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Design and Synthesis of (*R*)-1-Arylsulfonylpiperidine-2-carboxamides as 11β-Hydroxysteroid Dehydrogenase Type 1 Inhibitors

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Metabolic syndrome includes a series of associated metabolic abnormalities such as insulin resistance, type 2 diabetes (T2D), dyslipidemia, hypertension, and visceral obesity.[1] Studies have shown that cortisol levels in liver and adipose tissues of patients with metabolic syndrome tend to be higher than in healthy individuals.[2,3] There is also strong evidence that the glucocorticoid action relates to metabolic diseases. Glucocorticoid receptor (GR) signaling depends not only on circulating cortisol levels but also on the intracellular production of cortisol by reduction of cortisone, the inactive glucocorticoid. 11β-Hydroxysteroid dehydrogenase 1 (11β-HSD1), highly expressed in liver and adipose tissues, is the predominant enzyme responsible for converting cortisone to cortisol. Inhibition of 11β-HSD1 has the potential to control cortisol concentrations in the liver and adipose without affecting its systemic circulating concentration.[4] In clinical trials, 11β-HSD1 inhibitors such as AZD8329 (**1**), PF-915275 (**2**), and INCB-13739 (structure unknown) significantly improve insulin sensitivity in T2D patients, and lower triglyceride and cholesterol levels in patients with hyperlipidemia and hypertriglyceridemia.[5–7] Accumulation of preclinical and clinical results has made 11β-HSD1 a promising target for an inhibitor to combat metabolic disease.[8]

Several classes of 11β-HSD1 inhibitors such as amides, triazoles, thiazolones, and sulfonamides have been reported over the past decade.[9] We recently performed scaffold hopping studies and discovered a series of 1-arylsulfonylpiperidine-3-carboxamides **3** (Figure 1).[10] Interestingly, as part of our ongoing efforts in this program, piperidine-2-carboxamides also showed inhibitory activity against 11β-HSD1, and the *R* enantiomer **5** was found to be more active than the *S* enantiomer **4**. Through docking simulations, we found that the piperidine ring of compound **5** is situated in a sub-pocket formed by residues Tyr361, Leu364, Ile418, and Tyr421, whereas the piperidine group of compound **4** is not located in this hydrophobic sub-pocket and cannot make good van der Waals interactions with 11β-HSD1 (Figure 2). These contrasting interaction patterns may be the cause of the significant difference in their binding affinities. Using compound **5** as a starting point, we discovered and elaborated a series of (*R*)-1-arylsulfonylpiperi-

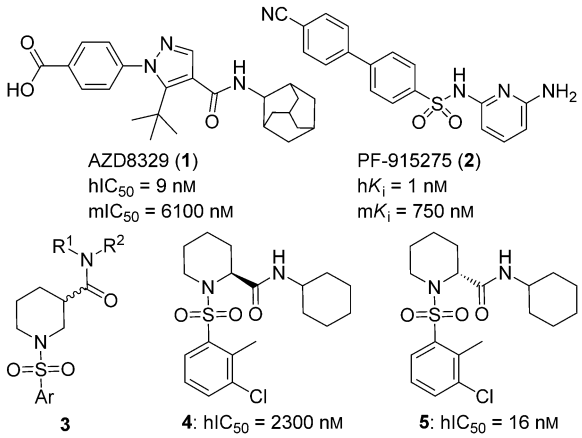

Figure 1. Sulfonamide 11β-HSD1 inhibitors **1** and **2**, and discovery of 1-arylsulfonylpiperidine-2-carboxamides **3**–**5** as novel 11β-HSD1 inhibitors.

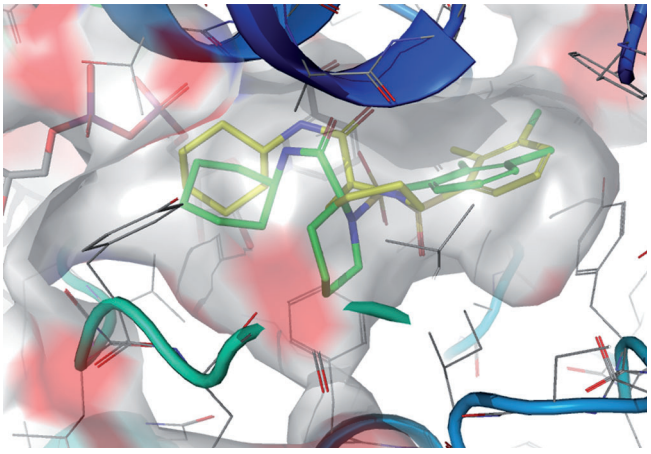

Figure 2. Docking study of compounds **4** and **5** carried out with the AutoDock Vina program[13] using default parameters. The structure of guinea pig 11β-HSD1 co-crystallized with PF-877423 (PDB ID: 3LZ6)[14] was used as the template for preparing the binding site. The NADPH cofactor and compounds **4** and **5** are shown in stick models, colored grey, yellow, and green, respectively.

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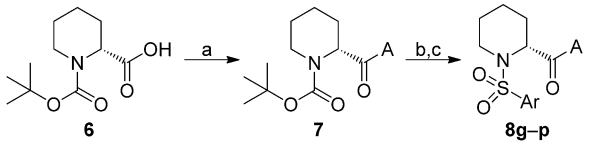
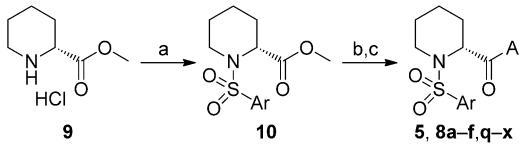
dine-2-carboxamides as potent and selective 11β-HSD1 inhibitors. Herein we report the synthesis and optimization of this series.

(*R*)-1-Arylsulfonylpiperidine-2-carboxamide analogues were prepared by two general methods, A and B. As shown in Scheme 1 (method A), (*R*)-1-(*tert*-butoxycarbonyl)piperidine-2-



Scheme 1. Synthesis of 1-arylsulfonyl-piperidine-2-carboxamides (method A). *Reagents and conditions*: a) amine, EDCI, HOBt, CH_2Cl_2, RT, 6 h; b) $HCl_{(g)}$/1,4-dioxane, CH_2Cl_2, RT, overnight; c) $ArSO_2Cl$, Et_3N, CH_2Cl_2, RT, 2–24 h. A = cycloheptylamino, Ar: see Table 2.

carboxylic acid (**6**) was condensed with various amines to provide corresponding amides **7**. After removing the protecting group under acidic conditions, the resulting product was then allowed to react with arylsulfonyl chlorides to give the target compounds **8g**–**p**. The other synthetic route, method B, is depicted in Scheme 2: sulfonylation of *R*-configured ester **9** with

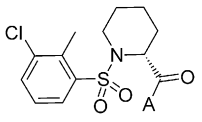


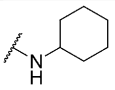
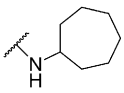
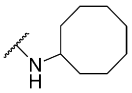
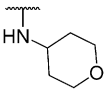
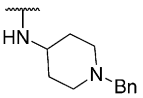
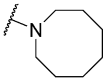
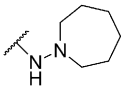
Scheme 2. Synthesis of 1-arylsulfonyl-piperidine-2-carboxamides (method B). *Reagents and conditions*: a) $ArSO_2Cl$, Et_3N, CH_2Cl_2, RT, 8 h; b) MeOH, 50% $NaOH_{(aq)}$, reflux, 5 h; c) amine, EDCI, HOBt, CH_2Cl_2, RT, 2–24 h. Ar = 3-chloro-2-methylphenyl, A: see Tables 1 and 3.

arylsulfonyl chloride provided (*R*)-benzenesulfonamide (**10**). Target compounds with varied amino moieties (**5**, **8a**–**f**, and **8q**–**x**) were obtained in two successive steps: the hydrolysis of ester **10** and the condensation of acid and primary amines.

The inhibitory activities of this compound series against human 11β-HSD1 (h11β-HSD1) and mouse 11β-HSD1 (m11β-HSD1) were determined by scintillation proximity assay (SPA),[11] and the results are listed in Tables 1–3. As summarized in Table 1, the cycloheptylamine and cyclooctylamine derivatives (**8a** and **8b**, respectively) showed improved potencies toward h11β-HSD1 over that of the cyclohexylamine derivative **5**. The tetrahydropyran-4-ylamine and 1-benzylpiperidin-4-ylamine derivatives **8c** and **8d** exhibited dramatically lower activities against the human enzyme, indicating the well-matched binding conformations of **8a** and **8b**. Whereas the azepan-1-ylamine analogue **8f** showed moderate activity, the azocane derivative **8e** did not show significant inhibition against h11β-HSD1. However, with the exception of **8b**, with an IC_{50} value of 173 nM against m11β-HSD1, all the cycloalkylamine compounds appear to show weak inhibition toward m11β-HSD1.

Table 1. In vitro activity of derivatives with varied cycloalkylamino groups.



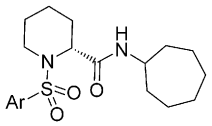
Compd	A	h11β-HSD1 IC_{50} [nM][a]	m11β-HSD1 Inhib. [%][b]
5		16	21
8a		3.7	32
8b		3.1	42[c]
8c		37[b]	12
8d		23[b]	14
8e		15[b]	11
8f		33	19

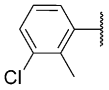
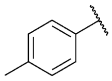
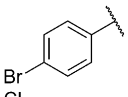
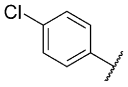
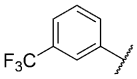
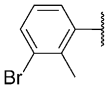
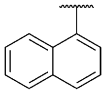
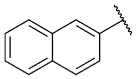
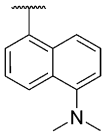
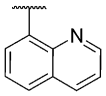
[a] Values are the average of three replicates, with a variance of $<15\%$. [b] Percent inhibition measured at 100 nM; values are the mean of two measurements. [c] $IC_{50} = 173$ nM.

Next, the effect of the aryl moiety on 11β-HSD1 inhibitory activity was investigated (Table 2). For compounds containing a cycloheptylamine moiety, only the naphthalen-2-yl and 5-dimethylaminonaphthalen-1-yl derivatives (**8n** and **8o**) showed nanomolar inhibitory activities similar to that of **8a**. Besides good activity toward human 11β-HSD1, all compounds exhibited low activity against m11β-HSD1 (inhibition ratio $<35\%$ at a concentration of 100 nM).

Human 11β-HSD1 shares ~79% sequence identity with the mouse enzyme, so it might be understandable that many known 11β-HSD1 inhibitors, including INCB-13739 and PF-915275, display species-dependent activity, which impedes the fast track of efficiencies of inhibitors within rodent models. From previously reported SAR information,[5,8] it is known that many 11β-HSD1 inhibitors with cross-species potencies have large lipophilic groups, such as 2-norbornyl in AMG221 and adamantyl in Merck-544. We conducted further modification on this series by introducing bulky fused ring systems onto the amino moiety in order to improve activity toward m11β-HSD1, in order to be able to perform in vivo studies in a rodent model. As listed in Table 3, (*R*)-(+)-bornylamine, 2-norbornylamine, and adamantyl-2-amine derivatives **8s**, **8t**, and **8v** displayed nanomolar inhibitory activities against h11β-HSD1 and m11β-HSD1. As the adamantane group is prone to oxidation

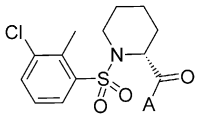
Table 2. In vitro activity of derivatives with varied aryl groups.

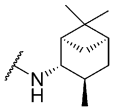
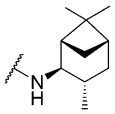
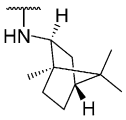
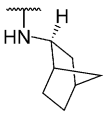
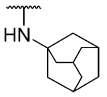
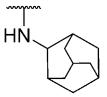
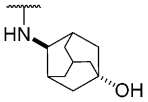
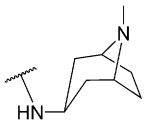


Compd	A	h11β-HSD1 IC_{50} [nM][a]	m11β-HSD1 Inhib. [%][b]
8a		3.7	32
8g		83	ND[c]
8h		29	18
8i		57	28
8j		12[b]	ND[c]
8k		11	25
8l		30	5
8m		35	24
8n		8.2	25
8o		9.7	16
8p		38	29

[a] Values are the average of three replicates, with a variance of $<15\%$. [b] Percent inhibition measured at 100 nM; values are the mean of two measurements. [c] Not determined.

Table 3. In vitro activity of bridged hydrocarbon amine derivatives.



Compd	A	h11β-HSD1 IC_{50} [nM][a]	m11β-HSD1 IC_{50} [nM][a]
8q		11	28[b]
8r		13	22[b]
8s		3.1	24
8t		6.0	47
8u		34	ND[c]
8v		1.5	13
8w		1.2	15
8x		32[b]	ND[c]

[a] Values are the average of three replicates, with a variance of $<15\%$. [b] Percent inhibition measured at 100 nM; values are the mean of two measurements. [c] Not determined.

Table 4. In vitro DMPK properties of representative compounds.[a]

Compd	HLM CL_{int} [$\mu L\,min^{-1}\,mg^{-1}$]	TDI	DI [%] 3A4	2D6	2C9
8a	393	No inhib.	93	49	62
8s	183	No inhib.	82	15	29
8v	175	No inhib.	72	34	0
8w	74	No inhib.	42	3	3

[a] The procedures for evaluating metabolic stability and CYP inhibition, including direct inhibition (DI) and time-dependent inhibition (TDI), are described in the Supporting Information.

in vivo, which could lead to rapid elimination of these compounds, we prepared **8w** with an additional hydroxy group at the vulnerable position of the adamantane ring in **8v**, and this compound maintained high potency against the human and rodent enzymes, similar to **8v**.

Based on the results of these enzyme assays, we selected the three most potent compounds **8s**, **8v**, and **8w**, together with **8a**, for studies of in vitro DMPK properties. As listed in Table 4, **8w** showed greater metabolic stability in human liver microsomes (HLM) and acceptable levels of cytochrome P450 (CYP) inhibition.

To evaluate the potential of compound **8w** as a lead candidate targeting 11β-HSD1, we performed pharmacokinetic/pharmacodynamic (PK/PD) studies in mice. As listed in Table 5, **8w** showed a high clearance rate and low oral bioavailability. However, the bioavailability via intraperitoneal (i.p.) injection was dramatically improved (41%), ~14-fold greater than oral bio-

Table 5. PK data for compound **8w** in mice.[a]

Parameter	Value
CL [mL min^{-1} kg^{-1}]	130
V_{dss} [L kg^{-1}]	0.76
p.o. *F* [%]	2.9
i.p. *F* [%]	41
i.p. AUC_{0-t} [ng h mL^{-1}]	760.0

[a] Inhibitor **8w** was dosed into male BALB/c mice by intravenous (i.v.) injection (1 mg kg^{-1}), oral route (p.o.) (5 mg kg^{-1}), and intraperitoneal (i.p.) injection (5 mg kg^{-1}); mean values averaged over three mice. Detailed procedures are described in the Supporting Information.

availability. This allowed us to select **8w** to observe the correlation between in vitro activity and in vivo inhibition. For the in vivo PD evaluation, normal mice were i.p. injected with **8w** (or vehicle). After 1 h, these mice were treated with an intravenous (i.v.) injection of the exogenous substrate prednisone (3 mg kg^{-1}), which would be transformed into prednisolone via 11β-HSD1 catalysis, to evaluate the effects of inhibitors on prednisolone turnover. As illustrated in Figure 3, i.p. treatment of BALB/c mice with **8w** at 3.75, 15, and 60 mg kg^{-1} dose-dependently decreased the formation of prednisolone, with respective inhibition ratios of 40, 72, and 88%.

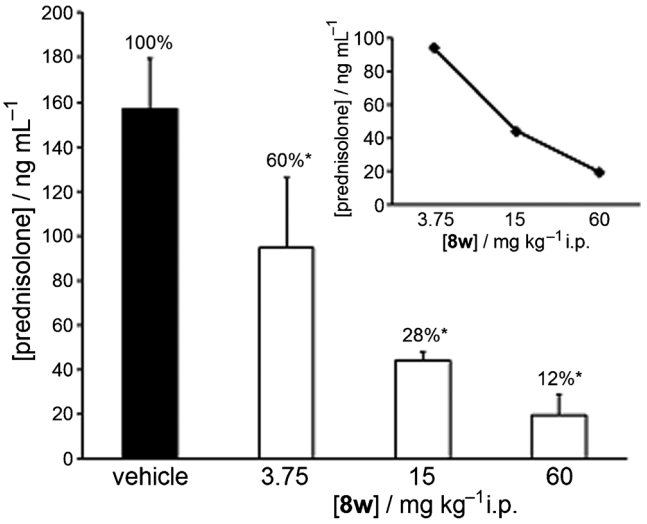


Figure 3. In vivo inhibitory activity of **8w** against 11β-HSD1 in BALB/c mice by measuring the turnover ratio and the concentration of prednisolone. The insert shows the mean prednisolone concentration values after treatment with three doses of inhibitor **8w**, as indicated. Student's *t*-test was used to compare the differences between the dosing group and vehicle; $^*p < 0.05$ vs. vehicle.

High intra-adipose tissue cortisol levels have been proposed to be a major determinant of metabolic diseases such as obesity, T2D, and metabolic syndrome, and thus it is desirable to discover adipose tissue-specific 11β-HSD1 inhibitors.[8,12] Therefore, we next measured the tissue distribution of **8w** in BALB/c mice (Figure 4). The concentration of **8w** in subcutaneous and celiac adipose as well as liver tissue remains high within

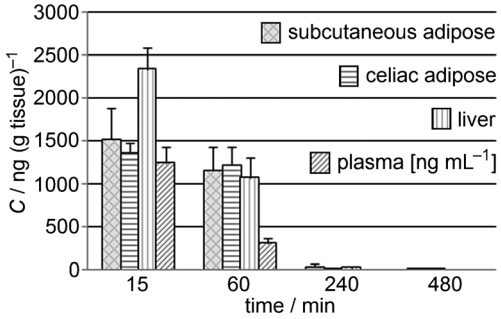


Figure 4. Tissue distribution of **8w** in BALB/c mice (i.v., 5 mg kg^{-1}).

1 h after i.v. treatment, whereas the concentration in plasma dramatically decreased 15 min after administration. Compound **8w** was also eliminated moderately in adipose and liver tissue over the subsequent 5 h, which may be the reason that **8w** showed its effects on decreasing prednisolone levels in the in vivo assays.

In summary, we report herein a series of 1-arylsulfonylpiperidine-2-carboxamides as 11β-HSD1 inhibitors. Initial enzyme assays indicated that the *R* enantiomer is much more potent than the *S* enantiomer, and compound **5** was selected as a starting point for optimization and SAR studies. Inhibitor **8w**, obtained from several rounds of optimizations, showed cross-species inhibition against human and mouse 11β-HSD1. It also displayed an acceptable DMPK profile in vitro, and was advanced to PK/PD evaluations in vivo. The results confirmed its dose-dependent activity in mice. Therefore, we have identified 1-arylsulfonylpiperidine-2-carboxamides as suitable compounds for further studies as promising inhibitors of 11β-HSD1 for the treatment of metabolic syndrome.

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