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ARTICLE

Synthesis and Characterization of Deshydroxy Posaconazole

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ABSTRACT

Posaconazole is a triazole antifungal drug and used for the treatment of infections caused by fungai. During the process development of posaconazole, the process related impurity deshydroxy posaconazole was identified as a critical impurity along with the final active pharmaceutical ingredient. The present work describes the synthesis and characterization of this deshydroxy posaconazole.

KEYWORDS

ICH, Antifungal, Impurity, Posaconazole.

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INTRODUCTION

A general scheme is set for the estimation of the impurities in bulk drug substances by the rational use of chromatographic, spectroscopic and analytical techniques. The various parameters to be fulfilled in an impurity profiling of drug substances are discussed. Impurity is defined as any substance coexisting with the original drug, such as starting material or intermediates or these formed, due to any side reactions. The presence of these unwanted chemicals, even in small amounts, may influence the efficacy and safety of pharmaceutical products. Impurity profiling (*i.e.*, the identity as well as the quantity of impurity in the pharmaceuticals), is now gaining critical attention from regulatory authorities. The different pharmacopoeias, such as British Pharmacopoeia (BP), United States Pharmacopeia (USP) and Indian Pharmacopoeia (IP) are slowly incorporating limits for allowable levels of impurities present in active pharmaceutical ingredients or formulations.

The process-related impurities in an active pharmaceutical ingredient (API) can have a significant impact on the quality and safety of drug products. The impurity levels in any drug substance are described as per its biological or toxicological data. It is quite important for "regulatory" aspect of drug approval to provide limitation of "related impurities." Therefore, it is necessary to study the impurity profile of any active pharmaceutical ingredient and control it during the manufacturing of a drug product. As per the ICH guidelines, impurities which are forming at a level of ≥ 0.10 % with respect to the active pharmaceutical ingredient should be identifed, synthesized and characterized thoroughly [1,2].

Posaconazole (POSA) 4-(4-(4-(4-(((3*R*,5*R*)-5-(2,4-difluorophenyl)-5-(1,2,4-triazol-1-ylmethyl)oxolan-3-yl)methoxy)phenyl)piperazin-1-yl)phenyl)-2-((2*S*,3*S*)-2-hydroxypentan-3-yl)-1,2,4-triazol-3-one (Fig. 1) is a triazole antifungal drug [3]. It is marketed in the United States, the European Union and in other countries by Schering-Plough under the trade name Noxafil [4]. In Canada, posaconazole is marketed by Schering-Plough under the trade name Posanol. It is used to treat invasive infections by *Candida* species, *Mucor* and *Aspergillus* species in severely immuno-compromised patients [5,6].

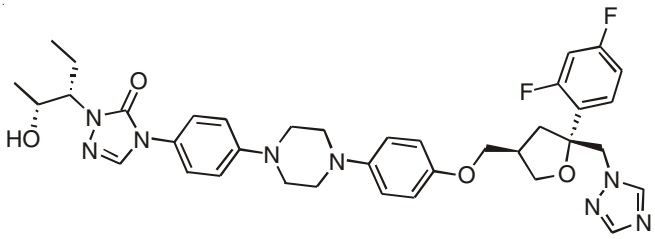


Fig. 1. Structure of posaconazole

In the synthesis of posaconazole, the process related impurities are identified by RA Chem pharma limited and they are 2-((2R,3S)-2-(benzyloxy)pentan-3-yl)-4-(4-(4-(4-hydroxyphenyl)piperazin-1-yl)phenyl)-2H-1,2,4-triazol-3(4H)-one or hydroxy triazole (Fig. 2), ((3S,5R)-5-((1H-1,2,4-triazol-1-yl)methyl)-5-(2,4-difluorophenyl)-tetrahydrofuran-3-yl)methyl 4-methylbenzenesulfonate or tosylated compound (Fig. 3), 4-(4-(4-(4-(((3R,5R)-5-((1H-1,2,4-triazol-1-yl)methyl)-5-(2,4-difluorophenyl)-tetrahydrofuran-3-yl)methoxy)phenyl)-piperazin-1-yl)phenyl)-2-(pentan-3-yl)-2H-1,2,4-triazol-3(4H)-one or deshydroxy posaconazole (Fig. 4), 2-((2R,3S)-2-hydroxypentan-3-yl)-4-(4-(4-(4-hydroxyphenyl)piperazin-1-yl)phenyl)-2H-1,2,4-triazol-3(4H)-one or debenzylated hydroxytriazole (Fig. 5) and 4-(4-(4-(4-(((3R,5R)-5-((1H-1,2,4-triazol-1-yl)methyl)-5-(2,4-difluorophenyl)-tetrahydrofuran-3-yl)methoxy)phenyl)piperazin-1-yl)phenyl)-2-((2R,3S)-2-(benzyloxy)pentan-3-yl)-2H-1,2,4-triazol-3(4H)-one or benzylated posaconazole (Fig. 6). The purpose of this work is for determining the impurities of posaconazole to ensure the quality, efficacy and safety of the active ingredient and final pharmaceutical formulation [7]. Among the five process related impurities, the deshydroxy posaconazole impurity was identified as a critical impurity and it was formed in the synthesis of posaconazole active pharmaceutical ingredient at the time of debenzylation reaction under acidic conditions.

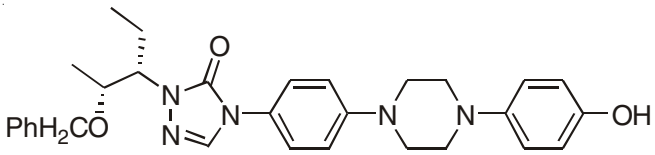


Fig. 2. Hydroxy triazole

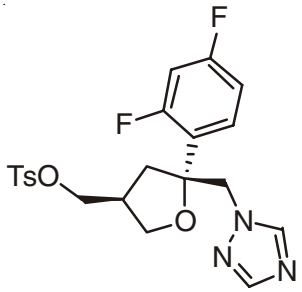


Fig. 3. Tosylated compound

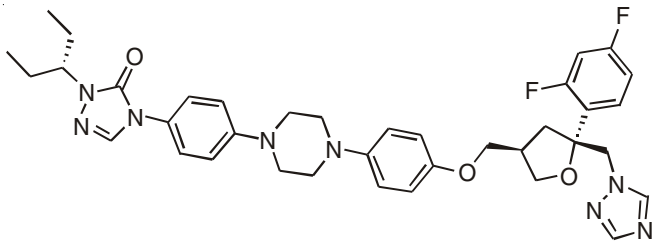


Fig. 4. Deshydroxy posaconazole

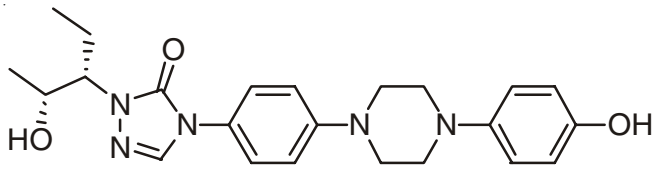


Fig. 5. Debenzylated hydroxy triazole

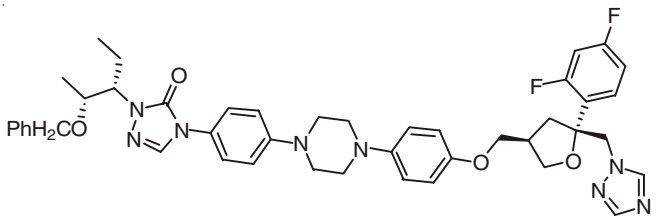


Fig. 6. Benzylated posaconazole

Sources of impurities

Hydroxy triazole: It is one of the key intermediates in the synthesis of posaconazole.

Tosylated compound: It is one of the key intermediates in the synthesis of posaconazole.

Bezylated posaconazole: It is the precursor for posaconazole active pharmaceutical ingredient. According to the literature [8], it was prepared by the reaction the hydroxy triazole compound with tosyled compound under basic conditions.

Debenzylated hydroxy triazole: If any unreacted hydroxy triazole compound is present in the benzylated posaconazole, it will further form debenzylated hydroxy triazole during the debenzylation reaction.

Deshydroxy posaconazole: It is one of the critical impurities in posaconazole active pharmaceutical ingredient. During the synthesis of posaconazole, acidic reagents (like HCl, formic acid and methane sulfonic acid *etc*.) were used for debenzylation reaction under hydrogenation condition. Due to this acidic condition under pressure dehydroxylation will happen to form the deshydroxy posaconazole impurity. It can be eliminated by using purification techniques.

The present article describes a simple and facile synthesis for deshydroxy posaconazole impurity. This may serve as a standard for impurity profiling in drug development.

EXPERIMENTAL

All ^{1}H NMR spectra were recorded on 400 MHz Bruker FT-NMR spectrometers. All chemical shifts are given as δ value with reference to tetramethyl silane as an internal standard. The chemicals and solvents were purchased from commercial suppliers and used without further purification.

Pentan-3-ol (2): To a stirred solution of 3-pentanone **(1)** (100 g, 1.16 mol) in methanol (200 mL) was added sodium borohydride (44 g, 1.16 mol) at 0-5 °C in 2-3 h. After completion of the addition, reaction mixture was allowed to warm up to 25-30 °C and the stirring was continued for 2-3 h at same temperature. After completion of the reaction, the reaction mass was poured in to ice water and extracted with dichloromethane (3 × 100 mL), total organic layer was washed with water, dried over sodium sulfate and evaporated to get 90 g of 3-pentanol (yield: 87.94 %), as a light pale yellow liquid.

Pentan-3-yl-4-methylbenzenesulfonate (3): To a stirred solution of 3-pentanol **(2)** (90 g, 1.02 mol) in pyridine (180 mL) was added catalytic amount of DMAP and *p*-toluene sulfonyl chloride (195 g, 1.02 mol) at 0-5 °C. After completion of the addition, the reaction mixture was allowed to warm up to 25-30 °C and the stirring was continued for 8-10 h at same temperature. After completion of the reaction, the reaction mass was diluted with water and extracted with dichloromethane (3 × 100 mL), total organic layer was washed with water, dried over sodium sulfate and evaporated to get crude compound. The crude product was crystallized in *n*-hexane to afford 125 g of pentan-3-yl 4-methylbenzenesulfonate (yield: 50.52 %), as a light pale yellow low melting solid.

4-(4-(4-(4-Methoxyphenyl)piperazin-1-yl)phenyl)-2-(pentan-3-yl)-2H-1,2,4-triazol-3(4H)-one (5): To a stirred solution of 4-(4-(4-(4-methoxyphenyl)piperazin-1-yl)phenyl)-2H-1,2,4-triazol-3(4H)-one (4) (50 g, 0.142 mol) in dimethyl sulfoxide (200 mL) was added potassium carbonate (40 g, 0.284 mol) and after 0.5 h pentan-3-yl 4-methylbenzenesulfonate (**3**) (52 g, 0.213 mol) then potassium iodide (12 g, 0.07 mol) was added at room temperature. After addition the reaction mixture was slowly heated to 80-85 °C and stirring continued for 50-60 h at the same temperature and progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mass was cooled to room temperature, diluted with water, extracted with chloroform (3 × 50 mL), total organic layer was washed with water, dried over sodium sulfate and evaporated to get crude compound. The crude product was purified by column chromatography to afford 30 g of 4-(4-(4-(4-methoxyphenyl) piperazin-1-yl) phenyl)-2-(pentan-3-yl)-2H-1,2,4-triazol-3(4H)-one (yield: 53.35 %), as a light brown solid.

4-(4-(4-(4-Hydroxyphenyl)piperazin-1-yl)phenyl)-2-(pentan-3-yl)-2H-1,2,4-triazol-3(4H)-one (6): To a stirred solution of 4-(4-(4-(4-methoxyphenyl)piperazin-1-yl)phenyl)-2-(pentan-3-yl)-2H-1,2,4-triazol-3(4H)-one (5) (20.0 g, 0.049 mol) was added 50 % aq-HBr (200 mL) at room temperature. After addition the reaction mixture was slowly heated to 90-100 °C, stirring continued for 5-6 h at the same temperature and progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mass was cooled to room temperature and stirring continued for 1-2 h at room temperature to get a precipitate. The precipitate was filtered, further slurried in water and dried to afford 14 g of 4-(4-(4-(4-hydroxyphenyl) piperazin-1-yl) phenyl)-2-(pentan-3-yl)-2H-1,2,4-triazol-3(4H)-one (yield: 72.42 %), as a off-white solid.

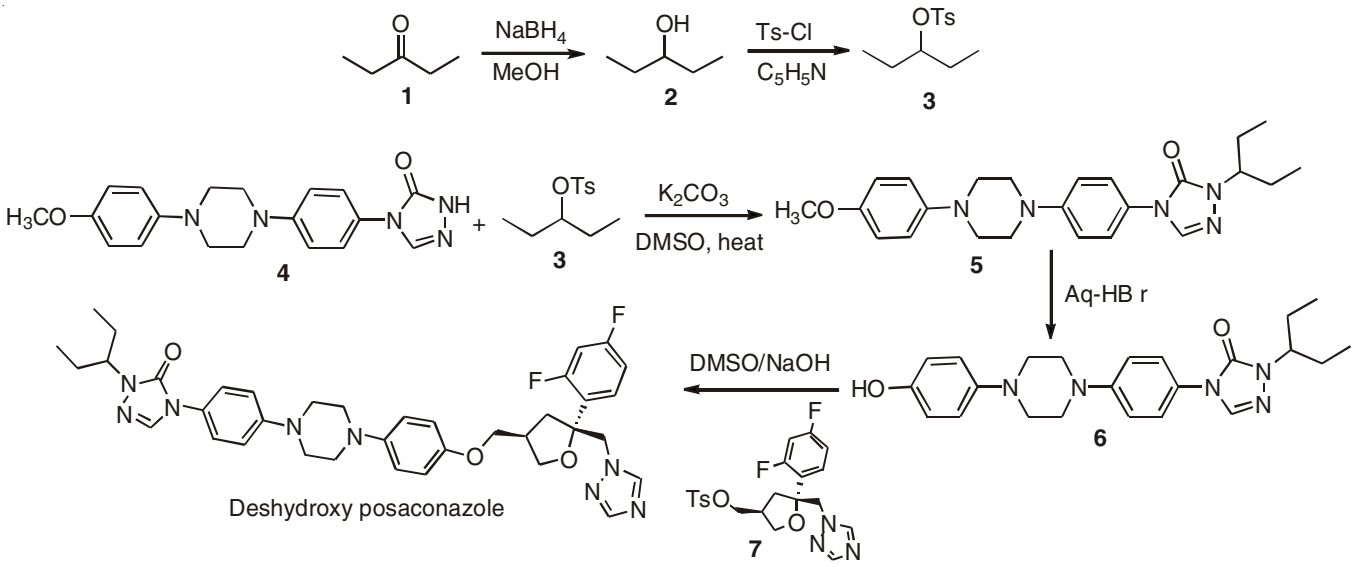
4-(4-(4-(4-(((3R,5R)-5-((1H-1,2,4-Triazol-1-yl)methyl)-5-(2,4-difluorophenyl)tetrahydrofuran-3-yl)methoxy)-phenyl)piperazin-1-yl)phenyl)-2-(pentan-3-yl)-2H-1,2,4-triazol-3(4H)-one or deshydroxy posaconazole (7): To a stirred solution of aqueous sodium hydroxide (2.0 g, 0.049 mol, in 5 mL water) in DMSO (100 mL) was added 4-(4-(4-(4-hydroxyphenyl) piperazin-1-yl) phenyl)-2-(pentan-3-yl)-2H-1,2,4-triazol-3(4H)-one (6) (10 g, 0.024 mol) and ((3S,5R)-5-((1H-1,2,4-triazol-1-yl)methyl)-5-(2,4-difluorophenyl)tetrahydrofuran-3-yl) methyl 4-methylbenzenesulfonate **(7)** (13 g,0.029 mol) at room temperature. After completion of the addition, the reaction mixture was slowly warmed to 40-45 °C and maintained for 20-24 h at this temperature till the reaction was completed (reaction was monitored by TLC). After completion of the reaction, the reaction mixture was cool to 25-30 °C, water was added (100 mL) and stirred for 2-3 h at 25-30 °C. The obtained solid was filtered and recrystallized in methanol to afford 7 g of deshydroxy posaconazole, as an off-white solid (yield: 41.66 % with HPLC purity: 98 %). ^{1}H NMR ($CDCl_3$): δ 8.11 (s, 1H), 7.99 (s, 1H), 7.64 (s, 1H), 7.46-7.34 (m, 3H), 7.03 (d, *J* = 9.0 Hz, 2H), 6.94-6.76 (m, 6H), 4.67-4.49 (m, 2H), 4.15-4.01 (m, 2H), 3.80-3.59 (m, 3H), 3.37-3.34 (m, 4H), 3.24-3.21 (m, 4H), 2.65-2.51 (m, 2H), 2.11-2.04 (m, 1H), 1.88-1.70 (m, 4H), 0.88 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR ($CDCl_3$): 10.20, 26.80, 37.54, 38.90, 50.67, 56.01, 58.85, 69.02, 70.81, 84.12, 104.66, 111.47, 115.21, 116.68, 118.52, 123.49, 125.50, 126.03, 128.68, 134.04, 144.60, 145.84, 151.10, 153.06, 157.48, 160.75, 161.23, 164.54. IR (KBr, ν_{max}, cm^{-1}): 3443.71, 3127.48, 2965.32, 2829.21, 1615.46, 1553.62, 1452.07, 1229.88, 1136.84, 1009.16, 786.19, 491.47, 464.73. Mass: (*m/z*)-685.1 (M+H peak).

RESULTS AND DISCUSSION

The overall synthesis of deshydroxy posaconazole was carried out through the following route of synthesis (**Scheme-I**). 3-Pentanone **(1)** was reduced with sodium borohydride to afford 3-pentanol **(2)** which was further reacted with *p*-toluene sulfonyl chloride to give the corresponding tosyl derivative **(3)**. The tosyl derivative was reacted with methoxy triazole compound **(4)** to afford the corresponding triazole alkylated derivative **(5)**, which was demethylated by using aqueous HBr to give the phenolic compound **(6)**. The phenolic compound **(6)** was reacted with tosyl derivative **(7)** under basic conditions to afford deshydroxy posaconzole. The obtained deshydroxy posaconazole structure was confirmed by ^{1}H NMR, ^{13}C NMR, IR and mass spectra.

Conclusion

The possible process-related impurity (deshydroxy posaconazole) of posaconazole was synthesized and confirmed by the characterization tools such as HPLC, ^{1}H NMR, ^{13}C NMR, IR and mass spectra.



Scheme-I: Deshydroxy posaconazole route of synthesis

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