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Synthesis and characterization of Rosuvastatin calcium impurity A; a HMG-CoA reductase inhibitor

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ABSTRACT

During the process development for multistep synthesis of Rosuvastatin calcium several impurities were obtained along with the final Rosuvastatin calcium. Out of this; synthesis of impurity A (acetone adduct) a minor impurity of Rosuvastatin calcium (3*R*,5*S*,6*E*)-7-[4-(4-fluorophenyl)-2-[[(2-hydroxy-2-methylpropyl)sulfonyl(methyl)amino]-6-(1-methylethyl)-pyrimidin-5-yl]-3,5-dihydroxyheptenoicacid hemicalcium salt, is described. The synthesis of impurity A has been accomplished in 6 steps; starting from formation of β-hydroxy sulfonamide as the key intermediate and followed by using convenient routes with overall yield of 13.5%. The target compound can be used as the reference substance of impurity of the Rosuvastatin calcium.

Introduction

Cardiovascular disease is one of the major public health problems which cause death worldwide; the high accumulation of cholesterol is the main reason for such disease.[1] Statins are called as HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase inhibitor; this catalyzes the conversion of HMG-CoA to mevalonate in the metabolic pathway that controls cholesterol in the biosynthesis.[2] In general these classes of compounds were used for reduce low density lipoprotein cholesterol levels and increase high density lipoprotein cholesterol.[3] Rosuvastatin calcium (RST, **1**) [Crestor, (*S*-(*R*,*S*-(*E*)))-7-(4-(4-Fluorophenyl)-6-(1-methylethyl)-2-(methyl(methylsulfonyl)amino)-5-pyrimidinyl)-3,5-dihydroxy-6-heptenoic acid, calcium salt (Fig. 1)] is a HMG-CoA reductase inhibitor by AstraZeneca; one of the therapeutic group of statin family also generally called "blockbuster drugs" which is one of the top 5 selling drug in U.S. market[4] and used in the treatment of patients with dyslipidemia,[5] hypercholesterolemia,[6] and hypertriglyceridemia.[7] It is also called as super statins because of, Rosuvastatin calcium is most potent HMG-CoA reductase inhibitor among the all available statins in the market.[8]

The impurities associated with APIs are classified into three categories as per the ICH guidance such as organic impurities (process and drug related), inorganic impurities (inorganic salts, ligands, and catalysts) and residual solvents impurities (solvent used).[9] The presence of impurities in an active pharmaceutical ingredient (API) can have significant impact on the quality and safety of the drug products. To commercialize and get approval from regulatory for a drug substance it is very important the level of impurities present. As per regulatory requirement, it is mandatory to identify and characterize all the unknown impurities that are present in it at a level as low as 0.05%.[10]

During the analysis of the laboratory batches of Rosuvastatin calcium crude, three main impurities (A–C) were detected in HPLC with its area of percentage ranging around 1.2% were detected (Fig. 1). These impurities were reported in the European Pharmacopoeia[11]; i.e. the impurity A is acetone adduct, impurity B (**3**) and its enantiomer, and finally impurity C (**4**) and so on.[11,12] Although significant methods have been reported for the preparation of Rosuvastatin calcium,[13] very less attention was focused on their impurities.[14] Herein, we wish to report the synthesis and characterization of the impurity A (acetone adduct) a process impurity,[12] which is present at a level of 0.2% in the bulk drug of Rosuvastatin calcium.[11] This synthesis starting from the assembly of key intermediate β-hydroxy sulfonamide; which was achieved

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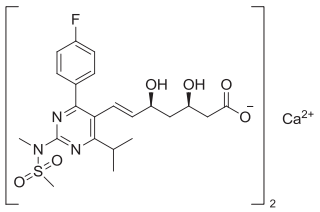
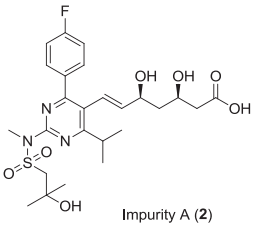
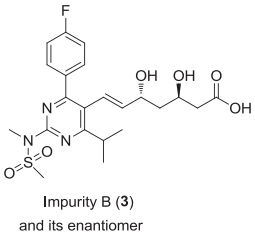






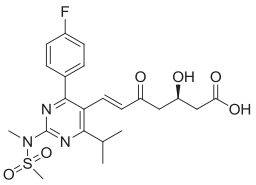
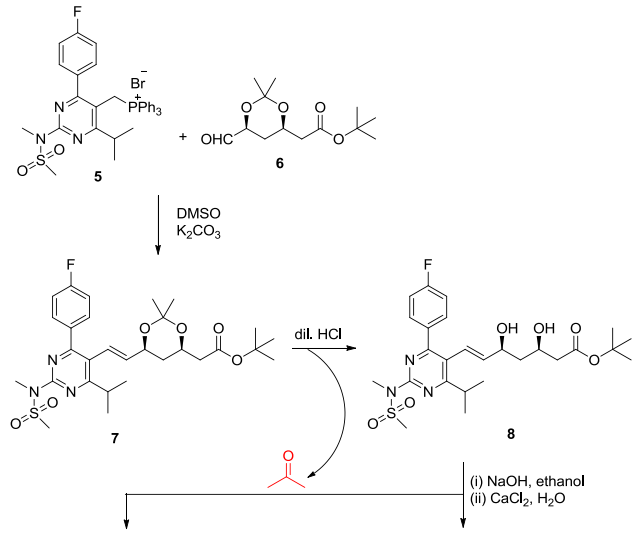


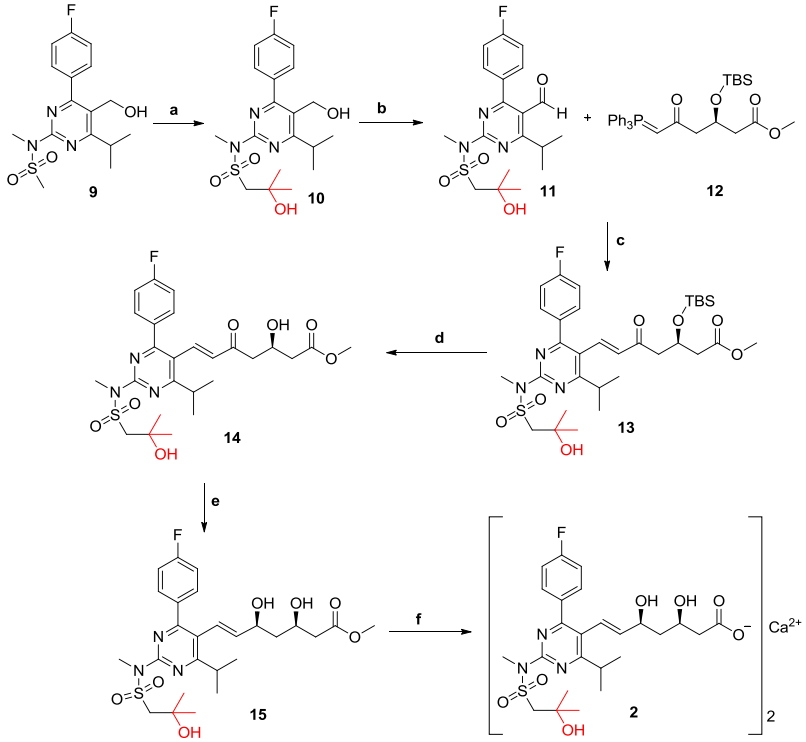
Fig. 1. Rosuvastatin calcium and its impurities.

from selective anionation at *N*-methylmethanesulfonamide followed by Aldol reaction with acetone.

Synthesis of Rosuvastatin calcium, one of the major method that utilized for the commercial purpose is the linear synthesis of Rosuvastatin calcium starting from commercially available materials **5** and **6** as outlined in Scheme 1. Synthetic sequence as follows Wittig reaction, followed by acetonide deprotection using mild acid condition delivered the dihydroxyester **7**. Then base mediated hydrolysis of ester followed by salt formation using calcium chloride delivered the final compound (**1**). We assumed that during the deprotection of acetonide **7** produces the by-product acetone



Scheme 1. Commercial method for the synthesis of Rosuvastatin calcium (**1**).



Scheme 2. Preparation of Rosuvastatin calcium impurity A (**2**). Reaction conditions: (a)16 2.0 M LDA in THF, acetone, THF, −10 °C, 4.5 h; (b) MnO_2, MC, reflux, 40 h; (c) ACN, reflux, 23 h; (d)17 HCl, H_2O, THF, r.t., 18 h; (e)17 1.0 M diethylmethoxyborane in THF, $NaBH_4$, THF, MeOH, −40 °C, 2 h; (f) i) NaOH, THF, H_2O, 25 °C, 1 h, ii) $CaCl_2{\cdot}2H_2O$, H_2O, 0–10 °C, 1 h.