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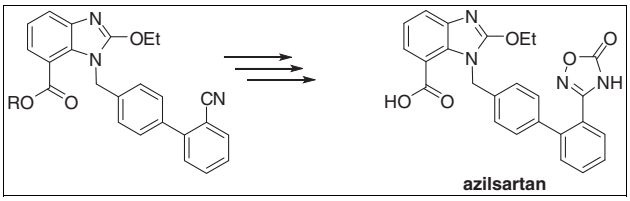

Synthesis of angiotensin II AT_1 receptor antagonist azilsartan is described. The results include reinvestigation of the described process as well as its novel modification. This new process includes transformation of the CN group into amidoxime moiety by aqueous hydroxylamine, its treatment with alkyl chloroformates and a base-initiated cyclization of the formed (alkoxycarbonyl-oxy)carbamimidoyl intermediates. Several so far undescribed side-products were identified and some of them were synthesized and duly characterized as potential impurities.

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INTRODUCTION

Angiotensin II AT_1 receptor antagonists, also called angiotensin receptor blockers (ARBs) 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, azilsartan medoxomil (**1**), was approved in 2011 as a prodrug form of azilsartan (**2**). (Figure 1).

When we started the 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 (**2**), and only patents [6] described transformation of azilsartan (**2**) into azilsartan medoxomil (**1**).

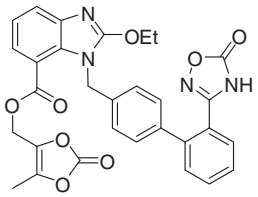
Synthetic pathway described in references [3–5] is shown in Scheme 1. In the first step, methyl ester **3a** is treated with hydroxylamine liberated *in situ* from its hydrochloride with either sodium methoxide or triethylamine giving 55% yield of amidoxime **4a** [5]. Treatment of **4a** with alkyl 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. In the last step, saponification of ester **6a** then provided azilsartan (**2**) in good yields. No side products explaining the low yields of the first steps are mentioned in the references.

The main goal of the generic active pharmaceutical ingredient (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 (**2**) development, we have found some inconsistencies in the data given in the aforementioned references. This paper explains the inconsistencies in the original references, describes our process of preparation of azilsartan (**2**), as well as synthesis and physico-chemical characteristics of selected side products.

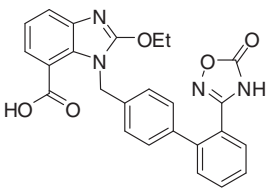
RESULTS AND DISCUSSION

Synthesis of amidoximes 5. First, the published reaction of **5a** with hydroxylamine hydrochloride under the described conditions (DMSO, 90 °C, MeONa or Et_3N) was repeated. We found, 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 **5a**, 32.3 and 44.2% of the product **6a**, and 17.6 and 19.7% of a side product, respectively. The liquid chromatography–mass spectrometry (LC–MS) suggested structure **7a** for this main side product, which was in accordance with the easy deethylation of candesartan reported earlier [7]. Surprisingly, no corresponding amidoxime **8a** was detected under these conditions. (Figure 2).

In attempts to optimize the reaction conditions, we tested several solvents [DMSO, *N*,*N*-dimethylformamide (DMF), *N*,*N*-dimethylacetamide (DMA), and NMP] and bases [MeONa, EtONa, *tert*-BuOK, NaOH, Na_2CO_3, K_2CO_3, $NaHCO_3$, $KHCO_3$, AcONa, Et_3N, *N*,*N*-Diisopropylethylamine (DIPEA), DBU, and proton

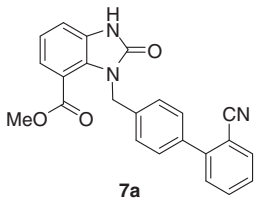


azilsartan medoxomil (1)

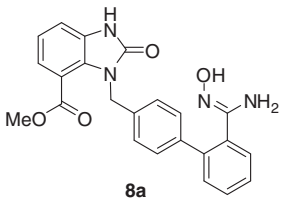


azilsartan (2)

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



7a



8a

Figure 2. Structures of 2-desethyl side products **7a** and **8a**.

sponge (1,8-bis(dimethylamino)naphthalene)] at temperatures ranging from 20 to 100 °C with little success. The best results were obtained using Et_3N and DMSO at 75 °C for 48 h. The results are given in Table 1.

Discouraged by the results, we decided to try also reactions of commercially available 50% aqueous hydroxylamine base. Using this reagent in combination with DMSO led to much better results; and therefore, we screened the reaction with a range of solvents [DMSO, DMF, DMA, NMP, 1,1,3,3-tetramethylurea (TMU), imidazolidin-2-one (DMI), and 1,3-dimethyl-3, 4,5,6- tetrahydro-2(1*H*)-pyrimidinone (DMPU)] at temperatures from 20 to 90 °C. Representative results at 75 °C are given in Table 2. In all cases, formation of compound **7a** was substantially suppressed. The best results in this respect were achieved in NMP; however, in this case, desethyl amidoxime **8a** was formed in about 6% amount.

Other impurities identified by LC–MS included the corresponding hydrolytic products—acid **9** and ester amide **10**. (Figure 3).

The heterocyclic moiety present in azilsartan, that is, 2-ethoxybenzimidazole-7-carboxylic acid, is also present in candesartan cilexetil (**11**), a prodrug of candesartan (**12**). For a review on candesartan cilexetil, see reference [8]. (Figure 4).

Because 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. Therefore, we decided to compare both of these potential starting compounds. For widening the scope of potential patent application, we also decided to prepare the corresponding benzyl **3c**, benzhydryl **3d**, and trityl **3e** esters. These compounds were synthesized from acid **13**, easily obtained by hydrolysis of methyl ester **3a**, by

Scheme 1

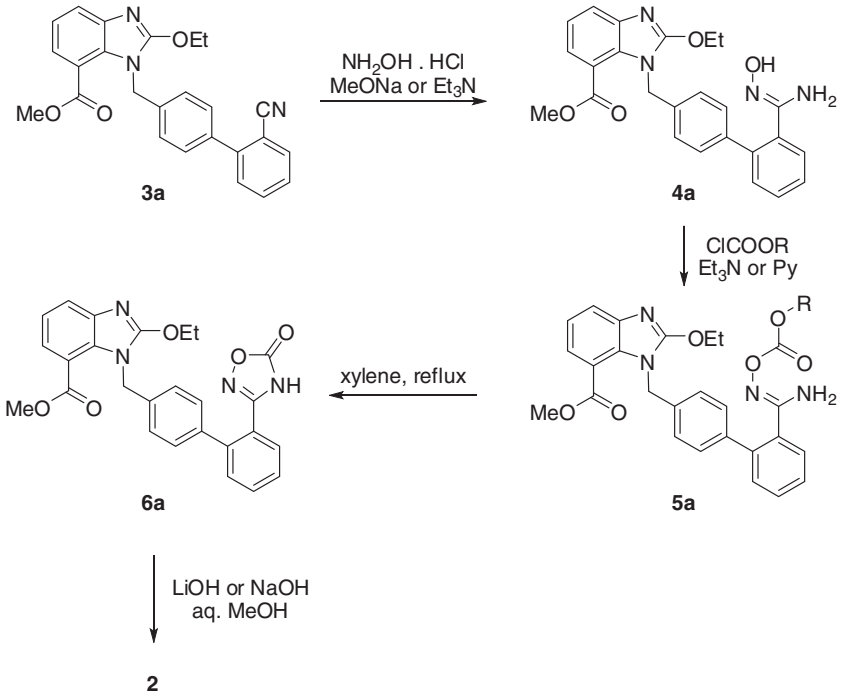


Table 1

HPLC results using Et_3N and DMSO—48 h.[a]

Temperature	% **3a**	% **4a**	% **7a**	% Others
20 °C	96.1	3.2	0.4	0.3
50 °C	49.6	33.1	11.7	5.6
75 °C	1.0	54.4	32.8	11.8

[a]The response factors were not considered.

Table 2

HPLC results using aqueous hydroxylamine (75 °C, 24 h).[a]

Solvent	% **3a**	% **4a**	% **7a**	Others
DMSO	7.6	84.3	2.2	5.9
DMF	16.1	61.9	13.7	8.3
DMA	37.1	45.3	15.0	2.5
NMP	15.1	76.2	0.6	8.1[b]
TMU	12.1	81.5	2.1	4.3
DMI	3.6	86.1	1.2	9.1
DMPU	7.6	84.3	2.2	5.9

[a]The response factors were not considered.
[b]5.8% of **8a** detected.

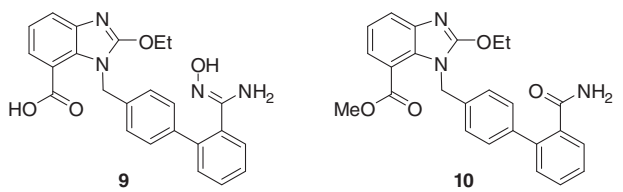


Figure 3. Structures of hydrolytic side products **9** and **10**.

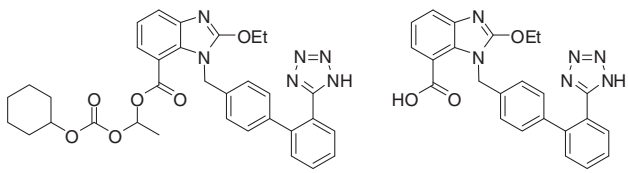


Figure 4. Structures of candesartan cilexetil (**11**) and candesartan (**12**).

alkylation with the corresponding bromides. We failed to get pure trityl ester **3e** because detritylation occurred during purification. (Scheme 2).

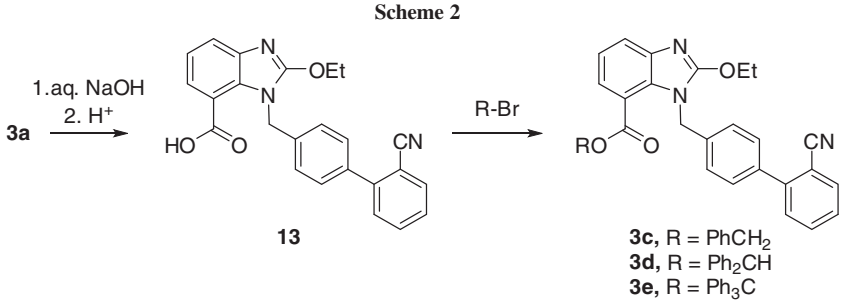
We have applied the conditions developed for methyl ester **3a** also for the reaction of esters **3b-3d** and obtained similar results. At last, slightly modified conditions using stirring with 50% aqueous hydroxylamine in DMSO at 90 °C for 15 h led to isolated yields of more than 95%.

Synthesis of (alkoxycarbonyloxy)carbamimidoyl derivatives 5 and their thermal cyclization. Again, we first repeated the literature procedures starting from methyl ester **4a** and ethyl or 2-ethylhexyl chloroformate under the conditions described in the literature [4–6]. The formed compounds were without purification used in the following step, that is, thermal cyclization in refluxing xylene. The yields after chromatography described in the literature are only 23 and 54%, respectively. Therefore, we were interested in the other products formed. We found that using ethyl chloroformate with triethylamine and cyclization in refluxing xylene for 1.5 h [6], the crude mixture contained according to HPLC 32.1% of **6a**, 36.4% of 2-desethyl derivative **14a**, and 9.6% of *N*-ethyl derivative **15a** (identified by LC–MS). Much better results were achieved using 2-ethylhexyl chloroformate, where the mixture contained 64.5% of **6a**, 6.2% of 2-desethyl derivative **14a**, and 4.1% of *N*-ethyl derivative **15a**. Formation of these impurities could be explained analogously as formation of similar candesartan cilexetil impurities described recently [7]. (Figure 5).

Base-mediated cyclization of (alkoxycarbonyloxy)-carbamimidoyl derivatives 5. Having in hands a series of compounds **5**, we decided to study their base-initiated cyclization in attempts to develop better process as well as better yields of compounds **6**.

We have screened the reaction in several solvents (DMSO, NMP, THF) using bases like *tert*-BuOK, MeONa (for methyl esters **5a**), EtONa (for ethyl esters **5b**), K_2CO_3, DBU, DIPEA, and DABCO. In general, the results were much better than results of thermal cyclization. However, in case of alcoholates, the starting substrates were partially transformed into compounds **4**. The best results were obtained using potassium carbonate in DMSO, providing often yields of the target compounds **6** of about 90% or higher.

Scheme 2



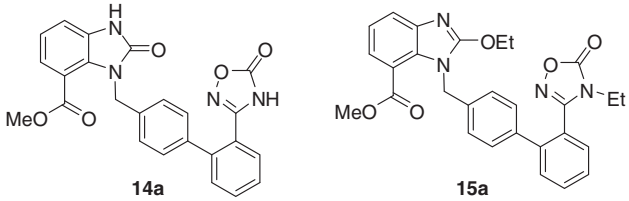


Figure 5. Structures of side products **14a** and **15a**.

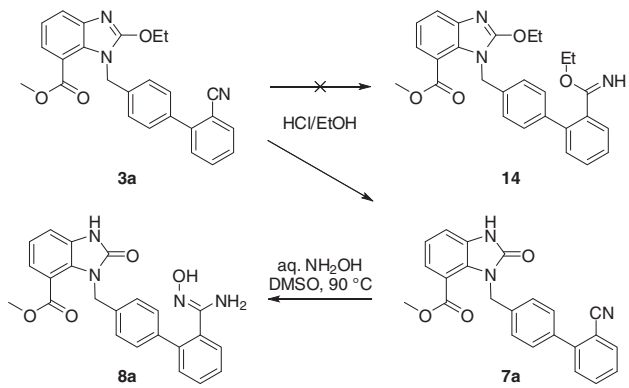
In case of using more than two equivalents of *tert*-BuOK in DMSO, azilsartan **2** was directly obtained. However, its purity was lower than in case of hydrolysis of purified esters **6**.

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 azilsartan (**2**).

Synthesis of standards of side products. One of the principal parts of documentation of any API is description of impurities and/or degradation products that can be present [9]. 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% [10]. Therefore, we have tried to synthesize all principal impurities/degradation products identified during the process development.

During our development, we have tried to prepare iminoether **14** by reaction of nitrile **3a** with methanolic hydrogen chloride. However, compound **7a** was isolated after usual workup. Analogously, also the corresponding ethyl ester **7b** was prepared (Scheme 3). Attempts to prepare **7a** by acid hydrolysis of **3a** led to a complex mixture containing also products of the CN group hydrolysis. Treatment of nitrile **7a** with aqueous hydroxylamine in NMP led to the corresponding potential impurity **8a**.

Scheme 3



CONCLUSION

We have developed robust processes for synthesis of azilsartan (**2**) starting from nitriles **3**, consisting of their treatment with aqueous hydroxylamine, followed by transformation of the formed amidoximes **4** into (alkoxycarbonyloxy) carbamimidoyl derivatives **5**. These compounds are then cyclized into azilsartan esters **6** and their final hydrolysis provides finally azilsartan (**2**).

We have also identified several side products that could be also impurities of the final product. Some of them, for example, compounds **7a**, **7b**, **8a**, **14a**, and **15a**, 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. Selected typical compounds were also characterized by their IR spectra.

EXPERIMENTAL

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 without purification.

Melting points were measured on a Kofler block and are uncorrected. NMR experiments were carried out on a Bruker Avance 500 (Bruker BioSpin Corporation, Billerica, MA, USA) at 500.13 MHz (1H), 125.77 MHz (^{13}C), and 50.70 MHz (^{15}N). Reference for ^{1}H δ ($CDCl_3$) = 7.26 ppm and for ^{13}C δ ($CDCl_3$) = 77.0 ppm. IR spectra were measured on an FTIR spectrometer Nicolet Nexus (Thermo Scientific, Waltham, MA, USA) using ZnSe attenuated total reflectance crystal technique by accumulation of 64 scans with two 1/cm resolution. The mass spectra [MS/MS; ionization mode APCI(+) (Atmospheric Pressure Chemical Ionization)] were measured on an API 3000 PE machine (Sciex Instruments, Applied Biosystems, Concord, Ontario, Canada). The purity of the prepared substances was evaluated by TLC on silica gel (FP KG F 254, Merck, Darmstadt, Germany) and by HPLC system HP Agilent 1050 (Agilent Technologies, Santa Clara, CA, USA) with UV detection (column Phenomenex Luna 5μ C18(2)) length: 0.25 m, internal diameter: 4.6 mm. 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. Flash chromatography was performed on silica gel Merck, particle size 0.04–0.063 mm. Centrifugally accelerated axial chromatography was carried out using Cyclograph instrument (Analtech Inc., Newark, DE, USA) with silica gel pre-scraped rotors.

***1-((2′-Cyanobiphenyl-4-yl)methyl)-2-ethoxy-1H*-benzo[*d*]-imidazole-7-carboxylic acid (13).** A mixture of **3a** (8.2 g, 20 mmol), ethanol (100 mL) and an aqueous solution of NaOH (4 g in 20 mL of water, 0.1 mol) was stirred at room temperature for 24 h. The solution was evaporated, dissolved in water (500 mL), acidified with acetic acid and the formed solid was filtered off and washed with water giving, after drying, 7.5 g (95%) of white solid; mp 174–176 °C. HPLC purity 96.8%. HRMS for $C_{24}H_{20}N_3O_3$ $(M+H)^+$ Calcd: 398.1505, found: 398.1528. ^{1}H NMR ($CDCl_3$) δ(ppm): 13.21 (bs, 1H, COOH), 7.72 (dd, J = 7.9, 1.2 Hz, 1H, Ar), 7.65 (dd, J = 7.6, 1.5 Hz, 1H, Ar), 7.55 (dd, J = 7.9, 1.2 Hz, 1H, Ar), 7.53 (ddd, J = 7.6, 1.5 Hz,

1H, Ar), 7.37 (dd, $J = 7.6$, 1.2 Hz, 1H, Ar), 7.35–7.31 (m, 1H, Ar), 7.31 (d, $J = 8.4$ Hz, 2H, Ar), 7.12 (t, $J = 7.9$ Hz, 1H, Ar), 7.07 (d, $J = 8.4$ Hz, 2H, Ar), 5.69 (s, 2H, N–C$\underline{H}_2$–Ar), 4.67 (q, $J = 7.1$ Hz, 2H, OC$\underline{H}_2$CH$_3$), 1.48 (t, $J = 7.1$ Hz, 3H, OCH$_2$C$\underline{H}_3$). ^{13}C NMR ($CDCl_3$) δ(ppm): 170.67, 158.60, 145.30, 141.72, 138.16, 136.85, 133.38, 132.87, 131.20, 129.79, 128.88, 127.48, 126.99, 123.99, 121.71, 120.95, 118.78, 117.27, 111.01, 66.78, 47.02, 14.65. IR: ν(C–H) 2987, ν(C≡N) 2227, ν(C=O) 1702, ν(C=C) + ν(C=N) 1609, 1547, ν(C–O) 1281, 1250, 1144 cm^{-1}. *Anal*. Calcd for $C_{24}H_{19}N_3O_3$: C, 72.53; H, 4.82; N, 10.57. Found: C, 72.11; H, 4.99; N, 10.33.

***Benzyl 1-((2′-cyanobiphenyl-4-yl)methyl)-2-ethoxy-1H*-benzo[*d*]imidazole-7-carboxylate (3c).** A mixture of **13** (4.0 g, 10 mmol), benzyl bromide (2.0 g, 11.7 mmol), K_2CO_3 (10 g, 72 mmol), and 2-butanone (100 mL) was refluxed for 4 h. The mixture was evaporated, diluted with water (150 mL), and extracted with dichloromethane. The extract was washed with water and dried with $MgSO_4$. The residue after evaporation was crystallized from acetonitrile to give 3.5 g (72%) of white crystals of **3c**; mp 111–114 °C. HPLC purity 99.3%. HRMS for $C_{31}H_{26}N_3O_3$ $(M + H)^+$ Calcd: 488. 1974, found: 488.1895. ^{1}H NMR (DMSO) δ(ppm): 7.92 (dd, $J = 7.6$, 1.5 Hz, 1H, Ar), 7.75 (ddd, $J = 7.6$, 1.5 Hz, 1H, Ar), 7.72 (dd, $J = 7.9$, 1.2 Hz, 1H, Ar), 7.56 (ddd, $J = 7.6$, 1.2 Hz, 1H, Ar), 7.51 (dd, $J = 7.9$, 1.2 Hz, 1H, Ar), 7.51–7.48 (m, 1H, Ar), 7.46 (d, $J = 8.4$ Hz, 2H, Ar), 7.38–7.27 (m, 5H, Ar), 7.20 (t, $J = 7.9$ Hz, 1H, Ar), 7.05 (d, $J = 8.4$ Hz, 2H, Ar), 5.60 (s, 2H, N–C$\underline{H}_2$–Ar), 5.24 (s, 2H, COOC$\underline{H}_2$-Ph), 4.62 (q, $J = 7.1$ Hz, 2H, OC$\underline{H}_2$CH$_3$), 1.41 (t, $J = 7.1$ Hz, 3H, OCH$_2$C$\underline{H}_3$). ^{13}C NMR (DMSO) δ(ppm): 165.44, 158.31, 143.89, 141.68, 137.62, 136.67, 135.69, 133.83, 133.44, 130.95, 129.98, 128.91, 128.42, 128.17, 128.14, 128.12, 126.61, 123.01, 121.79, 120.91, 118.44, 115.38, 110.02, 66.67, 66.55, 46.32, 14.35. *Anal*. Calcd for $C_{31}H_{25}N_3O_3$: C, 76.37; H, 5.17; N, 8.62. Found: C, 76.12; H, 5.33; N, 8.29.

***Benzhydryl 1-((2′-cyanobiphenyl-4-yl)methyl)-2-ethoxy-1H*-benzo[*d*]imidazole-7-carboxylate (3d).** A mixture of **13** (0.8 g, 2 mmol), benzhydryl bromide (0.55 g, 2.2 mmol), K_2CO_3 (2 g, 15 mmol), and 2-butanone (20 mL) was refluxed for 10 h and then stirred without heating overnight. The mixture was evaporated, diluted with water (50 mL), and extracted with dichloromethane. The extract was washed with water and dried with $MgSO_4$. The residue after evaporation (1.25 g) was crystallized from isopropyl acetate to give 1.05 g (93%) of white crystals of **3d**; mp 138–140 °C. HPLC purity 98.7%. HRMS for $C_{37}H_{30}N_3O_3$ $(M + H)^+$ Calcd: 564.2287, found: 564.3735. ^{1}H NMR (DMSO) δ(ppm): 7.91 (dd, $J = 7.8$, 1.4 Hz, 1H, Ar), 7.74 (dd, $J = 7.9$, 1.2 Hz, 1H, Ar), 7.76–7.70 (m, 2H, Ar), 7.55 (dd, $J = 7.6$, 1.2 Hz, 1H, Ar), 7.49–7.44 (m, 4H, Ar), 7.36–7.29 (m, 7H, Ar), 7.29–23 (m, 3H, Ar), 7.02 (s, 1H, COOC$\underline{H}$Ph$_2$), 6.96 (d, $J = 8.5$ Hz, 2H, Ar), 5.55 (s, 2H, N–C$\underline{H}_2$–Ar), 4.62 (q, $J = 7.1$ Hz, 2H, OC$\underline{H}_2$CH$_3$), 1.41 (t, $J = 7.1$ Hz, 3H, OCH$_2$C$\underline{H}_3$). ^{13}C NMR (DMSO) δ(ppm): 164.50, 158.34, 143.79, 141.76, 140.21, 137.41, 136.62, 133.81, 133.39, 131.17, 129.94, 128.85, 128.56, 128.15, 127.81, 126.80, 126.55, 123.14, 122.09, 121.07, 118.41, 115.18, 109.93, 77.45, 66.70, 46.21, 14.35. *Anal*. Calcd for $C_{37}H_{29}N_3O_3$: C, 78.84; H, 5.19; N, 7.46. Found: C, 78.57; H, 5.39; N, 7.11.

***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 18 h. 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$_2$C$\underline{H}_3$). ^{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).** Using the procedure described for the synthesis of **4a** starting from ethyl ester **3b**, 85% yield of **4b** was obtained; mp 209–211 °C (2-propanol). HPLC purity 98.0%. HRMS for $C_{26}H_{27}N_4O_4$ $(M + H)^+$ Calcd: 459.2032, found: 459.2189. ^{1}H NMR (DMSO) δ(ppm): 9.22 (s, 1H, OH), 7.74 (dd, $J = 7.9$, 1.2 Hz, 1H, Ar), 7.56 (dd, $J = 7.9$, 1.2 Hz, 1H, Ar), 7.44–7.31 (m, 3H, Ar), 7.28 (d, $J = 8.3$ Hz, 2H, Ar), 7.20 (dd, $J = 7.6$, 1.5 Hz, 1H, Ar), 7.02 (t, $J = 7.9$ Hz, 1H, Ar), 6.98 (d, $J = 8.3$ Hz, 2H, Ar), 6.54 (bs, 2H, NH_2), 5.66 (s, 2H, N–C$\underline{H}_2$–Ar), 4.68 (q, $J = 7.1$ Hz, 2H, OC$\underline{H}_2$CH$_3$), 4.24 (q, $J = 7.1$ Hz, 2H, OC$\underline{H}_2$CH$_3$), 1.52 (t, $J = 7.1$ Hz, 3H, OCH$_2$C$\underline{H}_3$), 1.27 (t, $J = 7.1$ Hz, 3H, OCH$_2$C$\underline{H}_3$). ^{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, 14.10. 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.

***Benzyl 2-ethoxy-1-((2′-(N′*-hydroxycarbamimidoyl)biphenyl-4-yl)methyl)-1*H*-benzo[*d*]imidazole-7-carboxylate (4c).** Using the procedure described for the synthesis of **4a** starting from benzyl ester **3c**, 82% yield of **4c** was obtained; mp 171–173 °C (2-propanol). HPLC purity 96.8%. HRMS for $C_{31}H_{29}N_4O_4$ $(M + H)^+$ Calcd: 521.2189, found: 521.2157. ^{1}H NMR (DMSO) δ(ppm): 9.19 (bs, 1H, OH), 7.69 (dd, $J = 7.9$, 1.2 Hz, 1H, Ar), 7.46 (dd, $J = 7.9$, 1.2 Hz, 1H, Ar), 7.45–7.32 (m, 3H, Ar), 7.35 (d, $J = 8.4$ Hz, 2H, Ar), 7.27 (dd, $J = 7.6$, 1.5 Hz, 1H, Ar), 7.19 (t, $J = 7.9$ Hz, 1H, Ar), 6.93 (d, $J = 8.4$ Hz, 2H, Ar), 5.55 (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$_3$),), 4.22 (q, $J = 7.1$ Hz, 2H, COOC$\underline{H}_2$CH$_3$), 1.42 (t, $J = 7.1$ Hz, 3H, OCH$_2$C$\underline{H}_3$), 1.18 (t, $J = 7.1$ Hz, 3H, COOCH$_2$C$\underline{H}_3$). ^{13}C NMR (DMSO) δ(ppm): 165.74, 158.26, 151.94, 141.59, 139.83, 139.78, 135.54, 133.18, 130.77, 130.03, 129.82, 128.86, 128.54, 126.91, 125.91, 122.84, 121.48, 120.78, 115.89, 66.62, 61.05, 46.20, 14.41, 13.93. *Anal*. Calcd for $C_{31}H_{28}N_4O_4$: C, 71.52; H, 5.42; N, 10.76. Found: C, 71.27; H, 5.55; N, 10.93.

***Benzhydryl 2-ethoxy-1-((2′-(N′*-hydroxycarbamimidoyl) biphe-nyl-4-yl)methyl)-1*H*-benzo[*d*]imidazole-7-carboxylate (4d).** Using the procedure described for the synthesis of **4a** starting from benzyl ester **3d**, 64% yield of **4d** was obtained; mp 234–237 °C (isopropyl acetate). HPLC purity 97.3%.

HRMS for $C_{37}H_{33}N_4O_4$ $(M+H)^+$ Calcd: 597.2502, found: 597.2657. ^{1}H NMR (DMSO) δ(ppm): 9.19 (s, 1H, OH), 7.76–7.70 (m, 2H, Ar), 7.53–7.44 (m, 4H, Ar), 7.42–7.28 (m, 9H, Ar), 7.25 (t, J = 7.9 Hz, 1H, Ar), 7.17 (d, J = 8.3 Hz, 2H, Ar), 7.10–6.99 (m, 2H, Ar), 6.82 (d, J = 8.3 Hz, 2H, Ar), 5.53 (bs, 2H, NH_2), 5.48 (s, 2H, N–C$\underline{H}_2$–Ar), 4.63 (q, J = 7.1 Hz, 2H, OC$\underline{H}_2$CH$_3$), 1.43 (t, J = 7.1 Hz, 3H, OCH$_2$C$\underline{H}_3$). ^{13}C NMR (DMSO) δ(ppm: 164.52, 158.37, 151.87, 141.76, 140.23, 139.83, 139.70, 135.23, 133.02, 131.15, 129.96, 129.88, 128.78, 128.63, 128.55, 127.91, 126.88, 126.60, 126.41, 123.18, 122.07, 121.01, 115.14, 77.58, 66.68, 46.07, 14.40. *Anal*. Calcd for $C_{37}H_{32}N_4O_4$: C, 74.48; H, 5.41; N, 9.39. Found: C, 74.33; H, 5.68; N, 9.57.

***Methyl 3-((2′-cyanobiphenyl-4-yl)methyl)-2-oxo-2,3-dihydro-1H*-benzo[*d*]imidazole-4-carboxylate (7a).** A mixture of **3a** (1 g, 2.4 mmol) and a saturated solution of hydrogen chloride in methanol (10 mL) was placed into Ace pressure tube and stirred at room temperature for 3 days. Then the tube was opened, the suspension poured into water (50 mL), the insoluble portion was filtered off, washed with water, and dried. The crude product was crystallized from ethanol to give 0.8 g (87%) of white crystals; mp 251–254 °C. HPLC purity 99.6%. HRMS for $C_{23}H_{18}N_3O_3$ $(M+H)^+$ Calcd: 384.1348, found: 384.1733. ^{1}H NMR ($CDCl_3$) δ(ppm): 10.21 (bs, 1H, NH), 7.74 (dd, J = 7.6, 1.5 Hz, 1H, Ar), 7.60 (ddd, J = 7.6, 1.5 Hz, 1H, Ar), 7.45 (d, J = 8.4 Hz, 2H, Ar), 7.46–7.42 (m, 1, Ar), 7.41 (dd, J = 7.6, 1.2 Hz, 1H, Ar), 7.38 (dd, J = 7.9, 1.2 Hz, 1H, Ar), 7.30 (dd, J = 7.9, 1.2 Hz, 1H, Ar), 7.22 (d, J = 8.4 Hz, 2H, Ar), 7.09 (t, J = 7.9 Hz, 1H, Ar), 5.59 (s, 2H, N–C$\underline{H}_2$–Ar), 3.71 (s, 3H, OCH_3). ^{13}C NMR (CDCl3) δ(ppm): 166.56, 156.27, 144.97, 137.63, 137.01, 133.76, 132.78, 130.00, 129.23 128.89, 128.09, 127.53, 127.07, 123.25, 121.14, 118.60, 115.97, 112.98, 111.18, 52.55, 45.77. *Anal*. Calcd for $C_{23}H_{17}N_3O_3$: C, 72.05; H, 4.47; N, 10.96. Found: C, 71.77; H, 4.71; N, 10.89.

***Ethyl 3-((2′-cyanobiphenyl-4-yl)methyl)-2-oxo-2,3-dihydro-1H*-benzo[*d*] imidazole-4-carboxylate (7b).** Using the procedure described for the synthesis of **7a** starting from ethyl ester **3b**, 94% yield of **7b** was obtained; mp 216–218 °C (ethanol). HPLC purity 99.4%. HRMS for $C_{24}H_{20}N_3O_3$ $(M+H)^+$ Calcd: 398.1505, found: 398.1583. ^{1}H NMR ($CDCl_3$) δ(ppm): 10.85 (bs, 1H, NH), 7.73 (dd, J = 7.6, 1.5 Hz, 1H, Ar), 7.60 (ddd, J = 7.6, 1.5 Hz, 1H, Ar), 7.46 (d, J = 8.3 Hz, 2H, Ar), 7.44–7.38 (m, 3H, Ar), 7.32 (dd, J = 7.9, 1.2 Hz, 1H, Ar), 7.22 (d, J = 8.3 Hz, 2H, Ar), 7.09 (t, J = 7.9 Hz, 1H, Ar), 5.63 (s, 2H, N–C$\underline{H}_2$–Ar), 4.19 (q, J = 7.1 Hz, 2H, OC$\underline{H}_2$CH$_3$), 1.20 (t, J = 7.1 Hz, 3H, OCH$_2$C$\underline{H}_3$). ^{13}C NMR ($CDCl_3$) δ(ppm): 166.10, 156.64, 144.92, 137.77, 136.93, 133.78, 132.76, 129.97, 129.37 128.88, 128.07, 127.49, 127.00, 123.24, 121.12, 118.59, 116.28, 113.11, 111.12, 61.51, 45.72, 14.09. IR: ν(C–H) 3060, 2930, ν(C≡N) 2230, ν(C═O) 1703, ν(C═C) + ν(C═N) 1623, 1458, ν(C–O) 1259, 1128 cm^{-1}. *Anal*. Calcd for $C_{24}H_{19}N_3O_3$: C, 72.53; H, 4.82; N, 10.57. Found: C, 72.38; H, 5.03; N, 10.79.

***Methyl 3-((2′-(N′*-hydroxycarbamimidoyl)biphenyl-4-yl) methyl)-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazole-4-carboxylate (8a).** A mixture of **7a** (0.38 g, 1. mmol), NMP (10 mL) and 50% aqueous hydroxylamine (0.4 mL) was stirred at 90 °C for 30 h. The mixture was poured into water, the insoluble portion was filtered off, washed with water, and dried to give 0.25 g (60%) of white solid. Crystallization from high volume of 2-propanol provided 0.13 g (31%) of **8a**; mp 231–232 °C. HPLC purity 97.7%. HRMS for $C_{23}H_{21}N_4O_4$ $(M+H)^+$ Calcd: 417.1563, found: 417.1611.^{1}H NMR (DMSO) δ(ppm): 11.47 (bs, 1H, NH), 9.19 (bs, 1H, OH), 7.50–7.33 (m, 3H, Ar), 7.35 (d, J = 8.2 Hz, 2H, Ar), 7.30 (dd, J = 7.6, 1.5 Hz, 1H, Ar), 7.27–7.23 (m, 2H, Ar), 7.09 (t, J = 7.9 Hz, 1H, Ar), 6.98 (d, J = 8.2 Hz, 2H, Ar), 5.54 (bs, 2H, NH_2), 5.28 (s, 2H, N–C$\underline{H}_2$–Ar), 3.66 (s, 3H, OC$\underline{H}_3$). ^{13}C NMR ($CDCl_3$) δ(ppm): 166.20, 154.96, 151.98, 139.95, 139.53, 135.71, 133.22, 130.02, 129.90, 129.85, 128.86, 128.43, 127.72, 126.88, 126.01, 121.91, 120.70, 114.62, 112.39, 52.36, 44.66. *Anal*. Calcd for $C_{23}H_{20}N_4O_4$: C, 66.34; H, 4.84; N, 13.43. Found: C, 66.11; H, 5.07; N, 13.62.

***Methyl 2-ethoxy-1-((2′-(N′*-(methoxycarbonyloxy)carbamimido-yl) biphenyl-4-yl)methyl)-1*H*-benzo[*d*]imidazole-7-carboxylate (5aa).** To a mixture of **4a** (5.8 g, 13 mmol), dry DMF (50 mL), and pyridine (1.4 g, 18 mmol) stirred in an ice bad was added dropwise a solution of methyl chloroformate (1.4 g, 15 mmol) in dry DMF (10 mL). The mixture was stirred at 0–5 °C for 3 h, and then the mixture was poured into water (150 mL), and the formed suspension was extracted with ethyl acetate. The combined organic layers were washed with water and dried with $MgSO_4$. The residue after evaporation (7.5 g) was dissolved in dichloromethane and purified by centrifugally accelerated axial chromatography (Cyclograph) using mixtures hexane-acetone 9 : 1 to 6 : 4. The fractions containing pure product were evaporated (4.9 g) and the residue was crystallized from methyl acetate yielding 3.9 g (60%) of **5aa**; mp 163–167 °C. HPLC purity 95.9%. HRMS for $C_{27}H_{27}N_4O_6$ $(M+H)^+$ Calcd: 503.1931, found: 503.2047. ^{1}H NMR (DMSO) δ(ppm): 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, 1H, Ar), 7.19 (t, J = 7.9 Hz, 1H, Ar), 6.95 (d, J = 8.3 Hz, 2H, Ar), 6.61 (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$_3$), 3.69 (s, 3H, OC$\underline{H}_3$), 3.67 (s, 3H, OCH_3), 1.41 (t, J = 7.1 Hz, 3H, OCH$_2$C$\underline{H}_3$). ^{13}C NMR (DMSO) δ(ppm): 166.22, 158.32, 158.08, 154.06, 141.61, 139.97, 138.78, 135.97, 130.83, 130.74, 130.06, 129.92, 129.84, 128.55, 126.99, 125.93, 122.79, 121.51, 120.80, 115.59, 66.61, 54.36, 52.20, 46.35, 14.36. *Anal*. Calcd for $C_{27}H_{26}N_4O_6$: C, 64.53; H, 5.22; N, 11.15. Found: C, 64.34; H, 5.37; N, 10.84.

***Ethyl 2-ethoxy-1-((2′-(N′*-(ethoxycarbonyloxy)carbamimido-yl)biphenyl-4-yl)methyl)-1*H*-benzo[*d*]imidazole-7-carboxylate (5bb).** Using the procedure described for the synthesis of **5aa** starting from ethyl ester **4b**, 78% yield of **5bb** was obtained; mp 145–147 °C (ethyl acetate). HPLC purity 97.3%. HRMS for $C_{29}H_{31}N_4O_6$ $(M+H)^+$ Calcd: 531.2244, found: 531.2297. ^{1}H NMR (DMSO) δ(ppm): 7.69 (d, J = 7.9 Hz, 1H, Ar), 7.50 (m, 1H, Ar), 7.45 (d, J = 7.7 Hz, 1H, Ar), 7.42–7.39 (m, 4H, Ar), 7.33 (d, J = 7.7, 1H, Ar), 7.19 (t, J = 7.9 Hz, 1H, Ar), 6.94 (d, J = 8.3 Hz, 2H, Ar), 6.57 (bs, 2H, NH_2), 5.54 (s, 2H, N–C$\underline{H}_2$–Ar), 4.61 (q, J = 7.0 Hz, 2H, OC$\underline{H}_2$CH$_3$), 4.19 (q, J = 7.1 Hz, 2H, OC$\underline{H}_2$CH$_3$), 4.12 (q, J = 7.0 Hz, 2H, OC$\underline{H}_2$CH$_3$), 1.40 (t, J = 7.0 Hz, 3H, OCH$_2$C$\underline{H}_3$), 1.21 (t, J = 7.1 Hz, 3H, OCH$_2$C$\underline{H}_3$), 1.16 (t, J = 7.1 Hz, 3H, OCH$_2$C$\underline{H}_3$). ^{13}C NMR (DMSO) δ(ppm): 165.73, 158.26, 157.87, 153.43, 141.58, 139.92, 138.83, 135.97, 130.79, 130.09, 129.91, 129.82, 128.58, 126.98, 125.94, 122.82, 121.45, 120.77, 115.90, 66.59, 63.30, 61.01, 46.25, 14.36, 14.16, 13.89. IR: ν(N–H) 3490, 3347, ν(C–H) 2977, ν(C═O) 1749, 1702, ν(C═C) + ν(C═N) 1618, 1547, ν(C–O) 1249, 1131 cm^{-1}. *Anal*. Calcd for $C_{29}H_{30}N_4O_6$: C, 65.65; H, 5.70; N, 10.56. Found: C, 65.41; H, 5.88; N, 10.33.

***Methyl 2-ethoxy-1-((2′-(N′*-(phenoxycarbonyloxy)carbamimido-yl)biphenyl-4-yl)methyl)-1*H*-benzo[*d*]imidazole-7-carboxylate (5ad).** Using the procedure described for the synthesis of **5aa** starting from methyl ester **4a**, 66% yield of **5ad** was obtained; mp 156–161 °C (ethyl acetate). HPLC purity 96.2%. HRMS for

$C_{32}H_{29}N_4O_6$ $(M+H)^+$ Calcd: 565.2087, found: 565.2091. ^1H NMR (DMSO) δ(ppm): 7.70 (dd, $J=7.9$, 1.2 Hz, 1H, Ar), 7.55–7.50 (m, 1H, Ar), 7.49–7.39 (m, 7H, Ar), 7.37 (dd, $J=7.7$, 1.4 Hz, 1H, Ar), 7.33–7.27 (m, 1H, Ar), 727–7.13 (m, 3H, Ar), 6.98 (d, $J=8.1$ Hz, 2H, Ar), 6.82 (bs, 2H, NH_2), 5.53 (s, 2H, N–CH_2–Ar), 4.61 (q, $J=7.1$ Hz, 2H, OCH_2CH_3), 3.68 (s, 3H, OCH_3), 1.40 (t, $J=7.1$ Hz, 3H, OCH_2CH_3). ^{13}C NMR (DMSO) δ(ppm): 16.23, 158.79, 158.32, 151.97, 150.79, 141.62, 140.03, 138.74, 136.04, 130.82, 130.48, 130.09, 129.97, 129.60, 128.58, 127.05, 126.21, 125.99, 125.98, 122.79, 121.51, 121.26, 120.80, 115.59, 66.61, 52.22, 46.35, 14.37. *Anal*. Calcd for $C_{32}H_{28}N_4O_6$: C, 68.07; H, 5.00; N, 9.92. Found: C, 67.71; H, 5.21; N, 9.72.

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

Method A) A mixture of **5aa** (1.0 g, 2 mmol), DMSO (10 mL), and K_2CO_3 (0.5 g, 3.6 mmol) was stirred at room temperature for 3 h. The mixture was poured into water (50 mL), and the formed solution was acidified with acetic acid. The formed precipitate was filtered off, washed with water, and dried to give 0.9 g (96%) of **6a**; mp 193–197 °C (ref. [5] mp 196–197 °C). HPLC purity 97.8%.

Method B) A mixture of **5ad** (1.8 g, 3.2 mmol), NMP (15 mL), and K_2CO_3 (0.5 g, 3.6 mmol) was stirred at room temperature for 2 h. The mixture worked up as in Method A providing 1.4 g (94%) of **6a** of HPLC purity 99.6%. HRMS for $C_{26}H_{23}N_4O_5$ $(M+H)^+$ Calcd: 471.1668, found: 471.1688. ^1H 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–CH_2–Ar), 4.62 (q, $J=7.1$ Hz, 2H, OCH_2CH_3), 3.69 (s, 3H, OCH_3), 1.39 (t, $J=7.1$ Hz, 3H, OCH_2CH_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, 66.31; H, 4.82; N, 11.77.

***Ethyl 2-ethoxy-1-((2′-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl)methyl)-1H*-benzo[*d*]imidazole-7-carboxylate (6b).** Using the procedure described for the synthesis of **6a** starting from ethyl ester **5bb**, 93% yield of **6b** was obtained; mp 179–182 °C. HPLC purity 97.8%. HRMS for $C_{27}H_{25}N_4O_5$ $(M+H)^+$ Calcd: 485.1825, found: 485.1798. ^1H 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, $COOCH_2CH_3$), 4.18 (q, $J=7.1$ Hz, 2H, OCH_2CH_3), 1.39 (t, $J=7.1$ Hz, 3H, $COOCH_2CH_3$), 1.16 (t, $J=7.1$ Hz, 3H, OCH_2CH_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, 66.77; H, 4.80; N, 11.49.

***Benzyl 2-ethoxy-1-((2′-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl)methyl)-1H*-benzo[*d*]imidazole-7-carboxylate (6c).** A solution of ethyl chloroformate (0.13 g, 1.2 mmol) in dry DMF (0.5 mL) was added via syringe to a mixture of **4c** (0.52 g, 1 mmol), dry DMF (2 mL), and pyridine (0.1 g, 1.3 mmol) stirred in an ice bath and the mixture was stirred for additional 1 h. Then the mixture was poured into water, extracted with dichloromethane, and dried with $MgSO_4$. The residue after evaporation containing crude compound **5cb** was dissolved in DMSO (2 mL); K_2CO_3 (0.1 g) was added and the mixture was stirred at room temperature for 10 h. The mixture was poured into water (10 mL), extracted with dichloromethane and dried with $MgSO_4$. The residue was purified by centrifugally accelerated axial chromatography (Cyclograph™) using mixtures hexane-acetone 9 : 1 to 6 : 4. The fractions containing pure product were evaporated to give 0.13 g (24%) of **6c**; mp 179–182 °C. HPLC purity 94.2%. HRMS for $C_{32}H_{27}N_4O_5$ $(M+H)^+$ Calcd: 547.1981, found: 547.1976. ^1H NMR (DMSO) δ(ppm): 12.40 (bs, 1H, NH), 7.70 (dd, $J=7.9$, 1.2 Hz, 1H, Ar), 7.68–7.62 (m, 2H, Ar), 7.57–7.52 (m, 1H, Ar), 7.51 (dd, $J=7.8$, 1.2 Hz, 1H, Ar), 7.45–7.30 (m, 6H, Ar), 7.19 (d, $J=8.2$ Hz, 2H, Ar), 7.19 (t, $J=7.8$ Hz, 1H, Ar), 6.96 (d, $J=8.3$ Hz, 2H, Ar), 5.55 (s, 2H, N–CH_2–Ar), 5.24 (s, 2H, $COOCH_2$-Ph), 4.61 (q, $J=7.1$ Hz, 2H, OCH_2CH_3), 1.40 (t, $J=7.1$ Hz, 3H, OCH_2CH_3). ^{13}C NMR (DMSO) δ(ppm): 165.44, 159.63, 158.36, 158.32, 141.68, 140.67, 137.79, 136.58, 135.76, 131.79, 130.99, 130.60, 130.18, 128.86, 128.45, 128.19, 128.15, 127.80, 126.49, 123.04, 122.23, 121.78, 120.87, 115.35, 66.64, 66.55, 46.30, 14.34. *Anal* Calcd. for $C_{32}H_{26}N_4O_5$: C, 70.32; H, 4.79; N, 10.25. Found: C, 70.04; H, 4.56; N, 10.03.

***2-Ethoxy-1-((2′-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl) biphenyl-4-yl)methyl)-1H*-benzo[*d*]imidazole-7-carboxylic acid, azilsartan (2).**

Method A) A mixture of **6a** (4.7 g, 10 mmol), methanol (50 mL), and aqueous NaOH (2 g in 10 mL of water, 50 mmol) was stirred at room temperature for 24 h. Then methanol was evaporated, the residue was diluted with water (20 mL), and acidified with 5% aqueous HCl. Formed precipitate was filtered off, washed with water, and dried in dark to give 4.4 g (96%) of azilsartan (**2**); mp 208–211 °C (ref. [5] mp 212–214 °C). HPLC purity 97.6%. HRMS for $C_{25}H_{21}N_4O_5$ (M^+) Calcd: 457.1512, found: 457.1597. ^1H 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–CH_2–Ar), 4.58 (q, $J=7.1$ Hz, 2H, OCH_2CH_3), 1.38 (t, $J=7.1$ Hz, 3H, OCH_2CH_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.

Method B) A solution of ethyl chloroformate (2.7 g, 25 mmol) in dry DMF (5 mL) was added by syringe pump during 30 min to a mixture of **4a** (10.6 g, 24 mmol), dry DMF (75 mL) and pyridine (2.3 g, 29 mmol) stirred in an ice bath and the mixture was stirred under nitrogen for additional 6 h. Then

the mixture was poured into water (150 mL), extracted with ethyl acetate and dried with $MgSO_4$. The residue after evaporation (12.7 g) was dissolved in DMSO (200 mL), the solution was placed into an ice bath, and *tert*-BuOK (8.0 g, 71 mmol) was added in portions during 30 min. The mixture was stirred at room temperature under nitrogen for 5 h, then the mixture was poured into water (750 mL), and the formed solution was acidified with 5% aqueous HCl. Insoluble product was filtered off, washed with water, and dried in dark. The crude product was crystallized from 2-propanol to give 9.3 g (85%) of azilsartan (**2**); mp 205–208 °C. HPLC purity 94.6%.

***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 (14a).** A mixture of **6a** (1 g, 2 mmol), acetone (10 mL), and concd. aqueous HCl (0.1 mL) was stirred at 50 °C for 24 h, the formed insoluble portion was filtered off to give 0.9 g of **14a** (HPLC purity 98.9%). Crystallization from methanol provided 0.7 g (74%) of **14a**; mp 295–298 °C. HPLC purity 99.7%. HRMS for $C_{24}H_{19}N_4O_5$ $(M+H)^+$ Calcd: 443.1355, found: 443.1349. ^{1}H NMR (DMSO) δ(ppm): 12.39 (bs, 1H, NH), 11.47 (bs, 1H, NH), 7.71–7.61 (m, 2H, Ar), 7.55 (ddd, J = 7.6, 1.2 Hz, 1H, Ar), 7.47 (d, J = 7.6, 1H, Ar), 7.27–7.22 (m, 2H, Ar), 7.24 (d, J = 8.2 Hz, 2H, Ar), 7.07 (t, J = 7.9 Hz, 1H, Ar), 7.04(d, J = 8.2 Hz, 2H, Ar), 5.29 (s, 2H, N–CH_2–Ar), 3.61 (s, 3H,CH_3). ^{1}H NMR (DMSO) δ (ppm): 166.11, 159.44, 158.26, 154.92, 140.84, 137.53, 136.82, 131.85, 130.63, 130.19, 129.89, 128.72, 127.77, 127.66, 126.36, 122.15, 121.90, 120.71, 114.60, 112.37, 52.20, 44.67. IR: ν(N–H) 3235, ν(C–H) 2973, 2730, ν(C═O) 1761, 1704, 1674, ν(C═C) + ν(C═N) 1495, ν(C–O) 1261, 1124 cm^{-1}. *Anal* Calcd. for $C_{24}H_{18}N_4O_5$: C, 65.15; H, 4.10; N, 12.66. Found: C, 65.11; H, 4.29; N, 12.31.

***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 (15a).** Iodoethane (2 mL) was added to a stirred mixture of **6a** (2 g, 4.1 mmol), K_2CO_3 (5 g, 36 mmol), and acetone (100 mL); and the mixture was stirred at room temperature for 24 h. Insoluble portion was filtered off and washed with acetone (10 mL). Residue after evaporation of the combined acetone fractions was extracted with a mixture of dichloromethane (50 mL) and water (25 mL), the organic layer was washed with water and dried with $MgSO_4$. Residue after evaporation was crystallized from ethyl acetate to provide 1.4 g (68%) of white crystals; mp 165–168 °C. HRMS for $C_{28}H_{27}N_4O_5$ $(M+H)^+$ Calcd: 499.1982, found: 499.2009. ^{1}H NMR (DMSO) δ(ppm): 7.74 (ddd, J = 7.6, 1.5 Hz, 1H, Ar), 7.69 (dd, J = 7.9, 1.5 Hz, 1H, Ar), 7.66 (dd, J = 7.6, 1.5 Hz, 1H, Ar),7.62–7.55 (m, 2H, Ar), 7.46 (dd, J = 7.9, 1.5 Hz, 1H, Ar), 7.28 (d, J = 8.2 Hz, 2H, Ar), 7.18 (t, J = 7.9 Hz, 1H, Ar), 7.00 (d, J = 8.2 Hz, 2H, Ar), 5.53 (s, 2H, N–CH_2–Ar), 4.59 (q, J = 7.1 Hz, 2H, O$\underline{C}H_2CH_3$), 3.69 (s, 3H, COO$\underline{C}H_3$), 2.93 (q, J = 7.2 Hz, 2H, N$\underline{C}H_2CH_3$), 1.38 (t, J = 7.1 Hz, 3H, $OCH_2\underline{C}H_3$), 0.58 (t, J = 7.2 Hz, 3H, $NCH_2\underline{C}H_3$). ^{13}C NMR ($CDCl_3$) δ(ppm): 166.04, 159.06, 158.33, 158.19, 141.66, 140.58, 137.31, 137.18, 132.47, 131.19, 130.96, 130.40, 128.68, 128.12, 126.70, 123.022, 121.67, 121.18, 120.83, 115.35, 66.59, 52.14, 46.35, 37.39, 14.32, 11.92. IR: ν(C–H) 2987, 2942, ν(C═O) 1785, 1761, 1703, ν(C═C) + ν(C═N) 1616, 1553, ν(C–O) 1278, 1249, 1131 cm^{-1}. *Anal* Calcd. for $C_{28}H_{26}N_4O_5$: C, 67.46; H, 5.26; N, 11.24. Found: C, 67.77; H, 5.49; N, 10.89.

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