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The synthesis and SAR of novel diarylsulfone 11β-HSD1 inhibitors

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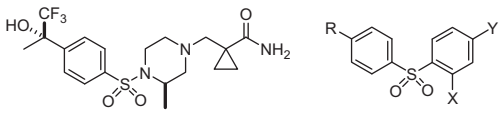
ABSTRACT

In this communication, human 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) inhibitory activities of a novel series of diarylsulfones are described. Optimization of this series resulted in several highly potent 11β-HSD1 inhibitors with excellent pharmacokinetic (PK) properties. Compound (*S*)-**25** showed excellent efficacy in a non-human primate ex vivo pharmacodynamic model.

Two isozymes, 11β-HSD1 and 11β-HSD2, catalyze the interconversion of the active glucocorticoid cortisol and the inactive glucocorticoid cortisone. In humans, the reductive, NADPH-dependent isozyme 11β-HSD1 is expressed mainly in liver, adipose, and brain tissue and converts the inactive glucocorticoid cortisone to active cortisol in a NADPH-dependent fashion.[1–4] 11β-HSD2 is expressed predominantly in the kidneys and catalyzes the reverse conversion. 11β-HSD1 knockout mice are resistant to diet-induced obesity and show improved hepatic insulin sensitivity and decreased glycogenolysis. Conversely, animals over-expressing 11β-HSD1 in adipose tissue develop central obesity and are hyperglycemic and insulin resistant. Pharmacologic inhibition of 11β-HSD1 in animals with type 2 diabetes improved insulin sensitivity.[5] These data suggested that selective inhibition of 11β-HSD1 activity may provide a viable treatment for the metabolic syndrome and type 2 diabetes.[6–12] As a therapeutic target, 11β-HSD1 has attracted a significant amount of attention in the pharmaceutical industry for the last decade.

Our group has published several communications on 11β-HSD1 inhibitors.[13] We previously described arylsulfonyl piperazine **1** (Fig. 1) as a potent inhibitor of 11β-HSD1 in biochemical and cellular assays, with efficacy in an ex vivo pharmacodynamic assay. In an effort to improve the pharmacokinetic (PK) properties of this sulfonamide series, several new central portions were designed and evaluated. In this communication, we report the successful structure-based design, synthesis, and evaluation of a novel series of HSD1 inhibitors based upon a diaryl sulfone replacement for the arylsulfonamide piperazine core present in **1**. These efforts led to the discovery of potent, selective, and orally bioavailable inhibitors with excellent efficacy in a cynomolgus monkey ex vivo enzyme inhibition model.

The target diarylsulfone analogs were prepared as outlined in Schemes 1–4.[14] The synthesis of compounds **2**–**16**, **18**–**19**, **21**, **23**–**31**, and **35**, is depicted in Scheme 1. The coupling of commercially available aryl halides and thiophenol in the presence of cesium carbonate in DMF, followed by Friedel–Crafts acylation at



1

hHSD1 IC_{50}: 0.83 nM
h293 IC_{50}: 7.3 nM
Rat PK :
CL (L/h/Kg): 1.4
MRT (h): 0.8
%F: 41

2-35 (Tables 1-5)

Figure 1. 11β-HSD1 inhibitors.

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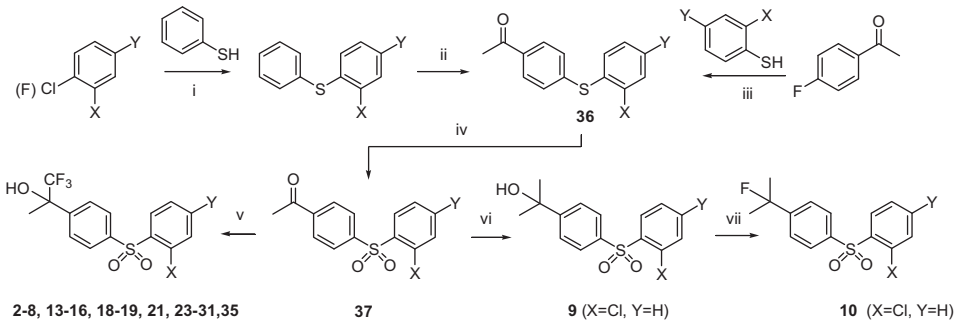
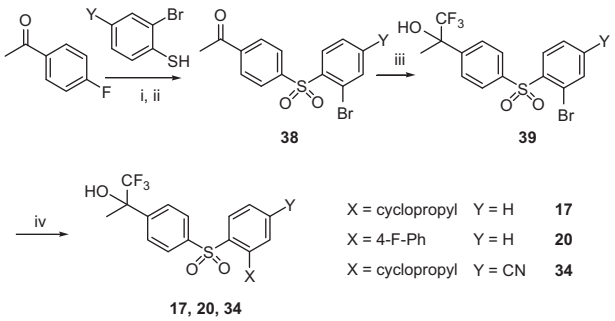
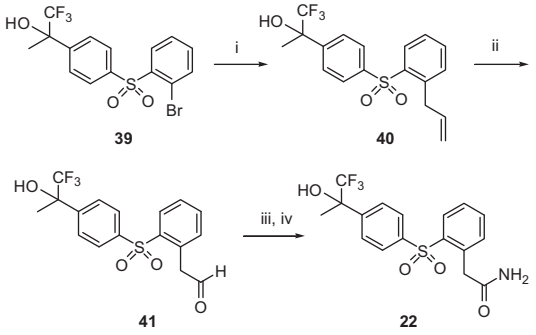


Cmpd	X	Y	Cmpd	X	Y	Cmpd	X	Y	Cmpd	X	Y	Cmpd	X	Y	Cmpd	X	Y
2	H	H	**3**	Cl	H	**4**	Me	H	**5**	3-Cl	H	**6**	H	OMe	**7**	H	F
8	H	NO_2	**13**	F	H	**14**	CF_3	H	**15**	Et	H	**16**	iPr	H	**18**	*t*Bu	H
19	CN	H	**21**	$C(CH_3)_2OH$	H	**23**	Cl	Cl	**24**	Cl	Br	**25**	Cl	CN	**26**	Cl	NO_2
27	Cl	4-CN-Ph	**28**	Cl	4-pyridyl	**29**	Cl	NH_2	**30**	Cl	$CONH_2$	**31**	Cl	$NHCONH_2$	**35**	CH_2CH_2F	CN

Scheme 1. Reagents and conditions: (i) Cs_2CO_3, DMF, 100 °C; 48–92%; (ii) acetyl chloride, $AlBr_3$, CS_2 0 °C, 24–86%; (iii) Cs_2CO_3, DMF, 100 °C; 37–89%; (iv) *m*CPBA, CH_2Cl_2, 69–83%; (v) TMS–CF_3, TBAF, THF, 20–75%; (vi) LiMe in Et_2O, THF, 0 °C, 54%; (vii) DAST, CH_2Cl_2, −78 °C, 45%.



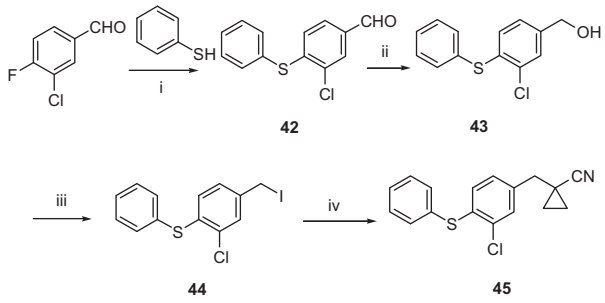
Scheme 2. Reagents and conditions: (i) Cs_2CO_3, DMF, 100 °C; 92%; (ii) *m*CPBA, CH_2Cl_2, 90%; (iii) TMS–CF_3, TBAF, THF, 59%; (iv) X-$B(OH)_2$, K_3PO_4, $Pd(PPh_3)_4$, toluene/H_2O, 20:1, 100 °C, 35–62%.



Scheme 3. Reagents and conditions: (i) allyltri-*n*-butyltin, $Pd(PPh_3)_4$, benzene, 100 °C, 96%; (ii) $NaIO_4$, OsO_4, MeOH/H_2O 1:1, 82%; (iii) Jones reagent, acetone, 72%; (iv) NH_3 in CH_2Cl_2, EDC, HOBt, CH_2Cl_2/DMF, 64%.

the 4-position with acetylchloride and aluminum tribromide generated intermediate **36**. Oxidation of **36** with *m*CPBA yielded sulfone **37**. Treatment of **37** with TMS–CF_3 in THF at room temperature gave the trifluoromethyl tertiary alcohol in moderate to excellent yield, while reaction of **37** with methyl lithium gave tertiary alcohol **9**. Analog **10** was obtained by treatment of tertiary alcohol **9** with DAST in CH_2Cl_2.

Compounds **17**, **20**, and **34** were prepared via the route described in Scheme 2. The coupling reaction of 4-fluoroacetophenone with 2-bromothiophenol proceeded under standard conditions, followed by oxidation with *m*CPBA to afford ketone **38**. Phenyl bromide **39** was generated upon treatment of **38** with TMS–CF_3 in THF. The target compounds **17**, **20**, and **34** were then obtained by Suzuki coupling of **39** with the appropriate boronic acids.



Scheme 4. Reagents and conditions: (i) Cs_2CO_3, DMF, 100 °C; 89%; (ii) $NaBH_4$, 0 °C, 95%; (iii) I_2, PPh_3, imidazole 70 °C, 20%; (iv) cyclopropanecarbonitrile, *n*-BuLi, iPr_2NH, THF, −78 °C, 28%.

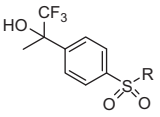
Phenyl bromide **39** was also used as the starting material for the synthesis of analogs **22** (Scheme 3). Stille coupling of **39** with allyltri-*n*-butyltin was followed by conversion to aldehyde **41**. Primary amide **22** was produced by further oxidation of **41** with Jones reagent, followed by amide coupling of the resultant acid with ammonia.

Scheme 4 shows the synthesis of the intermediate **45** necessary for making analogs **32** and **33** (Table 4). Accordingly, aldehyde **42**, which was generated by the coupling reaction of 3-chloro-4-fluorobenzaldehyde and thiophenol, was reduced to alcohol **43** with sodium borohydride. Conversion of the alcohol to the iodide furnished **44**. Treatment of **44** with cyclopropanecarbonitrile and LDA in THF gave intermediate **45**.

Compounds were evaluated in vitro for inhibition of human (h-HSD1) and mouse 11β-HSD1 enzymes, as well as in cell-based assays (h-293) using our previously published procedures: IC_{50} values were determined by scintillation proximity assay (SPA); h-293 = HEK 293 cells stably transfected with full length human 11β-HSD1.[13] The results are summarized in Tables 1–5.

In order to establish the minimum pharmacophore required for 11β-HSD1 inhibition, a small focused set of analogs was initially synthesized. This set demonstrated a steep SAR and, as shown in Tables 1 and 2-substitution was found to be quite important for

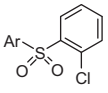
Table 1
Inhibition of 11β-HSD1 by selected analogs: initial sulfonamide replacements

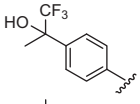
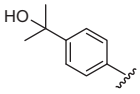
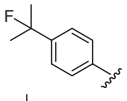
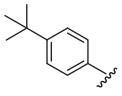
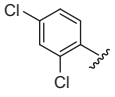


Compd	R	h-HSD1[a] IC_{50} (nM)	h-293 (cell)[a] IC_{50} (nM)
2	Ph	79	355
3	2-Cl–Ph	4.7	50
4	2-Me-Ph	4.4	56
5	3-Cl-Ph	18.1	317
6	4-OMe-Ph	28.7	229
7	4-F-Ph	36.6	240
8	4-NO_2-Ph	24	233

[a] IC_{50} determined by scintillation proximity assay (SPA). All potency data are reported as means of at least two determinations with variation around the mean <50%. h-293 = HEK 293 cells stably transfected with full length human 11β-HSD1. Compounds were tested as racemic mixtures.

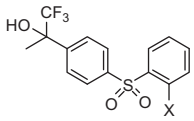
Table 2
Inhibition of 11β-HSD1 by selected analogs: modifications of the left-hand aryl ring



Compd	Ar	h-HSD1[a] IC_{50} (nM)	h-293[a] IC_{50} (nM)
3		4.7[b]	50[b]
9		102	—
10		30	—
11		20	455
12		>300	>3000

[a] All potency data are reported as means of at least two determinations with variation around the mean <50%.
[b] Compound tested as racemic mixtures.

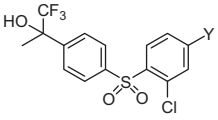
Table 3
Modification to the 2-position of the aryl ring of the right-hand side

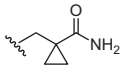


Compd	X	h-HSD1[a] IC_{50} (nM)	h-293[a] IC_{50} (nM)
3	Cl	4.7	50
13	F	11	129
4	Me	4.4	56
14	CF_3	7.5	145
15	Et	1.2	93
16	*i*Pr	4.1	1120
17	Cyclopropyl	1.2	28
18	*t*-Bu	11	280
19	CN	50	315
20	4-F-Ph	109	2410
21	$C(CH_3)_2OH$	144	>300
22	CH_2CONH_2	>300	>300

[a] All potency data are reported as means of at least two determinations with variation around the mean <50%. Compounds were tested as racemic mixtures.

Table 4
Inhibition of 11β-HSD1 by selected analogs: modification to the 4-position of the right-hand aryl ring



Compd	Y	h-HSD1[a,b] IC_{50} (nM)	h-293[a] IC_{50} (nM)
3	H	4.7	50
23	Cl	2	43
24	Br	1.8	59
25	CN	2.7	39
26	NO_2	3.2	105
27	4-CN-Ph	24	294
28	4-Pyridyl	7	110
29	NH_2	30	>300
30	$CONH_2$	18	>300
31	$NHCONH_2$	86	>300
32		9	184
33		30	650

[a] All potency data are reported as means of at least two determinations with variation around the mean <50%. Compounds were tested as racemic mixtures.

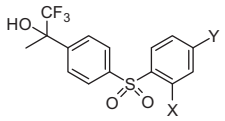
biochemical activity, while the unsubstituted phenyl analog **2** was significantly less active. Shifting the substitution to *meta*- and *para*-position also led to a drop in activity.

We then turned our attention to modifications on the left-hand side aryl ring of **3** (Table 2). In this limited set of analogs, replacement of the para-trifluoromethyl carbinol resulted, in varying degree, in a reduction in potency, consistent with our earlier SAR in the arylsulfonamide piperazine series.

The improved potency of the 2-substituted analogs prompted us to further investigate a more diversified set of derivatives (Table 3). Compound (**17**), containing a 2-cyclopropyl group, was found to be the most potent, with an IC_{50} of 1.2 nM, in the biochemical assay and 28 nM in the cellular assay, which was a 2 to 3-fold improvement over the parent (2-chloro) compound **3**. The 2-ethyl analog (**15**) gave a modest threefold improvement in biochemical potency but a twofold loss in cellular potency, while the slightly larger isopropyl (**16**) and *t*-butyl (**18**) groups led to decrease in activity, especially in the cellular assay. Replacement of the alkyl group with aryl substitution at C2 position (**20**) resulted in a significant decrease in activity, suggesting limited space in this region of the enzymes active site. The introduction of more polar groups (**21** and **22**) also resulted in a significant decrease in potency.

Previously reported structure–activity relationships in the arylsulfonylpiperazine series suggested that the substitution on the distal nitrogen of the piperazine (**1**) were well tolerated and gave compounds with sub-nanomolar inhibitory potency.[13] We applied the same strategy to the diarylsulfone series and made modifications at the *para*-position of the aryl ring (Table 4). Incorporation of a chloro, bromo, or cyano group (**23**–**25**) at the *para*-position of the aryl ring gave about twofold increase in human biochemical potency over **3**, although the cellular potency remained the same, while a nitro group (**26**) led to approximately a twofold reduction

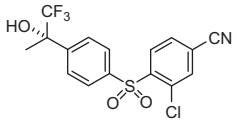
Table 5
Inhibition of 11β-HSD1 by selected analogs: effect of absolute stereochemistry at the trifluoromethylcarbinol moiety



Compd	X	Y	h-HSD1 [a] IC_{50} (nM)	h-293[a] IC_{50} (nM)
(*R*)-**25**	Cl	CN	14	165
(*S*)-**25**	Cl	CN	0.9	11
(*R*)-**34**	Cyclopropyl	CN	11.2	125
(*S*)-**34**	Cyclopropyl	CN	0.6	2.6
(*R*)-**35**	CH_2CH_2F	CN	36	376
(*S*)-**35**	CH_2CH_2F	CN	1.2	20.7

[a] All potency data are reported as means of at least two determinations with variation around the mean <50%.

Table 6
Pharmacokinetic profiles of compound (*S*)-**25**



Species	CL (iv, L/h/Kg)	AUC (po, μg h/L)	V_{dss} (iv, L/Kg)	MRT (iv, h)	*F* (po, %)
Rat[a,b]	0.49	1815	3.0	7.2	55
Dog[a,b]	0.02	33,800	1.7	100	73
Cyno[a,b]	0.43	630	1.4	6.5	13

[a] Dosed iv 0.5 mg/kg, po 2.0 mg/kg.
[b] Values are an average for three rats, dogs and monkeys.

in cellular potency. Aryl derivatives (**27** and **28**) had a 4 to 5-fold decrease in potency over the parent compound **3**. The introduction of more polar solubilizing groups (**29**–**31**) resulted in substantial loss of activity. We also modified the *para*-position with other solubilizing groups identified in our previous studies, such as the moiety from inhibitor **1** (**33**). In this case, such replacement led to a significant decrease in potency.

As observed in our previously reported trifluoromethylcarbinol containing analogs, the (*S*) configuration proved to have greater 11β-HSD1 inhibitory activity.[13] In the diarylsulfone series, the two enantiomers were also separated and their absolute configurations were determined by single crystal small molecule X-ray crystallography. As predicted from our earlier work, the (*S*)-enantiomers were found to be about 20 to 40 times more potent than the corresponding (*R*)-isomers in both the biochemical and cellular assays (Table 5).

Pharmacokinetic data for (*S*)-**25** is presented in Table 6. With the novel sulfone center core, (*S*)-**25** exhibited a significant improvement of in vivo metabolic stability and oral bioavailability compared to **1**.

In addition to the excellent potency and pharmacokinetic profile of (*S*)-**25**, this molecule had suitable activity against the cynomolgus monkey 11β-HSD1 enzyme (IC_{50} = 3 nM) and was selected for further evaluation in a cynomolgus monkey ex vivo pharmacodynamic model. In this study, cynomolgus monkeys were dosed orally with 2 and 10 mg/kg of inhibitor (*S*)-**25**. At 2 h post-dose, samples of mesenteric fat tissue were taken. Following 1 h incubation of these tissues in media containing [^{3}H]-cortisone, 11β-HSD1 activity was measured through detection of tritiated cortisol levels using a scintillation proximity assay.[13] Relative to controls, all dose groups showed a decrease in [^{3}H]-cortisol production in mesenteric fat (Fig 2). These results demonstrate that (*S*)-**25** was effective in lowering 11β-HSD1 adipose activity in non-human primates when administered orally.

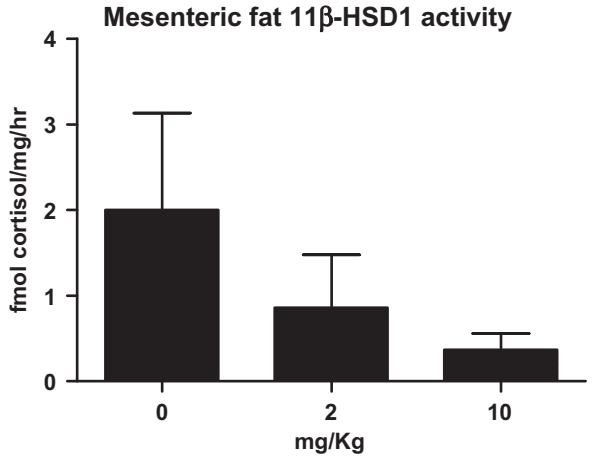


Figure 2. Ex vivo 11β-HSD1 enzyme activity in intact mesenteric fat collected from cynomolgus monkeys dosed orally with (*S*)-**25**. Plasma and mesenteric fat samples were collected 2 h after compound was administered orally in dosing vehicle (1% methylcellulose and 1% Tween 80 in sterile water). 11β-HSD1 enzyme activity was measured as the [^{3}H]-cortisol formed after 1 h incubation of fat samples at 37 °C in reaction buffer containing [^{3}H]-cortisone. Compound concentration in plasma and fat samples was determined by LC/MS/MS.

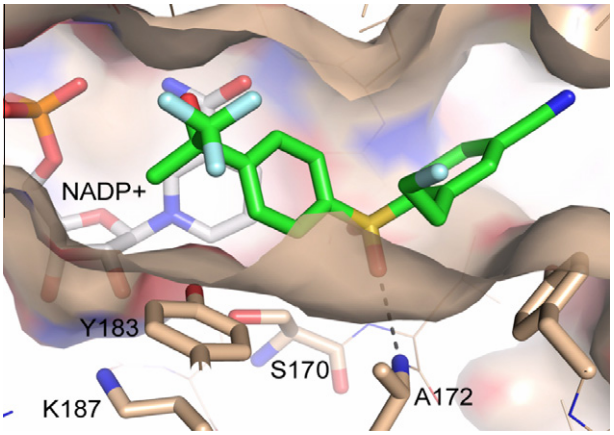


Figure 3. Co-crystal structure of compound (*S*)-**35** in human 11β-HSD1. The protein is shown in both stick and molecular surface representations which are color coded (red for oxygen atoms, blue for nitrogen, orange for sulfur, and wheat for carbon). The inhibitor and the cofactor NADP+ are shown in sticks and color coded gray for carbon atoms in NADP+ and green for the inhibitor. (PDB code: 3OQ1).

The structure of a representative diarylsulfone inhibitor bound to human 11β-HSD1 was determined by X-ray crystallography (Fig 3). The co-crystal structure of compound (*S*)-**35** with human 11β-HSD1 revealed that the inhibitor binds to the substrate site in a V-shape with its trifluoromethylcarbinol group pointing towards the cofactor NADP+ site. The central sulfonyl group makes a hydrogen bond from one of its oxygen atom to the backbone amide of Ala172, as well as Van der Waals contacts with Ser170 in the catalytic site.

In summary, we have developed a novel series of highly potent and selective 11β-HSD1 inhibitors (in all cases 11β-HSD2 IC_{50} >10 μM) with a diarylsulfonyl scaffold. The most potent inhibitors had sub-nanomolar IC_{50} values in the human biochemical assay and IC_{50} value <5 nM in the cellular assay. Representative compound (*S*)-**25** also had low clearance and excellent oral bioavailability (>50%) in both rats and dogs. Compound (*S*)-**25** was

selected for evaluation in a non-human primate ex vivo model and showed good efficacy when administered orally. Finally, X-ray co-crystallographic data of (*S*)-**35** with 11β-HSD1 revealed several key interactions for the inhibitor binding. Further investigation of the diarylsulfone class 11β-HSD1 inhibitors will be reported in due course.

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