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A transition metal-free approach towards synthesis of β-carboline tethered 1,3,4-oxadiazoles *via* oxidative C–O bond formation†

Dharmender Singh,[a] Sandip Kumar Tiwari[b] and Virender Singh *[a]

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An efficient protocol has been developed for one-pot synthesis of biologically interesting β-carboline substituted 1,3,4-oxadiazoles *via* an I_2-assisted oxidative C–O bond formation strategy. This metal-free sequential approach is found to be compatible with diversely substituted 1-formyl β-carbolines and aromatic as well as aliphatic hydrazides, providing access to a variety of multifunctional β-carboline linked 1,3,4-oxadiazole derivatives in good to excellent yields. The methodology was found to be applicable to gram scale synthesis of β-carboline substituted 1,3,4-oxadiazole derivatives. Additionally, β-carboline C1 linked 2-amino-1,3,4-oxadiazoles and bis-1,3,4-oxadiazoles were also synthesized using the same strategy.

Introduction

Naturally occurring β-carboline alkaloids and their synthetic derivatives are widely studied due to their broad spectrum of pharmacological properties, such as anticancer,[1] antibacterial, antimalarial, anti-HIV, anti-Alzheimer *etc.*[2] However, the majority of β-carboline alkaloids display anticancer properties *via* intercalation into DNA,[3] and inhibition of cyclin-dependent kinases,[4] topoisomerases[5] and IkK kinase complexes.[6] Importantly, the β-carboline alkaloids account for nearly one quarter of natural products (Fig. 1) and are also accommodated by several commercial drugs (Tadalfil, Abecarnil, Cipargamin *etc.*).[7]

Similarly, 1,3,4-oxadiazole is another high value added scaffold which has attracted considerable attention for decades owing to its pharmaceutical and biological activities, such as anti inflammatory, antibacterial, anticancer, anti-diabetic, analgesic, antiviral, antifungal *etc.*[8] Apart from this, 1,3,4-oxadiazole has demonstrated numerous applications in the field of materials science because of its excellent electron transporting and hole-blocking abilities.[9] The optoelectronic properties[10] of oxadiazole derivatives make them unique among the heterocyclic family. Moreover, the medicinal significance of this motif is evident from the fact that it is represented by numerous drugs such as Raltegravir[11] (antiretroviral), Zibotentan[12] (anticancer), Fenadiazole[13] (hypnotic), Nesapidil[14] (antihypertensive), ABT-751-oxadiazole and Furamizole[15] (Fig. 1) used for the treatment of various ailments.

The medicinal potential of these two privileged scaffolds inspired us to construct a new molecular hybrid containing both the frameworks. Interestingly, an analysis of the literature revealed the presence of one narrowly related previous report (Fig. 2) in the form of a patent where Guo *et al.* have disclosed the 8-step synthesis and anti-diabetic properties of tetrahydro-β-carbolines containing 1,3,4-oxadiazole for the treatment of type 2 diabetes mellitus (Fig. 2).[16] It was found that these molecular hybrids act as selective antagonists of the somatostatin subtype receptor 3 and could also be used for the treatment of depression, anxiety, insulin resistance, hyperglycemia, lipid disorders, obesity and hypertension. The literature revealed that dehydration of diacyl-hydrazines ($POCl_3$′ $SOCl_2$, PPA, H_2SO_4)[17] and oxidative cyclization of acylhydrazones utilizing oxidants[18] like HgO/I_2, PbO_2, IBX, DMP, chloramine T, $KMnO_4$, CAN, I_2, an Br_2 or transition metal catalysts ($Cu(OTf)_2$, $PdCl_2$(dppp), CuI, and $FeCl_3$) *via* C–O coupling reactions are two common approaches employed for the synthesis of 1,3,4-oxadiazoles.[19] Recently, the Xu group reported a novel Pd-assisted synthesis of 2-amino-1,3,4-oxadiazoles through isocyanide insertions into hydrazides.[20] Nevertheless, the major drawback associated with existing reports involves the use of expensive and hazardous reagents, harsh reaction conditions, multistep synthesis and non-scalability. Among these methods, annulation of acylhydrazides with carbonyl compounds is found to be a more effective approach[21] as disclosed by Yu and co-workers.[22] However, the substrate scope with acylhydrazides containing electron withdrawing substituents remains unexplored. Patel and co-workers have also developed a $Cu(OTf)_2$ assisted excellent approach toward synthesis of symmetrical and unsymmetrical oxadiazoles.[23] Our group has been involved in the

[a] *Department of Chemistry, Dr B R Ambedkar National Institute of Technology (NIT), Jalandhar, 144011, Punjab, India*
[b] *Drug Discovery and Molecular Synthesis Lab, Centre of Biomedical Research, SGPGIMS, Lucknow- 226014, Uttar Pradesh, India. E-mail: singhv@nitj.ac.in; Fax: +91 172-2214692*

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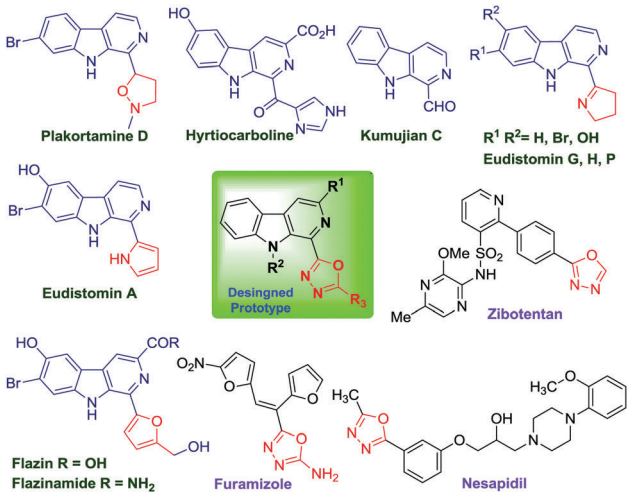


Fig. 1 Representative examples of biologically active β-carboline and 1,3,4-oxadiazole derivatives.

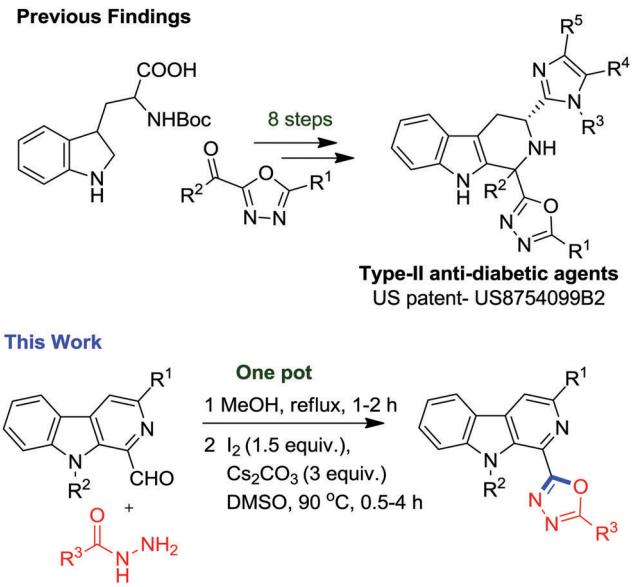


Fig. 2 Previous finding related to the synthesis of a designed prototype.

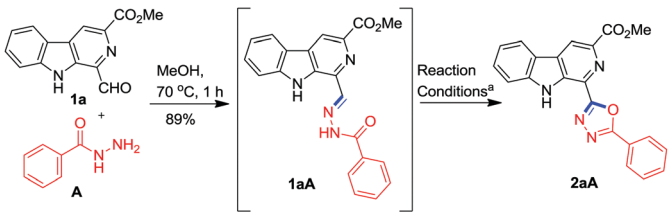
development of chemical libraries of β-carboline based molecular hybrids using sustainable approaches. In a recent finding, we have demonstrated the I_2-mediated synthesis of β-carboline N-fused imidazoles *via* decarboxylative oxidation of natural α-amino acids.[24a] In an extension to our research on the synthesis of β-carboline based privileged scaffolds, we have developed a surrogate approach for the synthesis of β-carboline substituted 1,3,4-oxadiazole derivatives *via* an iodine-mediated oxidative cyclisation process (Fig. 2). The details of these studies are presented here.

Results and discussion

To achieve the synthesis of the designed molecular hybrid, optimization of the reaction conditions was achieved using 1-formyl β-carboline **1a** and benzohydrazide **A** as the model substrates. The condensation of **1a** with **A** in methanol at 70 °C smoothly afforded the benzohydrazone **1aA** in 89% yield without any assistance of Bronsted acid. Next, we explored the oxidative cyclization of the isolated hydrazone **1aA** to generate the 1,3,4-oxadiazole framework. Recent studies have revealed that molecular iodine is one of the most versatile promoters and it offers numerous advantages over transition metal catalysts.[22,24] Therefore, it has been extensively used in organic synthesis for a variety of transformations. Accordingly, the isolated benzohydrazone **1aA** was treated with 1.5 equiv. of iodine in the presence of K_2CO_3 at 70 °C in MeOH. However, the reaction was very sluggish and it was not completed in 24 h (Table 1, entry 1). The purification of the reaction mixture *via* column chromatography afforded the desired product, β-carboline C1 substituted 1,3,4-oxadiazole, **2aA** in 25% yield as confirmed on the basis of spectroscopic data. Nevertheless, 60% of the starting substrate **1aA** was also recovered.

In a quest to improve the yield of product, various reaction parameters like reagent, base, solvent and the temperature were modified to obtain the optimum yield (Table 1). Accordingly,

Table 1 Reaction optimisation[a]



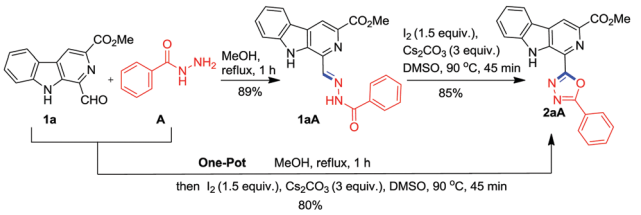
Entry	Reagents[b]	Base[c]	Solvent[d]	Temp (°C)	Time (h)	Yields[e] (%) **2aA**
1	I_2	K_2CO_3	MeOH	70	24	25% + **1a** (60%)
2	I_2	K_2CO_3	DMSO	90	1	77
3	I_2	$NaHCO_3$	DMSO	90	1.5	70
4	I_2	Cs_2CO_3	DMSO	rt	10	78
5	**I_2**	**Cs_2CO_3**	**DMSO**	**90**	**45 min**	**85**
6	I_2	Cs_2CO_3	DMSO	120	45 min	85
7	I_2	Cs_2CO_3	DMF	90	1.5	65
8	I_2	KOH	DMSO	90	1	75
9	I_2	—	DMSO	90	16	66 + polar impurity
10[f]	I_2	Et_3N	DMSO	90	24	NR
11[f]	I_2	DIPEA	DMSO	90	24	NR
12[f]	I_2	—	AcOH	90	16	NR
13[f]	TBAI	Cs_2CO_3	DMSO	90	16	NR
14	NCS	K_2CO_3	DMF	90	12	32 + polar impurity
15[f]	DMP	—	CH_2Cl_2	35	24	NR
16[f]	NH_4Cl	—	DMSO	90	12	NR
17[f,g]	$FeCl_3$	—	DMSO	90	12	NR
18[f,g]	CuI	Cs_2CO_3	DMSO	90	12	—
19[f,g]	$Cu(OTf)_2$	Cs_2CO_3	DMSO	90	12	—
20[f,g]	$La(OTf)_2$	Cs_2CO_3	DMSO	90	12	—

[a] Reaction conditions: All reactions were optimised with 0.134 mmol (1.0 equiv.) benzoylhydrazone **1aA** in 1 mL of solvent. [b] Molecular iodine (1.5 equiv.), KI (2.0 equiv.), TBAI (2.5 equiv.), NCS (2.0 equiv.), DMP (2.5 equiv.), NH_4Cl (2.0 equiv.) was used for oxidative cyclisation. [c] 3.0 equiv. of base was used. [d] Reactions were performed in anhydrous solvents (entries 1–21). [e] Isolated yields of the purified product. [f] NR = No reaction; the starting substrate **1aA** was recovered. [g] 20 mol% catalyst was used and decomposition of benzoylhydrazone **1aA** was observed.

when the reaction was examined in DMSO using K_2CO_3 as a base in the presence of iodine, **1aA** was completely consumed within 1 h and the yield of the anticipated product **2aA** was significantly improved (77%, Table 1, entry 2). Encouraged by these results, we screened various bases with DMSO as the solvent and molecular iodine as an oxidant. The reaction in the presence of $NaHCO_3$ could not enhance the yield and generated the desired product in 70% yield with some unidentified polar impurities (Table 1, entry 3). The reaction with 1.5 equiv. of iodine and 3.0 equiv. of Cs_2CO_3 in DMSO at ambient temperature afforded a clean reaction (82% yield) but required 10 h for completion (Table 1, entry 4). Interestingly, when the reaction was performed under similar conditions at 90 °C, it was completed within 45 min to give the product in 85% yield (Table 1, entry 5). However, when the temperature was further increased to 120 °C, no visible improvement was observed in the reaction time or yield of the product (Table 1, entry 6). It was realized that the use of Cs_2CO_3 took less time as compared to other bases and a clean reaction was obtained to yield the product in excellent yield. More importantly, treatment of the reaction mixture with cold water furnished the desired product as a solid and the analytically pure product could be obtained by simple filtration under vacuum followed by washing with diethyl ether.

It was further observed that the reaction in anhydrous DMF at 90 °C in the presence of molecular iodine completed in 1.5 h but the product was generated in 65% yield (Table 1, entry 7). The combination of KOH with DMSO in the presence of iodine also efficiently produced 1,3,4-oxadiazole **2aA** in 75% yield (Table 1, entry 8). To our surprise, I_2-mediated oxidative cyclisation in the absence of any base also generated the desired product **2aA** in 66% yield in 16 h but polar impurities were also formed (Table 1, entry 9). It was found that the use of organic bases (Et_3N or DIPEA) failed to deliver the desired product (Table 1, entries 10 and 11). Similarly, the corresponding product was not generated when TBAI was used as an iodide source (I^-) for this transformation instead of molecular iodine (Table 1, entry 13) indicating that the iodonium ion (I^+) was possibly driving the reaction. Recently, we found that NCS could be used for decarboxylative oxidation of tetrahydro-β-carbolines so it was planned to investigate its utility for oxidative cyclisation.[24a] Interestingly, NCS was able to provide the desired product albeit in low yield (32%) along with an unidentified polar impurity (Table 1, entry 14). The use of DMP, NH_4Cl and transition metal catalysts like $FeCl_3$, CuI, $Cu(OTf)_2$ and $La(OTf)_2$ failed to deliver the desired product (Table 1, entries 15–20). Eventually, the optimization investigations led to the inference that DMSO was the best solvent and Cs_2CO_3 was a suitable base for the oxidative cyclization of **1aA** in a short duration with 85% yield (Table 1, entries 5 and 6).

Next, it was considered worthwhile to develop a one-pot procedure for this transformation (Scheme 1). Accordingly, condensation of **1a** with **A** and successive oxidative cyclisation was attempted in MeOH using Cs_2CO_3 and I_2 at 70 °C but the formation of β-carboline substituted 1,3,4-oxadiazole **2aA** required more than 24 h due to the precipitation of hydrazone

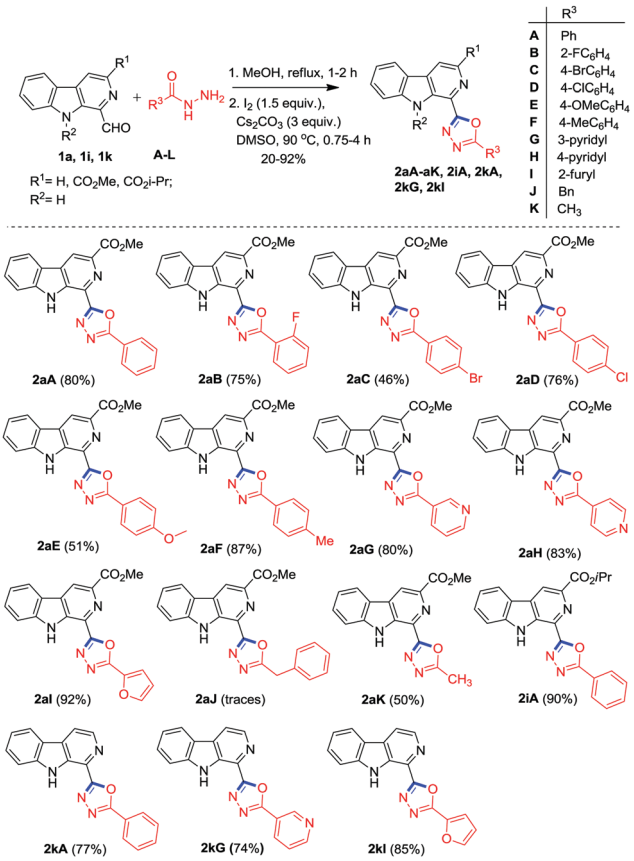


Scheme 1 Synthesis of β-carboline tethered 1,3,4-oxadiazole **2aA** from 1-formyl β-carboline (**1a**) and benzoic hydrazide (**A**).

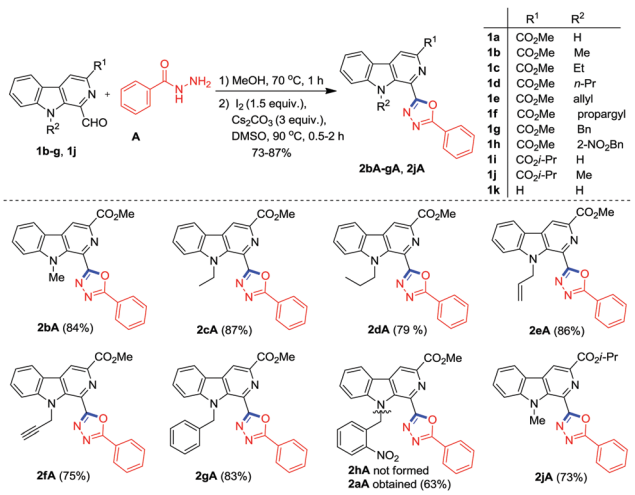
1aA from the reaction mixture and the desired product was obtained in 25% yield only. Then the one-pot assembly of reactants was executed in DMSO but condensation of **1a** and **A** was not completed even after 12 h. It was realised that MeOH was a suitable solvent for hydrazone synthesis **1aA** while DMSO was suited for oxidative cyclisation. Therefore, an alternate procedure was adopted where first hydrazone synthesis was achieved in MeOH within 1 h, then MeOH was evaporated and the hydrazone was re-dissolved in DMSO and subjected to oxidative cyclisation with 1.5 equiv. of iodine and 3.0 equiv. of Cs_2CO_3 at 90 °C for 45 min. To our delight, a clean reaction was observed and no column chromatographic separation was required.

With established conditions in hand, the scope of this one-pot procedure was investigated for condensation and oxidative cyclisation of 1-formyl β-carbolines[24] (**1a**, **1i** and **1k**) with substituted acylhydrazides (**A–L**) to afford the desired β-carboline substituted 1,3,4-oxadiazoles as depicted in Scheme 2. It was pleasing to see that the methodology worked well and smoothly yielded the anticipated products **2aA–aK**, **2iA**, **2kA**, **2kG**, **2kI** and **2kL** *via* oxidative cyclisation (C–O bond formation) within 1.75–5 h. The strategy was found compatible with a broad range of acylhydrazides (**A–K**) bearing electron withdrawing as well as electron donating groups. It was analysed that the acylhydrazides with an electron-donating group (**F**) reacted faster and afforded higher yield (87%) in comparisons to those bearing electron-withdrawing groups (**B–D**) (46–76%). The heteroaryl acylhydrazides (**G–I**) also reacted efficiently and furnished the corresponding products in good to excellent yields (74–92%). Furthermore, this method was extended to aliphatic hydrazides, such as acetylhydrazide **K** which generated the respective products **2aK** in 50% yield.

Encouraged by these results, we further extended our study by employing N-9 substituted 1-formyl β-carboline derivatives (**1b–h** and **1j**) for oxidative cyclisation with benzohydrazide **A**. To our delight, the reactions under optimum conditions easily yielded the corresponding β-carboline C1 substituted 1,3,4-oxadiazole derivatives **2bA–gA** and **2jA** within 1.5–3 h in good to excellent yield ranging from 73 to 87% (Scheme 3). It is important to mention that *N*-alkylated derivatives (except *N*-propargyl, **1f**) furnished the desired product in better yield and took less time for completion as compared to the free N–H derivative of β-carboline **1a**. Surprisingly, when **1h** was subjected to annulation with **A** under optimal reaction conditions, cleavage of the 2-nitrobenzyl group from the N-9 position of the β-carboline ring was observed and **2aA** was obtained as the



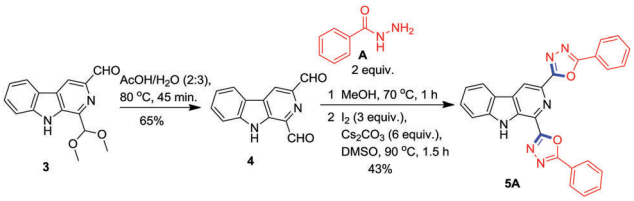
Scheme 2 Synthesis of β-carboline C-1 tethered 1,3,4-oxadiazole derivatives with the scope of variation in substituted acylhydrazides.



Scheme 3 Synthesis of *N*-alkylated β-carboline substituted 1,3,4-oxadiazole derivatives.

product instead of **2hA**. It is valuable to mention that the analytically pure products (**2bA–gA** and **2jA**) could be obtained by washing the crude product with diethyl ether and column chromatographic separation was not required.

Delighted by the successful synthesis of β-carboline C1 tethered 1,3,4-oxadiazoles, we examined the scope of this methodology for



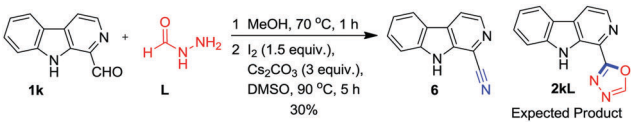
Scheme 4 Synthesis of β-carboline tethered bis-1,3,4-oxadiazole.

the synthesis of β-carboline tethered bis-oxadiazoles by employing β-carboline 1,3-dicarbaldehyde **4** as the precursor prepared from **3**.[25] The reaction of dialdehyde **4** with benzohydrazide **A** in the presence of I_2 and Cs_2CO_3 at 90 °C smoothly afforded the desired product **5A** in 43% yield (Scheme 4) after a silica gel column chromatographic separation.

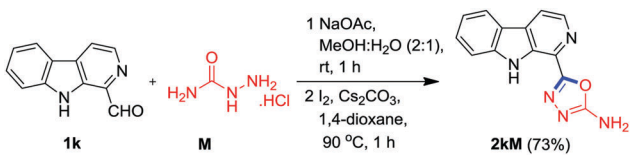
Surprisingly, when formic hydrazide **L** was used for oxidative annulation with **1k** (Scheme 5), the 1-cyano β-carboline **6** was obtained as the sole product instead of **2kL** as confirmed on the basis of ^{1}H-, ^{13}C-NMR and HRMS data.

Next, it was envisaged to further extend the scope of this practical methodology to prepare β-carboline containing 2-amino-1,3,4-oxadiazole derivatives by replacing benzohydrazide **A** with semicarbazide hydrochloride **M**. However, Kumujian C **1k** failed to react with semicarbazide hydrochloride **M** in the presence of I_2 and Cs_2CO_3 in DMSO. The screening of various solvents indicated that the desired product **2kM** could be isolated in 73% yield in 1,4-dioxane at 90 °C, as depicted in Scheme 6. In order to demonstrate the applicability of this protocol for industrial application, a one gram scale reaction was also conducted using **1a** and **A** as substrates and to our pleasure, the expected product **2aA** was obtained in an analytically pure form (77%) without column chromatographic purification (Scheme 7).

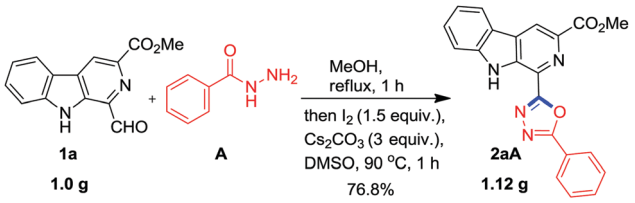
To probe the reaction mechanism, two control experiments were conducted where the isolated benzohydrazone **1bA** was separately reacted with iodine monochloride (source of I^+) and KI (source of I^-) in the presence of Cs_2CO_3 in DMSO under optimised conditions. It was found that ICl readily afforded the desired β-carboline substituted 1,3,4-oxadiazole, **2bA** within 2h while KI failed to execute the reaction (Scheme 8). These experiments



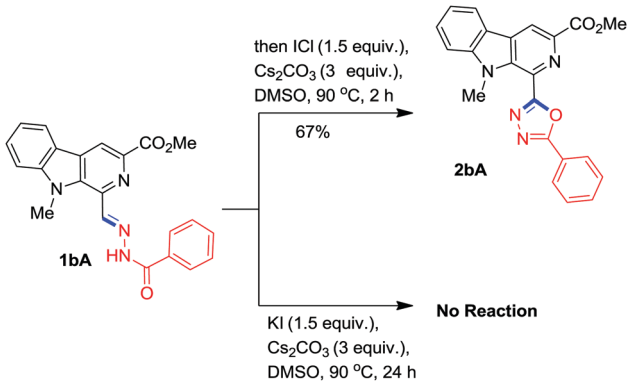
Scheme 5 Synthesis of 1-cyano β-carboline.



Scheme 6 Synthesis of β-carboline C1 tethered 2-amino 1,3,4-oxadiazole from semicarbazide.



Scheme 7 Gram scale synthesis of **2aA**.



Scheme 8 Control experiments.

indicated that the iodonium ion played a key role in initiation of this oxidative annulation process.

A plausible mechanism for the formation of β-carboline substituted 1,3,4-oxadiazoles is presented in Fig. 3 based on the results of the study. Initially, the condensation of 1-formyl β-carboline **1a** and benzohydrazide (**A**) resulted in the formation of isolable benzoylhydrazone **1aA**. Then, it is proposed that benzoylhydrazone **1aA** may undergo Cs_2CO_3 mediated oxidative C-iodination *via* route-I to generate the intermediate **6**. The successive formation of a new C–O bond *via* a S_N2-type intramolecular cyclization of **7** may result in the formation of 1,3,4-oxadiazole framework **2aA**. Alternatively, benzoylhydrazone **1aA** may undergo N-iodination *via* route-II to generate an N-iodo intermediate **8** which may follow base/heat mediated annulation with loss of 1 mole of HI to afford the 1,3,4-oxadiazole framework **2aA** as depicted in Fig. 2. The desired product could not be produced in the presence of Lewis acids ($FeCl_3$, $Cu(OTf)_2$ and $La(OTf)_2$) which are likely to follow route-II during annulation; therefore, there is good probability that the reaction is following route-I. The generation of HI during the course of reaction was confirmed by the pH study of a reaction medium which was performed in the absence of base (SI). It was observed that after completion of the reaction under base free conditions, the pH of the reaction medium was 2.61.

Conclusions

In summary, we have developed a transition metal-free approach for the synthesis of β-carboline C1 tethered 1,3,4-oxadiazoles as well as 2-amino 1,3,4-oxadiazoles *via* I_2 mediated oxidative cyclocondensation. This sequential one-pot synthetic procedure was found to be compatible for the annulation of diversely substituted hydrazides and 1-formyl β-carboline derivatives and desired 1,3,4-oxadiazoles could be isolated at a gram scale without column chromatographic purification. This methodology provides easy access to heterocycles with potential pharmaceutical applications. The investigation of the application of β-carboline linked 1,3,4-oxadiazoles as a ligand for complexation with metals and their development as analytical sensors is currently in progress in our laboratory.

Experimental section

General methods

The reagents and chemicals were procured from Sigma Aldrich and Spectrochem Ltd and used as such without additional purification. The anhydrous solvents (glacial AcOH, DCM, DMSO, DMF, and MeOH) were used as available commercially. TLC was examined on precoated aluminum plates (E. Merck; silica gel 60 PF254, 0.25 mm). The column chromatographic separation

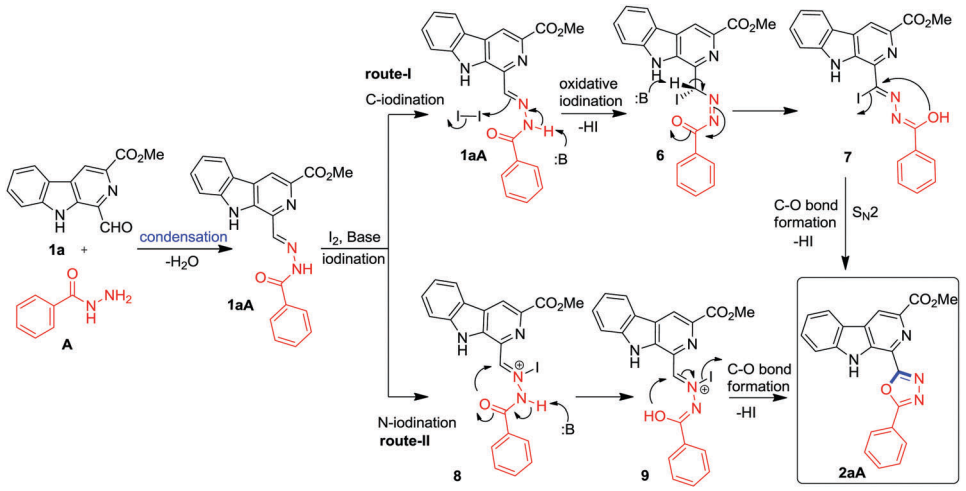


Fig. 3 The proposed mechanism for the construction of β-carboline substituted 1,3,4-oxadiazole.

was conducted on silica gel (SRL; 60–120 mesh). The melting points were recorded in open-ended capillary tubes on a Precision Digital melting-point apparatus (LABCO make) that contained silicon oil and are uncorrected. The IR spectra were recorded on an Agilent FTIR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on an Avance III Bruker spectrometer at operating frequencies of 400 MHz or 100 MHz (^{13}C), as mentioned in the individual spectrum, by using TMS as a standard. The HRMS spectra were recorded on Xevo G2-SQ TOF (Water; USA) or Thermo Finnigan LCQ Advantage, Ion-Trap Mass Spectrometer. Elemental analysis was performed on a Carlo–Erba 108 or an Elementar Vario EL III microanalyzer. During the study, room temperature varied between 25 and 40 °C. The multiplicity in the ^{1}H NMR spectra is mentioned as follows: s for singlet, d for doublet, t for triplet, q for quartet, dd for doublet of doublet, dt for doublet of triplet and m for multiplet.

General procedure (one-pot) for the synthesis of compounds 2aA–aK, 2iA, 2kA, 2kG, 2kI, 2kL, 2bA–hA and 2jA as exemplified for compound 2aA

The stirred solution of 1-formyl β-carboline **1a** (0.200 g, 0.787 mmol) and benzohydrazide **A** (0.112 g, 0.826 mmol) in MeOH (10 mL) was refluxed for 1 h. After the condensation was completed as monitored by TLC, the solvent was evaporated under reduced pressure. The resulting benzohydrazone **1aA** was re-dissolved in DMSO (5 mL), followed by addition of cesium carbonate (0.770 g, 2.362 mmol) and molecular iodine (0.300 g, 1.181 mmol) in sequence and the reaction mixture was stirred at 90 °C for 45 min; the conversion was monitored by the TLC technique. The reaction mixture was cooled to room temperature and then the content was poured into ice-cold water followed by treatment with 5% aq. $Na_2S_2O_3$ (20 mL), and light brown precipitates were obtained which were filtered and sintered under high vacuum to get a crude product which was triturated and washed with diethyl ether (twice) to afford the analytically pure product, β-carboline C1 tethered 1,3,4-oxadiazole **2aA** in 80% yield.

Methyl 1-(5-phenyl-1,3,4-oxadiazol-2-yl)-9*H*-pyrido[3,4-*b*] indole-3-carboxylate (2aA)

Yield: 80% (0.234 g from 0.200 g) as a light brown solid; m.p. 199–201 °C; R_f = 0.35 (hexane/EtOAc, 70 : 30, v/v); IR (neat): ν_{max} (cm^{-1}) = 3426 (NH), 1710 (CO_2CH_3), 1626 (C=N), 1261 (C–O), 1064 (C–O–C); ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6) δ = 4.02 (s, 3 H, CO_2CH_3), 7.31 (t, J = 7.5 Hz, 1 H, ArH), 7.46–7.52 (m, 3 H, ArH), 7.57 (t, J = 7.6 Hz, 1 H, ArH), 7.69 (d, J = 8.2 Hz, 1 H, ArH), 8.14 (d, J = 7.9 Hz, 1 H, ArH), 8.21 (d, J = 7.9 Hz, 2 H, ArH), 8.93 (s, 1 H, ArH), 10.87 (s, 1 H, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ = 52.8, 112.9, 119.6, 121.2, 121.6, 121.9, 123.1, 125.3, 127.5, 129.0, 129.8, 130.9, 132.2, 135.6, 137.4, 141.1, 163.1, 165.0, 165.8 ppm; HRMS (ESI) m/z: calcd for $C_{21}H_{14}N_4O_3$ [M + Na]: 393.0964, found: 393.1002.

Methyl 1-(5-(2-fluorophenyl)-1,3,4-oxadiazol-2-yl)-9*H*-pyrido [3,4-*b*]indole-3-carboxylate (2aB)

Yield: 75% (0.230 g from 0.200 g) as a light brown solid; m.p. 204–206 °C; R_f = 0.30 (hexane/EtOAc, 70 : 30, v/v); IR (neat): ν_{max} = 3565 (NH), 1701 (CO_2CH_3), 1620 (C=N), 1265 (C–O), 1058 (C–O–C); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.10 (s, 3 H, CO_2CH_3), 7.28–7.43 (m, 3 H, ArH), 7.59–7.67 (m, 3 H, ArH), 8.23 (dd, J_1 = 15.5 Hz, J_2 = 7.7 Hz, 2 H, ArH), 9.00 (s, 1 H, ArH), 10.48 (s, 1 H, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 53.0, 111.9 (d, J = 11 Hz), 112.7, 117.1 (d, J = 21 Hz), 119.8, 121.4, 122.0 (d, J = 34 Hz), 124.7, 124.8, 125.2, 130.2 (d, J = 20 Hz), 131.1, 134.1, 134.2, 135.9, 138.0, 141.2, 159.2, 162.5 (d, J = 143 Hz), 166.0 ppm; HRMS (ESI) m/z: calcd for $C_{21}H_{13}FN_4O_3$ [M + H$^+$]: 389.1050, found: 389.1077.

Methyl 1-(5-(4-bromophenyl)-1,3,4-oxadiazol-2-yl)-9*H*-pyrido [3,4-*b*]indole-3-carboxylate (2aC)

Yield: 46% (0.163 g from 0.200 g) as a pale yellow solid; m.p. > 260 °C; R_f = 0.45 (hexane/EtOAc, 70 : 30, v/v); IR (neat): ν_{max} = 3483 (NH), 1711 (CO_2CH_3), 1629 (C=N), 1277 (C–O), 1064 (C–O–C); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.12 (s, 3 H, CO_2CH_3), 7.43 (dt, J_1 = 8.0 Hz, J_2 = 4.1 Hz, 1 H, ArH), 7.68 (d, J = 3.8 Hz, 2 H, ArH), 7.70–7.72 (m, 2 H, ArH), 8.15–8.19 (m, 2 H, ArH), 8.24 (dd, J_1 = 7.9 Hz, J_2 = 0.7 Hz, 1 H, ArH), 9.02 (d, J = 0.5 Hz, 1 H, ArH), 10.45 (s, 1 H, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 53.1, 112.7, 120.0, 121.6, 122.0, 122.2, 122.4, 125.3, 127.3, 129.1, 130.3, 131.2, 132.6, 136.0, 138.1, 141.3, 163.5, 164.6, 166.0 ppm; HRMS (ESI) m/z: calcd for $C_{21}H_{13}BrN_4O_3$ [M + H$^+$]: 449.0249, found: 449.0194.

Methyl 1-(5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)-9*H*-pyrido [3,4-*b*]indole-3-carboxylate (2aD)

Yield: 76% (0.242 g from 0.200 g) as an off-white solid; m.p. 257–259 °C; R_f = 0.40 (hexane/EtOAc, 70 : 30, v/v); IR (neat): ν_{max} = 3512 (NH), 1707 (CO_2CH_3), 1626 (C=N), 1269 (C–O), 1067 (C–O–C); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.12 (s, 3 H, CO_2CH_3), 7.40–7.44 (m, 1 H, ArH), 7.54 (d, J = 8.3 Hz, 2 H, ArH), 7.68 (d, J = 3.9 Hz, 2 H, ArH), 8.23 (d, J = 8.3 Hz, 3 H, ArH), 9.01 (s, 1 H, ArH), 10.44 (s, 1 H, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 53.1, 112.7, 120.0, 121.6, 121.7, 122.0, 122.4, 125.3, 129.0, 129.6, 130.2, 131.2, 136.0, 138.0, 138.8, 141.2, 163.5, 164.5, 166.0 ppm; HRMS (ESI) m/z: calcd for $C_{21}H_{13}ClN_4O_3$ [M + H$^+$]: 405.0754, found: 405.0702.

Methyl 1-(5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (2aE)

Yield: 51% (0.161 g from 0.200 g) as an off-white solid; m.p. 254–256 °C; R_f = 0.40 (hexane/EtOAc, 70 : 30, v/v); IR (neat): ν_{max} = 3450 (NH), 1704 (CO_2CH_3), 1623 (C=N), 1266 (C–O), 1060 (C–O–C); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.92 (s, 3 H, OCH_3), 4.13 (s, 3 H, CO_2CH_3), 7.07 (d, J = 8.9 Hz, 2 H, ArH), 7.40–7.45 (m, 1 H, ArH), 7.68 (d, J = 3.3 Hz, 2 H, ArH), 8.23–8.27 (m, 3 H, ArH), 9.03 (s, 1 H, ArH), 10.51 (s, 1 H, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 53.1, 55.6, 112.6, 114.6, 115.7, 119.7, 121.6, 121.9, 122.3, 125.7, 129.6, 130.1, 131.0, 135.9, 137.9, 141.2, 162.9, 163.0, 165.3, 166.1 ppm; HRMS (ESI) m/z: calcd for $C_{22}H_{16}N_4O_4$ [M + H$^+$]: 401.1250, found: 401.1254.

Methyl 1-(5-(*p*-tolyl)-1,3,4-oxadiazol-2-yl)-9*H*-pyrido[3,4-*b*] indole-3-carboxylate (2aF)

Yield: 87% (0.263 g from 0.200 g) as a pale yellow solid; m.p. 233–235 °C; R_f = 0.37 (hexane/EtOAc, 70 : 30, v/v); IR (neat):

ν_{max} = 3412 (NH), 1709 (CO_2CH_3), 1618 (C═N), 1266 (C–O), 1126 (C–O–C); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.47 (s, 3 H, $ArCH_3$), 4.13 (s, 3 H, CO_2CH_3), 7.39 (d, J = 7.9 Hz, 2 H, ArH), 7.43 (dd, J_1 = 7.9 Hz, J_2 = 4.5 Hz, 1 H, ArH), 7.70 (d, J = 3.4 Hz, 2 H, ArH), 8.22 (d, J = 8.0 Hz, 2 H, ArH), 8.26 (d, J = 7.9 Hz, 1 H, ArH), 9.05 (s, 1 H, ArH), 10.52 (s, 1 H, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 21.7, 53.1, 100.1, 112.9, 119.8, 120.5, 121.6, 121.9, 122.3, 127.7, 127.8, 129.9, 130.1, 135.9, 138.0, 141.3, 143.1, 163.1, 165.5, 166.1 ppm; HRMS (ESI) *m*/*z*: calcd for $C_{22}H_{16}N_4O_3$ [M + H$^+$]: 385.1301, found: 385.1289.

Methyl 1-(5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (2aG)

Yield: 80% (0.235 g from 0.200 g) as a light brown solid; m.p. > 260 °C; R_f = 0.30 (hexane/EtOAc, 50 : 50, v/v); IR (neat): ν_{max} = 3392 (NH), 1714 (CO_2CH_3), 1595 (C═N), 1261 (C–O), 1107 (C–O–C); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.12 (s, 3 H, CO_2CH_3), 7.42–7.46 (m, 1 H, ArH), 7.52–7.55 (m, 1 H, ArH), 7.70 (d, J = 4.0 Hz, 2 H, ArH), 8.25 (d, J = 7.9 Hz, 1 H, ArH), 8.58 (dt, J_1 = 8.1 Hz, J_2 = 1.9 Hz, 1 H, ArH), 8.84 (dd, J_1 = 4.8 Hz, J_2 = 1.5 Hz, 1 H, ArH), 9.04 (s, 1 H, ArH), 9.55 (d, J = 1.9 Hz, 1 H, ArH), 10.47 (s, 1 H, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 53.2, 112.7, 119.9, 120.1, 121.5, 122.2, 122.4, 124.0, 125.1, 130.3, 131.3, 134.9, 136.0, 138.1, 141.3, 148.7, 153.0, 163.3, 163.8, 165.9 ppm; HRMS (ESI) *m*/*z*: calcd for $C_{20}H_{13}N_5O_3$ [M + H$^+$]: 372.1097, found: 372.1078.

Methyl 1-(5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (2aH)

Yield: 83% (0.243 g from 0.200 g) as a pale yellow solid; m.p. > 260 °C; R_f = 0.35 (hexane/EtOAc, 50 : 50, v/v); IR (neat): ν_{max} = 3399 (NH), 1719 (CO_2CH_3), 1623 (C═N), 1260 (C–O), 1107 (C–O–C); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.12 (s, 3 H, CO_2CH_3), 7.41–7.46 (m, 1 H, ArH), 7.70 (dd, J_1 = 5.9 Hz, J_2 = 1.0 Hz, 2 H, ArH), 8.16 (dd, J_1 = 4.5 Hz, J_2 = 1.6 Hz, 2 H, ArH), 8.24 (d, J = 8.0 Hz, 1 H, ArH), 8.88 (dd, J_1 = 4.5 Hz, J_2 = 1.6 Hz, 2 H, ArH), 9.04 (s, 1 H, ArH), 10.50 (s, 1 H, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 53.2, 112.8, 120.3, 121.0, 121.5, 122.1, 122.4, 124.9, 130.4, 130.5, 131.5, 136.1, 138.1, 141.3, 151.1, 163.5, 164.2, 165.9 ppm; HRMS (ESI) *m*/*z*: calcd for $C_{20}H_{13}N_5O_3$ [M + H$^+$]: 372.1097, found: 372.1114.

Methyl 1-(5-(furan-2-yl)-1,3,4-oxadiazol-2-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (2aI)

Yield: 92% (0.261 g from 0.200 g) as a pale yellow solid; m.p. 255–257 °C; R_f = 0.45 (hexane/EtOAc, 70 : 30, v/v); IR (neat): ν_{max} = 3393 (NH), 1712 (CO_2CH_3), 1624 (C═N), 1262 (C–O), 1128 (C–O–C); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.11 (s, 3 H, CO_2CH_3), 6.67 (dd, J_1 = 3.5 Hz, J_2 = 1.7 Hz, 1 H, ArH), 7.39–7.42 (m, 2 H, ArH), 7.65–7.73 (m, 3 H, ArH), 8.23 (d, J = 7.8 Hz, 1 H, ArH), 9.01 (s, 1 H, ArH), 10.49 (s, 1 H, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 53.1, 112.6, 112.7, 116.0, 120.0, 121.5, 122.0, 122.3, 125.2, 130.2, 131.2, 136.0, 138.0, 139.1, 141.3, 146.6, 158.0, 162.6, 166.0 ppm; HRMS (ESI) *m*/*z*: calcd for $C_{19}H_{12}N_4O_4$ [M + H$^+$]: 361.0937, found: 361.0874.

Methyl 1-(5-methyl-1,3,4-oxadiazol-2-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (2aK)

Yield: 50% (0.122 g from 0.200 g) as a light brown solid; m.p. 235–237 °C; R_f = 0.30 (hexane/EtOAc, 50 : 50, v/v); IR (neat): ν_{max} = 3391 (NH), 1712 (CO_2CH_3), 1587 (C═N), 1260 (C–O), 1086 (C–O–C); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.74 (s, 3 H, CH_3), 4.09 (s, 3 H, CO_2CH_3), 7.39–7.43 (m, 1 H, ArH), 7.66 (d, J = 3.8 Hz, 2 H, ArH), 8.22 (d, J = 7.9 Hz, 1 H, ArH), 8.99 (s, 1 H, ArH), 10.40 (s, 1 H, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 11.5, 53.2, 112.6, 119.8, 121.5, 121.9, 122.3, 125.5, 130.2, 131.1, 136.7, 137.8, 141.2, 163.6, 164.7, 166.0 ppm; HRMS (ESI) *m*/*z*: calcd for $C_{16}H_{12}N_4O_3$ [M + H$^+$]: 309.0988, found: 309.0999.

Isopropyl 1-(5-phenyl-1,3,4-oxadiazol-2-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (2iA)

Yield: 90% (0.255 g from 0.200 g) as a light brown solid; m.p. 197–199 °C; R_f = 0.50 (hexane/EtOAc, 50 : 50, v/v); IR (neat): ν_{max} = 3419 (NH), 1711 (CO_2i-Pr), 1598 (C═N), 1234 (C–O), 1108 (C–O–C); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.53 (d, J = 6.3 Hz, 6 H, $CH(CH_3)_2$), 5.41–5.47 (m, 1 H, $CH(CH_3)_2$), 7.40–7.44 (m, 1 H, ArH), 7.58 (d, J = 7.7 Hz, 3 H, ArH), 7.68 (dd, J_1 = 3.7 Hz, J_2 = 1.5 Hz, 2 H, ArH), 8.26 (d, J = 7.9 Hz, 1 H, ArH), 8.31 (dd, J_1 = 7.8 Hz, J_2 = 1.6 Hz, 2 H, ArH), 8.97 (s, 1 H, ArH), 10.49 (s, 1 H, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 22.2, 69.8, 112.7, 119.7, 121.6, 121.8, 122.3, 123.4, 125.7, 127.7, 129.2, 130.1, 131.0, 132.4, 135.9, 138.7, 141.3, 163.5, 164.9, 165.3 ppm; HRMS (ESI) *m*/*z*: calcd for $C_{23}H_{18}N_4O_3$ [M + H$^+$]: 399.1457, found: 399.1443.

2-Phenyl-5-(9*H*-pyrido[3,4-*b*]indol-1-yl)-1,3,4-oxadiazole (2kA)

Yield: 77% (0.245 g from 0.200 g) as a brown solid; m.p. 209–211 °C; R_f = 0.50 (hexane/EtOAc, 50 : 50, v/v); IR (neat): ν_{max} = 3465 (NH), 1630 (C═N), 1249 (C–O), 1088 (C–O–C); ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6) δ = 7.32 (t, J = 7.5 Hz, 1 H, ArH), 7.57–7.62 (m, 4 H, ArH), 7.80 (d, J = 8.2 Hz, 1 H, ArH), 8.14–8.18 (m, 2 H, ArH), 8.27 (d, J = 7.2 Hz, 2 H, ArH), 8.62 (d, J = 5.1 Hz, 1 H, ArH), 10.96 (s, 1 H, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ = 112.3, 116.6, 120.0, 120.2, 121.1, 122.9, 125.1, 126.7, 128.5, 128.7, 130.0, 131.5, 133.9, 138.3, 140.8, 163.1, 163.9 ppm; HRMS (ESI) *m*/*z*: calcd for $C_{19}H_{12}N_4O$ [M + H$^+$]: 313.1089, found: 313.1067.

2-(Pyridin-3-yl)-5-(9*H*-pyrido[3,4-*b*]indol-1-yl)-1,3,4-oxadiazole (2kG)

Yield: 74% (0.236 g from 0.200 g) as a brown solid; m.p. 213–215 °C; R_f = 0.35 (hexane/EtOAc, 50 : 50, v/v); IR (neat): ν_{max} = 1628 (C═N), 1225 (C–O), 1122 (C–O–C); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.34–7.38 (m, 1 H, ArH), 7.51 (dd, J_1 = 7.9 Hz, J_2 = 4.9 Hz, 1 H, ArH), 7.64 (d, J = 3.9 Hz, 2 H, ArH), 8.14 (d, J = 5.0 Hz, 1 H, ArH), 8.18 (d, J = 7.8 Hz, 1 H, ArH), 8.54 (d, J = 8.0 Hz, 1 H, ArH), 8.66 (d, J = 5.1 Hz, 1 H, ArH), 8.82 (d, J = 4.4 Hz, 1 H, ArH), 9.51 (s, 1 H, ArH), 10.18 (s, 1 H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 112.3, 117.6, 120.1, 121.0, 121.1, 122.1, 123.9, 125.2, 129.7, 130.9, 134.6, 134.8, 139.4, 140.9, 148.4, 152.8, 162.8, 164.3 ppm; HRMS (ESI) *m*/*z*: calcd for $C_{18}H_{11}N_5O$ [M + H$^+$]: 314.1042, found: 314.1042.

2-(Furan-2-yl)-5-(9*H*-pyrido[3,4-*b*]indol-1-yl)-1,3,4-oxadiazole (2kI)

Yield: 85% (0.262 g from 0.200 g) as a yellow solid; m.p. > 260 °C; R_f = 0.60 (hexane/EtOAc, 50 : 50, v/v); IR (neat): ν_{max} = 3409 (NH), 1640 (C=N), 1271 (C–O), 1118 (C–O–C); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.67 (dd, J_1 = 3.4 Hz, J_2 = 1.6 Hz, 1 H, ArH), 7.34–7.38 (m, 1 H, ArH), 7.42 (d, J = 3.5 Hz, 1 H, ArH), 7.62–7.66 (m, 2 H, ArH), 7.72 (d, J = 0.7 Hz, 1 H, ArH), 8.14 (d, J = 5.1 Hz, 1 H, ArH), 8.19 (d, J = 7.9 Hz, 1 H, ArH), 8.66 (d, J = 5.1 Hz, 1 H, ArH), 10.18 (s, 1 H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 112.3, 112.5, 115.4, 117.5, 121.1, 121.3, 122.1, 125.5, 129.7, 130.8, 134.9, 139.3, 139.6, 141.0, 146.4, 157.7, 163.2 ppm; HRMS (ESI) *m*/*z*: calcd for $C_{17}H_{10}N_4O_2$ [M + H$^+$]: 303.0882, found: 303.0870.

Methyl 9-methyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (2bA)

Yield: 84% (0.240 g from 0.200 g) as an off-white solid; m.p. 228–230 °C; R_f = 0.45 (hexane/EtOAc, 70 : 30, v/v); IR (neat): ν_{max} = 1711 (CO_2CH_3), 1588 (C=N), 1267 (C–O), 1129 (C–O–C); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.09 (s, 3 H, NCH_3), 4.10 (s, 3 H, CO_2CH_3), 7.45 (t, J = 7.5 Hz, 1 H, ArH), 7.58 (t, J = 7.6 Hz, 4 H, ArH), 7.74 (d, J = 7.5 Hz, 1 H, ArH), 8.25–8.28 (m, 3 H, ArH), 9.06 (s, 1 H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 33.5, 53.2, 110.6, 119.4, 121.0, 121.8, 122.0, 123.7, 126.4, 127.6, 129.2, 130.2, 132.3, 132.4, 137.3, 143.6, 162.0, 165.9, 166.0 ppm; HRMS (ESI) *m*/*z*: calcd for $C_{22}H_{16}N_4O_3$ [M + Na]: 407.1120, found: 407.1070.

Methyl 9-ethyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (2cA)

Yield: 87% (0.246 g from 0.200 g) as an off-white solid; m.p. 204–206 °C; R_f = 0.55 (hexane/EtOAc, 70 : 30, v/v); IR (neat): ν_{max} = 1714 (CO_2CH_3), 1586 (C=N), 1269 (C–O), 1119 (C–O–C); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.28 (t, J = 7.2 Hz, 3 H, NCH_2CH_3), 4.09 (s, 3 H, CO_2CH_3), 4.80 (q, J = 7.2 Hz, 2 H, NCH_2CH_3), 7.43 (t, J = 7.5 Hz, 1 H, ArH), 7.54–7.62 (m, 4 H, ArH), 7.69–7.73 (m, 1 H, ArH), 8.23–8.29 (m, 3 H, ArH), 9.06 (s, 1 H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.3, 40.2, 53.1, 110.7, 119.4, 121.3, 121.7, 122.0, 123.6, 126.2, 127.5, 129.2, 130.1, 132.3, 132.7, 136.1, 137.1, 142.6, 162.1, 165.9 ppm; HRMS (ESI) *m*/*z*: calcd for $C_{23}H_{18}N_4O_3$ [M + H$^+$]: 399.1457, found: 399.1457.

Methyl 1-(5-phenyl-1,3,4-oxadiazol-2-yl)-9-propyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (2dA)

Yield: 79% (0.110 g from 0.100 g) as an off-white solid; m.p. 201–202 °C; R_f = 0.65 (hexane/EtOAc, 70 : 30, v/v); IR (neat): ν_{max} = 1713 (CO_2CH_3), 1590 (C=N), 1261 (C–O), 1123 (C–O–C); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.73 (t, J = 7.1 Hz, 3 H, $NCH_2CH_2CH_3$), 1.62-1.67 (m, 2 H, $NCH_2CH_2CH_3$), 4.09 (s, 3 H, CO_2CH_3), 4.71 (t, J = 7.1 Hz, 2 H, $NCH_2CH_2CH_3$), 7.41 (t, J = 7.2 Hz, 1 H, ArH), 7.53–7.60 (m, 4 H, ArH), 7.67–7.71 (m, 1 H, ArH), 8.25 (d, J = 5.0 Hz, 3 H, ArH), 9.05 (s, 1 H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 11.2, 22.6, 46.6, 53.1, 110.9, 119.3, 121.1, 121.5, 121.6, 121.9, 123.6, 126.3, 127.5, 129.2, 130.0, 132.2, 132.5, 136.3, 137.1, 143.0, 162.0, 165.9 ppm; HRMS (ESI) *m*/*z*: calcd for $C_{24}H_{20}N_4O_3$ [M + H$^+$]: 413.1614, found: 413.1569.

Methyl 9-allyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (2eA)

Yield: 86% (0.240 g from 0.200 g) as a light brown solid; m.p. 160–162 °C; R_f = 0.45 (hexane/EtOAc, 70 : 30, v/v); IR (neat): ν_{max} = 1706 (CO_2CH_3), 1598 (C=N), 1297 (C–O), 1089 (C–O–C); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.10 (s, 3 H, CO_2CH_3), 4.57 (d, J = 16.7 Hz, 1 H, =C*H*H), 4.90 (dd, J_1 = 10.5 Hz, J_2 = 0.7 Hz, 1 H, =CH*H*), 5.48–5.51 (m, 2 H, NCH_2), 5.68–5.75 (m, 1 H, NCH_2CH), 7.45 (t, J = 7.6 Hz, 1 H, ArH), 7.55–7.60 (m, 4 H, ArH), 7.71 (t, J = 7.2 Hz, 1 H, ArH), 8.24 (dd, J_1 = 8.0 Hz, J_2 = 1.5 Hz, 2 H, ArH), 8.29 (d, J = 7.8 Hz, 1 H, ArH), 9.09 (s, 1 H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 47.2, 53.2, 110.9, 116.7, 119.4, 121.2, 121.9, 122.0, 123.7, 126.8, 127.6, 129.2, 130.2, 132.1, 132.2, 132.8, 136.3, 137.7, 143.1, 161.9, 165.8, 165.9 ppm; HRMS (ESI) *m*/*z*: calcd for $C_{24}H_{18}N_4O_3$ [M + H$^+$]: 411.1457, found: 411.1491.

Methyl 1-(5-phenyl-1,3,4-oxadiazol-2-yl)-9-(prop-2-yn-1-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (2fA)

Yield: 75% (0.105 g from 0.100 g) as a light brown solid; m.p. 205–207 °C; R_f = 0.50 (hexane/EtOAc, 70 : 30, v/v); IR (neat): ν_{max} = 1710 (CO_2CH_3), 1622 (C=N), 1275 (C–O), 1127 (C–O–C); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.00 (t, J = 2.4 Hz, 1 H, $CH_2C\equiv CH$), 4.11 (s, 3 H, CO_2CH_3), 5.74 (d, J = 2.4 Hz, 2 H, NCH_2), 7.47 (t, J = 7.5 Hz, 1 H, ArH), 7.55–7.60 (m, 3 H, ArH), 7.64 (d, J = 8.4 Hz, 1 H, ArH), 7.74 (t, J = 7.4 Hz, 1 H, ArH), 8.27 (dd, J_1 = 7.9 Hz, J_2 = 1.7 Hz, 3 H, ArH), 9.07 (s, 1 H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 35.3, 53.2, 73.3, 77.0, 110.7, 119.3, 121.5, 122.1, 122.3, 123.7, 127.0, 127.6, 129.2, 130.4, 132.3, 133.4, 135.8, 138.1, 142.6, 162.1, 165.8, 166.0 ppm; HRMS (ESI) *m*/*z*: calcd for $C_{24}H_{16}N_4O_3$ [M + H$^+$]: 409.1301, found: 409.1350.

Methyl 9-benzyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (2gA)

Yield: 83% (0.222 g from 0.200 g) as a light brown solid; m.p. 144–145 °C; R_f = 0.65 (hexane/EtOAc, 70 : 30, v/v); IR (neat): ν_{max} = 1714 (CO_2CH_3), 1628 (C=N), 1257 (C–O), 1149 (C–O–C); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.06 (s, 3 H, CO_2CH_3), 6.01 (s, 2 H, NCH_2), 6.53 (d, J = 7.3 Hz, 2 H, ArH), 6.90 (t, J = 7.3 Hz, 2 H, ArH), 6.95 (t, J = 7.1 Hz, 1 H, ArH), 7.48–7.51 (m, 3 H, ArH), 7.55 (d, J = 7.3 Hz, 1 H, ArH), 7.65 (d, J = 8.4 Hz, 1 H, ArH), 7.71–7.75 (m, 1 H, ArH), 8.00 (d, J = 7.1 Hz, 2 H, ArH), 8.35 (d, J = 7.8 Hz, 1 H, ArH), 9.12 (s, 1 H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 48.1, 53.2, 110.8, 119.4, 121.1, 122.1, 122.2, 123.6, 125.8, 127.2, 127.5, 128.7, 129.0, 130.4, 132.1, 132.9, 135.4, 136.1, 137.7, 143.8, 161.3, 165.8, 165.9 ppm; HRMS (ESI) *m*/*z*: calcd for $C_{28}H_{20}N_4O_3$ [M + H$^+$]: 461.1614, found: 461.1661.

Isopropyl 9-methyl-1-(5-phenyl-1,3,4-oxadiazol-2-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (2jA)

Yield: 73% (0.203 g from 0.200 g) as a pale yellow solid; m.p. 185–187 °C; R_f = 0.60 (hexane/EtOAc, 50 : 50, v/v); IR (neat): ν_{max} = 1707 (CO_2i-Pr), 1594 (C=N), 1255 (C–O), 1121 (C–O–C);

^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.50 (d, J = 6.2 Hz, 6 H, $CH(CH_3)_2$), 4.10 (s, 3 H, NCH_3), 5.38–5.45 (m, 1 H, $CH(CH_3)_2$), 7.43 (t, J = 7.2 Hz, 1 H, ArH), 7.56–7.59 (m, 4 H, ArH), 7.70–7.74 (m, 1 H, ArH), 8.25 (d, J = 1.8 Hz, 1 H, ArH), 8.27 (d, J = 7.8 Hz, 2 H, ArH), 8.98 (s, 1 H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 22.2, 33.5, 69.7, 110.6, 119.0, 121.1, 121.6, 121.9, 123.7, 126.5, 127.5, 129.2, 130.0, 132.2, 137.1, 137.9, 143.6, 162.2, 164.7, 165.8 ppm; HRMS (ESI) m/z: calcd for $C_{24}H_{20}N_4O_3$ [M + H$^+$]: 413.1614, found: 413.1637.

9*H*-Pyrido[3,4-*b*]indole-1-carbonitrile (6)

Yield: 30% (0.030 g from 0.100 g) as a light brown solid; m.p. 201–203 °C; R_f = 0.40 (hexane/EtOAc, 50 : 50, v/v); IR (neat): ν_{max} = 2239 (CN), 3404 (NH); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.38 (t, J = 7.4 Hz, 1 H, ArH), 7.61–7.69 (m, 2 H, ArH), 8.16 (dd, J_1 = 6.3 Hz, J_2 = 4.3 Hz, 2 H, ArH), 8.57 (d, J = 5.1 Hz, 1 H, ArH), 9.10 (s, 1 H, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 112.2, 116.1, 116.7, 118.4, 121.1, 121.6, 122.4, 130.4, 131.0, 138.8, 140.6 ppm; HRMS (ESI) m/z: calcd for $C_{12}H_7N_3$ [M + H$^+$]: 194.0718, found: 194.0780.

One pot procedure for the synthesis of 5A

A stirred solution of β-carboline 1,3-dicarbaldehyde **4** (0.150 g, 0.670 mmol) and benzohydrazide **A** (0.182 g, 1.339 mmol) in MeOH (10 mL) was refluxed for 1 h. After the condensation was completed as monitored by TLC, the solvent was evaporated under reduced pressure. The resulting benzohydrazone **4A** was re-dissolved in DMSO (5 mL), followed by addition of cesium carbonate (1.309 g, 4.017 mmol) and molecular iodine (0.510 g, 2.008 mmol) in sequence and the reaction mixture was stirred at 90 °C for 1.5 h; the conversion was monitored by the TLC technique. The reaction mixture was cooled to room temperature and then the content was poured into ice-cold water followed by treatment of 5% aq. $Na_2S_2O_3$ (20 mL), and light brown precipitates were obtained which were filtered and sintered under high vacuum to get a crude product which was purified through a short silica gel column chromatography using EtOAc : hexane (30 : 70, v/v) as an eluent to afford the analytically pure product, β-carboline tethered bis-1,3,4-oxadiazole **5A** in 43% yield.

5,5′-(9*H*-Pyrido[3,4-*b*]indole-1,3-diyl)bis(2-phenyl-1,3,4-oxadiazole) (5A)

Yield: 43% (0.131 g from 0.150 g) as a yellow solid; m.p. > 260 °C; R_f = 0.70 (hexane/EtOAc, 70 : 30, v/v); IR (neat): ν_{max} = 3393 (NH), 1565 (C=N), 1275 (C–O), 1139 (C–O–C); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.38–7.42 (m, 1 H, ArH), 7.57–7.61 (m, 6 H, ArH), 7.64–7.67 (m, 2 H, ArH), 8.22 (d, J = 7.9 Hz, 1 H, ArH), 8.27–8.31 (m, 4 H, ArH), 9.06 (s, 1 H, ArH), 10.45 (s, 1 H, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 112.6, 117.5, 121.3, 121.9, 122.4, 123.4, 124.1, 127.4, 127.7, 129.2, 129.3, 130.4, 131.3, 132.0, 132.5, 133.5, 135.4, 141.3, 163.4, 164.6, 165.3, 166.5 ppm; HRMS (ESI) m/z: calcd for $C_{27}H_{16}N_6O_2$ [M + H$^+$]: 457.1413, found: 457.1454.

General procedure for the synthesis of compound 2kM

To a stirred solution of semicarbazide hydrochloride **M** (0.085 g, 0.765 mmol) and sodium acetate (0.063 g, 0.765 mmol) in MeOH (7 mL), **1k** (0.150 g, 0.765 mmol) was added and stirring continued at room temperature for 1 h. After the condensation was completed as monitored by TLC, the solvent was evaporated under reduced pressure. The resulting residue was re-dissolved in 1,4-dioxane (5 mL), followed by addition of cesium carbonate (0.748 g, 2.295 mmol) and iodine (0.291 g, 1.147 mmol) in sequence and the reaction mixture was stirred at 90 °C for 1 h; the conversion was monitored by the TLC technique. The reaction mixture was cooled to room temperature and then, the reaction content was poured into ice-cold water followed by treatment with 5% aq. $Na_2S_2O_3$ (20 mL), and yellow precipitates were obtained which were filtered and sintered to get a crude product which was triturated and washed with diethyl ether (twice) to afford the analytically pure product **2kM** in 73% yield.

5-(9*H*-Pyrido[3,4-*b*]indol-1-yl)-1,3,4-oxadiazol-2-amine (2kM)

Yield: 73% (0.14 g from 0.150 g) as a pale yellow solid; m.p. > 260 °C; R_f = 0.30 (hexane/EtOAc, 20 : 80, v/v); ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.29 (d, J = 7.4 Hz, 1 H, ArH), 7.55 (s, 2 H, NH_2), 7.59 (d, J = 7.5 Hz, 1 H, ArH), 7.89 (d, J = 8.2 Hz, 1 H, ArH), 8.26 (dd, J_1 = 8.9 Hz, J_2 = 6.7 Hz, 2 H, ArH), 8.44 (d, J = 5.1 Hz, 1 H, ArH), 11.57 (s, 1 H, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 113.4, 116.2, 120.0, 120.4, 121.7, 126.8, 128.7, 129.4, 132.5, 138.0, 141.3, 157.1, 164.1 ppm; HRMS (ESI) m/z: calcd for $C_{13}H_9N_5O$ [M + H$^+$]: 252.0885, found: 252.0849.

Conflicts of interest

There are no conflicts to declare.

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