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# Commercial Synthesis of Azilsartan Kamedoxomil: An Angiotensin II Receptor Blocker

Srinivas Garaga,*[,†,‡] Nimesh C. Misra,[†] Ambati V. Raghava Reddy,[†] Koilpillai Joseph Prabahar,[†] Chandiran Takshinamoorthy,[†] Paul Douglas Sanasi,[‡] and Korupolu Raghu Babu[‡]

[†]Chemical Research and Development Department, Aurobindo Pharma Ltd., Survey No: 71&72, Indrakaran Village, Sangareddy Mandal, Medak District, Hyderabad, 502329 Andhra Pradesh, India

[‡]Department of Engineering Chemistry, A. U. College of Engineering (A), Andhra University, Visakhapatnam, 530 003 Andhra Pradesh, India

Supporting Information

**ABSTRACT:** A commercially viable process for the preparation of azilsartan kamedoxomil, an angiotensin II receptor blocker, has been developed. The present work describes the novel synthesis of azilsartan medoxomil from amidoxime methyl ester. The present work also describes the improved synthesis of amidoxime methyl ester and azilsartan kamedoxomil. This process features a high overall yield (36%) with 99.52% HPLC purity.

## INTRODUCTION

Azilsartan medoxomil belongs to the sartan class of drugs. Sartans inhibit the AT1 receptor of angiotensin II and modulate the rennin−angiotensin−aldosterone system.[1,2] Sartans are used to treat hypertension, heart failure, cardiovascular disease, stroke, and nephropathy. There are many sartan drugs available in the market, such as losartan, candesartan, telmisartan, valsartan, and others. Azilsartan medoxomil is an $AT_1$-subtype angiotensin II receptor blocker (ARB). Azilsartan medoxomil (Figure 1), a prodrug form of azilsartan (**8**), was approved in 2011 and is used for the treatment of hypertension. It is marketed by Takeda under the brand name Edarbi. Azilsartan medoxomil (**2**) 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-4yl]methyl}-1*H*-benzimidazole-7-carboxylate.

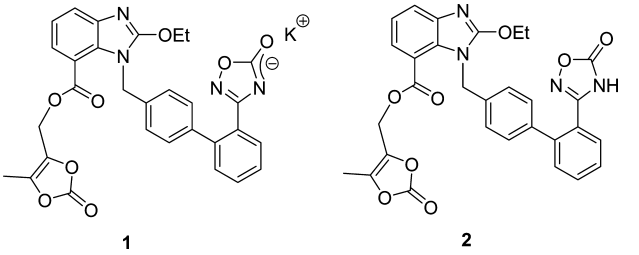


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**Figure 1.** Structures of azilsartan kamedoxomil (**1**) and azilsartan medoxomil (**2**).

There are very few reports for the synthesis of azilsartan kamedoxomil.[3−15] The synthetic route for azilsartan kamedoxomil (**1**), as disclosed in previous literature,[3] is 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**. Treatment of **6** with ethyl chloroformate in the presence of a base produces intermediate **6a**, which is cyclized in xylene at reflux to produce azilsartan methyl ester **7**. Hydrolysis of **7** in aqueous sodium hydroxide produces azilsartan (**8**). Finally, azilsartan (**8**) is treated with medoxomil alcohol (**4**; Figure 2) in the presence of tosyl chloride to produce azilsartan medoxomil (**2**). Azilsartan medoxomil (**2**) is treated with potassium 2-ethylhexanoate in acetone to produce azilsartan kamedoxomil (**1**) in 60% yield. The major disadvantage of this process is the formation of impurities like azilsartan methyl ester (**7**) and azilsartan ethyl ester (**10**) (Figure 3).[12] These impurities are process-related, and azilsartan methyl ester (**7**) also originates from methanol contained in the medoxomil alcohol.[12,16] These impurities are very difficult to remove, requiring repeated crystallizations to achieve the desired purity (below 0.1 level) and resulting in a low yield of azilsartan kamedoxomil; therefore, this is not suitable for commercial-scale preparations.

Another report[4] available for the preparation of azilsartan medoxomil involves reaction of azilsartan disodium salt with medoxomil chloride (**3**). The major disadvantage of this process is its poor yield due to the formation of byproducts, i.e., N-alkylation on the oxadiazole ring,[12] to produce N-alkylated impurity **11** and N,O-dialkylated impurity **12** (Figure 4). So, this process is also not suitable for commercialization of azilsartan kamedoxomil.

Hence, there is a need to develop an improved alternative route for the preparation of azilsartan kamedoxomil (**1**). The present invention relates to a novel, cost-effective, and commercially viable process for the preparation of azilsartan kamedoxomil (**1**).

## RESULTS AND DISCUSSION

The present article is covered by our patent[17] (Scheme 2) and involves the reaction of BEC methyl ester **5** with hydroxylamine hydrochloride in the presence of sodium bicarbonate to produce

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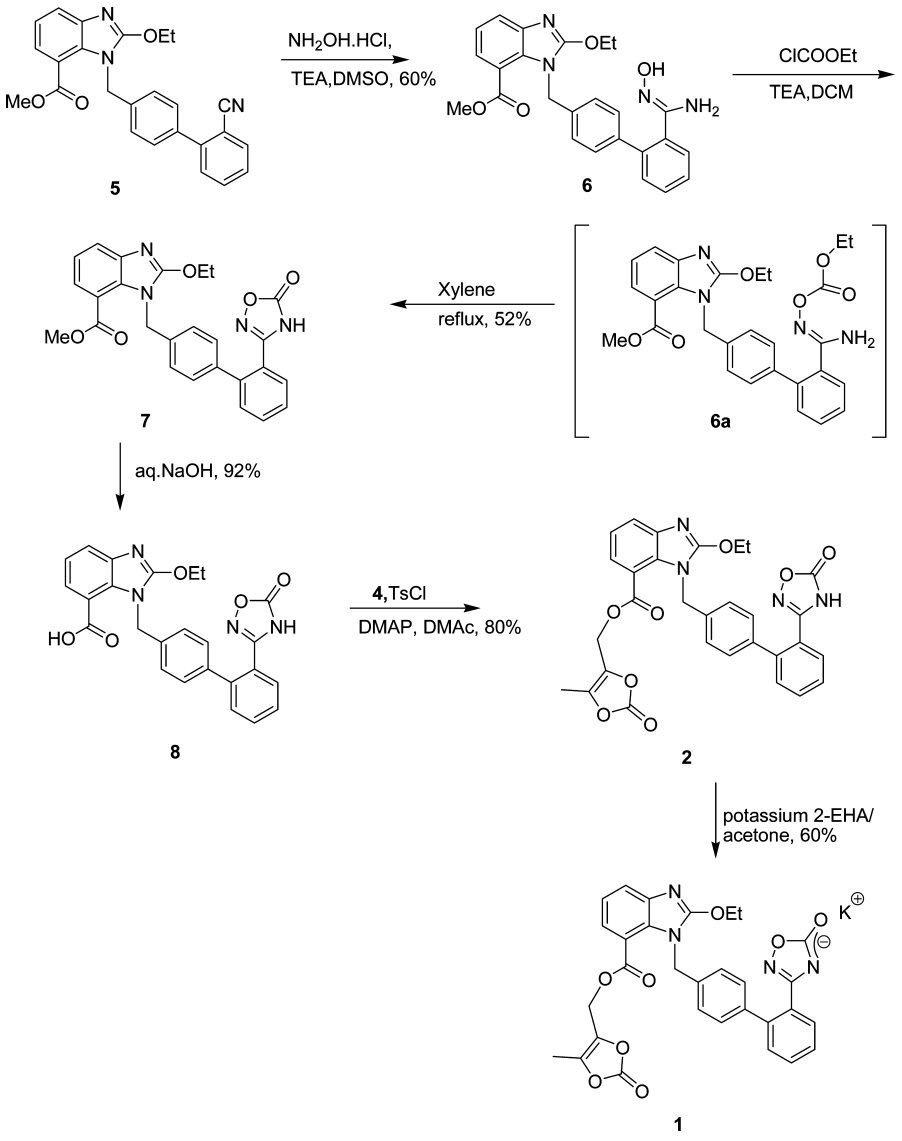
**Scheme 1. Synthetic Route for Azilsartan Kamedoxomil Reported in the Literature**



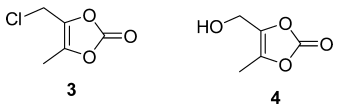




**Figure 2.** Structures of medoxomil chloride (**3**) and medoxomil alcohol (**4**).

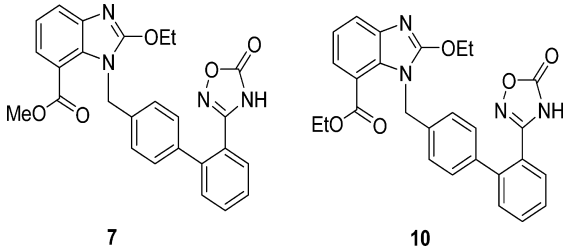



**Figure 3.** Structures of azilsartan methyl ester (**7**) and azilsartan ethyl ester (**10**).

amidoxime methyl ester **6**. Protection of compound **6** with trityl chloride produces trityl amidoxime methyl ester **15**. Hydrolysis of **15** provides trityl amidoxime sodium salt **16**, which is further

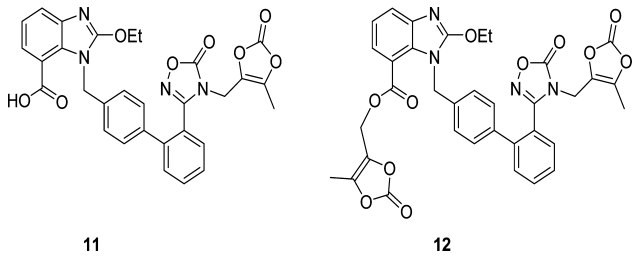



**Figure 4.** Structures of azilsartan *N*-medoxomil **11** and azilsartan dimedoxomil **12**.

condensed with medoxomil chloride (**3**) to produce trityl amidoxime medoxomil ester **17**. Deprotection of **17** with trifluoroacetic acid produces amidoxime medoxomil ester **18**. Compound **18** is cyclized with disuccinimidyl carbonate (DSC) to give azilsartan medoxomil (**2**). Finally, azilsartan medoxomil is treated with potassium 2-ethylhexanoate in tetrahydrofuran to give azilsartan kamedoxomil (**1**).

We have developed this process for the synthesis of azilsartan kamedoxomil (**1**) from amidoxime methyl ester **6**. The preparation of amidoxime methyl ester is known in the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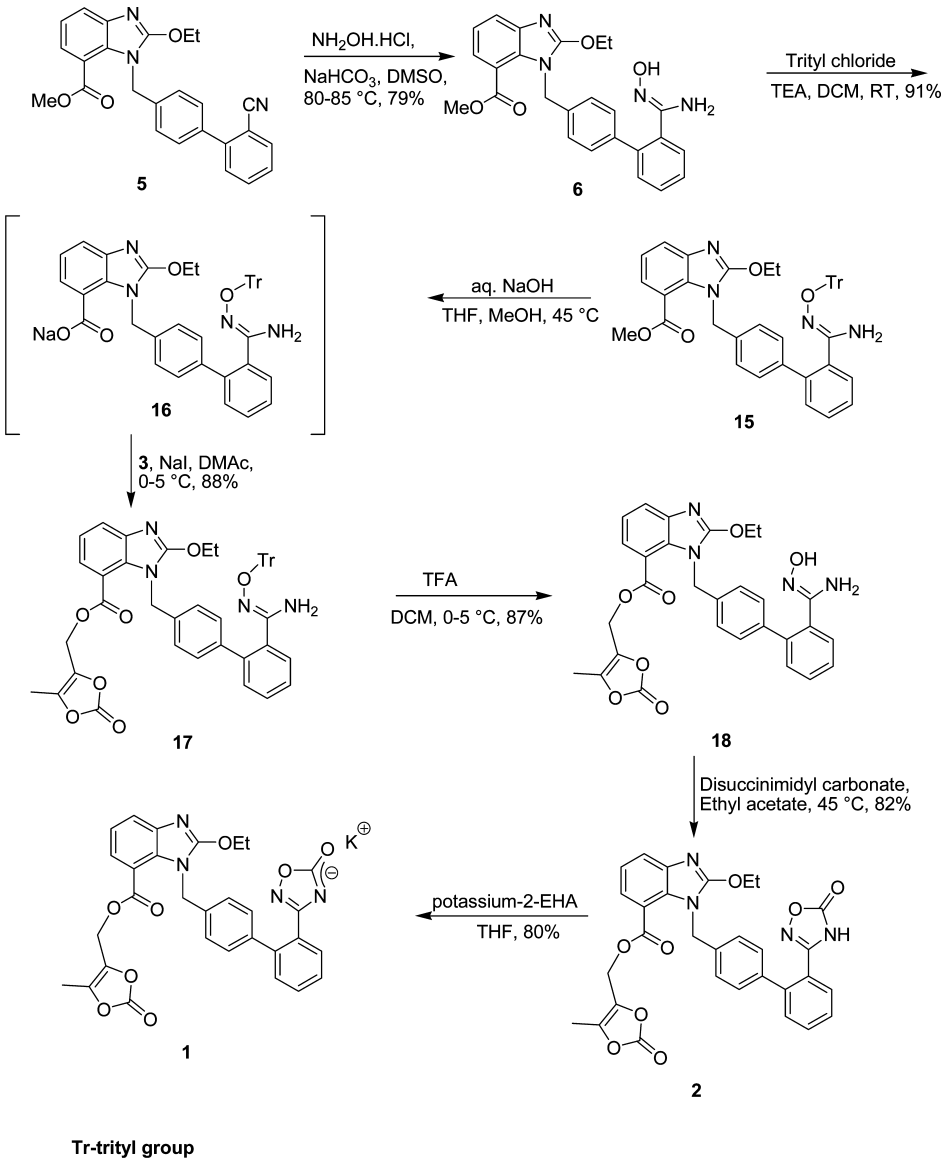
**Scheme 2. Improved and Alternate Synthetic Route for Azilsartan Kamedoxomil**




literature.[3−15] The formation of impurities (**13** and **14**; Figure 5) was observed during the synthesis of amidoxime methyl ester.

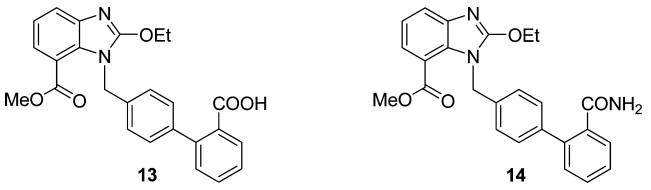



**Figure 5.** Structures of amidoxime acid **13** and amide methyl ester **14**.

There was a need to control these impurities in the reaction to obtain a higher yield. Our aim was to investigate the root cause of the formation of these impurities and to control their formation in the reaction. Most of the reported methods to prepare amidoxime methyl ester use excess hydroxylamine hydrochloride (18 to 25 mol equivalents). Hydroxylamine tends to decompose at higher temperature, giving ammonia as a byproduct.[18] This liberated ammonia reacts with BEC methyl ester **5**, giving amidoxime acid and amide methyl ester as related substances (**13** and **14**).

We controlled the formation of these impurities by using fewer moles of hydroxylamine hydrochloride (5 mol equivalents). Moreover, the liberated ammonia in the reaction is expelled by maintaining nitrogen purging. Under these conditions, we achieved 80−85% yield of amidoxime methyl ester **6** with an HPLC purity of more than 95%. The experimental details are tabulated in Table 1.

To protect amidoxime methyl ester **6**, we tested different protecting groups such as benzyl, DIBOC, and trityl (Tr). Among all of these protecting groups, trityl deprotection is easy to achieve with trifluoroacetic acid without affecting the 2-ethoxy group. To optimize the tritylation reaction, we tried different solvents such as *N*,*N*-dimethylformamide and dichloromethane. In these solvents, we observed the formation of diprotected amidoxime (ditritylated amidoxime methyl ester, **15a**; Figure 6) of around 10−12%. This ditritylated amidoxime subsequently reacts with medoxomil chloride in the next step and produces 10−12% ditritylated amidoxime medoxomil ester (**17a**; Figure 7). Finally, this ditritylated amidoxime medoxomil ester gives the



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**Table 1. Hydroxylamine and Base Screening Studies for Amidoxime Preparation Reaction to Control Formation 13 and 14**

| | | | | reaction monitoring results | | | |
|---|---|---|---|---|---|---|---|
| entry | $NH_2OH{\cdot}HCl$ moles | $NaHCO_3$ moles | temp (°C) | purity | acid (**13**) | amide (**14**) | yield (%) |
| 1 | 18 | 25 | 80−85 | 70.99 | 10.99 | 14.20 | 55 |
| 2 | 18 | 25 | 80−85 | 72.40 | 8.39 | 6.39 | 57 |
| 3 | 9 | 13 | 80−85 | 71.80 | 5.76 | 12.3 | 55 |
| 4 | 5 | 5.5 | 95−100 | 59.80 | 16.51 | 4.40 | 54 |
| 5[a] | 5 | 5.5 | 80−85 | 81.10 | 4.21 | 4.10 | 79 |

[a]Reaction performed under nitrogen purging.

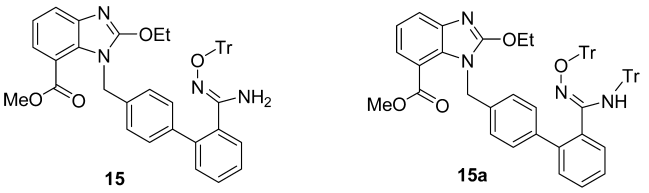


**Figure 6.** Structures of trityl amidoxime methyl ester **15** and ditrityl amidoxime methyl ester **15a**.

desired product, amidoxime medoxomil ester **18**, on deprotection.

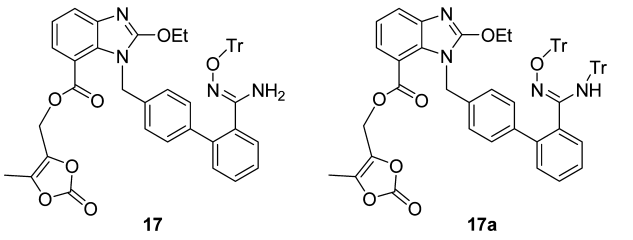


**Figure 7.** Structures of trityl amidoxime medoxomil ester **17** and ditrityl amidoxime medoxomil ester **17a**.

When we used *N*,*N*-dimethylformamide as solvent in the tritylation reaction, we observed the elimination of ditritylated product into the mother liquor during ethanol purification, and we achieved 65% yield with 97% HPLC purity, whereas with dichloromethane as a solvent, we achieved 91% yield with 85.95% (monotritylated) and 11.73% (ditritylated) HPLC purity. Therefore, dichloromethane was preferred for use as the solvent for the tritylation reaction because the ditritylated medoxomil ester also gives the desired amidoxime medoxomil ester **18** after deprotection. The experimental details are tabulated in Table 2.

To optimize the cyclization of amidoxime medoxomil ester **18** into azilsartan medoxomil (**2**), we explored different cyclization reagents such as carbonyldiimidazole (CDI), triphosgene, dimethyl carbonate (DMC), diethyl carbonate (DEC), diphenyl carbonate (DPC), and ethyl chloroformate (ECF). We identified the formation of azilsartan **8** with all of these reagents. The best results were achieved using disuccinimidyl carbonate (DSC) as the cyclization agent. Under these optimized conditions, an 82% yield of azilsartan medoxomil **2** with 99.6% HPLC purity was obtained. The experimental details are tabulated in Table 3.

**Table 2. Solvent Screening Studies for the Tritylation Reaction**

| | | reaction monitoring results | | purity by HPLC | | |
|---|---|---|---|---|---|---|
| entry | solvent | purity | ditritylated (**15a**) | purity | ditritylated (**15a**) | yield (%) |
| 1 | DMF | 84.23 | 11.50 | 97.05 | | 65 |
| 2 | DCM | 85.13 | 11.24 | 85.95 | 11.73 | 91 |

Finally, the preparation of azilsartan kamedoxomil (**1**) is known in the literature.[13−15] As per the literature, azilsartan medoxomil (**2**) is treated with potassium 2-ethylhexanoate in acetone to give azilsartan kamedoxomil (**1**) with 60% yield. However, the reported yields were very low. To overcome the low-yield problems associated with the reported process, we developed an improved process for the preparation of azilsartan kamedoxomil (**1**) in tetrahydrofuran. Herein, we report azilsartan kamedoxomil (**1**) preparation with 80% yield in tetrahydrofuran.

## CONCLUSIONS

A novel, efficient and commercially viable process for the preparation of azilsartan kamedoxomil (**1**) has been developed, resulting in 99.52% purity. The present process overcomes the previous problems of low yields of intermediate amidoxime methyl ester and azilsartan kamedoxomil (**1**). This improved process for the preparation of azilsartan kamedoxomil (**1**) involves the use of much cheaper medoxomil chloride instead of medoxomil alcohol. This modification makes the process cost effective.

## EXPERIMENTAL SECTION

Solvents and reagents were obtained from commercial sources and used without purification. The IR spectra ($\vartheta$max, $cm^{-1}$) were recorded in a solid-state KBr dispersion using a PerkinElmer FT-IR spectrometer. The $^1H$ and $^{13}C$ NMR spectra were recorded on Bruker Avance 300 and 500 MHz spectrometers. The chemical shifts were reported in $\delta$/ppm relative to TMS. The mass spectra were recorded on an API 2000 PerkinElmer PE-Sciex mass spectrometer. The reactions were monitored by HPLC. HPLC analysis was performed on a Waters instrument with a UV detector (250 nm) using a Sunfire C18 (250 mm × 4.6 mm, 5 $\mu$m) column. The column oven temperature was 25 °C. Mobile phase A was composed of 1 g of potassium dihydrogen phosphate dissolved in 1 L of water and adjusted to pH 3 with diluted orthophosphoric acid; mobile phase B, acetonitrile. The flow rate was 1.2 mL/min. A gradient (A/B) of 65:35 (0−30 min), 15:85 (30−50 min), and 65:35 (50−60 min) was used for stages 1 and 6. A gradient (A/B) of 65:35 (0−20 min), 15:85 (30−90 min), and 65:35 (91−100 min) was used for stages 2−5. Melting points were determined on a Polman melting point apparatus (model no. MP96) by open capillary method and are uncorrected.

**Methyl 2-Ethoxy-1-((2′-(*N*′-hydroxycarbamimidoyl)-biphenyl-4-yl)methyl)-1*H* benzo[*d*]imidazole-7-carboxylate (Amidoxime Methyl Ester, 6).** To a suspension of


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Table 3. Reagent Screening Studies for the Cyclization Reaction

| entry | cyclizing agent | solvent | temp (°C) | reaction monitoring results | | yield (%) |
|---|---|---|---|---|---|---|
| | | | | purity | azilsartan | |
| 1 | carbonyldiimidazole | ACN | 55−60 | 39.20 | 33.25 | |
| 2[a] | carbonyldiimidazole | ACN | 25−30 | 7.08 | 6.48 | |
| 3 | dimethyl carbonate | DMSO | 55−60 | 45.25 | 8.32 | |
| 4 | diphenyl carbonate | DMF | 75−80 | 95.27 | 3.52 | 75 |
| 5[b] | triphosgene | DCM | 25−30 | | | |
| 6 | disuccinimidyl carbonate | EA | 40−45 | 98.51 | 0.5 | 82 |

[a]No reaction. [b]No product formation.

hydroxylamine hydrochloride (5.07 kg, 72.99 mol) and sodium bicarbonate (6.74 kg, 80.29 mol) in dimethyl sulfoxide (30 L) was added compound BEC methyl ester **5** (6 kg, 14.59 mol) at 45−50 °C. The reaction mixture was stirred at 80−85 °C for 4 h under nitrogen purging. Then, water (60 L) was added to the reaction mixture at 25−30 °C, and the mixture was stirred for 1 h. The resulting product was filtered and purified with ethanol, yielding 5.1 kg (79%) of white crystals. mp 204−207 °C. HPLC purity: 97.74%. HRMS for $C_{25}H_{25}N_4O_4$: $(M + H)^+$ calcd 445.1876; found, 445.1879. $^1$H NMR (500 MHz, DMSO): $\delta$ 9.176 (s, 1H, OH), 7.704 (dd, J = 7, 1 Hz 1H, Ar), 7.466 (dd, J = 7.5, 1 Hz, 1H, Ar), 7.449−7.368 (m, 3H, Ar), 7.358 (d, J = 8 Hz, 2H, Ar), 7.297 (d, $J$ = 8 Hz, 1H, Ar), 7.195 (t, $J$ = 8.5 Hz, 1H, Ar), 6.942 (d, $J$ = 8 Hz, 2H, Ar), 5.539 (br s, 2H, $NH_2$), 5.507 (s, 2H, N-$\underline{CH_2}$-Ar), 4.644 (q, $J$ = 7 Hz, 2H, O$\underline{CH_2}CH_3$), 3.721 (s, 3H, $OCH_3$), 1.433 (t, $J$ = 7 Hz, 3H, $OCH_2\underline{CH_3}$). IR (KBr pellet): 3516, 3409, 3274, 2985, 1718, 1634, 1612, 1547, 1285, 1257, 1134 cm$^{-1}$.

**Methyl 2-Ethoxy-1-[(4-(2-(*N*′-(triphenylmethoxy)-carbamimidoyl)phenyl) phenyl)methyl]-1*H*-1,3-benzodiazole-7-carboxylate (Trityl Amidoxime Methyl Ester, 15).** To a solution of amidoxime methyl ester **6** (5 kg, 11.26 mol) in dichloromethane (25 L) were added triethylamine (1.99 kg, 19.7 mol) and trityl chloride (4.7 kg, 16.89 mol) at 25−30 °C. The reaction mixture was stirred for 16 h at 25−30 °C. DM water (30 L) was added to the above reaction mass and stirred for 30 min. The organic layer was separated and concentrated at 40 °C under reduced pressure. The resulting residue was purified with ethanol, yielding 7 kg (91%) of pure compound **15**. mp 190−193 °C. HPLC purity: 85.95 + 11.73% (ditrityl, **15a**). HRMS for $C_{44}H_{38}N_4O_4$: $(M + H)^+$ calcd, 687.2893; found, 687.2918. $^1$H NMR (500 MHz, DMSO): $\delta$ 7.727 (d, $J$ = 7.5 Hz, 1H, Ar), 7.453 (d, $J$ = 8 Hz, 1H, Ar), 7.378 (d, $J$ = 7.5 Hz, 1H, Ar), 7.312−7.217 (m, 6H, Ar), 7.201−7.117 (m, 15H, Ar), 6.843 (d, $J$ = 7.5 Hz, 2H, Ar), 5.825 (s, 2H, $NH_2$), 5.53 (s, 2H, N-$\underline{CH_2}$-Ar), 4.631 (q, $J$ = 7.5 Hz, 2H, O$\underline{CH_2}CH_3$), 3.668 (s, 3H, $OCH_3$), 1.398 (t, $J$ = 7 Hz, 3H, $OCH_2\underline{CH_3}$). $^{13}$C NMR (125 MHz, DMSO): $\delta$ 145.119, 129.989, 129.692, 129.13, 128.634, 128.545, 127.76, 127.501, 127.153, 126.828, 126.62, 126.495, 125.762, 122.927, 121.587, 120.839, 66.63, 52.232, 46.347, 39.833, 39.67, 39.5, 39.337, 39.167, 14.368. IR (KBr pellet):3478, 3371, 3000, 2951, 1720, 1630, 1616, 1549, 1280, 1248, 1149 cm$^{-1}$.

**Sodium 2-Ethoxy-1-[(4-(2-(*N*′-(triphenylmethoxy)-carbamimidoyl)phenyl) phenyl)methyl]-1*H*-1,3-benzodiazole-7-carboxylate (Trityl Amidoxime Sodium Salt, 16).** To a solution of trityl amidoxime methyl ester **15** (6.5 kg, 9.47 mol) in a mixture of tetrahydrofuran (39 L) and methanol (6.5 L) was added 20% aqueous sodium hydroxide (473 g, 11.84 mol) at 25−30 °C. The reaction mixture was stirred for 8 h at 40−45 °C to complete the reaction. Then, the reaction mixture was concentrated under reduced pressure at 50−55 °C, yielding 6.5 kg of **16** as a foamy solid. HPLC purity: 86.46 + 11.55% (ditrityl). HRMS for $C_{43}H_{35}N_4NaO_4$: $(M + H)^+$ calcd, 695.2556; found, 695.2579. $^1$H NMR (300 MHz, DMSO): $\delta$ 7.31−7.10 (m, 31H, Ar), 7.087 (m, 1H, Ar), 5.917 (s, 2H, N-$\underline{CH_2}$-Ar), 4.506 (q, $J$ = 6.9 Hz, 2H, O$\underline{CH_2}CH_3$), 1.337 (t, $J$ = 6.9 Hz, 3H, $OCH_2\underline{CH_3}$). IR (KBr pellet): 3392, 3023, 2978, 1751, 1616, 1545, 1276, 1251, 1154 cm$^{-1}$.

**(5-Methyl-2-oxo-2*H*-1,3-dioxol-4yl)methyl 2-ethoxy-1-[(4-(2-[*N*′-(triphenylmehoxy)cabamimidoyl]phenyl)-phenyl)methyl]-1*H*-1,3-benzodiazole-7-carboxylate (Trityl Amidoxime Medoxomil Ester, 17).** To a solution of trityl amidoxime sodium salt **16** in dimethylacetamide (32.5 L) were added sodium iodide (195 g, 3%) and medoxomil chloride **3** (1.55 kg, 10.42 mol) at 0−5 °C. The reaction mixture was stirred for 2 h at 0−5 °C to complete the reaction. Then, the reaction mixture was poured into a solvent mixture of water (260 L) and ethyl acetate (65 L), and the pH was adjusted to 7.0 with hydrochloric acid. The organic layer was separated and concentrated under reduced pressure at 50−55 °C. The resulting residue was crystallized with ethyl acetate (32.5 L), yielding 6.5 kg (88%) of **17** as a white compound. mp 90−93 °C. HPLC purity: 84.96 + 11.38% (ditrityl, **17a**). HRMS for $C_{48}H_{40}N_4O_7$: $(M + H)^+$ calcd, 785.2897; found, 785.2896. $^1$H NMR (300 MHz, DMSO): $\delta$ 7.769 (d, $J$ = 7.8 Hz, 1H, Ar), 7.518 (d, $J$ = 7.8 Hz, 1H, Ar), 7.383 (d, $J$ = 7.2 Hz, 1H, Ar), 7.303−7.101 (m, 24H, Ar), 6.81 (d, $J$ = 7.8 Hz, 2H, Ar), 5.829 (s, 2H, $NH_2$), 5.541 (s, 2H, N-$CH_2$-Ar), 5.074 (s, 2H, $CH_2$), 4.608 (q, $J$ = 7.2 Hz, 2H, O$\underline{CH_2}CH_3$), 2.111 (s, 3H, $CH_3$), 1.387 (t, $J$ = 6.9 Hz, 3H, $OCH_2\underline{CH_3}$). IR (KBr pellet): 3495, 3391, 2979, 1717, 1631, 1617, 1550, 1279, 1247, 1149, 1118 cm$^{-1}$.

**(5-Methyl-2-oxo-2*H*-1,3-dioxol-4yl)methyl 2-ethoxy-1-[(4-(2-[*N*-hydroxy carbamimidoyl]phenyl)phenyl)-methyl]-1*H*-1,3-benzodiazole-7-carboxylate (Amidoxime Medoxomil Ester, 18).** To a solution of trityl amidoxime medoxomil ester **17** (6.4 kg, 8.16 mol) in dichloromethane (64 L) was added trifluoroacetic acid (1.12 kg, 9.8 mol) at 0−5 °C. The reaction mixture was stirred for 6 h at 20−25 °C to complete the reaction. Thereafter, the reaction mixture was washed with saturated sodium bicarbonate solution (32 L). The organic layer was concentrated under reduced pressure at 35−40 °C. The resulting residue was crystallized with ethyl acetate (64 L), yielding 3.84 kg (87%) of **18** as a white compound. mp 179−181 °C. HPLC purity: 98.76%. HRMS for $C_{29}H_{26}N_4O_7$: $(M + H)^+$ calcd, 543.1859; found, 543.1871. $^1$H NMR (300 MHz, DMSO): $\delta$ 9.187 (s, 1H, OH), 7.742 (d, $J$ = 7.8 Hz, 1H, Ar), 7.53 (d, $J$ = 7.8 Hz, 1H, Ar), 7.398−7.213 (m, 7H, Ar), 6.944 (d, $J$ = 8.1 Hz, 2H, Ar), 5.554 (br s, 2H, $NH_2$), 5.532 (br s, 2H, N-$\underline{CH_2}$-Ar), 5.147 (s, 2H, $\underline{CH_2}$), 4.659 (q, $J$ = 6.9 Hz, 2H, O$\underline{CH_2}CH_3$), 2.179 (s, 3H, $CH_3$), 1.443 (t, $J$ = 6.9 Hz, 3H, $OCH_2\underline{CH_3}$). IR (KBr pellet): 3515, 3406, 3255, 2985, 1716, 1630, 1612, 1547, 1282, 1255, 1127 cm$^{-1}$.


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**(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-ethoxy-1*H*-benzimidazole-7-carboxylate (Azilsartan Medoxomil, 2).** To a solution of amidoxime medoxomil ester **18** (3.7 kg, 6.82 mol) in ethyl acetate (18.5 L) was added disuccinimidyl carbonate (1.92 kg, 7.5 mol) at 25−30 °C. The reaction mixture was stirred for 16 h at 40−45 °C to complete the reaction. Thereafter, DM water (7.4 L) was added to the reaction mixture at 25−30 °C, and the product was cooled to 5−10 °C. The product was filtered and purified with ethanol, yielding 3.14 kg (82%) of azilsartan medoxomil (**2**) as a white compound. mp 174−177 °C. HPLC purity: 99.60%. HRMS for $C_{30}H_{25}N_4O_8$: $(M + H)^+$ calcd, 569.1594; found, 569.1667. $^1$H NMR (500 MHz, DMSO): $\delta$ 12.374 (br s, 1H, NH), 7.737 (d, $J$ = 8 Hz, 1H, Ar), 7.68−7.562 (m, 2H, Ar), 7.549 (dd, $J$ = 7, 1 Hz, 1H, Ar), 7.531 (dd, $J$ = 7.5, 1 Hz, 1H, Ar), 7.514−7.467 (m, 1H, Ar), 7.231−7.20 (m, 3H, Ar), 7.007 (d, $J$ = 8.5 Hz, 2H, Ar), 5.554 (s, 2H, N-$\underline{CH_2}$-Ar), 5.116 (s, 2H, COO$\underline{CH_2}$), 4.606 (q, $J$ = 7 Hz, 2H, O$\underline{CH_2}CH_3$), 2.16 (s, 3H, $\underline{CH_3}$), 1.401 (t, $J$ = 7 Hz, 3H, OCH$_2\underline{CH_3}$). IR (KBr pellet): 3537, 3436, 2988, 1781, 1727, 1609, 1546, 1280, 1249, 1128 cm$^{-1}$.

**(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-ethoxy-1*H*-benzimidazole-7-carboxylate, Monopotassium Salt (Azilsartan Kamedoxomil, 1).** To a solution of azilsartan medoxomil **2** (3 kg, 5.28 mol) in tetrahydrofuran (300 L) was added activated carbon (150 g, 5%) at 25−30 °C. The slurry mass was stirred for 30 min at 40−45 °C. The reaction mass was filtered under hot conditions and then cooled to 20−25 °C. A tetrahydrofuran solution of potassium 2-ethylhexanoate (0.94 kg, 5.17 mol) was added to the above reaction mass at 20−25 °C. The slurry mass was stirred for 2 h at 20−25 °C. The product was filtered and washed with acetone (6 L), yielding 2.55 kg (80%) of **1** as a white compound. HPLC purity: 99.52%. HRMS for $C_{30}H_{24}KN_4O_8$: $(M + H)^+$ calcd, 607.1153; found, 607.1227. $^1$H NMR (500 MHz, DMSO): $\delta$ 7.732 (d, $J$ = 8 Hz, 1H, Ar), 7.501 (d, $J$ = 5.5, 1 Hz, 2H, Ar), 7.396−7.332 (m, 2H, Ar), 7.258 (d, $J$ = 7 Hz, 1H, Ar), 7.221−7.191 (m, 3H, Ar), 6.871 (d, $J$ = 8 Hz, 2H,Ar), 5.52 (s, 2H, N-$\underline{CH_2}$-Ar), 5.11 (s, 2H, COO$\underline{CH_2}$), 4.61 (q, 2H, O$\underline{CH_2}CH_3$), 2.16 (s, 3H, $\underline{CH_3}$), 1.42 (t,3H, OCH$_2\underline{CH_3}$). $^{13}$C NMR (125 MHz DMSO-$d_6$): $\delta$ 173.064, 168.793, 165.062, 158.414, 151.856, 141.685, 140.360, 140.315, 139.804, 135.096, 133.261, 131.047, 130.936, 129.974, 129.915, 128.893, 128.582, 126.798, 125.562, 123.223, 122.031, 120.832, 114.680, 66.697, 54.683, 46.370, 39.996, 39.922, 39.833, 39.752, 39.663, 39.589, 39.500, 39.419, 39.330, 39.167, 38.997, 14.391, 8.876. IR (KBr pellet): 3537, 3436, 2988, 1781, 1727, 1609, 1546, 1280, 1249, 1128 cm$^{-1}$.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

Characterization spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

## ■ AUTHOR INFORMATION

### Corresponding Author

*Tel.: +91-8455-223757; Fax: +91-8455-23044873; E-mail: srinivasgaraga@yahoo.com.

### Notes

The authors declare no competing financial interest.

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## ■ 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

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