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Synthesis and spectral characterization of related compounds of Losartan potassium, an anti-hypertensive drug substance

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ABSTRACT

Losartan potassium **(1)** is a known anti-hypertensive drug substance, recently appeared in the European pharmacopoeia with the several process related compounds/impurities. Out of **(12)** related compounds **(6)** were synthesized and characterized based on IR, NMR and MS spectral data, and same thing was described in this article.

KEYWORDS

Losartan;
Related compounds;
Hypertension;
Pharmacopoeia;
Non-peptide.

INTRODUCTION

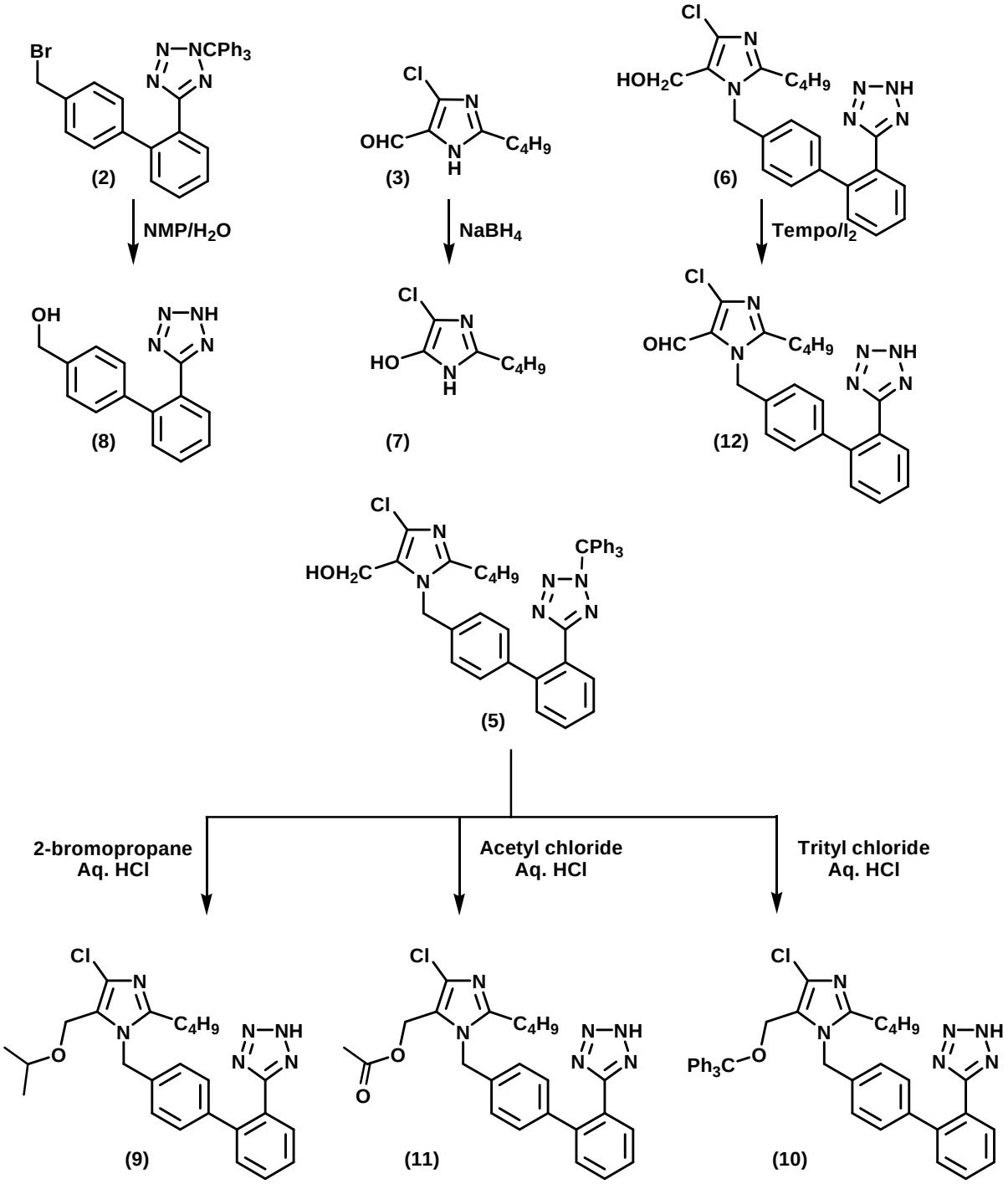
Losartan potassium **(1)**, a non-peptide molecule is chemically known as 2-butyl-4-chloro-1-[p-(o-1*H*-tetrazol-5-ylphenyl) benzyl] imidazole-5-methanol monopotassium salt, is used for the treatment of hypertension[1]. Recently, Losartan potassium appeared in the European pharmacopoeia[2] with 12 related compounds. Majority of these impurities were resulted as by-products from the reported synthetic pathway (Scheme 1) of Losartan potassium.

In this context, the present article describes synthesis[3] and spectral characterization of six critical pharmacopoeial impurities of losartan potassium. These related compounds are designated as (2-butyl-4-chloro-1*H*-imidazol-5-yl)methanol **(7)** / impurity A, [2′-(2H-tetrazol-5-yl) biphenyl-4-yl] methanol **(8)** /impurity B, 5-[4′-((2-butyl-4-chloro-5-(isopropoxymethyl)-1*H*-imidazol-1-yl) methyl) biphenyl-2-yl]-2H-tetrazole **(9)** /Impurity F, 5-[4′-((2-butyl-4-chloro-5-(trityloxymethyl)-1*H*-imidazol-1-yl)methyl)biphenyl-2-yl]-2*H*-tetrazole (10)/impurity **(I)**, (1-((2′-(2*H*-tetrazol-5-yl)biphenyl-4-yl)methyl)-2-butyl-4-chloro-1*H*-imidazol-5-yl) methyl acetate **(11)** /impurity **(J)** and 1-[(2′-(2*H*-tetrazol-5-yl)biphenyl-4-yl) methyl]-2-butyl-4-chloro-1*H*-imidazole carbaldehyde **(12)** /impurity **(K)**.

EXPERIMENTAL

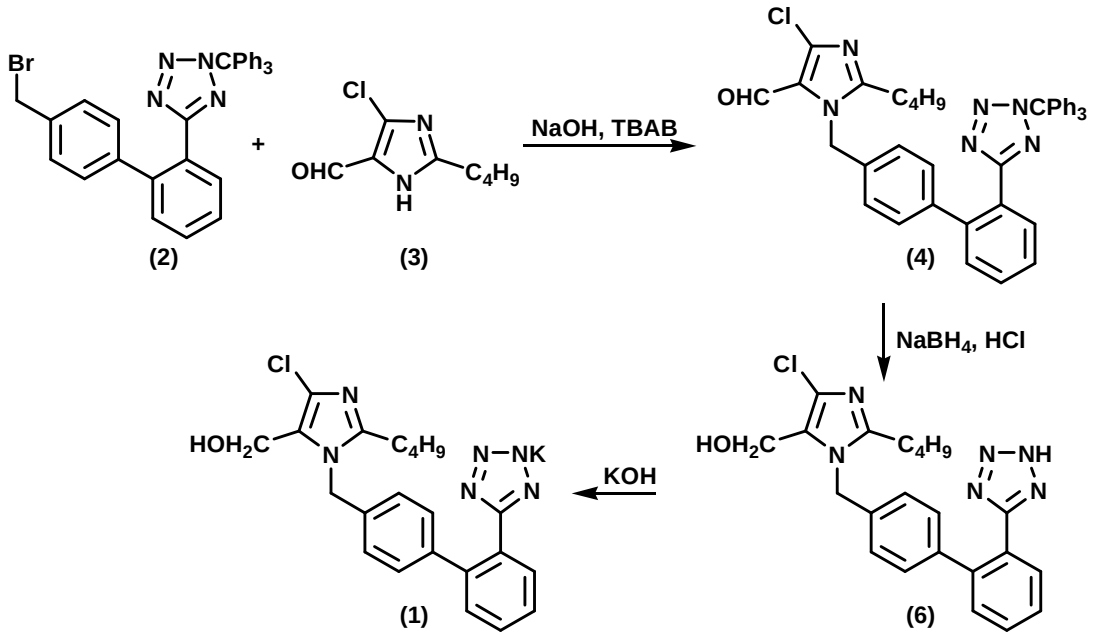
The ^{1}H NMR spectra recorded on a Gemini 400 MHz FT NMR spectrometer, the chemical shifts were reported on δ ppm relative to TMS. The IR spectra were recorded in the solid state as KBr dispersion using Perkin Elmer FT-IR spectrophotometer. The mass spectra recorded on Shimadzu LCMS-QP8000, LC-MS and AB-4000 Q-trap LC-MS/MS. Elemental analysis for CHN were performed on Perkin Elmer model 2400 CHNS/O analyzer at Dr. Reddy's Laboratories Ltd., Hyderabad.

(2-Butyl-4-chloro-1*H*-imidazol-5-yl) methanol **(7)**. To a mixture of 2-butyl-4-chloro-1*H*-imidazole-5-



Scheme 1 : Reported synthetic scheme for Losartan potassium

carbaldehyde (3, 5.0 g, 0.026 mol) and methanol (15 mL), sodium borohydride (0.49 g, 0.013 mol) was added portion wise over 30 min at–10°C. The reaction mixture was warmed to room temperature and to this, 2% aqueous acetic acid (30.0 mL) was added over 10 min at 20-25°C. After 15 minutes, the solid was filtered, washed with water (50 mL) and finally dried under vacuum at 60°C to afford the title compound **(7)** (4.75 g, yield: 94%, HPLC purity 99 %). IR (cm^{-1}): 3436 (OH); ^1H NMR (DMSO-d_6, δ ppm): 0.96 (t, 3H, CH_3), 1.35 (m, 2H, CH_2), 1.60 (m, 2H, CH_2), 2.55 (t, 2H, CH_2) 4.29 (s, 2H, CH_2); Mass: 189 (M^{+1}); C H N Analysis calcd. for $C_8H_{13}ClN_2O$: C, 50.93; H, 6.95; N, 14.85; Found: C, 50.98; H, 6.99; N, 14.89.



Scheme 2 : Synthetic scheme for Losartan potassium impurities preparation

[2′-(2*H*-tetrazol-5-yl)biphenyl-4-yl]methanol (8)

A solution of 5-(4′-(bromomethyl)biphenyl-2-yl)-2-trityl-2*H*-tetrazole (2, 5.0 g, 0.0158 mol) in 15 %(v/v) aqueous NMP (79.3 mL) was heated at 100-130°C and the reaction progress was monitored by TLC. After reaction completion, the mixture was cooled, diluted with water (160.0 ml) and extracted with dichloromethane (50.0 mL). The organic phase was washed with water (3×20.0 mL), dried over sodium sulphate and concentrated under vacuum on a rotary evaporator to yield the title compound **(8)** (2.0 g, yield: 88.5%, HPLC purity 99 %). IR (cm^{-1}): 3571-3406 (OH-NH broad); ^1H NMR (DMSO-d_6, δ ppm): 4.19 (s, 2H, CH2), 7.12 (d, 2H, Ar-H), 7.55 (d, 2H, Ar-H) 7.72 (d, 2H, Ar-H) 7.25 (d, 2H, Ar-H); Mass: 253 (M^{+1}); C H N Analysis calcd. for $C_{14}H_{12}N_4O$: C, 66.65; H, 4.79; N, 22.21; Found: C, 66.69; H, 4.82; N, 22.28.

5-(4′-((2-butyl-4-chloro-5-(isopropoxymethyl)-1*H*-imidazol-1-yl)methyl)biphenyl-2-yl)-2H-tetrazole (9)

To a mixture potassium hydroxide (8.4 g, 0.15 mol) and dimethylformamide (150.0 mL), 5 (10.0 g, 0.015 mol) was added at 25-35°C and stirred the mixture for 20 minutes. To the reaction mass, 2-bromopropane (18.3 g, 0.150 mol) was added and maintained until the reaction completion. The reaction mass concentrated under reduced pressure and the residual mass dissolved in acetonitrile (50 .0 mL), 10% aqueous HCl (100.0 mL) added and stirred at 20-25°C. Filtered the isolated solid and washed with acetonitrile (10 mL) to afford the title compound **(9)**. (3.0 g, yield: 85.7%, HPLC purity 97 %); IR (cm^{-1}): 1011 (C-O); ^1H NMR (DMSO-d_6, δ ppm): 0.96 (t, 3H, CH_3), 1.16 (d, 6H, CH3),1.35 (m, 2H, CH_2), 1.60 (m, 2H, CH_2), 2.55 (t, 2H, CH_2), 2.66 (m, 1H, CH), 4.35 (s, 2H, CH2), 7.12 (d, 2H, Ar-H), 7.55 (d, 2H, Ar-H) 7.72 (d, 2H, Ar-H) 7.25 (d, 2H, Ar-H); Mass: 465.2 (M^{+1}); C H N Analysis calcd. for $C_{25}H_{29}ClN_6O$: C, 64.58; H, 6.29; N, 18.07; Found: C, 64.55; H, 6.25; N, 18.02.

5-[4′-((2-butyl-4-chloro-5-(trityloxymethyl)-1*H*-imidazol-1-yl)methyl)biphenyl-2-yl]-2*H*-tetrazole (10)

To a mixture of **(5)** (5.0 g, 0.0075 mol) and toluene (60 mL), triethyl amine (5.0 g) was added under stirring at 20-25°C. The reaction mixture was heated to 80-85°C. Trityl chloride (2.9g, 0.010mol) was added at same temperature and maintained until the reaction completion. Reaction mass was concentrated under vacuum, the residual mass was triturated with acetonitrile (10 mL) and stirred at 25-35°C for 30-60 min. Filtered the resultant solid and washed with acetonitrile (5 mL). The resultant wet compound added to a mixture of acetonitrile (100 mL) and 10% aqueous HCl

solution (100.0 mL) and maintained at 20-25°C till the reaction completion. Filtered the solid compound, washed with acetonitrile (10 mL) and dried at 50-60°C to afford title compound **(10)**. (3.0 g yield: 60%, HPLC purity 97 %); IR (cm^{-1}): 1057 (C-O) and 3447 (NH); ^1H NMR (DMSO-d_6, δ ppm): 0.90 (t, 3H, CH_3), 1.20 (d, 6H, CH3),1.30 (m, 2H, CH_2), 1.60 (m, 2H, CH_2), 2.60 (t, 2H, CH_2), 2.80 (m, 1H, CH), 3.70 (s, 2H, CH2), 4.30 (s, 2H, CH2), 7.1-7.8 (s, 23H, Ar-H); Mass: 665.2 (M^{+1}); C H N Analysis calcd. for $C_{41}H_{37}ClN_6O$: C, 74.03; H, 5.61; N, 12.63; Found: C, 74.00; H, 5.58; N, 12.59.

[1-((2′-(2*H*-tetrazol-5-yl)biphenyl-4-yl)methyl)-2-butyl-4-chloro-1*H*-imidazol-5-yl]methyl acetate (11)

To a mixture of **(5)** (5.0 g, 0.0075 mol) and toluene (60 mL), triethyl amine (5.0 g) and acetyl chloride (1.47g, 0.0187 mol) was added at 25-35°C. The reaction mixture was heated to 80-85°C and maintained until the reaction completion. Solid compound filtered and washed with toluene (5.0 mL). Organic layer was concentrated under vacuum and the residual mass triturated with isopropyl alcohol (25.0 mL) for 30-60 min at 25-35°C, filtered the resultant solid and washed with isopropyl alcohol (5.0mL). The above wet compound added to mixture of acetonitrile (100 mL) and 10% aqueous HCl and stirred for 3 hours. Filtered the solid, washed with acetonitrile (5.0 mL) and dried at 50-60°C to yield the title compound **(11)**. (2.75 g, yield: 78.8, HPLC purity 97 %); IR (cm^{-1}): 1742(C=O) and 1227,1255 (O-C 2 bands); ^1H NMR (DMSO-d_6, δ ppm): 0.96 (t, 3H, CH_3),1.35 (m, 2H, CH_2), 1.60 (m, 2H, CH_2), 2.55 (t, 2H, CH_2), 4.20 (m, 3H, CH3), 4.35 (s, 2H, CH2), 5.00 (s, 2H, CH2), 7.12 (d, 2H, Ar-H), 7.55 (d, 2H, Ar-H) 7.72 (d, 2H, Ar-H) 7.25 (d, 2H, Ar-H); Mass: 465.2 (M^{+1}); C H N Analysis calcd. for $C_{24}H_{25}ClN_6O_2$: C, 62.00; H, 5.42; N, 18.08; Found: C, 62.05; H, 5.44; N, 18.11.

1-[(2′-(2*H*-tetrazol-5-yl)biphenyl-4-yl)methyl]-2-butyl-4-chloro-1*H*-imidazole-5-carbaldehyde (12)

A mixture of **(6)** (5 g, 0.0118 mol) and toluene (10 ml) was added to aqueous solution of sodium bicarbonate (2.98g, 0.035mol in 10 mL of water). Iodine (0.6g), solid TEMPO (0.18g, 0.0011 mol) added to the reaction mixture and stirred at 20-25°C until reaction completion. The mixture was cooled to 0-5°C, diluted with ethyl acetate (30 mL), aqueous sodium sulfite (3 g sodium sulfite in 5mL of water) solution added and layers were separated. The organic layer was dried over sodium sulfate, concentrated under vacuum and the residual mass triturated with cyclohexane (50 mL) to afford the title compound **(12)**. (4.0 g, yield: 80%, HPLC purity 97 %); IR (cm^{-1}): 1666 (C=O) and 2870,2734 2bands (C-H aldehyde); ^1H NMR (DMSO-d_6, δ ppm): 1.00 (t, 3H, CH_3),1.40 (m, 2H, CH_2), 1.70 (m, 2H, CH_2), 2.65 (t, 2H, CH_2), 4.40 (s, 2H, CH2), 5.00 (s, 2H, CH2), 7.12 (d, 2H, Ar-H), 7.55 (d, 2H, Ar-H) 7.72 (d, 2H, Ar-H) 7.25 (d, 2H, Ar-H); 9.61 (s, 1H, CH); Mass: 421.1 (M^{+1}); C H N Analysis calcd. for $C_{22}H_{21}ClN_6O$: C, 62.78; H, 5.03; N, 19.97; Found: C, 62.75; H, 5.00; N, 19.94.

RESULTS AND DISCUSION

If the compound **(4)** contains unreacted **(3)**, it is reacted with sodium borohydride in the second step of the Losartan process and leads to formation of impurity **(7)**. In the same fashion, said impurity was synthesized by treating the compound **(3)** with sodiumborohydride (Scheme 2). The mass spectrum of **(7)** displayed a protonated molecular ion at m/z 189, IR spectral pattern showed broadband at 3436 cm^{-1} corresponding to OH stretching and apart from this, disappearance of sharp carbonyl signal observed at 1666 cm^{-1}. In ^1H NMR spectrum, one singlet signal was observed at 4.29 δ ppm with two proton integration. This spectral data is in conformity with (2-butyl-4-chloro-1*H*-imidazol-5-yl) methanol **(7)** structure. Impurity 8 resulted from compound **(2)**, due to basic reaction conditions employed during the condensation step. This impurity (Scheme 2) prepared by the reaction of compound **(2)** with aqueous NMP (N-methyl pyrrolidine). The mass spectrum of **(8)** displayed a protonated molecule ion at m/z 253, IR spectral pattern is similar to that of compound **(2)** except two broad signals at 3571 cm^{-1} and at 3406 cm^{-1} corresponding to OH and NH stretching respectively. In ^1H NMR spectrum, singlet signal appeared at 4.50 δ ppm with one proton integration corresponding to NH. This spectral data is in conformity [2′-(2H-tetrazol-5-yl)biphenyl-4-yl]methanol

(8) structure.

The compound /impurity **(9)** was synthesized by treating **(5)** with aqueous HCl and 2-bromopropane (Scheme 2). The mass spectrum of **(9)** displayed a protonated molecule ion at m/z 465. The IR spectrum was similar to that of **(6)**, in addition to that disappearance of a broad band at 3500 cm^{-1} corresponding to -OH stretching was observed. In ^1H NMR spectrum, one multiplet signal at 2.66 δ ppm with one proton integration and one doublet at 1.16 δ ppm with six protons integration was observed. Based on the spectral data, the structure was confirmed as 5-[4′-((2-butyl-4-chloro-5-(isopropoxymethyl)-1*H*-imidazol-1-yl) methyl) biphenyl-2-yl]-2*H*-tetrazole **(9)**. Impurity 10 synthesized by treating the compound **(5)** with 10% HCl and trityl chloride (Scheme 2). The mass spectrum of **(10)** displayed a protonated molecule ion at m/z 665.2. IR spectrum showed broad band at 3447 cm^{-1} which was attributed to NH stretching and disappearance of a OH band at 3564 cm^{-1}. This spectral data is in conformity with the structure of **(10)**.

Impurity **(11)** quantitatively synthesized by the reaction of compound **(5)** with 10% HCl and acetyl chloride (Scheme 2). The mass spectrum of **(11)** displayed a protonated molecule ion at m/z 465.2. The IR spectra showed strong carbonyl absorption band at 1742 cm^{-1}. In ^1H NMR spectrum, singlet signal appeared at 2.22 δ ppm with three proton integration and singlet signal at 5.01 ppm with two proton integration. This spectral data is in conformity with structure of **(11)**. Finally, impurity **(12)** synthesized by treating the compound **(6)** with Tempo (2, 2, 6, 6-tetramethylpiperidine 1-oxyl) and I_2, followed by with 10% HCl (Scheme 2). The mass spectrum of **(12)** displayed a protonated molecule ion at m/z 421.1. IR spectral pattern was similar to that of **(5)**, in addition to that a band at 1666 cm^{-1} corresponding to C=O stretching was observed. In ^1H NMR spectrum, singlet signal appeared at 9.61 δ ppm with one proton integration. This spectral data confirms the structure of **(12)**.

CONCLUSION

In conclusion, we have provided synthesis and spectral characterization of six Losartan potassium pharmacopial impurities.

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