Chapter 2
New Synthetic Methodologies

Section A
Decarboxylative Method for the Synthesis of 2-Styryl Furans/Thiophenes

This section deals with the development of new routes for the synthesis of 2-styryl furans/thiophenes. It also discusses previous literature routes for the synthesis of this class of molecules.
2.1 Introduction

The formation of C-C bonds plays an important role in organic synthesis. There are numerous reports for the synthesis of various structural complex motifs via the effective use of transition metals. Palladium, which plays pivotal role in the Heck, Stille, and Sonogashira cross-coupling and in various cascade reactions. Palladium catalyzed cross-coupling reactions have emerged as an important tool for the carbon-carbon bond forming reactions. These reactions are better in scope selectivity, regio-specificity and chemo-selectivity as compared to other Fe, Ni, Cu metal catalyzed reactions. Direct cross-coupling between alkenes and aryl halides is well documented in literature.

The development of new carbon-carbon bond forming reactions is essential for the synthesis of important molecules. Over the past decades, Suzuki-Miyaura coupling is the most successful strategy for the synthesis of biaryls. Several biaryl derivatives possess their importance as drug molecules such as Felbinac 1, Losartan 2, Imatinib 3 and Boscalid 4 (Figure 1). However, these synthetic methods suffer from few drawbacks as they utilize stoichiometric amounts of organometallic partner.

Figure 1. Structure of few useful biaryl derivatives synthesized via Suzuki-Miyaura cross-coupling reactions.

There are few reports for the synthesis of biaryl derivatives. The first method involves conventional cross-coupling reaction between aryl halides and organometallic substrates. However, this method suffers from several drawbacks i.e. low yields and harsh reaction conditions. The second method employs direct arylation, using aryl halides and substrates having active C-H groups. However, C-H activation method has inherent problem of regio-selectivity.\(^7\)

A third and most promising approach consists of decarboxylative cross-coupling between aryl halide and arene carboxylic acid.\(^8\) The carboxylic group ensures regio-selectivity of the reaction and carbon dioxide is a by-product.

**Figure 2.** Previous reports for the synthesis of biaryl derivatives.

In 1966, Nilsson’s et al. first reported decarboxylative Ullmann coupling on the aryl iodides.\(^9\) Further advancements in this field came very recently. In 2002, Myers et al. carried out Heck type palladium catalyzed decarboxylative coupling between aryl carboxylic acid and olefins.\(^10\) Very recently, Gooßen et al.\(^11\) explored palladium catalyzed cross-coupling between heteroaromatic carboxylic acid and aryl halides. These reactions require catalytic amounts of copper or silver salts. Hence, still there exists a need for the development of new synthetic methodologies overcoming some of the short coming of the reported methods.

There are only very few methods in the literature for the synthesis of 2-styryl furans/thiophenes. These 2-styryl furans are highly conjugated analogs and possess
fluoroscent properties. While, 2-styryl thiophenes/polythiophenes can be useful in the synthesis of the conjugated polymers, these derivatives are highly sensitive to acidic conditions, hence there is still a need for development of new routes for these cross-coupled products (Scheme 1).

Scheme 1. Optimization of the reaction conditions for the synthesis of 2-styryl furans; Reagent and conditions: (a) Aryl halide, K$_2$CO$_3$, PdCl$_2$, 140 °C, 3Å molecular sieves, DMF, 15-60 min.

2.1.1 Previous reports

There are few reports in the literature for the synthesis of 2-styryl furans. In following section, each one of them has been briefly discussed.

2.1.1a Zeni’s et al. approach (2004)

Zeni et al.$^{12}$ utilized Negishi cross-coupling for the synthesis of 2-(Z-styryl)furan. The treatment of 2-furylzinc chloride $^{10}$ with Z-vinyllic tellurides $^{11}$ in presence of palladium chloride, and copper iodide resulted in the formation of 2-(Z-styryl)furan $^{12}$ in 75% yield (Scheme 2).

Scheme 2. Synthesis of 2-(Z-styryl)furan via Negishi cross-coupling reaction.

2.1.1b Bonadies’s et al. approach (2008)

Bonadies et al.$^{13}$ synthesized 2-styryl-furans $^{12}$ via the Wittig reaction. In this approach, triphenylbenzyl phosphonium bromide $^{13}$ was reacted with furan-2-carboxaldehyde $^{14}$ in presence of lithium hydroxide as a base to synthesize 2-(E-styryl)furan $^{15}$ in 98% yield (Scheme 3).


2.1.1c Bras’s et al. approach (2009)

Bras et al.\textsuperscript{14} utilized palladium catalyzed dehydrogenative cross-coupling between furan 16 and styrenes 17 to synthesize the 2-(E-styryl)furan 18. This method gave good to excellent yields, and is highly regio- and stereoselective (Scheme 4).

\textbf{Scheme 4.} Synthesis of 2-(E-styryl)furan via dehydrogenative cross-coupling.

2.2 Present Work: Objective and Rationale

Although derivatives of 2-styryl furans/thiophenes could be useful in the synthesis of various useful analogs, there are only a few methods in the literature for its synthesis. So, there is a need to develop new routes for the synthesis of these molecules.

2.3 Results and Discussion

We opined that 2-(E-styryl)furan 21 could be synthesized by reacting (E)-3-(furan-2-yl)-acrylic acid 19 and aryl halides 20 under palladium catalyzed conditions. An effective strategy for the regiospecific construction of 2-(E-styryl)furan 21, in which (E)-3-(furan-2-yl)-acrylic acid 19 undergoes decarboxylation to generate aryl palladium species which further acts as a nucleophilic intermediate in the cross-coupling with aryl halides and triflates. This system allows the coupling of furan carboxylic acids with aryl halides and triflates in the presence of palladium chloride at 140 °C using potassium carbonate as a mild base (Scheme 5).

\textbf{Scheme 5.} Optimization of reaction conditions for the Synthesis of 2-(E-styryl)furan.
The reaction conditions were optimized by heating a mixture of \((E)-3-(\text{furan-2-yl})\)-acrylic acid and various substituted aryl derivatives at 140 °C in DMF (Table 1). The other coupling substrates studied were boronic acids (entry 11), triflates (entry 10), sulphonyl chloride (entry 12), aromatic chlorides (entry 13), aromatic bromides (entries 2, 4-7) and aromatic iodides. Among all, it was observed that bromides and iodides afforded the desired 2-(\(E\)-styryl)furan 21 in 60 and 65% yields, respectively (entries 7 and 9). Initially, reactions were carried out at 120 °C, but it was observed that yields are low and prolonged heating were required as compared to reactions carried out at 140 °C. Palladium salts were screened from 0.1 mol % to 5 mol %. The better yields were obtained with 5 mol % of palladium catalysts. The screening of palladium catalysts were carried out under various conditions.

### Table 1. Optimization of reaction conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>X'</th>
<th>Palladium catalyst (0.05 eq)</th>
<th>Temp (°C)</th>
<th>Time (min)</th>
<th>Yield (%) b,c</th>
</tr>
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<td>1a</td>
<td>Cl</td>
<td>Pd/C</td>
<td>120</td>
<td>30</td>
<td>0d</td>
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<tr>
<td>2a</td>
<td>Br</td>
<td>Pd/C</td>
<td>120</td>
<td>30</td>
<td>0d</td>
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<tr>
<td>3a</td>
<td>I</td>
<td>Pd/C</td>
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<td>PdCl(_2)</td>
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<td>OTf</td>
<td>PdCl(_2)</td>
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\(a\) Reagent and reaction conditions: \((E)-3-(\text{furan-2-yl})\)-acrylic acid (1.0 eq.), K\(_2\)CO\(_3\) (2 eq.), palladium catalyst (0.05 eq.), powdered 3Å molecular sieves (200 mg), dry DMF (10 ml), were added and refluxed at 140 °C for the specified time mentioned in Table 2.

\(b\) Isolated yields; refers to isolated yields by silica gel column chromatography

\(c\) \(E/Z\) ratio are confirmed by \(^1\)H NMR.

\(d\) Starting materials were recovered quantitatively.

Among them, Pd(OAc)$_2$ (entry 5) afforded slightly lower yield (50%) of the product, while under the same reaction conditions PdCl$_2$ (entry 7) afforded 60% yield of the product. While, other Pd(0) salts resulted in either no reactions (entries 1-3) or in poor yields (entry 4). Inorganic as well as organic bases both were screened for the current methodology. Both these bases worked equally well under the present reaction conditions. In the present methodology, potassium carbonate was used as a base.

<table>
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<tr>
<th>Entry</th>
<th>Aromatic halides</th>
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<th>Product</th>
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<th>Yield (%)</th>
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<td>21a</td>
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<tr>
<td>2</td>
<td>19b</td>
<td>20a</td>
<td>21a</td>
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<tr>
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<td>19c</td>
<td>20a</td>
<td>21b</td>
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</tr>
<tr>
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<td>19d</td>
<td>20a</td>
<td>21c</td>
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<td>19e</td>
<td>20a</td>
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Table 2: Synthesis of 2-(E-styryl)furan/thiophenes via decarboxylative cross coupling.
<p>| | | | | | |</p>
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Both electron donating (EDG) and electron withdrawing groups (EWG) were well tolerated under the present reaction conditions. Remarkable functional group tolerability was observed in coupling reaction in the presence of nitro (entries 5, 6, 13, and 17), amino (entry 6), allyl esters (entry 12), methyl ethers (entries 7, 8, 11, 16, and 18), ketone (entries 14, 19), aldehyde (entries 15, 22), methyl ethers (entries 7, 8, 11, 16, and 18), boronic acids (entry 2), triflates (entries 9, 10), bicyclic bromides (entries 7, 9, 10, and 21) and cyano groups (entry 23) on the aromatic ring. Phenyl partners having free hydroxyl groups and N-heterocyclic arenes resulted in low yields of the corresponding product (Table 2). In order to prove the utility of \((E)-3-(\text{furan-2-yl})\text{-acrylic acid} \text{ 20a},\) cinnamic acid \text{20c} (entry 24) was subjected to present reaction conditions however substrate could not afforded the product. It can be concluded that \((E)-3-(\text{furan-2-yl})\text{-acrylic acid} \text{ 20a} \) or \((E)-3-(\text{thiophene-2-yl})\text{-acrylic acid} \text{ 20b} \) are needed for the present cross-coupling reaction. Two of the derivatives \text{21e} \ and \text{21u} \ were crystallized from methanol/DCM (1:9) and their single crystal X-ray structures of compound \text{21e} \ and \text{21u} \ are represented in Figure 3.
An important distinction between present studies from previously reported methods is that it highlights the ability to selectively perform the reaction in the presence of active C-H bond in an intermolecular fashion. Further, the present protocol is highly regio-specific as acid group directs the coupling. The present method was successfully extended to a variety of substituted aromatic halides having electron donating (EDG) and electron withdrawing groups (EWG) as shown in Table 2 and in all the cases reaction proceeded smoothly to furnish the corresponding product.

### 2.4 Postulated Mechanism

A postulated mechanism has been reported by the Bilodean et al.\textsuperscript{15} involving (E)-3-(furan-2-yl)-acrylic acid 20a or (E)-3-(thiophene-2-yl)-acrylic acid 20b and aryl bromides 19a. Since our substrate is similar, we also presumed that our decarboxylative cross-coupling reaction involving (E)-3-(furan-2-yl)-acrylic acid 20a or (E)-3-(thiophene-2-yl)-acrylic acid 20b and aryl bromides 19a under palladium (0)
species should have similar reaction mechanism. In the first step, palladium (0) species formed from the palladium (II) salts.

Scheme 6. Postulated mechanism for the synthesis of \((E)-3\text{-}(\text{furan-2-yl})\text{-acrylic acid}\) 20a or \((E)-3\text{-}(\text{thiophene-2-yl})\text{-acrylic acid}\) 20b.

The palladium (0) species then subsequently reacts with aromatic halides via oxidative addition to give intermediate (A). Shuffling of electrons from furan ring towards the 3-position of furan ring and attack by palladium yields adduct (B), which on decarboxylation gives intermediate (C), which easily regenerates the original palladium (0) (A) through the reductive elimination and gives the desired 2-styryl furans/thiophenes in good yields (Scheme 6).

2.5 Conclusion

In summary, an efficient decarboxylative cross-coupling reaction for preparing 2-styryl furans/thiophenes from \((E)-3\text{-}(\text{furan-2-yl})\text{-acrylic acid}\) 20a or \((E)-3\text{-}(\text{thiophene-2-yl})\text{-acrylic acid}\) 20b has been developed.
2.6 Experimental

(E)-3-(Furan-2-yl) acrylic acid (276 mg), aryl halide (1.0 eq.), potassium carbonate (551 mg, 2.0 eq.), palladium chloride (17.7 mg, 0.05 eq.), 3 Å molecular sieves (200 mg), and dry DMF (10 mL) were added and refluxed at 140 °C for the appropriate time (see Table 1). After cooling, reaction mixture was filtered over celite and the filtrate was extracted three times with ethyl acetate. The combined organic layers were washed sequentially with water and brine, and then dried over anhydrous Na₂SO₄. After removal of the solvent, the crude oil was passed through silica gel column chromatography (elution with PE/EA 90:10-70:30) to give corresponding product (20-80% yield).

(E)-2-Styrylfuran (21a)

Yield 60%; colorless oil; \( R_f = 0.60 \) (PE/EA, 7:3).

Mol. Formula \( \text{C}_{12}\text{H}_{10}\text{O} \)

IR (CHCl₃) \( \nu_{\text{max}} \text{ (cm}^{-1}) = 3020, 2400, 1532, 1352, 1215. \)

\(^1\text{H NMR} \) (CDCl₃, 200 MHz) \( \delta_H \text{ (ppm) = 7.75-6.83 (m, 8H, CH), 6.41-6.31 (m, 1H, CH)}. \)

\(^{13}\text{C NMR} \) (CDCl₃, 50 MHz) \( \delta_C \text{ (ppm) = 153.2 (CH), 142.1(CH), 136.9 \ (C), 128.6 (CH), 127.5 (CH), 127.1 (CH), 126.3 (CH), 123.8 (CH), 116.5 (CH), 111.6 (CH), 108.5 (CH)}. \)

Elemental analysis Caled for \( \text{C}_{12}\text{H}_{10}\text{O}: \text{C}, 84.68; \text{H}, 5.92 \)

Found: \( \text{C}, 84.50; \text{H}, 6.01 \).

(E)-2-(4-Ethyl)-styryl-furan (21b)

Yield 65%; colorless oil, \( R_f = 0.66 \) (PE/EA, 7:3).
### (E)-5-(2-(Furan-2-yl)vinyl)pyrimidine (21c)

<table>
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<tr>
<th>Property</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mol. Formula</strong></td>
<td>$\text{C}<em>{14}\text{H}</em>{14}\text{O}$</td>
</tr>
<tr>
<td><strong>IR (CHCl$_3$)</strong></td>
<td>$\nu_{\text{max}}$ (cm$^{-1}$) = 3019, 2932, 2400, 1777, 1604, 1418, 1215.</td>
</tr>
<tr>
<td><strong>$^1\text{H NMR}$ (CDCl$_3$, 200 MHz)</strong></td>
<td>$\delta_H$ (ppm) = 7.40-6.32 (m, 9H, CH), 2.58 (q, $J = 7.6$ Hz, 2H, CH$_2$), 1.20 (t, $J = 7.6$ Hz, 3H, CH$_3$).</td>
</tr>
<tr>
<td><strong>$^{13}\text{C NMR}$ (CDCl$_3$, 50 MHz)</strong></td>
<td>$\delta_C$ (ppm) = 153.5 (C), 143.1 (C), 141.9 (CH), 134.5 (C), 131.5 (CH) 130.0 (CH), 129.6 (CH), 128.2 (CH), 127.2 (CH), 126.3 (CH), 119.3 (CH), 115.7 (CH), 111.6 (CH), 108.1 (CH), 28.6 (CH$_2$), 15.4 (CH$_3$).</td>
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<td><strong>Elemental analysis</strong></td>
<td>Calcd for $\text{C}<em>{14}\text{H}</em>{14}\text{O}$: C, 84.81; H, 7.12.</td>
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<tr>
<td></td>
<td>Found: C, 84.73; H, 7.01.</td>
</tr>
<tr>
<td><strong>GC/MS (EI)</strong></td>
<td>198 [$\text{M}^+$], 183 [$\text{M-CH}_3]^+$, 169 [$\text{M-C}_2\text{H}_5]^+$.</td>
</tr>
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</table>

#### Yield

42%; colorless oil; $R_f = 0.40$ (PE/EA, 7:3).

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### (E)-2-(3-Nitrostyryl)furan (21d)

<table>
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<tr>
<th>Property</th>
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<tr>
<td><strong>Mol. Formula</strong></td>
<td>$\text{C}<em>{14}\text{H}</em>{14}\text{O}$</td>
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<tr>
<td><strong>IR (CHCl$_3$)</strong></td>
<td>$\nu_{\text{max}}$ (cm$^{-1}$) = 3411, 3019, 1604, 1405, 1214.</td>
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<tr>
<td><strong>$^1\text{H NMR}$ (CDCl$_3$, 200 MHz)</strong></td>
<td>$\delta_H$ (ppm) = 9.03 (s, 1H), 8.79 (s, 2H), 7.43 (s, 1H), 7.05-6.83 (m, 2H), 6.45 (s, 2H).</td>
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<tr>
<td><strong>$^{13}\text{C NMR}$ (CDCl$_3$, 50 MHz)</strong></td>
<td>$\delta_C$ (ppm) = 157.0 (CH), 153.5 (C), 154.0 (CH), 130.8 (CH), 143.3 (C), 120.0 (CH), 119.2 (CH), 112.0 (CH), 111.0 (CH).</td>
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<tr>
<td><strong>Elemental analysis</strong></td>
<td>Calcd for $\text{C}<em>{14}\text{H}</em>{14}\text{O}$: C, 69.76; H, 4.68.</td>
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<td></td>
<td>Found: C, 69.66; H, 4.53.</td>
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(E)-2-(2-(Furan-2-yl)vinyl)-5-nitroaniline (21e)

Yield 67%; brown solid; $R_f = 0.76$ (PE/EA, 7:3).
Melting Point 116.6-119.4°C
Mol. Formula C$_{12}$H$_9$NO$_3$
IR (CHCl$_3$) $\nu_{\text{max}}$ (cm$^{-1}$) = 3686, 3015, 2402, 1601, 1522, 1342, 1205.
$^1$H NMR (CDCl$_3$, 200 MHz) $\delta_H$ (ppm) = 8.28-8.26 (m, 1H, CH), 8.08-8.02 (m, 1H, CH), 7.74-7.68 (m, 1H, CH), 7.51-7.43 (m, 2H, CH), 7.0 (s, 1H, CH), 6.47-6.43 (m, 2H, CH).
$^{13}$C NMR (CDCl$_3$, 50 MHz) $\delta_C$ (ppm) = 152.2 (C), 148.6 (C), 142.9 (CH), 138.8 (C), 132.0 (CH), 129.5 (CH), 129.2 (CH), 124.2 (CH), 124.1 (CH), 123.4 (CH), 121.8 (CH), 120.5 (CH), 119.1 (CH), 111.8 (CH), 110.4 (CH).
Elemental analysis Calcd for C$_{12}$H$_9$NO$_3$: C, 66.97; H, 4.22; N, 6.51 Found: C, 66.86; H, 4.30; N, 6.56.

(E)-2-(2-(Furan-2-yl)vinyl)-5-nitroaniline (21e)

Yield 54%; brown solid; $R_f = 0.52$ (PE/EA, 7:3).
Melting Point 104.6-105.2°C
Mol. Formula C$_{12}$H$_9$NO$_3$
IR (CHCl$_3$) $\nu_{\text{max}}$ (cm$^{-1}$) = 3680, 3020, 2400, 1614, 1532, 1352, 1215.
$^1$H NMR (CDCl$_3$, 200 MHz) $\delta_H$ (ppm) = 7.82-7.61 (m, 4H, CH), 7.46 (s, 1H, CH), 7.17-7.04 (m, 2H, CH), 6.66-6.61 (m, 2H,
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\( ^{13}\text{C NMR} \) (CDCl\(_3\), 50 MHz)

\[
\delta_C (\text{ppm}) = 152.6 \ (C), \ 144.4 \ (C), \ 143.0 \ (CH),
\]

\[
129.3 \ (C), \ 128.3 \ (CH), \ 126.8 \ (CH), \ 125.8 \ (CH),
\]

\[
120.8 \ (CH), \ 120.0 \ (CH), \ 113.8 \ (CH), \ 112.0 \ (CH),
\]

\[
110.6 \ (CH), \ 110.4 \ (CH).
\]

Elemental analysis

Calcd for \( \text{C}_{12}\text{H}_9\text{NO}_3 \):  C, 62.60; H, 4.38

Found:  C, 62.58; H, 4.43.

GC/MS (EI)

230 \([\text{M}]^+\), 213 \([\text{M}-\text{NH}_2]^+\), 201 \([\text{M}-\text{C}_2\text{H}_5]^+\).

\((E)-2-(2-(2-\text{Methoxynaphthalen}-1-\text{yl})\text{vinyl})\text{furan (21f)}\)

![Diagram of 21f]

\( \text{Yield} \)

70%; brown semi-solid; \( R_f = 0.50 \) (PE/EA, 7:3).

\( \text{Mol. Formula} \)

\( \text{C}_{17}\text{H}_{14}\text{O}_2 \)

\( \text{IR (CHCl}_3\) \)

\( \nu_{\max} (\text{cm}^{-1}) = 3012, 2389, 1625, 1525, 1340, 1210. \)

\( ^1\text{H NMR} \) (CDCl\(_3\), 200 MHz)

\[
\delta_H (\text{ppm}) = 7.74-7.14 \ (m, \ 7H, \ CH), \ 6.54-6.26 \ (m, \ 2H, \ CH), \ 3.74 \ (s, \ 3H, \ OCH_3). \]

\( ^{13}\text{C NMR} \) (CDCl\(_3\), 50 MHz)

\[
\delta_C (\text{ppm}) = 153.6 \ (C), \ 150.6 \ (C), \ 144.6 \ (C), \ 132.9 \ (CH), \ 131.0 \ (C), \ 129.6 \ (CH), \ 129.2 \ (CH), \ 128.8 \ (CH), \ 127.9 \ (CH), \ 127.5 \ (CH), \ 127.4 \ (CH), \ 125.9 \ (CH), \ 124.1 \ (CH), \ 115.2 \ (CH), \ 114.6 \ (CH), \ 113.4 \ (CH) \ 112.1 \ (CH), \ 56.7 \ (OCH_3). \]

Elemental analysis

Calcd for \( \text{C}_{17}\text{H}_{14}\text{O}_2 \):  C, 81.58; H, 5.64

Found:  C, 81.64; H, 5.71.

\((E)-2-(3-\text{Methoxystyryl})\text{furan (21g)}\)

![Diagram of 21g]

Yield 83%; brown semi-solid; $R_f = 0.60$ (PE/EA, 7:3).

Mol. Formula $C_{13}H_{12}O_2$

IR (CHCl₃) $\nu_{\text{max}}$ (cm⁻¹) = 3012, 2392, 1612, 1521, 1323, 1205.

$^1$H NMR (CDCl₃, 200 MHz) $\delta_{\text{H}}$ (ppm) = 7.23-6.97 (m, 7H, CH), 6.83-6.77 (m, 2H, CH), 3.73 (s, 3H, OCH₃).

$^{13}$C NMR (CDCl₃, 50 MHz) $\delta_{\text{C}}$ (ppm) = 160.3 (C), 153.1 (C), 142.1 (CH), 138.4 (CH), 130.4 (C), 129.5 (CH), 127.0 (CH), 123.6 (CH), 122.7 (CH), 118.9 (CH), 117.1 (CH), 116.7 (CH) 113.2 (CH), 112.9 (CH), 111.6 (CH), 111.5 (CH), 108.6 (CH), 55.3 (OCH₃).

Elemental analysis Caled for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04

Found: C, 78.01; H, 5.98.


$(E)$-2-(2-(Naphthalen-2-yl)vinyl)furan (21h)

Yield 60%; yellow solid; $R_f = 0.51$(PE/EA, 7:3).

Melting Point 80.8-82.9°C

Mol. Formula $C_{16}H_{12}O$

IR (CHCl₃) $\nu_{\text{max}}$ (cm⁻¹) = 3005, 2405, 1610, 1514, 1350, 1220.

$^1$H NMR (CDCl₃, 200 MHz) $\delta_{\text{H}}$ (ppm) = 7.77-6.81 (m, 11H, CH), 6.29-6.22 (m, 2H, CH).

$^{13}$C NMR (CDCl₃, 50 MHz) $\delta_{\text{C}}$ (ppm) = 153.3 (C), 147.0 (C), 142.2 (CH), 134.5 (CH), 133.7 (CH), 133.3 (C), 133.0 (CH), 132.3 (C), 130.6 (CH), 128.3 (CH), 127.9 (CH), 127.8 (CH), 127.6 (CH), 127.5 (CH), 127.2 (CH), 127.1 (CH), 126.5 (CH), 126.3 (CH) 125.8 (CH), 123.2 (CH), 119.4 (CH), 119.1 (CH), 116.8 (CH),

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108.7 (CH).

Elemental analysis

Calcd for C\textsubscript{16}H\textsubscript{12}O: C, 87.25; H, 5.49

Found: C, 87.41; H, 5.40.

(E)-5-(2-(Furan-2-yl)vinyl)benzo[d][1,3]dioxale (21i)

\[
\begin{align*}
\text{Yield} & \quad 60\%; \text{ yellow syrup; } R_f = 0.55 \text{ (PE/EA, 7:3).} \\
\text{Mol. Formula} & \quad \text{C}_{13}\text{H}_{10}\text{O}_3 \\
\text{IR} (\text{CHCl}_3) & \quad \nu_{\text{max}} \text{ (cm}^{-1}) = 3030, 2465, 1625, 1520, 1325, 1212. \\
\text{\textsuperscript{1}H NMR} (\text{CDCl}_3, 200 \text{ MHz}) & \quad \delta_H \text{ (ppm)} = 7.38-7.37 \text{ (m, 1H, CH)}, 6.99-6.67 \text{ (m, 5H, CH)}, 6.41-6.39 \text{ (m, 1H, CH)}, 6.31-6.29 \text{ (m, 1H, CH)}, 5.96 \text{ (s, 2H, CH}_2). \\
\text{\textsuperscript{13}C NMR} (\text{CDCl}_3, 50 \text{ MHz}) & \quad \delta_C \text{ (ppm)} = 153.3 \text{ (C)}, 148.1 \text{ (C)}, 147.3 \text{ (CH)}, 141.9 \text{ (CH)}, 131.6 \text{ (CH)}, 126.9 \text{ (CH)}, 121.3 \text{ (CH)}, 115.0 \text{ (CH)}, 111.6 \text{ (CH)}, 108.4 \text{ (CH)}, 108.0 \text{ (CH)}, 105.3 \text{ (CH)}, 102.4 \text{ (CH)}, 101.1 \text{ (CH).}
\end{align*}
\]

Elemental analysis

Calcd for C\textsubscript{13}H\textsubscript{10}O\textsubscript{3}: C, 72.89; H, 4.71

Found: C, 72.82; H, 4.65.

(E)-Allyl 3-(furan-2-yl)acrylate (21k)

\[
\begin{align*}
\text{Yield} & \quad 60\%; \text{ yellow syrup; } R_f = 0.55 \text{ (PE/EA, 7:3).} \\
\text{Mol. Formula} & \quad \text{C}_{12}\text{H}_9\text{O} \\
\text{IR} (\text{CHCl}_3) & \quad \nu_{\text{max}} \text{ (cm}^{-1}) = 3023, 2932, 2404, 1735, 1625, 1525, 1418. \\
\text{\textsuperscript{1}H NMR} (\text{CDCl}_3, 200 \text{ MHz}) & \quad \delta_H \text{ (ppm)} = 7.45-7.34 \text{ (m, 2H, CH)}, 6.57-6.26 \text{ (m, 3H, CH)}, 6.03-5.84 \text{ (m, 1H, CH)}, 5.36-5.17 \text{ (m, 1H, CH).}
\end{align*}
\]

(E)-1-(4-(2-furan-2-yl)vinyl)phenyl)ethanone (21m)

\[ \delta_C \text{ (ppm)} = 166.4 \text{ (C)}, 150.7 \text{ (C)}, 144.7 \text{ (CH)}, \\
132.2 \text{ (CH)}, 115.3 \text{ (CH)}, 114.7 \text{ (CH)}, 112.1 \text{ (CH)}, \\
64.9 \text{ (CH\textsubscript{2})}. \]

Elemental analysis
Caled for C\textsubscript{12}H\textsubscript{9}O: C, 67.41; H, 5.66
Found: C, 67.35; H, 5.41.

GC/MS (EI) 178 \{M\}^+.

(E)-5-(2-furan-2-yl)vinyl)furan-2-carbaldehyde (21n)

\[ \delta_H \text{ (ppm)} = 7.92 \text{ (d, } J = 8.5 \text{ Hz, 2H, CH)}, 7.52 \text{ (d,} \\
J = 8.5 \text{ Hz, 2H, CH)}, 7.43 \text{ (m, 1H, CH)}, 7.02-7.01 \\
\text{ (m, 2H, CH)}, 6.44-6.43 \text{ (m, 2H, CH)}, 2.60 \text{ (s, 3H,} \\
\text{ CH\textsubscript{3})}. \]

Elemental analysis
Caled for C\textsubscript{14}H\textsubscript{12}O\textsubscript{2}: C, 79.22; H, 5.70
Found: C, 79.28; H, 5.78.

GC/MS (EI) 212 \{M\}^+.
Yield 40%; yellow solid; $R_f = 0.2$ (PE/EAm, 8:2).

Melting Point 120-122°C

Mol. Formula C₁₁H₈O₃

IR (CHCl₃) $\nu_{\text{max}}$ (cm⁻¹) = 3680, 3442, 2855, 2401, 1675, 1605, 1425, 1215, 1046.

$^1$H NMR (CDCl₃, 200 MHz) $\delta_H$ (ppm) = 9.57 (s, 1H, CHO), 7.53-7.45 (m, 1H, CH), 7.31-7.24 (m, 2H, CH), 7.18-7.15 (m, 1H, CH), 6.92-6.73 (m, 1H, CH), 6.55-6.46 (m, 2H, CH).

$^{13}$C NMR (CDCl₃, 50 MHz) $\delta_C$ (ppm) = 177.0 (CHO), 158.5 (C), 152.0 (C), 151.6 (C), 144.0 (CH), 143.5 (CH), 120.4 (CH), 113.0 (CH), 112.2 (CH), 111.9 (CH), 110.8 (CH), 109.6 (CH), 107.4 (CH).

Elemental analysis Calcd for C₁₁H₈O₃: C, 70.21; H, 4.29

Found: C, 70.29; H, 4.35.

GC/MS (EI) 415 [M]+.

(Ε)-2-(4-methoxystyryl)vinyl)thiophene (21o)

Yield 40%; orange solid; $R_f = 0.8$ (PE/EAm, 7:3).

Melting Point 100-104°C

Mol. Formula C₁₃H₁₂OS

IR (CHCl₃) $\nu_{\text{max}}$ (cm⁻¹) = 3012, 2923, 2843, 1604, 1571, 1508, 1461, 1279, 1248, 1215, 1178, 1111, 1078, 1034.

$^1$H NMR $\delta_H$ (ppm) = 7.54-6.83 (m, 8H, CH), 6.66-6.62 (m,
(E)-2-(3-nitrostyryl)vinyl)thiophene (21p)

\[
\begin{align*}
\text{Yield} & \quad 80\%; \text{orange solid; } R_f = 0.7 (\text{PE/EA, 7:3}). \\
\text{Melting Point} & \quad 102.7-104.7^\circ C \\
\text{Mol. Formula} & \quad \text{C}_{12}\text{H}_{9}\text{NO}_{2}\text{S} \\
\text{IR (CHCl}_3\text{) } & \quad \nu_{\text{max}} (\text{cm}^{-1}) = 3445, 3020, 2401, 1685, 1630, 1510, 1424, 1216, 1045. \\
\text{\^{1}H NMR (CDCl}_3\text{, 200 MHz) } & \quad \delta_{\text{H}} (\text{ppm}) = 8.32-8.25 (\text{m, } 1\text{H, } CH), 8.12-8.05 (\text{m, } 1\text{H, } CH), 7.76-7.65 (\text{m, } 1\text{H, } CH), 7.54-7.46 (\text{m, } 1\text{H, } CH), 7.40-7.26 (\text{m, } 2\text{H, } CH), 7.16-7.14 (\text{m, } 1\text{H, } CH), 7.08-6.85 (\text{m, } 2\text{H, } CH). \\
\text{\^{13}C NMR (CDCl}_3\text{, 50 MHz) } & \quad \delta_{\text{C}} (\text{ppm}) = 148.7 (\text{C}), 141.7 (\text{C}), 138.8 (\text{C}), 131.9 (\text{CH}), 129.6 (\text{C}), 128.6 (\text{CH}), 127.5 (\text{CH}), 125.6 (\text{CH}), 124.7 (\text{CH}), 121.9 (\text{CH}), 120.6 (\text{CH}). \\
\text{Elemental analysis} & \quad \text{Calcd for } \text{C}_{12}\text{H}_{9}\text{NO}_{2}\text{S: } \text{C, 62.32; H, 3.92} \\
\text{Found: } & \quad \text{C, 62.32; H, 3.98.} \\
\text{GC/MS (EI) } & \quad 231 [\text{M}]^+. 
\end{align*}
\]

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\[
\begin{align*}
\text{(E)-2-(3-methoxystyryl)vinyl)thiophene (21q)}
\end{align*}
\]

Yield 60%, orange solid; $R_f = 0.6$ (PE/EA, 7:3).

**Melting Point** 104.2-108.5°C

**Mol. Formula** C$_{14}$H$_{12}$OS

**IR (CHCl$_3$)** $\nu_{\text{max}}$ (cm$^{-1}$) = 3446, 3021, 2400, 1682, 1425, 1215, 1046.

**$^{1}$H NMR**

$\delta$H (ppm) = 7.88 (d, $J = 8.5$ Hz, 2H, CH), 7.46 (d, $J = 8.3$ Hz, 2H, CH), 7.21-6.83 (m, 5H, CH), 2.54 (s, 3H, CH$_3$).

**$^{13}$C NMR**

$\delta$C (ppm) = 197.3 (C), 142.2 (C), 141.6 (C), 135.7 (C), 128.9 (CH), 128.8 (CH), 127.7 (CH), 127.2

---

**Yield** 60%; orange solid; $R_f = 0.6$ (PE/EA, 7:3).

**Mol. Formula** C$_{14}$H$_{12}$OS

**IR (CHCl$_3$)** $\nu_{\text{max}}$ (cm$^{-1}$) = 3445, 3020, 2401, 1685, 1630, 1510, 1424, 1216, 1045.

**$^{1}$H NMR**

$\delta$H (ppm) = 7.23-6.84 (m, 9H, CH), 3.77 (s, 3H, OCH$_3$).

**$^{13}$C NMR**

$\delta$C (ppm) = 142.6 (C), 142.6 (C), 138.4 (C), 130.5 (CH), 123.7 (CH), 119.7 (CH), 117.1 (CH), 113.0 (CH), 111.4 (CH), 55.37 (OCH$_3$).

**Elemental analysis**

Calcd for C$_{14}$H$_{12}$OS: C, 62.32; H, 3.92

Found: C, 62.39; H, 3.98.

---

*(E)-1-(4-(2-(thiophene-2-yl)vinyl)phenyl)ethanone (21r)*
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(E)-2-styrylthiophene (21s)

CH, 127.1 (CH), 126.8 (CH), 126.2 (CH), 125.3 (CH), 124.3 (CH), 26.6 (CH₃).

Elemental analysis
Calcd for C₁₄H₁₂OS: C, 73.65; H, 5.30
Found: C, 73.71; H, 5.22.

GC/MS (EI)

(E)-2-styrylthiophene (21s)

\[
\text{\includegraphics{21s.png}}
\]

Yield
50%; orange solid; \( R_f = 0.5 \) (PE/EA, 7:3).

Mol. Formula
C₁₂H₁₀S

IR (CHCl₃)
νₘₐₓ (cm⁻¹) = 3446, 3021, 2400, 1682, 1425, 1215, 1046.

¹H NMR
(CDCl₃, 200 MHz) \( δ_H \) (ppm) = 7.65-7.14 (m, 8H, CH), 7.05-6.94 (m, 2H, CH).

¹³C NMR
(CDCl₃, 50 MHz) \( δ_C \) (ppm) = 143.0 (C), 136.9 (C), 131.5 (CH), 130.0 (CH), 128.9 (CH), 128.6 (CH), 128.3 (CH), 127.5 (CH), 127.1 (CH), 126.8 (CH), 126.2 (CH), 126.1 (CH), 125.6 (CH), 124.3 (CH), 121.7 (CH).

Elemental analysis
Calcd for C₁₂H₁₀S: C, 77.37; H, 5.41
Found: C, 77.31; H, 5.47.

GC/MS (EI)
186 [M⁺], 171 [M-CH₃]⁺.

(E)-2-(2-(naphthalen-2-yl)vinyl)thiophene (21t)

\[
\text{\includegraphics{21t.png}}
\]

Yield
70%; orange solid; \( R_f = 0.5 \) (PE/EA, 7:3).

Melting Point
143-144°C


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Mol. Formula
$C_{16}H_{12}S$

IR (CHCl$_3$)
$\nu_{\text{max}}$ (cm$^{-1}$) = 3681, 3843, 3743, 3678, 3648, 3619, 3055, 2921, 2851, 1740, 1706, 1694, 1647, 1625, 1531, 1511, 1463, 1427, 1213.

$^1$H NMR
(CDCl$_3$, 200 MHz)
$\delta_{\text{H}}$ (ppm) = 7.89-7.12 (m, 10H, CH), 7.03-6.93 (m, 2H, CH).

$^{13}$C NMR
(CDCl$_3$, 50 MHz)
$\delta_{\text{C}}$ (ppm) = 142.9 (C), 134.4 (C), 133.6 (C), 132.9 (C), 128.5 (CH), 128.4 (CH), 128.3 (CH), 127.9 (CH), 127.8 (CH), 127.7 (CH), 127.6 (CH), 126.4 (CH), 126.3 (CH), 126.2 (CH), 125.9 (CH), 125.8 (CH), 124.4 (CH), 123.2 (CH), 122.1 (CH).

Elemental analysis
Calcd for $C_{16}H_{12}S$: C, 81.31; H, 5.12
Found: C, 81.38; H, 5.19.

$(E)$-4-$(2-(\text{thiophene-2-yl})\text{vinyl})$benzaldehyde (21u)

Yield
80%; orange solid; $R_f$ = 0.6 (PE/EA, 7:3).

Melting Point
114°C

Mol. Formula
$C_{13}H_{10}OS$

IR (CHCl$_3$)
$\nu_{\text{max}}$ (cm$^{-1}$) = 3685, 3445, 2403, 1681, 1621, 1428, 1220, 1040.

$^1$H NMR
(CDCl$_3$, 200 MHz)
$\delta_{\text{H}}$ (ppm) = 9.91 (s, 1H, CHO), 7.78 (d, $J = 8.2$ Hz, 2H, CH), 7.52 (d, $J = 8.3$ Hz, 2H, CH), 7.20-7.19 (m, 1H, CH), 7.08-7.07 (m, 1H, CH), 6.97-6.95 (m, 1H, CH).

$^{13}$C NMR
(CDCl$_3$, 50 MHz)
$\delta_{\text{C}}$ (ppm) = 191.6 (CHO), 143.1 (C), 142.0 (C), 135.2 (C), 130.2 (CH), 127.8 (CH), 127.6 (CH), 126.7 (CH), 126.6 (CH), 125.7 (CH), 125.1 (CH).

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Elemental analysis  
Calcd for C_{13}H_{10}O:S: C, 72.87; H, 4.70  
Found: C, 72.81; H, 4.76.

(E)-2-(2-(thiophen-2-yl)vinyl)benzonitrile (21v)

![Structure of (E)-2-(2-(thiophen-2-yl)vinyl)benzonitrile (21v)]

Yield  
75%; orange solid; R_f = 0.7 (PE/EA, 7:3).

Melting Point  
129-131°C

Mol. Formula  
C_{13}H_{9}NS

IR (CHCl_3)  
ν_max (cm^{-1}) = 3678, 2922, 2852, 2224, 1770, 1740, 1724, 1706, 1693, 1647, 1625, 1595.

^1H NMR  
(CDCl_3, 200 MHz)  
δ_H (ppm) = 7.78-7.53 (m, 6H, CH), 7.36-7.25 (m, 2H, CH), 7.21-7.15 (m, 2H, CH).

^13C NMR  
(CDCl_3, 50 MHz)  
δ_C (ppm) = 143.3 (C), 139.8 (C), 139.7 (C), 136.9 (C), 134.5 (C), 133.6 (CH), 133.3 (CH), 133.1 (CH), 132.9 (CH), 132.8 (CH), 130.6 (CH), 129.5 (CH), 129.2 (CH), 129.1 (CH), 128.3 (CH), 127.8 (CH), 127.7 (CH), 125.7 (CH), 125.2 (CH), 124.5 (CH), 118.8 (CH), 117.8 (CH).

Elemental analysis  
Calcd for C_{13}H_{9}NS: C, 73.90; H, 4.29  
Found: C, 73.97; H, 4.34.

X-ray Crystal Analysis  

![X-ray Crystal Analysis Image]
Table 3. Crystal data and structure refinement for compound 21e.

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C₁₂H₁₀N₂O₃</td>
</tr>
<tr>
<td>Formula weight</td>
<td>230.22</td>
</tr>
<tr>
<td>Temperature</td>
<td>273(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P21/c</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 7.515(4) Å, α = 90°</td>
</tr>
<tr>
<td></td>
<td>b = 9.855(5) Å, β = 100.829 (8)°.</td>
</tr>
<tr>
<td></td>
<td>c = 15.415(8) Å, γ = 90°.</td>
</tr>
<tr>
<td>Volume</td>
<td>1121.3(10) Å³</td>
</tr>
<tr>
<td>Z</td>
<td>4</td>
</tr>
<tr>
<td>Density (Calcd)</td>
<td>1.364 Mg/m³</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>0.100 mm⁻¹</td>
</tr>
<tr>
<td>F(000)</td>
<td>480</td>
</tr>
<tr>
<td>Crystal size</td>
<td>210 x 113 x 10 mm³</td>
</tr>
<tr>
<td>Theta range for data collection</td>
<td>2.47 to 28.22°.</td>
</tr>
<tr>
<td>Index ranges</td>
<td>-9&lt;=h&lt;=9, -6&lt;=k&lt;=13, -19&lt;=l&lt;=20</td>
</tr>
<tr>
<td>Reflections collected</td>
<td>6432</td>
</tr>
<tr>
<td>Independent reflections</td>
<td>2540 [R(int) = 0.0360]</td>
</tr>
<tr>
<td>Completeness to theta = 28.22°</td>
<td>98.3 %</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>Semi-empirical from equivalents</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F²</td>
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<tr>
<td>Data / restraints / parameters</td>
<td>2540 / 0 / 154</td>
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<tr>
<td>Goodness-of-fit on F²</td>
<td>1.173</td>
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<tr>
<td>Final R indices [I&gt;2sigma(I)]</td>
<td>R1 = 0.0707, wR2 = 0.1541</td>
</tr>
<tr>
<td>R indices (all data)</td>
<td>R1 = 0.1111, wR2 = 0.1706</td>
</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>0.261 and -0.177 e. Å⁻³</td>
</tr>
</tbody>
</table>
Table 4. Crystal data and structure refinement for compound 21u.

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C_{13} H_{10} O S</td>
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<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P21/c</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>(a = 5.904(4) , \text{Å} \quad \alpha = 90°)</td>
</tr>
<tr>
<td></td>
<td>(b = 7.560(5) , \text{Å} \quad \beta = 97.837(10)^\circ)</td>
</tr>
<tr>
<td></td>
<td>(c = 12.324(9) , \text{Å} \quad \gamma = 90°)</td>
</tr>
<tr>
<td>Volume</td>
<td>544.9(6) Å</td>
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<tr>
<td>Z</td>
<td>2</td>
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<tr>
<td>Density (Calcd)</td>
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<tr>
<td>Absorption coefficient</td>
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<tr>
<td>F(000)</td>
<td>224</td>
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<tr>
<td>Crystal size</td>
<td>317 x 173 x 17 mm³</td>
</tr>
<tr>
<td>Theta range for data collection</td>
<td>1.67 to 28.03°</td>
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<tr>
<td>Index ranges</td>
<td>(-7 \leq h \leq 5, \ -9 \leq k \leq 9, \ -16 \leq l \leq 16)</td>
</tr>
<tr>
<td>Reflections collected</td>
<td>6798</td>
</tr>
<tr>
<td>Independent reflections</td>
<td>2596 [\text{R(int)} = 0.0376)]</td>
</tr>
<tr>
<td>Completeness to theta</td>
<td>28.03°</td>
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<tr>
<td>99.1 %</td>
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<td>Full-matrix least-squares on F²</td>
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<td>----------------------</td>
<td>-----------------</td>
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<tr>
<td>Extinction coefficient</td>
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2.7 References


## 2.8 Appendix D: Characterization data of synthesized compounds

<table>
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<td>Compound 21v</td>
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(E)-2-Styrylfuran (21a)

(E)-2-(4-Ethyl)styryl furan (21b)

(E)-5-(2-(Furan-2-yl)vinyl)pyrimidine (21c)
Chapter 2

$^1$H NMR

$^1$C NMR

DEPT

$(E)$-2-(3-Nitrostyryl)furan (21d)

(E)-2-(2-(Furan-2-yl)vinyl)-5-nitroaniline (21e)

(E)-2-(2-(2-Methoxynaphthalen-1-yl)vinyl)furan (21f)

(E)-2-(3-Methoxystyryl)furan (21g)

(E)-2-(2-(Naphthalen-2-yl)vinyl)furan (21h)

(E)-5-(2-(Furan-2-yl)vinyl)benzo[d][1,3]dioxale (21i)

(E)-Allyl 3-(furan-2-yl)acrylate (21k)

(E)-1-(4-(2-Furan-2-yl)vinyl)phenyl)ethanone (21m)

(E)-5-(2-Furan-2-yl)vinyl)furan-2-carbaldehyde (21n)

(E)-2-(4-Methoxystyryl)vinyl)thiophene (21o)

(E)-2-(3-Nitrostyryl)vinyl]thiophene (21p)

(E)-1-(4-(2-(Thiophene-2-yl)vinyl)phenyl)ethanone (21r)

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\[ ^1H \text{ NMR} \]

\[ ^{13}C \text{ NMR} \]

\[ \text{DEPT} \]

\((E)-2\text{-Styrylthiophene (21s)}\)

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\textbf{H NMR}

\textbf{13C NMR}

\textbf{DEPT}

\textbf{(E)-2-(2-(Naphthalen-2-yl)vinyl)thiophene (21t)}


178
(E)-4-(2-(Thiophene-2-yl)vinyl)benzaldehyde (21u)

(E)-2-(2-(Thiophen-2-yl)vinyl)benzonitrile (21v)

Section B

Synthesis of Biologically active Alpha-Aminophosphonates

This section deals with the development of new routes for the synthesis of Alpha-aminophosphonates. It also discusses previous literature routes for the synthesis of this class of molecules.
2.1 Introduction

α-Aminophosphonates are an important class of compounds due to their structural similarity to the corresponding α-amino acids and transition-state mimics of peptide hydrolysis. α-Aminophosphonates can act as enzyme inhibitors, peptide mimics, antibiotics and pharmacologic agents, herbicidal and haptens of catalytic antibodies.

The simplest natural aminophosphonic acid, 2-aminoethanephosphonic acid (AEP) 1, was isolated from ciliated sheep rumen protozoa in 1959 by Horiguchi and Kandatsu. This acid is also present in dietary and bacterial material in high amounts (Figure 1). AEP acts as marker of microbial nitrogen entering duodenum of sheep. Tyrosine plays crucial role in phosphorylation and dephosphorylation which is useful in cellular signal transduction and in cell growth control and carcinogenesis. The only naturally occurring aminophosphonic acid is (-)-1-amino-2-(4-hydroxy-phenyl)ethyolphosphonic acid 2 found to be useful for studying the mechanism of cell growth and carcinogenesis.

Alafosfalin 3, and renin inhibitor 4 are some synthetically designed examples of this class (Figure 2). Hassell and Allen et al. in 1979 designed and synthesized Alafosfalin (alaphosphin) 3. Compound 3 was found to be highly active against E. coli and moderately active against Serratia, Klebsiella, Enterobacter and Citrobacter bacterial strains. When Alafosfalin 3 was exposed to different bacterial strains, it resulted in the generation of alanine and 2-aminoethylphosphonic acid (AEP), 1. The latter compound inhibits the cell wall synthesis and hence resulting in antibacterial activity.

Figure 1. Structure of naturally occurring 2-aminoethane phosphonic acid (AEP) derivatives.
Compound 4 was designed and found to be renin inhibitor. This molecule has dipeptide of phenylalanine and leucine on one end and hydroxyl phosphonate on the other end. This compound after hydrolysis generates active hydroxyl phosphonate intermediate. This intermediate was found to act as potent renin inhibitor. So, in short aminophosphonic acid and esters possess different biological activities.7

Although the phosphonic and carboxylic acid groups differ considerably in terms of shape, size and acidity, derivatives of phosphonic acid are considered as structural analogues of natural α-amino acids. They are potent transition-state mimics of peptide hydrolysis like α-amino acids. They are known as “phosphorus analogues” of amino acids, in which the carboxylic acid group is replaced by a phosphonic acid group. These analogues are important in understanding the physiological processes in living organisms. These phosphonic acid derivatives have negligible mammalian toxicity. They can act as antimetabolites, which compete with their carboxylic acid counterparts for the active sites of enzymes and other cell receptors. They represent a promising class of potential drugs.5

Bismuth is 83rd element in the periodic table and known as heaviest stable element. The word Bismuth has been derived from the German word weisse masse ‘wismuth’ (white mass).8 Bismuth is isolated from the ores bismuthinite (bismuth sulphide) and bismite (bismuth oxide), and also isolated in its elemental form. Despite being heavy metal these salts are considered as non-toxic and non-carcinogenic. Many bismuth salts exhibits less toxicity than that of table salt (NaCl).8 Bismuth has an electronic configuration of [Xe]4f^{14}5d^{10}6s^{2}6p^{3} and due to weak

shielding exhibited by 4f electrons (Lanthanide contraction), bismuth salts (III) shows Lewis acid character. These salts are relatively less toxic and can tolerate small amounts of moisture.

Due to some of the above advantages several bismuth salts have gained tremendous applications in organic syntheses, chemical transformations etc. One of the bismuth salt, bismuth nitrate has emerged as an efficient Lewis acid. Bismuth nitrate (III), due to presence of nitrate ligands can act as a Lewis acid. Being a mild Lewis acid, it is relatively less toxic, cheaply available and tolerant towards trace amounts of water. Hence, Bi(NO₃)₃·5H₂O is considered as an Lewis acid.

2.1.1 Previous Reports

α-Aminophosphonates have attracted attention of organic and medicinal chemists due to their biological activities. In recent times, several synthetic approaches have been reported in the literature for the synthesis of α-aminophosphonates. Several synthetic approaches have been reported as discussed in Scheme 1.

---

Scheme 1. Synthetic routes to α-aminophosphonates.

The previous reports include (i) α-Heterofunctionalization, (ii) Catalytic hydrogenation, (iii) Nucleophilic addition, (iv) Alkylation, (v) Hydrophosphonation and (vi) Kabachnik-Field’s reaction for the synthesis of α-aminophosphonates.

2.1.1a α-Heterofunctionalization

In this approach, oxidative cross-dehydrogenative-coupling (CDC) method for C-H bond functionalization of N-aryl tetrahydroisoquinoline derivatives was carried out. This method provides excellent avenue from C-H bond oxidation to achieve C-P bond formed products. Here, molybdenum oxide acts as oxidant under aerobic conditions in order to facilitate the attack of diethylphosphite to furnish α-aminophosphonate (Scheme 2).

![Scheme 2. Synthesis of iso-quinoline phosphonates using α- heterofunctionalization.](image)

2.1.1b Catalytic hydrogenation

In this approach, Rh-catalyzed asymmetric hydrogenation of various substituted dimethyl R-enamido-phosphonate derivatives was carried out in the presence of phosphine (I) and aminophosphine ligands (Scheme 3).

![Scheme 3. Catalytic hydrogenation method for the synthesis of α-aminophosphonates.](image)
The enantioselective excesses (ee’s) largely depends on the type of chiral bidentate phosphorus ligand employed during the course of the reaction.

2.1.1c Nucleophilic addition

In this approach, N-acyl-iminophosphonates 10 were treated with silicone enolates 11 in the presence of diamine ligand (II) and copper triflate as catalyst to have α-aminophosphonates 12 in high enantiomeric excess 93% ee’s (Scheme 4).12

![Scheme 4. Enantioselective Michael addition to synthesize α-aminophosphonates.]

2.1.1d Alkylation

In this approach,13 α-aminophosphonate derivative 13, was brominated using N-bromosuccinimide to achieve bromo derivative 14. Bromo derivative 14 was reacted with base in the presence of various nucleophiles to furnish substituted α-aminophosphonate derivatives 15 (Scheme 5).13

![Scheme 5. Synthesis of α-aminophosphonates using alkylation method.]

2.1.1e Hydrophosphonylation

In this approach, imines 16 were treated with dialkyl phosphonates 17 in the presence of lewis acid based catalyst (II) in order to obtain α-aminophosphonates 18 in good to excellent enantiomeric excess (ee’s).7

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2.1.1f Kabachnik-Field’s reaction

Kabachnik and Field’s developed a new multicomponent reaction in which aldehydes or ketones 19, ammonia 20, and diethyl phosphonates 21 were treated in one pot to furnish α-aminophosphonates 22 (Scheme 7).14


2.2 Present Work: Rationale and Objective

α-aminophosphonates are the biologically important class of compounds and their synthesis has got world-wide attention in synthetic as well as in medicinal chemistry. Several synthetic approaches have been reported in the literature for the synthesis of α-aminophosphonates but the most preferred method is nucleophilic addition of phosphites to imines, which is either catalyzed by an alkali metal alkoxide or Lewis acid e.g. NaOEt or Lewis acids such as BF₃·Et₂O, SnCl₂, SnCl₄, ZnCl₂ and MgBr₂.15-16 However, one-pot protocols from a carbonyl compound, an amine and a phosphite could not proceed faster because the water, generated during the course of

reaction can decompose or deactivate Lewis acid. There are some recent advancements using lanthanide triflates/MgSO$_4$\textsuperscript{17}, InCl$_3$\textsuperscript{18}, ZrCl$_4$\textsuperscript{16} and TaCl$_5$-SiO$_2$ to eliminate these drawbacks.\textsuperscript{19} However, some of the major drawbacks are involvement of stoichiometric amount of catalysts, expensive reagents, longer reaction times, and in addition, many methods use harmful organic solvents such as CH$_2$Cl$_2$, THF or CH$_3$CN.\textsuperscript{20-25} Hence, there is still a room to develop an efficient, environment friendly and practically potent protocol for the synthesis of $\alpha$-aminophosphonates.

Bismuth nitrate is relatively less toxic, cheaply available and tolerant towards trace amounts of water. Hence, Bi(NO$_3$)$_3$.5H$_2$O is considered as an Lewis acid. A new Bi(NO$_3$)$_3$.5H$_2$O catalyzed one-pot synthesis of structurally diverse $\alpha$-aminophosphonates from carbonyl compounds, amines and diethylphosphite was developed. Being a mild Lewis acid, it can be used in several organic transformations like Michael conjugate addition, acylals synthesis, oxidation of secondary alcohols to aldehydes, oxidation of sulphides to sulphoxides, nitration of xylenes, Hantzsch oxidation of 1,4-dihydropyridines to pyridines, oxidation of acetals to aldehydes etc.\textsuperscript{9}

2.3 Results and Discussion

In literature very few reports deal with the synthesis of $\alpha$-aminophosphonates using mild Lewis acid catalyst. So, it is highly desirable to develop a synthetic method employing eco-friendly catalyst for the synthesis of $\alpha$-aminophosphonates. Bi(NO$_3$)$_3$.5H$_2$O being mild Lewis acid catalyst, was utilized in catalyzing one-pot synthesis of structurally diverse $\alpha$-aminophosphonates by reacting carbonyl compounds, amines and diethylphosphite in one pot. The role of bismuth atom is in coordination with the imine nitrogen and further facilitating the nucleophilic attack of diethylphosphite to render the desired product in excellent yields.

Initially, the reaction of benzaldehyde 19a with aniline 20a and diethylphosphite 21, was carried out at room temperature in the presence of Bi(NO$_3$)$_3$.5H$_2$O (10 mol %) (Scheme 8). The corresponding $\alpha$-aminophosphonate
22a was obtained in 93% yield and in 10 h time. The same reaction was carried out under Microwave irradiation (MWI) and the product was formed in 96% yield and in 4 minutes. The use of MWI greatly enhanced the yield and was reduced the reaction time. The synthesized α-aminophosphonate 22a was identified by its spectral data. The formation of α-aminophosphonate 22a was confirmed by the presence of peak in 1H-NMR at 4.76 ppm (d, JPH = 26.0 Hz, 1H) and in 13C-NMR 56.4 (d, JPC = 150.1 Hz, CH). IR stretching for 22a was observed at νmax 3300 (NH stretching), 1600 (C=O, stretching), 1214 (C-O, stretching) further confirms the formation of product.

Scheme 8. Bismuth nitrate catalyzed synthesis of α-aminophosphonates.

To establish versatility of the reaction various aldehydes (aliphatic/aromatic), amines (primary/secondary) and diethylphosphite were subjected to developed one-pot reaction conditions. The structurally diverse carbonyl compounds were subjected to this novel procedure in the presence of catalytic amount (10 mol %) of Bi(NO3)3.5H2O and converted to the corresponding α-aminophosphonates in high to excellent yields (see Table 1). In all the cases, the three-component reaction proceeded smoothly and furnished α-aminophosphonates.

Table 1. One-pot synthesis of α-aminophosphonates catalyzed by Bi(NO3)3.5H2O.
### Table 1.2.1: Product Formation Details

<table>
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<th>Sl. No.</th>
<th>RCHO</th>
<th>R’NH₂</th>
<th>Product</th>
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<th>Method B&lt;sup&gt;b&lt;/sup&gt;</th>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Time (h)</td>
<td>Yield (%)</td>
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<tr>
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<td>19a</td>
<td>20a</td>
<td>22a</td>
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<tr>
<td>2</td>
<td>19b</td>
<td>20a</td>
<td>22b</td>
<td>10</td>
<td>93</td>
</tr>
<tr>
<td>3</td>
<td>19c</td>
<td>20a</td>
<td>22c</td>
<td>10</td>
<td>94</td>
</tr>
<tr>
<td>4</td>
<td>19d</td>
<td>20a</td>
<td>22d</td>
<td>8</td>
<td>91</td>
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<tr>
<td>5</td>
<td>19e</td>
<td>20a</td>
<td>22e</td>
<td>8</td>
<td>90</td>
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</tbody>
</table>

*<sup>a</sup>* Time and yield for Method A

*<sup>b</sup>* Time and yield for Method B

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6.  
\[ \text{Phenyl-CHO} \quad \text{Phenyl-NH}_2 \quad \text{Et-P-OME} \]

7.  
\[ \text{Phenyl-CHO} \quad \text{Phenyl-CHNH}_2 \quad \text{Et-P-OME} \]

8.  
\[ \text{Phenyl-CHO} \quad \text{Phenyl-NH}_2 \quad \text{Et-P-OME} \]

9.  
\[ \text{Phenyl-CHO} \quad \text{Phenyl-NH}_2 \quad \text{Et-P-OME} \]

10.  
\[ \text{Phenyl-CHO} \quad \text{Phenyl-NH}_2 \quad \text{Et-P-OME} \]

---

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11

19i

20a

5 95 1 98

12

19j

20a

7 80 1 88

13

19k

20a

10 89 3 92

14

19l

20a

8 93 3 95

15

19m

20a

8 94 2 97

Method A: Reaction mixtures stirred at room temperature.

Method B: Reactions carried out under microwave irradiation (MWI).

*Yields refer to those of pure isolated products fully characterized by its spectral data.

Higher reactivity of aromatic aldehydes than aliphatic aldehydes, leads good to excellent yields of corresponding \( \alpha \)-aminophosphonates. However, conjugated aldehydes resulted in low yields of products. The reaction was compatible with various functional groups such as methylenedioxy, methoxy ethers, hydroxy, halides and olefinic groups. Electron-withdrawing groups at the \( \text{para} \)-position in the aldehyde ring resulted in higher yields while at the \( \text{meta} \)-position in lower yields. Electron-donating groups at the \( \text{para} \)-position in the aldehyde ring resulted in lower yields. Excellent yields were observed for substrates having halogen (entries 5, 13, 20) substituents. 1,4-conjugate addition was not found in case of cinnamaldehyde (entry 17), \( \text{O-Me} \) group (entries 4, 10, 11, 15, 19) was remained intact and sterically hindered aldehyde (entry 16) was well tolerated. Also, different substituted amines 2-aminophenol (entry 8), 2-cyano aniline (entries 19, 20, 21) and benzylamine (entry 7) were tolerated during the course of reaction. However, longer reaction times were needed for various sterically hindered substrates and electron deficient aromatic amines. The present reaction worked well on all substrates. The formation of \( \alpha \)-aminophosphonates was confirmed by the presence of peak in \( ^1 \)H NMR at 4.67-5.66 ppm (\( ^{1}J_{PH} = 23.1-26.1 \) Hz) and in \( ^{13} \)C NMR 51.2-55.8 (\( ^{1}J_{PC} = 149.2-153.8 \) Hz). This was further confirmed by the \( ^{31} \)P NMR peak at 18.92-20.69 ppm.

\( \alpha \)-Aminophosphonate 22t was crystallized from methanol/DCM (1:9) and its single crystal X-ray analysis proved the structure (Figure 3).
2.4 Postulated mechanism

The formation of $\alpha$-aminophosphonates generally follows two different reaction pathways \textit{i.e.} (i) formation of imine intermediate and nucleophilic attack of diethylphosphite or (ii) formation of hydroxyphosphonate and nucleophilic attack of phosphite yields the product. The synthesis of $\alpha$-aminophosphonates catalyzed by Bi(NO$_3$)$_3$.5H$_2$O could be described by the first mechanistic pathway. Initially, imine formed which further reacts with diethylphosphite to furnish the desired product. Detailed mechanistic studies were done on the Kabachnik-Field’s reaction and plausible mechanism is based on the observations by Cherkasov and Galkin using anilines and its substituted derivatives. A plausible mechanism for the formation of $\alpha$-aminophosphonates in one-pot catalyzed by Bi(NO$_3$)$_3$.5H$_2$O is depicted in Scheme 9. The reaction was started with imine formation which was generated by the treatment of aldehyde and amine. Then the lone pair of phosphorus attacked on the imine intermediate generating the desired $\alpha$-aminophosphonates.
2.5 Conclusion

In summary, Bismuth (III) nitrate pentahydrate was proved to be an efficient catalyst for three-component (3CR) one-pot reaction for the synthesis of \( \alpha \)-aminophosphonates. The advantages are such as (i) highly versatile and environmentally friendly catalyst, (ii) excellent yields (iii) solvent-free reaction condition, and (iv) the use of non-toxic reagent. This methodology provides better yields of products which will help in understanding the biological processes in detail. The present protocol is not only a potent method for the synthesis of biologically important class of compounds, but also an environmentally benign process.
2.6 Experimental

2.6.1 General procedures

Typical Experimental Procedure:

Method A: To a mixture of carbonyl compound (1 mmol), and amine (1 mmol), bismuth nitrate pentahydrate (10 mol%) was added and stirred at room temperature for 5 min and then slowly diethylphosphite (1 mmol) was added. The stirring of the reaction mixture was continued for the appropriate time (see Table 1) till the completion (TLC) of reaction. The reaction mixture was diluted with water and extracted with EtOAc. The EtOAc extract was washed with brine, dried (anhydrous Na$_2$SO$_4$), evaporated to furnish crude product, which was purified by column chromatography (PE/EA, 7:3) over silica gel to provide pure $\alpha$-aminophosphonates. All the products were characterized by spectral data.

Method B: To a mixture of carbonyl compound (1 mmol), amine (1 mmol), and diethylphosphite (1 mmol), bismuth nitrate (10 mol%) was added and the reaction mixture was irradiated with microwave (Kenstar Model No. OM-9918C; 2450 MHz, 2350 W) for the specified period of time in an open vessel. Work-up of the reaction was carried out as described in Method A.

Diethyl (phenyl(phenylamino)methyl)phosphonate (22a)

Yield 96%; colorless syrupy oil; $R_f = 0.20$ (PE/EA, 8:2).

Mol. Formula C$_{17}$H$_{22}$NO$_3$P

IR (CHCl$_3$) $\nu_{\text{max}}$ (cm$^{-1}$) = 3300, 1600, 1214.

$^1$H NMR (CDCl$_3$, 200 MHz) $\delta$H (ppm) = 7.49-7.06 (m, 7H), 6.72-.586 (m, 3H), 4.76 (d, $^1$J$_{PH}$ = 26.0 Hz, 1H), 4.16-3.61 (m, 4H),

Diethyl-(2-hydroxyphenylamino)(phenyl)methyl-phosphonate (22h)

\[ \text{C}_{17}\text{H}_{22}\text{NO}_{4}\text{P} \]

**\(^{13}\text{C}\) NMR**

(CDCl\(_3\), 50 MHz)

\( \delta_C \) (ppm) = 146.8 (s, Ph), 146.6 (s, Ph), 136.3 (s, Ph), 129.6 (s, Ph), 128.2 (s, Ph), 118.8 (s, Ph), 114.2 (s, Ph), 63.7 (d, \(^2\)J\(_{PC}\) = 7.0 Hz, -OCH\(_2\text{CH}_3\)), 56.4 (d, \(^1\)J\(_{PC}\) = 150.0 Hz, -CHP), 16.8 (d, \(^3\)J\(_{PC}\) = 5.8 Hz, -OCH\(_2\text{CH}_3\)), 16.6 (d, \(^3\)J\(_{PC}\) = 5.8 Hz, -OCH\(_2\text{CH}_3\)).

**Elemental analysis**

Calcd for C\(_{17}\)H\(_{22}\)NO\(_3\)P: C, 63.94; H, 6.94; N, 4.39

Found: C, 63.89; H, 6.99; N, 4.45.

**Yield**

91%; colorless syrupy oil; \( R_f = 0.20 \) (PE/EA, 6:4).

**Mol. Formula**

C\(_{17}\)H\(_{22}\)NO\(_4\)P

**IR (CHCl\(_3\))**

\( \nu_{\text{max}} \) (cm\(^{-1}\)) = 3687, 3018, 2399, 1215, 757.

**\(^1\text{H}\) NMR**

(CDCl\(_3\), 200 MHz)

\( \delta_H \) (ppm) = 7.46-6.46 (m, 9H), 4.89 (d, \(^1\)J\(_{PH}\) = 26.0 Hz, 1H), 4.33-3.61 (m, 4H), 1.30 (t, \( J = 7.0 \) Hz, 3H), 1.10 (t, \( J = 7.0 \) Hz, 3H).

**\(^{13}\text{C}\) NMR**

(CDCl\(_3\), 50 MHz)

\( \delta_C \) (ppm) = 145.2 (s, Ph), 135.6 (s, Ph), 134.7 (s, Ph), 128.4 (s, Ph), 128.4 (s, Ph), 128.1 (s, Ph), 127.8 (s, Ph), 127.7 (s, Ph), 119.7 (s, Ph), 118.1 (s, Ph), 114.3 (s, Ph), 111.8 (s, Ph), 64.2 (d, \(^2\)J\(_{PC}\) = 7.3 Hz, -OCH\(_2\text{CH}_3\)), 63.70 (d, \(^2\)J\(_{PC}\) = 7.0 Hz, -OCH\(_2\text{CH}_3\)), 55.8 (d, \(^1\)J\(_{PC}\) = 153.0 Hz, -CHP), 16.4 (d, \(^3\)J\(_{PC}\) = 5.5 Hz, -OCH\(_2\text{CH}_3\)), 16.0 (d, \(^3\)J\(_{PC}\) = 5.9 Hz, -OCH\(_2\text{CH}_3\)).

**Elemental analysis**

Calcd for C\(_{17}\)H\(_{22}\)NO\(_4\)P: C, 60.89; H, 6.61; N, 4.18
Diethylbenzo[\(d\)][1,3]dioxol-5-yl(phenylamino) methyl-phosphonate (22i)

\[
\text{Yield} \quad 98\%; \text{white solid; } R_f = 0.60 \text{ (PE/EA, 7:3).}
\]

\[
\text{Melting Point} \quad 112-3^\circ C
\]

\[
\text{Mol. Formula} \quad \text{C}_{18}\text{H}_{22}\text{NO}_5\text{P}
\]

\[
\text{IR (CHCl}_3) \quad \nu_{\text{max}} \text{ (cm}^{-1}) = 3380, 3001, 2400, 1210.
\]

\[
\text{\(^1\)H NMR (CDCl}_3, 200 MHz) \quad \delta_H \text{ (ppm) = 7.16-6.57 (m, 8H), 5.94 (s, 2H), 4.72 (d, } \frac{1}{J_{PH}} = 23.1 \text{ Hz, 1H), 4.17-3.70 (m, 4H), 1.30 (t, } \frac{1}{J_{PH}} = 7.0 \text{ Hz, 3H).}
\]

\[
\text{\(^{13}\)C NMR (CDCl}_3, 50 MHz) \quad \delta_C \text{ (ppm) = 146.9 (s, Ph), 146.8 (s, Ph), 146.4 (s, Ph), 146.1 (s, Ph), 145.4 (s, Ph), 128.9 (s, Ph), 127.1 (s, Ph), 127.0 (s, Ph), 120.8 (s, Ph), 120.7 (s, Ph), 114.4 (s, Ph), 113.7 (s, Ph), 110.2 (s, Ph), 63.3 (d, } \frac{2}{J_{PC}} = 7.0 \text{ Hz, } -\text{OCH}_2\text{CH}_3), 63.1 (d, } \frac{2}{J_{PC}} = 7.1 \text{ Hz, } -\text{OCH}_2\text{CH}_3), 55.7 (s, } -\text{OCH}_3), 55.5 (d, } \frac{1}{J_{PC}} = 152.1 \text{ Hz, } -\text{CCH}), 16.2 (d, } \frac{3}{J_{PC}} = 5.8 \text{ Hz, } -\text{OCH}_2\text{CH}_3), 16.1 (d, } \frac{3}{J_{PC}} = 6.0 \text{ Hz, } -\text{OCH}_2\text{CH}_3).
\]

\[
\text{Elemental analysis} \quad \text{Calcd for } \text{C}_{18}\text{H}_{22}\text{NO}_5\text{P: } C, 59.50; H, 6.10; N, 3.85 \quad \text{Found: } C, 59.32; H, 6.05; N, 3.78.
\]

Diethyl-(4-hydroxy-3-methoxyphenyl) (phenylamino) methylphosphonate (22k)

\[
\text{T. Kaur, PhD thesis, University of Pune, 2013}
\]
Diethyl-(2-hydroxy-6-methoxyphenyl) (phenylamino) methylphosphonate (22n)

**Yield**
98%; white solid; $R_f = 0.30$ (PE/EA, 7:3).

**Mol. Formula**
$C_{18}H_{22}NO_5P$

**IR (CHCl₃)**
$\nu_{\text{max}}$ (cm$^{-1}$) = 3308, 3012, 2401, 1200.

**$^1H$ NMR**
(CDCl₃, 200 MHz)
$\delta_H$ (ppm) = 7.14-6.58 (m, 8H), 4.67 (d, $^1J_{PH} = 24.0$ Hz, 1H), 4.16-3.67 (m, 4H), 3.83 (s, 3H), 1.27 (t, $J = 7.0$ Hz, 3H), 1.13 (t, $J = 7.0$ Hz, 3H).

**$^{13}C$ NMR**
(CDCl₃, 50 MHz)
$\delta_C$ (ppm) = 146.9 (s, Ph), 146.8 (s, Ph), 146.5 (s, Ph), 146.2 (s, Ph), 145.5 (s, Ph), 129.1 (s, Ph), 121.0 (s, Ph), 120.8 (s, Ph), 118.3 (s, Ph), 114.4 (s, Ph), 113.8 (s, Ph), 110.2 (s, Ph), 110.1 (s, Ph), 63.4 (d, $^2J_{PC} = 7.0$ Hz, -OCH₂CH₃), 63.2 (d, $^2J_{PC} = 7.3$ Hz, -OCH₂CH₃), 55.8 (s, OCH₃), 55.7 (d, $^1J_{PC} = 152.0$ Hz, -CH₃), 16.4 (d, $^3J_{PC} = 5.8$ Hz, -OCH₂CH₃), 16.2 (d, $^3J_{PC} = 5.8$ Hz, -OCH₂CH₃).

**Elemental analysis**
Calcd for $C_{18}H_{22}NO_5P$: C, 59.17; H, 6.62; N, 3.83
Found: C, 59.05; H, 6.45; N, 3.78.

**Yield**
95%; white solid; $R_f = 0.20$ (PE/EA, 7:3).

**Melting Point**
110-12°C

**Mol. Formula**
$C_{21}H_{24}NO_3P$

**IR (CHCl₃)**
$\nu_{\text{max}}$ (cm$^{-1}$) = 3302, 3010, 1209.

**$^1H$ NMR**
(CDCl₃, 200 MHz)
$\delta_H$ (ppm) = 8.26 (d, $J = 8.3$ Hz, 1H), 7.91-7.76 (m, 3H), 7.66-7.39 (m, 3H), 7.08-7.00 (m, 2H), 6.68-6.53 (m, 3H), 5.66 (d, $^1J_{PH} = 24.1$ Hz, 1H), 4.26-4.12 (m, 2H), 3.79-3.67 (m, 1H), 3.26-3.14 (m, 1H), 2.61-2.45 (m, 2H), 1.93-1.74 (m, 2H), 1.29-1.14 (m, 2H), 1.10-0.95 (m, 2H).

Chapter 2

Diethyl-(3-hydroxy-4-methoxyphenyl) (phenylamino) methylphosphonate (22o)

\[ \delta_{\text{C}} \text{ (ppm) = 146.1 (s, Ph), 145.8 (s, Ph), 133.7 (s, Ph), 133.6 (s, Ph), 131.6 (s, Ph), 131.5 (s, Ph), 131.4 (s, Ph), 131.3 (s, Ph), 129.0 (s, Ph), 128.4 (s, Ph), 128.3 (s, Ph), 126.1 (s, Ph), 125.5 (s, Ph), 125.4 (s, Ph), 125.3 (s, Ph), 125.2 (s, Ph), 122.8 (s, Ph), 122.7 (s, Ph), 118.1 (s, Ph), 113.4 (s, Ph), 63.3 (d, } J_{\text{PC}} = 7.3 \text{ Hz, -OCH}_2\text{CH}_3, 63.1 (d, } J_{\text{PC}} = 7.0 \text{ Hz, -OCH}_2\text{CH}_3, 51.2 (d, } J_{\text{PC}} = 152.6 \text{ Hz, -CHP), 16.3 (d, } J_{\text{PC}} = 5.9 \text{ Hz, -OCH}_2\text{CH}_3, 15.6 (d, } J_{\text{PC}} = 5.9 \text{ Hz, -OCH}_2\text{CH}_3.} \]

Elemental analysis

Calcd for C_{21}H_{24}NO_3P: C, 68.28; H, 6.55; N, 3.79

Found: C, 68.20; H, 6.50; N, 3.72.

Yield

97%; colorless syrupy liquid; \( R_f = 0.20 \) (PE/EA, 7:3).

Mol. Formula

C_{18}H_{24}NO_5P

IR (CHCl_3)

\( \nu_{\text{max}} \text{ (cm}^{-1}) = 3300, 3005, 2402, 1218. \)

\(^1\text{H NMR} \)

(CDCl_3, 200 MHz)

\( \delta_{\text{H}} \text{ (ppm) = 7.12-6.57 (m, 8H), 4.66 (d, } J_{\text{PH}} = 24.0 \text{ Hz, 1H), 4.15-3.68 (m, 4H), 3.79 (s, 3H), 1.26 (t, } J = 7.0 \text{ Hz, 3H), 1.12 (t, } J = 7.0 \text{ Hz, 3H).} \)

\(^{13}\text{C NMR} \)

(CDCl_3, 50 MHz)

\( \delta_{\text{C}} \text{ (ppm) = 146.7 (s, Ph), 146.3 (s, Ph), 146.0 (s, Ph), 128.8 (s, Ph), 128.2 (s, Ph), 119.3 (s, Ph), 119.1 (s, Ph), 118.0 (s, Ph), 114.3 (s, Ph), 113.7 (s, Ph),} \)
Chapter 2

Diethyl-[4-(2,3-dihydroxypropoxy) phenyl] (phenyl-amino)methylphosphonate (22r)

\[
\text{Ph), 110.8 (s, Ph), 63.3 (d, } J_{PC} = 7.0 \text{ Hz, } -OCH_2CH_3, 55.6 (s, -OCH_3), 55.2 (d, } J_{PC} = 153.8 \text{ Hz, } -CHP), 16.1 (d, } J_{PC} = 5.5 \text{ Hz, } -OCH_2CH_3), 15.9 (d, } J_{PC} = 5.8 \text{ Hz, } -OCH_2CH_3).
\]

**Elemental analysis**

Calcd for C_{18}H_{24}NO_{5}P: C, 59.17; H, 6.62; N, 3.83

Found: C, 59.12; H, 6.48; N, 3.78.

**Yield**

96%; colorless syrupy liquid; \( R_f = 0.40 \) (PE/EA, 1:9).

**Mol. Formula**

C_{20}H_{28}NO_{6}P

**IR (CHCl_3)**

\( \nu_{max} (\text{cm}^{-1}) = 3302, 3020, 2389, 1219. \)

**^1H NMR**

(CDCl_3, 200 MHz)

\( \delta_H (\text{ppm}) = 7.37-6.55 (m, 9H), 4.70 (d, } J_{PH} = 25.6 \text{ Hz, } 1H), 4.13-3.62 (m, 8H), 1.25 (t, } J = 7.0 \text{ Hz, } 3H), 1.11 (t, } J = 6.8 \text{ Hz, } 3H). \)

**^13C NMR**

(CDCl_3, 50 MHz)

\( \delta_C (\text{ppm}) = 158.3 (s, \text{ Ph}), 158.2 (s, \text{ Ph}), 146.4 (s, \text{ Ph}), 146.1 (s, \text{ Ph}), 129.1 (s, \text{ Ph}), 129.0 (s, \text{ Ph}), 127.9 (s, \text{ Ph}), 120.19 (s, \text{ Ph}), 118.4 (s, \text{ Ph}), 114.7 (s, \text{ Ph}), 114.6 (s, \text{ Ph}), 113.8 (s, \text{ Ph}), 70. 3 (s, -CHOH), 69.0 (s, -CH_2OH), 63.6 (d, } J_{PC} = 7.3 \text{ Hz, } -OCH_2CH_3), 63.4 (d, } J_{PC} = 7.3 \text{ Hz, } -OCH_2CH_3), 55.2 (d, } J_{PC} = 151.0 \text{ Hz, } -CHP), 16.3 (d, } J_{PC} = 5.5 \text{ Hz, } -OCH_2CH_3), 16.2 (d, } J_{PC} = 5.5 \text{ Hz, } -OCH_2CH_3). \)

**Elemental analysis**

Calcd for C_{20}H_{28}NO_{6}P: C, 58.67; H, 6.89; N, 3.42
Diethyl(((2-cyanophenyl)amino)(4-hydroxy-3-methoxyphenyl) methyl) phosphonate (22s)

Found:  C, 58.50; H, 6.78; N, 3.36.

Yield 98%; white solid; $R_f = 0.30$ (PE/EA, 7:3).

Melting Point 116°C

Mol. Formula $C_{19}H_{23}N_{2}O_{5}P$

IR (CHCl$_3$) $\nu_{\text{max}}$ (cm$^{-1}$) = 3396, 2984, 2931, 2400, 2213, 1604, 1215.

$^1H$ NMR (CDCl$_3$, 200 MHz) $\delta_H$ (ppm) = 7.49 (d, $J = 7.6$ Hz, 1H), 7.36-7.33 (m, 1H), 7.07 (s, 1H), 7.01-6.93 (m, 2H), 6.79 (t, $J = 7.3$ Hz, 3H), 6.63 (d, $J = 8.2$ Hz, 1H), 4.81 (d, $^1J_{PH} = 23.5$ Hz, 1H), 4.21-3.95 (m, 4H), 3.94 (s, 3H), 1.35 (t, $J = 7.0$ Hz, 3H), 1.30 (t, $J = 7.0$ Hz, 3H).

$^{13}C$ NMR (CDCl$_3$, 50 MHz) $\delta_C$ (ppm) = 148.8 (s, Ph), 148.7 (s, Ph), 147.0 (s, Ph), 145.8 (s, Ph), 134.0 (s, Ph), 132.7 (s, Ph), 126.0 (s, Ph), 120.7 (s, Ph), 120.6 (s, Ph), 118.0 (s, Ph), 117.3 (s, Ph), 114.6 (s, Ph), 112.4 (s, Ph), 112.3 (s, Ph), 109.8 (s, Ph), 97.4 (s, Ph), 63.6 (d, $^2J_{PC} = 7.3$ Hz, -OCH$_2$CH$_3$), 63.4 (d, $^2J_{PC} = 6.8$ Hz, -OCH$_2$CH$_3$), 55.9 (s, -OCH$_3$), 55.6 (d, $^1J_{PC} = 152.4$ Hz, -CHP), 16.3 (d, $^3J_{PC} = 5.5$ Hz, -OCH$_2$CH$_3$), 16.2 (d, $^3J_{PC} = 5.7$ Hz, -OCH$_2$CH$_3$).

$^{31}P$ NMR (CDCl$_3$, 200 MHz) $\delta_P$ (ppm) = 20.69.

Elemental analysis Calcd for $C_{19}H_{23}N_{2}O_{5}P$: C, 58.46; H, 5.94; N,
Diethyl (((2-cyanophenyl)amino)(3,5-dibromophenyl)methyl)phosphonate (22t)

Yield 96%; white solid; $R_f = 0.40$ (PE/EA, 7:3).

Melting Point 124°C

Mol. Formula C$_{19}$H$_{23}$Br$_2$N$_2$O$_5$P

IR (CHCl$_3$) $\nu$$_{\text{max}}$ (cm$^{-1}$) = 3843, 3619, 1922, 2215, 1740, 1693, 1646, 1246, 1214.

$^1$H NMR (CDCl$_3$, 200 MHz) $\delta_H$ (ppm) = 7.67-7.66 (m, 1H), 7.60 (s, 2H), 7.51 (d, $J$ = 6.1 Hz, 1H), 7.37-7.32 (m, 1H), 6.84 (t, $J$ = 7.3 Hz, 1H), 6.46 (d, $J$ = 8.5 Hz, 1H), 5.52-5.49 (m, 1H), 4.76 (d, $^1J_{PH}$ = 24.7 Hz, 1H), 4.23-4.06 (m, 4H), 1.36 (t, $J$ = 7.0 Hz, 3H), 1.34 (t, $J$ = 7.0 Hz, 3H).

$^{13}$C NMR (CDCl$_3$, 50 MHz) $\delta_C$ (ppm) = 148.1 (s, Ph), 148.0 (s, Ph), 139.3 (s, Ph), 139.2 (s, Ph), 134.3 (s, Ph), 134.1 (s, Ph), 134.0 (s, Ph), 133.0 (s, Ph), 129.2 (s, Ph), 129.1 (s, Ph), 123.4 (s, Ph), 123.3 (s, Ph), 118.6 (s, Ph), 117.0 (s, Ph), 112.0 (s, Ph), 97.8 (s, Ph), 64.0 (d, $^2J_{PC}$ = 7.5 Hz, -OCH$_2$CH$_3$), 63.7 (d, $^2J_{PC}$ = 7.0 Hz, -OCH$_2$CH$_3$), 55.2 (d, $^1J_{PC}$ = 149.2 Hz, -CHP), 16.4 (d, $^3J_{PC}$ = 5.7 Hz, -OCH$_2$CH$_3$), 16.2 (d, $^3J_{PC}$ = 5.9 Hz, -OCH$_2$CH$_3$).


7.18

Found: C, 58.40; H, 5.87; N, 7.10.

HRMS Calcd for C$_{19}$H$_{23}$N$_2$O$_5$P: 413.1242 (M+Na)$^+$

Found: 413.1240.
Chapter 2

$^{31}$P NMR

$\delta_P$ (ppm) = 18.92.

(CDCl$_3$, 200 MHz)

Elemental analysis

Calcd for C$_{18}$H$_{19}$Br$_2$N$_2$O$_3$P: C, 43.05; H, 3.81; N, 5.58

Found: C, 42.98; H, 3.89; N, 5.51.

HRMS (ESI)

Calcd for C$_{18}$H$_{19}$Br$_2$N$_2$O$_3$P: 522.9398 (M+Na)$^+$

Found: 522.9395.

(E)-Diethyl((2-cyanophenyl)amino)(4-(2-(thiophen-2-yl)vinyl)phenyl) methyl) phosphate (22u)

\[
\text{Yield} \quad 90\%; \text{ colorless syrupy liquid; } R_f = 0.30 \text{ (PE/EA, 7:3).}
\]

Mol. Formula

C$_{24}$H$_{25}$N$_2$O$_3$PS

IR (CHCl$_3$)

$\nu_{\text{max}}$ (cm$^{-1}$) = 3012, 2923, 2843, 2214, 1740, 1693, 1604, 1248, 1214, 1178, 1078.

$^1$H NMR

$\delta_H$ (ppm) = 7.22-7.19 (m, 5H), 7.09-6.96 (m, 3H), 6.86-6.76 (m, 2H), 6.68 (d, $J = 16$ Hz, 1H), 6.50 (t, $J = 7.8$ Hz, 1H), 6.30 (d, $J = 8.2$ Hz, 1H), 5.36 (d, $J = 16.9$ Hz, 1H), 4.65 (d, $^1$J$_{PH} = 24.3$ Hz, 1H), 3.92-3.72 (m, 4H), 1.08 (t, $J = 7.3$ Hz, 3H), 1.03 (t, $J = 6.9$ Hz, 3H).

$^{13}$C NMR

$\delta_C$ (ppm) = 148.4 (s, Ph), 148.3 (s, Ph), 142.3 (s, Ph), 136.8 (s, Ph), 136.7 (s, Ph), 133.9 (s, Ph), 133.6 (s, Ph), 132.6 (s, Ph), 127.7 (s, Ph), 127.6 (s, Ph), 127.4 (s, Ph), 127.3 (s, Ph), 127.1 (s, Ph), 126.4 (s, Ph), 126.2 (s, Ph), 124.4 (s, Ph), 122.1 (s, Ph), 117.8 (s, Ph), 117.1 (s, Ph), 111.9 (s, Ph), 97.1 (s, Ph), 63.4 (d, $^2$J$_{PC} = 7.7$ Hz, -OCH$_2$CH$_3$),
X-ray Crystal Structure

X-ray diffraction data for all the crystallized compounds were collected at \( T = 296 \) K, on SMART APEX CCD Single Crystal X-ray diffractometer using Mo-K\( \alpha \) radiation (\( \lambda = 0.7107 \) Å) to a maximum \( \theta \) range of 25.00°. Crystal to detector distance was 6.05 cm, 512 x 512 pixels / frame and other conditions used are oscillation / frame (-0.3°), maximum detector swing angle (-30.0°), beam center (260.2, 252.5) and in plane spot width (1.24). SAINT integration and SADABS correction were also applied. The structures were solved by direct methods using SHELXTL. All the data were corrected for Lorentzian, polarisation and absorption effects. SHELX-97 (ShelXTL) was used for structure solution and full matrix least squares refinement on F2. Hydrogen atoms were included in the refinement as per the riding model. The refinements were carried out using SHELXL-97.

Single crystals of the compound were found to grow best in solution mixture of ethanol and dichloromethane by slow evaporation. Colorless needle like crystal of approximate size 0.13 x 0.05 x 0.03 mm, was used for data collection. Multirun data acquisition, total scans (3), total frames (1818), exposure / frame (15.0 sec), \( \theta \) range (1.80 to 28.56°) and completeness to \( \theta \) of 28.56° (94%) were registered. The compound has molecular formula C\(_{18}\)H\(_{19}\)Br\(_2\)N\(_2\)O\(_3\) and molecular weight of 502.14. Crystals belong to Monoclinic system with P2\(_1\)/c space group with unit cell dimensions as \( a = 16.518 \) (12), \( b = 12.174 \) (9), \( c = 10.948 \) (8) Å. Other parameters like volume 2081(3) Å\(^3\), \( Z = 4 \), \( D_c = 1.603 \) g/cc, absorption coefficient \( \mu (\text{Mo–K}\alpha) = \)

Elemental analysis

Calcd for C\(_{24}\)H\(_{28}\)N\(_2\)O\(_3\): C, 63.7; H, 5.57; N, 6.19
3.991 mm$^{-1}$ were also recorded. 11542 reflections measured of which 2874 are unique. The final R indices \([I>2\sigma(I)]\) are R1 (0.0493) and wR2 (0.1332).

Table 2. Crystal data and structure refinement for compound 22t.

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<th>Property</th>
<th>Value</th>
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<td>Empirical formula</td>
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<td>β</td>
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<td>c</td>
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<td>90°</td>
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<td>Density (Calcd)</td>
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<td>Absorption coefficient</td>
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<td>F(000)</td>
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<td>Crystal size</td>
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<td>Theta range for data collection</td>
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<td>Index ranges</td>
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<td>Independent reflections</td>
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### Chapter 2

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<td>Completeness to theta = 28.56°</td>
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<td>Absorption correction</td>
<td>Semi-empirical from equivalents</td>
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<td>Refinement method</td>
<td>Full-matrix least-squares on F²</td>
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<td>Data / restraints / parameters</td>
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<tr>
<td>Goodness-of-fit on F²</td>
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<tr>
<td>Final R indices [I&gt;2sigma(I)]</td>
<td>R₁ = 0.0493, wR² = 0.1332</td>
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<tr>
<td>R indices (all data)</td>
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<td>Largest diff. peak and hole</td>
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2.7 References


### 2.8 Appendix E: Characterization data of synthesized compounds

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<th>Compound</th>
<th>Description</th>
<th>Page No.</th>
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<td>$^1$H NMR, $^{13}$C NMR, DEPT-NMR</td>
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<td>Compound 22i</td>
<td>$^1$H NMR, $^{13}$C NMR, DEPT-NMR</td>
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<td>Compound 22k</td>
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<td>Compound 22n</td>
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<td>$^1$H NMR, $^{13}$C NMR, DEPT-NMR, FT-IR, $^{31}$P NMR, HR-MS</td>
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<td>Compound 22t</td>
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</table>

Chapter 2

**$^1$H NMR**

![$^1$H NMR spectrum of Diethyl-(2-hydroxyphenylamino)(phenyl)methyl-phosphonate (22h)](image)

**$^{13}$C NMR**

![$^{13}$C NMR spectrum of Diethyl-(2-hydroxyphenylamino)(phenyl)methyl-phosphonate (22h)](image)

**DEPT**

![DEPT spectrum of Diethyl-(2-hydroxyphenylamino)(phenyl)methyl-phosphonate (22h)](image)

Diethyl-(2-hydroxyphenylamino)(phenyl)methyl-phosphonate (22h)

Diethylbenzo[d][1,3]dioxol-5-yl(phenylamino)methyl-phosphonate (22i)

Diethyl-(4-hydroxy-3-methoxyphenyl) (phenylamino) methylphosphonate (22k)

Chapter 2

$^1$H NMR

$^{13}$C NMR

DEPT

Diethyl(naphthalen-1-yl(phenylamino)methyl)phosphonate (22n)

Chapter 2

**H NMR**

<table>
<thead>
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<th>Chemical Shift</th>
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<tr>
<td>7.59</td>
<td>0.06</td>
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<td>7.58</td>
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<tr>
<td>7.57</td>
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<td>7.56</td>
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**C NMR**

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<td>148.77</td>
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<td>145.83</td>
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<td>134.04</td>
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<td>16.26</td>
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**DEPT**

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<td>16.33</td>
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**Diethyl(((2-cyanophenyl)amino)(4-hydroxy-3-methoxyphenyl)methyl)phosphonate (22s)**

Diethyl(((2-cyanophenyl)amino)(4-hydroxy-3-methoxyphenyl)methyl)phosphonate (22s)
Diethyl(((2-cyanophenyl)amino)(4-hydroxy-3-methoxyphenyl)methyl)phosphonate(22s)
Diethyl ((2-cyanophenyl)amino)(3,5-dibromophenyl)methyl)phosphonate (22t)

Diethyl (((2-cyanophenyl)amino)(3,5-dibromophenyl)methyl)phosphonate (22t)
Diethyl (((2-cyanophenyl)amino)(3,5-dibromophenyl)methyl)phosphonate (22t)
(E)-Diethyl(((2-cyanophenyl)amino)(4-(2-(thiophen-2-yl)vinyl)phenyl)methyl)phosphate (22u)