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Synthesis and Studies of Structure and Biological Properties of D-Homoanalogs of Steroid Estrogens

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Abstract—In order to estimate the potential of steroid estrogens modification, three D-homoanalogs of estrogens have been prepared; their structures and biological properties have been studied. The expansion of D-ring in such compounds has lead to strong decrease if the uterotropic action, however, the unfavorable hypertriglyceridemic effect has been retained. The latter has been eliminated by combined action of the studied steroids and ursolic acid; therewith the hypocholesterolemic activity has been retained.

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Studies on animal models revealed that the modified steroid estrogens prevent cardiovascular diseases. These results led to wide application of estrogens in the hormonal replacement therapy [1–3] despite some later recognized side effects. The most serious of them were increased risk of the tumor development [4, 5], thrombosis [6, 7], and other complications. At the same time, estrogens were found to avert the resistance of breast tumors towards clinically used tamoxifen [8] and inhibit the growth of large intestine cancer cells [9], they were to some extent useful in prostate cancer treatment [10]. The complex of revealed properties initiated the search of new drugs based on steroid estrogens with improved biological activity.

One of the promising directions of such search may be the preparation and analysis of biological activity of D-homoanalogs of the natural steroid estrogens, as they usually exhibit much weaker hormonal activity than the corresponding compounds with 5-membered D ring [11]. In this work, we chose a well known steroid **I** as the starting compound [12]. It was of interest to compare its biological properties with those of its 6-oxa (**II**) and 2-fluoro (**III**) derivatives. The steroid **II** was expected to show weaker hormonal activity as compared with the carbon analog **I** [13]. Compound **III** was selected for preparation and study because 2-fluoroestradiol was not carcinogenic as revealed in the animal experiments [14, 15].

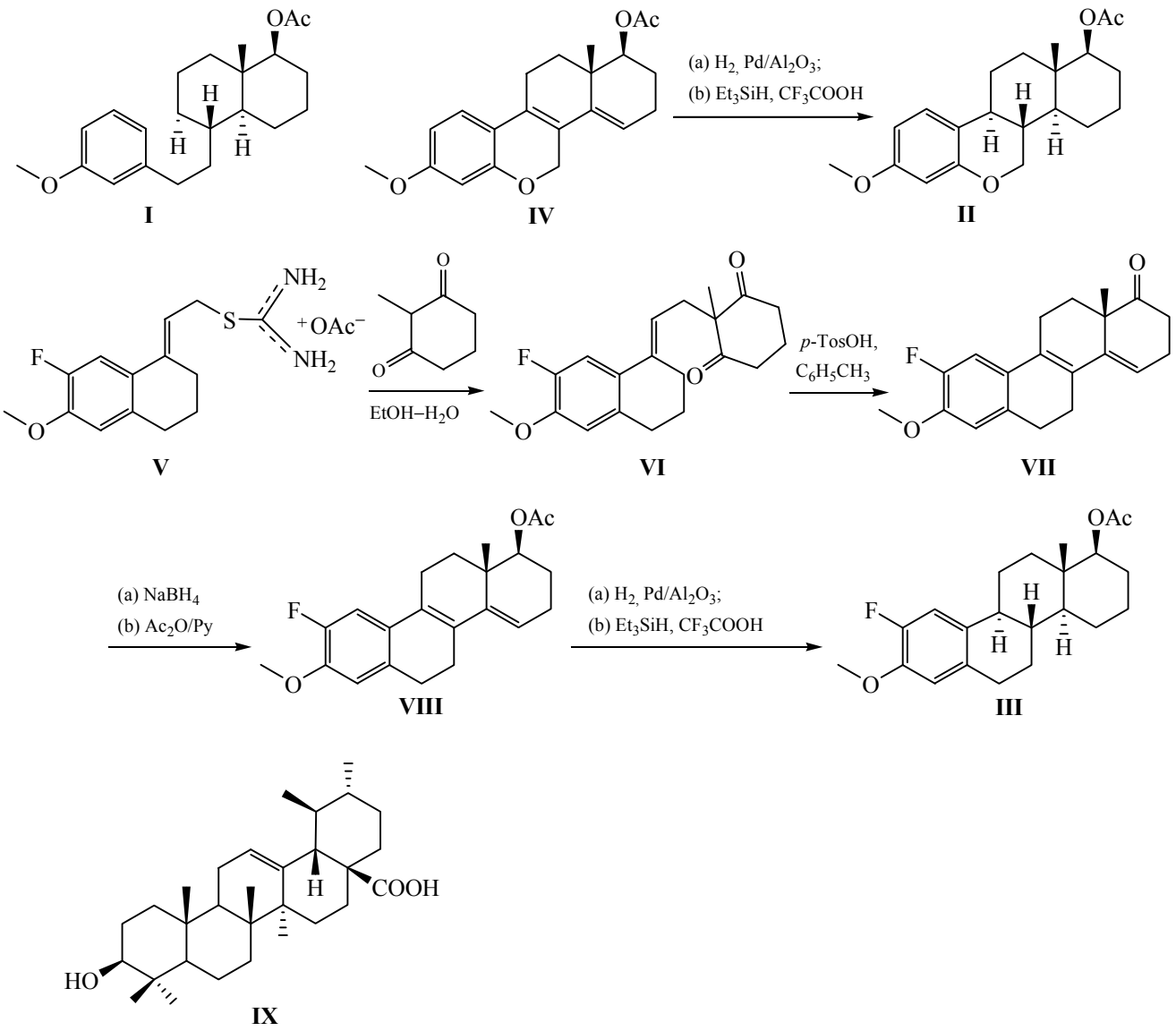
The model steroids were prepared via the Torgov–Avanchenko scheme [16] shown below.

Compound **I** was synthesized following a known procedure, its ^{1}H and ^{13}C NMR parameters corresponded to those reported previously [12].

In order to prepare **II**, the 14(15) double bond of the available estrapentaene **IV** [17] was selectively reduced in the presence of Pd/Al_2O_3, followed by the product hydrogenation by triethylsilane and trifluoroacetic acid. The target product yield was 67% (in two stages), noticeably higher than that in the case of direct ionic hydrogenation of the same substrate (25%, [17]).

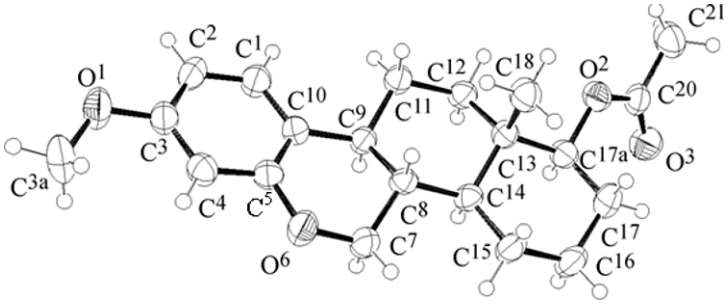
The structure of **II** was previously studied by XRD [18], however, detailed results were not published. In Tables 1 and 2 we present the torsion angles of **II** in the crystal; this data were used to calculate the distances between hydrogen atoms. The spatial structure of **II** is shown in the figure.

Further, we assigned the signals in the ^{1}H and ^{13}C NMR spectra of **II** applying the following methods: COSY-90, COSY-DQF, J-COSY, COLOC, NOESY, and DEPT-135 [19] that allowed calculation of some distances between hydrogen atoms in the solutions of **II** (Table 2). The tabulated data demonstrated that the conformations of **II** in the crystal and in the solution were identical, and were well in line with those calculated with the MM+ method. That proved that the MM+ method could be used to dock similar



compounds into the proteins structures for predicting the biological properties of the potentially interesting modified steroids.

Uterotropic activity of **I–III** was determined as described in [20, 21]. As was expected, all the modified estrogens revealed noticeably weaker hormonal activity as compared with the reference, 17α-ethynylestradiol. At the action of all model compounds, cholesterol concentration in blood serum decreased, however, triglycerides content increased. That was a serious drawback, as hypertriglyceridemia



General view of steroid **II** molecule according to X-Ray diffraction data.

Table 1. Torsion angles ω (deg) in compound **II**

Angle	ω	Angle	ω
$C^{10}C^{1}C^{2}C^{3}$	–0.4(7)	$C^{9}–C^{11}–C^{12}–C^{13}$	55.1(4)
$C^{11}C^{12}C^{13}C^{17a}$	–172.2(3)	$C^{3a}–O^{1}–C^{3}–C^{4}$	7.1(6)
$C^{11}C^{12}C^{13}C^{18}$	67.0(4)	$C^{3a}–O^{1}–C^{3}–C^{2}$	–172.3(4)
$C^{11}C^{12}C^{13}C^{14}$	–56.3(4)	$C^{1}–C^{2}–C^{3}–C^{4}$	–0.5(6)
$C^{7}C^{8}C^{14}C^{15}$	50.4(5)	$C^{1}–C^{2}–C^{3}–O^{1}$	178.9(4)
$C^{9}C^{8}C^{14}C^{15}$	171.7(3)	$O^{1}–C^{3}–C^{4}–C^{5}$	–178.9(4)
$C^{7}C^{8}C^{14}C^{13}$	178.0(3)	$C^{2}–C^{3}–C^{4}–C^{5}$	0.6(6)
$C^{9}C^{8}C^{14}C^{13}$	–60.7(4)	$C^{7}–O^{6}–C^{5}–C^{10}$	11.0(5)
$C^{12}C^{13}C^{14}C^{15}$	–172.9(3)	$C^{7}–O^{6}–C^{5}–C^{4}$	169.1(4)
$C^{17a}C^{13}C^{14}C^{15}$	–55.2(4)	$C^{3}–C^{4}–C^{5}–O^{6}$	–179.6(3)
$C^{18}C^{13}C^{14}C^{15}$	65.0(4)	$C^{3}–C^{4}–C^{5}–C^{10}$	0.3(6)
$C^{12}C^{13}C^{14}C^{8}$	58.3(4)	$C^{5}–O^{6}–C^{7}–C^{8}$	–40.6(5)
$C^{17a}C^{13}C^{14}C^{8}$	175.9(3)	$O^{6}–C^{7}–C^{8}–C^{9}$	60.3(4)
$C^{18}C^{13}C^{14}C^{8}$	–63.9(4)	$O^{6}–C^{7}–C^{8}–C^{14}$	–177.2(3)
$C^{8}C^{14}C^{15}C^{16}$	–177.7(3)	$C^{7}–C^{8}–C^{9}–C^{10}$	–50.0(4)
$C^{14}C^{15}C^{16}C^{17}$	–55.2(5)	$C^{14}–C^{8}–C^{9}–C^{10}$	–173.8(3)
$C^{15}C^{16}C^{17}C^{17a}$	55.6(5)	$C^{7}–C^{8}–C^{9}–C^{11}$	–177.7(3)
$C^{20}O^{2}C^{17a}C^{17}$	–73.0(4)	$C^{14}–C^{8}–C^{9}–C^{11}$	58.5(4)
$C^{20}O^{2}C^{17a}C^{13}$	163.1(3)	$O^{6}–C^{5}–C^{10}–C^{1}$	178.7(4)
$C^{16}C^{17}C^{17a}O^{2}$	–177.5(3)	$C^{4}–C^{5}–C^{10}–C^{1}$	–1.2(5)
$C^{16}C^{17}C^{17a}C^{13}$	–58.0(4)	$O^{6}–C^{5}–C^{10}–C^{9}$	–2.7(6)
$C^{12}C^{13}C^{17a}O^{2}$	–64.5(4)	$C^{4}–C^{5}–C^{10}–C^{9}$	177.4(4)
$C^{18}C^{13}C^{17a}O^{2}$	56.9(4)	$C^{2}–C^{1}–C^{10}–C^{5}$	1.2(6)
$C^{14}C^{13}C^{17a}O^{2}$	178.8(3)	$C^{2}–C^{1}–C^{10}–C^{9}$	–177.3(4)
$C^{12}C^{13}C^{17a}C^{17}$	173.5(3)	$C^{8}–C^{9}–C^{10}–C^{5}$	23.6(5)
$C^{18}C^{13}C^{17a}C^{17}$	–65.1(4)	$C^{11}–C^{9}–C^{10}–C^{5}$	149.1(3)
$C^{14}C^{13}C^{17a}C^{17}$	56.8(4)	$C^{8}–C^{9}–C^{10}–C^{1}$	–158.0(4)
$C^{17a}O^{2}C^{20}O^{3}$	–3.6(5)	$C^{11}–C^{9}–C^{10}–C^{1}$	–32.4(5)
$C^{17a}O^{2}C^{20}C^{21}$	175.5(3)	$C^{10}–C^{9}–C^{11}–C^{12}$	–179.7(3)
		$C^{8}–C^{9}–C^{11}–C^{12}$	–54.4(4)

Table 2. Bond lengths (Å) of hydrogen in steroid **II**

Bond	Method		
	X-Ray	NMR	MM+
$H^{1}–H^{11\alpha}$	2.15	2.10	2.16
$H^{1}–H^{11\beta}$	2.90		3.04
$H^{1}–H^{9\alpha}$	3.09	3.01	3.03
$H^{7\alpha}–H^{14\alpha}$	2.58	2.63	2.74
$H^{7\alpha}–H^{15\alpha}$	2.81		3.03
$H^{7\alpha}–H^{15\beta}$	3.93		4.11
$H^{7\beta}–H^{8\beta}$	2.43	2.45	2.53
$H^{7\beta}–H^{15\alpha}$	2.02	2.11	2.15
$H^{7\beta}–H^{15\beta}$	2.81	2.85	2.95
$H^{8\beta}–H^{11\beta}$	2.60		2.63
$H^{8\beta}–H^{15\beta}$	2.68		2.73
$H^{9\alpha}–H^{14\alpha}$	2.45	2.51	2.43
$H^{9\alpha}–H^{12\alpha}$	2.55	2.54	2.58
$H^{11\alpha}–H^{12\beta}$	2.48	2.42	2.47
$H^{11\beta}–H^{12\alpha}$	3.02		3.09
$H^{12\alpha}–H^{17a\alpha}$	2.40	2.34	2.36
$H^{12\alpha}–H^{14\alpha}$	2.52		2.53
$H^{14\alpha}–H^{16\alpha}$	2.49	2.41	2.45
$H^{15\alpha}–H^{16\beta}$	2.48		2.49
$H^{15\alpha}–H^{16\alpha}$	2.44		2.43
$H^{15\beta}–H^{17\beta}$	2.44		2.76
$H^{16\alpha}–H^{17a\alpha}$	2.46		2.62

was considered an independent risk factor related to cardiovascular diseases [22, 23].

As was shown previously, ursolic acid **IX** revealed hypotriglyceridemic and hypocholesteremic actions [24, 25]. That triterpenoid blocked the growth of various cancer cells, affecting, in particular, the stages of apoptosis [26] and angiogenesis [27]. Basing on that, we studied the effect of combined action of steroid **III** and ursolic acid. In the experiment, ursolic acid practically did not influence the hypocholesteremic and uterotropic activity of **III**; at the same time, in combination **III** and **IX** did not lead to hypertriglyceridemia.

In the course of prolonged action of antiestrogens in the hormone-dependent breast tumors, the tumor cells may become resistant to the corresponding drug; however, under action of estradiol the sensitivity to antiestrogens could be restored [8]. Thus, it is of interest to test further the action of steroids similar to **III** in combination with ursolic acid on the resistivity of the tumor cells towards antiestrogens.

EXPERIMENTAL

The compounds purity was checked by thin layer chromatography (Silufol plates, petroleum ether –

ethyl acetate 6:1, 4:1, or 3:1). All the prepared steroids were racemic mixtures.

NMR spectra of the solutions in $CDCl_3$ were recorded at 295 K with a spectrometer DPX-300 Bruker at 300.130 MHz (^1H) and 75.468 MHz (^{13}C); the signal of residual $CHCl_3$ was used as internal reference.

17aβ-Acetoxy-3-methoxy-D-homoestra-1,3,5(10)-triene (I) was prepared as described in [13], mp 167–169°C (mp 167–169°C [12]). The prepared compound did not show the melting point depression at mixing with a reference sample. ^1H NMR spectrum, δ, ppm: 7.21 (C^1H), 6.72 (C^2H), 6.62 (C^4H), 2.83 (C^6H^α), 2.83 (C^6H^β), 1.22 (C^7H^α), 2.06 (C^7H^β), 1.31 (C^8H^β), 2.27 (C^9H^α), 2.26 ($C^{11}H^\alpha$), 1.43 ($C^{11}H^\beta$), 1.30 ($C^{12}H^\alpha$), 1.81 ($C^{12}H^\beta$), 1.10 ($C^{14}H^\alpha$), 1.74 ($C^{15}H^\alpha$), 1.06 ($C^{15}H^\beta$), 1.39 ($C^{16}H^\alpha$), 1.83 ($C^{16}H^\beta$), 1.73 ($C^{17}H^\alpha$), 1.56 ($C^{17}H^\beta$), 4.57 ($C^{17a}H^\alpha$), 0.92 ($C^{18}H_3$), 3.78 (CH_3O), and 2.08 ($\underline{CH_3}CO$). ^{13}C NMR spectrum, δ, ppm: 126.2 (C^1), 111.5 (C^2), 157.3 (C^3), 113.3 (C^4), 137.7 (C^5), 30.0 (C^6), 26.3 (C^7), 38.3 (C^8), 43.2 (C^9), 132.7 (C^{10}), 25.8 (C^{11}), 36.8 (C^{12}), 38.1 (C^{13}), 48.6 (C^{14}), 22.8 (C^{15}), 23.8 (C^{16}), 26.5 (C^{17}), 81.3 (C^{17a}), 11.7 (C^{18}), 55.1 (CH_3O), 21.2, and 170.8 (CH_3CO). Found, %: C 77.11; H 8.97. $C_{22}H_{30}O_3$. Calculated, %; C 77.16; H 8.68.

17aβ-Acetoxy-3-methoxy-6-oxa-D-homoestra-1,3.5(10)-triene (II). 0.3 g of 5% Pd on aluminum oxide was added to a solution of 1 g of **IV** [26] in 100 mL of ethyl acetate; the hydrogenation was performed till uptake of 1 mol of hydrogen per 1 mol of substrate was reached. The catalyst was filtered off, and the solvent was evaporated on a rotary evaporator. The residue was dissolved in 20 mL of benzene; 10 mL of triethylsilane and 5 mL of trifluoroacetic acid were added. The reaction mixture was incubated at room temperature during 24 h, and then poured in 100 mL of water. After treating as usual, the target compound **II** was crystallized from chloroform–methanol mixture. Yield 0.68 g (67%), mp 175–177°C. ^1H NMR spectrum, δ, ppm: 7.06 (C^1H), 6.45 (C^2H), 6.34 (C^4H), 3.73 (C^7H^α), 4.37 (C^7H^β), 1.70 (C^8H^β), 2.37 (C^9H^α), 2.21 ($C^{11}H^\alpha$), 1.40 ($C^{11}H^\beta$), 1.30 ($C^{12}H^\alpha$), 1.82 ($C^{12}H^\beta$), 1.12 ($C^{14}H^\alpha$), 1.48 ($C^{15}H^\alpha$), 1.18 ($C^{15}H^\beta$), 1.34 ($C^{16}H^\alpha$), 1.80 ($C^{16}H^\beta$), 1.75 ($C^{17}H^\alpha$), 1.58 ($C^{17}H^\beta$), 4.57 ($C^{17a}H^\alpha$), 0.95 ($C^{18}H_3$), 3.75 (CH_3O), and 2.04 ($\underline{CH_3}CO$). ^{13}C NMR spectrum, δ_C, ppm: 126.0 (C^1), 106.4 (C^2), 159.0 (C^3), 101.0 (C^4), 154.5 (C^5), 67.9 (C^7), 35.8 (C^8), 39.5 (C^9), 118.0 (C^{10}), 24.6 (C^{11}), 36.2 (C^{12}), 38.0 (C^{13}), 45.4 (C^{14}), 22.7 (C^{15}), 23.6 (C^{16}), 26.4 (C^{17}), 80.7 (C^{17a}), 11.6 (C^{18}), 54.8 (CH_3O), 21.1, and 170.7 (CH_3CO). Found, %: C 73.27; H 8.33. $C_{21}H_{28}O_4$. Calculated, %: C 73.23; H 8.19.

17aβ-Acetoxy-3-methoxy-2-fluoro-D-homo-1,3,5(10)-estratriene (III). A mixture of 1.70 g of isothiuronium salt **V** [13] and 1.20 g of 2-methylcyclohexa-1,3-dione in 40 mL of ethanol–water (1:1) mixture was subjected to ultrasonic irradiation during 10 min till complete dissolution of solids, and then it was stirred at 40°C during 70 h. The formed precipitate was filtered off, washed with methanol, and dried in air. 0.92 g of secosteroid **VI** was obtained (56%), mp 108–110°C. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.28 s (3H, $C^{18}H_3$), 3.85 s (3H, CH_3O), 5.52 t (1H, $C^{11}H$, J 7.8 Hz), 6.61 d (1H, C^4H, $^4J_{HF}$ 8.8 Hz), 7.18 d (1H, C^1H, $^3J_{HF}$ 13.7 Hz). Found, %: C 72.80; H 6.96. $C_{20}H_{23}FO_3$. Calculated, %: C 72.71; H 7.02.

To a solution of 0.8 g of **VI** in 60 mL of toluene was added 0.05 g of *p*-toluenesulfonic acid monohydrate; the reaction mixture was refluxed during 30 min, cooled to room temperature, and washed with sodium hydrogen carbonate solution (5%). The organic layer was separated and the solvent was evaporated in a vacuum. To the residue 30 mL of ethanol was added, and the mixture was subjected to ultrasonic irradiation during 5 min. After cooling to –5°C, 0.2 g of sodium borohydride was added, and the mixture was left standing for 24 h. The reducer excess was decomposed by slow addition of acetic acid at stirring. After the usual treatment [20], the reduction products were dissolved in 5 mL of pyridine, 5 mL of acetic anhydride was added, and the reaction mixture was incubated at 40°C during 24 h. The acetylation product was then purified by column chromatography (silica gel: Merck, 40–63, eluent: hexane – diethyl ether 3:1). After crystallization from chloroform–methanol 1:5 mixture, 0.64 g (74%) of acetate **VIII** was obtained, mp. 138–140°C. Found, %: C 74.07; H 6.88. $C_{22}H_{25}FO_3$. Calculated, %: C 74.13; H 7.07.

To a solution of 0.3 g of acetate **VIII** in 20 mL of THF 200 mg of $Pd/CaCO_3$ (10%) was added; the hydrogenation was performed at room temperature till uptake of hydrogen was enough for saturating one double bond. The catalyst was filtered off and washed with methanol; the solutions were combined, and the solvents were evaporated in a vacuum. To a solution of 0.3 g of the hydrogenation product and 0.3 mL of triethylsilane in 7.5 mL of anhydrous methylene chloride was added at stirring at 0°C 2.5 mL of trifluoroacetic

acid; the mixture was incubated at room temperature during 4 days and then poured onto ice. The products were extracted with three portions of ether (50 mL each). The combined organic layers were washed with water, 2 M aqueous sodium hydrogen carbonate, water, and brine; then the mixture was dried over anhydrous sodium sulfate. After removal of the solvents, the semi-crystalline residue was washed with methanol and crystallized from methanol–chloroform 10:1 mixture. Yield of the target steroid **III** was 0.16 g (53%), mp 164–166°C, after additional purification via HPLC mp 168–169°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.92 s (3H, $C^{18}H_3$), 2.02 s (3H, CH_3C=O), 3.82 s (3H, CH_3O), 4.54 d. d (1H, $C^{17a}H$, *J* 4.6, 11.4 Hz), 6.63 d (1H, C^4H, $^4J_{HF}$ 8.6 Hz), 6.96 d (1H, C^1H, $^3J_{HF}$ 13.2 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 11.7 (C^{18}), 21.1 ($\underline{C}H_3CO$), 22.9 (C^{16}), 23.9 (C^{15}), 25.9 (C^{17}), 26.4 (C^7 or C^{11}), 26.6 (C^7 or C^{11}), 29.5(C^6), 36.9 (C^{12}), 38.1 (C^8 and C^{13}), 43.2 (C^9), 48.7 (C^{14}), 56.3 (CH_3O), 81.3 (C^{17a}), 112.9 d (C^1, $^2J_{CF}$ 17.5 Hz), 113.5 (C^4), 133.4 (C^5), 142.5 (C^3, $^2J_{CF}$ 11 Hz), 150.8 d (C^2, $^1J_{CF}$ 240 Hz), 170.9 (CH_3CO). Found, %: C 73.04; H 8.22. $C_{22}H_{29}FO_3$. Calculated, %: C 73.31; H 8.11.

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