Synthesis and Evaluation of 2′-Substituted 4-(4′-Carboxy- or 4′-carboxymethylbenzylidene)-*N*-acylpiperidines: Highly Potent and in Vivo Active Steroid 5α-Reductase Type 2 Inhibitors

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Sixteen compounds derived from *N*-acyl-4-benzylidenepiperidine-4′-carboxylic acids were synthesized and evaluated for inhibition of rat and human steroid 5α-reductase isozymes types 1 and 2. In the dicyclohexylacetyl series, fluorination in the 2-position of the benzene nucleus (**15**), exchange of the carboxy group by a carboxymethyl moiety (**20**), and combination of both structural modifications (**25**) led to highly active inhibitors of the human type 2 isozyme (IC_{50} values: **15**, 11 nM; **20**, 6 nM; **25**, 7 nM; finasteride, 5 nM). In vivo all compounds tested markedly reduced the prostate weights in castrated testosterone-treated rats. Oral activity was shown for compound **7**. From the finding that compound **15** is active in the rat, although it is a rather poor inhibitor of the rat enzyme and is a strong inhibitor of the human enzyme, it is concluded that it should be highly potent in men.

Introduction

Benign prostatic hyperplasia (BPH) is the most common benign tumor affecting over 50% of men above the age of 70.[1] The use of surgery (TURP) is effective in the treatment of BPH,[2] but its high cost and side effects (morbidity, mortality) led to a number of less invasive pharmacological approaches to be developed and assessed in the clinical setting. On the basis of the physiopathology of the disease, one of these strategies consisted of the inhibition of the steroid 5α-reductase (5αR), which is responsible for the reduction of testosterone (T) to dihydrotestosterone (DHT), the most potent androgen in men. DHT is believed to play a key role in BPH, since its concentration remains at a constant level in the prostate in elderly people despite a reduction of the plasma testosterone level.[3] The first and so far only inhibitor of 5αR on the market for treating BPH is finasteride. Its effective but limited use[4] is partly due to the specificity of finasteride to inhibit mainly one of two isozymes (type 2). Other disadvantages of this drug are the adverse effects associated with its use.[5] They are believed to be caused by its steroidal structure.[6] Searching for compounds with fewer side effects for the treatment of androgen-dependent disorders, we have synthesized several classes of nonsteroidal inhibitors of 5αR in the past years.[7−10] We discovered an attractive new series of compounds: N-substituted 4-benzylidenepiperidine-4′-carboxylic acids.[8] Some of these compounds (**3**, **6**, **7**, **9**; Figure 1) showed strong inhibitory activities toward the rat and human isozyme type 2 in vitro (for instance, for **7**, IC_{50} is 80 and 60 nM, respectively). Most importantly, they were also active in vivo, inhibiting the prostate weights of castrated testosterone-treated rats. Aiming at a further optimization in this class of compound, structural modifications of the parent compounds have been performed (Figure 1). In the following, we describe the synthesis of compounds **10**−**25** and their biological evaluation. The inhibition of the rat and human 5αR isozymes types 1 and 2 in vitro is reported as well as the determination of the in vivo activity of the most potent compounds in the rat.

Chemistry

Compounds **10**−**20** were prepared as described for the synthesis of the parent compounds[8] (Scheme 1). Briefly, the *N*-acylpiperidones (**3b**, **6b**, **7b**, **9b**, **28b**) were prepared from the corresponding acids as described.[8] After reaction with thionyl chloride, the acid chlorides were reacted with piperidone hydrochloride in a solution of triethylamine. The phosphonium bromides (**29b**−**33b**) necessary for Wittig olefination with **3b**, **6b**, **7b**, **9b**, and **28b** were obtained by bromination of their corresponding phenylalcanoic acids **29d**−**33d**[8,11−14] with NBS using benzoylperoxide or AIBN and subsequent reaction of **29c**−**33c** with triphenylphosphine.[8] The olefins obtained contained an ester moiety and were subsequently subjected to a saponification to give the target structures **10**−**20**. Compounds **21**−**24** were synthesized by alkylation of 4-hydroxybenzoic acid methyl ester (**24b**) with *N*-(*tert*-butoxycarbonyl)-4-piperidinol[15] (**24c**) under Mitsunobu conditions[16] (Scheme 2). Saponification of the resultant methyl ester led to the corresponding carboxylic acid (**24**). After removal of the Boc group, an acylation with several acid chlorides followed by saponification yielded the corresponding carboxylic acids (**21**−**23**). The first step in the synthesis of compound **25** (Scheme 3) was the preparation of the corresponding 2-fluoro-4-bromobenzyltriphenylphosphonium bromide salt **25c**, which was reacted with *N*-(dicyclohexyl)acetyl-4-piperidone (**7b**)[8] in a crown ether catalyzed variant of the Wittig reaction[17] to give the

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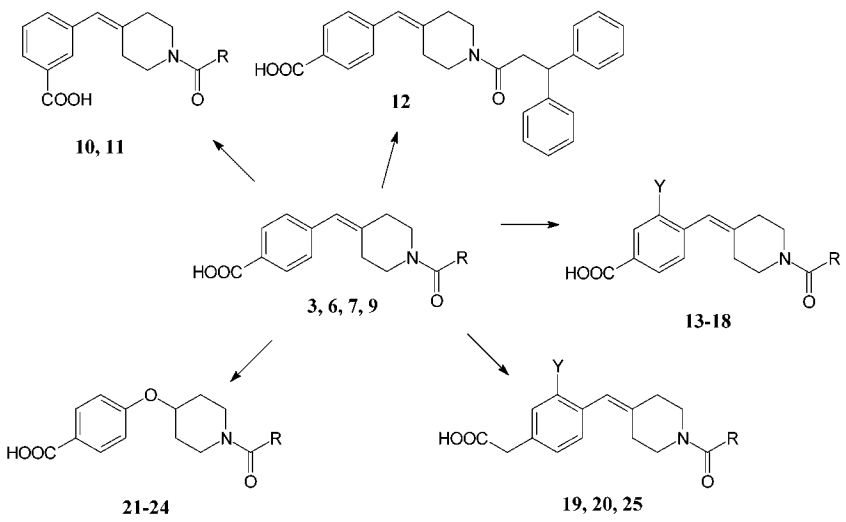


no	R, Y	no	R, Y	no	R, Y
3	1-Ada., –	**14**	$CH(Ph)_2$, OCH_3	**21**	$CH(Ph)_2$, –
6	$CH(Ph)_2$, –	**15**	$CH(Cyclohexyl)_2$, F	**22**	1-Ada, –
7	$CH(Cyclohexyl)_2$, –	**16**	$CH(Cyclohexyl)_2$, OCH_3	**23**	$N(Ph)_2$, –
9	$N(Ph)_2$, –	**17**	1-Ada., F	**24**	$OC(CH_3)_3$, –
10	$CH(Ph)_2$, –	**18**	1-Ada., OCH_3	**25**	$CH(Cyclohexyl)_2$, F
11	$CH(Cyclohexyl)_2$, –	**19**	$CH(Ph)_2$, –		
13	$CH(Ph)_2$, F	**20**	$CH(Cyclohexyl)_2$, –		

Figure 1. Parent compounds (**3**, **6**, **7**, **9**) and structural optimizations (**10**−**25**).

corresponding olefin **25b**. The latter was subjected to cross-coupling with trimethylsilylacetylene in the presence of $PdCl_2 \cdot 2PPh_3$ and cuprous iodide.[18] The hydroboration of the 1-alkynyl(trimethyl)silane **25a** obtained, followed by oxidation with aqueous NaOH and 35% hydrogen peroxide,[19] produced the corresponding carboxylic acid **25**.

Biological Results

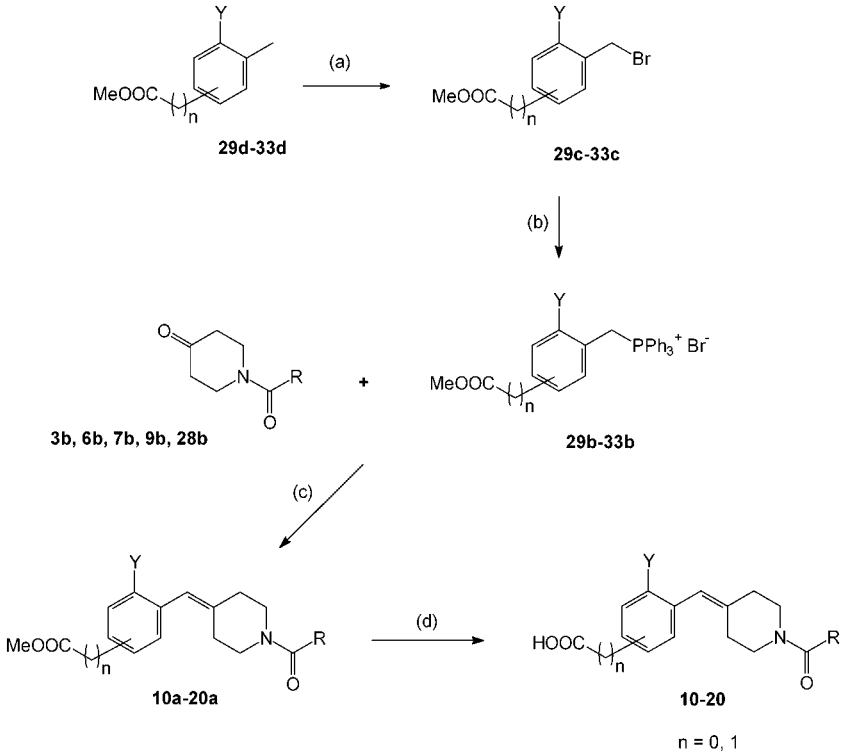
Inhibition of Rat and Human 5αR Isozymes Types 1 and 2 in Vitro. The inhibitory activities of compounds **3**, **6**, **7**, **9**, **10**−**25**, and finasteride as a reference were determined using rat prostate homogenates (pH 6.6, type 1; pH 5.5, type 2) and human prostate homogenate (BPH tissue for type 2) according to the method of Liang et al.[20] and the DU145 cell line (for human type 1 enzyme) as described in the literature.[21−23] The percent inhibition values at a concentration of 10 μM or, in case of more potent compounds, the IC_{50} values are presented in Tables 1−3.

Table 1 shows the effects of introducing F and OCH_3 substituents meta to the carboxylic acid group into the benzene ring of the parent compounds **3**, **6**, and **7**. This structural modification was performed because in the class of phenoxybenzoic acids halide and OCH_3 substituents are reported to enhance 5αR inhibition.[24] In the case of **6**, enlargement of the R substituent was performed by insertion of a CH_2 group between the carbonyl group and the diphenylmethyl moiety, leading to compound **12**. As can be seen, all modifications increased the inhibitory activities toward rat isozyme type 1. The only exception was the OCH_3 substituent, which decreased inhibition of this enzyme introduced into compound **3** (compound **18**). Regarding rat isozyme 2, however, the modifications led to a reduction of enzyme inhibition. In the case of the human type 1 isozyme, the weak inhibitory activities of the parent compounds were further diminished, mostly leading to inactive compounds.

In contrast, strong inhibition could be observed for the human type 2 enzyme. While OCH_3 substitution as well as insertion of a CH_2 spacer (**12**) led to a slight decrease of inhibition compared to the highly active parent compounds, the introduction of a fluorine substituent increased activity even further. In the case of the dicyclohexylmethyl compound **7**, this effect was strongest, leading to an enhancement by a factor of 5.5 (IC_{50} values: **7**, 60 nM; **15**, 11 nM).

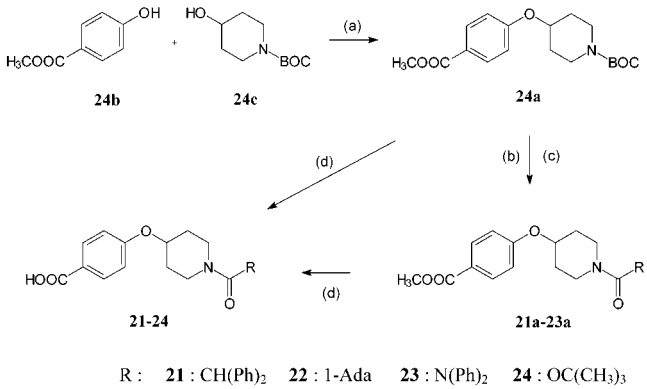
In Table 2, the effects of a transfer of the carboxylic acid group from the para to the meta position (**10**, **11**) and exchange of the −CH═ spacer between the two rings by an ether oxygen (**21**−**24**) are described as well as the insertion of a CH_2 spacer between the benzene ring and the carboxylic acid group (**19**, **20**). The latter

Scheme 1. Synthesis of Compounds **10**−**20**[a]



[a] Conditions: (a) 63%, NBS, DPBO or AIBN, CCl_4, refluxed 2 h; (b) 56−75%, PPh_3, toluene, refluxed 5 h; (c) 10−72%, *n*-BuLi (1.6 M), THF, −78 °C, then *N*-acylpiperidones (**3b, 6b, 7b, 9b, 28b**) in THF, room temp overnight; (d) 46−72%, K_2CO_3, MeOH/H_2O 9:1, refluxed 3 h, room temp overnight.

Scheme 2. Synthesis of Compounds **21**−**24**[a]



R : **21** : $CH(Ph)_2$ **22** : 1-Ada **23** : $N(Ph)_2$ **24** : $OC(CH_3)_3$

[a] Conditions: (a) 53%, DEAD, PPh_3, THF, 0 °C to room temp; (b) 74%, 4 N HCl; (c) 45−64%, RCOCl, NEt_3, CH_2Cl_2; (d) 30−64%, MeOH/H_2O, K_2CO_3 refluxed 3 h, room temp overnight.

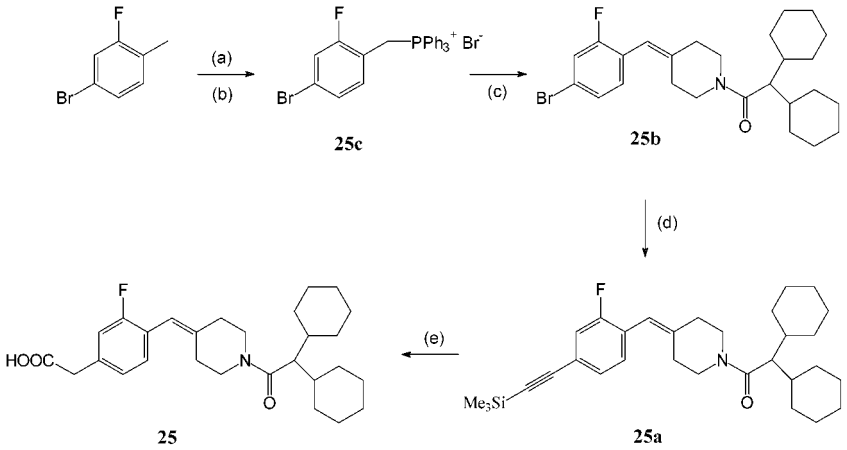
structural modification has been performed with steroidal inhibitors. Holt et al. have shown that 3-carboxymethyl steroids are as potent as 3-carboxy steroids.[25] All structural modifications reduced inhibition of the parent compounds toward both rat isozymes. The only exceptions to that rule were the phenylacetic acid derivatives **19** and **20**, which exhibited similar inhibitory activities. As observed with the aforementioned structural variations, compounds **9**, **10**, and **19**−**24** also were not active in the DU145 cells expressing human isozyme type 1. For the human type 2 enzyme, very interesting results were obtained. The compounds with an ether linkage (**21**−**24**) and the meta-substituted benzoic acids (**10**, **11**) showed a decrease in inhibition compared to their corresponding parent compounds. The phenylacetic acids **19** and **20**, however, exhibited a strong increase of enzyme inhibition by factors of 7 and 10, respectively (IC_{50} values: **6**, 530 nM; **19**, 75 nM; **7**, 60 nM; **20**, 6 nM). Most importantly, compound **20** reaches the activity of the highly active steroidal reference finasteride (IC_{50} values: 6 and 5 nM, respectively).

After we had found that both a fluorine group and a CH_2 spacer between the benzene ring and the carboxylic acid group enhanced inhibitory activity toward the human type 2 isozyme, we consequently combined the two structural modifications and synthesized compound **25**. As can be seen from Table 3, **25** is a highly potent inhibitor of the human type 2 isozyme. It is more active than its parent compound **15**; however, it does not exceed compound **20** (IC_{50} values: 7, 11, and 6 nM, respectively). Interestingly, compound **25** is much more potent toward both rat isozymes. This is especially true for the type 2 isozyme (IC_{50} values: **25**, 38 nM; **20**, ∼10 μM; **15**, 3 μM).

In Vivo Activity in the Rat. The in vivo activities of the most potent compounds were determined using juvenile castrated rats that were administered testosterone propionate. The androgen causes a stimulation of the prostatic weights (Table 4), which is due to the formation of DHT by 5αR. Accordingly, inhibitors of 5αR are capable of reducing this effect. Naturally, compounds showing not only a strong inhibition of the human prostatic isozyme but also a marked inhibition of the rat enzyme are reasonable for evaluation. Table 4 shows the data obtained with compounds **7**, **15**, and **25** as well as finasteride as a reference.

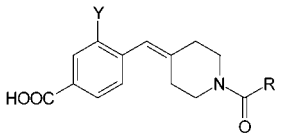
All compounds tested reduced the testosterone-induced stimulation of the prostatic weights. Importantly, compound **7** is also active when applied by the oral route. However, the activity is somewhat dimin-

Scheme 3. Synthesis of Compound **25**[a]



[a] Conditions: (a) NBS, CCl_4, AIBN, refluxed 2 h; (b) 75%, PPh_3, toluol, refluxed 5 h; (c) 65%, CH_2Cl_2, K_2CO_3, 18-crown-6, *N*-(dicyclohexyl)acetyl-4-piperidone (**7b**),[8] refluxed 3 days; (d) 90%, piperidine/THF 1:2, CuI, PPh_3, $PdCl_2 \cdot 2PPh_3$, trimethylsilylacetylene, refluxed 2 h; (e) 42%, BH_3, 1 M in THF, 3 h at room temp, MeOH, 3 N NaOH, 35% H_2O_2 at room temp, then 1 N HCl.

Table 1. Inhibition of Rat and Human 5αR Types 1 and 2 in Vitro by Compounds **3**, **6**, **7**, **12**−**18**, and Finasteride



3, **6**, **7**, **12-18**

			RVP:[a] % inhibition (10 μM) [IC_{50} (μM)]		human: % inhibition (10 μM) [IC_{50} (μM)]	
R	compd	Y	type 1[c]	type 2[c]	DU 145[b,c,e]	BPH[d,c]
$CH(Ph)_2$	**6**[f]	H	[3.4]	[0.37]	26	[0.53]
	13	F	[1.1]	[1.1]	2	[0.41]
	14	OCH_3	[1.9]	[0.94]	8	[3.5]
$CH_2CH(Ph)_2$	**12**	H	[1.6]	[0.88]	8	[1.1]
$CH(cyclohexyl)_2$	**7**[f]	H	51	[0.08]	46	[0.06]
	15	F	[1.8]	[3.0]	12	[0.011]
	16	OCH_3	55	43	5	[0.13]
1-adamantyl	**3**[f]	H	[5.6]	[2.5]	44	[0.26]
	17	F	[2.7]	[3.5]	20	[0.21]
	18	OCH_3	52	51	10	[1.2]
finasteride			[0.01]	[0.011]	[0.041]	[5 nM]

[a] Enzyme of rat ventral prostate, 250 μg of protein, substrate [1β, 2β-^{3}H]testosterone, 0.21 μM. [b] Substrate: [^{3}H]androstenedione, 5 nM. [c] Mean value; tests have been run in duplicate. The standard deviation for IC_{50} is 20%; for percent inhibition, it is ±10%. [d] Enzyme from BPH tissue (type 2), 125 μg of protein, substrate [1β,2β-^{3}H]testosterone, 0.21 μM. [e] Prostatic tumor cell line expressing type 1 enzyme. [f] See ref 8.

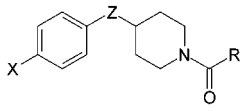
ished compared to the activity from subcutaneous application. Compound **15** is as active as **7**, whereas **25** is more potent than **15** and **7**. None of the compounds reached the potency of finasteride, which was applied in one-tenth the dose of the nonsteroidal inhibitors.

Discussion and Conclusion

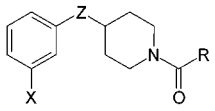
The present paper shows that the structural modifications performed were appropriate to further increase the inhibitory potency of the parent N-substituted 4-benzylidenepiperidine-4′-carboxylic acids. The most active compounds obtained (**15**, **20**, **25**) belong to the most potent inhibitors of isozyme type 2 described so far.

The structural modifications performed in this paper were based on recent results of our and other groups. We have shown that in the class of benzylidenepiperidines the nitrogen has to be part of an amide group and the double bond must not be derivatized.[8] In the class of 5αR-inhibiting biphenyl carboxylic acids, we have found that exchange of the benzoic acid moiety by a 1-methyl-2-pyridone group (as it is in the azasteroids) reduces enzyme inhibition[9] and thus have demonstrated that the benzoic acid moiety is a very appropriate mimic of the steroidal A ring. Holt et al. have shown that the exchange of the carboxylic acid in steroidal inhibitors by bioisosteric phosphonic and sulfonic acids did not enhance inhibition.[25] It becomes apparent from this paper that the transfer of the carboxylic acid group from the para to the meta position is not an appropriate strategy to improve inhibitory activity (**6**, **7** → **10**, **11**). For an optimal interaction with the carboxylate binding site, compounds **10** and **11** obviously are in a less favorable position in the active site of the enzyme. The exchange of the −CH═ linker by a bioisosteric oxygen also leads to a decrease of enzyme inhibition (**3**, **6**, **9** → **22**, **21**, **23**). Taking into consideration that the benzylidene compounds are conformationally less flexible,

Table 2. Inhibition of Rat and Human 5αR Types 1 and 2 in Vitro by Compounds **3**, **6**, **7**, **9**−**11**, **19**−**24**



3, **6**, **7**, **9**, **19-24**

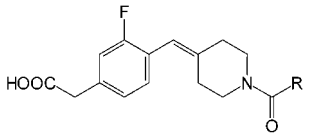


10, **11**

R	compd	X	Z	RVP:[a] % inhibition (10 μM) [IC_{50} (μM)] type 1[c]	RVP:[a] % inhibition (10 μM) [IC_{50} (μM)] type 2[c]	human: % inhibition (10 μM) [IC_{50} (μM)] DU 145[b,c,e]	human: % inhibition (10 μM) [IC_{50} (μM)] BPH[d,c]
$CH(Ph)_2$	**6**[f]	COOH	CH=	[3.4]	[0.37]	26	[0.53]
	10	COOH	CH=	49	43	6	57
	21	COOH	O	62	58	ni	[1.3]
	19	CH_2COOH	CH=	[4.5]	63	ni	[0.075]
$CH(cyclohexyl)_2$	**7**[f]	COOH	CH=	51	[0.08]	46	[0.06]
	11	COOH	CH=	35	25	ni	[0.70]
	20	CH_2COOH	CH=	66	56	6	[0.006]
1-adamantyl	**3**[f]	COOH	CH=	[5.6]	[2.5]	44	[0.26]
	22	COOH	O	18	21	7	[0.43]
$N(Ph)_2$	**9**[f]	COOH	CH=	[0.54]	[0.69]	22	[0.83]
	23	COOH	O	53	50	10	68
$OC(CH_3)_3$	**24**	COOH	O	4	12	2	[7.8]

[a] Enzyme of rat ventral prostate, 250 μg of protein, substrate [1β, 2β-^{3}H]testosterone, 0.21 μM. [b] Substrate: [^{3}H]androstenedione, 5 nM. [c] Mean value; tests have been run in duplicate. The standard deviation for IC_{50} is 20%; for percent inhibition, it is ±10%. [d] Enzyme from BPH tissue (type 2), 125 μg of protein, substrate [1β,2β-^{3}H]testosterone, 0.21 μM. [e] Prostatic tumor cell line expressing type 1 enzyme. [f] See ref 8.

Table 3. Inhibition of Rat and Human 5αR Types 1 and 2 in Vitro by Compound **25**



25

R	compd	RVP: % inhibition (10 μM) [IC_{50} (μM)] type 1[c]	RVP: % inhibition (10 μM) [IC_{50} (μM)] type 2[c]	human: % inhibition (10 μM) [IC_{50} (μM)] DU 145[b,c,e]	human: % inhibition (10 μM) [IC_{50} (μM)] BPH[d,c]
$CH(cyclohexyl)_2$	**25**	[3.2]	[0.038]	4	[0.007]

[a] Enzyme of rat ventral prostate, 250 μg of protein, substrate [1β, 2β-^{3}H]testosterone, 0.21 μM. [b] Substrate: [^{3}H]androstenedione, 5 nM. [c] Mean value; tests have been run in duplicate. The standard deviation for IC_{50} is 20%; for percent inhibition, it is ±10%. [d] Enzyme from BPH tissue (type 2), 125 μg of protein, substrate [1β,2β-^{3}H]testosterone, 0.21 μM. [e] Prostatic tumor cell line expressing type 1 enzyme.

Table 4. In Vivo Activity of Compounds **7**, **15**, **25**, and Finasteride on Ventral Prostate Weights in Juvenile Castrated Rats Treated with Testosterone Propionate

test group	in vivo: effect mean ± SEM[a]	in vivo: doses (mg/kg)	in vivo: % inhibition
vehicle (not castrated)	57.4 ± 7.9**		
vehicle (castrated)	13.7 ± 1.9**		
testosterone propionate (tp)	41.6 ± 1.9	1	
tp + **7**,[b] po	31.6 ± 1.7*	11.3	36
tp + **7**,[b] sc	27.9 ± 1.2**	11.3	49
tp + **15**,[b] sc	28.6 ± 1.0**	11.8	47
tp + **25**,[b] sc	26.4 ± 2.4**	12.2	55
tp + finasteride, sc	20.5 ± 1.5**	1	76

[a] In mg of prostate/100 g of body weight (mean values ± SEM). Significance according to Dunnett's test: (*) $P < 0.05$; (**) $P < 0.01$ [b] All compounds were applied in doses 10 times the equimolar value of 1 mg/kg finasteride. sc: subcutaneously. po: orally.

it is obvious that they have by nature a suitable three-dimensional structure for interacting with the active site. An overlay of compound **15** and compounds **A** and **B**, two highly active type 2 inhibitors described by others,[24,26] is shown in Figure 2. It becomes apparent that there is a very good fit. Interestingly, a pharmacophore model of type 2 inhibitors has recently been described by Chen et al.[27] using compounds **A** and **B** for the generation and validation, respectively. It consists of two hydrogen bond acceptors (HBA1/2) and three hydrophobic groups (HP1−3). The calculated distance constraints between any two features of compound **15** nicely fit into the described pharmacophore model (see Supporting Information). This finding confirms the validity of the model and explains the high activities of our compounds.

The finding that the insertion of a methylene spacer between the carbonyl group and the diphenylmethyl moiety decreases activity (**6** → **12**) leads to the conclusion that the hydrophobic pocket, which also accommodates the substituents in the 17-position of the steroidal inhibitors, is limited in size.

The introduction of substituents at the benzene ring led to interesting results. A decrease of activity was observed for OCH_3 groups (**3**, **6**, **7** → **18**, **14**, **16**), whereas an increase was discovered for fluorine substituents (**3**, **6**, **7** → **17**, **13**, **15**). This confirms the pharmacophore model describing that at this part of the molecule high lipophilicity is required for optimal interaction. The increase in activity observed for the exchange of the

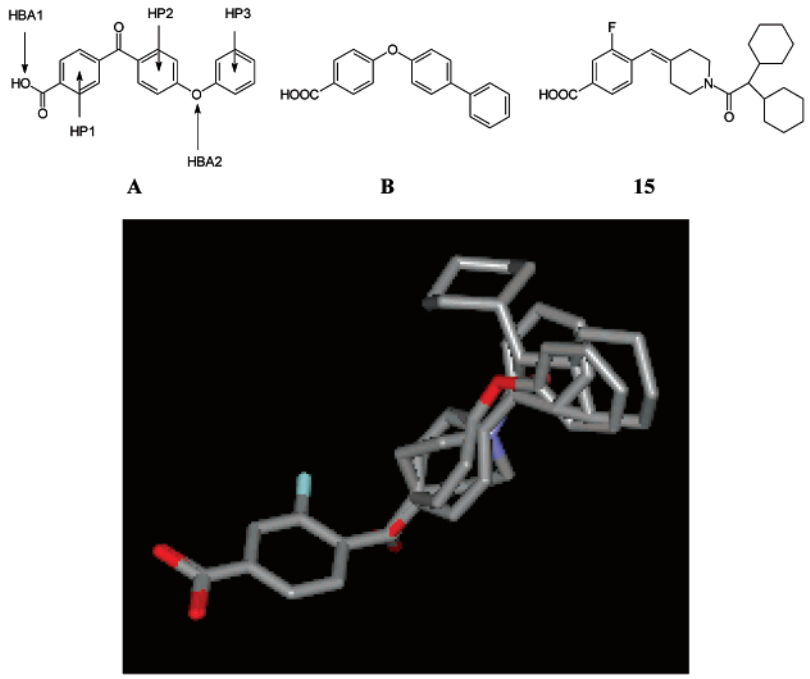


Figure 2. Superimposition of the lowest energy conformers of compounds **A**, **B**, and **15** (Hyperchem 5.0).

carboxy group by a carboxymethyl moiety (**6**, **7** → **19**, **20**) is an indication that the protein shows some conformational flexibility in this part of the active site. It is not caused by the higher acidity of the phenylacetic acid moiety, since in the case of steroidal inhibitors the strongly acidic phosphonic and sulfonic acids did not show higher activity compared to the corresponding less acidic carboxylic acids.[25]

Surprisingly the combination of F and carboxymethyl substituents (**25**, 7 nM) did not increase inhibitory activity above the non-fluorinated carboxymethyl compound **20** (6 nM). Obviously we are very near the maximum inhibition possible. This is supported by the facts that the activity of finasteride is in the same range (5 nM) and that compound **B** (IC_{50} value described to be 1.1 nM)[24] shows in our hands a similar activity (6 nM).

The results of the in vivo experiments are very encouraging. As demonstrated with **7**, the benzylidenepiperidines are orally active, a prerequisite for drug candidates. From a comparison of the potency of the title compounds with the reference finasteride, it seems at first glance that the steroidal inhibitor is superior to the nonsteroidal compounds. This is obviously true in the rat. For the prediction of the activity in men, one has to keep in mind that finasteride is much more potent toward the rat type 2 isozyme than, for example, compound **15** (factor of 300). Showing similar activity toward the human type 2 enzyme in vitro, compound **15** can be expected to be equally active as finasteride in male patients.

In conclusion, in the present investigation benzylidenepiperidines were structurally optimized to become highly potent in vitro inhibitors of the human 5αR isozyme type 2. In the rat, all compounds tested were active. In the case of one compound, oral activity was shown. Further preclinical and clinical studies will elucidate whether they are appropriate for overcoming the disadvantages of finasteride.

Experimental Section

^{1}H NMR spectra were recorded on a Bruker AM-400 (400 MHz) in DMSO-d_6 or $CDCl_3$. Chemical shifts are reported as δ values (ppm) relative to internal tetramethylsilane (δ 0 ppm). Elemental analyses were performed in the Department of Inorganic Chemistry, Saarland University. IR spectra were performed with KBr disks or films, as indicated, on a Perkin-Elmer 398 infrared spectrometer. Melting points were determined on a Kofler melting point apparatus thermopan (Reichert) and are uncorrected. Column chromatography was performed with Merck silica gel 60 (40−63 μm) or (50−200 μm). All reactions were followed by thin-layer chromatography using Alugram silica gel 60. Chemicals and solvents used were commercially available (Lancaster, Fluka, Acros, Fluorochem) and were used without further purification.

***N*-(3,3-Diphenyl)propanoyl-4-piperidone (28b).** A mixture of diphenylpropanoic acid (22.6 g, 0.10 mol), one drop of *N*,*N*-dimethylformamide (DMF), and thionyl chloride ($SOCl_2$) (50 mL) was refluxed for 2 h. After the mixture was cooled to ambient temperature, $SOCl_2$ was removed by distillation. The crude acid chloride was dissolved in 50 mL of dry CH_2Cl_2 and was added dropwise to a suspension of 4-piperidone monohydrate hydrochloride (18.0 g, 0.10 mol) and dry triethylamine (40 mL, 0.30 mol) in dry CH_2Cl_2 (170 mL). The solution was stirred for 3 h. The organic phase was washed with water (2 × 20 mL) and dried over $MgSO_4$. After filtration, the solvent was evaporated in vacuo to give **28b** as a crude product that was purified by recrystallization from hexane/ethyl acetate. Yield 51%, white crystals, mp 164−165 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.02 and 2.31 (2t, 4H, J = 6 Hz, pip. H), 3.14 (d, 2H, J = 7 Hz, $-CH_2CH-$), 3.60 and 3.80 (2t, 4H, J = 6 Hz, pip. H), 4.70 (t, 1H, J = 7 Hz, $-CH_2CH-$), 7.17−7.30 (m, 10H, diphenyl-H). IR (KBr): ν = 3400, 3040−2860 (several bands), 1710, 1650, 1500, 1450, 1310, 1270, 1240, 1200, 1080, 980, 760, 700 cm^{-1}. $C_{20}H_{21}NO_2$ (307.39).

Compounds **3b**, **6b**, **7b**, **9b** were prepared as previously described.[8]

Compounds **29c**,[11] **30c**,[12] **31c**,[13] **32c**,[14] **33c**[8] were prepared as described.

Synthesis of Compounds 29b−33b and 25c. [4-(Methoxycarbonylmethyl)benzyl]triphenylphosphonium Bromide (29b). A mixture of **29c**[11] (10.0 g, 41.0 mmol) and triphenylphosphine (10.8 g, 41.0 mmol) in dry toluene (350 mL) was refluxed for 5 h at 120 °C. The clear solution quickly

became turbid because of precipitation of salt. The solution was filtered to yield compound **29b**. No further purification was necessary. Yield 56%, white powder. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.54 (s, 2H, $-CH_2COOCH_3$), 3.67 (s, 3H, $-CH_2COOCH_3$), 5.40 (d, 2H, J(H, P) = 14 Hz, $-CH_2-PPh_3^+Br^-$), 7.02 and 7.07 (d, AA′BB′, 4H, J = 8 Hz, aromatic H), 7.60−7.78 (m, 15H, $-PPh_3^+Br^-$). $C_{28}H_{26}O_2BrP$ (505.39).

2-Methoxy-4-methoxycarbonylbenzyltriphenylphosphonium Bromide (30b). 30b was synthesized from 4-bromomethyl-3-methoxybenzoic acid methyl ester (**30c**).[12] It was used without further purification. Yield 62%, white powder, mp 219−220 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.27 (s, 3H, $-OCH_3$), 3.88 (s, 3H, $-COOCH_3$), 5.49 (d, 2H, J(H, P) = 15 Hz, $-CH_2-PPh_3^+Br^-$), 7.25 (d, 1H, J = 8 Hz, aromatic H), 7.49 (d, 1H, J = 8 Hz, aromatic H), 7.56−7.77 (m, 15H, $PPh_3^+Br^-$ overlapped with 1H, aromatic H). $C_{28}H_{26}O_3BrP$ (521.39).

2-Fluoro-4-methoxycarbonylbenzyltriphenylphosphonium Bromide (31b). 31b was synthesized from 4-bromomethyl-3-fluorobenzoic acid methyl ester (**31c**).[13] It was used without further purification. Yield 70%, white powder, mp 225−226 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.88 (s, 3H, $-COOCH_3$), 5.71 (d, 2H, J(H, P) = 15 Hz, $-CH_2-PPh_3^+Br^-$), 7.47 (d, 1H, J = 8 Hz, aromatic H), 7.62−7.84 (m, 15H, $PPh_3^+Br^-$ overlapped with 2H, aromatic H). $C_{27}H_{23}O_2BrPF$ (509.35).

3-Methoxycarbonylbenzyltriphenylphosphonium Bromide (32b). 32b was synthesized from 3-methoxycarbonylbenzyl bromide (**32c**).[14] Yield 67%, white powder, mp 204−206 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.79 (s, 3H, $-COOCH_3$), 5.59 (d, 2H, J(H, P) = 15 Hz, $-CH_2-PPh_3^+Br^-$), 7.28−7.40 (m, 4H, aromatic H), 7.61−7.84 (m, 15H, $PPh_3^+Br^-$). $C_{27}H_{24}O_2BrP$ (491.36).

4-(Methoxycarbonyl)benzyltriphenylphosphonium Bromide (33b). 33b was prepared as previously described.[8]

2-Fluoro-4-bromobenzyltriphenylphosphonium Bromide (25c). 25c was synthesized from 4-(bromomethyl)-3-fluorobromobenzene.[28] Yield 75%, white powder, mp 225 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.54 (d, 2H, J(H, P) = 15 Hz, $-CH_2-PPh_3^+Br^-$), 7.01 (d, 1H, J = 9 Hz, aromatic H), 7.15 (d, 1H, J = 9 Hz, aromatic H), 7.53 (m, 1H, aromatic H), 7.63−7.82 (m, 15H, $PPh_3^+Br^-$). $C_{25}H_{20}Br_2P$ (451.81).

Synthesis of Compounds 10a−20a. *N*-(Diphenyl)acetyl-4-[3-(methoxycarbonyl)benzylidene]piperidine (10a). Under nitrogen a solution of butyllithium (1.6 M in hexane, 5.60 mL, 8.14 mmol) was added dropwise at −78 °C to a suspension of 3-methoxycarbonylbenzyltriphenylphosphonium bromide (**32b**, 4.00 g, 8.14 mmol) in dry THF (40 mL). After 15 min, the solution changed to orange and a solution of *N*-(diphenyl)-acetyl-4-piperidone (**6b**)[8] (2.38 g, 8.14 mmol) in dry THF (30 mL) was added dropwise at room temperature. The solution was stirred overnight under nitrogen. The solvent was evaporated in vacuo, and the residue was dissolved in CH_2Cl_2 (75 mL) and was washed twice with water (20 mL). The solution was dried over $MgSO_4$. After filtration, the solvent was evaporated in vacuo and the crude compound was purified by column chromatography (CC) (hexane/ethyl acetate 7:3). Yield 37%, yellow paste. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.01−2.40 (4s, broad, 4H, pip. H), 3.51 and 3.62 (2s, broad, 4H, pip. H), 3.88 (s, 3H, $-COOCH_3$), 5.57 (s, 1H, $-COCH-$), 6.39 (s, 1H, vinyl-H), 7.21−7.33 (m, 10H, aromatic H), 7.35−7.46 (m, 2H, aromatic H), 7.70−7.78 (m, 2H, aromatic H). $C_{28}H_{27}NO_3$ (425.52).

***N*-(Dicyclohexyl)acetyl-4-[3-(methoxycarbonyl)benzylidene]piperidine (11a). 11a** was synthesized from *N*-(dicyclohexyl)acetyl-4-piperidone (**7b**)[8] and 3-methoxycarbonylbenzyltriphenylphosphonium bromide (**32b**). It was purified by flash column chromatography (FCC) (hexane/ethyl acetate 7:3). Yield 42%, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95−1.70 (m, 22H, cyclohexyl-H), 2.35 (s, broad, 1H, $-COCH-$), 2.38 and 2.48 (2s, broad, 4H, pip. H), 3.54−3.75 (3s, broad, 4H, pip. H), 3.92 (s, 3H, $-COOCH_3$), 6.40 (s, 1H, vinyl-H), 7.40 and 7.88 (m, 4H, aromatic H). $C_{28}H_{39}NO_3$ (437.62).

***N*-(3,3-Diphenyl)propanoyl-4-[4-(methoxycarbonyl)-benzylidene]piperidine (12a). 12a** was synthesized from *N*-(3,3-diphenyl)propanoyl-4-piperidone (**28b**) and 4-methoxycarbonylbenzyltriphenylphosphonium bromide (**33b**).[8] It was purified by FCC (hexane/ethyl acetate 6:4). Yield 36%, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.12−2.36 (4t, 4H, J = 6 Hz, pip. H), 3.09 (d, 2H, J = 7 Hz, $-CH_2CH-$), 3.32−3.62 (4t, 4H, J = 6 Hz, pip. H), 3.90 (s, 3H, $-COOCH_3$), 4.69 (t, 1H, J = 7 Hz, $-CH_2CH-$), 6.34 (s, 1H, vinyl-H), 7.19 and 7.98 (d, AA′BB′, 4H, J = 8 Hz, aromatic H), 7.24−7.28 (m, 10H, aromatic H). $C_{29}H_{29}NO_3$ (439.55).

***N*-(Diphenyl)acetyl-4-[(2-fluoro-4-methoxycarbonyl)-benzylidene]piperidine (13a). 13a** was synthesized from *N*-(diphenyl)acetyl-4-piperidone (**6b**)[8] and 2-fluoro-4-methoxycarbonylbenzyltriphenylphosphonium bromide (**31b**). It was purified by FCC (hexane/ethyl acetate 9:1). Yield 25%, white powder, mp 132−133 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.04−2.36 (4t, 4H, J = 6 Hz, pip. H), 3.46−3.78 (4t, 4H, J = 6 Hz, pip. H), 3.90 (s, 3H, $-COOCH_3$), 5.25 (s, 1H, $-COCH-$), 6.25 (s, 1H, vinyl-H), 7.13 (t, 1H, J = 8 Hz, aromatic H), 7.24−7.32 (m, 10H, aromatic H), 7.68−7.76 (m, 2H, aromatic H). IR (KBr): ν = 3400, 2940, 2860, 1710, 1640, 1480, 1430, 1270, 1240, 1200, 1080, 980, 960, 750, 700 cm^{-1}. $C_{28}H_{26}NO_3F$ (443.51).

***N*-(Diphenyl)acetyl-4-[(2-methoxy-4-methoxycarbonyl)-benzylidene]piperidine (14a). 14a** was synthesized from *N*-(diphenyl)acetyl-4-piperidone (**6b**)[8] and 2-methoxy-4-methoxycarbonylbenzyltriphenylphosphonium bromide (**30b**). It was purified by CC (hexane/ethyl acetate 7:3). Yield 10%, white powder, mp 141−142 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.08 and 2.39 (2s, broad, 4H, pip. H), 3.45−3.78 (4s, broad, 4H, pip. H), 3.86 (s, 3H, $-OCH_3$), 3.91 (s, 3H, $-COOCH_3$), 5.28 (s, 1H, $-COCH-$), 6.32 (s, 1H, vinyl-H), 7.13 (d, 1H, J = 8 Hz, aromatic H), 7.26−7.33 (m, 10H, aromatic H), 7.50−7.59 (m, 2H, aromatic H). IR (KBr): ν = 3000−2800, 1700, 1640, 1600, 1460, 1400, 1280, 1260, 1240, 1200, 1100, 1020, 980, 860, 750, 700 cm^{-1}. $C_{29}H_{29}NO_4$ (455.55).

***N*-(Dicyclohexyl)acetyl-4-[(2-fluoro-4-methoxycarbonyl)benzylidene]piperidine (15a). 15a** was synthesized from *N*-(dicyclohexyl)acetyl-4-piperidone (**7b**)[8] and 2-fluoro-4-methoxycarbonylbenzyltriphenylphosphonium bromide (**31b**). It was purified by CC (hexane/ethyl acetate 8:2) and recrystallized from hexane. Yield 34%, white powder, mp 122−123 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95−1.69 (m, 22H, cyclohexyl-H, overlapped with 1H, $-COCH-$), 2.36−2.50 (m, 4H, pip. H), 3.56−3.77 (3s, broad, 4H, pip. H), 3.90 (s, 3H, $-COOCH_3$), 6.31 (s, 1H, vinyl-H), 7.24 (m, 1H, aromatic H), 7.71 (d, 1H, J = 10 Hz, aromatic H), 7.77 (m, 1H, aromatic H). IR (KBr): ν = 3400, 2950, 2820, 1710, 1630, 1550, 1430, 1270, 1190, 1110, 1080, 980, 750 cm^{-1}. $C_{28}H_{38}NO_3F$ (455.61).

***N*-(Dicyclohexyl)acetyl-4-[(2-methoxy-4-methoxycarbonyl)benzylidene]piperidine (16a). 16a** was synthesized from *N*-(dicyclohexyl)acetyl-4-piperidone (**7b**)[8] and 2-methoxy-4-methoxycarbonylbenzyltriphenylphosphonium bromide (**30b**). It was purified by FCC (hexane/ethyl acetate 8:2). Yield 72%, white solid, mp 121−122 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.83−1.69 (m, 22 H, cyclohexyl-H, overlapped with 1H, $-COCH-$), 2.46 (t, 4H, J = 6 Hz, pip. H), 3.55−3.78 (3t, 4H, J = 6 Hz, pip. H), 3.88 (s, 3H, $-OCH_3$), 3.91 (s, 3H, $-COOCH_3$), 6.38 (s, 1H, vinyl-H), 7.17 (d, 1H, J = 7 Hz, aromatic H), 7.53 (s, 1H, aromatic H), 7.77 (t, 1H, J = 7 Hz, aromatic H). IR (KBr): ν = 3400, 2900, 2820, 1710, 1620, 1440, 1400, 1280, 1260, 1220, 1190, 1100, 980, 750 cm^{-1}. $C_{29}H_{41}NO_4$ (467.64).

***N*-(1-Adamantanoyl)-4-[(2-fluoro-4-methoxycarbonyl)-benzylidene]piperidine (17a). 17a** was synthesized from *N*-(1-adamantanoyl)-4-piperidone (**3b**)[8] and 2-fluoro-4-methoxycarbonylbenzyltriphenylphosphonium bromide (**31b**). It was purified by FCC (hexane/ethyl acetate 8:2). Yield 15%, white powder, mp 160 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.73 (s, 6H, ada H), 2.02, (s, 9H, ada H), 2.40 (m, 4H, pip. H), 3.66 and 3.76 (2t, 4H, J = 6 Hz, pip. H), 3.92 (s, 3H, $-COOCH_3$), 6.30 (s, 1H, vinyl-H), 7.24 (d, 1H, J = 8 Hz, aromatic H), 7.70 (d, 1H, J = 10 Hz, aromatic H), 7.77 (d, 1H, J = 9 Hz, aromatic H). IR (KBr): ν = 3400, 2900, 2840, 1720, 1610, 1550, 1430, 1410, 1270, 1200, 1080, 980, 900, 750 cm^{-1}. $C_{25}H_{30}NO_3F$ (411.51).

***N*-(1-Adamantanoyl)-4-[(2-methoxy-4-methoxycarbonyl)benzylidene]piperidine (18a). 18a** was synthesized from *N*-(1-adamantanoyl)-4-piperidone (**3b**)[8] and 2-methoxy-4-methoxycarbonylbenzyltriphenylphosphonium bromide (**30b**). It was purified by FCC (petrol ether/ethyl acetate 16:5). Yield 37%, white powder, mp 131−132 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.73 (s, 6H, ada H), 2.02, (s, 9H, ada H), 2.41 (t, 4H, J = 6 Hz, pip. H), 3.64 and 3.76 (2t, 4H, J = 6 Hz, pip. H), 3.89 (s, 3H, −OCH_3), 3.92 (s, 3H, −$COOCH_3$), 6.37 (s, 1H, vinyl-H), 7.17 (d, 1H, J = 8 Hz, aromatic H), 7.53 (s, 1H, aromatic H), 7.60 (dd, 1H, J = 8 Hz, J = 2 Hz, aromatic H). IR (KBr): ν = 3400, 2900, 2820, 1720, 1600, 1450, 1400, 1280, 1260, 1220, 1170, 1100, 1030, 980, 860, 750 cm^{-1}. $C_{26}H_{33}NO_4$ (423.55).

***N*-(Diphenyl)acetyl-4-[4-(methoxycarbonylmethyl)benzylidene]piperidine (19a). 19a** was synthesized from *N*-(diphenyl)acetyl-4-piperidone (**6b**)[8] and [4-(methoxycarbonylmethyl)benzyl]triphenylphosphonium bromide (**29b**). It was purified by CC (hexane/ethyl acetate 7:3). Yield 16%, white powder. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.04−2.47 (4s, broad, 4H, pip. H), 3.43−3.68 (m, 4H, pip. H, overlapped with 2H, −CH_2COOH), 3.70 (s, 3H, −$COOCH_3$), 5.25 (s, broad, 1H, −COCH−), 6.29 (s, broad, 1H, vinyl-H), 7.09 (s, broad, 2H, aromatic H), 7.20−7.33 (m, 10H, aromatic H, overlapped with 2H, aromatic H). $C_{29}H_{29}NO_3$ (439.55).

***N*-(Dicyclohexyl)acetyl-4-[4-(methoxycarbonylmethyl)-benzylidene]piperidine (20a). 20a** was synthesized from *N*-(dicyclohexyl)acetyl-4-piperidone (**7b**)[8] and [4-(methoxycarbonylmethyl)benzyl]triphenylphosphonium bromide (**29b**). It was purified by FCC (hexane/ethyl acetate 8:2). Yield 15%, white powder. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93−1.69 (m, 22 H, cyclohexyl-H), 2.36 (s, broad, 1H, −COCH−), 2.48 (s, broad, 4H, pip. H), 3.52−3.71 (m, 4H, pip. H), overlapped with 3.70 (s, 2H, −CH_2COOH), 3.73 (s, 3H, −$COOCH_3$), 6.35 (s, 1H, vinyl-H), 7.15 and 7.23 (d, AA′BB′, 4H, J = 8 Hz, aromatic H). $C_{29}H_{41}NO_3$ (451.64).

Synthesis of Compounds 10−20. *N*-(Diphenyl)acetylpiperidine-4-(benzylidene-3-carboxylic acid) (10). A mixture of *N*-(diphenyl)acetyl-4-[3-(methoxycarbonyl)benzylidene]-piperidine (**10a**) (0.50 g, 1.19 mmol) and potassium carbonate (0.70 g) in methanol/water 9:1 (50 mL) was refluxed for 3 h at 90 °C. The solution was stirred overnight at room temperature. After this, the reaction was acidified with 1 N hydrochloric acid. The compound was extracted with CH_2Cl_2 (3 × 30 mL), washed with water, and dried over $MgSO_4$. The solvent was evaporated in vacuo to yield **10** as a crude product that was purified by recrystallization from hexane/ethyl acetate. Yield 53%, white powder, mp 136−137 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.98−2.40 (4s, broad, 4H, pip. H), 3.52 and 3.60 (2s, broad, 4H, pip. H), 5.57 (s, 1H, −COCH−), 6.38 (s, 1H, vinyl-H), 7.21−7.33 (m, 10H, aromatic H), 7.37−7.45 (m, 2H, aromatic H), 7.70−7.78 (m, 2H, aromatic H), 12.77 (s, 1H, −COOH). IR (KBr): ν = 3050−2900, 1710, 1690, 1640, 1440, 1280, 1210, 1080, 1000, 920, 850, 750 cm^{-1}. Anal. ($C_{27}H_{25}NO_3$ (411.50)) C, H, N.

***N*-(Dicyclohexyl)acetylpiperidine-4-(benzylidene-3-carboxylic acid) (11). 11** was synthesized from *N*-(dicyclohexyl)acetyl-4-[3-(methoxycarbonyl)benzylidene]piperidine (**11a**). It was purified by recrystallization from hexane/ethyl acetate. Yield 65%, white powder, mp 214 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.90−1.65 (m, 22H, cyclohexyl-H), 2.28−2.41 (3s, broad, 4H, pip. H), 2.60 (s, broad, 1H, −COCH−), 3.56−3.65 (3s, broad, 4H, pip. H), 6.44 (s, 1H, vinyl-H), 7.47 (s, broad, 2H, aromatic H), 7.88 (s, broad, 2H, aromatic H), 12.99 (s, 1H, −COOH). IR (KBr): ν = 3400, 2920−2700 (broad), 2580, 1720, 1650, 1600, 1450, 1270, 1240, 1200, 1080, 980, 920, 850, 750, 700 cm^{-1}. Anal. ($C_{27}H_{37}NO_3$ (423.59)) C, H, N.

***N*-(3,3-Diphenyl)propanoylpiperidine-4-(benzylidene-4-carboxylic acid) (12). 12** was synthesized from *N*-(3,3-diphenyl)propanoyl-4-[4-(methoxycarbonyl)benzylidene]piperidine (**12a**). It was purified by recrystallization from hexane/ethyl acetate. Yield 61%, white powder, mp 191−192 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.20 and 2.29 (2s, broad, 4H, pip. H), 3.16 (t, 2H, J = 7 Hz, −CH_2CH−), 3.39−3.58 (4s, broad, 4H, pip. H), 4.51 (t, 1H, J = 7 Hz, −CH_2CH−), 6.39 (s, 1H, vinyl-H), 7.14 and 7.89 (d, AA′BB′, 4H, J = 8 Hz, aromatic H), 7.23−7.32 (m, 10H, aromatic H), 12.87 (s, 1H, −COOH). IR (KBr): ν = 3400 (broad), 2650, 2520, 1680, 1640, 1600, 1420, 1310, 1250, 1170, 1100, 980, 870, 750, 700 cm^{-1}. Anal. ($C_{28}H_{27}NO_3$ (425.52)) C, H, N.

***N*-(Diphenyl)acetylpiperidine-4-(2-fluorobenzylidene-4-carboxylic acid) (13). 13** was synthesized from *N*-(diphenyl)acetyl-4-[(2-fluoro-4-methoxycarbonyl)benzylidene]piperidine (**13a**). It was purified by recrystallization from hexane/ethyl acetate. Yield 52%, white powder, mp 217−218 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.98−2.29 (4s, broad, 4H, pip. H), 3.53 and 3.61 (2s, broad, 4H, pip. H), 5.58 (s, 1H, −COCH−), 6.29 (s, 1H, vinyl-H), 7.21−7.33 (m, 10H, aromatic H), 7.40 (t, 1H, J = 8 Hz, aromatic H), 7.62 (d, 1H, J = 8 Hz, aromatic H), 7.71 (t, 1H, J = 8 Hz, aromatic H), 13.18 (s, 1H, −COOH). IR (KBr): ν = 3440 (broad), 3050−2820, 1700, 1640, 1440, 1290, 1220, 1000, 940, 760, 700 cm^{-1}. Anal. ($C_{27}H_{24}NO_3F$ (429.49)) C, H, N.

***N*-(Diphenyl)acetylpiperidine-4-(2-methoxybenzylidene-4-carboxylic acid) (14). 14** was synthesized from *N*-(diphenyl)acetyl-4-[(2-methoxy-4-methoxycarbonyl)benzylidene]piperidine (**14a**). It was purified by recrystallization from hexane/ethyl acetate. Yield 46%, white powder, mp 215 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.97 and 2.28 (2s, broad, 4H, pip. H), 3.53 and 3.59 (2s, broad, 4H, pip. H), 3.80 (s, 3H, −OCH_3), 5.58 (s, 1H, −COCH−), 6.29 (s, 1H, vinyl-H), 7.13 (d, 1H, J = 8 Hz, aromatic H), 7.21−7.33 (m, 10H, aromatic H), 7.45−7.51 (m, 2H, aromatic H), 12.94 (s, 1H, −COOH). IR (KBr): ν = 2950, 2600 (broad), 1680, 1630, 1600, 1480, 1450, 1410, 1260, 1200, 1100, 1030, 980, 860, 750, 700 cm^{-1}. Anal. ($C_{28}H_{27}NO_4$ (441.52)) C, H, N.

***N*-(Dicyclohexyl)acetylpiperidine-4-(2-fluorobenzylidene-4-carboxylic acid) (15). 15** was synthesized from *N*-(dicyclohexyl)acetyl-4-[(2-fluoro-4-methoxycarbonyl)benzylidene]piperidine (**15a**). It was purified by recrystallization from hexane/ethyl acetate. Yield 65%, white powder, mp 195−196 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.95−1.69 (m, 22 H, cyclohexyl-H), 2.36−2.50 (m, 4H, pip. H), 2.62 (s, broad, 1H, −COCH−), 3.52−3.66 (m, 4H, pip. H), 6.35 (s, 1H, vinyl-H), 7.43 (t, 1H, J = 8 Hz, aromatic H), 7.64 (d, 1H, J = 10 Hz, aromatic H), 7.73 (d, 1H, J = 8 Hz, aromatic H), 13.20 (s, 1H, −COOH). IR (KBr): ν = 3400, 2940, 2860, 1720, 1580, 1460, 1430, 1260, 1210, 1080, 1000, 980, 900, 870, 750 cm^{-1}. Anal. ($C_{27}H_{36}NO_3F$ (441.58)) C, H, N.

***N*-(Dicyclohexyl)acetylpiperidine-4-(2-methoxybenzylidene-4-carboxylic acid) (16). 16** was synthesized from *N*-(dicyclohexyl)acetyl-4-[(2-methoxy-4-methoxycarbonyl)benzylidene]piperidine (**16a**). It was purified by recrystallization from hexane/ethyl acetate. Yield 72%, white powder, mp 197−198 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.90−1.65 (m, 22 H, cyclohexyl-H), 2.27 and 2.32 (2s, broad, 4H, pip. H), 2.60 (s, broad, 1H, −COCH−), 3.50−3.64 (4s, broad, 4H, pip. H), 3.83 (s, 3H, −OCH_3), 6.35 (s, 1H, vinyl-H), 7.26 (d, 1H, J = 8 Hz, aromatic H), 7.47 (s, 1H, aromatic H), 7.51 (d, 1H, J = 8 Hz, aromatic H), 12.96 (s, 1H, −COOH). IR (KBr): ν = 2940, 2840, 2600 (broad), 1720, 1680, 1630, 1600, 1450, 1410, 1250, 1200, 1110, 1040, 1000, 880, 760 cm^{-1}. Anal. ($C_{28}H_{39}NO_4$ (453.62)) C, H, N.

***N*-(1-Adamantanoyl)piperidine-4-(2-fluorobenzylidene-4-carboxylic acid) (17). 17** was synthesized from *N*-(1-adamantanoyl)-4-[(2-fluoro-4-methoxycarbonyl)benzylidene]-piperidine (**17a**). It was purified by recrystallization from hexane/ethyl acetate. Yield 62%, white powder, mp 250−251 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.68 (s, 6H, ada H), 1.92, (s, 6H, ada H), 1.98, (s, 3H, ada H), 2.31 and 2.35 (2s, broad, 4H, pip. H), 3.58 and 3.65 (2s, broad, 4H, pip. H), 6.33 (s, 1H, vinyl-H), 7.42 (t, 1H, J = 8 Hz, aromatic H), 7.64 (d, 1H, J = 10 Hz, aromatic H), 7.73 (d, 1H, J = 9 Hz, aromatic H), 12.96 (s, 1H, −COOH). IR (KBr): ν = 3200−2300, 1710, 1590, 1430, 1380, 1270, 1230, 1200, 1120, 1060, 980, 870, 740 cm^{-1}. Anal. ($C_{24}H_{28}NO_3F$ (397.48)) C, H, N.

***N*-(1-Adamantanoyl)piperidine-4-(2-methoxybenzylidene-4-carboxylic acid) (18). 18** was synthesized from

N-(1-adamantanoyl)-4-[(2-methoxy-4-methoxycarbonyl)benzylidene]piperidine (**18a**). It was purified by recrystallization from hexane/ethyl acetate. Yield 58%, white powder, mp 193−194 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.68 (s, 6H, ada H), 1.92 (s, 6H, ada H), 1.98 (s, 3H, ada H), 2.32 (s, broad, 4H, pip. H), 3.57 and 3.64 (2s, broad, 4H, pip. H), 3.83 (s, 3H, $-OCH_3$), 6.34 (s, 1H, vinyl-H), 7.25 (d, 1H, J = 8 Hz, aromatic H), 7.47 (s, 1H, aromatic H), 7.51 (d, 1H, J = 8 Hz, aromatic H), 12.93 (s, 1H, −COOH). IR (KBr): ν = 2900, 2820, 2650−2550, 1700, 1670, 1580, 1450, 1400, 1250, 1200, 1170, 1100, 1030, 980, 870, 750 cm^{-1}. Anal. ($C_{25}H_{31}NO_4$ (409.52)) C, H, N.

***N*-(Diphenyl)acetylpiperidine-4-(benzylidene-4-acetic acid) (19). 19** was synthesized from *N*-(diphenyl)acetyl-4-[4-(methoxycarbonylmethyl)benzylidene]piperidine (**19a**). It was purified by recrystallization from hexane/ethyl acetate. Yield 57%, white powder, mp 188 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.90−2.36 (4s, broad, 4H, pip. H), 3.50−3.58 (m, 4H, pip. H), overlapped with 3.54 (s, 2H, $-CH_2COOH$), 5.56 (s, 1H, −COCH−), 6.30 (s, 1H, vinyl-H), 7.07 and 7.13 (d, AA′BB′, 4H, J = 8 Hz, aromatic H), 7.17−7.33 (m, 10H, aromatic H), 12.27 (s, 1H, −COOH). IR (KBr): ν = 2920−2500, 1700, 1640, 1440, 1250, 1210, 1200, 1060, 980, 950, 860, 750, 700 cm^{-1}. Anal. ($C_{28}H_{27}NO_3$ (425.52)) C, H, N.

***N*-(Dicyclohexyl)acetylpiperidine-4-(benzylidene-4-acetic acid) (20). 20** was synthesized from *N*-(dicyclohexyl)-acetyl-4-[4-(methoxycarbonylmethyl)benzylidene]piperidine (**20a**). It was purified by recrystallization from hexane/ethyl acetate. Yield 65%, white powder, mp 114−115 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.89−1.65 (m, 22 H, cyclohexyl-H), 2.25−2.41 (4s, broad, 4H, pip. H), 2.60 (s, 1H, −COCH−), 3.40−3.64 (m, 4H, pip. H), overlapped with 3.54 (s, 2H, $-CH_2$-COOH), 6.35 (s, 1H, vinyl-H), 7.16 and 7.21 (d, AA′BB′, 4H, J = 8 Hz, aromatic H), 12.32 (s, 1H, −COOH). IR (KBr): ν = 2920, 2860, 1730, 1640, 1590, 1450, 1370, 1230, 1210, 990 cm^{-1}. Anal. ($C_{28}H_{39}NO_3$ (437.62)) C, H, N.

Methyl 4-(*N*-(*tert*-Butyloxycarbonyl)-4-piperidinyloxy)-benzoate (24a). Methyl 4-hydroxybenzoate (**24b**) (9.40 g, 61.0 mmol) and triphenylphosphine (22.5 g, 86.0 mmol) were dissolved in 200 mL of dry THF at 0 °C. To the stirred mixture was added dropwise, over a period of 2 h, a solution of *N*-(*tert*-butyloxycarbonyl)piperidin-4-ol[15] (**24c**) (17.3 g, 86.0 mmol) and diethylazodicarboxylate[29] (15.0 g, 86.0 mmol) in 160 mL of dry THF. The reaction mixture was stirred for 5 h at 0 °C and then warmed to room temperature for 18 h. The reaction mixture was diluted with 250 mL of ethyl acetate. The organic phase was washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated to give a semisolid. This material was suspended in 500 mL of hexane/ethyl acetate (9:1), stirred, and filtered to remove triphenylphosphine oxide. Evaporation of the filtrate under reduced pressure yielded an oil that was purified by FCC (hexane/ethyl acetate 8:2) to give an oil that solidified on standing. The residue obtained was recrystallized from hexane/ethyl acetate to yield compound **24a**. Yield 53%, white solid, mp 66−67 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.45 (s, 9H, $-OC(CH_3)_3$), 1.77 and 1.92 (2s, broad, 4H, pip. H), 3.36 and 3.68 (2s, broad, 4H, pip. H), 3.88 (s, 3H, $-COOCH_3$), 4.55 (m, 1H, −OCH−), 6.91 and 7.97 (d, AA′BB′, 4H, J = 9 Hz, aromatic H). IR (KBr): ν = 3400 (broad), 2900, 2820, 1700, 1600, 1500, 1460−1380, 1310−1240, 1160, 1120, 1000, 970, 850, 770, 700 cm^{-1}. $C_{18}H_{25}NO_5$ (335.40).

Methyl 4-(*N*-(Diphenyl)acetyl-4-piperidinyloxy)benzoate (21a). The above product (**24a**) was treated with 4.0 M HCl in dioxane (100 mL) at room temperature for 2 h. After evaporation, the residue was dissolved in 1 M HCl (100 mL) and impurities were extracted with CH_2Cl_2 (2 × 100 mL). The aqueous phase was basified (pH ≈ 8) with NH_4OH and extracted with CH_2Cl_2 (4 × 100 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, and evaporated to give 4′-(methoxycarbonylphenyloxy)-4-piperidine hydrochloride (**24′a**). Yield 74%, white powder, mp 82−83 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.96 (s, broad, 2H, pip. H), 2.19 (s, broad, 2H, pip. H), 2.35 (s, broad, 2H, pip. H), 3.69 (s, broad, 2H, pip. H), 3.88 (s, 3H, $-COOCH_3$), 4.74 (s, broad, 1H, −OCH−), 6.91 and 8.00 (d, AA′BB′, 4H, J = 9 Hz, aromatic H), 9.62 (s, broad, 1H, −NH). IR (KBr): ν = 3490, 3350, 2950−2720, 2550, 1720, 1610, 1530, 1480, 1430, 1330−1240, 1170, 1110, 1040, 970, 850, 780, 700 cm^{-1}. The latter (**24′a**) (1.20 g, 5.10 mmol) and triethylamine (1.20 g, 12.0 mmol) were dissolved in dry CH_2Cl_2. Diphenylacetyl chloride (1.40 g, 6.00 mmol) dissolved in dry CH_2Cl_2 was added dropwise, and the reaction mixture was stirred for 2 h at room temperature. The organic phase was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue obtained was purified by FCC (hexane/ethyl acetate 6:4) followed by recrystallization from hexane/ethyl acetate to give **21a**. Yield 64%, white solid, mp 135 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.54 and 1.86 (2s, broad, 4H, pip. H), 3.47−3.79 (3s, broad, 4H, pip. H), 3.87 (s, 3H, $-COOCH_3$), 4.54 (m, 1H, −OCH−), 5.22 (s, 1H, −COCH−), 6.86 and 7.95 (d, AA′BB′, 4H, J = 9 Hz, aromatic H), 7.24−7.33 (m, 10H, aromatic H). IR (KBr): ν = 3020, 2940, 1710, 1640, 1600, 1500, 1440, 1280, 1250, 1210, 1170, 1110, 1030, 1000, 940, 840, 750, 700 cm^{-1}. $C_{27}H_{27}NO_4$ (429.51).

Methyl 4-(*N*-Adamantanoyl-4-piperidinyloxy)benzoate (22a). 22a was synthesized from 4′-(methoxycarbonylphenyloxy)-4-piperidine hydrochloride (**24′a**) and adamantoyl chloride. It was purified by FCC (hexane/ethyl acetate 7:3). Yield 45%, white crystals, mp 131−132 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.72 (s, 6H, ada H), 1.83 and 1.99 (2s, broad, 4H, pip. H), 2.01 (s, 9H, ada H), 3.68 (s, broad, 2H, pip. H), 3.88 (s, 3H, $-COOCH_3$, overlapped with 2H, pip. H), 4.64 (s, broad, 1H, −OCH−), 6.91 and 7.98 (d, AA′BB′, 4H, J = 9 Hz, aromatic H). IR (KBr): ν = 3420 (broad), 2920, 2860, 1720, 1630, 1610, 1510, 1460, 1440, 1420, 1320, 1280, 1260, 1240, 1170, 1100, 1050, 850, 780, 700 cm^{-1}. $C_{24}H_{31}NO_4$ (397.51).

Methyl 4-(*N*-(Diphenyl)carbamoyl-4-piperidinyloxy)-benzoate (23a). 23a was synthesized from 4′-(methoxycarbonylphenyloxy)-4-piperidine hydrochloride (**24′a**) and diphenylcarbamoyl chloride. It was purified by FCC (hexane/ethyl acetate 7:3) and then recrystallized from hexane/ethyl acetate. Yield 64%, white crystals, mp 143−144 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.69 and 1.81 (2m, broad, 4H, pip. H), 3.38 and 3.59 (2m, broad, 4H, pip. H), 3.87 (s, 3H, $-COOCH_3$), 4.52 (m, 1H, −OCH−), 6.86 and 7.95 (d, AA′BB′, 4H, J = 9 Hz, aromatic H), 7.05 (d, 4H, J = 8 Hz, aromatic H), 7.13 (t, 2H, J = 8 Hz, aromatic H), 7.31 (t, 4H, J = 8 Hz, aromatic H). IR (KBr): ν = 3400, 3080, 2980, 2840, 1730, 1660, 1600, 1500, 1430, 1300−1210 (broad), 1170, 1100, 940, 850, 770, 700 cm^{-1}. $C_{26}H_{26}N_2O_4$ (430.50).

Compounds 21−24. Preparation of **21−24** was similar to the synthesis of compounds **10−20.**

4-(*N*-(Diphenyl)acetyl-4-piperidinyloxy)benzoic Acid (21). 21 was synthesized from methyl 4-(*N*-(diphenyl)acetyl-4-piperidinyloxy)benzoate (**21a**). It was purified by recrystallization from hexane/ethyl acetate. Yield 64%, white powder, mp 225 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.18−1.90 (4s, broad, 4H, pip. H), 3.30 (m, 2H, pip. H), 3.79 and 3.96 (2s, broad, 2H, pip. H), 4.65 (s, broad, 1H, −OCH−), 5.57 (s, 1H, −COCH−), 7.01 and 7.85 (d, AA′BB′, 4H, J = 9 Hz, aromatic H), 7.22−7.34 (m, 10H, aromatic H), 12.62 (s, 1H, −COOH). IR (KBr): ν = 3300−2700 (broad), 2680, 2540, 1680, 1640, 1600, 1500, 1430, 1100, 1270−1200 (broad), 1170, 1110, 1030, 950, 850, 750, 700, 630 cm^{-1}. Anal. ($C_{26}H_{25}NO_4$ (415.48)) C, H, N.

4-(*N*-Adamantanoyl-4-piperidinyloxy)benzoic Acid (22). 22 was synthesized from methyl 4-(*N*-adamantanoyl-4-piperidinyloxy)benzoate (**22a**). It was purified by recrystallization from hexane/ethyl acetate. Yield 30%, white crystals, mp 249−250 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.53 (s, broad, 2H, pip. H), 1.71 (s, 6H, ada H), 1.90 and 1.97 (2s, broad, 11H, [9H, ada H and 2H, pip. H]), 3.39 and 3.95 (2s, broad, 4H, pip. H), 4.74 (s, broad, 1H, −OCH−), 7.05 and 7.87 (d, AA′BB′, 4H, J = 9 Hz, aromatic H), 12.57 (s, 1H, −COOH). IR (KBr): ν = 3400−1900 (broad), 1720, 1640, 1580, 1500, 1460, 1440, 1270−1200 (broad), 1100, 1030, 960, 900, 840, 750, 620 cm^{-1}. Anal. ($C_{23}H_{29}NO_4$ (383.48)) C, H, N.

4-(*N*-(Diphenyl)carbamoyl-4-piperidinyloxy)benzoic Acid (23). 23 was synthesized from methyl 4-(*N*-(diphenyl)-carbamoyl-4-piperidinyloxy)benzoate (**23a**). It was purified by recrystallization from hexane/ethyl acetate. Yield 61%, white crystals, mp 225−226 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.41 and 1.80 (2s, broad, 4H, pip. H), 3.14 and 3.63 (2s, broad, 4H, pip. H), 4.62 (s, broad, 1H, −OCH−), 7.00 (d, 4H, J = 8 Hz, aromatic H), 7.01 (d, AA′BB′, 2H, J = 9 Hz, aromatic H), 7.14 (t, 2H, J = 8 Hz, aromatic H), 7.35 (t, 4H, J = 8 Hz, aromatic H), 7.84 (d, AA′BB′, 2H, J = 9 Hz, aromatic H), 12.59 (s, 1H, −COOH). IR (KBr): ν = 3400, 3080−2700, 1700, 1650, 1600, 1500, 1440, 1260, 1240, 1370, 1100, 1050, 940, 850, 760, 700, 630 cm^{-1}. Anal. ($C_{25}H_{24}N_2O_4$ (416.47)) C, H, N.

4-(*N*-(*tert*-Butyloxycarbonyl)-4-piperidinyloxy)benzoic Acid (24). 24 was synthesized from methyl 4-(*N*-(*tert*-butyloxycarbonyl)-4-piperidinyloxy)benzoate (**24a**). It was purified by recrystallization from hexane/ethyl acetate. Yield 56%, white powder, mp 183 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.40 (s, 9H, −OC(CH$_3$)$_3$), 1.53 and 1.91 (2s, broad, 4H, pip. H), 3.17 and 3.66 (2s, broad, 4H, pip. H), 4.67 (m, 1H, −OCH−), 7.05 and 7.87 (d, AA′BB′, 4H, J = 9 Hz, aromatic H), 12.57 (s, 1H, −COOH). IR (KBr): ν = 2980, 2860, 2680, 2560, 1700, 1600, 1510, 1430, 1360, 1300, 1280, 1250, 1230, 1170, 1130, 1040, 950, 860, 770 cm^{-1}. Anal. ($C_{17}H_{23}NO_5$ (321.37)) C, H, N.

***N*-(Dicyclohexyl)acetyl-4-[2-fluoro-4-bromobenzylidene]-piperidine (25b).** To 2-fluoro-4-bromobenzyltriphenylphosphonium bromide (**25c**) (3.00 g, 5.70 mmol) and potassium carbonate (782 mg, 5.70 mmol) in CH_2Cl_2 (25 mL) were added *N*-(dicyclohexyl)acetyl-4-piperidone (**7b**)[8] (1.50 g, 4.70 mmol) and 18-crown-6 (15 mg). The reaction mixture was refluxed for 3 days. The solvent was evaporated, and the residue obtained was purified by FCC (hexane/ethyl acetate 9:1) to give a white oil. The white oil was scratched with a Pasteur pipet and left in a refrigerator overnight. The solid obtained was recrystallized from hexane to give **25b**. Yield 65%, white powder, mp 101−102 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97−1.69 (m, 22H, cyclohexyl-H), 2.31 and 2.37 (2s, broad, 4H, pip. H), 2.47 (s, broad, 1H, −COCH−), 3.70 (t, broad, 4H, pip. H), 6.20 (s, 1H, vinyl H), 7.03 (t, 1H, J = 8 Hz, aromatic H), 7.23 (d, 2H, J = 8 Hz aromatic H). IR (KBr): ν = 3440 (broad), 3020, 2960, 2840, 1640, 1560, 1480, 1440, 1400, 1370, 1230, 1200, 1110, 1070, 1000, 900, 850, 820 cm^{-1}. $C_{26}H_{35}NOFBr$ (476.47).

***N*-(Dicyclohexyl)acetyl-4-[2-fluoro-4-trimethylsilylethynylbenzylidene]piperidine (25a).** A mixture of piperidine (2.5 mL), THF (5.0 mL), trimethylsilylacetylene (541 μL, 3.10 mmol, 1.5 equiv), *N*-(dicyclohexyl)acetyl-4-[2-fluoro-4-bromobenzylidene]piperidine (**25b**) (1.00 g, 2.10 mmol), finely powdered cuprous iodide (7.80 mg, 0.041 mmol), $PdCl_2$·2PPh_3 (7.80 mg, 0.011 mmol), and triphenylphosphane (7.80 mg, 0.029 mmol) was heated under nitrogen for 2 h under reflux. The solution changed from blue to yellow rapidly. The solvent was evaporated under reduced pressure, and the yellow oil was purified by CC (hexane/ethyl acetate 9:1) to give a brown oil. The residue was scratched with a Pasteur pipet and left overnight in the refrigerator. The solid obtained was recrystallized from hexane to give **25a**. Yield 90%, slightly yellow solid, mp 124−125 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.24 (s, 9H, −Si(CH$_3$)$_3$), 0.93−1.69 (m, 22H, cyclohexyl-H), 2.34 (s, broad, 4H, pip. H), 2.47 (s, broad, 1H, −COCH−), 3.65 (t, broad, 4H, pip. H), 6.26 (s, 1H, vinyl-H), 7.07−7.19 (m, 3H, aromatic H). IR (KBr): ν = 3440 (broad), 2940, 2860, 2160, 1630, 1550, 1500, 1450, 1410, 1360, 1250, 1200, 1100, 1000, 960, 850 (broad), 770, 650 cm^{-1}. $C_{31}H_{44}NOSiF$ (493.78).

***N*-(Dicyclohexyl)acetylpiperidine-4-(2-fluorobenzylidene-4-acetic acid) (25).** To a solution of *N*-(dicyclohexyl)-acetyl-4-[2-fluoro-4-trimethylsilylethynylbenzylidene]-piperidine (**25a**) (400 mg, 0.81 mmol) in dry THF was added under nitrogen at 0 °C BH_3 (1 M in THF, 891 μL, 1.1 equiv). After the mixture was stirred for 3 h at room temperature, methanol (405 μL) was added and the solution was oxidized at 40 °C with 3 N NaOH (405 μL) and 35% hydrogen peroxide (405 μL). The mixture was stirred at room temperature for 1 h, and an additional 405 μL of 3 N NaOH was added. The impurities were extracted with CH_2Cl_2 (2 × 10 mL), and the aqueous phase was acidified and extracted with CH_2Cl_2 (3 × 50 mL). The solvent was evaporated to give a slightly yellow oil that was purified by FCC (hexane/ethyl acetate 6:4) to give a colorless oil. Hexane (5 mL) was added to the oil, and the mixture was gently warmed to 50 °C. Then ethyl acetate was added until complete dissolution occurred. The clear solution was stored overnight in a refrigerator to precipitate compound **25**. Yield 42%, white crystals, mp 73−74 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.90−1.66 (m, 22H, cyclohexyl-H), 2.28 (t, broad, 4H, pip. H), 2.60 (s, broad, 1H, −COCH−), 3.50−3.65 (3s, broad, 4H, pip. H) overlapped with 3.59 (s, 2H, −CH_2COOH), 6.26 (s, 1H, vinyl-H), 7.06 (d, 1H, J = 7 Hz, aromatic H), 7.09 (d, 1H, J = 11 Hz, aromatic H), 7.21 (t, 1H, J = 8 Hz, aromatic H), 12.40 (s, 1H, −COOH). IR (KBr): ν = 3400 (broad), 2940, 2860, 1730, 1630, 1600, 1500, 1450, 1370, 1260−1100, 1000 cm^{-1}. Anal. ($C_{28}H_{38}NO_3F$ (455.61)) C, H, N.

Enzyme Inhibition Test. Reagents. [1,2-^{3}H]Androstenedione (4-androstene-3,17-dione, AD), and [1,2-^{3}H]testosterone (17β-hydroxy-4-androstene-3-one, T) were purchased from DuPont, Bad Homburg, Germany.

Preparation of Tissue. Rat prostatic enzyme was prepared according to the method of Liang et al.[20] with slight modifications.[8] Male rats were sacrificed, and prostates were taken within 5 min and put in ice-cold 0.9% 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, a total of 3 mL of 20 mM phosphate buffer, pH 6.6 (for type 1 enzyme), containing 0.32 mM sucrose and 1 mM DTT was added. For the preparation of type 2 enzyme, citrate buffer, pH 5.5, was used. The tissue was homogenized by 10 strokes (10 s each) at 20 500 rpm of an Ultraturax (IKA) at 60 s intervals, filtered through cheesecloth, and centrifuged for 60 min at 105000*g*. The pellet obtained was resuspended in phosphate buffer. The centrifugation was repeated, and the final pellet was resuspended in a minimum volume of phosphate buffer and stored in 300 μL portions at −70 °C. The 105000*g* pellet contains nuclei, mitochondria, and microsomes and is referred to as the enzyme preparation. The protein content was determined and was in the range 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[20] with modifications.[8] 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, type 1) or citrate buffer (40 mM, pH 5.5, type 2) was 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 of human protein), 200 μM NADPH (human enzyme: 100 μM NADPH), 0.21 μM T including 45 nCi [1,2-^{3}H]-T, and 2% DMSO with or without test compound (10 μM). The reaction was started by adding the prostatic enzyme preparation and stopped by addition of 50 μL of NaOH (10 M). The steroids were extracted using 500 μL of diethyl ether. The mixture was shaken for 10 min and centrifuged for 10 min at 4000 rpm. The water layer was frozen, and the ether layer was decanted into fresh tubes and evaporated to dryness.

Human Type 1 Inhibition: DU145 Assay.[13,22] Intact human prostatic carcinoma DU145 cells were used as the source of type 1 5α-reductase.[21−23] 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. Compounds to be tested were dissolved in DMSO, and 5 μL of each was added to the cells in a final volume of 0.5 mL of complete medium. Inhibitors were first

screened at concentrations of 10 μM in an initial test, and in the case of exceeding 80% inhibition, three concentrations were chosen for measurement of IC_{50} values. As controls for conversion (typically about 35% under these conditions), a triplicate of wells without inhibitors were 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 diethyl ether and the steroids were separated by HPLC. Results are expressed as the amount of formed androstanedione as a percentage of control values.

HPLC Procedure. The procedure was carried out[8] similar to the method of Cook et al.[30] The steroids were dissolved in 50 μL of methanol, and a total of 25 μL was injected into the computer-controlled HPLC system, which was checked before using labeled reference controls. Radioactivity was measured using a Berthold LB 506C monitor. When methanol/water (55:45, w/w) was used for T and DHT, with a flow of 0.4 mL/min and an additive flow of 1.0 mL for the scintillator, baseline separation of T and DHT was achieved within 20 min. For the steroids androstenedione and dihydroandrostenedione, methanol/water (50:50, w/w) was used.

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: $\%I = (1 - iv_{corr}/cv_{corr}) \times 100$.

In Vivo Assay.[31] One day after their arrival, 21 day-old male rats were castrated by scrotal incision under ether anesthesia. All animals were fed commercially available chow and housed in temperature controlled rooms with lights on between 8:00 and 18:00. Rats were divided in eight groups with eight rats each. One week after castration, oil solution of compounds (or vehicle) and testosterone propionate were applied either by separate subcutaneous injections (**7**, **15**, **25**) or by oral route (**7**) to the rats once daily for 4 days at doses of 11.3−12.2 mg/kg for title compounds and 1 mg/kg for testosterone propionate and finasteride. Twenty-four hours after the last application, the rats were sacrificed by CO_2 inhalation, and the ventral prostates were removed. The prostates were dissected free from fat and connective tissue and weighed. The mean percentage of inhibition of the T-induced hypertrophic response was calculated according to the equation

$$\% \text{ inhibition} = 100 \times (C_t - D)/(C_t - C_c)$$

where C_t, C_c, and D are the mean prostate weights of T-treated control, castrated control, and drug-treated group, respectively. Mean values and standard deviation were calculated. For determination of significance, Dunnett's test was used.

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Supporting Information Available: Table of calculated distance contraints between features of compound **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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