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Process for the purification of Latanoprostene Bunod

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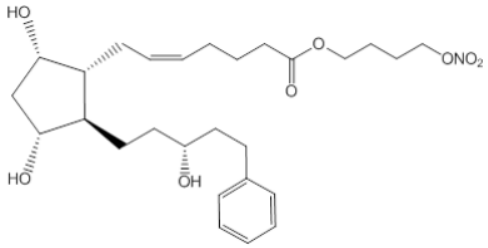
Latanoprostene bunod is chemically known as s 4-(Nitrooxy)butyl (5Z)-7-{(1R,2R,3R,5S)-3,5-dihydroxy-2-[(3R)-3-hydroxy-5-phenylpentyl]cyclopentyl}hept-5-enoate and it is a prostaglandin analog indicated for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension and which is approved the under the brand name of Vyzulta®. The chemical structure Latanoprostene bunod is as follows:



Latanoprostene bunod is an oil and its impurities cannot be removed by crystallization purification, but might be removed by chromatography.

Latanoprostene bunod preparation is described in various literatures like WO2005068421, WO2017093771, WO2019031774 and US11332433B2 but none of them provides a process of preparative HPLC purification of Latanoprostene bunod.

The present article provides an efficient purification of Latanoprostene bunod by preparative HPLC.

The intermediate (3aR,4R,5R,6aS)-4-((R)-3-hydroxy-5-phenylpentyl)-5-((triethylsilyl)oxy)hexahydro-2H-cyclopenta[b]furan-2-ol used in the article is prepared by methods known in the literature for example by the method reported in 789/CHE/2012.

Example-1: Preparation of Latanoprostene bunod

Potassium tertiary butoxide (24 g) and dried 4-carboxybutyl triphenyl phosphonium bromide (47.4 g) were added to tetrahydrofuran (150 ml) at 25-30°C and stirred at the same temperature. Cooled the reaction mixture to 0-5°C. A solution of (3aR,4R,5R,6aS)-4-((R)-3-hydroxy-5-phenylpentyl)-5-((triethylsilyl)oxy)hexahydro-2H-cyclopenta[b]furan-2-ol (15 g) in tetrahydrofuran (30 ml) was added and stirred at the same temperature. Water, ethyl acetate and aqueous sodium bisulfate solution added to the reaction mixture at 0-10°C, raised the temperature to 25-30°C and stirred at the same temperature. Separated the both organic and aqueous layers and aqueous layer was extracted with ethyl acetate. Combined the organic layers and dried over sodium sulphate solution. Distilled off the solvent completely from the organic layer to get the (Z)-7-((1R,2R,3R,5S)-3,5-dihydroxy-2-((R)-3-hydroxy-5-phenylpentyl)cyclopentyl)hept-5-enoic acid. Acetone (150 ml), potassium carbonate (29.56

g) and 4-bromobutyl nitrate (21.18 g) were added to the obtained (Z)-7-((1R,2R,3R,5S)-3,5-dihydroxy-2-((R)-3-hydroxy-5-phenylpentyl)cyclopentyl)hept-5-enoic acid compound at 25-30°C. Heated the reaction mixture to reflux temperature and stirred at the same temperature. Cooled the reaction mixture to 25-30°C, filtered and washed with acetone. Distilled off solvent completely from filterate. Ethyl acetate and water were added to the obtained compound at 25-30°C and stirred at the same temperature. Separated the both organic and aqueous layers and aqueous layer is extracted with ethyl acetate. Combined the organic layers, washed with water and dried over sodium sulphate solution. Distilled off the solvent completely from organic layer to get crude Latanoprostene bunod. Crude Latanoprostene bunod is purified by silica gel column chromatography by eluting with methyl tertiary butyl ether and acetone as a eluents.

Yield: 4.5 g; Purity by HPLC: 98.22%.

Example-2: Purification of Latanoprostene bunod by preparative HPLC {High performance liquid chromatography

Crude Latanoprostene bunod dissolved in acetonitrile: methanol (85: 15) was purified on preparative HPLC column was packed with DAC Chiral pak-IF 250x50 mm 10.0µ (manual filled) using acetonitrile: methanol (85:15) (as mobile phase) by isocratic elution method.The fractions were collected and purity of fractions were monitored by HPLC. Collected the pure fractions and distilled off the solvent completely. Dissolved the obtained compound in methanol (30 ml) at 25-30°C, filtered and distilled off the solvent to get the pure Latanoprostene bunod.

Yield: 3 g; Purity by HPLC: 99.77%.

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