RSC Advances

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Cite this: *RSC Adv.*, 2022, **12**, 30712

Synthesis of 5-aryl-3,3′-bis-indolyl and bis-7-aza-indolyl methanone derivatives from 5-bromo-7-azaindoles *via* sequential methylenation using microwave irradiation, CAN oxidation, and Suzuki coupling reactions†

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Received 16th September 2022
Accepted 18th October 2022

DOI: 10.1039/d2ra05849a

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A catalyst-free and green chemical method has been developed for the methylenation of indole and *N*-methyl-7-aza indoles with aqueous formaldehyde afforded respective *N*,*N*′-dimethyl-3,3′-bis-7-azaindolylmethanes under microwave irradiation in excellent yield. Subsequent oxidation of the products thus obtained, using one electron chemical oxidant CAN afforded *N*,*N*′-dimethyl-3,3′-bis-7-azaindolylmethanone derivatives in excellent yield. This resulted in methanone derivatives with halogen substitution at the aryl ring which when subjected to Suzuki coupling with aryl boronic acids furnished highly functionalized fluorescent biaryl derivatives. Plausible mechanisms, characterization including XRD, and evaluation of photophysical properties of the Suzuki coupled products are described.

Introduction

7-Azaindole and its derivatives exhibit significant biological activities and the framework has contributed to the development of new therapeutic agents.[1] For example, natural products, meriolin 1 (**1**) and meriolin 3 (**2**) showed improved potency, and several FDA-approved drugs such as vemurafenib (**3**) are used for the treatment of metastatic melanoma. Pexidartinib (**4**) is approved for the treatment of giant cell tumours associated with severe morbidity. Moreover, 7-azadindole derivative NVP-QAV680 (**5**) is known for the treatment of allergies and Zn-azaindole complex (**6**) has a bright blue emitter property. To demonstrate materials applications, and new functionality to enhance the performance of 7-azaindole derivatives, some of the triaryl boron functionalized compounds such as (**7**) and (**8**) have been reported as "bifunctional materials" in OLEDs (Fig. 1).[2]

Methylenation is a well-known structural modification reaction in organic synthesis.[3] Lewis acid-mediated synthesis of 3,3′-bis-7-azaindolylmethane derivatives using zinc- or acid-mediated cross-coupling reaction of 7-azaindoles with a number of diverse aldehydes provides the corresponding C3-linked methylenation products is reported.[4] However, the development of the synthesis of 3-methylenation products of indoles and 7-azaindoles by green chemistry protocol using a catalyst-free, aqueous, and microwave irradiation method would be an alternate and efficient method warranted.

Oxidation of benzylic methylene with various oxidizing agents offers functional derivatives such as alcohols, aldehydes and ketones depending upon the substrates and reagents used.[5] Development of synthetic methods based on utilizing green chemistry protocols such as green chemistry, clay, microwave irradiation techniques enzymatic method *etc.*, are of current interest in the synthetic organic chemistry.[6] Cerium(IV) ammonium nitrate (CAN) has emerged as a versatile reagent for

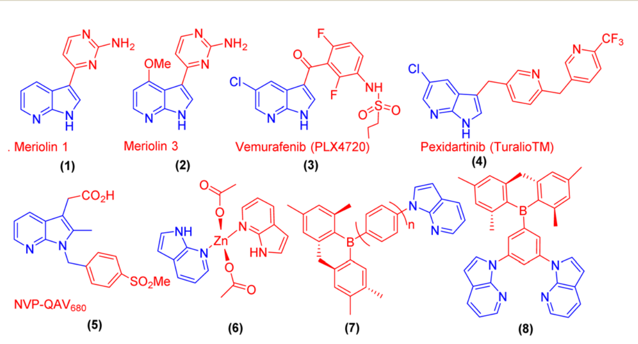

Fig. 1 Drugs and materials based on 7-aza indole cores.

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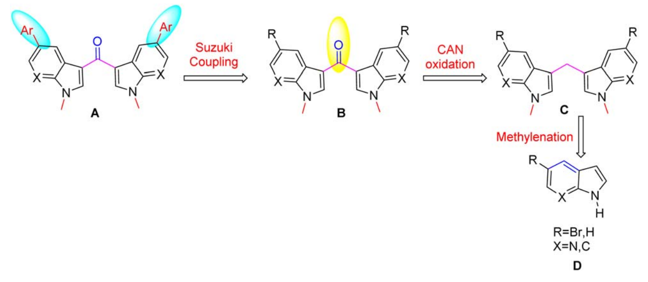
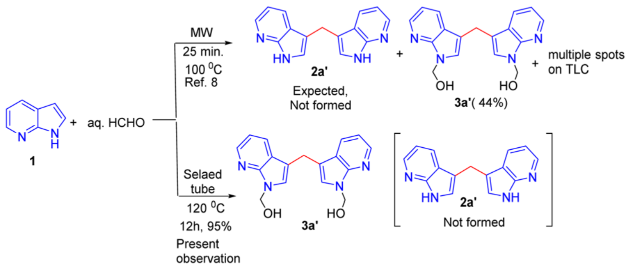
† Electronic supplementary information (ESI) available. Copies of ^{1}H NMR, ^{13}C NMR, DEPT-135, HRMS spectra for all the new compounds, and single-crystal XRD data for compounds **3b** and **4a** are provided. CCDC 2191474 and 2102023. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d2ra05849a



Scheme 1 Retrosynthetic route for the title compounds.



Scheme 2 Initial studies.

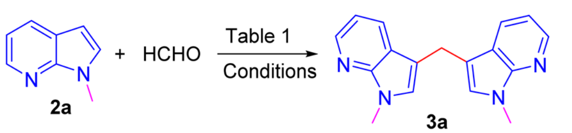
a variety of synthetic transformations which have been well documented.[7] Conversion of 3-methylenation products of indoles and 7-azaindoles to corresponding ketones are interesting synthetic modifications and no reports are available using mild and efficient reagents. Thus, we were interested to develop the oxidation of 3-methylenation products of indoles and 7-azaindoles using CAN as a one-electron oxidant into the corresponding ketones. Thus, herein we wish to report the details of the work carried out by initial methylenation, oxidation using CAN, and further synthetic utility of ketone products by using the Suzuki coupling reaction.

To synthesize the title compounds, a retrosynthetic analysis is shown in Scheme 1. Accordingly, the functionalized and fluorescent 3,3′-bis-7-azaindolylmethanone **B** derivatives were synthesized *via* steps involving microwave irradiated methylenation of 7-aza indoles **D** with aqueous formaldehyde would provide the *N*,*N*′-dimethyl-3,3′-bis-7-azaindolylmethane **C** followed by oxidation of compound **C** using CAN be followed by Suzuki coupling[8] of **C** with aryl boronic acids.

As per the retrosynthesis shown in Scheme 1, initially, we followed the reported procedure[9] for the synthesis of methylenated compound **2a′** from 7-azaindole **1** under microwave irradiation did not produce compound **2a′** but *N*-hydroxy methyl product in **3a′** was isolated in 44% yield and the reaction produced multiple spots and are inseparable by column chromatography. However, repeating the above reaction under sealed tube heating conditions produced 95% of a product *i.e.* methylated and *N*-hydroxy methyl product exclusively in **3a′** 95% yield (Scheme 2). The reaction suggests that when free N–H is available, under the reaction condition, it produces only *N*-hydroxy methyl compounds such as **3a′** and exclusive methylenated product is not observed.

Repeating the reaction of 1.0 equiv. of *N*-methyl-7-azaindole **2a** was treated with 3.0 equiv. of 37% aq. HCHO taken in a sealed tube was heated at a slightly lower temperature of 100 °C for 12 h and gave only a trace amount of bis(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)methane **3a**, as evidenced by spectroscopic data (Table 1, entry 1). To improve the yield of compound **3a**, reactions were carried out by varying parameters such as temperature, time, and catalyst load (Table 1). Increasing the temperature to 115 °C slightly improved the yield of **3a** to 35% and at 120 °C further improved the yield by 55% (Table 1, entries 2 and 3). Extending the reaction time to 15 h further improved the yield to 74% and the addition of 1 mmol amount of water to the reaction did not alter the yield (Table 1, entries 4 and 5). Repeating the reaction with paraformaldehyde at 120 °C for 12 h and 15 h afforded the expected product in 72 and 80% yields, respectively (Table 1, entries 6 and 7). Notably, to reduce the reaction time, and to improve the yield, when the mixture of **2a** and aqueous formaldehyde was irradiated in a microwave

Table 1 Optimization of synthesis of compound **3a**



Entry	Substrate	Reagent (3.0 equiv.)	Temp. (°C)	Time (h)	Yield of **3a**[a] (%)
1	**2a**	Aq. HCHO	100	12	Trace
2	**2a**	Aq. HCHO	115	12	35
3	**2a**	Aq. HCHO	120	12	55
4	**2a**	Aq. HCHO	120	15	74
5	**2a**	Aq. HCHO, H_2O	120	12	74
6	**2a**	$(HCHO)_n$	120	12	72
7	**2a**	$(HCHO)_n$	120	15	80
8	**2a**	Aq. HCHO	MW[b]	15 min	45
9	**2a**	Aq. HCHO, 50% w/w Mont. K-10	MW[b]	5 min	85

[a] Isolated yield. [b] Irradiated at 100 W using CEM Discover-300 microwave synthesizer.

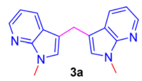
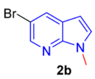
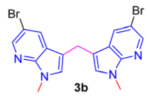
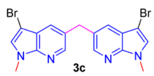
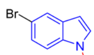
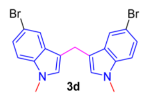
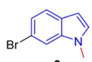
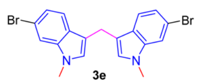
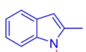
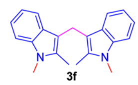
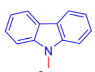
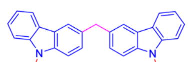
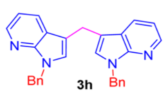
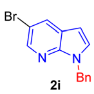
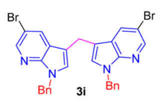
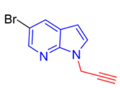
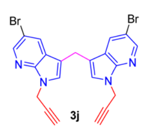
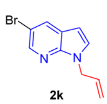
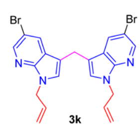
oven for 15 minutes and furnished product **3a** with a 45% yield. However, the best yield (85%) was obtained in a rapid reaction time of 5 min. microwave irradiation (100 °C, 150 psi, power 150) using 50% w/w montmorillonite K 10 clay as a solid acid catalyst, and this was found to be an optimum condition (Table 1, entry 9).

Encouraged by the preliminary results, the scope and diversity of the reaction were explored by selecting a number of *N*-alkyl-7-azaindole, indole, and carbazole **2b–k** (Table 2). Under optimized microwave irradiation conditions, all the reactions underwent smoothly to produce the corresponding methylenation products **3b–k** in very good to excellent yields (Table 2, entries 1–7). Further, diversify the methylenation reaction compound **2c** is also used as a substrate to produce a novel methylenation at C-5 position to produce compound **3c**. The structure of all the products was established by spectroscopic methods such as ^{1}H, ^{13}C NMR, DEPT-135, and HRMS.

The structure of new compounds was assigned from spectroscopic data and a representative compound **3b** structure and relative stereochemistry were assigned based on single-crystal X-ray analysis (Fig. 2).[10]

A plausible mechanism for the formation of bis(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)methane **3a** from *N*-methyl-7-aza indole **2a** with formaldehyde is shown in Scheme 3.[11] Under the influence of Mont. K-10 clay, the electrophilicity of the formaldehyde is increased and undergoes a facile conjugate

Table 2 Scope of the reaction for methylenation[a]

Entry	Substrate **2**	Product **3**	MW time[b,c] (min)	Yield (%)
1	 2a	 3a	5	74
2	 2b	 3b	8	80
3	 2c	 3c	8	85
4	 2d	 3d	5	84
5	 2e	 3e	5	82
6	 2f	 3f	6	80
7	 2g	 3g	12	79
8	 2h	 3h	9	75
9	 2i	 3i	7	78
10	 2j	 3j	10	80
11	 2k	 3k	10	75

[a] Optimized condition: aq. HCHO, 50% w/w Mont. K-10, MW, 100 W. [b] CEM Discover-300 microwave synthesizer was used. [c] Prolonged irradiation results in decomposition or charring.

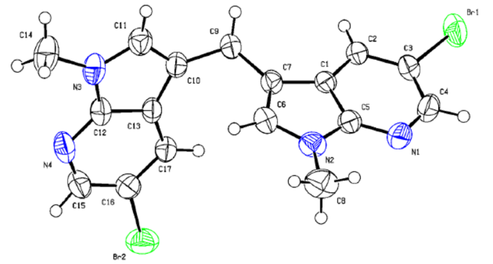
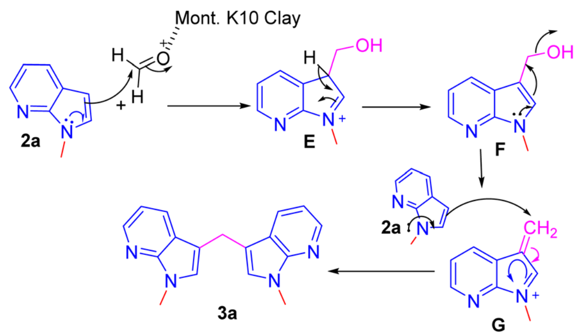
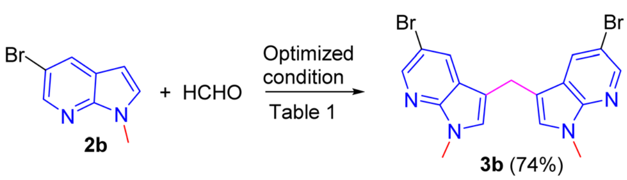


Fig. 2 ORTEP diagram of compound **3b** (CCDC-2191474†).



Scheme 3 A plausible mechanism for the formation of compounds 3a.

addition of 7-azaindole to provide hydroxy methylated intermediate **E**. Intermediate **E** upon elimination of water molecule *via* intermediate **F** to provide another intermediate **G**. Second addition of 7-azaindole to the intermediate **G** provides the product **3a**.



Scheme 4 Gram scale synthesis of compound **3b**.

To demonstrate scalability of the reaction a gram scale experiment has been carried out using substrate **2b** to afford the expected product in 74% yield (Scheme 4).

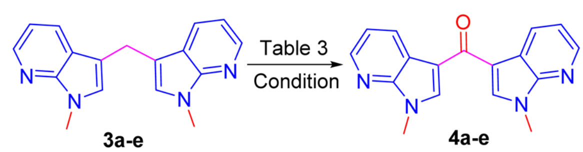
Direct oxidation of bis(1-methyl-1*H*-pyrrolo[2,3-*b*] pyridin-3-yl) methane **3a** into corresponding ketones **4a** are unknown in the literature. However, these ketones were reported by a two-step synthetic protocol starting from respective methylenes.[8,12] Hence, we were interested to develop a one-pot, mild and efficient procedure for this direct oxidation of **3a** into its ketone **4a.** To achieve the oxidation, initially, the benzylic oxidation of methylene carbon in compound **3a** was treated with peroxides such as 30% H_2O_2, and TBHP failed to provide ketone **4a** (Table 3, entries 1 and 2). To our dismay, another well-known oxidizing agent SeO_2 also failed to provide the ketone (Table 3, entry 3). In addition, Cs_2CO_3 also failed to provide the expected product (Table 3, entry 4).[13] However, a single electron chemical oxidant such as CAN was explored (Table 3, entry 5). Hence ketone **4a** was contained in 70% yield by reacting the compound **3a** with 3 equivalents of CAN in ACN–MeOH (1 : 3) solvent system for 30 minutes and was found as a suitable and optimized condition for the oxidation reaction. To diversify the methodology, Further under optimized condition compound **4c** was synthesized from the respective 3-bromo-*N*-methyl-5-methyledine-bis-7-azaindole.

Having followed the optimized CAN oxidizing condition, ketones **4a–e** were prepared in excellent yield from respective methylated compounds **3a–e** (Fig. 3).

The structure of all the new compounds **4a–e** was assigned from spectroscopic data and a representative compound **4a** structure and relative stereochemistry were assigned based on single-crystal X-ray analysis (Fig. 4).[14]

A plausible mechanism for the formation of compound **4** from the bis(1-methyl-1*H*-pyrrolo[2,3-*b*] pyridin-3-yl) methane **3a** by CAN is shown in Scheme 5.[12e] Initially, the CAN oxidizes the benzylic methylene group to benzylic radical cation intermediate **I**, which further undergoes second oxidation by CAN and by liberating H^+ ion to form the cation intermediate **J**.

Table 3 Synthesis and optimization of oxidation of compound **3a** using various oxidizing agents



Entry	Oxidizing agent (equiv.)	Solvent	Condition	Product **4a** (yield%)
1	30% H_2O_2 (5 equiv.)	MeOH	RT, 12 h	[a]
2	TBHP (4 equiv.)	CH_3CN	RT, 12 h	Trace
3	SeO_2 (2 equiv.)	1,4-Dioxane	120 °C, 12 h	Trace
4	Cs_2CO_3 (4 equiv.)	Dry DMSO	150 °C, 12 h	[b]
5	CAN (3 equiv.)	MeOH : CH_3CN	0 °C–RT, 0.5 h	70

[a] Decomposed. [b] SM recovered.

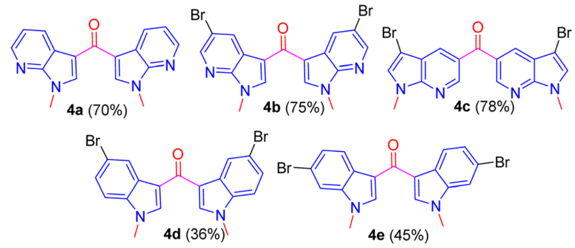


Fig. 3 Synthesized ketones **4a–e**.

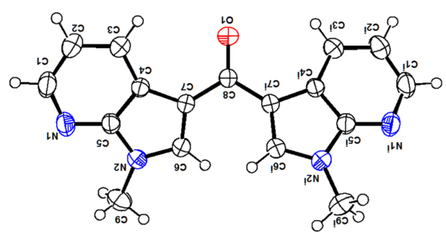
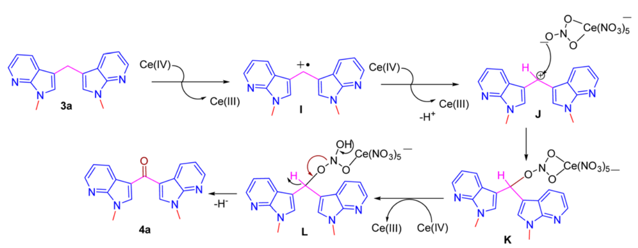


Fig. 4 ORTEP diagram of compound **4a** (CCDC-2102023†).



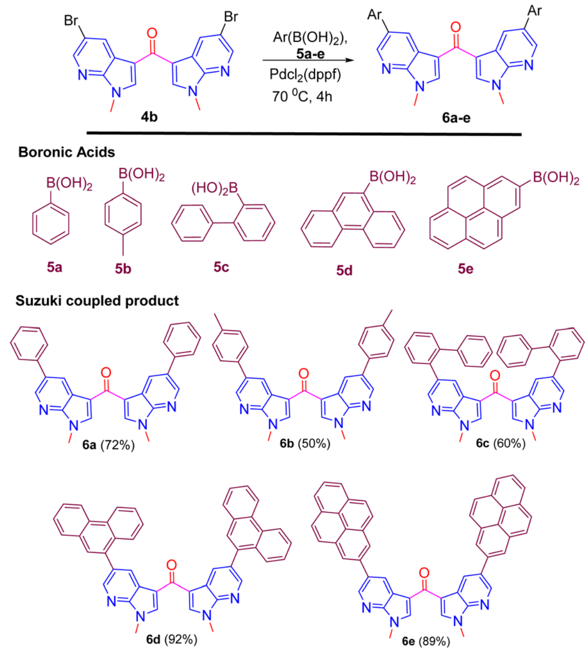
Scheme 5 A plausible mechanism for the formation of compounds 4a.

Intermediate **J** upon reaction with nitrate oxygen of CAN forms C–O bond intermediate **K**, and subsequent hydride ion elimination results the ketone **4** (Scheme 5).

The presence of bromine in product **4b** prompted us to derivatize its biphenyl derivatives by exploiting Suzuki coupling. Biphenyls and their derivatives are important structural motifs due to applications both in academic interest and in synthetic use of various carbo- and heterocyclic frameworks.[15] The asymmetric structural framework of biaryls has been effectively utilized as asymmetric catalysts, natural product synthesis, supramolecular assemblies, and organic materials.[16] Thus, the halogen on the aromatic substitution was successfully utilized for Suzuki coupling with several aryl boronic acids **5a–e** to provide aryl-substituted fluorescent 7-aza indole derivatives **6a–e** in excellent yield (Scheme 6).[17]

The nature of biaryl-based derivatives **6a–e** prompted us to evaluate the basic photophysical properties. The absorption measured in MeOH showed in the range of $\lambda_{\text{max.abs.}}$ 230–248, emission in the range of $\lambda_{\text{max.emi.}}$ 398–497, and large Stoke's shift (Table 4) has been evaluated. This basic data suggest that they are strong blue emitters (Table 4).

In conclusion, we have demonstrated a catalyst-free and green chemical method has been developed for the methylenation of indole and *N*-methyl-7-aza indoles with aqueous formaldehyde afforded respective *N*,*N'*-dimethyl-3,3'-bis-7-azaindolylmethane under MW in excellent yield. Subsequent oxidation of product using one electron chemical oxidant CAN afford *N*,*N'*-dimethyl-3,3'-bis-7-azaindolylmethanone derivatives in excellent yield. This resulted in methanone derivatives with halogen substitution at the aryl ring subjected to Suzuki coupling with aryl boronic acids furnished with highly functionalized biaryl derivatives. Plausible mechanisms, characterization including XRD, and evaluation of photophysical properties of the Suzuki coupled products are reported.



Scheme 6 Suzuki coupling of compound **4b** with several aryl boronic acids **5a–e**.

Experimental section

General remarks

All the reactions were carried out in oven-dried glassware. CEM Discover-300 microwave synthesizer was used for all the microwave irradiation reactions. The progress of the reactions was monitored by thin layer chromatography (TLC) using Merck pre-coated TLC plates (Merck 60 F254) Purification of the products was accomplished by column chromatography packed with silica gel 100–200 mesh. NMR spectra were recorded on a Bruker-400.3 MHz NMR spectrometer (400.3 MHz for ^{1}H NMR and 100.6 MHz for ^{13}C NMR) with $CDCl_3$/TMS as the solvent and TMS as the internal reference. Integrals are in accordance with assignments and coupling constants are reported in Hertz (Hz). All ^{13}C spectra are proton-decoupled. Multiplicity is indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublets), dt (doublet triplet), td (triplet of doublets), and br s (broad singlet). FTIR spectra were recorded on a PerkinElmer RX-IFT-IR spectrometer and absorbance values are reported in cm^{-1}. ESI HRMS was performed on

Table 4 Absorption and emission properties of compounds **3a**, **4b**, and **6a–e**

Entry	Product	Absorption[a] $\lambda_{max.abs.}$	Emission[a] $\lambda_{max.emi.}$	Stoke's shift $\Delta\bar{\upsilon}^{b}$ (cm^{-1})
1	**3b**	232, 299	412	18 831, 9173
2	**4b**	282, 316	398	10 335, 6520
3	**6a**	244, 326	406	16 353, 6044
4	**6b**	249, 328	463	18 562, 8889
5	**6c**	230, 324	408	18 969, 6355
6	**6d**	252, 325	497	19 562, 10 649
7	**6e**	274, 343	450	14 274, 6932

[a] All the spectra were recorded in MeOH at 2×10^{-5} M at 298 K concentration. [b] Stoke's shift = $\lambda_{max.abs.} - \lambda_{max.emi.}$ [cm^{-1}].

a Waters(R) Micromass(R) Q-TOF MicroTM mass spectrometer. Yields refer to quantities obtained after chromatography.

Experimental procedure

a. General procedure for the synthesis of methylated compounds 2a–c. In a 100 mL RB flask, under N_2 atm., compound **1a–c** (100 mg, 0.848 mmol) in DMF was treated with 1.1 equiv. of sodium hydride (NaH, 60% dispersed in paraffin oil) at 0 °C, and the mixture was allowed to attain RT (*ca.* 1 h), then 1.2 equiv. of methyl iodide was added. The reaction continued to stir at RT and the progress of the reaction was monitored by TLC. After completion of the reaction, the crude mixture was extracted with ethyl acetate and washed with distilled water and saturated brine solution. The organic phase was dried over anhydrous $MgSO_4$ and the solvent was removed under vacuum. The crude product was purified over silica gel (100–200 mesh) column chromatography using gradient elution with EtOAc–hexane to obtain the pure products **2a–c**.

b. General procedure for the synthesis of compounds 2d–f.[18] In a 100 mL RB flask, 1.2 equiv. powdered KOH was taken and DMF (2 mL) of solvent was added and allowed to stir for 5 min. at RT. Followed by compounds **1d–f** (100 mg, 0.510 mmol) was added portion-wise and allowed to stir under N_2 atm., for 5 min. The entire setup was cooled to 0 °C and CH_3I (1.5 equiv.) was added dropwise *via* syringe over a period of 5 minutes. Warm the reaction mixture to RT. After completion of the reaction, the crude reaction mixture was quenched with saturated cold brine solution and extracted with EtOAc. The organic phase was dried over anhydrous $MgSO_4$ and the solvent was removed under vacuum. The crude product was purified over a column chromatography of silica gel (100–200 mesh) using gradient elution with EtOAc–hexane to obtain the pure products **2d–f**.

c. General procedure for the synthesis of compounds 2g.[19] In a 100 mL RB flask, carbazole **1g** (100 mg, 0.598 mmol) in THF and potassium *tert*-butoxide (1.5 equiv.) were added and allowed to stir for 5 min., followed by iodomethane (1.5 equiv.) was added to the reaction mixture. Heat the reaction mixture at 50 °C for 2 h. Evaporated the solvent under reduced pressure and added water to the reaction mixture. A solid thus formed was collected by filtration and washed with cold methanol to obtain compound **2g** (white crystalline solid, 95 mg).

d. General procedure for the synthesis of compounds 3a–k. In a microwave tube, a mixture of *N*-methyl-7-aza indoles **2a–k** (100 mg, 0.7566 mmol), aq. HCHO (37%) (3 equiv.) and Mont K-10 (50 w/w) clay were microwave irradiated (100 °C, 150 W, 150psi for 5 min). After completion of the reaction (monitored by TLC), the reaction mixture was diluted with EtOAc and washed with water. The combined organic layer was dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude was purified by silica gel column chromatography by using gradient elution with EtOAc–hexane to obtain pure compounds **3a–k**.

e. General procedure for the synthesis of compound 4a–e. To a solution of 3,3′-bis-7-azaindolylmethane, **3a–e** (100 mg, 0.362 mmol) in MeOH : CH_3CN (2 : 1) was added cerium(IV) ammonium nitrate (3 equiv.) in a portion-wise at 0 °C to RT for 30 min. After the completion of the reaction (monitored by TLC), the reaction mixture was diluted with EtOAc and washed with distilled water. The combined organic layer was dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude mixture was purified on a silica gel column chromatography (eluent : hexane/EtOAc : 1/1) to afford the corresponding compounds **4a–e** in good yields.

f. Typical procedure for Suzuki coupling reaction. In a Schlenk tube, a mixture of bis(5-bromo-1-methyl-1*H*-pyrrolo [2,3-*b*] pyridin-3-1yl) methanone, **4b** (100 mg, 0.0223 mmol), aryl boronic acid (3 equiv.), $PdCl_2$(dppf) (20 mol%) and K_2CO_3 (3 equiv.) in dioxane : H_2O mixture (3 : 1, 2 mL) under N_2 atm., was heated at 70 °C for 22 h. After completion of the reaction (monitored by TLC), the mixture was allowed to attain room temperature. The mixture was diluted with EtOAc, filtered through a pad of Celite and concentrated under vacuum. The crude mixture was purified by silica gel column chromatography to afford products **6a–e**.

Spectroscopic data for synthesized compounds

Bis(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)methane (3a).[20] Nature: yellow solid; yield: 144 mg (74%); R_f (40% EtOAc–hexane): 0.21; FTIR (KBr) ν_{max}: 3052, 2940, 2829, 1533, 1478, 1403, 1260, 889, 845, 764, 591 cm^{-1}. ^{1}H NMR (400.3 MHz, $CDCl_3$/TMS): δ 8.24 (dd, J = 4.7, 1.4 Hz, 2H), 7.74 (dd, J = 7.8, 1.5 Hz, 2H), 6.92 (dd, J = 7.8, 4.7 Hz, 2H), 6.85 (s, 2H), 4.10 (s, 2H), 3.75 (s, 6H). ^{13}C NMR (101.6 MHz, $CDCl_3$/TMS): δ 148.2, 142.9, 127.2, 120.3, 115.0, 112.3, 31.1, 21.4. DEPT-135 (101.6 MHz, $CDCl_3$/TMS): δ 142.8, 127.3, 126.9, 114.9, 31.1, 21.3(↓). HRMS (ESI): calcd for $C_{17}H_{16}N_4$ $[M + H]^+$ m/z: 277.1453; found 277.1450.

Bis(5-bromo-1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)methane.[3b] Nature: white solid; yield: 165 mg (80%); R_f (40% EtOAc–hexane): 0.26; FTIR (KBr) ν_{max}: 3052, 2940, 2829, 1596, 1533, 1478, 1403, 1260, 1074, 889, 844, 768, 591 cm^{-1}. ^{1}H NMR (400.3 MHz, $CDCl_3$/TMS): δ 8.27 (d, J = 2.1 Hz, 2H), 7.84 (d, J = 2.1 Hz, 2H), 6.86 (s, 2H), 4.01 (s, 2H), 3.74 (s, 6H). ^{13}C NMR (101.6 MHz, $CDCl_3$/TMS): δ 146.4, 143.4, 129.3, 128.4, 121.5, 111.4, 111.0, 31.2, 21.1. DEPT-135 (101.6 MHz, $CDCl_3$/TMS): δ 146.5, 143.4, 129.3, 128.4, 121.5, 111.4, 111.0, 31.3, 21.1(↓). HRMS (ESI): calcd. for $C_{17}H_{14}Br_2N_4$ $[M + H]^+$ m/z: 432.9663; found 432.9636.

Bis(3-bromo-1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl) methane (3c). Nature: yellow solid; yield: 175 mg (85%); R_f (40% EtOAc–hexane): 0.23; FTIR (KBr) ν_{max}: 2918, 2860, 1471, 1400, 1257, 1140, 1075, 887, 841, 770, 602 cm^{-1}. ^{1}H NMR (400.3 MHz, $CDCl_3$/TMS): δ 8.26 (s, 2H), 7.84 (s, 2H), 6.86 (s, 2H), 4.01 (s, 2H), 3.74 (s, 6H). ^{13}C NMR (101.6 MHz, $CDCl_3$/TMS): δ 146.6, 143.5, 129.4, 128.5, 121.6, 111.5, 111.1, 31.4, 21.3. DEPT-135 (101.6 MHz, $CDCl_3$/TMS): δ 143.4, 129.3, 128.4, 31.3, 21.1(↓). HRMS (ESI): calcd. for $C_{17}H_{14}Br_2N_4$ $[M + H]^+$ m/z: 432.9663; found 432.9682.

Bis(5-bromo-1-methyl-1*H*-indol-3-yl)methane (3d).[21] Nature: pale pink powder; yield: 173 mg (84%); R_f (30% EtOAc–hexane): 0.42; ^{1}H NMR (400.3 MHz, $CDCl_3$/TMS): δ 7.71–7.65 (m, 2H), 7.32–7.23 (m, 2H), 7.17–7.10 (m, 2H), 6.76 (s, 2H), 4.08 (s, 2H), 3.68 (s, 6H). ^{13}C NMR (101.6 MHz, $CDCl_3$/TMS): δ 136.0, 129.6, 128.2, 124.5, 121.9, 113.7, 112.3, 110.8, 32.9, 20.8. DEPT-135 (101.6 MHz, $CDCl_3$/TMS): δ 128.1, 124.4, 121.7, 110.7, 32.8, 20.8(↓).

Bis(6-bromo-1-methyl-1*H*-indol-3-yl)methane (3e).[22] Nature: pale brown powder; yield: 169 mg (82%); R_f (30% EtOAc–hexane): 0.40; ^{1}H NMR (400.3 MHz, $CDCl_3$/TMS): δ 7.71–7.65 (m, 2H), 7.32–7.23 (m, 2H), 7.17–7.10 (m, 2H), 6.76 (s, 2H), 4.08 (s, 2H), 3.68 (s, 6H). ^{13}C NMR (101.6 MHz, $CDCl_3$/TMS): δ 136.0, 129.6, 128.2, 124.5, 121.9, 113.7, 112.3, 110.8, 32.9, 20.9. DEPT-135 (101.6 MHz, $CDCl_3$/TMS): δ 128.1, 124.4, 121.7, 110.7, 32.8, 20.8(↓).

Bis(1,2-dimethyl-1*H*-indol-3-yl)methane (3f).[23] Nature: white solid; yield: 167 mg (80%); R_f (8% EtOAc–hexane): 0.81; ^{1}H NMR (400.3 MHz, $CDCl_3$/TMS): δ 7.34 (d, J = 7.9 Hz, 2H), 7.13 (d, J = 8.1 Hz, 2H), 7.01 (t, J = 7.6 Hz, 2H), 6.88 (t, J = 7.4 Hz, 2H), 4.07 (s, 2H), 3.56 (s, 6H), 2.29 (s, 6H). ^{13}C NMR (101.6 MHz, $CDCl_3$/TMS): δ 136.7, 132.8, 128.2, 120.4, 118.6, 110.5, 108.5, 29.6, 20.1, 10.6. DEPT-135 (101.6 MHz, $CDCl_3$/TMS): δ 120.2, 118.5, 108.3, 29.5, 19.9(↓), 10.5.

Bis(9-methyl-9*H*-carbazol-3-yl)methane (3g).[24] Nature: white solid; yield: 164 mg (79%); R_f (8% EtOAc–hexane): 0.84; ^{1}H NMR (400.3 MHz, $CDCl_3$/TMS): δ 7.99–7.95 (m, 2H), 7.92–7.88 (m, 2H), 7.40–7.35 (m, 2H), 7.28 (dt, J = 20.0, 5.1 Hz, 6H), 7.11 (ddd, J = 8.0, 7.1, 1.0 Hz, 2H), 4.30 (s, 2H), 3.76 (s, 6H). ^{13}C NMR (101.6 MHz, $CDCl_3$/TMS): δ 141.4, 139.8, 132.9, 127.2, 125.7, 123.1, 122.9, 120.5, 118.8, 108.5, 42.1, 29.3. DEPT-135 (101.6 MHz, $CDCl_3$/TMS): δ 127.0, 125.5, 120.4, 118.6, 108.4, 41.9(↓), 29.1. HRMS (ESI): calcd for $C_{27}H_{22}N_2$ $[M + H]^+$ m/z: 375.1861; found 375.1843.

Bis(1-benzyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)methane (3h). Nature: pale yellow solid; yield: 155 mg (75%); R_f (50% EtOAc–hexane): 0.25; FTIR (KBr)ν_{max}: 3028, 2911, 1594, 1445, 1335, 1277, 111 722, 1024, 764, 705, 602 cm^{-1}. ^{1}H NMR (400.3 MHz, $CDCl_3$/TMS): δ 8.23 (dd, J = 4.7, 1.5 Hz, 2H), 7.68 (dd, J = 7.8, 1.6 Hz, 2H), 7.28–7.12 (m, 6H), 7.07 (dd, J = 7.7, 1.8 Hz, 4H), 6.98–6.78 (m, 4H), 5.36 (s, 4H), 4.07 (s, 2H). ^{13}C NMR (101.6 MHz, $CDCl_3$/TMS): δ 148.1, 143.0, 138.0, 128.6, 127.1, 125.7, 120.1, 115.2, 112.8, 47.5, 21.7. DEPT-135 (101.6 MHz, $CDCl_3$/TMS): δ 148.1, 143.0, 138.0, 128.6, 127.1, 125.7, 120.1, 115.2, 112.8, 47.5, 21.7. HRMS (ESI): calcd for $C_{29}H_{24}N_4$ $[M + H]^+$ m/z: 429.2079; found 429.2072.

Bis(1-benzyl-5-bromo-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)methane (3i). Nature: white solid; yield: 159 mg (78%); R_f (50% EtOAc–hexane): 0.21; FTIR (KBr) ν_{max}: 3028, 2911, 1723, 1594, 1445, 1335, 1277, 111 722, 1024, 764, 705, 602 cm^{-1}. ^{1}H NMR (400.3 MHz, $CDCl_3$/TMS): δ 8.25 (d, J = 2.1 Hz, 2H), 7.77 (d, J = 2.2 Hz, 2H), 7.35–7.12 (m, 6H), 7.13–6.99 (m, 4H), 6.89 (s, 2H), 5.33 (s, 4H), 3.99 (s, 2H). ^{13}C NMR (101.6 MHz, $CDCl_3$/TMS): δ 146.4, 143.6, 137.4, 129.4, 128.8, 127.7, 127.2, 121.4, 111.8, 111.2, 47.8, 21.6. DEPT-135 (101.6 MHz, $CDCl_3$/TMS): δ 143.6, 129.4, 128.8, 127.7, 127.2, 47.8, 21.6. HRMS (ESI): calcd for $C_{29}H_{22}Br_2N_4$ $[M + H]^+$ m/z: 584.0289; found 585.0286.

Bis(5-bromo-1-(prop-2-yn-1-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl) methane (3j). Nature: white solid; yield: 164 mg (80%); R_f (50% EtOAc–hexane): 0.22; FTIR (KBr) ν_{max}: 3287, 3105, 2954, 1536, 1467, 1423, 1341,1246, 1187, 1975, 927, 885, 832, 767, 690, 637. ^{1}H NMR (400.3 MHz, $CDCl_3$/TMS): δ 8.37 (d, J = 1.7 Hz, 2H), 7.93 (d, J = 1.9 Hz, 2H), 7.25 (d, J = 27.2 Hz, 2H), 5.05 (s, 4H), 4.14 (s, 2H), 2.41 (s, 2H). ^{13}C NMR (101.6 MHz, $CDCl_3$/TMS): δ 145.9, 143.8, 129.8, 126.5, 121.9, 112.4, 111.7, 73.5, 33.8, 21.6. DEPT-135 (101.6 MHz, $CDCl_3$/TMS): δ 143.7, 129.6, 126.4, 33.6, 21.5. HRMS (ESI): calcd for $C_{21}H_{14}Br_2N_4$ $[M + H]^+$ m/z: 479.9585; found 480.9702.

Bis(1-allyl-5-bromo-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)methane (3k). Nature: white solid; yield: 154 mg (75%) R_f (50% EtOAc–hexane): 0.24; ^{1}H NMR (400.3 MHz, $CDCl_3$/TMS): δ 8.25 (s, 2H), 7.81 (s, 2H), 6.92 (s, 2H), 5.93 (ddd, J = 22.2, 10.5, 5.4 Hz, 2H), 5.12 (d, J = 10.2 Hz, 2H), 4.98 (d, J = 17.1 Hz, 2H), 4.76 (d, J = 5.1 Hz, 4H), 4.02 (s, 2H). ^{13}C NMR (101.6 MHz, $CDCl_3$/TMS): δ 146.2, 143.6, 133.6, 129.5, 127.2, 121.6, 117.5, 111.5, 46.6, 29.8, 21.6. DEPT-135 (101.6 MHz, $CDCl_3$/TMS): δ 142.5, 132.4, 128.3, 126.0, 115.4, 20.4. HRMS (ESI): calcd for $C_{21}H_{18}Br_2N_4$ $[M + H]^+$ m/z: 483.9898; found 484.9649.

Bis(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)methanone (4a). Nature: white solid; yield: 73 mg (70%); R_f (50% EtOAc–hexane): 0.12; FTIR (KBr) ν_{max}: 3469, 3084, 2920, 1727, 1597, 1519, 1440, 1297, 1232, 1121, 1082, 847, 795, 736, 580 cm^{-1}. ^{1}H NMR (400.3 MHz, $CDCl_3$/TMS): δ 8.58 (dd, J = 7.9, 1.4 Hz, 2H), 8.38 (dd, J = 4.7, 1.4 Hz, 2H), 7.77 (s, 2H), 7.21 (dd, J = 8.6, 5.5 Hz, 2H), 3.95 (s, 6H). ^{13}C NMR (101.6 MHz, $CDCl_3$/TMS): δ 183.9, 148.2, 144.5, 134.2, 131.3, 119.9, 118.3, 115.6, 32.2. DEPT-135 (101.6 MHz, $CDCl_3$/TMS): δ 144.3, 134.1, 131.2, 118.2, 32.1. HRMS (ESI): calcd for $C_{17}H_{14}N_4O$ $[M + H]^+$ m/z: 291.1246; found 291.1277.

Bis(5-bromo-1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl) methanone (4b). Nature: brown powder; yield: 77 mg (75%); R_f (50% EtOAc–hexane): 0.19; FTIR (KBr) ν_{max}: 2919, 2849, 1718, 1584, 1520, 1455, 1213, 1098, 817, 727, 586 cm^{-1}. ^{1}H NMR (400.3 MHz, $CDCl_3$/TMS): δ 8.70 (d, J = 2.2 Hz, 2H), 8.39 (d, J =

2.2 Hz, 2H), 7.74 (s, 2H), 3.90 (s, 6H). ^{13}C NMR (101.6 MHz, $CDCl_3$/TMS): δ 182.9, 146.7, 145.5, 134.6, 132.9, 120.9, 114.6, 32.1. DEPT-135 (101.6 MHz, $CDCl_3$/TMS): δ 145.5, 134.6, 132.9, 32.1. HRMS (ESI): calcd for $C_{17}H_{12}Br_2N_4O$ [M + H]$^+$ *m*/*z*: 446.9456; found 446.9450.

Bis(3-bromo-1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl) methanone (4c). Nature: brown powder; yield: 80 mg (78%); R_f (50% EtOAc–hexane): 0.19; FTIR (KBr) ν_{max}: 3093, 2915, 2114, 1588, 1523, 1458, 1283, 1095, 887, 731 595 cm^{-1}. ^{1}H NMR (400.3 MHz, $CDCl_3$/TMS): δ 8.68 (s, 2H), 8.37 (s, 2H), 7.73 (s, 2H), 3.90 (s, 6H). ^{13}C NMR (101.6 MHz, $CDCl_3$/TMS): δ 183.0, 146.7, 145.5, 134.8, 133.1, 121.0, 114.7, 32.3. DEPT-135 (101.6 MHz, $CDCl_3$/TMS): δ 145.5, 134.8, 133.1, 32.3. HRMS (ESI): calcd for $C_{17}H_{12}Br_2N_4O$ [M + H]$^+$ *m*/*z*: 446.9456; found 446.9456.

Bis(5-bromo-1-methyl-1*H*-indol-3-yl)methanone (4d). Nature: brown powder; yield: 37 mg (36%); R_f (30% EtOAc–hexane): 0.10; FTIR (KBr) ν_{max}: 3509, 3431,3106, 2094, 1608, 1517, 1458, 1361, 1211, 1128, 1062, 836, 802, 595, 478 cm^{-1}. ^{1}H NMR (400.3 MHz, $CDCl_3$/TMS): δ 8.14 (d, *J* = 8.5 Hz, 2H), 7.47 (s, 2H), 7.42 (d, *J* = 1.5 Hz, 2H), 7.32 (dd, *J* = 8.5, 1.7 Hz, 2H), 3.74 (s, 6H). ^{13}C NMR (101.6 MHz, $CDCl_3$/TMS): δ 184.1, 138.3, 134.7, 126.1, 125.3, 123.8, 117.2, 112.8, 33.6, 29.8. DEPT-135 (101.6 MHz, $CDCl_3$/TMS): δ 134.6, 125.1, 123.6, 112.6, 33.4, 26.1. HRMS (ESI): calcd for $C_{19}H_{14}Br_2N_2O$ [M + H]$^+$ *m*/*z*: 443.9473; found 444.9549.

Bis(6-bromo-1-methyl-1*H*-indol-3-yl)methanone (4e). Nature: brown powder; yield: 46 mg (45%); R_f (75% EtOAc–hexane): 0.15; FTIR (KBr) ν_{max}: 2918, 2853, 1724, 1588, 1523, 1452, 1367, 1211, 1095, 816, 731, 666, 595 cm^{-1}. ^{1}H NMR (400.3 MHz, $CDCl_3$/TMS): δ 8.14 (d, *J* = 8.5 Hz, 2H), 7.46 (s, 2H), 7.41 (d, *J* = 1.4 Hz, 2H), 7.32 (dd, *J* = 8.5, 1.6 Hz, 2H), 3.73 (s, 6H). ^{13}C NMR (101.6 MHz, $CDCl_3$/TMS): δ 184.1, 138.3, 134.7, 126.1, 125.3 123.8, 117.5, 117.0, 112.8, 33.6. DEPT-135 (101.6 MHz, $CDCl_3$/TMS): δ 134.6, 125.2, 123.6, 112.6, 77.2, 33.5. HRMS (ESI): calcd for $C_{19}H_{14}Br_2N_2O$ [M + H]$^+$ *m*/*z*: 443.9473; found 444.9549.

Bis(1-methyl-5-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl) methanone (6a). Nature: brown powder; yield: 71 mg (72%); R_f (60% EtOAc–hexane): 0.20; FTIR (KBr) ν_{max}: 2928, 2857, 1996, 1724, 1594, 1530, 1452, 1368, 1258, 1129, 1083, 892, 770, 697 cm^{-1}. ^{1}H NMR (400.3 MHz, $CDCl_3$/TMS): δ 8.82 (d, *J* = 2.1 Hz, 2H), 8.63 (d, *J* = 2.1 Hz, 2H), 7.83 (s, 2H), 7.68–7.55 (m, 4H), 7.42 (t, *J* = 7.6 Hz, 4H), 7.32 (t, *J* = 7.4 Hz, 2H), 3.99 (s, 6H). ^{13}C NMR (101.6 MHz, DMSO) δ 138.6, 136.9, 129.5, 127.2, 119.4, 51.6, 31.7. DEPT-135 (101.6 MHz, $CDCl_3$) δ 144.0, 134.5, 129.2, 128.9, 127.5, 127.3, 32.0. HRMS (ESI): calcd for $C_{29}H_{22}N_4O$ [M + H]$^+$ *m*/*z*: 443.1872; found 443.1837.

Bis(1-methyl-5-(*p*-tolyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl) methanone (6b). Nature: yellow solid; yield: 52 mg (50%); R_f (75% EtOAc–hexane): 0.16; FTIR (KBr) ν_{max}: 3106, 3015, 2911, 2107, 1601, 1517, 1445, 1355, 1211, 1089, 887, 822, 738, 576, 524 cm^{-1}. ^{1}H NMR (400.3 MHz, $CDCl_3$/TMS): δ 8.79 (s, 2H), 8.61 (s, 2H), 7.80 (s, 2H), 7.52 (d, *J* = 7.6 Hz, 4H), 7.35–7.04 (m, 4H), 3.97 (s, 6H), 2.35 (s, 6H). ^{13}C NMR (101.6 MHz, DMSO) δ 182.6, 147.4, 146.4, 144.3, 143.1, 137.5, 137.0, 136.9, 135.6, 131.9, 130.8, 129.9, 127.6, 127.0, 120.9, 119.3, 113.5, 113.3, 112.9, 31.8, 20.8. DEPT-135 (101.6 MHz, $CDCl_3$) δ 143.9, 134.4, 129.6, 128.9, 127.4, 32.0, 21.1. HRMS (ESI): calcd for $C_{31}H_{26}N_4O$ [M + H]$^+$ *m*/*z*: 471.2185; found 471.2191.

Bis(5-([1,1′-biphenyl]-2-yl)-1-methyl-1*H*-pyrrolo[2,3-*b*] pyridin-3-yl)methanone (6c). Nature: white powder; yield: 79 mg (60%); R_f (60% EtOAc–hexane): 0.40; FTIR (KBr) ν_{max}: 3052, 2916, 1603, 1526, 1462, 1090, 897, 763, 737, 705, 577 cm^{-1}.^{1}H NMR (400.3 MHz, $CDCl_3$/TMS): δ 8.65 (d, *J* = 2.1 Hz, 2H), 8.06 (d, *J* = 2.1 Hz, 2H), 7.82 (s, 2H), 7.55–7.44 (m, 8H), 7.25–7.16 (m, 10H), 3.96 (s, 6H). ^{13}C NMR (101.6 MHz, $CDCl_3$/TMS): δ 183.9, 146.5, 141.4, 141.1, 137.9, 134.3, 132.4, 131.6, 131.5, 130.8, 130.2, 128.3, 127.9, 127.8, 126.8, 119.4, 115.7, 32.2. DEPT-135 (101.6 MHz, $CDCl_3$/TMS): δ 146.4, 134.2, 131.5, 131.3, 130.7, 130.0, 128.1, 127.8, 127.7, 126.6, 32.0. HRMS (ESI): calcd. for $C_{41}H_{30}N_4O$ [M + H]$^+$ *m*/*z*: 595.2498; found 595.2487.

Bis(1-methyl-5-(phenanthren-9-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)methanone (6d). Nature: white powder; yield: 132 mg (92%); R_f (75% EtOAc–hexane): 0.42; FTIR (KBr) ν_{max}: 3035, 2918, 2100, 1983, 1594, 1523, 1445, 1400, 1355, 1218, 1128, 1075, 978, 887, 738, 595 cm^{-1}. ^{1}H NMR (400.3 MHz, $CDCl_3$/TMS): δ 8.75 (d, *J* = 2.1 Hz, 2H), 8.70 (d, *J* = 8.2 Hz, 2H), 8.64 (d, *J* = 8.0 Hz, 2H), 8.54 (d, *J* = 2.1 Hz, 2H), 7.90 (s, 2H), 7.82 (td, *J* = 8.6, 1.2 Hz, 4H), 7.68 (s, 2H), 7.62–7.50 (m, 6H), 7.44 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 2H), 4.01 (s, 6H). ^{13}C NMR (101.6 MHz, $CDCl_3$/TMS): δ 183.9, 147.9, 146.2, 135.9, 134.7, 132.1, 131.4, 130.8, 130.2, 128.9, 126.7, 123.1, 122.7, 119.5, 115.8, 32.2. DEPT-135 (101.6 MHz, $CDCl_3$/TMS): δ 146.1, 134.6, 131.9, 128.8, 126.5, 123.0, 122.6, 32.1. HRMS (ESI): calcd for $C_{45}H_{30}N_4O$ [M + H]$^+$ *m*/*z*: 643.2498; found 643.2506.

Bis(1-methyl-5-(pyren-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl) methanone (6e). Nature: brown powder; yield: 137 mg (89%); R_f (75% EtOAc–hexane): 0.42; FTIR (KBr) ν_{max}: 2916, 2846, 1718, 1603, 1526, 1448, 1090, 833, 731 cm^{-1}. ^{1}H NMR (400.3 MHz, $CDCl_3$/TMS) δ 8.84 (d, *J* = 2.1 Hz, 2H), 8.63 (d, *J* = 2.1 Hz, 2H), 8.18–8.00 (m, 12H), 7.94 (dt, *J* = 9.6, 7.7 Hz, 8H), 4.04 (s, 6H). ^{13}C NMR (101.6 MHz, $CDCl_3$/TMS) δ 183.9, 147.8, 146.6, 134.7, 132.4, 131.8, 131.6, 131.0, 129.1, 128.4, 127.9, 127.7, 127.5, 126.2, 125.3, 125.0, 124.8, 119.5, 115.8, 32.2. Dept-135 (101.6 MHz, $CDCl_3$/TMS) δ 146.5, 134.6, 132.3, 128.3, 127.5, 126.0, 125.2, 124.7, 32.1. HRMS (ESI): calcd for $C_{49}H_{30}N_4O$ [M + H]$^+$ *m*/*z*: 691.2498; found 691.2485.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

PE thanks VIT, Vellore for the research fellowship. SK thanks VIT Management for providing infrastructure facilities and VIT SEED GRANT for carrying out this work.

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