Aryl Hetaryl Ketones and Thioketones as Efficient Inhibitors of Peptidyl-Prolyl *cis-trans* Isomerases

by **Thomas Hediger**[a]), **Walter Frank**[b]), **Michael Schumann**[c]), **Gunter Fischer***[c]), and **Manfred Braun***[a])

[a]) Institut für Organische und Makromolekulare Chemie, Universität Düsseldorf, Universitätsstrasse 1, DE-40225 Düsseldorf
(phone: +492118114731; fax +492118115079; e-mail: braunm@uni-duesseldorf.de)

[b]) Institut für Anorganische Chemie und Strukturchemie, Universität Düsseldorf, Universitätsstrasse 1, DE-40225 Düsseldorf

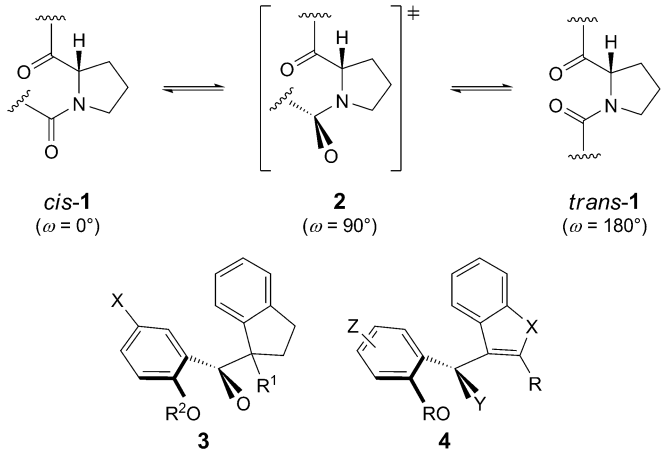
[c]) Max-Planck-Forschungsstelle für Enzymologie der Proteinfaltung, Weinbergweg 22, DE-06120 Halle
(phone: +493455522800; fax: +493455511972; e-mail: fischer@enzyme-halle.mpg.de)

Dedicated to Professor *Dieter Seebach* at the occasion of his 75th birthday

A series of 18 differently substituted new aryl hetaryl ketones and thioketones were synthesized in four to six steps from commercial starting materials. The new ketones were evaluated as inhibitors of the peptidyl-prolyl *cis-trans* isomerase hPin1 with K_i values ranging in the one-digit micromolar to sub-micromolar numbers. A crystal structure revealed the non-planar arrangement of the aryl residues at the carbonyl compound and supports the hypothesis that the new compounds might mimic the transition state of the enzymatic conversion.

Introduction. – The structure of proteins distinctly depends on the rigidity of the amide bond with only two energetically preferred conformational states, leading to *cis* and *trans* peptide-bond isomers **1**. The peptide bonds between 19 out of the 20 gene-coded amino acids overwhelmingly adopt the *trans*-conformation. In contrast, the imidic peptide bond preceding a proline residue realizes comparable thermodynamic stability for both isomers in unfolded polypeptide chains and also, in many cases, in native proteins. As a consequence, the presence of *cis* prolyl bonds can affect a variety of isomer-specific signaling processes in the cell. The activation barrier encountered with the rotation about this bond amounts to 75 to 100 kJ mol^{-1}. It is required to convert *cis*-**1** ($\omega = 0°$) to *trans*-**1** ($\omega = 180°$) through the transition state **2** with a perpendicular arrangement of the substituents at the amide bond ($\omega = 90°$) [1] (*Scheme 1*). The ubiquitously distributed peptidyl prolyl *cis*/*trans* isomerases (PPIases), discovered in 1984, catalyze the interconversion of *cis*-**1** and *trans*-**1** by substantially lowering the barrier to rotation [2]. Consequently, PPIases have been found to play a key role in accelerating slow steps in the refolding as well as in structural modifications in the native state of proteins. Three families of PPIases have been characterized: *i*) the cyclophilins, *ii*) the FK-506 binding proteins, and *iii*) the parvulins, the latter including human Pin1, a PPIase that is specific for phosphorylated serine and threonine preceding proline [3]. The role Pin1 plays in cell cycle, cancer pathogenesis, and *Alzheimer*'s disease has been studied intensively during the last decade [4], and Pin1 emerged as an 'anticancer drug target' [5]. It is, therefore, not surprising that

Scheme 1. cis-trans *Isomerization of Peptidyl–Prolyl Bonds.* Aryl indanyl ketones **3** and aryl hetaryl ketones, and thioketones **4** as transition-state analogs of the 'twisted amide' **2**.



various attempts have been made to develop peptidic and small-molecule inhibitors of Pin1 [6][7]. Despite intense efforts and remarkable progress in this area, there seems to be still a need for low-molecular-weight, cell-entering compounds with efficient Pin1 inhibition.

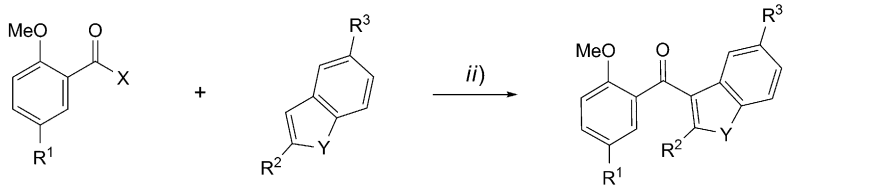
Guided by the idea to inhibit PPIases by mimicking the transition state **2** due to compounds that intrinsically feature a 'twisted' arrangement of residues at a carbonyl group, we developed (bi)aryl indanyl ketones **3** as PPIase inhibitors that turned out to be not only potent inhibitors of Pin1 [8], but also of cyclophilins with a remarkable selectivity towards the latter's isoforms [9]. MC/FEP calculations have confirmed the idea that aryl indanyl ketones also resemble the transition state of cyclophilin-A catalysis preferably by favorable stabilization of the residues Arg55 and Asn102 of the enzyme [10].

In the aryl-indanyl series, the individual enantiomers of **3** (R^1 = Me, X = F) were found not only to exhibit distinctly different inhibitory activities but also substantial differences in biochemical effects [8][9]. Racemic biaryl indanyl ketones **3** (R^1 = H, X = Aryl) lacking a stereogenic quaternary center were, according to our studies, in general more potent inhibitors than their (mono)aryl counterparts. Unfortunately, enantiomerically pure biaryl indanyl ketones of that type [11] underwent racemization through the corresponding enol under the conditions applied in the biochemical assay. Therefore, we decided to develop ketones without stereogenic center that form easily interconvertible atropisomers, assuming that the enzyme would incorporate preferably the better-fitting axially chiral stereoisomer. This requirement seems to be fulfilled in aryl or biaryl ketones and thioketones **4** (Y = O, S) with an additional 1-benzofuran, 1-benzothiophene, or 1*H*-indol moiety (X = O, S, MeN). Therein, an alkyl substituent C(2) was anticipated to prevent planarity of the aromatic rings, so that the concept of twisted ketones as mimics of the 'twisted amide' transition state **2** would be maintained in aryl hetaryl ketones and thioketones **4**. Thus, the series of aryl hetaryl ketones **11**, biaryl hetaryl ketones **10**, as well as thioketones **12** and **13** were synthesized, and the

inhibitory activities were determined on Pin1 and, additionally for one compound, on cyclophylin A.

Results and Discussion. – The heterocyclic starting materials **7** were either purchased or prepared by known procedures [12][1]). The *Friedel–Crafts* acylation of heterocycles **7** with the acyl chlorides **6**, obtained from commercially available carboxylic acids **5**, served for the preparation of the key intermediate ketones **8a**–**8h**. As expected, complete regiocontrol occurred in the acylation step, the heteroaromatic compounds being attacked at C(3) exclusively. The yields given in *Scheme 2* refer to two steps, and the lower yields observed in some cases are partly caused by demethylation occurring in the course of the *Friedel–Crafts* acylation. The corresponding phenolic ketones are readily removed by column chromatography, but isolated in the case of compound **11a** (see *Scheme 5*, below).

Scheme 2. *Synthesis of Key-Intermediate Ketones* **8**



	R^1	X			R^2	R^3	Y		R^1	R^2	R^3	Y	Yield [%]
5a	Br	OH	*i*)	**7a**	Me	H	O	**8a**	Br	Me	H	O	62
6a	Br	Cl		**7b**	Me	Me	O	**8b**	Br	Me	Me	O	65
5b	Me	OH	*i*)	**7c**	Me	$NC–CH_2$	O	**8c**	Br	Me	$NC–CH_2$	O	66
6b	Me	Cl		**7d**	Me	H	MeN	**8d**	Br	Me	H	MeN	35
5c	CF_3	OH	*i*)	**7e**	Me	H	S	**8e**	Br	Me	H	S	63
6c	CF_3	Cl		**7f**	Bu	H	S	**8f**	Br	Bu	H	S	74
								8g	Me	Me	Me	O	75
								8h	CF_3	Me	Me	O	12

i) $SOCl_2$, reflux, 3 h, 25°, 30 h. *ii*) $AlCl_3$, CH_2Cl_2, 25°, 30 h.

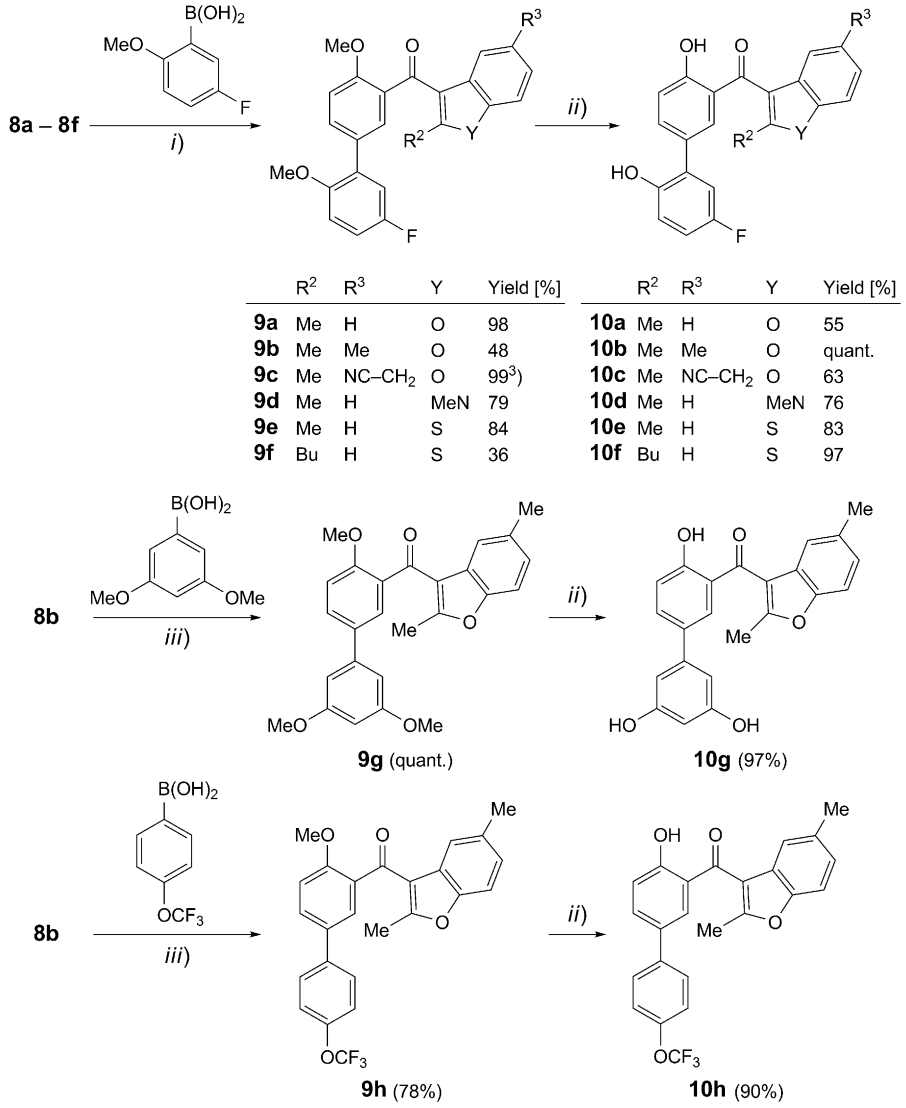
The substitution pattern of the aryl hetaryl ketones **8a**–**8f**, with Br in *para*-position to the MeO group, served as the key intermediates for the formation of a series of biaryl indanyl ketones, a structural motif that had proved as fruitful in the development of aryl indanyl ketones as PPIase inhibitors. Thus, *Suzuki* coupling reactions [13a][2]) of ketones **8a**–**8f** with (5-fluoro-2-methoxy)phenylboronic acid, (3,5-dimethoxy)phenylboronic acid, and (4-trifuoromethoxy)phenylboronic acid led to the formation of ketones **9a**–**9f**, **9g**, and **9h**, respectively. Complete cleavage of the phenolic ether groups occurred upon treatment with BBr_3, so that the ketones **10a**–**10h** were readily obtained (*Scheme 3*).

The Br-substituent in the ketone **8b** also allowed metal-catalyzed exchange reactions. Thus, a Pd-mediated reaction with potassium hexacyanoferrate(II) [14] led

[1]) 2-Butyl-1-benzothiophene (**7f**) was prepared by metallation of 1-benzothiophene with BuLi and subsequent treatment with 1-iodobutane.

[2]) A modified procedure was applied for the preparation of ketones **9c**, **9g**, and **9h** [13b].

Scheme 3. *Synthesis of Biaryl Hetaryl Ketones* **9** *by* Suzuki *Coupling and Deprotection to Phenols* **10**



	R^2	R^3	Y	Yield [%]
9a	Me	H	O	98
9b	Me	Me	O	48
9c	Me	NC–CH_2	O	99[3])
9d	Me	H	MeN	79
9e	Me	H	S	84
9f	Bu	H	S	36

	R^2	R^3	Y	Yield [%]
10a	Me	H	O	55
10b	Me	Me	O	quant.
10c	Me	NC–CH_2	O	63
10d	Me	H	MeN	76
10e	Me	H	S	83
10f	Bu	H	S	97

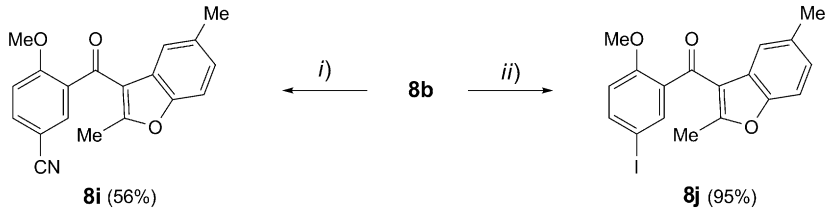
i) [Pd(dppf)Cl_2] (dppf = 1,1′-Bis(diphenylphosphino)ferrocene), $CsCO_3$, $MeO(CH_2)_2OMe/H_2O$ 1:1, reflux, 15 h. *ii*) BBr_3, CH_2Cl_2, −78° to 25°, 30 h. *iii*) $Pd(OAc)_2$, PPh_3, $PrOH/H_2O$ 5:1, reflux, 2 h; then 25°, 30 h.

to the formation of the nitrile **8i**. A Br/I exchange occurred upon treatment with NaI in the presence of CuI [15] to yield ketone **8j** (*Scheme 4*).

---

[3]) Modified conditions: $Pd(OAc)_2$, PPh_3, $PrOH/H_2O$ 5:1, reflux, 2 h, then: 25°, 30 h.

Scheme 4. *Synthesis of Aryl Hetaryl Ketones* **8j** *and* **8k**

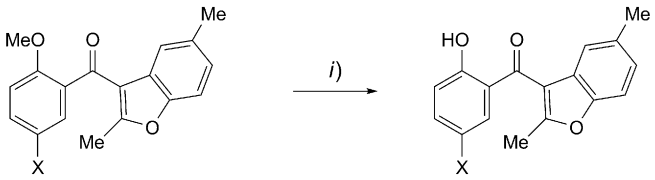


8i (56%) **8j** (95%)

i) [Pd(dppf)Cl_2], Na_2CO_3, $K_4[Fe(CN)_6]$, *N*-methylpyrrolidin-2-one (NMP), 120°, 20 h. *ii*) CuI, NaI, $MeNH(CH_2)_2NHMe$, 1,4-dioxane, reflux, 20 h.

The synthesis of phenolic compounds **11a**–**11e** featuring a monoaryl hetaryl ketone skeleton was again easily accomplished by demethylation of methoxy derivatives **8b** and **8g**–**8j** with BBr_3 (*Scheme 5*)[4]).

Scheme 5. *Synthesis of Monoaryl Hetaryl Ketones* **11a**–**11e**



			Y	Yield [%]
8b	Y = Br	**11a**	Br	[4])
8g	Y = Me	**11b**	Me	84
8h	Y = CF_3	**11c**	CF_3	77
8i	Y = CN	**11d**	CN	66
8j	Y = I	**11e**	I	80

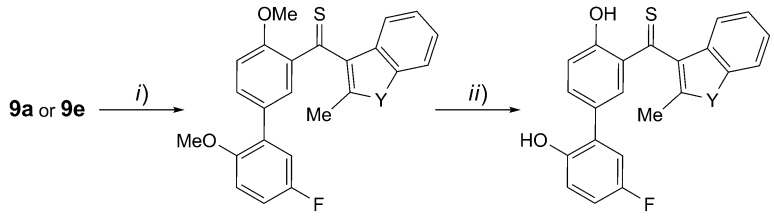
i) BBr_3, CH_2Cl_2, −78° to 25°, 30 h.

As we were interested whether the replacement of a C=O by a C=S moiety might be favorable for PPIase inhibition, selected ketones **9a** and **9e** were converted to thioketones **12a** and **12b**, respectively, by treatment with *Lawesson*'s reagent [16]. Here again, demethylation was performed with BBr_3 to give phenolic thioketones **13a** and **13b** (*Scheme 6*).

In addition to the analytical and spectroscopic characterization, the crystal structure of a representative biaryl indanyl ketone, **10b**, was determined. The structure shown in the *Figure* reveals a strong intramolecular H-bond of the chelated phenolic OH group with the C=O group. In addition, the OH substituent in *para*-position to the F-atom is engaged in the formation of a H-bridged dimer with a cyclic H-bond pattern $R_2^2(18)$ [17]. The crystal structure clearly reveals non-planarity of the 1-benzoforan ring and the phenyl residue at the CO group. The planes of both residues are twisted by *ca.* 53°, a value that results from the addition of the dihedral angle O1–C1–C12–C13 and O1–C1–C2–C9. Thus, the CO group is neither in plane with the phenyl nor with the

[4]) Obtained as a by-product in the *Friedel–Cratfs* acylation according to *Scheme 2.*

Scheme 6. *Synthesis of Thioketones* **12** *and* **13**



	Y	Yield [%]
12a	O	89
12b	S	73

	Y	Yield [%]
13a	O	64
13b	S	86

i) *Lawesson*'s reagent, toluene, reflux, 6 h. *ii*) BBr_3, $-78°$ to $25°$, 30 h.

furan ring. Although these ring skeletons are not arranged perpendicularly, their non-planarity might be sufficient to fulfil the requirement of mimicking the twisted-amide transition state **2**.

The inhibition of human Pin1 by biaryl hetaryl ketones **10a**–**10h**, monoaryl hetaryl ketones **11a**–**11e**, and thioketones **13a** and **13b** was determined in a protease-free PPIase assay with Suc-Ala-Glu-Pro-Phe-*p*-nitroanilide as the substrate [18]. As compiled in *Table 1*, all the compounds, except two, exhibit substantial inhibition of Pin1, most of them with K_i or IC_{50} values in the mono-digit μM range. First, a comparison of *Entries 1*, *4*, and *5* reveals that the heteroatom in the heterocyclic part only marginally influences the activity, in as far as that 1-benzofuran derivative **10a** (*Entry 1*) is as active as 1*H*-indole derivative **10d** (*Entry 4*), both being only slightly superior to the 1-benzothiophene derivative **10e** (*Entry 5*). The series of 1-benzofurans derivatives **10a**–**10c** (*Entries 1–3*) indicates that a lipophilic group (Me) at C(5) of the heterocyclic moiety seems to be more favorable than a polar one ($NCCH_2$). As indicated by the results of *Entries 5* and *6*, the size of the alkyl group at C(2) of the heterocycle has no substantial influence on the activity. It seems, when considering the crystal structure of compound **10b**, that a Me substituent is large enough to provide the

Table 1. *Inhibition Constants* K_i [μM] *or* IC_{50} *Values* [μM] (in brackets) *of Ketones* **10**–**11** *and Thioketones* **12** *and* **13**

Entry		K_i [μM] (IC_{50} [μM])	*Entry*		K_i [μM]
1	**10a**	2.10±0.27	*9*	**11a**	2.6±0.3
2	**10b**	(1.67±0.38)	*10*	**11b**	7.4±1.1
3	**10c**	(4.5±0.3)	*11*	**11c**	4.1±0.6
4	**10d**	2.22±0.51	*12*	**11d**	[a])
5	**10e**	3.70±0.66	*13*	**11e**	1.0±0.1
6	**10f**	3.66±0.86	*14*	**12a**	2.90±0.31
7	**10g**	(>10)	*15*	**13a**	1.80±0.21
8	**10h**	7.2±0.8	*16*	**13b**	0.60±0.17

[a]) Inactive.

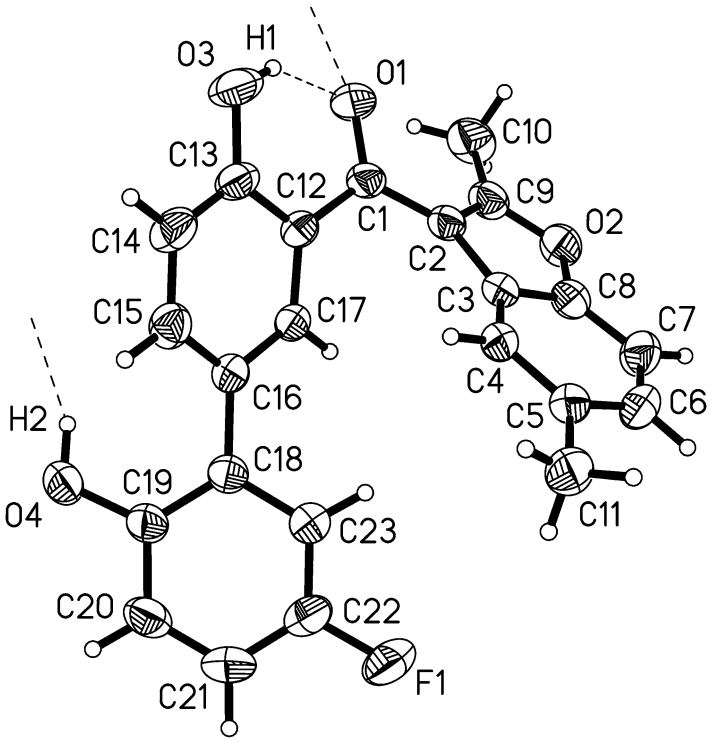


Figure. *Molecular structure of* **10b** *in the crystal.* Displacement ellipsoids are drawn at the 50% probability level, radii of H-atoms are chosen arbitrarily, and labels of H-atom bonded to C-atoms are omitted for clarity. Selected geometric parameters ([Å] and [°]): F1–C22, 1.369(3); O1–C1, 1.248(2); O2–C8, 1.385(3); O2–C9, 1.365(3); O3–C13, 1.357(3); O4–C19, 1.376(3); C1–C2, 1.468(3); C1–C12, 1.467(3); C2–C3, 1.458(3); C2–C9, 1.364(3); O1–C1–C2, 119.61(19); O1–C1–C12, 119.67(19); C2–C1–C12, 120.70(17); C1–C12–C13, 119.81(18); O3–C13–C12, 122.2(2); O4–C19–C18, 123.09(19); C2–C1–C12–C13, 154.52(19); O3–C13–C12–C1, 3.3(3); O1–C1–C12–C13, −23.6(3); O1–C1–C2–C9, −29.1(3); C1–C2–C9–C10, −4.6(4); C15–C16–C18–C19, 45.7(3); O3–H1, 0.93(3); H1···O1, 1.79(3); O3···O1, 2.610(3); O3–H1–O1, 145(3); O4–H2, 0.91(3), H2···O1, 1.98(4), O4···O1, 2.835(2); O4–H2–O1, 156(3) (symmetry code: $1-x$, $1-y$, $1-z$); dashed lines indicate the directions of H-bonding.

twisted conformation of the ketones. Concerning the residues in the biaryl moiety, the fluoro-phenolic pattern of ketones **10a**–**10f** is obviously superior to the CF_3O substituent in compound **10h** (*Entry 8*) and, in particular, to the accumulation of three phenolic OH groups in compound **10g** (*Entry 7*). As in the aryl indanyl ketone series, the ring-substituted biaryl pattern was always favorable for Pin1 inhibition, we were interested whether – in the aryl hetaryl ketones described here – the switch from the biaryl to the monoaryl pattern would influence the inhibitory activitiy. Generally, highly substituted ring systems were found to lead to potent non-peptidic Pin1 inhibitors [19].

It turned out that four out of the five monoaryl derivatives **11a**–**11e** act as inhibitors (*Entries 9–11* and *13*). The only exception is the benzonitrile **11d** (*Entry 12*) that did

not show any activity. Surprisingly, the replacement of the 'pseudohalogen' cyanide by Br (*Entry 9*) or I (*Entry 13*) leads to a remarkable enhancement of inhibition. The result of the latter compound, **11e**, with a K_i value of 1.0 μM indicates that the biaryl pattern is in this series of compounds not crucial for inhibitory activity.

Finally, the CO group was replaced by CS in compounds **12a**, **13a**, and **13b**, all of which were found to be inhibitors. A comparison of compounds **12a** and **13a** (*Entries 14* and *15*) clearly shows that the free phenolic group in the carboaromatic moiety is favorable, but not crucial for activity. Thioketone **13b**, finally, exhibits the highest inhibitory of the whole series, with its K_i value amounting to 0.6 μM (*Entry 16*). As it was considered the most promising compound, it was also tested for the inhibition of the PPIase cyclophylin A. Here also, thioketone **13b** provided inhibitory activity, the IC_{50} value amounting to 3.21 ± 0.38 μM. The finding that the large majority of the compounds prepared and tested act as PPIase inhibitors might support the hypothesis that the ketones are mimicking the 'twisted amide' transition state **2**.

Conclusions. – Based on the concept that aryl hetaryl ketones and thioketones have a non-planar arrangement of the aromatic moieties at the CO or CS group and, therefore, might function as transition-state analogs, a series of new potent inhibitors of human Pin1 have been synthesized. In view of their relatively simple structures, the inhibitory potency of the aryl hetaryl ketones and thioketones is remarkable, and it makes them suitable cell-penetrating agents for further biochemical studies, and promising candidates not only for the inhibition of Pin1 but also of cyclophilins.

We gratefully acknowledge the support of this work by *Deutsche Forschungsgemeinschaft* (Br 604/17-1,2)

Experimental Part

General. Toluene was freshly distilled from Na under N_2. THF and Et_2O were freshly distilled from Na with benzophenone as indicator under N_2. CH_2Cl_2 was freshly distilled from NaH under N_2. Other solvents were used as purchased. Column chromatography (CC): *Fluka* silica gel *60* (SiO_2; 230–400 mesh). TLC: *Merck* TLC silica gel *60 F254* aluminium sheets. M.p. (not corrected): *Büchi 540* melting-point apparatus. NMR Spectra ($CDCl_3$): *Bruker Avance DRX 200*, *DRX 300*, and *DRX 500* spectrometers. MS: *Thermo Finnigan Trace DSQ* apparatus (GC/MS), ion-trap *API* mass spectrometer *Finnigan LCQ Deca* (ESI), triple-quadrupole-mass spectrometer *Finnigan TSQ 7000* (EI), and sector field mass spectrometer *Finnigan MAT 8200* (EI, 70 eV), HR-MS: *FT-ICR APEX III* (7.0 T; MALDI), *Bruker UHR-QTOF maxis 4G* (ESI).

General Procedure for the Preparation of Ketones **8a**–**8h**. A mixture of the carboxylic acid **5** (4.33 mmol) and $SOCl_2$ (10 ml) was refluxed for 3 h in a 25-ml flask equipped with a magnetic stirrer and a reflux condenser with a drying tube. After stirring at r.t. overnight, the remaining $SOCl_2$ was removed by evaporation with an oil pump. The residual acid chloride **6** was used without further purification.

A 25-ml two-necked flask, equipped with a magnetic stirrer, a reflux condenser with a drying tube, and a pressure-equalizing dropping-funnel with a stopper was charged with $AlCl_3$ (0.659 g, 4.94 mmol) and CH_2Cl_2 (3 ml). The mixture was cooled in an ice bath, and a soln. of the crude acid chloride **6** (4.33 mmol), prepared as described above, in CH_2Cl_2 (4 ml) was added under vigorous stirring. Finally, a soln. of the heteroaromatic compound **7** (4.12 mmol) in CH_2Cl_2 (3 ml) was added dropwise at 0°. After stirring at r.t. for 25 h, the mixture was poured on to ice. In case of formation of a precipitate, it was dissolved by careful addition of conc. HCl. The layers were separated, and the aq. phase was extracted three times with CH_2Cl_2. The combined org. layers were washed with H_2O, 2% aq. NaOH, and H_2O, and

dried (Na_2SO_4). The crude products **8** obtained after evaporation of the solvent were purified by CC (yields refer to compounds **7**).

(*5-Bromo-2-methoxyphenyl)(2-methyl-1-benzofuran-3-yl)methanone* (**8a**). From **6a** (1.08 g, 4.33 mmol), **7a** (544.5 mg, 4.12 mmol), $AlCl_3$ (659 mg, 4.94 mmol), and CH_2Cl_2 (10 ml). Yield: 885 mg (62%). Yellow solid. R_f ($CHCl_3$) 0.63. M.p. 98–101°. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.5 (*s*, 3 H); 3.69 (*s*, 3 H); 6.80 (*d*, *J* = 8.8, 1 H); 7.19–7.22 (*m*, 1 H); 7.27–7.29 (*m*, 1 H); 7.43–7.46 (*m*, 1 H); 7.49 (*d*, *J* = 2.5, 1 H), 7.58 (*dd*, *J* = 2.5, *J* = 8.8, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 14.8; 56.0; 110.8; 113.1; 113.3; 117.6; 121.2; 124.0; 124.5; 126.2; 131.3; 132.5; 134.5; 153.5; 156.0; 163.9; 189.4. GC/EI-MS (70 eV): 346, 344 (75, M^+), 315, 313 (20), 265 (35), 234 (70), 215, 213 (40), 159 (100), 131 (25). Anal. calc. for $C_{17}H_{13}BrO_3$ (345.19): C 59.15, H 3.80; found: C 59.16, H 3.86.

(*5-Bromo-2-methoxyphenyl)(2,5-dimethyl-1-benzofuran-3-yl)methanone* (**8b**) From **6a** (3.23 g, 12.93 mmol), **7b** (1.8 g, 12.31 mmol), $AlCl_3$ (1.97 g, 14.77 mmol), and CH_2Cl_2 (30 ml). Yield: 2.89 g (65%). Yellow solid. R_f ($CHCl_3$) 0.54 . M.p. 110–113°. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.39 (*s*, 3 H); 2.41 (*s*, 3 H); 3.7 (*s*, 3 H); 6.89 (*d*, *J* = 8.8, 1 H); 7.08 (*dd*, *J* = 1.4, 8.4, 1 H); 7.31 (*d*, *J* = 8.4, 1 H); 7.4 (*s*, 1 H); 7.47 (*d*, *J* = 2.5, 1 H); 7.6 (*dd*, *J* = 2.5, 8.8, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 14.8; 21.4; 56.0; 110.2; 113.0; 113.3; 117.5; 121.3; 125.6; 126.2; 131.3; 132.6; 133.6; 134.4; 152.0; 155.9; 164.0; 189.5. GC/EI-MS (70 eV): 360, 358 (40, M^+), 329, 327 (14), 279 (24), 264 (18), 248 (62), 215, 213 (42), 173 (100), 145 (32). Anal. calc. for $C_{18}H_{15}BrO_3$ (359.21): C 60.18, H 4.21; found: C 59.94, H 4.37.

[3-(5-Bromo-2-methoxybenzoyl)-2-methyl-1-benzofuran-5-yl]acetonitrile (**8c**) From **6a** (793 mg, 3.18 mmol), **7c** (519 mg, 3.03 mmol), $AlCl_3$ (485 mg, 3.64 mmol), and CH_2Cl_2 (12 ml). Yield: 765 mg (66%). Colorless solid. R_f ($CHCl_3$) 0.54. M.p. 143–146°. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.46 (*s*, 3 H); 3.71 (*s*, 3 H); 3.77 (*s*, 2 H); 6.91 (*d*, *J* = 8.3, 1 H); 7.24–7.25 (*m*, 1 H); 7.44 (*d*, *J* = 8.4, 1 H); 7.49 (*d*, *J* = 2.3, 1 H); 7.53 (*s*, 1 H); 7.60 (*dd*, *J* = 2.4, 8.8, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 14.8; 23.6; 56.0; 111.4; 113.0; 113.2; 113.3; 117.5; 118.1; 121.0; 124.3; 125.8; 127.0; 131.3; 132.1; 134.8; 153.0; 156.9; 164.9; 189.2. GC/EI-MS (70 eV): 385, 383 (84, M^+), 354, 352 (18), 304 (40), 273 (40), 215, 213 (58), 198 (100), 185 (36), 170 (34), 115 (30). Anal. calc. for $C_{19}H_{14}BrNO_3$ (384.22): C 59.39, H 3.67, N 3.65; found: C 59.33, H 3.82, N 3.40.

(*5-Bromo-2-methoxyphenyl)(1,2-dimethyl-1*H*-indol-3-yl)methanone* (**8d**) From **6a** (1.08 g, 4.33 mmol), **7d** (598 mg, 4.12 mmol), $AlCl_3$ (659 mg, 4.94 mmol), and CH_2Cl_2 (10 ml). Yield: 509 mg (35%). Colorless solid. R_f (hexane/AcOEt 1:1) 0.35. M.p. 174–177°. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.62 (*s*, 3 H); 3.71 (*s*, 3 H); 3.73 (*s*, 3 H); 6.89 (*d*, *J* = 8.8, 1 H); 7.07–7.10 (*m*, 1 H); 7.20–7.24 (*m*, 1 H); 7.30–7.32 (*m*, 1 H); 7.41 (*d*, *J* = 2.5, 1 H); 7.54 (*dd*, *J* = 2.5, 8.8, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 12.5; 29.7; 56.0; 109.2; 113.0; 113.4; 113.8; 120.6; 122.2; 122.3; 126.8; 131.0; 133.2; 134.6; 146.4; 155.6; 189.2. EI-MS (70 eV): 359, 357 (34, M^+), 328, 326 (23), 247 (46), 172 (100), 144 (35). Anal. calc. for $C_{18}H_{16}BrO_2$ (358.23): C 60.35, H 4.50, N 3.91; found: C 60.29, H 4.51, N 3.90.

(5-Bromo-2-methoxyphenyl)(2-methyl-1-benzothiophen-3-yl)methanone (**8e**). From **6a** (1.08 g, 4.33 mmol), **7e** (611 mg, 4.12 mmol), $AlCl_3$ (659 mg, 4.94 mmol), CH_2Cl_2 (10 ml). Yield: 931 mg (63%). Yellow solid. R_f ($CHCl_3$) 0.5. M.p. 86–91°. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.49 (*s*, 3 H); 3.62 (*s*, 3 H); 6.85 (*d*, *J* = 9.5, 1 H); 7.29–7.31 (*m*, 2 H); 7.57–7.75 (*m*, 4 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 16.1; 56.1; 113.1; 113.7; 121.6; 123.3; 124.4; 125.0; 128.4; 129.2; 132.4; 135.4; 137.1; 138.7; 150.0; 156.8; 189.8. GC/EI-MS (70 eV): 362, 360 (45, M^+), 331, 329 (15), 281 (50), 266 (30), 250 (75), 215, 213 (25), 175 (100), 147 (85). Anal. calc. for $C_{17}H_{13}BrO_2S$ (361.25): C 56.52, H 3.63; found: C 56.38, H 3.62.

(5-Bromo-2-methoxyphenyl)(2-butyl-1-benzothiophen-3-yl)methanone (**8f**). From **6a** (1.62 g, 6.49 mmol), **7f** (1.18 g, 6.18 mmol), $AlCl_3$ (988 mg, 7.41 mmol), and CH_2Cl_2 (15 ml). Yield: 1.84 g (74%). Yellow oil. R_f ($CHCl_3$) 0.61. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.86 (*t*, *J* = 7.3, 3 H); 1.30 (*sext.*, *J* = 7.4, 2 H); 1.66 (*quint.*, *J* = 7.6, 2 H); 2.87 (*t*, *J* = 7.7, 2 H); 3.60 (*s*, 3 H); 6.84 (*d*, *J* = 8.6, 1 H); 7.22–7.30 (*m*, 2 H); 7.57–7.60 (*m*, 3 H); 7.75–7.77 (*m*, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 13.7; 22.4; 29.6; 33.9; 56.02; 113.0; 113.7; 121.7; 123.0; 124.2; 124.8; 132.1; 132.3; 132.7; 135.5; 137.3; 138.6; 155.2; 157.1; 190.0. EI-MS (70 eV): 404, 402 (40, M^+), 373, 371 (35), 323 (17), 292 (22), 280 (34), 215, 213 (100), 147 (68), 133 (37). Anal. calc. for $C_{20}H_{19}BrO_2S$ (403.33): C 59.56, H 4.75; found: C 59.34, H 5.01.

(2,5-Dimethyl-1-benzofuran-3-yl)(2-methoxy-5-methylphenyl)methanone (**8g**). From **6b** (530 mg, 2.87 mmol), **7b** (400 mg, 2.74 mmol), $AlCl_3$ (438 mg, 3.28 mmol), and CH_2Cl_2 (10 ml). Yield: 603 mg (75%). Yellow solid. R_f ($CHCl_3$) 0.46. M.p. 111–112°. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.33 (*s*, 3 H); 2.37 (*s*, 3 H); 2.38 (*s*, 3 H); 3.68 (*s*, 3 H); 6.88 (*d*, *J* = 8.4, 1 H); 7.06 (*d*, *J* = 8.3, 1 H); 7.17 (*d*, *J* = 1.8, 1 H); 7.26–7.28

(*m*, 1 H); 7.29 (*d*, *J* = 8.3, 1 H); 7.43 (*s*, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 14.6; 20.4; 21.4; 55.8; 110.0; 111.4; 117.9; 121.5; 125.4; 126.6; 129.1; 130.2; 130.7; 132.2; 133.3; 151.9; 154.8; 163.5; 191.6. GC/EI-MS (70 eV): 294 (88, M^+), 279 (74), 263 (58), 248 (22), 173 (38), 160 (18), 149 (100), 145 (20), 135 (22), 91 (40). Anal. calc. for $C_{19}H_{13}O_3$ (294.34): C 77.53, H 6.16; found: C 77.40, H 6.25.

(*2,5-Dimethyl-1-benzofuran-3-yl)[2-methoxy-5-(trifluoromethyl)phenyl]methanone* (**8h**). From **6c** (857 mg, 3.59 mmol), **7b** (500 mg, 3.42 mmol), $AlCl_3$ (547 mg, 4.10 mmol), and CH_2Cl_2 (15 ml). Yield: 140 mg (12%). Yellow oil. R_f ($CHCl_3$) 0.75 . ^{1}H-NMR (500 MHz, $CDCl_3$): 2.37 (*s*, 3 H); 2.40 (*s*, 3 H); 3.79 (*s*, 3 H); 7.08 (*d*, *J* = 8.6, 2 H); 7.32 (*d*, *J* = 8.4, 1 H); 7.34 (*s*, 1 H); 7.64 (*d*, *J* = 2.1, 1 H); 7.76 (*dd*, *J* = 2.1, 8.7, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 14.8; 21.4; 56.1; 109.1; 110.2; 111.4; 117.5; 121.3; 125.7; 126.2; 128.6; 129.0; 131.1; 131.2; 133.7; 152.0; 164.1; 168.9; 197.7. GC/EI-MS (70 eV): 348 (100, M^+), 317 (60), 305 (6), 279 (6), 248 (4), 203 (84), 173 (56), 160 (28), 145 (38), 115 (20). Anal. calc. for $C_{19}H_{15}F_3O_3$ (348.32): C 65.52, H 4.34; found: C 65.25, H 4.17.

General Procedure for the Preparation of Ketones **9a** *and* **9b***, and* **9d**–**9f**. A 100-ml two-necked flask, equipped with a magnetic stirrer, a reflux condenser, and a connection to the combined N_2/vacuum line, was charged with ketone **8** (1.45 mmol), (5-fluoro-2-methoxyphenyl)boronic acid, $CsCO_3$ (1.18 g, 3.6 mmol), and [Pd(dppf)Cl_2] (dppf = 1,1′-bis(diphenylphosphio)ferrocene) (58.25 mg, 0.0725 mmol). The flask was closed with a septum, and the air in the flask was replaced by N_2. A 3 : 1 mixture of 1,2-dimethoxyethane and H_2O (62.5 ml) was injected through the septum, and the mixture was refluxed under vigorous stirring for 15 h. After cooling to r.t., H_2O was added, and the mixture was extracted three times with $CHCl_3$. The combined org. layers were dried (Na_2SO_4), and the solvent was removed in a rotary evaporator. The crude products **9a** and **9b** and **9d**–**9g** thus obtained were purified by CC.

(*5′-Fluoro-2′,4-dimethoxy-1,1′-biphenyl-3-yl)(2-methyl-1-benzofuran-3-yl)methanone* (**9a**). From **8a** (500 mg,1.45 mmol), (5-fluoro-2-methoxyphenyl)boronic acid (246.4 mg, 1.45 mmol), Cs_2CO_3 (1.18 g, 3.63 mmol), [Pd(dppf)Cl_2] (58.25 mg, 0.0725 mmol), and 1,2-dimethoxyethane/H_2O 3 : 1 (62.5 ml). Yield: 558 mg (98%). Yellow oil. R_f (hexane/AcOEt 1 : 1) 0.58. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.52 (*s*, 3 H); 3.71 (*s*, 3 H); 3.77 (*s*, 3 H); 6.86 (*dd*, *J*(H,F) = 4.5, *J*(H,H) = 8.9, 1 H); 6.96 (*td*, *J*(H,H) = 3.1, *J*(H,F) = 8.3, 1 H); 7.02–7.06 (*m*, 3 H); 7.19–7.28 (*m*, 2 H); 7.43 (*d*, *J* = 8.2, 1 H); 7.57 (*d*, *J* = 1.7, 1 H); 7.62 (*dd*, *J* = 1.7, *J* = 8.6, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 14.7; 55.8; 56.1; 110.6; 111.3; 112.3 (*d*, *J*(C,F) = 8.6); 114.2 (*d*, *J*(C,F) = 22.7); 117.0 (*d*, *J*(C,F) = 23.2); 118.0; 121.5; 123.8; 124.3; 126.5; 130.0; 130.3; 132.7; 152.6; 153.5; 156.2; 163.7; 191.0. EI-MS (70 eV): 390 (100, M^+), 359 (32), 265 (58), 159 (92). Anal. calc. for $C_{24}H_{19}FO_4$ (390.40): C 73.84, H 4.91; found: C 73.67, H 5.01.

(*2,5-Dimethyl-1-benzofuran-3-yl)(5′-fluoro-2′,4-dimethoxy-1,1′biphenyl-3-yl)methanone* (**9b**). From **8b** (2.0 g,5.57 mmol), (5-fluoro-2-methoxy-1,1′-phenyl)boronic acid (946.2 mg, 5.57 mmol), Cs_2CO_3 (4.53 g, 13.93 mmol), [Pd(dppf)Cl_2] (223.8 mg, 0.278 mmol), and 1,2-dimethoxyethane/H_2O 3 : 1 (240 ml). Yield: 1.08 g (48%). Yellow solid. R_f (hexane/AcOEt 3 : 1) 0.5. M.p. 159–161°. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.38 (*s*, 3 H); 2.43 (*s*, 3 H); 3.72 (*s*, 3 H); 3.79 (*s*, 3 H); 6.85–6.88 (*m*, 1 H); 6.96 (*td*, *J*(H,H) = 3.0, *J*(H,F) = 8.6, 1 H); 7.02–7.08 (*m*, 3 H); 7.30 (*d*, *J* = 8.3, 1 H); 7.45 (*s*, 1 H); 7.55 (*d*, *J* = 2.0, 1 H); 7.63 (*dd*, *J* = 2.0, *J* = 8.7, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 14.7; 21.4; 55.9; 56.1; 110.0; 111.3; 112.4 (*d*, *J*(C,F) = 8.4); 114.2 (*d*, *J*(C,F) = 22.7); 117.0 (*d*, *J*(C,F) = 23.5); 117.8; 121.7; 125.5; 126.6; 129.9; 130.1; 130.4; 130.7; 132.6; 133.4; 152.0; 152.6; 156.1; 163.9; 191.1. EI-MS (70 eV): 404 (46, M^+), 389 (12), 373 (17), 279 (27), 259 (17), 173 (37), 145 (13), 135 (100). Anal. calc. for $C_{25}H_{21}FO_4$ (404.43): C 74.24, H 5.23; found: C 74.06, H 5.35.

*(1,2-Dimethyl-1*H*-indol-3-yl)(5′-fluoro-2′,4-dimethoxy-1,1′-biphenyl-3-yl)methanone* (**9d**). From **8d** (400 mg,1.12 mmol), (5-fluoro-2-methoxyphenyl)boronic acid (190 mg, 1.12 mmol), Cs_2CO_3 (910 mg, 2.8 mmol), [Pd(dppf)Cl_2] (45.0 mg, 0.056 mmol), and 1,2-dimethoxyethane/H_2O 3 : 1 (48 ml). Yield: 356 mg (79%). White solid. R_f (hexane/AcOEt 1 : 1) 0.25. M.p. 170–171°. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.64 (*s*, 3 H); 3.68 (*s*, 3 H); 3.73 (*s*, 3 H); 3.79 (*s*, 3 H); 6.84 (*dd*, *J*(H,F) = 4.5, *J*(H,H) = 8.9, 1 H); 6.91–6.95 (*m*, 1 H); 7.01 (*dd*, *J* = 3.1, *J*(H,F) = 9.1, 1 H); 7.05–7.09 (*m*, 2 H); 7.18–7.21 (*m*, H); 7.29–7.34 (*m*, H); 7.48 (*d*, *J* = 2.1, 1 H); 7.60 (*dd*, *J* = 2.1, *J* = 8.5, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 12.5; 29.6; 55.9; 56.2; 109.0; 111.3; 112.4 (*d*, *J*(C,F) = 8.6); 113.9 (*d*, *J*(C,F) = 22.5); 117.0; 121.0; 122.0 (*d*, *J*(C,F) = 20.8); 127.0; 129.7; 129.9; 131.2; 136.7; 139.9; 141.7; 157.0 (*d*, (C,F) = 268.4); 164.6; 173.7; 191.0. EI-MS (70 eV): 403 (62, M^+), 372 (90), 357 (15), 278 (50), 172 (100), 145 (56). HR-EI-MS: 403.1573 (M^+, $C_{25}H_{22}FNO_3^+$; calc. 403.1584).

(5′-Fluoro-2′,4-dimethoxy-1,1′-biphenyl-3-yl)(2-methyl-1-benzothiophen-3-yl)methanone (**9e**). From **8e** (500 mg,1.38 mmol), (5-fluoro-2-methoxyphenyl)boronic acid (235.2 mg, 1.38 mmol), Cs_2CO_3 (1.13 g, 3.46 mmol), [Pd(dppf)Cl_2] (55.6 mg, 0.069 mmol), and 1,2-dimethoxyethane/H_2O 3:1 (60 ml). Yield: 474 mg (84%). Yellow oil. R_f (hexane/AcOEt 1:1) 0.61. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.51 (*s*, 3 H); 3.68 (*s*, 3 H); 3.74 (*s*, 3 H); 6.84–7.82 (*m*, 10 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 16.0; 55.8; 56.0; 111.7; 112.2 (*d*, *J*(C,F) = 8.4); 114.2 (*d*, *J*(C,F) = 22.7); 117.0 (*d*, *J*(C,F) = 23.6); 121.5; 123.6; 124.2; 124.9; 129.9; 130.0; 130.4 (*d*, *J*(C,F) = 7.6); 131.4; 133.0; 133.7; 137.2; 139.0; 149.1; 152.5 (*d*, *J*(C,F) = 1.7); 157.1 (*d*, *J*(C,F) = 238.7); 157.2; 191.3. GC/EI-MS (70 eV): 406 (100, M^+), 391 (25), 375 (25), 281 (45), 175 (80), 147 (85). Anal. calc. for $C_{24}H_{19}FO_3S$ (406.47): C 70.92, H 4.71; found: C 70.55, H 4.69.

(2-Butyl-1-benzothiophen-3-yl)(5′-fluoro-2′,4-dimethoxy-1,1′-biphenyl-3-yl)methanone (**9f**). From **8f** (920 mg, 2.28 mmol), (5-fluoro-2-methoxyphenyl)boronic acid (387.5 mg, 2.28 mmol), Cs_2CO_3 (1.85 g, 5.7 mmol), [Pd(dppf)]Cl_2] (91.6 mg, 0.114 mmol), and 1,2-dimethoxyethane/H_2O 3:1 (98 ml). Yield: 366 mg (36%). Yellow oil. R_f (hexane/AcOEt 3:1) 0.42. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.84 (*t*, *J* = 7.3, 3 H); 1.25–1.34 (*m*, 2 H); 1.66 (*quint.*, *J* = 7.6, 2 H); 2.90 (*t*, *J* = 7.8, 2 H); 3.66 (*s*, 3 H); 3.71 (*s*, 3 H); 6.83–6.86 (*m*, 1 H); 6.93–7.03 (*m*, 3 H); 7.27–7.29 (*m*, 2 H); 7.64–7.67 (*m*, 3 H); 7.75–7.77 (*m*, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 13.7; 22.4; 29.6; 33.9; 55.9; 56.0; 11.6; 12.2 (*d*, *J*(C,F) = 8.7); 114.2 (*d*, *J*(C,F) = 22.6); 117.0 (*d*, *J*(H,F) = 23.6); 121.6; 123.4; 124.0; 124.7; 129.7; 129.9; 131.7; 133.0; 134.0; 137.3; 138.9; 152.0; 154.3; 156.1; 157.5; 158.0; 191.6. EI-MS (70 eV): 448 (34, M^+), 417 (16), 405 (36), 281 (25), 259 (53), 161 (50), 135 (100). Anal. calc. for $C_{27}H_{25}FO_3S$ (448.55): C 72.30, H 5.62; found: C 72.23, H 5.62.

General Procedure for the Preparation of Ketones **9c**, **9g**, *and* **9h**. A 25-ml two-necked, flask, equipped with a magnetic stirrer and a connection to the combined N_2/vacuum line, was charged with ketone **8** (0.26 mmol), arylboronic acid (0.274 mmol), and PrOH (5 ml). After the flask has been flushed with N_2, a mixture of $Pd(OAc)_2$ (0.18 mg, 0.78 μmol), PPh_3 (0.615 mg, 2.34 μmol), Na_2CO_3 (0.033 g, 0.312 mmol), and H_2O (1 ml) was added. The soln. was refluxed for 2 h and then stirred at r.t. overnight. After the addition of H_2O, the mixture was extracted three times with AcOEt. The combined org. layers were dried (Na_2SO_4), and the solvent was removed *in vacuo* to give crude product **9** that was submitted to CC.

{3-[(5′-Fluoro-2′,4-dimethoxy-1,1′-biphenyl-3-yl)carbonyl]-2-methyl-1-benzofuran-5-yl}acetonitrile (**9c**). From **8c** (100 mg, 0.26 mmol), (5-fluoro-2-methoxyphenyl)boronic acid (46.6 mg, 0.27 mmol), Na_2CO_3 (33 mg, 0.31 mmol), $Pd(OAc)_2$ (0.18 mg, 0.78 μmol), PPh_3 (0.62 mg, 2.34 μmol), and PrOH/H_2O 5:1 (6 ml). Yield: 111 mg (99%). Yellow solid. R_f ($CHCl_3$) 0.26. M.p. 164–166°. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.47 (*s*, 3 H); 3.73 (*s*, 3 H); 3.77 (*s*, 2 H); 3.78 (*s*, 3 H); 6.86–6.88 (*m*, 1 H); 6.97 (*td*, *J*(H,H) = 3.1, *J*(H,F) = 8.9, 1 H); 7.04–7.05 (*m*, 1 H); 7.07 (*d*, *J* = 8.7, 1 H); 7.24–7.26 (*m*, 1 H); 7.44 (*d*, *J* = 8.5, 1 H); 7.57 (*d*, *J* = 2.3, 1 H); 7.60 (*s*, 1 H); 7.65 (*dd*, *J* = 2.3, *J* = 8.6, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 14.7; 23.6; 55.8; 56.1; 111.3; 112.3 (*d*, *J*(C,F) = 8.3); 114.3 (*d*, *J*(C,F) = 22.7); 117.1 (*d*, *J*(C,F) = 23.1); 118.1; 121.4; 124.1; 125.6; 127.4; 129.8; 129.9; 130.2; 130.5; 133.0; 152.6; 153.1; 157.1 (*d*, *J*(C,F) = 246.4); 158.1; 164.7; 190.8. EI-MS (70 eV): 429 (1, M^+), 304 (14), 277 (100), 259 (18), 201 (24), 173 (32), 149 (26), 133 (25). HR-ESI-MS: 430.1451 ($[M+H]^+$, $C_{26}H_{21}FNO_4^+$; calc. 430.1449).

(2,5-Dimethyl-1-benzofuran-3-yl)(3′,4,5′-trimethoxy-1,1′-biphenyl-3-yl)methanone (**9g**). From **8b** (500 mg, 1.39 mmol), (3,5-dimethoxyphenyl)boronic acid (266 mg, 1.46 mmol), Na_2CO_3 (176 mg, 1.67 mmol), $Pd(OAc)_2$ (1.0 mg, 4.17 μmol), PPh_3 (3.3 mg, 12.51 μmol), PrOH/H_2O 5:1 (24 ml). Yield: 615 mg (quant.). Yellow solid. R_f ($CHCl_3$) 0.36. M.p. 144–146°. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.38; 2.42 (*s*, 3 H); 3.78 (*s*, 3 H); 3.82 (*s*, 6 H); 6.44 (*t*, *J* = 2.2, 1 H); 6.69 (*d*, *J* = 2.2, 2 H); 7.06 (*d*, *J* = 8.6, 1 H); 7.07 (*dd*, *J* = 1.8, 8.3, 1 H); 7.31 (*d*, *J* = 8.3, 1 H); 7.45 (*s*, 1 H); 7.60 (*d*, *J* = 2.4, 1 H); 7.70 (*d*, *J* = 2.4, 8.6, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 14.8; 21.5; 55.4; 55.9; 99.2; 99.3; 104.9; 105.4; 105.6; 110.1; 111.8; 117.8; 121.5; 125.5; 126.5; 127.4; 130.3; 142.0; 152.0; 156.5; 161.1; 163.9; 191.2. EI-MS (70 eV): 416 (100, M^+), 401 (14), 385 (50), 360 (21), 279 (37), 257 (36), 173 (31), 159 (11), 145 (11). HR-ESI-MS: 417.1696 ($[M+H]^+$, $C_{26}H_{25}O_5^+$; calc. 417.1697).

(2,5-Dimethyl-1-benzofuran-3-yl)[4-methoxy-4′-(trifluoromethoxy)-1,1′-biphenyl-3-yl]methanone (**9h**). From **8b** (500 mg, 1.39 mmol), [4-(trifluoromethoxy)phenyl]boronic acid (300.7 mg, 1.46 mmol), Na_2CO_3 (176 mg, 1.67 mmol), $Pd(OAc)_2$ (1.0 mg, 4.17 μmol), PPh_3 (3.3 mg, 12.51 μmol), and PrOH/H_2O 5:1 (24 ml). Yield: 478 mg (78%). Yellow solid. R_f ($CHCl_3$) 0.58. M.p. 116–117°. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.37 (*s*, 3 H), 2.43 (*s*, 3 H), 3.78 (*s*, 3 H), 7.08 (*d*, *J* = 8.3, 1 H); 7.08 (*d*, *J* = 8.7, 1 H); 7.25–7.27 (*m*,

2 H); 7.31 (*d*, *J* = 8.4, 1 H); 7.42 (*s*, 1 H); 7.55–7.58 (*m*, 2 H); 7.28 (*d*, *J* = 2.4, 1 H); 7.68 (*dd*, *J* = 2.4, *J* = 8.6, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 14.8; 21.4; 55.0; 110.2; 112.0; 117.8; 118.8; 121.4; 121.4; 125.6; 126.4; 127.3; 128.0; 130.2; 131.3; 132.5; 133.5; 138.6; 148.5; 152.0; 156.6; 163.9; 191.0. EI-MS (70 eV): 440 (100, M^+), 425 (16), 409 (75), 370 (16), 351 (13), 314 (36), 297 (41), 295 (70), 252 (20), 225 (15), 189 (31), 173 (68), 159 (36). HR-ESI-MS: 441.1309 ($[M+H]^+$, $C_{25}H_{20}F_3O_4^+$; calc. 441.1308).

3-[(2,5-Dimethyl-1-benzofuran-3-yl)carbonyl]-4-methoxybenzonitrile (**8i**). A 50-ml two-necked flask, equipped with a magnetic stirrer and a connection to the combined N_2/vacuum line, was charged with **8b** (0.637 g, 1.77 mmol), Na_2CO_3 (0.188 g, 1,77 mmol), $[Pd(dppf)Cl_2]$ (0.013 g, 0.0177 mmol), and pre-dried $K_4[Fe(CN)_6]$ (0.162 g, 0.44 mmol). The flask was closed with a septum, and the air in the flask was replaced by N_2. After the addition of *N*-methylpyrrolidin-2-one (20 ml), the soln. was refluxed to 120° for 20 h, cooled to r.t. and diluted with H_2O, brine, and CH_2Cl_2. The layers were separated. The org. phase was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by CC to give (300 mg, 56%). Yellow solid. **8i**. R_f ($CHCl_3$) 0.33. M.p. 151–153°. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.37 (*s*, 3 H); 2.43 (*s*, 3 H); 3.8 (*s*, 3 H); 7.08 (*d*, *J* = 8.7, 1 H); 7.08–7.10 (*m*, 1 H); 7.26 (*s*, 1 H); 7.32 (*d*, *J* = 8.4, 1 H); 7.66 (*d*, *J* = 2.1, 1 H); 7.80 (*dd*, *J* = 2.1, 8.7, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 14.9; 21.5; 56.2; 105.5; 110.4; 112.1; 117.3 (CN); 118.3; 121.0; 125.9; 125.9; 132.0; 132.5; 133.8; 136.0; 152.0; 159.9; 164.3; 188.6. GC/EI-MS (70 eV): 305 (100, M^+), 274 (60), 173 (50), 160 (75), 145 (40), 117 (35), 102 (20). Anal. calc. for $C_{19}H_{15}NO_3$ (305.33): C 74.74, H 4.95, N 4.59; found: C 74.55, H 5.23, N 4.41.

(2,5-Dimethyl-1-benzofuran-3-yl)(5-iodo-2-methoxyphenyl)methanone (**8j**). A 50-ml two-necked flask, equipped with a magnetic stirrer, a reflux condenser, and a connection to the combined N_2/vacuum line, was charged with **8b** (1.00 g, 2.78 mmol), CuI (0.0265 g, 0.139 mmol), and NaI (0.828 g, 5.56 mmol). The flask was closed with a septum, and the air in the flask was replaced by N_2. Dry 1,4-dioxane (15 ml) and *N*,*N*′-dimethylethylenediamine (0.03 ml, 0.278 mmol) were injected by syringes, and the mixture was refluxed for 20 h. After cooling to r.t., a concentrated soln. of NH_4OH (10 ml) was added, and the mixture was poured into H_2O and extracted three times (CH_2Cl_2). The combined org. layers were dried with (Na_2SO_4) and the solvent was removed in a rotary evaporator. The residue was submitted to CC to give **8j** (1.07 g, 95%). Yellow solid. R_f ($CHCl_3$) 0.66. M.p. 112–116°. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.39 (*s*, 3 H); 2.40 (*s*, 3 H); 3.70 (*s*, 3 H); 6.78 (*d*, *J* = 8.7, 1 H); 7.08 (*dd*, *J* = 1.4, 8.4, 1 H); 7.30 (*d*, *J* = 8.4, 1 H); 7.40 (*s*, 1 H); 7.63 (*d*, *J* = 2.3, 1 H); 7.75 (*dd*, *J* = 2.3, 8.7, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 14.8; 21.4; 55.9; 82.6; 110.1; 113.8; 117.5; 121.3; 125.6; 126.2; 133.1; 133.6; 137.0; 140.4; 151.9; 156.6; 164.0; 189.4. GC/EI-MS (70 eV): 406 (100, M^+), 375 (20), 279 (22), 261 (50), 248 (46), 173 (66), 159 (22). Anal. calc. for $C_{18}H_{15}IO_3$ (406.21): C 53.22, H 3.72; found: C 53.06, H 3.66.

General Procedure for Preparation of Thioketones **12**. A soln. of ketone **8a** or **8e** (0.68 mmol) and 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetan 2,4-disulfide (*Lawesson*'s reagent; 0.138 g, 0.34 mmol) in dry toluene (10 ml) was refluxed for 6 h. The solvent was removed in a rotary evaporator, and the residue was purified by CC.

(5′-Fluoro-2′,4-dimethoxybiphenyl-3-yl)(2-methyl-1-benzofuran-3-yl)methanethione (**12a**). From **9a** (1.1 g, 2.8 mmol), *Lawesson*'s reagent (566.3 mg, 1.4 mmol), and toluene (40 ml). Yield: 1.01 g (89%). Blue solid. R_f ($CHCl_3$) 0.77. M.p. 153–156°. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.37 (*s*, 3 H); 3.66 (*s*, 3 H); 3.75 (*s*, 3 H); 6.88 (*dd*, *J*(H,F) = 4.5, *J*(H,H) = 8.9, 1 H); 6.95–6.99 (*m*, 2 H); 7.07 (*dd*, *J* = 3.0, 9.0, 1 H); 7.22–7.30 (*m*, 2 H); 7.43 (*d*, *J* = 8.0, 1 H); 7.56 (*d*, *J* = 2.1, 1 H); 7.58 (*dd*, *J* = 2.2, 8.5, 1 H), 7.88–7.89 (*m*, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 15.8; 56.0; 56.2; 110.5; 111.2; 112.4 (*d*, *J*(C,F) = 8.4); 114.2 (*d*, *J*(C,F) = 22.6); 117.1 (*d*, *J*(C,F) = 23.7); 122.1; 124.2; 124.8; 128.3; 130.3; 130.4; 131.9; 139.1; 152.7; 153.5; 153.8; 156.2; 161.8; 215.7. EI-MS (70 eV): 406 (31, M^+), 373 (56), 342 (33), 249 (13), 213 (19), 149 (100), 131 (15). HR-EI-MS: 406.1037 (M^+, $C_{24}H_{19}FO_3S^+$; calc. 406.1039).

(5′-Fluoro-2′,4-dimethoxybiphenyl-3-yl)(2-methyl-1-benzothiophen-3-yl)methanethione (**12b**). From **9e** (277 mg, 0.68 mmol), *Lawesson*'s reagent (138 mg, 0.34 mmol), and toluene (10 ml). Yield: 210 mg (73%). Green oil. R_f ($CHCl_3$) 0.66. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.47 (*s*, 3 H); 3.47 (*s*, 3 H); 3.77 (*s*, 3 H); 6.85–6.91 (*m*, 3 H); 7.08–7.11 (*m*, 1 H); 7.22–7.28 (*m*, 2 H); 7.61–7.64 (*m*, 2 H); 7.71–7.73 (*m*, 1 H) 7.88 (*d*, *J* = 2.3, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 16.1; 56.1; 56.2; 111.7; 112.4 (*d*, *J*(C,F) = 9.1); 114.2 (*d*, *J*(C,F) = 22.4); 117.0 (*d*, *J*(C,F) = 23.5); 121.4; 123.2; 123.6; 124.2; 124.6; 124.9; 126.5; 131.5; 132.4; 133.7; 136.7; 153.4; 155.2; 157.6; 169.1. EI-MS (70 eV): 422 (44, M^+), 406 (40), 391 (53), 389 (100), 358 (89), 281 (20), 147 (71). HR-ESI-MS: 423.0881 ($[M+H]^+$, $C_{24}H_{20}FO_2S_2^+$; calc. 423.0883).

General Procedure for the Preparation of Phenolic Ketones **10** *and* **11***, and Thioketones* **13**. A 100-ml two-necked flask, equipped with a magnetic stirrer and a connection to the combined N_2/vacuum line, was charged with ketone **8b**, **8g**–**8j**, **9a**–**9h**, or thioketone **12**. The air in the flask was replaced by N_2, and the flask was closed with a septum. $CHCl_2$ (40 ml) was injected, the soln. was cooled to $-78°$, and BBr_3 was added dropwise by syringe. Stirring was continued overnight, while the mixture was allowed to reach r.t. H_2O and dil. HCl were added, the layers were separated, and the aq. phase was extracted three times with CH_2Cl_2. The combined org. layers were concentrated under reduced pressure, and the residue was purified by CC.

(5′-Fluoro-2′,4-dihydroxy-1,1′-biphenyl-3-yl)(2-methyl-1-benzofuran-3-yl)methanone (**10a**). From **9a** (903 mg, 2.31 mmol), BBr_3 (0.84 ml), and CH_2Cl_2 (50 ml). Yield: 463 mg (55%). Yellow solid. R_f (hexane/AcOEt 3:1) 0.37. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.61 (*s*, 3 H); 6.78–6.90 (*m*, 3 H); 7.20 (*d*, *J* = 8.6, 1 H); 7.25–7.33 (*m*, 2 H); 7.48–7.49 (*m*, 2 H); 7.65 (*dd*, *J* = 2.0, 8.6. 1 H); 7.79 (*d*, *J* = 2.0, 1 H); 12.10 (*s*, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 14.4; 111.1; 115.3 (*d*, *J*(C,F) = 23.0), 116.4 (*d*, *J*(C,F) = 23.5); 116.8 (*d*, *J*(C,F) = 8.3); 119.1; 120.6; 120.7; 123.8; 124.9; 126.6; 127.0; 127.8 (*d*, *J*(C,F) = 7.6); 133.2; 137.1; 148.4; 153.7; 157.0 (*d*, *J*(C,F) = 239.1); 160.4; 162.3; 195.8. EI-MS (70 eV): 362 (41, M^+), 347 (13), 345 (11), 230 (60), 132 (100). Anal. calc. for $C_{22}H_{15}FO_4$ (362.35): C 72.92, H 4.17; found: C 72.74, H 4.10.

(2,5-Dimethyl-1-benzofuran-3-yl)(5′-fluoro-2′,4-dihydroxy-1,1′-biphenyl-3-yl)methanone; (**10b**). From **9b** (500 mg,1.24 mmol), BBr_3 (0.45 ml), and CH_2Cl_2 (30 ml). Yield: 465 mg (quant.). Yellow solid. R_f (hexane/AcOEt 1:1) 0.64. M.p. 151–152°. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.41 (*s*, 3 H); 2.59 (*s*, 3 H); 6.79–6.89 (*m*, 3 H); 7.12 (*d*, *J* = 8.2, 1 H); 7.19 (*d*, *J* = 8.6, 1 H); 7.28 (*s*, 1 H); 7.35 (*d*, *J* = 8.4, 1 H); 7.66 (*dd*, *J* = 2.2, *J* = 8.6. 1 H); 7.80 (*d*, *J* = 2.2, 1 H); 12.11 (*s*, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 14.5; 21.3; 110.7; 115.2 (*d*, *J*(C,F) = 23.0); 116.2; 116.4 (*d*, *J*(C,F) = 23.5); 116.8 (*d*, *J*(C,F) = 8.2); 119.0; 120.5; 120.6; 126.0; 126.6; 127.0; 127.8 (*d*, *J*(C,F) = 8.1); 133.3; 133.5; 137.1; 152.1; 157.0 (*d*, *J*(C,F) = 238.7); 160.7; 162.3; 171.2; 195.9. EI-MS (70 eV): 376 (31, M^+), 359 (10), 230 (19), 173 (9), 146 (100). Anal. calc. for $C_{23}H_{17}FO_4$ (376.38): C 73.40, H 4.55; found: C 73.53, H 4.64.

{3-[(5′-Fluoro-2′,4-dihydroxy-1,1′-biphenyl-3-yl)carbonyl]-2-methyl-1-benzofuran-5-yl}acetonitrile (**10c**). From **9c** (111 mg, 0.26 mmol), BBr_3 (0.1 ml), and CH_2Cl_2 (5 ml). Yield: 66 mg (63%). Yellow oil. R_f (hexane/AcOEt 1:1) 0.52. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.62 (*s*, 3 H); 3.78 (*s*, 2 H); 6.78–6.81 (*m*, 1 H); 6.84–6.89 (*m*, 2 H); 7.20 (*d*, *J* = 8.6, 1 H); 7.24 (*dd*, *J* = 1.6, 8.5, 1 H); 7.48 (*d*, *J* = 8.6, 2 H); 7.66 (*dd*, *J* = 2.2, 8.6, 1 H); 7.77 (*d*, *J* = 2.2, 1 H); 12.0 (*s*, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 14.4; 23.5; 111.8; 115.2 (*d*, *J*(C,F) = 22.9); 116.3; 116.5 (*d*, *J*(C,F) = 23.4); 117.2 (*d*, *J*(C,F) = 8.3); 118.5; 119.1; 120.3; 120.4; 124.6; 125.4; 127.4; 127.6; 128.2; 133.1; 137.5; 148.5; 153.2; 157.0 (*d*, *J*(C,F) = 239.0); 161.6; 162.3; 195.5. EI-MS (70 eV): 401 (49, M^+), 384 (9), 371 (8), 291 (15), 274 (9), 230 (100), 191 (24), 171 (59), 149 (29), 115 (11). HR-ESI-MS: 402.1130 ($[M+H]^+$, $C_{24}H_{17}FNO_4^+$; calc. 402.1136).

*(1,2-Dimethyl-1*H*-indol-3-yl)(5′-fluoro-2′,4-dihydroxy-1,1′-biphenyl-3-yl)methanone*; (**10d**). From **9d** (250 mg, 0.62 mmol), BBr_3 (0.22 ml), and CH_2Cl_2 (15 ml). Yield: 176 mg (76%). Yellow solid. R_f (hexane/AcOEt 1:1) 0.44. M.p. 137–139°. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.61 (*s*, 3 H); 3.76 (*s*, 3 H); 6.77–6.86 (*m*, 3 H); 7.15–7.20 (*m*, 2 H); 7.24–7.35 (*m*, 2 H); 7.49 (*d*, *J* = 7.9, 1 H); 7.56 (*dd*, *J* = 2.2, 8.5, 1 H); 7.78 (*d*, *J* = 2.2, 1 H); 12.24 (*s*, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 12.4; 29.9; 109.5; 113.0; 115.1 (*d*, *J*(C,F) = 22.8); 116.4 (*d*, *J*(C,F) = 23.5); 116.7 (*d*, *J*(C,F) = 8.2); 119.0; 120.2; 121.8; 121.8; 122.5; 126.3; 128.0 (*d*, (C,F) = 7.7); 133.6; 135.8; 136.6; 143.6; 148.5; 156.7 (*d*, *J*(C,F) = 238.4); 161.9; 196.1. EI-MS (70 eV): 375 (5, M^+), 145 (100), 129 (8). Anal. calc. for $C_{23}H_{18}FNO_3$ (375.39): C 73.59, H 4.83, N 3.73; found: C 73.55, H 5.06, 3.64.

(5′-Fluoro-2′,4-dihydroxy-1,1′-biphenyl-3-yl)(2-methyl-1-benzothiophen-3-yl)methanone (**10e**). From **9e** (1.13 g, 2.77 mmol), BBr_3 (1.0 ml), CH_2Cl_2 (40 ml). Yield: 871 mg (83%). Yellow solid. R_f (hexane/AcOEt 1:1) 0.62. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.58 (*s*, 3 H); 6.75–6.87 (*m*, 3 H); 7.21 (*d*, *J* = 8.6, 1 H); 7.32–7.34 (*m*, 2 H); 7.52–7.54 (*m*, 1 H); 7.56 (*d*, *J* = 1.9, 1 H); 7.64 (*dd*, *J* = 1.9, 8.6, 1 H); 7.78–7.80 (*m*, 1 H); 12.3 (*s*, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 15.5; 115.3 (*d*, *J*(C,F) = 23.0); 116.4 (*d*, *J*(C,F) = 23.0); 116.8 (*d*, *J*(C,F) = 8.2); 119.3; 120.6; 122.1; 122.6; 124.7; 127.3; 127.6 (*d*, *J*(C,F) = 7.8); 128.0; 131.0; 133.6; 137.6; 138.1; 138.6; 144;7; 148.4; 157.0 (*d*, *J*(C,F) = 239.3); 162.7; 198.5. GC/EI-MS (70 eV): 378 (40, M^+), 345 (15), 230 (65), 148 (100). Anal. calc. for $C_{22}H_{15}FO_3S$ (378.42): C 69.83, H 4.00; found: C 68.56, H 4.14.

(2-Butyl-1-benzothiophen-3-yl)(5′-fluoro-2′,4-dihydroxy-1,1′-biphenyl-3-yl)methanone (**10f**). From **9f** (351 mg, 0.78 mmol), BBr_3 (0.28 ml), and CH_2Cl_2 (20 ml). Yield: 320 mg (97%). Yellow solid. R_f (hexane/AcOEt 1:1) 0.63. M.p. 119–120°. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.84 (*t*, *J* = 7.3, 3 H); 1.26 (*t*, *J* = 7.1, 2 H); 1.30–1.37 (*m*, 2 H); 2.92 (*t*, *J* = 7.7, 2 H); 6.74–6.77 (*m*, 2 H); 6.85 (*td*, *J* = 3.0, 8.4, 1 H); 7.21 (*d*, *J* = 8.6, 1 H); 7.30–7.34 (*m*, 2 H); 7.48–7.50 (*m*, 1 H); 7.53 (*d*, *J* = 2.2, 1 H); 7.64 (*dd*, *J* = 2.2, 8.6, 1 H); 7.80–7.82 (*m*, 1 H); 12.32 (*s*, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 13.7; 22.3; 29.4; 33.8; 115.2 (*d*, *J*(C,F) = 23.2); 116.3 (*d*, *J*(C,F) = 23.5); 116.8 (*d*, *J*(C,F) = 8.2); 119.2; 120.6; 122.2; 122.5; 124.6; 124.9; 127.3; 127.6; 133.5; 137.7; 138.0; 138.4; 139.7; 148.4; 150.7; 156.0; 162.7; 198.9. EI-MS (70 eV): 420 (30, M^+), 363 (100), 230 (37), 190 (54), 148 (91). Anal. calc. for $C_{25}H_{21}FO_3S$ (420.50): C 71.41, H 5.03; found: C 71.23, H 5.05.

(2,5-Dimethyl-1-benzofuran-3-yl)(3′,4,5′-trihydroxy-1,1′-biphenyl-3-yl)methanone (**10g**). From **9g** (300 mg, 0.72 mmol), BBr_3 (0.5 ml), and CH_2Cl_2 (16 ml). Yield: 261 mg (97%). Yellow solid. R_f (hexane/AcOEt 1:2) 0.56. M.p. 97–101°. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.41 (*s*, 3 H); 2.59 (*s*, 3 H); 6.26 (*t*, *J* = 2.2, 1 H); 6.46 (*d*, *J* = 2.2, 2 H); 7.14 (*dd*, *J* = 1.5, 8.3, 1 H); 7.14 (*d*, *J* = 8.7, 1 H); 7.33 (*s*, 1 H); 7.38 (*d*, *J* = 8.4, 1 H); 7.71 (*dd*, *J* = 2.3, 8.7, 1 H); 7.88 (*d*, *J* = 2.3, 1 H); 12.06 (*s*, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 14.6; 21.4; 101.6; 106.3; 110.7; 116.3; 118.7; 120.3; 120.7; 125.9; 126.8; 131.0; 131.1; 133.4; 135.0; 142.4; 152.2; 157.1; 160.6; 162.2; 196.0. EI-MS (70 eV): 374 (93, M^+), 359 (22), 357 (19), 228 (74), 186 (58), 146 (100). HR-ESI-MS: 375.1226 ($[M+H]^+$, $C_{23}H_{19}O_5^+$; calc. 375.1227).

(2,5-Dimethyl-1-benzofuran-3-yl)[4-hydroxy-4′-(trifluoromethoxy)-1,1′-biphenyl-3-yl]methanone (**10h**). From **9h** (150 mg, 0.34 mmol), BBr_3 (0.12 ml), and CH_2Cl_2 (10 ml). Yield: 130 mg (90%). Yellow solid. R_f (hexane/AcOEt 1:1) 0.82. M.p. 111–112°. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.40 (*s*, 3 H); 2.60 (*s*, 3 H); 7.14 (*dd*, *J* = 1.3, *J* = 8.4, 1 H); 7.17–7.21 (*m*, 3 H); 7.32 (*s*, 1 H); 7.39 (*d*, *J* = 8.4, 1 H); 7.40–7.43 (*m*, 2 H); 7.74 (*dd*, *J* = 2.4, 8.6, 1 H); 7.91 (*d*, *J* = 2.4, 1 H); 12.08 (*s*, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 14.5; 21.3; 110.7; 116.3; 119.0; 120.4; 120.6; 121.4; 126.0; 126.7; 127.7; 130.5; 131.2; 133.3; 135.0; 138.5; 147.6; 152.2; 155.1; 160.8; 162.2; 207.4. EI-MS (70 eV): 426 (34, M^+), 409 (12), 300 (18), 281 (28), 189 (6), 146 (100), 115 (8). HR-ESI-MS: 427.1156 ($[M+H]^+$, $C_{24}H_{18}F_3O_4^+$; calc. 427.1152).

(5-Bromo-2-hydroxyphenyl)(2,5-dimethyl-1-benzofuran-3-yl)methanone (**11a**). From **8b**. Yield: 1.4 g (21%). Yellow solid. R_f ($CHCl_3$) 0.66. M.p. 108–112°. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.42 (*s*, 3 H); 2.57 (*s*, 3 H); 6.99 (*d*, *J* = 8.8, 1 H); 7.13 (*d*, *J* = 8.5, 1 H); 7.28 (*s*, 1 H); 7.37 (*d*, *J* = 8.4, 1 H); 7.60 (*dd*, *J* = 2.4, 8.9, 1 H); 7.81 (*d*, *J* = 2.4, 1 H); 11.95 (*s*, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 14.7; 21.4; 110.3; 110.6; 120.3; 120.5; 126.1; 126.5; 132.2; 133.7; 134.8; 138.3; 139.0; 152.2; 160.8; 161.4; 195.0. GC/EI-MS (70 eV): 346, 344 (40, M^+), 331, 329 (35), 248 (10), 201, 199 (5), 173 (15), 146 (100). HR-ESI-MS: 345.0200 ($[M+H]^+$, $C_{17}H_{14}BrO_3^+$; calc. 345.0121).

(2,5-Dimethyl-1-benzofuran-3-yl)(2-hydroxy-5-methylphenyl)methanone (**11b**). From **8g** (230 mg, 0.78 mmol), BBr_3 (0.28 ml), and CH_2Cl_2 (17 ml). Yield: 184 mg (84%). Yellow solid. R_f (hexane/AcOEt 3:1) 0.6. M.p. 99–100°. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.23 (*s*, 3 H); 2.40 (*s*, 3 H); 2.55 (*s*, 3 H); 6.99 (*d*, *J* = 8.5, 1 H); 7.11 (*dd*, *J* = 1.3, 8.4, 1 H); 7.28 (*s*, 1 H); 7.33–7.35 (*m*, 1 H); 7.36 (*d*, *J* = 8.4, 1 H); 7.47 (*d*, *J* = 1.7, 1 H); 11.87 (*s*, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 14.5; 20.3; 21.4; 110.4; 116.5; 118.0; 120.1; 120.6; 125.7; 127.0; 128.0; 132.5; 133.3; 137.5; 152.1; 159.9; 160.5; 196.1. GC/EI-MS (70 eV): 280 (52, M^+), 265 (30), 263 (32), 248 (4), 173 (6), 146 (100), 135 (18). Anal. calc. for $C_{18}H_{16}O_3$ (280.32): C 77.12, H 5.75; found: C 76.94, H 5.84.

(2,5-Dimethyl-1-benzofuran-3-yl)[2-hydroxy-5-(trifluoromethyl)phenyl]methanone (**11c**). From **8h** (140 mg, 0.40 mmol), BBr_3 (0.14 ml), and CH_2Cl_2 (10 ml). Yield: 103 mg (77%). Orange solid. R_f (hexane/AcOEt 1:1) 0.69. M.p. 87–89°. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.39 (*s*, 3 H); 2.58 (*s*, 3 H); 7.14 (*d*, *J* = 8.4, 2 H); 7.18 (*d*, *J* = 8.8, 1 H); 7.25 (*s*, 1 H); 7.38 (*d*, *J* = 8.4, 1 H); 7.75 (*dd*, *J* = 1.9, 8.7, 1 H); 8.02 (*s*, 1 H); 12.36 (*s*, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 14.7; 21.3; 110.7; 115.9; 119.1; 119.7; 120.5; 121.0; 121.3; 126.2; 126.3; 130.4 (*q*, *J*(C,F) = 3.8); 132.6 (*q*, *J*(C,F) = 3.4); 133.7; 152.2; 161.4; 164.8; 195.2. GC/EI-MS (70 eV): 334 (100, M^+), 319 (85), 317 (80), 302 (5), 189 (30), 173 (20), 161 (20), 146 (100), 115 (25). HR-ESI-MS: 335.0890 ($[M+H]^+$, $C_{18}H_{14}F_3O_3^+$; calc. 335.0890).

3-[(2,5-Dimethyl-1-benzofuran-3-yl)carbonyl]-4-hydroxybenzonitrile (**11d**). From **8i** (738 mg, 2.42 mmol), BBr_3 (0.88 ml), and CH_2Cl_2 (50 ml). Yield: 468 mg (66%). Yellow solid. R_f (hexane/AcOEt 1:1) 0.63. M.p. 159–160°. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.41 (*s*, 3 H); 2.60 (*s*, 3 H); 7.14–7.19 (*m*, 1 H); 7.39 (*d*, *J* = 8.4, 1 H); 7.76 (*dd*, *J* = 2.1, 8.7, 1 H); 8.05 (*d*, *J* = 2.1, 1 H); 12.53 (*s*, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 14.6; 21.4; 102.5; 110.9; 115.6; 118.1; 120.0; 120.1; 126.1; 126.4; 134.0; 137.5; 138.8;

152.2; 165.7; 166.9; 194.9. GC/EI-MS (70 eV): 291 (74, M^+), 276 (46), 274 (44), 173 (10), 146 (100). Anal. calc. for $C_{18}H_{13}NO_3$ (291.30): C 74.22, H 4.50, N 4.81; found: C 74.17, H 4.68, N 4.30.

(2,5-Dimethyl-1-benzofuran-3-yl)(2-hydroxy-5-iodophenyl)methanone (**11e**). From **8j** (942 mg, 2.32 mmol), BBr_3 (0.84 ml), and CH_2Cl_2 (50 ml). Yield: 728 mg (80%). Yellow solid. R_f (hexane/AcOEt 3:1) 0.62. M.p. 125–127°. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.43 (*s*, 3 H); 2.57 (*s*, 3 H); 6.88 (*d*, *J* = 8.8, 1 H); 7.13 (*dd*, *J* = 1.3, 8.4, 1 H); 7.28 (*s*, 1 H); 7.37 (*d*, *J* = 8.4, 1 H); 7.76 (*dd*, *J* = 2.2, *J* = 8.8, 1 H); 7.99 (*d*, *J* = 2.2, 1 H); 11.97 (*s*, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 14.7; 21.4; 79.4; 110.1; 110.6; 116.0; 120.6; 120.7; 122.4; 126.1; 126.5; 133.7; 141.0; 144.6; 152.2; 161.0; 162.1; 194.8. GC/EI-MS (70 eV): 392 (45, M^+), 377 (15), 247 (10), 219 (5), 195 (10), 173 (10), 146 (100). Anal. calc. for $C_{17}H_{13}IO_3$ (392.19): C 52.06, H 3.34; found: C 52.31, H 3.15.

(5′-Fluoro-2′,4-dihydroxy-1,1′-biphenyl-3-yl)(2-methyl-1-benzofuran-3-yl)methanethione (**13a**). From **12a** (500 mg, 1.23 mmol), BBr_3 (0.44 ml), and CH_2Cl_2 (26 ml). Yield: 300 mg (64%). Brown solid. R_f (hexane/AcOEt 1:1) 0.64. M.p. 82–84°. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.47 (*s*, 3 H); 6.87–6.89 (*m*, 1 H); 6.94 (*td*, *J* = 3.0, 8.5, 1 H); 7.03 (*d*, *J* = 8.5, 1 H); 7.08 (*dd*, *J* = 2.9, 9.7, 1 H); 7.26–7.29 (*m*, 1 H); 7.31–7.35 (*m*, 1 H); 7.57–7.61 (*m*, 2 H), 7.63 (*d*, *J* = 2.2, 1 H); 7.67 (*dd*, *J* = 2.2, 8.5, 1 H); 9.54 (*s*, 1 H); 10.40 (*s*, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 14.4; 111.2; 115.2 (*d*, *J*(C,F) = 22.9); 116.3; 114.4 (*d*, *J*(C,F) = 23.7); 116.8 (*d*, *J*(C,F) = 8.2); 119.0; 120.6; 123.8; 124.8; 126.6; 127.2; 127.8 (*d*, *J*(C,F) = 7.5); 133.2; 137.2; 148.5; 153.7; 157.0 (*d*, *J*(C,F) = 239.0); 160.4; 162.2; 174.9; 195.9. EI-MS (70 eV): 378 (2, M^+), 362 (48), 345 (36), 230 (68), 159 (17), 132 (100). HR-EI-MS: 378.0743 (M^+, $C_{22}H_{15}FO_3S^+$; calc. 378.0726).

(5′-Fluoro-2′,4-dihydroxy-1,1′-biphenyl-3-yl)(2-methyl-1-benzothiophen-3-yl)methanethione (**13b**). From **12b** (150 mg, 0.36 mmol), BBr_3 (0.13ml), and CH_2Cl_2 (10 ml). Yield: 121 mg (86%). Red oil. R_f (hexane/AcOEt 1:1) 0.63. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.46 (*s*, 3 H); 6.69–6.74 (*m*, 2 H); 6.83 (*td*, *J* = 3.0, 8.3, 1 H); 7.28–7.37 (*m*, 4 H); 7.44 (*d*, 1 *J* = 2.2, 1 H); 7.61 (*dd*, *J* = 2.2, 8.6, 1 H); 7.77 (*d*, *J* = 7.2, 1 H); 13.44 (*s*, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 14.2; 115.3 (*d*, *J*(C,F) = 22.9); 116.2 (*d*, *J*(C,F) = 23.4); 116.9 (*d*, *J*(C,F) = 8.4); 119.2; 121.0; 122.0; 122.2; 124.5; 124.6; 125.0; 125.1; 128.7; 131.1; 133.7; 137.8; 148.2; 157.9; 162.8; 171.2. EI-MS (70 eV): 394 (1, M^+), 361 (100), 345 (3), 147 (10). HR-ESI-MS: 395.05703 ($[M+H]^+$, $C_{22}H_{16}FO_2S_2^+$; calc. 395.0570).

Crystal-Structure Determination of **10b**. A well-shaped crystal of **10b** was selected by means of an optical microscope and investigated at r.t. on an *Oxford Diffraction Xcalibur* (EOS) diffractometer, using graphite monochromatized MoK_α radiation. Unit cell parameters were determined by least-squares refinement on the positions of 13,715 reflections, distributed equally in reciprocal space in the

Table 2. *Crystal Data, X-Ray Measurement and Structure Determination Summary for Compound* **10b**

Empirical Formula		$C_{23}H_{17}FO_4$	Absorbtion coefficient [mm^{-1}]	0.101
Formular weight		376.37	$F(000)$	392
Crystal color; habit		colorless, plate	θ Range [°]	$2.76 \le \theta \le 25.00$
Crystal size [mm^3]		$0.30 \times 0.28 \times 0.18$	Index ranges	$-10 \le h \le 10$
Crystal system		triclinic		$-13 \le k \le 13$
Space group		$P\bar{1}$		$-12 \le l \le 13$
Unit cell dimensions	a [Å]	8.5156(12)	Reflections collected/unique	6276/263
	b [Å]	11.1887(13)	R_{int}	0.043
	c [Å]	11.2418(15)	Observed reflections [$I\,2\sigma(I)$]	2563
	α [°]	102.879(10)	Data/parameters	3057/263
	β [°]	108.594(11)	Goodness-of-fit on F^2	1.173
	γ [°]	107.431(10)	Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.057$
Volume [Å^3]		906.5(2)		$wR_2 = 0.107$
Z		2	R indices (all data)	$R_1 = 0.072$
Density (calc.; [g cm^{-3}])		1.379		$wR_2 = 0.112$
Temp. [K]		291(2)	Largest diff. peak/hole [e Å^{-3}]	0.158/−0.106
Wavelength [Å]		MoK_α, $\lambda = 0.71073$		

range $2.04^\circ < \theta < 29.82^\circ$. An anorthic lattice was found consistent with space group types $P1$ and $P\bar{1}$. In accordance with *E*-statistics, significantly better results were observed in the centrosymmetric space group type in the course of structure refinement. Crystal data as well as details of data collection and structure refinement are collected in *Table 2*. *Lorentz*-polarization corrections were applied to the collected data, and the structure was solved by direct methods [20] and subsequent difference *Fourier* syntheses. Approximate positions of all H-atoms were found. Refinement by full-matrix least-squares calculations on F^2 [21] converged (max. shift/esd: 0.000) giving the final quality indicators listed in *Table 2*. Refined parameters include positional parameters as well as anisotropic displacement parameters for all the atoms heavier than H. For H-atoms bonded to O-atoms, positional and isotropic displacement parameters were refined. With idealized bond lengths and angles assumed for all the CH and Me groups, the riding model was applied for the corresponding H-atoms, and their isotropic displacement parameters were constrained to 120 and 150% of the equivalent isotropic displacement parameters of the parent C-atoms, respectively. In addition, the H-atoms of the Me groups were allowed to rotate around the neighboring C–C bonds. CCDC-890359 contains the supplementary crystallographic data (excluding structure factors) for this article. These data can be obtained free of charge from *The Cambridge Crystallographic Data Centre via* www.ccdc.cam.ac.uk/data_request/cif.

REFERENCES

[1] G. Fischer, *Chem. Soc. Rev.* **2000**, *29*, 119; G. Fischer, *Angew. Chem.* **1994**, *106*, 1479; G. Fischer, *Angew. Chem., Int. Ed.* **1994**, *33*, 1415.

[2] G. Fischer, H. Bang, C. Mech, *Biomed. Biochim. Acta* **1984**, *43*, 1101.

[3] J. Fanghänel, *Angew. Chem.* **2003**, *115*, 506; J. Fanghänel, *Angew. Chem., Int. Ed.* **2003**, *42*, 490; Y. Zhang, *Mini-Rev. Org. Chem.* **2004**, *1*, 359; K. P. Lu, X. Z. Zhou, *Nat. Rev. Mol. Cell Biol.* **2007**, *8*, 904.

[4] A. Ryo, Y.-C. Liou, K. P. Lu, G. Wulf, *J. Cell Sci.* **2003**, *116*, 773; G. M. Wulf, A. Ryo, G. G. Wulf, S. W. Lee, T. Niu, V. Petkova, K. P. Lu, *EMBO J.* **2001**, *20*, 3459; Y.-C. Liou, A. Sun, A. Ryo, X. Z. Zhou, Z.-X. Yu, H.-K. Huang, T. Uchida, R. Bronson, G. Bing, X. Li, T. Hunter, K. P. Lu, *Nature* **2003**, *424*, 556; P.-J. Lu, G. Wulf, X. Z. Zhou, P. Davies, K. P. Lu, *Nature* **1999**, *399*, 784.

[5] G. G. Xu, F. A. Etzkorn, *Drug News Perspect.* **2009**, *22*, 399.

[6] L. Henning, C. Christner, M. Kipping, B. Schelbert, K. P. Rücknagel, S. Grabley, G. Küllertz, G. Fischer, *Biochemistry* **1998**, *37*, 5953; T. Uchida, M. Takamiya, M. Takahashi, H. Miyashita, H. Ikeda, T. Terada, Y. Matsuo, M. Shirouzu, S. Yokoyama, F. Fujimori, T. Hunter, *Chem. Biol.* **2003**, *10*, 15; H. C. Wang, K. Kim, R. Bakhtiar, J. P. Germanas, *J. Med. Chem.* **2001**, *44*, 2593; E. Bayer, M. Thutewohl, C. Christner, T. Tradler, F. Osterkamp, H. Waldmann, P. Bayer, *Chem. Commun.* **2005**, 516; D. Wildemann, F. Erdmann, B. Hernandez Alvarez, G. Stoller, X. Z. Zhou, J. Fanghänel, M. Schutkowski, K. P. Lu, G. Fischer, *J. Med. Chem.* **2006**, *49*, 2147; S. Zhao, F. A. Etzkorn, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6615; M. Braun, A. Hessamian-Alinejad, B. Féaux De Lacroix, B. Hernandez Alvarez, G. Fischer, *Molecules* **2008**, *13*, 995; B. Wu, M. F. Rega, J. Wei, H. Yuan, R. Dahl, Z. Zhang, M. Pellecchia, *Chem. Biol. Drug Des.* **2009**, *73*, 369; Y. Tatara, Y.-C. Lin, Y. Bamba, T. Mori, T. Uchida, *Biochem. Biophys. Res. Commun.* **2009**, *384*, 394; C. Guo, X. Hou, L. Dong, E. Dagostino, S. Greaseley, R. Ferre, J. Marakovits, M. C. Johnson, D. Matthews, B. Mroczkowski, H. Parge, T. Van Asdale, I. Popoff, J. Piraino, S. Margosiak, J. Thomson, G. Los, B. W. Murray, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5613; L. Dong, J. Marakovits, X. Hou, C. Guo, S. Greasley, E. Dagostino, R. Ferre, M. C. Johnson, E. Kraynov, J. Thomson, V. Pathak, B. W. Murray, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2210; T. Liu, Y. Liu, H.-Y. Kao, D. Pei, *J. Med. Chem.* **2010**, *53*, 2494; A. J. Potter, S. Ray, L. Gueritz, C. L. Nunns, C. J. Bryant, S. F. Scrace, N. Matassova, L. Baker, P. Dokurno, D. A. Robinson, A. E. Surgenor, B. Davis, J. B. Murray, C. M. Richardson, J. D. Moore, *Bioorg. Med. Chem Lett.* **2010**, *20*, 586; A. Potter, V. Oldfield, C. Nunns, C. Fromont, S. Ray, C. J. Northfield, C. J. Bryant, S. F. Scrace, D. Robinson, N. Matossova, L. Baker, P. Dokurno, A. E. Surgenor, B. Davis, C. M. Richardson, J. B. Murray, J. D. Moore, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6483; K. E. Duncan, B. R. Dempsey, L. E. Killip, J. Adams, M. L. Bailey, G. A. Lajoie, D. W. Litchfield, C. J. Brandl, G. S.

Shaw, B. H. Shilton, *J. Med. Chem.* **2011**, *54*, 3854; C. Liu, J. Jin, L. Chen, J. Zhou, X. Chen, D. Fu, H. Song, B. Xu, *Bioorg. Med. Chem.* **2012**, *20*, 2992.
[7] P. T. Flaherty, P. Jain, *Ann. Rep. Med. Chem.* **2011**, *46*, 337.
[8] S. Daum, F. Erdmann, G. Fischer, B. Féaux de Lacroix, A. Hessamian-Alinejad, S. Houben, W. Frank, M. Braun, *Angew. Chem.* **2006**, *118*, 7615; S. Daum, F. Erdmann, G. Fischer, B. Féaux de Lacroix, A. Hessamian-Alinejad, S. Houben, W. Frank, M. Braun, *Angew. Chem., Int. Ed.* **2006**, *45*, 7454.
[9] S. Daum, M. Schumann, S. Mathea, T. Aumüller, M. A. Balsley, S. L. Constant, B. Féaux de Lacroix, F. Kruska, M. Braun, C. Schiene-Fischer, *Biochemistry* **2009**, *48*, 6268.
[10] S. V. Sambasivarao, O. Acevedo, *J. Chem. Inf. Model*. **2011**, *51*, 475.
[11] J. Pietruszka, R. C. Simon, F. Kruska, M. Braun, *Eur. J. Org. Chem*. **2009**, 6217.
[12] H. W. Gschwend, H. R. Rodriguez, *Org. React.* **1979**, *26*, 1; P. Barker, P. Finke, K. Thompson, *Synth. Commun*. **1989**, *19*, 257; H. Sekizaki, K. Itoh, E. Toyota, K. Tanizawa, *Heterocycles* **2003**, *59*, 237.
[13] a) A. Suzuki, M. Miyaura, *J. Chem. Soc., Chem. Commun*. **1979**, 866; b) B. E. Huff, T. M. Koenig, D. Mitchell, M. A. Staszak, *Org. Synth.* **2004**, *Coll. Vol. 10*, 102.
[14] T. Schareina, A. Zapf, M. Beller, *Chem. Commun.* **2004**, 1388.
[15] A. Klapars, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 14844.
[16] I. Thomsen, K. Clausen, S. Scheibye, S.-O. Lawesson, *Org. Synth.* **1990**, *Coll. Vol. 7*, 372.
[17] M. C. Etter, J. C. MacDonald, J. Bernstein, *Acta Crystallogr., Sect. B* **1990**, *46*, 256.
[18] B. Janowski, S. Wöllner, M. Schutkowski, G. Fischer, *Anal. Biochem.* **1997**, *252*, 299.
[19] R. Siegrist, M. Zürcher, C. Baumgartner, P. Seiler, F. Diederich, S. Daum, G. Fischer, C. Klein, M. Dangl, M. Schwaiger, *Helv. Chim. Acta* **2007**, *90*, 217.
[20] G. M. Sheldrick, SHELXS86, Program for the Solution of Crystal Structures, University of Göttingen, Germany, 1985.
[21] G. M. Sheldrick, SHELXL97, Program for the Refinement of Crystal Structures, University of Göttingen, Germany, 1997.

Received July 17, 2012