Chapter-II

Sequential multicomponent synthesis of pyrrole-3-carboxaldehydes

2.1.1 Introduction

Nitrogen bearing heterocyclic compounds have gained significant attention in the area of material chemistry, pharmaceutical chemistry, and synthetic organic chemistry. Nitrogen heterocycles are probably more in number among the entire heterocyclic scaffold present in nature. One of the most relevant five-member nitrogen heterocyclic systems, i.e., pyrrole is present in an array of drug molecules and natural products. In 1834 pyrrole was detected as a component of coal tar by F. F. Runge,[1] latter in 1857, and it was isolated from the pyrolysate of bone. The name pyrrole came from Greek world Pyrrhus ("reddish, fiery") from the reaction applied to detect it the red color that it gives to wood when moistened with hydrochloric acid.[2]

2.1.2 Chemical properties

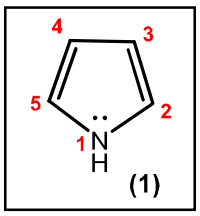


Figure 2.1 Structure of pyrrole

Pyrroles a five-membered nitrogen-containing aromatic heterocycle, nutty odor, colorless volatile liquid that readily darkens when exposed to air and generally purified by distillation just before use.[3] The $_pK_a$ of its conjugate base is −3.8 indicate that pyrrole is weakly basic in nature as well as poorly acidic at the N-H position with a pKa of 17.5. Pyrrole is an electron-rich species containing 6π-electron and five *p*-orbitals and obeys Huckel rule of aromaticity. Hence its reactivity is similar to aromatic compounds (**Figure 2.1**).

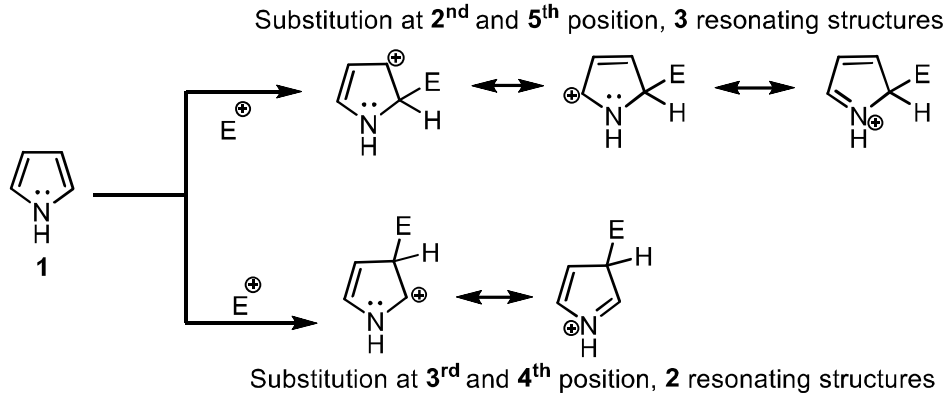


Figure 2.2 Electrophilic substitution on α and β position of pyrrole

Pyrroles usually undergo electrophilic substitution at α-position (C2 or C5) due to the more significant number of resonating hybrid structures that offer the highest degree of stability in intermediate compared to electrophilic replacement at β-position (C3 or C4) (**Figure 2.2**).

2.1.3 Importance of pyrrole

Pyrroles and its derivatives are one of the most often present five-membered heterocyclic systems in several useful scaffolds, which are essential building blocks in organic synthesis; as a result, it becomes potential starting materials for numerous organic transformations.[4-7] Pyrrole nucleus has simple natural abundance, and in many important biologically active molecules such as pyoluteorin and Pentabromopseudodiline, present predominantly as a fundamental unit, these bioactive molecules were isolated from marine natural products.[8] Functionalized pyrrole derivatives have shown full applications in numerous branches of science, such as pharmacology, biology, agrochemicals, material sciences, dyes, Flavor-components, photographic chemicals, and functionalized materials.[9-17] Several naturally occurring molecules are having pyrroles such as vitamin B_{12}, bile-pigment like bilirubin, biliverdin, and porphyrinogens, porphyrins of heme, bacteriochlorin, chlorophyll, chlorins.[18] Besides, other secondary metabolites containing pyrroles are ryanodine, Makalu amine M, PQQ, rhazinilam, sceptrin, myrmicacin, lamellarin, prodigious. Besides, medium-sized nitrogen heterocycles are privileged scaffolds present in numerous natural and unnatural compounds,[19-23] in particular; pyrrole derivatives show diverse physiological activities.[24] Such as anti-tubercular,[25-26] antiviral,[27] antibacterial,[28] anti-inflammatory,[29] Lamellarins and Ningalins are a large variety of antibiotics protease inhibitors and anticancer drugs, exhibit resistance reversal activity for multidrug against L1210 and HCT116 cell lines. Storniamide family where pyrrole is embedded in the center, isolated from a variety of marine organisms like mollusks, ascidians, sponges, showing potent activity as inhibitors of the multidrug resistance (MDR) phenomenon,[30-36] **(Figure 2.3).**[37-38]

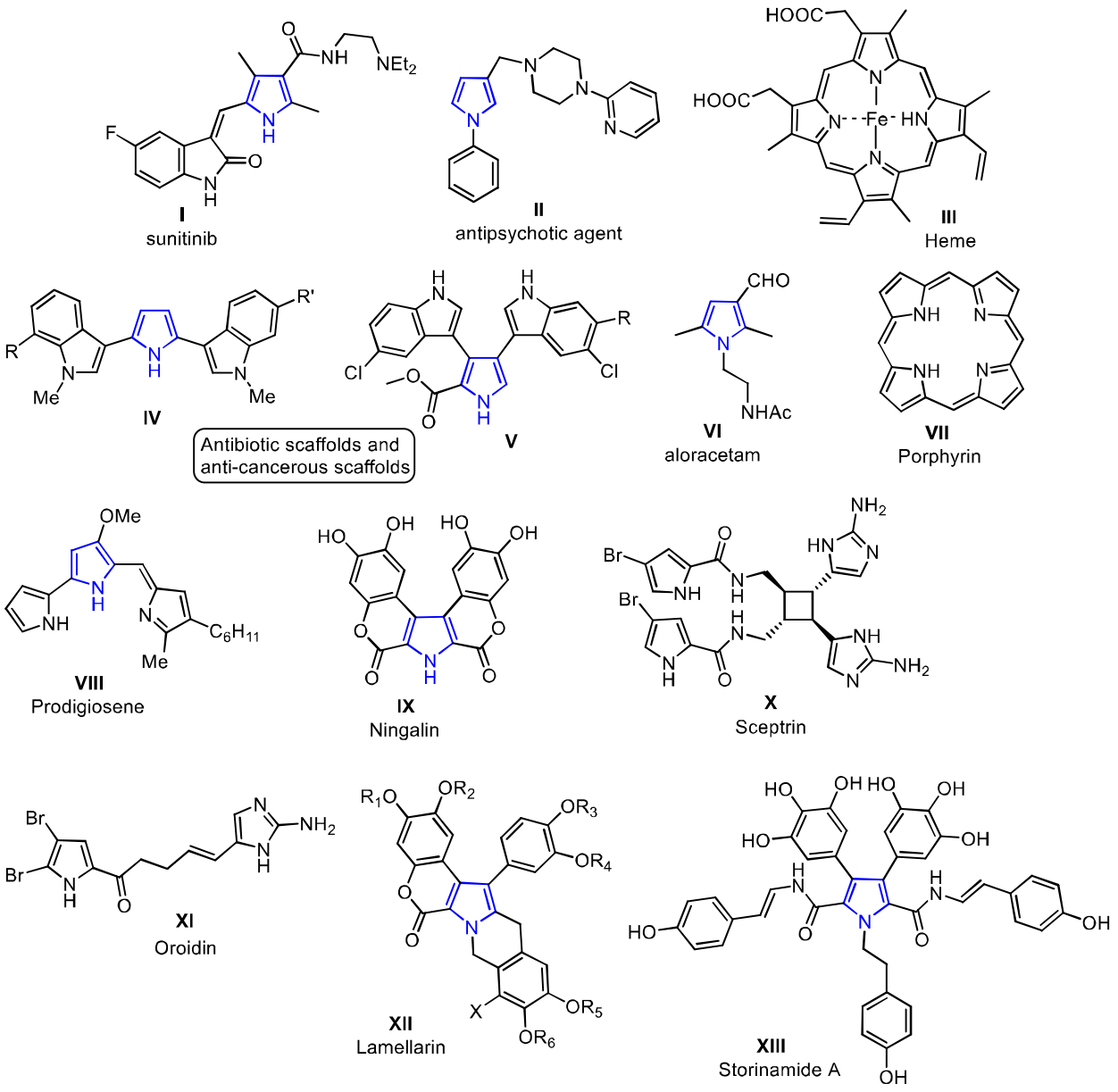
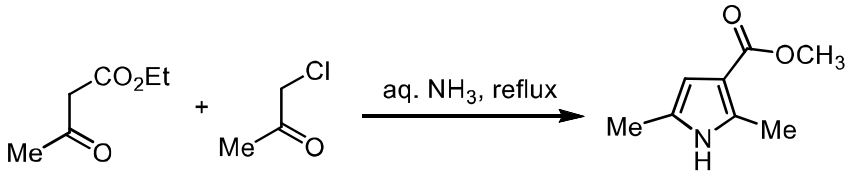


Figure 2.3 Some bioactive pyrroles and related derivatives

2.2 Basic idea and literature reports of multi-component reactions

Over the past few decades, several elegant methods to access functionalized pyrroles have been reported, which includes classical methods,[39-41] cycloadditions,[42] multi-component,[39,43] metal-catalyzed reactions,[44] and several others.[45-59] Particularly multicomponent reaction (MCRs) is also known as "Multi-component Assembly Process" (MCAP) is a chemical reaction in which more than two reacting substrates react sequentially to form a highly selective product, that retains the starting material in the majority.[60]

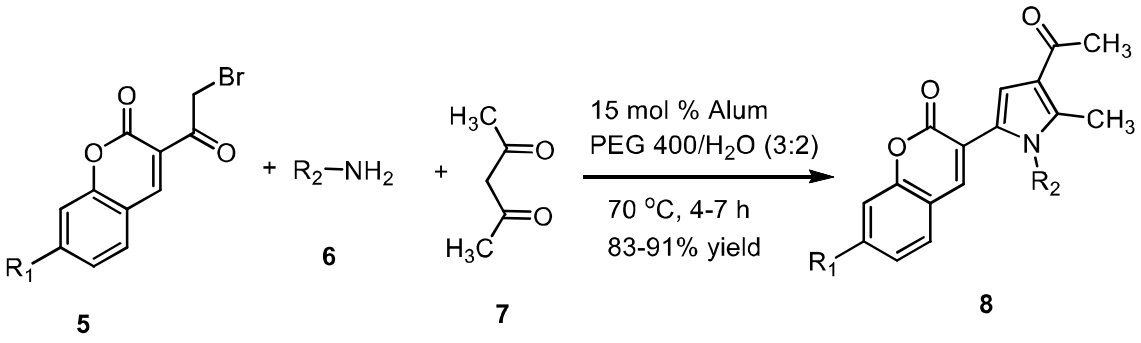
Strecker in 1850, developed the first multi-component reaction, called Strecker synthesis (synthesis of α-amino acids from α-amino cyanides). MCRs offer valuable benefits over conventional multi-step syntheses and produce a significant route for modern synthetic chemistry.[61,62] Broad substrate scope and several functional group tolerance capability make the MCRs as an important tool for synthesizing organic compounds with a high degree of molecular diversity.[63-65] Due to efficient synthetic efficiency and natural reaction designing strategy, one-pot multicomponent reactions (MCRs) have gained considerable attention in academics, ecology, and economic interest during the last two decades. This strategy constructs the libraries of small scaffolds with structural diversity like pharmaceutically active compounds, chromophores, and marine alkaloids.[66-76] Synthesis of pyrroles with diverse substitution by the multi-bond synthetic approach in one pot such as cascade/domino reactions, multi-component reactions (MCRs) is an important tool to synthesize complex molecules in one step. Numerous novel strategies have been developed for generating diversely substituted pyrrole *via* multi-component reactions.[39,77] For instance, in 1890, Hantzsch reported a brief note on the synthesis of pyrrole derivatives from the equimolecular mixture of acetoacetic ester **2** and chloroacetone **3** under reflux in concentrated aqueous ammonia (**scheme 2.1**).[78]



2 **3** **4**

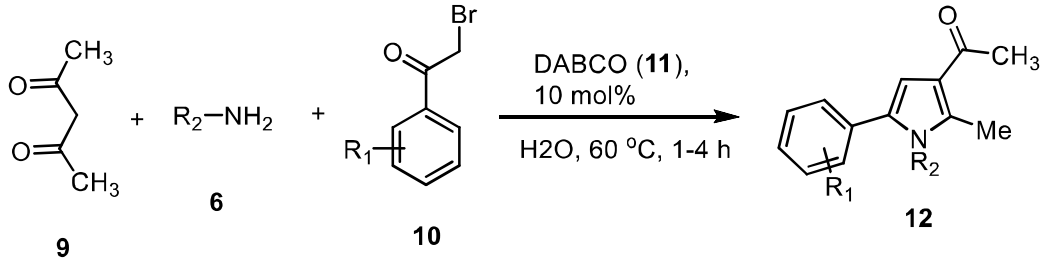
Scheme 2.1 First multi-component pyrrole synthesis describes by Rudolf Hantzsch

Das and co-workers reported one-pot three-component Hantzsch synthesis involving 3-bromoaceticcoumarin **5**, amines **6**, and pentanedione **7** to carry out tetrasubstituted pyrroles **8** syntheses (**Scheme 2.2**). A coumarin appended pyrrole was synthesized that may have pharmacological importance. An environmentally benign catalyst alum ($AlK(SO_4)_2.12H_2O$) was used in a mixture of polyethylene glycol (PEG) and water (3:2), which offered the platform for a catalyst to carried out the reaction. Al_3^+ work as active Lewis acidic species that facilitate both enaminone formation as well as C–Br bond polarization needed to facilitate the initial step of the Hantzsch reaction.[79].



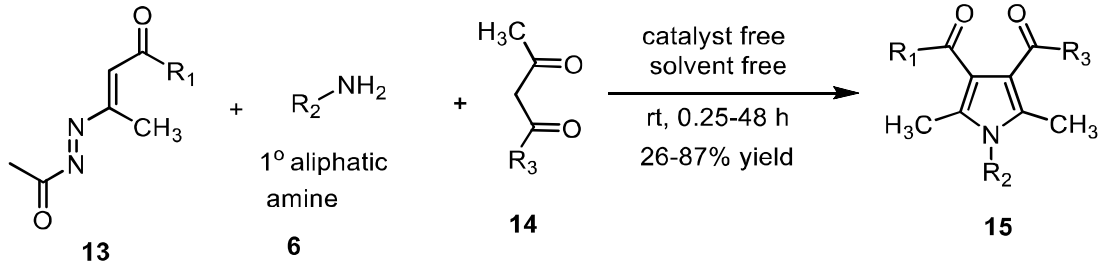
Scheme 2.2 Three-component Alum-catalyzed Hantzsch pyrrole synthesis in PEG–water

Meshram and co-workers described the base-catalyzed variation of the Hantzsch pyrrole synthesis, in which organic base 1,4-diazabicyclo[2,2,2]octane (DABCO) catalyzed this reaction in water, however, suffered from substrate scope as single diketone was utilized as substrate. As a result, positions 2,3 and 4, locked, and substitution could be changed at positions 1 and 5, by varying the phenacyl bromide and primary amine counterpart, respectively (**Scheme 2.3)**.[80]



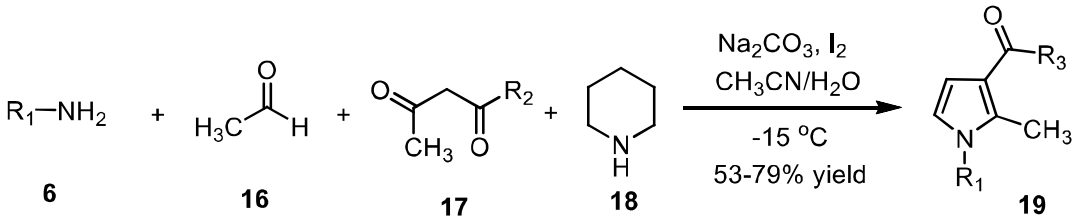
Scheme 2.3 Base-promoted Hantzsch pyrrole synthesis in the aqueous medium

Attanasi *et al*. have described the efficient three-component one-pot synthesis of densely substituted pyrroles **15** in solvent-free as we as catalyst-free fashion from 1,2-diaza-1,3-dienes**13**, amine **6,** and active methylene compounds**14** (**Scheme2.4**).[81]



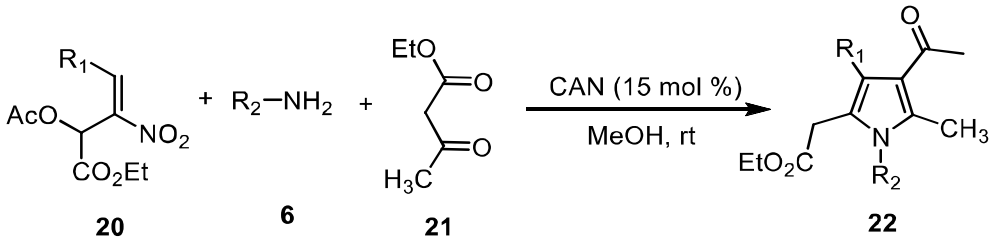
Scheme 2.4 Synthesis of polysubstituted pyrroles described by Attanasi

Zeng *et al.* reported a new and efficient one-pot two-step synthesis for 1,2,3-trisubstituted pyrroles **19** by using primary amines **6**, acetaldehyde **16**, 1,3-dicarbonyl compounds **17** and piperidine **18** and various 1,2,3-trisubstituted pyrroles were synthesized. The resulting pyrrole derivatives were obtained by the iodocyclization of several *β*-enaminoesters followed by dehydro-iodination (**Scheme 2.5**).[82]



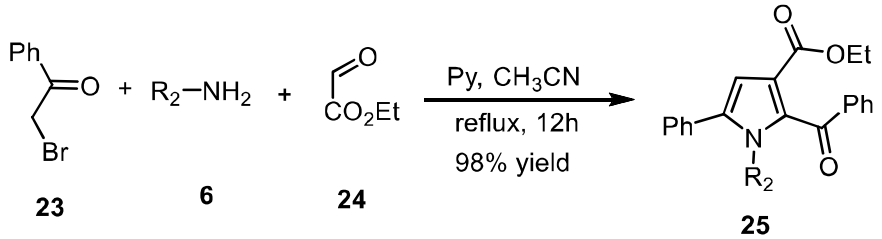
Scheme 2.5 Iodocyclization mediated 1,2,3-trisubstituted pyrrole synthesis

Chan group developed a ceric ammonium nitrate (CAN) catalyzed multicomponent methodology for fully substituted pyrrole **22** derivatives with diesters substituents from amine **6**, nitroallylic diacetates **20** and ethyl acetoacetate **21** (**Scheme 2.6**).[83]



Scheme 2.6 CAN catalyze the synthesis of pyrroles *via* three-component reaction

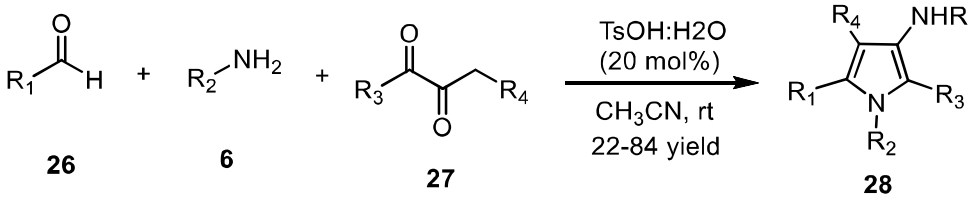
Wang *et al.* also made significant efforts for the synthesis of 1,2,3,5-tetrasubstituted pyrroles **25** by refluxing the solution of primary amine **6**, two equivalent of bromo-acetophenones **23** and ethyl glyoxylate **24** in CH_3CN (**Scheme 2.7**).[84]



Scheme 2.7 Base promoted synthesis of 2-acylpyrroles by Wang

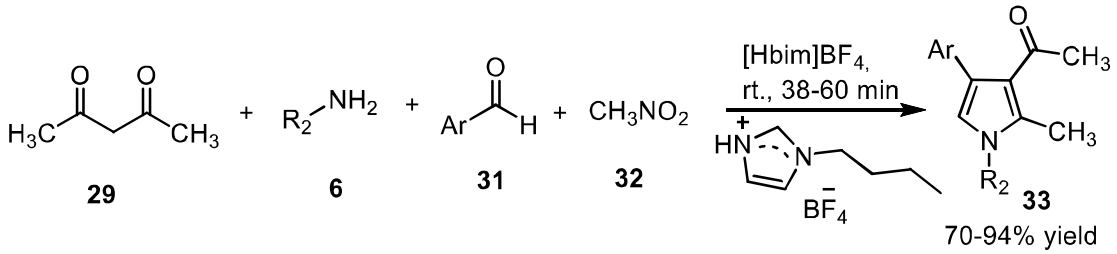
Under mild reaction conditions, Zhou and co-workers have reported an exciting approach to furnish multi-substituted pyrroles **28** afforded moderate to good yield up to 84% *via*

multi-component methodology from aromatic amine **6**, aldehydes **26**, 1,2-diones **27** **(Scheme 3.25)**.[85]



Scheme 2.8 Synthesis of multi-substituted pyrroles reported by Zhou and co-workers

Recently, Meshram's group described an ionic liquid mediated "catalyst-free" four-component synthesis of pyrroles. Tetrasubstituted pyrroles **32** thus obtained by coupling 1,3-pentadione **29**, amine **6**, aromatic aldehyde **30**, and nitromethane **31** in the presence of 1-*n*-butylimidazolium tetrafluoroborate ([Hbim]BF_4^-]) in short reaction time with good to excellent. Only traces of the desired pyrroles were obtained, when this was performed under neat conditions, and therefore it was assumed that the ionic liquid used as a solvent in reaction act as a catalyst. A wide variety of amines and aromatic aldehydes has been used, and the solvent can be reused up to three times without any noticeable decay in activity.[86]

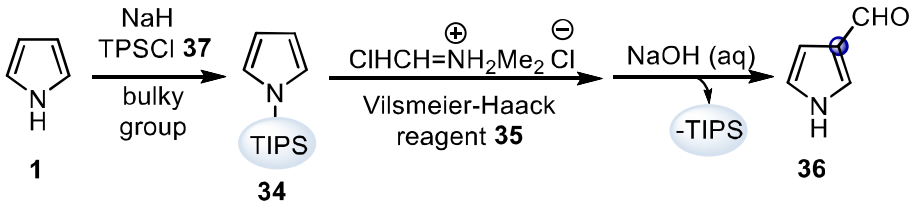


Scheme 2.9 Ionic-liquid promoted the four-component synthesis of pyrroles

Despite extensive efforts, the combination of C3-functionalized pyrroles is probably the most challenging task in organic synthesis and requires a specific strategy.[87-91] In particular, the regiospecific synthesis of pyrroles endowed with aldehyde group at C3-position is still very rare.[92-96] Pyrrole-3-carboxaldehydes **36** have mainly been synthesized by the use of sterically bulky triisopropyl silyl (TIPS) **37** as protecting group on the nitrogen of pyrrole followed by Vilsmeier formylation and deprotection as a multistep process **(Scheme 2.10)**,[92] along with other direct/indirect methods.[93-96] 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 **42**, to the best of our knowledge.

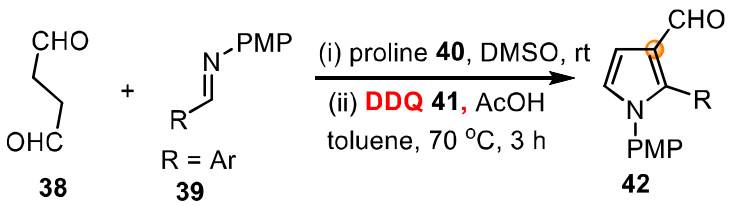
Earlier work: *approach for selective C3-formylation*



Scheme 2.10 Synthesis of 3-formyl pyrrole involving Vilsmeir-Haack reagent

The development of a 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, the aldehyde group at the C3-position of pyrroles can readily participate in numerous name reactions; thus, it holds significant promises to serve as a suitable intermediate to synthesize new medicinal agents and functionalized materials.[97-106] In continuation of our efforts to utilize using linear dialdehydes,[107] for the synthesis of medium-sized N-heterocycles under metal-free conditions.[108-115] We recently developed a two-pot protocol for the direct synthesis of pyrrole-3-carbaldehyde **42** from succinaldehyde **38** and imines **39.** This method resulted in a quick synthesis of pyrrole-3-aldehydes, though; it required the pre-assembled *N*-PMP protected aromatic and heteroaromatic aldimines and DDQ **41** as a harsh and toxic reagent for oxidative aromatization. This whole transformation proceeded through the organocatalytic direct Mannich reaction *via* formal [3+2] annulation cascade transformation followed by oxidative aromatization by DDQ **41 (Scheme 2.11).**[109]

our previous work: *two pot procedure*



Scheme 2.11 Two-pot synthesis of pyrrole-3-carboxaldehyde using DDQ

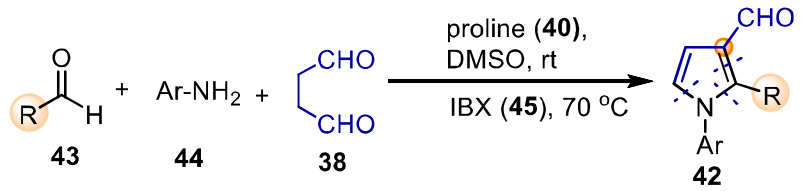
In spite of the rapid synthesis of pyrrole-3-carboxaldehyde**5** by this strategy, it is efficient to overcome several limitations that were associated with previous literature. This method also has some shortcomings, such as DDQ used as an oxidative aromatization agent, which is toxic and harsh, preform imine, and two pot syntheses, which is not economical. To refine this strategy further and to make this method more economical in every aspect, i.e., time, money, and environmentally benign herein, we modified our previous organocatalytic synthetic approach for the synthesis of functionalized 3-formylpyrrole by using multi-component one-pot tandem reaction *via* formal [3+2] direct Mannich cyclization reaction. The clear synthetic potential and novelty of this method to suitably functionalized pyrroles prompted us to explore similar transformation in one-pot sequential multi-component fashion under mild conditions. Besides, the social and environmental demands for more sustainable and practical synthetic protocols that need the use of less hazardous reagents/conditions have also gained much attention from the scientific community. In this context, multi-component reactions allow the rapid construction of new libraries of pharmaceutically active compounds and marine alkaloids. Thus, the development of such a protocol is always in demand.[8,62,68,70,71,72,76]

2.3 Results and discussion

Herein, we develop a simple and most rational sequential multi-component protocol for the synthesis of pyrrole-3-carboxaldehydes **42** *via in situ* imine formation between Ar/HetAr/Indole-aldehydes **43** and Ar-NH_2 **44**, followed by amine-catalyzed direct Mannich reaction-cyclization with succinaldehyde **38**, followed by IBX-mediated oxidative aromatization sequence in one-pot operation. IBX is a mild and versatile oxidizing agent that made this transformation greener, economical, efficient, as well as environmentally benign, unlike DDQ **(Scheme 2.12).** This improved method provides easy access to pyrrole-3-carboxaldehydes under mild and non-toxic conditions as compared to our previous two-pot protocol. Besides, *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.

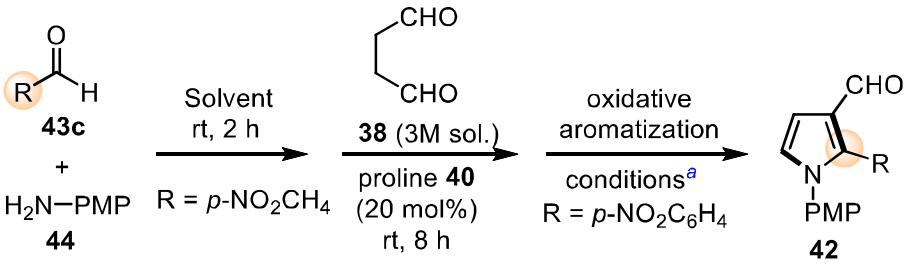
Scheme 2.12 One-pot multicomponent synthesis of pyrrole-3-carboxaldehyde

present work: one pot procedure



sequential multicomponent operation

Table 2.1 Optimization of reaction conditions[a]



Entry	Solvent	Conditions[a]	Yield (%)[b]
1	DMSO	$K_2S_2O_8$ (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_3CN	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_3CN	IBX (1.2 equiv.), 70 °C, 4 h	35
12[e]	DMSO	IBX (1.2 equiv.), 70 °C, 4 h	48

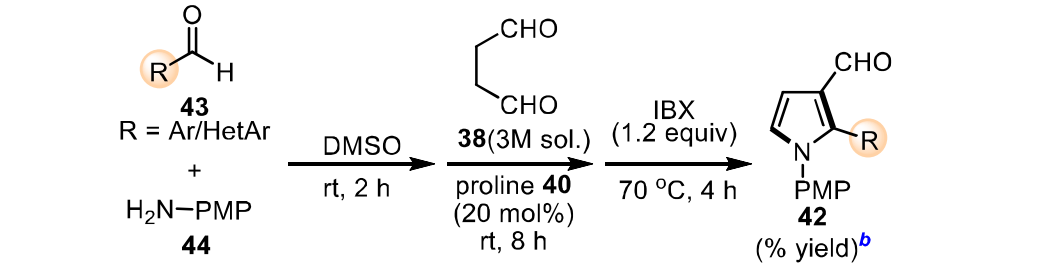
[a]Unless otherwise indicated, the reaction was carried out with (i) aldehyde **43** (0.3 mmol), *p*-anisidine **44** (0.3 mmol), succinaldehyde **38** (3M aqueous sol., 0.9 mmol), proline **40** (20 mol %), solvent (3.0 mL); (ii) IBX (1.1 equiv). [b]isolated yield of **42** refers to **43c**. [c]proline **40** (10 mol %). [d]EtOAc (3.0 mL) was added during IBX-mediated oxidative aromatization. [e]pyrrolidine (20 mol %), $PhCO_2H$ (20 mol %) were used in place of proline **40.**

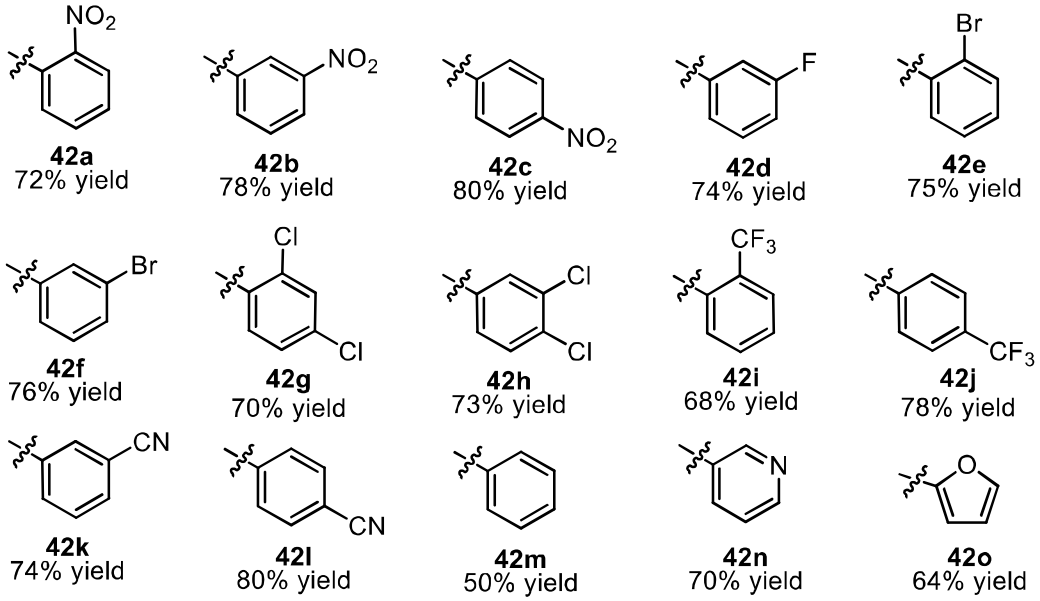
Based on our previous experience in this direction, we quickly optimized the designed reactions by choosing proline **40** (20 mol %) as a catalyst, *p*-nitrobenzaldehyde **43** as model substrates, along with *p*-anisidine **44**, and succinaldehyde **38** (3M aqueous sol.), in one-pot operation and the results are shown in (**Table 2.1)**. Initial experiments in DMSO as the choice of solvent along with the sequential addition of substrates, catalysts, and oxidant(s) gave **42** in low yield **(entry 1-2, Table 2.1)**. Our initial attempts were not successful to improve the yields by changing the solvents **(entries 2-4, Table 2.1)**. IBX **45** as the oxidant, also soluble in DMSO, showed good efficiency for this one-pot protocol at room temperature **(entry 5, Table 2.1)** and 50 ^{o}C **(entry 6, Table 2.1)**. Gratifyingly, an additional improvement in yields (80%) was observed when IBX-oxidation was carried out at 70 ^{o}C for 4 h **(entry 7, Table 2.1)**. However, additional efforts to increase the reaction yield by further increment in reaction temperature **(entry 8, Table 2.1)**, reduction in catalyst loading **(entry 9, Table 2.1)**, varying the reaction medium **(entries 10-11, Table 2.1)**, and changing the catalytic system **(entry 12, Table 2.1)** were ineffective. Thus, we prefer to perform this one-pot sequential transformation with the optimized conditions **(entry 7, Table 2.1)**.

The scope of the reaction was examined by employing various aromatic aldehydes. This one-pot sequential multi-component protocol works well in the case of aromatic aldehydes decorated with multiple groups (e.g., $-NO_2$, $-F$, $-Cl$, $-Br$, $-CN$ and CF_3) at the *ortho*-, *meta*-, or *para*-positions and resulted in 2-aryl-pyrrole-3-carbaldehydes in good to high yields (65-80%). The reaction works well with *in situ* generated simple aryl imine (**entry 42m, Table 2.2**), as well as with hetero-aryl imines (**entries 42n-42o, Table 2.2**) with good yields.

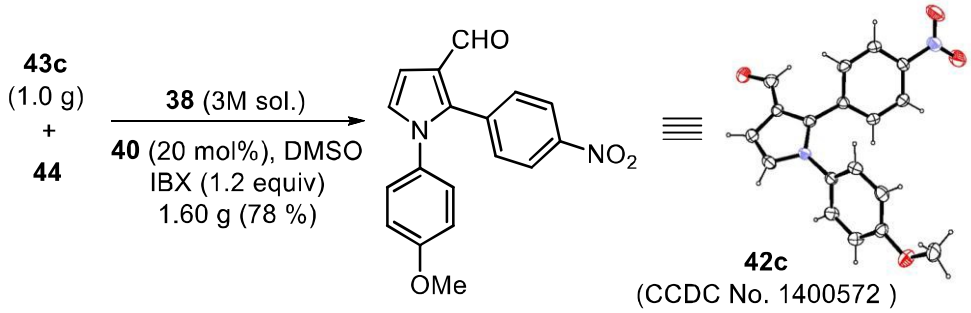
The feasibility of this protocol was also examined at the gram scale of **43c** (**1.0 g**) with other reactants under standardized conditions, and the corresponding product (**14c)** was obtained without much variation in yields (1.60 g, 78%). The structure of **42c** was further confirmed with single-crystal X-ray diffraction analysis (**Scheme 2.13**).

Table 2.2 Substrate scope concerning various Ar/HetAr-aldehydes**43**[a]



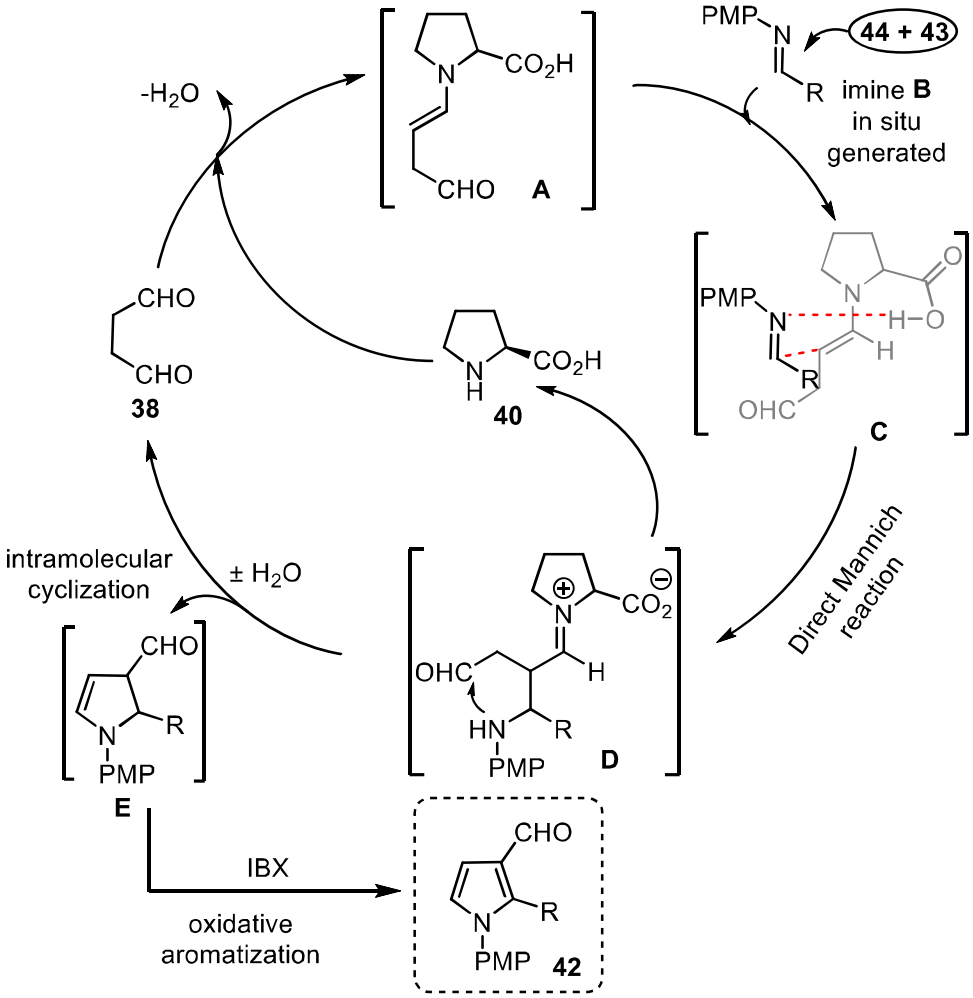


[a]Unless otherwise indicated, the reaction was carried out with (*i*) aldehyde **43** (0.3 mmol), *p*-anisidine **44** (0.3 mmol), DMSO (3.0 mL), rt, 2 h, (*ii*) Succinaldehyde **38** (3M aqueous sol., 0.9 mmol), proline **40** (20 mol %), 8 h, (*iii*) IBX (1.2 equiv), 70 °C, 4 h. [b]isolated yield of **42** refers to **43** (≤10% of aldehyde **43** was also recovered in all the cases).



Scheme 2.13 Single-crystal X-ray analysis of **42c** thermal ellipsoids is drawn at the 40% probability level.

Based on our study, a stepwise mechanism is proposed to account for this reaction. As shown in (**Scheme 2.14)**, the enamine **A** *in situ* generated from succinaldehyde **38** and catalyst **40**, reacts with *in situ* made *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 **40**. In the same pot, cyclic enamine-intermediate **E** underwent IBX-mediated oxidative aromatization to afford pyrrole-3-carboxaldehyde **42**.



Scheme 2.14 Proposed reaction mechanism for this study

2.3.2 Indolyl-3-pyrroles synthesis

The scope of this one-pot protocol was further was examined by employing various *in-situ* generated imines derived from indole-3-aldehydes **45**. Indole aldehyde is a very challenging substrate for direct aldol/Mannich reaction as its carbonyl carbon

electronically not deficient enough due to the conjugation of nitrogen lone-pair with the aldehydic moiety, to undergo these immediate reactions. Thus, an electron-withdrawing group (EWG) at the nitrogen of indole can make this moiety more electronically deficient for the further response (**Figure 2.3**). 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 as indole, and its derivatives are an essential unit in many alkaloids and other bioactive compounds. [116-121] Moreover, indole-tethered pyrrole derivatives (for example, **IV** and **V** in **Figure 2.3**) found in several synthetic compounds and marine alkaloids that showed remarkable bioactivities[122-129], therefore, the synthesis of these compounds is quite impressive.

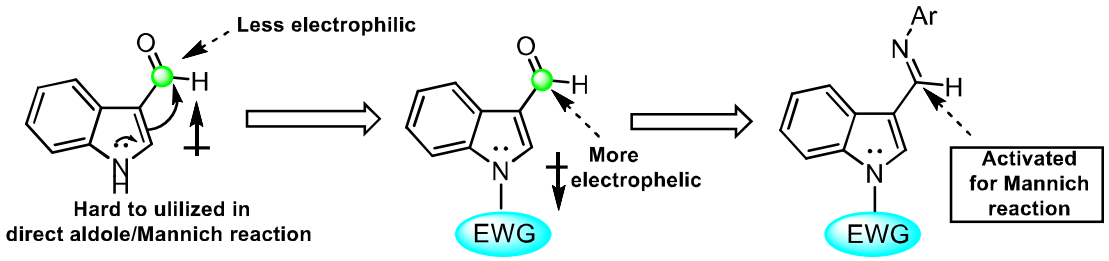
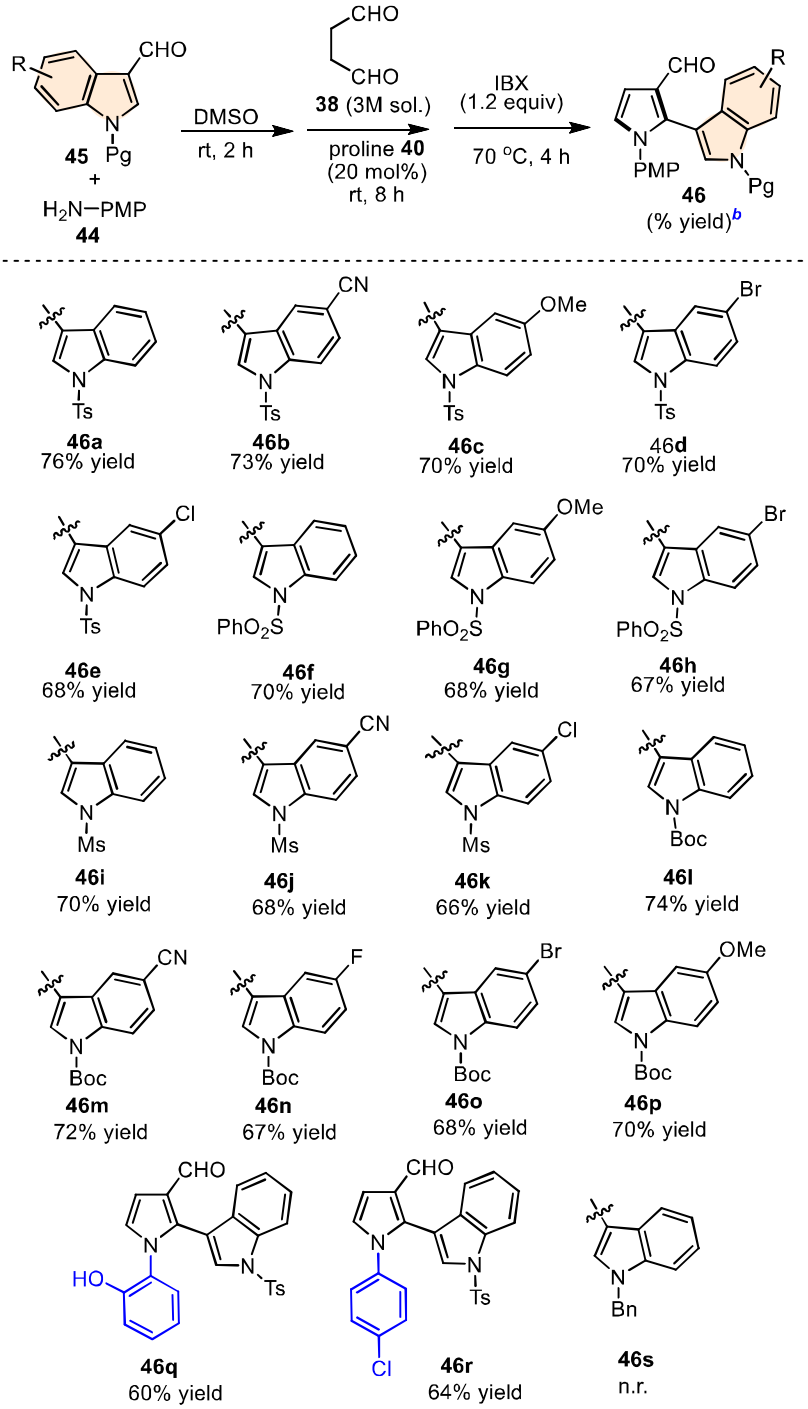


Figure 2.4 Presentation of electrophilic reactivity of indole aldehyde

In this context, a series of indolyl-pyrrole-3-carbaldehydes **46a-46p** were obtained with moderate to good yields, when *N*-Ts, -Ms, -SO_2Ph, and -Boc protected indole-3-aldehydes **45** were employed for this transformation with *p*-anisidine **44** and succinaldehyde **38** **(entries 46a-46p, Table 2.3)**. Besides, 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 46q-46r, Table 2.3)** were employed instead of *p*-anisidine for this one-pot transformation with *N*-Ts-indol-3-aldehyde **45a** and succinaldehyde **38**. However, reaction failed when a similar conversion was performed with *N*-benzyl-indole-3-aldehyde, probably because of the low reactivity of imine **(entry 46s, Table 2.3)**. ^{1}H and ^{13}C-NMR and mass-analysis confirm the structure of all compounds. Single crystal X-ray diffraction analysis of **46e** further established the product structure **(Figure 2.5)**.

Table 2.3 Substrate scope for various Indole-3-aldehydes **45**[a]



[a]Unless otherwise indicated, the reaction was carried out with (i) aldehyde **45** (0.3 mmol), *p*-anisidine**44** (0.3 mmol), DMSO (3.0 mL), rt, 2 h, (*ii*) Succinaldehyde **38** (3M aqueous sol., 0.9 mmol), proline **40** (20 mol %), 8 h, (*iii*) IBX (1.2 equiv), 70 °C, 4 h. [b]isolated yield refers to **46** (≤10% of aldehyde **45** was recovered in all the cases).

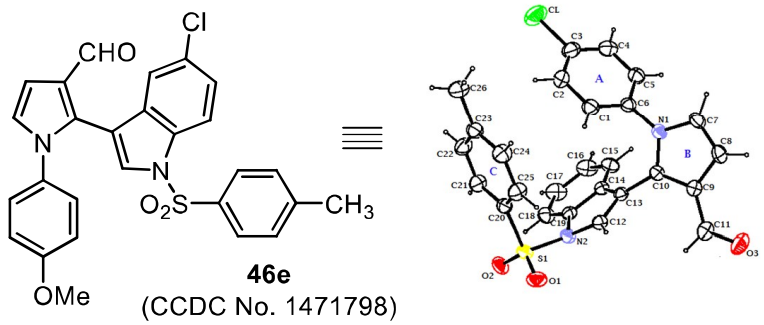
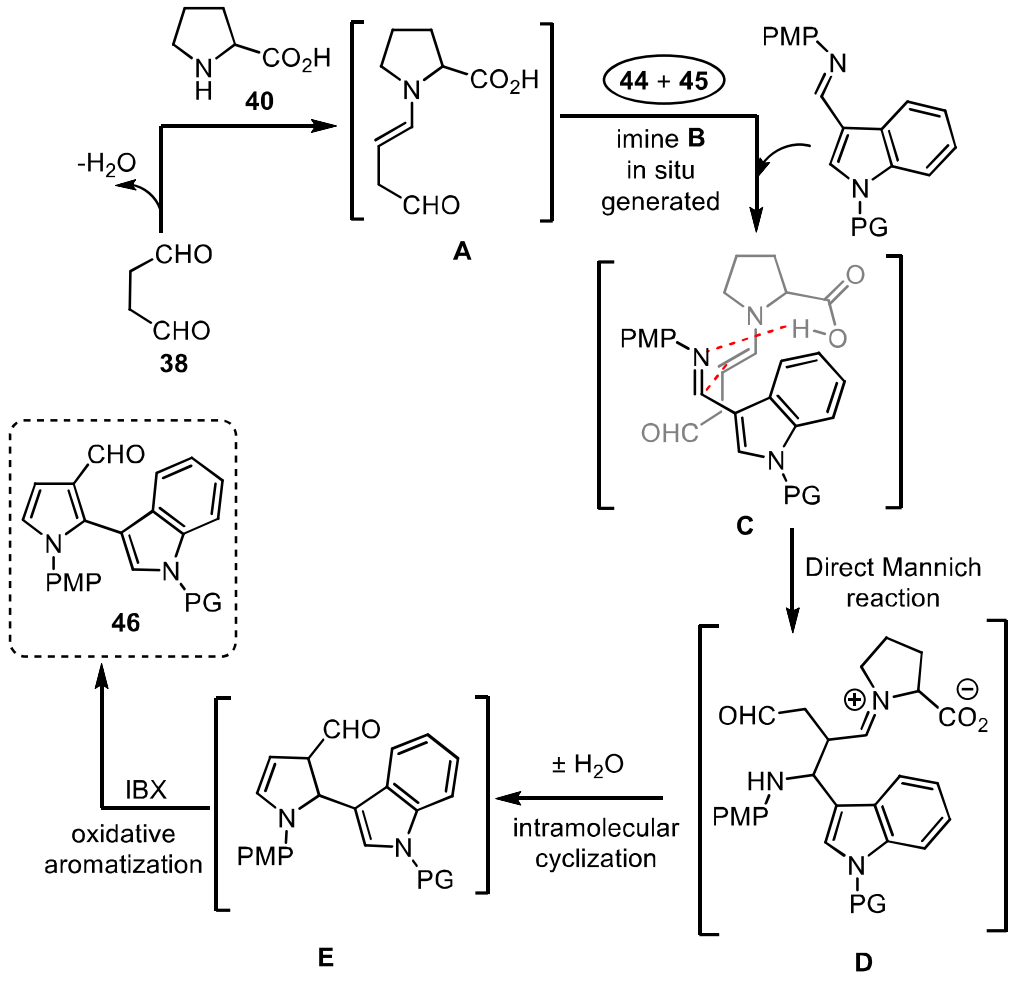


Figure 2.5 Single-crystal X-ray analysis of **46e.** Thermal ellipsoids are drawn at the 40% probability level.



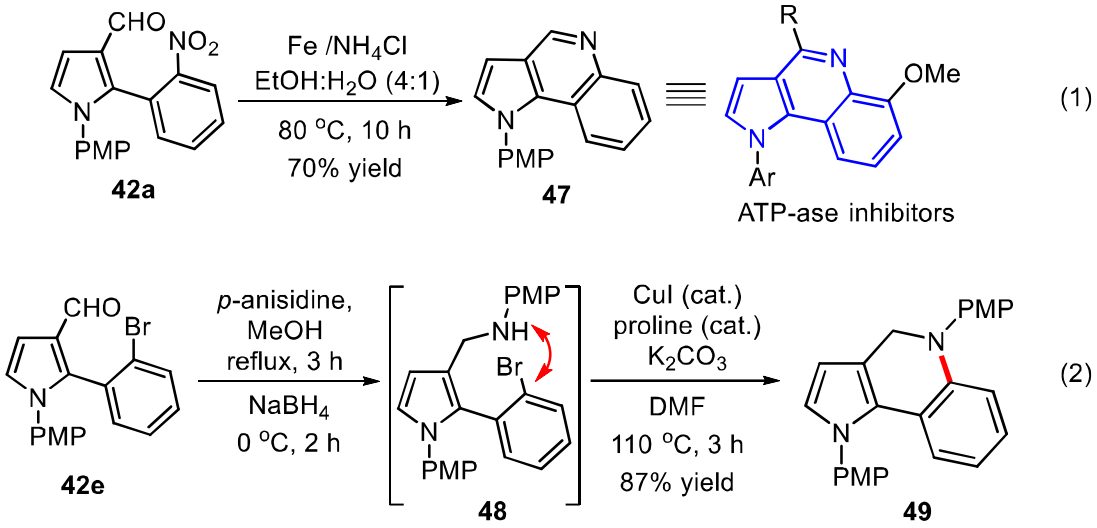
Scheme 2.15 Proposed reaction mechanism for this study

Based on our previous study, a stepwise mechanism is proposed to account for this reaction. As shown in **(Scheme 2.15)**, the enamine **A** *in situ* generated from succinaldehyde **38** and catalyst **40**, reacts with *in situ* generated *N*-PMP-imine **B** *via* a

direct *syn*-Mannich reaction model **C** to produced Mannich product **D**. The intermediate **D** underwent intramolecular cyclization to dihydropyrrole **E** with the simultaneous release of catalyst **40**. In the same pot, cyclic enamine-intermediate **E** underwent IBX-mediated oxidative aromatization to afford pyrrole-3-carboxaldehyde **46**.

2.4 Synthetic application

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 **47** was developed through reductive cyclization. This reaction proceeded *via in situ* amine formation through reduction of nitro-group of **42a** Fe/NH_4Cl in EtOH: H_2O (4:1), which underwent intramolecular cyclization with aldehyde group in the same pot with good yields (**eq.1, Scheme 2.16**). In another approach, the synthesis of pyrrole-dihydroquinoline **49** was accomplished through the reductive amination of **42e** with *p*-anisidine **44** in presence of $NaBH_4$ to generate *in situ* amine **48** which was further utilized for CuI-catalyzed intramolecular coupling (C-N) without purification to furnished **49** with high yield (87%) over two steps (**eq. 2, Scheme 2.16**).[130,131]

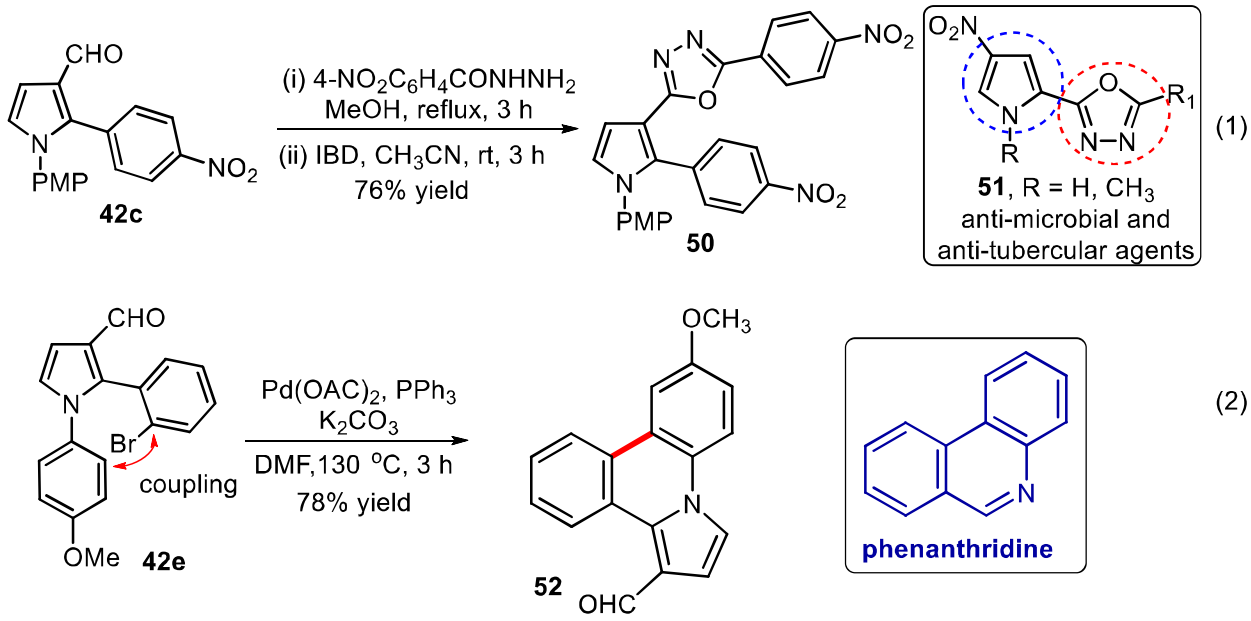


Scheme 2.16 Synthesis of pyrroloquinoline **47** and pyrrolo-dihydroquinoline**49**scaffolds

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.[132] The synthesized hybrid scaffolds resemble with various biologically active

molecules such as pyrrolo[3,2-*c*]-quinoline derivative, an ATP-ase inhibitor,[133] Pyrrolo[2,3-*c*]-quinoline derivative, a natural product with acetylcholinesterase-inhibiting activity,[134] and pyrrolo[3,4-*c*]quinoline derivative, a potent 5-HT4R antagonist with analgesic action.[135]

Further applications of our method were shown; (*i*) synthesis of pyrrole-oxadiazole**50** in good yield (76 %) over two steps from compound **42c** which was initially condensed with 4-nitrophenylhydrazide, followed by iodobenzenediacetate (IBD) mediated oxidative cyclization under the standardized conditions (**eq. 1, Scheme 2.17**),[136-138] and (*ii*) rapid and high yielding (78%) synthesis of pyrrole-phenanthridine (**52)** from **42e** through intramolecular C-C bond formation in presence $Pd(OAc)_2$, PPh_3 and K_2CO_3 in DMF at 130 ^oC **(eq. 2, Scheme 2.17)**. Interestingly, **52** 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.[139-144]



Scheme 2.17 Synthesis of pyrrole-oxadiazole **50**, and pyrrole-phenanthridine **52** moieties

2.5 Conclusions

In summary, we have developed a straight forwarded sequential multicomponent synthesis of substituted *N*-Aryl-pyrrole-3-carboxaldehydes. This one-pot protocol

proceeds through a 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, dihydropyrrooquinoline, and pyrrole-phenanthridines.

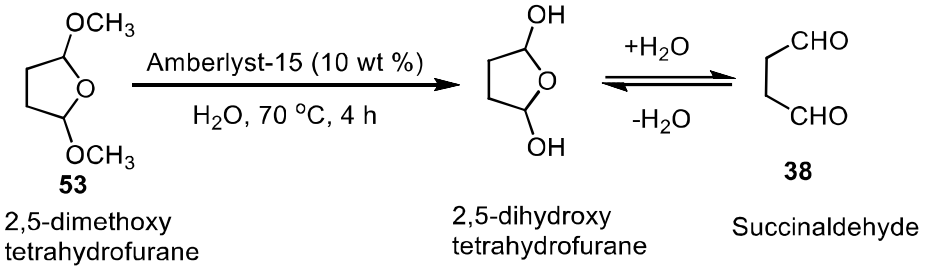
2.6 ExperimentalMethods

General Remark: 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. ^{1}H-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 ($CDCl_3$= δ 7.26 for ^{1}H, and 77.0 for ^{13}C-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. ^{13}C-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 ananalyzer. 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.

2.7 Preparation of succinaldehyde 6 (3M solution)

Amberist-15 (10 wt %) was added to the solution of 2,5-dimethoxytetrahydrofurane (2.0 g, 15.15 mmol) in H_2O (5.0 mL) followed by stirred along with heating for 4 h at 70 ^{o}C in

an open flask. The final solution obtained was very bitter in smell, cooled to room temperature and directly used for the above mentioned reaction.



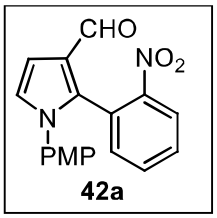
Scheme 2.18 Synthesis of succinaldehyde

2.8 Typical procedure for the synthesis of pyrrole-3-carboxaldehydes

To a stirred solution of Ar/HetAr-aldehyde **43** (0.3 mmol) or *N*-protected indole-3-aldehyde **45** (0.3 mmol) in DMSO (3.0 mL) was added *p*-anisidine **44** (0.3 mmol) and stirred initially for 2 hrs at rt. To this *in situ* generated-imine solution was added succinaldehyde **38** (0.3 mL, 0.9 mmol, 3M solution) and proline **40** (7.0 mg, 0.06 mmol) at the same temperature. The combined reaction mixture was stirred further for 8 hrs at rt. At that time, IBX (100 mg, 0.36 mmol, 1.2 equiv.) was added to the reaction mixture and heated at 70 ^{o}C for additional 3 hrs. The reaction was cooled to room temperature quenched with $NaHCO_3$solution (10% solution, 5 mL) and extracted with EtOAc (3 x 6 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 anhydrous, and concentrated under reduced pressure. Purification through silica gel column chromatography by eluting the mixture of hexane/EtOAc, gave pyrrole-3-carbaldehydes **42** or **46** 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.

2.9.1 Analytical data of synthesized compounds (42a-42o)

1-(4-methoxyphenyl)-2-(2-nitrophenyl)-1*H*-pyrrole-3-carbaldehyde (42a)

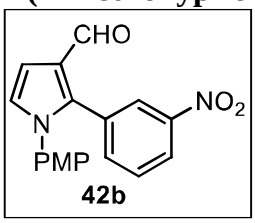


42a

Reddish semi-solid(70 mg, 72%); ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{18}H_{14}N_2O_4$(MH$^+$) 323.1032; Found 323.1033.

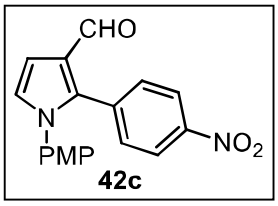
1-(4-methoxyphenyl)-2-(3-nitrophenyl)-1*H*-pyrrole-3-carbaldehyde (42b)



42b

Semi-solid (75 mg, 78%);^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{18}H_{14}N_2O_4$ (MH$^+$) 323.1032; Found 323.1033.

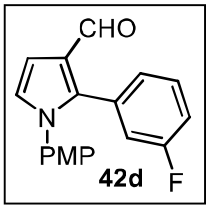
1-(4-methoxyphenyl)-2-(4-nitrophenyl)-1*H*-pyrrole-3-carbaldehyde (42c)



42c

pale yellow solid (M.P =102-104 ºC) (74 mg, 80%); ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (75MHz, $CDCl_3$) 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 $C_{18}H_{14}N_2O_4$ (MH$^+$) 323.1032; Found 323.1028.

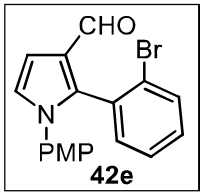
2-(3-fluorophenyl)-1-(4-methoxyphenyl)-1*H*-pyrrole-3-carbaldehyde (42d)



42d

Yellow semi-solid(65 mg, 74%);^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{18}H_{14}FNO_2$ (MH$^+$) 296.1087; Found 296.1070.

2-(2-bromophenyl)-1-(4-methoxyphenyl)-1*H*-pyrrole-3-carbaldehyde (42e)

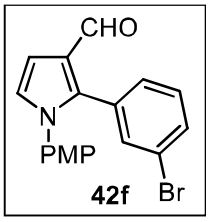


42e

Red viscous liquid (80 mg, 75%); ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (75

MHz, $CDCl_3$) 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 $C_{18}H_{14}BrNO_2$ (MH^+) 356.0286; Found 356.0295.

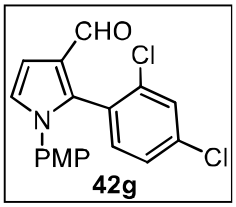
2-(3-bromophenyl)-1-(4-methoxyphenyl)-1*H*-pyrrole-3-carbaldehyde (42f)



42f

Brown semi-solid(81 mg, 76%); ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{18}H_{14}BrNO_2$ (MH^+) 356.0286; Found 356.0288.

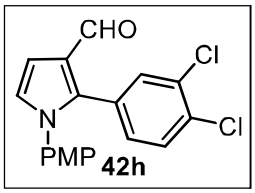
2-(2,4-dichlorophenyl)-1-(4-methoxyphenyl)-1*H*-pyrrole-3-carbaldehyde (42g)



42g

Yellow oily liquid (77 mg, 70%); ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{18}H_{13}Cl_2NO_2$ (MH^+) 346.0401; Found 346.0408.

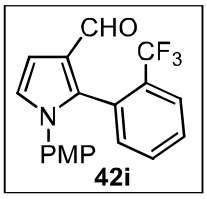
2-(3,4-dichlorophenyl)-1-(4-methoxyphenyl)-1*H*-pyrrole-3-carbaldehyde (42h)



42h

Yellow semi-solid(80 mg, 73%); ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{18}H_{13}Cl_2NO_2$ (MH^+) 346.0401; Found 346.0406.

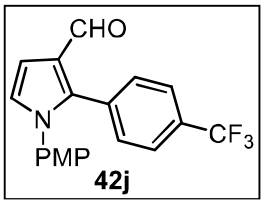
1-(4-methoxyphenyl)-2-(2-(trifluoromethyl)phenyl)-1*H*-pyrrole-3-carbaldehyde (42i)



42i

Yellow semi-solid(75 mg, 68%); ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{19}H_{14}F_3NO_2$ (MH^+) 346.1055; Found 346.1057.

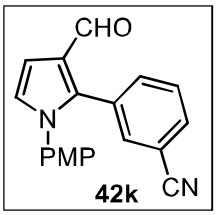
1-(4-methoxyphenyl)-2-(4-(trifluoromethyl)phenyl)-1*H*-pyrrole-3-carbaldehyde (42j)



42j

Yellow semi-solid(85 mg, 78%); ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{19}H_{14}F_3NO_2$ (MH^+)346.1055; Found 346.1053.

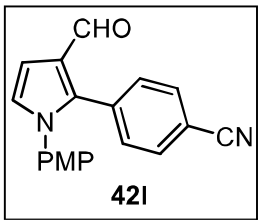
3-(3-formyl-1-(4-methoxyphenyl)-1*H*-pyrrol-2-yl)benzonitrile (42k)



42k

Yellow semi-solid(67 mg, 74%);^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{19}H_{14}N_2O_2$ (MH^+) 303.1134; Found 303.1134.

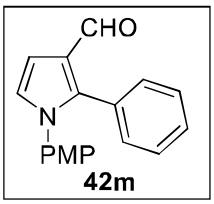
4-(3-formyl-1-(4-methoxyphenyl)-1*H*-pyrrol-2-yl) benzonitrile (42l)



42l

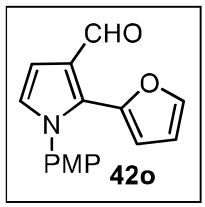
Pink semi-solid(72 mg, 80%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.81 (s, 3H), 6.85 (d, *J* = 8.9 Hz, 2H), 6.89 (d, *J* = 3.0 Hz, 1H), 6.94 (d, *J* = 2.5 Hz, 1H), 7.01 (d, *J* = 8.8 Hz, 2H), 7.32 (d, *J* = 8.3 Hz, 2H), 7.60 (d, *J* = 8.3 Hz, 2H), 9.72 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.5, 108.9, 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 $C_{19}H_{14}N_2O_2$ (MH^+) 303.1134; Found 303.1134.

1-(4-methoxyphenyl)-2-phenyl-1*H*-pyrrole-3-carbaldehyde (42m)



Yellow semi-solid(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 $C_{18}H_{15}NO_2$ (MH+) 278.1181; Found 278.1189.

1-(4-methoxyphenyl)-2-(pyridin-3-yl)-1*H*-pyrrole-3-carbaldehyde (42n) Red oily liquid (58 mg, 70%); ^{1}H 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 $C_{17}H_{14}N_2O_2$ (MH^+) 279.1133; Found 279.1140.

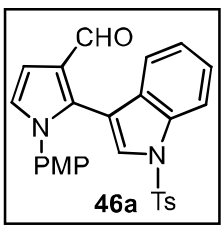


2-(furan-2-yl)-1-(4-methoxyphenyl)-1*H*-pyrrole-3-carbaldehyde (42o)

Red oily liquid (51 mg, 64%); ^{1}H 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 $C_{16}H_{13}NO_3$ (MH^+) 268.0974; Found 268.0980.

2.9.2Analytical data of synthesized compounds (46a-46r)

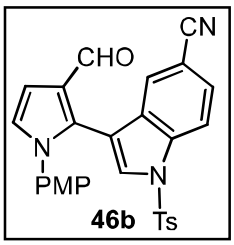
1-(4-methoxyphenyl)-2-(1-tosyl-1*H*-indol-3-yl)-1*H*-pyrrole-3-carbaldehyde (46a)



Yellow solid (107 mg, 76%, M.P. = 119-121 ^{o}C);^{1}H 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 $C_{27}H_{22}N_2O_4S$ (MH^+) 471.1378; Found 471.1382.

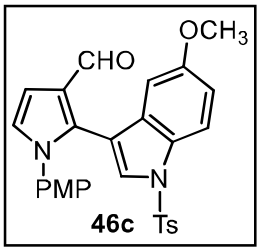
3-(3-formyl-1-(4-methoxyphenyl)-1*H*-pyrrol-2-yl)-1-tosyl-1*H*-indole-5-carbonitrile



46b

(46b) Brown solid (101 mg, 73%, M.P = 123-125 °C); ^{1}H 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), 7.00-703 (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 $C_{28}H_{21}N_3O_4S$ (MH^+) 496.1331; Found 496.1336.

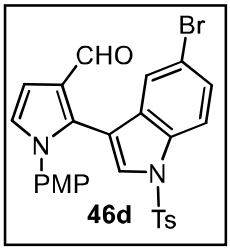
2-(5-methoxy-1-tosyl-1*H*-indol-3-yl)-1-(4-methoxyphenyl)-1*H*-pyrrole-3-



46c

carbaldehyde (46c) Red solid (105 mg, 70%, M.P = 127-129 °C); ^{1}H 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$C_{28}H_{24}N_2O_5S$ (MH^+) 501.1484; Found 501.1488.

2-(5-bromo-1-tosyl-1*H*-indol-3-yl)-1-(4-methoxyphenyl)-1*H*-pyrrole-3-carbaldehyde

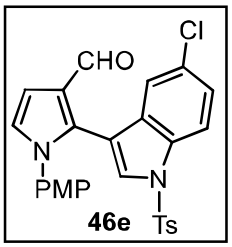


46d

(46d) Yellow solid (115 mg, 70%, M.P = 139-141 °C); ^{1}H 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

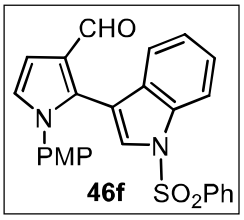
Hz , 1H), 9.57 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 29.6, 55.5, 108.5, 110.9, 114.4 (2C), 115.0, 117.5, 123.1, 125.8, 125.9, 126.6 (2C), 126.8 (2C), 128.3, 128.3, 130.1 (2C), 131.5, 131.8, 132.3, 133.1, 134.4, 145.7, 159.1, 185.8; IR (KBr)/cm^{-1} 2924, 2854, 1720, 1666, 1512, 1250, 1119; HRMS (ESI): Calcd for $C_{27}H_{21}BrN_2O_4S$ (MH^+) 549.0483; Found 549.0488.

2-(5-chloro-1-tosyl-1*H*-indol-3-yl)-1-(4-methoxyphenyl)-1*H*-pyrrole-3-carbaldehyde

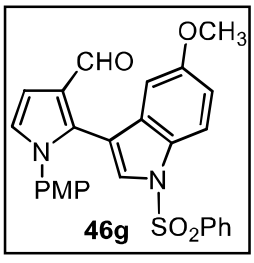


(46e) Brown solid (102 mg, 68%, M.P =134-136 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.17 (s, 3H), 3.58 (s, 3H), 6.52 (d, J = 8.9 Hz, 2H), 6.67 (d, J = 3.1 Hz, 1H), 6.76 (dd, J = 2.4 Hz, 1H), 6.80 (d, J = 8.9 Hz, 2H), 6.95 (d, J = 1.9 Hz, 1H), 7.02-7.05 (m, 4H), 7.40 (d, J = 8.4 Hz, 2H), 7.65 (d, J = 8.8 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 $C_{27}H_{21}ClN_2O_4S$ (MH^+) 505.0911; Found 505.0916.

1-(4-methoxyphenyl)-2-(1-(phenylsulfonyl)-1*H*-indol-3-yl)-1*H*-pyrrole-3-carbaldehyde (46f) Brown solid (96 mg, 70%, M.P = 117-119 °C); ^{1}H 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 $C_{26}H_{20}N_2O_4S$ (MH^+) 457.1222; Found 457.1226.

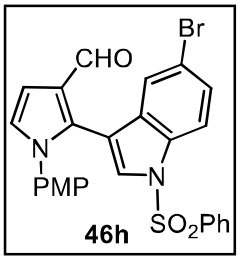


2-(5-methoxy-1-(phenylsulfonyl)-1*H*-indol-3-yl)-1-(4-methoxyphenyl)-1*H*-pyrrole-3-carbaldehyde (46g) Yellow viscous liquid (99 mg, 68%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.64 (s, 3H), 3.77 (s, 3H), 6.56 (d, J = 2.4 Hz, 1H), 6.70 (d, J = 8.9 Hz, 2H), 6.88-6.91 (m, 2H), 6.98 (d, J = 2.4 Hz, 1H), 7.00 (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

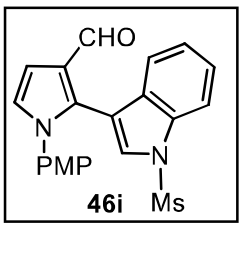


(75 MHz, $CDCl_3$) δ 55.4, 55.5, 102.0, 108.2, 111.8, 114.3 (2C), 114.5, 115.0, 125.6, 125.8, 126.3 (2C), 126.6 (2C), 127.8, 129.1, 129.3 (2C), 131.1, 131.7, 133.3, 134.0, 137.6, 156.9, 158.9, 186.1; IR (KBr)/cm^{-1} 2924, 2854, 1728, 1666, 1512, 1466, 1250, 1180; HRMS (ESI): Calcd for $C_{27}H_{22}N_2O_5S$ (MH^+) 487.1327; Found 487.1332.

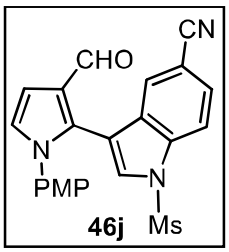
2-(5-bromo-1-(phenylsulfonyl)-1*H*-indol-3-yl)-1-(4-methoxyphenyl)-1*H*-pyrrole-3-carbaldehyde (46h) Brownish yellow gummy liquid (107 mg, 67%); ^1H NMR (400 MHz, $CDCl_3$) δ 3.82 (s, 3H), 3.76 (d, J = 8.9 Hz, 2H), 6.91 (d, J = 3.1 Hz, 1H), 7.00 (d, J = 3.1 Hz, 1H), 7.3 (d, J = 8.9 Hz, 2H), 7.35 (d, 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 $C_{26}H_{19}BrN_2O_4S$ (MH^+) 535.0319; Found 535.0325.



1-(4-methoxyphenyl)-2-(1-(methylsulfonyl)-1*H*-indol-3-yl)-1*H*-pyrrole-3-carbaldehyde (46i) Yellow semi-solid(82 mg, 70%); ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{21}H_{18}N_2O_4S$ (MH^+) 395.1065; Found 395.1070.

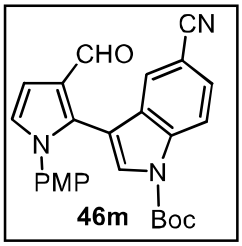


3-(3-formyl-1-(4-methoxyphenyl)-1*H*-pyrrol-2-yl)-1-(methylsulfonyl)-1*H*-indole-5-carbonitrile (46j) Brownish solid (85 mg, 68%, M.P = 114-116 ºC); ^1H NMR (400 MHz, $CDCl_3$) δ 3.17 (s, 3H), 3.77 (s, 3H), 6.8 (d, J = 8.9 Hz, 2H), 6.93 (d, J = 3.1 Hz, 1H), 7.03 (d, J = 2.6 Hz, 1H), 7.09 (d, J = 9.0 Hz, 2H), 7.53 (m,1H), 7.58 (d, J = 7.1 Hz, 1H), 7.99-8.03 (m, 2H), 9.73 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 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,

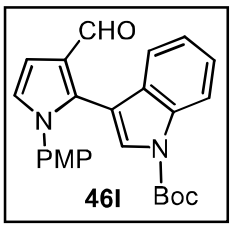


1180; HRMS (ESI): Calcd for $C_{22}H_{17}N_3O_4S$ (MH^+) 419.0940; Found 419.0946.

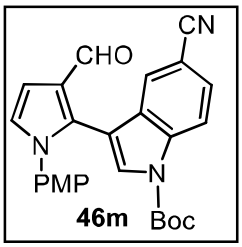
2-(5-chloro-1-(methylsulfonyl)-1*H*-indol-3-yl)-1-(4-methoxyphenyl)-1*H*-pyrrole-3-carbaldehyde (46k) Yellowish solid (85 mg, 66%, M.P = 126-128 ºC); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.07 (s, 3H), 3.77 (s, 3H), 6.79 (d, *J* = 8.9 Hz, 2H), 6.91 (d, *J* = 3.1 Hz, 1H), 7.01 (d, *J* = 2.8 Hz, 1H), 7.08 (d, *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); ^{13}C NMR (75 MHz, $CDCl_3$) *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 $C_{21}H_{17}ClN_2O_4S$ (MH^+) 429.0676; Found 429.0682.



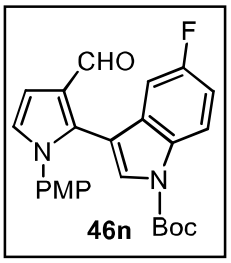
***tert*-butyl-3-(3-formyl-1-(4-methoxyphenyl)-1*H*-pyrrol-2-yl)-1*H*-indole-1-carboxylate (46l)** White solid, (92 mg, 74%, M.P = 117-119 ºC); ^{1}H NMR (400 MHz, $CdCl_3$), *δ* 1.67 (s, 9H), 3.74 (s, 3H), 6.66 (d, *J* = 9.0 Hz, 2H), 6.92 (d, *J* = 3.2 Hz, 1H), 6.98 (d, *J* = 2.5 Hz, 1H), 7.07-7.16 (m, 5H), 7.28-7.30 (m, 1H), 7.57 (s, 1H), 8.12 (d, *J* = 8.1 Hz, 1H), 9.36 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) *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 $C_{25}H_{24}N_2O_4$ (MH^+) 417.1814; Found 417.1820.



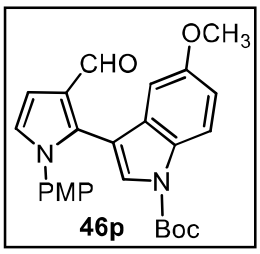
***tert*-butyl-5-cyano-3-(3-formyl-1-(4-methoxyphenyl)-1*H*-pyrrol-2-yl)-1*H*-indole-1-carboxylate (46m)** Reddish brown solid (95 mg, 72%, M.P =120-122 ºC); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 1.05 (s, 9H), 3.59 (s, 3H), 6.53 (d, *J* = 8.9 Hz, 2H), 6.70 (d, *J* = 3.1 Hz, 1H), 6.82 (d, *J* = 9.0 Hz, 3H), 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); ^{13}C NMR (75 MHz, $CDCl_3$) *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 $C_{26}H_{23}N_3O_4$ (MH^+) 442.1767; Found 442.1774.



***tert*-butyl-5-fluoro-3-(3-formyl-1-(4-methoxyphenyl)-1*H*-pyrrol-2-yl)-1*H*-indole-1-carboxylate (46n)** Yellow solid (87 mg, 67%, M.P119-121 ºC); ^{1}H NMR (400 MHz, $CDCl_3$) 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), ^{13}C-NMR (75 MHz, $CDCl_3$), *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 $C_{25}H_{23}FN_2O_4$ (MH^+) 435.1720; Found 435.1726.

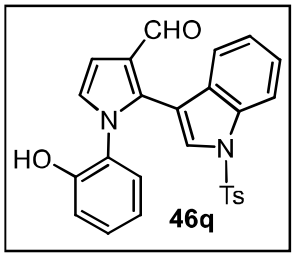


***tert*-butyl-5-bromo-3-(3-formyl-1-(4-methoxyphenyl)-1*H*-pyrrol-2-yl)-1*H*-indole-1-carboxylate (46o)** White solid (82 mg, 68%, M.P =129-131 ºC); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.66 (s, 9H), 3.02 (s, 3H), 6.79(d, *J* = 8.98 Hz, 2H), 6.90(d, *J* = 3.12 Hz, 1H), 6.98 (d,*J* = 3.9 Hz, 1H), 7.12 (d, *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), ^{13}C NMR (75 MHz, $CDCl_3$), *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 $C_{25}H_{23}BrN_2O_4$ (MH^+) 495.0919; Found 405.0924.



***tert*-butyl-3-(3-formyl-1-(4-methoxyphenyl)-1*H*-pyrrol-2-yl)-5-methoxy-1*H*-indole-1-carboxylate (46p)** dark brown solid (89 mg, 70%, M.P =124-126 ºC); (400 MHz, $CDCl_3$), *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); ^{13}C-NMR (100 MHz, $CDCl_3$) *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 $C_{26}H_{26}N_3O_5$ (MH^+) 425.1171; Found 425.1176.

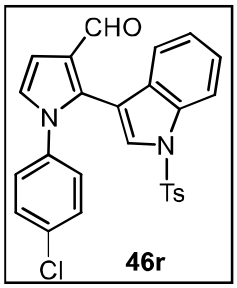
1-(2-hydroxyphenyl)-2-(1-tosyl-1*H*-indol-3-yl)-1*H*-pyrrole-3-carbaldehyde



46q

(46q) Light yellow solid (82 mg, 60%, M.P =118- 120 ºC); ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) *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 $C_{26}H_{20}N_2O_4S$ (MH^+) 457.1222; Found 457.1227.

1-(4-chlorophenyl)-2-(1-tosyl-1*H*-indol-3-yl)-1*H*-pyrrole-3-carbaldehyde (46r) Light

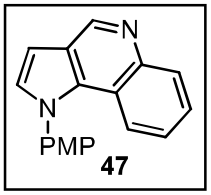


46r

pinkish solid (91 mg, 64%, M.P =132-134 ºC) ^{1}H NMR (400 MHz, $CDCl_3$) *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), ^{13}C NMR (75 MHz, $CDCl_3$) *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 $C_{26}H_{19}ClN_2O_3S$ (MH^+) 475.0883; Found 475.0888.

2.10 1-(4-methoxyphenyl)-1*H*-pyrrolo [3,2-*c*] quinoline (47)

To a stirred solution of **42a** (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 ºC 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 **47** as semi-solid yellow liquid (28 mg, 67% yield).



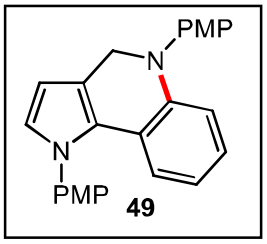
47

^{1}H 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 $C_{18}H_{14}N_2O(MH^+)$275.1185; Found 275.1190.

2.11 1,5-bis(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrrolo[3,2-*c*] quinoline (49)

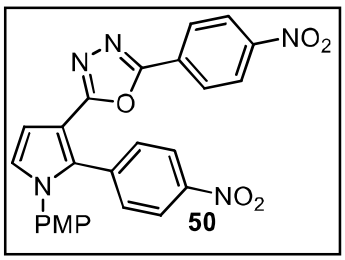
A mixture of **42e** (0.1g, 0.28 mmol, 1.0 equiv) and *p*-anisidine **44** (0.030g, 0.28 mmol, 1.0 equiv) in methanol (3 mL) was refluxed for 2 hrs at 80 ºC and followed by reductive amination in the presence of $NaBH_4$ at 0 ºC to obtain intermediate product. This crude intermediate **48** (0.1g, 0.22 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, 0.44mmol, 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 **49** as yellow semi-solid(70 mg, 87% yield).



49

^{1}H 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 $C_{25}H_{22}N_2O_2$ (MH^+) 383.1759; Found 383.1765.

2.12 2-(1-(4-methoxyphenyl)-2-(4-nitrophenyl)-1H-pyrrol-3-yl)-5-(4-nitrophenyl)



50

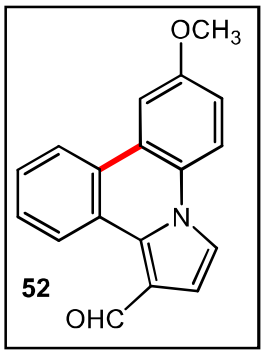
-1,3,4-oxadiazole (50) A mixture of **42c** (0.08g, 0.24 mmol, 1.0 equiv) and 4-nitrobenzohydrazide (0.044g, 0.24 mmol, 1.0 equiv) in methanol (3.0 mL) was stirred for 2 hours under 80 ºC and then concentrated *in vacuo*. The crude material was taken inCH_3CN (3.0mL) and IBD (0.08g, 0.24 mmol, 1.0 equiv.) was

added stirred at room temperature for one hour. The mixture was then concentrated in vacuo. To the residue was added H_2O (10mL) and the resulting mixture was extracted with ethylacetate (10 mLx3). 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 **50** as yellow solid (92 mg, 76% yield).

^{1}H NMR (400 MHz, $CDCl_3$) (MP = 112-115^{o}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 $C_{25}H_{17}N_5O_6$ (MH^+) 484.1258; Found 484.1263.

2.13 7-methoxypyrrolo [1, 2-*f*] phenanthridine-1-carbaldehyde (52)

A clean oven-dried 10 mL round-bottom flask was charged with **42e** (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 $Pd(OAc)_2$ (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 **52** as white solid (43 mg, 78% yield).



^{1}H 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 $C_{18}H_{13}BrNO_2$ (MH^+) 276.1024; Found 276.1029.

2.14.1 A representative ^{1}H and ^{13}C NMR of **(42h)** are shown in **(Figure 2.6)**.

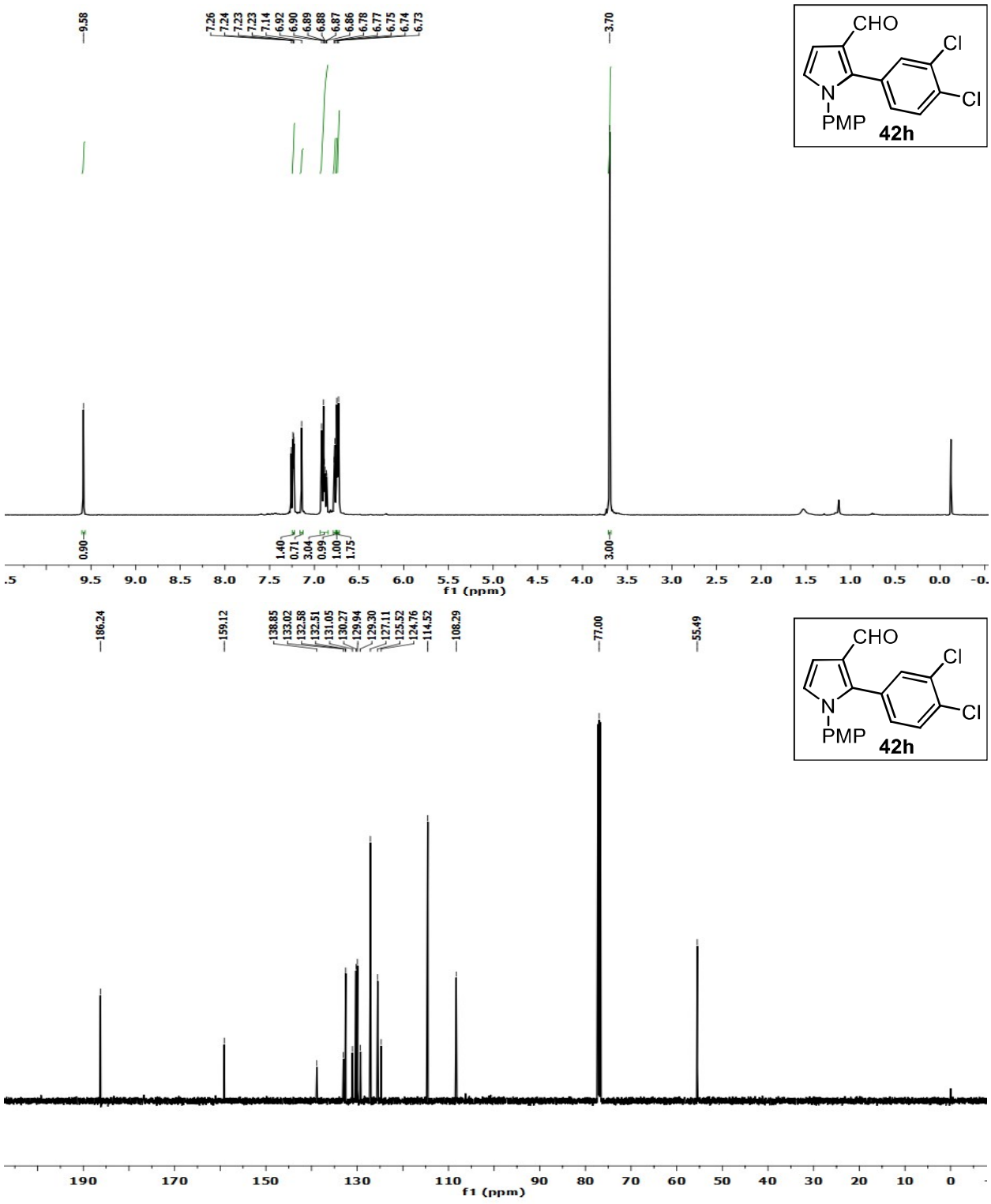


Figure 2.6 ^{1}H and ^{13}C NMR spectra of 2-(3,4-dichlorophenyl)-1-(4-methoxyphenyl)-1*H*-pyrrole-3-carbaldehyde **(42h)**

2.14.2 A representative ^{1}H and ^{13}C NMR of **(49)** are shown in **(Figure 2.7)**.

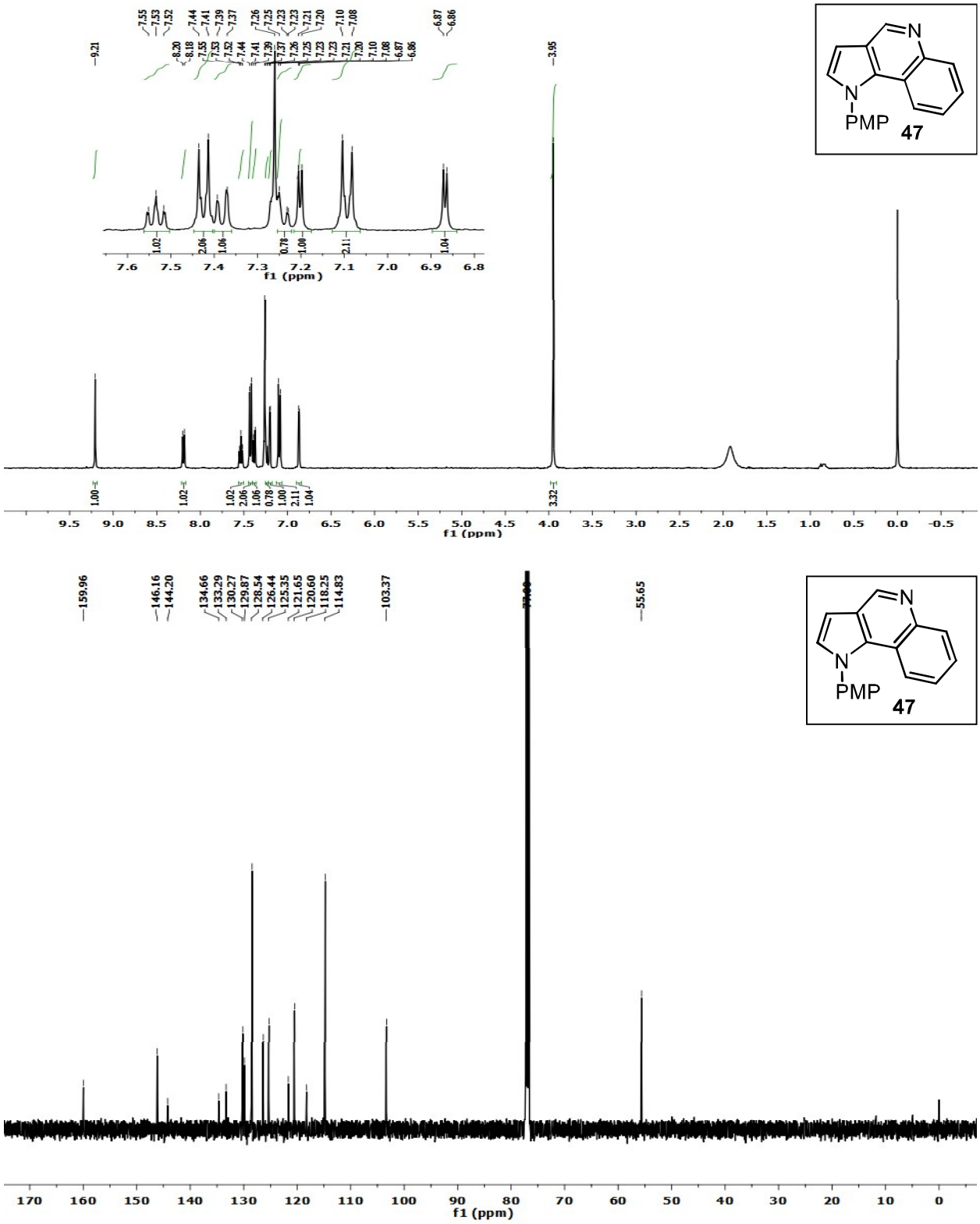


Figure 2.7 ^{1}H and ^{13}C NMR spectra of 1-(4-methoxyphenyl)-1*H*-pyrrolo [3,2-*c*] quinoline **(47)**

2.14.3 A representative ^{1}H and ^{13}C NMR of **(49)** are shown in **(Figure 2.8)**.

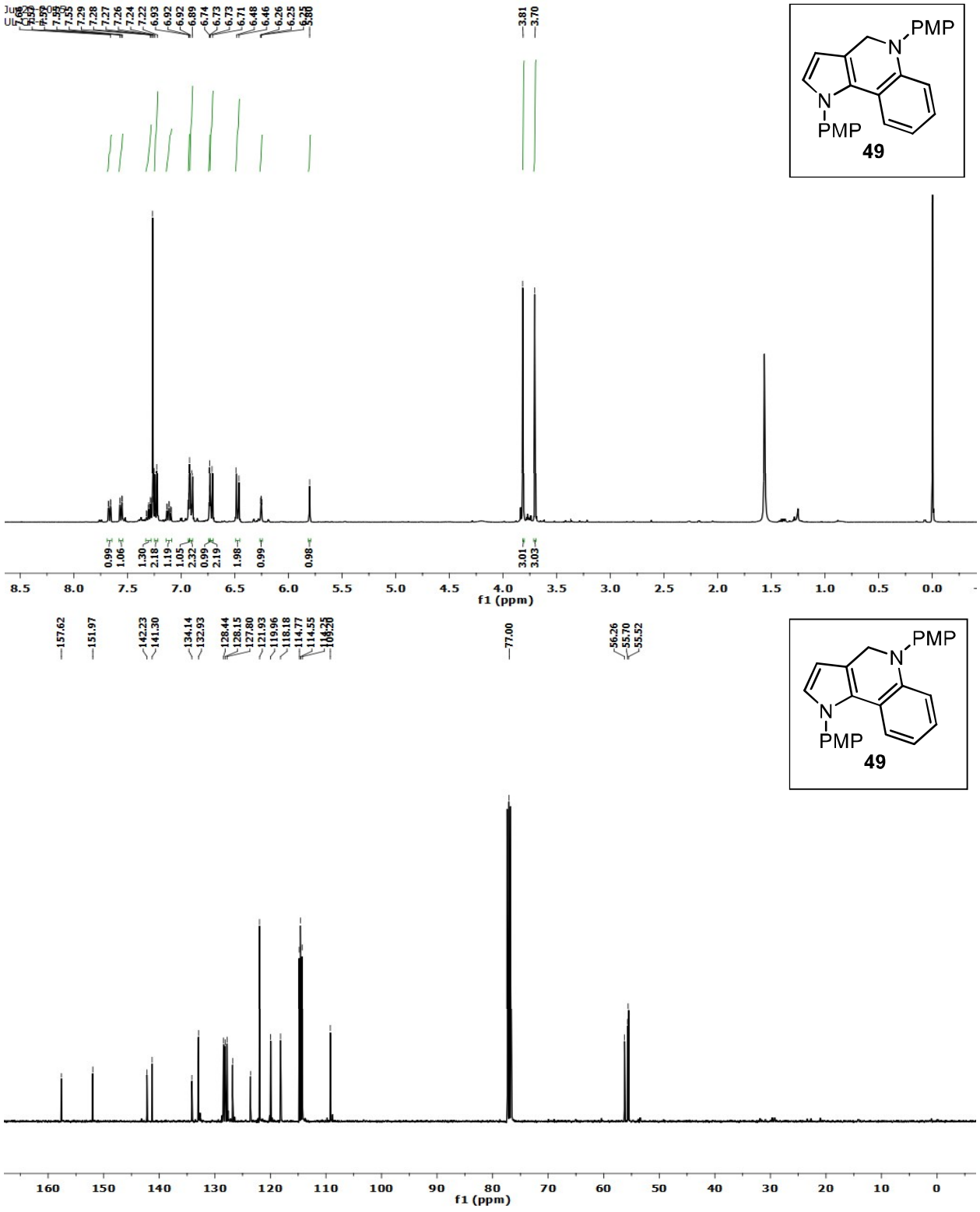


Figure 2.8 ^{1}H and ^{13}C NMR spectra of 1,5-bis(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrrolo[3,2-*c*] quinoline **(49)**

2.14.4 A representative ^{1}H and ^{13}C NMR of **(50)** are shown in **(Figure 2.9)**.

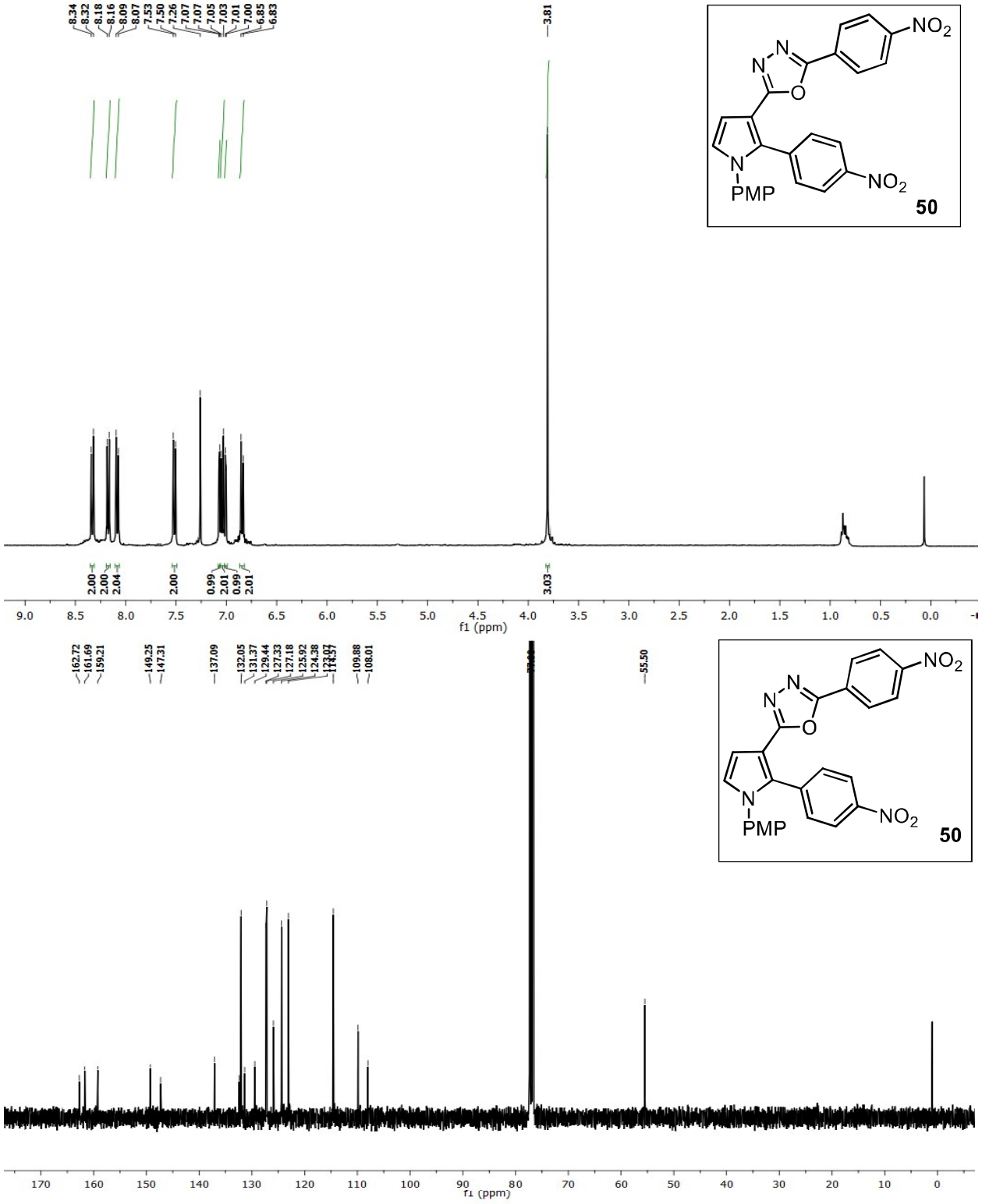


Figure 2.9 ^{1}H and ^{13}C NMR spectra of 2-(1-(4-methoxyphenyl)-2-(4-nitrophenyl)-1H-pyrrol-3-yl)-5-(4-nitrophenyl)-1,3,4-oxadiazole **(50)**

2.14.5 A representative ^{1}H and ^{13}C NMR of **(52)** are shown in **(Figure 2.10)**.

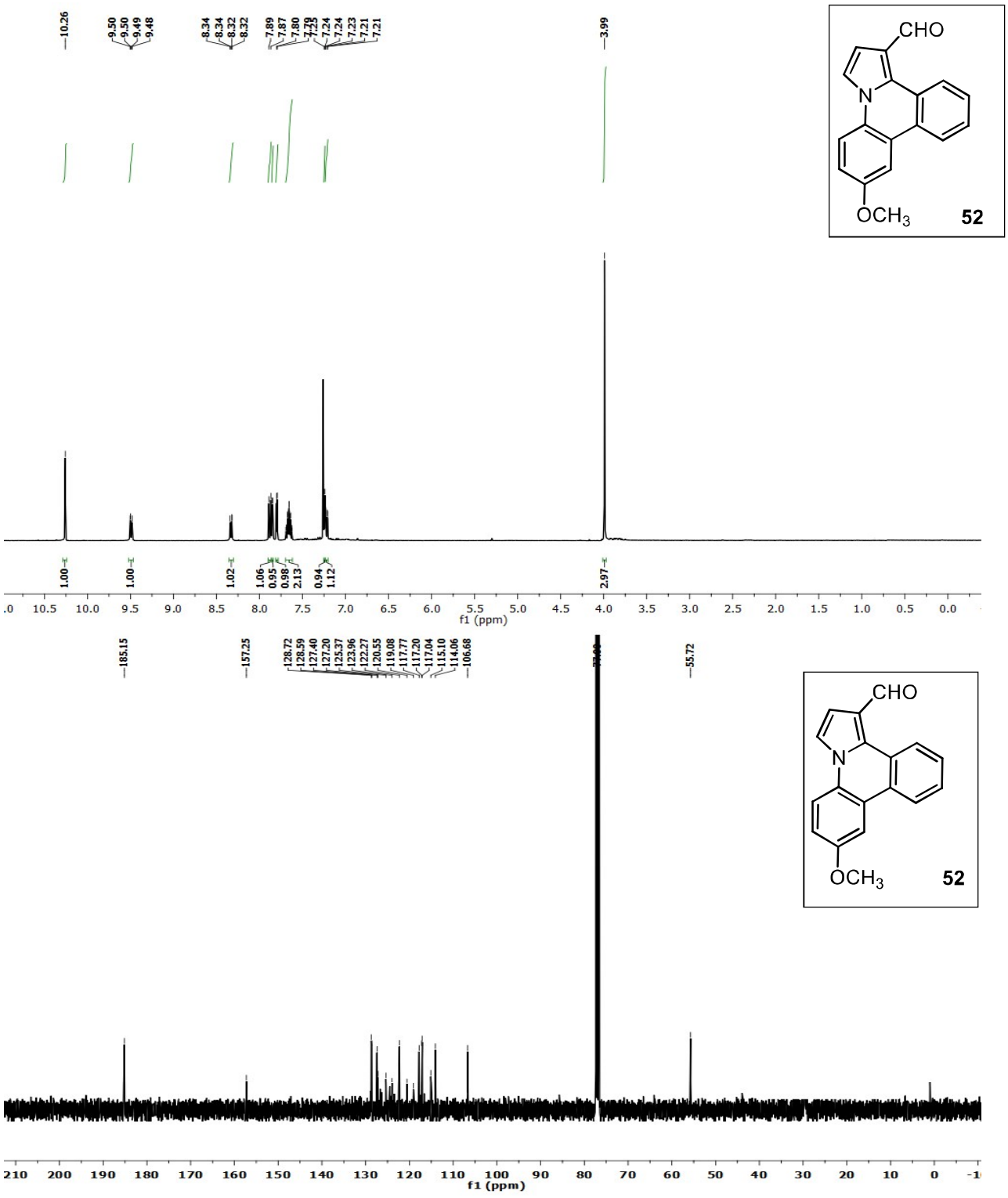


Figure 2.10 ^{1}H and ^{13}C NMR spectra of 7-methoxypyrrolo [1, 2-*f*] phenanthridine-1-carbaldehyde **(52)**

2.14.6 A representative ^{1}H and ^{13}C NMR of **(46g)** are shown in **(Figure 2.11)**.

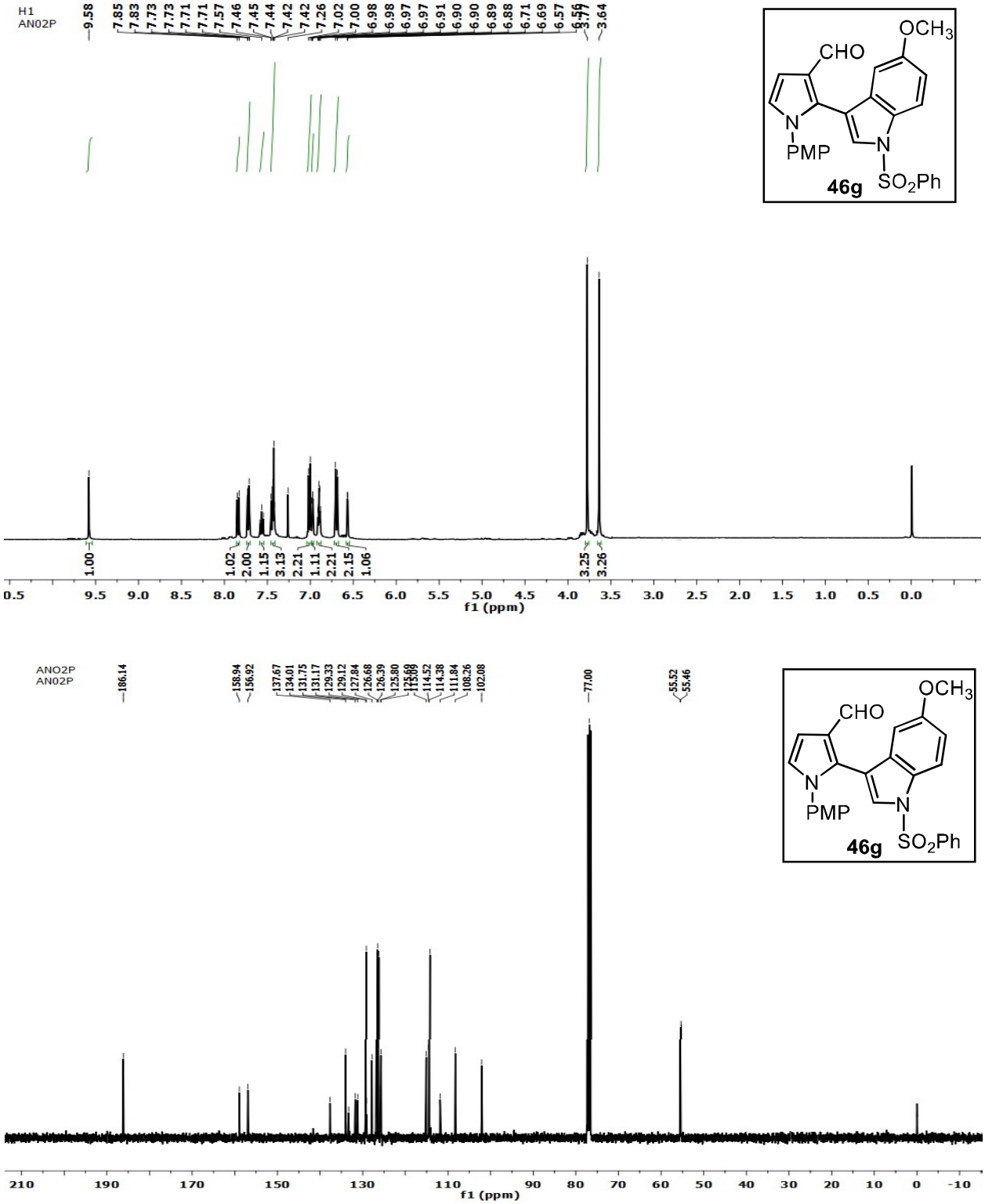
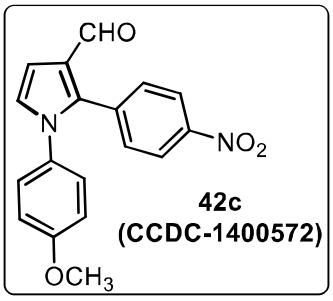


Figure 2.11 ^{1}H and ^{13}C NMR spectra of 2-(5-methoxy-1-tosyl-1*H*-indol-3-yl)-1-(4-methoxyphenyl)-1*H*-pyrrole-3-carbaldehyde **(46g)**

2.15.1 Crystal structure of 1-(4-methoxyphenyl)-2-(4-nitrophenyl)-1*H*-pyrrole-3-carbaldehyde (42c)



The compound 1-(4-methoxyphenyl)-2-(4-nitrophenyl)-1H-pyrrole-3-carbaldehyde, $C_{18}H_{14}N_2O_4$,crystallizes in the orthorhombic space group $P2_12_12_1$ with the unit-cell parameters: a= 8.0230(6), b= 10.5211(8), c= 18.4479(16) Å and Z = 4. The crystal structure was solved by direct methods using single-crystal X-ray diffraction data collected at room temperature and refined by full-matrix least-squares procedures to a final R-value of 0.0511 for 1184 observed reflections.

Crystal structure determination and refinement

X-ray intensity data of 4243 reflections (of which 1762 unique) were collected on *X'calibur*CCD area-detector diffractometer equipped with graphite monochromatedMoKα radiation (λ = 0.71073 Å). The crystal used for data collection was of dimensions 0.30 x 0.20 x 0.20 mm. The cell dimensions were determined by a least-squares fit of angular settings of 1096 reflections on the θ range 3.85 to 25.01°**.** The intensities were measured by ώ scan mode for θ ranges from 3.84 to 26.00°. 1184 reflections were treated as observed ($I > 2\sigma(I)$). Data were corrected for Lorentz, polarization and absorption factors. Direct methods SHELXS97 was used to solve this structure. All non-hydrogen atoms of the molecule were located in the best E-map. Full-matrix least-squares refinement was carried out using SHELXL97. The final refinement cycles converged to an R = 0.0511 and wR (F^2) = 0.0913 for the observed data. Residual electron densities ranged from $-0.194 < \Delta\rho < 0.143 eÅ^{-3}$. Atomic scattering factors were taken from International Tables for X-ray Crystallography (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4). The crystallographic data are summarized in **(Table 2.4)**. The geometry of the molecule was calculated using the WinGX, PARST, and PLATON software.

Table 2.4 Crystal and experimental data

CCDC	1400572
Crystal description	white block
Crystal size	0.3 X 0.2 X 0.2 mm
Empirical formula	$C_{18}H_{14}N_2O_4$
Formula weight	322.31
Radiation, Wavelength	Mo *K*α, 0.71073 Å
Unit cell dimensions	a= 8.0230(6), b= 10.5211(8),
c = 18.4479(16) Å	
Crystal system	orthorhombic
Space group	$P2_12_12_1$
Unit cell volume	1557.2(2)
No. of molecules per unit cell,	Z, 4
Temperature	293(2) K
Absorption coefficient	0.099 mm^{-1}
F(000)	672
Scan mode	ω scan
θ range for entire data collection	3.84 <θ<26.00
Range of indices	h= -8 to 9, k= -5 to 12, l= -13 to 22
Reflections collected / unique	4243/ 1762
Reflections observed (I > 2σ(I))	1184
R_{int}	0.0390
R_{sigma}	0.0639
Structure determination	Direct methods
Refinement	Full-matrix least-squares on F^2
No. of parameters refined	218
Final R	0.0511
wR(F^2)	0.0913
Weight	$1/[\sigma^2(F_o^2)+(0.0412 P)^2 +0.0000P]$
Where	$P=[F_o^2 +2F_c^2] / 3$

Goodness-of-fit	1.032
Final residual electron density	$-0.194<\Delta\rho<0.143 e Å^{-3}$
Measurement	*X'calibur system-Oxford diffraction make, U.K*
Software for structure solution:	SHELXS97 (Sheldrick, 2008)
Software for refinement:	SHELXL97 (Sheldrick, 2008)
Software for molecular plotting:	ORTEP-3 (Farrugia, 1997) PLATON
Software for geometrical calculation	PLATON (Spek, 2009) PARST (Nardelli, 1995)

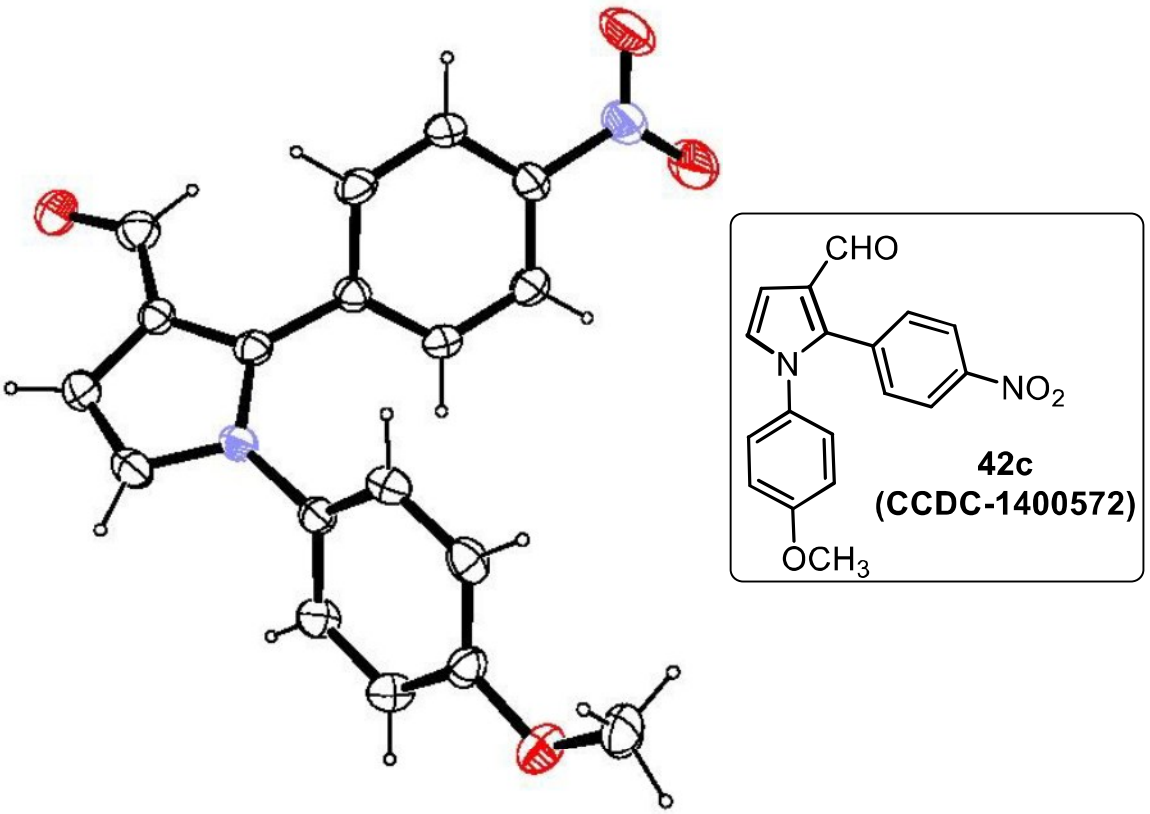
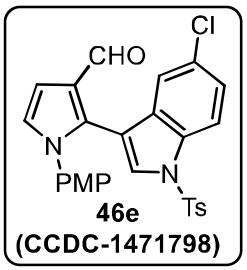


Figure 2.12 *ORTEP* view of the molecule with displacement ellipsoids drawn at 40%. H-atoms are shown as small spheres of arbitrary radii

2.15.2 Crystal structure of 2-(5-chloro-1-tosyl-1*H*-indol-3-yl)-1-(4-methoxyphenyl)-1*H*-pyrrole-3-carbaldehyde (46e)



The compound 2-(5-chloro-1-tosyl-1*H*-indol-3-yl)-1-(4-methoxyphenyl)-1*H*-pyrrole-3-carbaldehyde,$C_{27}H_{21}ClN_2O_4S$crystallizes in the monoclinic space group $P2_1/n$ with the following unit cell parameters: *a*=9.9462 (7), *b*= 15.4122 (9), *c*= 15.2477 (11) Å, β=96.432 (7)°and Z=4. The crystal structure was solved by direct methods and refined by full-matrix least-squares procedure to a final R-value of 0.051 for 2862 observed reflections.

Crystal structure determination and refinement

X-ray intensity data consisting of 10516 reflections were collected at 293(2) K, and 4546 reflections were found unique.A crystal of dimensions 0.30 x 0.20 x 0.20 mm was used for data collection on *X*'caliburCCD area-detector diffractometer, equipped with graphite monochromatedMo*Kα* radiation (λ=0.71073 Å).The intensities were measured by ω scan mode for θ ranges 3.7 to 26.0°. A total number of 2862 reflections were treated as observed [I>2σ(I)]. Data were corrected for Lorentz-polarization and absorption factors. Direct methods SHELXS97 was used to solve this structure.All non-hydrogen atoms of the molecule were located in the best E-map. All the hydrogen atoms were geometrically fixed and allowed to ride on the corresponding non-H atoms with C-H= 0.93-0.94 Å and U_{iso} = 1.2 U_{eq}(C), except for the methyl groups where U_{iso}(H) = 1.5U_{eq}(C). The refinement cycles converged the structure to a final *R*-factor of 0.0513 (w*R* (F^2) = 0.1128) for the 2862 observed reflections. Residual electron densities range from -0.271 to 0.270 eÅ^{-3}. Atomic scattering factors were taken from International Tables for X-ray Crystallography (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4). An ORTEPview of the compound with the atomic labeling scheme is shown in **Figure 2.7**. The geometry of the molecule was calculated using the PARSTandPLATONsoftware. Crystal data, along with data collection and structure refinement details are summarized (**Table 2.5)**

Table 2.5 Crystal and experimental Data

Chemical formula	$C_{26}H_{19}ClN_2O_3S$
CCDC No.	1471798
M_r	474.94
Crystal system, space group	Monoclinic, $p2_1/n$
Temperature (K)	293
a, b, c (Å)	9.9462 (7), 15.4122 (9), 15.2477 (11)
β (°)	96.432 (7)
V (Å^3)	2322.7 (3)
Z	4
Radiation type	Mo $K\alpha$
μ (mm^{-1})	0.29
Crystal size (mm)	0.30 × 0.20 × 0.20
T_{min}, T_{max}	0.625, 1.000
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	10516, 4546, 2862
R_{int}	0.041
$(\sin \theta/\lambda)_{max}$ (Å^{-1})	0.617
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.051, 0.113, 1.02
No. of reflections	4546
No. of parameters	311
No. of restraints	0
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.28, −0.27

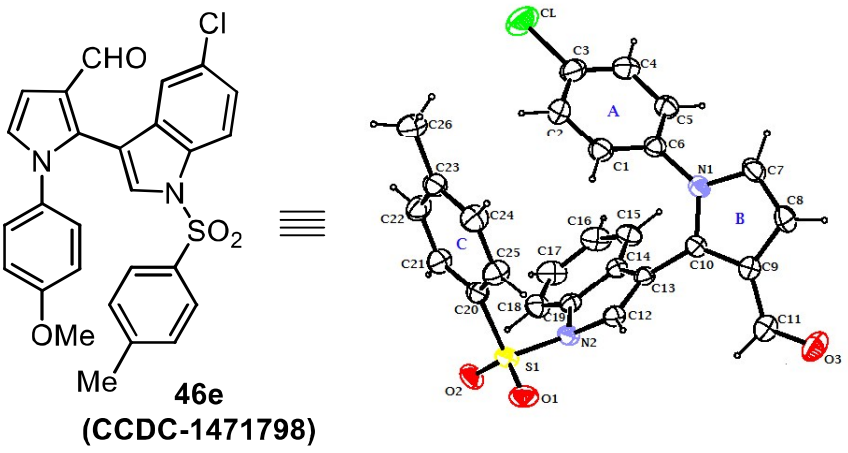


Figure 2.13 ORTEP view of the molecule with displacement ellipsoids drawn at the 40% probability level. H atoms are shown as small spheres of arbitrary radii.

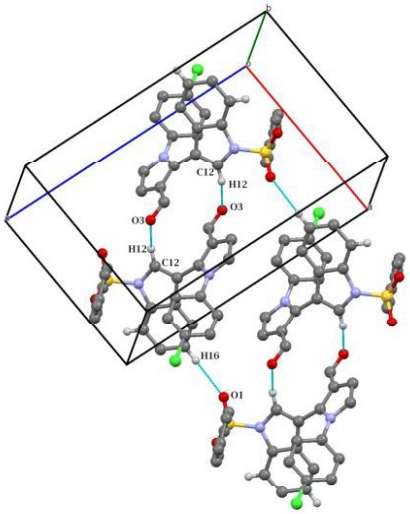


Figure 2.14 A dimer formed by intermolecular C-H…O hydrogen bonds

2.16 Notes and references

[1] Runge, F. F. *Ann. Physk*. **1834**, *31*, 67.

[2] Harreus, A. L. **2005**, "Pyrrole", *Ullmann's Encyclopedia of Industrial Chemistry*, Weinheim: Wiley-VCH, doi:10.1002/14356007.a22_453

[3] Armarego, W.; Chai, L. F.; Christina, L. L. Purification of Laboratory Chemicals (5th Ed.) Elsevier. **2003**, 346.

[4] Katritzky, A. R.; Huang, T. B.; Voronkov, M. V.; Wang, M.; Kolb, H. *J. Org. Chem*. **2000**, *65*, 8819.

[5] Martin, R.; Larsen, C. H.; Cuenca, A.; Buchwald, S. L. *Org. Lett*. **2007**, *9*, 3379.

[6] St. Cyr, D. J.; Arndtsen, B. A. *J. Am. Chem. Soc*. **2007**, *129*, 12366.

[7] Chiba, S.; Wang, Y. F.; Lapointe, G.; Narasaka, K. *Org. Lett*. **2008**, *10*, 313.

[8] Guillena, G.; Ramon, D. J.; Yus, M. *Tetrahedron: Asymmetry*. **2007**, *18*, 693.

[9] Raposo, M. M. M.; Fonseca, A. M. C.; Castro, M. C. R.; Belsley, M.; Cardoso, M. F. S.; Carvalho, L. M.; Coelho, P. J. *Dyes Pigm*. **2011**, *91*, 62.

[10] Takase, M.; Yoshida, N.; Narita, T.; Fujio, T.; Nishinaga, T.; Iyoda, M. *RSC Adv*. **2012**, *2*, 3221.

[11] Wienk, M. M.; Turbiez, M.; Gilot, J.; Janssen, R. A. *J. Adv. Mater*. **2008**, *20*, 2556.

[12] Wang, Y.; Sotzing, G. A.; Weiss, R. A. *Chem. Mater*. **2008**, *20*, 2574.

[13] Ibrahim, S. K.; Liu, X. M.; Tard, C.; Pickett, C. J. *Chem. Commun*. **2007**,1535.

[14] Higgins, S. J. *Chem. Soc. Rev*. **1997**, *26*, 247.

[15] Lee, C. F.; Yang, L. M.; Hwu, T. Y.; Feng, A. S.; Tseng, J. C.; Luh, T. Y.*J. Am. Chem. Soc.* **2000**, *122*, 4992.

[16] D'Silva, C.; Walker, D. A. *J. Org. Chem*. **1998**, *63*, 6715.

[17] Berlin, A.; Vercelli, B.; Zotti, G. *Polym. Rev*. **2008**, *48*, 493.

[18] Jusélius, Jonas; Sundholm, Dage. "The aromatic pathways of porphins, chlorins and bacteriochlorins, *Phys. Chem. Chem. Phys.* 2 (*10*): 2145]

[19] Joule, J. A.; Mills, K. *Heterocyclic Chemistry*. 4th ed., Blackwell, Oxford.2000.

[20] Eicher, T.; Hauptmann, S. *The Chemistry of Heterocycles*. Wiley-VCH, Weinheim.**2003**

[21] Katrizky, A. R.; Pozharskii, A. F. *Handbook of Heterocyclic Chemistry*. 2nd ed., Pergamon, Amsterdam. **2000**.

[22] Young, I. S.; Thornton, P. D.; Thompson, A. *Nat. Prod. Rep*. **2010**, *27*, 1801.

[23] Baumann, M.; Baxendale, I. R.; Ley, S. V.; Nikbin, N. *Beilstein J. Org. Chem*. **2011**, *7*, 442.

[24] Corvo, M. C.; Pereira, M. A. *Tetrahedron. Lett*. **2002**, *43*, 455.

[25] Biava, M.; Porretta, G. C.; Deidda, D.; Pompei, R.; Tafic, A.; Manettic, F. *Bioorg. Med. Chem*. **2004**, *12*, 1453.

[26] Protopopova, M.; Bogatcheva, E.; Nikonenko, B.; Hundert, S.; Einck L.; Nacy, C. A. *Med. Chem*. **2007**, *3*, 301.

[27] Teixeira, C.; Barbault, F.; Rebehmed, J.; Liu, K.; Xie, L.; Lu, H.; Jiang, S.; Fan B.; Maurel, F. *Bioorg. Med. Chem*. **2008**, *16*, 3039.

[28] Daidone, G.; Maggio, B.; Schillari, D. *Pharmazie*. **1990**, *45*, 441.

[29] Kaiser, D. G.; Glenn, E. M. *J. Pharm. Sci*. **1972**, *61*, 1908.

[30] Boger, D. L.; Boyce, C. W.; Labroli, M. A.; Sehon C. A.; Jin, Q. *J. Am. Chem. Soc*. **1999**, *121*, 54.

[31] Wiese, M.; Pajeva, I. K. *Curr. Med. Chem*. **2001**, *8*, 685.

[32] Ambudkar, S. V.; Dey, S.; Hrycyna, C. A.; Ramachandra, M.; Pastan, I.; Gottesman, M. M. *Annu. Rev. Pharmacol. Toxicol*. **1999**, *39*, 36.

[33] D. L.; Soenen, D.R.; Boyce, C.W.; Hedrick, M. P.; Jin, Q. *J. Org. Chem*. **2000**, *65*, 2479.

[34] Anderson, R. J.; Faulkner, D. J.; Cun-Heng, H.; Van Duyne, G. D.; Clardy, J. *J. Am. Chem. Soc*. **1985,** *107*, 5492.

[35] Davis, R. H.; Carroll, A. R.; Pierens, G. K.; Quinn, R. J. *J. Nat. Prod*. **1999**, *62*, 419.

[36] Ham, J.; Kang, H. *Bull. Korean. Chem. Soc*. **2002**, *23*, 163.

[37] Pyrroles, *The Chemistry of Heterocyclic Compounds*, ed. R. A. Jones, Wiley, New York, **1990**, 48, part I.

[38] Fan, H.; Peng, J.; Hamann, M. T.; Hu, J. F. *Chem. Rev*. **2008**, *108*, 264.

[39] Estevez, V.; Villacampa, M.; Menendez, J. C. *Chem. Soc. Rev*. **2010**, *39*, 4402.

[40] Bergman, J.; Janosik, T. *Modern Heterocyclic Chemistry*. **2011**, *1*, 269.

[41] Qi, X.; Xu, X.; Park, C. M. *Chem. Commun*. **2012**, *48*, 3996.

[42] Padwa, A.; Pearson, W. H. *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*, Wiley, New York, **2002**, 59.

[43] Balme, G.; Bouyssi, D.; Monteiro, N. *Heterocycles*. **2007**, *73*, 87.

[44] Gulevich, A. V.; Dudnik, A. S.; Chernyak, N.; Gevorgyan, V. *Chem. Rev*. **2013**, *113*, 3084.

[45] Chiba, S.; Wang, Y., Lapointe, G.; Narasaka, K. *Org. Lett*. **2008**, *10*, 313.

[46] Minetto, G.; Raveglia, L. F.; Sega, A.; Taddei, M. *Eur. J. Org. Chem*. **2005**,5277.

[47] Thirumalairajan, S.; Pearce, B. M.; Thompson, A. *Chem. Commun*. **2010**, *46*, 1797.

[48] Ngwerume, S.; Camp, J. E. *Chem. Commun.* **2011**, *47*, 1857.

[49] Attanasi, O. A.; Favi, G.; Mantellini, F.; Moscatelli, G.; Santeusanio, S. *J. Org. Chem*. **2011**, *76*, 2860.

[50] Zhang, M.; Zhang, J. *Chem. Commun.* **2012**, *48*, 6399.

[51] Meng, L., Wu, K.; Liu, C.; Lei, A. *Chem. Commun.***2013**, *49*, 5853.

[52] Estevez, V.; Villacampa, M.; Menendez, J. C. *Chem. Commun*. **2013**, *49*, 591.

[53] Wu, T.; Pan, L.; Xu, X.; Liu, Q. *Chem. Commun*. **2014**, *50*, 1797.

[54] Xu, Y. H.; He, T.; Zhang, Q. C.; Loh, T. P. *Chem. Commun*. **2014**, *50*, 2784.

[55] Zhou, C.; Ma, D. *Chem. Commun*. **2014**, *50*, 3085.

[56] Kalmode, H. P.; Vadagaonkar, K. S.; Murugan, K.; Chaskar, A. C.; *New. J. Chem.***2015**, *39*, 4631.

[57] Tan, W. W.; Yoshikai, N. *Chem. Sci*. **2015**, *6*, 6448.

[58] Wu, X.; Li, K.; Wang, S.; Liu, C.; Lei, A. *Org. Lett.***2016**, *18*, 56.

[59] Cogswell, T. J.; Donald, C. S.; Marquez, R. *Org. Biomol. Chem*. **2016**, *14*, 183.

[60] Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res*. **1996**, *29*, 123.

[61] Kumar, A.; Rao, V. K. *Synlett*. **2011**, 15, 2157.

[62] Guntreddi, T.; Allam, B. K.; Singh, K. N. *Synlett*. **2012**, *23*, 2635.

[63] Zhu, J.; Bienayme, H., In. Multicomponent. Reactions. Ed. Wiley-VCH Verlag GmbH & Co. KGa A**. 2005**, 35.

[64] Dömling, A.; Ugi, I. *Angew. Chem. Int. Ed*. **2000**, *39*, 3168.

[65] Dömling, A. *Chem. Rev*. **2005**, *106*, 17.

[66] Ugi, I.; Domling, A.; Werner, B. *J. Heterocycl. Chem*. **2000**, *37*, 647.

[67] Weber, L.; Illgen, K.; Almstetter, M. *Synlett*. **1999**, 366.

[68] Dömling, A.; Wang, W.; Wang, K. *Chem. Rev.* **2012,** *112*, 3083.

[69] Orru, R. V. A.; De Greef, M. *Synthesis*. **2003**, 1471.

[70] Tejedor, D.; Gonzalez-Cruz, D.; Santos-Exposito, A.; Marrero-Tellado, J. J.; De-Armas, P.; Garcıa-Tellado, F. *Chem. Eur. J*. **2005**, *11*, 3502.

[71] Toure, B. B.; Hall, D. G. *Chem*. *Rev*. **2009**, *109*, 4439.

[72] Shaabani, A.; Maleki, A.; Mofakham, H.; Khavasi, H. R. *J. Comb. Chem.* **2008**, *10*, 883.

[73] Weber, L. *Curr. Med. Chem*. **2002**, *9*, 2085.

[74] Hulme, C. Gore, V. *Curr. Med. Chem*. **2003**, *10*, 51.

[75] Roy, S. R.; Jadhavar, P. S.; Seth, K.; Sharma, K. K.; Chakraborti, A. K. *Synthesis*. **2011**, *48*, 2261.

[76] Benjamin, H.; Rotstein, S. Z.; Rai, V.; Andrei, K. Y. *Chem. Rev.***2014**, *114*, 8323.

[77] Balme, G. *Angew. Chem. Int. Ed*. **2004**, *43*, 6238.

[78] Hantzsch, A. *Chem. Ber*. **1890**, *23*, 1474.

[79] Pal, G.; Paul, S.; Das, A. R. *Synthesis*. **2013**, *45,* 1191.

[80] Meshram, H. M.; Bangade, V. M.; Reddy, B. C.; Kumar, G. S.; Thakur, P. B. *Int. J. Org. Chem*. **2012**, *2*, 159.

[81] Attanasi, O. A.; Favi, G.; Mantellini, F.; Moscatelli, G.; Santeusanio, S. *J. Org. Chem*. **2011**, *76*, 2860.

[82] Xu, P.; Huang, K.; Liu, Z.; Zhou, M.; Zeng, W. *Tetrahedron. Lett*. **2013**, *54*, 2929.

[83] Magar, D. R.; Ke, Y. J.; Chen, K. *Asian J. Org. Chem*. **2013**, *2*, 330.

[84] Lin, X.; Mao, Z.; Dai, X.; Lu, P.; Wang, Y. *Chem. Commun*. **2011**, *47*, 6620.

[85] Zheng, Y.; Wang, Y.; Zhou, Z. *Chem. Commun*. **2015**, *51*, 16652.

[86] Meshram, H. M.; Babu, B. M.; Kumar, G. S.; Thakur, P. B.; Bangade, V. M. *Tetrahedron. Lett*. **2013**, *54*, 2296.

[87] Andrieux, C. P.; Audebert, P.; Merz, A.; Schwarz, R. *New. J. Chem*. **1990**, *14*, 637.

[88] Méndez, J. M.; Flores, B.; León, F.; Martinez, M. E.; Vazquez, A.; Garcia, G. A.; Salmón, M. *Tetrahedron Lett*. **1996**, *37*, 4099.

[89] Pavri, N. P.; Trudell, M. L. *J. Org. Chem*. **1997**, *62*, 2649.

[90] Beecher, J. E.; Tirrell, D. A. *Tetrahedron Lett*. **1998**, *39*, 3927.

[91] Bunrit, A.; Sawadjoon, S.; Tšupova, S.; Sjöberg, P. J. R.; Samec, J. S. M. *J. Org. Chem*. 2016, **81**, 1450.

[92] Bray, B. L.; Mathies, P. H.; Naef, R.; Solas, D. R.; Tidwell, T. T.; Artis, D. R.; Muchowski, J. M. *J.Org. Chem*. **1990**, *55*, 6317.

[93] Hamdan, A.; Wasley, J. W. F. *Synth. Commun*. **1983**, *13*, 741.

[94] Dumoulin, H.; Fabis, F.; Dallemagne, P.; Roult, S.; Robba, M. *Synth. Commun*. **1994**, *24*, 1855.

[95] Haldar, P.; Guin, J.; Ray, J. K. *Tetrahedron Lett*. **2005**, *46*, 1071.

[96] Kelly, A. R.; Kerrigan, M. H.; Walsh, P. J. *J. Am. Chem. Soc*. **2008**, *130*, 4097.

[97] Jendralla, H.; Baader, E.; Bartmann, W.; Beck, G.; Bergmann, A.; Granzer, E.; Kerekjarto, B.; Kesseler, K.; Krause, R.; Schubert, W.; Wess, G., *J. Med. Chem*. **1990**, *33*, 61.

[98] Dumoulin, D.; Rault, S.; Robba, M. *J. Heterocycl. Chem*. **1996**, *33*, 255.

[99] He, R.; Zeng, L F.; He, Y.; Wu, L.; Gunawan, A. M.; Zhang, Z. Y. *Chem. Commun*. **2013**, *49*, 2064.

[100] Valente, S.; Tomassi, S.; Tempera, G.; Saccoccio, S.; Agostinelli, E.; Mai, A. *J. Med. Chem*. **2011**, *54*, 8228.

[101] Sigmund, W. M.; Weerasekera, G.; Marestin, C.; Styron, S.; Zhou, H.; Elsabee, M. Z.; Rühe, J.; Wegner, G.; Duran, R. S. *Langmuir*. **1999**, *15*, 6423.

[102] Martinnelli, F.; Palmieri, A.; Petrini, M. *Chem. Eur. J*. **2011**, *17*, 7183.

[103] Perez, L. J.; Karagounis, T. K.; Hurley, A.; Bassle, B. L.; Semmelhack, M. F. *Chem. Sci*. **2014**, ***5***, 151.

[104] Rivero, M. R.; Buchwald, S. L. *Org. Lett*. **2007**, *9*, 973.

[105] Butler, M. S. *J. Nat. Prod*. **2004**, 67, 2141.

[106] Toganoh, M.; Kawabe, Y.; Furuta, H. *J. Org. Chem*. **2011**, *76*, 7618.

[107] Kumar, I.; Ramaraju, P.; Mir, N. A.; Singh, A. *Org. Biomol. Chem*. **2015**, *13*, 1280.

[108] Kumar, I.; Mir, N. A.; Gupta, V. K.; Rajnikant. *Chem. Commun*. **2012**, *48*, 6975.

[109] Kumar, I.; Mir, N. A.; Ramaraju, P.; Wakhloo, B. P. *RSC Adv*. **2012**, *2*, 8922.

[110] Kumar, I.; Ramaraju, P.; Mir, N. A.; Singh, D.; Gupta, V. K.; Kant, R. *Chem. Commun.***2013**, *49*, 5645.

[111] Kumar, I.; Mir, N. A.; Ramaraju, P.; Singh, D.; Gupta, V. K.; Rajnikant. *RSC Adv*. **2014**, *4*, 34548.

[112] Ramaraju, P.; Mir, N. A.; Singh, D.; Gupta, V. K.; Kant, R; Kumar, I. *Org. Lett*.**2015**, *17*, 5582.

[113] Mir, N. A.; Choudhary, S.; Ramaraju, P.; Singh, D.; Kumar, I. *RSC Adv*. **2016**, *6*, 39741.

[114] Ramaraju, P.; Mir, N. A.; Singh, D.; Kumar, I. *RSC Adv*. **2016**, *6*, 60422.

[115] Ramaraju, P.; Mir, N. A.; Singh, D.; Sharma, P.; Kant, R.; Kumar, I. *Eur. J. Org. Chem*. **2017**,*2017*, 3461.

[116] Sundberg, R. J. *The Chemistry of Indoles*. Academic Press: New York, **1970**.

[117] Gribble, G. W. *In Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R.; Ress, C. W.; Scriven, E. F. V.; Bird, C. W. *Eds*.; Pergamon Press: Oxford. **1996**, *2*, 207.

[118] Faulkner, D. J. *Nat. Prod. Rep*. **2002**, *19*, 1.

[119] Bartoli, G.; Bencivenni, G.; Dalpozzo R. *Chem. Soc. Rev*. **2010**, *39*, 4449.

[120] Gul, W.; Hamann, M. T. *Life Sci*. **2005**, *78*, 442.

[121] Kochanowska-Karamyan, A. J. Hamann, M. T. *Chem. Rev*. **2010**, *110*, 4489.

[122] McArthur, K. A.; Mitchell, S. S.; Tsueng, G.; Rheingold, A.; White, D. J.; Grodberg, J.; Lam, K. S.; Potts, B. C. M. *J. Nat. Prod*. **2008**, *71*, 1732.

[123] Black, D. S.; Bowyer, M. C., Kumar, N. *Tetrahedron*. **1997**, *53*, 8573.

[124] Lehuédé, J.; Fauconneau, B.; Barrier, L.; Ourakow, M.; Piriou, A.; Vierfond, J. M. *Eur. J. Med. Chem.* **1999**, *34*, 991.

[125] Mohamed, M. S.; Kamel, R.; Fatahala, S. S. *Eur. J. Med. Chem*. **2011**, *46*, 3022.

[126] Williamson, N. R.; Fineran, P. C.; Gristwood, T.; Chawrai, S. R.; Leeper, F. J.; Salmond, G. P. C. *Future Microbiol*. **2007**, *2*, 605.

[127] Lavrado, J.; Moreira, R.; Paulo, A. *Curr. Med. Chem*. **2010**, *17*, 2348.

[128] Carbone, A.; Parrino, B.; Barraja, P.; Spanò, V.; Cirrincione, G.; Diana, P.; Maier, A.; Kelter, G.; Fiebig, H. H. *Mar. Drugs*. **2013**, *11*, 643.

[129] Zhang, W.; Liu, Z.; Li, S.; Yang, T.; Zhang, Q.; Ma, L.; Tian, X.; Zhang, H.; Huang, C.; Zhang, S.; Ju, J.; Shen, Y.; Zhang, C. *Org. Lett*. **2012**, *14*, 3364.

[130] Zhou, F.; Guo, J.; Liu, J.; Ding, K.; Yu, S.; Cai, Q. *J. Am. Chem. Soc.* **2012**, *134*, 14326.

[131] Wang, Z.; Baoand, W.; Jiang, Y. *Chem. Commun*. **2005**,2849.

[132] Goff, R. L.; Lawson, A. M.; Daich, A.; Comesse, S. *Org. Biomol. Chem*. **2013**, *11*, 1818.

[133] Brown, T. H.; Ife, R. J.; Keeling, D. J.; Laing, S. M.; Leach, C. A.; Parsons, M. E.; Price, C. A.; Reavill, D. R.; Wiggall, K. J. *J. Med. Chem*. **1990**, *33*, 527.

[134] Sangnoi, Y.; Sakulkeo, O.; Yuenyongsawad, S.; Kanjanaopas, A.; Ingkaninan, K.; Plubrukarn, A.; Suwanborirux, K. *Mar. Drugs*. **2008**, *6*, 578.

[135] Furlotti, G.; Alisi, M. A.; Apicella, C.; de Joannon, A. C.; Cazzolla, N.; Costi, R.; Crucitti, G. C.; Garrone, B.; Iacovo, A.; Magarò, G.; Mangano, G.; Miele, G.; Ombrato, R.; Pescatori, L.; Polenzani, L.; Rosi, F.; Vitiello, M.; Di Santo, R. *J. Med. Chem*. **2012**, *55*, 9446.

[136] Yang, R.Y.; Dai, L. X. *J. Org. Chem.***1993**, *58*, 3301.

[137] Rane, R. A.; Pavankumar, B.; Borhade, S. D.; Khandare, P. K. *Eur. J. Med. Chem*. **2013**, *70*, 49.

[138] Idhayadhulla, A.; Kumar, R. S.; Nasser, A. J. A.; Manilal, A. *Bull. Chem. Soc. Ethiop*. **2012**, *26*, 429.

[139] Ghosal, S.; Saini, K. S.; Frahm, A. W. *Phytochemistry*. **1983**, *22*, 2305.

[140] Ghosal, S.; Kumar, Y.; Chakrabarti, D. K.; Lal, J.; Singh, S. K. *Phytochemistry*. **1986**, *25*, 1097.

[141] Jin, Z. *Nat. Prod. Rep*. **2009**, *26*, 363.

[142] Merz, K. H.; Muller, T.; Vanderheiden, S.; Eisenbrand, G.; Marko, D.; Brase, S. *Synlett*. **2006**,*2006*, 3461.

[143] Ishikawa, T. *Med. Res. Rev*. **2001**, *21*, 61.

[144] Tsukamoto, H.; Kondo, S.; Mukudai, Y.; Nagumo, T.; Yasuda, A.; Kurihara, Y.; Kamatani, T.; Shintani, S. *Anticancer Res*. **2011**, *31*, 2841.