Discovery of 2-Alkyl-1-arylsulfonylprolinamides as 11β-Hydroxysteroid Dehydrogenase Type 1 Inhibitors

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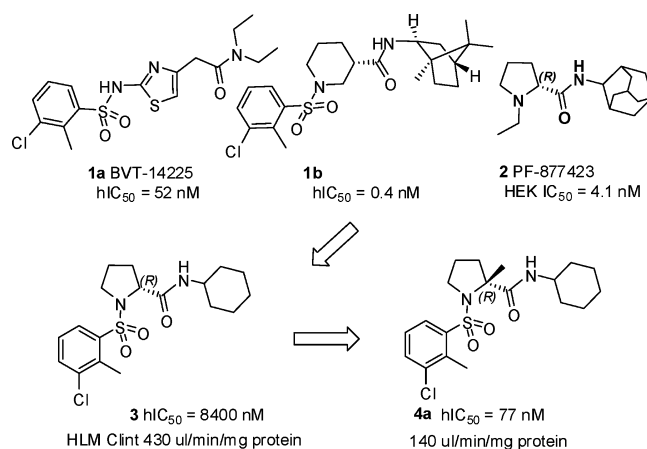
Ⓢ *Supporting Information*

ABSTRACT: On the basis of scaffold hopping, a novel series of 2-alkyl-1-arylsulfonylprolinamides was discovered as 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD-1) inhibitors. A representative compound **4ek**, obtained through SAR and structure optimization studies, demonstrates excellent in vitro potency against 11β-HSD-1 and dose-dependent in vivo inhibition of 11β-HSD-1 in a prednisone/prednisolone transformation biomarker study in mice.

4a human IC$_{50}$ = 77 nM
mouse IC$_{50}$ > 1,000 nM

4ek human IC$_{50}$ = 7.7 nM
mouse IC$_{50}$ = 11 nM
3T3L1 cell IC$_{50}$ = 11 nM

KEYWORDS: *metabolic syndrome, enzyme inhibitor, 11β-hydroxysteroid dehydrogenase type 1, sulfonamide, 2-alkylproline, prolinamide*
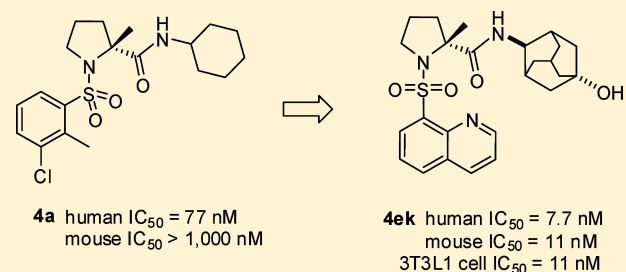
Glucocorticoid receptor (GR) signaling plays a significant role in metabolic regulation, and defects in this signaling pathway have been implicated in the development of several phenotypes of metabolic syndrome.[1] GR signaling depends not only on the circulating cortisol levels but also on the intracellular production of cortisol through reduction of cortisone, the inactive glucocorticoid. The enzymes catalyzing the conversion between cortisone and cortisol are 11β-hydroxysteroid dehydrogenases (11β-HSDs). Among them, the type 1 isoform (11β-HSD-1), highly expressed in liver and adipose tissue, predominantly reduces cortisone to cortisol, and the type 2 isoform (11β-HSD-2), primarily expressed in kidney, oxidizes cortisol to cortisone. A potential role for 11β-HSD-1 inhibitors in metabolic syndrome, type 2 diabetes, and obesity has been established using transgenic mice.[2−4] On the basis of these findings, in recent years, 11β-HSD-1 is recognized as a promising target in metabolic disease.[1−4]

In the past decade, industrial and academic researchers have reported several classes of 11β-HSD-1 inhibitors with varied scaffolds, including sulfonamides (e.g., BVT-14225, **1a**), amides (e.g., PF-877423, **2**) (Figure 1), triazoles (e.g., Merck 544), and thiazolones (e.g., AMG-221).[5−8] In a phase II clinical trial, 11β-HSD-1 inhibitor INCB-13739 (structure undisclosed) significantly improved insulin sensitivity in type 2 diabetes patients who failed on metformin treatment and lowered triglyceride and cholesterol levels of patients with hyperlipidaemia and hypertriglyceridemia.[9] Currently, other examples such as PF-915275, MK-0916, and AZD-4071 are being evaluated in phase

1a BVT-14225
hIC$_{50}$ = 52 nM

1b
hIC$_{50}$ = 0.4 nM

2 PF-877423
HEK IC$_{50}$ = 4.1 nM

3 hIC$_{50}$ = 8400 nM
HLM Clint 430 ul/min/mg protein

4a hIC$_{50}$ = 77 nM
140 ul/min/mg protein

Figure 1. 11β-HSD-1 inhibitors. Combining the arylsulfonyl moiety of **1a** or **1b** with the D-prolinamide moiety of PF-877423 (**2**) to discover 2-alkyl-1-arylsulfonylprolinamide **4a**.
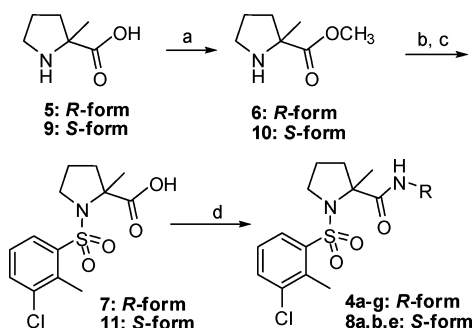
I/II trials for potential oral treatment of metabolic diseases.[10−12]

We recently disclosed a new series of sulfonamides (e.g., **1b**, Figure 1) with high inhibitory activity against 11β-HSD-1, and compound **1b** showed a short duration of action in a pharmacodynamics (PD) model.[13] As part of our continuing

Scheme 1. Synthesis of Compounds 4a−g and 8a,b,e[a]

[a]Reagents and conditions: (a) CH$_3$OH, SOCl$_2$, reflux, 1 h. (b) 3-Chloro-2-methylbenzene-1-sulfonyl chloride, triethylamine, CH$_2$Cl$_2$, rt, 2 h. (c) NaOH, THF, CH$_3$OH, H$_2$O, rt, overnight. (d) RNH$_2$, BOP-Cl, DIPEA, CH$_2$Cl$_2$, rt, 6 h.

Table 1. In Vitro Potency of (R)-2-Methyl Prolinamides with Varied Amino Groups

| Compound	R	h-11β-HSD-1 IC$_{50}$[a] (nM)	m-11β-HSD-1 IC$_{50}$[a] (nM)
4a		77	9.2%[b]
4b		6.4	13%[b]
4c		37%[b]	15%[b]
4d		1.5	64
4e		0.1	1.3
4f		35%[b]	18%[b]
4g		26	33%[b]

[a]Average of at least two replicates. [b]Percent inhibition at 100 nM, the mean of at least two experiments.

efforts to find novel and proprietary 11β-HSD-1 inhibitors, we combined the arylsulfonyl moiety of **1a** or **1b** with D-prolinamide moiety of **2** to form a new sulfonamide-D-prolinamide represented by **3** (Figure 1), which displayed only micromolar activity against human 11β-HSD-1 (h-11β-HSD-1) but poor liver microsome stability (HLM Clint 430

Table 2. In Vitro Potency of (S)-Enantiomers

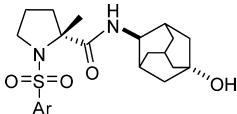| Compound	R	h-11β-HSD-1 IC$_{50}$[a] (nM)	m-11β-HSD-1 IC$_{50}$[a] (nM)
8a		4300	ND
8b		1800	ND
8e		3.1	63

[a]Average of at least two replicates; ND, not determined.
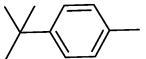
Scheme 2. Synthesis of Compounds 4eb−el[a]
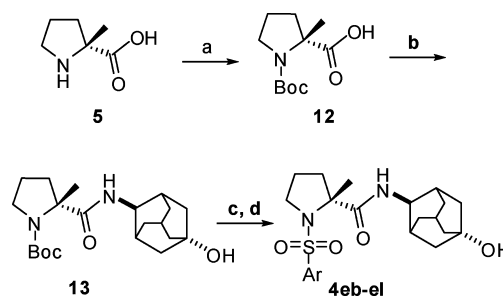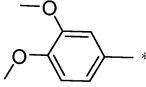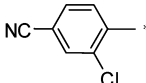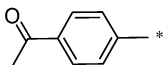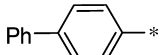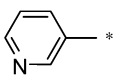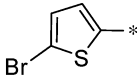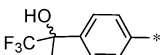
[a]Reagents and conditions: (a) (Boc)$_2$O, Na$_2$CO$_3$, dioxane, H$_2$O, rt, 0.5−2 h. (b) trans-4-Aminoadamantan-1-ol hydrochloride, BOP-Cl, DIPEA, CH$_2$Cl$_2$, rt, overnight. (c) CF$_3$COOH, CH$_2$Cl$_2$, rt, 1−6 h. (d) ArSO$_2$Cl, DIPEA, CH$_2$Cl$_2$, rt, 2−16 h.

μL/min/mg). In vitro metabolite identification studies indicated that the pyrrolidine ring of compound **3** was oxidized by HLM. We thought the substituent (e.g., alkyl) on the ring might be helpful to slow down the oxidization, so we first selected the commercially available (R)-α-methyl proline as a starting material and obtained compound **4a**. Interestingly, **4a** exhibited not only better HLM stability but also dramatically increased potency (IC$_{50}$ = 77 nM). Utilizing **4a** as a starting point, we discovered and elaborated a series of 2-alkyl-1-arylsulfonylprolinamides as potent and selective 11β-HSD-1 inhibitors. Herein, we report the synthesis, structure−activity relationship (SAR), and optimization of this series.

2-Alkyl-1-arylsulfonylprolinamide derivatives have been prepared according to Schemes 1−3. The inhibitory activity of this series of compounds against h-11β-HSD-1 and mouse 11β-HSD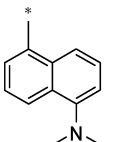-1 (m-11β-HSD-1) was determined by scintillation proximity assay (SPA) method,[13−15] and the results are listed in Tables 1−5. The selectivity over human 11β-HSD-2 (h-11β-HSD-2) and 3T3L1 cellular activity of some representative compounds was also tested.

As seen in Scheme 1, esterification of (R)-2-methylpyrrolidine-2-carboxylic acid (**5**) gave (R)-methyl 2-methylpyrrolidine-2-carboxylate (**6**). Typical sulfonylation of **6** and saponification of the resulting ester produced carboxylic acid

Table 3. In Vitro Potency and Liver Microsomal Stability of (R)-2-Methyl Prolinamides with Varied Arylsulfonyl Groups
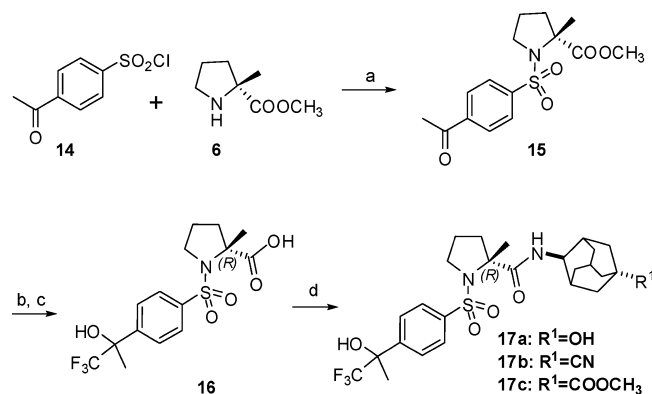

Compound	Ar	h-11β-HSD-1 IC$_{50}$[a] (nM)	m-11β-HSD-1 IC$_{50}$[a] (nM)	HLM Clint (μL/min/mg protein)
4e		0.1	1.3	106
4eb		9.5	3%[b]	132
4ec		7.2	12%[b]	ND
4ed		3.3	146	134
4ee		8.4	125	ND
4ef		5.5	16%[b]	12
4eg		11	37%[b]	87
4eh		17	17%[b]	55
4ei		12	112	15
4ej		8.2	97	57
4ek		7.7	11	51
4el		3.9	31%[b]	148
17a		6.0	26%[b]	64

[a]Average of at least two replicates. [b]Percent inhibition at 100 nM, the mean of at least two experiments; ND, not determined.

7, followed by coupling with varied primary amines using bis(2-oxo-3-oxazolidinyl)phosphonic chloride (BOP-Cl) to yield target molecules 4a–g. As summarized in Table 1, when a hydroxyl group is introduced to the 4-position of the cyclohexyl moiety, the potency toward h-11β-HSD-1 increased 12-fold (4b vs 4a); however, the methoxyl derivative 4c exhibited reduced activity (37% at a concentration of 100 nM), and all three compounds appeared to have very weak inhibition toward m-11β-HSD-1 (no more than 15% at a concentration of 100 nM). The adamant-2-yl-substituted 4d and 4e showed single-digit nanomolar and subnanomolar inhibition against human

enzyme (IC$_{50}$ = 1.5 and 0.1 nM); moreover, they were also potent inhibitors of rodent enzyme with IC$_{50}$ values of 64 and 1.3 nM, respectively. However, other bridged hydrocarbon substituents such as adamant-1-yl (4f) and 3-oxabicyclo[3.3.1]-nonane (4g) led to poor activity versus rodent enzyme.

For comparison, using (S)-acid 9 instead of (R)-acid 5, we synthesized (S)-form derivatives 8a, 8b, and 8e (Scheme 1). As shown in Table 2, although the (S)-derivatives had lower activity than the corresponding (R)-derivatives 4a, 4b, and 4e, the adamant-2-amino analogue 8e exhibited high activity toward both human and rodent 11β-HSD-1.

Scheme 3. Synthesis of Compounds 17a–c[a]

[a]Reagents and conditions: (a) Triethylamine, CH_2Cl_2, rt, 2 h. (b) TMS-CF_3, TBAF, THF, overnight. (c) NaOH, CH_3OH, THF, H_2O, rt, overnight. (d) 4-Aminoadamantane, BOP-Cl, DIPEA, CH_2Cl_2, 6 h.

Table 4. In Vitro Potency of Compounds 17a–c

compd	R^1	h-11β-HSD-1 IC$_{50}$[a] (nM)	m-11β-HSD-1 inh. at 100 nM[b] (%)
17a	OH	6.0	26
17b	CN	43	9.5
17c	COOMe	124	14

[a]Average of at least two replicates. [b]The mean of at least two experiments.

Table 5. In Vitro Potency of Compounds 18a,b

		IC$_{50}$[a] (nM)	
compd	R^2	h-11β-HSD-1	m-11β-HSD-1
4ek	−CH$_3$	7.7	11
18a	−CH$_2$CH$_3$	16	164
18b	−CH$_2$CH=CH$_2$	33%[b]	87

[a]Average of at least two replicates. [b]Percent inhibition at 100 nM, the mean of at least two experiments.

Because h-11β-HSD-1 enzyme shares only about 79% homology with the mouse enzyme, it might be understandable that many 11β-HSD-1 inhibitors displayed species-dependent activity.[5] Some clinical candidates, such as INCB-13739 and PF-915275, lack potency against rodent enzyme, so in vivo pharmacokinetics (PK)/PD studies of these compounds require primate models.[16] In our series, cross-species potencies of adamant-2-yl derivatives **4d** and **4e** allowed us to employ rodent model.

It is reported that the adamantane group is prone to oxidation in living organism, which could cause a rapid elimination of the compound, so substituted adamantanes

Table 6. Profile of the Two Lead Compounds

	4e	4ek
in vitro assay		
h-11β-HSD-1 IC$_{50}$[a]	0.1 nM	7.7 nM
m-11β-HSD-1 IC$_{50}$[a]	1.3 nM	11 nM
h-HSD-2 IC$_{50}$[a]	2.2 μM	>10 μM
selectivity ratio: h-HSD-2/h-11β-HSD-1 IC$_{50}$	22000	>1300
m-11β-HSD-1 3T3L1 cellular IC$_{50}$[a]	121 nM	11 nM
mice PK[b]		
CL [mL/(min kg)]	90	60
Vdss (L/kg)	0.51	0.63
iv $t_{1/2}$ (min)	14	14
po F (%)	9.1%	3.0%
ip F (%)	63%	33%
ip AUC0-t (ng h/mL)	597.0	939.0

[a]Average of at least two replicates. [b]Dosed iv (1 mg/kg), po (5 mg/kg), and ip (5 mg/kg) in male BALB/c mice; mean values over three mice.
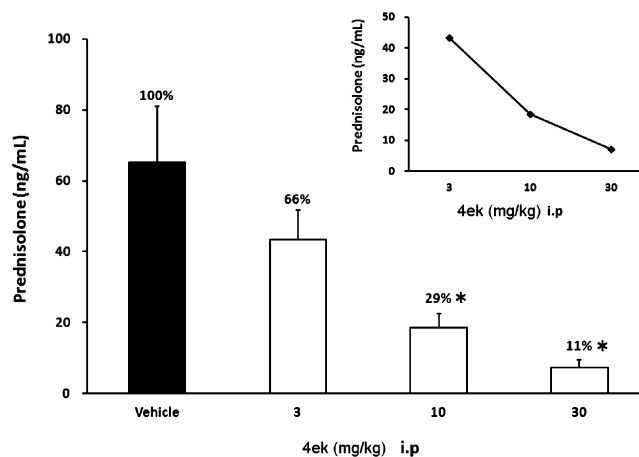

Figure 2. In vivo inhibitory activity of 11β-HSD-1 in BALB/c mice by **4ek**. Student's *t* test was used to compare the differences between the dosing group and the vehicle. *$P < 0.05$ vs vehicle.

have been used to prepare metabolically stable druglike molecules.[17−19] For example, introducing a hydroxyl group on the adamantane ring reduced Clog *P* and blocks metabolic soft spots.[6] In our test, hydroxylated adamant-2-yl derivative **4e** possessed better stability in HLM than unsubstituted adamant-2-yl derivative **4d** (HLM Cl$_{int}$ of **4e** vs **4d**: 106 vs 499 μL/min/mg protein). Consequently, we next focused our attention on the derivatization of **4e**.

Through the route depicted in Scheme 2, we synthesized more 4-amino-1-hydroxy-adamantyl derivatives. (*R*)-1-(*tert*-Butoxycarbonyl)-2-methyl pyrrolidine-2-carboxylic acid **12**, obtained from (*R*)-acid **5**, coupled with *trans*-4-amino-adamantan-1-ol hydrochloride to provide intermediate **13**. The target compounds (**4eb−el**) were then obtained by two successive steps from **13**: deprotection and sulfonylation. As listed in Table 3, most of the aryl or heteroaryl groups maintained high binding affinities to human enzyme with single-digit nanomolar IC$_{50}$ values, but some of them lose rodent enzyme activity.

To extend the SAR of this series, we next explored the effect of the R^1 group on adamantane. Noticing 4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzenesulfonamide reported in literature as a pharmacophore of 11β-HSD-1 inhibitors, we designed new

derivatives **17a−c** (Scheme 3 and Table 4).[20] As described in Scheme 3, sulfonylation of **6** afforded ketone **15**. Intermediate **16** was generated by treatment of **15** with (trifluoromethyl)-trimethylsilane (TMS-CF$_3$)/tetra-*n*-butylammonium fluoride (TBAF) in THF and a following hydrolysis step. The target compounds were then produced via condensation of **16** with the 1-substituted 4-aminoadamantanes. As listed in Table 4, the potency against human enzyme of **17b** (R^1 = CN) or **17c** (R^1 = COOMe) decreases 7- or 20-fold as **17a** (R^1 = OH). However, all three compounds display only weak activity on rodent enzyme at a concentration of 100 nM.

To investigate the effect of R^2 group on the pyrrolidine, **4ek** analogues **18a** and **18b** were designed (Table 5). The synthesis of **18a** and **18b** is analogous to **4ek**, replacing starting material **5** in Scheme 1 with (*R*)-2-ethyl and (*S*)-2-ally pyrrolidine-2-carboxylic acid.[21] As seen in Table 5, the methyl in the 2-position of pyrrolidine is superior to ethyl and allyl groups in terms of potency, but the 2-allyl analogue **18b** has higher affinity to rodent enzyme than human enzyme.

The potential for compounds **4e** and **4ek** to complete lead candidate criteria was further evaluated (Table 6). Both compounds were potent inhibitors of human and mouse 11β-HSD-1 and highly selective against human 11β-HSD-2. In the 3T3L1 cell-based assay, compound **4ek** was 11 times more potent than **4e**. In the mouse PK test, however, both **4e** and **4ek** showed high clearance, very short plasma half-life, and low oral bioavailability.

To look at the correlation between in vitro activity and in vivo inhibition, **4ek**, with higher cellular level activity than that of **4e**, was selected as a tool compound and progressed to an in vivo 11β-HSD-1 inhibition assay in mice. Because of the poor metabolic stability and low oral bioavailability of **4ek**, we at first selected intraperitoneal (ip) injection as administration route (Table 6, enhanced bioavailability after ip injection is 33%, 11 times of the po bioavailability). In this mechanistic biomarker study, normal mice were dosed with **4ek** (or vehicle) and then exogenous substrate prednisone, which transformed to prednisolone catalyzed by 11β-HSD1.[22] As illustrated in Figure 2, ip treatment of BALB/c mice with 3, 10, and 30 mg/kg **4ek** dose- dependently reduced the generation of predinisolone with inhibition of 34, 71, and 89%, respectively, and the corresponding plasma concentrations of **4ek** in mice were 28, 80, and 94 ng/mL.

In conclusion, we reported a new series of 2-alkyl-1-arylsulfonylprolinamides as human and rodent 11β-HSD-1 inhibitors. Primary optimization and SAR studies led to the discovering of compound **4ek**, which demonstrated potent and selective activity in vitro and in vivo inhibitory activity in a prednisone conversion experiment. Efforts to improve the PK profile of this series are under way and will be reported in the future.

ASSOCIATED CONTENT

S **Supporting Information**
Experimental procedures and characterization of new chemical entities. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions
§These authors contributed equally.

Notes
The authors declare no competing financial interest.

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ABBREVIATIONS

HSD, hydroxysteroid dehydrogenase; SAR, structure−activity relationship; HLM, human liver microsome; PK, pharmacokinetics; PD, pharmacodynamics; BOP-Cl, bis(2-oxo-3-oxazolidinyl)phosphonic chloride; TMS-CF$_3$, (trifluoromethyl)trimethylsilane; TBAF, tetra-*n*-butylammonium fluoride; DIPEA, *N,N*-diisopropylethylamine

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methyl pyrrolidone:32% β-cyclodextrin:normal saline = 1:6:3/V:V:V) or with 3, 10, and 30 mg/kg of **4ek**. One hour after the vehicle or drug treatment, mice were dosed by iv injection with 3 mg/kg of prednisone. Venous blood samples were collected from the retinal vein 2 min later. Plasma prednisone, prolnisolone, and **4ek** levels were measured using the LC/MS/MS method (Waters Acquity UPLC system coupled to Applied Biosystems/Sciex API 4000 Q-Trap tandem mass spectrometry).