



Cite this: *RSC Adv.*, 2018, 8, 15448

One-pot sequential multicomponent reaction between *in situ* generated aldimines and succinaldehyde: facile synthesis of substituted pyrrole-3-carbaldehydes and applications towards medicinally important fused heterocycles†

Anoop Singh,^{‡a} Nisar A. Mir,^{‡a} Sachin Choudhary,^a Deepika Singh,^b Preetika Sharma,^c Rajni Kant^c and Indresh Kumar^{id}*^a

An efficient sequential multi-component method for the synthesis of *N*-arylpyrrole-3-carbaldehydes has been developed. This reaction involved a proline-catalyzed direct Mannich reaction-cyclization sequence between succinaldehyde and *in situ* generated *Ar*/*HetAr*/indolyl-imines, followed by IBX-mediated oxidative aromatization in one-pot operation. The practical utility of this procedure is shown at gram-scale and the synthesis of diverse bioactive fused heterocyclic scaffolds such as pyrroloquinoline, pyrrolo-oxadiazole, dihydro pyrroloquinoline, and pyrrolo-phenanthridine.

Received 24th February 2018

Accepted 18th April 2018

DOI: 10.1039/c8ra01637b

rsc.li/rsc-advances

Introduction

Medium sized nitrogen heterocycles are privileged scaffolds present in numerous natural and unnatural compounds.¹ Among them, the pyrrole core is present in many important classes of natural products and its derivatives have been used as valuable intermediates for the synthesis of many drugs that exhibit interesting biological activities (Fig. 1).² In addition, functionalized pyrroles have shown wide applications in agrochemicals and flavor components, dyes, and functionalized materials.³ Over the past few decades, a number of elegant methods to access functionalized pyrroles have been reported, which includes classical methods,⁴ cycloadditions,⁵ multi-component,⁶ metal-catalyzed reactions,⁷ and several others.⁸ Despite the extensive efforts, the synthesis of C3-functionalized pyrroles is probably the most difficult task and required a special strategy.⁹ In particular, the regiospecific synthesis of pyrroles endowed with aldehyde group at C3-position is still very rare.¹⁰ Pyrrole-3-carbaldehydes have mainly been synthesized by the use of sterically bulky triisopropylsilyl (TIPS) as

protecting group on the nitrogen of pyrrole followed by Vilsmeier–Haack formylation and deprotection as a multistep process (eqn (1), Scheme 1),^{10a} along with other direct/indirect methods.^{10b–e} However, these reported approaches have one or more drawbacks, such as the requirement of specially designed substrates, multistep process with low yields, and harsh reaction conditions. Furthermore, none of these methods could directly yield 1,2-disubstituted pyrrole-3-carbaldehydes, to the best of our knowledge. The development of synthetic protocol, which directly produces the required functionality at the desired position of heterocyclic ring systems, has become a major contribution to the pharmaceutical industry. Thus, the development of modular and simple pot-economic protocol to strategically access substituted pyrrole-3-carbaldehydes from easily available materials is still in high demand. Notably,

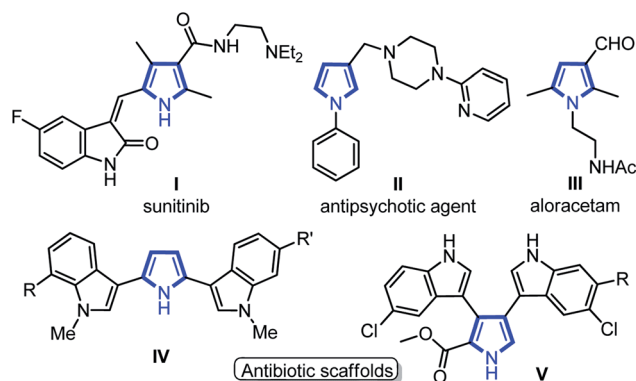


Fig. 1 Bioactive pyrroles and related derivatives.

^aDepartment of Chemistry, Birla Institute of Technology and Science, Pilani 333 031, Rajasthan, India. E-mail: indresh.chemistry@gmail.com; indresh.kumar@pilani.bits-pilani.ac.in

^bInstrumentation Division, IIM-CSIR Lab, Jammu 180 001, India

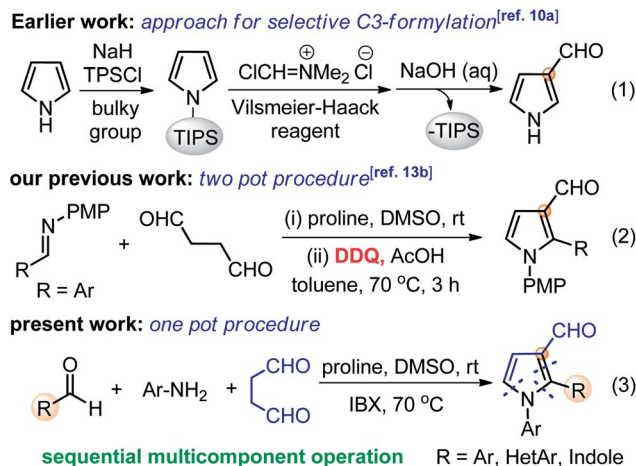
^cX-ray Crystallography Laboratory, Post-Graduate Department of Physics & Electronics, University of Jammu, Jammu 180 006, India

^dDepartment of Chemistry, Govt. Degree College for Puhwama-192301, J&K, India

† Electronic supplementary information (ESI) available. CCDC 1400572 and 1471798. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8ra01637b

‡ Both the authors contributed equally.





Scheme 1 Synthetic approaches for pyrrole-3-carbaldehydes.

aldehyde group at C3-position of pyrroles can readily participate in numerous name reactions, thus, holds significant promises to serve as a suitable intermediate to synthesize new medicinal agents and functionalized materials.¹¹

In continuation to our efforts to utilize using linear dialdehydes,¹² for the synthesis of medium-sized N-heterocycles under metal-free conditions,¹³ we recently developed a two-pot protocol for the direct synthesis of pyrrole-3-carbaldehyde

from succinaldehyde and imines (eqn (2), Scheme 1).^{13b} This method resulted in a quick synthesis of pyrrole-3-aldehydes, though, it required the pre-assembled imines and DDQ as a harsh and toxic reagent for oxidative aromatization. The clear synthetic potential and novelty of this method to suitably functionalized pyrroles prompted us to explore similar transformation in one-pot sequential multicomponent fashion under mild conditions. In addition, the social and environmental demands for more sustainable and practical synthetic protocols that need the use of less hazardous reagents/conditions has also gained much attention of the scientific community. In this context, multicomponent reactions allow the rapid construction of novel libraries of pharmaceutically active compounds and marine alkaloids, thus, the development of such protocol is always applauded.¹⁴ Herein, we report a simple and most rational sequential multicomponent protocol for the synthesis of pyrrole-3-carbaldehydes *via in situ* imine formation between Ar/HetAr/indole-aldehydes and Ar-NH₂, followed by amine-catalyzed direct Mannich reaction-cyclization with succinaldehyde, and IBX-mediated aromatization sequence in one-pot operation (eqn (3), Scheme 1). This improved method provides an easy access to pyrrole-3-carbaldehydes under mild and non-toxic condition as compare to our previous two-pot protocol. In addition, *in situ* generated imines derived from indole-3-aldehydes have been explored for the first time for such transformations to yield indole-based medicinally important scaffolds.

Results and discussion

Based on our previous experience in this direction, we quickly optimized the designed reactions by choosing proline **1** (20 mol%) as a catalyst, *p*-nitrobenzaldehyde **2c** as model substrates, along with *p*-anisidine **3**, and succinaldehyde **4** (3 M aqueous sol.), in one-pot operation and the results are shown in Table 1. Initial experiments in DMSO as the choice of solvent along with the sequential addition of substrates, catalyst, and oxidant(s) gave **5c** in low yield (entry 1 and 2, Table 1). Attempts were made to improve the yields by changing the solvents (entries 2–4, Table 1), however, failed. IBX as the oxidant, also soluble in DMSO, showed good efficiency for this one-pot protocol at rt (entry 5, Table 1) and at 50 °C (entry 6, Table 1). Gratifyingly, an additional improvement in yields (80%) was observed when IBX-oxidation was carried out at 70 °C for 4 h (entry 7, Table 1). However, additional efforts to increase the reaction yield by further increment in reaction temperature (entry 8, Table 1), reduction in catalyst loading (entry 9, Table 1), varying the reaction medium (entries 10 and 11, Table 1), and changing the catalytic system (entry 12, Table 1) were ineffective. Thus, we prefer to perform this one-pot sequential transformation with the optimized conditions (entry 7, Table 1).

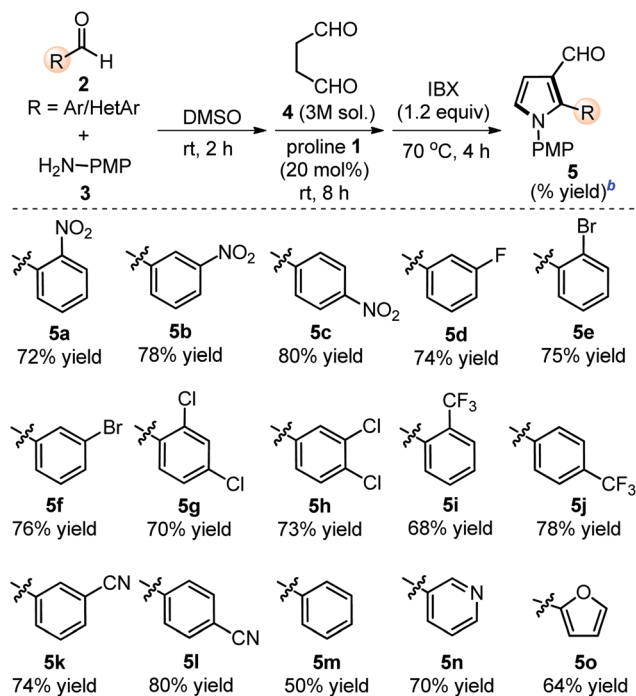
The scope of the reaction was examined by employing various aromatic aldehydes and the results are summarized in Table 2. This one-pot sequential multicomponent protocol works well in case of aromatic aldehydes decorated with various groups (*e.g.* –NO₂, –F, –Cl, –Br, –CN and CF₃) at the *ortho*-, *meta*-, or *para*-positions (entries **5a–5l**, Table 2) and resulted in 2-aryl-

Table 1 Optimization of reaction conditions^a

Entry	Solvent	Conditions ^a	Yield ^b (%)
1	DMSO	K ₂ S ₂ O ₈ (1.2 equiv.), rt, 8 h	35
2	DMSO	Oxone (1.2 equiv.), rt, 24 h	40
3	DMF	Oxone (1.2 equiv.), rt, 24 h	30
4	CH ₃ CN	Oxone (1.2 equiv.), rt, 24 h	<20
5	DMSO	IBX (1.2 equiv.), rt, 6 h	50
6	DMSO	IBX (1.2 equiv.), 50 °C, 6 h	64
7	DMSO	IBX (1.2 equiv.), 70 °C, 4 h	80
8	DMSO	IBX (1.2 equiv.), 90 °C, 4 h	75
9 ^c	DMSO	IBX (1.2 equiv.), 70 °C, 4 h	58
10	DMF	IBX (1.2 equiv.), 70 °C, 4 h	43
11 ^d	CH ₃ CN	IBX (1.2 equiv.), 70 °C, 4 h	35
12 ^e	DMSO	IBX (1.2 equiv.), 70 °C, 4 h	48

^a Unless otherwise indicated, the reaction was carried out with (i) aldehyde **2** (0.3 mmol), *p*-anisidine **3** (0.3 mmol), succinaldehyde **4** (3 M aqueous sol., 0.9 mmol), proline **1** (20 mol%), solvent (3.0 mL); (ii) IBX (1.2 equiv.). ^b Isolated yield of **5c** refers to **2c**. ^c Proline **1** (10 mol%). ^d EtOAc (3.0 mL) was added during IBX-mediated oxidative aromatization. ^e Pyrrolidine (20 mol%), PhCO₂H (20 mol%) were used in place of proline **1**.



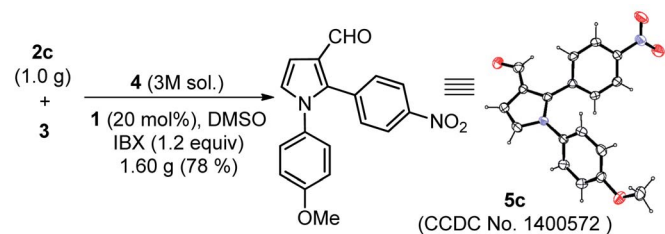
Table 2 Substrate scope with respect to various Ar/HetAr-aldehydes 2^a

^a Unless otherwise indicated, the reaction was carried out with (i) aldehyde **2** (0.3 mmol), *p*-anisidine **3** (0.3 mmol), DMSO (3.0 mL), rt, 2 h, (ii) succinaldehyde **4** (3 M aqueous sol., 0.9 mmol), proline **1** (20 mol%), 8 h, (iii) IBX (1.2 equiv.), 70 °C, 4 h. ^b Isolated yield of **5** refers to **2** ($\leq 10\%$ of aldehyde **2** was recovered in all the cases).

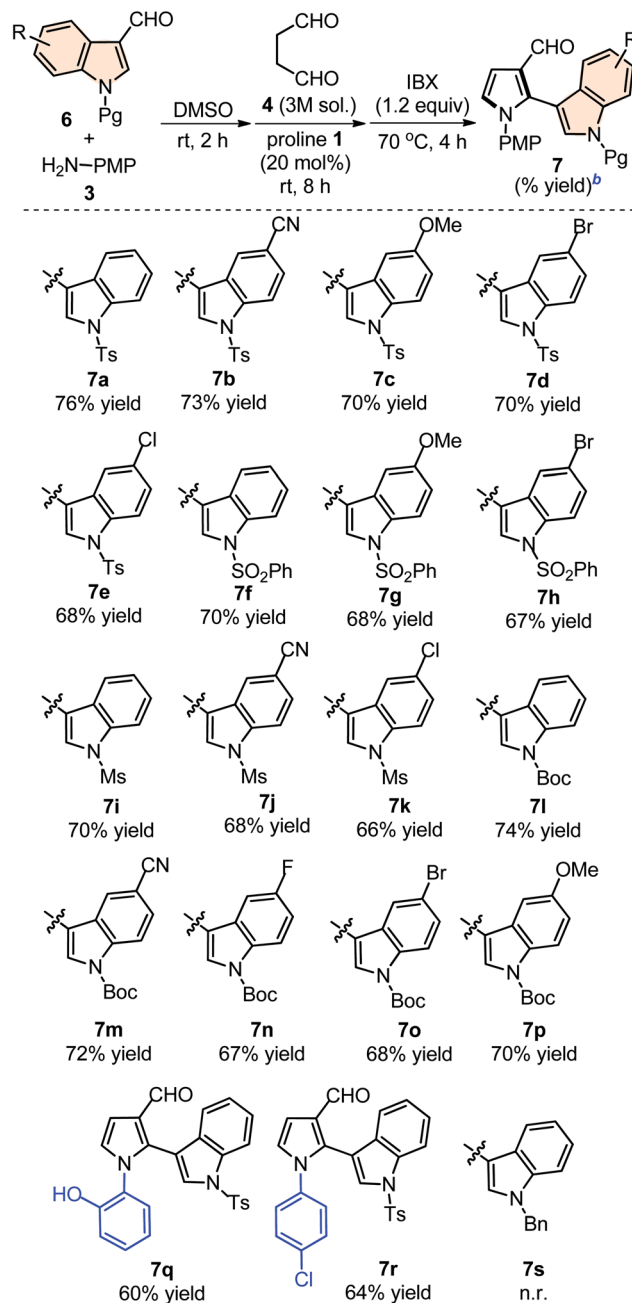
pyrrole-3-carbaldehydes in good to high yields (65–80%). The reaction works well with *in situ* generated simple aryl imine (entry **5m**, Table 2), as well as with hetero-aryl imines (entries **5n–5o**, Table 2) with good yields. The feasibility of this protocol was also examined at gram scale of **2c** (1.0 g) with other reactants under standardized conditions and corresponding product **5c** was obtained without much variation in yields (1.60 g, 78%). The structure of **5c** was further confirmed with single crystal X-ray diffraction analysis (Scheme 2).¹⁵

Indolyl-pyrroles synthesis

The scope of this one-pot protocol was further was examined by employing various *in situ* generated imines derived from indole-



Scheme 2 Single-crystal X-ray analysis of **5c**. Thermal ellipsoids are drawn at the 40% probability level.

Table 3 Substrate scope with respect to various indole-3-aldehydes 6^a

^a Unless otherwise indicated, the reaction was carried out with (i) aldehyde **6** (0.3 mmol), *p*-anisidine **3** (0.3 mmol), DMSO (3.0 mL), rt, 2 h, (ii) succinaldehyde **4** (3 M aqueous sol., 0.9 mmol), proline **1** (20 mol%), 8 h, (iii) IBX (1.2 equiv.), 70 °C, 4 h. ^b Isolated yield refers to **6** ($\leq 10\%$ of aldehyde **6** was recovered in all the cases).

3-aldehydes **6**. This extension to imines derived from indole-3-aldehydes could be motivating as these units have not been utilized for similar direct Mannich reaction and can lead to new structural scaffolds. Indole and its derivatives are an important family of alkaloid compounds and most abundant heterocycles found in nature, which possess interesting biological



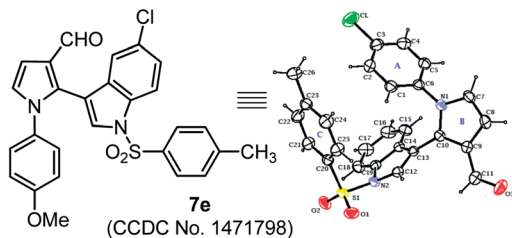
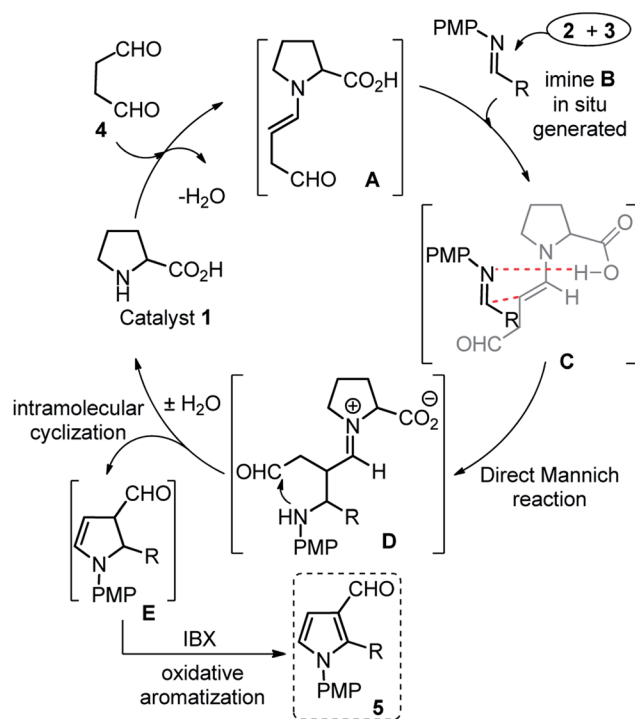


Fig. 2 Single-crystal X-ray analysis of **7e**. Thermal ellipsoids are drawn at the 40% probability level.



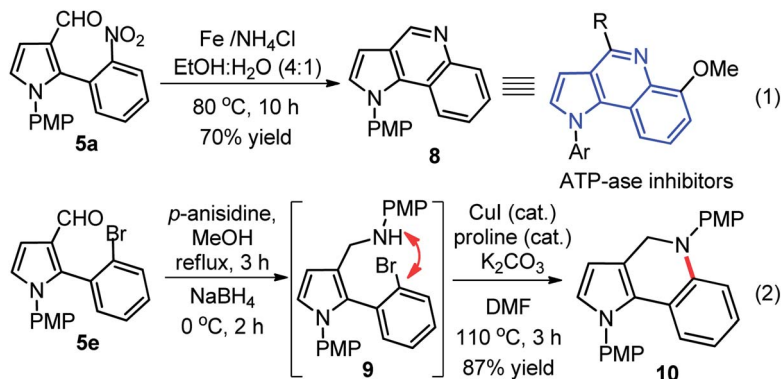
Scheme 3 Proposed reaction mechanism for this study.

activities.¹⁶ Moreover, indole-tethered pyrrole derivatives (for example **IV** and **V** in Fig. 1) found in several synthetic compounds and marine alkaloids that showed remarkable bioactivities,¹⁷ therefore, the synthesis of these compounds is

quite interesting. In this context, a series of indolyl-pyrrole-3-carboxaldehydes **7a–7p** were obtained with moderate to good yields, when *N*-Ts, Ms, SO₂Ph, Boc protected indole-3-aldehydes **6** were employed for this transformation with *p*-anisidine **3** and succinaldehyde **4** (entries **7a–7p**, Table 3). In addition, electron donating or withdrawing substitution on indole-ring did not alter the course of this transformation. Further, the reaction works quite well when other aryl-amines such as 2-aminophenol and 4-chloroaniline (entries **7q–7r**, Table 3) were employed instead of *p*-anisidine **3** for this one-pot transformation with *N*-Ts-indol-3-aldehyde **6a** and succinaldehyde **4**. However, reaction failed when the similar transformation was performed with *N*-benzyl-indole-3-aldehyde, probably because of low reactivity of imine (entry **7s**, Table 3). All compounds were well characterized by ¹H and ¹³C-NMR and mass-analysis. Single crystal X-ray diffraction analysis of **7e** further established the product structure (Fig. 2).¹⁵ Based on our study, a stepwise mechanism is proposed to account for this reaction. As shown in Scheme 3, the enamine **A** *in situ* generated from succinaldehyde **4** and catalyst **1**, reacts with *in situ* generated *N*-PMP-imine **B** *via* a direct Mannich reaction model **C** to produced Mannich product **D**. The intermediate **D** underwent intramolecular cyclization to dihydropyrrole **E** with the simultaneous release of catalyst **1**. In the same pot cyclic enamine-intermediate **E** underwent IBX-mediated oxidative aromatization to afford pyrrole-3-carboxaldehyde **4**.

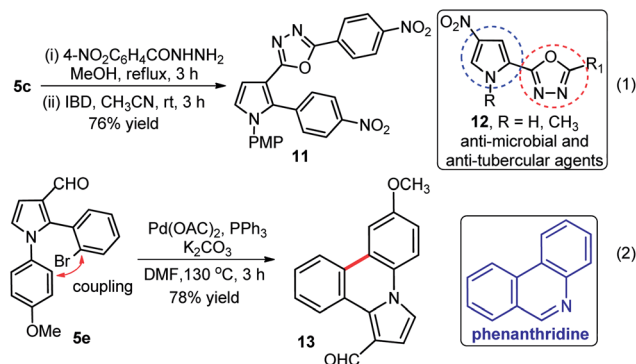
Synthetic applications

Substituted pyrrole-3-aldehydes could participate as suitable intermediates for further functionalization to many important and complex scaffolds, therefore, we developed interesting and useful synthetic applications of these compounds. In this context, a rapid synthesis of pyrrolo[3,2-*c*]quinoline **8** was developed through reductive cyclization. This reaction proceeded *via in situ* amine formation through reduction of nitro-group of **5a** Fe/NH₄Cl in EtOH : H₂O (4 : 1), which underwent intramolecular cyclization with aldehyde group in the same pot with good yields (eqn (1), Scheme 4). In another approach, the synthesis of pyrrole-dihydroquinoline **10** was accomplished through the reductive amination of **5e** with *p*-anisidine **3** in presence of NaBH₄ to generate *in situ* amine **9**, which was



Scheme 4 Synthesis of pyrroloquinoline **8** and pyrrolo-dihydroquinoline **10** scaffolds.





Scheme 5 Synthesis of pyrrole-oxadiazole **11**, and pyrrole-phenanthridine **13** moieties.

further utilized for CuI-catalyzed intramolecular coupling (C–N) without purification to furnish **10** with high yield (87%) over two steps (eqn (2), Scheme 4).¹⁸ The pyrroloquinoline moiety was found to be present in many natural/synthetic molecule with interesting bioactivity and our protocol may be better alternative to the previous procedure.¹⁹ The synthesized hybrid scaffolds resemble with various biologically active molecules such as pyrrolo[3,2-*c*]quinoline derivative, an ATP-ase inhibitor,^{20a} pyrrolo[2,3-*c*]quinoline derivative, a natural product with acetylcholinesterase-inhibiting activity,^{20b} and pyrrolo[3,4-*c*]quinoline derivative, a potent 5-HT4R antagonist with analgesic action.^{20c}

Further applications of our method were shown; (i) synthesis of pyrrole-oxadiazole **11** in good yield (76%) over two steps from compound **5c** which was initially condensed with 4-nitrophenylhydrazide, followed by iodobenzene diacetate (IBD) mediated oxidative cyclization under the standardized conditions (eqn (1), Scheme 5),²¹ and (ii) rapid and high yielding (78%) synthesis of pyrrole-phenanthridine **13** from **5e** through intramolecular C–C bond formation in presence Pd(OAc)₂, PPh₃ and K₂CO₃ in DMF at 130 °C as shown in (eqn (2), Scheme 5). Interestingly, **13** might exhibit interesting biological activities because phenanthridines serve as the core structure of natural products from Amaryllidaceae plants and received considerable attention from both chemists and biological scientists.²²

Conclusions

In summary, we have developed a straight forwarded sequential multicomponent synthesis of substituted *N*-aryl-pyrrole-3-carbaldehydes. This one-pot protocol proceeds through proline-catalyzed Mannich reaction-cyclization sequence between succinaldehyde and imines, *in situ* generated from Ar/HetAr/indole-aldehydes with aromatic amines, followed by IBX-mediated oxidative aromatization under mild conditions. Easy access to the starting materials and direct synthesis of pyrrole-3-carbaldehydes under metal-free conditions renders this method potentially useful in organic synthesis. Synthetic applicability of the developed method was established through; (i) at gram-scale synthesis, and (ii) the rapid access to the biologically important natural products analogous like-pyrrolo-quinoline,

pyrrolo-oxadiazole, dihydro pyrroloquinoline, and pyrrolo-phenanthridine.

Experimental

General remarks

Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification. All solvents employed in the reactions were distilled from appropriate drying agents prior to use. All reactions under standard conditions were monitored by thin-layer chromatography (TLC) on Merck silica gel 60 F254 pre-coated plates (0.25 mm). The column chromatography was performed on silica gel (100–200) using a mixture of hexane/EtOAc. Chemical yields refer to pure isolated substances. ¹H-NMR spectra were recorded on a BRUKER-AV400 (400 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (CDCl₃ = δ 7.26 for ¹H, and 77.0 for ¹³C-NMR). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = doublet of doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz) and integration. ¹³C-NMR spectra were recorded on a BRUKER-AV400 (75 MHz) spectrometer with complete proton decoupling. HRMS were performed employing an ESI+ ionization method and TOF as an analyzer. Infrared (FT-IR) spectra were recorded on an ABB Bomen MB 3000 FTIR Spectrophotometer system using KBr pellets. Melting points were determined in open capillary tubes with an EZ-Melt automated melting point apparatus and may be incorrect.

Typical procedure for the synthesis of pyrrole-3-carboxaldehydes

To a stirred solution of Ar/HetAr-aldehyde **2** (0.3 mmol) or N-protected indole-3-aldehyde **6** (0.3 mmol) in DMSO (3.0 mL) was added *p*-anisidine **3** (0.3 mmol) and stirred initially for 2 h at rt. To this *in situ* generated-imine solution was added succinaldehyde **4** (0.3 mL, 0.9 mmol, 3 M solution) and proline **1** (7.0 mg, 0.06 mmol) at the same temperature. The combined reaction mixture was stirred further for 8 h at rt. At that time, IBX (100 mg, 0.36 mmol, 1.2 equiv.) was added to the reaction mixture and heated at 70 °C for additional 3 h. The reaction was cooled to room temperature quenched with NaHCO₃ solution (10% solution, 5 mL) and extracted with EtOAc (3 × 6 mL). The combined organic extracts were washed with brine, dried over Na₂SO₄ anhydrous, and concentrated under reduced pressure. Purification through silica gel column chromatography by eluting the mixture of hexane/EtOAc, gave pyrrole-3-carbaldehydes **5** or **7** with 50–80% yields. In almost all the cases, we also obtained about <10% initial starting aldehyde due to cleavage of corresponding imine under these conditions.

1-(4-Methoxyphenyl)-2-(2-nitrophenyl)-1H-pyrrole-3-carbaldehyde (5a). Reddish pasty liquid (70 mg, 72%); ¹H NMR (400 MHz, CDCl₃) δ 3.77 (s, 3H), 6.77 (d, *J* = 8.9 Hz, 2H), 6.87 (d, *J* = 3.0 Hz, 1H), 6.94 (d, *J* = 3.0 Hz, 1H), 7.02 (d, *J* = 8.9 Hz, 2H), 7.45 (d, *J* = 6.5 Hz, 1H), 7.54 (t, *J* = 7.8 Hz, 1H), 7.62 (t, *J* = 6.6 Hz, 1H), 7.97 (d, *J* = 8.1 Hz, 1H), 9.60 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 55.4, 109.1, 114.3 (2C), 124.4, 124.8, 125.1, 125.2, 126.9 (2C), 130.1,



130.8, 132.7, 134.1, 135.8, 149.3, 159.1, 185.5; IR (KBr)/cm⁻¹, 2932, 1666, 1520, 1350, 1296, 1034; HRMS (ESI): calcd for C₁₈H₁₄N₂O₄ (MH⁺) 323.1032; found 323.1033.

1-(4-Methoxyphenyl)-2-(3-nitrophenyl)-1H-pyrrole-3-carbaldehyde (5b). Semi-solid (75 mg, 78%); ¹H NMR (400 MHz, CDCl₃) δ 3.73 (s, 3H), 6.77 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 3.0 Hz, 1H), 6.87 (d, *J* = 3.0 Hz, 1H), 6.97 (d, *J* = 8.0 Hz, 2H), 7.41–7.49 (m, 2H), 8.01 (t, *J* = 1.4 Hz, 1H), 8.11 (d, *J* = 8.0 Hz, 1H), 9.65 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 55.5, 108.8, 114.6 (2C), 123.2, 124.9, 125.5, 125.8, 127.3 (2C), 129.2, 130.8, 131.1, 136.6, 138.2, 147.9, 159.3, 186.0; IR (KBr)/cm⁻¹ 2920, 1746, 1680, 1244, 1172; HRMS (ESI): calcd for C₁₈H₁₄N₂O₄ (MH⁺) 323.1032; found 323.1033.

1-(4-Methoxyphenyl)-2-(4-nitrophenyl)-1H-pyrrole-3-carbaldehyde (5c). Pale yellow solid (mp = 102–104 °C) (74 mg, 80%); ¹H NMR (400 MHz, CDCl₃) δ 3.82 (s, 3H), 6.84 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 3.0 Hz, 1H), 6.94 (d, *J* = 3.0 Hz, 1H), 7.01 (d, *J* = 8.8 Hz, 2H), 7.35 (d, *J* = 8.8 Hz, 2H), 8.16 (d, *J* = 8.8 Hz, 2H), 9.73 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 55.4, 109.0, 114.6 (2C), 123.4 (2C), 125.1, 126.1, 127.1 (2C), 130.9, 131.6 (2C), 135.9, 138.2, 147.4, 159.3, 186.0; IR (KBr)/cm⁻¹ 2933, 1724, 1660, 1249, 1174; HRMS (ESI): calcd for C₁₈H₁₄N₂O₄ (MH⁺) 323.1032; found 323.1028.

2-(3-Fluorophenyl)-1-(4-methoxyphenyl)-1H-pyrrole-3-carbaldehyde (5d). Yellow pasty liquid (65 mg, 74%); ¹H NMR (400 MHz, CDCl₃) δ 3.80 (s, 3H), 6.83 (d, *J* = 8.9 Hz, 2H), 6.86 (d, *J* = 3.1 Hz, 1H), 6.89 (d, *J* = 2.8 Hz, 1H), 6.91 (t, *J* = 1.8 Hz, 1H), 7.00–7.06 (m, 4H), 7.28–7.32 (m, 1H), 9.70 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 55.4, 107.8, 114.3 (2C), 115.7, 117.9, 124.6, 125.2, 126.8, 127.0, (2C), 129.8, 129.9, 131.3, 140.4, 158.9, 161.2, 186.6; IR (KBr)/cm⁻¹, 2962, 1720, 1512, 1247, 1172; HRMS (ESI): calcd for C₁₈H₁₄FNO₂ (MH⁺) 296.1087; found 296.1070.

2-(2-Bromophenyl)-1-(4-methoxyphenyl)-1H-pyrrole-3-carbaldehyde (5e). Red viscous liquid (80 mg, 75%); ¹H NMR (400 MHz, CDCl₃) δ 3.77 (s, 3H), 6.78 (d, *J* = 8.9 Hz, 2H), 6.86 (d, *J* = 3.1 Hz, 1H), 6.92 (d, *J* = 3.0 Hz, 1H), 6.95 (d, *J* = 8.9 Hz, 2H), 6.98–7.00 (m, 1H), 7.56 (dd, *J* = 7.9, 4.3 Hz, 2H), 7.64 (d, *J* = 8.3 Hz, 1H), 9.51 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 55.4, 107.9, 114.2 (2C), 124.9, 125.1, 126.5 (2C), 126.9, 127.7, 129.7, 131.3, 134.0, 135.9, 136.1, 137.2, 158.9, 185.9; IR (KBr)/cm⁻¹, 3016, 1720, 1519, 1226, 1026; HRMS (ESI): calcd for C₁₈H₁₄BrNO₂ (MH⁺) 356.0286; found 356.0295.

2-(3-Bromophenyl)-1-(4-methoxyphenyl)-1H-pyrrole-3-carbaldehyde (5f). Brown pasty liquid (81 mg, 76%); ¹H NMR (400 MHz, CDCl₃) δ 3.81 (s, 3H), 6.84 (d, *J* = 2.1 Hz, 1H), 6.86 (d, *J* = 4.1 Hz, 2H), 6.89 (d, *J* = 3.0 Hz, 1H), 7.03 (d, *J* = 7.0 Hz, 2H), 7.08–7.11 (m, 1H), 7.17 (t, *J* = 7.8 Hz, 1H), 7.41 (t, *J* = 1.7 Hz, 1H), 7.45–7.48 (m, 1H), 9.69 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 55.5, 108.0, 114.4 (2C), 122.2, 122.8, 124.7, 125.3, 127.1 (2C), 129.5, 129.7, 131.3, 131.6, 133.7, 137.2, 159.0, 186.5; IR (KBr)/cm⁻¹, 2985, 1728, 1519, 1373, 1242, 1049; HRMS (ESI): calcd for C₁₈H₁₄BrNO₂ (MH⁺) 356.0286; found 356.0288.

2-(2,4-Dichlorophenyl)-1-(4-methoxyphenyl)-1H-pyrrole-3-carbaldehyde (5g). Yellow oily liquid (77 mg, 70%); ¹H NMR (400 MHz, CDCl₃) δ 3.78 (s, 3H), 6.80 (d, *J* = 8.9 Hz, 2H), 6.86 (d, *J* = 3.1 Hz, 1H), 6.94 (d, *J* = 2.9 Hz, 1H), 7.03 (d, *J* = 8.9 Hz, 2H), 7.24 (d, *J* = 1.7 Hz, 2H), 7.40 (s, 1H), 9.53 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 55.4, 107.9, 114.2 (2C), 124.9, 125.1, 126.5 (2C), 126.9, 127.7, 129.7, 131.3, 134.0, 135.9, 136.1, 137.2, 158.9,

185.9; IR (KBr)/cm⁻¹, 2954, 1668, 1514, 1469, 1246, 1031; HRMS (ESI): calcd for C₁₈H₁₃Cl₂NO₂ (MH⁺) 346.0401; found 346.0408.

2-(3,4-Dichlorophenyl)-1-(4-methoxyphenyl)-1H-pyrrole-3-carbaldehyde (5h). Yellow pasty liquid (80 mg, 73%); ¹H NMR (400 MHz, CDCl₃) δ 3.70 (s, 3H), 6.74 (d, *J* = 3.7 Hz, 2H), 6.75 (s, 1H), 6.78 (d, *J* = 3.1 Hz, 1H), 6.86–6.92 (m, 3H), 7.14 (s, 1H), 7.23 (t, *J* = 2.2 Hz, 2.0 Hz, 1H), 9.58 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 55.4, 108.2, 114.5 (2C), 124.7, 125.5, 127.1 (2C), 129.3, 129.9, 130.2, 131.0, 132.5, 132.5, 133.0, 138.8, 159.1, 186.2; IR (KBr)/cm⁻¹, 2962, 1697, 1514, 1253, 1031; HRMS (ESI): calcd for C₁₈H₁₃Cl₂NO₂ (MH⁺) 346.0401; found 346.0406.

1-(4-Methoxyphenyl)-2-(2-(trifluoromethyl)phenyl)-1H-pyrrole-3-carbaldehyde (5i). Yellow pasty liquid (75 mg, 68%); ¹H NMR (400 MHz, CDCl₃) δ 3.75 (s, 3H), 6.76 (d, *J* = 8.9 Hz, 2H), 6.85 (d, *J* = 3.1 Hz, 1H), 6.91 (d, *J* = 3.0 Hz, 1H), 7.03 (d, *J* = 8.8 Hz, 2H), 7.37 (t, *J* = 4.5 Hz, 1H), 7.51 (t, *J* = 4.9 Hz, 2H), 7.70 (t, *J* = 4.6 Hz, 1H), 9.41 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 55.3, 107.5, 114.1 (2C), 114.6, 117.6, 120.1, 121.5, 122.0, 124.8, 126.5, 127.0 (2C), 129.5, 131.1, 131.4, 134.0, 158.9, 186.0; IR (KBr)/cm⁻¹, 2955, 1666, 1520, 1311, 1250, 1119; HRMS (ESI): calcd for C₁₉H₁₄F₃NO₂ (MH⁺) 346.1055; found 346.1057.

1-(4-Methoxyphenyl)-2-(4-(trifluoromethyl)phenyl)-1H-pyrrole-3-carbaldehyde (5j). Yellow pasty liquid (85 mg, 78%); ¹H NMR (400 MHz, CDCl₃) δ 3.81 (s, 3H), 6.84 (d, *J* = 9.0 Hz, 2H), 6.89 (d, *J* = 3.1 Hz, 1H), 6.92 (d, *J* = 3.0 Hz, 1H), 7.02 (d, *J* = 8.9 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.58 (d, *J* = 8.1 Hz, 2H), 9.70 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 55.4, 108.3, 114.5 (2C), 124.9, 125.1, 125.2 (3C), 125.6, 127.1 (2C), 131.1 (2C), 131.2 (2C), 133.0, 159.1, 186.4; IR (KBr)/cm⁻¹, 2970, 1666, 1512, 1319, 1234; HRMS (ESI): calcd for C₁₉H₁₄F₃NO₂ (MH⁺) 346.1055; found 346.1053.

3-(3-Formyl-1-(4-methoxyphenyl)-1H-pyrrol-2-yl) benzonitrile (5k). Yellow pasty liquid (67 mg, 74%); ¹H NMR (400 MHz, CDCl₃) δ 3.81 (s, 3H), 6.84 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 3.1 Hz, 1H), 6.92 (d, *J* = 3.0 Hz, 1H), 7.01 (d, *J* = 8.9 Hz, 2H), 7.42–7.49 (m, 3H), 7.41 (d, *J* = 7.0 Hz, 1H), 9.69 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 55.4, 108.6, 112.6, 114.6 (2C), 118.0, 124.8, 125.7, 127.1 (2C), 129.1, 130.8, 130.9, 131.9, 134.0, 135.1, 138.4, 159.2, 186.0; IR (KBr)/cm⁻¹, 2932, 2230, 1659, 1512, 1443, 1250; HRMS (ESI): calcd for C₁₉H₁₄N₂O₂ (MH⁺) 303.1134; found 303.1134.

4-(3-Formyl-1-(4-methoxyphenyl)-1H-pyrrol-2-yl) benzonitrile (5l). Pink pasty liquid (72 mg, 80%); ¹H NMR (400 MHz, CDCl₃) δ 3.81 (s, 3H), 6.85 (d, *J* = 8.9 Hz, 2H), 6.89 (d, *J* = 3.0 Hz, 1H), 6.94 (d, *J* = 2.5 Hz, 1H), 7.01 (d, *J* = 8.8 Hz, 2H), 7.32 (d, *J* = 8.3 Hz, 2H), 7.60 (d, *J* = 8.3 Hz, 2H), 9.72 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 55.5, 108.9, 114.6 (2C), 118.2, 124.9, 125.0, 125.9, 127.1 (2C), 131.4 (2C), 131.9 (2C), 134.1, 138.8, 141.7, 159.3, 186.0; IR (KBr)/cm⁻¹, 2962, 2229, 1712, 1519, 1242; HRMS (ESI): calcd for C₁₉H₁₄N₂O₂ (MH⁺) 303.1134; found 303.1134.

1-(4-Methoxyphenyl)-2-phenyl-1H-pyrrole-3-carbaldehyde (5m). Yellow pasty liquid (42 mg, 50%); ¹H NMR (400 MHz, CDCl₃) δ 3.77 (s, 3H), 6.80 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 3.2 Hz, 1H), 6.87 (d, *J* = 3.2 Hz, 1H), 7.00 (d, *J* = 8.8 Hz, 2H), 7.18–7.20 (m, 2H), 7.28–7.32 (m, 3H), 9.67 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 55.3, 107.6, 114.2 (2C), 124.3, 124.9, 127.0 (2C), 128.1 (2C), 128.4, 129.1, 130.9 (2C), 131.6, 142.4, 158.7, 187.0; IR (KBr)/cm⁻¹, 2912, 1710, 1672, 1244, 1174; HRMS (ESI): calcd for C₁₈H₁₅NO₂ (MH⁺) 278.1181; found 278.1189.



1-(4-Methoxyphenyl)-2-(pyridin-3-yl)-1H-pyrrole-3-carbaldehyde (5n). Red oily liquid (58 mg, 70%); ^1H NMR (400 MHz, CDCl_3) δ 3.81 (s, 3H), 6.85 (d, $J = 8.9$ Hz, 2H), 6.91 (d, $J = 3.0$ Hz, 1H), 6.96 (d, $J = 2.9$ Hz, 1H), 7.04 (d, $J = 8.9$ Hz, 2H), 7.28 (t, $J = 3.7$ Hz, 1H), 7.54 (d, $J = 7.8$ Hz, 1H), 8.5 (bs, 1H), 8.58 (d, $J = 4.7$ Hz, 1H), 9.72 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 55.4, 108.4, 114.5 (2C), 122.9, 125.1, 125.7, 125.7, 127.3 (2C), 131.0, 137.8, 137.9, 149.4, 151.0, 159.2, 186.0; IR (KBr)/ cm^{-1} , 2954, 1666, 1512, 1242, 1033; HRMS (ESI): calcd for $\text{C}_{17}\text{H}_{14}\text{N}_2\text{O}_2$ (MH^+) 279.1133; found 279.1140.

2-(Furan-2-yl)-1-(4-methoxyphenyl)-1H-pyrrole-3-carbaldehyde (5o). Red oily liquid (51 mg, 64%); ^1H NMR (400 MHz, CDCl_3) δ 3.85 (s, 3H), 6.05 (d, $J = 3.3$ Hz, 1H), 6.37 (d, $J = 3.2$ Hz, 1H), 6.93 (d, $J = 8.8$ Hz, 2H), 7.18 (d, $J = 8.8$ Hz, 3H), 7.99 (d, $J = 7.7$ Hz, 1H), 8.05 (d, $J = 7.9$ Hz, 1H), 10.08 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 55.5, 108.1, 111.2, 111.7, 114.3 (2C), 126.0, 127.2 (2C), 127.9, 131.8, 133.1, 141.7, 143.4, 159.4, 187.4; IR (KBr)/ cm^{-1} , 2970, 1682, 1582, 1466, 1265, 1011; HRMS (ESI): calcd for $\text{C}_{16}\text{H}_{13}\text{NO}_3$ (MH^+) 268.0974; found 268.0980.

1-(4-Methoxyphenyl)-2-(1-tosyl-1H-indol-3-yl)-1H-pyrrole-3-carbaldehyde (7a). Yellow solid (107 mg, 76%, mp = 119–121 °C); ^1H NMR (400 MHz, CDCl_3) δ 2.37 (s, 3H), 3.78 (s, 3H), 6.71 (d, $J = 8.9$ Hz, 2H), 6.9 (d, $J = 3.1$ Hz, 1H), 6.97 (d, $J = 2.4$ Hz, 1H), 7.02 (d, $J = 8.9$ Hz, 2H), 7.12–7.16 (m, 1H), 7.23 (d, $J = 8$ Hz, 3H), 7.28–7.32 (m, 1H), 7.44 (s, 1H), 7.63 (d, $J = 8.3$ Hz, 2H), 7.95 (d, $J = 8.3$ Hz, 1H), 9.58 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 29.6, 55.4, 108.1, 111.5, 113.5, 114.3 (2C), 120.3, 123.9, 125.2, 125.7, 125.8, 126.5 (2C), 126.8 (2C), 127.1, 129.9 (2C), 130.2, 131.7, 133.3, 134.4, 134.7, 145.3, 158.9, 186.1; IR (KBr)/ cm^{-1} , 2924, 2854, 1659, 1597, 1512, 1173; HRMS (ESI): calcd for $\text{C}_{27}\text{H}_{22}\text{N}_2\text{O}_4\text{S}$ (MH^+) 471.1378; found 471.1382.

3-(3-Formyl-1-(4-methoxyphenyl)-1H-pyrrol-2-yl)-1-tosyl-1H-indole-5-carbonitrile (7b). Brown solid (101 mg, 73%, mp = 123–125 °C); ^1H NMR (400 MHz, CDCl_3) δ 2.40 (s, 3H), 3.79 (s, 3H), 6.73 (d, $J = 8.9$ Hz, 2H), 6.90 (d, $J = 3.1$ Hz, 1H), 7.00–7.03 (m, 3H), 7.28 (d, $J = 8.0$ Hz, 2H), 7.45 (d, $J = 8.8$ Hz, 1H), 7.52 (dd, $J = 7.1$ Hz, 1H), 7.64 (s, 1H), 7.67 (d, $J = 8.4$ Hz, 2H), 8.05 (d, $J = 8.1$ Hz, 1H), 9.60 (s, 1H); ^{13}C -NMR (75 MHz, CDCl_3) δ 29.6, 55.5, 109.1, 111.4, 114.4, 114.5 (2C), 125.4, 126.0, 126.5 (2C), 126.9 (2C), 128.1, 128.1, 129.1, 129.2, 129.8, 130.2, 130.3 (2C), 130.9, 131.3, 134.1, 136.0, 146.2, 159.1, 185.5; IR (KBr)/ cm^{-1} , 2924, 2854, 2230, 1720, 1666, 1512, 1173; HRMS (ESI): calcd for $\text{C}_{28}\text{H}_{21}\text{N}_3\text{O}_4\text{S}$ (MH^+) 496.1331; found 496.1336.

2-(5-Methoxy-1-tosyl-1H-indol-3-yl)-1-(4-methoxyphenyl)-1H-pyrrole-3-carbaldehyde (7c). Red solid (105 mg, 70%, mp = 127–129 °C); ^1H NMR (400 MHz, CDCl_3) δ 2.37 (s, 3H), 3.64 (s, 3H), 3.78 (s, 3H), 6.57 (d, $J = 2.4$ Hz, 1H), 6.71 (d, $J = 8.9$ Hz, 2H), 6.88–6.9 (m, 2H), 6.98 (d, $J = 2.7$ Hz, 1H), 7.02 (d, $J = 8.9$ Hz, 2H), 7.22 (d, $J = 8.2$ Hz, 2H), 7.43 (s, 1H), 7.62 (d, $J = 8.4$ Hz, 2H), 7.82 (d, $J = 9.1$ Hz, 1H), 9.58 (s, 1H); ^{13}C -NMR (75 MHz, CDCl_3) δ 21.5, 55.4, 55.5, 102.0, 108.2, 111.5, 114.3 (2C), 114.5, 115.0, 125.6, 125.8, 126.3 (2C), 126.7 (2C), 127.9, 129.1, 129.9 (2C), 131.1, 131.8, 132.4, 134.7, 145.2, 156.8, 158.9, 186.1; IR (KBr)/ cm^{-1} , 2924, 2854, 1720, 1659, 1512, 1173; HRMS (ESI): calcd for $\text{C}_{28}\text{H}_{24}\text{N}_2\text{O}_5\text{S}$ (MH^+) 501.1484; found 501.1488.

2-(5-Bromo-1-tosyl-1H-indol-3-yl)-1-(4-methoxyphenyl)-1H-pyrrole-3-carbaldehyde (7d). Yellow solid (115 mg, 70%, mp = 139–141 °C); ^1H NMR (400 MHz, CDCl_3) δ 2.38 (s, 3H), 3.79 (s, 3H), 6.72 (d, $J = 8.9$ Hz, 2H), 6.89 (d, $J = 3.2$ Hz, 1H), 6.97 (d, $J = 2.5$ Hz, 1H), 7.00 (d, $J = 8.9$ Hz, 2H), 7.24 (d, $J = 8.0$ Hz, 2H), 7.30 (d, $J = 1.7$ Hz, 2H), 7.37 (d, $J = 7.0$ Hz, 1H), 7.45 (s, 1H), 7.60 (d, $J = 8.4$ Hz, 2H), 7.81 (d, $J = 8.8$ Hz, 1H), 9.57 (s, 1H); ^{13}C NMR (400 MHz, CDCl_3) δ 29.6, 55.5, 108.5, 110.9, 114.4 (2C), 115.0, 117.5, 123.1, 125.8, 125.9, 126.6 (2C), 126.8 (2C), 128.3, 128.3, 130.1 (2C), 131.5, 131.8, 132.3, 133.1, 134.4, 145.7, 159.1, 185.8; IR (KBr)/ cm^{-1} , 2924, 2854, 1720, 1666, 1512, 1250, 1119; HRMS (ESI): calcd for $\text{C}_{27}\text{H}_{21}\text{BrN}_2\text{O}_4\text{S}$ (MH^+) 549.0483; found 549.0488.

2-(5-Chloro-1-tosyl-1H-indol-3-yl)-1-(4-methoxyphenyl)-1H-pyrrole-3-carbaldehyde (7e). Brown solid (102 mg, 68%, mp = 134–136 °C); ^1H NMR (400 MHz, CDCl_3) δ 2.17 (s, 3H), 3.58 (s, 3H), 6.52 (d, $J = 8.9$ Hz, 2H), 6.67 (d, $J = 3.1$ Hz, 1H), 6.76 (dd, $J = 2.4$ Hz, 1H), 6.80 (d, $J = 8.9$ Hz, 2H), 6.95 (d, $J = 1.9$ Hz, 1H), 7.02–7.05 (m, 4H), 7.40 (d, $J = 8.4$ Hz, 2H), 7.65 (d, $J = 8.8$ Hz, 1H), 9.36 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 29.7, 55.5, 108.4, 111.0, 114.4 (2C), 114.6, 120.0, 125.6, 125.8, 125.9, 126.6 (2C), 126.8 (2C), 128.5, 130.0, 130.1 (2C), 131.4, 131.5, 132.5, 132.8, 134.5, 145.6, 159.1, 185.8; IR (KBr)/ cm^{-1} , 2924, 2854, 1666, 1512, 1250, 1173; HRMS (ESI): calcd for $\text{C}_{27}\text{H}_{21}\text{ClN}_2\text{O}_4\text{S}$ (MH^+) 505.0911; found 505.0916.

1-(4-Methoxyphenyl)-2-(1-(phenylsulfonyl)-1H-indol-3-yl)-1H-pyrrole-3-carbaldehyde (7f). Brown solid (96 mg, 70%, mp = 117–119 °C); ^1H NMR (400 MHz, CDCl_3) δ 3.77 (s, 3H), 6.69 (d, $J = 8.93$ Hz, 2H), 6.89 (d, $J = 3.1$ Hz, 1H), 6.96 (d, $J = 3.3$ Hz, 1H), 7.00 (d, $J = 8.9$ Hz, 2H), 7.12–7.16 (m, 1H), 7.23 (d, $J = 7.6$ Hz, 1H), 7.28–7.32 (m, 1H), 7.42–7.46 (m, 3H), 7.54–7.59 (m, 1H), 7.72–7.74 (m, 2H), 7.96 (d, $J = 8.3$ Hz, 1H), 9.58 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 55.4, 108.1, 111.7, 113.4, 114.3 (2C), 120.3, 123.9, 125.3, 125.7, 126.5 (2C), 126.6 (2C), 127.1, 129.3 (2C), 130.2, 131.6, 132.2, 134.0, 134.4 (2C), 137.6, 158.8, 186.1; IR (KBr)/ cm^{-1} , 2932, 2839, 1720, 1666, 1512, 1225, 1180; HRMS (ESI): calcd for $\text{C}_{26}\text{H}_{20}\text{N}_2\text{O}_4\text{S}$ (MH^+) 457.1222; found 457.1226.

2-(5-Methoxy-1-(phenylsulfonyl)-1H-indol-3-yl)-1-(4-methoxyphenyl)-1H-pyrrole-3-carbaldehyde (7g). Yellow viscous liquid (99 mg, 68%); ^1H NMR (400 MHz, CDCl_3) δ 3.64 (s, 3H), 3.77 (s, 3H), 6.56 (d, $J = 2.4$ Hz, 1H), 6.70 (d, $J = 8.9$ Hz, 2H), 6.88–6.91 (m, 2H), 6.98 (d, $J = 2.4$ Hz, 1H), 7.00 (d, $J = 8.9$ Hz, 2H), 7.42–7.45 (m, 3H), 7.54–7.59 (m, 1H), 7.71–7.73 (m, 2H), 7.84 (d, $J = 9.1$ Hz, 1H), 9.58 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 55.4, 55.5, 102.0, 108.2, 111.8, 114.3 (2C), 114.5, 115.0, 125.6, 125.8, 126.3 (2C), 126.6 (2C), 127.8, 129.1, 129.3 (2C), 131.1, 131.7, 133.3, 134.0, 137.6, 156.9, 158.9, 186.1; IR (KBr)/ cm^{-1} , 2924, 2854, 1728, 1666, 1512, 1466, 1250, 1180; HRMS (ESI): calcd for $\text{C}_{27}\text{H}_{22}\text{N}_2\text{O}_5\text{S}$ (MH^+) 487.1327; found 487.1332.

2-(5-Bromo-1-(phenylsulfonyl)-1H-indol-3-yl)-1-(4-methoxyphenyl)-1H-pyrrole-3-carbaldehyde (7h). Brownish yellow gummy liquid (107 mg, 67%); ^1H NMR (400 MHz, CDCl_3) δ 3.82 (s, 3H), 3.76 (d, $J = 8.9$ Hz, 2H), 6.91 (d, $J = 3.1$ Hz, 1H), 7.00 (d, $J = 3.1$ Hz, 1H), 7.3 (d, $J = 8.9$ Hz, 2H), 7.35 (d, $J = 1.5$ Hz, 1H), 7.42 (d, $J = 6.9$ Hz, 1H), 7.48–7.51 (m, 3H), 7.60–7.65 (m, 1H), 7.74 (d, $J = 7.3$ Hz, 2H), 7.86 (d, $J = 8.8$ Hz, 1H), 9.60 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 55.5, 108.4, 111.1, 114.4 (2C), 114.9, 117.6, 123.1, 123.9,



125.8, 126.6 (2C), 126.7 (2C) 128.2, 128.4, 129.5 (2C), 131.4, 131.8, 132.1, 133.1, 134.3, 137.3, 159.0, 185.8; IR (KBr)/cm⁻¹, 2924, 2854, 1666, 1572, 1443, 1250, 1180; HRMS (ESI): calcd for C₂₆H₁₉BrN₂O₄S (MH⁺) 535.0319; found 535.0325.

1-(4-Methoxyphenyl)-2-(1-(methylsulfonyl)-1H-indol-3-yl)-1H-pyrrole-3-carbaldehyde (7i). Yellow pasty liquid (82 mg, 70%); ¹H NMR (400 MHz, CDCl₃) δ 3.07 (s, 3H), 3.75 (s, 3H), 6.77 (d, *J* = 9.0 Hz, 2H), 6.91 (d, *J* = 3.1 Hz, 1H), 7.01 (d, *J* = 2.4 Hz, 1H), 7.08 (d, *J* = 9.0 Hz, 2H), 7.21–7.25 (m, 1H), 7.31–7.34 (m, 2H), 7.35–7.39 (m, 1H), 7.90 (d, *J* = 8.4 Hz, 1H), 9.70 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 40.9, 55.4, 108.4, 113.0, 114.3 (2C), 120.7, 124.2, 125.3, 125.6, 125.7, 125.9, 126.5 (2C), 126.9, 130.2, 131.7, 132.9, 134.6, 159.1, 186.1; IR (KBr)/cm⁻¹ 2924, 2854, 1659, 1443, 1373, 1134; HRMS (ESI): calcd for C₂₁H₁₈N₂O₄S (MH⁺) 395.1065; found 395.1070.

3-(3-Formyl-1-(4-methoxyphenyl)-1H-pyrrol-2-yl)-1-(methylsulfonyl)-1H-indole-5-carbonitrile (7j). Brownish solid (85 mg, 68%, mp = 114–116 °C); ¹H NMR (400 MHz, CDCl₃) δ 3.17 (s, 3H), 3.77 (s, 3H), 6.8 (d, *J* = 8.9 Hz, 2H), 6.93 (d, *J* = 3.1 Hz, 1H), 7.03 (d, *J* = 2.6 Hz, 1H), 7.09 (d, *J* = 9.0 Hz, 2H), 7.53 (m, 1H), 7.58 (d, *J* = 7.1 Hz, 1H), 7.99–8.03 (m, 2H), 9.73 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 41.8, 55.5, 107.9, 109.6, 111.5, 114.1, 114.6 (2C), 118.6, 121.5, 125.8, 126.0, 126.5 (2C), 128.0, 128.4, 129.0, 131.3, 137.1, 141.7, 159.4, 185.6; IR (KBr)/cm⁻¹, 2924, 2854, 2230, 1659, 1512, 1381, 1180; HRMS (ESI): calcd for C₂₂H₁₇N₃O₄S (MH⁺) 419.0940; found 419.0946.

2-(5-Chloro-1-(methylsulfonyl)-1H-indol-3-yl)-1-(4-methoxyphenyl)-1H-pyrrole-3-carbaldehyde (7k). Yellowish solid (85 mg, 66%, mp = 126–128 °C); ¹H NMR (400 MHz, CDCl₃) δ 3.07 (s, 3H), 3.77 (s, 3H), 6.79 (d, *J* = 8.9 Hz, 2H), 6.91 (d, *J* = 3.1 Hz, 1H), 7.01 (d, *J* = 2.8 Hz, 1H), 7.08 (d, *J* = 8.9 Hz, 2H), 7.25 (d, *J* = 1.9 Hz, 1H), 7.31 (d, *J* = 6.8 Hz, 1H), 7.36 (s, 1H), 7.82 (d, *J* = 8.8 Hz, 1H), 9.70 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 40.1, 54.5, 107.8, 113.2, 113.4 (2C), 119.3, 121.6, 124.8, 124.9, 125.6 (2C), 126.0, 127.2, 129.2, 130.2, 130.4, 131.9, 135.6, 158.2, 184.8; IR (KBr)/cm⁻¹, 2924, 2854, 1666, 1572, 1443, 1250, 1180; HRMS (ESI): calcd for C₂₁H₁₇ClN₂O₄S (MH⁺) 429.0676; found 429.0682.

tert-Butyl-3-(3-formyl-1-(4-methoxyphenyl)-1H-pyrrol-2-yl)-1H-indole-1-carboxylate (7l). White solid, (92 mg, 74%, mp = 117–119 °C); ¹H NMR (400 MHz, CDCl₃) δ 1.67 (s, 9H), 3.74 (s, 3H), 6.66 (d, *J* = 9.0 Hz, 2H), 6.92 (d, *J* = 3.2 Hz, 1H), 6.98 (d, *J* = 2.5 Hz, 1H), 7.07–7.16 (m, 5H), 7.28–7.30 (m, 1H), 7.57 (s, 1H), 8.12 (d, *J* = 8.1 Hz, 1H), 9.36 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 28.1 (3C), 29.7, 55.44, 84.5, 108.0, 109.7, 114.3 (2C), 115.1, 120.1, 123.2, 124.9, 125.5, 125.9, 126.3 (2C), 127.2, 132.0, 134.7, 139.3, 149.2, 158.8, 186.7; IR (KBr)/cm⁻¹, 2934, 2860, 1726, 1666, 1512, 1250, 1157; HRMS (ESI): calcd for C₂₅H₂₄N₂O₄ (MH⁺) 417.1814; found 417.1820.

tert-Butyl-5-cyano-3-(3-formyl-1-(4-methoxyphenyl)-1H-pyrrol-2-yl)-1H-indole-1-carboxylate (7m). Reddish brown solid (95 mg, 72%, mp = 120–122 °C); ¹H NMR (400 MHz, CDCl₃) δ 1.05 (s, 9H), 3.59 (s, 3H), 6.53 (d, *J* = 8.9 Hz, 2H), 6.70 (d, *J* = 3.1 Hz, 1H), 6.82 (d, *J* = 9.0 Hz, 3H), 7.07 (d, *J* = 3.7 Hz, 1H), 7.09 (s, 1H), 7.32 (d, *J* = 1.4 Hz, 1H), 7.84 (d, *J* = 8.7 Hz, 1H), 9.40 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 29.7 (3C), 31.3, 55.5, 107.5, 109.1, 111.3, 114.5 (2C), 118.7, 125.5, 126.0, 126.5 (2C), 126.9, 128.1, 129.2, 129.9, 130.3, 131.0, 131.3, 134.1, 136.0, 146.2, 159.1, 185.6; IR (KBr)/

cm⁻¹, 2932, 2862, 2230, 1666, 1512, 1173, 1250; HRMS (ESI): calcd for C₂₆H₂₃N₃O₄ (MH⁺) 442.1767; found 442.1774.

tert-Butyl-5-fluoro-3-(3-formyl-1-(4-methoxyphenyl)-1H-pyrrol-2-yl)-1H-indole-1-carboxylate (7n). Yellow solid (87 mg, 67%, mp = 119–121 °C); ¹H NMR (400 MHz, CDCl₃) δ 1.66 (s, 9H), 3.75 (s, 3H), 6.74–6.79 (m, 3H), 6.90 (d, *J* = 3.1 Hz, 1H), 6.97–7.00 (m, 2H), 7.13 (d, *J* = 8.9 Hz, 2H), 7.62 (s, 1H), 8.07 (d, *J* = 5.9 Hz, 1H), 9.68 (s, 1H); ¹³C-NMR (75 MHz, CDCl₃) δ 28.1 (3C), 29.7, 55.4, 84.8, 105.6, 105.8, 108.2, 109.6, 112.8, 113.0, 114.4 (2C), 116.2, 125.6, 126.3 (2C), 128.6, 131.9, 134.0, 149.0, 158.9, 160.3, 186.5; IR (KBr)/cm⁻¹, 2924, 2854, 1736, 1666, 1450, 1366, 1250, 1172; HRMS (ESI): calcd for C₂₅H₂₃FN₂O₄ (MH⁺) 435.1720; found 435.1726.

tert-Butyl-5-bromo-3-(3-formyl-1-(4-methoxyphenyl)-1H-pyrrol-2-yl)-1H-indole-1-carboxylate (7o). White solid (82 mg, 68%, mp = 129–131 °C); ¹H NMR (400 MHz, CDCl₃) δ 1.66 (s, 9H), 3.02 (s, 3H), 6.79 (d, *J* = 8.98 Hz, 2H), 6.90 (d, *J* = 3.12 Hz, 1H), 6.98 (d, *J* = 3.9 Hz, 1H), 7.12 (d, *J* = 8.9 Hz, 2H), 7.22 (d, *J* = 1.7 Hz, 1H), 7.36 (d, *J* = 6.9 Hz, 1H), 7.75 (s, 1H), 7.99 (d, *J* = 8.4 Hz, 1H), 9.68 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 28.1 (3C), 29.7, 55.5, 85.8, 108.2, 109.1, 114.4 (2C), 116.6, 122.8, 125.6, 125.9, 126.4 (2C) 127.8, 128.2, 131.1, 131.8, 133.7, 133.8, 148.8, 159.0, 186.3; IR (KBr)/cm⁻¹, 2932, 2862, 1736, 1680, 1458, 1373, 1157; HRMS (ESI): calcd for C₂₅H₂₃BrN₂O₄ (MH⁺) 495.0919; found 405.0924.

tert-Butyl-3-(3-formyl-1-(4-methoxyphenyl)-1H-pyrrol-2-yl)-5-methoxy-1H-indole-1-carboxylate (7p). Dark brown solid (89 mg, 70%, mp = 124–126 °C); (400 MHz, CDCl₃) δ 1.66 (s, 9H), 3.64 (s, 3H), 3.75 (s, 3H), 6.51 (d, *J* = 2.4 Hz, 1H), 6.78 (d, *J* = 8.9 Hz, 2H), 6.87 (d, *J* = 6.6 Hz, 1H), 6.93 (d, *J* = 3.2 Hz, 1H), 7.00 (d, *J* = 2.4 Hz, 1H), 7.15 (d, *J* = 9 Hz, 2H), 7.57 (s, 1H), 7.99 (d, *J* = 8.7 Hz, 1H), 9.71 (s, 1H); ¹³C-NMR (100 MHz, CDCl₃) δ 28.1 (3C), 29.6, 55.4, 55.5, 84.3, 102.0, 108.0, 109.5, 114.3 (2C), 115.9, 125.4, 125.8, 126.1 (2C) 127.7, 129.6, 130.2, 132.2, 134.8, 149.1, 156.1, 158.8, 186.6; IR (KBr)/cm⁻¹, 2932, 2862, 1736, 1666, 1512, 1250, 1157; HRMS (ESI): calcd for C₂₆H₂₆N₃O₅ (MH⁺) 425.1171; found 425.1176.

1-(2-Hydroxyphenyl)-2-(1-tosyl-1H-indol-3-yl)-1H-pyrrole-3-carbaldehyde (7q). Light yellow solid (82 mg, 60%, mp = 118–120 °C); ¹H NMR (400 MHz, CDCl₃) δ 2.42 (s, 3H), 6.95 (d, *J* = 3.2 Hz, 1H), 7.07–7.01 (m, 3H), 7.22–7.15 (m, 3H), 7.25 (d, *J* = 7.4 Hz, 1H), 7.30 (d, *J* = 8.5 Hz, 2H), 7.36–7.38 (m, 1H), 7.46 (s, 1H), 7.67 (d, *J* = 8.4 Hz, 2H), 8.02 (d, *J* = 8.4 Hz, 1H), 9.63 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 21.6, 108.7, 111.0, 113.6, 120.1, 124.02, 125.2, 125.4, 126.3, 126.4 (2C), 126.7 (2C), 126.9, 127.0, 129.3 (2C), 130.0 (2C), 132.8, 133.5, 134.4, 134.6, 137.1, 145.5, 186.0; IR (KBr)/cm⁻¹, 3458, 2924, 2854, 1659, 1497, 1443, 1088; HRMS (ESI): calcd for C₂₆H₂₀N₂O₄S (MH⁺) 457.1222; found 457.1227.

1-(4-Chlorophenyl)-2-(1-tosyl-1H-indol-3-yl)-1H-pyrrole-3-carbaldehyde (7r). Light pinkish solid (91 mg, 64%, mp = 132–134 °C) ¹H NMR (400 MHz, CDCl₃) δ 2.35 (s, 3H), 6.70 (m, 1H), 6.78 (s, 1H), 6.87 (m, 2H), 6.97 (d, *J* = 7.9 Hz, 1H), 7.25–7.10 (m, 4H), 7.37–7.28 (m, 2H), 7.40 (d, *J* = 7.9 Hz, 1H), 7.56–7.50 (m, 2H), 7.90 (d, *J* = 8.4 Hz, 1H), 9.43 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 21.6, 108.4, 110.7, 113.4, 117.3, 120.0, 120.4, 123.9, 125.2, 125.2, 125.6, 126.1, 126.7 (2C), 127.0, 128.2, 129.9 (2C),



130.1, 130.3, 134.2, 134.6, 135.1, 145.1, 151.8, 186.0; IR (KBr)/ cm^{-1} , 2924, 2854, 1651, 1504, 1443, 1173; HRMS (ESI): calcd for $\text{C}_{26}\text{H}_{19}\text{ClN}_2\text{O}_3\text{S}$ (MH^+) 475.0883; found 475.0888.

1-(4-Methoxyphenyl)-1H-pyrrolo[3,2-c] quinoline (8). To a stirred solution of **5a** (50 mg, 0.15 mmol) in EtOH : H_2O (5 mL, 4 : 1) was added Fe-powder (86.9 mg, 1.55 mmol, 10.0 equiv.) and NH_4Cl (100 mg, 1.8 mmol, 12.0 equiv.) and combined mixture was heated at 80 °C for 10 h. The reaction progress was monitored by TLC, cooled and concentrated under reduced pressure once completed. The crude residue was extracted between EtOAc/ NaHCO_3 solutions. Organic layer dried over Na_2SO_4 and evaporated under reduced pressure followed by silica-gel chromatography purification by eluting the mixture of hexane/EtOAc, gave pure product **8** as pasty yellow liquid (28 mg, 67% yield). ^1H NMR (400 MHz, CDCl_3) δ 3.95 (s, 3H), 6.87 (d, $J = 3.1$ Hz, 1H), 7.09 (d, $J = 8.6$ Hz, 2H), 7.21 (d, $J = 3.1$ Hz, 1H), 7.23 (m, 1H), 7.38 (d, $J = 9.1$ Hz, 1H), 7.43 (d, $J = 8.8$ Hz, 2H), 7.53 (t, $J = 7.0$ Hz, 1H), 8.19 (d, $J = 8.3$ Hz, 1H), 9.21 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 55.6, 103.3, 114.8 (2C), 118.2, 120.6, 121.6, 125.3, 126.4, 128.5 (2C), 129.9, 130.2, 133.2, 134.6, 144.2, 146.1, 159.9; IR (KBr)/ cm^{-1} , 2924, 1713, 1512, 1366, 1250, 1034; HRMS (ESI): calcd for $\text{C}_{18}\text{H}_{14}\text{N}_2\text{O}$ (MH^+) 275.1185; found 275.1190.

1,5-Bis(4-methoxyphenyl)-4,5-dihydro-1H-pyrrolo[3,2-c] quinoline (10). A mixture of **5e** (0.1 g, 0.28 mmol, 1.0 equiv.) and *p*-anisidine **3** (0.030 g, 0.28 mmol, 1.0 equiv.) in methanol (3 mL) was refluxed for 2 h at 80 °C and followed by reductive amination in the presence of NaBH_4 at 0 °C to obtain intermediate product. This crude intermediate **9** (0.1 g, 0.22 mmol, 1.0 equiv.) was taken in oven-dried round-bottom flask dissolved in DMF (2 mL), followed by the addition of base K_2CO_3 (61 mg, 0.44 mmol, 2.0 equiv.), CuI (9 mg, 20 mol%), L-proline as ligand (10 mg, 40 mol%). The resulting solution was stirred at 110 °C for 3 h under an N_2 atmosphere. On completion, the residue was cooled to ambient temperature and then diluted with water (5 mL) and extracted with EtOAc (2×5 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated to dryness. The crude residue was purified by column chromatography by eluting the mixture of hexane/EtOAc, afford **10** as yellow pasty liquid (70 mg, 87% yield). ^1H NMR (400 MHz, CDCl_3) δ 7.67 (dd, $J = 7.8, 1.7$ Hz, 1H), 7.56 (dd, $J = 7.9, 1.2$ Hz, 1H), 7.28–7.33 (m, 1H), 7.23 (d, $J = 9.0$ Hz, 2H), 7.08–7.14 (m, 1H), 6.93 (d, $J = 2.4$ Hz, 1H), 6.90 (d, $J = 9.0$ Hz, 2H), 6.74 (d, $J = 1.8$ Hz, 1H), 6.72 (d, $J = 9.0$ Hz, 2H), 6.47 (d, $J = 8.9$ Hz, 2H), 6.25 (d, $J = 1.8$ Hz, 1H), 5.80 (s, 1H), 3.81 (s, 3H), 3.70 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 55.5, 55.7, 56.2, 109.2, 114.2 (2C), 114.5 (2C), 114.7 (2C), 118.1, 119.9, 121.9 (2C), 123.5, 126.7, 127.8, 128.1, 128.4, 132.9, 134.1, 141.3, 142.2, 151.9, 157.6; HRMS (ESI): calcd for $\text{C}_{25}\text{H}_{22}\text{N}_2\text{O}_2$ (MH^+) 383.1759; found 383.1765.

2-(1-(4-Methoxyphenyl)-2-(4-nitrophenyl)-1H-pyrrol-3-yl)-5-(4-nitrophenyl)-1,3,4-oxadiazole (11). A mixture of **5c** (0.08 g, 0.24 mmol, 1.0 equiv.) and 4-nitrobenzohydrazide (0.044 g, 0.24 mmol, 1.0 equiv.) in methanol (3.0 mL) was stirred for 2 hours under 80 °C and then concentrated *in vacuo*. The crude material was taken in CH_3CN (3.0 mL) and IBD (0.08 g, 0.24 mmol, 1.0 equiv.) was added stirred at room temperature for one hour. The mixture was then concentrated *in vacuo*. To

the residue was added H_2O (10 mL) and the resulting mixture was extracted with ethylacetate (10 mL \times 3). The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel by eluting the mixture of hexane/EtOAc, afford product **11** as yellow solid (92 mg, 76% yield). ^1H NMR (400 MHz, CDCl_3) (mp = 112–115 °C) δ 8.33 (d, $J = 9.0$ Hz, 2H), 8.17 (d, $J = 8.9$ Hz, 2H), 8.08 (d, $J = 9.0$ Hz, 2H), 7.52 (d, $J = 8.9$ Hz, 2H), 7.07 (d, $J = 3.0$ Hz, 1H), 7.04 (d, $J = 9.0$ Hz, 2H), 7.01 (d, $J = 3.0$ Hz, 1H), 6.84 (d, $J = 9.0$ Hz, 2H), 3.81 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 55.5, 108.0, 109.8, 114.5 (2C), 123.0 (2C), 124.3 (2C), 125.9, 127.1 (2C), 127.3 (2C), 129.4, 131.3, 132.0 (2C), 132.4, 137.0, 147.3, 149.2, 159.2, 161.6, 162.7; HRMS (ESI): calcd for $\text{C}_{25}\text{H}_{17}\text{N}_5\text{O}_6$ (MH^+) 484.1258; found 484.1263.

7-Methoxypyrrolo [1,2-f] phenanthridine-1-carbaldehyde (13). A clean oven-dried 10 mL round-bottom flask was charged with **5e** (70 mg, 0.19 mmol, 1.0 equiv.) in DMF (2 mL), K_2CO_3 (54 mg, 0.39 mmol, 2.0 equiv.), ligand PPh_3 (10 mg, 20 mol%), and $\text{Pd}(\text{OAc})_2$ (5 mg, 10 mol%). The resulting solution was stirred at 130 °C for 3 h under an N_2 atmosphere. On completion, the reaction mass was cooled to ambient temperature and then diluted with water (5 mL) and extracted with EtOAc (2×5 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated to dryness. The crude residue so obtained was purified by column chromatography by eluting the mixture of hexane/EtOAc, afford **13** as white solid (43 mg, 78% yield). ^1H NMR (400 MHz, CDCl_3) δ 10.26 (s, 1H), 9.49 (dd, $J = 7.1, 2.3$ Hz, 1H), 8.33 (dd, $J = 7.3, 2.2$ Hz, 1H), 7.88 (d, $J = 9.2$ Hz, 1H), 7.85 (d, $J = 2.7$ Hz, 1H), 7.80 (d, $J = 3.3$ Hz, 1H), 7.62–7.70 (m, 2H), 7.24 (d, $J = 3.3$ Hz, 1H), 7.22 (dd, $J = 9.1, 2.8$ Hz, 1H), 3.99 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 55.7, 106.6, 114.0, 115.1, 117.0, 117.2, 117.7, 119.0, 120.5, 122.2, 123.9, 125.3, 127.2, 127.4, 128.5, 128.7, 157.2, 185.1; HRMS (ESI): calcd for $\text{C}_{18}\text{H}_{13}\text{BrNO}_2$ (MH^+) 276.1024; found 276.1029.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by OPERA-grant of BITS Pilani and Department of Science & Technology, Science and Engineering Board (DST-SERB) New Delhi (EMR/2016/005599). AS thanks to UGC New Delhi for Research Fellowships. Authors are also grateful for generous support from the DST-FIST support to Department of Chemistry at BITS-Pilani.

Notes and references

- (a) J. A. Joule and K. Mills, *Heterocyclic Chemistry*, Blackwell, Oxford, 4th edn, 2000; (b) T. Eicher and S. Hauptmann, *The Chemistry of Heterocycles*, Wiley-VCH, Weinheim, 2003; (c) A. R. Katrizky and A. F. Pozharskii, *Handbook of Heterocyclic Chemistry*, Pergamon, Amsterdam, 2nd edn, 2000; (d) I. S. Young, P. D. Thornton and A. Thompson, *Nat. Prod. Rep.*, 2010, 27, 1801; (e) M. Baumann,



- I. R. Baxendale, S. V. Ley and N. Nikbin, *Beilstein J. Org. Chem.*, 2011, **7**, 442.
- 2 (a) *Pyrrroles, The Chemistry of Heterocyclic Compounds part I*, ed. R. A. Jones, Wiley, New York, 1990, vol. 48; (b) H. Fan, J. Peng, M. T. Hamann and J.-F. Hu, *Chem. Rev.*, 2008, **108**, 264; (c) V. Bhardwaj, D. Gumber, V. Abbot, S. Dhiman and P. Sharma, *RSC Adv.*, 2015, **46**, 15233.
- 3 (a) M. E. Mason, B. Johnson and M. Hamming, *J. Agric. Food Chem.*, 1966, **14**, 454; (b) M. M. M. Raposo, A. M. C. Fonseca, M. C. R. Castro, M. Belsley, M. F. S. Cardoso, L. M. Carvalho and P. J. Coelho, *Dyes Pigm.*, 2011, **91**, 62; (c) M. Takase, N. Yoshida, T. Narita, T. Fujio, T. Nishinaga and M. Iyoda, *RSC Adv.*, 2012, **2**, 3221; (d) M. M. Wienk, M. Turbiez, J. Gilot and R. A. J. Janssen, *Adv. Mater.*, 2008, **20**, 2556; (e) Y. Wang, G. A. Sotzing and R. A. Weiss, *Chem. Mater.*, 2008, **20**, 2574; (f) S. K. Ibrahim, X. M. Liu, C. Tard and C. J. Pickett, *Chem. Commun.*, 2007, 1535; (g) S. J. Higgins, *Chem. Soc. Rev.*, 1997, **26**, 247; (h) C.-F. Lee, L.-M. Yang, T.-Y. Hwu, A.-S. Feng, J.-C. Tseng and T.-Y. Luh, *J. Am. Chem. Soc.*, 2000, **122**, 4992; (i) C. D'Silva and D. A. Walker, *J. Org. Chem.*, 1998, **63**, 6715; (j) A. Berlin, B. Vercelli and G. Zotti, *Polym. Rev.*, 2008, **48**, 493.
- 4 For recent reviews, see (a) V. Estevez, M. Villacampa and J. C. Menendez, *Chem. Soc. Rev.*, 2010, **39**, 4402; (b) J. Bergman and T. Janosik, *Mod. Heterocycl. Chem.*, 2011, **1**, 269; (c) X. Qi, X. Xu and C.-M. Park, *Chem. Commun.*, 2012, **48**, 3996.
- 5 A. Padwa and W. H. Pearson, *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*, Wiley, New York, 2002, vol. 59.
- 6 For reviews on multicomponent reactions, see (a) V. Estèvez, M. Villacampa and J. C. Menéndez, *Chem. Soc. Rev.*, 2010, **39**, 4402; (b) G. Balme, D. Bouyssi and N. Monteiro, *Heterocycles*, 2007, **73**, 87.
- 7 For recent review see; A. V. Gulevich, A. S. Dudnik, N. Chernyak and V. Gevorgyan, *Chem. Rev.*, 2013, **113**, 3084.
- 8 (a) S. Chiba, Y. Wang, G. Lapointe and K. Narasaka, *Org. Lett.*, 2008, **10**, 313; (b) G. Minetto, L. F. Raveglia, A. Sega and M. Taddei, *Eur. J. Org. Chem.*, 2005, 5277; (c) S. Thirumalairajan, B. M. Pearce and A. Thompson, *Chem. Commun.*, 2010, **46**, 1797; (d) S. Ngwerume and J. E. Camp, *Chem. Commun.*, 2011, **47**, 1857; (e) O. A. Attanasi, G. Favi, F. Mantellini, G. Moscatelli and S. Santeusano, *J. Org. Chem.*, 2011, **76**, 2860; (f) M. Zhang and J. Zhang, *Chem. Commun.*, 2012, **48**, 6399; (g) L. Meng, K. Wu, C. Liu and A. Lei, *Chem. Commun.*, 2013, **49**, 5853; (h) V. Estevez, M. Villacampa and J. C. Menendez, *Chem. Commun.*, 2013, **49**, 591; (i) T. Wu, L. Pan, X. Xu and Q. Liu, *Chem. Commun.*, 2014, **50**, 1797; (j) Y. H. Xu, T. He, Q. C. Zhang and T. P. Loh, *Chem. Commun.*, 2014, **50**, 2784; (k) C. Zhou and D. Ma, *Chem. Commun.*, 2014, **50**, 3085; (l) H. P. Kalmode, K. S. Vadagaonkar, K. Murugan and A. C. Chaskar, *New J. Chem.*, 2015, **39**, 4631; (m) W. W. Tan and N. Yoshikai, *Chem. Sci.*, 2015, **6**, 6448; (n) X. Wu, K. Li, S. Wang, C. Liu and A. Lei, *Org. Lett.*, 2016, **18**, 56; (o) T. J. Cogswell, C. S. Donald and R. Marquez, *Org. Biomol. Chem.*, 2016, **14**, 183.
- 9 (a) C. P. Andrieux, P. Audebert, A. Merz and R. Schwarz, *New J. Chem.*, 1990, **14**, 637; (b) J. M. Méndez, B. Flores, F. León, M. E. Martínez, A. Vazquez, G. A. Garcia and M. Salmón, *Tetrahedron Lett.*, 1996, **37**, 4099; (c) N. P. Pavri and M. L. Trudell, *J. Org. Chem.*, 1997, **62**, 2649; (d) J. E. Beecher and D. A. Tirrell, *Tetrahedron Lett.*, 1998, **39**, 3927; (e) A. Bunrit, S. Sawadjoon, S. Tsupova, P. J. R. Sjöberg and J. S. M. Samec, *J. Org. Chem.*, 2016, **81**, 1450.
- 10 (a) B. L. Bray, P. H. Mathies, R. Naef, D. R. Solas, T. T. Tidwell, D. R. Artis and J. M. Muchowski, *J. Org. Chem.*, 1990, **55**, 6317; For direct method (b) A. Hamdan and J. W. F. Wasley, *Synth. Commun.*, 1983, **13**, 741; For indirect methods (c) H. Dumoulin, F. Fabis, P. Dallemagne, S. Roult and M. Robba, *Synth. Commun.*, 1994, **24**, 1855; (d) P. Haldar, J. Guin and J. K. Ray, *Tetrahedron Lett.*, 2005, **46**, 1071; (e) A. R. Kelly, M. H. Kerrigan and P. J. Walsh, *J. Am. Chem. Soc.*, 2008, **130**, 4097.
- 11 (a) H. Jendralla, E. Baader, W. Bartmann, G. Beck, A. Bergmann, E. Granzer, B. Kerekjarto, K. Kessler, R. Krause, W. Schubert and G. Wess, *J. Med. Chem.*, 1990, **33**, 61; (b) D. Dumoulin, S. Rault and M. Robba, *J. Heterocycl. Chem.*, 1996, **33**, 255; (c) R. He, L.-F. Zeng, Y. He, L. Wu, A. M. Gunawan and Z.-Y. Zhang, *Chem. Commun.*, 2013, **49**, 2064; (d) S. Valente, S. Tomassi, G. Tempera, S. Saccoccio, E. Agostinelli and A. Mai, *J. Med. Chem.*, 2011, **54**, 8228; (e) W. M. Sigmund, G. Weerasekera, C. Marestin, S. Styron, H. Zhou, M. Z. Elsabee, J. Rühle, G. Wegner and R. S. Duran, *Langmuir*, 1999, **15**, 6423; (f) F. Martinnelli, A. Palmieri and M. Petrini, *Chem.-Eur. J.*, 2011, **17**, 7183; (g) L. J. Perez, T. K. Karagounis, A. Hurley, B. L. Bassle and M. F. Semmelhack, *Chem. Sci.*, 2014, **5**, 151; (h) M. R. Rivero and S. L. Buchwald, *Org. Lett.*, 2007, **9**, 973; (i) M. S. Butler, *J. Nat. Prod.*, 2004, **67**, 2141; (j) M. Toganoh, Y. Kawabe and H. Furuta, *J. Org. Chem.*, 2011, **76**, 7618.
- 12 I. Kumar, P. Ramaraju, N. A. Mir and A. Singh, *Org. Biomol. Chem.*, 2015, **13**, 1280.
- 13 (a) I. Kumar, N. A. Mir, V. K. Gupta and Rajnikant, *Chem. Commun.*, 2012, **48**, 6975; (b) I. Kumar, N. A. Mir, P. Ramaraju and B. P. Wakhloo, *RSC Adv.*, 2012, **2**, 8922; (c) I. Kumar, P. Ramaraju, N. A. Mir, D. Singh, V. K. Gupta and Rajnikant, *Chem. Commun.*, 2013, **49**, 5645; (d) I. Kumar, N. A. Mir, P. Ramaraju, D. Singh, V. K. Gupta and Rajnikant, *RSC Adv.*, 2014, **4**, 34548; (e) P. Ramaraju, N. A. Mir, D. Singh, V. K. Gupta, R. Kant and I. Kumar, *Org. Lett.*, 2015, **17**, 5582; (f) N. A. Mir, S. Choudhary, P. Ramaraju, D. Singh and I. Kumar, *RSC Adv.*, 2016, **6**, 39741; (g) P. Ramaraju, N. A. Mir, D. Singh and I. Kumar, *RSC Adv.*, 2016, **6**, 60422; (h) P. Ramaraju, N. A. Mir, D. Singh, P. Sharma, R. Kant and I. Kumar, *Eur. J. Org. Chem.*, 2017, 3461.
- 14 (a) A. Shaabani, A. Maleki, H. Mofakham and H. R. Khavasi, *J. Comb. Chem.*, 2008, **10**, 883; (b) G. Guillena, D. J. Ramon and M. Yus, *Tetrahedron: Asymmetry*, 2007, **18**, 693; (c) D. Tejedor, D. Gonzalez-Cruz, A. Santos-Exposito,



- J. J. Marrero-Tellado, P. de-Armas and F. Garcia-Tellado, *Chem.-Eur. J.*, 2005, **11**, 3502; (d) B. B. Toure and D. G. Hall, *Chem. Rev.*, 2009, **109**, 4439; (e) A. Dömling, W. Wang and K. Wang, *Chem. Rev.*, 2012, **112**, 3083; (f) T. Guntreddi, B. K. Allam and K. N. Singh, *Synlett*, 2012, 2635; (g) S. R. Roy, P. S. Jadhavar, K. Seth, K. K. Sharma and A. K. Chakraborti, *Synthesis*, 2011, 2261; (h) H. Benjamin, S. Z. Rotstein, V. Rai and K. Y. Andrei, *Chem. Rev.*, 2014, **114**, 8323.
- 15 See ESI.†
- 16 (a) R. J. Sundberg, *The Chemistry of Indoles*, Academic Press, New York, 1970; (b) G. W. Gribble, in *Comprehensive Heterocyclic Chemistry II*, ed. A. R. Katritzky, C. W. Rens, E. F. V. Scriven and C. W. Bird, Pergamon Press, Oxford, 1996, vol. 2, p. 207; (c) D. J. Faulkner, *Nat. Prod. Rep.*, 2002, **19**, 1; (d) G. Bartoli, G. Bencivenni and R. Dalpozzo, *Chem. Soc. Rev.*, 2010, **39**, 4449; (e) W. Gul and M. T. Hamann, *Life Sci.*, 2005, **78**, 442; (f) A. J. Kochanowska-Karamyan and M. T. Hamann, *Chem. Rev.*, 2010, **110**, 4489.
- 17 (a) K. A. McArthur, S. S. Mitchell, G. Tsueng, A. Rheingold, D. J. White, J. Grodberg, K. S. Lam and B. C. M. Potts, *J. Nat. Prod.*, 2008, **71**, 1732; (b) D. S. Black, M. C. Bowyer and N. Kumar, *Tetrahedron*, 1997, **53**, 8573; (c) J. Lehuédé, B. Fauconneau, L. Barrier, M. Ourakow, A. Piriou and J. M. Vierfond, *Eur. J. Med. Chem.*, 1999, **34**, 991; (d) M. S. Mohamed, R. Kamel and S. S. Fatahala, *Eur. J. Med. Chem.*, 2011, **46**, 3022; (e) N. R. Williamson, P. C. Fineran, T. Gristwood, S. R. Chawrai, F. J. Leeper and G. P. C. Salmond, *Future Microbiol.*, 2007, **2**, 605; (f) J. Lavrado, R. Moreira and A. Paulo, *Curr. Med. Chem.*, 2010, **17**, 2348; (g) A. Carbone, B. Parrino, P. Barraja, V. Spanò, G. Cirrincione, P. Diana, A. Maier, G. Kelter and H.-H. Fiebig, *Mar. Drugs*, 2013, **11**, 643; (h) W. Zhang, Z. Liu, S. Li, T. Yang, Q. Zhang, L. Ma, X. Tian, H. Zhang, C. Huang, S. Zhang, J. Ju, Y. Shen and C. Zhang, *Org. Lett.*, 2012, **14**, 3364.
- 18 (a) F. Zhou, J. Guo, J. Liu, K. Ding, S. Yu and Q. Cai, *J. Am. Chem. Soc.*, 2012, **134**, 14326; (b) Z. Wang, W. Bao and Y. Jiang, *Chem. Commun.*, 2005, 2849.
- 19 R. L. Goff, A. M. Lawson, A. Daich and S. Comesse, *Org. Biomol. Chem.*, 2013, **11**, 1818.
- 20 (a) T. H. Brown, R. J. Iffe, D. J. Keeling, S. M. Laing, C. A. Leach, M. E. Parsons, C. A. Price, D. R. Reavill and K. J. Wiggall, *J. Med. Chem.*, 1990, **33**, 527; (b) Y. Sangnoi, O. Sakulkeo, S. Yuenyongsawad, A. Kanjanaopas, K. Ingkaninan, A. Plubrukarn and K. Suwanborirux, *Mar. Drugs*, 2008, **6**, 578; (c) G. Furlotti, M. A. Alisi, C. Apicella, A. C. de Joannon, N. Cazzolla, R. Costi, G. C. Crucitti, B. Garrone, A. Iacovo, G. Magarò, G. Mangano, G. Miele, R. Ombrato, L. Pescatori, L. Polenzani, F. Rosi, M. Vitiello and R. Di Santo, *J. Med. Chem.*, 2012, **55**, 9446.
- 21 (a) R. Y. Yang and L. X. Dai, *J. Org. Chem.*, 1993, **58**, 3301; (b) R. A. Rane, B. Pavankumar, S. D. Borhade and P. K. Khandare, *Eur. J. Med. Chem.*, 2013, **70**, 49; (c) A. Idhayadhulla, R. S. Kumar, A. J. A. Nasser and A. Manilal, *Bull. Chem. Soc. Ethiop.*, 2012, **26**, 429.
- 22 (a) S. Ghosal, K. S. Saini and A. W. Frahm, *Phytochemistry*, 1983, **22**, 2305; (b) S. Ghosal, Y. Kumar, D. K. Chakrabarti, J. Lal and S. K. Singh, *Phytochemistry*, 1986, **25**, 1097; (c) Z. Jin, *Nat. Prod. Rep.*, 2009, **26**, 363; (d) K. Merz, T. Muller, S. Vanderheiden, G. Eisenbrand, D. Marko and S. Brase, *Synlett*, 2006, 3461; (e) T. Ishikawa, *Med. Res. Rev.*, 2001, **21**, 61; (f) H. Tsukamoto, S. Kondo, Y. Mukudai, T. Nagumo, A. Yasuda, Y. Kurihara, T. Kamatani and S. Shintani, *Anticancer Res.*, 2011, **31**, 2841.

