Synthesis of \((E)-3\)-(4-fluorophenyl)-1-(2-hydroxyphenyl) prop-2-en-1-one and their oxidative cyclization to chromones under Ultrasonic irradiation.
PART-IV
4.1. Section A.:
Synthesis of \((E)\)-3-(4-fluorophenyl)-1-(2-hydroxyphenyl) prop-2-en-1-one from 4-fluorobenzaldehyde under ultrasound irradiation

4.1.1. Introduction:
Chalcones or 1, 3- diaryl-2-propen-1-ones are natural or synthetic compounds belonging to family of flavonoids. Chalcones possess a broad spectrum of biological activities which includes antibacterial, antihelminthic, amoebicidal, antiulcer, antiviral, insecticidal, antiprotozoal, anticancer, cytotoxic and immunosuppressive activities. [1, 2] The presence of heterocyclic moiety in these chalcones is essential and prime condition to express such activities [3]. Some of the derivatives of chalcones and flavones inhibit selectively different serotypes of rhinovirus [4-6]. Compounds such as 4’-ethoxy-2’-hydroxy-4, 6’-dimethoxy-chalcone and 4’, 6-dichloroflavan interact directly with specific sites on the viral capsid proteins, thereby uncoating and consequently liberation of viral RNA [7-9].

Fluorine can be considered as a nearly xenobiotic element as fluoroorganic compounds are extremely rare in nature. Surprisingly, when inserted in a molecule this halogen can induce as astonishingly wide variety of biological properties, ranging from the complete inertness to much metabolic process to the highest and most specific affinity for a given receptor. Due to the growing importance of fluorinated organic compounds in biochemical systems there is an existing and increasing demand for organic compounds containing fluorine atoms [10].

The use of ultrasonic waves is a field which alternatively provides non-conventional means in organic synthesis [11] and called as Sonoc hemistry. It is one of the useful technique which parallels microwave heating and mechanochemical grinding. Since the effects of ultrasound irradiation are similar to those created by ball-milling or microwave, one can achieve the same results that has been offered by the former or later. Thus, the examples for ultrasound promoted reactions include C-C and C-N bond forming reactions. Few examples of such reactions are Boc-protctions of amines [12], Baylis-Hillman reactions [13, 14] and organocatalytic Mannich reactions [15].

The mechanism of sonication is initiated by cavitation, which is process of creation, growth and collapse of micrometre-sized bubbles that are formed when an acoustic
pressure wave propagated through a liquid medium. According to “hot spot theory” extreme local conditions occur inside the cavitating bubbles and at their interfaces when they collapse. These have been estimated to be in the range of 4900-5200 K temperature and 1700 atm pressure [16, 17]. The interactions of acoustic waves with chemical systems lead to an energy transfer that can result in enhanced mechanical effects in heterogeneous processes thereby inducing new reactivities in molecules at unexpectedly high rates which ultimately results in cleaner reactions within short span of time. Thus Sonochemistry offer advantages at par when compared with conventional reaction processes.

4.1.2. Background of the work:
Fluoro-chalcones are biologically highly active molecules and their synthesis and activities are well described in literature.
Kromann and co-investigator [18] synthesized some fluoro-chalcones from 2’-fluorine-5’-methoxy acetophenone. (Scheme 4.01)

![Scheme 4.01](image)

C. S. Ramaa and D. H. Jadhav [19] have synthesized a series of 2’, 4’-difluorinated chalcones by Claisen- Schmidt condensation from 2’, 4’-difluoroacetophenone. (Scheme 4.02)

![Scheme 4.02](image)
Desai et al. [20] have reported synthesis of 2, 4- dichloro-5-fluoro chalcones from 2, 4-dichloro-5-fluoro acetophenone under microwave irradiation. These chalcones further cyclized to pyrazolines in successive step. (Scheme 4.03)

![Scheme 4.03](image)

Martin- Aranada and co-workers [21] have synthesized the chalcones under sonochemical irradiation by Claisen-Schmidt condensation using two basic activated carbons (Na and Cs-Norit). (Scheme 4.04)

![Scheme 4.04](image)

Gill et al. [22] have reported the synthesis of 1-(2-Hydroxy-phenyl)-3-piperidin-1-yl-propenones by Ultrasonic Irradiation. (Scheme 4.05)

![Scheme 4.05](image)

### 4.1.3. Present work:
Chalcones are biologically as well as synthetically useful entities and fluorine is most sought after element in medicinal chemistry, therefore our aim was to synthesize some fluorinated chalcones using 4-fluorobenzaldehyde under ultrasonication exploiting its advantages.

This section is related to the synthesis of (E)-3-(4-fluorophenyl)-1-(2-hydroxyphenyl) prop-2-en-1-ones (26a-g) from 4-fluorobenzaldehyde (25) and various substituted o-hydroxy acetophenone (10a-g) under ultrasound irradiation technique.
4.1.4. Experimental:

Synthesis of \((E)-1-(5\text{-bromo-2-hydroxyphenyl})-3-(4\text{-fluorophenyl})\text{ prop-2-en-1-one (26 f)\)}}

Aqueous KOH (0.530gm, 0.0094mol) solution was added to a suspension of 4'-bromo, 2'-hydroxy acetophenone \(10f\) (1.0gm, 0.0047mol) and 4-fluorobenzaldehyde \(25\) (0.58ml, 0.0047mol) in 10ml ethanol/ water. The mixture was irradiated in sonication bath of 33 KHz at 50° C for 30min. After completion of reaction, the mixture was poured into water and acidified with aqueous HCl (2M). The product was crystallized from alcohol, filtered off and dried.

The compounds \((26a-g)\) were prepared by following the above procedure and their % yields and physical constant were recorded in Table XII. Their structures have been confirmed by Mass, IR and H\(^1\)NMR spectra.

Table XII: Physical data of the compounds. 26(a-g)

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>(R_1)</th>
<th>(R_2)</th>
<th>Yield (%)</th>
<th>M.P.(°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>26a</td>
<td>H</td>
<td>Cl</td>
<td>96</td>
<td>182-184</td>
</tr>
<tr>
<td>26b</td>
<td>Cl</td>
<td>Cl</td>
<td>91</td>
<td>150-152</td>
</tr>
<tr>
<td>26c</td>
<td>CH(_3)</td>
<td>CH(_3)</td>
<td>90</td>
<td>84-86</td>
</tr>
<tr>
<td>26d</td>
<td>H</td>
<td>Cl</td>
<td>95</td>
<td>170-172</td>
</tr>
<tr>
<td>26e</td>
<td>H</td>
<td>CH(_3)</td>
<td>93</td>
<td>90-92</td>
</tr>
<tr>
<td>26f</td>
<td>H</td>
<td>Br</td>
<td>97</td>
<td>163-165</td>
</tr>
<tr>
<td>26g</td>
<td>H</td>
<td>H</td>
<td>86</td>
<td>------*</td>
</tr>
</tbody>
</table>

* Yellow semi-solid comp.
4.1.5. Spectral analysis:

\[
\begin{align*}
\text{H}^1\text{NMR:} & \quad \text{H}^1\text{NMR spectra were recorded in CDCl}_3 \text{ on a Brucker DRX-300 instrument at 400 MHz using TMS as an internal standard.} \\
\text{Comp. (26f)}: & \quad \delta \text{ppm } 6.93-6.95 \text{ (d, } J = 8.9 \text{ Hz, 1H, aromatic); } 7.12-7.17 \text{ (t, } J = 8.5 \text{ Hz, 2H); } 7.47 \text{ (d, } J = 15.4 \text{ Hz, 1H, ethylene proton); } 7.56 \text{ (dd, } J = 6.56 \text{ & 2.3 Hz, 1H); } 7.7 \text{ (dd, } J = 5.4 \text{ & 3.2Hz, 2H); } 7.9 \text{ (d, } J = 15.4 \text{ Hz, 1H, ethylene proton); } 7.97 \text{ (d, } J = 2.32 \text{ Hz, 1H); } 12.7 \text{ (s, 1H, OH)}
\end{align*}
\]

\[
\begin{align*}
\text{I.R.:} & \quad \text{IR spectra were recorded in KBr disc on Shimadzu FT-IR 8300 spectrophotometer.} \\
\text{Comp. (26f)}: & \quad (\text{KBr disc}) \text{ cm}^{-1} 3233 \text{ (OH); } 1683 \text{ (C=O); } 1641
\end{align*}
\]
H¹ NMR (Comp.26f)

I. R. (Comp.26f)
4.1.6. References:

4.2. Section B.:

Synthesis of substituted 2-(4-fluorophenyl)-4H-chromen-4-ones by oxidative cyclization under ultrasound irradiation

4.2.1. Introduction:
Chromones constitute an important class of oxygen heterocycles [1]. 2-substituted chromones i.e. Flavonoids are widely distributed in nature in plant kingdom. Increasingly, the chromone or flavonoid chemistry is the subject of medical research due to the inherent biological properties displayed by them. They have been reported to possess many useful properties, including ant-inflammatory activity, oestrogenic activity, enzyme inhibition, antimicrobial activity [2, 3], antiallergic activity, antioxidant activity [4], vascular activity and cytotoxic antitumor activity [5]. Some of the chromones, especially those having heterocyclic substituents at C-2 and C-3 positions have good pharmacological activities viz. coronary spasmolytic and bronchodilatory activities useful in the treatment of asthma [6-11]. The synthesis of 3-substituted chromones appears worthy of study because they are important natural products like isoflavones and in medicines such as ipriflavone, an antiosteoporosis drug [12, 13]. Selective induction of fluorine into organic molecules is important since fluorinated organic compounds have unique biological and physical properties [14].

4.2.2. Methods of synthesis of chromones:
Chromones and C-3 bearing chromones have been synthesized and investigated for long time. By and large, chromones are in general synthesized by oxidative cyclization of respective chalcones. In literature various reagents were described which can brought about this cyclization. The reagents include SeO$_2$ in amyl alcohol, sodium hypobromite, and catalytic iodine in DMSO. 3-halogenated chromones were obtained using different halogenating agents [15-18]. (Fig.1)
An overview about the synthesis of chromones is presented Part II, Sec. C. Jawed Iqbal and colleagues [19] described an unusual protocol for 3-methyl sulphide chromone using I$_2$-DMSO-H$_2$SO$_4$ system in a sealed tube. 2'-hydroxy-4, 4', 6'-trimethoxychalcone was first heated at 100°C for 15 min. with dimethyl sulfoxide and a small amount of sulfuric acid, then a catalytic amount of iodine was added, and the mixture was heated in a sealed tube at 100°C for 2h to get 3-methylthio-5, 7, 4'-trimethoxyflavone. (Scheme 4.04)
4.2.3. Background of the present work:
As chromone derivatives are associated with plenty of properties of biological importance and emergence of sonochemistry as non-conventional means of technique in organic synthesis, we synthesized chromones from chalcones of 4-fluorobenzaldehyde.

4.2.4. Present work:
The work describes the synthesis of substituted 2-(4-fluorophenyl)-4H-chromen-4-ones (28a-g) and substituted 2-(4-fluorophenyl)-3-(methylthio)-4H-chromen-4-one (29a-g) in ultrasound bath from substituted (E)-3-(4-fluorophenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one (26a-g) under oxidative cyclization using I2/DMSO and I2-DMSO-H2SO4 system respectively. But the interesting feature of the reaction was that in both the cases instead of formation of two individual products, only substituted 2-(4-fluorophenyl)-4H-chromen-4-ones (28a-g) were obtained.
4.2.5. Experimental:

Method A:

Synthesis of 6, 8-dichloro-2-(4-fluorophenyl)-4H-chromen-4-one (28b)

(0.1gm, 0.00032mol) of chalcone 26b was dissolved in 10ml of DMSO. To this reaction mixture catalytic amount of Iodine was added. Contents were irradiated in ultrasound bath for 15 min at 50°C and then the reaction mixture was left overnight. 10ml of cold water was slowly added to the flask and the separated product was filtered and washed with cold water followed by dil. Sodium thiosulphate solution for several times again it was washed with cold water, filtered and the product was crystallized from ethanol.

Method B:

Synthesis of 6, 8-dichloro-2-(4-fluorophenyl)-3-(methylthio)-4H-chromen-4-one (29b)

A mixture of chalcone 26b (0.1gm, 0.00032 mol) and sulfuric acid (60 mg) in Me₂SO (5 ml) was first heated at 50°C for 15 min. and then cooled to room temperature. After adding 2-crystals of iodine, the mixture was further heated in a sealed tube at 50°C for ~ 20min. It was then poured into ice-water and the precipitate was filtered, washed with water and dried to give a solid which was purified by crystallization using alcohol as solvent.

The compounds (28a-g) and (29a-g) were prepared by following the above procedures and their % yield and physical constant were recorded in Table XIII. Their structures have been confirmed by Mass, IR and H¹NMR spectra.

Table XIII: Physical data of the compounds 28(a-g).

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>R₁</th>
<th>R₂</th>
<th>Yield (%)</th>
<th>M. P. (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>28a</td>
<td>CH₃</td>
<td>Cl</td>
<td>52</td>
<td>132-134</td>
</tr>
<tr>
<td>28b</td>
<td>Cl</td>
<td>Cl</td>
<td>71</td>
<td>156-158</td>
</tr>
<tr>
<td>28c</td>
<td>CH₃</td>
<td>CH₃</td>
<td>82</td>
<td>146-148</td>
</tr>
<tr>
<td>28d</td>
<td>H</td>
<td>Cl</td>
<td>63</td>
<td>138-140</td>
</tr>
<tr>
<td>28e</td>
<td>H</td>
<td>CH₃</td>
<td>65</td>
<td>174-176</td>
</tr>
<tr>
<td>28f</td>
<td>H</td>
<td>Br</td>
<td>61</td>
<td>188-190</td>
</tr>
<tr>
<td>28g</td>
<td>H</td>
<td>H</td>
<td>74</td>
<td>150-152</td>
</tr>
</tbody>
</table>
4.2.6. Spectral analysis:

\[
\begin{align*}
\text{H}^1\text{NMR:} & \quad \text{H}^1\text{NMR spectra were recorded in CDCl}_3 \text{ on a Brucker DRX-300 instrument at 200 MHz using TMS as an internal standard.} \\
& \quad \text{Comp. (28a): } 2.5 \text{ (s, 3H, CH}_3\text{); 6.8 \text{ (s, 1H, pyrone ring proton); 7.22-7.3 \text{ (t, 2H, aromatic proton); 7.51 \text{ (s, 1H, aromatic proton); 7.92-7.99.(dd, J= 8.2 & 2 Hz, 2H); 8.1 \text{ (d, J= 3.2 Hz, 1H)}}} \\
\text{I.R.:} & \quad \text{IR spectra were recorded in KBr disc on Shimadzu FT-IR 8300 spectrophotometer.} \\
& \quad \text{Comp. (28a): (KBr disc) cm}^{-1}: 1650 (C=O); 1595 (C=C) \\
\text{Mass:} & \quad \text{Mass spectra were recorded on Water-Macromass Quattro-II mass spectrometer.} \\
& \quad \text{Comp. (28a) (m/z): 289 (M+1); 291(M+2)}
\end{align*}
\]
H\textsuperscript{1}NMR (Comp. 28a)

I. R. (Comp. 28a)
Mass (28a)
4.2.7. References:


PART-IV

4.3. Section C.:
Synthesis of substituted 1-(4-\((1H\text{-benzo}[d]\text{imidazol-2-yl})\text{ phenyl})-1H\text{-benzo}[d][1, 2, 3]\text{Triazoles}

4.3.1. Introduction:
Azoles are found widely in natural sources and there are several drugs available which contain azole ring. Triazoles are important five membered heterocyclic rings containing at least one nitrogen atom like isoxazole, thiazole, pyrazole and triazole. Triazoles are basically of two types i.e. 1, 2, 3 and 1, 2, 4 –triazoles. (Fig. 1)

![Fig. 1: Types of triazoles.](image)

Between the two triazoles, 1, 2, 4- triazoles are by far the best-known class of triazoles and consist of wide variety of medicinal activity. This extends from hypoglycemic activity, antimicrobial, anti-inflammatory, anticonvulsant, antitubercular to antidepressant activity [1]. The action of azole on mycotic biochemistry and physiology has been studied extensively. At high concentrations (micromolar) the azoles are fungicidal and at low concentrations (nanomolar) they are fungistatic. [2-4]

Benzotriazoles possess significant activity. Particularly, N1-substituted benzotriazole derivatives are highly desirable as they possess various activities. These compounds have been used as herbicides [5], insecticides, acaricides [6], and receptors in enzymatic reactions [7]. Moreover, they have been used in many organic transformations. [8]

Some of the important molecules of triazole are shown as follows. (Fig. 1)
4.3.2. Methods of synthesis of Benzotriazoles:

4.3.2.1. From o-phenylenediamine

The standard synthesis of benzotriazoles involves the cyclocondensation of o-phenylenediamines with sodium nitrite in acetic acid medium [9]. (Scheme 4.05)

Scheme 4.05

4.3.2.2. From o-chloro nitrobenzene and hydrazine hydrate

1-hydroxybenzotriazoles are obtained by condensation of 1-chloro-2-nitro benzene with hydrazine. (Scheme 4.06)

Scheme 4.06

4.3.2.3 By Ultrasonication

Pereira and co-workers [10] have synthesized few 1H-benzotriazoles and 1-acyl benzotriazoles in good yields from o-phenylenediamine and sodium nitrite in acetic acid under ultrasound irradiation within 10-15min. (Scheme 4.07)

Scheme 4.07
4.3.3. Present work:
This section describes the synthesis of 1-(4-(1\(H\)-benzo[\(d\]]imidazol-2-yl)phenyl)-1\(H\)-benzo[\(d\]][1,2,3]Triazole (33a-e) from 4-(1\(H\)-benzo[\(d\]][1,2,3]triazol-1-yl) benzaldehyde (31) by Phillips condensation with substituted o-phenylenediamines (32a-e) in 2\(N\) HCl.

4.3.4. Experimental:

**Synthesis of 4-(1\(H\)-benzo[\(d\]][1,2,3]triazol-1-yl) benzaldehyde (31)**
In DMF, (1.0gm, 0.0084mol) of 1, 2, 3-benzotriazole 30 was dissolved. To this solution K\(_2\)CO\(_3\) (2.3gm, 0.0168mol) was added and heated at 80°\(C\) with stirring. After, 30 min. (1ml, 0.0084mol) 4-fluorobenzaldehyde 25 was added and heating continued for 5-6h. On completion of reaction, the reaction mixture was cooled and added dropwise to ice-water. The separated product was filtered and dried. The product obtained was pure and used further without any purification.

**1-(4-(1\(H\)-benzo[\(d\]]imidazol-2-yl) phenyl)-1\(H\)-benzo[\(d\]][1, 2, 3] triazole (33a)**
The mixture of an aldehyde 31 (0.5gm, 0.0022mol) and 1, 2 phenylenediamine 32a (0.24gm, 0.0022mol) in 2N HCl (5ml) was refluxed at 110°\(C\) for 5-6h and was monitored by using TLC. After completion of reaction, the reaction mixture was cooled to room temperature and then stirred for 15-20 min at room temperature. The solid was filtered through buchner funnel and washed with chilled toluene. The solid obtained was triturated by diethyl ether, filtered and dried.
The compounds of this series were synthesized following the above mentioned procedure and their respective yield and physical constant recorded as shown in Table XIV.

Table XIV: Physical data of the compounds 33(a-e).

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>R</th>
<th>R'</th>
<th>Yield (%)</th>
<th>M. P. (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>33a</td>
<td>H</td>
<td>H</td>
<td>61</td>
<td>158-160</td>
</tr>
<tr>
<td>33b</td>
<td>F</td>
<td>F</td>
<td>57</td>
<td>134-136</td>
</tr>
<tr>
<td>33c</td>
<td>OCH₃</td>
<td>OCH₃</td>
<td>55</td>
<td>146-148</td>
</tr>
<tr>
<td>33d</td>
<td>CH₃</td>
<td>F</td>
<td>76</td>
<td>162-164</td>
</tr>
<tr>
<td>33e</td>
<td>H</td>
<td>F</td>
<td>52</td>
<td>140-142</td>
</tr>
</tbody>
</table>

4.3.5. Spectral analysis:

**H¹NMR:** H¹NMR spectra were recorded in DMSO- d₆ on a Varian AS instrument at 400 MHz using TMS as an internal standard.

Comp. (33a): δ ppm 7.47-7.51 (m, 3H, aromatic proton); 7.6-7.71 (dd, J = 8 & 2 Hz, 1H, aromatic proton); 7.8-8.25 (m, 6H, aromatic proton); 8.8 (d, J = 8 Hz, 1H); 8.7 (d, J = 8 Hz, 1H)

**I.R.:** I.R. spectra were recorded in KBr disc on Shimadzu FT-IR 8300 spectrophotometer.

Comp. (33a): cm⁻¹ 3328 (NH), 1628 (C=N)

**Mass:** Mass spectra were recorded on Water-Macromass Quattro-II mass spectrometer.

Comp. (33a): Mass (m/z) 312.2 (M+1); 310.2 (M-1)
H$^1$ NMR (Comp. 33a)

I. R. (Comp. 33a)
Mass (Comp. 33a)
4.3.6. References: