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# Synthesis of Fluphenazine Decanoate using Candida Antarctica Lipase B Enzyme

***Sachika Tomer, **Dhirsinh Rathod**
**Navrachana International School, Vadodara, Gujarat, India- 391 410*
***Nia Innovation LLP, Vadodara, Gujarat, India- 390 016*

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## ABSTRACT

In the present work, we have synthesized Fluphenazine Decanoate by using easily available starting materials like Fluphenazine, Decanoic acid and Lipase B Candida antarctica CALB enzyme. The process avoids the use of Decanoyl chloride which in turn is synthesized from Decanoic acid and toxic as well as corrosive chemicals, like thionyl chloride. This process is green and atom economic as compared to the other reported processes till date. Fluphenazine decanoate synthesized by this process is enough pure (purity 99.6%) for subsequent uses. The synthesized product is characterized by using HPLC, NMR and Mass spectroscopy.

**Keywords:** *Green synthesis; Fluphenazine decanoate; Lipase B Candida antarctica CALB; Esterification; Recycling of CALB*

## INTRODUCTION

Statistical data, in 2019 showed that one in eight people, or 970 million people in the world, were having some kind of mental disorder. This figure increased significantly about 26-28% in the next year 2020, probably due to COVID pandemic. There are different types of mental disorders, out of which schizophrenia is very common and affects approximately 24 million people globally[1]. The basic drugs used to treat this condition belong to the neuroleptic class[2]. Most antipsychotic medicines are taken orally. These medicines are prescribed to be taken regularly but are avoided if the individuals are having negative impacts or side effects. In 1960, depot injections were developed for long term maintenance[3]. Depot is an oily suspension of the derivative of the active pharmaceutical ingredient and it is administered intramuscularly.

Fluphenazine Decanoate was the first depot prepared from its oral antipsychotic counterpart Fluphenazine Hydrochloride. It is the decanoate ester of a trifluoromethyl phenothiazine derivative and has the following structural formula:

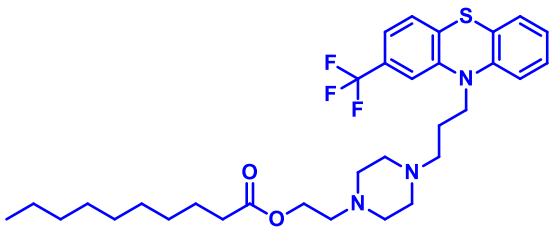


**Figure 1:** Chemical structure of Fluphenazine decanoate

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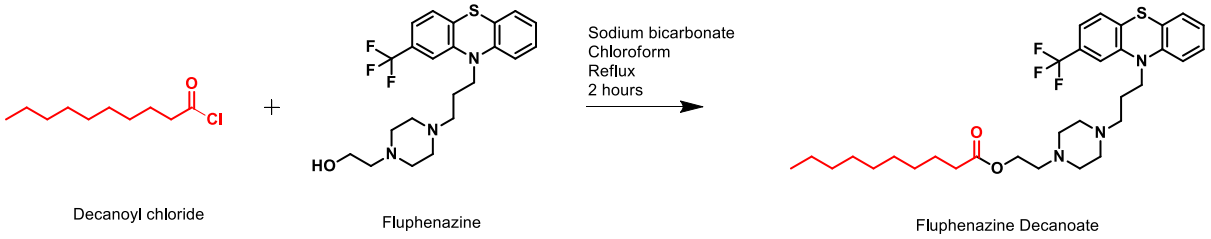
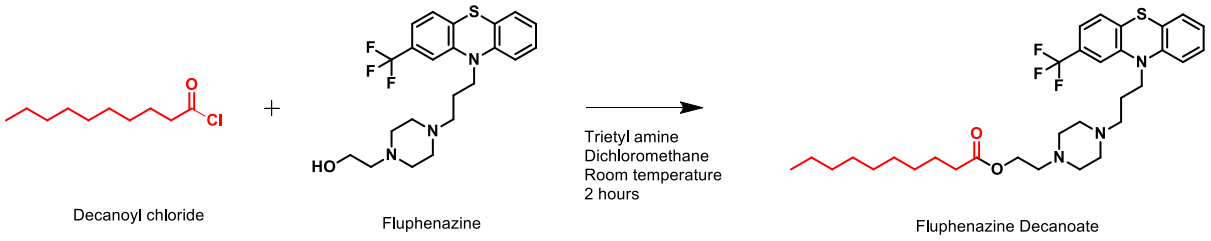
Fluphenazine Decanoate is similar in action to oral drug Fluphenazine Hydrochloride; the only difference is the duration of the effect. The decanoic ester of Fluphenazine only increases the duration of the drug without altering its desired activity.

The process for the preparation of Fluphenazine Decanoate was first reported in US3394131A (scheme-1). This involves the use of Decanoyl chloride to prepare the ester of Fluphenazine.




**Scheme 1**. Process for the preparation of Fluphenazine decanoate as described in patent US3394131A.

Later the following process was reported in IN201941043490 A by MSN Laboratories Private Limited and IN2014MU02033 A by Enaltec Labs Private Limited.




**Scheme 2.** Process for the preparation of Fluphenazine decanoate as described in patent IN201941043490 A and IN2014MU02033 A.

From the above description, it can be inferred that all the above reported processes are associated with the following drawbacks: i) Decanoyl chloride is used as one of the reactants. Decanoyl chloride is prepared from Decanoic acid reacting with one of the reagents: thionyl chloride, oxalyl chloride, phosphorous chlorides, etc. These reagents are corrosive in nature and are toxic to human health. For example, thionyl chloride is corrosive to the eyes, skin and respiratory tract. Inhalation of the fumes may cause lung oedema. When it reacts with water, it explodes and releases hydrochloric acid. ii) high temperature for the preparation of acid chloride and removal of solvents iii) the processes are lengthy and require tedious work up iv) the synthesized Fluphenazine Decanoate requires additional purification to meet the quality requirements v) the processes require multiple reactors, for the synthesis of acid chloride, reaction and work up vi) the processes are not atom economical.

Therefore, an atom economical green process which avoids the use of these toxic and corrosive chemicals is needed to be developed.

Literature survey was carried out to understand the other possible ways of the synthesis of an ester in a green manner. Emmanuel in 2019 reported the synthesis of ethyl butyrate by using Immobilized Lipase-B from Candida antarctica and in absence of solvent[4]. Julia Cassani in 2007 reported the esterification of phenylpropanoid and hydrophenylpropanoid acids, catalyzed by candida antarctica lipase B (CAL-B), with several alcohols[5]. Dounia Arcens described the synthesis of fatty acid glucose esters in the presence of Candida antarctica Lipase B (CALB) in Acetonitrile[6]. Anna Kundys reported Candida antarctica Lipase B as Catalyst for Cyclic Esters Synthesis[7]. Soni in 2017 reported monoesterification of symmetric diols catalyzed by CALB when the reaction was carried out in

diethyl ether with good yields[8]. There are numerous examples where ester is prepared from a carboxylic acid and an alcohol in the presence of CALB, with or without solvent.

Candida antarctica lipase B (CALB) is the most widely studied and used enzyme, due to its high selectivity and catalytic activity in organic solvents. Therefore, it was selected for the evaluation for the green preparation of Fluphenazine Decanoate.

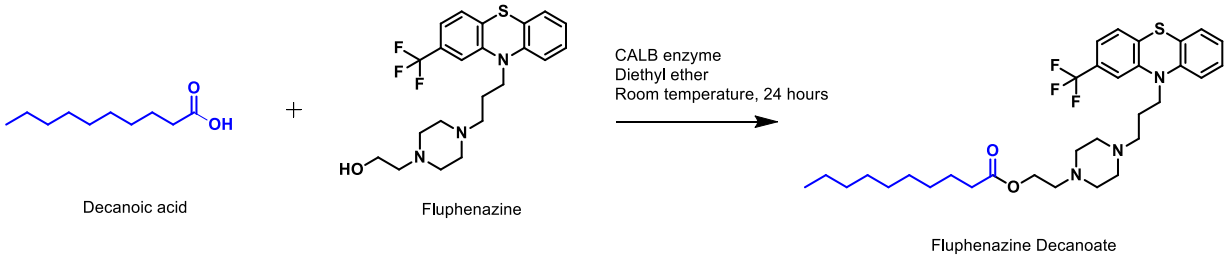
In the current work, we have prepared Fluphenazine Decanoate by using Fluphenazine and decanoic acid in diethyl ether in the presence of CALB with excellent yield. The product was enough pure for further use and was purified by column chromatography for analytical purpose only. The enzyme was filtered and reused many times. The present route is atom economical as compared to all the earlier route of synthesis.

## MATERIALS AND METHOD

Fluphenazine, Decanoic acid and Lipase B Candida antarctica (CALB) immobilized on Immobead 150, recombinant from yeast were purchased from Merck. Diethyl ether and silica (60-120mesh) was purchased from Spectrochem.

## RESULTS AND DISCUSSION

This work is carried out with the aim of synthesizing Fluphenazine decanoate from Fluphenazine and decanoic acid in the presence of Lipase B Candida antarctica CALB.




**Scheme 3.** Process for the preparation of Fluphenazine decanoate in the presence of CALB.

### Process

Fluphenazine (2g, 0.00457 moles) was added to Diethylether (30ml) at 25-30°C and the reaction mixture was stirred for 15 min at the same temperature till a clear solution is obtained. To this solution, Decanoic acid (0.79g, 0.00457 mol) and CALB enzyme (1g) were added. This suspension was stirred at the same temperature till completion of the reaction. The progress of the reaction was monitored by using thin layer chromatography.

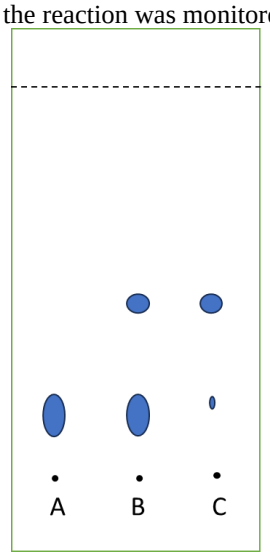



**Figure 2:** TLC image for the monitoring of the reaction.

Stationary phase: Silica gel coated on Aluminium plate
Mobile phase: 50% Ethyl acetate in Toluene
Spot A: Starting material (Fluphenazine)
Spot B: Mix spot of starting material (Fluphenazine) and reaction mixture.
Spot C: Reaction mixture.

After 24 hours, it was observed that there was no further progress in the reaction. The reaction mass was filtered through filter paper and the clear filtrate having the product was distilled to give crude product (2.6g) with 99.6% purity. The filtered enzyme was washed with Diethyl ether (5ml) and was stored for further cycles. The product was further purified (for analysis purpose only) by column chromatography using silica gel as stationary phase and 30% Ethyl acetate in Toluene as mobile phase. 2.4g of the pure product Fluphenazine Decanoate was obtained (0.00405 mol and 89% yield) as a viscous oil, having 99.93% purity.

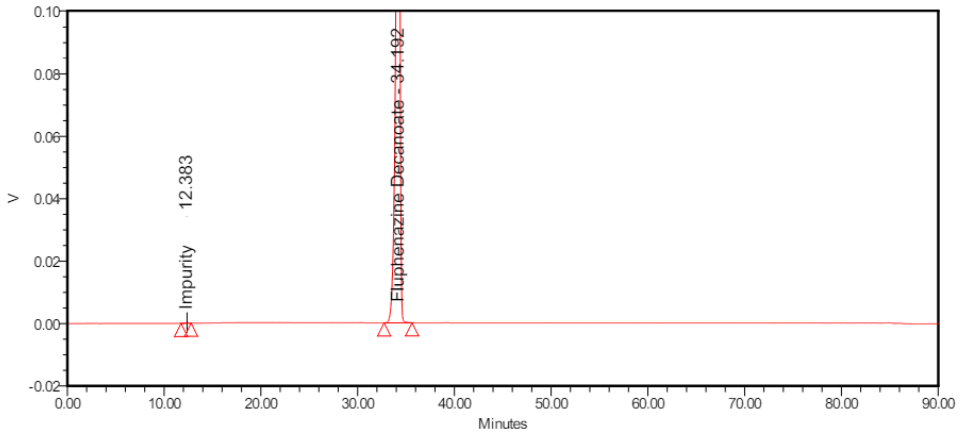



**Figure 3:** High performance liquid chromatography graph of Fluphenazine Decanoate. The Detection was carried out at 260nm.

The isolated product was characterized by NMR and mass spectroscopy. The mass obtained was in accordance to the structure. The NMR is as follows.

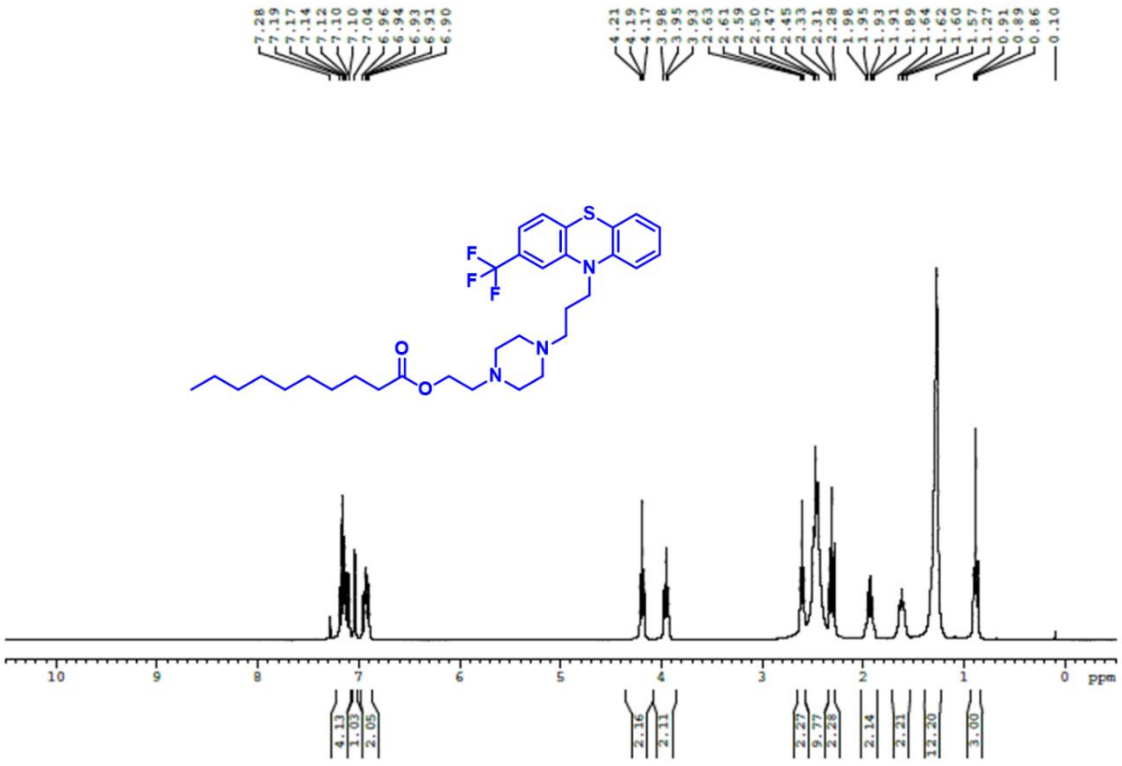



**Figure 4:** Nuclear magnetic resonance spectra of Fluphenazine decanoate.

The NMR of the product matches with the data of the standard.

**Recovery and reuse of CALB**

The recovered enzyme was stored at 2-8ºC till it was reused in the next cycle. The recovered enzyme was able to catalyze 4 more cycles of reaction without significant change in purity and molar yield. The data is as followed:

| Entry | Molar yield (%) | Chromatographic purity (% w/w) | Reaction/ Cycle |
|---|---|---|---|
| 1 | 96.2 | 99.60 | 1st reaction |
| 2 | 97.5 | 99.55 | 1st cycle |
| 3 | 94.6 | 99.53 | 2nd cycle |
| 4 | 94.6 | 99.72 | 3rd cycle |
| 5 | 92.8 | 99.81 | 4th cycle |

**Table 1**: Molar yield and chromatographic purity of Fluphenazine decanoate after the use of the recycled enzyme

**Atom economy**

It is the measurement of the desired product formed as compared to the amount of the starting materials used.
Existing process:

$$Fluphenazine + Decanoyl\ chloride + Triethyl\ amine \longrightarrow Fluphenazine\ decanoate$$

| | | | | |
|---|---|---|---|---|
| $Molecular\ Weight\ (g/mol)$ | 437.52 | 190.71 | 101.19 | 591.77 |

$$Atom\ economy = \frac{591.77}{729.42} \times 100 = \mathbf{81.13\%}$$

Newly developed process:

$$Fluphenazine + Decanoic\ acid \longrightarrow Fluphenazine\ decanoate$$

| | | | |
|---|---|---|---|
| $Molecular\ Weight\ (g/mol)$ | 437.52 | 172.26 | 591.77 |

$$Atom\ economy = \frac{591.77}{609.78} \times 100 = \mathbf{97.04\%}$$

**Calculation of Rf**

Rf, retention factor or retardation factor is the ratio of distance travelled by a component to the distance travelled by the solvent.

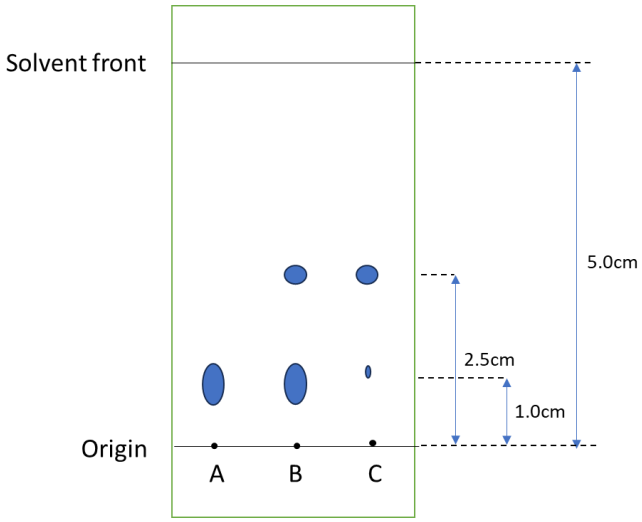



**Figure 5:** Calculation of retention factor

Rf of the starting material: $\frac{\text{Distance travelled by starting material}}{\text{Distance travelled by the solvent}} = \frac{1}{5} = 0.2$

Rf of the product: $\frac{\text{Distance travelled by the product}}{\text{Distance travelled by the solvent}} = \frac{2.5}{5} = 0.5$

**Scale up of the process**

To demonstrate the feasibility of the developed process at large scale, we carried out the synthesis at a pilot plant. The unit operations carried out for the synthesis by using Fluphenazine (250g) are shown in the Fig.:

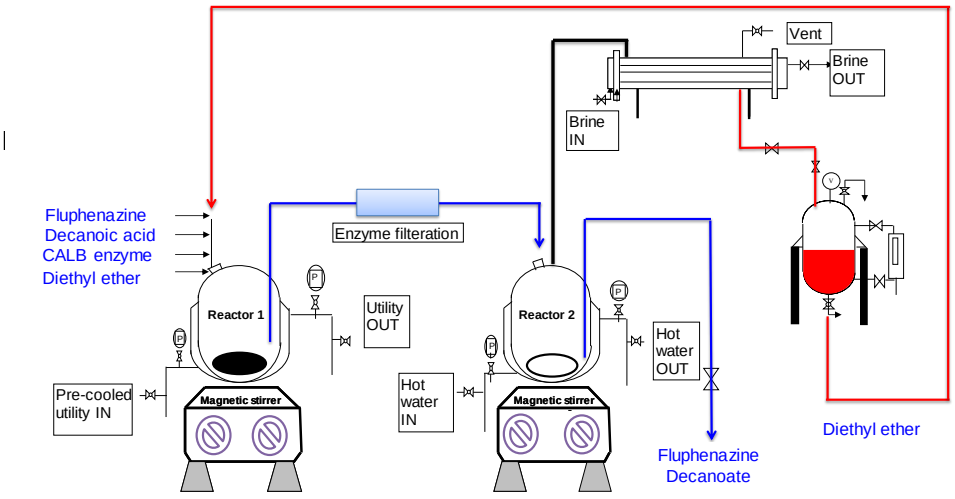



**Figure 6**: The engineering diagram of the pilot plant for the synthesis of Fluphenazine decanoate

## CONCLUSION

We have demonstrated the preparation of Fluphenazine decanoate from Fluphenazine and Decanoic acid in the presence of Lipase B Candida antarctica (CALB) enzyme. This process is green in true sense since it is atom economical and does not involve purification process or the use of corrosive reagents.

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