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Discovery and optimization of benzenesulfonanilide derivatives as a novel class of 11β-HSD1 inhibitors

Yosup Rew *, Michael DeGraffenreid, Xiao He, Juan C. Jaen †, Dustin L. McMinn, Daqing Sun, Hua Tu, Stefania Ursu, Jay P. Powers †

Amgen Inc., 1120 Veterans Boulevard, South San Francisco, CA 94080, USA

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ABSTRACT

A novel series of benzenesulfonanilide derivatives of 11β-HSD1 inhibitors were identified via modification of the sulfonamide core of the arylsulfonylpiperazine lead structures. The synthesis, in vitro biological evaluation, and structure–activity relationship of these compounds are presented. Optimization of this series rapidly resulted in the discovery of compounds (***S***)-**10** and (***S***)-**23** (11β-HSD1 SPA IC_{50} = 1.8 and 1.4 nM, respectively).

One of the key regulatory roles of glucocorticoids is glucose homeostasis. In this regard, glucocorticoids regulate gluconeogenesis in the liver and inhibit peripheral glucose uptake in muscle and adipose tissue. 11β-Hydroxysteroid dehydrogenase type 1 (11β-HSD1), a NADPH-dependent reductase, is a key enzyme that converts the inactive glucocorticoid cortisone to the active glucocorticoid hormone cortisol in liver, adipose, and brain. Excessive concentrations of glucocorticoids in the liver and adipose tissue can lead to glucose intolerance and insulin resistance.[1] In recent decades, selective inhibition of the 11β-HSD1 enzyme has been considered to be a promising strategy for improving insulin sensitivity and treating type II diabetes.[2]

Previous research within our laboratories described a series of arylsulfonylpiperazine derivatives,[3] exemplified by compound **1**, as potent 11β-HSD1 inhibitors (Fig. 1). Compound **1** was a potent, selective, and orally bioavailable inhibitor with efficacy in a cynomolgus monkey ex vivo enzyme inhibition model.[3a]

Compound **1** is known to bind to the substrate site in a V-shaped binding mode, and the central sulfonyl group is located near the catalytic triad residues of the enzyme.[3] We recently succeeded in the expansion of structural diversity and optimization of structurally distinguished amide[4] and sulfone[5] series as novel 11β-HSD1 inhibitors. Replacement of the central sulfonamide functional group with other isosteric core moieties has been continuously fascinating to us, and herein we report on another novel

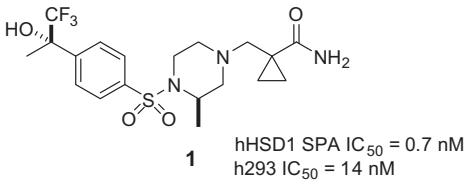
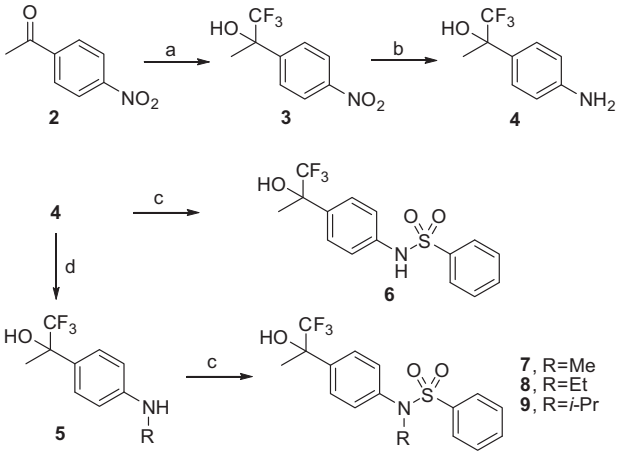


Figure 1. Representative arylsulfonylpiperazine 11β-HSD1 inhibitor.[3b]



Scheme 1. Reagents and conditions: (a) TMS-CF_3, TBAF, THF, 93%; (b) $SnCl_2$, EtOH, 94%; (c) benzenesulfonyl chloride, pyridine, DCM, 58–92%; (d) for R = Me and Et: (i) Boc_2O, $NaHCO_3$, THF/H_2O, 100%; (ii) NaH, MeI (85%) or EtBr (70%), DMF; (iii) TFA, 100%; for R = *i*-Pr: acetone, AcOH, $NaBH_3CN$, AcCN, 80%.

* Corresponding author. Tel.: +1 650 244 2682.
E-mail address: yrew@amgen.com (Y. Rew).
† Currently at ChemoCentryx, Inc., Mountain View, CA 94043, USA.

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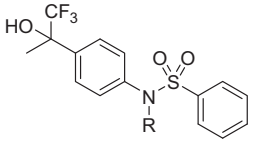
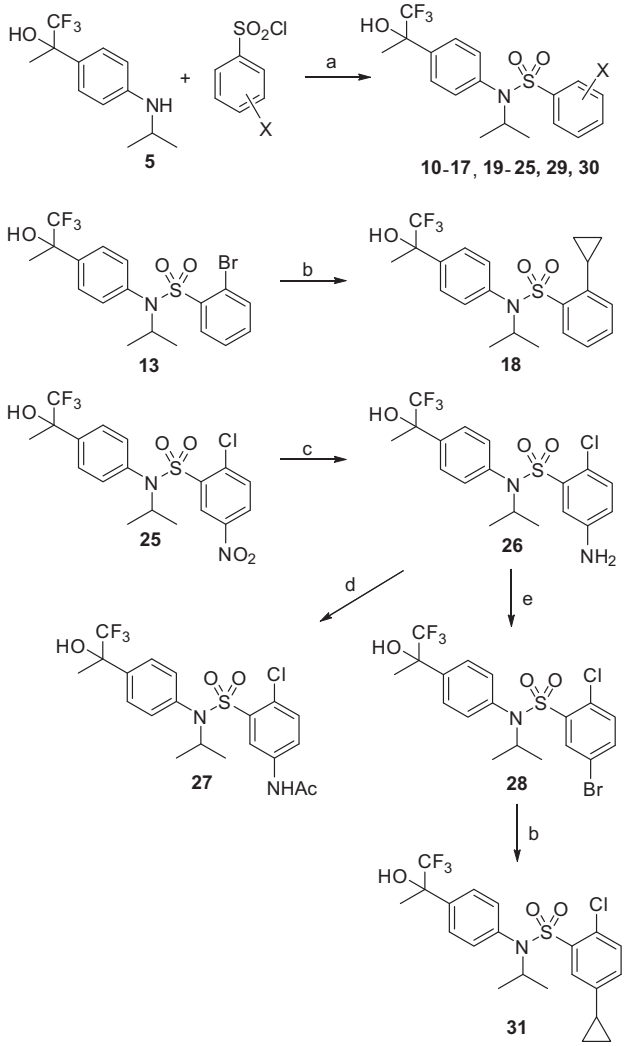
Table 1
Inhibition of 11β-HSD1 by selected analogs: initial N-alkylation



Compound[a]	R	hHSD1 SPA[b] IC_{50} (nM)
6	H	>1000
7	Me	>1000
8	Et	300
9	*i*-Pr	21.4

[a] All compounds were racemates and gave satisfactory ^1H NMR, HPLC, and MS data that were in full agreement with their proposed structures; purity (>95%) was determined by HPLC analysis.
[b] Potency data were reported as the average of at least two determinations and IC_{50} values determined by a scintillation proximity assay.

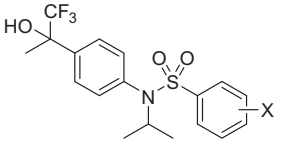


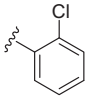
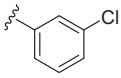
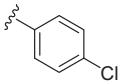
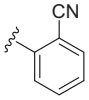
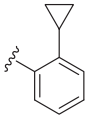
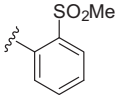
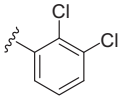
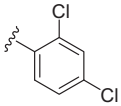
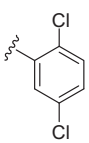
Scheme 2. Reagents and conditions: (a) pyridine, DCM, 16–76%; (b) cyclopropylboronic acid, K_3PO_4, $Pd(PPh_3)_4$, toluene/H_2O = 10/1, 81–96%; (c) $SnCl_2$, EtOH, quantitatively; (d) Ac_2O, DMF, 73%; (e) isoamylnitrite, $CuBr_2$, AcCN, 91%.

class of 11β-HSD inhibitors (**6**–**31** and **36**–**44**), which have a retro-inverso sulfonamide isosteric core.

As an initial SAR effort, a series of simple benzenesulfonanilides, compounds **6**–**9**, were synthesized as described in Scheme 1.

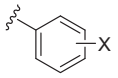
Table 2
Sulfonamide aryl modification



Compound[a]		hHSD1 SPA[b] IC_{50} (nM)	h293[c] (cell) IC_{50} (nM)	h293 (cell, 3% HSA[d]) IC_{50} (nM)
9		21.4	N/D	N/D
10		3.4	9.0	49
11		15	22	262
12		27.8	N/D	N/D
13		14	6.6	86
14		7.4	9.9	48
15		33	29	261
16		39	71	769
17		5.3	8.0	103
18		41	144	>1000
19		652	548	>1000
20		3.1	11.2	91
21		9.7	14	108
22		19.1	N/D	N/D
23		3.1	9.0	54

(*continued on next page*)

Table 2 (*continued*)

Compound[a]		hHSD1 SPA[b] IC_{50} (nM)	h293[c] (cell) IC_{50} (nM)	h293 (cell, 3% HSA[d]) IC_{50} (nM)
24		13	N/D	N/D
25		10	15	113
26		15	63	271
27		256	498	>1000
28		3.3	19	106
29		4.5	19	103
30		21	47	268
31		45	133	612

[a] All compounds were racemates and gave satisfactory ^{1}H NMR, HPLC, and MS data that were in full agreement with their proposed structures; purity (>95%) was determined by HPLC analysis.

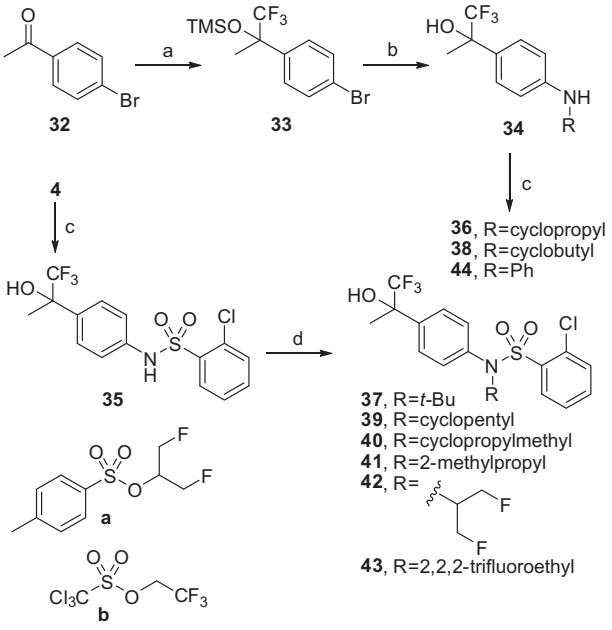
[b] IC_{50} values determined by a scintillation proximity assay (all potency data are reported as the average of at least two determinations).

[c] h293 = HEK 293 cells were stably transfected with full-length human 11β-HSD1 (all potency data are reported as the average of at least two determinations).

[d] HAS = human serum albumin (all potency data are reported as the average of at least two determinations).

Synthesis began with the conversion of 4′-nitroacetophenone **2** into the key intermediate aniline **4**. Treatment of **2** with TMS-CF_3, followed by reduction of the nitro group in **3** with $SnCl_2$ provided aniline **4**. Direct sulfonylation of **4** with benzenesulfonyl chloride afforded compound **6**. Preparation of *N*-monoalkyl anilines **5** by *N*-alkylation of a Boc-protected aniline (R = Me and Et) or direct reductive amination (R = *i*-Pr), followed by sulfonylation gave compounds **7**–**9**.

Compounds were evaluated for the inhibition of human 11β-HSD1 (Table 1).[6] The initial primary phenyl-sulfonamide, compound **6**, exhibited no activity as an enzyme inhibitor in the biochemical assay. However, as the size of the *N*-alkyl substituent increased, in vitro biochemical potency improved. Although the methyl analog (**7**) was inactive, the ethyl analog **8** displayed a moderate activity (IC_{50} = 300 nM). A 15-fold increase in the potency was observed when the ethyl group of compound **8** was replaced by the isopropyl group (compound **9**: IC_{50} = 21 nM).



Scheme 3. Reagents and conditions: (a) $TMSCF_3$ (1.5 equiv), TBAF (0.0075 equiv), THF, 77%; (b) for R = cyclopropyl and cyclobutyl: RNH_2, $Pd_2(dba)_3$, BINAP, *t*-BuONa, toluene; 1 M TBAF, 49–80%; for R = Ph: RNH_2, $Pd_2(dba)_3$, BINAP, Cs_2CO_3; 1 M TBAF, 43%; (c) 2-chlorobenzenesulfonyl chloride, pyridine, 12–92% (d) for **37** and **39**–**41**: RBr, K_2CO_3, DMF, 13–93%; for **42**: (a) K_2CO_3, DMF, 73%; for **43**: (b) K_2CO_3, DMF, 10%.

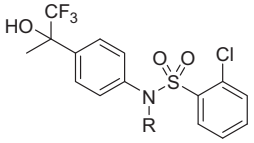
This interesting result led us to focus on further SAR with this benzenesulfonanilide series. To explore SAR of the aryl sulfonyl group systematically, we synthesized a variety of analogs with a modified aryl sulfonyl group (**10**–**31** in Scheme 2).

Most compounds (**10**–**17**, **19**–**25**, **29**, and **30**) were prepared by direct sulfonylation of **5** with a substituted benzenesulfonyl chloride. The Suzuki coupling reaction of **13** and **28** with cyclopropylboronic acid gave **18** and **31,** respectively. The nitro compound **25** was reduced to amine **26** under $SnCl_2$ conditions, and further acetylation gave **27**. Treatment of the diazonium salt, which was derived from **26,** with $CuBr_2$ provided **28**. Compounds were evaluated for the inhibition of human 11β-HSD1 enzymes in both biochemical assays and cell-based assays (Table 2).[6]

Screening a small focused library with a Cl substituent revealed that substitution at the 2-position improved11β-HSD1 inhibition (**9**–**12** in Table 2). Compound **10**, a 2-Cl analog, is significantly more potent than its unsubstituent phenyl analog (**9**). Shifting the substituent to the *meta*- and *para*-positions also led to a drop in activity (**11** and **12**).

Further derivatization at the 2-position was investigated (**13**–**20**). The 2-Cl analog (**10**) was still the most potent compound, and the 2-F and 2-Me analogs (**14** and **20**) showed potencies comparable to that of **10**. Additional substitutions at the 3, 4, 5, or 6 positions were then evaluated while preserving the 2-Cl substituent (**21**–**24**). Compound **23**, the 2,5-dichlorophenyl analog, showed potency similar to that of **10**; whereas the potency of all the other analogs was diminished. Lastly, we tried to replace the C-5 Cl group with other substituents (**25**–**31**) but none of those analogs was superior to **23** in terms of potency.

Table 3
N-alkyl modification



Compound[a]	R	hHSD1 SPA[b] IC_{50} (nM)	h293[c] (cell) IC_{50} (nM)	h293 (cell, 3% HSA[d]) IC_{50} (nM)
10		3.4	9.0	49
36		40	19	411
37		13	42	614
38		20	46	441
39		61	144	>1000
40		46	112	>1000
41		89	185	>1000
42		19	29	162
43		116	313	>1000
44		134	620	N/D

[a] All compounds were racemates and gave satisfactory ^{1}H NMR, HPLC, and MS data that were in full agreement with their proposed structures, and purity (>95%) was determined by HPLC analysis.
[b] IC_{50} values determined by a scintillation proximity assay (all potency data are reported as the average of at least two determinations).
[c] h293 = HEK 293 cells stably transfected with full length human 11β-HSD1 (all potency data are reported as the average of at least two determinations).
[d] HSA = human serum albumin (all potency data are reported as the average of at least two determinations).

With the discovery of the improved potency imparted by the 2-Cl phenyl group to sulfonyl functionality, we returned to investigate further modifications of the *N*-alkyl substituents in **10**. Compounds **36**–**44** were prepared as outlined in Scheme 3. Treatment of ketone **32** with TMS-CF_3, followed by the Buchwald-Hartwig coupling reaction with the primary amines of **33** and deprotection of the trifluoromethyl carbinol group provided **34**. Sulfonylation of **34** with 2-chlorobenzenesulfonyl chloride afforded compound **36**, **38**, and **44**. The other *N*-alkyl derivatives (**37** and **39**–**43**) were prepared by direct alkylation of the primary sulfonamide **35**. Unfortunately, in this broad set of analogs, replacement of the isopropyl group resulted in a reduction in potency (Table 3).

Chiral separation of the most potent analogs, **10** and **23**, was achieved by preparative normal phase chiral HPLC (Chiralpak AD) and, as observed in our previously reported trifluoromethyl carbinol containing analogs, the (*S*) configuration proved to have greater 11β-HSD1 inhibitory activity.[3–5] In this benzenesulfonanilide series, the absolute configuration of the trifluoromethyl carbinol was determined by single X-ray crystallography of the active isomer of compound **10** (Fig. 2) and the (***S***)-enantiomers are about over 60 times more potent than the corresponding (***R***)-isomers in both biochemical and cellular assays (Table 4).

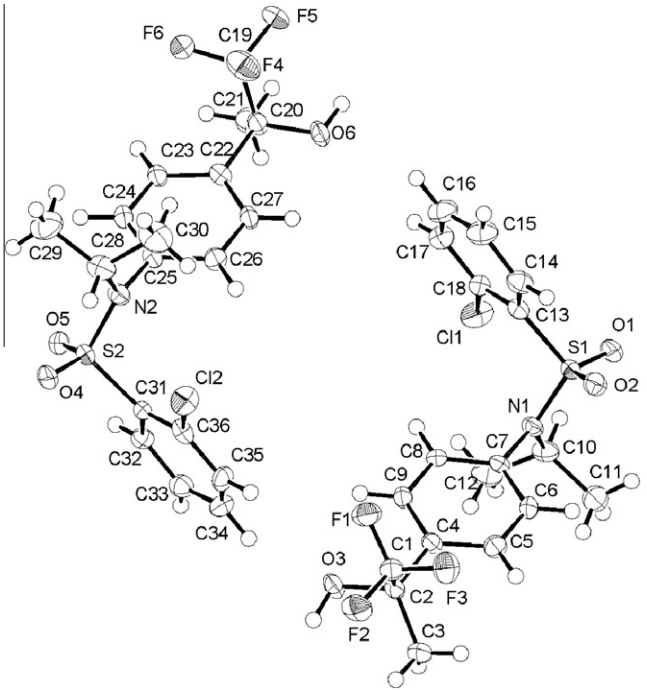
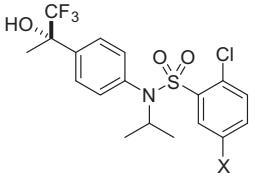


Figure 2. Single X-ray crystal structure of (***S***)-**10**.

Table 4
Effect of stereochemistry at the trifluoromethyl carbinol moiety



(***S***)-**10**, X = H
(***S***)-**23**, X = Cl

Compound[a]	X	hHSD1 SPA[b] IC_{50} (nM)	h293[c] (cell) IC_{50} (nM)	h293 (cell, 3% HSA[d]) IC_{50} (nM)
10	H	3.4	9.0	49
(*S*)-**10**	H	1.8	5.8	25
(*R*)-**10**	H	113	138	>1000
23	Cl	3.1	9.0	54
(*S*)-**23**	Cl	1.4	2.2	21
(*R*)-**23**	Cl	106	200	>1000

[a] All compounds gave satisfactory ^{1}H NMR, HPLC, and MS data that were in full agreement with their proposed structures, and purity (>95%) was determined by HPLC analysis.
[b] IC_{50} values determined by a scintillation proximity assay (all potency data are reported as the average of at least two determinations).
[c] h293 = HEK 293 cells stably transfected with full length human 11β-HSD1 (all potency data are reported as the average of at least two determinations).
[d] HSA = human serum albumin (all potency data are reported as the average of at least two determinations).

In summary, we have identified a novel class of benzenesulfonanilide inhibitors of the human 11β-HSD1. Optimization of this series rapidly resulted in the discovery of compounds (***S***)-**10** and (***S***)-**23**, with single-digit nanomolar potency in both biochemical and cell-based assays.

Acknowledgements

The authors would like to thank Dr. Frederick Hollander at the University of California, Berkeley for solving the single X-ray crystal structure of compound **(*S*)-10**.

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6. 11β-HSD1 enzyme activity was determined by measuring the conversion of [^{3}H]-cortisone to [^{3}H]-cortisol. Product [^{3}H]-cortisol, captured by an anti-cortisol monoclonal antibody conjugated to scintillation proximity assay (SPA) beads, was quantified with a microscintillation plate reader. Biochemical enzyme assays were performed with Baculovirus-produced recombinant full-length human or mouse 11β-HSD1 as the enzyme source and NADPH as cofactor. Cell-based enzyme assays (h293) utilized HEK293 cells stably expressing recombinant human full-length 11β-HSD1 as the enzyme source without supplementation of NADPH. IC_{50} values for enzyme inhibition were calculated with a dose response curve fitting algorithm with at least duplicate sets of samples. In the cellular assay, selected compounds were tested in the presence of human serum albumin (HSA) to measure the impact of protein binding.