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Synthesis of telmisartan impurity B

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Telmisartan is an antihypertensive drug and is a specific angiotensin II receptor (AT1) antagonist. According to European Pharmacopoeia 7 Edition 2008 telmisartan quality standard, there are seven impurities in telmisartan. Impurity B which is not available commercially and no synthetic method is published so far. We report herein the first synthesis of impurity B. The structure of impurity B was confirmed by ^{1}H NMR, ^{13}C NMR and MS data. These findings should be important for quality control purposes in the manufacture and quality control of telmisartan.

1. Introduction

Telmisartan is an antihypertensive drug developed by the German Boehringer Ingelheim company. Its chemical name is 4'-[[4-methyl-6-(1-methyl-1*H*-benzimidazol-2-yl)-2-propyl-1*H*-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid. It was introduced in the US in 1992 under the brand name of Micardis. Telmisartan is a non-peptide angiotensin II receptor converting enzyme antagonist (Merlos et al. 1997; Hauel et al. 1997; Venkataraman et al. 2007; Ries et al. 1993). It has high bioavailability, long half life, good security, few side effects, so it can be used as a first-line drug in the treatment of hypertension. According to the European Pharmacopoeia 7 Edition 2008 telmisartan quality standard, there are seven impurities in the telmisartan [PhEur 7.0]. Impurity B is not available commercially and no synthesis method is reported. Thus, this study provides a method for preparing telmisartan impurity B for reference in the the quality control of telmisartan (Snjeev Kumar et al. 2009; Hauel et al. 2004).

2. Investigations, results and discussion

The synthesis procedure comprises seven steps. Compound **1** as the raw material, under alkaline conditions, gave compound **2** which was chlorinated (compound **3**). This intermediate reacted with *N*-Methyl-o-phenylenediamine dihydrochloride under alkaline condition and gave compound **4**. In organic acid as solvent, and at a reaction temperature of 80−130 °C, compound **5** was prepared. With 4'-bromomethyl-biphenyl-2-carbonitrile, in an organic solvent, and with alkali as catalyst, at a temperature of 10 −80 °C, compound **6** was synthesized. In 50–130 °C acid solution compound **6** was reduced using a metal reductant to compound **7**. Under alkaline conditions, with an organic solvent and water, **7** was hydrolysed at 30–180 °C to obtain impurity B (Fig. 2).

3. Experimental

3.1. General

All commercially available reagents and solvents were used without further purification, unless specified. Solvents were dried and re-distilled prior to use according to standard methods. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker ARX 300 MHz instrument, using DMSO-*d*6 as solvent and TMS as the internal standard. Mass spectra were obtained on an Agilent 1100 mass spectrometer. Column chromatography (CC) was performed on silica gel H and analytical TLC on silica gel HF254.

3.2. First step: 4-(Butyrylamino)-3-methyl-5-nitrobenzoic acid (2)

A solution of 4-(butyrylamino)-3-methyl-5-nitrobenzoate (28.0 g), NaOH (8.0 g)in H_2O (70 ml) and methanol (70 ml), was placed into a 250 mL 4-necked round-bottom flask. The resulting solution was allowed to react for 3 h while maintaining the temperature at 60 °C. The reaction progress was monitored by thin-layer chromatography (dichloromethane: methanol = 10:1) until the starting material was consumed completely. The reaction was then quenched by water (70 ml) and the pH value of the solution was adjusted to 5 with glacial acetic acid. The solids were filtered out. This resulted in 25.0 g (93%) of 4-(butyrylamino)-3-methyl-5- nitrobenzoic acid as a white solid. ESI-MS:267$[M+1]^{+}$

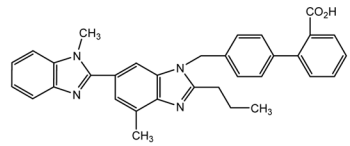
3.3. Second step: 4-(Butyrylamino)-3-methyl-5- nitrobenzoyl chloride (3)

A solution of 4-(butyrylamino)-3-methyl-5-nitrobenzoic acid (**2**, 24.0 g) in dichloromethane (120 ml) was placed into a 250 ml 4-necked round-bottom flask. Thionyl chloride (21.4 g) was added dropwise to the solution while maintaining the temperature at 0–10 °C (about 1 h until completion). The resulting solution was allowed to react for 8 h while maintaining the temperature at 45 °C. The reaction progress was monitored by thin-layer chromatography (dichloromethane: methanol = 20:1) until the starting material was consumed completely. The solution was concentrated by evaporation under vacuum using a rotary evaporator. The product (25.6 g, purity: 95%, yield: 90%) of 4-(butyrylamino)-3-methyl-5-nitrobenzoyl chloride (**3**) was obtained as a pale yellow solid. The material was used in the next step without any further purification.

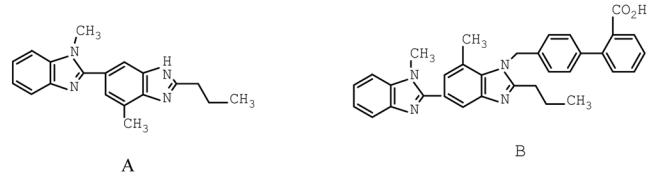
3.4. Third step: 4-Butyrylamino-3-methyl-N-(2-methylamino-phenyl)-5-nitro-benzamide (4)

A solution of *N*-methyl-o-phenylenediamine dihydrochloride (35.1 g) in dichloromethane(175 ml) and water (210 ml) was placed into a 250-mL 4-necked round-bottom flask. Sodium bicarbonate (37.8 g) in batches was added to the above solution at room temperature. A solution of 4-(butyrylamino)-3-methyl-5-nitrobenzoyl chloride (**3**, 25.6 g) in dichloromethane (128 ml) was added dropwise to the solution while maintaining the temperature at 0–10 °C (about 1 h until completion). The reaction mixture was stirred to reflux for 1 h and the reaction progress was monitored by thin-layer chromatography (dichloromethane: methanol = 20:1)

Structures of telmisartan

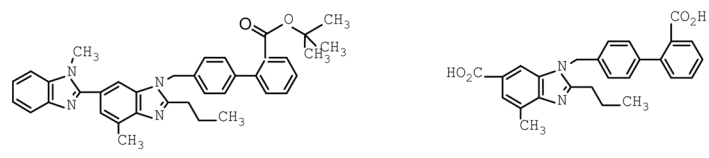


Structures of Impurity A and B



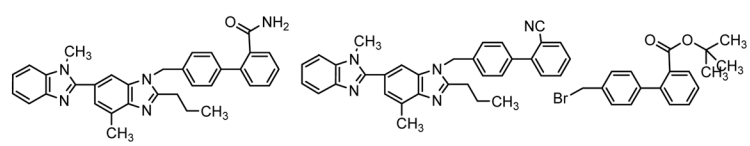
A B

Structures of Impurity C and D



C D

Structures of Impurity F、G and H

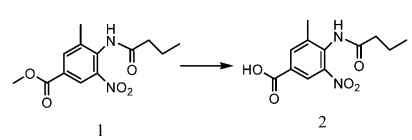


F G H

Fig. 1: Structures of telmisartan and 7 impurities

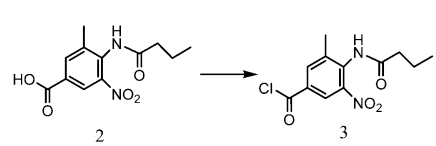
until the starting material was consumed completely. The resulting solution was extracted with dichloromethane (2 × 100 ml) and the organic layers were combined. The resulting mixture was washed with 10% acetic acid aqueous solution (100 ml × 2) and saturated brine (1 x 100 ml). The organic phase was dried over anhydrous sodium sulfate and concentrated under vacuum. This resulted in 25.9 g (78%) of 4-butyrylamino-3-methyl-*N*-(2-methylamino-phenyl)-5-nitro-benzamide (**4**) as dark solid. ESI-MS: 371 $[M+1]^+$

The first step: 4-(butyrylamino)-3-Methyl-5- Nitrobenzoic acid



1 2

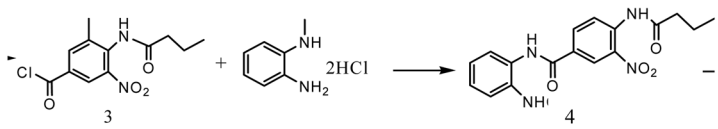
The second Step: 4-(butyrylamino)-3-Methyl-5- Nitrobenzoyl chloride



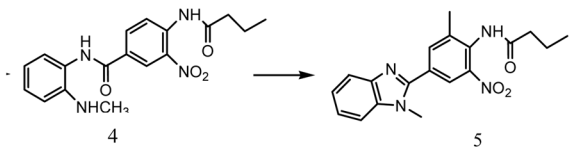
2 3

Fig. 2: Synthetic route to impurity B

The third Step: 4-Butyrylamino-3-methyl-N-(2-methylamino-phenyl)-5-nitro-benzamide

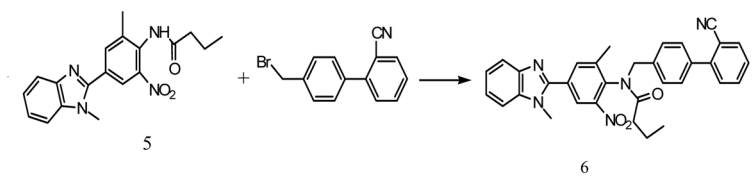


The fourth Step: N-[2-Methyl-4-(1-methyl-1H-benzoimidazol-2-yl)-6-nitro-phenyl]-butyramide

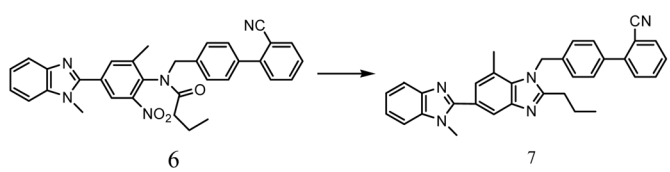


The fifth Step:

N-(2'-Cyano-biphenyl-4-ylmethyl)-N-[2-methyl-4-(1-methyl-1H-benzoimidazol-2-yl)-6-nitro-phenyl]-butyramide



The sixth step:
4´-[[7-Methyl-5-(1-methyl-1H-benzimidazol-2-yl)-2-propyl-1H-benzimidazol-1-yl]methyl]biphenyl-2-carbonitrile



The seventh step: the preparation of impurity B

4´-[[7-Methyl-5-(1-methyl-1H-benzimidazol-2-yl)-2-propyl-1H-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

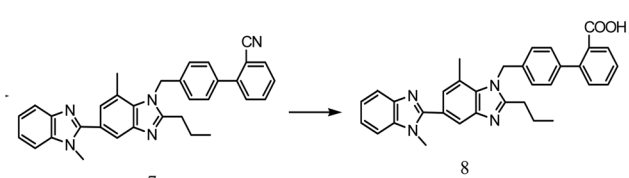


Fig. 2: (Continued)

3.5. N-[2-Methyl-4-(1-methyl-1H-benzoimidazol-2-yl)-6-nitro-phenyl]-butyramide (5)

A solution of 4-butyrylamino-3-methyl-*N*-(2-methylamino-phenyl)-5-nitro-benzamide (**4**, 25.9 g) in acetic acid (130 ml) was placed into a 250 ml 4-necked round-bottom flask. The mixture was stirred to reflux for 2 h. The reaction progress was monitored by thin-layer chromatography (dichloromethane: methanol = 20:1) until the starting material was consumed completely. The acetic acid solvent was removed under reduced pressure using a rotary evaporator. The residue was purified by flash chromatography on silica gel (dichloromethane:methanol = 50:1). The final product **5** (21.2 g, yield:86%) was obtained as a white solid. M.p. 151 - 153 °C, ESI-MS: 353 $[M+1]^+$

3.6. Fifth step: N-(2'-Cyano-biphenyl-4-ylmethyl)-N-[2-methyl-4-(1-methyl-1H-benzoimidazol-2-yl)-6-nitro-phenyl]-butyramide (6)

A solution of *N*-[2-methyl-4-(1-methyl-1*H*-benzoimidazol-2-yl)-6-nitro-phenyl]-butyramide (**5**, 21.2 g), potassium hydroxide (16.6 g) in *N,N*-dimethylformamide (106 ml) was placed into a 250 mL 4-necked round-bottom flask. The mixture was stirred for 30 min at room temper-

ature. 4'-Bromomethyl-biphenyl-2-carbonitrile (19.2 g) was added to the mixture which was then stirred at room temperature for 1 h. The reaction progress was monitored by thin-layer chromatography (dichloromethane: methanol = 20:1) until the starting material was consumed completely. The reaction was then quenched by water (500 ml). A filtration was performed. The filter cake was washed with water (100 ml × 3). The product (28.8 g, yield:83%) of *N*-(2'-cyano-biphenyl-4-ylmethyl)-*N*-[2-methyl-4-(1-methyl-1*H*-benzoimidazol-2-yl)-6-nitro-phenyl]-butyramide (**6**) was obtained as a white solid. The material was used in the next step without any further purification. ESI-MS: 544 $[M+1]^+$

3.7. Sixth step: 4-[[7-Methyl-5-(1-methyl-1H-benzimidazol-2-yl)-2-propyl-1H-benzimidazol-1-yl]methyl]biphenyl-2-carbonitrile (7)

A solution of *N*-(2'-cyano-biphenyl-4'-ylmethyl)-*N*-[2-methyl-4-(1-methyl-1*H*-benzoimidazol-2-yl)-6-nitro-phenyl]-butyramide (**6**, 28.8 g), iron (8.4 g) and acetic acid (144 ml) was placed into a 250-mL 4-necked round-bottom flask. The mixture was stirred to reflux for 2 h at 130 °C. The reaction progress was monitored by thin-layer chromatography (dichloromethane: methanol = 20:1) until the starting material was consumed completely. A filtration was performed to remove iron mud. The acetic acid solvent was removed under reduced pressure using a rotary evaporator. The residue was purified by flash chromatography on silica gel (ethyl acetate: petroleum ether = 1:3). The final product (**7**, 21.2 g, yield:80%) was obtained as a white solid. M.p. 205-207 °C ^{1}H NMR (300 MHz, CDCl3): δ 8.02(s, 1H), 7.85–7.89(m, 1H), 7.76(d, J = 6.9 Hz, 2H), 7.59(m, 7H), 7.40∼7.67(m, 7H), 7.30∼7.36(m, 2H), 7.07(d, J = 8.4 Hz, 2H), 5.68(s, 2H), 3.97(s, 3H), 2.87(t, J = 8.4 Hz, 2H), 2.58(s. 3H), 1.85–1.97(m, 2H), 1 .05(t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.90, 157.63, 154.47, 144.97, 142.49, 143.31, 138.39, 138.09, 136.74, 135.14, 134.29, 133.46, 130.48, 130.16, 128.35, 127.81, 126.03, 123.92, 123.20, 122.38, 119.70, 119.06, 118.60, 111.63, 110.23, 48.36, 32.47, 29.69. 21.75, 21.50, 18.78, 14.45. ESI-MS: 495 $[M+1]^+$

3.8. Seventh step: Preparation of impurity B: 4'-[[7-methyl-5-(1-methyl-1H-benzimidazol-2-yl)-2-propyl-1H-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

A solution of 4ĭ-[[7-methyl-5-(1-methyl-1*H*-benzimidazol-2-yl)-2-propyl-1*H*-benzimidazol-1-yl]methyl]biphenyl-2-carbonitrile (**7**, 4.96 g, 0.01 mmol), potassium hydroxide (2.8 g, 0.05 mmol) in ethylene glycol (25 ml) and water (1 ml) was placed into a 50 mL 4-necked round-bottom flask. The reaction mixture was stirred to reflux for 24 h at 160 °C. The reaction progress was monitored by thin-layer chromatography (dichloromethane: methanol = 10:1) until the starting material was consumed completely. The reaction was then quenched by 50 ml water and 25 ml ethanol. The pH value of the solution was adjusted to 5 with glacial acetic acid. A filtration was performed. The filter cake was washed once with mixed solution (ethanol: water = 1:2) and washed once with water (25 ml). The final product (4.2 g, yield:82.4%) was obtained as a white solid.^{1}H NMR (300 MHz, DMSO-d6): δ 12.65 (s, 1H), 7.93 (s, 1H), 7.65–7.73 (m, 2H), 7.52–7.61 (m, 2H), 7.41–7.46 (m, 2H), 7.21–7.37 (m, 5H), 6.99 (d, J = 8.1 Hz, 2H), 5.76 (s, 2H), 3.93 (s, 3H), 2.86 (t, J = 7.5 Hz, 2H), 2.54 (s, 3H), 1.78–1.90 (m, 2H), 1.00 (t, J = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, DMSO-d6): δ 170.47, 157.89, 154.80, 143.76, 143.48, 141.46, 140.93, 138.29, 137.59, 135.52, 133.21, 131.80, 131.35, 130.07, 129.89, 128.27, 126.82, 125.87, 124.33, 122.94, 122.70, 122.32, 119.65, 118.64, 111.33, 48.02, 32.73, 29.52. 21.22, 18.83, 14.79 ESI-MS: 515$[M+1]^+$

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