Chapter – 3

Multicomponent site-selective synthesis of 4-iodo and 5-iodo-pyrrole-3-carboxaldehyde

3.1 Introduction:

From the perspective of green chemistry, the progress of organic transformations for the synthesis of bioactive *N*-containing heterocyclic scaffolds in a minimum number of synthetic steps with high molecular complexity and diversity is an eternal demand in organic chemistry. In this direction, One-pot Multicomponent reactions (MCRs)[1-13] and cascade reactions[14-16] are important tools to meet these goals, because several bonds forming steps are combined in a single reaction vessel to form a new product containing portions of all components. MCRs are also explained as convergent chemical processes where two or more reactants are shared in such a way that the final compound retains significant portions of all starting materials. MCRs increases the molecular diversity and complexity in a straightforward approach via the bonding of three or more reactants in a single synthetic process with high atom economy and bond-forming efficiency. These reactions also allow the construction of novel small sized drug-like moiety that is an integral part of biologically active compounds and marine alkaloids.[17-26]MCRs are mainly one-pot protocol to form a product displaying features of all inputs without isolating the intermediates, have become an important tool for synthesizing organic compounds with a high degree of molecular diversity.[27-29]Therefore, MCRs play an important role in modern synthetic chemistry and offer significant advantages over conventional multi-step syntheses along with the broad substrate scope and capability to tolerate diverse functionalities.[30-32]

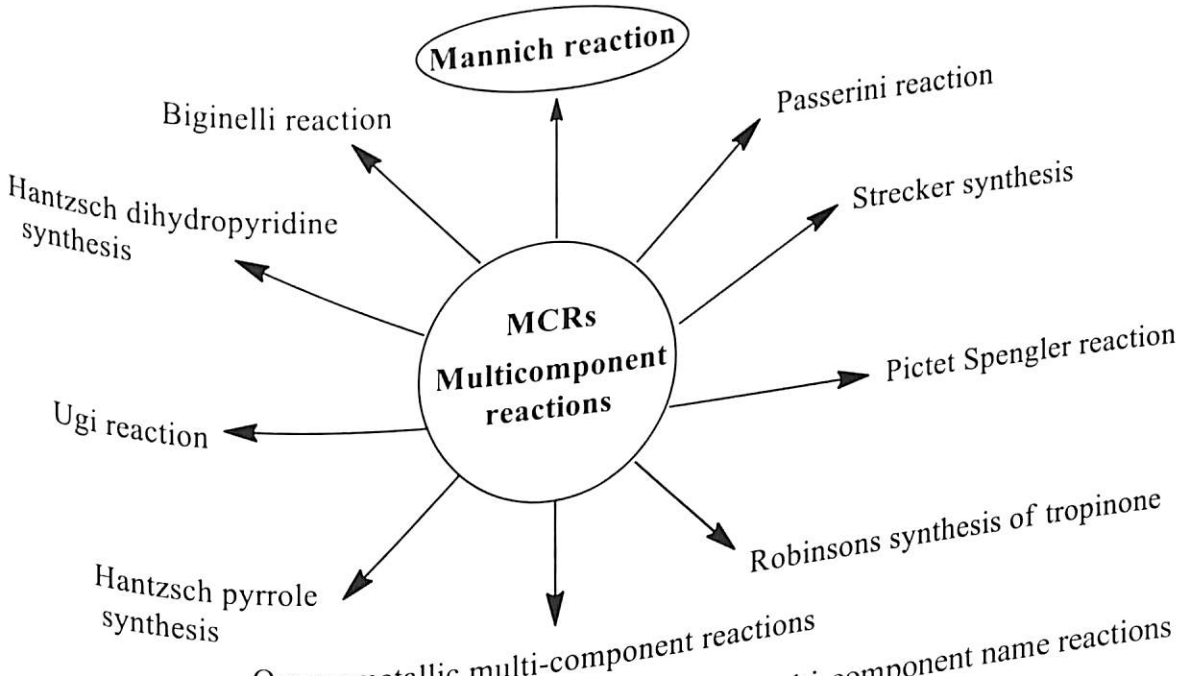


Figure 3.1 Overall representation of a various one-pot multi-component name reactions

Literature is flooded with the articles of MCRs which show their strength in the synthetic field. Among them the most studied classical MCRs are Mannich reaction,[33] Strecker synthesis,[34]Robinsons synthesis of tropinone,[35] Biginelli reaction,[36] Ugi reaction,[37] Passerini reaction,[38] organometallic multi-component reactions,[39] Pictet-Spengler reaction,[40] Hantzsch pyrrole synthesis [41] and Hantzsch dihydropyridine synthesis[42] which are described in the below mentioned Figure 3.1.

In this fashion, the unprecedented blossom of reports has been published on MCRs which delivered either potential bioactive motifs in a reduced number of synthetic steps or new libraries for biological screenings. In addition, there are several reports where these multi-component reactions are fused with other valuable C-C as well as C-heteroatom bond forming reactions in a domino sequence to form complex structures in a single step.[43-44]In addition, the novelty of cascade/domino-reactions has been a challenging facet of organic reactions. These reactions are a powerful tool for construction of polycyclic scaffolds. A wide variety of domino reaction has been carried out in different reactions like nucleophilic/electrophilic attack, organometallic reaction, organocatalytic reaction, pericyclic reaction, transition metal reaction, radical and cascade reactions. Through the cascade reactions, just one solvent, one workup process, and one purification step are required, thus cascade reactions make it more efficient.

Novel and under-explored heterocyclic compounds show remarkable biological activity and are vital for the drug discovery and development process. Efficient synthetic approaches towards such scaffolds are instrumental to the rapid synthesis and evaluation of these compounds.

In particular, the formation of variously substituted pyrroles involving one-pot multi-bond approaches such as multicomponent reactions, cascade reactions, and one-pot synthetic sequences is an efficient and practical tool to access these moieties in one-pot. A number of novel approaches have been established to generate variously substituted pyrrole scaffolds *via* multicomponent approach.[45-46]

3.2 Importance of halo-pyrroles

Among the nitrogen-containing heterocycles, pyrrole based skeleton is widely prevalent in drug-like compounds, biologically active natural compounds, synthetic medicinal agents and exhibit significant applications in materials science.[47-67] Pyrrole and their derivatives are found as a pharmaceutical class of nitrogen heterocyclic framework because of their significant anti-viral,[68]anti-bacterial,[69]anti-tumor,[70]anti-inflammatory,[71]antioxidant activities,[72]anticancer

and immunosuppressive agents.[73] Moreover, polysubstituted pyrroles have also been used as conducting polymers,[74-75] pyrrolic macrocyclesring system, for example, calyx-[4]-pyrroles, [76-82] promising pharmacophores in medicinal chemistry,[83-84] and agrochemicals.[85-88] Polypyrroles such as Neolamellarin A, a metabolite isolated from the sponge Dendrilla nigra exhibits confirmed antitumor activity.[89]Fludioxonil is a contact broad-spectrum fungicide structurally related to pyrrolnitrin.[90] Apricoxib, a cyclooxygenase-2 inhibitor, shows antitumor activity.[91] The progress of efficient methods for formation of polypyrroles have found significant attention due to the potential applications of this type of compounds and have emerged as an attractive synthetic motif since these are frequently found in natural products and compounds incorporating such a motif possess numerous types of biological activities(Figure 3.2).A number of methods including classical ones have been developed by synthetic chemists,[92-95] like multicomponent reactions,[96-97] metal catalyzed reactions [98] cycloaddition reactions,[99] and other synthetic methods.[100-112]

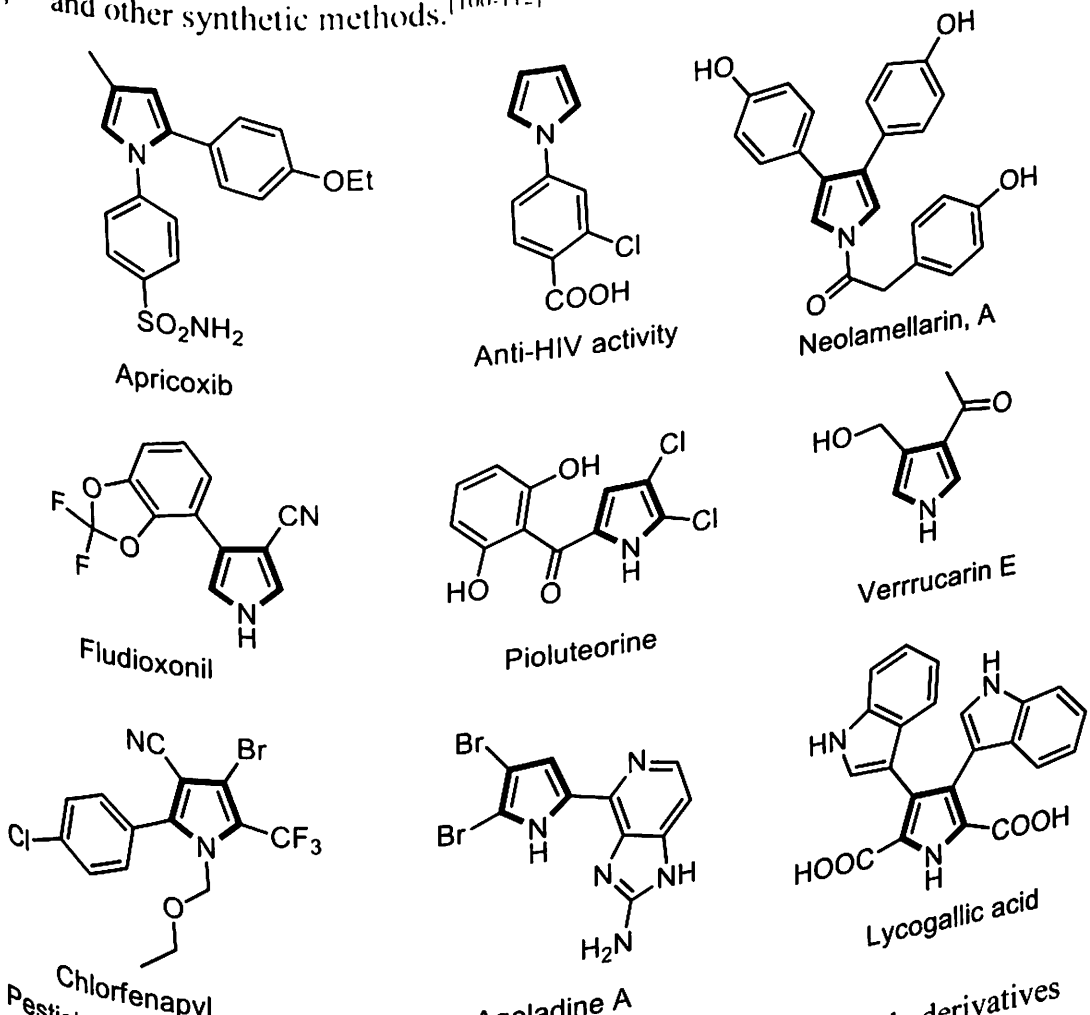
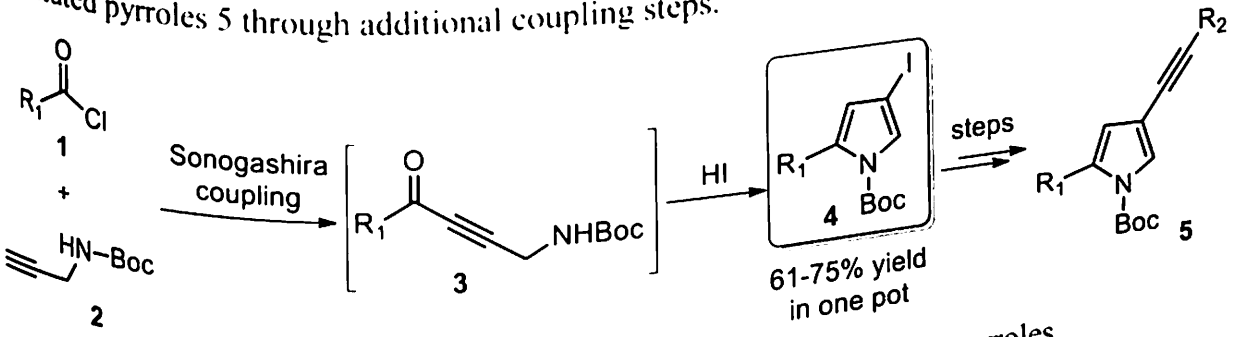


Figure 3.2 Representative examples of biological active pyrrole derivatives

3.3 General Synthesis of iodo-pyrrole derivatives

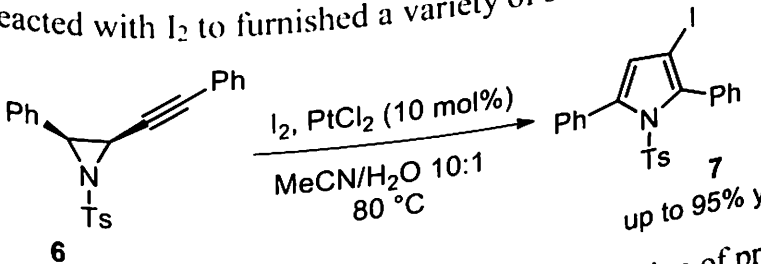
Though, there are enormous methods are available to access functionalized pyrroles, however, a limited number of methods are available to access 4-iodo- and 5-iodo-pyrroles. Herein, we are providing a detailed literature survey on the synthesis of iodo-pyrroles.

The very first method for the direct synthesis *N*-Boc-4-iodopyrroles**5**was developed by Merkul and co-workers. As shown in Scheme 3.1, variously aryl-, heteroaryl, alkenyl-, and alkyl-substituted acid chlorides **1**underwent Sonogashira coupling with *N*-Boc-protected propargylamine**2** under mild conditions, followed by cyclization with HI gave *corresponding* 4-iodopyrroles**5**in good yields.[113]Product **4** was utilized further for the rapid synthesis of alkynyl-substituted pyrroles 5 through additional coupling steps.



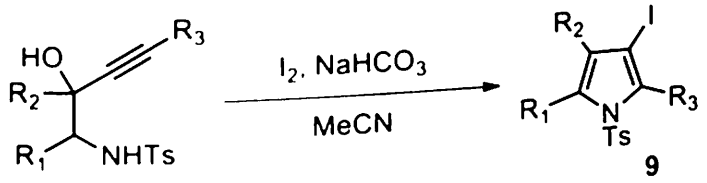
Scheme 3.1 Multi component approach for*N*-Boc-4-iodopyrroles

Yoshida and co-workers developed a Pt-catalyzed rearrangement of propargylic aziridines **6**with $I_2$to access 3-iodopyrroles**7**with high yields as shown in Scheme 3.2.[114]In this reaction *N*-tosyl-propargylic aziridines**6** was rearranged with Pt-catalysts to intermediate dihydropyrrole, which was subsequently reacted with I_2 to furnished a variety of substituted 3-iodopyrrole derivatives.



Scheme 3.2 Substituted 3-iodopyrroles using cycloisomerization of propargylicaziridines

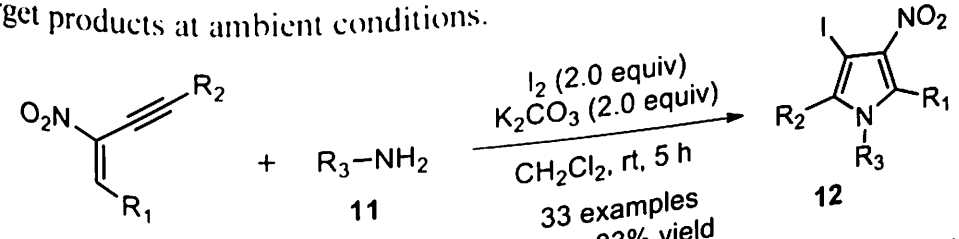
Gabriele and co-workers reported a novel and general method for the direct synthesis of 3-iodo pyrroles**11**through the iodocyclization of **8**, followed by dehydration to yield **9** in good yields.[115] As shown in Scheme 3.3, this reaction was carried out under mild conditions in the presence of an excess of $I_2$and MeCN as the solvent along with $NaHCO_3$. This method was also successfully applied to synthesize substituted pyrroles, furans and thiophenes derivatives without affecting the alkynyl group at C-3.



8 9

Scheme 3.3 Synthesis of substituted 3-iodopyrroles by iodocyclization with Iodine

Recently, Punniyamurthy and co-workers developed a new method for the synthesis of fully substituted 3-iodo-pyrroles**12** from simple starting materials.[116] In this reaction, molecular I2mediated cyclization of Michael-addition intermediate of 1,3-enynes **10**and amines **11**, followed by oxidative aromatization under mild conditions furnished fully substituted 3-iodo-pyrroles**12** in good to high yields as shown in Scheme 3.4. The protocol is simple and efficient to afford the target products at ambient conditions.

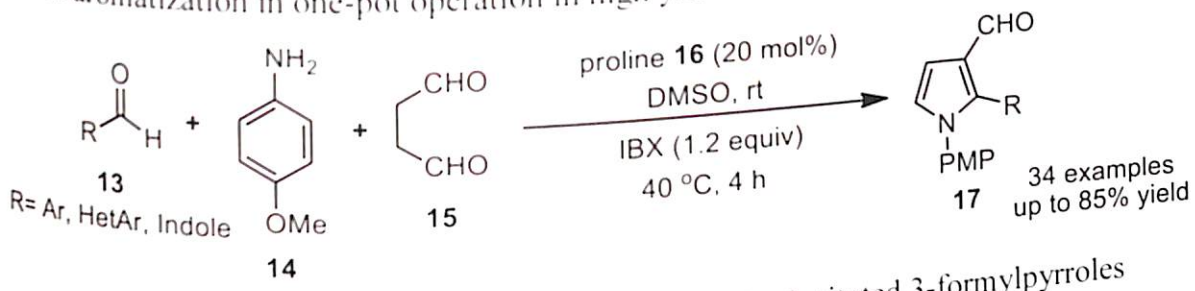


10 11 12

Scheme 3.4 Synthesis of pyrrole by 5-endo-dig cyclization of 1,3-enynes with amines

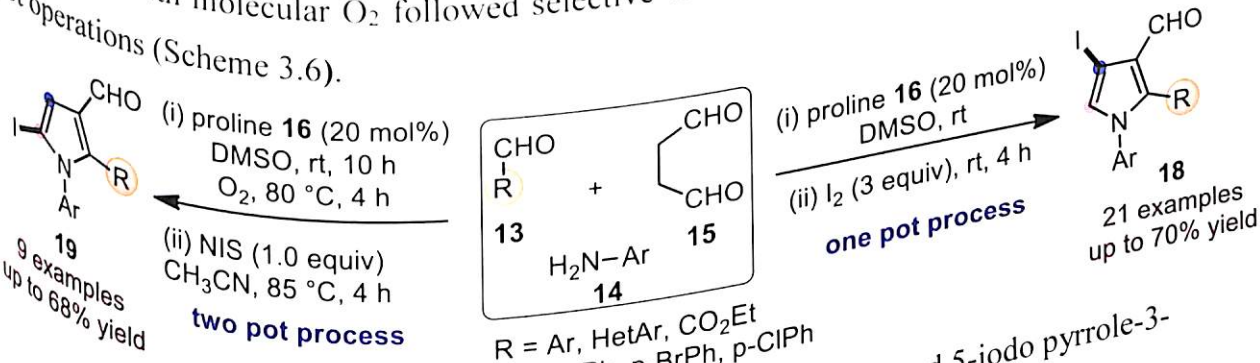
These existing methods provide an access to 3-iodo-, and 4-iodo-pyrroles, however, required a use of elaborately designed starting materials, suffer from low efficiency and selectivity and sometimes require harsh conditions. Therefore, the development of a method for the site-selective synthesis of iodo-pyrroles is required and herein, we describe our study in the direction. The direct synthesis of pyrroles holding two-electrophilic groups like –CHO, and –I at the C3 and C4 position is a difficult task to achieve as an electrophilic substitution at existing pyrrole mainly takes place at C-2 and C-5positions. Thus, a general approach for the formation of 4-iodo and 5-iodo pyrrole-3-carboxaldehyde from simple and common starting materials with minimal synthetic steps is highly required. Recently, organocatalytic reactions involving two or more selective approaches using single or multiple catalyzes, act as a effective tools for synthesis through reducing the overall number of synthetic steps.[71-74]In this context, our group have recently developed an efficient sequential multi-component method for the synthesis of *N*-arylpyrrole-3-carbaldehydes**17**, from aryl-aldehydes **13**, aryl-amines **14**, and succinaldehyde **15** in a one-pot fashion. This [3+2] annulation protocol involved proline-catalyzed direct Mannich reaction-cyclization sequence between succinaldehyde**15** and *in situ* generated Ar/HetAr/indolyl-

imines (Imines derived from aromatic aldehydes**13** and Anisidine**14**), followed by IBX-mediated oxidative aromatization in one-pot operation in high yield as shown in Scheme 3.5. [117]



Scheme 3.5 One-pot multicomponent synthesis of substituted 3-formylpyrroles

With the idea of cascade transformations of substituted pyrroles in mind, we applied our methodology for the synthesis of substituted 4-iodo and 5-iodo pyrrole-3-carboxaldehydes from succinaldehyde and imines. Importantly, imines have not been explored earlier to synthesize substituted iodo-pyrroles. Moreover, it is also motivating to develop a novel approach with a variation where 1,4-dicarbonyl compounds serve as a source of three atoms and the further two atoms could be obtained from imines for the pyrrole ring moiety. This synthetic approach will be different from Paal-Knorr which also involves 1,4-dicarbonyl compounds. In this chapter, we have developed a simple protocol for the synthesis of 4-iodo-, and 5-iodo-pyrrole-3-carboxaldehyde using the common starting materials under metal-free conditions. The synthesis of substituted 4-iodo-pyrrole-3-carboxaldehyde **18** through direct Mannich reaction-cyclization sequence between succinaldehyde**14** and situ generated imines (derived from aldehyde **13**and amine**14**), followed by I_2 mediated iodination at C4-position and aromatization in one-pot operation, whereas 5-iodo-pyrrole-3-carboxaldehyde **19** was prepared through the oxidative atomization with molecular O_2 followed selective iodination using NIS at C5-positions in two-pot operations (Scheme 3.6).

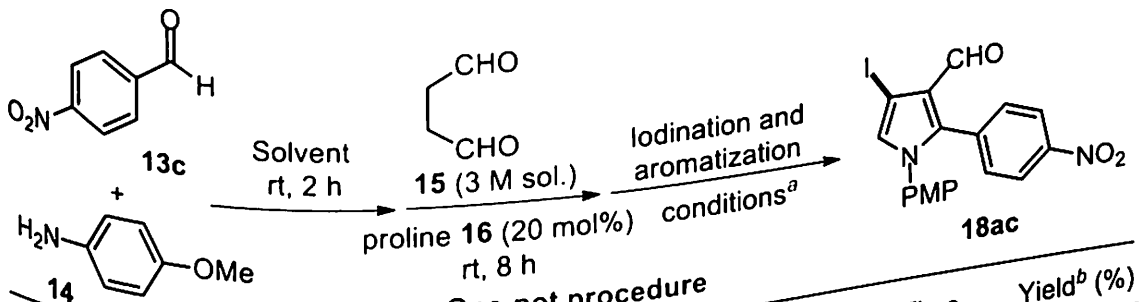


Scheme 3.6 Regioselective synthesis of substituted 4-iodo-, and 5-iodo pyrrole-3-carboxaldehydes from common starting materials

3.4 Results and discussion

As part of our interest for the synthesis of heterocyclic compounds, earlier we utilized aqueous succinaldehyde **15**, a synthetically useful 1,4-dicarbonyl unit, for the synthesis of pyrrole-3-carboxaldehydes. In this chapter, we report a sequential multicomponent synthesis of 4-iodo-**18**, and 5-iodo-pyrrole-3-carboxaldehyde **19**. In this context, we initially established the amine-catalyzed reaction protocol for 4-iodo-pyrrole-3-carboxaldehyde **18** by choosing *p*-nitrobenzaldehyde **13c** as a model substrate along with *p*-anisidine **14**, and succinaldehyde **15** in DMSO as overall [3+2] annulation. This reaction proceeds through proline **16** catalyzed direct Mannich/cyclization sequence between succinaldehyde **15**and in situ generated imine, followed by I_2 mediated iodination and oxidative aromatization in one-step sequence and results are shown in Table 3.1.

Table 3.1: Optimization of Reaction Conditions for **18ac**



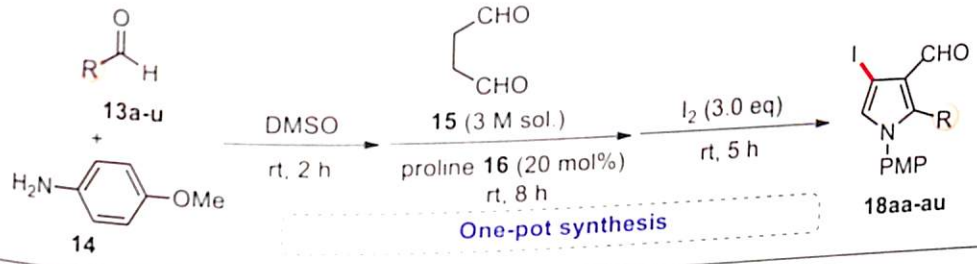
Entry	Solvent	Iodinating agent	Temperature	Time	Yield[b] (%)
1	DMSO	I_2 (2 eq.)	rt	5 h	40
2	DMSO	NIS (2 eq.)	rt	5 h	35
3	DMF	I_2 (2 eq.)	rt	6 h	20
4	CH_3CN	I_2 (2 eq.)	rt	10 h	24
5	toluene	NIS (2 eq.)	80 °C	10 h	40
6	$CHCl_3$	I_2 (2 eq.)	70 °C	10 h	20
7	DMSO	NIS (3 eq.)	rt	5 h	49
8	**DMSO**	**I_2 (3 eq.)**	**rt**	**5 h**	**85**
9	DMSO	I_2 (4 eq.)	rt	5 h	83
10[c]	DMSO	I_2 (3 eq.)	rt	5 h	65

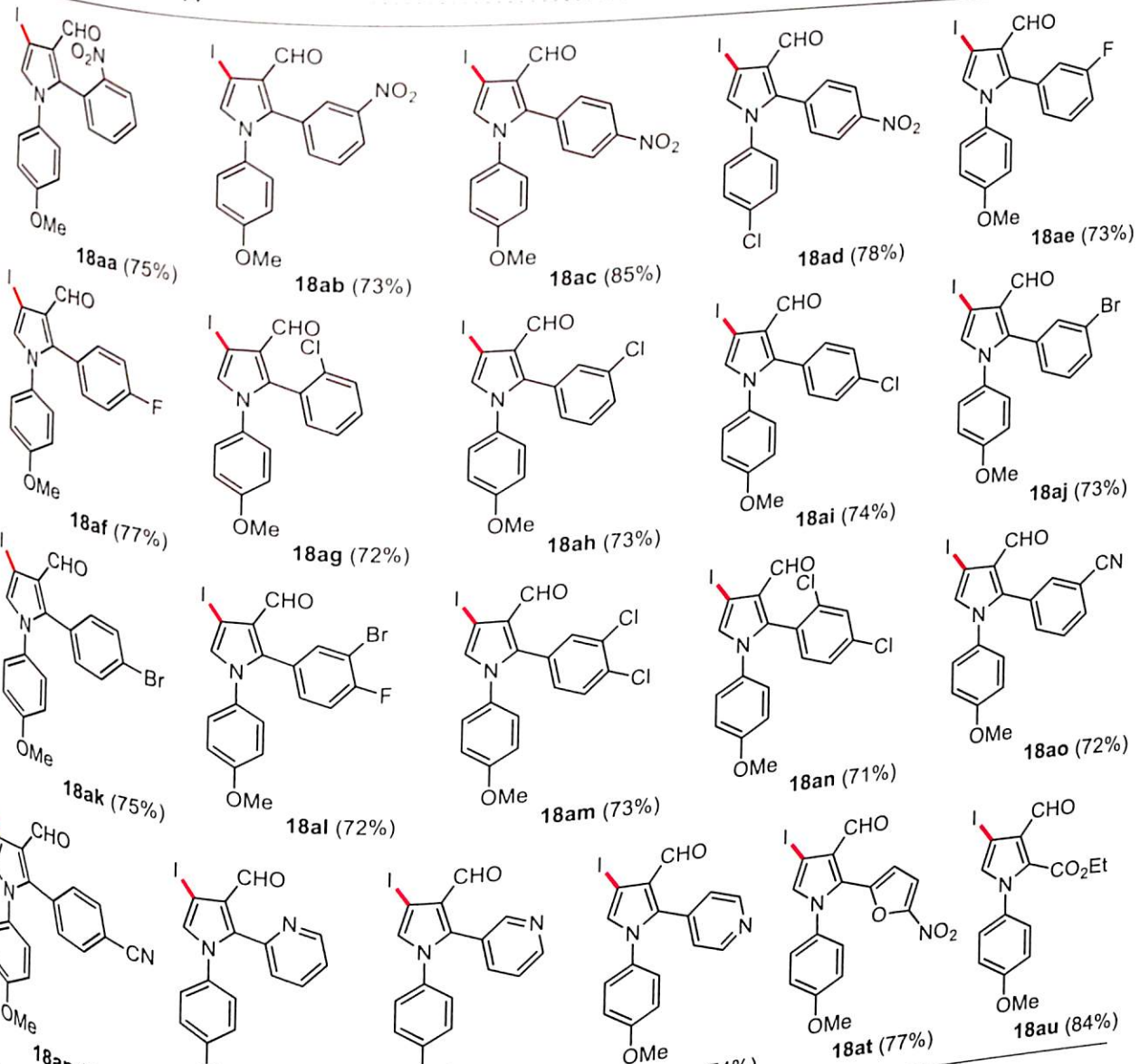
[a] (i) **13c**(0.3 mmol), **14** (0.3 mmol), and **15**(3 M sol, 0.9 mmol), catalyst **16** (20 mol%), solvent (3.0 mL).[b]Isolated yield of **18ac** refer to **13c**.[c] catalyst **16** (10 mol %).

In our initial experiments, 4-iodo-pyrrolecarbaldhdyes**18ac** was obtained in 40% and 28% yields, when hemiaminal (enamine) intermediate, generated through Mannich reaction-cyclization sequence between **15** (3 M sol) and in situ generated imine, was reacted with molecular I_2(2.0 equiv.) and NIS ((2.0 equiv.), respectively, in same-pot (entries 1-2, Table 3.1). Further, other solvents like CH_3CN and DMF and iodinating agents were screened(entries3-6, Table 3.1) for the same transformation, however, failed to improve in the overall yield. Next, a slight improvement in the yields was observed when NIS (3.0 equiv.) was used in DMSO (entry 7, Table 3.1). Pleasingly, product **18ac** was obtained in high yield when molecular I_2 (3.0 equiv.) was used as iodinating as an aromatizing reagent in DMSO (entry 8, Table 3.1). However, further efforts to improve the reaction yields, either by increasing the amount of I_2 (3.0 equiv.) (entry 9, Table 3.1) or by varying the catalysts loading (entry 10, Table 3.1) were not successful Thus, we preferred to perform the reaction under optimizing conditions (entry 8, Table 3.1).

Next, we examined the generality of the developed protocol by employing variously substituted aromatic/hetero-aromatic aldehydes **13** and the results are summarized in Table 3.2. This one pot protocol worked well with a series of aromatic/heteroaromatic aldehydes bearing various substituents at the ortho-, meta-, or para-positions. Nitro-benzaldehydes**13a-c** gave resulting product **18aa-au** in high yields under optimized conditions with *p*-$OCH_3C_6H_4NH_2$**14**. In addition, product **18ad** was also obtained in high yield when *p*-$ClC_6H_4NH_2$ was employed with 13c. Subsequently, other halo-benzaldehydes (substituted with –F, –Cl, –Br) at ortho-/meta-/para-positions gave corresponding products in good to high yields. Product **18ao-ap** were also obtained nicely when *m*-CN-/*p*-CN-benzaldehydes were used under optimized conditions (Table 3.2). In addition, this protocol was also successful with heteroaromatic aldehydes **13q**, **13r**, **13s**, and **13t**were employed and corresponding pyrroles **18aq**, **18ar**, **18as**, and **18at** were obtained in good yields, (Table 3.2). Interestingly, 4-iodo-pyrrole-3-carboxaldehyde **18u** was obtained in high yield with ethyl glyoxylate **13u** was employed for the same reaction under standardized conditions with extracted succinaldehyde (without water) (Table 3.2). Moreover, we got a poor yield of this product **18au** in presence of aqueous succinaldehyde (3M sol), probably because of the low stability of the in situ generated imine in presence of water. This reaction is limited to electron deficient aldehydes as the reaction failed in the case of electronically rich aryl as well as in aliphatic aldehydes.

Table 3.2: Library of the molecules synthesized **18aa-18au**



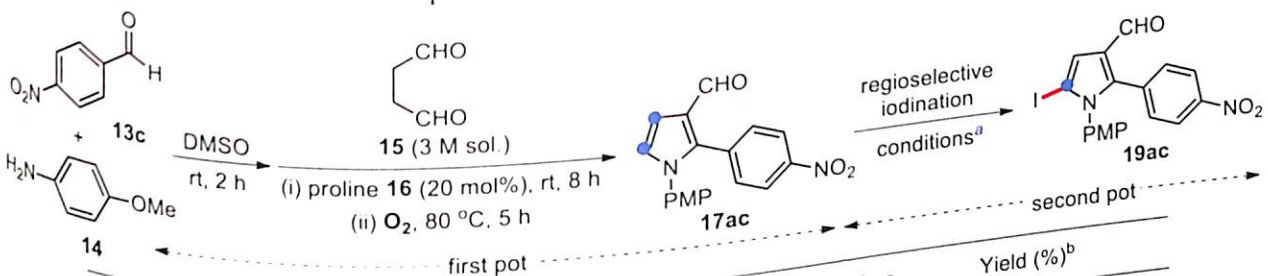


[a](i) aldehyde **13** (0.3 mmol), Ar-NH_2 **14** (0,3 mmol), **15** (3M sol, 0.9 mmol), proline **16** (20 mol%), DMSO (3.0 mL) (ii) I_2 (3 eq.)[b] isolated yield refer to **18**.

Having developed an efficient protocol for the direct synthesis of 4-iodo-pyrrole-3-carboxaldehyde **18**, we turn our attention to synthesize 5-iodo-pyrrole-3-carboxaldehyde **19** from

the same set of starting materials. This was feasible if we perform the regioselective iodination of the preformed pyrrole-3-carboxaldehyde under mild conditions. To achieve this task, we screened the reaction conditions for the selective iodination with an iodinating agent at the pyrrole-3-carboxaldehyde **17**, prepared through our modified protocol in which we have used molecular oxygen for oxidative-aromatization, instead of IBX, which makes this protocol more practical. In this context, initially pyrrole-3-carboxaldehyde **17ac** was prepared using our earlier developed sequential multicomponent protocol for proline-catalyzed Direct Mannich reaction-cyclization and aromatization with O_2 at 85 °C. This in situ generated **17ac** was utilized without purification for the regioselective iodination at C5-position and the results are shown in Table 3.3.

Table 3.3: Optimization of reaction conditions for **19ac**



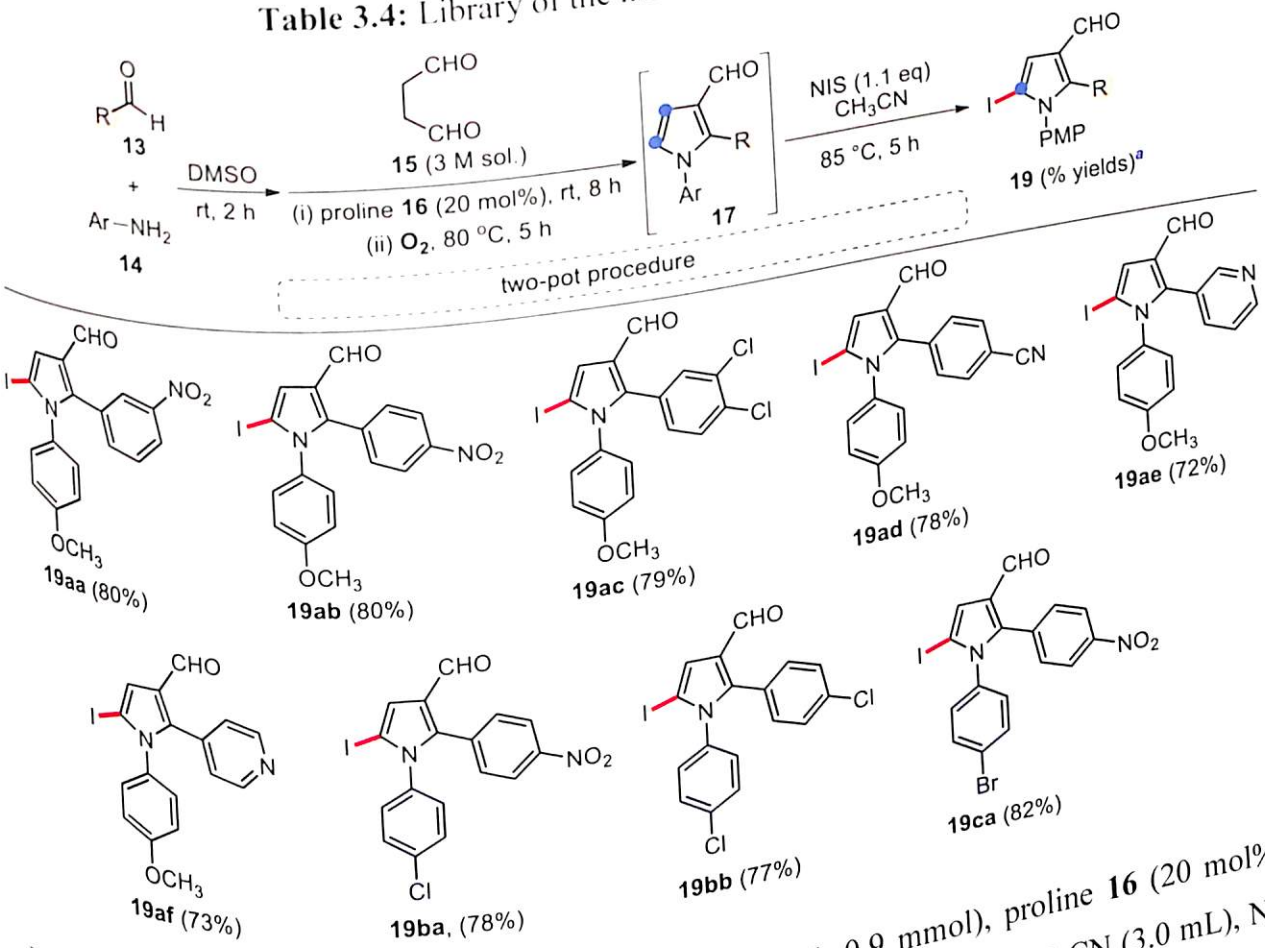
Entry	Solvents	Temperature	Iodinating agent	Time	Yield (%)[b]
1	DMSO	rt	I_2	10 h	30
2	DMSO	rt	NIS	10 h	45
3	CH_3CN	rt	I_2	10 h	52
4	CH_3CN	rt	NIS	6 h	65
5	**CH_3CN**	**85 °C**	**NIS**	**4h**	**80**
6	CH_3CN	95 °C	NIS	4 h	78
7	CH_3CN	85 °C	I_2	4 h	45
8	DMF	85 °C	I_2	4 h	43
9	DMF	85 °C	NIS	4 h	56
10	dioxane	85 °C	NIS	4 h	45

First pot: (i) **13c** (0.3 mmol), **14** (0,3 mmol), **15** (3M sol, 0.9 mmol), proline **16** (20 mol%), DMSO (3.0 mL) (ii) Molecular O2 (purged), 85 °C, 5 h. Second-pot: [a]Solvent (3.0 mL), Iodinating agents (NIS/I_2) (0.32 mmol), [b]isolated yield of **19ac** refer to **13c**.

Initially, efforts were made to make this reaction as one-pot transformation by using the iodinating agent after aromatization with molecular oxygen. In this context, 5-iodo-pyrrole-3-carboxaldehyde **19ac** was obtained in fewer yields (30%, entry 1, table 3.3) and (45%, entry 2,

Table 3.3) when I_2 and NIS were was added to **17ac**, respectively, in the same pot. The reaction was fairly good (52%) when I_2 was added to extracted **17ac** in CH_3CN at rt in a two-pot fashion. (entry 3, Table 3.3). The reaction yield (65%) of **19ac** for this two-pot protocol was further improved when NIS was employed in CH_3CN at rt (entry 4, Table 3.3). Pleasingly, **19ac** was obtained with a high yield (80%) when the reaction was warmed to 85°C for 5 h (entry 5, Table 3.3). Further increment in the reaction temperature (entry 6, Table 3.3) and change in the iodinating agent (entry 7, Table 3.3) did not provide an improvement in the reaction yields. Additional efforts to improve the reaction yields by changing the solvents or iodinating agents were failed (entries 8-10, Table 3.3). Thus, we perform this reaction under our best conditions (entry, Table 3.3).

Table 3.4: Library of the molecules synthesized **19**



First pot: (i) **13c** (0.3 mmol), **14** (0,3 mmol), **15** (3M sol, 0.9 mmol), proline **16** (20 mol%), DMSO (3.0 mL) (ii) Molecular O_2 (purged), 85 °C, 5 h. Second pot: (iii) CH_3CN (3.0 mL), NIS (1.1 eq, 0.32 mmol), [a]isolated yield of **19** refer to **13**.

Next, we examined the generality of this two-pot protocol for the regioselective synthesis of 5-iodo-pyrrole-3-carboxaldehydes **19** with respect to various aromatic aldehydes **13** and amine **14**, and the results are shown in Table 3.4. It is clear from the results that this method worked very well with variously substituted aromatic/heteroaromatic aldehydes **13** along with *p*–methoxy aniline and corresponding **19aa-19af** were obtained in good to high yields (Table 3.4). We also varied aromatic amines like; *p*-chloro-, and *p*-bromo-anilines and corresponding **19ba-bc** were obtained in good yields with overall two-step protocol. Thus, we could synthesize a series of 4-iodo-pyrrole-3-carboxaldehydes **18** and 5-iodo-pyrrole-3-carboxaldehydes **19** from the common starting materials by altering the reaction conditions, makes this protocol practically viable.

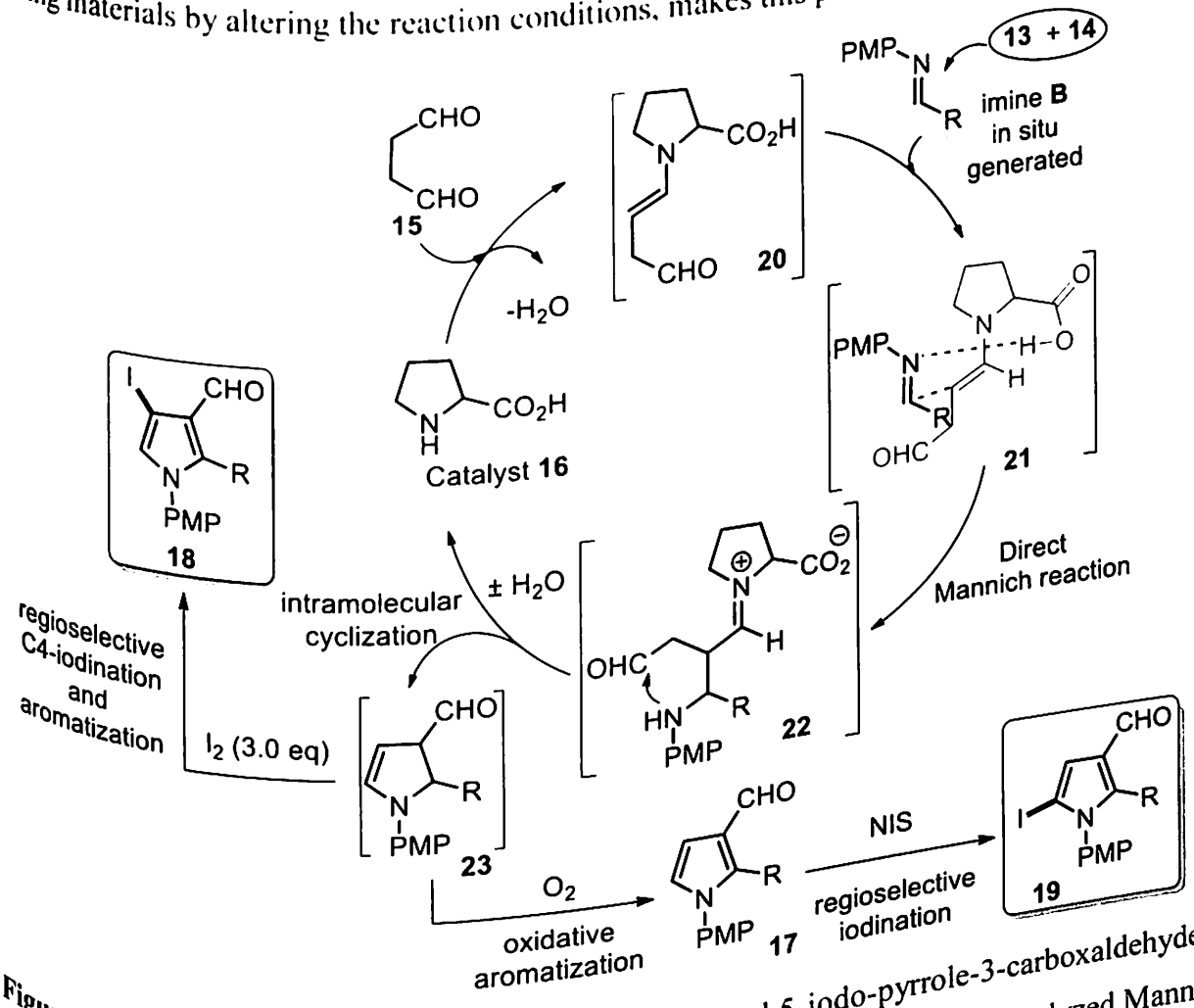
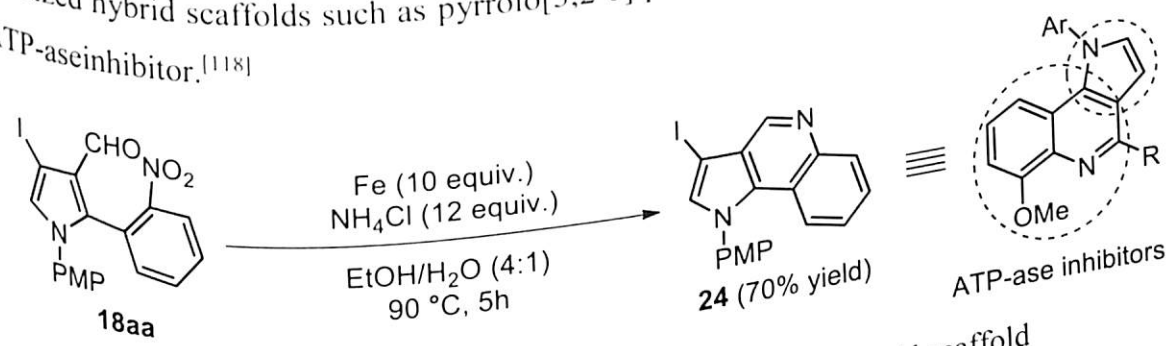


Figure 3.3: Plausible reaction mechanism for 4-iodo-, and 5-iodo-pyrrole-3-carboxaldehydes

Based on our previous study in this direction and literature reports on proline-catalyzed Mannich reaction, a stepwise plausible mechanism is proposed and shown in Figure 3.3. Initially, enamine **20**, generated by the reaction of succinaldehyde **15** and proline **16**, reacts with *N*-PMP aldimine, in situ derived from aromatic aldehyde **13** and *p*-methoxyaniline **14**, produce a direct Mannich

reaction intermediate **22**. This intermediate **22** undergoes intramolecular cyclization to dihydropyrrole (enamine) **23**, with the subsequent release of catalyst **16**. The dihydropyrrole intermediate **23** now underwent two different transformations; (*i*) I_2-mediated regioselective iodination at C4-position, and simultaneous aromatization to yield 4-iodo-pyrrole-3-carboxaldehydes **18**, while (*ii*) first oxidative aromatization with molecular O_2-followed by regioselective iodination with NIS at C5-positions of intermediate pyrrole **17** to 5-iodo-pyrrole-3-carboxaldehydes **19**. Thus, a series of 4-iodo- and 5-iodo-pyrrole-3-carboxaldehydes were obtained in good to high yields from a common set of starting materials. All the synthesized compounds were fully characterized by ^1H NMR, ^{13}C NMR, IR, single X-ray analysis and HRMS mass-data.

In addition, the application of our developed protocol was also established through the quick synthesis of iodo-pyrrolo-[3,2-*c*]quinolone **24**. This scaffolds was prepared through the in situ reduction of $-NO_2$ group at **18aa** with Fe–NH_4Cl in EtOH:H_2O (4:1), followed by intramolecular cyclization in the same pot to furnished **24** in 70% yield as shown in Scheme 3.7. The synthesized hybrid scaffolds such as pyrrolo[3,2-*c*]quinoline showed interesting bioactivity such as ATP-aseinhibitor.[118]



Scheme 3.7 Synthesis of pyrroloquinoline based hybrid scaffold

3.5 Conclusions

In conclusion of this chapter, we have developed a simple and practical methods for synthesis of 4-iodo- pyrrole-3-carboxaldehydes **18** and 5-iodo-pyrrole-3-carboxaldehydes **19** by tuning the reaction condition from common set of starting materials. These reaction proceeds through the sequential multicomponent reaction between succinaldehyde and in situ generated imine (from aromatic/hetroaromatic aldehydes and aromatic amines) to generate dihydropyrrole intermediate through proline catalyzed direct Mannich reaction-cyclizations. Next, dihydropyrrole then underwent two different site-selective transformations; (*i*) I_2-mediated regioselective iodination at C4-position, and simultaneous aromatization to yield 4-iodo-pyrrole-3-carboxaldehydes in

one-pot operation, and (*ii*) oxidative-aromatization with molecular O_2, followed by regioselective iodination with NIS at C5-positions to 5-iodo-pyrrole-3-carboxaldehydes in two-pot fashion. Thus, a series of 4-iodo-, and 5-iodo-pyrrole-3-carboxaldehdyes were synthesized in good to high yields from common set of starting materials.

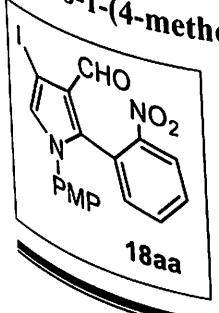
3.6 General Experimental Methods

Unless otherwise stated, all commercially available compounds were used as received without further purification. All solvents employed in the reactions were distilled from appropriate drying agents. All reactions under standard conditions were monitored by thin-layer chromatography (TLC) on Merck silica gel 60 F254 pre-coated plates (0.25 mm). Column chromatographic purification was performed on silica gel (100-200 mesh) using a mixture of hexane/EtOAc. Chemical yields refer to pure isolate substances. ^{1}H, ^{13}C-NMR spectra were recorded in $CDCl_3$ solution and spectral data were reported in ppm relative to tetramethylsilane (TMS) as an internal standard. ^{13}C-NMR spectra were recorded on a BRUKER-AV400 (100MHz) spectrometer with complete proton decoupling. High-resolution mass spectra were recorded using the quadrupole electrospray ionization (ESI) technique.

3.7 Typical procedure for the synthesis of 4-iodo-pyrrole-3-carboxaldehydes (18):

To a stirred solution of **13** (0.3 mmol) in DMSO (3.0 mL) was added **14** (0.3 mmol) and stirred at rt for 2 h. Subsequently, after the in situ imine formation, **15** (0.3 mL, 0.9 mmol, 3M sol) and proline **16** (6.9 mg, 0.06 mmol) were added and additionally stirred at the same temperature for 8 h. After that, molecular I_2 (0.9 mmol) was added to the same flask and stirred additionally for 5 h at the same temperature. The reaction was quenched by with sodium thiosulfate (saturated solution, 10 mL) and stirred with EtOAc (15.0 mL). The organic layer was separated and washed with brine solution, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude material was purified with silica-gel column chromatography by eluting with hexane:EtOAc (4:1) to yield **18** with high yields (69-85%).

3.8 Analytical data of (18aa-18au)

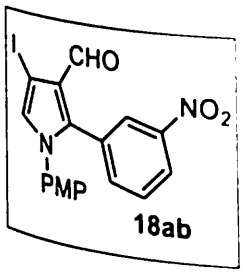


18aa

4-iodo-1-(4-methoxyphenyl)-2-(2-nitrophenyl)-1*H*-pyrrole-3-carbaldehyde (18aa): (100 mg, 75%, red viscous liquid); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76 (s, 3H), 6.76 (d, J = 9.0 Hz, 2H), 7.03 (d, J = 9.0 Hz, 2H), 7.06 (s, 1H), 7.29 (dd, J = 7.5 Hz,1.8 Hz, 1H), 7.54 (m, 2H), 8.02 (dd, J = 7.5, 1.8 Hz, 1H), 9.63 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.4, 64.2, 114.4 (2C), 116.1, 121.1, 123.4, 124.3,

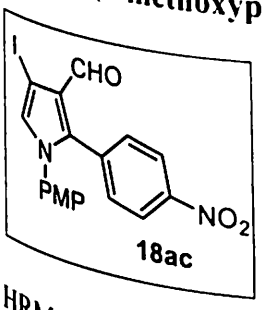
124.6, 124.8, 126.9 (2C), 129.7, 130.1, 132.8, 133.6, 159.4, 186.9.HRMS (ESI-TOF)*m/z*[M + H$^+$] Calcd for $C_{18}H_{13}IN_2O_4$ 448.9998; Found 448.9998.

4-iodo-1-(4-methoxyphenyl)-2-(3-nitrophenyl)-1*H*-pyrrole-3-carbaldehyde (18ab): (97 mg, 73%, yellow oily liquid): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (s, 3H), 6.82 (d, *J* = 8.9 Hz, 2H), 6.99 (d, *J* = 8.9 Hz, 2H), 7.08 (s, 1H) 7.47-7.55 (m, 2H), 8.05 (t, *J* = 1.78 Hz, 1H), 8.18 (d, *J* = 7.11 Hz, 1H), 9.74 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.5, 63.4, 114.7 (2C), 121.7, 123.6, 125.7, 127.2 (2C), 129.1, 130.0, 130.2, 130.7, 136.8, 138.3, 147.7, 159.5, 186.56. HRMS (ESI-TOF) *m/z* [M + H$^+$] Calcd for $C_{18}H_{13}IN_2O_4$ 448.9998; Found 448.9999.



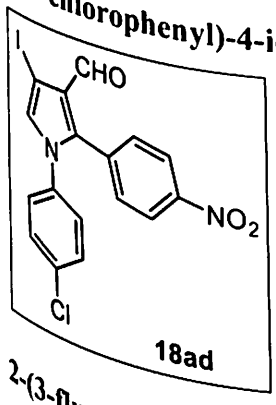
18ab

4-iodo-1-(4-methoxyphenyl)-2-(4-nitrophenyl)-1*H*-pyrrole-3-carbaldehyde (18ac): (113 mg, 85%, yellow solid) (mp =130-132 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 3H), 6.83 (d, *J* = 9.0 Hz, 2H), 6.97 (d, *J* = 9.0 Hz, 2H), 7.09 (s, 1H), 7.36 (d, *J* = 8.9 Hz, 2H), 8.15 (d, *J* = 8.9 Hz, 2H), 9.75 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.5, 63.7, 114.7 (2C), 121.8, 123.2 (2C), 127.1 (2C), 130.1, 131.0, 131.8 (2C), 135.0, 138.4, 147.7, 159.5, 186.5. HRMS (ESI-TOF) *m/z* [M + H$^+$] Calcd for $C_{18}H_{13}IN_2O_4$448.9998; Found 448.9996.



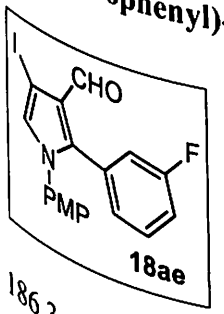
18ac

1-(4-chlorophenyl)-4-iodo-2-(4-nitrophenyl)-1*H*-pyrrole-3-carbaldehyde (18ad): (104 mg, 78%, white solid) (mp =138-140°C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, *J* = 8.8 Hz, 2H), 7.12 (s, 1H), 7.33 (d, *J* = 8.8 Hz, 2H), 7.37 (d, *J* = 8.9 Hz, 2H), 8.17 (d, *J* = 8.9 Hz, 2H), 9.75 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 64.3, 123.4 (2C), 124.2, 127.0 (2C), 129.9 (2C), 130.6, 131.8 (2C), 134.5, 134.8, 135.8, 138.0, 147.8, 186.4.HRMS (ESI-TOF) *m/z* [M + H$^+$] Calcd for $C_{17}H_{10}ClIN_2O_3$452.9503; Found 452.9510.



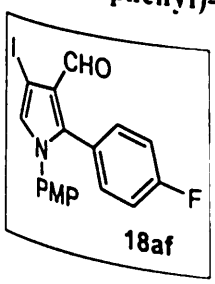
18ad

2-(3-fluorophenyl)-4-iodo-1-(4-methoxyphenyl)-1*H*-pyrrole-3-carbaldehyde (18ae): (91 mg, 73%, brown oily liquid); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 3H), 6.82 (d, *J* = 9.0 Hz, 2H), 6.99 (d, *J* = 9.0 Hz 2H), 7.04 (s, 1H), 7.31–7.27 (m, 1H), 7.49–7.42 (m, 1H), 7.77 (d, *J* = 10.7 Hz, 1H), 7.89 (d, *J* = 7.7 Hz, 1H), 9.71 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.4, 61.2, 114.6 (2C), 115.9, 116.1, 117.8, 118.0, 121.1, 127.0 (2C), 129.80, 129.88, 130.2, 130.5, 141.2, 159.3, 186.3. HRMS (ESI-TOF) *m/z* [M + H$^+$] Calcd for $C_{18}H_{13}FINO_2$ 422.0053; Found 422.0068.



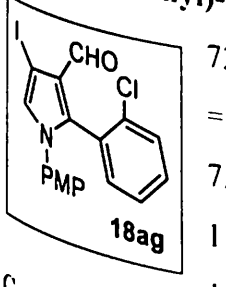
18ae

2-(4-fluorophenyl)-4-iodo-1-(4-methoxyphenyl)-1*H*-pyrrole-3-carbaldehyde (18af): (96 mg, 77%, pasty liquid); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (s, 3H), 6.81 (d, *J* = 9.00 Hz, 2H), 6.97 (d, *J* = 9.04 Hz, 2H), 7.00 (s, 1H), 7.03 (d, *J* = 3.43 Hz, 2H), 7.16 (dd, *J* = 8.88 Hz, 2H), 9.69 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.4, 61.3, 114.4 (2C), 115.3, 115.5, 121.5, 124.0, 127.1 (2C), 130.0, 130.3, 130.6, 132.8, 132.9, 141.9, 159.2, 186.4.HRMS (ESI-TOF) *m/z* [M + H$^+$] Calcd for $C_{18}H_{13}FINO_2$ 422.0053; Found 422.0053.



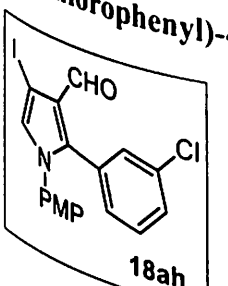
18af

2-(2-chlorophenyl)-4-iodo-1-(4-methoxyphenyl)-1*H*-pyrrole-3-carbaldehyde (18ag): (94 mg, 72%, white oily liquid); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76 (s, 3H), 6.77 (d, *J* = 9.01 Hz, 2H), 7.02 (d, *J* = 9.02 Hz, 2H), 7.07 (s, 1H), 7.23-7.24 (m, 2H), 7.29-7.38 (m, 2H), 9.58 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.4, 61.1, 114.2 (2C), 122.2, 126.52, 126.58 (2C), 128.1, 129.7, 129.9, 130.7, 130.8, 133.2, 135.2, 139.5, 159.1, 186.0. HRMS (ESI-TOF) *m/z* [M + H$^+$] Calcd for $C_{18}H_{13}ClINO_2$ 437.9757; Found 437.9765.



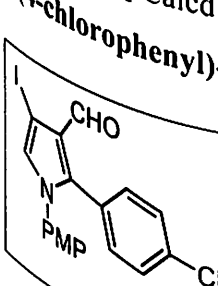
18ag

2-(3-chlorophenyl)-4-iodo-1-(4-methoxyphenyl)-1*H*-pyrrole-3-carbaldehyde (18ah): (95 mg, 73%, brown oily liquid); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (s, 3H), 6.82 (d, *J* = 8.97 Hz, 2H), 6.98 (d, *J* = 8.97 Hz, 2H), 7.02-7.03 (m, 2H), 7.20-7.24 (m, 2H), 7.31 (d, *J* = 9.04 Hz, 1H), 9.70 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.5, 61.3, 114.5 (2C), 121.7, 127.0 (2C), 129.1, 129.4, 129.9, 130.0, 130.4, 130.6, 130.9, 134.1, 141.2, 159.3, 186.2.HRMS (ESI-TOF) *m/z* [M + H$^+$] Calcd for $C_{18}H_{13}ClINO_2$ 437.9757; Found 437.9760.



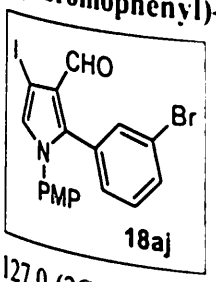
18ah

2-(4-chlorophenyl)-4-iodo-1-(4-methoxyphenyl)-1*H*-pyrrole-3-carbaldehyde (18ai): (96 mg, 74%, brown oily liquid); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 3H), 6.82 (d, *J* = 8.99 Hz, 2H), 6.97 (d, *J* = 9.02 Hz, 2H), 7.03 (s, 1H), 7.11 (d, *J* = 8.64 Hz, 2H), 7.28 (d, *J* = 8.64 Hz, 2H), 9.70 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.4, 61.6, 114.5 (2C), 121.5, 127.0 (2C), 128.5 (2C), 128.7, 128.9, 130.5, 132.2 (2C), 135.2, 141.4, 159.2, 186.3.HRMS (ESI-TOF) *m/z* [M + H$^+$] Calcd for $C_{18}H_{13}ClINO_2$ 437.9757; Found 437.9765.



18ai

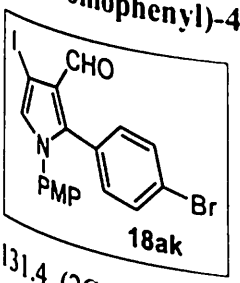
2-(3-bromophenyl)-4-iodo-1-(4-methoxyphenyl)-1*H*-pyrrole-3-carbaldehyde (18aj): (105



18aj

mg, 73%, Reddish viscous oil); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 3H), 6.83 (d, *J* = 9.0 Hz, 2H), 6.99 (d, *J* = 9.0 Hz, 2H), 7.04 (s, 1H), 7.06-7.08 (m, 1H), 7.16 (t, *J* = 7.9 Hz, 1H), 7.37 (s, 1H), 7.45-7.48 (m, 1H), 9.70 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.4, 61.3, 114.5 (2C), 121.7, 122.1, 127.0 (2C), 129.5, 129.6, 130.1, 130.4, 130.6, 132.0, 133.8, 141.1, 159.3, 186.2. HRMS (ESI-TOF) *m/z* [M + H$^+$] Calcd for $C_{18}H_{13}BrINO_2$ 481.9252, Found 481.9252.

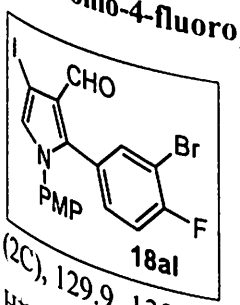
2-(4-bromophenyl)-4-iodo-1-(4-methoxyphenyl)-1*H*-pyrrole-3-carbaldehyde (18ak): (107



18ak

mg, 74%, yellow viscous oil); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 3H), 6.82 (d, *J* = 9.01 Hz, 2H), 6.97 (d, *J* = 9.02 Hz, 2H), 7.04 (d, *J* = 8.44 Hz, 3H), 7.43 (d, *J* = 8.62 Hz, 2H), 9.69 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.4, 61.7, 114.2, 114.5 (2C), 121.5, 123.5, 127.0 (2C), 129.9, 130.5, 131.4 (2C), 132.4 (2C), 141.4, 159.2, 186.3. HRMS (ESI-TOF) *m/z* [M + H$^+$] Calcd for $C_{18}H_{13}BrINO_2$ 481.9252; Found 481.9260.

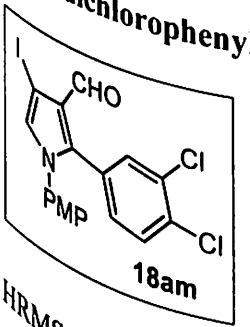
2-(3-bromo-4-fluorophenyl)-4-iodo-1-(4-methoxyphenyl)-1*H*-pyrrole-3-carbaldehyde



18al

(18al): (108 mg, 72%, reddish oily liquid); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.81 (s, 3H), 6.84 (d, *J* = 9.0 Hz, 2H), 6.98 (d, *J* = 9.0 Hz, 2H), 7.03 (s, 1H), 7.05 (s,1H), 7.43 (dd, *J* = 6.6 Hz,1.9 Hz, 2H), 9.70 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.5, 62.1, 114.6 (2C), 116.2, 116.4, 121.6, 127.1 (2C), 129.9, 130.2, 130.5, 131.5, 131.6, 136.0, 139.6, 159.4, 186.3. HRMS (ESI-TOF) *m/z* [M + H$^+$] Calcd for $C_{18}H_{12}BrFINO_2$ 499.9158; Found 499.9165.

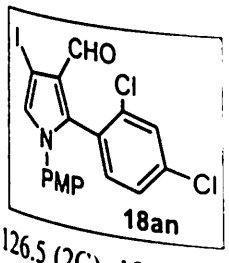
2-(3,4-dichlorophenyl)-4-iodo-1-(4-methoxyphenyl)-1*H*-pyrrole-3-carbaldehyde (18am):



18am

(102 mg, 73%, white viscous oil); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.81 (s, 3H), 6.84 (d, *J* = 9.00 Hz, 2H), 6.99 (d, *J* = 9.01 Hz, 2H), 7.04 (s, 1H), 7.32 (d, *J* = 2 Hz, 1H), 7.35 (d, *J* = 8.31 Hz, 1H), 9.71 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.5, 62.3, 114.6 (2C), 121.6, 127.0 (2C), 128.2, 130.0, 130.1, 130.2, 130.6, 132.5, 132.6, 133.4, 139.3, 159.4, 186.2. HRMS (ESI-TOF) *m/z* [M + H$^+$] Calcd for $C_{18}H_{12}Cl_2INO_2$ 471.9368; Found 471.9375.

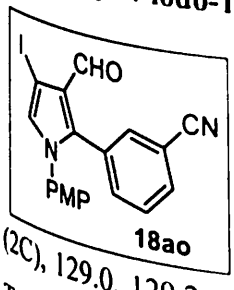
2-(2,4-dichlorophenyl)-4-iodo-1-(4-methoxyphenyl)-1*H*-pyrrole-3-carbaldehyde (18an): (99



18an

mg, 71%, reddish viscous oil); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 3H), 6.80 (d, J = 9.0 Hz, 2H), 7.00 (d, J = 9.0 Hz, 2H), 7.07 (s, 1H), 7.16 (s, 1H), 7.22 (dd, J = 8.3 Hz, 2.0 Hz, 1H), 7.38 (d, J = 2.0 Hz, 1H), 9.60 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.4, 62.2, 114.3 (2C), 122.2, 126.5 (2C), 127.0, 127.7, 129.6, 130.0, 130.4, 133.7, 136.0, 136.1, 137.4, 159.3, 186.1. HRMS (ESI-TOF) m/z [M + H$^+$] Calcd for $C_{18}H_{12}Cl_2INO_2$ 471.9368; Found 471.9368.

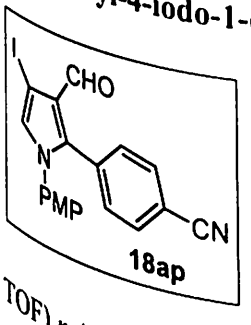
3-(3-formyl-4-iodo-1-(4-methoxyphenyl)-1*H*-pyrrol-2yl)benzonitrile (18ao): (92 mg, 72%,



18ao

yellow pasty liquid); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 3H), 6.83 (d, J = 9.0 Hz, 2H), 6.96 (d, J = 9.0 Hz, 2H), 7.06 (s, 1H), 7.43 (s, 1H), 7.45 (d, J = 1.8 Hz, 2H), 7.61 (dd, J = 8.7 Hz, 1.9 Hz, 1H), 9.71 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.5, 63.1, 114.6 (2C), 117.9, 121.7, 127.1 (2C), 129.0, 129.2, 129.4, 129.9, 130.0, 130.6, 131.4, 132.2, 134.1, 135.2, 186.4. HRMS (ESI-TOF) m/z [M + H$^+$] Calcd for $C_{19}H_{13}IN_2O_2$ 429.0100; Found 429.0110.

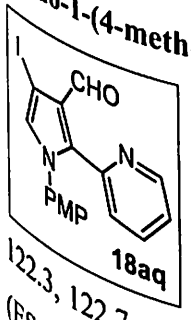
4-(3-formyl-4-iodo-1-(4-methoxyphenyl)-1*H*-pyrrol-2yl)benzonitrile (18ap): (96 mg, 76%,



18ap

orange pasty liquid); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 3H), 6.83 (d, J = 9.0 Hz, 2H), 6.96 (d, J = 9.0 Hz, 2H), 7.08 (s, 1H), 7.30 (d, J = 8.6 Hz, 2H), 7.58 (d, J = 8.6 Hz, 2H), 9.73 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.5, 63.3, 114.6 (2C), 118.2, 118.5, 121.7, 127.0 (2C), 129.8, 130.2, 130.9, 131.5 (2C), 131.8 (2C), 133.1, 159.5, 186.5. HRMS (ESI-TOF) m/z [M + H$^+$] Calcd for $C_{19}H_{13}IN_2O_2$ 429.0100; Found 429.0100.

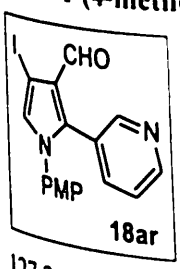
4-iodo-1-(4-methoxyphenyl)-2-(pyridin-2-yl)-1*H*-pyrrole-3-carbaldehyde (18aq): (83 mg,



18aq

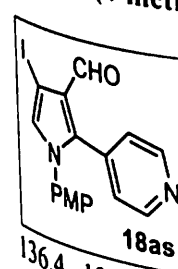
69%, light red oily liquid); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (s, 3H), 6.68 (s, 1H), 6.81 (d, J = 9.0 Hz, 2H), 7.03 (d, J = 9.1 Hz, 3H), 7.18 (d, J = 7.8 Hz, 1H), 7.21 – 7.25 (m, 1H), 7.61 (td, J = 7.8 Hz, 1.8 Hz, 1H), 8.57 – 8.58 (m, 1H), 9.86 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.0, 61.9, 115.0 (2C), 122.3, 122.7, 127.6 (2C), 130.1, 130.3, 130.7, 131.1, 132.5, 134.3, 141.6, 159.8, 186.8. HRMS (ESI-TOF) m/z [M + H$^+$] Calcd for $C_{17}H_{13}IN_2O_2$ 405.0100; Found 405.0100.

4-iodo-1-(4-methoxyphenyl)-2-(pyridine-3-yl)-1*H*-pyrrole-3-carbaldehyde (18ar): (86 mg, 72%, red oily liquid); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (s, 3H), 6.82 (d, *J* = 9.0 Hz, 2H), 6.99 (d, *J* = 9.0 Hz, 2H), 7.08 (s, 1H), 7.28 (s, 1H), 7.52–7.57 (m, 1H), 8.41 (d, *J* = 2.8 Hz, 1H), 8.55 (dd, *J* = 4.9 Hz, 1.6 Hz, 1H), 9.73 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.4, 62.7, 114.6 (2C), 121.9, 122.9, 124.8, 127.2 (2C), 128.6, 130.2, 130.8, 138.2, 149.6, 151.0, 159.5, 186.3. HRMS (ESI-TOF) *m/z* [M + H$^+$] Calcd for $C_{17}H_{13}IN_2O_2$ 405.0100; Found 405.0105.



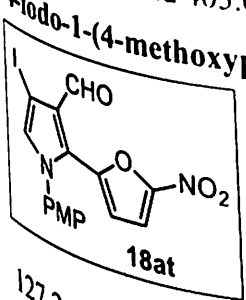
18ar

4-iodo-1-(4-methoxyphenyl)-2-(pyridin-4-yl)-1*H*-pyrrole-3-carbaldehyde (18as): (74 mg, 74%, red pasty liquid); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 3H), 6.83 (d, *J* = 9.0 Hz, 2H), 6.98 (d, *J* = 9.0 Hz, 2H), 7.09 (d, *J* = 2.3 Hz, 2H), 7.10 (s, 1H), 8.55 (d, *J* = 6.1 Hz, 2H), 9.76 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.5, 62.8, 114.6 (2C), 122.0, 123.8, 125.2 (2C), 127.0 (2C), 130.2, 131.2 (2C), 136.4, 138.5, 149.6, 159.6, 186.2. HRMS (ESI-TOF) *m/z* [M + H$^+$] Calcd for $C_{17}H_{13}IN_2O_2$ 405.0100; Found 405.0105.



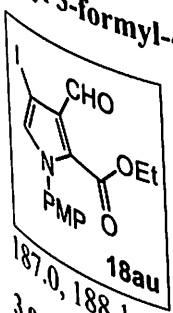
18as

4-iodo-1-(4-methoxyphenyl)-2-(5-nitrofuran-2-yl)-1*H*-pyrrole-3-carbaldehyde (18at): (100 mg, 77%, yellow oily liquid); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.86 (s, 3H), 6.67 (d, *J* = 3.85 Hz, 1H), 6.95 (d, *J* = 8.99 Hz, 2H), 7.09 (s, 1H), 7.19 (d, *J* = 9.28 Hz, 2H), 7.25 (d, *J* = 3.84 Hz, 1H), 10.02 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.6, 64.5, 112.3, 114.0, 114.7 (2C), 115.2, 124.0, 126.9, 127.2 (2C), 130.6, 132.9, 145.0, 160.3, 186.4. HRMS (ESI-TOF) *m/z* [M + H$^+$] Calcd for $C_{16}H_{11}IN_2O_5$ 438.9791, Found 438.9791.



18at

Ethyl 3-formyl-4-iodo-1-(4-methoxyphenyl)-1*H*-pyrrole-2-carboxylate (18au): (98 mg, 84%, colorless oily liquid); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (t, *J* = 7.1 Hz, 3H), 3.86 (s, 3H), 4.21 (q, *J* = 7.1 Hz, 2H), 6.95 (d, *J* = 9.0 Hz, 2H), 7.01 (s, 1H), 7.19 (d, *J* = 9.0 Hz, 2H), 10.41 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6, 29.6, 55.4, 61.48, 114.0 (2C), 144.3, 127.0 (2C), 131.7, 134.0, 134.5, 159.7, 187.0, 188.1. HRMS (ESI-TOF) *m/z* [M + H$^+$] Calcd for $C_{15}H_{14}INO_4$ 400.0046; Found 400.0050.



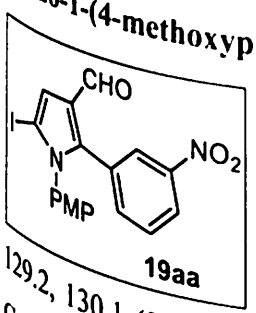
18au

3.9 Typical procedure for the synthesis of 5-iodo-pyrrole-3-carboxaldehydes (19):

To a stirred solution of **13** (0.3 mmol) in DMSO (3.0 mL) was added **14** (0.3 mmol) and stirred at rt for 2 h. Subsequently, after the in situ imine formation, **15** (0.3 mL, 0.9 mmol, 3M sol) and proline **16** (6.9 mg, 0.06 mmol) were added and additionally stirred at the same temperature for 8

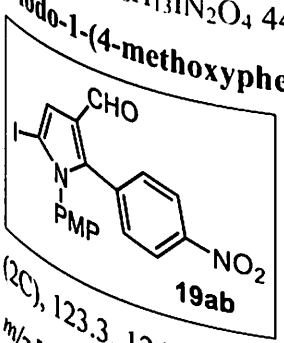
h. After that, molecular oxygen was purged into the same flask and heated at 80 °C for 5 h. The reaction mixture was cooled and stirred between CH_2Cl_2 (10.0 mL) and $NaHCO_3$ (10% aqueous sol., 5.0 mL), organic layer was separated and concentrated under reduced pressure. The crude pyrrole-3-carboxaldehdye **17** was used further for regioselective iodination without purification. Therefore, to the stirred solution of crude **17** in CH_3CN (3.0 mL) was added NIS (1.1 eq, 0.33 mmol) and stirred at 85 °C for 4 h. The reaction was cooled and stirred between by $Na_2S_2O_3$ (saturated sodium, 5.0 mL) and EtOAc (5.0 mL). The organic layer was separated and again extracted with EtOAc (5.0 mL), the combined organic layer was washed with brine solution, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude material was purified with silica-gel column chromatography by eluting with hexane:EtOAc (4:1) to yield **19** with high yields (72-82%).

3.10 Analytical data of (19aa-19ca)



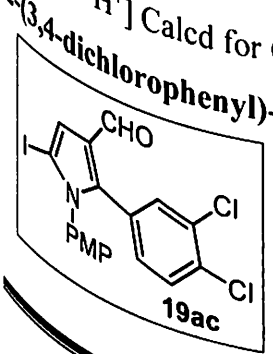
19aa

5-iodo-1-(4-methoxyphenyl)-2-(3-nitrophenyl)-1*H*-pyrrole-3-carbaldehyde (19aa): (106 mg, 80%, red oily liquid); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.81 (s, 3H), 6.87 (d, J = 8.9 Hz, 2H), 7.05 (d, J = 8.9 Hz, 2H), 7.13 (s, 1H), 7.53 7.45 (m, 2H), 8.04 (t, J = 1.8 Hz, 1H), 8.17–8.13 (m, 1H), 9.58 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.4, 78.6, 114.4 (2C), 118.6, 123.5, 125.4, 126.6, 129.2, 130.1 (2C), 131.1, 136.4, 141.8, 147.8, 160.0, 184.6. HRMS (ESI-TOF) *m/z* [M + H$^+$] Calcd for $C_{18}H_{13}IN_2O_4$ 448.9998; Found 448.9990.



19ab

5-iodo-1-(4-methoxyphenyl)-2-(4-nitrophenyl)-1*H*-pyrrole-3-carbaldehyde (19ab): (106 mg, 80%, yellow solid) (mp =130-132 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82 (s, 3H), 6.88 (d, J = 9.0 Hz, 2H), 7.03 (d, J = 9.0 Hz, 2H), 7.14 (s, 1H), 7.33 (d, J = 8.9 Hz, 2H), 8.13 (d, J = 8.9 Hz, 2H), 9.59 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.4, 79.1, 114.3 (2C), 118.8, 123.1 (2C), 123.3, 124.4, 129.8 (2C), 130.0, 131.5 (2C), 131.7, 135.3, 160.0, 185.9. HRMS (ESI-TOF) *m/z* [M + H$^+$] Calcd for $C_{18}H_{13}IN_2O_4$448.9998; Found 448.9996.

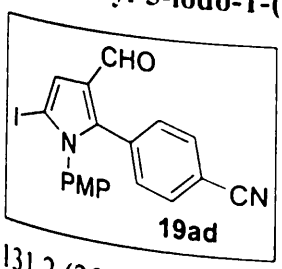


19ac

2-(3,4-dichlorophenyl)-5-iodo-1-(4-methoxyphenyl)-1*H*-pyrrole-3-carbaldehyde (19ac): (110 mg, 79%, yellow pasty liquid); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.83 (s, 3H); 6.89 (d, J = 8.9 Hz, 2H), 6.96 (dd, J = 8.3 Hz, 2.1 Hz, 1H), 7.03 (d, J = 8.9 Hz, 2H), 7.09 (s, 1H), 7.29 (d, J = 2.0 Hz, 1H), 7.33 (d, J = 8.3 Hz, 1H), 9.55 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.4,

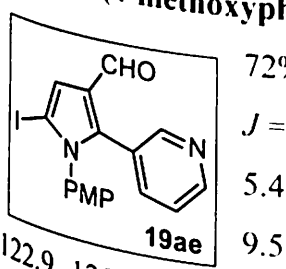
78.2, 114.3 (2C), 118.2, 126.4, 129.2, 129.7, 130.0 (2C), 130.1, 130.6, 132.4, 132.5, 133.3, 142.4, 159.9, 184.8.HRMS (ESI-TOF) *m/z* [M + H$^+$] Calcd for $C_{18}H_{12}Cl_2INO_2$ 471.9368; Found 471.9375.

4-(3-formyl-5-iodo-1-(4-methoxyphenyl)-1*H*-pyrrol-2-yl)benzonitrile (19ad): (99 mg, 78%, orange pasty liquid); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.81 (s, 3H), 6.86 (d, *J* = 9.0 Hz, 2H), 7.00 (d, *J* = 9.0 Hz, 2H), 7.10 (s, 1H), 7.24 (d, 2H), 7.55 (d, *J* = 8.6 Hz, 2H), 9.54 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.4, 78.8, 114.3 (2C), 118.0, 118.6, 126.6, 127.0, 130.0 (2C), 130.5, 131.2 (2C), 131.4, 131.8 (2C), 133.9, 160.0, 184.7. HRMS (ESI-TOF) *m/z* [M + H$^+$] Calcd for $C_{19}H_{13}IN_2O_2$ 429.0100; Found 429.0100.



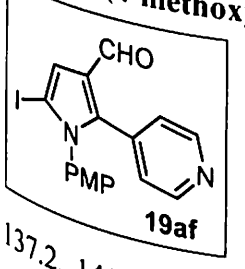
19ad

5-iodo-1-(4-methoxyphenyl)-2-(pyridin-3-yl)-1*H*-pyrrole-3-carbaldehyde (19ae): (86 mg, 72%, red pasty liquid); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 3H), 6.84 (d, *J* = 8.9 Hz, 2H), 7.01 (d, *J* = 8.9 Hz, 2H), 7.09 (s, 1H), 7.21 (dd, *J* = 7.8 Hz, 5.4 Hz, 1H), 7.46 (d, *J* = 7.8 Hz, 1H), 8.43 (s, 1H), 8.49 (d, *J* = 9.1 Hz, 1H), 9.50 (s, 1H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.3, 78.5, 114.2 (2C), 118.2, 122.9, 125.6, 126.7, 130.1 (2C), 130.4, 137.9, 141.3, 149.3, 150.5, 159.8, 184.7. HRMS (ESI-TOF) *m/z* [M + H$^+$] Calcd for $C_{17}H_{13}IN_2O_2$405.0100, Found 405.0105.



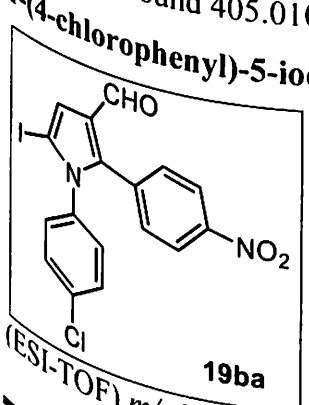
19ae

5-iodo-1-(4-methoxyphenyl)-2-(pyridin-4-yl)-1*H*-pyrrole-3-carbaldehyde (19af): (87 mg, 73%, orange oily liquid); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.83 (s, 3H), 6.88 (d, *J* = 8.9 Hz, 2H), 7.03 (d, *J* = 8.9 Hz, 2H), 7.06 (d, *J* = 6.1 Hz, 2H), 7.13 (s, 1H), 8.53 (d, *J* = 5.3 Hz, 2H), 9.60 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.4, 79.1, 114.3 (2C), 118.6, 124.9 (2C), 126.7 (2C), 129.9, 130.0 (2C), 137.2, 141.6, 149.62, 160.0, 184.7. HRMS (ESI-TOF) *m/z* [M + H$^+$] Calcd for $C_{17}H_{13}IN_2O_2$ 405.0100; Found 405.0105.



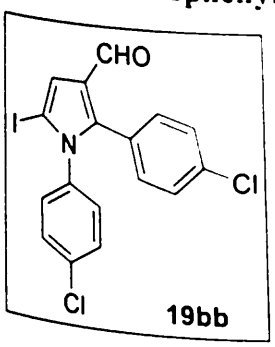
19af

1-(4-chlorophenyl)-5-iodo-2-(4-nitrophenyl)-1*H*-pyrrole-3-carbaldehyde (19ba): (105 mg, 78%, white solid) (mp =138-140 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (d,*J* = 8.8 Hz, 2H), 7.15 (s, 1H), 7.33 (d, *J* = 8.9 Hz, 2H), 7.38 (d, *J* = 8.8 Hz, 2H), 8.15 (d, *J* = 8.9 Hz, 2H), 9.59 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 78.0, 119.4, 123.5 (2C), 123.6, 127.0, 129.6 (2C), 130.2 (2C), 131.4 (2C), 135.3, 136.2, 141.7, 147.7, 184.6. HRMS (ESI-TOF) *m/z* [M + H$^+$] Calcd for $C_{17}H_{10}ClIN_2O_3$ 452.9503; Found 452.9510.

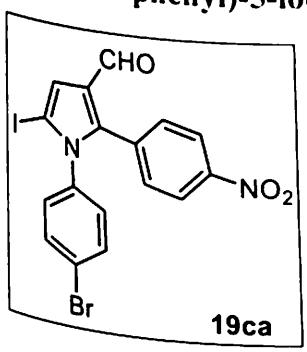


19ba

1,2-bis(4-chlorophenyl)-5-iodo-1*H*-pyrrole-3-carbaldehyde (19bb): (102 mg, 77%, white solid) (mp = 139-141 °C); ^{1}H NMR (400 MHz, CDCl3) δ 7.06 (d, *J* = 6.9 Hz, 2H), 7.08 (d, *J* = 6.8 Hz, 2H), 7.12 (s, 1H), 7.29 (d, *J* = 8.2 Hz, 2H), 7.37 (d, *J* = 8.7 Hz, 2H), 9.53 (s, 1H); ^{13}C NMR (100 MHz, CDCl3) δ 76.6, 118.6, 126.5, 127.3, 128.7 (2C), 129.4 (2C), 130.3 (2C), 131.9 (2C), 135.3, 135.4, 136.6, 144.0, 185.0. HRMS (ESI-TOF) *m/z* [M + H$^+$] Calcd for $C_{17}H_{10}Cl_2INO$ 441.9262; Found 441.9263.

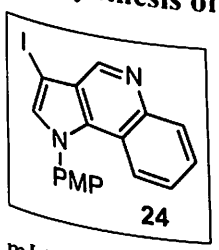


1-(4-bromophenyl)-5-iodo-2-(4-nitrophenyl)-1*H*-pyrrole-3-carbaldehyde (19ca): (122 mg, 82%,white solid) (mp =140-142 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, *J* = 8.7 Hz, 2H), 7.16 (s, 1H), 7.33 (d, *J* = 8.9 Hz, 2H), 7.54 (d, *J* = 8.7 Hz, 2H), 8.16 (d, *J* = 8.9 Hz, 2H), 9.60 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 77.9, 119.4, 123.5 (2C), 123.8, 127.0, 130.5 (2C), 131.4 (2C), 132.6 (2C), 135.2, 136.7, 141.6, 147.7, 184.5. HRMS (ESI-TOF) *m/z* [M + H$^+$] Calcd for $C_{17}H_{10}BrIN_2O_3$ 496.8997; Found 496.8998.



3.11 Synthesis of 3-iodo-1-(4-methoxyphenyl)-1*H*-pyrrolo[3,2-*c*]quinolone 24:

To a stirred solution of **18aa** (50 mg, 0.13 mmol) in EtOH:H2O (5 mL, 4:1) was added Fe powder (86.9 mg, 1.3 mmol, 10.0 equiv.) and NH_4Cl (100 mg, 1.8 mmol, 12.0 equiv.) and heated at 90 °C for 10 h. The reaction mixture was cooled and extracted between EtOAc (10.0 mL) and aqueous $NaHCO_3$ (5.0 mL). The combined organic layer was separated and concentrated under reduced pressure followed by purification through a pad of silica-gel by eluting with hexane/EtOAc (3:1) afforded **24** (83 mg, 70% yield) as yellow solid.



(31 mg, 70%, yellow solid) (M.P =130-132 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.95 (s, 3H), 7.09 (d, *J* = 8.9 Hz, 2H), 7.29 (s, 1H), 7.33 (d, *J* = 8.4 Hz, 1H), 7.40 (d, *J* = 8.9 Hz, 2H), 7.55–7.59 (m, 2H), 8.21 (d, *J* = 8.3 Hz, 1H), 8.98 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.6, 57.4, 114.9 (2C), 117.4, 120.4, 123.0, 125.7, 126.9, 128.4 (2C), 130.3, 132.5, 133.9, 135.6, 145.1, 146.5, 160.2. HRMS (ESI-TOF) *m/z* [M + H$^+$] Calcd for $C_{18}H_{13}IN_2O$ 401.0151; Found 401.0151.

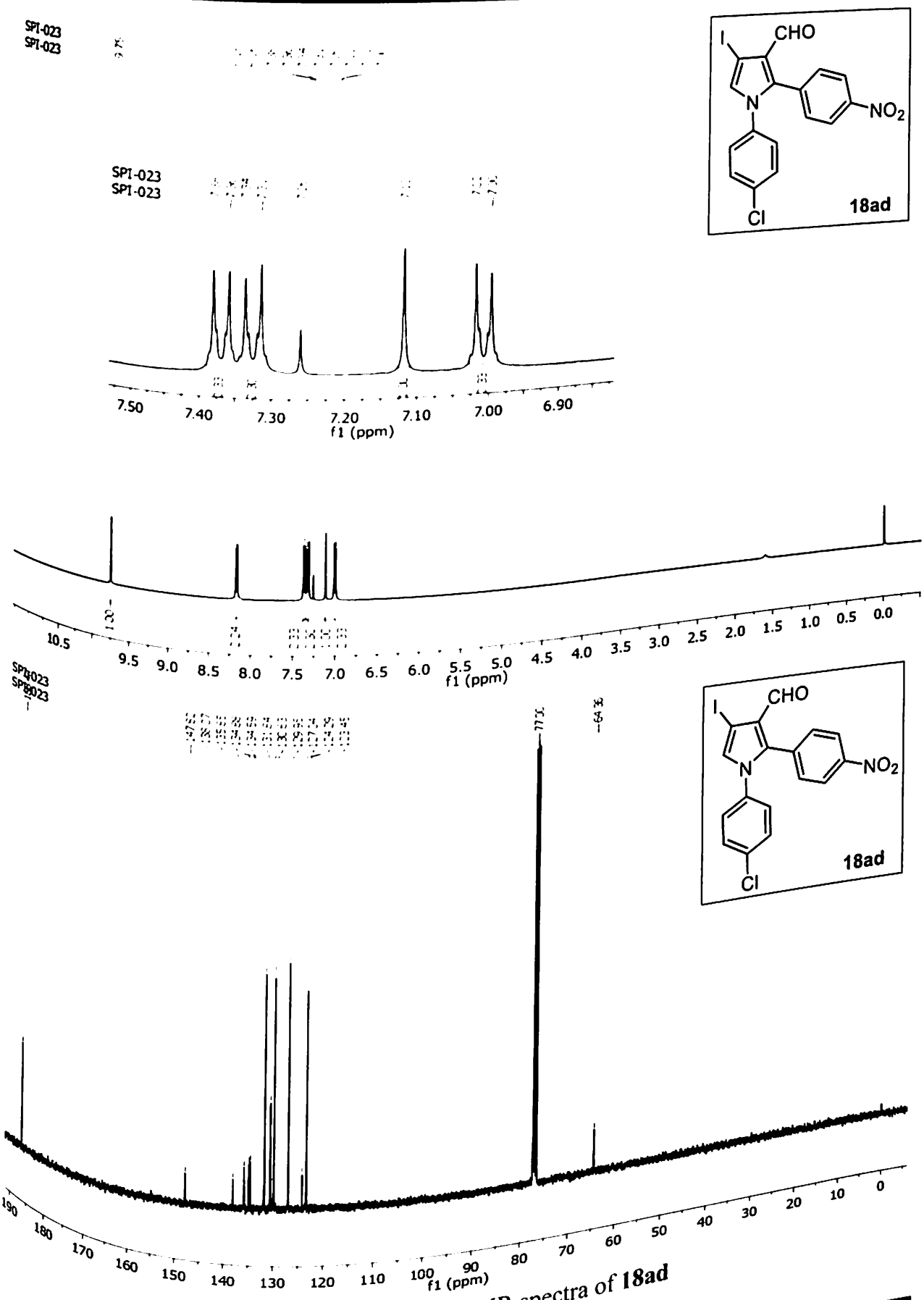
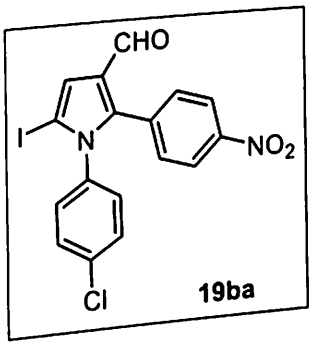
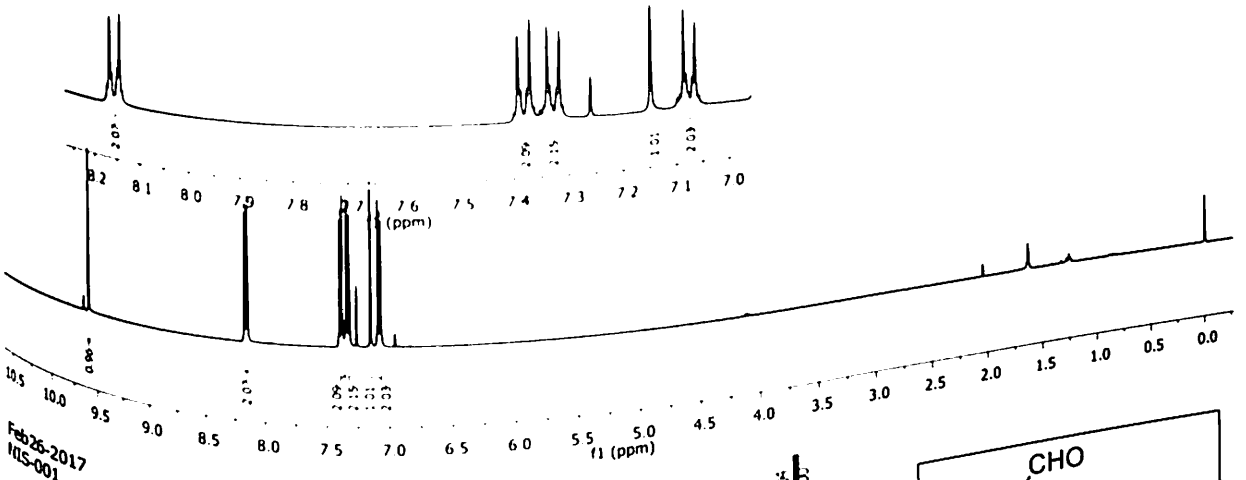


Figure 3.4 ^{1}H and ^{13}C NMR spectra of **18ad**





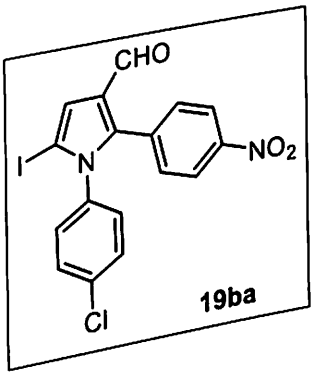


Figure 3.5 ^{1}H and ^{13}C NMR spectra of **19ba**

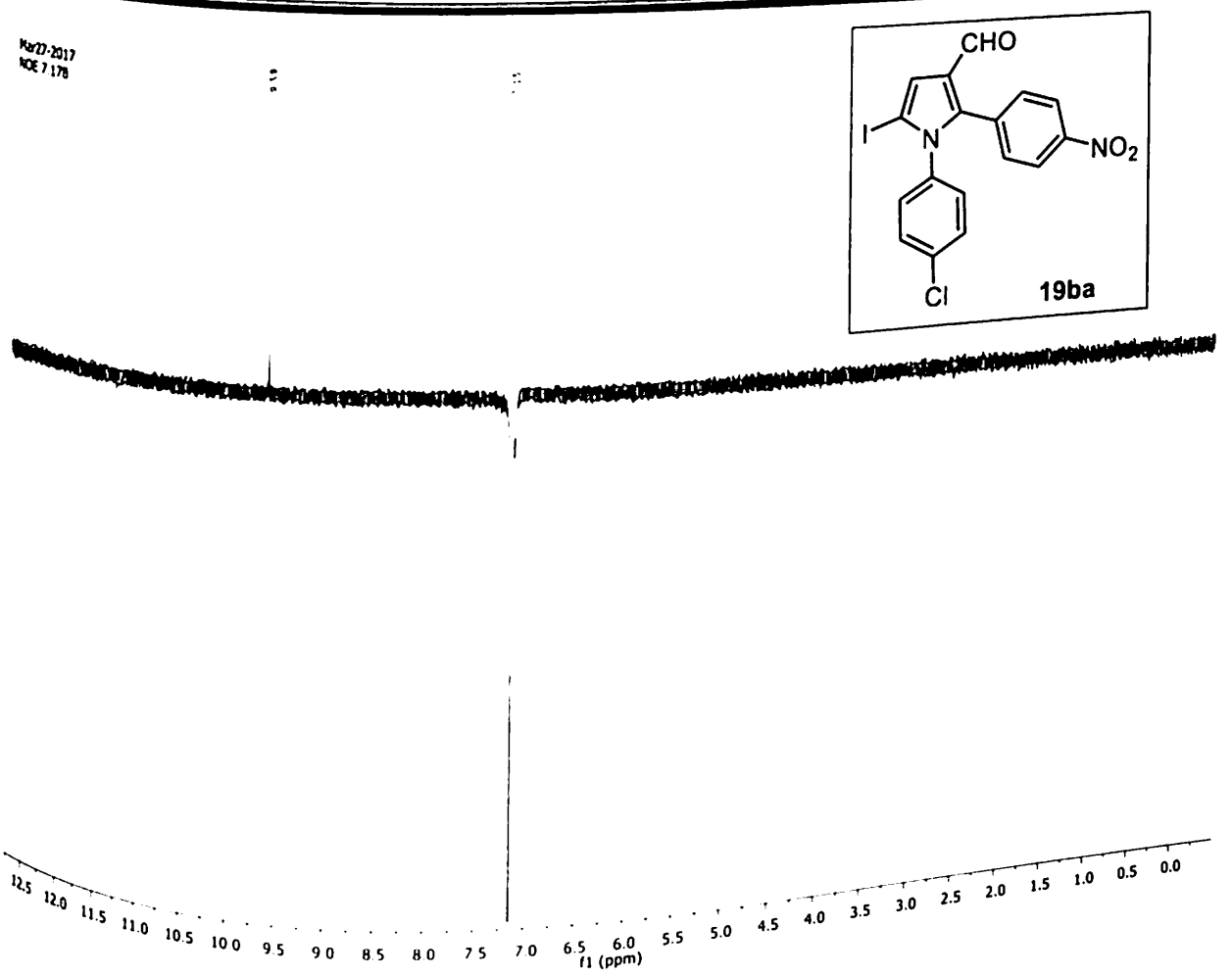
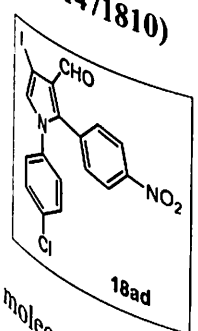


Figure 3.6 NOE spectra of **19ba**

3.12 Crystal structure data for (18ad): 1-(4-chlorophenyl)-4-iodo-2-(4-nitrophenyl)-1H-pyrrole-3-carbaldehyde (18ad): (CCDC NO. 1471810)



The title compound1-(4-chlorophenyl)-4-iodo-2-(4-nitrophenyl)-1H-pyrrole-3-carbaldehyde (**18ad**), $C_{17}H_{10}ClIN_2O_3$ crystallizes in the Orthorhombic space group*Pca2*with unit cell parameters *a*= 18.4757(12), *b*= 9.7925(5),*c*= 18.6956(13)Å and Z=8. The X-ray analysis reveals that the asymmetric unit of the title compound comprises of two crystallographically independent molecules, A and B, with similar geometries. The crystal packing of the molecule is governed by four intermolecular hydrogen bonding [one C-H...Cl and three C-H...O]. Block-shaped crystal selected for intensity data collection was of dimensions 0.30 x 0.20 x 0.10 mm. Accurate cell parameters were determined from 2042 reflections with $3.7<\theta<27.31°$. X-ray intensity data of 8495 reflections (of which 5369 were unique) were collected on a computer controlled single crystal X-

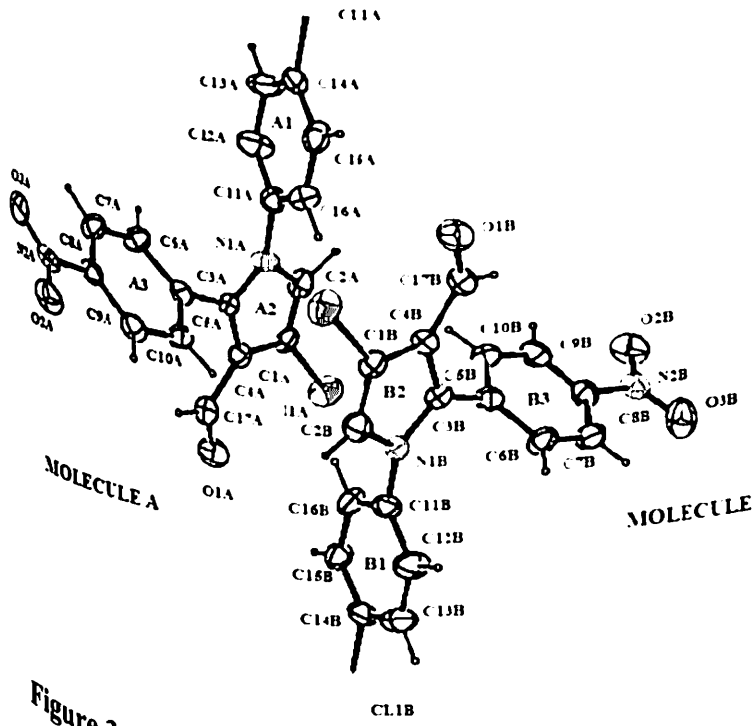
ray diffractometer with graphite monochromated Mo $K\alpha$ radiation (λ = 0.71073 Å) in ω scan mode. The number of reflections after applying the limiting criterion I >2σ(I) converged to 3531 which were considered as observed ($-21 \leq h \leq 22$, $-12 \leq k \leq 5$, $-23 \leq l \leq 21$). Data were corrected for Lorentz-polarization and multi-scan absorption corrections. The crystal structure was solved by direct methods using SHELXS97 software [2]. Full-matrix least-squares refinement was carried out using SHELXL97 software. All H atoms [except H4b] were positioned geometrically and were treated as riding on their parent C atoms, with C–H distances of 0.93–0.97 Å and with $U_{iso}(H) = 1.2U_{eq}(C)$ or $1.5U_{eq}$(methyl C). The final refinement cycles converged R = 0.0452 and w$R(F^2)$ = 0.0987. Atomic scattering factors were taken from International Tables for X-ray Crystallography (1992, Vol. C, Tables4.2.6.8 and 6.1.1.4). The crystallographic data are summarized in Table 3.5. A general view of the molecule indicating atom-numbering scheme (thermal ellipsoids are drawn at 40% probability level) is shown in Figure 3.6. ORTEP-3for Windows software was used for making the thermal ellipsoids. The geometry of the molecule was calculated using PLATON and PARST software. The asymmetric unit of the title compound comprises of two crystallographically independent molecules, A and B, with similar geometries. Each molecule comprises three rings chlorophenyl, pyrrole and nitrophenyl ring. These rings are labeled as A1, A2, A3 and B1, B2, B3 with respect to molecule A and molecule B. All bond lengths and angles are normal and correspond to those observed in the literature.

Table 3.5 Crystal and experimental data for **18ad**

CCDC NO.	**1471810**
Crystal description	Block
Crystal colour	White
Crystal size	0.3 x 0.2 x 0.1 mm
Empirical formula	$C_{17}H_{10}ClIN_2O_3$
Formula weight	452.62
Radiation, Wavelength	Mo $K\alpha$, 0.71073 Å
Crystal system	Orthorhombic
Space group	*Pca2*
Hall symbol	*P2c -2ac*

No. of molecules per unit cell, Z	8
Unit cell dimensions	a= 18.4757(12), b= 9.7925(5),c= 18.6956(13)Å
Unit cell volume	3382.5(4)Å^3
D_x	1.273 g cm^{-3}
Temperature	293(2) K
Absorption coefficient	2.07 mm^{-1}
F(000)	1760
θ range for collection of cell parameters	3.716 <θ<27.3100 º
Measurement	X'calibur system–*Oxford diffraction make, U.K.* [Oxford Diffraction, 2010]
Structure determination	Direct methods
Range of indices	h=-21 to 22, k= -12 to 5, l= -23 to 21
Reflections collected / unique	8495 / 5369
Reflections observed ($I > 2\sigma(I)$)	3531
R_{int}	0.027
R_{sigma}	0.0518
Scan mode	ω scan
θ_{max}	26.00°
θ_{min}	3.73°
T_{min}, T_{max}	0.39569, 1.0000
Absorption correction	multi-scan[*CrysAlisRED*; Oxford Diffraction, 2010]
Refinement	Full-matrix least squares on F^2
No. of parameters refined	441
Final R	0 .0452
$wR(F^2)$	0.0987
Weight	$w=1/[\sigma^2(F_o^2)+(0.0494P)^2+0.00P]$ where $P=[F_o^2+2F_c^2]/3$.
Goodness-of-fit	1.028
$(\Delta/\sigma)_{max}$	0.001

Final residual electron density	-0.706< $\Delta\rho$<0.073e Å^{-3}
Software for structure solution	SHELXS97 [Sheldrick, 2008]
Software for refinement	SHELXL97 [Sheldrick, 2008]
Software for molecular plotting	ORTEP-3[Farrugia,2012]; PLATON [Spek,2009]
Software for geometrical calculation	PLATON [Spek, 2009]; PARST [Nardelli, 1995]



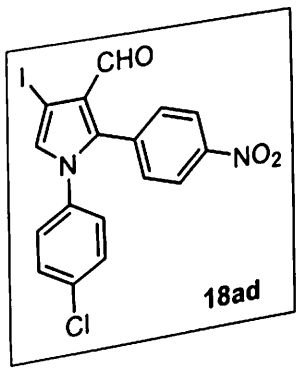
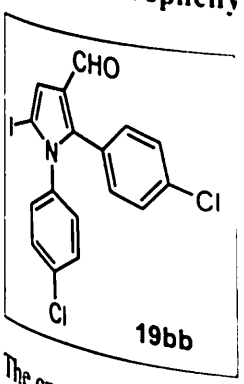


Figure 3.7: ORTEP plot of the molecule (**18ad**) with 40% probability thermal ellipsoids. H-atoms are shown as small spheres of arbitrary radii (**CCDC NO. 1471810**)

3.13 Crystal structure data for (19bb):

1,2-bis(4-chlorophenyl)-4-iodo-1H-pyrrole-3-carbaldehyde (19bb): (CCDC NO. 1573099)



19bb

The title compound1,2-bis(4-chlorophenyl)-4-iodo-1H-pyrrole-3-carbaldehyde (**19bb**), $C_{17}H_{10}N_1O_1Cl_2I_1$,crystallizes in the monoclinic space group P2$_1$/n with unit cell parameters: a = 6.6656(7), b = 19.4376(15), c = 13.2403(13)Å, β = 104.291(11)° and Z= 4. The crystal structure was solved by direct methods using single-crystal X-ray diffraction data and refined to R = 0.0383 for 2288 observed reflections. The crystal packing is stabilized by Vander Waal's interactions.

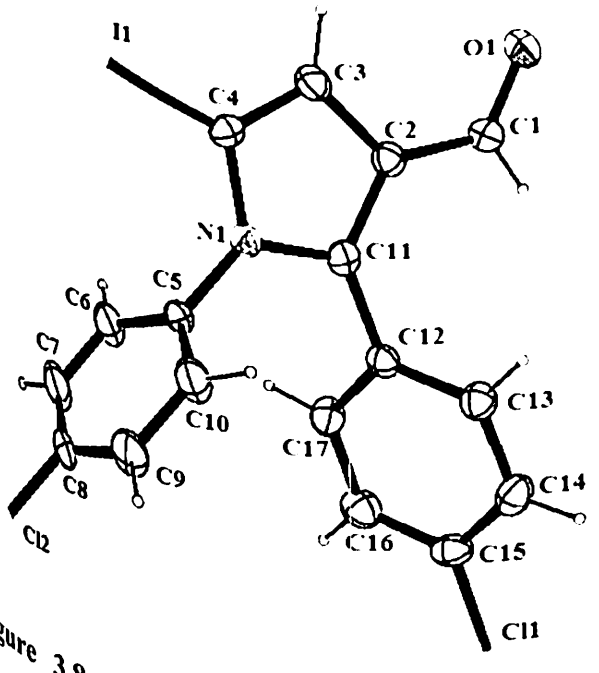
Crystal Structure Determination and Refinement

X-ray intensity data of the crystal of the dimension 0.30 X 0.20 X 0.20 mm^3 having well-defined morphology was collected on *Xcalibur* CCD area-detector diffractometer equipped with graphite monochromated Mo*Kα* radiation (λ = 0.71073 Å). X-ray intensity data of 4614 reflections (of which 3039 unique) were collected at 293(2)K. The cell dimensions were determined by a least-squares fit of angular settings of 1559 reflections in the θ range 3.66 to 29.07 °. The intensities were measured by oscan mode forθ ranges 3.99 to 27.01 °. 2288 reflections were treated as observed (I> 2σ(I)). Data were corrected for Lorentz and polarization factors. The structure was solved by direct methods using SHELXS97. All non-hydrogen atoms of the molecule were located in the best E-map. Full-matrix least-squares refinement was carried out using SHELXL97. All the hydrogen atoms were geometrically fixed and allowed to ride on their parent carbon atoms with C-H= 0.93 Å with $U_{iso}(H) = 1.2U_{eq}(C)$. The final refinement cycles converged to an R = 0.0383 and wR (F^2) = 0.0853 for the observed data. Residual electron densities ranged from -0.613 to 0.560 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 3.6. An ORTEP view of the title compound with atomic labeling is shown in Fig.3.7. The geometry of the molecule was calculated using the PLATON and PARST software's. Bond lengths and bond angles are within expected values.

Table 3.6 Crystal and experimental data for **19bb**

CCDC No	1573099
Crystal description	Block shaped
Crystal colour	White
Crystal size	0.3 x 0.2 x 0.2 mm
Empirical formula	$C_{17}H_{10}N_1O_1Cl_2I_1$
Formula weight	442.06
Radiation, Wavelength Mo Kα,	0.71073 Å
Unit cell dimensions	a= 6.6656(7), b= 19.4376(15), c= 13.2403(13)Å,
	β= 104.291(11)°
Crystal system	Monoclinic
Space group	$P2_1/n$
Unit cell volume	1662.4(3)
No. of molecules per unit cell, Z	4
Temperature	293(2)
Absorption coefficient	2.247 mm^{-1}
F(000)	856
Scan mode	ω scan
θ range for entire data collection	3.79<θ<25.99 º
Range of indices	h= -8 to 7, k= -23 to 23, l= -11 to 16
Reflections collected / unique	4614 / 3039
Reflections observed ($I > 2\sigma(I)$)	2288
R_{int}	0.0507
R_{sigma}	0.0285
Structure determination	Direct methods
Refinement	Full-matrix least-squares on F^2
No. of parameters refined	200
Final R	0.0383
$wR(F^2)$	0.0853
Weight	$1/[\sigma^2(F_o^2)+(0.0367P)^2+0.3021P]$ where $P=[F_o^2+2F_c^2]/3$

Goodness-of-fit	1.069
$(\Delta/\sigma)_{max}$	0.002 (for U33 C7)
Final residual electron density	$-0.613 < \Delta\rho < 0.560$ eÅ^{-3}
Measurement	*X'calibur system – Oxford diffraction make, U.K.*
Software for structure solution:	SHELXS97 (Sheldrick, 2008)
Software for refinement:	SHELXL97 (Sheldrick, 2015)
Software for molecular plotting:	ORTEP-3 (Farrugia, 2012) PLATON (Spek, 2009)
Software for geometrical calculation	PLATON (Spek, 2009)



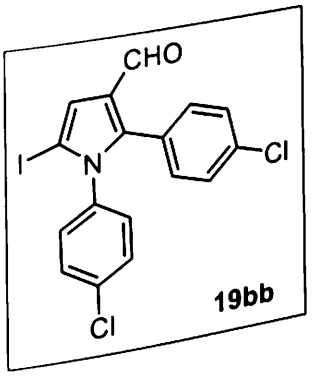


Figure 3.8: *ORTEP* view of the molecule (**19bb**), showing the atom-labeling scheme. Displacement ellipsoids are drawn at the 50% probability level and H-atoms are shown as small spheres of arbitrary radii **(CCDC NO. 1573099)**

3.14 References

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