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Synthesis and 11β hydroxysteroid dehydrogenase 1 inhibition of thiazolidine derivatives with an adamantyl group

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ABSTRACT

A new series of thiazolidine derivatives with an adamantyl group was synthesized and evaluated for their ability to inhibit 11β-hydroxysteroid dehydrogenase 1 (11β-HSD1). Our initial compound **5a** showed a weak inhibitory activity. Significant improvements in potency were achieved by substituent modification. The potent compound **8g (E)** showed good in vitro inhibitory activity toward human 11β-HSD1, selectivity toward 11β-HSD2, metabolic stability, pharmacokinetic, and safety profile. Furthermore, this compound significantly inhibited 11β-HSD1 activity in rat and monkey models, and showed improved glycemic control in KKAy mice.

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 relationship 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, several classes of 11β-HSD1 inhibitors have been reported.[6–12] Among the classes of 11β-HSD1 inhibitors, adamantyl group is one of the most popular and promising skeletons.[9–12] Therefore, we searched our chemical library for a new 11β-HSD1 inhibitor with an adamantyl group and adamantyl thiazolidine-2-carboxamide (**5a**) was discovered as a hit (Fig. 2).

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

A series of thiazolidine derivatives with an adamantyl group was synthesized according to Schemes 1 and 2. Cysteamine hydrochloride was cyclized using ethyl glyoxalate in toluene to provide ethyl thiazolidine-2-carboxylate **1**. After Boc-protection, *N*-Boc protected thiazolidine ester was hydrolyzed with LiOH to yield the corresponding acid **2**. This compound was subsequently coupled with 2-adamantylamine to afford compound **3**, which was deprotected by 4 M HCl and further derivatized with diverse electrophiles to afford thiazolidine derivatives with an adamantyl group (**5**).

Compound **1** was derivatized with sulfonyl chlorides or benzyl bromide to yield the compound **6**, which was hydrolyzed and amidated with substituted adamantyl amines to finally produce **8**. Racemic ethyl thiazolidine-2-carboxylate **1** was converted to the chiral compound **9** through crystallization induced dynamic resolution using tartaric acid.[13] The next steps were to derivatize

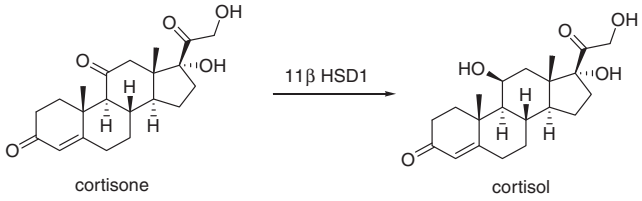

Figure 1. The role of 11β-HSD1 between cortisone and cortisol.

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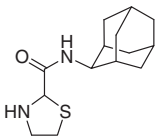
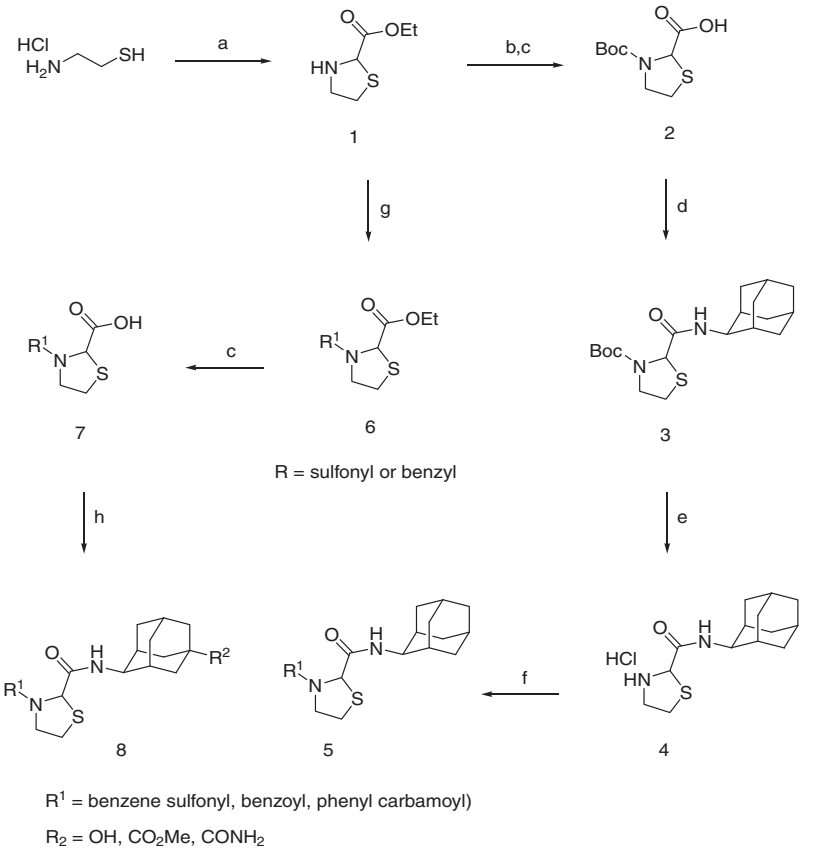
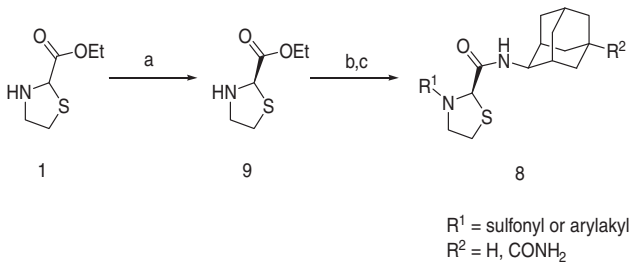


Figure 2. Chemical structure of **5a**.



Scheme 1. Reagents and conditions: (a) ethyl glyoxalate, $NaHCO_3$, toluene, H_2O, 5 °C to room temperature, 16 h; (b) $(Boc)_2O$, CH_2Cl_2, room temperature, 12 h; (c) LiOH, H_2O, MeOH, THF, room temperature, 4 h; (d) 2-adamantylamine, EDCI, HOBT, DIPEA, *i*-PrOH, room temperature; (e) 4 M HCl in 1,4-dioxane, CH_2Cl_2, room temperature, 12 h; (f) R-X, DMAP, TEA, CH_2Cl_2, 4 h; (g) R-X, DMAP, TEA, CH_2Cl_2, 4 h or K_2CO_3, acetone, reflux, 3 h; (h) adamantylamines, EDCI, HOBT, DIPEA, DMSO, *i*-PrOH, room temperature, 5 h.



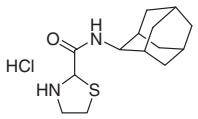
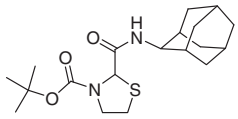
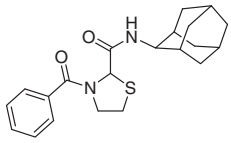
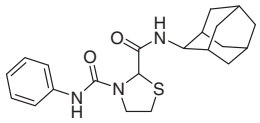
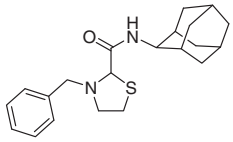
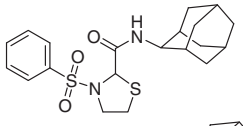
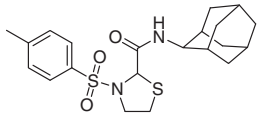
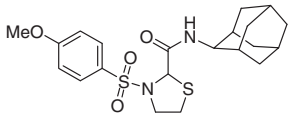
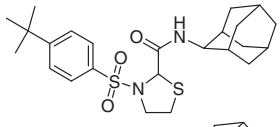
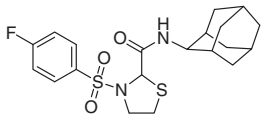
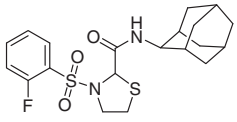
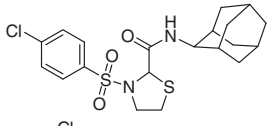
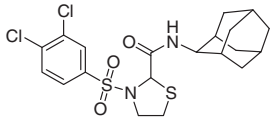
Scheme 2. Reagents and conditions: (a) (i) D-tartaric acid, ethanol, diethyl ether, 5 days; (ii) 10% sodium bicarbonate, ether, 10 °C; (b) (i) R-X, DMAP, TEA, CH_2Cl_2, 4 h; (ii) LiOH, H_2O, MeOH, THF, room temperature, 4 h; (c) 2-adamantyl amine or *N*-[5-(aminocarbonyl)tricyclo[3,3,1,13,7]dec-2-yl]amine, EDCI, HOBT, DIPEA, DMSO, *i*-PrOH, room temperature, 5 h.

compound **9** with N-substitution and amidation with adamantyl derivatives including *N*-[5-(aminocarbonyl)tricycle[3,3,1,13,7]-dec-2-yl]amine to afford a variety of isomers **8** including *R*/*S* at the 2-position of thiazolidine and *E*/*Z* at the adamantyl group.

The in vitro inhibitory activity of 11β-HSD1 was assessed with the use of a HTRF cortisol assay. CHO cells overexpressing human 11β-HSD1 were incubated with cortisone, and chemical compound. The IC_{50} values of compounds were determined from concentration-dependent inhibition curves. Carbenoxolone was used as a reference compound.[14]

Thaizolidine-2-carboxylic acid adamantylamide **5a** was identified as a hit with an IC_{50} value of 2.13 μM. First, the substituent effects of nitrogen on thiazolidine were evaluated as shown in Table 1. *N*-Boc substituted thiazolidine (**5b**, IC_{50} = 0.554 μM) was found to be nearly four times greater than that of compound **5a**. In addition, the in vitro potency of the benzoyl derivative **5c** was nine times better than compound **5b** with an IC_{50} value of 63 nM. However, the activity of the urea compound **5d** was significantly reduced. Although benzyl derivatives **5e** showed good inhibitory activity (IC_{50} = 20 nM), sulfonyl derivatives **5f** exhibited the best in vitro potency among the compounds of this series with an IC_{50} value of 10 nM. Therefore, sulfonyl derivatives were further investigated. Sulfonyl derivatives with electron donating groups such as methyl and methoxy (**5g** and **5h**) showed similar or weaker inhibitory activity than unsubstituted phenyl derivative. Furthermore, *t*-butylphenyl sulfonyl substituent seemed to be detrimental to the inhibitory activity (**5i**). Introduction of fluoride and chloride resulted in good in vitro potencies around 10 nM (**5k**–**5m**). Among

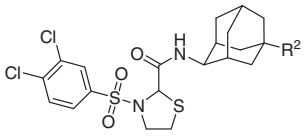
Table 1
In vitro human 11β-HSD1 inhibitory activity of thiazolidine derivatives with adamantyl group

Compound	Structure	IC_{50}[a] (μM)
5a		2.13
5b		0.554
5c		0.063
5d		0.945
5e		0.020
5f		0.010
5g		0.020
5h		0.055
5i		0.149
5j		0.020
5k		0.010
5l		0.010
5m		0.010
Carbenoxolone		0.5

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

them, we chose **5m** to further evaluate the functionalized adamantyl amide derivatives and the results are summarized in Table 2.

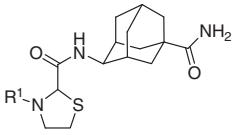
Table 2
In vitro human 11β-HSD1 inhibitory activity of sulfonyl thiazolidine derivatives with adamantyl group

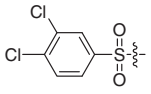
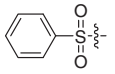
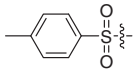
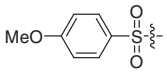
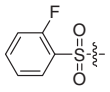
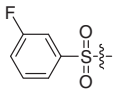
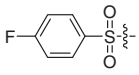


Compound	R^2	IC_{50}[a] (μM)
5m	H	0.010
8a	OH	0.683
8b	CO_2Me	0.170
8c	$CONH_2$	0.005

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

Table 3
In vitro 11β-HSD1 inhibitory activity of sulfonyl thiazolidine derivatives with adamantyl group



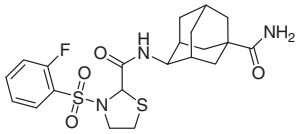
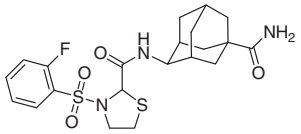
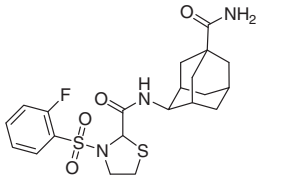
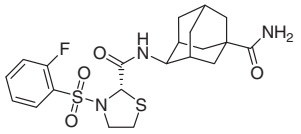
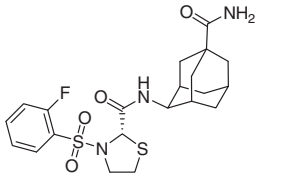
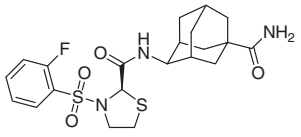
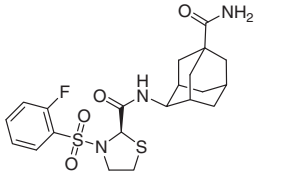
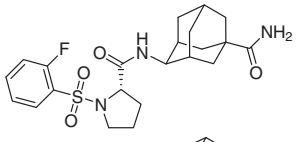
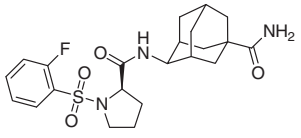
Compound	R1	hHSD1 IC_{50}[a] (nM)	mHSD1 IC_{50}[a] (nM)
8c		5	6
8d		67	842
8e		8	57
8f		16	171
8g		4	4
8h		11	76
8i		11	27
Carbenoxolone		500	250

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

Hydroxy-adamantyl analog (**8a**) showed a weak in vitro activity with an IC_{50} value of 683 nM. Also, methoxycarbonyladamantyl derivative (**8b**) exhibited a moderate potency (170 nM). Fortunately, amide derivative (**8c**) showed the best in vitro activity with an IC_{50} value of 5 nM. From these results, we selected the carbamoyladamantyl group for further derivatization.

Thiazolidine derivatives with a carbamoyladamantyl group were evaluated for their in vitro potency against human and mouse cell lines and the results are summarized in Table 3. 3,4-Dichlorophenylsulfonyl derivative **8c** showed good in vitro potency in both human and mouse cell lines with an IC_{50} value of 5 and 6 nM, respectively. However, the unsubstituted phenyl compound **8d** exhibited a relatively weak activity in human as well as mouse

Table 4
In vitro human 11β-HSD1 inhibitory activity of sulfonyl thiazolidine derivatives with adamantyl group

Compound	Structure	IC_{50}[a] (μM)
8g (*E*/*Z*)		0.004
8g (*E*)		0.003
8g (*Z*)		7.95
8g (*S*) (*E*)		0.012
8g (*S*) (*Z*)		38.7
8g (*R*) (*E*)		0.002
8g (*R*) (*Z*)		1.34
10		0.037
11		0.010
Carbenoxolone		0.5

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

cell lines (67 and 842 nM, respectively). Tosyl derivatives showed IC_{50} value of 8 nM in human cell lines. Lastly, the 2-fluorophenylsulfonyl derivative **8g** was the most active in this series with an IC_{50} value of 4 nM in both the human and mouse system.

Compound **8g** has several isomers including the *E*/*Z* isomer at the adamantyl group and *R*/*S* isomer at the 2-position of thiazolidine. Therefore, we synthesized each isomer and evaluated their activities as shown in Table 4. *E*-Isomer [**8g (E)**] of compound **8g** showed better activity than the *E*/*Z* mixture (**8g**). Whereas, the *Z*-isomer [**8g (Z)**] of **8g** exhibited a very weak in vitro inhibitory activity. The thiazolidine derivative with *R* at the 2-position of thiazolidine showed higher in vitro potency when compared with *S*-configuration. Compound [**8g (R) (E)**] combining an *R*-configuration at the 2-position of thiazolidine and an *E*-isomer at the adamantyl group exhibited the highest activity, with an IC_{50} value of 2 nM. The in vitro potency of proline derivatives (**10** and **11**) was tested. (*R*)-Isomer (**10**) showed better activity than (*S*)-isomer (**11**) with IC_{50} value of 10 nM. Although the proline derivatives also showed relatively high in vitro potency, the thiazolidine derivative exhibited an even higher potency.

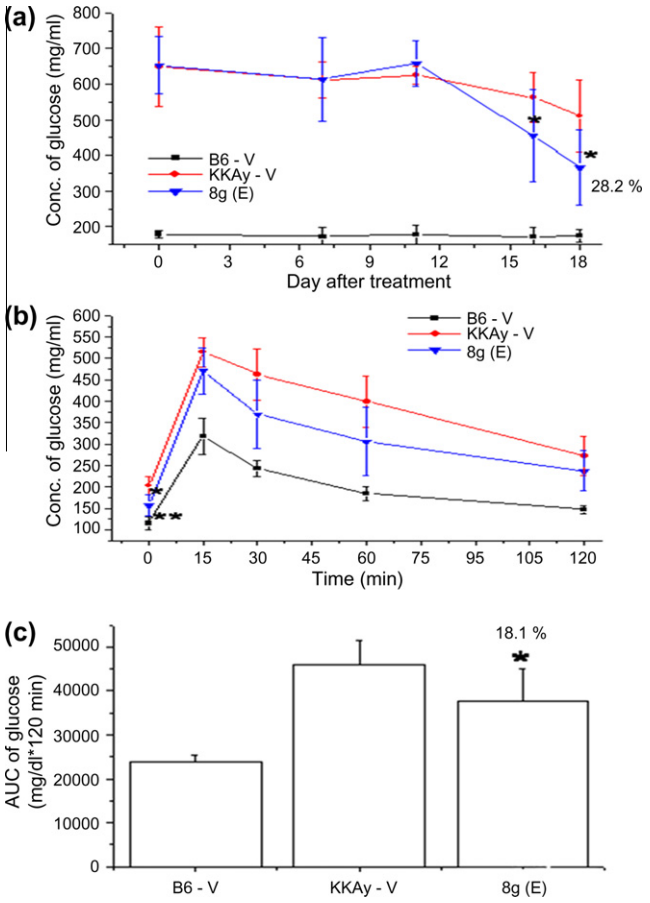


Figure 3. Anti-diabetic efficacy of compound **8g (E)** in KKAy mice. (a) Non-fasting blood glucose levels; (b) glucose level after an oral glucose tolerance test; (c) glucose AUC determined from 0 to 120 min. Results are expressed as means ± SEM for $n = 7$ mice/group. $^{*}P < 0.05$, $^{**}P < 0.01$.

We chose three representative compounds (**8c**, **8e**, and **8g (E)**) for further biological evaluations, which covered selectivity, microsomal stability, hERG, CYP assay, PK, and in vivo study. According to Table 5, compounds **8c**, **8e**, and **8g (E)** exhibited a good selectivity toward 11β-HSD2. Furthermore, compounds **8e** and **8g (E)** showed acceptable liver microsomal stability, no hERG binding and CYP inhibition. Also pharmacokinetic (PK) and in vivo 11β-HSD1 inhibition study in inguinal fat and liver tissues were performed. Compound **8g (E)** exhibited reasonable PK profile and in vivo inhibition of approximately 65–67% in inguinal fat and liver tissues.

Compound **8g (E)** was dosed orally in KKAy mice, displayed significant higher blood glucose level compared with its lean littermates (C57BL6j mice), at 100 mg/kg for 18 days. The non-fasting blood glucose level was reduced by 28.2% compared with vehicle mice after 18 days (Fig. 3a). The oral glucose tolerance test (OGTT) was performed after 18 days. The plasma glucose levels, determined on the basis of AUC of the glucose concentration, were reduced by 18.1% compared to vehicle (Fig. 3b and c).

Table 5
In vitro inhibition, metabolic stability, hERG, and PK study of thiazolidine derivatives

Entry	hHSD1 IC_{50}[a] (nM)	mHSD1 IC_{50}[a] (nM)	hHSD2 IC_{50}[a] (nM)	Microsomal stability 30 min after	hERG	CYP inhibition % at 10 μM	PK (rat)	In vivo 11β-HSD1 inhibition
8c	2	6	47% at 10 μM	43% (h)				
8e	8	57	0% at 10 μM	53% (h)	>100 μM	1A2 0% 2C19 21% 2D6 0% 3A4 24%	PO C_{max} = 0.65 g/mL Cl (L/h/Kg) = 2.6 *F* = 16%	PO (40mpk) *F* (51%) *L* (51%)
8g (E)	3	3	0% at 10 μM	77% (h)	>100 μM	1A2 0% 2C19 25% 2D6 0% 3A4 21%	PO C_{max} = 1.2 g/mL PO $AUC_{0-8\ h}$ = 1.11 μg h/mL Cl (L/h/Kg) = 2.9 *F* = 32%	PO (40mpk) *F* (67%) *L* (65%)

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

Table 6
Ex vivo pharmacodynamic data of compound **8g (E)**[a]

% inhibition of HSD1 in fat 2 h	% inhibition of HSD1 in liver 2 h
62%	57%

[a] Compound was administered at 20 mg/kg oral.

Compound **8g (E)** was administered in a cynomolgus monkey pharmacodynamic model, evaluating the activity of 11β-HSD1 in adipose and liver tissues. When dosed PO at 20 mg/kg, 62% of 11β-HSD1 was inhibited after 2 h in fat and 57% in liver tissues (Table 6).

In conclusion, we have identified a series of thiazolidine derivatives with an adamantyl group as 11β-HSD1 inhibitors. Our initial compound **5a** showed a weak inhibitory activity. Significant improvements in its potency were achieved by substituent modification. In particular, compound **8g (E)** showed good in vitro inhibitory activity toward human 11β-HSD1, selectivity toward 11β-HSD2, metabolic stability, good PK, and safety profile such as hERG and CYP. Further, this compound significantly inhibited 11β-HSD1 activity in rat and monkey models, and showed improved glycemic control in KKAy mice.

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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.2010.10.123.

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