CHAPTER 5

Synthesis of substituted imidazoles as anti-inflammatory agents
5.1. Section A

Synthesis of 4-[1-(4-Fluoro-phenyl)-4-(5-Substituted-[1,3,4]oxadiazol-2-yl)-1H-imidazol-2-yl]-pyridine as p38 MAP kinase inhibitors.

5.1.1. Introduction.

Benzimidazole derivatives are of wide interest because of their diverse biological activities and clinical applications\textsuperscript{1} \textit{a-g} are depicted in Figure 5.1.1. This ring system is present in numerous antiparasitic, fungicidal, anthelmintic and anti-inflammatory drugs.\textsuperscript{2-5} Some benzimidazole nucleosides, particularly 5,6-dichlorobenzimidazole-1-\(\beta\)-D-ribofuranoside (DRB) and its 2-substituted derivatives show activity against human cytomegalovirus.\textsuperscript{6}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{images/figure_5.1.1}
\caption{Imidazole based drug molecules}
\end{figure}
It is also known that 5,6-dinitrobenzimidazole can substitute 5,6-dimethylbenzimidazole in the vitamin B-12 molecule in *Corynebacterium diphteriae*. Most recently, antiprotozoal activity of substituted 2-trifluorobenzimidazoles has been reported. Recently 5,6-dinitro and 2-trifluoromethyl derivatives, are found to be promising candidates for antimicrobial drugs.

Various Imidazole based selective p38 MAP Kinase (Figure 5.1.2.) inhibitors have been reported for treatment of chronic inflammatory disorders. SmithKline Beecham demonstrated early on that an orally active small molecule, SB203580 (h) could reduce TNFα levels in vivo, validating the pyridinylimidazole structural class. Significant improvements to the kinase selectivity and whole blood potency of (h) were subsequently accomplished at Merck with the discovery of the (S)-sec-phenethylamine moiety represented in the second-generation pyridinylimidazole L-790070 (i). Several other pyridine imidazole based lead molecules e.g., SB242235 (j) RWJ67657 (k), SK&F86002 (l), VK19911 (m) have been advanced to preclinical or clinical studies.

**Figure 5.1.2.** Schematic representation of imidazole based p38 MAP Kinase inhibitors
Taking SB203580 (h) (Figure 5.1.2.) as the basis for designing we have tried replacing 4-thiomethyl phenyl ring with 2-thioalkyl substituted-1,3,4-heterodiazole keeping outer pyridine and fluorophenyl ring intact. Positioning of imidazole was changed. (Figure 5.1.3.)

\[
\begin{align*}
\text{SB203580} & \quad \text{Where } X = O, S; \ Y = O, S, SO, SO_2; \ R = CH_3, CH_2CH_3
\end{align*}
\]

Figure 5.1.3.
5.1.2. Present Work:

The basic core was synthesized by following Scheme 5.1.1. Amidine 3 was obtained by reaction of sodium salt of \( p \)-fluoro aniline 1 on 4-pyridine cabonitrile 2 in tetrahydrofuran. Amidine was further reacted to ethylbromo formate in isopropanol at reflux to get 1-(4-fluoro-phenyl)-4-hydroxy-2-pyridin-4-yl-4,5-dihydro-1H-imidazole-4-carboxylic acid ethyl ester 4.

![Scheme 5.1.1. Reagents and Conditions: A. THF, NaH, 25-65°C; B. Ethyl bromoformate, Isopropanol, NaHCO\(_3\), Reflux; C. Toluene, \( p \)-toluene sulphonic acid, reflux; D. Hydrazine Hydrate, Ethanol, Reflux.](image)

The ester was further dehydrated using \( p \)-toluene sulphonic acid in toluene at reflux to get 1-(4-fluoro-phenyl)-2-pyridin-4-yl-1H-imidazole-4-carboxylic acid ethyl ester 5. Aromatized ester was converted into required hydrazide 6 by reacting with hydrazine hydrate in ethanol.

The hydrazide was used for preparation of 2 substituted-1,3,4-hetrodiazoles. (Scheme 5.1.2.)
Hydrazide was reacted with cyanogen bromide in presence of sodium bicarbonate to get 2-amino-1,3,4-oxadiazole 7. 2-hydroxy-1,3,4-oxadiazole 8 was obtained by reacting hydrazide with triphosgene in dichloromethane and triethylamine as base. The Carbon disulfide and potassium hydroxide in methanol were reacted with hydrazide at 0 °C and then refluxed to furnish 2-mercapto-1,3,4-oxadiazole 9. 2-mercaptoalkyl-1,3,4-thiadiazole 10a,b were obtained by first preparing alkyl thiosemicarbazide derivative of hydrazide using carbon disulfide and alkyl iodide followed by cyclising it in toluene promoted by p-toluene sulphonic acid at reflux.
Mercapto-1,3,4-oxadiazole was alkylated by methyl iodide and ethyl iodide in methanol using potassium-t-butoxide as base (Scheme 5.1.3.) Mercapto alkyl compounds were further oxidized to sulfoxide derivatives using m-chloroperoxybenzoic acid as oxidizing agent below 0 °C.

5.1.3. COX-2 inhibition assay.21
Inhibition of Cyclooxygenases and therefore prostaglandin production is the common mechanism of action of NSAIDs (Nonsteroidal anti-inflammatory drugs). COX exists as two isoforms COX-1 and COX-2. Cyclooxygenase-1 is constitutive whereas Cyclooxygenases 2 is induced by pro-inflammatory cytokines and endotoxin such as Lipopolysachharide (LPS) in cells. Arachidonic acid is stored esterified in phospholipids of cell membranes. It is released from the cell membrane upon demand via phospholipase A2. The free Arachidonic acid is then oxygenated by cyclooxygenase or lipoxygenase pathway. Thromboxane is the end product of Cyclooxygenase pathways and a measure of COX activity.
Selected Compounds were screened for its ability to inhibit Human whole blood COX-2 at the concentration of 10 µM in duplicates using Assay Designs TXB2 EIA kit (Cat. No. 900-002). These compounds were compared with Diclofenac sodium at 20 µM concentration. The results are summarized in Table 5.1.1.

**Assay procedure**
To the heparinized blood, aspirin was added at a conc. of 12µg/mL, to inactivate COX-1 and incubated for 6h, following which blood was half diluted and treated with 10 µM concentration of test compounds 1 hour at 37 °C/5% CO₂ in a 96-well plate. After preincubation with test compound, LPS was added at a final con of 10µg/mL and incubated for another 18 hrs. 250 µL of 1:1 diluted blood was added for both the tests, and 50 µL of 7X concentration of LPS and test compounds were added to make a final volume of 350µL. The TXB2 assay is based on the competitive binding technique in which TXB2 present in a sample competes with a fixed amount of alkaline phosphatase-labeled TXB2 for sites on a rabbit polyclonal antibody. During the incubation, the polyclonal antibody binds to the goat anti-rabbit antibody coated onto the microplate. Following a wash to remove excess conjugate and unbound sample, a substrate solution is added to the wells to determine the bound enzyme activity. The color development is stopped and the absorbance is read at 405 nm. The intensity of the color is inversely proportional to the concentration of TXB2 in the sample. The assay includes following controls:
- **Blank**: Background absorbance caused by the substrate (p-nitrophenyl phosphate).
- **TA (Total Activity)**: Total enzymatic activity of the alkaline phosphatase conjugated to TXB2.
- **NSB (Non-Specific Binding)**: Non-immunological binding of the conjugated TXB2 to the well.
- **B0 (Maximum Binding)**: Maximum amount of TXB2 conjugate bound by the antiserum in the absence of free analyte.

**Standards**: A 3-fold serial dilution was done starting with highest standard (3333pg/mL) in assay buffer. Standards # 1 (3333pg/mL) serves as highest and Std # 7 (13.7pg/mL) as lowest.
Table 5.1.1. Results of selected imidazole derivatives for % inhibition of COX-2 in human whole blood at 10 µM.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Test Compound</th>
<th>% inhibition of COX-2&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>12a</td>
<td>X=O, R= CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>-3</td>
</tr>
<tr>
<td>12b</td>
<td>X=O, R= CH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>4</td>
</tr>
<tr>
<td>13a</td>
<td>X=S, R= CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>-9</td>
</tr>
<tr>
<td>13b</td>
<td>X=S, R= CH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>-12</td>
</tr>
<tr>
<td>Control</td>
<td>Control</td>
<td>0</td>
</tr>
<tr>
<td>STD</td>
<td>Diclofenac</td>
<td>99&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Data are indicated as percentage of inhibition at 10 µM mean of 2 tests. <sup>b</sup> Diclofenac was assayed at 20 µM for COX-2.

The selected compounds tested for their ability to inhibit COX-2 *in-vitro* were inactive.
5.1.4. Experimental & Spectral Data:

The melting points were determined on a Veego apparatus and are uncorrected. Infrared spectra were recorded on a Bruker spectrophotometer in a KBr disc, and the absorption bands are expressed in cm$^{-1}$. $^1$H-NMR spectra were recorded on a Varian AS 400 MHz spectrometer in CDCl$_3$/DMSO-d-6, chemical shifts (δ) are in ppm relative to TMS, and coupling constants (J) are expressed in hertz (Hz). Mass spectra were taken on a Macro mass spectrometer (Waters) by electro-spray method (ES).

$N$-(4-fluoro-phenyl)-isonicotinamidine. (3)
The sodium hydride (3.9 g, 90 mmol) was charged to 100 mL tetrahydrofuran under argon atmosphere. The 4-fluoro aniline (10 g, 90 mmol) in 50 mL tetrahydrofuran was charged to it below 0 °C using addition funnel. The reaction mixture was warmed to room temperature. 4-pyridine carbonitrile (9.36 g, 90 mmol) in 50 mL tetrahydrofuran was charged to it and stirred at 25-30 °C for 18 hrs and further heated at reflux for 2 hours. Tetrahydrofuran was concentrated on rotavap under reduced pressure. Yellow oily residue obtained was partitioned in 150 mL water and 150 mL ethyl acetate. Aq. layer was re-extracted with 2×50 mL ethyl acetate. Organic extracts were combined, dried over sodium sulfate and concentrated to get semisolid product 3 (18 g, 93 %): IR (KBr) 3497, 3313, 3063, 1610, 1597 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-d$_6$) δ 8.66 (d, 2H), 7.87 (d, 2H), 7.14 (t, 2H), 6.86 (q, 2H), 6.52 (bs, 2H); ESI-MS (m/z): 216.0 [M+H]; Molecular Weight:- 215; Molecular Formula:- C$_{12}$H$_{10}$FN$_3$.

1-(4-fluoro-phenyl)-4-hydroxy-2-pyridin-4-yl-4,5-dihydro-1H-imidazole-4-carboxylic acid ethyl ester (4).
To Amidine 3 (10 g, 46.5 mmole) dissolved in 100 mL isopropanol was charged (7.8 g, 93 mmol) sodium bicarbonate and heated to 50°C. Ethyl bromoformate (10.88 g, 55.8 mmole) was charged to the reaction mixture under argon atmosphere using addition funnel. Reaction mixture was heated at reflux 80-85°C, reaction was monitored by TLC for completion of reaction [ethyl acetate: hexane (1:1)] Reaction was cooled to room temperature and IPA was removed under reduced pressure. Residue obtained was partitioned in 150 mL water and 150 mL ethyl acetate. Aq. layer was re-extracted with 2×50 mL ethyl acetate. Organic extracts were combined dried over sodium sulfate and
concentrated to get semisolid product. Purified by column chromatography using silica gel 100-200 mesh size to get 4 as off-white solid (5 g, 32.8%)

:mp 152-154 °C; IR (KBr) 3079, 2992, 2872, 1752, 1611, 1580, 1502 cm\(^{-1}\); \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 8.58 (d, \(J = 6\) Hz, 2H), 7.35 (d, \(J = 6\) Hz, 2H), 7.11 (m, 2H), 6.98 (m, 2H), 6.75 (bs, 1H), 4.45 (d, \(J = 12\) Hz, 1H), 4.18 (bs, 2H), 3.78 (d, \(J = 12\) Hz, 1H), 1.23 (t, 3H). ESI-MS (m/z): 330.1 [M+H]; Molecular Weight:- 329; Molecular Formula:- C\(_{17}\)H\(_{16}\)FN\(_3\)O\(_3\).

1-(4-fluoro-phenyl)-2-pyridin-4-yl-1H-imidazole-4-carboxylic acid ethyl ester (5)

Hydroxy dihydro imidazole 4 (5 g, 15.1 mmole) was charged to 100 mL toluene, \(p\)-toluene sulfonic acid (260 mg, 1.51 mmole) was charged to it and heated to reflux using Dean-Stark apparatus to remove water under argon atmosphere. The reaction was monitored by TLC for completion of reaction [ethyl acetate: hexane (1:1)]. Reaction was cooled to room temperature and toluene was removed under reduced pressure. Residue obtained was partitioned in 100 mL water and 100 mL ethyl acetate. Aq. layer was re-extracted with 2×25 mL ethyl acetate. Organic extracts were combined dried over sodium sulfate and concentrated to get semisolid product. Purified by column chromatography using silica gel 100-200 mesh size to get 5 as off-white solid (3g, 63.8%)

:mp 128-129 °C; IR (KBr) 3488, 3323, 3063, 1745, 1614, 1598 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.54 (q, 2H), 7.83 (s, 1H), 7.31 (q, 2H), 7.25 (d, 2H), 7.20 (d, 2H), 4.46 (q, 2H), 1.40 (t, 3H). ESI-MS (m/z): 312.2 [M+H]; Molecular Weight:- 311; Molecular Formula:- C\(_{17}\)H\(_{14}\)FN\(_3\)O\(_2\).

1-(4-fluoro-phenyl)-2-pyridin-4-yl-1H-imidazole-4-carboxylic acid hydrazide (6)

The ester 6 (3 g, 9.6 mmole) was charged to 30 mL ethanol and refluxed with 2 mL hydrazine hydrate for 4 hours. Reaction mixture was cooled to room temperature. Ethanol was concentrated on rotavap under reduced pressure. Yellow solid residue obtained was stirred in 150 mL water for 30 mins. Solid precipitates were filtered under suction on Buchner funnel. Product was washed with 50 mL water twice followed by 50 mL hexane wash. Yellow colored powder obtained 6 (2.5 g, 87%): mp 154-156 °C; IR (KBr) 3488, 3066, 1619, 1597, 1511 cm\(^{-1}\); \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 9.33 (bs, 1H) 8.53 (d, 2H), 8.00 (s, 1H), 7.50 (q, 2H), 7.38 (d, 2H), 7.27 (q, 2H), 4.41 (bs, 2H); ESI-MS (m/z): 298.1 [M+H]; Molecular Weight:- 297; Molecular Formula:- C\(_{15}\)H\(_{12}\)FN\(_5\)O.
5-[1-(4-fluoro-phenyl)-2-pyridin-4-yl-1H-imidazol-4-yl]-[1,3,4]oxadiazol-2-ylamine (7)
Sodium bicarbonate (141 mg, 1.6 mmol) in 15 mL of water was added to a room temperature solution of 6 (250 mg, 0.84 mmol) in 20 mL of dioxane. After the mixture was stirred at room temperature for 5 min cyanogen bromide (106 mg, 1.02 mmol) was added. After 3 h the volatiles were removed in vacuum. Residue obtained was stirred in 10 mL water and precipitate was removed by filtration to provide 7 as off-white solid (201 mg, 74%): mp 220-222 °C; IR (KBr) 3475, 3061, 1611, 1597, 1510 cm⁻¹; ¹H NMR (400 MHz, DMSO- d6) δ 8.54 (d, 2H), 8.02 (s, 1H), 7.52 (q, 2H), 7.40 (d, 2H), 7.29 (q, 2H); ESI-MS (m/z): 323.2 [M+H]; Molecular Weight:- 322; Molecular Formula:- C₁₆H₁₁FN₆O.

5-[1-(4-Fluoro-phenyl)-2-pyridin-4-yl-1H-imidazol-4-yl]-[1,3,4]oxadiazol-2-ol (8)
Triphosgene (99 mg, 0.36 mmol) was added to a 0 °C solution of 6 (250 mg, 0.84 mmol) and triethylamine (360 µL, 2.5 mmol) in 10 mL of tetrahydrofuran. The reaction mixture was stirred at 0 °C for 2 h, warm to room temperature overnight. The volatiles were removed under reduced pressure and the residue was dissolved in ethyl acetate. The ethyl acetate solution was washed consecutively saturated sodium bicarbonate, and brine. The organic layer was dried over sodium sulfate, filtered and concentrated in vacuum. Off-white solid 8 was obtained. (224 mg, 80 %): mp 220-222 °C; IR (KBr) 3480, 3065, 1619, 1595, 1510 cm⁻¹; ¹H NMR (400 MHz, DMSO- d6) δ 8.54 (d, 2H), 8.00 (s, 1H), 7.54 (q, 2H), 7.38 (d, 2H), 7.29 (q, 2H); ESI-MS (m/z): 324.2 [M+H]; Molecular Weight:- 323; Molecular Formula:- C₁₆H₁₀FN₅O₂.

5-[5-(4-chloro-phenyl)-1-phenyl-1H-pyrazol-3-yl]-[1,3,4]oxadiazole-2-thiol (9)
The hydrazide 6 (250 mg, 0.84 mmol) was dissolved in 20 mL of methanol, and the solution was cooled to 0 °C. Carbon disulfide (100 mg, 1.33 mmol) was added, followed by potassium hydroxide (58 mg, 0.84 mmol). The solution was stirred at 25-30 °C for 1 hr heated at reflux for 4 hr and allowed to cool to room temperature overnight. The solution was concentrated in vacuum and the residue charged in water. The resulting solids were extracted by ethyl acetate. The organic layer was dried over magnesium sulfate, filtered and concentrated in vacuum. Provided off-white solid 9 (190 mg 66 %):
mp 113-116 °C; IR (KBr) 3481, 3066, 1611, 1595, 1515 cm\(^{-1}\); \(^1^H\) NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 8.54 (d, 2H), 8.04 (s, 1H), 7.56 (q, 2H), 7.38 (d, 2H), 7.28 (q, 2H); ESI-MS (m/z): 340.2 [M+H]; Molecular Weight:- 339; Molecular Formula:- C\(_{16}\)H\(_{10}\)FN\(_5\)OS.

4-[1-(4-fluoro-phenyl)-4-(5-methylsulfanyl-[1,3,4]thiadiazol-2-yl)-1H-imidazol-2-yl]-pyridine (10a)
Carbon disulfide (274 mg, 3.70 mmol) was added to a 0 °C suspension of 6 (1 g, 3.36 mmol) in 5 mL of methanol. Potassium hydroxide (235 mg, 0.84 mmol) was then added, and the reaction mixture was stirred at 0 °C for 30 min and then at room temperature for 5 h. Iodomethane (478mg, 3.36 mmol) was added and stirring continued overnight. The solution was concentrated in vacuum and partitioned between ethyl acetate and water. The organic layer was washed with saturated sodium bicarbonate and then dried over magnesium sulfate. The residue was purified by column chromatography, using silica gel 100-200 mesh size eluting with hexane-ethyl acetate (1:1), to provide 558 mg of methyl thiosemicarbazide intermediate.

A solution of intermediate (558 mg) and p-toluenesulfonic acid (638 mg, 3.36 mmol) in 20 mL of toluene was heated at reflux for 2 h under argon atmosphere. The solution was concentrated in Vacuum and purified by column chromatography using silica gel 100-200 mesh size eluting with hexane-ethyl acetate (7:3). The solid was stirred with hexane and collected by filtration to give (408 mg, 33 %) of 10a

mp 124-126 °C; IR (KBr) 3066, 1610, 1595, 1515 cm\(^{-1}\); \(^1^H\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.56 (d, 2H), 7.87 (s, 1H), 7.18-7.32 (m, 6H), 2.80 (s, 3H); ESI-MS (m/z): 370 [M+H]; Molecular Weight:- 369; Molecular Formula:- C\(_{17}\)H\(_{12}\)FN\(_5\)S\(_2\).

4-[4-(5-ethylsulfanyl-[1,3,4]thiadiazol-2-yl)-1-(4-fluoro-phenyl)-1H-imidazol-2-yl]-pyridine (10b)
The compound 10b was prepared using similar procedure for 10a only iodoethane was used as alkylating agent.

mp 143-145 °C; IR (KBr) 3109, 1574, 1509, 1472, 1337 cm\(^{-1}\); \(^1^H\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.56 (d, 2H), 7.87 (s, 1H), 7.21-7.32 (m, 6H), 3.39 (q, 2H), 1.52 (t, 3H); ESI-MS (m/z): 384.0 [M+H]. Molecular Weight:- 383; Molecular Formula:- C\(_{18}\)H\(_{14}\)FN\(_5\)S\(_2\).
4-[1-(4-fluoro-phenyl)-4-(5-methylsulfanyl-[1,3,4]oxadiazol-2-yl)-1H-imidazol-2-yl]-pyridine (11a)

The 2-mercapto-oxadiazole 9 (500 mg, 1.47 mmol) was dissolved in tetrahydrofuran to this was added potassium t-butoxide (97 mg, 1.47 mmol) and cooled to 0 °C under argon atmosphere. Iodomethane (229 mg, 1.61 mmol) was added and stirring continued overnight. The solution was concentrated in vacuum and partitioned between ethyl acetate and water. The organic layer was washed with saturated sodium bicarbonate and then dried over sodium sulfate. The residue was purified by column chromatography using silica gel 100-200 mesh size, eluting with hexane-ethyl acetate (1:1), to provide 11a

mp 161-163 °C; IR (KBr) 3066, 1619, 1597, 1511, 1468 cm⁻¹; ¹H NMR (400 MHz, DMSO- d6) δ 8.55 (d, J = 6.4 Hz, 2H), 8.44 (s, 1H), 7.56 (m, 2H) 7.41 (t, 2H) 7.29 (d, J = 6 Hz, 2H), 2.75 (s, 3H); ESI-MS (m/z): 354.2 [M+H]; Molecular Weight:- 353; Molecular Formula:- C₁₇H₁₂FN₅OS.

4-[1-(4-fluoro-phenyl)-4-(5-Ethylsulfanyl-[1,3,4]oxadiazol-2-yl)-1H-imidazol-2-yl]-pyridine (11b)

The compound 11b was prepared using similar procedure for 11a only iodoethane was used as alkylating agent.

mp 145-147 °C; IR (KBr) 3066, 1619, 1597, 1511, 1468 cm⁻¹; ¹H NMR (400 MHz, DMSO- d6) δ 8.55 (d, J = 6.4 Hz 2H), 8.44 (s, 1H), 7.56(d, 2H) 7.41 (t, 2H) 7.29 (d, J = 6 Hz 2H), 3.38 (q, 2H), 1.44 (t, 3H); ESI-MS (m/z): 368.2 [M+H]; Molecular Weight:- 367; Molecular Formula:- C₁₈H₁₄FN₅OS.

General procedure for synthesis of sulfoxide analogue of 2-alkylsulfanyl-1,3,4-oxadiazoles and thiadiazoles. (12a, 12b, 13a, 13b)

The alkylsulfanyl heterodiazoles 250 mg (1 mole. eq) was dissolved in DCM and cooled to 0 °C. m-chloro perbenzoic acid (1 mole. eq) was added and stirring continued overnight at 25-30 °C. The reaction was quenched by adding saturated sodium bicarbonate. The organic layer was washed with brine and then dried over magnesium sulfate. The residue was purified by column chromatography using silica gel 100-200 mesh size, eluting with hexane-ethyl acetate (1:1), to provide respective sulfoxides.
4-[1-(4-fluoro-phenyl)-4-(5-methanesulfinyl-[1,3,4]oxadiazol-2-yl)-1H-imidazol-2-yl]-pyridine. (12a)
mp 161-163 °C; IR (KBr) 3066, 1619, 1597, 1511, 1468, 1370 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.61 (d, J = 6.4 Hz, 2H), 8.01 (s, 1H), 7.20-7.31(m, 6H), 3.14 (s, 3H); ESI-MS (m/z): 370.1 [M+H]; Molecular Weight:- 369; Molecular Formula:- C₁₇H₁₂FN₅O₂S.

4-[1-(4-fluoro-phenyl)-4-(5-Ethanesulfinyl-[1,3,4]oxadiazol-2-yl)-1H-imidazol-2-yl]-pyridine. (12b)
mp 148-150 °C; IR (KBr) 3066, 1619, 1597, 1511, 1468 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.54 (d, J = 6.4 Hz, 2H), 8.00 (s, 1H), 7.20 (m, 6H), 3.39 (q, 2H), 1.52 (t, 3H); ESI-MS (m/z): 384.0 [M +H]; Molecular Weight:- 384; Molecular Formula:- C₁₈H₁₄FN₅O₂S.

4-[1-(4-fluoro-phenyl)-4-(5-methanesulfinyl-[1,3,4]thiadiazol-2-yl)-1H-imidazol-2-yl]-pyridine (13a)
mp 164-166 °C; IR (KBr) 3065, 1615, 1598, 1518 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.56 (d, 2H), 7.88 (s, 1H), 7.20-7.34 (m, 6H) 3.11 (s, 3H); ESI-MS (m/z): 386.1 [M+H]; Molecular Weight:- 385; Molecular Formula:- C₁₇H₁₂FN₅OS₂.

4-[1-(4-fluoro-phenyl)-4-(5-Ethanesulfinyl-[1,3,4]thiadiazol-2-yl)-1H-imidazol-2-yl]-pyridine (13b)
mp 151-153 °C; IR (KBr) 3066, 1614, 1597, 1510 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.56 (d, 2H), 7.88 (s, 1H), 7.22-7.31 (m, 6H), 3.40 (q, 2H), 1.53 (t, 3H); ESI-MS (m/z): 400 [M+H]; Molecular Weight:- 399; Molecular Formula:- C₁₈H₁₄FN₅OS₂.
$^1$H NMR (4)

![H NMR Image]

MS (4)

![Mass Spectrometry Image]
IR (4)

\[ ^1H \text{ NMR (10b)} \]
MS (12a)

IR (12a)
5.2. Section B:
Development of new synthetic methodologies for Benzimidazole, Imidazopyridine, Benzoheteroazolones and 2-Aminobenzothiazoles.

1. Lithium bromide catalyzed solvent free method for synthesis of 2-substituted benzimidazoles and imidazopyridines.

5.2.1. Introduction.

The benzimidazole moiety is an important heterocyclic nucleus which has been used extensively in medicinal chemistry. Current clinical examples include the antihistamine astemizole\textsuperscript{16}, the anti-ulcerative esomeprazole\textsuperscript{17} and albendazole\textsuperscript{18}, which is used to treat parasitic diseases. Benzimidazoles are a component of vitamin B12 and are related to the DNA base purine and the stimulant caffeine. Bisbenzimidazoles are being developed as DNA minor groove binding agents with antitumor activity\textsuperscript{19} and can act as ligands to transition metals for modeling biological systems\textsuperscript{20}.

Due to their great importance, many synthetic strategies have been developed. The most popular synthetic approach generally involves the condensation of an arylenediamine with a carboxylic acid or its derivative under harsh dehydrating reaction conditions\textsuperscript{21}. Another method is the condensation of an aldehyde with arylenediamine\textsuperscript{22}. Some methods using transition metal catalyzed coupling reactions to construct the benzimidazole nucleus have also been reported. Those involved a palladium-catalyzed intramolecular N-arylation of (\textit{O}-bromophenyl)-amidine\textsuperscript{23}. A method starting from arylenediamine and orthoester in the presence of Yb(OTf)\textsubscript{3}\textsuperscript{24}, zeolite \textsuperscript{25}, or KSF clay\textsuperscript{26} at high temperature was also used for the synthesis of benzimidazole derivatives. Very recently, literature survey reveals several methods for synthesis of benzimidazole and its derivatives using hypervalent iodine as oxidant\textsuperscript{27}, oxalic acid\textsuperscript{28}, H\textsubscript{2}O\textsubscript{2}/HCl\textsuperscript{29}, TiCl\textsubscript{4}\textsuperscript{30}, PPA\textsuperscript{31}, SOCl\textsubscript{2}/SiO\textsubscript{2},\textsuperscript{32} (bromodimethyl)sulphonium bromide\textsuperscript{33}, L-proline\textsuperscript{34}, sulfamic acid\textsuperscript{35}, FeBr\textsubscript{3}\textsuperscript{36}. However in many of these methodologies, acids and aldehydes were used to condense with arylenedimine and suffer from one or more disadvantages, such as low yields, lack of easy availability of the starting materials, use of high boiling corrosive solvents, requirement of excess of catalysts, special apparatus, and harsh reaction conditions.
conditions. Thus, there is a need for simple and efficient processes for the synthesis of benzimidazole derivatives using starting materials other than acids and aldehyde.

5.2.2. Present work.

Another important retro-synthetic approach for synthesis of benzimidazole is condensation of substituted esters with arylenediamine, this has not been explored effectively till date. We therefore took this opportunity to explore this aspect of chemistry as an alternative method for synthesis of 2-substituted benzimidazoles and imidazopyridines.

In our ongoing project for synthesis of 2-substituted imidazopyridines as antihistamine compounds, we started as per the method for reported example\(^3\). Condensation of neat ethyl lactate with 2,3-diamino pyridine (Scheme 5.2.1.) gave very less yield, reaction was incomplete after 48 hours heating at 110-115\(^\circ\)C. In order to improve in both the parameters we employed the addition of Lewis acids to enhance the nucleophilicity of amine by polarizing the ester as given in the proposed mechanism. The various different Lewis acids were used to catalyze a solvent free condensation of ethyl lactate with 2,3-diamino pyridine. This brought us to conclusion that lithium bromide was the best among different Lewis acids used (Table 5.2.1).

![Scheme 5.2.1.](image)

Lithium bromide is a versatile reagent often used basically as nucleophilic brominating reagent\(^3\). It has also been used as Lewis acid catalyst\(^3\) and also as mediator in various other different reactions\(^4\).

In a typical experiment arylenediamine was heated at 110-115 °C in neat substituted ethyl or methyl esters. Alcohol, nitriles and etheral esters were easily condensed (Table 5.2.2).
Table 5.2.1. Effect of Lewis acid (1 mole) on condensation of Ethyl lactate with 2,3 diamino pyridine.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis acid</th>
<th>Time (h)</th>
<th>Yield (%)\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BF\textsubscript{3}-ethrate</td>
<td>12</td>
<td>35</td>
</tr>
<tr>
<td>2</td>
<td>FeCl\textsubscript{3}</td>
<td>15</td>
<td>47</td>
</tr>
<tr>
<td>3</td>
<td>SnCl\textsubscript{4}</td>
<td>13</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>ZnBr</td>
<td>12</td>
<td>40</td>
</tr>
<tr>
<td>5</td>
<td>TiCl\textsubscript{4}</td>
<td>18</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>LiBr</td>
<td>6</td>
<td>80</td>
</tr>
</tbody>
</table>

\textsuperscript{a}2,3-diamino pyridine (1 mole), ethyl lactate (10 mole), solvent free, 115 °C; \textsuperscript{b}isolated yield.

The yields obtained were more in case of alcohol esters than nitrile and ethereal esters. Nitrile esters react slowly in absence of lithium bromide (18, 21, Table 5.2.2.), addition of lithium bromide increases the rate of reaction but various different side products were observed. Plane aliphatic esters without second hetero atom failed to give the required product (23, Table 5.2.2.), this suggest the requirement of another hetero atom oxygen, nitrogen for proper chelation of lithium ion in cyclic five membered or sixmembered transition state supporting the idea of proposed mechanism (Scheme 5.2.2) in first step. Further cyclisation where aromatization and removal of water molecule is the driving force.
Scheme 5.2.2.
Table 5.2.2.

Lithium bromide catalyzed synthesis of 2- substituted imidazopyridines and benzimidazoles. Using 2,3-diamino pyridine and ortho diamino benzene as reactants with different esters.$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ester</th>
<th>Product</th>
<th>Yield$^b$</th>
<th>Time (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>O</td>
<td>![Product Image]</td>
<td>85</td>
<td>7</td>
</tr>
<tr>
<td>15</td>
<td>O</td>
<td>![Product Image]</td>
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<tr>
<td>16</td>
<td>O</td>
<td>![Product Image]</td>
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<td>8</td>
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<tr>
<td>17</td>
<td>O</td>
<td>![Product Image]</td>
<td>75</td>
<td>9</td>
</tr>
<tr>
<td>18</td>
<td>O</td>
<td>![Product Image]</td>
<td>70</td>
<td>14$^c$</td>
</tr>
<tr>
<td>19</td>
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<td>20</td>
<td>O</td>
<td>![Product Image]</td>
<td>83</td>
<td>8</td>
</tr>
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<td>21</td>
<td>O</td>
<td>![Product Image]</td>
<td>70</td>
<td>18$^c$</td>
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<tr>
<td>22</td>
<td>O</td>
<td>![Product Image]</td>
<td>70</td>
<td>10</td>
</tr>
<tr>
<td>23</td>
<td>O</td>
<td>No reaction</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

$^a$ Standard conditions: (1 mole) Arylenediamine, (10 mole) ester, (1 mole) LiBr, 110-115°C; $^b$ Isolated yields based upon starting 2,3-diamino pyridine; $^c$ Reaction without addition of LiBr.
2,3-Diamino pyridine showed slow condensation with substituted esters without LiBr, whereas orthodiamino benzene remain unreacted in absence of LiBr. This concludes that LiBr improves the reactivity of 2,3-diaminopyridine, whereas ortho diaminobenzene reacts easily with substituted esters to get respective condensed product. The excess unreacted alcohol, ethereal esters used can be easily recovered by high vacuum distillation of the reaction mixture.

Thiols and keto esters failed to give required product which is one of the drawbacks of this methodology. Surprisingly reaction of ethyl thioglycolate with 2, 3-diaminopyridine gave 2-methylimidazopyridine as product (16, Table 5.2.2.).

In conclusion we report a unique method for solvent free condensation of esters with arylendiamine using lithium bromide as catalyst to obtain benzimidazoles and imidazopyridines in good to excellent yields.
5.2.3. Experimental work:

General procedure for synthesis of 2-substituted benzimidazoles and imidazopyridines.

Arylenediamine (1 mole. eq), substituted ester (10 mole. eq), LiBr (1 mole eq) were taken in single neck round bottom flask. Reaction mixture was heated to 110-115°C. Progress of the reaction was monitored on TLC. After completion of reaction crude product was purified by flash chromatography to obtain corresponding 2-substituted benzimidazoles and imidazopyridines compounds these were characterized by $^1$H NMR and mass.

1-(3-H-Imidazo[4,5-b]pyridin-2-yl)-ethanol. (15): off white solid; mp °C: 155-157; $^1$H NMR (D$_2$O, 400 MHz): $\delta$ 1.53-1.51 (d, 3H), 5.08-5.02 (q, 1H), 7.22–7.18 (q, 1H, 4 Hz, 8Hz), 7.88-7.86(d, 1H, 8Hz), 8.21-8.20 (2d, 1H, 4Hz); MS (EI, 70 eV): m/z 163.9 (M+H).

(2-Ethoxy-ethyl)-3H-imidazo[4, 5-b]-pyridine. (17): yellow solid. mp °C: 95-97; $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 1.28 (t, 3H), 3.22 (t, 2H), 3.62 (q, 2H), 3.84 (t, 2H), 7.20–7.17 (q, 1H, 4 Hz, 8 Hz), 7.97-7.95 (d, 1H, 8 Hz), 8.30-8.29(d, 1H, 4 Hz); MS (EI, 70 eV): m/z 192.1 (M+H).

1-(1H-Benzimidazol-2-yl)-ethanol. (20): yellow solid. mp °C: 173-175; $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 1.73 (d, 3H), 5.22 (d, 1H), 7.26–7.24 (q, 2H, 4 Hz, 8 Hz), 7.60-7.57 (q, 2H, 4Hz, 8 Hz); MS (EI, 70 eV): m/z 163.0 (M+H).
$^1\text{H NMR (D}_2\text{O)} \ (15) $  

![NMR spectrum of compound in D$_2$O](image1)

$^1\text{H NMR (DMSO)} \ (15) $  

![NMR spectrum of compound in DMSO](image2)
MS (15)

$^{1}$HNMR (17)
MS (17)
2. Lithium bromide catalyzed unique reaction of alkyl cyanoformate with 1-amino 2-heteroaryl substrates and its application towards synthesis of benzoheteroazolones and 2-aminobenzothiazoles.

5.2.2.1. Introduction.

The benzimidazolone\textsuperscript{41}, benzooxazolone\textsuperscript{42}, 2-aminothiazole\textsuperscript{43}, 2-substituted imidazopyridines\textsuperscript{44} moieties are important heterocyclic nucleus, which have been extensively used in organic and medicinal field. 2-benzimidazolone\textsuperscript{45}, 2-benzooxazolone\textsuperscript{46}, 2-amino-thiazole\textsuperscript{47} have been synthesized using various different methods reported. All these methods have one or more drawbacks in its preparation. A close look at the described procedures led us to identify several points to be addressed, as this could be of some help in establishing a reliable and high-yielding synthesis of different azolones and thiazoles. We report here a very unique and simple method for synthesis of various benzoheteroazolones and 2-aminobenzothiazoles.

Ethyl cyanoformate and methyl cyanoformate have been used effectively in organic synthesis\textsuperscript{48} as building blocks. These are also used as nitrile ions source in various reactions like Streker’s reaction\textsuperscript{49}. Ethyl cyanoformates in combination with hydrogen peroxide has also been used for epoxidation\textsuperscript{50} of olefins. There are few reports of its use as source of COOEt synthons\textsuperscript{51}. Taking into account of its use as a source of COOEt and CN synthon we planned to use this information to our benefit and use it to react with various different 1,2 disubstituted arylenes substrates. We came across very interesting observations during this study, which would be unfolded in this report.

We were successful in developing a solvent free method for synthesis of 2-substituted benzimidazoles and imidazoles using lithium bromide as a Lewis acid catalyst\textsuperscript{52}. This knowledge was also used in developing this method.
5.2.2.2. Present work.

In a typical experiment 1-amino-2-heteroaryl substrates were heated at 110-115 °C in neat ethyl cyanoformate in presence of lithium bromide for 1 hour (Scheme 5.2.2.1) to give a unique alkyl

\[
\begin{align*}
\text{NH}_2 & \quad \text{O} \quad \text{CN} \\
& \quad \text{LiBr} \\
110-115^\circ C & \quad 1\text{hr}
\end{align*}
\]

\[
\begin{align*}
X = \text{NH}_2, \text{OH}, \text{SH}; \quad Y = \text{NCOOEt}, \text{O}, \text{S}; \quad Z = \text{NH}, \text{O}, \text{S}; \quad R = \text{O,NH} \quad 8 \text{ examples}
\end{align*}
\]

Scheme 5.2.2.1

carbamate protected benzoheteroazolones. 1, 2-diamino benzene on above reaction produced 2-Oxo-benzoimidazole-1, 3-dicarboxylic acid diethyl ester (24a, Table 5.2.2.1.), which on heating with potassium carbonate in ethanol gave 2-benzimidazolone (24b, Table 5.2.2.1.). 2-amino-phenol under above given condition gave 2-Oxo-benzoazole-3-carboxylic acid ethyl ester (25a, Table 5.2.2.1.) this on further reaction with \( K_2\text{CO}_3 \) in ethanol gave 2-benzooxazolone (25b, Table 5.2.2.1.). A different trend was observed in case of 2-amino benzenethiol under standard conditions we expected similar trend but surprisingly in this case 2-Imino-benzothiazole-3-carboxylic acid ethyl ester (26a, Table 5.2.2.1.) was obtained. This intermediate on hydrolysis with stronger base like KOH in water shows conversion of imino intermediate into starting material, 2-amino-benzothiazole and other degraded products.

Ethylcyanoformate in coordination with lithium bromide provides 2 different possible electrophiles CN, COOEt for attack of a nucleophile (Proposed mechanism Scheme 5.2.2.2.). Attack is governed by the hetero group present in the 1-amino-2 heteroaryl substrate. In case of diamino and amino phenol substrates nitrogen acts as a nucleophile on COOEt group, whereas amino thiol substrates sulphur acts as a nucleophile on CN
electrofile. The only drawback of this method is the possible generation of nitrile ion as per the proposed mechanism. Wherein the nitrile ion removed could possibly liberate HCN. All the necessary precaution should be taken in order to avoid hazards. Taking into account the possible mechanism, if we use 1 eq of alkyl cyanoformates with 1-amino-2-heteroaryl substrates we could stop the reaction at step 2 and step

![Chemical Reaction](image)

Scheme 5.2.2.2

2a (Proposed mechanism Scheme 5.2.2.2.) to 2-benzimidazolone and 2-benzooxazolones, as well as a very green, safe and effective method for synthesis of 2-amino-benzothiazoles.

We performed experiment under above ideology, heating 1-amino 2-heteroaryl substrates with 1 mole ethylcyanoformate and 1 mole lithium bromide in 1, 4 dioxan gave us the expected result. We were able to synthesize different heteroazolones in single step and (Table 5.2.2.2.) in good yields.
In case of 2,3 diamino pyridine (30a Table 5.2.2.1.) we observed another major change in the trend under similar conditions it produced 2-Ethoxy-imidazo[4,5-b]pyridine-3-carboxylic acid ethyl ester. Subsequent reaction with K$_2$CO$_3$ in ethanol gave 2-ethoxy imidazopyridine. Di-ethyl carbamate intermediate formed undergoes cyclisation with removal of water molecule where aromatization is the driving force for the reaction (Proposed mechanism for diamino pyridine Scheme 5.2.2.3). Aliphatic 1, 2 diamino cyclohexane failed to give the cyclised product (31a).

In conclusion we report a unique method for synthesis of carbamate protected as well as free 2-benimidazolone, 2-benooxazolone in good yields. We also report a green and safe method for synthesis of 2-amino-benzothiazole.

Scheme 5.2.2.3
**Table 5.2.2.1:** Lithium bromide catalyzed reaction of 1-amino-2-heteroaryl substrates with ethyl cyanoformate to get intermediate 24a-30a and further reaction with K$_2$CO$_3$ in ethanol to get 24b, 25b, 27b, 28b, 30b$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting</th>
<th>Intermediate 24a-31a</th>
<th>Product 24b-31b</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>( \begin{array}{c} \text{NH}_2 \ \text{NH}_2 \end{array} )</td>
<td>( \begin{array}{c} \text{NH} \ \text{NH} \end{array} )</td>
<td>( \begin{array}{c} \text{O} \ \text{O} \ \text{O} \ \text{O} \end{array} )</td>
<td>85$^c$</td>
</tr>
<tr>
<td>25</td>
<td>( \begin{array}{c} \text{NH}_2 \ \text{OH} \end{array} )</td>
<td>( \begin{array}{c} \text{NH} \ \text{OH} \end{array} )</td>
<td>( \begin{array}{c} \text{O} \ \text{O} \ \text{O} \end{array} )</td>
<td>82$^c$</td>
</tr>
<tr>
<td>26</td>
<td>( \begin{array}{c} \text{NH}_2 \ \text{SH} \end{array} )</td>
<td>( \begin{array}{c} \text{NH} \ \text{SH} \end{array} )</td>
<td>( \begin{array}{c} \text{O} \ \text{O} \ \text{S} \ \text{O} \end{array} )</td>
<td>88$^b$</td>
</tr>
<tr>
<td>27</td>
<td>( \begin{array}{c} \text{NH}_2 \ \text{NH}_2 \end{array} )</td>
<td>( \begin{array}{c} \text{NH} \ \text{NH} \end{array} )</td>
<td>( \begin{array}{c} \text{O} \ \text{O} \ \text{O} \end{array} )</td>
<td>78$^c$</td>
</tr>
<tr>
<td>28</td>
<td>( \begin{array}{c} \text{NH}_2 \ \text{OH} \end{array} )</td>
<td>( \begin{array}{c} \text{NH} \ \text{OH} \end{array} )</td>
<td>( \begin{array}{c} \text{Cl} \ \text{O} \ \text{O} \end{array} )</td>
<td>80$^c$</td>
</tr>
<tr>
<td>29</td>
<td>( \begin{array}{c} \text{NH}_2 \ \text{SH} \end{array} )</td>
<td>( \begin{array}{c} \text{NH} \ \text{SH} \end{array} )</td>
<td>( \begin{array}{c} \text{O} \ \text{O} \ \text{S} \end{array} )</td>
<td>76$^b$</td>
</tr>
<tr>
<td>30</td>
<td>( \begin{array}{c} \text{NH}_2 \ \text{NH}_2 \end{array} )</td>
<td>( \begin{array}{c} \text{NH} \ \text{NH} \end{array} )</td>
<td>( \begin{array}{c} \text{N} \ \text{H} \ \text{Cl} \end{array} )</td>
<td>80$^c$</td>
</tr>
<tr>
<td>31</td>
<td>( \begin{array}{c} \text{NH}_2 \ \text{NH}_2 \end{array} )</td>
<td>( \begin{array}{c} \text{NH} \ \text{NH} \end{array} )</td>
<td>( \begin{array}{c} \text{O} \ \text{O} \ \text{O} \end{array} )</td>
<td>No cyclised product 90$^d$</td>
</tr>
</tbody>
</table>

$^a$ Standard conditions: A. 1-amino-2-heteroaryl and 1-amino-2-hetarylcyclic substrates (1 mole), ethyl cyanoformate (5 mole), lithium bromide (1 mole), 110-115°C Reaction time 1 hr; B. Potassium carbonate (1 mole), ethanol, reflux; $^b$ Yield for intermediate 3a, 6a for single step cyclisation with ethyl cyanoformate; $^c$ Isolated overall yields after two steps based upon starting substrates; $^d$ Yield for intermediate 8a non cyclised product obtained.
Table 5.2.2.2: Lithium bromide catalyzed reaction of 1-amino-2-hetoroaryl substrates with 1 eq ethyl cyanoformate.\

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting</th>
<th>Product 24b-26b</th>
<th>Yield(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td><img src="image1" alt="Structure" /></td>
<td><img src="image2" alt="Structure" /></td>
<td>78</td>
</tr>
<tr>
<td>25</td>
<td><img src="image3" alt="Structure" /></td>
<td><img src="image4" alt="Structure" /></td>
<td>75</td>
</tr>
<tr>
<td>26</td>
<td><img src="image5" alt="Structure" /></td>
<td><img src="image6" alt="Structure" /></td>
<td>68</td>
</tr>
</tbody>
</table>

\(^a\) Standard conditions: 1-amino-2-hetoroaryl (1 mole), ethyl cyanoformate (1 mole), Lithium bromide (1 mole), 1,4 dioxan 2 v/w. 110-115°C Reaction time 1 hr; \(^b\) Isolated overall yields based upon starting substrates.
5.2.2.3. Experimental and spectral data.

$^1$H NMR spectra were recorded on a 400 MHz Varian-Mercury Plus spectrometer and are reported as parts per million (ppm) downfield from a tetramethylsilane internal standard. The following abbreviations are used: singlet (s), doublet (d), triplet (q), multiplet (m) and broad (b). Mass spectra were taken with Micromass-QUATTRO-II of WATER mass spectrometer. All chemicals were obtained from commercial suppliers and were used without purification.

*General procedure for synthesis of ethyl carbamate protected 2-benzimidazolones, 2-benzooxazolone and 2-imino benzothiazoles. (24a-30a)*

1-amino-2-hetroaryl substrates (1 mole. eq), ethyl cyanoformate (5 mole eq), LiBr (1 mole. eq) were taken in single neck round bottom flask. Reaction mixture was heated to 110-115°C for 1 hr. Progress of the reaction was monitored on TLC. After completion of reaction crude reaction mixture was quenched in saturated ferrous sulfate solution and extracted with ethyl acetate. Ethylacetate extracts were dried on anhydrous Na$_2$SO$_4$ and volatiles were removed under reduced pressure to get corresponding alkyl carbamate protected intermediate (24a-30a).

*General procedure for synthesis of 2-benzimidazolone, 2-benzooxazolone from ethyl carbamate protected intermediates. (24b, 25b, 27b, 28b)*

Carbamate protected 2-benzimidazolone, 2-benzooxazolone substrates (1 mole. eq) were taken in 10 volumes Ethanol to this was charged potassium carbonate (1 mole. eq) and heated to reflux in a single neck round bottom flask. Progress of the reaction was monitored on TLC. After completion of reaction ethanol was removed under reduced pressure and residue was stirred in 2 volume water to obtain precipitates of respective product (24b, 25b, 27b, 28b). Filtered and dried till constant weight at 45-50°C.

*Procedure for synthesis of Dihydrochloride salt of 2-ethoxy-3H-imidazo[4,5-b]pyridine from ethyl carbamate protected intermediate.(30b)*

The 2-ethoxy-imidazo[4,5-b]pyridine-1-carboxylic acid ethyl ester (1 mole. eq) was taken in 10 v/w 2N HCl and stirred at 50-55°C. Progress of the reaction was monitored
on TLC. After completion of the reaction water was removed under reduced pressure. Residue obtained was stirred in 10 v/w ethanol to get hydrochloride salt of 7b. Filtered and dried under vacuum.

*General procedure for synthesis of 2-benzimidazolones, 2-benooxazolones and 2-amino benzothiazoles. (24a-26a)*

1-amino-2-heteroaryl substrates (1 mole. eq), Ethyl cyanoformate (1 mole. eq), LiBr (1 mole. eq) in 2v/w 1,4 dioxan were taken in single neck round bottom flask. Reaction mixture was heated at 100-105 °C for 1 hr. Progress of the reaction was monitored on TLC. After completion of reaction crude reaction mixture was quenched in saturated ferrous sulfate solution and extracted with ethylacetate. Ethyl acetate extracts were dried on anhydrous Na₂SO₄ and volatiles were removed under reduced pressure to get 2-benzimidazolones, 2-benooxazolone and 2-amino benzothiazole (24b-26b).

*2-oxo-benzoimidazole-1,3-dicarboxylic acid diethyl ester. (24a):* off white solid; mp °C: 130-132; ¹H NMR (DMSO-d₆, 400 MHz, δ, ppm): 1.45-1.49 (t, 6H), 4.50-4.55 (q, 4H), 7.24-7.27 (m, 2H), 7.92-7.94 (m, 2H); MS (EI, 70 eV): m/z 279.1 (M+H).

*2-oxo-benooxazole-3-carboxylic acid ethyl ester. (25a):* off white solid. mp °C: 80-82; ¹H NMR (DMSO-d₆, 400 MHz, δ, ppm): 1.37-1.34 (t, 3H), 4.40-4.45 (q, 2H), 7.24-7.29 (m, 2H), 7.36-7.38 (m, 1H), 7.67-7.70 (m, 1H); MS (EI, 70 eV): m/z 208. (M+H).

*2-imino-benzothiazole-3-carboxylic acid ethyl ester. (26a):* off white solid. mp °C: 123-125; ¹H NMR (DMSO-d₆, 400 MHz, δ, ppm): 1.24-1.27 (t, 3H), 4.20-4.25 (q, 2H), 7.22–7.26 (m, 1H), 7.36-7.40 (m, 1H), 7.65-7.67 (d, 1H), 7.91-7.93 (d, 1H), 11.97 (bs, 1H, NH); MS (EI, 70 eV): m/z 223.0 (M+H).

*2-ethoxy-imidazo[4,5-b]pyridine-1-carboxylic acid ethyl ester. (30a):* off white solid. mp °C: 106-107; ¹H NMR (CDCl₃, 400 MHz, δ, ppm): 1.43-1.47 (t, 3H), 1.49-1.52 (t, 3H), 4.33-4.39 (q, 2H), 4.47-4.52 (q, 2H), 6.70–6.74 (t, 1H), 7.28–7.30 (dd, 1H.), 7.79-7.81 (d, 1H), 7.91-7.93 (d, 1H); MS (EI, 70 eV): m/z 236.1 (M+H).
1,3-dihydro-benzoimidazol-2-one. (24b): off white solid; mp °C: 254-256; 1H NMR (DMSO-d6, 400 MHz, δ, ppm): 6.89 (s, 4H), 10.53 (bs, 2H, NH); MS (EI, 70 eV): m/z 136.8 (M+2H), 132.9 (M-H).

3H-benzooxazol-2-one. (25b): off white solid; mp °C: 184-185; 1H NMR (DMSO-d6, 400 MHz, δ, ppm): 7.18–7.22 (m, 2H), 7.34-7.40 (m, 2H); MS (EI, 70 eV): m/z 135 (M+H).

Benzothiazol-2-ylamine. (26b): off white solid; mp °C: 130-132; 1H NMR (DMSO-d6, 400 MHz, δ, ppm): 7.11 -7.14 (m, 2H,), 7.25- 7.32 (m, 1H,), 7.54-7.60 (d, 1H, 8Hz), 5.34 (bs, 2H); MS (EI, 70 eV): m/z 151.0 (M+H).

Dihydrochloride salt of 2-ethoxy-3H-imidazo[4,5-b]pyridine. (30b): off white solid; mp °C: 228-230; 1H NMR (D₂O, 400 MHz, δ, ppm): 7.61 (m, 1H), 7.34 (m, 1H), 6.91 (m, 1H); MS (EI, 70 eV): m/z 163.9 (M+H)+.
$^1$H NMR (26a)

MS (26a)
$^1$H NMR (30a)

MS (30a)
1H NMR (30b)

MS (30b)
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