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Discovery and optimization of adamantyl carbamate inhibitors of 11β-HSD1

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ABSTRACT

Synthesis of 2-adamantyl carbamate derivatives of piperidines and pyrrolidines led to the discovery of **9a** with an IC_{50} of 15.2 nM against human 11β-HSD1 in adipocytes. Optimization for increased adipocyte potency, metabolic stability and selectivity afforded **11k** and **11l**, both of which were >25% orally bioavailable in rat.

11β-hydroxysteroid dehydrogenase (11β-HSD1) is a member of the short chain dehydrogenase/reductase (SDR) superfamily.[1,2] 11β-HSD1 increases local tissue concentrations of the active glucocorticoid cortisol by NADPH-dependent reduction of the 11-keto group of inactive cortisone to the (11*S*)-alcohol, cortisol. 11β-HSD1 is primarily expressed in liver and adipose tissue, and its elevated expression in adipose tissue has been linked to obesity, insulin resistance, metabolic syndrome, diabetes and cardiovascular disease in humans.[3–7] Moreover, the phenotype of transgenic mice overexpressing 11β-HSD1 in adipose tissue includes visceral obesity, insulin resistance and hypertension,[8,9] while 11β-HSD1 knockout mice are resistant to diet induced obesity and have increased insulin sensitivity.[10–12] Thus, a selective inhibitor of 11β-HSD1 may be useful for the treatment of diabetes and has potential for positive effects on multiple cardiovascular risk parameters.

Since 2002,[13] several classes of selective, synthetic inhibitors of 11β-HSD1 have been reported (Fig. 1).[14–16] Triazole **1** increased insulin sensitivity and decreased fasting glucose, cholesterol, and adipose tissue mass in mice.[17] Oral dosing of thiazolone **2** increased plasma adiponectin levels and decreased fasting glucose levels in KKA$^{\gamma}$ mice.[18,19] Sulfonamide **3** reduced fed glucose and fasted insulin in mice when incorporated into a high fat diet at 30 mg/kg/day.[20] Racemic adamantyl amide **4** lowered plasma glucose levels after 3 weeks of oral administration to ob/ob mice at 30 mg/kg b.i.d.[21] The activity of these compounds in animal models

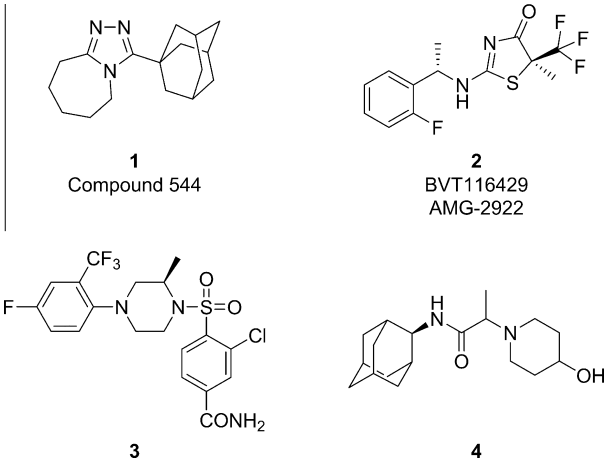

Figure 1. Literature 11β-HSD1 inhibitors.

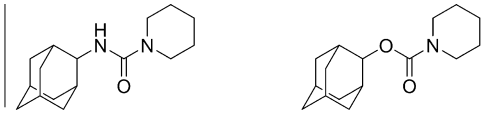

Figure 2. Adamantyl urea and carbamate 11β-HSD1 inhibitors.

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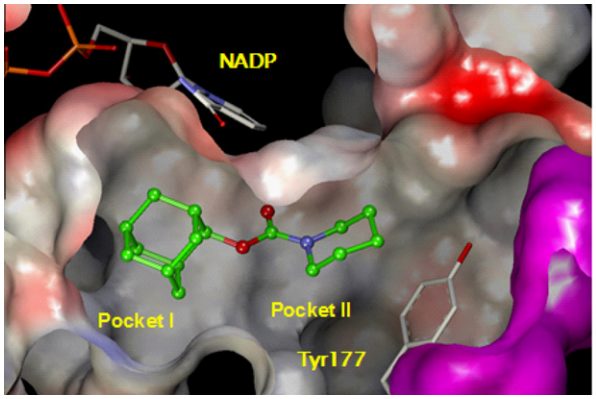


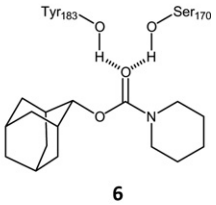


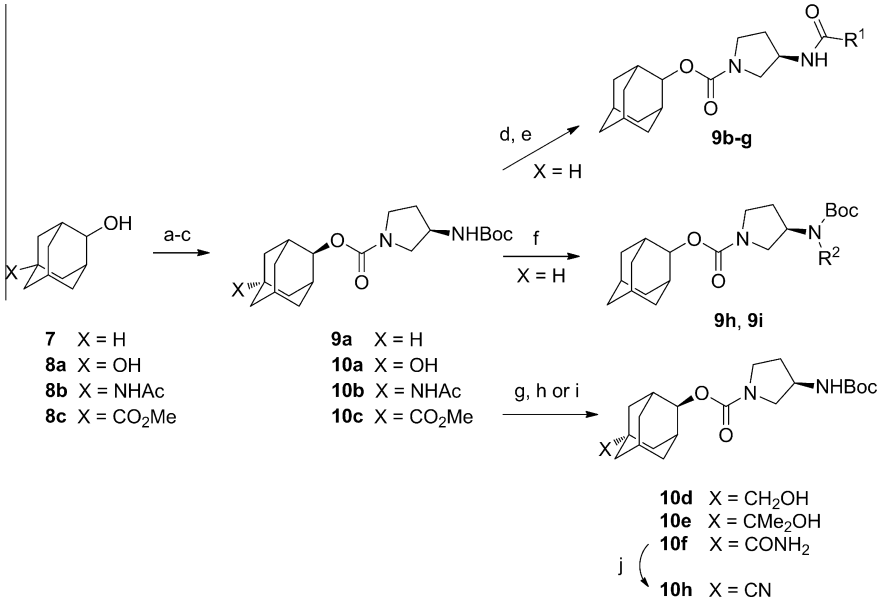
Figure 3. Model of **6** in the 11β -HSD1 binding site. The surface of the dimeric enzyme shown with residues 213–233 excluded to provide a clear view of the active site. Tyr 177 is highlighted to show the hydrophobic interaction with the piperidine ring. The solvent accessible surface due to monomer A is colored according to the electrostatic surface properties and that of monomer B is shown in magenta. The carbonyl of compound **6** interacts with the catalytic residues Tyr183 and Ser170.

further validates the potential for selective inhibition of 11β-HSD1 as a treatment for diabetes.

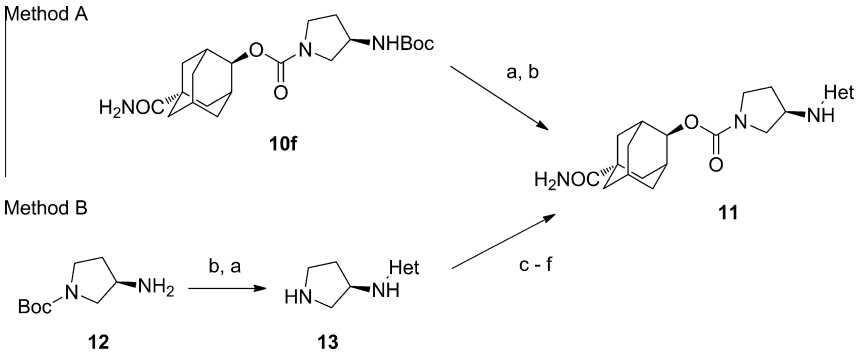
We previously described the discovery of *N*-(2-adamantyl)ureas such as **5** (Fig. 2).[22] Our model of **5** bound to 11β-HSD1, based on the ligand in PDB code 2IRW,[23] indicated that the urea NH did not participate in a hydrogen bond with the protein. Replacement of the urea NH with O gave carbamate **6** resulting in a 3× improvement in enzyme potency but a 1.5× decrease in cell potency. Our model of **6** bound to 11β-HSD1 is depicted in Figure 3. Whereas the adamantyl group filled the large, mainly hydrophobic pocket adjacent to the cofactor (Pocket I), the piperidine ring of **6** only partially filled Pocket II, suggesting that larger groups would be tolerated in this region and might increase potency. The low MW of **6** (263 da) also permitted additional substitution on the molecule, although the high clog $D_{7.0}$ (calculated log D at pH 7.0) and low PSA (polar surface area) of the molecule dictated that polar substituents would be required to improve the solubility and drug-likeness of the compounds synthesized.[24–26] The medicinal chemistry program commenced with the synthesis of a small library of 2-adamantyl carbamates of readily available pyrrolidines and piperidines which included **9a** (Scheme 1).

The synthesis of analogs **9a**–**i** is depicted in Scheme 1. 2-Adamantyl alcohol **7** was converted to its chloroformate by treatment with triphosgene in the presence of pyridine and reacted with (3*R*)-(3-*t*-butoxycarbonylamino)pyrrolidine to afford carbamate **9a**. Removal of the Boc group, followed by acylation of the resulting amine, gave analogs **9b**–**g**. Alternatively, the BocNH group of **9a** was alkylated with MeI or BnBr to afford **9h** and **9i**, respectively.

Similar chemistry was employed to prepare analogs of general structure **10** in which the adamantane ring system was substituted at the 5-position (Scheme 2). The *E* and *Z* adamantane isomers were separated by preparative HPLC to afford **10a**–**c**. In all cases, the desired *E* isomer had a longer retention time on reverse phase HPLC. The chemical shift of the proton on the oxygen-substituted carbon of the adamantane in the *E* isomer was downfield by ~0.03 ppm compared to the *Z* isomer. The assignment of the *E* geometry was subsequently confirmed when X-ray structures of **11k** and **11l** bound to 11β-HSD1 were obtained (data not shown).



Scheme 1. Synthesis of compounds **9** and **10**. For complete substituent definitions see Tables 1 and 3. Reagents and conditions: (a) triphosgene, pyridine, CH_2Cl_2, 0–5 °C, 3 h; (b) (3*R*)-(3-*t*-butoxycarbonylamino)pyrrolidine, *i*-Pr2NEt, CH_2Cl_2, 0 °C→rt, 16 h; (c) preparative HPLC (X ≠ H); (d) 4 M HCl in dioxane, CH_2Cl_2, rt, 1 h or 1:4 TFA/CH_2Cl_2, rt, 1 h; (e) R^1COCl, *i*-Pr_2NEt, CH_2Cl_2, 0 °C→rt; (f) MeI or BnBr, NaH, DMF; (g) $LiBH_4$ to give **10d**; (h) MeMgBr to give **10e**; (i) LiOH, H_2O, MeOH followed by NH_3 in dioxane, EDC, HOBt, *i*-Pr_2NEt, CH_2Cl_2, 0 °C→rt, 16 h to give **10f**; (j) $(CF_3CO)_2O$, pyridine, CH_2Cl_2, 0 °C to rt.



Scheme 2. Methods for the synthesis of compounds of general structure **11**. See Table 4 for definitions of Het. Reagents and conditions: (a) HCl, dioxane, CH_2Cl_2, rt, 1 h; (b) Het-X, *i*-Pr_2NEt, *n*-PrOH, Δ, microwave; (c) 5-(methoxycarbonyl)-2-adamantyl chloroformate, *i*-Pr_2NEt, CH_2Cl_2, 0 °C to rt; (d) LiOH, H_2O, MeOH, rt, 16 h; (e) NH_3 in dioxane, EDC, HOBt, *i*-Pr_2NEt, CH_2Cl_2, 0 °C→rt, 16 h; (f) preparative HPLC.

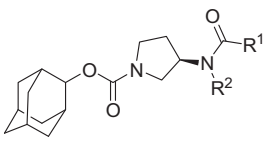
Reduction of ester **10c** with $LiBH_4$ led to primary alcohol **10d**, while treatment with excess MeMgBr gave tertiary alcohol **10e**. Hydrolysis of the ester, followed by EDC coupling with ammonia, gave carboxamide **10f**. Analog **10g**, the (*S*) isomer of **10f**, was prepared in the same fashion employing (3*S*)-(3-*t*-butoxycarbonylamino)pyrrolidine. Dehydration of **10f** afforded nitrile **10h**.

Analogs of general structure **11** were prepared by two closely related methods (Scheme 2). Removal of the Boc group from **10f**, followed by S_NAr reaction of the primary amine with electron deficient haloheterocycles gave **11** (Method A, Scheme 2). Alternatively, Boc protected 3-aminopyrrolidine **12** was reacted with a haloheterocycle under S_NAr conditions and deprotected to afford a 3-(heterocyclylamino)pyrrolidine **13** which was reacted with 1-(methoxycarbonyl)-4-adamantyl chloroformate. Ester hydrolysis and carboxamide preparation, followed by preparative HPLC to separate the *E* and *Z* adamantane isomers, gave target compounds **11** (Method B, Scheme 2). Analogs with the (*S*) stereochemistry at the 3-position of the pyrrolidine ring were prepared from **10g** following Method A or from the (*S*) isomer of **12** following Method B.

The first phase of the medicinal chemistry program led to the identification of **9a** (Table 1) which had superior enzyme and cell potency to the prototype compound **6**. The presence of additional polar atoms in **9a** was considered to be an attractive feature although the plasma shift was only marginally reduced compared to **6**, and metabolic stability remained poor (Table 2).

Replacement of the *t*-butoxy group in **9a** with smaller alkoxy groups (**9b**–**d**) reduced the enzyme potency. The isobutoxy compound **9e** was equiactive, while the benzyloxy compound **9f** was less active. A more substantial reduction in activity occurred when the ether oxygen of the *t*-butoxy group in **9a** was replaced with a CH_2 group to give amide **9g**. These results suggested that the *t*-butoxy group is optimal at R^1 and that the ether oxygen plays an important role. N-methylation (**9h**) was well tolerated, while N-benzylation (**9i**) reduced potency.

Table 1
Carbamates **9**



Compound	R1	R^2	Enzyme IC_{50}[a] (nM)	Adipocyte IC_{50}[a] (nM)
6			5	53
9a	O*t*-Bu	H	2.7	15.2
9b	OEt	H	12.0	65.5
9c	O*i*-Pr	H	6.4	36.3
9d	O*n*-Pr	H	5.4	40.2
9e	O*i*-Bu	H	2.0	19.2
9f	OBn	H	9.0	84.8
9g	CH_2*t*-Bu	H	68	—
9h	O*t*-Bu	Me	2.9	24.7
9i	O*t*-Bu	Bn	15.3	290

[a] See Ref. 32.

Table 2
Calculated physical properties and biological data for selected compounds

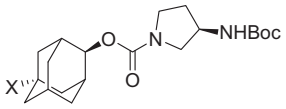
Compound	MW (da)	$clogD_{7.0}$[a]	PSA[a] (Å^2)	Plasma shift[b]	RLM $t_{1/2}$[c] (min)
6	263	3.4	30	28.4	2
9a	365	3.2	68	20.9	2
10f	408	1.9	111	1.2	30
11k	409	1.4	121	2.7	>60
11l	409	1.4	121	2.2	46

[a] Calculated using Pipeline Pilot, Accelrys, San Diego, CA.
[b] Ratio of enzyme IC_{50} measured in the presence and absence of 50% human plasma.
[c] RLM $t_{1/2}$ is rat liver microsome half life. See Ref. 33.

Changes to the substituent on the pyrrolidine ring initially failed to identify analogs with improved potency over **9a** and rapid metabolism of **9a** was shown to occur predominantly on the adamantyl ring system. Therefore, we turned our attention to modifications of the adamantane ring. Amides of 2-aminoadamantane have previously been studied as inhibitors of 11β-HSD1.[23,27–30] In these molecules, polar substituents at the *trans*-5-position of the adamantane ring were reported to be compatible with potency while improving metabolic stability.[29] Hydroxyadamantyl analog **10a** retained comparable enzyme and cell potency to **9a**, while acetamido analog **10b** was 6× less active (Table 3). Ester **10c** was 100× less potent than **9a**. Primary alcohol **10d** regained considerable enzyme potency; however, tertiary alcohol **10e** had little activity. The carboxamide group in **10f** improved cell potency to 7.5 nM. Compound **10g**, the (*S*) isomer of **10f**, was 2–3× less potent in cells than **10f**. Nitrile **10h** was also 3× less potent in cells than **10f** from which it was derived.

Compound **10f** exhibited a reduction in clog $D_{7.0}$ and an increase in PSA compared to both **9a** and the original carbamate **6** (Table 2). Compound **10f** was selected for further evaluation in vitro. The compound suffered <2× loss in enzyme potency in the presence of 50% human plasma, had an improved RLM $t_{1/2}$, and exhibited a selective profile with IC_{50} values for the hydroxysteroid dehydrogenases 11β-HSD2, 3β-HSD2 and 17β-HSD1 of >10,000 nM. Its EC_{50} values against FXR and GR were >10,000 nM, and its IC_{50} values on CYP3A4, CYP2C9 and CYP2D6 were all >30,000 nM. Despite these desirable features, **10f** was deemed to have inadequate adipocyte potency.

Table 3
Substituted adamantyl compounds **10**



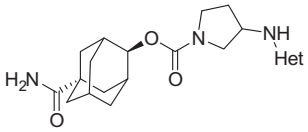
Compound	X	Enzyme IC_{50}[a] (nM)	Adipocyte IC_{50}[a] (nM)
9a	H	2.7	15.2
10a	OH	3.8	15.7
10b	NHAc	15.7	66.9
10c[b]	CO_2Me	289	>100
10d	CH_2OH	5.8	26.5
10e	CMe_2OH	98.0	>100
10f	$CONH_2$	3.4	7.5
10g[c]	$CONH_2$	4.4	17.6
10h	CN	7.4	24.1

[a] See Ref. 32.
[b] 1:1 *E*/*Z* mixture.
[c] (*S*) isomer of **10f**.

In a further effort to improve the cellular potency of **10f**, we reinvestigated substituents on the pyrrolidine ring by replacing the *t*-butoxycarbonyl group with heterocycles. A 2-pyrimidinyl group was initially selected since it recapitulates many of the hydrogen bond accepting features of the *t*-butoxycarbonyl group. Compound **11a**, the first analog prepared, suffered a 2× loss in cellular potency compared to **10f** (Table 4); however, the regioisomeric 4-pyrimidinyl compound **11b** demonstrated potency equivalent to **10f**. Replacement of the electron withdrawing CF_3 group in **11b** with dimethyl substituents (**11c**) reduced enzyme potency by 10×. These results led us to focus on CF_3 substituted heterocycles.

Replacement of the pyrimidine ring with a CF_3 substituted 1,3,4-thiadiazole (**11d**) reduced potency; however, three of the four isomeric trifluoromethylpyridyl analogs (**11e**, **11g** and **11h**) had enzyme potency <1 nM and cellular potency <5 nM. Compounds with the (*S*) stereochemistry on the pyrrolidine ring were also investigated: **11i** and **11j** had comparable enzyme and cellular potency to epimers **11e** and **11g**. Analogs with cellular IC_{50} <5 nM were further profiled for metabolic stability in rat liver microsomes (RLM) and for inhibition of selected CYP isozymes (Table 5). Half lives in the presence of RLM varied considerably with **11j** emerging as the only trifluoromethylpyridyl compound with $t_{1/2}$ >60 min. All the trifluoromethylpyridyl compounds profiled had unacceptable IC_{50} values of <10 μM against CYP3A4 with the exception of **11j**.

Table 4
Heteroaryl compounds **11**



Compound	Het	Stereo	Enzyme IC_{50}[a] (nM)	Adipocyte IC_{50}[a] (nM)
11a	4-CF_3-2-pyrimidinyl	R	5.2	16.4
11b	2-CF_3-4-pyrimidinyl	R	1.9	7.0
11c	2,6-diMe-4-pyrimidinyl	R	20.7	>100
11d	5-CF_3-2-(1,3,4-thiadiazolyl)	R	21.3	>100
11e	3-CF_3-2-pyridyl	R	0.55	1.1
11f	4-CF_3-2-pyridyl	R	3.1	14. 7
11g	5-CF_3-2-pyridyl	R	0.82	5.0
11h	6-CF_3-2-pyridyl	R	0.67	1.4
11i	3-CF_3-2-pyridyl	S	0.63	0.5
11j	5-CF_3-2-pyridyl	S	0.74	2.7
11k	3-CN-2-pyridyl	R	0.87	0.4
11l	5-CN-2-pyridyl	R	1.5	2.7
11m	3-CN-2-pyridyl	S	2.6	7.6
11n	5-CN-2-pyridyl	S	1.7	5.2

[a] See Ref. 32.

Table 5
Metabolic stability and CYP inhibition of heteroaryl compounds **11**

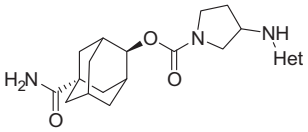
Compound	RLM $t_{1/2}$[a] (min)	CYP3A4 IC_{50} (nM)	CYP2C9 IC_{50} (nM)	CYP2D6 IC_{50} (nM)
7	2	>30,000	22,000	>30,000
9a	2	>30,000	11,400	>30,000
10f	30	>30,000	>30,000	>30,000
11e	30	3300	9400	—
11g	47	7200	4100	11,600
11h	7	4800	2400	5900
11i	11	8500	8000	>30,000
11j	>60	10,300	2400	11,600
11k	>60	17,100	>30,000	>30,000
11l	46	14,200	23,100	25,000
11m	25	18,600	>30,000	>30,000
11n	25	26,600	20,000	16,600

[a] See Ref. 33.

Replacement of the trifluoromethyl substituent in **11e** and **11g** with the more polar, but still electron withdrawing, cyano group gave **11k** and **11l**, respectively. The cyano group improved adipocyte potency (Table 4), maintained good metabolic stability, and reduced CYP inhibition (Table 5). The (*R*) isomers **11k** and **11l** were more potent and stable in RLM than the corresponding (*S*) isomers **11m** and **11n** (Table 5); thus, the (*R*) isomers were selected for further characterization.

Compounds **11k** and **11l** had drug-like clog $D_{7.0}$ and PSA values (Table 2), and desirable in vitro and in vivo profiles. They experienced <3× loss in potency when assayed in the presence of 50% human plasma and exhibited >1000× selectivity over three other hydroxysteroid dehydrogenases, including 11β-HSD2 (Table 6). Despite their stability in RLM, both compounds experienced mod-

Table 6
In vitro characterization of **11k** and **11l**



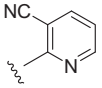
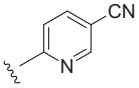
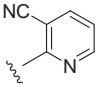
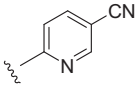
Het		 **11k**	 **11l**
Enzyme + plasma IC_{50}	(nM)	2.4	3.2
11β-HSD2 IC_{50}	(nM)	7350	8650
3β-HSD2 IC_{50}	(nM)	>10,000	>10,000
17β-HSD1 IC_{50}	(nM)	>10,000	>10,000
Rat hepatocyte CL	(mL/min/kg)	41	33

Table 7
Rat pharmacokinetics of **11k** and **11l**[a]

Het		 **11k**	 **11l**
IV AUC	(nM h)	398	209
V_{ss}	(L/kg)	0.70	2.2
MRT disp	(h)	0.3	0.5
IV CL	(mL/min/kg)	42	80
F	(%)	42	27

[a] IV dose = 1 μmol/kg, PO dose = 5 μmol/kg.

erate clearance in cultured rat hepatocytes. Both **11k** and **11l** were orally bioavailable. The IV clearance of **11k** in rat was consistent with clearance in rat hepatocytes suggesting that metabolism is the major mechanism of clearance; however, **11l** was cleared more rapidly in vivo than predicted from its in vitro data, suggesting that mechanisms other than metabolism were operative (Table 7).

We have described the optimization of **6**, a hydrophobic molecule with good enzyme potency but poor metabolic stability, into **11k** and **11l** with moderate lipophilicity, improved enzyme and cellular potency, reduced plasma shift[31] and improved metabolic stability. These two compounds are selective over three related hydroxysteroid dehydrogenases, do not inhibit CYP isozymes commonly involved in drug metabolism, and are orally bioavailable in rat.

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32. Compounds were assayed for inhibition of 11β-HSD1 in enzyme- and cell-based assays. Both assays measured the conversion of [^{3}H]-cortisone to [^{3}H]-cortisol, which was quantified using SPA beads and a microscintillation plate reader.[32] Biochemical assays used recombinant 11β-HSD1 isolated as a microsomal preparation from transfected CHO cells. Assays were performed in 25 mM HEPES, pH 7.4, 50 mM KCl, 2.5 mM NaCl, 1 mM $MgCl_2$, 1 mM NADPH and 80 nM [^{3}H]-cortisone at room temperature for 1 h. Cell-based potency was assessed in differentiated human adipocytes by the addition of cortisone (80 nM [^{3}H]-cortisone) followed by incubation at 37 °C for 2 h. IC_{50} values represent the mean of at least duplicate assays and were generated from an 8-point dose–response curve. Solly, K.; Mundt, S. S.; Zokian, H. J.; Ding, G. J.-F.; Hermanowski-Vosatka, A.; Strulovici, B.; Zheng, W. *Assay Drug Dev. Technol.* **2005**, *3*, 377.
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