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One-pot synthesis of *N*-fused benzimidazo- β -carbolines through sequential propargylation/*aza*-cycloisomerization approach

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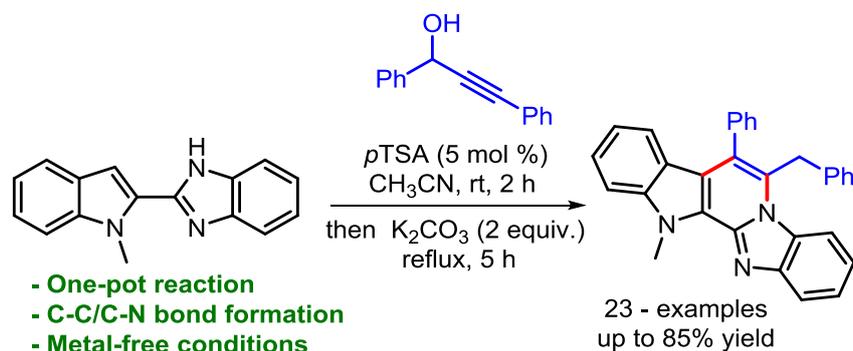
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ABSTRACT: The first sequential acid-catalyzed propargylation/base-mediated *aza*-cycloisomerization between indolyl-benzimidazoles and propargylic alcohols is described. This protocol enables the one-pot construction of *N*-fused benzimidazo- β -carbolines in good yields. The synthetic utility of this approach is demonstrated by the assembly of an *aza*-helicene and also by a gram scale reaction.

KEYWORDS: Propargylation • *aza*-annulation • β -carboline • Propargylic alcohol • Cycloisomerization

INTRODUCTION

β -Carbolines are one of the important scaffolds embedded in many bioactive natural products and/or pharmaceutical agents, such as 9-methyl harmine (**I**), methylated 7-bromoedistomin D (**II**), Chaetogline F (**III**) etc. as representative examples (Figure 1).¹⁻⁴ Further, *aza*-heterocyclic fused β -carbolines are also encountered as key motifs with important pharmacological properties (Figure 1). For instance, 2-methoxy-13-methyl-rutaecarpine (**IV**, fused quinazoline tetrahydro- β -carboline) alkaloid exhibits significant anti-malarial activity,⁵ Isogranulatimide A (**V**, fused imidazole β -carboline) showcases a G2 Checkpoint Inhibitor⁶ and Fascapsylin C (**VI**, fused β -carboline) displays strong cytotoxic activity against leukemia cells.⁷ Benzimidazole is also one of the frequent heterocycles in pharmaceuticals. Therefore, we became interested to explore the construction of a novel hybrid skeleton, *N*-fused benzimidazo- β -carboline.⁸ To the best of our knowledge, there are only two methods known in the literature towards the synthesis of benzimidazo- β -carbolines with limited examples. In the first method, copper-catalyzed intramolecular cyclization of *N*-propargylated benzimidazole **VII** provides the corresponding benzimidazo- β -carboline **VIII**

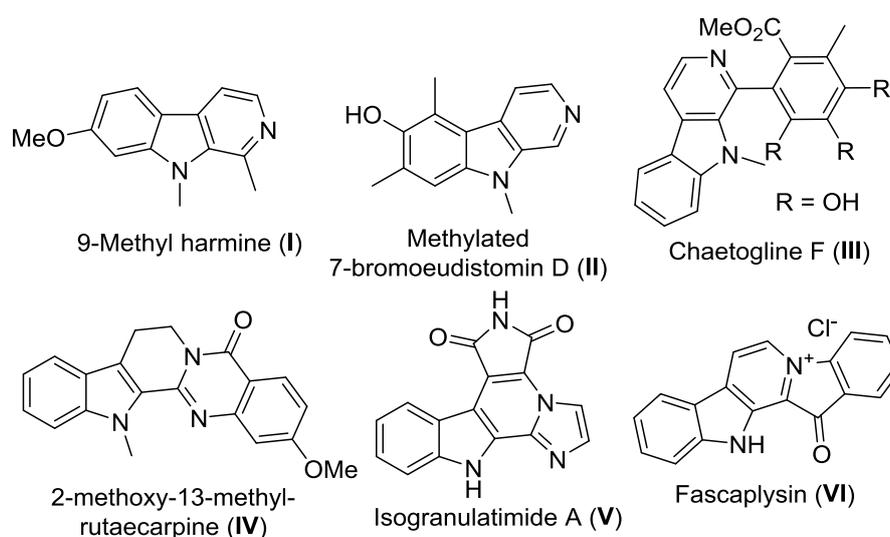
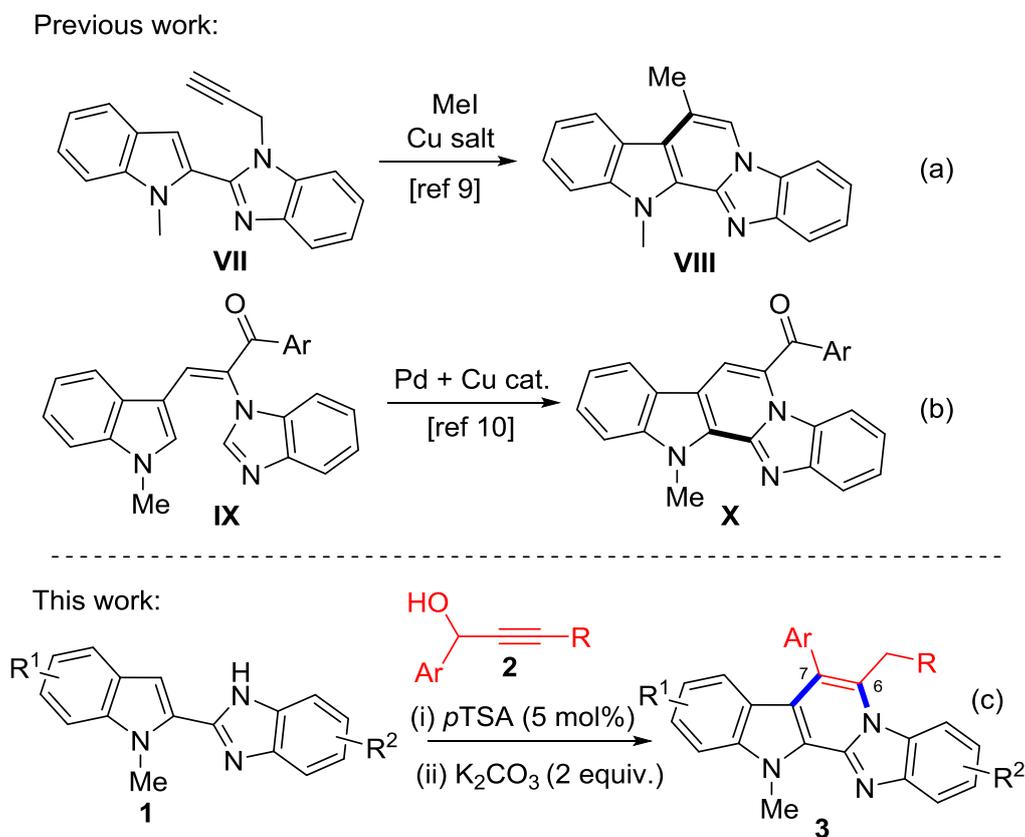


Figure 1: Representative examples of β -carboline and *N*-fused β -carboline

(Scheme 1a).⁹ The other method involves a transition metal-mediated C-C bond formation of indolyl-propenone **IX**, generated by the Knoevenagel condensation between azoles and indole carboxaldehydes, to give benzimidazo- β -carboline **X** (Scheme 1b).¹⁰ Hence, a general and efficient method for the construction of diversely substituted benzimidazo- β -carbolines remains desirable.

On the other hand, 1-aryl propargyl alcohols have emerged as effective precursors in sequential nucleophilic substitution/annulation reactions for the assembly of heterocycles as well as carbocycles.¹¹ Based on our previous research on the use of propargylic alcohols as reaction partners in annulation reactions,¹² we anticipated their reactivity with easily accessible indolyl-benzimidazoles (**1**) to offer targeted *N*-fused benzimidazo- β -carbolines (**3**). Herein, we describe the first sequential propargylation/*aza*-cycloisomerization approach for the assembly of *N*-fused benzimidazo- β -carbolines (Scheme 1c).

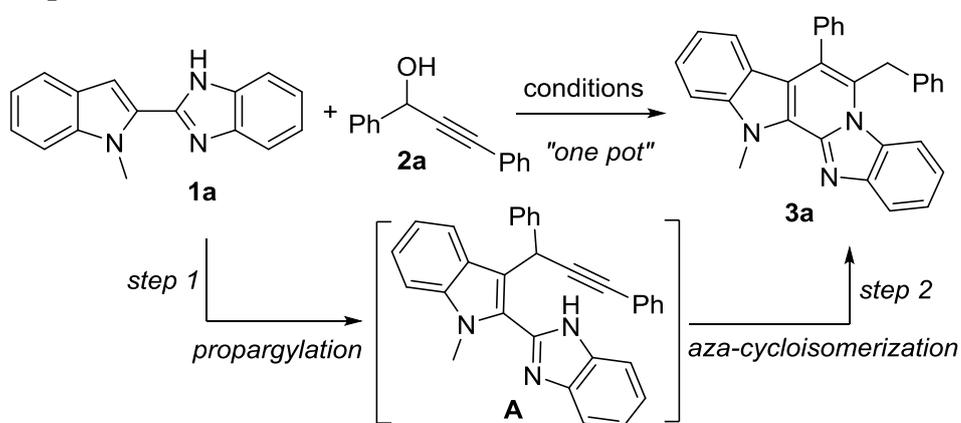


Scheme 1: Synthesis of *N*-fused benzimidazo- β -carbolines

RESULTS AND DISCUSSION

The indolyl-benzimidazole **1a** and propargylic alcohol **2a** were selected as model substrates to explore the feasibility of the envisaged propargylation followed by *aza*-cycloisomerization and to further optimize the reaction conditions (Table 1). Initially, various acid catalysts were screened for the propargylation of **1a** with **2a**. Among triflates, copper (II) triflate gave poor yield of **A** (20%, entry 1) whereas scandium (III) triflate gave satisfactory yield of 70% (entry 2). Indium (III) triflate performed well affording the intermediate **A** in 80% (entry 3).

Table 1. Optimization of the reaction conditions



entry	propargylation (acid, 5 mol%) [step 1]	benzannulation (base, temp, time) [step 2]	product	yield (%) ^b
1	Cu(OTf) ₂ , 2 h	---	A	20
2	Sc(OTf) ₃ , 2 h	---	A	70
3	In(OTf) ₃ , 2 h	---	A	80
4	FeCl ₃ , 2 h	---	A	78
5	BF ₃ · Et ₂ O, 2 h	---	A	65
6	<i>p</i> TSA, 2 h	---	A	95
7	-	NaHCO ₃ , 80 °C, 12 h	3a	10
8	-	DBU, 80 °C, 12 h	3a	20
9	-	K ₂ CO ₃ , 80 °C, 5 h	3a	85
10^c	<i>p</i>TSA, 2 h	K₂CO₃, 80 °C, 5 h	3a	82 [80]^d

^a(entries 1 to 6): Reactions were performed using 0.5 mmol of **1a** with 0.5 mmol of **2a** in 3 mL of CH₃CN and acid (5 mol%) at rt for 2 h; (entries 7 to 9): Reaction of **A** with 2 equiv. of base in CH₃CN at 80 °C for 3-12 h; ^bIsolated yield; ^cOne-pot reaction; ^dGram-scale reaction (4 mmol scale).

FeCl₃ gave a promising yield of **A** in 78% (entry 4) and BF₃.Et₂O was found to be less efficient (65% yield of **A**, entry 5). To our delight, *p*-toluene sulfonic acid (*p*TSA) proved to be the best catalyst for the C-propargylation to afford **A** in 95% yield (entry 6). Having the successful formation of C3-propargylated indole derivative **A**, its *aza*-cycloisomerization was tested using different bases. Sodium bicarbonate gave expected fused β -carboline **3a** in 10%, (entry 7) and DBU proved to be equally inefficient for this reaction (20% yield of **3a**, entry 8). To our satisfaction, potassium carbonate was the base of choice for this *aza*-annulation and subsequent isomerization affording the target molecule **3a** in 85% yield (entry 9). Next, a one-pot conversion *via* a sequential addition of *p*TSA followed by K₂CO₃ was also attempted and we were pleased to obtain **3a** in an overall yield of 82% (entry 10). We have also tested the scalability of the reaction on gram scale (4 mmol of **1a**) to afford **3a** in 80% yield (1.41g). The structure of benzimidazo- β -carboline **3a** and **3h** were also established by single-crystal X-ray diffraction studies (Figure 2).

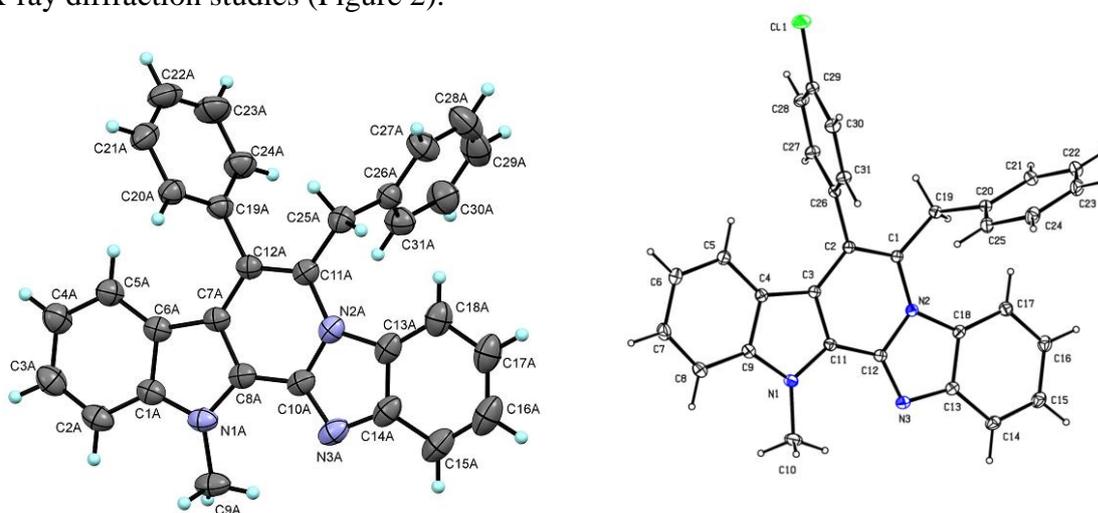
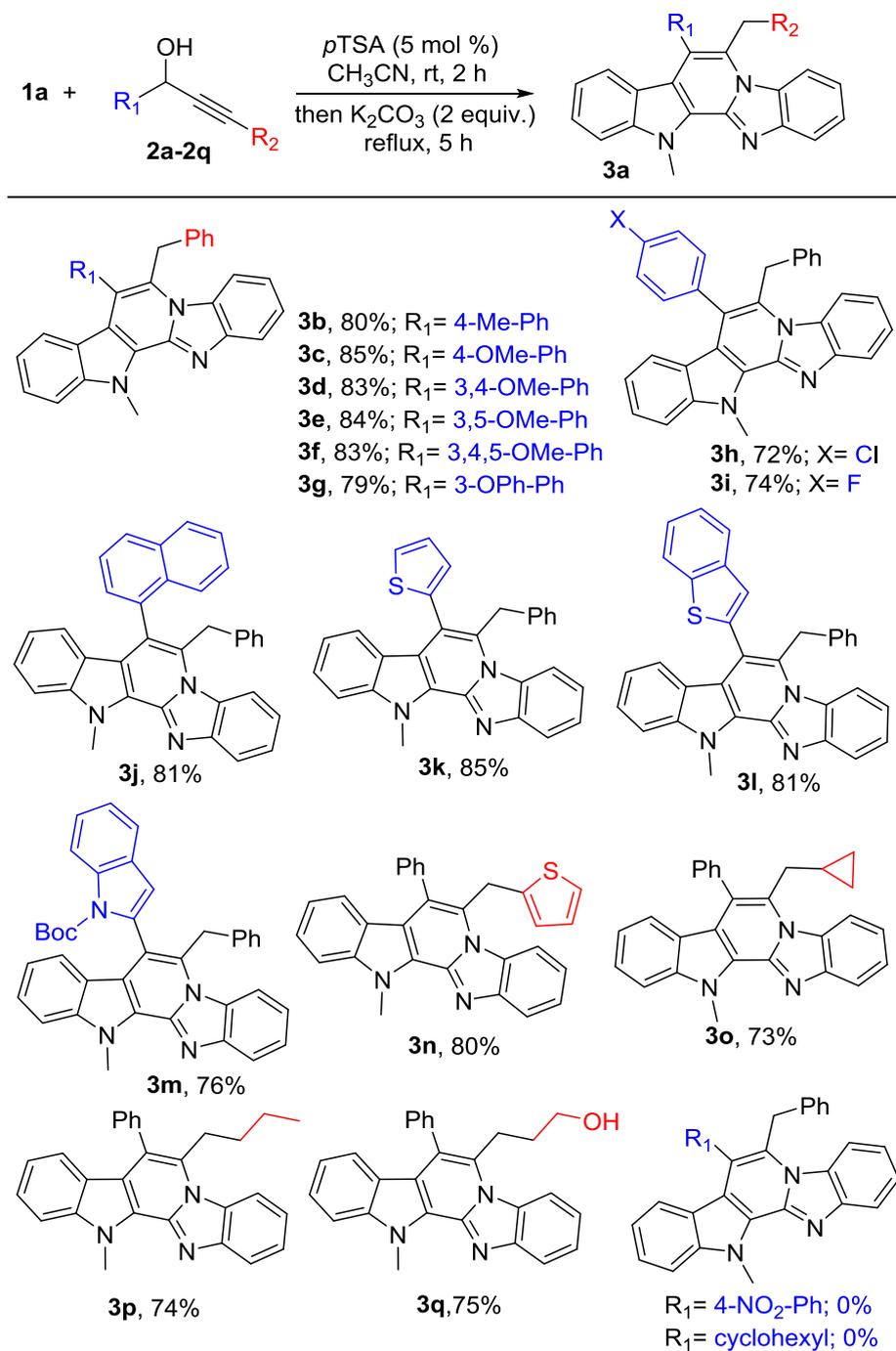


Figure 2: X-ray structure of **3a** (CCDC No. 2309870) and **3h** (CCDC No. 2326484)

Having defined the optimal reaction conditions, we probed the scope and limitations of this one-pot protocol. Initially, the scope of propargylic alcohols was studied and the results are shown in Scheme 2. As expected, the propargylic alcohols with electron-rich aryl (R¹)

substitutions holding methyl, methoxy and phenoxy groups performed well in this one-pot transformation affording the desired *aza*-fused benzimidazo- β -carbolines **3b** to **3g** in good

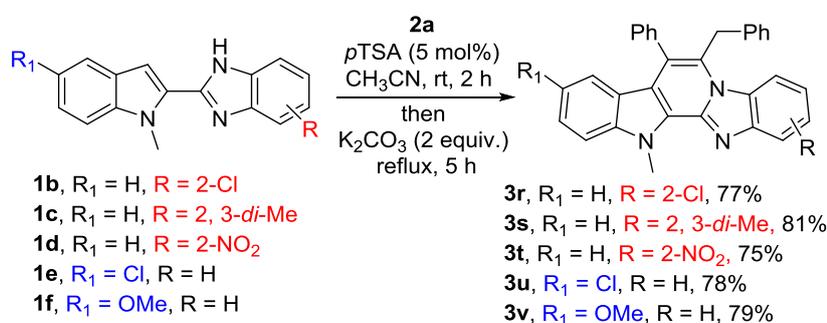


Reaction conditions: a) A mixture of **1a** (0.3 mmol) and **2a** (0.3 mmol) in the presence of *p*TSA (5 mol%) in 3 mL of CHCl₃ was stirred at rt for 2 hours followed by addition of K₂CO₃ (2 equiv.) and stirred at 80 °C till the reaction was complete; b) All the yields given are isolated yields; c) For the structures of **2a-2q**, see the supporting information.

Scheme 2: Scope and limitations regarding propargylic alcohols substrates^{a-c}

yields. Halogen substituted propargylic alcohols also gave the products **3h** and **3i** in 72% and 74% yields, respectively. Propargylic alcohol generated from 1-naphthaldehyde suited well to offer the corresponding fused β -carboline **3j** in 81% yield. Likewise, the heterocyclic substrates containing thiophene, benzothiophene and *N*-Boc-indole rings found to be well suited, affording the corresponding products **3k** to **3m** in good yield. As far as the other side of the propargylic alcohol is concerned (R^2 group linked to the alkyne), all the studied substrates were successful in providing the desired products. A thiophene group on the alkyne was perfectly compatible with the reaction, providing **3n** in 80% yield. Similarly, a cyclopropylated alcohol gave the annulated β -carboline **3o** in 73% yield while the propargylic alcohols having *n*-propyl group on the alkyne offered the product **3p** in 74% yield. The substrate with *tert*-butyldiphenylsilyl ether was also participated in this one-pot reaction affording the desilylated β -carboline **3q** in 75% yield. Not surprisingly, the substrates generated from 4-nitro benzaldehyde (electron-withdrawing group) and aliphatic aldehydes were found to be ineffective for acid-catalyzed propargylation reaction, which can be attributed to the formation of non-stabilized carbocation intermediate.

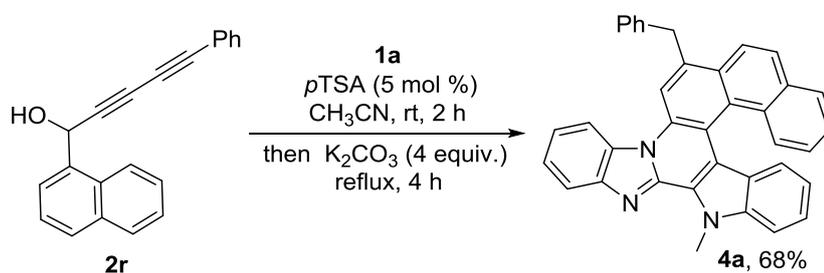
Next, we turned our attention to verify the substrate scope pertaining to the indolyl-benzimidazoles (Scheme 3). Substitutions (electron-donating as well as electron-withdrawing) on the benzimidazole ring such as chloro (**1b**), dimethyl (**1c**) and nitro (**1d**) groups were well tolerated in reaction with **2a** providing the fused benzimidazo-carbolines **3r**



Scheme 3: Scope and limitations regarding benzimidazole and indole moieties

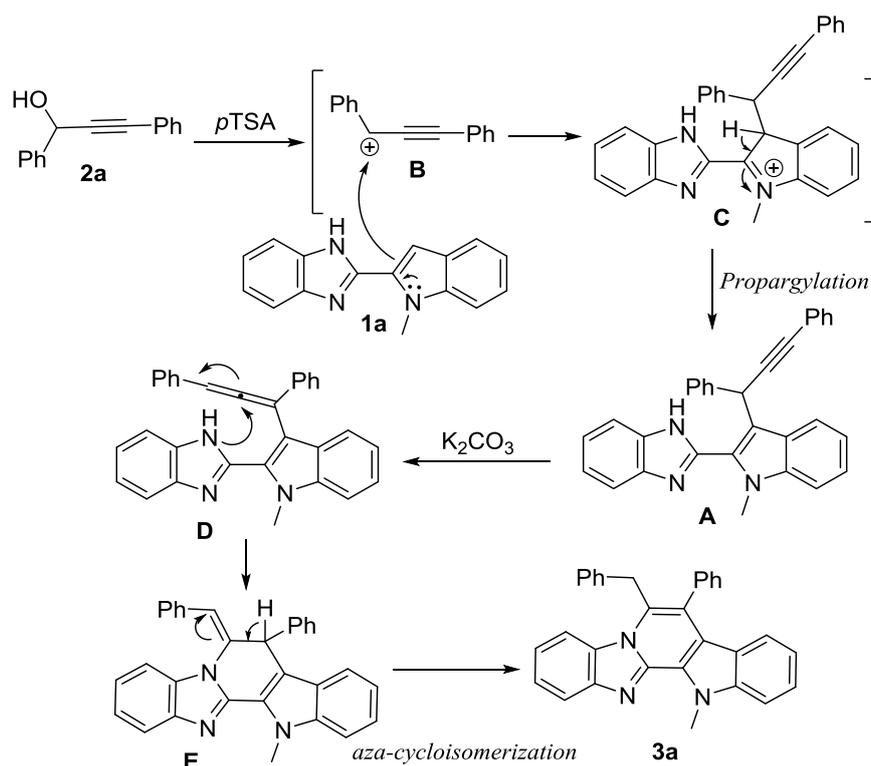
(77%), **3s** (81%) and **3t** (75%), respectively. Similarly, the effect of substitutions on the indole ring was also tested. The substrates having chloro (**1e**) and methoxy (**1f**) groups on indole participated in reaction with **2a** affording **3u** (78%) and **3v** (79%), respectively.

To further examine the versatility of this one-pot strategy, we investigated the reaction of diyne-ol **2r** with **1a** anticipating a double annulation. To our pleasure, the sequential propargylation/*aza*-cycloisomerization/benzannulation was feasible to deliver the corresponding *aza*-helicene **4a** in 68% yield (Scheme 4). The helicity of **4a** was established by chiral HPLC analysis, which revealed the existence of a pair of enantiomers.



Scheme 4: Synthesis of **4a**

Based on the aforesaid outcomes and relevant literature reports,^{12c} a possible reaction mechanism is proposed (Scheme 5). Initially, carbocation **B** is generated from **2a** in the presence of *p*TSA which reacts with nucleophile **1a** leading to propargylated indole **A** via intermediate **C**. Then, base-promoted formation of allene intermediate **D** and subsequent intramolecular regioselective *aza*-cyclization produced the intermediate **E**. Lastly, intramolecular isomerization of **E** through 1,3-H shift under basic conditions furnished the desired product **3a**. The intermediate **A** was also isolated, characterized and independently treated with base to obtain the product **3a**.



Scheme 5: Proposed mechanism

CONCLUSION

In conclusion, we have developed a convenient and straightforward approach for the synthesis of unprecedented *aza*-fused benzimidazo- β -carbolines from readily accessible starting materials. The strategy involves a sequential acid-catalysed C-propargylation/base-mediated *aza*-cycloisomerization. A variety of 1-aryl propargylic alcohols as well as indolyl benzimidazoles are found to be competent participants. Furthermore, this protocol could be extended to diyne-ol leading to a double annulation process affording the fused carbo- and hetero-aromatic structural framework (helicene). With interesting advantages such as metal-free, operationally easy conditions, good substrate scope and yield of the products, this method would find application in organic synthesis.

EXPERIMENTAL SECTION

General information:

All the reactions were performed in oven-dried glass apparatus. For reactions sensitive to air and moisture, an inert atmosphere (nitrogen) was employed, and freshly distilled anhydrous solvents were used. Commercially available reagents (*p*TSA, K₂CO₃) were utilized without additional purification. Thin-layer chromatography performed on silica plates and visualized under UV light and anisaldehyde was used to monitor all reactions. Column chromatography, using hexane and ethyl acetate as the eluent, was carried out on silica gel (100–200 mesh). The ¹H NMR spectra were recorded in CDCl₃ at 500 and 400 MHz, while the ¹³C NMR spectra were recorded at 126 and 101 MHz. ¹H NMR was recorded in CDCl₃ at 400 and 500 MHz, and ¹³C NMR was recorded at 126 and 101 MHz. δ 7.26, δ 77 and δ 2.5, δ 39.5 correspond to CDCl₃ and DMSO-*d*₆ in ¹H NMR and ¹³C NMR, respectively, and δ 1.56 and δ 3.3 are related to the moisture present in CDCl₃ and DMSO-*d*₆. Chemical shifts are reported in δ (ppm) relative to TMS as an internal standard, and *J* values are expressed in Hz. Multiplicity is denoted as s (singlet), d (doublet), t (triplet), m (multiplet), dd (doublet of doublets), etc. High-resolution mass spectra (HRMS) [ESI]⁺ were obtained using either a TOF or a double focusing spectrometer. Melting point of all solid compounds was determined using a melting point apparatus.

Procedures for the Preparation of Starting Materials:

All the basic starting materials **1a**¹ and **2a-2q** and **2v**, **2w** and **2r** were prepared based on literature reports² and the spectral data was compared.

General procedure for the preparation of indolyl benzimidazoles (1)

5-Chloro-2-(1-methyl-1H-indol-2-yl)-1H-benzo[d]imidazole (1b)

Off white solid, 138 mg, 78% yield, mp 180 – 182 °C; R_f = 0.3 (*n*-hexane: ethyl acetate = 9:1); ¹H NMR (400 MHz, DMSO) δ 13.10 (d, *J* = 11.1 Hz, 1H), 7.77 – 7.67 (m, 2H), 7.58 –

7.53 (m, 2H), 7.30 – 7.21 (m, 3H), 7.13 (t, $J = 7.4$ Hz, 1H), 4.28 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, DMSO) δ 147.7, 139.4, 129.3, 127.1, 123.8 (2C), 123.0, 121.5 (2C), 120.7 (2C), 110.9, 104.5, 32.5; HRMS (ESI): m/z calcd for $\text{C}_{16}\text{H}_{13}\text{N}_3\text{Cl}$ $[\text{M} + \text{H}]^+$: 282.0798, found 282.0785.

5,6-Dimethyl-2-(1-methyl-1H-indol-2-yl)-1H-benzo[d]imidazole (1c)

Off white solid, 138 mg, 80%, mp 250 – 252 °C; $R_f = 0.3$ (*n*-hexane: ethyl acetate = 9:1); ^1H NMR (400 MHz, DMSO) δ 12.59 (s, 1H), 7.59 (d, $J = 7.9$ Hz, 1H), 7.48 (d, $J = 8.3$ Hz, 1H), 7.32 (s, 2H), 7.21 – 7.17 (m, 1H), 7.15 (s, 1H), 7.09 – 6.99 (m, 1H), 4.22 (s, 3H), 2.27 (s, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, DMSO) δ 145.5, 139.2, 130.2, 127.2, 123.3 (2), 121.3 (3), 120.5 (2), 110.7 (2), 103.4 (2), 32.4, 20.5 (2); HRMS (ESI): m/z calcd for $\text{C}_{18}\text{H}_{17}\text{N}_3$ $[\text{M} + \text{H}]^+$: 276.1501, found 276.1494.

2-(1-methyl-1H-indol-2-yl)-5-nitro-1H-benzo[d]imidazole (1d)

Yellow solid, 129 mg, 78%, mp 265 – 270 °C; $R_f = 0.2$ (*n*-hexane: ethyl acetate = 9:1); ^1H NMR (500 MHz, DMSO) δ 13.59 (s, 1H), 8.49 (s, 1H), 8.16 (d, $J = 8.8$ Hz, 1H), 7.78 (d, $J = 7.9$ Hz, 1H), 7.72 (d, $J = 7.9$ Hz, 1H), 7.61 (d, $J = 8.4$ Hz, 1H), 7.39 (s, 1H), 7.33 (t, $J = 7.6$ Hz, 1H), 7.16 (t, $J = 7.4$ Hz, 1H), 4.32 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, DMSO) δ 150.7, 143.2, 139.7, 128.6, 127.0, 124.2 (2), 121.8 (2), 120.9 (2), 118.7, 111.0 (2), 105.7, 32.6; HRMS (ESI): m/z calcd for $\text{C}_{16}\text{H}_{13}\text{N}_4\text{O}_2$ $[\text{M} + \text{H}]^+$: 293.1039, found 293.1029.

2-(5-Chloro-1-methyl-1H-indol-2-yl)-1H-benzo[d]imidazole (1e)

Off white solid, 133 mg, 75% yield, mp 223 – 225 °C; $R_f = 0.3$ (*n*-hexane: ethyl acetate = 9:1); ^1H NMR (400 MHz, DMSO) δ 13.02 (s, 1H), 7.77 (d, $J = 2.0$ Hz, 1H), 7.74 (d, $J = 7.8$ Hz, 1H), 7.60 (d, $J = 8.8$ Hz, 1H), 7.56 (d, $J = 7.7$ Hz, 1H), 7.30 – 7.27 (m, 2H), 7.26 – 7.21 (m, 2H), 4.31 (s, 3H); δ $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, DMSO) δ 145.8, 144.1, 137.7, 134.6,

131.3, 128.2, 125.2, 123.6, 123.4, 122.3, 120.4, 119.6, 112.5, 111.7, 103.5, 32.8; HRMS (ESI): m/z calcd for $C_{16}H_{13}N_3Cl$ $[M + H]^+$: 282.0798, found 282.0784.

2-(5-Methoxy-1-methyl-1H-indol-2-yl)-1H-benzo[d]imidazole (1f)

Off white solid, 121 mg, 70%, mp 243 – 245 °C; R_f = 0.3 (*n*-hexane: ethyl acetate = 9:1); 1H NMR (400 MHz, DMSO) δ 12.80 (s, 1H), 7.64 (d, J = 7.0 Hz, 1H), 7.47 (d, J = 7.3 Hz, 1H), 7.40 (d, J = 8.9 Hz, 1H), 7.19 – 7.14 (m, 2H), 7.11 – 7.10 (m, 2H), 6.86 – 6.84 (m, 1H), 4.21 (s, 3H), 2.44 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO) δ 154.6, 146.4, 144.2, 134.7, 134.5, 130.0, 127.5, 123.3, 122.2, 119.4, 114.2, 111.7, 111.5, 103.6, 102.4, 55.8, 32.6; HRMS (ESI): m/z calcd for $C_{17}H_{16}N_3O$ $[M + H]^+$: 278.1293, found 278.1283.

General procedure for the preparation of aza-fused benzimidazo- β -carbolines (3)

To the solution of indolyl benzimidazole (1) (0.40 mmol, 1.0 equiv) in CH_3CN (3 mL), propargylic alcohol 2 (0.40 mmol, 1.0 equiv) and *p*TSA (0.02 mmol, 5 mol %) were added and stirred at rt for 2h affording intermediate A. It was further treated with K_2CO_3 (0.80 mmol, 2 equiv) and stirred at 80 °C in an oil bath till the completion of the reaction as indicated by TLC. The reaction mixture was diluted with water (10 mL) and extracted by EtOAc (10 mL x 2). The organic layers were combined, washed by water (10 mL x 2), and brine solution (10 mL), dried over Na_2SO_4 , and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to afford substituted *N*-fused benzimidazo- β -carbolines (3).

2-(3-(1,3-diphenylprop-2-yn-1-yl)-1-methyl-1H-indol-2-yl)-1H-benzo[d]imidazole (A)

Yellow solid, 167 mg, 95% yield, mp 225 – 230 °C; R_f = 0.3 (*n*-hexane: ethyl acetate = 9:1); 1H NMR (400 MHz, $CDCl_3$) δ 9.85 (s, 1H), 7.84 (s, 1H), 7.65 (d, J = 8.1 Hz, 1H), 7.52 (d, J = 7.9 Hz, 2H), 7.41 (d, J = 8.4 Hz, 1H), 7.34 (dd, J = 7.0, 1.0 Hz, 1H), 7.31 – 7.23 (m, 10H),

7.20 (dd, $J = 11.4, 4.3$ Hz, 1H), 7.17 – 7.11 (m, 1H), 5.86 (s, 1H), 4.01 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 144.1, 140.3, 138.2, 131.6 (2), 128.7, 128.3, 128.3, 127.4 (2), 127.1, 127.0, 126.2, 123.7, 122.9, 122.7, 120.3, 120.1, 120.0, 120.0, 116.4, 110.8, 110.2, 89.7, 85.0, 34.0, 31.7; HRMS (ESI): m/z calcd for $\text{C}_{31}\text{H}_{24}\text{N}_3$ $[\text{M} + \text{H}]^+$: 438.1965, found 438.1970.

6-Benzyl-12-methyl-7-phenyl-12H-benzo[4',5']imidazo[1',2':1,2]pyrido[3,4-b]indole (3a)

Off-white solid, 145 mg, 82% yield, mp 217 – 219 °C; $R_f = 0.5$ (*n*-hexane: ethyl acetate = 9:1); ^1H NMR (400 MHz, CDCl_3) δ 7.93 (d, $J = 8.1$ Hz, 1H), 7.71 (d, $J = 8.5$ Hz, 1H), 7.47 (d, $J = 8.3$ Hz, 1H), 7.44 – 7.39 (m, 3H), 7.37 – 7.31 (m, 4H), 7.17 – 7.11 (m, 2H), 7.10 – 7.08 (m, 1H), 7.04 – 6.97 (m, 3H), 6.93 – 6.86 (m, 1H), 6.50 (d, $J = 8.1$ Hz, 1H), 4.64 (s, 3H), 4.58 (s, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 144.8, 142.2, 140.9, 138.0, 137.2, 130.0, 129.8, 128.9, 128.9, 128.3, 127.9, 127.5, 126.5, 125.7, 125.4, 124.3, 122.7, 122.5, 121.8, 120.9, 120.1, 119.4, 117.8, 115.2, 109.7, 35.5, 32.2; HRMS (ESI): m/z calcd for $\text{C}_{31}\text{H}_{24}\text{N}_3$ $[\text{M} + \text{H}]^+$: 438.1970, found 438.1981.

6-Benzyl-12-methyl-7-(*p*-tolyl)-12H-benzo[4',5']imidazo[1',2':1,2]pyrido[3,4-b]indole (3b)

Off - white solid, 146 mg, 80% yield, mp 220 – 222 °C, $R_f = 0.5$ (*n*-hexane: ethyl acetate = 8:2); ^1H NMR (400 MHz, CDCl_3) δ 7.99 (d, $J = 8.1$ Hz, 1H), 7.78 (d, $J = 8.5$ Hz, 1H), 7.54 (d, $J = 8.3$ Hz, 1H), 7.45 – 7.36 (m, 2H), 7.30 – 7.25 (m, 4H), 7.23 – 7.14 (m, 3H), 7.10 – 7.06 (m, 3H), 6.99 (t, $J = 7.6$ Hz, 1H), 6.66 (d, $J = 8.1$ Hz, 1H), 4.70 (s, 3H), 4.66 (s, 2H), 2.47 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 144.9, 142.3, 141.00, 138.2, 137.9, 134.1, 129.9, 129.8, 129.6, 128.9, 128.0, 127.5, 126.5, 125.7, 125.3, 124.2, 122.7, 122.6, 121.9, 120.8, 120.0, 119.4, 117.9, 115.2, 109.7, 35.5, 32.2, 21.5; HRMS (ESI): m/z calcd for $\text{C}_{32}\text{H}_{26}\text{N}_3$ $[\text{M} + \text{H}]^+$: 452.2127, found 452.2146.

6-Benzyl-7-(4-methoxyphenyl)-12-methyl-12H-benzo[4',5']imidazo[1',2':1,2]pyrido[3,4-b]indole (3c)

Yellow solid, 161 mg, 85% yield, mp 226 – 228 °C, R_f = 0.5 (*n*-hexane: ethyl acetate = 9:1); ^1H NMR (500 MHz, CDCl_3) δ 7.99 (d, J = 8.0 Hz, 1H), 7.78 (d, J = 8.5 Hz, 1H), 7.55 (d, J = 8.3 Hz, 1H), 7.45 – 7.40 (m, 2H), 7.32 (d, J = 8.6 Hz, 2H), 7.23 – 7.15 (m, 3H), 7.10 – 7.06 (m, 3H), 7.01 (t, J = 7.5 Hz, 3H), 6.70 (d, J = 8.1 Hz, 1H), 4.71 (s, 3H), 4.67 (s, 2H), 3.90 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 159.5, 140.1, 138.1, 131.1 (2), 129.8, 129.3, 128.9 (2), 128.3, 127.5, 126.5, 125.6, 125.4, 124.3, 122.6, 122.4, 121.1, 120.9, 120.1, 119.3, 115.2, 114.3 (2), 109.7, 55.3, 35.5, 32.2; HRMS (ESI): m/z calcd for $\text{C}_{32}\text{H}_{26}\text{N}_3\text{O}$ $[\text{M}+\text{H}]^+$: 468.2078, found 468.2065.

6-Benzyl-7-(3,4-dimethoxyphenyl)-12-methyl-12H-benzo[4',5']imidazo [1',2':1,2] pyrido [3,4-b]indole (3d)

Off white solid, 167 mg, 83% yield, mp 227–229°C, R_f = 0.5 (*n*-hexane: Ethyl acetate = 9:1); ^1H NMR (400 MHz, CDCl_3) δ 7.80 (d, J = 8.1 Hz, 1H), 7.57 (d, J = 8.5 Hz, 1H), 7.34 (d, J = 8.3 Hz, 1H), 7.26 – 7.21 (m, 2H), 7.05 – 6.96 (m, 3H), 6.92 – 6.84 (m, 3H), 6.82 – 6.77 (m, 3H), 6.67 (d, J = 1.2 Hz, 1H), 6.62 (d, J = 8.1 Hz, 1H), 4.52 (s, 1H), 4.48 (s, 3H), 4.36 (d, J = 17.8 Hz, 1H), 3.78 (s, 3H), 3.36 (s, 3H).; $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 148.9, 148.8, 144.9, 142.2, 140.9, 138.6, 129.9, 129.5, 128.9, 128.3, 127.6, 126.5, 125.7, 125.4, 124.3, 122.5, 122.3, 122.2, 122.0, 120.9, 120.2, 119.4, 117.8, 115.2, 113.1, 111.3, 109.7, 55.9, 55.6, 35.7, 32.2; HRMS (ESI): m/z calcd for $\text{C}_{33}\text{H}_{28}\text{N}_3\text{O}_2$ $[\text{M} + \text{H}]^+$: 498.2182 found: 498.2186.

6-Benzyl-7-(3,5-dimethoxyphenyl)-12-methyl-12H-benzo[4',5']imidazo[1',2':1,2] pyrido [3,4-b]indole (3e)

White solid, 169 mg, 84% yield, mp 187 – 189 °C, $R_f = 0.5$ (*n*-hexane: ethyl acetate =9:1); ^1H NMR (300 MHz, CDCl_3) δ 7.94 (d, $J = 8.0$ Hz, 1H), 7.72 (d, $J = 8.5$ Hz, 1H), 7.50 (d, $J = 8.3$ Hz, 1H), 7.40 – 7.34 (m, 2H), 7.19 – 7.10 (m, 3H), 7.08 – 6.95 (m, 4H), 6.91 (s, 2H), 6.77 – 6.73 (m, 2H), 4.71 (s, 1H), 4.65 (s, 3H), 4.54 (d, $J = 18.0$ Hz, 1H), 3.92 (s, 3H), 3.48 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 148.9, 148.8, 144.9, 142.3, 140.9, 138.6, 129.9, 129.4, 128.9, 128.4, 127.6, 126.5, 125.7, 125.4, 124.3, 122.5, 122.3, 122.2, 122.0, 120.9, 120.2, 119.4, 117.8, 115.2, 113.1, 111.3, 109.7, 55.9, 55.6, 35.7, 32.2; HRMS (ESI): m/z calcd for $\text{C}_{33}\text{H}_{28}\text{N}_3\text{O}_2$ $[\text{M}+\text{H}]^+$: 498.2182, found 498.2186.

6-Benzyl-12-methyl-7-(3,4,5-trimethoxyphenyl)-12H-benzo[4',5']imidazo[1',2':1,2]pyrido[3,4-*b*]indole (3f)

White solid, 177 mg, 83% yield, mp 185-187 °C, $R_f = 0.5$ (*n*-hexane: ethyl acetate = 8:2); ^1H NMR (400 MHz, CDCl_3) δ 8.01 (d, $J = 8.1$ Hz, 1H), 7.80 (d, $J = 8.5$ Hz, 1H), 7.56 (d, $J = 8.3$ Hz, 1H), 7.50 – 7.40 (m, 2H), 7.23 (d, $J = 7.6$ Hz, 2H), 7.17 (t, $J = 7.2$ Hz, 1H), 7.15 – 7.04 (m, 4H), 6.91 (d, $J = 8.1$ Hz, 1H), 6.60 (s, 2H), 4.71 (s, 3H), 4.65 (s, 2H), 3.98 (s, 3H), 3.58 (s, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 153.3, 144.9, 142.1, 140.9, 138.8, 137.7, 132.3, 129.9, 128.9, 128.1, 127.6, 126.5, 125.7, 125.4, 124.3, 122.7, 122.3, 122.00, 120.9, 120.3, 119.5, 117.4, 115.1, 109.7, 107.0, 61.2, 55.9, 35.8, 32.1; HRMS (ESI): m/z calcd for $\text{C}_{34}\text{H}_{30}\text{N}_3\text{O}_3$ $[\text{M}+\text{H}]^+$: 528.2287, found 528.2289.

6-Benzyl-12-methyl-7-(3-phenoxyphenyl)-12H-benzo[4',5']imidazo[1',2':1,2]pyrido[3,4-*b*]indole (3g)

Yellow solid, 169 mg, 79% yield, mp 177 – 179 °C, $R_f = 0.5$ (*n*-hexane: ethyl acetate = 9:1); ^1H NMR (400 MHz, CDCl_3) δ 7.91 (d, $J = 8.1$ Hz, 1H), 7.68 (d, $J = 8.5$ Hz, 1H), 7.47 (d, $J = 8.3$ Hz, 1H), 7.40 – 7.31 (m, 3H), 7.15 – 7.08 (m, 7H), 7.05 – 6.98 (m, 2H), 6.97 – 6.90 (m, 4H), 6.84 (d, $J = 7.8$ Hz, 2H), 6.67 (d, $J = 8.1$ Hz, 1H), 4.60 (s, 3H), 4.58 (s, 2H); $^{13}\text{C}\{^1\text{H}\}$

NMR (101 MHz, CDCl₃) δ 157.76, 156.65, 144.85, 142.16, 140.90, 138.87, 137.79, 130.38, 129.82 (2), 129.03, 127.87, 127.42, 126.59, 125.70, 125.39, 124.79, 124.30, 123.44, 122.38, 121.99, 121.77, 120.89, 120.16, 120.01, 119.44, 119.05, 118.82, 117.36, 115.18, 109.76, 35.48, 32.15; HRMS (ESI): m/z calcd for C₃₇H₂₈N₃O [M+H]⁺ : 530.2232, found 530.2212.

6-Benzyl-7-(4-chlorophenyl)-12-methyl-12H-benzo[4',5']imidazo[1',2':1,2]pyrido[3,4-b]indole (3h)

Off- white solid, 137 mg, 72% yield, mp 241 – 243 °C , R_f = 0.5(*n*-hexane: ethyl acetate = 9:1); ¹H NMR (400 MHz, CDCl₃) δ 8.04 (d, J = 8.1 Hz, 1H), 7.75 (d, J = 8.5 Hz, 1H), 7.56 – 7.51 (m, 2H), 7.49 (d, J = 4.9 Hz, 2H), 7.44 (t, J = 8.7 Hz, 3H), 7.28 – 7.18 (m, 3H), 7.17 – 7.11 (m, 1H), 7.10 – 7.04 (m, 3H), 6.72 (d, J = 8.1 Hz, 1H), 4.65 (s, 3H), 4.54 (s, 2H); ¹³C{¹H} (75 MHz, CDCl₃) δ 144.9, 142.1, 140.9, 137.8, 135.7, 134.3, 131.5, 129.8, 129.2, 129.0, 128.1, 127.4, 126.7, 125.7, 125.4, 124.4, 122.3, 121.6, 121.3, 121.0, 120.3, 119.5, 117.2, 115.2, 109.8, 35.4, 32.1; HRMS (ESI): m/z calcd for C₃₁H₂₃N₃Cl [M+H]⁺ : 472.1581, found 472.1591.

6-Benzyl-7-(4-fluorophenyl)-12-methyl-12H-benzo[4',5']imidazo[1',2':1,2]pyrido[3,4-b]indole (3i)

Yellow solid, 136 mg, 74% yield, mp 224 – 226 °C, R_f = 0.5 (*n*-hexane: ethyl acetate = 9:1); ¹H NMR (400 MHz, CDCl₃) δ 8.00 (d, J = 8.1 Hz, 1H), 7.77 (d, J = 8.5 Hz, 1H), 7.56 (d, J = 8.3 Hz, 1H), 7.46 – 7.43 (m, 2H), 7.41 – 7.36 (m, 2H), 7.26 – 7.15 (m, 5H), 7.10 (t, J = 7.8 Hz, 1H), 7.08 – 6.97 (m, 3H), 6.63 (d, J = 8.1 Hz, 1H), 4.71 (s, 3H), 4.64 (s, 2H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 162.8 (d, J = 247.3 Hz), 161.5, 144.9, 142.2, 140.9, 137.9, 133.1 (d, J = 2.9 Hz), 131.8 (d, J = 8.0 Hz), 129.8, 129.0, 128.2, 127.5, 126.6, 125.8, 125.4, 124.3, 122.4, 121.6, 121.5, 120.9, 120.2, 119.5, 117.5, 116.5, 116.0 (d, J = 21.3 Hz), 115.2, 109.8,

35.4, 32.1; ^{19}F NMR (376 MHz, CDCl_3) δ -71.12; HRMS (ESI): m/z calcd for $\text{C}_{31}\text{H}_{23}\text{N}_3\text{F}$ $[\text{M}+\text{H}]^+$: 456.1876, found 456.1895.

6-Benzyl-12-methyl-7-(naphthalen-1-yl)-12H-benzo[4',5']imidazo[1',2':1,2]pyrido[3,4-*b*]indole (3j)

Yellow solid, 159 mg, 81%, mp 280 – 282 °C, R_f = 0.5 (*n*-hexane: ethyl acetate = 8:2); ^1H NMR (400 MHz, CDCl_3) δ 8.10 – 7.93 (m, 3H), 7.80 (d, J = 8.5 Hz, 1H), 7.54 – 7.49 (m, 4H), 7.48 – 7.39 (m, 2H), 7.34 – 7.30 (m, 1H), 7.24 – 7.20 (m, 1H), 7.21 – 7.07 (m, 4H), 7.01 (d, J = 6.9 Hz, 2H), 6.74 (t, J = 7.3 Hz, 1H), 6.06 (d, J = 8.1 Hz, 1H), 4.77 – 4.72 (m, 4H), 4.40 (d, J = 17.8 Hz, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 144.9, 142.5, 140.9, 137.9, 134.3, 133.8, 132.6, 129.9, 128.9, 128.8 (2), 128.4, 127.9, 127.5 (2), 126.6, 126.5, 126.3, 125.8, 125.7, 125.3, 124.4, 122.3, 121.5, 120.9, 120.4, 120.2, 119.5, 118.1, 115.3, 109.6, 35.7, 32.2; HRMS (ESI): m/z calcd for $\text{C}_{35}\text{H}_{26}\text{N}_3$ $[\text{M}+\text{H}]^+$: 488.2127, found 488.2135.

6-Benzyl-12-methyl-7-(thiophen-2-yl)-12H-benzo[4',5']imidazo[1',2':1,2]pyrido[3,4-*b*]indole (3k)

Yellow solid, 153 mg, 85% yield, mp 252 – 254 °C, R_f = 0.5 (*n*-hexane: ethyl acetate = 9:1); ^1H NMR (400 MHz, CDCl_3) δ 7.92 (d, J = 8.1 Hz, 1H), 7.74 (d, J = 8.5 Hz, 1H), 7.49 (d, J = 8.3 Hz, 1H), 7.44 (dd, J = 5.2, 1.1 Hz, 1H), 7.41 – 7.34 (m, 2H), 7.18 – 7.13 (m, 2H), 7.13 – 7.08 (m, 2H), 7.07 – 6.96 (m, 5H), 6.67 (d, J = 8.1 Hz, 1H), 4.73 (t, J = 15.4 Hz, 2H), 4.64 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 144.9, 142.3, 140.9, 137.8, 137.5, 130.3, 129.8, 129.00, 128.6, 127.5, 127.5, 127.0, 126.6, 125.5, 125.4, 124.5, 122.3, 121.7, 121.0, 120.4, 119.5, 118.2, 115.2, 114.9, 109.7, 35.6, 32.1; HRMS (ESI): m/z calcd for $\text{C}_{29}\text{H}_{22}\text{N}_3\text{S}$ $[\text{M}+\text{H}]^+$: 444.1534, found 444.1548.

**7-(Benzo[b]thiophen-2-yl)-6-benzyl-12-methyl-12H-benzo[4',5']imidazo[1',2':1,2] pyrido
[3,4-b]indole (3l)**

Off- white solid, 162 mg, 81% yield, mp 245 – 247 °C, $R_f = 0.5$ (*n*-hexane: ethyl acetate = 8:2); ^1H NMR (500 MHz, CDCl_3) δ 8.03 (d, $J = 8.1$ Hz, 1H), 7.99 (d, $J = 8.2$ Hz, 1H), 7.81 (d, $J = 8.5$ Hz, 1H), 7.54 (d, $J = 8.3$ Hz, 1H), 7.46 – 7.43 (m, 1H), 7.40 – 7.36 (m, 3H), 7.33 (d, $J = 8.0$ Hz, 1H), 7.25 – 7.18 (m, 3H), 7.17 (d, $J = 7.4$ Hz, 1H), 7.15 – 7.09 (m, 1H), 7.07 (d, $J = 7.2$ Hz, 2H), 6.90 – 6.79 (m, 1H), 6.43 (d, $J = 8.1$ Hz, 1H), 4.81 (d, $J = 17.7$ Hz, 1H), 4.74 (s, 3H), 4.48 (d, $J = 17.8$ Hz, 1H).; $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 144.9, 142.4, 140.9, 139.9, 139.1, 138.1, 132.1, 129.9, 129.8, 129.00, 127.5, 126.6, 125.8, 125.8, 125.4, 124.9, 124.7, 124.5, 123.1, 122.9, 122.0, 121.6, 121.0, 120.3, 119.5, 117.7, 115.6, 115.2, 109.6, 35.7, 32.2; HRMS (ESI): m/z calcd for $\text{C}_{33}\text{H}_{24}\text{N}_3\text{S}$ $[\text{M}+\text{H}]^+$: 494.1691, found 494.1689.

***tert*-Butyl 2-(6-benzyl-12-methyl-12H-benzo[4',5']imidazo[1',2':1,2]pyrido[3,4-b]indol-7-yl)-1H-indole-1-carboxylate (3m)**

Off - white solid, 177 mg, 76% yield, mp 220-222 °C, $R_f = 0.5$ (*n*-hexane: ethyl acetate = 9:1); ^1H NMR (400 MHz, CDCl_3) δ 8.31 (d, $J = 8.0$ Hz, 1H), 8.03 (d, $J = 8.0$ Hz, 1H), 7.84 (d, $J = 8.5$ Hz, 1H), 7.55 (d, $J = 8.3$ Hz, 1H), 7.52 – 7.33 (m, 4H), 7.23 (d, $J = 7.5$ Hz, 2H), 7.20 – 7.14 (m, 2H), 7.13 – 7.08 (m, 4H), 6.93 – 6.86 (m, 1H), 6.81 (d, $J = 8.0$ Hz, 1H), 4.89 (d, $J = 17.7$ Hz, 1H), 4.75 (s, 3H), 4.56 (d, $J = 17.8$ Hz, 1H), 1.59 (s, 9H).; $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 149.5, 140.9, 138.6, 135.3, 135.2, 130.5, 130.0, 129.9, 128.9, 127.5, 127.4, 126.6, 125.8, 125.4, 125.2, 125.1, 125.0, 124.5, 123.2, 122.1, 121.0, 120.5, 120.2, 119.5, 117.9, 116.4, 115.3, 115.2, 113.3, 109.6, 83.9, 36.0, 32.2, 28.1; HRMS (ESI): m/z calcd for $\text{C}_{38}\text{H}_{33}\text{N}_4\text{O}_2$ $[\text{M}+\text{H}]^+$: 577.2604, found 577.2608.

12-Methyl-7-phenyl-6-(thiophen-2-ylmethyl)-12H-benzo[4',5']imidazo[1',2':1,2]pyrido[3,4-b]indole (3n)

Off white solid, 143 mg, 80% yield, mp 239–241 °C, $R_f = 0.3$ (*n*-hexane: ethyl acetate = 9:1); ^1H NMR (400 MHz, CDCl_3) δ 8.01 (d, $J = 8.1$ Hz, 1H), 7.79 (d, $J = 8.5$ Hz, 1H), 7.53 – 7.47 (m, 4H), 7.46 – 7.39 (m, 4H), 7.26 – 7.25 (m, 1H), 7.16 – 7.12 (m, 1H), 6.99 – 6.95 (m, 1H), 6.88 (dd, $J = 5.0, 1.2$ Hz, 1H), 6.72 (dd, $J = 2.8, 1.3$ Hz, 1H), 6.57 (d, $J = 8.1$ Hz, 1H), 4.68 (s, 3H), 4.54 (s, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 144.9, 142.2, 140.9, 138.4, 137.2, 130.1, 129.9, 128.9, 128.5, 128.3, 127.3, 126.5, 125.7, 125.3, 124.3, 122.5, 122.0, 121.8, 121.3, 120.9, 120.1, 119.5, 117.7, 115.2, 109.7, 32.1, 31.3; HRMS (ESI): m/z calcd for $\text{C}_{29}\text{H}_{22}\text{N}_3\text{S}$ $[\text{M}+\text{H}]^+$: 444.1534 found: 444.1544.

6-(Cyclopropylmethyl)-12-methyl-7-phenyl-12H-benzo[4',5']imidazo[1',2':1,2]pyrido[3,4-b]indole (3o)

Off white solid, 118 mg, 73% yield, mp 256 – 258 °C, $R_f = 0.5$ (*n*-hexane: ethyl acetate = 8:2); ^1H NMR (500 MHz, CDCl_3) δ 8.42 (d, $J = 8.5$ Hz, 1H), 8.11 (d, $J = 8.0$ Hz, 1H), 7.58 – 7.56 (m, 4H), 7.55 – 7.52 (m, 1H), 7.49 – 7.47 (m, 2H), 7.41 (t, $J = 7.6$ Hz, 2H), 6.96 (t, $J = 7.3$ Hz, 1H), 6.50 (d, $J = 8.1$ Hz, 1H), 4.70 (s, 3H), 3.21 (d, $J = 5.8$ Hz, 2H), 1.27 – 1.25 (m, 1H), 0.52 – 0.48 (m, 2H), 0.08 – 0.07 (m, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 141.1, 137.4, 131.5, 130.9, 130.1, 129.9, 128.9, 128.7, 128.3, 125.6, 124.7, 122.4, 121.9, 121.3, 121.1, 120.1, 119.3, 115.5, 115.4, 109.7, 109.6, 33.3, 32.3, 9.4, 5.4; HRMS (ESI): m/z calcd for $\text{C}_{28}\text{H}_{24}\text{N}_3$ $[\text{M}+\text{H}]^+$: 402.1970, found: 402.1964.

6-Butyl-12-methyl-7-phenyl-12H-benzo[4',5']imidazo[1',2':1,2]pyrido[3,4-b]indole (3p)

White solid, 121 mg, 74% yield, mp 180 – 182 °C, $R_f = 0.5$ (*n*-hexane: ethyl acetate = 9:1); ^1H NMR (400 MHz, CDCl_3) δ 8.06 (dd, $J = 8.0, 5.7$ Hz, 2H), 7.61 – 7.58 (m, 3H), 7.56 –

7.52 (m, 2H), 7.50 – 7.46 (m, 2H), 7.42 – 7.35 (m, 2H), 6.95 (t, $J = 7.6$ Hz, 1H), 6.51 (d, $J = 8.1$ Hz, 1H), 4.67 (s, 3H), 3.22 – 3.18 (m, 2H), 1.81 – 1.73 (m, 2H), 1.44 – 1.38 (m, 2H), 0.85 (t, $J = 7.4$ Hz, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 144.8, 142.3, 140.9, 137.7, 132.0, 130.4, 130.1, 128.9, 128.1, 125.2, 125.1, 124.3, 122.5, 121.8, 120.9, 120.7, 119.9, 119.7, 118.2, 114.7, 109.6, 32.2, 30.4, 29.1, 22.4, 13.7; HRMS (ESI): m/z calcd for $\text{C}_{28}\text{H}_{26}\text{N}_3$ $[\text{M}+\text{H}]^+$: 404.2120, found 404.2121.

3-(12-Methyl-7-phenyl-12H-benzo[4',5']imidazo[1',2':1,2]pyrido[3,4-b]indol-6-yl)propan-1-ol (3q)

White solid, 123 mg, 75%, mp 217 – 219 °C, $R_f = 0.5$ (*n*-hexane: ethyl acetate = 8:2); ^1H NMR (400 MHz, CDCl_3) δ 7.83 (d, $J = 7.9$ Hz, 1H), 7.56 (d, $J = 8.0$ Hz, 1H), 7.45 – 7.43 (m, 2H), 7.32 (dd, $J = 11.6, 4.5$ Hz, 1H), 7.26 – 7.24 (m, 1H), 7.22 – 7.17 (m, 1H), 7.18 – 7.14 (m, 3H), 7.12 – 7.08 (m, 3H), 4.54 (s, 1H), 4.44 (s, 3H), 4.29 – 4.24 (m, 1H), 2.60 – 2.53 (m, 1H), 2.26 – 2.07 (m, 4H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 145.1, 144.7, 139.6, 138.3, 133.6, 128.9, 128.2, 127.2, 125.7, 125.2, 123.9, 123.3, 122.3, 120.3, 119.5, 119.4, 116.5, 112.6, 110.1, 101.2, 69.9, 50.7, 40.2, 31.9, 25.3; HRMS (ESI): m/z calcd for $\text{C}_{27}\text{H}_{24}\text{N}_3\text{O}$ $[\text{M}+\text{H}]^+$: 406.1919, found 406.1903.

6-Benzyl-2-chloro-12-methyl-7-phenyl-12H-benzo[4',5']imidazo[1',2':1,2]pyrido[3,4-b]indole (3r)

Off white solid, 129 mg, 77% yield, mp 251 – 253 °C, $R_f = 0.5$ (*n*-hexane: Ethyl acetate = 8:2); ^1H NMR (400 MHz, CDCl_3) δ 7.95 (d, $J = 2.1$ Hz, 1H), 7.65 (d, $J = 9.0$ Hz, 1H), 7.56 – 7.54 (m, 1H), 7.52 – 7.46 (m, 3H), 7.44 – 7.40 (m, 3H), 7.25 – 7.15 (m, 3H), 7.04 – 7.01 (m, 3H), 7.00 – 6.96 (m, 1H), 6.57 (d, $J = 8.1$ Hz, 1H), 4.68 (s, 3H), 4.62 (s, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 145.8, 143.0, 141.0, 137.6, 136.9, 129.9 (2), 129.1, 129.0, 128.4, 128.4, 127.7, 127.4, 126.7, 125.6, 125.5, 123.2, 122.4, 121.9, 121.0, 120.2, 118.9, 118.1, 115.9,

109.7, 35.2, 32.1; HRMS (ESI): m/z calcd for $C_{31}H_{23}N_3Cl$ $[M+H]^+$: 472.1581, found: 472.1569.

6-Benzyl-2,3,12-trimethyl-7-phenyl-12H-benzo[4',5']imidazo[1',2':1,2]pyrido[3,4-b] indole (3s)

White solid, 136 mg, 81% yield, mp 278 – 280 °C, R_f = 0.5 (*n*-hexane: ethyl acetate = 9:1); 1H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.58 – 7.52 (m, 2H), 7.49 – 7.43 (m, 4H), 7.35 (d, J = 6.7 Hz, 3H), 7.17 – 7.13 (m, 2H), 6.98 – 6.93 (m, 3H), 6.51 – 6.49 (m, 1H), 4.70 (s, 3H), 4.66 (d, J = 13.1 Hz, 2H), 2.32 (s, 3H), 2.15 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 141.12, 138.02, 137.04, 130.42, 129.97, 128.98, 128.34, 127.98, 127.91, 127.47, 126.57, 125.64, 122.39, 121.85, 120.21, 118.72, 115.52, 109.72, 35.58, 32.45, 20.79, 20.35; HRMS (ESI): m/z calcd for $C_{33}H_{28}N_3$ $[M+H]^+$: 466.2283, found: 466.2263.

6-benzyl-12-methyl-2-nitro-7-phenyl-12H-benzo[4',5']imidazo[1',2':1,2]pyrido[3,4-b]indole (3t)

Yellow solid, 120 mg, 73%, mp 315 – 320 °C; R_f = 0.3 (*n*-hexane: ethyl acetate = 9:1); 1H NMR (400 MHz, $CDCl_3$) δ 8.82 (d, J = 2.0 Hz, 1H), 8.27 (dd, J = 9.1, 2.1 Hz, 1H), 7.88 (d, J = 9.1 Hz, 1H), 7.54 (d, J = 8.3 Hz, 1H), 7.52 – 7.47 (m, 3H), 7.46 – 7.42 (m, 3H), 7.23 (s, 1H), 7.19 (s, 1H), 7.14 – 7.10 (m, 3H), 6.98 (t, J = 7.2 Hz, 1H), 6.57 (d, J = 8.1 Hz, 1H), 4.68 (s, 2H), 4.66 (s, 3H); $^{13}C\{H\}$ NMR (126 MHz, $CDCl_3$) δ 149.2, 145.4, 141.5, 141.1, 136.5, 136.2, 129.8, 129.3 (2), 129.2, 128.7, 128.6, 128.4, 127.5, 127.0, 126.5, 125.3, 124.5, 122.2, 120.6, 120.1, 119.8, 118.6, 113.0, 109.9, 35.6, 32.2; HRMS (ESI): m/z calcd for $C_{31}H_{23}N_4O_2$ $[M + H]^+$: 483.1821, found 483.1799.

6-Benzyl-9-chloro-12-methyl-7-phenyl-12H-benzo[4',5']imidazo[1',2':1,2]pyrido[3,4-b]indole (3u)

Off white solid, 130 mg, 78% yield, mp 235 – 237 °C, $R_f = 0.5$ (*n*-hexane: ethyl acetate = 9:1); ^1H NMR (400 MHz, CDCl_3) δ 8.20 (d, $J = 7.6$ Hz, 1H), 7.83 (d, $J = 8.6$ Hz, 1H), 7.58 – 7.48 (m, 5H), 7.44 – 7.39 (m, 3H), 7.26 – 7.16 (m, 4H), 7.06 (d, $J = 7.0$ Hz, 2H), 6.49 (d, $J = 1.9$ Hz, 1H), 4.75 (s, 3H), 4.71 (s, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 139.6, 137.5, 136.2, 129.7 (2), 129.4, 129.2 (2), 129.1, 128.8, 128.6, 127.4 (2), 126.8, 126.3, 126.0, 125.6, 125.2, 123.3, 123.2, 121.8, 121.5, 119.0, 115.4, 110.9, 35.5, 32.7; HRMS (ESI): m/z calcd for $\text{C}_{31}\text{H}_{23}\text{N}_3\text{Cl}$ $[\text{M}+\text{H}]^+$: 472.1575, found: 472.1573.

6-Benzyl-9-methoxy-12-methyl-7-phenyl-12H-benzo[4',5']imidazo[1',2':1,2]pyrido[3,4-*b*]indole (3v)

White solid, 133 mg, 79% yield, mp 208 – 210 °C, $R_f = 0.5$ (*n*-hexane: ethyl acetate = 9:1); ^1H NMR (400 MHz, CDCl_3) δ 7.99 (d, $J = 8.1$ Hz, 1H), 7.78 (d, $J = 8.5$ Hz, 1H), 7.50 – 7.48 (m, 3H), 7.45 – 7.39 (m, 4H), 7.24 – 7.17 (m, 3H), 7.11 – 7.05 (m, 4H), 5.94 (d, $J = 2.4$ Hz, 1H), 4.69 (s, 2H), 4.68 (s, 3H), 3.48 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 154.0, 144.9, 142.4, 138.1, 137.2, 136.2, 130.2, 129.9, 128.9, 128.9, 128.2, 127.5, 127.3, 126.5, 126.1, 124.2, 122.7, 122.6, 120.8, 119.4, 117.2, 115.8, 115.1, 110.4, 103.0, 55.3, 35.5, 32.3; HRMS (ESI): m/z calcd for $\text{C}_{32}\text{H}_{26}\text{N}_3\text{O}$ $[\text{M}+\text{H}]^+$: 468.2076, found 468.2057.

19-benzyl-11-methyl-11H-benzo[4,5]imidazo[1,2-*a*]indolo[2,3-*c*]naphtho[1,2-*f*]quinoline (4a)

Yellow solid, 140 mg, 68% yield, mp 258 – 260 °C, $R_f = 0.5$ (*n*-hexane: Ethyl acetate = 8:2); ^1H NMR (400 MHz, CDCl_3) δ 9.08 (dd, $J = 7.6, 2.0$ Hz, 1H), 8.42 (d, $J = 8.3$ Hz, 1H), 8.31 (s, 1H), 8.20 – 8.15 (m, 1H), 7.98 (d, $J = 8.1$ Hz, 1H), 7.85 (d, $J = 8.4$ Hz, 1H), 7.65 – 7.57 (m, 2H), 7.56 (d, $J = 8.2$ Hz, 1H), 7.49 – 7.45 (m, 3H), 7.40 – 7.31 (m, 6H), 7.27 – 7.20 (m, 2H), 4.68 (s, 3H), 4.62 (s, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 145.0, 142.2, 141.0, 139.7, 136.0, 130.9, 130.2, 129.7, 129.6, 129.5, 129.4, 129.0, 128.7, 128.1, 127.3, 127.1,

126.7, 126.0, 125.2, 125.0, 124.2, 123.9, 123.8, 123.3, 122.2, 120.2, 119.9, 116.4, 114.1, 113.9, 110.2, 39.0, 32.3; HRMS (ESI): m/z calcd for C₃₇H₂₆N₃ [M + H]⁺ : 512.2127, found: 512.2128.

ASSOCIATED CONTENT:

• Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

• Supporting Information Statement.

The Supporting Information is available free of charge on the ACS Publications website at DOI: Copies of ¹H, ¹³C and ¹⁹F NMR spectra for all the new compounds as well as X-ray crystallographic data of **3a** and **3h**.

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References and Notes:

- (a) Thatikayala, M.; Wadhwa, P.; Kaur, P.; Singh, P. K.; Yadav, A.; Kaushik, M.; Sahu, S. K. Beta-carboline as a promising heterocyclic nucleus: Synthetic aspects, pharmacological potential and structure activity relationship. *Eur. J. Med. Chem. Rep.* **2022**, *6*, 100096. (b) Aaghaz, S.; Sharma, K.; Jain, R.; Kamal, A. β-Carbolines as potential anticancer agents. *Eur. J. Med. Chem.* **2021**, *216*, 113321. (c) Luo, B.; Song, X. A comprehensive overview of b-carbolines and its derivatives as anticancer agents. *Eur. J. Med. Chem.* **2021**, *224*, 113688. (d) Piechowska, P.; Zawirska-Wojtasiak, R.; Mildner-Szkudlarz, S. Bioactive β-Carbolines in Food: A Review. *Nutrients.* **2019**, *11*, 814.
- Vignoni, M.; Erra-Balsells, R.; Epe B.; Cabrerizo, F. M. Intra- and extra-cellular DNA damage by harmine and 9-methyl-harmine *J. Photoch and Photob B: Bio.*, **2014**, *132*, 66-71.

3. Ishiyama, H.; Ohshita, K.; Abe, T.; Nakata, H.; Kobayashi, J. Synthesis of eudistomin D analogues and its effects on adenosine receptors. *Bioorg. & Med. Chem.*, **2008**, *16*, 3285-3830.
4. Shi, Y.; Xu, Z.; Tan, R.; Lei, X. Divergent total synthesis of chaetoglines C to F. *J. Org. Chem.*, **2019**, *84*, 9766-8770.
5. Christopher, E.; Bedir, E.; Dunbar, C.; Khan, I. A.; Okunji, C. O.; Schuster, B. M.; Iwu, M. M. Indoloquinazoline alkaloids from *Araliopsis tabouensis*. *Helv. Chim. Acta* **2003**, *86*, 2914-2918.
6. (a) Wang, C.; Wang, S.; Li, H.; Hou, Y.; Cao, H.; Hua, H.; Li, D. Marine-Derived Lead Fascaplysin: Pharmacological Activity, Total Synthesis, and Structural Modification. *Mar. Drugs*. **2023**, *21*, 226. (b) Liang, Y.; Quan, H.; Bu, T.; Li, X.; Liu, X.; Wang, S.; He, D.; Jia, Q.; Zhang, Y. Comparison of the Inhibitory Binding Modes Between the Planar Fascaplysin and Its Nonplanar Tetrahydro- β -carboline Analogs in CDK4. *Front. Chem.* **2021**, *9*, 614154.
7. Hotha, S.; Yarrow, J. C.; Yang, J. G.; Garrett, S.; Renduchintala, K. V.; Mayer, T. U.; Kapoor, T. M. HR22C16: A Potent Small-Molecule Probe for the Dynamics of Cell Division. *Angew. Chem. Int. Ed.* **2003**, *42*, 2379 – 2382.
8. (a) Racane, L.; Zlatar, I.; Perin, N.; Cindric, M.; Radovanovic, V.; Banjanac, M.; Shanmugham, S.; Stojkovic, M. R.; Brajsa, K.; Hranjec, M. Biological Activity of Newly Synthesized Benzimidazole and Benzothiazole 2,5-Disubstituted Furane Derivatives. *Molecules* **2021**, *26*, 4935. (b) Brishty, S. R.; Hosain, M. J.; Khandakar, M. D.; Faruque, M. R. I.; Osman, H.; Rahman, S. M. A. A comprehensive account on recent progress in pharmacological activities of benzimidazole derivatives. *Front. Pharmacol.* **2021**, *12*,

762807. (c) Chintakunta, R.; Meka, G. Synthesis, in silico studies and antibacterial activity of some novel 2-substituted benzimidazole derivatives. *Futur. J. Pharm. Sci.* **2020**, *6*, 128.

9. Ramesh, S.; Nagarajan, R. Copper-catalyzed hydroarylation of alkynes for the synthesis of Fascaplysin, Rutacarpine and Granulatimide analogues. *Synthesis* **2015**, *47*, 3573- 3582.

10. Shinde, V. N.; Dhiman, S.; Krishnan, R.; Kumar D.; Kumar, A. Synthesis of imidazopyridine-fused indoles *via* one-pot sequential Knoevenagel condensation and cross dehydrogenative coupling. *Org. Biomol. Chem.* **2018**, *16*, 6123- 6132.

11. (a) Qian, H.; Huang, D.; Bi, Y.; Yan, G. 2-Propargyl Alcohols in Organic Synthesis. *Adv. Synth. Catal.* **2019**, *361*, 3240- 3280. (b) Roy, R.; Saha, S. Scope and advances in the catalytic propargylic substitution reaction. *RSC Adv.* **2018**, *8*, 31129- 31193. (c) Reddy, R. C.; Ranjan, R.; Kumaraswamy, P.; Reddy, D. M.; Gree, R. 1-Aryl propargylic alcohols as handy synthons for the construction of heterocycles and carbocycles. *Curr. Org. Chem.* **2014**, *18*, 2603–2645.

12. (a) Reddy, C. R.; Aila, M.; Subbarao, M.; Warudikar, K.; Gree, R. Domino Reaction of 2,4-Diyn-1-ols with 1,3-Dicarbonyl Compounds: Direct Access to Aryl/Heteroaryl-Fused Benzofurans and Indoles. *Org. Lett.* **2021**, *23*, 4882–4887. (b) Reddy, C. R.; Subbarao, M.; Sathish, P.; Kolgave, D. H.; Donthiri, R. R. One-pot assembly of 3-hydroxycarbazoles via Uninterrupted Propargylation/Hydroxylative Benzannulation Reactions. *Org. Lett.* **2020**, *22*, 689–693. (c) Reddy, C. R.; Valleti, R. R.; Dilipkumar, U. One-pot sequential propargylation/cycloisomerization: A Facile [4+2]-Benzannulation approach to carbazoles. *Chem. Eur. J.* **2016**, *22*, 2501–2506.