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Synthesis and biological evaluation of α-sulfonamido-*N*-adamantanecarboxamide derivatives as 11β-HSD1 inhibitors

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Introduction

Glucocorticoids (e.g., cortisol, corticosterone) are ubiquitous hormones that regulate energy metabolism, stress, cardiovascular homeostasis, immune and inflammatory responses.[1] Excessive concentration of intracellular glucocorticoids (Cushing's syndrome) leads to obesity, insulin resistant, hypertension, type 2 diabetes, dyslipidemia and cardiovascular impairments.[2,3] Intracellular production of cortisol levels is controlled by 11β-hydroxysteroid dehydrogenase (11β-HSDs) enzymes. Among the two isozymes of 11β-HSD that have been identified, 11β-HSD1 predominantly expressed in the liver, adipose tissue and catalyzes the conversion of inactive cortisone to active cortisol. In contrast, 11β-HSD2 is present in kidney and catalyzes the reverse reaction. In recent decades, much attention has been focused on the development of 11β-HSD1 inhibitors due to their promising ability to reduce metabolic syndromes.[4-6]

Type 2 diabetes is a chronic metabolic disorder, affecting 350 million people globally and the prevalence has been increasing all over the world.[7] Although a number of therapeutic treatments are available to reduce this health burden, still there is an unmet need for the development of potential and improved antidiabetic agents.

Studies have been demonstrated the influence of 11β-HSD1 inhibition on type 2 diabetes in mice. For instance, 11β-HSD1 knockout mice have shown enhanced insulin sensitivity, reduced fasting blood glucose levels and decreased gluconeogenesis.[8,9] In contrast,

overexpressed 11β-HSD1 has displayed insulin resistant, hyperglycemia and central obesity.[10,11] Consequently, inhibition of 11β-HSD1 could be a promising treatment for type 2 diabetes and other metabolic disorders.

Many groups and institutions have reported a variety of synthetic small molecules as 11β-HSD1 inhibitors.[12,13] Also, we previously identified sulfonamidothiazolidine[14] and sulfamide derivative with adamantaneamide group[15](Fig 1). Recently, Ahn et al[16] reported sulfonamidoadamantanecarboxamide derivatives as a 11β-HSD1 inhibitor (Fig 1).

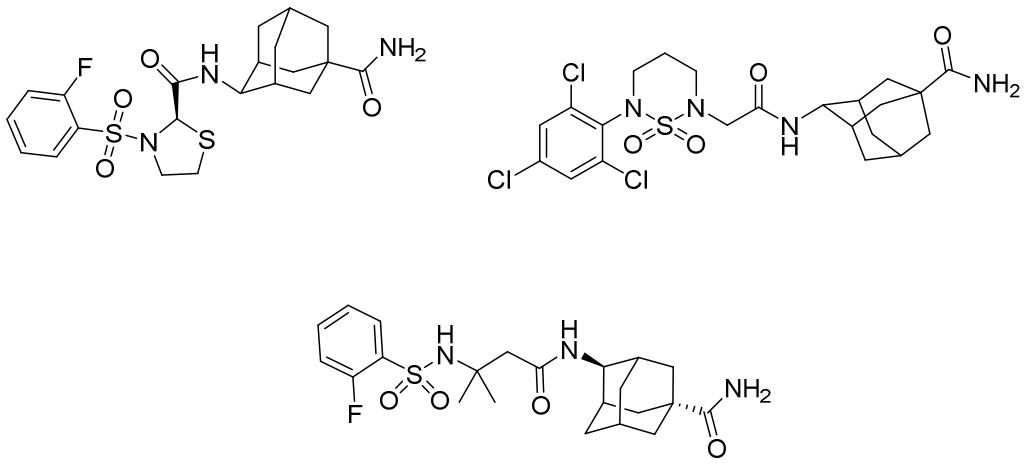


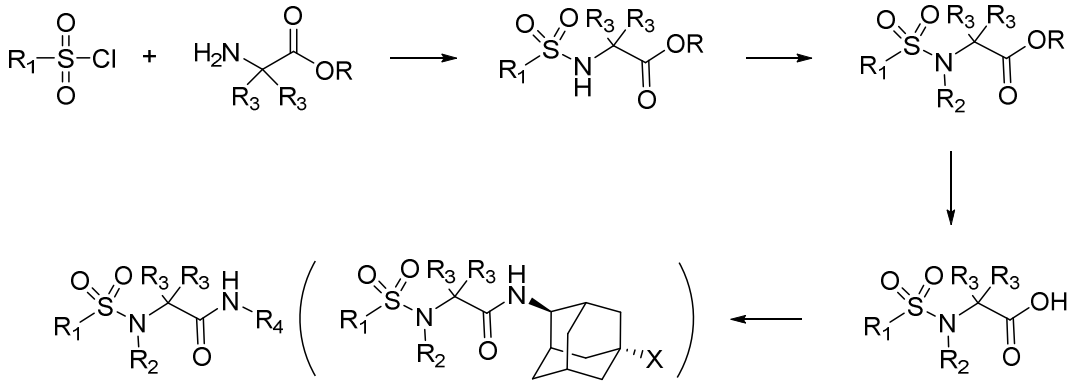
Fig 1. Previously identified 11β-HSD1 inhibitors with an adamantaneamide group and β-sulfonamidoadamantanecarboxamide.

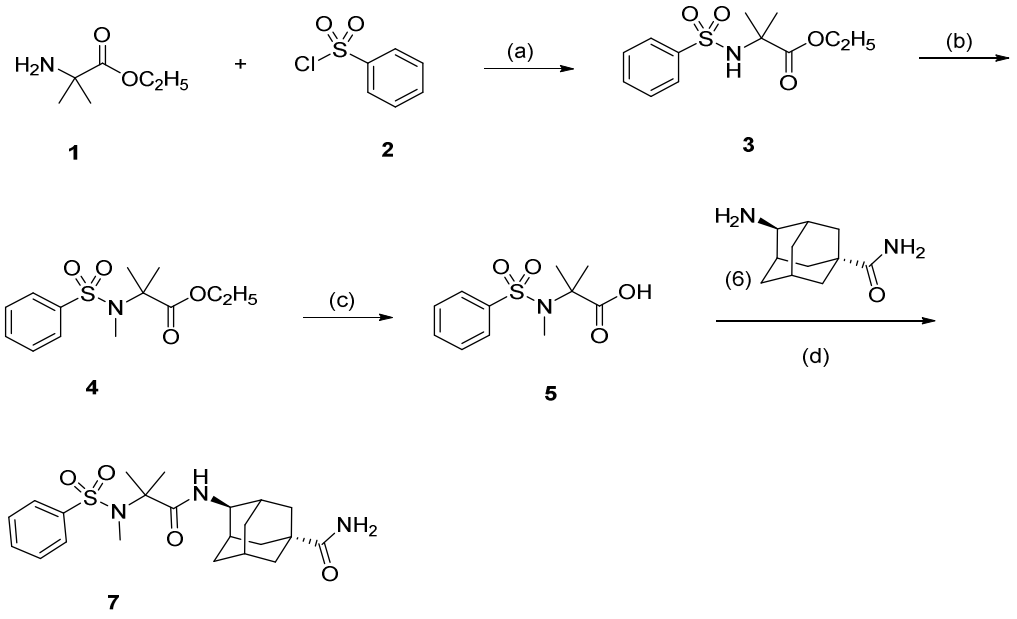
The importance of sulfonamides and adamatanecarboxamide in the inhibitory effects on 11β-HSD1 and our previous results prompted us to develop α-sulfonamidoamide derivatives. Herein we wish to report the potent α-sulfonamidoamide derivatives and their inhibitory activities against human and mouse 11β-HSD1 enzymes.

Chemistry

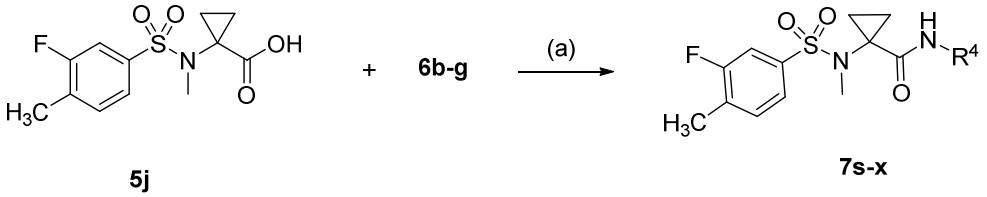
The general and detailed synthetic route for the synthesis of compound **7** and its derivatives is presented in Scheme 1. Ethyl 2-methyl-2-(phenylsulfonamido)propanoate (**3**) was obtained from the reaction of ethyl 2-amino-2-methylpropanoate (**1**) with benzenesulfonyl chloride (**2**) in the presence of triethylamine under room temperature. *N*-Alkylation followed by subsequent hydrolysis afforded corresponding propanoic acid (**5**). Coupling of compound **5** with aminoadamantane-1-carboxamide (**6**) in the presence of EDCI and HOBt resulted in a series of substituted phenylsulfonamido-propanamido-adamantane-1-carboxamide (**7**) in good yields. Similarly, 2-amino-2-cyclopropylpropanoate, 2-amino-2-cyclobutylpropanoate, 2-amino-2-cyclopentylpropanoate were treated with substituted benzenesulfonyl chlorides and subsequent reactions afforded carboxamides (**7a-r**). Compounds **7s-x** were synthesized as shown in scheme 2, accordingly, coupling reaction of phenylsulfonamido-cyclopropane-1-carboxylic acid **5j** with various amino adamantanes such as adamantan-2-amine(**6b**), adamantan-1-amine (**6c**), 4-aminoadamantan-1-ol (**6d**), 4-aminoadamantane-1-carboxylic acid (**6e**), 4-aminoadamantane-1-carboxylate (**6f**) and with bicyclo[2.2.1]heptan-2-amine (**6g**) afforded compounds **7s-x** (Scheme 2).

General scheme





Scheme 1. Reagents and conditions: (a) DMAP, TEA, CH_2Cl_2, rt; (b) MeI, K_2CO_3, DMF; (c) LiOH, THF, H_2O, EtOH, rt; (or 1M BBr_3 in DCM for compound **4d**); (d) DIPEA, HOBt, EDCI, DMSO, 2-propanol, rt.



Scheme 2. Reagents and conditions: (a) DIPEA, HOBt, EDCI, DMSO, 2-propanol, rt.

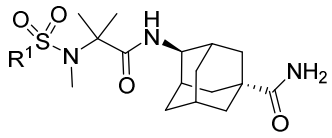
Results and discussion

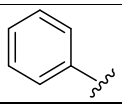
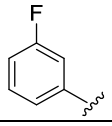
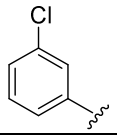
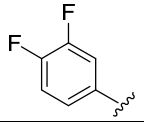
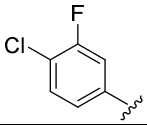
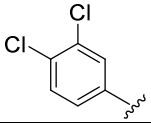
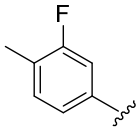
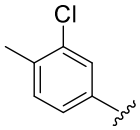
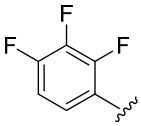
The *in vitro* 11β-HSD1 inhibitory effects of the synthesized compounds (**7a-i**) are presented in Table 1. Most of the derivatives showed significant potency toward human 11β-HSD1, whereas, displayed well to moderate inhibitory potency toward mouse 11β-HSD1. The unsubstituted phenyl sulfonamide, compound **7a** exhibited reasonable potency in human 11β-HSD1 (IC_{50}: 89 nM) and showed moderate activity in mouse 11β-HSD1 (IC_{50}: 159 nM).

The potency of the tested compounds was improved by adopting the substitutions on the sulfonamide phenyl ring. A 3 fold increase in inhibitory potency was observed by phenyl mono substituted analogues (**7b** IC_{50}: 26 nM; **7c** IC_{50}: 32 nM) toward human 11β-HSD1. Whereas, they displayed further improvement in potency was achieved by disubstituted

derivatives. Compound **7g** (IC_{50}: 11 nM) exhibited the most potent inhibition of the human enzyme and showed reduced effect to the mouse 11β-HSD1 (IC_{50}: 111 nM). Compound **7h** (human IC_{50}: 15 nM, mouse IC_{50}: 31 nM) showed notable inhibitory potency on both 11β-HSD1.

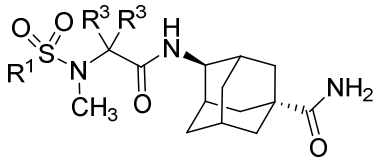
Table 1. In vitro inhibitory activity of compounds **7a-i** against human and mouse 11β-HSD1

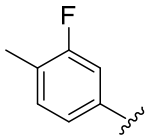
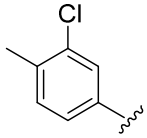
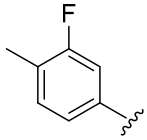


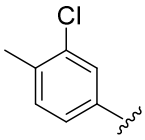
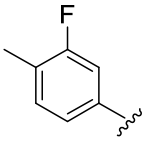
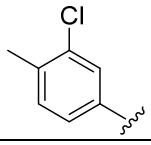
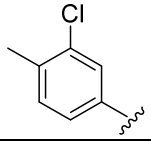
No	Compound	R^1	Human 11βHSD1 IC_{50} (nM)	Mouse 11βHSD1 IC_{50} (nM)
1	**7a**		89	159
2	**7b**		26	105
3	**7c**		32	75
4	**7d**		12	156
5	**7e**		57	254
6	**7f**		25	64
7	**7g**		11	111
8	**7h**		15	31
9	**7i**		22	58

After the discovery of the potency imparted by the substitution such as fluoro or chloro at the 3rd position and methyl at the 4th position of the phenyl sulfonamide ring, we turned to modify the substitutions at the α-position of the carboxamide. Significant improvement in potency was observed by replacing the dimethyl substitution at the α-potion of the carboxamide with a cyclopropyl group (Table 2). Accordingly, compound **7j** (IC_{50}: 8 nM) displayed most promising inhibitory effect toward human 11β-HSD1 and showed good potency toward mouse 11β-HSD1 (IC_{50}: 49 nM). Similarly, improved potency was observed with compound **7k** in human (IC_{50}: 10.5 nM) and slightly reduced effects in mouse 11β-HSD1 (IC_{50}: 46 nM) compared with compound **7h**. However, the other substitutions (**7l**, **7m** & **7n**) such as cyclobutyl and cyclopentyl derivatives of compounds **7g** & **7h** exhibited reduced inhibitory effects on both the microsomes.

Table 2. In vitro inhibitory activity of compounds **7j-n** against human and mouse 11β-HSD1 and comparison with **7g** & **7h.**



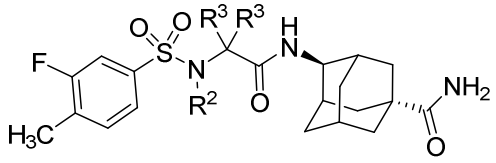
No	Compound	R^1	R^3	Human 11βHSD1 IC_{50} (nM)	Mouse 11βHSD1 IC_{50} (nM)
1	**7g**			11	111
2	**7h**			15	31
3	**7j**			8	49

4	**7k**			10.5	46
5	**7l**			40	40
6	**7m**			40	30
7	**7n**			60	130

Further modification at *N*-alkyl group of compound **7j** led to the reduction in inhibitory on both 11β-HSD1. As shown in table 3, compound **7o** having no substitution on nitrogen of the sulfonamide displayed less potency. *N*-propyl (**7q**) derivative showed reasonable inhibitory effect. Whereas, *N*-ethyl (**7p**) and *N*-isopropyl (**7r**) derivatives exhibited reduced effects on both 11β-HSD1.

To demonstrate the importance of adamantanecarboxamide in the 11β-HSD1 inhibitory potency, substituted adamantane derivatives (**7s-x**) such as adamantan-2-amine, adamantan-1-amine, 4-aminoadamantan-1-ol, 4-aminoadamantane-1-carboxylic acid and bicyclo[2.2.1]heptan-2-amine were assayed for inhibition and found reduced activity (Table 4).

Table 3. In vitro inhibitory activity of compounds **7o-r** against human and mouse 11β-HSD1 and comparison with **7j**.



No	Compound	R^2	R^3	Human 11βHSD1 IC_{50} (nM)	Mouse 11βHSD1 IC_{50} (nM)

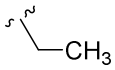
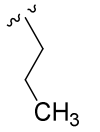
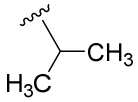
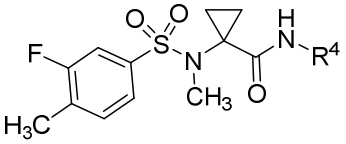
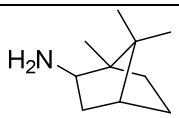
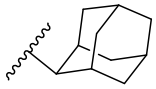
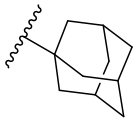
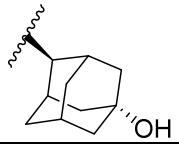
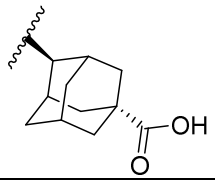
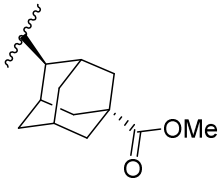
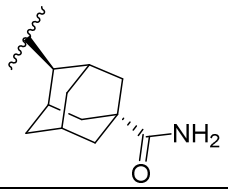
1	**7j**			8	49
2	**7o**			459	823
3	**7p**			1515	451
4	**7q**			201	218
5	**7r**			648	1227

Table 4. In vitro inhibitory activity of compounds **7s-x** against human and mouse 11β-HSD1 and comparison with **7j**.



No	Compound	R^4	Human 11βHSD1 IC_{50} (nM)	Mouse 11βHSD1 IC_{50} (nM)
1	**7s**		2659	na
2	**7t**		1078	105
3	**7u**		na	na
4	**7v**		267	2958

5	**7w**		3853	na
6	**7x**		12180	na
7	**7j**		8	49

From the results of our in vitro data, **7j** was selected as the prototype compound. Next, compound **7j** was investigated for its stability, permeability, CYP and hERG inhibition. As shown in Table 5, compound **7j** showed reasonable liver microsomal stability in human with ~ 57% of the parent compound remaining after 30 min incubation, good plasma stability (~95%) and exhibited medium level of permeability in PAMPA. In CYP inhibition assays with several CYP subtypes, compound **7j** did not significantly inhibit CYP. Compound **7j** showed no hERG inhibition (29% at 10 μM). The compound 7j was characterized for its pharmacokinetic property in rats. 7j displayed moderate blood concentration (AUC: 8.95 μg.hr/mL(iv), 2.66 μg.hr/mL(oral)), clearance (1.19 L/Kg/hr) and volume of distribution (0.63L/kg). The oral bioavailability is 28%.

Table 5. Stability, permeability, CYP, hERG and PK parameters of **7j**.

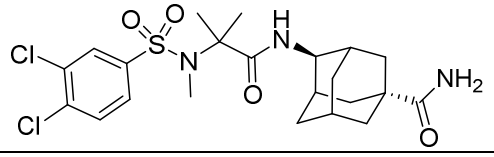
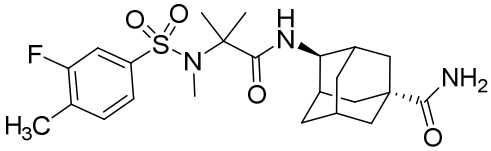
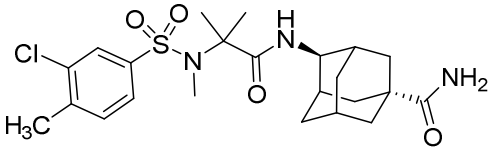
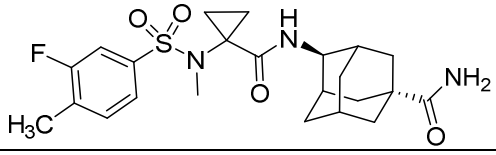
Assay	**Results**	
Liver microsomal stability (Human)	56.6 ± 4.06 % (parent was remained after 30 min incubation)	
Plasma stability (human)	95.3 ± 1.50 % (parent was remained after 2h incubation at 37 ^{o}C)	

Permeability in PAMPA assay	- logPe (mean±SD) = -4.19±0.030	* -logPe (high: > -4.07, medium: -4.07 ~ -4.87, low: < -4.87)
CYP inhibition assay	1A2: IC_{50} > 50 μM 2C9: IC_{50} > 50 μM 2C19: IC_{50} > 50 μM 2D6: IC_{50} > 50 μM 3A4: IC_{50} > 50 μM	
hERG assay (patch clamp)	29% inhibition at 10 μM 42% inhibition at 100 μM	
In vivo PK in rats	Iv dose (mg/kg) 10 $T_{1/2}$ (hr) 0.93 AUC (μg·hr/mL) 8.95 CL (L/kg/hr) 1.19 Vss (L/kg) 0.64 Po dose (mg/kg) 10 Tmax (hr) 0.67 Cmax (μg/mL) 1.32 AUC (μg·hr/mL) 2.66 F (%) 28	

We performed in vivo 11β-HSD1 inhibition study in normal mice with several active compounds including **7j** (Table 6). After 20 mpk oral dosing, 11β-HSD1 inhibition was measured in fat and liver tissues. Among the active derivatives, compound **7j** was most effective, and exhibited approximately 79% inhibition in mouse liver and fat tissues.

Table 6. In vivo 11 β-HSD 1 inhibition of **7f-h** & **7j**.

No	**Compound**	**Structure**	**In vivo 11βHSD1 inhibition**	**In vivo 11βHSD1 inhibition**

			(%) Liver	(%) Fat
1	7f		43	52
2	7g		78	16
3	7h		78	59
4	7j		79	79

The oral in vivo efficacy (Table 6) observed with this compound provided further impetus to continue studies in this α-sulfonamido-N- adamantanecarboxamide series in order to further improve pharmacokinetic properties.

Conclusion

In conclusion, we have identified a series of α-sulfonamido-*N*-adamantanecarboxamide derivatives as 11β-HSD1 inhibitors. Several compounds with R^1, R^2 and R^3 substituents were found to be potent 11β-HSD1 inhibitors. Among them, compound **7j** was the most active with an IC_{50} value of 8 nM in human. Compound **7j** exhibited reasonable stability, permeability and safety profiles (CYP and hERG). Compound **7j** showed good in vivo 11 β-HSD1 inhibition with ~80% inhibition after 20 mpk oral dosing. Further investigations of promising compounds are under process and will be reported in due course.

Acknowledgments

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the project of the Korea Research Institute of Chemical Technology, the Ministry of Knowledge Economy, Republic of Korea.

Experimental Section

General Information.

All the commercial chemicals and solvents were reagent grade and used without further purification. Products from all reactions were purified by flash column chromatography using the silica gel 60 (230-400 mesh Kieselgel 60) or crystallization. 1H-NMR spectra were obtained on FT-NMR Varian Gemini-300FT or Bruker AVANCE-300 with TMS as internal reference. LC/MS spectra were obtained on the Agilent and high resolution mass spectrum (HRMS) was obtained on the Autospec magnetic sector mass spectrometer (Micromass, Manchester, UK).

Synthetic procedures of compound 7d

(*E*)-4-(2-((3,4-difluoro-*N*-methylphenyl)sulfonamido)-2-methylpropanamido)-adamantane-1-carboxamide (**7d**). To a solution of 3,4-difluorobenzenesulfonyl chloride (**2d**, 1.45 mmol, 308 mg) in CH_2Cl_2 (7 mL), were added ethyl 2-amino-2-methylpropanoate . hydrochloride (**1a**, 2.17 mmol, 364 mg), DIPEA (4.35 mmol, 561 mg) and DMAP (1.74 mmol, 212 mg). The reaction mixture was stirred for 3 h at room temperature, and extracted with 2N-HCl/CH_2Cl_2. The organic layer was washed with water and brine, dried over anhydrous MgSO4 and concentrated. The residue was purified by silica gel column chromatography to give ethyl 2-(3,4-difluorophenylsulfonamido)-2-methylpropanoate (**3d**, 409 mg, 92%). To a solution of ethyl 2-(3,4-difluorophenylsulfonamido)-2-methylpropanoate (**3d**, 1.3 mmol, 409 mg) in DMF (7 mL), were added K_2CO_3 (10 mmol, 1503 mg) and CH_3I (2.0 mmol, 276 mg). The mixture was stirred for 4 hr at 80 ℃, and extracted with sat.NH_4Cl and ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous MgSO4 and concentrated. The residue was purified by silica gel column chromatography to give ethyl 2-(3,4-difluoro-*N*-methylphenylsulfonamido)-2-methylpropanoate (**4d**) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93-7.87 (m, 1H), 7.82-7.77 (m, 1H), 7.33-7.25 (m, 1H), 4.27 (q, J = 7.1 Hz, 2H), 2.71 (s, 3H), 1.56 (s, 6H), 1.33 (t, J = 7.1 Hz, 3H).

To a solution of ethyl 2-(3,4-difluoro-*N*-methylphenylsulfonamido)-2-methylpropanoate (**4d**,

300 mg) in CH_2Cl_2 (10 mL), was added BBr_3 (2.5 mL) at 0 ^{0}C. The reaction mixture was stirred for 1 hr at room temperature, quenched with MeOH and H_2O at 0 ^{0}C, and exctracted with CH_2Cl_2. The organic layer was washed with water and brine, dried over anhydrous MgSO4 and concentrated. The residue was purified by silica gel column chromatography to give 2-(3,4-difluoro-*N*-methylphenylsulfonamido)-2-methylpropanoic acid as a white solid (**5d**, 248 mg, 91%), ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77-7.66 (m, 2H), 7.36-7.23 (m, 1H), 4.16 (s, 2H), 2.55-2.48 (m, 1H), 0.88-0.81 (m, 2H), 0.79-0.72 (m, 2H).

To a solution of adamantyl amine.HCl salt (**6a**, 0.3 mmol, 69 mg) and DIPEA (252 mg, 1.95 mmol) in DMSO (2 mL), were added isopropanol (~ 6 mL), 2-(3,4-difluoro-*N*-methylphenylsulfonamido)-2-methylpropanoic acid (**5d**, 88 mg, 0.3 mmol), EDC (118 mg, 0.6 mmol) and HOBt (48 mg, 0.36 mmol) at room temperature. The mixture was stirred for 3 hr, and then evaporated at 50 ℃ for 20-30 min. The residue was extracted with sa.NH_4Cl and ethyl acetate, dried over anhydrous MgSO4 and concentrated. The residue was purified by silica gel column chromatography to give (*E*)-4-(2-((3,4-difluoro-*N*-methylphenyl)sulfonamido)-2-methylpropanamido)adamantane-1-carboxamide (**7d**, 50.6mg, 36%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80-7.76 (m, 1H), 7.72-7.70 (m, 1H), 7.37-7.31 (m, 1H), 6.76 (d, J = 7.5 Hz, 1H), 4.01 (d, J = 7.5 Hz, 1H), 2.89 (s, 3H), 2.11-1.83 (m, 11H), 1.67-1.64 (m, 2H), 1.49 (s. 6H); HRMS (EI) m/z calcd for $[C_{22}H_{29}F_2N_3O_4S]^+$ 469.1847, found 469.1834.

(*E*)-4-(2-methyl-2-(*N*-methylphenylsulfonamido)propanamido)adamantane-1-carboxamide (**7a**). Yield (83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89-7.86 (m, 2H), 7.63-7.58 (m, 1H), 7.56-7.51 (m, 2H), 6.94 (d, J = 8.0 Hz, 1H), 5.59 (br, 1H), 5.30 (br, 1H), 4.03 (m, 1H), 2.94 (s, 3H), 2.10-1.85 (m, 11H), 1.65-1.60 (m, 2H), 1.44 (s, 6H); HRMS (EI) m/z calcd for $[C_{22}H_{31}N_3O_4S]^+$ 433.2035, found 433.2044.

(*E*)-4-(2-((3-fluoro-*N*-methylphenyl)sulfonamido)-2-methylpropanamido)adamantane-1-carboxamide (**7b**). Yield (68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71-7.51 (m, 3H), 7.33-7.27 (m, 1H), 7.56-7.51 (m, 2H), 6.82 (d, J = 8.0 Hz, 1H), 5.59 (br, 1H), 5.36 (br, 1H), 4.02 (m, 1H), 2.94 (s, 3H), 2.10-1.83 (m, 11H), 1.65-1.62 (m, 2H), 1.47 (s, 6H); HRMS (EI) m/z calcd for $[C_{22}H_{30}FN_3O_4S]^+$ 451.1941, found 451.1931.

(*E*)-4-(2-((3-chloro-*N*-methylphenyl)sulfonamido)-2-methylpropanamido)adamantane-1-carboxamide (**7c**). Yield (79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7,57 (d, J = 8.0 Hz, 1H), 7.48 (t, J = 8.0 Hz, 1H), 6.80 (d, J = 7.6 Hz, 1H), 5.59 (br, 1H), 5.35 (br, 1H), 4.03 (m, 1H), 2.94 (s, 3H), 2.10-1,82 (m, 11H), 1.66-1.63 (m, 2H), 1.47 (s. 6H); HRMS (EI) m/z calcd for $[C_{22}H_{30}ClN_3O_4S]^+$ 467.1646, found 467.1638.

(*E*)-4-(2-((4-chloro-3-fluoro-*N*-methylphenyl)sulfonamido)-2-methylpropanamido)adamantane-1-carboxamide (**7e**). Yield (80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71-7.64 (m, 2H), 7.59-7.55 (m, 1H), 6.71 (d, J = 8.0 Hz, 1H), 5.78 (br, 1H), 5.28 (br, 1H), 4.03 (m, 1H), 2.91 (s, 3H), 2.10-1.82 (m, 11H), 1.66-1.63 (m, 2H), 1.48 (s, 6H); HRMS (EI) m/z calcd for $[C_{22}H_{29}ClFN_3O_4S]^+$ 485.1551, found 485.1550.

(*E*)-4-(2-((3,4-dichloro-*N*-methylphenyl)sulfonamido)-2-methylpropanamido)adamantane-1-carboxamide (**7f**). Yield (53%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.74 (d, J = 8.5 Hz, 1H), 7.63 (d, J = 8.5 Hz, 1H), 6.76 (d, J = 7.5 Hz, 1H), 4.01 (d, J = 7.5 Hz, 1H), 2.91 (s, 3H), 2.10-1.82 (m, 11H), 1.67-1.64 (m, 2H), 1.49 (s. 6H); HRMS (EI) m/z calcd for $[C_{22}H_{29}Cl_2N_3O_4S]^+$ 501.1256, found 501.1263.

(*E*)-4-(2-((3-fluoro-*N*,4-dimethylphenyl)sulfonamido)-2-methylpropanamido)adamantane-1-carboxamide (**7g**). White solid, 54 mg, Yield 39%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57-7.51 (m, 2H), 7.37-7.35 (m, 1H), 6.87 (d, J = 7.6 Hz, 1H), 5.63 (br, 1H), 5.42 (br, 1H), 4.03 (d, J = 7.6 Hz, 1H), 2.93 (s, 3H), 2.36 (s, 3H), 2.09-1.84 (m, 11H), 1.65-1.63 (m, 2H), 1.45 (s. 6H); HRMS (EI) m/z calcd for $[C_{23}H_{32}FN_3O_4S]^+$ 465.2098, found 465.2075.

(*E*)-4-(2-((3-chloro-*N*,4-dimethylphenyl)sulfonamido)-2-methylpropanamido)adamantane-1-carboxamide (**7h**). Yield (66%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.66 (d, J = 8.0 Hz, 1H), 7.39 (d, J = 8.0 Hz, 1H), 6.85 (d, J = 7.8 Hz, 1H), 5.61 (br, 1H), 5.36 (br, 1H), 4.03 (d, J = 7.8 Hz, 1H), 2.93 (s, 3H), 2.46 (s, 3H), 2.10-1.83 (m, 11H), 1.65-1.63 (m, 2H), 1.46 (s. 6H); HRMS (EI) m/z calcd for $[C_{23}H_{32}ClN_3O_4S]^+$ 481.1802, found 481.1802.

(*E*)-4-(2-methyl-2-((2,3,4-trifluoro-*N*-methylphenyl)sulfonamido)propanamido)adamantane-1-carboxamide (**7i**). White soild, 93 mg, Yield 64%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72-7.67 (m, 1H), 7.15-7.12 (m, 1H), 6.93 (d, J = 7.8 Hz, 1H), 5.63 (br, 1H), 5.45 (br, 1H), 4.01 (d, J = 7.8 Hz, 1H), 3.06 (s, 3H), 2.08-1.81 (m, 11H), 1.66-1.64 (m, 2H), 1.48 (s. 6H); HRMS (EI) m/z calcd for $[C_{22}H_{28}F_3N_3O_4S]^+$ 487.1753, found 487.1738.

Synthetic procedures of compound 7j

(*E*)-4-(1-((3-fluoro-*N*,4-dimethylphenyl)sulfonamido)cyclopropane-1-carboxamido)adamantane-1-carboxamide (**7j**).

To a solution of 3-fluoro-4-methylbenzenesulfonyl chloride (**2j**, 1.40 mmol, 292 mg) in CH_2Cl_2 (7 mL), were added ethyl 1-aminocyclopropane-1-carboxylate.hydrochloride (**1b**, 2.17 mmol, 358 mg), DIPEA (4.35 mmol, 561 mg) and DMAP (1.74 mmol, 212 mg). The reaction mixture was stirred for 3 h at room temperature, and extracted with 2N-HCl/CH_2Cl_2. The organic layer was washed with water and brine, dried over anhydrous MgSO4 and concentrated. The residue was purified by silica gel column chromatography to give ethyl 1-((3-fluoro-4-methylphenyl)sulfonamido)cyclopropane-1-carboxylate (**3j**, 396 mg, 94%). To a solution of ethyl 1-((3-fluoro-4-methylphenyl)sulfonamido)cyclopropane-1-carboxylate (**3j**, 1.3 mmol, 390 mg) in DMF (7 mL), were added K_2CO_3 (10 mmol, 1503 mg) and CH_3I (2.0 mmol, 276 mg). The mixture was stirred for 4 hr at 80 ^{0}C, and extracted with sat.NH_4Cl/ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous MgSO4 and concentrated. The residue was purified by silica gel column chromatography to give ethyl 1-(3-fluoro-*N*,4-dimethylphenylsulfonamido)cyclopropanecarboxylate (**4j**). To a solution of ethyl 1-(3-fluoro-*N*,4-dimethylphenylsulfonamido)cyclopropanecarboxylate (**4j**) in THF (5 mL) and MeOH (5 mL), was added LiOH.H_2O (193 mg) in H_2O (3.0 mL). The mixture was stirred for 12 hr at 80 ℃, evaporated at 50 ℃, neutralized with 2N-HCl and extracted with ethyl acetate. The organic layer was dried over MgSO4 to give 1-(3-fluoro-*N*,4-dimethylphenylsulfonamido)cyclopropanecarboxylic acid as a white solid (**5j**, 263.6mg, 83.4%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.50-7.42 (m, 2H), 7.34-7.28 (m, 1H), 2.98 (s, 3H), 2.34 (s, 3H), 1.99-1.69 (m, 2H), 1.52-1.33 (m, 1H), 1.27-1.06 (m, 1H).

To a solution of adamantyl amine.HCl salt (**6a**, 0.3 mmol, 69 mg) and DIPEA (252 mg, 1.95 mmol) in DMSO (2 mL), were added isopropanol (~6 mL), 1-(3-fluoro-*N*,4-

dimethylphenylsulfonamido)cyclopropanecarboxylic acid (**5j**, 89 mg, 0.31 mmol), EDC (118 mg, 0.6 mmol) and HOBt (48 mg, 0.36 mmol) at room temperature. The mixture was stirred for 3 hr, and then evaporated at 50 ^{0}C for 20-30 min. The residue was extracted with sa.NH_4Cl and ethyl acetate, dried over anhydrous MgSO4 and concentrated. The residue was purified by silica gel column chromatography to give (*E*)-4-(1-((3-fluoro-*N*,4-dimethylphenyl)sulfonamido)cyclopropane-1-carboxamido)adamantane-1-carboxamide as a white solid (**7j**, 108 mg, 75%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.56-7.48 (m, 3H), 3.96 (s, 1H), 2.98 (s, 3H), 2.36 (d, J = 2.4 Hz, 3H), 2.05-2.19 (m, 11H), 1.68-1.64 (m, 2H), 1.51 (m, 2H), 1.21 (m, 2H); HRMS (EI) m/z calcd for $[C_{23}H_{30}FN_3O_4S]^+$ 463.1941, found 463.1941.

(*E*)-4-(1-((3-chloro-*N*,4-dimethylphenyl)sulfonamido)cyclopropane-1-carboxamido)adamantane-1-carboxamide (**7k**) White solid, 75 mg, Yield 52%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.55 (d, J = 8.0 Hz, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.22 (d, J = 7.6 Hz, 1H), 5.61 (br, 1H), 5.35 (br, 1H), 4.04 (d, J = 7.6 Hz, 1H), 2.96 (s, 3H), 2.46 (s, 3H), 2.12-1.92 (m, 13H), 1.66-1.64 (m, 4H); HRMS (EI) m/z calcd for $[C_{23}H_{30}ClN_3O_4S]^+$ 479.1646, found 479.1620.

(*E*)-4-(1-((3-fluoro-*N*,4-dimethylphenyl)sulfonamido)cyclobutane-1-carboxamido)adamantane-1-carboxamide (**7l**). White solid, 90 mg, Yield 63%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, J = 8.2 Hz, 1H), 7.48 (d, J = 2.4 Hz, 1H), 7.39-7.36 (m, 2H), 5.61 (br, 1H), 5.36 (br, 1H), 4.06 (d, J = 7.7 Hz, 1H), 2.83 (s, 3H), 2.59-2.56 (m, 2H), 2.38 (s, 3H), 2.26-2.19 (m, 2H), 2.12-1.82 (m, 11H), 1.65-1.62 (m, 3H); HRMS (EI) m/z calcd for $[C_{24}H_{32}FN_3O_4S]^+$ 477.2098, found 477.2100.

(*E*)-4-(1-((3-chloro-*N*,4-dimethylphenyl)sulfonamido)cyclobutane-1-carboxamido)adamantane-1-carboxamide (**7m**). White solid, 79 mg, Yield 53%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.19 (d, J = 8.0 Hz, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.37 (d, J = 7.6 Hz, 1H), 5.61 (br, 1H), 5.35 (br, 1H), 4.07 (d, J = 7.6 Hz, 1H), 2.83 (s, 3H), 2.60-2.57 (m, 2H), 2.47 (s, 3H), 2.26-2.19 (m, 2H), 2.13-1.92 (m, 11H), 1.86-1.80 (m, 1H), 1.65-1.63 (m, 3H); HRMS (EI) m/z calcd for $[C_{24}H_{32}ClN_3O_4S]^+$ 493.1802, found 493.1811.

(*E*)-4-(1-((3-chloro-*N*,4-dimethylphenyl)sulfonamido)cyclopentane-1-carboxamido)adamantane-1-carboxamide (**7n**). White solid, 73 mg, Yield 48%. ^{1}H NMR

($CDCl_3$, 300 MHz) δ 7.77 (s, 1H), 7.58 (d, J = 8.1 Hz, 1H), 7.45 (d, J = 8.1 Hz, 1H), 7.38 (s, 1H), 5.62 (br, 1H), 5.38 (br, 1H), 4.03-4.01 (m, 1H), 3.06 (s, 3H), 2.46 (s, 3H), 2.09-1.47 (m, 21H); HRMS (EI) m/z calcd for $[C_{25}H_{34}ClN_3O_4S]^+$ 507.1959, found 507.1967.

(*E*)-4-(1-((3-fluoro-4-methylphenyl)sulfonamido)cyclopropane-1-carboxamido)adamantane-1-carboxamide (**7o**) Yield (52%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.57-7.54 (m, 1H), 7.51-7.45 (m, 2H), 3.88 (s, 1H), 3.35 (s, 3H), 2.36 (d, J = 2.4 Hz, 3H), 1.98-1.92 (m, 11H), 1.65-1.62 (m, 2H), 1.30 (q, J = 4.8, 3.6 Hz, 2H), 0.88 (q, J = 4.8, 3.6 Hz, 2H); HRMS (EI) m/z calcd for $[C_{22}H_{28}FN_3O_4S]^+$ 449.1785, found 449.1786.

(*E*)-4-(1-((*N*-ethyl-3-fluoro-4-methylphenyl)sulfonamido)cyclopropane-1-carboxamido)adamantane-1-carboxamide (**7p**). Yield (82%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.56-7.47 (m, 3H), 3.98 (s, 1H), 3.69 (m, 1H), 3.13 (m, 1H), 2.36 (d, J = 2.4 Hz, 3H), 2.05-1.93 (m, 11H), 1.69-1.66 (m, 2H), 1.51-1.50 (m, 2H), 1.26 (t, J = 6.8 Hz, 3H), 1.58 (m, 2H); HRMS (EI) m/z calcd for $[C_{24}H_{32}FN_3O_4S]^+$ 477.2098, found 477.2076.

(*E*)-4-(1-((3-fluoro-4-methyl-*N*-propylphenyl)sulfonamido)cyclopropane-1-carboxamido)adamantane-1-carboxamide (**7q**). Yield (80%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.56-7.47 (m, 3H), 3.96 (s. 1H), 3.50 (m, 1H), 3.00 (m, 1H), 2.37 (d, J = 2.4 Hz, 3H), 2.05-1.93 (m, 11H), 1.72-1.62 (m, 4H), 1.49-1.48 (m, 2H), 1.14 (m, 2H), 0.92 (t, J = 6.8 Hz, 3H); HRMS (EI) m/z calcd for $[C_{25}H_{34}FN_3O_4S]^+$ 491.2254 found 491.2256.

(*E*)-4-(1-((3-fluoro-*N*-isopropyl-4-methylphenyl)sulfonamido)cyclopropane-1-carboxamido)adamantane-1-carboxamide (**7r**). Yield (50%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.60-7.49 (m, 3H), 4.28-4,21 (m, 1H0, 3.98 (s, 1H), 2.37 (d, J = 2.4 Hz, 3H), 2.08-1.92 (m, 11H), 1.68 (m, 4H), 1.37-1.34 (m, 6H), 1.02 (m, 2H); HRMS (EI) m/z calcd for $[C_{25}H_{34}FN_3O_4S]^+$ 491.2254, found 491.2256.

1-((3-fluoro-*N*,4-dimethylphenyl)sulfonamido)-*N*-((1R,2R,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)cyclopropane-1-carboxamide (**7s**). Yield (83%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.55-7.46 (m, 3H), 4.22-4.16 (m, 0.5H), 3.86-3.80 (m, 0.5H), 2.97 (s, 3H), 2.36 (s, 3H), 1.89-1.64 (m, 3H), 1.62-1.47 (m, 2H), 1.34-1.21 (m, 3H), 1.20-0.83 (m, 8H); HRMS (EI) m/z calcd for $[C_{22}H_{31}FN_2O_3S]^+$ 422.2039, found 422.2045.

***N*-((1R,3S,5r,7r)-adamantan-2-yl)-1-((3-fluoro-*N*,4-dimethylphenyl)sulfonamido)cyclopropane-1-carboxamide** (**7t**). Yield (75%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.55-7.48 (m, 3H), 3.98 (m, 1H), 2.97 (s, 3H), 2.36 (d, J =2.4 Hz, 3H), 2.05-2.01 (m, 2H), 1.94-1.82 (m, 10), 1.72-1.69 (m, 2H), 1.50 (m, 2H), 1.20 (m, 2H); HRMS (EI) m/z calcd for $[C_{22}H_{29}FN_2O_3S]^+$ 420.1883, found 420.1878.

***N*-((3s,5s,7s)-adamantan-1-yl)-1-((3-fluoro-*N*,4-dimethylphenyl)sulfonamido)cyclopropane-1-carboxamide** (**7u**). Yield (85%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.55-7.48 (m, 3H), 2.95 (s, 3H), 2.36 (d, J =2.0 Hz, 3H), 2.07 (m, 3H), 2.00-1.99 (m, 6H), 1.74-1.73 (m, 6H), 1.43 (m, 2H), 1.17 (m, 2H); HRMS (EI) m/z calcd for $[C_{22}H_{29}FN_2O_3S]^+$ 420.1883, found 420.1839.

1-((3-fluoro-*N*,4-dimethylphenyl)sulfonamido)-*N*-((*E*)-5-hydroxyadamantan-2-yl)cyclopropane-1-carboxamide (**7v**). Yield (89%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.55-7.48 (m, 3H), 3.93 (m, 1H), 2.97 (s, 3H), 2.36 (d, J = 2.4 Hz, 3H), 2.15-2.10 (m, 3H), 1.97-1.78 (m, 8H), 1.58-1.51 (m, 4H), 1.20 (m, 2H); HRMS (EI) m/z calcd for $[C_{22}H_{29}FN_2O_4S]^+$ 436.1832, found 436.1848.

(*E*)-4-(1-((3-fluoro-*N*,4-dimethylphenyl)sulfonamido)cyclopropane-1-carboxamido)adamantane-1-carboxylic acid (**7w**). Yield (96%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.55-7.48 (m, 3H), 3.96 (m, 1H), 2.98 (s, 3H), 2.36 (d, J = 2.0 Hz, 3H), 2.03-1.95 (m, 11H), 1.67-1.64 (m, 2H), 1.52 (m, 2H), 1.21 (m, 2H); HRMS (EI) m/z calcd for $[C_{23}H_{29}FN_2O_5S]^+$ 464.1781, found 464.1733.

Methyl (*E*)-4-(1-((3-fluoro-*N*,4-dimethylphenyl)sulfonamido)cyclopropane-1-carboxamido)adamantane-1-carboxylate (**7x**). Yield (91%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.55-7.48 (m, 3H), 3.95 (m, 1H), 3.66 (s, 3H), 2.97 (s, 3H), 2.36 (d, J = 2.0 Hz, 3H), 2.04-1.95 (m, 11H), 1.67-1.64 (m, 2H), 1.52 (m, 2H), 1.21 (m, 2H); HRMS (EI) m/z calcd for $[C_{24}H_{31}FN_2O_5S]^+$ 478.1938, found 478.1939.

In vitro assay for 11β-HSD1 activity

Human and mouse 11β-HSD1 overexpressing CHO-K1 cells or adipocytes were seeded at 2 × 10^4 cells/well (11β-HSD1 overexpressing CHO-K1 cells) or 5 × 10^4 cells/well (adipocytes) onto 96 or 24-well plates and were incubated in a medium containing 160 nM cortisone in the presence or absence of compounds for 3 h (human and mouse 11β-HSD1 overexpressing CHO-K1 cells) or 24 h (adipocytes). Small aliquots (10 μl) of the reaction mixtures were removed and subjected to a homogeneous time-resolved fluorescence (HTRF) cortisol assay in accordance with the manufacturer's instructions (Nihon Schering, Tokyo, Japan). The HTRF assay is based on the competition between free cortisol and XL665-conjugated cortisol for binding to an anti-cortisol antibody labeled with europium (Eu^{3+}) cryptate. Eu^{3+} cryptate and XL665 act as a donor and acceptor, respectively. If the two fluorophores are in close proximity, fluorescence resonance energy transfer (FRET) occurs upon excitation. The specific signal is expressed as the percentage of Delta F, which is the value calculated from the ratio of 665 nm/615 nm $[(R_{sample} - R_{negative})/R_{negative} \times 100]$, and is inversely proportional to the concentration of cortisol in the sample or the calibrator. The cortisol concentration was calculated from the calibration curve obtained from Delta F versus the standard solution. The IC_{50} values of the compounds were determined from concentration-dependent inhibition curves obtained using GraphPad Prism software (GraphPad Software Inc., La Jolla, CA, USA).

In vivo 11β-HSD1 inhibition assay in mice

Male C57Bl/6 lean mice, 12 weeks old, were orally gavaged with vehicle (0.5% carboxymethylcellulose sodium (CMC)/0.1% Tween 80 in H_2O) or compound at 20 mg/kg and sacrificed 2 h post dose, n = 4 per group. Liver and fat pads were removed and sectioned into three 30−40 mg samples and placed into 24-well Falcon plates containing prewarmed assay media that consisted of 1 μM cortisone and 100 nM NADPH in DMEM. Plates were then transferred to a 37 °C/CO_2 incubator and incubated for 3 h. Then cortisol product in the media was quantitated using a cortisol ELISA kit (Assay Designs Inc., Ann Arbor, MI). Enzyme activity is expressed as pg/mL of product formed per mg wet tissue weight.

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