# Synthesis of Novel Oximes of 2-Aryl-6-methoxy-3,4-dihydronaphthalene and Their Evaluation as Inhibitors of 17α-Hydroxylase-C17,20-Lyase (P450 17)

Yan Zhuang and Rolf W. Hartmann*

Fachrichtung 12.1 Pharmazeutische Chemie, Universität des Saarlandes, P.O. Box 15 11 50, D-66041 Saarbrücken, Germany

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## Summary

The synthesis and biological evaluation of oximes of 2-aryl-6-methoxy-3,4-dihydronaphthalene (**7a, 7b, 14a, 14b**) as nonsteroidal inhibitors of 17α-hydroxylase-C17,20-lyase (P450 17, CYP 17) is described. The target compounds were synthesized and identified by $^1$H NMR and MS. The preparation of the key intermediates **5a** and **5b** was accomplished by coupling **4a** and **4b** with **1** (2-hydroxy-6-methoxy-3,4-dihydronaphthalene-2-trifluoromethanesulfonate) using the palladium complex $Pd(PPh_3)_4$ as catalyst. Hydrolysis of **5a** and **5b** in THF-HCl solution at room temperature gave the corresponding keto compounds **6a** and **6b**. The other important intermediates – the substituted (*E*)-2-methylene-1-tetralones **10a** and **10b** – were obtained by condensation of 1-tetralone with the corresponding aromatic aldehydes (**9a** and **9b**). Hydrogenation ($H_2$), followed by reduction ($NaBH_4$), and subsequent hydrolysis and elimination led to the keto compounds **13a** and **13b**. The title compounds, the oximes **7a, 7b** and **14a**, **14b** were formed by reaction of hydroxylamine hydrochloride with the corresponding keto compounds. Using a microsomal fraction of human testicular enzyme, **7a, 7b, 14a,** and **14b** inhibited the target enzyme only marginally.

## Introduction

The steroidal enzyme 17α-hydroxylase-C17,20-lyase (P450 17) is a cytochrome P450 monooxygenase that catalyzes the conversion of progesterone and pregnenolone into the androgens, androstenedione and dehydroepiandrosterone (DHEA), respectively [1,2]. As androgens have been implicated in the development and progression of several diseases, most notably prostatic cancer, a promising alternative to treatment with antihormones and LHRH analogues might be the use of selective inhibitors of P450 17 [3,4]. Recently we have shown [3,5,6] that a dihydro- or tetrahydro-naphthalene 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**, Chart 1[6]). While the heterocyclic N complexes 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 [7,8] that an oxime group at the substituent in C-17 position also leads to potent inhibitors (e.g., **II**, Chart 1[7]). The first attempt to obtain the nonsteroidal oximes as inhibitors of P450 17 has recently been published (e.g., **III**, Chart 1[9]). The present paper describes a further attempt to synthesize of the nonsteroidal oximes (**7a, 7b, 14a**, and **14b**, Chart 1) designated as inhibitors of P450 17 and their biological evaluation.

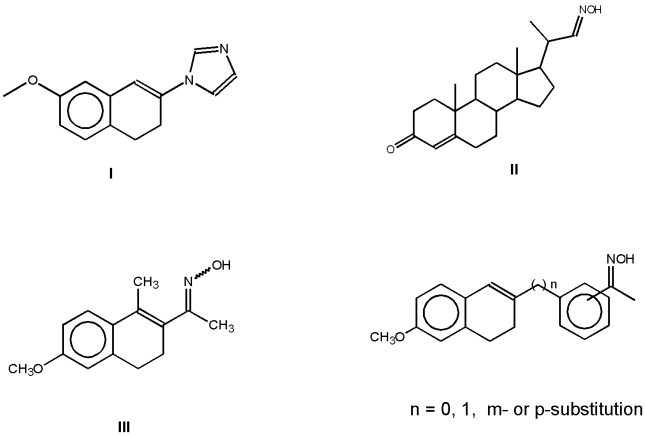


**Chart 1**: Selected inhibitors of P450 17 (**I, II**, and **III**) and the title compounds.

## Synthesis

6-Methoxy-2-tetralone was used as starting material to react with trifluoromethanesulfonic acid anhydride to yield **1** (2-hydroxy-6-methoxy-3,4-dihydronaphthalene-2-trifluoromethanesulfonate). The keto group of 3- or 4-bromoacetophenone was protected by refluxing ethylene glycol in toluene to give **3a** and **3b** which were used to react with t-BuLi and $ZnCl_2$ to produce **4a** and **4b**. Coupling of **1** with **4a** and **4b** using the palladium complex $Pd(PPh_3)_4$ as catalyst afforded **5a** and **5b**. Hydrolysis of **5a** and **5b** in THF-HCl solution at room temperature gave the corresponding keto compounds **6a** and **6b**. The other important intermediates – the substituted (*E*)-2-methylene-1-tetralones (**10a** and **10b**) – were obtained by condensation of 1-tetralone with the corresponding aromatic aldehydes (**9a** and **9b**) which were synthesized by nucleophilic substitution of DMF with **3a** and **3b** in the presence of n-BuLi. Through two steps of reaction, hydrogenation ($H_2$) and reduction ($NaBH_4$), **10a** and **10b** were turned into **12a** and **12b**. Hydrolysis and elimination of **12a** and **12b** in a refluxing THF-HCl solution gave the corresponding keto compounds **13a** and **13b**. The title compounds, the oximes **7a, 7b, 14a,** and **14b** were formed by reaction with hydroxylamine hydrochloride.

## Results and Discussion

Compounds **7a, 7b, 14a,** and **14b** were tested for inhibition of P450 17 using human testicular enzyme as well as progesterone as a substrate (25 μM) employing the procedure re-

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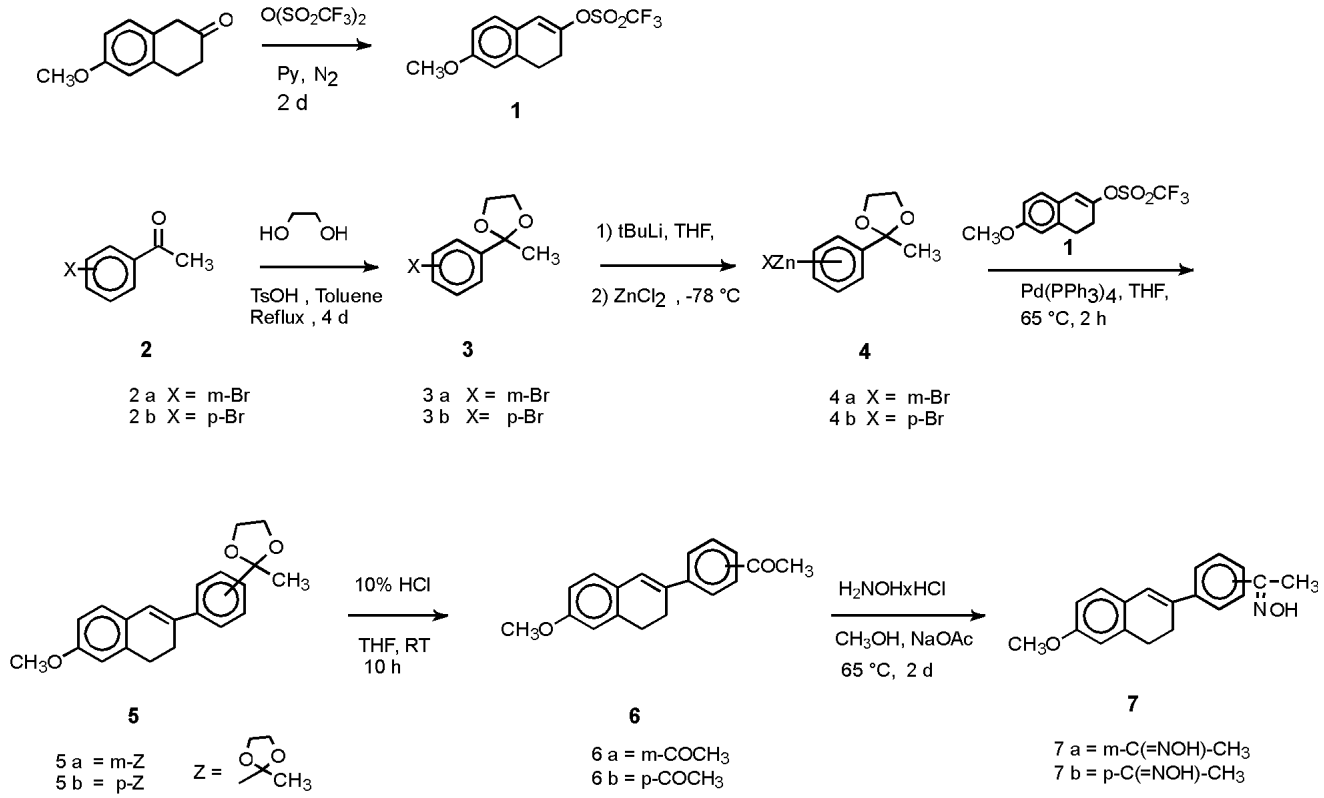


**Scheme 1:** Synthesis of **7a** and **7b**.

cently described [9]. Tested at a concentration of 2.5 μM, the title compounds showed only marginal inhibitory activity (**7a,** 1.3%, **7b,** 5.4%, **14a,** 2.1%, and **14b**, 4.5%). This disappointing result is probably due to the fact that there is no energetically preferred conformation of these oximes to fit properly into the active site of the enzyme.

## Acknowledgements

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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 carried out on a HP G1800A GCD. $^1$H-NMR spectra were measured on a Bruker AM 400 (400 MHz) and Bruker AW 80 (80 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**)*

5.4 ml (32 mmol) trifluoromethanesulfonic acid anhydride was added slowly to a stirred solution of 4.2 g (24 mmol) 6-methoxy-2-tetralone and 3.2 g (40 mmol) pyridine in 250 ml $CH_2Cl_2$ 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)-2-methyl-1,3-dioxolane (**3a**)*

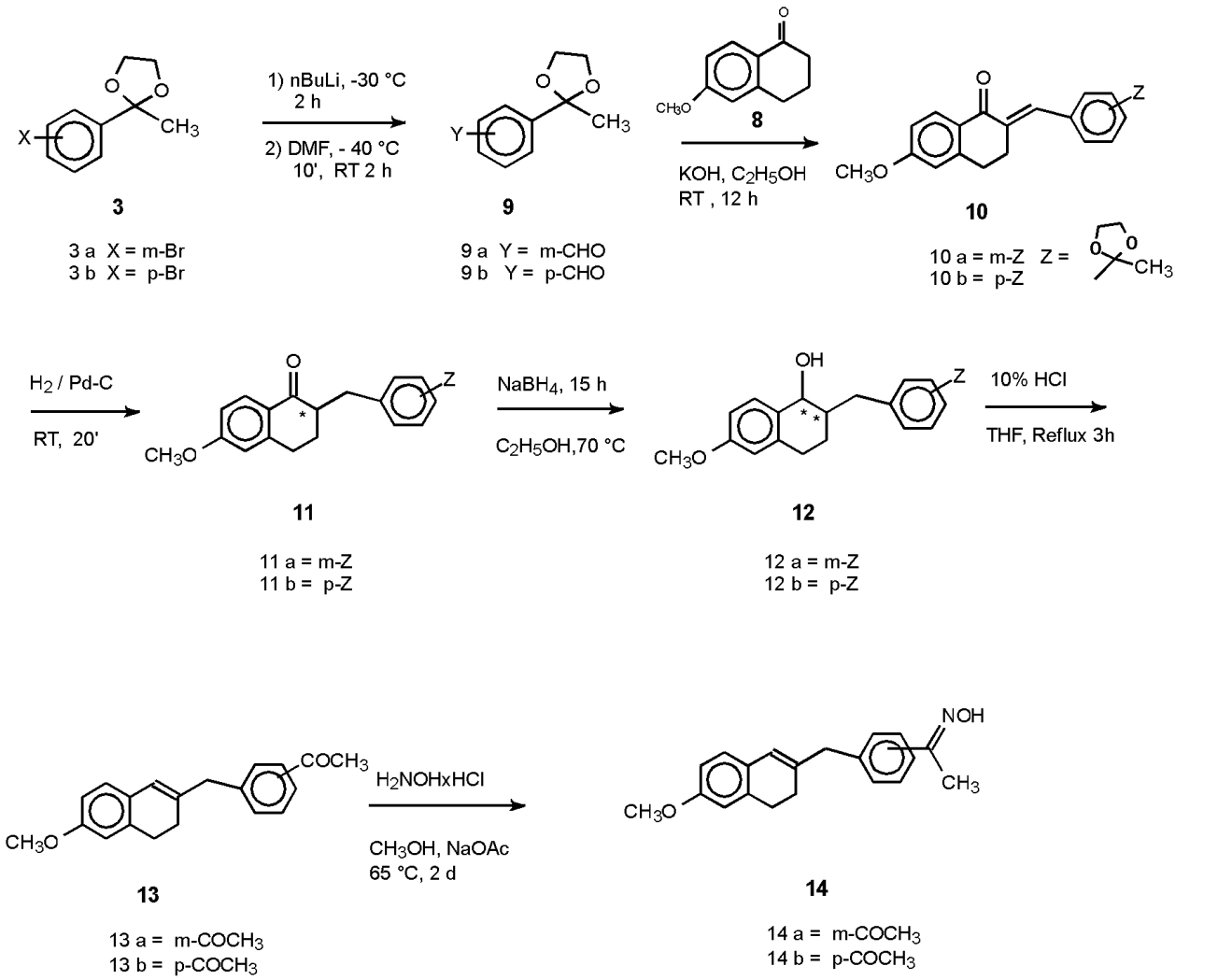
A mixture of 3-bromoacetophenone **2a** (25 g, 126 mmol), ethylene glycol (14 g, 226 mmol) and p-TsOH·$H_2O$ (714 mg, 3.75 mmol) in 200 ml of toluene was heated at reflux in a flask equipped with a Dean-Stark apparatus. After 8 h, ethylene glycol (4.65 g, 75 mmol) was added and the mixture was refluxed for 4 days. The reaction mixture was cooled to room temperature, washed with 1N $NaHCO_3$, brine, dried over $Na_2SO_4$ and after the solvent was removed *in vacuo*, the residue was distilled to give 25.5 g (83.6%) of **3a**. (oil, bp 105–107 °C/0.25–0.28 Torr).– $^1$H NMR ($CDCl_3$): δ = 1.71 (s, 3H, $CH_3$), 3.83 (t, *J* = 7.1 Hz, 2H, $OCH_2$), 4.07 (t, *J* = 7.1 Hz, 2H, $OCH_2$), 7.40–7.72 (m, 3H, Ar-H, -H4, -H5, -H6), 7.33 (s, 1H, Ar-H, -H2).

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

25g of **2b** gave 24.5 g of **3b** (80.1%) colorless prisms. bp 70–75 °C / 0.15 Torr, mp 40–42 °C.– $^1$H NMR ($CDCl_3$): δ = 1.63 (s, 3H, $CH_3$), 3.74–3.77 (t, *J* = 6.9 Hz, 2H, $OCH_2$), 4.02–4.05 (t, *J* = 6.9 Hz, 2H, $OCH_2$), 7.36 (d, *J* = 8.4 Hz, 2H, Ar-H, -H2, -H6), 7.46 (d, *J* = 8.4, Hz, 2H, Ar-H, -H3, -H5).

*6-Methoxy-2-[3-(2-methyl-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 first with t-BuLi (20 ml, 30 mmol, 5 eq) under dry nitrogen at –75 °C, then with a slurry of $ZnCl_2$ (2.04 g, 15 mmol, 2.5 eq) in THF (10 ml). The mixture was cooled 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 the mixture heated




**Scheme 2**: Synthesis of **14a** and **14b**.

under reflux for 2 h. The reaction mixture 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 1.4 g (74%) of **5a**. mp 101–102 °C.– $^1$H NMR ($CDCl_3$): δ = 1.69 (s, 3H, $CH_3$), 2.74 (t, *J* = 8.4 Hz, 2H, $ArCH_2CH_2$), 2.94 (t, *J* = 8.4 Hz, 2H, $ArCH_2$), 3.82 (s, 3H, $OCH_3$), 3.80–3.83 (m, 2H, $CH_2O$), 4.04–4.06 (m, 2H, $CH_2O$), 6.72 (m, 2H, Ar-H, -H5, -H7), 6.85 (s, 1H, =CH), 7.08 (m, 1H, Ar-H, -H8), 7.34 (d, *J* = 7.5 Hz, 1H, Ar′-H, -H5′), 7.37–7.39 (d, *J* = 7.1 Hz, 1H, Ar′-H, -H6′), 7.45–7.47 (d, *J* = 7.1 Hz, 1H, Ar′-H, -H4′), 7.65 (s, 1H, Ar′-H, -H2′).– MS *m/z* (%) = 322 (100) ($M^+$), 307 (70) ($M^+ - CH_3$), 87 (68).

*6-Methoxy-2-[4-(2-methyl-1,3-dioxolan-2-yl)phenyl]-3,4-dihydro-naphthalene (***5b***)*

3.65g of **3b** gave 1.5g of **5b** (77.3%) white solid, mp 114–116°C.– $^1$H NMR ($CDCl_3$): δ = 1.67 (s, 3H, $CH_3$), 2.72 (t, *J* = 8.4 Hz, 2H, $ArCH_2CH_2$), 2.93 (t, *J* = 8.4 Hz, 2H, $ArCH_2$), 3.83 (s, 3H, $OCH_3$), 3.81–3.82 (m, 2H, $CH_2O$), 4.03–4.07 (m, 2H, $CH_2O$), 6.72–6.74 (m, 2H, Ar-H, -H5, -H7), 6.83 (s, 1H, =CH),), 7.05-7.08 (d, *J* = 10.6 Hz, 1H, Ar-H, -H8), 7.46–7.53 (m, 4H, Ar′-H, -H2′, -H3′, -H5′, -H6′).– MS *m/z* (%) = 322 (67) ($M^+$), 307 (100) ($M^+ - CH_3$), 131(40).

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

5ml 10% HCl was added to a stirred solution of 0.5 g (1.55 mmol) **5a** in 20 ml of THF. The mixture was stirred at room temperature for 15 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** (0.406 g, 94.1 %) which was purified by recrystallization from EtOAc/petroleum ether. mp 71–73°C. IR (KBr): ν = 3030 (w), 3010 (w), 2920 (m, CH), 1678 (s, C=O), 1605 (s, C=C), 1590 (s, C=C) (vs)$cm^{-1}$.– $^1$H NMR ($CDCl_3$): δ = 2.64 (s, 3H, $CH_3$), 2.66 (t, *J* = 8.2 Hz, 2H, $ArCH_2CH_2$), 2.96 (t, *J* = 8.2 Hz, 2H, $ArCH_2$), 3.82 (s, 3H, $OCH_3$), 6.73–6.75 (m, 2H, Ar-H, -H5, -H7), 6.88 (s, 1H, =CH), 7.09 (d, *J* = 8.0 Hz, 1H, Ar-H, H8), 7.46 (t, *J* = 7.74 Hz, 1H, Ar′-H, -H5′), 7.72 (d, *J* = 8.0 Hz, 1H, Ar′-H, -H6′), 7.83 (d, *J* = 8.0, 1H, Ar′-H, -H4′), 8.09 (s, 1H, Ar′-H, -H2′).– MS *m/z* (%) = 278 (95) ($M^+$), 145 (100), 43 (50).

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

0.5 g of **5b** gave 0.41 g of **6b** (95.1%, yellow crystals). mp 117–119°C. IR (KBr): ν = 3020 (w), 2840–2950 (m, CH), 1675 (s, C=O), 1600 (s, C=C), 1570 (s, C=C) (vs)$cm^{-1}$.– $^1$H NMR ($CDCl_3$): δ = 2.61 (s, 3H, $CH_3$), 2.75 (t, *J* = 10.2 Hz, 2H, $ArCH_2CH_2$), 2.95 (t, *J* = 10.2 Hz, 2H, $ArCH_2$), 3.83 (s, 3H, $OCH_3$), 6.73–6.76 (m, 2H, Ar-H, -H5, -H7), 6.94 (s, 1H, =CH), 7.11 (d, *J* = 10.8 Hz, 1H, Ar-H, -H8), 7.59 (d, *J* = 10.2 Hz, 2H, Ar′-H, -H2′, -H6′), 7.96 (d, *J* = 10.2 Hz, 2H, Ar′-H, -H3′, -H5′).– MS *m/z* (%) = 278 (95) ($M^+$), 145 (100), 131 (40) 43 (50).

*2-[3-(1-Hydroximinoethyl)phenyl]-6-methoxy-3,4-dihydronaphthalene (**7a**)*

A mixture of 0.27 g (0.97 mmol) **6a**, 0.2 g (2.9 mmol) $NH_2OH{\cdot}HCl$, 0.4 g (4.9 mmol) NaOAc and 30 ml $CH_3OH$ was stirred and heated at 65 °C for 2 days. The solution was poured into 150 ml water and extracted three times with $CH_2Cl_2$ (50 ml). The organic layer was washed with $H_2O$ and dried over $Na_2SO_4$. After evaporation of the solvent *in vacuo*, the crude product **7a** (270 mg, 94.9 %) was obtained, which was purified by recrystallization from EtOAc / petroleum ether. mp 92–93.5 °C. IR (KBr): ν = 3250 (s, OH), 3010 (w), 2840–2960 (m, CH), 1620 (s, C=C), 1575 (s, C=C) (vs) $cm^{-1}$.– $^1H$ NMR (DMSO($d_6$)): δ ppm: 2.22 (s, 3H, $CH_3$), 2.69 (t, *J* = 8.0 Hz, 2H, $ArCH_2\mathit{CH_2}$), 2.91 (t, *J* = 8.0 Hz, 2H, $ArCH_2$), 3.78 (s, 3H, $OCH_3$), 6.78 (d, *J* = 8.0, 1H, Ar-H, -H7), 6.82 (s, 1H, Ar-H, -H5), 6.98 (s, 1H, =CH), 7.17 (d, *J* = 8.0, 1H, Ar-H, -H8), 7.41 (m, 1H, Ar′-H, -H5′), 7.57 (m, 2H, Ar′-H, -H4′, -H6′), 7.83 (s, 1H, Ar′-H, -H2′), 11.23 (s, 1H, =NOH).– MS *m/z* (%) = 275 (100) ($M^+$ – $H_2O$), 260 (45), 189 (30). Anal. ($C_{19}H_{19}NO_2$) C,H,N.

*2-[4-(1-Hydroximinoethyl)phenyl]-6-methoxy-3,4-dihydronaphthalene (**7b**)*

0.3 g (1.1 mmol) **6b,** 0.25 g (3.6 mmol) $NH_2OH{\cdot}HCl$, 0.45 g (5.5 mmol) NaOAc, gave 0.3 g yellow needle crystals of **7b** (95.3%). mp 192–194 °C. IR (KBr): ν = 3240 (s, OH), 3090 (w), 2840–2960 (m, CH), 1610, 1575 (s, C=C) (vs)$cm^{-1}$.– $^1H$ NMR (DMSO($d_6$)): δ ppm: 2.12 (s, 3H, $CH_3$), 2.62 (t, *J* = 8.4 Hz, 2H, $ArCH_2\mathit{CH_2}$), 2.82 (t, *J* = 8.4 Hz, 2H, $ArCH_2$), 3.72 (s, 3H, $OCH_3$), 6.72 (m, 2H, Ar-H, -H5, -H7), 6.96 (s, 1H, =CH), 7.10 (d, *J* = 8.0, 1H, Ar-H, -H8), 7.54 (m, 2H, Ar′-H, -H2′, -H6′), 7.63 (m, 2H, Ar′-H, -H3′, -H5′), 11.16 (s, 1H, =NOH).– MS *m/z* (%) = 275 (90) ($M^+$- $H_2O$), 260 (50), 189 (25), 18 (100). Anal. ($C_{19}H_{19}NO_2$) C,H,N.

*3-(2-Methyl-1,3-dioxolan-2-yl)-benzaldehyde (**9a**)*

To a stirred solution of **3a** (2.43 g, 0.01mol) in THF (30 ml) under dry nitrogen at –30 °C was added n-BuLi (0.011 mol) and stirred for 2 h. Then 1.2 ml (0.015 mol) DMF was added at –40 °C and subsequently stirred at room temperature for 2 h. The reaction mixture was worked up with 1N HCl and extracted three times with $CH_2Cl_2$ (100 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 **9a** (1.48 g, 77%, liquid) which was used without further purification for the next reaction.

*4-(2-Methyl-1,3-dioxolane-2-yl)-benzaldehyde (**9b**)*

2.43 g of **3b**, gave 1.51 g of **9b** (78.6%).

*(2E)-[3-(2-Methyl-1,3-dioxolan-2-yl)benzylidene]-6-methoxy-1-tetralone (**10a**)*

To a stirred solution of KOH in EtOH (13 ml, 4%) were added 6-methoxy-1-tetralone (**8**) (1.3 g, 7.4 mmol) and **9a** (1.4 g, 7.3 mmol) successively and stirred for 12 h at room temperature. After the end of reaction was shown by TLC control, 100 ml of $H_2O$ was added and the mixture was extracted three times with $CH_2Cl_2$ (100 ml). The organic layer was washed with 1N HCl, $H_2O$ and dried over $Na_2SO_4$. After 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 0.9 g (35.2%) of **10a** (colorless crystals). mp 115–7°C. IR (KBr): δ = 3050 (w), 2820–2980 (m, CH), 1660 (s, C=O), 1610 (s, C=C), 1600 (s, C=C) (vs) $cm^{-1}$.– $^1H$ NMR ($CDCl_3$): δ = 1.68 (s, 3H, $CH_3$), 2.93 (t, *J* = 6.4 Hz, 2H, $ArCH_2\mathit{CH_2}$), 3.12 (t, *J* = 6.4 Hz, 2H, $ArCH_2$), 3.80–3.83 (m, 2H, $CH_2O$), 3.88 (s, 3H, $OCH_3$), 4.05–4.08 (m, 2H, $CH_2O$), 6.70 (s, 1H, Ar-H, -H5), 6.89 (d, *J* = 8.4 Hz, 1H, Ar-H, -H7), 7.35–7.41 (m, 2H, Ar′-H, -H4′, -H5′), 7.46–7.48 (d, *J* = 7.1 Hz, 1H, Ar′-H, -H6′), 7.56 (s, 1H, Ar′-H, -H2′), 7.84 (s, 1H, =CH), 8.12 (d, *J* = 8.8 Hz, 1H, Ar-H, -H8).– MS *m/z* (%) = 350 (10) ($M^+$), 349 (15) ($M^+$ – 1), 335 (60), 87 (100).

*(2E)-[4-(2-Methyl-1,3-dioxolan-2-yl)benzylidene]-6-methoxy-1-tetralone (**10b**)*

1.3 g (7.4 mmol) of 6-methoxy-1-tetralone and **9b** (1.4 g, 7.3 mmol) were dissolved in 13 ml 4% KOH/EtOH, and stirred 12 h at room temperature to give 1.0 g of **10b** (39.1%, white crystals). mp 127–128 °C. IR (KBr): ν = 3005 (w), 2840–2980 (m, CH), 1665 (s, C=O), 1610 (s, C=C), 1595 (s, C=C), 1570 (s, C=C) (vs) $cm^{-1}$.– $^1H$ NMR ($CDCl_3$): δ = 1.68 (s, 3H, $CH_3$), 2.92 (t, *J* = 6.4 Hz, 2H, $ArCH_2\mathit{CH_2}$), 3.12 (t, *J* = 6.4 Hz, 2H, $ArCH_2$), 3.82 (t, *J* = 7.5 Hz, 2H, $CH_2O$), 3.87 (s, 3H, $OCH_3$), 4.06 (t, *J* = 7.5 Hz, 2H, $CH_2O$), 6.71 (s, 1H, Ar-H, -H5), 6.87 (d, *J* = 8.4 Hz, 1H, Ar-H, -H7), 7.40 (d, *J* = 8.4 Hz, 2H, Ar′-H, -H3′, -H5′), 7.52 (d, *J* = 8.4 Hz, 2H, Ar′-H, -H2′, -H6′), 7.82 (s, 1H, =CH), 8.11 (d, *J* = 8.4 Hz, 1H, Ar-H, -H8).– MS *m/z* (%) = 350 (12) ($M^+$), 349 (14) ($M^+$ – 1), 335 (100), 87(80).

*6-Methoxy-2-[3-(2-methyl-1,3-dioxolan-2-yl)benzyl]-1-tetralone (**11a**)*

A mixture of **10a** (400 mg, 1.14 mmol), 10% Pd/C (40 mg) and absolute $CH_3OH$ (50 ml) was hydrogenated at normal pressure for 20 min until an equimolar amount of $H_2$ was absorbed. The mixture was filtered and the filtrate was evaporated under reduced pressure to give 370 mg (92.0%) of **11a**. Recrystallization from EtOH yielded a white solid. mp 89–91 °C. IR (KBr): ν = 3040 (w), 2800–2960 (m, CH), 1670 (s, C=O), 1610 (s, C=C), 1590 (s, C=C) (vs) $cm^{-1}$.– $^1H$ NMR ($CDCl_3$): δ = 1.67 (s, 3H, $CH_3$), 1.76–1.81 (m, 1H, $ArCH_2\mathit{CH_2}CH$), 2.07 (m, 1H, $ArCH_2\mathit{CH_2}CH$), 2.62 (m, 2H, Ar′$CH_2$), 2.90 (m, 2H, $ArCH_2$), 3.50–3.53 (m, 1H, ArCOCH), 3.77–3.80 (m, 2H, $CH_2O$), 3.85 (s, 3H, $OCH_3$), 4.02–4.06 (m, 2H, $CH_2O$), 6.67 (s, 1H, Ar-H, -H5), 6.83–6.84 (d, *J* = 8.8 Hz, 1H, Ar-H, -H7), 7.17 (d, *J* = 7.5 Hz, 1H, Ar′-H, -H6′), 7.27 (d, *J* = 7.5 Hz, 1H, Ar′-H, -H4′), 7.34 (m, 2H, Ar′-H, -H2′, -H5′), 8.05 (d, *J* = 8.8 Hz, 1H, Ar-H, -H8).

*6-Methoxy-2-[4-(2-methyl-1,3-dioxolan-2-yl)benzyl]-1-tetralone (**11b**)*

A mixture of **10b** (400 mg, 1.14 mmol), 10% Pd/C (40 mg) and absolute $CH_3OH$ (50 ml) was hydrogenated at normal pressure for 20 min until an equimolar amount of $H_2$ was absorbed. The mixture was filtered and the filtrate was evaporated under reduced pressure to give 380 mg (94.5%) of **11b**. Recrystallization from EtOH yielded a white solid. mp 101–103 °C. IR (KBr): ν = 3060 (w), 2840–2960 (m, CH), 1670 (s, C=O), 1610 (s, C=C), 1590 (s, C=C) (vs) $cm^{-1}$.– $^1H$ NMR ($CDCl_3$): δ = 1.66 (s, 3H, $CH_3$), 2.03–2.09 (m, 2H, $ArCH_2\mathit{CH_2}CH$), 2.73 (m, 2H, Ar′$CH_2$), 2.90 (m, 2H, $ArCH_2$), 3.50–3.53 (m, 1H, ArCOCH), 3.77–3.80 (m, 2H, $CH_2O$), 3.85 (s, 3H, $OCH_3$), 4.04 (m, 2H, $CH_2O$), 6.67 (s, 1H, Ar-H, -H5), 6.83-6.84 (d, *J* = 8.8 Hz, 1H, Ar-H, -H7), 7.34 (d, *J* = 8.4, 2H, Ar′-H, -H2′, -H6′), 7.90 (d, *J* = 8.4, 2H, Ar′-H, -H3′, -H5′), 8.04 (d, *J* = 8.8 Hz, 1H, Ar-H, -H8)

*1-Hydroxy-6-methoxy-2-[3-(2-methyl-1,3-dioxolan-2-yl)benzyl]-1-tetralin (**12a**)*

To a suspension of 100 mg (2.64 mmol) $NaBH_4$ in 30 ml $C_2H_5OH$ was added 300 mg (0.85 mmol) **11a** in 5 ml $C_2H_5OH$ and the mixture was stirred at 70 °C for 15 h. After the end of reaction was shown by TLC control, the solution was poured into 150 ml water and extracted three times with $CH_2Cl_2$ (50ml). The organic layer was washed with $H_2O$ and dried over $Na_2SO_4$. After evaporation of the solvent *in vacuo*, the crude product **12a** (270 mg, 90%, liquid) was obtained and used without further purification for the next reaction. IR (KBr): ν = 3450 (s, OH), 3050 (w, Ar-H), 2870-2960 (m, CH), 1610 (s, C=C), 1580 (w, C=C) (vs) $cm^{-1}$.– $^1H$ NMR ($CDCl_3$): δ = 1.65 (s, 3H, $CH_3$), 2.01–2.09(m, 2H, $ArCH_2\mathit{CH_2}$), 2.47–2.52 (m, 1H, $ArCH_2CH_2\mathit{CH}$) 2.71–2.73 (m, 2H, $ArCH_2$), 2.77–2.83 (m, 1H, Ar′$CH_2$), 2.95–3.04 (m, 1H, Ar′$\mathit{CH_2}$), 3.74–3.77 (m, 2H, $CH_2O$), 3.77(m, 1H, OH), 3.78 (s, 3H, $OCH_3$), 4.0–4.03 (m, 2H, $CH_2O$), 4.44–4.48(m, 1H, Ar$\mathit{CH}$OH), 6.65 (s, 1H, Ar-H, -H5), 6.79 (m, 1H, Ar-H, -H7), 7.13–7.17 (m, 1H, Ar′-H, -H6′), 7.31–7.32 (m, 2H, Ar′-H, -H2′, -H4′), 7.34 (m, 1H, Ar′-H, -H5′), 7.40 (m, 1H, Ar-H, -H8).

*1-Hydroxy-6-methoxy-2-[4-(2-methyl-1,3-dioxolan-2-yl)benzyl]-1-tetralin (**12b**)*

To a suspension of 100 mg (2.64 mmol) $NaBH_4$ in 30 ml $C_2H_5OH$, 300 mg (0.85 mmol) **11b** in 5 ml $C_2H_5OH$ was added. Reaction was performed at 70 °C for 15 h and gave 285 mg **12b** (94.5 %). mp 108–110 °C. IR (KBr): ν = 3400 (s, OH), 3030 (w, Ar-H), 2890–2960 (m, CH), 1610 (s, C=C), 1590 (s, C=C) (vs) $cm^{-1}$.– $^1H$ NMR ($CDCl_3$): δ = 1.66 (s, 3H, $CH_3$), 1.97–2.05 (m, 2H, $ArCH_2CH_2$), 2.47–2.52 (m, 1H, $ArCH_2CH_2CH$), 2.72–2.75 (m, 2H, $ArCH_2$), 2.77–2.83 (m, 1H, $Ar'CH_2$), 2.97–3.02 (m, 1H, $Ar'CH_2$), 3.76 (m, 1H, OH), 3.79 (s, 3H, $OCH_3$), 3.80–3.83 (m, 2H, $CH_2O$), 4.03 (m, 2H, $CH_2O$), 4.45 (m, 1H, ArCHOH), 6.62 (s, 1H, Ar-H, -H5), 6.79 (m, 1H, Ar-H, -H7), 7.17 (d, *J* = 8.0, 2H, Ar′-H, -H2′, -H6′), 7.39 (m, 1H, Ar-H, -H8), 7.41–7.43 (m, 2H, Ar′-H, -H3′, -H5′).

*2-(3-Acetylbenzyl)-6-methoxy-3,4-dihydronaphthalene (**13a**)*

To a stirred solution of 0.27 g (0.76 mmol) **12a** in THF (20 ml) was added 3 ml 10% HCl and the solution was refluxed for 3 h. The reaction mixture was poured into 150 ml water and extracted three times with $CH_2Cl_2$ (50 ml). The organic layer was washed with saturated $NaHCO_3$, $H_2O$ and dried over $Na_2SO_4$. Evaporation of the solvent *in vacuo* gave the crude product, which was purified by silica gel column chromatography using 4% EtOAc/petroleum ether as eluent to give 200 mg (89.8%) of **13a** (colorless liquid). IR (KBr): ν = 3030 (w), 3010 (w), 2820–2920 (m, CH), 1685 (s, C=O), 1610 (s, C=C), 1570 (s, C=C), 1500 (s, C=C) (vs)$cm^{-1}$.– $^1H$ NMR ($CDCl_3$): δ = 2.16 (t, *J* = 8.2, 2H, $ArCH_2CH_2$), 2.60 (s, 3H, $CH_3$), 2.75 (t, *J* = 8.2 Hz, 2H, $ArCH_2$), 3.54 (s, 2H, $Ar'CH_2$), 3.78 (s, 3H, $OCH_3$), 6.21(s, 1H, =CH), 6.66–6.69 (m, 2H, Ar-H, -H5, -H7), 6.92 (d, *J* = 7.52 Hz, 1H, Ar-H, -H8), 7.38–7.41(t, *J* = 7.52 Hz, 1H, Ar′-H, -H5′), 7.45 (d, *J* = 7.48 Hz, 1H, Ar′-H, -H6′), 7.80–7.83 (m, 2H, Ar′-H, -H2′, -H4′).– MS *m/z* (%) = 292 (75) ($M^+$), 159 (100), 144 (49).

*2-(4-Acetylbenzyl)-6-methoxy-3,4-dihydronaphthalene (**13b**)*

280 mg (0.79 mmol) of **12 b** gave 210 mg of **13 b** (91 %, yellow crystals). mp 66–68 °C. IR (KBr): ν = 3010 (w) 2840–2950 (m, CH), 1675 (s, C=O), 1610 (s, C=C), 1570 (s, C=C) (vs) $cm^{-1}$.– $^1H$ NMR ($CDCl_3$): δ = 2.13–2.17 (t, *J* = 8.4, 2H, Ar $CH_2CH_2$), 2.59 (s, 3H, $CH_3$), 2.75 (t, *J* = 8.4 Hz, 2H, $ArCH_2$), 3.54 (s, 2H, $Ar'CH_2$), 3.78 (s, 3H, $OCH_3$), 6.22 (s, 1H, =CH), 6.66–6.69 (m, 2H, Ar-H, -H5, -H7), 6.93 (d, *J* = 8.4 Hz, 1H, Ar-H, -H8), 7.33 (d, *J* = 8.4 Hz, 2H, Ar′-H, -H2′, -H6′), 7.89 (d, *J* = 8.4 Hz, 2H, Ar′-H, -H3′, -H5′).– MS *m/z* (%) = 292 (73) ($M^+$), 159 (100), 144 (50).

*2-[3-(1-Hydroximinoethyl)benzyl]-6-methoxy-3,4-dihydronaphthalene (**14a**)*

A mixture of 0.19 g (0.65 mmol) of **13a**, 0.2 g (2.9 mmol) of $NH_2OH{\cdot}HCl$, 0.4 g (4.9 mmol) of NaOAc and 30 ml $CH_3OH$ was stirred and heated at 65 °C for 2 days. The solution was poured into 150ml water 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 **14a** (0.19 g, 95.2 %) which was purified by recrystallization from EtOAc / petroleum ether. mp 110.5–112 °C; IR (KBr): ν = 3260 (s, OH), 3100 (w), 2840–2960 (m, CH), 1615 (s, C=C), 1575 (s, C=C) (vs) $cm^{-1}$.– $^1H$ NMR (DMSO($d_6$)): δ ppm: 2.10 (t, *J* = 8.0 Hz, 2H, $ArCH_2CH_2$), 2.14 (s, 3H, $CH_3$), 2.68 (t, *J* = 8.0 Hz, 2H, $ArCH_2$), 3.48 (s, 2H, $Ar'CH_2$), 3.71 (s, 3H, $OCH_3$), 6.25 (s, 1H, =CH), 6.68 (m, 2H, Ar-H, -H5, -H7), 6.93 (d, *J* = 7.52 Hz, 1H, Ar-H, -H8), 7.23 (d, *J* = 7.52 Hz, 1H, Ar′-H, -H6′), 7.32 (t, *J* = 7.74 Hz, 1H, Ar′-H, -H5′), 7.47(d, *J* = 7.96 Hz, 1H, Ar′-H, -H4′), 7.55 (s, 1H, Ar′-H, -H2′), 11.13 (s, 1H, =NOH).– MS *m/z* (%) = 307 (44) ($M^+$), 290 (52) ($M^+$ – OH), 159 (63), 132 (100). Anal. ($C_{20}H_{21}NO_2$) C,H,N.

*2-[4-(1-Hydroximinoethyl)benzyl]-6-methoxy-3,4-dihydro-naphthalene (**14b**)*

A mixture of 0.20 g (0.685 mmol) of **13b**, 0.22 g (3.16 mmol) of $NH_2OH{\cdot}HCl$, 0.4 g (4.9 mmol) of NaOAc and 30 ml $CH_3OH$ was stirred and heated at 65 °C for 2 days. The solution was poured into 150ml water 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 **14b** (0.20 g, 95.1%) which was purified by recrystallization from EtOAc / petroleum ether. mp 134–136 °C; IR (KBr): ν = 3240 (s, OH), 3080 (w), 2840–2960 (m, CH), 1610 (s, C=C), 1570 (s, C=C) (vs) $cm^{-1}$.– $^1H$ NMR (DMSO($d_6$)): δ ppm: 2.08 (t, *J* = 8.0 Hz, 2H, $ArCH_2CH_2$), 2.14 (s, 3H, $CH_3$), 2.68 (t, *J* = 8.0 Hz, 2H, $ArCH_2$), 3.47 (s, 2H, $Ar'CH_2$), 3.71 (s, 3H, $OCH_3$), 6.23 (s, 1H, =CH), 6.66 (s, 1H, Ar-H, -H5), 6.67 (d, *J* = 8.0 Hz, 1H, Ar-H, -H7), 6.93 (d, *J* = 8.0 Hz, 1H, Ar-H, H8), 7.25 (d, *J* = 8.4 Hz, 2H, Ar′-H, -H2′, -H6′), 7.59 (d, *J* = 8.4 Hz, 2H, Ar′-H, -H3′, -H5′), 11.12 (s, 1H, =NOH).– MS *m/z* (%) = 307 (36) ($M^+$), 290 (30) ($M^+$ – OH), 159 (100), 144 (44). Anal. ($C_{20}H_{21}NO_2$) C,H,N.

*Biological Methods*

**Enzyme Preparation**: The enzyme was prepared according to a described method using human testes.[10] The determination of enzyme inhibition was performed according to the same literature. The 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 1N HCl). 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%.

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