Full Paper

CYP17 Inhibitors. Annulations of Additional Rings in Methylene Imidazole Substituted Biphenyls: Synthesis, Biological Evaluation and Molecular Modelling

Mariano A. E. Pinto-Bazurco Mendieta[1], Matthias Negri[1], Qingzhong Hu[1], Ulrike E. Hille[1], Carsten Jagusch[1], Kerstin Jahn-Hoffmann[1], Ursula Müller-Vieira[2], Dirk Schmidt[3], Thomas Lauterbach[3], and Rolf W. Hartmann[1]

[1] Pharmaceutical and Medicinal Chemistry, Saarland University, Saarbrücken, Germany
[2] Pharmacelsus CRO, Science Park, Saarbrücken, Germany
[3] Schwarz Pharma, Monheim, Germany

Twenty-one novel compounds originating from two classes of annulated biphenyls were synthesized as mimetics of the steroidal A- and C-rings and examined for their potency as inhibitors of human CYP17. Selected compounds were tested for inhibition of the hepatic CYP enzyme 3A4. Potent CYP17 inhibitors were found for each class, compound **9** (17 and 71% at 0.2 and 2 μM, respectively) and **21** (591 nM). Compound **21** showed only weak inhibition of CYP3A4 (32 and 64% at 2 and 10 μM, respectively). Both compounds, however, exhibited moderate to strong inhibition of the glucocorticoid-forming enzyme CYP11B1. The most interesting compounds were docked into our protein model. They bound into one of the modes which we have previously published. New interaction regions were identified.

Keywords: CYP3A4 / Docking studies / 17α-Hydroxylase-17,20-lyase (CYP17) inhibitors / Prostate cancer / Steroidomimetics

Received: December 6, 2007; accepted: January 18, 2008

DOI 10.1002/ardp.200700251

Introduction

Prostate cancer is a major cause of death in elderly men worldwide [1]. It is widely demonstrated that high androgen levels (testosterone and dihydrotestosterone) stimulate tumor growth in prostate cancer [2]. Thus, androgen receptor antagonists [3] and gonadotropin-releasing hormone analogues [4] are used as a standard therapy. The major drawback of these therapies is the fact that they do not reduce androgen concentrations or only affect testicular androgen production, allowing androgens still to be produced in the adrenals.

Correspondence: Prof. Dr. Rolf W. Hartmann, Pharmaceutical and Medicinal Chemistry, Saarland University, P.O. Box 151150, D66041 Saarbrücken, Germany.
E-mail: rwh@mx.uni-saarland.de
Fax: +49 681 302 4386

Abbreviations: 1,1′-carbonyldiimidazole (CDI); 4-(dicyanomethylene)-2-methyl-6-(*p*-dimethylaminostyryl)-4-*H*-pyran (DCM); *N*-methyl-2-pyrrolidone (NMP); tetrabutylammonium bromide (TBAB)

Therefore, a new promising target is 17α-hydroxylase-17,20-lyase (CYP17), the key enzyme for the biosynthesis of androgens. It is catalyzing the conversion of pregnenolone or progesterone to DHEA or androstenedione, respectively. Even more, this target has already clinically proven success with the antimicotic ketoconazole which is also a weak inhibitor of CYP17 [5]. In previous works, we could demonstrate *in-vitro* and *in-vivo* activity for steroidal [6] and non-steroidal [7–10, 11] compounds. Some of these compounds had been designed as mimetics of the steroidal AC-rings (Fig. 1) [10, 11]. Since they had shown a high activity and a good selectivity, we chose them for further optimizations.

Very recently [12], we found new highly potent and selective compounds, which showed better pharmacokinetic and pharmacodynamic profiles than abiraterone, a CYP17 inhibitor currently undergoing clinical phase II [13], by replacing the A-ring-mimicking benzene nucleus with different heterocycles.

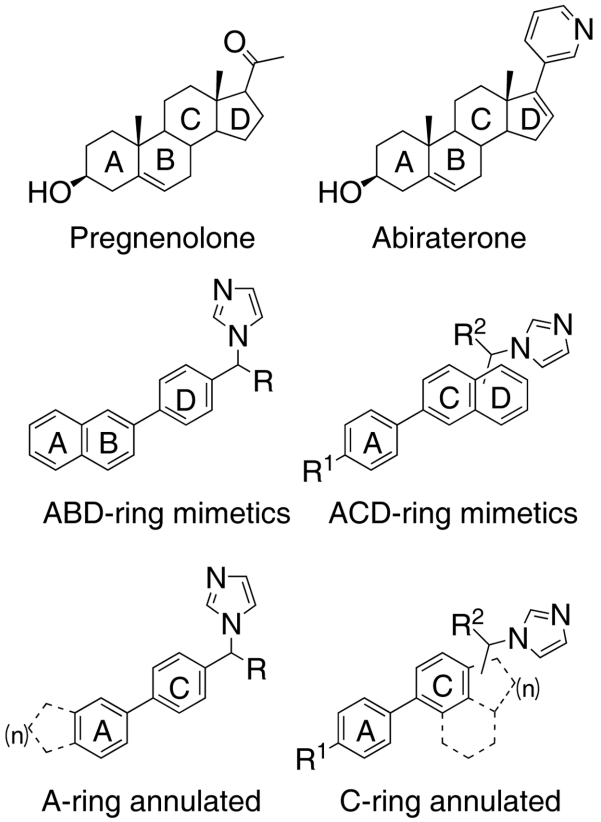
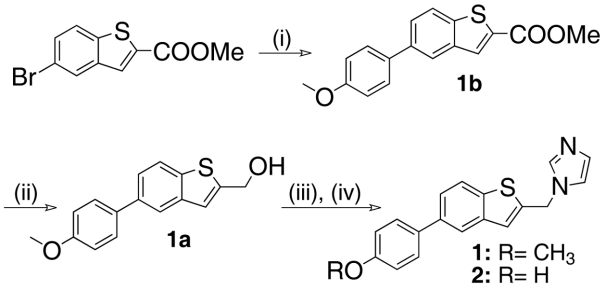


Figure 1. Substrate, abiraterone, described ABD- and ACD-ring mimetic CYP17 inhibitors, and A- and C-ring-annulated compounds of the present study.



Reagent and conditions: (i) a: 4-bromo-anisole, *t*-BuLi, THF, −78°C, 30 min; b: $ZnCl_2$, 0°C, 30 min; c: $PdCl_2(PPh_3)_2$, 16 h. (ii) $LiBH_4$, toluene, THF, Et_2O, 110°C, 16 h. (iii) Method A1: CDI, imidazole, NMP, 180°C, 16 h. (iv) Method B: BBr_3, DCM, -78°C to 0°C, 16 h.

Scheme 1. Synthesis route of compounds **1** and **2**.

In order to further explore the spatial limitations surrounding the A- and C-ring binding regions, in this work, we expand the corresponding biphenyl rings by annulation of different aromatic and non-aromatic rings. In this way, two different compound classes were synthesized (Fig. 2), by either annealing the C-ring (compounds **1**–**11**) or by otherwise annealing the A-ring (compounds **12**–**21**). Like in previous works [10–12], 1-imidazole linked with a methylene spacer was introduced as nitrogen-bearing heterocycle, since the complexation of the heme iron by an aromatic nitrogen is an important prerequisite for inhibition of cytochrome P450 enzymes [14]. We have also shown [10–12] that the introduction of a fluorine, hydroxy, and methoxy group in the A-ring strongly contributed to a better inhibition of our target enzyme. In the following, the synthesis, CYP17 inhibitory activities, and molecular modelling studies are presented and these data are compared to the ones recently obtained with ABD- and ACD-ring mimetics (Fig. 1) [9]. Besides, for reasons of selectivity, inhibition of the most crucial hepatic CYP enzyme CYP3A4 was monitored, and for selected compounds inhibition of the glucocorticoid-forming enzyme CYP11B1 was also determined. The most promising compounds were docked into our protein model, and the key interactions with the enzyme were elucidated.

Results

Chemistry

The syntheses of compounds **1**–**21** are shown in Schemes 1–7. In persuing our aim to explore the binding regions surrounding the A- and C-rings, different aro-

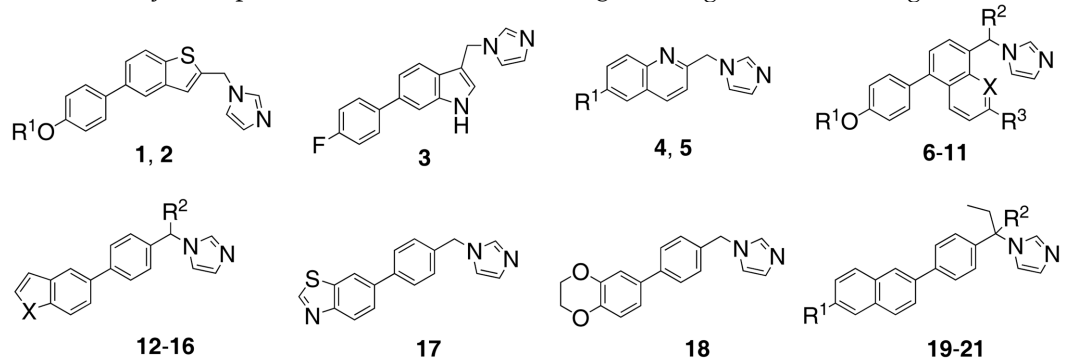
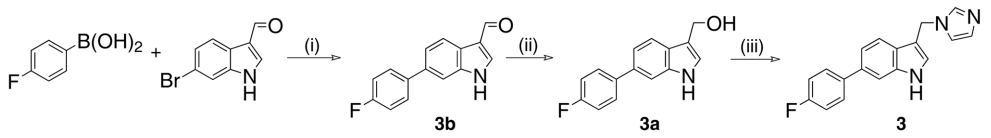
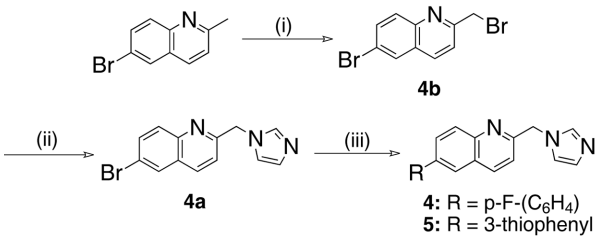


Figure 2. List of synthesized compounds **1**–**21**.



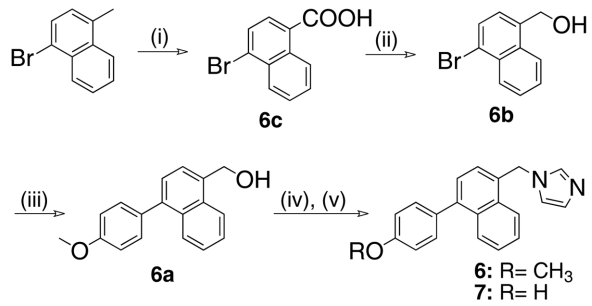
Reagent and conditions: (i) Method C1: Na_2CO_3, $Pd(PPh_3)_4$, toluene/EtOH/H_2O, reflux, 5 h; (ii) Method D: $NaBH_4$, MeOH, rt, 2 h; (iii) Method A2: CDI, acetonitrile, reflux, 18 h.

Scheme 2. Synthesis route of compound 3.



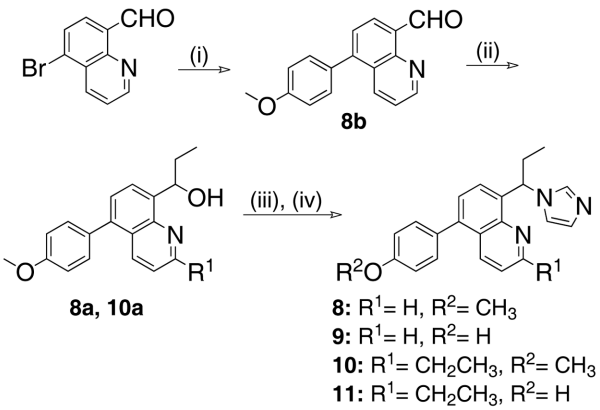
Reagents and conditions: (i) NBS, CCl_4, 75°C, 16 h; (ii) Imidazole, K_2CO_3, 18-crown-6, acetonitrile, 100°C, 16 h; (iii) Method C1: 4-fluorophenylboronic acid (**5**: 3-thiophenylboronic acid), Na_2CO_3, $Pd(PPh_3)_4$, toluene/MeOH/H_2O, 70°C, 5 h.

Scheme 3. Synthesis route of compounds **4** and **5**.



Reagents and conditions: (i) $KMnO_4$, pyridine, H_2O, 50°C, 4 d; (ii) $LiAlH_4$, Et_2O, 35°C, 16 h; (iii) Method C2: 4-methoxyphenylboronic acid, Cs_2CO_3, $Pd(OAc)_2$, TBAB, toluene/EtOH/H_2O, 110°C, 16 h: (iv) Method A1: CDI, imidazole, NMP, 180°C, 2 d; (v) Method B: BBr_3, DCM, -78°C to 0°C, 16 h.

Scheme 4. Synthesis route of compounds **6** and **7**.



Reagents and conditions: (i) Method C2: 4-methoxyphenylboronic acid, Cs_2CO_3, $Pd(OAc)_2$, TBAB, toluene/EtOH/H_2O, 110°C, 16 h; (ii) Method E: EtMgBr, THF, 0°C to rt, 16 h; (iii) Method A1: CDI, imidazole, NMP, 180°C, 1 – 2.5 d; (iv) Method B: BBr_3, DCM, -78°C to – °C, 16 h.

Scheme 5. Synthesis route of compounds **8 – 11**.

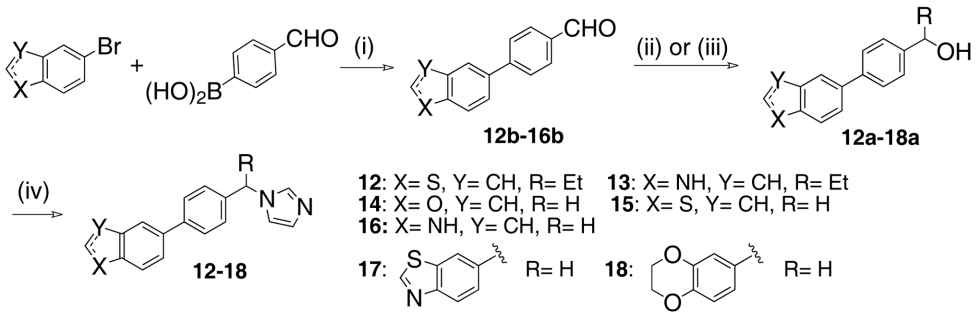
matic and non-aromatic moieties were annulated to the A (Schemes 1 – 5) or C (Schemes 6, 7) ring. The coupling of the biphenylic moiety was achieved by means of Suzuki coupling [15] (method C) except for the synthesis of compounds **1** and **2** (Scheme 1) where a Negishi coupling had to be applied. When the necessary bromides for the couplings were not commercially available, they were prepared by bromination using NBS (*N*-bromosuccinimide) (Scheme 3). The imidazoles were introduced by performing a S_Nt reaction with 1,1′-carbonyldiimidazole (CDI) and the corresponding alcohol [16] (method A) or via S_N2 reaction of an alkyl bromide with imidazole (Scheme 3). The alcohols were obtained from either the carboxylic derivatives (Schemes 1, 4) or from the aldehydes (methods D, E). In most cases, the methoxy-substituted compounds were submitted to an ether cleavage (method B). For the preparation of compound **21**, the hydroxyl group on the naphthalene had to be protected before the Suzuki coupling due to otherwise very low yields [15].

Biological results

Inhibition of CYP17 was evaluated using human enzyme expressed in *E. coli* [17]. The percent inhibition values of the compounds were determined with the 50 000 *g* sediment of the *E. coli* homogenate, progesterone (25 μM) as substrate and the inhibitors at concentrations of 0.2 and 2.0 μM. Separation of substrate and product was accomplished by HPLC using UV detection [7].

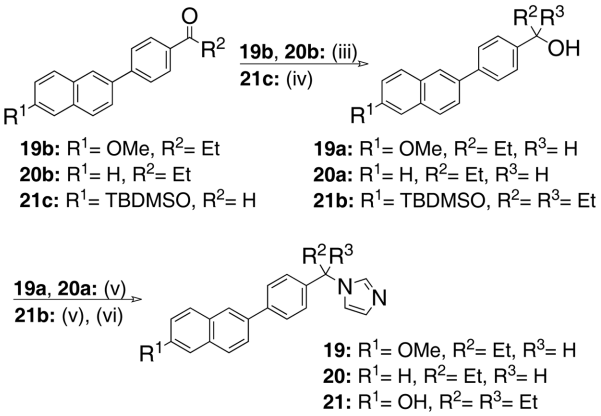
In contrast to the reference compound ketoconazole, the C-ring-annulated compounds (**1 – 11**, Table 1) mostly showed moderate to no inhibition with exception of the quinoline compound **9**, which showed 71% inhibition at 2 μM. The prolongation of the C-ring in compounds **1 – 5** led to non-active compounds. The quinolines **8 – 11** bearing an ethyl moiety at the methylene linker showed an overall better activity than the naphthalenes **6** and **7**.

The A-ring-annulated compounds (**12 – 21**, Table 2) showed moderate to good activities. However, they did



Reagents and conditions: (i) Method C1: $Pd(PPh_3)_4$, TBAB, Na_2CO_3, toluene/EtOH/H_2O, reflux, 16 h; (ii) Method E: **12a**–**13a**: EtMgBr, THF, 0°C to rt, 16 h: (iii) Method D: **14a**–**18a**: $NaBH_4$, MeOH, reflux, 2 h; (iv) Method A1: CDI, NMP, reflux, 3 h.

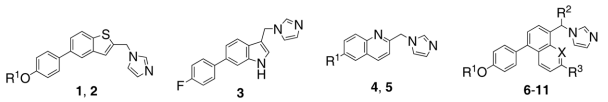
Scheme 6. Synthesis route of compounds **12**–**18**.



Reagents and conditions: (i) TBDMSCl (tert-Butylchlorodimethylsilane), CH_2Cl_2, imidazole, rt, 4 h; (ii) Method C1: boronic acid, Na_2CO_3, $Pd(PPh_3)_4$, toluene/MeOH/H_2O, 70°C, 5 h: (iii) Method D: **19b**, **20b**: $NaBH_4$, MeOH, reflux, 2 h: (iv) Method E: **21c**: EtMgBr, THF, rt, 5 h; (v) Method A1: **19a**, **20a**: CDI, NMP, 170°C, 7 h; (vi) **21b**: TBAF, THF, rt, 4 h.

Scheme 7. Synthesis route of compounds **19**–**1**.

Table 1. Inhibition of CYP17 by C-ring-annulated compounds **1**–**11**.



Comp.	Structures				CYP17 % Inhibition[a]	
	R^1	R^2	R^3	X	(0.2 μM)	**(2 μM)**
1	Me				0	18
2	H				6	13
3					0	12
4	p-F-(C_6H_4)				1	12
5	3-thiophenyl				0	11
6	Me	H	H	CH	0	5
7	H	H	H	CH	1	12
8	Me	Et	H	N	3	32
9	H	Et	H	N	17	71[b]
10	Me	Et	Et	N	6	57
11	H	Et	Et	N	5	57
KTZ[c]					29	

[a] Data shown were obtained by performing the tests in duplicate. The deviations were below ± 5%. Concentration of progesterone (substrate) was 25 μM.

[b] IC_{50} = 817 nM.

[c] KTZ: ketoconazole.

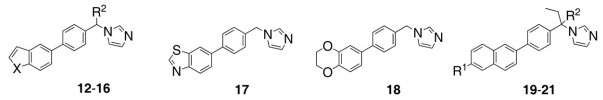
not exceed the activity of compound **9**. The most active compounds in this class showing percent-inhibition values of more than 70% at 2 μM are compound **13** bearing an indole (H-bond donor) and compounds **19** and **21** bearing a methoxy group (H-bond acceptor) or a hydroxy group (H-bond acceptor and donor), respectively, at the the 6-position of a naphthalene. Absence of these substituents in the latter compounds diminishes the inhibitory activity (compound **20**). The introduction of an ethyl moiety at the methylene linker led to an increase in activity for compounds **15** to **12** and **16** to **13**. All other aromatic heterocycles resulted in only moderate inhibitors.

When comparing the activities of the compounds of this study to the ones of the parent compounds [11], it must be mentioned that the structural modifications did not increase activities.

Regarding selectivity against other CYP enzymes, a broader spectrum of our compounds was tested for inhibition of the hepatic enzyme CYP3A4. This enzyme is responsible for the metabolism of lipophilic substances and, therefore, responsible for about 50% of current prescription drugs [18]. While compounds **12**–**19** showed a strong inhibition of this enzyme (>85% inhibition at 2 μM), compound **21** exhibited low inhibitory activity toward CYP3A4 (32% at 2 μM and 64% at 10 μM).

Thus, compound **21** together with the most promising compound **9** of the C-ring-annulated class of compounds, were further tested for inhibition of the steroidogenic enzyme CYP11B1. Its importance relies on the fact that it

Table 2. Inhibition of CYP17 by A-ring-annulated compounds **12**–**21**.



Comp.	Structures			CYP17 % Inhibition[a]	
	R^1	R^2	X	(0.2 μM)	(2 μM)
12		Et	S	7	40
13		Et	NH	21	75[b]
14		H	O	5	27
15		H	S	0	21
16		H	NH	2	39
17				5	39
18				0	17
19	OMe	H		19	74
20	H	H		7	43
21	OH	Et		16	74*
KTZ[c]				29	

[a] Data shown were obtained by performing the tests in duplicate. The deviations were below ± 5%. Concentration of progesterone (substrate) was 25 μM.
[b] IC_{50} = 667 nM.
[c] KTZ: ketoconazole.
[d] IC_{50} = 703 nM.
* IC_{50} = 591 nM.

catalyzes the last step in glucocorticoid formation, namely the transformation of 11-deoxycortisol into cortisol. For the assay [19], V79MZh11B1 cells expressing human CYP11B1 were used. Both compounds showed strong inhibition of the enzyme at the tested concentrations (**9**: 86 and 94% at 0.2 and 2 μM; **21**: 81 and 95% at 0.2 and 2 μM).

Molecular modelling studies

Using selected compounds, we explored the binding modes of the A- and C-ring-annulated biphenyls. Several active and less active compounds (C-ring: **6**–**11** (R, S); A-ring: **13** (R, S), **16**, **17**, **19** (R, S) and **21**) were docked by means of the GOLD v 3.0.1 software [20] in the active site of our homology model of CYP17 [12].

Aware of the limitations of docking [21], the resulting poses of each compound were clustered with AClAP (autonomous hierarchical agglomerative cluster analysis) [22] and the representative poses of each cluster were subjected to a critical visual inspection. H-bonds, π-π, and hydrophobic interactions, as well as steric clashes were measured and evaluated. The necessity of iron-nitrogen complexation [14] for inhibitory activity was also considered. Furthermore, the GOLD v 3.0.1 software, used with a slightly modified GOLDSCORE, was tested on different crystallized CYP enzymes. This program could reproduce quite well the correct orientation of co-crystallized ligands (data not shown). Moreover, GOLD v 3.0.1 produced reliable poses for abiraterone in our CYP17 model [12], oriented like described for pregnenolone [23]. With these findings, the obtained results can be considered very probable.

All compounds principally showed poses in BM1 – one of two binding modes we have identified for biphenyl type inhibitors [12] – with the modified biaryl-skeleton oriented almost parallel to the I-helix (Fig. 3). Furthermore, the observed increase in activity caused by the ethyl group at the methylene spacer can be explained by the anchoring function of this substituent, namely by hydrophobic interactions with the tiny hydrophobic pocket next to the heme, as already described [12].

Regarding the docked C-ring annulated compounds, both enantiomers of compounds **6**–**11** showed mainly one binding mode, except for compounds **6** and **7**, which switch the annealed ring toward or opposite the I-helix (Fig. 3A). The annealed ring is directed toward the kink of the I-helix [12], stabilized in its orientation by π-π and hydrophobic interactions with the residues Phe114, Gly301-Ala302, Glu305, Thr306, Ile371, and Val482 (Fig. 3A). Nevertheless, for all three compound couples sterical hindrance, changing in its extend from pair to pair (**8**–**9** < **6**–**7** < **10**–**11**) between the annulated C-ring and the surrounding amino acids, was observed. The extension of the annealed ring system, like the introduction of a space-demanding group, *e.g.* ethyl was crucial, as seen by the reduced activity of compounds **10** and **11** with respect to **8** and **9**.

For the inhibitory activity of compounds **8**–**11**, the presence of the aromatic nitrogen in the annealed C-ring was striking; it delocalizes the negative charge of the ring system and is capable of H-bond formation with the catalyticly important Thr306 and the 1-N of the imidazole.

Compounds **6**–**11** (R, S) showed the ability of forming an H-bond net between the R^1 substituent of the A-ring (Table 1) and the amino acids Arg109 and His235, as it was already observed for their parent compounds [9]. OH showed the highest activity values, leading to the conclusion that an H-bond donor group in this position was necessary.

As for the A-ring annulated compounds, **13** (R, S), **16** (R, S), **17**, **19** (R, S) and **21** were docked into our homology model (Fig 3B). Even these elongated compounds are basically oriented in BM1. However, the extension of the A-ring caused a shift in the interaction area. The substituent R^1 showed H-bond formations with Asn202, Lys231, His235, and, eventually, Arg109, but even hydrophobic

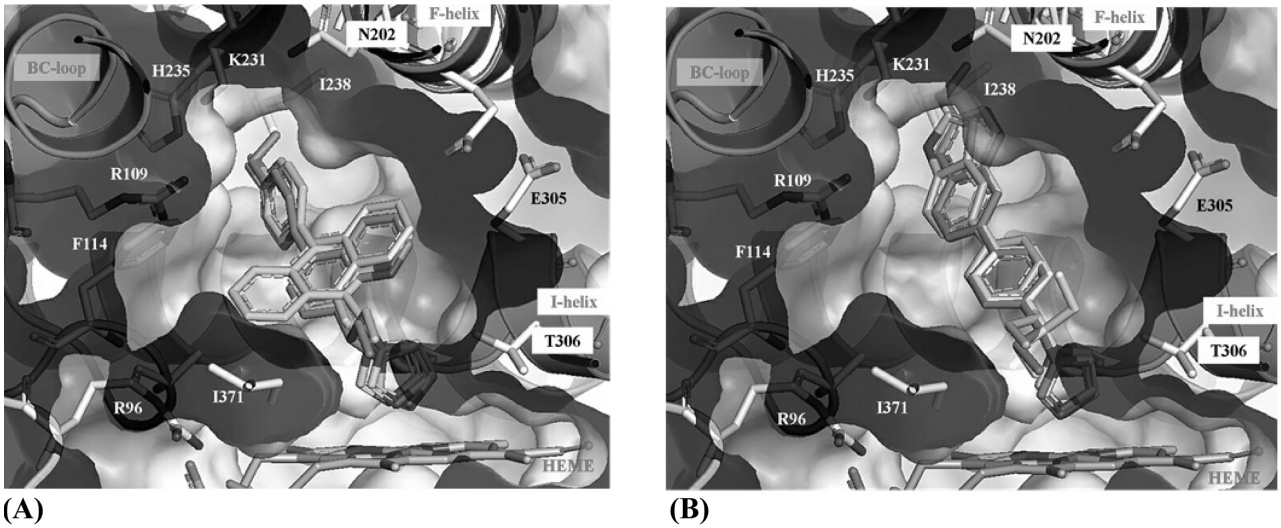


Figure 3. A cross-section of the solvent-accessible surface of CYP17 is shown, revealing the active-site cavity with docked: (**A**) C-ring-annulated **6** (green), **7** (yellow), **8** (magenta), and **9** (cyano), and (**B**) A-ring-annulated compounds **13** (cyan), **19** (magenta), and **21** (yellow). Further, heme, interacting residues, and ribbon-rendered tertiary structure of the active site are shown. Figures were generated with Pymol (http://www.pymol.org).

interactions between the OMe group in R^1 and Ile198 and Ile238. Almost the same hydrophobic interactions, as reported previously [12], between the aromatic core structure and the prevalently hydrophobic surroundings of the active site could be observed. Additionally, the extended A-ring can undergo π-π and hydrophobic interactions with Phe114, Ile205, His235, Gly297, and Thr294. Comparing compounds **13** and **16**–**17**, the presence of a H-bond donor hetero-atom in the annealed A-ring appeared necessary for H-bond formation with His235 and Asn202, with the intent to mimic the *para*-OH of some of the most active parent compounds [9].

Discussion

Similar to our ABD-mimetics [9], the annulation at the A-ring led mostly to low to moderately active compounds with exception of **9** which showed good inhibition of CYP17. On the other hand, the annealing of an additional ring at the C-ring resulted in moderately to highly active compounds, similar to our findings in the class of ACD-ring mimetic inhibitors [9].

The best compounds in terms of activity in each class are **9** for the A-ring-expanded and **21** for the C-ring-annulated compounds. Compound **21** is also selective against CYP3A4. Based on both biological results and molecular modelling studies (Fig. 3), we conclude that space occupancy in both the A-ring and the C-ring area is appropriate for the design of new lead structures. The presence of specific heteroatoms, especially N in the annealed rings, is recommended, since this structure modification is capable of H-bond formation and of modifying the electrostatic properties of the annealed ring system. The importance for CYP17 activity of an ethyl substituent at the methylene linker was reiterated as well.

One of our goals in this work was the discovery of a new, more complex lead structure, with the aim of increasing potency and selectivity toward other CYP enzymes. This was achieved with compounds **9** and **21**. For further increasing the activity of compound **9**, we suggest an lead structure optimized by substitution of the annealed ring with a 5-membered aromatic ring bearing a heteroatom, like imidazole, or the exchange of the whole bicyclic structure at the C-ring with a 7-membered ring. These modified compounds are likely to better fit in the active site, due to reduced steric hindrance and hydrophobic repulsion.

We thank the Fonds der Chemischen Industrie for financial support. U. E. H. is grateful to the European Postgraduate School 532 (DFG) for a scholarship. We also thank Dr. J. J. R. Hermans, Cardiovascular Research Institute, University of Maastricht (The Netherlands), for providing us with V79MZh11B1 cells.

The authors have declared no conflict of interest.

Experimental

CYP17 preparation and assay: As source of human CYP17, our *E. coli* system [17] (co-expressing human CYP17 and NADPH-P450 reductase) was used and the assay was performed as previously

described [7] taking unlabeled progesterone as substrate and applying HPLC with UV-detection for separation.

Inhibition of hepatic CYP enzymes: The recombinantly expressed enzymes from baculovirus-infected insect microsomes (supersomes) were used and the manufacturer's instructions (www.gentest.com) were followed.

Inhibition of CYP11B1: V79MZh11B1 cells expressing the respective human enzyme were used and our assay procedure using [4-^{14}C]-11-deoxycorticosterone was applied [19].

Chemistry

General

Melting points were determined on a Mettler FP1 (Mettler-Toledo, Greifensee, Switzerland) melting point apparatus and are uncorrected. IR spectra were recorded neat on a Bruker Vector 33FT-infrared spectrometer (Bruker Bioscience, Billerica, MA, USA). ^{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 ionisation) mass spectra were determined on a TSQ quantum (Thermo Electron Corporation, Bremen, Germany) 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, Düren, Germany). Boronic acids and bromoaryls used as starting materials were commercially obtained (CombiBlocks, USA; Chempur, Karlsruhe, Germany; Aldrich, München, Germany, Acros, Germany).

*Methyl 5-(4-methoxyphenyl)benzo[b]thiophene-2-carboxylate **1b***

To a solution of 1-bromo-4-methoxybenzene (1.32 mL, 10.52 mmol) in dry THF (20 mL) cooled at −78°C, *t*-BuLi (1.5 M, 14.48 mL, 21.72 mmol) was slowly added. After 30 min $ZnCl_2$ (0.5 M, 24.53 mL, 12.26 mmol) was carefully added and after 10 min it was let to warm up to rt. After additional 20 min, methyl 5-bromobenzo[*b*]thiophene-2-carboxylate (1.90 g, 7.00 mmol) and bis-(triphenylphosphine)-palladium (II)-dichloride (0.49 g, 0.70 mmol) were prepared in dry THF (30 mL) under nitrogen atmosphere and the reagent was added at 0°C and the reaction mixture left stirring overnight; yield: 1.45 g (69%); R_f = 0.77 (hexane / EtOAc, 7 : 3); d_H ($CDCl_3$, 500 MHz) 3.87 (s, 3H), 3.96 (s, 3H), 7.01 (d, J = 8.8 Hz, 2H), 7.58 (d, J = 8.8 Hz, 2H), 7.67 (dd, J = 1.8 Hz, J = 8.5 Hz, 1H), 7.89 (d, J = 8.5 Hz, 1H), 8.01 (s, 1H), 8.09 (s, 1H).

*(5-(4-Methoxyphenyl)benzo[b]thiophen-2-yl)methanol **1a***

To a solution of **1b** (0.55 g, 1.84 mmol) in THF (30 mL), toluene (15 mL) and diethyl ether (15 mL) $LiBH_4$ (0.05 g, 2.21 mmol) was added and heated to reflux for 2 h; yield: 0.47 g (95%); R_f = 0.44 (hexane / EtOAc, 7 : 3); d_H ($CDCl_3$, 500 MHz) 3.87 (s, 3H), 4.95-5.01 (m, 2H), 6.99-7.01 (m, 3H), 7.53 (dd, J = 1.8 Hz, J = 8.4 Hz, 1H), 7.56-7.59 (m, 2H), 7.85 (d, J = 8.4 Hz, 1H), 7.88 (s, 1H).

Method A: CDI reaction

To a solution of the corresponding alcohol (1 eq) in NMP (*N*-methyl-2-pyrrolidone) (method A1) or acetonitrile (method A2) (10 mL/mmol) CDI (5 eq) was added. Then, the solution was heated to reflux for 4 to 18 hours. After cooling to ambient temperature, it 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. Then the desired product was purified by chromatography on silica gel.

*1-((5-(4-Methoxyphenyl)benzo[b]thiophen-2-yl)methyl)-1H-imidazole **1***

Synthesized according to method A1 using **1a** (0.25 g, 0.93 mmol) and CDI (1.20 g, 7.40 mmol); yield: 0.20 g (68%); white solid: m.p. 169°C; R_f = 0.40 (DCM / MeOH, 95 : 5); IR (ATR) ν (cm^{-1}) 3106 (w), 1607 (w), 1516 (m), 1453 (w), 1436 (w), 1277 (m), 1254 (m), 1231 (m), 1194 (w), 1072 (w), 1031 (m), 1015 (w), 908 (w), 806 (s), 744 (s), 667 (m); d_H ($CDCl_3$, 500 MHz) 3.86 (s, 3H), 5.35 (s, 2H), 6.99 – 7.01 (m, 3H), 7.12 (s, 1H), 7.17 (s, 1H), 7.52 – 7.56 (m, 3H), 7.62 (s, 1H), 7.80 (d, J = 8.4 Hz, 1H), 7.86 (s, 1H); d_C ($CDCl_3$, 125 MHz) 46.3, 55.3, 114.3, 119.1, 121.5, 122.6, 123.3, 124.2, 128.3, 130.0, 133.4, 137.2, 137.9, 138.3, 139.8, 139.8, 159.1.

*3-(1H-Imidazol-1-ylmethyl)-6-(4-fluorophenyl)-1H-indole **3***

Synthesized according to method A2 using **3a** (0.25 g, 1.04 mmol) and CDI (0.34 g, 2.08 mmol); yield: 0.15 g (52%); brown solid: m.p. 171 – 173°C; R_f = 0.24 (EtOAc / MeOH, 95 : 5); d_H ($CDCl_3$, 500 MHz) 5.29 (s, 2H), 6.91 (bs, 1H), 7.02 (bs, 1H), 7.06 (t, J = 8.8 Hz, 2H), 7.18 (dd, J = 1.7 Hz, J = 8.3 Hz, 1H), 7.28 (d, J = 2.5 Hz, 1H), 7.41 (d, J = 8.5 Hz, 1H), 7.50 (d, J = 1.7 Hz, 1H), 7.52 (dd, J = 5.3 Hz, J = 8.8 Hz, 2H), 7.71 (bs, 1H), 10.90 (bs, 1H); d_C ($CDCl_3$, 125 MHz) 42.8 (CH_2), 110.1 (CH), 115.5 (CH), 118.4 (CH), 119.3 (CH), 119.8 (CH), 121.8 (C_q), 124.7 (CH), 125.5 (C_q), 128.7 (CH), 128.9 (CH), 135.1 (CH), 136.8 (C_q), 137.2 (C_q), 138.0 (C_q), 162.1 (CF); MS (ESI): m/z = 292 [M^+ + H].

*1-(4-(4-Methoxyphenyl)naphthalen-1-ylmethyl)-1H-imidazole **6***

Synthesized according to method A1 using **6a** (0.38 g, 1.42 mmol) and CDI (1.84 g, 11.35 mmol); yield: 0.37 g (83%); white solid: m.p. 192°C; R_f = 0.54 (DCM / MeOH, 95 : 5); IR (ATR) ν (cm^{-1}) 3109 (w), 1609 (m), 1507 (s), 1460 (w), 1392 (w), 1284 (m), 1246 (s), 1176 (w), 1108 (w), 1076 (w), 1031 (m), 830 (m), 770 (m), 735 (w), 664 (w); d_H ($CDCl_3$, 500 MHz) 3.89 (s, 3H), 5.61 (s, 2H), 6.97 (s, 1H), 7.04 (d, J = 8.6 Hz, 2H), 7.11 (s, 1H), 7.19 (d, J = 7.3 Hz, 1H), 7.36 (d, J = 7.3 Hz, 1H), 7.39 (d, J = 8.6 Hz, 2H), 7.46 – 7.49 (m, 1H), 7.53 – 7.56 (m, 1H), 7.61 (s, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.99 (d, J = 8.4 Hz, 1H); d_C ($CDCl_3$, 125 MHz) 48.8, 53.4, 55.3, 113.8, 119.4, 122.5, 125.7, 126.1, 126.4, 126.7, 127.3, 129.6, 130.4, 131.0, 131.1, 132.2, 132.5, 137.5, 141.2, 159.1; (ESI): m/z = 315 [M^+ + H].

*8-(1-(1H-Imidazol-1-yl)propyl)-5-(4-methoxyphenyl)-quinoline **8***

Synthesized according to method A1 using **8a** (0.40 g, 1.36 mmol) and CDI (0.88 g, 5.45 mmol); yield: 0.24 g (51%); white solid: m.p. 135°C; R_f = 0.42 (DCM / MeOH, 95 : 5); IR (ATR) ν (cm^{-1}) 2967 (w), 1609 (m), 1515 (s), 1465 (w), 1284 (m), 1248 (s), 1176 (m), 1110 (w), 1074 (w), 1031 (m), 824 (s), 735 (w), 666 (m), 541 (w), 530 (w), 514 (w); d_H ($CDCl_3$, 500 MHz) 1.06 (t, J = 7.3 Hz, 3H), 2.33 – 2.49 (m, 2H), 3.89 (s, 3H), 6.64 – 6.67 (m, 1H), 7.04 (d, J = 8.7 Hz, 2H), 7.06 (s, 1H), 7.13 (m, 1H), 7.35 (d, J = 8.7 Hz, 2H), 7.38 (dd, J = 4.1 Hz, J = 8.6 Hz, 1H), 7.43 (d, J = 7.5 Hz, 1H), 7.55 (d, J =

7.5 Hz, 1H), 7.79 (s, 1H), 8.25 (dd, *J* = 1.7 Hz, *J* = 8.6 Hz, 1H), 8.94 (dd, *J* = 1.7 Hz, *J* = 4.1 Hz, 1H);d_C ($CDCl_3$, 125 MHz) 11.4, 28.2, 55.4, 57.0, 114.0, 118.0, 121.2, 125.3, 126.8, 127.0, 128.9, 131.0, 131.4, 134.7, 137.1, 137.8, 140.3, 145.7, 149.4, 159.3; (ESI): *m/z* = 344 [M^+ + H].

8-(1-(1H-Imidazol-1-yl)propyl)-2-ethyl-5-(4-methoxyphenyl)quinoline ***10***

Synthesized according to method A1 using **10a** (0.40 g, 1.25 mmol) and CDI (1.61 g, 9.96 mmol); yield: 0.27 g (59%); white solid: m.p. 157°C; R_f = 0.56 (DCM / MeOH, 95 : 5); IR (ATR) ν (cm^{-1}) 2969 (w), 1609 (s), 1576 (w), 1517 (s), 1498 (w), 1460 (w), 1285 (w), 1247 (s), 1177 (m), 1110 (w), 1072 (w), 1032 (m), 825 (w), 738 (m), 664 (m); d_H ($CDCl_3$, 500 MHz) 1.08 (t, *J* = 7.3 Hz, 3H), 1.47 (t, *J* = 7.6 Hz, 3H), 2.37-2.51 (m, 2H), 3.06 (q, *J* = 7.6 Hz, *J* = 15.1 Hz, 2H), 3.91 (s, 3H), 6.69 (m, 1H), 7.05 (d, *J* = 8.7 Hz, 2H), 7.14 (s, 1H), 7.27 (d, *J* = 3.8 Hz, 1H), 7.35–7.39 (m, 3H), 7.55 (d, *J* = 7.5 Hz, 1H), 7.82 (s, 1H), 8.15 (d, *J* = 8.7 Hz, 1H); d_C ($CDCl_3$, 125 MHz) 11.4, 13.2, 28.0, 31.9, 55.4, 57.1, 113.9, 117.9, 121.1, 125.1, 125.3, 125.8, 128.8, 131.0, 131.7, 134.7, 137.1, 137.2, 140.0, 145.2, 159.2, 162.6; (ESI): *m/z* = 372 [M^+ + H].

1-(1-(4-(Benzo[b]thiophen-5-yl)phenyl)propyl)-1H-imidazole ***12***

Synthesized according to method A1 using **12a** (1.33 g, 4.94 mmol) and CDI (4.00 g, 24.7 mmol); yield: 0.51 g (32%); white solid: m.p. 101-103°C; R_f = 0.24 (DCM / MeOH, 20 : 1); IR (ATR) ν (cm^{-1}) 1496 (m), 1223 (m), 1073 (m), 805 (vs), 758 (s), 702 (s), 663 (s); d_H ($CDCl_3$, 500 MHz) 0.98 (t, *J* = 7.3 Hz, 3H, CH_3), 2.28 (q, *J* = 7.3, 7.6 Hz, 2H, CH_2), 5.08 (t, *J* = 7.6 Hz, 1H, CH), 7.00 (s, 1H), 7.13 (s, 1H), 7.29 (d, *J* = 8.1 Hz, 2H), 7.39 (d, *J* = 5.4 Hz, 1H), 7.49 (d, *J* = 5.4 Hz, 1H), 7.55 (dd, *J* = 1.7, 8.4 Hz , 1H), 7.64 (dd, *J* = 1.7, 8.3 Hz, 2H), 7.73 (s, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 8.00 (s, 1H); d_C ($CDCl_3$, 125 MHz) 11.1 (CH_3), 28.6 (CH_2), 63.3 (CH), 117.8, 120.0, 121.9, 122.8, 123.7, 124.0, 127.0, 127.2, 127.8, 128.7, 136.1, 136.7, 138.8, 139.1, 139.4, 140.2, 141.3; MS (ESI): m/z = 319 [M^+ + H].

5-(4-(1-(1H-Imidazol-1-yl)propyl)phenyl)-1H-indole ***13***

Synthesized according to method A1 using **13a** (1.10 g, 4.38 mmol) and CDI (3.55 g, 21.88 mmol); yield: 0.33 g (25%); white solid: m.p. 158-159°C; R_f = 0.15 (DCM / MeOH, 20 : 1); IR (ATR) ν (cm^{-1}) 3143 (br), 1593 (w), 1471 (w), 1222 (w), 1075 (m), 891 (s), 805 (s), 772 (s), 739 (s), 660 (m), 574 (w), 539 (w); d_H ($CDCl_3$, 500 MHz) 0.86 (t, *J* = 7.3, 3H, CH_3), 2.15 (q, *J* = 7.23, 7.6 Hz, 2H, CH_2), 4.93 (t, *J* = 7.6 Hz, 1H, CH), 6.50 (s, 1H), 6.90 (s, 1H), 7.04 (s, 1H), 7.13–7.17 (m, 3H), 7.30 (dd, *J* = 8.5, 9.5 Hz, 2H), 7.52 (d, *J* = 8.3 Hz, 2H), 7.67 (s, 1H), 7.74 (s, 1H), 8.89 (s, 1H); d_C ($CDCl_3$, 125 MHz) 11.0 (CH_3), 28.4 (CH_2), 63.5 (CH), 102.6, 111.4, 119.0,121.4, 125.2, 127.7, 128.4, 130.8, 132.1, 135.6, 135.8, 137.3, 142.6; MS (ESI): m/z = 302 [M^+ + H].

1-(4-(Benzofuran-5-yl)benzyl)-1H-imidazole ***14***

Synthesized according to method A1 using **14a** (0.50 g, 2.23 mmol) and CDI (1.81 g, 11.1 mmol); yield: 0.26 g (43%); white solid: m.p. 127–129°C; R_f = 0.22 (DCM / MeOH, 20 : 1); IR (ATR) ν (cm^{-1}) 3109 (w), 1511 (m), 1463 (m), 1439 (m), 1249 (m), 1130 (m), 1107 (m), 1083 (m), 1028 (s), 909 (m), 876 (m), 836 (m), 802 (vs), 779 (s), 748 (vs), 704 (m), 662 (vs), 631 (m), 523 (s); d_H ($CDCl_3$, 500 MHz) 5.17 (s, 2H, CH_2), 6.82 (d, *J* = 3.0 Hz, 1H), 6.95 (s, 1H), 7.12 (s, 1H), 7.23 (d, *J* = 8.1 Hz, 2H), 7.49 (d, *J* = 5.4 Hz, 1H), 7.55–7.60 (m, 4H), 7.66 (d, *J* = 8.4 Hz, 1H), 7.76 (s, 1H); d_C ($CDCl_3$, 125 MHz) 50.5 (CH_2), 119.7, 123.8, 127.7, 127.9, 129.9, 135.5, 137.4, 141.7,145.7; MS (ESI): m/z = 275 [M^+ + H].

1-(4-(Benzo[b]thiophen-5-yl)benzyl)-1H-imidazole ***15***

Synthesized according to method A1 using **15a** (0.7 g, 2.91 mmol) and CDI (2.36 g, 14.6 mmol); yield: 0.18 g (21%); white solid: m.p. 164–165°C; R_f = 0.25 (DCM / MeOH, 20 : 1); IR (ATR) ν (cm^{-1}) 1434 (w), 908 (m), 807 (m), 759 (m), 708 (m), 663 (m); d_H ($CDCl_3$, 500 MHz) 5.18 (s, 2H, CH_2), 6.95 (s, 1H), 7.12 (s, 1H), 7.25 (d, *J* = 8.1 Hz, 2H), 7.38 (d, *J* = 5.4 Hz, 1H), 7.49 (d, *J* = 5.4 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.59 (s, 1H), 7.64 (d, *J* = 8.3 Hz, 2H), 7.93 (d, *J* = 8.4 Hz, 1H), 8.00 (s, 1H); d_C ($CDCl_3$, 125 MHz) 50.5 (CH_2), 119.3, 121.93, 122.83, 123.7, 124.1, 127.3, 127.9, 129.9, 135.0, 139.1, 140.2, 141.4; MS (ESI): m/z = 291 [M^+ + H].

5-(4-(1H-Imidazol-1-ylmethyl)phenyl)-1H-indole ***16***

Synthesized according to method A1 using **16a** (0.80 g, 3.58 mmol) and CDI (3.55 g, 21.88 mmol); yield: 0.24 g (25%); white solid: m.p. 217–218°C; R_f = 0.16 (DCM / MeOH, 20 : 1); IR (ATR) ν (cm^{-1}) 1509 (m), 1232 (m), 1099 (m), 1072 (m), 915 (m), 883 (m), 801 (m), 732 (s), 662 (m), 619 (m), 574 (s), 528 (m); d_H ($CDCl_3$, 500 MHz) 5.16 (s, 2H, CH_2), 6.61–6.63 (m, 1H), 6.97 (s, 1H), 7.13 (s, 1H), 7.22 (d, *J* = 8.4 Hz, 2H), 7.25 (s, 1H), 7.43 (dd, *J* = 8.4, 9.4 Hz, 2H), 7.61 (s, 1H), 7.63 (d, *J* = 8.3 Hz, 2H), 7.84 (s, 1H), 8.31 (s, 1H); d_C ($CDCl_3$, 125 MHz) 50.6 (CH_2), 103.0, 111.3, 119.2, 121.6, 127.6, 127.8, 128.4, 130.8, 132.4, 134.0, 135.5, 140.53, 142.63; MS (ESI): m/z = 274 [M^+ + H].

6-(4-(1H-Imidazol-1-ylmethyl)phenyl)benzo[d]thiazole ***17***

Synthesized according to method A1 using **17a** (0.40 g, 1.66 mmol) and CDI (2.15 g, 13.26 mmol); yield: 0.29 g (70%); white solid: m.p. 143°C; R_f = 0.38 (DCM / MeOH, 95 : 5); IR (ATR) ν (cm^{-1}) 3370 (w), 2927 (w), 2856 (w), 1708 (w), 1506 (m), 1468 (m), 1441 (m), 1391 (m), 1284 (w), 1232 (m), 1108 (w), 1077 (m), 1030 (w), 886 (w), 813 (s), 739 (s), 697 (w), 663 (s); d_H ($CDCl_3$, 500 MHz) 5.18 (s, 2H), 6.95 (s, 1H), 7.13 (s, 1H), 7.23 (d, *J* = 8.3 Hz, 2H), 7.64 (bs, 1H), 7.71 (dd, *J* = 1.8 Hz, *J* = 8.5 Hz, 1H), 8.12 (m, 1H), 8.18 (d, *J* = 8.5 Hz, 1H); d_C ($CDCl_3$, 125 MHz) 50.6, 119.3, 120.1, 123.8, 125.8, 127.9, 128.0, 134.6, 135.3, 138.1, 140.6, 152.7, 154.3.

1-((4-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)phenyl)-methyl)-1H-imidazole ***18***

Synthesized according to method A1 using **18a** (0.13 g, 0.54 mmol) and CDI (0.70 g, 4.30 mmol); yield: 0.06 g (43%); white solid: m.p. 149°C; R_f = 0.52 (DCM / MeOH, 95 : 5); IR (ATR) ν (cm^{-1}) 3112 (w), 3041 (w), 2930 (w), 2877 (w), 1728 (w), 1677 (w), 1588 (w), 1497 (s), 1309 (s), 1284 (m), 1246 (m), 1068 (s), 897 (m), 876 (w), 807 (m), 748 (m), 699 (w), 662 (w), 530 (w); d_H ($CDCl_3$ + CD_3OD, 500 MHz) 5.13 (s, 2H), 6.88 (d, *J* = 8.3 Hz, 1H), 6.96 (bs, 1H), 7.00–7.04 (m, 3H), 7.18 (d, *J* = 8.0 Hz, 2H), 7.36 (s, 1H), 7.48 (d, *J* = 8.0 Hz, 2H), 7.64 (s, 1H); d_C ($CDCl_3$ + CD_3OD, 125 MHz) 17.8, 29.8, 31.0, 51.1, 64.8, 64.8, 116.0, 117.9, 120.1, 120.3, 127.6, 128.2, 128.9, 134.1, 134.5, 137.6, 141.1, 143.8, 144.1; (ESI): *m/z* = 293 [M^+ + H].

1-(1-(4-(6-Methoxynaphthalen-2-yl)phenyl)propyl)-1H-imidazole ***19***

Synthesized according to method A1 using **19a** (0.75 g, 1.71 mmol) and CDI (1.50 g, 9.30 mmol); yield: 0.23 g (39%);

white solid: m.p. 136 – 138°C; R_f = 0.27 (DCM / MeOH, 95 : 5); IR (ATR) ν (cm^{-1}), 2936 (w), 1676 (s), 1602 (m), 1502 (m), 1462 (m), 1200 (s), 1021 (m), 844 (s), 814 (s), 665 (s), 532 (m); d_H ($CDCl_3$, 500 MHz) 0.98 (t, *J* = 7.25 Hz, 3H, CH_3), 2.27 – 2.30 (m, 2H, CH_2), 3.94 (s, 3H, OCH_3), 5.06 (t, *J* = 7.61 Hz, 1H, CH), 6.99 (s, 1H, Im-H5), 7.11 (s, 1H, Im-H4), 7.16 – 7.19 (m, 2H, aromat), 7.28 (d, *J* = 8.19 Hz, 2H, aromat), 7.65 (s, 1H, Im-H2), 7.66 – 7.68 (m, 3H, aromat), 7.80 (t, *J* = 8.51 Hz, 2H, aromat), 7.95 (d, *J* = 1.26 Hz, 1H, aromat); d_C ($CDCl_3$, 125 MHz) 11.1 (CH_3), 28.6 (CH_2), 55.3 (CH), 63.0 (OCH_3), 105.6 (C-5′), 117.7 (Im-C4), 119.2 (C-7′), 125.6, 125.7 (Im-C5, C-3′), 127.0, 127.3 (C-1′, C-4′), 127.6 (C-3, C-5), 129.1 (C-2, C-6), 129.7 (C-8), 133.9 (C-2′), 135.4 (C-4), 139.0 (C-1), 141.0 (Im-C2), 157.9 (C-6′); MS (ESI): *m/z* = 343 [M^+ - H].

1-(1-(4-(Naphthalen-2-yl)phenyl)propyl)-1H-imidazole ***20***

Synthesized according to method A1 using **20a** (0.50 g, 1.9 mmol) and CDI (1.50 g, 9.30 mmol); yield: 0.23 g (39%); white solid: m.p. 136 – 138°C; R_f = 0.29 (DCM / MeOH, 95 : 5); IR (ATR) ν (cm^{-1}), 1687 (m), 1499 (s), 1223 (m), 1072 (m), 1015 (m), 809 (vs), 758 (s), 733 (s), 662 (s); d_H ($CDCl_3$, 500 MHz) 0.98 (t, *J* = 7.25 Hz, 3H, CH_3), 2.24-2.33 (m, 2H, CH_2), 5.08 (t, *J* = 7.56 Hz, 1H, CH), 7.00 (t, *J* = 1.26 Hz, 1H, Im-H5), 7.11 (t, *J* = 1.26 Hz, 1H, Im-H4), 7.30 (d, *J* = 7.88 Hz, 2H, aromat), 7.47 – 7.53 (m, 2H, aromat), 7.65 (s, 1H, Im-H2), 7.69 – 7.72 (m, 3H, aromat), 7.85 – 7.92 (m, 3H, aromat), 8.01 (d, *J* = 1.57 Hz, 1H, aromat); d_C ($CDCl_3$, 125 MHz) 11.1 (CH_3), 28.6 (CH_2), 63.1 (CH), 117.7 (Im-C4), 125.3 (C-3′), 125.8, 126.1, 126.4 (Im-C5, C-7′, C-8′), 127.1 (C-1′), 127.6, 127.8, 128.1, 128.5 (C-3, C-5, C-5′, C-8′), 129.6 (C-4′), 132.7, 132.6 (C-2, C-6), 136.4 (C-4, C-2′), 137.6 (C-1), 139.4 (Im-C2); MS (ESI): *m/z* = 313 [M^+ + H].

1-(3-(4-(6-(tert-Butyldimethylsilyloxy)naphthalen-2-yl)phenyl)pentan-3-yl)-1H-imidazole ***21a***

Synthesized according to method A1 using **21b** (1.00 g, 2.5 mmol) and CDI (2.06 g, 12.7 mmol); brown oil; the crude product was directly used in the next step without further purification and analysis.

Method B: Ether cleavage with BBr_3

To a solution of the corresponding ether (1 eq) in DCM at −78°C was added 1 M boron tribromide in DCM (5 eq). The resulting mixture was stirred at rt for 16 hours. Then, water (25 mL) was added and the emulsion was stirred for further 30 min. The resulting mixture was extracted with ethyl acetate (3 × 25 mL). The combined organic phases were washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure. Then the desired product was purified by chromatography on silica gel.

4-(2-(1H-Imidazol-1-ylmethyl)benzo[b]thiophen-5-yl)phenol ***2***

Synthesized according to method B using **1** (0.15 g, 0.47 mmol) and BBr_3 (2.35 mL, 2.34 mmol); yield: 0.05 g (32%); white solid: m.p. 211°C; R_f = 0. 25 (DCM / MeOH, 95 : 5); IR (ATR) ν (cm^{-1}) 3349 (w), 2959 (w), 1733 (w), 1609 (w), 1515 (s), 1448 (w), 1277 (s), 1242 (w), 1231 (w), 1194 (w), 1108 (m), 1030 (w), 951 (w), 885 (w), 809 (s), 749 (s), 658 (m), 547 (w); d_H ($CDCl_3$ + CD_3OD, 500 MHz) 5.43 (s, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 7.02 (bs, 1H), 7.11 (bs, 1H), 7.25 (s, 1H), 7.44 – 7.52 (m, 3H), 7.72 (bs, 1H), 7.76 (d, *J* = 8.4 Hz, 1H), 7.85 (s, 1H); d_C ($CDCl_3$ + CD_3OD, 125 MHz) 116.3, 122.0, 123.1, 124.4, 124.8, 128.9, 133.1, 138.9, 138.9, 140.3, 140.6, 157.2.

4-(4-(1H-Imidazol-1-ylmethyl)naphthalen-1-yl)phenol ***7***

Synthesized according to method B using **6** (0.15 g, 0.48 mmol) and BBr_3 (1.90 mL, 1.90 mmol); yield: 0.08 g (52%); white solid: m.p. 197°C; R_f = 0.27 (DCM / MeOH, 95 : 5); IR (ATR) ν (cm^{-1}) 3600 – 2900 (w), 1610 (w), 1509 (m), 1437 (w), 1391 (w), 1264 (s), 1214 (w), 1172 (w), 1091 (m), 951 (w), 834 (s), 770 (w), 734 (s), 654 (w), 574 (w); d_H ($CDCl_3$ + CD_3OD, 500 MHz) 6.89 (d, *J* = 8.4 Hz, 2H), 7.04 (s, 1H), 7.15 (s, 1H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.28 – 7.30 (m, 1H), 7.31 (s, 1H), 7.36 – 7.39 (m, 1H), 7.44-7.47 (m, 1H), 7.82 (d, *J* = 8.4 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.29 (bs, 1H); d_C ($CDCl_3$ + CD_3OD, 125 MHz) 115.3, 122.4, 126.3, 126.4, 127.2, 127.6, 131.1, 131.3, 132.5, 156.6; (ESI): *m/z* = 301 [M^+ + H].

4-(8-(1-(1H-Imidazol-1-yl)propyl)quinolin-5-yl)phenol ***9***

Synthesized according to method B using **8** (0.10 g, 0.29 mmol) and BBr_3 (1.46 mL, 1.46 mmol); yield: 0.06 g (63%); white solid: m.p. 174°C; R_f = 0.29 (DCM / MeOH, 95: 5); IR (ATR) ν (cm^{-1}) 3500-2600 (w), 1610 (m), 1515 (s), 1458 (w), 1397 (w), 1269 (s), 1227 (w), 1172 (w), 1108 (w), 1089 (w), 826 (s), 797 (w), 736 (s), 669 (w); d_H ($CDCl_3$ + CD_3OD, 500 MHz) 0.95 (t, *J* = 7.2 Hz, 3H), 2.30 – 2.41 (m, 2H), 6.58 (m, 1H), 6.91 (d, *J* = 8.5 Hz, 2H), 6.07 (bs, 1H), 7.14 (bs, 1H), 7.18 (d, *J* = 8.5 Hz, 2H), 7.28 – 7.32 (m, 1H), 7.37 (d, *J* = 7.5 Hz, 1H), 7.57 (d, *J* = 7.5 Hz, 1H), 7.99 (bs, 1H), 8.22 (d, *J* = 8.5 Hz, 1H), 8.81 (m, 1H); d_C ($CDCl_3$ + CD_3OD, 125 MHz) 11.3, 27.8, 57.8, 60.7, 115.5, 115.6, 119.0, 121.4, 125.8, 125.9, 126.8, 127.2, 127.3, 130.0, 131.1, 131.1, 135.3, 135.9, 137.3, 141.4, 145.7, 149.6, 157.1; (ESI): *m/z* = 330 [M^+ + H].

4-(8-(1-(1H-Imidazol-1-yl)propyl)-2-ethylquinolin-5-yl)phenol ***11***

Synthesized according to method B using **10** (0.15 g, 0.40 mmol) and BBr_3 (2.00 mL, 2.00 mmol); yield: 0.09 g (58%); white solid: m.p. 142°C; R_f = 0.31 (DCM / MeOH, 95 : 5); IR (ATR) ν (cm^{-1}) 3600 – 2800 (w), 2968 (w), 2932 (w), 1733 (s), 1608 (s), 1579 (w), 1518 (s), 1457 (w), 1398 (w), 1269 (s), 1225 (m), 1172 (m), 1108 (w), 951 (w), 824 (s), 734 (m), 659 (w); d_H ($CDCl_3$ + CD_3OD, 500 MHz) 0.94 (t, *J* = 7.2 Hz, 3H), 1.30 (t, *J* = 7.5 Hz, 3H), 2.29 – 2.43 (m, 2H), 2.89 – 2.93 (m, 2H), 6.57 – 6.60 (m, 1H), 6.88 (d, *J* = 8.1 Hz, 2H), 6.99 (s, 1H), 7.12 (s, 1H), 7.15-7.18 (m, 3H), 7.29 (d, *J* = 7.4 Hz, 1H), 7.53 (d, *J* = 7.4 Hz, 1H), 8.08 (d, *J* = 8.7 Hz, 1H), 8.13 (s, 1H); d_C ($CDCl_3$ + CD_3OD, 125 MHz) 11.0, 13.0, 27.1, 31.6, 58.1, 115.2, 119.1, 121.0, 125.2, 125.33, 125.34, 126.2, 130.2, 130.8, 134.2, 134.8, 137.5, 141.0, 145.0, 156.4, 162.9; (ESI): *m/z* = 358 [M^+ + H].

Method C: Suzuki-coupling

The corresponding brominated aromatic compound (1 eq) was dissolved in toluene (7 mL/mmol), an aqueous 2.0 M Na_2CO_3 (method C1) or Cs_2CO_3 solution (method C2) (3.2 mL/mmol) and an ethanolic solution (3.2 mL/mmol) of the corresponding boronic acid (1.5 – 2.0 eq) were added. For method C2, TBAB (Tetrabutylammonium bromide; 1 eq) was also added to the reaction mixture. The mixture was deoxygenated under reduced pressure and flushed with nitrogen. After repeating this cycle several times, $Pd(PPh_3)_4$ (method C1) or $Pd(OAc)_2$ (method C2) (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 and the organic phase was separated. 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 celite1, and evaporated

under reduced pressure. The compounds were purified by flash chromatography on silica gel.

6-(4-Fluorophenyl)-1H-indole-3-carbaldehyde ***3b***

Synthesized according to method C1 using 6-bromo-1*H*-indole-3-carbaldehyde (0.45 g, 2.00 mmol) and 4-fluorophenylboronic acid (0.57 g, 4.05 mmol); yield: 0.35 g (73%); yellow oil; R_f = 0.57 (hexane / EtOAc, 1 : 2); IR (ATR) ν (cm^{-1}) 3228 (m), 2806 (w), 1646 (s), 1618 (m), 1518 (m), 1386 (m), 1198 (m), 1110 (s), 1083 (s), 811 (s), 670 (s), 593 (m), 517 (s); d_H ($CDCl_3$, 500 MHz) 6.84 (t, *J* = 8.8 Hz, 2H), 7.15 (dd, *J* = 1.6 Hz, 8.2 Hz, 1H), 7.30 (dd, *J* = 5.4 Hz, 8.8 Hz, 2H), 7.33 (m, 1H), 7.63 (d, *J* = 3.2 Hz, 1H), 7.96 (d, *J* = 8.2 Hz, 1H), 9.71 (s, 1H), 11.42 (bs, 1H); d_C ($CDCl_3$, 125 MHz) 109.7 (CH), 114.8 (CH), 118.0 (C_q), 121.0 (C_q), 121.1 (CH), 123.0 (C_q), 128.1 (CH), 135.3 (C_q), 136.8 (CH), 137.1 (C_q), 137.3 (C_q), 161.4 (CF), 184.2 (CH); MS (ESI): m/z = 238 [M^+ − H].

2-(1H-Imidazol-1-ylmethyl)-6-(4-fluorophenyl)quinoline ***4***

Synthesized according to method C1 using **4a** (0.24 g, 0.84 mmol) and 4-fluorophenylboronic acid (0.23 g, 1.68 mmol); yield: 0.23 g (92%); yellow solid: m.p. 106°C; R_f = 0.15 (EtOAc / MeOH 9 : 1); IR (ATR) ν (cm^{-1}) 3125 (w), 3094 (w), 2926 (w), 1602 (m), 1515 (m), 1498 (m), 1431 (m), 1224 (s), 824 (s), 771 (m), 657 (m); d_H ($CDCl_3$, 500 MHz) 5.43 (s, 2H), 7.04 (t, *J* = 1.3 Hz, 1H), 7.08 (d, *J* = 8.5 Hz, 1H), 7.15 (bs, 1H), 7.18 (t, *J* = 8.5, 2H), 7.66 (m, 2H), 7.69 (bs, 1H), 7.93 (d, *J* = 2.2 Hz, 1H), 7.96 (dd, *J* = 2.2, 8.5 Hz, 1H), 8.12 (d, *J* = 8.8 Hz, 1H), 8.16 (d, *J* = 8.5 Hz, 1H); d_C ($CDCl_3$, 125 MHz) 53.2 (CH_2), 115.9 (d, $^2J_{CF}$ = 22 Hz, CH), 119.1 (CH), 119.6 (CH), 125.1 (CH), 127.6 (CH), 128.3 (C_q), 128.4 (CH), 129.0 (d, $^3J_{CF}$ = 7.7 Hz, CH), 129.6 (CH), 129.7 (CH), 130.2 (CH), 136.2 (d, $^4J_{CF}$ = 2.9 Hz, C_q), 137.7 (CH), 137.8 (CH), 138.8 (C_q), 146.9 (C_q), 156.2 (C_q), 162.8 (d, $^1J_{CF}$ = 248.0 Hz, CF); MS (ESI): *m/z* = 304 [M^+ + H].

2-(1H-Imidazol-1-ylmethyl)-6-(thiophen-3-yl)quinoline ***5***

Synthesized according to method C1 using **5a** (0.24 g, 0.84 mmol) and 3-thiophenylboronic acid (0.22 g, 1.68 mmol); yield: 0.22 g (88%); yellow solid: m.p. 128°C; R_f = 0.11 (EtOAc / MeOH 9 : 1); IR (ATR) ν (cm^{-1}) 3104 (w), 2963 (w), 2926 (m), 1597 (m), 1506 (m), 1318 (m), 1068 (m), 828 (s), 782 (s), 753 (s), 660 (s); d_H ($CDCl_3$, 500 MHz) 5.43 (s, 2H), 7.04 (t, *J* = 1.3 Hz, 1H), 7.06 (d, *J* = 8.5 Hz, 1H), 7.15 (t, *J* = 0.9 Hz, 1H), 7.46 (dd, *J* = 2.8, 5.0 Hz, 1H), 7.52 (dd, *J* = 1.6, 5.0 Hz, 1H), 7.62 (dd, *J* = 1.3, 2.8 Hz, 1H), 7.69 (bs, 1H), 7.99 (d, *J* = 1.9 Hz, 1H), 8.02 (dd, *J* = 2.2, 8.8 Hz, 1H), 8.09 (d, *J* = 8.8 Hz, 1H), 8.14 (d, *J* = 8.5 Hz, 1H); d_C ($CDCl_3$, 125 MHz) 53.2 (CH_2), 119.1 (CH), 119.6 (CH), 121.5 (CH), 124.2 (CH), 126.3 (CH), 126.8 (CH), 127.7 (C_q), 129.4 (CH), 129.6 (CH), 130.2 (CH), 134.4 (C_q), 137.6 (CH), 137.8 (CH), 141.2 (C_q), 146.9 (C_q), 155.9 (C_q); MS (ESI): *m/z* = 292 [M^+ + H].

(4-(4-Methoxyphenyl)naphthalen-1-yl)methanol ***6a***

Synthesized according to method C2 using **6b** (0.40 g, 1.69 mmol) and 4-methoxyphenylboronic acid (0.39 g, 2.53 mmol); yield: 0.42 g (94%); m.p. 112°C; R_f = 0.50 (hexane / EtOAc, 7 : 3); d_H ($CDCl_3$, 500 MHz) 3.90 (s, 3H), 5.20 (s, 2H), 7.04 (d, *J* = 8.7 Hz, 2H), 7.38 (d, *J* = 7.2 Hz, 1H), 7.40 (d, *J* = 8.7 Hz, 2H), 7.45-7.48 (m, 1H), 7.56 (d, *J* = 7.2 Hz, 2H), 7.96 (d, *J* = 8.4 Hz, 1H), 8.20 (d, *J* = 8.4 Hz, 1H); d_C ($CDCl_3$, 125 MHz) 55.4, 63.8, 113.7, 123.9, 125.0, 125.9, 126.2, 126.4, 126.9, 131.1, 131.5, 132.2, 133.0, 135.4, 140.5, 159.0.

5-(4-Methoxyphenyl)quinoline-8-carbaldehyde ***8b***

Synthesized according to method C2 using 6-bromo-1*H*-indole-3-carbaldehyde (3.00 g, 12.71 mmol) and 4-methoxyphenylboronic acid (2.90 g, 19.06 mmol); yield: 2.75 g (82%); white solid: m.p. 159°C; R_f = 0.56 (hexane / EtOAc, 7 : 3); d_H ($CDCl_3$, 500 MHz) 7.06 (d, *J* = 8.7 Hz, 2H), 7.41 (d, *J* = 8.7 Hz, 2H), 7.45 (d, *J* = 4.1 Hz, *J* = 8.6 Hz, 1H), 7.61 (d, *J* = 7.5 Hz, 1H), 8.33 – 8.34 (m, 2H), 9.03-9.04 (m, 1H), 11.48 (s, 1H); d_C ($CDCl_3$, 125 MHz) 55.4, 114.1, 121.5, 121.8, 126.2, 126.7, 126.9, 128.8, 129.3, 130.5, 130.9, 131.0, 134.2, 134.8, 136.3, 146.7, 148.1, 150.9, 151.3, 159.8, 192.6.

4-(Benzo[b]thiophen-5-yl)benzaldehyde ***12b***

Synthesized according to method C1 using 5-bromobenzo[*b*]thiophene (1.90 g, 8.92 mmol) and 4-formylphenylboronic acid (1.74 g, 11.6 mmol); yield: 1.71 g (80%); brown oil; R_f = 0.35 (hexane / EtOAc, 5 : 1); d_H ($CDCl_3$, 500 MHz) 7.41 (d, *J* = 5.4 Hz, 1H), 7.51 (d, *J* = 5.4 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 1H), 7.82 (d, *J* = 7.9 Hz, 2H), 7.97 (d, *J* = 8.2 Hz, 3H), 8.07 (s, 1H), 10.07 (s, 1H, CHO); d_C ($CDCl_3$, 125 MHz) 122.3, 123.0, 123.6, 124.0, 127.5, 127.8, 130.3, 135.0, 126.1, 139.9, 140.2, 147.3, 191.9.

4-(1H-Indol-5-yl)benzaldehyde ***13b***

Synthesized according to method C1 using 5-bromo-*1H*-indole (0.10 g, 0.51 mmol) and 4-formylphenylboronic acid (0.1 g, 0.66 mmol); yield: 0.07 g (65%); yellow oil; R_f = 0.25 (hexane / EtOAc, 5 : 1); d_H ($CDCl_3$, 500 MHz) 6.64 (t, *J* = 2.8 Hz, 1H), 7.27 (t, *J* = 3.1 Hz, 1H), 7.48 (s, 1H), 7.74 (dd, *J* = 1.8, 8.5 Hz, 2H), 7.92 (s, 1H), 8.04 (dd, *J* = 1.8, 8.5 Hz, 2H), 8.29 (s, br, 1H), 10.05 (s, 1H, CHO); d_C ($CDCl_3$, 125 MHz) 103.2, 111.4, 119.6, 121.7, 125.1, 127.2, 128.4, 128.5, 132.0, 135.8, 147.0, 192.1.

4-(Benzofuran-5-yl)benzaldehyde ***14b***

Synthesized according to method C1 using 5-bromobenzofuran (1.90 g, 9.64 mmol) and 4-formylphenylboronic acid (1.88 g, 12.5 mmol); yield: 0.53 g (25%); yellow oil; R_f = 0.33 (hexane / EtOAc, 5 : 1); d_H ($CDCl_3$, 500 MHz) 6.83 – 6.84 (m, 1H), 7.54 – 7.60 (m, 2H), 7.68 (d, *J* = 2.2 Hz, 1H), 7.76 (d, *J* = 8.2 Hz, 2H), 7.84 (d, *J* = 1.6 Hz, 1H), 7.94 (dd, *J* = 1.8, 8.4 Hz, 2H), 10.05 (s, 1H, CHO); d_C ($CDCl_3$, 125 MHz) 106.8, 111.8, 120.1, 123.9, 127.8, 130.2, 134.8, 145.9, 147.6, 155.0, 191.9.

(4-(Benzo[d]thiazol-6-yl)phenyl)methanol ***17a***

Synthesized according to method C1 using 6-bromobenzo[*d*]thiazole (0.50 g, 2.34 mmol) and 4-(hydroxymethyl)phenylboronic acid (0.53 g, 3.50 mmol); yield: 0.50 g (89%); yellow oil; R_f = 0.22 (hexane / EtOAc, 7 : 3); d_H ($CDCl_3$, 500 MHz) 4.77 (s, 2H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.64 – 7.68 (m, 3H), 7.74 (dd, *J* = 1.8 Hz, *J* = 8.5 Hz, 1H), 8.15 (s, 1H), 8.20 (d, *J* = 8.5 Hz, 1H), 9.03 (s, 1H); d_C ($CDCl_3$, 125 MHz) 64.9, 120.1, 123.6, 125.9, 127.6, 127.6, 128.5, 128.6, 132.0, 132.0, 132.1, 132.1, 134.5, 138.8, 139.7, 140.4.

(4-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)phenyl)methanol ***18a***

Synthesized according to method C1 using 6-bromo-2,3-dihydrobenzo[*b*][1,4]dioxine (0.50 g, 2.33 mmol) and 4-(hydroxymethyl)-phenyl-boronic acid (0.53 g, 3.49 mmol); yield: 0.15 g (27%); brown oil; R_f = 0.53 (hexane / EtOAc, 7 : 3); d_H ($CDCl_3$, 500 MHz) 4.29 (s, 1H), 4.71 (s, 1H), 6.93 (d, *J* = 8.3 Hz, 1H), 7.08 (dd, *J* = 2.2 Hz, *J* = 8.3 Hz, 1H), 7.12 (d, *J* = 2.2 Hz, 1H), 7.40 (d, *J* = 8.3 Hz, 2H), 7.53

(d, J = 8.3 Hz, 2H); d_C ($CDCl_3$, 125 MHz) 64.4, 64.4, 65.1, 115.8, 117.5, 120.1, 126.9, 127.4, 134.4, 139.4, 140.0, 143.2, 143.7.

Method D: Reduction with $NaBH_4$

To an ice cooled solution of the corresponding aldehyde or ketone (1 eq) in methanol (5 mL/mmol) was added $NaBH_4$ (2 eq). Then, the resulting mixture was heated to reflux for 30 min. After cooling to ambient temperature, the solvent was distilled off under reduced pressure. Then water (10 mL) was added, and the resulting mixture 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, followed by purification of the desired product by chromatography on silica gel.

*(6-(4-Fluorophenyl)-1H-indol-3-yl)methanol **3a***

Synthesized according to method D using **3b** (0.30 g, 1.25 mmol) and $NaBH_4$ (0.86 g, 2.26 mmol); yield: 0.27 g (89%); R_f = 0.55 (hexane / EtOAc, 1 : 2); the crude product was directly used in the next step without further purification and analysis.

*(4-(Benzofuran-5-yl)phenyl)methanol **14a***

Synthesized according to method D using **14b** (0.50 g, 2.25 mmol) and $NaBH_4$ (0.17 g, 4.50 mmol); yield: 0.46 g (91%); R_f = 0.33 (hexane / EtOAc, 2 : 1); the crude product was directly used in the next step without further purification and analysis.

*(4-(Benzo[b]thiophen-5-yl)phenyl)methanol **15a***

Synthesized according to method D using **15b** (0.30 g, 1.26 mmol) and $NaBH_4$ (0.10 g, 2.52 mmol); yield: 0.28 g (92%); R_f = 0.30 (hexane / EtOAc, 2 : 1); the crude product was directly used in the next step without further purification and analysis.

*1-(4-(6-Methoxynaphthalen-2-yl)phenyl)propan-1-ol **19a***

Synthesized according to method E using **19b** (1.93 g, 6.40 mmol) and $NaBH_4$ (0.48 g, 12.8 mmol); yield: 0.711 g (38%); R_f = 0.59 (DCM / MeOH, 98 : 2); the crude product was directly used in the next step without further purification and analysis.

*1-(4-(Naphthalen-2-yl)phenyl)propan-1-ol **20a***

Synthesized according to method E using **20b** (1.80 g, 6.40 mmol) and $NaBH_4$ (0.48 g, 12.8 mmol); yield: 1.34 g (80%); R_f = 0.62 (DCM / MeOH, 98 : 2); the crude product was directly used in the next step without further purification and analysis.

*6-Bromo-2-(bromomethyl)quinoline **4b***

6-Bromo-2-methylquinoline (3.00 g, 13.5 mmol) was dissolved in 40 mL of dry carbon tetrachloride. To this solution was added NBS (2.63 g, 14.8 mmol) and dibenzoyl peroxide (0.16 g, 0.70 mmol) and the mixture was refluxed over night. After cooling, the succinimide was removed by filtration and the filtrate was concentrated under vacuum. The crude product was further purified by flash column chromatography on silica gel using petroleum ether / EtOAc (95 : 5) as eluent; yield: 1.71 g (42%); lachrymatory lilac oil; R_f = 0.46 (hexane / EtOAc 95 : 5); IR (ATR) ν (cm^{-1}) 3054 (w), 3038 (w), 2928 (w), 2855 (w), 1589 (m), 1484 (s), 1373 (m), 1304 (m), 1200 (s), 1190 (s), 1060 (s), 899 (s), 830 (s), 792 (s), 775 (m), 735 (s), 694 (s), 597 (s), 550 (s); d_H ($CDCl_3$, 500 MHz) 4.68 (s, 2H), 7.59 (d, J = 8.5 Hz, 1H), 7.79 (dd, J = 2.1, 9.1 Hz, 1H), 7.93 (d, J = 8.8 Hz, 1H), 7.98 (d, J = 2.1 Hz, 1H), 8.08 (d, J = 8.5 Hz, 1H); d_C ($CDCl_3$, 125 MHz) 34.0 (CH_2), 121.0 (CH), 122.0 (CH), 128.4 (C_q), 129.6 (CH), 131.0 (CH), 133.4 (CH), 136.2 (C_q), 157.4 (C_q), 157.9 (C_q); MS (ESI): m/z =302 [M^+ + H].

*2-(1H-Imidazol-1-ymethyl)-6-bromoquinoline **4a***

The α-brominated compound **4b** (1.89 g, 6.28 mmol), imidazole (0.86 g, 12.55 mmol), anhydrous K_2CO_3 (1.29 g, 9.42 mmol) and a catalytical amount of 18-crown-6 in dry acetonitrile were heated under reflux over night. After the solution was cooled down, the solvent was removed under reduced pressure. The residue was dissolved with water (10 mL/eq) and extracted three times with CH_2Cl_2 (15 mL/eq). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and evaporated. The crude material was purified by flash chromatography on silica-gel, using 5% MeOH in CH_2Cl_2; yield: 1.1 g (61%); R_f = 0.23 (EtOAc / MeOH 9 : 1); IR (ATR) ν (cm^{-1}) 3098 (w), 1593 (m), 1488 (s), 1291 (m), 1235 (m), 1086 (m), 1030 (m), 824 (s), 733 (s), 658 (s); d_H ($CDCl_3$, 500 MHz) 5.39 (s, 2H), 7.01 (t, J = 1.3 Hz, 1H), 7.06 (d, J = 8.5 Hz, 1H), 7.13 (t, J = 1.3 Hz, 1H), 7.66 (s, 1H), 7.79 (dd, J = 2.2, 9.1 Hz, 1H), 7.91 (d, J = 9.1 Hz, 1H), 7.96 (d, J = 2.2 Hz, 1H), 8.03 (d, J = 8.5 Hz, 1H)); d_C ($CDCl_3$, 125 MHz) 55.0 (CH_2), 119.5 (CH), 119.5 (CH), 120.9 (CH), 129.6 (C_q), 130.2 (CH), 130.8 (CH), 133.6 (CH), 136.6 (CH), 137.7 (C_q), 146.2 (C_q), 156.6 (C_q); MS (ESI): m/z = 289 [M^+ + H].

*4-Bromo-1-naphthoic acid **6c***

4-Bromo-1-methyl naphthalene (20.0 g, 88.65 mmol) was preheated to 90°C in a water / pyridine 1 : 1 mixture (170 mL) and $KMnO_4$ (57.2 g, 354.6 mmol) was added over a period of 3 h every 30 min in equal portions; yield: 1.60 g (7%); R_f = 0.61 (hexane / EtOAc, 7 : 3); d_H ($CDCl_3$ + CD_3OD, 500 MHz) 7.56-7.61 (m, 2H), 7.78 (d, J = 7.9 Hz, 1H), 8.00 (d, J = 7.9 Hz, 1H), 8.26 – 8.28 (m, 1H), 8.91 – 8.93 (m, 1H); d_C ($CDCl_3$ + CD_3OD, 125 MHz) 126.5, 127.6, 127.7, 128.4, 128.7, 129.1, 130.5, 132.3, 132.6.

*(4-Bromonaphthalen-1-yl)methanol **6b***

To a solution of **6c** (0.60 g, 2.39 mmol) in THF (10 mL), $LiAlH_4$ (0.91 g, 3.90 mmol) in THF (5 mL) was added slowly and heated to reflux overnight; yield: 1.65 g (83%); R_f = 0.49 (hexane / EtOAc, 7 : 3); d_H ($CDCl_3$, 500 MHz) 5.12 (s, 2H), 7.37 (d, J = 7.6 Hz, 1H), 7.58-7.64 (m, 2H), 7.76 (d, J = 7.6 Hz, 1H), 8.11 (d, J = 7.8 Hz, 1H), 8.31 (d, J = 7.8 Hz, 1H); d_C ($CDCl_3$, 125 MHz) 123.2, 124.0, 125.5, 127.1, 127.2, 127.9, 129.4, 132.1, 132.3, 136.3.

Method E: Grignard reaction

Under exclusion of air and moisture, a 1.0 M EtMgBr (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 over night at rt. Then, ethyl acetate (10 mL) and water (10 mL) were added and the organic phase was separated. The organic phase was extracted with water and brine, dried over Na_2SO_4, and evaporated under reduced pressure. The crude products were purified by flash chromatography on silica gel.

*1-(5-(4-Methoxyphenyl)quinolin-8-yl)propan-1-ol **8a***

Synthesized according to method E using **8b** (1.00 g, 3.80 mmol) and a 1.0 M ethylmagnesium bromide solution in THF (15.20 mL, 15.20 mmol); yield: 0.47 g (43%); R_f = 0.53 (hexane / EtOAc, 7 : 3); d_H ($CDCl_3$, 500 MHz) 1.05 (t, J = 7.4 Hz, 3H), 1.97 –

2.20 (m, 2H), 3.90 (s, 3H), 5.04 – 5.07 (m, 1H), 7.04 (d, J = 8.6 Hz, 2H), 7.35 – 7.38 (m, 3H), 7.43 (d, J = 7.3 Hz, 1H), 7.56 (d, J = 7.3 Hz, 1H), 8.30 (d, J = 8.6 Hz, 1H), 8.82 – 8.83 (m, 1H); d_C ($CDCl_3$, 125 MHz) 11.0, 31.9, 55.4, 113.9, 120.6, 126.8, 127.1, 127.4, 131.1, 131.5, 135.4, 139.2, 139.5, 146.8, 147.9, 150.3.

1-(2-Ethyl-5-(4-methoxyphenyl)quinolin-8-yl)propan-1-ol ***10a***

Synthesized according to method E using **8b** (1.00 g, 3.80 mmol) and a 1.0 M ethylmagnesium bromide solution in THF (15.20 mL, 15.20 mmol); yield: 0.43 g (39%); R_f = 0.71 (hexane / EtOAc, 7 : 3); d_H ($CDCl_3$, 500 MHz) 1.03 (t, J = 7.4 Hz, 3H), 1.41 (t, J = 7.6 Hz, 3H), 2.02-2.19 (m, 2H), 2.98-3.03 (m, 2H), 3.89 (s, 3H), 4.95 – 4.98 (m, 1H), 7.03 (d, J = 8.6 Hz, 2H), 7.24 (d, J = 8.8 Hz, 1H), 7.34 – 7.36 (m, 3H), 7.48 (d, J = 7.3 Hz, 1H), 8.19 (d, J = 8.8 Hz, 1H).

1-(4-(Benzo[b]thiophen-5-yl)phenyl)propan-1-ol ***12a***

Synthesized according to method E using **12b** (0.35 g, 1.47 mmol) and a 1.0 M ethylmagnesium bromide solution in THF (1.91 mL, 1.91 mmol); yield: 0.34 g (85%); R_f = 0.30 (hexane / EtOAc, 2 : 1); the crude product was directly used in the next step without further purification and analysis.

1-(4-(1H-Indol-5-yl)phenyl)propan-1-ol ***13a***

Synthesized according to method E using **13b** (0.50 g, 2.26 mmol) and a 1.0 M ethylmagnesium bromide solution in THF (2.94 mL, 2.94 mmol); yield: 0.51 g (89%); R_f = 0.30 (hexane / EtOAc, 2 : 1); the crude product was directly used in the next step without further purification and analysis.

3-(4-(6-(tert-Butyldimethylsilyloxy)naphthalen-2-yl)phenyl)pentan-3-ol ***21b***

Synthesized according to method E using **21c** (6.07 g, 16.7 mmol) and EtMgBr (1 M, 18.4 mL, 18.4 mmol, 1.1 eq); yield: 1.37 g (21%); yellow solid; R_f = 0.73 (hexane / EtOAc, 7 : 3); the crude product was directly used in the next step without further purification and analysis.

(6-Bromonaphthalen-2-yloxy)(tert-butyl)dimethylsilane ***21d***

To a solution of 6-bromonaphthalen-2-ol (10 g, 44.8 mmol) and imidazole (3.4 g, 49.3 mmol, 1.1 eq) in dichloromethane was slowly added a solution of *tert*-butyldimethylsilyl chloride (7.4 g, 49.3 mmol, 1.1 eq) in dichloromethane. 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 lead to a pale oil, which was purified by chromatography on silica gel; yield: 14.5 g, (96%); yellow oil; R_f = 0.63 (hexane); d_H ($CDCl_3$, 500 MHz) 0.25 (s, 6H), 1.02 (s, 9H), 7.09 (dd, J = 2.2, 8.8 Hz, 1H), 7.15 (d, J = 2.2 Hz, 1H), 7.48 (dd, J = 2.2, 8.8 Hz, 1H), 7.56 (d, J = 8.8 Hz, 1H), 7.63 (d, J = 8.8 Hz, 1H), 7.92 (d, J = 2.2 Hz, 1H); d_C ($CDCl_3$, 125 MHz) -4.3 (CH_3), 18.2 (C_q), 25.7 (CH_3), 114.9 (CH), 117.3 (C_{Br}), 123.1 (CH), 128.3 (CH), 128.4 (C_q), 129.4 (CH), 129.6 (CH), 130.3 (CH), 133.1 (C_q), 153.8 (C_{OR}); MS (ESI): m/z = 337 [M^+ + H].

6-(4-(3-(1H-Imidazol-1-yl)pentan-3-yl)phenyl)naphthalen-2-ol ***21***

To a solution of the silyl-protected phenol **21a** (crude product, 2.5 mmol) in anhydrous tetrahydrofuran (25 mL) was added tetrabutylammonium fluoride (3 mL, 1 M) and the solution was stirred for 4 h. The reaction was terminated with the addition of methanol and the solvent was removed under reduced pressure. Then, the desired product was purified by chromatography on silica gel; yield = 50 mg (6%); brown solid; R_f = 0.31 (EtOAc / MeOH 95 : 5); IR (ATR) ν (cm^{-1}) 2975 (w), 2874 (w), 1602 (s), 1510 (m), 1498 (m), 1251 (s), 1205 (s), 858 (s), 831 (s); d_H ($CDCl_3$, 500 MHz) 0.65 (t, J = 7.3 Hz, 6H), 2.27 – 2.31 (m, 4H), 6.94 (bs, 1H), 7.06 (bs, 1H), 7.10 (dd, J = 2.4 Hz, J = 8.8 Hz, 1H), 7.14 (d, J = 2.4 Hz, 1H), 7.22 (d, J = 8.8 Hz, 2H), 7.70 – 7.76 (m, 4H), 7.80 (bs, 1H), 7.82 (d, J = 8.8 Hz, 1H), 8.07 (bs, 1H), 9.84 (s, 1H); d_C ($CDCl_3$, 125 MHz) 7.6 (CH_3), 28.9 (CH_2), 65.7 (CH), 108.4 (CH), 117.1 (CH), 118.4 (CH), 119.0 (CH), 125.0 (CH), 125.0 (CH), 126.2 (CH), 126.6 (CH), 126.7 (CH), 127.9 (C_q), 128.1 (C_q), 129.7 (CH), 133.5 (C_q), 133.8 (C_q), 139.0 (C_q), 142.9 (CH), 155.5 (C_{OH}); MS (ESI): m/z = 357 [M^+ + H].

Molecular modelling

All molecular modelling studies were performed on Intel(R) P4 CPU 3.00GHz running Linux Suse 10.1.

Ligands

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 [24] as implemented in Sybyl. The resulting geometries for our compounds were then subjected to *ab initio* calculation employing the B3LYP functional [25] in combination with a 6-31G* basis set using the package Gaussian03 (Gaussian, Inc., Pittsburgh, PA, USA, 2003).

Docking

Various inhibitors of Tables 1 and 2 were docked into our CYP17 homology model by means of the GOLD v 3.0.1 software [20]. 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 its radius was set equal to 19 Å. The automatic active site detection was switched on. Furthermore, a distance constraint of a minimum of 1.9 and a maximum of 2.5 Å between the sp^2-hybridised nitrogen of the imidazole and the iron of the heme was set. Additionally, 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 [20]. 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 [22] and the representative structure of each significant cluster was selected. The quality of the docked representative poses was evaluated based on the GOLDSCORE values, which give a good measure of the found binding mode, and on visual inspection of the putative binding modes of the ligands, as outcome of docking simulations and cluster analysis.

References

[1] A. Jemal, R. Siegel, E. Ward, T. Murray, *et al., CA Cancer J. Clin.* **2007**, *57*, 43 – 66.

[2] C. Huggins, *J. Urol.* **1952**, *68*, 875 – 884.

[3] F. Labrie, A. Dupont, A. Belanger, F. A. Lefebvre, *et al.*, *J. Steroid Biochem*. **1983**, *19*, 999 – 1007.

[4] I. Huhtaniemi, H. Nikula, M. Parvinen, S. Rannikko, *Am. J. Clin. Oncol.* **1988**, *11*, S11 – S15.

[5] K. A. Harris, V. Weinberg, R. A. Bok, M. Kakefuda, E. J. Small, *J. Urol.* **2002**, *168*, 542 – 545; J. Eklund, M. Kozloff, J. Vlamakis, A. Starr, *et al.*, *Cancer* **2006**, *106*, 2459 – 2465.

[6] V. C. O. Njar, M. Hector, R. W. Hartmann, *Bioorg. Med. Chem.* **1996**, *4*, 1447 – 1453; R. W. Hartmann, M. Hector, S. Haidar, P. B. Ehmer, *et al.*, *J. Med. Chem.* **2000**, *43*, 4266 – 4277; R. W. Hartmann, M. Hector, B. G. Wachall, A. Paluszcak, *et al.*, *J. Med. Chem.* **2000**, *43*, 4437 – 4445; S. Haidar, R. W. Hartmann, *Arch. Pharm. Pharm. Med. Chem.* **2002**, *335*, 526 – 534.

[7] T. Sergejew, R. W. Hartmann, *J. Enzym. Inhib.* **1994**, *8*, 113 – 122.

[8] R. W. Hartmann, G. A. Wächter, T. Sergejew, R. Würtz, J. Düerkop, *Arch. Pharm. (Weinheim)* **1995**, *328*, 573 – 575; G. A. Wächter, R. W. Hartmann, T. Sergejew, G. L. Grün, D. Ledergerber, *J. Med. Chem.* **1996**, *39*, 834 – 841; Y. Zhuang, R. W. Hartmann, *Arch. Pharm. Pharm. Med. Chem.* **1999**, *332*, 25 – 30; R. W. Hartmann, P. B. Ehmer, S. Haidar, M. Hector, *et al.*, *Arch. Pharm. Pharm. Med. Chem.* **2002**, *335*, 119 – 128; S. Haidar, P. B. Ehmer, S. Barassin, C. Batzl – Hartmann, R. W. Hartmann, *J. Steroid. Biochem. Mol. Biol.* **2003**, *84*, 555 – 562; O. O. Clement, C. M. Freeman, R. W. Hartmann, A. Paluszcak, *et al.*, *J. Med. Chem.* **2003**, *46*, 2345 – 2351.

[9] M. A. E. Pinto-Bazurco Mendieta, M. Negri, C. Jagusch, U. E. Hille, *et al.*, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 267 – 273.

[10] B. G. Wachall, M. Hector, Y. Zhuang, R. W. Hartmann, *Bioorg. Med. Chem.* **1999**, *7*, 1913 – 1924.

[11] Y. Zhuang, B. G. Wachall, R. W. Hartmann, *Bioorg. Med. Chem.* **2000**, *8*, 1245 – 1252; F. Leroux, T. U. Hutschenreuter, C. Charrière, R. Scopelliti, R. W. Hartmann, *Helv. Chim. Acta* **2003**, *86*, 2671 – 2686; T. U. Hutschenreuter, P. B. Ehmer, R. W. Hartmann, *J. Enzym Inhib. Med. Chem.* **2004**, *18*, 17 – 32.

[12] C. Jagusch, M. Negri, U. E. Hille, Q. Hu, *et al.*, *Bioorg. Med. Chem.* **2008**, *in press*, doi:10.1016/j.bmc.2007.10.094.

[13] R. A. Madan, P. M. Arlen, *IDrugs* **2006**, *9*, 49 – 55.

[14] J. B. Schenkman, S. G. Sligar, D. L. Cinti, *Pharmacol Ther.* **1981**, *12*, 43 – 71.

[15] N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457 – 2483.

[16] Y. Tang, Y. Dong, J. L. Vennerstrom, *Synthesis* **2004**, *15*, 2540 – 2544.

[17] P. B. Ehmer, J. Jose, R. W. Hartmann, *J. Steroid Biochem. Mol. Biol.* **2000**, *75*, 57 – 63.

[18] J. Hodgson, *Nat. Biotechnol.* **2001**, *19*, 722 – 726.

[19] S. Ulmschneider, U. Müller – Vieira, C. D. Klein, I. Antes, *et al.*, *J. Med. Chem.* **2005**, *48*, 1563 – 1575.

[20] G. Jones, P. Willett, R. C. Glen, A. R. Leach, R. Taylor, *J. Mol. Biol.* **1997**, *267*, 727 – 748.

[21] G. Warren, C. Andrews, A. – M. Capelli, B. Clarke, *et al.*, *J. Med. Chem.* **2006**, *49*, 5912 – 5931.

[22] G. Bottegoni, A. Cavalli, M. Recanatini, *J. Chem. Inf. Model* **2006**, *46*, 852 – 862; G. Bottegoni, W. Rocchia, M. Recanatini, A. Cavalli, *Bioinformatics* **2006**, *22*, e58 – e65.

[23] D. Lin, L. Zhang, E. Chiao, W. L. Miller, *Mol. Endocrinol.* **1994**, *8*, 392 – 402; R. J. Auchus, W. L. Miller, *Mol. Endocrinol.* **1999**, *13*, 1169 – 1182; A. P. Mathieu, J.-G. LeHoux, R. Auchus, *Biochim. Biophys. Acta* **2003**, *1619*, 291 – 300.

[24] T. A. Halgren, *J. Comput. Chem*. **1999**, *20*, 730 – 748.

[25] A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648 – 5652; P. J. Stevens, J. F. Devlin, C. F. Chabalowski, M. J. Frisch, *J. Phys. Chem*. **1994**, *98*, 11623 – 11627.

