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Improved Process for Azilsartan Medoxomil: A New Angiotensin Receptor Blocker

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ABSTRACT - An improved process for the active pharmaceutical ingredient of a new angiotensin II AT_1 receptor antagonist azilsartan medoxomil has been developed. The results include reinvestigation of the described process as well as its novel modifications. This new process includes transformation of the CN group into amidoxime moiety by aqueous hydroxylamine, its cyclization into the corresponding oxadiazole by treatment with dialkyl carbonates and the following hydrolysis of the ester and transformation into the medoxomil ester. Several so far undocumented side-products were identified and some of them were synthesized and duly characterized as potential impurities. Formation and control of critical possible impurities is described.

1. INTRODUCTION

Angiotensin II AT_1 receptor antagonists, called also ARB's (Angiotensin Receptor Blockers) or sartans, are drugs interacting with the renin-angiotensin-aldosterone system.[1,2] Most of them are widely used in the treatment of hypertension and some other cardiovascular diseases. The last

addition to this therapeutic class, a prodrug form of azilsartan (**1**) azilsartan medoxomil (**2**), was approved in 2011 and marketed under the trade name Edarbi (Figure 1).

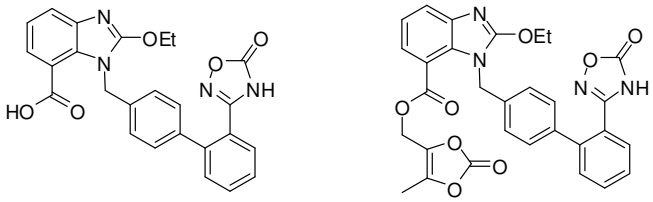
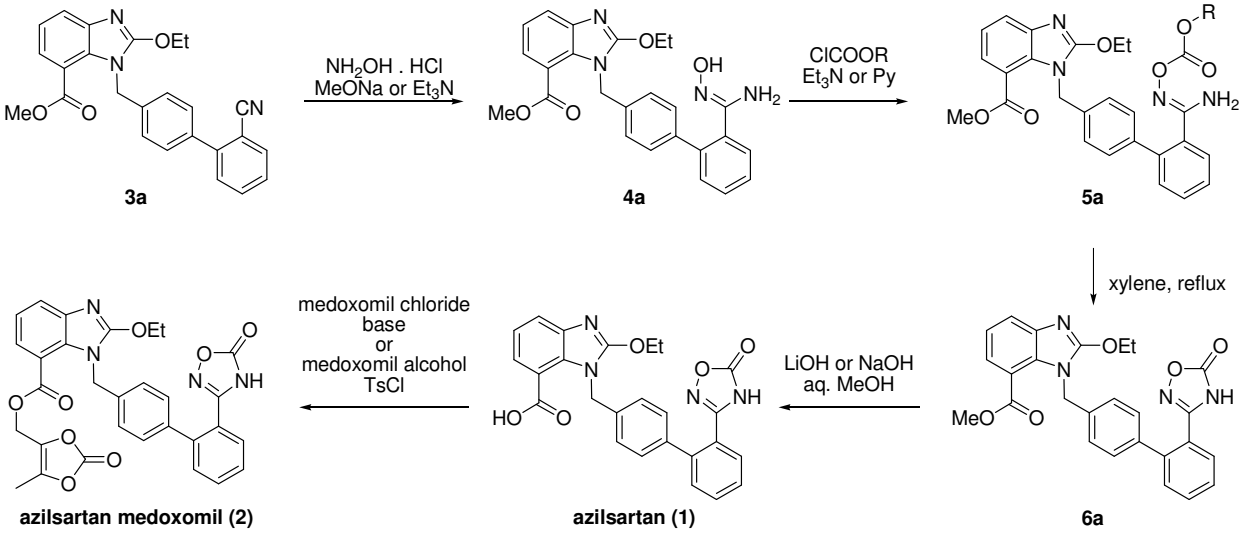


Figure 1. Strucures of azilsartan (**1**) and azilsartan medoxomil (**2**)

When we started development of a generic equivalent of azilsartan medoxomil, only very limited information of its synthesis was available. Original patents[3] and papers[4,5] provided only basic facts on the synthesis of azilsartan (**1**) and only patents[6] described transformation of azilsartan (**1**) into azilsartan medoxomil (**2**). The reported route is schown in Scheme 1.

Scheme 1. Reported Synthetic Scheme for Azilsartan Medoxomil



A literature review revealed only limited variations of the synthesis of azilsartan medoxomil. Synthetic pathway described in references[3-6] is shown in Scheme 1. In the first step, methyl ester **3a** is treated with hydroxylamine liberated *in situ* from its hydrochloride with either sodium

methoxide or triethylamine giving 55 % yield of amidoxime **4a** (Ref. [5]). Treatment of **4a** with alkyl chloroformates in the presence of triethylamine or pyridine provided then crude intermediates **5a**, which were without purification thermally cyclized to provide only low yields of methyl ester **6a**. The described yields of 23 % (for R = Et)[3] and 52 % (R = 2-ethylhexyl)[5] after chromatography are not acceptable for commercial production. No side products explaining the low yields of the first steps are mentioned in the references. In the next step, saponification of ester **6a** then provided azilsartan (**1**) in good yields. Two possible routes of transformation of azilsartan (**1**) into azilsartan medoxomil (**2**) were described in ref.[6] The first is based on reaction of azilsartan (**1**) with medoxomil chloride (**7**) using either pre-formed disodium salt of azilsartan or *in situ* formed salt with triethylamine. In both cases, only low yields (14-22 %) of azilsartan medoxomil (**2**) were reported.[6] The second procedure uses medoxomil alcohol (**8**), which, after proper activation of azilsartan (**1**) either with TBz-Cl or TsCl, provided azilsartan medoxomil (**2**) in good yields. Of course, no information about possible impurities is given either in the patent or in other literature sources.

7 **8**

Figure 2. Strucures of medoxomil chloride (**7**) and medoxomil alcohol (**8**)

To overcome the problems associated with the reported processes and to find reasons for the low yields in critical steps, we planned to study process of Scheme 1 in details. Herein we report an improved and scalable process for the preparation of azilsartan (**1**) and azilsartan medoxomil (**2**). In addition, an impurity profile study including conditions for the formation and control of impurities is discussed.

The main goal of the generic API development is developing an economic, safe and robust patent non-infringing process, which can be used in the production of commercial batches of the products. During the development, formed impurities and/or degradation products are identified and very often their standards are either isolated or synthesized. During the initial phase of the azilsartan (**1**) development we have found some inconsistencies in the data given in the above mentioned references. This paper explains the inconsistencies in the original references, describes our process of preparation of azilsartan medoxomil (**2**), as well as synthesis and physico-chemical characteristics of selected side products.[i]

2. RESULTS AND DISCUSSION

2.1. Synthesis of amidoximes 4. First the published reaction of **3a** with hydroxylamine hydrochloride under the described conditions [DMSO (dimethyl sulfoxide), 90 °C, MeONa or Et_3N] was repeated. We found,[7] that after the reaction time indicated in the original references (4 h for MeONa and 15 h for Et_3N), the mixtures contained 49.9 % and 35.2 % of the starting compound **3a**, 32.3 % and 44.2 % of the product **4a**, and 17.6 % and 19.7 % of a side product, respectively. The side product was identified[7] as **9a** which was in accordance with the easy

[i] There are some inconsistencies in the Takeda publications. For example, ref.[3] describes preparation of **4a** using $NH_2OH.HCl$/MeONa in DMSO in 90 % yield after 4h heating at 90 °C. In our hands, only about 70 % conversion was achieved under these conditions and beside about 40 % of the product, the mixture contained also about 30 % of **9a**. In all other Takeda publications, the best yields achieved were 55% using Et_3N instead of MeONa. Though they obtained in some steps very low yields, no side products explaining the low yields are mentioned. Two possible routes of transformation of azilsartan into azilsartan medoxomil were described in ref.[6] The first is based on reaction of azilsartan with medoxomil chloride using either pre-formed disodium salt of azilsartan or in situ formed salt with triethylamine. In both cases, only low yields (14-22 %) of azilsartan medoxomil were reported. The fact, that alkylation on the oxadiazole ring is taking place is not given.

deethylation of candesartan reported earlier.[8] Surprisingly, no corresponding amidoxime **10a** was detected under these conditions (Figure 3). Independent synthesis of these compounds has already been reported.[7]

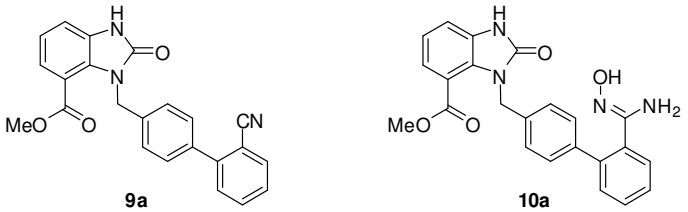


Figure 3. Structures of 2-desethyl side products **9a** and **10a**

In attempts to optimize the reaction conditions, we tested several solvents [DMSO (dimethyl sulfoxide), DMF (*N,N*-dimethylformamide), DMA (*N,N*-dimethylacetamide), NMP (*N*-methylpyrrolidone)] and bases [MeONa, EtONa, *tert*-BuOK, NaOH, Na_2CO_3, K_2CO_3, $NaHCO_3$, $KHCO_3$, AcONa, Et_3N, DIPEA (*N,N*-Diisopropylethylamine), DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), proton sponge (1,8-bis(dimethylamino)naphthalene)] at temperatures ranging from 20 °C to 100 °C with little success. No improvement was achieved by replacing hydroxylamine hydrochloride with other commercially available hydroxylamine salts (sulfate, phosphate). Finally we succeeded using commercially available 50 % aqueous hydroxylamine base in combination with DMSO. The results of this optimization have been reported recently.[7]

The heterocyclic moiety present in azilsartan, *i.e.*, 2-ethoxybenzimidazole-7-carboxylic acid, is also present in candesartan cilexetil (**11**), a prodrug of candesartan (**12**) (For a review on candesartan cilexetil, see ref.[9]). Since generic candesartan cilexetil is available in some countries, also intermediates for its production are available. Besides methyl ester **3a** used by Takeda, the corresponding ethyl ester **3b**, which is widely used by generic API producers, is also

commercially available. We found, that using our procedure, both of these potential starting compounds provided similar results, but yields were consistently better with the ethyl ester.[7]

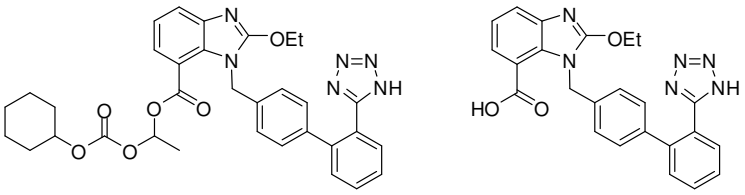


Figure 4. Structures of candesartan (**12**) and candesartan cilexetil (**11**)

2.2. Cyclization of amidoximes 4 with phosgene equivalents. Another problem of the original synthesis was transformation of amidoxime **4a** to oxadiazole **6a** *via* the corresponding (alkoxycarbonyloxy)carbamimidoyl derivatives **5**. In case of the reported thermal cyclization of **5**, the reported yields for ethoxycarbonyl and 2-ethylhexoxycarbonyl derivative were only 23 and 54 %, respectively. We identified main impurities as the corresponding 2-desethyl and *N*-ethyl derivatives of **6a**, the fact which was consistent with our observations with candesartan.[8] Based on these findings, we also developed an efficient base-initiated cyclization of **5** into oxadiazoles **6**.[7] However, the direct transformation of amidoximes **4** into oxadiazoles **6** was our ultimate goal.

In our attempts to develop shorter and more efficient direct cyclization of **4** into **6**, we suggested using a phosgene equivalent. Due to the high sensitivity of the 2-ethoxy group, it was evident that such a process would not be compatible with either high temperatures or acid conditions. Therefore we screened only methods of the 1,2,4-oxadiazol-5(4*H*)-one synthesis proceeding under mild conditions. As the phosgene equivalents we considered diphosgene, triphosgene, 1,1'-carbonyldiimidazole (CDI) and methyl, ethyl and phenyl dicarbonates. Since solubility of the starting amidoximes is limited, only some dipolar aprotic solvents could be

effectively used. We tested common solvents of this type as DMSO, DMF, DMA, NMP and HMPA, but also some cyclic urea derivatives as 1,1,3,3-tetramethylurea (TMU), 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) and their mixtures. We also screened a range of organic and inorganic bases, including amines [triethylamine, diisopropylethylamine (DIPEA) 1,4-diazabicyclo[2.2.2]octane (DABCO), 8-diazabicyclo[5.4.0.]undec-7-en (DBU), 1,8-bis-(dimethylamino)naphthalene, 1-methylmorpholine, 1-ethylpiperidine], alcoholates (MeONa, MeOK, EtONa, *tert*-BuONa, *tert*-BuOK, *tert*-AmONa), carbonates (Na_2CO_3, K_2CO_3, Cs_2CO_3), hydrogen carbonates ($NaHCO_3$, $KHCO_3$), and acetates (NaOAc, KOAc).

Very quickly we identified 1,1'-carbonyldiimidazole and dicarbonates as suitable phosgene equivalents and therefore more detailed screening was done only for these reagents. In case of combination of 1,1'-carbonyldiimidazole/DBU, the best results were achieved using DMSO, NMP and DMPU as solvents (Table 1).[ii]

Table 1. Solvent Screening for Cyclization with 1,1'-carbonyldiimidazole/DBU

Entry	Solvent	Yield (%)	HPLC Purity of **6a** (%)
A	DMSO	85	96.6
B	NMP	81	94.7
C	DMI	68	97.8
D	DMPU	77	89.9
E	THF	55	52.1[a]

[ii] A Patent Application (added as ref.[15]) describing the cyclization using CDI/DBU in THF giving 68% yield of **6a** appeared when our laboratory development was already finished and this manuscript submitted. We have extensively studied the reaction using CDI with both methyl (as described in the Patent Application) and ethyl ester using not only DBU, but also a range of bases. In our hands, THF was much worse than most of the tested solvents (as you can see in our Table 1).

[a] - 40.4 % of **4a** detected (HPLC).

Though only slightly lower yields (5-12 %) were obtained using some other bases (DIPEA, 1-methylmorpholine, 1-ethylpiperidine) under similar conditions, the present impurity profiles were different and more complicated. We applied combination of CDI/DBU in DMSO and obtained compounds **6a** or **6b** in high yields. Since DBU is quite expensive, we tried to replace it by a cheap base. Finally we succeeded with simple potassium carbonate. Finally we found the conditions providing comparable results as using DBU. Under these conditions, 85 % yield of **6a** of HPLC purity higher than 99% was repeatedly obtained.

Dialkyl carbonates are considered as cheap and green compounds used even as solvents and therefore we have paid our attention to their use as reagents for the cyclization. Initial screening done in DMSO revealed that in case of diphenyl carbonate (DPC) the reaction proceeds with potassium carbonate, DBU, *tert*-BuOK and MeONa. On the other hand, dimethyl (DMC) and diethyl carbonate (DEC) reacted only using *tert*-BuOK or MeONa. One of the screening conditions (results are given in Table 2) consisted in simple stirring of the reaction components in DMSO in vials at room temperature and the following HPLC analysis (in entries C, F, and I peaks of phenole were not integrated).

Table 2. Reagent and Base Screening for Cyclization in DMSO

Entry	Reagent	Base	HPLC (%)	
			4a	**6a**
A	DMC	K_2CO_3	73.4	0.75
B	DEC	K_2CO_3	76.2	0.0
C	DPC	K_2CO_3	0.0	84.6
D	DMC	DBU	76.6	0.0
E	DEC	DBU	75.6	0.0

Entry	Reagent	Base	HPLC (%)	
			4a	**6a**
F	DPC	DBU	0.0	79.2
G	DMC	EtONa	48.4	24.2
H	DEC	EtONa	6.6	9.1
I	DPC	EtONa	0.0	35.0

For the above mentioned reasons, we first considered diphenyl carbonate (DPC) as a reagent of choice. When the reaction was done in DMSO using potassium carbonate at room temperature, the reaction was complete after 4 h. Simple workup consisted in addition of water and acidification with acetic acid, filtration of the crude product and final crystallization. Though the yields of the crude product were very good and the purity after crystallization was about 99 %, the product still contained small amounts of phenol. In addition, in larger scales (up to 50 g), the yields were gradually lower. Therefore we decided to check the possibility of using dimethyl or diethyl carbonate in combination with the corresponding sodium alkoxide. If the reaction of methyl ester **4a** with dimethyl carbonate was done in methanol, several days of reflux was required to complete conversion. In addition, a range of side products was formed. When the reaction was done at 100 °C in a pressure flask for 24 h, the reaction was complete, but the mixture contained about 16 % of impurities (HPLC). Surprisingly, when the reaction was done in DMSO at room temperature, the reaction was complete after 30 minutes and the crude mixture after simple dilution with water, acidification and filtration contains more than 90 % of **6a**. In this case, the yields of about 90 % of crude **6a** with purity of about 98 % were obtained. After recrystallization from acetone yields of 85-90 % and purity higher than 99 % were routinely achieved. Even better results were obtained using ethyl ester **4b** in combination with diethyl

carbonate and EtONa providing nearly quantitative yields of **6b**. Quite surprisingly, we found that reaction with ethyl ester **4b** in combination of dimethyl carbonate and MeONa provided methyl ester **6a**. The corresponding ethyl ester **6b** was present only in amounts ranging from 0 to 5 %, depending on the reaction time. The work-up consisted in simple dilution with water, acidification and filtration of the product. Since we were interested in the background of the reaction, we also tested reactions of **4b** with dimethyl carbonate/EtONa and diethyl carbonate/MeONa. In both cases, mixtures of **6a** and **6b** were obtained.

Finally we evaluated the tested possibilities of the synthesis of azilsartan esters **6a** and **6b**, and selected for further development compound **4b** as the starting substrate (higher yields in the first step) in combination with dimethyl carbonate (cheap and green reagent) and sodium methoxide (cheap and commercially available). We have also optimized amount of DMSO with regards of reaction time at room temperature and purity of the crude product.

2.3. Hydrolysis of esters 6. Esters **6a** and **6b** were easily hydrolyzed using aqueous NaOH, KOH, or LiOH. We have not noticed any substantial difference in yields or purity of the formed azilsartan (**1**).

2.4. Transformation of azilsartan (1) into azilsartan medoxomil (2). Since medoxomil chloride (**7**) is used for the synthesis of olmesartan medoxomil[12] and therefore is commercially available at reasonable price, we first tested possibility of using this compound as a medoxomil group source. However, under all the conditions tested, both the carboxy group and the oxadiazole group were alkylated. Therefore the possibility of using medoxomil alcohol (**8**) was further studied.

Besides the activation of azilsartan with 2,4,6-trichlorobenzoyl chloride (TBz-Cl) or TsCl reported in the patent literature,[6] we also tested some other known literature methods. However,

we found the use of tosyl chloride activation the most appropriate, since the reagent is cheap, and both the yields and the purity are acceptable. In order to understand the reaction background in more details, we checked the reaction mixture by HPLC. To our surprise, a very complex mixture was initially formed, but after some time, the reaction mixture containing about 90 % of azilsartan medoxomil (**2**) was obtained. HPLC results of this study are shown in Figure 5. Peak corresponding to azilsartan (**1**) quickly disappeared and after 15 min two main peaks, one of them corresponding to tosyl chloride, were present (See Fig. 5A). After 30 min, the mixture was even more complex (see Fig. 5B). Composition of the mixture after 1, 1.5 and 2 hours is shown as Figs 5C, 5D, and 5E, respectively. Finally, after 3 h, the composition of the mixture was much more reasonable with the only major peak corresponding to the expected product (Fig. 5F).[iii]

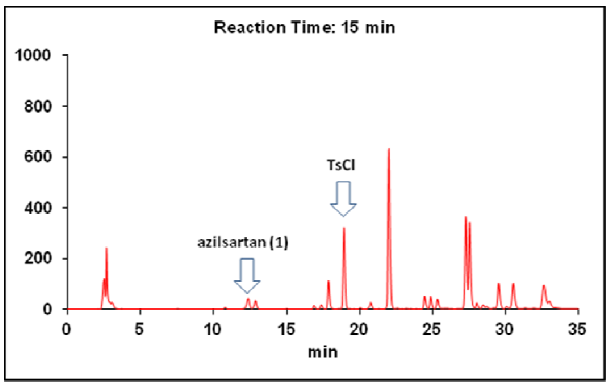


Fig. 5A

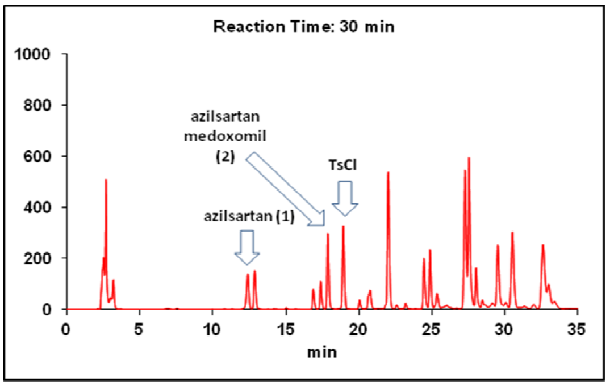


Fig. 5B

[iii] The changes of the HPLC content were so fast that we have not tried to track them by LCMS. We do not have any explanation but the results were repeatedly obtained.

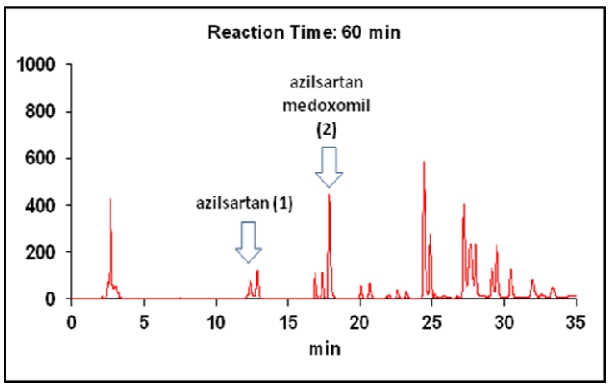


Fig. 5C

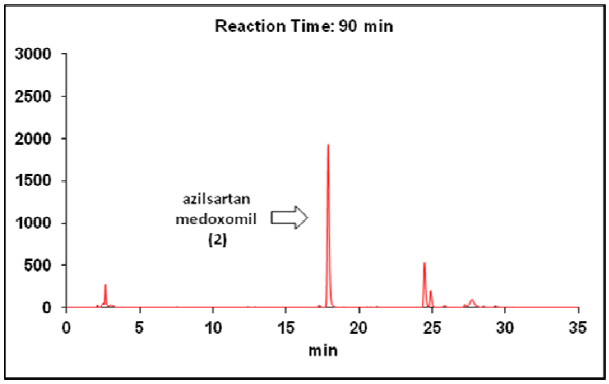


Fig. 5D

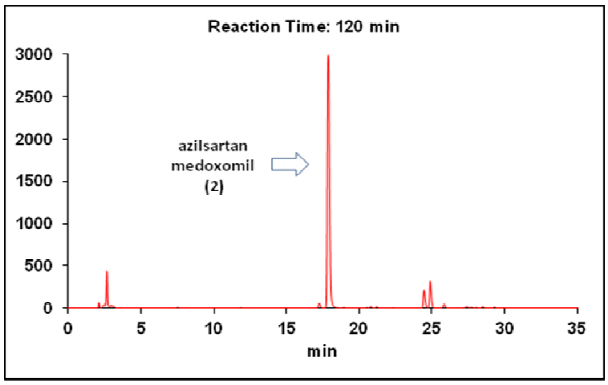


Fig. 5E

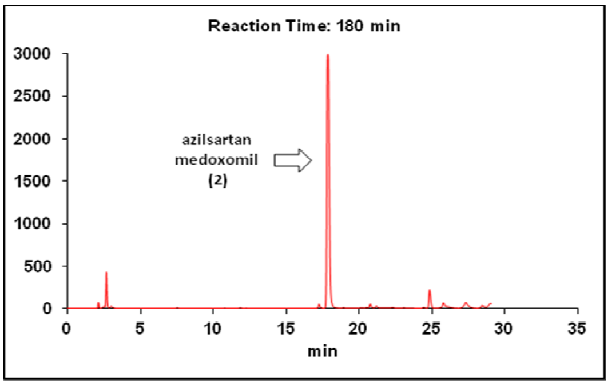


Fig. 5F

Figure 5. HPLC changes during the reaction of azilsartan (**1**) with medoxomil alcohol (**8**)

We found that quality of the used azilsartan (**1**) as well as medoxomil alcohol (**8**) is crucial. When azilsartan purified by crystallization from an alcohol was used, even after thorough drying, the corresponding ester of azilsartan was detected as an impurity. Therefore we finally purified azilsartan (**1**) by stirring its suspension in acetone. Formation of methyl ester **6a** was also observed using medoxomil alcohol (**8**) from one supplier and subsequent GC analysis found methanol as a residual solvent in this material. Since the most medoxomil alcohol (**8**) producers probably use the literature procedure[13] where the last step is done in methanol, the methanol content should be carefully checked.

We also found that the compound forms solvates with a range of solvents[14] and some of them, *i.e.,* solvates with acetone, THF or DMA, could be used for its purification. This method is suitable for removing most of the impurities, including methyl ester **6** and dimeric impurities **15** and **17.** Final desolvating is then done by stirring the slurry with aqueous acetone under reflux. X-Ray powder diffraction (XRPD) spectra and differential scanning calorimetry (DSC) of azilsartan medoxomil (**2**) and its solvate with *N,N*-dimethylacetamide are shown in Figures 6 and 7, respectively.

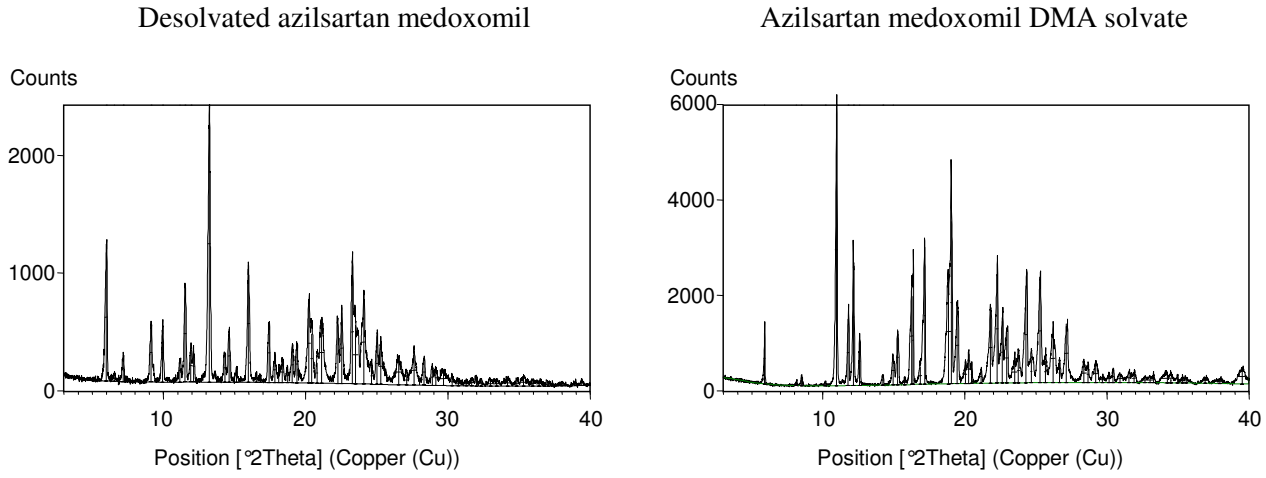


Figure 6. XRPD of azilsartan medoxomil and its solvate with *N,N*-dimethylacetamide

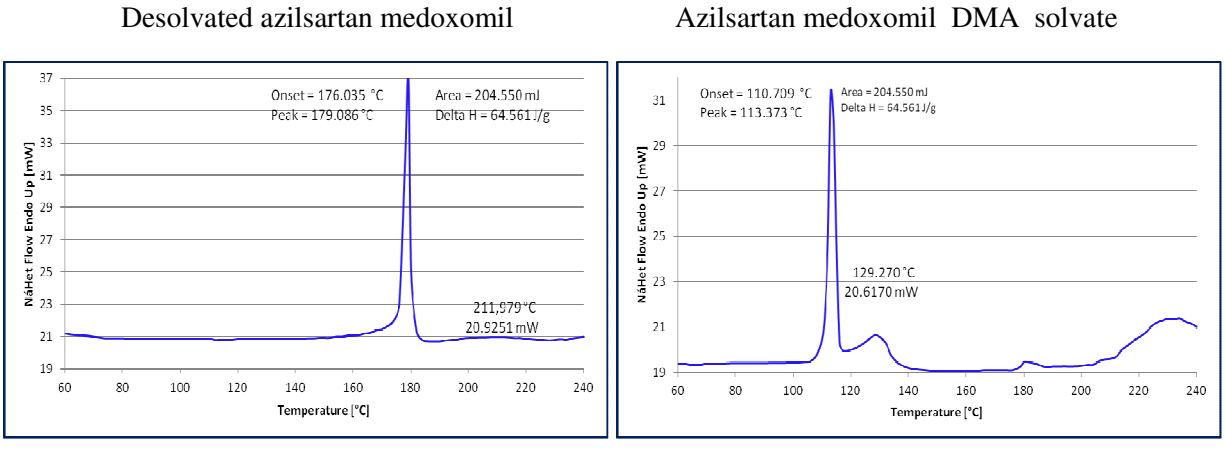


Figure 7. DSC of azilsartan medoxomil and its solvate with *N,N*-dimethylacetamide

2.5. Synthesis of standards of impurities. One of the principal parts of documentation of any active pharmaceutical ingredient (API) is description of impurities and/or degradation products which can be present.[10] Identified impurities should be included in the specification when they are present at a level higher than the identification threshold, which is usually 0.10 %. These impurities must be not only identified but also either isolated or independently synthesized. Recently, the drug registration authorities are increasingly interested even in pharmaceutical impurities in the range 0.01–0.1% (Ref.[11]). To anticipate possible problems associated with the reported processes, we planned to study reactions of Schemes 1 and 2 in detail. Consequently, we have tried to synthesize all principal impurities/degradation products identified during the process development.

Having some experience with impurities of similar candesartan cilexetil (**11**),[8] as well as with impurities formed in the first steps of the original synthesis,[7] compounds **13** and **14** should be the logical impurities of azilsartan medoxomil (Figure 8), which could be even product related degradation products formed during a long-term storage. Therefore these compounds were also synthesized. Treatment of azilsartan medoxomil (**2**) with HCl in acetone provided compound **13**. Compound **14** was prepared by simple alkylation of **2** with ethyl iodide in the presence of K_2CO_3.

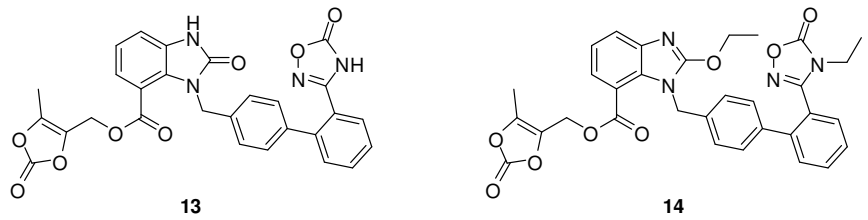
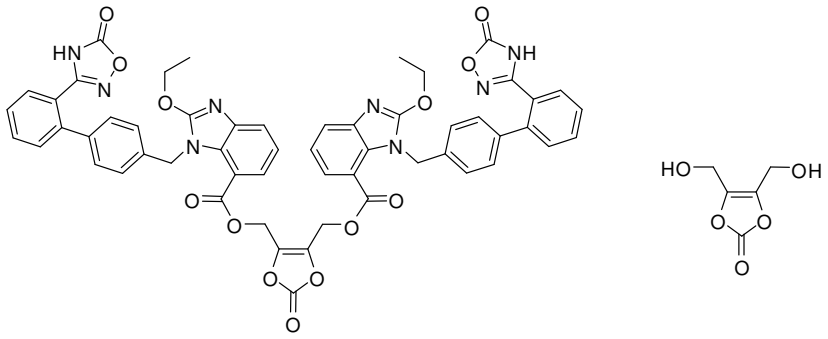


Figure 8. Structures of potential impurities of azilsartan medoxomil **13** and **14**

Analysis of crude azilsartan medoxomil (**2**) revealed only trace amounts of **13** and **14** and small amount of methyl ester **6a**.[iv] However, the product contained also 2 more critical impurities. One of them was identified by LC-MS as compound with molecular formula $C_{55}H_{42}N_8O_{13}$, which could be easily explained by structural formula **15** (Figure 9). Therefore, content of the corresponding diol **16** in medoxomil alcohol (**8**) is even more critical than the methanol content.

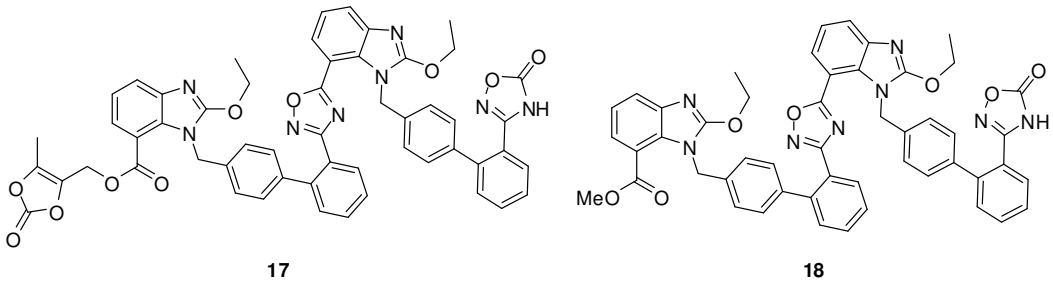


15 **16**

Figure 9. Structure of potential impurity **15** and the corresponding diol **16**

The second critical impurity has molecular formula $C_{54}H_{42}N_8O_{10}$, which can be explained by structural formula **17**. This assumption is supported by the fact, that compound of formula $C_{50}H_{40}N_8O_7$, which corresponds to structure **18**, was also identified by MS in crude compound **6a**. The corresponding acid of formula $C_{49}H_{38}N_8O_7$ was also present in small amounts in azilsartan (**1**). Independent synthesis of the mentioned impurities **15**, **17** and **18** is underway and will be published elsewhere.

[iv] The amounts lower than 0.03 %, if detected.



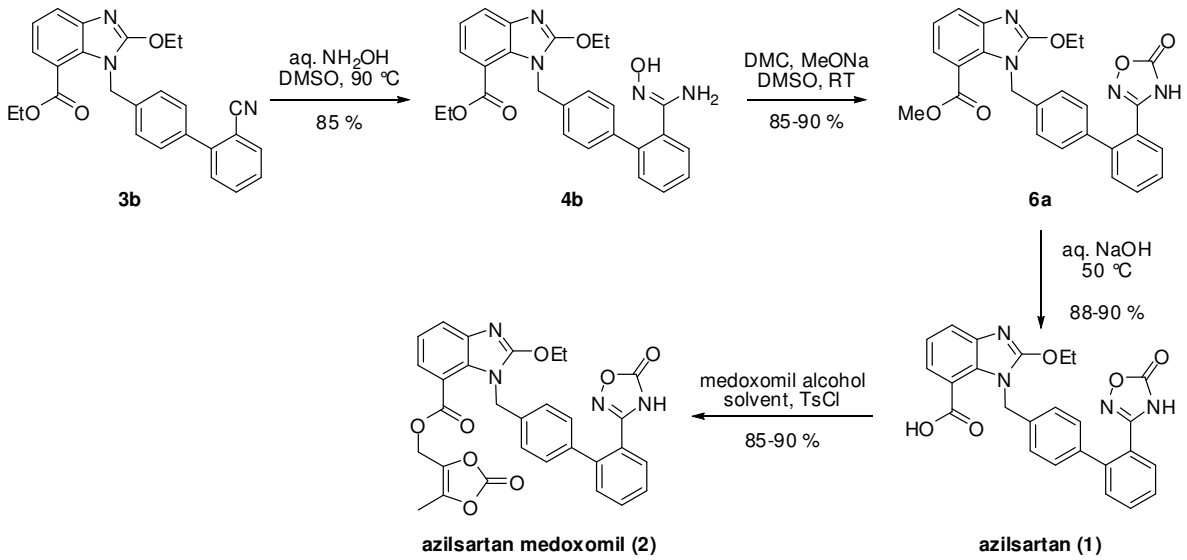
17 18

Figure 10. Structure of potential impurity **17** and the corresponding ester **18**

3. SUMMARY

We have developed robust processes for synthesis of azilsartan medoxomil (**2**) starting from nitriles **3**, consisting of their treatment with aqueous hydroxylamine, followed by transformation of the formed amidoximes **4** into azilsartan esters **6** using phosgene equivalents, advantageously dialkyl carbonates**.** These compounds are then hydrolyzed to azilsartan (**1**), which is consequently treated with medoxomil alcohol (**8**) providing the final compound. The selected route starting from ethyl ester **3b** has been repeatedly checked in amounts of hundreds of grams. The reactions were routinely done in jacketed laboratory reactors with mechanical stirring (Radleys) with internal temperature control.

Scheme 2. Synthetic Scheme of the Zentiva Process of Azilsartan Medoxomil Production



We have also detected and/or identified several potential impurities of the final product. Some of them, e.g., compounds **13** and **14**, were also synthesized as standards for analytical development. All of them were also duly characterized by ^{1}H NMR, ^{13}C NMR, MS, and elemental analysis. We believe that this information would be of interest of process chemists working in this area.

The article reports results of our laboratory development and due to the patent expiration time, the scale-up at Zentiva is not planned in the near future. Of course, additional aspects should be duly studied during further development. These include safety testing of the particular reaction steps, conditions for crystallizations of the intermediates as well as the final product (cooling times, possible seeding, crystal forms, filterability, particle size, etc)[v]. It must be stressed that the article describes preparation of the azilsartan medoxomil API, while in the final formulation of

[v] Generally the seeding was not necessary and the cooling times were not crucial to get good yields with acceptable filtration times.

Takeda, the corresponding potassium salt of azilsartan medoxomil is used. In this case, preparation of the salt is correctly described in the Takeda patents[6] and can be used by generic companies.

4. EXPERIMANTAL SECTION

Methyl and ethyl 1-((2'-cyanobiphenyl-4-yl)methyl)-2-ethoxy-1*H*-benzo[*d*]imidazole-7-carboxylate (**3a**) and (**3b**), respectively, were obtained from Zhejiang Tianyu Pharmaceutical Company (http://www.tianyupharma.com). Other chemicals used in the synthesis were purchased from Sigma-Aldrich and were used as supplied.

Melting points were measured on a Kofler block and are uncorrected. NMR experiments were carried out on a Bruker Avance 500 at 500.13 MHz (1H) and 125.77 MHz (^{13}C). Reference for ^{1}H δ ($CDCl_3$) = 7.26 ppm, for ^{13}C δ ($CDCl_3$) = 77.0 ppm. IR spectra were measured on a FTIR spectrometer Nicolet Nexus (Thermo, USA) using ZnSe ATR crystal technique by accumulation of 64 scans with 2 1/cm resolution. The Mass spectra (MS/MS; ionization mode APCI(+)) were measured on an API 3000 PE machine (Sciex Instruments, Applied Biosystems). XRPD Spectra were measured on PANalytical's X'Pert PRO Materials Research Diffractometer with graphite monochromator using CuKα radiation (λ=1.542 Å). DSC measurements were done on a Perkin Elmer Pyris 1 Differential Scanning Calorimeter. The purity of the prepared substances was evaluated by TLC on silica gel (FP KG F 254, Merck) and by HPLC system HP Agilent 1050 [column Phenomenex Luna 5μ C18(2) length: 0.25 m, internal diameter 4.6 mm] with UV detection (240 nm). Gradient elution with mobile phase A (phosphate buffer [1. 2 g NaH_2PO_4 diluted in 1000 mL of water, pH adjusted to 3.0 with 50% phosphoric acid), and mobile phase B (methanol) was used. The results are given as LCAP (liquid chromatography area percent). Flash chromatography was performed on silica gel Merck, particle size 0.04-0.063 mm. Centrifugally

accelerated axial chromatography was done using Cyclograph™ instrument (Analtech) with silica gel pre-scraped rotors.

Methyl 2-Ethoxy-1-((2'-(*N*'-hydroxycarbamimidoyl)biphenyl-4-yl)methyl)-1*H*-benzo[*d*]imidazole-7-carboxylate (**4a**). A mixture of **3a** (10 g, 2.4 mmol), DMSO (75 mL), and 50 % aqueous hydroxylamine (5 mL) was stirred at 90 °C for 18h. Then the mixture was poured into water (250 mL), the mixture was stirred for 30 min, the insoluble portion was filtered off and washed with water providing, after drying, 10.6 g of white precipitate containing according to HPLC 91.5 % **3a**. The solid was crystallized from 2-propanol to give 8.0 g (75 %) of white crystals; Mp: 203-206 °C (ref.[5] Mp: 207-209 °C). HPLC purity 97.5 %. HRMS for $C_{25}H_{25}N_4O_4$ $(M+H)^+$ Calcd: 445.1876, found: 445.1992. ^{1}H NMR (DMSO) δ (ppm): 9.18 (s, 1H, OH), 7.70 (dd, *J* = 7.9, 1.2 Hz, 1H, Ar), 7.46 (dd, *J* = 7.9, 1.2 Hz, 1H, Ar), 7.45-7.33 (m, 3H, Ar), 7.35 (d, *J* = 8.3 Hz, 2H, Ar), 7.29 (dd, *J* = 7.6, 1.5 Hz, 1H, Ar), 7.19 (t, *J* = 7.9 Hz, 1H, Ar), 6.94 (d, *J* = 8.3 Hz, 2H, Ar), 5.55 (bs, 2H, NH_2), 5.51 (s, 2H, N-C$\underline{H}_2$-Ar), 4.62 (q, *J* = 7.1 Hz, 2H, OC$\underline{H}_2$CH$_3$), 3.71 (s, 3H, OCH_3), 1.42 (t, *J* = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$). ^{13}C NMR (DMSO) δ (ppm): 166.22, 158.33, 151.96, 141.63, 139.85, 139.74, 135.54, 133.20, 130.83, 130.02, 129.85, 128.85, 128.52, 126.90, 125.92, 122.85, 121.55, 120.81, 115.56, 66.62, 52.32, 46.29, 14.40. Anal. Calcd. for $C_{25}H_{24}N_4O_4$: C, 67.55; H, 5.44; N, 12.60. Found: C, 67.27; H, 5.72; N, 12.87.

Ethyl 2-Ethoxy-1-((2'-(*N*'-hydroxycarbamimidoyl)biphenyl-4-yl)methyl)-1*H*-benzo[*d*]imidazole-7-carboxylate (**4b**). 50 % Aqueous hydroxylamine (240 mL) was added to a stirred suspension of **3b** (400 g, 941 mmol) in DMSO (2400 mL) and the mixture was stirred at 90 °C for 15 h. Then the mixture was diluted with water (400 mL) and slowly cooled down to 15 °C under stirring and then stirred at this temperature for 1 h. The insoluble portion was filtered off and washed with *i*-PrOH (5 x 1 L). The crude product was dried in a vacuum drier

(35 °C/50 mbar) to provide 386.4 g (90 %) of white precipitate containing according to HPLC 97.8 % **4b**; Mp: 209-211 °C (2-propanol). HRMS for $C_{26}H_{27}N_4O_4$ $(M+H)^+$ Calcd: 459.2032, found: 459.2189. ^{1}H NMR (DMSO) δ (ppm): 9.19 (bs, 1H, OH), 7.70 (dd, *J* = 7.9, 1.2 Hz, 1H, Ar), 7.46 (dd, *J* = 7.9, 1.2 Hz, 1H, Ar), 7.42-7.34 (m, 5H, Ar), 7.27 (dd, *J* = 7.6, 0.9 Hz, 1H, Ar), 7.19 (dd, *J* = 7.6, 1.5 Hz, 1H, Ar), 6.92 (d, *J* = 8.4 Hz, 2H, Ar), 5.57 (bs, 2H, NH_2), 5.53 (s, 2H, N-C$\underline{H}_2$-Ar), 4.62 (q, *J* = 7.1 Hz, 2H, OC$\underline{H}_2$CH$_3$), 4.21 (q, *J* = 7.1 Hz, 2H, OC$\underline{H}_2$CH$_3$), 1.42 (t, *J* = 7.1 Hz, 3H, OCH$_2$C$\underline{H}_3$), 1.17 (t, *J* = 7.1 Hz, 3H, OCH$_2$C$\underline{H}_3$). ^{13}C NMR (DMSO) δ (ppm): 165.74, 158.26, 151.92, 141.58, 139.83, 139.78, 135.53, 133.20, 130.77, 130.03, 129.82, 128.85, 128.54, 126.91, 125.91, 122.84, 121.48, 120.78, 115.89, 66.62, 61.05, 46.20, 14.41, 13.93. IR: ν(N-H) 3515, 3407, ν(O-H) 3254, ν(C-H) 2986, ν(C=O) 1703, ν(C=C) + ν(C=N) 1634, 1611, 1545, ν(C-O) 1284, 1256, 1136 cm^{-1}. Anal. Calcd. for $C_{26}H_{26}N_4O_4$: C, 68.11; H, 5.72; N, 12.22. Found: C, 67.78; H, 5.88; N, 12.54.

Methyl 2-Ethoxy-1-((2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl)methyl)-1*H*-benzo[*d*]imidazole-7-carboxylate (6a).

Method A) A mixture of **4a** (8 g, 18 mmol), DMSO (70 mL), 1,1'-carbonyldiimidazole (3.5 g, 21.6 mmol), and DBU (3.5 g, 23 mmol) was stirred at room temperature for 4 h. The mixture was poured into water (300 mL) and the solution was acidified with 5% HCl to pH about 4-5. The formed precipitate was filtered off, washed with water and dried on air to provide 8.4 g of white precipitate. Its crystallization from acetone provided 7.7 g (91 %) of white crystals was obtained; Mp: 192-196 °C. HPLC purity 99.1 %.

Method B) A mixture of **4a** (20 g, 45 mmol), DMSO (130 mL), 1,1'-carbonyldiimidazole (8 g, 50 mmol), and K_2CO_3 (9 g, 65 mmol) was stirred at room temperature for 3 h. The mixture was poured into water (500 mL) and the solution was acidified with 5% HCl. The formed

precipitate was filtered off, washed with water and dried to provide 22.2 g of white precipitate. Its crystallization from acetone provided 18.1 g (85 %) of white crystals was obtained; Mp: 194-198 °C. HPLC purity 99.3 %.

Method C) Diphenyl carbonate (0.32 g, 1.5 mmol) was added to a mixture of **4a** (0.44 g, 1 mmol) and potassium carbonate (0.2 g, 1.4 mmol) in DMSO (10 mL) and the mixture was stirred at room temperature for 4 h. The mixture was poured into water (25 mL), acidified with acetic acid and the formed precipitate was filtered off, washed with water and dried providing 0.43 g (91 %) of white precipitate of HPLC purity 93.2 %. Its crystallization from ethyl acetate provided 0.33 g (74 %) of white crystals; Mp: 194-197 °C. HPLC purity 98.8 %.

Method D) A 30% (w/w) solution of MeONa in MeOH (31 mL) was added dropwise (10 minutes) to a solution of **4a** (36 g, 81 mmol) and dimethyl carbonate (20.5 mL = 22 g, 244 mmol) in DMSO (205 mL) stirred at temperature of about 10 °C. The cooling bath was removed and the mixture was stirred for 20 minutes (temperature of about 21 °C). The mixture was added into cold water (1 L, 5 °C) and acidified with 5% aqueous HCl. The formed precipitate was filtered off, washed with cold water and dried to provide 38.7 g of white precipitate. Its crystallization from acetone provided 33.1 g (87 %) of white crystals was obtained; Mp: 195-198 °C. HPLC purity 98.7 %.

Method E) A 30% (w/w) solution of MeONa in MeOH (190 mL) was added dropwise (15 minutes) to a mixture of **4b** (190 g, 414 mmol) and dimethyl carbonate (112 g, 1243 mmol) in DMSO (900 mL) stirred under cooling at inner temperature not exceeding 25 °C. The cooling bath was removed and the mixture was stirred for 2 h (temperature of about 20-25 °C). Cold water (5 °C, 3.6 L) was added, the mixture was cooled down to 15 °C and an aqueous HCl (prepared from 72 mL of concd. HCl and 72 mL of water) was added during 1 h. The formed

mixture was stirred at 15 °C for 1 h, the precipitate was filtered off, washed with water (3 x 300 mL) and dried in a vacuum drier (35 °C/50 mbar) to provide 201.5 g of white precipitate. The crude product of HPLC purity of 88.4 % containing also 4.1 % of ethyl ester **6b** and 4.4 % of azilsartan (**1**) was used for the next step (hydrolysis) without further purification. A sample purified by crystallization from acetone (HPLC purity 98.3 %) melted at 194-198 °C. HRMS for $C_{26}H_{23}N_4O_5$ $(M+H)^+$ Calcd: 471.1668, found: 471.1688. ^{1}H NMR (DMSO) δ (ppm): 12.39 (s, 1H, NH), 7.70 (dd, *J* = 7.9, 1.1 Hz, 1H, Ar), 7.68-7.63 (m, 2H, Ar), 7.55 (td, *J* = 7.4, 1.1 Hz, 1H, Ar), 7.46 (m, 2H, Ar), 7.24 (d, *J* = 8.1, 2H, Ar), 7.19 (t, *J* = 7.9 Hz, 1H, Ar), 7.00 (d, *J* = 8.1 Hz, 2H, Ar), 5.54 (s, 2H, N-C$\underline{H}_2$-Ar), 4.62 (q, *J* = 7.1 Hz, 2H, OC$\underline{H}_2$CH$_3$), 3.69 (s, 3H, OCH$_3$), 1.39 (t, *J* = 7.1 Hz, 3H, OCH$_2$C$\underline{H}_3$). ^{13}C NMR (DMSO) δ (ppm): 166.15, 159.45, 158.32, 158.26, 141.64, 140.78, 137.73, 136.73, 131.85, 130.90, 130.60, 130.16, 128.81, 128.80, 126.24, 122.91, 122.18, 121.58, 120.82, 115.50, 66.61, 52.18, 46.38, 14.35. Anal. Calcd. for $C_{26}H_{22}N_4O_5$: C, 66.37; H, 4.71; N, 11.91. Found: C, 66.22; H, 4.93; N, 11.66.

Ethyl 2-Ethoxy-1-((2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl)methyl)-1*H*-benzo[*d*]imidazole-7-carboxylate (6b). Using the procedure described for the synthesis of **6a** from **4a** (Method A) and starting from ethyl ester **4b**, 98 % yield of **6b** was obtained; Mp: 179-182 °C (acetone). HPLC purity 97.7 %. HRMS for $C_{27}H_{25}N_4O_5$ $(M+H)^+$ Calcd: 485.1825, found: 485.1798. ^{1}H NMR (DMSO) δ (ppm): 12.40 (s,1H, NH), 7.69 (dd, *J* = 7.9, 1.2 Hz, 1H, Ar), 7.50 (m, 1H, Ar), 7.44 (dd, *J* = 7.9, 1.2 Hz, 1H, Ar), 7.43-7.40 (m, 4H, Ar), 7.35 (d, *J* = 7.7 Hz, 1H, Ar), 7.19 (t, *J* = 7.9 Hz, 1H, Ar), 6.95 (d, *J* = 8.3 Hz, 2H, Ar), 5.57 (s, 2H, N-CH$_2$-Ar), 4.60 (q, *J* = 7.1 Hz, 2H, COOC$\underline{H}_2$CH$_3$), 4.18 (q, *J* = 7.1 Hz, 2H, OC$\underline{H}_2$CH$_3$), 1.39 (t, *J* = 7.1 Hz, 3H, COOCH$_2$C$\underline{H}_3$), 1.16 (t, *J* = 7.1 Hz, 3H, OCH$_2$C$\underline{H}_3$). ^{13}C NMR (DMSO) δ (ppm): 165.70, 159.46, 158.26, 158.23, 141.60, 140.76, 137.76, 136.74, 131.84, 130.86,

130.60, 130.18, 128.84, 127.80, 126.23, 122.92, 122.17, 121.51, 120.79, 115.83, 66.60, 61.01, 46.30, 14.35, 13.85. IR: ν(C-H) 2979, ν(C=O) 1771, 1713, ν(C=C) + ν(C=N) 1610, 1544, ν(C-O) 1275, 1124 cm^{-1}. Anal. Calcd. for $C_{27}H_{24}N_4O_5$: C, 66.93; H, 4.99; N, 11.56. Found: C, 66.69; H, 4.73; N, 11.27.

2-Ethoxy-1-((2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl)methyl)-1*H*-benzo[*d*]imidazole-7-carboxylic Acid, Azilsartan (1). A mixture of crude **6a** obtained by Method E (200 g, 425 mmol) and aqueous NaOH (100 g in 2 L of water, 2.5 mol) was stirred at 50 °C for 3 h (HPLC checking). The mixture was diluted with acetone (1 L) and acidified with acetic acid (about 150 mL) at 45 °C. Then the mixture was diluted with water (700 mL), slowly cooled down to 20°C (4 h) and stirred for additional 1 h at this temperature. The formed precipitate was filtered off, washed with a mixture of acetone - water (200 mL, 1 : 2 v/v) and dried in dark in a vacuum drier (35 °C/50 mbar) overnight to provide 185.6 g of off white precipitate (HPLC purity 95.7 %). This product was suspended in acetone (360 mL) and stirred under reflux for 1 h. After cooling to room temperature, the insoluble material was filtered off to get 173.2 g (89 %) of azilsartan (**1**); Mp: 208-211 °C (ref.[5] m. p. 212-214 °C). HPLC purity 98.9 %. HRMS for $C_{25}H_{21}N_4O_5$ (M^+) Calcd: 457.1512, found: 457.1597. ^{1}H NMR (DMSO) δ (ppm): 13.17 (bs, 1H, OH or NH), 12.42 (bs, 1H, OH or NH), 7.70-7.60 (m, 3H, Ar), 7.57-7.50 (m, 2H, Ar), 7.50-7.44 (m, 1H, Ar), 7.23 (d, *J* = 8.3 Hz, 2H, Ar), 7.18 (t, *J* = 7.9 Hz, 1H, Ar), 7.05 (d, *J* = 8.3 Hz, 2H, Ar), 5.68 (s, 2H, N-C$\underline{H}_2$-Ar), 4.58 (q, *J* = 7.1 Hz, 2H, OC$\underline{H}_2$CH$_3$), 1.38 (t, *J* = 7.1 Hz, 3H, OCH$_2$C$\underline{H}_3$). ^{13}C NMR (DMSO) δ (ppm): 167.51, 159.49, 158.27, 158.26, 141.63, 140.70, 137.71, 137.16, 131.87, 131.26, 130.65, 130.20, 128.85, 127.81, 126.61, 123.47, 122.13, 121.45, 120.69, 116.57, 66.48, 46.34, 14.36. Anal. Calcd. for $C_{25}H_{20}N_4O_5$: C, 65.78; H, 4.42; N, 12.27. Found: C, 65.55; H, 4.66; N, 11.92.

(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)-1*H*-benzo[*d*]imidazole-7-carboxylate, Azilsartan Medoxomil (2), solvate with *N,N*-dimethylacetamide (1:1)

Potassium carbonate (23 g, 167 mmol), 4-toluenesulfonyl chloride (27.5 g, 144 mmol) and DMAP (2.0 g, 16 mmol) was added to a solution of azilsartan (**1**; 50 g, 110 mmol) and medoxomil alcohol (**8**; 18.8 g, 144 mmol) in *N,N*-dimethylacetamide (500 mL) at 30 °C and the mixture was stirred for 3 h at this temperature. The mixture was diluted with water (300 mL), acidified with concentrated aqueous hydrochloric acid to pH about 5 and a seed (0.1 g) was added. The formed white crystals were filtered off to give 63.6 g (88.5 %) of crude product as a solvate with *N,N*-dimethylacetamide after drying in *vacuo* at 45°C for 5 h. Mp: 111-114 °C; mp (onset temperature) by DSC: 110 °C. HPLC purity 99.2 %. ^{1}H NMR (500 MHz, DMSO) δ (ppm): 12.37 (bs, 1H, NH), 7.73 (dd, *J* = 7.9, 1.2 , 1H, Ar), 7.69-7.61 (m, 2H, Ar), 7.55 (dd, *J* = 7.6, 1.2, 1H, Ar), 7.52 (dd, *J* = 7.9, 1.2 , 1H, Ar), 7.50-7.44 (m, 1H, Ar), 7.22 (d, *J* = 8.2 Hz, 2H, Ar), 7.21 (t, *J* = 7.7 Hz, 1H, Ar), 7.00 (d, *J* = 8.2 Hz, 2H, Ar), 5.55 (s, 2H, N-$\underline{CH_2}$-Ar), 5.12 (s, 2H, COO$\underline{CH_2}$-R), 4.60 (q, *J* = 7.0 Hz, 2H, O$\underline{CH_2}CH_3$), 2.94 (s, 3H, $CH_3CON(\underline{CH_3})_2$), 2.78 (s, 3H, $CH_3CON(\underline{CH_3})_2$), 2.16 (s, 3H, CH_3),), 1.95 (s, 3H, $\underline{CH_3}CON(CH_3)_2$), 1.38 (t, *J* = 7.0 Hz, 3H, $OCH_2\underline{CH_3}$). ^{13}C NMR (500 MHz, $CDCl_3$) δ (ppm): 169.54, 165.04, 159.43, 158.38, 158.21, 151.77, 141.70, 140.73, 140.35, 137.81, 136.66, 133.12, 131.83, 131.17, 130.60, 130.12, 128.82, 127.82, 126.36, 123.42, 122.17, 122.14, 120.87, 114.48, 66.67, 54.67, 46.43, 37.41, 34.45, 21.37, 14.32, 8.83.

(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)-1*H*-benzo[*d*]imidazole-7-carboxylate, Azilsartan Medoxomil (2)

The isolated crystals of solvate (63 g) were suspended in a mixture of acetone (200 mL) and water (400 mL) and the formed suspension was stirred at 40 °C for 3 h. Then the mixture was cooled down to 25°C, stirred at this temperature for 1 h and the insoluble portion was filtered off, washed with water (200 mL) and dried under reduced pressure at 40 °C to provide 51.2 g (93.7 %) of the final desolvated product. HPLC purity 99.5 %. Residual solvents (acetone: 100 ppm; *N,N*-dimethylacetamide: 50 ppm). Mp 177 - 179 °C; mp (onset temperature) by DSC 176 °C. HRMS for $C_{30}H_{25}N_4O_8$ $(M+H)^+$ Calcd: 569.1594, found: 569.1599. ^{1}H NMR (500 MHz, DMSO) δ (ppm): 12.37 (bs, 1H, NH), 7.73 (dd, *J* = 7.9, 1.2, 1H, Ar), 7.69-7.62 (m, 2H, Ar), 7.55 (dd, *J* = 7.6, 1.2, 1H, Ar), 7.52 (dd, *J* = 7.9, 1.2, 1H, Ar), 7.50-7.44 (m, 1H, Ar), 7.22 (d, *J* = 8.2 Hz, 2H, Ar), 7.24-7.19 (m, 1H, Ar), 7.00 (d, *J* = 8.2 Hz, 2H, Ar), 5.55 (s, 2H, N-$\underline{CH_2}$-Ar), 5.12 (s, 2H, COO$\underline{CH_2}$-R), 4.60 (q, *J* = 7.0 Hz, 2H, O$\underline{CH_2}CH_3$), 2.16 (s, 3H, CH_3), 1.38 (t, *J* = 7.0 Hz, 3H, $OCH_2\underline{CH_3}$). ^{13}C NMR (500 MHz, $CDCl_3$) δ (ppm): 165.04, 159.43, 158.38, 158.21, 151.77, 141.70, 140.73, 140.35, 137.81, 136.66, 133.12, 131.83, 131.17, 130.60, 130.12, 128.82, 127.82, 126.36, 123.42, 122.17, 122.14, 120.87, 114.48, 66.67, 54.67, 46.43, 14.32. Anal. Calcd. for $C_{28}H_{20}N_4O_8$: C, 71.42; H, 4.79; N, 11.10. Found: C, 71.42; H, 4.79; N, 11.10.

(5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl 2-Oxo-3-((2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl)methyl)-2,3-dihydro-1H-benzo[d]imidazole-4-carboxylate (13). A mixture of **1** (0.57 g, 1 mmol), acetone (5 mL) and concentrated aqueous HCl (0.1 mL) was refluxed for 1 h. After cooling, the insoluble portion was filtered off, washed with water and dried to give 0.48 g of **13** (HPLC purity 97.4 %). Crystallization from *i*-PrOH provided 0.40 g (73 %) of **13** of HPLC purity 98.6 %. Mp: 164-168 °C. HRMS for $C_{28}H_{21}N_4O_8$ $(M+H)^+$ Calcd: 541.1359, found: 541.1473. ^{1}H NMR (500 MHz, DMSO) δ (ppm): 12.38 (bs, 1H, NH), 11.51 (bs, 1H, NH), 7.67 (ddd, *J* = 7.6, 1.4 Hz, 1H, Ar), 7.65-7.62 (m, 1H, Ar), 7.55

(ddd, *J* = 7.6, 1.2 Hz, 1H, Ar), 7.50-7.45 (m, 1H, Ar), 7.30 (dd, *J* = 7.9, 1.2 Hz, 1H, Ar), 7.28 (dd, *J* = 7.9, 1.2 Hz, 1H, Ar), 7.22 (d, *J* = 8.2 Hz, 2H, Ar), 7.09 (t, *J* = 7.9 Hz, 1H, Ar), 7.04 (d, *J* = 8.2 Hz, 2H, Ar), 5.36 (s, 2H, N-$\underline{CH_2}$-Ar), 5.04 (s, 2H, COO$\underline{CH_2}$-R), 2.08 (s, 3H, CH_3). ^{13}C NMR (500 MHz, $CDCl_3$) δ (ppm): 164.95, 159.46, 158.24, 154.90, 151.75, 140.73, 140.33, 137.62, 136.75, 133.05, 131.83, 130.63, 130.14, 129.98, 128.76, 128.04, 127.78, 126.46, 122.35, 122.10, 120.76, 113.52, 112.93, 54.69, 44.68, 8.83. Anal. Calcd. for $C_{28}H_{20}N_4O_8$: C, 62.22; H, 3.73; N, 10.37. Found: C, 61.91; H, 3.89; N, 10.03.

(5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl 2-Ethoxy-1-((2'-(4-ethyl-5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl)methyl)-1H-benzo[d]imidazole-7-carboxylate (14). A mixture of **1** (0.57 g, 1 mmol), acetone (10 mL), K_2CO_3 (0.25 g, 1.8 mmol) and ethyl iodide (0.2 mL) was stirred in a closed flask for 24 h. The insoluble portion was filtered off through a celite pad, washed with acetone and the filtrate was evaporated. The residue after evaporation was mixed with water (15 mL) and extracted with dichloromethane (3 x 20 mL). The extract was washed with water and dried with $MgSO_4$. The filtrate was evaporated (0.68 g) to give an oily product, which was purified by crystallization from ethyl acetate to give 0.35 g (59 %) of white crystals. Mp: 164-170 °C (HPLC purity 96.8). HRMS for $C_{32}H_{29}N_4O_8$ $(M+H)^+$ Calcd: 597.1985, found: 597.1736. ^{1}H NMR (500 MHz, DMSO) δ (ppm): 7.78-7.70 (m, 2H, Ar), 7.68-7.64 (m, 1H, Ar), 7.63-7.56 (m, 2H, Ar), 7.52 (dd, *J* = 7.9, 1.2 , 1H, Ar), 7.26 (d, *J* = 8.3 Hz, 2H, Ar), 7.21 (t, *J* = 7.9 Hz, 1H, Ar), 7.01 (d, *J* = 8.3 Hz, 2H, Ar), 5.53 (s, 2H, N-$\underline{CH_2}$-Ar), 5.13 (s, 2H, COO$\underline{CH_2}$-R), 4.58 (q, *J* = 7.1 Hz, 2H, O$\underline{CH_2}$$CH_3$), 2.93 (q, *J* = 7.2 Hz, 2H, N$\underline{CH_2}$$CH_3$), 2.16 (s, 3H, CH_3), 1.36 (t, *J* = 7.1 Hz, 3H, O$CH_2\underline{CH_3}$), 0.58 (t, *J* = 7.2 Hz, 3H, N$CH_2\underline{CH_3}$). ^{13}C NMR (500 MHz, $CDCl_3$) δ (ppm): 165.00, 159.06, 158.40, 158.20, 151.75,

141.72, 140.54, 140.35, 137.28, 137.24, 133.08, 132.47, 131.25, 131.18, 130.36, 128.66, 128.14, 126.83, 123.50, 122.22, 121.17, 120.90, 114.38, 66.63, 54.65, 46.43, 37.40, 14.30, 11.86, 8.82. Anal. Calcd. for $C_{32}H_{28}N_4O_8$: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.77; H, 4.81; N, 9.07.

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Notes

The authors declare no competing financial interest.

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ABBREVIATIONS

CDI, 1,1'-carbonyldiimidazole; DABCO, 1,4-diazabicyclo[2.2.2]octane; DBU, 8-diazabicyclo[5.4.0.]undec-7-en; DEC, diethyl carbonate; DIPEA (*N,N*-Diisopropylethylamine); DMA, *N,N*-dimethylacetamide; DMC, dimethyl carbonate; DMF, *N,N*-dimethylformamide; NMP, *N*-methylpyrrolidone; DMPU, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone; DMSO, dimethyl sulfoxide; DPC, diphenyl carbonate; DSC, differential scanning calorimetry; HPLC, high-performance liquid chromatography; TBz-Cl, 2,4,6-trichlorobenzoyl chloride; TLC, thin layer chromatography; TMU, 1,1,3,3-tetramethylurea; TsCl, 4-toluenesylfonyl chloride; XRPD, X-ray powder diffraction.

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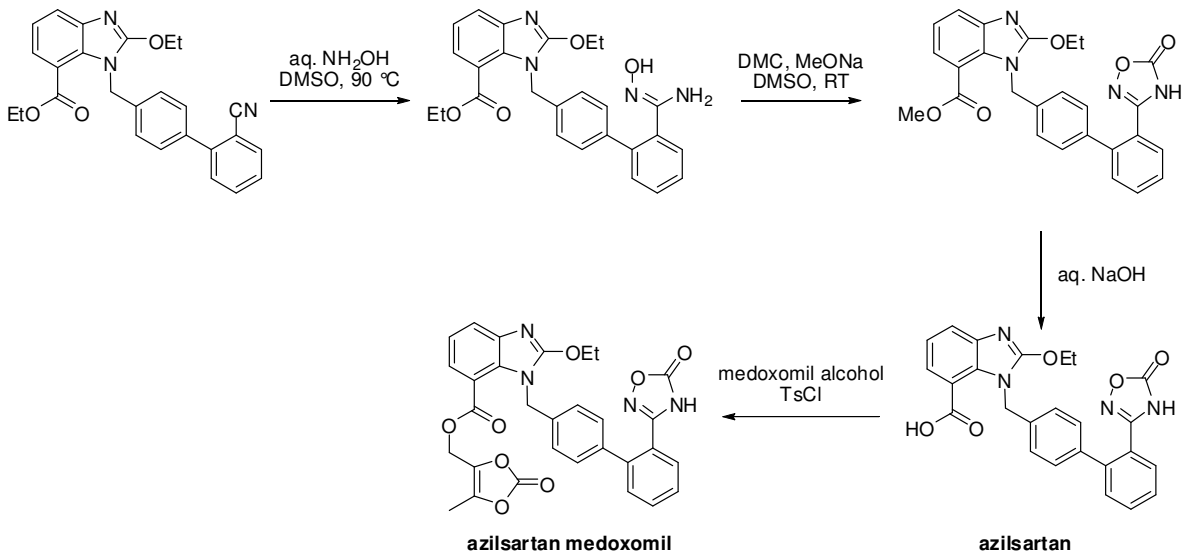
GRAPHICAL ABSTRACT

Improved Process for Azilsartan Medoxomil: A New Angiotensin Receptor Blocker

Stanislav Rádl, Josef Černý, Jan Stach, and Zuzana Gablíková


aq. NH2OH
DMSO, 90 °C
DMC, MeONa
DMSO, RT
aq. NaOH
medoxomil alcohol
TsCl
azilsartan medoxomil
azilsartan