Synthesis of related substances of olmesartan medoxomil, anti-hypertensive drug#

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Abstract

Olmesartan medoxomil **1** is the latest angiotensin receptor antagonist approved by the FDA for the treatment of hypertension. During the process development of olmesartan medoxomil, four related substances (impurities) were observed along with the final API. Those impurities were identified as olmesartan acid, 4-acetyl olmesartan, 5-acetyl olmesartan, and dehydro olmesartan. Present work describes the synthesis and characterization of all these four impurities.

Keywords: Active pharmaceutical ingredients, angiotensin receptor antagonists, olmesartan medoxomil, related substances, synthesis

Introduction

The presence of impurities, also called as, related substances in an active pharmaceutical ingredient (API) can have a significant impact on the quality and safety of the drug products. Therefore, it is necessary to study the impurity profile of any API and control it during the manufacturing of a drug product. As per the ICH guidelines any impurities, which are forming at a level of ≥ 0.10% with respect to the API should be identified, synthesized and characterized thoroughly.[1] Olmesartan medoxomil **1** [Benicar®, Sankyo pharma] is the latest angiotensin receptor antagonist[2,3] approved by the FDA for the treatment of hypertension (Figure 1).[4] The drug works by inhibiting the effects of angiotensin II, a potent vasoconstrictor and one of the key contributors to cardiovascular and renal disease.[5] During the process for the synthesis of **1**, four unknown impurities were observed. However, as far as we are aware, the syntheses of these four

impurities were not reported so far. Herein, we wish to discuss identification, synthesis, and characterization of these new four impurities of **1**.

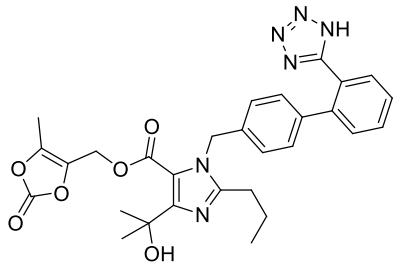

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Figure 1. Molecular framework of olmesartan medoxomil **1**.

Very recently, we have described an efficient, industrial scale synthesis of olmesartan medoxomil **1**.[6] During the synthesis of **1**, we came across many process related impurities and some of them were captured in our prior report.[7] To comprehend the complete impurity profile of olmesartan medoxomil **1** and to compare the extent of contamination of the impurities in **1**, we have decided to synthesize all the possible impurities. The HPLC chromatogram, Figure 2, shows the impurity profile of **1**.

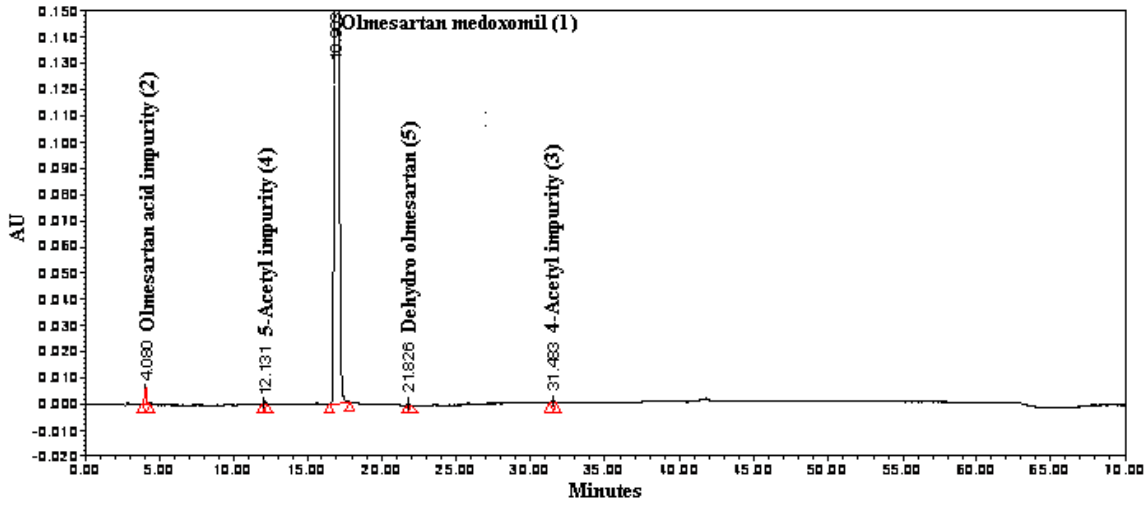


Figure 2. HPLC Chromatogram of olmesartan medoxomil.

Initially, **1** was subjected to LCMS to learn about the number of contaminants associated with it. Apart from the molecular ion peak of **1**, four more peaks with distinct molecular ions were observed in LCMS (Figure 3). Based on the molecular ion peaks, the following four structures **2** – **5** were proposed (Figure 4). Although, the structure of impurity **2** has been already

reported in the literature, surprisingly its synthesis was not accounted.[8] Other impurities **3**, **4** and **5** are process related new impurities and were not reported elsewhere. In this report, syntheses and characterization of all the four impurities of **1** will be discussed in detail.

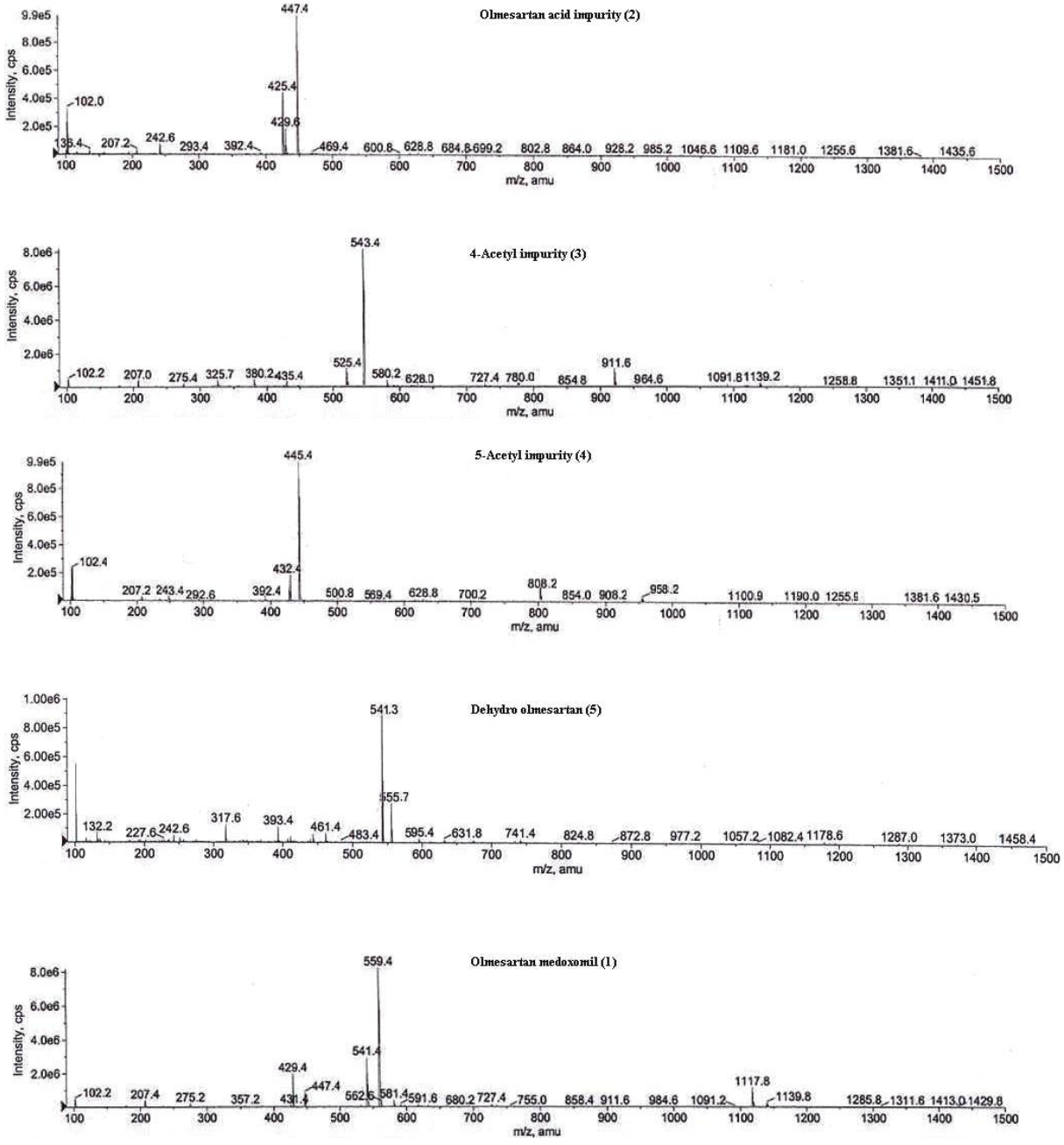


Figure 3. LC-MS Spectrum of olmesartan medoxomil and its related substances.

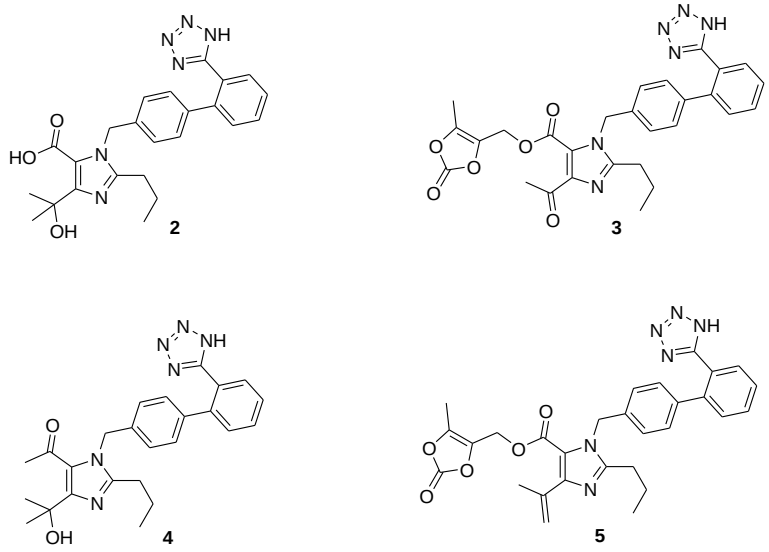
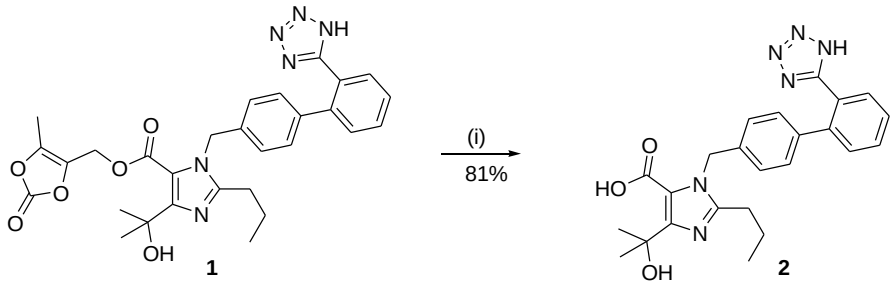


Figure 4. Related substances of olmesartan medoxomil **1**.

Results and Discussion

The synthesis of impurity **2**, also known as olmesartan acid impurity, is described in Scheme 1. Olmesartan medoxomil **1** was subjected to basic hydrolysis using sodium hydroxide in methanol at ambient reaction conditions afforded the impurity **2** in good yield and 99% HPLC purity. The structure of **2** was confirmed by spectral analysis.



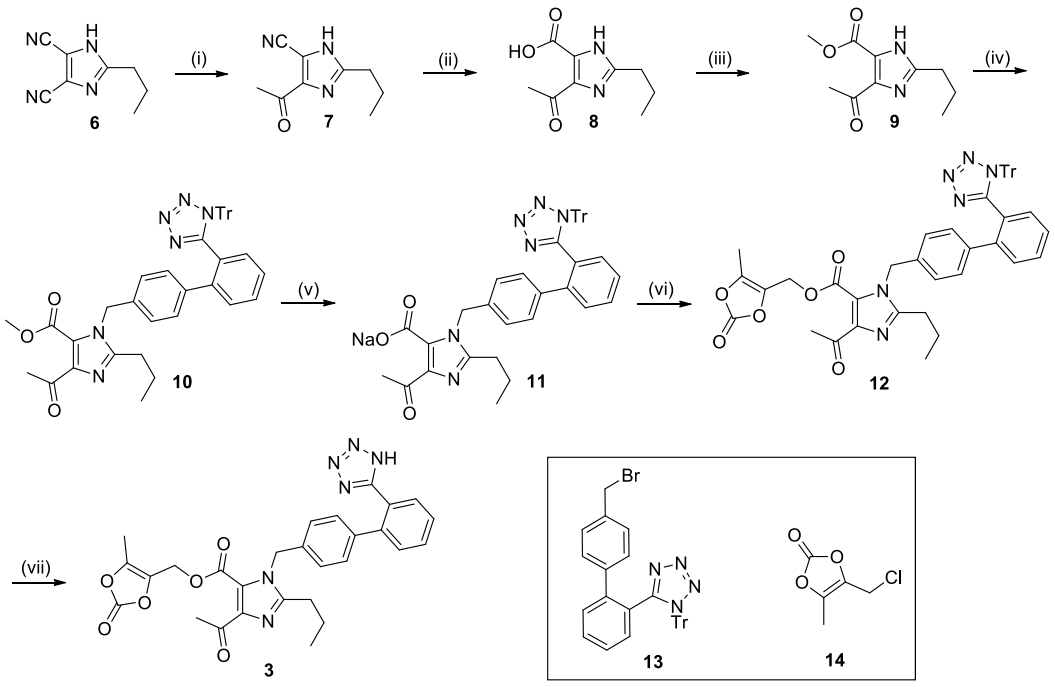
Reagents and conditions: (i) NaOH, MeOH, RT, 20 h

Scheme 1. Synthesis of impurity **2**.

The 4-acetyl impurity **3** has been synthesized according to the synthetic sequence shown in Scheme 2. Treatment of dicyanoimidazole **6** with methyl magnesium chloride in THF followed by acidic work up afforded the corresponding acetyl derivative 7, which on acid hydrolysis under reflux provided the corresponding acid **8**. The imidazole acid **8** on esterification with methanol and HCl provided the methyl ester of 4-acetyl propyl imidazole carboxylic acid **9**. The acetyl

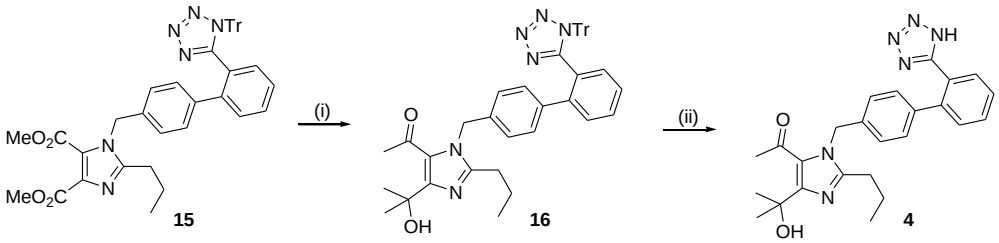
imidazole derivative **9** was then condensed with biphenyl derivative **13** in presence of potassium carbonate in refluxing acetone to provide the *N*-alkylated acetyl imidazole derivative **10**, which on further hydrolysis using aqueous NaOH in acetone gave the sodium salt **11**. Alkylation of **11** with 4-chloromethyl-5-methyl-1,3-dioxolen-2-one[9]**14** provided the medoxomil ester **12**. Finally, deprotection of trityl group in **12** with acetic acid afforded 4-acetyl impurity of olmesartan medoxomil **3.**

The synthesis of **5**-acetyl impurity **4** commenced from the *N*-alkylated imidazole derivative **15**, which is one of the intermediates in the synthesis of **1** (Scheme 3). The Grignard reaction of **15** with excess moles of methyl magnesium chloride in anhydrous toluene afforded 5-acetyl derivative of N-alkylated imidazole **16**, which on deprotection using acetic acid provided 5-acetyl impurity **4** in good yield and purity. The structure of **4** was confirmed by standard spectral analysis.



Reagents and conditions: (i) CH_3MgCl, THF. (ii) aq. HCl. (iii) Methanol/HCl. (iv) **13**, K_2CO_3, acetone,reflux. (v)NaOH/ H_2O/acetone. (vi) **14**, $NaHCO_3$/DMF at 45-50 ^oC. (vii) Acetic acid/Acetone at 50-60 ^oC

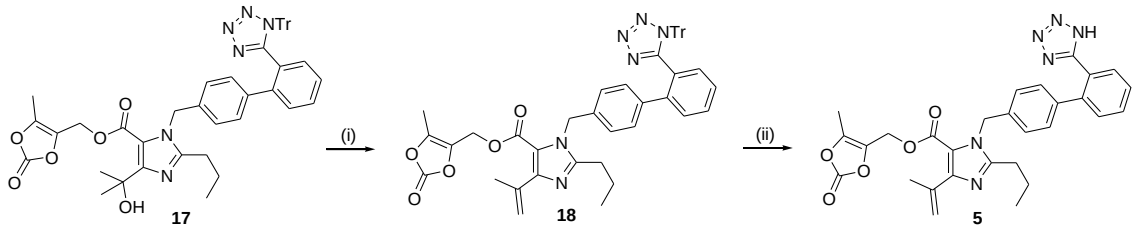
Scheme 2. Synthesis of impurity **3**.



Reagents and conditions: (i) 15eq.CH_3MgCl, THF (ii) Acetic acid at 55-60^oC

Scheme 3. Synthesis of impurity **4**.

Preparation of dehydro olmesartan impurity **5**, originated from the medoxomil ester derivative of *N*-alkylated imidazole **17**. Dehydration of **17** with *p*-toluenesulphonic acid in toluene under reflux conditions provided the corresponding dehydro derivative **18**, which on deprotection with acetic acid provided dehydro olmesartan impurity **5** in good purity.



Reagents and conditions: (i) PTSA/Toluene (ii) Aceticacid at 55-60^oC

Scheme 4. Synthesis of impurity **5**.

Finally, all the impurities **2** – **5** were individually co-injected with the API **1** in the HPLC and the HPLC data was compared with that of the API **1**. As expected, all the impurities were matching with the impurity profile of **1**.

Conclusions

We have demonstrated the synthesis and complete characterization of some of the critical impurities of olmesartan medoxomil **1**. This investigation helped us to establish the impurity profile of **1**.

Experimental Section

General. ^1H NMR spectra were recorded at 400 MHz Varian FT NMR Spectrometer. The chemical shifts are reported in δ ppm relative to TMS. The IR spectra were obtained using Perkin

Elmer, Spectrum One FT IR spectrophotometer, with substances being pressed in a KBr pellet. The mass analyses have been performed on AB-4000 Q-trap LC-MS/MS mass spectrometer (MDS SCIEX, Applied Bio systems, California, USA). All the solvents and reagents were used without further purification.

Synthesis of olmesartan acid impurity 2

To a solution of olmesartan medoxomil **1** [10.0 g, 0.0179 mol] in 200.0 mL of methanol was added a solution of sodium hydroxide (1.5 g, 0.0075 mol) in water (25.0mL) and the reaction mixture was stirred at 25-30 °C for 15-20 h. After completion of the reaction, methanol was distilled off completely at 45-50 °C and diluted with water. It was then washed with ethyl acetate (100.0 mL x 1). The aqueous layer was separated and the pH was adjusted to 8.0-8.5 using 10% HCl solution. The resulting solution was stirred for 15-30 minutes at 25-30 °C. The separated solid was filtered and washed with water and dried under vacuum to get the olmesartan acid **2** (5.7 g, yield 90%; purity by HPLC 95%); FT IR (KBr) 3429, 3066, 1637 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) 0.8 (t, J = 5.6 Hz, 3H), 1.6 (s, 6H), 1.4-1.7 (m, 2H), 2.6 (t, J = 5.4 Hz, 2H), 5.7 (s, 2H), 6.9-7.2 (m, 4H), 7.5-7.8 (m, 4H); MS (EI) *m/z* 447.0 (M^+ + 1); CHN Analysis: calcd. for $C_{24}H_{26}N_6O_3$: C, 64.56; H, 5.87; N, 18.82; Found: C, 64.78; H, 5.98; N, 18.91.

Synthesis of 4-acetyl impurity 3

2-Propylimidazole-4-acetyl-5-carbonitrile (7). To a solution of 2-propylimidazole-4,5-dicarbonitrile (**6**, 25.0 g, 0.156 mol) in THF (250.0 mL) was added a solution of methyl magnesium chloride in tetrahydrofuran (24.5 %, 142.5 mL, 0.47 mol) at room temperature and stirred for 1-2 h. After completion of the reaction, the reaction mass was quenched with 10% acetic acid (315.0 mL) and the mixture was extracted with toluene (100.0 mL). Combined the organic layers were washed with 25% sodium chloride solution (3 x 125.0 mL). Solvent was distilled off under reduced pressure to obtain the title compound **7** as a residue (29.7 g, yield 80 %; purity by HPLC 94%); IR (KBr): 3166, 2235, 1678 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 0.9 (t, J = 7.5 Hz, 3H), 1.7-1.9 (m, 2H), 2.6 (s, 3H), 2.7 (t, J = 7.4 Hz, 2H); MS *m/z* (EI): 178.0 (M^+ + 1); CHN Analysis: calcd. for $C_9H_{11}N_3O$: C, 61.00; H, 6.26; N, 23.71; Found: C, 61.23; H, 6.31; N, 23.80.

2-Propylimidazole-4-acetyl-5-carboxylic acid (8). A solution of **7** (40.0 g, 0.225 mol) in conc. HCl (90.0 mL) was refluxed for 24 h. After cooling to room temperature was added water (100.0 mL) and the pH of the solution was adjusted to 4 using 10% sodium hydroxide solution (100.0 mL) and the precipitated solid was filtered. The filtrate was extracted with ethyl acetate (4 x 150.0 mL). The solvent was removed by vacuum distillation to get the crude material, which was recrystalized using cyclohexane (50.0 mL) to yield **8** (9.5 g, yield 22 %; purity by HPLC 91%); IR (KBr): 3394, 1696 cm^{-1}; ^1H-NMR (400 MHz, DMSO-d_6) δ 0.9 (t, J = 7.48 Hz, 3H), 1.6-1.8 (m, 2H), 2.4-2.6 (m, 2H), 2.65 (s, 3H), 13.8 (br, s, 1H): MS *m/z* (EI): 197.0 (M^+ +1); CHN Analysis: calcd. for $C_9H_{12}N_2O_3$: C, 55.09; H, 6.16; N, 14.28; Found: C, 55.28; H, 6.22; N, 14.40.

Methyl-4-acetyl-2-propylimidazole-5-carboxylate (9). A solution of 2-propylimidazole-4-acetyl-5-carboxylic acid (**8**, 20.0 g, 0.102 mol) in CH_3OH/HCl (246.0 mL, 0.612 mol) was stirred vigorously for 4h at room temperature. After completion of the reaction, methanol was distilled off completely. To the residue was added ethyl acetate (100.0 mL) followed by water (100.0 mL) and the resulting mixture was stirred for 10 minutes. The layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 60.0 mL). The combined the organic layers were washed with water (50.0 mL) and the resulting organic layer was dried over sodium sulphate. Removal of solvent under reduced pressure gave a residue, which was recrystallized in cyclohexane to provide **9** (15.2 g, yield 65 %; purity by HPLC 97%); IR (KBr) 3432, 1728, 1663 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 0.9 (t, J = 7.5 Hz, 3H), 1.7-1.9 (m, 2H), 2.6-3.0 (m, 2H), 2.8 (s, 3H), 3.9 (s, 3H); MS *m/z* (EI): 211.0 (M^+ + 1); CHN Analysis calcd. for $C_{10}H_{14}N_2O_3$: C, 57.13; H, 6.71; N, 13.13; Found: C, 57.28; H, 6.93; N, 13.23.

Compound 10. To a solution of methyl-4-acetyl-2-propylimidazole-5-carboxylate (**9**, 14.0 g, 0.066 mol) in acetone (70.0 mL) were added *N*,*N*-dimethylacetamide (14.0 mL) followed by 11 (37.1 g, 0.066 mol) and potassium carbonate (18.4g, 0.133 mol). The reaction mixture was heated to reflux and maintained for 8-9 h. Quench the reaction mass with water (140.0 mL). It was extracted with ethyl acetate (140.0 mL). The organic layer was washed with saturated brine solution (2 x 70.0 mL). Solvent was distilled off under reduced pressure to obtain a residue. The residue was further purified by column chromatography (30% ethyl acetate in hexane) to obtain compound **10** as a brown solid (7.3 g, yield 16%; purity by HPLC 97%); IR (KBr): 3061, 2964, 1715, 1690 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 0.9 (t, J = 7.6 Hz, 3H), 1.6-1.8 (m, 2H), 2.5 (t, J = 7.6 Hz, 2H), 2.6 (s, 3H), 3.7 (s, 3H), 5.3 (s, 2H), 6.9 (d, J = 8.0 Hz, 2H), 6.9-7.2 (m, 8H), 7.2-7.6 (m, 13H); MS *m/z* (EI): 687.0 (M^+ + 1); CHN Analysis: calcd. for $C_{43}H_{38}N_6O_3$: C, 75.20; H, 5.58; N, 12.24; Found: C, 75.23; H, 5.74; N, 12.33.

Compound 11. To the stirred solution **10** (3.5 g, 0.0051 mol) in acetone (70.0 mL), sodium hydroxide (0.4 g, 0.01 mol) in water (17.5 mL) was added at 20-25 °C and the resulting solution was stirred for 5-6 hrs. After completion of the reaction, reaction mass was diluted with saturated brine solution and extracted with ethyl acetate (75.0 mL). Solvent was distilled off under reduced pressure to obtain the title compound **11** as a residue. It was further purified by column chromatography using 40% ethyl acetate in hexanes to yield **10** (1.0 g, yield 29%; purity by HPLC 94%); IR (KBr): 3058, 1717, 1621 cm^{-1}; ^1H NMR (400 M Hz, DMSO-d_6) δ 0.9 (t, J = 7.6 Hz, 3H), 1.6-1.9 (m, 2H), 2.5-2.6 (m, 2H), 2.8 (s, 3H), 5.7 (s, 2H), 6.6-7.6 (m, 22H), 7.9-8.0 (m, 1H), 15.2 (brs, 1H); MS *m/z* (EI): 673.0 (M^+ + 1); CHN Analysis: calcd. for $C_{42}H_{35}N_6O_3$: C, 72.61; H, 5.08; N, 12.10; Found: C, 72.73; H, 5.11; N, 12.13.

Compound 12. To a solution of **11** (3.0 g, 0.0043 mol) in of *N*,*N*-dimethylacetamide (9.0 mL), sodium carbonate (0.27 g, 0.0025 mol) and 4-chloromethyl-5- methyl-1,3-dioxolen-2-one (0.83 g, 0.005 mol, **14**) were added and the resulting mixture was heated to 45–50 °C and maintained for 9-10 h. It was cooled to rt and aqueous sodium chloride solution (10%, 15.0 mL) and toluene (15.0 mL) were added to the reaction mixture. The pH of the reaction mixture was adjusted to 7–8 with 10% aqueous hydrochloric acid. The aqueous layer was separated and extracted with

toluene (6.0 mL). The combined organic layers were washed with 10% sodium chloride solution (15.0 mL). The solvent was evaporated under reduced pressure to get the title compound **12** as a white solid (2.5 g, yield 28%; purity by HPLC 94%); IR (KBr): 3051, 1822, 1716, 1446 cm^{-1}; ^1H NMR (400 M Hz, DMSO-d_6) δ 0.9 (t, J = 7.5 Hz, 3H), 1.6-1.75 (m, 2H), 2.0 (s, 3H), 2.5-2.6 (m, 2H), 2.6 (s, 3H), 4.85 (s, 2H), 5.2 (s, 2H), 6.7-7.5 (m, 22H), 7.9 (d, J = 8.0 Hz, 1H); MS *m/z* (EI): 785.0 (M^+ + 1); CHN Analysis: calcd. for $C_{47}H_{40}N_6O_6$: C, 71.92; H, 5.14; N, 10.71; Found: C, 72.18; H, 5.21; N, 10.83.

Compound 3. A solution of **12** (10.0 g, 0.013 mol) in 40% aqueous acetic acid (300.0 mL) was heated at 55–60 °C for 1–2 h. The reaction mass was cooled to room temperature and diluted with water (100.0 mL). The precipitated solids were filtered off, and the filtrate was extracted with dichloromethane (550.0 mL). The organic layer was washed with a mixture of 5% aqueous sodium bicarbonate solution (100.0 mL) and 5% sodium chloride solution (450.0 mL). Removal of the solvent followed by isolation in cyclohexane (30.0 mL) gave the pure product **3** as a white solid (3.3 g, yield 48%; purity by HPLC 98%); IR (KBr),) 3062, 1823, 1717, 1446 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 0.9 (t, J = 7.2 Hz, 3H), 1.6-1.75 (m, 2H), 2.1 (s, 3H), 2.5-2.6 (m, 2H), 2.65 (s, 3H), 4.9 (s, 2H), 5.2 (s, 2H), 7.0-7.5 (m, 8H), 14.2 (brs, 1H); MS *m/z* (EI): 543.0 (M^+ + 1); CHN Analysis: calcd. for $C_{28}H_{26}N_6O_6$: C, 61.99; H, 4.83; N, 15.49; Found: C, 62.11; H, 4.92; N, 15.55.

Synthesis of 5-acetyl impurity 4

Compound 16. To a solution of **15** (35.0 g, 0.05 mol) in toluene (105.0 mL) was added a solution of methyl magnesium chloride in tetrahydrofuran (24.5 %, 228.0 mL, 0.45 mol) at room temperature and maintained for 6-7 h. After completion of the reaction, the reaction mass was quenched with 10% acetic acid (460.0 mL) and extracted with toluene (35.0 mL). The organic layer was washed with saturated brine solution (105.0 mL). Solvent was distilled off under reduced pressure to obtain the title compound **16** as a residue. The residue was further purified by column chromatography in 10% ethyl acetate in hexane to provide pure compound **16** as a white solid (12.0 g, yield 34%; purity by HPLC 99%); IR (KBr) 3337, 3059-3034, 1624 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 0.92 (t, J = 7.5 Hz, 3H), 1.57 (s, 6H), 1.58-1.63 (m, 2H), 1.9 (s, 2H), 2.3 (s, 3H), 2.7-2.8 (m, 2H), 5.3 (s, 2H), 6.9-7.6 (m, 23H); MS *m/z* (EI): 687.0 (M^+ + 1); CHN Analysis: calcd. for $C_{44}H_{42}N_6O_2$: C, 76.94; H, 6.16; N, 12.24; Found: C, 77.12; H, 6.31; N, 12.30.

Synthesis of impurity 4

A solution of **16** (10.0 g, 0.013 mol) in 40% aqueous acetic acid (300.0 mL) was heated at 55–60 °C for 1–2 h. The reaction mass was cooled to room temperature and diluted with water (100.0 mL). The precipitated solids were filtered and washed with 40% aqueous acetic acid (10.0 mL), and the filtrate was extracted with dichloromethane (550.0 mL). The organic layer was washed with a mixture of 5% aqueous sodium bicarbonate solution (100.0 mL) and 5% sodium chloride solution (450.0 mL). Removal of the solvent followed by isolation in cyclohexane (30.0 mL)

gave the pure product **4** as a white solid (3.3 g, yield 52%; purity by HPLC 98%); IR (KBr): 3337, 3060, 1669 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 0.92 (t, J = 7.6 Hz, 3H), 1.5 (s, 6H), 1.6-1.8 (m, 2H), 2.4 (s, 3H), 2.72 (t 2H), 5.3 (s, 2H), 6.8-7.6 (m, 8H); MS *m/z* (EI): 445.0 (M^+ + 1); CHN Analysis: calcd. for $C_{44}H_{42}N_6O_2$: C, 67.55; H, 6.35; N, 18.91; Found: C, 67.60; H, 6.44; N, 18.94.

Synthesis of dehydro olmesartan (5)

Compound 18. To a stirred solution of **17** (3.0 g, 0.043 mol) in toluene (9.0mL) was added water (0.83 mL, 0.005mol) and *p*TSA (0.27 g, 0.0025mol) and the resulting mixture was refluxed in a Dean-Stark reaction set up for 8-10 h. The solvent was distilled off completely at 60 °C to obtain the title compound **18** as a residue. The residue was further purified by column chromatography using 10% ethyl acetate in hexane to provide pure compound **18** as a white solid (1.3 g, yield 45%; purity by HPLC 96%); IR (KBr) 3060, 1823, 1706 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 0.9 (t, J = 7.6 Hz, 3H), 1.6-1.7 (m, 2H), 2.1 (s, 3H), 2.2 (s, 3H), 2.5 (t, J = 7.5 Hz, 2H), 4.85 (s, 2H), 5.3 (s, 2H), 5.4 (s, 2H), 6.7-6.8 (m, 2H), 6.7-7.9 (m, 23H); MS *m/z* (EI): 783.0 (M^+ + 1); CHN Analysis: calcd. for $C_{48}H_{42}N_6O_5$: C, 73.64; H, 5.41; N, 10.73; Found: C, 73.71; H, 5.48; N, 10.79.

Dehydro olmesartan (5). To a stirred solution of 18 (9.0 g, 0.11 mol) in 40% aqueous acetic acid (270.0 mL) was heated at 55–60 °C for 2–3 h. The reaction mass was cooled to room temperature and diluted with 5% sodium chloride solution (135.0 mL). The precipitated solids were filtered off and washed with 40% aqueous acetic acid (10.0 mL), and the filtrate was extracted with dichloromethane (270.0 mL). The organic layer was washed with a mixture of 5% aqueous sodium bicarbonate solution (100.0 mL) and 5% sodium chloride solution (100.0 mL). The solvent was removed under reduced pressure and the residue was isolated from 1:1 mixture of acetone and *n*-heptane (100.0 mL) to give the pure product **5** (5.6 g, yield 90%; purity by HPLC 98%); IR (KBr) 2928, 1824, 1714 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 0.9 (t, J = 7.6 Hz, 3H), 1.4-1.6 (m, 2H), 2.2 (s, 3H), 2.5 (s, 3H), 2.6-2.8(m, 2H), 5.0 (s, 2H), 5.2 (s, 2H), 5.4 (s, 2H), 6.8-7.8 (m, 8H); MS *m/z* (EI): 541.0 (M^+ + 1); CHN Analysis: calcd. for $C_{29}H_{28}N_6O_5$: C, 64.43; H, 5.22; N, 15.55; Found: C, 64.52; H, 5.29; N, 15.61.

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References

1. International conference on harmonization (ICH) Guidelines, Q_3A (R) Impurities in New Drug Substances, February 2002.
2. Fukuda, M.; Yamanaka, T.; Mizuno, M.; Motokawa, M.; Shirasawa, Y.; Miyagi, S.; Nishio, T.; Yoshida, A.; Kimura, G. *J. Hypertens*. **2008**, *26*, 583.
3. Nobuya, K.; Miwa, S.; Shoko, K.; Keisuke, Y.; Hirokazu, I.; *Br. J. Pharmacol*. **2003**, *139*, 1085.
4. Yanagisawa, H.; Amemiya, Y.; Kanazaki, T.; Shimoji, Y.; Fujimoto, K.; Kitahara, Y.; Sada, T.; Mizuno, M.; Ikeda, M.; Miyamoto, S.; Furukawa, Y.; Koike, H. *J. Med. Chem.* **1996**, *39*, 323.
5. Gardner, S. F.; Franks, A. M. *Ann. Pharmacother.* **2003**, *37*, 99.
6. Babu, K. S.; Reddy, M. S.; Tagore, A. R.; Reddy, G. S.; Sebastian, S. WO 2007/047838 A2, 2007.
7. Babu, K. S.; Reddy, M. S.; Tagore, A. R.; Reddy, G. S.; Sebastian, S.; Varma, M. S.; Anand, R. V. *Syn. Commun.* **2009**, *39*, 291.
8. Teng, J.; Fukuda, N.; Suzuki, R.; Takagi, H.; *J. Cardiovas. Pharmacol.* **2002**, *39*, 161.
9. Ismail, M. A. H.; Barker, S.; Abou El Ella, D. A.; Abouzid, K. A. M.; Toubar, R. A.; Todd, M. H. *J. Med. Chem.* **2006**, *49*, 1526.