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(2015) European Journal of Medicinal Chemistry, 89, pp. 597-605.

1-Phenylsulfinyl-3-(pyridin-3-yl)naphthalen-2-ols: A New Class of Potent and Selective Aldosterone Synthase Inhibitors

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RECEIVED DATE (to be automatically inserted after your manuscript is accepted if required according to the journal that you are submitting your paper to)

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[a] Abbreviations: *m*-CPBA, 3-chloroperoxybenzoic acid; CYP, cytochrome P450; CYP11B1, 11β-hydroxylase; CYP11B2, aldosterone synthase; CYP17, 17α-hydroxylase-17,20-lyase; CYP19, aromatase; HPLC, high performance liquid chromatography; MR, mineralocorticoid receptor; RAAS, renin-angiotensin-aldosterone system; SF, selectivity factor, $IC_{50\ CYP11B1}$ / $IC_{50\ CYP11B2}$.

Abstract

1-Phenylsulfinyl-3-(pyridin-3-yl)naphthalen-2-ols and related compounds were synthesized and evaluated for inhibition of aldosterone synthase (CYP11B2), a potential target for cardiovascular diseases associated with elevated plasma aldosterone levels like congestive heart failure and myocardial fibrosis. Introduction of substituents at the phenylsulfinyl moiety and changes of the substitution pattern at the naphthalene core were examined. Potent compounds were further examined for selectivity versus other important steroidogenic CYP enzymes, i.e. the highly homologous 11β-hydroxylase (CYP11B1), CYP17 and CYP19. The most potent compound (IC_{50} = 14 nM) discovered was the *meta*-trifluoromethoxy derivative **11**, which also exhibited excellent selectivity toward CYP11B1 (SF = 415), and showed no inhibition of CYP17 and CYP19.

Keywords: Aldosterone, aldosterone synthase, 1-Phenylsulfinyl-3-(pyridin-3-yl)naphthalen-2-ols, 11β-hydroxylase, selectivity.

1. Introduction

The mineralocorticoid aldosterone plays a crucial role in the salt and water homeostasis. Its release is mainly controlled by angiotensin-II via the renin-angiotensin-aldosterone system (RAAS) and potassium plasma levels. Chronically elevated plasma aldosterone levels are linked to the development and progression of certain cardiovascular diseases such as hypertension, congestive heart failure, and myocardial fibrosis. [1] In clinical studies, the mineralocorticoid receptor (MR) antagonists like spironolactone and eplerenone reduce mortality in patients with congestive heart failure and post acute myocardial infarction, [2] thereby showing the detrimental role of aldosterone in the pathophysiology of cardiovascular diseases and the therapeutic benefit of blocking its action. However, the influence of the unaffected elevated plasma aldosterone levels leading to an up-regulation of mineralocorticoid receptor expression [3] and to nongenomic aldosterone effects is not yet fully explained. [4] Therefore, the mitochondrial cytochrome P450 enzyme aldosterone synthase has been highlighted as a potential pharmacological target, and it was proposed that CYP11B2 inhibitors could serve as drugs for the aforementioned cardiovascular diseases. [5,6,7] CYP11B2 is located in the zona glomerulosa of the adrenal cortex. It catalyzes the last steps in aldosterone biosynthesis, i.e. in humans the conversion of 11-deoxycorticosterone to aldosterone via corticosterone and 18-hydroxycorticosterone. [8] The inhibition of CYP11B2 reduces the production of aldosterone and is therefore a treatment option for related diseases.

In the development of CYP inhibitors, a crucial point is the selectivity over other CYP enzymes, especially steroidogenic and hepatic CYPs. The most challenging task is to achieve selectivity versus the highly homologous (> 93%) [9] 11β-hydroxylase (CYP11B1), which plays a key role in glucocorticoid biosynthesis by catalyzing the formation of cortisol from 11-deoxycortisol. [Fehler: Referenz nicht gefunden] Despite of these difficulties, selective inhibitors of CYP11B1 [10] and CYP11B2 have been successfully identified. Several classes of CYP11B2 inhibitors were derived from the anaesthetic *R*-etomidate or unselective CYP19 inhibitor fadrozole. For example, Hermans *et al*. describe a class of *N*-benzyl-1*H*-imidazoles, [11] and several patents disclose, for example,

imidazo[1,5]pyridine, [12] 4-imidazolyl-1,2,3,4-tetrahydroquinoline [13] derivatives or heterocyclic spiro-compounds [14] as aldosterone synthase inhibitors. One of these inhibitors, LCI699, has been investigated in clinical trials for the treatment of primary hyperaldosteronism and hypertension. However, in order to avoid the potential impairment of cortisol biosynthesis that could result from CYP11B1 inhibition by this compound, low doses (< 1.3 mg daily) were applied, and consequently only moderate curative effects were observed. [15]

In our group, in 2003 a drug discovery program based on a biological screening of known CYP inhibitors had been performed. [Fehler: Referenz nicht gefunden] Utilizing the broad experience gained in the development of inhibitors of other CYP enzymes, such as aromatase (CYP19) [16] or CYP17, [17] several classes of nonsteroidal highly potent and selective *h*CYP11B2 inhibitors were obtained by subsequent optimization strategies, i.e. imidazolyl- and pyridylmethylenetetrahydronaphthalenes and -indanes, [18,19] heterocycle substituted naphthalenes, dihydronaphthalenes [20-22] and 3,4-dihydro-1*H*-quinolin-2-ones. [23]

In this study, we describe the synthesis and biological properties of a series of 1-phenylsulfinyl-2-hydroxy-3-pyridyl substituted naphthalenes and structurally related compounds (Chart 1). This class of compounds was obtained by oxidation of 1-(phenylthio)-3-(pyridin-3-yl)naphthalen-2-ols, which were readily accessible by a new $S_{N,Ar}$ reaction recently described by us. [24] The novel compounds revealed themselves as potent and selective CYP11B2 inhibitors. Structure activity relationships of different substituents on the phenylsulfinyl moiety were established considering the potency toward human and the selectivity versus human CYP11B1, CYP17 and CYP19. Compound **11** was further investigated in a pharmacokinetic study in male Wistar rats.

2. Results

2.1 Chemistry. Recently, the synthesis of sulfides **1a-4a** was described by us (Scheme 1). [Fehler: Referenz nicht gefunden] 2-Methoxynaphthalene is converted into the boronic acid via *ortho*-lithiation [25] and subsequently transferred into 3-(3-methoxynaphthalen-2-yl)-pyridine by a *Suzuki* reaction. [20, 26] Cleavage of the methyl ether by refluxing in aqueous hydrobromic acid and reaction of the obtained

alcohol with triflate anhydride led to intermediate **1b**. [Fehler: Referenz nicht gefunden] Reaction of the triflate **1b** with substituted thiophenols or thiophene-2-thiol under aromatic nucleophilic substitution conditions afforded 1-arylthio-2-hydroxy-3-pyridyl naphthalenes **1a**-**22a** in 34-90% yield. Oxidation to the sulfoxides **1**-**22** was carried out using one equivalent of *m*-CPBA. The 3- and 4-mercaptobenzonitriles were prepared from 3- [27] and 4-cyanophenol [28] with the method of Newman and Karnes. [29]

As for the synthesis of compounds **23**-**24** (Scheme 2), 1-Fluoronaphthalene was first brominated at 3-position in two steps as previously described. [30] *Suzuki* reaction with 3-pyridine boronic acid and subsequent microwave facilitated nucleophilic substitution of the fluorine by thiophenol yielded compound **23**. Oxidation with one equivalent *m*-CPBA at room temperature afforded **24**.

Compound **25** was prepared as depicted in Scheme 3. Based on a route described by Li *et al*., **25b** was synthesized from 2-methoxynaphthalene via *ortho*-lithiation, followed by *in situ* addition of benzene-sulfonyl fluoride [31] and subsequent cleavage of the methyl ether in refluxing aqueous hydrobromic acid. Reaction of the obtained alcohol with triflate anhydride afforded **25a**. Despite applying different *Suzuki* reaction protocols, cross coupling was not successful with 3-pyridine boronic acid. However, *Negishi* reaction [32] with pyridin-3-ylmagnesium chloride - prepared from 3-bromopyridine with *i*-PrMgCl·LiCl solution [33] - led to **25** in moderate yield. Attempts to reduce the sulfone moiety with $LiAlH_4$ [34] or diisobutylaluminium hydride [35] failed and resulted in the decomposition of the molecule.

2.2 Biological Results. The inhibition of human adrenal corticoid producing enzymes CYP11B2 and CYP11B1 was determined in V79MZ cells, stably expressing either human CYP11B2 or CYP11B1 (Table 1). [6,36] The V79MZ cells were incubated with [^{3}H]-11-deoxycorticosterone as substrate and products formations were monitored by HPLC using a radio flow detector. Fadrozole, an unselective suppresser of adrenal corticoid formation, [37] was used as a reference (CYP11B2, IC_{50} = 0.8 nM; CYP11B1, IC_{50} = 6.3 nM).

Table 1. Inhibition of *human* CYP11B2 and CYP11B1 *in vitro*.

compd	R	X	% inhibition[a]	IC$_{50}$ (nM)[b]		Selectivity factor[e]
			V79MZ *h*CYP11B2[c]	V79MZ *h*CYP11B2[c]	V79MZ h*C*YP11B1[d]	
1a	H		22	nd	nd	nd
2a	4-OMe		22	nd	nd	nd
3a	3-OMe		20	nd	nd	nd
4a	2-OMe		18	nd	nd	nd
1	H		85	33	6712	203
2	4-OMe		80	48	4196	87
3	3-OMe		87	27	7315	271
4	2-OMe		86	64	1096	17
5	4-Cl		84	22	8947	407
6	3-Cl		90	60	4797	80
7	2-Cl		90	22	4487	204
8	4-F		84	33	5549	168
9	3-F		85	39	6548	168
10	4-OCF_3		88	32	7427	232
11	3-OCF_3		83	14	5812	415
12	2-OCF_3		77	56	4710	84
13	4-CF_3		81	25	6189	248
14	3-CF_3		88	43	6674	155
15	2-CF_3		86	53	5076	96
16	4-CN		47	nd	nd	nd
17	3-CN		84	46	8550	186
18	3,4-di-Cl		90	33	8333	253
19	3,5-di-CF_3		78	33	9346	283
20	3,5-di-Cl		87	47	4717	100
21	3-Cl-4-F		91	53	6534	123
22			79	192	6164	32
23		S	15	nd	nd	nd
24		SO	33	nd	nd	nd
25			16	nd	nd	nd
fadrozole				0.8	6.3	8

[a] Mean value of at least two experiments; inhibitor concentration, 500 nM. [b] Mean value of at least three experiments, standard deviation usually less than 25%, nd = not determined. [c] Hamster fibroblasts expressing human CYP11B2; substrate deoxycorticosterone, 100 nM. [d] Hamster fibroblasts expressing

human CYP11B1; substrate deoxycorticosterone, 100 nM. [e] $IC_{50\ CYP11B1}$ / $IC_{50\ CYP11B2}$, nd = not determined. [f] Mean value of at least two experiments; inhibitor concentration, 2 µM.

The 1-phenylthiol-3-(pyridin-3-yl)naphthalen-2-ols **1a-4a** show only low inhibition of CYP11B2 (< 25 %), whereas the corresponding sulfoxides are potent inhibitors of CYP11B2 (**1-4**, IC_{50} = 27-64 nM). Other sulfoxide derivatives with Cl, F, OCF_3, and CN substituted on the phenylsulfinyl moiety (**5-21**) also exhibit strong CYP11B2 inhibition (IC_{50} values ranging 14 to 60 nM). Exceptions are the *p*-cyano-phenylsulfinyl substituted compound **16** (47 % inhibition, c = 500 nM) and thiophen-2-ylsulfinyl **22** (IC_{50} = 192 nM), which turn out to be only moderate CYP11B2 inhibitors. The selectivity factors (SF = $IC_{50\ CYP11B1}$ / $IC_{50\ CYP11B1}$) toward CYP11B1 range from low for compounds **4** and **22** (SF = 17 and 32, respectively) to good for compounds **2**, **6**, **12**, **15**, **20** and **21** (SF = 80-123). Other sulfoxides (**1**, **3**, **7-10**, **13**, **14**, **17-19**) exhibit rather high selectivity (SF = 155-283). Compounds **5** and **11** even show SF of more than 400. Taking together, the 3-trifluoromethoxy compound **11** is the most potent (IC_{50} = 14 nM) and selective (SF = 415) CYP11B2 inhibitor within this series.

Removal of the hydroxyl group in 2-position (compound **24**) leads to a strong decrease in inhibitory potency (33 % inhibition), and the exchange of sulfoxide to sulfide (compound **23**) also only results in 15 % inhibition. Shift of the linker from position 1 to position 2 and oxidation, as accomplished in sulfone **25**, also results in a strong loss of inhibitory potency toward CYP11B2 (16 % inhibition).

The sulfoxides **1-15** and **17-22** were evaluated for their selectivity versus the steroidogenic enzymes CYP17 and CYP19. Inhibition of CYP17 was determined using the 50,000 *g* sediment of an *E. coli* homogenate recombinantly expressing human CYP17 with progesterone as substrate.[38] All compounds demonstrate almost no inhibition (< 5 %) at an inhibitor concentration of 2 µM. The inhibition of CYP19 was evaluated *in vitro* with human placental microsomes using [1β-^{3}H]androstenedione (500 nM) as substrate[39] All compounds show hardly any aromatase inhibition (< 5 %) at an inhibitor concentration of 500 nM.

The pharmacokinetic profile of compound **11** was determined by intravenous and per-oral application in a dosage of 1 mg/kg bodyweight to male Wistar rats (3 animals). Plasma samples were collected

during 24 h and compound concentrations were determined using HPLC-MS/MS. The compound was fast absorbed after oral application reaching the maximal concentration (c_{max} = 40.4 ng/ml) after 0.5 hours. Terminal half lives were calculated to be 4 hours for intravenous and 7 hours for per-oral application, respectively. Areas under the curve were shown as 1776 and 335 ng·h/ml for intravenous and per-oral application, respectively. Accordingly, bioavailability of 19 % was observed.

2.3 Docking study. Compound **11** as the most potent and selective CYP11B2 inhibitor in this series was docked into the crystal structure of CYP11B2 (PDB ID: 4DVQ) [40] to further investigate its binding to the enzyme. This compound coordinated to the heme iron with its pyridyl N in a nearly perpendicular manner (Figure 1); while the hydrophobic core pointed to β2-sheet in a mode similar to that of the natural substrate deoxycorticosterone. The naphthalenyl moiety formed π-π interactions with Phe381 and Phe487 in perpendicular and parallel ways, respectively. An intra-molecular hydrogen bond between the sulfoxide oxygen and the hydroxyl group was observed, which can also be found in the crystal of compound **1** (Figure 2). [24] With this intra-molecular hydrogen bond, the compound was folded into a twisted shape, in which the phenyl sulfoxide stretched out perpendicularly with regard to the naphthalenyl core (Figure 1). Such a conformation not only avoided steric clashes with the enzyme, but also facilitated the forming of a π-π interaction between phenyl sulfoxide moiety and Phe130. This observation is in accordance with and well explains the facts that analogues unable to form intra-molecular hydrogen bonds (**1a**-**4a**, **23** and **24**) exhibited low inhibitory potency. Substituents on phenyl sulfoxide moiety were accommodated in a small hydrophobic pocket confined by Met111-Ile112-Leu113-Val117-Leu131, however, no further interactions can be identified, which could be the reason for the observation that compounds with different substituents showed similar potency.

3. Discussion and conclusion

This paper describes 1-phenylsulfinyl-3-(pyridin-3-yl)naphthalen-2-ols as a new class of potent and selective *human* CYP11B2 inhibitors.

3-(Pyridin-3-yl)naphthalene as the common sub-structure of all synthesized compounds has already been shown to be a potent CYP11B2 inhibitor. [20] This fact together with the comparison of the biological results of sulfides **1a-4a** (18-22 % inhibition, c = 500 nM) with sulfoxides **1-4** (IC_{50} = 27-64 nM) exhibits the importance of the oxygen for CYP11B2 inhibition. Moreover, the hydroxyl group in 2-position seems to be fundamental for the binding affinity. Omission of the hydroxyl group, as accomplished in compound **24**, results in a significantly reduced CYP11B2 inhibition of only 33 %. Both facts could indicate that the intra-molecular hydrogen bridge between the sulfoxide oxygen and the hydroxyl group, as observed in the crystal structure of compound **1** (Figure 2), [24] still exist after binding to the protein. This hydrogen bond limits steric flexibility and thereby improves the inhibitory potency towards CYP11B2 but not towards other CYP enzymes. In the sulfoxide series the effects of the substituents on the phenyl moiety were investigated (compounds **1**-**22**). Surprisingly, all tested substituents were found to exhibit strong CYP11B2 inhibition. Only in case of *para*-cyano substitution, as accomplished in **16** and bioisosteric exchange of phenyl by thiophene (compound **22**), there is a sharp loss of inhibitory potency. For the other compounds, no clear structure activity relationship is observed. The introduction of the electron donating methoxy substituent into the *meta*-position leads to one of the best compounds of this series (**3**, IC_{50} = 27 nM, SF = 271), whereas a methoxy in *para* or *ortho* position results in a significant decrease in selectivity versus CYP11B1 (**2**, SF = 87 and **4**, SF = 17). The same trend was observed after replacing methoxy by trifluoromethoxy, which led to the best compound of this series, i.e. the *meta*-trifluoromethoxy derivative **11** (IC_{50} = 14 nM, SF = 415). Several other electron withdrawing substituents (e.g. *ortho*- and *para*-chloro) lead to almost equally potent CYP11B2 inhibitors (**7**, IC_{50} = 22 nM, SF = 204; **5**, IC_{50} = 22 nM, SF = 407) with excellent selectivities over CYP11B1.

It is no doubt that the inhibition of CYP11B2 is a promising treatment for primary aldosteronism, hypertension, congestive heart failure, myocardial fibrosis and diabetic nephropathy. [7] The application of CYP11B2 inhibition can also be expanded to other indications because elevation of aldosterone levels is suspected as a side effect in breast cancer patients receiving aromatase (CYP19) inhibitors as

well as prostate cancer patients under androgen deprivation therapy. Therefore, administration of CYP11B2 inhibitors as adjuvant agents to these therapies or the employment of selective dual inhibitors of CYP19/CYP11B2 [41] and CYP17/CYP11B2 [42] should be superior treatments for breast and prostate cancer patients as they reduce the risks of cardiovascular diseases.

In this study, we have shown that 1-phenylsulfinyl-3-(pyridin-3-yl)naphthalen-2-ols are a new class of potent and selective human aldosterone synthase inhibitors. The most active compound, the *meta*-trifluoromethoxy substituted derivative **11**, exhibits an IC_{50} value of 14 nM and excellent selectivity over the highly homologous CYP11B1 (SF = 415). It shows no inhibition of CYP17 (< 5 % inhibition, c = 2 μM) and CYP19 (< 5 % inhibition, c = 500 nM) and a bioavailability after peroral application of about 20 %. This compound was chosen as a new lead compound in order to optimize pharmacokinetic parameters for further pharmacodynamic investigations *in vivo*.

4. Materials and Methods

4.1 Chemical and Analytical Methods. Melting points were measured on a Mettler FP1 melting point apparatus and are uncorrected. ^{1}H-NMR and ^{13}C-NMR were recorded on a Bruker AM500 spectrometer 500 MHz and 125 MHz, respectively, at 300 K. Chemical shifts (δ) are reported in parts per million (ppm), by reference to the hydrogenated residues of the deuterated solvent as internal standard. All coupling constants (*J*) are given in Hertz (*Hz*). Mass spectra (LC/UV/MS: ESI) were recorded on a SpectraSystem/MSQ Plus (ThermoFinnigan) instrument with a RP18-100-3 or a RP18-100-5 column (Macherey-Nagel). A water/acetonitrile gradient was used as eluent system. All compounds are > 95 % chemical pure as measured by LC/UV trace at 254 nm. Reagents were used as obtained from commercial suppliers without further purification. Solvents were distilled before use. Dry DMF was obtained by distillation from CaH_2 prior to use. CH_2Cl_2 was dried over molecular sieves (4 Å). Flash chromatography was performed on silica gel 40 (35/40–63/70 μM) and reaction progress was monitored by thin-layer chromatography on TLC Silica Gel 60 F_{254} (Merck KGaA). Visualization was accomplished with UV light. Microwave irradiation experiments were carried out in a CEM-Discover monomode microwave apparatus.

The following compounds were prepared similar to previously described procedures: 1-(phenylsulfinyl)-3-(pyridin-3-yl)naphthalen-2-ol (**1**), [Fehler: Referenz nicht gefunden] 1-(phenylthio)-3-(pyridin-3-yl)naphthalen-2-ol (**1a**), [Fehler: Referenz nicht gefunden] 1-(4-methoxyphenylthio)-3-(pyridin-3-yl)naphthalen-2-ol (**2a**), [Fehler: Referenz nicht gefunden] 1-(3-methoxyphenylthio)-3-(pyridin-3-yl)naphthalen-2-ol (**3a**), [Fehler: Referenz nicht gefunden] 1-(2-methoxyphenylthio)-3-(pyridin-3-yl)naphthalen-2-ol (**4a**), [Fehler: Referenz nicht gefunden] 3-(pyridin-3-yl)naphthalen-2-yl trifluoromethane sulfonate (**1b**), [21] 3-methoxynaphthalen-2-yl)pyridine, [20] 3-(pyridin-3-yl)naphthalen-2-ol, [21] 3-methoxynaphthalen-2-ylboronic acid, [Fehler: Referenz nicht gefunden] 3-bromo-1-fluoronaphthalene (**23b**), [Fehler: Referenz nicht gefunden] and 2-methoxy-3-(phenylsulfonyl)naphthalene (**25b**). [Fehler: Referenz nicht gefunden]

Synthesis of the target compounds. Procedure A. [Fehler: Referenz nicht gefunden] Dry K_2CO_3 (2 eq.) and subsequently substituted thiophenol (1.2 eq.) was added to a solution of **1b** (1 eq.) in dry DMF under an atmosphere of nitrogen. The mixture was stirred at 100 °C until the conversion was complete (0.5 to 3 h, monitored by TLC). After cooling to room temperature, the crude mixture was partitioned between ethyl acetate and water and the aqueous layer was exhaustingly extracted with ethyl acetate. The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. Then, the solvents were removed under reduced pressure. The products were obtained after flash chromatography on silica gel (petroleum ether/ethyl acetate or CH_2Cl_2/methanol mixtures).

Procedure B. [Fehler: Referenz nicht gefunden] *m*-CPBA (1 eq.) was added in portions to a solution of the sulfide (1 eq.) in CH_2Cl_2. The mixture was stirred at room temperature until the conversion was complete (0.5 to 3 h, monitored by TLC). Then, it was washed with saturated aqueous Na_2CO_3 and subsequently with brine, before it was dried over anhydrous $MgSO_4$. Evaporation of the solvents under reduced pressure and purification by flash chromatography on silica gel (CH_2Cl_2/methanol mixtures) afforded the sulfoxides.

1-(Phenylthio)-3-(pyridin-3-yl)naphthalen-2-ol (1a). Compound **1a** was obtained according to procedure A using **1b** (530 mg, 1.50 mmol) and thiophenol (184 µl, 1.80 mmol) in DMF (15 ml) after

flash chromatography (petroleum ether/ethyl acetate 3/1) as colorless solid (425 mg, 1.29 mmol, 86 %), Anal. C21H15NOS (C, H, N, O), mp 105 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.09 (dd, ^{3}J = 7.3 Hz, ^{4}J = 1.3 Hz, 2H), 7.13 (dd, ^{3}J = ^{3}J = 7.4 Hz, 1H), 7.20 (dd, ^{3}J = ^{3}J = 7.4 Hz, 2H), 7.38-7.44 (m, 2H), 7.53 (ddd, ^{3}J = ^{3}J = 7.7 Hz, ^{4}J = 1.4 Hz, 1H), 7.57 (s, 1H), 7.87 (d, ^{3}J = 8.2 Hz, 1H), 7.97 (s, 1H), 8.06 (ddd, ^{3}J = 7.8 Hz, ^{4}J = ^{4}J = 2.0 Hz, 1H), 8.24 (d, ^{3}J = 8.2 Hz, 1H), 8.64 (dd, ^{3}J = 4.7 Hz, ^{4}J = 1.6 Hz, 1H), 8.94 (d, ^{4}J = 1.9 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 122.9, 124.5, 124.8, 126.2, 126.6, 126.8, 128.3, 128.8, 129.3, 129.3, 133.0, 133.5, 134.9, 135.2, 136.9, 148.7, 149.0, 150.1, 154.5. MS *m/z* 329.94 (MH^+).

1-(4-Methoxyphenylthio)-3-(pyridin-3-yl)naphthalen-2-ol (2a). Compound **2a** was obtained according to procedure A using **1b** (707 mg, 2.00 mmol) and 4-methoxythiophenol (295 µl, 2.40 mmol) in DMF (20 ml) after flash chromatography (petroleum ether/ethyl acetate 2/1) and crystallization from ethanol as colorless solid (303 mg, 0.48 mmol, 42 %), Anal. C22H17NO2S (C, H, N, O), mp 164 °C. MS *m/z* 360.02 (MH^+).

1-(3-Methoxyphenylthio)-3-(pyridin-3-yl)naphthalen-2-ol (3a). Compound **3a** was obtained according to procedure A using **1b** (707 mg, 2.00 mmol) and 3-methoxythiophenol (297 µl, 2.40 mmol) in DMF (20 ml) after flash chromatography (petroleum ether/ethyl acetate 3/1) and crystallization from ethanol as colorless solid (446 mg, 1.24 mmol, 62 %), Anal. C22H17NO2S (C, H, N, O), mp 157 °C. MS *m/z* 360.01 (MH^+).

1-(2-Methoxyphenylthio)-3-(pyridin-3-yl)naphthalen-2-ol (4a). Compound **4a** was obtained according to procedure A using **1b** (556 mg, 1.57 mmol) and 2-methoxythiophenol (230 µl, 1.89 mmol) in DMF (20 ml) after flash chromatography (CH_2Cl_2/methanol 99/1) and crystallization from ethanol as colorless solid (191 mg, 0.53 mmol, 34 %), Anal. C22H17NO2S (C, H, N, O), mp 167-168 °C. MS *m/z* 359.99 (MH^+).

1-(Phenylsulfinyl)-3-(pyridin-3-yl)naphthalen-2-ol (1). Compound **1** was obtained according to procedure B using **1a** (165 mg, 0.50 mmol) and *m*-CPBA (123 mg, 0.50 mmol) in CH_2Cl_2 (10 ml) after flash chromatography (CH_2Cl_2/methanol 99/1) as colorless solid (129 mg, 0.37 mmol, 75 %), Anal.

C21H15NO2S (C, H, N, O), mp 142 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36 (ddd, ^{3}J = 7.9 Hz, ^{3}J = 4.9 Hz, ^{5}J = 0.8 Hz, 1H), 7.42-7.48 (m, 4H), 7.58 (ddd, ^{3}J = ^{3}J = 7.7 Hz, ^{4}J = 1.3 Hz, 1H), 7.74-7.76 (m, 2H), 7.83 (d, ^{3}J = 8.2 Hz, 1H), 7.91 (s, 1H), 8.01 (ddd, ^{3}J = 7.9 Hz, ^{4}J = ^{4}J = 2.1 Hz, 1H), 8.04 (dd, ^{3}J = 8.4 Hz, ^{4}J = 0.8 Hz, 1H), 8.61 (dd, ^{3}J = 4.9, ^{4}J = 1.7 Hz, 1H), 8.83 (dd, ^{4}J = 2.4 Hz, ^{4}J = 0.8 Hz, 1 H), 11.99 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 113.9, 120.3, 122.8, 124.6, 125.2, 128.4, 129.1, 129.6, 129.9, 130,8, 131.7, 132.3, 134.0, 137.1, 142.8, 148.8, 150.1, 158.0. MS *m/z* 346.01 (MH^+).

1-(4-Methoxyphenylsulfinyl)-3-(pyridin-3-yl)naphthalen-2-ol (2). Compound **2** was obtained according to procedure B using **2a** (145 mg, 0.40 mmol) and *m*-CPBA (100 mg, 0.40 mmol) in CH_2Cl_2 (10 ml) after flash chromatography (CH_2Cl_2/methanol 99/1) and crystallization with HCl (2N in diethyl ether) as colorless solid (117 mg, 0.28 mmol, 71 %), Anal. C22H17NO3S (C, H, N, O), mp 161 °C. MS *m/z* 375.95 (MH^+).

1-(3-Methoxyphenylsulfinyl)-3-(pyridin-3-yl)naphthalen-2-ol (3). Compound **3** was obtained according to procedure B using **3a** (100 mg, 0.29 mmol) and *m*-CPBA (72 mg, 0.29 mmol) in CH_2Cl_2 (5 ml) after flash chromatography (CH_2Cl_2/methanol 99/1) as colorless solid (70 mg, 0.19 mmol, 64 %), Anal. C22H17NO3S (C, H, N, O), mp 126 °C. MS *m/z* 376.12 (MH^+).

1-(2-Methoxyphenylsulfinyl)-3-(pyridin-3-yl)naphthalen-2-ol (4). Compound **4** was obtained according to procedure B using **4a** (100 mg, 0.29 mmol) and *m*-CPBA (72 mg, 0.29 mmol) in CH_2Cl_2 (5 ml) after flash chromatography (CH_2Cl_2/methanol 99/1) as colorless solid (92 mg, 0.25 mmol, 84 %), Anal. C22H17NO3S (C, H, N, O), mp 138 °C. MS *m/z* 375.98 (MH^+).

1-(4-Chlorophenylsulfinyl)-3-(pyridin-3-yl)naphthalen-2-ol (5). Compound **5** was obtained according to procedure B using **5a** (143 mg, 0.39 mmol) and *m*-CPBA (97 mg, 0.39 mmol) in CH_2Cl_2 (5 ml) after flash chromatography (CH_2Cl_2/methanol 99/1) as colorless foam (101 mg, 0.27 mmol, 68 %), Anal. C21H14ClNO2S (C, H, N, O), mp 144 °C. MS *m/z* 379.93 ($M^{35}ClH^+$), 381.66 ($M^{37}ClH^+$).

1-(3-Chlorophenylsulfinyl)-3-(pyridin-3-yl)naphthalen-2-ol (6). Compound **6** was obtained according to procedure B using **6a** (272 mg, 0.75 mmol) and *m*-CPBA (184 mg, 0.75 mmol) in CH_2Cl_2

(15 ml) after flash chromatography (CH_2Cl_2/methanol 98/2) as colorless solid (181 mg, 0.48 mmol, 48 %), Anal. C21H14ClNO2S (C, H, N, O), mp 150 °C. MS *m/z* 379.83 ($M^{35}ClH^+$), 382.00 ($M^{37}ClH^+$).

1-(2-Chlorophenylsulfinyl)-3-(pyridin-3-yl)naphthalen-2-ol (7). Compound **7** was obtained according to procedure B using **7a** (302 mg, 0.83 mmol) and *m*-CPBA (205 mg, 0.83 mmol) in CH_2Cl_2 (15 ml) after flash chromatography (CH_2Cl_2/methanol 99/1 and petroleum ether/ethyl acetate 2/1) and crystallization with HCl as colorless solid (131 mg, 0.31 mmol, 38 %), Anal. C21H14ClNO2S (C, H, N, O), mp (HCl salt) 202 °C. MS *m/z* 379.91 ($M^{35}ClH^+$), 381.83 ($M^{37}ClH^+$).

1-(4-Fluorophenylsulfinyl)-3-(pyridin-3-yl)naphthalen-2-ol (8). Compound **8** was obtained according to procedure B using **8a** (192 mg, 0.55 mmol) and *m*-CPBA (136 mg, 0.55 mmol) in CH_2Cl_2 (10 ml) after flash chromatography (CH_2Cl_2/methanol 98/2) as colorless foam (113 mg, 0.31 mmol, 56 %), Anal. C21H14FNO2S (C, H, N, O), mp 132 °C. MS *m/z* 364.02 (MH^+).

1-(3-Fluorophenylsulfinyl)-3-(pyridin-3-yl)naphthalen-2-ol (9). Compound **9** was obtained according to procedure B using **9a** (241 mg, 0.69 mmol) and *m*-CPBA (171 mg, 0.69 mmol) in CH_2Cl_2 (10 ml) after flash chromatography (CH_2Cl_2/methanol 98/2) as colorless foam (193 mg, 0.53 mmol, 77 %), Anal. C21H14FNO2S (C, H, N, O), mp 141 °C. MS *m/z* 363.88 (MH^+).

3-(Pyridin-3-yl)-1-(4-(trifluoromethoxy)phenylsulfinyl)naphthalen-2-ol (10). Compound **10** was obtained according to procedure B using **10a** (254 mg, 0.61 mmol) and *m*-CPBA (151 mg, 0.61 mmol) in CH_2Cl_2 (12 ml) after flash chromatography (CH_2Cl_2/methanol 99/1) as yellow foam (144 mg, 0.34 mmol, 55 %), Anal. C22H14F3NO3S (C, H, N, O), mp 106 °C, MS *m/z* 429.93 (MH^+).

3-(Pyridin-3-yl)-1-(3-(trifluoromethoxy)phenylsulfinyl)naphthalen-2-ol (11). Compound **11** was obtained according to procedure B using **11a** (270 mg, 0.67 mmol) and *m*-CPBA (166 mg, 0.67 mmol) in CH_2Cl_2 (7 ml) after flash chromatography (CH_2Cl_2/methanol 98/2) as off-white solid (155 mg, 0.36 mmol, 54 %), Anal. C22H14F3NO3S (C, H, N, O), mp 101 °C. MS *m/z* 430.00 (MH^+).

3-(Pyridin-3-yl)-1-(2-(trifluoromethoxy)phenylsulfinyl)naphthalen-2-ol (12). Compound **12** was obtained according to procedure B using **12a** (278 mg, 0.67 mmol) and *m*-CPBA (166 mg, 0.67 mmol)

in CH_2Cl_2 (10 ml) after flash chromatography (CH_2Cl_2/methanol 98.5/1.5) as yellow solid (102 mg, 0.24 mmol, 38 %), Anal. C22H14F3NO3S (C, H, N, O), mp 118 °C. MS *m/z* 429.93 (MH^+).

3-(Pyridin-3-yl)-1-(4-(trifluoromethyl)phenylsulfinyl)naphthalen-2-ol (13). Compound **13** was obtained according to procedure B using **13a** (238 mg, 0.60 mmol) and *m*-CPBA (148 mg, 0.60 mmol) in CH_2Cl_2 (10 ml) after flash chromatography (CH_2Cl_2/methanol 99/1) as yellow solid (123 mg, 0.30 mmol, 50 %), Anal. C22H14F3NO2S (C, H, N, O), mp 117 °C. MS *m/z* 413.98 (MH^+).

3-(Pyridin-3-yl)-1-(3-(trifluoromethyl)phenylsulfinyl)naphthalen-2-ol (14). Compound **14** was obtained according to procedure B using **14a** (235 mg, 0.59 mmol) and *m*-CPBA (145 mg, 0.59 mmol) in CH_2Cl_2 (10 ml) after flash chromatography (CH_2Cl_2/methanol 99/1) as off-white solid (99 mg, 0.24 mmol, 41 %), Anal. C22H14F3NO2S (C, H, N, O), mp 124 °C. MS *m/z* 413.98 (MH^+).

3-(Pyridin-3-yl)-1-(2-(trifluoromethyl)phenylsulfinyl)naphthalen-2-ol (15). Compound **15** was obtained according to procedure B using **15a** (178 mg, 0.45 mmol) and *m*-CPBA (110 mg, 0.45 mmol) in CH_2Cl_2 (5 ml) after flash chromatography (CH_2Cl_2/methanol 99/1) as colorless foam (69 mg, 0.17 mmol, 37 %), Anal. C22H14F3NO2S (C, H, N, O), mp 62 °C. MS *m/z* 413.85 (MH^+).

4-(2-Hydroxy-3-(pyridin-3-yl)naphthalen-1-ylsulfinyl)benzonitrile (16). Compound **16** was obtained according to procedure B using **16a** (215 mg, 0.61 mmol) and *m*-CPBA (150 mg, 0.61 mmol) in CH_2Cl_2 (5 ml) after flash chromatography (CH_2Cl_2/methanol 98/2) as off-white solid (103 mg, 0.28 mmol, 46 %), Anal. C22H14N2O2S (C, H, N, O), mp 150 °C. MS *m/z* 370.87 (MH^+).

3-(2-Hydroxy-3-(pyridin-3-yl)naphthalen-1-ylsulfinyl)benzonitrile (17). Compound **17** was obtained according to procedure B using **17a** (126 mg, 0.36 mmol) and *m*-CPBA (88 mg, 0.36 mmol) in CH_2Cl_2 (4 ml) after flash chromatography (CH_2Cl_2/methanol 98/2) as off-white solid (77 mg, 0.21 mmol, 58 %), Anal. C22H14N2O2S (C, H, N, O), mp 155 °C. MS *m/z* 370.87 (MH^+).

1-(3,4-Dichlorophenylsulfinyl)-3-(pyridin-3-yl)naphthalen-2-ol (18). Compound **18** was obtained according to procedure B using **18a** (153 mg, 0.38 mmol) and *m*-CPBA (95 mg, 0.38 mmol) in CH_2Cl_2 (8 ml) after flash chromatography (CH_2Cl_2/methanol 98/2) as yellow foam (86 mg, 0.19 mmol, 51 %), Anal. C21H13Cl2NO2S (C, H, N, O), mp 144 °C. MS *m/z* 413.84 ($M^{35}ClH^+$), 415.45 ($M^{37}ClH^+$).

1-(3,5-Bis(trifluoromethyl)phenylsulfinyl)-3-(pyridin-3-yl)naphthalen-2-ol (19). Compound **19** was obtained according to procedure B using **19a** (169 mg, 0.36 mmol) and *m*-CPBA (90 mg, 0.36 mmol) in CH_2Cl_2 (13 ml) after flash chromatography (CH_2Cl_2/methanol 99/1) as yellow solid (70 mg, 0.15 mmol, 40 %), Anal. C23H13F6NO2S (C, H, N, O), mp 118 °C. MS *m/z* 481.99 (MH^+).

1-(3,5-Dichlorophenylsulfinyl)-3-(pyridin-3-yl)naphthalen-2-ol (20). Compound **20** was obtained according to procedure B using **20a** (170 mg, 0.43 mmol) and *m*-CPBA (106 mg, 0.43 mmol) in CH_2Cl_2 (7 ml) after flash chromatography (CH_2Cl_2/methanol 98/2) as colorless solid (97 mg, 0.24 mmol, 54 %), Anal. C21H13Cl2NO2S (C, H, N, O), mp 124 °C. MS *m/z* 413.91 ($M^{35}ClH^+$), 415.73 ($M^{37}ClH^+$).

1-(3-Chloro-4-fluorophenylsulfinyl)-3-(pyridin-3-yl)naphthalen-2-ol (21). Compound **21** was obtained according to procedure B using **21a** (170 mg, 0.43 mmol) and *m*-CPBA (106 mg, 0.43 mmol) in CH_2Cl_2 (10 ml) after flash chromatography (CH_2Cl_2/methanol 99/1) as colorless solid (104 mg, 0.26 mmol, 61 %), Anal. C21H13ClFNO2S (C, H, N, O), mp 123 °C. MS *m/z* 397.74 ($M^{35}ClH^+$), 399.91($M^{37}ClH^+$).

3-(Pyridin-3-yl)-1-(thiophen-2-ylsulfinyl)naphthalen-2-ol (22). Compound **22** was obtained according to procedure B using **22a** (62 mg, 0.18 mmol) and *m*-CPBA (46 mg, 0.18 mmol) in CH_2Cl_2 (4 ml) after flash chromatography (CH_2Cl_2/methanol 98.5/1.5) as off-white solid (36 mg, 0.10 mmol, 57 %), C19H13NO2S2 (C, H, N, O), mp 107 °C. MS *m/z* 351.91 (MH^+).

3-(4-(Phenylthio)naphthalen-2-yl)pyridine hydrochloride (23). Compound **23a** (450 mg, 2.02 mmol), thiophenol (227 µl, 2.22 mmol) and K_2CO_3 (306 mg, 2.22 mmol) in DMF (5 ml) were suspended in a 10 ml septum-capped tube. The mixture was irradiated in the microwave at a temperature of 150 °C and an initial irradiation power of 150 W for 40 min. After cooling to room temperature, the mixture was diluted with water and extracted with ethyl acetate. The combined extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Purification by flash chromatography (CH_2Cl_2/methanol 99/1), crystallization with HCl (2N in diethyl ether) and recrystallization from ethanol yielded **23** as colorless solid (74 mg, 0.21 mmol, 9 %), Anal. Anal. C21H15NS (C, H, N, O), mp (HCl salt) 188 °C. MS *m/z* 314.10 (MH^+).

3-(4-(Phenylsulfinyl)naphthalen-2-yl)pyridine (24). Compound **24** was obtained according to procedure B using **23** (free base, 142 mg, 0.45 mmol) and *m*-CPBA (112 mg, 0.45 mmol) in CH_2Cl_2 (3 ml) after flash chromatography (CH_2Cl_2/methanol 99/1) as colorless solid (61 mg, 0.19 mmol, 41 %), Anal. C21H15NOS (C, H, N, O), mp 143 °C. MS *m/z* 330.06 (MH^+).

3-(3-(Phenylsulfonyl)naphthalen-2-yl)pyridine (25). A 0.5 M solution of $ZnCl_2$ in THF (6.8 ml, 3.38 mmol) was added to a solution of **25a** (1.28 g, 3.07 mmol) and $Pd(PPh_3)_4$ (178 mg, 0.15 mmol, 5 mol %) in THF (10 ml). After stirring for 1 h at room temperature a Grignard solution, freshly prepared from 3-bromopyridine (390 µl, 4.00 mmol) and 0.96 M *i*-PrMgCl·LiCl solution (4.5 ml, 4.3 mmol) at -10 °C, was added slowly at 50 °C. The resulting mixture was stirred at 50 °C for 5 h, then allowed to reach room temperature, before 2 M HCl was added. The organic layer was separated. Then, the aqueous solution was washed with *n*-hexane and afterwards neutralised with aqueous Na_2CO_3 solution, before it was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$ and concentrated. Compound **25** (349 mg, 1.01 mmol, 33 %) was obtained after purification by flash chromatography (CH_2Cl_2/methanol 99/1) as off-white solid, Anal. C21H15NO2S (C, H, N, O), mp 152 °C. MS *m/z* 346.03 (MH^+).

4.2 Biological test assays.

Activity and selectivity assays using V79 Cells. V79MZ*h*CYP11B1, V79MZ*h*CYP11B2 or V79MZ*r*CYP11B2 cells [6,Fehler: Referenz nicht gefunden,37] were preincubated with 500 nM of inhibitor (*h*CYP11B) or 2 µM (*r*CYP11B2) at 37 °C for 1 h. For determination of IC_{50} values, at least three different inhibitor concentrations were used. The reaction was started by addition of 100 nM (*h*CYP11B) or 500 nM (*r*CYP11B2) [^{3}H]-11-deoxycorticosterone as substrate. After incubation for 25 min (*h*CYP11B1), 45 min (*h*CYP11B2) or 7 h (*r*CYP11B2), the enzyme reactions were stopped by extracting the supernatant with ethyl acetate. Samples were centrifuged (10,000 x g, 5 min), and the ethyl acetate was separated.18 The steroids were separated by HPLC and analyzed with radio flow detection.

Selectivity tests versus *h*CYP17 and *h*CYP19. *h*CYP17 [Fehler: Referenz nicht gefunden] and *h*CYP19 [Fehler: Referenz nicht gefunden] enzyme preparations and assay procedures were performed as previously described.

In vivo pharmacokinetics. The animal study was conducted in accordance with German animal welfare guidelines. Adult male Wistar rats (243-275 g) were housed in a temperature-controlled room (20-24 °C) and maintained in a 12 h light/12 h dark cycle. The animals were catheterized in the jugular vein 2-3 days prior to the blood sampling. They were fasted ~14-16 h before application and fed again 6 hours after application. Water was available ad libitum. Prior to the first blood sampling, the rats were connected to a counterbalanced system and tubing to perform blood sampling in the freely moving animal. Compound **11** was dissolved in PEG400/water (1:1), was administered intravenous (1 mg/kg, 2 ml/kg, 3 rats) or peroral (1 mg/kg, 5 ml/kg, 3 rats). At time 0, **11** was applied and blood samples (250 µl) were taken at different time points between 5 min and 24 h postdose. Plasma was harvested and kept at -20 °C until being assayed. HPLC-MS/MS analysis and quantification of the samples was carried out on a Surveyor HPLC system coupled with a TSQ Quantum (ThermoFisher) triple quadrupole mass spectrometer equipped with an electrospray ioninterface (ESI). The mean of absolute plasma concentrations (± SEM) was calculated for the three rats and the regression was performed on group mean values. The pharmacokinetic analysis was performed by applying a non-compartment model using the PK Solutions 2.0 software (Summit Research Services, Montrose, USA).

4.3 Docking study

The CYP11B2 crystal (PDB ID: 4DVQ) was processed as described previously, [43] including the removal of redundant protein copies, substrate and water as well as the addition of hydrogens and partial charges. Ligand was built and its energy was minimized in the MMFF94s force field using MOE. The docking study was performed with GOLD in automatic active-site detection mode. Heme iron was defined as the origin of active-site with a radius of 19 Å. The distance between the *sp*2 hybrid N and the iron was constrained to 1.9 to 2.5 Å. 50 independent genetic algorithm iterations for each run were set. The resulted poses were further analyzed according to fitness in MOE.

Acknowledgment. The authors thank Gertrud Schmitt and Jeannine Jung for the help in performing the *in vitro* tests. We are grateful to Prof. J. J. Rob Hermans, University of Maastricht, The Netherlands, for supplying the V79MZ*h*CYP11B1 cells, and to Prof. Rita Bernhardt, Saarland University, for supplying the V79MZ*h*CYP11B2 cells. We thank Dr. M. Heydel for helpful discussions during writing the manuscript. The PK-study was conducted by Pharmacelsus GmbH financed by the grant 0315478A from BMBF Germany.

Supplementary Data. NMR spectroscopic data of target compounds **2a**-**4a** and **2-25**, full experimental details and spectroscopic characterization of intermediates **5a-23a** and **25a** as well as the ^{1}H and ^{13}C spectra of the most potent and selective compounds **3**, **5**, **11**, **13**, **18** and **19**.

References

Chart 1. Title compounds: 1-Phenylsulfinyl-2-hydroxy-3-heterocycle substituted naphthalenes and related compounds.

Scheme 1. Synthesis of compounds **1-22**[a]

[a]Reagents and conditions: (i) *n*-BuLi, $B(OMe)_3$, THF -78 °C, then HCl/water; (ii) 3-bromopyridine, $Pd(PPh_3)_4$, aq. Na_2CO_3, toluene/ethanol, reflux; (iii) HBr (48 %) in water, reflux; (iv) Tf_2O, pyridine, CH_2Cl_2, 0 °C to rt; (v) Procedure A: substituted thiophenol or thiophene-2-thiol, K_2CO_3, DMF, 100 °C; (vi) Procedure B: *m*-CPBA, CH_2Cl_2, rt.

Scheme 2. Synthesis of compounds **23**,**24**[a]

[a]Reagents and conditions: (i) *s*-BuLi, hexane, -78 °C, then Br_2; (ii) *n*-BuLi, 2,2,6,6-tetramethylpiperidine, THF/hexane, -78 °C; (iii) 3-bromopyridine, $Pd(PPh_3)_4$, aq. Na_2CO_3, toluene/ethanol 4/1, reflux; (iv) thiophenol, K_2CO_3, DMF, μw, 200 °C; (v) Procedure B: *m*-CPBA, CH_2Cl_2, rt.

Scheme 3. Synthesis of compound **25**[a]

[a]Reagents and conditions: (i) *n*-BuLi, THF, 0 °C, then $PhSO_2F$; (ii) HBr (48 %) in water, reflux; (iii) Tf_2O, pyridine, CH_2Cl_2, 0 °C to rt; (iv) $Pd(PPh_3)_4$, $ZnCl_2$, THF, rt, then pyridin-3-ylmagnesium bromide, 50 °C.

Figure 1. The binding of compound **11** in the crystal of CYP11B2 (PDB ID: 4DVQ).

Figure 2. The hydrogen bridge between the sulfoxide oxygen and the hydroxyl group in compound **1** (CCDC 936617). [24]

[1][] Weber, K. T. Mechanisms of disease: Aldosterone in congestive heart failure. *N. Engl. J. Med.* **2001**, *345*, 1689-1697.

[2][] (a) Pitt, B.; Zannad, F.; Remme, W. J.; Cody, R.; Castaigne, A.; Perez, A.; Palensky, J.; Wittes, J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N. Engl. J. Med.* **1999**, *341*, 709-717. (b) Pitt, B.; Remme, W.; Zannad, F.; Neaton, J.; Martinez, F.; Roniker, B.; Bittman, R.; Hurley, S.; Kleiman, J.; Gatlin, M. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N. Engl. J. Med.* **2003**, *348*, 1309-1321.

[3][] Delcayre, C.; Swynghedauw, B. Molecular mechanisms of myocardial remodeling. The role of aldosterone. *J. Mol. Cell Cardiol.* **2002**, *34*, 1577-1584.

[4][] Funder, J. W. The nongenomic actions of aldosterone. *Endocr. Rev.* **2005**, *26*, 313-321.

[5][] Ehmer, P. B.; Bureik, M.; Bernhardt, R.; Müller, U.; Hartmann, R. W. Development of a test system for inhibitors of human aldosterone synthase (CYP11B2): Screening in fission yeast and evaluation of selectivity in V79 cells. *J. Steroid Biochem. Mol. Biol.* **2002**, *81*, 173-179.

[6][] Hartmann, R. W.; Müller, U.; Ehmer, P. B. Discovery of selective CYP11B2 (aldosterone synthase) inhibitors for the therapy of congestive heart failure and myocardial fibrosis. *Eur. J. Med. Chem.* **2003**, *38*, 363-366.

[7][] Hu, Q.; Yin, L.; Hartmann, R. W. Aldosterone synthase inhibitors as promising treatments for mineralocorticoid dependent cardiovascular and renal diseases. *J. Med. Chem.* **2014**, *57*, 5011–5022.

[8][] Kawamoto, T.; Mitsuuchi, Y.; Toda, K.; Yokoyama, Y.; Miyahara, K.; Miura, S.; Ohnishi, T.; Ichikawa, Y.; Nakao, K.; Imura, H.; Ulick, S.; Shizuta, Y. Role of steroid 11β-hydroxylase and steroid 18-hydroxylase in the biosynthesis of glucocorticoids and mineralocorticoids in humans. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 1458-1462.

[9][] Mornet, E.; Dupont, J.; Vitek, A.; White, P. C. Characterization of two genes encoding human steroid 11*β*-hydroxylase (P-450 11*β*). *J. Biol. Chem.* **1989**, *264*, 20961-20967.

[10][] (a) Yin, L.; Lucas, S.; Maurer, F.; Kazmaier, U.; Hu, Q.; Hartmann, R. W. Novel imidazol-1-ylmethyl substituted 1,2,5,6-tetrahydro-pyrrolo[3,2,1-ij]quinolin-4-ones as potent and selective CYP11B1 inhibitors for the treatment of Cushing's syndrome. *J. Med. Chem.* **2012**, *55*, 6629–6633. (b) Emmerich, J.; Hu, Q.; Hanke, N.; Hartmann, R. W. Cushing's syndrome: Development of highly potent and selective CYP11B1 inhibitors of the (pyridylmethyl)pyridine type. *J. Med. Chem.* **2013**, *56*, 6022–6032. (c) Hille, U. E.; Zimmer, C.; Vock, C. A.; Hartmann, R. W. Discovery of the first selective steroid-11β-hydroxylase (CYP11B1) inhibitors for the treatment of cortisol dependent diseases. *ACS Med. Chem. Lett.* **2011**, *2*, 2–6. (d) Zhu, W.; Hu, Q.; Hanke, N.; van Koppen, C. J.; Hartmann, R. W. Potent 11β-hydroxylase inhibitors with inverse metabolic stability in human plasma and hepatic S9 fractions to promote wound healing. *J. Med. Chem.* **2014**, *57*, 7811–7817.

[11][] Roumen, L.; Peeters, J. W.; Emmen, J. W. A.; Beugels, I. P. E.; Custers, E. M G.; de Gooyer, M.; Plate, R.; Pieterse, K.; Hilbers, P. A. J.; Smits, J. F. M.; Vekemans, J. A. J.; Leysen, D.; Ottenheijm, H. J. C.; Janssen, H. M.; Hermans, J. J. R. Synthesis, biological evaluation, and molecular modelling of 1-benzyl-1*H*-imidazoles as selective inhibitors of aldosterone synthase (CYP11B2), *J. Med. Chem,* **2010**, *53*, 1712–1725.

[12][] Firooznia, F. Preparation of imidazo[1,5*a*]pyridine derivatives for treatment of aldosterone mediated diseases, PCT Int. Appl. WO2004046145, 2004.

[13][] Hu, Q.-Y.; Ksander, G. 4-Imidazolyl-1,2,3,4-tetrahydroquinoline derivatives and their use as aldosterone synthase/11-beta-hydroxylase inhibitors. PCT Int. Appl. WO2008076860, 2008.

[14][] (a) Herold, P.; Mah, R.; Tschinke, V.; Stojanovic, A.; Marti, C.; Jotterand, N.; Schumacher, C.; Quirmbach, M. Heterocyclic spiro-compounds as aldosterone synthase inhibitors, PCT Int. Appl. WO2006128853, 2006. (b) Herold, P.; Mah, R.; Tschinke, V.; Stojanovic, A.; Marti, C.; Jotterand, N.; Schumacher, C.; Quirmbach, M. Heterocyclic spiro-compounds, PCT Int. Appl.

WO2006128852, 2006. (c) Herold, P.; Mah, R.; Tschinke, V.; Stojanovic, A.; Marti, C.; Jotterand, N.; Schumacher, C.; Quirmbach, M. Fused imidazole derivatives and use thereof as aldosterone synthase inhibitors, PCT Int. Appl. WO2006128851, 2006.

[15][] (a) Menard, J.; Watson, C.; Rebello, S.; Zhang, Y. M.; Dole, W. P., Hormonal and electrolyte responses to the aldosterone synthase inhibitor LCI699 in soduim depleted healthy subjects. *J. Am. Coll. Cardiol*. **201**0, *55*, A61.E583-A61.E583. (b) White, W. B.; Calhoun, D. A.; Krum, H.; Guo, W.; Trapani, A. J.; Lefkowitz, M.; Menard, J., Blockade of aldosterone production as a novel approach to the management of high blood pressure: Efficacy and tolerability of the aldosterone synthase inhibitor LCI699 in patients with stage 1-2 hypertension. *J. Am. Coll. Cardiol.* **2010**, *55*, A61.E582-A61.E582.

[16][] (a) Gobbi, S.; Cavalli, A.; Negri, M.; Schewe, K. E.; Belluti, F.; Piazzi, L.; Hartmann, R. W.; Recanatini, M.; Bisi, A. Imidazolylmethylbenzophenones as highly potent aromatase inhibitors. *J. Med. Chem.* **2007**, *50*, 3420–3422. (b) Gobbi, S.; Hu, Q.; Negri, M.; Zimmer, C.; Belluti, F.; Rampa, A.; Hartmann, R. W.; Bisi, A. Modulation of cytochromes P450 with xanthone-based molecules: from aromatase to aldosterone synthase and steroid 11β-hydroxylase inhibition. *J. Med. Chem.* **2013**, *56*, 1723–1729. (c) Leze, M. P.; Le Borgne, M.; Pinson, P.; Palusczak, A.; Duflos, M.; Le Baut, G.; Hartmann, R. W. Synthesis and biological evaluation of 5-[(aryl)(1H-imidazol-1-yl)methyl]-1H-indoles: potent and selective aromatase inhibitors. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1134–1137.

[17][] (a) Hille, U. E.; Hu, Q.; Vock, C.; Negri, M.; Bartels, M.; Müller-Vieira, U.; Lauterbach, T.; Hartmann, R. W. Novel CYP17 inhibitors: Synthesis, biological evaluation, structure–activity relationships and modelling of methoxy- and hydroxy-substituted methyleneimidazolyl biphenyls. *Eur. J. Med. Chem.* **2009**, *44,* 2765-2775. (b) Hu, Q.; Negri, M.; Jahn-Hoffmann, K.; Zhuang, Y.; Olgen, S.; Bartels, M.; Müller-Vieira, U.; Lauterbach, T.; Hartmann, R. W. Synthesis, biological evaluation, and molecular modeling studies of methylene imidazole substituted biaryls as inhibitors

of human 17α-hydroxylase-17,20-lyase (CYP17)-Part II: Core rigidification and influence of substituents at the methylene bridge. *Bioorg. Med. Chem.* **2008**, *16*, 7715–7727. (c) Yin, L.; Hu, Q.; Hartmann, R. W. Recent progress in pharmaceutical therapy for castration-resistant prostate cancer. *Int. J. Mol. Sci.* **2013**, *14*, 13958–13978. (d) Hartmann, R. W.; Frotscher, M.; Ledergerber, D.; Wächter, G. A.; Grün, G. L.; Sergejew, T. F. Synthesis and evaluation of azole-substituted tetrahydronaphthalenes as inhibitors of P450 arom, P450 17, and P450 TxA_2. *Arch. Pharm. (Weinheim)* **1996**, *329,* 251-261. (e) Hu, Q.; Yin, L.; Jagusch, C.; Hille, U. E.; Hartmann, R. W. Isopropylidene substitution increases activity and selectivity of biphenyl methylene 4-pyridine type CYP17 inhibitors. *J. Med. Chem.* **2010**, *53*, 5049–5053.

[18][] Ulmschneider, S.; Müller-Vieira, U.; Klein, C. D.; Antes, I.; Lengauer, T.; Hartmann, R. W. Synthesis and evaluation of (pyridylmethylene)tetrahydronaphthalenes/-indanes and structurally modified derivatives: potent and selective inhibitors of aldosterone synthase. *J. Med. Chem*. **2005**, *48*, 1563-1575.

[19][] Ulmschneider, S.; Müller-Vieira, U.; Mitrenga, M.; Hartmann, R. W.; Oberwinkler-Marchais, S.; Klein, C. D.; Bureik, M.; Bernhardt, R.; Antes, I.; Lengauer, T. Synthesis and evaluation of imidazolylmethylenetetrahydronaphthalenes and imidazolylmethyleneindanes: potent inhibitors of aldosterone synthase. *J. Med. Chem*. **2005**, *48*, 1796-1805.

[20][] (a) Heim, R.; Lucas, S.; Grombein, C. M.; Ries, C.; Schewe, K. E.; Negri, M.; Müller-Vieira, U.; Birk, B.; Hartmann, R. W. Overcoming undesirable CYP1A2 inhibition of pyridylnaphthalene type aldosterone synthase inhibitors: Influence of heteroaryl derivatization on potency and selectivity. *J. Med. Chem*. **2008**, *51*, 5064-5074. (b) Yin, L.; Hu, Q.; Hartmann, R. W. 3-Pyridinyl substituted aliphatic cycles as CYP11B2 inhibitors: aromaticity abolishment of the core significantly increased selectivity over CYP1A2. *PLoS ONE* **2012**, 7(11), e48048. doi:10.1371/journal.pone.0048048.

[23][] Lucas, S.; Heim, R.; Ries, C.; Schewe, K. E.; Birk, B.; Hartmann, R. W. In Vivo Active Aldosterone Synthase Inhibitors with Improved Selectivity: Lead Optimization providing a Series of Pyridine Substituted 3,4-dihydro-1*H*-quinolin-2-one derivatives. *J. Med. Chem.* **2008**, *51*, 8077-8087.

[24][] Grombein, C. M.; Hu, Q.; Heim, R.; Huch, V.; Hartmann, R. W. Unexpected results of a $S_{N,Ar}$-reaction. A novel synthetic approach to 1-arylthio-2-naphtols. *Tetrehedron Lett.* **2013**, *54*, 6615–6618.

[25][] Chowdhury, S.; Georghiou, P. E. Synthesis and properties of a new member of the calix-naphthalene family: A C_2-symmetrical *endo*-calix[*4*]naphthalene. *J. Org. Chem.* **2002**, *67*, 6808-6811.

[26][] Miyaura, N.; Suzuki, A. Palladium-catalyzed cross-coupling reactions of organoboron compounds. *Chem. Rev*. **1995**, *95*, 2457-2483.

[27][] Samreth, S.; Millet, J.; Bellamy, F.; Bajgrowicz, J.; Barberousse, V.; Renaut, P. Nouveaux beta-D-phényl-thioxylosides, leur procédé de préparation et leur utilisation en thérapeutique. Eur. Patent Appl. EP0365397, 1990.

[28][] Sheley, C. F. A convenient synthesis of 4-alkyl and 4-cyano thiophenols. *Mol. Cryst. Liq. Cryst.* **1978**, *44*, 193-196.

[29][] Newman, M. S.; Karnes, H. A. The conversion of phenols to thiophenols *via* dialkylthio-carbamates. *J. Org. Chem.* **1966**, *31*, 3980-3984.

[30][] Leroux, F.; Mangano, G.; Schlosser, M. The abnormal behavior of an atropisomer: 3,3'-Dibromo-1,1'-difluoro-2,2'-binaphthyl reacting with alkyllithium compounds. *Eur. J. Org. Chem.* **2005**, *2005*, 5049-5054.

[31][] Li, X.; Hewgley, J. B.; Mulrooney, C. A.; Yang, J.; Kozlowski, M. C. Enantioselective oxidative biaryl coupling reactions catalyzed by 1,5-diazadecalin metal complexes: Efficient formation of chiral functionalized BINOL derivatives. *J. Org. Chem.* **2003**, *68*, 5500–5511.

[32][] Erdik, E. Transition metal catalyzed reactions of organozinc reagents. *Tetrahedron* **1992,** *48*, 9577-9648.

[33][] Krasovskiy, A.; Knochel, P. A LiCl-mediated Br/Mg exchange reaction for the preparation of functionalized aryl- and heteroarylmagnesium compounds from organic bromides. *Angew. Chem. Int. Ed.* **2004**, *43*, 3333 - 3336.

[34][] Bordwell, F. G.; McKellin, W. H. The Reduction of Sulfones to Sulfides. *J. Am. Chem. Soc.* **1951**, *73*, 2251-2253.

[35][] Gardner, J. N.; Kaiser, S.; Krubiner, A.; Lucas, H. A facile reduction of sulfones to sulfides. *Can. J. Chem.* **1973**, *51*, 1419-1421.

[36][] Denner, K.; Doehmer, J.; Bernhardt, R. Cloning of CYP11B1 and CYP11B2 from normal human adrenal and their functional expression in COS-7 and V79 chinese hamster cells. *Endocr. Res.* **1995**, *21*, 443–448.

[37][] Demers, L. M.; Melby, J. C.; Wilson, T. E.; Lipton, A.; Harvey, H. A.; Santen, R. J. The effects of CGS 16949A, an aromatase inhibitor on adrenal mineralocorticoid biosynthesis. *J. Clin. Endocrinol. Metab.* **1990**, *70*, 1162–1166.

[38][] Ehmer, P. B.; Jose, J.; Hartmann, R. W. Development of a simple and rapid assay for the evaluation of inhibitors of human 17α-hydroxylase-C17,20-lyase (P450c17) by coexpression of P450c17 with NADPH-cytochrome-P450-reductase in Escherichia coli. *J. Steroid Biochem. Mol. Biol.* **2000**, *75*, 57–63.

[39][] (a) Hartmann, R. W.; Batzl, C. Aromatase inhibitors. Synthesis and evaluation of mammary tumor inhibiting activity of 3-alkylated 3-(4-aminophenyl)piperidine-2,6-diones. *J. Med. Chem.* **1986**, *29*, 1362–1369. (b) Thompson, E. A.; Siiteri, P. K. Utilization of oxygen and reduced nicotinamide adenine dinucleotide phosphate by human placental microsomes during aromatization of androstenedione. *J. Biol. Chem.* **1974**, *249*, 5364–5372.

[40][] Strushkevich, N.; Gilep, A. A.; Shen, L.; Arrowsmith, C. H.; Edwards, A. M.; Usanov, S. A.; Park, H. W. Structural insights into aldosterone synthase substrate specificity and targeted inhibition. *Mol. Endocrinol.* **2013**, *27*, 315–324.

[41][] (a) Hu, Q.; Yin, L.; Hartmann, R. W. Selective dual inhibitors of CYP19 and CYP11B2: targeting cardiovascular diseases hiding in the shadow of breast cancer. *J. Med. Chem.* **2012**, *55*, 7080–7089. (b) Yin, L.; Hu, Q.; Hartmann, R. W. Tetrahydropyrroloquinolinone type dual inhibitors of aromatase / aldosterone synthase as a novel strategy for breast cancer patients with elevated cardiovascular risks. *J. Med. Chem.* **2013**, *56*, 460–470.

[42][] Pinto-Bazurco Mendieta, M. A. E.; Hu, Q.; Engel, M.; Hartmann, R. W. Highly potent and selective non-steroidal dual inhibitors of CYP17 / CYP11B2 for the treatment of prostate cancer to reduce risks of cardiovascular diseases. *J. Med. Chem.* **2013**, *56,* 6101–6107.

[43] Yin, L.; Hu, Q.; Emmerich, J.; Lo, M. M.; Metzger, E.; Ali, A.; Hartmann, R. W. Novel pyridyl- or isoquinolinyl- substituted indolines and indoles as potent and selective aldosterone synthase inhibitors. *J. Med. Chem.* **2014**, *57,* 5179–5189.