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# Synthesis, biological evaluation, and molecular modeling studies of methylene imidazole substituted biaryls as inhibitors of human 17α-hydroxylase-17,20-lyase (CYP17)—Part II: Core rigidification and influence of substituents at the methylene bridge

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ABSTRACT

Thirty-five novel substituted imidazolyl methylene biphenyls have been synthesized as CYP17 inhibitors for the potential treatment of prostate cancer. Their activities have been tested with recombinant human CYP17 expressed in *Escherichia coli*. Promising compounds were tested for selectivity against CYP11B1, CYP11B2, and hepatic CYP enzymes 3A4, 1A2, 2B6 and 2D6. The core rigidified compounds (**30**–**35**) were the most active ones, being much more potent than Ketoconazole and reaching the activity of Abiraterone. However, they were not very selective. Another rather potent and more selective inhibitor (compound **23**, $IC_{50}$ = 345 nM) was further examined in rats regarding plasma testosterone levels and pharmacokinetic properties. Compared to the reference Abiraterone, **23** was more active in vivo, showed a longer plasma half-life (10 h) and a higher bioavailability. Using our CYP17 homology protein model, docking studies with selected compounds were performed to study possible interactions between inhibitors and amino acid residues of the active site.



## 1. Introduction

It has been illuminated that the growth of up to 80% of prostate carcinoma, the most common malignancy and cause of death for male elders, depends on androgen stimulation. Thus, inhibition of androgen formation or prevention of androgens unfolding activity will effectively prevent cancer cell proliferation. Currently, the standard therapy for prostate carcinoma is the so-called 'combined androgen blockade' (CAB), which means orchidectomy or treatment with gonadotropin-releasing hormone (GnRH) analogues (chemical castration) combined with androgen receptor antagonists.[1] Anti-androgens are used to prevent adrenal androgens, which are not affected by the former strategies from unfolding stimulatory effects. However, CAB often leads to resistance, which can be associated with androgen receptor mutations. The mutated androgen receptor recognizes antagonists as agonists, and the efficiency of this therapy is whittled away. Total blockage of the androgen biosynthesis could be a more promising alternative, which brings CYP17 and its central role in the androgen biosynthesis into focus. CYP17, located in both testicular and adrenal tissues,[2] is the key enzyme catalyzing 17α-hydroxylation and subsequent C17–C20 bond cleavage of pregnenolone and progesterone to form DHEA and androstenedione, which are then converted to testosterone and DHT.[3]

From Ketoconazole, the first medication that has been used clinically as CYP17 inhibitor, to Abiraterone, which entered into phase II clinical trial very recently, several types of CYP17 inhibitors have been synthesized and tested (representative structures are shown in Chart 1). Almost all the inhibitors, steroidal or non-steroidal, are mimics of the natural substrates pregnenolone and

*Abbreviations:* CYP, cytochrome P450; CAB, combined androgen blockade; GnRH, gonadotropin-releasing hormone; CYP17, 17α-hydroxylase-17,20-lyase; DHEA, dehydroepiandrosterone; DHT, dihydrotestosterone; CDI, 1,1-carbonyl diimidazole; TBDMS, *tert*-butyldimethylsilyl; TBDPS, *tert*-butyldiphenylsilyl; Boc, *tert*-butoxycarbonyl; NMP, *N*-methylpyrrolidone; ATR, attenuated total reflectance; PE, petroleum ether; BM, binding mode; GA, genetic algorithm.

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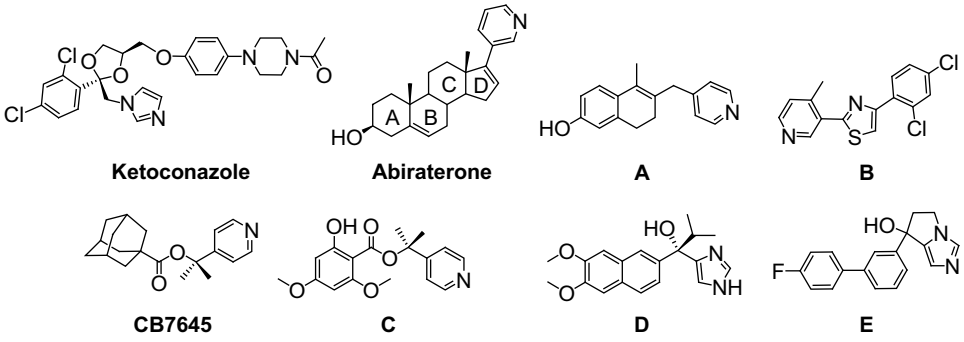
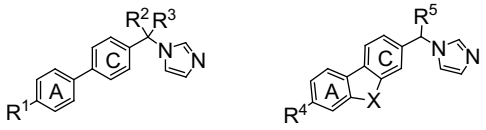



**Chart 1.** Structures of typical CYP17 inhibitors.



$R^1$ = H, OH, F, alkyl, amino, amido, CN, $CF_3$
$R^2$ = H, alkyl, phenyl, biphenyl
$R^3$ = H, Me, Et

$R^4$ = H, F
$R^5$ = H, Me
X = NH, $CH_2$

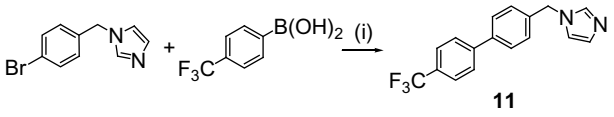
**Chart 2.** General structures of synthesized compounds **1**–**35**.

progesterone. Although lots of steroidal inhibitors are very potent,[4] especially Abiraterone,[5] the potential drawback of these compounds should not be ignored: the relative short half-life or poor bioavailability,[6] the first pass effect when orally administered[7] and the affinity towards steroid receptors, which might result in side effect no matter acting as agonists or antagonists. All of these shortcomings indicated the necessity to develop non-steroidal CYP17 inhibitors. In the past decade, a wide variety of non-steroidal compounds have been described, the most important of these were tetrahydronaphthalenes (A),[8] *m*-pyridinyl substituted esters (CB7645 and C),[9] 1*H*-imidazol-4-yl substituted alcohols (D and E),[10] and 1-(*m*-pyridinyl)-3-phenyl substituted heterocycles (B).[11]

Our group has reported a series of imidazolyl and triazolyl substituted biphenyls as potent CYP17 inhibitors.[12] Recently heterocyclic modifications of the core structure were performed with the more promising biphenyl methylene imidazoles. They have been published recently as part I of this study to further improve biological properties. [13] In the present paper, modifications such as the introduction of different substituents at the methylene bridge as well as the A ring and core rigidifications have been made leading to compounds **1**–**35** (general structures shown in Chart 2). Besides the syntheses and the determination of inhibitory activities towards human CYP17, the inhibitions of selected compounds against CYP11B1, CYP11B2, and hepatic CYP enzymes 3A4, 1A2, 2B6, and 2D6 are described. Furthermore, compound **23**, as the most selective inhibitor, was examined for its potency of reducing plasma testosterone concentration and its pharmacokinetic properties in rats. Moreover, molecular docking studies with both enantiomers of selected compounds, if existing, were carried out using our homology model of CYP17[13] for getting a closer insight into the interaction between active site amino acids and the ligands.

## 2. Chemistry

For the synthesis of compounds **1–10** and **12–35** (Schemes 1–7), basically the following strategy was used: the corresponding ketone or aldehyde intermediates were obtained commercially or



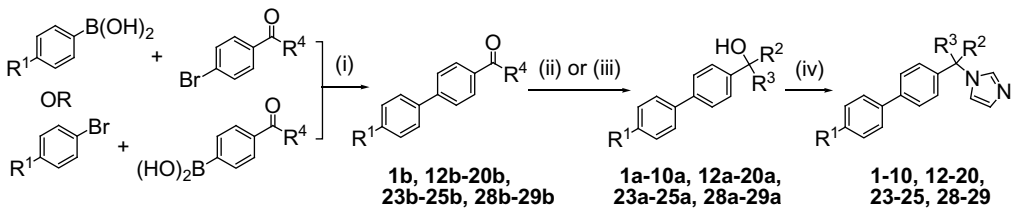

**Scheme 1.** Reagents and conditions: (i) *Method C:* $Pd(PPh_3)_4$, $Na_2CO_3$, toluene/EtOH/$H_2O$, reflux, 16 h.

synthesized by Suzuki coupling (Method C) from the corresponding bromides and boronic acids.[14] Subsequently, they were converted to the alcohols by reduction with $NaBH_4$ (Method D) or Grignard reaction (Method B). The alcohol intermediates were reacted with 1,1-carbonyl diimidazole (CDI) (Method A), in a $S_Nt$ reaction, to give the racemic mixtures of the desired products,[15] which were tested for their inhibitory potencies without further separation. In the case of some sensitive intermediates, certain protecting groups were employed and subsequently removed: *tert*-butyldimethylsilyl (TBDMS) or *tert*-butyldiphenylsilyl (TBDPS) for hydroxy groups and *tert*-butoxycarbonyl (Boc) for amino groups. The conversion of the hydroxy compound **26** to the chloro compound **27** was achieved using $SOCl_2$ (Scheme 5). In some cases, the carbazole core was constructed by ring closure of the *o*-nitro substituted biphenyl refluxed with phosphorous acid triethyl ester (Scheme 7). The only exception from this strategy was the synthesis of compound **11** (Scheme 1). This compound was simply prepared from 1-(4-bromobenzyl)-1*H*-imidazole and 4-trifluoromethylphenylboronic acid by means of Suzuki coupling (Method C).

## 3. Biological results, modeling studies, and discussion

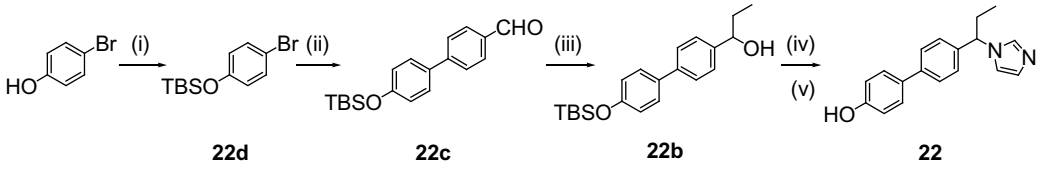
CYP17 inhibition of all compounds was evaluated using the 50,000*g* sediment after homogenation of *Escherichia coli* expressing human CYP17 as well as cytochrome P450 reductase.[12d] The assay was run with progesterone (25 μM) as substrate and NADPH as cofactor. Separation of substrate and product was accomplished by HPLC using UV detection.[16a] $IC_{50}$ values are presented in comparison to Ketoconazole and Abiraterone in Tables 1–4.

Inheriting from ref. compound **1**,[12b] the influence of different substituents on the methylene bridge was investigated (Table 1). From the inhibitory activity values, it becomes apparent that increasing the length of $\mathbf{R}^2$ would largely influence the potency. The introduction of two-carbon alkyl substituents, like Et (**1**), and even more bulky ones like *i*-Pr (**3**) and *t*-Bu (**6**), increased the potency of the compounds compared to ref. compound **1** ($IC_{50}$ = 910 nM), resulting in inhibitors with $IC_{50}$ values in a range from 300 to 450 nM. Interestingly, the further prolongation of the alkyl chain by another carbon atom led to moderate (**2**, $\mathbf{R}^2$: *n*-Pr, $IC_{50}$ = 580 nM) or low active inhibitors (**5**, $\mathbf{R}^2$: *i*-Bu, $IC_{50}$ = 2100 nM). However, adding another C atom to the alkyl $\mathbf{R}^2$

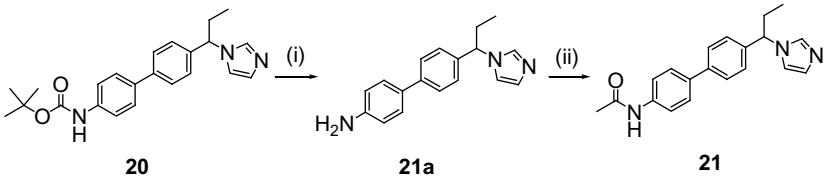



**1**: $R^1$ = H, $R^2$ = Et, $R^3$ = $R^4$ = H;
**2**: $R^1$ = H, $R^2$ = n-Pr, $R^3$ = $R^4$ = H;
**3**: $R^1$ = H, $R^2$ = i-Pr, $R^3$ = $R^4$ = H;
**4**: $R^1$ = H, $R^2$ = n-Bu, $R^3$ = $R^4$ = H;
**5**: $R^1$ = H, $R^2$ = i-Pr, $R^3$ = $R^4$ = H;
**6**: $R^1$ = H, $R^2$ = t-Bu, $R^3$ = $R^4$ = H;
**7**: $R^1$ = H, $R^2$ = cyclohexyl, $R^3$ = $R^4$ = H;
**8**: $R^1$ = H, $R^2$ = benzyl, $R^3$ = $R^4$ = H;
**9**: $R^1$ = H, $R^2$ = phenyl, $R^3$ = $R^4$ = H;
**10**: $R^1$ = H, $R^2$ = biphenyl, $R^3$ = $R^4$ = H;
**12**: $R^1$ = $OCF_3$, $R^2$ = Et, $R^3$ = $R^4$ = H;
**13**: $R^1$ = SMe, $R^2$ = Et, $R^3$ = $R^4$ = H;
**14**: $R^1$ = CN, $R^2$ = Et, $R^3$ = $R^4$ =H ;
**15**: $R^1$ = Me, $R^2$ = $R^4$ = Et, $R^3$ = H;
**16**: $R^1$ = Et, $R^2$ = $R^4$ = Et, $R^3$ = H;
**17**: $R^1$ = $N(Me)_2$, $R^2$ = Et, $R^3$ = $R^4$ = H;
**18**: $R^1$ = $N(Et)_2$, $R^2$ = Et, $R^3$ = $R^4$ = H;
**19**: $R^1$ = morpholino, $R^2$ = Et, $R^3$ = $R^4$ = H;
**20**: $R^1$ = NHBoc, $R^2$ = Et, $R^3$ = $R^4$ = H;
**23**: $R^1$ = F, $R^2$ = $R^4$ = Et, $R^3$ = H;
**24**: $R^1$ = F, $R^2$ = Me, $R^3$ = $R^4$ = Me;
**25**: $R^1$ = F, $R^2$ = Et, $R^3$ = $R^4$ = Et;
**28**: $R^1$ = F, $R^2$ = $CH=CH_2$, $R^3$ = $R^4$ = H;
**29**: $R^1$ = H, $R^2$ = $CH=CH_2$, $R^3$ = $R^4$ = H;

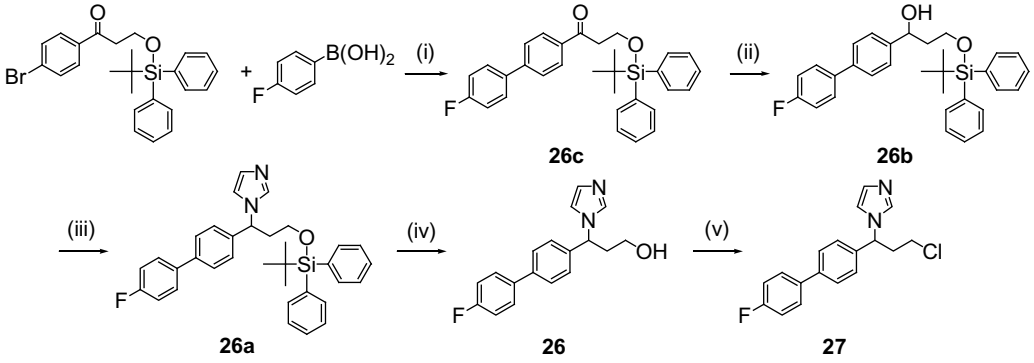
**Scheme 2.** Reagents and conditions: (i) *Method C:* $Pd(PPh_3)_4$, $Na_2CO_3$, toluene, reflux 6 h; (ii) *Method D:* **15b**–**16b**, **23b**: $NaBH_4$, MeOH; (iii) *Method B:* **1b**, **12b**–**14b**, **17b**–**20b**, **24b**–**25b**, **28b**–**29b**: corresponding Grignard reagent, THF; (iv) *Method A:* CDI, NMP.




**Scheme 3.** Reagents and conditions: (i) TBSCl, Imidazole; (ii) *Method C:* 4-formylphenylboronic acid, $Pd(PPh_3)_4$, $Na_2CO_3$, toluene, reflux 6 h; (iii) *Method B:* EtMgBr, THF; (iv) *Method A:* CDI, NMP; (v) TBAF, THF, rt.



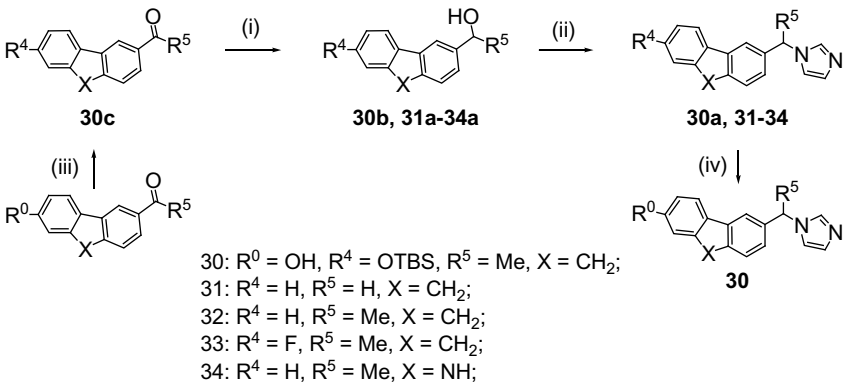

**Scheme 4.** Reagents: (i) TFA, DCM (ii) AcCl, $N(Et)_3$, DMAP, THF.



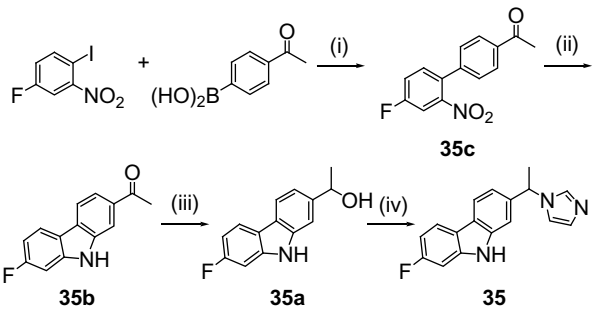

**Scheme 5.** Reagents and conditions: (i) *Method C:* $Pd(PPh_3)_4$, $Na_2CO_3$, toluene, reflux 6 h; (ii) *Method D:* $NaBH_4$, MeOH; (iii) *Method A:* CDI, NMP, reflux, 3 h; (iv) TBAF, THF; (v) $SOCl_2$, DCM.

gave again a very potent compound (**4**, $\mathbf{R}^2$: *n*-Bu, $IC_{50}$ = 300 nM). Furthermore, it could be observed that the activity of the compounds with a bulky group was reduced dramatically as expected, like benzyl, phenyl (**8** and **9** with $IC_{50}$ values around 800 nM), cyclohexyl (**7**, $IC_{50}$ = 1050 nM), and biphenyl (**10**, $IC_{50}$ = 2300 nM).

In the modeling studies, it was observed that all docked compounds showed two binding modes, named **BM1** and **BM2**, which were identified previously for other biaryl type inhibitors.[13,17] These binding modes are different from the proposed substrate binding mode.[18,19] In **BM1** the biaryl plane is oriented almost parallel to the I-helix, and principally ligands bearing a $\mathbf{R}^1$-substituent were found in this mode (in Fig. 1, compound **22** is taken as an example). The substituted A-ring is located next to a polar pocket[18] delimitated by Arg109, Lys231, His235, and Asp298, which tolerates different substitution patterns. On the other hand, in **BM2** the biaryl plane crosses the I-helix, avoiding the interaction with

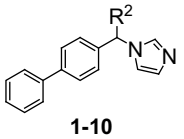



**Scheme 6.** Reagents and conditions: (i) *Method D:* $NaBH_4$, MeOH; (ii) *Method A:* CDI, NMP, reflux, 3 h; (iii) TBSCl, imidazole; (iv) TBAF, THF.




**Scheme 7.** Reagents and conditions: (i) *Method C:* $Pd(PPh_3)_4$, $Na_2CO_3$, toluene, reflux 6 h; (ii) $P(OEt)_3$, reflux; (iii) *Method D:* $NaBH_4$, THF, MeOH; (iv) *Method A:* CDI, NMP, reflux, 3 h.

**Table 1**
Inhibition of CYP17 by compounds **1**–**10**



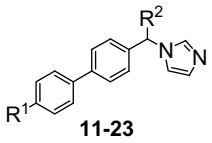

| Compound | $R^2$ | CYP17 $IC_{50}$[b] (nM) |
|---|---|---|
| Ref. **1** | Me | 910 |
| **1** | Et | 450 |
| **2** | *n*-Pr | 580 |
| **3** | *i*-Pr | 310 |
| **4** | *n*-Bu | 300 |
| **5** | *i*-Bu | 2100 |
| **6** | *t*-Bu | 460 |
| **7** | Cyclohexyl | 1050 |
| **8** | Benzyl | 780 |
| **9** | Phenyl | 790 |
| **10** | Biphenyl | 2300 |
| KTZ[a] | | 2780 |
| ABT[a] | | 72 |

[a] KTZ, Ketoconazole; ABT, Abiraterone.
[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%.

the polar pocket. It is a less permissive binding mode, which tolerates only planar ligands with an un- or fluorine substituted A-ring (compound **2** shown in Fig. 1).

Nonetheless, for both binding orientations similar hydrophobic and π–π interactions can be observed,[13,17] namely between the biphenyl core and Phe114 as well as between the biphenyl moiety and apolar parts of amino acids of the F-helix (Asn202 and Ile206) and I-helix (Gly301, Ala302, Val304, and Glu305) (Fig. 1).

**Table 2**
Inhibition of CYP17 by compounds **11**–**23**



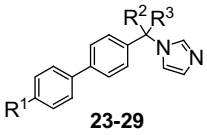

| Compound | $R^1$ | $R^2$ | CYP17 $IC_{50}$[b] (nM) |
|---|---|---|---|
| **11** | $CF_3$ | H | >5000 |
| **12** | $OCF_3$ | Et | >5000 |
| **13** | SMe | Et | 3100 |
| **14** | CN | Et | >5000 |
| **15** | Me | Et | >5000 |
| **16** | Et | Et | 2000 |
| **17** | $N(Me)_2$ | Et | ≫5000 |
| **18** | $N(Et)_2$ | Et | ≫5000 |
| **19** | Morpholino | Et | 2200 |
| **20** | NHBoc | Et | 1700 |
| **21** | NHAc | Et | >5000 |
| **22** | OH | Et | 375 |
| **23** | F | Et | 345 |
| KTZ[a] | | | 2780 |
| ABT[a] | | | 72 |

[a] KTZ, Ketoconazole; ABT, Abiraterone.
[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%.

Compounds **1**, **2**, **4**, **5**, **6**, and ref. compound **1** were docked into our CYP17 model with the aim of explaining the influence of the different $\mathbf{R}^2$ substituents. For all *R*-enantiomers bearing a short alkyl substituent (Et, *i*-Pr, *t*-Bu or Me) at the methylene bridge, the preferred binding mode was **BM1**; whereas for the corresponding *S*-enantiomers, **BM2** seemed to be the most probable. Based on the requisites for each binding mode, [13,17] both orientations seem to be possible for compounds **1**, **6**, and ref. compound **1**. On the other hand, although poses in **BM2** could also be observed, the preferred orientations for compounds **2**, **4**, and **5** seem to be **BM1**, regardless of which enantiomer was considered. This might be caused by the presence of a longer and bulkier substituent on the methylene bridge.

The results revealed an orientation of the $\mathbf{R}^2$ group towards a tiny hydrophobic pocket, formed by amino acids Ala367-Pro368-Met369-Leu370-Ile371 (Fig. 2A). Et, *i*-Pr, and *t*-Bu substituents can undergo hydrophobic interactions with this apolar environment close to the heme without steric clashes due to their reduced length. However, for compounds **2** (*n*-Pr) and **5** (*i*-Bu) steric hindrance and hydrophobic repulsion perish the possibility of additional hydrophobic interactions, thus reducing their inhibitory potencies. As for compound **4**, the results indicate that the *n*-Bu

**Table 3**
Inhibition of CYP17 by compounds **23–29**

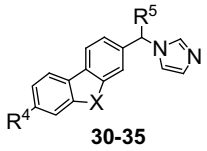



**23-29**

| Compound | $R^1$ | $R^2$ | $R^3$ | CYP17 $IC_{50}$[b] (nM) |
|---|---|---|---|---|
| Ref. **2** | F | Me | H | 1100 |
| **23** | F | Et | H | 345 |
| **24** | F | Me | Me | 3800 |
| **25** | F | Et | Et | 1300 |
| **26** | F | $(CH_2)_2OH$ | H | >5000 |
| **27** | F | $(CH_2)_2Cl$ | H | 756 |
| **28** | F | $CH{=}CH_2$ | H | >5000 |
| **29** | H | $CH{=}CH_2$ | H | 1400 |
| KTZ[a] | | | | 2780 |
| ABT[a] | | | | 72 |

[a] KTZ, Ketoconazole; ABT, Abiraterone.
[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%.

**Table 4**
Inhibition of CYP17 by compounds **30–35**




**30-35**

| Compounds | $R^4$ | $R^5$ | X | CYP17 $IC_{50}$[b] (nM) |
|---|---|---|---|---|
| **30** | OH | Me | $CH_2$ | 99 |
| **31** | H | H | $CH_2$ | 388 |
| **32** | H | Me | $CH_2$ | 112[c] |
| **33** | F | Me | $CH_2$ | 168 |
| **34** | H | Me | NH | 282 |
| **35** | F | Me | NH | 118 |
| KTZ[a] | | | | 2780 |
| ABT[a] | | | | 72 |

[a] KTZ, Ketoconazole; ABT, Abiraterone.
[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] $IC_{50}$ = 4 nM, reported in Ref. 23.

group can interact not only with amino acids Ile371 and Ala367, like *n*-Pr does, but also with Val366, Pro368, and Val382 as additional contacts. This leads to the stabilization of its orientation, and makes it a potent inhibitor (Fig. 2A).

It can also be observed that different $\mathbf{R}^1$ substituents on the A ring show a strong influence on the activity of the imidazole substituted biphenyls. Exhibiting the same ethyl group at the methylene bridge, the A ring substitution dispersed the inhibitory potency of the corresponding compounds strongly ranging from no to strong inhibition (Table 2). It becomes apparent that hydrophobic and electronegative groups in $\mathbf{R}^1$ led to almost inactive compounds. However, when $\mathbf{R}^1$ is a small polar substituent, capable of H-bond formation, the compounds turned out to be very active (**22**, $\mathbf{R}^1$ = OH, $IC_{50}$ = 375 nM; **23**, $\mathbf{R}^1$ = F, $IC_{50}$ = 345 nM).

Docking of both enantiomers of ligands **22** and **23** into the active site of our CYP17 model revealed that **BM1** is preferred for *S*-**22**, *R*-**22**, and *R*-**23**. There is obviously hydrogen bond formation between $\mathbf{R}^1$ and the polar surrounding of Arg109, Asp298, Lys231, and His235 (Fig. 2B). However, the *S*-enantiomer of compound **23** was found to bind in **BM2** as long as the small H-bond accepting fluorine group can interact with Gln199 and Asn202 (Fig. 2B).

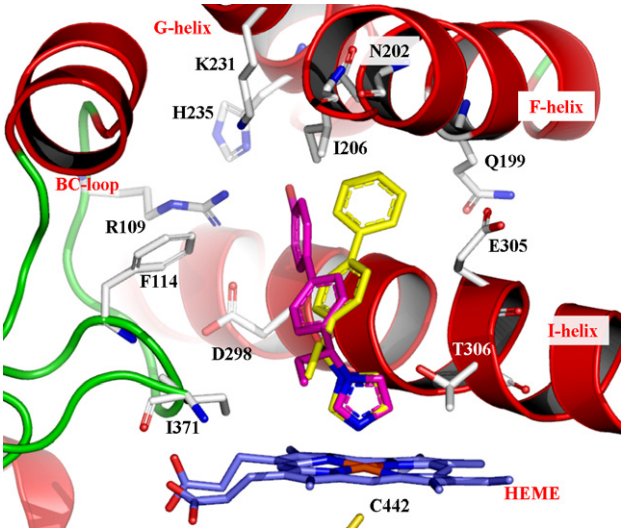



**Figure 1.** Presentation of the two found binding modes **BM1** and **BM2**, exemplified by compounds **22** (magenta, **BM1**) and **2** (yellow, **BM2**). Furthermore, heme, interacting residues and ribbon rendered tertiary structure of the active site are shown. Figures were generated with Pymol (http://www.pymol.org).

As it is known that fluorine compounds are more stable in vivo than hydroxy compounds, $\mathbf{R}^1$ was sustained to be fluorine, and the influence of substituents at the methylene bridge was further investigated (Table 3). Interestingly, the single ethyl group turned out to be the best, while twin alkyl substituted analogues (**24**–**25**) showed lower inhibitory potency than their single substituted analogues (**23**, ref. compound **2**). This is obviously due to the steric clashes with amino acids of the I-helix kink and the reduced flexibility of these ligands. Moreover, the similar activity of compound **27** (2-chloroethyl, $IC_{50}$ = 756 nM) and compound **2** (*n*-Pr) and the total loss of activity for the 2-hydroxylethyl analogue (**26**) demonstrate the necessity of a hydrophobic side chain on the methylene bridge.

Rigidification of the biphenyl core to form a carbazole or 9*H*-fluorene ring (Table 4) led to the most potent series of compounds (**30**–**35**). The planar conjugated scaffolds apparently contributed most to the inhibitory potency, probably due to the reduced degrees of freedom. Once again, inhibitors furnished with groups capable of forming hydrogen bonds turned out to be more active, with the hydroxy substituted 9*H*-fluorene analogue (**30**) being the most potent compound of this study ($IC_{50}$ = 99 nM, 28-fold more potent than Ketoconazole). Moreover, the importance of an alkyl substituent on the spacer has been demonstrated again, as can be seen from the higher activity of the methyl compound **32** showing an $IC_{50}$ value of 112 nM (for this compound an $IC_{50}$ value of 4 nM is reported[23]) compared to the corresponding non-substituted analogue **31** ($IC_{50}$ = 388 nM).

For the docking studies of selected compounds from Table 4 (**30**, **32**, and **35**), similar results were achieved as obtained for the non-rigidified compounds. Two binding modes, **BM1** and **BM2**, were identified. The former seemed to be preferred, based on the internal energies of the docked inhibitors and the visual inspection of possible interactions, regardless which enantiomer was considered. The same H-bond interactions were found as described above (Figs. 1 and 2B). Moreover, the poses were also stabilized by the electrostatic interactions with carbon chain of Glu305 (Fig. 3).

The inhibition of selected compounds towards hepatic CYP enzymes was determined (Table 5), because of their important role in drug metabolism and drug–drug interaction. Although the com-

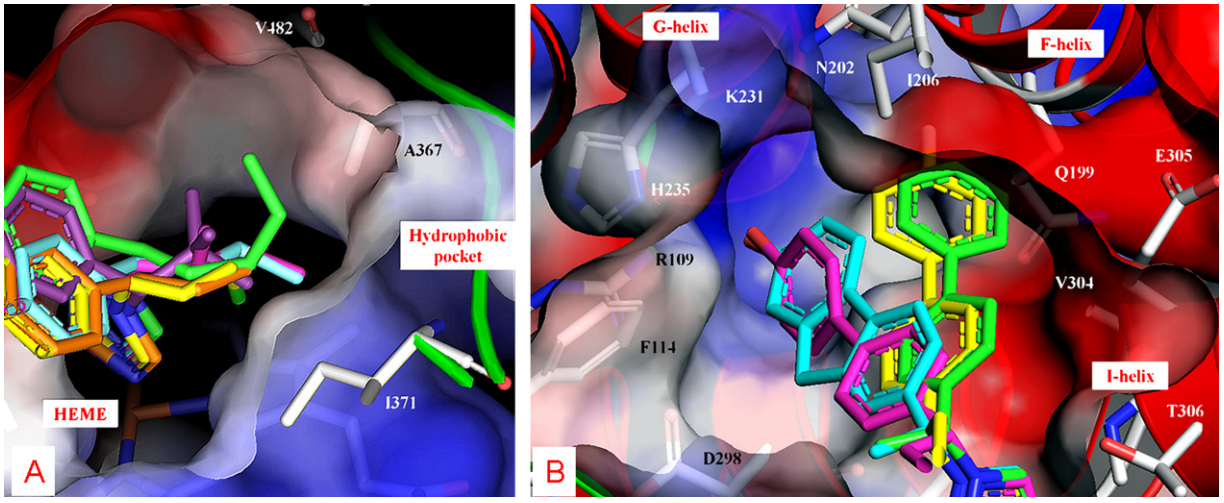



**Figure 2.** A cross-section of the solvent accessible surface of the active site is given with a (A) closer look to the orientation of the $R^2$ methylene linker substituents (compounds **2** (light blue), **4** (green), **5** (magenta), **6** (violet), **23** (orange), and **27** (yellow)) with their surrounding amino acids and a (B) more in-depth view of the A-ring substituents (compounds **30** (cyan), *S*-**23** (yellow), *R*-**22** (magenta) and ref. compound **1** (R; green) and interacting residues.

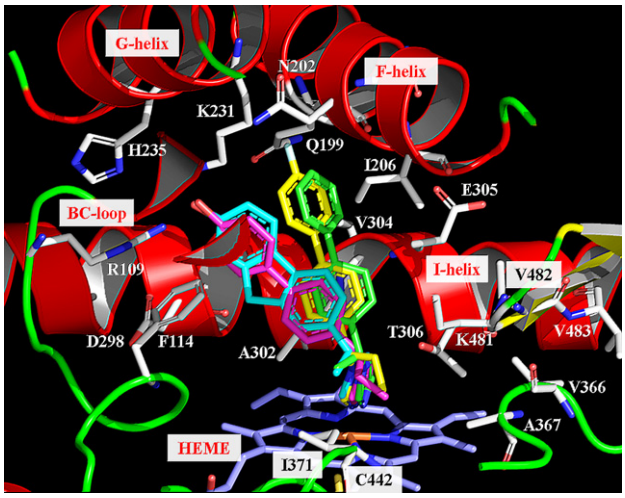



**Figure 3.** Docking complex between CYP17 and compounds **30** (cyan), *S*-**23** (yellow), *R*-**22** (magenta), and ref. compound **1** (R; green). Heme, interacting residues and ribbon rendered tertiary structure of the active site are shown.

**Table 5**
Inhibition of hepatic CYP enzymes by selected compounds

| Compounds | % Inhibition[b] | | | |
|---|---|---|---|---|
| | CYP3A4 | CYP1A2 | CYP2B6 | CYP2D6 |
| **20** | 52 | nd[a] | nd | nd |
| **23** | 88 | 97 | 46 | 54 |
| **25** | 95 | 51 | nd | nd |
| **27** | 86 | 96 | 34 | 32 |
| **30** | 89 | 93 | nd | nd |
| **32** | 89 | 98 | nd | nd |
| **34** | 88 | 99 | nd | nd |
| **35** | 75 | nd | nd | nd |
| KTZ[a] | 96 | 8 | 11 | 1 |
| ABT[a] | 27 | 36 | 2 | 7 |

[a] KTZ, Ketoconazole; ABT, Abiraterone; nd, not determined.
[b] Inhibition at a concentration of 1 μM; standard deviations were within <±5%; All the data are the mean values of at least three independent tests.

pounds tested showed inhibition of CYP3A4, it was lower than that of Ketoconazole. Interestingly, compound **20** showed only little inhibition (52% at 1 μM), possibly due to the bulky *t*-Boc amino group it bears. However, CYP1A2 inhibition shown by the test compounds was much higher than that of Ketoconazole. Compounds **23** and **27** showed good selectivity towards CYP2B6 and 2D6.

Furthermore, selectivity towards CYP11B1 and CYP11B2—the most important steroidogenic enzymes being responsible for adrenal corticoid biosynthesis—has been determined as another criterion to decide which compound should be tested further in vivo. CYP11B1 catalyzes 11β-hydroxylation in cortisol biosynthesis, whereas CYP11B2 is responsible for the final three steps (11β-hydroxylation, 18-hydroxylation and 18-oxidation) in aldosterone biosynthesis. Inhibition of these two enzymes could cause hyponatremia, hyperkalemia, and a series of recessive disorders, such as adrenal hyperplasia and hypovolemic shock.[20] The most interesting compounds of this series, **23** and **30**, were tested at a concentration of 0.2 μM. As compound **23** showed less inhibition on both enzymes (11B2: 66%; 11B1: 66%, compound **30**, 11B1: 96%; 11B2: 98%), it was further tested in rats.

The in vivo evaluation of compound **23**, including the ability of reducing plasma testosterone concentration (Table 6) and the determination of pharmacokinetic properties (Table 7), was performed in male Wistar rats after oral application using Abiraterone as reference compound. The plasma concentrations of testosterone were determined by ELISA, and plasma drug concentrations were measured using LC–MS. Although applied as acetate, only the signals of the free Abiraterone were monitored. It is obvious that both compounds significantly reduced the plasma testosterone concentration. It is striking that compound **23**, which was less active in vitro, was much more active in vivo than Abiraterone at each time point checked. Importantly, after 24 h compound **23** still showed strong inhibitory activity, while Abiraterone exhibited at this time point plasma testosterone concentrations six fold higher than that of the untreated control. This activity profile can be explained by the pharmacokinetic properties of the compounds. Compound **23** exhibited a plasma half-life of 10 h, while Abiraterone only showed 1.6 h. The fact that Abiraterone had to be administrated as acetate prodrug, which is inactive as CYP17 inhibitor, could explain the reduced inhibitory activity of the steroidal compound. However, application of the acetate should prolong the plasma half-life having no influence on the AUC of the parent compound. The superiority of compound **23** becomes apparent by comparing the AUCs of the two compounds, leading to the conclusion that the bioavailability of compound **23** is much better.

**Table 6**
Reduction of the plasma testosterone concentrations in rats by compound **23**[a]

| Compounds | Relative plasma testosterone level (%) [b] | | | | | |
|---|---|---|---|---|---|---|
| | 1 h | 2 h | 4 h | 6 h | 8 h | 24 h |
| Control | 143.1 ± 13.3 | 76.4 ±13.3 | 81.4 ± 24.6 | 109.6 ± 31.7 | 90.6 ± 22.8 | 80.6 ± 21.0 |
| **23** | 16.5 ± 5.7[d] | 11.7 ± 5.0[d] | 13.9 ± 8.0[d] | 13.9 ± 7.1[d] | 13.4 ± 6.2 [d] | 36.7 ± 27.4[d] |
| ABT[e] | 92.5 ± 43.1[d] | 44.0 ± 14.7[d] | 43.5 ± 12.4[d] | 43.3 ±12.8[c] | 35.6 ± 9.7[d] | 476.0 ± 238.6 |

[a] Compound **23** was applied at a dose of 50 mg/kg body weight; Abiraterone was administrated as Abiraterone acetate (56 mg/kg body weight, equivalent to Abiraterone 50 mg/kg body weight). Five to six intact adult male Wistar rats were employed for each treatment group; each sample was tested for three times.
[b] The average plasma testosterone concentrations (1.81 ng/mL) at pre-treatment time points (−1, −0.5, and 0 h) were set to 100%. The values shown are the relative levels compared to the pre-treatment value.
[c] $P < 0.05$.
[d] $P < 0.01$.
[e] ABT, Abiraterone.

**Table 7**
Pharmacokinetic properties of compound **23**[a]

| Compound | $t_{1/2z}$[b] (h) | $t_{max}$[b] (h) | $C_{max}$[b] (ng/mL) | $AUC_{0-\infty}$[b] (ng h/mL) | $Cl_{int}$[b] (l/kg/h) |
|---|---|---|---|---|---|
| 23 | 10.0 | 6.0 | 3288 | 70,729 | 0.7 |
| Abiraterone | 1.6 | 2.0 | 592 | 4015 | 11.2 |

[a] Compound 23 was applied at a dose of 50 mg/kg body weight; Abiraterone was administrated as Abiraterone acetate (56 mg/kg body weight, equivalent to Abiraterone 50 mg/kg body weight). Five to six intact adult male Wistar rats were employed for each treatment group; each sample was tested for three times.
[b] $t_{1/2z}$, terminal half-life; $t_{max}$, time of maximal concentration; $C_{max}$, maximal concentration; $AUC_{0-\infty}$, area under the curve; $Cl_{int}$, intrinsic hepatic clearance.

## 4. Conclusion

Herein, we reported the synthesis and evaluation of bioactivity of a series of substituted and core rigidified biphenyl methylene imidazoles as CYP17 inhibitors. We found clearer SAR for biphenyl type CYP17 inhibitors, comparing to previous work,[12,13] that alkyl groups at the methylene bridge, if in suitable length, can strongly improve the inhibitory potency. Analogues substituted with polar substituents at the A ring, capable of H-bond formation, always led to potent inhibitors. Besides, rigidification of the biphenyl core to form a carbazole or 9*H*-fluorene ring also significantly elevated the activity to give a series of CYP17 inhibitors more potent than previously reported, [12,13] probably due to their planar conjugated scaffolds. Moreover, one of the best compounds in vitro, compound **23** showed potent activity in vivo, a long plasma half-life and a high bioavailability.

However, further structure modifications have to be performed with the aim of reducing the CYP1A2 inhibition—the enzyme responsible for the metabolism of approximately 10% of the prescription drugs—before a candidate for the treatment of prostate cancer can be propagated. Furthermore, because of being tested as racemic mixtures, it is likely that one enantiomer of compound **23** would be more potent and selective than the other. A separation of the enantiomers is presently being performed.

## 5. Experimental

### 5.1. CYP17 preparation and assay

Human CYP17 was expressed in *E. coli* (coexpressing human CYP17 and cytochrome P450 reductase) and the assay was performed as previously described.[12d,16a]

### 5.2. 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.

### 5.3. Inhibition of CYP11B1 and CYP11B2

V79MZh cells expressing human CYP11B1 or CYP11B2 were incubated with [4-$^{14}$C]-11-deoxycorticosterone as substrate. The assay was performed as previously described.[16c,d]

### 5.4. In vivo study

The in vivo tests were performed with intact adult male Wistar rats (Harlan Winkelmann, Germany), 5–6 for each treatment group. These rats were cannulated with silicone tubing via the right jugular vein. Compound **23** was applied po at 50 mg/kg body weight, while Abiraterone was administrated as acetate at 56 mg/kg body weight (equivalent to Abiraterone at 50 mg/kg body weight). The concentrations of testosterone in the rat plasma were determined using the Testosterone ELISA (EIA-1559) from DRG Instruments according to the manufacturer's instructions. The plasma drug levels were measured by LC–MS. Non-compartmental pharmacokinetic analysis of concentration versus time data were performed for each compound on the mean plasma level using a validated computer program (PK solution 2 software; Summit Research Services, Montrose, USA). Plasma concentrations below the limit of detection were assigned a value of zero.

### 5.5. Chemistry

#### 5.5.1. 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 and $^{13}$C 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 Hertz. 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. The purities of the final compounds were controlled by Surveyor®-LC-system. Purities were greater than 98%. 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 commercially obtained (CombiBlocks, Chempur, Aldrich, Acros).

### 5.5.2. Method A: CDI reaction

To a solution of the corresponding alcohol (1 equiv) in *N*-methylpyrrolidone (NMP) or acetonitrile (10 mL/mmol) was added CDI (5 equiv). Then, the solution was heated to reflux for 4–18 h. 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.

**5.5.2.1. 1-(1-Biphenyl-4-yl-propyl)-1*H*-imidazole (1).** Synthesized according to Method A using **1a** (0.50 g, 2.36 mmol) and CDI (1.91 g, 11.78 mmol); yield: 0.13 g (21%); yellow solid: mp 75–77 °C; $R_f$ = 0.31 (DCM/MeOH, 10:1); $\delta_H$ ($CDCl_3$, 500 MHz) 0.99 (t, *J* = 7.5 Hz, 3H, $CH_3$), 2.26–2.32 (m, 2H, $CH_2$), 5.09 (t, *J* = 7.5 Hz, 1H, CH), 6.99 (s, 1H), 7.11 (s, 1H), 7.25 (d, *J* = 8.4 Hz, 2H), 7.33–7.37 (m, 1H), 7.42–7.46 (m, 2H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.69 (s, 1H); MS (ESI): *m/z* = 263 [$M^+$+H].

**5.5.2.2. 1-(1-Biphenyl-4-yl-butyl)-1*H*-imidazole (2).** Synthesized according to Method A using **2a** (0.50 g, 2.21 mmol) and CDI (1.79 g, 11.05 mmol); yield: 0.16 g (27%); brownish oil; $R_f$ = 0.29 (DCM/MeOH, 10:1); $\delta_H$ ($CDCl_3$, 500 MHz) 0.98 (t, *J* = 7.5 Hz, 3H, $CH_3$), 1.31–1.39 (m, 2H, $CH_2$), 2.14–2.28 (m, 2H, $CH_2$), 5.17 (t, *J* = 7.5 Hz, 1H, CH), 6.99 (s, 1H), 7.10 (s, 1H), 7.26 (d, *J* = 8.0 Hz, 1H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.45 (dd, *J* = 7.5, 8.4 Hz, 2H), 7.54–7.57 (m, 4H), 7.66 (s, 1H); MS (ESI): *m/z* = 277 [$M^+$+H].

**5.5.2.3. 1-(1-Biphenyl-4-yl-2-methyl-propyl)-1*H*-imidazole (3).** Synthesized according to Method A using **3a** (0.50 g, 2.36 mmol) and CDI (1.91 g, 11.78 mmol); yield: 0.20 g (33%); white solid: mp 124–125 °C; $R_f$ = 0.31 (DCM/MeOH, 10:1); $\delta_H$ ($CDCl_3$, 500 MHz) 0.95 (t, *J* = 7.5 Hz, 6H, $(CH_3)_2$), 2.56–2.65 (m, 1H, $CH(Me)_2$), 4.67 (d, *J* = 7.5 Hz, 1H, CH), 7.05 (s, 1H), 7.07 (s, 1H), 7.32–7.38 (m, 3H), 7.42–7.45 (m, 2H), 7.55–7.58 (m, 4H), 7.67 (s, 1H); MS (ESI): *m/z* = 277 [$M^+$+H].

**5.5.2.4. 1-(1-Biphenyl-4-yl-pentyl)-1*H*-imidazole (4).** Synthesized according to Method A using **4a** (0.50 g, 2.08 mmol) and CDI (1.69 g, 10.40 mmol); yield: 0.15 g (25%); brownish oil; $R_f$ = 0.30 (DCM/MeOH, 10:1); $\delta_H$ ($CDCl_3$, 500 MHz) 0.89 (t, *J* = 7.5 Hz, 3H, $CH_3$), 1.28–1.37 (m, 2H, $CH_2$), 1.39–1.43 (m, 2H, $CH_2$), 2.20–2.26 (m, 2H, $CH_2$), 5.14 (t, *J* = 7.7 Hz, 1H, CH), 6.99 (s, 1H), 7.12 (s, 1H), 7.26 (d, *J* = 8.4 Hz, 2H), 7.35 (m, 1H), 7.43 (dd, *J* = 7.9, 8.4 Hz, 2H), 7.54–7.57 (m, 4H), 7.68 (s, 1H); MS (ESI): *m/z* = 291 [$M^+$+H].

**5.5.2.5. 1-(1-Biphenyl-4-yl-3-methyl-butyl)-1*H*-imidazole (5).** Synthesized according to Method A using **5a** (0.50 g, 2.08 mmol) and CDI (1.69 g, 10.40 mmol); yield: 0.16 g (27%); brownish oil; $R_f$ = 0.30 (DCM/MeOH, 10:1); $\delta_H$ ($CDCl_3$, 500 MHz) 0.96 (d, *J* = 7.5 Hz, 6H, $C(CH_3)_2$), 1.46–1.53 (m, 1H, $CH(Me)_2$), 1.99–2.20 (m, 2H, $CH_2$), 5.14 (t, *J* = 9.5 Hz, 1H, CH), 6.99 (s, 1H), 7.09 (s, 1H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.35 (m, 1H), 7.43 (dd, *J* = 7.9, 8.4 Hz, 2H), 7.54–7.57 (m, 4H), 7.65 (s, 1H); MS (ESI): *m/z* = 291 [$M^+$+H].

**5.5.2.6. 1-(1-Biphenyl-4-yl-2,2-dimethyl-propyl)-1*H*-imidazole (6).** Synthesized according to Method A using **6a** (0.50 g, 2.08 mmol) and CDI (1.69 g, 10.40 mmol); yield: 0.15 g (25%); white solid: mp 150-151 °C; $R_f$ = 0.30 (DCM/MeOH, 10:1); $\delta_H$ ($CDCl_3$, 500 MHz) 1.07 (s, 9H, $C(CH_3)_3$), 4.92 (s, 1H, CH), 7.08 (s, 1H), 7.24 (s, 1H), 7.32–7.36 (m, 1H), 7.41–7.45 (m, 4H), 7.55–7.57 (m, 4H), 7.72 (s, 1H); MS (ESI): *m/z* = 291 [$M^+$+H].

**5.5.2.7. 1-(1-Biphenyl-4-yl-cyclohexyl-methyl)-1*H*-imidazole (7).** Synthesized according to Method A using **7a** (0.50 g, 1.87 mmol) and CDI (1.52 g, 9.34 mmol); yield: 0.19 g (32%); white solid: mp 118–121 °C; $R_f$ = 0.32 (DCM/MeOH, 10:1); $\delta_H$ ($CDCl_3$, 500 MHz) 0.89–1.03 (m, 2H, cyclohexyl), 1.15–1.28 (m, 3H, cyclohexyl), 1.52–1.60 (m, 2H, cyclohexyl), 1.71–1.77 (m, 3H, cyclohexyl), 2.22–2.23 (m, 1H, cyclohexyl), 4.72 (t, *J* = 10.1 Hz, 1H, CH), 7.04 (s, 1H), 7.06 (s, 1H), 7.32–7.37 (m, 3H), 7.43 (dd, *J* = 7.5, 8.8 Hz, 2H), 7.54–7.57 (m, 4H), 7.63 (s, 1H); MS (ESI): *m/z* = 317 [$M^+$+H].

**5.5.2.8. 1-(1-Biphenyl-4-yl-2-phenyl-ethyl)-1*H*-imidazole (8).** Synthesized according to Method A using **8a** (0.50 g, 1.82 mmol) and CDI (1.48 g, 9.11 mmol); yield: 0.14 g (23%); yellow solid: mp 99–101 °C [ref. 98–100 °C[21]]; $R_f$ = 0.29 (DCM/MeOH, 10:1); $\delta_H$ ($CDCl_3$, 500 MHz) 3.50 (d, *J* = 7.5 Hz, 2H, $CH_2$), 5.09 (t, *J* = 7.5 Hz, 1H, CH), 6.95(s, 1H), 7.01 (d, *J* = 8.0 Hz, 2H), 7.06 (s, 1H), 7.22–7.24 (m, 3H), 7.28 (d, *J* = 8.4 Hz, 2H), 7.35–7.37 (m, 1H), 7.42–7.45 (m, 2H), 7.48 (s, 1H), 7.56–7.58 (m, 4H); MS (ESI): *m/z* = 325 [$M^+$+H].

**5.5.2.9. 1-(1-Biphenyl-4-yl-2-phenyl-methyl)-1*H*-imidazole (9).** Synthesized according to Method A using **9a** (0.50 g, 1.92 mmol) and CDI (1.56 g, 9.60 mmol); yield: 0.07 g (12%); yellow oil; [ref. mp 142 °C[22]]; $R_f$ = 0.35 (DCM/MeOH, 10:1); $\delta_H$ ($CDCl_3$, 500 MHz) 6.57 (s, 1H, CH), 6.89 (s, 1H), 7.13–7.19 (m, 5H), 7.35–7.38 (m, 4H), 7.42–7.47 (m, 3H), 7.56–7.59 (m, 4H); MS (ESI): *m/z* = 311 [$M^+$+H].

**5.5.2.10. 1-(Bis-biphenyl-4-yl-methyl)-1*H*-imidazole (10).** Synthesized according to Method A using **10a** (0.50 g, 1.49 mmol) and CDI (1.21 g, 7.43 mmol); yield: 0.07 g (13%); yellow oil; [ref. mp 120 °C[22]]; $R_f$ = 0.37 (DCM/MeOH, 10:1); $\delta_H$ ($CDCl_3$, 500 MHz) 6.95 (s, 1H), 7.16 (s, 1H), 7.21–7.23 (m, 4H), 7.35–7.38 (m, 2H), 7.43–7.47 (m, 4H), 7.55–7.61 (m, 10H); MS (ESI): *m/z* = 387 [$M^+$+H].

**5.5.2.11. 1-(1-(4′-(Trifluoromethoxy)biphenyl-4-yl)propyl)-1*H*-imidazole (12).** Synthesized according to Method A using **12a** (0.50 g, 2.10 mmol) and CDI (2.00 g, 12.40 mmol); yield: 0.16 g (21%); brownis oil; $R_f$ = 0.51 (DCM/MeOH, 95:5); $\delta_H$ ($CDCl_3$, 500 MHz) 0.99 (t, *J* = 7.5 Hz, 3H, $CH_3$), 2.26-2.32 (m, 2H, $CH_2$), 5.09 (t, *J* = 7.5 Hz, 1H, CH), 7.00 (s, 1H), 7.13 (s, 1H), 7.28–7.31 (m, 4H), 7.54–7.59 (m, 4H), 7.66 (s, 1H); $\delta_C$ ($CDCl_3$, 125 MHz) 11.1 ($CH_3$), 28.6 ($CH_2$), 63.0 (CH), 117.6 (CH), 119.5($CF_3$), 121.2 (CH), 127.0 (Im-C5), 127.5 (CH) 127.6 (CH), 128.4 (CH), 129.5 ($C_q$), 136.4 ($C_q$), 139.1 ($C_q$), 139.7, 139.8 ($C_q$) 148.8 ($C_q$); MS (ESI): *m/z* = 347 [$M^+$+H].

**5.5.2.12. 1-(1-(4′-(Methylsulfanyl)biphenyl-4-yl)propyl)-1*H*-imidazole (13).** Synthesized according to Method A using **13a** (0.67 g, 2.6 mmol) and CDI (2.00 g, 12.40 mmol); yield: 0.12 g (15%); beige solid; $R_f$ = 0.44 (DCM/MeOH, 95:5); $\delta_H$ ($CDCl_3$, 500 MHz) 0.96 (t, *J* = 7.0 Hz, 3H, $CH_3$), 2.24–2.28 (m, 2H, $CH_2$), 2.52 (s, 3H, $SCH_3$), 5.04 (t, *J* = 7.0 Hz, 1H, CH), 6.97 (s, 1H), 7.10 (s, 1H), 7.23–7.26 (m, 2H), 7.30–7.33 (m, 2H), 7.47–7.50 (m, 2H), 7.52–7.54 (m, 2H), 7.63 (s, 1H); $\delta_C$ ($CDCl_3$, 125 MHz) 11.1 ($CH_3$), 15.8 ($SCH_3$), 28.6 ($CH_2$), 63.0 (CH), 117.7 (Im-C4), 126.9 (CH), 127.0 (CH), 127.2 (CH), 127.4 (CH), 129.5 ($C_q$), 136.4 ($C_q$), 137.1 ($C_q$), 138.0 ($C_q$), 139.2 (CH), 140.4 (CH); MS (ESI): *m/z* = 309 [$M^+$+H].

**5.5.2.13. 4′-(1-(1*H*-Imidazol-1-yl)propyl)biphenyl-4-carbonitrile (14).** Synthesized according to Method A using **14a** (0.46 g, 1.93 mmol) and CDI (1.5 g, 9.30 mmol); yield: 0.14 g (25%); brown oil; $R_f$ = 0.40 (DCM/MeOH, 95:5); $\delta_H$ ($CDCl_3$, 500 MHz) 0.98 (t, $J$ = 7.0 Hz, 3H, $CH_3$), 2.22–2.30 (m, 2H, $CH_2$), 5.08 (t, $J$ = 7.0 Hz, 1H, CH), 6.97 (s, 1H), 7.10 (s, 1H), 7.29 (d, $J$ = 8.5 Hz, 2H), 7.56 (d, $J$ = 8.5 Hz, 2H), 7.61–7.68 (m, 3H), 7.73 (d, $J$ = 8.0 Hz, 2H); $\delta_C$ ($CDCl_3$, 125 MHz) 11.1 ($CH_3$), 28.5 ($CH_2$), 62.9 (CH), 111.2 (C-4′), 117.6 (C-N), 118.7 (Im-C4), 127.2 (CH), 127.6 (CH), 129.6 ($C_q$), 132.6 (CH), 136.3 ($C_q$), 139.0 (CH), 140.9 ($C_q$), 144.7 ($C_q$); MS (ESI): $m/z$ = 288 [$M^+$+H].

**5.5.2.14. 1-(1-(4′-Methylbiphenyl-4-yl)propyl)-1*H*-imidazole (15).** Synthesized according to Method A using **15a** (0.57 g, 2.5 mmol) and CDI (2.0 g, 12.50 mmol); yield: 0.20 g (29%); yellow solid: mp 71-72 °C; $R_f$ = 0.26 (EtOAc); $\delta_H$ ($CDCl_3$, 500 MHz) 0.88 (t, $J$ = 7.3 Hz, 3H, $CH_3$), 2.16 (q, $J$ = 7.3 Hz, 2H, $CH_2$), 2.30 (s, 3H, $PhCH_3$), 4.95 (t, $J$ = 7.3 Hz, 1 H, CH), 6.89 (s, 1H), 7.00 (s, 1H), 7.12-7.18 (m, 4H), 7.37 (d, $J$ = 8.2 Hz, 2H), 7.45 (d, $J$ = 8.2 Hz, 2H), 7.54 (s, 1H); $\delta_C$ ($CDCl_3$, 125 MHz) 11.1 ($CH_3$), 21.0 ($PhCH_3$), 28.5 ($CH_2$), 63.0 (CH), 117.6, 126.81, 126.86, 127.3, 129.5, 136.3, 137.3, 138.9, 140.9, 142.1; MS (ESI): $m/z$ = 277 [$M^+$+H].

**5.5.2.15. 1-(1-(4′-Ethylbiphenyl-4-yl)propyl)-1*H*-imidazole (16).** Synthesized according to Method A using **16a** (0.64 g, 2.6 mmol) and CDI (2.1 g, 13.12 mmol); yield: 0.14 g (18%); yellowish oil; $R_f$ = 0.30 (EtOAc); $\delta_H$ ($CDCl_3$, 500 MHz) 0.89 (t, $J$ = 7.3 Hz, 3H, $CH_3$), 1.20 (t, $J$ = 7.6 Hz, 3H, $CH_3$), 2.18 (quint, $J$ = 7.3 Hz, 2H, $CH_2$), 2.61 (q, $J$ = 7.6 Hz, 2H, $CH_2$), 4.97 (t, $J$ = 7.3 Hz, 1H, CH), 6.90 (s, 1H), 7.02 (s, 1H), 7.14-7.21 (m, 4H), 7.41 (d, $J$ = 8.2 Hz, 2H), 7.47 (d, $J$ = 8.5 Hz, 2H), 7.57 (s, 1H); $\delta_C$ ($CDCl_3$, 125 MHz) 10.1 ($CH_3$), 14.5 ($CH_3$), 27.5 ($CH_2$), 27.6 ($CH_2$), 62.1 (CH), 116.7, 125.9, 126.0, 126.4, 127.3, 128.3, 135.3, 136.7, 137.8, 140.0, 142.1; MS (ESI): $m/z$ = 291 [$M^+$+H].

**5.5.2.16. [4′-(1*H*-Imidazol-1-yl-propyl)-biphenyl-4-yl]-dimethyl-amine (17).** Synthesized according to Method A using **17a** (0.59 g, 2.31 mmol) and CDI (0.56 g, 3.47 mmol); yield: 0.18 g (25%); white solid: mp 117–119 °C; $R_f$ = 0.33 (DCM/MeOH, 20:1); $\delta_H$ ($CDCl_3$, 500 MHz) 0.95 (t, $J$ = 7.3 Hz, 3 H, $CH_3$), 2.24 (q, $J$ = 7.3, 7.6 Hz, 2H, $CH_2$), 2.99 (s, 6H, N-$CH_3$), 5.01 (t, $J$ = 7.6 Hz, 1H, CH), 6.78 (d, $J$ = 9.1 Hz, 2H), 6.97 (s, 1H), 7.09 (s, 1H), 7.20 (d, $J$ = 8.5 Hz, 2H), 7.47 (d, $J$ = 8.8 Hz, 2H), 7.51 (d, $J$ = 8.2 Hz, 2H), 7.62 (s, 1H); $\delta_C$ ($CDCl_3$, 125 MHz) 11.1 ($CH_3$), 28. 6 ($CH_2$), 40.4 (N-$CH_3$), 63.0 (CH), 112.6, 117.6, 126.5, 126.8, 127.6, 129.4, 136.4, 137.7, 141.0, 150.1; MS (ESI): $m/z$ = 306 [$M^+$+H].

**5.5.2.17. Diethyl-[4′-(1*H*-imidazol-1-yl-propyl)-biphenyl-4-yl]-amine (18).** Synthesized according to Method A using **18a** (0.70 g, 2.47 mmol) and CDI (0.61 g, 3.70 mmol); yield: 0.16 g (19%); white solid: mp 109–111 °C; $R_f$ = 0.33 (DCM/MeOH, 20:1); $\delta_H$ ($CDCl_3$, 500 MHz) 0.95 (t, $J$ = 7.3 Hz, 3H, $CH_3$), 1.19 (t, $J$ = 6.9 Hz, 6H, N-$CH_3$), 2.24 (q, $J$ = 7.3, 7.6 Hz, 2H, $CH_2$), 3.39 (q, $J$ = 6.9 Hz, 4H, N-$CH_2$), 5.01 (t, $J$ = 7.6 Hz, 1H, CH), 6.73 (d, $J$ = 9.1 Hz, 2H), 6.97 (s, 1H), 7.09 (s, 1H), 7.19 (d, $J$ = 8.5 Hz, 2H), 7.45 (d, $J$ = 8.8 Hz, 2H), 7.50 (d, $J$ = 8.2 Hz, 2H), 7.62 (s, 1H); $\delta_C$ ($CDCl_3$, 125 MHz) 11.1 ($CH_3$), 12.6 (N-$CH_3$), 28.6 ($CH_2$), 44.3 (N-$CH_2$), 63.0 (CH), 111.8, 117.6, 126.3, 126.8, 127.7, 129.4, 136.4, 137.5, 141.1, 147.3; MS (ESI): $m/z$ = 334 [$M^+$+H].

**5.5.2.18. 4-[4′-(1*H*-Imidazol-1-yl-propyl)-biphenyl-4-yl]-morpholine (19).** Synthesized according to Method A using **19a** (0.70 g, 2.37 mmol) and CDI (0.58 g, 3.55 mmol); yield: 0.27 g (33%); white solid: mp 119–121 °C; $R_f$ = 0.17 (DCM/MeOH, 20:1); $\delta_H$ ($CDCl_3$, 500 MHz) 0.95 (t, $J$ = 7.3 Hz, 3H, $CH_3$), 2.24 (q, $J$ = 7.3, 7.6 Hz, 2H, $CH_2$), 3.20 (t, $J$ = 4.7 Hz, 4H), 3.86 (t, $J$ = 4.7 Hz, 4H), 5.02 (t, $J$ = 7.6 Hz, 1H, CH), 6.92–6.95 (m, 3H), 7.08 (s, 1H), 7.21 (d, $J$ = 8.5 Hz, 2H), 7.49 (d, $J$ = 8.8 Hz, 2H), 7.51 (d, $J$ = 8.5 Hz, 2H), 7.61 (s, 1H); $\delta_C$ ($CDCl_3$, 125 MHz) 11.1 ($CH_3$), 28.5 ($CH_2$), 48.9, 62.9 (CH), 66.7, 115.6, 117.6, 126.7, 126.8, 127.6, 129.4, 131.5, 136.3, 138.3, 140.5, 150.6; MS (ESI): $m/z$ = 348 [$M^+$+H].

**5.5.2.19. [4′-(1*H*-Imidazol-1-yl-propyl)-biphenyl-4-yl]-carbamic acid *tert*-butyl ester (20).** Synthesized according to Method A using **20a** (1.23 g, 3.75 mmol) and CDI (0.91 g, 5.63 mmol); yield: 0.33 g (23%); white solid: mp 204–206 °C; $R_f$ = 0.29 (DCM/MeOH, 20:1); $\delta_H$ ($CDCl_3$, 500 MHz) 0.97 (t, $J$ = 7.3 Hz, 3H, $CH_3$), 1.53 (s, 9H, t-Bu), 2.26 (q, $J$ = 7.3, 7.6 Hz, 2H, $CH_2$), 5.04 (t, $J$ = 7.6 Hz, 1H, CH), 6.57 (s, 1H, CONH), 6.97 (s, 1H), 7.09 (s, 1H), 7.24 (d, $J$ = 8.2 Hz, 2H), 7.42 (d, $J$ = 8.5 Hz, 2H), 7.51–7.53 (m, 4H), 7.62 (s, 1H); $\delta_C$ ($CDCl_3$, 125 MHz) 11.1 ($CH_3$), 28.3 (*t*-Bu), 28.6 ($CH_2$), 63.0 (CH), 118.8, 126.9, 127.1, 127.5, 129.5, 137.9, 138.8, 140.5; MS (ESI): $m/z$ = 378 [$M^+$+H].

**5.5.2.20. 1-[1-(4′-Fluoro-biphenyl-4-yl)-propyl]-1*H*-imidazole 23.** Synthesized according to Method A using **23a** (1.23 g, 5.34 mmol) and CDI (4.33 g, 26.70 mmol); yield: 0.52 g (35%); brown oil; $R_f$ = 0.6 (DCM/MeOH, 95:5); $\delta_H$ ($CDCl_3$, 500 MHz) 0.97 (t, $J$ = 7.3 Hz, 3H, $CH_3$), 2.27 (q, $J$ = 7.3, 7.6 Hz, 2H, $CH_2$), 5.06 (t, $J$ = 7.6 Hz, 1H, CH), 6.97 (s, 1H), 7.09–7.14 (m, 3H), 7.25 (d, $J$ = 8.9 Hz, 2H), 7.51–7.53 (m, 4H), 7.62 (s, 1H); $\delta_C$ ($CDCl_3$, 125 MHz) 11.1 ($CH_3$), 28.6 ($CH_2$), 63.0 (CH), 115.6, 115.7, 117.7, 127.0, 127.4, 128.6, 128.7, 129.5, 136.4, 136.5, 139.3, 140.1, 161.6, 163.6; MS (ESI): $m/z$ = 281 [$M^+$+H].

**5.5.2.21. 1-(2-(4′-Fluorobiphenyl-4-yl)propan-2-yl)-1*H*-imidazole 24.** Synthesized according to Method A using **24a** (0.23 g, 1.0 mmol) and CDI (0.36 g, 2.20 mmol); yield: 0.05 g (19%); $R_f$ = 0.27 (DCM/MeOH, 95:5); $\delta_H$ ($CDCl_3$, 500 MHz) 1.94 (s, 6H, $CH_3$), 6.94–6.96 (m, 1H), 7.10–7.15 ( m, 5H), 7.47–7.36 (m, 4H), 7.67–7.69 (m, 1H); $\delta_C$ ($CDCl_3$, 125 MHz) 31.5 ($CH_3$), 60.3 (CH), 116.1, 117.0, 125.2, 127.3, 129.2, 132.6, 139.4, 145.4, 163.7; MS (ESI): $m/z$ = 281 [$M^+$+H].

**5.5.2.22. 1-(3-(4′-Fluorobiphenyl-4-yl)pentan-3-yl)-1*H*-imidazole (25).** Synthesized according to Method A using **25a** (0.26 g, 1.00 mmol) and CDI (0.36 g, 2.20 mmol); yield: 0.13 g (43%); $R_f$ = 0.33 (DCM/MeOH, 95:5); $\delta_H$ ($CDCl_3$, 500 MHz) 0.75 (s, 6H, $CH_3$), 2.26–2.30 (q, 4H, $CH_2$), 6.84–6.86 (m, 1H), 7.08–7.09 (m, 1H), 7.10–7.13 (m, 2H), 7.17–7.20 (m, 2H), 7.48–7.55 (m, 4H), 7.62–7.63 (m, 1H); $\delta_C$ ($CDCl_3$, 125 MHz) 8.3 ($CH_3$), 30.5 ($CH_2$), 66.1 (CH), 116.3, 119.7, 127.6, 129.9, 136.2, 139.1, 142.8; MS (ESI): $m/z$ = 309 [$M^+$+H].

**5.5.2.23. 1-(1-(4′-Fluorobiphenyl-4-yl)allyl)-1*H*-imidazole (28).** Synthesized according to Method A using **28a** (1.14 g, 5.00 mmol) and CDI (1.80 g, 10.10 mmol); yield: 0.57 g (41%); $R_f$ = 0.27 (DCM/MeOH, 95:5); $\delta_H$ ($CDCl_3$, 500 MHz) 4.73–4.74 (m, 2H, $CH_2$), 6.30–6.35 (m, 1H, CH), 6.54–6.57 (m, 1H, CH), 6.98 (s, 1H), 7.10–7.12 (m, 3H), 7.42–7.44 (m, 2H), 7.50–7. 56 (m, 5H); $\delta_C$ ($CDCl_3$, 125 MHz) 49.3 (CH), 116.5, 124.9, 127.4, 128.6, 130.8, 133.2, 135.2, 137.0, 140.3, 161.7; MS (ESI): $m/z$ = 279 [$M^+$+H].

**5.5.2.24. 1-(1-(Biphenyl-4-yl)allyl)-1*H*-imidazole (29).** Synthesized according to Method A using **29a** (0.30 g, 1.00 mmol) and CDI (0.36 g, 2.20 mmol); yield: 0.09 g (32%); $R_f$ = 0.21 (DCM/MeOH, 95:5); $\delta_H$ ($CDCl_3$, 500 MHz) 4.73–4.75 (m, 2H, $CH_2$), 6.30–6.35 (m, 1H, CH), 6.56–6.57 (m, 1H, CH), 6.98 (s, 1H), 7.12–7.13 (m, 1H), 7.34–7.37 (m, 1H), 7.43–7.46 (m, 4H), 7.56–7.60 (m, 5H); $\delta_C$ ($CDCl_3$, 125 MHz) 49.3 (CH), 119.4 (=$CH_2$), 123.8, 127.0, 129.4, 133.2, 134.5, 137.7, 140.9; MS (ESI): $m/z$ = 297 [$M^+$+H].

**5.5.2.25. 1-((9*H*-Fluoren-2-yl)methyl)-1*H*-imidazole (31).** Synthesized according to Method A using **31a** (0.32 g, 1.63 mmol) and CDI (0.53 g, 3.26 mmol); yield: 0.16 g (40%); $R_f$ = 0.31 (MeOH/EtOAc, 5:95); colorless solid: mp 183–185 °C; $\delta_H$ ($CDCl_3$, 500 MHz) 3.87 (s, 2H, $CH_2$), 5.18 (s, 2H), 6.94 (br s, 1H), 7.11 (br s, 1H), 7.19 (d, *J* = 8.5 Hz, 1H), 7.30–7.33 (m, 2H), 7.38 (dd, *J* = 7.3, 7.6 Hz, 1H), 7.54 (d, *J* = 7.6 Hz, 1H), 7.59 (br s, 1H), 7.75 (d, *J* = 7.9 Hz, 1H), 7.77 (d, *J* = 7.6 Hz, 1H); $\delta_C$ ($CDCl_3$, 125 MHz) 36.8 ($CH_2$), 51.0 ($CH_2$), 119.3 (CH), 120.0 (CH), 120.2 (CH), 124.0 (CH), 125.1 (CH), 126.1 (CH), 126.8 (CH), 127.1 (CH), 129.7 (CH), 134.4 ($C_q$), 137.4 (CH), 140.9 ($C_q$), 141.9 ($C_q$), 143.3 ($C_q$), 144.1 ($C_q$); MS (ESI): *m/z* = 247 [$M^+$+H].

**5.5.2.26. 1-((9*H*-Fluoren-2-yl)ethyl)-1*H*-imidazole (32).** Synthesized according to Method A using **32a** (1.00 g, 4.70 mmol) and CDI (1.53 g, 9.50 mmol); yield: 0.62 g (51%); $R_f$ = 0.58 (MeOH/EtOAc, 5:95); light yellow solid: mp 109–110 °C [ref. no mp reported[23]]; $\delta_H$ ($CDCl_3$, 500 MHz) 1.90 (d, *J* = 6.9 Hz, 3H, $CH_3$), 3.86 (s, 2H, $CH_2$), 5.41 (q, *J* = 6.9 Hz, 1H, CH), 6.96 (t, *J* = 1.3 Hz, 1H), 7.10 (br s, 1H), 7.17–7.19 (m, 1H), 7.29 (br s, 1H), 7.31 (dd, *J* = 1.3, 7.6 Hz, 1H), 7.37 (t, *J* = 7.8 Hz, 1H), 7.53 (bd, *J* = 7.6 Hz, 1H), 7.63 (bs, 1H), 7.74 (d, *J* = 7.9 Hz, 1H), 7.76 (d, *J* = 7.6 Hz, 1H); $\delta_C$ ($CDCl_3$, 125 MHz) 22.2 ($CH_3$), 36.9 ($CH_2$), 56.8 (CH), 118.0 (CH), 120.0 (CH), 120.1 (CH), 122.6 (CH), 124.8 (CH), 125.0 (CH), 126.8 (CH), 127.0 (CH), 129.2 (CH), 136.0 (CH), 139.9 ($C_q$), 140.9 ($C_q$), 141.8 ($C_q$), 143.3 ($C_q$), 144.0 ($C_q$); MS (ESI): *m/z* = 261 [$M^+$+H].

**5.5.2.27. 1-[1-(7-Fluoro-9*H*-fluoren-2-yl)-ethyl]-1*H*-imidazole (33).** Synthesized according to Method A using **33a** (1.00 g, 4.38 mmol) and CDI (1.87 g, 1.16 mmol); yield: 0.44 g (36%); $R_f$ = 0.24 (MeOH/EtOAc, 5:95); yellow oil; $\delta_H$ ($CDCl_3$, 500 MHz) 1.90 (d, *J* = 6.9 Hz, 3H, $CH_3$), 3.85 (s, 2H, $CH_2$), 5.41 (q, *J* = 7.0 Hz, 1H, CH), 6.96 (s, 1H), 7.05–7.09 (m, 2H), 7.18 (d, *J* = 7.9 Hz, 1H), 7.22 (dd, *J* = 1.8, 8.6 Hz, 1H), 7.28 (br s, 1H), 7.63 (br s, 1H), 7.67–7.70 (m, 2H); $\delta_C$ ($CDCl_3$, 125 MHz) 22.2 ($CH_3$), 36.9 ($CH_2$), 56.8 (CH), 112.4 (d, CH), 114.1 (d, CH), 118.0 (CH), 119.8 (CH), 120.9 (CH), 122.6 (CH), 125.0 (CH), 129.2 (CH), 136.0 (CH), 137.0 (Cq), 139.7 (Cq), 141.0 (Cq), 143.7 (Cq), 145.5 (Cq), 161.6 ($C_q$); MS (ESI): *m/z* = 279 [$M^+$+H].

**5.5.2.28. 2-(1-Imidazol-1-yl-ethyl)-9*H*-carbazole (34).** Synthesized according to Method A using **34a** (0.22 g, 1.02 mmol) and CDI (0.33 g, 2.04 mmol); yield: 0.08 g (29%); [ref. 157–158 °C[23]]; $R_f$ = 0.40 (MeOH/EtOAc, 5:95); $\delta_H$ ($CDCl_3$, 500 MHz) 1.90 (d, *J* = 6.9 Hz, 3H), 5.46 (q, *J* = 6.9 Hz, 1H), 6,97 (br s, 1H), 7.05–7.07 (m, 2H), 7.11 (br s, 1H), 7.22 (ddd, *J* = 1.9, 6.4, 8.0 Hz, 1H), 7.38–7.43 (m, 2H), 7.65 (br s, 1H), 8.02 (d, *J* = 8.5 Hz, 1H), 8.05 (d, *J* = 7.9 Hz, 1H); $\delta_C$ ($CDCl_3$, 125 MHz) 22.4 ($CH_3$), 57.2 (CH), 108.0 (CH), 110.8 (CH), 117.3 (CH), 118.3 (CH), 119.4 (CH), 120.3 (CH), 120.5 (CH), 122.7 ($C_q$), 123.1 ($C_q$), 126.0 (CH), 128.8 (CH), 136.0 (CH), 139.2 ($C_q$), 140.0 ($C_q$), 140.2 ($C_q$); MS (ESI): *m/z* = 262 [$M^+$+H].

**5.5.2.29. 2-(1-(1*H*-Imidazol-1-yl)ethyl)-7-fluoro-9*H*-carbazole (35).** Synthesized according to Method A using **35a** (0.30 g, 1.30 mmol) and CDI (0.42 g, 2.60 mmol); yield: 0.08 g (23%); $R_f$ = 0.11 (EtOAc); $\delta_H$ ($CDCl_3$, 500 MHz) 1.93 (d, *J* = 7.0 Hz, 3H), 5.64 (q, *J* = 7.0 Hz, 1H), 6.90 (ddd, *J* = 2.2, 8.5, 9.6 Hz, 1H), 6.99 (t, *J* = 1.3 Hz, 1H), 7.07 (ddd, *J* = 0.6, 1.6, 8.2 Hz, 1H), 7.11 (dd, *J* = 2.2, 9.6 Hz, 1H), 7.18 (t, *J* = 1.3 Hz, 1H), 7.28 (d, *J* = 1.6 Hz, 1H), 7.80 (br s, 1H), 7.96–7.99 (m, 2H); $\delta_C$ ($CDCl_3$, 125 MHz) 22.5 ($CH_3$), 58.6 (CH), 98.2 (d, CH), 107.9 (d, CH), 109.4 (CH), 118.6 (CH), 119.7 (CH), 120.6 ($C_q$), 121.1 (CH), 122.2 (CH), 123.8 ($C_q$), 128.9 (CH), 137.4 (CH), 140.4 ($C_q$), 142.2 ($C_q$), 142.8 ($C_q$), 163.5 ($C_q$); MS (ESI): *m/z* = 280 [$M^+$+H].

### 5.5.3. Method B: Grignard reaction

Under exclusion of air and moisture a 1.0 M Grignard reagent (1.2 equiv) solution in THF was added dropwise to a solution of the aldehyde or ketone (1 equiv) in THF (12 mL/mmol). The mixture was stirred at room temperature overnight. Subsequently 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.

**5.5.3.1. 1-Biphenyl-4-yl-3-methyl-butan-1-ol (5a).** Synthesized according to Method B using Biphenyl-4-carbaldehyde (1.00 g, 5.48 mmol) and a 1.0 M iso-butylmagnesiumbromide solution in THF (7.13 mL, 7.13 mmol); yield: 0.96 g (73%); $R_f$ = 0.28 (PE/EtOAc, 5:1); $\delta_H$ ($CDCl_3$, 500 MHz) 0.97 (d, *J* = 4.9 Hz, 6H, $CH_3$), 1.51–1.58 (m, 1H, CH), 1.72 (s, br, 1H, OH), 1.75–1.81 (m, 2H, $CH_2$), 4.79 (t, *J* = 2.7 Hz, 1H, CH), 7.33 (t, *J* = 7.5 Hz, 1H), 7.43 (d, *J* = 8.4 Hz, 4H), 7.57 (d, *J* = 8.4 Hz, 4H); MS (ESI): *m/z* = 241 [$M^+$+H].

**5.5.3.2. 1-[4′-(*tert*-Butyl-dimethyl-silanyloxy)-biphenyl-4-yl]-propan-1-ol (22b).** Synthesized according to method B using **22c** (3.30 g, 10.6 mmol) and 1.0 M EtMgBr (12.7 mL). Yield: 1.89 g (52%); $R_f$ = 0.40 (PE/EtOAc, 9:1); $\delta_H$ ($CDCl_3$, 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].

**5.5.3.3. 3-(4′-Fluorobiphenyl-4-yl)pentan-3-ol (25a).** Synthesized according to Method B using **23b** (0.58 g, 2.53 mmol) and a 1.0 M ethylmagnesiumbromide solution in THF (25.0 mL, 25.0 mmol); yield: 0.58 g (89%); $R_f$ = 0.28 (DCM); $\delta_H$ ($CDCl_3$, 500 MHz): 0.79–0.92 (s, 6H, $CH_3$), 1.68 (s, br, 1H, OH), 1.82–1.93 (m, 4H, $CH_2$), 7.10–7.14 (m, 2H), 7.43–7.45 (m, 2H), 7.51–7.58 (m, 4H); MS (ESI): *m/z* = 259 [$M^+$+H].

### 5.5.4. Method C: Suzuki coupling

The corresponding brominated aromatic compound (1 equiv) was dissolved in toluene (7 mL/mmol), and an aqueous 2.0 M $Na_2CO_3$ solution (3.2 mL/mmol) and an ethanolic solution (3.2 mL/mmol) of the corresponding boronic acid (1.5–2.0 equiv) were added. The mixture was deoxygenated under reduced pressure and flushed with nitrogen. After repeating 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, 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 Celite®, and evaporated under reduced pressure. The compounds were purified by flash chromatography on silica gel.

**5.5.4.1. 1-((4′-(Trifluoromethyl)biphenyl-4-yl)methyl)-1*H*-imidazole (11).** Synthesized according to Method C using 1-(4-bromobenzyl)-1*H*-imidazole (0.24 g, 1.00 mmol) and 4-trifluoromethylphenylboronic acid (0.38 g, 2.00 mmol); yield: 0.24 g (80%); brown oil; $R_f$ = 0.14 (EtOAc); $\delta_H$ ($CDCl_3$, 500 MHz) 5.17 (s, 2H, $CH_2$), 6.93 (br s, 1H), 7.11 (br s, 1H), 7.24 (d, *J* = 7.9 Hz, 2H), 7.57 (d, *J* = 7.9 Hz, 2H), 7.59 (br s, 1H), 7.65 (d, *J* = 8.5 Hz, 2H), 7.68 (d, *J* = 8.5 Hz, 2H); $\delta_C$ ($CDCl_3$, 125 MHz) 50.4 ($CH_2$), 119.2 (CH), 123.1 ($C_q$), 125.2 ($C_q$), 125.7 (CH), 127.3 (CH), 127.7 (CH), 127.8 (CH), 129.8 (CH), 136.2 ($C_q$), 137.4 (CH), 139.7 ($C_q$), 143.8 ($C_q$); MS (ESI): *m/z* = 303 [$M^+$+H].

**5.5.4.2. 1-(4′-Fluorobiphenyl-4-yl)propan-1-one (23b).** Synthesized according to Method C using 4-bromopropiophenone (1.23 g, 6.65 mmol) and 4-fluorophenylboronic acid (1.38 g, 6.47 mmol); yield: 1.20 g (79%); $R_f$ = 0.45 (Hex/EtOAc, 10:1); $\delta_H$ ($CDCl_3$, 500 MHz) 1.24–1.27 (t, $J$ = 7.3 Hz, 3H, $CH_3$), 3.01–3.06 (m, 2H, $CH_2$), 6.97–7.01 (m, 1H), 7.06–7.11 (m, 1H), 7.58–7.61 (m, 2H), 8.02–8.04 (m, 2H); MS (ESI): $m/z$ = 229 [$M^+$+H].

**5.5.4.3. 1-(4′-Fluoro-2′-nitrobiphenyl-4-yl)ethanone (35c).** Synthesized according to Method C using 4-fluoro-1-iodo-2-nitrobenzene (1.20 g, 4.50 mmol) and 4-acetylbenzeneboronic acid (1.48 g, 9.00 mmol); yield: 1.01 g (87%); $R_f$ = 0.19 (petrolether/EtOAc, 10:1); $\delta_H$ ($CDCl_3$, 500 MHz) 2.64 (s, 3H, $CH_3$), 7.38 (d, $J$ = 8.5 Hz, 2H), 7.39–7.41 (m, 1H), 7.43 (dd, $J$ = 5.5, 8.5 Hz, 1H), 7.67 (dd, $J$ = 2.5, 8.0 Hz, 1H), 8.01 (d, $J$ = 8.5 Hz, 2H); $\delta_C$ ($CDCl_3$, 125 MHz) 26.6 ($CH_3$), 112.1 (d, CH), 119.9 (d, CH), 128.3 (CH), 128.7 (CH), 131.7 ($C_q$), 133.2 (CH), 136.8 ($C_q$), 141.3 ($C_q$), 161.6 (d, $C_q$), 197.4 ($C_q$ ); MS (ESI): $m/z$ = 259 [$M^+$-H].

### 5.5.5. Method D: reduction with $NaBH_4$

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

**5.5.5.1. 1-(4′-Fluoro-biphenyl-4-yl)-propan-1-ol (23a).** Synthesized according to Method D using **22b** (1.20 g, 5.26 mmol) and $NaBH_4$ (0.30 g, 7.89 mmol); yield: 1.15 g (95%); the compound was directly used in the next step without further purification and characterization.

**5.5.5.2. 1-(9*H*-Carbazol-2-yl)ethanol (34a).** Synthesized according to Method D using 1-(9*H*-carbazol-2-yl)ethanone (0.50 g, 2.39 mmol) and $NaBH_4$ (0.16 g, 4.30 mmol); yield: 0.42 g (83%); $R_f$ = 0.12 (petrolether/EtOAc, 5:1); light yellow solid: mp 192–194 °C; $\delta_H$ ($CDCl_3$, 500 MHz) 1.41 (d, $J$ = 6.6 Hz, 3H, $CH_3$), 3.13 (br s, 1H), 4.88 (q, $J$ = 6.6 Hz, 1H), 7.03 (ddd, $J$ = 1.2, 7.3, 7.9 Hz, 1H), 7.07 (dd, $J$ = 1.6, 8.2 Hz, 1H), 7.22 (ddd, $J$ = 1.2, 7.2, 8.2 Hz, 1H), 7.30 (dt, $J$ = 1.0, 8.2 Hz, 1H), 7.37–7.39 (m, 1H), 7.85 (d, $J$ = 8.2 Hz, 1H), 7.88 (d, $J$ = 7.9 Hz, 1H), 9.62 (br s, 1H); $\delta_C$ ($CDCl_3$, 125 MHz) 25.5 ($CH_3$), 69.9 ($CH_2$), 107.3 (CH), 110.4 (CH), 116.4 (CH), 118.4 (CH), 119.5 (CH), 119.6 (CH), 121.8 ($C_q$), 122.6 ($C_q$), 124.9 (CH), 139.7 ($C_q$), 139.8 ($C_q$), 144.4 ($C_q$); MS (ESI): $m/z$ = 210 [$M^+$−OH].

**5.5.5.3. 1-(7-Fluoro-9*H*-carbazol-2-yl)ethanol (35a).** Synthesized according to Method D using **35b** (0.25 g, 1.12 mmol) and $NaBH_4$ (0.08 g, 2.02 mmol); yield: 0.21 g (82%); $R_f$ = 0.19 (petrolether/EtOAc, 5:1); $\delta_H$ ($CDCl_3$, 500 MHz) 1.50 (d, $J$ = 6.4 Hz, 3H), 4.94 (q, $J$ = 6.4 Hz, 1H), 6.85 (ddd, $J$ = 2.3, 8.5, 8.8 Hz, 1H), 7.08 (dd, $J$ = 2.3, 9.8 Hz, 1H), 7.15 (dd, $J$ = 1.2, 8.2 Hz, 1H), 7.43 (br s, 1H), 7.91 (d, $J$ = 8.5 Hz, 1H), 7.93 (dd, $J$ = 5.5, 8.5 Hz, 1H); $\delta_C$ ($CDCl_3$, 125 MHz) 26.0 ($CH_3$), 71.5 (CH), 98.0 (d, CH), 107.5 (d, CH), 108.6 (CH), 118.2 (CH), 120.5 (CH), 120.8 ($C_q$), 121.8 (d, CH), 123.2 ($C_q$), 142.2 ($C_q$), 142.4 ($C_q$), 145.1 ($C_q$), 163.2 (d, $C_q$); MS (ESI): $m/z$ = 212 [$M^+$−OH].

**5.5.5.4. 4′-(1*H*-Imidazol-1-yl-propyl)-biphenyl-4-ylamine (21a).** To a solution of **20** (0.32 g, 0.85 mmol) in DCM (10 mL) was added TFA (0.63 mL, 8.5 mmol) slowly in an ice bath. Subsequently it was stirred at room temperature overnight. DCM (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; yield: 0.22 g (95%); $R_f$ = 0.35 (PE/EtOAc, 2:1); the compound was directly used in the next step without further purification and analysis.

**5.5.5.5. N-[4′-(1*H*-Imidazol-1-yl-propyl)-biphenyl-4-yl]-acetamide (21).** To a solution of **21a** (0.07 g, 0.25 mmol) in THF (10 mL) were added DMAP (0.02 g, 0.13 mmol) and triethylamine (0.1 mL). After cooling to 0 °C in an ice bath, acetyl chloride was dropped into the reaction solution slowly. Then, it was stirred in the ambient temperature overnight. After being neutralized to pH 7 with sodium bicarbonate in an ice bath, 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; yield: 0.33 g (23%); white solid: mp 221–223 °C; $R_f$ = 0.27 (DCM/MeOH, 20:1); $\delta_H$ ($CDCl_3$, 500 MHz) 0.97 (t, $J$ = 7.3 Hz, 3H, $CH_3$), 2.20 (s, 3H, $CH_3CO$), 2.26 (q, $J$ = 7.3, 7.6 Hz, 2H, $CH_2$), 5.05 (t, $J$ = 7.6 Hz, 1H, CH), 6.99 (s, 1H), 7.11 (s, 1H), 7.23 (d, $J$ = 8.2 Hz, 2H), 7.49–7.58 (m, 6H), 7.72 (s, 1H); $\delta_C$ ($CDCl_3$, 125 MHz) 11.0 ($CH_3$), 24.6 ($CH_3CO$), 28.5 ($CH_2$), 63.2 (CH), 120.1, 126.9, 127.5, 127.5, 135.9, 137.6, 140.5, 168.4; MS (ESI): $m/z$ = 320 [$M^+$+H].

**5.5.5.6. 4′-(1*H* -Imidazol-1-yl-propyl)-biphenyl-4-ol (22).** To a solution of **22a** (0.85 g, 2.16 mmol) in anhydrous THF (20 mL) was added TBAF (2.4 mL, 2.4 mmol), and subsequently the solution was stirred at room temperature for 4 h. The reaction were 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: 0.22 g (37%); Yellow solid; $R_f$ = 0.21 (Hex/EtOAc, 5:1); $\delta_H$ (DMSO-$d_6$, 500 MHz) 0.82 (t, $J$ = 7.3 Hz, 3H), 2.21 (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); $\delta_C$ (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].

**5.5.5.7. 3-(4′-Fluorobiphenyl-4-yl)-3-(1*H*-imidazol-1-yl)propan-1-ol (26).** Compound **26a** (0.241 g, 0.45 mmol) was dissolved by slowly adding dropwise to 15 mL THF and 1 M TBAF (0.55 mL, 0.55 mmol) in THF. One hour later, according to TLC (DCM/methanol, 95:5), the deprotection was quantitative. The batch was diluted with a large quantity of ethyl acetate and extracted three times with water and once with brine, then dried over $MgSO_4$, and the solvent removed under reduced pressure. The crude product was subsequently purified by column chromatography; yield: 0.09 g (67%); $R_f$ = 0.34 (DCM/MeOH, 9:1); $\delta_H$ ($CDCl_3$, 500 MHz) 2.43–2.49 (m, 2H, $CH_2$), 3.50–3.54 (m, 1H), 3.68–3.72 (m, 1H), 5.56–5.59 (q, 1H, CH), 6.98 (m, 1H), 7.08 (m, 1H′), 7.1–7.14 (m, 2H), 7.26–7.29 (m, 2H), 7.48–7.51 (m, 4H), 7.56 (m, 1H); $\delta_C$ ($CDCl_3$, 125 MHz) 37.1 ($CH_2$), 50.5 (CH), 57.7 ($CH_2$-OH), 116.3, 127.6, 128.6, 129.8, 136.8, 137.2, 139.9, 140.0, 161.4; MS (ESI): $m/z$ = 297 [$M^+$+H].

**5.5.5.8. 1-(3-Chloro-1-(4′-fluorobiphenyl-4-yl)propyl)-1*H*-imidazole (27).** Compound **26** (0.044 g, 0.148 mmol) was dissolved in 10 mL dry DCM and mixed with 13 μL thionyl chloride. The batch was stirred for 2 h at room temperature; according to the TLC control, the reaction was quantitative (DCM as solvent). The batch was diluted with a large quantity of DCM and water. The organic phase was separated off and extracted five times with water and once with brine, then dried over $MgSO_4$, and the solvent removed under

reduced pressure; yield: 0.05 g (99%); $R_f$ = 0.63 (DCM/MeOH, 9:1); $\delta_H$ ($CDCl_3$, 500 MHz) 2.87–2.97 (m, 2H, $CH_2$), 3.50–3.60 (m, 2H, $CH_2Cl$), 5.80–5.83 (m, 1H, CH), 7.11–7.16 (m, 2H), 7.16–7.17 (m, 1H), 7.35–7.37 (m, 1H), 7.49–7.53 (m, 4H), 7.58–7.60 (m, 2H), 9.51–9.53 (m, 1H); $\delta_C$ ($CDCl_3$, 125 MHz) 34.2 ($CH_2$), 41.4 ($CH_2Cl$), 61.8 (CH), 119.6, 122.9, 116.5, 128.4, 129.4, 135.7, 136.3, 137.6, 136.4, 142.5, 163.5; MS (ESI): *m/z* = 315 [$M^+$+H].

**5.5.5.9. 1-(7-(*tert*-Butyldimethylsilyloxy)-9*H*-fluoren-2-yl)ethanone, (30c).** Imidazole (0.17 g, 2.45 mmol) and 1-(7-hydroxy-9*H*-fluoren-2-yl)ethanone (0.50 g, 2.23 mmol) were dissolved in 20 mL DCM. Then, *tert*-butyldimethylsilylchloride (0.37 g, 2.45 mmol) dissolved in 3 mL DCM was slowly added. The resulting mixture was stirred for 18 h at room temperature. Afterwards the mixture was extracted with water and brine. The organic phase was separated, dried over $Na_2SO_4$ and evaporated; yield: 0.58 g (77%); $R_f$ = 0.40 (petrolether/EtOAc, 10:1); MS (ESI): *m/z* = 339 [$M^+$+H].

**5.5.5.10. 7-(1-(1*H*-imidazol-1-yl)ethyl)-9*H*-fluoren-2-ol (30).** Compound 30a (0.16 g, 0.40 mmol) was dissolved in 10 mL THF, and 1 M TBAF (0.41 mL, 0.41 mmol) solution in THF was added dropwise. After 1 h according to TLC (DCM/methanol 95:5) the deprotection was quantitative. The batch was diluted with a large quantity of ethyl acetate and extracted three times with water and once with brine, then dried over $MgSO_4$, and the solvent removed under reduced pressure; yield: 0.10 g (90%); $R_f$ = 0.12 (MeOH/EtOAc, 5:95); orange solid: mp 217–218 °C; $\delta_H$ ($CDCl_3$, 500 MHz) 1.81 (d, *J* = 6.9 Hz, 3H), 3.70 (s, 2H), 5.31 (q, *J* = 6.9 Hz, 1H), 6.77 (dd, *J* = 2.2, 8.2 Hz, 1H), 6.90 (s, 1H), 6.93 (s, 1H), 6.95 (s, 1H), 7.06 (d, *J* = 7.9 Hz, 1H), 7.18 (s, 1H), 7.50 (d, *J* = 8.2 Hz, 1H), 7.52 (d, *J* = 7.9 Hz, 1H), 7.55 (s, 1H); $\delta_C$ ($CDCl_3$, 125 MHz) 21.9 ($CH_3$), 36.6 ($CH_2$), 56.9 (CH), 112.0 (CH), 114.1 (CH), 118.1 (CH), 118.8 (CH), 120.6 (CH), 122.4 (CH), 124.7 (CH), 128.2 (CH), 132.8 ($C_q$), 135.6 (CH), 137.9 ($C_q$), 142.0 ($C_q$), 143.2 ($C_q$), 145.2 ($C_q$), 156.6 ($C_q$); MS (ESI): *m/z* = 277 [$M^+$+H].

**5.5.5.11. 1-(7-Fluoro-9*H*-carbazol-2-yl)ethanone (35b).** 35c was dissolved in 3 mL $P(OEt)_3$ and refluxed for 16 h. The resulting mixture was directly purified using column chromatography; yield: 0.28 g (53%); $R_f$ = 0.13 (petrolether/EtOAc, 5:1); $\delta_H$ ($CDCl_3$, 500 MHz) 2.54 (s, 3H), 6.79 (ddd, *J* = 2.3, 8.6, 9.5 Hz, 1H), 7.01 (dd, *J* = 2.3, 9.6 Hz, 1H), 7.65 (dd, *J* = 1.6, 8.2 Hz, 1H), 7.85 (dd, *J* = 5.4, 8.5 Hz, 1H), 7.87 (d, *J* = 8.5 Hz, 1H), 7.93 (dd, *J* = 0.6, 1.6 Hz, 1H), 10.53 (br s, 1H); $\delta_C$ ($CDCl_3$, 125 MHz) 26.5 ($CH_3$), 97.4 (d, CH), 107.3 (d, CH), 110.9 (CH), 118.4 ($C_q$), 119.0 (CH), 119.2 (CH), 121.6 (d, CH), 126.2 ($C_q$), 133.6 ($C_q$), 139.7 ($C_q$), 142.0 (d, $C_q$), 162.2 (d, $C_q$), 197.8 ($C_q$); MS (ESI): *m/z* = 227 [$M^+$+H].

### 5.5.6. Docking studies

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

**5.5.6.1. 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[24a] as implemented in Sybyl. The resulting geometries for our compounds were then subjected to ab initio calculation employing the B3LYP functional[24b,c] in combination with a 6-31G* basis set using the package Gaussian03 (Gaussian, Inc., Pittsburgh, PA, 2003).

**5.5.6.2. Docking.** Various inhibitors were docked into our CYP17 homology model by means of the GOLD v3.0.1 software.[25] Since it is known that non-steroidal inhibitors of CYP enzymes primarily interact by complexation of the heme iron with their $sp^2$ hybridized nitrogen[16b] a distance constraint of a minimum of 1.9 and a maximum of 2.5 Å between the nitrogen of the imidazole and the iron was set.

Ligands were docked in 50 independent genetic algorithm (GA) runs using GOLD. Heme iron was chosen as active-site origin, while the active site 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. Furthermore, 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. 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[26], 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. Further the different interaction patterns were manually analyzed using Silver 1.1,[25b] a program included for use with GOLD and used to post-process docking results.

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## Supplementary data

The synthetic procedures and characterization of further intermediates and IR spectra of all compounds as well as the purities of final compounds by element analysis or HPLC can be found, in the online version, at doi:10.1016/j.bmc.2008.07.011.

## References and notes

1. (a) Smith, J. A. *J. Urol.* **1987**, *137*, 1; (b) Crawford, E. D.; Eisenberger, M. A.; McLeod, D. G.; Spaulding, J. T.; Benson, R.; Dorr, F. A.; Blumstein, B. A.; Davis, M. A.; Goodman, P. J. *N. Engl. J. Med.* **1989**, *321*, 419.
2. Chung, B. C.; Picardo-Leonard, J.; Hanui, M.; Bienkowski, M.; Hall, P. F.; Shively, J. E.; Miller, W. L. *Proc. Natl. Acad. Sci. U.S.A.* **1987**, *84*, 407.
3. (a) Swinney, M.; Mak, A. Y. *Biochemistry* **1994**, *33*, 2185; (b) Akhtar, M.; Corina, D. L.; Miller, S. L.; Shyadehi, A. Z.; Wright, J. N. *Biochemistry* **1994**, *33*, 4410.
4. (a) Hartmann, R. W.; Hector, M.; Haidar, M.; Ehmer, P. B.; Reichert, W.; Jose, J. *J. Med. Chem.* **2000**, *43*, 4266; (b) Hartmann, R. W.; Hector, M.; Wachall, B. G.; Palusczak, A.; Palzer, M.; Huch, V.; Veith, M. *J. Med. Chem.* **2000**, *43*, 4437; (c) Njar, V. C. O.; Hector, M.; Hartmann, R. W. *Bioorg. Med. Chem.* **1996**, *4*, 1447.
5. (a) Potter, G. A.; Barrie, S. E.; Jarman, M.; Rowlands, M. G. *J. Med. Chem.* **1995**, *38*, 2463; (b) Jarman, M.; Barrie, S. E.; Lera, J. M. *J. Med. Chem.* **1998**, *41*, 5375.
6. (a) Gambertoglio, J. G.; Amend, W. J., Jr.; Benet, L. Z. *J. Pharmacokinet. Biopharm.* **1980**, *8*, 1; (b) Fotherby, K. *Contraception* **1996**, *54*, 59; (c) Steiner, J. F. *Clin. Pharmacokinet.* **1996**, *30*, 16; (d) Hameed, A.; Brothwood, T.; Bouloux, P. *Curr. Opin. Investig. Drugs* **2003**, *4*, 1213.
7. (a) Buster, J. E.; Casson, P. R.; Straughn, A. B.; Dale, D.; Umstot, E. S.; Chiamovi, N.; Abraham, G. E. *Am. J. Obstet. Gynecol.* **1992**, *166*, 1163; (b) Peterson, R. E. Metabolism of adrenal cortical steroids. In *The Human Adrenal Cortex*; Christy, N. P., Ed.; Harper & Row: New York, 1997; pp 87–189.
8. (a) Wächter, G. A.; Hartmann, R. W.; Sergejew, T.; Grün, G. L.; Ledergerber, D. *J. Med. Chem.* **1996**, *39*, 834; (b) Zhuang, Y.; Hartmann, R. W. *Archiv. Pharm.* **1998**, *331*, 36; (c) Zhuang, Y.; Hartmann, R. W. *Archiv. Pharm.* **1998**, *331*, 25; (d) Hartmann, R. W.; Wachall, B. WO9918075, 1998.

9. (a) Rowlands, M. G.; Barrie, S. E.; Chan, F.; Houghton, J.; Jarman, M.; McCague, R.; Potter, G. A. *J. Med. Chem.* **1995**, *38*, 4191; (b) Chan, F. C. Y.; Potter, G. A.; Barrie, S. E.; Haynes, B. P.; Rowlands, M. J.; Houghton, G.; Jarman, M. *J. Med. Chem.* **1996**, *39*, 3319.
10. (a) Matsunaga, N.; Kaku, T.; Itoh, T.; Tanaka, T.; Hara, T.; Miki, H.; Iwasaki, M.; Aono, T.; Yamaoka, M.; Kusaka, M.; Tasaka, A. *Bioorg. Med. Chem.* **2004**, *12*, 2251; (b) Matsunaga, N.; Kaku, T.; Ojida, A.; Tanaka, T.; Hara, T.; Yamaoka, M.; Kusaka, M.; Tasaka, A. *Bioorg. Med. Chem.* **2004**, *12*, 4313; (c) Tasaka, A.; Hitaka, T.; Matsunaga, N.; Kusaka, M.; Adachi, M.; Aoki, I.; Ojida, A. WO02040484, 2002.
11. (a) Bierer, D.; Mcclue, A.; Fu, W.; Achebe, F.; Ladouceur, G. H.; Burke, M. J.; Bi, C.; Hart, B.; Dumas, J.; Sibley, R.; Scott, W. J.; Johnson, J.; Asgari, D. WO03027085, 2003.; (b) Ladouceur, G. H.; Burke, M. J.; Wong, W. C.; Bierer, D. WO03027094, 2003.
12. (a) Wachall, B. G.; Hector, M.; Zhuang, Y.; Hartmann, R. W. *Bioorg. Med. Chem.* **1999**, *7*, 1913; (b) Zhuang, Y.; Wachall, B. G.; Hartmann, R. W. *Bioorg. Med. Chem.* **2000**, *8*, 1245; (c) Leroux, F.; Hutschenreuter, T. U.; Charriere, C.; Scopelliti, R.; Hartmann, R. W. *Helv. Chim. Acta* **2003**, *86*, 2671; (d) Hutschenreuter, T. U.; Ehmer, P. E.; Hartmann, R. W. *J. Enzyme Inhibit. Med. Chem.* **2004**, *19*, 17.
13. Jagusch, C.; Negri, M.; Hille, U. E.; Hu, Q.; Bartels, M.; Jahn-Hoffmann, K.; Pinto-Bazurco Mendieta, M. A. E.; Rodenwaldt, B.; Müller-Vieira, U.; Schmidt, D.; Lauterbach, T.; Recanatini, M.; Cavalli, A.; Hartmann, R. W. *Bioorg. Med. Chem.* **2008**, *16*, 1992.
14. Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
15. Tang, Y.; Dong, Y.; Vennerstrom, J. L. *Synthesis* **2004**, *15*, 2540.
16. (a) Ehmer, P. B.; Jose, J.; Hartmann, R. W. *J. Steroid Biochem. Mol. Biol.* **2000**, *75*, 57; (b) Hartmann, R. W.; Bayer, H.; Gruen, G. *J. Med. Chem.* **1994**, *37*, 1275; (c) Denner, K.; Bernhardt, R. Inhibition studies of steroid conversions mediated by human CYP11B1 and CYP11B2 expressed in cell cultures. In *Oxygen Homeostasis and Its Dynamics*; Ishimura, Y., Shimada, H., Suematsu, M., Eds.; Springer-Verlag: Tokyo, Berlin, Heidelberg, New York, 1998; pp 231–236; (d) Böttner, B.; Denner, K.; Bernhardt, R. *Eur. J. Biochem.* **1998**, *252*, 458.
17. Pinto-Bazurco Mendieta, M. A. E.; Negri, M.; Jagusch, C.; Hille, U. E.; Müller-Vieira, U.; Schmidt, D.; Hansen, K.; Hartmann, R. W. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 267.
18. (a) Lin, D.; Zhang, L.; Chiao, E.; Miller, L. W. *Mol. Endocrinol.* **1994**, *8*, 392; (b) Auchus, R. J.; Miller, W. L. *Mol. Endocrinol.* **1999**, *13*, 1169.
19. Mathieu, A. P.; LeHoux, J.-G.; Auchus, R. J. *Biochim. Biophys. Acta* **2003**, *1619*, 291.
20. White, P. C.; Curnow, K. M.; Pascoe, L. *Endocr. Rev.* **1994**, *15*, 421.
21. Cuberes, M. R.; Moreno-Manas, M.; Trius, A. *Synthesis* **1985**, *3*, 302.
22. Regel, E.; Draber, W.; Buechel, K. H.; Plempel, M. US4118487, 1978.
23. Okada, M.; Yoden, T.; Kawaminami, E.; Shimada, Y.; Ishihara, T.; Kudou, M. US5807880, 1994.
24. (a) Halgren, T. A. *J. Comput. Chem.* **1999**, *20*, 730; (b) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648; (c) Stevens, P. J.; Devlin, J. F.; Chabalowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 11623.
25. (a) Jones, G.; Willett, P.; Glen, R. C.; Leach, A. R.; Taylor, R. *J. Mol. Biol.* **1997**, *267*, 727; (b) http://www.ccdc.cam.ac.uk/products/life_sciences/gold/.
26. (a) Bottegoni, G.; Cavalli, A.; Recanatini, M. *J. Chem. Inf. Model.* **2006**, *46*, 852; (b) Bottegoni, G.; Rocchia, W.; Recanatini, M.; Cavalli, A. *Bioinformatics* **2006**, *22*, e58.