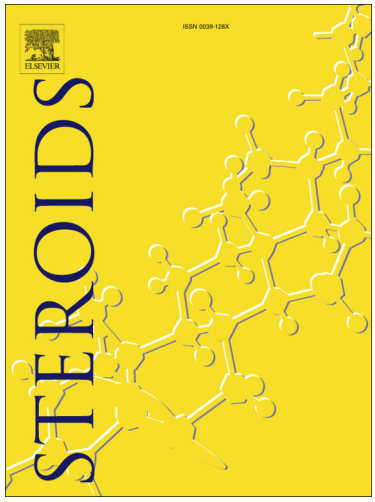

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PII: S0039-128X(17)30093-4
DOI: http://dx.doi.org/10.1016/j.steroids.2017.05.014
Reference: STE 8111

To appear in: *Steroids*

Received Date: 14 February 2017
Revised Date: 25 April 2017
Accepted Date: 31 May 2017

Please cite this article as: Górecki, M., Dziedzic, A., Luboradzki, R., Ostaszewska, A., Frelek, J., Szczepek, W.J., Synthesis and Comprehensive Structural and Physicochemical Characterization of Dutasteride Hydrochloride Hydrate Solvates, *Steroids* (2017), doi: http://dx.doi.org/10.1016/j.steroids.2017.05.014

Synthesis and Comprehensive Structural and Physicochemical Characterization of Dutasteride Hydrochloride Hydrate Solvates

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Abstract

Four crystalline dutasteride hydrochloride hydrate solvates containing respectively methanol, ethanol, acetone and acetonitrile molecules were obtained. All samples were characterized by extensive spectroscopic analysis with infrared spectroscopy (FT-IR), differential scanning calorimetry (DSC) and ^{1}H as well as ^{13}C NMR techniques. For three solvates, *i.e.* methanol, ethanol and acetone solvates, the single crystal X-ray diffraction (SCXRD) experiments were possible, and their respective crystal and molecular structures were determined. The present study allowed to unambiguously establish the molecular composition of solvates as consisting of a dutasteride : hydrogen chloride : water : solvent in a molar ratio of 1:1:1:1 and confirm that they are isostructural. Beyond providing the full spectroscopic characteristic of the compounds, the results obtained have also allowed clarifying of some appearing inconsistencies in published literature regarding the appropriate attribution of IR absorption bands to the relevant molecular vibrations.

Keywords:

Dutasteride

Dutasteride hydrochloride hydrate solvates

Single crystal X-ray analysis

NMR spectroscopy

IR spectroscopy

Differential scanning calorimetry

Chemical compounds

Chemical compounds studied in this article:

- Dutasteride, *i.e*. *N*-[2,5-bis(trifluoromethyl)phenyl]-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide, (PubChem CID: 6918296);
- Finasteride, *i.e*. *N-tert*-butyl-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide, (PubChem CID: 57363);
- Dihydrofinasteride, *i.e*. *N-tert*-butyl-3-oxo-4-aza-5α-androstane-17β-carboxamide, (PubChem CID: 9864387);
- Dihydrodutasteride, *i.e*. *N-tert*-butyl-3-oxo-4-aza-5α-androstane-17β-carboxamide, (PubChem CID: 58077530);
- 3-Oxo-4-aza-5α-androstane-17β-carboxylic acid (PubChem CID: 9818495).

1.Introduction

Dutasteride (**1**), *i.e. N*-[2,5-bis(trifluoromethyl)phenyl]-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide, is the next following the finasteride (**2**) a 4-azasteroid drug that inhibits human 5α-reductase which converts testosterone into the more potent 5α-dihydrotestosterone (DHT). As an analogue of finasteride, it was approved for treatment of benign prostatic hyperplasia (BPH), commonly known as enlarged prostate, in 2002 [1]. From a structural point of view, finasteride and dutasteride are *N*-substituted derivatives of 3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide with 1,1-dimethylethyl (*tert*-butyl) and 2,5-bis(trifluoromethyl)phenyl substituent at N21 atom, respectively (Fig. 1). Although the therapeutic effectiveness of both drugs is considered to be very similar, control studies demonstrated that dutasteride as being a triple inhibitor of 5α-reductase types 1, 2 and 3, more efficiently reduces the concentration of active DHT in comparison to finasteride which is, in turn, a dual inhibitor of 5α-reductase isoforms 2 and 3 (94-97% *vs*. 68-85%, respectively) [2].

Within an extensive variety of works concerning the crystalline forms of dutasteride, we turned our attention to the paper by Nanubolu *et al.* [3] concerning dutasteride hydrochloride hydrate ethanol solvate. Inspired by this publication, we decided to check which kind of product will be formed as a result of treatment dutasteride with concentrated hydrochloric acid in other water miscible solvents. Our motivation was also caused by the fact that drugs frequently exist in solvated forms. Therefore, their characteristics are the subject of basic research often requiring a systematic and comprehensive study [4]. As good solvents for this purpose methanol, acetone, acetonitrile and acetic acid were chosen. We expected a possibility of the following product types formation:

(a) “hydrochloride”, as in the case of linezolid dihydrochloride [5];

(b) “hydrated hydrochloride”, as in the case of calix[4]arene tetramethylamide hydrochloride trihydrate [6];

(c) “solvated hydrochloride hydrate”, as in the case of calix[4]arene tetramethylamide hydrochloride hydrate dichloromethane solvate [6] and dutasteride hydrochloride hydrate ethanol solvate reported by Nanubolu *et al.* [3] or

(d) other(s).

For comparison with the Nanubolu *et al.* [3] results, also repetition of the synthesis of dutasteride hydrochloride hydrate ethanol solvate was planned. Next, we decided to perform full physicochemical characterization of synthesized compounds using infrared spectroscopy

(IR) in KBr, Nuclear Magnetic Resonance spectroscopy (^{1}H and ^{13}C NMR) in solution and differential scanning calorimetry (DSC). In the case of obtaining suitable crystals, single crystal X-ray diffraction (SCXRD) analysis was also planned.

To facilitate proper attribution of absorption bands in the IR spectra of newly synthesized dutasteride hydrochloride solvates and to simplify comparison with the existing literature data we decided to synthesize two appropriate model compounds, namely, dihydrofinasteride **4** and dihydrodutasteride **5** (Fig. 1). Measuring their infrared spectra combined with theoretical simulation of the IR spectrum of dutasteride form I having one dutasteride molecule in the asymmetric unit [7] should lead to an unambiguous assignment of the individual absorption bands to the corresponding vibrations.

2. Experimental

2.1. General

Melting points were recorded on MEL-TEMP II apparatus (Laboratory Devices Inc., Box 6402, Holliston MA 01746-6402 USA). FT-IR spectra were recorded using JASCO FTIR-6200 spectrometer equipped with DLATGS detector and temperature regulator. The spectra were obtained using KBr pressed pellets (~1 mg per 300 mg KBr) in the range of 4000-400 cm^{-1} with 4 cm^{-1} resolution. Theoretical IR spectrum was calculated for the simplest model (single molecule) in vacuum using the Gaussian09 program [8] at the B3LYP/TZVP level of theory. As an input structure optimized geometry of the dutasteride form I taken from the literature X-ray data [7] was used. The spectrum was simulated with Lorentzian line shapes of 8 cm^{-1} half-widths at half-height, and no scaling factor was applied. DSC measurement was conducted on a Universal V4.3A TA Instrument. All samples were tested in the temperature range of 30 to 300 °C. Argon was used as a purge gas at an ambient mode. The heating rate was kept constant at 5 or 10 °C min^{-1}. Aluminum sample pans were used for all samples. A single point calibration was carried out using indium as a standard sample. Single crystal X-ray diffraction (SCXRD) measurements were carried out using Agilent Supernova diffractometer, at 100 K with monochromated Cu K_α radiation (1.54184 Å). The data reduction was made using CrysAlisPRO [9] software. The structures were solved by direct methods and refined on F^2 by full-matrix least squares by using SHELXS97 and SHELXL97 [10]. All non-hydrogen atoms were refined as anisotropic while hydrogen atoms were placed

in calculated positions and refined in riding mode. Nuclear Magnetic Resonance (^{1}H NMR, ^{13}C NMR) in solution were performed using Bruker DRX 500 Avance spectrometer at 303 K operating at 500.13 MHz for ^{1}H and 125.76 MHz for ^{13}C spectra, Varian VNMRS 500 spectrometer at 298 K operating at 499.83 MHz for ^{1}H and 125.68 MHz for ^{13}C spectra and Varian VNMRS 600 spectrometer at 298 K operating at 599.84 MHz for ^{1}H spectra. 5 mm TBI 1H/13C/BB Z-GRD (inverse type) probe was used in both cases. TMS was used as an internal reference for proton spectra. The standard procedures were used for acquisition and processing of the data.

Commercially available reagents [*tert*-butylamine (*tert*-$BuNH_2$), 4-(*N,N*-dimethylamino)pyridine (DMAP), *N,N*-dimethylformamide (DMF), pyridine (Py), thionyl chloride ($SOCl_2$) and 2,5-bis(trifluoromethyl)aniline] and pure solvents [acetic acid, acetone, acetonitrile, ethanol (99.8%), chloroform, dichloromethane, ethyl acetate, heptanes, methanol and toluene] were used without additional purification in the preparation of dutasteride hydrochloride solvates as well as in the synthesis of model compounds **4** and **5**. Both the dutasteride (**1**, purity 99.27%) and 3-oxo-4-aza-5α-androstane-17β-carboxylic acid (**3**) are commercially available from Afine Chemicals Ltd. and Hangzhou Imaginochem Co. Ltd., respectively.

Commercial dutasteride was purified by column chromatography and finally was crystallized from a mixture of ethyl acetate-heptane [11] to give anhydrous crystalline form I, called in this work sample **D I**. **IR**, ν_{max} (cm^{-1}): 3470, 3170, 3096, 1714, 1680, 1652, 1592, 1540, 1435, 1333, 1318, 1258, 1173, 1141, 1113, 1088, 1038, 828 (lit. [12], 3470, 3171, 3096, 1714, 1679, 1652, 1592, 1540, 1435, 1332, 1318, 1259, 1173, 1141, 1113, 1087, 1038, 828). **^{1}H NMR** (500 MHz, $CDCl_3$) see Table 1.

Commercial 3-oxo-4-aza-5α-androstane-17β-carboxylic acid (**3**) has **IR**, ν_{max} (cm^{-1}): 3261, 3190, 1729, 1636, 1482, 1439, 1397, 1359, 1212, 1184, 1160, 1119, 720 (lit. [13], 3585, 3261, 3193, 1728, 1636, 1482, 1400, 1360, 1212, 1189, 1163, 1120, 721).

2.2. Preparation of mono(dutasteride) monohydrochloride monohydrate mono(solvent) solvates

2.2.1. First attempt of mono(dutasteride) monohydrochloride monohydrate mono(ethanol) solvate preparation

To a stirred solution of dutasteride (**D I**, 0.32 g) in ethanol 99.8% (48 mL) concentrated hydrochloric acid (44 drops) was added at room temperature (r.t.). The obtained solution was

left standing in an open flask at r.t. under normal pressure for 4 days. The formed crystals were filtered off and dried at r.t. under reduced pressure to yield sample **D III** (295 mg; 91%) of the dutasteride form III, *i.e*. so-called "dutasteride hemihydrate" [3,14]. **IR**, ν_{max} (cm^{-1}): 3463, 3427, 3198, 1717, 1693, 1674, 1594, 1533, 1432, 1333, 1317, 1262, 1175, 1146, 1127, 1085, 1040, 822 (lit. [14], 3465, 3428, 3202, 3100, 3048, 1717, 1694, 1675, 1594, 1534, 1433, 1333, 1318, 1264, 1179, 1146, 1129, 1086, 1042, 824). **^{1}H NMR** (600 MHz, $CDCl_3$) see Table 1.

2.2.2. Second attempt of mono(dutasteride) monohydrochloride monohydrate mono(ethanol) solvate preparation

To a warm (~35 °C) and stirred solution of dutasteride (**D I**, 1.169 g) in ethanol (8.5 mL) concentrated hydrochloric acid (0.19 mL; 1 eq) was added. The obtained solution was left standing in an open flask at r.t. under normal pressure for 19 hours. The crystals were filtered off, washed with ethanol and dried at r.t. under reduced pressure to yield sample **D II** (818 mg) of the dutasteride form II (hydrated dutasteride [7,15]). **IR**, ν_{max} (cm^{-1}): 3464, 3448, 3388, 3293, 3194, 1712, 1697, 1685, 1672, 1593, 1539, 1526, 1432, 1332, 1316, 1263, 1181, 1170, 1146, 1127, 1087, 1040, 836, 818 (lit. [16], 3450, 3391, 3296, 3197, 1712, 1674, 1594, 1540, 1467, 1435, 1318, 1263, 1181, 1146, 1088, 1041, 836, 818). **^{1}H NMR** (600 MHz, $CDCl_3$) see Table 1.

*2.2.3. Mono(dutasteride) monohydrochloride monohydrate mono(ethanol) solvate $C_{27}H_{30}F_6N_2O_2 \cdot HCl \cdot H_2O \cdot C_2H_5OH$ (sample **D 1**)*

To a hot (~50 °C) and stirred solution of dutasteride (**D I**, 1.08 g) in ethanol (10.0 mL) concentrated hydrochloric acid (8.0 mL; 45.6 eq) was added. The obtained solution was left standing at r.t. under normal pressure for four days. The crystals were filtered off, washed with ethanol and dried at r.t. under reduced pressure to yield sample **D 1** (1.118 g; 87%). **IR**, ν_{max} (cm^{-1}): 3437, 3115, 3044, 1653, 1591, 1529, 1433, 1336, 1319, 1182, 1150, 1132, 1122, 1082 (lit. [3], 3462.4, 3199.8, 1717.6, 1672.8, 1594.1, 1531.6. **^{1}H NMR** (500 MHz, $CDCl_3$) see Table 1. **^{1}H NMR** (500 MHz, DMSO-d_6) see Table 5. **^{13}C NMR** (125 MHz, DMSO-d_6) see Table 6. **Elemental analysis** for $C_{29}H_{39}ClF_6N_2O_4$: calcd (%) C, 55.37; H, 6.25; Cl, 5.64; F, 18.12; N, 4.45, found (%) C, 55.15; H, 6.21; Cl, 5.76; F, 17.61; N, 4.44.

*2.2.4. Mono(dutasteride) monohydrochloride monohydrate mono(methanol) solvate $C_{27}H_{30}F_6N_2O_2 \cdot HCl \cdot H_2O \cdot CH_3OH$ (sample **D 2**)*

To a hot (~50 °C) and stirred solution of dutasteride (**D I**, 1.09 g) in methanol (10.0 mL) concentrated hydrochloric acid (8.0 mL; 45 eq) was added. The obtained solution was left standing overnight at r.t. The crystals were filtered off, washed with methanol and dried at r.t. under reduced pressure to yield sample **D 2** (0.912 g; 72%). **IR**, ν_{max} (cm^{-1}): 3451, 3114, 3062, 3044, 1652, 1590, 1531, 1432, 1335, 1317, 1266, 1171, 1149, 1129, 1082, 1032. **^{1}H NMR** (500 MHz, DMSO-d_6) see Table 5. **^{13}C NMR** (125 MHz, DMSO-d_6) see Table 6. **Elemental analysis** for $C_{28}H_{37}ClF_6N_2O_4$: calcd (%) C, 54.68; H, 6.06; Cl, 5.76; F, 18.53; N, 4.55, found (%) C, 54.58; H, 6.25; Cl, 5.76; F, 18.06; N, 4.43.

The filtrate deposited a second crop of crystals. They were filtered off, washed with methanol and dried at r.t. under reduced pressure to yield an impure sample of the mono(dutasteride) monohydrochloride monohydrate mono(methanol) solvate (sample **D 2a**; 0.165 g; *ca*. 13%). **IR**, ν_{max} (cm^{-1}): 3452, 3221, 3107, 1682, 1652, 1590, 1556, 1531, 1431, 1335, 1317, 1264, 1172, 1147, 1128 and 1082.

*2.2.5. Mono(dutasteride) monohydrochloride monohydrate mono(acetone) solvate $C_{27}H_{30}F_6N_2O_2 \cdot HCl \cdot H_2O \cdot (CH_3)_2CO$ (sample **D 3**)*

To a hot (~45 °C) and stirred solution of dutasteride (**D I**, 1.09 g) in acetone (15.0 mL) concentrated hydrochloric acid (8.0 mL; 45 eq) was added. The obtained solution was left standing overnight at r.t. The crystals were filtered off, washed with acetone and dried at r.t. under reduced pressure to yield sample **D 3** (1.017 g; 77%). **IR**, ν_{max} (cm^{-1}): 3106, 1712, 1655, 1590, 1524, 1428, 1316, 1167, 1146, 1126, 1083. **^{1}H NMR** (500 MHz, DMSO-d_6) see Table 5. **^{13}C NMR** (125 MHz, DMSO-d_6) see Table 6. **Elemental analysis** for $C_{30}H_{39}ClF_6N_2O_4$: calcd (%) C, 56.20; H, 6.13; Cl, 5.53; F, 17.78; N, 4.37, found (%) C, 55.95; H, 6.14; Cl, 5.53; F, 17.92; N, 4.33.

*2.2.6. Mono(dutasteride) monohydrochloride monohydrate mono(acetonitrile) solvate $C_{27}H_{30}F_6N_2O_2 \cdot HCl \cdot H_2O \cdot CH_3CN$ (sample **D 4**)*

To a hot (~50 °C) and stirred solution of dutasteride (**D I**, 1.6 g) in acetonitrile (20.0 mL) concentrated hydrochloric acid (24.0 mL; 92.3 eq) was added. The obtained solution was stirred for 1 hour. The crystals were filtered off, washed with acetonitrile and dried at r.t. under reduced pressure to yield mono(dutasteride) monohydrochloride monohydrate mono(acetonitrile) solvate, sample **D 4** (1.529 g; 81%). **IR**, ν_{max} (cm^{-1}): 3114, 2258, 1658, 1591, 1529, 1430, 1335, 1316, 1265, 1169, 1146, 1127, 1084. **^{1}H NMR** (500 MHz, DMSO-d_6) see Table 5. **^{13}C NMR** (125 MHz, DMSO-d_6) see Table 6. **Elemental analysis** for

$C_{29}H_{36}ClF_6N_3O_3$: calcd (%) C, 55.81; H, 5.81; Cl, 5.68; F, 18.27; N, 6.73, found (%) C, 55.58; H, 5.81; Cl, 5.69; F, 17.88; N, 6.50.

The filtrate was left standing at r.t. overnight. The formed crystals were filtered off, washed with acetonitrile and dried at r.t. under reduced pressure to yield a sample **D 4a** (0.197 g), which does not contain dutasteride. **IR**, ν_{max} (cm^{-1}): 3141, 3044, 2808, 2006, 1756 and 1402 (all very broad bands).

2.2.7 The attempted preparation of mono(dutasteride) monohydrochloride monohydrate mono(acetic acid) solvate

To a hot (~70 °C) and stirred solution of dutasteride (**D I**, 2.25 g) in acetic acid (8.0 mL) concentrated hydrochloric acid (20.0 mL; 54.7 eq) was added. The obtained solution was left standing overnight at r.t. The crystals were filtered off, washed with a mixture of acetic acid-water (2:5, 28 mL) and dried at r.t. under reduced pressure to yield impure mono(dutasteride) monohydrochloride monohydrate mono(acetic acid) solvate, sample **D 5** (2.271 g). **IR**, ν_{max} (cm^{-1}): 3162, 1766, 1742, 1713, 1661, 1591, 1524, 1495, 1432. **^{1}H NMR** (500 MHz, DMSO-d_6), δ (ppm): 0.67 (3H, s, H-18), 0.87 (3H, s, H-19), 1.93 (2.27H, s, $C\underline{H_3}COOH$), 2.61 (1H, t, J~9.3 Hz, H-17α), 3.22 (1H, dd, J~12.6 and 3.0 Hz, H-5α), 5.67 (1H, d, J~9.9 Hz, H-2), 6.88 (1H, d, J~9.9 Hz, H-1), 7.15 (vbr s, $CH_3COO\underline{H}$), 7.58 (br s, H-N4), 7.79 (1H, d, J~8.2, H-4'), 7.94 (1H, s, H-6'), 7.98 (1H, d, J~8.2, H-3'), 9.46 (1H, s, H-N21). **Elemental analysis** for $C_{29}H_{37}ClF_6N_2O_5$: calcd (%) C, 54.16; H, 5.80; Cl, 5.51; F, 17.73; N, 4.36, found (%) C, 55.11; H, 5.84; Cl, 4.88; F, 19.08; N 4.60.

*2.3. Synthesis of the known compounds **4** and **5** as models for IR bands assignment*

*2.3.1. N-(tert-butyl)-3-oxo-4-aza-5α-androstane-17β-carboxamide (dihydrofinasteride, **4**)*

Lactam-acid **3** (3.00 g, 9.40 mmol, 1eq) was treated with chloroform (80 mL), pyridine (3.8 mL, 47.17 mmol, 5.02 eq) and *N,N*-dimethylformamide (500 µL), and stirred at r.t. for 30 min. Then the reaction mixture was cooled (−8 °C) and thionyl chloride (1.7 mL, 23.3 mmol, 2.48 eq) was added. The cooling bath was removed, and stirring was continued at r.t. for 3 hours. DMAP (80 mg) and *tert*-butylamine (7.2 mL, 67.96 mmol, 7.23 eq) were added, and the reaction mixture was stirred at r.t. for 20 hours. The reaction mixture was treated with water (80 mL), and the organic phase was separated. The aqueous phase was re-extracted with chloroform (30 mL), and the organic layer was separated. The organic extracts were combined, washed with water (100 mL), dried over anhydrous $MgSO_4$, filtered and

concentrated under reduced pressure. The obtained residue (3.30 g) was purified by column chromatography on silica gel, eluting with methylene chloride-methanol mixtures (98:2 and 95:5). The fractions containing main product (TLC) were combined and evaporated to dryness. Crystallization of the residue from dichloromethane-ethyl acetate yielded lactam-amide **4** (2.65 g; 84%). **Mp**: 270-272 °C (lit.[18], 276-277 °C, lit. [19], 280-284 °C). **IR**, ν_{max} (cm^{-1}): 3425, 3195, 3095, 1698, 1670, 1631, 1502, 1451, 1404, 1367, 1360, 1309, 1256, 1232 (lit. [16], 3425, 1698, 1670, 1502, 1367). **^{1}H NMR** (500 MHz, $CDCl_3$), δ (ppm): 0.69 (3H, s, H-18), 0.79 (1H, td, J *ca.* 11.5 and 3.9 Hz), 0.90 (3H, s, H-19), 1.35 [9H, s, -C($C\underline{H}_3$)$_3$], 1.94 (1H, m), 2.01 (1H, t, J *ca.* 9 Hz, H-17α), 2.15 (1H, m), 2.41 (2H, m), 3.05 (1H, dd, J *ca.* 12.3 and 3.7 Hz, H-5α), 5.08 (1H, s, NH), 6.17 (1H, s, NH) (lit. [18], 0.69 (H-19), 0.91 (H-18), 1.35 (C($C\underline{H}_3$)$_3$, 3.04 (H-5α), 5.39 (H-N4), 6.07 (H-N21), lit. [19], 0.69 (3H, s), 0.70-0.90 (1H, m), 0.91 (3H, s), 1.35 (9H, s), 2.12 (2H, m), 2.41 (2H, m), 3.07 (1H, dd), 5.07 (1H, brs), 5.66 (1H, brs)).

*2.3.2. N-[2,5-bis(trifluoromethyl)phenyl]-3-oxo-4-aza-5α-androstane-17β-carboxamide (dihydrodutasteride, **5**)*

Lactam-acid **3** (3.00 g) was treated with toluene (100 mL) and heated under reflux for 30 min. Then 20 mL of toluene were distilled off. The resulting mixture was cooled to 2 °C, pyridine (1.9 mL) and thionyl chloride (0.85 mL) were added, and the resulting mixture was stirred at r.t. for 2.5 h. Next, 2,5-bis(trifluoromethyl)aniline (1.6 mL) was added, and the reaction mixture was stirred at room temperature for 8 days. Then the mixture was diluted with chloroform (100 mL), treated with water (100 mL) and acidified with 5 M hydrochloric acid. The organic layer was separated. The aqueous layer was re-extracted with chloroform (50 mL). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$ and filtered. The filtrate was evaporated to dryness, and the residue was chromatographed on silica gel. Fractions eluted with a mixture dichloromethane-methanol (98:2), containing the product, were collected and evaporated to dryness. The residue was crystallized from ethanol to yield lactam-amide **5** (2.80 g; 56%). **Mp**: 244-246 °C (lit. [11], 245-247 °C, lit.[20], 250-252 °C). **IR**, ν_{max} (cm^{-1}): 3466, 1705, 1665, 1592, 1538, 1474, 1434, 1335, 1318, 1262, 1179, 1131, 1086, 1040. **^{1}H NMR** (500 MHz, $CDCl_3$), δ (ppm): 0.79 (3H, s, H-18), 0.84 (1H, m), 0.91 (3H, s, H-19), ~2.08 (2H, m), 2.28 (1H, m), 2.36 (1H, t, J *ca.* 9.1 Hz, H-17α), 2.40 (2H, m), 3.07 (1H, dd, J *ca.* 12.2 and 3.5 Hz, H-5α), 6.27 (1H, s, H-N4), 7.45 (1H, d, J=8.2 Hz, H-4'), 7.52 (1H, s, H-6'), 7.73 (1H, d, J=8.2 Hz, H-3'), 8.77 (1H, s, H-

N21) (lit. [20], 0.79 (3H, s, H-18), 0.84 (1H, m, H-9), 0.92 (3H, s, H-19), 2.36 (1H, t, H-17), 3.07 (1H, dd, H-5), 6.07 (1H, br, H-N4), 7.45 (1H, d, H-4'), 7.51 (1H, br s, H-N21), 7.73 (1H, d, H-3'), 8.78 (1H, br s, H-6')).

3. Results and discussion

3.1. Preparation of dutasteride hydrochloride salts

The first attempt to obtain known "dutasteride hydrochloride hydrate ethanol solvate" by a procedure based on that described by Nanubolu *et al.* [3] failed. In our hands, however, treatment of an ethanolic solution of dutasteride with concentrated hydrochloric acid at r.t. gave a clear solution from which crystals were dropped out due to evaporation at r.t. under normal pressure. The IR spectrum shows the main absorption bands at 3463, 3198, 1717, 1674, 1594 and 1533 cm^{-1} *i.e.*, at practically the same positions as reported by Nanubolu *et al.* for "dutasteride hydrochloride hydrate ethanol solvate" (3462.4, 3199.8, 1717.6, 1672.8, 1594.1 and 1531.6 cm^{-1}, respectively) [3]. However, to our surprise, the shape of the spectrum recorded by us was the same as that published for dutasteride form III [14]. The ^{1}H NMR spectrum of the obtained crystals recorded in $CDCl_3$ displays signals belonging to dutasteride and absence of signals coming from ethanol and differed distinctly from the spectrum of the mono(dutasteride) monohydrochloride monohydrate mono(ethanol) solvate (sample **D 1)** also recorded in $CDCl_3$ (see Table 1). Therefore, in the current work, the isolated crystals are called sample **D III**.

It is well known, that formation of salts in many cases requires higher reaction temperatures, as in the case, for example, of the creation of linezolid salts [5]. Therefore, in the second attempt, the warm (~35 °C) solution of dutasteride in ethanol was treated with ~1 equivalent of concentrated hydrochloric acid. Unexpectedly, evaporation of the obtained solution at r.t. under normal pressure gave crystals identified by their FT-IR spectrum as dutasteride form II. The shape of the IR spectrum was the same as that published for this compound [16]. The ^{1}H NMR spectrum of the obtained crystals recorded in $CDCl_3$ shows signals belonging to dutasteride and presents only traces of signal coming from methylene (-CH_2-) group of ethanol at *ca.* 3.7 ppm. It differs from the spectrum of the mono(dutasteride) monohydrochloride monohydrate mono(ethanol) solvate (sample **D 1**) also recorded in $CDCl_3$ (see Table 1). Therefore, in this work, the isolated crystals are called sample **D II**.

The IR and ^{1}H NMR experiments clearly show that the formation of expected compounds requires both higher temperature and a large excess of concentrated hydrochloric acid. Thus, next experiments in solvents such as ethanol, methanol, acetone, acetonitrile and acetic acid were carried out at higher temperatures and with the use of *ca.* 45-93 equivalents of concentrated hydrochloric acid. In each case, except for the experiment in acetic acid, the first crop of crystals (**D 1**, **D 2**, **D 3,** and **D 4**, respectively) gave the expected pure mono(dutasteride) monohydrochloride monohydrate mono(solvent) solvates. The composition of the obtained crystals was confirmed by elemental analysis (see Experimental) and ^{1}H NMR (Table 5) as well as ^{13}C NMR (Table 6) spectra in DMSO-d_6 solution.

In the case of acetic acid, the formed crystals gave incorrect elemental analysis which indicated the too high content of C, N and F, and too low content of Cl than required for pure mono(dutasteride) monohydrochloride monohydrate mono(acetic acid) solvate. ^{1}H NMR spectrum of this sample in DMSO-d_6 showed dutasteride : acetic acid molar ratio *ca.* 1 : 0.75. Therefore, this product we have excluded from further consideration.

The filtrates from reactions in methanol and acetonitrile left overnight at r.t. produced the second crop of crystals. In the case of methanol, isolated crystals **D 2a** were impure mono(dutasteride) monohydrochloride monohydrate mono(methanol) solvate. In acetonitrile, however, an unknown crystalline substance **D 4a** not containing dutasteride was isolated and was not investigated further.

*3.2. Synthesis of the model compounds **4** and **5***

Starting from the commercially available lactam-acid **3** two model compounds necessary for the IR spectra comparisons were synthesized (Fig. 1). The two amides **4** and **5** were obtained by treatment of the generated *in situ* intermediate acyl chloride with *tert*-butylamine and 2,5-bis(trifluoromethyl)aniline, respectively. Both compounds were purified by column chromatography. The structures of amides **4** and **5** were determined by FT-IR and ^{1}H NMR spectra and confirmed by comparison with the data reported in the literature.

3.3. Single crystal X-ray diffraction (SCXRD) analysis

The crystal structures of the obtained solvates **D 1**, **D 2**, and **D 3** are shown in Fig. 2. Crystallographic data [17] presented in Table 2 and particularly the values of torsion angles and bond lengths given in Table 3 show that the investigated by us sample of

mono(dutasteride) monohydrochloride monohydrate mono(ethanol) solvate (**D 1**) has the same crystal form as that previously described by Nanubolu *et al*. [3]. Thus our and literature IR (KBr) data for this compound should be practically the same.

All examined structures **D 1**, **D 2**, and **D 3** exhibit similar arrangement of the dutasteride molecules. Also, in all cases both amide N atoms bind to Cl^- ions, making N-H…Cl^- hydrogen bonds. Water molecules form hydrogen bonds with Cl^- ions and dutasteride O atom of lactam carbonyl, which results in identical hydrogen bond networks in all structures. Thus, with small deviations in the cell parameters (see Table 2), all those structures may be assumed as isostructural. This may be clearly seen with overlaying fragments of the examined structures, as it is shown in Fig. 3.

Data presented in Table 3 shows that C-N bond distances for lactam (C3-N4) and phenylamide (C20-N21) moieties in hydrochloride salts **D 1**, **D 2**, and **D 3** are shortened (1.292-1.317 Å and 1.342-1.355 Å, respectively), compared to those of non-protonated and non-solvated form I [7] (1.334 Å and 1.385 Å, respectively). Also, the C2-C3 bond distances of hydrochloride salts (1.455-1.471 Å) are shorter compared to that of form I (1.486 Å). However, the C=O bond lengths for lactam (C3=O) and phenylamide (C20=O) moieties in hydrochloride salts are lengthened (1.277-1.290 Å and 1.223-1.238 Å, respectively) compared to those of form I [7] (1.241 Å and 1.215 Å, respectively). Greater lengthening of the lactam C=O bond clearly shows that all investigated dutasteride hydrochlorides are protonated at lactam carbonyl oxygen atom as it was stated by Nanubolu *et al*. [3].

*3.4. Infrared spectroscopy of dutasteride hydrochloride hydrate solvates **D 1 – D 4***

The dutasteride hydrochloride hydrate solvates show four characteristic absorption bands over 1510 cm^{-1}. The first one, very broad, located at 3110±5 cm^{-1} corresponds to N-H (ene-lactam and phenylamide) and O-H (water) stretching vibrations. In the carbonyl absorption region, all of them have one absorption band at *ca.* 1657±5 cm^{-1}. However, the frequencies of these two absorption bands strongly differ from the values reported in the chemical literature for "dutasteride hydrochloride hydrate ethanol solvate" (3462.4, 3199.8, 1717.6 and 1672.8 for phenylamide N-H, cyclic amide N-H, phenylamide C=O and lactam C=O, respectively) [3]. The third characteristic band lies at *ca.* 1590 cm^{-1}. Its origin was deduced from analysis of the IR spectra of compounds **1**–**5**. The IR spectra of lactam-acid **3** (see Table 4) and dihydrofinasteride **4** (see Table 4) show no absorption band at *ca.* 1596±6 cm^{-1} whereas finasteride **2** polymorphs reveal the absorption band at *ca.* 1600 cm^{-1} [21]. Therefore this band

is associated with the presence of the C1=C2 double bond. However, both dihydrodutasteride **5** (see Table 4) and dutasteride **1** crystalline forms **D I**, **D II**, and **D III** absorb at *ca.* 1593 cm^{-1}. In this case, the absorption band is associated with the presence of phenyl ring for dihydrodutasteride **5**, and with the C1=C2 double bond and phenyl ring for dutasteride **1**. Therefore, the third band lying at *ca.* 1590 cm^{-1} in the dutasteride hydrochloride solvates corresponds to stretching vibrations of C1=C2 double bond and C=C in arene ring. The last absorption band of the dutasteride hydrochloride solvates lies in the range 1524-1532 cm^{-1}. It is absent in the spectra of lactam-acid **3** and *N*-*tert*-butylamides **4** and **2** [21] but is present in the spectra of *N*-phenylamides **5** and **1** at 1538 and 1526-1540 cm^{-1}, respectively. This band is probably associated with the presence of the phenylamide moiety (most likely amide N-H bending).

Theoretical IR spectrum was calculated for dutasteride crystalline form I having one dutasteride molecule in the asymmetric unit to prove the accuracy of the assignments for the third and fourth band (see Figure 4). The simulated IR spectrum shows that the experimental band of the solvates peaking at *ca.* 1590 cm^{-1} is composed of two oscillations coming from the C1=C2 double bond and $C=C_{ar}$ (with the participation of phenylamide N-H). It also suggests that the next experimental band peaking in the range 1524-1532 cm^{-1} can be specified as phenylamide N-H bending with the contribution of the second C=C absorption band of the arene. The bands at *ca.* 1590 cm^{-1} and in the 1524-1532 cm^{-1} range were earlier incorrectly ascribed to phenylamide N-H bending and lactam N-H bending [3], respectively.

Moreover, the spectra of the solvates show absorption bands originating from incorporated solvents. The absorption bands at *ca.* 3445±10 cm^{-1} characteristic only for ethanol (**D 1**) and methanol (**D 2**) solvates of dutasteride hydrochloride are absent in the remaining solvates. Consequently, these bands correspond to O-H stretching of alcohol. The acetone solvate (**D 3**) shows intensive absorption band characteristic of acetone C=O bond at 1712 cm^{-1} and acetonitrile solvate (**D 4**) – a weak absorption band characteristic of the non-conjugated C≡N bond at 2258 cm^{-1}.

Based on the results mentioned above, it is highly plausible that the earlier published IR data ascribed to the "dutasteride hydrochloride hydrate ethanol solvate" [3] belong in fact to the dutasteride form III, *i.e.* bis(dutasteride) monohydrate (previously called "dutasteride hemihydrate" [14]).

3.5. Differential scanning calorimetry (DSC)

The dutasteride hydrochloride solvates were further characterized by DSC. The DSC curves characterize one (sample **D 3**), two (samples **D 2** and **D 4**) or three (sample **D 1**) endotherms within the 30-160 °C range. Moreover, there appears an additional exotherm at *ca.* 160-180 °C range corresponding to the crystallization of dutasteride anhydrous form I. Finally, the form I melts within the narrow range 251.2-252.6 °C (for peaks). The literature melting point is 244-245 °C [11], 249.08 °C (DSC, peak) [12] and 251 °C (DSC, peak) [22]. In the case of **D 2** and **D 3**, a small endotherm of unknown origin is additionally visible at 193.8 °C and 193.3 °C, respectively.

3.6. Solution ^{1}H and ^{13}C NMR spectra of the solvates

The dutasteride hydrochloride hydrate solvates were also characterized by ^{1}H NMR and ^{13}C NMR spectra in DMSO-d_6 solution. The ^{1}H NMR data presented in Table 5 shows the presence of an incorporated solvent in each isolated solvate. The observed chemical shifts of protons coming from the incorporated solvents agree well with the published data [23], except for the water. Its signal is not observed at *ca.* 3.33 ppm but is visible in the 5.7-7.0 ppm range. All prepared solvates have a dutasteride to a solvent molar ratio of 1:1.

^{13}C NMR data (Table 6) also shows the presence of incorporated solvents and their carbon chemical shifts agree well with the published data [23]. The signal assignment of skeletal carbon atoms was accomplished by comparison with the assignment done for dutasteride in DMSO-d_6 solution in patent application [13] and the literature [12].

3.7. Site of protonation in $CDCl_3$ solution in the light of the ^{1}H NMR data in this solvent

Comparison of the chemical shifts for protons in the spectra recorded in $CDCl_3$ solution (Table 1) evidently shows that H-5α, H-2 and H-1 proton signals in protonated sample **D 1** are deshielded compared to non-solvated form **D I**. However, the chemical shifts of these protons are practically unaffected in hydrated forms **D II** and **D III** by solvation with water (compare the data for samples **D II** and **D II** with **D I**). In the case of $CDCl_3$ solutions the phenylamide N-H proton (H-N21) shows practically constant chemical shift (*ca.* 8.76 ppm), whereas cyclic amide N-H proton (H-N4) is deshielded after protonation of dutasteride. Additionally, it was found that the chemical shift of this proton in **D I** probably depends on sample concentration or the presence of traces of water in $CDCl_3$ solution. The similar effects

are not seen in the ^{1}H NMR spectra of form I and solvates **D 1**–**D 4** in DMSO-d_6 solution (see Table 5).

The data presented shows that in $CDCl_3$ solution the protonation occurs at oxygen atom of the C3 carbonyl group, similarly as in the solid state. In the C3-carbocation thus formed the positive charge is delocalized not only on N4 nitrogen atom (Figure 5) but also on the C1=C2 double bond. From this it follows that the protonation of the N4 nitrogen atom is much less important.

4. Conclusions

Following the modified procedure four crystalline mono(dutasteride) monohydrochloride monohydrate mono(solvent) solvates were obtained. They were thoroughly characterized by FT-IR in KBr pressed pellets, DSC as well as by solution ^{1}H and ^{13}C NMR data in DMSO-d_6. Preparation of three solvates containing ethanol, methanol and acetone produced crystals suitable for the SCXRD measurements. Then, their crystal structures were solved and refined. The SCXRD measurements revealed that in the solid state the dutasteride hydrochloride solvates are protonated at oxygen atom of α,β-unsaturated δ-lactam. Moreover, two model compounds, derivatives of 3-oxo-4-aza-5α-androstane-17β-carboxylic acid with different 17β-substituents, were synthesized. Their FT-IR data were necessary, and they proved to be particularly helpful in the discussion of the assignment of the absorption bands to the appropriate vibrations. Comparison of ^{1}H NMR spectra of mono(dutasteride) monohydrochloride monohydrate mono(ethanol) solvate and dutasteride crystalline forms I, II and III showed that the protonation in the $CDCl_3$ solution also occurs at oxygen atom of α,β-unsaturated δ-lactam. Both the N4 nitrogen atom and C1=C2 double bond participate in the delocalization of positive charge appearing at C3. Summarizing, our comprehensive research on dutasteride hydrochloride hydrate solvates has provided valuable information about this group of compounds. Based on the results obtained, correction of incompatibilities in published literature related to the assignment of IR absorption bands to the corresponding molecular vibrations was ultimately possible.

Acknowledgments

This work was supported by The National Centre for Research and Development (Poland), Grant No. INNOTECH-K2/IN2/65/182982/NCBR/13 and Grant No. UMO-2011/03/N/ST4/02426 from the National Science Centre (Poland). All computational calculations were performed at the Interdisciplinary Centre for Mathematical and Computational Modeling (ICM) of University of Warsaw (Grant No. G34-15).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at .....

Appendix B. CIF file for mono(dutasteride) monohydrochloride monohydrate mono(ethanol) solvate (sample **D 1**), CCDC **1061655.**

Appendix C. CIF file for mono(dutasteride) monohydrochloride monohydrate mono(methanol) solvate (sample **D 2**), CCDC **1063084.**

Appendix D. CIF file for mono(dutasteride) monohydrochloride monohydrate mono(acetone) solvate (sample **D 3**), CCDC **1061654.**

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Table 1
Comparison of ^{1}H NMR chemical shifts for **D I**, **D II, D III**, and **D 1** in $CDCl_3$ solution.
$\Delta\delta_{D\,II}$= **D II–D I**, $\Delta\delta_{D\,III}$= **D III–D I**, $\Delta\delta_{D\,1}$= **D 1–D I**

	D I[20]	**D I**	**D II**	$\Delta\delta_{D\,II}$	**D III**	$\Delta\delta_{D\,III}$	**D 1**	$\Delta\delta_{D\,1}$
Dutasteride								
18-H (3H, s)	0.81	0.80	0.80	0.00	0.80	0.00	0.81	+0.01
19-H (3H, s)	1.00	0.99	0.99	0.00	0.99	0.00	1.00	+0.01
17α-H (1H, t, J~9.3 Hz)	2.39	2.38	2.37	–0.01	2.37	–0.01	2.38	0.00
5α-H (1H, dd, J~12.6 and 3.7 Hz)	**3.36**	**3.35**	**3.35**	0.00	**3.35**	0.00	**3.46**	**+0.11**
2-H (1H, d, J~9.9 Hz)	**5.83**	**5.83**	**5.82**	–0.01	**5.82**	–0.01	**5.99**	**+0.16**
1-H (1H, d, J~9.9 Hz)	**6.81**	**6.81**	**6.80**	–0.01	**6.80**	–0.01	**7.07**	**+0.26**
4'-H (1H, d, J~8.2 Hz)	7.47	7.45	7.45	0.00	7.45	0.00	7.46	+0.01
3'-H (1H, d, J~8.2 Hz)	7.75	7.73	7.73	0.00	7.73	0.00	7.74	+0.01
6'-H (1H, s)	8.79[a]	7.53	7.51	–0.02	7.51	–0.02	7.51	–0.02
N4-H (br s)	**5.74**	**6.40**	**5.70**	–0.70	**5.76**	–0.64	**8.21**	**+1.81**
N21-H (1H, s)	7.52[a]	8.77	8.78	+0.01	8.75	–0.02	8.76	–0.01
Others								
CH_3, t, J=7.1 Hz							1.25	
CH_2, q, J=7.1 Hz							3.747[b]	
?							4.46[c]	
?							4.87[d]	

[a] should be interchanged; [b] 2.67H; [c] br, 3.23H; [d] br, 0.33H

Table 2
Crystallographic data and structure refinement for the dutasteride hydrochloride solvates.

	D1 [3] **CCDC 849483**	**D1**$^{\text{current work}}$ [17] **CCDC 1061655**	**D2** [17] **CCDC 1063084**	**D3** [17] **CCDC 1061654**
Empirical formula	$C_{27}H_{30}F_6N_2O_2{\cdot}HCl{\cdot}H_2O{\cdot}C_2H_6O$	$C_{27}H_{30}F_6N_2O_2{\cdot}HCl{\cdot}H_2O{\cdot}C_2H_6O$	$C_{27}H_{30}F_6N_2O_2{\cdot}HCl{\cdot}H_2O{\cdot}CH_4O$	$C_{27}H_{30}F_6N_2O_2{\cdot}HCl{\cdot}H_2O{\cdot}C_3H_6O$
Formula weight	629.07	629.07	615.05	641.09
Temperature		100 K	100 K	100 K
Wavelength		1.54184	1.54184	1.54184
Crystal system	triclinic	triclinic	triclinic	triclinic
Space group	*P*1	*P*1	*P*1	*P*1
Unit cell dimensions				
a	7.9357(7)	7.8843(6)	7.9036(3)	7.9287(6)
b	9.1050(8)	8.9625(6)	8.9867(5)	9.1620(9)
c	11.1952(9)	11.0748(7)	10.8511(4)	11.3759(8)
α	73.7460(10)	74.793(6)	74.832(4)	69.698(8)
β	88.6870(10)	88.179(6)	87.201(3)	89.921(6)
γ	86.1930(10)	85.976(6)	84.425(4)	89.239(7)
Volume	774.85(11)	753.24(9)	740.14(6)	774.97(12)
Z, calculated density	1, 1.348 g cm^{-3}	1, 1.385g cm^{-3}	1, 1.373g cm^{-3}	1, 1.372g cm^{-3}
Absorption coefficient [mm^{-1}]		1.782	1.801	1.744
F(000)	330	329	319	335
Theta range for data collection		4.14 - 72.18	4.22 - 72.09	4.14 - 72.15
Limiting indices		–9 ≤h≤ 9 –10 ≤k≤ 10 –11 ≤l≤ 13	–9 ≤h≤ 9 –10 ≤k≤ 10 –11 ≤l≤ 12	–9 ≤h≤ 3 –11 ≤k ≤11 –14 ≤l≤ 11
Reflections Collected/unique		4641/3396	6077/3739	2633/2190
Absorption correction		multi-scan*	multi-scan*	multi-scan*
Refinement method		Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/restraints/				

parameters		3396/3/391	3739/3/374	2190/3/395
Goodness-of-fit on F^2	1.072	1.048	1.200	1.062
Final R indices [I>2 sigma(I)]	0.0448	0.0264	0.0694	0.0277
R indices (all data)		R_1 = 0.0269	R_1 = 0.0695	R_1 = 0.0278
		wR_2 = 0.0705	wR_2 = 0.2387	wR_2 = 0.0751
Largest diff. peak and hole		0.28 –0.25	0.94 –0.46	0.21 –0.24

* CrysAlisPro, Agilent Technologies, Version 1.171.35.15 (release 03-08-2011 CrysAlis171 .NET) (compiled Aug 3 2011,13:03:54). Empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm

Table 3

Selected torsion angles [°] and bond lengths [Å] for the dutasteride forms I (**D I**) [7] and III (**D III**) [3] and dutasteride hydrochloride solvates **D 1**, **D 2**, and **D 3**.

Sample	**D I** [7]	**D III** [3]		**D 1** [3]	**D 1**[current work] [17]	**D 2** [17]	**D 3** [17]
CCDC	**1032001**	**849482**		**849483**	**1061655**	**1063084**	**1061654**
		two molecules					
A ring torsion angles							
5-10-1-2	+33.8	+37.5	+31.6	+35.4	+35.7	+33.0	+37.7
10-1-2-3	+0.0	–0.1	+1.1	–1.9	–2.3	–0.2	–2.1
1-2-3-4	–15.0	–18.9	–14.0	–16.1	–15.7	–16.2	–18.7
2-3-4-5	–9.5	–5.5	–11.8	–5.5	–5.6	–5.2	–2.5
3-4-5-10	+45.4	+45.0	+46.6	+41.1	+40.9	+39.1	+40.4
4-5-10-1	–53.3	–56.3	–52.1	–51.9	–52.0	–49.6	–54.2
O=3-4-5	+172.6	+177.7	+169.0	+174.8	+174.8	+173.9	+177.0
A ring bond lengths							
C10-C1	1.517	1.511	1.512	1.511	1.512	1.506	1.515
C1=C2	1.333	1.316	1.316	1.323	1.334	1.350	1.339
C2-C3	**1.486**	**1.468**	**1.456**	**1.455**	**1.467**	**1.464**	**1.471**
C3-N4	**1.334**	**1.320**	**1.333**	**1.292**	**1.306**	**1.317**	**1.303**
N4-C5	1.459	1.461	1.454	1.464	1.473	1.466	1.470
C5-C10	1.539	1.530	1.545	1.538	1.543	1.540	1.539
C3=O	**1.241**	**1.245**	**1.243**	**1.277**	**1.285**	**1.277**	**1.290**
Side chain torsion angles							
16-17-20-21	+18.0	+159.6	+149.1	+154.7	+155.8	+152.4	+152.5
17-20-21-1’	+170.1	–169.8	–177.6	–176.1	–175.8	–177.0	–175.2
20-21-1’-2’	–169.7	–155.3	–130.7	–123.7	–124.1	–126.1	–115.2
O=20-21-1’	–7.0	+9.8	+3.6	+6.4	+5.9	+4.2	+6.9
Side chain bond lengths							
C20-N21	**1.385**	**1.372**	**1.351**	**1.342**	**1.350**	**1.355**	**1.355**
N21-C1’	1.410	1.402	1.418	1.420	1.422	1.436	1.425
C20=O	**1.215**	**1.194**	**1.201**	**1.223**	**1.236**	**1.229**	**1.238**

Table 4

IR absorption bands of compounds **1** – **5** and **D 1** – **D 4** at *ca.* 1596±6 and 1532±8 cm^{-1}.

Compound, form (sample)	Ring A	17β-Substituent	Band at *ca.* 1596±6 cm^{-1}	Band at *ca.* 1532±8 cm^{-1}
3	lactam	carboxyl	-	-
4	lactam	*N*-alkylcarboxamide	-	-
2, form I (S1) [21]	ene-lactam	*N*-alkylcarboxamide	1600	-
2, form II (S4) [21]	ene-lactam	*N*-alkylcarboxamide	1598	-
2, form III (S6) [21]	ene-lactam	*N*-alkylcarboxamide	1601	-

5	lactam	*N*-arylcarboxamide	1592	1538
1 form I (**D I**)	ene-lactam	*N*-arylcarboxamide	1592	1540
1, form II (**D II**)	ene-lactam	*N*-arylcarboxamide	1593	1539 1526[a]
1 form III (**D III**)	ene-lactam	*N*-arylcarboxamide	1594	1533
D 1	ene-lactam	*N*-arylcarboxamide	1591	1529
D 2	ene-lactam	*N*-arylcarboxamide	1590	1531
D 3	ene-lactam	*N*-arylcarboxamide	1590	1524
D 4	ene-lactam	*N*-arylcarboxamide	1591	1529

[a] two distinctly visible absorption bands corresponding mainly to phenylamide N-H bending

Table 5

^{1}H NMR chemical shifts (δ [ppm]) for **D I** and **D 1** – **D 4** in DMSO-d_6.

H	**D I** [12,13]	**D 1**	**D 2**	**D 3**	**D 4**
	Dutasteride				
H-18 (3H, s)	0.64	0.66	0.66	0.67	0.66
H-19 (3H, s)	0.85	0.87	0.87	0.87	0.87
H-12β (1H, dm, J *ca.* 12.4 Hz)	1.96	1.98	1.98	1.98	1.98
H_B-16 (1H, m)	2.10	2.10	2.10	2.09[a]	*ca.* 2.1[a]
H-17α (1H, t, J~9.3 Hz)	2.55	2.59	2.58	2.61	2.61
H-5α (1H, dd, J~12.6 and 3.0 Hz)	3.18	3.21	3.20	3.21	3.21
H-2 (1H, d, J~9.9 Hz)	5.60	5.64	5.63	5.66	5.66
H-1 (1H, d, J~9.9 Hz)	6.83	6.86	6.86	6.87	6.87
H-N4 (br s)	7.40	7.47	7.42	7.51	7.54
H-4' (1H, d, J~8.2)	7.79	7.80	7.81	7.80	7.80
H-6' (1H, s)	7.92	7.93	7.92	7.94	7.93
H-3' (1H, d, J~8.2)	7.97	7.99	7.99	7.98	7.98
H-N21 (1H, s)	9.36	9.43	9.42	9.45	9.47
	Solvents and water				
H_2O in DMSO at ~3.33 ppm					
		EtOH	MeOH	Me_2CO	MeCN
$C\underline{H}_3$-		1.06 3H, t J~7.0 Hz	3.17 3H, s	2.09[a] 6H, s	2.09[a] 3H, s
-$C\underline{H}_2$-		3.45 2H, q J~7.0 Hz	-	-	-
water from solvate and DMSO-d_6		5.94 br s	5.70 br s	6.98 br s	6.62 br s

[a] overlapping signals

Table 6

^{13}C NMR chemical shifts (δ [ppm]) for **D I** and **D 1** – **D 4** in DMSO-d_6.

C	**D I** [12,13]	**D 1**	**D 2**	**D 3**	**D 4**
	Skeletal carbon atoms				
20	172.4	172.5	172.4	172.5	172.6
3	165.1	165.2	165.2	165.3	165.4
1	150.4	150.7	150.6	150.8	150.9
2	123.1	123.0	123.0	122.9	122.9
5	59.1	59.1	59.1	59.1	59.2
17	55.4	55.4	55.4	55.4	55.5
14	55.3	55.3	55.3	55.3	55.3

9	47.1	47.1	47.1	47.2	47.2
13	44.3	44.3	44.3	44.3	44.4
10	38.6	38.7	38.6	38.7	38.7
12	37.0	37.0	36.9	37.0	37.0
8	34.8	34.9	34.8	34.9	34.9
7	29.1	29.1	29.1	29.1	29.2
6	25.1	25.1	25.0	25.1	25.1
15	24.0	24.0	24.0	24.1	24.1
16	23.7	23.7	23.7	23.8	23.8
11	20.6	20.6	20.6	20.7	20.7
18	13.3	13.3	13.3	13.4	13.4
19	11.8	11.8	11.8	11.8	11.8
	CF_3 and aromatic carbon atoms				
1’	137.0	137.1	137.0	137.1	137.1
5’	133.0	133.0	132.9	133.0	133.0
3’	127.9	127.9	127.9	127.9	128.0
2’	127.9	127.9	127.9	127.9	128.0
6’	126.4	126.4	126.4	126.3	126.4
5’-CF_3	123.1	123.1	123.1	123.2	123.2
4’	123.0	123.0	123.0	123.0	123.1
2’-CF_3	122.8	122.8	122.8	122.9	122.9
	Carbon atoms of solvent				
	-	EtOH	MeOH	Me_2CO	MeCN
	-	56.0	48.6	206.4	118.1
	-	18.5	-	30.7	1.2

Figure legends

Fig. 1. Molecular structures of dutasteride (**1**), finasteride (**2**), 3-oxo-4-aza-5α-androstane-17β-carboxylic acid (**3**), dihydrofinasteride (**4**), and dihydrodutasteride (**5**).

Fig. 2. The crystal structures of investigated solvates **D1** - **D3**. Chlorine anion and water molecule have been drawn in two positions to show their interactions with both amide N atoms or both carbonyl oxygen atoms, respectively.

Fig. 3. Structural overlay: for clarity only dutasteride molecules were shown (solvent, water molecules, Cl^- ions as well as all H atoms were omitted). (Left) Overlay of three dutasteride molecules observed in **D 1** (yellow), **D 2** (red) and **D 3** (green). (Middle) View along the x axes. (Right) View perpendicular to dutasteride plane: **D 1** (yellow), **D 2** (red) and **D 3** (green).

Fig. 4. Simulated IR spectrum of dutasteride **1** form **I** at the B3LYP/TZVP level of theory with Lorentzian line shapes of 8 cm^{-1} half-width at half-height in the 1300-1900 cm^{-1} range.

Fig. 5. Resonance structures of protonated ene-lactam in $CDCl_3$ solution.

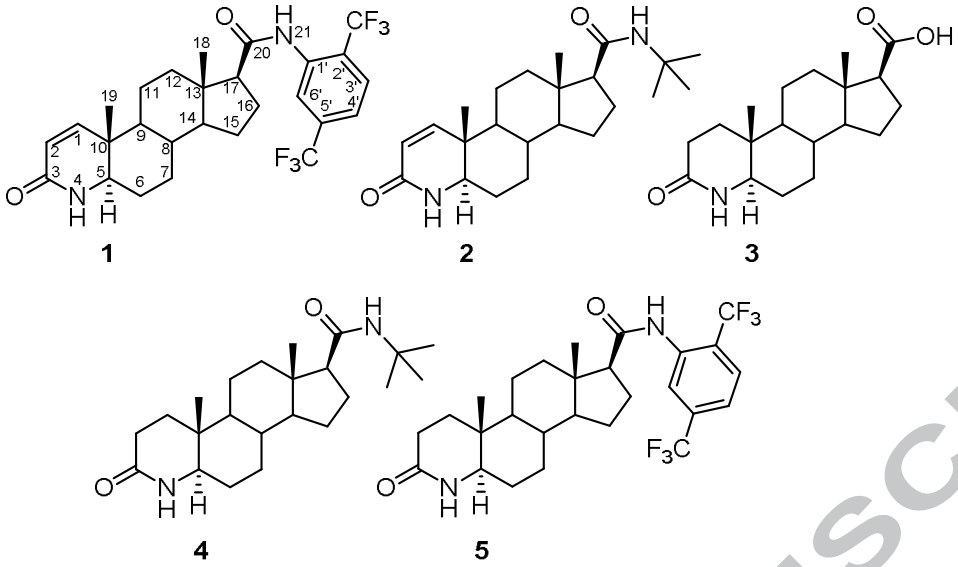

Fig. 1.

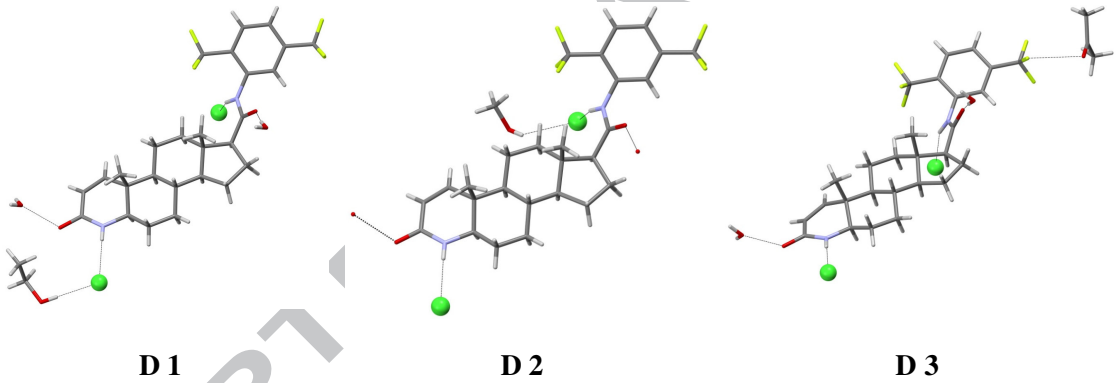

Fig. 2.

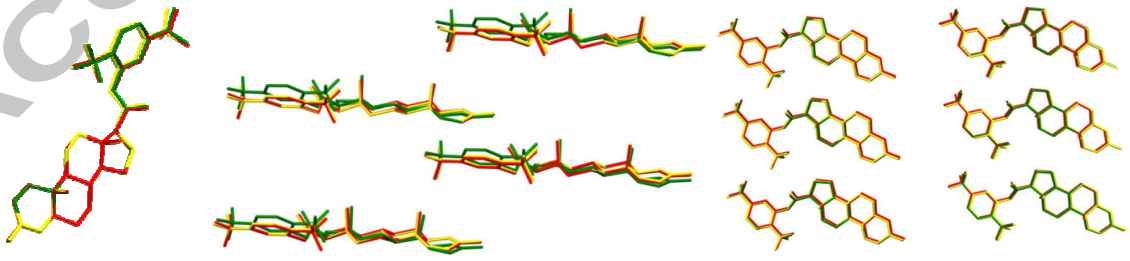

Fig. 3.

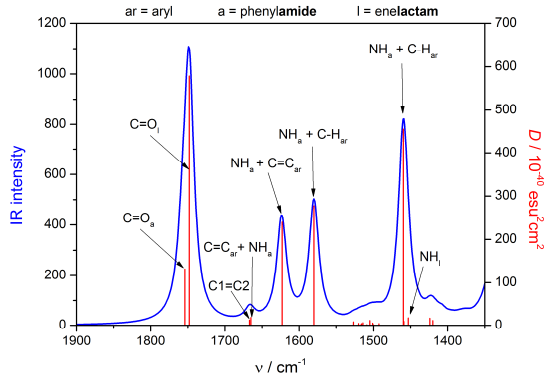

Fig. 4.

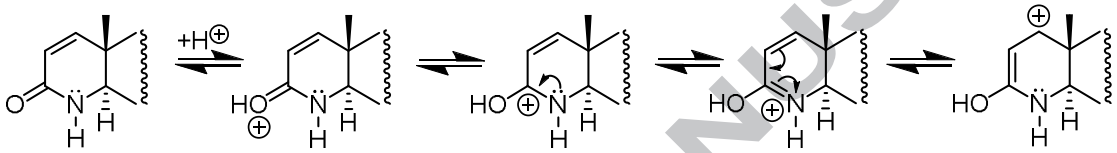

Fig. 5.

Highlights

Preparation of dutasteride hydrochloride hydrate solvates is described.
Five dutasteride hydrochloride hydrate solvates are fully spectroscopically characterized.
Thermal decomposition of dutasteride hydrochloride hydrate solvates leads to dutasteride ~~form I~~.