Chapter -3

One-pot Synthesis of Polyhydroquinolines
3.1. Introduction

In this chapter we have discussed one-pot synthesis of polyhydroquinoline derivatives. Polyhydroquinoline derivatives are of considerable interest in the academics as well as industry owing to their diverse biological activity. Polyhydroquinolines contain 1,4-dihydropyridine as basic skeleton. The dihydropyridine (DHP) nucleus is common to numerous bioactive compounds which include calcium channel blockers, vasodilators, bronchodilators, anti-atherosclerosis, hepatoprotective, geroprotective and anti-diabetic agents. The clinically available calcium antagonists includes Nifidipine, Nitrendipine, Nimodipine, Amlodipine and Efonidipine are currently used to treat cardiovascular disorders, including angina, pectons and hypertension.

The second generation calcium antagonists include dihydropyridine derivatives with improved bioavailability, tissue selectivity and stability such as antihypertensive or antianginal drugs, Elgodipine, Furnidipine, Darodipine, Pranidipine, Lamildipine, Lacidipine and Benzidipine. Bay K 8644 and number of dihyropyridine calcium agonists are working as drug candidates for treatment of congestive heart failure. Furthermore, studies have revealed several other therapeutic applications that include neuroprotectant, platelet-anti aggregator activity,
cerebral anti-ischemic activity in the treatment of Alzheimer’s disease and as a chemo-sensitizer in tumor therapy.\textsuperscript{66} The recent biological studies reveal that calcium antagonists as a class may also prevent artherosclerosis. These families of polyhydroquinoline are being used as anti-malarial, anti-inflammatory, anti-asthmatic, anti-bacterial and tyrosine kinase inhibiting agents.\textsuperscript{67}

\begin{center}
\includegraphics[width=0.7\textwidth]{figure3.1.png}
\end{center}

\textbf{Figure 3.1.} 1,4-dihydropyridine motif containing few drugs which are available in the market.
These examples indicate the potential of novel 1,4-dihydropyridine and polyhydroyquinoline derivatives as important drug candidates and useful intermediates in the organic synthesis. The recent examples highlight the level of ongoing interest towards new DHP derivatives and have prompted us to explore this chemistry further.

3.1.1. Review of synthetic approaches of polyhydroyquinolines:

A decade ago Arthur Hantzsch described the preparation of 1, 4-dihydropyrimidines. In recent year’s organic chemical synthesis have reached high degree of skillfulness. The classical methods for the synthesis of 1, 4-dihydropyrimidines is one pot condensation of aldehydes with ethyl acetoacetate and ammonia either in acetic acid or by refluxing in alcohol. However, this method involves longer reaction time, harsh conditions and generally gives lower yields of the products. Although a number of modified methods under improved conditions have been reported in the literature and some of these methods are discussed in the following paragraphs.

a. V.K Ahluwalia et al. described synthesis of polyhyroquinoline from dimethyl cyclohexanedione (13), benzaldehyde (14), and methyl β-aminocrotonoate (15) under refluxed condition in methanol to get the desired product.

Scheme 1. Reagents and conditions: (a) Methanol, reflux.

In this approach, dimethyl cyclohexanedione (13), reacted with aldehydes (14), ethyl acetoacetate (17) and liquor ammonia in refluxing methanol to get the desired product.
In another approach, mixture of ethyl 2-(2-nitrobenzylidene) acetoacetate, dimethyl cyclohexanedione (13) and liquor ammonia in methanol was refluxed to get the product.

b. Donlsen et al.\textsuperscript{71} used Scandium triflate as a catalyst for the synthesis of polyhydroquinoline. In this process is a mixture of aldehydes (14), dinedone (13), ethyl acetoacetate (19), ammonium acetate and scandium triflate in ethanol were stirred at room temperature to get the product.
c. Kade et al.\textsuperscript{72} used L-proline as an organo catalyst for the synthesis of polyhydroquinoline. In this process a mixture of aldehydes (14), dimedone (13), ethyl acetoacetate (19), ammonium acetate, L-proline in ethanol was stirred at reflux temperature to obtain the product.

\textbf{Scheme 5. Reagents and conditions:} (a) NH\textsubscript{4}OAc, L-Proline, Ethanol, reflux.

d. Guoyong Song et al.\textsuperscript{73} used Montmorillonite K10 clay as solid catalyst for the one pot synthesis of polyhydroquinolines in ethanol at 80 °C.

\textbf{Scheme 6. Reagents and conditions:} (a) NH\textsubscript{4}OAc, Montmorillonite-K10, Ethanol, 80 °C.

e. Atul Kumar et al.\textsuperscript{74} used Baker’s yeast as a catalyst for one pot synthesis of polyhydroquinoline in ethanol at room temperature for longer hours.
**Scheme 7.** *Reagents and conditions:* (a) NH$_4$OAc, Baker’s yeast, Phosphate buffer, 25 °C.

**f. Su et al.*$^{75}$** reported synthesis of polyhydroquinoline derivatives *via* four component coupling reaction of aldehydes (14), dinedone (13), active methylene compound (19) and ammonium bicarbonate in the presence of 5-pyrrolidin-2-yl-tetrazole as a catalyst under solvent free conditions.

**Scheme 8.** *Reagents and conditions:* (a) NH$_4$HCO$_3$, 5-pyrrolidin-2-yltetrazole, 25 °C.

**g. Maheswara M et al.*$^{76}$** reported synthesis of polyhydroquinoline derivatives *via* Hantzsch condensation using HClO$_4$-SiO$_2$ as heterogeneous catalyst at 90 °C.

**Scheme 8.** *Reagents and conditions:* (a) NH$_4$OAc, HClO$_4$-SiO$_2$, 90 °C.

**3.1.2. Disadvantages of previous synthetic approaches of polyhyrdoquinolines:**

Although a number of modified methods under improved conditions have been reported, many of them suffer from drawbacks such as unsatisfactory yields, high temperature, longer reaction time and use of expensive catalyst/reagents. Moreover, disadvantage of almost all
existing methods is that the excess Lewis acids/catalyst are destroyed in the aqueous quench, liberating large amount of harmful mixtures containing metal ions and organic wastes that are detrimental to our delicate eco-system and the catalyst is destroyed in the work-up procedure and cannot be recovered or reused. Furthermore, the use of soluble metal catalysts in these systems often necessitates a tedious catalyst separation step. Therefore, the ideal synthesis is shown lead the product with good yields, environmentally compatible reagent, operational simplicity, reusability, economic viability and greater selectivity. Consequently, there is a need for a greater catalytically efficient method for these transformations which might work under mild and more economical and environmentally benign conditions.

3.2. Results and discussion

In the current tool box of organic chemist’s requirements for clean, fast, efficient, and selective processes have increased the demand for metal based reaction promoters especially the ones that can be applied in catalytic amounts and /or that are recyclable. However, many catalysts are derived from heavy or rare metals and their toxicity and prohibitive prices constitute severe drawbacks for large-scale application. In contrast, Iron is one of the most abundant metals on earth and consequently one of the most inexpensive and environmentally friendly ones. Moreover, many iron salts and complexes are commercially available and described in the literature. Despite its advantages, it is surprising that until recently many research groups have ignored this metal in organic syntheses. Iron was relatively under represented in the field of catalysis compared to other transition metals. However, the last few years have seen a rise of its use and some very efficient processes able to compete with other metal catalyzed ones have emerged, also in the field of asymmetric catalysis. This development encouraged us to use of iron catalysts in organic synthesis as part of the PhD programme. Iron-catalyzed systems for C–H oxidation, nonheme mimics system olefin epoxidation, and the chemistry of Fe-porphyrins has well studied. Among the different iron sources, FeF$_3$ is the most widely known fluoride of iron. It is white in
color and the crystal has a rhombic structure. The most important industrial application of the FeF$_3$ is in the manufacturing of Fe–Co–Nd magnets,\textsuperscript{77a} hydro-cracking,\textsuperscript{77b} preparation of perfluoroacyl fluorides,\textsuperscript{77c} hydrorefining of lubricating oils,\textsuperscript{77d} fluorinating agent,\textsuperscript{77e} pin-hole prevention in cast iron,\textsuperscript{77f} for xenon–fluorine compounds,\textsuperscript{77g} and as a catalyst for aromatization, dealkylation, polymerization and conversion of vinylidene chloride to the fluoride.\textsuperscript{77h} The chemistry of FeF$_3$ in organic synthesis has recently received increasing attention over its companion reagents like FeCl$_3$, FeBr$_3$, and FeI$_3$ owing to its stability in water and air actively utilized as a catalyst for various types of organic syntheses. FeF$_3$ has been utilized as an effective catalyst for bis-indolylmethanes,\textsuperscript{78a} chemo selective addition of cyanotrimethylsilane to aldehydes,\textsuperscript{78b} cross-coupling reactions,\textsuperscript{78c,78d} sulenylation and selenation reaction.\textsuperscript{78e,78f}

In addition the growing concern for the influence of the chemical reagents on the environment as well as on human body, recovery and reusability of the chemical reagents has attracted the attention of synthetic organic chemists. More importantly pharmaceutical industry has given more importance towards recovery and reuse of chemical reagents to reduce the cost of a product as well as the environmental burden. As part of continuing effort in our laboratory towards the development of new methods in organic synthesis, we became interested in the possibility of developing a one-pot synthesis of polyhydroquinoline derivatives catalyzed by FeF$_3$. In this chapter we present our results about a FeF$_3$ catalyzed four-component Hantzsch reaction in ethanol as a solvent.

We report herein an efficient one-pot synthesis of polyhydroquinoline derivatives from four component coupling of aromatic aldehyde, alkyl acetoacetate, β-keto compounds and ammonium acetate in the presence of a catalytic amount of Iron(III) fluoride catalyst in ethanol at 75–80 °C in excellent yield in shorter reaction time 1 h. The general scheme for synthesis of polyhydroquinoline derivatives is shown in scheme 9.
**Scheme 9.** *Reagents and conditions:* (a) FeF$_3$, ethanol, 75-80 °C

In an initial endeavor (Scheme 10), 1.0 equiv each of benzaldehyde (14a), dimedone (13a), ethyl acetoacetate (19) and ammonium acetate (20) were heated under reflux in ethanol without any catalyst. No reaction was observed even after 12 h, only dimedone/aldehyde adduct was isolated. However, addition of a catalytic amount of FeF$_3$ to this mixture has rapidly induced four component condensations in 1 hr (Table 3.1).

**Scheme 10.** *Reagents and conditions:* (a) FeF$_3$, ethanol, 75-80 °C

**Table 3.1.** The reaction of benzaldehyde, ethylacetoacetate, dimedone and ammonium acetate: effect of catalyst$^a$
<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Catalyst (mol%)</th>
<th>Time (h)</th>
<th>Yield&lt;sup&gt;b&lt;/sup&gt; (%)</th>
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<td>50</td>
</tr>
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<td>5</td>
<td>24</td>
<td>none</td>
</tr>
<tr>
<td>12</td>
<td>Fe(SO&lt;sub&gt;4&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;.nH&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>5</td>
<td>24</td>
<td>none</td>
</tr>
</tbody>
</table>

<sup>a</sup>All reactions were carried out in ethanol at 75-80 °C.

<sup>b</sup>Isolated yield.

<sup>c</sup>Major product isolated was dimedone/aldehyde adduct.

Hantzsch condensation of dimedone, benzaldehyde, ethylacetoacetate and ammonium acetate in the presence of catalytic amount of FeF<sub>3</sub> (5 mol%) at 75-80 °C in ethanol results in the formation of ethyl 2-methyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (Table 3.1, entry 8) in 92% yield. To the best of our knowledge this is the first report for the polyhydroquinoline synthesis using FeF<sub>3</sub> as a homogeneous catalyst. We have not observed any fluorination while FeF<sub>3</sub> is used in the one-pot synthesis. In an attempt to improve the catalytic activity of the reactions we have examined other Lewis acids and iron salts such as FeBr<sub>3</sub>, FeCl<sub>3</sub>, FeI<sub>3</sub>, Fe<sub>2</sub>(NO<sub>3</sub>)<sub>.9H</sub> <sub>2</sub>O, Fe(SO<sub>4</sub>)<sub>3</sub>.nH<sub>2</sub>O for the synthesis of polyhydroquinolines (Table 3.1, entries 4, 5, 10-12). It was found that conventional Lewis acids such as AlCl<sub>3</sub> (Table 3.1, entry 2), ZnCl<sub>2</sub> (Table 3.1, entry 3), and FeCl<sub>3</sub> (Table 3.1, entry 5) showed poor effect to the yield and reaction time. This is probably due to their poor water tolerance of the reagents under the reaction condition we studied. Even large amount of catalyst was used, the results were still
unsatisfactory and many side reactions were observed. When 5 mol% of FeBr₃, FeCl₃, FeI₃, Fe₂(NO₃)₉H₂O and Fe(SO₄)₃.nH₂O (Table 3.1, entries 4, 5, 10-12) was used for the synthesis of polyhydroquinolines, only 45, 60, 50 and 0% yield of the corresponding product were obtained. FeF₃ emerged as the best catalyst in terms of conversion and reaction rates (Table 3.1, entries 6-9). While adding 100mol % of FeF₃ into the system under similar reaction conditions, the speed of the reaction was obviously accelerated, but the yield was not yet satisfactory (Table 3.1, entry 6). Further studies showed that decreasing the amount of FeF₃ improve the reaction significantly. Inspired by the results, we changed the amount from 100mol % to 10mol % and 5mol %, finding that 5 mol % of FeF₃ was good enough (Table 3.1, entry 8) to obtained very high yield of the product in shorter reaction time.

FeF₃ showed higher catalytic activity than other Fe-catalyst due to the high acidity, high thermal stability and high water tolerance. The acidity of 5 mol% FeF₃ measured in water and found the pH ~2.7. The catalytic process of FeF₃ using different solvents was also investigated. The reaction of benzaldehyde (14a), dimedone (13), ethyl acetoacetate (19) and ammonium acetate (20) was chosen as a model reaction for comparison of solvents, the results are shown in Table 3.2. In each case, the reactants were mixed together with 5 mol% of FeF₃ stirred with 5 mL solvent. The polar solvents such as ethanol and acetonitrile were found to be better solvents than the non-polar solvents like toluene, dichloromethane, cyclohexane etc. Obviously, the results could be attributed to the better solubility of the catalyst and the reagents in the polar solvents. Among the two solvents viz. ethanol and acetonitrile, ethanol stands out as the solvent of choice, with its fast conversion, high yield and low toxicity.

Table 3.2. The reaction of benzaldehyde, ethylacetoacetate, dimedone and ammonium acetate: effect of solvent and temperature.a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Yield (%)b</th>
</tr>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Entry</td>
<td>Catalyst (Fluoride source)</td>
<td>Temp. (°C)</td>
<td>Time (h)</td>
<td>Yield (%)^b</td>
</tr>
<tr>
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<td>---------------------------</td>
<td>------------</td>
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</tr>
<tr>
<td>1</td>
<td>CaF$_2$</td>
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<td>12</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>FeF$_3$</td>
<td>80</td>
<td>1</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td>KF</td>
<td>80</td>
<td>12</td>
<td>35</td>
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<tr>
<td>5</td>
<td>NH$_4$F</td>
<td>80</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>6</td>
<td>TBAF</td>
<td>Reflux</td>
<td>12</td>
<td>30</td>
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</table>

^aConditions: benzaldehyde (1 mmol), ethylacetoacetate (1 mmol), dimedone (1 mmol), and ammonium acetate (1 mmol), catalyst (5 mol%), ethanol (5 mL), heating.

^bIsolated yield.
To check the catalytic behavior of FeF$_3$, we decided to check the physical properties of FeF$_3$, recovered FeF$_3$ and comparison reagent FeCl$_3$ by XRD to know more about the crystalline behavior. The powder X-ray diffraction pattern of FeF$_3$, recovered FeF$_3$ (after 5$^{th}$ run) and FeCl$_3$ (Figure 3.2) were recorded on a Rigaku D/Max-2200 model diffractometer equipped with horizontal goniometer in $\theta/2\theta$ geometry. The Copper K$\alpha$(\(\lambda=1.5418 \text{ A}^\circ\)) radiation was used and the sample was scanned between 3-45 degrees 2$\theta$. The sharp peaks in the diffractogram indicate that the FeF$_3$ and recovered FeF$_3$ (after 5$^{th}$ run) are crystalline in nature. FeCl$_3$ showing absence of any sharp peak in XRD pattern confirms the amorphous nature.

![XRD profile of FeF$_3$, recovered FeF$_3$ (after 5$^{th}$ run) and FeCl$_3$.](image)

After completion of the reaction (TLC), the product was extracted with ethyl acetate and the catalyst was recovered from the aqueous layer. FeF$_3$ is more soluble in water than that in organic solvents. The catalyst was recovered almost quantitatively from the aqueous layer, which was
subsequently reused for several runs. As indicated in Figure 3.3, it showed almost no loss of activity after five successive runs. The yields obtained were from 90, 89, 89, 88 and 87% in the first, second, third, fourth and fifth run respectively. In view of environment friendly methodologies, recovery and reuse of the catalyst is highly preferable. More importantly pharmaceutical industry has given more importance towards recovery and reuse of chemical reagents to reduce the cost of a product as well as the environmental burden.

![Figure 3.3. Recycling and reuse of FeF$_3$ for polyhydroquinoline synthesis.](image)

Thus, we selected the optimized reaction condition to examine the universality of this catalyst’s application with different electron rich and deficient substrates. Variously substituted aromatic aldehydes, $\beta$-keto esters and dimerdone undergo the Hantzsch reaction in the presence of catalytic amount of FeF$_3$ (5 mol%) in ethanol at 75-80 °C (Scheme 10). The results of this study are summarized in Table 3.4. It was indicated that both electron deficient (Table 3.4, entry 1, 2, 4, 8, 10-13, 15 & 16) and electron rich aromatic aldehydes (Table 3.4, entry 5-7, 9 & 14) worked well, giving high yields of the product in shorter reaction time. Next, we investigated the effect
of substitution in 1,3-cyclohexadione (dimedone) system. Aromatic aldehydes such as 3-nitro benzaldehyde (Table 3.4, entry 1), 4-chloro benzaldehyde (Table 3.4, entry 2), 4-nitro benzaldehyde (Table 3.4, entry 3), 3,4-dimethoxy benzaldehyde (Table 3.4, entry 5), 4-trifluoro benzaldehyde (Table 3.4, entry 6), 3,4-dihydroxy benzaldehyde (Table 3.4, entry 7) react with 5,5-dimethyl-1,3-cyclohexadione, ethyl acetoacetate and ammonium acetate in the presence of FeF₃ (5 mol%) in ethanol at 75-80 °C to afford the products in excellent yields. Interestingly, 1,3-cyclohexadione (dimedone) reacted with aromatic aldehyde (Table 3.4, entry 15 & 16), ethyl acetoacetate and ammonium acetate in the presence of FeF₃ (5 mol%) with little lower yield. Aromatic aldehydes (Table 3.4, entry 11-14) react with 5,5-dimethyl-1,3-cyclohexadione, methyl acetoacetate and ammonium acetate in the presence of FeF₃ (5 mol%) in shorter reaction time with high yields. As seen from the Table 3.4 the methodology tolerates most of the substrates.

Reagents and conditions: (a) FeF₃, Ethanol, 75-80 °C

Table 3.4. FeF₃ catalyzed synthesis of polyhydroquinoline derivatives.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)</th>
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<td>CH₃</td>
<td>C₂H₅</td>
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<tr>
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<td>4-ClC₆H₄</td>
<td>CH₃</td>
<td>CH₃</td>
<td>C₂H₅</td>
<td>1.0</td>
<td>16b</td>
<td>92ᵇ</td>
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<td>CH₃</td>
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<td>R2</td>
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<td>H</td>
<td>C₂H₅</td>
<td>1.5</td>
<td>16p</td>
<td>85</td>
</tr>
</tbody>
</table>

a Yields refer to isolated pure products.

b Catalyst has been reused 4 times.

Products were characterized by IR, ¹H, ¹³C, Mass spectroscopy and compared with authentic samples.

### 3.3. Nature of the products and product characterization

Various compounds were synthesized in this research work, which are stable at room temperature and could be handled safely. All the compounds (16a-16p) are obtained as solids. All the synthesized compounds are characterized by spectroscopic data (IR, ¹H NMR, ¹³C NMR, and mass) and HRMS data. A
A plausible mechanism for the product formation is shown in Figure 3.4. Polyhydroquinoline derivatives 16 may be formed via steps I-III or via steps IV-VI. The role of FeF₃ comes in steps I and IV, where it catalyzes the Knovenagel type coupling of aldehydes with active methylene compounds and in steps III and VI, where it catalyzes 22, 23 and 24, 25 to give the product 16. The isolated products prepared under the reaction conditions we studied are racemic.
Figure 3.4. Proposed mechanism for the Hantzsch polyhydroquinoline derivatives catalyzed by FeF$_3$.

3.4. Conclusion

In conclusion, we have developed an easy and efficient method to prepare a variety of polyhydroquinolines from the reaction of different aryl aldehydes, β-keto compounds, including 1,3-cyclohexanedione or 5,5-dimethyl-1,3-cyclohexanedione, alkyl acetoacetate and ammonium acetate in the presence of catalytic amount of FeF$_3$ at 75-80 °C. The higher catalytic activity of FeF$_3$ described due to its high acidity, thermal stability and water tolerance. Also the superiority of use of FeF$_3$ towards the synthesis of polyhydroquinoline is compared with other Lewis acids, Fe-salts, fluoride sources. The mildness of the conversion, experimental simplicity, compatibility with various functional groups, high yields of the reaction product, shorter reaction time and the easy workup procedure etc, emphasizes this procedure is attractive to synthesize a variety of these derivatives. Moreover, FeF$_3$ can be recovered
and reused for several times, which makes it a useful and attractive catalyst for synthesis of these classes of compounds for economic viability and greater selectivity.

3.5. Experimental Section

3.5.1. Typical procedure for the synthesis of polyhydroquinoline derivatives

In a typical experimental procedure, a mixture of aldehyde (14) (1 mmol), dimedone (13) (1 mmol), alkyl acetoacetate (19) (1 mmol), ammonium acetate (20) (1 mmol), FeF₃ (5 mol %) and ethanol (5 mL) was placed in a 25 mL round bottomed flask equipped with a cold water condenser and calcium chloride guard tube. The reaction mixture was slowly heated to 75-80 °C. Typically the reaction completed within one hour. After confirming the complete consumption of starting material by TLC, the mixture was cooled and 15 mL of ethyl acetate and 5 mL of water was added to the flask. The ethyl acetate layer was separated and washed with cold water (20 mL). The organic layer was then dried over anhydrous sodium sulfate, filtered and the solvent distilled under vacuum to afford the crude product. The crude product was finally recrystallized from ethanol to afford the pure products 16a-16p. The aqueous layer containing the catalyst (FeF₃) was evaporated under reduced pressure to give a solid (slight pale pink in color). The IR spectrum of the recovered catalyst was identical to that of the commercially available catalyst (Aldrich), which was further reused for the next reaction without loss in activity. The catalyst has been recovered and reused five times (reaction yields: 90, 89, 89, 88% and 87%).

Ethyl 2,7,7-trimethyl-4-(3-nitrophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (16a).
Pale yellow solid; **MP**: 173-175 °C; **IR** (KBr): 3289, 2959, 1702, 1528, 1349, 1217, 1073, 683;

**H NMR** (400 MHz, DMSO-$d_6$): $\delta$ 9.24 (s, 1H, NH), 7.98 (m, 2H), 7.62-7.50 (m, 2H), 4.96 (s, 1H), 3.98 (q, $J = 7.2$ Hz, 2H), 2.48 (d, $J = 17.2$ Hz, 1H), 2.38 (m, 4H), 2.21 (d, $J = 16.0$ Hz, 1H), 2.00 (d, $J = 16.4$ Hz, 1H), 1.13 (t, $J = 7.2$ Hz, 3H), 1.01 (s, 3H), 0.83 (s, 3H);

**C NMR** (50 MHz, DMSO-$d_6$): $\delta$ 194.19, 166.28, 150.30, 149.64, 147.29, 146.03, 134.22, 129.33, 121.92, 120.82, 109.15, 102.58, 59.20, 49.99, 36.38, 32.16, 29.01, 26.32, 18.32, 14.00; **MS (ES)**: m/z 385.10 (M+H); **ESI-HRMS**: m/z [M+H]$^+$ calculated for C$_{21}$H$_{25}$N$_2$O$_5$: 385.1763; found 385.1769.

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**Ethyl 4-(4-chlorophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (16b).**

Off-white solid; **MP**: 233-235 °C; **IR** (KBr): 3275, 2958, 1706, 1604, 1488, 1381, 1214, 1214, 1071, 844, 534 cm$^{-1}$; **H NMR** (400 MHz, DMSO-$d_6$): $\delta$ 9.12 (s, 1H, NH), 7.25 (d, $J = 8.0$ Hz, 2H), 7.16 (d, $J = 8.4$ Hz, 2H), 4.83 (s, 1H), 3.99 (q, $J = 7.2$ Hz, 2H), 2.43 (d, $J = 17.2$ Hz, 1H), 2.25-2.28 (m, 4H), 2.19 (d, $J = 16.0$ Hz, 1H), 1.99 (d, $J = 16.0$ Hz, 1H), 1.13 (t, $J = 7.2$ Hz, 3H), 1.00 (s, 3H), 0.83 (s, 3H); **C NMR** (50 MHz, DMSO-$d_6$): $\delta$ 194.09, 166.53, 149.49, 146.45, 145.29, 130.08, 129.22, 127.58, 109.58, 103.04, 59.04, 50.13, 35.55, 32.08, 29.03, 26.40, 18.25, 14.08; **MS (ES)**: m/z 374.00 (M+H); **ESI-HRMS**: m/z [M+H]$^+$ calculated for C$_{21}$H$_{25}$NO$_3$Cl: 374.1763; found 374.1756.
Ethyl 2,7,7-trimethyl-4-(4-nitrophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (16c).

Yellow solid; **MP**: 242-245 °C; **IR** (KBr): 3295, 2959, 1699, 1605, 1517, 1482, 1345, 1218, 1073, 836, 694 cm\(^{-1}\); \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) 9.23 (s, 1H, NH), 8.10 (d, \(J = 8.8\) Hz, 2H), 7.42 (d, \(J = 8.8\) Hz, 2H), 4.96 (s, 1H), 3.98 (q, \(J = 7.2\) Hz, 2H), 2.45 (d, \(J = 16.4\) Hz, 1H), 2.27-2.31 (m, 4H), 2.20 (d, \(J = 16.0\) Hz, 1H), 1.99 (d, \(J = 16.0\) Hz, 1H), 1.12 (t, \(J = 7.2\) Hz, 3H), 1.00 (s, 3H), 0.82 (s, 3H); \(^{13}\)C NMR (50 MHz, DMSO-\(d_6\)): \(\delta\) 194.08, 166.27, 154.87, 149.97, 146.03, 145.55, 128.65, 123.03, 108.95, 102.30, 59.17, 50.03, 36.59, 32.09, 28.95, 26.41, 18.30, 14.04; **MS (ES)**: \(m/z\) 385.10 (M+H); **ESI-HRMS**: \(m/z\) [M+H]\(^+\) calculated for C\(_{21}\)H\(_{25}\)N\(_2\)O\(_5\): 385.1763; found 385.1756.

Ethyl 4-(4-cyanophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (16d).

Ash solid; **MP**: 140-142 °C; **IR** (KBr): 3296, 2959, 2226, 1697, 1606, 1488, 1379, 1219, 1074, 845, 555 cm\(^{-1}\); \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) 9.19 (s, 1H, NH), 7.68 (d, \(J = 8.0\) Hz, 2H), 7.34 (d, \(J = 8.0\) Hz, 2H), 4.90 (s, 1H), 3.98 (q, \(J = 7.2\) Hz, 2H), 2.44 (d, \(J = 17.2\) Hz, 1H), 2.30-2.26 (m, 4H), 2.19 (d, \(J = 16.4\) Hz, 1H), 1.99
Ethyl 4-(3,4-dimethoxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (16e).

White solid; **MP**: 204-206 °C; **IR** (KBr): 3279, 2957, 1695, 1604, 1491, 1379, 1216, 1139, 1031, 788, 730 cm⁻¹; **¹H NMR** (400 MHz, DMSO-d₆): δ 9.02 (s, 1H, NH), 6.77-6.74 (m, 2H), 6.63 (dd, J = 2.0 & 8.4 Hz 1H), 4.79 (s, 1H), 4.02 (q, J = 7.2 Hz, 2H), 3.66 (s, 3H, OCH₃), 3.65 (s, 3H, OCH₃), 2.44 (d, J = 17.2 Hz, 1H), 2.30-2.26 (m, 4H), 2.19 (d, J = 16.4 Hz, 1H), 2.00 (d, J = 16.4 Hz, 1H), 1.17 (t, J = 7.2 Hz, 3H), 1.01 (s, 3H), 0.88 (s, 3H); **¹³C NMR** (50MHz, DMSO-d₆): δ 194.24, 166.87, 149.31, 147.91, 146.88, 144.50, 140.42, 119.17, 111.67, 111.42, 109.99, 103.81, 58.97, 55.37, 55.27, 50.26, 35.11, 32.08, 29.19, 26.40, 18.24, 14.23; **MS (ES)**: m/z 400.50 (M+H); **ESI-HRMS**: m/z [M+H]⁺ calculated for C₂₃H₃₆NO₅: 400.2124; found 400.2127.
Ethyl 2,7,7-trimethyl-5-oxo-4-(4-(trifluoromethyl)phenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (16f).

Pale yellow solid; **MP:** 188-190 °C; **IR (KBr):** 3281, 2938, 1710, 1603, 1496, 1382, 1324, 1216, 1136, 1065, 862, 598, 531 cm⁻¹; **¹H NMR** (400 MHz, DMSO-d₆): δ 9.17 (s, 1H, NH), 7.57 (d, J = 7.6 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 4.93 (s, 1H), 3.99 (q, J = 7.2 Hz, 2H), 2.45 (d, J = 16.4 Hz, 1H), 2.32 (m, 4H), 2.19 (d, J = 16.4 Hz, 1H), 2.00 (d, J = 16.0 Hz, 1H), 1.13 (t, J = 7.2 Hz, 3H), 1.00 (s, 3H), 0.83 (s, 3H); **¹³C NMR** (50 MHz, DMSO-d₆): δ 194.14, 166.45, 151.97, 149.80, 145.67, 128.19, 124.65, 124.58, 109.32, 102.75, 59.12, 50.09, 36.28, 32.12, 28.99, 26.45, 18.30, 14.06; **MS (ES):** m/z 408.50 (M+H); **ESI-HRMS:** m/z [M+H]⁺ calculated for C₂₂H₂₅NO₃F₃: 408.1787; found 408.1786.

Ethyl 4-(3,4-dihydroxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (16g).
Light brown solid; **MP**: 216-218 °C; **IR** (KBr): 3504, 3276, 2960, 1681, 1603, 1487, 1380, 1286, 1217, 1074, 814, 659 cm⁻¹; **¹H NMR** (400MHz, DMSO-d₆): δ 8.94 (s, 1H, NH), 8.56 (s, 1H, OH), 8.45 (s, 1H, OH), 6.57 (d, J = 2.0 Hz, 1H), 6.51 (d, J = 8.0 Hz 1H), 6.39 (dd, J = 2.0 & 8.4 Hz 1H), 4.68 (s, 1H), 4.00 (q, J = 7.2 Hz, 2H), 2.40 (d, J = 17.2 Hz, 1H), 2.27 (m, 4H), 2.16 (d, J = 16.0 Hz, 1H), 1.99 (d, J = 16.0 Hz, 1H), 1.16 (t, J = 7.2 Hz, 3H), 1.00 (s, 3H), 0.87 (s, 3H); **¹³C NMR** (100 MHz, DMSO-d₆): δ 194.28, 167.10, 149.01, 144.35, 144.12, 143.11, 138.59, 118.13, 115.18, 114.83, 110.31, 104.12, 58.94, 50.37, 34.78, 32.11, 29.16, 26.58, 18.25, 14.20; **MS (ES)**: m/z 372.60 (M+H); **ESI-HRMS**: m/z [M+H]+ calculated for C₂₁H₂₆NO₅: 372.1811; found 372.1817.

**Ethyl 4-(5-hydroxy-2-nitrophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (16h).**

Yellow solid; **MP**: 167-169 °C; **IR** (KBr): 3486, 3310, 2956, 1698, 1607, 1494, 1280, 1218, 1066, 856, 613 cm⁻¹; **¹H NMR** (400 MHz, DMSO-d₆): δ 10.37 (s, 1H, OH), 9.06 (s, 1H, NH), 7.69 (d, J = 8.8 Hz, 1H), 6.75 (d, J = 2.4 Hz, 1H), 6.62 (dd, J = 2.4 & 8.8 Hz, 1H), 5.77 (s, 1H), 3.94 (q, J = 7.2 Hz, 2H), 2.42 (d, J = 16.8 Hz, 1H), 2.29 (s, 3H), 2.25 (d, J = 16.8 Hz, 1H), 2.13 (d, J = 15.6 Hz, 1H), 1.92 (d, J = 15.6 Hz, 1H), 1.00 (t, J = 7.2 Hz, 3H), 0.98 (s, 3H), 0.79 (s, 3H); **¹³C NMR** (100 MHz, DMSO-d₆): δ 193.93, 166.70, 149.01, 145.88, 145.40, 140.14, 126.36, 116.58, 113.32, 110.03, 103.59, 90.03, 50.15, 32.06, 31.75, 28.89, 26.38, 18.29, 13.82; **MS (ES)**: m/z 401.50 (M+H); **ESI-HRMS**: m/z [M+H]+ calculated for C₂₁H₂₅N₂O₆: 401.1713; found 401.1721.
**Ethyl 4-(4-methoxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (16i).**

White solid; **MP:** 250-252 °C; **IR (KBr):** 3279, 2958, 1699, 1605, 1492, 1380, 1214, 1072, 1031, 849, 762, 536 cm\(^{-1}\); **\(^1\)H NMR (400 MHz, DMSO-\(d_6\)):** \(\delta\) 9.00 (s, 1H, NH), 7.05 (d, \(J = 8.4\) Hz, 2H), 6.74 (d, \(J = 8.4\) Hz, 2H), 4.78 (s, 1H), 3.99 (q, \(J = 7.2\) Hz, 2H), 3.67 (s, 3H, OCH\(_3\)), 2.43 (d, \(J = 16.8\) Hz, 1H), 2.29 (m, 4H), 2.17 (d, \(J = 16.0\) Hz, 1H), 1.98 (d, \(J = 16.0\) Hz, 1H), 1.15 (t, \(J = 7.2\) Hz, 3H), 1.00 (s, 3H), 0.85 (s, 3H); **\(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)):** \(\delta\) 194.24, 166.91, 157.25, 149.20, 144.59, 139.99, 128.37, 113.05, 110.18, 103.90, 58.96, 54.80, 50.25, 34.90, 32.09, 29.13, 26.47, 18.24, 14.15; **MS (ES):** m/z 370.50 (M+H); **ESI-HRMS:** m/z [M+H]\(^+\) calculated for C\(_{22}\)H\(_{28}\)NO\(_4\): 370.2018; found 370.2025.

**Ethyl 4-(2-chloro-3-(trifluoromethyl)phenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (16j).**

White solid; **MP:** 104-106 °C; **IR (KBr):** 3297, 2961, 1701, 1614, 1492, 1380, 1312, 1216, 1133, 803, 735, 597 cm\(^{-1}\); **\(^1\)H NMR (400 MHz, DMSO-\(d_6\)):** \(\delta\) 9.17 (s, 1H, NH), 7.59 (m, 2H), 7.40 (m, 1H), 5.31 (s, 1H), 3.99
Methyl 2,7,7-trimethyl-4-(4-nitrophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (16k).

Pale yellow solid; **MP:** 229-232 °C; **IR** (KBr): 3277, 2959, 1709, 1605, 1491, 1345, 1217, 1075, 866, 833, 533 cm⁻¹; **¹H NMR** (400 MHz, DMSO-d₆): δ 9.26 (s, 1H, NH), 8.10 (d, J = 8.8 Hz, 2H), 7.42 (d, J = 8.8 Hz, 2H), 4.98 (s, 1H), 3.52 (s, 3H, OCH₃), 2.46 (d, J = 17.2 Hz, 1H), 2.32 (m, 4H), 2.21 (d, J = 16.4 Hz, 1H), 2.00 (d, J = 16.4 Hz, 1H), 1.00 (s, 3H), 0.81 (s, 3H); **¹³C NMR** (50 MHz, DMSO-d₆): δ 194.13, 166.80, 154.74, 150.01, 146.32, 145.59, 128.51, 123.15, 108.99, 102.03, 50.75, 50.04, 36.42, 32.11, 28.99, 26.39, 18.37; **MS (ES):** m/z 371.50 (M+H); **ESI-HRMS:** m/z [M+H]+ calculated for C₂₀H₂₃N₂O₅: 371.1607; found 371.1616.
Methyl 4-(4-chlorophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (16l).

White solid; **MP:** 243-245 °C; **IR** (KBr): 3288, 2959, 1682, 1606, 1489, 1381, 1226, 1074, 1013, 840, 776, 538 cm$^{-1}$; **$^1$H NMR** (400 MHz, DMSO-$d_6$): δ 9.14 (s, 1H, NH), 7.25 (d, $J = 8.4$ Hz, 2H), 7.15 (d, $J = 8.4$ Hz, 2H), 4.85 (s, 1H), 3.52 (s, 3H, OCH$_3$), 2.44 (d, $J = 17.2$ Hz, 1H), 2.29 (m, 4H), 2.19 (d, $J = 16.0$ Hz, 1H), 1.99 (d, $J = 16.0$ Hz, 1H), 1.00 (s, 3H), 0.82 (s, 3H); **$^{13}$C NMR** (50 MHz, DMSO-$d_6$): δ 194.14, 167.02, 149.49, 146.30, 145.59, 130.14, 129.05, 127.68, 109.62, 102.69, 50.64, 50.13, 35.36, 32.08, 29.04, 26.37, 18.29; **ESI-HRMS:** $m/z$ [M+H]$^+$ calculated for C$_{20}$H$_{23}$NO$_3$Cl: 360.1366; found 360.1373.

Methyl 4-(4-cyanophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (16m).

White solid; **MP:** 220-222 °C; **IR** (KBr): 3276, 2960, 2226, 1708, 1607, 1493, 1379, 1217, 1074, 858, 553 cm$^{-1}$; **$^1$H NMR** (400 MHz, DMSO-$d_6$): δ 9.22 (s, 1H, NH), 7.68 (d, $J = 8.0$ Hz, 2H), 7.33 (d, $J = 8.0$ Hz, 2H), 4.92 (s, 1H), 3.51 (s, 3H, OCH$_3$), 2.45 (d, $J = 17.2$ Hz, 1H), 2.31 (m, 4H), 2.20 (d, $J = 16.0$ Hz, 1H), 2.00 (d, $J = 16.0$ Hz, 1H), 1.00 (s, 3H), 0.80 (s, 3H); **$^{13}$C NMR** (50 MHz, DMSO-$d_6$): δ 194.12, 166.84, 152.62, 149.90,
MS (ES): m/z 351.50 (M+H); ESI-HRMS: m/z [M+H]^+ calculated for C_{21}H_{23}N_{2}O_{3}: 351.1709; found 351.1705.

Methyl 4-(3,4-dimethoxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (16n).

White solid; MP: 209-211 °C; IR (KBr): 3276, 2945, 1699, 1602, 1492, 1379, 1217, 1137, 1030, 858, 788, 768, 733, 657 cm⁻¹; \(^1\)H NMR (400 MHz, DMSO-d\(_6\)): δ 9.04 (s, 1H, NH), 6.77 (m, 2H), 6.61 (d, J = 8.0 Hz, 1H), 4.80 (s, 1H), 3.67 (s, 3H, OCH\(_3\)), 3.65 (s, 3H, OCH\(_3\)), 3.55 (s, 3H, OCH\(_3\)), 2.44 (d, J = 17.2 Hz, 1H), 2.30 (m, 4H), 2.20 (d, J = 16.0 Hz, 1H), 2.01 (d, J = 16.0 Hz, 1H), 1.01 (s, 3H), 0.87 (s, 3H); \(^{13}\)C NMR (50 MHz, DMSO-d\(_6\)): δ 194.27, 167.32, 149.29, 148.01, 146.89, 144.81, 140.23, 118.93, 111.48, 110.00, 103.44, 55.37, 55.29, 50.55, 50.24, 34.92, 32.07, 29.18, 26.37, 18.23; MS (ES): m/z 386.50 (M+H); ESI-HRMS: m/z [M+H]^+ calculated for C_{22}H_{28}NO_{5}: 386.1967; found 386.1971.
Ethyl 2-methyl-4-(3-nitrophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (16o).

Yellow solid; **MP**: 204-206 °C; **IR** (KBr): 3297, 2940, 1703, 1608, 1527, 1480, 1346, 1222, 1182, 1076, 718, 680, 525 cm\(^{-1}\); **\(^1\)H NMR** (400MHz, CDCl\(_3\)): δ 8.09 (m, 1H), 7.99 (dd, \(J = 2.0 \& 8.0\) Hz, 1H), 7.74 (d, \(J = 7.6\) Hz, 1H), 7.39 (m, 1H), 6.06 (s, 1H, NH), 5.18 (s, 1H), 4.08 (q, \(J = 7.2\) Hz, 2H), 2.50-2.47 (m, 2H), 2.42 (s, 3H), 2.39-2.32 (m, 2H), 2.05-1.92 (m, 2H), 1.19 (t, \(J = 7.2\) Hz, 3H); **\(^13\)C NMR** (50 MHz, CDCl\(_3\)): δ 195.78, 166.89, 150.82, 149.31, 148.20, 144.51, 134.73, 128.53, 121.17, 112.22, 104.88, 60.00, 36.87, 27.22, 20.99, 19.24, 14.15; **MS (ES)**: \(m/z\) 357.50 (M+H); **ESI-HRMS**: \(m/z\) [M+H]\(^+\) calculated for C\(_{19}\)H\(_{21}\)N\(_2\)O\(_5\): 357.1450; found 357.1467.

Ethyl 4-(2-chloro-4-(trifluoromethyl)phenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (16p).

Pale yellow solid; **MP**: 92-94 °C; **IR** (KBr): 3295, 2979, 1698, 1614, 1490, 1315, 1225, 1184, 1130, 977, 736, 697, 530 cm\(^{-1}\); **\(^1\)H NMR** (400 MHz, CDCl\(_3\)): δ 7.63 (d, \(J = 7.6\) Hz, 1H), 7.49 (d, \(J = 7.6\) Hz, 1H), 7.24 (t, \(J = 7.6\) Hz, 1H), 6.00 (s, 1H, NH), 5.51 (s, 1H), 4.05 (q, \(J = 7.2\) Hz, 2H), 2.45-2.37 (m, 2H), 2.34 (s, 3H), 2.32-2.28 (m, 2H), 2.01-1.89 (m, 2H), 1.16 (t, \(J = 7.2\) Hz, 3H); **\(^13\)C NMR** (50 MHz, CDCl\(_3\)): δ 195.68, 167.14, 151.16, 146.52, 144.28, 135.81, 125.75, 125.58, 125.46, 111.77, 104.67, 59.90, 36.99, 36.54, 27.32, 20.96, 19.19, 14.11; **MS (ES)**: \(m/z\) 414.40 (M+H); **ESI-HRMS**: \(m/z\) [M+H]\(^+\) calculated for C\(_{20}\)H\(_{20}\)NO\(_3\)Cl\(_3\): 414.1084; found 414.1072.
3.6. Spectral data of selected compounds (\(^1\)H NMR and \(^{13}\)C NMR)

Figure 3.5. \(^1\)H NMR Spectra of compound 16a
Figure 3.6. $^{13}$C NMR Spectra of compound 16a
Figure 3.7. $^1$H NMR Spectra of compound 16d

Figure 3.8. $^{13}$C NMR Spectra of compound 16d
Figure 3.9. $^1$H NMR Spectra of compound 16g
Figure 3.10. $^{13}$C NMR Spectra of compound 16g

Figure 3.11. $^1$H NMR Spectra of compound 16h
Figure 3.12. $^{13}$C NMR Spectra of compound 16h
Figure 3.13. $^1$H NMR Spectra of compound 16i
Figure 3.14. $^{13}$C NMR Spectra of compound 16i
Figure 3.15. $^1$H NMR Spectra of compound 16k

Figure 3.16. $^{13}$C NMR Spectra of compound 16k
Figure 3.17. $^1$H NMR Spectra of compound 16l
Figure 3.18. $^{13}$C NMR Spectra of compound 16l

Figure 3.19. $^1$H NMR Spectra of compound 16n
Figure 3.20. $^{13}$C NMR Spectra of compound 16n
Figure 3.21. $^1$H NMR Spectra of compound 16o

Figure 3.22. $^{13}$C NMR Spectra of compound 16o