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Biphenyls as Surrogates of the Steroidal Backbone. Part 2: Discovery of a Novel Family of Non-steroidal 5-α-Reductase Inhibitors

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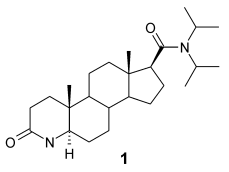
Abstract—A new family of non-steroidal 5-α-reductase inhibitors was designed by replacing the steroid skeleton of an inhibitor related to estrone by a biphenyl moiety. This hypothesis originated from the reported estrogenic activity of a few biphenyl compounds (see Part 1 of this paper; Lesuisse et al. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1709). Two compounds turned out to be potent type 2 5-α-reductase inhibitors with IC_{50}'s of inhibition in the nanomolar range. These are to our knowledge amongst the most potent non-steroidal 5-α-reductase inhibitors described to date.

Introduction

Steroid 5-α-reductase (EC 1.3.99.5) is the enzyme that catalyzes the conversion of testosterone to di-hydrotestosterone (DHT), the most potent prostatic androgen. Finasteride **1**,[1] one of the first described inhibitors of this enzyme, is currently marketed worldwide as a treatment for BPH. A few years ago, Holt and coworkers described a new class of steroidal inhibitors of 5-α-reductase, **2**, incorporating the estradiol skeleton.[2] Based on these new potent estrone-derived inhibitors of the 5-α-reductase, we hypothesized that by introducing appropriate substituents non-steroidal estrogens could be tailored into 5-α-reductase inhibitors. We had recently identified a new family of estrogens based on the biphenyl scaffold.[3] The best compounds in these series were the 2′,6′-dibromo- and dichlorobiphenyls **3** and **4**. Based on these findings, we speculated that similar compounds where the 4-hydroxy and the 4′-hydroxymethyl groups would be replaced by 4-carboxylic acid and 4′-carboxamidomethyl groups, respectively, as in **5** could potentially be good 5-α-reductase inhibitors.

The objective of this paper is to describe the synthesis of this new series of compounds and the results we have obtained using this approach.



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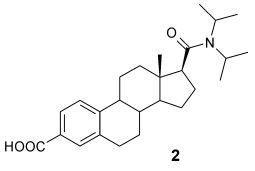

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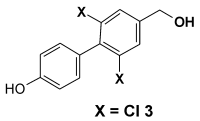

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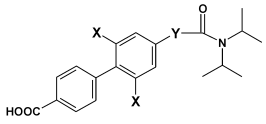
X = Br 4



5

Chemistry[4] and Biology[5]

We decided to first check the validity of the hypothesis by synthesizing the simplest derivative of **5** incorporating the desired functionalities (X = H, Y = —). Diisopropyl 4-hydroxy benzamide **6**[6] was transformed into its triflate[7] and condensed with tolyl boronic acid using standard conditions.[8] The methyl group of **7** was

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oxidized using potassium permanganate in pyridine[9] to afford the desired carboxylic acid **8** with a good yield (Scheme 1). Even this simple compound proved to inhibit human prostate 5-α-reductase[5] by about 30% at 1 μM (compared to Finasteride **1**[10] ($IC_{50} = 1.2\ 10^{-8}$ M) and **2**[11] ($IC_{50} = 10^{-9}$ M)) (Table 1).

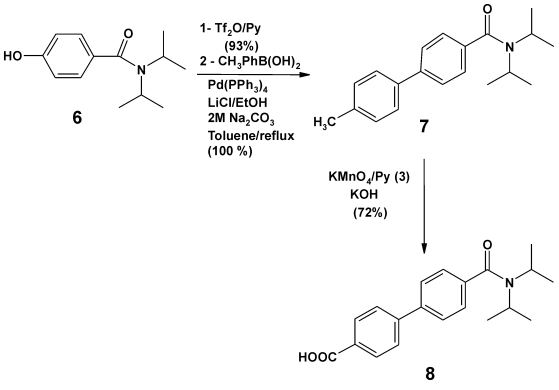
Comforted by this first result, we embarked on the synthesis of an analogue of **8** incorporating the required *ortho* disubstitution (**5**, X = Br, Y = —). The synthesis proved to be not as straightforward as envisaged. The way we finally succeeded in obtaining the desired compound was by the Ullmann coupling[12] of diisopropyl 4-chloro-3,5-dinitro benzamide **9** with methyl 4-iodobenzoate, followed by reduction, diazotation[13] and hydrolysis to give desired compound **12** (Scheme 2). The dinitro biphenyl **10** was also elaborated into the nitro- and amino-derivatives **14** and **16** and the iodo-derivatives **13** and **15** (see Table 1) using methods reported previously.[3]

To our surprise, none of the *ortho* disubstituted biphenyls **12–16** gave any detectable inhibition of the 5-α-reductase at 1 μM (Table 1).

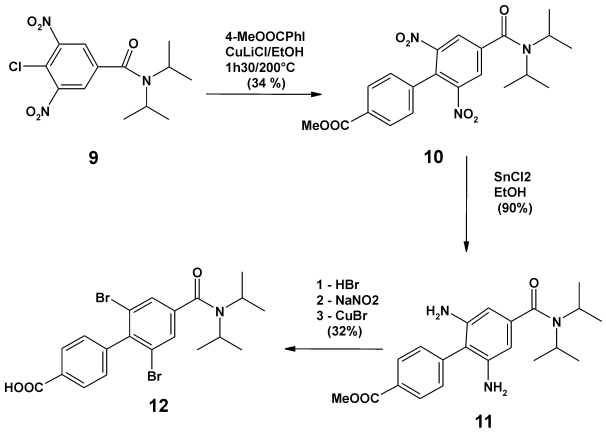
Because our experience in the field of biphenyls and estrogens[3] had taught us that the chain mimicking the 17-position of the steroid nucleus had to be tailored to the appropriate length, we evaluated the inhibition behaviour of compounds obtained by varying the Y linker between the biphenyl and the amide portion. The compounds **17–19** were obtained uneventfully.[14] Of all unsubstituted biphenyl derivatives (Table 2), **19** inhibited the enzyme best and therefore we decided to keep this moiety for reinvestigating the biphenyl substitution.

In view of our initial hypothesis, we invested again most of our effort into the synthesis of *ortho* disubstituted halogen derivatives of **19**. To this end, we used biphenyl intermediates we had prepared for our estrogen binding studies.[3] Protected *ortho* halogenobiphenyls **20–25** incorporating a carboxylic acid function precursor were transformed by alkylation of the deprotected phenol with diisopropylamino-1-bromoacetamide **26**. Oxidation or hydrolysis gave the desired carboxylic acids **27–32** (Scheme 3, Table 3). The new derivatives were evaluated against 5-α-reductase in comparison with **19**. The results confirmed the trend seen with derivatives **12–16**. No improvement of the inhibition properties was seen upon introduction of any halogen or methyl group in the *ortho*, *ortho*′ position of either aromatic ring (Table 5).

Evidently, the criteria for estrogen receptor binding affinity of 4-hydroxy-4′-hydroxymethyl biphenyls which very stringently required 2′,6′-disubstitution of the second aromatic ring mainly with chlorine and bromine, were not determinant for 5-α-reductase inhibition. In the absence of structural information on the active site of 5-α-reductase, we embarked on a wider exploration of the biphenyl substitution to improve the inhibition

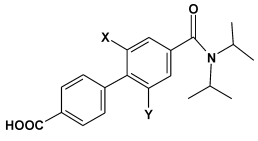


Scheme 1.



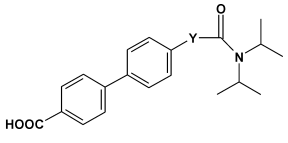
Scheme 2.

Table 1. 5-α-Reductase inhibition by 2′, 6′-disubstituted biphenyl derivatives of **8**

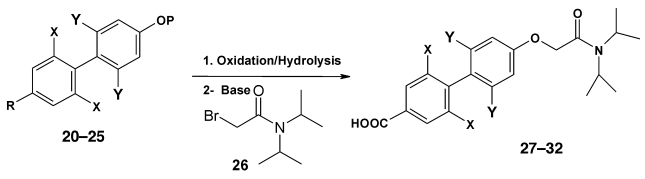


X	Y	Compound	% Inhib. (10^{-6} M)
H	H	**8**	32.5
Br	Br	**12**	0
NO_2	I	**13**	0
H_2N	NH_2	**14**	0
I	I	**15**	0
NO_2	NO_2	**16**	0

Table 2. Influence of the length of the side chain on 5-α-reductase inhibition



X	Compound	% Inhib. (10^{-6} M)
—	**8**	32.5
CH_2	**17**	37
CH(Me)	**18**	26.9
OCH_2	**19**	57.5



Scheme 3.

Table 3. Synthesis of *o*-disubstituted biphenyl derivatives **27–32** from **20–25**

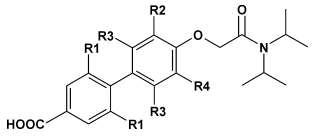
Starting compound	R	X	Y	P	Conditions (yield)	Compound
20	CH_2OH	F	—	Bn	(1) Jones (76%); (2) H_2/Pd/C (93%); (3) **26**/NaOH/DMSO (49%)	**27**
21	CHO	Cl	—	tBuPh$_2$Si	(1) TBAF (Q); (2) **26**/NaH/THF (68%); (3) $NaClO_2/H_2NSO_3H$ (61%)	**28**
22	CHO	Me	—	tBuPh$_2$Si	(1) TBAF(Q); (2) **26**/NaOH/DMSO (75%); (3) $NaClO_2/H_2NSO_3H$ (71%)	**29**
23	COOMe	—	Cl	tBuMe$_2$Si	(1) TBAF(Q); (2) **26**/NaOH/DMSO (20%)	**30**
24	COOMe	Cl,H	—	Bn	(1) H_2/Pd/C (99%); (2) **26**/NaOH/DMSO (15%)	**31**
25	CHO	CF3,H	—	Bn	(1) H_2/Pd/C (Q); (2) Jones (95%); (3) **26**/NaOH/DMSO (16%)	**32**

pattern. Some of the chemistry and results are summarized hereunder. Hydroquinones **33** and **34** were transformed into suitably functionalized candidates by sequential reactions with diisopropylamino-1-bromoacetamide **26** and triflic anhydride followed by biphenyl coupling reactions of the resulting triflates with 4-formylphenyl boronic acid. Oxidation of the resulting aldehydes gave carboxylic acids **37** and **38**. The same sequence of reactions was undertaken for the 4-bromophenol derivatives **35** and **36** where coupling was performed right after alkylation with diisopropylamino-1-bromoacetamide **26** to afford new compounds **39** and **40** (Scheme 4, Table 4).

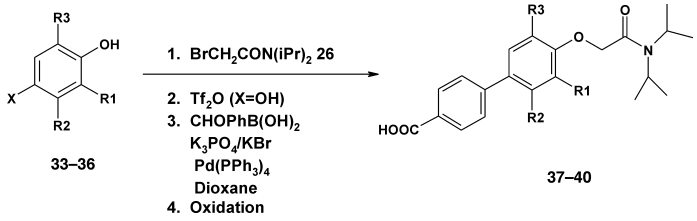
2-Ethyl-1,4-hydroquinone was converted to both compounds **41** and **42** by an analogous sequence of reactions (data not shown).

All new compounds displayed inhibition of 5-α-reductase to some extent (Table 5). Substitution of the first aromatic ring brought about no increase of inhibition compared to the unsubstituted compound (Table 5, cf. **27**–**29**, **31**, and

Table 5. 5-α-Reductase inhibition by polysubstituted biphenyl derivatives of **19**



R1	R2	R3	R4	IC_{50}	Compound
H	—	—		$8.3.10^{-7}$ M	**19**
F	—	—		$>10^{-6}$ M	**27**
Cl	—	—		$>10^{-6}$ M	**28**
Me	—	—		$>10^{-6}$ M	**29**
—	—	Cl		$>10^{-6}$ M	**30**
Cl,H	—	—	—	$8.7.10^{-7}$ M	**31**
CF_3,H	—	—	—	$5.7.10^{-7}$ M	**32**
—		–CH=CH–CH=CH–		—	37
—	—	CN,H	CN	—	**38**
—	IPr	—	IPr	$7.1.10^{-8}$ M	**39**
—	F	—	NO_2	$9.8.10^{-9}$ M	**40**
—	—	Et,H	—	2.10^{-6} M	**41**
—	—	—	Et	$3.5.10^{-7}$ M	**42**
				4.10^{-8} M	**1**
				2.10^{-9} M	**2**



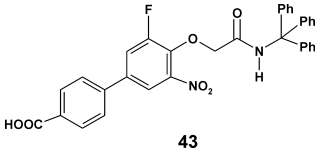
Scheme 4.

Table 4. Synthesis of polysubstituted biphenyl derivatives **37–40** from **33–36**

Starting compound	R1	R2	R3	X	Conditions (yield)	Compound
33	–CH=CH–CH=CH–		—	OH	(1) KH/DMF (38%); (2) 2,6-tBu$_2$Pyridine/CH_2Cl_2 (69%); (3) (51%); (4) Jones/acetone (24%)	**37**
34	CN	CN	—	OH	(1) NaH/DMF (60%); (2) IPr$_2$Net/CH_3CN (50%); (3) (13%); (4) PDC/DMF (40%)	**38**
35	iPr	—	iPr	Br	(1) NaH/DMF (96%); (3) (30%); (4) Ag_2O/NaOH 1 N/THF (14%)	**39**
36	NO_2	—	F	Br	(1) MeOK/DMSO (51%); (3) (17%); (4) Ag_2O/NaOH 1 N/THF (88%)	**40**

32 with **19**). Furthermore monosubstitution at the *ortho* position of the second aromatic ring had a detrimental effect on the inhibition (cf. **37**, **38**, and **41** to **19**). Finally, introduction of substituents *ortho* to the amide function had a dramatic effect on the inhibition (**39**, **40**). A fluorine and a nitro group in these positions improved the inhibition by 100-fold over the unsubstituted derivative **19**. These new compounds now displayed better inhibition than the reference Finasteride (see Table 5).

Finally, we tried to further improve **40** by replacing the diisopropylamide moiety by a trityl amide. Frye had described this as the optimal side chain for 5-α-reductase inhibition by 6-azasteroid derivatives.[15] However, in our case the resulting compound **43** was about 10-fold less active than the diisopropylamide analogue ($IC_{50} = 92$ nM vs 9.8 nM).



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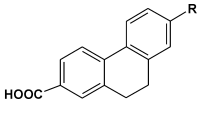
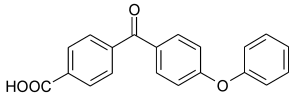
Conclusion

Our study was initiated by our initial observations of the excellent estrogen receptor binding affinity of a series of 2′,6′-disubstituted 4-hydroxy-4′-hydroxymethyl biphenyl derivatives.[1] This observation led us to hypothesize that a similar biphenyl scaffold suitably tailored could be a useful steroid replacement in other areas of steroid receptors and biosynthesis. Our study demonstrates that this is at least the case in the field of dihydrotestosterone biosynthesis with the discovery of a potent non-steroidal inhibitor of the type 2 5-α-reductase enzyme. Compound **40** is amongst the most potent non-steroidal inhibitor of the enzyme reported. Noteworthy in this regard is a publication by Abell of inhibitors somewhat chemically related like **44** and devoid of inhibitory activity on type 2 isoenzyme.[16] The same team was also able to identify chemically related inhibitors like **45** by high throughput screening.[17]



44 (R = H, Cl, Br)



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A compound like **40** could be of value in the treatment of diseases related to the function of this enzyme.

Acknowledgements

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References and Notes

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