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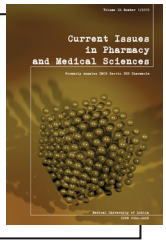

An alternative synthesis of Azilsartan: an angiotensin II receptor blocker

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ABSTRACT

This paper provides a description of an alternative, novel and commercially viable process which has been developed for the preparation of Azilsartan, a pro-drug of Azilsartan medoxomil, an angiotensin II receptor blocker. The present work also provides a primary account of the synthesis and characterization of the novel intermediates (**6, 7 & 10**) of Azilsartan, with their spectral data.

INTRODUCTION

Azilsartan medoxomil is an AT1-subtype angiotensin II receptor blocker (ARB), wherein, angiotensin II is formed from angiotensin I in a reaction catalyzed by the angiotensin converting enzyme. Angiotensin II is the principal pressor agent of the rennin-angiotensin system [1,2], with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Azilsartan medoxomil blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in many tissues, such as the vascular smooth muscle and the adrenal gland. Azilsartan medoxomil, a pro-drug 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 medoxomil **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-4yl]methyl}-1H-benzimidazole-7-carboxylate. Azilsartan **2** is chemically known as 2-ethoxy-1-{[2`-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl) biphenyl-4yl]methyl}-1H-benzimidazole-7-carboxylic acid.

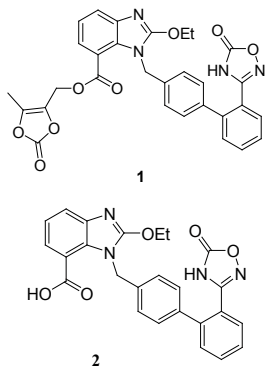

Figure 1. Structures of Azilsartan medoxomil 1 and Azilsartan 2

Several references [3-13] have described the synthesis of azilsartan, but very few references [14] have been found for the synthesis of azilsartan from 4'-(bromomethyl) -1,1'-biphenyl-1,2,4-oxadiazol-5(2H)-one **11**.

The synthetic pathway, as described in the previous literature [11], is given in Scheme 1. In the first step, methyl 2-tert-butoxycarbonyl amino-3-nitrobenzoate 3, when condensed with 2-(4-bromomethyl phenyl)benzonitrile 4, gives compound **5**. The subsequent de-protection of compound **5** with trifluoroacetic acid, gives compound **6**. Reduction of compound **6** with stannous chloride, gives compound **7**. Compound **7** is then cyclized with tetraethyl orthocarbonate, giving BEC methyl ester 8. BEC methyl ester is

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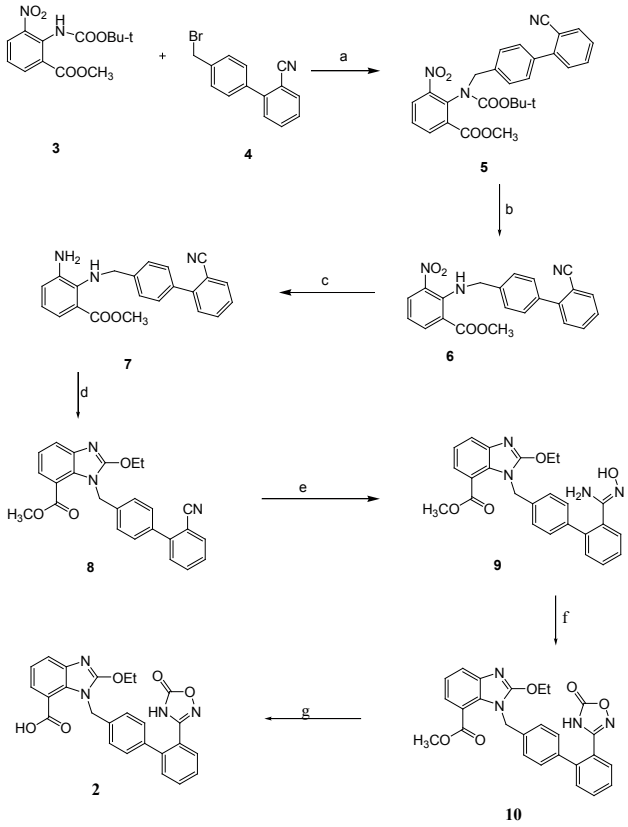
subsequently treated with hydroxylamine hydrochloride, giving amidoxime **9**. Compound **9** is treated with ethyl chloroformate resulting in an intermediate, which is further cyclized to provide azilsartan methyl ester 10 in xylene. Finally, azilsartan methyl ester 10 is hydrolyzed with sodium hydroxide, giving azilsartan 2.



Scheme 1. Reported synthetic route for Azilsartan

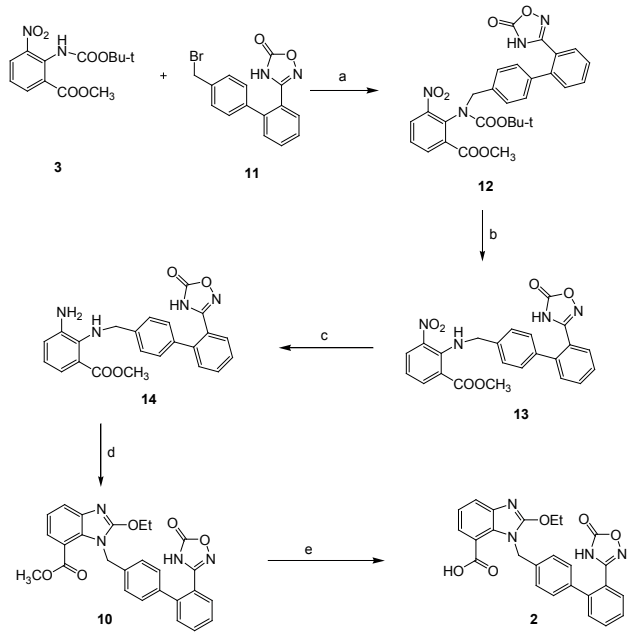
Reagents and conditions: (a) K_2CO_3, acetonitrile, 80-85°C (b) TFA, DCM, 20-25°C, 66% (c) $SnCl_2$, THF, 60-65°C, 80% (d) tetraethyl orthocarbonate, acetic acid, methanol, 20-25°C, 73% (e) NH2OH, NaOMe, DMSO, 55% (f) ethylchloroformate, TEA,DCM, Xylene,110°C, 50% (g) NaOH, H_2O, 40-45°C, 95%.

The main draw back of the aforementioned process, is its low yields (55% and 50%) at the amidoxime production stage, and the cyclization steps necessarily undertaken due to the formation of impurities. To overcome these low yields problems, we have developed an alternative synthesis. This is from 4'-(bromomethyl)-1,1'-biphenyl-1,2,4-oxadiazol-5(2H)-one **11**. This process is mainly noted for both generating high yields and incorporating simple work up procedures.

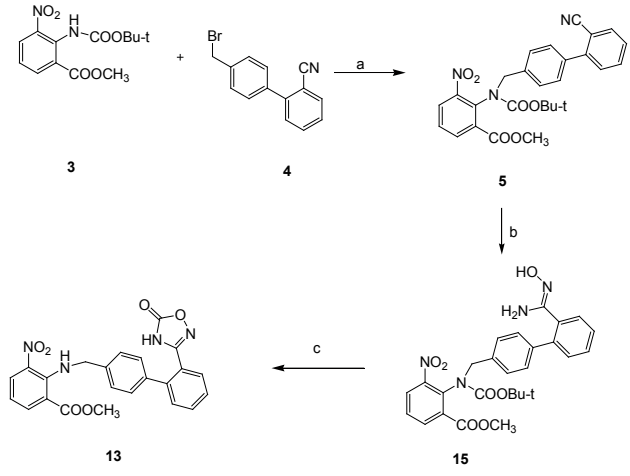
The present invention relates to the synthesis of azilsartan by using commercially available starting materials such as methyl 2-tert-butoxycarbonyl amino-3-nitrobenzoate 3 and 4'-(bromomethyl) -1,1'-biphenyl-1,2,4-oxadiazol-5(2H)-one **11**. Within this unconventional process, compounds **13**, **14** and **15** are novel, and, hence, we are reporting their synthesis and characterization for the first time, along with their spectral data. The main goal of this work was to develop a safe, economic and non-infringing process for the synthesis of Azilsartan **2**.

RESULTS AND DISCUSSION

In our approach (as shown in Scheme 2), we bring about the condensation of compound **3** with **11**, in the presence of potassium carbonate, giving compound **12**. Compound **12** is then de-protected with trifluoroacetic acid, yielding a corresponding nitro compound **13**. Compound **13** is subsequently reduced with stannous chloride, giving a corresponding amino compound **14**. Compound **14** is then cyclized with tetraethyl orthocarbonate, generating azilsartan methyl ester **10**. Finally, azilsartan methyl ester **10** is hydrolysed by using sodium hydroxide, resulting in the targeted molecule azilsartan **2**.



Scheme 2. Novel synthetic route for the synthesis of Azilsartan 2. Reagents and conditions: (a) K2CO3, acetonitrile, 80-85°C, (b) TFA, DCM, 20-25°C, 66% (c) SnCl2, THF, 60-65°C, 80% (d) tetraethyl orthocarbonate, acetic acid, methanol, 20-25°C, 73% (e) NaOH, H2O, 40-45°C, 95%



Scheme 3. Novel synthetic route for the synthesis of compound **13**. Reagents and conditions: (a) K_2CO_3, acetonitrile, 80-85°C (b) $NH_2OH.HCl$, $NaHCO_3$, 80-85°C, 75% (c) CDI, DBU, THF, 20-25°C , 94%

Our unconventional way towards generating azilsartan **2** (as shown in scheme 3), comes about by condensing **13** with 2-(4-bromomethyl phenyl)benzonitrile **4,** yielding compound **5**. Compound **5** is then treated with hydroxylamine hydrochloride in the presence of sodium bicarbonate giving **15**. Cyclization of compound **15** with carbonyldiimidazole, subsequently generates nitro compound **13**. Of note: during the work-up process of cyclization of **15,** we used aqueous sodium bisulfite washing to remove the imidazole by-product. But surprisingly, in so doing, we observed the de-protection of the t-butyl group by way of this sodium bisulfite washing, and, discovered that we could therefore directly obtain nitro compound **13**.

The aforementioned compounds **3** and **4** are known in the literature [14], and we prepared these compounds by using known literature methods. Compound **5** is also known in the literature.[15,16], thus we prepared this compound by using known literature methods.

Synthesis of the Amidoxime intermediate (compound 15)

In this sub-process, compound **5** was treated with hydroxylamine hydrochloride in the presence of a base at a higher temperature, resulting in an amidoxime intermediate **15**. To develop a suitable amidoxime reaction, we tried different bases such as sodium methoxide, triethylamine and sodium bicarbonate. Of all these bases, the best results were obtained by employing sodium bicarbonate. The mass spectrum of compound **15** showed a molecular ion at m/z 521.2039, while the NMR spectrum revealed a singlet at δ 5.47, δ 9.19, corresponding to the NH_2 and OH protons in the amidoxime intermediate **15**. In addition, the infrared (IR) spectrum showed absorptions at 3499, 3398 and 3196. These correspond to -NH_2 and -OH stretching, respectively, confirming the assigned structure.

Synthesis of Nitro compound 13

Compound **13** was prepared from compound **15** by using a cyclizing agent. To develop this cyclization reaction, we tried different reagents. Among these were carbonyldiimidazole, triphosgene, diphenyl carbonate, disuccinimidyl carbonate, diethyl carbonate and dimethyl carbonate. We found that the best results were obtained by using carbonyldiimidazole. The mass spectrum of compound **13** showed a molecular ion at m/z 447.1313, while the NMR spectrum revealed a broad singlet at δ 12.4, corresponding to the NH proton in an oxadiazole ring. The absence of NH_2 and OH protons also confirmed the structure. Moreover, the infrared (IR) spectrum showed absorptions at 3438 and 1537, corresponding to -NH and -NO stretching, respectively, and confirming the assigned structure.

Synthesis of Amino compound 14

Compound **14** was prepared by the reduction of compound **13**. So as to develop this reduction, we tried different reducing agents. Among these being stannous chloride, ferric chloride and Raney nickel. In this work, the best results were obtained by using stannous chloride. The mass spectrum of compound **14** showed a molecular ion at m/z 417.1558, and the NMR spectrum revealed broad singlets at δ 4.92 and 6.17, which correspond to the NH_2 and NH protons in amino compound **14**. What is more, the Infrared (IR) spectrum showed absorptions at 3499. This corresponds to -NH_2, while the absence of N-O stretching at 1537 also confirms the assigned structure.

Synthesis of Azilsartan methyl ester 10

Compound **10** was prepared from compound **14**, by cyclizing it with tetraethyl orthocarbonate. The mass spectrum of compound **10** revealed a molecular ion at m/z 471.1638, and the NMR spectrum showed a triplet at δ 1.36 and a quartet at δ 4.606, corresponding to the CH_3 and CH_2 protons.

All these reported reaction procedures are very simple to undertake, and they provided excellent yields of the products. Thus, this process is economic and useful for the commercial manufacture of Azilsartan **2**.

CONCLUSION

To the extension of our previous work [17], we have developed a non-infringing process for the synthesis of Azilsartan **2**, beginning from methyl 2-tert-butoxycarbonyl amino-3-nitrobenzoate **3** and 4'-(bromomethyl)-1,1'-biphenyl-1,2,4-oxadiazol-5(2*H*)-one **11**. The present work also describes the synthesis and characterization of novel intermediates of Azilsartan, along with their spectral data.

EXPERIMENTAL

The solvents and reagents were obtained from commercial sources and used without purification. The IR spectra (ϑ_{max}, cm^{-1}) were recorded in solid state KBr dispersion, using a Perkin Elmer FT-IR spectrometer. The ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker-Avance 300 MHz, 500 MHz and 125 MHz spectrometer. The chemical shifts were reported in δ ppm relative to TMS. The mass spectra were recorded on an API 2000 Perkin Elmer PE-Sciex mass spectrometer. In addition, the reactions were monitored by Thin–layer chromatography (TLC), while melting points were determined on a polman melting point apparatus (Model No MP96), by way of the open capillary method, and are uncorrected.

Methyl 3-nitro-2-[[4-[2-(5-oxo-4*H*-1,2,4-oxadiazol-3-yl) phenyl]phenyl] methyl amino]benzoate (13)

To a suspension of compound **3** (100 g, 337.8 mmol) and **11** (110 g, 334.4 mmol) in acetonitrile (1000 mL), we added potassium carbonate (140 g, 1011.3 mmol) at 20-25°C. The reaction mixture was stirred for 12 h at 80-85°C, then the resulting salts were removed by filtration, and the filtrate was concentrated under reduced pressure, resulting in a residue which contains compound 12. The residue was subsequently dissolved in dichloromethane (100 mL), while trifluoroacetic acid (37.6 g, 329.6 mmol) was added at 20-25°C. The reaction mixture was then stirred for 4 h, at room temperature. Subsequently, water (500 mL) was added to the reaction mass, and the PH was adjusted to 6 with saturated sodium bicarbonate solution. Following this, the organic layer was separated and concentrated under reduced pressure, resulting in residue **13** (102 g, 66%). HRMS for $C_{23}H_{18}N_4O_6$ $(M + H)^+$:

calculated: 447.1260, found: 447.1313. 1H-NMR (DMSO) d (ppm): 12.36 (bs, 1H, NH), 8.11 (m, 1H, Ar), 8.03 (m, 1H, Ar), 7.6 (m, 4H,Ar), 7.57 (m, 1H, Ar), 7.47 (m, 1H, Ar), 7.18 (m, 4H, Ar), 4.61 (d, J = 15 Hz, 1H, N-CH_2-Ar), 4.54 (d, J = 14.5 Hz, 1H, N-CH_2-Ar), 3.6 (s, 3H, $COOCH_3$). ^{13}C-NMR (DMSO) d (ppm): 164.51, 159.62, 158.31, 153.13, 148.17, 141.01, 138.21, 135.49, 134.89, 133.67, 132.06, 131.65, 130.61, 129.47, 129.09, 128.97, 128.05, 127.77, 122.34, 80.12, 67.31, 63.35, 52.65, 40.09. IR (KBr pellet): 3438, 2978, 1708, 1603, 1577, 1295, 1129 Cm^{-1}.

Methyl 3-amino-2-[[4-[2-(5-oxo-4*H*-1,2,4-oxadiazol-3-yl) phenyl]phenyl] methyl amino]benzoate (14)

To a solution of compound **13** (100 g, 224.2 mmol) in tetrahydrofuran (1000 mL), we added stannous chloride (101.1 g, 448.4 mmol) at 25-30°C. The reaction mixture was then stirred at 60-65°C, for 6 h. Subsequently, we diluted the reaction mixture with water (500 mL) and ethylacetate (1000 mL). We followed this up by adjusting the pH of the reaction mixture to 12, with 20% w/w sodium hydroxide solution, and the organic layer was separated. This organic layer was washed with saturated sodium bicarbonate solution (1000 mL) and saturated sodium chloride solution (1000 mL). We then concentrated the organic layer under reduced pressure. This yielded a residue, which, when crystallized with diisopropyl ether, resulted in a pale yellow colored compound **14** (75 g, 80%). HRMS for $C_{23}H_{20}N_4O_4$ $(M + H)^+$: calculated: 417.1518, found: 417.1558. 1H-NMR (DMSO) d (ppm): 7.65 (m, 2H, Ar), 7.51 (m, 2H, Ar), 7.37 (m, 2H, Ar), 7.29 (m, 1H, Ar), 7.188 (m, 1H, Ar), 7.04 (m, 1H, Ar), 6.92 (m, 1H, Ar), 6.78 (m, 1H, Ar), 6.17 (bs, 1H, NH), 4.92 (bs, 2H, NH_2), 4.12 (s, 2H, N-CH_2-Ar), 3.775 (s, 3H, OCH_3). ^{13}C-NMR (DMSO) d (ppm): 166.40, 162.78, 160.91, 154.59, 145.76, 142.56, 140.89, 139.446, 137.99, 137.63, 137.23, 131.14, 130.90, 130.51, 129.23, 128.95, 127.99, 127.65, 127.12, 125.59, 124.26, 121.81, 120.46, 119.13, 119.06, 118.55, 117.95, 78.69, 67.30, 51.81, 48.85, 40.00. IR (KBr pellet): 3514, 3407, 3268, 2985, 1718, 1634, 1612, 1547, 1284, 1257, 1133 Cm^{-1}.

Methyl2-ethoxy-3-[[4-[2-(5-oxo-4H-1,2,4-oxadiazol-3-yl) phenyl]phenyl] methyl]benzimidazole-4-carboxylate (Azilsartan methyl ester 10)

To a mixture of compound **14** (100 g, 240 mmol) in tetraethyl orthocarbonate (92.3 g, 480 mmol), we added acetic acid (28.8 g, 480 mmol) at 25-30°C. The reaction mass was then heated to reflux for 3 h. Subsequently, the reaction mass was diluted with methanol (300 mL), water (400 mL) and 30 % sodium hydroxide solution (30 mL). The reaction mass was then stirred at 25-30°C, for 2 h, and the PH neutralized to 7. We followed this up by cooling the solution to 5-10°C, and filtering the precipitated product, yielding a white colored compound 10 (82 g, 73%). HPLC purity: 99.49%. HRMS for $C_{26}H_{22}N_4O_5$ $(M + H)^+$: calculated: 471.1624, found: 471.1638. 1H-NMR (DMSO) d (ppm): 12.383 (bs, 1H, NH), 7.7-7.63 (m, 3H, Ar), 7.56 (m, 1H, Ar), 7.47 (m, 2H, Ar), 7.246 (d, J = 1.5 Hz, 2H, Ar), 7.196 (t, J = 8 Hz, 1H, Ar), 7.0 (d, J = 8.5 Hz, 2H, Ar) 5.529 (s, 2H, N-CH_2-Ar), 4.628 (q, 2H, OCH_2CH_3), 3.68 (s, 3H, OCH_3), 1.38 (t, J = 7.5 Hz, 3H, OCH_2CH_3). IR (KBr pellet):2983, 1779, 1720, 1609, 1547, 1281, 1133 Cm^{-1}.

2-ethoxy-1-{[2`-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl) biphenyl-4yl]methyl}-1*H*-benzimidazole-7-carboxylica-cid (Azilsartan 2)

Compound 10 (100 g, 212.7 mmol) was added to aqueous sodium hydroxide (25.5 g in 200 mL of water, 638.2 mmol) at room temperature and mixture was stirred for 6 h at 40-45°C. Then the reaction mixture was acidified with aqueous hydrochloric acid to 4 pH. The precipitated product was filtered and wash with water results a white compound 2 (92 g, 95%) mp: 210-213°C. HPLC purity: 99.48%. HRMS for $C_{25}H_{20}N_4O_5$ $(M + H)^+$ Calcd: 457.1467, found: 457.1479. ^{1}H-NMR (DMSO) δ (ppm): 13.15 (bs, 1H, NH), 12.4 (bs, 1H, OH), 7.68-7.63 (m, 3H, Ar), 7.56-7.55 (m, 2H, Ar), 7.52-7.46 (m, 1H, Ar), 7.245 (d, J=8.3 Hz, 2H, Ar), 7.197 (t, 1H, Ar), 7.05 (d, J=8.3 Hz, 2H, Ar) 5.67 (s, 2H, N-CH2-Ar), 4.578 (q, 2H, OCH2CH3), 1.38 (t, J=7.1 Hz, 3H, OCH_2CH_3). IR (KBr pellet): 2989, 1774, 1733, 1613, 1552, 1286, 1145 Cm-1.

Methyl 2-[tert-butoxycarbonyl[[4-[2-(*N*'-hydroxycar-bamimidoyl) phenyl] phenyl] methyl]amino] 3-nitro-benzoate 15

To a suspension of hydroxylamine hydrochloride (84.55 g, 1216.5 mmol) and sodium bicarbonate (112.4 g, 1338 mmol) in DMSO (500 mL), we added compound **5** (100 g, 205.3 mmol) at 45-50°C. The reaction mixture was then stirred at 80-85°C, for 24 h. We followed this up by pouring the mixture into water (2000 mL) and stirring this solution for 1 h. The resulting product was then filtered and purified with ethanol, yielding a white compound **15** (80 g, 75 %). HRMS for $C_{27}H_{28}N_4O_7$ $(M + H)^+$: calculated: 521.1992, found: 521.2039. ^{1}H-NMR (DMSO) δ (ppm): 9.197 (s, 1H, OH), 8.159 (m, 1H, Ar), 8.142 (m, 1H, Ar), 7.656 (m, 1H, Ar), 7.447 (m, 1H, Ar), 7.41 (m, 2H, Ar), 7.308 (m, 3H, Ar), 7.087 (m, 2H, Ar), 5.474 (bs, 2H, NH_2), 4.633 (dd, J = 14, 14.5 Hz, 2H, N-CH_2-Ar), 3.61 (s, 3H, OCH_3), 1.479 (s, 9H, t-Bu). ^{13}C-NMR (DMSO) δ (ppm): 164.53, 153.52, 153.23, 152.10, 148.63, 140.04, 139.96, 135.00, 134.73, 133.15, 132.27, 131.85, 130.06, 129.94, 128.94, 128.39, 126.95, 52.73, 39.66, 39.44, 27.95, 27.55. IR (KBr pellet): 3499, 3398, 3196, 2976, 1698, 1647, 1600, 1536, 1288, 1270, 1124 Cm^{-1}.

Methyl 3-nitro-2-[[4-[2-(5-oxo-4*H*-1,2,4-oxadiazol-3-yl) phenyl]phenyl]methyl amino]benzoate (13) from 15

To a solution of compound **15** (100 g, 192.3 mmol) in tetrahydrofuran (1000 mL), we added carbonyldiimidazole (51.5 g, 317.3 mmol) and DBU (44.5 g, 292.3 mmol) at 20-25°C. We then stirred the reaction mixture for 2 h, at 20-25°C. Subsequently, we diluted the reaction mixture with ethyl acetate (1000 mL) and washed it with saturated sodium bisulfite solution (1000 mL), followed by saturated sodium chloride solution (1000 mL). The organic layer was then separated and concentrated under reduced pressure at 35-40°C to obtain a residue **13** (80 g, 94%). HRMS for $C_{23}H_{18}N_4O_6$ (M + H)+: calculated: 447.1260, found: 447.1313. ^{1}H-NMR (DMSO) δ (ppm): 12.36 (bs, 1H, NH), 8.11 (m, 1H, Ar), 8.03 (m, 1H, Ar), 7.6 (m, 4H,Ar), 7.57 (m, 1H, Ar), 7.47 (m, 1H, Ar), 7.18 (m, 4H, Ar), 4.61 (d, 1H, N-CH_2-Ar), 4.54 (d, 1H, N-CH_2-Ar), 3.6 (s, 3H, $COOCH_3$). ^{13}C-NMR

(DMSO) δ (ppm): 164.51, 159.62, 158.31, 153.13, 148.17, 141.01, 138.21, 135.49, 134.89, 133.67, 132.06, 131.65, 130.61, 129.47, 129.09, 128.97, 128.05, 127.77, 122.34, 80.12, 67.31, 63.35, 52.65, 40.09. IR (KBr pellet): 3438, 2978, 1708, 1603, 1577, 1295, 1129 Cm^{-1}.

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ABBREVIATIONS

DMSO, dimethyl sulfoxide; DMAc, N,N-dimethylacetamide; DMF, N,N-dimethylformamide; DSC, disuccinimidyl carbonate; TFA, trifluoroacetic acid; DIBOC, Di-tert-butyl dicarbonate; DMC, dimethyl carbonate; DEC, diethyl carbonate; DPC, diphenyl carbonate; CDI, carbonyldiimidazole; DBU, 1,8-diazabicyclo 5.4.0 undec-7-ene.

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