IDENTIFICATION, SYNTHESIS AND STRUCTURAL DETERMINATION OF SOME IMPURITIES OF CANDESARTAN CILEXETIL

Jaroslav HAVLÍČEK[a1,*], Zuzana MANDELOVÁ[a2], Ruediger WEISEMANN[b], Ivo STŘELEC[a3], Lukáš PLAČEK[a4] and Stanislav RÁDL[a5]

[a] *Zentiva, U kabelovny 130, 102 37 Prague 10, Czech Republic; e-mail: [1] jaroslav.havlicek@zentiva.cz, [2] zuzana.mandelova@zentiva.cz, [3] ivo.strelec@zentiva.cz, [4] lukas.placek@zentiva.cz, [5] stanislav.radl@zentiva.cz*

[b] *Bruker BioSpin GmbH, Silberstreifen, 76287 Rheinstetten, Germany; e-mail: ruediger.weisemann@bruker-biospin.de*

Received April 17, 2008
Accepted July 3, 2008
Published online February 18, 2009

All principal candesartan cilexetil impurities and/or degradation products were synthesized and identified. The differentiation of N-1 and N-2 ethylated candesartan cilexetil derivatives was performed using 1D and 2D NMR experiments. The influence of the magnetic field on the resolution and sensitivity of NMR experiments is shown. Selective hydrolysis of these compounds then provided corresponding producrs of hydrolysis of the ethoxy group.

Keywords: Candesartan cilexetil; Impurity identification; Impurity synthesis; Tetrazoles; Benzimidazoles; NMR spectroscopy; ^{1}H-^{15}N HMBC; MS.

Candesartan cilexetil **1**, a prodrug of candesartan **2**, is a member of a modern therapeutic group of drugs known as angiotensin II receptor antagonists (AIIRAs) used in the treatment of hypertension (high blood pressure). The drug is marketed by AstraZeneca and Takeda Pharmaceuticals, under the trade names Blopress, Atacand, Amias, and Ratacand[1,2].

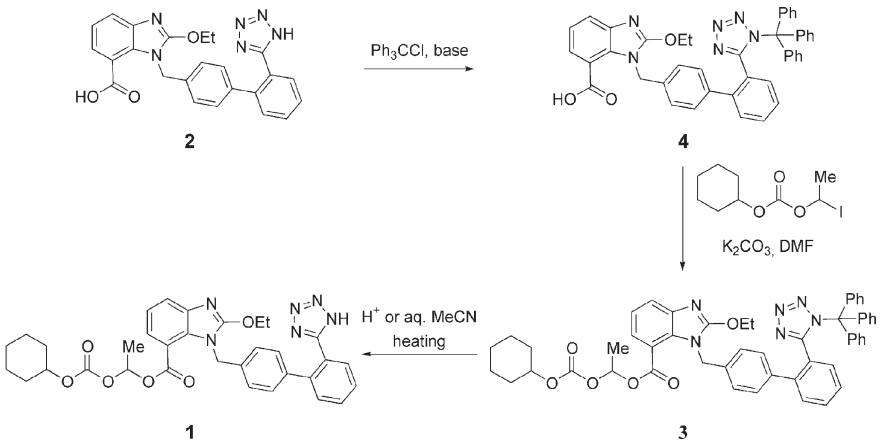
Trityl candesartan cilexetil **3**, a key intermediate of the synthesis of candesartan cilexetil, can be prepared according to the patent literature[3] from candesartan **2** in two steps via trityl candesartan **4**. Detritylation of **3** under various conditions has been described in numerous patents (Scheme 1).

In spite of the strict requirements regarding the purity of drugs in developed countries, the presence of both process-related impurities and degradation products cannot be completely eliminated. Therefore, the principal knowledge needed for any drug registration is that of its impurities and/or degradation products. The specified impurities can be either identified or unidentified. Identified impurities should be included in the specification

Collect. Czech. Chem. Commun. 2009, Vol. 74, No. 2, pp. 347–362

doi:10.1135/cccc2008072

when they are present at a level higher than the identification threshold, which is usually 0.10%. These impurities must not only be identified but also independently synthesized. In general, the impurities could be either process-related or formed by degradation of the drug.



SCHEME 1
Synthesis of candesartan cilexetil **1** from candesartan **2**

Considering the structure of candesartan cilexetil **1**, candesartan **2**, can be expected as the major degradation product. However, this is true only under alkaline conditions; otherwise usually three other degradation products are detected in higher amounts. LC-MS technique identified their probable structures **5**–**7** (Fig. 1). Compound **5** was described in patent literature[4] and quite recently, both a patent[5] and a paper[6] listing compounds **5**–**7** as impurities of candesartan cilexetil have appeared. However, neither properties nor the structure elucidation of these compounds have been published. Even though Rao et al.[6] have described an isocratic HPLC for the separation of candesartan cilexetil and its impurities, the positions of the *N*-ethyl group in the tetrazole ring is not apparent from the paper. Therefore, we would like to report the synthesis and structure determination of impurities **5**–**7** by several 1D and 2D NMR experiments.

Literature search has not revealed the presence of compounds **8**, **9** having common structural features with of **5** and **6**/**7**. Therefore, we also decided to synthesize these compounds and compare them to minor impurities formed during the candesartan cilexetil synthesis.

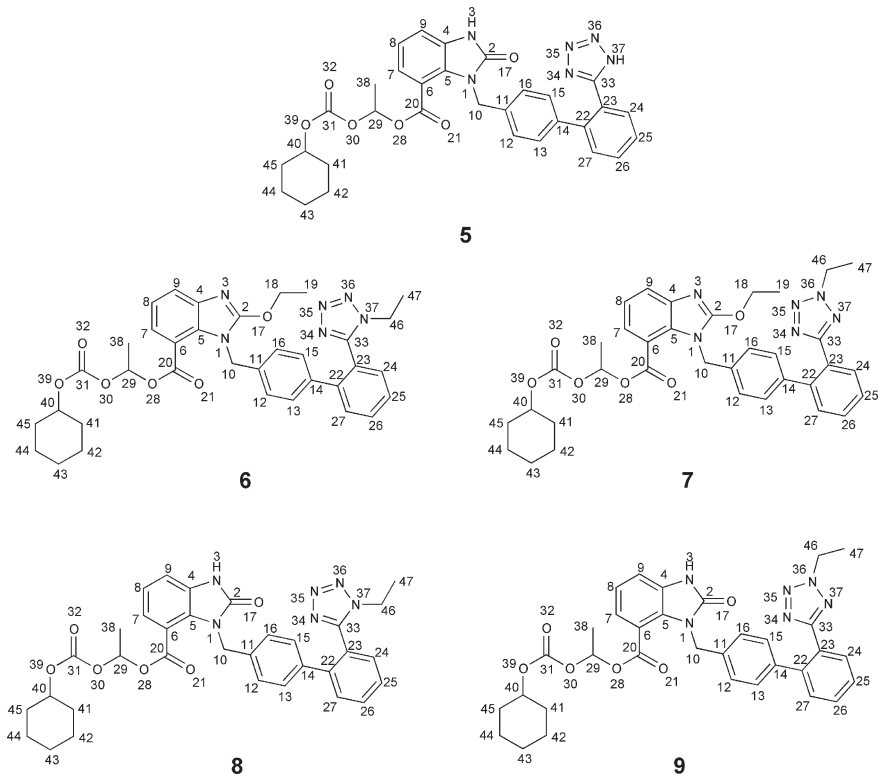


FIG. 1
Structures of the discussed impurities **5**–**9**

RESULTS AND DISCUSSION

*Identification of Impurities **5**–**9***

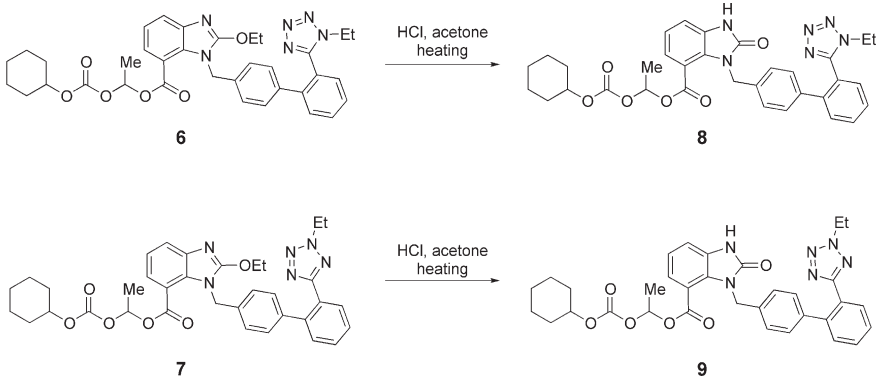
Impurities **5**–**7** are present both in the commercially available active pharmaceutical ingredient of candesartan cilexetil and in the drugs on the market. These impurities are also formed during the stability tests under all tested conditions. LC-MS provided $[M + H]^+$ masses of impurities **5**–**7** in TIC scan mode (*m/z* 583 for impurity **5** and *m/z* 639 for impurities **6** and **7**). Compounds **5**–**7** were synthesized and characterized. The $[M + H]^+$ values were specified using high-resolution MS for elemental composition; *m/z* 583.2297 corresponding to $C_{31}H_{31}N_6O_6$ (impurity **5**). Similarly, the *m/z* values of 639.2930 and 639.2931 for impurities **6** and **7**, respectively, cor-

responding to $C_{35}H_{39}N_6O_6$, were obtained. Analogously, high-resolution MS of the potential impurities **8** and **9** provided $[M + H]^+$ *m/z* values of 611.26147 and 611.26154 corresponding to $C_{33}H_{35}N_6O_6$. All compounds **5**–**9** were detected by UPLC in the crude reaction mixtures of candesartan cilexetil obtained from **3** by both acidic deprotection[3] and deprotection under neutral conditions[7] (Table III).

*Synthesis of Impurities **5**–**9***

Compound **5** is formed as the major side product in amounts up to 10% during acidic detritylation of **3**. The patented procedures for the acidic detritylation include, among other conditions, heating in aqueous hydrochloric acid[3] or in ethanolic hydrogen chloride[8]. Prolonged heating under the mentioned conditions leads to complex mixtures containing also products of solvolysis of the relatively unstable cilexetil ester group. First, we tried to obtain **5** by chromatographic purification of these mixtures but we failed to obtain pure samples. However, extensive screening of the conditions revealed that acidic hydrolysis of **3** in aqueous acetone provided relatively pure compound **5** and trityl alcohol, and subsequent chromatographic purification provided good yield of **5**. The same treatment of candesartan cilexetil **1** provided even better yield (88%) of **5** without chromatographic purification.

Compounds **6** and **7**, identified by LC-MS as ethyl derivatives of **1**, were prepared by simple ethylation of **1** with iodoethane in acetone in the presence of potassium carbonate at ambient temperature. The formed isomers **6**



6 **8**

7 **9**

SCHEME 2
Synthesis of impurities **8** and **9**

and **7** were isolated by flash chromatography but their structure elucidation was not trivial and required the use of advanced NMR methods described in the following paragraph.

For the synthesis of compounds **8** and **9**, acidic hydrolysis of the respective *N*-ethyl derivatives **6** and **7** using the conditions developed for the synthesis of **5** was used (Scheme 2).

*Structure Elucidation of Impurities **5**–**9***

For the assignment of protons and carbons, advanced 2D NMR techniques were used. The ^{1}H-^{15}N HMBC NMR spectra of impurities **6** and **7** are shown in Figs 3 and 4. Chemical shifts of ^{1}H and ^{13}C of compounds **6** and **7** are given in Tables I and II, respectively. The influence of the magnetic field on the resolution and sensitivity of the NMR experiments is shown in Fig. 2. The differentiation of impurities **6** and **7** of candesartan cilexetil was performed using 2D ^{1}H-^{15}N HMBC experiments. In ^{1}H-^{15}N HMBC, three cross peaks (35-46, 36-46, 37-46) for the tetrazole ring were found in impurity **7**, while in the case of impurity **6**, the cross peak 35-46 was not observed.

By analogy with the discussed structures of compounds **6** and **7**, the NMR spectra of compounds **5**, **8** and **9** were interpreted (see Experimental).

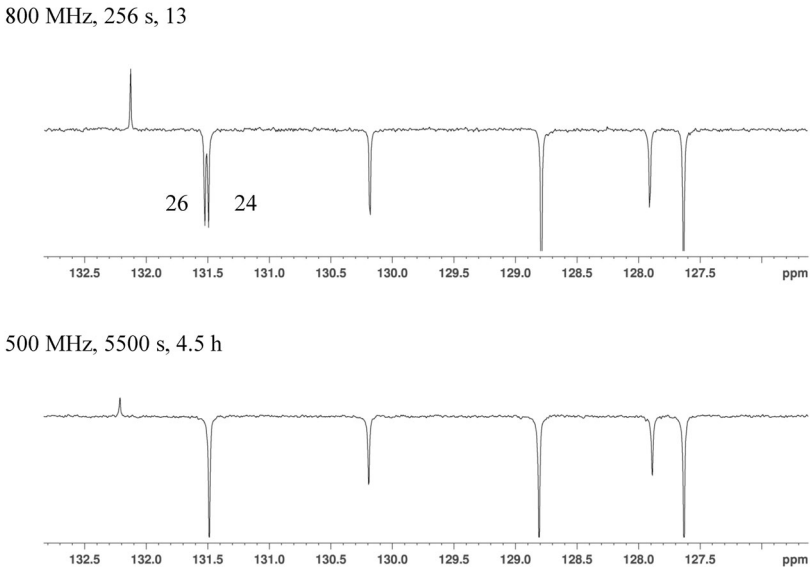


FIG. 2
^{13}C-APT NMR spectrum of impurity **6** at two magnetic fields

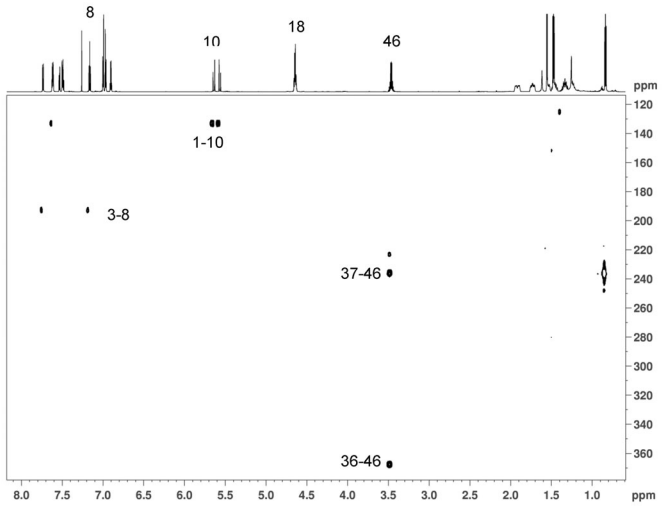


FIG. 3
^{1}H-^{15}N HMBC spectrum of impurity **6** in $CDCl_3$, $J_{N(XH)}$ = 4 Hz

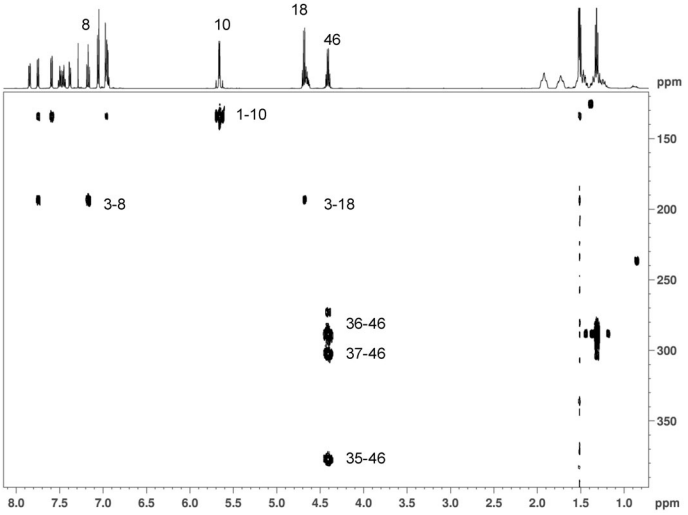


FIG. 4
^{1}H-^{15}N HMBC spectrum of impurity **7** in $CDCl_3$, $J_{N(XH)}$ = 4 Hz

TABLE I
^{1}H, ^{13}C and ^{15}N NMR assignments for impurity **6** (500 MHz, $CDCl_3$)

Position	δ_C	δ_H	δ_N	Multiplicity	$J_{H,H}$
1	–	–	132.5		
2	158.84	–			
3	–	–	192.5		
4	142.14	–			
5	132.22	–			
6	114.34	–			
7	124.28	7.62		dd	7.9; 1.2
8	120.89	7.16		t	7.9
9	122.90	7.73		dd	7.9; 1.2
10	46.95	5.64		d	15.9
		5.57		d	15.9
11	137.48	–			
12	127.64	6.97		d	8.3
13	128.82	7.00		d	8.3
14	137.93	–			
15	128.82	7.00		d	8.3
16	127.64	6.97		d	8.3
18	66.81	4.64		q	7.2
19	14.63	1.47		t	7.2
20	164.01	–			
22	141.25	–			
23	122.89	–			
24	131.50	7.52		m	
25	130.20	7.51		m	
26	131.52	7.61		m	
27	127.90	7.49		m	
29	91.82	6.90		q	5.4
31	152.56	–			

TABLE I
(*Continued*)

Position	δ_C	δ_H	δ_N	Multiplicity	$J_{H,H}$
33	154.26	–			
34	–	–	not found		
35	–	–	not found		
36	–	–	368.2		
37	–	–	236.7		
38	19.63	1.56		d	5.5
40	77.53	4.61		m	
41	31.43[a]	1.98		m	
		1.44		m	
42	23.60	1.73		m	
		1.34		m	
43	25.14	1.51		m	
		1.25		m	
44	23.60	1.73		m	
		1.34		m	
45	31.40[a]	1.98		m	
		1.44		m	
46	42.37	3.47		q	7.3
47	13.59	0.84		t	7.3

[a] Interchangeable.

TABLE II
^{1}H, ^{13}C and ^{15}N NMR assignments for impurity **7** (500 MHz, $CDCl_3$)

Position	δ_C	δ_H	δ_N	Multiplicity	$J_{H,H}$
1	–	–	134.9		
2	158.77	–			
3	–	–	193.3		
4	142.02	–			
5	131.89	–			
6	114.60	–			
7	123.85	7.58		dd	7.9; 1.2
8	120.60	7.16		dd	7.9
9	122.48	7.74		dd	7.9; 1.2
10	46.86	5.67		d	15.9
		5.63		d	15.9
11	116.33	–			
12	126.52	7.00		d	8.2
13	129.30	7.05		d	8.2
14	135.83	–			
15	129.30	7.05		d	8.2
16	126.52	7.00		d	8.2
18	66.65	4.67		q	7.1
19	14.56	1.49		t	7.0
20	163.95	–			
22	141.50	–			
23	126.30	–			
24	130.20	7.83		m	
25	127.40	7.44		dt	1.5; 7.6
26	129.78	7.48		dt	1.5; 7.6
27	130.53			m	
29	91.71	6.94		q	5.4
31	152.49	–			

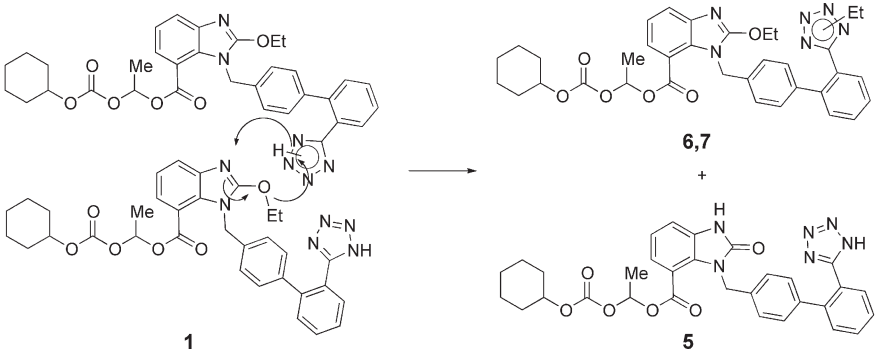
TABLE II
(*Continued*)

Position	δ_C	δ_H	δ_N	Multiplicity	$J_{H,H}$
33	164.92	–			
34	–	–	not found		
35	–	–	377.2		
36	–	–	288.9		
37	–	–	302.6		
38	19.51	1.50		d	5.5
40	77.42			m	
41[a]	31.31	1.91		m	
	31.30	1.43		m	
42[a]	23.49	1.72		m	
	23.46	1.27		m	
43	25.05	1.46		m	
		1.22		m	
44[a]	23.49	1.72		m	
	23.46	1.27		m	
45[a]	31.31	1.91		m	
	31.30	1.43		m	
46	47.92	4.40		q	7.3
47	14.22	1.30		t	7.3

[a] Interchangeable.

*Proposed Mode of Formation of Impurities **5**–**7***

Formation of candesartan cilexetil impurities **5**–**7** occurs during both the deprotection of trityl candesartan cilexetil **3** leading to candesartan cilexetil **1** and the purification of **1**. Since no apparent ethylation agent is present, the only reasonable explanation of the formation of these impurities is that the ethoxy group of **1** serves as an alkylation species, and alkylates, in an intermolecular fashion, positions N-1 and N-2 of the tetrazole ring providing compounds **6** and **7**, respectively (Scheme 3). To the best of our knowledge, no similar intermolecular *N*-alkylation by an acyclic ether has been reported.



SCHEME 3
Proposed mechanism of formation of impurities **5**–**7**

While under acidic conditions, compound **5** is formed mainly by the hydrolysis of the ethoxy group of candesartan cilexetil or trityl candesartan cilexetil (see Experimental, preparation of **5**), the hydrolysis does not play an important role under neutral conditions. This was proven by heating candesartan cilexetil solutions in various solvents (see, e.g., Experimental, Heating of candesartan cilexetil **1** in aqueous acetone). Similarly, formation of impurities **8** and **9** from compounds **6** and **7**, respectively, can be explained.

CONCLUSIONS

Five impurities of candesartan cilexetil **5**–**9** were identified and synthesized. The complex structures of the two *N*-ethyl substituted impurities were determined by several 1D and 2D NMR experiments. In ^{1}H-^{15}N HMBC, three

cross-peaks (35-46, 36-46, 37-46) for the tetrazole ring were found in impurity **7**, while in the case of impurity **6**, the cross-peak 35-46 was not observed. The advantage of higher magnetic field is not only in the improvement of sensitivity (shorter experimental time), but also in better resolution of ^{1}H and ^{13}C NMR spectra.

EXPERIMENTAL

Samples and Reagents

Trityl candesartan cilexetil **3** was obtained from Zhejiang Tianyu Pharmaceutical (http://www.tianyupharma.com). Other chemicals used in the synthesis were purchased from Sigma–Aldrich and were used without purification.

Synthesis

Melting points were measured on a Kofler block and are uncorrected. The UV spectra were recorded on a Hewlett–Packard 8452A spectrophotometer (ethanol) in the range 190–400 nm. Flash chromatography was performed on silica gel Merck, particle size 0.04–0.063 mm. The purity of the substances prepared was evaluated by TLC on silica gel (FP KG F 254, Merck) and by Ultra Performance Liquid Chromatography (UPLC) using a UPLC system Waters Acquity with UV detection (column length 0.1 m, internal diameter 2.1 mm, stationary phase UPLC BEH-C8, temperature 35 °C). Gradient elution with mobile phase A (phosphate buffer: 1.32 g $(NH_4)_2HPO_4$ in 1000 ml of H_2O, pH adjusted to 3.0 with 50% phosphoric acid), and mobile phase B (acetonitrile) was used.

1-{[(Cyclohexyloxy)carbonyl]oxy}ethyl 2-Ethoxy-1-{[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl}-1*H*-benzimidazole-7-carboxylate (**1**)

A stirred mixture of trityl candesartan cilexetil **3** (100 g, 117 mmol), acetonitrile (1000 ml) and water (125 ml) was heated at reflux for 10 h and the mixture was stirred at ambient temperature for additional 2 h (UPLC results given in Table III, entry 1). Water (800 ml) was then added and the mixture was stirred for additional 10 h. The precipitate was filtered off, mixed with ethyl acetate (250 ml) and stirred at 50 °C for 2 h. After cooling, the precipitate was filtered off (Table III, entry 2) and repeatedly crystallized from aqueous acetone to provide 45.7 g (63.9%) of **1**, m.p. 172–174 °C. The UPLC purity is given in Table III, entry 3. UV (EtOH), λ (log ε): 214 (4.73), 254 (4.28), 304 (3.76). HRMS: *m/z* calculated for $C_{35}H_{39}N_6O_6$ $[M + H]^+$ 639.2931, found 639.2930.

1-{[(Cyclohexyloxy)carbonyl]oxy}ethyl 3-{[2′-(1*H*-Tetrazol-5-yl)biphenyl-4-yl]methyl}-2-oxo-2,3-dihydro-1*H*-benzimidazole-4-carboxylate (**5**)

Method A. A mixture of **3** (2 g, 2.34 mmol), acetone (16 ml), water (4 ml) and concentrated hydrochloric acid (0.2 ml) was heated at reflux for 6 h. The mixture was evaporated, and the residue was purified by flash chromatography (hexane–acetone 8:2) to provide 0.95 g (69.7%) of **5**, m.p. 246–248 °C (97.4% purity, RRT 0.66). ^{1}H NMR (for numbering, see Fig. 1): 1.22 m, 1 H (H-43); 1.31 m, 2 H (H-42, H-44); 1.35 d, 3 H, J = 5.5 (H-38); 1.39 m,

2 H (H-41, H-45); 1.46 m, 1 H (H-43); 1.63 m, 2 H (H-42, H-44); 1.83 m, 2 H (H-41, H-45); 4.57 m, 1 H (H-40); 5.24 d, 1 H, *J* = 16.2 (H-10); 5.33 d, 1 H, *J* = 16.2 (H-10); 6.72 q, 1 H, *J* = 5.4 (H-29); 6.93 d, 1 H, *J* = 8.4 (H-12, H-16); 7.00 d, 2 H, *J* = 8.4 (H-13, H-15); 7.09 dd, 1 H, *J* = 7.9 (H-8); 7.26 dd, 1 H, *J* = 7.9, 1.2 (H-7); 7.28 dd, 1 H, *J* = 7.9, 1.2 (H-9); 7.54 ddd, 1 H, *J* = 15.0, 7.6, 1.5 (H-25); 7.49 dd, 1 H, *J* = 7.9, 1.5 (H-27); 7.63 m, 1 H (H-24); 7.64 m, 1 H (H-26); 11.50 bs, 1 H (N-3). ^{13}C NMR (for numbering, see Fig. 1): 18.98 (C-38); 22.86 (C-42 or C-44); 22.89 (C-42 or C-44); 24.51 (C-43); 30.70 (C-41 or C-45); 30.73 (C-41 or C-45); 44.50 (C-10); 76.74 (C-40); 91.83 (C-29); 113.00 (C-6); 113.18 (C-9); 120.70 (C-8); 122.24 (C-7); 123.42 (C-23); 126.42 (C-12, C-16); 127.66 (C-25); 128.28 (C-5); 128.93 (C-13, C-15); 130.00 (C-4); 130.47 (C-27); 130.55 (C-24); 130.91 (C-26); 136.22 (C-11); 138.02 (C-14); 140.90 (C-22); 151.84 (C-31); 154.83 (C-2); 154.83 (C-33); 163.40 (C-20). UV (EtOH), λ (log ε): 212 (4.74), 254 (4.27), 316 (3.73). HRMS: *m/z* calculated for $C_{31}H_{31}N_6O_6$ $[M + H]^+$ 583.2305, found 583.2297.

Method B. A mixture of **1** (2 g, 3.28 mmol), acetone (16 ml), water (4 ml) and concentrated hydrochloric acid (0.2 ml) was heated at reflux for 6 h. The mixture was evaporated, and the residue was crystallized from acetone to provide 1.68 g (87.9%) of **5**, m.p. 248 °C (99.8% purity, RRT 0.66).

TABLE III
Purity of candesartan cilexetil prepared by detritylation in aqueous acetonitrile[7]

Entry	UPLC in % (RRT)[a]						
	1 (1.00)	**3** (2.42)	**5** (0.66)	**6** (1.33)	**7** (1.58)	**8** (0.90)	**9** (1.13)
1	93.91	4.11	0.14	0.42	1.14	0.02	0.06
2	96.18	3.50	0.09	0.06	0.17	–	–
3	99.87	0.07	0.02	0.01	0.03	–	–

[a] The formed trityl alcohol was not integrated.

1-{[(Cyclohexyloxy)carbonyl]oxy}ethyl 2-Ethoxy-1-{[2′-(1-ethyl-1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl}-1*H*-benzimidazole-7-carboxylate (**6**) and 1-{[(Cyclohexyloxy)carbonyl]oxy}-ethyl 2-Ethoxy-1-{[2′-(2-ethyl-2*H*-tetrazol-5-yl)biphenyl-4-yl]methyl}-1*H*-benzimidazole-7-carboxylate (**7**)

Potassium carbonate (2.5 g) was added to a solution of **1** (6.1 g, 10 mmol) in acetone (150 ml) and the mixture was stirred under nitrogen at ambient temperature for 1 h. Iodoethane (1 ml) was then added, and the mixture was stirred for additional 24 h. The insoluble portion was filtered off and washed with acetone (25 ml), the filtrate was evaporated (8.2 g) and separated by flash chromatography (hexane–acetone 8:2) to provide 2.9 g of fraction I containing 99.9% of compound **7** (RRT 1.58, m.p 109–112 °C), 0.8 g of combined fraction II containing 54.3% of compound **6** (RRT 1.33) and 45.6% of compound **7** (RRT 1.58), and 2.5 g

of fraction III containing 99.75% of compound **6** (RRT 1.33) and 0.22% of compound **7** (RRT 1.58, m.p. 102–103 °C).

1-{[(Cyclohexyloxy)carbony]loxy}ethyl 2-ethoxy-1-{[2′-(1-ethyl-1H-tetrazol-5-yl)biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylate (**6**). UV, λ (log ε): 214 (4.65), 254 (4.25), 308 (3.68). HRMS: *m/z* calculated for $C_{35}H_{39}N_6O_6$ $[M + H]^+$ 639.2931, found 639.2930.

1-{[(Cyclohexyloxy)carbonyl]oxy}ethyl 2-ethoxy-1-{[2′-(2-ethyl-2H-tetrazol-5-yl)biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylate (**7**). UV, λ (log ε): 216 (4.68), 258 (4.15), 304 (3.67). HRMS: *m/z* calculated for $C_{35}H_{39}N_6O_6$ $[M + H]^+$ 639.2931, found 639.2931.

1-{[(Cyclohexyloxy)carbonyl]oxy}ethyl 3-{[2′-(1-Ethyl-1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl}-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazole-4-carboxylate (**8**)

A mixture of **6** (0.2 g, 0.31 mmol), acetone (2 ml), water (0.5 ml) and concentrated hydrochloric acid (0.02 ml) was stirred in a vial at 75 °C for 6 h. The mixture was evaporated and the residue was crystallized from a mixture of diethyl ether–acetone to provide 0.13 g (68.8%) of **8**, m.p. 189–192 °C (99.6% purity, RRT 0.90). ^{1}H NMR (for numbering, see Fig. 1): 0.85 t, 3 H, *J* = 7.3 (H-47); 1.25 m, 1 H (H-43); 1.35 m, 2 H (H-42, H-44); 1.46 m, 2 H (H-41, H-45); 1.50 d, 3 H, *J* = 5.4 (H-38); 1.53 m, 1 H (H-43); 1.74 m, 2 H (H-42, H-44); 1.93 m, 2 H (H-41, H-45); 3.45 q, 2 H, *J* = 7.3, (H-46); 4.65 m, 1 H (H-40); 5.49 d, 1 H, *J* = 15.9 (H-10); 5.53 d, 1 H, *J* = 15.9 (H-10); 6.85 q, 1 H, *J* = 5.4 (H-29); 7.02 d, 2 H, *J* = 8.4 (H-13, H-15); 7.08 d, 1 H, *J* = 8.4 (H-12, H-16); 7.08 dd, 1 H, *J* = 7.9 (H-8); 7.31 dd, 1 H, *J* = 7.9, 1.1 (H-7); 7.45 dd, 1 H, *J* = 7.9, 1.1 (H-9); 7.49 ddd, 1 H, *J* = 15.0, 7.6, 1.5 (H-25); 7.50 m, 1 H (H-27); 7.62 ddd, 1 H, *J* = 15.0, 7.6, 1.5 (H-26); 7.83 dd, 1 H, *J* = 7.6, 1.5 (H-24); 10.27 bs, 1 H (N-3). ^{13}C NMR (for numbering, see Fig. 1): 13.61 (C-47); 19.56 (C-38); 23.60 (C-42, C-44); 25.11 (C-43); 31.39 (C-41 or C-45); 31.44 (C-41 or C-45); 45.69 (C-10); 52.41 (C-46); 77.64 (C-40); 91.94 (C-29); 113.88 (C-9); 114.31 (C-6); 121.12 (C-8); 122.85 (C-23); 123.86 (C-7); 127.88 (C-25); 127.91 (C-12, C-16); 128.83 (C-13, C-15); 128.95 (C-5); 129.49 (C-4); 130.20 (C-27); 131.51 (C-26); 131.55 (C-24); 137.17 (C-11); 137.91 (C-14); 141.20 (C-22); 152.51 (C-31); 154.27 (C-33); 156.42 (C-2); 163.61 (C-20). UV, λ (log ε): 212 (4.70), 254 (4.28), 312 (3.70). HRMS: *m/z* calculated for $C_{33}H_{35}N_6O_6$ $[M + H]^+$ 611.26181, found 611.26147.

1-{[(Cyclohexyloxy)carbonyl]oxy}ethyl 3-{[2′-(2-Ethyl-1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl}-2-oxo-2,3-dihydro-1*H*-benzimidazole-4-carboxylate (**9**)

Using the procedure described for the synthesis of **8**, but starting from *N*-ethyl derivative **7**, 0.14 g (74.0%) of **9** was prepared, m.p. 173–176 °C (99.9% purity, RRT 1.13). ^{1}H NMR (for numbering, see Fig. 1): 1.24 m, 1 H (H-43); 1.32 m, 2 H (H-42, H-44); 1.34 t, 3 H, *J* = 7.4 (H-47); 1.44 d, 3 H, *J* = 5.4 (H-38); 1.46 m, 2 H (H-41, H-45); 1.53 m, 1 H (H-43); 1.73 m, 2 H (H-42, H-44); 1.92 m, 2 H (H-41, H-45); 3.42 q, 2 H, *J* = 7.4 (H-46); 4.64 m, 1 H (H-40); 5.46 d, 1 H, *J* = 16.0 (H-10); 5.61 d, 1 H, *J* = 16.0 (H-10); 6.86 q, 1 H, *J* = 5.4 (H-29); 7.04 m, 4 H (H-12, H-13, H-15, H-16); 7.05 m, 1 H (H-8); 7.29 dd, 1 H, *J* = 7.9, 1.0 (H-7); 7.36 dd, 1 H, *J* = 7.6, 1.5 (H-27); 7.41 dd, 1 H, *J* = 7.9, 1.0 (H-9); 7.45 ddd, 1 H, *J* = 15.6, 7.6, 1.6 (H-25); 7.48 ddd, 1 H, *J* = 15.0, 7.6, 1.6 (H-26); 7.82 dd, 1 H, *J* = 15.6, 7.6 (H-24); 10.24 bs, 1 H (N-3). ^{13}C NMR (for numbering, see Fig. 1): 14.36 (C-47); 19.51 (C-38); 23.57 (C-42 or C-44); 23.59 (C-42 or C-44); 25.12 (C-43); 31.39 (C-41 or C-45); 31.41 (C-41 or C-45); 45.71 (C-10); 48.06 (C-46); 77.63 (C-40); 91.93 (C-29); 113.51 (C-9); 114.71 (C-6); 120.89 (C-8); 123.59 (C-7); 126.38 (C-23); 126.52 (C-12); 126.72 (C-13, C-15); 127.46 (C-25); 128.86 (C-5); 129.35 (C-4); 129.41 (C-16); 129.85 (C-26); 130.32 (C-24); 130.62 (C-27); 135.56 (C-11);

139.97 (C-14); 141.61 (C-22); 151.10 (C-2); 152.53 (C-31); 163.67 (C-20); 165.15 (C-33). UV, λ (log ε): 214 (4.74), 256 (4.20), 306 (3.62). HRMS: *m/z* calculated for $C_{33}H_{35}N_6O_6$ $[M + H]^+$ 611.26181, found 611.26154.

Heating of Candesartan Cilexetil **1** in Aqueous Acetone

Candesartan cilexetil **1** (1.0 g) was heated at reflux in a mixture of acetone (8 ml) and water (2 ml) for 24 h. The reaction mixture was analyzed by UPLC and the results are given in Table IV.

TABLE IV
Heating of candesartan cilexetil **1** in aqueous acetone

Time h	UPLC in % (RRT)					
	1 (1.00)	**5** (0.66)	**6** (1.33)	**7** (1.58)	**8** (0.90)	**9** (1.13)
0	99.80	0.02	0.03	0.05	–	–
1	98.77	0.55	0.16	0.52	–	–
4	98.68	0.60	0.18	0.54	–	–
24	89.30	4.91	1.31	4.00	0.12	0.36

MS Experiments

Impurities **5**–**7** were identified by LC-MS using a Perkin–Elmer 200 series HPLC system coupled to a Sciex API 3000 mass spectrometer with positive atmospheric pressure ionization (TurboIonspray) and by high-resolution MS technique using an LTQ Orbitrap hybrid mass spectrometer with direct injection into APCI source in the positive mode. HPLC system (C8 symmetry 5 μm, 4.6 × 250 mm column, 25 °C) in gradient elution (mobile phase A: 10 mM ammonium formate in water, pH adjusted to 3.5 with formic acid, mobile phase B: acetonitrile, 0.8 ml/min) was used.

NMR Experiments

NMR experiments were carried out on a Bruker Avance 500 (Bruker Biospin GmbH) at 500.13 MHz (^{1}H), 125.77 MHz (^{13}C) and 50.70 MHz (^{15}N). Reference for ^{1}H δ_{CDCl3} 7.26 ppm, for ^{13}C δ_{CDCl3} 77.0 ppm and for ^{15}N δ_{NH4+} 0 ppm. Coupling constants (*J*) are given in Hz. To improve spectral resolution and sensitivity, a Bruker Avance-III 800 MHz spectrometer operating at frequencies of 800.13 MHz (^{1}H), 201.19 MHz (^{13}C) and 81.11 MHz (^{15}N) was used for selected experiments. All experiments were performed in $CDCl_3$ at 298 K. COSY, HSQC, ^{1}H-^{13}C HMBC and ^{1}H-^{15}N HMBC spectra were recorded using pulse programs from the Bruker NMR standard library. At 500 MHz, standard 5 mm TXO (triple-nucleus X-observe) and TBI (triple-broadband inverse) probeheads equipped with *z*-gradient coils were employed for all measurements. At 800 MHz, a Bruker 5 mm TCI (triple C-optimized inverse)

cryoprobe equipped with a z-gradient was used to record gradient-enhanced heteronuclear experiments, i.e. ^{1}H-^{13}C HSQC, ^{1}H-^{13}C HMBC and ^{1}H-^{15}N HMBC, at high sensitivity. For the ^{1}H-^{13}C HSQC, a dataset was acquired with 8 scans for each t1 increment at a resolution of 2048 and 256 points in the F_2 and F_1 dimensions, respectively. The time domain data were zero-filled to 2048 and 1024 data points in F_2 and F_1 dimensions, and multiplied with a sinusoidal squared sine-bell window function in both dimensions prior to Fourier transform. The gradient-selected ^{1}H-^{13}C HMBC and ^{1}H-^{15}N HMBC data sets were recorded with 4 K and 512 points in the F_2 and F_1 dimensions, respectively. The magnetization transfer in the ^{1}H-^{13}C HMBC experiment was optimized for a three-bond coupling constant ^{3}J(C,H) of 8 Hz. The corresponding ^{1}H-^{15}N HMBC was optimized for a long-range coupling constant of 6 Hz. 1 K increments of 2 K data points were recorded with 128 scans for each increment. The data were subsequently processed employing zero-filling to 2 K and 1 K data points in the F_1 and F_2 dimensions, using a sinusoidal squared sine-bell window function for apodization prior to Fourier transform in both dimensions.

REFERENCES

1. Gohlke P., Jürgensen T., van Kügelgen S., Unger T.: *Drugs Today* **1999**, *35*, 105.
2. Hansson L.: *Drugs Today* **1999**, *35*, 117.
3. Naka T., Nishikawa K., Kato T. (Takeda Chemical Industries, Ltd.): U.S. 5196444; *Chem. Abstr.* **1992**, *116*, 128924.
4. Etinger M. Yu., Niddam-Hildesheim V., Fedotev B., Dolitzky B.-Z. (TEVA Pharmarmaceutical Industries, Ltd.): WO 2005/111021; Chem. Abstr. **2005**, *143*, 4483142.
5. Kurgan Z., Pesachovich M. (TEVA Pharmarmaceutical Industries, Ltd.): WO 2006/122254; *Chem. Abstr.* **2007**, *145*, 445638.
6. Rao D. V. S., Radhakrishnanand P., Suryanarayana M. V., Himabindu V.: *Chromatographia* **2007**, *66*, 499.
7. Rádl S., Stach J. (Zentiva a.s.): WO 2007/048361; *Chem. Abstr.* **2007**, *146*, 462268.
8. Shida Y., Kokichi Y. (Takeda Chemical Industries, Ltd.): U.S. 5578733; *Chem. Abstr.* **1995**, *123*, 340152.