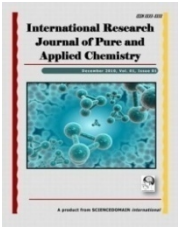

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Synthesis and Characterization of Impurities of a Common and Advanced Intermediate of Candesartan and Azilsartan Antihypertensive Drugs

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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ABSTRACT

Six impurities were identified in the lab development batches during the course of benzimidazole intermediate (1) synthesis by reverse phase HPLC method. Intermediate 1 is used as a common and advanced intermediate in the synthesis of candesartan and azilsartan. All the impurities were characterized by IR, NMR, LC/MS and CHN analyses, which included an isomer of intermediate 11 (impurity 19), desethyl analogue of 1 (impurity 20), desethoxy analogue of 1 (impurity 21), methyl analogue of 1 (impurity 22), cyanobiphenyl benzimidazole (impurity 25) and cyanobiphenyl derivative of 1 (impurity 26). The synthesis and characterization of these impurities are presented.

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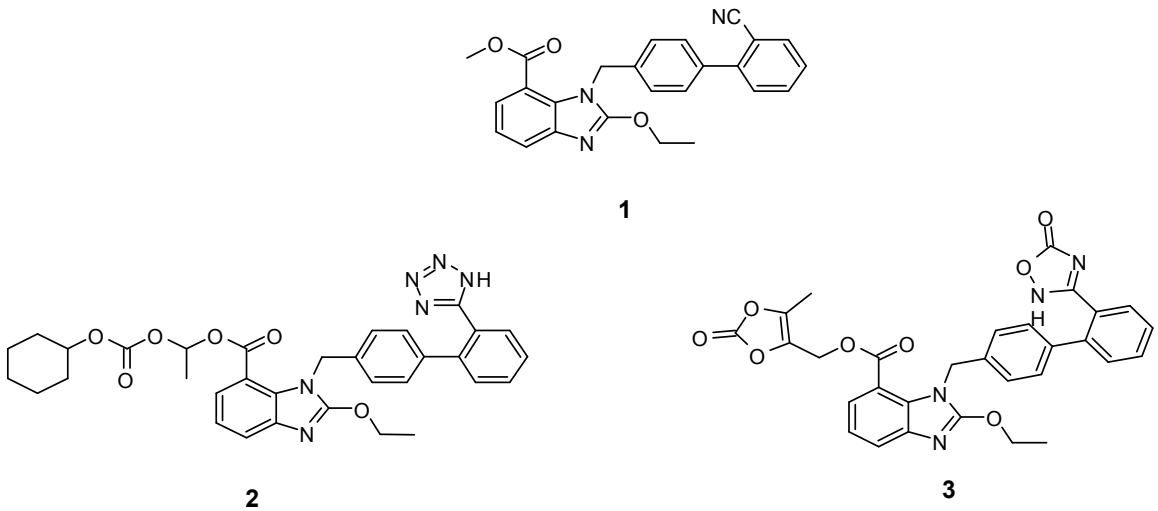
Keywords: Candesartan; azilsartan; benzimidazole; impurity; API and intermediate.

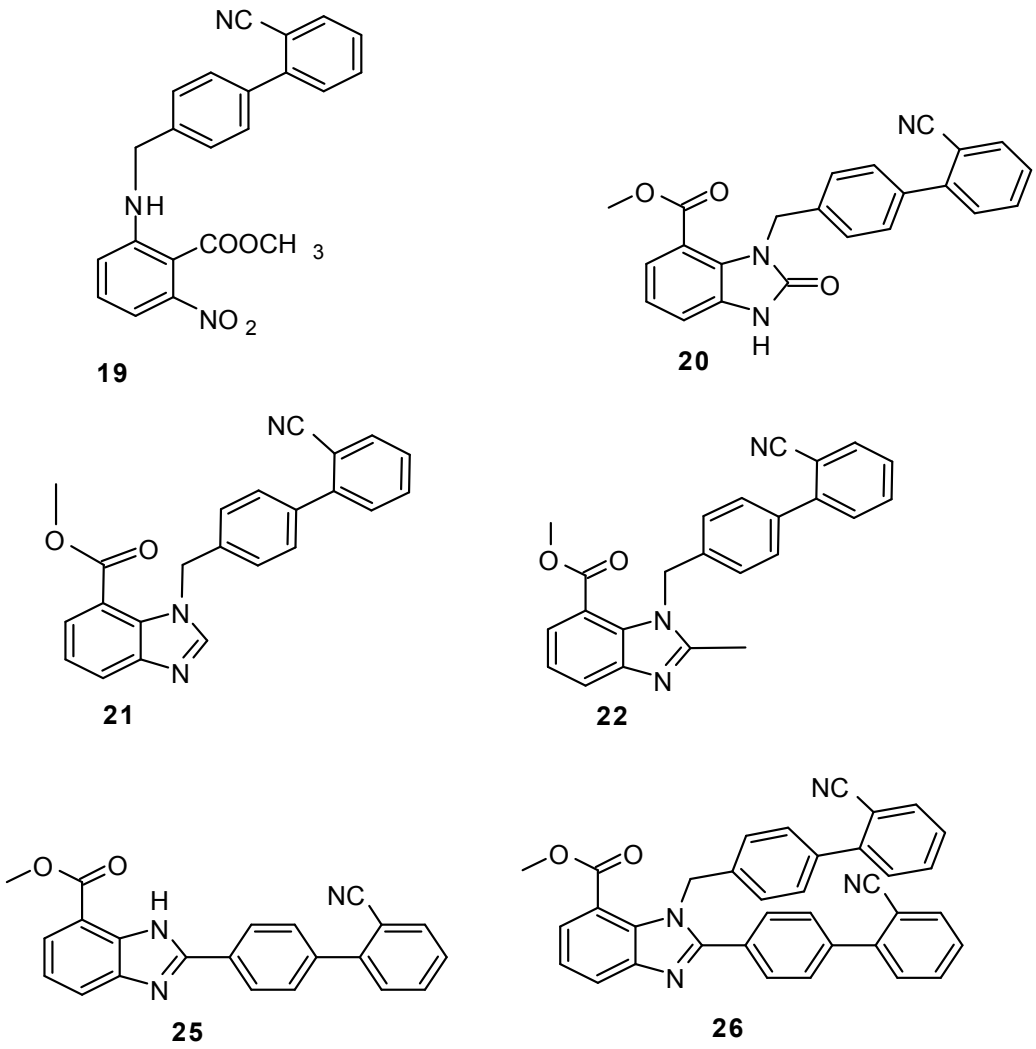
1. INTRODUCTION

The identification, characterization and control of both the processes and degradation related impurities in Active Pharmaceutical Ingredients (APIs) or drug substances are the essential aspects of drug development. Complete elimination of impurities for safe human consumption has been the goal of both pharmaceutical companies and various regulatory agencies. Consequently, for any drug registration, one of the principal requirements is to specify both identified and unidentified impurities in drug substance/drug product as per ICH guidelines Q3A(R), Q3B(R) and Q3C [1]. Characterization of impurities is required, particularly when they are present at a level higher than the identification threshold to control their levels in the final API or drug product [2]. Benzimidazole intermediate (**1**) is an advanced common intermediate used in the synthesis of candesartan cilexetil (**2**) [3, 4] and azilsartan medoxomil (**3**) [4-8] (Scheme **1**). Candesartan and azilsartan are angiotensin II receptor antagonists that modulate the renin-angiotensin-aldosterone system. These sartans are used in the treatment of hypertension, diabetic nephropathy and congestive heart failure [9-11]. Candesartan cilexetil and Azilsartan medoxomil are sold under the brand names Atacand and Edabyclor, respectively. Candesartan is administered alone or in combination with other hypertensive agents, while Edabyclor is a combination of azilsartan medoxomil and chlorthalidone.

The synthesis, structural elucidation and LC (liquid chromatography) method for few potential impurities of candesartan cilexetil [2, 12-14] and Azilsartan medoxomil [5] have been documented before now in the literature but nowhere the synthesis and characterization of impurities of Benzimidazole intermediate has been described in writings till now. In this paper, we present synthesis and characterization of six impurities identified in the lab development batches of intermediate **1** synthesis. They include methyl 2-{[(2'-cyanobiphenyl-4-yl) methyl] amino}-6-nitrobenzoate (impurity **19**), methyl3-[(2'-cyanobiphenyl-4-yl)methyl]-2-oxo-2,3-dihydro-1*H*-benzimidazole-4-carboxylate (impurity **20**), methyl 1-[(2'-cyanobiphenyl-4-yl)methyl]-1*H*-benzimidazole-7-carboxylate (impurity **21**), methyl 1-[(2'-cyanobiphenyl-4-yl)methyl]-2-methyl-1*H*-benzimidazole-7-carboxylate(impurity **22**), methyl 2-(2'-cyanobiphenyl-4-yl)-1*H*-benzimidazole-7-carboxylate (impurity **25**) and methyl 2-(2'-cyanobiphenyl-4-yl)-1-[(2'-cyanobiphenyl-4-yl)methyl]-1*H*-benzimidazole-7-carboxylate (impurity **26**) (Scheme **2**).



Scheme 1. Chemical structures of benzimidazole intermediate, candesartan and azilsartan



Scheme 2. Chemical structures of the impurities characterized in this study

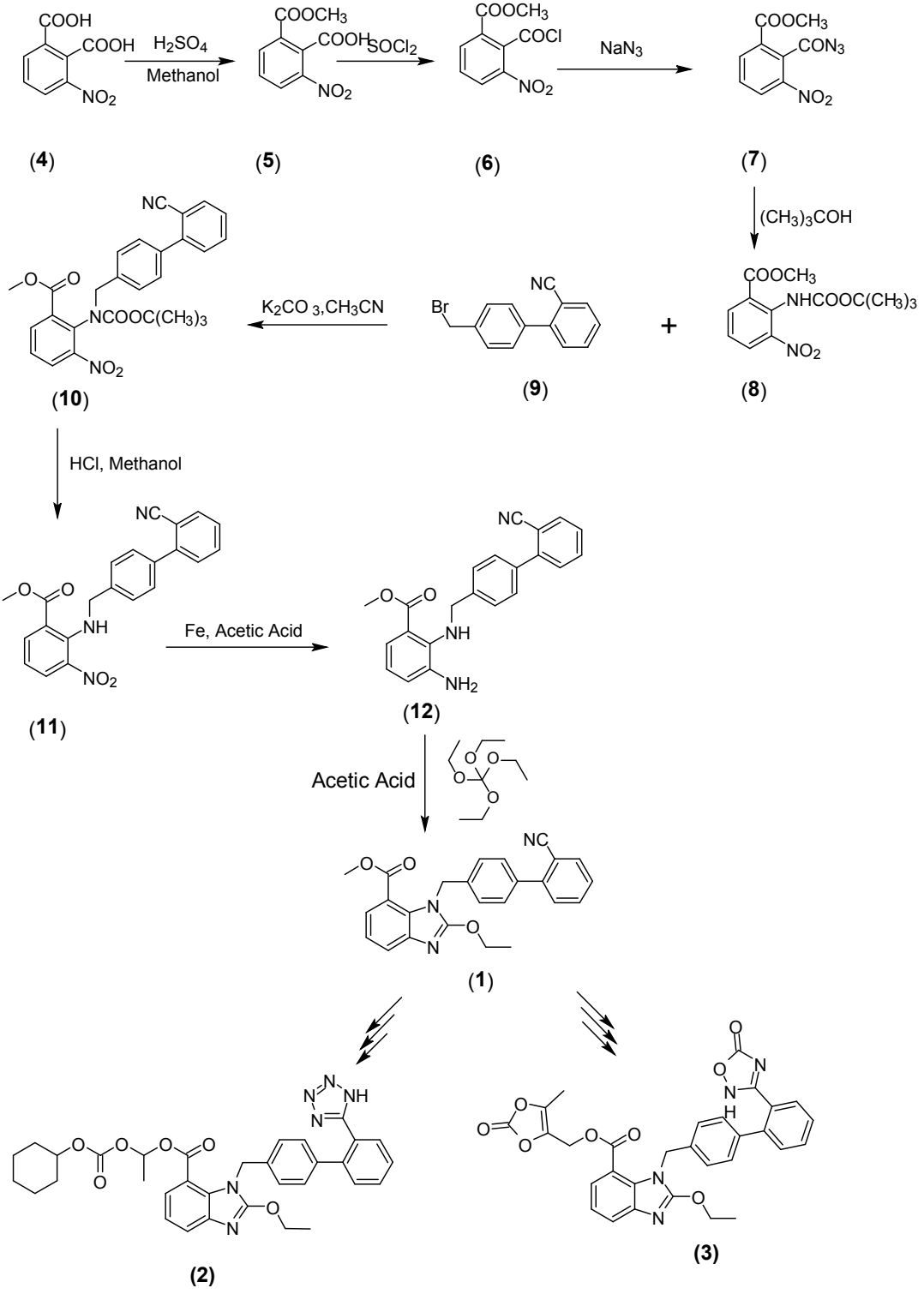
2. MATERIALS AND METHODS

HPLC (Agilent Technologies) with a UV detector, Empower software and NuGenesis UNIFY 7.1 print system was used for chromatographic analyses. Hypersil MOS-1 column (5µm particle size, 150mm × 4.6mm column size) and KH_2PO_4 buffer (pH 6.5)/acetonitrile gradient were used as the dormant and active phase, respectively, with flow rates of 1.5-2.5 ml/min. THF was used as a diluent and the UV absorptions were measured at 254 nm. IR spectra were recorded on Perkin-Elmer Spectrum One FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100.6 MHz, respectively using TMS as an internal standard. Signals from OH groups in ^{1}H NMR spectra recorded in $CDCl_3$ and DMSO were verified by the D_2O exchange. LCMS data was generated by using QTRAP LC/MS/MS system (Applied Biosystems). The mass spectral analysis was done by way of Ion Spray in positive ion mode using API 2000 LC/MS/MS system (Applied Biosystems). Perkin Elmer CHNS/O analyzer 2400 was used for CHN analysis. Analytical TLCs were performed on pre-coated mark silica gel 60 F_{254} plates and the spots were detected under UV light. Silica Gel (300-400 mesh) was used for column chromatography. All the chemicals were obtained from commercial suppliers and were used without any further purification.

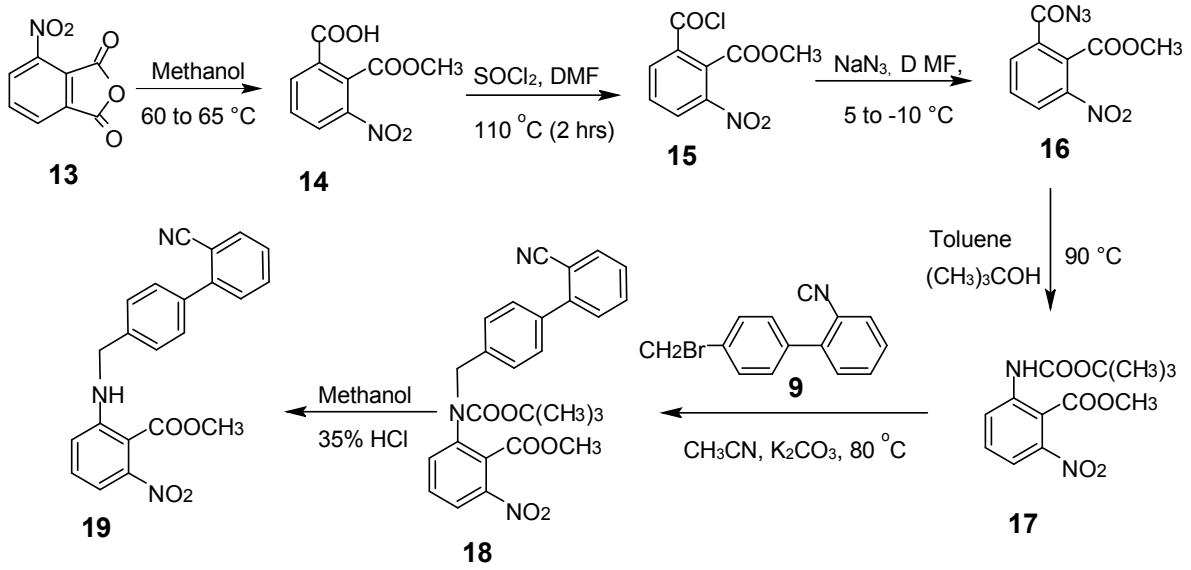
3. EXPERIMENTAL

A total of six impurities (Scheme **2**), were synthesized and characterized. A general route for preparation of benzimidazole intermediate (**1**) is shown in (Scheme **3)**. Impurity **19** was generated at step 6 (Scheme **4**), while the rest of

the impurities (**20**, **21**, **22**, **25** and **26**) were generated in the final step. Except for the impurity **19**, which was synthesized in six steps (Scheme **4**), all the other impurities were synthesized in one go process (Schemes **5**-**8**).



Scheme 3. Scheme for the synthesis of the benzimidazole intermediate (1) which is a common intermediate used in the synthesis of Candesartan (2) and azilsartan (3)



Scheme 4. Scheme for the synthesis of impurity 19, an isomer of intermediate 11 (Scheme 1)

3.1 Methyl 2-{[(2'-cyanobiphenyl-4-yl) methyl] amino}-6-nitrobenzoate (18)

Impurity 19 was synthesized in six steps starting from 4-nitro-2-benzofuran-1,3-dione (**13**). The key step is the formation of the undesired isomer (**14**, Scheme **4**) of intermediate **5** (Scheme **3**). The rest of the synthetic procedure is similar to that of intermediate **11** starting from compound **5**.

*2-(Methoxycarbonyl)-3-nitrobenzoic acid (**14**):* This is synthesized as per the reported procedures [15]. It involves the ring opening reaction of **13** under reflux conditions in methanol (Scheme **4**). 15 g of **13** was dissolved in 190 mL of methanol at RT and the resulting clear solution was stirred at 65 °C for 16 h. Methanol was completely distilled off at 50 °C under vacuum and the solid material (**14**) was dried at 50 °C under vacuum for about 16 h. Yield: 93.4%.

*Methyl 2-[(tert-butoxycarbonyl) amino]-6-nitrobenzoate (**17**):* Compound **17** is synthesized in three steps starting from **14** (Scheme **4**). 7 g of 2-(Methoxycarbonyl)-3-nitrobenzoic acid (**14**) was suspended in 25 ml toluene. 0.35 mL dimethylformamide (DMF) and 4.7 mL thionyl chloride were added to it. The resulting mixture was stirred at 110 °C for 2 h. The solvents were completely distilled off at 60 °C under vacuum. 70 mL toluene was added to the residue and the solvent was distilled off at 60 °C under vacuum and this process was repeated twice or thrice to remove the non-reacting thionyl chloride. 2-(Chlorocarbonyl)-6-nitrobenzoate (**15**) was isolated as a solid when the residue was cooled down to RT. Meanwhile, 3.1 g of sodium azide was suspended in 11 mL of DMF and the mixture was cooled down to -5 to -10 °C. Compound **15** was added to the sodium azide suspension and the resulting mixture was stirred at 10 to 15 °C for 1 h. Chilled mixture of toluene (28 mL) and water (42 ml) was added to the suspension and the resulting mixture was stirred at RT for 15 minutes. The organic layer was washed with water and dried over sodium sulphate to yield **16** dissolved in toluene. 10.5 mL tert-butanol was added to the toluene solution and the resulting solution was stirred at 90 °C for 6 h. Solvents were completely distilled off at 70 °C under vacuum and the residue was crystallized from IPA (7 mL). The product (**17**) was dried at 45 °C under vacuum for 5 h. Yield: 80.0%.

Finally, the impurity **19** was prepared from **17** in two steps (Scheme **4**). 5.45 g of **9**, 6.0 g of **17** and 3.15 g of potassium carbonate were suspended in 18 mL of acetonitrile. The resulting mixture was stirred at 80 °C for 13 h. Solvents were completely distilled off at 50 °C under vacuum to yield a yellow colored sticky crude compound (**18**). 50 mL methanol was added to it followed by the addition of 14.2 mL of 35% HCl slowly over a period of 10 minutes at RT. The resultant mixture was then stirred at 65 °C for 1 h. Yellow solids were filtered. The material was washed with 15 ml water and subsequently with 5 ml of chilled methanol. The resulting material was dried at 50 °C under vacuum for 16 h. Impurity **19** was obtained as a light yellow solid (yield = 89.4%); IR (KBr) V_{max} (in cm^{-1}): 3436 (N-H, stretching), 2225(C≡N stretching), 1688 (C=O

stretchings) 1539 and 1243 (N-O stretchings), 807 and 759 (C-H bending vibrations); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.84 (3H, s, C17-H, *J* = 7.1 Hz), 4.53 (2H, d, C8-H, *J* = 5.7 Hz), 6.83 (1H, d, Ar-H, *J* = 8.6 Hz), 6.97(1H, d, Ar-H, *J* = 7.8 Hz), 7.19 (1H, t, N-H, *J* = 5.3, 5.4 Hz), 7.31 (1H, t, Ar-H, *J* = 8.2 Hz), 7.43-7.57 (6H, Ar-H), 7.65 (1H, t, Ar-H, *J* = 7.7 Hz), 7.77 (1H, d, Ar-H, *J*= 7.7 Hz); ^{13}CNMR (100.6 MHz, $CDCl_3$): δ 47.12, 52.74, 106.58, 111.24, 112.46, 115.65, 120.37, 127.22,127.67, 129.30, 131.40, 132.70, 132.88, 133.79, 137.49, 138.34, 144.94, 149.0, 149.26, 152.14, 166.49 (CO); Mass: 388.5 $[M + H]^+$; MS/MS: 356.2, 192.2; CHN data: C-67.88, H-4.28, N-10.66. Theoretical CHN: C(68.21%), H(4.42%), N(10.85%).

3.2 Methyl3-[(2'-cyanobiphenyl-4-yl)methyl]-2-oxo-2,3-dihydro-1*H*-benzimidazole-4-carboxylate (20)

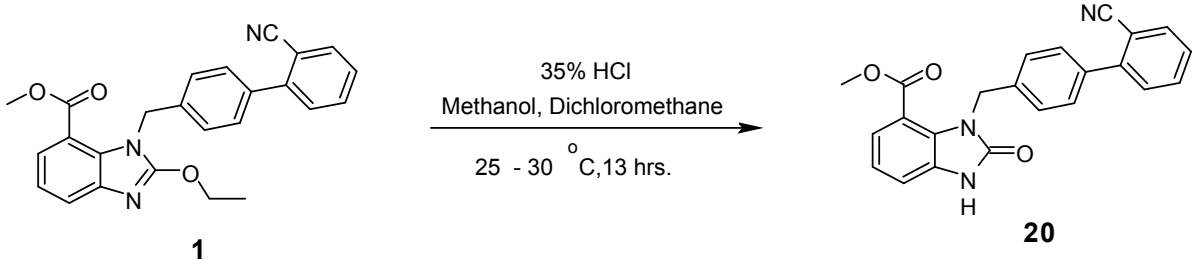
Impurity **20** was synthesized by the acidic degradation of the benzimidazole intermediate (**1**) (Scheme **5**).

4.0 g of **1** was dissolved in a mixture of 8 mL of methanol and 40 ml of dichloromethane. 8.5 ml of 35% HCl was added to it slowly over a period of 20 minutes at RT. The resulting clear solution was stirred at RT for 12 h and then stirred at 10 °C for 1 h. The solids were filtered through and washed with chilled methanol (2 mL). White solid of **20** was obtained after drying the material at 50 °C under vacuum for 12 h. (yield = 92.7%); IR (KBr) V_{max} (in cm^{-1}): 3436 (N-H stretching), 2223 (C≡N stretching), 1734 (C=O stretchings), 832 and 756 (C-H bending vibrations); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.71 (3H, s, C20-H), 5.58 (2H, s, C10-H), 7.09 (1H, t, *J* = 7.9 Hz, Ar-H), 7.21 (2H, d, *J* = 8.4 Hz, Ar-H), 7.29 (1H, d, Ar-H, *J* = 6.8 Hz), 7.37-7.47 (5H, m, Ar-H), 7.61 (1H, t, C25-H, *J* = 7.7, 7.8 Hz), 7.74 (1H, d, C23-H, *J* = 7.8 Hz), 9.97 (1H, s, N-H); ^{13}CNMR (100.6 MHz, $CDCl_3$): δ 45.80, 52.54, 111.22, 113.04, 115.99, 118.60, 121.17, 123.27, 127.09, 127.54, 128.13, 128.91, 129.32, 130.02, 132.78, 133.77, 137.05, 137.70, 145.02, 156.38 (CO), 166.58 (CO); Mass: 384.2 $[M + H]^+$, 401.2 $[M + NH_4]^+$; MS/MS: 352.1, 192.0, 165.2; CHN data: C-71.91,H-4.48, N-10.94. Theoretical CHN: C (72.05%), H (4.47%), N (10.96%), O (12.52%).

3.3 Methyl 1-[(2'-cyanobiphenyl-4-yl)methyl]-1*H*-benzimidazole-7-carboxylate(21)

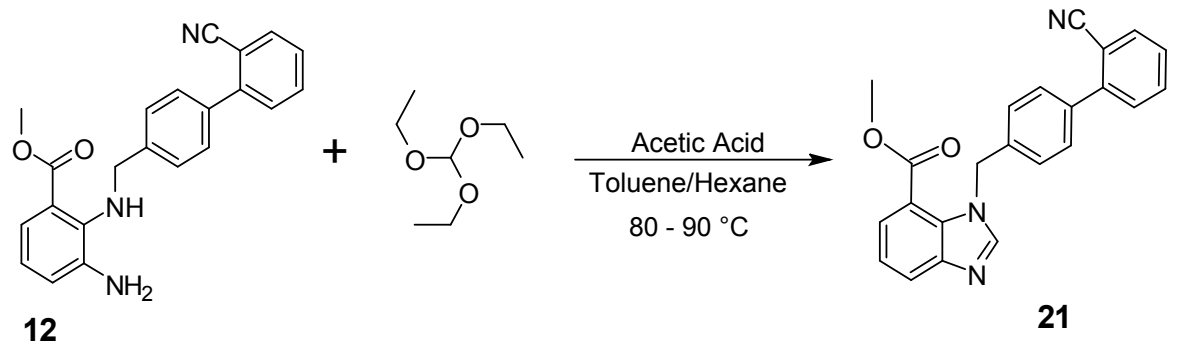
Impurity **21** was prepared by cyclizing the intermediate **12** in the presence of triethyl orthoformate (Scheme **6**) instead of tetraethyl orthocarbonate which leads to the formation of the intermediate **1** (Scheme **3**).

1.6 g of **12**, 1.62 mL of triethyl orthoformate and 0.3 g of acetic acid were added to 1.6 mL (1T) of toluene. The mixture was stirred at 90 °C for 2 h and then at -15 °C for 14 h. The resultant solids were filtered, washed with 10 mL of chilled toluene/hexane (1:1 v/v) and dried at 50 °C under vacuum for about 16 h to yield a light yellow solid (impurity **21**) (yield = 64.5%); IR (KBr) V_{max} (in cm^{-1}): 2223 (C≡N stretching), 1719 (C=O, stretching), 1604, 1595, 1502, 1436 (C=C, skeletal vibration), 853, 814, 756 (C-H bending vibrations); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.73 (3H, s, C19-H), 5.84 (2H, s, C10-H), 7.05 (2H, d, Ar-H, *J* = 8.3 Hz), 7.32 (1H, t, Ar-H, *J* = 7.8 Hz), 7.50 (2H, d, Ar-H, *J* = 8.3 Hz), 7.54-7.58 (2H, m, Ar-H), 7.63 (1H, d, C7-H, *J* = 7.6 Hz), 7.76 (1H, t, Ar-H, *J* = 7.5, 7.9 Hz), 7.92 (1H, d, Ar-H, *J* = 8.1 Hz), 7.98 (1H, d, Ar-H, *J* = 8.0 Hz), 8.61 (1H, s, C2-H);^{13}C NMR (100.6 MHz, $CDCl_3$): δ 49.68, 52.33, 110.11, 117.03, 118.39, 121.35, 124.37, 125.04, 126.57, 128.19, 128.87, 129.99, 130.66, 133.43, 133.78, 136.85, 137.92, 143.95, 145.80, 147.69, 166.08 (CO); Mass: 368.1 $[M + H]^+$; MS/MS: 192.1, 190.1, 165.1;CHN: C-72.86, H-5.05, N-10.81. Theoretical CHN: C (75.19%), H (4.66%), N (11.44%), O (8.71%),



1 **20**

Scheme 5. Scheme for the synthesis of impurity 20, a desethyl analogue of 1



Scheme 6. Scheme for the synthesis of impurity 21, a desethoxy analogue of 1

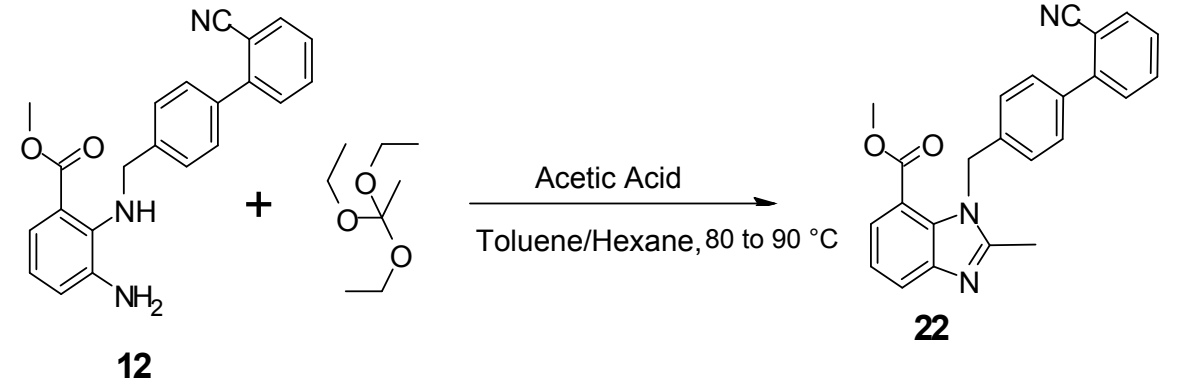
3.4 Methyl 1-[(2'-cyanobiphenyl-4-yl)methyl]-2-methyl-1*H*-benzimidazole-7-carboxylate (22)

Impurity **22** was prepared by cyclizing the intermediate **12** in the presence of triethyl orthoacetate (Scheme **7**), instead of tetraethyl orthocarbonate and triethyl orthoformate to yield intermediate **1** (Scheme **3**) and impurity **21** (Scheme **6**), respectively.

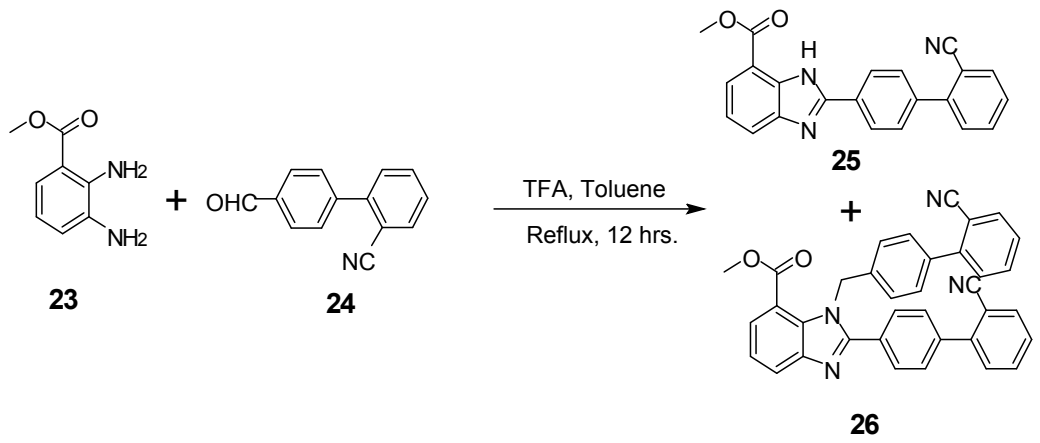
1.6 g of **12**, 1.8 mL of triethyl orthoacetate and 0.3 g of acetic acid were added to 1.6 ml of toluene. The resultant clear solution was stirred at 90 °C for 2 h and then stirred at -5 to -10 °C for 1 h. The solid material was filtered, washed with chilled toluene/hexane (1:1, v/v) and dried at 50 °C under vacuum for about 16 h to yield white solid of impurity **22** (yield: 74.2%); IR (KBr) V_{max}(in cm^{-1}): 2226 (C≡N, stretching), 1710 (C=O stretching), 1595, 771, 758 (C-H bending vibrations); 1H NMR (400 MHz, CDCl3): δ 2.61 (3H, s, C17-H), 3.68 (3H, s, C20-H), 5.76 (2H, s, C10-H), 7.02 (2H, d, Ar-H, *J* = 8.2, 8.3 Hz), 7.26 (1H, t, Ar-H, *J* = 7.8 Hz), 7.46-7.71 (5H, Ar-H), 7.76 (1H, t, Ar-H, *J* = 4.7, 7.5 Hz), 7.85 (1H, d, Ar-H, *J* = 7.7 Hz), 7.93 (1H, d, Ar-H, *J* = 8.0 Hz);^{13}C NMR (100.6 MHz, $CDCl_3$): 14.15, 48.10, 52.27, 110.10, 116.48, 118.42, 120.96, 122.97, 124.25, 126.19, 128.19, 128.93, 130.01, 132.10, 133.46, 133.80, 136.67, 137.78, 143.98, 144.13, 154.67, 166.32 (CO); Mass: 382.5 $[M + H]^+$; MS/MS: 350.0, 192.1; CHN data: C-73.86, H-5.02, N-10.67. Theoretical CHN: C (75.57%), H (5.02%), N (11.02%).

3.5 Methyl 2-(2'-cyanobiphenyl-4-yl)-1*H*-benzimidazole-7-carboxylate (25) and methyl 2-(2'-cyanobiphenyl-4-yl)-1-[(2'-cyanobiphenyl-4-yl)methyl]-1*H*-benzimidazole-7-carboxylate (26)

Both impurities, **25** and **26**, (Scheme **8**) were prepared in a single step by condensing the diamino derivative **23** and 4-bromomethyl biphenyl derivative **24** in the presence of trifluoroacetic acid by following the reported procedure for the preparation of the related compounds [16].



Scheme 7. Scheme for the synthesis of impurity 22, a methyl analogue of 1



23 **24** **25** **26**

Scheme 8. Scheme for the synthesis of cyanobiphenylbenzimidazole (impurity 25) and cyanobiphenyl derivative of 1 (impurity 26)

0.5 g of **23** and 1.2 g of **24** were added in 5 mL of toluene and stirred the mixture at RT. After 5 minutes, 0.25 ml of trifluoroacetic acid was further added and the clear solution was stirred further under the reflux conditions for 12 h. After cooling the mixture to RT, 20 mL of ethyl acetate and 10 mL of water was added to it. The organic layer was washed with a sodium bicarbonate solution and finally with a brine solution. The solvents were completely distilled off at 40 ^{o}C under vacuum to yield 0.95 g of a solid mixture of **25** and **26**, which were separated by flash chromatography using ethyl acetate/hexane gradient from 30% ethyl acetate to 100%. Yield: **25 (**off white solid): 0.32 g and **26** (off white solid): 0.24 g.

25: IR (KBr) V_{max}(in cm^{-1}): 3464 (N-H stretching), 2221 (C≡N stretching), 1718 (C=O stretching), 1600, 1543, 1478, 1438 (C=C aromatic skeletal vibration), 778, 753, 745 (C-H bending vibrations); ^{1}H NMR (400 MHz, $CDCl_3$): δ (in ppm) 4.03 (3H, s, C18-H), 7.37 (1H, t, Ar-H, *J* = 7.8, 7.8 Hz), 7.64(1H, t, Ar-H, *J* = 7.4, 7.5 Hz), 7.70 (1H, d, Ar-H, *J* = 7.8 Hz), 7.73-7.89 (4H, m, Ar-H), 8.01 (2H, d, Ar-H, *J* = 7.5 Hz), 8.47 (2H, d, Ar-H, *J* = 7.4 Hz), 12.5 (1H, s, N-H);^{13}C NMR (100.6 MHz, $CDCl_3$): 52.14, 110.14, 114.06, 118.48, 124.44, 124.74, 128.01, 128.56, 129.06, 129.59, 129.71, 129.75, 130.09, 130.60, 133.94, 134.24, 139.38, 143.72, 144.86, 152.63, 165.60 (CO); Mass: 354.4 $[M + H]^+$, 707.4 $[2M + H]^+$; MS/MS: 513.1, 192.0; CHN data: C -74.17%, H -4.48%, N -11.29%. Theoretical CHN: C (74.78%), H (4.28%), N (11.89%).

26: IR (KBr) V_{max} (in cm^{-1})*:* 3438 (N-H stretching), 2223 (C≡N stretchings), 1710 (C=0, stretching), 1608, 1596, 1471, 1430 (C=C aromatic skeletal vibration), 825, 847, 759, (C-H bending vibrations); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.94 (3H, s, C25-H), 5.81 (2H, s, C10-H), 7.19 (2H, d, Ar-H, *J* = 8.1 Hz), 7.40 (1H, t, Ar-H, *J* = 7.8 Hz), 7.55 (4H, d,d, Ar-H, *J* = 7.5, 8.0 Hz), 7.64 (1H, t, Ar-H, *J* = 7.6 Hz), 7.71-7.89 (7H, Ar-H), 7.92 (1H, d, Ar-H, *J* = 7.7 Hz), 7.96 (2H, d, Ar-H, *J* = 8.2 Hz), 8.0 (1H, d, Ar-H, *J* = 7.7 Hz);^{13}C NMR (100.6 MHz, $CDCl_3$): 47.40, 51.92, 110.03, 110.22, 115.90, 118.39, 118.44, 121.11, 122.35, 124.84, 126.53, 128.24, 128.63, 129.20, 129.60, 129.98, 130.04, 130.14, 133.48, 133.61, 133.83, 133.92, 137.02, 137.05, 137.17, 139.40, 141.26, 143.57, 143.80, 154.18, 166.24 (CO). Mass: 546.2 $[M + H]^+$; MS/MS: 545.5, 514.4, 193.3, 192.2; CHN data: C-78.26, H-4.51, N-10.11. Theoretical CHN: C (79.39%), H (4.44%), N (10.29%).

4. RESULTS AND DISCUSSION

Identification and characterization of impurities in key raw materials and/or intermediates is necessary to control their levels in the final API. Benzimidazole derivative **1** is one of the common and advanced intermediates for the synthesis of candesartan (**2**) [3-4] and azilsartan [4-8]. Various routes of synthesis of candesartan using 3-nitrobenzene-1, 2-dicarboxylic acid (**4**) as a key starting material via the benzimidazole intermediate were also reported [17-22]. In the present study, we have followed the procedure as reported by Kubo et al. to synthesize benzimidazole intermediate **1** and subsequently candesartan in three additional steps (Scheme 3) [20]. The reverse phase HPLC analysis of various lab development batches of benzimidazole derivative (**1**) revealed the presence ofsix impurities at the levels up to 1-2%

of which five were hitherto unknown. These impurities included impurity **19**, an isomer of intermediate **11**; impurity **20**, desethyl analogue of **1**; impurity **21**, desethoxy analogue of **1**; impurity **22**, methyl analogue of **1**; impurity **25**, cyanobiphenyl benzimidazole and impurity **26**, cyanobiphenyl derivative of **1**. The impurities were found to carrying forward the API stage of the lab batches of candesartan synthesis. Hence, controlling all the impurities at the benzimidazole intermediate stage itself can be a good strategy. The reverse phase HPLC separation of the impurities was based on gradient elution with potassium dihydrogen orthophosphate buffer (pH 6.5) and acetonitrile on Hypersil MOS–1 column. All the six impurities were characterized on the basis of their chemistry and fragmentation patterns in LC/MS-MS and their structures were further confirmed by IR, ^{1}H NMR, ^{13}C NMR, Mass/MS-MS and elemental analysis (Analytical spectra's has been attached as supplementary material).

The origin of impurity **19**, an isomer of intermediate **11**, can be traced back to step 1 in (Scheme **3)**, wherein esterification of any one of the carboxylic groups is equally possible. Impurity **19** is formed at step 6 in the synthesis of intermediate **1** (Scheme **3**). The efforts to separate these closely related isomers (**11** and **19**, (Schemes **3** and **4)**, respectively) using column chromatography were unsuccessful. Therefore, attempts were made to directly synthesize this impurity (**19**) from **14**, which in turn was prepared by subjecting 3-nitro phthalic anhydride (**13**) to the ring opening conditions (Scheme **4**). Synthesis of **19** (isomer of **11**) starting from **14** (isomer of **5**) is similar to that of the desired isomer (**11**) starting from **5** (Schemes **3** and **4**).

Impurities **20**, **21**, **22**, **25** and **26** are formed in the final step of the synthesis of intermediate **1** (Scheme **3)**. Compound **20** has been previously identified to be an impurity of candesartan cilexetil (**2**) [23]. However, its synthesis was not reported. In the present work, we have synthesized it by decomposing **1** with conc. HCl at RT (Scheme **5**). It is possible that the impurities **21** and **22**, desethoxy and methyl analogues of **1**, respectively, can be formed as a result of the reaction of **12** with the respective triethyl orthoformate and triethyl orthoacetate impurities present in tetraethyl orthocarbonate. This was indeed realized when they were synthesized by reacting **12** with triethyl orthocarbonate and triethyl orthoacetate separately in the presence of acetic acid (Schemes **6** and **7**). However, the origin of the last two impurities (**25** and **26**) is not clear from (Scheme **3)**. But some clues on the mechanism of their formation can be found in the reported synthesis of the related compounds [16]. These impurities were synthesized in one pot by following the reported procedure (Scheme **8**) [16] and subsequently they were separated by flash column chromatography.

5. CONCLUSION

We have presented synthesis and characterization of six impurities that were found to be in range of 1-2% in the lab batches of the benzimidazole intermediate synthesis, which is one of the common and advanced intermediates used in the synthesis of candesartan and azilsartan. All the six impurities, five of which were hitherto unknown, were separately synthesized in one-step processes, except for the isomer of intermediate **11**, which was synthesized in six steps. The data generated in the present work will be very useful in controlling these impurities in candesartan and azilsartan final API.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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