5.1. Introduction

The term enaminones usually refers to the compounds that contain the conjugate system N-C=C-C=O, sometimes they are referred to as β-aminovinyl ketones, β-aminoenones or α-enaminoketones. Enaminones are classified as primary (1°), secondary (2°) and tertiary (3°) enaminones based on the degree of substitution on the nitrogen atom (Fig 15). Enaminones are very stable chemical entities and can be easily synthesized from easily available starting materials, therefore they become an attractive intermediates for the synthesis of various heterocycles.

Figure-15

β-enaminones are the useful building blocks in the synthetic organic chemistry. These compounds have reactive sites for nucleophile attack at C-1 and C-3 and carbonyl oxygen and C-2 for electrophile attack. In the following section, methods for the synthesis and applications (or reactions) of β-enaminones is described.

5.2. Synthesis and applications of β-enaminones: A short review

5.2.1. Synthesis of β-enaminones

5.2.1.1. Amination of 1,3-electrophilic 3-carbon selection

Direct condensation of 1,3-dicarbonyl compounds with amines in benzene or toluene at reflux temperature with azeotropic removal of water is one of the classical method for the synthesis of β-enaminones. To enhance the product yield and speed up of the
reaction various catalysts or mediators have been used such as NiO, silica sulfuric acid, CeCl₃.7H₂O, iodine, Ga(OTf)₃, Vo(acac)₂, Bi(TFA)₃, HCl, H₂SO₄, PTSA, AcOH, HClO₄, TMSOTf, montmorillonite KIO, BF₃.Et₂O, Al₂O₃, Zn(ClO₄)₂.6H₂O, NaAuCl₄, Erbium(III) triflate, natural clay, InBr₃, KHSO₄, Yb(OTf)₃ and ionic liquid medium (Scheme 98).

**Scheme-98**

All the above mentioned methods for the synthesis of enaminones from 1,3-diketones and amines are limited to symmetrical diketones. While, unsymmetrical 1,3-diketones give mixture of regioisomeric enaminones.

Sanjay S. Palimkar and coworkers have reported the synthesis of various β-enaminones through Michael addition of different amines into acylacetylenes under solvent free condition (Scheme 99).

**Scheme-99**

Yunyun Liu and coworkers have reported highly stereoselective synthesis of Z-enaminones bearing reactive secondary amino group has been successfully performed in water using tertiary amino group functionalized enaminones under ambient conditions (Scheme 100).
Scheme-100

Hegedus and Bozell\textsuperscript{28} have reported the palladium catalyzed synthesis of β-enaminones from α,β-unsaturated ketones, esters and nitriles in presence of \textit{p}-benzoquinone in THF (Scheme 101).

Scheme-101

Shinzo Seko and Nobuhiro Tani\textsuperscript{29} have reported a two step synthesis of enaminoketones from the addition of methoxyamine to 1,3-diaryl-2-propen-1-one followed by the base induced β-elimination to furnish corresponding enaminoketones in moderate to good yields (Scheme 102).

Scheme-102

Yu-Gui Si and coworkers\textsuperscript{30} have described the addition reaction of amines to the triple bond in α,α,α-trichloro-methylpropargyl mesylate to give α,α-dichloromethyleneaminones (Scheme 103).
Skattebol and Hofslokken\textsuperscript{31} have reported the synthesis of β-enaminones from the reaction between 3-oxo-2,3-dihydrothiophene-1,1-dioxide derivatives with amines. The reaction took place with extrusion of SO\textsubscript{2} at room temperature (Scheme 104).

Okubo and coworkers\textsuperscript{32} have reported the synthesis of enaminones by the substitution of Grignard complexes of amines to the enones with methoxy group at β-position (Scheme 105).

Donald and Marks\textsuperscript{33} have studied the reaction of HN\textsubscript{3} and a chalcone bearing electron withdrawing substituent, which yielded N-aryl enaminone in good yields (Scheme 106).
Srinivasa Reddy and coworkers\textsuperscript{34} have reported lewis acid catalyzed reaction of alkyl azides with enones to afford enaminones (Scheme 107).

Cunha and Gomes\textsuperscript{35} have reported the reaction of benzalacetones and dibenzalacetones with benzyl azide promoted by BF\textsubscript{3}.OEt\textsubscript{2} afforded Z and E densely substituted acyclic α-aryl enaminones in good yields (Scheme 108).

Katritzky and coworkers\textsuperscript{36} have developed a protocol for the synthesis of enaminoketones by reacting silyl enol ethers with imidoylbenzotriazoles in presence of t-BuOK in THF (Scheme 109).
Matsumura and coworkers\textsuperscript{37} have reported the synthesis of enaminones from silyl enol ethers and oxime sulfonates catalyzed by diethyl aluminium chloride (Scheme 110).

Kostrikova and Sosnovskikh\textsuperscript{38} have reported the formation of enaminones by the reaction of nitriles with acetyl ketones in the presence of lithium diisopropyl amide (Scheme 111).

5.2.1.3. Miscellaneous methods

James A. Kenar\textsuperscript{39} has reported raney nickel catalyzed reductive ring-opening protocol for the synthesis of long-chain compounds containing β-enaminone from their corresponding long chain 3,5-disubstituted isoxazole precursors (Scheme 112).
Ilia and coworkers\textsuperscript{40} have reported the reaction of lithioamino anions with α-oxoketone dithioketals in the presence of BF$_3$.OEt$_2$ as catalyst afforded the corresponding enaminones in moderate to good yields (Scheme 113).

\textbf{Scheme-113}

Anthony R. Haight and coworkers\textsuperscript{41} have reported the condensation of N,N-dibenzyl α-amino esters with the anion of acetonitrile followed by the addition of a Grignard reagent to afford α-amino enaminones in one pot operation (Scheme 114).

\textbf{Scheme-114}

\textbf{5.2.2. Applications of enaminones}

Jie Huang and coworkers\textsuperscript{42} have reported a convenient and efficient synthesis of highly substituted pyrrolin-4-ones via the Phenylidonium(III) bis(trifluoroacetate)-mediated cyclization reactions of readily available enaminones (Scheme 115).

\textbf{Scheme-115}
Roberta Bernini and coworkers\textsuperscript{43} have reported an efficient copper-catalyzed approach to the construction of a multisubstituted indole skeleton from readily available N-aryl enamines (Scheme 116).

Scheme-116

Valeriya S. Velezheva\textsuperscript{44} and coworkers have reported a Lewis acid-catalyzed method for the Nenitzescu synthesis of 5-hydroxyindoles with a range of substituents at N-1 and C-3 and symmetric 5,5-dihydroxydiindoles (Scheme 117).

Scheme-117

Zheng-Hui Guan and coworkers\textsuperscript{45} have reported Iron-catalyzed aryl C–H and vinyl C–H bonds activation to give valuable substituted indole products with high functional group tolerance (Scheme 118).

Scheme-118
Ru-Long Yan and coworkers\textsuperscript{46} have described straightforward method for the synthesis of polysubstituted pyrroles was achieved easily from oxidative cyclization of β-enamino ketones and alkynoates catalyzed by CuI in the presence of O\textsubscript{2} (Scheme 119).

Scheme-119

Alessandro Palmieri and coworkers\textsuperscript{47} have reported one-pot synthesis of polyfunctionalized pyrroles from the reaction between β-nitroacrylates and β-enaminones at room temperature under solvent- and promoter-free conditions (Scheme 120).

Scheme-120

Mamta Suri and coworkers\textsuperscript{48} have reported an efficient, atom economic and greener method for the regioselective synthesis of tetrasubstituted pyrazoles catalyzed by copper with molecular oxygen as the sole oxidant (Scheme 121).

Scheme-121
Miao Zhao and coworkers\textsuperscript{49} have synthesized tetrasubstituted pyrroles via the cross-dehydrogenative coupling between enamino esters and acetone using silver carbonate as an effective oxidant (Scheme 122).

\textbf{Scheme-122}

Li and coworkers\textsuperscript{50} have demonstrated Iodine catalyzed intramolecular dehydrogenative coupling reactions of enamines under transition metal free reaction conditions (Scheme 123).

\textbf{Scheme-123}

Jiang and coworkers\textsuperscript{51} have reported the synthesis of quinolines via an unexpected formation of enaminone by the reaction of amines to triple bond in $\alpha,\alpha,\alpha$-trichloromethyl propargyl mesylate (Scheme 124).

\textbf{Scheme-124}
5.3. Results and discussion

5.3.1. Regiospecific synthesis of β-enaminones

The required β-enaminones 3 were synthesized by base catalyzed condensation of glycine ethyl/methyl esters 2a/2b or aminoacetonitrile 2c with β-thioxoketones 1 in ethanol at room temperature (Scheme 125). Both ethyl/methyl glycine esters and aminoacetonitrile 2a-c undergo facile condensation reaction with 1,3-monothio-β-diketones 1a-n to afford corresponding enaminones 3a-p in good yields (Table 8). The chemical shift value of >11.0 corresponds to NH confirmed that the enaminones exists in more stable intra-molecularly hydrogen bonded Z configuration form.

Scheme 125. Synthesis of β-enaminones
**Table 8.** Reaction scope of 1,3-monothio-β-diketones for the synthesis of β-enaminones

<table>
<thead>
<tr>
<th>Entry</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>86</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>2a</td>
<td></td>
<td>85</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>2a</td>
<td></td>
<td>79</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>2a</td>
<td></td>
<td>81</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
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<td>---</td>
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<tr>
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<td>78</td>
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<tr>
<td>6</td>
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<td>2a</td>
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<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>2a</td>
<td>77</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>2a</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>9</td>
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<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>2a</td>
<td>69</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td></td>
<td>2a</td>
<td>74</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>1d</td>
<td></td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>1g</td>
<td></td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td></td>
<td>2c</td>
<td>83</td>
<td></td>
</tr>
</tbody>
</table>
5.3.2. Synthesis of 2,3,5 tri-substituted pyrrole derivatives from β-enaminones

Base catalyzed condensation of 1,3-monothio-β-diketones 1a-n with the appropriate amines 2a-c in ethanol at room temperature afforded the desired enamiones 3a-p (Scheme 125). Initially we have started the synthesis of pyrrole derivatives starting directly from 1,3-monothio-β-diketones in one pot operation. The monothio-β-diketone 1a was selected as a model substrate for optimizing the reaction conditions for the formation of pyrrole F41 in the presence of various bases and solvents at different temperature and time intervals (Table 9, Scheme 126). Thus treatment of 1a with glycine ethyl ester hydrochloride in presence of cesium carbonate in DMF under reflux condition (Table 9, Entry 10) was found to be better reaction condition for the synthesis of pyrrole with only 41% yield. Unfortunately we could not able to improve the product yield even with the different bases like triethyl amine, sodium ethoxide, sodium hydride, potassium tertiarybutoxide, DBU, potassium carbonate and sodium acetate under different reaction conditions (Table 9 entry 1-11).
**Scheme 126.** Synthesis of Ethyl 3,5-diphenyl-1H-pyrrole-2-carboxylate

**Table 9.** Optimization of reaction condition for the formation of Pyrrole F41 in one pot condition

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base (equiv)</th>
<th>Solvent</th>
<th>T(°C)</th>
<th>t(h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TEA (2.0)</td>
<td>DMF</td>
<td>80</td>
<td>8</td>
<td>trace</td>
</tr>
<tr>
<td>2</td>
<td>NaOEt (2.0)</td>
<td>Ethanol</td>
<td>90</td>
<td>12</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>NaH (2.0)</td>
<td>DMF</td>
<td>100</td>
<td>8</td>
<td>25</td>
</tr>
<tr>
<td>4</td>
<td>NaH (2.5)</td>
<td>DMF</td>
<td>100</td>
<td>8</td>
<td>24</td>
</tr>
<tr>
<td>5</td>
<td>t-BuOK(2.0)</td>
<td>t-butanol</td>
<td>80</td>
<td>10</td>
<td>trace</td>
</tr>
<tr>
<td>6</td>
<td>DBU(2.0)</td>
<td>DMF</td>
<td>120</td>
<td>8</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>K$_2$CO$_3$(2.0)</td>
<td>Ethanol</td>
<td>90</td>
<td>8</td>
<td>20</td>
</tr>
<tr>
<td>8</td>
<td>K$_2$CO$_3$ (2.0)</td>
<td>DMF</td>
<td>120</td>
<td>6</td>
<td>30</td>
</tr>
<tr>
<td>9</td>
<td>CS$_2$CO$_3$ (2.0)</td>
<td>DMF</td>
<td>120</td>
<td>6</td>
<td>40</td>
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<tr>
<td>10</td>
<td>CS$_2$CO$_3$ (2.5)</td>
<td>DMF</td>
<td>120</td>
<td>8</td>
<td>41</td>
</tr>
<tr>
<td>11</td>
<td>NaOAc (2.0)</td>
<td>Ethanol</td>
<td>90</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

An attempt for one pot synthesis of pyrroles from 1,3-monothio-β-diketones was not much successful, so we have decided to isolate the intermediate β-enaminoes and to perform a base catalyzed condensation of β-enaminoes for the synthesis of pyrroles. Initially enaminone 3b was selected as a model reactant for the synthesis of pyrrole F42 in the presence of various bases and solvents in different reaction conditions.
Chapter-5

(Table 10, Scheme 127). Thus the condensation of 3b with different bases like K$_2$CO$_3$, Cs$_2$CO$_3$ and NaH doesn’t gave the desired product F42 in appreciable yield (Table 10, entry 1, 2 & 4). When the reaction was performed in presence of potassium tertiary butoxide, only trace amount of desired product was observed (Table 10, entry 3). Then we got a quantitave yield of pyrrole F42 in presence of sodium ethoxide in ethanol (Table 10, entry 5), when the condensation reaction was performed with the triethyl amine as a base in DMF solvent, the reaction doesn’t yield the product F42. However, dramatic increase in the yield (65%) of pyrrole F42 was observed when DBU (1,8-Diazabicyclo[5.4.0]undec-7-ene) was used as a base in DMF solvent under reflux condition (Table 10, Entry 7), probably due to enhanced base strength of DBU. Similarly pyrrole F42 was obtained in an improved yield, when the reaction was conducted in toluene as solvent and DBU as a base (Table 10, Entry 8). Attempt to further improvement of the product yield of F42 by varying the reaction time was not successful (Table 10, Entry 8).
Table 10. Optimization of reaction condition for the formation of Pyrrole derivatives from β-keto enaminones.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base(equiv)</th>
<th>Solvent</th>
<th>T(°C)</th>
<th>t(h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>K₂CO₃(1.0)</td>
<td>DMF</td>
<td>100</td>
<td>8</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>CS₂CO₃(1.0)</td>
<td>DMF</td>
<td>120</td>
<td>8</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>t-BuOK(1.0)</td>
<td>t-butanol</td>
<td>80</td>
<td>12</td>
<td>Trace</td>
</tr>
<tr>
<td>4</td>
<td>NaH(1.0)</td>
<td>DMF</td>
<td>120</td>
<td>8</td>
<td>35</td>
</tr>
<tr>
<td>5</td>
<td>NaOEt(1.0)</td>
<td>Ethanol</td>
<td>90</td>
<td>8</td>
<td>40</td>
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<td>6</td>
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<td>7</td>
<td>DBU(1.0)</td>
<td>DMF</td>
<td>120</td>
<td>12</td>
<td>65</td>
</tr>
<tr>
<td>8</td>
<td>DBU(1.0)</td>
<td>Toluene</td>
<td>100</td>
<td>12</td>
<td>76</td>
</tr>
<tr>
<td>9</td>
<td>DBU(1.5)</td>
<td>Toluene</td>
<td>100</td>
<td>16</td>
<td>75</td>
</tr>
</tbody>
</table>

With the optimized reaction conditions in hand, we next explored the generality of the protocol for the synthesis of other substituted pyroles F41 and F43-56 (Scheme 128) from the corresponding enaminones 3a-p as shown in the Table 4. The enaminones derived from ethyl/methyl glycine ester and amino acetonitrile underwent cyclocondensation smoothly in presence of DBU in toluene at reflux condition. Thus the enaminones bearing various electron donating substituents on the different position of aryl ring such as methoxy, dimethoxy, trimethoxy, methyl, chloro and bromo groups gave the desired product in good yield (Table 11, Entry 2, 7, 9, 11, 12 & 15). Similarly, the enaminones bearing electron withdrawing substituents on the different position of aryl ring such as nitro, cyano and trifluoromethyl groups have also gave the considerable product yield (Table 11, Entry 4, 5, 10, 13 & 16). On the otherhand, the pyroles bearing 2-furyl/2-thienyl/3-pyridyl and 4-pyridyl groups at 3 and 5 positions were obtained in appreciable yields from the corresponding
enaminones (Table 11, Entry 3, 6, 8 and 14). It is noteworthy to mention that, it was possible to install three different heterocyclic ring at 3\textsuperscript{rd} and 5\textsuperscript{th} position of pyrrole ring by employing this protocol.

**Scheme 128.** Synthesis of pyrroles from enaminones

**Table 11.** Synthesis of 3,5-bis(het)aryl-2-carboxylate/nitrile pyrroles F41-56 from enaminones

<table>
<thead>
<tr>
<th>Entry</th>
<th>Enaminone</th>
<th>Product</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td>78</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td>76</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td>70</td>
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</tr>
<tr>
<td>4</td>
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<td>68</td>
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<td>8</td>
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<td></td>
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<tr>
<td>9</td>
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<td>80</td>
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<td>10</td>
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<td>11</td>
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</tr>
<tr>
<td>12</td>
<td></td>
<td>59</td>
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</tr>
</tbody>
</table>
5.4. Conclusion

In conclusion, we have developed an efficient base catalyzed regioselective route to \( \beta \)-enaminones 3 from readily available 1,3-bis(het)aryl-1,3-monothio diketones 1 and used these enaminones 3 to develop a simple and convenient approach for the synthesis of 3,5-bis(het)aryl-2-carboxylate/nitrile pyrroles F41-56. The present protocol allowed us to synthesis novel 2,3,5 tri substituted pyrroles with full control over 3\textsuperscript{rd} & 5\textsuperscript{th} position on pyrrole ring. Although the product yields are moderate to
good, the method offers a facile regioselective entry to 2,3,5 trisubstituted pyrroles, thus overcoming the limitations of literature reported methods in which they have reported the mixture of regioisomers. The probable mechanism for the formation of pyrroles looks to be simple as depicted in scheme 129. Base induced intramolecular cyclization of enaminones with the elimination of water molecule affords pyrroles in good yield.

**Scheme 129.** Probable mechanism for the formation of pyrroles

### 5.5. Experimental Section

#### 5.5.1. General

Reactions were monitored by TLC using precoated sheets of silica gel G/UV-254 of 0.25 mm thickness (Merck 60F254) using UV light for visualization. $^1$H and $^{13}$C NMR spectra were recorded on an NMR spectrometer operating at 400 and 100 MHz, respectively, using the residual solvent peaks as reference relative to SiMe$_4$. Mass spectra were recorded using high resolution mass spectrometer (HRMS). Infrared spectra were recorded on Shimadzu FT-IR model 8300 spectrophotometer.
5.5.2. General procedure for the synthesis of β-enaminones 3a-p

To a solution of 1,3-bis(het)arylmethiodiketones 1 (5 mmol) and ethyl/methyl glycine ester or amino acetonitrile 2 (5 mmol) in EtOH (25 mL), NaOAc (7.5 mmol) was added at room temperature and stirred for 3-4 h (monitored by TLC). The solvent was removed under reduced pressure and the residue was diluted with EtOAc (100 mL) and water (100 mL). The organic layer was separated and washed with brine (50 mL), then dried over anhydrous sodium sulfate and concentrated to give crude products which were purified by column chromatography over silica gel using hexane:ethylacetate mixture as eluent.

5.5.3. General procedure for the synthesis of pyrroles F41-56

To a solution of enaminone 3 (1.0 mmol) in toluene, DBU (1.0 mmol) was added at room temperature and the reaction mixture was heated at 100°C for 12-14 h (monitored by TLC). The solvent was removed under reduced pressure and the residue was diluted with EtOAc (10 mL) and water (10 mL). The organic layer was separated and washed with brine (10 mL), then dried over anhydrous sodium sulfate and concentrated to give crude products which were purified by column chromatography over silica gel using hexane:ethylacetate mixture as eluent.
5.5.4. Characterization data of isolated enaminones

(Z)-ethyl 2-(3-oxo-1,3-diphenylprop-1-enylamino)acetate (3a)

Yellow solid (88%): mp 68-70°C; Rf 0.4 (3:7 EtOAc : Hexane); IR (KBr, Cm⁻¹) 3461, 3053, 2979, 1740, 1582, 1438, 1219, 1156, 1025, 896, 698; ¹H NMR (400 MHz, CDCl₃) δ 11.44 (s, 1H, NH), 7.94-7.92 (m, 2H, ArH), 7.48-7.38 (m, 8H, ArH), 5.89 (s, 1H, CH), 4.22-4.17 (q, J = 7.2 Hz, 2H, OCH₂CH₃), 3.97-3.95 (d, J = 6.4 Hz, 2H, CH₂), 1.27-1.23 (t, J = 7.0 Hz, 3H, OCH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 189.1, 169.3, 165.8, 139.8, 135.0, 130.8, 129.5, 128.5, 128.0, 127.6, 127.1, 94.6, 61.3, 46.2, 13.9; HRMS (ESI) m/z Calcd for C₁₉H₁₉NO₃ [M + Na]⁺ 332.3591, found 332.3609.

(Z)-ethyl 2-(1-(4-methoxyphenyl)-3-oxo-3-m-tolylprop-1-enylamino)acetate (3b)

Brown solid (80%): mp 100-102°C; Rf 0.5 (3:7 EtOAc : Hexane); IR (KBr, Cm⁻¹) 3460, 3054, 2980, 2928, 1742, 1580, 1555, 1440, 1388, 1220, 1158, 1075, 864, 590. ¹H NMR (400 MHz, CDCl₃) δ 11.50 (s, 1H, NH), 7.97-7.95 (d, J = 8.8 Hz, 2H, ArH), 7.38-7.25 (m, 3H, ArH), 6.96-6.94 (d, J = 8.8 Hz, 2H, ArH), 6.75 (s, 1H, ArH), 5.89 (s, 1H, CH), 4.19-4.14 (q, J = 7.2 Hz, 2H, OCH₂CH₃), 4.01-3.99 (d, J = 8.0 Hz, 2H, CH₂), 3.97 (s, 3H, OCH₃), 2.43 (s, 3H, CH₃), 1.43-1.40 (t, J = 7.0 Hz, 3H, OCH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 186.1, 169.3, 167.5, 150.1, 149.1, 147.1, 136.3, 127.0, 120.9, 120.6, 111.2, 110.8, 94.3, 61.6, 56.0, 46.5, 21.8, 14.0; HRMS (ESI) m/z Calcd for C₂₁H₂₃NO₄ [M + Na]⁺ 376.1627, found 376.1645.
(Z)-ethyl 2-(3-(furan-2-yl)-1-(4-methoxyphenyl)-3-oxoprop-1-enylamino)acetate (3c)

Pale yellow solid (78%): mp 107-109°C; Rf 0.4 (3:7 EtOAc : Hexane); IR (KBr, Cm

\(^{-1}\)) 3425, 2994, 2942, 2847, 1746, 1606, 1575, 1517, 1331, 1262, 1222, 1125, 1074, 1017, 862, 678, 639. \(^1\)H

NMR (400 MHz, CDCl\(_3\)) \(\delta\) 11.07 (s, 1H, NH), 8.36-8.34 (d, \(J = 8.0\) Hz, 1H, ArH), 8.00-7.98 (d, \(J = 8.0\) Hz, 2H, ArH), 7.34-7.32 (d, \(J = 8.0\) Hz, 1H, ArH), 6.95-6.93 (d, \(J = 8.0\) Hz, 2H, ArH), 5.77 (s, 1H, CH), 4.09-4.01 (q, \(J = 7.6\) Hz, 2H, OCH\(_2\)CH\(_3\)), 3.88-3.86 (d, \(J = 6.8\) Hz, 2H, CH\(_2\)), 3.82 (s, 3H, OCH\(_3\)), 1.28-1.25 (t, \(J = 7.2\) Hz, 3H, OCH\(_2\)CH\(_3\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 182.0, 169.8, 167.9, 140.0, 138.3, 129.8, 127.7, 124.7, 119.2, 118.5, 93.9, 60.6, 55.8, 41.8, 14.23; HRMS (ESI) \(m/z\) Calcd for C\(_{18}\)H\(_{19}\)NO\(_5\) [M + Na]\(^+\) 352.1263, found 352.1297.

(Z)-ethyl 2-(3-(3-nitrophenyl)-3-oxo-1-p-tolylprop-1-enylamino)acetate (3d)

Pale yellow solid (76%): mp 111-113°C; Rf 0.45 (3:7 EtOAc : Hexane); IR (KBr, Cm

\(^{-1}\)) 3450, 2989, 2985, 2917, 1716, 1435, 1298, 1098, 1035, 858, 777, 520; \(^1\)H

NMR (400 MHz, CDCl\(_3\)) \(\delta\) 11.53 (s, 1H, NH), 8.68 (s, 1H, ArH), 8.29-8.23 (m, 2H, ArH), 7.60-7.56 (t, \(J = 8.0\) Hz, 1H, ArH), 7.30-7.25 (m, 4H, ArH), 5.83 (s, 1H, CH), 4.23-4.18 (q, \(J = 7.0\) Hz, 2H, OCH\(_2\)CH\(_3\)), 3.99-3.98 (d, \(J = 4.0\) Hz, 2H, CH\(_2\)), 2.42 (s, 3H, CH\(_3\)), 1.29-1.25 (t, \(J = 7.0\) Hz, 3H, OCH\(_2\)CH\(_3\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 185.4, 168.8, 167.3, 141.5, 140.1, 132.9, 131.8, 129.4, 129.1, 128.7, 127.5, 127.4, 125.9, 96.1, 61.5, 46.4, 21.4, 14.1; HRMS (ESI) \(m/z\) Calcd for C\(_{20}\)H\(_{20}\)N\(_2\)O\(_5\) [M + Na]\(^+\) 391.1372, found 391.1379.
(Z)-ethyl 2-(3-(4-cyanophenyl)-3-oxo-1-p-tolylprop-1-enylamino)acetate (3e)

Yellow solid (85%): mp 122-124°C; Rf 0.45 (3:7 EtOAc : Hexane); IR (KBr, Cm⁻¹) 3443, 2996, 2980, 226, 1712, 1560, 1453, 1356, 1285, 1162, 1096, 857, 709, 618, 519; ¹H NMR (400 MHz, CDCl₃) δ 11.50 (s, 1H, NH), 7.91-7.89 (d, J = 6.8 Hz, 2H, ArH), 7.61-7.60 (d, J = 6.8 Hz, 2H, ArH), 7.22-7.17 (m, 4H, ArH), 5.73 (s, 1H, CH), 4.10-4.15 (q, J = 7.2 Hz, 2H, OCH₂CH₃), 3.93-3.91 (d, J = 6.4 Hz, 2H, CH₂), 2.33 (s, 3H, CH₃), 1.19-1.16 (t, J = 7.2 Hz, 3H, OCH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 186.4, 169.1, 167.4, 143.7, 140.3, 132.0, 131.6, 129.4, 127.6, 127.4, 118.5, 113.9, 94.4, 61.6, 46.4, 21.2, 14.0; HRMS (ESI) m/z Calcd for C₂₁H₂₀N₂O₃ [M + Na⁺] 371.3951, found 371.3957.

(Z)-ethyl 2-(1-(4-chlorophenyl)-3-(naphthalen-2-yl)-3-oxoprop-1-enylamino)acetate (3f)

Yellow solid (83%): mp 119-121°C; Rf 0.45 (3:7 EtOAc : Hexane); IR (KBr, Cm⁻¹) 3461, 3052, 2979, 1900, 1741, 1582, 1439, 1387, 1219, 895, 591; ¹H NMR (400 MHz, CDCl₃) δ 11.33 (s, 1H, NH), 8.32 (s, 1H, ArH), 7.94-7.92 (d, J = 8.0 Hz, 1H, ArH), 7.84-7.75 (m, 3H, ArH), 7.46-7.17 (m, 6H, ArH), 5.92 (s, 1H, CH), 4.09-4.14 (q, J = 7.2 Hz, 2H, OCH₂CH₃), 3.85-3.87 (d, J = 6.4 Hz, 2H, CH₂), 1.19-1.15 (t, J = 7.2 Hz, 3H, OCH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 189.2, 169.3, 164.6, 137.1, 135.9, 134.7, 133.6, 132.7, 129.23, 129.21, 129.0, 127.9, 127.7, 127.6,
127.3, 126.2, 124.1, 95.1, 61.6, 46.3, 14.1; HRMS (ESI) m/z Calcd for C_{23}H_{20}ClNO_{3}[M + Na]^+ 416.8628, found 416.8631.

(Z)-ethyl 2-(3-oxo-1,3-di(thiophen-2-yl)prop-1-enylamino)acetate (3g)

Pale brown solid (75%): mp 96-98^0C; R_f 0.35 (3:7 EtOAc : Hexane); IR (KBr, Cm\(^{-1}\))

3311, 3124, 2934, 2855, 1615, 1516, 1386, 1271, 1182, 1118, 1079, 1037, 933, 856, 837, 785, 723, 482; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 11.06 (s, 1H, NH), 7.58 - 7.57 (d, \(J = 3.6\) Hz, 1H, ArH), 7.46 - 7.42 (m, 2H, ArH), 7.25 - 7.24 (d, \(J = 4.4\) Hz, 1H, ArH), 7.10 - 7.03 (m, 2H, ArH), 5.89 (s, 1H, CH), 4.24 - 4.19 (q, \(J = 7.2\) Hz, 2H, O\(\text{CH}_2\)CH\(_3\)), 4.11 - 4.09 (d, \(J = 6.4\) Hz, 2H, CH\(_2\)), 1.30 - 1.27 (t, \(J = 7.2\) Hz, 3H, O\(\text{CH}_2\)CH\(_3\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 185.3, 168.9, 167.2, 140.0, 133.0, 129.5, 128.7, 127.6, 127.5, 126.0, 93.9, 61.4, 42.0, 14.2; HRMS (ESI) m/z Calcd for C_{15}H_{15}NO_{3}S_{2}[M + Na]^+ 344.0493, found 344.0499.

(Z)-ethyl 2-(1-(3,4-dimethoxyphenyl)-3-oxo-3-(4-(trifluoromethyl)phenyl)prop-1-enyl amino) acetate (3i)

Pale yellow solid (82%): mp 104-106^0C; R_f 0.35 (3:7 EtOAc : Hexane); IR (KBr, Cm\(^{-1}\))

1) 3425, 2993, 2940, 1747, 1605, 1572, 1445, 1329, 1259, 1224, 1073, 859, 595, 477; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 11.44 (s, 1H, NH), 7.93 - 7.91 (d, \(J = 8.4\) Hz, 2H, ArH), 7.58 - 7.56 (d, \(J = 8.4\) Hz, 2H, ArH), 6.93 - 6.90 (m, 1H, ArH), 6.86 - 6.84 (m, 2H, ArH), 5.78 (s, 1H, CH), 4.15 - 4.10 (q, \(J = 7.2\) Hz, 2H, O\(\text{CH}_2\)CH\(_3\)), 3.94 - 3.92 (d, \(J = 6.4\) Hz, 2H, CH\(_2\)), 3.85 (s, 3H, OCH\(_3\)), 3.81 (s, 3H, OCH\(_3\)), 1.20 - 1.16 (t, \(J = 7.2\) Hz, 3H, O\(\text{CH}_2\)CH\(_3\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 187.1, 169.6, 166.9, 196
150.4, 149.0, 132.3, 132.0, 128.1, 127.4, 127.1, 125.2, 125.18, 125.14, 125.10, 124.7, 122.9, 120.6, 111.0, 94.5, 61.5, 55.99, 55.98, 46.5, 14.3; HRMS (ESI) m/z Calcd for C_{22}H_{22}F_{3}NO_{5} [M + Na]^+ 460.4090, found 460.4094.

(Z)-ethyl 2-(1-(3,4-dimethoxyphenyl)-3-oxo-3-(pyridin-4-yl)prop-1-enylamino) acetate (3j)

Light brown solid (72%): mp 124-126°C; R_f 0.4 (5:5 EtOAc : Hexane); IR (KBr, Cm^−1) 3316, 3106, 3072, 2978, 2928, 1715, 1662, 1538, 1481, 1453, 1413, 1323, 1286, 1197, 1105, 1026, 832, 741; 1H NMR (400 MHz, CDCl_3) δ 11.58-11.55 (t, J = 5.8 Hz, 1H, NH), 8.69-8.68 (d, J = 6.0 Hz, 2H, ArH), 7.71-7.70 (d, J = 4.0 Hz, 2H, ArH), 6.99-6.90 (m, 3H, ArH), 5.83 (s, 1H, CH), 4.24-4.18 (q, J = 7.2 Hz, 2H, OCH_2CH_3), 4.02-4.01 (d, J = 6.4 Hz, 2H, CH_3), 3.93 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 1.29-1.26 (t, J = 7.2 Hz, 3H, OCH_2CH_3); 13C NMR (100 MHz, CDCl_3) δ 186.3, 169.1, 167.3, 150.0, 149.0, 146.6, 126.9, 120.8, 120.5, 111.0, 110.6, 96.0, 61.5, 55.94, 55.90, 46.5, 14.1; HRMS (ESI) m/z Calcd for C_{20}H_{22}N_2O_5 [M + Na]^+ 393.1529, found 393.1536.

(Z)-2-(1-(4-methoxyphenyl)-3-oxo-3-(thiophen-2-yl)prop-1-enylamino) acetonitrile (3n)

Yellow viscous solid (80%): R_f 0.55 (3:7 EtOAc : Hexane); IR (ATR, Cm^−1) 3449, 3247, 3056, 2926, 2219, 1639, 1507, 1458, 1387, 1269, 1098, 1017, 836, 799, 738, 504; 1H NMR (400 MHz, CDCl_3) δ 10.82-10.81 (d, J = 6.0 Hz, 1H, NH), 7.61-7.60 (d, J = 4.0 Hz, 1H, ArH), 7.54-7.52 (d, J = 5.2 Hz, 1H, ArH), 7.43-7.40 (m, 2H, ArH), 7.10-7.08 (t, J = 5.0 Hz, 1H, ArH), 7.03-
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7.00 (m, 2H, ArH), 5.84 (s, 1H, CH), 4.07-4.05 (d, \( J = 7.2 \) Hz, 2H,CH\(_2\)), 3.88 (s, 3H, OCH\(_3\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 182.8, 164.6, 161.3, 146.1, 131.4, 129.4, 129.0, 127.9, 125.9, 116.1, 114.5, 96.7, 55.4, 32.7; HRMS (ESI) \( m/z \) Calcd for C\(_{16}\)H\(_{14}\)N\(_2\)O\(_2\)S [M + Na]\(^{+}\) 321.0776, found 321.0785.

5.5.5. Characterization data of isolated pyrroles F41-56

**Ethyl 3,5-diphenyl-1H-pyrrole-2-carboxylate (F41)**

Off white solid (78%): mp 140-142\(^0\)C (lit 139-140\(^0\)C); \( R_f \) 0.5 (2:8 EtOAc : Hexane);

IR (KBr, Cm\(^{-1}\)) 3311, 2978, 1661, 1603, 1462, 1437, 1365, 1268, 1134, 819, 764, 657, 505; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 9.42 (s, 1H, NH), 7.60-7.59 (m, 4H, ArH), 7.43-7.38 (m, 4H, ArH), 7.34-7.32 (m, 2H, ArH), 6.629-6.622 (d, \( J = 2.8 \) Hz, 1H, C\(_4\)H), 4.28-4.26 (q, \( J = 2.0 \) Hz, 2H, OCH\(_2\)CH\(_3\)), 1.25-1.23 (t, \( J = 7.2 \) Hz, 3H, OCH\(_2\)CH\(_3\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 161.2, 135.3, 135.0, 133.4, 131.0, 129.5, 129.0, 127.9, 127.6, 127.0, 124.7, 118.5, 109.9, 60.3, 14.1; HRMS (ESI) \( m/z \) Calcd for C\(_{19}\)H\(_{17}\)NO\(_2\) [M + Na]\(^{+}\) 314.3438, found 314.3439.

**Ethyl 5-(4-methoxyphenyl)-3-m-tolyl-1H-pyrrole-2-carboxylate (F42)**

White solid (76%): mp 130-132\(^0\)C; \( R_f \) 0.6 (3:7 EtOAc : Hexane); IR (KBr, Cm\(^{-1}\))

3314, 2999, 2833, 1664, 1476, 1448, 1297, 1266, 1242, 1016, 802, 719, 530; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \)

9.24 (s, 1H, NH), 7.54-7.51 (m, 2H, ArH), 7.41-7.39 (d, \( J = 9.6 \) Hz, 2H, ArH), 7.29-7.26 (t, \( J = 7.8 \) Hz, 1H, ArH), 7.148-7.144 (m, 1H, ArH), 6.98-6.95 (m, 2H,
ArH), 6.52-6.652 (d, J = 3.2 Hz, 1H, C₄H), 4.29-4.26 (q, J = 3.2 Hz, 2H, OCH₂CH₃), 3.86 (s, 3H, OCH₃), 2.39 (s, 3H, CH₃), 1.29-1.26 (t, J = 7.6 Hz, 3H, OCH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 161.4, 151.9, 137.4, 135.7, 134.7, 133.9, 130.2, 127.7, 127.5, 126.6, 126.3, 126.0, 114.4, 109.0, 60.2, 55.3, 21.4, 14.1; HRMS (ESI) m/z Calcd for C₂₁H₂₁NO₃ [M + Na]+ 358.3963, found 358.3965.

Ethyl 3-(furan-2-yl)-5-(4-methoxyphenyl)-1H-pyrrole-2-carboxylate (F43)

Pale pink solid (70%): mp 134-136°C; Rf 0.65 (2:8 EtOAc : Hexane); IR (KBr, Cm⁻¹) 3339, 2984, 2839, 1667, 1483, 1467, 1271, 1237, 1186, 1026, 828, 747, 523; ¹H NMR (400 MHz, CDCl₃) δ 9.07 (s, 1H, NH), 7.54-7.52 (m, 2H, ArH), 7.45-7.45 (m, 1H, ArH), 7.21-7.22 (d, J = 2.7 Hz, 1H, ArH), 6.95-6.97 (d, J = 2.5 Hz, 2H, ArH), 6.86-6.85 (d, J = 2.5 Hz, 1H, ArH), 4.43-4.38 (q, J = 5.8 Hz, 2H, OCH₂CH₃), 3.85 (s, 3H, OCH₃), 1.44-1.41 (t, J = 5.7 Hz, 3H, OCH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 160.5, 159.5, 148.8, 141.2, 135.5, 126.1, 123.6, 122.9, 116.6, 114.4, 111.5, 109.4, 106.1, 60.5, 55.3, 14.5; HRMS (ESI) m/z Calcd for C₁₈H₁₇NO₄ [M + Na]+ 334.3319, found 334.3321.

Ethyl 3-(3-nitrophenyl)-5-p-tolyl-1H-pyrrole-2-carboxylate (F44)

Yellow solid (71%): mp 148-150°C; Rf 0.65 (2:8 EtOAc : Hexane); IR (KBr, Cm⁻¹) 3327, 2923, 2853, 1536, 1345, 1268, 1205, 1096, 1024, 883, 869, 685, 508; ¹H NMR (400 MHz, CDCl₃) δ 9.37 (s, 1H, NH), 8.50-8.49 (t, J = 1.6 Hz, 1H, ArH), 8.18-8.16 (m, 1H, ArH), 7.94-7.92 (m, 1H, ArH), 7.55-7.49 (m, 3H, ArH), 7.26-7.25 (m, 2H, ArH), 6.629-6.623 (d, J =
2.3 Hz, 1H, C(CH3)3), 4.31-4.27 (q, J = 5.8 Hz, 2H, OCH2CH3), 2.39 (s, 3H, CH3), 1.27-1.24 (t, J = 5.8 Hz, 3H, OCH2CH3); 13C NMR (100 MHz, CDCl3) δ 161.0, 147.8, 138.3, 136.8, 136.6, 130.8, 129.8, 128.5, 128.4, 127.7, 127.6, 124.7, 124.5, 118.2, 109.2, 60.7, 21.2, 14.1; HRMS (ESI) m/z Calcd for C20H18N2O4 [M + Na]+ 373.3679, found 373.3683.

**Ethyl 3-(4-cyanophenyl)-5-p-tolyl-1H-pyrrole-2-carboxylate (F45)**

White solid (69%): mp 196-198°C; Rf 0.65 (2:8 EtOAc : Hexane); IR (KBr, Cm⁻¹) 3311, 3110, 2924, 2854, 2227, 1661, 1503, 1476, 1445, 1289, 1207, 1135, 1112, 1081, 729, 560; 1H NMR (400 MHz, CDCl3) δ 9.34 (s, 1H, NH), 7.71-7.69 (m, 2H, ArH), 7.67-7.65 (m, 2H, ArH), 7.49-7.47 (d, J = 6.6 Hz, 2H, ArH), 7.26-7.24 (d, J = 7.2 Hz, 2H, ArH), 6.587-6.581 (d, J = 2.3 Hz, 1H, C(CH3)3), 4.30-4.27 (q, J = 5.6 Hz, 2H, OCH2CH3), 2.39 (s, 3H, CH3), 1.29-1.25 (t, J = 5.2 Hz, 3H, OCH2CH3); 13C NMR (100 MHz, CDCl3) δ 160.7, 140.0, 138.3, 136.0, 131.4, 131.3, 130.1, 129.8, 127.7, 124.7, 119.2, 118.5, 110.4, 109.2, 60.6, 21.2, 14.2; HRMS (ESI) m/z Calcd for C21H18N2O2 [M + Na]+ 353.3798, found 353.3799.

**Ethyl 5-(4-chlorophenyl)-3-(naphthalen-2-yl)-1H-pyrrole-2-carboxylate (F46)**

White solid (75%): mp 142-144°C; Rf 0.7 (2:8 EtOAc : Hexane); IR (KBr, Cm⁻¹) 3320, 2976, 2926, 1673, 1480, 1384, 1283, 1139, 1028, 900, 647, 504, 477; 1H NMR (400 MHz, CDCl3) δ 9.34 (s, 1H, NH), 8.049-8.045 (m, 1H, ArH), 7.86-7.83 (m, 3H, ArH), 7.73-7.70 (d, J = 8.2 Hz, 1H, ArH), 7.56-7.54 (m, 2H, ArH), 7.49-7.47 (m, 2H, ArH), 7.42-7.40 (m,
2H, ArH), 6.71-6.70 (d, J = 2.5 Hz, 1H, C₄H), 4.30-4.26 (q, J = 5.7 Hz, 2H, OCH₂CH₃), 1.25-1.22 (t, J = 5.6 Hz, 3H, OCH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 161.2, 133.7, 133.3, 132.5, 132.3, 129.5, 129.2, 128.1, 128.07, 128.00, 127.5, 126.9, 125.9, 125.8, 119.1, 110.4, 60.5, 14.2; HRMS (ESI) m/z Calcd for C₂₃H₁₈ClNO₂ [M + Na]⁺ 398.8475, found 398.8479.

Ethyl 3,5-di(thiophen-2-yl)-1H-pyrrole-2-carboxylate (F47)

Off white solid (68%): mp 104-106°C; Rₓ 0.6 (3:7 EtOAc : Hexane); IR (KBr, Cm⁻¹)
3302, 3103, 2993, 2934, 1665, 1590, 1514, 1456, 1276, 1166, 1078, 939, 502, 474; ¹H NMR (400 MHz, CDCl₃) δ 9.07 (s, 1H, NH), 7.57-7.56 (m, 1H, ArH), 7.30-7.28 (m, 2H, ArH), 7.24-7.23 (m, 1H, ArH), 7.09-7.05 (m, 2H, ArH), 6.63-6.62 (d, J = 2.3 Hz, 1H, C₄H), 4.40-4.35 (q, J = 5.6 Hz, 2H, OCH₂CH₃), 1.39-1.36 (t, J = 5.6 Hz, 3H, OCH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 160.5, 136.0, 133.6, 129.9, 127.9, 127.1, 127.0, 125.6, 125.1, 124.9, 123.4, 117.6, 109.9, 60.7, 14.4; HRMS (ESI) m/z Calcd for C₁₅H₁₃NO₂S₂ [M + Na]⁺ 326.3992, found 326.3997.

Ethyl 3-(4-bromophenyl)-5-(thiophen-2-yl)-1H-pyrrole-2-carboxylate (F48)

Off white solid (66%): mp 174-176°C; Rₓ 0.55 (3:7 EtOAc : Hexane); IR (KBr, Cm⁻¹)
3315, 3100, 2976, 2926, 1712, 1659, 1530, 1478, 1409, 1320, 1199, 1023, 829, 706, 645, 482; ¹H NMR (400 MHz, CDCl₃) δ 9.16 (s, 1H, NH), 7.50-7.44 (m, 4H, ArH), 7.29-7.28 (m, 1H, ArH), 7.23-7.22 (m, 1H, ArH), 7.08-7.07 (m, 1H, ArH), 6.486-6.480 (d, J = 2.3 Hz, 1H, C₄H), 4.30-4.26
(q, \( J = 5.6 \) Hz, 2H, OCH\(_2\)CH\(_3\)), 1.26-1.29 (t, \( J = 5.7 \) Hz, 3H, OCH\(_2\)CH\(_3\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 160.8, 133.8, 133.6, 132.0, 131.1, 130.7, 130.0, 127.9, 124.9, 123.3, 121.2, 118.1, 110.0, 60.5, 14.2; HRMS (ESI) \( m/z \) Calcd for C\(_{17}\)H\(_{14}\)BrNO\(_2\)S [M+ Na]\(^{+}\) 399.2676, found 399.2679 [M+2+ Na]\(^{+}\).

**Ethyl 5-(3,4-dimethoxyphenyl)-3-(4-(trifluoromethyl)phenyl)-1H-pyrrole-2-carboxylate (F49)**

Pale yellow solid (80%): mp 120-122\(^{0}\)C; \( R_f \) 0.65 (3:7 EtOAc : Hexane); IR (KBr, Cm\(^{1}\)) 3325, 2980, 2839, 1671, 1617, 1461, 1294, 1152, 1078, 845, 730, 634, 534; \(^{1}\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 9.27 (s, 1H, NH), 7.71-7.69 (d, \( J = 6.8 \) Hz, 2H, ArH), 7.65-7.62 (m, 2H, ArH), 7.16-7.14 (m, 1H, ArH), 7.074-7.070 (m, 1H, ArH), 6.94-6.92 (d, \( J = 6.6 \) Hz, 1H, ArH), 6.538-6.532 (d, \( J = 2.3 \) Hz, 1H, C\(_4\)H), 4.30-4.26 (q, \( J = 5.6 \) Hz, 2H, OCH\(_2\)CH\(_3\)), 3.96 (s, 3H, OCH\(_3\)), 3.93 (s, 3H, OCH\(_3\)), 1.27-1.24 (t, \( J = 5.6 \) Hz, 3H, OCH\(_2\)CH\(_3\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 160.7, 149.0, 132.4, 132.0, 128.0, 127.4, 127.1, 125.2, 125.19, 125.15, 125.13, 125.11, 120.5, 111.0, 110.7, 109.4, 109.2, 61.5, 55.99, 55.95, 14.0; HRMS (ESI) \( m/z \) Calcd for C\(_{22}\)H\(_{20}\)F\(_3\)NO\(_4\) [M+ Na]\(^{+}\) 442.3937, found 442.3935.

**Ethyl 5-(3,4-dimethoxyphenyl)-3-(pyridin-4-yl)-1H-pyrrole-2-carboxylate (F50)**

Yellow solid (54%): mp 136-138\(^{0}\)C; \( R_f \) 0.5 (1:1 EtOAc : Hexane); IR (KBr, Cm\(^{1}\)) 3442, 3060, 2934, 2852, 2721, 1707, 1605, 1509, 1440, 1294, 1235, 1112, 832, 803, 766, 670, 466; \(^{1}\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 9.49 (s,
1H, NH), 8.62 (s, 2H, ArH), 7.56-7.54 (m, 2H, ArH), 7.18-7.16 (t, \( J = 5.2 \) & 2.8 Hz, 1H, ArH), 7.09 (s, 1H, ArH), 6.95-6.92 (m, 1H, ArH), 6.58-6.57 (d, \( J = 3.2 \) Hz, 1H, C\(_4\)H), 4.32-4.29 (q, \( J = 3.2 \) Hz, 2H, O\( \text{CH}_2\text{CH}_3 \)), 3.969 (s, 3H, OCH\(_3\)), 3.960 (s, 3H, OCH\(_3\)), 1.29-1.27 (t, \( J = 3.6 \) Hz, 3H, O\( \text{CH}_2\text{CH}_3 \)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 160.8, 149.4, 149.0, 148.9, 136.1, 124.2, 124.1, 123.7, 118.6, 117.5, 111.6, 108.9, 108.3, 56.0, 55.9, 14.1; HRMS (ESI) \( m/z \) Calcd for C\(_{20}\)H\(_{20}\)N\(_2\)O\(_4\) [M+ Na]\(^+\) 375.3835, found 375.3837.

**Ethyl 3-(thiophen-2-yl)-5-(3,4,5-trimethoxyphenyl)-1H-pyrrole-2-carboxylate (F51)**

Pale brown solid (62%): mp 100-102\(^0\)C; R\(_f\) 0.6 (3:7 EtOAc : Hexane); IR (KBr, Cm\(^{-1}\)) 3315, 3100, 2926, 1712, 1659, 1530, 1478, 1450, 1320, 1283, 1199, 1023, 829, 706, 522; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 9.18 (s, 1H, NH), 7.56-7.55 (m, 1H, ArH), 7.31-7.29 (m, 1H, ArH), 7.08-7.06 (m, 1H, ArH), 6.76 (s, 2H, ArH), 6.65-6.64 (d, \( J = 2.5 \) Hz, 1H, C\(_4\)H), 4.41-4.36 (q, \( J = 5.8 \) Hz, 2H, O\( \text{CH}_2\text{CH}_3 \)), 3.94 (s, 6H, (OCH\(_3\))\(_2\)), 3.88 (s, 3H, OCH\(_3\)), 1.40-1.37 (t, \( J = 5.6 \) Hz, 3H, O\( \text{CH}_2\text{CH}_3 \)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 161.4, 152.4, 151.9, 137.5, 135.7, 134.7, 133.8, 130.0, 127.7, 127.5, 126.6, 126.3, 114.3, 109.2, 60.0, 55.3, 54.4, 14.1; HRMS (ESI) \( m/z \) Calcd for C\(_{20}\)H\(_{21}\)NO\(_5\)S [M+ Na]\(^+\) 410.4494, found 410.4497.

**Methyl 3-(3-nitrophenyl)-5-p-tolyl-1H-pyrrole-2-carboxylate (F52)**

Pale yellow solid (66%): mp 144-146\(^0\)C; R\(_f\) 0.6 (2:8 EtOAc : Hexane); IR (KBr, Cm\(^{-1}\)) 3329, 2919, 2857, 1536, 1343, 1271, 1208, 1096, 1009, 883, 685, 508; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 9.32 (s,
1H, NH), 8.50-8.48 (d, J = 8.0 Hz, 1H, ArH), 8.18-8.16 (d, J = 8.0 Hz, 1H, ArH), 7.56-7.49 (m, 3H, ArH), 7.27-7.25 (d, J = 7.8 Hz, 2H, ArH), 7.25-7.23 (d, J = 8.0 Hz, 2H, ArH), 6.64-6.63 (d, J = 2.5 Hz, 1H, C4H), 3.82 (s, 3H, OCH3), 2.41 (s, 3H, CH3).

HRMS (ESI) m/z Calcd for C_{19}H_{16}N_{2}O_{4} [M+ Na]^{+} 359.1110, found 359.1116.

3,5-di(thiophen-2-yl)-1H-pyrrole-2-carbonitrile (F53)

White solid (71%): mp 188-190\(^{0}\)C; Rf 0.65 (3:7 EtOAc : Hexane); IR (KBr, Cm\(^{-1}\)) 3447, 3053, 3014, 2924, 2218, 1635, 1505, 1384, 1267, 1014, 797, 505, 469; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 9.46 (s, 1H, NH), 7.94-7.92 (d, J = 7.6 Hz, 2H, ArH), 7.55-7.51 (t, J = 8.8 Hz, 2H, ArH), 7.44-7.43 (d, J = 6.8 Hz, 1H, ArH), 6.88 (s, 1H, C4H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta 142.4, 138.0, 128.6, 128.2, 127.6, 126.5, 126.3, 126.0, 125.5, 112.1, 106.6, 100.0; HRMS (ESI) m/z Calcd for C_{13}H_{8}N_{2}S_{2} [M+ Na]^{+} 279.3460, found 279.3470.

5-(4-methoxyphenyl)-3-(thiophen-2-yl)-1H-pyrrole-2-carbonitrile (F54)

Pale yellow solid (72%): mp 197-199\(^{0}\)C; Rf 0.7 (3:7 EtOAc : Hexane); IR (KBr, Cm\(^{-1}\)) 3658, 3310, 3069, 2932, 2205, 1613, 1438, 1269, 1115, 1033, 931, 832, 722, 574, 478; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 9.20 (s, 1H, NH), 7.50-7.48 (d, J = 6.8 Hz, 3H, ArH), 7.30-7.29 (m, 1H, ArH), 7.13-7.10 (m, 1H, ArH), 6.98-6.96 (d, J = 7.6 Hz, 2H, ArH), 6.60 (s, 1H, C4H), 3.85 (s, 3H, OCH3); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta 160.0, 130.0, 129.1, 135.1, 134.0, 127.8, 126.3, 124.0, 124.1, 114.3, 110.5, 104.5, 55.7; HRMS (ESI) m/z Calcd for C_{16}H_{12}N_{2}OS [M+ Na]^{+} 303.3443, found 303.3449.
5-(4-methoxyphenyl)-3-(naphthalen-2-yl)-1H-pyrrole-2-carbonitrile (F55)

Pale yellow solid (78%): mp 183-185°C; Rf 0.75 (3:7 EtOAc : Hexane); IR (KBr, Cm⁻¹) 3688, 3300, 2926, 2844, 2204, 1712, 1452, 1260, 1080, 1035, 829, 756, 626, 579, 473; ¹H NMR (400 MHz, CDCl₃) δ 9.22 (s, 1H, NH), 8.20 (s, 1H, ArH), 7.91-7.85 (m, 4H, ArH), 7.54-7.50 (m, 4H, ArH), 7.00-6.98 (d, J = 6.8 Hz, 2H, ArH), 6.80 (s, 1H, C₄H), 3.86 (s, 3H, OCH₃); ¹³C NMR (100 MHz, CDCl₃) δ 160.0, 139.1, 135.9, 134.7, 133.6, 132.7, 129.23, 129.21, 129.0, 127.9, 127.7, 127.6, 127.3, 126.2, 124.1, 114.2, 105.7, 55.3; HRMS (ESI) m/z Calcd for C₂₂H₁₆N₂O₃ [M+ Na]⁺ 347.3752, found 347.3765.

5-(3,4-dimethoxyphenyl)-3-(4-(trifluoromethyl)phenyl)-1H-pyrrole-2-carbonitrile (F56)

Yellow solid (82%): mp 193-195°C; Rf 0.7 (3:7 EtOAc : Hexane); IR (KBr, Cm⁻¹) 3689, 3297, 2924, 2854, 2211, 1700, 1601, 1519, 1473, 1445, 1383, 1330, 1257, 1074, 1022, 846, 768, 662, 607; ¹H NMR (400 MHz, CDCl₃) δ 9.51 (s, 1H, NH), 7.85-7.83 (d, J = 7.6 Hz, 2H, ArH), 7.71-7.69 (d, J = 7.2Hz, 2H, ArH), 7.16-7.08 (m, 2H, ArH), 6.95- 6.94 (d, J = 7.6 Hz, 1H, ArH), 6.706 (s, 1H, C₄H), 3.97 (s, 3H, OCH₃), 3.93 (s, 3H, OCH₃); ¹³C NMR (100 MHz, CDCl₃) δ 150.7, 149.2, 137.5, 135.8, 129.9, 128.9, 128.2, 127.9, 127.6, 126.9, 126.6, 125.5, 124.0, 114.6, 104.8, 103.8, 56.9; HRMS (ESI) m/z Calcd for C₂₀H₁₅F₃N₂O₂ [M+ Na]⁺ 395.3405, found 395.3436.
5.6. References


Appendices
$^1$H NMR Spectrum of compound 3d
\( ^{13}\text{C} \) NMR Spectrum of compound 3d
HRMS of compound 3d
\(^1\)H NMR Spectrum of compound 3n
$^{13}$C NMR Spectrum of compound 3n
HRMS of compound 3n
$^1$H NMR Spectrum of compound F43
$^{13}$C NMR Spectrum of compound F43
HRMS of compound F43
$^1$H NMR Spectrum of compound F45
$^{13}$C NMR Spectrum of compound F45
HRMS of compound F45
$^1$H NMR Spectrum of compound F49
$^{13}$C NMR Spectrum of compound F49
HRMS of compound F49
$^1$H NMR Spectrum of compound F55
$^{13}$C NMR Spectrum of compound F55
HRMS of compound F55