European Journal of Medicinal Chemistry 47 (2012) 1–17

Contents lists available at SciVerse ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Discovery of a new class of bicyclic substituted hydroxyphenylmethanones as 17β-hydroxysteroid dehydrogenase type 2 (17β-HSD2) inhibitors for the treatment of osteoporosis

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ARTICLE INFO

Article history:
Received 11 May 2011
Received in revised form
31 August 2011
Accepted 2 September 2011
Available online 8 September 2011

Keywords:
17β-HSD2
Osteoporosis
Non steroidal inhibitors
Steroidomimetics

ABSTRACT

E2 deficiency in elderly people has directly an effect on the skeleton and can lead to osteoporosis. As 17β-hydroxysteroid dehydrogenase type 2 (17β-HSD2) catalyses the conversion between active 17β-hydroxysteroid estradiol (E2) and testosterone (T) into their less active 17-ketosteroid and has been found in bones, 17β-HSD2 inhibitor may provide a new approach in the onset of osteoporosis. Bicyclic substituted hydroxyphenylmethanone derivatives were synthesised as steroidomimetics of the substrate E2 and were evaluated for their 17β-HSD2 inhibition and their selectivity toward 17β-HSD1, catalysing the reverse reaction the conversion of estrone (E1) into E2. Highly selective compounds (**11**, **12**, **14**, **21** and **22**) have been identified, the most promising one (**12**) showing an IC_{50} value in the low nanomolar range (101 nM) and a selectivity factor of 13 toward 17β-HSD1. These results make compound **12** an interesting candidate for further biological evaluation.

1. Introduction

Healthy bones are continuously regenerated by a mechanism of balance between osteoblasts (OBs) and osteoclasts (OCs), which are responsible for bone formation and bone resorption, respectively. The abnormal increase of the activity of OCs compared to the one of OBs in elderly people leads to osteoporosis [1]. Osteoporosis is a silent and systemic skeletal disease, characterised by reduced bone mineral density and increased risk of fractures often at the hips, spine and wrist. Bone loss often takes place in post-menopausal women and elderly men, after the level of active sex steroids 17β-estradiol (hereafter "estradiol" or E2) or testosterone (T) (Chart 1) has dropped down.

Several drugs can be administered for the treatment of osteoporosis. Among the antiresorptive agents, the bisphosphonate alendronate [2] is the most potent one used, but reduces the risk of hip fractures only by 50% in post-menopausal women [2,3] and elderly men [4]. Raloxifene [5], a selective estrogen receptor modulator (SERM) is also often used to treat osteoporosis, but leads to various adverse effects as increased risk of thromboembolism [6], hot flushes or leg cramps. Denosumab [7], an inhibitor of the receptor activator of nuclear factor κB ligand (RANKL) [8] inhibits the osteoclastogenesis (OC differentiation) by binding to RANKL. It has proven its efficacy [7,9] in post-menopausal women and elderly men with high risk of fractures but is associated with high cholesterol levels, muscle pain and bladder infection. Among all current marketed osteoporosis drugs, none of them offers a complete cure, there is therefore a need to develop new drugs for this disease with higher efficiency.

Estrogens [10] and androgens [10] play a key role in the development of the disease. It has been show that administration of E2 can help in the treatment of osteoporosis, but has adverse effects. Mechanism by which estrogens act on bones is not well understood yet, but one theory points out the importance of RANKL and

Abbreviations: 17β-HSD1, 17β-hydroxysteroid dehydrogenase type 1; 17β-HSD2, 17β-hydroxysteroid dehydrogenase type 2; A-dione, 4-androstene-3,17-dione; BMD, bone mineral density; E1, estrone; E2, 17β-estradiol; EDG, electron donating group; equiv, equivalent; ER, estrogen receptor; EWG, electron withdrawing group; HPLC, high pressure liquid chromatography; KO, knockout; NAD(H), nicotinamide adenine dinucleotide; OB, osteoblast; OC, osteoclast; OPG, osteoprotegerin; RBA, relative binding affinity; RANK(L), receptor activator of nuclear factor κB (ligand); SAR–activity relationship, structure; SERM, selective estrogen receptor modulator; SF, selectivity factor; T, testosterone.

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doi:10.1016/j.ejmech.2011.09.004

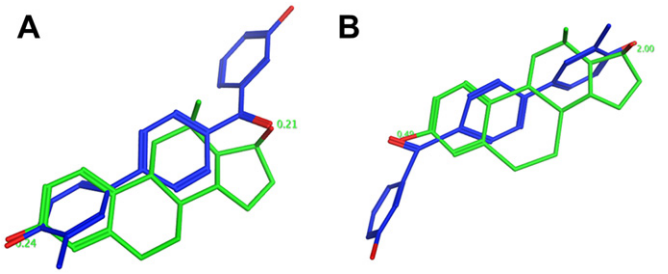


Fig. 1. Superimposition of compound **2** (green) and E2 (blue); (A) carbonyl group of 2 mimicks the C17(OH) of E2 and the OH of the phenyl A ring the C3(OH) of the steroid; (B) carbonyl group of **2** mimicks the C3(OH) of E2 and the OH of the phenyl A ring the C17(OH) of the steroid. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

osteoprotegerin (OPG) [11]. The production of OPG is stimulated by E2 in the OBs. Binding of OPG to RANKL inhibits the activation of the RANK receptor on osteoclasts, limiting the resorptive activity of OCs. OPG and RANKL knockout (KO) mice confirm the possible involvement of OPG and RANKL in bone regulation, as OPG KO mice [12,13] exhibit severe osteoporosis due to an increase of osteoclastogenesis, while RANKL KO mice [14] show serious osteopetrosis and a complete lack of OCs. A drug which could increase the concentration of estrogens in bones, would raise OPG levels, and thus might diminish bone resorption and should have favorable effects on osteoporosis.

17β-Hydroxysteroid dehydrogenase type 2 (17β-HSD2) is an enzyme converting the highly active E2 and T into their less active form, estrone (E1) and 4-androstene-3,17-dione (A-dione), respectively, using NAD^+ as cofactor (Chart 1). It is mainly localised in placenta, liver, small intestine and can be found in osteoblastic cells [15]. Inhibitors of 17β-HSD2 could therefore maintain a high level of E2 and T in bones, and protect them against bone loss. Considering that systemic and intracellular modulation of hormone concentrations has already been successfully applied for the treatment of breast and prostate cancer and begnign prostatic hyperplasia by inhibition of the steroidogenic enzymes aromatase [16–18], CYP17 [19–22] and 5α-reductase [23–25], respectively, or – as in case of 17β-HSD1 [26–34] – is considered beneficial for endometriosis therapy, inhibition of 17β-HSD2 could be a new approach for the treatment of osteoporosis.

Few inhibitors of 17β-HSD2 have been identified until now [35–40]. Among them, the pyrrolidinone **A** [38] (Chart 2) is the most potent one described in the literature ($IC_{50} = 10$ nM). Efficacy of a derivative of **A** has been evaluated *in vivo* in an osteoporotic monkey model [41]. This study proved that inhibition of 17β-HSD2

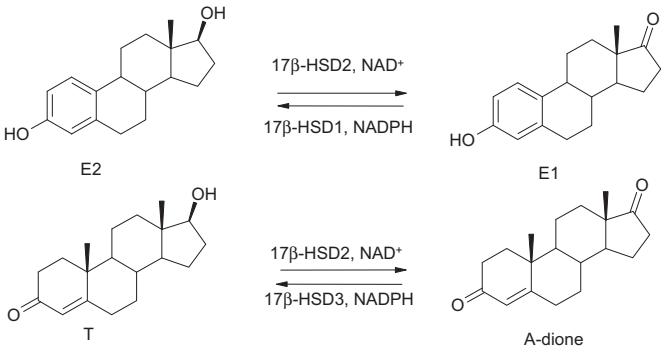


Chart 1. Interconversion of 17β-estradiol (E2) to estrone (E1) by 17β-HSD2 and 17β-HSD1 and of testosterone (T) to androstenedione (A-dione) by 17β-HSD2 and 17β-HSD3.

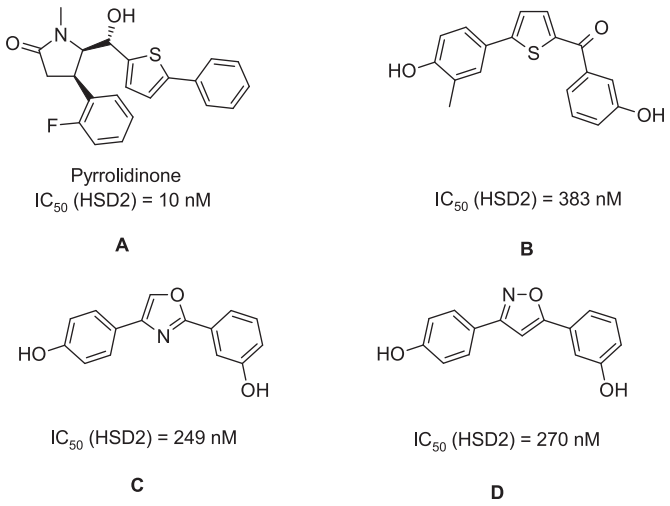


Chart 2. Inhibitors of 17β-HSD2.

recovers the balance between bone formation and bone resorption. A strong variability is observed, certainly due to non appropriate pharmacokinetic properties of this compound. New 17β-HSD2 inhibitors with good pharmacokinetic properties should be identified for further *in vivo* experiments.

In the frame of our 17β-HSD1 project, the hydroxyphenylketothiophene **B** (Chart 2) was identified [32] as moderate 17β-HSD2 inhibitor ($IC_{50} = 382$ nM). The scaffold of **B** can therefore be considered as an interesting starting point for development of a new class of 17β-HSD2 inhibitors. Optimisation of HSD2 activity and gain in selectivity toward HSD1 might be obtained by (1) exchange of the thiophene ring by bioisosteres, (2) exchange of the methyl substituent on the A ring, and (3) introduction of substituents on the B moiety. Convenience of these compounds is the easy four steps synthesis and purification, contrary to the pyrrolidinone **A**, which requires a separation of stereoisomers.

In this paper, we will report on the synthesis and the biological evaluation of a novel class of 17β-HSD2 inhibitors, with a bicyclic substituted hydroxyphenylmethanone core structure.

2. Results

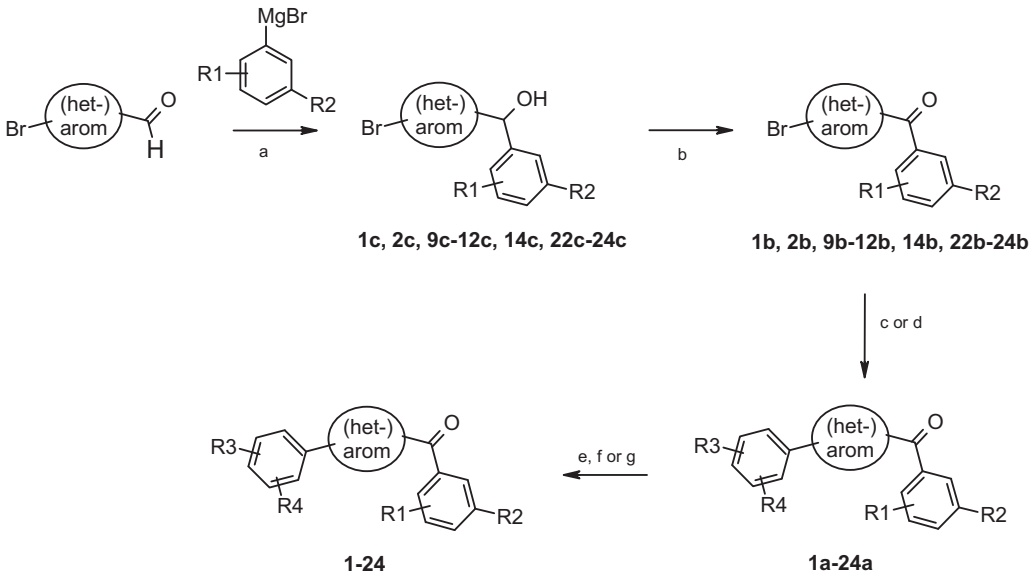
2.1. Chemistry

The synthesis of compounds **1**–**24** was achieved in a four step procedure and is depicted in Scheme 1. First, the nucleophilic addition of Grignard reagent (phenylmagnesiumbromide derivatives) to the appropriate aromatic carbaldehyde (Method A) afforded the alcohol intermediates **1c**, **2c**, **9c**–**12c**, **14c** and **22c**–**24c**. Then the OH-group was further oxidized into the corresponding ketone with 2-iodoxybenzoic acid (Method B). Subsequent Suzuki cross couplings [42] with different substituted phenylboronic acids led to compounds **1a**–**24a** (Method C or D). Ether cleavage [43] was performed using boron tribromide for compounds **1**, **2**, **10**, **11**, **14**–**19** and **21**, (method E), boron trifluoride dimethylsulfide complex for compounds **3**, **5**, **6**, **13** and **23** (method F) or pyridinium hydrochloride for compounds **4**, **7**–**9**, **12**, **20**, **22** and **24** (method G).

2.2. Biological results

2.2.1. Inhibition of human 17β-HSD2 and selectivity toward 17β-HSD1 and estrogen receptors (ERs)

17β-HSD2 and 17β-HSD1 inhibitory activities of the synthesised compounds were evaluated. As 17β-HSD1 catalyses the reduction



Scheme 1. Synthesis of compounds **1**–**24**. *Reagents and conditions*: a. anhydrous THF, 80 °C, 3 h, Method A; b. 2-iodoxybenzoic acid, anhydrous THF, 60 °C, overnight, Method B; c. Na_2CO_3, $Pd(PPh_3)_4$, $RB(OH)_2$, DME/water (2:1), microwave irradiation (25 min, 150W, 150 °C, 15 bar), for compounds **15a**–**17a**, Method C; d. Cs_2CO_3, $Pd(PPh_3)_4$, $RB(OH)_2$, DME/water (2:1), 80 °C, overnight, for compounds **1a**–**14a, 18a**–**24a**, Method D; e. BBr_3, CH_2Cl_2, −78 °C to rt, overnight, for compounds **1, 2, 10, 11, 14**–**19** and **21**, Method E; f. $BF_3 \cdot SMe_2$, CH_2Cl_2, rt, overnight, for compounds **3, 5, 6, 13** and **23**, Method F; g. pyridinium hydrochloride, 180 °C, 2 h, for compounds **4, 7**–**9, 12, 20, 22** and **24**, Method G.

of E1 to E2, it should not be affected by 17β-HSD2 inhibitors. Moreover, inhibitors of 17β-HSD2 should have no affinity for the estrogen receptors (ER) α and β, as most E2 effects are ER mediated.

Human placental enzymes were used for both assays and were obtained according to described methods [44–46]. Briefly, in the 17β-HSD2 assay, incubations were run with microsomal fractions, tritiated E2, cofactor and inhibitor. The separation of substrate and product was accomplished by HPLC. The 17β-HSD1 assay was performed similarly using tritiated E1 as substrate and the cytosolic fraction. The percent inhibition values of compounds **1**–**24** are shown in Table 1, and the IC_{50} values determined for selected compounds are reported in Table 2. Compounds showing less than 10% inhibition tested at a concentration of 1 μM were considered to be inactive. The spiro-δ-lactone described by Poirier et al. [36] was taken as external reference (65% at 1 μM in our test; 62–66% at 1 μM in their test).

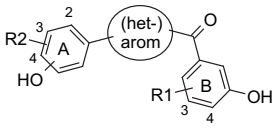
In a previous work [32], focusing on the development of 17β-HSD1 inhibitors, compound **B** has been identified as an interesting scaffold for 17β-HSD2 inhibition with an IC_{50} value of 382 nM. The goal of this study was to increase the 17β-HSD2 inhibitory activity and reverse selectivity in favor of HSD2. The thiophene ring of **B** was first exchanged by the bioisostere benzene with 1,3- and 1,4-substitution pattern to afford compounds **1** and **2**, respectively. **1** turned out to be a moderate 17β-HSD2 inhibitor ($IC_{50} = 379$ nM), while the 1,4-substituted compound **2** is a very active compound ($IC_{50} = 132$ nM). Compound **2** also shows a slight selectivity toward 17β-HSD1 (SF: 3). Thus, exchange of the thiophene ring by a 1,4-substituted benzene reverses the selectivity of the starting compound **B** toward 17β-HSD2. These results encouraged us to extend this SAR study on bicyclic substituted hydroxyphenylmethanones by changing the methyl group on the A ring (compounds **3**-**5**) and by adding further substituents on the B ring (compounds **6**–**9**) to improve their activity for 17β-HSD2.

Replacement of the electron donating methyl group (EDG) of **2** by an electron withdrawing group (EWG) like a fluoro (**3**) is not well tolerated by the enzyme, as compound **3** showed only 68% inhibition at 1 μM. Exchange of the lipophilic methyl group (**2**) by a bioisosteric chlorine (**5**) led to a similar affinity to the enzyme and a similar selectivity factor toward 17β-HSD1 (90% vs. 92% inhibition at 1 μM, respectively). Advantageously compound **5** with a chlorine should be less susceptible to metabolic oxidation compared to the CH_3 compound **2**. Shifting the chlorine to the *ortho* position (**4**) led to a small loss in activity (80% and 92% 17β-HSD2 inhibition at 1 μM for **4**: 2-Cl and **5**: 3-Cl, respectively). As the exchange of the methyl group of **2** did not improve selectivity, additional substituents were added on the phenyl moiety B. Introduction of a fluorine (compounds **6**–**8**) leads to highly active 17β-HSD2 inhibitors (IC_{50} values between 24 and 34 nM), but only a small selectivity toward 17β-HSD1 (SF between 2 and 9). Better selectivity is achieved in presence of the methyl group on the A ring (**6**, SF = 9) compared to the chlorinated analog **7** (SF = 2). Exchanging the *m*-OH group in the B ring by fluorine led to a completely inactive compound (11% inhibition at 1 μM for **9**). New potent 17β-HSD2 inhibitors have been identified in the class of 1,4-disubstituted benzenes, but none of them is highly selective toward 17β-HSD1 (compounds **2**–**8**).

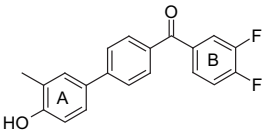
In a previous study [28], oxazole **C** and isoxazole **D** (Chart 2) were identified as inhibitors of 17β-HSD2 ($IC_{50} = 249$ nM for **C** and 270 nM for **D**), indicating that polar moieties like O and N are well tolerated in the central core of this class of inhibitor. With the hypothesis that these two classes of compounds bind in the same area of HSD2 and trying to increase the selectivity of this new class of 17β-HSD2 inhibitors, a nitrogen was introduced in the 1,4-disubstituted central benzene ring leading to 3,6-pyridine **10**, 2,5-pyridine **11** and 2,6-pyridine **14**. These compounds turned out to be very active (84%, 73% and 84% 17β-HSD2 inhibition at 1 μM for **10**, **11** and **14**, respectively). In addition, the selectivity of **11** and **14** toward 17β-HSD1 was much increased compared to the 1,4- and 1,3-disubstituted benzenes (SF = 21 and 75 for **11** and **14**, respectively, to be compared with SF = **3** and **1** for **2** and **1**, respectively). In the 2,5-pyridine class, activity of **11** can be increased by addition of fluorine to the B phenyl moiety (compounds **12** and **13**, $IC_{50} = 101$ nM and 153 nM respectively), but selectivity toward 17β-HSD1 dropped down in case of compound **13**.

2,6-Substituted pyridine **14**, the most selective compound of the pyridine class was further modified trying to increase its activity. Shifting the CH_3-group from the *meta*- to the *ortho*-position of the phenyl is detrimental for the activity (18% and 84% 17β-HSD2 inhibition at 1 μM for **18**: 2-CH_3 and **14**: 3-CH_3, respectively).

Table 1
Inhibition of human 17β-HSD2 and 17β-HSD1 by compounds **1**–**24**.



B, 1-8, 10-24



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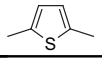
Compd	(Het-) arom	R1	R2	Position of the OH group in A ring	Inhibition of 17β-HSD2[a] [%] at 1 μM	Inhibition of 17β-HSD1[b] [%] at 1 μM
Spiro-δ-lactone	–	–	–	–	69	n.i.
B		H	3-CH_3	4	75	94
1		H	3-CH_3	4	77	50
2		H	3-CH_3	4	90	58
3		H	3-F	4	68	26
4		H	2-Cl	4	80	43
5		H	3-Cl	4	92	66
6		4-F	3-CH_3	4	98	79
7		4-F	3-Cl	4	100	95
8		3-F	3-CH_3	4	100	84
9		–	–		11	16
10		H	3-CH_3	4	84	58
11		H	3-CH_3	4	73	24
12		4-F	3-CH_3	4	84	47
13		4-F	3-Cl	4	87	50
14		H	3-CH_3	4	84	n.i.
15		H	H	2	n.i.	n.i.
16		H	H	3	n.i.	n.i.
17		H	H	4	16	n.i.
18		H	2-CH_3	4	18	n.i.
19		H	2-F	4	56	64
20		H	3-F	4	40	47
21		H	3-Cl	4	55	n.i.
22		4-F	3-CH_3	4	62	n.i.
23		4-CH_3	3-CH_3	4	28	n.i.
24		3-F	3-CH_3	4	57	n.i.

n.i.: no inhibition (inhibition < 10%).
[a] Human placental, microsomal fraction, substrate [^{3}H]-E2 + E2 [500 nM], NAD^+ [1.5 mM], mean value of three determinations, relative standard deviation < 10%.
[b] Human placental, cytosolic fraction, substrate [^{3}H]-E1 + E1 [500 nM], NADH [0.5 mM], mean value of three determinations, relative standard deviation < 10%.

Exchange of the methyl by an EWG like fluorine (**19**: 2-F and **20**: 3-F) or chlorine (**21**: 3-Cl) led to a regain of activity (56%, 40% and 55% 17β-HSD2 inhibition at 1 μM, respectively), but these compounds are not able to reach the activity of compound **14** (84% inhibition at 1 μM). Furthermore, addition of an EWG (compounds **22** and **24**) or an EDG (compound **23**) group in the 3-hydroxyphenyl B moiety is detrimental for the activity, as the compounds show a weaker inhibition compared to the parent compound **14** (62%, 28% and 58% 17β-HSD2 inhibition at 1 μM, respectively), independently of the position of the fluorine (62% and 57% 17β-HSD2 inhibition at 1 μM for **22**: 4-F and **24**: 5-F, respectively).

As none of the substituted 2,6-pyridines reached the activity of **14**, the position of the OH group on the A ring has been studied in absence of the 3-methyl group to investigate whether the *para*–*meta* OH substitution pattern of **14** is the best one for a high 17β-HSD2 inhibitory activity. Compounds **15**–**17** as well as their analogs with methoxy groups (data not shown) turned out to be only weak HSD2 inhibitors. It can be concluded that the methyl group next to the OH in the A ring plays an important role for the inhibition of 17β-HSD2 and should not be omitted.

Eleven compounds were identified as highly active 17β-HSD2 inhibitors with IC_{50} values below 300 nM, with three of them selective toward 17β-HSD1 (SF > 10). The most potent compounds have been evaluated for their binding affinities to the ERα and β, expressed as relative binding affinity (RBA). The RBA represents the ligand affinity to ER, relative to the one of E2, which is arbitrarily set up at 100%. The tested compounds showed very low affinities to both ER subtypes (<0.1%).

Table 2
IC_{50} values, selectivity factor for selected compounds.

Compd	Cell-free assay		
	17β-HSD2 IC_{50}[a] [nM]	17β-HSD1 IC_{50}[b] [nM]	Selectivity factor[c]
B	382	8	0.02
1	379	475	1
2	132	413	3
3	525	2429	5
4	176	1764	11
5	153	571	4
6	34	289	9
7	24	53	2
8	31	159	5
10	220	567	3
11	260	5482	21
12	101	1272	13
13	153	1013	7
14	263	19646	75
21	752	60638	81
22	757	22395	30

[a] Human placental, microsomal fraction, substrate [^{3}H]-E2 + E2 [500 nM], cofactor NAD^+ [1.5 mM], mean value of three determinations, relative standard deviation < 10%.
[b] Human placental, cytosolic fraction, substrate [^{3}H]-E1 + E1 [500 nM], cofactor NADH [0.5 mM], mean value of three determinations, relative standard deviation < 10%.
[c] IC_{50} (17β-HSD1)/IC_{50} (17β-HSD2).

3. Discussion and conclusion

In this study, starting from compound **B** [32] as moderate 17β-HSD2 inhibitor, we have developed a new class of active and selective 17β-HSD2 inhibitors. Exchange of the thiophene moiety of **B** by a six-membered ring (benzene or pyridine) with different substitution patterns inverses the selectivity of **B** in favor of 17β-HSD2 and leads to highly potent 17β-HSD2 inhibitors.

The best inhibitory activity was obtained when the core structure is a 1,4-substituted benzene (compound **2**). Changing the substitution pattern to 1,3-substituted benzene leads to a loss in activity, indicating that the linear geometry of the inhibitors suits better to the enzyme binding pocket. Furthermore, the compounds are believed to be steroidomimetics as the 1,4-substituted benzene derivatives superimpose well with the substrate E2 (Fig. 1): because of the pseudosymmetry the inhibitors can overlay with E2 in two ways: either the carbonyl group of **2** mimicks the C17(OH) of E2 and the OH of the phenyl A ring the C3(OH) of the steroid (Fig. 1A) or *vice versa* (Fig. 1B).

Introduction of a fluorine on the B ring in compounds bearing the 1,4- substitution pattern results in highly potent inhibitors (compounds **6**–**8**, **12** and **13**). This fluorine might interact with amino acids of the active site via H-bond interaction, which could stabilise the binding of the inhibitor. Interestingly, the position of the fluorine is not important for activity, as compounds **6** and **8** show similar HSD2 inhibition. As the 3D-structure of 17β-HSD2 is unknown, it is not possible to discuss the binding interactions of the compounds with the enzyme in more detail.

Regarding the pyridine derivatives (compounds **10**, **11** and **14**), the introduction of a nitrogen in the phenyl ring decreases inhibitory activity. None of these compounds is as active as the corresponding 1,4-benzene derivative. With the aim to increase activity in the pyridine class, the best hydroxyphenyl substitution pattern was investigated in the class of the 2,6-pyridines (compounds **15**–**17**) in absence of the methyl group. These compounds showed either very low activity (**17**) or were inactive (**15** and **16**). A similar compound to **15** with the OH group in *ortho*-position of the A ring was described by Oster et al. [32], with a 2,5-thiophene as central core. This compound is a highly potent 17β-HSD2 inhibitor (IC_{50} = 18 nM, SF = 5), while compound **15** is inactive. Comparison of these results indicates that the 2,5-thiophene and the 2,6-pyridine derivatives do not bind in the same way in the enzyme active site. Furthermore, the inactivity of **17** shows that the methyl group on the A ring plays a key role for the binding of the compound in the enzyme. The methyl group might be located in a small lipophilic pocket and might form Van der Waals interactions. In the 1,4-benzene class (compounds **2**, **5**, **6** and **7**) and 2,5-pyridine class (compounds **12** and **13**), the methyl could be replaced by a chlorine without loss of activity, confirming that the amino acids around this region of the enzyme should be lipophilic.

Interestingly, the nitrogen of the pyridine seems to be responsible for the high selectivity observed toward 17β-HSD1. A similar effect of the nitrogen on selectivity was already identified in the frame of our 17β-HSD1 inhibitors development: polar atoms are not tolerated in the active site of 17β-HSD1 [28] while they are advantageous in 17β-HSD2 (compounds **C** and **D**) [28,47]. The position of the nitrogen on the central core also plays a key role for the selectivity. Compound **10**, with the nitrogen next to the A ring is an unselective 17β-HSD2 inhibitor, while compound **11** with the nitrogen next to the B ring is a highly selective inhibitor.

In the optimisation process of the 2,5-pyridine class, activity of **11** can be increased by introduction of a fluorine into the B ring, thereby leading to the identification of the highly active and selective compound **12** as most promising 17β-HSD2 inhibitor in this study. This compound as well as the most interesting molecules identified (**2**, **5**, **6**, **7**, **8**, **11** and **14**) show a negligible affinity to both receptors ERα and β.

In this paper, we described the synthesis and the biological evaluation of a new class of 17β-HSD2 inhibitors, derived from substituted bicyclic hydroxyphenylmethanones. The influence of different six-membered rings as central core and different small substituents on the phenyl moieties A and B were investigated. Structural optimisation of the starting compound **B** led to new highly potent 17β-HSD2 inhibitors (compounds **6**, **7**, **8**, **12** and **13**) with inhibitory activities in the low nanomolar range. Selectivity was achieved by introduction of a nitrogen in the central core, while activity was increased by addition of a fluorine in the B ring. Thereby, compound **12** was identified as the most promising derivative of this series with activity in the low nanomolar range, a striking selectivity toward 17β-HSD1 and no affinity on both ERs. This inhibitor seems to be the best candidate for being further evaluated for its pharmacokinetic profile and for its *in vivo* activity in a disease-oriented model to validate the concept of 17β-HSD2 inhibition.

4. Experimental section

4.1. Chemical methods

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DRX-500 instrument in $CDCl_3$ or acetone-d_6. Chemicals shifts are reported in δ values (ppm), the hydrogenated residues of deuterated solvent were used as internal standard ($CDCl_3$: δ = 7.26 ppm in ^{1}H NMR and δ = 77 ppm in ^{13}C NMR, acetone-d_6: δ = 2.05 ppm in ^{1}H NMR and δ = 30.8 ppm and 206.3 ppm in ^{13}C NMR). Signals are described as s, br, d, t, dd, ddd, dt and m for singlet, broad, doublet, triplet, doublet of doublets, doublet of doublet of doublets, doublet of triplets and multiplet, respectively. All coupling constants (J) are given in Hertz.

Tested compounds are ≥95% chemical purity as measured by HPLC. The Surveyor®-LC-system consisted of a pump, an autosampler, and a PDA detector. Mass spectrometry was performed on a TSQ® Quantum (ThermoFisher, Dreieich, Germany). The triple quadrupole mass spectrometer was equipped with an electrospray interface (ESI) and atmospheric pressure chemical ionisation

(APCI), respectively. The system was operated by the standard software Xcalibur®. A RP C18 NUCLEODUR® 100-5 (3 mm) column (Macherey-Nagel GmbH, Dühren, Germany) was used as stationary phase. All solvents were HPLC grade. In a gradient run the percentage of acetonitrile (containing 0.1% trifluoroacetic acid) in 0.1% trifluoroacetic acid in was increased from an initial concentration of 5% at 0 min to 100% at 15 min and kept at 100% for 5 min. The injection volume was 20 μL and flow rate was set to 800 μL/min. MS analysis was carried out at a needle voltage of 3000 V and a capillary temperature of 350 °C. Mass spectra were acquired in positive mode and in negative mode when required from 100 to 1000 *m*/*z* and UV spectra were recorded at the wavelength of 254 nm and in some cases at 360 nm.

GC/MS spectra were measured on a GCD Series G1800A (Hewlett Packard) instrument with an Optima-5-MS (0.25 μM, 30 m) column (Macherey-Nagel).

All microwave irradiation experiments were carried out in a CEM-Discover microwave apparatus.

Melting points were measured on a Stuart Scientific SMP3 apparatus.

Flash chromatography was performed on silica gel 40 (35/40–63/70 μM) with hexane/ethyl acetate mixtures as eluents, and the reaction progress was determined by thin-layer chromatography analyses on Alugram SIL G/UV254 (Macherey-Nagel). Visualization was accomplished with UV light. Purification by preparative TLC was performed on 1 mm SIL G-100 UV_{254} glass plates (Macherey-Nagel). Purification with preparative HPLC were carried out on a Agilent 1200 series HPLC system from Agilent Technologies, using a RP C18 Nucleodur 100-5 column (30·100 mm/50 μm – from Macherey-Nagel GmbH) as stationary phase with acetonitrile/water or isopropanol/water as solvent in a gradient from 20:80 to 100:0 in 40 min.

Starting materials were used as obtained from Aldrich, Acros, Alfa Aeser and Combi-blocks without further purification. No attempts were made to optimise yields.

4.2. General procedure for alcohol formation

4.2.1. Method A

To a mixture of aldehyde (1 equiv) in dry THF was added the magnesiumbromide derivative (2.2 equiv) under nitrogen. The reaction mixture was heated to 80 °C and stirred for 3 h at 80 °C. The reaction mixture was cooled to room temperature, quenched with brine and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered and concentrated to dryness. The product was purified by column chromatography.

4.3. General procedure for oxidation of alcohol in ketone

4.3.1. Method B

To a mixture of alcohol (1 equiv) in dry THF was added 2-iodoxybenzoic acid (2 equiv). The reaction mixture was stirred at 60 °C overnight, cooled to room temperature and quenched with $Na_2S_2O_3$. The aqueous layer was extracted with ethyl acetate and the organic layer was washed with water, neutralised with 0.5N NaOH and dried over sodium sulfate, filtered and concentrated to dryness. The product was purified by column chromatography or by recrystallisation.

4.4. General procedures for Suzuki coupling

4.4.1. Method C

A mixture of arylbromide (1 equiv), boronic acid (1.2 equiv), sodium carbonate (2 equiv), and tetrakis(triphenylphosphine) palladium (0.02 equiv) was suspended in a degazed DME/water (2:1) solution. The reaction mixture was exposed to microwave irradiation (25 min, 150 W, 150 °C, 15 bar). After reaching room temperature, water was added to quench the reaction and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated to dryness. The product was purified by column chromatography.

4.4.2. Method D

A mixture of arylbromide (1 equiv), boronic acid (1.2 equiv), cesium carbonate (4 equiv), and tetrakis(triphenylphosphine) palladium (0.02 equiv) was suspended in a DME/water (2:1) solution and the mixture was degazed. The mixture was heated to 80 °C and stirred overnight at 80 °C under nitrogen. The reaction mixture was cooled to room temperature, quenched by water and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, filtered and concentrated to dryness. The product was purified by column chromatography or by recrystallisation.

4.5. General procedures for ether cleavage

4.5.1. Method E

To a solution of methoxy derivative (1 equiv) in dry dichloromethane cooled at −78 °C under nitrogen was slowly added boron tribromide (1 M solution in dichloromethane, 5 equiv per methoxy function). The reaction mixture was stirred at −78 °C for 1 h and then allowed to warm to room temperature overnight. The reaction was quenched by water and extracted with ethyl acetate. The combined organic layers were washed with brine and dried over sodium sulfate, filtered, evaporated to dryness under reduced pressure and purified by column chromatography.

4.5.2. Method F

To a solution of methoxy derivative (1 equiv) in dry dichloromethane, boron trifluoride dimethylsulfide complex (35 equiv per methoxy function) was added dropwise at room temperature. The reaction mixture was stirred at room temperature overnight. Water was added to quench the reaction and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, evaporated to dryness under reduced pressure and purified by column chromatography.

4.5.3. Method G

To pyridinium hydrochloride (100 equiv) at 190 °C was added the methoxy derivative (1 equiv). The reaction mixture was stirred for 2 h, cooled to room temperature and then stirred with 1N HCl for 1 h. The mixture was extracted in ethyl acetate. The combined organic layers were washed with water, dried over sodium sulfate, filtered, evaporated to dryness under reduced pressure and purified by column chromatography or by recrystallisation.

4.6. Detailed synthesis procedure

4.6.1. (3-Bromophenyl)-(3-methoxyphenyl)-methanol (***1c***)

The title compound was prepared by reaction of 3-bromophenyl carboxaldehyde (500 mg, 2.71 mmol, 1 equiv) with 3-methoxyphenylmagnesiumbromide (1 M in THF) (1.35 g, 5.95 mL, 5.95 mmol, 2.2 equiv) according to method A. The product was used in the next step without further purification. $C_{14}H_{13}BrO_2$; MW 293.

*4.6.2. (3-Bromophenyl)-(3-methoxyphenyl)-methanone (**1b**)*

The title compound was prepared by reaction of (3-bromophenyl)-(3-methoxyphenyl)-methanol **1c** (460 mg, 1.57 mmol, 1 equiv) with 2-iodoxybenzoic acid (885 mg, 3.14 mmol, 2 equiv) according to method B. The product was purified by column chromatography (hexane/ethyl acetate 9:1) to give 200 mg (44%) of the analytically pure compound as a yellow oil. $C_{14}H_{11}BrO_2$; MW 291; ^{1}H NMR (acetone-d_6): δ 7.92–7.90 (m, 1H), 7.82 (ddd, J = 0.9 Hz, J = 1.9 Hz, J = 7.9 Hz, 1H), 7.76–7.73 (m, 1H), 7.50 (t, J = 8.2 Hz, 1H), 7.48–7.44 (m, 1H), 7.34–7.30 (m, 2H), 7.23 (ddd, J = 1.3 Hz, J = 2.5 Hz, J = 8.2 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (acetone-d_6): δ 195.8, 161.7, 141.6, 140.1, 136.9, 134.0, 132.2, 131.4, 130.4, 124.1, 123.9, 120.6, 116.2, 56.8.

*4.6.3. (4′-Methoxy-3′-methylbiphenyl-3-yl)-(3-methoxyphenyl)-methanone (**1a**)*

The title compound was prepared by reaction of (3-bromophenyl)-(3-methoxyphenyl)-methanone **1b** (200 mg, 0.69 mmol, 1 equiv) with 4-methoxy-3-methylphenylboronic acid (137 mg, 0.82 mmol, 1.2 equiv) according to method D. The product was purified by column chromatography (hexane/ethyl acetate 95:5) to afford 200 mg (88%) of the analytically pure compound as a yellow oil. $C_{22}H_{20}O_3$; MW 332; ^{1}H NMR (acetone-d_6): δ 8.00–7.98 (m, 1H), 7.90–7.87 (m, 1H), 7.71–7.68 (m, 1H), 7.59 (t, J = 7.9 Hz, 1H), 7.52–7.45 (m, 3H), 7.38–7.35 (m, 2H), 7.25–7.21 (m, 1H), 7.02 (d, J = 9.1 Hz, 1H), 3.87 (s, 6H), 2.25 (s, 3H); ^{13}C NMR (acetone-d_6): δ 196.3, 160.7, 158.8, 142.0, 140.0, 139.2, 134.8, 132.0, 131.2, 130.4, 130.0, 129.7, 128.7, 128.4, 127.6, 126.4, 123.2, 119.3, 115.2, 111.4, 55.9, 55.8, 16.4.

*4.6.4. (4′-Hydroxy-3′-methylbiphenyl-3-yl)-(3-hydroxyphenyl)-methanone (**1**)*

The title compound was prepared by reaction of (4′-methoxy-3′-methylbiphenyl-3-yl)-(3-methoxyphenyl)-methanone **1a** (200 mg, 0.60 mmol, 1 equiv) with boron tribromide (6 mmol, 10 equiv) according to method E. The product was purified by column chromatography (hexane/ethyl acetate 8:2) then by preparative TLC (hexane/ethyl acetate 7:3) to afford 44 mg (24%) of the analytically pure compound as a yellow oil. $C_{20}H_{16}O_3$; MW 304; ^{1}H NMR (acetone-d_6): δ 8.72 (s, br, 1H), 8.38 (s, br, 1H), 7.97–7.95 (m, 1H), 7.86–7.83 (m, 1H), 7.67–7.65 (m, 1H), 7.57 (t, J = 7.6 Hz, 1H), 7.46 (d, J = 2.2 Hz, 1H), 7.40–7.35 (m, 2H), 7.33–7.31 (m, 1H), 7.30–7.28 (m, 1H), 7.14 (dd, J = 2.5 Hz, J = 7.9 Hz, 1H), 6.94 (d, J = 8.2 Hz, 1H), 2.28 (s, 3H); ^{13}C NMR (acetone-d_6): δ 197.3, 159.1, 157.3, 143.0, 140.8, 140.1, 132.9, 131.8, 131.2, 131.1, 130.4, 129.3, 129.0, 127.1, 126.6, 122.9, 121.3, 117.9, 116.9, 17.1; IR: 3320, 1641, 1581, 1476, 1358, 1220 cm^{-1}; LC/MS m/z: 305 $(M + H)^+$.

*4.6.5. (4-Bromophenyl)-(3-methoxyphenyl)-methanol (**2c**)*

The title compound was prepared by reaction of 4-bromophenyl carboxaldehyde (1 g, 5.41 mmol, 1 equiv) with 3-methoxyphenylmagnesiumbromide (1 M in THF) (2.70 g, 11.9 mmol, 11.9 mL, 2.2 equiv) according to method A. The product was purified by column chromatography (hexane/ethyl acetate 9:1) to afford 1.58 g (100%) of the analytically pure compound as a colorless oil. $C_{14}H_{13}BrO_2$; MW 292; ^{1}H NMR (acetone-d_6): δ 7.50–7.47 (m, 2H), 7.41–7.38 (m, 2H), 7.23 (t, J = 7.9 Hz, 1H), 7.06–7.04 (m, 1H), 7.00–6.97 (m, 1H), 6.81 (ddd, J = 0.9 Hz, J = 2.5 Hz, J = 8.2 Hz, 1H), 5.81 (d, J = 4.0 Hz, 1H), 5.01 (d, J = 4.0 Hz, 1H), 3.76 (s, 3H); ^{13}C NMR (acetone-d_6): δ 160.8, 147.5, 145.7, 132.0, 130.2, 129.4, 121.2, 119.6, 113.3, 113.1, 75.5, 55.5.

*4.6.6. (4-Bromophenyl)-(3-methoxyphenyl)-methanone (**2b**)*

The title compound was prepared by reaction of (4-bromophenyl)-(3-methoxyphenyl)-methanol **2c** (1.5 g, 5.12 mmol, 1 equiv) with 2-iodoxybenzoic acid (2.88 mg, 10.2 mmol, 2 equiv) according to method B. The product was purified by column chromatography (hexane/ethyl acetate 95:5) to afford 1.39 g (94%) of the analytically pure compound as a colorless oil. $C_{14}H_{11}BrO_2$; MW 290; ^{1}H NMR (acetone-d_6): δ 7.73–7.70 (m, 4H), 7.46–7.42 (m, 1H), 7.32–7.29 (m, 2H), 7.21 (ddd, J = 0.9 Hz, J = 2.5 Hz, J = 8.2 Hz, 1H), 3.85 (s, 3H); ^{13}C NMR (acetone-d_6): δ 195.3, 160.7, 139.5, 137.5, 132.5, 130.4, 127.7, 123.1, 119.5, 115.2, 55.9; IR: 3003, 2834, 1651, 1575, 1234 cm^{-1}.

*4.6.7. (4′-Methoxy-3′-methylbiphenyl-4-yl)-(3-methoxyphenyl)-methanone (**2a**)*

The title compound was prepared by reaction of (4-bromophenyl)-(3-methoxyphenyl)-methanone **2b** (410 mg, 1.41 mmol, 1 equiv) with 4-methoxy-3-methylphenylboronic acid (281 mg, 1.69 mmol, 1.2 equiv) according to method D. The product was used in the next step without further purification. $C_{22}H_{20}O_3$; MW 332.

*4.6.8. (4′-Hydroxy-3′-methylbiphenyl-4-yl)-(3-hydroxyphenyl)-methanone (**2**)*

The title compound was prepared by reaction of (4′-methoxy-3′-methylbiphenyl-4-yl)-(3-methoxyphenyl)-methanone **2a** (460 mg, 1.38 mmol, 1 equiv) with boron tribromide (13.8 mmol, 10 equiv) according to method E. The product was purified by column chromatography (hexane/ethyl acetate 8:2) then by preparative TLC (hexane/ethyl acetate 7:3 + 10 drops of HCOOH) to afford 120 mg (29%) of the analytically pure compound as an orange solid. $C_{20}H_{16}O_3$; MW 304; ^{1}H NMR (acetone-d_6): δ 8.68 (s, br, 1H), 8.46 (s, br, 1H), 7.85–7.82 (m, 2H), 7.77–7.74 (m, 2H), 7.54 (d, J = 2.2 Hz, 1H), 7.44 (dd, J = 1.9 Hz, J = 7.9 Hz, 1H), 7.37 (t, J = 7.9 Hz, 1H), 7.29–7.24 (m, 2H), 7.13 (ddd, J = 0.9 Hz, J = 2.5 Hz, J = 8.2 Hz, 1H), 6.96 (d, J = 8.2 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (acetone-d_6): δ 196.9, 159.3, 157.9, 146.9, 141.3, 137.3, 132.7, 132.3, 131.5, 131.3, 127.8, 127.5, 126.8, 122.9, 121.2, 118.0, 117.1, 17.3; IR: 3363, 1641, 1588, 1449 cm^{-1}; LC/MS m/z: 305 $(M + H)^+$.

*4.6.9. (3′-Fluoro-4′-methoxybiphenyl-4-yl)-(3-methoxyphenyl)-methanone (**3a**)*

The title compound was prepared by reaction of (4-bromophenyl)-(3-methoxyphenyl)-methanone **2b** (200 mg, 0.69 mmol, 1 equiv) with 3-fluoro-4-methoxyphenylboronic acid (141 mg, 0.81 mmol, 1.2 equiv) according to method D. The product was used in the next step without further purification. $C_{21}H_{17}FO_3$; MW 336.

*4.6.10. (3′-Fluoro-4′-hydroxybiphenyl-4-yl)-(3-hydroxyphenyl)-methanone (**3**)*

The title compound was prepared by reaction of (3′-fluoro-4′-methoxy-biphenyl-4-yl)-(3-methoxyphenyl)-methanone **3a** (20 mg, 0.06 mmol, 1 equiv) with boron trifluoride dimethylsulfide complex (4.2 mmol, 70 equiv) according to method F. The product was purified by column chromatography (hexane/ethyl acetate 1:1). Yield: 8 mg (43%). $C_{19}H_{13}FO_3$; MW 308; ^{1}H NMR (acetone-d_6): δ 8.88 (s, br, 1H), 8.68 (s, br, 1H), 7.87–7.80 (m, 4H), 7.55 (dd, J = 2.3 Hz, J = 12.2 Hz, 1H), 7.47 (ddd, J = 0.9 Hz, J = 2.1 Hz, J = 8.4 Hz, 1H), 7.39 (t, J = 7.8 Hz, 1H), 7.28–7.25 (m, 2H), 7.16–7.12 (m, 2H); ^{13}C NMR (acetone-d_6): δ 195.9, 144.5, 140.1, 137.0, 131.3, 130.4, 127.0, 124.2, 121.9, 120.3, 116.9, 115.5, 115.4; IR: 3333, 2981, 1637, 1305 cm^{-1}; GC/MS m/z: 308 $(M)^+$.

*4.6.11. (2′-Chloro-4′-methoxybiphenyl-4-yl)-(3-methoxyphenyl)-methanone (**4a**)*

The title compound was prepared by reaction of (4-bromophenyl)-(3-methoxyphenyl)-methanone **2b** (262 mg, 0.90 mmol, 1 equiv) with 2-chloro-4-methoxyphenylboronic acid (201 mg, 1.08 mmol, 1.2 equiv) according to the method D. The product was recrystallised in ethanol to afford 193 mg (61%) of the analytically pure compound as white crystals. $C_{21}H_{17}ClO_3$; MW 353; mp: 119–121 °C; ^{1}H NMR ($CDCl_3$): δ 7.88–7.85 (m, 2H), 7.56–7.53 (m, 2H), 7.41–7.38 (m, 3H), 7.29 (d, J = 8.5 Hz, 1H),

7.17–7.13 (m, 1H), 7.05 (d, J = 2.5 Hz, 1H), 6.91 (dd, J = 2.8 Hz, J = 8.8 Hz, 1H), 3.89 (s, 3H), 3.86 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 196.1, 159.8, 143.4, 139.0, 136.3, 133.9, 131.9, 131.8, 129.9, 129.5, 129.2, 122.8, 118.8, 115.4, 114.3, 113.3, 55.6, 55.5; IR: 2954, 1647, 1597, 1034 cm^{-1}; GC/MS m/z: 352 $(M)^+$.

4.6.12. (2′-Chloro-4′-hydroxybiphenyl-4-yl)-(3-hydroxyphenyl)-methanone (**4**)

The title compound was prepared by reaction of (2′-chloro-4′-methoxybiphenyl-4-yl)-(3-methoxyphenyl)-methanone **4a** (100 mg, 0.28 mmol, 1 equiv) with pyridinium hydrochloride (28 mmol, 100 equiv) according to method G. The product was purified by recrystallisation in hexane to afford 67 mg (74%) of the analytically pure compound as a brown solid. $C_{19}H_{13}ClO_3$; MW 325; mp: 212–214 °C; ^{1}H NMR (acetone-d_6): δ 8.67 (s, br, 1H), 7.87–7.83 (m, 2H), 7.61–7.58 (m, 2H), 7.42–7.37 (m, 1H), 7.33 (d, J = 8.2 Hz, 1H), 7.31–7.29 (m, 1H), 7.27 (ddd, J = 0.9 Hz, J = 1.6 Hz, J = 7.6 Hz, 1H), 7.14 (ddd, J = 0.9 Hz, J = 2.5 Hz, J = 8.2 Hz, 1H), 7.05 (d, J = 2.5 Hz, 1H), 6.95 (dd, J = 2.5 Hz, J = 8.5 Hz, 1H); ^{13}C NMR (acetone-d_6): δ 159.0, 158.3, 144.3, 140.0, 137.3, 133.1, 131.5, 130.4, 122.0, 120.4, 117.6, 117.0, 115.7; IR: 3292, 1645, 1589, 1451 cm^{-1}; LC/MS m/z: 325 $(M + H)^+$.

4.6.13. (3′-Chloro-4′-hydroxybiphenyl-4-yl)-(3-methoxyphenyl)-methanone (**5a**)

The title compound was prepared by reaction of (4-bromophenyl)-(3-methoxyphenyl)-methanone **2b** (200 mg, 0.69 mmol, 1 equiv) with 3-chloro-4-hydroxyphenylboronic acid (143 mg, 0.83 mmol, 1.2 equiv) according to method D. The product was purified by column chromatography (hexane/ethyl acetate 7:3) to afford 120 mg (51%) of the analytically pure compound. $C_{20}H_{15}ClO_3$; MW 338; ^{1}H NMR (acetone-d_6): δ 9.03 (s, br, 1H), 7.86–7.83 (m, 2H), 7.80–7.77 (m, 2H), 7.74 (d, J = 2.2 Hz, 1H), 7.57 (dd, J = 2.2 Hz, J = 8.5 Hz, 1H), 7.47–7.41 (m, 1H), 7.33–7.30 (m, 2H), 7.20 (ddd, J = 0.9 Hz, J = 2.7 Hz, J = 8.2 Hz, 1H), 7.14–7.11 (m, 1H), 3.85 (s, 3H); ^{13}C NMR (acetone-d_6): δ 194.9, 159.8, 153.3, 143.4, 139.2, 136.0, 132.4, 130.5, 130.0, 129.4, 128.5, 126.9, 126.8, 126.2, 122.1, 121.0, 118.2, 117.3, 114.3, 54.9.

4.6.14. (3′-Chloro-4′-hydroxybiphenyl-4-yl)-(3-hydroxyphenyl)-methanone (**5**)

The title compound was prepared by reaction of (3′-chloro-4′-hydroxybiphenyl-4-yl)-(3-methoxyphenyl)-methanone **5a** (60 mg, 0.18 mmol, 1 equiv) with boron trifluoride dimethylsulfide complex (6.2 mmol, 35 equiv) according to method F. The product was purified by column chromatography (hexane/ethyl acetate 1:1). Yield: 40 mg (69%). $C_{19}H_{13}ClO_3$; MW 324; ^{1}H NMR (acetone-d_6): δ 9.00 (s, br, 1H), 8.67 (s, br, 1H), 7.84–7.81 (m, 2H), 7.79–7.75 (m, 2H), 7.73 (d, J = 2.2 Hz, 1H), 7.56 (dd, J = 2.2 Hz, J = 8.4 Hz, 1H), 7.35 (t, J = 7.9 Hz, 1H), 7.25–7.21 (m, 2H), 7.12 (d, J = 8.5 Hz, 1H), 7.09 (ddd, J = 1.1 Hz, J = 2.5 Hz, J = 8.2 Hz, 1H); ^{13}C NMR (acetone-d_6): δ 195.9, 158.3, 154.2, 144.2, 140.2, 137.1, 133.3, 131.4, 130.4, 129.3, 127.7, 127.1, 121.9, 121.8, 120.3, 118.2, 117.0; GC/MS m/z: 324–326 $(M)^+$.

4.6.15. (4-Bromophenyl)-(4-fluoro-3-methoxyphenyl)-methanol (**6c**)

To a solution of 5-bromo-2-fluoroanisole (547 mg, 2.67 mmol, 1 equiv) in anhydrous THF was added granules of magnesium (68 mg, 2.80 mmol, 1.05 equiv) under nitrogen. The mixture was heated to 60 °C for 2 h. After cooling to room temperature, 4-bromobenzaldehyde (592 mg, 3.20 mmol, 1.2 equiv) was added and the reaction mixture was stirred at 80 °C overnight. The reaction was cooled to room temperature, quenched with brine and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered and concentrated to dryness under vacuum. The product was used in the next step without further purification. $C_{14}H_{12}BrFO_2$; MW 311.

4.6.16. (4-Bromophenyl)-(4-fluoro-3-methoxyphenyl)-methanone (**6b**)

The title compound was prepared by reaction of (4-bromophenyl)-(4-fluoro-3-methoxyphenyl)-methanol **6c** (468 mg, 1.50 mmol, 1 equiv) with 2-iodoxybenzoic acid (3.00 mmol, 2 equiv) according to method B. The product was purified by column chromatography (hexane/ethyl acetate 7:3) to afford 280 mg (60%) of the analytically pure compound. $C_{14}H_{10}BrFO_2$; MW 309; ^{1}H NMR (acetone-d_6): δ 7.77–7.72 (m, 4H), 7.56 (dd, J = 1.9 Hz, J = 8.5 Hz, 1H), 7.39–7.36 (m, 1H), 7.33–7.28 (m, 1H), 3.96 (s, 3H); ^{13}C NMR (acetone-d_6): δ 194.3, 137.5, 134.8, 132.5, 132.4, 127.6, 124.6, 118.6, 117.8, 116.6, 116.5, 115.5, 56.7; GC/MS m/z: 308–310 $(M)^+$.

4.6.17. (4-Fluoro-3-methoxyphenyl)-(4′-methoxy-3′-methylbiphenyl-4-yl)-methanone (**6a**)

The title compound was prepared by reaction of (4-bromophenyl)-(4-fluoro-3-methoxyphenyl)-methanone **6b** (142 mg, 0.46 mmol, 1 equiv) with 4-methoxy-3-methylphenylboronic acid (92 mg, 0.55 mmol, 1.2 equiv) according to method D. The product was recrystallised in ethanol to afford 98 mg (61%) of the analytically pure compound as a white solid. $C_{22}H_{19}FO_3$; MW 350; mp: 145–146 °C; ^{1}H NMR (acetone-d_6): δ 7.87–7.84 (m, 2H), 7.81–7.78 (m, 2H), 7.60–7.56 (m, 3H), 7.40 (ddd, J = 1.9 Hz, J = 4.4 Hz, J = 8.2 Hz, 1H), 7.30 (dd, J = 8.2 Hz, J = 11.0 Hz, 1H), 7.05 (d, J = 8.2 Hz, 1H), 3.97 (s, 3H), 3.90 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (acetone-d_6): δ 194.7, 159.2, 148.8, 148.7, 145.7, 136.3, 138.6, 135.6, 132.3, 131.3, 130.1, 127.7, 127.0, 126.6, 124.4, 124.3, 116.5, 115.5, 111.4, 56.7, 55.8, 16.4; IR: 2922, 1645, 1601, 1027 cm^{-1}; GC/MS m/z: 350 $(M)^+$.

4.6.18. (4-Fluoro-3-hydroxyphenyl)-(4′-hydroxy-3′-methylbiphenyl-4-yl)-methanone (**6**)

The title compound was prepared by reaction of (4-fluoro-3-methoxyphenyl)-(4′-methoxy-3′-methylbiphenyl-4-yl)-methanone **6a** (98 mg, 0.30 mmol, 1 equiv) with pyridinium hydrochloride (30 mmol, 100 equiv) according to method G. The product was recrystallised in hexane to afford 40 mg (41%) of the analytically pure compound as a green powder. $C_{20}H_{15}FO_3$; MW 322; mp: 203–205 °C; ^{1}H NMR (acetone-d_6): δ 9.04 (s, br, 1H), 8.47 (s, br, 1H), 7.84–7.76 (m, 4H), 7.54 (d, J = 1.8 Hz, 1H), 7.48 (dd, J = 2.0 Hz, J = 8.6 Hz, 1H), 7.46 (dd, J = 2.2 Hz, J = 8.2 Hz, 1H), 7.34–7.28 (m, 2H), 6.96 (d, J = 8.3 Hz, 1H), 2.29 (s, 3H); ^{13}C NMR (acetone-d_6): δ 194.7, 156.9, 156.0, 154.0, 145.9, 145.7, 136.2, 135.7, 131.7, 131.2, 130.5, 126.8, 126.5, 125.9, 123.3, 123.2, 120.1, 116.8, 116.1, 16.3; IR: 3307, 1642, 1592, 1429 cm^{-1}; LC/MS m/z: 323 $(M + H)^+$.

4.6.19. (3′-Chloro-4′-hydroxybiphenyl-4-yl)-(4-fluoro-3-methoxyphenyl)-methanone (**7a**)

The title compound was prepared by reaction of (4-bromophenyl)-(4-fluoro-3-methoxyphenyl)-methanone **6b** (127 mg, 0.41 mmol, 1 equiv) with 3-chloro-4-hydroxyphenylboronic acid (85 mg, 0.49 mmol, 1.2 equiv) according to method D. The product was used in the next step without further purification. $C_{20}H_{14}ClFO_3$; MW 357.

4.6.20. (3′-Chloro-4′-hydroxybiphenyl-4-yl)-(4-fluoro-3-hydroxyphenyl)-methanone (**7**)

The title compound was prepared by reaction of (3′-chloro-4′-hydroxybiphenyl-4-yl)-(4-fluoro-3-methoxyphenyl)-methanone **7a** (126 mg, 0.35 mmol, 1 equiv) with pyridinium hydrochloride (35 mmol, 100 equiv) according to method G. The product was purified by column chromatography (hexane/ethyl acetate 7:3) then by preparative HPLC (isopropanol/water) to afford 38 mg

(32%) of the analytically pure compound as a yellow solid. $C_{19}H_{12}ClFO_3$; MW 343; ^{1}H NMR (acetone-d_6): δ 9.04 (s, br, 1H), 9.02 (s, br, 1H), 7.86–7.83 (m, 2H), 7.82–7.80 (m, 2H), 7.76 (d, J = 2.2 Hz, 1H), 7.60 (dd, J = 2.2 Hz, J = 8.5 Hz, 1H), 7.48 (dd, J = 1.9 Hz, J = 8.5 Hz, 1H), 7.34–7.31 (m, 1H), 7.31–7.26 (m, 1H), 7.16 (d, J = 8.5 Hz, 1H); ^{13}C NMR (acetone-d_6): δ 193.8, 153.3, 143.3, 136.1, 134.6, 132.4, 130.4, 128.4, 127.5, 126.2, 122.4, 121.0, 119.2, 118.5, 118.4, 117.3, 117.0, 116.0, 115.8; IR: 3320, 1650, 1593, 1058 cm^{-1}; LC/MS m/z: 344–346 $(M + H)^+$.

4.6.21. (4-Bromophenyl)-(3-fluoro-5-methoxyphenyl)-methanol (**8c**)

To a solution of 3-bromo-5-fluoroanisole (500 mg, 2.44 mmol, 1 equiv) in anhydrous THF was added granules of magnesium (64 mg, 2.56 mmol, 1.05 equiv) under nitrogen. The mixture was heated to 60 °C for 2 h. After reaching room temperature, 4-bromobenzaldehyde (542 mg, 2.93 mmol, 1.2 equiv) was added and the reaction mixture was stirred at 80 °C overnight. The reaction was cooled to room temperature, quenched with brine and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered and concentrated to dryness under vacuum. The product was used in the next step without further purification. $C_{14}H_{12}BrFO_2$; MW 311.

4.6.22. (4-Bromophenyl)-(3-fluoro-5-methoxyphenyl)-methanone (**8b**)

The title compound was prepared by reaction of (4-bromophenyl)-(3-fluoro-5-methoxyphenyl)-methanol **8c** (306 mg, 0.98 mmol, 1 equiv) with 2-iodoxybenzoic acid (553 mg, 1.96 mmol, 2 equiv) according to method B. The product was used in the next step without further purification. $C_{14}H_{10}BrFO_2$; MW 309.

4.6.23. (3-Fluoro-5-methoxyphenyl)-(4′-methoxy-3′-methylbiphenyl-4-yl)-methanone (**8a**)

The title compound was prepared by reaction of (4-bromophenyl)-(3-fluoro-5-methoxyphenyl)-methanone **8b** (175 mg, 0.57 mmol, 1 equiv) with 4-methoxy-3-methylphenylboronic acid (113 mg, 0.68 mmol, 1.2 equiv) according to method D. The product was used in the next step without further purification. $C_{22}H_{19}FO_3$; MW 350.

4.6.24. (3-Fluoro-5-hydroxyphenyl)-(4′-hydroxy-3′-methylbiphenyl-4-yl)-methanone (**8**)

The title compound was prepared by reaction of (3-fluoro-5-methoxyphenyl)-(4′-methoxy-3′-methylbiphenyl-4-yl)-methanone **8a** (100 mg, 0.29 mmol, 1 equiv) with pyridinium hydrochloride (29.0 mmol, 100 equiv) according to method G. The product was purified by preparative HPLC (gradient water/isopropanol) to afford 5 mg (5%) of the analytically pure compound. $C_{20}H_{15}FO_3$; MW 322; ^{1}H NMR (acetone-d_6): δ 9.17 (s, br, 1H), 8.48 (s, br, 1H), 7.87–7.84 (m, 2H), 7.80–7.77 (m, 2H), 7.56–7.54 (m, 1H), 7.45 (ddd, J = 0.6 Hz, J = 2.5 Hz, J = 8.2 Hz, 1H), 7.10–7.08 (m, 1H), 6.99 (ddd, J = 1.3 Hz, J = 2.5 Hz, J = 8.8 Hz, 1H), 6.96 (d, J = 8.5 Hz, 1H), 6.87 (dt, J = 2.2 Hz, J = 10.4 Hz, 1H), 2.29 (s, 3H); ^{13}C NMR (acetone-d_6): δ 195.7, 160.9, 158.0, 147.3, 142.7, 142.6, 136.7, 132.6, 132.3, 131.5, 127.9, 127.5, 126.9, 117.1, 114.6, 109.1, 108.2, 108.0, 17.3; LC/MS m/z: 323 $(M + H)^+$.

4.6.25. (4-Bromophenyl)-(3,4-difluorophenyl)-methanol (**9c**)

To a solution of 1-bromo-3,4-difluorobenzene (1.00 g, 0.59 mL, 5.18 mmol, 1 equiv) in anhydrous THF was added granules of magnesium (132 mg, 5.44 mmol, 1.05 equiv) under nitrogen. The mixture was heated to 60 °C for 2 h. After cooling to room temperature, 4-bromobenzaldehyde (592 mg, 3.20 mmol, 1.2 equiv) was added and the reaction mixture was stirred at 80 °C overnight. The reaction was cooled to room temperature, quenched with brine and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered and concentrated to dryness under vacuum. The product was used in the next step without further purification. $C_{13}H_9BrF_2O$; MW 299.

4.6.26. (4-Bromophenyl)-(3,4-difluorophenyl)-methanone (**9b**)

The title compound was prepared by reaction of (4-bromophenyl)-(3,4-difluorophenyl)-methanol **9c** (589 mg, 1.97 mmol, 1 equiv) with 2-iodoxybenzoic acid (1.38 g, 4.93 mmol, 2.5 equiv) according to method B. The product was purified by recrystallisation in ethanol to afford 140 mg (24%) of the analytically pure compound as a white powder. $C_{13}H_7BrF_2O$; MW 297; mp: 74–77 °C; ^{1}H NMR (acetone-d_6): δ 7.79–7.74 (m, 5H), 7.70–7.66 (m, 1H), 7.56–7.50 (m, 1H); ^{13}C NMR (acetone-d_6): δ 193.3, 151.9, 151.8, 136.9, 135.5, 132.7, 132.4, 128.3, 128.2, 128.0, 119.8, 119.6, 118.6; IR: 1650, 1604, 1280 cm^{-1}; GC/MS m/z: 296–298 $(M)^+$.

4.6.27. (3,4-Difluorophenyl)-(4′-methoxy-3′-methylbiphenyl-4-yl)-methanone (**9a**)

The title compound was prepared by reaction of (4-bromophenyl)-(3,4-difluorophenyl)-methanone **9b** (168 mg, 0.52 mmol, 1 equiv) with 4-methoxy-3-methylphenylboronic acid (103 mg, 0.62 mmol, 1.2 equiv) according to method D. The compound was recrystallised in ethanol to obtain 157 mg of the analytically pure product as a white powder. $C_{21}H_{16}F_2O_2$; MW 338; mp: 123–125 °C; ^{1}H NMR (acetone-d_6): δ 7.88–7.84 (m, 2H), 7.82–7.79 (m, 2H), 7.75 (ddd, J = 2.2 Hz, J = 7.9 Hz, J = 11.0 Hz, 1H), 7.71–7.67 (m, 1H), 7.61–7.57 (m, 2H), 7.56–7.50 (m, 1H), 7.06 (d, J = 8.2 Hz, 1H), 3.90 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (acetone-d_6): δ 193.6, 159.3, 146.1, 135.7, 131.4, 130.1, 128.1, 128.0, 127.8, 127.2, 126.7, 119.7, 119.5, 111.4, 55.9, 16.4; IR: 2930, 1645, 1596, 1141 cm^{-1}; GC/MS m/z: 338 $(M)^+$.

4.6.28. (3,4-Difluorophenyl)-(4-hydroxy-3′-methylbiphenyl-4-yl)-methanone (**9**)

The title compound was prepared by reaction of (3,4-difluorophenyl)-(4′-methoxy-3-methylbiphenyl-4-yl)-methanone **9a** (100 mg, 0.30 mmol, 1 equiv) with pyridinium hydrochloride (30 mmol, 100 equiv) according to method G. The product was purified by recrystallisation in hexane to afford 35 mg (36%) of the analytically pure compound as a yellow solid. $C_{20}H_{14}F_2O_2$; MW 324; mp: 174–176 °C; ^{1}H NMR (acetone-d_6): δ 8.54 (s, br, 1H), 7.86–7.83 (m, 2H), 7.80–7.77 (m, 2H), 7.77–7.74 (m, 1H), 7.71–7.67 (m, 1H), 7.56–7.50 (m, 2H), 7.45 (ddd, J = 0.6 Hz, J = 2.5 Hz, J = 8.2 Hz, 1H), 6.96 (d, J = 8.2 Hz, 1H), 2.29 (s, 3H); ^{13}C NMR (acetone-d_6): δ 193.7, 157.1, 152.7, 152.6, 151.8, 149.9, 146.4, 135.5, 131.4, 130.5, 127.0, 126.5, 119.7, 119.5, 118.4, 118.3, 116.2, 16.3; IR: 3427, 1645, 1594, 1287 cm^{-1}; GC/MS m/z: 324 $(M)^+$.

4.6.29. (6-Bromopyridin-3-yl)-(3-methoxyphenyl)-methanol (**10c**)

The title compound was prepared by reaction of 6-bromopyridin-3-yl carboxaldehyde (500 mg, 2.69 mmol, 1 equiv) with 3-methoxyphenylmagnesiumbromide (1 M in THF) (1.35 g, 5.91 mmol, 2.2 equiv) according to method A. The product was purified by column chromatography (hexane/ethyl acetate 7:3) to afford 700 mg (89%) of the analytically pure compound as a colorless oil. $C_{13}H_{12}BrNO_2$; MW 294; ^{1}H NMR (acetone-d_6): δ 8.45–8.43 (m, 1H), 7.71 (ddd, J = 0.6 Hz, J = 2.5 Hz, J = 8.2 Hz, 1H), 7.52 (d, J = 8.8 Hz, 1H), 7.25 (t, J = 8.2 Hz, 1H), 7.06–7.04 (m, 1H), 7.00–6.97 (m, 1H), 6.82 (ddd, J = 0.9 Hz, J = 2.8 Hz, J = 8.2 Hz, 1H), 5.89 (d, J = 4.1 Hz, 1H), 5.21 (d, J = 4.1 Hz, 1H), 3.77 (s, 3H); ^{13}C NMR (acetone-d_6): δ 161.8, 150.4, 147.6, 142.4, 142.0, 139.0, 131.3, 129.5, 120.3, 114.6, 113.8, 74.3, 56.5.

*4.6.30. (6-Bromopyridin-3-yl)-(3-methoxyphenyl)-methanone (**10b**)*

The title compound was prepared by reaction of (6-bromopyridin-3-yl)-(3-methoxyphenyl)-methanol **10c** (700 mg, 2.38 mmol, 1 equiv) with 2-iodoxybenzoic acid (1.34 g, 4.76 mmol, 2 equiv) according to method B. The product was purified by column chromatography (hexane/ethyl acetate 9:1) to give 520 mg (75%) of the analytically pure compound as a colorless oil. $C_{13}H_{10}BrNO_2$; MW 292; ^{1}H NMR (acetone-d_6): δ 8.70 (d, J = 1.8 Hz, 1H), 8.07 (dd, J = 2.4 Hz, J = 8.2 Hz, 1H), 7.80 (dd, J = 0.6 Hz, J = 8.2 Hz, 1H), 7.51–7.47 (m, 1H), 7.38–7.35 (m, 2H), 7.26 (ddd, J = 0.9 Hz, J = 2.7 Hz, J = 8.2 Hz, 1H), 3.87 (s, 3H); ^{13}C NMR (acetone-d_6): δ 161.8, 152.9, 147.2, 141.5, 139.8, 134.6, 131.6, 129.9, 124.2, 121.2, 116.0, 56.9.

*4.6.31. [6-(4-Methoxy-3-methylphenyl)-pyridin-3-yl]-(3-methoxyphenyl)-methanone (**10a**)*

The title compound was prepared by reaction of (6-bromopyridin-3-yl)-(3-methoxyphenyl)-methanone **10b** (520 mg, 1.80 mmol, 1 equiv) with 4-methoxy-3-methylphenylboronic acid (359 mg, 2.16 mmol, 1.2 equiv) according to method D. The product was purified by column chromatography (hexane/ethyl acetate 9:1) to afford 536 mg (89%) of the analytically pure compound as a yellow oil. $C_{21}H_{19}NO_3$; MW 333; ^{1}H NMR (acetone-d_6): δ 8.74 (dd, J = 0.9 Hz, J = 2.2 Hz, 1H), 7.91 (dd, J = 2.2 Hz, J = 8.2 Hz, 1H), 7.83–7.80 (m, 2H), 7.74 (dd, J = 0.6 Hz, J = 8.5 Hz, 1H), 7.28–7.24 (m, 1H), 7.17–7.14 (m, 2H), 7.02 (ddd, J = 1.3 Hz, J = 2.5 Hz, J = 8.5 Hz, 1H), 6.81 (d, J = 9.1 Hz, 1H), 3.68 (s, 3H), 3.66 (s, 3H), 2.05 (s, 3H); ^{13}C NMR (acetone-d_6): δ 195.5, 161.7, 161.5, 152.6, 140.6, 139.7, 131.9, 131.5, 131.3, 128.4, 128.2, 124.0, 120.6, 120.3, 116.0, 112.0, 56.9, 56.8, 17.5.

*4.6.32. [6-(4-Hydroxy-3-methylphenyl)-pyridin-3-yl]-(3-hydroxyphenyl)-methanone (**10**)*

The title compound was prepared by reaction of [6-(4-methoxy-3-methylphenyl)-pyridin-3-yl]-(3-methoxyphenyl)-methanone **10a** (466 mg, 1.40 mmol, 1 equiv) with boron tribromide (14.0 mmol, 10 equiv) according to method E. The product was purified by column chromatography (hexane/ethyl acetate 8:2) to give 321 mg (75%) of the analytically pure compound as a yellow powder. $C_{19}H_{15}NO_3$; MW 305; ^{1}H NMR (acetone-d_6): δ 8.94 (dd, J = 0.6 Hz, J = 2.1 Hz, 1H), 8.73 (s, br, 2H), 8.14 (dd, J = 2.1 Hz, J = 8.2 Hz, 1H), 8.04 (dd, J = 0.6 Hz, J = 2.1 Hz, 1H), 7.99 (dd, J = 0.6 Hz, J = 8.2 Hz, 1H), 7.94 (dd, J = 2.1 Hz, J = 8.5 Hz, 1H), 7.44–7.39 (m, 1H), 7.32–7.29 (m, 2H), 7.17–7.14 (m, 1H), 6.97 (d, J = 8.2 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (acetone-d_6): δ 194.7, 160.7, 158.4, 151.5, 139.7, 138.7, 131.4, 130.9, 130.6, 130.4, 127.1, 125.6, 122.0, 120.7, 119.2, 116.9, 115.9, 16.3; IR: 3431, 1648, 1582, 1473, 1268 cm^{-1}; LC/MS m/z: 306 $(M + H)^+$.

*4.6.33. (5-Bromopyridin-2-yl)-(3-methoxyphenyl)-methanol (**11c**)*

The title compound was prepared by reaction of 5-bromopyridin-2-yl carboxaldehyde (500 mg, 2.69 mmol, 1 equiv) with 3-methoxyphenylmagnesiumbromide (1 M in THF) (1.35 g, 5.9 mL, 5.91 mmol, 2.2 equiv) according to method A. The product was purified by column chromatography (hexane/ethyl acetate 8:2) to give 490 mg (62%) of the analytically pure compound as a red oil. $C_{13}H_{12}BrNO_2$; MW 294; ^{1}H NMR (acetone-d_6): δ 8.57 (dd, J = 0.6 Hz, J = 2.5 Hz, 1H), 7.94 (dd, J = 2.5 Hz, J = 8.5 Hz, 1H), 7.56–7.53 (m, 1H), 7.21 (t, J = 7.9 Hz, 1H), 7.07–7.05 (m, 1H), 7.04–7.00 (m, 1H), 6.79 (ddd, J = 0.9 Hz, J = 2.5 Hz, J = 8.2 Hz, 1H), 5.80 (d, J = 4.4 Hz, 1H), 5.25 (d, J = 4.4 Hz, 1H), 3.76 (s, 3H); ^{13}C NMR (acetone-d_6): δ 192.6, 164.4, 161.6, 151.0, 147.2, 141.2, 131.0, 124.0, 120.6, 114.4, 114.0, 77.3, 56.4.

*4.6.34. (5-Bromopyridin-2-yl)-(3-methoxyphenyl)-methanone (**11b**)*

The title compound was prepared by reaction of (5-bromopyridin-2-yl)-(3-methoxyphenyl)-methanol **11c** (490 mg, 1.67 mmol, 1 equiv) with 2-iodoxybenzoic acid (940 mg, 3.33 mmol, 2 equiv) according to method B. The product was purified by column chromatography (hexane/ethyl acetate 9:1) to afford 365 mg (75%) of the analytically pure compound as a colorless oil. $C_{13}H_{10}BrNO_2$; MW 292; ^{1}H NMR (acetone-d_6): δ 8.80 (dd, J = 0.6 Hz, J = 2.2 Hz, 1H), 8.25 (dd, J = 2.2 Hz, J = 8.2 Hz, 1H), 7.97 (dd, J = 0.6 Hz, J = 8.2 Hz, 1H), 7.65–7.61 (m, 2H), 7.45–7.41 (m, 1H), 7.21 (ddd, J = 0.9 Hz, J = 2.5 Hz, J = 8.2 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (acetone-d_6): δ 193.7, 161.3, 155.6, 151.3, 141.9, 139.3, 131.0, 127.7, 125.7, 125.3, 120.7, 117.3, 56.8.

*4.6.35. [5-(4-Methoxy-3-methylphenyl)-pyridin-2-yl]-(3-methoxyphenyl)-methanone (**11a**)*

The title compound was prepared by reaction of (5-bromopyridin-2-yl)-(3-methoxyphenyl)-methanone **11b** (365 mg, 1.25 mmol, 1 equiv) with 4-methoxy-3-methylphenylboronic acid (249 mg, 1.50 mmol, 1.2 equiv) according to method D. The product was purified by column chromatography (hexane/ethyl acetate 9:1) to give 362 mg (87%) of the analytically pure compound as yellow solid. $C_{21}H_{19}NO_3$; MW 333; ^{1}H NMR (acetone-d_6): δ 8.95 (dd, J = 0.6 Hz, J = 2.2 Hz, 1H), 8.18 (dd, J = 2.5 Hz, J = 8.2 Hz, 1H), 8.06 (dd, J = 0.6 Hz, J = 8.2 Hz, 1H), 7.75–7.71 (m, 2H), 7.62–7.59 (m, 2H), 7.45–7.41 (m, 1H), 7.20 (ddd, J = 0.9 Hz, J = 2.8 Hz, J = 8.2 Hz, 1H), 7.06 (dd, J = 2.2 Hz, J = 7.3 Hz, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (acetone-d_6): δ 194.1, 161.3, 160.6, 154.9, 148.0, 140.3, 140.0, 136.1, 131.1, 130.8, 130.3, 129.0, 127.9, 126.2, 125.4, 120.2, 117.6, 112.6, 56.8, 56.7, 17.4.

*4.6.36. [5-(4-Hydroxy-3-methylphenyl)-pyridin-2-yl]-(3-hydroxyphenyl)-methanone (**11**)*

The title compound was prepared by reaction of [5-(4-methoxy-3-methylphenyl)-pyridin-2-yl]-(3-methoxyphenyl)-methanone **11a** (362 mg, 1.09 mmol, 1 equiv) with boron tribromide (10.9 mmol, 10 equiv) according to method E. The product was purified by column chromatography (hexane/ethyl acetate 8:3) then by preparative TLC (hexane/ethyl acetate 7:3) to give 127 mg (45%) of the analytically pure compound as yellow powder. $C_{19}H_{15}NO_3$; MW 305; mp: 178–180 °C; ^{1}H NMR (acetone-d_6): δ 8.93 (d, J = 1.8 Hz, 1H), 8.62 (s, br, 1H), 8.61 (s, br, 1H), 8.19 (dd, J = 2.1 Hz, J = 8.2 Hz, 1H), 8.04 (d, J = 8.2 Hz, 1H), 7.63–7.58 (m, 3H), 7.50 (dd, J = 1.8 Hz, J = 8.2 Hz, 1H), 7.37–7.32 (m, 1H), 7.13–7.09 (m, 1H), 7.00 (d, J = 8.2 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR (acetone-d_6): δ 194.4, 158.9, 158.4, 154.9, 147.8, 140.6, 140.1, 135.9, 131.6, 130.9, 129.7, 127.7, 127.3, 126.2, 124.3, 121.5, 119.2, 117.4, 17.3; IR: 3350, 1644, 1580, 1514, 1240 cm^{-1}; LC/MS m/z: 306 $(M + H)^+$.

*4.6.37. (5-Bromopyridin-2-yl)-(4-fluoro-3-methoxyphenyl)-methanol (**12c**)*

To a solution of 5-bromo-2-fluoroanisole (1.00 g, 4.88 mmol, 1 equiv) in anhydrous THF was added granules of magnesium (125 mg, 5.12 mmol, 1.05 equiv) under nitrogen. The mixture was heated to 60 °C for 2 h. After cooling to room temperature, 5-bromo-2-formylpyridine (1.09 g, 5.86 mmol, 1.2 equiv) was added and the reaction mixture was stirred at 80 °C overnight. The reaction was cooled to room temperature, quenched with brine and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered and concentrated to dryness under vacuum. The product was used in the next step without further purification. $C_{13}H_{11}BrFNO_2$; MW 312.

*4.6.38. (5-Bromopyridin-2-yl)-(4-fluoro-3-methoxyphenyl)-methanone (**12b**)*

The title compound was prepared by reaction of (5-bromopyridin-2-yl)-(4-fluoro-3-methoxyphenyl)-methanol **12c** (463 mg, 1.48 mmol, 1 equiv) with 2-iodoxybenzoic acid (2.96 mmol, 2 equiv) according to method B. The product was purified by column chromatography (hexane) to afford 354 mg (77%) of the analytically pure compound as a yellow oil. $C_{13}H_9BrFNO_2$; MW 310; ^{1}H NMR (acetone-d_6): δ 6.28 (dd, J = 2.2 Hz, J = 8.2 Hz, 1H), 8.06–8.03 (m, 2H), 7.99 (dd, J = 0.9 Hz, J = 8.5 Hz, 1H), 7.89 (dd, J = 2.2 Hz, J = 8.5 Hz, 1H), 7.77 (ddd, J = 1.9 Hz, J = 4.4 Hz, J = 8.5 Hz, 1H), 3.96 (s, 3H); ^{13}C NMR (acetone-d_6): δ 191.4, 167.6, 154.5, 150.3, 141.1, 133.8, 130.4, 129.3, 126.8, 126.2, 116.6, 116.2, 56.7; IR: 2835, 1678, 1601, 1290 cm^{-1}; LC/MS m/z: 310–312 $(M + H)^+$.

*4.6.39. (4-Fluoro-3-methoxyphenyl)-[5-(4-methoxy-3-methylphenyl)-pyridin-2-yl]-methanone (**12a**)*

The title compound was prepared by reaction of (5-bromopyridin-2-yl)-(4-fluoro-3-methoxyphenyl)-methanone **12b** (300 mg, 0.97 mmol, 1 equiv) with 4-methoxy-3-methylphenylboronic acid (193 mg, 1.16 mmol, 1.2 equiv) according to method D. The product was recrystallised in acetonitrile to afford 279 mg (82%) of the analytically pure compound as a yellow powder. $C_{21}H_{18}FNO_3$; MW 351; mp: 141–143 °C; ^{1}H NMR ($CDCl_3$): δ 8.89 (dd, J = 0.6 Hz, J = 2.2 Hz, 1H), 8.09 (dd, J = 0.6 Hz, J = 8.2 Hz, 1H), 8.02 (dd, J = 2.5 Hz, J = 8.2 Hz, 1H), 7.82 (dd, J = 2.2 Hz, J = 8.5 Hz, 1H), 7.77 (ddd, J = 2.2 Hz, J = 4.4 Hz, J = 8.5 Hz, 1H), 7.46 (dd, J = 2.5 Hz, J = 8.2 Hz, 1H), 7.44–7.42 (m, 1H), 7.15 (dd, J = 8.5 Hz, J = 10.7 Hz, 1H), 6.94 (d, J = 8.2 Hz, 1H), 3.95 (s, 3H), 3.88 (s, 3H), 2.30 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 192.0, 158.9, 156.8, 153.0, 147.9, 147.8, 146.7, 139.2, 134.7, 133.3, 129.7, 128.8, 126.1, 125.8, 125.2, 115.9, 115.8, 110.8, 56.6, 55.7, 16.6; GC/MS m/z: 351 $(M)^+$.

*4.6.40. (4-Fluoro-3-hydroxyphenyl)-[5-(4-hydroxy-3-methylphenyl)-pyridin-2-yl]-methanone (**12**)*

The title compound was prepared by reaction of (4-fluoro-3-methoxyphenyl)-[5-(4-methoxy-3-methylphenyl)-pyridin-2-yl]-methanone **12a** (70 mg, 0.20 mmol, 1 equiv) with pyridinium hydrochloride (20.0 mmol, 100 equiv) according to method G. The product was purified by preparative HPLC (isopropanol/water) to give 21 mg (33%) of the analytically pure compound as a yellow powder. $C_{19}H_{14}FNO_3$; MW 323; mp: 221–223 °C; ^{1}H NMR (acetone-d_6): δ 8.94 (dd, J = 0.6 Hz, J = 2.2 Hz, 1H), 8.64 (s, br, 1H), 8.20 (dd, J = 2.2 Hz, J = 8.2 Hz, 1H), 8.05 (dd, J = 0.9 Hz, J = 8.2 Hz, 1H), 7.87 (dd, J = 2.2 Hz, J = 8.8 Hz, 1H), 7.74 (ddd, J = 2.2 Hz, J = 4.4 Hz, J = 8.5 Hz, 1H), 7.60 (dd, J = 0.6 Hz, J = 2.2 Hz, 1H), 7.50 (ddd, J = 0.6 Hz, J = 2.5 Hz, J = 8.2 Hz, 1H), 7.24 (dd, J = 8.5 Hz, J = 11.0 Hz, 1H), 7.00 (d, J = 8.2 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (acetone-d_6): δ 192.7, 158.3, 157.2, 154.6, 147.6, 140.5, 135.9, 131.5, 129.5, 127.5, 127.1, 126.1, 125.7, 125.6, 122.3, 117.3, 117.2, 117.1, 17.1; IR: 3179, 2971, 1607, 1511, 1124 cm^{-1}; LC/MS m/z: 324 $(M + H)^+$.

*4.6.41. (4-Fluoro-3-methoxyphenyl)-[5-(3-chloro-4-hydroxyphenyl)-pyridin-2-yl]-methanone (**13a**)*

The title compound was prepared by reaction of (5-bromopyridin-2-yl)-(4-fluoro-3-methoxyphenyl)-methanone **12b** (150 mg, 0.48 mmol, 1 equiv) with 3-chloro-4-hydroxyphenylboronic acid (100 mg, 0.58 mmol, 1.2 equiv) according to method D. The product was recrystallised in ethyl acetate to afford 72 mg (42%) of the analytically pure product as a yellow solid. $C_{19}H_{13}ClFNO_3$; MW 357; mp: 195–197 °C; ^{1}H NMR (acetone-d_6): δ 9.20 (s, br, 1H), 9.00 (dd, J = 0.6 Hz, J = 2.2 Hz, 1H), 8.28 (dd, J = 2.5 Hz, J = 8.2 Hz, 1H), 8.11 (dd, J = 0.6 Hz, J = 8.2 Hz, 1H), 7.97 (dd, J = 2.2 Hz, J = 8.5 Hz, 1H), 7.88–7.84 (m, 2H), 7.67 (dd, J = 2.2 Hz, J = 8.5 Hz, 1H), 7.28 (dd, J = 8.2 Hz, J = 11.4 Hz, 1H), 7.20 (d, J = 8.5 Hz, 1H), 3.97 (s, 3H); ^{13}C NMR (acetone-d_6): δ 191.6, 154.8, 154.3, 147.0, 138.2, 135.5, 130.2, 129.6, 128.0, 126.2, 126.1, 125.4, 122.2, 118.4, 116.8, 116.3, 116.1, 56.6; GC/MS m/z: 356–358 $(M)^+$.

*4.6.42. (4-Fluoro-3-hydroxyphenyl)-[5-(3-chloro-4-hydroxyphenyl)-pyridin-2-yl]-methanone (**13**)*

The title compound was prepared by reaction of (4-fluoro-3-methoxyphenyl)-[5-(3-chloro-4-hydroxyphenyl)-pyridin-2-yl]-methanone **13a** (59 mg, 0.17 mmol, 1 equiv) with boron trifluoride dimethylsulfide complex (5.95 mmol, 35 equiv) according to method F. The product was purified by column chromatography (hexane/ethyl acetate 6:4) then by preparative HPLC (isopropanol/water) to afford 10 mg (17%) of the analytically pure product. $C_{18}H_{11}ClFNO_3$; MW 343; ^{1}H NMR (acetone-d_6): δ 9.10 (s, br, 2H), 8.98 (d, J = 2.2 Hz, 1H), 8.27 (dd, J = 2.5 Hz, J = 7.9 Hz, 1H), 8.09–8.06 (m, 1H), 7.87 (dd, J = 2.2 Hz, J = 8.8 Hz, 1H), 7.84 (d, J = 2.2 Hz, 1H), 7.73 (ddd, J = 1.9 Hz, J = 4.4 Hz, J = 8.5 Hz, 1H), 7.66 (dd, J = 2.2 Hz, J = 8.5 Hz, 1H), 7.25 (dd, J = 8.5 Hz, J = 10.7 Hz, 1H), 7.20 (d, J = 8.5 Hz, 1H); ^{13}C NMR (acetone-d_6): δ 191.8, 156.4, 154.8, 154.4, 147.0, 145.5, 145.4, 138.2, 135.5, 134.4, 129.6, 128.0, 125.3, 122.2, 121.4, 119.4, 118.4, 116.5; IR: 3355, 1647, 1578, 1517, 1265 cm^{-1}; LC/MS m/z: 344–346 $(M + H)^+$.

*4.6.43. (6-Bromopyridin-2-yl)-(3-methoxyphenyl)-methanol (**14c**)*

The title compound was prepared by reaction of 6-bromopyridin-2-yl carboxaldehyde (1 g, 5.41 mmol, 1 equiv) with 3-methoxyphenylmagnesiumbromide (1 M in THF) (2.70 g, 11.9 mL, 11.9 mmol, 2.2 equiv) according to method A. The product was purified by column chromatography (hexane/ethyl acetate 8:2) to afford 936 mg (59%) of the analytically pure product. $C_{13}H_{12}BrNO_2$; MW 294; ^{1}H NMR (acetone-d_6): δ 7.57 (t, J = 7.6 Hz, 1H), 7.49 (d, J = 7.6 Hz, 1H), 7.30 (d, J = 7.9 Hz, 1H), 7.08 (t, J = 8.2 Hz, 1H), 6.93–6.90 (m, 1H), 6.87 (d, J = 7.6 Hz, 1H), 6.66 (dd, J = 2.4 Hz, J = 8.2 Hz, 1H), 5.63 (d, J = 4.5 Hz, 1H), 5.05 (d, J = 4.5 Hz, 1H), 3.62 (s, 3H); ^{13}C NMR (acetone-d_6): δ 165.5, 159.8, 145.1, 140.4, 139.7, 129.2, 126.4, 119.4, 118.8, 112.5, 75.5, 54.5.

*4.6.44. (6-Bromopyridin-2-yl)-(3-methoxyphenyl)-methanone (**14b**)*

The title compound was prepared by reaction of (6-bromopyridin-2-yl)-(3-methoxyphenyl)-methanol **14c** (930 mg, 3.19 mmol, 1 equiv) with 2-iodoxybenzoic acid (1.80 g, 6.39 mmol, 2 equiv) according to method B. The product was purified by column chromatography (hexane/ethyl acetate 9:1) to afford 727 mg (78%) of the analytically pure compound as a yellow solid. $C_{13}H_{10}BrNO_2$; MW 292; ^{1}H NMR (acetone-d_6): δ 8.02 (dd, J = 1.6 Hz, J = 7.6 Hz, 1H), 7.99 (t, J = 7.3 Hz, 1H), 7.86 (dd, J = 1.6 Hz, J = 7.3 Hz, 1H), 7.65–7.61 (m, 2H), 7.47–7.43 (m, 1H), 7.23 (ddd, J = 0.9 Hz, J = 2.5 Hz, J = 8.2 Hz, 1H), 3.87 (s, 3H); ^{13}C NMR (acetone-d_6): δ 193.5, 160.4, 156.7, 141.2, 141.1, 138.0, 131.9, 124.4, 120.1, 119.2, 116.3, 115.2, 55.8; IR: 1667, 1425, 1254, 1032 cm^{-1}; LC/MS m/z: 292–294 $(M + H)^+$.

*4.6.45. [6-(4-Methoxy-3-methylphenyl)-pyridin-2-yl]-(3-methoxyphenyl)-methanone (**14a**)*

The title compound was prepared by reaction of (6-bromopyridin-2-yl)-(3-methoxyphenyl)-methanone **14b** (410 mg, 1.40 mmol, 1 equiv) with 4-methoxy-3-methylphenylboronic acid (280 mg, 1.69 mmol, 1.2 equiv) according to method D. The product was purified by column chromatography (hexane/ethyl acetate 9:1) to give 432 mg (92%) of the analytically pure compound as a yellow powder. $C_{21}H_{19}NO_3$; MW 333; ^{1}H NMR (acetone-d_6): δ 8.10 (dd, J = 0.9 Hz, J = 7.9 Hz, 1H), 8.07–8.03 (m, 1H), 7.99–7.95 (m, 2H), 7.89 (dd, J = 0.9 Hz, J = 7.6 Hz, 1H), 7.80–7.78 (m, 1H), 7.75 (dt, J = 0.9 Hz,

J = 7.6 Hz, 1H), 7.48 (t, J = 7.9 Hz, 1H), 7.24 (ddd, J = 0.9 Hz, J = 2.8 Hz, J = 8.2 Hz, 1H), 7.02 (d, J = 8.2 Hz, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (acetone-d_6): δ 193.6, 160.4, 160.1, 156.5, 155.7, 139.0, 138.9, 131.3, 129.9, 127.3, 126.7, 124.5, 122.6, 122.5, 119.8, 116.4, 111.1, 55.9, 55.8, 16.5.

4.6.46. [6-(4-Hydroxy-3-methylphenyl)-pyridin-2-yl]-(3-hydroxyphenyl)-methanone (**14**)

The title compound was prepared by reaction of [6-(4-methoxy-3-methylphenyl)-pyridin-2-yl]-(3-methoxyphenyl)-methanone **14a** (341 mg, 1.02 mmol, 1 equiv) with boron tribromide (10.2 mmol, 10 equiv) according to method E. The product was purified by column chromatography (hexane/ethyl acetate 8:2) then by preparative TLC (hexane/ethyl acetate 65:35) to afford 120 mg (38%) of the analytically pure compound as a yellow solid. $C_{19}H_{15}NO_3$; MW 305; ^{1}H NMR (acetone-d_6): δ 8.64 (s, br, 1H), 8.54 (s, br, 1H), 8.06 (dd, J = 1.3 Hz, J = 7.9 Hz, 1H), 8.04–8.00 (m, 1H), 7.93 (d, J = 2.2 Hz, 1H), 7.85–7.81 (m, 2H), 7.67–7.63 (m, 2H), 7.41–7.37 (m, 1H), 7.14 (ddd, J = 0.9 Hz, J = 2.5 Hz, J = 7.9 Hz, 1H), 6.91 (d, J = 8.2 Hz, 1H), 2.27 (s, 3H); ^{13}C NMR (acetone-d_6): δ 195.1, 157.0, 140.1, 140.0, 131.9, 131.6, 131.2, 127.8, 126.6, 124.5, 123.4, 123.3, 121.9, 119.5, 117.0, 17.5; IR: 3372, 1642, 1581, 1426 cm^{-1}; LC/MS m/z: 306 $(M + H)^+$.

4.6.47. (3-Methoxyphenyl)-[6-(2-methoxyphenyl)-pyridin-2-yl]-methanone (**15a**)

The title compound was prepared by reaction of (6-bromopyridin-2-yl)-(3-methoxyphenyl)-methanone **14b** (100 mg, 0.34 mmol, 1 equiv) with 2-methoxyphenylboronic acid (62 mg, 0.41 mmol, 1.2 equiv) according to method C. The product was purified by column chromatography (hexane/ethyl acetate 8:2) to afford 53 mg (49%) of the analytically pure product as a light yellow oil. $C_{20}H_{17}NO_3$; MW 319; ^{1}H NMR (acetone-d_6): δ 8.19 (dd, J = 0.9 Hz, J = 7.9 Hz, 1H), 8.05 (t, J = 7.9 Hz, 1H), 7.94 (dd, J = 1.2 Hz, J = 7.7 Hz, 1H), 7.86 (dd, J = 1.8 Hz, J = 7.7 Hz, 1H), 7.78–7.76 (m, 1H), 7.76–7.73 (m, 1H), 7.46–7.40 (m, 2H), 7.21 (ddd, J = 1.0 Hz, J = 2.6 Hz, J = 8.2 Hz, 1H), 7.17 (dd, J = 0.9 Hz, J = 8.5 Hz, 1H), 7.05 (dt, J = 1.2 Hz, J = 7.6 Hz, 1H), 3.93 (s, 3H), 3.86 (s, 3H); ^{13}C NMR (acetone-d_6): δ 193.6, 160.4, 158.4, 155.8, 155.6, 138.9, 137.9, 131.9, 131.3, 129.9, 128.9, 128.3, 124.5, 122.9, 121.6, 119.7, 116.4, 112.7, 56.0, 55.8; LC/MS m/z : 320 $(M + H)^+$.

4.6.48. (3-Hydroxyphenyl)-[6-(2-hydroxyphenyl)-pyridin-2-yl]-methanone (**15**)

The title compound was prepared by reaction of (3-methoxyphenyl)-[6-(2-methoxyphenyl)-pyridin-2-yl]-methanone **15a** (40 mg, 0.13 mmol, 1 equiv) with boron tribromide (1.3 mmol, 10 equiv) according to method E. The product was purified by preparative TLC (hexane/ethyl acetate 1:1). Yield: 30 mg (79%). White oil. $C_{18}H_{13}NO_3$; MW 291; ^{1}H NMR (acetone-d_6): δ 8.42 (d, J = 7.9 Hz, 1H), 8.28–8.24 (m, 1H), 8.06 (dd, J = 1.5 Hz, J = 8.1 Hz, 1H), 7.94 (dd, J = 0.7 Hz, J = 7.5 Hz, 1H), 7.43–7.41 (m, 3H), 7.35–7.30 (m, 1H), 7.19–7.16 (m, 1H), 6.97–6.93 (m, 1H), 6.88 (dd, J = 1.2 Hz, J = 8.2 Hz, 1H); GC/MS m/z: 291 $(M)^+$.

4.6.49. (3-Methoxyphenyl)-[6-(3-methoxyphenyl)-pyridin-2-yl]-methanone (**16a**)

The title compound was prepared by reaction of (6-bromopyridin-2-yl)-(3-methoxyphenyl)-methanone **14b** (150 mg, 0.51 mmol, 1 equiv) with 3-methoxyphenylboronic acid (94 mg, 0.62 mmol, 1.2 equiv) according to method C. The product was purified by column chromatography (hexane/ethyl acetate 8:2). Yield: 70 mg (43%). $C_{20}H_{17}NO_3$; MW 319; ^{1}H NMR (acetone-d_6): δ 8.19 (dd, J = 1.1 Hz, J = 7.9 Hz, 1H), 8.12 (t, J = 7.9 Hz, 1H), 7.99 (dd, J = 0.9 Hz, J = 7.6 Hz, 1H), 7.79–7.74 (m, 3H), 7.70 (ddd, J = 0.9 Hz, J = 1.8 Hz, J = 7.9 Hz, 1H), 7.48 (t, J = 7.9 Hz, 1H), 7.40 (t, J = 8.1 Hz, 1H), 7.24 (ddd, J = 0.9 Hz, J = 2.6 Hz, J = 8.2 Hz, 1H), 7.02 (ddd, J = 0.7 Hz, J = 2.6 Hz, J = 8.7 Hz, 1H), 3.87 (s, 3H), 3.85 (s, 3H); ^{13}C NMR (acetone-d_6): δ 193.4, 161.3, 160.4, 156.2, 155.6, 140.7, 139.3, 138.8, 130.7, 130.0, 124.5, 123.6, 119.9, 119.6, 116.6, 116.2, 113.0, 55.8, 55.6; IR: 2981, 1658, 1579, 1234 cm^{-1}; GC/MS m/z: 319 $(M)^+$.

4.6.50. (3-Hydroxyphenyl)-[6-(3-hydroxyphenyl)-pyridin-2-yl]-methanone (**16**)

The title compound was prepared by reaction of (3-methoxyphenyl)-[6-(3-methoxyphenyl)-pyridin-2-yl]-methanone **16a** (50 mg, 0.16 mmol, 1 equiv) with boron tribromide (1.6 mmol, 10 equiv) according to method E. The product was purified by preparative TLC (hexane/ethyl acetate 1:1) to afford 32 mg (69%) of the analytically pure product as a beige powder. $C_{18}H_{13}NO_3$; MW 291; ^{1}H NMR (acetone-d_6): δ 8.68 (s, br, 1H), 8.50 (s, br, 1H), 8.13 (dd, J = 1.3 Hz, J = 7.9 Hz, 1H), 8.11–8.07 (m, 1H), 7.90 (dd, J = 1.3 Hz, J = 7.3 Hz, 1H), 7.66–7.63 (m, 2H), 7.63–7.62 (m, 1H), 7.61 (ddd, J = 0.9 Hz, J = 1.6 Hz, J = 7.6 Hz, 1H), 7.41–7.37 (m, 1H), 7.32 (t, J = 8.2 Hz, 1H), 7.14 (ddd, J = 0.9 Hz, J = 2.5 Hz, J = 8.2 Hz, 1H), 6.93 (ddd, J = 0.9 Hz, J = 2.5 Hz, J = 8.2 Hz, 1H); ^{13}C NMR (acetone-d_6): δ 193.9, 158.8, 156.4, 156.1, 139.1, 138.7, 130.7, 130.1, 123.4, 123.3, 120.9, 119.0, 118.2, 117.4, 114.6; IR: 3282, 1641, 1581, 1325, 1213 cm^{-1}; LC/MS m/z: 292 $(M + H)^+$.

4.6.51. [6-(4-Hydroxyphenyl)-pyridin-2-yl]-(3-methoxyphenyl)-methanone (**17a**)

The title compound was prepared by reaction of (6-bromopyridin-2-yl)-(3-methoxyphenyl)-methanone **14b** (150 mg, 0.51 mmol, 1 equiv) with 4-hydroxyphenylboronic acid (84 mg, 0.61 mmol, 1.2 equiv) according to method C. The product was purified by column chromatography (hexane/ethyl acetate 8:2). Yield: 45% (70 mg). $C_{19}H_{15}NO_3$; MW 305; ^{1}H NMR (acetone-d_6): δ 8.73 (s, br, 1H), 8.09 (dd, J = 1.2 Hz, J = 8.0 Hz, 1H), 8.06 (d, J = 7.5 Hz, 1H), 8.04–8.01 (m, 2H), 7.87 (dd, J = 1.5 Hz, J = 7.3 Hz, 1H), 7.76–7.72 (m, 2H), 7.47 (t, J = 7.8 Hz, 1H), 7.23 (ddd, J = 1.0 Hz, J = 2.7 Hz, J = 8.3 Hz, 1H), 6.97–6.93 (m, 2H), 3.87 (s, 3H); ^{13}C NMR (acetone-d_6): δ 193.7, 160.4, 159.9, 156.5, 155.7, 139.0, 138.9, 130.7, 130.0, 129.2, 124.5, 122.4, 122.3, 119.8, 116.5, 116.2, 55.8; GC/MS m/z: 305 $(M)^+$.

4.6.52. (3-Hydroxyphenyl)-[6-(4-hydroxyphenyl)-pyridin-2-yl]-methanone (**17**)

The title compound was prepared by reaction of [6-(4-hydroxyphenyl)-pyridin-2-yl]-(3-methoxyphenyl)-methanone **17a** (30 mg, 0.10 mmol, 1 equiv) with boron tribromide (0.50 mmol, 5 equiv) according to method E. The product was recrystallised in ethyl acetate to afford 15 mg (51%) of the analytically pure compound. $C_{18}H_{13}NO_3$; MW 291; mp: 177–179 °C; ^{1}H NMR (acetone-d_6 + MeOH): δ 8.21–8.16 (m, 1H), 8.15–8.11 (m, 1H), 7.94 (d, J = 8.9 Hz, 2H), 7.90 (s, 1H), 7.52 (d, J = 7.9 Hz, 1H), 7.50–7.48 (m, 1H), 7.35 (t, J = 8.1 Hz, 1H), 7.11–7.08 (m, 1H), 6.91 (d, J = 8.5 Hz, 2H); IR: 3140, 1605, 1453, 1340, 1193 cm^{-1}; LC/MS m/z: 292 $(M + H)^+$.

4.6.53. [6-(4-Methoxy-2-methylphenyl)-pyridin-2-yl]-(3-methoxyphenyl)-methanone (**18a**)

The title compound was prepared by reaction of (6-bromopyridin-2-yl)-(3-methoxyphenyl)-methanone **14b** (200 mg, 0.68 mmol, 1 equiv) with 4-methoxy-2-methylphenylboronic acid (136 mg, 0.82 mmol, 1.2 equiv) according to method D. The product was purified by column chromatography (hexane/ethyl acetate 7:3) to afford 100 mg (44%) of the analytically pure compound. $C_{21}H_{19}NO_3$; MW 333; ^{1}H NMR (acetone-d_6): δ 8.08 (t, J = 7.9 Hz, 1H), 7.94 (dd, J = 0.9 Hz, J = 7.6 Hz, 1H), 7.73 (dd,

J = 0.9 Hz, J = 7.9 Hz, 1H), 7.70–7.66 (m, 2H), 7.46–7.43 (m, 1H), 7.43–7.39 (m, 1H), 7.18 (ddd, J = 1.3 Hz, J = 2.5 Hz, J = 8.2 Hz, 1H), 6.87–6.84 (m, 2H), 3.84 (s, 3H), 3.83 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (acetone-d_6): δ 160.4, 159.4, 155.7, 139.0, 138.5, 138.4, 132.1, 129.8, 127.2, 124.3, 122.4, 119.5, 117.2, 117.1, 116.3, 112.2, 112.1, 55.7, 55.5, 14.4; IR: 2959, 1661, 1579, 1450, 1237 cm^{-1}; GC/MS m/z: 333 $(M)^+$.

4.6.54. [6-(4-Hydroxy-2-methylphenyl)-pyridin-2-yl]-(3-hydroxyphenyl)-methanone (**18**)

The title compound was prepared by reaction of [6-(4-methoxy-2-methylphenyl)-pyridin-2-yl]-(3-methoxyphenyl)-methanone **18a** (90 mg, 0.27 mmol, 1 equiv) with boron tribromide (2.7 mmol, 10 equiv) according to method E. The product was purified by column chromatography (hexane/ethyl acetate 7:3) to afford 45 mg (55%) of the analytically pure compound as a brown oil. $C_{19}H_{15}NO_3$; MW 305; ^{1}H NMR (acetone-d_6): δ 8.60 (s, br, 1H), 8.43 (s, br, 1H), 8.05–8.00 (m, 1H), 7.85 (dd, J = 1.1 Hz, J = 7.8 Hz, 1H), 7.69 (dd, J = 0.9 Hz, J = 7.8 Hz, 1H), 7.55–7.50 (m, 2H), 7.35–7.28 (m, 2H), 7.07 (dd, J = 0.9 Hz, J = 8.1 Hz, 1H), 6.76–6.69 (m, 2H), 2.32 (s, 3H); ^{13}C NMR (acetone-d_6): δ 158.6, 158.0, 138.3, 132.3, 129.9, 127.0, 123.2, 122.1, 120.7, 118.4, 118.0, 113.8, 21.2; IR: 3255, 2924, 1689, 1583, 1219 cm^{-1}; LC/MS m/z: 306 $(M + H)^+$.

4.6.55. [6-(2-Fluoro-4-methoxyphenyl)-pyridin-2-yl]-(3-methoxyphenyl)-methanone (**19a**)

The title compound was prepared by reaction of (6-bromopyridin-2-yl)-(3-methoxyphenyl)-methanone **14b** (170 mg, 0.58 mmol, 1 equiv) with 2-fluoro-4-methoxyphenylboronic acid (119 mg, 0.70 mmol, 1.2 equiv) according to method D. The product was used in the next step without further purification. $C_{20}H_{16}FNO_3$; MW 337.

4.6.56. [6-(2-Fluoro-4-hydroxyphenyl)-pyridin-2-yl]-(3-hydroxyphenyl)-methanone (**19**)

The title compound was prepared by reaction of [6-(2-fluoro-4-methoxyphenyl)-pyridin-2-yl]-(3-methoxyphenyl)-methanone **19a** (100 mg, 0.3 mmol, 1 equiv) with boron tribromide (3.0 mmol, 10 equiv) according to method E. The product was recrystallised in ethyl acetate to afford 50 mg (54%) of the analytically pure product as a yellow powder. $C_{18}H_{12}FNO_3$; MW 309; mp: 246–248 °C; ^{1}H NMR (acetone-d_6): δ 8.27–8.22 (m, 1H), 8.11–8.08 (m, 1H), 7.98–7.95 (m, 1H), 7.84 (t, J = 8.2 Hz, 1H), 7.49 (dt, J = 1.1 Hz, J = 7.8 Hz, 1H), 7.47–7.45 (m, 1H), 7.33 (t, J = 7.9 Hz, 1H), 7.11–7.07 (m, 1H), 6.77–6.73 (m, 1H), 6.69–6.64 (m, 1H); ^{13}C NMR (acetone-d_6): δ 158.7, 137.0, 133.3, 130.8, 129.7, 128.9, 125.9, 122.8, 122.3, 119.3, 119.2, 118.4, 118.2, 117.5, 113.7, 108.2, 104.7; IR: 3251, 3027, 1608, 1468, 1235 cm^{-1}; LC/MS m/z: 310 $(M + H)^+$.

4.6.57. [6-(3-Fluoro-4-methoxyphenyl)-pyridin-2-yl]-(3-methoxyphenyl)-methanone (**20a**)

The title compound was prepared by reaction of (6-bromopyridin-2-yl)-(3-methoxyphenyl)-methanone **14b** (150 mg, 0.51 mmol, 1 equiv) with 3-fluoro-4-methoxyphenylboronic acid (104 mg, 0.61 mmol, 1.2 equiv) according to method D. The product was recrystallised in ethanol to afford 130 mg (76%) of the analytically pure compound as a white powder. $C_{20}H_{16}FNO_3$; MW 337; mp: 100–102 °C; ^{1}H NMR (acetone-d_6): δ 8.17 (dd, J = 1.3 Hz, J = 8.2 Hz, 1H), 8.10 (t, J = 7.6 Hz, 1H), 7.97–7.94 (m, 2H), 7.92 (dd, J = 1.3 Hz, J = 5.7 Hz, 1H), 7.74–7.70 (m, 2H), 7.50–7.46 (m, 1H), 7.28–7.23 (m, 2H), 3.95 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (acetone-d_6): δ 193.5, 160.5, 155.7, 155.1, 152.4, 149.9, 139.3, 138.8, 132.4, 130.0, 124.4, 123.9, 123.2, 122.8, 119.9, 116.2, 115.1, 114.9, 56.6, 55.8; IR: 2926, 1662, 1581, 1283 cm^{-1}; GC/MS m/z: 337 $(M)^+$.

4.6.58. [6-(3-Fluoro-4-hydroxyphenyl)-pyridin-2-yl]-(3-hydroxyphenyl)-methanone (**20**)

The title compound was prepared by reaction of [6-(3-fluoro-4-methoxyphenyl)-pyridin-2-yl]-(3-methoxyphenyl)-methanone **20a** (120 mg, 0.36 mmol, 1 equiv) with pyridinium hydrochloride (36 mmol, 100 equiv) according to method G. The analytically pure product was obtained after recrystallisation with hexane and ethyl acetate as a brown solid. Yield: 103 mg (94%). $C_{18}H_{12}FNO_3$; MW 309; mp: 224–226 °C; ^{1}H NMR (acetone-d_6): δ 8.32 (d, J = 1.9 Hz, 1H), 7.89–7.87 (m, 1H), 7.75–7.74 (m, 1H), 7.38 (dd, J = 2.2 Hz, J = 8.2 Hz, 1H), 7.21 (t, J = 1.6 Hz, 1H), 7.19 (dd, J = 0.6 Hz, J = 8.2 Hz, 1H), 7.15 (t, J = 1.6 Hz, 1H), 6.80 (dd, J = 0.6 Hz, J = 1.6 Hz, 1H), 6.60 (dd, J = 0.9 Hz, J = 1.9 Hz, 1H), 5.35 (d, J = 8.2 Hz, 1H); ^{13}C NMR (acetone-d_6): δ 183.5, 164.7, 161.0, 160.4, 156.5, 149.4, 147.7, 143.6, 143.3, 139.0, 132.2, 129.5, 120.9; IR: 3225, 3027, 1608, 1468, 1285 cm^{-1}; LC/MS m/z: 310 $(M + H)^+$.

4.6.59. [6-(3-Chloro-4-hydroxyphenyl)-pyridin-2-yl]-(3-methoxyphenyl)-methanone (**21a**)

The title compound was prepared by reaction of (6-bromopyridin-2-yl)-(3-methoxyphenyl)-methanone **14b** (200 mg, 0.68 mmol, 1 equiv) with 3-chloro-4-hydroxyphenylboronic acid (141 mg, 0.82 mmol, 1.2 equiv) according to method D. The product was purified by column chromatography (hexane/ethyl acetate 7:3) to afford 120 mg (50%) of the analytically pure compound as white oil. $C_{19}H_{14}ClNO_3$; MW 339; ^{1}H NMR (acetone-d_6): δ 9.13 (s, br, 1H), 8.18 (d, J = 2.2 Hz, 1H), 8.15 (dd, J = 0.8 Hz, J = 8.0 Hz, 1H), 8.10 (t, J = 7.7 Hz, 1H), 7.97 (dd, J = 2.1 Hz, J = 8.4 Hz, 1H), 7.93 (dd, J = 0.9 Hz, J = 7.5 Hz, 1H), 7.76–7.74 (m, 1H), 7.73–7.70 (m, 1H), 7.48 (t, J = 8.0 Hz, 1H), 7.25 (ddd, J = 0.6 Hz, J = 2.8 Hz, J = 8.2 Hz, 1H), 7.13 (d, J = 8.5 Hz, 1H), 3.88 (s, 3H); ^{13}C NMR (acetone-d_6): δ 193.5, 155.7, 155.2, 155.1, 139.3, 132.1, 130.0, 129.3, 128.5, 127.5, 126.9, 124.4, 123.0, 122.7, 120.0, 118.0, 117.9, 116.2, 55.8; GC/MS m/z: 339–341 $(M)^+$.

4.6.60. [6-(3-Chloro-4-hydroxyphenyl)-pyridin-2-yl]-(3-hydroxyphenyl)-methanone (**21**)

The title compound was prepared by reaction of [6-(3-chloro-4-hydroxyphenyl)-pyridin-2-yl]-(3-methoxyphenyl)-methanone **21a** (200 mg, 0.59 mmol, 1 equiv) with pyridinium hydrochloride (59 mmol, 100 equiv) according to method G. The product was purified by recrystallisation in ethanol and ethyl acetate to give 82 mg (43%) of the analytically pure compound as a green powder. $C_{18}H_{12}ClNO_3$; MW 325; mp: 206–208 °C; ^{1}H NMR (acetone-d_6): δ 9.10 (s, br, 1H), 8.76 (s, br, 1H), 8.17 (d, J = 2.2 Hz, 1H), 8.13 (dd, J = 0.9 Hz, J = 7.9 Hz, 1H), 8.10–8.06 (m, 1H), 7.97 (dd, J = 2.2 Hz, J = 8.5 Hz, 1H), 7.88 (dd, J = 0.9 Hz, J = 7.6 Hz, 1H), 7.64–7.60 (m, 2H), 7.42–7.38 (m, 1H), 7.15 (ddd, J = 1.3 Hz, J = 2.2 Hz, J = 7.9 Hz, 1H), 7.13 (d, J = 8.5 Hz, 1H); ^{13}C NMR (acetone-d_6): δ 193.8, 158.1, 156.0, 155.2, 155.1, 139.2, 132.2, 130.1, 129.4, 127.5, 123.3, 122.9, 122.5, 121.8, 120.9, 118.2, 117.8; IR: 3345, 1639, 1580, 1324, 1290 cm^{-1}; LC/MS m/z: 326 $(M + H)^+$.

4.6.61. (6-Bromopyridin-2-yl)-(4-fluoro-3-methoxyphenyl)-methanol (**22c**)

To a solution of 5-bromo-2-fluoroanisole (200 mg, 0.98 mmol, 1 equiv) in anhydrous THF was added granules of magnesium (24 mg, 0.98 mmol, 1 equiv) under nitrogen. The mixture was heated to 60 °C for 2 h. After reaching room temperature, 6-bromopyridin-2-yl carboxaldehyde (182 mg, 0.98 mmol, 1 equiv) was added and the reaction mixture was heated to 80 °C and stirred overnight at 80 °C. The reaction was cooled to room temperature, quenched with brine and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered and concentrated to dryness under vacuum. The product was used

in the next step without further purification. $C_{13}H_{11}BrFNO_2$; MW 312.

4.6.62. (6-Bromopyridin-2-yl)-(4-fluoro-3-methoxyphenyl)-methanone (**22b**)

The title compound was prepared by reaction of (6-bromopyridin-2-yl)-(4-fluoro-3-methoxyphenyl)-methanol **22c** (150 mg, 0.48 mmol, 1 equiv) with 2-iodoxybenzoic acid (269 mg, 0.96 mmol, 2 equiv) according to method B. The product was purified by column chromatography (hexane/ethyl acetate 7:3) to afford 130 mg (87%) of the analytically pure compound as orange oil. $C_{13}H_9BrFNO_2$; MW 310; ^{1}H NMR (acetone-d_6): δ 8.05 (dd, J = 1.3 Hz, J = 7.6 Hz, 1H), 8.02 (t, J = 7.6 Hz, 1H), 7.94 (dd, J = 2.2 Hz, J = 8.5 Hz, 1H), 7.89 (dd, J = 1.3 Hz, J = 7.6 Hz, 1H), 7.74 (ddd, J = 2.2 Hz, J = 4.4 Hz, J = 8.5 Hz, 1H), 7.33–7.28 (m, 1H), 3.98 (s, 3H); ^{13}C NMR (acetone-d_6): δ 190.3, 157.4, 156.5, 148.5, 141.3, 141.0, 133.4, 132.0, 126.0, 124.5, 116.7, 108.3, 56.6; IR: 3058, 1686, 1585, 1514, 1421, 1293 cm^{-1}; LC/MS m/z: 310–312 $(M + H)^+$.

4.6.63. (4-Fluoro-3-methoxyphenyl)-[6-(4-methoxy-3-methylphenyl)-pyridin-2-yl]-methanone (**22a**)

The title compound was prepared by reaction of (6-bromopyridin-2-yl)-(4-fluoro-3-methoxyphenyl)-methanone **22b** (100 mg, 0.32 mmol, 1 equiv) with 4-methoxy-3-methylphenylboronic acid (64 mg, 0.39 mmol, 1.2 equiv) according to method D. The product was purified by column chromatography (hexane/ethyl acetate 7:3) to give 70 mg (62%) of the analytically pure compound. $C_{21}H_{18}FNO_3$; MW 351; ^{1}H NMR (acetone-d_6): δ 8.13 (dd, J = 1.1 Hz, J = 7.8 Hz, 1H), 8.09–8.04 (m, 2H), 7.99 (dd, J = 2.3 Hz, J = 8.6 Hz, 1H), 7.97 (d, J = 1.7 Hz, 1H), 7.91 (dd, J = 1.0 Hz, J = 7.6 Hz, 1H), 7.88–7.84 (m, 1H), 7.35–7.30 (m, 1H), 7.05 (d, J = 8.6 Hz, 1H), 3.97 (s, 3H), 3.90 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (acetone-d_6): δ 190.1, 160.1, 156.5, 155.5, 139.1, 129.8, 127.4, 126.7, 126.1, 122.7, 122.6, 117.0, 116.4, 116.2, 111.1, 56.6, 55.9, 16.5; LC/MS m/z: 352 $(M + H)^+$.

4.6.64. (4-Fluoro-3-hydroxyphenyl)-[6-(4-hydroxy-3-methylphenyl)-pyridin-2-yl]-methanone (**22**)

The title compound was prepared by reaction of (4-fluoro-3-methoxyphenyl)-[6-(4-methoxy-3-methylphenyl)-pyridin-2-yl]-methanone **22a** (30 mg, 0.09 mmol, 1 equiv) with pyridinium hydrochloride (9 mmol, 100 equiv) according to method G. The analytically pure product was obtained after purification by column chromatography (hexane/ethyl acetate 7:3) and preparative HPLC using isopropanol/water as eluent in 66% yield (19 mg). $C_{19}H_{14}FNO_3$; MW 323; ^{1}H NMR (acetone-d_6): δ 9.01 (s, br, 1H), 8.57 (s, br, 1H), 8.07 (dd, J = 1.3 Hz, J = 8.2 Hz, 1H), 8.05–8.01 (m, 1H), 7.93 (dd, J = 0.6 Hz, J = 2.2 Hz, 1H), 7.90 (dd, J = 2.2 Hz, J = 8.8 Hz, 1H), 7.85–7.82 (m, 2H), 7.75 (ddd, J = 2.2 Hz, J = 4.7 Hz, J = 8.5 Hz, 1H), 7.32–7.27 (m, 1H), 6.93 (d, J = 8.2 Hz, 1H), 2.27 (s, 3H); ^{13}C NMR (acetone-d_6): δ 193.2, 163.8, 158.0, 157.9, 156.8, 155.6, 139.0, 130.5, 126.6, 124.9, 122.4, 122.3, 122.2, 118.8, 116.6, 116.5, 115.9, 16.4; IR: 3332, 1656, 1583, 1181 cm^{-1}; LC/MS m/z: 324 $(M + H)^+$.

4.6.65. (6-Bromopyridin-2-yl)-(3-methoxy-4-methylphenyl)-methanol (**23c**)

To a solution of 5-bromo-2-methylanisole (200 mg, 0.99 mmol, 1 equiv) in anhydrous THF was added granules of magnesium (24 mg, 0.99 mmol, 1 equiv) under nitrogen. The mixture was heated to 60 °C for 2 h. After cooling down to room temperature, 6-bromopyridin-2-yl carboxaldehyde (182 mg, 0.99 mmol, 1 equiv) was added and the reaction mixture was heated to 80 °C and stirred overnight at 80 °C. The reaction was cooled to room temperature, quenched with brine and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered and concentrated to dryness under vacuum. The product was purified by column chromatography (hexane/ethyl acetate 8:2) to afford the analytically pure compound in 76% yield (232 mg) as a yellow oil. $C_{14}H_{14}BrNO_2$; MW 308; ^{1}H NMR (acetone-d_6): δ 7.71 (t, J = 7.8 Hz, 1H), 7.60 (d, J = 7.7 Hz, 1H), 7.44 (d, J = 7.9 Hz, 1H), 7.07–7.04 (m, 2H), 6.89 (dd, J = 1.3 Hz, J = 7.5 Hz, 1H), 5.75 (d, J = 4.5 Hz, 1H), 5.11 (d, J = 4.5 Hz, 1H), 3.80 (s, 3H), 2.12 (s, 3H); ^{13}C NMR (acetone-d_6): δ 166.6, 158.6, 143.4, 141.3, 140.6, 131.0, 127.2, 126.0, 120.3, 119.2, 109.3, 76.5, 55.6, 16.0; IR: 3396, 2923, 1581, 1555, 1252 cm^{-1}; GC/MS m/z: 307–309 $(M)^+$.

4.6.66. (6-Bromopyridin-2-yl)-(3-methoxy-4-methylphenyl)-methanone (**23b**)

The title compound was prepared by reaction of (6-bromopyridin-2-yl)-(3-methoxy-4-methylphenyl)-methanol **23c** (60 mg, 0.19 mmol, 1 equiv) with 2-iodoxybenzoic acid (106 mg, 0.38 mmol, 2 equiv) according to method B. The product was purified by column chromatography (hexane/ethyl acetate 8:2) to afford the analytically pure compound in 98% yield (57 mg) as a yellow powder. $C_{14}H_{12}BrNO_2$; MW 306; ^{1}H NMR (acetone-d_6): δ 8.03–8.01 (m, 1H), 8.00 (d, J = 1.4 Hz, 1H), 7.89–7.85 (m, 1H), 7.69 (d, J = 1.4 Hz, 1H), 7.58 (dd, J = 1.5 Hz, J = 7.7 Hz, 1H), 7.30 (dd, J = 0.9 Hz, J = 7.7 Hz, 1H), 3.92 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (acetone-d_6): δ 191.5, 158.5, 157.1, 141.2, 141.1, 135.7, 133.6, 131.6, 131.0, 124.8, 124.3, 112.4, 55.8, 16.6; IR: 2929, 1651, 1553, 1302, 1247 cm^{-1}; LC/MS m/z: 306–308 $(M + H)^+$.

4.6.67. (3-Methoxy-4-methylphenyl)-[6-(4-methoxy-3-methylphenyl)-pyridin-2-yl]-methanone (**23a**)

The title compound was prepared by reaction of (6-bromopyridin-2-yl)-(3-methoxy-4-methylphenyl)-methanone **23b** (50 mg, 0.16 mmol, 1 equiv) with 4-methoxy-3-methylphenylboronic acid (31 mg, 0.19 mmol, 1.2 equiv) according to method D. The product was purified by column chromatography (hexane/ethyl acetate 7:3) to afford the analytically pure compound in 68% yield (38 mg) as an orange powder. $C_{22}H_{21}NO_3$; MW 347; ^{1}H NMR (acetone-d_6): δ 8.11 (dd, J = 0.9 Hz, J = 8.1 Hz, 1H), 8.05 (t, J = 7.5 Hz, 1H), 8.01–7.97 (m, 2H), 7.86 (dd, J = 0.9 Hz, J = 7.5 Hz, 1H), 7.82 (d, J = 1.6 Hz, 1H), 7.71 (dd, J = 1.4 Hz, J = 7.7 Hz, 1H), 7.32 (dd, J = 0.6 Hz, J = 7.7 Hz, 1H), 7.04 (d, J = 8.5 Hz, 1H), 3.91 (s, 3H), 3.90 (s, 3H), 2.29 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (acetone-d_6): δ 193.2, 160.1, 158.4, 156.4, 156.1, 139.0, 133.0, 131.4, 130.8, 129.8, 127.3, 125.0, 122.5, 122.4, 113.3, 112.6, 112.1, 111.1, 55.9, 55.8, 16.6, 16.5; IR: 2916, 1651, 1566, 1233 cm^{-1}; LC/MS m/z: 348 $(M + H)^+$.

4.6.68. (3-Hydroxy-4-methylphenyl)-[6-(4-hydroxy-3-methylphenyl)-pyridin-2-yl]-methanone (**23**)

The title compound was prepared by reaction of (3-methoxy-4-methylphenyl)-[6-(4-methoxy-3-methylphenyl)-pyridin-2-yl]-methanone **23a** (30 mg, 0.09 mmol, 1 equiv) with boron trifluoride dimethylsulfide complex (6.3 mmol, 70 equiv) according to method F. The product was purified by column chromatography (hexane/ethyl acetate 7:3) then by preparative HPLC with isopropanol/water as eluent to afford 10 mg (35%) of the analytically pure compound as a white powder. $C_{20}H_{17}NO_3$; MW 319; ^{1}H NMR (acetone-d_6): δ 8.60 (s, br, 2H), 8.05 (dd, J = 1.4 Hz, J = 8.0 Hz, 1H), 8.01 (t, J = 8.3 Hz, 1H), 7.94–7.92 (m, 1H), 7.84 (dd, J = 2.1 Hz, J = 8.4 Hz, 1H), 7.77 (dd, J = 1.3 Hz, J = 7.3 Hz, 1H), 7.66 (d, J = 1.6 Hz, 1H), 7.61 (dd, J = 1.8 Hz, J = 7.8 Hz, 1H), 7.27 (d, J = 7.8 Hz, 1H), 6.93 (d, J = 8.3 Hz, 1H), 2.31 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (acetone-d_6): δ 190.9, 174.6, 161.0, 138.8, 131.2, 130.4, 126.6, 123.7, 122.0, 121.9, 118.8, 16.5, 16.4; IR: 3340, 1671, 1585 cm^{-1}; LC/MS m/z: 320 $(M + H)^+$.

*4.6.69. (6-Bromopyridin-2-yl)-(5-fluoro-3-methoxyphenyl)-methanol (**24c**)*

To a solution of 3-bromo-5-fluoroanisole (250 mg, 1.22 mmol, 1 equiv) in anhydrous THF was added granules of magnesium (32 mg, 1.28 mmol, 1.05 equiv) under nitrogen. The mixture was heated to 60 °C for 2 h. After cooling down to room temperature, 6-bromopyridin-2-yl carboxaldehyde (271 mg, 1.47 mmol, 1.2 equiv) was added and the reaction mixture was stirred at 80 °C overnight. The reaction was cooled to room temperature, quenched with brine and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered and concentrated to dryness under vacuum. The product was purified by column chromatography (hexane/ethyl acetate 8:2) to afford the analytically pure compound in 21% yield (80 mg). $C_{13}H_{11}BrFNO_2$; MW 312; ^{1}H NMR (acetone-d_6): δ 7.74 (t, J = 7.6 Hz, 1H), 7.64–7.61 (m, 1H), 7.47 (dd, J = 0.9 Hz, J = 7.2 Hz, 1H), 6.92–6.90 (m, 1H), 6.81 (ddd, J = 0.6 Hz, J = 1.3 Hz, J = 9.1 Hz, 1H), 6.59 (dt, J = 2.5 Hz, J = 10.7 Hz, 1H), 5.77 (d, J = 4.7 Hz, 1H), 5.35 (d, J = 4.7 Hz, 1H), 3.79 (s, 3H); ^{13}C NMR (acetone-d_6): δ 165.8, 165.3, 140.8, 127.5, 120.3, 109.4, 106.1, 105.9, 101.0, 100.8, 75.8, 56.0; LC/MS m/z: 312–314 $(M + H)^+$.

*4.6.70. (6-Bromopyridin-2-yl)-(5-fluoro-3-methoxyphenyl)-methanone (**24b**)*

The title compound was prepared by reaction of (6-bromopyridin-2-yl)-(5-fluoro-3-methoxyphenyl)-methanol **24c** (190 mg, 0.61 mmol, 1 equiv) with 2-iodoxybenzoic acid (342 mg, 1.22 mmol, 2 equiv) according to method B. The product was purified by column chromatography (hexane/ethyl acetate 17:3) to afford 150 mg (79%) of the analytically pure compound as a brown solid. $C_{13}H_9BrFNO_2$; MW 310; ^{1}H NMR (acetone-d_6): δ 8.08 (dd, J = 0.9 Hz, J = 7.6 Hz, 1H), 8.03 (t, J = 7.6 Hz, 1H), 7.91 (dd, J = 0.9 Hz, J = 7.6 Hz, 1H), 7.53–7.51 (m, 1H), 7.41 (ddd, J = 1.3 Hz, J = 2.5 Hz, J = 9.1 Hz, 1H), 7.05 (dt, J = 2.2 Hz, J = 10.4 Hz, 1H), 3.91 (s, 3H); ^{13}C NMR (acetone-d_6): δ 190.6, 164.9, 161.9, 161.8, 141.4, 132.2, 124.6, 110.2, 107.0, 56.4; IR: 3080, 2980, 1668, 1555, 1152 cm^{-1}; LC/MS m/z: 310–312 $(M + H)^+$.

*4.6.71. (5-Fluoro-3-methoxyphenyl)-[6-(4-methoxy-3-methylphenyl)-pyridin-2-yl]-methanone (**24a**)*

The title compound was prepared by reaction of (6-bromopyridin-2-yl)-(5-fluoro-3-methoxyphenyl)-methanone **24b** (80 mg, 0.26 mmol, 1 equiv) with 4-methoxy-3-methylphenylboronic acid (52 mg, 0.31 mmol, 1.2 equiv) according to method D. The analytically pure product was obtained after purification by column chromatography (gradient hexane/ethyl acetate from 1:0 to 8:2) in 81% yield (74 mg). $C_{21}H_{18}FNO_3$; MW 351; ^{1}H NMR (acetone-d_6): δ 8.13 (dd, J = 1.3 Hz, J = 8.2 Hz, 1H), 8.07 (t, J = 7.9 Hz, 1H), 7.99–7.96 (m, 2H), 7.93 (dd, J = 0.9 Hz, J = 7.6 Hz, 1H), 7.66–7.64 (m, 1H), 7.54 (ddd, J = 1.3 Hz, J = 2.5 Hz, J = 9.5 Hz, 1H), 7.06–7.05 (m, 1H), 7.04–7.02 (m, 1H), 3.91 (s, 3H), 3.90 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (acetone-d_6): δ 192.1, 161.8, 161.7, 160.2, 154.9, 139.2, 131.2, 129.9, 127.4, 126.7, 123.0, 122.7, 113.5, 111.1, 110.7, 110.5, 106.7, 106.5, 56.4, 55.9, 16.5; LC/MS m/z: 352 $(M + H)^+$.

*4.6.72. (5-Fluoro-3-hydroxyphenyl)-[6-(4-hydroxy-3-methylphenyl)-pyridin-2-yl]-methanone (**24**)*

The title compound was prepared by reaction of (5-fluoro-3-methoxyphenyl)-[6-(4-methoxy-3-methylphenyl)-pyridin-2-yl]-methanone **24a** (39 mg, 0.11 mmol, 1 equiv) with pyridinium hydrochloride (11 mmol, 100 equiv) according to method G. The product was purified by column chromatography (hexane/ethyl acetate 6:4) to give 10 mg (28%) of the analytically pure compound as a yellow solid. $C_{19}H_{14}FNO_3$; MW 323; ^{1}H NMR (acetone-d_6): δ 9.14 (s, br, 1H), 8.58 (s, br, 1H), 7.86 (dd, J = 1.3 Hz, J = 8.2 Hz, 1H), 7.84–7.80 (m, 1H), 7.72–7.70 (m, 1H), 7.65 (dd, J = 0.9 Hz, J = 7.3 Hz, 1H), 7.63–7.59 (m, 1H), 7.32–7.30 (m, 1H), 7.22 (ddd, J = 1.3 Hz, J = 2.2 Hz, J = 9.5 Hz, 1H), 6.71 (d, J = 8.5 Hz, 1H), 6.68 (dt, J = 2.2 Hz, J = 10.4 Hz, 1H), 2.27 (s, 3H); ^{13}C NMR (acetone-d_6): δ 192.4, 164.9, 159.6, 159.5, 155.1, 140.1, 140.0, 139.0, 130.6, 130.5, 126.6, 122.7, 122.3, 115.9, 115.1, 109.6, 109.4, 107.8, 16.4; IR: 3399, 2921, 1613, 1584, 1146 cm^{-1}; LC/MS m/z: 324 $(M + H)^+$.

4.7. Biological assays

[2,4,6,7-^{3}H]-E2 and [2,4,6,7-^{3}H]-E1 were bought from Perkin–Elmer, Boston. Quickszint Flow 302 scintillator fluid was bought from Zinsser Analytic, Frankfurt. 17β-HSD2 and 17β-HSD1 were obtained from human placenta according to previously described procedures [46,48,49]. Fresh human placenta was homogenised and centrifuged. The pellet fraction contains the microsomal 17β-HSD2, while 17β-HSD1 was obtained after precipitation with ammonium sulfate from the cytosolic fraction.

4.7.1. Inhibition of 17β-HSD2

Inhibitory activities were evaluated by a well established method with minor modifications [44,46,48,50]. Briefly, the microsomal enzyme was incubated with NAD^+ [1500 μM] in the presence of potential inhibitors at 37 °C in a phosphate buffer (50 mM) supplemented with 20% of glycerol and EDTA 1 mM. Inhibitor stock solutions were prepared in DMSO. Final concentration of DMSO was adjusted to 1% in all samples. The enzymatic reaction was started by addition of a mixture of unlabeled- and [2,4,6,7-^{3}H]-E2 (final concentration: 500 nM, 0.11 μCi). After 20 min at 37 °C, the incubation was stopped with $HgCl_2$ and the mixture was extracted with ether. After evaporation, the steroids were dissolved in acetonitrile/water (45:55). E1 and E2 were separated using acetonitrile/water (45:55) as mobile phase in a C18 rp chromatography column (Nucleodur C18 Gravity, 3 μm, Macherey-Nagel, Düren) connected to a HPLC-system (Agilent 1100 Series, Agilent Technologies, Waldbronn). Detection and quantification of the steroids were performed using a radioflow detector (Berthold Technologies, Bad Wildbad). The conversion rate was calculated according to following equation: %conversion = (%(E1)/(%(E1) + %(E2))) × 100. Each value was calculated from at least three independent experiments.

4.7.2. Inhibition of 17β-HSD1

The 17β-HSD1 inhibition assay was performed similarly to the 17β-HSD2 procedure. The cytosolic fraction was incubated with NADH [500 μM], test compound and a mixture of unlabeled- and [2,4,6,7-^{3}H]-E1 (final concentration: 500 nM, 0.15 μCi) for 10 min. Further treatment of the samples and HPLC separation was carried out as mentioned above.

4.7.3. ER affinity

The binding affinity of selected compounds to the ERα and ERβ was determined according to Zimmermann et al. [51] using recombinant human proteins. Briefly, 0.25 pmol of ERα or ERβ, respectively, were incubated with [^{3}H]-E2 (10 nM) and test compound for 1 h at room temperature. The potential inhibitors were dissolved in DMSO (5% final concentration). Evaluation of non-specific-binding was performed with diethylstilbestrol (10 μM). After incubation, ligand–receptor complexes were selectively bound to hydroxyapatite (5 g/60 mL TE-buffer). The formed complex was separated, washed and resuspended in ethanol. For radiodetection, scintillator cocktail (Quickszint 212, Zinsser Analytic, Frankfurt) was added and samples were measured in a liquid scintillation counter (Rack Beta Primo 1209, Wallac, Turku). From these results the percentage of [^{3}H]-E2 displacement by the compounds was calculated. The plot of % displacement versus

compound concentration resulted in sigmoidal binding curves. The compound concentration to displace 50% of the receptor bound [^{3}H]-E2 were determined. Unlabeled E2 was used as a reference. For determination of the relative binding affinity the ratio was calculated according to the following equation: RBA[%] = (IC_{50}(E2) /IC_{50}(compound)) × 100 [52]. This results in an RBA value of 100% for E2. After the assay was established and validated a modification was made to increase throughput. Compounds were tested at concentrations of 1000 × IC_{50}(E2). Compounds with less than 50% displacement of [^{3}H]-E2 at a concentration of 1000 × IC_{50}(E2) were classified as RBA <0.1%.

Acknowledgments

We are grateful to the Deutsche Forschungsgemeinschaft for financial support (HA1315/12-1). We thank Victoria Krämer, Jeannine Jung, Laura Schrobildgen and Jörg Haupenthal for their help in performing the enzyme inhibition tests (17β-HSD2, 17β-HSD1) and the ER tests.

References

[1] J.E. Compston, Sex steroids and bone, Physiol. Rev. 81 (2001) 419–447.
[2] U.A. Liberman, S.R. Weiss, J. Bröll, H.W. Minne, H. Quan, N.H. Bell, J. Rodriguez-Portales, R.W. Downs Jr., J. Dequeker, M. Favus, E. Seeman, R.R. Recker, T. Capizzi, A.C.I. Santora, A. Lombardi, R.V. Shah, L.J. Hirsch, D.B. Karpf, Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. The Alendronate Phase III Osteoporosis Treatment Study Group, N. Engl. J. Med. 333 (1995) 1437–1443.
[3] D.C. Bauer, D.M. Black, P. Garnero, M. Hochberg, S. Ott, J. Orloff, D.E. Thompson, S.K. Ewing, P.D. Delmas, Change in bone turnover and hip, non-spine, and vertebral fracture in alendronate-treated women: the fracture intervention trial, J. Bone Miner. Res. 19 (2004) 1250–1258.
[4] E. Orwoll, M. Ettinger, S. Weiss, P. Miller, D. Kendler, J. Graham, S. Adami, K. Weber, R. Lorenc, P. Pietschmann, K. Vandormael, A. Lombardi, Alendronate for the treatment of osteoporosis in men, N. Engl. J. Med. 343 (2000) 604–610.
[5] B. Ettinger, D.M. Black, B.H. Mitlak, R.K. Knickerbocker, T. Nickelsen, H.K. Genant, C. Christiansen, P.D. Delmas, J.R. Zanchetta, J. Stakkestad, C.C. Glüer, K. Krueger, F.J. Cohen, S. Eckert, K.E. Ensrud, L.V. Avioli, P. Lips, S.R. Cummings, Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators, JAMA 282 (1999) 637–645.
[6] E. Barrett-Connor, L. Mosca, P. Collins, M.J. Geiger, D. Grady, M. Kornitzer, M.A. McNabb, N.K. Wenger, Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women, N. Engl. J. Med. 355 (2006) 125–137.
[7] R. Rizzoli, U. Yasothan, P. Kirkpatrick, Denosumab, Nat. Rev. Drug Discov. 9 (2010) 591–592.
[8] M. McClung, Role of RANKL inhibition in osteoporosis, Arthritis Res. Ther. 9 (Suppl. 1) (2007) 3.
[9] S. Boonen, J.D. Adachi, Z. Man, S.R. Cummings, K. Lippuner, O. Törring, J.C. Gallagher, J. Farrerons, A. Wang, N. Franchimont, J. San Martin, A. Grauer, M. McClung, Treatment with Denosumab reduces the incidence of new vertebral and hip fractures in postmenopausal women at high risk, J. Clin. Endocrinol. Metab. 96 (2011) 1727–1736.
[10] R.T. Turner, B.L. Riggs, T.C. Spelsberg, Skeletal effects of estrogen, Endocr. Rev. 15 (1994) 275–300.
[11] E.F. Eriksen, Cellular mechanisms of bone remodeling, Rev. Endocr. Metab. Disord. 11 (2010) 219–227.
[12] A. Mizuno, N. Amizuka, K. Irie, A. Murakami, N. Fujise, T. Kanno, Y. Sato, N. Nakagawa, H. Yasuda, S. Mochizuki, T. Gomibuchi, K. Yano, N. Shima, N. Washida, E. Tsuda, T. Morinaga, K. Higashio, H. Ozawa, Severe osteoporosis in mice lacking osteoclastogenesis inhibitory factor/osteoprotegerin, Biochem. Biophys. Res. Commun. 247 (1998) 610–615.
[13] N. Bucay, I. Sarosi, C.R. Dunstan, S. Morony, J. Tarpley, C. Capparelli, S. Scully, H.L. Tan, W. Xu, D.L. Lacey, W.J. Boyle, W.S. Simonet, Osteoprotegerin-deficient mice develop early onset osteoporosis and arterial calcification, Genes Dev. 12 (1998) 1260–1268.
[14] Y.Y. Kong, H. Yoshida, I. Sarosi, H.L. Tan, E. Timms, C. Capparelli, S. Morony, A.J. Oliveira-dos-Santos, G. Van, A. Itie, W. Khoo, A. Wakeham, C.R. Dunstan, D.L. Lacey, T.W. Mak, W.J. Boyle, J.M. Penninger, OPGL is a key regulator of osteoclastogenesis, lymphocyte development and lymph-node organogenesis, Nature 397 (1999) 315–323.
[15] Y. Dong, Q.Q. Qiu, J. Debear, W.F. Lathrop, D.R. Bertolini, P.P. Tamburini, 17Beta-hydroxysteroid dehydrogenases in human bone cells, J. Bone Miner. Res. 13 (1998) 1539–1546.
[16] A. Cavalli, A. Bisi, C. Bertucci, C. Rosini, A. Paluszcak, S. Gobbi, E. Giorgio, A. Rampa, F. Belluti, L. Piazzi, P. Valenti, R.W. Hartmann, M. Recanatini, Enantioselective nonsteroidal aromatase inhibitors identified through a multidisciplinary medicinal chemistry approach, J. Med. Chem. 48 (2005) 7282–7289.
[17] M.P. Leze, M. Le Borgne, P. Pinson, A. Palusczak, M. Duflos, G. Le Baut, R.W. Hartmann, Synthesis and biological evaluation of 5-[(aryl)(1H-imidazol-1-yl)methyl]-1H-indoles: potent and selective aromatase inhibitors, Bioorg. Med. Chem. Lett. 16 (2006) 1134–1137.
[18] S. Gobbi, A. Cavalli, M. Negri, K.E. Schewe, F. Belluti, L. Piazzi, R.W. Hartmann, M. Recanatini, A. Bisi, Imidazolylmethylbenzophenones as highly potent aromatase inhibitors, J. Med. Chem. 50 (2007) 3420–3422.
[19] S. Haidar, P.B. Ehmer, S. Barassin, C. Batzl-Hartmann, R.W. Hartmann, Effects of novel 17alpha-hydroxylase/C17, 20-lyase (P450 17, CYP 17) inhibitors on androgen biosynthesis *in vitro* and *in vivo*, J. Steroid Biochem. Mol. Biol. 84 (2003) 555–562.
[20] F. Leroux, T.U. Hutschenreuter, C. Charrière, R. Scopelliti, R.W. Hartmann, *N*-(4-biphenylmethyl)imidazoles as potential therapeutics for the treatment of prostate cancer: metabolic robustness due to fluorine substitution? Helv. Chim. Acta 86 (2003) 2671–2686.
[21] C. Jagusch, M. Negri, U.E. Hille, Q. Hu, M. Bartels, K. Jahn-Hoffmann, M.A. Pinto-Bazurco Mendieta, B. Rodenwaldt, U. Müller-Vieira, D. Schmidt, T. Lauterbach, M. Recanatini, A. Cavalli, R.W. Hartmann, Synthesis, biological evaluation and molecular modelling studies of methyleneimidazole substituted biaryls as inhibitors of human 17alpha-hydroxylase-17,20-lyase (CYP17). Part I: heterocyclic modifications of the core structure, Bioorg. Med. Chem. 16 (2008) 1992–2010.
[22] U.E. Hille, Q. Hu, C. Vock, M. Negri, M. Bartels, U. Müller-Vieira, T. Lauterbach, R.W. Hartmann, Novel CYP17 inhibitors: synthesis, biological evaluation, structure–activity relationships and modelling of methoxy- and hydroxy-substituted methyleneimidazolyl biphenyls, Eur. J. Med. Chem. 44 (2009) 2765–2775.
[23] E. Baston, R.W. Hartmann, *N*-substituted 4-(5-indolyl)benzoic acids. Synthesis and evaluation of steroid 5alpha-reductase type I and II inhibitory activity, Bioorg. Med. Chem. Lett. 9 (1999) 1601–1606.
[24] F. Picard, E. Baston, W. Reichert, R.W. Hartmann, Synthesis of *N*-substituted piperidine-4-(benzylidene-4-carboxylic acids) and evaluation as inhibitors of steroid-5alpha-reductase type 1 and 2, Bioorg. Med. Chem. 8 (2000) 1479–1487.
[25] E. Baston, A. Palusczak, R.W. Hartmann, 6-Substituted 1H-quinolin-2-ones and 2-methoxy-quinolines: synthesis and evaluation as inhibitors of steroid 5alpha reductases types 1 and 2, Eur. J. Med. Chem. 35 (2000) 931–940.
[26] M. Frotscher, E. Ziegler, S. Marchais-Oberwinkler, P. Kruchten, A. Neugebauer, L. Fetzer, C. Scherer, U. Müller-Vieira, J. Messinger, H. Thole, R.W. Hartmann, Design, synthesis, and biological evaluation of (hydroxyphenyl)naphthalene and -quinoline derivatives: potent and selective nonsteroidal inhibitors of 17beta-hydroxysteroid dehydrogenase type 1 (17beta-HSD1) for the treatment of estrogen-dependent diseases, J. Med. Chem. 51 (2008) 2158–2169.
[27] S. Marchais-Oberwinkler, P. Kruchten, M. Frotscher, E. Ziegler, A. Neugebauer, U. Bhoga, E. Bey, U. Müller-Vieira, J. Messinger, H. Thole, R.W. Hartmann, Substituted 6-phenyl-2-naphthols. Potent and selective nonsteroidal inhibitors of 17beta-hydroxysteroid dehydrogenase type 1 (17beta-HSD1): design, synthesis, biological evaluation, and pharmacokinetics, J. Med. Chem. 51 (2008) 4685–4698.
[28] E. Bey, S. Marchais-Oberwinkler, P. Kruchten, M. Frotscher, R. Werth, A. Oster, O. Algül, A. Neugebauer, R.W. Hartmann, Design, synthesis and biological evaluation of bis(hydroxyphenyl) azoles as potent and selective non-steroidal inhibitors of 17beta-hydroxysteroid dehydrogenase type 1 (17beta-HSD1) for the treatment of estrogen-dependent diseases, Bioorg. Med. Chem. 16 (2008) 6423–6435.
[29] E. Bey, S. Marchais-Oberwinkler, R. Werth, M. Negri, Y.A. Al-Soud, P. Kruchten, A. Oster, M. Frotscher, B. Birk, R.W. Hartmann, Design, synthesis, biological evaluation and pharmacokinetics of bis(hydroxyphenyl) substituted azoles, thiophenes, benzenes, and aza-benzenes as potent and selective nonsteroidal inhibitors of 17beta-hydroxysteroid dehydrogenase type 1 (17beta-HSD1), J. Med. Chem. 51 (2008) 6725–6739.
[30] E. Bey, S. Marchais-Oberwinkler, M. Negri, P. Kruchten, A. Oster, T. Klein, A. Spadaro, R. Werth, M. Frotscher, B. Birk, R.W. Hartmann, New insights into the SAR and binding modes of bis(hydroxyphenyl)thiophenes and -benzenes: influence of additional substituents on 17beta-hydroxysteroid dehydrogenase type 1 (17beta-HSD1) inhibitory activity and selectivity, J. Med. Chem. 52 (2009) 6724–6743.
[31] A. Oster, T. Klein, R. Werth, P. Kruchten, E. Bey, M. Negri, S. Marchais-Oberwinkler, M. Frotscher, R.W. Hartmann, Novel estrone mimetics with high 17beta-HSD1 inhibitory activity, Bioorg. Med. Chem. 18 (2010) 3494–3505.
[32] A. Oster, S. Hinsberger, R. Werth, S. Marchais-Oberwinkler, M. Frotscher, R.W. Hartmann, Bicyclic substituted hydroxyphenylmethanones as novel inhibitors of 17beta-hydroxysteroid dehydrogenase type 1 (17beta-HSD1) for the treatment of estrogen-dependent diseases, J. Med. Chem. 53 (2010) 8176–8186.
[33] A. Oster, T. Klein, C. Henn, R. Werth, S. Marchais-Oberwinkler, M. Frotscher, R.W. Hartmann, Bicyclic substituted hydroxyphenylmethanone type inhibitors of 17 beta-hydroxysteroid dehydrogenase type 1 (17 beta-HSD1): the role of the bicyclic moiety, ChemMedChem 6 (2011) 476–487.

[34] S. Marchais-Oberwinkler, M. Wetzel, E. Ziegler, P. Kruchten, R. Werth, C. Henn, R.W. Hartmann, M. Frotscher, New drug-like hydroxyphenylnaphthol steroidomimetics as potent and selective 17beta-hydroxysteroid dehydrogenase type 1 inhibitors for the treatment of estrogen-dependent diseases, J. Med. Chem. 54 (2011) 534–547.
[35] K. Sam, F. Labrie, D. Poirier, *N*-Butyl-*N*-methyl-11-(3′-hydroxy-21′, 17′-carbolactone-19′-nor-17′alpha-pregna-1′,3′, 5′(10′)-trien-7′alpha-yl)-undecanamide: an inhibitor of type 2 17beta-hydroxysteroid dehydrogenase that does not have oestrogenic or androgenic activity, Eur. J. Med. Chem. 35 (2000) 217–225.
[36] D. Poirier, P. Bydal, M.R. Tremblay, K.M. Sam, V. Luu-The, Inhibitors of type II 17beta-hydroxysteroid dehydrogenase, Mol. Cell. Endocrinol. 171 (2001) 119–128.
[37] P. Bydal, S. Auger, D. Poirier, Inhibition of type 2 17beta-hydroxysteroid dehydrogenase by estradiol derivatives bearing a lactone on the D-ring: structure–activity relationships, Steroids 69 (2004) 325–342.
[38] J. Wood, C.M. Bagi, C. Akuche, A. Bacchiocchi, J. Baryza, M.L. Blue, C. Brennan, A.M. Campbell, S. Choi, J.H. Cook, P. Conrad, B.R. Dixon, P.P. Ehrlich, T. Gane, D. Gunn, T. Joe, J.S. Johnson, J. Jordan, R. Kramss, P. Liu, J. Levy, D.B. Lowe, I. McAlexander, R. Natero, A.M. Redman, W.J. Scott, C. Town, M. Wang, Y. Wang, Z. Zhang, 4,5-Disubstituted cis-pyrrolidinones as inhibitors of type II 17beta-hydroxysteroid dehydrogenase. Part 3. Identification of lead candidate, Bioorg. Med. Chem. Lett. 16 (2006) 4965–4968.
[39] S. Marchais-Oberwinkler, C. Henn, G. Möller, T. Klein, M. Negri, A. Oster, A. Spadaro, R. Werth, M. Wetzel, K. Xu, M. Frotscher, R.W. Hartmann, J. Adamski, 17beta-Hydroxysteroid dehydrogenases (17beta-HSDs) as therapeutic targets: protein structures, functions, and recent progress in inhibitor development, J. Steroid Biochem. Mol. Biol. (2011).
[40] M. Wetzel, S. Marchais-Oberwinkler, R.W. Hartmann, 17beta-HSD2 inhibitors for the treatment of osteoporosis: identification of a promising scaffold, Bioorg. Med. Chem. 19 (2011) 807–815.
[41] C.M. Bagi, J. Wood, D. Wilkie, B. Dixon, Effect of 17beta-hydroxysteroid dehydrogenase type 2 inhibitor on bone strength in ovariectomized cynomolgus monkeys, J. Musculoskelet. Neuronal Interact. 8 (2008) 267–280.
[42] N. Miyaura, A. Suzuki, Palladium-catalyzed cross-coupling reactions of organoboron compounds, Chem. Rev. 95 (1995) 2457–2483.
[43] M.V. Bhatt, S.U. Kulkarni, Cleavage of ethers, Synthesis 1983 (1983) 249–282.
[44] K.M. Sam, S. Auger, V. Luu-The, D. Poirier, Steroidal spiro-gamma-lactones that inhibit 17beta-hydroxysteroid dehydrogenase activity in human placental microsomes, J. Med. Chem. 38 (1995) 4518–4528.
[45] W. Qiu, R.L. Campbell, A. Gangloff, P. Dupuis, R.P. Boivin, M.R. Tremblay, D. Poirier, S.X. Lin, A concerted, rational design of type 1 17beta-hydroxysteroid dehydrogenase inhibitors: estradiol-adenosine hybrids with high affinity, Faseb J. 16 (2002) 1829–1831.
[46] P. Kruchten, R. Werth, S. Marchais-Oberwinkler, M. Frotscher, R.W. Hartmann, Development of a biological screening system for the evaluation of highly active and selective 17beta-HSD1-inhibitors as potential therapeutic agents, Mol. Cell. Endocrinol. 301 (2009) 154–157.
[47] Y.A. Al-Soud, E. Bey, A. Oster, S. Marchais-Oberwinkler, R. Werth, P. Kruchten, M. Frotscher, R.W. Hartmann, The role of the heterocycle in bis(hydroxyphenyl)triazoles for inhibition of 17beta-hydroxysteroid dehydrogenase (17beta-HSD) type 1 and type 2, Mol. Cell. Endocrinol. 301 (2009) 212–215.
[48] S.X. Lin, F. Yang, J.Z. Jin, R. Breton, D.W. Zhu, V. Luu-The, F. Labrie, Subunit identity of the dimeric 17 beta-hydroxysteroid dehydrogenase from human placenta, J. Biol. Chem. 267 (1992) 16182–16187.
[49] D.W. Zhu, X. Lee, R. Breton, D. Ghosh, W. Pangborn, W.L. Duax, S.X. Lin, Crystallization and preliminary X-ray diffraction analysis of the complex of human placental 17beta-hydroxysteroid dehydrogenase with $NADP^+$, J. Mol. Biol. 234 (1993) 242–244.
[50] K.M. Sam, R.P. Boivin, M.R. Tremblay, S. Auger, D. Poirier, C16 and C17 derivatives of estradiol as inhibitors of 17beta-hydroxysteroid dehydrogenase type 1: chemical synthesis and structure–activity relationships, Drug Des. Discov. 15 (1998) 157–180.
[51] J. Zimmermann, R. Liebl, E. von Angerer, 2,5-Diphenylfuran-based pure antiestrogens with selectivity for the estrogen receptor alpha, J. Steroid Biochem. Mol. Biol. 94 (2005) 57–66.
[52] R.W. Hartmann, Influence of alkyl chain ramification on estradiol receptor binding affinity and intrinsic activity of 1,2-dialkylated 1,2-bis(4- or 3-hydroxyphenyl)ethane estrogens and antiestrogens, J. Med. Chem. 29 (1986) 1668–1674.