*Scientific paper*

# Synthesis and Identification of Some Impurities of Irbesartan

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***Dedicated to Professor Branko Stanovnik on the occasion of his 70th birthday***

## Abstract

Synthesis of two principal impurities of irbesartan prepared via its *N*-trityl derivative is described. The impurities were isolated and unambiguouesly identified by NMR techniques. Spectral characteristics (IR, UV, MS) of these compounds are also given.

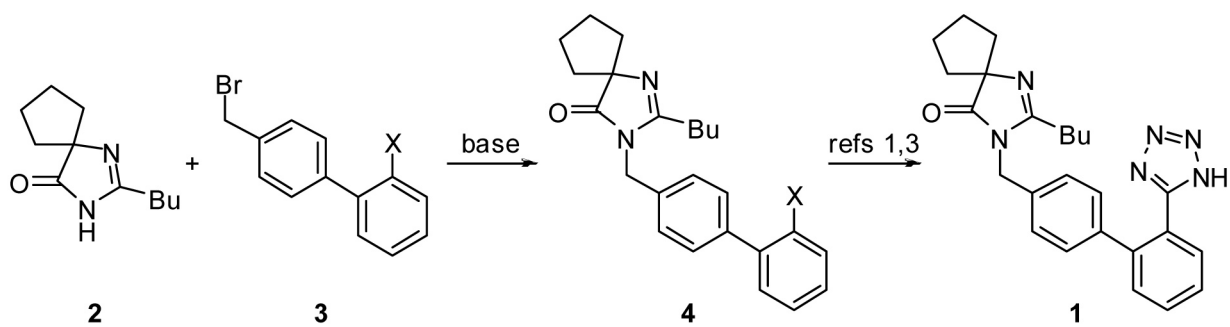
**Keywords:** Irbesartan, Impurities, Identification, NMR, LC MS, IR, UV.

## 1. Introduction

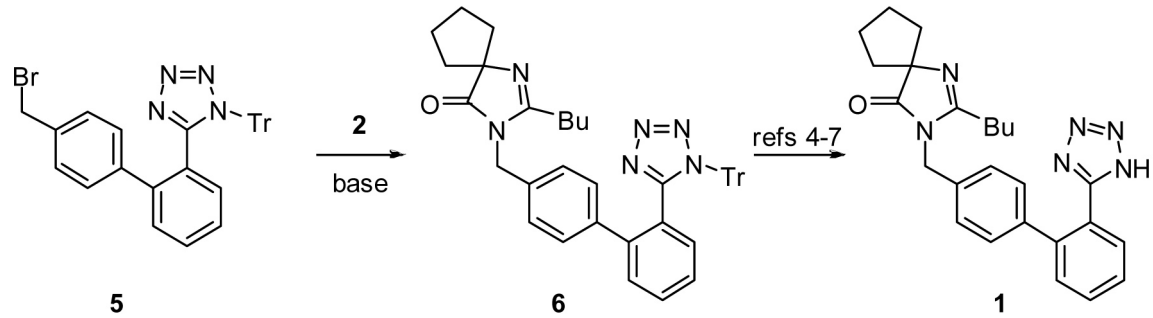
Irbesartan (**1**, SR 47436) is a member of a modern therapeutic group of drugs known as Angiotensin II Receptor Antagonists (AIIRAs) used in treatment of hypertension.[1,2] Clinical results have shown that the blood pressure lowering ability of irbesartan is significantly better than that of losartan (Cozaar®), the first marketed AIIRA. Irbesartan is marketed by two different companies under the names Avapro® (Bristol-Myers Squibb) and Karvea® (Sanofi-Winthrop).

One of the principal parts of documentation of any active pharmaceutical ingredient (API) is description of impurities and/or degradation products which can be present. The specified impurities can be either identified or unidentified. 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 independently synthesized. In general, the impurities could be either process-related or formed by degradation of the drug.

The originally described methods[1,3] of preparation of irbesartan are based on N-alkylation of spiroimidazolone **2** with biphenyl derivatives **3** and the formed intermediates **4** are then converted in several steps into irbesartan (Scheme 1).




**Scheme 1**




**Scheme 2**

More recent procedures[4–6] use 5-(4'-(bromomethyl) biphenyl-2-yl)-1-trityl-1*H*-tetrazole (**5**, BBTT), a common intermediate used in the sythesis of various sartans (Scheme 2). Intermediate tritylirbesartan (**6**) is then detritylated, usually under acid conditions, to provide irbesartan (**1**) and trityl alcohol. Recently we have developed more advantageous method of detritylation in boiling methanol providing irbesartan (**1**) and methyl trityl ether.[7]

## 2. Results and Discussion

Irbesartan APIs produced by these different procedures have different impurity profiles. While two papers describing impurities related to the process shown in Scheme 1 have been published,[8,9] no such report on impurities of the process of Scheme 2 has appeared. In irbesartan API prepared by the procedure, two principle impurities are frequently detected by HPLC. The HPLC-MS data suggested two isomeric structures **7** and **8**. Formation of these impurities is easily explainable by partial deprotection of either **5** or **6** during the alkylation of **2** and the following alkylation of the tetrazole ring providing finaly the mixture of possible tritylated isomers **9** and **10**. The final detritylation then provides impurities **7** and **8**. Structures of impurities **7-10** are given in Fig. 1.

For more precise HPLC determination of the impurity profile of irbesartan we needed to prepare these impurities for establishing their correction factors. Synthesis of both isomers was quite straightforward; it started with irbesartan (**1**), which was alkylated by protected tetrazole derivative (**5**) in acetonitrile/*N*-ethyldiisopropylamine to give a mixture of protected isomers **9** and **10**, containing 53% of **9** and 35% of **10** (HPLC). This result is quite surprising since similar ethylation of candesartan cilexetil with iodoethane[10] gave a mixture of the N-1 and N-2 iso-

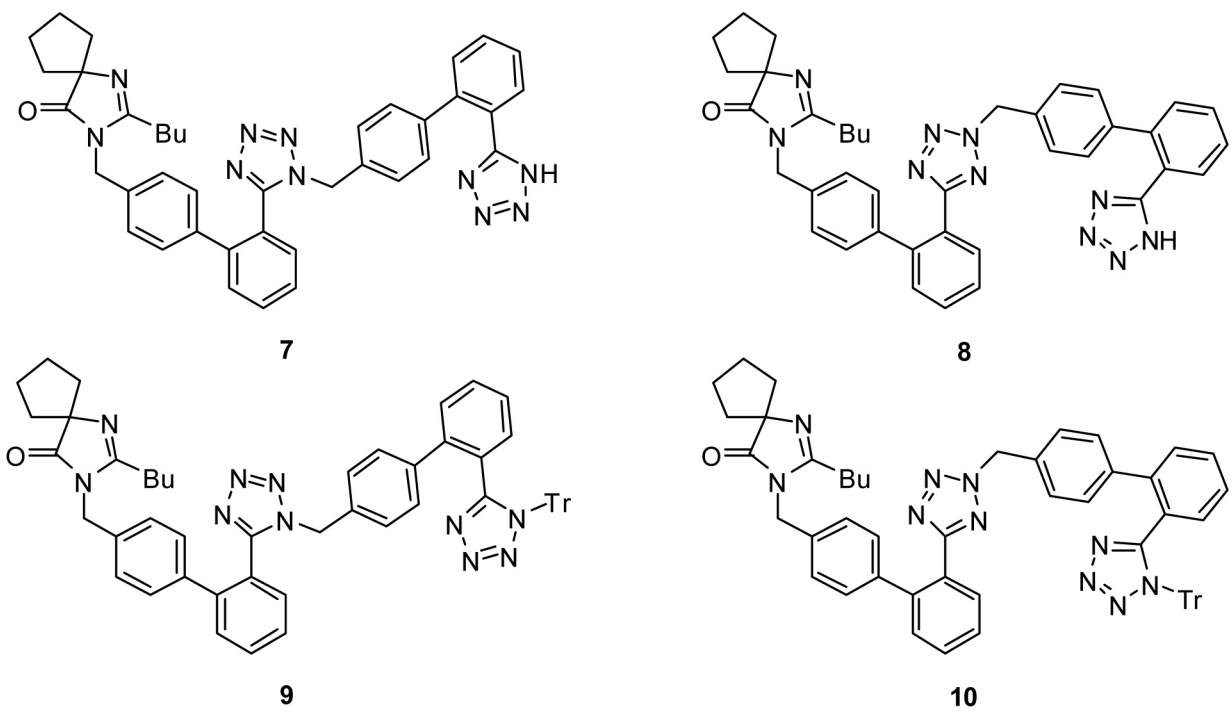



**Figure 1.** Structures of the discussed impurities **7**–**10**.

mers in a ratio of 2 : 3 and with much bulkier (2'-(1-trityl-1*H*-tetrazol-5-yl)biphenyl-4-yl)methyl substituent we expected compound **10** as the major product. Attempts to separate compounds **9** and **10** by flash chromatography provided mixed fractions containing both compounds and only small amount of **9**. A part of the mixture was subjected to centrifugally accelerated axial chromatography to get a minor fraction containing **9**, major mixed fractions containing **9** and **10**, and small amount of **10**. Both compounds **9** and **10** were recrystalized and fully characterized (m.p., $^1$H NMR, $^{13}$C NMR, IR, UV, HRMS). Deprotection of compound **9** in boiling methanol provided the correspon-

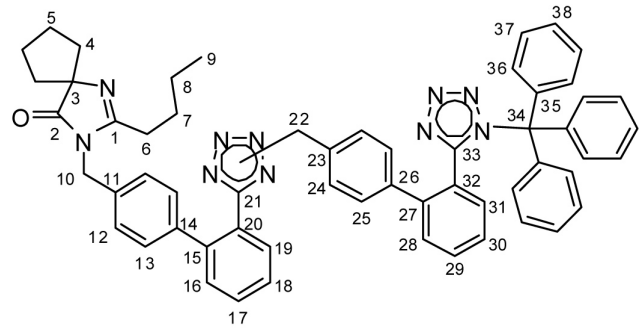


**Figure 2.** Numbering used for the discussed impurities **7**–**10**.

**Table 1.** $^1$H and $^{13}$C NMR assignments for impurities **7** and **9**.

| Position | $\delta_{(c)}$ [ppm] | | $\delta_{(H)}$ [ppm] multiplicity[a] | | Integ. H | $J_{(H,H)}$ | |
|---|---|---|---|---|---|---|---|
| | **9** | **7** | **9** | **7** | | **9** | **7** |
| 1 | 161.35 | 162.32 | | | | | |
| 2 | 186.69 | 186.78 | | | | | |
| 3 | 76.55 | 76.44 | | | | | |
| 4 | 37.40 | 37.31 | 1.80–2.10 m | 1.75 m | 2H | | |
| | | | 1.80–2.10 m | 1.92 m | 2H | | |
| 5 | 26.06 | 25.98 | 1.80–2.10 m | 1.85 m | 4H | | |
| 6 | 28.74 | 28.39 | 2.28 t | 2.19 t | 2H | 7.6 | 7.5 |
| 7 | 27.68 | 27.66 | 1.57 qn | 1.51 qn | 2H | 7.6 | 7.9 |
| 8 | 22.27 | 22.10 | 1.32 sx | 1.30 sx | 2H | 7.6 | 7.5 |
| 9 | 13.68 | 13.55 | 0.86 t | 0.85 t | 3H | 7.3 | 7.3 |
| 10 | 43.18 | 43.23 | 4.66 s | 4.68 s | 2H | | |
| 11 | 136.59 | 135.93 | | | | | |
| 12 | 127.20 | 126.85 | 7.10 m | 7.03 d | 1H | | 8.3 |
| 13 | 129.20 | 129.47 | 7.10 m | 7.11 d | 1H | | 8.3 |
| 14 | 138.41 | 138.41 | | | | | |
| 15 | 141.03[b] | 141.07 | | | | | |
| 16 | 130.20 | 130.54 | 7.52 dd | 7.58 dd | 1H | 7.7, 1.3 | 7.8, 1.2 |
| 17 | 131.61 | 131.81 | 7.60 dt | 7.70 dt | 1H | 7.7, 1.3 | 7.6, 1.3 |
| 18 | 128.10 | 128.19 | 7.37 dt | 7.54 dt | 1H | 7.7, 1.3 | 7.6, 1.3 |
| 19 | 131.29 | 130.97 | 7.25 m | 7.42 dd | 1H | | 7.8, 1.1 |
| 20 | 122.70 | 122.38 | | | | | |
| 21 | 154.38 | 154.52 | | | | | |
| 22 | 50.54 | 50.44 | 4.70 s | 4.87 s | 2H | | |
| 23 | 131.62 | 132.29 | | | | | |
| 24 | 127.20 | 128.14 | 6.55 d | 6.65 d | 2H | 8.1 | 8.3 |
| 25 | 129.60 | 129.31 | 6.94 d | 6.99 d | 2H | 8.1 | 8.3 |
| 26 | 141.59 | 139.88 | | | | | |
| 27 | 141.04[b] | 140.69 | | | | | |
| 28 | 130.50 | 130.40 | 7.26 m | 7.37 dd | 1H | | 7.8, 1.1 |
| 29 | 130.01 | 131.09 | 7.48 m | 7.59 dt | 1H | | 7.6, 1.3 |
| 30 | 127.78 | 128.07 | 7.44 m | 7.51 dt | 1H | | 7.6, 1.3 |
| 31 | 130.30 | 130.72 | 7.89 dd | 7.78 dd | 1H | 7.5, 1.6 | 7.8, 1.2 |
| 32 | 126.23 | 123.41 | | | | | |
| 33 | 163.86 | 155.49 | | | | | |
| 34 | 82.91 | – | | – | | | |
| 35 | 141.19 | – | | – | | | |
| 36 | 130.18 | – | 6.94 d | – | 6H | 8.1 | |
| 37 | 127.59 | – | 6.55 d | – | 6H | 8.1 | |
| 38 | 128.25 | – | 7.31 t | – | 3H | 7.4 | |

[a] – Standard abbreviation used: s = singlet, d = doublet, t = triplet, qn = quintet, sx = sextet, m = complex multiplet; [b] – Interchangeable.

ding compound **7**. The combined fractions were evaporated, the residue was deprotected by refluxing in methanol, and the formed mixture of **7** and **8** was successfully separated by flash chromatography on silica gel to provide pure compounds **7** and **8**. Structures of these complex tetrazole isomers were determined by NMR experiments; the used numbering is shown in Fig. 2.

For the assignment of protons and carbons, several advanced 1D and 2D NMR techniques (COSY, HSQC, HMBC, ROESY, 1D NOESY) were used. D NOESY of impurities **7** and **8** are shown in Figs 3 and 4, respectively. Chemical shifts of protons and carbons are given in Tables 1 and 2, respectively. The differentiation of both impurities of irbesartan were performed using 1D NOESY experiments. In both cases proton 22 was excitated. While for impurity **7** signals of protons 13, 19 and 24 were found (Fig. 3), in the case of impurity **8** (Fig. 4) signals of aliphatic protons 6, 8, 9, in addition to the signals of protons 24, appear.

# 3. Experimental

2-Butyl-1,3-diazaspiro[4.4]non-1-en-4-one (**2**) and 5-(4'-(bromomethyl)biphenyl-2-yl)-1-trityl-1*H*-te-

**Table 2.** $^{1}$H and $^{13}$C NMR assignments for impurities **8** and **10**.

| Position | $\delta_{(c)}$ [ppm] | | $\delta_{(H)}$ [ppm] multiplicity[a] | | Integ. H | $J_{(H,H)}$ | |
|---|---|---|---|---|---|---|---|
| | 10 | 8 | 10 | 8 | | 10 | 8 |
| 1 | 161.66 | 164.76 | | | | | |
| 2 | 186.61 | 184.95 | | | | | |
| 3 | 76.45 | 75.63 | | | | | |
| 4 | 37.36 | 37.36 | 1.80–2.10 m | 1.43 m | 2H | | |
| | | | 1.80–2.10 m | 1.84 m | 2H | | |
| 5 | 26.02 | 22.50 | 1.80–2.10 m | 1.61 m | 2H | | |
| | | | 1.80–2.10 m | 1.84 m | 2H | | |
| 6 | 28.73 | 28.67 | 2.36 t | 1.76 t | 2H | 7.6 | 6.9 |
| 7 | 27.68 | 27.60 | 1.61 qn | 1.26 m | 2H | 7.6 | |
| 8 | 22.22 | 22.50 | 1.37 sx | 1.23 m | 2H | 7.6 | |
| 9 | 13.65 | 13.46 | 0.91 t | 0.82 t | 3H | 7.3 | 7.0 |
| 10 | 43.32 | 43.31 | 4.71 s | 4.76 s | 2H | | |
| 11 | 135.30 | 134.59 | | | | | |
| 12 | 126.30 | 125.69 | 7.10 d | 7.12 d | 2H | 8.2 | 7.9 |
| 13 | 129.68[b] | 130.02 | 7.18 d[c] | 7.33 d | 2H | | 7.9 |
| 14 | 140.43 | 141.66 | | | | | |
| 15 | 141.30 | 141.07 | | | | | |
| 16 | 130.75 | 130.84 | 7.46 m | 7.44 m | 1H | | |
| 17 | 129.91[d] | 130.44 | 757 m | 7.58 m | 1H | | |
| 18 | 127.55[c] | 128.09 | 7.49 m | 7.54 m | 1H | | |
| 19 | 130.45 | 129.90 | 7.83 dd | 8.17 m | 1H | 7.8, 1.1 | |
| 20 | 126.25 | 125.80 | | | | | |
| 21 | 165.41 | 164.85 | | | | | |
| 22 | 56.12 | 55.13 | 5.59 s | 5.61 s | 2H | | |
| 23 | 131.78 | 133.54 | | | | | |
| 24 | 127.50 | 125.91 | 7.05 d | 6.74 d | 2H | 8.2 | 8.6 |
| 25 | 129.72[b] | 129.53 | 7.18 d[c] | 7.03 d | 2H | | 8.2 |
| 26 | 141.73 | 139.46 | | | | | |
| 27 | 141.20 | 140.66 | | | | | |
| 28 | 130.65 | 130.44 | 7.43 m | 7.39 dd | 1H | | 7.9, 0.8 |
| 29 | 129.94[d] | 131.25 | 7.56 m | 7.61 dd | 1H | | 7.5, 1.2 |
| 30 | 127.70 | 128.25 | 7.53 m | 7.57 m | 1H | | |
| 31 | 130.20 | 131.21 | 8.02 dd | 7.75 dd | 1H | 7.4, 1.8 | 7.7, 1.1 |
| 32 | 126.12 | 123.90 | | | | | |
| 33 | 163.80 | 154.58 | | | | | |
| 34 | 82.90 | – | | – | | | |
| 35 | 141.11 | – | | – | | | |
| 36 | 130.17 | – | 6.94 d | – | 6H | 7.3 | |
| 37 | 127.55[d] | – | 7.27 t | – | 6H | 8.0 | |
| 38 | 128.18 | – | 7.35 m | – | 3H | 7.6 | |

[a] – Standard abbreviation used: s = singlet, d = doublet, t = triplet, qn = quintet, sx = sextet, m = complex multiplet; [b] –Interchangeable; [c] – Overlap; [d] – Interchangeable.

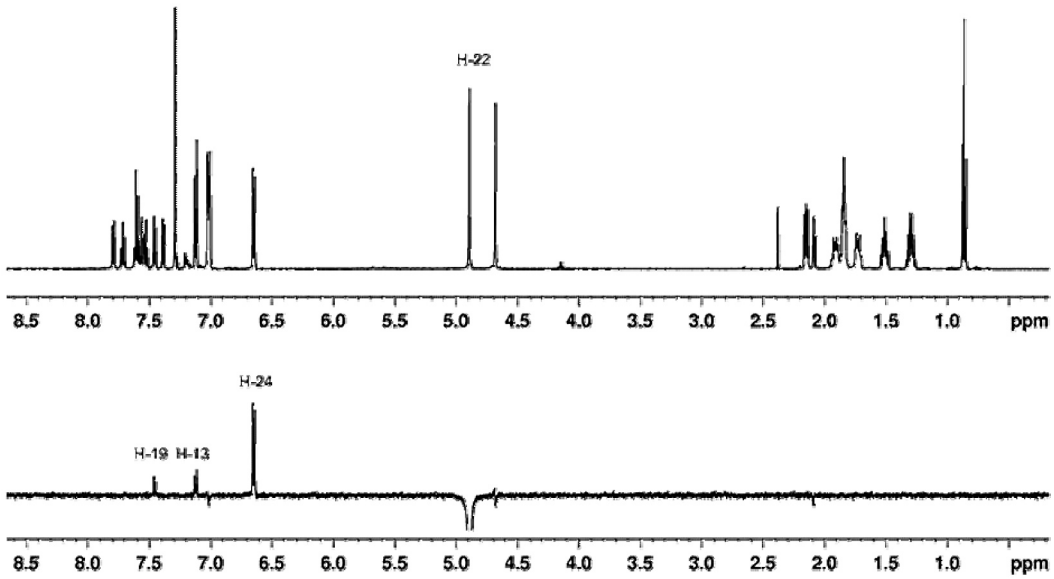



**Figure 3.** 1D NOESY of impurity **7**.

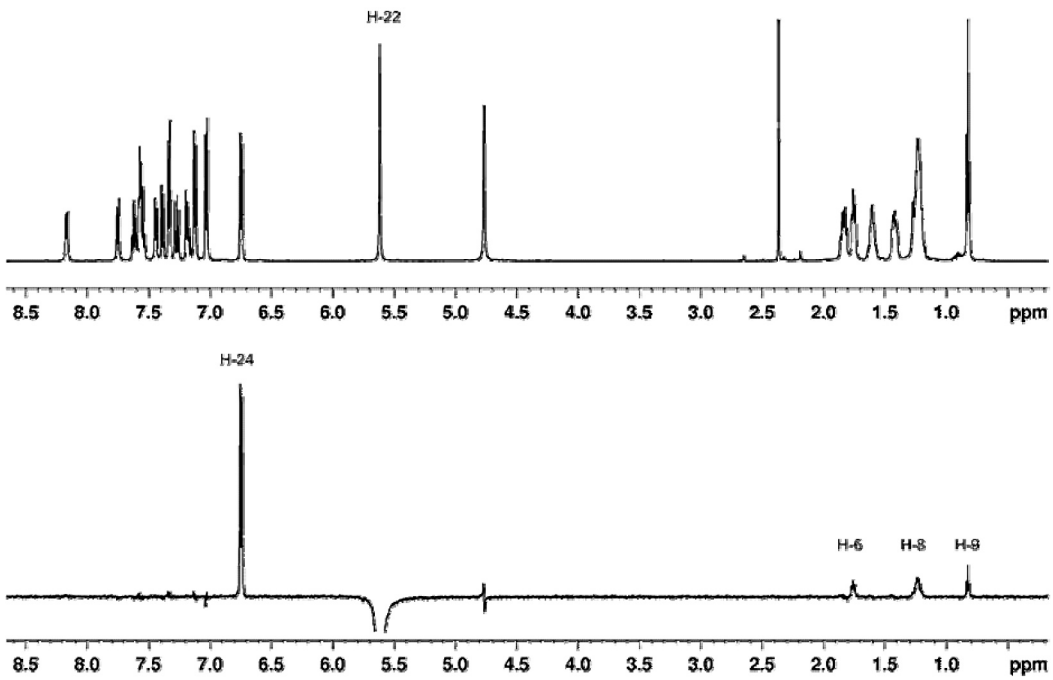



**Figure 4.** 1D NOESY of impurity **8**.

trazole (**5**, BBTT) 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. The IR spectra were measured on a Perkin Elmer Spectrum BX FT-IR machine by the diffuse reflectance method (KBr), wavenumbers are given in $cm^{-1}$. The UV spectra were recorded on a Hewlett-Packard 8452A spectrophotometer (ethanol) in the range 190–400 nm. NMR experiments were carried out on a Bruker Avance 500 at 500.13 MHz ($^1H$), 125.77 MHz ($^{13}C$) and 50.70 MHz ($^{15}N$). Reference for $^1H$ δ ($CDCl_3$) = 7.26 ppm, for $^{13}C$ δ ($CDCl_3$) = 77.0 ppm. All experiments were performed in $CDCl_3$ at 298 K. COSY, HSQC, $^1H$,$^{13}C$ HMBC and $^1H$, $^{15}N$ 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 in-

verse) probeheads equipped with z-gradient coils were employed for all measurements. 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 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 data was 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. The ROESY spinlock was 200 ms. The mixing time for 1D NOESY was optimized to 800 ms.

The Mass spectra (MS/MS; ionization mode AP-CI(+)) were measured on an API 3000 PE machine (Sciex Instruments, Applied Biosystems). The purity of the prepared substances was evaluated by TLC on silica gel (FP KG F 254, Merck) and by 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 $(NH_4)_2HPO_4$ diluted in1000 mL of $H_2O$, pH adjusted to 3.0 with 50% phosphoric acid), and mobile phase B (acetonitrile) was used. Flash chromatography was performed on silica gel Merck, particle size 0.04–0.063 mm. Centrifugally accelerated axial chromatography was done using Cyclograph™ instrument (Analtech) with silica gel pre-scraped rotors.

2-Butyl-3-((2'-(1-((2'-(1-trityl-1*H*-tetrazol-5-yl)biphenyl-4-yl)methyl)-1*H*-tetrazol-5-yl)biphenyl-4-yl)methyl)-1,3-diazaspiro[4.4]non-1-en-4-one (**9**) and 2-Butyl-3-((2'-(1-((2'-(2-trityl-2*H*-tetrazol-5-yl)biphenyl-4-yl)methyl)-1*H*-tetrazol-5-yl)biphenyl-4-yl)methyl)-1,3-diazaspiro[4.4]non-1-en-4-one (**10**).

A mixture of irbesartan (**1**; 2.5 g, 5.8 mmol), 5-(4'-(bromomethyl)biphenyl-2-yl)-1-trityl-1*H*-tetrazole (**5**; 3.4 g, 6.1 mmol) and *N*-ethyldiisopropylamine (1.7 g, 13 mmol) in acetonitrile (30 mL) was stirred at 90 °C under nitrogen for 5 hrs. The mixture was evaporated, the residue was dissolved in ethyl acetate (100 mL), the cloudy solution was washed with water (3 × 20 mL) and dried with magnesium sulfate. The residue after evaporation (5.17 g) contained 4.2% of **5**, 53.1% of **9** and 35.5% of **10** (HPLC). The mixture was subjected to flash chromatography (silica gel; dichloromethane – ethyl acetate 50 : 1) to provide **5** (0.15 g), a mixture of **9** and **10** (3.4 g) and **9** (0.6 g). A part of the mixture (1.0 g) was subjected to centrifugally accelerated axial chromatography using Cyclograph™ (silica gel, from dichloromethane to dichloromethane – ethyl acetate 20 : 1) to give **10** (0.1 g), a mixture of **9** and **10** (0.75 g), and **9** (0.1 g). All mixed fractions were combined, evaporated (4.1 g) and used for further reaction. Both fractions of **9** (0.7 g) were crystallized from methylcyclohexane to give 0.55 g of white crystals. Compound **10** was characterized as obtained without further purification.

*Data for compound **9**:* m.p. 88–92 °C (from methylcyclohexane). $^{1}H$ and $^{13}C$ NMR ($CDCl_3$): See Table 1. IR (KBr): 697 ($\delta_{Ar}$), 746 ($\delta_{Ar}$), 1006 ($\delta_{=CH}$), 1027 ($\delta_{=CH}$), 1343 ($\delta_{CH}$), 1444 ($\delta_{CH}$), 1630 ($\nu_{Ar}$), 1720 ($\nu_{C=O}$), 2848 ($\nu_{CH}$), 2924 ($\nu_{CH}$) $cm^{-1}$. UV (EtOH), $\lambda_{max}$ (log ε): 206.0 (4.99); $\lambda_{infl}$ 252.0 (4.23). HRMS *m/z* calcd for $C_{58}H_{53}N_{10}O$ $[M+H]^+$ 905.44038, found 905.43988.

*Data for compound **10**:* m.p. 73–75 °C (from methylcyclohexane); $^{1}H$ and $^{13}C$ NMR ($CDCl_3$): See Table 2. IR (KBr): 697 ($\delta_{Ar}$), 746 ($\delta_{Ar}$), 1006 ($\delta_{=CH}$), 1032 ($\delta_{=CH}$), 1342 ($\delta_{CH}$), 1444 ($\delta_{CH}$),1629 ($\nu_{Ar}$), 1722 ($\nu_{C=O}$), 2870 ($\nu_{CH}$), 2960 ($\nu_{CH}$) $cm^{-1}$. UV (EtOH), $\lambda_{max}$ (log ε): 206.0 (4.94). HRMS *m/z* calcd for $C_{58}H_{53}N_{10}O$ $[M+H]^+$ 905.44038, found 905. 43951.

3-((2'-(1-((2'-(1*H*-Tetrazol-5-yl)biphenyl-4-yl)methyl)-1*H*-tetrazol-5-yl)biphenyl-4-yl)methyl)-2-butyl-1,3-diazaspiro[4.4]non-1-en-4-one (**7**) and 3-((2'-(2-((2'-(1*H*-Tetrazol-5-yl)biphenyl-4-yl)methyl)-2*H*-tetrazol-5-yl)biphenyl-4-yl)methyl)-2-butyl-1,3-diazaspiro[4.4]non-1-en-4-one (**8**).

A mixture of **9** and **10** (4 g, 4.4 mmol) was refluxed in methanol (75 mL) for 6 h, the mixture was evaporated and the residue was separated by flash chromatography (silica gel; dichloromethane – methanol 20 : 1) to provide compound **7** (1.55 g, 53%) and **8** (0.95 g, 33%).

*Data for compound **7**:* m.p. 218–223 °C (methylcyclohexane – ethyl acetate 1 : 1); $^{1}H$ and $^{13}C$ NMR ($CDCl_3$): See Table 1. IR (KBr): 697 ($\delta_{Ar}$), 746 ($\delta_{Ar}$), 1006 ($\delta_{=CH}$), 1032 ($\delta_{=CH}$), 1337 ($\delta_{CH}$), 1403 ($\delta_{CH}$), 1620 ($\nu_{Ar}$), 1729 ($\nu_{C=O}$), 42857 ($\nu_{CH}$), 2962 ($\nu_{CH}$) $4cm^{-1}$. UV (EtOH), $\lambda_{max}$ (log ε): 206.4 (4.77), 248.8 (4.36). HRMS *m/z* calcd for $C_{39}H_{39}N_{10}O$ $[M+H]^+$ 663.33083, found 663.33044.

*Data for compound **8**:* m.p. 111–114 °C (methylcyclohexane); $^{1}H$ and $^{13}C$ NMR ($CDCl_3$): See Table 2. IR (KBr): 691 ($\delta_{Ar}$), 758 ($\delta_{Ar}$), 1006 ($\delta_{=CH}$), 1033 ($\delta_{=CH}$), 1345 ($\delta_{CH}$), 1436 ($\delta_{CH}$), 1622 ($\nu_{Ar}$), 1732 ($\nu_{C=O}$) 2871 ($\nu_{CH}$), 2956($\nu_{CH}$) $cm^{-1}$. UV (EtOH), $\lambda_{max}$ (log ε): 206.6 (4.84), 252.3 (4.42). HRMS *m/z* calcd for $C_{39}H_{39}N_{10}O$ $[M+H]^+$ 663.33083, found 663.33026.

3-((2'-(2-((2'-(1*H*-Tetrazol-5-yl)biphenyl-4-yl)methyl)-2*H*-tetrazol-5-yl)biphenyl-4-yl)methyl)-2-butyl-1,3-diazaspiro[4.4]non-1-en-4-one (**7**).

A mixture of **9** (0.4 g, 0.44 mmol) and methanol (10 mL) was refluxed for 6 h. The mixture was evaporated and separated by Cyclograph™ (silica gel, from dichloromethane to dichloromethane-ethyl acetate 10 : 1) to provide 0.25 g (85%) of **8**.

## 4. Conclusion

Two principal impurities of irbesartan API prepared *via* its *N*-trityl derivatives are described. The impurities were identified as isomeric N-1 and N-2 (2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl)methyl derivatives of irbesartan. Both compounds were unambigouesly identified by NMR techniques. For assignments of proton and carbon NMR spectra, COSY, HSQC, and HMBC experiments were used. The differentiation of both impurities of irbesartan was performed using 1D NOESY experiments. In both cases proton H-22 was excitated. While for impurity **7** signals of protons 13, 19 and 24 were found, in the case of impurity **8** signals of aliphatic protons 6, 8, and 9 appear. Spectral characteristics (IR, UV, MS) of these compounds are also given.

## 5. Acknowledgements

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## Povzetek

Opisana je sinteza dveh glavnih nečistoč irbesartana prek njegovega *N*-tritilnega derivata. Nečistoče so bile izolirane in nedvoumno identificirane z NMR spektroskopskimi tehnikami. Podana je tudi IR, UV in MS spektroskopska karakterizacija omenjenih spojin.