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Synthesis, structure, and screening of estrogenic and antiestrogenic activity of new 3,17-substituted-16,17-seco-estratriene derivatives

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Abstract

The starting compound for synthesis of new 16,17-seco-estratriene derivatives was 3-benzyloxy-17-hydroxy-16,17-secoestra-1,3,5(10)-triene-16-nitrile (**1b**), obtained from estrone in several synthetic steps. 17-Tosyl, -chloro-, bromo-, and -iodo- derivatives **2b**, **4b**, **5b**, and **6b** were prepared directly from secocyanoalcohol **1b**, while the 17-fluoro-derivative **3b** was obtained from tosylate **2b** in the reaction with tetrabutyl ammonium fluoride. The corresponding 3-hydroxy derivatives of these compounds were produced by action of hydrogen in presence of Pd/C, except the 3-hydroxy-17-iodo derivative **6a**, which was obtained from 3-hydroxy-17-tosyloxy derivative **2a**. All the newly synthesized compounds in biological tests on experimental animals exhibited an almost total loss of estrogenic activity, while most of them even prevented the action of endogenous estrogens. On the other hand, most of them, except compounds **3a** and **6b**, partially hindered the action of estradiol benzoate, behaving as moderate antagonists.

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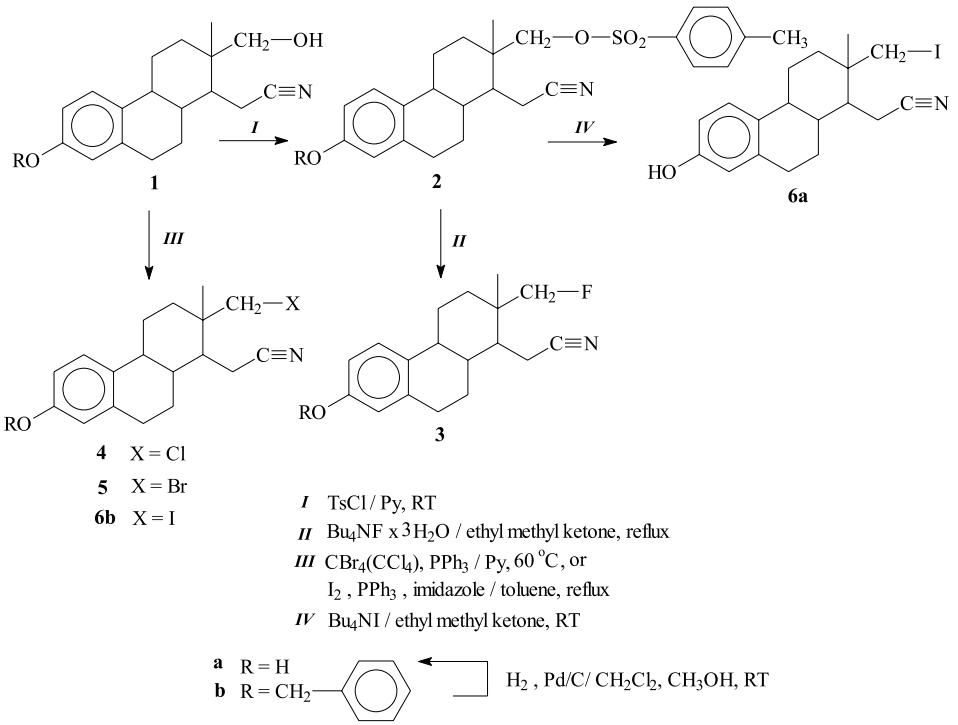
1. Introduction

A broader project, directed towards preparation of potential antiestrogens, resulted in the synthesis of series of new 16,17-seco-estrone derivatives [1–5]. Among them the behaviour of 3-benzyloxy-17-hydroxy-16,17-secoestra-1,3,5(10)-triene-16-nitrile (**1b**, Scheme 1), and its corresponding 3-hydroxy derivative (**1a**) were of special interest. Namely, compound **1b** showed a very low estrogenic activity, exhibiting a significant antihormonal property. On the other hand, its 3-hydroxy equivalent **1a** showed a complete loss of estrogenic activity, but a less antiestrogenic effect [5,6]. These facts prompted us to further chemical transformations of **1**, in order to study the influence of the nature of functional groups at C-3 and C-17 on biological action of the new compounds. Accordingly, the aim of this paper was the synthesis of a series of new 3-benzyloxy-16,17-secoestratriene derivatives with different substituents at C-17, as well as their 3-hydroxy analogs, and testing their biological activity on experimental animals.



Scheme 1.

2. Materials and methods

2.1. Synthesis and characterization of the newly synthesized compounds

2.1.1. General

Melting points were determined in open capillary tubes on a Büchi SMP apparatus and the values are uncorrected. Infrared spectra (ν in cm^{-1}) were recorded in KBr pellets or as films on a Perkin–Elmer M457 or Carl Zeiss Specord 75 spectrophotometer. NMR-spectra were taken on a Bruker AC 250E spectrometer operating at 250 Hz (proton) and 62.9 Hz (carbon), using standard Bruker software. The signals are reported in parts per million downfield from a tetramethylsilane internal standard (δ 0.00); symbols s, bs, d, dd, q, and m denote singlet, broad singlet, doublet, double doublet, quartet, and multiplet, respectively. Mass spectra were recorded on a Finnigan-Math 8230 instrument, using electron impact (70 eV) or chemical ionization (*iso*-butane) techniques; the first number denotes *m/z* value, and the ion abundances are given in parentheses. The diffraction data of the compound **1a** were collected using Siemens P4 diffractometer and the structure was solved by the molecular-mechanic calculations (MMC), using PCMODEL (Serena Software, 1989). Crystallographic data were deposited at the Cambridge Crystallographic Data Centre (CCDC 205270). The starting compound, **1b**, was synthesized by known procedure [2], as well as compound **1a**, whose crystal structure we present. All reagents used were of analytical grade commercially available substances.

2.1.2. 3-Benzyloxy-17-tosyloxy-16,17-secoestra-1,3,5(10)-triene-16-nitrile (*2b*)

To the solution of 3-benzyloxy-17-hydroxy-16,17-secoestra-1,3,5(10)-triene-16-nitrile (**1b**, 1 g, 2.67 mmol) in absolute pyridine (10 mL) *p*-toluenesulphonyl chloride (0.8 g, 4.2 mmol) was added and the mixture was kept at room temperature for 50 h. After completion of the reaction, the resulting solution was poured into dilute HCl (1:1, 100 mL), crude product was filtered off, washed with water until neutral, and air-dried. Column chromatography on silica gel (100 g, dichloromethane–*n*-hexane 9:1) of the crude *p*-toluenesulphonate ester **2b** afforded 0.84 g (84%) of pure 3-benzyloxy-17-tosyloxy-16,17-secoestra-1,3,5(10)-triene-16-nitrile (**2b**) in the form of an amorphous mass.

IR: 3060, 2980, 2300, 1420, 1375, 1260, 1180, 890, 750.

^{1}H NMR spectrum ($CDCl_3$): 0.96 (s, 3H, CH_3, H-18); 2.50 (s, 3H, CH_3 from Ts); 3.67 (d, 1H, H_a–C-17); 3.92 (d, 1H, H_b–C-17, $J_{gem} = 10.1$ Hz); 5.08 (s, 2H, O–C**H**$_2$–C_6H_5); 6.75–7.88 (group of signals, 12H, aromatic protons).

^{13}C NMR spectrum ($CDCl_3$): 15.36 (C-15); 15.91 (C-18); 22.57 (CH_3 from Ts); 76.26 (O–**C**H_2–C_6H_5); 118.77 (C≡N); 156.92 (C-3).

Mass spectrum: 587 (8; (M+*i*-Bu)$^+$); 586 (13; (M+*i*-Bu-1)$^+$); 530 (4; (M+1)$^+$); 415 (47); 358 (54; (M+*i*-Bu-OTs)$^+$); 324 (100); 268(2).

2.1.3. 3-Benzyloxy-17-fluoro-16,17-secoestra-1,3,5(10)-triene-16-nitrile (*3b*)

3-Benzyloxy-17-tosyloxy-16,17-secoestra-1,3,5(10)-triene-16-nitrile (**2b**, 1 g, 1.90 mmol) and tetrabutyl ammonium fluoride trihydrate (3 g, 9.52 mmol) were dissolved

in ethylmethyl ketone (30 mL) and the reaction mixture was refluxed during 12 h. Reaction mixture was then poured into ice-cold water (100 mL) and the formed emulsion was extracted with ether (3×30 mL). The collected extracts were dried over anhydrous sodium sulphate and evaporated to dryness. The dark-brown oily product was purified by column chromatography on silica gel (100 g, dichloromethane–*n*-hexane 9:1), whereby 0.36 g (70.4%) of pure 3-benzyloxy-17-fluoro-16, 17-secoestra-1,3,5(10)-triene-16-nitrile (**3b**, mp 127–129 °C) was obtained, and 0.29 g (29%) of *p*-toluenesulphonate ester **2b** was recovered.

IR: 2920, 1600, 1500, 1450, 1375, 1310, 1180, 940, 670, 550.

^{1}H NMR spectrum ($CDCl_3$): 1.05 (s, 3H, CH_3, H-18); 2.53 (dd, 1H, H_a–C-15, $J_{gem} = 21.01$ Hz, $J_{15a,14} = 3.25$ Hz); 2.72 (dd, 1H, H_b–C-15, $J_{15b,14} = 5.0$ Hz); 4.16 (dd, 1H, H_a–C-17, $J_{gem} = 9.6$ Hz, $J_{17a,F} = 39.66$ Hz); 4.36 (dd, 1H, H_b–C-17, $J_{17b,F} = 40.79$ Hz); 5.10 (s, 2H, O–C**H**$_2$–C_6H_5); 6.81–7.52 (group of signals, 8H, aromatic protons).

^{13}C NMR spectrum ($CDCl_3$): 14.67 (d, C-15, $J_{C,F} = 6.29$ Hz); 15.78 (d, C-18, $J_{C,F} = 2.96$ Hz); 34.99 (d, C-12, $J_{C,F} = 3.90$ Hz); 38.34 (d, C-13, $J_{C,F} = 15.91$ Hz); 41.91 (d, C-14, $J_{C,F} = 1.76$ Hz); 69.82 (O–**C**H$_2$–C_6H_5); 90.68 (d, **C**H$_2$–F, $J_{C,F} = 176.37$ Hz); 119.19 (C≡N); 156.87 (C-3).

Mass spectrum: 434 (42; $(M+i\text{-Bu-1})^+$); 378 (100; $(M+1)^+$).

Anal. Calcd for $C_{25}H_{28}FNO$: C, 79.54; H, 7.47; N, 3.71. Found: C, 79.26; H, 7.52; N, 3.59.

*2.1.4. 3-Benzyloxy-17-chloro-16,17-secoestra-1,3,5(10)-triene-16-nitrile (**4b**) and 3-benzyloxy-17-bromo-16,17-secoestra-1,3,5(10)-triene-16-nitrile (**5b**)*

3-Benzyloxy-17-hydroxy-16,17-secoestra-1,3,5(10)-triene-16-nitrile (**1b**, 1 g, 2.67 mmol) was dissolved in absolute pyridine (30 mL) at room temperature. The solution was cooled to 0 °C and triphenylphosphine (1.72 g, 6.6 mmol) and carbon tetrachloride or tetrabromide (3.25 mmol) were added in several portions. The reaction mixture was heated for 2.5 h at 60 °C, then cooled and methanol (10 mL) was added, to eliminate the excess of reagents, and poured into icy 2 M HCl (100 mL). The emulsion was extracted with dichloromethane (2×50 mL), collected extracts were washed with water, dried over anhydrous sodium sulphate and evaporated to dryness. The oily crude products were purified by column chromatography on silica gel (100 g, toluene–ethyl acetate 95:5), whereby pure compounds **4b**, i.e. **5b** were obtained.

*3-Benzyloxy-17-chloro-16,17-secoestra-1,3,5(10)-triene-16-nitrile (**4b**).* Yield: 53.6%, mp 148.5–149.5 °C.

IR: 2925–2860, 2250, 1605, 1500, 1240, 1020, 740.

^{1}H NMR spectrum ($CDCl_3$): 1.09 (s, 3H, CH_3, H-18); 2.35 (m, 3H, H_a–C-15 and 2H from the skeleton); 2.61 (dd, 1H, H_b–C-15, $J_{gem} = 17.9$ Hz, $J_{15b,14} = 5.2$ Hz); 3.42 (d, 1H, H_a–C-17, $J_{gem} = 10.95$ Hz); 3.59 (d, 1H, H_b–C-17); 5.08 (s, 2H, O–C**H**$_2$–C_6H_5); 6.78–7.52 (group of signals, 8H, aromatic protons).

^{13}C NMR spectrum ($CDCl_3$): 15.18 (C-15); 18.00 (C-18); 69.85 (O–**C**H$_2$–C_6H_5); 118.93 (CN); 156.90 (C-3).

Mass spectrum: 452 (37; (M+*i*-Bu)$^+$); 451 (52; (M+*i*-Bu-1)$^+$); 450 (100; (M+*i*-Bu-2)$^+$); 394 (74; M$^+$); 360 (17).

Anal. Calcd for $C_{25}H_{28}ClNO$: C, 76.34; H, 7.12; N, 3.56. Found: C, 75.88; H, 7.18; N, 4.01.

*3-Benzyloxy-17-bromo-16,17-secoestra-1,3,5(10)-triene-16-nitrile (**5b**).* Yield: 84%, mp 157–157.5 °C.

IR: 3030, 2930, 2250, 1605, 1503, 1240, 1015.

^{1}H NMR spectrum ($CDCl_3$): 1.13 (s, 3H, CH_3, H-18); 2.38 (m, 3H, H_a–C-15 and 2H from the skeleton); 2.62 (dd, 1H, H_b–C-15, $J_{gem} = 17.8$ Hz, $J_{15b,14} = 5.2$ Hz); 3.35 (d, 1H, H_a–C-17, $J_{gem} = 10.9$ Hz); 3.45 (d, 1H, H_b–C-17); 5.06 (s, 2H, O–C**H**$_2$–C_6H_5); 6.75–7.44 (group of signals, 8H, aromatic protons).

^{13}C NMR spectrum ($CDCl_3$): 15.15 (C-15); 18.29 (C-18); 69.83 (O–**C**H$_2$–C_6H_5); 118.88 (CN); 156.87 (C-3).

Mass spectrum: 438 (16; M$^+$); 437 (18); 91 (100).

Anal. Calcd for $C_{25}H_{28}BrNO$: C, 68.50 H, 6.39, N, 3.19. Found: C, 68.39; H, 6.53; N, 3.23.

*2.1.5. 3-Benzyloxy-17-iodo-16,17-secoestra-1,3,5(10)-triene-16-nitrile (**6b**)*

The mixture of compound **1b** (1g, 2.67 mmol), triphenylphosphine (2 g, 7.5 mmol), imidazole (0.53 g, 0.8 mmol), and iodine (1.32 g, 5.2 mmol) in toluene (70 mL) was refluxed during 3 h. After cooling, methanol (10 mL) was added, and the resulting solution was poured into water (50 mL). The organic layer was separated, washed with water, dried over anhydrous sodium sulphate, and evaporated to dryness. Column chromatography of the dark-brown oily crude product on silica gel (100 g, dichloromethane–*n*-hexane 9:1), yielded the pure 3-benzyloxy-17-iodo-16,17-secoestra-1,3,5(10)-triene-16-nitrile (**6b**, 1.24 g, 96%, mp 139–140 °C).

IR: 3040, 2920, 2250, 1605, 1500, 1240, 1020.

^{1}H NMR spectrum ($CDCl_3$): 1.17 (s, 3H, CH_3, H-18); 2.35 (m, 3H, H_a–C-15 and 2H from the skeleton); 2.58 (dd, 1H, H_b–C-15, $J_{gem} = 17.8$ Hz, $J_{15b,14} = 5.1$ Hz); 3.30 (s, 1H, CH_2–I); 5.07 (s, 2H, O–C**H**$_2$–C_6H_5); 6.78–7.44 (group of signals, 8H, aromatic protons).

^{13}C NMR spectrum ($CDCl_3$): 15.21 (C-15); 18.11 (C-18); 23.96 (CH_2–I); 69.89 (O–**C**H$_2$–C_6H_5); 118.80 (C≡N); 156.93 (C-3).

Mass spectrum: 543 (100; (M+*i*-Bu)$^+$); 542 (48; (M+*i*-Bu-1)$^+$); 487 (22; (M+1)$^+$).

Anal. Calcd for $C_{25}H_{28}INO$: C, 61.86 H, 5.82, N, 2.89. Found: C, 61.42; H, 5.95; N, 3.31.

*2.1.6. General procedure for deprotection of the 3-hydroxy function of compounds **2b–5b***

To the solution of the corresponding benzyl ether **2b**–**5b** (1 mmol) in ethyl acetate (10 mL) or in the dichloromethane–methanol mixture (2:1, 10 mL), 10% Pd/C (10%) was added. The suspensions were stirred at room temperature for 12–24 h in an atmosphere of hydrogen. After the removal of the catalyst, the solvent was evaporated to dryness and the crude products were purified by column chromatography (25 g,

toluene–ethyl acetate, 4:1), yielding the appropriate 3-hydroxy-17-substituted derivatives (**2a**–**5a**).

3-Hydroxy-17-iodide-16,17-secoestra-1,3,5(10)-triene-16-nitrile (**6a**) could not be obtained by this procedure. It was synthesized from 3-hydroxy-17-tosyloxy-16,17-secoestra-1,3,5(10)-triene-16-nitrile (**2a**), in the reaction with tetrabutyl ammonium iodide in ethylmethyl ketone.

2.2. Biological tests

Immature Wistar strain female rats (21–23 days old) were randomly divided into groups of six to eight animals each. The animals were treated by subcutaneous injection once a day for 3 days with 0.1 mL of a solution of the test compound in olive oil, either solely or in combination with estradiol benzoate (EB). The control group obtained the vehicle only. The total administered amount of tested compounds was 5 mg/kg of body weight (b.w.), except in case of tamoxifen, used as a comparator, where doses were 5 mg/kg b.w., i.e. 25 mg/kg b.w., whereas the EB dose was 30 μg/kg b.w. The animals were sacrificed on the fourth day. The uteri were removed, dissected free of adhering fat and blotted dry after expulsion of uterine fluid and the wet weights were recorded.

The uterotrophic assay was carried out in six different experiments, where every experiment had its own control and EB treated group. The means of the relative uteri weights in control groups from different experiments were comparable, as well as in the EB treated groups.

Percentage of agonist and antagonist activity in immature rat uterine weight assays were calculated from the ratio of values recorded in the treated and control animals, thus

$$\% \text{ agonism} = (C - A) \times 100/(B - A),$$

$$\% \text{ antagonism} = (B - D) \times 100/(B - A),$$

where A, B, C, and D are uterine wet weights, corrected for differences in body weights, i.e. (mg/100 g body weight) for vehicle alone, EB, test compound alone, or test compound plus EB, respectively.

3. Results and discussion

The starting compound, 3-benzyloxy-17-hydroxy-16,17-secoestra-1,3,5(10)-triene-16-nitrile (**1b**, Scheme 1) was synthesized in several synthetic steps, starting from estrone [1,2].

Action of tosyl chloride in dry pyridine upon compound **1b** afforded the corresponding 17-tosyl ester **2b**, in 84% yield. The substitution reaction of the 17-tosyloxy function of **2b** with tetrabutyl ammonium fluoride in refluxing ethylmethyl ketone afforded the 17-fluoro derivative **3b**, in a 70.4% yield.

On the other hand, 17-chloro-, bromo-, and -iodo-derivatives were obtained in high yields directly from secocyanoalcohol **1b**, in the substitution reaction of the 17-hydroxy function, with the appropriate reagents. Namely, the chloro-(**4b**) and bromo-(**5b**) derivatives were prepared from **1b** by the action of carbon tetrachloride, i.e., tetrabromide, in the presence of triphenylphosphine [3]. The iodo-(**6b**) derivative was formed by treating of compound **1b** with a mixture of triphenylphosphine, imidazole and iodine in toluene at reflux temperature [4].

The deprotection of the 3-hydroxy function of compounds **2b**–**5b** was performed by hydrogenolysis at room temperature and low hydrogen pressure, using Pd/C as a catalyst, whereby 3-hydroxy-16,17-seco-estrone derivatives **2a**–**5a** were obtained in satisfactory yields [5].

On the other hand, 3-hydroxy-17-iodo derivative **6a** could not be obtained by hydrogenolysis from the corresponding benzyl ether **6b**, probably due to some kind of long-range effect. Namely, this compound did not react at all under the mentioned reaction conditions, even if the reaction mixture was acidified (perchloric acid) and/or heated. Therefore, the derivative **6a** was synthesized by substitution of the tosyloxy function of compound **2a** with tetrabutyl ammonium iodide in ethyl methyl ketone [5].

The estrogenic and antiestrogenic effects of compounds **2a**–**6a** and **2b**–**6b** were tested on experimental animals, using the uterotrophic and antiuterotrophic assay [6]. The differences in uteri weights of treated and control animals served for the calculation of the agonistic and antagonistic effects [7], which are presented in Table 1.

As can be seen from Table 1, all the newly synthesized compounds exhibited an almost total loss of estrogenic activity, while many of them even prevented the action of endogenous estrogens.

It is known that the estrogens act at the level of estrogen receptors (ER), whereby the presence of free hydroxyl group at the aromatic moiety is necessary [8,9].

Table 1
Agonistic and antagonistic effects of compounds **2a**–**6a**, **2b**–**6b**, and tamoxifen

Compound	Dose (mg/kg)	*n*	Estrogenic effect (%, mean ± SEM)	*n*	Antiestogenic effect (%, mean ± SEM)
1a	5	6	−2.06 ± 1.06	8	21.13 ± 2.05
1b	5	7	0.71 ± 0.90	8	31.47 ± 2.26
2a	5	6	4.52 ± 5.72	7	26.34 ± 3.49
2b	5	7	−3.51 ± 0.36	7	23.37 ± 3.05
3a	5	6	0.48 ± 2.08	8	0.04 ± 6.44
3b	5	6	−4.21 ± 2.07	8	25.08 ± 2.26
4a	5	6	1.71 ± 0.70	7	32.95 ± 5.37
4b	5	7	−2.97 ± 0.88	7	25.13 ± 2.61
5a	5	7	0.80 ± 0.84	7	32.02 ± 3.52
5b	5	7	−0.19 ± 0.79	7	22.28 ± 4.08
6a	5	6	3.55 ± 4.77	7	16.08 ± 2.95
6b	5	6	−5.64 ± 1.29	7	3.62 ± 5.70
Tamoxifen	5	7	39.78 ± 3.13	—	—
Tamoxifen	25	8	39.36 ± 4.09	7	62.80 ± 2.13

Many of steroidal and nonsteroidal compounds with a phenolic function, even simple molecules, such as tetrahydronaphtol [9], show high affinity for binding to ER. However, this binding does not lead to the activation of the receptor, i.e., such derivatives do not express estrogenic action. For activation of the receptor, besides 3-OH function, the steroidal skeleton, as well as the presence of a 17-hydroxy group, is crucial.

It was expected that compound **1a**, fulfilling the mentioned requirements, will show estrogenic activity, but, surprisingly, it even hindered the action of endogenous estrogens. In order to explain such behaviour, we submitted the crystals of **1a** to X-ray structural analysis. The stereo diagram of the molecular structure of **1a** and its relevant crystal data are given in Fig. 1, i.e., Table 2. Selected torsion angles are given in Table 3. As it can be seen, in compound **1a** the 17-OH function has an opposite orientation in comparison to the 17β-OH group of estradiol, which is essential for ER activation.

The crystal packing arrangement of this compound could be seen in Table 4. It consists of coils formed by O1···N and O2···O1W hydrogen bonds along *b* axis. The coils are linked by O1W···O1 hydrogen bond.

On the other hand, the synthesized compounds, except **3a** and **6b**, expressed moderate antiestrogenic effects, which were regularly higher in the case of compounds with a free 3-OH function, than those bearing the 3-benzyloxy group. The biological action of 3-benzyloxy derivatives could be explained in two ways. Namely, it can be assumed that the animal etherases slowly deprotect the 3-OH group, giving the corresponding more active compound, or that the benzyl function is capable to bind to an allosteric site of ER via hydrophobic interaction, leading to conformational changes of the ER, which slightly hinder the binding of estradiol to the binding site.

With an aim to clarify these presumptions, experiments on in vitro systems will be undertaken. Furthermore, on the basis of molecular modelling data, synthesis of new derivatives of compound **1a**, directed towards obtaining of compounds with higher antagonistic effect will be performed.

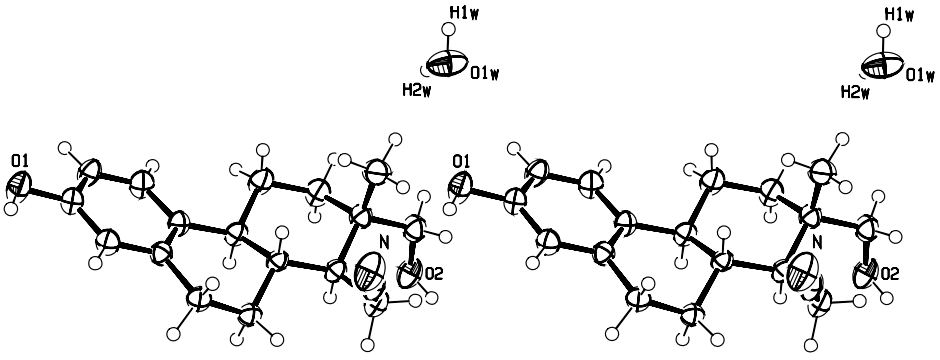


Fig. 1. The stereo diagram of the molecular structure of compound **1a** with the atomic labelling scheme. Displacement ellipsoids are drawn at the 30% probability level and the H atoms are shown as small spheres of arbitrary radii.

Table 2
Crystal data, data collection, and refinement parameters for compound **2a**

Crystal data	Data collection	Refinement parameters
$C_{18}H_{23}NO_2 + H_2O$	Siemens P4 diffractometer	Refinement on F^2
$M_r = 303.39$	$2\theta/\omega$ scans	$R[F^2 > 2\sigma(F^2)] = 0.0349$
Orthorhombic, $P2_12_12_1$	4392 Measured reflections	$wR(F^2) = 0.0848$, $w = 1/[\sigma^2(F_o^2) + (0.0443P)^2 + 0.3945P]$, where $P = (F_o^2 + 2F_c^2)/3$
$a = 8.0576(6)$ Å	3654 Independent reflections	
$b = 9.3546(7)$ Å	3287 Reflections with $I > 2\sigma(I)$	$S = 1.014$
$c = 21.1293(14)$ Å	$\theta_{min} = 2.38$	3654 Reflections
$V = 1592.6(2)$ Å^3	$\theta_{max} = 27.50$	299 Parameters
$Z = 4$	$h = -1 \rightarrow 10$	H-atom parameters constrained
$D_x = 1.265$ Mg m^{-3}	$k = 0 \rightarrow 12$	$(\Delta/\sigma)_{max} = 0.001$
Mo Kα radiation	$l = -27 \rightarrow 27$	$(\Delta\rho)_{max} = 0.162$ e Å^3
Cell parameters from 50 reflections	Three standard reflections	$(\Delta\rho)_{min} = -0.131$ e Å^3
$\theta = 7.677°$–$27.263°$	Frequency: 197 min	
$\mu = 0.085$ mm^{-1}	Intensity decay: none	
$T = 293(1)$ K		
Irregular ellipsoid, colourless		
$0.046 \times 0.044 \times 0.044$ mm		

Table 3
Selected torsion angles (°)

C_{13}–C_{14}–C_{15}–C_{16}	88.2(2)
C_{18}–C_{13}–C_{17}–O_2	171.5(1)

Table 4
Hydrogen-bonding geometry

D–H···A	*D*–H (Å)	H···A (Å)	*D*···A (°)	*D*–H···A (°)
O1–H1···N^{i}	0.83	2.24	3.004(2)	154(2)
O2–H2···O1W^{ii}	0.83	1.79	2.653(2)	179(3)
O1W–H2W···O1^{iii}	0.83	1.91	2.765(2)	172(2)

Symmetry code: (i) $1-x,\ 1/2+y,\ 1/2-z$; (ii) $1-x,\ -1/2+y,\ 1/2-z$; and (iii) $-x,\ -1/2+y,\ 1/2-z$.

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