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## Synthesis and characterization of related substances of Azilsartan Kamedoxomil

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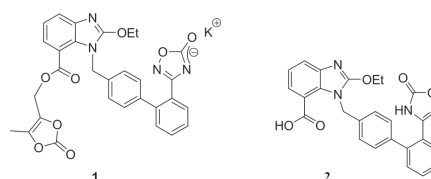
### ABSTRACT

Azilsartan Kamedoxomil is an AT<sub>1</sub>-subtype angiotensin II receptor blocker (ARB). During the laboratory synthesis of Azilsartan Kamedoxomil, four related substances of Azilsartan Kamedoxomil were observed and identified. These were 2-Ethoxy-3-[[4-[2-[(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl]-5-oxo-1,2,4-oxadiazol-3-yl]phenyl]phenyl]methyl] benzimidazole-4-carboxylic acid (azilsartan N-medoxomil, **9**), (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 2-ethoxy-3-[[4-[2-[(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl]-5-oxo-1,2,4-oxadiazol-3-yl]phenyl]phenyl]methyl] benzimidazole-4-carboxylate (azilsartan dimedoxomil, **10**), (5-methyl-2-oxo-1,3-dioxo-4-yl)methyl 1-[2'-(4,5-dihydro-5-oxo-4H-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl]-2-methoxy-1H-benzimidazole-7-carboxylate (methoxy analogue of azilsartan medoxomil, **11**), Methyl 1-((2'-amidobiphenyl-4-yl)methyl)-2-ethoxy-1H-benzo[d]imidazole-7-carboxylate (amide methyl ester, **12**). The present work describes the origin, synthesis and characterization of these related substances.

### INTRODUCTION

Azilsartan Kamedoxomil is an AT<sub>1</sub>-subtype angiotensin II receptor blocker (ARB). Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin converting enzyme, and angiotensin II is the principal pressor agent of the rennin-angiotensin system [1,12], with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Azilsartan Kamedoxomil blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT<sub>1</sub> receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Azilsartan Kamedoxomil, a prodrug form of azilsartan **2**, was approved in 2011, and is used for the treatment of hypertension. It is marketed by Takeda under the brand name of Edarbi®. Azilsartan Kamedoxomil **1** is chemically known as (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 2-ethoxy-1-[[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylate potassium salt. Azilsartan **2** is chemically known as

2-ethoxy-1-[[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylic acid.



**Figure 1.** Structures of Azilsartan Kamedoxomil **1** and Azilsartan **2**

The presence of impurities in an Active Pharmaceutical Ingredient (API) will influence the quality and safety of the drug product. In the regulatory guidelines of the International Conference on Harmonization (ICH), it is recommended that impurities amounting to more than 0.1% [5] should be identified and characterized. Impurities are required to be in pure form to check the analytical performance characteristics such as specificity, linearity, range, accuracy, precision, limit of detection (LOD), limit of quantification, robustness, system suitability testing and relative retention factor [4].

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During the process development of Azilsartan Kamedoxomil **1** in our laboratory, we observed the formation of four substances that are related to Azilsartan Kamedoxomil. These unknown related substances were identified, as well as monitored, and their structures were tentatively assigned on the basis of their fragmentation patterns in LC-MS. In the present work, the identified related substances of Azilsartan Kamedoxomil **1** were synthesized and then characterized by various spectroscopic techniques. Moreover, they were further confirmed by co-injection studies using qualitative HPLC analysis.

## EXPERIMENTAL

Solvents and reagents were obtained from commercial source and used without purification. The IR spectra ( $9\text{max}$ ,  $\text{cm}^{-1}$ ) were recorded in solid state KBr dispersion, using a Perkin Elmer FT-IR spectrometer. The  $^1\text{H-NMR}$  and  $^{13}\text{C-NMR}$  spectra were recorded on a Bruker-Avance 300 MHz, 500 MHz and a 125 MHz spectrometer. The chemical shifts were reported in  $\delta/\text{ppm}$  relative to TMS. The mass spectra were then recorded on a API 2000 Perkin Elmer PE-Sciex mass spectrometer. The reactions were monitored by High pressure liquid chromatography (HPLC). Melting points were determined via a polman melting point apparatus (Model No MP96) by the open capillary method, and are uncorrected.

### 2-Ethoxy-3-[[4-[2-[4-[(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl]-5-oxo-1,2,4-oxadiazol-3-yl]phenyl]phenyl]methyl]benzimidazole-4-carboxylic acid (azilsartan N-medoxomil, **9**)

To a solution of Azilsartan (10 g, 21.92 mmol) in DMF (30 mL), we added medoxomil chloride (2.6 g, 17.53 mmol) at 25-30°C. The reaction mass was stirred for 1 h and the reaction mass was poured into DM water (300 mL). We then stirred the reaction mass for 1 h, filtered the product and dried the white colored compound results **9** (7 g, 57%). The analytical results are as followed: HPLC Purity: 98.36 %; IR (KBr pellet): 3662, 2990, 1778, 1730, 1614, 1552, 1287, 1221, 1132  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (500 MHz,  $\text{DMSO-}d_6$ )  $\delta$ : 7.7603-7.722 (m, 5H, Ar), 7.49-7.519 (m, 1H, Ar), 7.172-7.255 (m, 3H, Ar), 7.007-7.034 (d, 2H, Ar), 5.635(s, 2H, N- $\text{CH}_2$ -Ar), 4.574-4.597 (q, 2H,  $\text{COOCH}_2$ ), 4.152 (s, 2H,  $\text{OCH}_2\text{CH}_3$ ), 1.620 (s, 3H,  $\text{CH}_3$ ), 1.352-1.399 (t, 3H,  $\text{OCH}_2\text{CH}_3$ );  $^{13}\text{C NMR}$  (125 MHz,  $\text{DMSO-}d_6$ )  $\delta$ : 167.50, 158.26, 158.11, 157.77, 151.23, 141.62, 140.71, 139.07, 137.60, 136.92, 132.58, 131.20, 131.12, 131.04, 130.51, 128.55, 128.18, 126.99, 123.29, 121.37, 120.46, 116.67, 66.48, 46.33, 40.00, 39.83, 39.66, 39.50, 39.16, 38.99, 34.68, 14.31, 8.08; HRMS for  $\text{C}_{30}\text{H}_{25}\text{N}_4\text{O}_8$  ( $\text{M} + \text{H}$ )<sup>+</sup>. Calcd: 569.1628; found: 569.1688.

(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 2-ethoxy-3-[[4-[2-[4-[(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl]-5-oxo-1,2,4-oxadiazol-3-yl]phenyl]phenyl]methyl]benzimidazole-4-carboxylate (azilsartan dimedoxomil, **10**).

To a solution of azilsartan (10 g, 21.92 mmol) in DMF (25 mL), we added potassium carbonate (3.78 g, 27.4 mmol) and potassium iodide (0.6 g, 6%) at 25-30°C. We then raised the reaction mass temperature to 40-45°C and added medoxomil chloride (4.1 g, 27.4 mmol). The reaction mass

was first stirred for 2 h at 40-45°C, then poured into DM water (250 mL) at 20-25°C, and the pH adjusted to 7.2 with diluted hydrochloric acid. We stirred the product for 1 h, and filtered and dried the results: a white colored compound **12** (9.6 g, 65%). The analytical results are as follows: IR (KBr pellet): 3635, 3413, 2983, 1780, 1717, 1616, 1551, 1279, 1226, 1119  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (500 MHz,  $\text{DMSO-}d_6$ )  $\delta$ : 7.728-7.744 (m, 3H, Ar), 7.713-7.717 (m, 2H, Ar), 7.516-7.519 (d, 1H, Ar), 7.213-7.240 (m, 3H, Ar), 6.966-6.994 (d, 2H, Ar) 5.527(s, 2H, N- $\text{CH}_2$ -Ar), 5.113 (s, 2H,  $\text{CH}_2$ ) 4.562-4.632 (q, 2H,  $\text{COOCH}_2$ ), 4.154 (s, 2H,  $\text{OCH}_2\text{CH}_3$ ), 2.138 (s, 3H,  $\text{CH}_3$ ), 1.401 (s, 3H,  $\text{CH}_3$ ), 1.354-1.393 (t, 3H,  $\text{OCH}_2\text{CH}_3$ ); HRMS for  $\text{C}_{35}\text{H}_{29}\text{N}_4\text{O}_{11}$  ( $\text{M} + \text{H}$ )<sup>+</sup>. Calcd: 681.1788; found: 681.1823.

### (5-methyl-2-oxo-1,3-dioxo-4yl)methyl 1-[2'-(4,5-dihydro-5-oxo-4H-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl]-2-methoxy-1H-benzimidazole-7-carboxylate a (methoxy analogue of azilsartan medoxomil, **11**)

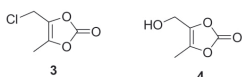
To a solution of methoxy analogue of azilsartan (10 g, 22.62 mmol) in dimethylacetamide (100 mL), we added medoxomil alcohol (4.11 g, 31.67 mmol) at 25-30°C. We then cooled the reaction mass to -10°C to -15°C, and added *p*-toluenesulfonyl chloride (6.15 g, 32.34 mmol), DMAP (0.6 g, 4.97 mmol) and potassium carbonate (4.12 g, 29.8 mmol) at -10 to -15°C. Subsequently, we raised the reaction mass temperature to 10-15°C, stirred the reaction mass for 2 h, then poured the reaction mass into DM water (500 mL) and adjusted pH to 4.0 with diluted hydrochloric acid. We then stirred the product for 1 h, filtered and dried the results: a white compound **11** (10.2 g, 80%). The analytical results are as follows: HPLC Purity: 95.23 %; IR (KBr pellet): 3662, 3010, 1785, 1731, 1617, 1297, 1229, 1109  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (500 MHz,  $\text{DMSO-}d_6$ )  $\delta$ : 7.678-7.693 (m, 2H, Ar), 7.651-7.664 (m, 1H, Ar), 7.548-7.577 (m, 2H, Ar), 7.211-7.379 (m, 1H, Ar), 7.179-7.194 (m, 3H, Ar), 7.048-7.065 (d, 2H, Ar), 5.382 (s, 2H, N- $\text{CH}_2$ -Ar), 5.061 (s, 2H,  $\text{CH}_2$ ), 3.473 (s, 3H,  $\text{CH}_3$ ) 2.17 (s, 3H,  $\text{CH}_3$ ); HRMS for  $\text{C}_{29}\text{H}_{23}\text{N}_4\text{O}_8$  ( $\text{M} + \text{H}$ )<sup>+</sup>. Calcd: 555.1471; found: 555.1776.

### Methyl 1-((2'-amidobiphenyl-4-yl)methyl)-2-ethoxy-1H-benzol[d]imidazole-7-carboxylate (amide methyl ester **12**)

To a solution of BEC methyl ester (10 g, 24.33 mmol) in dimethyl sulfoxide (50 mL), we added a 30% w/w hydrogen peroxide (8.2 g, 72.92 mmol) solution at room temperature. We then stirred the reaction mixture for 24 h at 25-30°, and poured the reaction mass in to DM water (300 mL). The resulting solid was subsequently filtered and purified, giving the titled compound **12** (5 g, 50%). This was characterized as follows: HPLC purity: 97.59%;  $^1\text{H NMR}$  (300 MHz,  $\text{DMSO-}d_6$ )  $\delta$ : 7.11-7.684 (d, J = 8.1 Hz, 1H, Ar), 7.618 (s, 1H, Ar), 7.465-7.389 (m, 4H, Ar), 7.339-7.194 (m, 5H, Ar), 6.965-6.938 (d, J = 8.1 Hz, 2H,  $-\text{CONH}_2$ ), 5.518 (s, 2H, N- $\text{CH}_2$ -Ar), 4.587-4.657 (q, 2H,  $\text{OCH}_2\text{CH}_3$ ), 3.707 (s, 3H,  $\text{OCH}_3$ ), 1.394-1.441 (t, J = 6.9, 4.8 Hz, 3H,  $\text{OCH}_2\text{CH}_3$ ); IR (KBr pellet): 2994, 1768, 1717, 1614, 1542, 1281, 1135  $\text{cm}^{-1}$ .

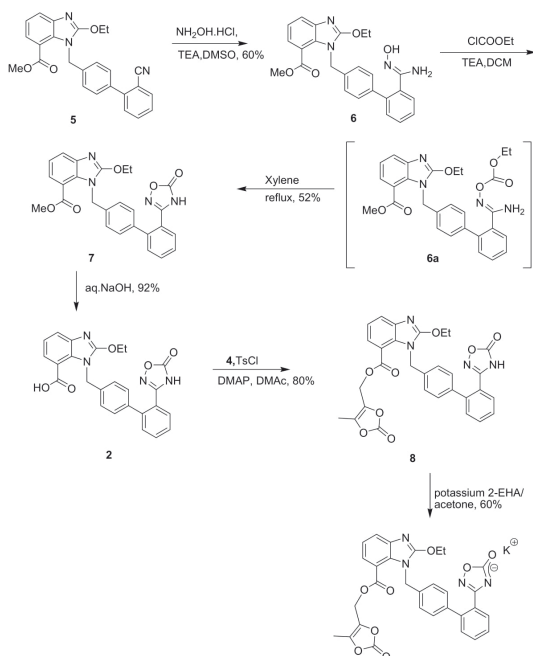
## RESULTS AND DISCUSSION

Several routes are available in literature [2,3,6-11,13, 15,16,20] for the synthesis of Azilsartan Kamedoxomil, the synthetic route [13] for azilsartan kamedoxomil **1** being shown in Scheme 1. The process involves the reaction of methyl 1-((2'-cyanobiphenyl-4-yl)methyl)-2-ethoxy-1*H*-benzo[d]imidazole-7-carboxylate (BEC methyl ester, **5**) with hydroxylamine hydrochloride in the presence of sodium methoxide, to produce amidoxime **6**. The treatment of **6** with ethyl chloroformate in the presence of a base produces an intermediate **6a**, which is cyclized in xylene at reflux to produce azilsartan methyl ester **7**. Hydrolysis of **7** in aqueous sodium hydroxide subsequently produces Azilsartan **2**.



**Figure 2.** Structures of medoxomil chloride (**3**) and medoxomil alcohol (**4**)

Finally, azilsartan (**2**) treated with medoxomil alcohol (**4**) in the presence of tosyl chloride produces azilsartan medoxomil (**8**). Azilsartan medoxomil (**8**) is then treated with potassium 2-ethylhexanoate in acetone to produce azilsartan kamedoxomil **1**, with a 60% yield.



**Scheme 1.** Synthesis of Azilsartan Kamedoxomil **1**

Only a few references [15,17-20] were found in the literature for the related substances of Azilsartan Kamedoxomil **1**. During the synthesis of Azilsartan Kamedoxomil in laboratory, we observed the presence of four related substances. The identified were related substances of Azilsartan Kamedoxomil, and their structures and chemical names were confirmed as:

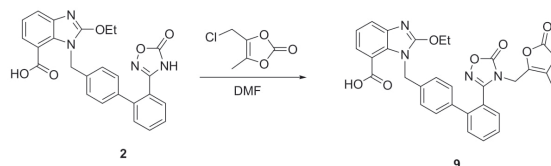
1. 2-Ethoxy-3-[[4-[2-[4-[(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl]-5-oxo-1,2,4-oxadiazol-3-yl]phenyl]phenyl]methyl]benzimidazole-4-carboxylic acid (azilsartan N-medoxomil, **9**).

2. (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 2-ethoxy-3-[[4-[2-[4-[(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl]-5-oxo-1,2,4-oxadiazol-3-yl]phenyl]phenyl]methyl]benzimidazole-4-carboxylate (azilsartan dimedoxomil, **10**).
3. (5-methyl-2-oxo-1,3-dioxo-4yl)methyl 1-[2'-(4,5-dihydro-5-oxo-4*H*-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl]-2-methoxy-1*H*-benzimidazole-7-carboxylate (methoxy analogue of azilsartan medoxomil, **11**).
4. Methyl 1-((2'-amidobiphenyl-4-yl)methyl)-2-ethoxy-1*H*-benzo[d]imidazole-7-carboxylate (amide methyl ester, **12**).

The origin, synthesis and characterization of these related substances are described individually below. The synthetically prepared related substances were characterized by conventional spectroscopic studies, and the presence of these related substances in the Azilsartan Kamedoxomil batch was confirmed by spiking the related substances individually with Azilsartan Kamedoxomil. These studies confirmed the formation of related substances (**9-12**) during the standard manufacturing process of Azilsartan Kamedoxomil **1**.

### Origin and synthesis of compound **9** (Azilsartan N-medoxomil)

Compound **9** is formed due to condensation of medoxomil chloride **3** at the isoxazole ring in azilsartan **2**.

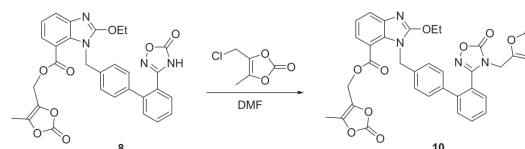


**Scheme 2.** Synthesis of Azilsartan N-medoxomil **9**

Compound **9** was confirmed by IR, Mass, NMR spectral data and co-injection with an authentic sample. The mass spectrum of compound **9** showed a molecular ion at  $m/z$  569.1688. The NMR spectrum showed a singlet at  $\delta$  4.15, corresponding to  $-N-CH_2$ , and a broad singlet at  $\delta$  13, corresponding to  $-COOH$ . Furthermore, the infrared (IR) spectrum showed absorptions at 1614, corresponding to  $C=O$  stretching – also confirming the assigned structure.

### Origin and synthesis of compound **10** (Azilsartan dimedoxomil)

Compound **10** is formed due to the condensation of medoxomil chloride **3** at the isoxazole ring in azilsartan medoxomil **8**.



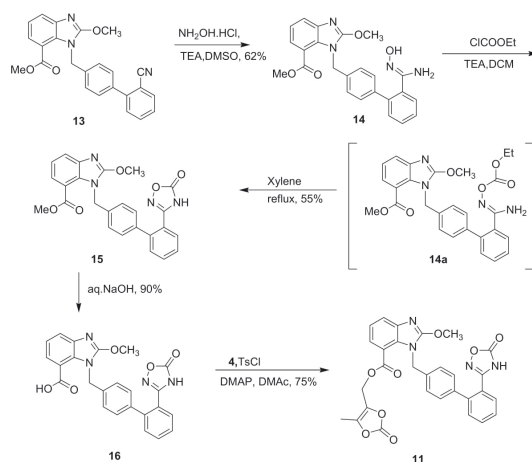
**Scheme 3.** Synthesis of Azilsartan dimedoxomil **10**

Compound **10** was confirmed by IR, Mass, NMR spectral data and co-injection with an authentic sample. The mass spectrum of compound **10** showed a molecular ion at  $m/z$  681.1823. In addition, the NMR spectrum showed a singlet at  $\delta$  4.15, 5.11, 1.61 & 2.15 corresponding to  $-N-CH_2$ ,

–O-CH<sub>2</sub> and two –CH<sub>3</sub> of the medoxomil group, while the Infrared (IR) spectrum showed absorptions at 1616, corresponding to –C=O stretching – also confirming the assigned structure **10**.

#### Origin and synthesis of compound **11** (Methoxy analogue of Azilsartan medoxomil)

Compound **11** originates from BEC methyl ester raw material. The methoxy analogue of BEC methyl ester is present as an impurity in BEC methyl ester raw material, and may undergo all the reactions employed in the synthesis of Azilsartan medoxomil, to give compound **11**.

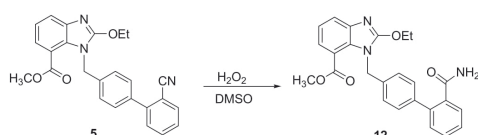


**Scheme 4.** Synthesis of Methoxy analogue of Azilsartan medoxomil **11**

Compound **11** was confirmed by IR, Mass, NMR spectral data and co-injection with an authentic sample. The mass spectrum of compound **11** showed a molecular ion at *m/z* 555.1776. What is more, the NMR spectrum showed a singlet at  $\delta$  12.42, corresponding to –NH, and the absence of –OCH<sub>2</sub> protons - also confirming the assigned structure. Moreover, the Infrared (IR) spectrum showed absorptions at 1617, corresponding to –C=O stretching – also confirming the assigned structure.

#### Origin and synthesis of compound **12** (Amide methyl ester)

Compound **12** is a major impurity in amidoxime methyl ester **6** preparation. It comes about because most of the reported methods for preparing amidoxime methyl ester **6** use an excess of hydroxylamine hydrochloride (18 to 25 mole equivalents). Hydroxylamine tends to decompose at higher temperature by giving ammonia as a by-product. This ammonia then reacts with BEC methyl ester **5**, to give amide methyl ester **12** as a related substance. In our work, the amide methyl ester was independently prepared by treating BEC methyl ester **5** with hydrogen peroxide in dimethyl sulfoxide.



**Scheme 5:** Synthesis of Amide methyl ester **12**

Compound **12** was confirmed by IR, Mass, NMR spectral data (experimental section 3.6) and co-injection with an authentic sample. The mass spectrum of compound **12** showed a molecular ion at *m/z* 430.1769. In comparison with BEC methyl ester **5**, the NMR spectrum showed a singlet at  $\delta$  6.938 corresponding to –CONH<sub>2</sub>, while the Infrared (IR) spectrum showed absorptions at 3518 and 1622, corresponding to –NH<sub>2</sub> and –C=O stretching – also confirming the assigned structure.

#### CONCLUSION

The process related substances in Azilsartan Kamedoxomil were identified, synthesized and characterized by using <sup>1</sup>H NMR, <sup>13</sup>C NMR, MS and IR techniques. Further, these related substances were co-injected with Azilsartan Kamedoxomil to confirm the retention time in HPLC. This related substances study of Azilsartan Kamedoxomil is, hence, useful to the pharmaceutical industry.

#### ABBREVIATIONS

TsCl, Para-toluenesulfonyl chloride;  
 DMSO, dimethyl sulfoxide;  
 DMAP, dimethylaminopyridine;  
 DMAc, N,N-dimethylacetamide;  
 DMF, N,N-dimethylformamide;  
 TrCl, Trityl chloride;  
 DSC, disuccinimidyl carbonate;  
 TFA, trifluoroacetic acid;  
 DIBOC, Di tert-butyl dicarbonate;  
 DMC, dimethyl carbonate;  
 DEC, diethyl carbonate;  
 DPC, diphenyl carbonate;  
 CDI, carbonyldiimidazole;  
 ECF, ethyl chloroformate;  
 HPLC, High pressure liquid chromatography;  
 LCMS, Liquid chromatography-mass spectrometry.

#### ACKNOWLEDGMENTS

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