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Novel Imidazolyl and Triazolyl Substituted Biphenyl Compounds: Synthesis and Evaluation as Nonsteroidal Inhibitors of Human 17α-Hydroxylase-C17, 20-Lyase (P450 17)

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Abstract—The synthesis of a new series of P450 17 inhibitors is described. The imidazol-1-yl compounds **5** showed strong inhibition of P450 17 rat and especially human enzyme, the most active compounds being **5ax**, **5ay** and **5bx** with IC_{50} values of 0.17, 0.24 and 0.25 μM, respectively (ketoconazole: 0.74 μM). The 1,2,4-triazol-1-yl compounds **6** were less active, while the 1,2,4-triazol-4-yl compounds **7** were inactive. The title compounds showed little inhibition of P450 arom. The most active P450 17 inhibitors **5ax** and **5ay** markedly decreased the testosterone plasma concentration of SD rats 2 h after application of 0.019 mmol/kg. After 6 h, **5ay** still exhibited a strong effect.

Introduction

Inhibitors of enzymes involved in the key steps of androgen synthesis are important for the treatment of prostatic diseases, such as benign prostatic hyperplasia (BPH) and prostatic cancer.[1–4] 17α-Hydroxylase-C17,20-lyase (P450 17) produces androstenedione and dehydro*epi*androsterone (DHEA), the immediate precursors of testosterone, from progesterone and pregnenolone, in both testes and adrenals.[5,6] We have shown[2,7,8] that a dihydro- or tetrahydronaphthalene is appropriate to give — after linkage with an N containing heterocycle, like imidazole, pyrazine or pyridine — highly potent inhibitors of P450 17 (e.g., **I** and **II**, Chart 1[8]). While the heterocyclic N is complexing the heme iron of P450 17, the rest of the molecule interacts with the apoprotein moiety. In the case of steroidal compounds, it has been shown recently,[9,10] that an imidazole ring at the C-17 position leads to potent inhibitors as well (e.g., **III**, Chart 1[10]). Very recently we found in the class of N-imidazolylmethyl-substituted biphenyls highly potent inhibitors of P450 17 (like **IV**, Chart 1[11]). To further increase in vitro activity and in vivo efficacy we describe in the present paper the synthesis of the imidazolyl and triazolyl substituted biphenyl compounds **5ax**–**5az**, **5bx**–**5bz**, **6ax**–**6az**, **6bx**–**6bz**, **7ax**–**7az** and **7bx**–**7bz**. Inhibition of P450 17 rat and human enzyme and human P450 arom by the test compounds and the influence of selected compounds on testosterone plasma concentration in rats are presented.

Chemistry

As starting materials for the synthesis of the imidazolyl and triazolyl substituted biphenyl compounds **5**, **6** and **7**, 4-bromo-acetophenone **2a** or 5-bromo-1-indanone **2b** and different para-substituted benzeneboronic acids (**1x**, **1y**, **1z**) were used (Scheme 1). The two series of important intermediates, the 4-phenyl-acetophenones **3ax**–**3az** and the 5-phenyl-1-indanones **3bx**–**3bz**, were obtained by fluoride-mediated boronic acid coupling reaction using the palladium complex $Pd(PPh_3)_4$ as catalyst (Method A).[12] The title compounds, the imidazole substituted racemic biphenyls **5** were prepared by reaction of **4** with CDI (1,1′-carbonyldiimidazole) (Method C)[13] and the triazole substituted racemic biphenyls **6** and **7** were produced by similar reaction of **4** with 1,1′-carbonyldi(1,2,4-triazole) (CDT; Method D). The alcohols **4** were obtained as racemates by reduction of **3** with $NaBH_4$ (Method B).[13] The isomers **6** and **7** were separated by silica gel column chromatography using CH_2Cl_2:CH_3OH (19:1) as eluent.

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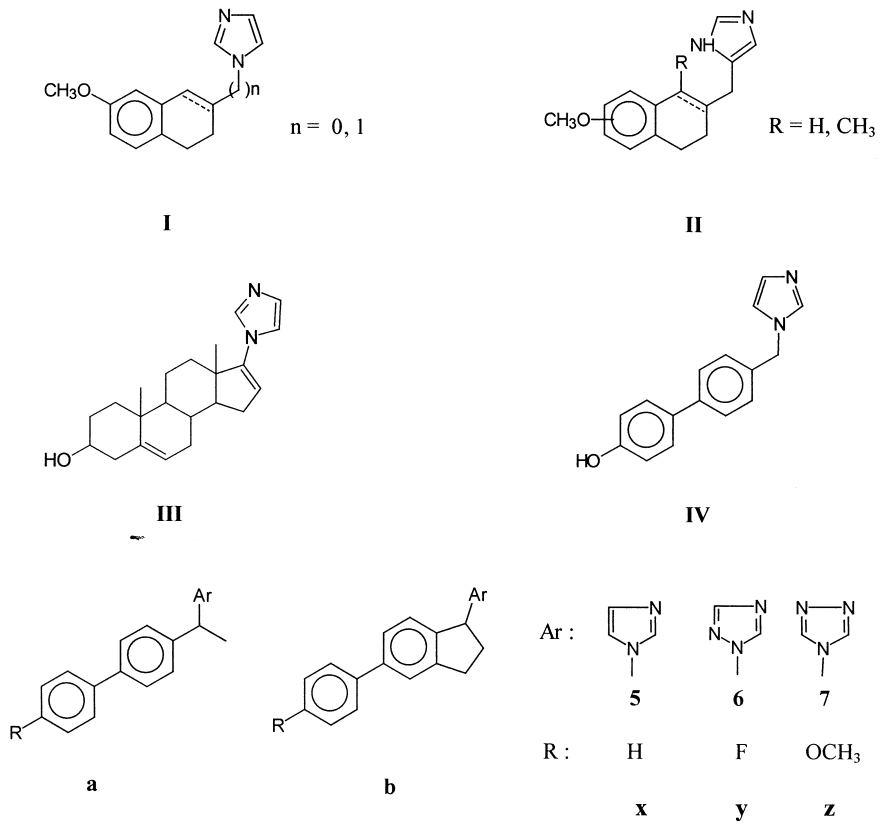


Chart 1. Selected inhibitors of P450 17 (**I**–**IV**) and the title compounds.

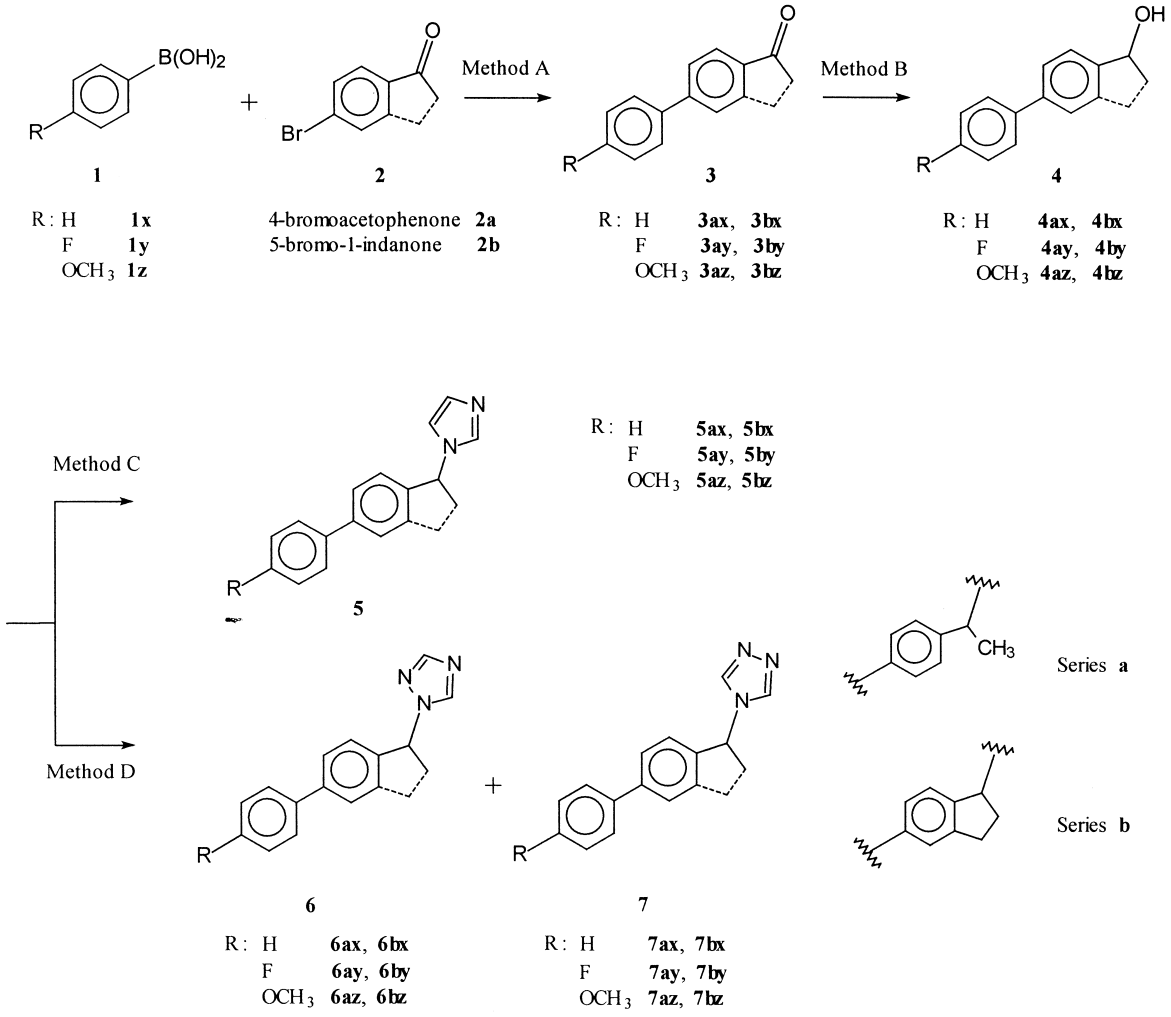
Results and Discussion

Table 1 shows the IC_{50} values and the inhibitory potencies of the compounds towards P450 17 relative to ketoconazole (**KTZ**; rp values). P450 17 from rat and human origin was used as it is known that there is no correlation between inhibition data obtained from these species.[11] Testicular enzyme and progesterone as substrate were employed using the procedure recently described by us.[14] The imidazolyl compounds showed strong inhibitory activity toward the human enzyme exhibiting IC_{50} values of 0.17 μM (**5ax**), 0.24 μM (**5ay**), and 0.25 μM (**5bx**), respectively. They were clearly more potent than the reference ketoconazole (0.74 μM). It is striking that the indane compounds were less active than the corresponding open ring compounds. Similar results were observed in the rat enzyme test (**5ax**, **5ay** and **5bx** with IC_{50} values of 1.2, 0.54 and 2.1 μM, respectively, ketoconazole: 67 μM). The 1,2,4-triazol-1-yl compounds **6** were less active, while the 1,2,4-triazol-4-yl compounds **7** were inactive. Methoxy substitution of the phenyl ring decreases activity in both series **5a** and **5b**, while fluorine substitution leads to an increase in the rat and to a decrease in the human enzyme.

In order to find an explanation for the results, molecular modeling studies were performed using energy-minimized conformations of the title compounds. Superimposition of the unsubstituted compounds (**x** series) is shown in Figure 1. It becomes apparent that the orientation of the heterocycle is different in the indane and the open ring class of compounds. The energy difference from the low energy conformation of the open ring compounds (**a** series) to the conformation which corresponds to the indane structure is approximately 3 kcal/mol. From the fact that the indane compounds are less active than the corresponding open ring compounds, it can be concluded that the cyclic conformation of the indane compounds (**b** series) is less appropriate for optimal interaction with the enzyme. The fact that the imidazolyl compounds (series **5**) are more active than the triazolyl compounds (series **6** and **7**) might be explained by the different atomic charges of the nitrogens (Table 1) being responsible for the interaction with the heme iron.

As P450 arom plays an important role in androgen metabolism it should not be inhibited by the title compounds to avoid accumulation of testosterone. Therefore the compounds were tested for inhibition of P450 arom (Table 1). Most imidazolyl compounds **5** inhibited P450 arom only in high concentrations of approximately 20 μM. As observed with P450 17, the triazole compounds **6** and **7** were even less active. The only compounds clearly more potent than the reference compound aminoglutethimide were the methoxy substituted phenylindanes **5bz** and **7bz**.

The most active inhibitiors of P450 17 rat and human enzyme compounds **5ax**, **5ay** were tested for reduction of the plasma testosterone concentration in male Sprague–Dawley rats (Table 2).



Scheme 1. Synthesis of the title compounds **5**, **6** and **7**. Method A: CsF, $Pd(PPh_3)_4$, DME, reflux 12 h; B: $NaBH_4$, THF, CH_3OH, rt 1 h; C: 1,1′-carbonyldiimidazole (CDI), THF, 80–90 °C, 3–4 days; D: 1,1′-carbonyldi(1,2,4-triazole) (CDT), THF, 80–90 °C, 1 day followed by 140–150 °C, 7 days.

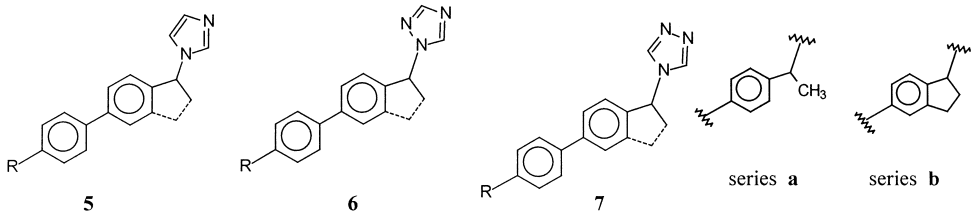
The two compounds were clearly superior to the reference compound ketoconazole. Compound **5ax** strongly inhibited testosterone concentration 2 h after application. As observed after ketoconazole, **5ax** led to a stimulation of the testosterone concentration above control after 6 h. This phenomenon has already been observed[11,15] and is probably due to hypothalamic pituitary feedback. In contrast to **5ax**, **5ay** reduced testosterone concentration to castration level after 2 h and still exhibits strong activity after 6 h.

Comparing the results of the present study with the data obtained for the correspondingly H, F or OCH_3 substituted imidazolylmethyl substituted biphenyls (Type **IV** compounds, Chart 1),[11] it becomes apparent that the introduction of a methyl group into the methylene spacer between imidazole and biphenyl moiety increases P450 17 inhibitory activity in both species. Ring closure leading to the corresponding phenylindanes, however, reduces inhibition of the target enzymes. The most active compound toward P450 17 rat enzyme (**5ay**) showed a marked in vivo activity. It reduced plasma testosterone concentration to a stronger extent than the corresponding imidazolylmethyl compound.[11] Thus, it has to be concluded that **5ay** might be a new lead for the development of a drug candidate for the treatment of prostate cancer.

Experimental

Melting points were determined on a Kofler melting point Thermopan apparatus and are uncorrected. IR Spectra were recorded on a Perkin–Elmer 398 Infrared spectrometer as KBr disks or films as indicated. ^1H NMR spectra were measured on a Bruker AM-400 instrument (400 MHz). Chemical shifts are given in parts per million, and TMS was used as an internal standard for spectra obtained in $CDCl_3$. All J values are given in Hz. Purity was checked by GC–MS on HP G1800A GCD system. Reagents and solvents were used as obtained from commercial suppliers without further purification. Column chromatography was performed using silica-gel 60 (50–200 μm), and reaction progress was determined by TLC analysis on ALUGRAM® SILG/UV_{254} (Macherey and Nagel). Boronic acids and bromoaryls used as starting materials were commercially obtained (Lancaster, Fluka, Acros).

Table 1. Structures, atomic charges and inhibition of steroidogenic P450 enzymes (P450 17, P450 arom) by heterocyclic substituted biphenyls and phenylindanes



5 **6** **7**

Compound no.	R	a.c.[b] N1/N3/N4	P450 17 (rat)			P450 17 (human)			P450 arom (human)		
			% Inhibition[c]	IC_{50} [μM][d]	r.p.[e]	% Inhibition[g]	IC_{50} [μM][d]	r.p.[e]	% Inhibition[h]	IC_{50} [μM][d]	r.p.[i]
5ax	H	−0.204		1.2	56		0.17	4.4		22	0.84
5ay	F	−0.205		0.54	124		0.24	3.1		21	0.88
5az	OCH_3	−0.206		2.51	27		1.8	0.41		25	0.74
5bx	H	−0.205		2.1	32		0.25	3.0		20	0.93
5by	F	−0.204		1.7	39		1.11	0.67		21	0.88
5bz	OCH_3	−0.205		10	6.7		2.1	0.35		5.1	3.6
6ax	H	−0.221	n.i.[f]			48			18		
6ay	F	−0.219		11	6.1	37			21		
6az	OCH_3	−0.220	n.i.			30			22		
6bx	H	−0.220		42	1.6	35			25		
6by	F	−0.221		24	2.8	30			26		
6bz	OCH_3	−0.222	41			11				26	0.71
7ax	H	−0.144	n.i.			n.i.			20		
7ay	F	−0.144	n.i.			12			7.1		
7az	OCH_3	−0.144	n.i.			n.i.			17		
7bx	H	−0.142	n.i.			n.i.			35		
7by	F	−0.141	n.i.			n.i.				27	0.68
7bz	OCH_3	−0.142	n.i.			n.i.				3.7	5.0
III				0.18	372		0.04	19			
IV				2.6	26		0.31	2.4			
KTZ[a]				67	1		0.74	1			
AG[a]										18.5	1

[a]**KTZ**: ketoconazole; **AG**: aminoglutethimide; **III**, **IV**: see Chart 1.
[b]a.c.: atomic charges; N3: for imidazolyl compound (series **5**); N4: for 1,2,4-triazol-1-yl compounds (series **6**); N1: for 1,2,4-triazol-4-yl compounds (series **7**).
[c]Concentration of inhibitors for rat enzyme: 125 μM, concentration of progesterone (substrate): 25 μM.
[d]Concentration of inhibitors required to give 50% inhibition. The given values are mean values of at least two experiments. The deviations were within ±10%.
[e]r.p.: relative potency (against ketoconazole (**KTZ**), rp KTZ = 1).
[f]n.i.: no inhibition: values ≤10%.
[g]Concentration of inhibitors for human enzyme: 2.5 μM, concentration of progesterone (substrate): 25 μM.
[h]Human placental microsomes, concentration of inhibitors: 25 μM, concentration of testosterone (substrate): 2.5 μM, (1β,2β-^{3}H)-testosterone: 0.225 μCi.
[i]r.p.: relative potency (against aminoglutethimide (**AG**): r.p. AG = 1).

Method A. 5-Phenyl-1-indanone (3bx). To a stirred mixture of benzeneboronic acid (**1x**, 0.25 g, 2.01 mmol), 5-bromo-1-indanone (**2b**, 0.4 g, 1.90 mmol), and powdered CsF (0.61 g, 4.0 mmol) in 20 mL of DME (dimethoxyethane) was added 68 mg (58.8 μmol) of $Pd(PPh_3)_4$. Under nitrogen the reaction mixture was refluxed until no more starting material was detected by TLC. The reaction mixture was worked up with 1 N HCl and extracted three times with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4 and the solvent was removed in vacuo. The crude product was purified by silica gel column chromatography using 4% EtOAc/petroleum ether as eluent to give 0.38 g (91%) of **3bx** as a white solid: mp 103–105 °C; IR 3080, 2950, 1710, 1610, 1580, 1510 (vs)cm^{-1}; ^{1}H NMR ($CDCl_3$) 2.74–2.77 (t, J = 6.2 Hz, 2H, H2), 3.19–3.22 (t, J = 6.2 Hz, 2H, H3), 7.40–7.43 (m, 1H, Ar′-H, H4′), 7.47–7.50 (dd, J = 8.4 Hz, 2H, Ar′-H, H3′, H5′), 7.60–7.62 (d, J = 7.96 Hz, 1H, Ar-H, H6), 7.63–7.65 (dd, J = 8.4 Hz, 2H, Ar′-H, H2′, H6′), 7.68 (s, 1H, H4), 7.82–7.84 (d, J = 7.96 Hz, 1H, Ar-H, H7).

5-(4-Fluorophenyl)-1-indanone (3by). Compound **1y** (0.56 g, 4.0 mmol) gave 0.72 g (80%) of **3by** as white crystals: mp 91–93 °C; IR 3030, 2960, 1710, 1605, 1500 (vs)cm^{-1}; ^{1}H NMR ($CDCl_3$) 2.74–2.77 (t, J = 6.2 Hz, 2H, H2), 3.19–3.22 (t, J = 6.2 Hz, 2H, H3), 7.15–7.19 (dd, J = 8.84 Hz, 2H, Ar′-H, H2′, H6′), 7.54–7.57 (d, J = 7.96 Hz, 1H, Ar-H, H7), 7.58–7.62 (dd, J = 8.84 Hz, 2H, Ar′-H, H3′,H5′), 7.63 (s, 1H, H4), 7.81–7.83 (d, J = 7.96 Hz, 1H, Ar-H, H6).

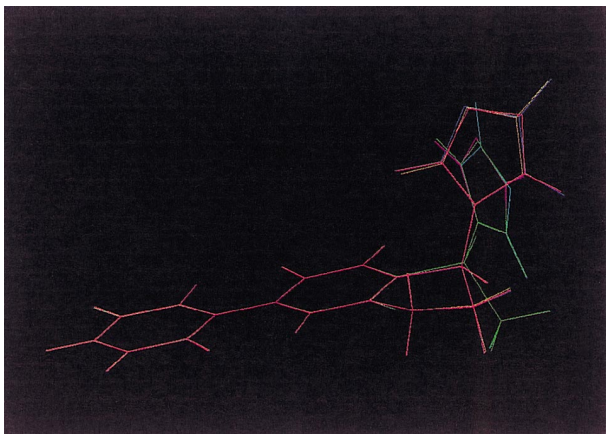


Figure 1. Superimposition of the title compounds (**x** series): indane compounds (**b** series, pink) show different orientation of their heterocycles compared to open ring compounds (**a** series, blue).

Table 2. Reduction of the plasma testosterone concentrations in Sprague–Dawley rats by select compounds[a]

Compound	Plasma testosterone level (ng/mL)	
	2 h	6 h
Control	4.54±1.58	0.94±0.77
KTZ	1.69±0.61[b]	3.13±1.73[b]
5ax	0.24±0.15[b]	4.11±1.94[b]
5ay	0.028±0.046[b]	0.34±0.27[c]

[a]All compounds were applied equimolar to 10 mg/kg KTZ (0.019 mmol/kg) intraperitoneally. Blood was taken by cardiac puncture. Testosterone plasma concentrations were determined by RIA. Each group consisted of 7–8 animals. Significant difference from control group (Wilcoxon); [b]$P < 0.01$; [c]$P < 0.05$.

Compounds **3ax**,[16] **3ay**,[17] **3az**[18] and **3bz**,[19] prepared by literature methods, provided spectral and analytical data as described.[16–19]

Method B. 5-Phenyl-1-indanol (4bx). A solution of $NaBH_4$ (120 mg, 3.17 mmol) in methanol (10 mL) was added dropwise to a solution of **3bx** (110 mg, 0.53 mmol) in THF (10 mL). The reaction mixture was stirred at room temperature for 1 h. Water was added and the solution was extracted three times with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4 and the solvent was removed in vacuo. The crude product was purified by recrystallization from diethyl ether and gave 92 mg (83%) of **4bx** as light brown crystals: mp 105–107 °C. IR 3400, 3020, 2960, 2870, 1615, 1600, 1570, 1480 (vs)cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.57 (s, 1H, OH), 1.97–2.05 (m, 1H, H2a), 2.50–2.59 (m, 1H, H2b), 2.84–2.92 (m, 1H, H3a), 3.09–3.16 (m, 1H, H3b), 5.28–5.31 (t, J = 5.32 Hz, 1H, H1), 7.32–7.36 (m, 1H, Ar′-H, H4′), 7.41–7.43 (d, J = 7.96 Hz, 1H, H6), 7.43–7.45 (d, J = 8.4 Hz, 1H, Ar′-H, H2′), 7.47–7.56 (m, 3H, Ar-H, H4, H7, Ar′-H, H6′), 7.56–7.58 (m, 2H, Ar′-H, H3′, H5′).

5-(4-Fluorophenyl)-1-indanol (4by). Compound **3by** (0.4 g, 1.17 mmol) gave 0.37 g (92%) of **4by** as white crystals: mp 100–102 °C; IR 3400, 3020, 2960, 2880, 1610, 1510, 1490 (vs)cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.76 (s, 1H, OH), 1.96–2.05 (m, 1H, H2a), 2.50–2.59 (m, 1H, H2b), 2.84–2.92 (m, 1H, H3a), 3.08–3.15 (m, 1H, H3b), 5.28–5.31 (t, J = 5.96 Hz, 1H, H1), 7.09–7.13 (dd, J = 8.84 Hz, 1H, Ar′-H, H2′, H6′), 7.41–7.42 (m, 2H, Ar-H, H4, H6), 7.47–7.49 (d, J = 8.4 Hz, 1H, Ar-H, H7), 7.51–7.54 (dd, J = 8.84 Hz, 2H, Ar′-H, H3′, H5′).

Compounds **4ax**,[20] **4ay**,[17] **4az**[17] and **4bz**,[19] prepared by literature methods, provided spectral and analytical data as described.[17,19,20]

Method C. 4-[1-(1*H*-Imidazolyl)ethyl]biphenyl (5ax). Compound **4ax** (178 mg, 0.9 mmol) and 300 mg (1.85 mmol) of CDI (1,1′-carbonyldiimidazole) in dry THF (20 mL) were stirred at 70 °C for 4 days. Water was added and the reaction mixture was extracted three times with CH_2Cl_2 (50 mL). The organic layer was washed with brine, dried over Na_2SO_4 and the solvent was removed in vacuo. The crude product was purified by silica gel column chromatography (CH_2Cl_2:CH_3OH: 19:1) and the resulting solid was recrystallized from *n*-hexane/ethyl acetate to give 130 mg (58%) of **5ax** as a light white solid: mp 102–103 °C. IR 3110, 3080, 3020, 2960, 2940, 1580, 1500, 1485 (vs)cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.90–1.91 (d, J = 7.04 Hz, 3H, CH_3), 5.38–5.43 (q, J = 7.08 Hz, 1H, CH), 6.97 (s, 1H, imidazole-H5), 7.11 (s, 1H, imidazole-H4), 7.21–7.23 (d, J = 8.4 Hz, 2H, Ar-H, H3, H5), 7.34–7.38 (m, 1H, Ar′-H, H4′), 7.42–7.46 (m, 2H, Ar′-H, H2′, H6′), 7.55–7.58 (m, 4H, Ar-H, H2, H6, Ar′-H, H3′, H5′), 7.64 (s, 1H, imidazole-H2); GC–MS m/z (M^+): 248.3 (calcd 248.3).

4′-Fluoro-4-[1-(1*H*-imidazolyl)ethyl]biphenyl (5ay). Compound **4ay** (200 mg, 0.93 mmol) gave 142 mg (61%) of **5ay** as a light white solid: mp 81–83 °C. IR 3110, 3050, 2950, 1605, 1500 (vs)cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.89–1.91 (d, J = 7.08 Hz, 3H, CH_3), 5.37–5.42 (q, J = 7.08 Hz, 1H, CH), 6.97 (s, 1H, imidazole-H5), 7.10 (s, 1H, imidazole-H4), 7.13–7.15 (d, J = 8.84 Hz, 2H, Ar-H, H3, H5), 7.20–7.22 (d, J = 8.4 Hz, 2H, Ar′-H, H2′, H6′), 7.50–7.53 (m, 4H, Ar-H, H2, H6, Ar′-H, H3′, H5′), 7.63 (s, 1H, imidazole-H2); GC–MS m/z (M^+): 266.3 (calcd 266.3).

4′-Methoxy-4-[1-(1*H*-imidazolyl)ethyl]biphenyl (5az). Compound **4az** (175 mg, 0.77 mmol) gave 170 mg (80%) of **5az** as a light white solid: mp 130–131 °C. IR 3100, 3040, 2960, 1610, 1580, 1500 (vs)cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.89–1.90 (d, J = 6.64 Hz, 3H, CH_3), 3.85 (s, 3H, OCH_3), 5.36–5.41 (q, J = 6.64 Hz, 1H, CH), 6.96–6.99 (m, 3H, Ar′-H, H3′, H5′, imidazole-H5), 7.10 (s, 1H, imidazole-H4), 7.18–7.20 (d, J = 7.96 Hz, 2H, Ar-H, H3, H5), 7.49–7.53 (dd, J = 8.84 Hz, 4H, Ar-H, H2, H6, Ar′-H, H2′, H6′), 7.63 (s, 1H, imidazole-H2); GC–MS m/z (M^+): 278.4 (calcd 278.4).

1-(1*H*-Imidazolyl)-5-phenylindane (5bx). Compound **4bx** (80 mg, 0.38 mmol) gave 60 mg (60%) of **5bx** as a light green oil. IR 3110, 3040, 2970, 2850, 1610, 1570, 1490 (vs)cm^{-1}; ^{1}H NMR ($CDCl_3$) 2.22–2.31 (m, 1H, H2a), 2.72–2.81 (m, 1H, H2b), 3.0–3.08 (m, 1H, H3a), 3.16–3.23

(m, 1H, H3b), 5.69–5.73 (t, $J=7.08$ Hz, 1H, H1), 6.88 (s, 1H, imidazole-H5), 7.09 (s, 1H, imidazole-H4), 7.17–7.19 (d, $J=7.96$ Hz, 1H, H7), 7.35–7.38 (m, 1H, Ar′-H, H4′), 7.43–7.47 (d, $J=7.96$ Hz, 2H, Ar′-H, H2′, H6′), 7.47 (s, 1H, Ar-H, H4), 7.55 (s, 1H, imidazole-H2), 7.57–7.60 (m, 3H, Ar-H, H6, Ar′-H, H3′, H5′); GC–MS m/z (M^+): 260.3 (calcd 260.3).

1-(1*H*-Imidazolyl)-5-(4-fluorophenyl)indane (5by). Compound **4by** (0.19 g, 0.81 mmol) gave 0.15 g (67%) of **5by** as a light brown oil. IR 3110, 3040, 2970, 2850, 1610, 1520, 1490 (vs)cm^{-1}; ^{1}H NMR ($CDCl_3$) 2.22–2.30 (m, 1H, H2a), 2.72–2.80 (m, 1H, H2b), 2.99–3.07 (m, 1H, H3a), 3.15–3.22 (m, 1H, H3b), 5.69–5.72 (t, $J=7.06$ Hz, 1H, H1), 6.87 (s, 1H, imidazole-H5), 7.10 (s, 1H, Ar-H, H4), 7.11–7.16 (dd, $J=8.84$ Hz, 2H, Ar′-H, H2′, H6′), 7.16–7.18 (d, $J=7.96$ Hz, 1H, Ar-H, H7), 7.39–7.41 (d, $J=7.96$ Hz, 1H, Ar-H, H6), 7.50 (s, 1H, imidazole-H4), 7.52–7.55 (dd, $J=8.84$ Hz, 2H, Ar′-H, H3′, H5′), 7.57 (s, 1H, imidazole-H2);GC–MS m/z (M^+): 278.3 (calcd 278.3).

1-(1*H*-Imidazolyl)-5-(4-methoxyphenyl)indane (5bz). Compound **4bz** (0.04 g, 0.17 mmol) gave 37 mg (77%) of **5bz** as white crystals: mp 130–131 °C; IR 3120, 3040, 2970, 2850, 1610, 1590, 1525, 1490 (vs)cm^{-1}; ^{1}H NMR ($CDCl_3$) 2.21–2.30 (m, 1H, H2a), 2.71–2.80 (m, 1H, H2b), 3.0-3.08 (m, 1H, H3a), 3.14–3.22 (m, 1H, H3b), 3.86 (s, 3H, OCH_3), 5.69–5.72 (t, $J=7.08$ Hz, 1H, H1), 6.88 (s, 1H, imidazole-H5), 6.98–7.00 (d, $J=8.84$ Hz, 2H, Ar′-H, H3′, H5′), 7.10 (s, 1H, imidazole-H4), 7.15–7.17 (d, $J=7.96$ Hz, 1H, Ar-H, H6), 7.41–7.43 (d, $J=7.96$ Hz, 1H, Ar-H, H7), 7.51 (s, 1H, Ar-H, H4), 7.55–7.54 (d, $J=8.84$ Hz, 2H, Ar′-H, H2′, H6′), 7.59 (s, 1H, imidazole-H2); GC–MS m/z (M^+): 290.4 (calcd 290.4).

Method D. 4-[1-(1*H*-Tri-1,2,4-azolyl)ethyl]biphenyl (6ax) and 4-[1-(4*H*-tri-1,2,4-azolyl)ethyl]biphenyl (7ax). Compound **4ax** (120 mg, 0.61 mmol) and 600 mg (3.7 mmol) of 1,1′-carbonyldi(1,2,4-triazole)(CDT) in dry THF (20 mL) were refluxed for 1 day. The solvent was removed by distillation and the residue heated at 140–150 °C for 7 days. Water was added and the reaction mixture was extracted three times with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4 and the solvent was removed in vacuo. The crude product was purified by silica gel column chromatography using CH_2Cl_2:CH_3OH (19:1) as eluent to give 75 mg (50%) of **6ax** as a light white solid: mp 68–70 °C. IR 3105, 3030, 2990, 2940, 1500 (versus) cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.97–1.99 (d, $J=7.08$ Hz, 3H, CH_3), 5.58–5.64 (q, $J=7.08$ Hz, 1H, CH), 7.33–7.35 (d = 7.96 Hz, 2H, Ar′-H, H3′, H5′), 7.43–7.46 (m, 2H, Ar′-H, H4′, triazole-H5), 7.56–7.58 (d, $J=8.4$ Hz, 2H, Ar-H, H2, H6), 7.59–7.61 (d, $J=8.4$ Hz, 2H, Ar′-H, H2′, H6′), 8.0–8.02 (d, $J=8.4$ Hz, 2H, Ar-H, H3, H5), 8.11 (s, 1H, triazole-H3); GC–MS m/z (M^+): 249.3 (calcd 249.3) and 60 mg (40%) of **7ax** as white crystals: mp 66–68 °C. IR 3100, 3015, 2990, 2940, 1530, 1485 (vs)cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.95–1.97 (d, $J=7.08$ Hz, 3H, CH_3), 5.44–5.49 (q, $J=7.08$ Hz, 1H, CH), 7.25–7.27 (m, 2H, Ar′-H, H3′, H5′), 7.36–7.40 (m, 1H, Ar′-H, H4′), 7.44–7.48 (m, 2H, Ar-H, H2, H6), 7.56–7.58 (m, 2H, Ar′-H, H2′, H6′), 7.60–7.62 (d, $J=8.4$ Hz, 2H, Ar-H, H3, H5), 8.23 (s, 2H, triazole-H2, triazole-H5); GC–MS m/z (M^+): 249.3 (calcd 249.3).

4′-Fluoro-4-[1-(1*H*-tri-1,2,4-azolyl)ethyl]biphenyl (6ay) and 4′-fluoro-4-[1-(4*H*-tri-1,2,4-azolyl)ethyl]biphenyl (7ay). Compound **4ay** (360 mg, 1.67 mmol) gave 177 mg (40%) of **6ay** as a light white solid: mp 60–62 °C. IR 3100, 3060, 2950, 2940, 1600, 1500 (vs)cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.96–1.98 (d, $J=7.08$ Hz, 3H, CH_3), 5.57–5.63 (q, $J=7.08$ Hz, 1H, CH), 7.10–7.12 (d, $J=8.84$ Hz, 2H, Ar-H, H3, H5), 7.32–7.34 (d, $J=8.4$ Hz, 2H, Ar′-H, H2′, H6′), 7.50–7.52 (d, $J=8.84$ Hz, 2H, Ar-H, H2, H6), 7.53–7.55 (d, $J=8.4$ Hz, 2H, Ar′-H, H3′, H5′), 7.99 (s, 1H, triazole-H5), 8.10 (s, 1H, triazole-H3); GC–MS m/z (M^+): 267.3 (calcd 267.3) and 101 mg (23%) of **7ay** as white crystals: mp 122–124 °C. IR 3100, 3030, 2980, 1600, 1515, 1500 (vs)cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.96–1.98 (d, $J=7.08$ Hz, 3H, CH_3), 5.49–5.54 (q, $J=7.08$ Hz, 1H, CH), 7.12–7.16 (d, $J=8.84$ Hz, 2H, Ar-H, H3, H5), 7.26–7.28 (d, $J=7.96$ Hz, 2H, Ar′-H, H2′, H6′), 7.51–7.54 (d, $J=8.84$ Hz, 2H, Ar-H, H2, H6), 7.56–7.58 (d, $J=7.96$ Hz, 2H, Ar′-H, H3′, H5′), 8.34 (s, 2H, triazole-H2, triazole-H5); GC–MS m/z (M^+): 267.3 (calcd 267.3).

4′-Methoxy-4-[1-(1*H*-tri-1,2,4-azolyl)ethyl]biphenyl (6az) and 4′-methoxy-4-[1-(4*H*-tri-1,2,4-azolyl)ethyl]biphenyl (7az). Compound **4az** (140 mg, 0.61 mmol) gave 77 mg (45%) of **6az** as a light white solid: mp 128–130 °C. IR 3100, 3030, 2960, 2940, 1610, 1500 (vs)cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.96–1.98 (d, $J=7.08$ Hz, 3H, CH_3), 3.85 (s, 3H, OCH_3), 5.57–5.62 (q, $J=7.08$ Hz, 1H, CH), 6.97–6.99 (d, $J=8.84$ Hz, 2H, Ar′-H, H3′, H5′), 7.31–7.33 (d, $J=8.4$ Hz, 2H, Ar-H, H2, H6), 7.50–7.52 (d, $J=8.84$ Hz, 2H, Ar′-H, H2′, H6′), 7.54–7.56 (d, $J=8.4$ Hz, 2H, H3, H5), 7.99 (s, 1H, triazole-H5), 8.10 (s, 1H, triazole-H3); GC–MS m/z (M^+): 279.3 (calcd 279.3) and 38 mg (22%) of **7az** as white crystals: mp 208–210 °C. IR 3100, 3020, 2960, 1650, 1600, 1500 (vs)cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.93–1.95 (d, $J=7.08$ Hz, 3H, CH_3), 3.85 (s, 3H, OCH_3), 5.41–5.46 (q, $J=7.08$ Hz, 1H, CH), 6.97–6.99 (d, $J=8.84$ Hz, 2H, Ar′-H, H3′, H5′), 7.21–7.23 (d, $J=8.4$ Hz, 2H, Ar-H, H2, H6), 7.49–7.51 (d, $J=8.84$ Hz, 2H, Ar′-H, H2′, H6′), 7.55–7.57 (d, $J=8.4$ Hz, 2H, H3, H5), 8.20 (s, 2H, triazole-H2, triazole-H5); GC–MS m/z (M^+): 279.3 (calcd 279.3).

5-Phenyl-1-(1*H*-tri-1,2,4-azolyl)indane (6bx) and 5-phenyl-1-(4*H*-tri-1,2,4-azolyl)indane (7bx). Compound **4bx** (400 mg, 1.9 mmol) gave 227 mg (46%) of **6bx** as green solid: mp 109–111 °C. IR 3110, 3030, 2990, 2940, 2860, 1610, 1540, 1500 (vs)cm^{-1}; ^{1}H NMR ($CDCl_3$) 2.45–2.53 (m, 1H, H2a), 2.73–2.82 (m, 1H, H2b), 3.04–3.11 (m, 1H, H3a), 3.21–3.28 (m, 1H, H3b), 5.95–5.98 (t, $J=6.2$ Hz, 1H, H1), 7.25–7.27 (d, $J=7.96$ Hz, 1H, H7), 7.35–7.39 (m, 1H, Ar′-H, H4′), 7.43–7.49 (m, 3H, Ar-H, H6, Ar′-H, H3′, H5′), 7.57–7.60 (m, 3H, Ar-H, H4, Ar′-H, H2′, H6′), 8.01 (s, 1H, triazole-H5), 8.05 (s, 1H, triazole-H3); GC–MS m/z (M^+): 261.3 (calcd 261.3) and 57 mg (11%) of **7bx** as a light green oil. IR 3120, 3040, 2980, 2960, 1630, 1610, 1560, 1520 (vs)cm^{-1}; ^{1}H NMR

($CDCl_3$) 2.20–2.30 (m, 1H, H2a), 2.78–2.87 (m, 1H, H2b), 3.05–3.12 (m, 1H, H3a), 3.18–3.26 (m, 1H, H3b), 5.78–5.81 (t, $J=6.2$ Hz, 1H, H1), 7.20–7.22 (d, $J=7.96$ Hz, 1H, H7), 7.36–7.41 (m, 1H, Ar′-H, H4′), 7.44–7.51 (m, 3H, Ar-H, H6, Ar′-H, H3′, H5′), 7.58–7.60 (m, 3H, Ar-H, H4, Ar′-H, H2′, H6′), 8.17 (s, 2H, triazole-H2, triazole-H5); GC–MS m/z (M^+): 261.3 (calcd 261.3).

5-(4-Fluorophenyl)-1-(1*H*-tri-1,2,4-azolyl)indane (6by) and 5-(4-fluorophenyl)-1-(4*H*-tri-1,2,4-azolyl)indane (7by). Compound **4by** (235 mg, 1.0 mmol) gave 143 mg (50%) of **6by** as light white solid: mp 80–82 °C; IR 3110, 3040, 2960, 1600, 1500 (vs)cm^{-1}; ^1H NMR ($CDCl_3$) 2.46–2.54 (m, 1H, H2a), 2.74–2.82 (m, 1H, H2b), 3.04–3.11 (m, 1H, H3a), 3.21–3.29(m, 1H, H3b), 5.96–5.99 (t, $J=7.48$ Hz, 1H, H1), 7.11–7.16 (m, 2H, H2′, H6′), 7.25–7.27 (d, $J=7.96$ Hz, 1H, Ar-H, H7), 7.42–7.44 (d, $J=7.96$ Hz, 1H, Ar-H, H6), 7.51–7.57 (m, 3H, Ar-H, H4, Ar′-H, H3′, H5′), 8.04 (s, 1H, triazole-H5), 8.13 (s, 1H, triazole-H3); GC–MS m/z (M^+): 279.3 (calcd 279.3) and 32 mg (11%) of **7by** as white solid: mp 153–155 °C; IR 3120, 2980, 2960, 1600, 1580, 1530, 1490 (vs)cm^{-1}; ^1H NMR ($CDCl_3$) 2.16–2.30 (m, 1H, H2a), 2.79–2.87 (m, 1H, H2b), 3.04–3.12 (m, 1H, H3a), 3.18–3.26 (m, 1H, H3b), 5.79–5.80 (t, $J=7.12$ Hz, 1H, H1), 7.12–7.17 (m, 2H, H2′, H6′), 7.19–7.27 (d, $J=7.96$ Hz, 1H, Ar-H, H7), 7.44–7.46 (d, $J=7.96$ Hz, 1H, Ar-H, H6), 7.53–7.56 (m, 3H, Ar-H, H4, Ar′-H, H3′, H5′), 8.18 (s, 2H, triazole-H2, triazole-H5); GC–MS m/z (M^+): 279.3 (calcd 279.3).

5-(4-Methoxyphenyl)-1-(1*H*-tri-1,2,4-azolyl)indane (6bz) and 5-(4-methoxyphenyl)-1-(4*H*-tri-1,2,4-azolyl)indane (7bz). Compound **4bz** (200 mg, 0.83 mmol) gave 142 mg (58%) of **6bz** as a light white solid: mp 134–136 °C. IR 3110, 3020, 2960, 2940, 1610, 1590, 1510, 1500 (vs)cm^{-1}; ^1H NMR ($CDCl_3$) 2.43–2.51 (m, 1H, H2a), 2.71–2.80 (m, 1H, H2b), 3.02–3.09 (m, 1H, H3a), 3.19–3.27 (m, 1H, H3b), 3.86 (s, 3H, OCH_3), 5.93–5.96 (m, 1H, H1), 6.97–7.00 (d, $J=8.84$ Hz, 2H, Ar′-H, H3′, H5′), 7.23–7.25 (d, $J=7.96$ Hz, 1H, Ar-H, H6), 7.43–7.45 (d, $J=7.96$ Hz, 1H, Ar-H, H7), 7.51–7.53 (m, 3H, Ar-H, H4, Ar′-H, H2′, H6′), 8.00 (s, 1H, triazole-H3), 8.02 (s, 1H, triazole-H5); GC–MS m/z (M^+): 291.4 (calcd 291.4) and 51 mg (21%) of **7bz** as a light white solid: mp 139–140.5 °C. IR 3105, 3020, 2970, 2940, 1610, 1590, 1520, 1490 (vs)cm^{-1}; ^1H NMR ($CDCl_3$) 2.21–2.29 (m, 1H, H2a), 2.78–2.87 (m, 1H, H2b), 3.04–3.11 (m, 1H, H3a), 3.17–3.25 (m, 1H, H3b), 3.86 (s, 3H, OCH_3), 5.80–5.83 (t, $J=6.64$ Hz, 1H, H1), 6.99–7.01 (d, $J=8.84$ Hz, 2H, Ar′-H, H3′, H5′), 7.18–7.20 (d, $J=7.96$ Hz, 1H, Ar-H, H6), 7.45–7.47 (d, $J=7.96$ Hz, 1H, Ar-H, H7), 7.52–7.54 (m, 3H, Ar-H, H4, Ar′-H, H2′, H6′), 8.22 (s, 2H, triazole-H2, triazole-H5); GC–MS m/z (M^+): 291.4 (calcd 291.4).

Biological methods

Enzyme preparations and assays. The enzymes were prepared according to described methods: human and rat testicular P450 17[14] and human placental P450 arom.[21] Enzyme assays were performed as described: human P450 17,[11] rat P450 17[14] and P450 arom.[21]

Determination of plasma testosterone concentration. Tests were performed with adult male Sprague–Dawley rats (each group consisted of 7–8 animals). All compounds were dissolved in 0.1 N HCl and administered once i.p. equimolar to 10 mg/kg ketoconazole (0.019 mmol/kg). Blood samples were taken by cardiac puncture under diethyl ether anesthesia after 2 and 6 h. Plasma testosterone values were determined by commercially available RIA and are given in ng/mL plasma±standard deviation.

Molecular modeling

HyperChem molecular modeling software[22] was used to build and minimize the structures of the title compounds. Molecular mechanics calculations employed the MM+ force field[23] and the structures were refined using a conjugate gradient (Polak-Ribiere) method. Conformations were optimized by molecular dynamics simulations using the heating-cooling-heating procedure.[24] Each molecule was heated several times to 1000 K and then cooled down to 0 K (5, 10, 5 ps). Between each cycle, the molecule was reminimized using the MM+ force field and the procedure was iterated until it provided the minimum energy conformation. Molecular Similarity fitting operation was performed between two molecules, matching the pairs of atoms, using energy-minimized **5ax** as a template and C1, C3, CH_2 or C5, C7, C1 as fit atoms for biphenyl and indane compounds, respectively (Fig. 1). The charges of compounds were obtained, after minimization, by the semiempirical CNDO approximation.[25]

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