Synthesis and Evaluation of Azole-substituted 2-Aryl-6-methoxy-3,4-dihydronaphthalenes and -naphthalenes as Inhibitors of 17α-Hydroxylase-C17,20-Lyase (P450 17)☆

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Summary

The synthesis and biological evaluation of azole-substituted 3,4-dihydronaphthalenes (**7a**, **7b**, **14a**, **14b**) and naphthalenes (**12a**, **12b**, **16a**, **16b**) as nonsteroidal inhibitors of 17α-hydroxylase-C17,20-lyase (P450 17, CYP 17) are described. In the case of the dihydronaphthalenes, introduction of the phenyl substituent into the 2-position was accomplished by coupling 2-hydroxy-3,4-dihydronaphthalene-2-trifluoromethanesulfonate **1** with the corresponding aryl-Zn-bromides **4a** and **4b** in the presence of $Pd(PPh_3)_4$ as catalyst yielding **5a** and **5b** as key intermediates. In the case of the naphthalenes, 2-bromonaphthalene **9** was reacted with the corresponding Grignard reagents yielding **10a** and **10b**. After transformation of the intermediate acetals **5a**, **5b**, **10a**, **10b** into the corresponding aldehydes, the latter compounds were reacted with tosylmethyl isocyanide and K_2CO_3 to give the oxazoles **7a**, **7b**, **12a**, and **12b**. The imidazoles **14a**, **14b**, **16a**, and **16b** were prepared by heating the corresponding 4-tosyloxazolines in ammonia, which were prepared by reacting the aldehydes with tosylmethyl isocyanide and NaCN. Using a microsomal fraction of human testicular enzyme, the title compounds did not inhibit the target enzyme.

Introduction

Two strategies are conceivable for the therapy of hormone dependent tumors: The use of hormone antagonists and the application of inhibitors of hormone biosynthesis. In the case of estrogen dependent breast cancer both methods have been realized in the meantime[1]. As an alternative to antiestrogen treatment[2], highly potent inhibitors of estrogen biosynthesis have been developed recently, some of which already have been admitted to the market (fadrozole, anastrozole, letrozole)[3–5]. Efforts are currently being undertaken to develop inhibitors of androgen biosynthesis[6,7], as alternatives to antiandrogens (flutamide, cyproterone acetate)[8,9] and GnRH analogs (such as busereline)[10]. The enzyme in question is 17α-hydroxylase-C17,20-lyase (P450 17) which catalyzes the conversion of progesterone and pregnenolone into the androgens, androstenedione and dehydro*epi*androsterone (DHEA), respectively[11,12]. Recently we have shown[6,13,14] that a dihydro- or tetrahydronaphthalene nucleus is able to give – after linkage with an N containing heterocycle such as imidazole, pyrazine, or pyridine – highly potent inhibitors of P450 17 (e.g., **I** and **II**, Chart 1[6]). While the heterocyclic N is complexing the heme iron of P450 17, the rest of the molecule interacts with the apoprotein moiety. In the case of steroidal compounds, it has recently been shown[7,15] that an imidazole ring at the C-17 position leads to potent inhibitors as well (e.g., **III**, Chart 1[7]). The present paper describes the synthesis of imidazole and oxazole-substituted 3,4-dihydronaphthalenes and naphthalenes (**7a**, **7b**, **12a**, **12b**, **14a**, **14b**, **16a**, and **16b**, Chart 1) and their biological evaluation. A phenyl ring instead of a methylene group is used as a spacer between the two ring systems leading to conformationally constrained compounds.

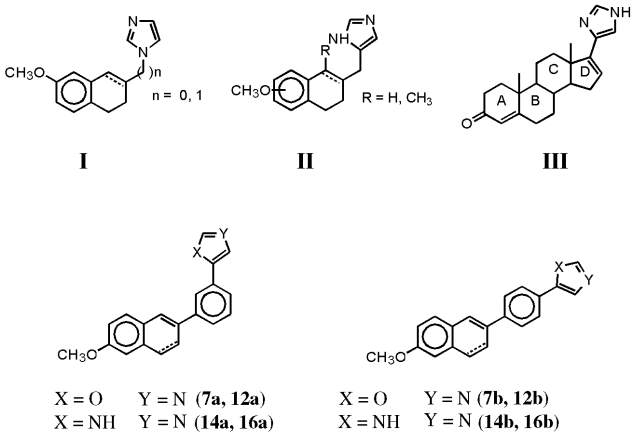

Chart 1. Selected inhibitors of P450 17 (**I**–**III**) and the title compounds.

Synthesis

6-Methoxy-2-tetralone was used as starting material for the synthesis of the dihydronaphthalenes **7** and **14** (Scheme 1). Reaction with trifluoromethanesulfonic acid anhydride gave the corresponding trifluoromethanesulfonate **1**[16]. After protection of the aldehyde group in the bromo compounds **2a** and **2b**, the corresponding acetals **3a** and **3b** were reacted with t-BuLi and $ZnCl_2$. Using a described procedure[17], the *in situ* formed compounds **4a** and **4b** were converted with **1**, using the palladium complex $Pd(PPh_3)_4$ as catalyst, to yield compounds **5a** and **5b**. After deprotection, the aldehydes **6a** and **6b** were either transformed to the oxazole compounds **7a** and **7b** using equimolar quantities of tosylmethyl isocyanide (TosMIC) [18], or were converted to the imidazole derivatives **14a** and **14b**. For the synthesis of the latter compounds, reaction of the aldehydes **6a** and **6b** with TosMIC and sodium cyanide to yield the corresponding 4-tosyloxazolines **13a** and **13b** and subsequent heating of **13a** and **13b** in saturated methanolic ammonia was performed[19].

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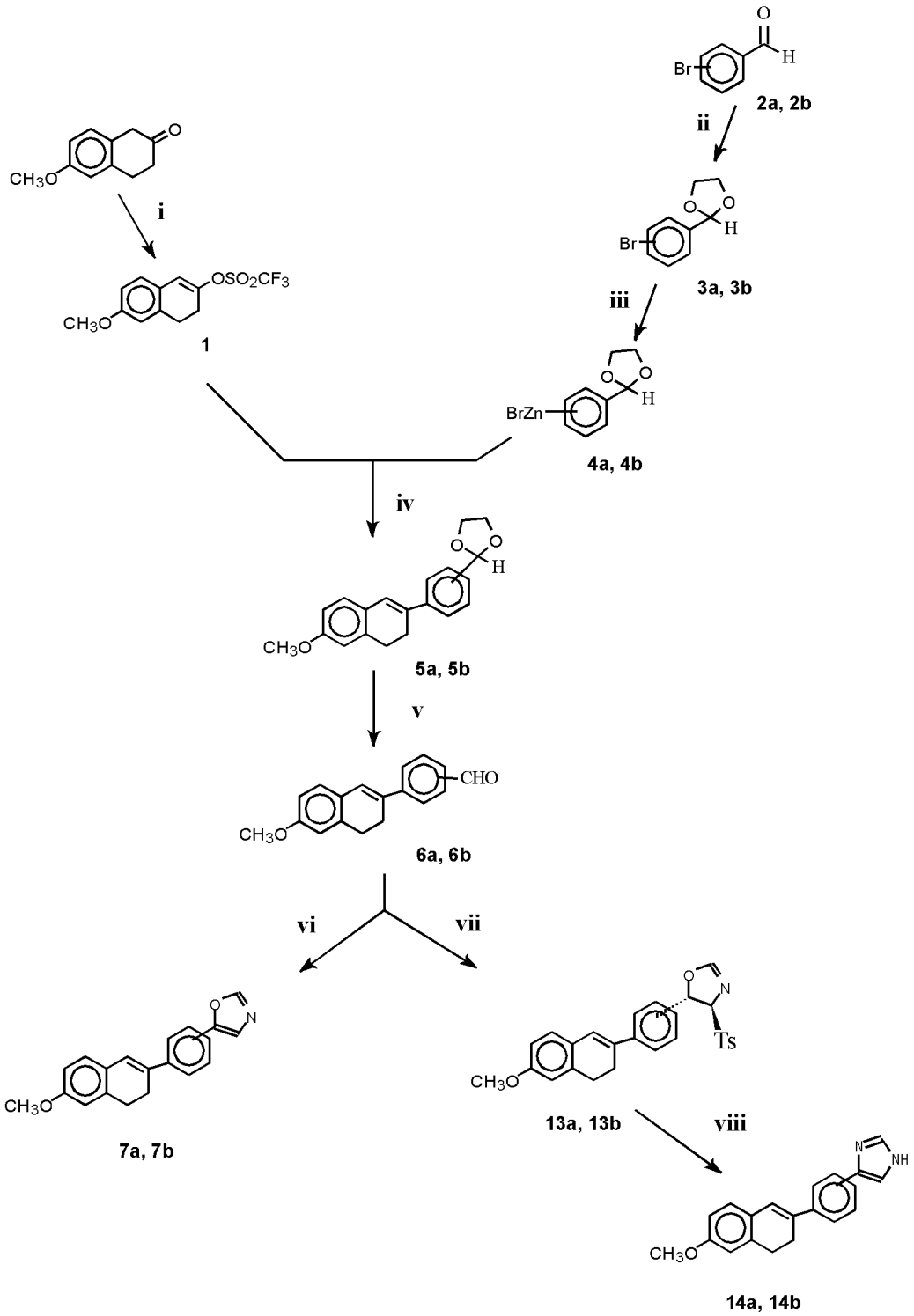
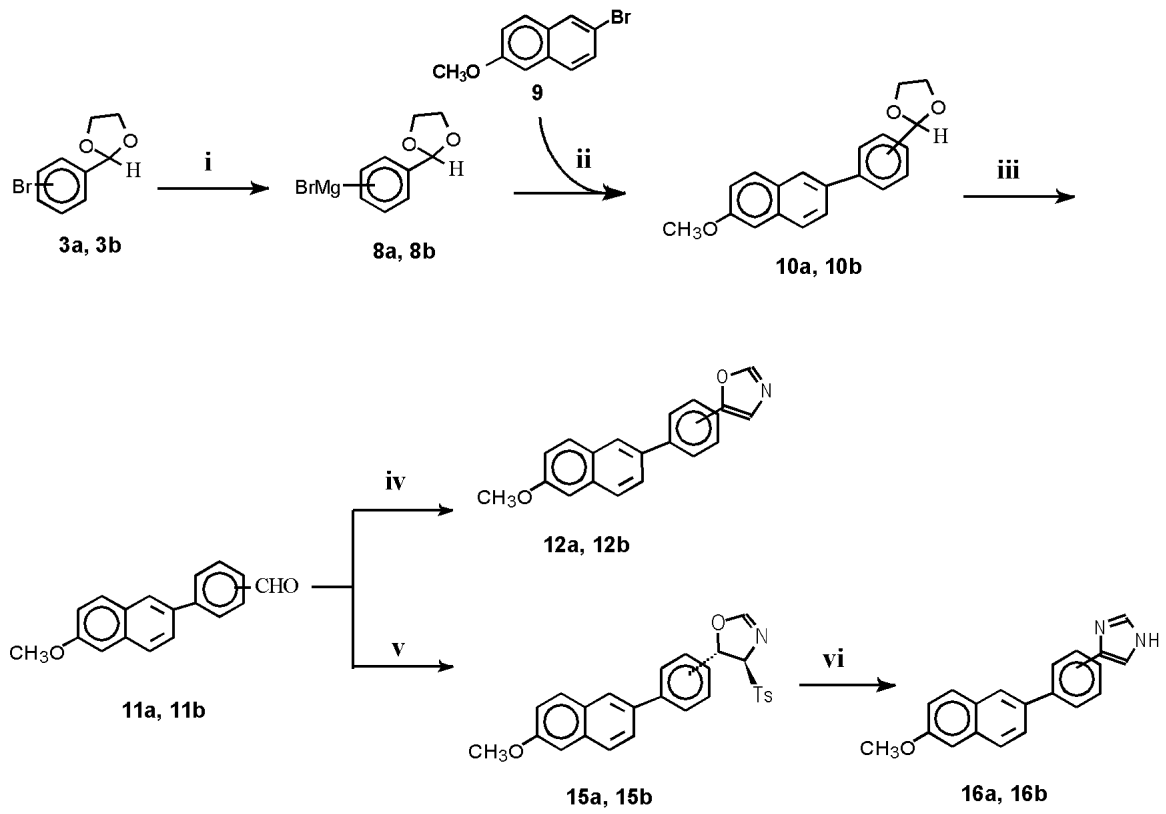


a: meta substitution **b**: para substitution **Ts**: p-tolylsulfonyl

i) $O(SO_2CF_3)_2$, Py, CH_2Cl_2, N_2, rt, 2 d; **ii)** ethylene glycol, TsOH, toluene, reflux, 4 d;
iii) t-BuLi, $ZnCl_2$, THF, N_2, –78 °C; **iv)** $Pd(PPh_3)_4$, THF, N_2, 65 °C, 2 h;
v) 10% HCl, THF, rt, 10 h; **vi)** TosMIC, K_2CO_3, CH_3OH, reflux, 3 h;
vii) TosMIC, NaCN, EtOH, THF, 0 °C , 2 h; **viii)** NH_3, CH_3OH, THF, 110–120 °C, 24 h.

Scheme 1. Synthesis of **7a**, **7b**, **14a**, and **14b**.



a: meta substitution **b**: para substitution **Ts**: p-tolylsulfonyl

i) Mg, I_2, THF, N_2, rt, 2 h; **ii)** $Pd(PPh_3)_4$, THF, N_2, 65 °C, 2 h;
iii) 10% HCl, THF, rt, 10 h; **iv)** TosMIC, K_2CO_3, CH_3OH, reflux, 3 h;
v) TosMIC, NaCN, EtOH, THF, 0 °C , 2 h; **vi)** NH_3, CH_3OH, THF, 110–120 °C, 24 h.

Scheme 2. Synthesis of **12a**, **12b**, **16a**, and **16b**.

For the synthesis of the naphthalene compounds **12** and **16**, a different coupling reaction was used (Scheme 2). The acetals **3a** and **3b** were converted to the Grignard reagents **8a** and **8b** which were reacted with 2-bromo-6-methoxynaphthalene **9** using $Pd(PPh_3)_4$ as catalyst. The resulting 2-arylnaphthalenes **10a** and **10b** were further converted to the title compounds using the same reactions as for the dihydronaphthalenes.

Results and Discussion

Compounds **7a**, **7b**, **12a**, **12b**, **14a**, **14b**, **16a**, and **16b** were tested for inhibition of P450 17 using human testicular enzyme as well as progesterone as substrate (25 μM) employing the procedure recently described[20]. Tested at a concentration of 2.5 μM, the title compounds showed no inhibitory activity (**7a**, –19.6%, **7b**, –13.5%, **12a**, –10.2% and **12b**, 3.9%, **14a**, –4.0%, **14b**, –9.9%, **16a**, –4.6% and **16b**, 2.8%). This result is probably due to the fact that there is no energetically preferred conformation of these azoles to fit properly into the active site of the enzyme. In order to find an explanation for this, molecular modeling studies were performed using energy-minimized conformations of the title compounds and the highly potent steroidal inhibitor **III**. Superimposition of these compounds is shown in Figure 1. It becomes apparent that the D ring and the heterocycle of the meta substituted compounds fit well with the steroidal template. A large difference, however, can be seen with respect to the A and B ring systems. This is true for the para substituted compounds as well. The different orientation of the keto group of the steroidal compound **III** and the methoxy group of the title compounds seems to be a plausible reason for their poor inhibitory activity.

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Experimental Section

Melting points were determined on a Kofler microscope (Reichert; Vienna) and are not corrected. Elemental analyses were performed at the Inorganic Chemistry Department of the Universität des Saarlandes and were within ±0.4% of the calculated values. Mass spectra (EI) were recorded on

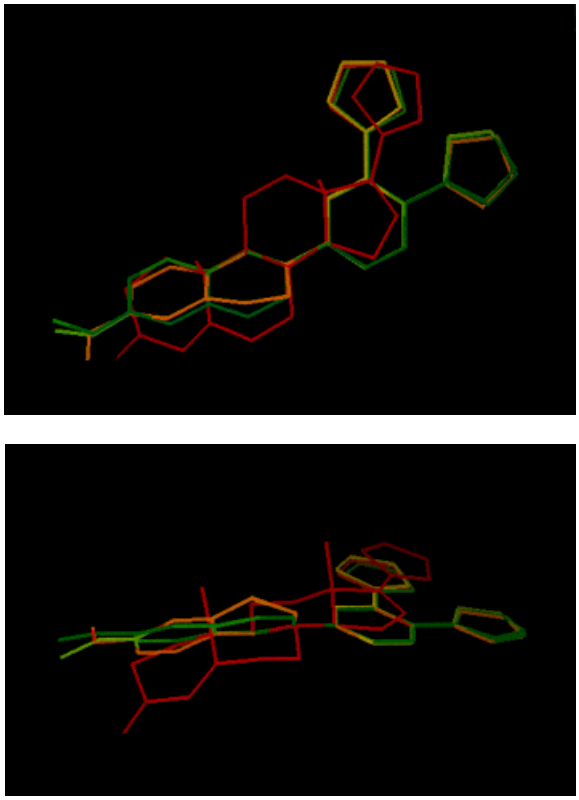

Figure 1. Superimposition of the lowest-energy conformation of the title compounds with **III** (red); top: from β side; bottom: from front side.

a HP G1800A GCD. ^{1}H-NMR spectra were measured on a Bruker AM 400 (400 MHz) and are consistent with the assigned structures. IR spectra of KBr disks were measured on a Perkin-Elmer Infrared Spectrometer 398. Silica gel 60 from Macherey & Nagel was used for column chromatography. Petroleum ether refers to petroleum ether (40-60 °C).

*2-Hydroxy-6-methoxy-3,4-dihydronaphthalene-2-trifluoromethanesulfonate (**1**)*

Trifluoromethanesulfonic acid anhydride (5.4 ml, 32 mmol) was added slowly to a stirred solution of 6-methoxy-2-tetralone (4.2 g, 24 mmol) and pyridine (3.2 g, 40 mmol) in CH_2Cl_2 (250 ml) under nitrogen atmosphere at 0 °C. The mixture was stirred at room temperature for 2 days. The end of reaction was determined by TLC control. Then 200 ml water was added slowly in an ice-bath. The reaction mixture was worked up with saturated $NaHCO_3$ and extracted three times with CH_2Cl_2 (150 ml). The organic layer was washed with H_2O, dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was purified by silica gel column chromatography using 4% EtOAc / petroleum ether as eluent to give 4.3 g (60%) of compound **1**.– Mp 35–37 °C.– ^{1}H NMR ($CDCl_3$): δ = 2.66 (t, *J* = 8.4 Hz, 2H, $ArCH_2CH_2$), 3.03 (t, *J* = 8.4 Hz, 2H, $ArCH_2$), 3.80 (s, 3H, OCH_3), 6.43 (s, 1H, HC=), 6.68 (m, 2H, Ar-H, -H5, -H7), 6.70 (d, *J* = 8.4, Hz, 1H, Ar-H, -H8).

*2-(3-Bromophenyl)-1,3-dioxolane (**3a**)*

A mixture of 3-bromobenzaldehyde **2a** (39.8 g, 25 ml, 214 mmol), ethylene glycol (14 g, 226 mmol), and toluene sulfonic acid (p-TsOH-H_2O) (714 mg, 3.75 mmol) in toluene (200 ml) was heated at reflux in a flask equipped with a Dean-Stark apparatus. After 8 h, ethylene glycol (4.65 g, 75 mmol) was added and the mixture was refluxed for 4 days. The reaction mixture was cooled to room temperature, washed with 1N $NaHCO_3$, brine, and dried over Na_2SO_4. After the solvent was removed *in vacuo*, the residue was distilled to give 33 g (68%) of **3a**, oil, bp 132–133 °C/8.0 Torr.

*2-(4-Bromophenyl)-1,3-dioxolane (**3b**)*

23 g (124 mmol) of **2b** gave 24.5 g of **3b** (86%), oil, bp 107 °C/2 Torr.

*6-Methoxy-2-3-(1,3-dioxolan-2-yl)phenyl-3,4-dihydronaphthalene (**5a**)*

A stirred solution of **3a** (3.65 g, 15 mmol, 2.5 eq) in THF (50 ml) was treated with t-BuLi (20 ml, 30 mmol, 5 eq) under dry nitrogen at –75 °C. Then a slurry of $ZnCl_2$ (2.04 g, 15 mmol, 2.5 eq) in THF (10 ml) was added. The mixture was warmed to room temperature, before triflate **1** (1.85 g, 6.0 mmol, 1 eq) and $Pd(PPh_3)_4$ (0.23 g, 0.2 mmol) were added and then heated under reflux for 2 h. The solution was worked up with 3 N HCl and extracted three times with CH_2Cl_2 (100 ml). The organic layer was washed with brine, dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was purified by silica gel column chromatography using 4% EtOAc/petroleum ether as eluent to give 1.3 g (70%) of **5a** (white crystals).– Mp 98–99 °C.– IR (KBr): ν = 3020 (w, Ar-H), 3000 (m, CH), 2960 (m, CH), 2880 (m, CH), 1600 (s), 1570 (s, C=C), 1500 (s, C=C) (vs)cm^{-1};– ^{1}H NMR ($CDCl_3$): δ = 2.73 (t, *J* = 8.4 Hz, 2H, $ArCH_2CH_2$), 2.93 (t, *J* = 8.4 Hz, 2H, $ArCH_2$), 3.82 (s, 3H, OCH_3), 4.06 (t, *J* = 7.08 Hz, 2H, CH_2O), 4.16 (t, *J* = 7.08 Hz, 2H, CH_2O), 5.85(s, 1H, $HC(OCH_2)_2$), 6.72 (d, *J* = 7.96 Hz, 1H, Ar-H, -H7), 6.74 (s, 1H, Ar-H, -H5), 6.84 (s, 1H, =CH), 7.07 (d, *J* = 7.96 Hz, 1H, Ar-H, -H8), 7.37–7.38 (m, 2H, Ar′-H, -H4′, -H6′), 7.52 (m, 1H, Ar′-H, -H5′), 7.64 (s, 1H, Ar′-H, -H2′);– MS *m/z* (%) = 308 (100) (M^+), 145 (70), 73 (50).

*6-Methoxy-2-4-(1,3-dioxolan-2-yl)phenyl-3,4-dihydronaphthalene (**5b**)*

3.65 g (15.9 mmol) of **3b** gave 1.2 g of **5b** (65%, white crystals).– Mp 112–114 °C;– IR (KBr): ν = 3000 (w, Ar-H), 2980 (m, CH), 2800 (m, CH), 1600 (s), 1570 (s), 1500 (s, C=C) (vs) cm^{-1};– ^{1}H NMR ($CDCl_3$): δ = 2.72 (t, *J* = 8.4 Hz, 2H, $ArCH_2CH_2$), 2.95 (t, *J* = 8.4 Hz, 2H, $ArCH_2$), 3.82 (s, 3H, OCH_3), 4.03–4.06 (t, *J* = 6.86 Hz, 2H, CH_2O), 4.13–4.17 (t, *J* = 6.86 Hz, 2H, CH_2O), 5.83 (s, 1H, $HC(OCH_2)_2$), 6.71–6.73 (d, *J* = 7.96 Hz, 1H, Ar-H, -H7), 6.73 (s, 1H, Ar-H, -H5), 6.83 (s, 1H, =CH),), 7.06–7.08 (d, *J* = 7.96 Hz, 1H, Ar-H, -H8), 7.46-7.48 (d, *J* = 8.4 Hz, 2H, Ar′-H, -H2′, -H6′), 7.53–7.56 (d, *J* = 8.4 Hz, 2H, Ar′-H, -H3′, -H5′);– MS *m/z* (%) = 308 (100) (M^+), 236 (60), 145 (70), 91(40).

*6-Methoxy-2-3-(1,3-dioxolan-2-yl)phenylnaphthalene (**10a**)*

3a (1.7 g, 7.4 mmol) was slowly added to a solution containing Mg (0.18 g, 7.4 mmol) in THF (5 ml)under dry nitrogen at 90 °C with a trace of I_2 as catalyst. The mixture was stirred under reflux for 2 h, then cooled to room temperature, prior to addition of **9** (2-bromo-6-methoxynaphthalene) (0.85 g, 3.5 mmol) and $Pd(PPh_3)_4$ (0.23 g, 0.2 mmol). The mixture was then heated under reflux for another 2 h. The solution was worked up with 1 N HCl and extracted three times with CH_2Cl_2 (100 ml). The organic layer was washed with brine, dried over Na_2SO_4, and the solvent was removed *in vacuo*. The crude product was purified by silica gel column chromatography using 4% EtOAc/petroleum ether as eluent to give 0.55 g (50%) of **10a** (white crystals).– Mp 118–119.5 °C.– IR (KBr): ν = 3030 (w, Ar-H), 2980, 2890 (m, CH), 1630, 1610 (s, C=C), 1600, 1490 (s, C=C) (vs)cm^{-1};– ^{1}H NMR ($CDCl_3$): δ = 3.95 (s, 3H, OCH_3), 4.08 (m, 2H, CH_2O), 4.17 (m, 2H, CH_2O), 5.92 (s, 1H, $HC(OCH_2)_2$), 7.16 (s, 1H, Ar-H, -H5), 7.17 (d, *J* = 7.96 Hz, 1H, Ar-H, -H7), 7.48 (m, 1H, Ar-H, -H4), 7.49 (d, *J* = 7.96 Hz, 1H, Ar-H, -H8), 7.70–7.73 (m, 2H, Ar-H, -H3, Ar′-H, -H5′), 7.79–7.82 (m, 3H, Ar′-H, -H2′, -H4′, -H6′), 7.99 (s, 1H, Ar-H, -H1).

*6-Methoxy-2-4-(1,3-dioxolan-2-yl)phenylnaphthalene (**10b**)*

1.4 g (6.1 mmol) of **3b** gave 0.52 g (55%) of **10b** (white crystals).– Mp 151–153 °C.– IR (KBr): ν = 3020 (w, Ar-H), 2960, 2880 (m, CH), 1630, 1610 (s, C=C), 1600 (s, C=C) (vs) cm^{-1};– ^{1}H NMR ($CDCl_3$): δ = 3.96 (s, 3H, OCH_3), 4.03–4.06 (m, 2H, CH_2O), 4.17 (m, 2H, CH_2O), 5.89 (s, 1H, $HC(OCH_2)_2$), 7.18 (s, 1H, Ar-H, -H5), 7.20 (d, *J* = 8.84 Hz, 1H, Ar-H, -H7), 7.74 (d, *J* = 8.84 Hz, 1H, Ar-H, -H8), 7.81–7.84 (m, 2H, Ar-H, -H3, -H4), 7.87 (d, *J* = 8.4 Hz, 2H, Ar′-H, -H3′, -H5′), 7.98 (d, *J* = 8.4 Hz, 2H, Ar′-H, -H2′, -H6′), 8.05 (s, 1H, Ar-H, -H1).

*2-(3-Formylphenyl)-6-methoxy-3,4-dihydronaphthalene (**6a**)*

10% HCl (5 ml) was added to a stirred solution of **5a** (1.0 g, 3.24 mmol)in THF (20 ml). The mixture was stirred at room temperature for 10 h, before it was worked up with saturated $NaHCO_3$ and extracted three times with CH_2Cl_2 (50 ml). The organic layer was washed with H_2O and dried over

Na_2SO_4. Evaporation of the solvent *in vacuo* gave the crude product **6a** (0.81 g, 95%) which was purified by recrystallization from EtOH.– Mp 52–53°C (white crystals).– IR (KBr): ν = 3010 (w, Ar-H), 2990 (m, CH), 2890 (m, CH), 2720 (m, CHO), 1700 (s, C=O), 1610, 1600, 1500 (s, C=C) (vs)cm^{-1};– ^{1}H NMR ($CDCl_3$): δ = 2.76 (t, *J* = 8.18 Hz, 2H, $ArCH_2CH_2$), 2.96 (t, *J* = 8.18 Hz, 2H, $ArCH_2$), 3.83 (s, 3H, OCH_3), 6.74 (d, *J* = 7.96 Hz, 1H, Ar-H, -H7), 6.76 (s, 1H, Ar-H, -H5), 6.91 (s, 1H, =CH), 7.09 (d, *J* = 7.96 Hz, 1H, Ar-H, -H8), 7.52 (t, *J* = 7.52 Hz, 1H, Ar′-H, -H5′), 7.75 (d, *J* = 7.52 Hz, 1H, Ar′-H, -H4′), 7.79 (d, *J* = 7.52, 1H, Ar′-H, -H6′), 8.02 (s, 1H, Ar′-H, -H2′), 10.05 (s, 1H, -CHO);– MS *m/z* (%) = 264 (95) (M^+), 145 (100), 119 (30).

*2-(4-Formylphenyl)-6-methoxy-3,4-dihydronaphthalene (***6b***)*

0.46 g of **5b** gave 0.375 g of **6b** (95%, yellow crystals).– Mp 85–87 °C.– IR (KBr): ν = 3020 (w), 2950, 2840 (m, CH), 1700 (s, C=O), 1600, 1570 (s, C=C) (vs)cm^{-1};– ^{1}H NMR ($CDCl_3$): δ = 2.77 (t, *J* = 8.18 Hz, 2H, $ArCH_2CH_2$), 2.96 (t, *J* = 8.18 Hz, 2H, $ArCH_2$), 3.83 (s, 3H, OCH_3), 6.74 (d, *J* = 8.4 Hz, 1H, Ar-H, -H7), 6.76 (s, 1H, Ar-H, -H5), 6.98 (s, 1H, =CH), 7.11 (d, *J* = 8.4 Hz, 1H, Ar-H, -H8), 7.67 (d, *J* = 8.4 Hz, 2H, Ar′-H, -H2′, -H6′), 7.87 (d, *J* = 8.4 Hz, 2H, Ar′-H, -H3′, -H5′), 10.0 (s, 1H, CHO);– MS *m/z* (%) = 264 (70) (M^+), 145 (100).

*2-(3-Formylphenyl)-6-methoxynaphthalene (***11a***)*

0.55 g (1.8 mmol) of **10a** gave the crude product **11a** (0.35 g, 75%) which was purified by recrystallization from EtOAc / petroleum ether (white crystals).– Mp 102–104°C;– IR (KBr): ν = 3040 (w, Ar-H), 2960 (m, CH), 2800 (m, CH), 2720 (m, CHO), 1710 (s, C=O), 1620, 1600 (s, C=C), 1585 (s, C=C) (vs)cm^{-1};– ^{1}H NMR ($CDCl_3$): δ = 3.95 (s, 3H, OCH_3), 7.19 (s, 1H, Ar-H, -H5), 7.20 (d, *J* = 8.4 Hz, 1H, Ar-H, -H7), 7.64 (t, *J* = 7.52 Hz, 1H, Ar′-H, -H5′), 7.74 (d, *J* = 8.4 Hz, 1H, Ar-H, -H8), 7.82 (d, *J* = 8.4 Hz, 1H, Ar-H, -H4), 7.84-7.88 (m, 2H, Ar′-H, -H4′, -H6′), 7.98 (d, *J* = 8.4 Hz, 1H, Ar-H, -H3), 8.02 (s, 1H, Ar′-H, -H2′), 8.21 (s, 1H, Ar-H, -H1), 10.12 (s, 1H, -CHO);– MS *m/z* (%) = 262 (100) (M^+), 219 (50), 189 (30).

*2-(4-Formylphenyl)-6-methoxynaphthalene (***11b***)*

0.47 g (1.54 mmol) of **10b** gave 0.35 g of **11b** (86%, white crystals).– Mp 141–143 °C.– IR (KBr): ν = 3020 (w, Ar-H), 2980 (m, CH), 2940 (m, CH), 2840 (m, CHO), 1690 (s, C=O), 1620, 1600 (s, C=C), 1565 (s, C=C) (vs)cm^{-1};– ^{1}H NMR ($CDCl_3$): δ = 3.96 (s, 3H, OCH_3), 7.18 (s, 1H, Ar-H, -H5), 7.20 (d, *J* = 8.84 Hz, 1H, Ar-H, -H7), 7.74 (d, *J* = 8.84 Hz, 1H, Ar-H, -H8), 7.81–7.84 (m, 2H, Ar-H, -H3, -H4), 7.87 (d, *J* = 8.4 Hz, 2H, Ar′-H, -H2′, -H6′), 7.97 (d, *J* = 8.4 Hz, 2H, Ar′-H, -H3′, -H5′), 8.05 (s, 1H, Ar-H, -H1), 10.07 (s, 1H, -CHO);– MS *m/z* (%) = 262 (100) (M^+), 219 (60), 189 (40).

*6-Methoxy-2-3-(5-oxazolyl)phenyl-3,4-dihydronaphthalene (***7a***)*

Tosylmethyl isocyanide (TosMIC) (0.27 g, 1.4 mmol) was added to a stirred solution of **6a** (0.37 g, 1.4 mmol) and of K_2CO_3 (0.28 g, 2.0 mmol)in 20 ml of CH_3OH. The mixture was refluxed for 3 h, before it was worked up with saturated $NaHCO_3$ and extracted three times with CH_2Cl_2 (50 ml). The organic layer was washed with H_2O and dried over Na_2SO_4. Evaporation of the solvent *in vacuo* gave 0.39 g of **7a** (92%, white crystals).– Mp 112.5–114 °C;– IR (KBr): ν = 3020 (w, Ar-H), 2980 (w), 2900 (m, CH), 1600 (s), 1570 (s, C=C), 1500 (s, C=C) (vs)cm^{-1};– ^{1}H NMR ($CDCl_3$): δ = 2.76 (t, *J* = 7.96 Hz, 2H, $ArCH_2CH_2$), 2.96 (t, *J* = 7.96 Hz, 2H, $ArCH_2$), 3.83 (s, 3H, OCH_3), 6.74 (d, *J* = 7.96 Hz, 1H, Ar-H, -H7), 6.75 (s, 1H, Ar-H, -H5), 6.88 (s, 1H, =CH), 7.10 (d, *J* = 7.96 Hz, 1H, Ar-H, -H8), 7.40 (s, 1H, oxazole–H4), 7.42 (t, *J* = 7.52 Hz, 1H, Ar′-H, -H5′), 7.50 (d, *J* = 7.52 Hz, 1H, Ar′-H, -H6′), 7.54 (d, *J* = 7.52, 1H, Ar′-H, -H4′), 7.80 (s, 1H, oxazole-H2), 7.96 (s, 1H, Ar′-H, -H2′);– MS *m/z* (%) = 303 (98) (M^+), 158 (35), 145 (100); Anal. ($C_{20}H_{17}NO_2$) C,H,N.

*6-Methoxy-2-4-(5-oxazolyl)phenyl-3,4-dihydronaphthalene (***7b***)*

0.3 g (1.14 mmol) of **6b** gave 0.32 g of **7b** (93%, yellow crystals).– Mp 167–169 °C;– IR (KBr): ν = 3080, 3030 (w, Ar-H), 2960 (w), 2890 (m, CH), 1610, 1600, 1570, 1500 (s, Ar) (vs)cm^{-1};– ^{1}H NMR ($CDCl_3$): δ = 2.76 (t, *J* = 7.96 Hz, 2H, $ArCH_2CH_2$), 2.95 (t, *J* = 7.96 Hz, 2H, $ArCH_2$), 3.83 (s, 3H, OCH_3), 6.74 (d, *J* = 7.96 Hz, 1H, Ar-H, -H7), 6.75 (s, 1H, Ar-H, -H5), 6.89 (s, 1H, =CH), 7.09 (d, *J* = 7.96 Hz, 1H, Ar-H, -H8), 7.37 (s, 1H, oxazole–H4), 7.59 (d, *J* = 8.4 Hz, 2H, Ar′-H, -H2′, -H6′), 7.65 (d, *J* = 7.52, 2H, Ar′-H, -H3′, -H5′), 7.95 (s, 1H, oxazole-H2);– MS *m/z* (%) = 303 (95) (M^+), 158 (100), 145 (41); Anal. ($C_{20}H_{17}NO_2$) C,H,N.

*6-Methoxy-2-3-(5-oxazolyl)phenylnaphthalene (***12a***)*

0.1 g (0.38 mmol) of **11a** gave 104 mg of **12a** (90%, white crystals).– Mp 164–165.5 °C;– IR (KBr): ν = 3120 (w), 3100 (w, Ar-H), 2900 (m, CH), 1630, 1610, 1600 (s), 1580 (s), 1500 (s, Ar) (vs)cm^{-1};– ^{1}H NMR ($CDCl_3$): δ = 3.96 (s, 3H, OCH_3), 7.18 (s, 1H, Ar-H, -H5), 7.20 (d, *J* = 8.4 Hz, 1H, Ar-H, -H7), 7.45 (s, 1H, oxazole-H4), 7.53 (t, *J* = 7.96 Hz, 1H, Ar′-H, -H5′), 7.65 (d, *J* = 7.96 Hz, 1H, Ar′-H, -H6′), 7.68 (d, *J* = 7.96, 1H, Ar′-H, -H4′), 7.74 (d, *J* = 8.4 Hz, 1H, Ar-H, -H8), 7.82 (d, *J* = 7.96 Hz, 1H, Ar-H, -H3), 7.84 (d, *J* = 7.96 Hz, 1H, Ar-H, -H4), 7.97 (s, 1H, oxazole-H2), 7.98 (s, 1H, Ar′-H, -H2′), 8.01 (s, 1H, -H1);– MS *m/z* (%) = 301 (100) (M^+), 258 (45), 202 (35); Anal. ($C_{20}H_{15}NO_2$) C,H,N.

*6-Methoxy-2-4-(5-oxazolyl)phenylnaphthalene (***12b***)*

0.35 g (1.33 mmol) of **11b** gave 0.37 g of **12b** (92%, yellow crystals).– Mp 222.5–224 °C (dec.);– IR (KBr): ν = 3120 (w), 3005 (w, Ar-H), 2980 (m, CH), 1630, 1600 (s), 1500 (s, Ar) (vs)cm^{-1};– ^{1}H NMR (DMSO(d_6)): δ = 3.92 (s, 3H, OCH_3), 7.21 (d, *J* = 7.96 Hz, 1H, Ar-H, -H7), 7.34 (s, 1H, Ar-H, -H5), 7.68 (s, 1H, oxazole-H4), 7.82-7.84 (m, 3H, Ar-H, -H8, Ar′-H, -H2′, -H6′), 7.89-7.93 (m, 4H, Ar-H, -H3, -H4, Ar′-H, -H3′, -H5′), 8.18 (s, 1H, Ar-H, -H1), 8.38 (s, 1H, oxazole-H2);– MS *m/z* (%) = 301 (100) (M^+), 258 (40), 202 (25); Anal. ($C_{20}H_{15}NO_2$) C,H,N.

*6-Methoxy-2-3-(4-tosyl-5-oxazolinyl)phenyl-3,4-dihydronaphthalene (***13a***)*

To a stirred suspension of tosylmethyl isocyanide (TosMIC) (0.38 g, 2.0 mmol) and **6a** (0.5 g, 2.1 mmol) in dry ethanol (15 ml) and THF (5 ml) was added finely powdered sodium cyanide (10 mg, 0.2 mmol). Within minutes the slightly exothermic reaction mixture became clear, and white crystals of oxazoline quickly began to deposit from solution (20 min). Stirring was continued for an additional 2 h. The mixture was filtered and the crystals were washed with diethyl ether:*n*-hexane (1:1) (15 ml) to give, after drying, 0.68 g of **13a** (71%, white powder).– Mp 139–141 °C;– IR (KBr): ν = 3020 (w, Ar-H), 2940 (m, CH), 1620 (s), 1600, 1500 (s) (Ar), 1380 (s), 1320, 1150 (SO_2) (vs)cm^{-1}.

*6-Methoxy-2-4-(4-tosyl-5-oxazolinyl)phenyl-3,4-dihydronaphthalene (***13b***)*

475 mg (1.8 mmol) of **6b** gave 0.64 g of **13b** (78%, white powder).– Mp 134–135 °C;– IR (KBr): ν = 3060, 3020 (w, Ar-H), 2940 (m, CH), 1620 (s), 1600, 1540 (s) (Ar), 1495, 1320 (SO_2), 1250, 1140 (SO_2) (vs)cm^{-1}.

*6-Methoxy-2-3-(4-tosyl-5-oxazolinyl)phenylnaphthalene (***15a***)*

0.3 g (1.14 mmol) of **11a** gave 0.41 g of **15a** (78%, white powder).– Mp 134–135 °C;– IR (KBr): ν = 3060 (w, Ar-H), 2920 (m, CH), 1620 (s), 1600, 1500 (s)(Ar), 1320, 1140 (SO_2) (vs)cm^{-1}.

*6-Methoxy-2-4-(4-tosyl-5-oxazolinyl)phenylnaphthalene (***15b***)*

0.25 g (0.95 mmol) of **11b** gave 0.68 g of **15b** (69%, white powder).– Mp 138–140 °C;– IR (KBr): ν = 3060 (w, Ar-H), 2970 (m, CH), 1630 (s), 1605, 1500 (s)(Ar), 1320, 1130 (SO_2) (vs)cm^{-1}.

*2-3-(4-Imidazolyl)phenyl-6-methoxy-3,4-dihydronaphthalene (***14a***)*

In a resealable pressure tube, a solution of **13a** (0.6 g, 1.3 mmol) and a saturated solution of ammonia in dry methanol (20 ml) and dry THF (20 ml) was heated between 100–120 °C for 24 h. TLC (CH_2Cl_2/MeOH: 9/1) of the reaction mixture indicated a clean transformation. Concentration and chromatography (CH_2Cl_2/MeOH: 9/1) of the residue gave 123 mg of **14a** (31%, light brown powder).– Mp 176–178 °C;– IR (KBr): ν = 3100(s, NH), 3020 (w, Ar-H), 2940 (m, CH), 1600, 1580, 1500 (s) (Ar), 1465 (s), 1250 (s) (vs)cm^{-1};– ^{1}H NMR (DMSO(d_6)): δ = 2.70 (t, *J* = 8.4 Hz, 2H, $ArCH_2CH_2$),

2.90 (t, *J* = 8.4 Hz, 2H, $ArCH_2$), 3.77 (s, 3H, OCH_3), 6.76 (d, *J* = 7.96 Hz, 1H, Ar-H, -H7), 6.81 (s, 1H, Ar-H, -H5), 6.97 (s, 1H, =CH), 7.15 (d, *J* = 7.96 Hz, 1H, Ar-H, -H8), 7.34–7.37 (m, 2H, Ar′-H, -H5′, imidazole–H2), 7.68–7.70 (m, 3H, Ar′-H, -H4′, -H6′, imidazole–H5), 7.80 (s, 1H, Ar′-H, -H2′);– MS *m/z* (%) = 302 (100) (M^+), 207 (80), 157 (43); Anal. ($C_{20}H_{18}N_2O$) C,H,N.

*2-4-(4-Imidazolyl)phenyl-6-methoxy-3,4-dihydronaphthalene (***16b***)*

0.62 g (1.35 mmol) of **13b** gave 95 mg of **14b** (23%, light yellow powder).– Mp 243–245 °C;– IR (KBr): ν = 3120 (NH), 3060 (w, Ar-H), 2930 (m, CH), 1610, 1570, 1500 (s) (Ar), 1430 (s), 1250 (s) (vs)cm^{-1};– ^1H NMR (DMSO(d_6)): δ = 2.66 (t, *J* = 8.4 Hz, 2H, $ArCH_2CH_2$), 2.88 (t, *J* = 8.4 Hz, 2H, $ArCH_2$), 3.76 (s, 3H, OCH_3), 6.74 (d, *J* = 7.96 Hz, 1H, Ar-H, -H7), 6.78 (s, 1H, Ar-H, -H5), 6.92 (s, 1H, =CH), 7.11 (d, *J* = 7.96 Hz, 1H, Ar-H, -H8), 7.51 (d, *J* = 8.4 Hz, 1H, imidazole–H2), 7.55 (d, *J* = 8.4 Hz, 2H, Ar′-H, -H2′, -H6′), 7.66 (s, 1H, imidazole–H5), 7.74 (d, *J* = 8.4 Hz, 2H, Ar′-H, -H3′, -H5′);– MS *m/z* (%) = 302 (100) (M^+), 287 (15), 207 (20), 157 (70); Anal. ($C_{20}H_{18}N_2O$) C,H,N.

*2-3-(4-Imidazolyl)phenyl-6-methoxynaphthalene (***16a***)*

0.8 g (1.75 mmol) of **15a** gave 126 mg of **15a** (24%, brown powder).– Mp 197–199 °C;– IR (KBr): ν = 3120 (NH), 3060, 3000 (w, Ar-H), 2940 (m, CH), 1630, 1610, 1580 (s) (Ar), 1485, 1460 (s), 1240 (s) (vs)cm^{-1};– ^1H NMR (DMSO(d_6)): δ = 3.90 (s, 3H, OCH_3), 7.11 (s, 1H, Ar-H, -H5), 7.12 (d, *J* = 8.4 Hz, 1H, Ar-H, -H7), 7.36 (s, 1H, imidazole–H5), 7.42 (d, *J* = 7.96 Hz, 1H, Ar′-H, -H3′), 7.55 (d, *J* = 7.96 Hz, 1H, Ar′-H, -H4′), 7.63 (d, *J* = 7.96 Hz, 1H, Ar′-H, -H5′), 7.68 (d, *J* = 8.4 Hz, 2H, Ar-H, -H3, -H8), 7.72 (s, 1H, imidazole–H2), 7.74 (d, *J* = 8.4 Hz, 1H, Ar-H, -H4), 7.95 (s, 1H, Ar′-H, -H2′), 8.05 (s, 1H, Ar-H, -H1);– MS *m/z* (%) = 300 (100) (M^+), 285 (10), 257 (32), 150 (30); Anal. ($C_{20}H_{16}N_2O$) C,H,N.

*2-4-(4-Imidazolyl)phenyl-6-methoxynaphthalene (***16b***)*

0.2 g (0.44 mmol) of **15b** gave 43 mg of **16b** (33%, light yellow powder).– Mp 266–268 °C;– IR (KBr): ν = 3120 (NH), 3040 (w, Ar-H), 2995 (m, CH), 1635, 1605, 1500 (s) (Ar), 1250 (s), 1200 (s) (vs)cm^{-1};– ^1H NMR (DMSO(d_6)): δ = 3.90 (s, 3H, OCH_3), 7.19 (d, *J* = 8.84 Hz, 1H, Ar-H, -H7), 7.35 (s, 1H, Ar-H, -H5), 7.68 (s, 1H, imidazole–H5), 7.73 (s, 1H, imidazole–H2), 7.78 (d, *J* = 8.4 Hz, 2H, Ar′-H, -H2′, -H6′), 7.83 (d, *J* = 8.4 Hz, 1H, Ar-H, -H3), 7.90 (d, *J* = 8.4 Hz, 1H, Ar-H, -H4), 7.91 (d, *J* = 8.4 Hz, 2H, Ar′-H, -H3′, -H5′), 7.92 (d, *J* = 8.84 Hz, 1H, Ar-H, -H8), 8.17 (s, 1H, Ar-H, -H1);– MS *m/z* (%) = 300 (100) (M^+), 285 (18), 257 (40), 150 (45); Anal. ($C_{20}H_{16}N_2O$) C,H,N.

Biological Methods

Enzyme Preparation: The enzyme was prepared using human testes. For the determination of enzyme inhibition, microsomes were incubated with excess progesterone as substrate (25 μM), NADPH (500 μM) and inhibitor (2.5 μM) in phosphate buffer (temperature: 32 °C, termination after 20 min by addition of 1 N HCl)[20]. After extraction of the steroids, fluorocortisol acetate was added as internal standard. The samples were submitted to HPLC (RP-8 column, $CH_3OH:H_2O$ = 1:1, v/v) and detected by UV. Peak areas (fluorocortisol, progesterone, 17α-hydroxyprogesterone, androstenedione and testerone) were determined using a data evaluation software (JCL 6000, Chromatography Data System, Vision 5.07).

Statistical limits: The inhibitory activity data are mean values of two experiments. The deviations were within ±10%.

Molecular Modeling

The energy minimization of the compounds was carried out using CHARm22 in Quanta-Release 97 software package, run on Silicon Graphics INDY (SGI) O2 with R 10000 workstation with default setting value. Molecular Similarity (rigid and flexible method) fitting operation was selected to perform a least-squares fit between two molecules, matching the pairs of atoms, using energy-minimized steroid **III** as a template and C8, C9, C14 as fit atoms.

References

☆ Dedicated to Professor Kallmayer on the occasion of his 60th birthday.

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