European Journal of Medicinal Chemistry 44 (2009) 2765–2775

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Novel CYP17 inhibitors: Synthesis, biological evaluation, structure–activity relationships and modelling of methoxy- and hydroxy-substituted methyleneimidazolyl biphenyls

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ARTICLE INFO

Article history:
Received 30 May 2008
Received in revised form
17 November 2008
Accepted 8 January 2009
Available online 19 January 2009

Keywords:
Prostate cancer
Androgens
17α-Hydroxylase-17,20-lyase (CYP17)
inhibitors
Steroidomimetics
CYP3A4
CYP11B1

ABSTRACT

Recently, the steroidal CYP17 inhibitor Abiraterone entered phase II clinical trial for the treatment of androgen-dependent prostate cancer. As 17α-hydroxylase-17,20-lyase (CYP17) catalyzes the last step in androgen biosynthesis, inhibition of this target should affect not only testicular but also adrenal androgen formation. Therefore CYP17 inhibitors should be advantageous over existing therapies, for example with GnRH analogues. However, steroidal drugs are known for side effects which are due to affinities for steroid receptors. Therefore we decided to synthesize non-steroidal compounds mimicking the natural CYP17 substrates pregnenolone and progesterone. The synthesis and biological evaluation of a series of 15 novel and highly active non-steroidal CYP17 inhibitors are reported. The compounds were prepared via Suzuki-cross-coupling, *Grignard* reaction and CDI-assisted S_Nt-reaction with imidazole and their inhibitory activity was examined with recombinant human CYP17 expressed in *Escherichia coli*. Promising compounds were further tested for their selectivity against the hepatic enzyme CYP3A4 and the glucocorticoid-forming enzyme CYP11B1. All compounds turned out to be potent CYP17 inhibitors. The most active compounds **7** and **8** were much more active than Ketoconazole showing activity comparable to Abiraterone (IC_{50} values of 90 and 52 nM vs. 72 nM). Most compounds also showed higher selectivities than Ketoconazole, but turned out to be less selective than Abiraterone. Docking studies using our CYP17 protein model were performed with selected compounds to study the interactions between the inhibitors and the amino acid residues of the active site.

1. Introduction

Prostate cancer (PC) is the most prevalent cancer in men in the US and Europe [1]. Since about 80% of patients with PC have androgen-dependent disease and respond to hormonal ablation, the presently used treatment is surgical castration (orchidectomy) or its medical equivalent, the application of gonadotropin-releasing hormone (GnRH) analogs to suppress testicular androgen biosynthesis [2]. However, only testicular production of androgens is affected by these strategies, the adrenal formation of androstendione is not and even after 3 months treatment with a GnRH agonist, prostate levels of testosterone and dihydrotestosterone are still about 25 and 10%, respectively [3]. Therefore, there is frequent combination with anti-androgens to counteract the stimulatory effect of androgens on the androgen receptor [4]. However, it is speculated that due to mutations in the androgen receptor, anti-androgens might be recognized as agonists [5,6], making this so-called "combined androgen blockade" therapy not suitable for all patients.

A promising novel target for the treatment of prostate cancer is 17α-hydroxylase-17,20-lyase (CYP17), the cytochrome b_5 modulated key enzyme [7] for the biosynthesis of androgens, catalyzing the 17α-hydroxylation of pregnenolone and progesterone and the subsequent cleavage of the C 20,21-acetyl group to yield the corresponding androgens dehydroepiandrosterone and androstendione (Fig. 1) [8]. Proof of principle was achieved by the antimycotic Ketoconazole, which clinically turned out to be a good adjuvant therapeutic capable of reducing testosterone levels through unspecific inhibition of CYP17 [9,10]. Nevertheless, the side

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doi:10.1016/j.ejmech.2009.01.002

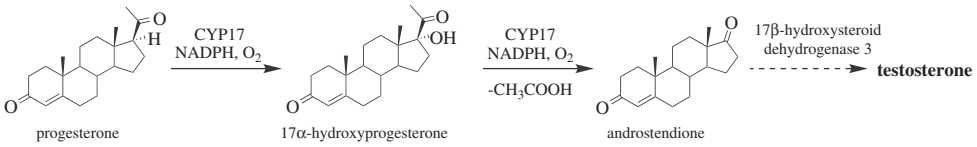


Fig. 1. The role of CYP17 in androgen biosynthesis.

effects it showed were the reason why it was not generally accepted [4]. These drawbacks motivated us and others to look for more active and selective CYP17 inhibitors (for reviews see: Refs. [11–16]). Recently, the steroidal CYP17 inhibitor Abiraterone (Fig. 2) passed phase II clinical trials showing high activity in post-docetaxel castration refractory PC patients and seems to have no dose-limiting toxicity [17].

In previous works, we described novel in vitro and in vivo active steroidal [18–22] and non-steroidal [22–35] CYP17 inhibitors. Important for the mode of action of these compounds is a nitrogen-bearing heterocycle which is capable of complexing the heme iron of the enzyme. Very recently we demonstrated that some imidazole-methyl substituted biphenyls designed as AC-ring steroidal mimetics are good CYP17 inhibitors showing moderate selectivity toward other CYP enzymes [32].

In this work, in order to further increase the inhibitory activity of these compounds, different substitution patterns of methoxy- and hydroxy-groups in the A-ring and further selected functional groups in the A- and C-ring were examined. Methyl and ethyl substituents were introduced into the methylene bridge between the biphenyl moiety and the imidazole ring, as we found in previous works [30], that these substituents increase inhibitory potency.

In the following we report about the synthesis of compounds **1**–**15** (Table 1) and the evaluation of their inhibitory activities toward CYP17 and, for reasons of selectivity, the hepatic enzyme CYP3A4 and the glucocorticoid-forming enzyme CYP11B1. Furthermore molecular modelling studies were performed with selected compounds.

2. Chemistry

The syntheses of compounds **1**–**15** are shown in Schemes 1 and 2. Regarding the functional groups attached to the A-ring, the substances can be divided in alkoxy- and hydroxy-substituted compounds. In case of the methoxy- and ethoxy-substituted compounds **1**, **2** and **9**–**12** (Scheme 1), commercially available substituted phenylboronic acids were coupled to bromopropiophenone in a *Suzuki*-reaction [36] yielding the ketones **9b**–**12b**, and were subsequently reduced with $NaBH_4$ to the corresponding secondary alcohols **1a**, **2a** and **9a**–**12a**. The ketones **1b** and **2b** were commercially available.

The hydroxy-substituted compounds **3**–**8** and **13**–**15** (Scheme 2) were also prepared via *Suzuki*-cross-coupling reaction using phenylboronic acids carrying the carbonyl function and substituted bromophenols to yield the ketones **3b**–**8b**, **13c**–**14c** and **15b**. Most of the bromophenols (**3d**, **4d**, **13d**–**15d**) were commercially available. Demethylation of bromoveratrole and 1-bromo-3,5-dimethoxybenzene was achieved with BBr_3 (Method A) to yield **5d** and **6d**. The introduction of the ethyl substituent at the methylene bridge between the biphenylic core and the imidazole was performed by *Grignard* reaction, yielding the desired secondary alcohols **3a**–**8a** and **13a**–**15a**.

All these secondary alcohols **1a**–**15a** were subjected to a S_N1 reaction with *N*,*N*′-carbonyldiimidazole (CDI) to give the imidazole-substituted compounds **1**–**15** as racemates [37].

The phenolic OH-groups had to be silyl-protected before the *Grignard* reaction. In most cases this synthetic step was performed before the Suzuki-reaction, as the chromatographic purification after the cross-coupling was easier with the protected compounds. For the final deprotection of the silylated compounds, TBAF was used as standard reagent.

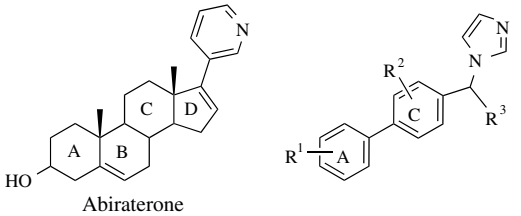
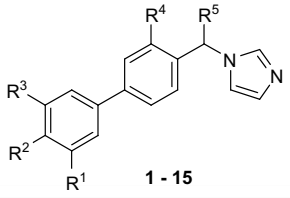


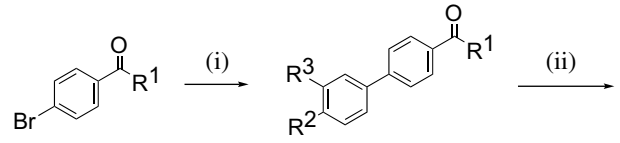
Fig. 2. Schematic presentation of Abiraterone and the scaffold of our biaryl inhibitors.

Table 1
Inhibition of CYP17 by compounds **1**–**15**.

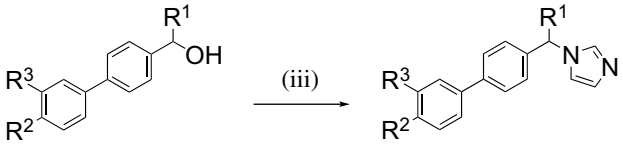


Comp.	Structures					CYP17		
	R^1	R^2	R^3	R^4	R^5	% Inhibition[a]		IC_{50}[b] [nM]
						0.2 μM	2 μM	
Ref1[c]	H	OH	H	H	H	1	32	
1	H	OMe	H	H	Me	9	40	
2	OMe	H	H	H	Me	8	59	
3	H	OH	H	H	Et	27	80	231
4	OH	H	H	H	Et	55	89	164
5	OH	OH	H	H	Et	56	91	152
6	OH	H	OH	H	Et	48	90	195
7	H	OH	H	F	Et	64	94	90
8	OH	OH	H	F	Et	69	95	52
9	H	OMe	H	H	Et	2	36	
10	OMe	H	H	H	Et	31	83	188
11	OMe	OMe	H	H	Et	9	58	
12	H	OEt	H	H	Et	3	25	
13	Me	OH	Me	H	Et	28	78	379
14	Me	OH	H	H	Et	45	89	261
15	Cl	OH	H	H	Et	44	89	217
KTZ[d]								2780
ABT[d]								72

[a] Concentration of progesterone (substrate): 25 μM; standard deviations were within <±5%.
[b] Concentration of inhibitors required to give 50% inhibition. The given values are mean values of at least three experiments. The deviations were within ±10%.
[c] From Ref. [32]; the IC_{50} value of 0.31 μM cited therein was obtained using a different source of the enzyme: human testicular microsoma.
[d] **KTZ**: Ketoconazole, **ABT**: Abiraterone.



1b: R^1= Me, R^2= OMe, R^3= H
2b: R= Me, R^2= H, R^3= OMe
9b: R^1= Et, R^2= OMe, R^3= H
10b: R^1= Et, R^2= H, R^3= OMe
11b: R^1= Et, R^2= R^3= OMe
12b: R^1= Et, R^2= OEt, R^3= H



1a: R^1= Me, R^2= OMe, R^3= H
2a: R^1= Me, R^2= H, R^3= OMe
9a: R^1= Et, R^2= OMe, R^3= H
10a: R^1= Et, R^2= H, R^3= OMe
11a: R^1= Et, R^2= R^3= OMe
12a: R^1= Et, R^2= OEt, R^3= H

1: R^1= Me, R^2= OMe, R^3= H
2: R^1= Me, R^2= H, R^3= OMe
9: R^1= Et, R^2= OMe, R^3= H
10: R^1= Et, R^2= H, R^3= OMe
11: R^1= Et, R^2= R^3= OMe
12: R^1= Et, R^2= OEt, R^3= H

Scheme 1. Reagents and conditions: (i) $R^2R^3C_6H_3B(OH)_2$, Na_2CO_3, $Pd(PPh_3)_4$, toluene/MeOH/H_2O, 70 °C, 5 h; (ii) $NaBH_4$, MeOH, reflux, 2 h; (iii) CDI, NMP, 170 °C, 7 h.

3. Results

3.1. Biological results

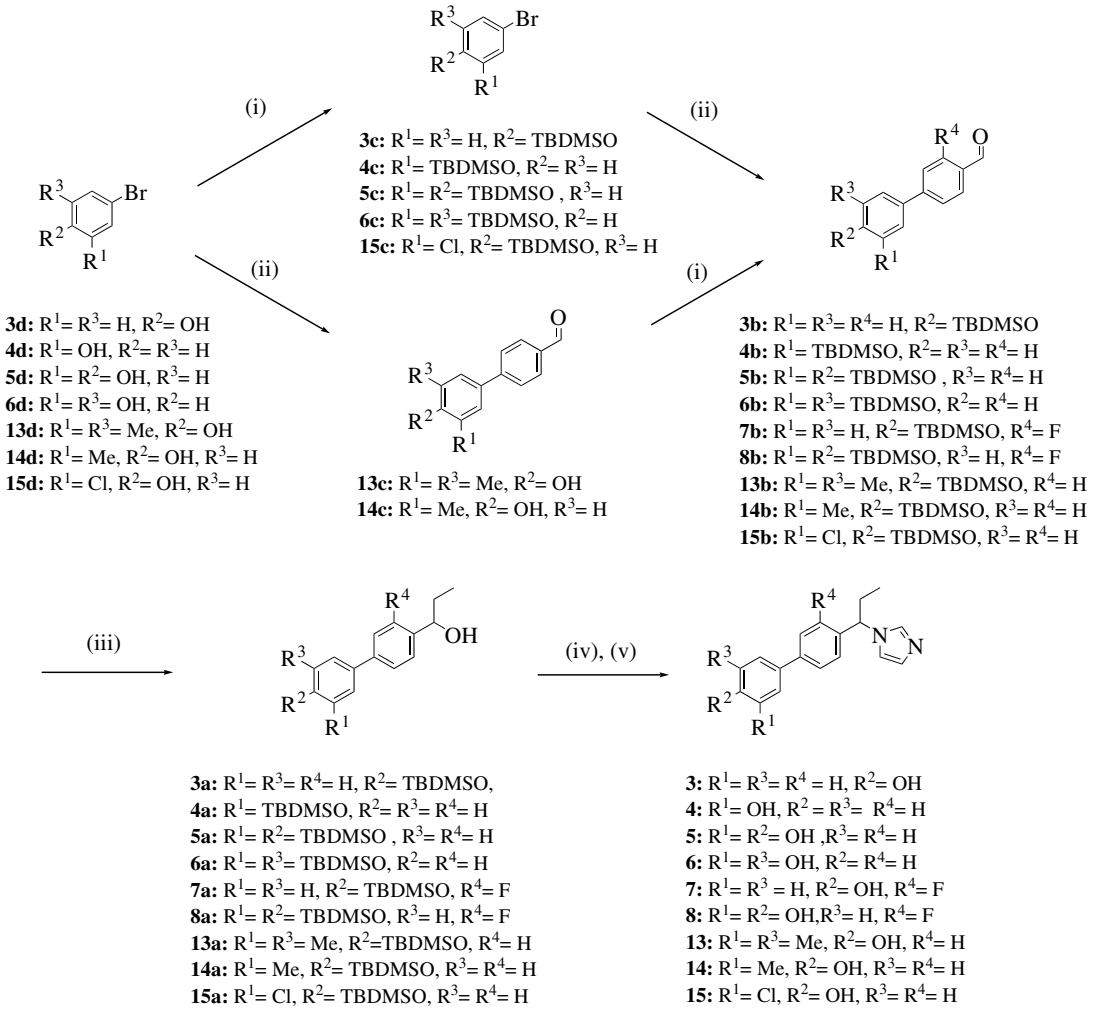
Inhibition of human CYP17 was determined by performing our previously described assay [33] at inhibitor concentrations of 0.2 and 2 μM. In case of the most potent inhibitors IC_{50} values were determined. As source of human CYP17, our *Escherichia coli* system [38] stably expressing human CYP17 and NADPH-P450 reductase was used. After homogenisation the 50,000 g sediment was incubated with progesterone (25 μM) as substrate and NADPH as previously described [27]. Separation of the product was accomplished by HPLC using UV detection.

The inhibitory activities of compounds **1**–**15** and the reference compounds Abiraterone, Ketoconazole and **Ref1** [32] toward human CYP17 are shown in Table 1. The compounds can be divided in two classes according to the substituents at the A-ring, namely hydroxy and methoxy derivatives and also in two classes regarding substitution at the methylene bridge, in methyl and ethyl bearing compounds. All compounds were tested as racemates and showed inhibitory activity. The methoxy-substituted compounds turned out to be weaker inhibitors compared to the corresponding hydroxy analogues. An exception to this is the 3-OCH_3 compound **10** which showed a similar high activity than the corresponding hydroxy compound **4** (IC_{50} = 188 nM and 164 nM). Comparing **10** which bears an ethyl group at the methylene bridge with the correspondingly substituted methyl compound **2** clearly showed the significance of the alkyl substitution in this position, which we already have seen with similar compounds [30,32,34,39]. Furthermore it is striking that methoxy substitution in para position (R^2) is not tolerated as the corresponding compounds **1**, **9** and **11** showed little activities.

The hydroxy compounds **3**–**8** and **13**–**15** showed very high inhibition (IC_{50} = 379–52 nM) with up to fifty fold better IC_{50} values than the reference Ketoconazole (IC_{50} = 2780 nM). They also turned out to be much more active than **Ref1** which is certainly due to the ethyl group at the methylene linker. The additional introduction of substituents in compound **3** led to interesting findings. In case of the A-ring, substitution with another OH group is favourable (**5**), while CH_3 or Cl groups did not increase activity (**13**–**15**). Introduction of an F in the C-ring, however, increased the potency and led to the most active inhibitors of this study, compounds **7** and **8** (IC_{50} = 90 and 52 nM), the latter even exceeding Abiraterone (IC_{50} = 72 nM).

Regarding selectivity against other CYP enzymes, most compounds were tested for inhibition of the hepatic enzyme CYP3A4 at concentrations of 1 and 10 μM. This enzyme is involved in the metabolism of 50% of the drugs. Its inhibition leads to drug–drug interactions by prolonging the half-lives of other co-administered drugs. All of the tested compounds showed inhibition of CYP3A4. The ones carrying only one hydroxy substituent at the A-ring (**Ref1** and compounds **3**, **4**, **7**; IC_{50} > 100 nM, data shown in Supplementary material) were less potent than Ketoconazole (IC_{50} = 72 nM), which means they are more selective than the reference. The methoxy-substituted compounds **9**, **10** and **11** were even more selective (IC_{50} > 200 nM), however, not reaching Abiraterone (IC_{50} = 2704 nM).

Additionally, the most promising compounds were tested for inhibition of the steroidogenic CYP enzyme CYP11B1, which is catalyzing the key step in glucocorticoid biosynthesis. For the assay [40], V79MZh11B1 cells expressing human CYP11B1 were used and the compounds were tested at concentrations 0.2 and 2 μM. While compounds **3**, **4**, **6**, **7**, **14** and **15** showed high inhibition of this enzyme at both concentrations (>89% at 0.2 μM and >95% at 2.0 μM, data shown in Supplementary material), compounds **5**, **8** and **13** exhibited less inhibitory activity toward this enzyme (38–51% at 0.2 μM). Interestingly, in contrast to the inhibition of CYP3A4, here the compounds with two vicinal OH-groups showed a very high selectivity and were better than Ketoconazole (61% at 0.2 μM). However, they did not reach Abiraterone (IC_{50} = 1608 nM). Because of this lack of selectivity, the compounds were not further tested for inhibition of other steroidogenic CYP enzymes like CYP11B2 and CYP19.



Scheme 2. Reagents and conditions: (i) TBDMSCl, CH_2Cl_2, imidazole, rt, 12 h; (ii) $CHOR^4C_6H_3B(OH)_2$, Na_2CO_3, $Pd(PPh_3)_4$, toluene/MeOH/H_2O, 70 °C, 5 h; (iii) EtMgBr, THF, rt, 5 h; (iv) CDI, NMP, 170 °C, 7 h; (v) TBAF, THF, rt, 12 h.

3.2. Molecular modelling studies

Both enantiomers, if existing, of selected energy-minimized compounds (**3**–**11**, **13**–**15**) were docked into our CYP17 model by means of the GOLD v3.2 software [41] running Linux CentOS 5.1 on Intel(R) P4 CPU 3.00 GHz. A slightly modified GOLDSCORE function with goldscore.P450_pdb.parameters, for better evaluation of hydrophobic interactions, was used. The experimentally proven complexation of the heme iron with sp^2 hybridized nitrogen [22] was considered in these studies by applying a distance constraint between those two atoms.

For both enantiomers of almost all docked compounds the statistical significant binding mode was **BM1** – the alternative mode **BM2** was less prevalent (Fig. 3). These two binding modes could be previously identified by us for biphenylic CYP17 inhibitors [26,32]. In **BM1** the biaryl skeleton is oriented parallel to the I-helix pointing the A-ring next to a polar area. Hydrophobic and π–π interactions between the conjugated biphenyl core and Phe114 as well as apolar amino acid residues (Gly301, Ala302, Glu305, Ala367 and Ile371) were observed for all compounds.

The ethyl group at the methylene spacer has an important stabilizing role, as already described by us [34]. It anchors in a tiny hydrophobic pocket next to the heme, delimitated in its extend by Val366 and Ile371.

The analysis of the docking results was focused on the interaction of the A-ring with the corresponding amino acid residues, since most of the variations on the compounds presented in this article are located here. Regarding the substituents in para position, it can be observed that a hydroxy group is involved in a H-bond net with Arg109, Lys231, His235 and Asp298. In contrast to this, for a methoxy group there is steric hindrance due to His235, Arg109 and the proximal I-helix residues. Depending on the different kind of substituents at the Meta position, the R^1 group is oriented toward the F-/G-helix (Asn202, Lys231), if R^1 is MeO or Me or toward Asp298 for OH. The latter group forms a strong H-bond with the carboxylate ($r = 1.9$ Å). In case of the Cl substituent, it was not possible to determine an unequivocal orientation, because of the bivalent interaction character of this halogen. Looking at the exact orientation of the MeO group, it becomes apparent that it is oriented toward a small hydrophobic pocket, delimitated in its extent by Ile238, Lys231, Ile206, Asn202 and Gln199. Its methyl group is placed at about 3.5–5 Å from the hydrophobic interaction partners of the mentioned amino acids, while its oxygen showed a reasonable H-bond with Lys231.

Striking for compounds **7** and **8** is the influence of the fluorine in the C-ring which reduces its electrostatic potential. Thus interactions with the backbone atoms of Gly301, Ala302 and Val304 are formed as we already have observed with other inhibitors of this class [32].

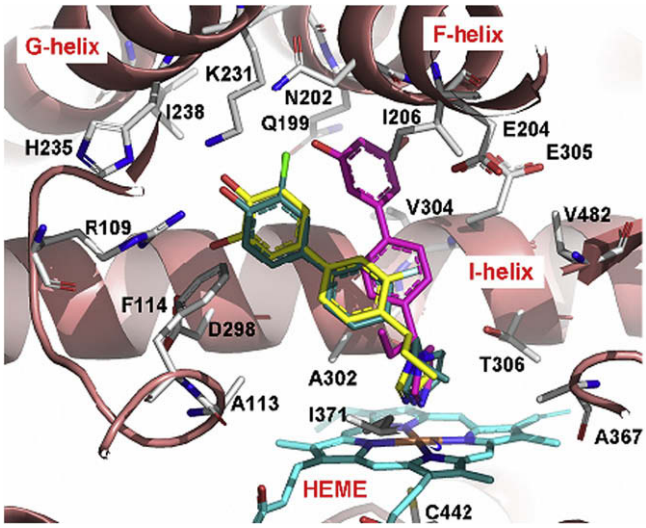


Fig. 3. Presentation of the two found binding modes **BM1** (compounds **8** yellow and **15** green-blue) and **BM2** (compound **6** magenta). Heme (cyan), interacting residues and ribbon rendered tertiary structure of the active site are shown. Figure was generated with Pymol (http://www.pymol.org) (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.).

4. Discussion and conclusion

CYP17 is the pivotal enzyme in the biosynthesis of androgens, which are known to promote prostatic tumor growth. GnRH analogs have been shown to be useful in the treatment of prostate cancer by reducing the androgen formation. As outlined above inhibitors of CYP17 could be more efficient therapeutics as they should not only affect testicular androgen formation but also adrenal biosynthesis.

The present work describes a series of new imidazole-substituted biphenyls. As they are very potent inhibitors of the target enzyme, our search for new substitution patterns increasing the activity of known biphenylic compounds [30–35,39] (e.g. **Ref1**) was successful. Regarding the structure–activity relationships obtained in this study, the importance of an ethyl substituent at the methylene bridge was demonstrated and could be explained in the modelling study. With respect to A-ring substitution a strong enhancement of the inhibitory activity was achieved by introduction of hydroxy groups, especially by two vicinal groups in R^1 and R^2. A very important role plays the fluorine substituent in the C-ring. Its introduction leads to the most active compounds **7** and **8**.

All synthesised compounds are much more potent than the reference Ketoconazole and two compounds reached the inhibitory activity of Abiraterone, which is under clinical investigation. Regarding selectivity toward the hepatic CYP3A4 and the glucocorticoid forming CYP11B1, most of the compounds turned out to be superior to Ketoconazole. However, none of the novel compounds reached the selectivity of the steroidal inhibitor Abiraterone. Therefore further structural optimization has to be performed to overcome this weakness. In our opinion this should be worthwhile as non-steroidal inhibitors should not interfere with steroid hormone receptors as steroidal drugs do. These studies are presently being performed. The structurally modified compounds will not only be tested for CYP3A4 and CYP11B1 selectivity but also for inhibition of other important hepatic CYP enzymes and steroidogenic CYPs like CYP11B2 and CYP19. As the enantioselectivity of the enzyme is an interesting aspect, the enantiomeric separation of the structural optimized compounds will be performed and the enantiomers will be evaluated.

5. Experimental section

5.1. CYP17 preparation and assay

As source of human CYP17, our *E. coli* system [38] co-expressing human CYP17 and NADPH-P450 reductase was used and the assay was performed as previously described [27] using unlabeled progesterone as substrate and applying HPLC with UV-detection for separation.

5.2. Inhibition of hepatic enzyme CYP3A4

The recombinantly expressed enzyme from baculovirus-infected insect microsomes (Supersomes) was used and the manufacturer's instructions (www.gentest.com) were followed.

5.3. Inhibition of CYP11B1

V79MZh11B1 cells expressing CYP11B1 were used and our assay procedure with [4-^{14}C]-11-deoxycorticosterone was applied [42].

5.4. Chemistry section

5.4.1. General

Melting points were determined on a Mettler FP1 melting point apparatus and are uncorrected. IR spectra were recorded neat on a Bruker Vector 33FT-infrared spectrometer. ^{1}H NMR spectra were measured on a Bruker DRX-500 (500 MHz). Chemical shifts are given in parts per million (ppm), and TMS was used as an internal standard for spectra obtained in $CDCl_3$. All coupling constants (J) are given in Hz. ESI (electrospray ionization) mass spectra were determined on a TSQ quantum (Thermo Electron Corporation) instrument. Elemental analyses were performed at the Department of Instrumental Analysis and Bioanalysis, Saarland University. Column chromatography was performed using silica gel 60 (50–200 μM), and reaction progress was determined by TLC analysis on Alugram® SIL G/UV$_{254}$ (Macherey-Nagel). Boronic acids and bromoaryls used as starting materials were obtained commercially (CombiBlocks, Chempur, Aldrich, Acros).

5.4.2. Method A: boron tribromide cleavage of phenolic methyl ethers

To a solution of the corresponding methyl ether in dichloromethane (300 mL) cooled in an ice bath was added BBr_3 (1.5 eq per MeO) dropwise. After 2 h, the mixture was allowed to warm to room temperature and then stirred overnight. Methanol (10 mL) was added dropwise to terminate the reaction, the mixture was poured into water and stirred for another 2 h. Then saturated $NaHCO_3$-solution (100 mL) was added, and the mixture was extracted with dichloromethane. The extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated. The resulting crude product was subjected to flash chromatography using silica gel.

*5.4.2.1. 4-Bromo-benzene-1,2-diol (**5d**).* Synthesised according to Method A using 4-bromo-1,2-dimethoxybenzene (8.00 g, 36.9 mmol) and BBr_3 (25.00 g, 100 mmol); pale oil; yield: 6.57 g (94%); $R_f = 0.38$ (hexane/EtOAc, 9:1); δ_H ($CDCl_3$, 500 MHz): 5.18 (s, 1H), 5.33 (s, 1H), 6.74 (d, $J = 8.5$ Hz, 1H), 6.93 (dd, $J = 2.2$, 8.5 Hz, 1H), 7.02 (d, $J = 2.2$ Hz, 1H); δ_C ($CDCl_3$, 125 MHz): 112.6, 116.7, 118.7, 124.0, 142.7, 144.4; MS (ESI): $m/z = 190$ [$M^+ + H$].

*5.4.2.2. 5-Bromo-benzene-1,3-diol (**6d**).* Synthesised according to Method A using 1-bromo-3,5-dimethoxybenzene (8.00 g, 36.9 mmol) and BBr_3 (25.00 g, 100 mmol); pale oil; yield: 6.77 g (97%). $R_f = 0.38$

(DCM/MeOH, 98:2); δ_H ($CDCl_3$, 500 MHz): 5.20 (s, 2H), 6.28 (t, $J = 2.2$ Hz, 1H), 6.67 (d, $J = 2.2$ Hz, 2H); MS (ESI): $m/z = 190$ [$M^+ + H$].

5.4.3. Method B: protection of phenols as TBDMS ethers

To a solution of the corresponding phenol and imidazole (1.1 eq per OH) in dichloromethane, a solution of *tert*-butyl-dimethylsilyl chloride in dichloromethane was slowly added (1.1 eq per OH). After being stirred for 4 h at rt, the reaction mixture was poured into water, extracted with dichloromethane, washed with water and brine and dried over Na_2SO_4. Solvent removal under reduced pressure led to a pale oil, which was purified by chromatography on silica gel.

5.4.3.1. (4-Bromo-phenoxy)-tert-*butyl-dimethyl-silane (**3c**).* Synthesised according to Method B using 4-bromophenol (**3d**) (3.00 g, 17.3 mmol); pale oil; yield: 4.80 g (94%); $R_f = 0.84$ (hexane/EtOAc, 9:1); δ_H ($CDCl_3$, 500 MHz): 0.19 (s, 6H), 0.98 (s, 9H), 6.72 (d, $J = 8.8$ Hz, 2H), 7.32 (d, $J = 8.8$ Hz, 2H); δ_C ($CDCl_3$, 125 MHz): −4.5, 18.2, 25.6, 113.6, 121.9, 132.3, 154.8; MS (ESI): $m/z = 288$ [$M^+ + H$].

5.4.3.2. (3-Bromo-phenoxy)-tert-*butyl-dimethyl-silane (**4c**).* Synthesised according to Method B using 3-bromophenol (**4d**) (5.00 g, 28 mmol); pale oil; yield: 8.21 g (quant.); $R_f = 0.81$ (hexane/EtOAc, 9:1); δ_H ($CDCl_3$, 500 MHz): 0.19 (s, 6H), 0.98 (s, 9H), 6.79–6.81 (m, 1H), 7.01–7.12 (m, 3H); MS (ESI): $m/z = 288$ [$M^+ + H$].

*5.4.3.3. 4-Bromo-1,2-bis-(*tert-*butyl-dimethyl-silanyloxy)-benzene (**5c**).* Synthesised according to Method B using **5d** (3.57 g, 18.9 mmol); pale oil; yield: 6.64 g (84%); $R_f = 0.59$ (hexane); δ_H ($CDCl_3$, 500 MHz): 0.19 (s, 6H), 0.21 (s, 6H), 0.98 (s, 9H), 0.99 (s, 9H), 6.69 (d, $J = 8.5$ Hz, 1H), 6.92 (dd, $J = 2.5$, 8.5 Hz, 1H), 6.95 (d, $J = 2.5$ Hz, 1H); δ_C ($CDCl_3$, 125 MHz): −4.18, −4.14, 18.42, 18.44, 25.86, 25.89, 112.7, 122.2, 124.2, 124.3, 146.4, 147.9; MS (ESI): $m/z = 418$ [$M^+ + H$].

*5.4.3.4. 1-Bromo-3,5-bis-(*tert-*butyl-dimethyl-silanyloxy)-benzene (**6c**).* Synthesised according to Method B using **6d** (7.17 g, 38.0 mmol); pale oil; yield: 14.45 g (91%); $R_f = 0.73$ (hexane); δ_H ($CDCl_3$, 500 MHz): 0.20 (s, 12H), 0.97 (s, 18H), 6.26 (t, $J = 2.2$ Hz, 1H), 6.63 (d, $J = 2.2$ Hz, 2H); MS (ESI): $m/z = 418$ [$M^+ + H$].

*5.4.3.5. 4′-(*tert-*Butyl-dimethyl-silanyloxy)-3′,5′-dimethyl-biphenyl-4-carbaldehyde (**13b**).* Synthesised according to Method B using **13c** (0.92 g, 4.07 mmol); white solid; yield: 1.32 g (93%); $R_f = 0.33$ (hexane/EtOAc, 10:1); δ_H ($CDCl_3$, 500 MHz): 0.25 (s, 6H), 1.08 (s, 9H), 2.31 (s, 6H), 7.28 (s, 2H), 7.70 (d, $J = 8.3$ Hz, 2H), 7.89 (d, $J = 8.3$ Hz, 2H), 10.01 (s, 1H, CHO); δ_C ($CDCl_3$, 125 MHz): −3.2, 17.6, 18.4, 25.8, 126.7, 127.4, 128.9, 129.8, 132.0, 134.2, 146.7, 152.6, 191.4; MS (ESI): $m/z = 227$ [$M^+ + H$].

*5.4.3.6. 4′-(*tert-*Butyl-dimethyl-silanyloxy)-3′-methyl-biphenyl-4-carbaldehyde (**14b**).* Synthesised according to Method B using **14c** (0.96 g, 4.07 mmol); white solid; yield: 1.40 g (95%); $R_f = 0.33$ (hexane/EtOAc, 10:1); δ_H ($CDCl_3$, 500 MHz): 0.26 (s, 6H), 1.04 (s, 9H), 2.29 (s, 3H), 6.85 (d, $J = 8.3$ Hz, 1H), 7.36 (dd, $J = 2.3$, 8.3 Hz, 1H), 7.44 (s, 1H), 7.70 (d, $J = 8.3$ Hz, 2H), 7.91 (d, $J = 8.4$ Hz, 2H), 10.03 (s, 1H); δ_C ($CDCl_3$, 125 MHz): −4.4, 16.8, 25.5, 118.6, 125.4, 126.8, 130.0, 134.3, 146.8, 154.4, 191.7; MS (ESI): $m/z = 227$ [$M^+ + H$].

5.4.3.7. (4-Bromo-2-chloro-phenoxy)-tert-*butyl-dimethyl-silane (**15c**).* Synthesised according to Method B using 4-bromo-2-chloro phenol (**15d**) (1.00 g, 4.82 mmol); white solid; yield: 1.40 g (91%); $R_f = 0.45$ (hexane/EtOAc, 20:1); δ_H ($CDCl_3$, 500 MHz): 0.22 (s, 6H), 1.02 (s, 9H), 6.75 (d, $J = 8.6$ Hz, 1H), 7.23 (dd, $J = 2.5$, 8.6 Hz, 1H), 7.48 (d, $J = 2.5$ Hz, 1H); δ_C ($CDCl_3$, 125 MHz): −4.7, 25.3, 112.9, 121.6, 126.6, 130.2, 132.5, 150.7; MS (ESI): $m/z = 322$ [$M^+ + H$].

5.4.4. Method C: Suzuki coupling

To a solution of the corresponding bromo-benzene derivative (1.0 eq) in toluene (7 mL/mmol), an aqueous Na_2CO_3 solution (2.0 M; 3.2 mL/mmol) and an ethanolic solution (3.2 mL/mmol) of the corresponding boronic acid (1.5–2.0 eq) were added. The mixture was deoxygenated under reduced pressure and flushed with nitrogen. After having repeated this cycle several times, $Pd(PPh_3)_4$ (4 mol%) was added, and the resulting suspension was heated under reflux for 8 h. After cooling, ethyl acetate (10 mL) and water (10 mL) were added. The organic phase was separated and the water phase was extracted with ethyl acetate (2 × 10 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered over a short plug of Celite® and evaporated under reduced pressure. The compounds were purified by flash chromatography using silica gel.

*5.4.4.1. 4′-(*tert-*Butyl-dimethyl-silanyloxy)-biphenyl-4-carbaldehyde (**3b**).* Synthesised according to Method C using **3c** (4.80 g, 16.7 mmol) and 4-formylphenylboronic acid (5.01 g, 33.4 mmol); yellow solid; yield: 3.80 g (73%); $R_f = 0.65$ (hexane/EtOAc, 9:1); δ_H ($CDCl_3$, 500 MHz): 0.25 (s, 6H), 1.02 (s, 9H), 6.94 (d, $J = 8.8$ Hz, 2H), 7.53 (d, $J = 8.8$ Hz, 2H), 7.71 (d, $J = 8.2$ Hz, 2H), 7.92 (d, $J = 8.2$ Hz, 2H), 10.03 (s, 1H); δ_C ($CDCl_3$, 125 MHz): −4.4, 18.2, 25.6, 120.6, 127.0, 127.6, 128.4, 130.2, 134.7, 146.8, 156.4, 191.8; MS (ESI): $m/z = 297$ [$M^+ + H$].

*5.4.4.2. 3′-(*tert-*Butyl-dimethyl-silanyloxy)-biphenyl-4-carbaldehyde (**4b**).* Synthesised according to Method C using **4c** (6.66 g, 22.9 mmol) and 4-formylphenylboronic acid (5.10 g, 34.5 mmol); yellow solid; yield: 3.70 g (52%); $R_f = 0.60$ (hexane/EtOAc 9/1); the compound was directly used in the next step without further purification and analysis.

*5.4.4.3. 3′,4′-Bis-(*tert-*butyl-dimethyl-silanyloxy)-biphenyl-4-carbaldehyde (**5b**).* Synthesised according to Method C using **5c** (5.30 g, 12.7 mmol) and 4-formylphenylboronic acid (2.80 g, 19.0 mmol); yellow solid; yield: 3.30 g (58%); $R_f = 0.40$ (hexane/EtOAc, 9:1); the compound was directly used in the next step without further purification and analysis.

*5.4.4.4. 3′,5′-Bis-(*tert-*butyl-dimethyl-silanyloxy)-biphenyl-4-carbaldehyde (**6b**).* Synthesised according to Method C using **6c** (11.0 g, 26.3 mmol) and 4-formylphenylboronic acid (6.00 g, 39.4 mmol); yellow solid; yield: 7.67 g (66%); $R_f = 0.59$ (hexane/EtOAc, 9:1); the compound was directly used in the next step without further purification and analysis.

*5.4.4.5. 4′-(*tert-*Butyl-dimethyl-silanyloxy)-3-fluoro-biphenyl-4-carbaldehyde (**7b**).* Synthesised according to Method C using **3c** (3.50 g, 11.9 mmol) and 3-fluor-4-formylphenylboronic acid (3.00 g, 17.9 mmol); yellow solid; yield: 3.80 g (73%); $R_f = 0.47$ (hexane/EtOAc, 9:1); the compound was directly used in the next step without further purification and analysis.

*5.4.4.6. 3′,4′-Bis-(*tert-*butyl-dimethyl-silanyloxy)-3-fluoro-biphenyl-4-carbaldehyde (**8b**).* Synthesised according to Method C using **5c** (5.0 g, 12.0 mmol) and 3-fluor-4-formylphenylboronic acid (3.00 g, 17.9 mmol); yellow solid; yield: 3.70 g (67%); $R_f = 0.68$ (hexane/EtOAc, 9:1); the compound was directly used in the next step without further purification and analysis.

*5.4.4.7. 1-(4′-Methoxy-biphenyl-4-yl)-propan-1-one (**9b**).* Synthesised according to Method C using 4′-bromopropiophenone (2.0 g, 9.4 mmol) and 4-methoxyphenylboronic acid (2.14 g, 14.1 mmol); yellow solid; yield: 2.12 g (94%); $R_f = 0.29$ (DCM/hexane, 1:1); δ_H ($CDCl_3$, 500 MHz): 1.25 (t, $J = 7.3$ Hz, 3H), 3.02 (q, $J = 7.3$ Hz, 2H), 3.86 (s, 3H), 7.00 (d, $J = 8.8$ Hz, 2H), 7.57 (d, $J = 8.8$ Hz, 2H), 7.63 (d, $J = 8.5$ Hz, 2H), 8.01 (d, $J = 8.5$ Hz, 2H); δ_C ($CDCl_3$, 125 MHz): 8.3, 31.8, 55.4, 114.4, 126.6, 128.3, 128.6, 132.3, 135.0, 145.1, 159.9, 200.4; MS (ESI): $m/z = 241$ [$M^+ + H$].

*5.4.4.8. 1-(3′-Methoxy-biphenyl-4-yl)-propan-1-one (**10b**).* Synthesised according to Method C using 4′-bromopropiophenone (2.0 g, 9.4 mmol) and 3-methoxyphenylboronic acid (2.14 g, 14.1 mmol); orange solid; yield: 2.30 g (96%); $R_f = 0.29$ (DCM/hexane, 1:1); δ_H ($CDCl_3$, 500 MHz): 1.25 (t, $J = 7.3$ Hz, 3H), 3.04 (q, $J = 7.3$ Hz, 2H), 3.88 (s, 3H), 6.95 (ddd, $J = 0.6$, 2.5, 8.2 Hz, 1H), 7.15 (t, $J = 2.5$ Hz, 1H), 7.20–7.22 (m, 1H), 7.39 (t, $J = 8.2$ Hz, 1H), 7.67 (d, $J = 8.5$ Hz, 2H), 8.03 (d, $J = 8.5$ Hz, 2H); δ_C ($CDCl_3$, 125 MHz): 8.3, 31.8, 55.3, 113.0, 113.5, 119.7, 127.3, 128.5, 130.0, 135.8, 141.4, 160.0, 200.4; MS (ESI): $m/z = 241$ [$M^+ + H$].

*5.4.4.9. 1-(3′,4′-Dimethoxy-biphenyl-4-yl)-propan-1-one (**11b**).* Synthesised according to Method C using 4′-bromopropiophenone (2.00 g, 9.4 mmol) and 3,4-dimethoxyphenylboronic acid (2.57 g, 14.1 mmol); orange solid; yield: 2.41 g (95%); $R_f = 0.37$ (DCM); δ_H ($CDCl_3$, 500 MHz): 1.25 (t, $J = 7.3$ Hz, 3H), 3.03 (q, $J = 7.3$ Hz, 2H), 3.94 (s, 3H), 3.97 (s, 3H), 6.97 (d, $J = 8.2$ Hz, 1H), 7.14 (d, $J = 2.2$ Hz, 1H), 7.20 (dd, $J = 2.2$, 8.2 Hz, 1H), 7.64 (d, $J = 8.5$ Hz, 2H), 8.02 (d, $J = 8.5$ Hz, 2H); MS (ESI): $m/z = 271$ [$M^+ + H$].

*5.4.4.10. 1-(4′-Ethoxy-biphenyl-4-yl)-propan-1-one (**12b**).* Synthesised according to Method C using 4′-bromopropiophenone (0.86 g, 4.0 mmol) and 4-ethoxyphenylboronic acid (1.00 g, 6.02 mmol); yellow solid; yield: 0.96 g (94%); $R_f = 0.32$ (hexane/EtOAc, 9:1); δ_H ($CDCl_3$, 500 MHz): 1.25 (t, $J = 7.3$ Hz, 3H), 1.45 (t, $J = 6.9$ Hz, 3H), 3.03 (q, $J = 7.3$ Hz, 2H), 4.10 (q, $J = 6.9$ Hz, 2H), 6.68 (d, $J = 8.8$ Hz, 2H), 7.50 (d, $J = 8.8$ Hz, 2H), 7.64 (d, $J = 8.2$ Hz, 2H), 8.01 (d, $J = 8.2$ Hz, 2H); MS (ESI): $m/z = 255$ [$M^+ + H$].

*5.4.4.11. 4′-Hydroxy-3′,5′-dimethyl-biphenyl-4-carbaldehyde (**13c**).* Synthesised according to Method C using 4-bromo-2,6-dimethylphenol (**13d**) (1.00 g, 4.97 mmol) and 4-formylphenylboronic acid (0.89 g, 5.9 mmol); white solid; yield: 0.92 g (82%); $R_f = 0.30$ (hexane/EtOAc, 5:1); δ_H ($CDCl_3$, 500 MHz): 2.33 (s, 6H), 4.81 (bs, 1H), 7.28 (s, 2H), 7.69 (d, $J = 8.3$ Hz, 2H), 7.90 (d, $J = 8.3$ Hz, 2H), 10.03 (s, 1H); δ_C ($CDCl_3$, 125 MHz): 15.8, 126.4, 126.8, 127.4, 130.0, 131.4, 134.3, 152.7, 191.7; MS (ESI): $m/z = 227$ [$M^+ + H$].

*5.4.4.12. 4′-Hydroxy-3′-methyl-biphenyl-4-carbaldehyde (**14c**).* Synthesised according to Method C using 4-bromo-2-methylphenol (**14d**) (1.00 g, 5.35 mmol) and 4-formylphenylboronic acid (0.96 g, 6.4 mmol); white solid; yield: 0.96 g (85%); $R_f = 0.31$ (hexane/EtOAc, 5:1); δ_H ($CDCl_3$, 500 MHz): 2.34 (s, 3H), 5.23 (bs, 1H), 6.89 (d, $J = 8.3$ Hz, 1H), 7.37 (dd, $J = 2.3$, 8.3 Hz, 1H), 7.43 (bs, 1H), 7.70 (d, $J = 8.3$ Hz, 2H), 7.91 (d, $J = 8.4$ Hz, 2H), 10.03 (s, 1H); δ_C ($CDCl_3$, 125 MHz): 15.7, 115.2, 124.3, 125.9, 126.8, 130.1, 131.9, 134.3, 146.8, 154.4, 191.9 (CHO); MS (ESI): $m/z = 213$ [$M^+ + H$].

*5.4.4.13. 4′-(*tert*-Butyl-dimethyl-silanyloxy)-3′-chloro-biphenyl-4-carbaldehyde (**15b**).* Synthesised according to Method C using **15c** (1.40 g, 4.35 mmol) and 4-formylphenylboronic acid (0.78 g, 5.5 mmol); white solid; yield: 1.22 g (81%); $R_f = 0.33$ (hexane/EtOAc, 10:1); δ_H ($CDCl_3$, 500 MHz): 0.27 (s, 6H), 1.06 (s, 9H), 6.98 (d, $J = 8.4$ Hz, 1H), 7.41 (dd, $J = 2.3$, 8.4 Hz, 1H), 7.65 (d, $J = 2.3$ Hz, 1H), 7.69 (d, $J = 8.3$ Hz, 2H), 7.93 (d, $J = 8.4$ Hz, 2H), 10.04 (s, 1H); δ_C ($CDCl_3$, 125 MHz): −4.4, 25.6, 121.1, 126.4, 127.1, 129.1, 130.3, 133.7, 135.1, 145.6, 152.1, 191.8; MS (ESI): $m/z = 348$ [$M^+ + H$].

5.4.5. Method D: Grignard reaction

Under exclusion of air and moisture, a EtMgBr (1.0 M in THF, 1.2 eq) solution in THF was added dropwise to a solution of the aldehyde or ketone (1 eq) in THF (12 mL/mmol). The mixture was stirred overnight at rt. Then water (10 mL) and ethyl acetate (10 mL) were added. The organic phase was separated and washed with water and brine, dried over Na_2SO_4, and evaporated under reduced pressure. The crude products were purified by flash chromatography using silica gel.

*5.4.5.1. 1-[4′-(*tert*-Butyl-dimethyl-silanyloxy)-biphenyl-4-yl]-propan-1-ol (**3a**).* Synthesised according to Method D using **3b** (3.30 g, 10.6 mmol) and EtMgBr (1.0 M in THF, 12.7 mL, 12.7 mmol); white solid; yield: 1.89 g (52%); $R_f = 0.40$ (hexane/EtOAc, 9:1); δ_H ($CDCl_3$, 500 MHz): 0.23 (s, 6H), 0.95 (t, $J = 7.3$ Hz, 3H), 1.00 (s, 9H), 1.76–1.89 (m, 2H), 4.64 (t, $J = 6.6$ Hz, 1H), 6.90 (d, $J = 8.5$ Hz, 2H), 7.38 (d, $J = 8.5$ Hz, 2H), 7.46 (d, $J = 8.5$ Hz, 2H), 7.54 (d, $J = 8.5$ Hz, 2H); MS (ESI): $m/z = 344$ [$M^+ + H$].

*5.4.5.2. 1-[3′-(*tert*-Butyl-dimethyl-silanyloxy)-biphenyl-4-yl]-propan-1-ol (**4a**).* Synthesised according to Method D using **4b** (3.70 g, 11.9 mmol) and EtMgBr (1.0 M, 14.3 mL, 14.3 mmol); white solid; yield: 2.02 g (45%); $R_f = 0.40$ (hexane/EtOAc, 9:1); δ_H ($CDCl_3$, 500 MHz): 0.27 (s, 6H), 0.97 (t, $J = 7.3$ Hz, 1H), 1.05 (s, 9H), 1.76–1.91 (m, 2H), 2.15–2.38 (m, 1H), 4.65 (t, $J = 6.6$ Hz, 1H), 6.86 (m, 1H), 7.11 (m, 1H), 7.21 (d, J = 7.9 Hz, 1H), 7.31 (t, $J = 7.9$ Hz, 1H), 7.41 (d, $J = 8.2$ Hz, 2H), 7.57 (d, $J = 8.2$ Hz, 2H); δ_C ($CDCl_3$, 125 MHz): −4.4, 9.9, 21.2, 25.7, 29.2, 77.1, 118.8, 119.0, 120.1, 126.9, 127.1, 129.6, 139.6, 140.5, 142.2, 156.0; MS (ESI): $m/z = 344$ [$M^+ + H$].

*5.4.5.3. 1-[3′,4′-Bis-(*tert*-butyl-dimethyl-silanyloxy)-biphenyl-4-yl]-propan-1-ol (**5a**).* Synthesised according to Method D using **5b** (6.09 g, 13.7 mmol) and EtMgBr (1.0 M, 16.4 mL, 16.4 mmol); white solid; yield: 1.55 g (25%); $R_f = 0.62$ (hexane/EtOAc, 7:3); δ_H ($CDCl_3$, 500 MHz): 0.22 (s, 6H), 0.23 (s, 6H), 0.88 (t, $J = 7.3$ Hz, 3H),1.00 (s, 9H), 1.01 (s, 9H), 1.68–1.81 (m, 2H), 2.51 (bs, 1H), 4.52 (t, $J = 6.6$ Hz, 1H), 6.86 (d, $J = 8.2$ Hz, 1H), 7.02 (dd, $J = 2.2$, 8.2 Hz, 1H), 7.08 (d, $J = 2.2$ Hz, 1H), 7.31 (d, $J = 8.2$ Hz, 2H), 7.45 (d, $J = 8.2$ Hz, 2H); δ_C ($CDCl_3$, 125 MHz): −4.08, −4.12, 10.1, 18.38, 18.39, 25.90, 25.92, 31.7, 75.5, 119.7, 119.9, 121.2, 126.3, 126.5, 134.3, 139.8, 143.1, 146.4, 146.9; MS (ESI): $m/z = 474$ [$M^+ + H$].

*5.4.5.4. 1-[3′,5′-Bis-(*tert*-butyl-dimethyl-silanyloxy)-biphenyl-4-yl]-propan-1-ol (**6a**).* Synthesised according to Method D using **6b** (6.85 g, 15.5 mmol) and EtMgBr (1.0 M, 18.6 mL, 18.6 mmol); yellow solid; yield: 3.60 g (49%); the compound was directly used in the next step without further purification and analysis.

*5.4.5.5. 1-[4′-(*tert*-Butyl-dimethyl-silanyloxy)-3-fluoro-biphenyl-4-yl]-propan-1-ol (**7a**).* Synthesised according to Method D using **7b** (3.01 g, 9.10 mmol) and EtMgBr (1.0 M, 10.9 mL, 10.9 mmol); white solid; yield: 1.30 g (40%); $R_f = 0.48$ (hexane/EtOAc, 9:1); δ_H ($CDCl_3$, 500 MHz): 0.25 (s, 6H), 0.98 (t, $J = 7.3$ Hz, 3H), 1.03 (s, 9H), 1.79–1.89 (m, 2H), 2.33 (bs, 1H), 4.94–4.97 (m, 1H), 6.91 (d, $J = 8.8$ Hz, 2H), 7.20 (dd, $J = 1.9$, 12.0 Hz, 1H), 7.33 (dd, $J = 1.9$, 8.2 Hz, 1H), 7.44–7.46 (m, 3H); MS (ESI): $m/z = 361$ [$M^+ + H$].

*5.4.5.6. 1-[3′,4′-Bis-(*tert*-butyl-dimethyl-silanyloxy)-3-fluoro-biphenyl-4-yl]-propan-1-ol (**8a**).* Synthesised according to Method D using **8b** (3.71 g, 8.00 mmol) and EtMgBr (1.0 M, 9.6 mL, 9.6 mmol); yellow solid; yield: 1.36 g (35%); $R_f = 0.34$ (hexane/EtOAc, 9:1); the

compound was directly used in the next step without further purification and analysis.

*5.4.5.7. 1-[4′-(*tert*-Butyl-dimethyl-silanyloxy)-3′,5′-dimethyl-biphenyl-4-yl]-propan-1-ol (**13a**).* Synthesised according to Method D using **13b** (1.32 g, 3.88 mmol) and EtMgBr (1.0 M, 4.65 mL, 4.65 mmol) solution in THF. Yield: 1.24 g (86%); $R_f = 0.15$ (hexane/EtOAc, 10:1); white solid; δ_H ($CDCl_3$, 500 MHz): 0.24 (s, 6H), 0.95 (t, $J = 7.4$ Hz, 3H), 1.08 (s, 9H), 1.77–1.88 (m, 2H), 1.93 (bs, 1H), 2.29 (s, 6H), 4.62 (t, $J = 6.5$ Hz, 1H), 7.23 (s, 2H), 7.37 (d, $J = 8.3$ Hz, 2H), 7.54 (d, $J = 8.3$ Hz, 2H); δ_C ($CDCl_3$, 125 MHz): −3.2, 9.9, 17.7, 25.8, 31.5, 75.5, 125.9, 126.4, 127.1, 128.6, 133.4, 140.0, 142.5, 151.6; MS (ESI): $m/z = 227$ [$M^+ + H$].

*5.4.5.8. 1-[4′-(*tert*-Butyl-dimethyl-silanyloxy)-3′-methyl-biphenyl-4-yl]-propan-1-ol (**14a**).* Synthesised according to Method D using **14b** (1.40 g, 4.29 mmol) with EtMgBr (1.0 M, 4.71 mL, 4.71 mmol) solution in THF; white solid; yield: 1.24 g (81%); $R_f = 0.15$ (hexane/EtOAc, 10:1); the compound was directly used in the next step without further purification and analysis.

*5.4.5.9. 1-[4′-(*tert*-Butyl-dimethyl-silanyloxy)-3′-chloro-biphenyl-4-yl]-propan-1-ol (**15a**).* Synthesised according to Method D using **15b** (1.22 g, 3.52 mmol) with EtMgBr (1.0 M, 3.87 mL, 3.87 mmol) solution in THF; white solid; yield: 1.05 g (79%); $R_f = 0.18$ (hexane/EtOAc, 10:1); the compound was directly used in the next step without further purification and analysis.

5.4.6. Method E: reduction with $NaBH_4$

To an ice-cooled solution of the corresponding aldehyde or ketone (1.0 eq) in methanol (5 mL/mmol) was added $NaBH_4$ (2.0 eq). The resulting mixture was heated to reflux for 30 min. After cooling to ambient temperature, the solvent was distilled off under reduced pressure. Water (10 mL) was added, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. The desired product was purified by chromatography using silica gel.

*5.4.6.1. 1-(4′-Methoxy-biphenyl-4-yl)-ethanol (**1a**).* Synthesised according to Method E using 1-(4′-methoxy-biphenyl-4-yl)ethanone (**1b**) (0.23 g, 1.00 mmol) and $NaBH_4$ (0.15 g, 3.98 mmol); colourless solid; yield: 0.13 g (58%); $R_f = 0.16$ (hexane/EtOAc, 10:1); the compound was directly used in the next step without further purification and analysis.

*5.4.6.2. 1-(3′-Methoxy-biphenyl-4-yl)-ethanol (**2a**).* Synthesised according to Method E using 1-(3′-methoxy-biphenyl-4-yl)ethanone (**2b**) (0.62 g, 2.71 mmol) and $NaBH_4$ (0.19 g, 4.88 mmol); colourless solid; yield: 0.45 g (72%); $R_f = 0.17$ (hexane/EtOAc, 10:1); IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3388 (m), 1600 (m), 1481 (m), 1295 (m), 1214 (s), 1053 (m), 832 (s), 777 (s), 695 (m); δ_H ($CDCl_3$, 500 MHz): 1.54 (d, $J = 6.4$ Hz, 3H), 1.77 (bs, 1H), 3.87 (s, 3H), 4.96 (q, $J = 6.4$ Hz, 1H), 6.90 (dd, $J = 2.2$, 8.2 Hz, 1H), 7.12 (bt, $J = 2.2$ Hz, 1H), 7.17–7.19 (m, 1H), 7.36 (t, $J = 7.9$ Hz, 1H), 7.45 (d, $J = 8.2$ Hz, 2H), 7.58 (d, $J = 8.2$ Hz, 2H); δ_C ($CDCl_3$, 125 MHz): 25.1, 55.3, 70.1, 112.6, 112.8, 119.6, 125.8, 127.3, 129.7, 140.3, 142.4, 145.0, 159.9; MS (ESI): $m/z = 211$ [$M^+ + H - H_2O$].

*5.4.6.3. 1-(4′-Methoxy-biphenyl-4-yl)-propan-1-ol (**9a**).* Synthesised according to Method E using **9b** (2.12 g, 8.80 mmol) and $NaBH_4$ (0.64 g, 17 mmol); white solid; yield: 1.85 g (87%); $R_f = 0.37$ (DCM); δ_H ($CDCl_3$, 500 MHz): 0.95 (t, $J = 7.6$ Hz, 3H), 1.77–1.89 (m, 3H), 3.85 (s, 3H), 4.64 (t, $J = 6.6$ Hz, 1H), 6.98 (d, $J = 8.5$ Hz, 2H), 7.39 (d, $J = 8.5$ Hz, 2H), 7.52–7.55 (m, 4H); δ_C ($CDCl_3$, 125 MHz): 10.2, 31.8, 55.3, 75.8, 114.2, 126.4, 126.7, 128.1, 133.4, 140.1, 143.0, 159.1; MS (ESI): $m/z = 243$ [$M^+ + H$].

*5.4.6.4. 1-(3′-Methoxy-biphenyl-4-yl)-propan-1-ol (**10a**).* Synthesised according to Method E using **10b** (2.30 g, 9.00 mmol) and $NaBH_4$ (0.76 g, 20 mmol); white solid; yield: 1.87 g (86%); $R_f = 0.37$ (DCM); δ_H ($CDCl_3$, 500 MHz): 0.95 (t, $J = 7.3$ Hz, 3H), 1.78–1.90 (m, 3H), 3.88 (s, 3H), 4.65 (t, $J = 6.4$ Hz, 1H), 6.98 (ddd, $J = 0.6$, 2.5, 8.2 Hz, 1H), 7.17 (t, $J = 2.5$ Hz, 1H), 7.22–7.24 (m, 2H), 7.71 (d, $J = 8.5$ Hz, 2H), 8.06 (d, $J = 8.5$ Hz, 2H); δ_C ($CDCl_3$, 125 MHz): 10.3, 31.8, 55.3, 76.1, 113.0, 113.4, 119.7, 127.4, 128.2, 130.0, 135.8, 141.4, 159.9; MS (ESI): $m/z = 243$ [$M^+ + H$].

*5.4.6.5. 1-(3′,4′-Dimethoxy-biphenyl-4-yl)-propan-1-ol (**11a**).* Synthesised according to Method E using **11b** (2.41 g, 8.90 mmol) and $NaBH_4$ (0.76 g, 20 mmol); yellow solid; yield: 2.03 g (84%); $R_f = 0.31$ (DCM); δ_H ($CDCl_3$, 500 MHz): 0.99 (t, $J = 7.3$ Hz, 3H), 1.81–1.90 (m, 3H), 3.82 (s, 3H), 3.84 (s, 3H), 4.59 (t, $J = 6.6$ Hz, 1H), 6.94 (d, $J = 8.2$ Hz, 1H), 7.07 (d, $J = 2.2$ Hz, 1H), 7.11 (dd, $J = 2.2$, 8.2 Hz, 1H), 7.30 (d, $J = 8.2$ Hz, 2H), 7.55 (d, $J = 8.2$ Hz, 2H); MS (ESI): $m/z = 273$ [$M^+ + H$].

*5.4.6.6. 1-(4′-Ethoxy-biphenyl-4-yl)-propan-1-ol (**12a**).* Synthesised according to Method E using **12b** (1.32 g, 5.20 mmol) and $NaBH_4$ (0.39 g, 10 mmol); white solid; yield: 1.14 g (86%); $R_f = 0.16$ (hexane/EtOAc 9:1); δ_H ($CDCl_3$, 500 MHz): 0.95 (t, $J = 7.3$ Hz, 3H), 1.42 (t, $J = 6.6$ Hz, 3H), 2.22–2.29 (m, 2H), 4.07 (q, $J = 6.6$ Hz, 2H), 5.03 (t, $J = 7.7$ Hz, 1H), 6.97 (d, $J = 8.8$ Hz, 2H), 7.40 (d, $J = 8.2$ Hz, 2H), 7.53–7.56 (m, 4H); MS (ESI): $m/z = 257$ [$M^+ + H$].

*5.4.7. Method F: CDI reaction (compounds **1**, **2**, **9**–**12**)*

To a solution of the corresponding alcohol (1.0 eq) in *N*-methyl-2-pyrrolidon (NMP) or acetonitrile (10 mL/mmol), CDI (5.0 eq) was added at rt. The solution was heated to reflux for 4–18 h. After cooling to ambient temperature, the reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified via chromatography using silica gel.

*5.4.7.1. 1-[1-(4′-Methoxy-biphenyl-4-yl)-ethyl]-1H-imidazole (**1**).* Synthesised according to Method F using **1a** (0.20 g, 0.88 mmol) and CDI (0.28 g, 1.8 mmol) in acetonitrile; colourless solid; yield: 0.12 g (49%); $R_f = 0.15$ (EtOAc); IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1605 (m), 1595 (s), 1247 (s), 1209 (m), 1185 (m), 1036 (m), 822 (s), 747 (m), 664 (s); δ_H ($CDCl_3$, 500 MHz): 1.89 (d, $J = 6.9$ Hz, 3H), 3.84 (s, 3H), 5.37 (q, $J = 6.9$ Hz, 1H), 6.96 (bs, 1H), 6.97 (d, $J = 9.0$ Hz, 2H), 7.10 (bs, 1H), 7.18 (d, $J = 8.2$ Hz, 2H), 7.49 (d, $J = 9.0$ Hz, 2H), 7.52 (d, $J = 8.2$ Hz, 2H), 7.61 (bs, 1H); δ_C ($CDCl_3$, 125 MHz): 22.0 (CH_3), 55.3 (CH), 56.3 (CH_3), 114.3 (CH), 117.9 (CH), 126.4 (CH), 127.1 (CH), 128.1 (CH), 129.4 (CH), 132.8 (C_q), 136.1 (CH), 139.8 (C_q), 140.7 (C_q), 159.4 (C_q); MS (ESI): $m/z = 279$ [$M^+ + H$].

*5.4.7.2. 1-[1-(3′-Methoxy-biphenyl-4-yl)-ethyl]-1H-imidazole (**2**).* Synthesised according to Method F using **2a** (0.39 g, 1.7 mmol) and CDI (0.55 g, 3.4 mmol) in acetonitrile; colourless oil; yield: 0.21 g (44%); $R_f = 0.31$ (EtOAc/MeOH, 95:5); IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1599 (w), 1566 (w), 1481 (m), 1296 (m), 1260 (m), 1220 (s), 1031 (s), 1013 (s), 787 (s); δ_H ($CDCl_3$, 500 MHz): 1.89 (d, $J = 6.9$ Hz, 3H), 3.85 (s, 3H), 5.39 (q, $J = 6.9$ Hz, 1H), 6.90 (ddd, $J = 1.0$, 2.5, 8.2 Hz, 1H), 6.97 (bs, 1H), 7.08 (dd, $J = 1.6$, 2.5 Hz, 1H), 7.09 (bs, 1H), 7.14 (ddd, $J = 1.0$, 1.6, 7.9 Hz, 1H), 7.20 (d, $J = 8.2$ Hz, 2H), 7.35 (t, $J = 7.9$ Hz, 1H), 7.55 (d, $J = 8.2$ Hz, 2H), 7.63 (bs, 1H); δ_C ($CDCl_3$, 125 MHz): 21.0 (CH_3), 55.3 (CH_3), 56.3 (CH), 112.8 (CH), 112.9 (CH), 118.0 (CH), 119.5 (CH), 126.4 (CH), 127.6 (CH), 129.3 (CH), 129.8 (CH), 136.0 (CH), 140.5 (C_q), 141.0 (C_q), 141.8 (C_q), 160.0 (C_q); MS (ESI): $m/z = 279$ [$M^+ + H$].

*5.4.7.3. 1-[1-(4′-Methoxy-biphenyl-4-yl)-propyl]-1H-imidazole (**9**).* Synthesised according to Method F using **9a** (2.12 g, 8.8 mmol) and CDI (7.29 g, 45.0 mmol) in NMP; yellow solid; yield: 0.28 g (11%) $R_f = 0.52$ (EtOAc/NH_3 (aq, 25%) 97.5:2.5); IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2962 (w), 2932 (w), 1605 (m), 1497 (s), 1254 (s), 818 (s); δ_H ($CDCl_3$, 500 MHz): 0.97 (t, $J = 7.3$ Hz, 3H), 2.24–2.30 (m, 2H), 3.84 (s, 3H), 5.10 (t, $J = 7.6$ Hz, 1H), 6.96 (d, $J = 8.5$ Hz, 2H), 7.00 (bs, 1H), 7.13 (bs, 1H), 7.25 (d, $J = 8.5$ Hz, 2H), 7.49 (d, $J = 8.5$ Hz, 2H), 7.52 (d, $J = 8.5$ Hz, 2H), 7.89 (bs, 1H); δ_C ($CDCl_3$, 125 MHz): 11.0 (CH_3), 28.4 (CH_2), 55.3 (O-CH_3), 63.4 (CH), 114.3 (CH), 117.9 (CH), 127.0 (CH), 127.1 (CH), 127.9 (C_q), 128.0 (CH), 132.7 (C_q), 136.0 (CH), 137.9 (C_q), 140.9 (C_q), 159.4 (C_{OMe}); MS (ESI): $m/z = 293$ [$M^+ + H$].

*5.4.7.4. 1-[1-(3′-Methoxy-biphenyl-4-yl)-propyl]-1H-imidazole (**10**).* Synthesised according to Method F using **10a** (2.30 g, 9.0 mmol) and CDI (7.29 g, 45.0 mmol) in NMP; yellow solid; yield: 0.89 g (30%); $R_f = 0.52$ (EtOAc/NH_3 (aq, 25%) 97.5:2.5); IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2967 (w), 2935 (w), 1503 (s), 1249 (s), 1218 (s), 1024 (s), 806 (s); δ_H ($CDCl_3$, 500 MHz): 0.95 (t, $J = 7.3$ Hz, 3H), 2.22–2.28 (m, 2H), 3.84 (s, 3H), 5.05 (t, $J = 7.9$ Hz, 1H), 6.89 (dd, $J = 2.2$, 8.2 Hz, 1H), 6.98 (bs, 1H), 7.08 (t, $J = 2.2$ Hz, 1H), 7.10 (bs, 1H), 7.13 (d, $J = 7.9$ Hz, 1H), 7.24 (d, $J = 7.9$ Hz, 2H), 7.34 (t, $J = 7.9$ Hz, 1H), 7.54 (d, $J = 8.2$ Hz, 2H), 7.69 (bs, 1H); δ_C ($CDCl_3$, 125 MHz): 11.0 (CH_3), 28.5 (CH_2), 55.2 (CH_3-O), 63.0 (CH), 112.8 (CH), 112.8 (CH), 117.7 (CH), 119.5 (CH), 126.0 (CH), 127.5 (CH), 129.0 (C_q), 129.8 (CH), 136.2 (C_q), 139.2 (C_q), 140.9 (C_q), 141.7 (CH), 159.9 (C_{OMe}); MS (ESI): $m/z = 293$ [$M^+ + H$].

*5.4.7.5. 1-[1-(3′,4′-Dimethoxy-biphenyl-4-yl)-propyl]-1H-imidazole (**11**).* Synthesised according to Method F using **11a** (2.41 g, 8.90 mmol) and CDI (7.29 g, 45.0 mmol) in NMP; amber oil; yield: 0.69 g (24%); $R_f = 0.47$ (EtOAc/NH_3 (aq, 25%) 97.5:2.5); IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2967 (w), 2937 (w), 2875 (w), 2838 (w), 1668 (m), 1604 (m), 1583 (m), 1480 (s), 1294 (s), 1101 (s), 816 (s), 778 (s), 743 (s); δ_H ($CDCl_3$, 500 MHz): 0.99 (t, $J = 7.3$ Hz, 3H), 2.28–2.35 (m, 2H), 3.92 (s, 3H), 3.94 (s, 3H), 5.21 (t, $J = 7.9$ Hz, 1H), 6.94 (d, $J = 8.2$ Hz, 1H), 7.05 (bs, 1H), 7.07 (d, $J = 2.2$ Hz, 1H), 7.11 (dd, $J = 2.2$, 8.2 Hz, 1H), 7.21 (bs, 1H), 7.30 (d, $J = 8.2$ Hz, 2H), 7.55 (d, $J = 8.2$ Hz, 2H), 8.29 (bs, 1H); δ_C ($CDCl_3$, 125 MHz): 11.0 (CH_3), 28.5 (CH_2), 55.9 (O-CH_3), 55.9 (O-CH_3), 62.9 (CH), 110.3 (CH), 111.4 (CH), 117.6 (CH), 119.3 (CH), 126.9 (CH), 127.1 (CH), 129.4 (CH), 133.2 (C_q), 136.3 (CH), 138.7 (C_q), 140.8 (C_q), 148.8 (C_q), 149.1 (C_q); MS (ESI): $m/z = 323$ [$M^+ + H$].

*5.4.7.6. 1-[1-(4′-Ethoxy-biphenyl-4-yl)-propyl]-1H-imidazole (**12**).* Synthesised according to Method F using **12a** (1.14 g, 4.45 mmol) and CDI (3.61 g, 22.3 mmol) in NMP; brown solid; yield: 0.60 g (45%); $R_f = 0.66$ (EtOAc/MeOH 95:5); IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3115 (w), 2976 (w), 2936 (w), 2877 (w), 1606 (m), 1497 (s), 1245 (s), 1043 (s), 827 (s), 815 (s), 784 (s), 740 (s), 665 (s); δ_H ($CDCl_3$, 500 MHz) 0.95 (t, $J = 7.3$ Hz, 3H), 1.42 (t, $J = 6.9$ Hz, 3H), 2.22–2.29 (m, 2H), 4.07 (q, $J = 6.9$ Hz, 2H), 5.03 (t, $J = 7.7$ Hz, 1H), 6.95 (d, $J = 8.8$ Hz, 2H), 6.97 (bs, 1H), 7.09 (bs, 1H), 7.22 (d, $J = 8.2$ Hz, 2H), 7.48 (d, $J = 8.8$ Hz, 2H), 7.52 (d, $J = 8$,2 Hz, 2H), 7.63 (bs, 1H); δ_C ($CDCl_3$, 125 MHz): 11.1 (CH_3), 14.8 (CH_3), 28.6 (CH_2), 63.1 (CH), 63.5 (CH_2), 114.8 (CH), 117.7 (CH), 126.9 (CH), 127.0 (CH), 128.0 (CH), 129.3 (C_q), 132.6 (CH), 136.3 (CH), 138.4 (C_q), 140.7 (C_q), 158.7 (C_q); MS (ESI): $m/z = 307$ [$M^+ + H$].

*5.4.8. Method G: CDI reaction and deprotection with TBAF (compounds **3**–**8**, **13**–**15**)*

To a solution of the corresponding alcohol (1.0 eq) in NMP (10 mL/mmol) CDI (5.0 eq) was added at rt. The solution was heated to reflux for 4–18 h. After cooling to ambient temperature, the reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. The crude intermediate of the silyl-protected phenol was directly diluted in anhydrous THF, tetrabutylammonium fluoride solution was added (1.0 M in THF, 1.1 eq per TBDMS), and the reaction mixture was stirred for 4 h. The reaction was quenched by addition of methanol, and the solvent was removed under reduced pressure. The crude product was purified by chromatography using silica gel.

*5.4.8.1. 4′-(1-Imidazol-1-yl-propyl)-biphenyl-4-ol (**3**).* Synthesised according to Method G using **3a** (0.85 g, 2.16 mmol); yellow solid; yield: 0.22 g (37%); $R_f = 0.21$ (hexane/EtOAc, 5:1); IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2963 (w), 2930 (w), 2364 (w),1607 (m), 1588 (m), 1498 (s), 1272 (m), 1070 (s), 808 (s), 748 (m), 658 (m); δ_H (DMSO-d_6, 500 MHz): 0.82 (t, $J = 7.3$ Hz, 3H), 2.21–2.25 (m, 2H), 5.23 (t, $J = 7.3$ Hz, 1H), 6.82 (d, $J = 8.8$ Hz, 2H), 6.90 (s, 1H), 7.37 (d, $J = 8.5$ Hz, 2H), 7.46 (d, $J = 8.8$ Hz, 2H), 7.54 (d, $J = 8.5$ Hz, 2H), 7.82 (s, 1H), 9.55 (s, 1H); δ_C (DMSO-d_6, 125 MHz): 10.9 (CH_3), 27.4 (CH_2), 61.5 (CH), 115.6 (CH), 117.7 (CH), 126.0 (CH), 127.1 (CH), 127.6 (CH), 128.4 (C_q), 130.3 (CH), 130.7 (C_q), 139.3 (CH), 139.5 (C_q), 157.1 (C_q); MS (ESI): $m/z = 279$ [$M^+ + H$].

*5.4.8.2. 4′-(1-Imidazol-1-yl-propyl)-biphenyl-3-ol (**4**).* Synthesised according to Method G using **4a** (1.32 g, 3.36 mmol); yellow solid; yield: 0.20 g (21%); $R_f = 0.13$ (EtOAc/MeOH, 9:1); IR (ATR) $\tilde{\nu}$ (cm^{-1}) 2963 (w), 2361 (w), 1583 (m), 1564 (m), 1477 (s), 817 (s), 781 (s), 740 (s); δ_H (DMSO-d_6, 500 MHz): 0.83 (t, $J = 7.3$ Hz, 3H), 2.17–2.22 (m, 2H), 5.24–5.26 (m, 1H), 6.73–6.76 (m, 1H), 6.91 (bs, 1H), 6.99 (t, $J = 2.2$ Hz, 1H), 7.04 (ddd, $J = 0.9$, 2.2, 7.6 Hz, 1H), 7.23 (t, $J = 7.6$ Hz, 1H), 7.33 (t, $J = 1.3$ Hz, 1H), 7.41 (d, $J = 8.2$ Hz, 2H), 7.56 (d, $J = 8.2$ Hz, 2H), 7.83 (t, $J = 0.9$ Hz, 1H), 9.55 (s, 1H); δ_C (DMSO-d_6, 125 MHz): 10.9 (CH_3), 27.4 (CH_2), 61.5 (CH), 113.4 (CH), 114.4 (CH), 117.4 (CH) 117.7 (CH), 126.7 (CH), 127.1 (CH), 128.5 (CH), 129.8 (CH), 136.4 (CH), 140.4 (C_q), 141.0 (C_q), 157.7 (C_{OH}); MS (ESI): $m/z = 279$ [$M^+ + H$].

*5.4.8.3. 4′-(1-Imidazol-1-yl-propyl)-biphenyl-3,4-diol (**5**).* Synthesised according to Method G using **5a** (1.00 g, 1.92 mmol); yellow solid; yield: 0.19 g (34%); $R_f = 0.31$ (EtOAc/MeOH. 95:5); IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3285 (m), 3157 (m), 2963 (m), 2931 (m), 2874 (m), 2828 (m), 1770 (m), 1952 (s), 1945 (s), 1495 (s), 1304 (s), 1219 (s), 1086 (s), 805 (s), 755 (s); δ_H (DMSO-d_6, 500 MHz): 0.81 (t, $J = 7.3$ Hz, 3H), 2.18–2.24 (m, 2H), 5.20–5.23 (m, 1H), 6.79 (d, $J = 8.2$ Hz, 1H), 6.88–6.92 (m, 2H), 7.00 (d, $J = 2.2$ Hz, 1H), 7.31 (t, $J = 1.3$ Hz, 1H), 7.35 (d, $J = 8.2$ Hz, 2H), 7.48 (d, $J = 8.2$ Hz, 2H), 7.82 (bs, 1H), 9.01 (bs, 1H), 9.06 (bs, 1H); MS (ESI): $m/z = 295$ [$M^+ + H$].

*5.4.8.4. 4′-(1-Imidazol-1-yl-propyl)-biphenyl-3,5-diol (**6**).* Synthesised according to Method G using **6a** (2.00 g, 3.83 mmol); yellow solid; yield: 0.06 g (5%); $R_f = 0.38$ (EtOAc/MeOH, 95:5); IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2975 (w), 1595 (m), 1488 (m), 1351 (m), 1167 (s), 1111 (m), 1091 (m), 1077 (m), 1014 (m), 831 (s), 820 (s), 803 (s), 742 (s); δ_H (DMSO-d_6, 500 MHz) 0.82 (t, $J = 7.3$ Hz, 3H), 2.15–2.28 (m, 2H), 5.23–5.26 (m, 1H), 6.21 (t, $J = 2.1$ Hz, 1H), 6.44 (d, $J = 2.1$ Hz, 2H), 6.91 (s, 1H), 7.31 (s, 1H), 7.38 (d, $J = 8.2$ Hz, 2H), 7.49 (d, $J = 8.2$ Hz, 2H), 7.82 (s, 1H), 9.36 (s, 2H); δ_C (DMSO-d_6, 125 MHz): 10.9 (CH_3), 27.5 (CH_2), 61.5 (CH), 101.7 (CH), 104.7 (CH), 117.7 (CH), 126.6 (CH), 127.0 (CH), 128.5 (CH), 132.5 (C_q), 136.4 (CH), 139.9 (C_q), 141.5 (C_q), 158.7 (C_{OH}); MS (ESI): $m/z = 295$ [$M^+ + H$].

*5.4.8.5. 3′-Fluoro-4′-(1-imidazol-1-yl-propyl)-biphenyl-4-ol (**7**).* Synthesised according to Method G using **7a** (crude product); yellow solid; yield: 0.05 g; $R_f = 0.4$ (EtOAc/MeOH, 95:5); IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2974 (w), 2360 (m), 2341 (m), 1607 (m), 1494 (s), 1283 (m), 1223 (m), 1077 (m), 840 (m), 827 (s), 765 (m); δ_H (DMSO-d_6, 500 MHz): 0.84 (t, $J = 7.3$ Hz, 3H), 2.14–2.32 (m, 2H), 5.47–5.50 (m, 1H), 6.83 (d, $J = 8.5$ Hz, 2H), 6.90 (bs, 1H), 7.30 (t, $J = 1.3$ Hz, 1H), 7.41–7.44 (m, 3H),

7.51 (d, $J = 8.5$ Hz, 2H), 7.81 (bs, 1H), 9.67 (s, 1H); MS (ESI): $m/z = 297$ $[M^+ + H]$.

*5.4.8.6. 3′-Fluoro-4′-(1-imidazol-1-yl-propyl)-biphenyl-3,4-diol (**8**).* Synthesised according to Method G using **8a** (crude product); yellow solid; yield: 0.05 g; $R_f = 0.45$ (EtOAc/MeOH, 95:5); IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1500 (s), 1413 (m), 1279 (m), 1264 (s), 1109 (s), 1089 (s), 859 (s), 812 (s), 785 (m), 742 (m); δ_H ($CDCl_3$, 500 MHz): 1.00 (t, $J = 7.3$ Hz, 3H), 2.26–2.32 (m, 2H), 5.35 (t, $J = 7.9$ Hz, 1H), 6.93–6.97 (m, 2H), 7.01 (t, $J = 1.3$ Hz, 1H), 7.03 (d, $J = 1.9$ Hz, 1H), 7.10 (t, $J = 1.3$ Hz, 1H), 7.14 (dd, $J = 1.9$, 12.0 Hz, 1H), 7.17 (d, $J = 7.9$ Hz, 1H), 7.24 (dd, $J = 1.9$, 8.2 Hz, 1H), 7.78 (s, 1H); MS (ESI): $m/z = 313$ $[M^+ + H]$.

*5.4.8.7. 4′-(1-Imidazol-1-yl-propyl)-3,5-dimethyl-biphenyl-4-ol (**13**).* Synthesised according to Method G using **13a** (0.30 g, 0.71 mmol) and TBAF solution (1.0 M in THF, 0.78 mL, 0.78 mmol); white solid; yield: 0.19 g (85%); $R_f = 0.22$ (hexane/EtOAc, 5:1); IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2927 (w), 1705 (w), 1484 (s), 1188 (m), 1076 (w), 923 (m), 817 (w), 731 (s), 662 (s), 543 (w); δ_H ($CDCl_3$, 500 MHz): 0.95 (t, $J = 7.3$ Hz, 3H, CH_3), 2.23–2.26 (m, 2H), 2.31 (s, 6H), 5.04 (t, $J = 7.6$ Hz, 1H), 6.97 (s, 1H), 7.09 (s, 1H), 7.18 (s, 2H), 7.20 (d, $J = 8.2$ Hz, 2H), 7.49 (d, $J = 8.2$ Hz, 2H), 7.63 (s, 1H); δ_C ($CDCl_3$, 125 MHz): 11.1 (CH_3), 16.2 (CH_2), 28.6 (CH_3), 30.9 (CH_3), 63.1 (CH), 117.7 (CH), 126.8 (C_q), 127.1 (CH), 127.2 (CH), 129.3 (CH), 136.3 (C_q), 138.2 (C_q), 141.1 (C_q); MS (ESI): $m/z = 307$ $[M^+ + H]$.

*5.4.8.8. 4′-(1-Imidazol-1-yl-propyl)-3-methyl-biphenyl-4-ol (**14**).* Synthesised according to Method G using **14a** (0.24 g, 0.59 mmol) and TBAF solution (1.0 M in THF, 0.89 mL, 0.89 mmol); white solid; yield: 0.14 g (83%); $R_f = 0.22$ (hexane/EtOAc, 5:1); IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2933 (w), 2361 (w), 1602 (m), 1499 (s), 1398 (m), 1278 (s), 1129 (w), 1087 (w), 1075 (m), 927 (w), 815 (s), 739 (m), 659 (m); δ_H ($CDCl_3$, 500 MHz): 0.97 (t, $J = 7.3$ Hz, 3H), 2.23–2.29 (m, 2H), 2.32 (s, 3H), 5.04 (t, $J = 7.6$ Hz, 1H), 6.81 (d, $J = 8.3$ Hz, 1H), 7.01 (s, 1H), 7.13 (s, 1H), 7.19-7.23 (m, 3H), 7.33 (d, $J = 1.9$ Hz, 1H), 7.50 (d, $J = 8.3$ Hz, 2H), 7.67 (s, 1H); δ_C ($CDCl_3$, 125 MHz): 11.1 (CH_3), 16.2 (CH_2), 28.5 (CH_3), 63.3 (CH), 115.2 (CH), 117.9 (CH), 124.8 (CH), 125.4 (CH), 126.8, 127.0 (CH), 128.9 (CH), 129.6 (CH), 131.1 (CH), 136.2 (C_q), 137.9 (C_q), 141.2 (C_q), 154.9 (C_{OH}); MS (ESI): $m/z = 293$ $[M^+ + H]$.

*5.4.8.9. 3-Chloro-4′-(1-imidazol-1-yl-propyl)-biphenyl-4-ol (**15**).* Synthesised according to Method G using **15a** (0.27 g, 0.63 mmol) and TBAF solution (1.0 M in THF, 0.91 mL, 0.91 mmol); white solid; yield: 0.18 g (86%); $R_f = 0.25$ (hexane/EtOAc, 5:1); IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2360(m), 1497 (s), 1293 (s), 1054 (m), 810 (s), 735 (m), 659 (m); δ_H ($CDCl_3$, 500 MHz): 0.96 (t, $J = 7.3$ Hz, 3H), 2.23–2.29 (m, 2H), 5.04 (t, $J = 7.3$ Hz, 1H), 6.99 (d, $J = 8.3$ Hz, 1H), 7.04 (s, 1H), 7.13 (s, 1H), 7.19–7.23 (m, 3H), 7.47 (d, $J = 1.9$ Hz, 1H), 7.52 (d, $J = 8.3$ Hz, 2H), 7.80 (s, 1H); δ_C ($CDCl_3$, 125 MHz): 11.0 (CH_3), 28.4 (CH_2), 63.5 (CH), 116.9 (CH), 118.1 (CH), 126.6 (CH), 127.0 (CH), 127.1(CH), 127.9 (CH), 135.8 (C_q), 139.9 (C_q); MS (ESI): $m/z = 313$ $[M^+ + H]$.

5.5. Docking studies

5.5.1. Ligands

All molecular modelling studies were performed on Intel(R) P4 CPU 3.00 GHz running Linux Suse 10.1. The structures of the inhibitors were built with SYBYL 7.3.2 (Sybyl, Tripos Inc., St. Louis, Missouri, USA) and energy-minimized in MMFF94s force field [43] as implemented in Sybyl. The resulting geometries for our compounds were then subjected to *ab initio* calculation employing the B3LYP functional [44,45] in combination with a 6-31G* basis set using the package Gaussian03 (Gaussian, Inc., Pittsburgh, PA, 2003).

5.5.2. Docking

Molecular docking calculations were performed for various inhibitors of Table 1. Since the GOLD docking program allows flexible docking of the compounds, no conformational search was employed to the ligand structures. GOLD gave the best poses by a genetic algorithm (GA) search strategy, and then various molecular features were encoded as a chromosome.

Ligands were docked in 50 independent genetic algorithm (GA) runs using GOLD. Heme iron was chosen as active-site origin, while the radius was set equal to 19 Å. The automatic active-site detection was switched on. A distance constraint of a minimum of 1.9 and a maximum of 2.5 Å between the sp^2-hybridized nitrogen of the imidazole and the iron was set. Further, some of the GOLDSCORE parameters were modified to improve the weight of hydrophobic interaction and of the coordination between iron and nitrogen. The genetic algorithm default parameters were set as suggested by the GOLD authors [41]. On the other hand, the annealing parameters of fitness function were set at 3.5 Å for hydrogen bonding and 6.5 Å for Van der Waals interactions.

All 50 poses for each compound were clustered with ACIAP [46,47] and the representative structure of each significant cluster was selected. The quality of the docked representative poses was evaluated based on visual inspection of the putative binding modes of the ligands, as outcome of docking simulations and cluster analysis.

Acknowledgement

This work was supported by the Fonds der Chemischen Industrie. U. E. H. is grateful to the European Postgraduate School 532 (DFG) for a scholarship. We thank Professor J. Hermans, Cardiovascular Research Institute (University of Maastricht, The Netherlands), for providing us with V79MZh11B1 cells expressing human CYP11B1. Thanks are due to G. Schmitt, T. Scherzberg and J. Jung for technical assistance.

Appendix. Supplementary information

Supplementary data regarding CYP3A4 and CYP11B1 (one table) can be found in the online version, at doi:10.1016/j.ejmech.2009.01.002.

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