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A Convenient Method for the Preparation of Losartan Active Metabolite (EXP-3174)

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Losartan is an angiotensin antagonist with a 5-carboxylate active metabolite (EXP-3174). This active metabolite is the result of the oxidation of 5-hydroxymethyl group to the corresponding 5-carboxyl group in liver. The active metabolite (EXP-3174) is important in pharmacological and biopharmaceutical studies of parent drug. Therefore, a convenient two steps procedure has been developed based on the oxidation of hydroxymethyl group of losartan to aldehyde and subsequent oxidation to carboxylate using different oxidizing reagents. H_2O_2-KOH reagent was found the most convenient and efficient method.

Key Words: Synthesis, Losartan active metabolite, EXP-3174, Oxidation.

INTRODUCTION

Losartan is an angiotensin II type 1 receptor antagonist that inhibits the actions of angiotensin II on the renin-angiotensin-aldosterone system. The renin-angiotensin system (RAS) plays an important role in the pathogenesis of heart failure and hypertension. Angiotensin II type 1 receptor antagonists (angiotensin receptor blockers) are highly effective in reducing blood pressure, exhibit renoprotective properties and have placebo-like tolerability[1].

After oral administration, losartan is mainly converted to an active metabolite EXP-3174 (**Scheme-I**). This active metabolite is the consequences of the oxidation of 5-hydroxymethyl group to the corresponding 5-carboxaldehyde (EXP-3179) and finally 5-carboxylic acid group. The isoenzymes of cytochrome P450 in liver are responsible for metabolism and conversion of losartan to its major active metabolite. The EXP-3174 metabolite of losartan is 10 to 40 times more potent than its parent compound and the most of the pharmacological activity of losartan relates to this metabolite[2]. On the other hand, 5-carboxaldehyde metabolite (EXP-3179) is responsible for antiinflammatory and antiaggregatory activities of losartan[3].

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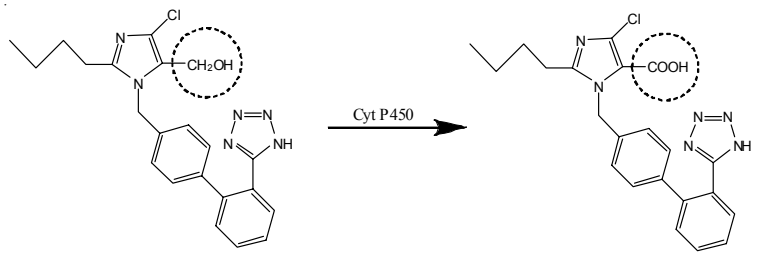


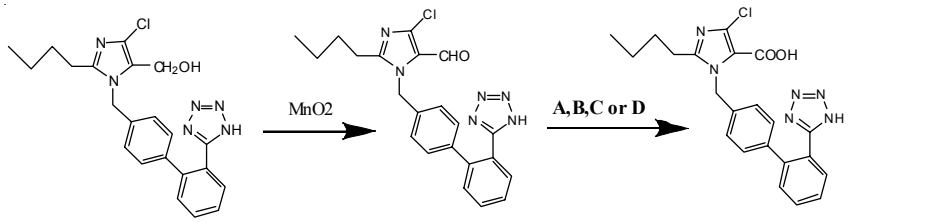
Losartan **EXP-3174**

Scheme-I: Metabolism of losartan in liver and conversion to its active metabolite EXP-3174

Since the EXP-3174 is important in pharmacological and biopharmaceutical studies of losartan[4] and there are several reports on determination of losartan and its metabolites[5,6]. We have developed a convenient two steps procedure for preparation of EXP-3174 through its carboxaldehyde intermediate (EXP-3179), using MnO_2 and subsequent oxidation to carboxylate using different oxidizing reagents. The aldehyde intermediate is also a useful reagent for preparation of the biologically active compounds[7,8].

EXPERIMENTAL

Losartan was used as starting material for all experiments and the target compound EXP-3174 was synthesized through the 5-carboxaldehyde intermediate. The 5-carboxaldehyde intermediate was prepared using the mild oxidizing agent, MnO_2[9-11]. Subsequent oxidation of aldehyde to the corresponding 5-carboxylate was performed by oxidation of the aldehyde with other reagents such as silver nitrate[12], hydrogen peroxide[13], oxone[14-16] and Pd/C[17] (**Scheme-II**).



Losartan **Losartan 5-carboxaldehyde (EXP-3179)** **Losartan 5-carboxylic acid (EXP-3174)**

Procedure	Reagents	Time (h)	Solvent	Yield (%)
A	$AgNO_3$	1.0	H_2O	51
B	H_2O_2, KOH	0.5	MeOH	71
C	Oxone	5.0	DMF	65
D	Pd/C, $NaBH_4$, KOH, air	Overnight	MeOH/H_2O	57

Scheme-II: Synthesis of active metabolite of losartan using different oxidizing reagents

The purity of the synthesized compounds was confirmed by thin layer chromatography using various solvents of different polarities. Merck silica gel 60 F_{254} plates were applied for analytical TLC. Column chromatography was performed on Merck silica gel (70-230 mesh). ^{1}H NMR spectra were measured using a Bruker 500 spectrometer and chemical shifts are expressed as δ (ppm) with tetramethylsilane as internal standard. Melting points were determined on a Kofler hot stage apparatus and are uncorrected. The mass spectra were run on a Finigan TSQ-70 spectrometer (Finigan, USA) at 70 eV. Elemental analyses were carried out on a CHN-O-rapid elemental analyzer (GmbH-Germany) for C, H and N and the results are within ± 0.4 % of the theoretical values.

Synthesis of 2-*n*-butyl-4-chloro-5-formyl-1-[{2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl}methyl]imidazole: A mixture of losartan (10 g, 0.024 mol) and excess of MnO_2 (50 g) in 200 mL $CHCl_3$ was stirred at room temperature for 10 h. The reaction monitored by thin layer chromatography. After the completion of reaction, the mixture was passed through a short pad of diatomatous earth and washed with chloroform. Chloroform was evaporated and the residue was purified by column chromatography using chloroform as mobile phase.

Spectral data and physicochemical properties: White solid, m.p. 153-155 ºC, ^{1}H NMR (DMSO-d_6): 9.67 (s, 1H), 7.69 (d, 1H, *J* = 8 Hz), 7.65 (t, 1H, *J* = 8 Hz), 7.56 (t, 1H, *J* = 8 Hz), 7.52 (d, 1H, *J* = 8 Hz), 7.11 (d, 2H, *J* = 8.5), 7.04 (d, 2H, *J* = 8.5 Hz), 5.55 (s, 2H), 2.62 (t, 2H, *J* = 7Hz), 1.8-1.1 (m, 4H), 0.85 (t, 3H, *J* = 7Hz). MS (m/z): 419 (M^+, 5%).

Synthesis of 2-*n*-butyl-4-chloro-5-carboxy-1-[{2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl}methyl]imidazole

Procedure A: A mixture of 4.5 g (0.011 mol) of losartan 5-carboxaldehyde and 2.25 g (0.056 mol) of NaOH in 100 mL of water was stirred for 15 min. Then 0.1 g of $AgNO_3$ was dissolved in warm water and was added to the reaction mixture and the resulting mixture was refluxed overnight. The mixture was filtered and acidified by HCl. The obtained yellowish precipitate was filtered and was crystallized from ethanol.

Procedure B: Hydrogen peroxide (30 %, 5.7 mL, 56.8 mmol) was added dropwise to a stirring solution of aqueous KOH 50 % (3.2 mL, 28.4 mmol) and losartan 5-carboxaldehyde (3 g, 7.1 mmol) in methanol (25 mL) at 65 ºC and the mixture was stirred for 20 min. After the completion of reaction, the reaction was cooled and was acidified with concentrated HCl to obtain 2.9 g of 5-carboxylate derivative.

Procedure C: A mixture of 1.5 g (3.6 mmol) of losartan 5-carboxaldehyde and 0.55 g (3.6 mmol) of oxone (potassium peroxymonosulfate) was dissolved in 10 mL of DMF and the reaction mixture was stirred for 5 h. The reaction was monitored by thin layer chromatography. After the completion of reaction, the solvent was evaporated and the residue was purified by acid base workup and was crystallized from ethanol.

Procedure D: A catalytic amount of Pd/C was added to 10 mL of H_2O and 0.6 mmol of $NaBH_4$ was slowly added to this suspension followed by 1 g (18 mmol) of KOH. Then, 2.5 g (5.9 mmol) losartan 5-carboxaldehyde was added to the suspension and reaction mixture was stirred overnight under the air at room temperature for 10 h. The completion of the reaction was controlled by thin layer chromatography. After the completion, the reaction mixture was neutralized with 0.1 M HCl solution. The obtained mixture was extracted with 10 mL of ethyl acetate 3 times and the organic layers were combined and evaporated. The residue was purified by acid base workup and was crystallized from ethanol.

Spectral data and physico-chemical properties: White solid, m.p. 175-177 °C, ^{1}H NMR (DMSO-d_6): 7.71(d, 1H, J = 8 Hz), 7.68 (t, 1H, J = 8 Hz), 7.57 (t, 1H, J = 8Hz), 7.54 (d, 1H, J = 8 Hz), 7.10 (d, 2H, J = 8.5), 7.01 (d, 2H, J = 8.5 Hz), 5.57 (s, 2H), 2.59 (t, 2H, J = 7 Hz), 2.1-1.3 (m, 4H), 1.1 (t, 3H, J = 7Hz). MS (m/z): 435 (M^+, 6 %).

RESULTS AND DISCUSSION

A microwave-assisted synthesis of an active metabolite of losartan (EXP-3174) using excess of MnO_2 is reported by Santagada *et al.*[18]; however, the purification procedure was performed using preparative RP-HPLC. Recent report by Schmidt and Schieffer[19] indicated a procedure for synthesis of EXP-3179 in the presence of $RuCl_3$ and H_2O_2 with 16 % yield.

In all procedures reported in this study, the aldehyde intermediate was used for the preparation of EXP-3174. In the first procedure, A, the 5-carboxylate derivative was synthesized using a selective reagent for the oxidation of aldehydes to related carboxylic acids. Silver nitrate as oxidizing agent was used concurrently with NaOH in water for this conversion[10]. This procedure had the lowest yield in comparison with other methods. **Procedure B** (H_2O_2, KOH) is an efficient and rapid method for oxidation of aldehydes to carboxylic acids[13]. The reagents of this procedure are convenient and inexpensive and the time of 0.5 h is a positive point and an advantage of this procedure. **Procedure C** (oxone)[14-16] was also found as an efficient method for obtaining active metabolite of losartan from its aldehyde intermediate. In the presence of oxone as an oxidizing agent in dimethyl formamide the reaction was completed after 5 h. **Procedure D** (Pd/C, $NaBH_4$ and KOH)[17] is a good method for the oxidation of losartan 5-carboxaldehyde to EXP-3174. Stirring overnight is necessary for the completion of the reaction.

In summary, we have developed four methods for the synthesis of losartan active metabolite (EXP-3174) from its aldehyde intermediate (EXP-3179).

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