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# PHARMACEUTICAL SYNTHETIC REVIEW OF ROSUVASTATIN CALCIUM

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## ABSTRACT

Rosuvastatin is a member of the drug class of statins, used to treat high cholesterol and related conditions, and to prevent cardiovascular disease. It was developed by Shionogi. The primary uses of rosuvastatin are for the treatment of dyslipidemia. It is recommended to be used only after other measures such as diet, exercise, and weight reduction have not improved cholesterol levels. Rosuvastatin has multiple contraindications which include hypersensitivity to rosuvastatin or any component of the formulation, active liver disease, and elevation of serum transaminases, pregnancy, or breast-feeding.

**KEYWORDS:** Rosuvastatin is a member or breast-feeding.

## INTRODUCTION

Rosuvastatin Calcium is a white or almost white, hygroscopic powder, slightly soluble in water, freely soluble in methylene chloride, practically insoluble in anhydrous ethanol. Store in airtight container, protected from light, at temperature of 2°C to 8°C. Rosuvastatin Calcium (ROS-Ca); is chemically known as [(3R,5S,6E)-7-[4-(4-fluorophenyl)-6-(1-methyleythyl) -2- [methyl (methyl sulfonyl) amino] pyrimidine-5- yl]-3,5-dihydroxyhept-6-enoate]. It has a molecular formula of $C_{44}H_{45}CaF_2N_6O_{12}S_2$ and a molecular weight of 1001[1-2] (Fig 1).

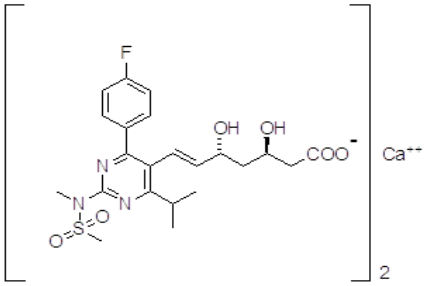



**Fig 1: Rosuvastatin Calcium.**

In 1971, Akira Endo[3-5], a Japanese biochemist working for the pharmaceutical company Sankyo, began the search for a cholesterol-lowering drug. Research had already shown that cholesterol is mostly manufactured by the body in the liver, using an enzyme known as HMG-CoA reductase. Endo and his team reasoned that certain microorganisms may produce inhibitors of the enzyme to defend themselves against other organisms, as mevalonate is a precursor of many substances required by organisms for the maintenance of their cell wall (ergosterol) or cytoskeleton (isoprenoids).The first agent they identified was mevastatin (ML-236B), a molecule produced by the fungus Penicilliumcitrinum.[6]

Studies in 1975 by Japanese biochemist Akira Endo, working at Sankyo Pharmaceuticals, found potent HMGCR inhibitors produced in the fermentation broth of certain molds and yeasts, leading to the isolation of the compound mevastatin, from the fungus Penicillium citrinum. Mevastatin (compactin) was further tested in animals and in human clinical trials in Japan. It was effective at reducing serum cholesterol levels, but the long-term toxic side effects were unacceptably negative; thus it was never marketed for use in humans.

The pharmaceutical giant Merck picked up on the Japanese research in 1976, and by 1978 isolated statin from the mold Aspergillus terreus, an effective HMGCR inhibitor, and eventually the first commercially available statin in 1987.

**Statins in Nature**

**Picture I: Oyster Mushroom Picture II: Red Yeast Rice.**

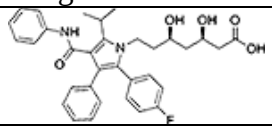
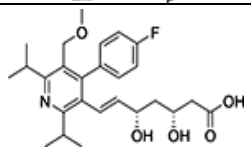
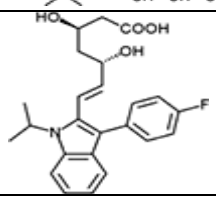
The oyster mushroom (Pleurotus ostreatus), a widely consumed culinary mushroom, naturally contains lovastatin, the first marketed statin. Some types of statins are naturally occurring, being found in such foods as oyster mushrooms and red yeast rice. Source: Wikimedia Commons (Jean-Pol Grandmont).

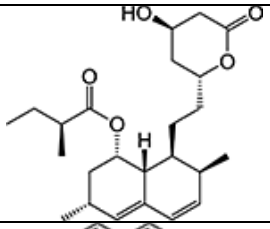
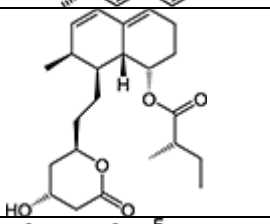
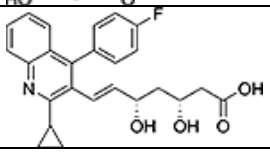
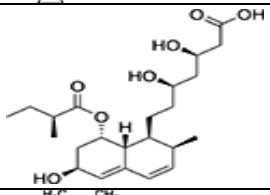
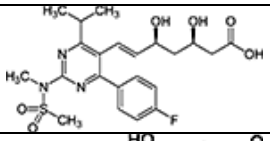
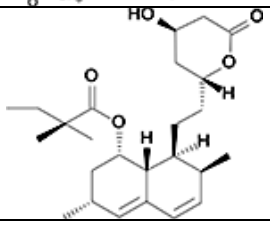
The early statin drugs were derived from natural sources—from food products or other natural organisms. Another rich source was red rice yeast, common in many Asian cooking recipes and in Chinese red barbecue pork. Red rice yeast also contains the molecule lovastatin, the same as found in Merck's first marketed statin drug Mevacor. Dried grain red yeast rice (red fermented rice, red kojic rice, red koji rice, anka, or ang-kak), is a bright reddish purple fermented rice, which acquires its color as white rice is cultivated with the mold Monascus purpureus. Red yeast rice naturally contains lovastatin.

LDL-lowering potency varies between agents. Cerivastatin is the most potent, (withdrawn from the market in August, 2001 due to risk of serious Rhabdomyolysis) followed by (in order of decreasing potency), rosuvastatin, atorvastatin, simvastatin, lovastatin, pravastatin, and fluvastatin. The relative potency of pitavastatin has not yet been fully established. Some types of statins are naturally occurring and can be found in such foods as oyster mushrooms and red yeast rice.

The statins are divided into two groups: fermentation-derived and synthetic. They are listed, along with brand names as following table.

**Table : Significant Statins**

| Statin | Image | Brand Name | Derivation | Metabolism |
|---|---|---|---|---|
| Atorvastatin |  | Lipitor, Torvast | Synthetic | CYP3A4 |
| Cerivastatin |  | Lipobay, Baycol (withdrawn in 2001 due to risk of rhabdomyolysis) | Synthetic | various CYP3A isoforms |
| Fluvastatin |  | Lescol, Lescol XL | Synthetic | CYP2C9 |

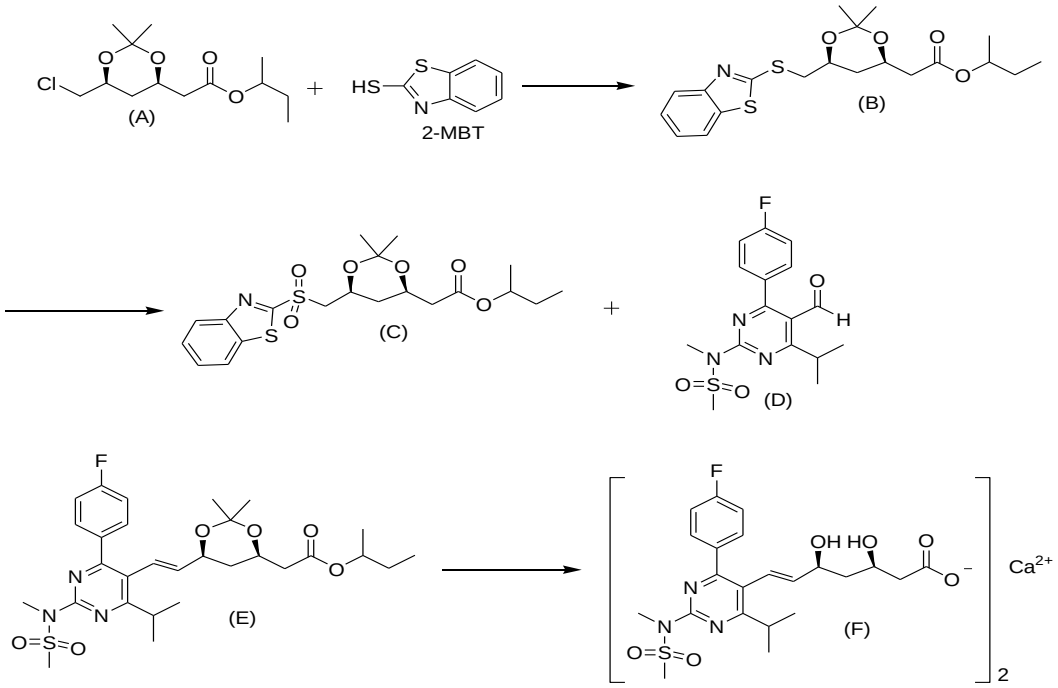
| | | | | |
|---|---|---|---|---|
| Lovastatin |  | Mevacor, Altocor, Altoprev | Fermentation-derived. Naturally occurring compound. Found in oyster mushrooms and red yeast rice. | CYP3A4 |
| Mevastatin |  | Compactin | Naturally occurring compound. Found in red yeast rice. Not marketed. | CYP3A4 |
| Pitavastatin |  | Livalo, Pitava | Synthetic | |
| Pravastatin |  | Pravachol, Selektine, Lipostat | Fermentation-derived (a fermentation product of bacterium Nocardia autotrophica) | Non CYP |
| Rosuvastatin |  | Crestor | Synthetic | CYP2C9 and CYP2C19 |
| Simvastatin |  | Zocor, Lipex | Fermentation-derived. (Simvastatin is a synthetic derivate of a fermentation product of Aspergillus terreus) | CYP3A4 |
| Simvastatin+ Ezetimibe | | Vytorin | Combination therapy | |
| Lovastatin+ Niacin | | Advicor | Combination therapy | |
| Atorvastatin+ Amlodipine Besylate | | Caduet | Combination therapy: cholesterol + blood Pressure | |
| Simvastatin+ Niacin extended-release | | Simcor | Combination therapy | |

Randomized controlled trials found them to be effective, but the quality of the trials was low. Most of the block-buster branded statins will be generic by 2012, including atorvastatin, the largest selling branded drug. Research continues into other areas where statins also appear to have a favorable effect, including dementia, lung cancer, nuclear cataracts, hypertension and prostate cancer. Rosuvastatin is an antihyper chlolesterolemic drug, is chemically known as

(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid calcium salt.

**WO20130296561A1[7]**

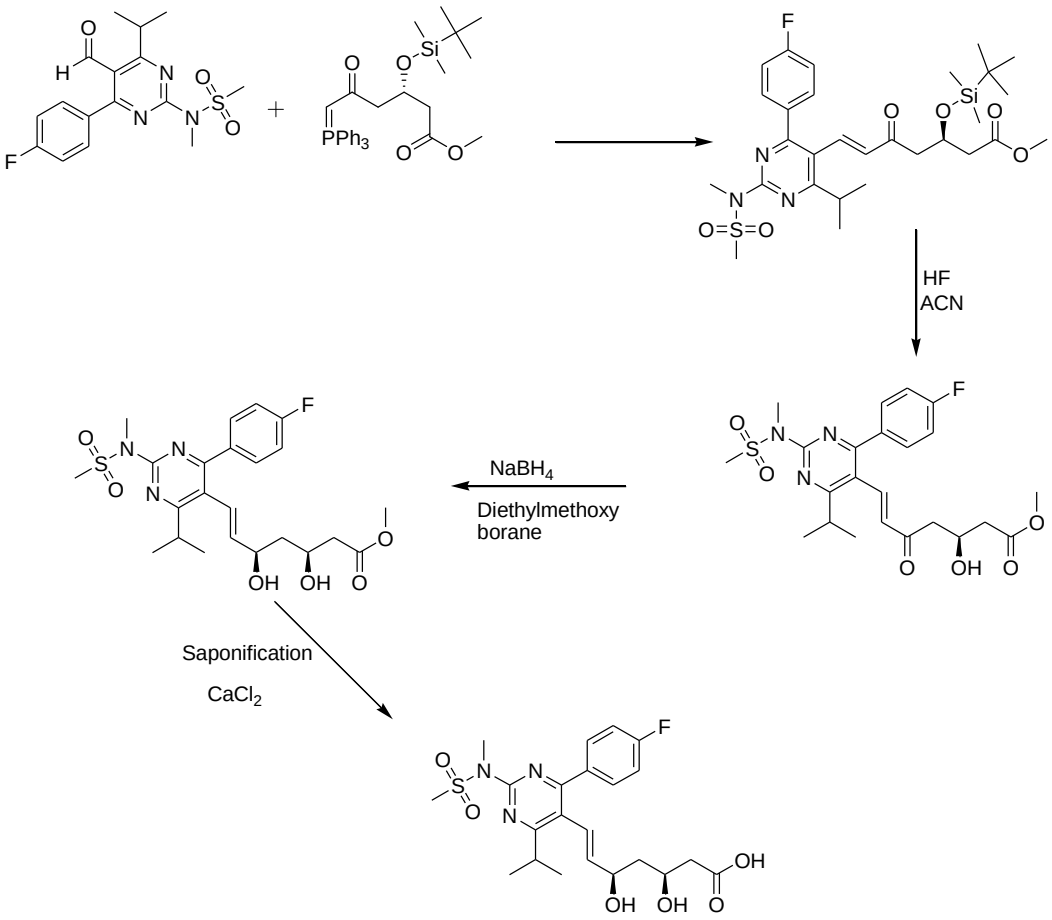
The significance of rosuvastatin as a lipid-lowering agent, several synthetic methods have been reported in the literature to prepare rosuvastatin, some of which are summarized below The present invention described to a process for the preparation of statins via a Julia-Kocienski reaction between an aldehyde and a sulfone derivative in the presence of an alkaline metal alkoxy base. The resulting derivatives are suitable as building blocks for statin type compounds rosuvastatin calcium as shown in scheme- 1.




**Scheme-1.**

**1. WO2012176218A1[8]**

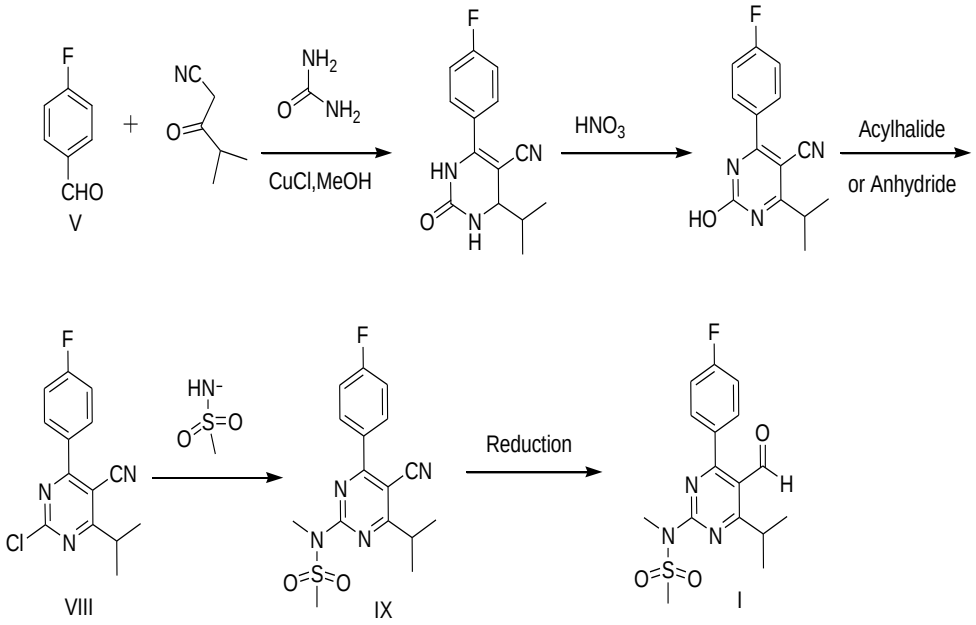
The present invention describe a process for preparing pure rosuvastatin, or pharmaceutically acceptable salts thereof through rosuvastatin l-(l-naphthyl)ethyl salt wherein represent (R), (S) stereochemistry or racemate thereof as shown in scheme-.2.




**Scheme-2.**

## 2. WO 2008/151510 A1[9]

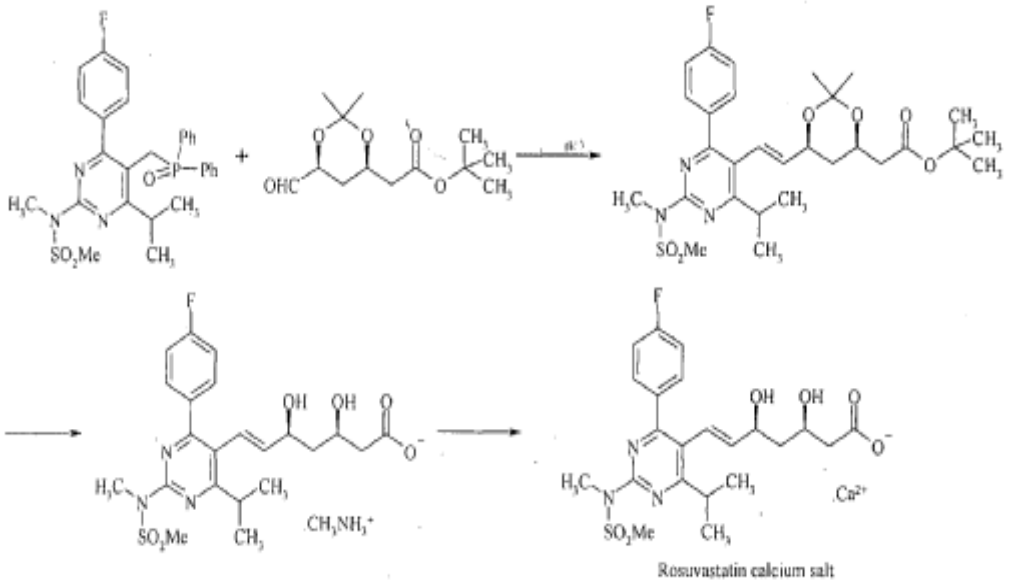
Describe a process for the preparation of pyramid derivative. as shown in scheme-.3




**Scheme-3**

### 3. US6844437 B1[10]

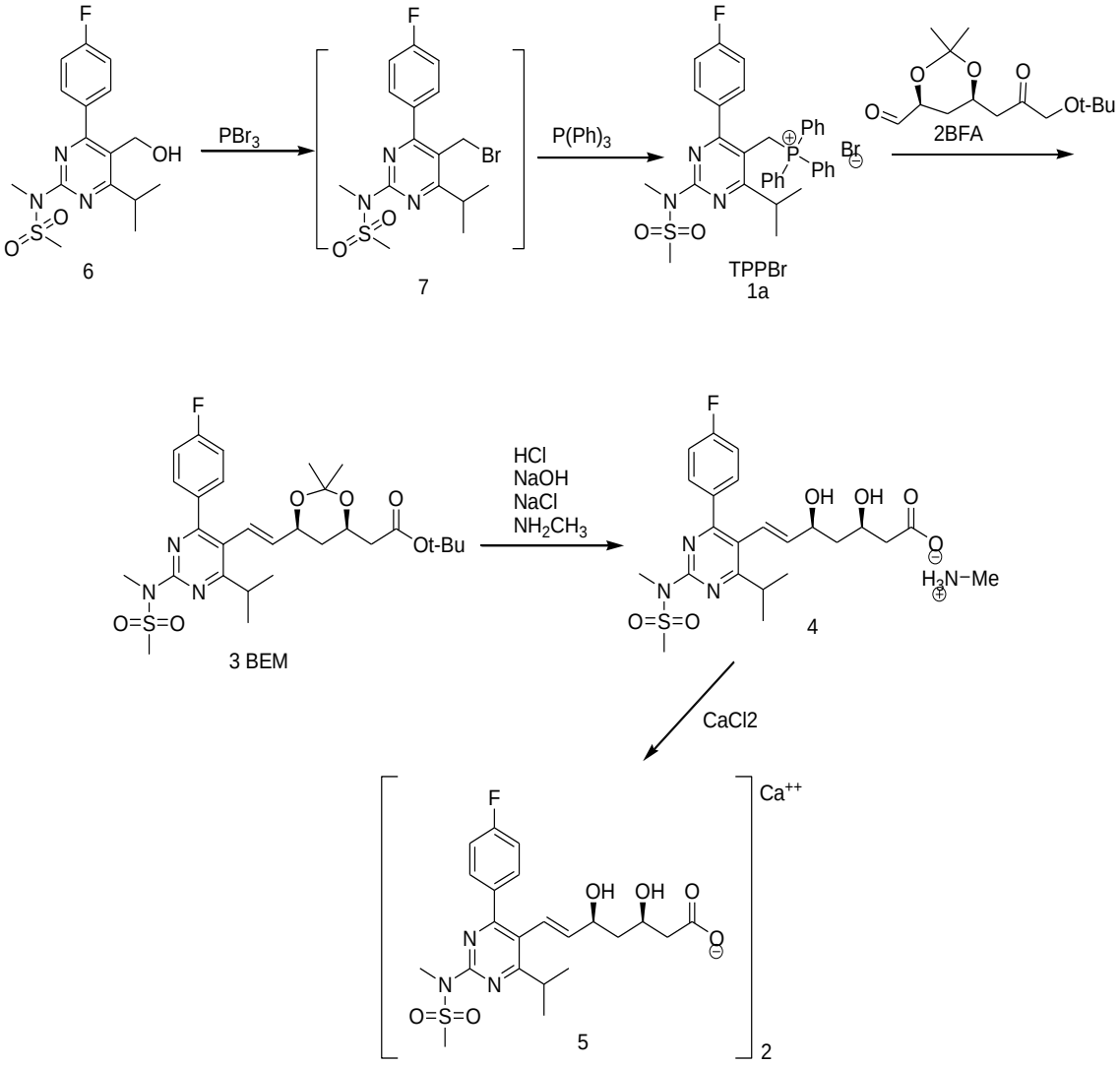
A process for the preparation of rosuvastatin calcium described in this method, the diphenyl phosphine oxide is coupled with an aldehyde in presence of a base to get the acetonide protected tert-butyl ester. The acetonide protecting group is then deprotection in an acidic medium and the tert-butyl group is hydrolyzed in a basic medium to get sodium salt is treated with methylamine to obtain a methyl ammonium salt of rosuvastatin. Rosuvastatin calcium is prepared from the methyl ammonium salt via its sodium salt as shown in scheme-.4.




**Scheme-4**

### 4. US7312329B2[11]

This process includes the steps of (a) reacting an alcohol of Formula 6 with $PBr_3$ to get bromide compound (7); (b) reacting the bromide intermediate (7) with $P(Ph)_3$to get the Wittig reagent TPPBr (1a); (c) reacting TPPBr (1a) with BFA (2) to form BEM (3); (d) treating the BEM (3) with hydrochloric acid, sodium hydroxide, sodium chloride and methylamine to obtained the methylammonium salt of rosuvastatin (4); and (e) reacting the methylammonium salt of rosuvastatin (4) with calcium chloride to get the calcium salt of rosuvastatin (5) as shown in scheme-.5.

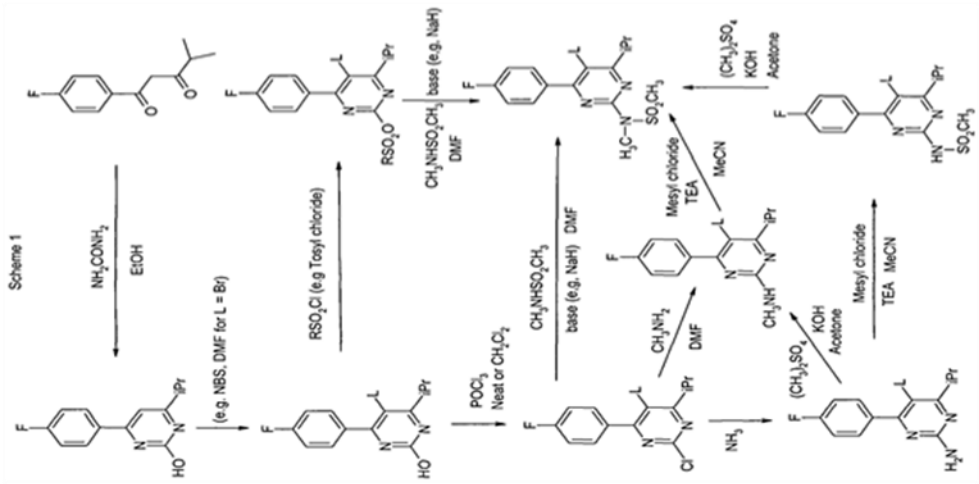



**Scheme-5**

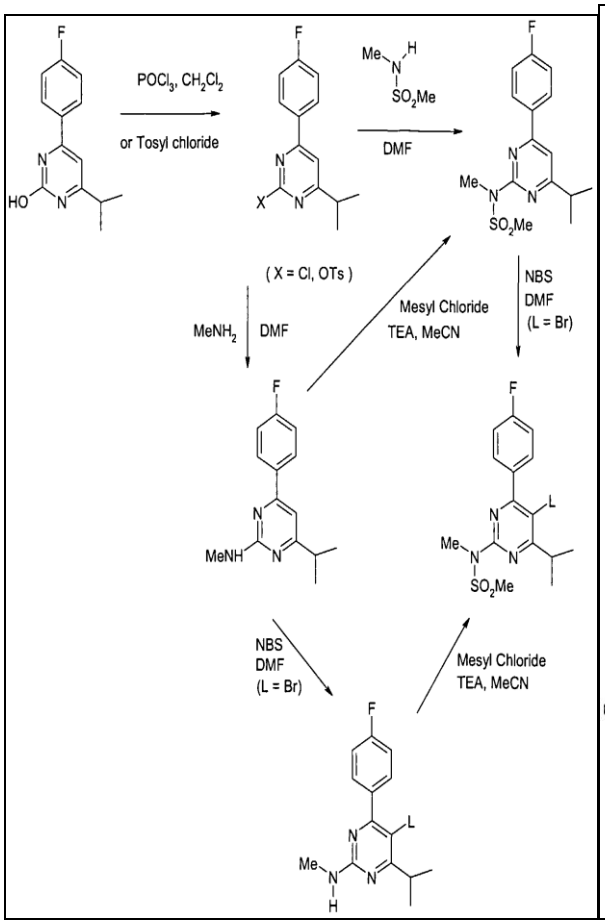
## 5. WO2006067456A2[12]

Starting materials of the formula II may be obtained, and conversion of a group Y into a group Z may be carried out, for example, as illustrated in the examples or as shown in Schemes 1 to 5 below, or by analogy therewith. It will be appreciated that when a compound of the formula II, wherein X is a group Y, is reacted with a compound of the formula III, then the intermediate obtained will include, for example, a compound as set out in Schemes 1 to 5 bearing the group -L, but in which the group -L is replaced by - CH=CH-A. The group Y may then be converted to the group $CH_3SO_2N(CH_3)$- using one or more of the synthetic chemical steps illustrated in Schemes 1 to 5. In Schemes 1 to 5 and elsewhere herein, the following abbreviations are used: as shown in scheme-.6.

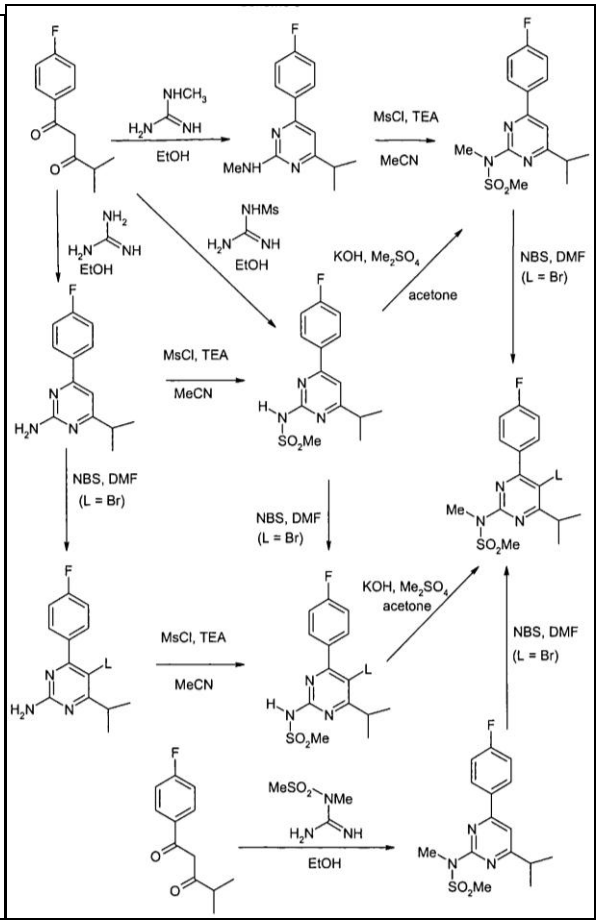
EtOH = ethanol; NBS = N-bromosuccinimide; DMF = N,N-dimethylformamide; TEA = triethylamine; MeCN = acetonitrile; MsCl = mesyl chloride; TsCl = tosyl chloride; OTs = tosyloxy; THF = tetrahydrofuran; IPA = isopropanol; DCM = dichloromethane NaH).



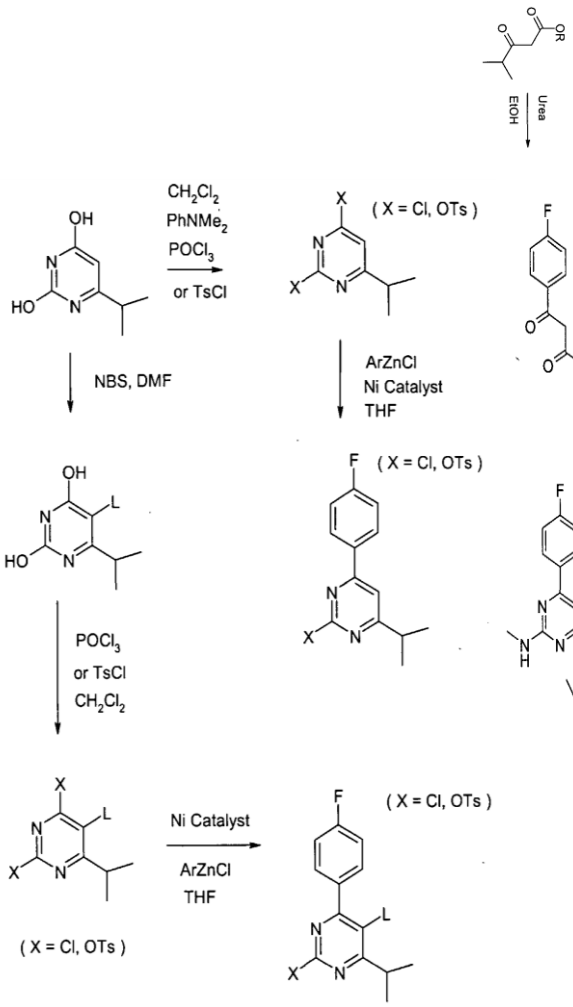
Scheme-6



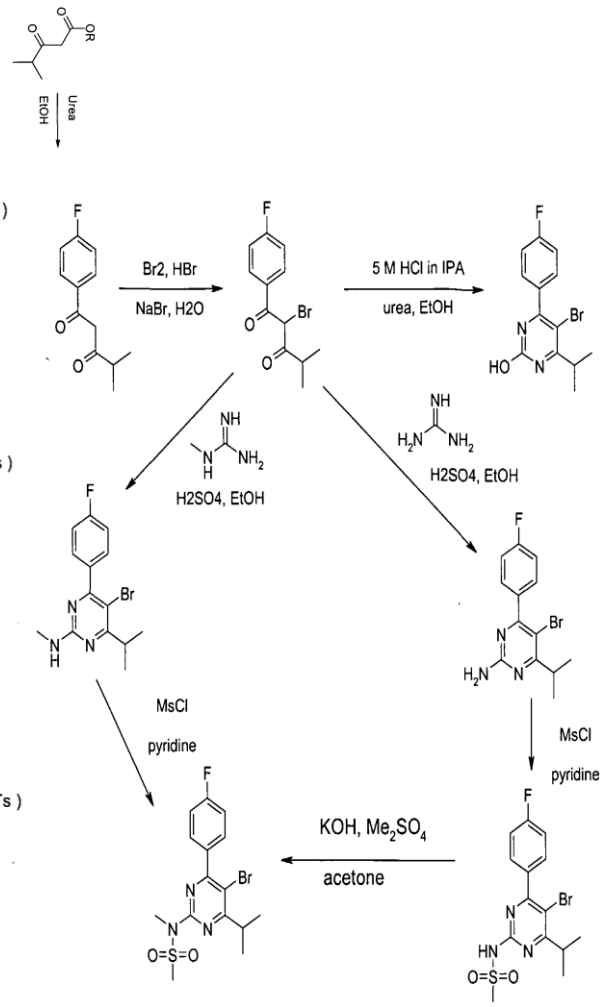
**Scheme-7**



**Scheme 8**



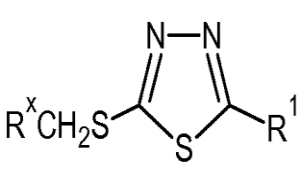
**Scheme 9**

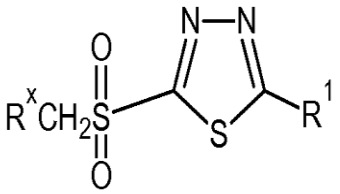


**Scheme-10**

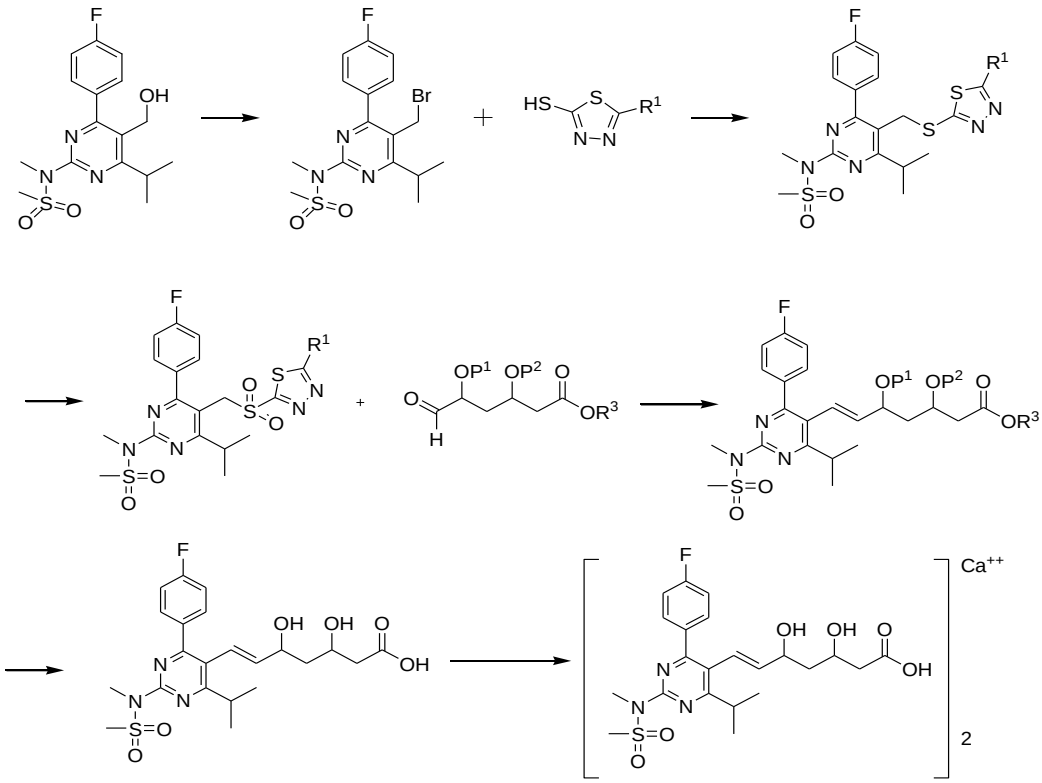
### 6. WO 2011132172 A1[13]

The present invention described a process for preparing novel intermediates of rosuvastatin calcium.





wherein, $R^1$ can be hydrogen, $C_1$-$C_4$ alkyl, halogen, nitro, hydroxy, or $C_1$-$C_4$ alkoxy; $R^x$ is a hydrophobic residue of HMG-CoA reductase inhibitors including as shown in scheme-11.,



**Scheme-11**

A. Ramu et al gave a oral route of drug administration is the most common and preferred method of delivery due to convenience and ease of ingestion. From a patient's perspective, swallowing a dosage form is a comfortable and a familiar means of taking medication.[14-16]

Debaditya Saha et al review here the Solid dispersions of Rosuvastatin calcium which prepared by employing starch-5-phosphate as carrier showed marked enhancement in the dissolution rate of Rosuvastatin calcium. Farther solid dispersions could be formulated into compressed tablets retaining their fast dissolution characteristics and fulfilling official standards. Thus starch-5-phosphate, a new modified starch was found to be a promising disintegrant in tablet formulations and can be used in the concentration of 5-10% as an effective disintegrant.[17]

Sarwar Beg and coworkers describes the systematic development and characterization of nanolipospheres (NLPs) loaded with phospholipid complex of rosuvastatin for enhanced oral drug absorption trough lymphatic pathways. The construction of Job's plot revealed 3:1 as the apt stoichiometric ratio for formation of complex between the drug and phospholipid.[18] Rosuvastatin calcium, (primarily referred to as rosuvastatin) is an antihyperlipidemic agent, which competitively inhibits the hydroxymethyl glutaryl coenzyme A (HMG-CoA) reductase

and decreases the biosynthesis of cholesterol[19] It is primarily indicated for treatment of dyslipidemia, hypercholesterolemia and hypertriglyceridemia like conditions.[20]

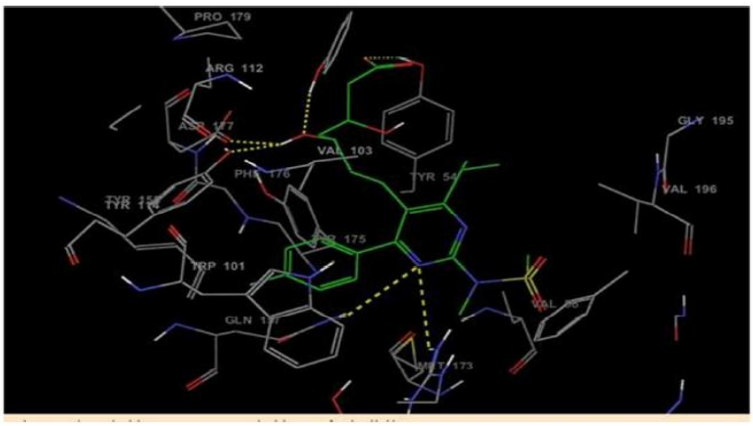



**Fig1-Molecular docking images depicting binding of rosuvastatin with phosphatidylcholine transfer protein.**

N. Dudhipala and K. Veerabrahma were made investigation to improve pharmacokinetic (PK) and pharmacodynamic (PD) effects of Rosuvastatin calcium (RC) by solid lipid nanoparticles (SLNs). RC is antihyperlipidemic drug with low oral bioavailability (20%) due to first-pass metabolism. Hot homogenization followed by ultrasonication method was used to prepare RC-SLNs with stearic acid, glyceryl behenate and glyceryl trilaurate as lipid matrices, egg lecithin and poloxamer 188 as surfactants. The prepared SLNs were tested for particle size, PDI, zeta potential (ZP), entrapment efficiency (EE), drug content and in vitro release. Further, PK and PD studies were conducted on selected SLNs.[21] Srinivasarao Koppala were identified by liquid chromatography –tandem mass spectrometry using electrospray ionization source and Q-trap mass analyzer (LC–ESI–QT/MS/MS) fig-2.[22]

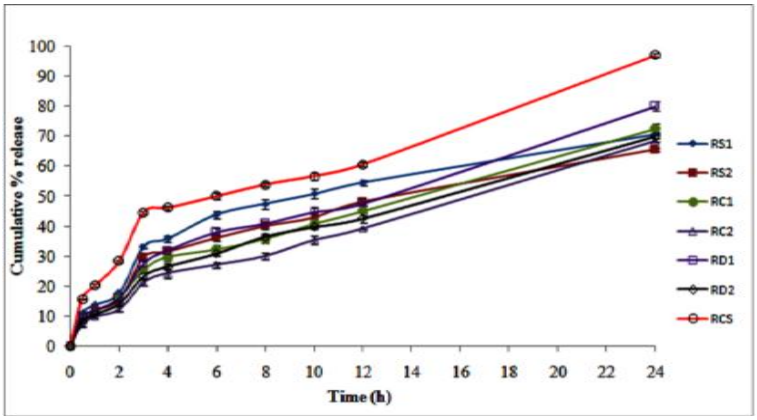
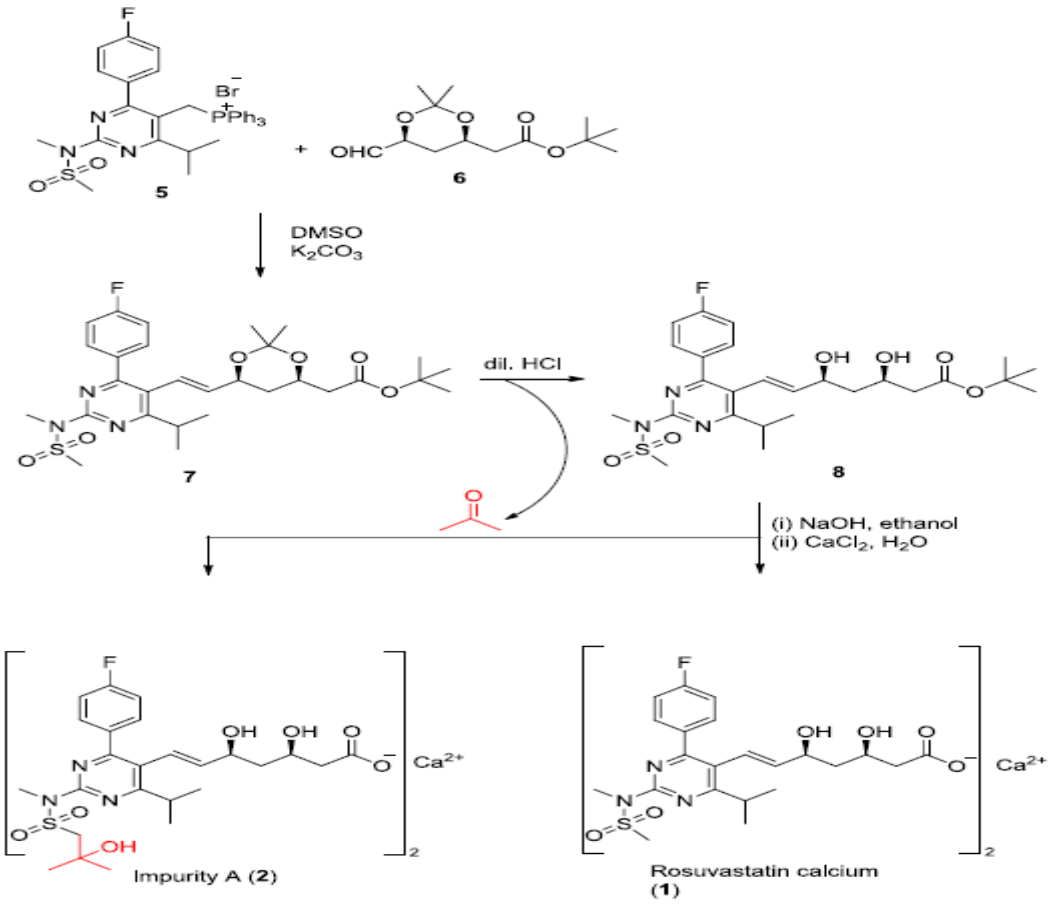



**Fig 3: In-vitro release profiles of rosuvastatin calcium from RC-SLNs and RCS in 0.1N HCl followed by pH 6.8 phosphate buffer (mean±SD, n=3).**

have made an effort towards the synthesis of Rosuvastatin calcium impurity A in overall 13.5% yield; which was successfully accomplished by a linear strategy utilizing bhydroxy sulfonamide formation, oxidation, Wittig reaction, deprotection followed by reduction and finally salt formation as shown in scheme-12.[23]




**Scheme-12**

Chamarthi R P Kishore and Dr.G.V. Krishna Mohan studied the precise, accurate, specific, linear, rugged and robust analytical method and developed and validated for estimation of process and degradant impurities of Rosuvastatin calcium (RSC) in Rosuvastatin calcium tablets. 150mm length column, 4.6mm diameter and 3.5µ particle size with C18 stationary phase and pH3.0 phosphate buffer as mobile phase.[24]

Doaa H. Alshora et al studied solubility of rosuvastatin calcium (ROSCa) in seven different neat solvents such as water, ethanol, 1-butanol, 2-butanol, ethylene glycol (EG), isopropyl alcohol (IPA) and propane-1,2-diol (PG) was measured at five different temperatures i.e. T = (298.15 to 318.15) K and atmospheric pressure. Values of the experimental solubility of

ROSCa were correlated with Apelblat and ideal models which showed good correlation and model fitting. The solubility (as mole fraction) of ROSCa was recorded highest in PG (1.89 10-2 at T = 318.15 K) followed by 1-butanol (8.20 . $10^{-4}$ at T = 318.15 K), ethanol (6.81 $10^{-4}$ at T = 318.15 K), IPA (5.66 . $10^{-4}$ at T = 318.15 K), EG (5.03 . $10^{-4}$ at T = 318.15 K), 2-butanol (1.08 . $10^{-4}$ at T = 318.15 K) and water (1.40 . $10^{-5}$ at T = 318.15 K).[25]

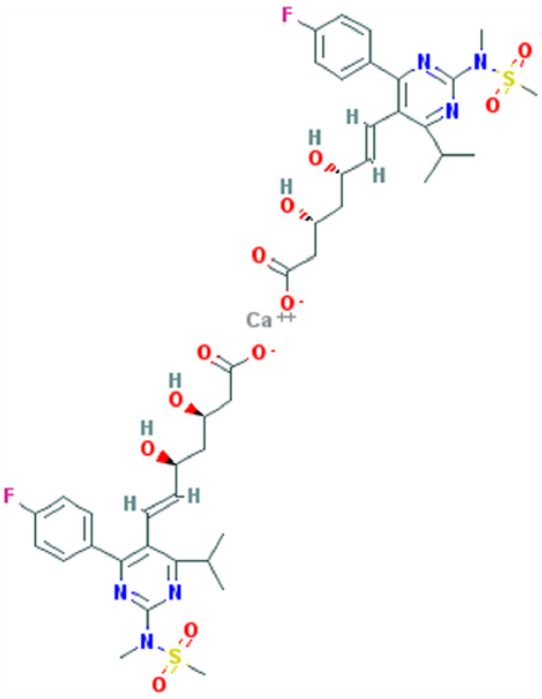
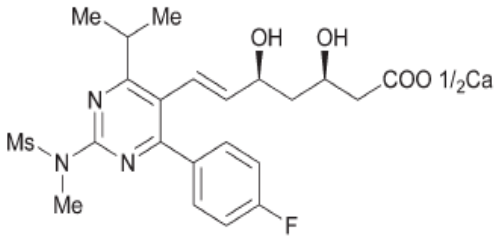


**Fig-4**

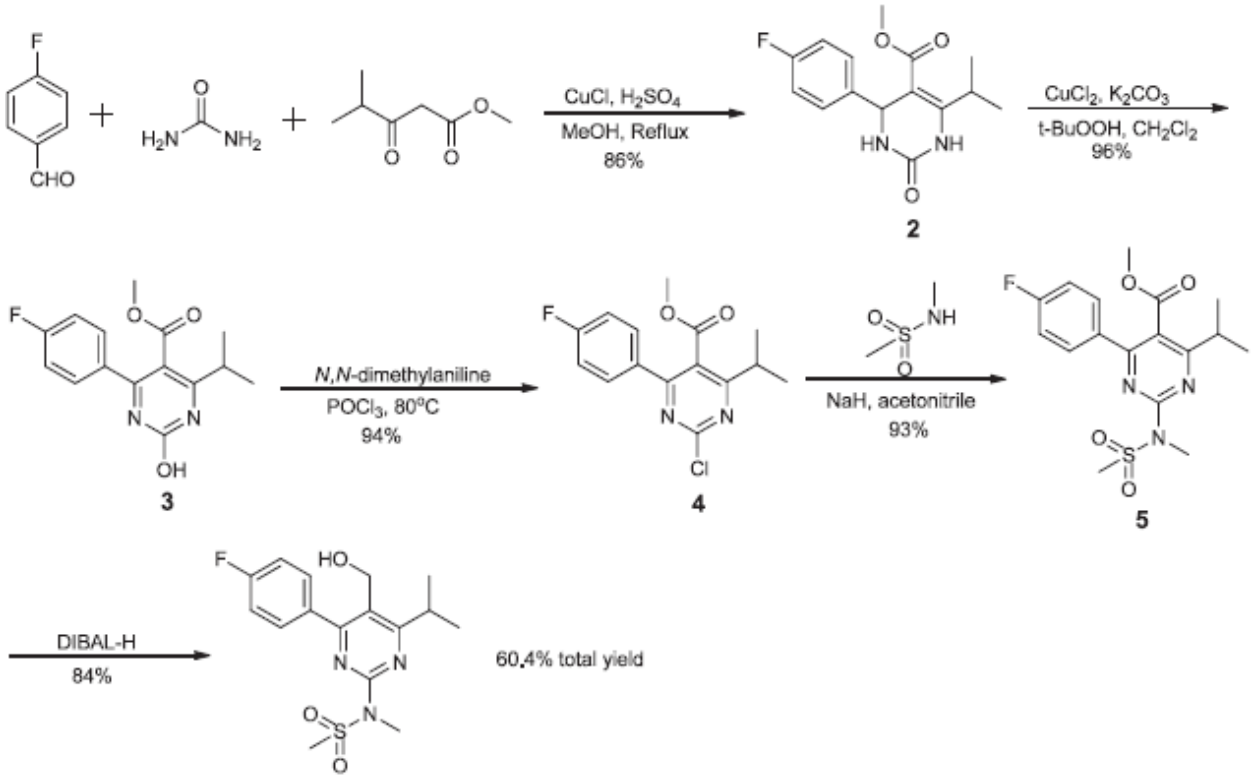
Fangjun Xiong et al gave synthesis of a novel, stereoselective approach towards rosuvastatin calcium from the known (S)-homoallylic alcohol. This synthesis is highlighted by a regio- and stereocontrolled ICl-induced intramolecular cyclization of chiral homoallylic carbonate to deliver the C6-formyl statin side chain with a syn- 1,3-diol moiety.[26]




Structure of rosuvastatin calcium (1).

**Fig-5**

A novel and efficient five-step synthetic route, including a Biginelli reaction, dehydrogenation, chlorination, sulfonamidation, and reduction, for the core of Rosuvastatin was established. All steps were systematically studied. Tert-butylhydroperoxide aqueous solution was applied in the dehydrogenation instead of nitric acid. N,N-dimethylaniline was employed as a catalyst to accelerate the chlorination proceeding smoothly, and its catalytic mechanism is discussed. In the sulfonamidation as shown in scheme-13.[27]




**Scheme-13.**

Mohamed El-Kassem M Hassouna and Hafsa Omar Salem developed new RP-HPLC method were validated for the determination of Rosuvastatin calcium (ROS-Ca) in pure and tablets dosage forms. The method is validated as per ICH guidelines and USP requirements for new methods, which include accuracy, precision, specificity, LOD, LOQ, robustness, ruggedness, linearity and range. Hence this RP-HPLC method is suitable for quality control of raw materials and finished products.[28]

N. Dudhipala, K. Veerabrahma used by solid lipid nanoparticles (SLNs).to improve pharmacokinetic (PK) and pharmacodynamic (PD) effects of Rosuvastatin calcium (RC) RC is antihyperlipidemic drug with low oral bioavailability (20%) due to first-pass metabolism. Hot homogenization followed by ultrasonication method was used to prepare RC-SLNs with

stearic acid, glyceryl behenate and glyceryl trilaurate as lipid matrices, egg lecithin and poloxamer 188 as surfactants.[29]

Voltammetric and liquid chromatographic (LC) methods have been developed for the simultaneous determination of amlodipine besylate (AML) and rosuvastatin calcium (ROS) for the first time. Detailed electrochemical behavior and simultaneous voltammetric determination of AML and ROS were investigated in detail using glassy carbon electrode (GCE). High-performance liquid chromatography (HPLC) and ultra-performance liquid chromatography (UPLC) were also developed for the comparison.[30] A.P. Rajput et have worked on Vilsmeier-Haack reaction for drugs containing Nitrogen centre.[32-34]

## CONCLUSION

Rosuvastatin Calcium originated as lifesaving drugs by reducing the risk of heart diseases, they are also known to produce minor side effects such as constipation, heartburn, dizziness, sleeplessness, depression, joint pain, cough, memory loss or forgetfulness, confusion. The current review article emphasizes broadly over several scalable approaches carried out toward the syntheses of Rosuvastatin drug which are commercially available in the market and this should serve the purpose for those who aspire to come out with cost effective, ecofriendly and robust alternative approaches towards synthesis of existing Rosuvastatin drugs. This article also provides a way forward for new insights in design and development of new upcoming Rosuvastatin drugs. There also a broad scope in the development of Rosuvastatin drugs and further research is needed to come out with new Rosuvastatin drug hybrids which can reduce the risk of cardiovascular disease with minimal or zero side effects, caused with their intake.

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