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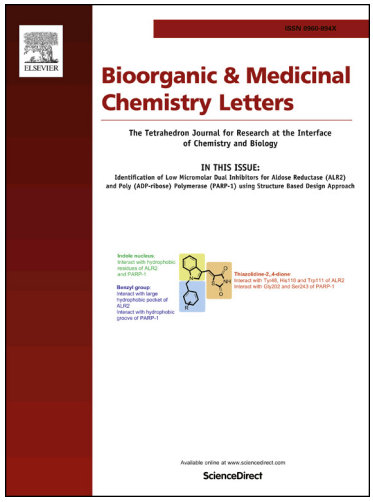

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Phenyl benzenesulfonates and -sulfonamides as 17β-hydroxysteroid dehydrogenase type 2 inhibitors: synthesis and SAR-analysis

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Abstract

17β-Hydroxysteroid dehydrogenase type 2 (17β-HSD2) converts the potent estrogen estradiol into the weakly active keto form estrone. Because of its expression in bone, inhibition of 17β-HSD2 provides an attractive strategy for the treatment of osteoporosis, a condition that is often caused by a decrease of the active sex steroids. Currently, there are no drugs on the market targeting 17β-HSD2, but in multiple studies, synthesis and biological evaluation of promising 17β-HSD2 inhibitors have been reported. Our previous work led to the identification of phenylbenzene-sulfonamides and -sulfonates as new 17β-HSD2 inhibitors by ligand-based pharmacophore modeling and virtual screening. In this study, new molecules representing this scaffold were synthesized and tested *in vitro* for their 17β-HSD2 activity to derive more profound structure-activity-relationship rules.

Keywords: 17β-HSD2, Inhibitor, Osteoporosis, Virtual screening, Estrogen

The microsomal enzyme 17β-hydroxysteroid dehydrogenase 2 (17β-HSD2) regulates the intracellular concentrations of the sex steroid hormones estradiol and testosterone. It is responsible for the oxidative inactivation of estradiol into estrone and inactivation of testosterone into Δ4-androstene-3,17-dione (androstenedione), respectively (Figure 1)[1, 2]. Additionally, 17β-HSD2 is involved in the inactivation of 5α-dihydrotestosterone into 5α-androstanedione and conversion of androstenediol into dehydroepiandrosterone[2, 3].

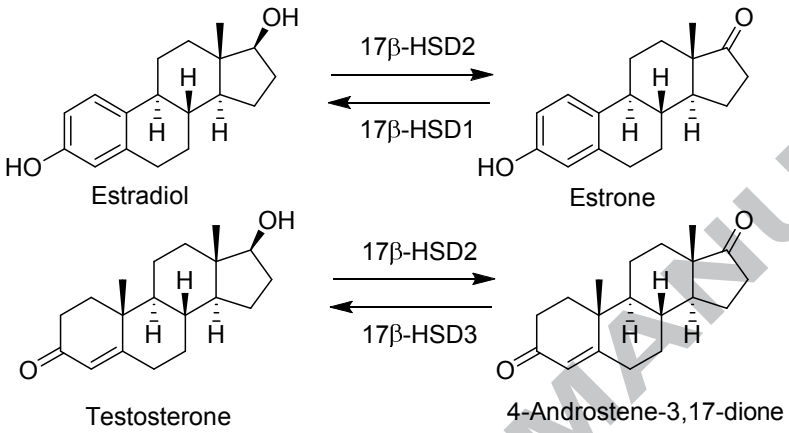


Figure 1: Reactions catalyzed by 17β-HSD2.

17β-HSD2 is expressed only in a few tissues: placenta,[4] endometrium,[4, 5] prostate,[6] small intestine,[7] and bone[1]. Inhibition of 17β-HSD2 is an attractive way to increase local estradiol concentrations only in the target tissues, without affecting estrogen receptor signaling in tissues where it is not expressed. This is thought to be especially beneficial in the treatment of osteoporosis, a condition where reduced bone density increases the fracture risk. The onset of osteoporosis is often connected with the age-related decrease of estradiol in women and decrease of testosterone in men[8]. Currently, osteoporosis is treated by estrogen replacement therapy, bisphosphonates, monoclonal antibodies against receptor activator of nuclear factor kappa-B ligand (RANKL), and selective estrogen receptor modulators (SERMs)[9-11]. All of these treatments have their disadvantages: Hormone replacement therapies and SERMs have been associated with cardiovascular complications and bisphosphonate therapy suffers from low oral bioavailability[12]. Because of the challenges in the current treatment options, there is a considerable demand for novel therapies such as 17β-HSD2 inhibitors. In fact, there is evidence from a study in ovariectomized cynomolgus

monkeys that 17β-HSD2 inhibition lowered bone resorption, although the effects were moderate and only observed at the highest dose tested (25 mg/kg/day)[13]. Additionally, treatment with 17β-HSD2 inhibitor reversed the ovariectomy-dependent decrease in bone strength at 5 mg/kg and 25 mg/kg. Nevertheless, the selectivity of the inhibitor used as well as inhibitor concentration reached in the bone needs to be further assessed. To the best of our knowledge, there are currently no 17β-HSD2 inhibitors in clinical trials or already on the market. However, there are multiple studies on the discovery and development of 17β-HSD2 inhibitors[14-17].

Our recently published study described 17β-HSD2 inhibitors that were discovered by ligand-based pharmacophore modeling and virtual screening[18]. In total, three pharmacophore models representing the common chemical features of 17β-HSD2 inhibitors were developed and used for virtual screening of the commercial SPECS database (www.specs.net) containing about 200000 small synthetic chemicals. From the hit molecules, 27 were purchased and biologically evaluated for 17β-HSD2 inhibition. Seven of these compounds inhibited 17β-HSD2 by more than 70% at a concentration of 20 µM. Four of these compounds represented the phenyl benzene-sulfonate and –sulfonamide scaffold and were found by the most successful model (Figure 2). To further explore the phenylbenzene-sulfonamide- and -sulfonate scaffold, 16 derivatives and additional 14 virtual hits representing this scaffold were purchased. From these compounds, six inhibited 17β-HSD2. In total, ten 17β-HSD2 inhibitors representing phenylbenzene sulfonamides and –sulfonates were discovered. From these compounds, the most active ones are depicted in Figure 3. The full series has been published previously[18].

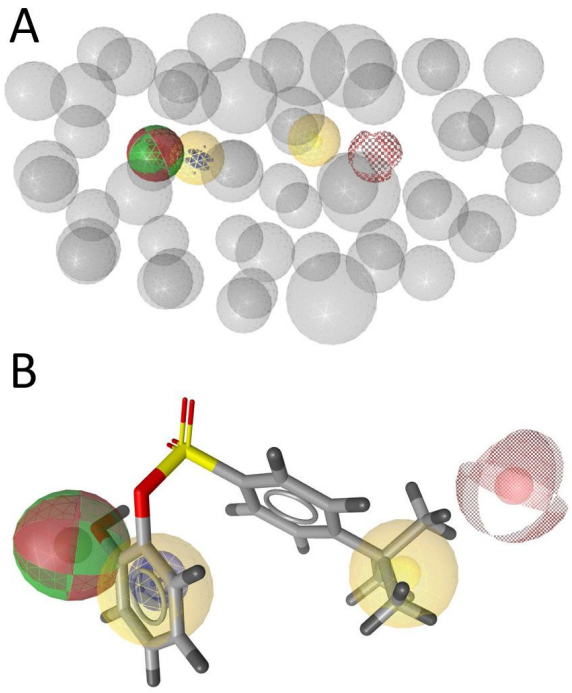


Figure 2: (A) Pharmacophore model correctly predicting phenylbenzene-sulfonamides and -sulfonates as 17β-HSD2 inhibitors. This model consists of six pharmacophore features: two hydrophobic areas (yellow), two hydrogen bond acceptors (red), of which one was optional (scattered representation), one hydrogen bond donor (green), an aromatic ring (blue rings), and 54 exclusion volumes (grey) mimicking spatial restrictions by the binding site. (B) Compound **1** fitted into the model.

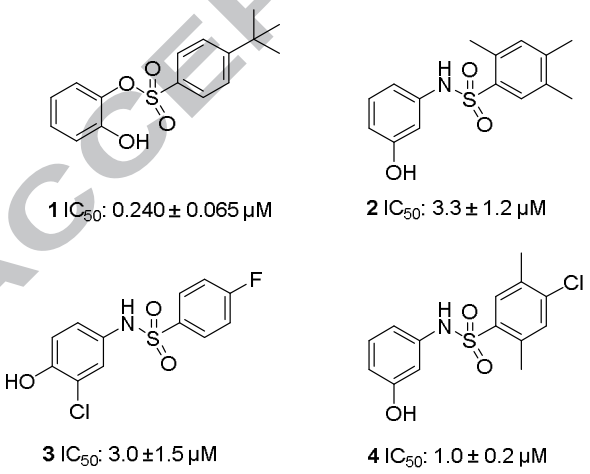


Figure 3: The most active phenylbenzene-sulfonamides and –sulfonates from Vuorinen et al. [18] with their IC_{50}-values.

This follow-up study aims at a more comprehensive structure-activity relationship analysis (SAR) analysis of this scaffold by synthesis of derivatives of the most active compounds. An additional aim was to replace the phenolic hydroxy group that is an attractive metabolic site and toxicologically not favorable[19, 20].

In total, 20 derivatives of the most active compounds shown in Figure 3 were synthesized (Table 1) from the corresponding 1,2-phenylendiamine or 2-hydroxyaniline and 4-*tert.*-butylbenzenesulfonylchloride (see Figure 4). These compounds were tested for 17β-HSD2 inhibition in a cell-free radioligand binding assay using the same test system as reported in Vuorinen et al.[18]. Ten of them inhibited 17β-HSD2 by more than 70% at a concentration of 20 µM, and IC_{50} values were determined subsequently. These compounds inhibited 17β-HSD2 with low micromolar IC_{50} values, with the most active compound **17** exhibiting an IC_{50} of 0.80 ± 0.22 µM.

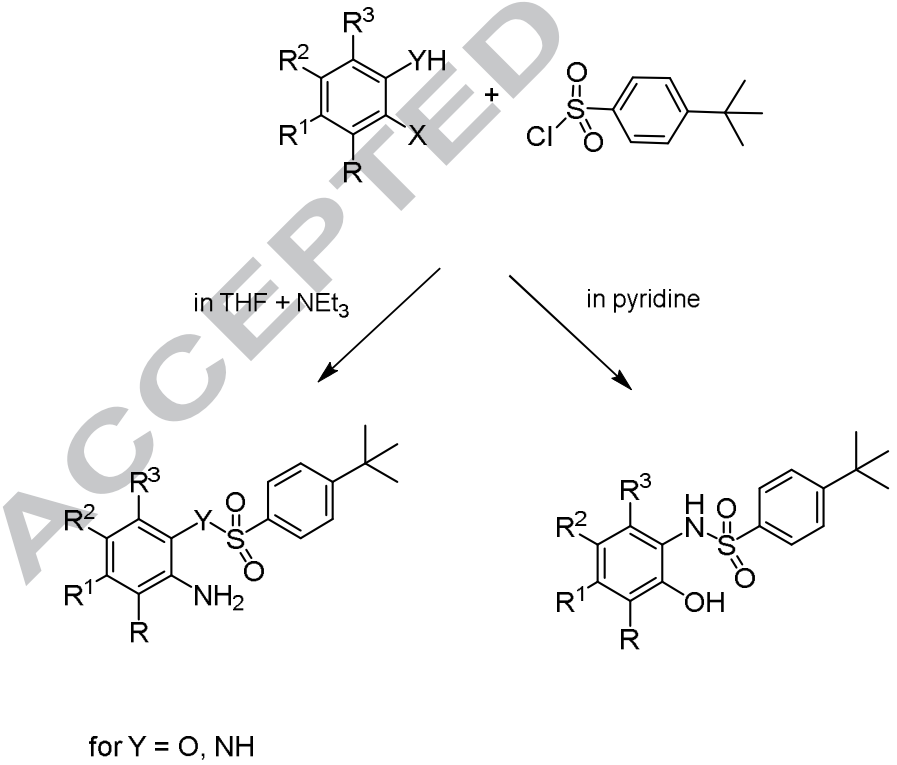
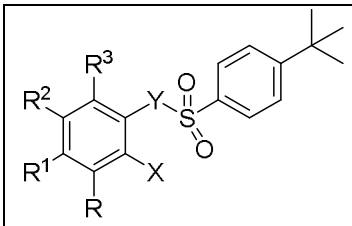


Figure 4. Schematic synthesis of compounds **5**-**24**.

Table 1: Structures and activities of the newly synthesized compounds.



Compound	X	Y	R	R^1	R^2	R^3	Activity[1]
5	NH_2	NH	H	H	H	H	46 ± 5%
6	NH_2	O	H	CH_3	H	H	37 ± 1%
7	NH_2	O	H	H	H	H	33 ± 4%
8	NH_2	NH	H	Cl	Cl	H	11 ± 4% 4.65 ± 0.35 µM
9	NH_2	NH	H	CH_3	CH_3	H	58 ± 7%
10	NH_2	O	H	Cl	H	H	44 ± 2%
11	NH_2	O	H	CH_3	H	CH_3	49 ± 3%
12	NH_2	O	H	H	CH_3	H	36 ± 3%
13	NH_2	O	Bn		H	H	43 ± 1%
14	NH_2	O	H	Ph	H	H	86 ± 3%
15	OH	NH	H	H	H	H	5 ± 3% 1.23 ± 0.35 µM
16	OH	NH	H	H	CH_3	H	13 ± 3% 4.09 ± 0.49 µM
17	OH	NH	H	H	Cl	H	6 ± 4% 0.80 ± 0.22 µM
18	OH	NH	CH_3	H	CH_3	H	18 ± 7% 5.19 ± 0.92 µM
19	OH	NH	H	CH_3	H	H	22 ± 1% 4.40 ± 0.79 µM
20	OH	NH	H	H	Ph	H	2 ± 2% 1.25 ± 0.09 µM
21	OH	NH	H	H	Bn		7 ± 3% 2.90 ± 0.69 µM

22	NH_2	NH	H	H	Cl	H	28 ± 6% 5.58 ± 1.09 µM
23	NH_2	NH	H	Cl	H	H	35 ± 4%
24	NH_2	NH	H	F	H	H	36 ± 2%
4 (positive control)							10 ± 3% 1.0 ± 0.2 µM

[1]Given as remaining enzyme activity at a compound concentration of 20 µM (%) or as IC_{50}

As already observed in the previous publication, the phenolic hydroxyl group is advantageous for the activity. However, this functionality is an attractive site for metabolic modification [19, 20] and therefore exchanging this feature with a bioisosteric group would be beneficial for the in vivo half-life of the molecule and may address possible toxicological concerns. Nevertheless, replacing the phenolic hydroxy group by an amino group results in the formation of anilines, which also need to be evaluated for their toxic potential. The previous work revealed a decreased activity upon methylation of the phenol group, suggesting that a hydrogen bond donor is needed for the activity. Therefore, the hydroxyl group was replaced by an amine. Unfortunately, the activity was decreased (compounds **5** and **7**). Introducing an electronegative substituent, such as chlorine or fluorine, to the sulfonamide compounds increased the activity, as can be concluded from the comparison of activities of the unhalogenated compound **5** and the corresponding halogenated derivatives **8**, **22**, **23** and **24**. In the sulfonamide series, methyl substituents in any position of the benzene ring reduced the inhibitory ability (compounds **16** and **18-19**) compared to compound **15**, however the activity was not completely lost. The position of the single methyl substituents did not make a significant difference in the activity of the compounds, as represented by their IC_{50} values. Interestingly, in the sulfonamide series, large aromatic ring substituents were tolerated by the enzyme (**20-21**); however, this was not the case in the sulfonate series. Whether the linker between the benzene rings was a sulfonamide or a sulfonate did not play a major role in the activity: Compounds **23** and **10** were equipotent. However, the sulfonate-compound **1** was six times more active than the respective sulfonamide compound **15**. Still, compound **15** was more active than the sulfonamide **5** and the sulfonate **7**, respectively.

To demonstrate the observed SAR, a refined pharmacophore model representing the common chemical functionalities of our lead compound **1** and the most active compound from the new series (**17**) was generated. An addition of a phenyl and benzo anellation were tolerated (Figure

5A and 5B), however, without significant effect on the potency of the compounds (compare compounds **7** vs. **13** and **15** vs. **21**). Substitution with a phenyl in para position to the amino group (position R^2 in Table 1) was tolerated in the sulfonamide **20**. However, in the sulfonate **14**, a phenyl in the para position to the linker (R^1 in Table 1) led to a loss of activity (Figure 5C). Therefore, the position of the phenyl substituent makes a difference in the activity. However, this loss of activity in compound **14** could also be caused by the hydroxyl-amino group exchange and by the different linker. It is speculated that the reason for the activity loss of **14** may lie in the spatial properties of the binding site in this position. Still, without structural data for 17β-HSD2, this is rather an assumption. A chlorine substituent at position R^2 in Table 1 is well tolerated, as compounds **15** and **17** are similarly active (Figure 5D), and they both fit to the model well.

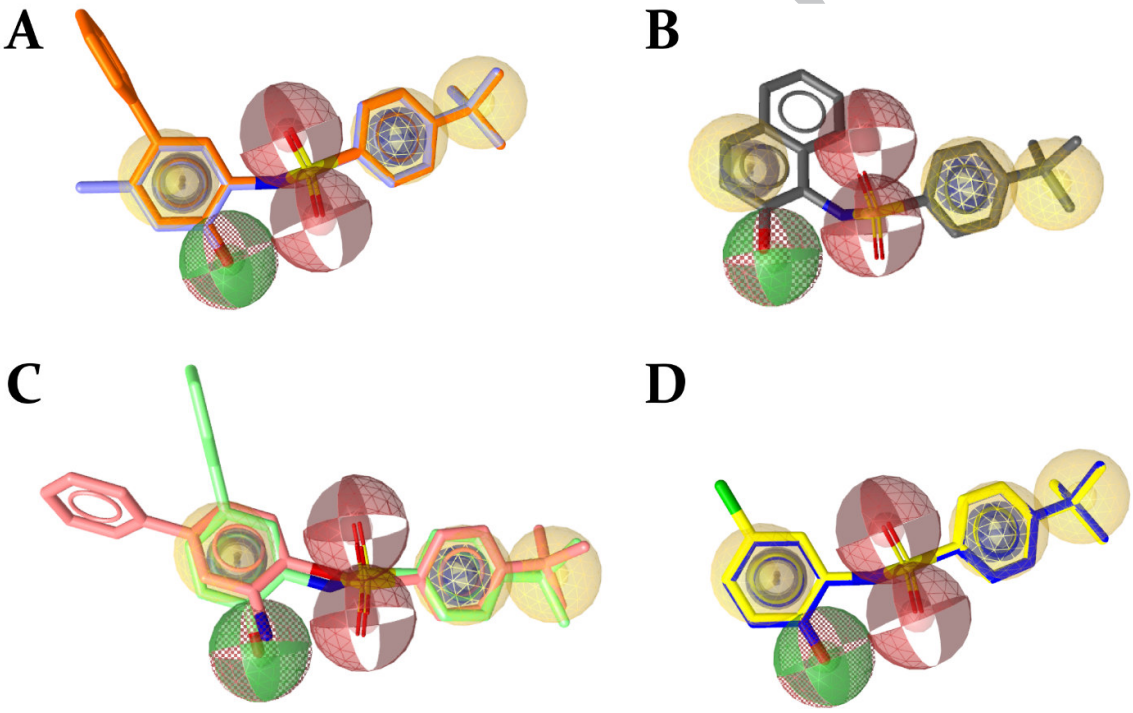


Figure 5: New SAR-pharmacophore model with selected compounds: (A) **19** (light blue) and **20** (orange), (B) **21** (gray), (C) **14** (red) and **20** (green), (D) **15** (blue) and **17** (yellow). The pharmacophore features are color-coded: hydrogen bond acceptor –red, hydrogen bond donor green, aromatic ring – blue, hydrophobic – yellow. In case a feature is optional, it is depicted in a scattered style. Exclusion volumes were not generated.

The previous report also depicted a predictive SAR-model for this scaffold [18]. The new compounds were fitted into this model as well. In fact, when the tolerance area of the hydrogen bond donor (HBD) functionality of the model was slightly increased by 0.15 Å, the following compounds could fit into the model: **15-17**, **19-20**, and **22** (Figure 6A). Our previously published predictive SAR-model found most of the active compounds, but most remarkably, it was able to exclude the weakly active ones. The newly synthesized and biologically evaluated compounds were also fitted to our previously established pharmacophore model, the one that initially identified the scaffold. If screened without the exclusion volume spheres, three of the compounds: **15**, **16**, and **20** fitted into that model (Figure 6B).

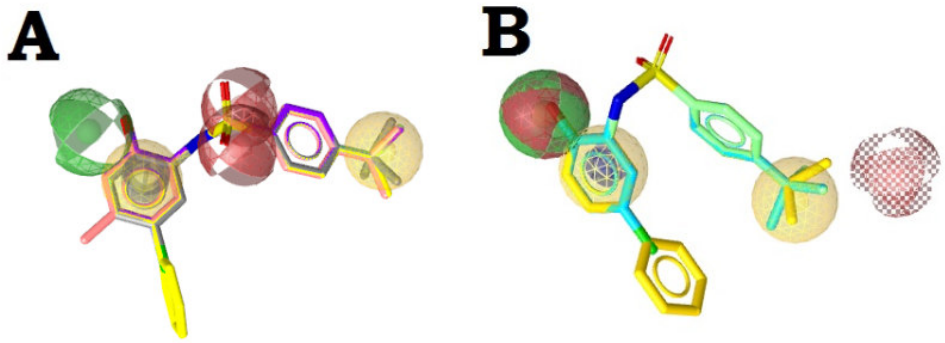


Figure 6: (A) **15** (purple), **16** (green), **17** (blue), **19** (red), **20** (yellow), and **22** (grey) with the predictive SAR-model described previously [18]. (B) Compounds **16** (green), **17** (cyan), and **20** (yellow) fitted into the original pharmacophore model. The pharmacophore features are color coded: hydrogen bond acceptor –red, hydrogen bond donor green, aromatic ring – blue, hydrophobic – yellow. In case a feature is optional, it is depicted in a scattered style. Exclusion volumes are not shown for clarity.

Additionally, the most active compounds were also tested against other HSDs (Table 2) that are structurally and functionally close to 17β-HSD2. Unfortunately, four of the new 17β-HSD2 inhibitors were also active on 17β-HSD1, the enzyme that is responsible for the reductive activation of estrone into estradiol[21]. Two of the compounds (**17** and **20**) also potently inhibited 11β-HSD2. This enzyme converts cortisol into cortisone in kidneys and is considered as an antitarget because its inhibition causes cardiovascular complications such as hypokalemia and hypertension[22]. Therefore, these compounds should be optimized for better selectivity. Compounds **19, 21, 22** and **24** inhibited 11β-HSD1, which activates

cortisone to cortisol. Importantly, compound **15** could be considered as a relatively selective 17β-HSD2 inhibitor, indicating the feasibility to develop potent and selective compounds from this class.

Table 2: Qualitative selectivity assessment of the active compounds represented as % of control at the inhibitor concentration of 20 µM.

Compound	17β-HSD2	17β-HSD1	SI	11β-HSD1	SI	11β-HSD2	SI
8	11 ± 4%	23 ± 3%[a]	2.1	74 ± 4%	6.7	21 ± 11%	1.9
15	5 ± 3%	41 ± 6%	8.2	37 ± 5%	7.4	83 ± 9%	16.6
16	13 ± 3%	38 ± 6%	2.9	46 ± 2%	3.5	63 ± 12%	4.8
17	6 ± 4%	15 ± 6%	2.5	35 ± 3%	5.8	7 ± 4%	1.2
18	18 ± 7%	19 ± 8%	1.1	43 ± 2%	2.4	37 ± 10%	2.1
19	22 ± 1%	35 ± 9%	1.6	24 ± 4%	1.1	62 ± 9%	2.8
20	2 ± 2%	13 ± 3%	6.5	62 ± 5%	31	3 ± 3%	1.5
21	7 ± 3%	46 ± 7%	8.6	21 ± 4%	3	21 ± 4%	3
22	22 ± 6%	46 ± 10%	2.1	28 ± 7%	1.3	75 ± 8%	3.4
24	36 ± 2%	56 ± 11%	1.6	26 ± 8%	0.7	97 ± 4%	2.7
positive controls	10 ± 3% (**4**)	11 ± 3% (apigenin)[23]		5 ± 1% (glycyrrhetinic acid)[24]		7 ± 2% (glycyrrhetinic acid)[24]	

[a] % residual enzyme activity compared to non-inhibited control at 20 µM concentration. SI = selectivity index (residual HSD activity / residual 17β-HSD2 activity)

In this study, 20 phenylbenzene-sulfonamides and -sulfonates were synthesized and tested for 17β-HSD2 inhibition. In total, nine of them inhibited the enzyme with low micromolar IC_{50} values. Even though none of these new compounds was more active than the parental compound **1**, they allowed for establishing more comprehensive SAR-rules for this scaffold. In addition, these compounds provide also valuable information on the selectivity towards related enzymes.

Acknowledgements

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