N-(4-Biphenylmethyl)imidazoles as Potential Therapeutics for the Treatment of Prostate Cancer: Metabolic Robustness Due to Fluorine Substitution?

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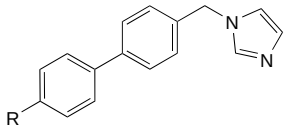
3,3′,5,5′- And 2,2′,6,6′-tetrafluoro-substituted 1-[(1,1′-biphenyl]-4-yl)methyl]-1*H*-imidazoles were synthesized as inhibitors of 17α-hydroxylase-C17,20-lyase (P450 17, CYP 17). P450 17 is the key enzyme of androgen biosynthesis. Its inhibition is a novel therapeutic approach for treatment of prostate cancer. To increase the so-far insufficient *in vivo* lifetime of such compounds, the metabolically sensitive positions were blocked by F-substitution. The *meta*- and *ortho*-F-substituted compounds were prepared by selective metallation or halogen/metal permutation reactions performed on symmetrically substituted 1,1′-biphenyls. Compared with the halogen-free compounds, the *ortho*-F-substituted derivatives did not match the activity, whereas the *meta*-F-substituted isomers equaled or surpassed the latter.

1. Introduction. – 17α-Hydroxylase-C17,20-lyase (P450 17, CYP 17, androgen synthase), a cytochrome P450 monooxygenase, is the key enzyme of androgen biosynthesis. It produces androstenedione and dehydroepiandrosterone from progesterone and pregnenolone, respectively. As androgens are implicated in the development of prostatic cancer, it is a promising alternative to the treatment with antiandrogens to develop selective inhibitors of this enzyme [1–7].

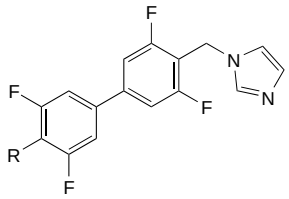
1-[([1,1′-Biphenyl]-4-yl)methyl]-substituted 1*H*-imidazoles **1** are highly potent inhibitors of CYP 17 and of CYP 19 (aromatase) [8–11]. Unfortunately, the very encouraging *in vitro* results are contrasted by a lack of *in vivo* activity, due to rapid degradation of the compounds by metabolic oxidation. We were able to isolate and identify the major metabolites by means of biomimetic methods.



1a R = H
1b R = Me
1c R = MeO
1d R = HO

Fluorine, the only element capable of mimicking hydrogen by virtue of comparable size ('isosterism') [12][13], may not only induce very specific properties to molecules, due to its electron-withdrawing power, but also confer metabolic stability, and, in addition, enhance the lipophilicity, and, as a corollary, facilitate cell-membrane permeation [14–20]. Thus, fluorine appeared to us to be the ideal molecular tool for fine-tuning the mechanical and biological properties of these compounds [15].

Therefore, we have embarked on the synthesis of fluorinated 1-[([1,1′-biphenyl]-4-yl)methyl]-1*H*-imidazoles **2** (F in the *meta*-positions) and **3** (F in the *ortho*-positions), wherein metabolically sensitive positions were blocked by F-atoms.



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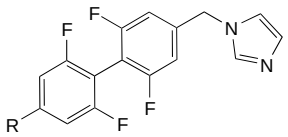


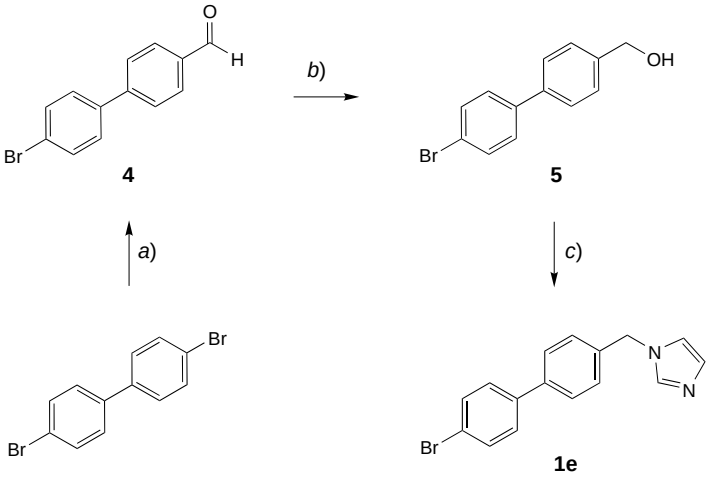
3a R = H
3b R = Me
3c R = MeO
3d R = HO

2. Results and Discussion. – *Synthesis.* The two series of dissymmetrically substituted 1,1′-biphenyls **2** and **3** could be prepared by the classical cross-coupling processes such as *Suzuki–Miyaura*, *Negishi*, *Kumada–Tamao–Corriu*, or *Stille* coupling [21], as we have shown in the case of the non-fluorinated parent compounds [9]. In all these cases, an efficient access to the corresponding fluorinated aryl nucleophiles and aryl halides is imperative. As this is not always the case, we decided to develop a different approach, based on the development of specific organometallic methods to transform symmetrically substituted 1,1′-biphenyls in dissymmetrically ones [22]. The symmetrically substituted 1,1′-biphenyls were prepared according to a modern modification [23–25] of the classical *Ullmann* reaction [26].

The crucial question was whether a symmetrically substituted 1,1′-biphenyl undergoes selective metallation or selective Br/metal permutation. This kind of reaction is far from being obvious, as one might expect a statistical mixture of zero-, mono-, and dimetallated intermediates. *Gilman et al.* reported in 1940 that 4,4′-dibromo-1,1′-biphenyl gives, after treatment with BuLi under various conditions, roughly a 2:1 mixture of the mono- and dicarboxylic acids after trapping with dry ice [27]. In 1997, *Ferreira* and co-workers reported on the formation of 4′-bromo[1,1′-biphenyl]-4-carbaldehyde after treatment of 4,4′-dibromo[1,1′-biphenyl] with BuLi in THF at $-75°$ and subsequent addition of DMF [28]. Applying these reaction conditions, a 69:31 mixture of the mono- and dicarbaldehyde, as determined by gas chromatography, was obtained. Contrarily, when the Br/Li permutation was performed in THF at $-100°$, followed by trapping of the aryllithium intermediate with DMF, the aldehyde **4** was selectively formed in a ratio of 96:4 for the mono- and dicarbaldehyde (see *Exper. Part*). After reduction of **4** to the alcohol **5** (96%), followed by conversion to the sulfonate and condensation with 1*H*-imidazole, the target compound **1e** was obtained in a yield of 56% (*Scheme 1*).

Encouraged by these findings, we decided to prepare the *m*-F-substituted compounds **2** by metallation of 3,3′,5,5′-tetrafluoro[1,1′-biphenyl] (**6**; *Scheme 2*). In a model reaction, with *s*-BuLi, in the presence of *N,N,N′,N″,N″*-pentamethyldiethylenetriamine (PMDTA) at $-75°$ in THF, followed by addition of DMF as electrophile, a mixture of mono- and dicarbaldehyde in a ratio of 94:6 was obtained (see compound

Scheme 1. *Selective Br/Li Permutation Performed on 4,4′-Dibromo[1,1′-biphenyl]*

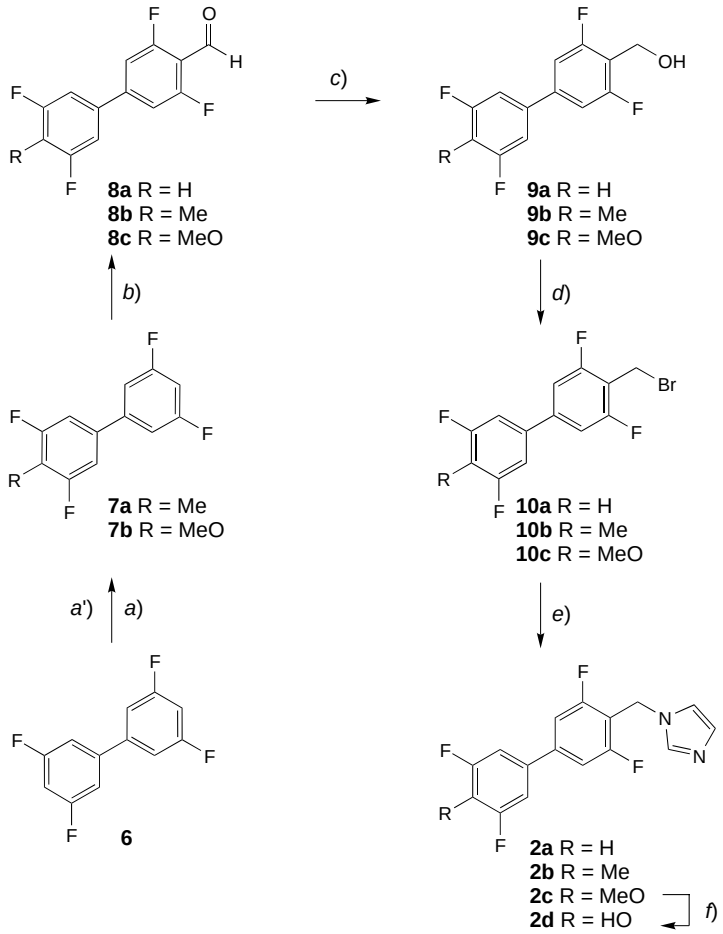


a) 1. LiC_4H_9, THF, – 100°; 2. DMF; 91%. *b*) $NaBH_4$, MeOH/THF, 25°, 12 h; 96%. *c*) 1. $MeSO_2Cl$, Et_3N, CH_2Cl_2, 0°, 1 h; 2. 1*H*-Imidazole, K_2CO_3, 18-crown-6, acetone, reflux, 2 h; 56%.

8a in *Exper. Part*). In the same way, the 1,1′-biphenyl core was functionalized by trapping the organometallic intermediate with Me_2SO_4 to the methyl derivative **7a** (79%) or addition of $FB(OMe)_2 \cdot OEt_2$, followed by oxidation to the phenol and treatment with MeI to yield the MeO derivative **7b** (64%). These 1,1′-biphenyls were metallated for a second time, under the same reaction conditions. After addition of DMF, the aldehydes **8b** (82%) and **8c** (87%) were obtained. The alcohols **9a**–**9c**, obtained after reduction with $NaBH_4$ (up to 95%) were converted to the bromides **10a** (88%), **10b** (89%), and **10c** (83%). Condensation with 1*H*-imidazole resulted in the target compounds **2a** (74%), **2b** (69%), and **2c** (71%). The phenolic compound **2d** was synthesized from the corresponding MeO-substituted 1,1′-biphenyl **2c** by ether cleavage with Br_3B in a yield of 62%.

To obtain the *o*-F-substituted compounds **3**, 1-bromo-3,5-difluorobenzene was used as the starting material. Metallation with lithium diisopropylamide (LDA) and addition of I_2 gave 5-bromo-1,3-difluoro-2-iodobenzene (**11**; 82%). I/Li exchange, transmetallation, and oxidation yielded 4,4′-dibromo-2,2′,6,6′-tetrafluoro[1,1′-biphenyl] (**12**; 79%; *Scheme 3*). Selective Br/Li permutation performed on **12** with BuLi in Et_2O at – 100° and trapping of the organometallic intermediate with DMF afforded the aldehyde **13** in a 92:8 ratio for mono- and dicarbaldehyde (see *Exper. Part*). After reduction to the alcohol **14a** (89%) and protection with the $(i\text{-}Pr)_3Si$ group to **15a** (92%), the 1,1′-biphenyl unit was further functionalized by Br/Li exchange and interception of the lithiated intermediate with Me_2SO_4 or $FB(OMe)_2 \cdot OEt_2$ to yield the Me- and MeO-substituted compounds **15b** (74%) and **15c** (63%), respectively. Cleavage of the $(i\text{-}Pr)_3Si$ groups with Bu_4NF gave the alcohols **14b** (85%) and **14c** (83%), respectively. Bromination of the alcohols **14a**, **14b**, and **14c** resulted in the formation of the bromides **16a** (81%), **16b** (78%), and **16c** (77%), respectively. After

Scheme 2. *Preparation of the* m-*F-Substituted Derivatives* **2**

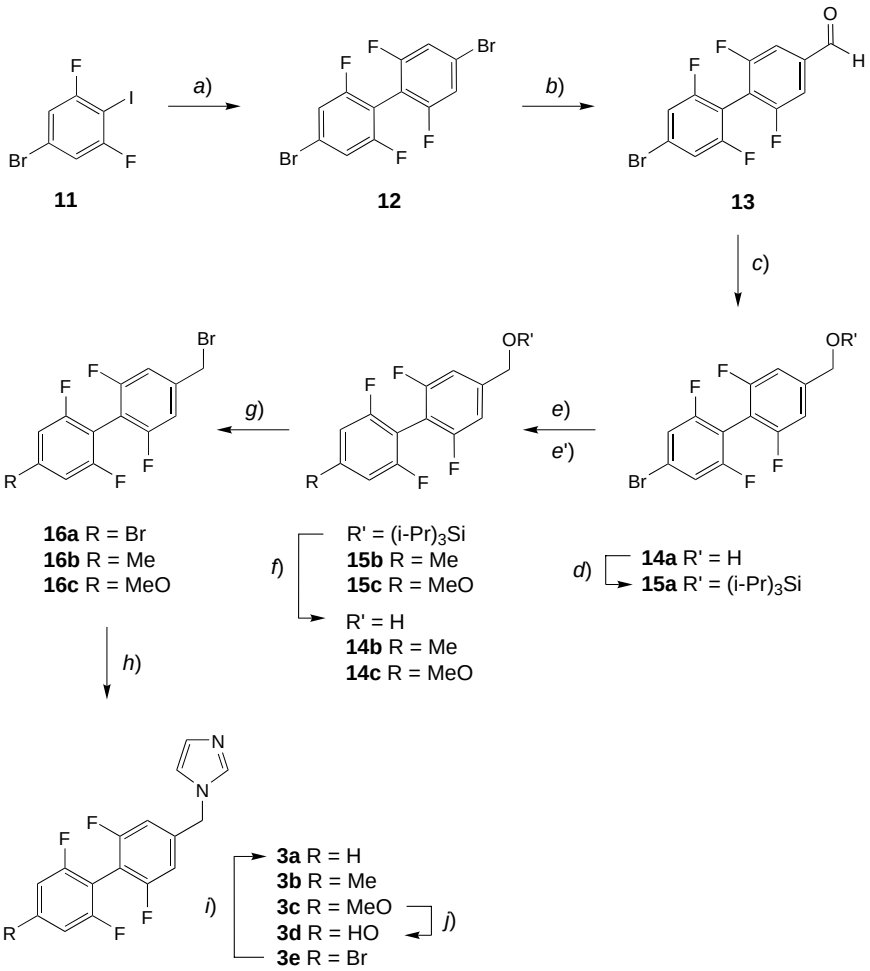


a) 1. LiC(Me)Et, *N,N,N′,N″,N″-pentamethyldiethylenetriamine* (PMDTA), THF, −75°, 2 h; 2. Me_2SO_4; 79% of **7a**, *a′*) 1. LiC(Me)Et, PMDTA, THF, −75°, 2 h; 2. $FB(OMe)_2 \cdot OEt_2$; 3. NaOH, H_2O_2; 4. MeI, KOH, DMSO, 64% of **7b**. *b*) 1. LiC(Me)Et, PMDTA, THF, −75°, 2 h; 2. DMF; 75% of **8a**; 82% of **8b**; 87% of **8c**. *c*) $NaBH_4$, MeOH/THF, 25°, 12 h; 94% of **9a**; 88% of **9b**; 79% of **9c**. *d*) Ph_3P, Br_2, MeCN, 50°, 6 h; 88% of **10a**; 89% of **10b**; 83% of **10c**. *e*) 1*H*-Imidazole, K_2CO_3, 18-crown-6, acetone, reflux, 2 h; 74% of **2a**; 69% of **2b**; 71% of **2c**. *f*) Br_3B, CH_2Cl_2, 25°, 12 h; 62%.

condensation with 1*H*-imidazole the 2,2′,6,6′-tetrafluoro-substituted 1-[([1,1′-biphenyl]-4-yl)methyl]-1*H*-imidazoles **3b** (62%), **3c** (64%), and **3e** (67%), respectively, were obtained. The 4-Br-substituted compound **3e** can be submitted to another Br/Li permutation and, after addition of MeOH, the debrominated compound **3a** was obtained in a yield of 93%. Ether cleavage of the methoxy derivative **3c** with Br_3B gave the alcohol **3d** (64%).

These results show that, in the symmetrically substituted 1,1′-biphenyls **6** and **12**, the H- or Br-atoms play the role of a kind of joker, which can be successively replaced by

Scheme 3. *Preparation of the* o-*F-Substituted Derivatives* **3**



a) 1. BuLi, Et_2O, $-75°$; 2. $CuBr_2$, 45 min; 3. nitrobenzene; 79%. *b*) 1. BuLi, Et_2O, $-100°$; 2. DMF; 86%. *c*) $NaBH_4$, MeOH/THF, 25°, 12 h; 89%. *d*) $(i\text{-}Pr)_3SiCl$ (TIPSCl), 1*H*-imidazole, DMF, 25°, 20 h; 92%. *e*) 1. BuLi, THF, $-75°$; 2. Me_2SO_4; 74% of **15b**. *e'*) 1. BuLi, THF, $-75°$; 2. $FB(OMe)_2 \cdot OEt_2$; 3. NaOH, H_2O_2; 4. MeI, KOH, DMSO; 63% of **15c**. *f*) Bu_4NF, THF, 25°, 15 min; 85% of **14b**; 83% of **14c**. *g*) Ph_3P, Br_2, MeCN, 50°, 6 h; 81% of **16a**; 78% of **16b**; 77% of **16c**. *h*) 1*H*-Imidazole, K_2CO_3, 18-crown-6, acetone, reflux, 2 h; 62% of **3b**; 64% of **3c**; 67% of **3e**. *i*) 1. *t*-BuLi, THF, $-100°$; 2. MeOH; 93%. *j*) Br_3B, CH_2Cl_2, 25°, 12 h; 64%.

any electrophile, after selective metallation (H/metal interconversion) or Br/Li permutation, opening access to dissymmetrically substituted biaryls.

X-Ray-Diffraction Studies. It makes a striking difference whether the two pairs of F-atoms are introduced at the 2,2′,6,6′- or the 3,3′,5,5′-positions of the 1,1′-biphenyl core. Although the oxidation potentials should be quite similar in both series, the structures do not resemble each other. The unsubstituted 1,1′-biphenyl is twisted in the gas phase

with a torsion angle of 45° [29]. In the solid state, the two phenyl rings are absolutely coplanar [30–32].

The introduction of the F-atoms into the *meta*-positions of the phenyl ring should change neither the form nor the shape of the molecules compared to the non-fluorinated analogs. This prediction was supported by single-crystal X-ray-diffraction studies (*Fig. 1* and *Table 2* in *Exper. Part*). The 1,1′-biphenyl core in compounds **2** is only slightly twisted around the central C–C axis. Compound **2c** has a torsion angle C(2)–C(1)–C(7)–C(12) of 11.1(5)° and C(6)–C(1)–C(7)–C(8) of 12.3(5)°. The torsional barriers of such 1,1′-biphenyls falls in the range of $E^{\pm}_{tors} \approx 3$ kcal/mol [32].

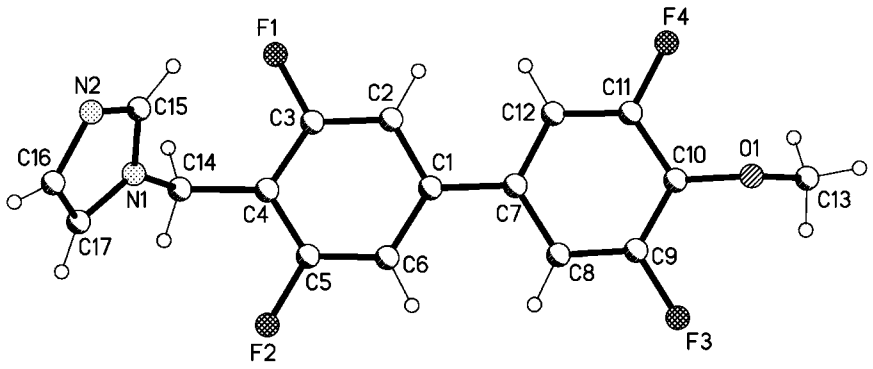


Fig. 1. *X-Ray crystal structure of the* m-*F-substituted derivative* **2c**

By dislocating the F-atoms from the *meta*- to the *ortho*-positions, the two aryl rings of the 1,1′-biphenyl unit are forced to occupy distinctly separated planes. Single-crystal X-ray-diffraction studies of **3c** (*Fig. 2* and *Table 2* in *Exper. Part*) revealed a torsion angle C(2)–C(1)–C(7)–C(12) of 64.1(4)° and C(6)–C(1)–C(7)–C(8) of 61.4(4)°. This was anticipated by the torsion angle of 59.7° [33] for perfluoro[1,1′-biphenyl] and even 57.6° [34] for 2,2′-difluoro[1,1′-biphenyl]. The barrier to planarization is too high ($E^{\pm}_{tors} = 26$ kcal/mol) to be surmounted at ambient temperature [35].

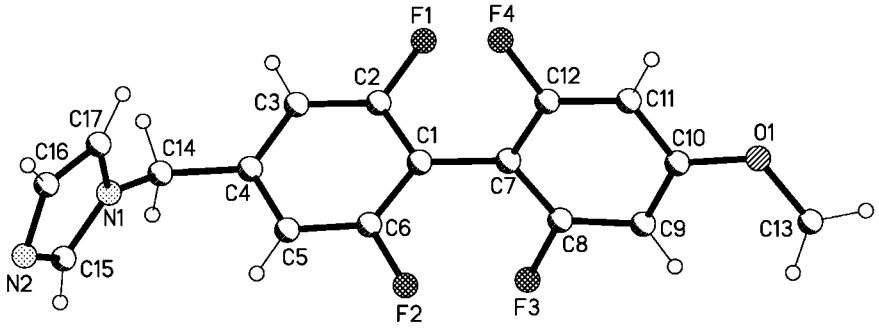


Fig. 2. *X-Ray crystal structure of the* o-*F-substituted derivative* **3c**

Biological Studies. The newly synthesized compounds were tested for their inhibitory activity towards CYP 17 and CYP 19 by the methods described in [9][36], and their inhibitory activities were compared with those of the non-fluorinated parent compounds. When the inhibitory activities exceeded 80%, the IC_{50} values were determined.

The derivatives, which have the best inhibitory activity towards CYP 17, were also tested in a kinetic study for their *in vitro* stability [37]. Phenol and the unfluorinated parent compound were used as reference substances. In these experiments, the compounds were incubated with rat liver microsomes for 120 min, samples were taken at stated time intervals, and the remaining concentrations of the parent compounds were determined by high-pressure liquid chromatography.

Inhibition of CYP 19 and SAR. The fluorinated 1,1′-biphenyl derivatives exhibit poor-to-moderate inhibitory activity towards CYP 19 (see *Table 1*). The influence of the introduction of F-atoms in the *meta*- and *ortho*-positions of the 1,1′-biphenyl unit was inconsistent. However, in two cases (**3b** and **3d**) the introduction of the F-atoms in the *ortho*-positions resulted in an increased activity of more than 20%, compared to the non-fluorinated analogs.

Table 1. *Inhibition of CYP 17 and CYP 19 by the Fluorinated ([1,1′-Biphenyl]ylmethyl)-1*H*-imidazoles in Comparison to the Non-Fluorinated Parent Compounds*

Compound	R	Inhibition of CYP 17 [%] (IC_{50} [μM])[a])	Inhibition of CYP 19[b]) [%]
1a [9]	H	(0.96)	66
2a	H	(0.37)	57
3a	H	73	66
1b [9]	Me	36	51
2b	Me	39	66
3b	Me	38	72
1c [9]	MeO	43	62
2c	MeO	46	53
3c	MeO	4	48
1d [9]	OH	(0.31)	31
2d	OH	(0.38)	29
3d	OH	75	68
1e	Br	27	49
3e	Br	16	40

[a]) 25 μM progesterone; 250 μM NADPH; 2.5 μM inhibitor [b]) 4.4 pM [1β2β^{3}H]-testosterone + 2.5 μM testosterone; 10 μM glucose-6-phosphate; 1 μM $NADP^{\oplus}$; 2 U/ml glucose-6-phosphate dehydrogenase; 25 μM inhibitor.

Inhibition of CYP 17 and SAR. The strongly twisted *o*-F-substituted 1,1′-biphenyls **3** did not match the activity of the halogen-free parent compounds. Only the poor inhibitor **3b** was as potent as its non-fluorinated congener. On the other hand, the flattened *m*-F-substituted isomers **2** equaled or surpassed the inhibitory activity of the non-fluorinated parent compounds (see *Table 1*). Compound **2a** showed an almost threefold higher activity towards CYP 17 (IC_{50} value of 0.37 μM), compared to the non-fluorinated analogue **1a** with an IC_{50} value of 0.96 μM.

Already 1-[(3′-fluoro[1,1′-biphenyl]-4-yl)methyl]-1*H*-imidazole, a monofluorinated derivative, has an inhibitory activity of 0.66 μM towards CYP 17 [9]. Apparently, the introduction of one or more F-atoms in the 3′-position of the 1,1′-biphenyl unit increases the inhibitory activity significantly.

The introduction of a non-hydrophilic *p*-substituent decreases the inhibition potency in the case of the non-fluorinated parent compounds as in the case of the fluorinated derivatives. However, the introduction of the OH group at the *para*-position increases the inhibition of CYP 17 by a factor of three. These observations are identical to the results for the non-fluorinated compounds [9]. Thus, the introduction of F-atoms in the *meta*-positions of the 1,1′-biphenyl unit has only marginal effects on the inhibitory activity towards CYP 17. The inhibition potency is affected mainly by the nature of the *p*-substituent.

These results indicate that the different torsion angles for the *m*- and *o*-F-substituted 1,1′-biphenyls have a significant influence on the inhibitory activity. The *o*-F-substituted 1,1′-biphenyls seem to be too 'bulky' to interact well with the active site of the target enzyme. In addition, the torsional barrier for planarization of the 1,1′-biphenyl unit is to high to be surmounted in the enzyme pocket. On the other hand, the effect of the F-atoms in the *meta*-positions are negligible if one looks at the *in vitro* activity.

Effects of Fluorination on the Metabolic Stability. Next, we studied the effect of the F-substitution on the metabolic stability of the [(biphenylyl)methyl]-1*H*-imidazoles. Therefore, the two fluorinated OH isomers with the highest inhibitory activity towards CYP 17 (**2d** and **3d**) were tested for their metabolic stability in an *in vitro* study. Phenol and the unsubstituted analogue were used as reference compounds (*Fig. 3*).

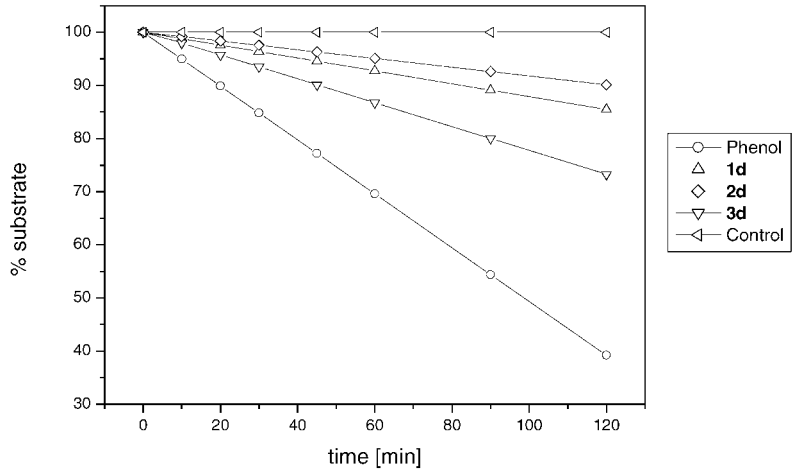


Fig. 3. In vitro *biodegradation of the* m-*F-substituted derivative* **2d** *and the* o-*F-substituted derivative* **3d** *compared with the unfluorinated compound* **1d** *and phenol* (control experiments are without NADPH-generating system)

Controls without added NADPH-generating system remained unaffected indicating no NADPH-independent reactions. The biodegradation of the (1*H*-imidazol-1-

yl)methyl-substituted 1,1′-biphenyls is slower than the degradation of the reference phenol, since most of the 1*H*-imidazol-1-yl-substituted compounds are inhibitors of many hepatic CYPs [38–40]. As expected, the *m*-F-substituted derivative **2d** showed a significantly reduced *in vitro* metabolism ($P < 0.005$, $n = 6$) compared to its non-fluorinated congener **1d**. Surprisingly, the *o*-F-substituted compound **3d** was metabolized faster than the non-fluorinated parent compound **1d**. In the HPLC chromatogram of the incubation of **1d**, a catechol derivative (4′-[(1*H*-imidazol-1-yl)methyl][1,1′-biphenyl]-3,4-diol) was detected (t_R 3.8 min).

In phenolic compounds the *ortho*-position is susceptible to hydroxylation. In addition, this position is acidified in compound **3d** due to the neighboring F-atom. This finding may explain the faster biodegradation of **3d** in comparison to the non-fluorinated analogue **1d**. In the derivative **2d**, however, this position is blocked by F-substitution.

3. Conclusions. – Two sets of model compounds were investigated to control metabolism of 1-[([1,1′-biphenyl]-4-yl)methyl]-1*H*-imidazoles. One set contained the F-atoms in the *meta*-positions of the 1,1′-biphenyl unit and the second set in the *ortho*-positions. All fluorinated 1,1′-biphenyl derivatives exhibit poor inhibitory activity towards aromatase (CYP 19), but proved potent towards 17α-hydroxylase-C17,20-lyase (CYP 17). Compared with the halogen-free compounds, the *o*-F-substituted derivatives did not match the activity, whereas the *m*-F-substituted isomers equaled or surpassed the latter. The phase-I metabolism of these compounds can be slowed down by the introduction of F-atoms in the *meta*-positions.

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Experimental Part

General. THF and Et_2O were distilled from sodium benzophenone and stored under N_2 in *Schlenk* burettes. DMF was dried by azeotropic distillation with toluene. BuLi, *s*-BuLi, and *t*-BuLi were supplied by *CheMetall AG*, D-38685 Langelsheim. Other reagents were obtained from commercial sources and checked by comparison of refraction index for liquids and melting points for solids. Air- and moisture-sensitive compounds were stored in *Schlenk* tubes or *Schlenk* burettes. Reactions at low temp. were performed by using cold baths: H_2O/ice at 0°, EtOH/dry ice at −75°, and Et_2O/liquid N_2 at −100°. The temp. EtOH/dry ice is consistently indicated at −75° and 'room temperature' as 25°. Melting ranges (M.p.) are reproducible after resolidification unless otherwise stated (dec.), and were corrected by using a calibration curve. ^{1}H-NMR: *Bruker DPX-400*; chemical shifts δ in ppm relative to TMS ($\delta = 0.00$) or relative to deuterated solvent. Elementary analysis: *Ilse Beetz*, Microanalytisches Laboratorium, D-96301 Kronach, or *F. Hoffmann-La Roche AG*, CH-4070 Basel.

4′-Bromo[1,1′-biphenyl]-4-carbaldehyde (**4**). At −100°, BuLi (0.10 mol) in hexanes (63 ml) was added dropwise during 10 min to a soln. of 4,4′-dibromo[1,1′-biphenyl] (31 g, 0.10 mol) in THF (0.50 l). After 15 min, DMF (7.7 ml, 7.3 g, 0.10 mmol) was added, and the mixture was allowed to reach 25°. After addition of H_2O (50 ml) and extraction with Et_2O (3 × 50 ml), a 96:4 mixture, according to GC (30 m, *DB-1*, 180°), of the aldehyde **1** and the dicarbaldehyde was obtained. The combined org. layers were evaporated and crystallized from AcOEt/hexanes to provide **4** (23.9 g, 91%). Colorless needles. M.p. 140–142° ([41]: 137–140°). ^{1}H-NMR ($CDCl_3$, 400 MHz): 10.06 (*s*, 1 H); 7.95 (*d*, $J = 8.4$, 2 H); 7.70 (*d*, $J = 8.3$, 2 H); 7.61 (*d*, $J = 8.6$, 2 H); 7.49 (*d*, $J = 8.5$, 2 H).

4′-Bromo[1,1′-biphenyl]-4-methanol (**5**). $NaBH_4$ (7.6 g, 0.20 mol) was added to **4** (13 g, 50 mmol) in MeOH/THF 1:1 (*v*/*v*) (0.20 l). After 12 h at 25°, a 2.0M aq. soln. of HCl (50 ml) was carefully added, followed by extraction with Et_2O (4 × 50 ml). The org. layer was washed with brine (50 ml), dried, and evaporated.

Crystallization from AcOEt/hexanes afforded **5** (12.6 g, 96%). Colorless needles. M.p. 130–132° ([42]: 130.5–131.5°). ^{1}H-NMR ($CDCl_3$, 400 MHz): 7.57 (*d*, *J* = 8.5, 2 H); 7.55 (*d*, *J* = 8.3, 2 H); 7.46 (*d*, *J* = 8.7, 2 H); 7.43 (*d*, *J* = 8.0, 2 H); 4.74 (*s*, 2 H); 1.76 (br. *s*, 1 H).

*1-[(4′-bromo[1,1′-biphenyl]-4-yl)methyl]-1*H*-imidazole* (**1e**). At 0°, MsCl (3.9 ml, 5.7 g, 50 mmol) and Et_3N (10 ml, 7.6 g, 75 mmol) were added consecutively to **5** (6.6 g, 25 mmol) in CH_2Cl_2 (0.12 l). After 1 h, the volatiles were removed *in vacuo*, and the residue was dissolved in dry acetone (0.12 l). 1*H*-Imidazole (6.9 g, 0.10 mol), 18-crown-6 (0.26 g, 1.0 mmol), and anh. K_2CO_3 (28 g, 0.20 mol) were added consecutively, and the mixture was heated under reflux for 2 h. At 25°, the precipitate was removed by filtration, washed with more acetone (50 ml), and the combined filtrates were evaporated. After the addition of H_2O (0.10 l), the mixture was extracted with a 1:5 (*v*/*v*) mixture MeOH/AcOEt (2 × 50 ml). The org. phase was extracted with a 0.10M aq. soln. of HCl (5 × 50 ml). The combined aq. layers were alkalinized with a sat. aq. soln. of Na_2CO_3 (0.20 l) and again extracted with a 1:5 (*v*/*v*) mixture MeOH/AcOEt (4 × 50 ml). The combined org. layers were dried and evaporated. The residue was crystallized from AcOEt/hexanes to afford **1e** (4.38 g, 56%). Colorless needles. M.p. 116–117°. ^{1}H-NMR ($CDCl_3$, 400 MHz): 7.59 (*s*, 1 H); 7.56 (*d*, *J* = 8.5, 2 H); 7.53 (*d*, *J* = 8.2, 2 H); 7.43 (*d*, *J* = 8.5, 2 H); 7.22 (*d*, *J* = 8.3, 2 H); 7.11 (*s*, 1 H); 6.95 (*s*, 1 H); 5.17 (*s*, 2 H). Anal. calc. for $C_{16}H_{13}BrN_2$ (313.20): C 61.36, H 4.18; found: C 61.32, H 4.36.

3,3′,5,5′-Tetrafluoro[1,1′-biphenyl] (**6**). At −75°, 1-bromo-3,5-difluorobenzene (39 g, 0.20 mol), $CuBr_2$ (45 g, 0.20 mol), and, 45 min later, $PhNO_2$ (20 ml, 25 g, 0.20 ml) were added consecutively to a soln. of BuLi (0.20 mol) in hexanes (0.11 l) and Et_2O (0.40 l). The mixture was allowed to reach 25° during 2 h. The suspension was poured into a 12% aq. solution of NH_3 (0.20 l). The org. layer was separated, and the aq. phase was extracted with Et_2O (2 × 0.20 l). The combined org. layers were dried and evaporated. Crystallization from MeOH afforded **6** (19.9 g, 88%). Colorless needles. M.p. 86–88° ([43]: 85.5–87°). ^{1}H-NMR ($CDCl_3$, 400 MHz): 7.06 (sym. *m*, 4 H); 6.85 (*tt*, *J* = 8.9, 2.6, 2 H).

3,3′,5,5′-Tetrafluoro-4-methyl[1,1′-biphenyl] (**7a**). At −100°, *s*-BuLi (50 mmol) in cyclohexane (39 ml) was added dropwise during 15 min to **6** (11 g, 50 mmol) and *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (PMDTA; 10 ml, 8.7 g, 50 mmol) in THF (0.25 l). After the addition was completed, the mixture was kept 2 h at −75°, followed by the addition of Me_2SO_4 (4.8 ml, 6.3 g, 50 mmol). The volatiles were evaporated, and H_2O (50 ml) was added. After extraction with Et_2O (3 × 50 ml), drying, and evaporation, the residue was crystallized from MeOH to afford **7a** (9.49 g, 79%). Colorless needles. M.p. 77–79°. ^{1}H-NMR ($CDCl_3$, 400 MHz): 7.1 (*m*, 4 H); 6.82 (*tt*, *J* = 8.8, 2.5, 1 H); 2.41 (*t*, *J* = 1.7, 3 H). Anal. calc. for $C_{13}H_8F_4$ (240.20): C 65.01, H 3.36; found: C 65.18, H 3.26.

3,3′,5,5′-Tetrafluoro-4-methoxy[1,1′-biphenyl] (**7b**). The reaction was initially conducted as described for **7a**, Me_2SO_4 being replaced by $FB(OMe)_2 \cdot OEt_2$ [44][45] (9.4 ml, 8.2 g, 50 mmol). At 0°, a 3.0M aq. soln. of NaOH (18 ml) and a 30% aq. H_2O_2 soln. (5.0 ml, 1.7 g, 50 mmol) were added consecutively. The mixture was neutralized with a 2.0M aq. soln. of HCl (50 ml) and extracted with Et_2O (3 × 50 ml). The combined org. layers were washed with a 10% aq. soln. of Na_2SO_3 (50 ml), dried, and evaporated. The residue was dissolved in Me_2SO (0.10 l), before MeI (3.8 ml, 8.5 g, 60 mmol) and KOH powder (3.4 g, 60 mmol) were added. After 1 h, H_2O (0.25 l) was added, followed by extraction with Et_2O (3 × 50 ml). The combined org. layers were washed with brine (3 × 50 ml), dried, and evaporated. Crystallization from EtOH gave **7b** (8.20 g, 64%). Colorless needles. M.p. 87–88°. ^{1}H-NMR ($CDCl_3$, 400 MHz): 7.09 (*d*, *J* = 9.3, 2 H); 7.01 (*dd*, *J* = 8.4, 2.2, 2 H); 6.80 (*tt*, *J* = 8.8, 2.3, 1 H); 4.05 (*t*, *J* = 1.1, 3 H). Anal. calc. for $C_{13}H_8F_4O$ (256.20): C 60.95, H 3.15; found: C 61.13, H 2.99.

3,3′,5,5′-Tetrafluoro[1,1′-biphenyl]-4-carbaldehyde (**8a**). The same metallation conditions described for **7a** were applied, followed by addition of DMF (3.2 ml, 3.0 g, 50 mmol). The mixture was allowed to reach 25°. H_2O (50 ml) was added, followed by extraction with Et_2O (3 × 50 ml). A 96:4 mixture of **8a** and the dicarbaldehyde was obtained (according to GC, 30 m, *DB-1*, 150°). Concentration and crystallization from AcOEt/hexanes gave **8a** (9.53 g, 75%). Colorless needles. M.p. 128–129°. ^{1}H-NMR ($CDCl_3$, 400 MHz): 10.37 (*s*, 1 H); 7.20 (*d*, *J* = 9.4, 2 H); 7.11 (sym. *m*, 2 H); 6.92 (*tt*, *J* = 8.5, 2.3, 1 H). Anal. calc. for $C_{13}H_6F_4O$ (254.18): C 61.43, H 2.38; found: C 61.35, H 2.53.

3,3′,5,5′-Tetrafluoro-4′-methyl[1,1′-biphenyl]-4-carbaldehyde (**8b**). At −100°, *s*-BuLi (50 mmol) in cyclohexane (39 ml) was added dropwise during 15 min to **7a** (12 g, 50 mmol) and PMDTA (10 ml, 8.7 g, 50 mmol) in THF (0.25 l). After the addition was completed, the mixture was kept 2 h at −75°, followed by the addition DMF (3.2 ml, 3.0 g, 50 mmol). The mixture was allowed to reach 25°. H_2O (50 ml) was added, followed by extraction with Et_2O (3 × 50 ml). The org. layers were dried and evaporated. The residue was crystallized from AcOEt/hexanes to afford **8b** (11.0 g, 82%). Colorless needles. M.p. 143–145°. ^{1}H-NMR ($CDCl_3$, 400 MHz): 10.35 (*s*, 1 H); 7.17 (*d*, *J* = 9.7, 2 H); 7.09 (*d*, *J* = 8.0, 2 H); 2.27 (*t*, *J* = 1.6, 3 H). Anal. calc. for $C_{14}H_8F_4O$ (268.21): C 62.69, H 3.01; found: C 62.84, H 3.08.

3,3′,5,5′-Tetrafluoro-4′-methoxy[1,1′-biphenyl]-4-carbaldehyde- (**8c**). Compound **8c** was obtained from **7b** (13 g, 50 mmol) as described above after crystallization from AcOEt/hexanes (12.4 g, 87%). Colorless needles. M.p. 113–114°. ^{1}H-NMR ($CDCl_3$, 400 MHz): 10.37 (*s*, 1 H); 7.15 (*d*, *J* = 9.5, 2 H); 7.12 (*d*, *J* = 9.7, 2 H); 4.08 (*t*, *J* = 1.5, 3 H). Anal. calc. for $C_{14}H_8F_4O_2$ (284.12): C 59.17, H 2.84; found: C 58.81, H 2.76.

3,3′,5,5′-Tetrafluoro[1,1′-biphenyl]-4-methanol (**9a**). $NaBH_4$ (7.6 g, 0.20 mol) was added to **8a** (13 g, 50 mmol) in a 1:1 (*v*/*v*) mixture MeOH/THF (0.20 l). After 12 h at 25°, a 2.0M aq. soln. of HCl (0.20 l) was carefully added. The mixture was extracted with Et_2O (4 × 50 ml), and the combined org. layers were washed with brine (50 ml), dried, and evaporated. Crystallization from AcOEt/hexanes afforded **9a** (12.0 g, 94%). Colorless needles. M.p. 106–108°. ^{1}H-NMR ($CDCl_3$, 400 MHz): 7.10 (*d*, *J* = 8.3, 2 H); 7.04 (*dd*, *J* = 8.4, 2.3, 2 H); 6.84 (*tt*, *J* = 8.7, 2.4, 1 H); 4.81 (*s*, 2 H); 2.04 (*s*, 1 H). Anal. calc. for $C_{13}H_8F_4O$ (256.20): C 60.95, H 3.15; found: C 60.58, H 3.33.

3,3′,5,5′-Tetrafluoro-4′-methyl[1,1′-biphenyl]-4-methanol (**9b**). The same reaction and workup conditions as described for **9a** were applied to **8b** (13 g, 50 mmol). Compound **9b** was obtained after crystallization from AcOEt/hexanes (11.9 g, 88%). Colorless needles. M.p. 151–152°. ^{1}H-NMR ($CDCl_3$, 400 MHz): 7.09 (*d*, *J* = 8.3, 2 H); 7.03 (*d*, *J* = 7.8, 2 H); 4.81 (*s*, 2 H); 2.22 (*s*, 3 H). Anal. calc. for $C_{14}H_{10}F_4O$ (270.23): C 62.23, H 3.73; found: C 62.14, H 3.79.

3,3′,5,5′-Tetrafluoro-4′-methoxy[1,1′-biphenyl]-4-methanol (**9c**). Compound **9c** was obtained from **8c** (14 g, 50 mmol) as described above after crystallization from AcOEt/hexanes (11.3 g, 79%). Colorless needles. M.p. 127–128°. ^{1}H-NMR ($CDCl_3$, 400 MHz): 7.09 (*d*, *J* = 9.4, 2 H); 7.05 (*d*, *J* = 8.3, 2 H); 4.81 (*s*, 2 H); 4.05 (*s*, 3 H). Anal. calc. for $C_{14}H_{10}F_4O_2$ (286.23): C 58.75, H 3.52; found: C 58.86, H 3.43.

4-(Bromomethyl)-3,3′,5,5′-tetrafluoro[1,1′-biphenyl] (**10a**). Br_2 (1.5 ml, 4.8 g, 30 mmol) and **9a** (7.7 g, 30 mmol) were added consecutively to a suspension of Ph_3P (11 g, 30 mmol) in MeCN (0.15 ml). The mixture was kept at 50° for 6 h. After evaporation, the residue was suspended in hexanes (0.10 l), filtered over a pad of silica gel, and washed with more hexanes (0.10 l). Evaporation and crystallization from AcOEt/hexanes afforded **10a** (8.42 g, 88%). Colorless needles. M.p. 102–104°. ^{1}H-NMR ($CDCl_3$, 400 MHz): 7.11 (*d*, *J* = 8.2, 2 H); 7.05 (*dd*, *J* = 8.3, 2.2, 2 H); 6.86 (*tt*, *J* = 8.6, 2.1, 1 H); 4.55 (*s*, 2 H). Anal. calc. for $C_{13}H_7BrF_4$ (319.10): C 48.93, H 2.21; found: C 48.93, H 2.11.

4-(Bromomethyl)-3,3′,5,5′-tetrafluoro-4′-methyl[1,1′-biphenyl] (**10b**). Compound **10b** was obtained from **9b** (8.11 g, 30 mmol) as described above after crystallization from AcOEt/hexanes (8.89 g, 89%). Colorless needles. M.p. 104–105°. ^{1}H-NMR ($CDCl_3$, 400 MHz): 7.09 (*d*, *J* = 8.2, 2 H); 7.03 (*d*, *J* = 7.3, 2 H); 4.55 (*s*, 2 H); 2.23 (*s*, 3 H). Anal. calc. for $C_{14}H_9BrF_4$ (333.12): C 50.48, H 2.72; found: C 50.43, H 2.61.

4-(Bromomethyl)-3,3′,5,5′-tetrafluoro-4′-methoxy[1,1′-biphenyl] (**10c**). When the reaction and workup conditions described above were applied to **9c** (8.6 g, 30 mmol), the **10c** (8.69 g, 83%) was obtained after crystallization from AcOEt/hexanes. Colorless needles. M.p. 99–101°. ^{1}H-NMR ($CDCl_3$, 400 MHz): 7.09 (*d*, *J* = 9.5, 2 H); 7.05 (*d*, *J* = 8.4, 2 H); 4.55 (*s*, 2 H); 4.05 (*s*, 3 H). Anal. calc. for $C_{14}H_9BrF_4O$ (349.12): C 48.16, H 2.30; found: C 48.40, H 2.51.

*1-[(3,3′,5,5′-Tetrafluoro[1,1′-biphenyl]-4-yl)methyl]-1*H-*imidazole* (**2a**). 1*H*-Imidazole (6.8 g, 0.10 mol), the **10a** (8.0 g, 25 mmol), 18-crown-6 (0.26 g, 1.0 mmol), and anh. K_2CO_3 (28 g, 0.20 mol) in dry acetone (0.12 l) were heated under reflux for 2 h. At 25°, the precipitate was removed by filtration, washed with more acetone (50 ml), and the combined filtrates were evaporated. After the addition of H_2O (0.10 l), the mixture was extracted with a 1:5 (*v*/*v*) mixture MeOH/AcOEt (2 × 50 ml). The org. phase was extracted with a 0.10M aq. soln. of HCl (4 × 50 ml). The combined aq. layers were alkalinized with a sat. aq. soln. of Na_2CO_3 (0.20 l) and again extracted with a 1:5 (*v*/*v*) mixture MeOH/AcOEt (4 × 50 ml). The combined org. layers were dried and evaporated. The residue was crystallized from AcOEt/hexanes to afford **2a** (5.67 g, 74%). Colorless needles. M.p. 117–118°. ^{1}H-NMR ($CDCl_3$, 400 MHz): 7.62 (*s*, 1 H); 7.14 (*d*, *J* = 8.3, 2 H); 7.0 (*m*, 4 H); 6.86 (*tt*, *J* = 7.6, 2.3, 1 H); 5.21 (*s*, 2 H). Anal. calc. for $C_{16}H_{10}F_4N_2$ (306.26): C 62.75, H 3.29; found: C 62.65, H 3.21.

*1-[(3,3′,5,5′-Tetrafluoro-4′-methyl[1,1-biphenyl]-4-yl)methyl]-1*H-*imidazole* (**2b**). When the same reaction and workup conditions described above were applied to **10b** (5.0 g, 15 mmol), **2b** (3.32 g, 69%) was obtained after crystallization from AcOEt/hexanes. Colorless needles. M.p. 112–113°. ^{1}H-NMR ($CDCl_3$, 400 MHz): 7.62 (*s*, 1 H); 7.11 (*d*, *J* = 8.2, 2 H); 7.0 (*m*, 4 H); 5.20 (*s*, 2 H); 2.23 (*s*, 3 H). Anal. calc. for $C_{17}H_{12}F_4N_2$ (320.29): C 63.75, H 3.78; found: C 63.62, H 3.72.

*1-[(3,3′,5,5′-Tetrafluoro-4′-methoxy[1,1′-biphenyl]-4-yl)methyl]-1*H-*imidazole* (**2c**). When the same reaction and workup conditions described above were applied to **10c** (7.0 g, 20 mmol), **2c** (4.78 g, 71%) was obtained after crystallization from AcOEt/hexanes. Colorless cubes. M.p. 108–111°. ^{1}H-NMR ($CDCl_3$, 400 MHz): 7.61 (*s*, 1 H); 7.09 (*d*, *J* = 8.2, 2 H); 7.06 (*d*, *J* = 9.3, 2 H); 7.04 (*s*, 1 H); 7.00 (*s*, 1 H); 5.19 (*s*, 2 H); 4.04 (*s*, 3 H). Anal. calc. for $C_{17}H_{12}F_4N_2O$ (336.29): C 60.72, H 3.60; found: C 61.01, H 3.63.

*3,3′,5,5′-Tetrafluoro-4′-[(1*H*-imidazole-1-yl)methyl][1,1′-biphenyl]-4-ol* (**2d**). Br_3B (0.95 ml, 2.5 g, 10 mmol) was added to a soln. of **2c** (1.7 g, 5.0 mmol) in dry CH_2Cl_2 (25 ml). After 12 h at 25°, MeOH (5.0 ml) was added, and the volatiles were evaporated. A sat. aq. soln. of $NaHCO_3$ (10 ml) was added, and the product was collected by filtration. Crystallization from MeOH afforded **2d** (1.00 g, 62%). Colorless cubes. M.p. 242–244° (dec.). ^{1}H-NMR (D_3CCOCD_3, 400 MHz): 7.67 (*s*, 1 H); 7.43 (*d*, *J* = 8.4, 4 H); 7.11 (*s*, 1 H); 6.93 (*s*, 1 H); 5.36 (*s*, 2 H); 2.83 (*s*, 1 H). Anal. calc. for $C_{16}H_{10}F_4N_2O$ (322.26): C 59.63, H 3.13; found: C 59.49, H 3.22.

5-Bromo-1,3-difluoro-2-iodobenzene (**11**). At −75°, $(i\text{-}Pr)_2NH$ (16 ml, 10 g, 0.10 mol) and 1-bromo-3,5-difluorobenzene (12 ml, 19 g, 0.10 mol) were added consecutively to a soln. of BuLi (0.10 mol) in THF (0.20 l) and hexanes (60 ml). After 2 h at −75°, a soln. of I_2 (25 g, 0.10 mol) in THF (50 ml) was added. The solvents were evaporated, and the residue was dissolved in Et_2O (0.10 l). After washing with a 10% aq. soln. of $Na_2S_2O_3$ (2 × 50 ml), the org. layer was dried and evaporated. Crystallization from EtOH afforded **11** (26.1 g, 82%). Colorless platelets. M.p. 41–43°. ^{1}H-NMR ($CDCl_3$, 400 MHz): 7.08 (*m*, sym., 2 H). Anal. calc. for $C_6H_2BrF_2I$ (318.85): C 22.60, H 0.63; found: C 22.76, H 0.78.

4,4′-Dibromo-2,2′,6,6′-tetrafluoro[1,1′-biphenyl] (**12**). At −75°, BuLi (0.10 mol) in hexanes (0.62 l), $CuBr_2$ (22 g, 0.10 mol), and, 45 min later, $PhNO_2$ (10 ml, 12 g, 0.10 mol) were added consecutively to a soln. of **11** (32 g, 0.10 mol) in Et_2O (0.50 l). The mixture was allowed to reach 25° during 2 h. The suspension was poured into a 12% aq. soln. of NH_3 (0.10 l). The org. layer was separated, and the aqueous phase was extracted with Et_2O (2 × 0.10 l). The combined org. layers were dried and evaporated. Crystallization from MeOH afforded **12** (15.2 g, 79%). Colorless platelets. M.p. 106–108°. ^{1}H-NMR ($CDCl_3$, 400 MHz): 7.22 (sym. *m*, 4 H). Anal. calc. for $C_{12}H_4Br_2F_4$ (383.96): C 37.54, H 1.05; found: C 37.48, H 1.10.

4-Bromo-2,2′,6,6′-tetrafluoro[1,1′-biphenyl]-4-carbaldehyde (**13**). At −100°, BuLi (0.10 mol) in hexanes (63 ml) was added dropwise during 10 min to a suspension of **12** (38 g, 0.10 mol) in Et_2O (0.50 l). After 15 min, DMF (7.7 ml, 7.3 g, 0.10 mmol) was added, and the mixture was allowed to reach 25°. After addition of H_2O (50 ml) and extraction with Et_2O (3 × 50 ml), a 92:8 mixture (according to GC, 30 m, DB-1, 100° (10 min) → 200°, heating rate 30°/min) of **13** and the dicarbaldehyde was obtained. Concentration and crystallization from AcOEt/hexanes gave **13** (28.6 g, 86%). Colorless needles. M.p. 94–96°. ^{1}H-NMR ($CDCl_3$, 400 MHz): 10.00 (*t*, *J* = 1.6, 1 H); 7.55 (*d*, *J* = 6.8, 2 H); 7.26 (*d*, *J* = 6.9, 2 H). Anal. calc. for $C_{13}H_5BrF_4$ (333.08): C 46.88, H 1.51; found: C 47.14, H 1.20.

4′-Bromo-2,2′,6,6′-tetrafluoro-[1,1′-biphenyl]-4-methanol (**14a**). $NaBH_4$ (7.6 g, 0.20 mol) was added to **13** (17 g, 50 mmol) in a 1:1 (*v*/*v*) mixture MeOH/THF (0.20 l). After 12 h at 25°, a 2.0M aq. soln. of HCl (50 ml) was carefully added, followed by extraction with Et_2O (4 × 50 ml). The combined org. layers were washed with brine (50 ml), dried, and evaporated. Crystallization from AcOEt/hexanes afforded **14a** (14.9 g, 89%). Colorless needles. M.p. 74–75°. ^{1}H-NMR ($CDCl_3$, 400 MHz): 7.21 (*d*, *J* = 6.7, 2 H); 7.03 (*d*, *J* = 8.2, 2 H); 4.74 (*s*, 2 H). Anal. calc. for $C_{13}H_7BrF_4O$ (335.09): C 46.60, H 2.11; found: C 46.96, H 1.96.

Bromo-2,2′,6,6′-tetrafluoro-4′-[[(triisopropylsilyl)oxy]methyl][1,1′-biphenyl] (**15a**). The alcohol **14a** (17 g, 50 mmol), $(i\text{-}Pr)_3SiCl$ (13 ml, 12 g, 60 mmol), and 1*H*-imidazole (8.8 g, 0.13 mol) were dissolved in DMF (25 ml). After 20 h at 25°, the mixture was poured into H_2O and extracted with CH_2Cl_2 (3 × 50 ml). The volatiles were evaporated, and the residue was crystallized from MeOH to afford **15a** (22.6 g, 92%). Colorless needles. M.p. 57–59°. ^{1}H-NMR ($CDCl_3$, 400 MHz): 7.21 (*d*, *J* = 6.6, 2 H); 7.02 (*d*, *J* = 8.3, 2 H); 4.85 (*s*, 2 H); 1.2 (*m*, 3 H); 1.11 (*d*, *J* = 6.8, 18 H). Anal. calc. for $C_{22}H_{27}BrF_4OSi$ (491.44): C 53.77, H 5.54; found: C 53.91, H 5.35.

2,2′,6,6′-Tetrafluoro-4-methyl-4′-{[(triisopropylsilyl)oxy]methyl][1,1′-biphenyl] (**15b**). At −75°, **15a** (37 g, 75 mmol) and Me_2SO_4 (7.1 ml, 9.5 g, 75 mmol) were added consecutively to a soln. of BuLi (75 mmol) in hexanes (33 ml) and THF (0.15 l). After evaporation, H_2O (50 ml) was added, and the product was extracted with Et_2O (3 × 50 ml). The combined extracts were dried and evaporated. Crystallization from MeOH afforded **15b** (23.7 g, 74%). Colorless needles. M.p. 67–68°. ^{1}H-NMR ($CDCl_3$, 400 MHz): 7.01 (*d*, *J* = 8.3, 2 H); 6.83 (*d*, *J* = 8.0, 2 H); 4.85 (*s*, 2 H); 2.40 (*s*, 3 H); 1.2 (*m*, 3 H); 1.11 (*d*, *J* = 6.7, 18 H). Anal. calc. for $C_{23}H_{30}F_4OSi$ (426.57): C 64.76, H 7.09; found: C 64.42, H 6.88.

2,2′,6,6′-Tetrafluoro-4-methoxy-[4′-{[(triisopropylsilyl)ary]methyl[1,1′-biphenyl] (**15c**). The reaction was conducted as described for **15b**, Me_2SO_4 being replaced with $FB(OMe)_2 \cdot OEt_2$ [44][45] (14 ml, 12 g, 75 mmol). At 0°, a 3.0M aq. soln. of NaOH (27 ml) and 30% H_2O_2 (7.5 ml, 2.7 g, 75 mmol) were added consecutively. At 25°, the mixture was acidified with 2.0M solution of HCl (0.10 l) and extracted with Et_2O (3 × 0.10 l). The combined org. layers were washed with a 10% aq. soln. of $Na_2S_2O_3$ (0.10 ml), dried, and evaporated. The residue was dissolved in Me_2SO (0.15 l) before MeI (5.6 ml, 13 g, 90 mmol) and KOH powder (5.0 g, 90 mmol) were added consecutively. After 1 h, H_2O (0.50 l) was added, and the product was extracted with Et_2O (3 × 0.10 l). The org. layers were dried and evaporated. Crystallization from MeOH afforded **15c** (20.9 g, 63%). Colorless

needles. M.p. 73–75°. ^{1}H-NMR ($CDCl_3$, 400 MHz): 7.00 (*d*, *J* = 8.2, 2 H); 6.58 (*d*, *J* = 9.1, 2 H); 4.85 (*s*, 2 H); 3.84 (*s*, 3 H); 1.2 (*m*, 3 H); 1.11 (*d*, *J* = 6.4, 18 H). Anal. calc. for $C_{23}H_{30}F_4O_2Si$ (442.52): C 62.42, H 6.83; found: C 62.50, H 6.71.

2,2′,6,6′-Tetrafluoro-4′-methyl[1,1′-biphenyl]-4-methanol (**14b**). The protected alcohol **15b** (11 g, 25 mmol) was dissolved in THF (25 ml) and treated with a 1.0M soln. of Bu_4NF (26 mmol) in THF (26 ml). After 15 min, H_2O (50 ml) was added, and the aq. layer was extracted with Et_2O (3 × 50 ml). The combined org. layers were dried and evaporated. Crystallization from AcOEt/hexanes gave **14b** (5.74 g, 85%). Colorless needles. M.p. 92–94°. ^{1}H-NMR ($CDCl_3$, 400 MHz): 7.03 (*d*, *J* = 7.6, 2 H); 6.83 (*d*, *J* = 8.2, 2 H); 4.75 (*s*, 2 H); 2.40 (*s*, 3 H). Anal. calc. for $C_{14}H_{10}F_4O$ (270.23): C 62.23, H 3.73; found: C 62.31, H 3.67.

2,2′,6,6′-Tetrafluoro-4′-methoxy[1,1′-biphenyl]-4-methanol (**14c**). When the reaction and workup conditions described above were applied to **15c** (11 g, 25 mmol), **14c** (5.94 g, 83%) was obtained after crystallization from AcOEt/hexanes. Colorless needles. M.p. 89–90°. ^{1}H-NMR ($CDCl_3$, 400 MHz): 7.02 (*d*, *J* = 8.0, 2 H); 6.57 (*d*, *J* = 9.4, 2 H); 4.75 (*s*, 2 H); 3.84 (*s*, 3 H). Anal. calc. for $C_{14}H_{10}F_4O_2$ (286.22): C 58.75, H 3.52; found: C 58.77, H 3.51.

4-Bromo-4′-(bromomethyl)-2,2′,6,6′-tetrafluoro[1,1′-biphenyl] (**16a**). Br_2 (1.5 ml, 4.8 g, 30 mmol) and **14a** (10 g, 30 mmol) were added consecutively to a suspension of Ph_3P (11 g, 30 mmol) in (0.15 l). The mixture was kept at 50° for 6 h. After evaporation, the residue was suspended in hexanes (0.15 l), filtered over a pad of silica gel, and washed with more hexanes (0.10 l). After evaporation, the residue was crystallized from AcOEt/hexanes to afford **16a** (9.67 g, 81%). Colorless needles. M.p. 63–64°. ^{1}H-NMR ($CDCl_3$, 400 MHz): 7.22 (*d*, *J* = 6.8, 2 H); 7.07 (*d*, *J* = 7.8, 2 H); 4.45 (*s*, 2 H). Anal. calc. for $C_{13}H_6Br_2F_4$ (397.99): C 39.23, H 1.52; found: C 39.42, H 1.59.

4-(Bromomethyl)-2,2′,6,6′-tetrafluoro-4′-methyl[1,1′-biphenyl] (**16b**). When the reaction and workup conditions described above were applied to **14b** (8.1 g, 30 mmol), **16b** (7.79 g, 78%) was obtained after crystallization from AcOEt/hexanes. Colorless needles. M.p. 92–93°. ^{1}H-NMR ($CDCl_3$, 400 MHz): 7.05 (*d*, *J* = 7.8, 2 H); 6.83 (*d*, *J* = 8.3, 2 H); 4.45 (*s*, 2 H); 2.41 (*s*, 3 H). Anal. calc. for $C_{14}H_9BrF_4$ (333.12): C 50.48, H 2.72; found: C 50.46, H 2.62.

4-(Bromomethyl)-2,2′,6,6′-tetrafluoro-4′-methoxy[1,1′-biphenyl] (**16c**). When the reaction and workup conditions described above were applied to **14c** (8.6 g, 30 mmol), **16c** (8.06 g, 77%) was obtained after crystallization from AcOEt/hexanes. Colorless needles. M.p. 91–92°. ^{1}H-NMR ($CDCl_3$, 400 MHz): 7.04 (*d*, *J* = 8.1, 2 H); 6.56 (*d*, *J* = 9.3, 2 H); 4.44 (*s*, 2 H); 3.85 (*s*, 3 H). Anal. calc. for $C_{14}H_9BrF_4O$ (349.12): C 48.16, H 2.60; found: C 48.41, H 2.58.

*1-[(2,2′,6,6′-Tetrafluoro-4′-methyl[1,1′-biphenyl]-4-yl)methyl]-1*H-*imidazole* (**3b**). 1*H*-Imidazole (6.9 g, 0.10 mol), **16b** (8.3 g, 25 mmol), 18-crown-6 (0.26 g, 1.0 mmol), and anh. K_2CO_3 (28 g, 0.20 mol) in dry acetone (0.12 l) were heated under reflux for 2 h. At 25°, the precipitate was removed by filtration, washed with more acetone (50 ml), and the combined filtrates were evaporated. After the addition of H_2O (0.10 l), the mixture was extracted with a 1:5 (*v*/*v*) mixture MeOH/AcOEt (2 × 50 ml). The org. phase was extracted with a 0.10M aq. soln. of HCl (4 × 50 ml). The combined aq. layers were alkalinized with a sat. aq. soln. of Na_2CO_3 (0.20 l) and again extracted with a 1:5 (*v*/*v*) mixture MeOH/AcOEt (4 × 50 ml). The combined org. layers were dried and evaporated. The residue was crystallized from AcOEt/hexanes to afford **3b** (4.96 g, 62%). Colorless needles. M.p. 112–113°. ^{1}H-NMR ($CDCl_3$, 400 MHz): 7.59 (*s*, 1 H); 7.16 (*s*, 1 H); 6.96 (*s*, 1 H); 6.83 (*d*, *J* = 8.3, 2 H); 6.75 (*d*, *J* = 7.2, 2 H); 5.16 (*s*, 2 H); 2.39 (*s*, 3 H). Anal. calc. for $C_{17}H_{12}F_4N_2$ (320.29): calc. (%): C 63.75, H 3.78; found: C 63.62, H 3.52.

*1-[(2,2′,6,6′-Tetrafluoro-4′-methoxy[1,1′-biphenyl]-4-yl)methyl]-1*H-*imidazole* (**3c**). When the reaction and workup conditions described for **3b** were applied to **16c** (7.0 g, 20 mmol), **3c** (4.30 g, 64%) was obtained after crystallization from AcOEt/hexanes. Colorless needles. M.p. 88–89°. ^{1}H-NMR ($CDCl_3$, 400 MHz): 8.06 (*s*, 1 H); 7.21 (*s*, 1 H); 6.99 (*s*, 1 H); 6.81 (*d*, *J* = 8.1, 2 H); 6.57 (*d*, *J* = 9.2, 2 H); 5.26 (*s*, 2 H); 3.83 (*s*, 3 H). Anal. calc. for $C_{17}H_{12}F_4N_2O$ (336.29): C 60.72, H 3.60; found: C 60.68, H 3.46.

*1-[(4′-bromo-2,2′,6,6′-tetrafluoro[1,1′-biphenyl]-4-yl)methyl]-1*H-*imidazole* (**3e**). Compound **3e** was obtained from **16a** (9.9 g, 25 mmol) and isolated as described above from AcOEt/hexanes (6.45 g, 67%). Colorless needles. M.p. 120–121°. ^{1}H-NMR ($CDCl_3$, 400 MHz): 7.60 (*s*, 1 H); 7.22 (*d*, *J* = 6.5, 2 H); 7.17 (*s*, 1 H); 6.96 (*s*, 1 H); 6.77 (*d*, *J* = 7.3, 2 H); 5.19 (*s*, 2 H). Anal. calc. for $C_{16}H_9BrF_4N_2$ (385.16): C 49.90, H 2.36; found: C 50.04, H 2.33.

*1-[(2,2′,6,6′-Tetrafluoro[1,1′-biphenyl]-4-yl)methyl]-1*H-*imidazole* (**3a**). At −100°, **3e** (1.9 g, 5.0 mmol) was added to a soln. of *t*-BuLi (10 mmol) in Et_2O (50 ml) and pentanes (7.1 ml). After 5 min, MeOH (0.50 ml) was added, and the volatiles were evaporated. The residue was crystallized from AcOEt/hexanes to afford **3a** (1.42 g, 93%). Colorless needles. M.p. 107–109°. ^{1}H-NMR ($CDCl_3$, 400 MHz): 8.20 (*s*, 1 H); 7.41 (*m* symm., 1 H); 7.22

(*s*, 1 H); 7.02 (*t*, *J* = 7.9, 2 H); 7.00 (*s*, 1 H); 5.30 (*s*, 2 H). Anal. calc. for $C_{16}H_{10}F_4N_2$ (306.26): C 62.75, H 3.29; found: C 62.71, H 3.16.

*2,2′,6,6′-Tetrafluoro-4′-[(1*H*-imidazol-1-yl)methyl][1,1′-biphenyl]-4-ol* (**3d**). Br_3B (0.95 ml, 2.5 g, 10 mmol) was added to **3c** (1.7 g, 5.0 mmol) in dry CH_2Cl_2 (25 ml). The mixture was kept at 25° for 12 h. MeOH (5.0 ml) was added, and the volatiles were evaporated. A sat. aq. soln. of $NaHCO_3$ (10 ml) was added, and the product was collected by filtration. Crystallization from MeOH afforded **3d** (1.03 g, 64%). Colorless cubes. M.p. 228–230° (dec.). ^{1}H-NMR (D_3CCOCD_3, 400 MHz): 7.85 (*s*, 1 H); 7.27 (*s*, 1 H); 7.05 (*d*, *J* = 7.9, 2 H); 7.04 (*s*, 1 H); 6.64 (*d*, *J* = 9.3, 2 H); 5.42 (*s*, 2 H). Anal. calc. for $C_{16}H_{10}F_4N_2O$ (322.26): C 59.63, H 3.13; found: C 59.53, H 3.06.

Inhibition of CYP 17. The inhibition of human CYP 17 of the synthesized compounds was determined as described in [9].

Inhibition of CYP 19. According to the method of *Hartmann* and *Batzl* [36], the compounds were tested for their inhibitory activity toward CYP 19.

Preparation of Rat Liver Microsomes. Six adult male *Sprague–Dawley* rats were sacrificed by CO_2. The livers were removed, pooled, washed twice with an ice-cold 0.90% aq. soln. of NaCl, weighed, and frozen at −70° until they were further processed.

The defrosted livers were homogenized in buffer (pH 7.4) containing 0.25M sucrose, 10 mM tris(hydroxymethyl)aminomethane (*Tris*), and 1.0 mM ethylenediaminetetraacetic acid (EDTA; 3 ml per g tissue). The homogenate was centrifuged at $1.2 \cdot 10^4$ g for 30 min in order to remove cell debris and mitochondria. The resulting supernatant was subsequently centrifuged at $1.0 \cdot 10^5$ g for 1 h. The pelleted microsomes were washed once with 0.10M Na_3PO_4 buffer (pH 7.4) and suspended in 0.10M Na_3PO_4 buffer containing 20% glycerol (15 ml). All steps were carried out at 4° [1]. Protein concentrations were determined by the method of *Lowry et al.* [46] with bovine serum albumin as standard. Cytochrome P450 concentrations were measured according to the method described by *Omura* and *Sato* [47]. Aliquots of this enzyme preparation were frozen at −70° until used.

Test of the in vitro *Stability.* Rat liver microsomal suspension containing 0.40 μM of P450 (0.41 nM of P450 · (mg of protein)$^{-1}$) and 1.0 μM of one of the compounds (**1d**, **2d**, **3d**, or phenol; dissolved in a 7:3 (*v*/*v*) mixture of a 0.10M aq. HCl soln. and Me_2SO, diluted 1:10) was mixed in 1440 μl of 50 mM Na_3PO_4 buffer (pH 7.4, containing 1.0 mM $MgCl_2$, 1.0 mM EDTA, and 0.10 mM dithiothreitol) at 4° in a 2.0-ml micro test tube. After 5 min of preincubation at 37°, the reaction was started by the addition of 60 μl of NADPH-generating system (2.0 U/ml glucose-6-phosphate dehydrogenase, 10 mM glucose-6-phosphate, and 1.0 mM $NADP^{\oplus}$ (preincubated for 30 min at 37°)) and vigorous mixing [37]. Control incubations were performed in absence of the NADPH-generating system. At 0, 10, 20, 30, 45, 60, 90, and 120 min, samples of 150 μl were taken and pipetted into 80 μl of a 91:9 (*v*/*v*) mixture of MeCN and AcOH to stop the reaction. After 15 min at 0°, the precipitated proteins were separated by microcentrifugation. Samples of 50 μl of the supernatant were transferred into a safe-lock vial and stored at −70° until the HPLC analysis.

HPLC Analysis. The HPLC system consisted of an isocratic high-pressure pump (*Jasco 870-PU*, D-64823 Groß-Umstadt), an autosampler (*Jasco 851-AS*, D-64823 Groß-Umstadt), and a UV-detector (*Jasco 870-UV*, D-64823 Groß-Umstadt). A CC 125 × 3 mm *Nucleodur Gravity 120-3 C18* column with column holder and an analogue guard column (*Macherey Nagel*, D-52355 Düren) operated at ambient temp. was used to separate the compounds at a flow rate of 0.85 ml/min. Different ratios of ammonium acetate buffer (20 mM, pH 4.0) and MeCN were used as eluents (for **1d**: 91:9 (G/G), t_R 7.9 min; for **2d**, **3d**, and phenol: 84:16 (G/G), t_R 7.5, 5.1, and 7.0 min, resp.). UV Absorbance was monitored at 254 nm.

X-Ray Crystal-Structure Determination of **2c** *and* **3c** (*Table 2*). Diffraction data were collected at 140 K (**2c**) and 293 K (**3c**) with MoK_α radiation on different equipments: an *Oxford Diffraction* diffractometer with a kappa geometry equipped with a *Sapphire CCD* detector (**2c**) and a *mar345* imaging plate detector (**3c**). Data reduction was performed with *CrysAlis RED 1.6.9β* [48] and *marHKL 1.9.1* [49]. Structure solutions were determined with *ab initio* direct methods [50]. All structures were refined with full-matrix least-squares on F^2 with all non-H-atoms anisotropically defined. The H-atoms were placed in calculated positions by the 'riding model' with $U_{iso} = aU_{eq}$(C) (where *a* is 1.5 for Me H-atoms and 1.2 for other atoms and C is the parent C-atom). Space-group determination, structure refinement, geometric calculations, and graphical representations were carried out on all structures with SHELXTL software package, release 5.1 [51]. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the *Cambridge Crystallographic Data Centre* as deposition No. CCDC-203256 (**2c**) and deposition No. CCDC-203257 (**3c**). Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ UK (fax: +44 (1223) 336033; e-mail: deposit@ccdc.cam.ac.uk).

Table 2. *Crystallographic Data for the Compounds* **2c** *and* **3c**

	2c	**3c**
Empirical formula	$C_{17}H_{12}F_4N_2O$	$C_{17}H_{12}F_4N_2O$
Formula weight	336.29	336.29
Crystal size [mm]	$0.30 \times 0.13 \times 0.10$	$0.20 \times 0.15 \times 0.12$
Crystal system	monoclinic	monoclinic
Space group	$P2_1/n$	$P2_1/c$
a [Å]	16.0021(18)	6.9734(14)
b [Å]	4.2789(10)	8.848(5)
c [Å]	21.648(3)	24.125(8)
β [°]	96.239(10)	92.16(2)
Volume [Å^3]	1473.5(4)	1487.5(10)
Z	4	4
Density [g m^{-3}]	1.516	1.502
Temp. [K]	140(2)	293(2)
Absorption coeff. [mm^{-1}]	0.130	0.129
θ Range [°]	3.79–25.03	3.42 to 25.02
Index ranges	$-19 \rightarrow 18$, $-4 \rightarrow 4$, $-25 \rightarrow 25$	$-7 \rightarrow 8$, $-10 \rightarrow 10$, $-28 \rightarrow 28$
Refl. collected	7389	8589
Independent reflect.	2477 ($R_{int} = 0.0607$)	2495 ($R_{int} = 0.0489$)
Absorption correction	none	none
Data/restraints/parameters	2477/0/218	2495/0/218
Goodness-of-fit on F^2	1.144	0.991
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0715$, $wR2 = 0.1508$	$R1 = 0.0590$, $wR2 = 0.1600$
R Indices (all data)	$R1 = 0.0854$, $wR2 = 0.1573$	$R1 = 0.0856$, $wR2 = 0.1886$
Largest diff. peak/hole [e A^{-3}]	0.264 and -0.235	0.260 and -0.297

REFERENCES

[1] T. Sergejew, R. W. Hartmann, *J. Enzyme Inhib*. **1994**, *8*, 113 (*Chem. Abstr*. **1995**, *122*, 71366).
[2] S. E. Barrie, M. Jarman, *Endocr. Relat. Cancer* **1996**, *3*, 25 (*Chem. Abstr*. **1996**, *125*, 25360).
[3] M. Jarman, H. J. Smith, P. J. Nicholls, C. Simons, *Nat. Prod. Rep*. **1998**, *15*, 495.
[4] G. A. Wächter, R. W. Hartmann, T. Sergejew, G. L. Grün, D. Ledergerber, *J. Med. Chem*. **1996**, *39*, 834.
[5] F. Chan, G. A. Potter, S. E. Barrie, B. P. Haynes, M. G. Rowlands, J. Houghton, M. Jarman, *J. Med. Chem*. **1996**, *39*, 3319.
[6] J. P. Van Wauve, P. A. J. Janssen, *J. Med. Chem*. **1989**, *32*, 2231.
[7] R. W. Hartmann, B. G. Wachall, M. Yoshihama, M. Nakakoshi, S. Nomoto, Y. Ikeda, U.S. Pat. Appl., US 2002/0032211 A1, 2002.
[8] R. W. Hartmann, *Eur. J. Pharm. Sci*. **1994**, *2*, 15; *Chem. Abstr.* **1994**, *121*, 292816.
[9] B. G. Wachall, M. Hector, Y. Zhuang, R. W. Hartmann, *Biorg. Med. Chem*. **1999**, *7*, 1913.
[10] Y. Zhuang, B. G. Wachall, R. W. Hartmann, *Biorg. Med. Chem*. **2000**, *8*, 1245.
[11] R. W. Hartmann, P. B. Ehmer, S. Haidar, M. Hector, J. Jose, C. D. P. Klein, S. B. Seidel, T. Sergejew, G. A. Wächter, Y. Zhuang, *Arch. Pharm. Pharm. Med. Chem*. **2002**, *335*, 119.
[12] M. Schlosser, *Tetrahedron* **1978**, *34*, 3.
[13] M. Schlosser, D. Michel, *Tetrahedron* **1996**, *52*, 99.
[14] M. Schlosser, *Angew. Chem*. **1998**, *111*, 1538; *Angew. Chem*., *Int. Ed*. **1998**, *37*, 1496.
[15] M. Schlosser, in 'Enantiocontrolled Synthesis of Fluoroorganic Compounds: Stereochemical Challenges and Biomedicinal Targets', Ed. V. A. Soloshonok, Wiley, Chichester, 1999, 613–659.
[16] J.-N. Volle, M. Schlosser, *Eur. J. Org. Chem*. **2000**, 823.
[17] D. Michel, M. Schlosser, *Tetrahedron* **2000**, *56*, 4253.
[18] M. Schlosser, L. Guio, F. Leroux, *J. Am. Chem. Soc*. **2001**, *123*, 3822.
[19] E. Marzi, F. Mongin, A. Spitaleri, M. Schlosser, *Eur. J. Org. Chem*. **2001**, 2911.

[20] B. K. Park, N. R. Kitteringham, *Drug Metab. Rev.* **1994**, *26*, 605.
[21] F. Diederich, P. J. Stang, 'Metal-Catalyzed Cross-Coupling Reactions', Wiley-VCH, Weinheim, 1998.
[22] M. Schlosser, in 'Organometallics in Synthesis: A Manual', Ed. M. Schlosser, 2nd edn., Wiley, Chichester, 2002, p. 1 – 252, spec. 121 – 122.
[23] M. S. Kharasch, O. Reinmuth, 'Grignard Reactions of Nonmetallic Substances', Prentice Hall, Englewood Cliffs, 1954.
[24] A. Rajca, A. Safronov, S. Rajca, C. R. Ross, J. J. Stezowski, *J. Am. Chem. Soc.* **1996**, *118*, 7272.
[25] J. Hassan, M. Sévignon, C. Gozzi, E. Schulz, M. Lemaire, *Chem. Rev.* **2002**, *102*, 1359.
[26] P. Fanta, *Synthesis* **1974**, 9.
[27] H. Gilman, W. Langham, F. W. Moore, *J. Am. Chem. Soc.* **1940**, *62*, 2327.
[28] P. S. van Heerden, B. C. B. Bezuidenhoudt, D. Ferreira, *J. Chem. Soc., Perkin Trans. 1* **1997**, *8*, 1141.
[29] A. Almenningen, O. Bastiansen, L. Fernholt, B. N. Cyvin, S. J. Cyvin, S. Samdal, *J. Mol. Struct. (THEOCHEM)* **1985**, *128*, 59.
[30] G.-P. Charbonneau, Y. Delugeard, *Acta Crystallogr., Sect. B* **1976**, *32*, 1420.
[31] G.-P. Charbonneau, Y. Delugeard, *Acta Crystallogr., Sect. B* **1977**, *33*, 1586.
[32] F. Grein, *J. Phys. Chem. A* **2002**, *106*, 3823.
[33] W. B. Gleason, D. Britton, *Cryst. Struct. Commun.* **1976**, *5*, 483 (*Chem. Abstr.* **1976**, *85*, 102761).
[34] B. Aldridge, G. De Luca, M. Edgar, S. J. Edgar, J. W. Emsley, M. I. C. Furby, M. Webster, *Liq. Cryst.* **1998**, *24*, 569 (*Chem. Abstr.* **1998**, *128*, 302405).
[35] N. Hasaka, M. Okigawa, I. Kouno, N. Kawano, *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3828.
[36] R. W. Hartmann, C. Batzl, *J. Med. Chem.* **1986**, *29*, 1363.
[37] P. Valadon, P. M. Dansette, J.-P. Girault, C. Amar, D. Mansuy, *Chem. Res. Toxicol.* **1996**, *9*, 1403.
[38] R. A. McKinnon, A. M. Evans, *Aust. J. Hosp. Pharm.* **2000**, *30*, 146 (*Chem. Abstr.* **2000**, *134*, 157065).
[39] K. E. Thummel, G. R. Wilkinson, *Annu. Rev. Pharmacol. Toxicol.* **1998**, *38*, 389 (*Chem. Abstr.* **1998**, *129*, 35991).
[40] R. Zuber, E. Anzenbacherova, P. Anzenbacher, *J. Cell. Mol. Med.* **2002**, *6*, 189.
[41] F. Fleck, H. Kittl, S. Valenti, Ger. Offen. DE 2262340 (to Sandoz Ltd.; filed on 20 December 1972; issued on 28 June 1973) (*Chem. Abstr.* **1973**, *79*, 147435).
[42] M. I. Dawson, P. D. Hobbs, K. Derdzinski, R. L.-S. Chan, J. Gruber, W.-r. Chao, S. Smith, R. W. Thies, L. J. Schiff, *J. Med. Chem.* **1984**, *27*, 1516.
[43] V. Courtois, R. Barhdadi, M. Troupel, J. Périchon, *Tetrahedron* **1997**, *53*, 11569.
[44] G. Rauchschwalbe, M. Schlosser, *Helv. Chim. Acta* **1975**, *58*, 1094.
[45] M. Schlosser, L. Franzini, *Synthesis* **1998**, 707.
[46] O. H. Lowry, N. J. Rosebrough, A. L. Farr, R. J. Randall, *J. Biol. Chem.* **1951**, *193*, 265.
[47] T. Omura, R. Sato, *J. Biol. Chem.* **1964**, *239*, 2370.
[48] *Oxford Diffraction Ltd.*, Abingdon, Oxfordshire, U.K., 2001.
[49] Z. Otwinowski, W. Minor, in 'Methods in Enzymology', Eds. C. W. Carter, R. M. Sweet, Academic Press, New York, 1997, Vol. 276, p. 307 – 326.
[50] G. M. Sheldrick, *Acta Crystallogr., Sect. A* **1983**, *39*, 158.
[51] G. M. Sheldrick, *Bruker AXS, Inc.*, Madison, Wisconsin, USA, 1997.

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