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Pyridyl-Substituted Naphthalenes and 3,4-dihydro-1H-quinolin-2-ones as Fluorinated Aldosterone Synthase (CYP11B2) Inhibitors for the Differential Diagnosis of Primary Aldosteronism

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Abstract

Aldosterone synthase (CYP11B2) is specifically expressed in aldosterone-producing tissue of the adrenal cortex. It catalyzes the final steps in aldosterone synthesis and is pathophysiologically relevant in primary aldosteronism. Therefore, it presents an excellent PET imaging target for the localization of aldosterone excess. To expand compound library for the development of an appropriate F-18 labelled radiotracer, we synthesized fluorinated derivatives of pyridyl-substituted naphthalenes **1** and 3,4-dihydro-1H-quinolin-2-ones **2**. Despite the high homology of CYP11B2 with the cortisol-producing enzyme 11β-hydroxylase (CYP11B1) both classes of compounds are well known as selective CYP11B2 inhibitors. Some of the 30 substances prepared proved to be highly potent CYP11B2 inhibitors (IC_{50} < 10 nM) in in vitro evaluation using transfected Y1 cells and NCI-H295 cells. Moreover, several compounds exhibited outstanding selectivity over CYP11B1 and thus deserve further biological investigations of their F-18 labelled analogues.

Keywords: Primary aldosteronism; Molecular imaging; Naphthyl pyridines; Dihydroisoquinolinones; Fluorinated CYP11B2 inhibitors; NCI-H295 cells

Introduction

Aldosterone is a steroid hormone that acts on the kidneys to increase sodium reabsorption and potassium excretion, which helps in regulating blood pressure, blood volume, and electrolyte balance. Furthermore, aldosterone can indirectly affect hydrogen ion secretion, aiding in the management of acid-base balance in the body. The biosynthesis of aldosterone is performed by the enzyme aldosterone synthase (CYP11B2) which converts corticosterone into aldosterone in three successive catalytic reactions: 11β-hydroxylation, 18-hydroxylation, and 18-oxidation. Aldosterone synthase is primarily found in the zona glomerulosa of the adrenal cortex and regulated by various factors, namely angiotensin II, plasma potassium levels and to a lesser extent by the adrenocorticotropic hormone (ACTH). Excessive autonomous aldosterone production leads to primary aldosteronism (Conn's syndrome), a condition characterized by treatment-resistant hypertension, hypokalemia and an elevated risk for cardiovascular diseases, kidney damage and stroke [1]. One of the major diagnostic challenges in confirmed primary aldosteronism is localizing the main source of aldosterone excess [2,3]. If the cause is unilateral, typically due to a unilateral aldosterone-producing adenoma (APA), surgery may offer a potential cure and beneficial effects on long-term mortality

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[4]. In contrast, bilateral aldosterone excess necessitates lifelong medication management, typically involving mineral-ocorticoid receptor antagonists like spironolactone or eplerenone [2]. These pharmaceuticals act by blocking the mineralocorticoid receptor that is the site of action of aldosterone. Another approach is to inhibit the activity of CYP11B2, thereby reducing the production of aldosterone. However, the development of selective CYP11B2 inhibitors has been challenging due to the similarity between CYP11B2 and CYP11B1, the enzyme relevant for cortisol synthesis. The two enzymes share 93% homology, differing in only 29 amino acids, most of which are not inside the active sites of enzymes. The high selectivity of the CYP11B2 inhibitors is necessary to avoid affecting cortisol production, which can lead to dangerous side effects like adrenal insufficiency.

The development of selective CYP11B2 inhibitors was pioneered by the group of R.W. Hartmann, who published many compounds with 3,5-disubstituted pyridines as the pharmacophore [5-10]. Later, other N-containing heterocycles (imidazoles, isoxazoles, pyrimidines and pyrazines) were discovered [11-15]. A recently published review provides a good overview of the very numerous inhibitors [16]. Due to the research activities of big pharmaceutical companies (e.g. Novartis, Roche, Merck, AstraZeneca, Eli Lilly) several CYP11B2 inhibitors have entered clinical trials, aiming to provide a therapeutic option for primary aldosteronism without the side effects of non-selective mineralocorticoid receptor antagonists like spironolactone, namely FAD286 [17,18], LCI699 [19], baxdrostat [20], lorundrostat [21] (Figure 1), LY3045697 [22] and BI 690517 [23] (chemical structures not disclosed). Nevertheless, none of them have approved marketing authorization at the moment, apart from LCI-699 which was repurposed as a CYP11B1 inhibitor and approved for therapy of Cushing´s syndrome under the trade name Isturisa® in the United States and in the European Union [24]. This underlines the difficulty of developing suitable CYP11B2 inhibitors.

In contrast to the numerous CYP11B2 inhibitors for therapeutic purposes described above, only few radiolabelled CYP11B2 inhibitors were described for diagnostic purposes, although there is a great clinical need for these as well: Traditional imaging techniques have limitations when it comes to differentiating between unilateral and bilateral causes of PA, particularly in patients over 40 years old [25]. This limitation arises from the increasing detection of hormonally inactive adrenal masses with age and the potential presence of very small aldosterone-producing adenomas (< 5 mm), which can evade detection through these imaging modalities [26,27].

Consequently, the current gold standard for further diagnosis involves bilateral blood sampling and analysis from the adrenal veins [2]. However, this method is invasive, associated with side effects, and requires a skilled clinician. It is only available in a limited number of medical centers [28,29]. Additionally, adrenal vein sampling entails significant radiation exposure, making it an area in need of improvement [30,31]. Molecular imaging of CYP11B2 expression using a radiolabelled inhibitor holds great promise as a non-invasive diagnostic tool for distinguishing between bilateral hyperplasia and APA. Especially positron emission tomography (PET) provides excellent spatial resolution and tracer uptake quantification [32]. Clinical studies involving the non-selective radiotracer [^{11}C]Metomidate have produced varying results regarding its ability to differentiate between unilateral and bilateral disease [33,34] (Figure 2). Due to the short half-life time of carbon-11 (20 min), a radiofluorinated derivative, [^{18}F]CETO was recently introduced into a clinical trial of patients with primary aldosteronism [35,36]. The first selective radiofluorinated CYP11B2 inhibitor, [^{18}F]CDP2230, was introduced, but it showed only moderate selectivity (15.8) towards CYP11B2 and was not further developed for clinical use [37]. [^{18}F]AldoView, on the other hand, seems to be very promising, even if this tracer cannot be labelled using conventional labelling methods [38].

Recently, we presented numerous 3-(4-cyano-3-fluorophenyl)pyridines and 3-(4-cyano-3-fluorophenyl) pyrazines as highly potent and selective CYP11B2 inhibitors [39]. In order to expand the reservoir of compounds that can be considered for the development of a selective radiofluorinated tracer, we decided to prepare fluoro-substituted derivatives of two further compound classes, namely of the pyridyl-substituted naphthalenes **1** and the 3,4-dihydro-1H-quinolin-2-ones **2** that were both investigated by Hartmann et al. [7,40] (Figure 3). Apparently, the 3,4-dihydro-1H-quinolin-2-ones

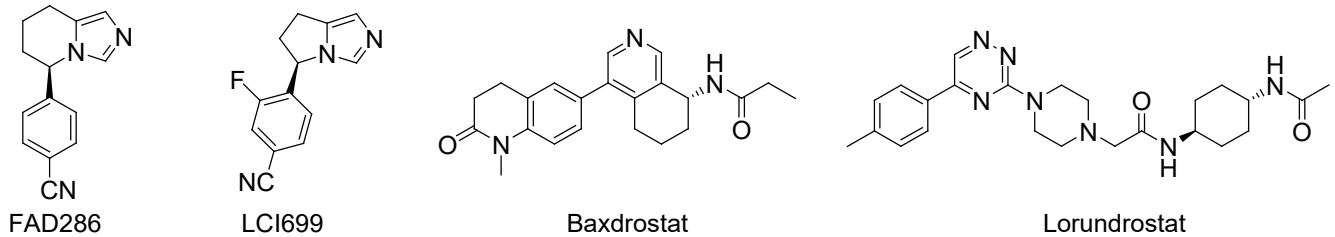

Figure 1: Structures of selective CYP11B2 inhibitors in different stages of clinical trials.

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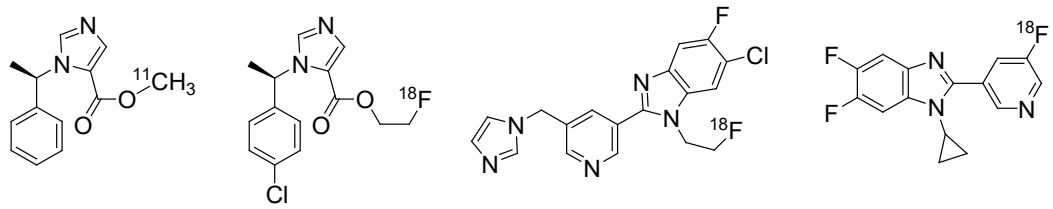

Figure 2: Structures of unselective ([^{11}C]Metomidate, [^{18}F]CETO), a moderate selective ([^{18}F]CDP2230) and a highly selective ([^{18}F]AldoView) labelled CYP11B2 inhibitor for PET.

presented in [7] were later developed into Baxdrostat. Favored by the absence of protic functions a one-step radiosynthesis of analogue F-18 labelled PET tracers by nucleophilic aliphatic F-18 fluorination of suitable labelling precursors is viable. Therefore, the fluoro substituent of most of our target compounds was introduced in an alkyl side chain (R_f). All synthesized compounds were analyzed for their potential in the inhibition of CYP11B1 and CYP11B2 enzymes using in vitro assays of transfected Y1 cells, and some were also tested on the human NCI-H295 cell line.

Results and Discussion

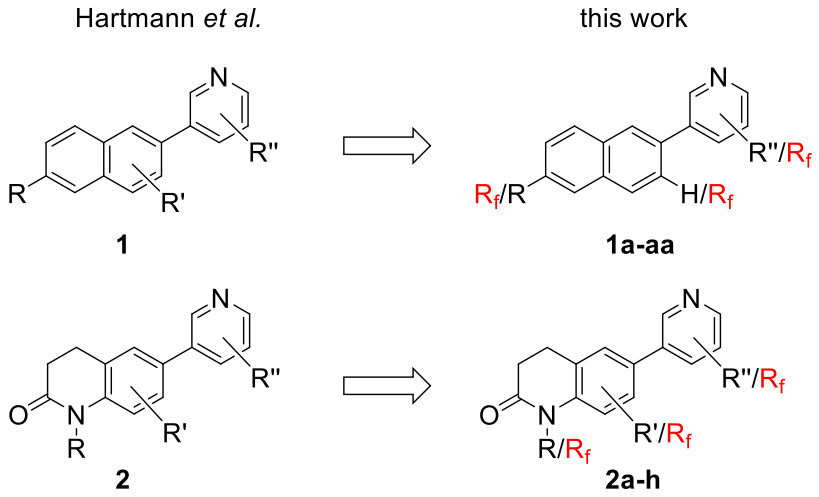

Figure 3: CYP11B2 inhibitors **1** and **2** as well as the derived fluorinated title compounds **1a-aa** and **2a-h**; R_f = fluoro-containing substituent.

Preparation of the fluorinated target compounds

The syntheses of naphthyl pyridines are shown in Schemes 1 and 2. Generally, the target compounds were prepared by Suzuki-Miyaura reactions as a key step. The required naphthalene reactants **3a-g** were either commercially available or easily accessible by synthesis according to known procedures [41-43]. Coupling with a variety of pyridines **4a-u** provided the biaryl compounds **1a-w** (Scheme 1). Almost all of the pyridine precursors are also commercially available or could be prepared in a fast way according to known procedures [10,44-48]. If necessary, the coupling reactions were examined with different combinations of solvents and bases known from the literature, since none of the conditions used provided reliably good yields for all of the target compounds (Methods A-D) [49-51]. Moreover, the yields were apparently independent of the functionalization of both coupling building blocks; neither the boron-containing transmetalation reagents nor the halogen substituted electrophiles proved to be superior for the naphthalene and the pyridine compound species. However, the isolated amounts were sufficient for in vitro studies of the potential new CYP11B2 inhibitors or for further conversion.

Compound **1l** was extended by another Suzuki coupling with pyridine boronic acids **4v** and **4w** to furnish ortho-fluorine substituted teraryls **1x** and **1y**, respectively (Scheme 2). With regard to our further research intentions this represents a proper position for F-18 labelling of the corresponding nitro compounds. Methyl ester **1n** was transformed in a reduction-alkylation sequence to ether **1aa**, using lithium aluminum hydride in tetrahydrofurane to form the benzylic alcohol intermediate **1z** and 2-fluoroethyl tosylate with sodium hydride for the subsequent strong base mediated alkylation.

Taking into account our original research interest, the

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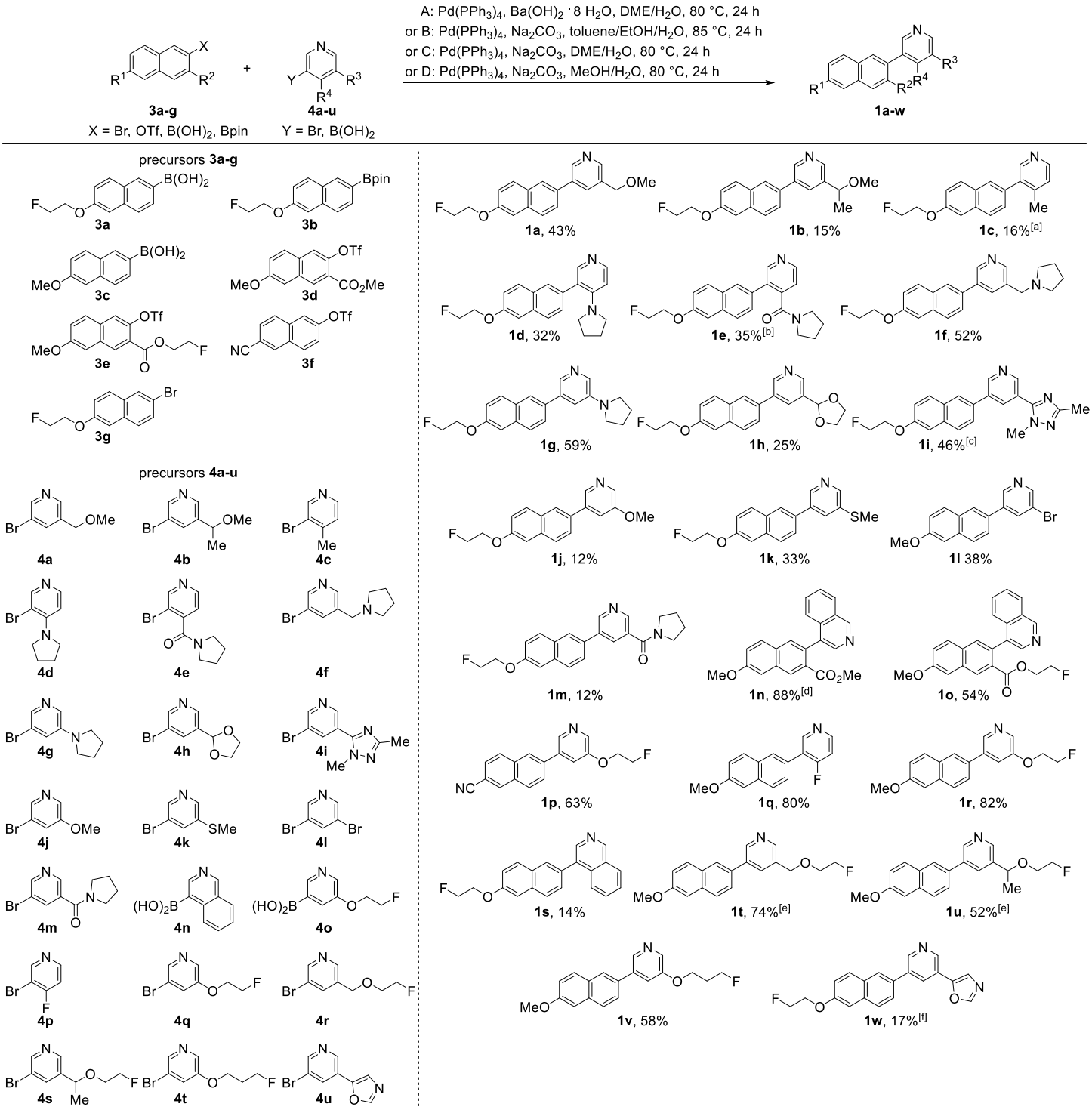

Scheme 1: Synthesis of pyridyl-substituted naphthalenes **1a-w** by Suzuki cross-coupling reactions of naphthyl compounds **3a-g** with different pyridyl bromides or boronic acids **4a-u**. Reaction conditions unless otherwise noted: Method A: 1.0 equiv. **3a**, 0.8 equiv. **4a-c**, 3.2 mol% $Pd(PPh_3)_4$, 1.25 equiv. $Ba(OH)_2$ * 8 H_2O, or 1.0 equiv. **3b**, 1.0 equiv. **4d-l**, 3.6 mol% $Pd(PPh_3)_4$, 1.4 equiv. $Ba(OH)_2$ * 8 H_2O, DME/H_2O, 80 °C, 24h, 12-59% for **1a-l**; Method B: 1.0 equiv. **3a**, **3d** or **3e**, 1.0-1.6 equiv. **4m** or **4n**, 7.0-8.1 mol% $Pd(PPh_3)_4$, 2.15 equiv. Na_2CO_3, toluene/EtOH/H_2O, 85 °C, 24 h, 12-88% for **1m-o**; Method C: 1.0 equiv. **3c**, 1.0 equiv. **4o**, 2.1 mol% $Pd(PPh_3)_4$, 2.2 equiv. Na_2CO_3 or 1.0 equiv. **3f**, 0.8 equiv. **4p**, 4.3 mol% $Pd(PPh_3)_4$, 3.4 equiv. Na_2CO_3, DME/H_2O, 80 °C, 24 h, 63-80% for **1p/q**; Method D: 1.0 equiv. **3c** or **3g**, 0.4-1.0 equiv. **4o-t**, 3.7 mol% $Pd(PPh_3)_4$, 6.2-6.5 equiv. Na_2CO_3, MeOH/H_2O, 80 °C, 24 h, 24-82% for **1r-v**. [a] 1.5 equiv. $Ba(OH)_2$ * 8 H_2O. [b] 0.9 equiv. **4e**. [c] 0.8 equiv. **4i**. [d] 1.8 equiv. Na_2CO_3. [e] 3.9 mol% $Pd(PPh_3)_4$. [f] reaction conditions: 1.0 equiv. **3b**, 1.0 equiv. **4u**, 6.0% $Pd(PPh_3)_4$, 1.1 equiv. Ag_2CO_3, benzene, Δ, 48 h.

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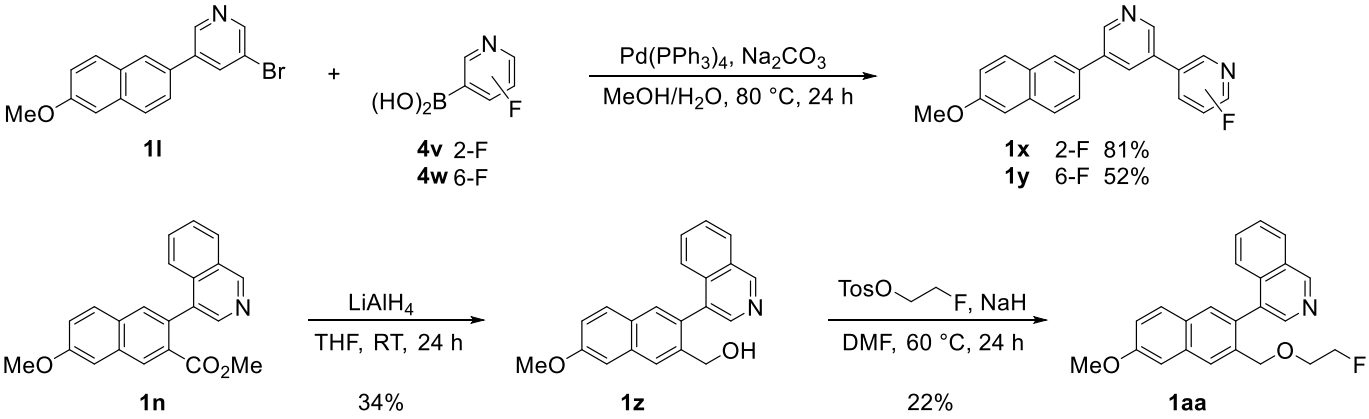
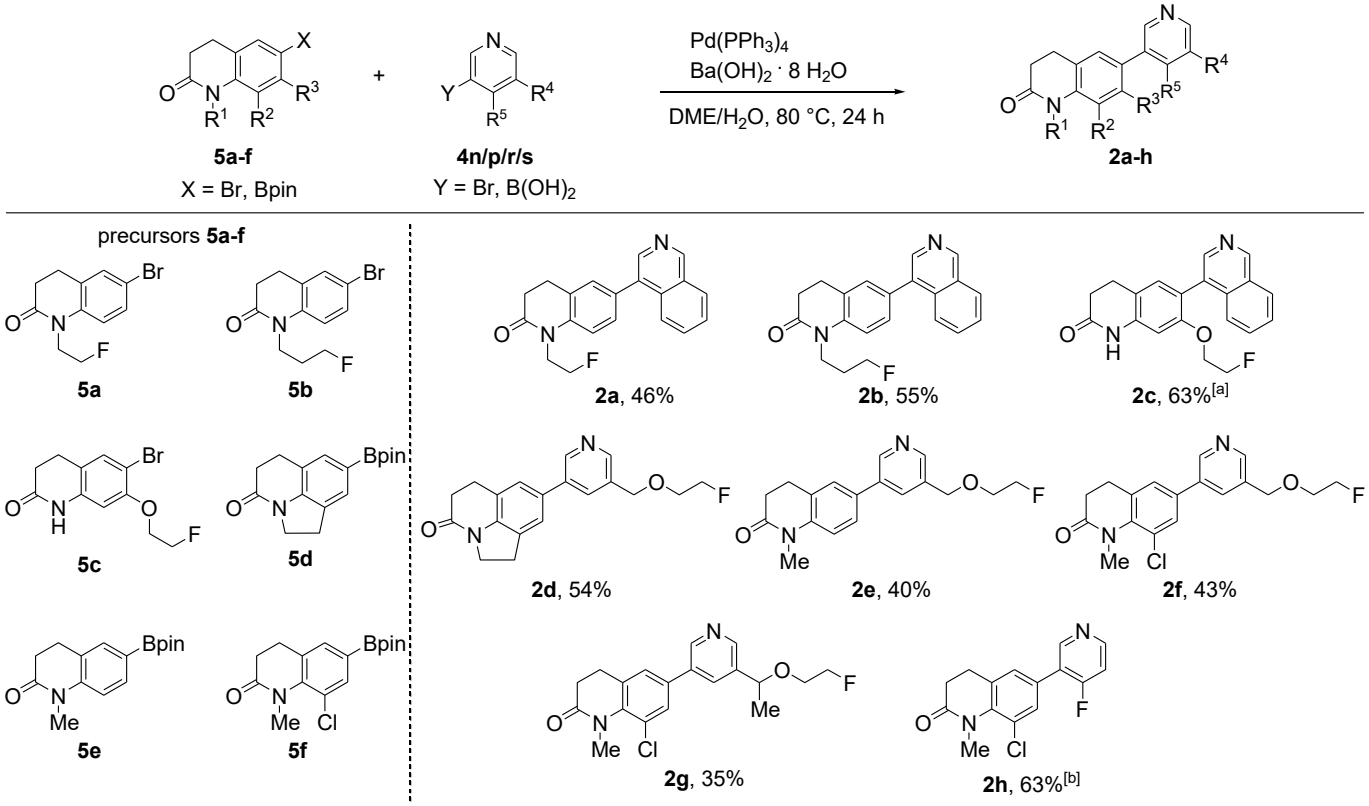


Scheme 2: Synthesis of naphthyl pyridines **1x**, **1y** and **1aa** by conversion of the coupling products **1l** and **1n**.

The second type of our target compounds were pyridyl and isoquinolyl substituted 3,4-dihydro-1H-quinolin-2-ones **2a-h**. Their preparation was accomplished again by a Suzuki coupling as the key synthetic transformation by means of the connection of 3,4-dihydro-1H-quinolin-2-ones **5a-f** with isoquinolyl-4-boronic pinacol ester **4n** or pyridines **4p**, **4r** and **4s**, respectively (Scheme 3). Compounds **5a-f** were obtained by successive generation of the bicyclic system, bromination and borylation reactions according to known procedures [7,43,52,53].



Scheme 3: Synthesis of pyridyl- and isoquinolyl-substituted dihydro-1H-quinolin-2-ones **2a-h** by Suzuki cross-coupling reactions of dihydroquinolinones **5a-f** with pyridyl bromides **4p**, **4r** or **4s** or pyridyl boronic acid **4n**. Reaction conditions unless otherwise noted: 1.0 equiv. **5**, 0.9-1.3 equiv. **4**, 3.5-4.2 mol% $Pd(PPh_3)_4$, 1.3-1.65 equiv. $Ba(OH)_2$ * 8 H_2O, DME/H_2O, 80 °C, 24 h. [a] reaction conditions: 1.6 equiv. **4n**, 8.2% $Pd(PPh_3)_4$, 2.15 equiv. Na_2CO_3, toluene/EtOH/H_2O, 85 °C, 18 h. [b] reaction conditions: 5.8% $Pd(PPh_3)_4$, 4.6 equiv. Na_2CO_3, DME/H_2O, 80 °C, 24 h.

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majority of the target compounds **1a-w** as well as **2a-h** contain a fluorinated aliphatic group for which the analogue radioactive form can be expected to be synthesized rapidly in one-step radiolabelling by commonly used nucleophilic F-18 fluorination of corresponding bromo or nitro precursors.

In vitro enzymatic inhibitory assays

For the evaluation of in vitro inhibitory activities of the compounds against either human CYP11B1 or CYP11B2 we applied assays of Y1 cells stably transfected with one of the two genes (Table 1). The cell line Y1 is derived from a murine adrenal adenocarcinoma with naturally low expression levels of both murine CYP11B enzymes and is therefore ideally suited for such investigations. FAD286 was used as positive control agent and displayed inhibitory activities for CYP11B1 and CYP11B2 comparable to reported data, with a selectivity factor of 5.8 [54]. Several of the novel tested compounds were potent and selective CYP11B2 inhibitors, and as expected, the position of substituents in both aryl moieties is one of the decisive factors. In this context, the pyridyl substituted naphthalenes **1c**, **1d**, **1e** and **1q** with substituents in 4-position of the pyridine ring showed moderate affinities and no or only very low selectivities towards CYP11B1. Contrarily, substitution in the 5-position provided many compounds exhibiting good or even excellent inhibitory activities at the target enzyme CYP11B2, with **1b** being the most potent (IC_{50} = 6.0 nM). Moreover, heteroaromatic moieties in the 5-position, even with sterically demanding residues, led to reasonable affinities and very good selectivities (**1i**, **1w**). On the other hand, for teraryl derivatives **1x** and **1y**, representative for compounds with an ortho substituted pyridine ring, no inhibition effect on CYP11B1 could be observed, but the affinities for CYP11B2 were also considerably diminished. Furthermore, replacement of the substituent in 5-position by an annulated aromatic fragment in terms of a isoquinoline resulted in a good IC_{50} value and strong selectivity for CYP11B2 (**1s**). The attachment of an additional chain in 3-position of the naphthalene unit, however, caused a significant loss of potency for compounds **1aa** and **1o**. Regarding the electronic properties of the substituents, a similar tendency was disclosed as for related CYP11B2 inhibitors previously [7,39,55]. Electron-donating residues obviously promote CYP11B2 inhibitory activity, and the best results were achieved for derivatives bearing an electron-donating chain both in 5-position of the pyridine ring and in 6-position of the naphthalene moiety. The affinity and selectivity values are preserved even after a mutual exchange of both chains as demonstrated in the case of naphthyl pyridines **1r** and **1j**, whereas an exchange of the methoxy group of compound **1r** by a cyano substituent decreased both the affinity and the selectivity for **1p** towards CYP11B2 confirming the unfavorable effect of electron-withdrawing substituents. The 3,4-dihydro-1H-quinolin-2-ones also exhibited a broad range of IC_{50} values. Isoquinolyl substituted compounds **2a-c** were characterized by a low CYP11B2 inhibition and were only poorly selective towards CYP11B1. As already found for the analogous naphthyl pyridines described above, in particular the alkyl chain in 7-position ortho to the isoquinoline moiety induced almost a complete loss of enzyme inhibition and selectivity. Such an analogy of comparatively low potency could also be determined for compound **2h** with a 4-substituted pyridine ring. Likewise the inhibitory effects of compounds **2d-g** on CYP11B2 were moderate to very good and partially outstanding selective towards CYP11B1, and therefore consistent with recent studies on 3,5-disubstituted pyridines as well as on 8-chloro-substituted 3,4-dihydro-1H-quinolin-2-ones [7,39]. Encouraged by the good results of several compounds in the inhibition experiments on the transfected Y1 cells, we further assessed the potency of some of the best derivatives on NCI-H295 cells (Table 2). This human cell line is considered a standard tool for adrenal cortical research issues, since it contains the whole cascade of enzymes for producing all adrenocortical steroids [56,57]. In comparison to the transfected Y1 cells, the selectivities towards CYP11B1 were somewhat lower, but binding affinities on CYP11B2 remained essentially on the same level or increased up to the subnanomolar IC_{50} value for compound **1a**.

Materials and Methods

General Chemistry and analytical methods

All chemicals and solvents were purchased from commercial sources (Sigma-Aldrich, Deisenhofen, Germany; Merck, Darmstadt, Germany; ChemPUR, Karlsruhe, Germany) and were used without further purification. The progress of chemical reactions was monitored by thin layer chromatography (TLC) on precoated 0.2 mm silica gel 60 sheets (Macherey-Nagel, Düren, Germany). Developed TLC sheets were visualized with UV light at 254 nm. Separations of organic products by column chromatography were carried out with silica gel 60 (0.03-0.2 mm, Carl Roth, Karlsruhe, Germany). ^{1}H-NMR spectra were recorded on a 250 MHz Bruker NMR spectrometer with tetramethylsilane as internal standard. The chemical shifts δ are presented in parts per million (ppm) using the residual protic solvent as internal reference: $CDCl_3$ (δ = 7.26). Signal multiplicities are characterized as follows: s = singlet, d = doublet, t = triplet, q =quartet, m = multiplet. Mass spectra were obtained on a Bruker Daltonics microtof focus. Melting points were measured on a Büchi Melting Point B-540 apparatus and are uncorrected.

Synthesis of the fluorinated target compounds

General procedure for Suzuki coupling

A suspension of an aryl halide or trifluoromethanesulfonate, an aryl boronic acid or ester, and a base in an appropriate

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Table 1: Inhibitory potency (IC_{50} values for inhibition of CYP11B1 and CYP11B2) and selectivity factors of selected compounds in Y1 cells stably transfected with either human CYP11B1 or human CYP11B2.

Compound	IC_{50} (nM)[a]		sf[b]		Compound	IC_{50} (nM)[a]		sf[b]
	CYP11B1	CYP11B2				CYP11B1	CYP11B2	
1a	1237 ± 379	14.2 ± 4.3	87.4		**1s**	1375 ± 534	15.4 ± 3.7	89.3
1b	514 ± 557	6.0 ± 4.2	86.2		**1t**	1185 ± 398	9.8 ± 3.5	121
1c	56.0 ± 11.6	23.6 ± 7.7	2.4		**1u**	241 ± 578	7.1 ± 1.2	33.8
1d	2900	395 ± 454	7.4		**1v**	585 ± 249	36.4± 24.3	16.1
1e	16.4	60.4±77.1	0.27		**1w**	1460 ± 181	24.9 ± 3.2	58.6
1f	1020	105± 24.8	9.8		**1x**	> 5000	259 ± 344	-
1g	1380± 53.7	87.2	15.8		**1y**	> 10000	70.0± 21.4	-
1h	850 ± 11.6	23.2±33.9	36.6		**1aa**	520 ± 683	> 10000	-
1i	> 1000	29.2±23.8	-		**2a**	2200 ± 807	82.9± 19.5	26.5
1j	1620 ± 151	35.0±14.8	46.3		**2b**	> 10000	708 ± 356	-
1k	1430 ± 149	25.2 ± 5.5	56.7		**2c**	2400 ± 1743	1100± 531	2.2
1m	581 ± 820	480 ± 373	1.2		**2d**	856 ± 320	24.4± 17.5	38.2
1o	> 5000	210	-		**2e**	601 ± 268	8.8 ± 9.9	68.3
1p	1130 ± 232	76.6±25.6	14.9		**2f**	> 5000	61.9± 18.0	-
1q	56.0 ± 35.0	119 ± 165	0.47		**2g**	655 ± 492	15.7± 12.4	41.7
1r	> 1000	21.8 ± 4.1	-		**2h**	1380 ± 1937	192 ± 263	7.2
FAD286[c]	79.1	13.5	5.8					

[a] IC_{50} values determined from n ≥ 1; for compounds with n > 1 the mean value ± standard deviation is given. [b] sf: selectivity factor = IC_{50}(CYP11B1) / IC_{50}(CYP11B2). [c] FAD286: *R*-enantiomer of fadrozole.

Table 2: Inhibitory potency (IC_{50} values for inhibition of CYP11B1 and CYP11B2) and selectivity factors of selected compounds in NCI-H295 cells expressing CYP11B1 and CYP11B2.

Compound	IC_{50} (nM)[a]		sf[b]		Compound	IC_{50} (nM)[a]		sf[b]
	CYP11B1	CYP11B2				CYP11B1	CYP11B2	
1r	163 ± 73.6	31.3 ± 6.5	5.2		**1a**	18.9 ± 15.8	0.95 ± 0.25	19.8
1s	1094± 75.6	17.0 ± 6.2	64		**1b**	90.8 ± 23.0	8.8 ± 4.8	10.3
1t	435 ± 199	64.8 ± 14.6	6.7		**2a**	1260±1330	172 ± 43.8	7.3
1u	128 ± 102	5.6 ± 1.4	23		**2g**	958 ± 144	9.5 ± 7.4[c]	101
FAD286[d]	102 ± 38.1	50.1 ± 4.4	2.0					

[a] Mean value ± standard deviation of at least three experiments. [b] sf: selectivity factor = IC_{50}(CYP11B1) / IC_{50}(CYP11B2). [c] n = 2. [d] FAD286: *R*-enantiomer of fadrozole.

solvent (A: $Ba(OH)_2$ * 8 H_2O in DME/H_2O; B: Na_2CO_3 in toluene/EtOH/H_2O; C: Na_2CO_3 in DME/H_2O; D: Na_2CO_3 in MeOH/H_2O) was degassed by an argon stream for 15 min. After addition of the catalyst $Pd(PPh_3)_4$ the reaction mixture was stirred at elevated temperature for 3-24 h under an argon atmosphere, then cooled to room temperature and the reaction solvent was removed in vacuum. The residue was reconstituted in H_2O, the resulting mixture was extracted several times (solvent noted) and the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel afforded the desired compounds.

Synthesis of Naphthalene Compounds 1a-aa

5-[6-(2-Fluoroethoxy)-2-naphthalenyl]-3-(methoxymethyl)pyridine (**1a**): Prepared according to the general procedure method A from 6-(2-Fluoroethoxy)-2-naphthaleneboronic acid (**3a**, 562 mg, 2.40 mmol), 3-Bromo-5-(methoxymethyl)pyridine (**4a**, 404 mg, 2.00 mmol), $Ba(OH)_2$ * 8 H_2O (948 mg, 3.00 mmol) and $Pd(PPh_3)_4$ (88.0 mg, 76.2 µmol) in DME (12 mL) and H_2O (2 mL); reaction time: 24 h. After work-up (H_2O (50 mL), extraction with $CHCl_3$ (5 x 50 mL), column chromatography CH_2Cl_2/CH_3OH = 98:2) compound **1a** was obtained as a colorless solid (270 mg, 43%), mp: 111-113 °C. ^{1}H-NMR ($CDCl_3$, 250 MHz): δ = 3.47 (s, 3H, OCH_3), 4.29-4.44 (m, 2H, OCH_2), 4.57 (s, 2H, $ArCH_2O$), 4.74-4.96 (m, 2H, CH_2F), 7.17-7.28 (m, 2H), 7.68-7.73 (m, 1H), 7.81-7.87 (m, 2H), 7.97-8.02 (m, 2H), 8.56 (m, 1H), 8.89 (m, 1H). MS (DIP-APCI, +): *m/z* (%): calcd. for $C_{19}H_{19}FNO_2$ $[M+H]^+$: 312.1394; found: 312.1396 ($[M+H]^+$).

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5-[6-(2-Fluoroethoxy)-2-naphthalenyl]-3-(1-methoxyethyl)pyridine (**1b**): Prepared according to the general procedure method A from 6-(2-Fluoroethoxy)-2-naphthaleneboronic acid (**3a**, 562 mg, 2.40 mmol), 3-Bromo-5-(1-methoxyethyl)pyridine (**4b**, 432 mg, 2.00 mmol), $Ba(OH)_2 \cdot 8\ H_2O$ (948 mg, 3.00 mmol) and $Pd(PPh_3)_4$ (88.0 mg, 76.2 µmol) in DME (12 mL) and H_2O (2 mL); reaction time: 24 h. After work-up (H_2O (50 mL), extraction with $CHCl_3$ (5 x 50 mL), column chromatography CH_2Cl_2/CH_3OH = 98:2) compound **1b** was obtained as a yellowish solid (97.4 mg, 15%). ^{1}H-NMR ($CDCl_3$, 250 MHz): δ = 1.54 (d, ^3J = 7.6 Hz, 3H, CHCH_3), 3.32 (s, 3H, OCH_3), 4.29-4.48 (m, 3H, OCH_2 and CHCH$_3$ superimposed), 4.74-4.96 (m, 2H, CH_2F), 7.17-7.28 (m, 2H), 7.63-7.73 (m, 2H), 7.82-7.87 (m, 2H), 7.94-7.98 (m, 1H), 8.01 (m, 1H), 8.53 (m, 1H), 8.89 (m, 1H). MS (DIP-APCI, +): *m/z* (%): calcd. for $C_{20}H_{21}FNO_2$ $[M+H]^+$: 326.1551; found: 326.1556 ($[M+H]^+$).

3-[6-(2-Fluoroethoxy)-2-naphthalenyl]-4-methylpyridine (**1c**): Prepared according to the general procedure method A from 6-(2-Fluoroethoxy)-2-naphthaleneboronic acid (**3a**, 281 mg, 1.20 mmol), 3-Bromo-4-methylpyridine (**4c**, 172 mg, 111 µL, 1.00 mmol), $Ba(OH)_2 \cdot 8\ H_2O$ (474 mg, 1.50 mmol) and $Pd(PPh_3)_4$ (44.0 mg, 38.1 µmol) in DME (6 mL) and H_2O (1 mL); reaction time: 24 h. After work-up (H_2O (50 mL), extraction with $CHCl_3$ (5 x 30 mL), column chromatography CH_2Cl_2/CH_3OH = 98:2) compound **1c** was obtained as a yellow oil (46.0 mg, 16%). ^{1}H-NMR ($CDCl_3$, 250 MHz): δ = 2.35 (s, 3H, CH_3), 4.30-4.45 (m, 2H, OCH_2), 4.74-4.97 (m, 2H, CH_2F), 7.20 (m, 1H), 7.23-7.28 (m, 2H), 7.41 (dd, ^3J = 8.4 Hz, ^4J = 1.8 Hz, 1H), 7.72 (m, 1H), 7.79 (m, 1H), 7.83 (m, 1H), 8.48 (d, ^3J = 5.2 Hz, 1H), 8.53 (m, 1H). MS (DIP-APCI, +): *m/z* (%): calcd. for $C_{18}H_{17}FNO$ $[M+H]^+$: 282.1289; found: 282.1290 ($[M+H]^+$).

3-[6-(2-Fluoroethoxy)-2-naphthalenyl]-4-(1-pyrrolidinyl)pyridine (**1d**): Prepared according to the general procedure method A from 6-(2-Fluoroethoxy)-2-naphthaleneboronic acid pinacol ester (**3b**, 316 mg, 1.00 mmol), 3-Bromo-4-(1-pyrrolidinyl)pyridine (**4d**, 227 mg, 1.00 mmol), $Ba(OH)_2 \cdot 8\ H_2O$ (430 mg, 1.36 mmol) and $Pd(PPh_3)_4$ (42.0 mg, 36.3 µmol) in DME (5 mL) and H_2O (0.9 mL); reaction time: 24 h. After work-up (H_2O (200 mL), extraction with $CHCl_3$ (3 x 50 mL), column chromatography CH_2Cl_2/CH_3OH = 98:2) compound **1d** was obtained as a brown oil (107 mg, 32%). ^{1}H-NMR ($CDCl_3$, 250 MHz): δ = 1.72-1.78 (m, 2H, NCH_2CH_2), 2.96-3.03 (m, 2H, NCH_2), 4.28-4.43 (m, 2H, OCH_2), 4.73-4.95 (m, 2H, CH_2F), 6.60 (d, ^3J = 6.0 Hz, 1H), 7.17 (m, 1H), 7.24 (dd, ^3J = 8.9 Hz, ^4J = 2.5 Hz, 1H, superimposed with CDCl3 residual peak), 7.44 (dd, ^3J = 8.5 Hz, ^4J = 1.8 Hz, 1H), 7.69-7.74 (m, 2H), 7.77 (d, ^3J = 9.0 Hz, 1H), 8.18 (s, 1H), 8.22 (d, ^3J = 5.9 Hz, 1H). MS (DIP-APCI, +): *m/z* (%): calcd. for $C_{21}H_{22}FN_2O$ $[M+H]^+$: 337.1711; found: 337.1718 ($[M+H]^+$).

2-[6-(2-Fluoroethoxy)-2-naphthalenyl]isonicotinic acid pyrrolidinyl amide (**1e**): Prepared according to the general procedure method A from 6-(2-Fluoroethoxy)-2-naphthaleneboronic acid pinacol ester (3**b**, 316 mg, 1.00 mmol), 3-Bromoisonicotinic acid pyrrolidinyl amide (**4e**, 230 mg, 902 µmol), $Ba(OH)_2 \cdot 8\ H_2O$ (430 mg, 1.36 mmol) and $Pd(PPh_3)_4$ (42.0 mg, 36.3 µmol) in DME (5 mL) and H_2O (0.9 mL); reaction time: 24 h. After work-up (H_2O (200 mL), extraction with $CHCl_3$ (3 x 50 mL), column chromatography CH_2Cl_2/CH_3OH = 98:2) compound **1e** was obtained as a yellow oil (116 mg, 35%). ^{1}H-NMR ($CDCl_3$, 250 MHz): δ = 1.38-1.65 (m, 4H, NCH_2CH_2), 2.71-2.77 (m, 2H, NCH_2), 3.38-3.44 (m, 2H, NCH_2), 4.29-4.43 (m, 2H, OCH_2), 4.73-4.95 (m, 2H, CH_2F), 7.17 (m, 1H), 7.25 (dd, ^3J = 8.9 Hz, ^4J = 2.6 Hz, 1H, superimposed with $CDCl_3$ residual peak), 7.37 (m, 1H), 7.60 (dd, ^3J = 8.4 Hz, ^4J = 1.8 Hz, 1H), 7.77-7.85 (m, 2H), 7.92 (m, 1H), 8.67 (d, ^3J = 4.9 Hz, 1H), 8.81 (s, 1H). MS (DIP-APCI, +): *m/z* (%): calcd. for $C_{22}H_{22}FN_2O_2$ $[M+H]^+$: 365.1660; found: 365.1669 ($[M+H]^+$).

5-[6-(2-Fluoroethoxy)-2-naphthalenyl]-3-(1-pyrrolidinylmethyl)pyridine (**1f**): Prepared according to the general procedure method A from 6-(2-Fluoroethoxy)-2-naphthaleneboronic acid pinacol ester (**3b**, 152 mg, 481 µmol), 3-Bromo-5-(1-pyrrolidinylmethyl)pyridine (**4f**, 116 mg, 481 µmol), $Ba(OH)_2 \cdot 8\ H_2O$ (210 mg, 666 µmol) and $Pd(PPh_3)_4$ (20.2 mg, 17.5 µmol) in DME (3 mL) and H_2O (0.5 mL); reaction time: 24 h. After work-up (H_2O (200 mL), extraction with $CHCl_3$ (3 x 50 mL), column chromatography hexane/EtOAc = 1:1) compound **1f** was obtained as a brownish solid (88.0 mg, 52%). ^{1}H-NMR ($CDCl_3$, 250 MHz): δ = 1.79-1.85 (m, 4H, NCH_2CH_2), 2.55-2.61 (m, 4H, NCH_2CH_2), 3.73 (s, 2H, $ArCH_2N$), 4.28-4.43 (m, 2H, OCH_2), 4.73-4.95 (m, 2H, CH_2F), 7.16 (m, 1H), 7.24 (dd, ^3J = 9.0 Hz, ^4J = 2.8 Hz, 1H, superimposed with $CDCl_3$ residual peak), 7.71 (dd, ^3J = 8.5 Hz, ^4J = 1.9 Hz, 1H), 7.80-7.85 (m, 2H), 7.99-8.02 (m, 2H), 8.52 (d, ^4J = 2.1 Hz, 1H), 8.84 (d, ^4J = 2.5 Hz, 1H). MS (DIP-APCI, +): *m/z* (%): calcd. for $C_{22}H_{24}FN_2O$ $[M+H]^+$: 351.1867; found: 351.1884 ($[M+H]^+$).

3-[6-(2-Fluoroethoxy)-2-naphthalenyl]-5-(1-pyrrolidinyl)pyridine (**1g**): Prepared according to the general procedure method A from 6-(2-Fluoroethoxy)-2-naphthaleneboronic acid pinacol ester (**3b**, 316 mg, 1.00 mmol), 3-Bromo-5-(1-pyrrolidinyl)pyridine (**4g**, 227 mg, 1.00 mmol), $Ba(OH)_2 \cdot 8\ H_2O$ (430 mg, 1.36 mmol) and $Pd(PPh_3)_4$ (42.0 mg, 36.3 µmol) in DME (5 mL) and H_2O (0.9 mL); reaction time: 24 h. After work-up (H_2O (200 mL), extraction with $CHCl_3$ (3 x 50 mL), column chromatography hexane/EtOAc = 1:1 → 1:4) compound **1g** was obtained as a yellowish solid (200 mg, 59%), mp: 153-155 °C. ^{1}H-NMR ($CDCl_3$, 250 MHz): δ = 2.04-2.11 (m, 2H, NCH_2CH_2), 3.37-3.43 (m, 2H, NCH_2), 4.36 (m, 2H, OCH_2), 4.85 (m, 2H, CH_2F), 7.11-7.27 (2m superimposed, 3H), 7.62-7.71 (m,

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2H), 7.80-7.85 (m, 2H), 7.94-7.99 (m, 2H), 8.24 (m, 1H). MS (DIP-APCI, +): *m/z* (%): calcd. for $C_{21}H_{22}FN_2O$ $[M+H]^+$: 337.1711; found: 337.1723 ($[M+H]^+$).

3-(1,3-Dioxolan-2-yl)-5-[6-(2-fluoroethoxy)-2-naphthalenyl]pyridine (**1h**): Prepared according to the general procedure method A 6-(2-Fluoroethoxy)-2-naphthaleneboronic acid pinacol ester (**3b**, 632 mg, 2.00 mmol), 3-Bromo-5-(1,3-dioxolan-2-yl)pyridine (**4h**, 460 mg, 2.00 mmol), $Ba(OH)_2 \cdot 8\ H_2O$ (860 mg, 2.73 mmol) and $Pd(PPh_3)_4$ (84.0 mg, 72.7 µmol) in DME (10 mL) and H_2O (1.8 mL); reaction time: 24 h. After work-up (H_2O (200 mL), extraction with $CHCl_3$ (3 x 50 mL), column chromatography heptane/EtOAc = 1:1) compound **1h** was obtained as a yellowish oil (172 mg, 25%). ^{1}H-NMR ($CDCl_3$, 250 MHz): δ = 4.11-4.19 (m, 4H, OCH_2CH_2O), 4.30-4.45 (m, 2H, OCH_2CH_2F), 4.74-4.97 (m, 2H, CH_2F), 5.99 (s, 1H, OCHO), 7.19 (m, 1H), 7.27 (dd, ^3J = 8.9 Hz, ^4J = 2.6 Hz, 1H, superimposed with $CDCl_3$ residual peak), 7.70 (dd, ^3J = 8.5 Hz, ^4J = 1.8 Hz, 1H), 7.86 (2d superimposed, ^3J = 8.9 Hz, ^3J = 8.4 Hz, 2H), 8.02 (m, 1H), 8.25 (m, 1H), 8.72 (m, 1H), 8.97 (d, ^4J = 2.1 Hz, 1H). MS (DIP-APCI, +): *m/z* (%): calcd. for $C_{20}H_{19}FNO_3$ $[M+H]^+$: 340.1364; found: 340.1344 ($[M+H]^+$).

3-(1,3-Dimethyl-1,2,4-triazol-5-yl)-5-[6-(2-fluoroethoxy)-2-naphthalenyl]pyridine (**1i**): Prepared according to the general procedure method A from 6-(2-Fluoroethoxy)-2-naphthaleneboronic acid pinacol ester (**3b**, 316 mg, 1.00 mmol), 3-Bromo-5-(1,3-dimethyl-1,2,4-triazol-5-yl)pyridine (**4i**, 196 mg, 774 µmol), $Ba(OH)_2 \cdot 8\ H_2O$ (430 mg, 1.36 mmol) and $Pd(PPh_3)_4$ (42.0 mg, 36.3 µmol) in DME (5 mL) and H_2O (1 mL); reaction time: 24 h. After work-up (H_2O (100 mL), extraction with $CHCl_3$ (3 x 50 mL), column chromatography heptane/EtOAc = 1:1) compound **1i** was obtained as a colorless solid (130 mg, 46%), mp: 154-157 °C. ^{1}H-NMR ($CDCl_3$, 250 MHz): δ = 2.47 (s, 3H, CCH_3), 4.03 (s, 3H, NCH_3), 4.30-4.45 (m, 2H, OCH_2), 4.75-4.97 (CH_2F), 7.19 (m, 1H), 7.28 (dd, ^3J = 9.0 Hz, ^4J = 2.6 Hz, 1H, superimposed with $CDCl_3$ residual peak), 7.73 (dd, ^3J = 8.5 Hz, ^4J = 2.0 Hz, 1H), 7.86 (2d superimposed, ^3J = 9.0 Hz, ^3J = 8.5 Hz, 2H), 8.06 (m, 1H), 8.34 (m, 1H), 8.87 (m, 1H), 9.07 (d, ^4J = 1.8 Hz, 1H). MS (DIP-APCI, +): *m/z* (%): calcd. for $C_{21}H_{20}FN_4O$ $[M+H]^+$: 363.1616; found: 363.1622 ($[M+H]^+$).

5-[6-(2-Fluoroethoxy)-2-naphthalenyl]-3-methoxypyridine (**1j**): Prepared according to the general procedure method A from 6-(2-Fluoroethoxy)-2-naphthaleneboronic acid pinacol ester (**3b**, 316 mg, 1.00 mmol), 3-Bromo-5-methoxypyridine (**4j**, 188 mg, 1.00 mmol), $Ba(OH)_2 \cdot 8\ H_2O$ (430 mg, 1.36 mmol) and $Pd(PPh_3)_4$ (42.0 mg, 36.3 µmol) in DME (5 mL) and H_2O (1 mL); reaction time: 24 h. After work-up (H_2O (100 mL), extraction with $CHCl_3$ (3 x 50 mL), column chromatography heptane/EtOAc = 1:1) compound **1j** was obtained as a beige solid (36.0 mg, 12%), mp: 117-120 °C. ^{1}H-NMR ($CDCl_3$, 250 MHz): δ = 3.95 (s, 3H, OCH_3), 4.29-4.43 (m, 2H, OCH_2), 4.73-4.96 (m, 2H, CH_2F), 7.18 (m, 1H), 7.25 (dd, ^3J = 8.9 Hz, ^4J = 2.7 Hz, 1H, superimposed with $CDCl_3$ residual peak), 7.47 (dd, ^4J = 2.8 Hz, ^4J = 1.9 Hz, 1H), 7.73 (dd, ^3J = 8.4 Hz, ^4J = 1.8 Hz, 1H), 7.81 (m, 1H), 7.85 (m, 1H), 7.97 (d, ^4J = 1.5 Hz, 1H), 8.31 (d, ^4J = 2.9 Hz, 1H), 8.57 (d, ^4J = 1.8 Hz, 1H). MS (DIP-APCI, +): *m/z* (%): calcd. for $C_{18}H_{17}FNO_2$ $[M+H]^+$: 298.1238; found: 298.1248 ($[M+H]^+$).

5-[6-(2-Fluoroethoxy)-2-naphthalenyl]-3-(methylthio) pyridine (**1k**): Prepared according to the general procedure method A from 6-(2-Fluoroethoxy)-2-naphthaleneboronic acid pinacol ester (**3b**, 316 mg, 1.00 mmol), 3-Bromo-5-(methylthio)pyridine (**4k**, 204 mg, 1.00 mmol), $Ba(OH)_2 \cdot 8\ H_2O$ (430 mg, 1.36 mmol) and $Pd(PPh_3)_4$ (42.0 mg, 36.3 µmol) in DME (5 mL) and H2O (1 mL); reaction time: 24 h. After work-up (H_2O (100 mL), extraction with $CHCl_3$ (3 x 50 mL), column chromatography heptane/EtOAc = 1:1) compound **1k** was obtained as a greyish solid (102 mg, 33%), mp: 118-121 °C. ^{1}H-NMR ($CDCl_3$, 250 MHz): δ = 2.59 (s, 3H, SCH_3), 4.29-4.44 (m, 2H, OCH_2), 4.74-4.96 (m, 2H, CH_2F), 7.18 (m, 1H), 7.26 (dd, ^3J = 8.9 Hz, ^4J = 2.4 Hz, 1H, superimposed with $CDCl_3$ residual peak), 7.66 (dd, ^3J = 8.5 Hz, ^4J = 1.8 Hz, 1H), 7.81-7.87 (m, 3H), 7.97 (m, 1H), 8.49 (m, 1H), 8.71 (m, 1H). MS (DIP-APCI, +): *m/z* (%): calcd. for $C_{18}H_{16}FNOS$ $[M+H]^+$: 314.1009; found: 314.1013 ($[M+H]^+$).

3-Bromo-5-(6-methoxy-2-naphthalenyl)pyridine (**1l**): Prepared according to the general procedure method A from 6-Methoxynaphthalene-2-boronic acid (**3c**, 2.32 g, 11.48 mmol), 3,5-Dibromopyridine (**4l**, 2.72 g, 11.48 mmol), $Ba(OH)_2 \cdot 8\ H_2O$ (4.95 g, 15.67 mmol) and $Pd(PPh_3)_4$ (482 mg, 417 µmol) in DME (68 mL) and H_2O (11 mL); reaction time: 24 h. After work-up (H_2O (100 mL), extraction with CH_2Cl_2 (3 x 100 mL), column chromatography (CH_2Cl_2/CH_3OH = 98:2) compound **1l** was obtained as a yellowish solid (687 mg, 38%), mp: 160-162 °C. ^{1}H-NMR ($CDCl_3$, 250 MHz): δ = 3.96 (s, 3H, OCH_3), 7.17-7.24 (m, 2H), 7.62-7.67 (dd, ^3J = 8.5 Hz, ^4J = 2.1 Hz, 1H), 7.80-7.88 (m, 2H), 7.96 (m, 1H), 8.13-8.15 (m, 1H), 8.66 (d, ^3J = 2.3 Hz, 1H), 8.87 (d, ^3J = 2.0 Hz, 1H).

5-[6-(2-Fluoroethoxy)-2-naphthalenyl]nicotinic acid pyrrolidinyl amide (**1m**): Prepared according to the general procedure method B from 6-(2-Fluoroethoxy)-2-naphthaleneboronic acid pinacol ester (**3b**, 632 mg, 2.00 mmol), 3-Bromonicotinic acid pyrrolidinyl amide (**4m**, 510 mg, 2.00 mmol), Na_2CO_3 (456 mg, 4.30 mmol) and $Pd(PPh_3)_4$ (180 mg, 156 µmol) in toluene (18 mL), EtOH (3 mL) and H_2O (3 mL). After work-up (H_2O (50 mL), extraction with $CHCl_3$ (5 x 30 mL), column chromatography hexane/EtOAc = 1:1) compound **1m** was obtained as brownish

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solid (88.0 mg, 12%), mp: 152-154 °C. ^{1}H-NMR ($CDCl_3$, 250 MHz): δ = 1.92-2.04 (m, 4H, NCH_2CH_2), 3.54 (m, 2H, NCH_2), 3.70 (m, 2H, NCH_2), 4.29-4.44 (m, 2H, OCH_2), 4.74-4.96 (m, 2H, CH_2F), 7.18 (m, 1H), 7.26 (dd, ^3J = 9.0 Hz, ^4J = 2.6 Hz, 1H, superimposed with $CDCl_3$ residual peak), 7.69 (dd, ^3J = 8.5 Hz, ^4J = 1.8 Hz, 1H), 7.81-7.86 (m, 2H), 8.01 (m, 1H), 8.17 (m, 1H), 8.75 (m, 1H), 9.00 (m, 1H). MS (DIP-APCI, +): *m/z* (%): calcd. for $C_{22}H_{22}FN_2O_2$ $[M+H]^+$: 365.1660; found: 365.1665 ($[M+H]^+$).

Methyl 3-(4-isoquinolinyl)-7-methoxy-2-naphthoate (**1n**): Prepared according to the general procedure method B from Methyl 7-methoxy-3-(trifluoromethylsulfonyloxy)-2-naphthoate (**3d**, 1.00 g, 2.75 mmol), Isoquinoline-4-boronic acid (**4n**, 645 mg, 3.73 mmol), Na_2CO_3 (530 mg, 5.00 mmol) and $Pd(PPh_3)_4$ (220 mg, 191 µmol) in a mixture of toluene (20 mL), EtOH (5 mL) and H_2O (5 mL); reaction time: 24 h. After work-up (H_2O (200 mL), extraction with $CHCl_3$ (5 x 100 mL), column chromatography CH_2Cl_2/CH_3OH = 98:2) compound **1n** was obtained as a colorless solid (826 mg, 88%). ^{1}H-NMR ($CDCl_3$, 250 MHz): δ = 3.43 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 7.27-7.32 (m, 2H), 7.52-7.61 (m, 3H), 7.74-7.79 (m, 2H), 7.99-8.06 (m, 1H), 8.47 (s, 1H), 8.56 (s, 1H), 9.28 (s, 1H).

2-Fluoroethyl 3-(4-isochinolinyl)-7-methoxy-2-naphthoate (**1o**)**:** Prepared according to the general procedure method B from 2-Fluoroethyl 7-methoxy-3-(trifluoromethylsulfonyl)-2-naphthoate (**3e**, 250 mg, 630 µmol), Isoquinoline-4-boronic acid (**4n**, 174 mg, 1.00 mmol), Na_2CO_3 (143 mg, 1.36 mmol) and $Pd(PPh_3)_4$ (60.0 mg, 51.0 µmol) in toluene (6 mL), EtOH (1 mL) and H_2O (1 mL); reaction time: 24 h. After work-up (H_2O (50 mL), extraction with $CHCl_3$ (3 x 25 mL), column chromatography (first column: CH_2Cl_2/CH_3OH = 98:2, second column: hexane/EtOAc = 1:4)) compound **1o** was obtained as a colorless solid (128 mg, 54%), mp: 119-121 °C. ^{1}H-NMR ($CDCl_3$, 250 MHz): δ = 3.98-4.07 (m, 2H, OCH_2) superimposed with 3.99 (s, 3H, OCH_3), 4.13-4.22 (m, 2H, CH_2F), 7.29-7.35 (m, 2H), 7.50-7.63 (m, 3H), 7.77-7.82 (m, 2H), 8.02-8.08 (m, 1H), 8.49 (s, 1H), 8.61 (s, 1H), 9.30 (s, 1H). MS (EI): *m/z* (%): calcd. for $C_{23}H_{18}FNO_3$ $[M]^{+\cdot}$: 375.1; found: 375.1 (100, $[M]^{+\cdot}$).

3-[6-Cyano-2-naphthalenyl]-5-(2-fluoroethoxy)pyridine (**1p**): Prepared according to the general procedure method C from 6-Cyano-2-naphthalenyl trifluoromethanesulfonate (**3f**, 301 mg, 1.00 mmol), 5-(2-Fluoroethoxy)-3-pyridineboronic acid (**4o**, 185 mg, 1.00 mmol), Na_2CO_3 (235 mg, 2.22 mmol) and $Pd(PPh_3)_4$ (24.0 mg, 20.8 µmol) in DME (11 mL) and H_2O (1 mL); reaction time: 3 h. After work-up (H_2O (50 mL), extraction with EtOAc (3 x 40 mL), column chromatography hexane/EtOAc = 1:1) compound **1p** was obtained as a colorless solid (157 mg, 63%), mp: 139-143 °C. ^{1}H-NMR ($CDCl_3$, 250 MHz): δ = 4.32-4.46 (m, 2H, OCH_2), 4.72-4.94 (m, 2H, CH_2F), 7.55 (dd, ^4J = 2.8 Hz, ^4J = 1.9 Hz, 1H), 7.67 (dd, ^3J = 8.5 Hz, ^4J = 1.6 Hz, 1H), 7.83 (dd, ^3J = 8.7 Hz, ^4J = 1.8 Hz, 1H), 7.97-8.04 (m, 2H), 8.08 (m, 1H), 8.28 (m, 1H), 8.40 (d, ^4J = 2.8 Hz, 1H), 8.62 (d, ^4J = 1.8 Hz, 1H). MS (DIP-APCI, +): *m/z* (%): calcd. for $C_{18}H_{14}FN_2O$ $[M+H]^+$: 293.1085; found: 293.1099 ($[M+H]^+$).

4-Fluoro-3-(6-methoxy-2-naphthalenyl)pyridine (**1q**): Prepared according to the general procedure method C from 6-Methoxynaphthalene-2-boronic acid (**3c**, 289 mg, 1.43 mmol), 3-Bromo-4-fluoropyridine (**4p**, 199 mg, 1.13 mmol), Na_2CO_3 (509 mg, 4.80 mmol) and $Pd(PPh_3)_4$ (71.0 mg, 61.4 µmol) in DME (7 mL) and H_2O (2 mL); reaction time: 18 h. After work-up (H_2O (50 mL), extraction with methyl *tert*-butyl ether (3 x 25 mL), column chromatography heptane/EtOAc = 1:1) compound **1q** was obtained as a greyish solid (230 mg, 80%), mp: 134-136 °C. ^{1}H-NMR ($CDCl_3$, 250 MHz): δ = 3.95 (s, 3H, OCH_3), 7.01-7.06 (m, 1H), 7.15-7.24 (m, 2H), 7.62 (dd, ^3J = 8.5 Hz, ^4J = 2.0 Hz, 1H), 7.77-7.87 (m, 2H), 7.92 (m, 1H), 8.02-8.11 (m, 1H), 8.50-8.54 (m, 1H). MS (DIP-APCI, +): *m/z* (%): calcd. for $C_{16}H_{13}FNO$ $[M+H]^+$: 254.0976; found: 254.0975 ($[M+H]^+$).

3-(2-Fluoroethoxy)-5-(6-methoxy-2-naphthalenyl) pyridine (**1r**): Prepared according to the general procedure method D from 6-Methoxynaphthalene-2-boronic acid (**3c**, 642 mg, 3.18 mmol), 3-Bromo-5-(2-fluoroethoxy)pyridine (**4q**, 605 mg, 2.75 mmol), Na_2CO_3 (2.10 g, 19.81 mmol) and $Pd(PPh_3)_4$ (137 mg, 119 µmol) in MeOH (31 mL) and H_2O (9 mL); reaction time: 24 h. After work-up (H_2O (5 mL), extraction with CH_2Cl_2 (3 x 50 mL), column chromatography CH_2Cl_2/CH_3OH = 100:0 → 98:2) compound **1r** was obtained as a colorless solid (669 mg, 82%), mp: 139-141 °C. ^{1}H-NMR ($CDCl_3$, 250 MHz): δ = 3.95 (s, 3H, OCH_3), 4.30-4.44 (m, 2H, OCH_2), 4.71-4.94 (m, 2H, CH_2F), 7.16-7.23 (m, 2H), 7.51-7.54 (m, 1H), 7.67 (dd, ^3J = 8.5 Hz, ^4J = 1.8 Hz, 1H), 7.79-7.86 (m, 2H), 7.97 (m, 1H), 8.34 (d, ^4J = 2.7 Hz, 1H), 8.61 (d, ^4J = 1.6 Hz, 1H). MS (DIP-APCI, +): *m/z* (%): calcd. for $C_{18}H_{17}FNO_2$ $[M+H]^+$: 298.1238; found: 298.1246 ($[M+H]^+$).

4-[6-(2-Fluoroethoxy)-2-naphthalenyl]isoquinoline (**1s**): Prepared according to the general procedure method D from 2-Bromo-6-(2-fluoroethoxy)naphthalene (**3g**, 778 mg, 2.89 mmol), Isoquinoline-4-boronic acid (**4n**, 500 mg, 2.89 mmol), Na_2CO_3 (1.90 g, 17.93 mmol) and $Pd(PPh_3)_4$ (125 mg, 108 µmol) in MeOH (27 mL) and H_2O (8 mL); reaction time: 24 h. After work-up (H_2O (100 mL), extraction with CH_2Cl_2 (3 x 80 mL), column chromatography hexane/CH_2Cl_2 = 1:1 → 100:0) compound **1s** was obtained as a brownish solid (132 mg, 14%), mp: 107 °C. ^{1}H-NMR ($CDCl_3$, 250 MHz): δ = 4.32-4.47 (m, 2H, OCH_2), 4.76-4.98 (m, 2H, CH_2F), 7.23-7.31 (m, 2H), 7.59-7.74 (m, 3H), 7.82-8.00 (m, 4H), 8.04-8.09 (m, 1H), 8.58 (s, 1H), 9.29 (s, 1H). MS (DIP-APCI, +): *m/z* (%): calcd. for $C_{21}H_{17}FNO_2$ $[M+H]^+$: 318.1289; found: 318.1295 ($[M+H]^+$).

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3-(2-Fluoroethoxymethyl)-5-(6-methoxy-2-naphthalenyl) pyridine (**1t**): Prepared according to the general procedure method D from 6-Methoxynaphthalene-2-boronic acid (**3c**, 345 mg, 1.71 mmol), 3-Bromo-5-(2-fluoroethoxymethyl) pyridine (**4r**, 400 mg, 1.71 mmol), Na_2CO_3 (1.17 g, 11.04 mmol) and $Pd(PPh_3)_4$ (77.0 mg, 66.6 µmol) in MeOH (17 mL) and H_2O (5 mL); reaction time: 24 h. After work-up (H_2O (100 mL), extraction with CH_2Cl_2 (3 x 80 mL), column chromatography CH_2Cl_2/CH_3OH = 98:2) compound **1t** was obtained as a colorless solid (393 mg, 74%), mp: 120-124 °C. ^{1}H-NMR ($CDCl_3$, 250 MHz): δ = 3.75-3.90 (m, 2H, OCH_2), 3.95 (s, 3H, OCH_3), 4.53-4.76 (m, 2H, CH_2F) superimposed with 4.72 (s, 2H, $ArCH_2O$), 7.16-7.23 (m, 2H), 7.70 (dd, ^3J = 8.6 Hz, ^4J = 1.9 Hz, 1H), 7.80-7.87 (m, 2H), 7.99-8.03 (m, 2H), 8.57 (m, 1H), 8.90 (m, 1H). MS (DIP-APCI, +): *m/z* (%): calcd. for $C_{19}H_{19}FNO_2$ $[M+H]^+$: 312.1394; found: 318.1399 ($[M+H]^+$).

3-[1-(2-Fluoroethoxy)ethyl]-5-(6-methoxy-2-naphthalenyl)pyridine (**1u**): Prepared according to the general procedure method D from 6-Methoxynaphthalene-2-boronic acid (**3c**, 345 mg, 1.71 mmol), 3-Bromo-5-[1-(2-fluoroethoxy)ethyl]pyridine (**4s**, 170 mg, 685 µmol), Na_2CO_3 (1.17 g, 11.04 mmol) and $Pd(PPh_3)_4$ (77.0 mg, 66.6 µmol) in MeOH (17 mL) and H_2O (5 mL); reaction time: 24 h. After work-up (H_2O (100 mL), extraction with CH_2Cl_2 (3 x 80 mL), column chromatography CH_2Cl_2/CH_3OH = 98:2) compound **3u** was obtained as a colorless solid (117 mg, 52%), mp: 111 °C. ^{1}H-NMR ($CDCl_3$, 250 MHz): δ = 1.58 (d, ^3J = 6.5 Hz, 3H, $CHCH_3$), 3.51-3.78 (m, 2H, OCH_2), 3.95 (s, 3H, OCH_3), 4.47-4.69 (m, 3H, CH_2F and $CHCH_3$ superimposed), 7.17-7.24 (m, 2H), 7.68-7.73 (m, 1H), 7.80-7.89 (m, 2H), 7.99-8.04 (m, 2H), 8.53 (m, 1H), 8.89, 9.14 (m, 1H). MS (EI): *m/z* (%): calcd. for $C_{20}H_{20}FNO_2$ $[M]^{+\cdot}$: 325.2; found: 325.1 (100, $[M]^{+\cdot}$).

3-(2-Fluoropropoxy)-5-(6-methoxy-2-naphthalenyl) pyridine (**1v**): Prepared according to the general procedure method D from 6-Methoxynaphthalene-2-boronic acid (**3c**, 321 mg, 1.59 mmol), 3-Bromo-5-(3-fluoropropoxy)pyridine (**4t**, 372 mg, 1.59 mmol), Na_2CO_3 (1.05 g, 9.97 mmol) and $Pd(PPh_3)_4$ (69.0 mg, 59.7 µmol) in MeOH (15 mL) and H_2O (4 mL); reaction time: 24 h. After work-up (H_2O (50 mL), extraction with CH_2Cl_2 (3 x 40 mL), column chromatography CH_2Cl_2/CH_3OH = 100:0 → 95:5) compound **1v** was obtained as a colorless solid (287 mg, 58%), mp: 130-131 °C. ^{1}H-NMR ($CDCl_3$, 250 MHz): δ = 2.14-2.34 (m, 2H, OCH_2CH_2), 3.95 (s, 3H, OCH_3), 4.25 (t, ^3J = 6.1 Hz, 2H, OCH_2), 4.58-4.82 (dt, $^2J_{F,H}$ = 39.5 Hz, ^3J = 6.1 Hz, 2H, CH_2F), 7.16-7.23 (m, 2H), 7.50 (dd, ^4J = 2.7 Hz, ^4J = 1.8 Hz, 1H), 7.67 (dd, ^3J = 8.6 Hz, ^4J = 1.8 Hz, 1H), 7.79-7.86 (m, 2H), 7.97 (d, ^4J = 2.0 Hz, 1H), 8.31 (d, ^4J = 2.8 Hz, 1H), 8.61 (d, ^4J = 1.7 Hz, 1H). MS (DIP-APCI, +): *m/z* (%): calcd. for $C_{19}H_{19}FNO_2$ $[M+H]^+$: 312.1394; found: 312.1399 ($[M+H]^+$).

5-[6-(2-Fluoroethoxy)-2-naphthalenyl]-3-(1,3-oxazol-5-yl)pyridine (**1w**): A suspension of 6-(2-Fluoroethoxy)-2-naphthaleneboronic acid pinacol ester (**3b**, 357 mg, 1.13 mmol), 3-Bromo-5-(1,3-oxazol-5-yl)pyridine (**4u**, 254 mg, 1.13 mmol) and Ag_2CO_3 (345 mg, 1.25 mmol) in benzene (15 mL) was degassed with argon. $Pd(PPh_3)_4$ (78.0 mg, 67.5 µmol) was added and the reaction mixture was stirred under reflux for 24 h. After cooling to room temperature H_2O (100 mL) was added and the mixture was extracted with methyl *tert*-butyl ether (3 x 50 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure. Purification of the residue by column chromatography (heptane/EtOAc = 1:1) yielded compound **1w** as a colorless solid (64.0 mg, 17%), mp: 143-145 °C. ^{1}H-NMR ($CDCl_3$, 250 MHz): δ = 4.30-4.44 (m, 2H, OCH_2), 4.74-4.96 (m, 2H, CH_2F), 7.19 (d, ^4J = 2.6 Hz, 1H), 7.27 (dd, ^3J = 8.9 Hz, ^4J = 2.5 Hz, 1H, superimposed with $CDCl_3$ residual peak), 7.56 (s, 1H), 7.63 (d, ^4J = 1.7 Hz, 1H), 7.86, 7.87 (2d superimposed, ^3J = 9.0 Hz, ^3J = 8.9 Hz, 2H), 8.03 (m, 2H), 8.24 (m, 1H), 8.91 (m, 2H). MS (EI): *m/z* (%): calcd. for $C_{20}H_{15}FN_2O_2$ $[M]^{+\cdot}$: 334.1; found: 334.1 (100, $[M]^{+\cdot}$).

5-(6-Methoxy-2-naphthalenyl)-3-(2-fluoro-3-pyridyl) pyridine (**1x**): Prepared according to the general procedure method D from 3-Bromo-5-(6-methoxy-2-naphthalenyl) pyridine (**1l**, 314 mg, 1.00 mmol), 2-Fluoropyridine-3-boronic acid (**4v**, 155 mg, 1.10 mmol), Na_2CO_3 (657 mg, 6.20 mmol) and $Pd(PPh_3)_4$ (45.0 mg, 38.9 µmol) in MeOH (10 mL) and H_2O (3 mL); reaction time: 24 h. After work-up (H_2O (50 mL), extraction with CH_2Cl_2 (3 x 40 mL), column chromatography (CH_2Cl_2/CH_3OH = 98:2) compound **1x** was obtained as a beige solid (267 mg, 81 %), mp: 192 °C. ^{1}H-NMR ($CDCl_3$, 250 MHz): δ = 3.96 (s, 3H, OCH_3), 7.18-7.24 (m, 2H), 7.38 (ddd, ^3J = 7.5 Hz, ^3J = 4.9 Hz, ^4J = 1.8 Hz, 1H), 7.72 (dd, ^3J = 8.7 Hz, ^4J = 1.8 Hz, 1H), 7.82-7.90 (m, 2H), 7.96-8.04 (m, 2H), 8.22 (dd, ^3J = 4.0 Hz, ^4J = 2.1 Hz, 1H), 8.31 (ddd, ^3J = 4.9 Hz, ^4J = 2.0 Hz, ^5J = 1.2 Hz, 1H), 8.79 (m, 1H), 9.00 (d, ^3J = 2.3 Hz, 1H). MS (DIP-APCI, +): *m/z* (%): calcd. for $C_{21}H_{16}FN_2O$ $[M+H]^+$: 331.1241; found: 331.1268 ($[M+H]^+$).

5-(6-Methoxy-2-naphthalenyl)-3-(6-fluoro-3-pyridyl) pyridine (**1y**): Prepared according to the general procedure method D from 3-Bromo-5-(6-methoxy-2-naphthalenyl) pyridine (**1l**, 314 mg, 1.00 mmol), 6-Fluoropyridine-3-boronic acid (**4w**, 155 mg, 1.10 mmol), Na_2CO_3 (657 mg, 6.20 mmol) and $Pd(PPh_3)_4$ (45.0 mg, 38.9 µmol) in MeOH (10 mL) and H_2O (3 mL); reaction time: 24 h. After work-up (H_2O (50 mL), extraction with CH_2Cl_2 (3 x 40 mL), column chromatography (CH_2Cl_2/CH_3OH = 98:2) compound **1y** was obtained as a beige solid (267 mg, 52%), mp: 219 °C. ^{1}H-NMR ($CDCl_3$, 250 MHz): δ = 3.97 (s, 3H, OCH_3), 7.09-7.14 (m, 1H), 7.19-7.26 (m, 2H), 7.71-7.75 (m, 1H), 7.84 (d, ^3J = 8.9 Hz, 1H), 7.90 (d, ^3J = 8.7 Hz, 1H), 8.05-8.12 (m, 2H),

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8.17 (m, 1H), 8.54 (m, 1H), 8.79 (d, ^4J = 2.1 Hz, 1H), 9.0 (d, ^4J = 2.0 Hz, 1H). MS (DIP-APCI, +): *m/z* (%): calcd. for $C_{21}H_{16}FN_2O$ $[M+H]^+$: 331.1241; found: 331.1252 ($[M+H]^+$).

4-(3-Hydroxymethyl-6-methoxy-2-naphthalenyl) isoquinoline (**1z**): To a suspension of $LiAlH_4$ (1.33 g, 35.0 mmol) in THF (10 mL) a solution of **1n** (826 mg, 2.40 mmol) in THF (10 mL) was added dropwise. After stirring at room temperature for 24 h H_2O (20 mL) and H_2SO_4 (5 mL) were added successively. The resulting solution was neutralized with 1 N NaOH and extracted with $CHCl_3$ (5 x 25 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography CH_2Cl_2/CH_3OH = 98:2) afforded compound **1z** as a brownish solid (260 mg, 34%). ^{1}H-NMR ($CDCl_3$, 250 MHz): δ = 2.50 (s, 1H, OH), 3.96 (s, 3H, OCH_3), 4.51 (s, 2H, CH_2OH), 7.17-7.26 (m, 2H), 7.45-7.50 (m, 1H), 7.55-7.65 (m, 2H), 7.66 (s, 1H), 7.73 (d, ^3J = 9.4 Hz, 1H), 7.99-8.06 (m, 2H), 8.40 (s, 1H), 9.22 (s, 1H).

4-[3-(2-Fluoroethoxymethyl)-6-methoxy-2-naphthalenyl] isoquinoline (**1aa**): A solution of **1z** (260 mg, 824 µmol), 2-Fluoroethyl p-toulenesulfonate (358 mg, 1.64 mmol) and NaH (60% dispersion in mineral oil, 150 mg, 3.75 mmol) in DMF (4 mL) was stirred at 60 °C for 24 h. The reaction mixture was allowed to come to room temperature and the solvent was removed in vacuo. The residue was taken up in H_2O (50 mL). Extraction with $CHCl_3$ (3 x 50 mL), drying over Na_2SO_4, evaporation of the solvent in vacuo and column chromatography CH_2Cl_2/CH_3OH = 95:5) compound **1aa** was obtained as a brownish solid (65.0 mg, 22%). ^{1}H-NMR ($CDCl_3$, 250 MHz): δ = 3.38-3.55 (m, 2H, OCH_2), 3.97 (s, 3H, OCH_3), 4.25-4.49 (m, 2H, CH_2F) superimposed with 4.39 (s, 2H, $ArCH_2O$), 7.20 (dd, ^3J = 8.9 Hz, ^4J = 2.5 Hz, 1H), 7.26 (m, 1H), 7.48-7.51 (m, 1H), 7.59-7.64 (m, 2H), 7.70-7.76 (m, 2H), 8.01 (s, 1H), 8.04-8.08 (m, 1H), 8.50 (s, 1H), 9.31 (s, 1H). MS (DIP-APCI, +): *m/z* (%): calcd. for $C_{23}H_{21}FNO_2$ $[M+H]^+$: 362.1551; found: 362.1559 ($[M+H]^+$).

Synthesis of Dihydroquinolinone Compounds 2a-h

1-(2-Fluoroethyl)-6-(isoquinolin-4-yl)-3,4-dihydro-2(1H)-quinolinone (**2a**): Prepared according to the general procedure method A from 6-Bromo-1-(2-fluoroethyl)-3,4-dihydro-2(1*H*)-quinolinone (**5a**, 268 mg, 985 µmol), Isoquinoline-4-boronic acid (**4n**, 190 mg, 1.10 mmol), $Ba(OH)_2 \cdot 8\ H_2O$ (474 mg, 1.50 mmol) and $Pd(PPh_3)_4$ (44.0 mg, 38.1 µmol) in DME (6 mL) and H_2O (1 mL); reaction time: 24 h. After work-up (H_2O (50 mL), extraction with $CHCl_3$ (5 x 30 mL), column chromatography CH_2Cl_2/CH_3OH = 95:5) compound **2a** was obtained as an orange oil (145 mg, 46%). ^{1}H-NMR ($CDCl_3$, 250 MHz): δ = 2.73-2.79 (m, 2H, CH_2), 2.98-3.04 (m, 2H, CH_2), 4.11-4.25 (dt, $^3J_{F,H}$ = 24.6 Hz, ^3J = 5.0 Hz, 2H, CH_2CH_2F), 4.58-4.81 (dt, $^2J_{F,H}$ = 47.4 Hz, ^3J = 5.0 Hz, 2H, CH_2F), 7.28-7.33 (m, 2H), 7.37-7.42 (m, 1H), 7.62-7.69 (m, 2H), 7.90-7.95 (m, 1H), 8.02-8.06 (m, 1H), 8.46 (s, 1H), 9.24 (s, 1H).

1-(3-Fluoropropyl)-6-(isoquinolin-4-yl)-3,4-dihydro-2(1H)-quinolinone (**2b**): Prepared according to the general procedure method A from 6-Bromo-1-(2-fluoropropyl)-3,4-dihydro-2(1*H*)-quinolinone (**5b**, 260 mg, 909 µmol), Isoquinoline-4-boronic acid (**4n**, 208 mg, 1.20 mmol), $Ba(OH)_2 \cdot 8\ H_2O$ (474 mg, 1.50 mmol) and $Pd(PPh_3)_4$ (44.0 mg, 38.1 µmol) in DME (6 mL) and H_2O (1 mL); reaction time: 24 h. After work-up (H_2O (50 mL), extraction with $CHCl_3$ (5 x 30 mL), column chromatography CH_2Cl_2/CH_3OH = 98:2) compound **2b** was obtained as a yellowish resin (166 mg, 55%). ^{1}H-NMR ($CDCl_3$, 250 MHz): δ = 2.03-2.24 (m, 2H, NCH_2), 2.69-2.75 (m, 2H, CH_2), 2.95-3.01 (m, 2H, CH_2), 4.12-4.18 (m, 2H, CH_2CH_2F), 4.46-4.70 (dt, $^2J_{F,H}$ = 47.1 Hz, ^3J = 5.6 Hz, 2H, CH_2F), 7.18 (d, ^3J = 8.4 Hz, 1H), 7.32 (m, 1H), 7.40 (dd, ^3J = 8.4 Hz, ^3J = 2.2 Hz, 1H), 7.64-7.69 (m, 2H), 7.90-7.95 (m, 1H), 8.01-8.05 (m, 1H), 8.45 (s, 1H), 9.23 (s, 1H).

7-(2-Fluoroethoxy)-6-(isoquinolin-4-yl)-3,4-dihydro-2(1H)-quinolinone (**2c**): Prepared according to the general procedure method B from 6-Bromo-7-(2-fluoroethoxy)-3,4-dihydro-2(1*H*)-quinolinone (**5c**, 134 mg, 465 µmol), Isoquinoline-4-boronic acid (**4n**, 129 mg, 746 mmol), Na_2CO_3 (106 mg, 1.00 mmol) and $Pd(PPh_3)_4$ (44.0 mg, 38.1 µmol) in toluene (6 mL), EtOH (1 mL) and H_2O (1 mL); reaction time: 18 h. After work-up (H_2O (50 mL), extraction with $CHCl_3$ (5 x 30 mL), column chromatography CH_2Cl_2/CH_3OH = 98:2) compound **2c** was obtained as a salmon solid (99.0 mg, 63%). ^{1}H-NMR ($CDCl_3$, 250 MHz): δ = 2.04-2.11 (m, 2H, NCH_2CH_2), 3.37-3.43 (m, 2H, NCH_2), 4.36 (m, 2H, OCH_2), 4.85 (m, 2H, CH_2F), 7.11-7.27 (2m superimposed, 3H), 7.62-7.71 (m, 2H), 7.80-7.85 (m, 2H), 7.94-7.99 (m, 2H), 8.24 (m, 1H).

8-[5-(2-Fluoroethoxymethyl)pyridine-3-yl]-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ij]-4-quinoli-none (**2d**): Prepared according to the general procedure method A from 1,2,5,6-tetrahydro-4*H*-pyrrolo[3,2,1-*ij*]-4-quinolinone-8-boronic acid pinacol ester (**5d**, 471 mg, 1.57 mmol), 3-Bromo-5-(2-fluoroethoxymethyl)pyridine (**4r**, 322 mg, 1.38 mmol), $Ba(OH)_2 \cdot 8\ H_2O$ (645 mg, 2.04 mmol) and $Pd(PPh_3)_4$ (64.0 mg, 55.4 µmol) in DME (8.5 mL) and H_2O (1.3 mL); reaction time: 24 h. After work-up (H_2O (50 mL), extraction with $CHCl_3$ (3 x 25 mL), column chromatography CH_2Cl_2/CH_3OH = 95:5) compound **2d** was obtained as an off-white solid (277 mg, 54%), mp: 138-140 °C. ^{1}H-NMR ($CDCl_3$, 250 MHz): δ = 2.69-2.76 (m, 2H, CH_2), 3.02-3.08 (m, 2H, CH_2), 3.23-3.29 (m, 2H, CH_2), 3.72-3.88 (OCH_2CH_2F), 4.11-4.17 (m, 2H, CH_2), 4.52-4.74 (m, 2H, CH_2F) superimposed with 4.68 (s, 2H, $ArCH_2O$), 7.22 (m, 1H), 7.30 (m, 1H), 7.85 (m, 1H), 8.52 (d, ^4J = 2.1 Hz, 1H), 8.72 (d, ^4J = 2.4 Hz, 1H). MS (DIP-APCI, +): *m/z* (%): calcd. for $C_{19}H_{20}FN_2O_2$ $[M+H]^+$: 327.1503; found: 327.1519 ($[M+H]^+$).

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6-[5-(2-fluoroethoxymethyl)pyridin-3-yl]-1-methyl-3,4-dihydro-2(1H)-quinolinone (**2e**): Prepared according to the general procedure method A from 1-Methyl-3,4-dihydro-2(1*H*)-quinolinone-6-boronic acid pinacol ester (**5e**, 369 mg, 1.28 mmol), 3-Bromo-5-(2-fluoroethoxymethyl)pyridine (**4r**, 301 mg, 1.28 mmol), $Ba(OH)_2 \cdot 8\ H_2O$ (605 mg, 1.92 mmol) and $Pd(PPh_3)_4$ (60.0 mg, 51.9 µmol) in DME (8 mL) and H_2O (1.3 mL); reaction time: 24 h. After work-up (H_2O (50 mL), extraction with $CHCl_3$ (3 x 25 mL), column chromatography (first column: CH_2Cl_2/CH_3OH = 95:5, second column: hexane/EtOAc = 1:3) compound **2e** was obtained as an off-white solid (163 mg, 40%). ^{1}H-NMR ($CDCl_3$, 250 MHz): δ = 2.67-2.73 (m, 2H, CH_2), 2.96-3.02 (m, 2H, CH_2), 3.40 (s, 3H, NCH_3), 3.73-3.88 (OCH_2CH_2F), 4.52-4.74 (m, 2H, CH_2F) superimposed with 4.68 (s, 2H, $ArCH_2O$), 7.08 (d, ^3J = 8.4 Hz, 1H), 7.39-7.43 (m, 1H), 7.49 (dd, ^3J = 8.4 Hz, ^4J = 2.3 Hz, 1H), 7.90 (m, 1H), 8.53 (d, ^4J = 2.1 Hz, 1H), 8.76 (d, ^4J = 2.2 Hz, 1H).

8-Chloro-6-[5-(2-fluoroethoxymethyl)pyridin-3-yl]-1-methyl-3,4-dihydro-2(1H)-quinoli-none (**2f**): Prepared according to the general procedure method A from 8-Chloro-1-methyl-3,4-dihydro-2(1*H*)-quinolinone-6-boronic acid pinacol ester (**5f**, 322 mg, 1.00 mmol), 3-Bromo-5-(2-fluoroethoxymethyl)pyridine (**4r**, 216 mg, 923 µmol), $Ba(OH)_2 \cdot 8\ H_2O$ (432 mg, 1.37 mmol) and $Pd(PPh_3)_4$ (44.0 mg, 38.1 µmol) in DME (6 mL) and H_2O (0.9 mL); reaction time: 24 h. After work-up (H_2O (50 mL), extraction with $CHCl_3$ (3 x 25 mL), column chromatography CH_2Cl_2/MeOH = 95:5) compound **2f** was obtained as a yellowish oil (139 mg, 43%). ^{1}H-NMR ($CDCl_3$, 250 MHz): δ = 2.60-2.66 (m, 2H, CH_2), 2.90-2.96 (m, 2H, CH_2), 3.49 (s, 3H, NCH_3), 3.72-3.88 (m, 2H, OCH_2CH_2F), 4.51-4.74 (m, 2H, CH_2F), 4.68 (s, 2H, $ArCH_2O$), 7.32 (m, 1H), 7.50 (d, ^4J = 2.1 Hz, 1H), 7.86 (m, 1H), 8.56 (d, ^4J = 2.1 Hz, 1H), 8.73 (d, ^4J = 2.3 Hz, 1H).

8-Chloro-6-{5-[1-(2-fluoroethoxy)ethyl]pyridin-3-yl}-1-methyl-3,4-dihydro-2(1H)-quinolino-ne (**2g**): Prepared according to the general procedure method A from 8-Chloro-1-methyl-3,4-dihydro-2(1*H*)-quinolinone-6-boronic acid pinacol ester (**5f**, 322 mg, 1.00 mmol), 3-Bromo-5-[1-(2-fluoroethoxy)ethyl]pyridine (**4s**, 218 mg, 879 mmol), $Ba(OH)_2 \cdot 8\ H_2O$ (432 mg, 1.37 mmol) and $Pd(PPh_3)_4$ (44.0 mg, 38.1 µmol) in DME (6 mL) and H_2O (0.9 mL); reaction time: 24 h. After work-up (H_2O (50 mL), extraction with $CHCl_3$ (3 x 25 mL), column chromatography CH_2Cl_2/MeOH = 95:5) compound **2g** was obtained as a yellowish oil (112 mg, 35%). ^{1}H-NMR ($CDCl_3$, 250 MHz): δ = 1.55 (d, ^3J = 6.4 Hz, 3H, $CHCH_3$), 2.62-2.67 (m, 2H, CH_2), 2.92-2.97 (m, 2H, CH_2), 3.51 (s, 3H, NCH_3), 3.54-3.72 (m, 2H, OCH_2CH_2F), 4.45-4.69 (m, 2H, CH_2F) superimposed with 4.61 (q, ^3J = 6.4 Hz, 1H, $CHCH_3$), 7.33 (m, 1H), 7.51 (d, ^4J = 2.3 Hz, 1H), 7.86 (m, 1H), 8.54 (d, ^4J = 2.0 Hz, 1H), 8.74 (d, ^4J = 2.1 Hz, 1H). MS (EI): *m/z* (%): calcd. for $C_{19}H_{20}ClFN_2O_2$ $[M]^{+\cdot}$: 362.1; found: 277.0 (100, $[M\text{-}CH_2CH_2CONCH_3]^+$), 362.0 (29, $[M]^{+\cdot}$).

8-Chloro-6-(4-fluoropyridin-3-yl)-1-methyl-3,4-dihydro-2(1H)-quinolinone (**2h**): Prepared according to the general procedure method C from 8-Chloro-1-methyl-3,4-dihydro-2(1*H*)-quinolinone-6-boronic acid pinacol ester (**5f**, 338 mg, 1.05 mmol), 3-Bromo-4-fluoropyridine (**4p**, 199 mg, 1.13 mmol), Na_2CO_3 (509 mg, 4.80 mmol) and $Pd(PPh_3)_4$ (71.0 mg, 61.4 µmol) in DME (7 mL) and H_2O (2 mL); reaction time: 24 h. After work-up (H_2O (50 mL), extraction with methyl *tert*-butyl ether (3 x 25 mL), column chromatography heptane/EtOAc = 1:1) compound **2h** was obtained as a colorless solid (191 mg, 63%), mp: 127-129 °C. ^{1}H-NMR ($CDCl_3$, 250 MHz): δ = 2.61-2.67 (m, 2H, CH_2), 2.91-2.97 (m, 2H, CH_2), 3.50 (s, 3H, NCH_3), 6.99-7.05 (m, 1H), 7.26 (m, 1H, superimposed with $CDCl_3$ residual peak), 7.45 (d, ^4J = 2.1 Hz, 1H), 7.90-7.97 (m, 1H), 8.37-8.41 (m, 1H).

Cell Cultures

The primary human adrenocortical cell line NCI-H295 was purchased commercially from ATCC via LGC Standards GmbH (Wesel, Germany) and was cultured in RPMI 1640 medium supplemented with 10% FCS, 5 µg/ml insulin, 100 µg/ml transferrin and 5.2 ng/ml sodium selenite at 37 °C in a humidified atmosphere (95%) with 5% CO_2. The medium was exchanged every 48 hours, with approximately 30% of the old medium being reused to preserve synthesized growth factors. Alternately, the cells were passaged every four to five days. The murine adrenocortical tumour Y1 cell line was purchased commercially from CLS Cell Lines Service GmbH (Eppelheim, Germany). Y1 cells stably transfected with human CYP11B1 (Y1-CYP11B1) and Y1 cells stably transfected with CYP11B2 (Y1-CYP11B2) were cultured in DMEM AQ (Dulbeccos Modified Eagle Medium) supplemented with 4.5 g/l glucose, 10% FCS and 1 mg/ml of the cell culture antibiotic zeocin at 37 °C in a humidified atmosphere (95%) with 5% CO_2. The Y1-CYP11B1 and the Y1-CYP11B2 cells were passaged every 48 hours. All cell culture media and supplements were obtained from Sigma-Aldrich (Deisenhofen, Germany).

Evaluation of CYP11B1 and CYP11B2 inhibition in NCI-H295 cells and Y1 cells

To evaluate CYP11B1 and CYP11B2 inhibition of all synthesized compounds, Y1-CYP11B1 and Y1-CYP11B2 cells were subcultured on 6-well plates (5 x 10^5 cells per well) in 2 ml of culture medium. The enzyme reaction was started after 24 h by the addition of 1 ml culture medium containing either 11-deoxycortisol (RSS) or deoxycorticosterone (DOC) (obtained from Sigma, Deisenhofen, Germany) as enzyme substrate and the corresponding inhibitor. RSS and DOC were added because the Y1 cells do not contain the whole cascade of enzymes to produce cortisol and aldosterone, and were dissolved in ethanol prior to addition to the cell culture

medium. The final concentrations were 1 µM for the substrate and, for the determination of IC_{50} values, 0.1 nM - 10 µM for the corresponding inhibitor before incubating for 48 h at 37 °C in a humidified atmosphere (95%) with 5% CO_2. Y1-CYP11B1 and Y1-CYP11B2 cells treated in the same way but without inhibitors served as negative controls.

Selected inhibitors were evaluated for their CYP11B1 and CYP11B2 inhibition using cells of the adrenocortical cell line NCI-H295 subcultured on 6-well plates (1 x 10^6 cells/well) in culture medium. NCI-H295 cells contain the whole cascade of enzymes to produce cortisol and aldosterone. For determination of IC_{50} values, the inhibitors were added to the culture medium at final concentrations between 0.1 nM - 10 µM before incubating for 48 h at 37 °C in a humidified atmosphere (95%) with 5% CO_2. NCI-H295 cells treated in the same way without inhibitors served as negative controls.

At the end of incubation time, cortisol and aldosterone concentrations were determined in the cell supernatant by commercially available radioimmunoassays (DPC Biermann, Bad Nauheim, Germany; IBL international, Hamburg, Germany). The intra-assay variance of both assays was <8%, the inter-assay variance was <12%.

Conclusions

In conclusion, we report the synthesis and in vitro evaluation of fluorinated pyridyl-substituted naphthalenes and 3,4-dihydro-1H-quinolin-2-ones. Several compounds from both classes were found to act as highly potent aldosterone synthase (CYP11B2) inhibitors up to low nanomolar affinities using assays of stably transfected murine Y1 cells and the human adrenocortical NCI-H295 cell line. In addition, many of these inhibitors showed good or even excellent selectivity values owing to weak binding affinities on CYP11B1. The observed correlations between their substitution patterns and potency largely aligns with recent findings for similar compounds, such as the beneficial substitution of the 5-position of the pyridine moiety compared to the 4-position [39]. Based on these promising results, the organic synthesis of suitable precursors for F-18 fluorination, along with the respective labelling chemistry and preclinical evaluation of the most promising radiotracers are well underway.

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Author Contributions

Conceptualization, A.S., S.H. and B.H.; methodology, P.M., M.S., S.G., S.R. and B.H.; formal analysis, P.M., A.S. and B.H.; writing – original draft preparation: P.M. and A.S.; writing - review and editing, A.S., P.M. and S.H.; supervision, A.S. and S.H.; project administration, A.S. and B.H.; funding acquisition, A.S. and S.H. All authors have read and agreed to the published version of the manuscript.

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Declarations

Competing interests

AS and SH filed a patent application: PET radiopharmaceuticals for the differential diagnosis between bilateral and unilateral conditions of primary hyperaldosteronism. WO/2011/151411. All other authors declare no conflict of interest.

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