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Discovery of cyclicsulfonamide derivatives as 11β-hydroxysteroid dehydrogenase 1 inhibitors

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ABSTRACT

A new series of cyclic sulfonamide derivatives was synthesized and evaluated for their ability to inhibit 11β-HSD1. Cyclic sulfonamides with phenylacetyl substituents at the 2-position showed nanomolar inhibitory activities. Among them, compound **4e** exhibited a good in vitro inhibitory activity and selectivity toward human 11β-HSD2.

11β-Hydroxysteroid dehydrogenase type 1 (11β-HSD1) is an endoplasmic reticulum-associated enzyme that acts as NADPH-dependent reductase and converts inactive cortisone to the active glucocorticoid cortisol (Fig. 1).[1]

The connection between 11β-HSD1 and type 2 diabetes has been demonstrated in mouse genetic models. Mice overexpressing 11β-HSD1 in adipose showed metabolic syndrome-like phenotypes such as central obesity, glucose intolerance, and insulin resistance.[2,3] In contrast, 11β-HSD1 deficient mice were resistant to the development of high-fat diet-induced obesity and exhibited improved insulin sensitivity and lipid profiles.[4,5] These data suggest that 11β-HSD1 could be a drug target for the treatment of metabolic syndrome as well as type 2 diabetes.

During the last few years, small molecule inhibitors for 11β-HSD1 have been reported,[6–11] and Incyte and Amgen's compounds are in clinical trials. Although a number of small molecule inhibitors were introduced, the discovery of a new scaffold is still very important. Therefore, the search for new 11β-HSD1 inhibitor through high throughput screening (HTS) using the chemical library of Korea Chemical Bank was performed and compound **1a**[12] was discovered as a hit (Fig. 2).

We now wish to report the synthesis of cyclic sulfonamide derivatives and their biological study for 11β-HSD1 inhibitors. A series of cyclic sulfonamide derivatives was synthesized according to Schemes 1–3. Saccharin sodium salt **2** was reacted with α-bromo ketone or ester in DMF to provide the alkylated product **3**. It is on reaction with sodium in ethanol resulted ring expansion to provide compound **1** (including hit **1a**, R^1 = phenyl) and its derivatives, which were further derivatized with diverse alkyl halides and α-halo ketones to result in the coupled product **4** (Scheme 1).

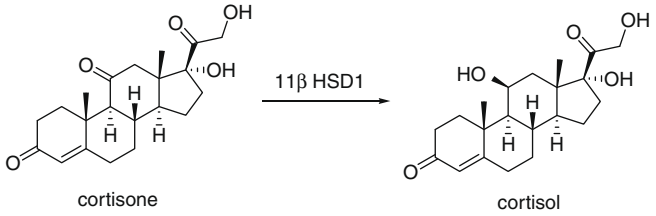
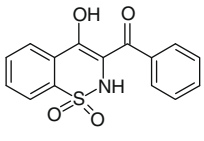


Figure 1. The role of 11β-HSD1 between cortisone and cortisol.



1a

Figure 2. Chemical structure of compound **1a**.

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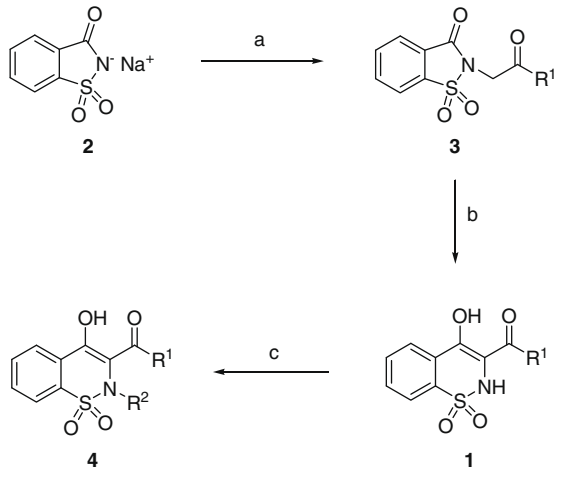
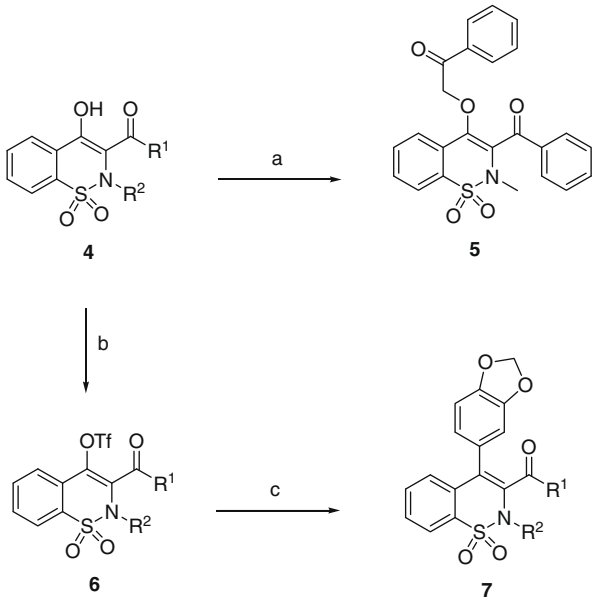


Scheme 1. Reagents and conditions: (a) $BrCH_2COR^1$ (R^1 = methyl, phenyl, OEt), DMF, 100 °C, 4 h (78–88%); (b) Na, EtOH, reflux, 4 h (53–60%); (c) 1 M NaOH, X-R^2 (R^2 = methyl, benzyl, phenethyl, CH_2COAr), room temperature, 12 h (47–60%).

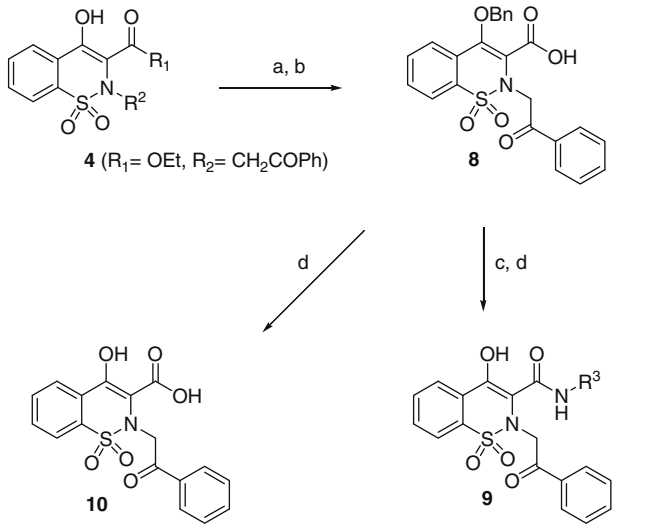


Scheme 2. Reagents and conditions: (a) bromoacetophenone, K_2CO_3, acetone, room temperature, 3 h (71%); (b) trifluoromethanesulfonic anhydride, pyridine, CH_2Cl_2, room temperature, 2 h (90%); (c) 3,4-methylenedioxyphenyl boronic acid, K_2CO_3, $Pd(PPh_3)_4$, toluene/DMF, reflux, 2 h (75%).

As shown in Scheme 2, compound **4** was further derivatized with α-bromoacetophenone to give the O-alkylated compound **5**. Also, compound **4** was converted to triflate **6**, followed by Suzuki reaction with a boronic acid derivative to give **7**.

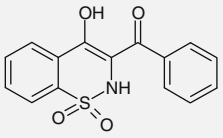
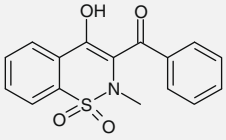
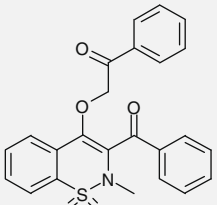
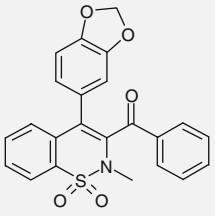
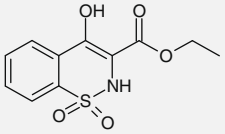
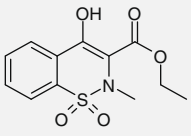
Compound **4** (R^1 = OEt, R^2 = CH_2COPh) was converted to carboxylic acid or amide derivatives (Scheme 3). Benzylation of compound **4** followed by treatment with lithium hydroxide afforded the corresponding acid **8**. The compound **8** was directly converted to the carboxylic acid **10** under acidic debenzylation condition or amidated with aniline or benzyl amine to give amide derivatives, followed by debenzylation under acidic condition afforded the corresponding amide **9**.

In vitro inhibition activity of 11β-HSD1 was assessed by a HTRF cortisol assay. Human microsomes were incubated with cortisone, NADPH, and chemical compound. The IC_{50} values of compounds were determined from concentration-dependent inhibition curves. Carbenoxolone was used as a reference compound.[13]



Scheme 3. Reagents and conditions: (a) benzyl bromide, K_2CO_3, toluene, 100 °C, 12 h (80%); (b) LiOH, THF/EtOH/H_2O, room temperature, 6 h (90%); (c) aniline or benzyl amine, EDCI, DMAP, CH_2Cl_2, room temperature, 12 h (41–53%); (d) 15% aq HCl/dioxane, reflux, 3–6 h (60–85%).

Table 1
In vitro 11β-HSD1 inhibitory activity of cyclic sulfonamide derivatives

Compound	Structure	IC_{50}[a] (μM)
1a		14.8
4a		0.388
5		0.547
7		Not active 35% at 10 μM
1b		Not active 23% at 10 μM
4b		4.5
Carbenoxolone		0.5

[a] IC_{50} values were determined by GraphPad Prism software.

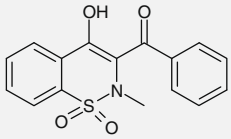
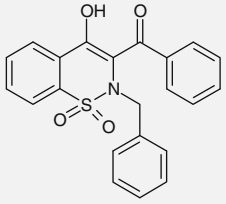
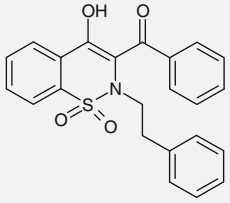
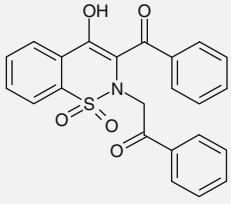
A high throughput screen was conducted to discover new 11β-HSD1 inhibitors. Cyclic sulfonamide **1a** was identified as a hit with an IC_{50} value of 14.8 μM. First, the substituent effects of cyclic sulfonamide at the 2-, 3-, and 4-position were evaluated as shown in Table 1. N-Methylated cyclic sulfonamide (**4a**, IC_{50} = 0.388 μM) was shown to have a nearly 50-fold greater potency than that of the hit compound **1a**. However, further O-alkylated compound **5** and 3,4-methyldioxyphenyl substituent at the 4-position **7** exhibited decrease of in vitro activities. Also, substitution of benzoyl moiety to ester (ethyl ester) at the 3-position **1b** and **4b** led to decrease in vitro potency.

Next, the substituent effect at the 2-position was further evaluated as shown in Table 2. The methyl analogue **4a** showed an IC_{50} value of 388 nM. Benzyl and phenethyl derivative (**4c** and **4d**) had an approximately twofold greater potency than the methyl substituent (254 and 234 nM, respectively). Furthermore, compound **4e** having phenylacetyl group at the 2-position exhibited a good in vitro potency with an IC_{50} value of 31 nM. The phenylacetyl group at the 2-position was fixed, and other substituent effects were studied and the results were summarized (Table 3). Substitution of the benzoyl group to the acetyl group (**4f**) at the 3-position resulted in a loss of activity. Also the masking of OH at the 4-position showed a decrease of in vitro potency (**6**). An introduction of acid derivative at the 3-position was found to be detrimental (**4g**–**4j**). Compound **4e** was still the most potent, therefore a further modification at the 2-position was performed.

The substituent effect on the phenyl group at the 2-position, mouse 11β-HSD1 inhibition potency, selectivity, metabolic stability, and PK study were investigated (Table 4). Compound **4e** and other phenyl derivatives (**4k**–**4n**) except acid substituent (**4o**) showed good in vitro activities toward human 11β-HSD1 with IC_{50} values in the range of 28–40 nM. On the other hand, toward mouse 11β-HSD1, compound **4e** was the most potent with a moderate inhibitory activity (7.8 μM).

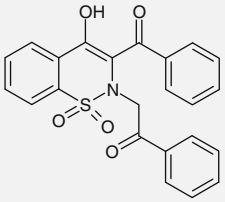
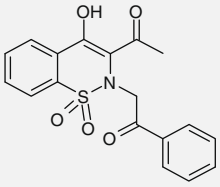
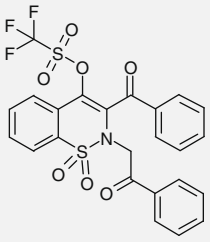
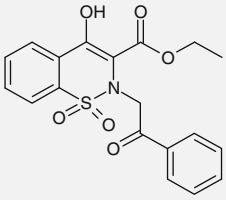
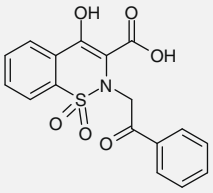
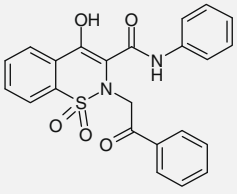
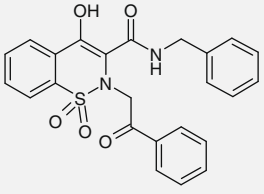
11β-HSD2 oxidizes cortisol to cortisone utilizing NAD as a cofactor and is primarily expressed in the kidney, colon, and other tissues.[14,15] Inhibition of 11β-HSD2 might lead to sodium retention, hypokalemia, and hypertension,[14] indicating that inhibitors for 11β-HSD1 must be selective over 11β-HSD2. Compound **4e** showed a good selectivity against human 11β-HSD2 enzyme. Also,

Table 2
In vitro 11β-HSD1 inhibitory activity of cyclic sulfonamide derivatives

Compound	Structure	IC_{50}[a] (μM)
4a		0.388
4c		0.254
4d		0.234
4e		0.031
Carbenoxolone		0.5

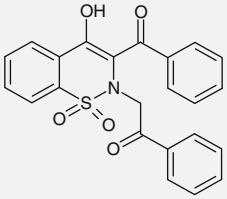
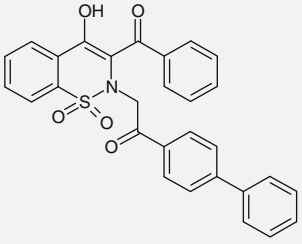
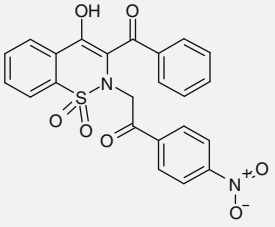
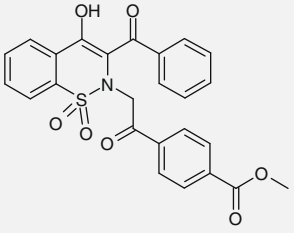
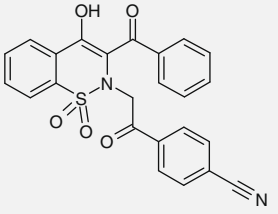
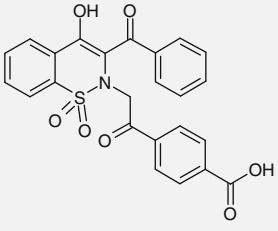
[a] IC_{50} values were determined by GraphPad Prism software.

Table 3
In vitro 11β-HSD1 inhibitory activity of cyclic sulfonamide derivatives

Compound	Structure	IC_{50}[a] (μM)
4e		0.031
4f		Not active 18% at 10 μM
6		0.74
4g		3.0
4h		Not active 24% at 10 μM
4i		Not active 21% at 10 μM
4j		Not active 38% at 10 μM
Carbenoxolone		0.5

[a] IC_{50} values were determined by GraphPad Prism software.

Table 4
In vitro inhibition, metabolic stability, hERG and PK study of cyclic sulfonamide derivatives

Compound	Structure	hHSD1 IC_{50}[a] (μM)	mHSD1 IC_{50}[a] (μM)	hHSD2 IC_{50}[a] (μM)	Microsomal stability ($t_{1/2}$)	hERG	PK
4e		0.031	7.8	6% at 20 μM	Human 74.88 min	>100 μM	PO C_{max} = 1.1 μg/mL $t_{1/2}$ = 5.5 h Cl (L/h/Kg) = 0.4 *F* = 48.7%
4k		0.028	36% at 10 μM	NT[b]	NT	NT	
4l		0.030	38% at 10 μM	NT	NT	NT	
4m		0.031	43% at 10 μM	NT	NT	NT	
4n		0.040	9.0	NT	NT	NT	
4o		0.72	9.7% at 10 μM	NT	NT	NT	
Carbenoxolone		0.5					

[a] IC_{50} values were determined by GraphPad Prism software.
[b] Not tested.

4e was moderately stable in human liver microsomes and exhibited no binding with hERG (>100 μM). The rat PK profiles of compound **4e** showed moderately good systemic exposure and oral bioavailability with an acceptable clearance and half-life.

In conclusion, we have identified a series of cyclic sulfonamide derivatives as 11β-HSD1 inhibitors through the screening of a small-molecule library. Our initial hit compound **1a** showed weak inhibitory activity. Significant improvements in potency were achieved by modification at the 2-position. The most potent compound **4e** showed good in vitro activity and selectivity. Further investigation for increasing both human and mouse 11β-HSD1 inhibition activity is in progress.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.12.035.

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