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6-Substituted 3,4-Dihydro-naphthalene-2-carboxylic Acids: Synthesis and Structure–Activity Studies in a Novel Class of Human 5α Reductase Inhibitors

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Novel 3,4-dihydro-naphthalene-2-carboxylic acids were synthesized and evaluated for 5α reductase inhibitory activity. This enzyme exists in two isoforms and is a pharmacological target for the treatment of benign prostatic hyperplasia, male pattern baldness and acne. In the present study non-steroidal compounds capable of mimicking the transition state of the steroidal substrates were prepared. The synthetic strategy for the preparation of compounds 1–6 consisted of triflation followed by subsequent Heck-type carboxylation or methoxy carbonylation for 6-phenyl-3,4-dihydro-naphthalen-2(1H)-one 1c. A Negishi-type coupling reaction between 6-(trifluoro-methanesulfonyloxy)-3,4-dihydro-naphthalene-2-carboxylic acid methyl ester 7b and various aryl bromides led, after further transformations, to 6-substituted 3,4-dihydro-naphthalene-2-carboxylic acids 7–15. In a similar way the corresponding naphthalene-2-carboxylic acids 16 and 17 were obtained. The DU 145 cell line and prostate homogenates served as enzyme sources for the human type 1 and type 2 isozymes, whereas ventral prostate was employed to evaluate rat isozyme inhibitory potency. The most active inhibitors identified in this study were 6-[4-(*N*,*N*-dicyclohexylaminocarbonyl)-phenyl]-3,4-dihydro-naphthalene-2-carboxylic acid (3) (IC_{50} = 0.09 μM, rat type 1), 6-[3-(*N*,*N*-dicyclohexylaminocarbonyl)phenyl]-3,4-dihydro-naphthalene-2-carboxylic acid (13) (IC_{50} = 0.75 μM, human type 2; IC_{50} = 0.81 μM, human type 1) and 6-[4-(*N*,*N*-diisopropylamino-carbonyl)phenyl]naphthalene-2-carboxylic acid (16) (IC_{50} = 0.2 μM, human type 2). The latter compound was shown to deactivate the enzyme in an uncompetitive manner (Ki = 90 nM; Km, Testosterone = 0.8–1.0 μM) similar to the steroidal inhibitor Epristeride. Select inhibitors (13 and 16) were tested *in vivo* using testosterone propionate-treated, juvenile, orchiectomized SD-rats. None of the compounds was active at a dose of 25 mg/kg. This result might in part be ascribed to the relatively poor *in vitro* rat isozyme inhibitory potency.

Keywords: 5α-reductase inhibitors; Dual non-steroidal inhibitors; Rat and human steroid 5α-reductase isozymes 1 and 2; 6-Substituted 3,4-dihydro-naphthalene-2-carboxylic acids; Benign prostatic hyperplasia

INTRODUCTION

5α Reductase (EC 1.3.99.5) is a NADPH-dependent, membrane bound enzyme, which catalyzes the conversion of testosterone (T) to the more potent androgen dihydrotestosterone (DHT).[1] DHT is believed to be the causative agent in a variety of diseases, including benign prostatic hyperplasia (BPH), acne, hirsutism and androgenetic alopecia (AGA).[2–4] Two different 5α reductase isozymes named type 1 and type 2 have been identified, which are characterized by distinct molecular genetics, structural and biochemical properties and by different tissue localization.[5–7] Finasteride (Proscar®) and Epristeride (Chart 1) are highly potent rather selective type 2 steroidal inhibitors. Due to their relatively poor type 1 inhibitory potency they do not completely suppress DHT formation, which might be a reason for the limited benefit when treating BPH patients with Finastreride.[2] Combination of Finasteride with a selective type 1 isozyme inhibitor (MK-386),[8] resulted in nearly complete suppression of serum DHT (90% compared to 70% without type 1 isozyme inhibitor).[9] Another approach to obtain compounds with inhibitory activity against both isozymes is the development of so-called dual inhibitors.[10–15] One of these, Dutasteride (Chart 1), produced a nearly complete (>90%) suppression of

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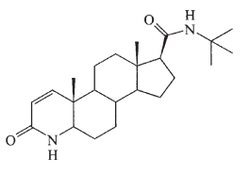
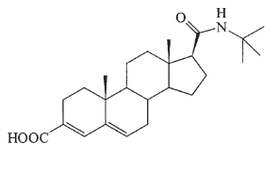
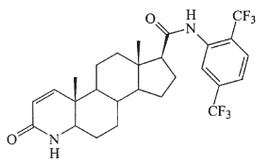
serum DHT in healthy male subjects and is in an advanced stage of clinical development for the treatment of BPH and AGA.[16–18] Due to these results, dual inhibition is now considered to be a promising strategy for a more effective treatment of BPH with 5α reductase inhibitors.



Finasteride

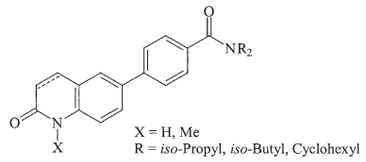


Epristeride



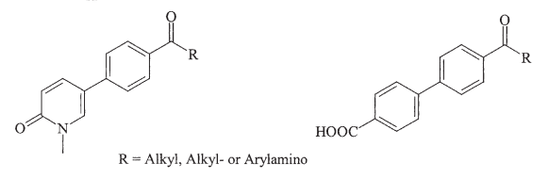
Dutasteride

Because of the side effects of steroidal compounds,[19] which we think at least in part are due to the steroidal framework, we have been attempting to develop non-steroidal 5α reductase inhibitors with dual inhibition towards both human isozymes.[20–28] An interesting class of compounds are the 6-substituted 1H-quinolin-2-ones (**A**, Chart 2) as their lactam ring mimics the steroidal A ring of Finasteride.[29] Furthermore, we have recently demonstrated,[30] that in the class of A–C ring steroidomimetics the biphenyl-4-carboxylic acids (**C**) were more appropriate for 5α reductase inhibition than the 5-phenyl-1-methyl-2-pyridones (**B**, Chart 2). As a consequence of these recent structure–activity studies we focussed in the present paper on 3,4-dihydro-naphthalene-2-carboxylic acids (**1**–**15**) and naphthalene-2-carboxylic acids (**16**, **17**, Chart 3), which are structurally based on the steroidal inhibitor Epristeride. In the following paragraphs we describe the synthesis of a series of novel 6-substituted compounds and their evaluation of rat and human 5α reductase isozyme 1 and 2 inhibition. Using selected compounds studies on the mode of inhibition and *in vivo* activity are presented.



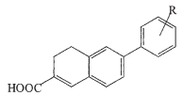
X = H, Me
R = *iso*-Propyl, *iso*-Butyl, Cyclohexyl

A

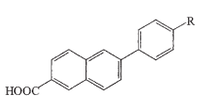


R = Alkyl, Alkyl- or Arylamino

B **C**



1-15



16,17

compd	R	compd	R	compd	R
1	H	7	4-OMe	13	3-CON(Cyclohexyl)$_2$
2	4-CON(*iso*-Propyl)$_2$	8	4-*tert*-Butyl	14	3-CONHCPh$_3$
3	4-CON(Cyclohexyl)$_2$	9	4-Phenyl	15	3-OMe
4	4-CONH(1-Adamantyl)	10	4-Benzoyl	16	CON(*iso*-Propyl)$_2$
5	4-CONH(*tert*-Butyl)	11	4-*iso*-Valeroyl	17	CON(Cyclohexyl)$_2$
6	4-CONHPh	12	3-CON(*iso*-Propyl)$_2$		

EXPERIMENTAL SECTION

General

Unless otherwise indicated, materials obtained from commercial suppliers were used without further purification. Solvents for reactions under anhydrous conditions were dried according to standard procedures. All reactions, except those involving water as a reagent, were performed under nitrogen atmosphere. Melting points were determined on a Reichert Thermometer hot stage microscope and are uncorrected. Silica gel TLC and column chromatography were performed on Merck TLC 60F-254 (0.25 mm) and Merck Kieselgel 60 (40–63 μm or 50–200 μm). IR spectra were measured using a Perkin Elmer Infrared Spectrometer 398 (KBr). ^{1}H NMR spectra were measured on a Bruker AM 400 at 400 MHz in $CDCl_3$ or DMSO-d_6 solution and chemical shifts are reported in δ parts per million downfield from tetramethylsilane. Mass spectra (EI, 70 ev) were determined on a HP G1800A GCD. Elemental analyses indicated by the symbols of the elements were within ±0.4% of the theoretical values and were performed by the Institute of Inorganic Chemistry, Saarland University, Saarbrücken, Germany.

[1β-^{3}H]Androstenedione (4-androstene-3,17-dione, AD) 27.5 Ci/mmol, and [1β,2β-^{3}H]Testosterone (17β-hydroxy-4-androstene-3-one, T) 54 Ci/mmol were purchased from DuPont, Bad Homburg, Germany.

6-Phenyl-3,4-dihydro-naphthalen-2(1H)-one (1c)

Compound **1c** was prepared in analogy to the two-step procedure of Cereghetti *et al.*[31] Starting with biphenyl-4-acetic acid. Mp 81–82°C (lit. 81–81.7°C).[31] IR (KBr): $\nu = 3020, 2960, 1720, 1605, 1480, 1240, 1165, 1045, 760\,cm^{-1}$. ^{1}H NMR ($CDCl_3$) δ 2.59 (t, 2H); 3.13 (t, 2H); 3.63 (s, 2H); 7.19–7.59 (m, 8H).

N,N-Diisopropyl-4-(6-oxo-5,6,7,8-tetrahydro-naphthalen-2-yl)-benzamide (2c)

$AlCl_3$ (8.0 g, 60 mmol) was gradually added to a mixture of 6-phenyl-3,4-dihydro-naphthalen-2(1H)-one (**1c**) (4.4 g, 19.8 mmol) and oxalyl chloride (3.36 mL, 40 mmol) in dichloromethane (80 mL) at 0°C. The mixture was stirred at 5–10°C for 30 min, then poured onto ice (100 g) and was immediately extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with water (30 mL) and dried (magnesium sulfate). The solvent was evaporated and the remaining crude acid chloride (red brownish oil) was used without further purification. A solution of the crude acid chloride (4.5 g) in dichloromethane was added dropwise within 10 min to a solution of diisopropylamine (5 g, 50 mmol) in dichloromethane (50 mL). The mixture was stirred for 30 min at 25°C, then water (50 mL) and dichloromethane (100 mL) were added. The phases were separated and the organic layer was washed with water (40 mL) and dried (magnesium sulfate). The solvent was evaporated and the residue purified by column chromatography (silica gel) eluting with hexane-ethyl acetate (6:4). Yield: 22%, pale pink crystals, mp: 160–165°C. IR (KBr): $\nu =$ 2960, 2930, 1725, 1625, 1440, 1340, 1210, 1165, 1040, 860, 770 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.33 (m, 12H); 2.57 (t, 2H, $J = 6.62$ Hz); 3.11 (t, 2H, $J = 6.84$ Hz); 3.61 (s, 2H); 7.18 (d, 1H, $J = 7.48$ Hz); 7.38 and 7.57 (dd, 4H, $J = 7.96$ Hz); 7.43 (m, 2H). Anal. ($C_{23}H_{27}NO_2$) C, H, N.

Compound **3c** was prepared following the same procedure described for the synthesis of **2c**:

N,N-*Dicyclohexyl-4-(6-oxo-5,6,7,8-tetrahydro-naphthalen-2-yl)-benzamide (3c)*

Purified by column chromatography (silica gel) using dichloromethane-ethyl acetate of increasing polarity. Yield: 14%, pale brownish crystals, mp 200–205°C. IR (KBr): $\nu = 2930$, 2850, 1720, 1630, 1435, 1370, 1320, 1130, 895 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.00–2.05 (2m, 20H); 2.60 (t, 2H, $J = 6.64$ Hz); 3.14 (t, 2H, $J = 6.64$ Hz); 3.45 (m, 2H); 3.64 (s, 2H); 7.22 (d, 1H, $J = 7.52$ Hz); 7.38 and 7.59 (dd, 4H, $J = 8.40$ Hz); 7.48 (m, 2H). Anal. ($C_{29}H_{35}NO_{2)}$ C, H, N.

2-Trifluoro-methanesulfonic Acid 6-phenyl-3,4-dihydro-naphthalen-2-yl Ester (1b)

Trifluoromethanesulfonic anhydride (2.35 mL, 14.2 mmol) was added dropwise to a solution of 6-phenyl-3,4-dihydro-naphthalen-2(1H)-one (**1c**) (2.22 g, 10.0 mmol) and 2,6-di-*tert*-butyl-4-methyl-pyridine (2.25 g, 11.0 mmol) in anhydrous dichloromethane (20 mL) at 0°C. The mixture was warmed to room temperature and stirred for 30 h. Ethyl acetate (100 mL) was added and the organic layer was washed once with diluted hydrochloric acid (5%) and then with brine (25 mL). It was then dried over $MgSO_4$ and the organic solvent evaporated. The brown residue was purified by flash chromatography eluting with hexane-chloroform (9:1). Yield: 73%, colourless crystals, mp. 88–89°C. IR (KBr): $\nu =$ 2480, 1660, 1420, 1220, 1140, 760, 700 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.74 (t, 2H, $J = 8.40$ Hz); 3.13 (t, 2H, $J = 8.40$ Hz); 6.53 (s, 1H); 7.14–7.58 (m, 8H).

Compounds **2b**–**3b** were prepared in a similar way as described for **1b**:

Trifluoro-methanesulfonic Acid 6-[4-(N,N-diisopropylaminocarbonyl)phenyl]-3,4-dihydro-naphthalen-2-yl Ester (2b)

Synthesized from compound **2c**. The reaction mixture was stirred for 30 h at 25°C and the residue was purified by column chromatography (silica gel) eluting with hexane-ethyl acetate (7:3). Yield: 27%, pale yellow solid, mp: 180–181°C. ^1H NMR ($CDCl_3$) δ 1.35 (d, 12H); 2.73–3.11 (m, 4H); 3.69 (m, 2H); 6.50 (s, 1H); 6.97–7.71 (m, 7H).

Trifluoro-methanesulfonic Acid 6-[4-(N,N-dicyclohexylaminocarbonyl)phenyl]-3,4-dihydro-naphthalen-2-yl Ester (3b)

Synthesized from compound **3c**. The reaction mixture was stirred at 25°C for 48 h and the residue was purified by column chromatography (silica gel) eluting with petroleum ether (40–60°C)-ethyl acetate (7:3). Yield: 22%, colourless solid, mp: 208–210°C. ^1H NMR ($CDCl_3$) δ 1.25–1.68 (2m, 20H); 2.74 (t, 2H, $J = 8.40$ Hz); 3.13 (t, 2H, $J = 8$,40 Hz); 3.72 (m, 2H); 6.53 (s, 1H); 7.22 (d, 1H, $J = 7.92$ Hz); 7.37 and 7.56 (dd, 4H, $J = 7.95$ Hz); 7.40 and 7.44 (2m, 2H).

6-[4-(N,N-Diisopropylaminocarbonyl)phenyl]-3,4-dihydro-naphthalene-2-carboxylic Acid Methyl Ester (2a)

A mixture of trifluoro-methanesulfonic acid 6-[4-(*N*,*N*-diisopropyl-aminocarbonyl)phenyl]-3,4-dihydro-naphthalen-2-yl ester (**2b**) (241 mg, 0.50 mmol), triethylamine (0.14 mL, 1.00 mmol), palladium acetate (3.50 mg, 15.0 μmol), triphenylphosphine (10.0 mg, 30.0 μmol), methanol (0.90 mL, 20.0 mmol) and *N*,*N*-dimethylformamide (2 mL) was purged with carbon monoxide for 5 min and then stirred for 20 h at 25°C under a carbon monoxide atmosphere. Water (50 mL) was added and the mixture was extracted with ether (4 × 50 mL). The combined organic layers were washed with hydrochloric acid (5%, 25 mL) and water until neutral and dried over Na_2SO_4. The solvent was evaporated and the residue was purified by flash chromatography eluting with

hexane- ethyl acetate (7:3) Yield: 59%, colourless crystals, mp. 148–149°C. IR (KBr): $\nu = 3020$, 2960, 1710, 1630, 1610, 1440, 1340, 1210, 1070, 1035, 830, 770, 725 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.26 (m, 12H), 2.66 (t, 2H, $J = 8.40$ Hz), 2.94 (t, 2H, $J = 8.2$ Hz), 3.83 (s, 3H), 7.57 (s, 1H), 7.38 and 7.60 (dd, 4H, $J = 7.96$ Hz); 7.26–7.45 (m, 3H). MS (154°C): $m/z = 391$ (M^+, 29%), 291 (100%), 45 (60%), 348 (59%), 57 (58%), 61 (50%), 292 (38%).

Compound **1a** was prepared in analogy to **2a**:

6-Phenyl-3,4-dihydro-naphthalene-2-carboxylic Acid Methyl Ester (1a)

Synthesized from compound **1b**. The reaction mixture was stirred for 3 h at 25°C under a carbon monoxide atmosphere. Ethyl acetate (100 mL) was added. The organic layer was washed once with diluted hydrochloric acid (10%, 30 mL), then with saturated $NaHCO_3$ solution (50 mL), water and brine until neutral. The organic layer was dried over $MgSO_4$ and the solvent evaporated. The remaining solid was purified by flash chromatography eluting with hexane-ethyl acetate (12:1). Yield: 81%, colourless crystals, mp: 116–117°C. IR (KBr): $\nu = 2945$, 1710, 1440, 1295, 1220, 1070, 1010, 770, 700 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.66 (t, 2H, $J = 8.40$ Hz); 2.94 (t, 2H, $J = 8.20$ Hz); 3.83 (s, 3H); 7.26–7.61 (m, 9H).

6-Phenyl-3,4-dihydro-naphthalene-2-carboxylic Acid (1)

2-Trifluoro-methanesulfonic acid 6-phenyl-3,4-dihydro-naphthalen-2-yl ester (**1b**) (0.35 g, 1 mmol), potassium acetate (0.39 g, 4 mmol), palladium(II)acetate (9 mg), and triphenyl-phosphine (21 mg) were stirred in *N,N*-dimethylformamide (10 mL) under CO-atmosphere at 25°C for 14 h. Water (30 mL) was added and the solution was acidified with diluted hydrochloric acid (20 mL, 0.5 N). The mixture was extracted with dichloromethane (3 × 25 mL) and the combined organic layers were washed with brine (25 mL), dried (magnesium sulfate) and the solvent was evaporated. The remaining brownish residue was dissolved in diluted sodium hydroxide solution (0.5 N, 50 mL) and extracted with diethylether (2 × 25 mL). The aqueous layer was acidified (HCl, 2 N, 30 mL) and extracted with diethylether (3 × 25 mL), dried (magnesium sulfate) and evaporated. The residue was purified by column chromatography (silica gel) using ethyl acetate and subsequent recrystallization from petroleum ether (40–60°C)/ethyl acetate (1:1). Yield: 26%, pale yellow crystals, mp: 210–215°C. IR (KBr): $\nu = 3000$, 1675, 1430, 1300, 1230, 890, 830, 770, 700 cm^{-1}. ^1H NMR (DMSO-d_6) δ 2.50 (m, 2H); 2.89 (t, 2H, $J = 8.18$ Hz); 7.42 (s, 1H); 7.35–7.69 (m, 8H); 12.40 (s, 1H). Anal. ($C_{17}H_{14}O_2$) C, H, N.

Compounds **2** and **3** were prepared in a similar way as described for **1**:

6-[4-(N,N-Diisopropylaminocarbonyl)phenyl]-3,4-dihydro-naphthalene-2-carboxylic Acid (2) Synthesized from Compound 2b

Yield: 36%, colourless crystals, mp (ethyl acetate): 275–276°C. IR (KBr): $\nu = 3000$, 2960, 1670, 1630, 1435, 1370, 1340, 1225, 1040, 1015, 825, 770 cm^{-1}. ^1H NMR (DMSO-d_6) δ 1.28 (m, 12H); 2.50 (t, 2H, $J = 8.40$ Hz); 2.90 (t, 2H, $J = 8.00$ Hz); 3.65 (s, 2H); 7.52 (s, 1H); 7.35 and 7.73 (dd, 4H, $J = 8.40$ Hz); 7.41–7.70 (m, 3H). Anal. ($C_{24}H_{27}NO_3$) C, H, N.

6-[4-(N,N-Dicyclohexylaminocarbonyl)phenyl]-3,4-dihydro-naphthalene-2-carboxylic Acid (3)

Synthesized from compound **3b**. Yield: 28%, colourless crystals, mp (ethyl acetate): 265–266°C. ^1H NMR (DMSO-d_6) δ 1.09 and 1.66 (2m; 20H); 2.50 (t, 2H, $J = 8.29$ Hz); 2.90 (t, 2H, $J = 8.29$ Hz); 7.34 and 7.75 (dd, 4H, $J = 8.22$ Hz); 7.43 (d, 1H, $J = 7.77$ Hz); 7.52 (s, 1H); 7.58 (m, 2H). Anal. ($C_{30}H_{35}NO_3 \cdot 1.2\ H_2O$) C, H, N.

Compound **2** was also prepared by saponification of **2a**:

A mixture of 6-[4-(*N,N*-Diisopropylaminocarbonyl)phenyl]-3,4-dihydro-naphthalene-2-carboxylic acid methyl ester (**2a**) (110 mg. 0.28 mmol) and K_2CO_3 (78.0 mg, 2.00 mmol), in methanol–water (9:1) (5 mL) was heated under reflux for 6 h. The reaction was cooled to 25°C, diluted with water (30 mL) and acidified with diluted hydrochloric acid (10%). The precipitated acid was filtered, washed thoroughly with water, dried and recrystallized from ethyl acetate. Yield: 47%, colourless crystals, mp. 280–281°C. IR (KBr): $\nu = 3000$, 2960, 1670, 1630, 1435, 1370, 1335, 1225, 1039, 825, 770 cm^{-1}. ^1H NMR (DMSO-d_6) δ 1.28 (m, 12 H); 2.52 (t, 2H,); 2.90 (t, 2H, $J = 8.20$ Hz); 3.66 (s, 2H); 7.52 (s, 1H); 7.36 and 7.73 (dd, 4H, $J = 8.40$ Hz); 7.41–7.57 (m, 3H). Anal. ($C_{24}H_{27}NO_3$) C, H, N.

6-[4-(N-tert-Butylaminocarbonyl)phenyl]-3,4-dihydro-naphthalene-2-carboxylic Acid Methyl Ester (5a)

$AlCl_3$ (1.20 g, 9.00 mmol) was gradually added to a mixture of 6-phenyl-3,4-dihydro-naphthalene-2-carboxylic acid methyl ester (**1a**) (0.79 g, 3.00 mmol), and oxalyl chloride (0.51 mL, 6.00 mmol) in anhydrous dichloromethane (12 mL) at 0°C. The mixture was stirred at 5–10°C for 30 min, poured onto ice (15 g), and immediately extracted with ethyl acetate (3 × 30 mL). The combined organic layers were

washed with water (7 mL) and dried over $MgSO_4$. The solvent was evaporated and the remaining crude acid chloride was used without further purification. A solution of the crude acid chloride in anhydrous dichloromethane (10 mL) was added dropwise to a solution of *tert*-butylamine (316 μL, 3.00 mmol) and triethylamine (1.25 mL, 9.00 mmol) in anhydrous dichloromethane (20 mL). The mixture was stirred for 1 h at 5–10°C. Water (30 mL) and ethyl acetate (50 mL) were added, the phases were separated and the organic layer was washed once with hydrochloric acid (10%), $NaHCO_3$ solution and water until neutral and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by flash chromatography eluting with hexane–ethyl acetate (7:3). Yield: 68%, colourless crystals, mp: 189–190°C. IR (KBr): $\nu = 3380, 3300, 2980, 1710, 1640, 1610, 1550, 1440, 1280, 1220, 1080, 1000, 830, 775, 730\ cm^{-1}$. ^1H NMR ($CDCl_3$) δ 1.50 (s, 9H); 2.67 (t, 2H, $J = 8.20$ Hz); 2.95 (t, 2H, $J = 8.20$ Hz); 3.84 (s, 3H); 5.97 (s, 1H); 7.63 and 7.78 (dd, 4H, $J = 8.40$ Hz); 7.27–7.46 (m, 3H). MS (135°C) m/z: 363 (M^+, 78%), 291 (100%), 307 (57%), 57 (76%), 55 (60%), 149 (50%), 69 (44%), 71 (39%).

Compounds **4a** and **6a** were synthesized in analogy to **5a**:

6-[4-(N-(1-Adamantyl)aminocarbonyl)phenyl]-3,4-dihydro-naphthalene-2-carboxylic Acid Methyl Ester (4a)

Yield: 60%, colourless crystals, mp: 191–192°C. IR (KBr): $\nu = 3415, 2910, 2845, 1710, 1660, 1610, 1505, 1305, 1215, 1075, 1005, 830, 770, 730\ cm^{-1}$. ^1H NMR ($CDCl_3$) δ 1.74 (s, 6H); 2.15 (s, 9H); 2.67 (t, 3H, $J = 7.74$ Hz); 2.95 (t, 2H, $J = 8.20$ Hz), 3.83 (s, 3H); 5.82 (s, 1H); 7.27–7.44 (m, 3H); 7.64 and 7.79 (dd, 4H, $J = 8.20$ Hz). Anal. ($C_{29}H_{31}NO_3$) C, H, N.

6-[4-(N-Phenylaminocarbonyl)phenyl]-3,4-dihydro-naphthalene-2-carboxylic Acid Methyl Ester (6a)

Yield: 57%, colourless crystals, mp: 226–227°C. IR (KBr): $\nu = 3280, 2945, 1715, 1650, 1600, 1535, 1440, 1330, 1300, 1215, 1075, 825, 770, 690\ cm^{-1}$. ^1H NMR ($CDCl_3$) δ 2.67 (t, 2H, $J = 8.40$ Hz); 2.95 (t, 2H, $J = 8.20$ Hz); 3.83 (s, 3H); 7.58 (s, 1H); 7.71 and 7.95 (dd, 4H, $J = 8.40$ Hz); 7.14–7.68 (m, 8H); 7.92 (s, 1H). Anal. ($C_{25}H_{21}NO_3$) C, H, N.

6-[4-(N-(1-Adamantyl)aminocarbonyl)phenyl]-3,4-dihydro-naphthalene-2-carboxylic Acid (4)

A mixture of 6-[4-(*N*-(1-adamantyl)aminocarbonyl)-phenyl]-3,4-dihydro-naphthalene-2-carboxylic acid methyl ester (**4a**) (443 mg, 1.00 mmol)) and K_2CO_3 (415 mg, 3.00 mmol) in methanol–water (9:1) (18 mL) was heated under reflux for 18 h. The reaction mixture was cooled to 25°C and acidified with hydrochloric acid (10%). The precipitate was filtered off, washed with water and dried. The remaining solid was recrystallized from dimethylsulfoxide. Yield: 94%, pale yellow crystals, mp: 294–295°C. IR (KBr): $\nu = 3420, 3020, 2845, 2900, 1680, 1660, 1610, 1500, 1300, 1225, 1010, 830, 770\ cm^{-1}$. ^1H NMR (DMSO-d_6) δ 1.69 (s, 6H); 2.11 (m, 9H); 2.53 (t, 2H); 2.92 (t, 2H, $J = 8.20$ Hz); 5.82 (s, 1H); 7.70 and 7.87 (dd, 4H, $J = 8.20$ Hz); 8.20 (s, 1H); 7.37–7.50 (m, 4H). Anal. ($C_{28}H_{29}NO_3$) C, H, N.

Compounds **5** and **6** were obtained in analogy to **4**.

6-[4-(N-tert-Butylaminocarbonyl)phenyl]-3,4-dihydro-naphthalene-2-carboxylic Acid (5)

Synthesized from compound **5a**. Yield: 97%, colourless crystals, mp: 291–92°C. IR (KBr): $\nu = 3320, 2980, 1700, 1630, 1550, 1300, 1220, 1015, 770, 730\ cm^{-1}$. ^1H NMR (DMSO-d_6) δ 1.40 (s, 9H); 2.52 (t, 2H, $J = 8.20$ Hz); 2.91 (t, 2H, $J = 8.20$ Hz); 7.75 and 7.88 (dd, 4H, $J = 8.20$ Hz); 7.79 (s, 1H); 7.52 (s, 1H); 7.42–7.60 (m, 3H); 12.48 (s, broad; 1H). Anal. ($C_{22}H_{23}NO_3$) C, H, N.

6-[4-(N-Phenylaminocarbonyl)phenyl]-3,4-dihydro-naphthalene-2-carboxylic Acid (6)

Synthesized from compound **6a**. Yield: 80%, pale yellow crystals, mp: 296-297°C. IR (KBr): $\nu = 3300, 3020, 2900, 1680, 1635, 1590, 1520, 1430, 1310, 1290, 1220, 810, 760, 680\ cm^{-1}$. ^1H NMR (DMSO-d_6) δ 2.54 (t, 2H, $J = 7.74$ Hz); 2.92 (t, 2H, $J = 8.40$ Hz); 7.87 and 8.06 (dd, 4H, $J = 8.40$ Hz); 7.53 (s, 1H); 7.09-7.81 (m, 8H); 10.28 (s, 1H). MS (206°C) m/z: 369 (M^+, 5%), 197 (100%), 253 (86%), 318 (64%), 57 (56%), 149 (40%).

6-Methoxy-1-oxo-1,2,3,4-tetrahydro-naphthalene-2-carboxylic Acid Ethyl Ester (7f)

A solution of 6-methoxy-1-tetralone (7.5 g, 42.6 mmol) in tetrahydrofuran (80 mL) was slowly added to a mixture of sodium hydride (3.75 g, 156 mmol) and diethyl carbonate (10.05 g, 85 mmol) in tetrahydrofuran (30 mL) under reflux. The mixture was stirred for 30 h under reflux, cooled to 25°C and treated with water (100 mL) and glacial acetic acid (10 mL) and subsequently extracted with diethyl-ether (3 × 100 mL). The combined organic layers were washed with brine (50 mL), dried (magnesium sulfate) and evaporated. The oily residue was chromatographed (silica gel) using hexane-ethyl acetate (8:2). Yield: 65%, colourless solid, mp: 50–52°C. IR (KBr): $\nu = 2990, 2950, 1740, 1680, 1610, 1505, 1470, 1370, 1315, 1280, 1260, 1225, 1180, 1160, 1110, 1060, 1035, 1020\ cm^{-1}$. ^1H NMR ($CDCl_3$) δ 1.27 (t, 3H, $J = 8.0$ Hz); 2.16–2.61 (m, 2H); 2.79–3.14 (m, 2H); 3.40–3.57 (m, 1H, CH-CO); 3.82 (s, 3H); 4,22

(q, 2H, $J = 7.2$ Hz); 6.56–6.89 (m, 2H); 7.95–8.09 (m, 1H); 12.51 (s, 1H, HO–C = C–).

1-Hydroxy-6-methoxy-1,2,3,4-tetrahydro-naphthalene-2-carboxylic Acid Ethyl Ester (7e)

Sodium borohydride (0.2 g, 5.2 mmol) was suspended in ethanol (10 mL) and a solution of **7f** (4.4 g, 17.7 mmol) in ethanol (20 mL) was added slowly at 0°C. The mixture was stirred at 25°C for 2 h, poured onto cracked ice (50 g), acidified with diluted hydrochloric acid (1 N, 30 mL) and extracted with diethylether (3 × 50 mL). The ethereal extracts were dried (magnesium sulfate) and evaporated to yield a yellow oil, which was purified by column chromatography (silica gel) eluting with petroleum ether (40–60°C)–ethyl acetate (1:1). Yield: 64%, colourless oil. IR (Film): $\nu = 3450$, 2940, 1730, 1615, 1505, 1470 cm^{-1}. ^1H NMR (DMSO-d_6) δ 1.22 (t, 3H, $J = 7.60$ Hz); 1.73–2.08 (m, 2H); 2.41–2.91 (m, 3H); 3.37 (s, 1H); 3.70 (s, 3H); 4.10 (q, 2H, $J = 8.0$ Hz); 5.0 (s, 1H); 6.53–6.82 (m, 2H); 7.09–7.32 (m, 1H).

6-Methoxy-3,4-dihydro-naphthalene-2-carboxylic Acid Ethyl Ester (7d)

Compound **7e** (1.6 g, 6.4 mmol) and p-toluene sulfonic acid (0.1 g) in toluene were heated under reflux until no more water was formed (1.5 h). The mixture was cooled to 25°C, the solvent was evaporated and the oily residue was chromatographed (silica gel) using hexane–ethyl acetate (4:1) as eluants. Yield: 92%, colourless oil. IR (film): $\nu =$ 2940, 1745, 1710, 1635, 1615, 1580, 1510, 1440, 1385, 1310, 1280, 1250, 1210, 1080, 1045 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.32 (t, 3H, $J = 7.20$ Hz); 2.42–3.04 (m, 4H); 3.77 (s, 3H); 4.25 (q, 2H, $J = 7.60$ Hz); 6.56–6.81 (m, 2H); 7.00–7.25 (m, 1H); 7.48 (s, 1H).

6-Hydroxy-3,4-dihydro-naphthalene-2-carboxylic Acid Methyl Ester (7c)

Boron tribromide (30 g, 120 mmol) was added slowly to a solution of **7d** (7.0 g, 30 mmol) in dichloromethane (200 mL) at −75°C. The solution was kept for 2 h at −75°C and for 2 h at 25°C. Dry methanol (25 mL) was then added very slowly and the solution was washed with water (3 × 25 mL), dried (magnesium sulfate) and filtered over celite. The residue that remained upon evaporation of the solvent was chromatographed (silica gel) using hexane–ethyl acetate (3:2) as eluants. Yield: 45%, colourless solid, mp: 140–142°C. IR (KBr): $\nu = 3400$, 2960, 1680, 1615, 1580, 1440, 1290, 1220, 1160, 1080, 1010, 825 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.58 (t, 2H, $J = 7.96$ Hz); 2.82 (t, 2H, $J = 8.20$ Hz); 3.81 (s, 3H); 5.22 (s, 1H); 6.67 (m, 2H); 7.08 (d, 1H, $J = 8.84$ Hz); 7.49 (s, 1H).

Compound **12c** was prepared following the same procedure described for **7c**:

6-(3-Hydroxy-phenyl)-3,4-dihydro-naphthalene-2-carboxylic Acid Methyl Ester (12c)

Synthesized from compound **15a**. Yield: 76%, colourless solid, mp: 145–146°C. IR (KBr): $\nu = 3400$, 2950, 1685, 1585, 1480, 1445, 1310, 1270, 1220, 1160, 1140, 1080, 935, 840, 780 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.66 (t, 2H, $J = 8.40$ Hz); 2.93 (t, 2H, $J = 8.20$ Hz); 3.87 (s, 3H); 5.00 (s, 1H); 6.83 (dd, 1H, $J = 7.96$ Hz, $J = 2.24$ Hz); 7.07 (t, 1H, $J = 2.20$ Hz); 7.17 (d, 1H, $J = 7.96$ Hz); 7.25 (d, 1H); 7.31 (t, 1H, $J = 7.74$ Hz); 7.38 (s, 1H); 7.41 (d, 1H, $J = 7.48$ Hz); 7.57 (s, 1H).

6-(Trifluoro-methanesulfonyloxy)-3,4-dihydro-naphthalene-2-carboxylic Acid Methyl Ester (7b)

Trifluoromethanesulfonic anhydride (1 mL, 5.75 mmol) was added to a solution of **7c** (1.02 g, 5 mmol) in dichloromethane (20 mL) and pyridine (2 mL). After 30 min dichloromethane (100 mL) and water (30 mL) were added, the phases were separated and the organic layer was washed with diluted hydrochloric acid (5 N, 2 × 30 mL) and water (50 mL). After drying (magnesium sulfate) and evaporation of the solvent, the residue was purified by filtration over silica gel eluting with hexane–ethyl acetate (7:3). Yield: 67%, pale yellow crystals, mp: 48–50°C. IR (KBr): $\nu = 3050$, 2950, 1705, 1585, 1425, 1310, 1275, 1250, 1210, 1150, 1130, 1110, 1010, 910, 830 cm^{-1}. ^1H NMR (DMSO-d_6) δ 2.53 (t, 2H, $J = 8.40$ Hz); 2.90 (t, 2H, $J = 8.40$ Hz); 3.75 (s, 3H); 7.36 (dd, 1H, $J = 8.4$ Hz, $J = 2.2$ Hz); 7.41 (s, 1H); 7.56 (m, 2H).

Compounds **12b**, **16a** and **17a** were prepared in a similar way as described for compound **7b**:

6-[3-(Trifluoro-methanesulfonyloxy)-phenyl]-3,4-dihydro-naphthalene-2-carboxylic Acid Methyl Ester (12b)

Synthesized starting from compound **12c**. Yield: 81%, colourless solid, mp: 84–85°C. ^1H NMR ($CDCl_3$) δ 2.67 (t, 2H, $J = 8.40$ Hz); 2.95 (t, 2H, $J = 8.40$ Hz); 3.84 (s, 3H); 7.26 (m, 1H); 7.30 (d, 1H, $J = 7.96$ Hz); 7.37 (s, 1H); 7.41 (d, 1H, $J = 7.96$ Hz); 7.48 (s, 1H); 7.52 (t, 1H, $J = 7.96$ Hz); 7.57 (s, 1H, H-5); 7.61 (d, 1H, $J = 7.96$ Hz). Anal. ($C_{19}H_{15}F_3O_5S$) C, H.

Trifluoro-methanesulfonic Acid 6-[4-(N,N-diisopropylaminocarbonyl)phenyl]naphthal-en-2-yl Ester (16a)

Synthesized starting from compound **16b**.Yield: 84%, yellow solid, mp: 201–202°C. ^1H NMR ($CDCl_3$) δ 1.40 (m, 12H); 3.60 (m, 2H); 7.41 (dd, $J = 9.06$ Hz,

$J = 2.46$ Hz, 1H); 7.45 and 7.72 (4H, $J = 8.18$ Hz); 7.78 (d, 1H, $J = 2.20$ Hz); 7.84 (dd, 1H, $J = 8.40$ Hz, $J = 1.80$ Hz, 1H); 7.97 (2d, 2H, $J = 9.72$ Hz,); 8.09 (s, 1H).

Trifluoro-methanesulfonic Acid 6-[4-(N,N-dicyclo hexylaminocarbonyl)phenyl]naphthal-en-2-yl Ester (17a)

Synthesized starting from compound **17b**.Yield: 58%, yellow solid, mp: 211–212°C. ^{1}H NMR ($CDCl_3$) δ 1.00–1.90 (m, 20H); 2.60–3.00 (2m, 2H); 7.41 (dd, 1H, $J = 2.68$ Hz); 7.43 and 7.71 (dd, 4H, $J = 8.40$ Hz); 7.78 (d, 1H, $J = 2.20$ Hz); 7.86 (dd, 1H, $J = 8.40$ Hz, $J = 1.76$ Hz); 7.98 (m, 2H); 8.11 (s, 1H).

6-[4-(2-Phenyl-[1,3]dioxolan-2-yl)phenyl]-3,4-dihydro-naphthalene-2-carboxylic Acid Methyl Ester (10b)

tert-Butyllithium (2 mL, 3.2 mmol, solution in pentane) was injected via a syringe into a solution of 2-(4-bromophenyl)-2-phenyl-[1,3]dioxolane (0.45 g, 1.5 mmol) in tetrahydrofuran (20 mL) at −78°C. Then carefully dried zinc(II)chloride (0.2 g, 1.5 mmol) was added and the mixture warmed to 25°C within 1 h. Compound **7b** (0.2 g, 0.6 mmol) and tetra-kistriphenylphosphino palladium (0) (50 mg) were added. The mixture was heated under reflux for 2 h, cooled to 25°C, evaporated and treated with water (20 mL) and dichloromethane (50 mL). The phases were separated, the organic layer was dried over sodium sulfate and the solvent was distilled off. The oily residue was purified by column chromatography (silica gel) eluting with hexane–ethyl acetate (7:3). Yield: 63%, colourless solid, mp: 128–130°C. ^{1}H NMR ($CDCl_3$) δ 2.65 (t, 2H, $J = 8.20$ Hz); 2.92 (t, 2H, $J = 8.40$ Hz); 3.82 (s, 3H); 4.10 (s, 4H); 7.24–7.59 (2m, 13H).

11b was prepared in a similar way as described for compound **10b**:

6-[4-(2-iso-Butyl-[1,3]dioxolan-2-yl)phenyl]-3,4-dihydro-naphthalene-2-carboxylic Acid Methyl Ester (11b)

Yield: 66%, colourless oil. ^{1}H NMR ($CDCl_3$) δ 0.91 (d, 6H, $J = 6.64$ Hz); 1.69 (m, 1H); 1.86 (d, 2H, $J = 6.20$ Hz); 2.65 (t, 2H, $J = 7.30$ Hz); 2.91 (t, 2H, $J = 8.43$ Hz); 3.78 and 4.03 (2t, 4H, $J = 6.43$ Hz); 3.83 (s, 3H); 7.41 (s, 1H); 7.10–7.70 (m, 7H).

6-(4-Benzoyl-phenyl)-3,4-dihydro-naphthalene-2-carboxylic Acid Methyl Ester (10a)

Compound **10b** (4.33 g, 10.5 mmol) was dissolved in ethanol (20 mL) and dilute hydrochloric acid (120 mL, 3%) was added. The mixture was stirred at 90°C for 5 h and was then extracted with ethyl acetate (3 × 50 mL) after being cooled to 25°C. The combined organic layers were washed with water (2 × 50 mL), dried (magnesium sulfate) and the solvent was evaporated. Yield: 56%, colourless solid, mp: 163–165°C. ^{1}H NMR ($CDCl_3$) δ 2.68 (t, 2H, $J = 7.96$ Hz); 2.96 (t, 2H, $J = 8.18$ Hz); 3.84 (s, 3H); 7.31 (d, 1H, $J = 7.96$ Hz); 7.46 (s, 1H); 7.50 (m, 3H); 7.59 (m, 2H); 7.83 (d, 2H, $J = 7.52$ Hz); 7.71 and 7.89 (dd, 4H, $J = 7.96$ Hz).

11a was prepared in a similar way as described for compound **10a**:

6-[4-(3-Methyl-butyryl)phenyl]-3,4-dihydro-naphthalene-2-carboxylic Acid Methyl Ester (11a)

Synthesized from compound **11b**. The reaction mixture was refluxed for 6 h, cooled to 25°C and extracted with dichloromethane (3 × 50 mL). The combined organic layers were washed with water (2 × 50 mL), dried (magnesium sulfate) and evaporated. The resulting residue was purified by digestion with petroleum ether (60–80°C). Yield: 34%, colourless crystals (platelets), mp: 105–110°C. ^{1}H NMR ($CDCl_3$) δ 1.02 (d, 6H, $J = 6.64$ Hz); 2.33 (m, 1H); 2.67 (t, 2H, $J = 8.18$ Hz); 2.86 (d, 2H, $J = 6.64$ Hz); 2.96 (t, 2H, $J = 8.18$ Hz); 3.83 (s, 3H); 7.30 (d, 1H, $J = 7.52$ Hz); 7.44 (s, 1H); 7.48 (d, 1H, $J = 7.96$ Hz); 7.58 (s, 1H); 7.68 and 8.02 (dd, 4H, $J = 8.18$ Hz).

6-(4-Methoxyphenyl)-3,4-dihydro-naphthalene-2-carboxylic Acid Methyl Ester (7a)[32]

6-(4-tert-Butylphenyl)-3,4-dihydro-naphthalene-2-carboxylic Acid Methyl Ester (8a)[32]

6-Biphenyl-4-yl-3,4-dihydro-naphthalene-2-carboxylic Acid Methyl Ester (9a)[32]

6-(3-Methoxyphenyl)-3,4-dihydro-naphthalene-2-carboxylic Acid Methyl Ester (15a)[32]

N,N-Diisopropyl-4-[6-(tert-butyl-dimethyl-silyloxy)naphthalen-2-yl]benzamide (16c)

Synthesized from compounds *16d* and *16e*. Yield: 63%, colourless oil. ^{1}H NMR ($CDCl_3$) δ 0.23 (s, 6H); 1.03 (s, 9H); 1.40 (s, broad, 12H); 3.63 (s, broad, 2H); 7.11 (dd, 1H, $J = 8.85$ Hz, $J = 2.20$ Hz); 7.67 (dd, 1H, $J = 1.76$ Hz; 7.22 (d, 1H, $J = 2.24$ Hz); 7.97 (s, 1H); 7.42 and 7.70 (dd, 4H, $J = 8.18$ Hz); 7.77 (d, 1H, $J = 8.40$ Hz); 7.78 (d, 1H, $J = 8.84$ Hz).

N,N-Dicyclohexyl-4-[6-(tert-butyl-dimethyl-silyloxy)naphthalen-2-yl]benzamide (17c)

Synthesi-zed from compounds **16d** and **17e**. Yield: 59%, colourless oil. ^{1}H NMR ($CDCl_3$) δ 0.23 (s, 6H); 1.02 (s, 9H); 1.00–1.90 (m, broad, 20H); 2.60 and 3.14

(2s, broad, 2H); 7.11 (dd, 1H, $J = 8.84$ Hz, $J = 2.20$ Hz); 7.67 (dd, 1H, $J = 7.96$ Hz, $J = 1.76$ Hz); 7.19 and 7.50 (dd, 4H, $J = 8.40$ Hz); 7.22 (d, 1H, $J = 2.24$ Hz); 7.99 (s, 1H); 7.77 (d, 1H, $J = 8.84$ Hz); 7.78 (d, 1H, $J = 8.88$ Hz).

6-(4-Methoxy-phenyl)-3,4-dihydronaphthalene-2-carboxylic Acid (7)

A mixture of **7a** (1.47 g, 5 mmol) and potassium carbonate (0.83 g, 6 mmol) in methanol–water (9:1) (100 mL) was heated under reflux for 25 h. The reaction mixture was cooled to 25°C, acidified with dilute hydrochloric acid (5N, 20 mL) and then extracted with dichloromethane (4 × 30 mL). The combined organic layers were washed with brine (30 mL), dried (magnesium sulfate) and the solvent was evaporated. The remaining solid was recrystallized from petroleum ether (40–60°C)–ethyl acetate of increasing polarity. Yield: 74%, colourless crystals, mp: 256°C. IR (KBr): $\nu = 3000$, 2950, 1680, 1625, 1600, 1550, 1520, 1430, 1300, 1250, 1225, 1180, 1040, 1025, 925, 815, 670 cm^{-1}. ^1H NMR (DMSO-d_6) δ 2.50 (t, 2H, $J = 8.36$ Hz); 2.87 (t, 2H, $J = 8.44$ Hz); 7.02 and 7.64 (dd, 4H, $J = 8.78$ Hz); 7.37 (d, 1H, $J = 7.60$ Hz); 7.49 (m, 3H); 12.41 (s, 1H). Anal. ($C_{18}H_{16}O_3 \cdot 0.2\ H_2O$) C, H.

Compounds **8**–**15** were prepared in analogy to **7**:

6-(4-tert-Butyl-phenyl)-3,4-dihydro-naphthalene-2-carboxylic Acid (8)

Synthesized from compound **8a**. Yield: 29%, colourless crystals, mp: 288–290°C. IR (KBr): $\nu = 3000$, 2960, 1670, 1605, 1550, 1430, 1300, 1220, 825 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.37 (s, 9H); 2.68 (t, 2H, $J = 8.40$ Hz); 2.96 (t, 2H, $J = 8.40$ Hz); 7.29 (d, 1H, $J = 7.96$ Hz); 7.42 (s, 1H); 7.45 (d, 1H, $J = 7.48$ Hz); 7.47 and 7.55 (dd, 4H, $J = 8.40$ Hz); 7.70 (s, 1H). Anal. ($C_{21}H_{22}O_2 \cdot 0.3\ H_2O$) C, H.

6-Biphenyl-4-yl-3,4-dihydro-naphthalene-2-carboxylic Acid (9)

Synthesized from compound **9a**. Yield: 37%, colourless crystals, mp: >300°C. IR (KBr): $\nu = 3000$, 1680, 1625, 1480, 1435, 1305, 1230, 825, 765, 730, 690 cm^{-1}. ^1H NMR (DMSO-d_6) δ 2.52 (t, 2H, $J = 7.52$ Hz); 2.91 (t, 2H, $J = 7.96$ Hz); 7.53 (s, 1H); 7.37–7.82 (m, 12H); 12.48 (s, 1H). Anal. ($C_{23}H_{18}O_2 \cdot 0.2\ H_2O$) C, H.

6-(4-Benzoyl-phenyl)-3,4-dihydro-naphthalene-2-carboxylic Acid (10)

Synthesized from compound **10a**. Yield: 31%, white powder, mp: 272–274°C. IR (KBr): $\nu = 3000$, 1680, 1650, 1605, 1430, 1300, 1290, 1230, 940, 925, 830, 695 cm^{-1}. ^1H NMR (DMSO-d_6) δ 2.53 (t, 2H, $J = 8.50$ Hz); 2.92 (t, 2H, $J = 8.30$ Hz); 7.47 (d, 1H, $J = 7.70$ Hz); 7.54 (s, 1H); 7.64 (m, 2H); 7.59–7.76 (m, 5H); 7.84 and 7.91 (dd, 4H, $J = 8.42$ Hz); 12.50 (s, 1H). Anal. ($C_{24}H_{18}O_3$) C, H.

6-(4-(3-Methyl-butyryl)phenyl]-3,4-dihydro-naphthalene-2-carboxylic Acid (11)

Synthesized from compound **11a**. Yield: 43%, white powder, mp: 210–213°C. IR (KBr): $\nu = 3000$, 2950, 1680, 1605, 1430, 1365, 1295, 1220, 820 cm^{-1}. ^1H NMR (DMSO-d_6) δ 0.95 (d, 6H, $J = 6.60$ Hz); 2.17 (sext, 1H; $J = 6.64$ Hz); 2.53 (t, 2H, $J = 7.96$ Hz); 2.91 (t, 2H, $J = 7.72$ Hz); 7.45 (d, 1H, $J = 7.96$ Hz); 7.53 (s, 1H); 7.62 (d, 1H, $J = 8.40$ Hz); 7.64 (s, 1H); 7.85 and 8.04 (dd, 4H, $J = 8.40$ Hz); 12.49 (s, 1H). Anal. ($C_{22}H_{22}O_3 \cdot 0.3\ H_2O$) C, H.

6-[3-(N,N-Diisopropylaminocarbonyl)phenyl]-3,4-dihydro-naphthalene-2-carboxylic Acid (12)

Synthesized from compound **12a**. Yield: 34%, colourless crystals, mp: 283–285°C. IR (KBr): $\nu = 3000$, 2960, 1665, 1630, 1540, 1430, 1300, 1280, 1230, 815, 700 cm^{-1}. ^1H NMR (DMSO-d_6) δ 1.18 (m, 12H); 2.50 (t, 2H, $J = 8.40$ Hz); 2.92 (t, 2H, $J = 8.40$ Hz); 7.53 (s, 1H); 7.43–8.34 (m, 7H); 12.49 (s, 1H). Anal. ($C_{24}H_{27}NO_3$) C, H.

6-[3-(N,N-Dicyclohexylaminocarbonyl)phenyl]-3,4-dihydro-naphthalene-2-carboxylic Acid (13)

Synthesized from compound **13a**. Yield: 38%, colourless solid, mp: 235–236°C. IR (KBr): $\nu = 3050$, 2940, 2840, 1695, 1605, 1580, 1450, 1370, 1280, 1210, 1140, 915, 895, 800, 710 cm^{-1}. ^1H NMR (DMSO-d_6) δ 0.90–1.80 (m, 20H); 2.51 (t, 2H, $J = 8.40$ Hz); 2.90 (t, 2H, $J = 8.40$ Hz); 7.24 (d, 1H, $J = 7.52$ Hz); 7.42 (d, 1H, $J = 7.52$ Hz); 7.48–7.54 (m, 4H); 7.56 (s, 1H); 7.73 (d, 1H, $J = 7.96$ Hz); 12.47 (s, 1H). ($C_{30}H_{35}NO_3 \cdot 0.8\ H_2O$) C, H.

6-[3-(N-Triphenylmethylaminocarbonyl)phenyl]-3,4-dihydro-naphthalene-2-carboxylic Acid (14)

Synthesized from compound **14a**. Yield: 42%, colourless crystals, mp: 258–260°C. IR (KBr): $\nu = 3000$, 1680, 1490, 1450, 1305, 1280, 1230 cm^{-1}. ^1H NMR (DMSO-d_6) δ 2.49 (t, 2H); 2.91 (t, 2H, $J = 8.40$ Hz); 7.16–7.59 (m, 22H); 7.83 (d, 1H, $J = 7.52$ Hz); 9.15 (s, 1H). Anal. ($C_{37}H_{29}NO_3 \cdot 0.7\ H_2O$) C, H.

6-(3-Methoxy-phenyl)-3,4-dihydro-naphthalene-2-carboxylic Acid (15)

Synthesized from compound **15a**. Yield: 45%, colourless crystals, mp: 174–175°C. IR (KBr): $\nu = 3000$, 2940, 1670, 1610, 1585, 1555, 1485, 1430, 1290, 1220,

1170, 1040, 920, 870, 840, 775, 690 cm^{-1}. ^1H NMR (DMSO-d_6) δ 2.50 (t, 2H, $J = 8.20$ Hz); 2.89 (t, 2H, $J = 8.30$ Hz); 3.83 (s, 3H); 6.95 (dd, 1H, $J = 8.10$ Hz, $J = 2.46$ Hz); 7.21 (t, 1H, $J = 2.16$ Hz); 7.25 (d, 1H, $J = 7.94$ Hz); 7.39 (m, 2H); 7.53 (m, 3H). Anal. ($C_{18}H_{16}O_3$) C, H.

6-[3-(N,N-Diisopropylaminocarbonyl)phenyl]-3,4-dihydro-naphthalene-2-carboxylic Acid Methyl Ester (12a)

A mixture of **12b** (0.1 g, 0.24 mmol), palladium(II) acetate (2 mg), 1,1′-bis(diphenylphosphino)ferrocene (8 mg) and diisopropylamine (0.5 g, 5 mmol) in dry *N,N*-dimethylformamide (2 mL) was stirred for 2 h at 80°C under an atmosphere of carbon monoxide. After cooling to 25°C water (20 mL) was added and the mixture was extracted with diethylether (3 × 30 mL). The combined organic layers were washed with dilute hydrochloric acid (1 N, 30 mL) and dried over magnesium sulfate. The solvent was evaporated and the residue purified by column chromatography (silica gel) eluting with petroleum ether (40–60°C)–acetone of increasing polarity. Yield: 24%, colourless solid, mp: 179–180°C. ^1H NMR ($CDCl_3$) δ 1.40 (m, 12H); 2.66 (t, 2H, $J = 8.57$ Hz); 2.95 (t, 2H, $J = 8.36$ Hz); 3.84 (s, 3H); 7.44 (s, 1H); 7.28–7.98 (m, 7H).

Compounds **13a** and **14a** were prepared in a similar way as described for **12a**:

6-[3-(N,N-Dicyclohexylaminocarbonyl)phenyl]-3,4-dihydro-naphthalene-2-carboxylic Acid Methyl Ester (13a)

Yield: 32%, colourless oil. ^1H NMR ($CDCl_3$) δ 1.05–1.90 (2m, 20H); 2.66 (t, 2H, $J = 8.40$ Hz); 2.94 (t, 2H, $J = 8.40$ Hz); 3.40 (s, 2H); 3.83 (s, 3H); 7.41 (s, 1H); 7.26–7.60 (m, 7H).

6-[3-(N-Triphenylmethylaminocarbonyl)phenyl]-3,4-dihydro-naphthalene-2-carboxylic Acid Methyl Ester (14a)

Yield: 58%, colourless oil. ^1H NMR ($CDCl_3$) δ 2.67 (t, 2H, $J = 8.40$ Hz); 2.93 (t, 2H, $J = 8.40$ Hz); 3.83 (s, 3H); 7.16–7.80 (m, 23H); 8.10 (s, 1H).

6-Bromo-2-tert-butyl-dimethyl-silyloxy-naphthalene (16d)

tert-Butyldimethylsilylchloride (13.6 g, 0.09 mol) was added in 3 portions to a solution of 6-bromo-2-naphthol (20.1 g, 0.09 mol), triethylamine (12.5 mL, 0.09 mol) and 4-dimethylaminopyridine (0.5 g) in dry *N,N*-dimethylformamide (100 mL) at 25°C. After 12 h the mixture was poured onto ice water (300 mL) and extracted with diethylether (4 × 150 mL). The combined organic extracts were washed with water (50 mL) and dried over magnesium sulfate. Evaporation of the solvent yielded an oil, that crystallized immediately and was purified by column chromatography (silica gel) eluting with hexane-ethyl acetate of increasing polarity. Yield: 66%, yellow crystals, mp: 58–60°C. ^1H NMR ($CDCl_3$) δ 0.11 (s, 6H); 1.01 (s, 9H); 7.09 (dd, 1H, $J = 8.84$ Hz, $J = 2.64$ Hz); 7.47 (dd, 1H, $J = 8.84$ Hz, $J = 1.76$ Hz); 7.15 (d, 1H, $J = 1.76$ Hz); 7.91 (d, 1H, $J = 1.76$ Hz); 7.56 (d, 1H, $J = 8.84$ Hz); 7.62 (d, 1H, $J = 8.84$ Hz).

4-(6-Hydroxy-naphthalen-2-yl)-N,N-diisopropyl-benzamide (16b)

Tetrabutylammonium-fluoride (4.8 mL, 4.8 mmol, 1 M solution in THF) was added to a solution of **16c** in tetrahydrofuran (30 mL). After 2 h at 25°C ice water (100 mL) was added and the mixture was extracted with diethylether (3 × 100 mL). The combined organic layers were dried over magnesium sulfate and the remaining oil crystallized from hexane–ethyl acetate. Yield: 58%, colourless crystals, mp: 263–264°C (dec). IR (KBr): $\nu = 3200$, 2950, 1600, 1450, 1375, 1350, 1210, 870, 850, 840, 805 cm^{-1}. ^1H NMR (DMSO-d_6) δ 1.29 (s, broad, 12H); 3.69 (s, broad, 2H); 7.12 (dd, 1H, $J = 8.84$ Hz, $J = 2.20$ Hz); 7.74 (dd, 1H, $J = 8.40$ Hz, $J = 1.76$ Hz); 7.15 (s, 1H); 8.12 (s, 1H); 7.38 and 7.80 (dd, 4H, $J = 8.18$ Hz); 7.78 (d, 1H, $J = 9.28$ Hz); 7.85 (d, 1H, $J = 8.84$ Hz); 9.79 (s, 1H). Anal. ($C_{23}H_{25}NO_2$) C, H, N.

Compound **17b** was prepared in a similar way as described for **16b**:

4-(6-Hydroxy-naphthalen-2-yl)-N,N-dicyclohexyl-benzamide (17b)

Synthesized from compound **17c**. Yield: 52%, colourless crystals, mp: 267–268°C. IR (KBr): $\nu = 3250$, 2920, 2850, 1730, 1600, 1480, 1440, 1370, 1315, 1230, 1200, 1120, 990, 920, 895, 850 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.10–1.90 (m, 20H); 3.10 and 3.50 (2s, broad, 2H); 6.90 (dd, 1H, $J = 8.84$ Hz, $J = 2.20$ Hz); 7.45 (dd, 1H, $J = 8.40$ Hz, $J = 1.80$ Hz); 6.96 (s, 1H); 7.67 (s, 1H); 7.33 and 7.51 (dd, 4H, J = 7.96 Hz); 7.52 (m, 2H). Anal. ($C_{29}H_{33}NO_2$) C, H, N.

6-[4-(N,N-Diisopropylaminocarbonyl) phenyl]naphthalene-2-carboxylic Acid (16)

A mixture of **16a** (239 mg, 0.5 mmol), potassium acetate (196 mg, 2 mmol), palladium(II)acetate (60 mg, 0.25 mmol) and 1,1′-bis(diphenylphosphino)-ferrocene (56 mg 0.1 mmol) in dry dimethyl-sulfoxide (15 mL) was stirred at 65°C for 3 h under an atmosphere of carbon monoxide. After cooling to 25°C water (50 mL) and then dilute hydrochloric acid (1 N, 25 mL) were added and the mixture was

extracted with dichloromethane (4 × 50 mL). The combined organic layers were extracted with a sodium hydroxide solution (1 N, 3 × 50 mL) and the combined basic extracts were acidified with concentrated hydrochloric acid. The aqueous layer was extracted with dichloromethane (3 × 50 mL). The combined organic layers were washed with water (2 × 50 mL) and dried over magnesium sulfate. The solvent was evaporated and the residue recrystallized from ethyl acetate. Yield: 42%, colourless crystals, mp: 286–287°C. IR (KBr): $\nu = 2970$, 1680, 1635, 1440, 1370, 1340, 1300, 1040, 1015, 855, 770 cm^{-1}. ^1H NMR (DMSO-d_6) δ 1.50 (s, broad, 12H); 3.70 (s, broad); 7.43 and 7.90 (dd, 4H, $J = 8.18$ Hz); 7.98 (dd, 1H, $J = 8.84$ Hz, $J = 1.32$ Hz); 8.01 (dd, 1H, $J = 8.84$ Hz, $J = 1.32$ Hz); 8.10 (d, 1H, $J = 8.40$ Hz); 8.22 (d, 1H, $J = 8.40$ Hz); 8.36 (s, 1H); 864 (s, 1H); 13.05 (s, 1H). Anal. ($C_{24}H_{25}NO_3$) C, H, N.

Compound **17** was prepared in the same way as described for compound **16**:

6-[4-(N,N-Dicyclohexylaminocarbonyl) phenyl]naphthalene-2-carboxylic Acid (17)

Synthesized from compound **17a**. Yield: 38%, colourless crystals, mp: 285–286°C. IR (KBr): $\nu = 3050$, 2930, 2850, 1690, 1630, 1435, 1365, 1315, 1190, 1170, 1120, 725, 705 cm^{-1}. ^1H NMR (DMSO-d_6) δ 0.80–1.90 (m, 20H); 3.30 (m, 2H); 7.41 and 7.91 (dd, 4H, $J = 7.96$ Hz); 8.00 (2 dd); 8.10 (d, 1H, $J = 8.84$ Hz); 8.22 (d, 1H, $J = 8.44$ Hz); 8.34 (s, 1H); 8.64 (s, 1H); 13.11 (s, 1H). Anal. ($C_{30}H_{33}NO_3$) C, H, N.

Inhibition of 5α Reductase *In Vitro*

Enzyme Inhibition Test

Preparation of Tissue

Rat prostatic enzyme was prepared according to the method of Liang *et al.*[33] with slight modifications.[30] Male rats were sacrified and prostates were taken within 5 min and put in ice cold 0.9% aqueous NaCl solution. All the following operations were performed at 0–4°C. The prostates were dissected free from fat and connective tissue, cut into pieces and weighed. Per 1 g of tissue, 3 ml of 20 mM phosphate buffer, pH 6.6, containing 0.32 mM sucrose and 1 mM dithiothreitol (DTT) was added. The tissue was homogenized by 10-s strokes at 20,500 rpm of an ultraturax (IKA) in 60-s intervals, filtered through cheesecloth and centrifuged for 60 min at 105,000 g. The pellet obtained was resuspended in phosphate buffer. The centrifugation was repeated, the final pellet resuspended in a minimum volume of phosphate buffer and stored in 300 μL portions at −70°C. The 105,000 g pellet contains nuclei, mitochondria and microsomes and is referred to as the enzyme preparation. The protein content was determined by Lowry's method[34] and was in the range of 15–25 mg/ml. Human prostatic tissue from BPH patients was processed in the same way using citrate buffer, pH 5.5.

Incubation Procedure

The assay was performed as described[33] with modifications.[30] All values were run in duplicate. The incubation was carried out for 30 min at 37°C in a total volume of 250 μL. In the case of rat enzyme preparation phosphate buffer (40 mM, pH 6.6 for type 1) or citrate buffer (40 mM, pH 5.5 for type 2) were used. In the case of human enzyme preparation citrate buffer (40 mM, pH 5.5) was used. The incubation mixture contained approximately 250 μg of rat protein (125 μg human protein), 200 μM NADPH (human enzyme, 100 μM NADPH), 0.21 μM testosterone (T) including 100 nCi [1β,2β-^{3}H]T and 2% DMSO with or without test compound (10 μM). Where inhibition exceeded 60%, three concentrations were chosen for the determination of IC_{50} values. The reaction was started by adding the prostatic enzyme preparation and terminated by addition of 50 μL aqueous solution of NaOH (10 M). The steroids were extracted with diethyl ether (500 μL) by shaking for 10 min. Subsequent centrifugation was performed for 10 min at 4000 rpm. The water layer was frozen and the ether layer was decanted in fresh tubes and evaporated to dryness.

Human Type 1 Inhibition: DU 145-assay[35]

Intact human prostatic carcinoma DU145 cells were used as the source of type 1 5α reductase.[36,37] The inhibitory potencies of the compounds were determined by monitoring the conversion of the tritiated substrate androstenedione (5 nM) to androstanedione during an incubation period of 6 h. A day before the experiment, DU145 cells were seeded in a 24-multiwell-plate at a density of 180.000 cells/well and allowed to become adherent overnight in 1 mL RPMI-1640 medium (with 10% FCS). Appropriate concentrations (10 μM final concentration in initial tests) of inhibitors dissolved in dimethylsulfoxide (DMSO) were applied in duplicates. Growth medium was replaced by 500 μL of fresh medium containing 5 μL of the inhibitor and 5 nM [^{3}H]androstenedione as substrate. Inhibitors were first screened at concentrations of 10 μM in an initial test and in cases exceeding 80% inhibition, three concentrations were chosen for measurement of IC_{50} values. As a control of conversion (typically about 35% under these conditions) a triplicate of wells without inhibitors was used and as a positive control for inhibition **Finasteride** (80, 60, 40, 20 nM) was used. After the 6 h incubation period in 5% CO_2 at 37°C the medium samples were extracted twice with 1 mL of diethylether and the steroids were separated

by HPLC. Results are expressed as amount of formed androstanedione as percentage of control values.

HPLC Procedure

Steroid separation was performed[30] similar to the method of Cook *et al.*[38] The steroids were dissolved in 50 μL methanol and 25 μL were injected into the computer-controlled HPLC system, which was checked before using labelled reference controls. Radioactivity was measured using a Berthold LB 506C monitor, using methanol/water (55/45, w/w) for T and DHT with a flow rate of 0.4 ml/min and an additive flow of 1.0 mL for scintillator, base-line separation of T and DHT was achieved within 20 min. For the steroids androstenedione and androstanedione methanol/water (50/50, w/w) was used and the retention time's were 11.2 min and 17.5 min respectively.

Calculation Procedure

The amount of DHT formed was calculated (% DHT). The zero value was subtracted from the control (cv) and inhibition (iv) values (cv_{corr} and iv_{corr}). Inhibition (I) was calculated using the following equation: $\% I = (1 - iv_{corr}/cv_{corr})100$.

Ki Values Determination

For the determination of Ki values, the inhibitor was tested at 2 concentrations (250 and 125 nM) near its IC_{50} value with variable substrate concentrations (0.21, 0.51, 1.01 and 2.02 μM T). The kinetic parameters were calculated using the following equations:

$$\frac{1}{V} = \frac{Km}{Vmax} \cdot \frac{1}{S} + \frac{1}{Vmax} \quad (1)$$

$$\frac{1}{V} = \frac{Km}{Vmax} \cdot \frac{1}{S} + \frac{1}{Vmax}\left(1 + \frac{I}{Ki}\right) \quad (2)$$

The first equation represents a modification of the Lineweaver–Burk relation according to Lee and Wilson with V (reaction velocity), Vmax (maximum velocity), Km (Michaelis–Menten constant) and S (mean substrate concentration). Equation (2) describes uncompetitive inhibitory patterns.[39]

Inhibition of 5α Reductase In Vivo[40]

Juvenile, male, orchiectomized Sprague–Dawley rats (age 21 days) were divided into groups of 6–8 animals. For 4 consecutive days, testosterone propionate (1 mg/kg) and the test compounds in doses equimolar to Finasteride were subcutaneously administered as solution or suspension in olive oil. One group received vehicle only a second one only testosterone propionate, but no inhibitor. On the fifth day the animals were sacrificed by CO_2-inhalation. The ventral prostates were quickly removed, dissected free from adhering adipose tissue and weighed (prostate wet weight).

RESULTS

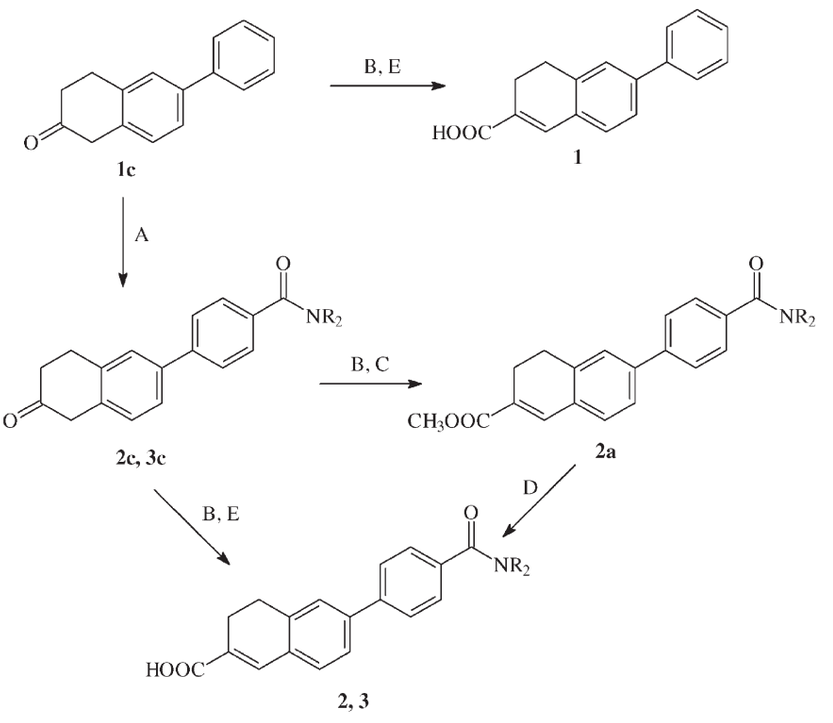
Chemistry

6-Phenyl-3,4-dihydro-naphthalen-2(1H)-one (**1c**)[31] was applied as the precursor for the 6-aryl substituted 3,4-dihydro-naphthalene-2-carboxylic acids **1**–**6** using two pathways (Schemes 1 and 2):

In the first (Scheme 1), **1c** was regioselectively acylated using oxalyl chloride and aluminium chloride, with phosgene generated *in situ* acting as acylating agent.[41] The correct regioselective para-orientation could be achieved by choosing dichloromethane as a solvent. The acid chloride obtained was directly converted to the desired amides **2c** and **3c** by quenching the reaction mixture with the appropriate amine. For the synthesis of the carboxylic acids **1**–**3**, the ketones **1c**–**3c** were transferred into the enol triflates **1b**–**3b** using 2,6-di-*tert*-butyl-4-methylpyridine as sterically hindered base and trifluoromethanesulfonic anhydride.[42,43] These were carboxylated using carbon monoxide, potassium acetate and catalytic amounts of $Pd(OAc)_2/PPh_3$ according to a procedure recently developed by Cacchi.[44] Alternatively, the acid **2** was synthesized by methoxy carbonylation[45,46] of the triflate **2b** with carbon monoxide and methanol under palladium catalysis to yield the methyl ester **2a** followed by saponification.

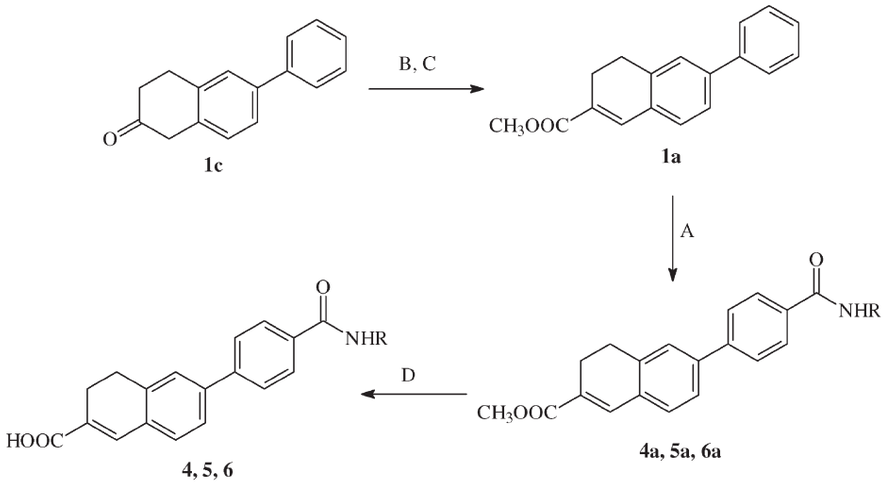
Carboxylic acids **4**–**6** with secondary amide substituents were synthesized using a different route (Scheme 2) to avoid the unwanted reaction of Tf_2O with the secondary amide. Triflation and methoxy carbonylation of the ketone **1c** yielded the methyl ester **1a**. Reacting **1a** with oxalyl chloride/$AlCl_3$ followed by the appropriate amine produced the amides **4a**–**6a**. Subsequent saponification led to carboxylic acids **4**–**6**.

For the preparation of compounds **7**–**11**, which are not carrying an amide substituent in the para-position, a different strategy was developed that involved the construction of the biphenyl skeleton. Using this procedure a larger variety of substituents could be introduced. The preparation of the key precursor **7b** (Scheme 3) started from 6-methoxy-1-tetralone, which was subjected to a Stobbe condensation with diethylcarbonate yielding the ß-ketoester **7f**.[47] Reduction with sodium borohydride and elimination using p-toluene sulfonic acid gave compound **7d** in high yield. Ether cleavage with boron tribromide at −78°C, followed by methanolysis and reaction with trifluoromethanesulfonic anhydride in pyridine resulted in the aryl triflate **7b**.



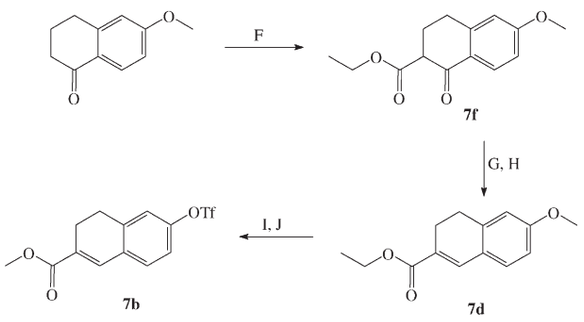
2 : R = *iso*-Propyl **3** : R = Cyclohexyl

SCHEME 1 Synthesis of compounds **1**–**3**. Reagents and conditions: A: oxalyl chloride, $AlCl_3$, CH_2Cl_2 then H_2NR, NEt_3,CH_2Cl_2, 25°C; B: Tf_2O, 2,6-di-(*tert*-butyl)-4-methylpyridine, CH_2Cl_2, 25°C; C: CO, MeOH, NEt_3, cat. $Pd(OAc)_2$, cat. PPh_3, DMF, and **2b**, 25°C; D: K_2CO_3, ethanol/water (9/1), reflux; E: CO, KOAc, cat. $Pd(OAc)_2$, cat. PPh_3, and **1b**, **2b** or **3b**, DMF, 25°C.



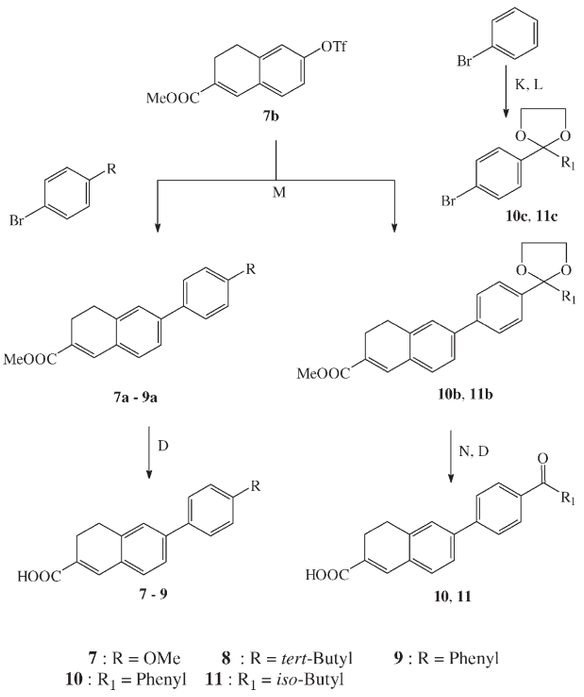
4 : R = 1-Adamantyl **5** : R = *tert*-Butyl **6** : R = Phenyl

SCHEME 2 Synthesis of compounds **4**–**6**. Reagents and conditions: B: Tf_2O, 2,6-di-(*tert*-butyl)-4-methylpyridine, CH_2Cl_2, 25°C; C: CO, MeOH, NEt_3, cat. $Pd(OAc)_2$, cat. PPh_3, DMF, 25°C; A: oxalyl chloride, $AlCl_3$, CH_2Cl_2 then H_2NR, NEt_3, CH_2Cl_2, 25°C; D: K_2CO_3, methanol/water (9/1), reflux.



SCHEME 3 Synthesis of intermediate **7b**. Reagents and conditions: F: diethylcarbonate, NaH, THF, reflux, 30 h; G: $NaBH_4$, ethanol, 25°C, 2 h; H: p-Tos-OH, toluene, reflux, 1.5 h; I: BBr_3, CH_2Cl_2, −78°C, then dry methanol; J: Tf_2O, CH_2Cl_2, pyridine, 0–5°C.

According to our published procedure,[32] the triflate **7b** was converted to various biphenyls (Scheme 4). First the required arylbromides were transformed to the lithium species using two equivalents of *tert*-butyl lithium at −78°C in tetrahydrofuran and then transmetalated with zinc(II)chloride. A Negishi-type coupling reaction with triflate **7b** yielding the biphenyl system gave access to compounds **7a**–**9a**, **10b** and **11b**. The latter were first deprotected using diluted hydrochloric acid and subsequently saponificated with potassium carbonate resulting in carboxylic acids *7*–**11**.



SCHEME 4 Synthesis of compounds **7**–**11**. Reagents and conditions: K: acyl chloride, $AlCl_3$, 55°C, 3 h; L: ethyleneglycol, p-Tos-OH, benzene, reflux, 48 h; M: *tert*-BuLi (2 eq), THF, −78°C, then $ZnCl_2$ (−78°C to 25°C) and **7b**, $Pd(PPh_3)_4$, reflux, 2 h; N: HCl (3 %)/ethanol (6/1), 90°C; D: K_2CO_3, methanol/water (9/1), reflux.

Also in the described way the meta-substituted compound **15a** (Scheme 5) was obtained, which proved to be appropriate for further transformations, giving access to analogs with an amide substituent in the meta-position. Ether cleavage with boron tribromide yielded the phenol **12c**, which was converted to the triflate **12b**. This compound was directly transformed to the desired amides **12a**–**14a** according to an excellent method developed by Cacchi.[45] With palladium(II)acetate, 1,1′-bis(diphenylphosphino)ferrocene, and the corresponding amines in *N*,*N*-dimethylformamide under a carbon monoxide atmosphere, the corresponding amides **12a**–**14a** were obtained in an acceptable yield. Subsequent saponification gave the carboxylic acids **12**–**15**.

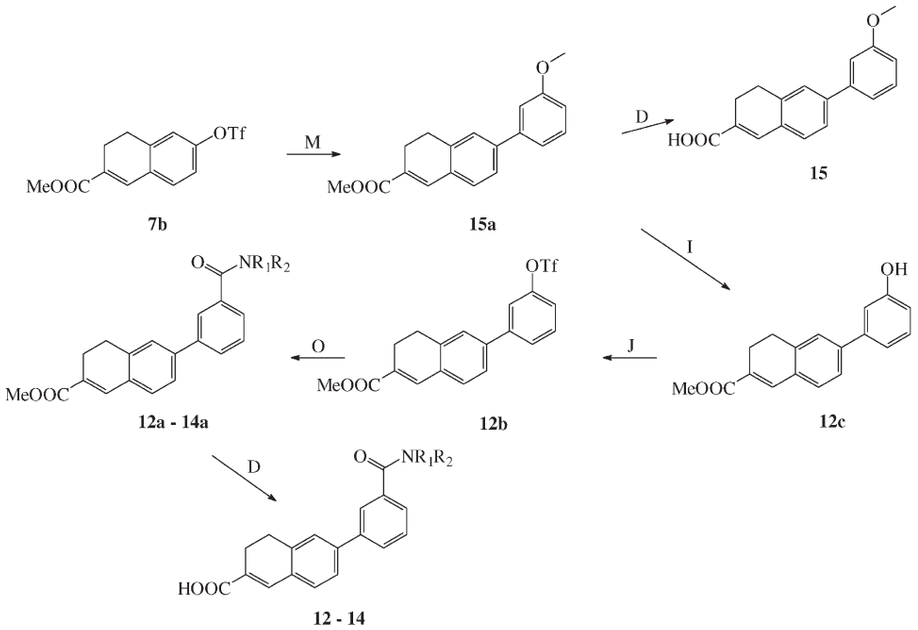
In a similar way as described for compounds **7**–**11** the 6-aryl substituted naphthalene-2-carboxylic acids **16** and **17** were obtained (Scheme 6). The zinc chloride intermediate was generated from the *tert*-butyl-dimethylsilyl protected naphthol derivative **16d**, which was subjected to palladium (0) catalyzed cross coupling with aryl bromides **16e** and **17e**. The obtained biphenyl derivatives **16c** and **17c** were deprotected (**16b**, **17b**) and subsequently converted to the corresponding aryl triflates **16a** and **17a**. Upon treating these compounds with palladium(II)acetate and carbon monoxide in dimethylsulfoxide[44] the carboxylic acids **16** and **17** were obtained.

Biological Results

Inhibition of 5α Reductase In Vitro:

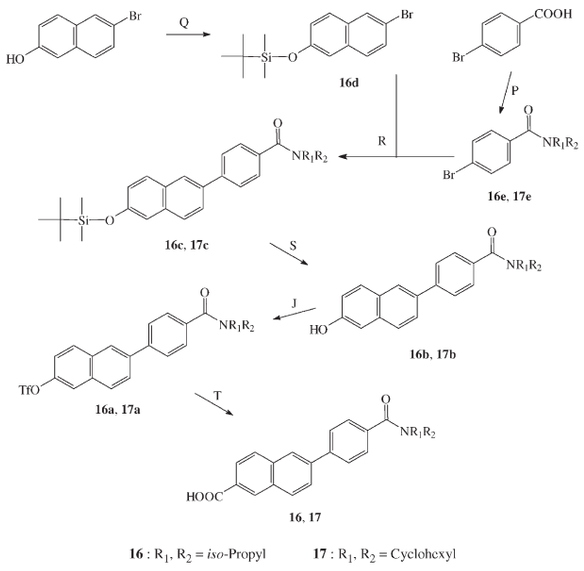
The synthesized compounds were tested for inhibitory potency using prostate homogenates for the human type 2 isozyme and the DU 145 cell line—a prostate cancer metastasis of the brain—for the human type 1 isozyme.[48,49] For both rat isozymes the ventral prostate was used as a source.

As can be seen from the pH-dependency of enzyme activity employing preparations from rat liver and rat ventral prostate (Figure 1), a selective testing for either isozyme is possible by variation of the pH. It has to be taken into account that in these enzyme preparations some part of the DHT produced by the target protein is further transformed into 3α-or 3β, 17β androstanediol. Rat liver protein is known to contain exclusively type 1 isozyme.[50,51] Here maximum activity is observed at pH 6.6, whereas at pH 5.5 only marginal enzyme activity was detected. As rat ventral prostate contains both type 1 (epithelium) and type 2 (stroma) 5α reductase,[52] we considered this source to be suitable for both isozymes, with the possibility of evaluating inhibitors for either isozyme by choosing



12 : R_1, R_2 = *iso*-Propyl
13 : R_1, R_2 = Cyclohexyl
14 : R_1 = H, R_2 = CPh_3

SCHEME 5 Synthesis of compounds **12**–**14**. Reagents and conditions: M: 3-bromoanisole, *tert*-BuLi (2 eq), THF, −78°C, then $ZnCl_2$ (−78°C to 25°C) and **7b**, $Pd(PPh_3)_4$, reflux, 2 h; I: BBr_3, CH_2Cl_2, −78°C, then dry methanol; J: Tf_2O, CH_2Cl_2, pyridine, 0–5°C; O: Pd (II)OAc_2, dppf, R_1R_2NH, CO, DMF, 80°C, 2 h; D: K_2CO_3, methanol/water (9/1), reflux.



16 : R_1, R_2 = *iso*-Propyl **17** : R_1, R_2 = Cyclohexyl

SCHEME 6 Synthesis of compounds **16**–**17**. Reagents and conditions: P: $SOCl_2$, then HNR_1R_2, CH_2Cl_2, NEt_3; Q: TBDMSCl, DMAP, NEt_3, DMF, 25°C, R: *tert*-BuLi (2 eq), THF, −78°C, then $ZnCl_2$ (−78°C to 25°C), then **16e** or **17e**, $Pd(PPh_3)_4$, reflux, 2 h; S: NBu_4F, THF, 25°C, 2 h; J: Tf_2O, CH_2Cl_2, pyridine, 0–5°C; 12 h;T: KOAc, Pd(II)OAc_2, dppf, CO, DMSO, 65°C, 3 h.

the appropriate pH value. Type 2 inhibitory potency was tested at pH 5.5 and type 1 was evaluated at pH 6.6. Following this procedure at least 80% of enzyme activity at pH 5.5 comes from type 2 isozyme, whereas at least 80% of enzyme activity at pH 6.6 comes from type 1 isozyme. Only compounds which proved to be inhibitors at both pH-values were selected for *in vivo* testing.

Finasteride, Epristeride and 4-MA (Table I) served as reference compounds and proved to be highly active for both human and rat isozymes. Only Epristeride was significantly less active for the human type 1 isozyme.

Due to the high enolization tendency of 6-aryl substituted-2-tetralones, which might lead to a favorable interaction with the enzyme's electropositive residue, the tetralones **2c** and **3c** were included in the assay. With these compounds however, only marginal inhibitory activity was observed. Contrarily, the corresponding 3,4-dihydro-naphthalene-2-carboxylic acids **2** and **3** showed high activity. On replacing the diisopropyl-aminocarbonyl side chain in **2** by the bulkier dicyclohexyl-aminocarbonyl group (compound **3**), an increase in activity for

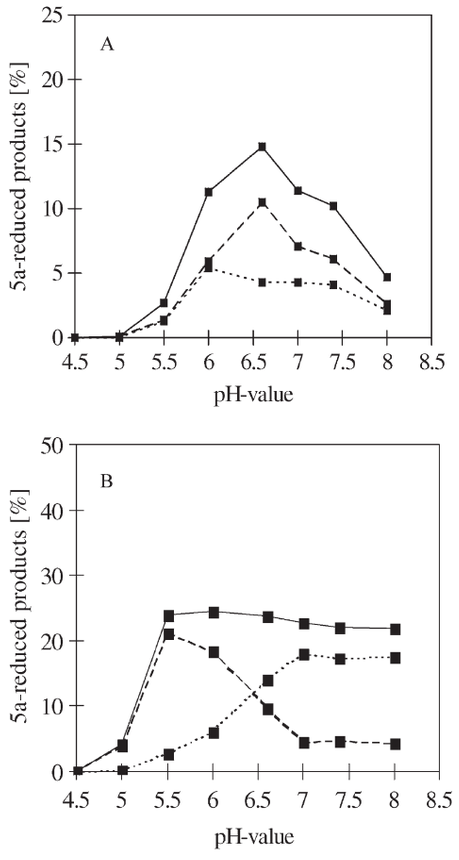


FIGURE 1 pH-Dependency of rat 5α reductase activity for liver (A) and ventral prostate (B). (—) %DHT and 3α/3β 17β-androstanediol, (- - -) %3α/3β 17β-androstanediol, (···) %DHT. Activity of the enzyme is described by %DHT + 3α/3β 17β-androstanediol. [1*B*,2*B*-^{3}H]testosterone 0.21 μM. **A**: Rat liver protein; 5 μg, NADPH 50 μM, incubation time; 6 min. **B**: Rat ventral prostate protein; 160 μg, NADPH 1 mM, incubation time; 30 min.

both human (IC_{50} = 1.23 μM) and rat type 1 isoform (IC_{50} = 0.09 μM) was observed. The striking differences between rat and human enzymes demonstrate that it is important to determine the rat data, if an *in vivo* test using rat models is taken into consideration. Attempts for further optimization, by replacement of the tertiary amide with secondary amide substituents (1-adamantyl-, *tert*-butyl- or phenyl-aminocarbonyl) resulted in potent human type 2 inhibitors (compounds **4**–**6**). However, their activities did not surpass compound **2**, not even by using the *tert*-butyl-aminocarbonyl moiety (compound **5**) which in the steroidal inhibitors Finasteride and Epristeride is essential for high potency. Despite the fact that the phenyl-aminocarbonyl compound **6** is only a moderate inhibitor of human isozyme 2, it is the most potent inhibitor in this class of compounds toward the rat isozyme 2 (IC_{50} = 0.84 μM). With the exception of compound **4**, bearing the highly lipophilic adamantyl-aminocarbonyl substituent, no other compound showed a marked inhibition of human isozyme 1.

In the series of compounds **7**–**11**, the amide substituents were replaced by different "non-amide" groups. Especially in the case of compound **7** carrying a methoxy group which represents a good mimetic of the steroidal ketone or hydroxy groups of the natural substrate, we had expected high inhibitory potency as such a strategy strongly enhanced inhibition of non steroidal aromatase inhibitors.[53–56] However, with the exception of the *iso*-valeroyl derivative **11**, no reasonable inhibitors could be identified.

In compounds **12**–**15** the position of the substituents was changed from para to meta which in case of compound **13** increased activity for both human isoforms in comparison to compound **3**. On the other hand inhibitory activity for the rat isoforms dropped significantly. The meta-diisopropyl-aminocarbonyl compound **12** surprisingly turned out to be nearly inactive for all isozymes. Replacement of the dicyclohexyl-aminocarbonyl group by a trityl-aminocarbonyl substituent (compound **14**) led to a slight increase in human type 1 inhibitory potency, but to a strong decrease with respect to human type 2 inhibition.

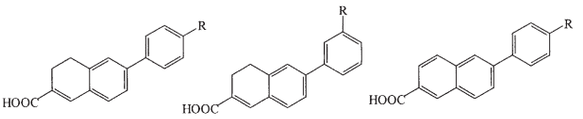
The influence of an aromatic steroidal A-ring mimetic was investigated using compounds **16** and **17**. Here again the phenol precursors **16a** and **17a** were included in the test. However, as already observed for the 2-tetralones **2c** and **3c** no inhibitory activity was found. The carboxylic acid **16** with a para diisopropyl-aminocarbonyl group, was the most active inhibitor for the human type 2 isoform identified in this study (IC_{50} = 0.2 μM), also possessing inhibitory activity for the human type 1 isoform (IC_{50} = 1.71 μM). Surprisingly the replacement of the diisopropyl-aminocarbonyl moiety by a dicyclohexyl-aminocarbonyl group did not only decrease human type 2 inhibition but also human type 1 inhibitory activity (compound **17**).

To get further insight into the mode of action, the Ki-value of compound **16** was determined (Figure 2). As described for Epristeride,[57,58] an uncompetitive inhibition (Ki = 90 nM) versus the substrate testosterone was found.

Inhibition of 5α Reductase In Vivo:

To evaluate, whether the title compounds are able to reduce DHT-formation *in vivo*, two inhibitors were selected for further examination. As shown in Table II, testosterone propionate when administered to juvenile, orchiectomized Sprague–Dawley rats strongly increases prostate weights. An inhibitor of 5α reductase should dose-dependently antagonize this effect.[40] Compound **13**, the most active dual inhibitor for the human isozymes and **16**, the most

TABLE I Inhibition of human and rat steroid 5α reductase isoenzymes by 6-substituted 3,4-dihydronaphthalene-2-carboxylic acids **1**–**15** and 6-substituted naphthalene-2-carboxylic acids **16** and **17**.



1-11 **12-15** **16,17**

Compd	R	Human: %inhibition (10 μM) [IC_{50}, μM] Type 2*§	Type 1†¶	RVP: %inhibition (10 μM) [IC_{50}, μM] (pH 5.5)‡§	(pH 6.6)‡§
1	H	[13.8]	n.d.	n.d.	[47.6]
2c	4-CON(*iso*-Propyl)$_2$	10	n.d.	n.d.	18
2	4-CON(*iso*-Propyl)$_2$	[0.46]	35	73 [1.39]	99 [0.3]
3c	4-CON(Cyclohexyl)$_2$	7	20	n.d.	28
3	4-CON(Cyclohexyl)$_2$	[1.4]	93 [1.23]	84 [2.82]	98 [0.09]
4	4-CONH(1-Adamantyl)	[3.93]	47	56	[0.31]
5	4-CONH(*tert*-Butyl)	[2.46]	14	[1.44]	89 [1.12]
6	4-CONHPh	[4.04]	15	[0.84]	[0.33]
7	4-Ome	11	33	n.d.	26
8	4-*tert*-Butyl	n.i.	n.d.	n.d.	n.i.
9	4-Phenyl	n.i.	n.d.	n.d.	29
10	4-Benzoyl	36	n.d.	n.d.	38
11	4-*iso*-Valeroyl	53	66	n.d.	40
12	3-CON(*iso*-Propyl)$_2$	36	n.d.	n.d.	13
13	3-CON(Cyclohexyl)$_2$	99 [0.75]	94 [0.81]	51 [9.55]	65 [5.8]
14	3-CONHCPh$_3$	94 [1.53]	94 [0.68]	n.d.	17
15	3-Ome	26	n.d.	n.d.	13
16a	4-CON(*iso*-Propyl)$_2$	n.i.	26	n.d.	n.i.
16	4-CON(*iso*-Propyl)$_2$	93 [0.2]	80 [1.71]	78 [1.55]	91 [1.21]
17a	4-CON(Cyclohexyl)$_2$	n.i.	n.d.	n.d.	n.i.
17	4-CON(Cyclohexyl)$_2$	43 [11.7]	41	41	95 [0.88]
Finasteride		[0.005]	[0.045]	[0.011]	[0.01]
Epristeride		[0.003]	[1.10]	[0.04]	[0.045]
4-MA		[0.005]	[0.007]	[0.005]	[0.018]

*Human prostate homogenates; 125 μg protein, pH 5.5. †DU 145 cell line. ‡Rat ventral prostate; 200–250 μg protein. §Substrate [1β,2β-^{3}H]testosterone 210 nM. ¶Substrate [^{3}H]androstenedione 5 nM. n.i.: no inhibition. n.d.: not determined.

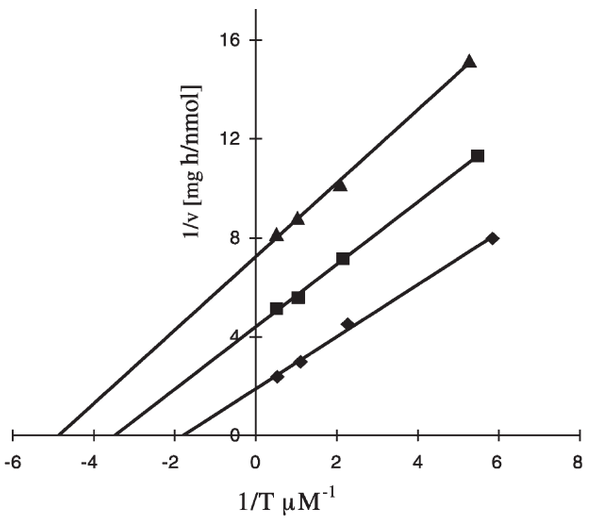


FIGURE 2 Inhibitory analysis of 6-[4-(*N*,*N*-diisopropylaminocarbonyl)phenyl]naphthalene-2-carboxylic acid (**16**) versus human type 2 5α reductase. [For details concerning the determination of the Ki-value and the type of inhibition see Experimental Section (Ki, uncompetitive (**16**): 90 ± 15 nM). The indicated data points represent the mean of at least 3 experiments. Inhibitor concentrations: –▲– 250 nM, –■– 125 nM, –◆– control; testosterone concentrations: 0.21 μM, 0.51 μM, 1.01 μM, 2.01 μM].

potent compound for the human type 2 isozyme were tested at a dose of 25 mg/kg. However, no significant reduction in prostate weight was observed. Contrarily, Epristeride and Finasteride effectively reduced prostate weights at a dose of 1 mg/kg. This disappointing result can only in part be explained by the rather low *in vitro* activity of the compounds for the rat enzyme which is in contrast to that for the steroidal inhibitors.

TABLE II Effect of 13, 16, Epristeride and Finasteride on the prostate weights of juvenile, orchiectomized SD-rats

treatment group	Effect (means ± SD)*	% inhibition
Control	17.6 ± 3.7	
Testosterone propionate†	61.4 ± 9.6	
Epristeride‡	35.5 ± 8.0¶	59
Finasteride‡	31.0 ± 9.0¶	86
13§	53.8 ± 5.5£	17
16§	54.7 ± 15.5£	15

*Prostate wet weight (mg)/ body weight (g) × 100. †1 mg/kg. ‡1 mg/kg equimolar to Finasteride + testosterone propionate 1 mg/kg. §25 mg/kg equimolar to Finasteride + testosterone propionate 1 mg/kg. ¶Significantly different from testosterone propionate stimulated control (U-test according to Wilcoxon, Mann and Whitney), $p < 0.01$. £Not significant.

DISCUSSION AND CONCLUSION

The present study shows that in the class of the title compounds potent inhibitors of human and rat 5α reductase isozymes 1 and 2 could be obtained. Apparently the 3,4-dihydronaphthalene- and naphthalene-2-carboxylic acid moiety mimicking the steroidal A-B ring is appropriate for generating potent transition state analogs of the steroidal substrates testosterone and androstenedione. The most potent inhibitors of the human enzyme—showing IC_{50} values in the nM range—were compounds **2**, **13** and **16** for the type 2 enzyme and compounds **13** and **14** for the type 1 enzyme. Compound **13** turned out to be a potent dual inhibitor of both isozymes. The title compounds clearly exceeded similarly substituted 1H-quinolin-2-ones[29] in their inhibitory activities. This was to be expected since we have found that in the class of biphenyl type inhibitors a benzoic acid moiety is superior to a 2-pyridone structure as a steroidal A ring mimetic.[30] As a matter of fact the most active inhibitor of the human type 2 isozyme in this study (the *N*,*N*-diisopropylaminocarbonyl compound **2**) is equipotent to the most active biphenyl-4-carboxylic acid (4′-dicyclohexyl-methylcarbonyl compound[30]). The compounds of the present study have the advantage that they additionally inhibit the human type 1 isozyme. Remarkable is the strong influence of the type and the position of the substituents at the 6-phenyl group as well as the absence or presence of a double bond in 1 position on the activity of the compounds. The strong differences in their inhibitory activities towards type 1 and type 2 isozyme in the case of single compounds demonstrate that they are appropriate to elaborate the structural requirements for a selective inhibition of type 1 or type 2 enzyme or a dual inhibition of both isozymes. Furthermore it is notable that the most potent inhibitors of the rat isozymes were different from the most active inhibitors of the human isozymes: inhibition in the nM range was shown by compound **6** for rat type 2 isozyme, and by compounds **2**–**4**, **6** and **17** for rat type 1 isozyme. The most potent compound of this study was compound **3** showing IC_{50} values of 90 nM for rat type 1 isozyme. The finding that compound **16** exhibited an uncompetitive type of inhibition was not surprising, since the α,β-unsaturated steroidal carboxylic acid Epristeride had shown the same inhibition type.[57,58]

However, the finding that compounds **13** and **16** only showed a weak, not significant *in vivo* activity is somewhat disappointing. It might be due in part to the rather weak inhibition of the rat isozymes by these compounds, especially by **13**, giving rise to the expectation of a stronger effect of this compound in the human. A further explanation might be the low bioavailability of this type of inhibitor. In a similar class of compounds we have recently observed that carboxylic acids are less appropriate for permeating an intact cell membrane than the corresponding esters. Consequently we are presently trying to obtain derivatives of the title compounds with improved permeation properties.

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