Chapter – 4

Metal-free synthesis of tetracyclic oxazepine-fused pyrroles

4.1 Introduction

Fused-nitrogen heterocycles are not only found in numerous natural products that exhibit interesting biological activities but also have wide applications in the field of materials science.[1-5] For instance, dibenzo[*b*,*f*][1,4]oxazepine (DBO), as well as their derivatives, are regarded as "privileged scaffolds" in medicinal chemistry.[6] Dibenzoxazepine scaffold is present in marketed antidepressants drugs such as Amoxapine, and several other related compounds[7-14] that possess a wide range of biological activity such as anti-HIV [15-18] anti-inflammatory,[19-20] antihistaminic,[21] antidepressant,[22-24] anti-psychotics,[25] progesterone receptor agonists,[26-27] and histone deacetylase inhibitors[28] as well as several others such as psychotropic activity, prostaglandin receptor antagonism, MAP kinase inhibition, ion channel modulation and muscarinic cholinergic receptor agonists.[29-34] Owing to their widespread prevalence as pharmacophores in medicinal chemistry, a number of methods have been explored for the synthesis of 1,4-dibenzoxazepines in asymmetric and non-asymmetric fashion.[35-36] In particular, heterocyclic *ortho*-fused dibenz[*b*,*f*][1,4]oxazepines, resembles the tetracyclic anti-depressants (TeCAs),[37] with similar and interesting bioactivities[38-41] are attractive targets to explore further as drugs candidates, some of them are shown in Figure 1. Despite high medicinal importance of *ortho*-fused dibenz[*b*,*f*][1,4]oxazepines, a limited number of methods are available for their synthesis.

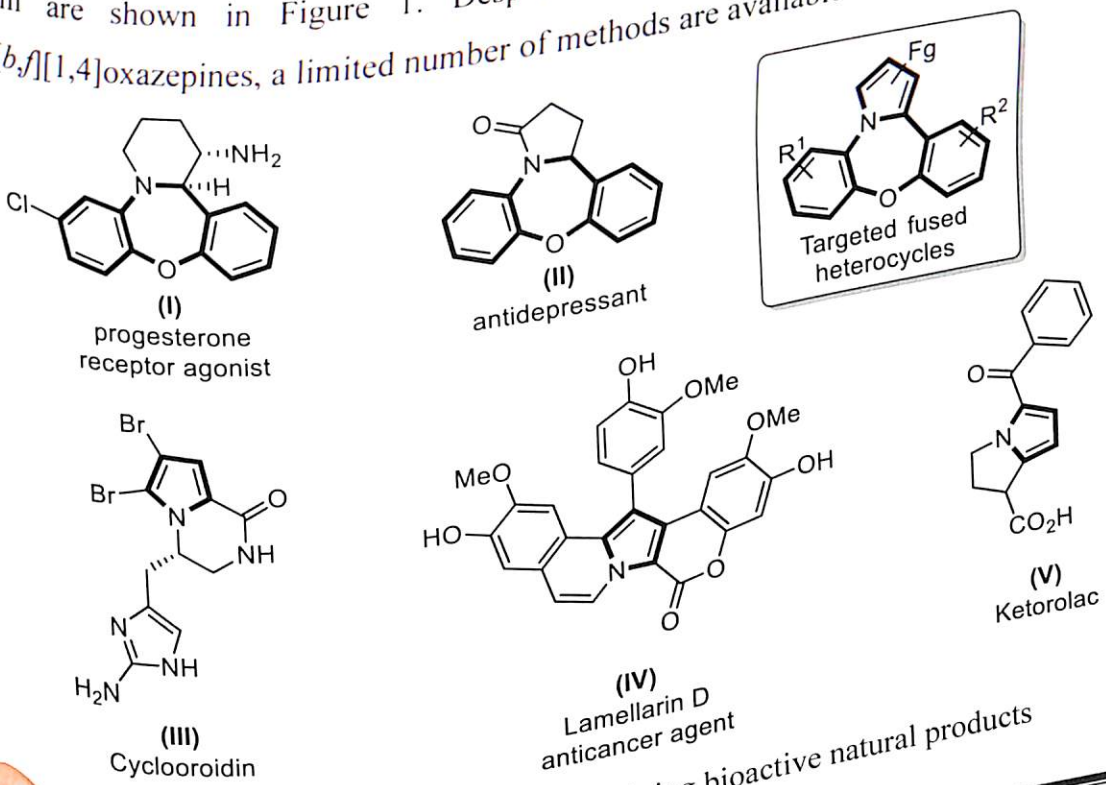


Figure 4.1: Some fused pyrrole-containing bioactive natural products

4.1 Introduction

Fused-nitrogen heterocycles are not only found in numerous natural products that exhibit interesting biological activities but also have wide applications in the field of materials science.[1-9] For instance, dibenzo[*b*,*f*][1,4]oxazepine (DBO), as well as their derivatives, are regarded as "privileged scaffolds" in medicinal chemistry.[6] Dibenzoxazepine scaffold is present in marketed antidepressants drugs such as Amoxapine, and several other related compounds[7-14] that possess a wide range of biological activity such as anti-HIV,[15-18] anti-inflammatory,[19-20] antihistaminic,[21] antidepressant,[22-24] anti-psychotics,[25] progesterone receptor agonists,[26-27] and histone deacetylase inhibitors[28] as well as several others such as psychotropic activity, prostaglandin receptor antagonism, MAP kinase inhibition, ion channel modulation and muscarinic cholinergic receptor agonists.[29-34] Owing to their widespread prevalence as pharmacophores in medicinal chemistry, a number of methods have been explored for the synthesis of 1,4-dibenzoxazepines in asymmetric and non-asymmetric fashion.[35-36] In particular, heterocyclic *ortho*-fused dibenz[*b*,*f*][1,4]oxazepines, resembles the tetracyclic anti-depressants (TeCAs),[37] with similar and interesting bioactivities[38-41] are attractive targets to explore further as drugs candidates, some of them are shown in Figure 1. Despite high medicinal importance of *ortho*-fused dibenz[*b*,*f*][1,4]oxazepines, a limited number of methods are available for their synthesis.

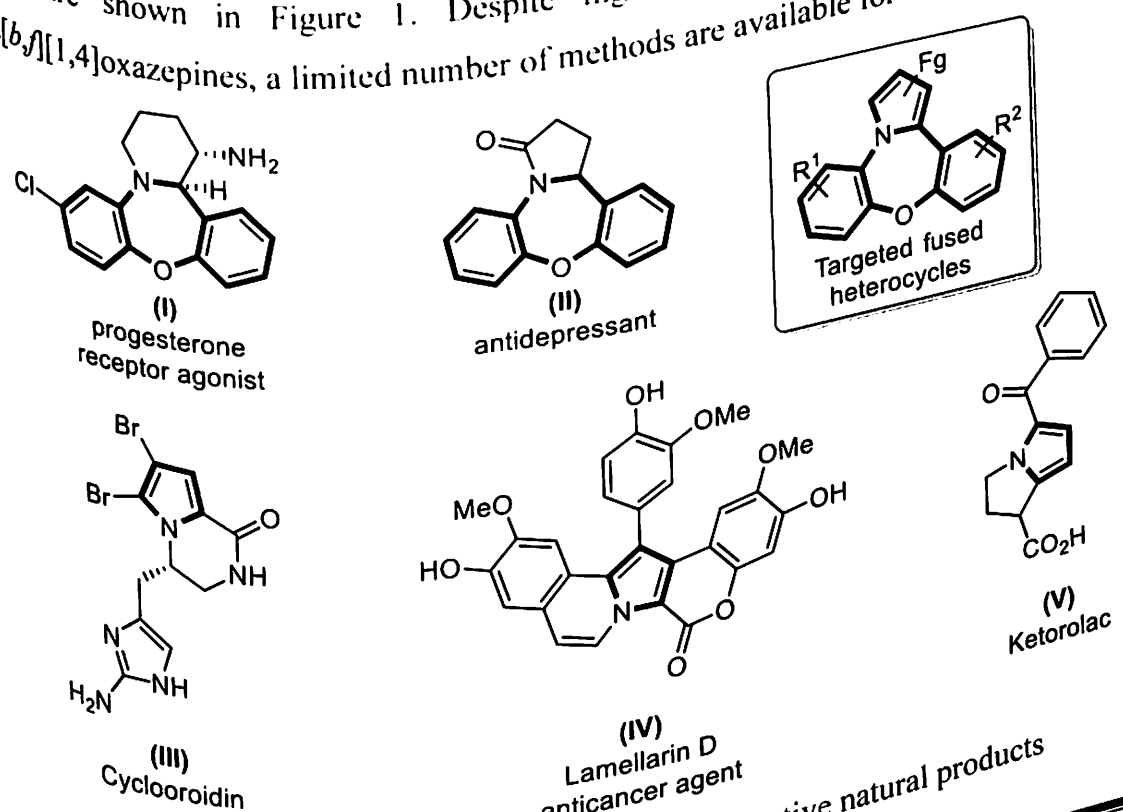
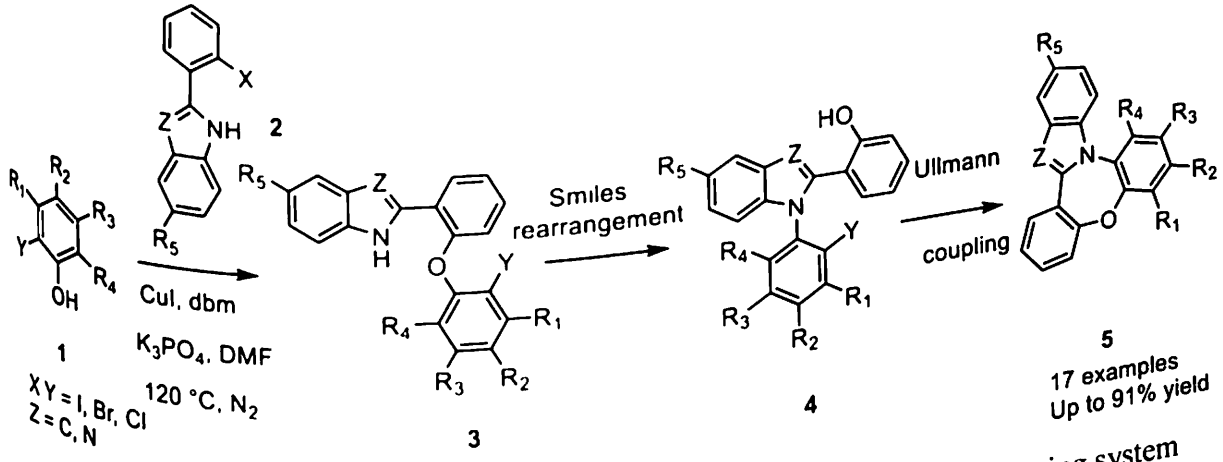


Figure 4.1: Some fused pyrrole-containing bioactive natural products

4.2 Synthetic approaches for the tetracyclic fused dibenzo[*b*,*f*][1,4]oxazepines

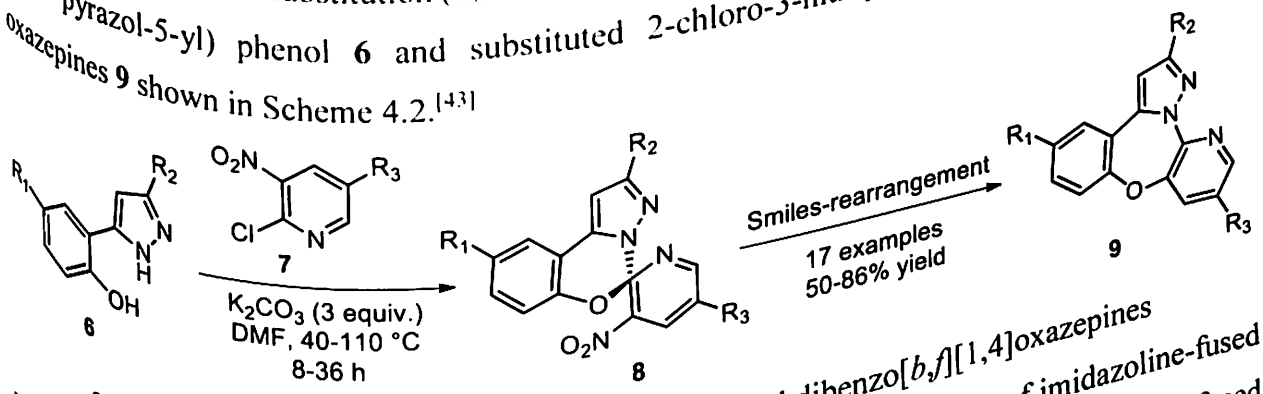
4.2.1 Methods using a direct synthesis of the seven-membered ring system

Zhang and co-workers developed an efficient transformation of copper catalysis for the one-pot synthesis of fused dibenzo[*b*,*f*][1,4]oxazepines **5** in good yields with regioselectivity. This protocol involves an Ullmann coupling and Smiles rearrangement between 2-halophenols **1** and 2-(2-halophenyl)-1*H*-indoles **2** giving the fused oxazepines shown in Scheme 4.1.[42]



Scheme 4.1: Highly regioselective synthesis of the fused seven-membered ring system

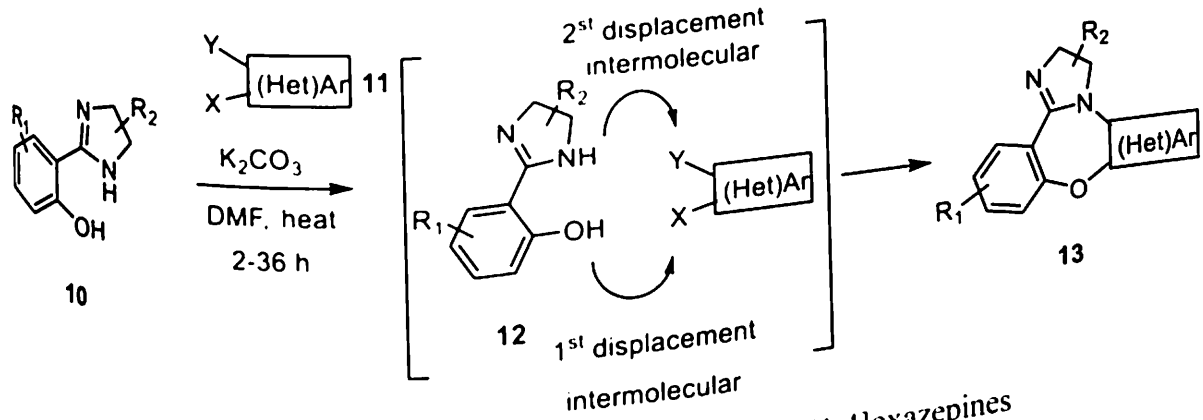
Krasavin and co-workers developed a synthetic methodology for the one-pot synthesis of fused dibenzo[*b*,*f*][1,4]oxazepines **9** in high yield. This protocol involves three tandem chemical events ~nucleophilic aromatic substitution (SNAr), Smiles rearrangement and denitrocyclization between 2-(1*H*-pyrazol-5-yl) phenol **6** and substituted 2-chloro-3-nitropyridine **7** giving the fused oxazepines **9** shown in Scheme 4.2.[43]



Scheme 4.2: One-pot synthesis of tetracyclic fused dibenzo[*b*,*f*][1,4]oxazepines

Krasavin and co-workers developed an efficient method for the preparation of imidazoline-fused [1,4]oxazepines **13** with aromatic and heteroaromatic groups in high yields. Imidazoline-fused oxazepines **13** scaffolds were synthesized from substituted 2-hydroxyphenyl imidazolines **10** and

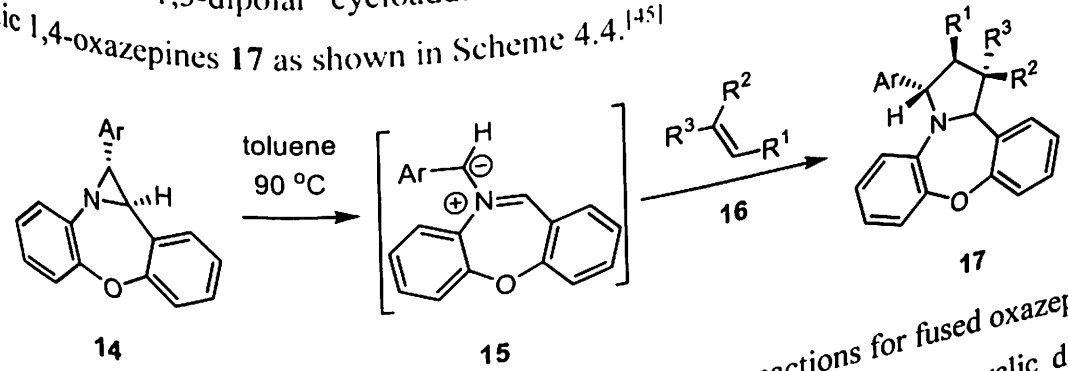
bis-electrophilic aromatic substrates **11** in a reaction involving sequential nucleophilic aromatic substitution steps and a Smiles rearrangement as shown in Scheme 4.3.[44]



Scheme 4.3: Synthesis of imidazoline-fused [1,4]oxazepines

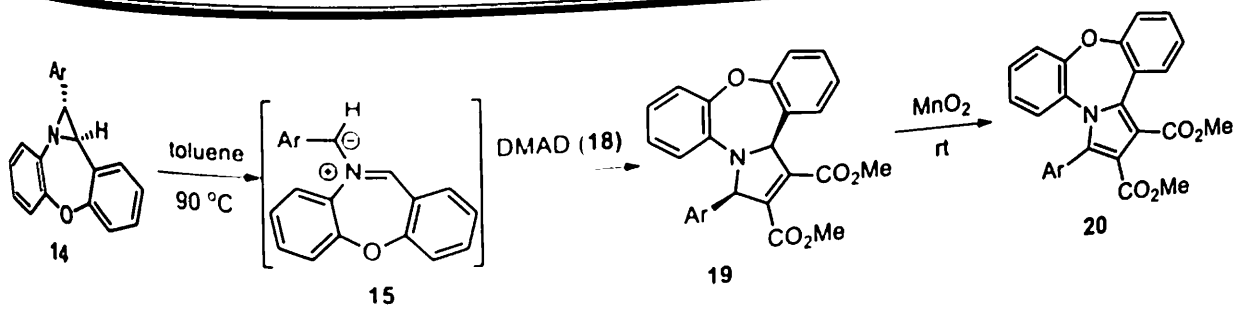
4.2.2 Methods using a preformed seven-membered ring system

Khlebnikov and co-workers developed a novel approach for tetracyclic oxazepine system through the use of preformed azirino-fused compounds such as 1-aryl-1,11b-dihydoazirino[1,2-*d*]dibenz[*b*,*f*][1,4]oxazepines **14** which on heating in situ generated azomethine ylides **15** for 1,3-dipolar cycloadditions with an activated dienophile. Here, the ylides **15** undergoes stereospecific and stereoselective 1,3-dipolar cycloadditions with activated olefins **16** to produce fused tetracyclic 1,4-oxazepines **17** as shown in Scheme 4.4.[45]



Scheme 4.4: Facile access and 1,3-dipolar cycloadditions reactions for fused oxazepines

Similarly, the same group has extended this work for the synthesis of tetracyclic dibenzo[*b*,*f*]pyrrolo-[1,2-*d*][1,4]oxazepinecarboxylates **20**. In this transformation initially stereoselective 1,3-dipolar cycloaddition of azomethine ylides **15**, took place with dimethylbut-2-ynedioate **18** to give cycloadduct **19**. Followed by a smooth aromatization under mild conditions furnished tetracyclic oxazepine-fused pyrrole derivatives **20** shown in Scheme 4.5.[46]



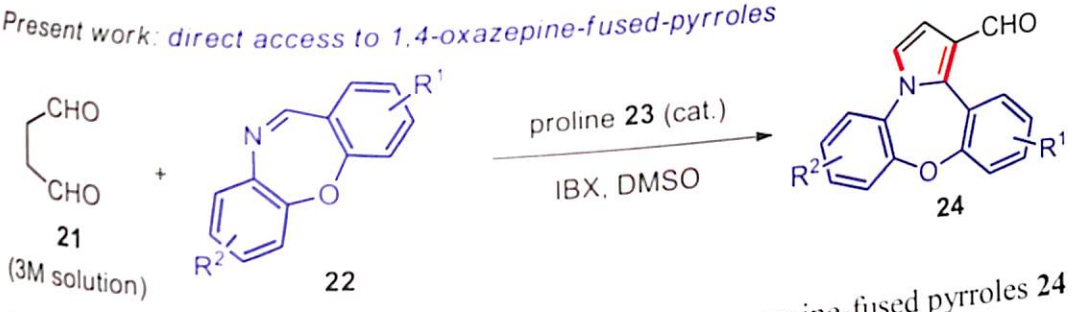
14 15 19 20

Scheme 4.5: Synthesis of tetracyclic 3-aryldibenzo[*b,f*]pyrrolo[1,2-d][1,4]oxazepines

Although these existing methods provide an access to *ortho*-fused-oxazepines, some of them suffer due to the multistep process from starting materials and have limited substrate scope. Thus, the development of a simple protocol to access new tetracyclic pyrrolo-oxazepines from easily available materials is highly required.

On the other hand, multi-substituted and fused pyrroles are present as a main structural unit in various biological active natural and synthetic compounds as shown in Figure 1.[47-53] Polycyclic pyrroles are not only present in agrochemicals[54] and functionalized materials,[55-59] but also showed a wide range of biological activities.[60-68] Consequently, the design and development of fused pyrroles have remained one of the popular and demanding areas in medicinal and organic chemistry during the last decade.[69-76] A number of elegant methods have been developed to access fused pyrroles during last decade[77-81] which mainly involve direct decoration on the pyrrole ring,[82-84] intermolecular cycloadditions,[85-86] intramolecular cyclo-isomerization reactions, etc.[87] However, some of these methods involved multi-step processes and direct synthesis of fused polycyclic pyrroles with required functionality from easily available materials are limited. Moreover, the development of economical and efficient catalytic protocols that directly produce the required functionality at the desired position of fused heterocyclic ring systems are of great importance to the pharmaceutical industry. Herein, we present an efficient method for the one-pot synthesis of novel tetracyclic pyrrolo-oxazepines **24** with aldehyde functionality under proline **23** catalyzed Mannich reaction-cyclization, followed by IBX-mediated oxidative aromatization sequence between succinaldehyde **21** and dibenzoxazepine-imines **22** (Scheme 4.6). Interestingly, these fused pyrroles hold significant promises to serve as a suitable intermediate to synthesize new polycyclic medicinal agents as aldehyde group can participate in various name reactions.

Present work: direct access to 1,4-oxazepine-fused-pyrroles

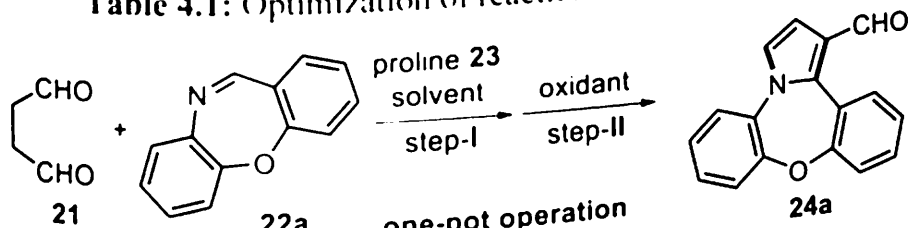


Scheme 4.6: Direct one-pot synthesis of tetracyclic oxazepine-fused pyrroles **24**

4.3 Results and discussion

Earlier, we developed a protocol to prepare functionalized pyrroles using the reaction of aldimines and succinaldehyde.[88] The clear synthetic potential of the earlier protocol to functionalized pyrroles, that could serve as an alternative to a traditional Paal-Knorr method involving 1,4-dicarbonyls,[89-90] prompted us to explore similar transformation by employing dibenzoxazepines, seven-membered cyclic imines, as suitable substrates to access polycyclic pyrroles. Having this idea in mind, we quickly established reaction conditions for a proline-catalyzed direct Mannich/cyclization/aromatization sequence as [3+2] annulation between 1,4-dibenzoxazepine **22a** as model substrate and succinaldehyde **21** in DMSO as the choice of solvent. As shown in Table 4.1, tetracyclic oxazepine-fused pyrrole **24a** was obtained in 35% yield when DDQ was used as an oxidizing agent at rt in the same pot (entry 1, Table 4.1). Next, we examined other oxidants like SeO_2, IBX, $K_2S_2O_8$, and oxone in combinations with DMSO and other solvents (entries 2–8, Table 4.1). Initially, one-pot reaction with IBX as an oxidant (1.2 equiv.) in DMSO at rt gave **24a** in 50% yield (entry 3, Table 4.1). In addition, an improved yield of **24a** (74%) was observed when IBX-mediated oxidative aromatization was carried out at 50 °C (entry 9, Table 4.1). Consequently, tetracyclic pyrrole **24a** was obtained with 90% yield (entry 6, Table 4.1) when further heated up to 70 °C with IBX for 4 h (entry 10, Table 4.1). Any additional change in the reaction conditions caused a loss in the overall yield of the protocol (entries 11-13, Table 4.1). Thus, we preferred to use this one-pot methodology under the optimized conditions (entry 10, Table 4.1). Interestingly, this one-pot protocol became highly feasible due to the high solubility of IBX in DMSO as well as its ability to dehydrogenate carbonyls into the corresponding α,β-unsaturated moieties. Next, the substrate scope for this one-pot protocol was investigated with various 1,4-dibenzoxazepine imines **22** under optimized conditions and the results are shown in Table 4.2. In general, a wide range of cyclic aldimines **22**, decorated with both electron-donating and electron withdrawing substituents at different positions of the two aryl rings, afforded the desired tetracyclic pyrroles **24**

Table 4.1: Optimization of reaction conditions for **24a**

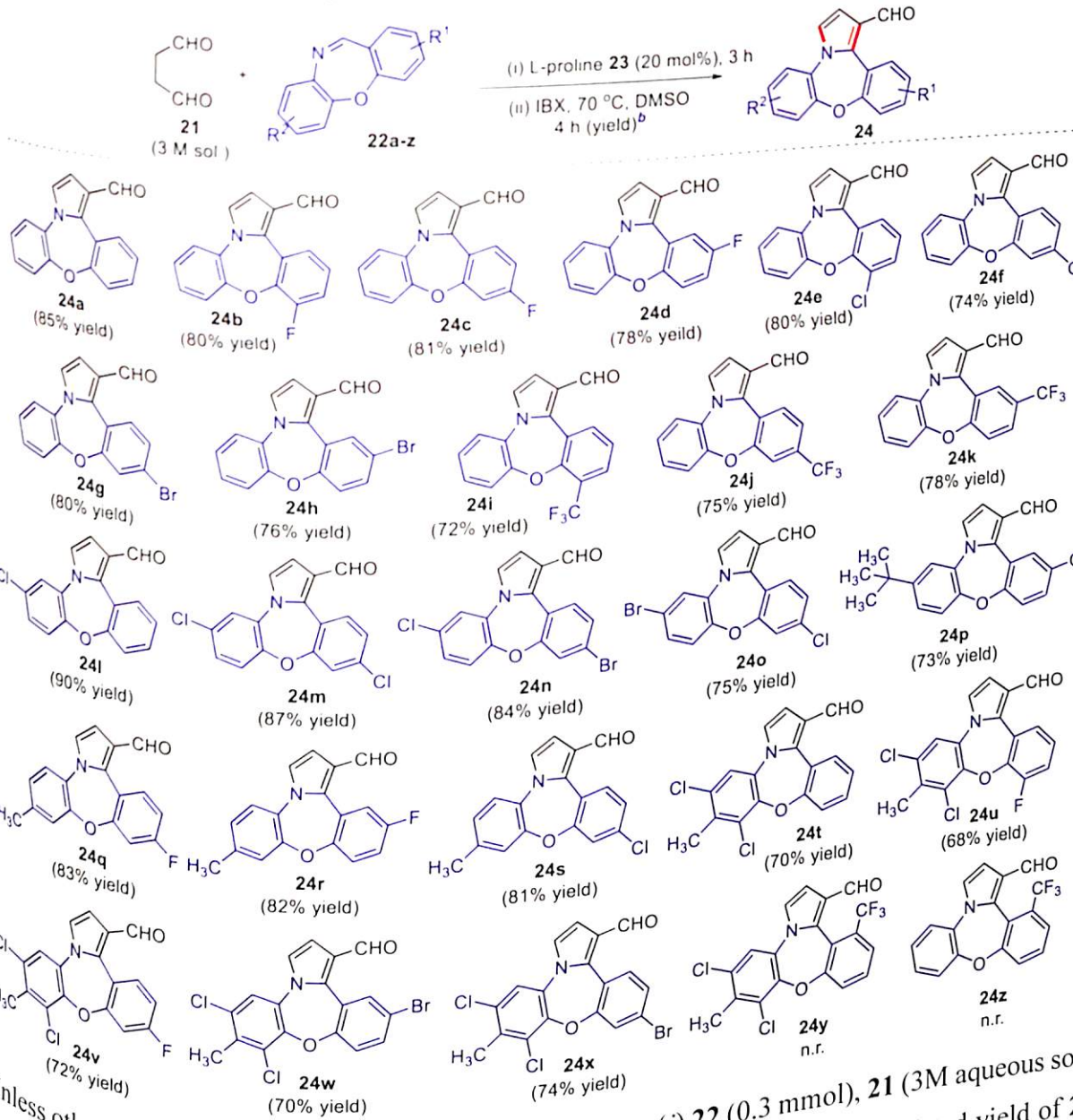


entry	step-I	step-II	yield (%)[b]
1	DMSO, rt, 3 h	DDQ, rt, 6 h	35
2	DMSO, rt, 3 h	SeO_2, rt, 6 h	<20
3	DMSO, rt, 3 h	IBX (1.2 equiv.), rt, 6 h	50
4	DMSO, rt, 3 h	$K_2S_2O_8$ (1.2 equiv.), rt, 8 h	32
5	DMSO, rt, 3 h	Oxone (1.2 equiv.), rt, 24 h	<20
6	DMF, rt, 8 h	Oxone (1.2 equiv.), rt, 24 h	<10
7	DMF, rt, 8 h	IBX (1.2 equiv.), 50 °C, 4 h	40
8	CH_3CN, rt, 8 h	IBX (1.2 equiv.), 50 °C, 4 h	35
9	DMSO, rt, 3 h	IBX (1.2 equiv.), 50 °C, 4 h	74
10	**DMSO, rt, 3 h**	**IBX** (1.2 equiv.), **70 °C, 4 h**	**90**
11	DMSO, rt , 3 h	IBX (1.2 equiv.), 90 °C, 4 h	81
12[c]	DMSO, rt, 3 h	IBX (1.2 equiv.), 70 °C, 4 h	78
13[d]	DMSO, rt, 3 h	IBX (1.2 equiv.), 70 °C, 4 h	48

[a]Unless otherwise indicated, the reaction was carried out at (*i*) **22a** (0.3 mmol), succinaldehyde **21** (3M aqueous sol., 0.9 mmol), proline **23** (20 mol %), solvent (3.0 mL); (*ii*) oxidant (120 mol %).[b]Isolated yield of **24a** refer to **22a**. [c]reaction was carried out with extracted succinaldehyde **21** (0.9 mmol). [d]reaction was carried out using proline **23** (10 mol %).

with good to excellent yields. Initially, the imines **22a-22k**, derived from 2-aminophenol and variously substituted 2-fluorobenzaldehydes resulted in products **24a-24k** (Table 4.2) with high yields. Additionally, cyclic-imines **22l-22s**, prepared from substituted 2-aminophenols and substituted 2-fluorobenzaldehydes, decorated with F, Cl, Br, CH_3, and *tert*-butyl substituents at different positions of the two aryl rings which also furnished corresponding fused pyrroles **24l-24s** with high yields (up to 90% yield) (Table 4.2).

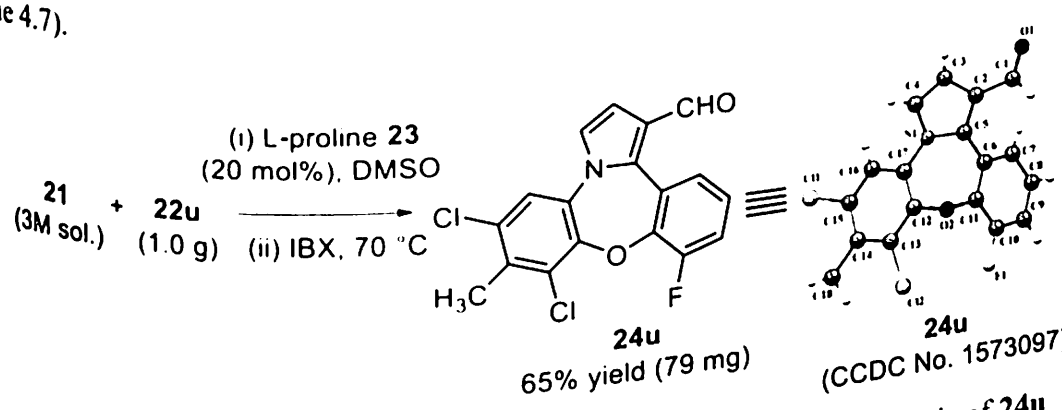
Table 4.2: Generality with respect to various dibenzo[*b*,*f*][1,4]oxazepines **22**



[a]Unless otherwise indicated the reaction was carried out at (*i*) **22** (0.3 mmol), **21** (3M aqueous sol., 0.9 mmol), proline **23** (20 mol %), DMSO (3.0 mL), (*ii*) IBX (120 mol %). [b]Isolated yield of **24** refer to **22**.

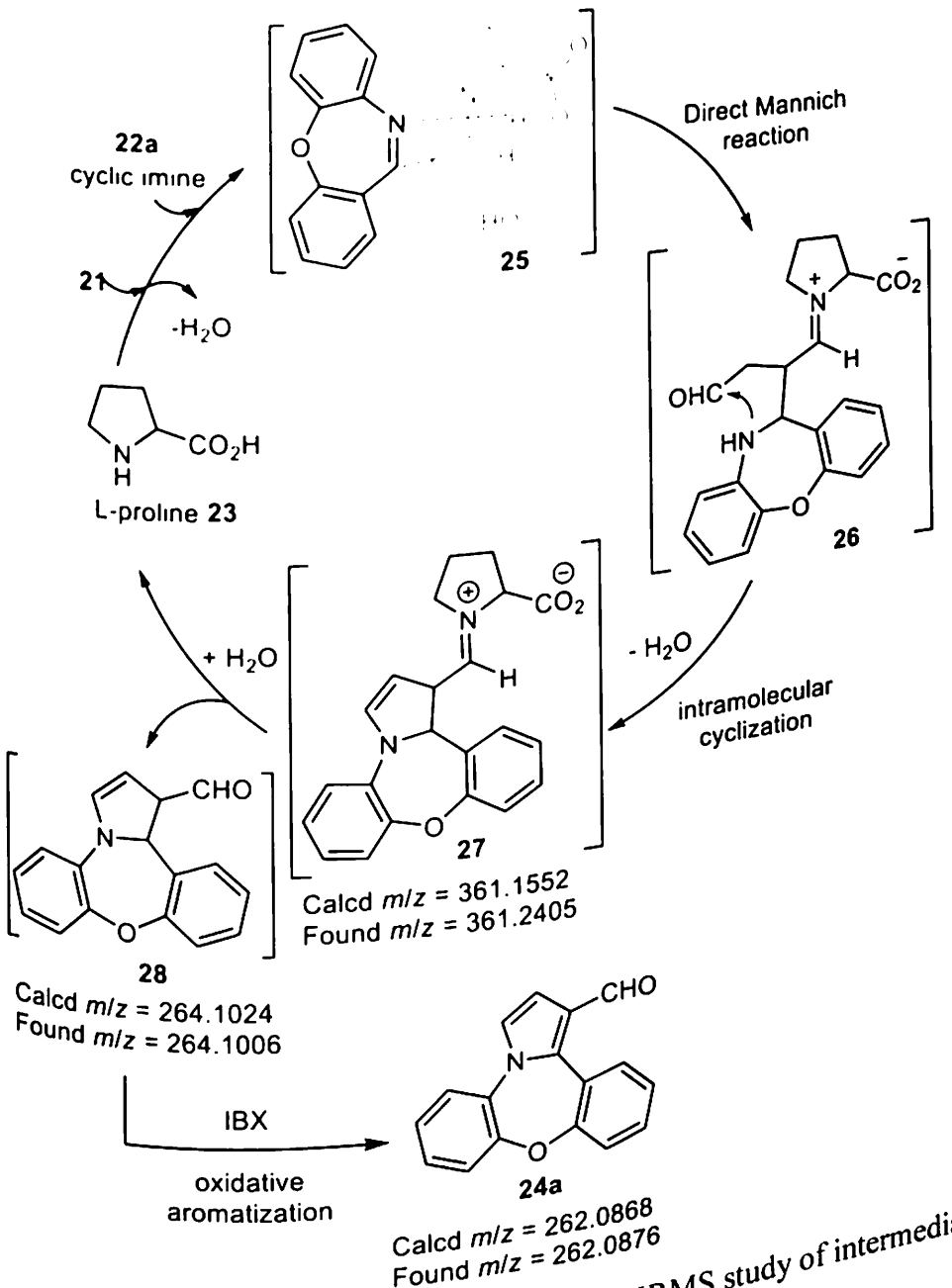
Moreover, the densely substituted oxazepine-imines **22t-22x** also furnished corresponding tetracyclic fused-pyrroles **24t-24x** (Table 4.2). However, the reaction failed to give desired products **24y** and **24z**, when exceedingly substituted 1,4-oxazepine imines **22y** and **22z** were employed for the similar transformation under standardized conditions, probably due to the steric bulkiness of -CF_3 group at the *ortho*-position (Table 4.2). All compounds were well characterized by ^{1}H and ^{13}C-NMR and Mass-analysis.

To demonstrate the practical use of this method, the feasibility was examined at gram scale of **22u** (1.0 g) and furnished tetracyclic pyrrole **24u** (79 mg, 65% yield) without much variation in yield under the standardized conditions. Further, single crystal X-ray diffraction analysis confirms the structure of tetracyclic pyrrole **24u** and structure of other product was assigned by analogy (Scheme 4.7).



Scheme 4.7: Gram-scale synthesis and single-crystal X-ray analysis of **24u**

Based on our study and literature reports on proline-catalyzed Mannich reaction, a stepwise mechanism has been proposed by monitoring predicted intermediate structures and their confirmation through in situ HRMS (See ESI). As shown in Scheme 4.8, enamine **25** is generated from aqueous succinaldehyde **21** and proline **23**, underwent direct Mannich reaction with cyclic imine **22** to produce intermediate **26**. The intramolecular cyclization of intermediate **26** with the removal of H_2O gave intermediate **27**, which was in situ confirmed by HRMS (ESI-TOF) m/z $[M + H^+]$ = 361.2305). The subsequent release of catalyst **23** from iminium-ion intermediate **27** to dihydropyrrole intermediate **28**, was also in situ confirmed by HRMS (ESI-TOF) m/z $[M + H^+]$ = 264.1006). In the same pot, intermediate **28** underwent IBX-mediated oxidative aromatization to afford tetracyclic 1,4-dibenzoxazepine-fused pyrrole **24** HRMS (ESI-TOF) m/z $[M + H^+]$ = 262.0876 in high yields. Easy availability of starting materials and metal-free access to tetracyclic oxazepine-fused pyrroles **24** makes this approach quite tempting.

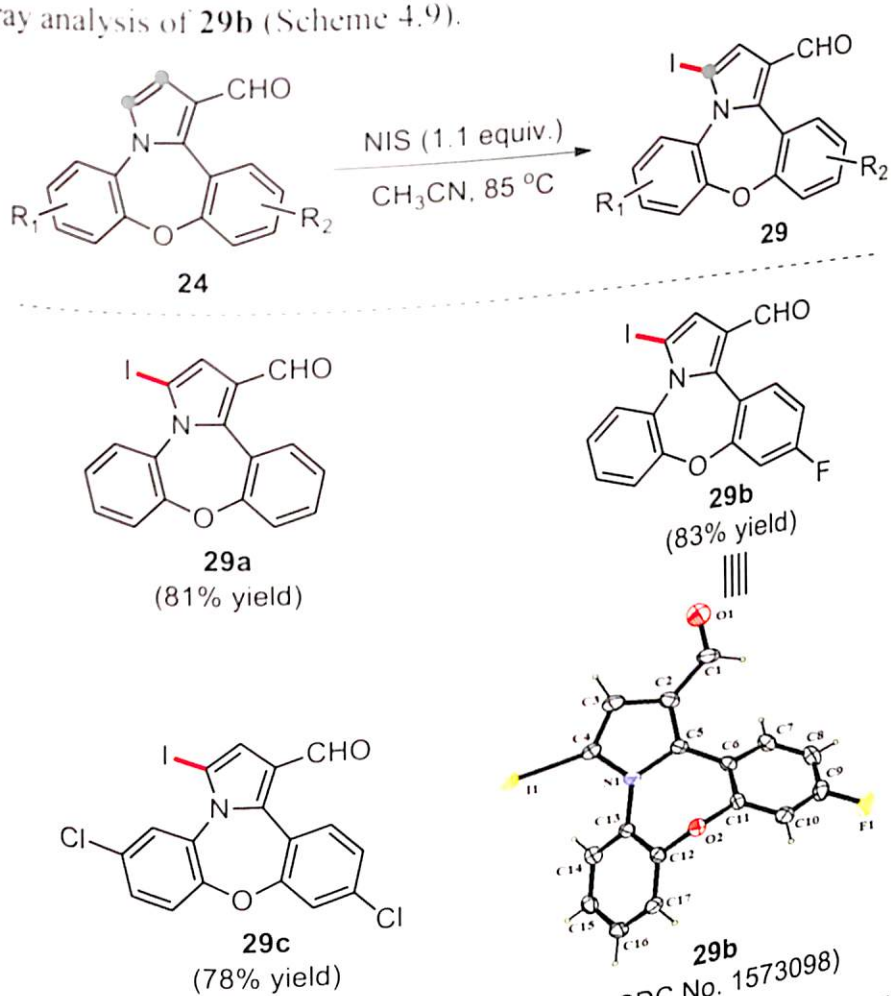


Scheme 4.8: Proposed reaction mechanism having in situ HRMS study of intermediate structures

4.4 Synthesis of tetracyclic 2-iodo-4-formyl-pyrroles

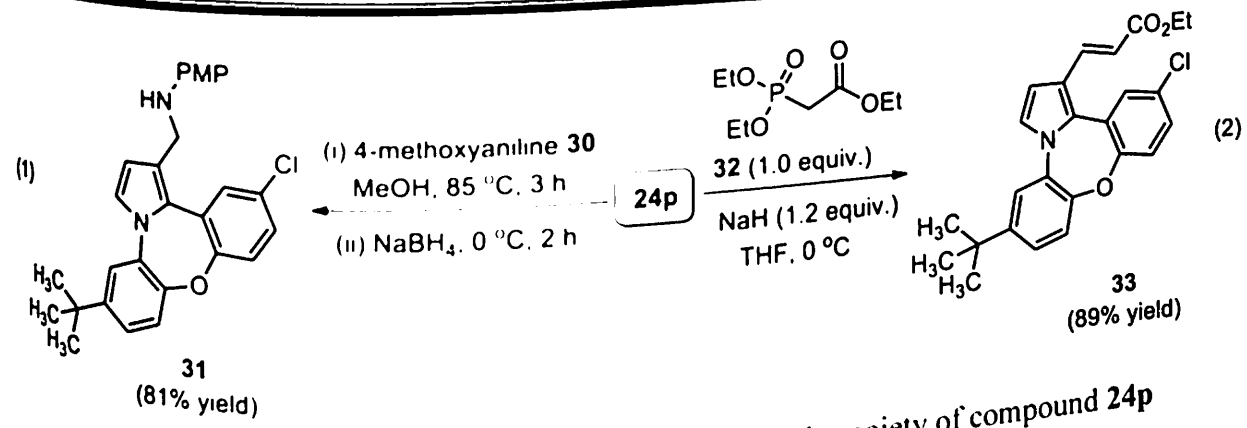
Tetracyclic 1,4-oxazepine-fused pyrroles could participate as a suitable substrate for further additional functionalizations to more important scaffolds, therefore, we developed interesting and useful synthetic transformations of these compounds. In this context, we initially developed a regioselective synthesis of 1,4-oxazepines-fused 2-Iodo-4-formyl-pyrroles **29** through electrophilic substitution reactions using standard condition. The treatment of tetracyclic pyrroles **24** with *N*-iodosuccinamide (NIS, 1.1 equiv.) in CH_3CN at 85 °C furnished corresponding 2-iodo-substituted pyrroles (**29a-29c**)

with good yields. Furthermore, regioselectivity of this reaction was further confirmed through the single-crystal X-ray analysis of **29b** (Scheme 4.9).



Scheme 4.9: Regioselective iodination at the C-2 position of aldehyde-tethered fused-pyrroles

Next, some extensive transformations on the aldehyde-moiety present on tetracyclic pyrroles was developed to showcase the additional applications of our protocol. In this context, aldehyde moiety of **24p** was converted to amino-methyl functionality through the reductive amination with PMP-NH_2 **30** in presence of $NaBH_4$ to generate corresponding amine compound **31** (eq 1, Scheme 4.10), with 81% overall yield. Further, the treatment of **24p** with triethyl phosphonoacetate **32** (1.0 equiv.) and NaH (1.2 eq) in dry THF at 0 °C for Horner–Wadsworth–Emmons reaction gave corresponding α,β-unsaturated ester **33** in 89% yield (eq 2, Scheme 4.10).



Scheme 4.10: Synthetic transformations with aldehyde-moiety of compound **24p**

4.5 Conclusions

In summary, we have established a conceptually simple method for the synthesis of tetracyclic dibenzo[*b*,*f*][1,4]oxazepine-fused pyrroles. High to excellent yields of polycyclic pyrroles were obtained upon treatment of succinaldehyde under proline-catalysis with seven membered1,4-oxazepines through direct Mannich/cyclization, followed by IBX-mediated oxidative aromatization in the same pot. The practical utility of this method was shown at gram-scale. Further, the applications of this protocol were developed for the regioselective synthesis of tetracyclic 2-iodo-4-formylpyrroles and additional functionalizations like (*i*) reductive amination, and (*ii*) Wittig-reaction on aldehyde moiety on fused pyrroles were also described.

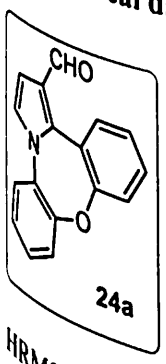
4.6 Experimental section

General Methods: Unless otherwise stated, all commercially available compounds were used as received without further purification. Cyclic 1,4-oxazepine-imines **22** were synthesized using the literature procedure. All solvents employed in the reactions were distilled from appropriate drying agents and the reactions were monitored by thin-layer chromatography (TLC) under standard conditions on Merck silica gel 60 F254 pre-coated plates (0.25 mm). Column chromatography was performed on silica gel (100–200 mesh) using a mixture of hexane/EtOAc. Chemical yields refer to the pure isolated product. ^{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 (100 MHz) spectrometer with complete proton decoupling. Melting points were determined by EZ–Melt, Automated Melting Point Apparatus. High-resolution mass spectra were recorded using the quadrupole electrospray ionization (ESI) technique.

4.7 Typical procedure for the synthesis fused tetracyclic pyrrole-3-carbaldehdye 24:

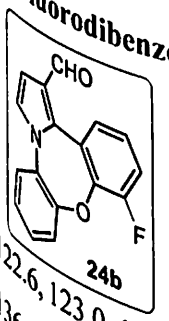
To a stirred solution of dibenzo[*b,f*][1,4]oxazepines **22** (0.3 mmol) in DMSO (3.0 mL) was added succinaldehyde **21** (3M, 0.9 mmol) and proline **23** (6.8 mg, 0.06 mmol) at rt. The reaction mixture was further stirred at the same temperature for 3 h until the dibenzo[*b,f*][1,4]oxazepines **22** was consumed as monitored by TLC. *o*-Iodoxybenzoic acid (IBX, 1.2 equiv., 0.35 mmol) was added into the same flask and further heated at 70 °C for 4 h. The reaction was quenched with $NaHCO_3$ (10 mL of 10% solution) slowly and stirred with ethyl acetate (10 mL) for 10 minutes. The organic layer was separated and the aqueous solution was again extracted with ethyl acetate (2 x 10 mL) and combined organic extracts were washed with brine once, dried over anhydrous Na_2SO4 and concentrated under reduced pressure. Purification was performed by a silica gel column and eluted with EtOAc/hexane. Tetracyclic fused pyrroles product **24** were obtained in good to high yields (up to 90%).

4.8 Analytical data of (24a-24x)



24a

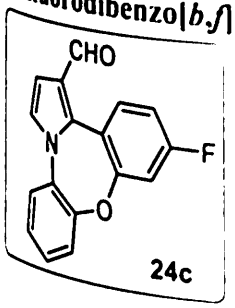
Dibenzo[*b,f*]pyrrolo[1,2-*d*][1,4]oxazepine-1-carbaldehyde (24a). White solid (67 mg, 85% yield, M.P = 175-176 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, *J* = 3.2 Hz, 1H), 7.14 (d, *J* = 3.9 Hz, 1H), 7.26–7.30 (m, 2H), 7.30–7.41 (m, 3H), 7.41–7.47 (m, 2H), 7.53 (dd, *J* = 7.6 Hz, 1.6 Hz, 1H), 9.94 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 110.1, 121.2, 122.1, 122.3, 122.5, 123.2, 124.7, 125.6, 126.2, 128.6, 131.1, 131.8, 132.1, 137.7, 153.3, 158.8, 186.2; HRMS (ESI-TOF) *m/z*: [M + H$^+$] Calcd for $C_{17}H_{12}NO_2$ 262.0868; Found. 262.0876.



24b

10-Fluorodibenzo[*b,f*]pyrrolo[1,2-*d*][1,4]oxazepine-1-carbaldehyde (24b). Semi solid (66 mg, 80% yield, mp = 173-174 °C), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, *J* = 3.2 Hz, 1H),7.18 (d, *J* = 3.6 Hz, 1H), 7.20–7.25 (m, 2H), 7.28–7.33 (m, 2H), 7.37 (td, *J* = 7.7 Hz, 1.8 Hz, 1H), 7.46 (dd, *J* = 7.8 Hz, 1.7 Hz, 1H), 7.50 (dd, *J* = 7.9 Hz, 1.2 Hz, 1H), 9.95 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 110.3, 117.7, 122.6, 123.0, 123.4, 124.7, 125.1, 125.8 (d, *J* = 8.0 Hz), 126.6, 126.8 (d, *J* = 4.0 Hz), 128.7, 131.79, 136.2 (d, *J* = 3.0 Hz), 146.0 (d, *J* = 14.0 Hz), 153.1, 155.5, 186.0. HRMS (ESI-TOF) *m/z*: [M + H$^+$] Calcd for $C_{17}H_{11}FNO_2$ 280.0774; Found. 280.0774.

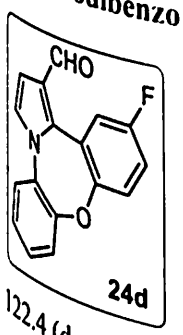
11-fluorodibenzo[*b*,*f*]pyrrolo[1,2-*d*][1,4]oxazepine-1-carbaldehyde (24c). Light yellow solid



24c

(67 mg, 81% yield, mp 177-178 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (d, *J* 3.2 Hz, 1H), 6.99–7.13 (m, 2H), 7.14 (d, *J* = 3.2 Hz, 1H), 7.28–7.33 (m, 1H), 7.33–7.41 (m, 2H), 7.45 (dd, *J* = 7.5 Hz, 1.7 Hz, 1H), 7.52 (dd, *J* = 8.6 Hz, 6.2 Hz, 1H), 9.89 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.3(d, *J* 24.0 Hz), 110.4, 113.0 (d, *J* = 22.0 Hz), 118.5 (d, *J* = 4.0 Hz), 122.2, 122.5, 123.4, 124.6, 126.6, 128.7, 131.6, 132.9 (d, *J* = 9.0 Hz), 136.5, 152.8, 159.6 (d, *J* = 3.2 Hz), 163.9 (d, *J* = 251.0 Hz), 185.9. HRMS (ESI-TOF) *m/z*: [M + H$^+$] Calcd for $C_{17}H_{11}FNO_2$ 280.0774; Found. 280.0778.

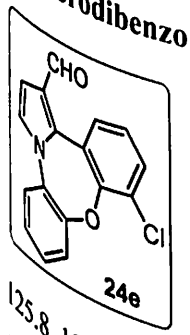
12-fluorodibenzo[*b*,*f*]pyrrolo[1,2-*d*][1,4]oxazepine-1-carbaldehyde (24d). Light yellow



24d

solid(65 mg, 78% yield, mp = 172-173 °C).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, *J* = 3.2 Hz, 1H), 7.11 (m, 1H), 7.16 (d, *J* = 3.2 Hz, 1H), 7.24 (dd, *J* = 8.6 Hz, 3.0 Hz, 1H), 7.26–7.32 (m, 2H), 7.34 (dd, *J* = 5.8 Hz, 3.2 Hz, 1H), 7.37 (t, *J* = 2.1 Hz, 1H), 7.44 (dd, *J* = 7.8 Hz, 1.5 Hz, 1H), 9.97 (s, 1H).^{13}C NMR (100 MHz, $CDCl_3$) δ 110.5, 117.4 (d, *J* = 23.0 Hz), 118.2 (d, *J* = 25.0 Hz), 122.1, 122.4 (d, *J* = 9.0 Hz), 122.9, 123.4, 123.5 (d, *J* = 10 Hz), 125.0, 126.4, 128.8, 131.6, 135.8 (d, *J* = 2.0 Hz), 153.3, 154.6 (d, *J* = 3.0 Hz), 159.5 (d, *J* = 243.0 Hz), 185.7. HRMS (ESI-TOF) *m/z*: [M + H$^+$] Calcd for $C_{17}H_{11}FNO_2$ 280.0774; Found. 280.0782.

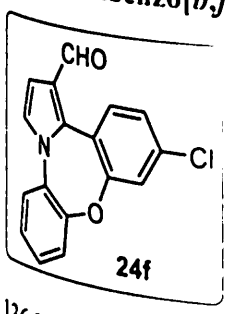
10-chlorodibenzo[*b*,*f*]pyrrolo[1,2-*d*][1,4]oxazepine-1-carbaldehyde (24e). Light yellow solid



24e

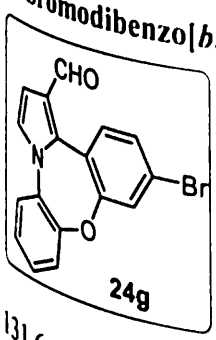
(70 mg, 80% yield, mp = 170-172 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, *J* = 3.2 Hz, 1H), 7.16 (d, *J* = 3.2 Hz, 1H), 7.19 (t, *J* = 7.9 Hz, 1H), 7.27–7.38 (m, 2H), 7.41 (dd, *J* = 7.8 Hz, 1.6 Hz, 1H), 7.45 (dd, *J* = 7.8 Hz, 1.7 Hz, 1H), 7.49 (dd, *J* = 8.0 Hz, 1.6Hz, 1H), 7.61 (dd, *J* = 8.0 Hz, 1.5 Hz, 1H), 9.92 (s, 1H).^{13}C NMR (100 MHz, $CDCl_3$) δ 110.3, 122.8, 123.0, 123.1, 124.0,125.1, 125.8, 126.6, 127.0, 128.6, 130.4, 131.1, 131.6, 136.3, 152.7, 153.8, 185.8. HRMS (ESI-TOF) *m/z*: [M + H$^+$] Calcd for $C_{17}H_{11}ClNO_2$ 296.0478; Found. 296.0484.

11-chlorodibenzo[*b*,*f*]pyrrolo[1,2-*d*][1,4]oxazepine-1-carbaldehyde (24f). Yellow solid(65 mg, 74% yield, mp = 165-166 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, *J* = 3.2 Hz, 1H), 7.16 (d, *J* = 3.7 Hz, 1H), 7.27–7.37 (m, 3H), 7.38 (t, *J* = 2.0 Hz, 1H), 7.40 (d, *J* = 2.0 Hz, 1H), 7.45 (dd, *J* = 7.8 Hz, 1.6 Hz, 1H), 7.48 (d, *J* = 8.3 Hz, 1H), 9.90 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 110.6, 120.8, 121.9, 122.3, 122.8, 123.4, 124.8, 126.0, 126.6, 128.8, 131.6, 132.5, 136.2, 136.4, 152.9, 158.9, 185.8; HRMS (ESI-TOF) *m/z*: [M + H$^+$] Calcd for $C_{17}H_{11}ClNO_2$ 296.0478; Found. 296.0476.



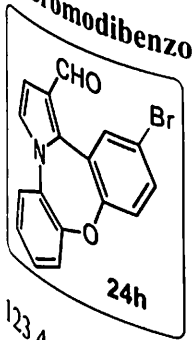
24f

11-bromodibenzo[*b*,*f*]pyrrolo[1,2-*d*][1,4]oxazepine-1-carbaldehyde (24g). Yellow solid(89 mg, 80% yield, mp = 183-184 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, *J* = 3.2 Hz, 1H), 7.16 (d, *J* = 3.2 Hz, 1H), 7.28–7.33 (m, 1H), 7.38 (dt, *J* = 9.0 Hz, 3.5 Hz, 2H), 7.40–7.44 (m, 2H), 7.45 (dd, *J* = 7.8 Hz, 1.6 Hz, 1H), 7.56 (d, *J* = 1.7 Hz, 1H), 9.91 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 110.6, 121.3, 122.3, 122.8, 123.4, 124.2, 124.80, 124.84, 126.6, 128.8, 128.9, 131.6, 132.7, 136.2, 152.9, 158.8, 185.8. HRMS (ESI-TOF) *m/z*: [M + H$^+$] Calcd for $C_{17}H_{11}BrNO_2$ 339.9973; Found. 339.9977.



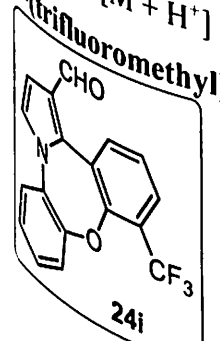
24g

12-Bromodibenzo[*b*,*f*]pyrrolo[1,2-*d*][1,4]oxazepine-1-carbaldehyde (24h). Yellow solid (84 mg, 76% yield, mp = 182-183 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (d, *J* = 3.2 Hz, 1H), 7.19 (d, *J* = 3.2 Hz, 1H),7.28 (d, *J* = 1.9 Hz, 1H), 7.33 (dd, *J* = 7.6Hz, 2.2 Hz, 1H), 7.38 (d, *J* = 1.6 Hz, 1H), 7.39 (s, 1H), 7.47 (dd, *J* = 7.8 Hz, 1.5 Hz, 1H), 7.55 (dd, *J* = 8.6 Hz, 2.4 Hz, 1H), 7.67 (d, *J* = 2.4 Hz, 1H), 9.98 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 110.5, 118.4, 122.2, 122.9, 123.0, 123.4, 124.0, 125.0, 126.5, 128.8, 131.6, 133.7, 134.2, 135.7, 153.0, 157.7, 185.8. HRMS (ESI-TOF) *m/z*: [M + H$^+$] Calcd for $C_{17}H_{11}BrNO_2$ 339.9973; Found. 339.9975.



24h

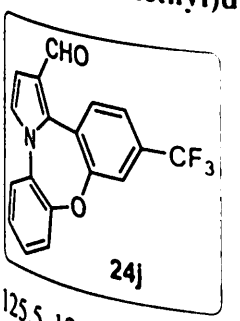
10-(trifluoromethyl)dibenzo[*b*,*f*]pyrrolo[1,2-*d*][1,4]oxazepine-1-carbaldehyde (24i). Light orange solid (71 mg, 72% yield, mp = 170-172 °C), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (d, *J* = 3.2 Hz, 1H), 7.17 (d, *J* = 3.2 Hz, 1H), 7.32–7.40 (m, 3H), 7.47 (dd, *J* = 7.7 Hz, 1.9 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 7.8 Hz, 2H), 9.86 (s, 1H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 111.0, 121.2, 122.0, 122.8 (q, *J* = 4.0 Hz), 123.0, 124.7 (q, *J* = 270.0 Hz), 125.6 (q, *J* = 72.0 Hz),



24i

126.2, 128.0 (q, J = 50 Hz), 128.8, 131.4 (q, J = 10.0 Hz), 131.6, 135.7, 136.1, 152.6, 156.4, 185.8. HRMS (ESI-TOF) m/z: [M + H$^+$] Calcd for $C_{18}H_{11}F_3NO_2$ 330.0742; Found. 330.0744.

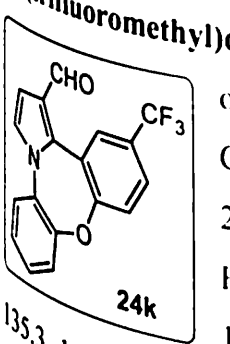
11-(trifluoromethyl)dibenzo[*b*,*f*]pyrrolo[1,2-*d*][1,4]oxazepine-1-carbaldehyde (24j). Light



24j

orange solid (74 mg, 75% yield, mp = 173-174 °C), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (d, J = 3.2 Hz, 1H), 7.20 (d, J = 2.9 Hz, 1H), 7.30–7.40 (m, 2H), 7.45 (m,2H), 7.55 (d, J = 8.0 Hz, 1H), 7.63 (s, 1H), 7.68 (d, J = 8.0 Hz, 1H), 9.94 (s, 1H). ^{13}C NMR(100 MHz, $CDCl_3$) δ 111.0, 118.6 (q, J = 7.0 Hz), 122.3 (q, J = 4.0 Hz), 122.4, 123.2 (q, J = 271.0 Hz), 123.4, 124.2, 125.5, 125.8, 126.7, 129.0, 131.5, 132.4, 132.7 (q, J = 33.0 Hz), 135.2, 152.9, 158.5, 185.7. HRMS (ESI-TOF) m/z: [M + H$^+$] Calcd for $C_{18}H_{11}F_3NO_2$ 330.0742; Found. 330.0748.

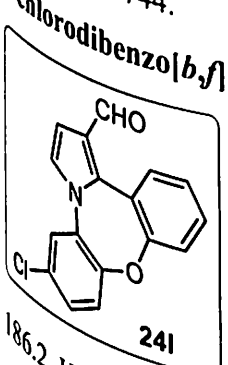
12-(trifluoromethyl)dibenzo[*b*,*f*]pyrrolo[1,2-*d*][1,4]oxazepine-1-carbaldehyde (24k). Light



24k

orange solid (77 mg, 78% yield, mp= 170-172 °C), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (d, J = 3.2 Hz, 1H), 7.18 (d, J = 3.2 Hz, 1H), 7.29–7.35 (m, 2H), 7.38 (td, J = 5.1 Hz, 2.4 Hz,3H), 7.43 (s, 1H), 7.47 (dd, J = 7.6 Hz, 1.6 Hz, 1H), 9.95 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 110.8, 122.2, 122.4, 123.0, 123.4, 123.5, 123.6, 124.4, 125.1, 126.1, 126.2, 126.6, 128.9, 131.6, 135.3, 153.0, 156.9, 185.6. HRMS (ESI-TOF) m/z: [M + H$^+$]Calcd for $C_{18}H_{11}F_3NO_2$ 330.0742; Found. 330.0744.

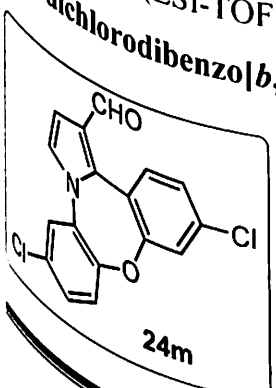
6-chlorodibenzo[*b*,*f*]pyrrolo[1,2-*d*][1,4]oxazepine-1-carbaldehyde (24l). White solid(79 mg,



24l

90% yield, mp= 165-166 °C), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, J = 3.2 Hz, 1H), 7.12 (d, J = 3.2 Hz, 1H), 7.27–7.31 (m, 2H), 7.32 (s, 1H), 7.35 (d, J = 8.5 Hz, 1H), 7.42–7.48 (m, 2H), 7.52 (d, J = 9.2 Hz, 1H), 9.93 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 110.6, 121.1, 121.8, 122.4, 122.8, 123.3, 123.4, 125.0, 125.9, 128.4, 131.3, 132.2, 132.6, 137.6, 151.7, 158.5, 186.2. HRMS (ESI-TOF) m/z: [M + H$^+$] Calcd for $C_{17}H_{11}ClNO_2$ 296.0478; Found. 296.0474.

6,11-dichlorodibenzo[*b*,*f*]pyrrolo[1,2-*d*][1,4]oxazepine-1-carbaldehyde (24m). White solid(86

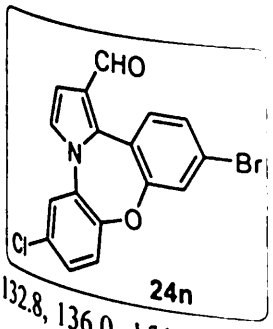


24m

mg, 87% yield, mp = 160-162 °C),^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, J = 3.2 Hz, 1H), 7.13 (d, J = 3.8 Hz, 1H), 7.27–7.31 (m, 2H), 7.32 (s, 1H), 7.38 (d, J = 2.0 Hz, 1H), 7.44 (s, 1H), 7.47 (d, J = 8.3 Hz, 1H), 9.90 (s, 1H).^{13}C NMR (100 MHz, $CDCl_3$) δ 111.0, 120.5, 121.8, 122.6, 123.4, 123.4, 125.1, 126.2, 128.6, 131.7, 132.4, 132.6, 136.0, 136.6,

151.3, 158.5, 185.7.HRMS (ESI-TOF) *m/z*: [M + H⁺] Calcd for $C_{17}H_{10}Cl_2NO_2$ 330.0088; Found. 330.0096.

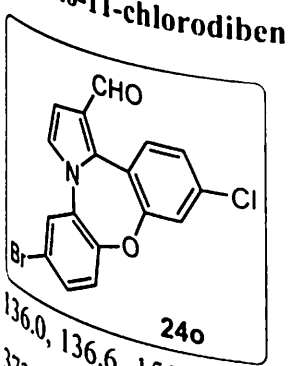
11-bromo-6-chlorodibenzo[*b*,*f*]pyrrolo[1,2-*d*][1,4]oxazepine-1-carbaldehyde (24n). White



24n

solid (94 mg, 84% yield, mp = 178-180 °C), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, *J* = 3.2 Hz, 1H), 7.13 (d, *J* = 3.2 Hz, 1H), 7.32 (d, *J* = 1.7 Hz, 2H), 7.42 (s, 1H), 7.44 (d, *J* = 1.8 Hz, 2H), 7.54 (d, *J* = 1.8 Hz, 1H), 9.90 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 111.1, 121.0, 122.7, 123.47, 123.49, 124.4, 124.7, 125.1, 128.6, 129.2, 131.7, 132.4, 132.8, 136.0, 151.3, 158.5, 185.6. HRMS (ESI-TOF) *m/z*: [M + H⁺] Calcd for $C_{17}H_{10}BrClNO_2$ 373.9583; Found. 373.9595.

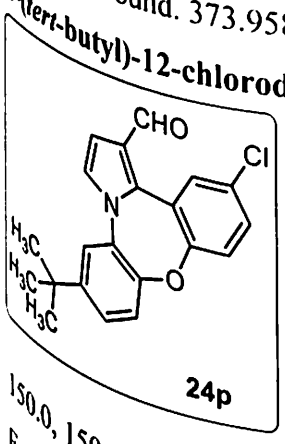
6-bromo-11-chlorodibenzo[*b*,*f*]pyrrolo[1,2-*d*][1,4]oxazepine-1-carbaldehyde (24o). White



24o

solid (83 mg, 75% yield, mp = 180-182 °C), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, *J* = 3.2 Hz, 1H), 7.13 (d, *J* = 3.3 Hz, 1H), 7.27–7.31 (m, 2H), 7.37 (d, *J* = 2.0 Hz, 1H), 7.44–7.50 (m, 2H), 7.59 (d, *J* = 2.3 Hz, 1H), 9.90 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 111.1, 119.0, 120.5, 121.8, 122.6, 123.8, 125.1, 126.31, 126.38, 131.6, 132.6, 132.7, 136.0, 136.6, 151.8, 158.5, 185.6. HRMS (ESI-TOF) *m/z*: [M + H⁺] Calcd for $C_{17}H_{10}BrClNO_2$ 373.9583; Found. 373.9587.

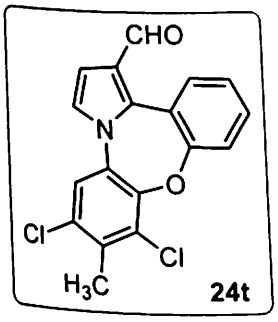
6-(*tert*-butyl)-12-chlorodibenzo[*b*,*f*]pyrrolo[1,2-*d*][1,4]oxazepine-1-carbaldehyde (24p). Light



24p

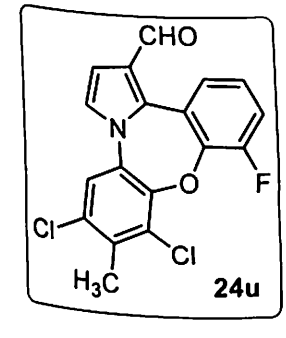
red solid (77 mg, 73% yield, mp = 185-187 °C), ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (s, 9H), 7.01 (d, *J* = 3.2 Hz, 1H), 7.17 (d, *J* = 7.9 Hz, 1H), 7.20 (d, *J* = 3.2 Hz, 1H), 7.39 (m, 2H), 7.43 (d, *J* = 2.3 Hz, 1H), 7.48 (dd, *J* = 8.0 Hz, 1.5 Hz, 1H), 7.51 (d, *J* = 8.5 Hz, 1H), 9.92 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.2 (3C), 34.6, 110.1, 120.1, 122.2, 122.8, 124.1, 125.0, 125.6, 125.7, 126.9, 130.4, 130.8, 131.0, 136.4, 150.0, 150.5, 154.0, 185.9. HRMS (ESI-TOF) *m/z*: [M + H⁺] Calcd for $C_{21}H_{19}ClNO_2$ 352.1104; Found. 352.1108.

6,8-dichloro-7-methyldibenzo[*b*,*f*]pyrrolo[1,2-*d*][1,4]oxazepine-1-carbaldehyde (24t). Orange solid (71 mg, 70% yield, mp = 165-167 °C), ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.51 (s, 3H), 7.00 (d, *J* = 3.2 Hz, 1H), 7.11 (d, *J* = 3.1 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.40 (s, 1H), 7.47 (t, *J* = 7.8 Hz, 1H), 7.54 (dd, *J* = 7.6 Hz, 1.5 Hz, 1H), 7.60 (d, *J* = 7.4 Hz, 1H), 9.94 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.8, 110.6, 121.5, 121.9, 122.0, 122.4, 125.0, 126.1, 129.3, 131.0, 131.2, 131.4, 132.0, 134.9, 137.3, 147.6, 158.1, 186.1. HRMS (ESI-TOF) *m/z*: [M + H$^+$] Calcd for $C_{18}H_{12}Cl_2NO_2$ 344.0245; Found. 344.0239.



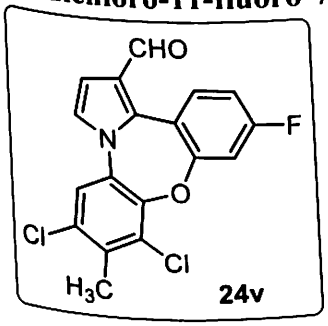
24t

6,8-dichloro-10-fluoro-7-methyldibenzo[*b*,*f*]pyrrolo[1,2-*d*][1,4]oxazepine-1-carbaldehyde (24u). Orange solid (73 mg, 68% yield, mp = 175-176 °C), ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.53 (s, 3H), 7.01 (d, *J* = 3.2 Hz, 1H), 7.12 (d, *J* = 3.1 Hz, 1H), 7.28 (dd, *J* = 7.1 Hz, 1.9 Hz, 3H), 7.41 (s, 1H), 9.93 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.9, 110.9, 118.4 (d, *J* = 19.0 Hz), 121.5, 122.9, 124.3, 125.5, 126.4 (d, *J* = 8.0 Hz), 126.7 (d, *J* = 4.0 Hz), 129.4, 130.9, 131.8, 135.4, 135.8 (d, *J* = 3.0 Hz), 145.4 (d, *J* = 14.0 Hz), 148.0, 153.9 (d, *J* = 252.0 Hz), 185.8. HRMS (ESI-TOF) *m/z*: [M + H$^+$] Calcd for $C_{18}H_{11}Cl_2FNO_2$ 362.0151; Found. 362.0155.



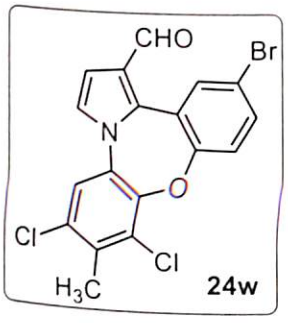
24u

6,8-dichloro-11-fluoro-7-methyldibenzo[*b*,*f*]pyrrolo[1,2-*d*][1,4]oxazepine-1-carbaldehyde (24v). Orange solid (78 mg, 72% yield, mp= 177-178 °C), ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.51 (s, 3H), 6.99 (d, *J* = 3.2 Hz, 1H), 7.03–7.08 (m, 1H), 7.10 (d, *J* = 3.2 Hz, 1H), 7.33 (dd, *J* = 8.6 Hz, 2.6 Hz, 1H), 7.40 (s, 1H), 7.54 (dd, *J* = 8.6 Hz, 6.1 Hz, 1H), 9.89 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.8, 110.2 (d, *J* = 24.0 Hz), 110.9, 113.6 (d, *J* = 22.0 Hz), 118.3 (d, *J* = 4.0 Hz), 121.6, 122.3, 124.9, 129.2, 130.8, 131.8, 132.8 (d, *J* = 10.0 Hz), 135.1, 136.1, 147.2, 158.7 (d, *J* = 11.0 Hz), 163.9 (d, *J* = 252.0 Hz) 185.7. HRMS (ESI-TOF) *m/z*: [M + H$^+$] Calcd for $C_{18}H_{11}Cl_2FNO_2$ 362.0151; Found. 362.0157.



24v

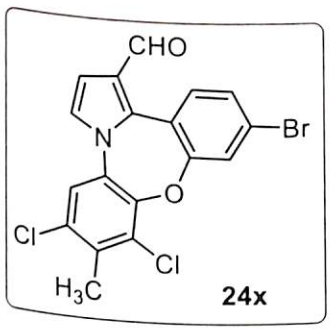
12-bromo-6,8-dichloro-7-methyldibenzo[*b,f*]pyrrolo[1,2-*d*][1,4]oxazepine-1-carbaldehyde



24w

(24w). Light yellow solid (88 mg, 70% yield, mp = 180-181 °C), ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.51 (s, 3H), 7.00 (d, *J* = 3.2 Hz, 1H), 7.11 (d, *J* = 3.2 Hz, 1H), 7.40 (s, 1H), 7.46 (d, *J* = 8.6 Hz, 1H), 7.55 (dd, *J* = 8.6 Hz, 2.4 Hz, 1H), 7.66 (d, *J* = 2.4 Hz, 1H), 9.96 (s, 1H).^{13}C NMR (100 MHz, $CDCl_3$) δ 17.8, 110.9, 119.0, 121.6, 122.8, 123.6, 123.8, 125.3, 129.2, 130.7, 131.7, 133.8, 134.2, 135.26, 135.27, 147.3, 156.9, 185.5. HRMS (ESI-TOF) *m/z*: [M + H$^+$] Calcd for $C_{18}H_{11}BrCl_2NO_2$ 421.9350; Found. 421.9356.

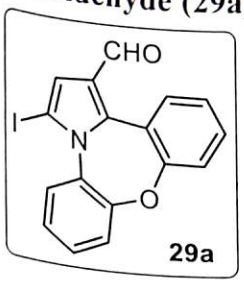
11-bromo-6,8-dichloro-7-methyldibenzo[*b,f*]pyrrolo[1,2-*d*][1,4]oxazepine-1-carbaldehyde



24x

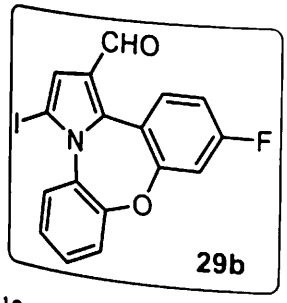
(24x). Light yellow solid (93 mg, 74% yield, mp= 177-178 °C), ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.52 (s, 3H), 7.00 (d, *J* = 3.2 Hz, 1H), 7.12 (d, *J* = 3.1 Hz, 1H), 7.40 (s, 1H), 7.44 (d, *J* = 8.3 Hz, 1H), 7.76 (d, *J* = 1.7 Hz, 1H), 9.91 (s, 1H).^{13}C NMR (100 MHz, $CDCl_3$) δ 17.8, 111.1, 121.0, 121.6, 122.6, 124.4, 125.1, 125.5, 129.3, 130.7, 130.8, 131.8, 132.6, 135.2, 135.8, 147.2, 158.0, 185.6. HRMS (ESI-TOF) *m/z*: [M + H$^+$] Calcd for $C_{18}H_{11}BrCl_2NO_2$ 421.9350; Found. 421.934.

4.9 General procedure for the synthesis of 3-iododibenzo[*b,f*]pyrrolo[1,2-*d*][1,4]oxazepine-1-carbaldehyde (29a). To a stirred solution of compound **24a** (52 mg, 0.20 mmol) in dry CH_3CN (4.0 mL) was added *N*-iodosuccinimide (NIS, 1.1 equiv.) and stirred at 85 °C for 4 h. The reaction was quenched with saturated $Na_2S_2O_3$ solution (5.0 mL) and stirred with EtOAc (10 mL). Organic layer was separated and aqueous layer was further extracted with EtOAc (10 mL) and combined organic layer was washed with saturated brine solution (10 mL) and dried over anhydrous Na_2SO_4followed by evaporated in vacuum after filtration. Purification on silica gel column chromatography using Hexane:EtOAc as eluent furnished tetracyclic regioselective iodinated-pyrrole **29a** (62 mg, 81% yield). White solid, mp = 182-183 °C,^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.30 (m, 2H),7.34–7.40 (m, 3H), 7.40 (s, 1H), 7.42–7.47 (m, 1H), 7.51 (dd, *J* = 1.6, 7.6 Hz, 1H), 7.69 (d, *J* = 9.1 Hz, 1H), 9.78 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 72.3, 121.0, 121.8, 122.0, 122.1, 125.1, 125.5, 125.9, 128.2, 129.5, 130.4, 131.4, 131.6, 140.9, 155.0, 159.9, 185.2. HRMS (ESI-TOF) *m/z*: [M + H$^+$] Calcd for $C_{17}H_{11}INO_2$ 387.9834; Found. 387.9839.



29a

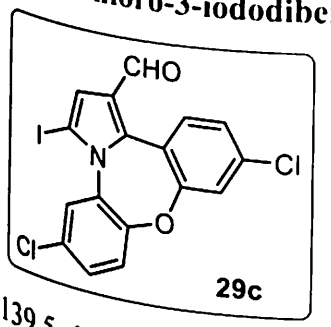
11-fluoro-3-iododibenzo[*b*,*f*]pyrrolo[1,2-*d*][1,4]oxazepine-1-carbaldehyde (29b). White solid



29b

(66 mg, 83% yield, mp = 190-192 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99–7.04(m, 1H), 7.12 (dd, J = 8.7 Hz, 2.5 Hz, 1H), 7.25 (s, 1H), 7.29–7.34 (m, 1H), 7.37–7.42 (m, 2H), 7.51 (dd, J = 8.6 Hz, 6.1 Hz, 1H), 7.70 (dd, J = 8.0 Hz, 1.3 Hz, 1H), 9.74 (s, 1H).^{13}C NMR (100 MHz, $CDCl_3$) δ 72.1, 109.1 (d, J = 23.0 Hz), 112.9 (d, J = 22.0 Hz), 118.2 (d, J = 4.0 Hz), 121.9, 122.4, 122.8, 125.4, 125.9, 128.3, 129.6, 132.3 (d, J = 10.0 Hz), 139.8, 154.6, 160.8 (d, J = 11.0 Hz), 164.2(d, J = 252.0 Hz), 184.8. HRMS (ESI-TOF) *m/z*: [M + H$^+$] Calcd for $C_{17}H_{10}FINO_2$ 405.9740; Found. 405.9746.

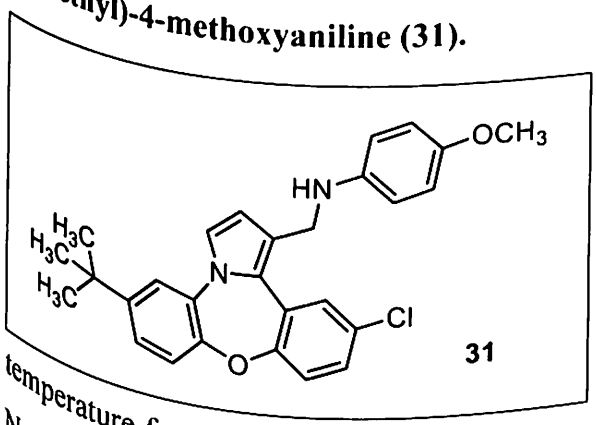
6,11-dichloro-3-iododibenzo[*b*,*f*]pyrrolo[1,2-*d*][1,4]oxazepine-1-carbaldehyde (29c). White



29c

solid (70 mg, 78% yield, mp= 181-182 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (s, 1H), 7.29–7.33 (m, 1H), 7.40 (s, 2H), 7.41 (d, J = 1.8 Hz, 1H), 7.55 (d, J = 1.7 Hz, 1H), 7.69 (dd, J = 8.0 Hz, 1.0 Hz, 1H), 9.76 (s, 1H).^{13}C NMR (100 MHz, $CDCl_3$) δ 72.6, 120.8, 122.0, 122.6, 124.6, 124.7, 125.4, 126.0, 128.3, 128.8, 129.7, 130.2, 132.0, 139.5, 154.6, 159.9, 184.7. HRMS (ESI-TOF) *m/z*: [M + H$^+$] Calcd for $C_{17}H_9Cl_2INO_2$ 455.9055; Found. 455.9059.

4.10 Synthesis of *N*-((6-(tert-butyl)-12-chlorodibenzo[*b*,*f*]pyrrolo[1,2-*d*][1,4]oxazepin-1-yl)methyl)-4-methoxyaniline (31).

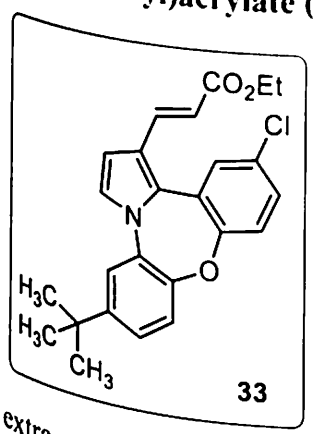


31

To a stirred solution of compound **24p** (88 mg, 0.25 mmol) dry MeOH (4.0 mL) was added 4-methoxyaniline **30** (1.0 equiv.) and stirred at 85 °C for 3 h. The reaction was taken to 0°C and was added $NaBH_4$ (1.0 equiv.) portion wise in the same pot. The reaction was stirred at the same temperature for 1 h and allowed to come to room temperature. The reaction was quenched with $NaHCO_3$ solution (20% sol, 10 mL) and stirred with EtOAc (10 mL). Organic layer was separated and aqueous solution was again extracted with EtOAc (10 mL). The combined organic extracts was washed with brine, dried over anhydrous Na_2SO_4 and concentrated in a vacuum after filtration. Purification on silica gel column chromatography using EtOAc/hexane furnished **31** (85 mg, 81% yield). White solid, mp = 180-181 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (s, 9H), 3.77 (s, 3H),

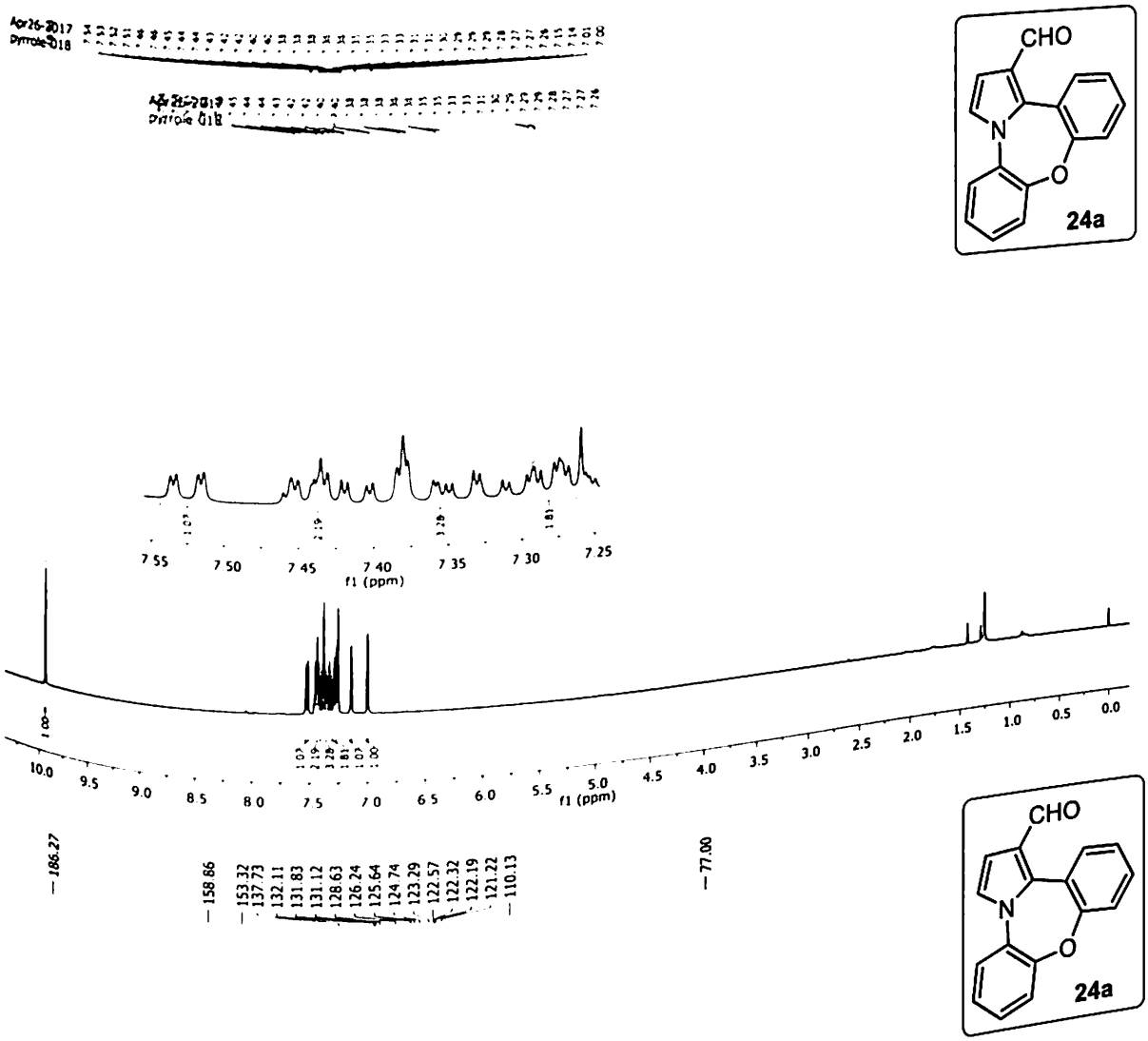
4.22 (s, 2H), 6.53 (d, J = 2.9 Hz, 1H), 6.67 (d, J = 8.9 Hz, 2H), 6.83 (d, J = 8.9 Hz, 2H), 7.07 (t, J = 7.9 Hz, 1H), 7.16 (d, J = 3.0 Hz, 1H), 7.29 (dd, J = 8.5 Hz, 2.3 Hz, 1H), 7.33 (dd, J = 8.0 Hz, 1.5 Hz, 1H), 7.38 (d, J = 2.3 Hz, 1H), 7.53–7.49 (s, 1H), 7.51 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.35(3C), 34.6, 42.2, 55.8, 111.8, 114.1 (2C), 114.9 (2C), 120.1, 120.9, 122.0, 122.1, 124.3, 125.7, 126.3, 126.5, 126.8, 128.1, 128.8, 132.2, 142.5, 149.6, 150.3, 152.2, 152.94.HRMS (ESI-TOF) *m/z*: [M + H$^+$] Calcd for $C_{28}H_{28}ClN_2O_2$ 459.1839; Found. 459.1843.

4.11 Synthesis of Ethyl(E)-3-(6-(*tert*-butyl)-12-chlorodibenzo[*b,f*]pyrrolo[1,2-*d*][1,4]-oxazepin-1-yl)acrylate (33).



33

To a stirred solution of compound **24p** (88 mg, 0.25 mmol) in dry THF (4.0 mL) at 0 °C was added triethyl phosphono acetate **32** (1.0 equiv.) followed by NaH (1.2 equiv.) slowly under inert atmosphere. The reaction was stirred at the same temperature for 1 hand allowed to come to room temperature with additional stirring for 2 h. The reaction was quenched with $NaHCO_3$ (10 % solution) and stirred with EtOAc (10 mL). The organic layer was separated and the aqueous layer was further extracted with EtOAc (10 mL). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4 followed by evaporated in vacuum after filtration. Purification on silica gel column chromatography using EtOAc/hexane furnished **33** (93 mg, 89%yield). Yellow colored solid, mp= 190-191 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (s, 3H), 1.32 (s, 9H), 4.24 (q, J = 7.1 Hz, 2H), 6.32 (d, J= 15.6 Hz, 1H), 6.75 (d, J = 3.1 Hz, 1H), 7.16–7.18 (m, 1H), 7.19 (d, J = 8.0 Hz, 1H), 7.29–7.34 (m, 2H), 7.36–7.44 (m, 2H), 7.49 (d, J = 8.5 Hz, 1H), 7.79 (d, J = 15.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 31.3 (3C), 34.7, 60.1, 108.8, 116.0, 119.8, 120.7, 122.2, 122.5, 124.9, 125.4, 125.8, 126.8, 129.6, 129.9, 130.7, 131.5, 137.6, 149.8, 150.3, 153.6, 167.7; HRMS (ESI-TOF) *m/z*: [M + H$^+$] Calcd for $C_{25}H_{25}ClNO_3$ 422.1523; Found. 422.1529.



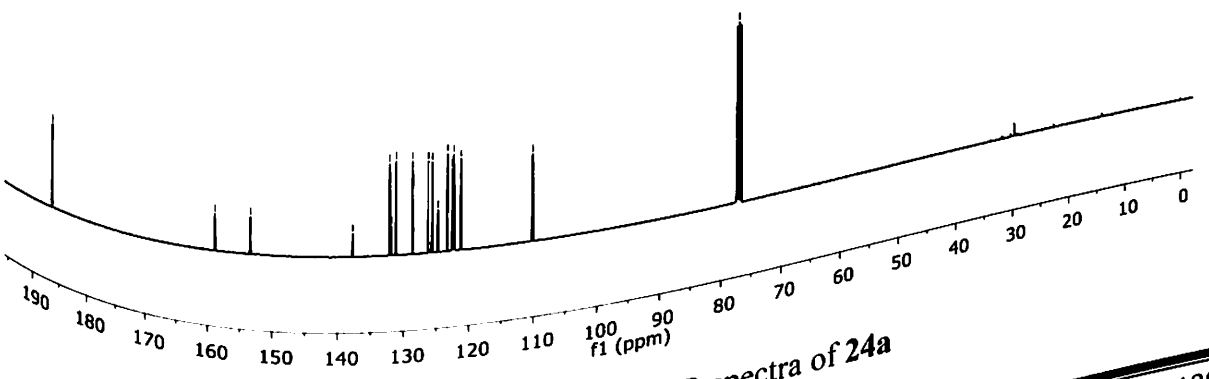
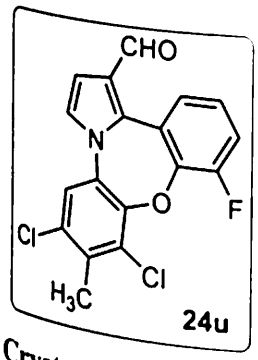


Figure 4.2 ^{1}H and ^{13}C NMR spectra of **24a**

4.12 Crystal structure data for 6,8-dichloro-10-fluoro-7-methyldibenzo[*b,f*]pyrrolo[1,2-*d*][1,4]oxazepine-1-carbaldehyde (24u) (CCDC NO. 1573097):



24u

The title compound, 6,8-dichloro-10-fluoro-7-methyl dibenzo[b,f] pyrrolo [1,2-d][1,4]oxazepine-1-carbaldehyde (**24u**), $C_{18}H_{10}Cl_2FNO_2$, crystallizes in the monoclinic space group $P2_1/c$ with unit cell parameters: a =16.6493(13), b = 13.1167(11), c = 7.0767(7)Å, β = 98.220(9)° and Z= 4. The crystal structure was solved by direct methods using single-crystal X-ray diffraction data and refined to R = 0.0626 for 2041 observed reflections.

Crystal Structure Determination and Refinement

X-ray intensity data of the crystal of the dimension 0.20 X 0.20 X 0.10 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 6007 reflections (of which 3003 unique) were collected at 293(2)K. The cell dimensions were determined by a least-squares fit of angular settings of 1757 reflections in the θ range 3.88 to 27.55°. The intensities were measured by ωscan mode for θ ranges 3.66 to 25.99°. 2041 reflections were treated as observed (I > 2σ(I)). Data were corrected for Lorentz and polarisation 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 – 0.96 Å with *U*iso = 1.5*U*eq of the attached C atom for methyl H atoms and1.2*U*eq for other H atoms.The final refinement cycles converged to an R = 0.0626 and wR (F^2) = 0.1607 for the observed data. Residual electron densities ranged from -0.325 to 0.377 $eÅ^{-3}$. 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 4.3.

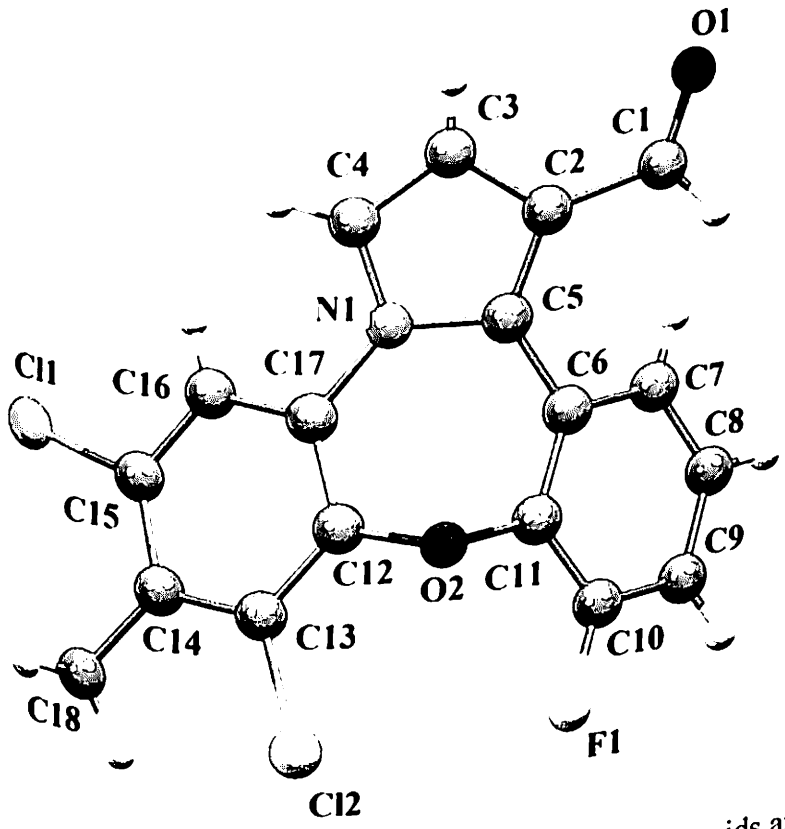
An ORTEP view of the title compound with atomic labeling is shown in Figure 4.3. The geometry of the molecule was calculated using the PLATON and PARST software. Bond lengths and bond angles are within expected values.

Table 4.3 Crystal and experimental data for **24u**

CCDC	1573097
Crystal description	Plate shaped

Crystal colour	Orange
Crystal size	0.2 x 0.2 x 0.1 mm
Empirical formula	$C_{18}H_{10}Cl_2FNO_2$
Formula weight	362.17
Radiation, Wavelength	Mo Kα, 0.71073 Å
Unit cell dimensions	a =16.6493(13), b = 13.1167(11), c = 7.0767(7)Å,
	β= 98.220(9)°
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell volume	1529.6(2)
No. of molecules per unit cell, Z	4
Temperature	293(2)
Absorption coefficient	0.446 mm^{-1}
F(000)	736
Scan mode	ω scan
θ range for entire data collection	3.66<θ<25.99 °
Range of indices	h= -20 to 20, k= -16 to 11, l= -8 to 4
Reflections collected / unique	6007 / 3003
Reflections observed (I > 2 (I))	2041
R_{int}	0.0605
R_{sigma}	0.0430
Structure determination	Direct methods
Refinement	Full-matrix least-squares on F^2
No. of parameters refined	219
Final R	
$wR(F^2)$	0.0626
Weight	0.1607
	$1/[\sigma^2(F_o^2)+(0.0725P)^2+0.8139P]$
	where $P=[F_o^2+2F_c^2]/3$
Goodness-of-fit	1.104
$(\Delta/\sigma)_{max}$	0.002 (for tors H18A)
Final residual electron density	$-0.325 < \Delta\rho < 0.377$ eÅ^{-3}

Measurement	*Xcalibur 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)



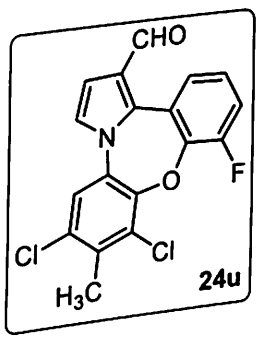
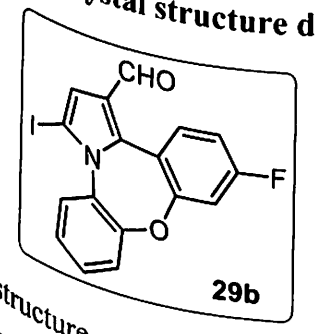


Figure 4.3: *ORTEP* view of **24u** with Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii. **(CCDC NO. 1573097)**

4.13 Crystal structure data for 11-fluoro-3-iododibenzo[b,f]pyrrolo[1,2-d][1,4]oxazepine-1-carbaldehyde (29b) (CCDC NO. 1573098):



The title compound 11-fluoro-3-iododibenzo[b,f]pyrrolo[1,2-d][1,4]oxazepine-1-carbaldehyde **29b**, $C_{17}H_9N_1O_2F_1I_1$,crystallizes in the orthorhombic space group Pbca with unit cell parameters: a = 17.5729(13), b = 9.1432(10), c = 17.8218(13)Å, and Z= 8. The crystal structure was solved by direct methods using single-crystal X-ray diffraction data and refined to R = 0.0406 for 2081 observed reflections.

Crystal Structure Determination and Refinement

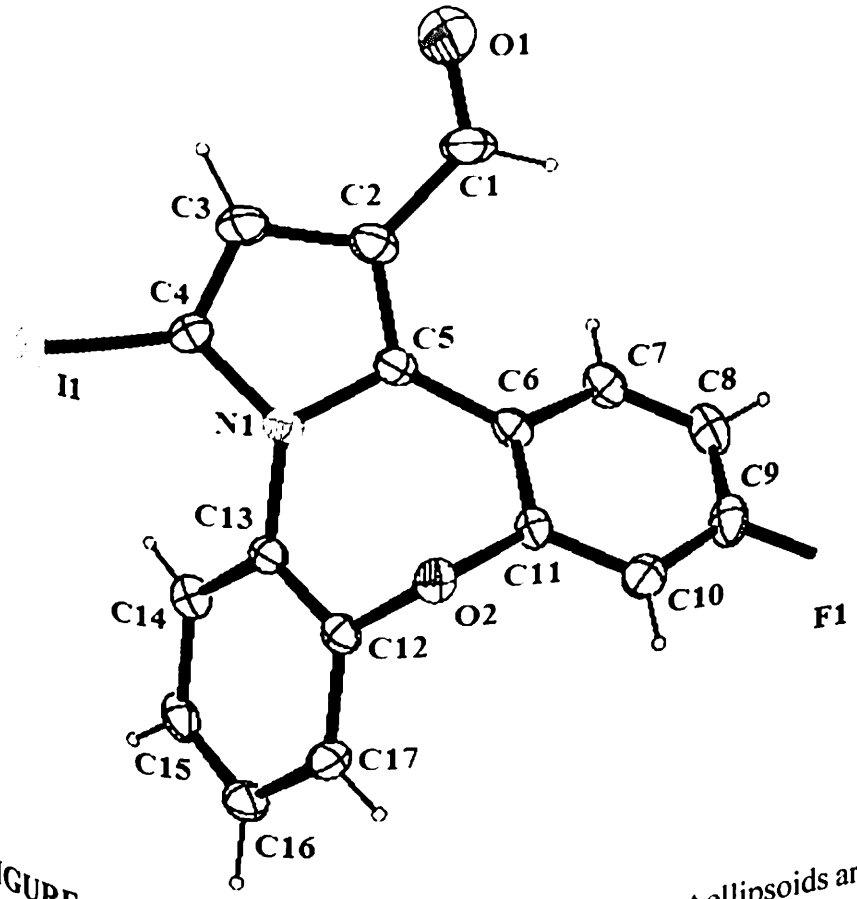
X-ray intensity data of the crystal of the dimension 0.30 X 0.20 X 0.20 mm^3 having well-defined morphology was collected on *Xcalibur* CCD area-detector diffractometer equipped with graphite monochromated Mo*Kα* radiation (λ = 0.71073 Å).X-ray intensity data of 7316 reflections (of which 2808 unique) were collected at 293(2)K. The cell dimensions were determined by a least-squares fit of angular settings of 2367 reflections in the θ range 4.11 to 28.88°. The intensities were measured by ω scan mode for θ ranges 3.95 to 26.00°. 2081 reflections were treated as observed (I > 2σ(I)). Data were corrected for Lorentz and polarisation 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 = 0.0406 and wR (F^2) = 0.0914 for the observed data. Residual electron densities ranged from -0.571 to 0.665eÅ^{-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 4.4**.

An ORTEP view of the title compound with atomic labeling is shown in **Fig. 4.4**. The geometry of the molecule was calculated using the PLATON and PARST software. Bond lengths and bond angles are within expected values.

Table 4.4 Crystal and experimental data for **29b**

CCDC	**1573098**
Crystal description	Block shaped
Crystal colour	Orange
Crystal size	0.3 x 0.2 x 0.2 mm
Empirical formula	$C_{17}H_9N_1O_2F_1I_1$
Formula weight	405.15
Radiation, Wavelength	Mo *Kα*, 0.71073 Å
Unit cell dimensions	a= 17.5729(13), b= 9.1432(10), c= 17.8218(13)Å,
Crystal system	Orthorhombic
Space group	Pbca

Unit cell volume	2863.5(4)
No. of molecules per unit cell, Z	8
Temperature	293(2)
Absorption coefficient	2.254 mm^{-1}
F(000)	1568
Scan mode	ω scan
θrange for entire data collection	$3.95<\theta<26.00^{\circ}$
Range of indices	h= -21 to 14, k= -11 to 11, l= -17 to 21
Reflections collected / unique	1568 / 2808
Reflections observed ($I > 2\sigma(I)$)	2081
R_{int}	0.0423
R_{sigma}	0.0361
Structure determination	Direct methods
Refinement	Full-matrix least-squares on F^2
No. of parameters refined	200
Final R	0.0406
$wR(F^2)$	0.0914
Weight	$1/[\sigma^2(F_o^2)+(0.0363 P)^2+3.3228P]$ where $P=[F_o^2 +2F_c^2] / 3$
Goodness-of-fit	1.125
$(\Delta/\sigma)_{max}$	0.002 (forU22 C5)
Final residual electron density	$-0.571 < \Delta\rho < 0.665$ 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)



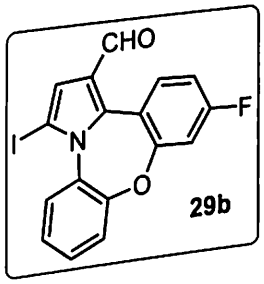


FIGURE 4.4: *ORTEP* view of **29b**, with Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii. **(CCDC NO. 1573098)**

4.14 References

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