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Original article

Novel *N*-methylsulfonamide and retro-*N*-methylsulfonamide derivatives as 17β-hydroxysteroid dehydrogenase type 2 (17β-HSD2) inhibitors with good ADME-related physicochemical parameters

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ABSTRACT

Under physiological conditions healthy bones are maintained by a well tightened balance between osteoclast (OCs) and osteoblast (OBs) activity. Disruption of this balance leads to osteoporosis characterized by decline in bone function and skeletal rigidity. Inhibition of 17β-hydroxysteroid dehydrogenase type 2 (17β-HSD2) could help maintaining the appropriate bone mass density by increasing the level of estradiol and testosterone in bone. Herein, we described the synthesis, the physicochemical properties and the biological evaluation of novel *N*-methylsulfonamide and retro-*N*-methylsulfonamide derivatives as 17β-HSD2 inhibitors showing high potency (compound **10f**, IC_{50} = 23 nM), with a good selectivity toward 17β-HSD1 (the isoenzyme responsible of the reverse reaction), and a likely good *in vitro* ADME profile. It was also shown that the acidity of the phenolic hydroxy correlates with the inhibitory potency, suggesting p*K*a as a predictive parameter for the activity of this class of inhibitors.

1. Introduction

Bone is formed and maintained by two cell types: osteoblasts (OB), which are the cells that synthesize and mineralize the bone matrix and osteoclasts (OC), which resorb or remove the calcified tissues. OB and OC work together regulating the balance of bone remodeling process. Deregulation in this equilibrium often leads to diseases like osteopenia [1] or osteoporosis [2].

Osteoporosis is a common systemic bone disease characterized by a loss or decrease in bone mineral density (osteopenia) and deterioration of the bone microarchitecture. It comes from an increased OC activity and/or a decreased OB activity, which leads to bone fragility and high bone fracture risk [3].

The decrease in active sex steroids level (estradiol E2 and testosterone T, e.g. in women at menopause) [4,5] has been described among the factors responsible for the development of osteoporosis. The antiresorptive bisphosphonates, like alendronate, are the most frequently administered therapeutic treatment. It is effective in both postmenopausal women [6] and men [7,8]. However, it leads to reduction of only 50% of fracture risks.

Osteoporosis is an aged-dependent disease. It is estimated that 40% of all women worldwide over the age of 50 will experience an osteoporotic fracture during their life time. As the population is

Abbreviation: OB, osteoblast; OC, osteoclast; 17β-HSD2, 17β-hydroxysteroid dehydrogenase type 2; 17β-HSD1, 17β-hydroxysteroid dehydrogenase type 1; E2, estradiol; T, testosterone; A-dione, androstenedione; SF, selectivity factor; ADME, absorption, distribution, metabolism and elimination; MW, molecular weight; tPSA, topological polar surface area.

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getting older and as this disease is a real issue in public/family care and health costs, development of new therapeutic strategies for this disease are urgently needed.

17β-Hydroxysteroid dehydrogenase type 2 (17β-HSD2, EC1.1.1.51 [9]) catalyzes the NAD^+-dependent oxidation of the biologically active sex steroids E2 and T into their less active forms estrone (E1) and androstenedione (A-dione), respectively (Fig. 1). 17β-HSD2 is a membrane-associated protein located in the endoplasmic reticulum [10], and the 3D-structure of this enzyme remains unknown. This enzyme is expressed in a broad variety of tissues such as placenta, liver, small intestine, endometrium, urinary tracts and to a lesser extends also in kidney, pancreas, colon, uterus, breast and prostate. 17β-HSD2 is also present in OB [10–13]. Inhibition of this enzyme will lead to an intracellular E2 and T increase, which can replenish the reduced endogenous hormone levels in osteoporotic patients and thus can be beneficial for the treatment of osteoporosis.

So far, only few 17β-HSD2 inhibitors have been described in the literature [14,15]. Bagi et al. have validated the concept of improving bone quality by inhibiting 17β-HSD2 using a monkey osteoporosis model [5]. They synthesized several 2,3-disubstituted-*cis*-pyrrolidinone derivatives substituted by a thiophene moiety **1** or a phenyl ring **2a**–**b** and evaluated *in vivo* the activity of the *cis*-pyrrolidinone derivative **1** (Fig. 2) [16–18]. However, this compound only led to minor effects on bone mass, which might be due to its poor pharmacokinetic profile, eventually due to its poor solubility. Thus, there is a need to develop new potent 17β-HSD2 inhibitors with a better pharmacokinetic profile. The new compounds should not inhibit 17β-HSD1, the isoenzyme catalyzing the reverse reaction (reduction of E1 into E2 (Fig. 1) as this would be contraproductive for the aim to increase E2).

Our group has been working for twenty years on the development of inhibitors of steroidogenic enzymes (e.g. 5α-reductase [19], aromatase [20–23], CYP17 [24,25], CYP11B2 [26–29], CYP11B1 [30,31]) and in the last years a lot of experience was gained in the design of potent and selective 17β-HSD1 [32–37] and 17β-HSD2 [38–44] inhibitors. Recently, we described [40,44] 3- and 4-phenyl-*N*-methyl benzamide derivatives (compound **3**–**8**, Fig. 2) as new 17β-HSD2 inhibitors. These compounds all have a phenyl central core **B**. They differ in the substitution pattern of the phenyl **B**: compounds **3**, **4** are 1,4-disubstituted while compounds **5**–**8** are 1,3-disubstituted. They differ also in the size of the linker *n* ($n = 0$ for **5** and **6**, $n = 1$ for **3**, **4**, **7** and **8**) between the phenyl **C** and the amide moiety. They can bear two hydroxy (**4**, **6** and **8**) or two methoxy groups (**3**, **5** and **7**) on the phenyls **A** and **C**. The methoxylated **3** and **5** and the hydroxylated **8** show a moderate 17β-HSD2 inhibitory activity with an IC_{50} around 500 nM, independent of the 1,3 or 1,4-substitution pattern of the central core **B**. As these derivatives present additionally a good selectivity toward 17β-HSD1 (selectivity factor between 8 and 200, Table 1), they were considered as interesting hits for further optimization.

The ADME (absorption, distribution, metabolism and elimination) profile of a compound describes its disposition in the tissues *in vivo*. Recently, prediction of ADME parameters has become an important tool in drug development to anticipate the suitability of a molecule for *in vivo* evaluation in order to combat drug attrition during clinical phase development. As the physical chemical properties can be controlled through structure modification, ADME parameters can be adjusted, when necessary, in an early stage of development in parallel to efficacy optimization.

The aim of this project was to develop 17β-HSD2 inhibitors to be used *in vivo* for a proof of principle in an animal model and, hopefully, later in human. Therefore in addition to pursue good potency and selectivity, acceptable ADME properties of the compounds to be developed are in our focus to increase the success of *in vivo* application.

In this study, we describe new 17β-HSD2 inhibitors of the biphenyl class derived from **3** to **8**, bearing a sulfonamide moiety instead of the carboxamide, with improved potency. The design of the molecules was guided by selection of the ones with favorable ADME parameters only. The biological evaluation of the synthesized compounds is reported as well as their physicochemical properties (calculated and experimentally determined). In addition it will be shown that the acidity of the molecules correlates well with their biological activity, highlighting the p*K*a as an important parameter to be taken into account in the design of inhibitors in this class.

2. Rationale and design

Within the most relevant predicting ADME parameters, the following were selected and calculated for compounds **3**–**8**: molecular weight (MW), lipophilicity (log *P*), acidity (p*K*a), topological polar surface area (tPSA), number of rotatable bonds and number of H-bond donors (HD) and acceptors (HA) (Table 1).

According to their calculated ADME profile, molecules **3**–**8** are small (MW around 400 Da) with a good lipophilicity (*c*log *P* around 3), an adequate polar surface area (tPSA <75 $Å^2$) and a reduced flexibility (small number of rotatable bounds). They were therefore

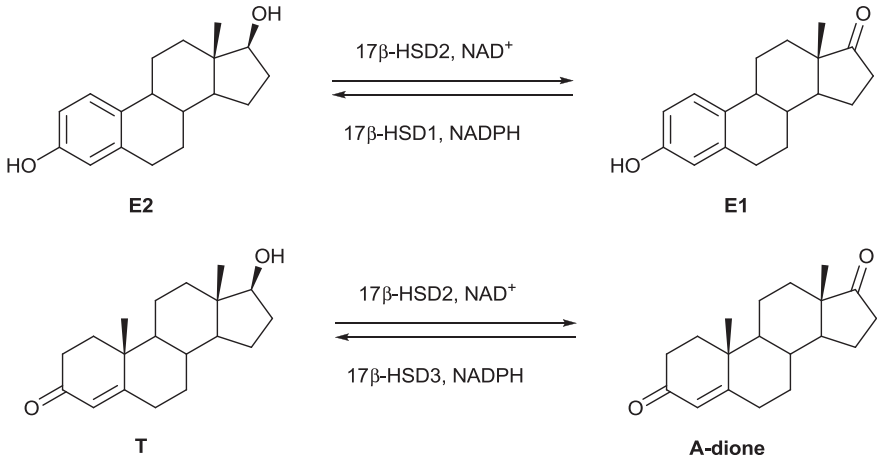


Fig. 1. Interconversion of estradiol (E2) to estrone (E1) by 17β-HSD2 and 17β-HSD1, and testosterone (T) to androstenedione (A-dione) by 17β-HSD2 and 17β-HSD3.

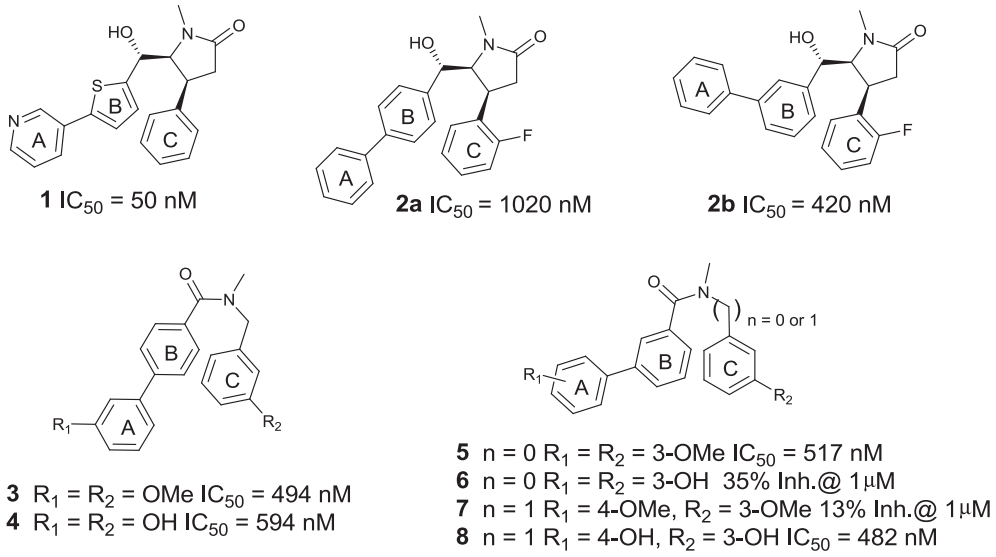


Fig. 2. Described 17β-HSD2 inhibitors.

considered as interesting hits and good starting points for optimization of their potency.

The 3- and 4-phenyl-*N*-methyl benzamide derivatives **3**–**8** (Fig. 2) present a certain structural similarity to the equipotent 2,3-disubstituted *cis*-pyrrolidinones **2a**–**b** (Fig. 2) developed by Bagi et al. sharing the aromatic ring **C**, the biphenyl moiety **A** and **B** and the *N*-methyl amide function, which is essential for activity. **2a**–**b** differ from **3**–**8** for the presence of a secondary hydroxy group (*versus* the amide bond in **3**–**8**) and of the pyrrolidinone moiety. The tetrahedral geometry of the alcohol in **2a**–**b** might allow different H-bond interactions (HA and HD) compared to the planar *N*-methylamido group of **3**–**8** (only HA), and this might be more favorable for the stabilization of the enzyme–inhibitor complex. In this study, a ligand-based strategy was used to design a series of new 17β-HSD2 inhibitors by replacement of the planar amide for the bioisosteric tetrahedral sulfonamide and retrosulfonamide moieties (compounds **9a**–**r** and **10a**–**d**, Fig. 3).

As both 1,3- and 1,4-substitution pattern on the central phenyl **B** (1,4- in case of **3** and **4** and 1,3- in case of **5**–**8**) led to equipotent compounds, the sulfonamides/retrosulfonamides were designed with both 1,3-(**10a**–**d**) and 1,4-(**9a**–**r**) substitution pattern. In addition, the length of the linker was also varied ($n = 0$ or 1) to explore different areas in the enzyme active site.

The physicochemical properties of compounds **3**–**8**, bearing either hydroxy or methoxy groups, span a good range. The same substituents were introduced on the sulfonamide at different positions on the phenyl **A** and **C** to identify the best substitution pattern. In the previous study of the 2,5-thiophene carboxamide class (compound **11**, Fig. 4), the positive influence of an additional substituent like a F on the **A** ring was demonstrated [40,44]. In this study, we wanted to investigate the influence of an additional fluorine on the phenyl **C** ring on the activity, as it will modify the acidity of the hydroxy group next to it. The phenyl ring **A** was also replaced by its bioisostere thiophene and pyridine rings to decrease the lipophilicity of the molecule.

3. Results

3.1. Chemistry

The synthesis of the sulfonamides **9a**–**p** and **10a**, **10b** was achieved in a three-step pathway as depicted in Scheme 1 starting

Table 1
Predicted ADME-related physicochemical parameters and biological activities of compounds **3**–**8**.

Cpd	MW	*c*log *P*[a]	*cpKa*[b]	tPSA[c]	Rotat. bonds	HD[d]	HA[e]	17β-HSD2[f]	17β-HSD1[g]	SF[h]
3	361	4.30	–	39	6	0	4	494 nM	>100,000 nM	>202
4	333	3.14	9.8 (A) 9.6 (C)	61	4	2	4	594 nM	13,009 nM	22
5	347	3.94	–	39	5	0	4	517 nM	>60,000 nM	>115
6	319	3.29	9.6 (A) 9.6 (C)	61	3	2	4	35%@1 μM	13%@1 μM	nd
7	361	4.28	–	39	6	0	4	13%@1 μM	3%@1 μM	nd
8	333	3.08	9.8 (A) 9.7 (C)	61	4	2	4	482 nM	3801 nM	22

[a] Calculated log *P*, values determined with ACD/Labs Percepta 2012 Release using GALAS method.
[b] Calculated p*Ka* values for the OH phenyl A ring (A) and OH phenyl C ring (C) determined with ACD/Labs Percepta 2012 Release using the classic method.
[c] Total polar surface area (Å^2), determined with ACD/Labs Percepta 2012 Release.
[d] HA: number of H-bond acceptors.
[e] HD: number of H-bond donors.
[f] 17β-HSD2 potency, IC_{50} or % inhibition@1 μM, human placental, microsomal fraction, substrate E2 [500 nM], cofactor NAD^+ [1500 nM], mean value of three determinations, standard deviation less than 15%.
[g] 17β-HSD1 potency, IC_{50} or % inhibition@1 μM human placental, cytosolic fraction, substrate E1 [500 nM], cofactor NADH [500 nM], mean value of three determinations, standard deviation less than 15%.
[h] SF: selectivity factor, ratio IC_{50} (HSD1)/IC_{50} (HSD2).

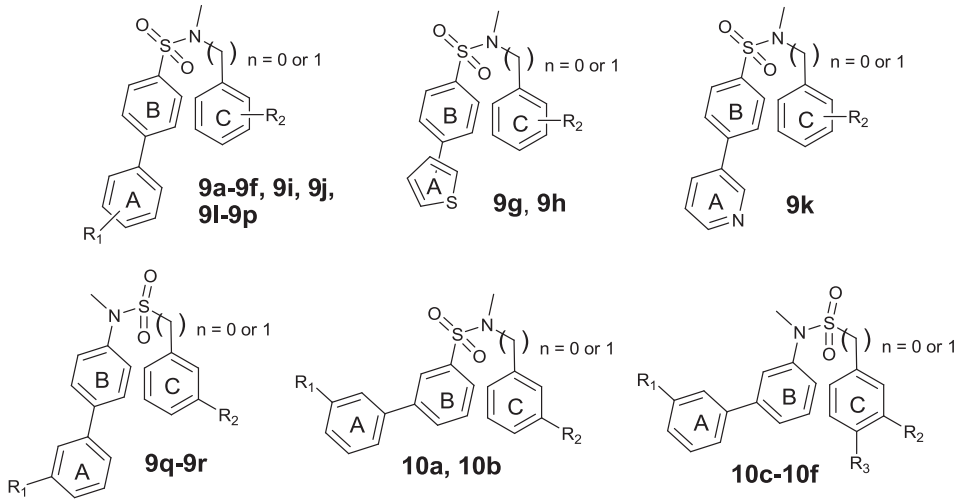


Fig. 3. Chemical structure of the designed compounds **9a**–**r** and **10a**–**f**.

from 4- and 3-bromobenzenesulfonyl chloride **14a** and **15a**, respectively. The synthesis of the retrosulfonamides **9q**, **9r** and **10c**–**f** was performed in a three-step pathway as depicted in Scheme 2, similar to the synthesis of the sulfonamide but starting from the 4- and 3-bromo-*N*-methylaniline **14b** and **15b**.

Compounds **14a**, **15a** and **14b**, **15b** were reacted with corresponding-methylaniline and chlorosulfonyl derivatives, respectively, to afford the bromo-*N*-methylsulfonamide intermediates **12a**–**g** and **13a**–**c** in very good yields. Then, a Suzuki–Miyaura cross coupling performed under microwave irradiation with differently substituted phenylboronic acids led to compounds **9a**–**k**, **9m**, **9o** and **9q** and **10a**, **10c** and **10e**. Finally, ether cleavage using boron trifluoride methyl sulfide complex $BF_3 \cdot SMe_2$ in presence of triethylamine resulted in the final compounds **9l**, **9n**, **9p** and **9r** and **10b**, **10d** and **10f**. Ether cleavage failed when boron tribromide, pyridium hydrochloride salt and boron trifluoride methyl sulfide complex without triethylamine were used.

3.2. Biological results

The synthesized compounds were tested for their ability to inhibit 17β-HSD2 and 17β-HSD1 enzymes from human placental source as previously described [45]. Results are reported in Table 2 as percentage of inhibition and as IC_{50} values for compounds exceeding 50% inhibition at a concentration of 1 μM. Compounds showing an inhibitory activity below 10% were considered inactive.

In the 1,4-phenyl class three moderately active compounds bearing a sulfonamide moiety could be identified, **9n** and **9p** with an IC_{50} around 1 μM and the retrosulfonamide **9r** with an IC_{50} value of 511 nM. Replacement of the carboxamido by the sulfonamido group resulted in a loss of activity in both methoxylated (**9o**, no inhibition at 1 μM *vs* **3**, IC_{50} = 494 nM) and hydroxylated compounds (**9p**, IC_{50} = 934 nM *vs* **4**, IC_{50} = 594 nM). This could be an indication that the tetrahedral sulfonamide cannot achieve additional H-bond interactions in case of the methoxylated derivatives in contrast to the carboxamido group and that compounds with a sulfonamido group combined with a methoxy group are not accepted by the enzyme while they are tolerated when they bear hydroxy groups. An explanation for this could be that the methoxylated and hydroxylated molecules might not bind in the same area of the enzyme.

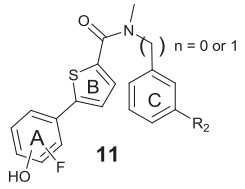


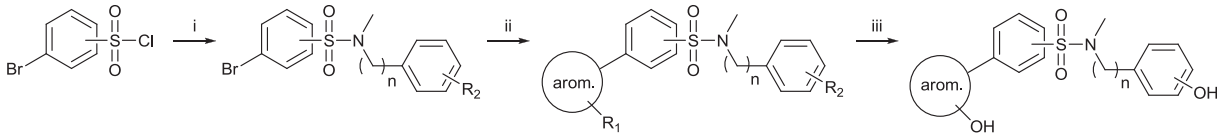
Fig. 4. 2,5-Thiophene amide **11** as 17β-HSD2 inhibitor.

In the 1,3-phenyl series, one moderately active sulfonamide (**10b**, IC_{50} = 540 nM) and two highly active retrosulfonamides (**10d** and **10f**, IC_{50} = 159 and 23 nM, respectively) could be identified. Considering the sulfonamides only, a decrease in activity was observed with the methoxylated derivatives (**10a**, 26% inhibition at 1 μM *vs* **5**, IC_{50} = 517 nM) compared to the carboxamides while an increase was found with the hydroxylated compounds (**10b**, IC_{50} = 540 nM *vs* **6**, 35% inhibition at 1 μM). These activity differences also support our assumption that in presence of the sulfonamido group the hydroxylated and methoxylated compounds might bind in a different way/area, therefore exhibiting different structure–activity relationships.

Independently of the 1,3- or 1,4-substitution pattern the retrosulfonamide derivatives are superior to the sulfonamides when the compounds are hydroxylated (**9r**, IC_{50} = 511 nM *vs* **9n**, IC_{50} = 1179 nM or **10d**, IC_{50} = 159 nM *vs* **10b**, IC_{50} = 540 nM). In the case of the methoxylated compounds a weak inhibitory activity without differences between the sulfonamides or the retrosulfonamides was observed.

Comparing the contribution of the substituents, it is clear that the hydroxylated compounds are always more active than the methoxylated derivatives independent of the linker size (for $n = 0$, **9b** OMe, 27% inhibition at 1 μM *vs* **9n** OH, IC_{50} = 1179 nM, for $n = 1$ **9o** OMe, no inhibition at 1 μM *vs* **9p** OH, IC_{50} = 934 nM), the substitution pattern of the **B** ring, 1,3-phenyl or 1,4-phenyl, and the sulfonamide or retrosulfonamide linker (**10a** OMe, 26% inhibition at 1 μM *vs* **10b** OH, IC_{50} = 540 nM, **9q** OMe, 25% inhibition at 1 μM *vs* **9r** OH, IC_{50} = 511 nM, **10c** OMe, 14% inhibition at 1 μM *vs* **10d** OH, IC_{50} = 159 nM).

Introduction of a fluorine substituent in ortho of the hydroxy group on the phenyl **C** ring increased the inhibitory activity leading to highly potent **10f** (IC_{50} = 23 nM). On the other hand a fluorine substituent had no influence on the activity of the methoxy derivative (**10e** inactive at 1 μM) highlighting the importance of acidity of the OH group for activity.



14a
15a

12a-12f
13a

9a-9k, 9m, 9o
10a

9l, 9n, 9p
10b

1,4-disubstituted (starting from **14a**):

$R_1 = R_2 = OMe$
9a-9f, **9i**, **9j**, **9m**, **9l**, **9n**: n = 0, arom. = phenyl
9g: n = 0, arom. = 2-thienyl
9h: n = 0, arom. = 3-thienyl
9k: n = 0, arom. = 3-pyridinyl
9o, **9p**: n = 1, arom. = phenyl

1,3-disubstituted (starting from **15a**):

$R_1 = R_2 = OMe$
10a: n = 0, arom. = phenyl
10b: n = 1, arom. = phenyl

Scheme 1. Synthesis of compounds **9a**–**p**, **10a**, **10b**, **12a**–**f** and **13a**. Reagents and conditions: (i) Bu_4HSO_4, NaOH 50%, CH_2Cl_2, r.t., 3h. (ii) Boronic acid, $Pd(PPh_3)_4$, Cs_2CO_3, DME/EtOH/H_2O (1:1:1), microwave irradiation (150 °C, 150 W, 20 min). (iii) $BF_3{\cdot}SMe_2$, Et_3N, CH_2Cl_2, 0 °C to r.t.

The influence of the linker length was also investigated: longer linkers, $n = 1$, are slightly more favorable than shorter linkers ($n = 0$) in case of the hydroxylated compound (**9p**, $n = 1$, $IC_{50} = 934$ nM *vs* **9m**, $n = 0$, 38% inhibition at 1 μM).

The most active compounds identified, i.e., **9n**, **9p**, **9r**, **10b** and **10d** showed a weak selectivity (selectivity factors, SFs, between 2 and 6) for 17β-HSD1 except **10f**, which exhibited a SF = 10.

3.3. Physicochemical properties determination

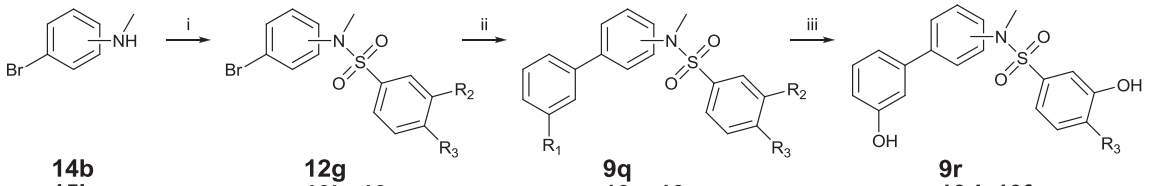
The relevant physicochemical parameters of the most potent compounds were both calculated and experimentally determined as shown in Table 3.

In silico predictions of physicochemical parameters were performed using ACD/Labs Percepta 2012 Release software. The logarithm of partition constant *P* (log *P*) was used as quantitative descriptor of lipophilicity. The negative logarithm of the acid dissociation constant K_a (p*K*a) were used as the measure of the acidity. Lipophilicity and acidity calculated parameters are indicated in Table 3 as *c*log *P* and *c*p*K*a, respectively.

The experimental determination of the physicochemical parameters log *P*, log *S* (*S* is the aqueous solubility expressed in mmol/L) and p*K*a, are reported in Table 3 as *e*log *P*, *e*log *S* and *e*p*K*a, respectively for the most potent compounds. Measurements were performed on a SiriusT3 instrument from Sirius Analytical using an automated potentiometric titration as described in Table 3.

The molecular weight (355 Da < MW < 373 Da) of the synthesized molecules was small and within the allowed range for drug-likeness.

The lipophilicity (characterized by log *P*), which is an important parameter as it affects absorption, distribution, metabolism, excretion, toxicity and *in vivo* pharmacological properties, was first calculated for all the compounds during the design step in order to focus only on the ones with a good profile. As there is a high variation in the predicted *c*log *P* depending on the program used, the log *P* of the most interesting compounds was determined experimentally (*e*log *P*). The *c*log *P* turned out to be always lower than the *e*log *P*, which was found to be between 3.7 and 4.4 (Table 3), an acceptable range, except for compound **9p**, which has a very high *e*log *P* of 5.41. The increase in lipophilicity for this compound comes from the presence of the additional methylene linker ($n = 1$) between the sulfonamide function and the phenyl **C** ring. This result indicates that compounds from this class with a linker $n = 1$ do not have an optimum profile and were therefore not further investigated. The sulfonamide **10b** (*e*log $P = 4.34$) was slightly more lipophilic than the corresponding carboxamide **6**



14b
15b

12g
13b, 13c

9q
10c, 10e

9r
10d, 10f

1,4-disubstituted (starting from **14b**):

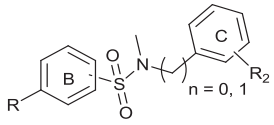
9q: $R_1 = R_2 = OMe$, $R_3 = H$
9r: $R_3 = H$

1,3-disubstituted (starting from **15b**):

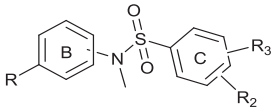
10c: $R_1 = R_2 = OMe$, $R_3 = H$
10d: $R_3 = H$
10e: $R_1 = R_2 = OMe$, $R_3 = F$
10f: $R_3 = F$

Scheme 2. Synthesis of compounds **9q**, **9r**, **10c**–**f**, **12g**, **13b** and **13c**. Reagents and conditions: (i) Bu_4HSO_4, NaOH 50%, CH_2Cl_2, r.t., 3h. (ii) Boronic acid, $Pd(PPh_3)_4$, Cs_2CO_3, DME/EtOH/H_2O (1:1:1), microwave irradiation (150 °C, 150 W, 20 min). (iii) $BF_3{\cdot}SMe_2$, Et_3N, CH_2Cl_2, 0 °C to r.t.

Table 2
In vitro 17β-HSD2 and 17β-HSD1 inhibitory potencies of substituted *N*-methylsulfonamide and retro-*N*-methylsulfonamide derivatives **9a**–**r** and **10a**–**f**.



9a-9p
10a, 10b



9q, 9r
10c-10f

Cpd	Central core	*n*	R	R_2	R_3	% Inhibition at 1 μM (IC_{50})		SF[d]
						17β-HSD2[a,b]	17β-HSD1[a,c]	
9a		0	2-OMePh	3-OMe	H	23	10	–
9b		0	3-OMePh	3-OMe	H	27	n.i.	–
9c		0	4-OMePh	3-OMe	H	13	n.i.	–
9d		0	2-OMePh	–	H	10	17	–
9e		0	3-OMePh	2-OMe	H	10	n.i.	–
9f		0	3-OMePh	4-OMe	H	22	n.i.	–
9g		0	2-Thienyl	3-OMe	H	32	n.i.	–
9h		0	3-Thienyl	3-OMe	H	23	n.i.	–
9i		0	3-OMePh	3-OH	H	18	15	–
9j		0	3-MePh	3-OH	H	22	14	–
9k		0	3-Pyridinyl	3-OH	H	15	n.i.	–
9l		0	2-Thienyl	3-OH	H	31	15	–
9m		0	3-OHPh	3-OMe	H	38	14	–
9n		0	3-OHPh	3-OH	H	50 (1179 nM)	45 (2031 nM)	2
9o		1	3-OMePh	3-OMe	H	n.i.	n.i.	–
9p		1	3-OHPh	3-OH	H	57 (934 nM)	18 (4299 nM)	5
9q		0	3-OMePh	3-OMe	H	25	16	–
9r		0	3-OHPh	3-OH	H	66 (511 nM)	22 (3282 nM)	6
10a		0	3-OMePh	3-OMe	H	26	n.i.	–
10b		0	3-OHPh	3-OH	H	68 (540 nM)	42 (1308 nM)	2
10c		0	3-OMePh	3-OMe	H	14	14	–
10d		0	3-OHPh	3-OH	H	88 (159 nM)	68 (427 nM)	3
10e		0	3-OMePh	3-OMe	4-F	n.i.	17	–
10f		0	3-OHPh	3-OH	4-F	96 (23 nM)	80 (238 nM)	10

[a] Mean value of three determinations, standard deviation less than 15%.
[b] Human placental, microsomal fraction, substrate E2 [500 nM], cofactor NAD^+ [1500 nM].
[c] Human placental, cytosolic fraction, substrate E1 [500 nM], cofactor NADH [500 nM].
[d] SF: selectivity factor, ratio IC_{50} (17β-HSD1)/IC_{50} (17β-HSD2).

(*e*log $P = 3.78$) but exchange of one moiety for the other should not have critical effect on the *in vivo* behavior of the compounds.

The aqueous solubility S of the most interesting compounds, expressed in mmol/L, was determined experimentally at pH = 7.4 and at 25 °C in KCl 0.15 M solution (*e*log *S*, Table 3). It was in a good range for compounds **9n**, **9r**, **10b**, **10d** and **10f** ($-2.6 >$ *e*log $S > -4.1$, corresponding to concentrations in the range: 2.51 mM > $S > 7.94 \cdot 10^{-2}$ mM) while was too low for **9p** (*e*log $S = -5.9$, $S = 1.26 \cdot 10^{-3}$ mM). As solubility is affected by lipophilicity, the high *e*log *S* value was expected as **9p** exhibited a high *e*log *P*. This confirms that **9p** is inappropriate for further development. The solubilities of the sulfonamide **10b** and of the corresponding carboxamide analog **6** were in a similar range. Exchange of the carboxamido for the sulfonamido moiety should not change significantly the lipophilicity of the compounds *in vivo*.

Molecular flexibility, polar surface area and hydrogen bond donor and acceptor counts are important determinants of oral bioavailability [46]. The tPSA was calculated using the program Advance Chemistry Development, Inc. (ACD/Labs) Percepta 2012 Release and all values are reported in Table 3. It can be seen that for all synthesized compounds the tPSA is <140 $Å^2$, the compounds possess less than 10 rotatable bonds and less than 12 hydrogen bonds (acceptors and donors), fulfilling the requirements of the Veber [46]/Lipinski [47] rule for a good oral bioavailability.

The p*K*a of a compound is indicative of its ionizability, which is a major determinant of solubility and permeability. The p*K*a values of the most interesting compounds were calculated (*c*p*K*a) and determined experimentally (*ep*K*a*) for each phenolic group. The calculated value helped the assignment of the experimental values obtained. The *ep*K*a*s of the hydroxy groups from the **A** ring and from the **C** ring are differentiated in Table 3 by the letter (A) or (C), respectively. In addition, to verify the good correlation between calculated and experimental p*K*a values and proceed with the correct acid group assignment (OH in phenyl A or phenyl C ring), the *c*p*K*a and *ep*K*a* of **9i** and of **9m** bearing only one OH group, either on the phenyl **A** or phenyl **C** ring, was determined. The OH on phenyl **C** ring appears to be more acidic (*ep*K*a* **9i** = 8.9) than the OH phenyl **A** ring (*ep*K*a* **9m** = 9.5). This was confirmed in all the sulfonamides bearing two OH moieties: **10b**, **9n** and **9p**, where the *ep*K*a* of OH on the phenyl **C** varied between 8.8 and 8.9 whereas the *ep*K*a* of OH on the phenyl **A** varied between 9.2 and 9.4. Within the retrosulfonamides **9r** and **10d**, the *ep*K*a* of OH on the phenyl **C** varied between 8.2 and 8.5, resulting slightly more acidic than the one of the sulfonamides, because of the electron withdrawing effect of the SO_2 moiety directly attached to the **C** ring. Comparison of the *ep*K*a* of the carboxamide **6** with the corresponding sulfonamide **10b** indicates that the carboxamido and the sulfonamido groups have a different effect on the acidity of the OH group of phenyl **A** ring or OH group of phenyl **C** ring. Introduction of the electron withdrawing fluorine on the retrosulfonamide phenyl **C** ring resulted in a stronger increase in acidity of the OH next to the F atom (*ep*K*a* of OH on the phenyl *C* = 6.9 for **10f** compared to the *ep*K*a* of OH on the phenyl *C* = 8.2 for **10d**).

4. Discussion and conclusion

The main goal of this work was to develop new active and selective 17β-HSD2 inhibitors with a good *in vitro* ADME profile. Starting from the moderately active biphenylcarboxamides **3**–**8** and exchanging the amide moiety for a sulfonamido/retrosulfonamido group, a new class of biphenyl derivatives was designed, prepared and tested. In the 1,4-phenyl class with linker *n* = 1, replacement of the carboxamido by a sulfonamido/retrosulfonamido group led to a decreased activity for hydroxy compound **9p** and a loss of activity for methoxy compound **9o**. Three moderately active compounds **9n**, **9c** and **9r** could be identified with an IC_{50} between 500 nM and 1 μM with linker *n* = 0. In the 1,3-phenyl class, a reduction of the activity was observed for the methoxylated sulfonamide **10a** while an increase was seen with the hydroxylated retrosulfonamide **10b**.

The retrosulfonamides were superior to the sulfonamides, independent of their 1,3- or 1,4-substitution pattern, as seen with **10d**

Table 3
Physicochemical properties calculated and experimentally determined for compounds **6**, **9i**, **9m**, **9n**, **9p**, **9r**, **10b**, **10d** and **10f**.

Cpd	MW	*c*log *P*[a]	*e*log *P*[b]	*e*log *S*[c]	cp*K*a[d]	ep*K*a[e]	tPSA[f]	Rotat. bonds[g]	HD	HA
6	319	3.29	3.78	−2.81	9.6 (A) 9.6 (C)	9.4 (A) 9.0 (C)	61	3	2	4
9i	369	3.80	n.d.[h]	n.d.[h]	9.4 (A)	9.5 (A)	75	5	1	5
9m	369	3.80	n.d.[h]	n.d.[h]	9.4 (C)	8.9 (C)	75	5	1	5
9n	355	3.31	4.17	−4.09	9.5 (A) 9.4 (C)	9.5 (A) 8.8 (C)	86	4	2	5
9p	369	3.20	5.41	−5.90	9.7 (A) 9.5 (C)	9.2 (A) 8.8 (C)	86	5	2	5
9r	355	3.53	3.72	−3.29	9.7 (A) 8.7 (C)	9.8 (A) 8.5 (C)	86	4	2	5
10b	355	3.32	4.34	−3.18	9.6 (A) 9.4 (C)	9.4 (A) 8.9 (C)	86	4	2	5
10d	355	3.48	4.08	−3.27	9.7 (A) 8.7 (C)	9.8 (A) 8.2 (C)	86	4	2	5
10f	373	3.50	4.42	−2.64	9.7 (A) 7.4 (C)	9.3 (A) 6.9 (C)	86	4	2	5

[a] Calculated log *P*, values determined with ACD/Labs Percepta 2012 Release using GALAS method.
[b] Experimental log *P* using SiriusT3 instrument.
[c] Experimental log *S* using SiriusT3 instrument, value of *e*log *S* at pH = 7.4.
[d] Calculated p*K*a values for the OH phenyl A ring (A) and OH phenyl C ring (C) determined with ACD/Labs Percepta 2012 Release using the classic method.
[e] Experimental log *P* using SiriusT3 instrument.
[f] Topological polar surface area (Å^2) determined with ACD/Labs Percepta 2012 Release.
[g] Rotatable bonds determined with ACD/Labs Percepta 2012 Release.
[h] Not determined due to a too high lipophilicity of the compound.

and **10f**, leading to highly active compounds, the latter being the most potent 17β-HSD2 inhibitors described in this class of compounds. We hypothesized that the SO_2 moiety, next to the phenyl **C** ring in the retrosulfonamides was responsible for this increased activity as it caused an enhancement of the acidity of the **C** ring hydroxy group. In order to verify this hypothesis, the retrosulfonamide bearing an additional electron withdrawing fluorine at the **C** ring, compound **10f**, was designed and synthesized. This compound turned out to be even more active, confirming the hypothesis that the retrosulfonamides were superior to the sulfonamides because of the electron withdrawing effect of the sulfonyl group. In addition, the acidity of the OH group of phenyl **C** correlated well with the potency of the compounds, highlighting the p*K*a as an important physicochemical parameter for the design of new molecular entities and as predicting molecular descriptor for inhibitory activity. In previous studies [40,44] of 2,5-thiophene carboxamide class **11**, the increased acidity of the OH phenyl on **A** was also correlated with an enhanced activity.

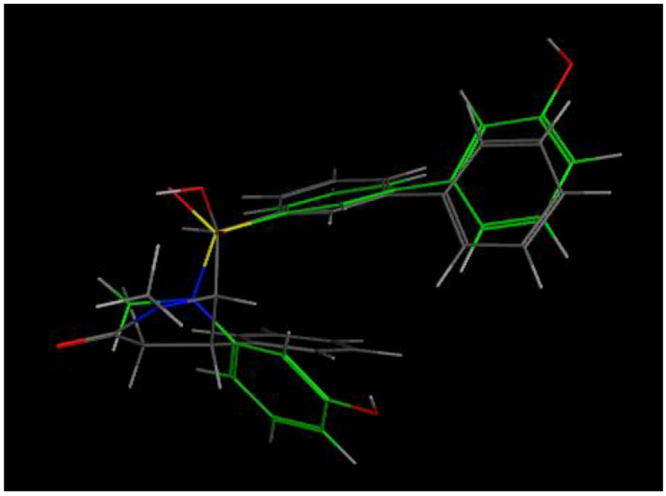


Fig. 5. Molecular superimposition of low-energy conformations of compounds **10b** (green) and **2b** (gray). The picture was generated using MOE 2010.10. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Increasing the acidity of one phenolic OH enhanced the strength of the hydrogen bond interaction achieved by this group and therefore might lead to a greater stabilization of the enzyme–inhibitor complex. In case of compound **10f**, it can be assumed that the OH bond is mostly ionized (*ep*K*a* = 6.9) because of the combined strong electron withdrawing effects of F and SO_2 on the acidity of the OH on phenyl **C**. In this case it might participate in ionic interactions with basic nitrogens of lysines (p*K*a values between 10 and 10.5) or arginines (p*K*a values of 12–13) present in the active site.

Potency comparison of carboxamides *versus* sulfonamides suggests that the planar amide bond results in a better stabilization of the compound than the tetrahedral $-SO_2N-$ moiety, indicating that the geometry of hydrogen bonding interaction is more favorable in case of the −CON−. The sulfonamide moiety has one more H-bond acceptor atom, which is obviously not involved in the stabilization of the compound. Interestingly, the amides **3**, **4** and **5** were more potent than their sulfonamide analogs **9o**, **9p** and **10a**, respectively, except **6** which resulted weaker than **10b**. This missing correlation in the activities between the carboxamide and sulfonamide classes might be explained by a likely different binding mode of these two series of compounds in the enzyme active site.

Comparison of the new sulfonamides (1,4-: **9a**–**9r**, 1,3-: **10a**–**10f**) with the Bagi compounds (1,4-: **2a**, 1,3-: **2b**) highlights striking similarities: in each of these two compound classes the 1,3-phenyl substitution is approximately two times better than the 1,4-phenyl, leading to moderate 17β-HSD2 inhibitors with an IC_{50} around 500 nM for **2b** and **10b**. In addition, the tetrahedral $-SO_2N-$ moiety might mimic the tetrahedral secondary OH of **2b**. Superimposition of these two compounds (Fig. 5) shows that the phenyl **C** rings do not cover the same area in both classes and the pyrrolidinone moiety of **2b** overlaps with the *N*-methyl group of the sulfonamide. In case that both compounds have the same binding mode, this might indicate that the *cis*-pyrrolidinone moiety is not highly necessary and that the phenyl **C** ring does not achieve crucial interactions. Interestingly, exchange of the central phenyl **B** for a 2,5-thiophene ring in the pyrrolidinone derivative **2b** leading to compound **1** and in the carboxamido class **6** to **11** (where R_1 = 3-OH, R_2 = 3-OH without F) results in a gain in activity in both classes of compounds.

The *in vitro* ADME profile of a compound reflects its *in vivo* pharmacokinetic behavior that can be related to its chemical properties. The prediction of the ADME parameters has become an accepted strategy in modern drug development to reduce the number of synthesized molecules and speed up the drug discovery process reducing the attrition rate during clinical trials. For all synthesized compounds reported herein, ADME-related physicochemical parameters were proved to span a good range. Some of these parameters were determined experimentally because of the high variability of the predictions obtained using different *in silico* programs. All of the most potent compounds turned out to exhibit good ADME-related parameters in an acceptable range.

The best compound identified in this study, **10f**, is the most potent 17β-HSD2 inhibitor described in this class of compounds with a very good activity ($IC_{50} = 23$ nM). Moreover, its calculated and experimentally determined ADME parameters (MW = 373 Da, *e*log $P = 4.42$, tPSA = 86 Å^2, 4 rotatable bonds, 2 HD, 4 HA) are in very good range, predicting a good bioavailability. Especially its good solubility (*e*log S = −2.64, $S = 2.28$ mM) makes it appropriate for *in vivo* application. It exhibited also a good selectivity toward 17β-HSD1 (SF: 10). The metabolic stability of **10f** as well as its pharmacokinetics will be determined in order to verify whether it can be successfully tested in animal models of osteoporosis. In this report we also demonstrated that there was a correlation between the acidity of the phenolic hydroxy on **C** ring and the inhibitory potency, and this suggests that p*K*a could be used as a useful parameter to guide the design of new class of inhibitors.

5. Experimental section

5.1. Chemical methods

Chemical names follow IUPAC nomenclature.

Starting materials were purchased from Aldrich, Acros, Combi-Blocks or Fluka and were used without purification. No attempts were made to optimize reaction yields.

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

Melting points (mp) were measured on a Stuart Scientific SMP3 apparatus and are uncorrected.

Column chromatography was performed on silica gel (70–200 μm) with hexane/ethyl acetate mixtures as eluents, and the reaction progress was monitored by thin-layer chromatography analysis (TLC) on Alugram SIL G/UV254 (Macherey–Nagel). Visualization was accomplished with UV light.

^{1}H NMR and ^{13}C NMR spectra were measured on a Bruker DRX-500 spectrometer (at 500 MHz and 125 MHz, respectively) at 300 K in acetone-d_6. Chemical shifts are reported in δ (parts per million: ppm), by reference to the hydrogenated residues of deuterated solvent as internal standard: 2.05 ppm (^{1}H NMR) and 29.8 and 206.3 ppm (^{13}C NMR) for acetone-d_6. The spectral splitting patterns are designated as follows: s, singlet; d, doublet; dd, doublet of doublets; ddd, doublet of doublet of doublets, t, triplet; q, quartet; m, multiplet; br s, broad singlet.

IR spectra were recorded neat on a Perkin Elmer Spectrum 100 FTIR spectrophotometer.

All tested compounds exhibited ≥95% chemical purity assessed by HPLC/MS.

Mass spectrometry measurements were performed on a TSQ® Quantum (ThermoFisher, Dreieich, Germany). The triple quadrupole mass spectrometer was equipped with an electrospray interface (ESI). The Surveyor®-LC-system consisted of a pump, an auto sampler, and a PDA detector. 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 was increased from an initial concentration of 0% at 0 min to 100% at 15 min and kept at 100% for 5 min. The injection volume was 15 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 from 100 to 1000 *m*/*z* and UV spectra were recorded at the wave length of 254 nm and in some cases at 360 nm.

GC/MS spectra were measured on a DSQ II Mass Spectrometer® (ThermoFisher) with an Optima-5-MS (0.25 μM, 30 m) column (Macherey–Nagel GmbH, Dühren, Germany).

Synthesis of compound **6** was made as described in the literature [40].

5.2. General procedures

5.2.1. General procedure for sulfonamides preparation (method A)

To a solution of substituted *N*-methylaniline (1 mmol) in CH_2Cl_2 (5 mL) was added aqueous NaOH 25 M (1 mL) followed by tetrabutylammonium hydrogen sulfate (0.15 mmol). After 5 min of vigorous stirring, the substituted benzenesulfonyl chloride (1 mmol) was added to the reaction mixture. The solution was stirred either for 3 h or overnight at room temperature. Water was added to quench the reaction. Aqueous layer was extracted with CH_2Cl_2 (3 × CH_2Cl_2). The organic layer was washed once with brine and once with water, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography using a mixture of *n*-hexane and ethyl acetate as solvent to afford the desired compound.

5.2.2. General procedure for Suzuki–Miyaura coupling (method B)

In a sealed tube was introduced the previously prepared bromo-*N*-methylsulfonamide derivative (1 eq.) followed by the corresponding boronic acid (1.5 eq.), cesium carbonate (3 eq.), tetrakis(triphenylphosphine)palladium (0.02 eq.) and a mixture of DME/EtOH/H_2O (1:1:1, v:v:v, 3 mL) as solvent. The reactor was flushed with N_2 and submitted to microwave irradiation (150 °C, 150 W) for 20 min. After cooling, a mixture of EtOAc/H_2O (1:1, v:v, 2 mL) was added to stop the reaction. The aqueous layer was extracted with EtOAc (3 × EtOAc). The organic layer was washed once with brine and once with water, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography using a mixture of *n*-hexane and ethyl acetate as solvent to afford the desired compound.

5.2.3. General procedure for ether cleavage (method C)

To a solution of substituted methoxysulfonamide derivative (1 eq.) in CH_2Cl_2 (10 mL) at 0 °C was added, Et_3N (6 eq. per methoxy group) followed by boron trifluoride methyl sulfide complex (6 eq. per methoxy group). The reaction was warmed to room temperature and stirred overnight. The reaction was monitored by TLC and when necessary an extra portion of Et_3N and $BF_3{\cdot}SMe_2$ was added to complete the reaction. The reaction mixture was cooled at 0 °C and methanol was added to quench the reaction. After warming up to room temperature for 1 h, the solvent was carefully removed under reduced pressure (temperature of bath was 25 °C). Cold water was added to the residue and the aqueous layer was extracted with CH_2Cl_2 (3 × CH_2Cl_2). The organic layer was washed once with water, dried over $MgSO_4$, filtered and evaporated to dryness under reduced pressure. The residue was purified by column chromatography using a mixture of hexanes and ethyl acetate as solvent to afford the desired compound.

5.3. Detailed synthesis procedure for the preparation of compounds

5.3.1. 4-Bromo-N-methyl-N-phenylbenzenesulfonamide (**12b**)

The title compound was prepared by reaction of *N*-methylaniline (643 mg, 6 mmol) in CH_2Cl_2 (18 mL) and NaOH 25 M (6 mL) with 4-bromobenzenesulfonyl chloride (**14a**) (1.533 g, 6 mmol) and tetrabutylammonium hydrogen sulfate (306 mg, 0.9 mmol) as phase transfer catalyst according to method A. The residue was purified by silica gel column chromatography using *n*-hexane and EtOAc as eluent (*n*-hexane/EtOAc 90:10) to afford **12b** (1.91 g, 5.86 mmol, 98%) as colorless crystal. $C_{13}H_{12}BrNO_2S$; mp 98–100 °C; IR (neat): 1346, 1158 cm^{-1}; ^1H NMR (acetone-d_6): δ 3.22 (s, 3H), 7.15–7.17 (m, 2H), 7.28–7.37 (m, 3H), 7.45–7.48 (m, 2H), 7.75–7.78 (m, 2H); ^{13}C NMR (acetone-d_6): δ 38.6, 127.4, 128.1, 128.2, 129.1, 129.8, 130.4, 131.2, 133.1, 137.0, 142.4; GC–MS (EI) *m*/*z*: $[M]^+$ 326.27, 328.37.

5.3.2. 4-Bromo-N-(2-methoxyphenyl)-N-methylbenzenesulfonamide (**12c**)

The title compound was prepared by reaction of 2-methoxy-*N*-methylaniline (274 mg, 2 mmol) in CH_2Cl_2 (6 mL) and NaOH 25 M (2 mL) with 4-bromobenzenesulfonyl chloride (**14a**) (511 mg, 2 mmol) and tetrabutylammonium hydrogen sulfate (102 mg, 0.3 mmol) as phase transfer catalyst according to method A. The residue was purified by silica gel column chromatography using *n*-hexane and EtOAc as eluent (*n*-hexane/EtOAc 90:10) to afford **12c** (282 mg, 0.79 mmol, 40%) as colorless solid. $C_{14}H_{14}BrNO_3S$; mp 123–125 °C; IR (neat): 1339, 1152 cm^{-1}; ^1H NMR (acetone-d_6): δ 3.20 (s, 3H), 3.44 (s, 3H), 6.93–6.97 (m, 2H), 7.27 (ddd, J = 0.6, 1.6, 5.5 Hz, 1H), 7.31–7.34 (m, 1H), 7.57–7.60 (m, 2H), 7.76–7.79 (m, 2H); ^{13}C NMR (acetone-d_6): δ 38.2, 55.4, 113.0, 121.3, 127.4, 129.7, 130.2, 130.7, 132.6, 132.7, 140.1, 157.3; GC–MS (EI) *m*/*z*: $[M]^+$ 356.23, 358.27.

5.3.3. 4-Bromo-N-(3-methoxyphenyl)-N-methylbenzenesulfonamide (**12a**)

The title compound was prepared by reaction of 3-methoxy-*N*-methylaniline (274 mg, 2 mmol) in CH_2Cl_2 (5 mL) and NaOH 25 M (1 mL) with 4-bromobenzenesulfonyl chloride (**14a**) (511 mg, 2 mmol) and tetrabutylammonium hydrogen sulfate (102 mg, 0.3 mmol) as phase transfer catalyst according to method A. The residue was purified by silica gel column chromatography using *n*-hexane and EtOAc as eluent (*n*-hexane/EtOAc 90:10) to afford **12a** (641 mg, 1.80 mmol, 90%) as brown solid. $C_{14}H_{14}BrNO_3S$; mp 72–76 °C; IR (neat): 1356, 1165 cm^{-1}; ^1H NMR (acetone-d_6): δ 3.21 (s, 3H), 3.75 (s, 3H), 6.70 (ddd, J = 0.9, 2.0, 7.9 Hz, 1H), 6.74 (t, J = 2.4 Hz, 1H), 6.87 (ddd, J = 0.9, 2.6, 8.3 Hz, 1H), 7.23 (t, J = 8.1 Hz, 1H), 7.49–7.52 (m, 2H), 7.75–7.79 (m, 2H); ^{13}C NMR (acetone-d_6): δ 38.6, 55.0, 113.4, 113.8, 119.2, 128.2, 129.1, 130.4, 130.5, 133.1, 143.5, 160.9; GC–MS (EI) *m*/*z*: $[M]^+$ 356.21, 358.19.

5.3.4. 4-Bromo-N-(4-methoxyphenyl)-N-methylbenzenesulfonamide (**12d**)

The title compound was prepared by reaction of 4-methoxy-*N*-methylaniline (274 mg, 2 mmol) in CH_2Cl_2 (5 mL) and NaOH 25 M (1 mL) with 4-bromobenzenesulfonyl chloride (**14a**) (511 mg, 2 mmol) and tetrabutylammonium hydrogen sulfate (102 mg, 0.3 mmol) as phase transfer catalyst according to method A. The residue was purified by silica gel column chromatography using *n*-hexane and EtOAc as eluent (*n*-hexane/EtOAc 90:10) to afford **12d** (697 mg, 1.96 mmol, 98%) as pale brown viscous solid. $C_{14}H_{14}BrNO_3S$; IR (neat): 1345, 1154 cm^{-1}; ^1H NMR (acetone-d_6): δ 3.17 (s, 3H), 3.79 (s, 3H), 6.86–6.89 (m, 2H), 7.02–7.06 (m, 2H), 7.44–7.49 (m, 2H), 7.75–7.78 (m, 2H); ^{13}C NMR (acetone-d_6-d_6): δ 38.9, 55.8, 114.9, 128.9, 129.1, 130.5, 131.1, 133.0, 134.9, 159.9; GC–MS (EI) *m*/*z*: $[M]^+$ 356.20, 358.22.

5.3.5. 4-Bromo-N-(3-hydroxyphenyl)-N-methylbenzenesulfonamide (**12e**)

The title compound was prepared by reaction of 4-bromo-*N*-(3-methoxyphenyl)-*N*-methylbenzenesulfonamide (**12a**) (754 mg, 2.12 mmol) with Et_3N (1.77 mL, 12.72 mmol) and $BF_3{\cdot}SMe_2$ (1.34 mL, 12.72 mmol) in CH_2Cl_2 (10 mL) according to method C. The residue was purified by silica gel column chromatography using *n*-hexane and EtOAc as eluent (*n*-hexane/EtOAc 80:20) to afford **12e** (693 mg, 2.03 mmol, 96%) as pale brown solid. $C_{13}H_{12}BrNO_3S$; mp 104–106 °C; IR (neat): 3378, 1331, 1153 cm^{-1}; ^1H NMR (acetone-d_6): δ 3.18 (s, 3H), 6.58 (ddd, J = 0.9, 2.2, 8.0 Hz, 1H), 6.67 (t, J = 2.3 Hz, 1H), 6.78 (ddd, J = 1.0, 2.3, 8.2 Hz, 1H), 7.14 (t, J = 8.2 Hz, 1H), 7.49–7.52 (m, 2H), 7.75–7.78 (m, 2H), exchange of hydroxy proton with deuterated solvent; ^{13}C NMR (acetone-d_6): δ 38.6, 114.6, 115.2, 118.0, 128.1, 130.4, 130.5, 133.0, 137.0, 143.5, 158.5; GC–MS (EI) *m*/*z*: $[M]^+$ 342.45, 344.49.

5.3.6. 4-Bromo-N-(3-methoxybenzyl)-N-methylbenzenesulfonamide (**12f**)

The title compound was prepared by reaction of 1-(3-methoxyphenyl)-*N*-methylmethanamine (558 mg, 3.69 mmol) in CH_2Cl_2 (5 mL) and NaOH 25 M (1 mL) with 4-bromobenzenesulfonyl chloride (**14a**) (943 mg, 3.69 mmol) and tetrabutylammonium hydrogen sulfate (188 mg, 0.55 mmol) as phase transfer catalyst according to method A. The residue was purified by silica gel column chromatography using *n*-hexane and EtOAc as eluent (*n*-hexane/EtOAc 80:20) to afford **12f** (1.285 g, 3.47 mmol, 94%) as yellow viscous solid. $C_{15}H_{16}BrNO_3S$; IR (neat): 1340, 1157 cm^{-1}; ^1H NMR (acetone-d_6): δ 2.64 (s, 3H), 3.78 (s, 3H), 4.18 (s, 2H), 6.86–6.89 (m, 1H), 6.90–6.93 (m, 2H), 7.24 (t, J = 7.9 Hz, 1H), 7.81–7.87 (m, 4H); ^{13}C NMR (acetone-d_6): δ 34.9, 55.6, 55.5, 114.1, 114.7, 121.3, 127.9, 130.0, 130.2, 131.2, 138.0, 138.6, 161.0; GC–MS (EI) *m*/*z*: $[M]^+$ 370.06, 372.12.

5.3.7. N-(4-Bromophenyl)-3-methoxy-N-methylbenzenesulfonamide (**12g**)

The title compound was prepared by reaction of 4-bromo-*N*-methylaniline (558 mg, 3 mmol) in CH_2Cl_2 (9 mL) and NaOH 25 M (3 mL) with 3-methoxybenzenesulfonyl chloride (**15a**) (425 μL, 3 mmol) and tetrabutylammonium hydrogen sulfate (153 mg, 0.45 mmol) as phase transfer catalyst according to method A. The residue was purified by silica gel column chromatography using *n*-hexane and EtOAc as eluent (*n*-hexane/EtOAc 80:20) to afford **12g** (985 mg, 2.77 mmol, 92%) as yellow oil. $C_{14}H_{14}BrNO_3S$; IR (neat): 1350, 1151 cm^{-1}; ^1H NMR (acetone-d_6): δ 3.19 (s, 3H), 3.79 (s, 3H), 7.00 (dd, J = 1.7, 2.5 Hz, 1H), 7.11–7.14 (m, 3H), 7.23 (ddd, J = 1.0, 2.6, 8.4 Hz, 1H), 7.48 (t, J = 8.1 Hz, 1H), 7.50–7.53 (m, 2H); ^{13}C NMR (acetone-d_6): δ 38.3, 56.0, 113.3, 120.1, 120.7, 121.1, 129.1, 131.1, 132.7, 138.4, 142.1, 160.8; GC–MS (EI) *m*/*z*: $[M]^+$ 356.38, 358.42.

5.3.8. 3-Bromo-N-(3-methoxyphenyl)-N-methylbenzenesulfonamide (**13a**)

The title compound was prepared by reaction of 3-methoxy-*N*-methylaniline (823 mg, 6 mmol) in CH_2Cl_2 (18 mL) and NaOH 25 M (6 mL) with 3-bromobenzenesulfonyl chloride (**15a**) (1.533 g, 6 mmol) and tetrabutylammonium hydrogen sulfate (306 mg, 0.9 mmol) as phase transfer catalyst according to method A. The residue was purified by silica gel column chromatography using *n*-hexane and EtOAc as eluent (*n*-hexane/EtOAc 80:20) to afford **13a** (2.112 g, 5.93 mmol, 99%) as brown oil. $C_{14}H_{14}BrNO_3S$; IR (neat): 1351, 1149 cm^{-1}; ^1H NMR (acetone-d_6): δ 3.22 (s, 3H), 3.75 (s, 3H), 6.71 (ddd, J = 0.9, 2.2, 7.9 Hz, 1H), 6.73 (t, J = 2.3 Hz, 1H), 6.89 (ddd,

J = 0.9, 2.5, 8.4 Hz, 1H), 7.25 (t, J = 8.0 Hz, 1H), 7.53–7.60 (m, 2H), 7.65 (t, J = 2.1 Hz, 1H), 7.86–7.88 (m, 1H); ^{13}C NMR (acetone-d_6): δ 38.7, 55.8, 113.4, 114.1, 119.3, 123.1, 125.8, 127.5, 130.5, 131.1, 132.0, 136.8, 143.4, 161.0; GC–MS (EI) m/z: $[M]^+$ 356.18, 358.25.

5.3.9. N-(3-Bromophenyl)-3-methoxy-N-methylbenzenesulfonamide (**13b**)

The title compound was prepared by reaction of 3-bromo-*N*-methylaniline (558 mg, 3 mmol) in CH_2Cl_2 (9 mL) and NaOH 25 M (3 mL) with 3-methoxybenzenesulfonyl chloride (**15a**) (425 μL, 3 mmol) and tetrabutylammonium hydrogen sulfate (153 mg, 0.45 mmol) as phase transfer catalyst according to method A. The residue was purified by silica gel column chromatography using *n*-hexane and EtOAc as eluent (*n*-hexane/EtOAc 80:20) to afford **13b** (880 mg, 2.47 mmol, 82%) as yellow oil. $C_{14}H_{14}BrNO_3S$; IR (neat): 1351, 1152 cm^{-1}; ^{1}H NMR (acetone-d_6): δ 3.21 (s, 3H), 3.79 (s, 3H), 6.99 (dd, J = 1.7, 2.5 Hz, 1H), 7.15 (ddd, J = 1.0, 2.2, 7.6 Hz, 1H), 7.18 (ddd, J = 1.0, 2.2, 8.2 Hz, 1H), 7.24 (ddd, J = 1.0, 2.6, 8.4 Hz, 1H), 7.30 (t, J = 8.0 Hz, 1H), 7.36 (t, J = 2.1 Hz, 1H), 7.46–7.51 (m, 2H); ^{13}C NMR (acetone-d_6): δ 38.4, 56.1, 113.2, 120.3, 120.7, 122.4, 126.1, 130.2, 131.0, 131.1, 131.3, 138.4, 144.2, 160.8; GC–MS (EI) m/z: $[M]^+$ 356.20, 358.22.

5.3.10. N-(3-Bromophenyl)-4-fluoro-3-methoxy-N-methylbenzenesulfonamide (**13c**)

The title compound was prepared by reaction of 3-bromo-*N*-methylaniline (744 mg, 4 mmol) in CH_2Cl_2 (12 mL) and NaOH 25 M (4 mL) with 2-fluoro-3-methoxybenzenesulfonyl chloride (899 μL, 4 mmol) and tetrabutylammonium hydrogen sulfate (204 mg, 0.6 mmol) as phase transfer catalyst according to method A. The residue was purified by silica gel column chromatography using *n*-hexane and EtOAc as eluent (*n*-hexane/EtOAc 80:20) to afford **13c** (1.00 g, 2.68 mmol, 67%) as pale yellow solid. $C_{14}H_{13}BrFNO_3S$; mp 94–98 °C; IR (neat): 1348, 1152 cm^{-1}; ^{1}H NMR (acetone-d_6): δ 3.22 (s, 3H), 3.85 (s, 3H), 7.12 (dd, J = 2.2, 7.9 Hz, 1H), 7.19–7.22 (m, 2H), 7.33 (t, J = 8.0 Hz, 1H), 7.35 (t, J = 8.5 Hz, 1H), 7.38 (t, J = 2.0 Hz, 1H), 7.50 (ddd, J = 0.9, 1.8, 8.0 Hz, 1H); ^{13}C NMR (acetone-d_6): δ 38.4, 56.8, 113.74, 113.76, 117.1, 117.3, 122.09, 122.15, 122.4, 126.3, 130.4, 131.1, 131.4, 133.50, 133.53, 144.2, 148.9, 149.0, 154.9, 156.9; GC–MS (EI) m/z: $[M]^+$ 374.48, 376.51.

5.3.11. 2′-Methoxy-N-(3-methoxyphenyl)-N-methyl-[1,1′-biphenyl]-4-sulfonamide (**9a**)

The title compound was prepared by reaction of 4-bromo-*N*-(3-methoxyphenyl)-*N*-methylbenzenesulfonamide (**12a**) (150 mg, 0.43 mmol) with 2-methoxyphenylboronic acid (96 mg, 0.63 mmol), cesium carbonate (411 mg, 1.26 mmol) and tetrakis(-triphenylphosphine)palladium (10 mg, 8.65×10^{-3} mmol) in DME/EtOH/H_2O (3 mL) according to method B. The residue was purified by silica gel column chromatography using *n*-hexane and EtOAc as eluent (*n*-hexane/EtOAc 80:20) to afford **9a** (84 mg, 0.22 mmol, 51%) as pale brown crystal. $C_{21}H_{21}NO_4S$; mp 82–83 °C; IR (neat): 1347, 1165, 1150 cm^{-1}; ^{1}H NMR (acetone-d_6): δ 3.23 (s, 3H), 3.74 (s, 3H), 3.84 (s, 3H), 6.23 (t, J = 2.2 Hz, 1H), 6.76 (ddd, J = 0.9, 2.0, 7.9 Hz, 1H), 6.87 (ddd, J = 0.9, 2.5, 8.3 Hz, 1H), 7.07 (dt, J = 1.2, 7.6 Hz, 1H), 7.14 (dd, J = 1.0, 8.4 Hz, 1H), 7.24 (t, J = 8.1 Hz, 1H), 7.36 (dd, J = 1.6, 7.6 Hz, 1H), 7.38–7.42 (m, 1H), 7.59–7.62 (m, 2H), 7.70–7.72 (m, 2H); ^{13}C NMR (acetone-d_6): δ 38.7, 55.7, 56.0, 112.6, 113.1, 113.8, 119.4, 121.9, 128.3, 129.4, 130.3, 130.7, 130.8, 131.5, 136.0, 143.9, 144.4, 157.5, 160.9; HPLC–MS (ESI) m/z: $[M + H]^+$ 383.85.

5.3.12. 3′-Methoxy-N-(3-methoxyphenyl)-N-methyl-[1,1′-biphenyl]-4-sulfonamide (**9b**)

The title compound was prepared by reaction of 4-bromo-*N*-(3-methoxyphenyl)-*N*-methylbenzenesulfonamide (**12a**) (150 mg, 0.43 mmol) with 2-methoxyphenylboronic acid (96 mg, 0.63 mmol), cesium carbonate (411 mg, 1.26 mmol) and tetrakis(-triphenylphosphine)palladium (10 mg, 8.65×10^{-3} mmol) in DME/EtOH/H_2O (3 mL) according to method B. The residue was purified by silica gel column chromatography using *n*-hexane and EtOAc as eluent (*n*-hexane/EtOAc 80:20) to afford **9b** (79 mg, 0.21 mmol, 48%) as yellow oil. $C_{21}H_{21}NO_4S$; IR (neat): 1338, 1160, 1147 cm^{-1}; ^{1}H NMR (acetone-d_6): δ 3.23 (s, 3H), 3.74 (s, 3H), 3.88 (s, 3H), 6.72–6.76 (m, 2H), 6.87 (ddd, J = 1.0, 2.5, 8.4 Hz, 1H), 7.01 (ddd, J = 0.9, 2.6, 8.3 Hz, 1H), 7.24 (t, J = 8.0 Hz, 1H), 7.27 (t, J = 1.9 Hz, 1H), 7.29 (ddd, J = 0.9, 1.6, 7.7 Hz, 1H), 7.42 (t, J = 8.1 Hz, 1H), 7.64–7.66 (m, 2H), 7.84–7.87 (m, 2H); ^{13}C NMR (acetone-d_6): δ 38.6, 55.68. 55.70, 113.3, 113.6, 113.7, 115.0, 119.2, 120.3, 128.2, 129.2, 130.3, 131.1, 136.7, 141.4, 143.9, 146.1, 160.9, 161.3; HPLC–MS (ESI) m/z: $[M + H]^+$ 383.65.

5.3.13. 4′-Methoxy-N-(3-methoxyphenyl)-N-methyl-[1,1′-biphenyl]-4-sulfonamide (**9c**)

The title compound was prepared by reaction of 4-bromo-*N*-(3-methoxyphenyl)-*N*-methylbenzenesulfonamide (**12a**) (150 mg, 0.43 mmol) with 4-methoxyphenylboronic acid (96 mg, 0.63 mmol), cesium carbonate (411 mg, 1.26 mmol) and tetrakis(-triphenylphosphine)palladium (10 mg, 8.65×10^{-3} mmol) in DME/EtOH/H_2O (3 mL) according to method B. The residue was purified by silica gel column chromatography using *n*-hexane and EtOAc as eluent (*n*-hexane/EtOAc 80:20) to afford **9c** (104 mg, 0.27 mmol, 63%) as colorless crystal. $C_{21}H_{21}NO_4S$; mp 130–132 °C; IR (neat): 1342, 1159, 1148 cm^{-1}; ^{1}H NMR (acetone-d_6): δ 3.22 (s, 3H), 3.74 (s, 3H), 3.87 (s, 3H), 6.72–6.76 (m, 2H), 6.87 (ddd, J = 0.9, 2.5, 8.3 Hz, 1H), 7.06–7.09 (m, 2H), 7.23 (t, J = 8.2 Hz, 1H), 7.60–7.63 (m, 2H), 7.68–7.72 (m, 2H), 7.79–7.82 (m, 2H); ^{13}C NMR (acetone-d_6): δ 38.6, 55.66, 55.72, 113.3, 113.6, 115.4, 119.2, 127.4, 129.25, 129.27, 130.3, 132.1, 135.7, 143.9, 145.9, 160.9, 161.3; HPLC–MS (ESI) m/z: $[M + H]^+$ 384.21.

5.3.14. 2′-Methoxy-N-methyl-N-phenyl-[1,1′-biphenyl]-4-sulfonamide (**9d**)

The title compound was prepared by reaction of 4-bromo-*N*-methyl-*N*-phenylbenzenesulfonamide (**12b**) (326 mg, 1 mmol) with 2-methoxyphenylboronic acid (228 mg, 1.5 mmol), cesium carbonate (978 mg, 3 mmol) and tetrakis(triphenylphosphine) palladium (23 mg, 19.90×10^{-3} mmol) in DME/EtOH/H_2O (3 mL) according to method B. The residue was purified by silica gel column chromatography using *n*-hexane and EtOAc as eluent (*n*-hexane/EtOAc 80:20) to afford **9d** (239 mg, 0.68 mmol, 68%) as yellow oil. $C_{20}H_{19}NO_3S$; IR (neat): 1347, 1172, 1152 cm^{-1}; ^{1}H NMR (acetone-d_6): δ 3.24 (s, 3H), 3.84 (s, 3H), 7.07 (dt, J = 1.0, 7.6 Hz, 1H), 7.15 (dd, J = 0.9, 8.4 Hz, 1H), 7.18–7.20 (m, 2H), 7.27–7.31 (m, 1H), 7.33–7.42 (m, 4H), 7.56–7.59 (m, 2H), 7.69–7.72 (m, 2H); ^{13}C NMR (acetone-d_6): δ 38.5, 56.0, 112.7, 121.8, 127.3, 128.0, 128.3, 129.4, 129.7, 130.7, 130.8, 131.5, 136.0, 142.8, 144.3, 157.5; HPLC–MS (ESI) m/z: $[M]^+$ 353.78.

5.3.15. 3′-Methoxy-N-(2-methoxyphenyl)-N-methyl-[1,1′-biphenyl]-4-sulfonamide (**9e**)

The title compound was prepared by reaction of 4-bromo-*N*-(2-methoxyphenyl)-*N*-methylbenzenesulfonamide (**12c**) (270 mg, 0.76 mmol) with 3-methoxyphenylboronic acid (173 mg, 1.14 mmol), cesium carbonate (743 mg, 2.28 mmol) and tetrakis(-triphenylphosphine)palladium (18 mg, 15.58×10^{-3} mmol) in DME/EtOH/H_2O (3 mL) according to method B. The residue was purified by silica gel column chromatography using *n*-hexane and EtOAc as eluent (*n*-hexane/EtOAc 80:20) to afford **9e** (275 mg, 0.72 mmol, 94%) as yellow oil. $C_{21}H_{21}NO_4S$; IR (neat): 1342, 1171, 1152 cm^{-1}; ^{1}H NMR (acetone-d_6): δ 3.22 (s, 3H), 3.39 (s, 3H), 3.88 (s, 3H), 6.92–6.96 (m, 2H), 7.01 (ddd, J = 0.9, 2.6, 8.3 Hz, 1H), 7.27–7.33 (m, 4H), 7.43 (t, J = 8.2 Hz, 1H), 7.71–7.73 (m, 2H), 7.82–7.85 (m,

2H); ^{13}C NMR (acetone-d_6): δ 38.3, 55.4, 55.7, 113.0, 113.7, 114.7, 120.4, 121.3, 128.0, 128.9, 130.0, 130.5, 131.1, 132.7, 139.6, 141.8, 145.6, 157.5, 161.3; HPLC–MS (ESI) *m*/*z*: $[M + H]^+$ 383.89.

5.3.16. 3′-Methoxy-N-(4-methoxyphenyl)-N-methyl-[1,1′-biphenyl]-4-sulfonamide (**9f**)

The title compound was prepared by reaction of 4-bromo-*N*-(4-methoxyphenyl)-*N*-methylbenzenesulfonamide (**12d**) (356 mg, 1 mmol) with 3-methoxyphenylboronic acid (228 mg, 1.5 mmol), cesium carbonate (978 mg, 3 mmol) and tetrakis(triphenylphosphine)palladium (23 mg, 19.90×10^{-3} mmol) in DME/EtOH/H_2O (3 mL) according to method B. The residue was purified by silica gel column chromatography using *n*-hexane and EtOAc as eluent (*n*-hexane/EtOAc 80:20) to afford **9f** (305 mg, 0.80 mmol, 80%) as pale brown solid. $C_{21}H_{21}NO_4S$; mp 86–87 °C; IR (neat): 1345, 1170, 1153 cm^{-1}; ^{1}H NMR (acetone-d_6): δ 3.19 (s, 3H), 3.79 (s, 3H), 3.88 (s, 3H), 6.85–6.89 (m, 2H), 7.02 (ddd, *J* = 1.0, 2.6, 8.3 Hz, 1H), 7.04–7.07 (m, 2H), 7.27–7.28 (m, 1H), 7.29–7.31 (m, 1H), 7.42 (t, *J* = 8.1 Hz, 1H), 7.60–7.63 (m, 2H), 7.83–7.86 (m, 2H); ^{13}C NMR (acetone-d_6): δ 38.9, 55.7, 55.8, 113.6, 114.8, 115.0, 120.4, 128.2, 128.9, 129.3, 131.1, 135.3, 136.7, 141.4, 146.0, 159.7, 161.3; HPLC–MS (ESI) *m*/*z*: $[M + H]^+$ 383.97.

5.3.17. N-(3-Methoxyphenyl)-N-methyl-4-(thiophen-2-yl) benzenesulfonamide (**9g**)

The title compound was prepared by reaction of 4-bromo-*N*-(3-methoxyphenyl)-*N*-methylbenzenesulfonamide (**12a**) (356 mg, 1 mmol) with 2-thiopheneboronic acid (192 mg, 1.5 mmol), cesium carbonate (978 mg, 3 mmol) and tetrakis(triphenylphosphine) palladium (23 mg, 19.90×10^{-3} mmol) in DME/EtOH/H_2O (3 mL) according to method B. The residue was purified by silica gel column chromatography using *n*-hexane and EtOAc as eluent (*n*-hexane/EtOAc 80:20) to afford **9g** (253 mg, 0.70 mmol, 70%) as pale brown solid. $C_{18}H_{17}NO_3S_2$; mp 79–81 °C; IR (neat): 1341, 1153 cm^{-1}; ^{1}H NMR (acetone-d_6): δ 3.22 (s, 3H), 3.74 (s, 3H), 6.73 (ddd, *J* = 0.9, 2.1, 8.1 Hz, 1H), 6.76 (t, *J* = 2.3 Hz, 1H), 6.87 (ddd, *J* = 0.9, 2.6, 8.4 Hz, 1H), 7.19 (dd, *J* = 3.8, 5.1 Hz, 1H), 7.23 (t, *J* = 8.1 Hz, 1H), 7.58–7.61 (m, 3H), 7.65 (dd, *J* = 1.0, 3.6 Hz, 1H), 7.83–7.86 (m, 2H); ^{13}C NMR (acetone-d_6): δ 37.7, 54.7, 112.4, 112.7, 118.2, 125.4, 125.5, 127.1, 128.58, 128.63, 129.4, 135.2, 138.5, 141.8, 142.9, 159.9; GC–MS (EI) *m*/*z*: $[M]^+$ 359.35.

5.3.18. N-(3-Methoxyphenyl)-N-methyl-4-(thiophen-3-yl) benzenesulfonamide (**9h**)

The title compound was prepared by reaction of 4-bromo-*N*-(3-methoxyphenyl)-*N*-methylbenzenesulfonamide (**12a**) (300 mg, 0.84 mmol) with 3-thiopheneboronic acid (162 mg, 1.26 mmol), cesium carbonate (821 mg, 3 mmol) and tetrakis(triphenylphosphine) palladium (19 mg, 16.44×10^{-3} mmol) in DME/EtOH/H_2O (3 mL) according to method B. The residue was purified by silica gel column chromatography using *n*-hexane and EtOAc as eluent (*n*-hexane/EtOAc 80:20) to afford **9h** (144 mg, 0.40 mmol, 48%) as pale brown solid. $C_{18}H_{17}NO_3S_2$; mp 92–94 °C; IR (neat): 1344, 1156 cm^{-1}; ^{1}H NMR (acetone-d_6): δ 3.22 (s, 3H), 3.74 (s, 3H), 6.72 (ddd, *J* = 0.9, 2.0, 7.9 Hz, 1H), 6.76 (t, *J* = 2.4 Hz, 1H), 6.87 (ddd, *J* = 0.9, 2.5, 8.4 Hz, 1H), 7.23 (t, *J* = 8.1 Hz, 1H), 7.58–7.64 (m, 4H), 7.89–7.92 (m, 2H), 7.96 (dd, *J* = 1.6, 2.7 Hz, 1H); ^{13}C NMR (acetone-d_6): δ 38.6, 55.7, 113.3, 113.6, 119.2, 123.8, 127.0, 127.3, 128.1, 129.4, 130.3, 136.0, 140.8, 141.2, 143.4, 160.9; GC–MS (EI) *m*/*z*: $[M]^+$ 359.24.

5.3.19. N-(3-Hydroxyphenyl)-3′-methoxy-N-methyl-[1,1′-biphenyl]-4-sulfonamide (**9i**)

The title compound was prepared by reaction of 4-bromo-*N*-(3-hydroxyphenyl)-*N*-methylbenzenesulfonamide (**12e**) (90 mg, 0.26 mmol) with 3-methoxyphenylboronic acid (59 mg, 0.39 mmol), cesium carbonate (258 mg, 0.79 mmol) and tetrakis(triphenylphosphine)palladium (6 mg, 5.19×10^{-3} mmol) in DME/EtOH/H_2O (3 mL) according to method B. The residue was purified by silica gel column chromatography using *n*-hexane and EtOAc as eluent (*n*-hexane/EtOAc 50:50) to afford **9i** (87 mg, 0.24 mmol, 91%) as pale brown solid. $C_{20}H_{19}NO_4S$; mp 125–126 °C; IR (neat): 3377, 1342, 1167, 1148 cm^{-1}; ^{1}H NMR (acetone-d_6): δ 3.19 (s, 3H), 3.87 (s, 3H), 6.60 (ddd, *J* = 0.9, 2.2, 8.1 Hz, 1H), 6.70 (t, *J* = 2.3 Hz, 1H), 6.76 (ddd, *J* = 0.9, 2.3, 8.2 Hz, 1H), 7.00 (ddd, *J* = 0.9, 2.6, 8.3 Hz, 1H), 7.14 (t, *J* = 8.1 Hz, 1H), 7.27 (t, *J* = 1.8 Hz, 1H), 7.29 (ddd, *J* = 1.0, 1.7, 7.7 Hz, 1H), 7.42 (t, *J* = 8.0 Hz, 1H), 7.62–7.65 (m, 2H), 7.83–7.86 (m, 2H), 8.49 (s, 1H); ^{13}C NMR (acetone-d_6): δ 38.6, 55.7, 113.5, 114.6, 115.0, 115.1, 117.9, 120.3, 128.2, 129.2, 130.3, 131.1, 136.7, 141.4, 143.8, 146.0, 158.5, 161.3; HPLC–MS (ESI) *m*/*z*: $[M + H]^+$ 369.91.

5.3.20. N-(3-Hydroxyphenyl)-N,3′-dimethyl-[1,1′-biphenyl]-4-sulfonamide (**9j**)

The title compound was prepared by reaction of 4-bromo-*N*-(3-hydroxyphenyl)-*N*-methylbenzenesulfonamide (**12e**) (200 mg, 0.58 mmol) with 3-tolylboronic acid (118 mg, 0.87 mmol), cesium carbonate (567 mg, 1.74 mmol) and tetrakis(triphenylphosphine) palladium (13 mg, 11.25×10^{-3} mmol) in DME/EtOH/H_2O (3 mL) according to method B. The residue was purified by silica gel column chromatography using *n*-hexane and EtOAc as eluent (*n*-hexane/EtOAc 70:30) to afford **9j** (98 mg, 0.28 mmol, 48%) as brown oil. $C_{20}H_{19}NO_3S$; IR (neat): 3376, 1341, 1163, 1147 cm^{-1}; ^{1}H NMR (acetone-d_6): δ 2.42 (s, 3H), 3.20 (s, 3H), 6.60 (ddd, *J* = 0.9, 2.2, 8.0 Hz, 1H), 6.70 (t, *J* = 2.3 Hz, 1H), 6.77 (ddd, *J* = 1.0, 2.5, 8.2 Hz, 1H), 7.13 (t, *J* = 8.1 Hz, 1H), 7.25–7.28 (m, 1H), 7.39 (t, *J* = 7.7 Hz, 1H), 7.51–7.54 (m, 1H), 7.56–7.57 (m, 1H), 7.64 (dt, *J* = 2.0, 8.7, 2H), 7.84 (dt, *J* = 2.0, 8.7, 2H), 8.70 (br s, 1H); ^{13}C NMR (acetone-d_6): δ 21.4, 38.6, 114.6, 115.1, 117.9, 125.2, 128.0, 128.8, 129.2, 129.9, 130.1, 130.3, 136.5, 139.6, 139.9, 143.8, 146.2, 158.6; HPLC–MS (ESI) *m*/*z*: $[M + H]^+$ 353.90.

5.3.21. N-(4-Hydroxyphenyl)-N-methyl-4-(pyridin-3-yl) benzenesulfonamide (**9k**)

The title compound was prepared by reaction of 4-bromo-*N*-(3-hydroxyphenyl)-*N*-methylbenzenesulfonamide (**12e**) (200 mg, 0.58 mmol) with pyridine-3-boronic acid (107 mg, 0.87 mmol), cesium carbonate (567 mg, 1.74 mmol) and tetrakis(-triphenylphosphine)palladium (13 mg, 11.25×10^{-3} mmol) in DME/EtOH/H_2O (3 mL) according to method B. The residue was purified by silica gel column chromatography using EtOAc as eluent to afford **9k** (134 mg, 0.39 mmol, 69%) as colorless crystal. $C_{18}H_{16}N_2O_3S$; mp 165–168 °C; IR (neat): 3380, 1341, 1165, 1152 cm^{-1}; ^{1}H NMR (acetone-d_6): δ 3.21 (s, 3H), 6.61 (ddd, *J* = 0.9, 2.1, 8.0 Hz, 1H), 6.71 (t, *J* = 2.3 Hz, 1H), 6.78 (ddd, *J* = 0.9, 2.5, 8.2 Hz, 1H), 7.14 (t, *J* = 8.1 Hz, 1H), 7.51 (ddd, *J* = 0.9, 4.9, 8.1 Hz, 1H), 7.70 (dt, *J* = 1.9, 8.5 Hz, 2H), 7.92 (dt, *J* = 1.9, 8.5 Hz, 2H), 8.12 (ddd, *J* = 1.7, 2.4, 4.1 Hz, 1H), 8.64 (dd, *J* = 1.5, 4.8 Hz, 1H), 8.94 (d, *J* = 2.1 Hz, 1H), exchange of hydroxyl proton with deuterated solvent; ^{13}C NMR (acetone-d_6): δ 38.6, 114.6, 115.2, 117.9, 124.7, 128.3, 129.4, 130.4, 135.3, 135.4, 137.4, 143.1, 143.7, 149.1, 150.5, 158.6; HPLC–MS (ESI) *m*/*z*: $[M + H]^+$ 340.98.

5.3.22. N-(3-Hydroxyphenyl)-N-methyl-4-(thiophen-2-yl) benzenesulfonamide (**9l**)

The title compound was prepared by reaction of 4-bromo-*N*-(3-hydroxyphenyl)-*N*-methylbenzenesulfonamide (**12e**) (200 mg, 0.58 mmol) with 2-thiopheneboronic acid (111 mg, 0.87 mmol), cesium carbonate (567 mg, 1.74 mmol) and tetrakis(-triphenylphosphine)palladium (13 mg, 11.25×10^{-3} mmol) in DME/EtOH/H_2O (3 mL) according to method B. The residue was purified

by silica gel column chromatography using *n*-hexane and EtOAc as eluent (*n*-hexane/EtOAc 70:30) to afford **9l** (124 mg, 0.36 mmol, 62%) as pale brown crystal. $C_{17}H_{15}NO_3S_2$; mp 146–148 °C; IR (neat): 3379, 1336, 1158, 1138 cm^{-1}; ^1H NMR (acetone-d_6): δ 3.19 (s, 3H), 6.61 (ddd, $J = 0.9$, 2.2, 8.1 Hz, 1H), 6.70 (t, $J = 2.3$ Hz, 1H), 6.77 (ddd, $J = 0.9$, 2.4, 8.2 Hz, 1H), 7.13 (t, $J = 8.1$ Hz, 1H), 7.19 (dd, $J = 3.6$, 5.1 Hz, 1H), 7.57–7.61 (m, 3H), 7.65 (dd, $J = 1.0$, 3.6 Hz, 1H), 7.85 (dt, $J = 2.0$, 8.7 Hz, 2H), 8.53 (br s, 1H); ^{13}C NMR (acetone-d_6): δ 38.6, 114.6, 115.2, 118.0, 126.3, 126.4, 128.0, 129.5, 129.6, 130.3, 136.2, 139.4, 142.8, 143.8, 158.5; HPLC–MS (ESI) *m/z*: $[M]^+$ 345.92.

5.3.23. 3′-Hydroxy-N-(3-methoxyphenyl)-N-methyl-[1,1′-biphenyl]-4-sulfonamide (**9m**)

The title compound was prepared by reaction of 4-bromo-*N*-(3-methoxyphenyl)-*N*-methylbenzenesulfonamide (**12a**) (356 mg, 1 mmol) with 3-hydroxyphenylboronic acid (207 mg, 1.5 mmol), cesium carbonate (978 mg, 3 mmol) and tetrakis(triphenylphosphine)palladium (23 mg, 19.90×10^{-3} mmol) in DME/EtOH/H_2O (3 mL) according to method B. The residue was purified by silica gel column chromatography using *n*-hexane and EtOAc as eluent (*n*-hexane/EtOAc 60:40) to afford **9m** (246 mg, 0.67 mmol, 67%) as colorless crystal. $C_{20}H_{19}NO_4S$; mp 109–112 °C; IR (neat): 3378, 1339, 1162, 1147 cm^{-1}; ^1H NMR (acetone-d_6): δ 3.22 (s, 3H), 3.73 (s, 3H), 6.71–6.74 (m, 2H), 6.86 (ddd, $J = 0.9$, 2.5, 8.4 Hz, 1H), 6.91 (ddd, $J = 0.9$, 2.5, 8.2 Hz, 1H), 7.16–7.19 (m, 2H), 7.20–7.24 (m, 1H), 7.30–7.34 (m, 1H), 7.62–7.65 (m, 2H), 7.78–7.81 (m, 2H), 8.55 (s, 1H); ^{13}C NMR (acetone-d_6): δ 38.6, 55.7, 113.3, 113.7, 114.9, 116.4, 119.2, 119.3, 128.0, 129.2, 130.3, 131.1, 136.5, 141.4, 143.9, 146.2, 158.9, 160.9; GC–MS (EI) *m/z*: $[M]^+$ 369.29.

5.3.24. 3′-Hydroxy-N-(3-hydroxyphenyl)-N-methyl-[1,1′-biphenyl]-4-sulfonamide (**9n**)

The title compound was prepared by reaction of 3′-methoxy-*N*-(3-methoxyphenyl)-*N*-methyl-[1,1′-biphenyl]-4-sulfonamide (**9b**) (254 mg, 0.66 mmol) with Et_3N (1.47 mL, 10.56 mmol) and with $BF_3 \cdot SMe_2$ (1.11 mL, 10.56 mmol) in CH_2Cl_2 (10 mL) according to method C. The residue was purified by silica gel column chromatography using *n*-hexane and EtOAc as eluent (*n*-hexane/EtOAc 60:40) to afford **9n** (230 mg, 0.65 mmol, 98%) as colorless crystal. $C_{19}H_{17}NO_4S$; mp 120–124 °C; IR (neat): 3380, 1335, 1160, 1146 cm^{-1}; ^1H NMR (acetone-d_6): δ 3.20 (s, 3H), 6.61 (ddd, $J = 0.9$, 2.0, 8.0 Hz, 1H), 6.70 (t, $J = 2.3$ Hz, 1H), 6.77 (ddd, $J = 0.8$, 2.4, 8.1 Hz, 1H), 6.92 (ddd, $J = 1.0$, 2.3, 8.1 Hz, 1H), 7.13 (t, $J = 8.1$ Hz, 1H), 7.17–7.20 (m, 2H), 7.33 (t, $J = 7.8$ Hz, 1H), 7.62–7.65 (m, 2H), 7.79–7.81 (m, 2H), 8.50 (s, 1H), 8.57 (s, 1H); ^{13}C NMR (acetone-d_6): δ 38.6, 114.6, 114.9, 115.1, 116.4, 118.0, 119.3, 128.0, 129.2, 130.3, 131.1, 136.5, 141.4, 143.8, 146.1, 158.5, 158.9; GC–MS (EI) *m/z*: $[M]^+$ 355.26.

5.3.25. 3′-Methoxy-N-(3-methoxybenzyl)-N-methyl-[1,1′-biphenyl]-4-sulfonamide (**9o**)

The title compound was prepared by reaction of 4-bromo-*N*-(3-methoxybenzyl)-*N*-methylbenzenesulfonamide (**12f**) (356 mg, 1 mmol) with 3-methoxyphenylboronic acid (228 mg, 1.5 mmol), cesium carbonate (978 mg, 3 mmol) and tetrakis(triphenylphosphine)palladium (23 mg, 19.90×10^{-3} mmol) in DME/EtOH/H_2O (3 mL) according to method B. The residue was purified by silica gel column chromatography using *n*-hexane and EtOAc as eluent (*n*-hexane/EtOAc 80:20) to afford **9o** (254 mg, 0.64 mmol, 64%) as orange oil. $C_{22}H_{23}NO_4S$; IR (neat): 1338, 1158 cm^{-1}; ^1H NMR (acetone-d_6): δ 2.65 (s, 3H), 3.77 (s, 3H), 3.90 (s, 3H), 4.20 (s, 2H), 6.87 (ddd, $J = 0.6$, 2.5, 8.2 Hz, 1H), 6.91–6.95 (m, 2H), 7.03 (ddd, $J = 0.9$, 2.6, 8.3 Hz, 1H), 7.28 (t, $J = 7.7$ Hz, 1H), 7.30 (t, $J = 1.7$ Hz, 1H), 7.32 (ddd, $J = 1.0$, 1.6, 7.6 Hz, 1H), 7.45 (t, $J = 8.1$ Hz, 1H), 7.92–7.97 (m, 4H); ^{13}C NMR (acetone-d_6): δ 35.0, 54.7, 55.5, 55.7, 113.6, 114.1, 114.6, 115.0, 120.4, 121.3, 128.6, 128.9, 130.5, 131.1, 137.5, 138.8, 141.5, 146.0, 161.0, 161.3; HPLC–MS (ESI) *m/z*: $[M + H]^+$ 397.79.

5.3.26. 3′-Hydroxy-N-(3-hydroxybenzyl)-N-methyl-[1,1′-biphenyl]-4-sulfonamide (**9p**)

The title compound was prepared by reaction of 3′-methoxy-*N*-(3-methoxybenzyl)-*N*-methyl-[1,1′-biphenyl]-4-sulfonamide (**9o**) (240 mg, 0.6 mmol) with Et_3N (1.67 mL, 12 mmol) and with $BF_3 \cdot SMe_2$ (1.26 mL, 12 mmol) in CH_2Cl_2 (10 mL) according to method C. The residue was purified by silica gel column chromatography using *n*-hexane and EtOAc as eluent (*n*-hexane/EtOAc 60:40) to afford **9p** (202 mg, 0.55 mmol, 91%) as pale brown solid. $C_{20}H_{19}NO_4S$; mp 180–181 °C; IR (neat): 3285, 2976, 2923, 2880, 2856, 1590, 1483, 1453, 1321, 1304, 1296, 1148, 1085, 835, 768, 694, 584 cm^{-1}; ^1H NMR (acetone-d_6): δ 2.65 (s, 3H), 4.15 (s, 2H), 6.78 (ddd, $J = 0.8$, 2.5, 8.2 Hz, 1H), 6.80–6.83 (m, 1H), 6.87–6.89 (m, 1H), 6.94 (ddd, $J = 0.9$, 2.4, 8.2 Hz, 1H), 7.18 (t, $J = 7.9$ Hz, 1H), 7.21 (t, $J = 2.1$ Hz, 1H), 7.22 (ddd, $J = 0.9$, 1.6, 7.6 Hz, 1H), 7.33–7.37 (m, 1H), 7.89 (dt, $J = 2.2$, 8.7 Hz, 2H), 7.94 (dt, $J = 2.2$, 8.7 Hz, 2H), 8.37 (br s, 1H), 8.58 (br s, 1H); ^{13}C NMR (acetone-d_6): δ 34.9, 54.6, 114.9, 115.6, 115.9, 116.4, 119.3, 120.2, 128.5, 128.9, 130.5, 131.1, 137.5, 138.8, 141.6, 146.1, 158.6, 159.0; HPLC–MS (ESI) *m/z*: $[M + 1]^+$ 369.77.

5.3.27. 3-Methoxy-N-(3′-methoxy-[1,1′-biphenyl]-4-yl)-N-methylbenzenesulfonamide (**9q**)

The title compound was prepared by reaction of *N*-(4-bromophenyl)-3-methoxy-*N*-methylbenzenesulfonamide (**12g**) (356 mg, 1 mmol) with 3-methoxyphenylboronic acid (228 mg, 1.5 mmol), cesium carbonate (978 mg, 3 mmol) and tetrakis(-triphenylphosphine)palladium (23 mg, 19.90×10^{-3} mmol) in DME/EtOH/H_2O (3 mL) according to method B. The residue was purified by silica gel column chromatography using *n*-hexane and EtOAc as eluent (*n*-hexane/EtOAc 50:50) to afford **9q** (237 mg, 0.62 mmol, 62%) as orange oil. $C_{21}H_{21}NO_4S$; IR (neat): 1349, 1171, 1151 cm^{-1}; ^1H NMR (acetone-d_6): δ 3.23 (s, 3H), 3.76 (s, 3H), 3.87 (s, 3H), 6.94 (ddd, $J = 0.9$, 2.6, 8.2 Hz, 1H), 7.01 (dd, $J = 1.7$, 2.5 Hz, 1H), 7.17–7.23 (m, 4H), 7.24 (dt, $J = 2.1$, 8.7 Hz, 2H), 7.36 (t, $J = 7.9$ Hz, 1H), 7.48 (t, $J = 8.0$ Hz, 1H), 7.64 (dt, $J = 2.1$, 8.7 Hz, 2H); ^{13}C NMR (acetone-d_6): δ 38.4, 55.6, 56.0, 113.2, 114.0, 120.01, 120.05, 120.7, 127.5, 128.1, 130.8, 131.0, 138.8, 140.5, 142.1, 142.3, 160.7, 161.2; HPLC–MS (ESI) *m/z*: $[M]^+$ 383.83.

5.3.28. 3-Hydroxy-N-(3′-hydroxy-[1,1′-biphenyl]-4-yl)-N-methylbenzenesulfonamide (**9r**)

The title compound was prepared by reaction of 3-methoxy-*N*-(3′-methoxy-[1,1′-biphenyl]-4-yl)-*N*-methylbenzenesulfonamide (**9q**) (200 mg, 0.52 mmol) with Et_3N (1.67 mL, 12 mmol) and with $BF_3 \cdot SMe_2$ (1.26 mL, 12 mmol) in CH_2Cl_2 (10 mL) according to method C. The residue was purified by silica gel column chromatography using *n*-hexane and EtOAc as eluent (*n*-hexane/EtOAc 60:40) to afford **9r** (157 mg, 0.44 mmol, 85%) as pale brown crystal. $C_{19}H_{17}NO_4S$; mp 150–154 °C; IR (neat): 3376, 2973, 2939, 2880, 2814, 1739, 1690, 1602, 1592, 1478, 1450, 1338, 1306, 1260, 1210, 1168, 1146, 1088, 837, 785, 685, 588 cm^{-1}; ^1H NMR (acetone-d_6): δ 3.22 (s, 3H), 6.85 (ddd, $J = 1.0$, 2.2, 8.2 Hz, 1H), 7.02 (t, $J = 1.9$ Hz, 1H), 7.08 (ddd, $J = 1.0$, 1.7, 7.7 Hz, 1H), 7.11–7.14 (m, 3H), 7.23 (dt, $J = 2.2$, 8.7 Hz, 2H), 7.28 (t, $J = 8.2$ Hz, 1H), 7.39 (t, $J = 7.7$ Hz, 1H), 7.59 (dt, $J = 2.2$, 8.7 Hz, 2H), 8.72 (br s, 2H); ^{13}C NMR (acetone-d_6): δ 38.5, 114.5, 115.2, 115.5, 118.9, 119.7, 120.9, 127.5, 127.9, 130.9, 131.0, 138.8, 140.4, 142.0, 142.3, 158.6, 158.8; HPLC–MS (ESI) *m/z*: $[M]^+$ 355.82.

5.3.29. 3′-Methoxy-N-(3-methoxyphenyl)-N-methyl-[1,1′-biphenyl]-3-sulfonamide (**10a**)

The title compound was prepared by reaction of 3-bromo-*N*-(3-methoxyphenyl)-*N*-methylbenzenesulfonamide (**13a**) (356 mg,

1 mmol) with 3-methoxyphenylboronic acid (228 mg, 1.5 mmol), cesium carbonate (978 mg, 3 mmol) and tetrakis(triphenylphosphine)palladium (23 mg, 19.90 × 10^{-3} mmol) in DME/EtOH/H_2O (3 mL) according to method B. The residue was purified by silica gel column chromatography using *n*-hexane and EtOAc as eluent (*n*-hexane/EtOAc 80:20) to afford **10a** (271 mg, 0.71 mmol, 71%) as yellow oil. $C_{21}H_{21}NO_4S$; IR (neat): 1349, 1165, 1149 cm^{-1}; ^1H NMR (acetone-d_6): δ 3.22 (s, 3H), 3.73 (s, 3H), 3.85 (s, 3H), 6.74–6.76 (m, 2H), 6.89 (ddd, J = 1.0, 2.3, 8.3 Hz, 1H), 6.97 (ddd, J = 0.9, 2.6, 8.2 Hz, 1H), 7.06 (t, J = 2.0 Hz, 1H), 7.11 (ddd, J = 0.9, 1.6, 7.6 Hz, 1H), 7.26 (t, J = 8.1 Hz, 1H), 7.39 (t, J = 8.1 Hz, 1H), 7.61–7.68 (m, 3H), 7.95 (ddd, J = 1.3, 1.9, 7.6 Hz, 1H); ^{13}C NMR (acetone-d_6): δ 38.6, 55.71, 55.72, 113.36, 113.38, 113.7, 114.7, 119.3, 120.2, 126.9, 127.4, 130.35, 130.43, 131.0, 132.4, 138.0, 141.5, 142.6, 143.9, 160.9, 161.3; HPLC–MS (ESI) m/z: $[M + H]^+$ 383.85.

5.3.30. 3′-Hydroxy-N-(3-hydroxyphenyl)-N-methyl-[1,1′-biphenyl]-3-sulfonamide (**10b**)

The title compound was prepared by reaction of 3′-methoxy-*N*-(3-methoxyphenyl)-*N*-methyl-[1,1′-biphenyl]-3-sulfonamide (**10a**) (261 mg, 0.68 mmol) with Et_3N (1.67 mL, 12 mmol) and with $BF_3 \cdot SMe_2$ (1.26 mL, 12 mmol) in CH_2Cl_2 (10 mL) according to method C. The residue was purified by silica gel column chromatography using *n*-hexane and EtOAc as eluent (*n*-hexane/EtOAc 60:40) to afford **10b** (221 mg, 0.62 mmol, 91%) as orange oil. $C_{19}H_{17}NO_4S$; IR (neat): 3380, 2961, 2934, 2863, 2816, 1699, 1594, 1484, 1462, 1457, 1412, 1338, 1308, 1206, 1161, 1146, 1083, 1065, 999, 944, 910, 865, 779, 692, 637, 593, 576 cm^{-1}; ^1H NMR (acetone-d_6): δ 3.21 (s, 3H), 6.61 (ddd, J = 1.0, 2.2, 8.1 Hz, 1H), 6.71 (t, J = 2.2 Hz, 1H), 6.78 (ddd, J = 0.9, 2.5, 8.2 Hz, 1H), 6.89 (ddd, J = 0.9, 2.5, 8.2 Hz, 1H), 7.03–7.06 (m, 2H), 7.15 (t, J = 8.1 Hz, 1H), 7.29 (dt, J = 0.4, 7.7 Hz, 1H), 7.57 (ddd, J = 1.2, 1.8, 7.8 Hz, 1H), 7.65 (dt, J = 0.6, 7.9 Hz, 1H), 7.69 (t, J = 1.9 Hz, 1H), 7.91 (ddd, J = 1.3, 1.9, 7.8 Hz, 1H), 8.52 (br s, 1H), 8.53 (br s, 1H); ^{13}C NMR (acetone-d_6): δ 38.6, 116.66, 116.75, 115.2, 116.1, 117.9, 119.1, 126.7, 127.3, 130.32, 130.35, 131.1, 132.1, 138.2, 141.5, 142.6, 143.8, 158.6, 158.9; HPLC–MS (ESI) m/z: $[M]^+$ 355.95.

5.3.31. 3-Methoxy-N-(3′-methoxy-[1,1′-biphenyl]-3-yl)-N-methylbenzenesulfonamide (**10c**)

The title compound was prepared by reaction of *N*-(3-bromophenyl)-3-methoxy-*N*-methylbenzenesulfonamide (**13b**) (356 mg, 1 mmol) with 3-methoxyphenylboronic acid (228 mg, 1.5 mmol), cesium carbonate (978 mg, 3 mmol) and tetrakis(-triphenylphosphine)palladium (23 mg, 19.90 × 10^{-3} mmol) in DME/EtOH/H_2O (3 mL) according to method B. The residue was purified by silica gel column chromatography using *n*-hexane and EtOAc as eluent (*n*-hexane/EtOAc 80:20) to afford **10c** (302 mg, 0.79 mmol, 79%) as yellow oil. $C_{21}H_{21}NO_4S$; IR (neat): 1349, 1166, 1150 cm^{-1}; ^1H NMR (acetone-d_6): δ 3.27 (s, 3H), 3.75 (s, 3H), 3.85 (s, 3H), 6.94 (ddd, J = 0.9, 2.6, 8.3 Hz, 1H), 7.00 (dd, J = 1.8, 2.5 Hz, 1H), 7.06 (t, J = 1.8 Hz, 1H), 7.11 (ddd, J = 1.0, 1.6, 7.6 Hz, 1H), 7.17–7.21 (m, 2H), 7.23 (ddd, J = 0.9, 2.6, 8.3 Hz, 1H), 7.33–7.35 (m, 1H), 7.36 (t, J = 7.9 Hz, 1H), 7.43 (t, J = 7.9 Hz, 1H), 7.50 (t, J = 8.0 Hz, 1H), 7.58 (ddd, J = 1.0, 1.7, 7.8 Hz, 1H); ^{13}C NMR (acetone-d_6): δ 38.6, 55.6, 56.0, 113.3, 113.4, 114.1, 120.0, 120.1, 120.8, 125.8, 126.6, 126.7, 130.1, 130.8, 131.0, 138.7, 142.4, 142.6, 143.3, 160.7, 161.2; HPLC–MS (ESI) m/z: $[M + H]^+$ 383.88.

5.3.32. 3-Hydroxy-N-(3′-hydroxy-[1,1′-biphenyl]-3-yl)-N-methylbenzenesulfonamide (**10d**)

The title compound was prepared by reaction of 3-methoxy-*N*-(3′-methoxy-[1,1′-biphenyl]-3-yl)-*N*-methylbenzenesulfonamide (**10c**) (275 mg, 0.72 mmol) with Et_3N (1.67 mL, 12 mmol) and with $BF_3 \cdot SMe_2$ (1.26 mL, 12 mmol) in CH_2Cl_2 (10 mL) according to method C. The residue was purified by silica gel column chromatography using *n*-hexane and EtOAc as eluent (*n*-hexane/EtOAc 60:40) to afford **10d** (136 mg, 0.38 mmol, 53%) as orange oil. $C_{19}H_{17}NO_4S$; IR (neat): 3379, 2941, 2873, 2814, 2696, 1690, 1598, 1590, 1577, 1474, 1450, 1418, 1338, 1306, 1259, 1231, 1164, 1146, 1088, 1072, 996, 937, 900, 856, 782, 751, 699, 685, 607, 582 cm^{-1}; ^1H NMR (acetone-d_6): δ 3.26 (s, 3H), 6.85 (ddd, J = 0.9, 2.5, 8.1 Hz, 1H), 7.02–7.05 (m, 3H), 7.08 (ddd, J = 1.0, 1.6, 7.6 Hz, 1H), 7.11–7.14 (m, 2H), 7.26 (dt, J = 0.5, 7.3 Hz, 1H), 7.37–7.42 (m, 3H), 7.53 (ddd, J = 1.0, 1.8, 7.8 Hz, 1H), 8.62 (br s, 1H), 8.84 (br s, 1H); ^{13}C NMR (acetone-d_6): δ 38.6, 114.7, 115.2, 115.6, 119.0, 119.7, 120.9, 125.9, 126.0, 126.4, 130.0, 130.8, 131.0, 138.8, 142.5, 142.6, 143.3, 158.6, 158.8; HPLC–MS (ESI) m/z: $[M]^+$ 355.88.

5.3.33. 4-Fluoro-3-methoxy-N-(3′-methoxybiphenyl-3-yl)-N-methylbenzenesulfonamide (**10e**)

The title compound was prepared by reaction of *N*-(3-bromophenyl)-4-fluoro-3-methoxy-*N*-methylbenzenesulfonamide (**13c**) (374 mg, 1 mmol) with 3-methoxyphenylboronic acid (228 mg, 1.5 mmol), cesium carbonate (978 mg, 3 mmol) and tetrakis(triphenylphosphine)palladium (23 mg, 19.90 × 10^{-3} mmol) in DME/EtOH/H_2O (3 mL) according to method B. The residue was purified by silica gel column chromatography using *n*-hexane and EtOAc as eluent (*n*-hexane/EtOAc 80:20) to afford **10e** (308 mg, 0.77 mmol, 77%) as yellow oil. $C_{21}H_{20}FNO_4S$; IR (neat): 1345, 1169, 1150 cm^{-1}; ^1H NMR (acetone-d_6): δ 3.27 (s, 3H), 3.78 (s, 3H), 3.85 (s, 3H), 6.94 (ddd, J = 0.7, 2.5, 8.3 Hz, 1H), 7.05–7.08 (m, 1H), 7.10–7.14 (m, 2H), 7.20 (ddd, J = 0.8, 2.0, 8.0 Hz, 1H), 7.22–7.25 (m, 1H), 7.31–7.40 (m, 3H), 7.45 (t, J = 7.9 Hz, 1H), 7.58–7.61 (m, 1H); ^{13}C NMR (acetone-d_6): δ 38.6, 55.6, 56.7, 113.3, 113.85. 113.88, 114.2, 117.0, 117.2, 120.1, 122.06, 122.13, 126.0, 126.6, 126.8, 130.2, 130.8, 133.76, 133.79, 142.4, 142.6, 143.2, 148.7, 148.8, 154.7, 156.7, 161.2; HPLC–MS (ESI) m/z: $[M]^+$ 401.76.

5.3.34. 4-Fluoro-3-hydroxy-N-(3′-hydroxybiphenyl-3-yl)-N-methylbenzenesulfonamide (**10f**)

The title compound was prepared by reaction of 4-fluoro-3-methoxy-*N*-(3′-methoxybiphenyl-3-yl)-*N*-methylbenzenesulfonamide (**10e**) (308 mg, 0.77 mmol) with Et_3N (1.67 mL, 12 mmol) and with $BF_3 \cdot SMe_2$ (1.26 mL, 12 mmol) in CH_2Cl_2 (10 mL) according to method C. The residue was purified by silica gel column chromatography using *n*-hexane and EtOAc as eluent (*n*-hexane/EtOAc 70:30) to afford **10f** (204 mg, 0.55 mmol, 71%) as colorless solid. $C_{19}H_{16}FNO_4S$; mp 148–150 °C; IR (neat): 3380, 2959, 2868, 1348, 1310, 1231, 1171, 1151 cm^{-1}; ^1H NMR (acetone-d_6): δ 3.26 (s, 3H), 6.85 (ddd, J = 0.9, 2.5, 8.1 Hz, 1H), 7.03–7.06 (m, 2H), 7.10–7.15 (m, 2H), 7.18 (dd, J = 2.3, 8.1 Hz, 1H), 7.25–7.33 (m, 2H), 7.39–7.43 (m, 2H), 7.54 (ddd, J = 1.0, 1.8, 7.6 Hz, 1H), 8.48 (br s, 1H), 9.36 (br s, 1H); ^{13}C NMR (acetone-d_6): δ 38.5, 114.7, 115.6, 117.35, 117.51, 118.24, 118.27, 119.0, 121.06, 121.12, 125.96, 126.1, 126.5, 130.1, 130.9, 133.96, 133.99, 142.4, 142.6, 143.1, 146.1, 146.2, 154.1, 156.1, 158.8; HPLC–MS (ESI) m/z: $[M]^+$ 373.91.

5.4. Physicochemical properties determination

The log *P* and p*K*a values were calculated from ACD/Labs Percepta 2012 Release program and experimentally determined using SiriusT3 apparatus from Sirius Analytical Instruments.

The logarithm of partition constant P (log *P*) was calculated using the "GALAS" method (Global, Adjusted Locally According to Similarity). The program predicts *c*log *P* by comparing the molecule with structurally similar molecules where experimental data are known. The logarithm of dissociation constant K_a (p*K*a) was obtained using the classical method where Hammet-type equations and electronic substituent constants (σ) are used to calculate p*K*a values for ionizable groups.

The solubility *e*log *S* was experimentally determined using SiriusT3 apparatus from Sirius Analytical Instruments at 25 °C in a solution of in KCl 1.15 M solution. Solubility *S* was given in mol/L and it was obtained using the following equation: $S = 10^{logS}$.

5.5. Biological methods

[2,4,6,7-^{3}H]-E2 and [2,4,6,7-^{3}H]-E1 were purchased from Perkin–Elmer, Boston. Quickszint Flow 302 scintillator fluid was bought from Zinsser Analytic, Frankfurt. Other chemicals were purchased from Sigma, Roth or Merck.

5.5.1. 17β-HSD1 and 17β-HSD2 enzyme preparations

Cytosolic (17β-HSD1) and microsomal (17β-HSD2) fractions were obtained from human placenta according to previously described procedures [45,48,49]. Fresh tissue was homogenized and the enzymes were separated by fractional centrifugation at 1000 *g*, 10,000 *g* and 150,000 *g*. The pellet fraction containing the microsomal 17β-HSD2 was used for the determination of 17β-HSD2 inhibition, while 17β-HSD1 was obtained after precipitation with ammonium sulfate from the cytosolic fraction to be used for testing of 17β-HSD1 inhibition. Aliquots containing 17β-HSD1 or 17β-HSD2 were frozen for storage.

5.5.2. Inhibition of 17β-HSD2 in cell-free assay

Inhibitory activities were evaluated by an established method with minor modifications [50–52]. Briefly, the enzyme preparation 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 [^{3}H]-E2 (final concentration: 500 nM, 0.11 μCi). After 20 min, 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, 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 radio flow detector (Berthold Technologies, Bad Wildbad). The conversion rate was calculated according to the following equation: % conversion = (%E1/(%E1 + % E2)) × 100. Each value was calculated from at least three independent experiments.

5.5.3. Inhibition of 17β-HSD1 in cell-free assay

The 17β-HSD1 inhibition assay was performed similarly to the 17β-HSD2 test. The microsomal fraction was incubated with NADH [500 μM], test compound and a mixture of unlabeled- and [^{3}H]-E1 (final concentration: 500 nM, 0.15 μCi) for 10 min at 37 °C. Further treatment of the samples and HPLC separation was carried out as mentioned above for 17β-HSD2.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.ejmech.2013.08.026. These data include MOL files and InChiKeys of the most important compounds described in this article.

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