**INSTITUTE OF INTELLECTUAL PROPERTY RESEARCH & DEVELOPMENT**

IFAIA Centre, S/20-22, Greater Noida Shopping Plaza, Greater Noida - 201308, India
Phone: +91.120.2342010, 3104849, Fax: 2342011 Website: www.iiprd.com
Email: iiprd@iiprd.com

**NON-CONFIDENTIAL TECHNOLOGY SUMMARY**

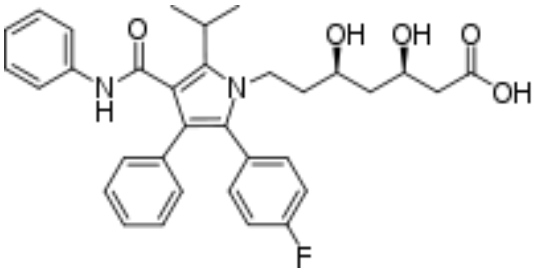
# PREPARATION PROCESS OF A KEY INTERMEDIATE USED IN SYNTHESIS OF ATORVASTATIN AND ISOLATION & CHARACTERIZATION OF A NOVEL IMPURITY

**INVENTORS: A Group of scientists from Arch Pharma**

## Background & Introduction:

Atorvastatin is a member of drug class known as statins, a drug useful for lowering blood cholesterol, stabilizing plaque and preventing stroke through anti-inflamatory and other mechanisms.

Atorvastatin is a competitive inhibitor of HMG-CoA reductase.



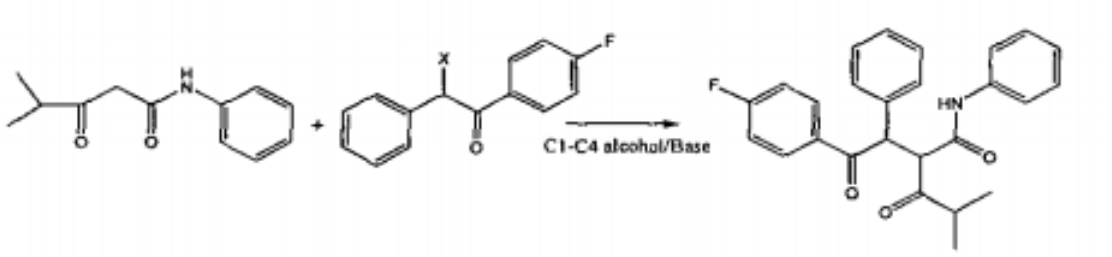

Atorvastatin is used for the treatment of dyslipidemia and the prevention of cardiovascular disease.

Intermediates play an important role in the efficiency, cost and the percentage of impurities. Earlier known synthetic processes report desfluoro and difluoro as impurities that affect the purity of Atorvastatin. The present process by Arch Pharma prepares the key intermediate in 99:1 diastereoisomeric mixture comprising up to 1% total impurities with the desfluoro impurity of about 0.1% and the difluoro impurity about 0.05%.

## Description:

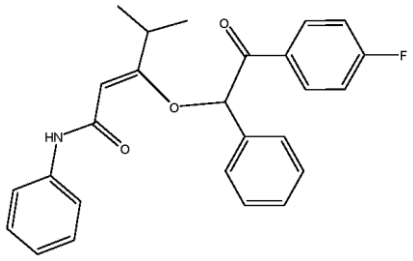
The technology relates to a preparation process of 4-fluoro-.alpha.-[2-methyl-1-oxopropyl]-y-oxo-n-beta-diphenylbenzenebutanamide (DKT III), a key intermediate for the synthesis of Atorvastatin.

The process comprising reacting a compound of Formula II with a compound of Formula III in C3-C5 alcohol as a solvent in the presence of a base. The inventors have studied and revealed that O-alkylation of enol tautomer to form O-alkylated impurity will affect the purity and yield of DKT III considerably.




**Formula II** **Formula III** **DKT III**

This technology discloses a method of isolation and characterization of a novel impurity (F-IV) formed during the process of preparation of the intermediate DKT III and it is up to 0.1%.



**F-IV**

Claims a process of preparation of intermediate (formula-II), without using a solvent and it is isolated in less than one day. The same intermediate isolation takes 10 days and uses solvent when other/earlier methods are employed for the synthesis.

Also, Claims a process for preparation of Atorvastatin and its calcium salts using the above mentioned intermediates.

## Advantages:

- Efficient and economic process.
- Final product is free of impurity.
- Total impurities is upto 1% with desfluoro impurity of about 0.1% and the difluoro impurity about 0.05%.
- Product(Intermediate, DKT III) is Isolated in Solid form.
- The process isolates and characterizes unknown impurities of DKT III, which is up to 0.1%.

## Development Status:

The above process was implemented in the laboratory on a small scale and resulted in the Purity 99.69% with 0.047% of Desfluoro impurity, Difluoro almost nil and O-alkylated impurity to be 0.1% with yield of 73%.

## Patent Status

- Indian Application Number: 1152/MUM/2008.
- US Granted Patent Numbered 7872154.
- Also, a US Granted Patent 8163959, claiming(Product Claim) for a novel impurity **Formula-IV**.
- European Application No. EP2279167.

## For more information please contact:

Tarun Khurana
Partner, IIPRD
Phone: +91 9810617992,
Fax : +91-(120) 2342011
E-mail: tarun@iiprd.com

**About IIPRD**

IIPRD is a premier Intellectual Property Consulting and Commercialization/Licensing Firm with a diversified business practice providing services in the domain of Commercialization, Valuation, Licensing, Transfer of Technology and Due-Diligence of Intellectual Property Assets along with providing complete IP and Patent Analytics and Litigation Support Services to International Corporates and Global IP Law Firms.