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Synthesis and Biological Evaluation of Cyclic Sulfamide Derivatives as 11β-Hydroxysteroid Dehydrogenase 1 Inhibitors

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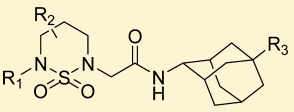
Supporting Information

ABSTRACT: A new series of cyclic sulfamide derivatives were synthesized and evaluated for their ability to inhibit 11β-HSD1. Among this series, **18e** showed good in vitro activity toward human 11β-HSD1, selectivity against 11β-HSD2, microsomal stability, and pharmacokinetic and safety profiles (hERG, CYP, and acute toxicity). Additionally, **18e** exhibited good in vivo efficacy in rat and monkey models.



KEYWORDS: *diabetes, antidiabetic agents, 11β-hydroxysteroid dehydrogenase type 1, cyclic sulfamide, adamantyl group*

An endoplasmic reticulum-associated enzyme, 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1), acts predominantly as an NADPH-dependent reductase in vivo and converts inactive cortisone to the active glucocorticoid cortisol[1] (Figure 1).

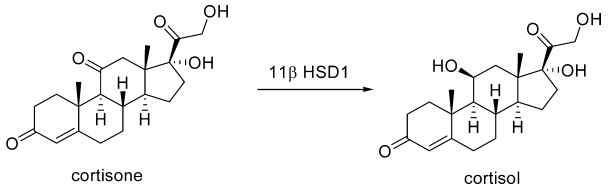
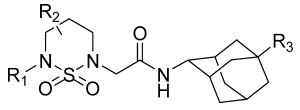


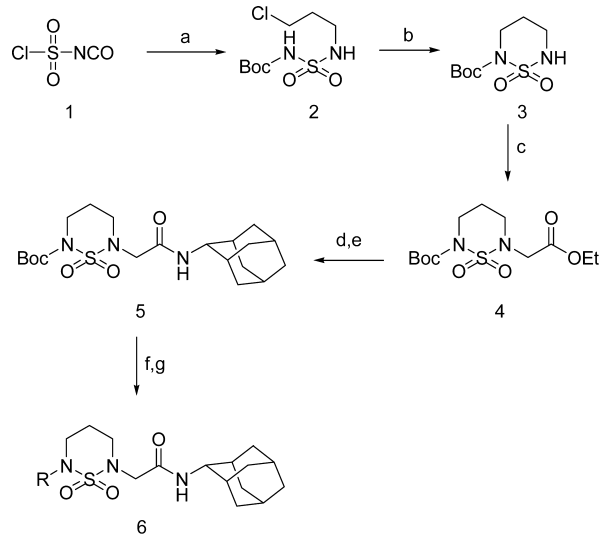
Figure 1. Role of 11β-HSD1 between cortisone and cortisol.



The relationship between 11β-HSD1 and type 2 diabetes has been demonstrated in genetic mouse models. Mice overexpressing 11β-HSD1 in adipose tissues 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 past few years, a number of small molecule 11β-HSD1 inhibitors have been reported,[6−15] and several candidates including Incyte's compound are in clinical trials.[8]

Among the classes of 11β-HSD1 inhibitors, the adamantyl group is one of the most popular and promising skeletons.[9−13] Therefore, we looked for a new 11β-HSD1 inhibitor with an adamantyl group and found a promising cyclic sulfamide skeleton with an adamantyl group.

Scheme 1[a]



[a]Reagents and conditions: (a) *tert*-Butyl alcohol, CH_2Cl_2, 0 °C and then triethylamine, 3-chloropropylamine, 5 °C, 2 h. (b) K_2CO_3, DMSO, 0 °C to room temperature, 4 h. (c) Ethyl bromoacetate, K_2CO_3, DMF, room temperature, 4 h. (d) LiOH, H_2O, MeOH, THF, room temperature, 3 h. (e) 2-Adamantylamine, EDCI, CH_2Cl_2, room temperature, 5 h. (f) 4 M HCl in 1,4-dioxane, room temperature, 4 h. (f) R-X, K_2CO_3, DMF, 4 h.

We now report the synthesis of cyclic sulfamide derivatives with an adamantyl group and their biological evaluation as 11β-HSD1 inhibitors.

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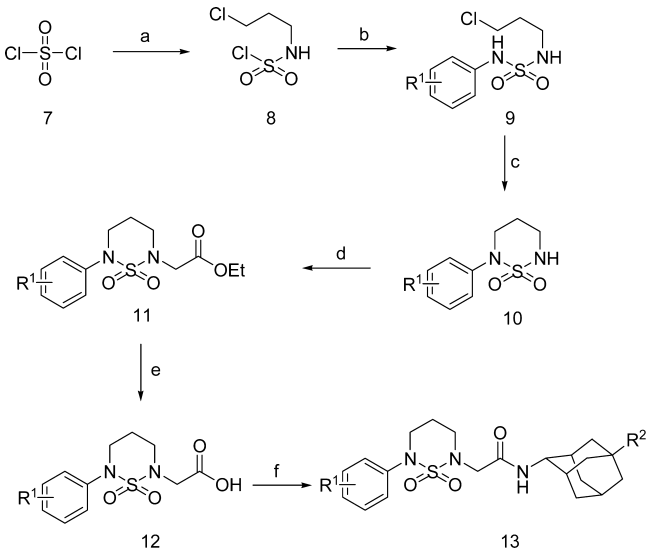
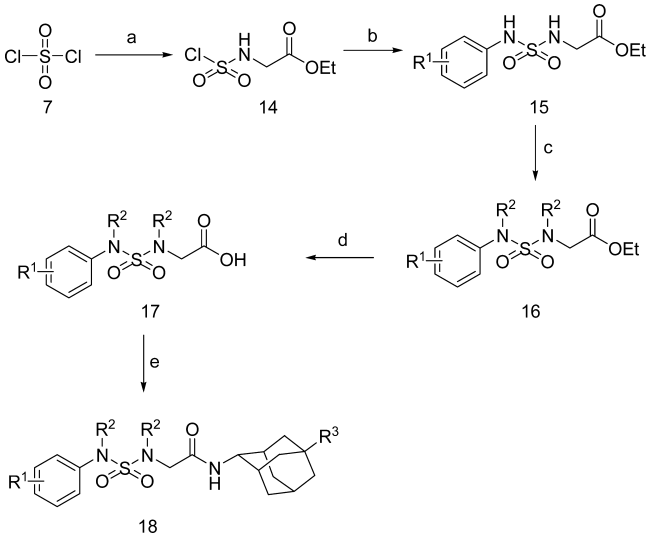
Scheme 2[a]



[a]Reagents and conditions: (a) 3-Chloropropylamine hydrochloride, acetonitrile, room temperature to 80 °C, 18 h. (b) Anilines, triethylamine, diethyl ether, room temperature, 4 h. (c) K_2CO_3, DMSO, 0 °C to room temperature, 2 h. (d) Ethyl bromoacetate, K_2CO_3, DMF, room temperature, 4 h. (d) LiOH, H_2O, MeOH, THF, room temperature, 3 h. (f) Oxalyl chloride, 50 °C and then adamantylamines, $NaHCO_3$, THF, H_2O, room temperature, 1 h.

Scheme 3[a]



[a]Reagents and conditions: (a) Glycine ethyl ester hydrochloride, acetonitrile, room temperature to 80 0 °C, 18 h. (b) Anilines, triethylamine, diethyl ether, room temperature, 4 h. (c) Dihaloalkane, K_2CO_3, acetonitrile, reflux, 12 h or diols, PPh_3, DIAD, THF room temperature, 3 h. (d) LiOH, H_2O, MeOH, THF, room temperature, 3 h. (e) 4-Aminoadamantane-1-carboxamide hydrochloride, EDCI, DIPEA, HOBT, DMSO, isopropyl alcohol, room temperature, 5 h.

A series of cyclic sulfamide derivatives were synthesized according to Schemes 1−3. Chlorosulfonyl isocyanate **1** was reacted sequentially with *tert*-butyl alcohol and chloropropylamine to provide **2**, which was cyclized under basic condition to give Boc-cyclic sulfamide **3**. Compound **3** was alkylated with ethyl bromoacetate to produce compound **4**. Alkaline hydrolysis then provided an acid, which was amidated with 2-adamantyl amine to obtain compound **5**. Compound **5** was deprotected by 4 M HCl and alkylated to produce the arylalkyl cyclic sulfamide derivatives **6**.

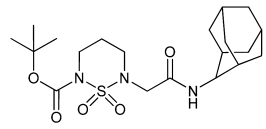
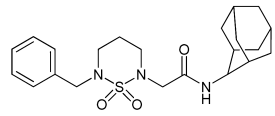
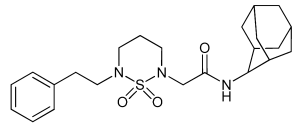
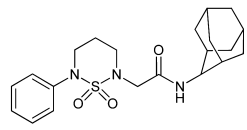
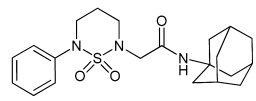
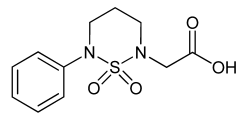
N-Phenyl cyclic sulfamide derivatives were synthesized according to Scheme 2. Sulfuryldichloride **7** was coupled with 3-chloropropylamine and anilines to give compound **9**, which was cyclized under basic condition to give **10**. Compound **10** was coupled with ethyl bromoacetate to give **11**, which was hydrolyzed and amidated by adamantyl amines to produce final compound **13**.

Analogues bearing substitution on the sulfamide-containing ring were obtained as shown in Scheme 3. Sulfuryl dichloride **7** was coupled with glycine ethyl ester and anilines to give compound **15**, which was N-substituted by alkylation or Mitsunobu reaction to obtain compound **16**. Compound **16** was then hydrolyzed and coupled with adamantyl amines to produce the final compound **18**.

In vitro inhibition activity of 11β-HSD1 was assessed by a HTRF cortisol concentration assay. Human and mouse 11β-HSD1 overexpressed cells were incubated with cortisone and each compound for 3 h. The IC_{50} values of the compounds were determined from concentration-dependent inhibition curves. Carbenoxolone was used as a standard 11β-HSD1 inhibitor.

First, Boc-protected cyclic sulfamide derivative with 2-adamantyl group (**5**) showed nanomolar inhibitory activity with an IC_{50} value of 363 nM toward 11β-HSD1. Therefore, we further

Table 1. In Vitro Human 11β-HSD1 Inhibitory Activity of Cyclic Sulfonamide Derivatives

Compound	Structure	IC_{50}, μM[a]
5		0.363
6a		0.360
6b		1.66
13a		0.012
13b		3.37
12		Not active
Carbenoxolone		0.5

[a]IC_{50} values were determined by GraphPad Prism software. Results are expressed as means ± SEMs of triplicate experiments.

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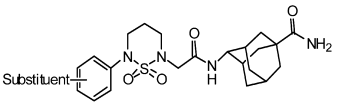
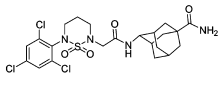
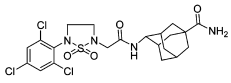
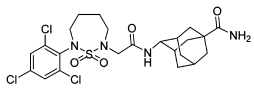
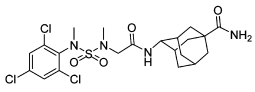
Table 2. In Vitro 11β-HSD1 Inhibitory Activity of Cyclic Sulfonamide Derivatives

compound	structure[a]	IC_{50}, μM[b] human	IC_{50}, μM[b] mouse
			
13c	H	0.017	0.207
13d	2-fluoro	0.014	0.17
13e	3-fluoro	0.050	0.14
13f	4-fluoro	351	15.5
13g	2,4,6-trifluoro	0.020	0.157
13h	2,4,6-trichloro	0.001	0.004
carbenoxolone		0.5	

[a](*E*)-Adamantylcarboxamide isomer. [b]IC_{50} values were determined by GraphPad Prism software.

Table 3. In Vitro 11β-HSD1 Inhibitory Activity, Liver Microsomal Stability, and 11β-HSD Inhibition of Cyclic Sulfonamide Derivatives

Compound	Structure[a]	IC_{50}, μM[b] human	IC_{50}, μM[b] mouse	MS[c] 30 min incubation	In vivo 11β-HSD1 inhibition 20 mpk (2h) (ex-vivo)
13h		0.001	0.004	61% (h) 57%(r)	fat 92.1±1.0%*** liver 83.7±1.1%***
18a		0.187	0.409	ND	
18b		0.001	0.001	40%(h) 26%(r)	fat 59.9±4.5%*** liver 51.4±4.5%***
18c		0.001	0.002	21%(h) 7%(r)	fat 33.3±3.8% liver 57.8±6.6%**
carbenoxolone		0.5			

[a](*E*)-Adamantylcarboxamide isomer. [b]IC_{50} values were determined by GraphPad Prism software. [c]Liver microsomal stability. Results of ex vivo 11β-HSD1 inhibition are expressed as means ± SEMs for n = 4 mice per group. $^{**}P < 0.01$, $^{***}P < 0.001$ vs vehicle group.

modified sulfamide scaffold by replacing the Boc group. Instead of Boc, the benzyl substituent **6a** showed similar activity as that with Boc; however, the phenethyl substituent **6b** displayed weak inhibitory activity (1.66 μM). Indeed, phenyl substituent

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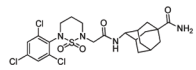
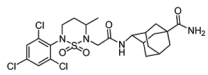
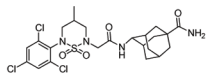
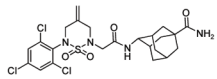
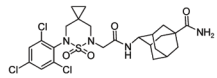
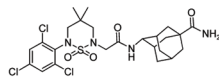
Table 4. In Vitro 11β-HSD1 Inhibitory Activity, Liver Microsomal Stability, and 11β-HSD 1 Inhibition of Cyclic Sulfonamide Derivatives

Compound	Structure[a]	IC_{50}, μM[b] human	IC_{50}, μM[b] mouse	In vivo 11β-HSD1 inhibition (po) after 2 h (ex-vivo)	MS 30min incubation
13h		0.001	0.004	(20mpk) fat (92.1±1.0%)***	61% (h) 57%(r)
18d[c]		0.001	0.070	(20mpk) fat (74.5±4.0%)***	94% (h) 70%(r)
18e[c]		0.001	0.002	(20 mpk) fat (95.9±0.8%)***	93% (h) 78%(r)
18f		0.014	0.008	(20mpk) fat (82.1± 4.3%)**	ND
18g		0.005	0.023	(20mpk) fat (39.6 ±6.7%)	ND
18h		0.005	0.026	(20mpk) fat (29.9 ± 17.9%)	ND
carbenoxolone		0.5			

[a](*E*)-Adamantylcarboxamide isomer. [b]IC_{50} values were determined by GraphPad Prism software. [c]The chirality of methyl is racemic. Results of in vivo 11β-HSD1inhibition are expressed as means ± SEMs for n = 4 mice per group. $^{**}P < 0.01$, $^{***}P < 0.001$ vs vehicle group.

Table 5. Selectivity, Stability, CYP Inhibition, hERG, Solubility, and Acute Toxicity of 18e

entry	hHSD2 inhibition	plasma stability	CYP inhibition	hERG	aqueous solubility	acute toxicity
18e	20% at 10 μM	100% after 30 min incubation	1A2 > 100 μM 2C9 > 100 μM 2C19 > 100 μM 2D6 > 100 μM 3A4 > 100 μM	36.9 μM	361 μM	LD_{50} > 1000 mpk

Table 6. In Vivo PK and PD Study of 18e[a]

rat PK (10 mpk)	in vivo 11β-HSD1 inhibition (po) in mice (ex vivo)	monkey PK (10 mpk)	in vivo 11β-HSD1 inhibition (po) in monkey (ex vivo)
po C_{max} = 3.1 μg/mL	(1 mpk) fat (76.6 ± 2.8%)	po C_{max} = 6.4 ug/mL	10 mpk
$t_{1/2}$ = 3.8 h	(5 mpk) fat (90.4 ± 0.6%)*	$t_{1/2}$ = 3.4 h	shoulder fat 87%
AUC = 15.7 μg h/mL	(10 mpk) fat (90.7 ± 2.6%)*	AUC = 35.6 μg h/mL	Inguinal fat 83%
Cl (L/h/kg) = 0.7	(20 mpk) fat (95.9 ± 0.8%)***		abdominal cavity fat 81%
F = 68.8%			

[a]Results of in vivo 11β-HSD1 inhibition in rats (?) are expressed as means ± SEMs for n = 4 mice per group. In in vivo 11β-HSD1 inhibition in monkeys, results are expressed as means for n = 2 monkey per group $^{*}P < 0.05$, and $^{***}P < 0.001$ vs vehicle group.

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13a showed good in vitro activity with an IC_{50} value of 12 nM. However, 1-adamantyl derivative **13b** and acid compound **12** were weakly active and not active, respectively.

We focused our attention on N-phenylsubstituted cyclic sulfamide with adamantylcarboxamide (**13c**), which has better microsomal stability than unsubstituted adamantyl group,[16] and the results are summarized in Table 2. Compounds **13c−h** are *E* isomers, which showed better in vitro activity than the *Z* isomers; therefore, we focused on the *E* isomer. Unsubstituted phenyl derivative with adamantylcarboxamide (**13c**) showed good in vitro activity with an IC_{50} value of 17 nM for human 11β-HSD1 and moderate activity with an IC_{50} value of 207 nM for mouse 11β-HSD1. Although 3-fluoro (**13e**), 4-fluoro (**13f**), and 2,4,6-trifluorophenyl (**13g**) derivatives showed moderate to good in vitro activities, 2,4,6-trichlorophenyl derivative (**13h**) was the most active in this series with 1 and 4 nM for human and mouse 11β-HSD1, respectively.

The compound **13h** showed good in vitro activities; therefore, we performed in vivo 11β-HSD1 inhibition study in normal mice. After 20 mpk oral dosing, 11β-HSD1 inhibition was measured in fat and liver tissues. Compound **13h** showed 86 and 85% 11β-HSD1 inhibitions in the fat and liver tissues after 2 h, respectively. However, human and rat liver microsomal stabilities of **13h** were moderate with 61 and 57% of the parent compound remaining after 30 min of incubation. To improve the liver microsomal stability, we changed the six-membered ring to five- or seven-membered ring and ring-opening structure. Unfortunately, the five-memered ring (**18a**) exhibited reduced activity with submicromolar potency. Moreover, although the seven-membered ring (**18b**) and ring-opened dimethyl derivative (**18c**) showed good in vitro potencies, their in vivo 11β-HSD1 inhibitions and liver microsomal stabilities were not improved.

Therefore, we further modified the six-membered ring with diverse substituents, and the results are summarized in Table 4. 2-Methyl substituent (**18d**) showed improved metabolic stability in human and rat liver microsome. Furthermore, **18e** was the most potent in this series exhibiting good in vitro activities with 1 and 2 nM toward human and mouse 11β-HSD1, respectively, as well as liver microsomal stability (93 and 78% after 30 min of incubation). Compound **18e** exhibited the best in vivo 11β-HSD1 inhibition efficacy with 95% inhibition after 20 mpk oral administration.

As shown in Table 5, **18e** exhibited good selectivity against 11β-HSD2 and plasma stability. Additionally, **18e** showed no significant inhibition any of the major CYP isoforms (main cytochrome P450 enzymes, 1A2, 2C9, 2C19, 2D6, and 3A4). Moreover, it showed weak inhibition of the hERG channel (36.9 μM), reasonable solubility (361 μM), and a LD_{50} value of over 1000 mpk.

The PK and PD profiles of **18e** were evaluated in rat and monkey and are summarized in Table 6. Compound **18e** showed good bioavailability (69%) and moderate clearance (CL = 0.7) in rat. The compound **18e** significantly and dose dependently reduced 11β-HSD1 activity in fat tissues in 2 h by 77, 90, 91, and 96% at 1, 5, 10, and 20 mpk, respectively. Additionally, a nonhuman primate (cynomologous monkey) was dosed orally with **18e** at 10 mpk and exhibited over 80% 11β-HSD1 inhibition in three fat depots in 2 h and a good blood exposure level.

In conclusion, we have developed a series of cyclic sulfamide derivative with an adamantyl group as 11 β-HSD1 inhibitors. Compound **18e** showed good in vitro activity toward human and mouse 11β-HSD1, selectivity toward 11β-HSD2, metabolic stability, good PK and safety profiles such as hERG, CYP, and acute toxicity. Additionally, **18e** also showed good in vivo efficacy in a primate model.

■ ASSOCIATED CONTENT

Supporting Information

Synthetic procedures and details of biological assay. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

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Author Contributions

[§]These authors contributed equally.

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Notes

The authors declare no competing financial interest.

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