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Discovery of adamantane ethers as inhibitors of 11β-HSD-1: Synthesis and biological evaluation

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Abstract—A novel class of adamantane ethers 11β-hydroxysteroid hydrogenase type I inhibitors has been discovered. These compounds have excellent HSD-1 potency and selectivity against HSD-2. The structure–activity relationships, selectivity, metabolism, PK, ex vivo pharmacodynamic data, and an X-ray crystal structure of one of these inhibitors bound to h-HSD-1 are discussed.

The combination of risk factors for cardiovascular disease such as insulin resistance, dyslipidemia, obesity, and hypertension is referred to as metabolic syndrome.[1] Glucocorticoids (GCs) are important regulators of glucose and lipid homeostasis. At the cellular level, GCs bind to the glucocorticoid receptor and activate, or repress, downstream target genes leading to increased hepatic glucose production and lipolysis in adipose tissue. GCs circulate in an active (cortisol in humans, corticosterone in rodents) and an inactive form (cortisone in humans, dehydrocortisone in rodents). Conversion between two forms is catalyzed by the enzymes 11β-hydroxysteroid dehydrogenase type-1 (11β-HSD-1) and type-2 (11β-HSD-2). While 11β-HSD-1 reduces cortisone to cortisol and is highly expressed in liver and adipose tissue, 11β-HSD-2 oxidizes cortisol to cortisone and is primarily expressed in the kidney.[2–4]

The hypothesis that the inhibition of 11β-HSD-1, mediated GC amplification may be therapeutically relevant for metabolic syndrome is supported by rodent experiments.[5,6] Improved hepatic insulin sensitivity and lipid profiles were observed in 11β-HSD-1 knockout mice. It is expected that the inhibition of 11β-HSD-1 in the liver and fat will improve glucose and lipid metabolism disorders.

Multiple classes of 11β-HSD-1 inhibitors have been reported.[7–12] Potent and selective inhibitors of human 11β-HSD-1 have been discovered recently.[13] These compounds have excellent potency against human 11β-HSD-1 and selectivity over 11β-HSD-2, but frequently lack the desired rodent potency against m-11β-HSD-1 and selectivity over m-11β-HSD-2, for preclinical evaluation.

We sought to discover compounds with improved potency (<30 nM) and selectivity (>100-fold) in rodents. We have identified adamantane aryl ethers as potent and selective inhibitors of human and mouse 11β-HSD-1, and report their optimization in this paper.

Reductive amination of adamantane ketone **1** gave an amine intermediate, which was acylated to give amide **2** as a mixture of trans- and cis- isomers (4:1, Scheme 1). The trans-isomer was isolated by chromatography and was treated with oleum and formic acid, followed by

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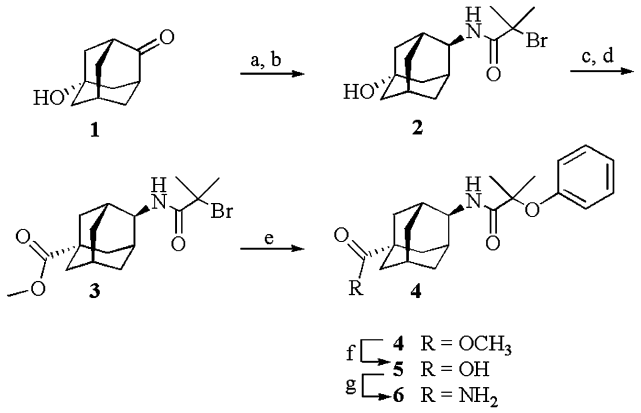
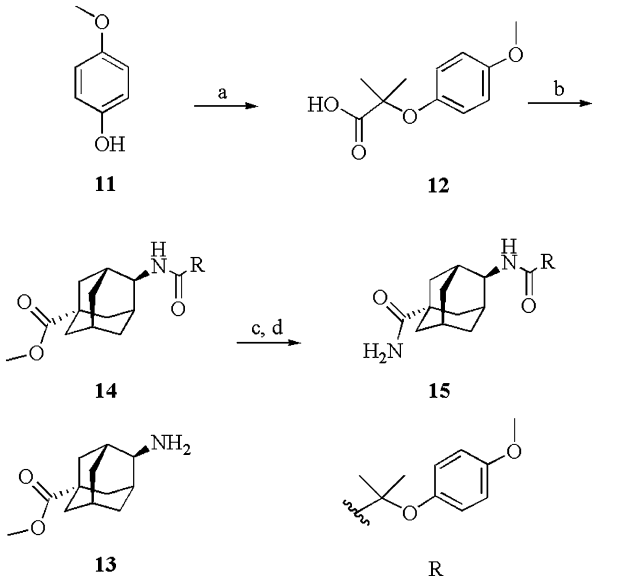


Scheme 1. Reagents and conditions: (a) i—NH_4OH, CH_3OH, rt; ii—$NaBH_3$, rt, 98%; (b) 2-bromo-2-methylpropanoyl bromide, TEA, DCM, rt, 48%; (c) oleum, formic acid, 60 °C, 71%; (d) $SOCl_2$, CH_3OH, 0 °C, 83%; (e) phenol, NaH, toluene, 100 °C, 29%; (f) NaOH, THF, EtOH, H_2O, rt, 97%; (g) 30% NH_4OH, EDAC, HOBT, DCM, rt, 57%.



Scheme 2. Reagents and conditions: (a) 1,1,1-trichloro-2-methylpropan-2-ol, NaOH, acetone, rt, 65%; (b) **13**, TBTU, DIEA, DMF, rt, 87%; (c) NaOH, THF, EtOH, H_2O, rt, 90%; (d) 30% NH_4OH, EDAC, HOBT, DCM, rt, 85%.

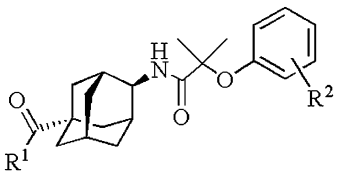
thionyl chloride and methanol, to yield the bromide **3**. Phenol was pretreated with sodium hydride then bromide **3** was added and reaction mixture was heated to provide ether **4**. The ester in **4** was hydrolyzed to provide acid **5**, which was then converted into amide **6**. Compounds with substituted aryl ether (**7**–**10**, Table 1) were synthesized using these procedures as exemplified by **5** and **6**.

In some cases, the O-alkylation (using bromide **3**) as described above gave poor yields. In these cases, the acids like **12** were prepared (Scheme 2).[14] Amine **13** was synthesized by reductive amination of 4-oxo-adamantane-1-carboxylic acid followed by esterification. Coupling of **12** and **13** provided ester **14**, which was then hydrolyzed and the resulting acid was converted into the amide **15**.

Secondary amides were synthesized as shown in Scheme 3. Acid **9** and methyl 4-(aminomethyl)benzoate were coupled using TBTU and DIEA, and the resulting ester was hydrolyzed to furnish acid **16**. Further condensation with methyl sulfonamide yielded acylsulfonamide **17**. Similarly, acid **9** and 4-(aminomethyl)benzonitrile were coupled to yield an intermediate nitrile, which was further reacted with sodium azide and triethylamine hydrochloride to provide tetrazole **18**. Compounds **19**–**22** were synthesized by similar procedures.

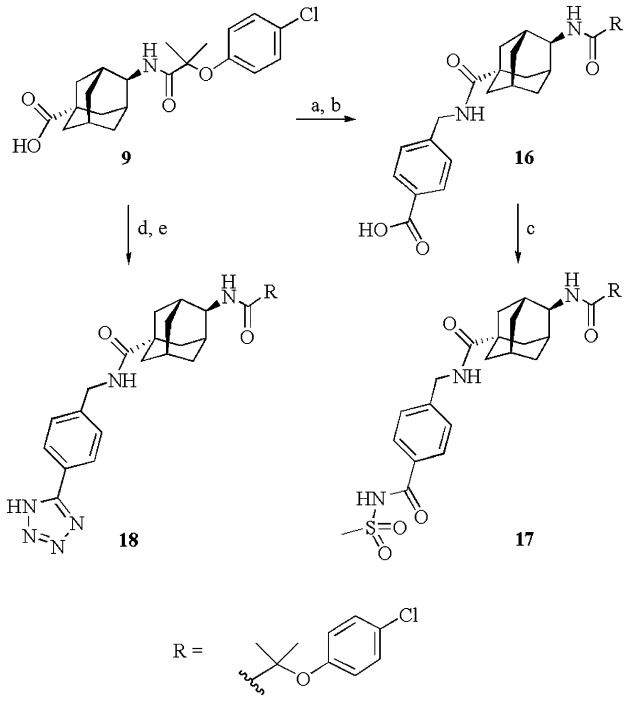
Synthesis of compounds prepared in an effort to replace primary amide at C-5 of the adamantane is shown in Scheme 4. Acid **9** was converted to amide **23** and was also reduced to alcohol **24**, which was alkylated to afford acid **25**. The amide **10** was dehydrated and the intermediate nitrile was converted to tetrazole **26** using sodium

Table 1. In vitro inhibition and metabolic stability data for **5**–**10** and **15**

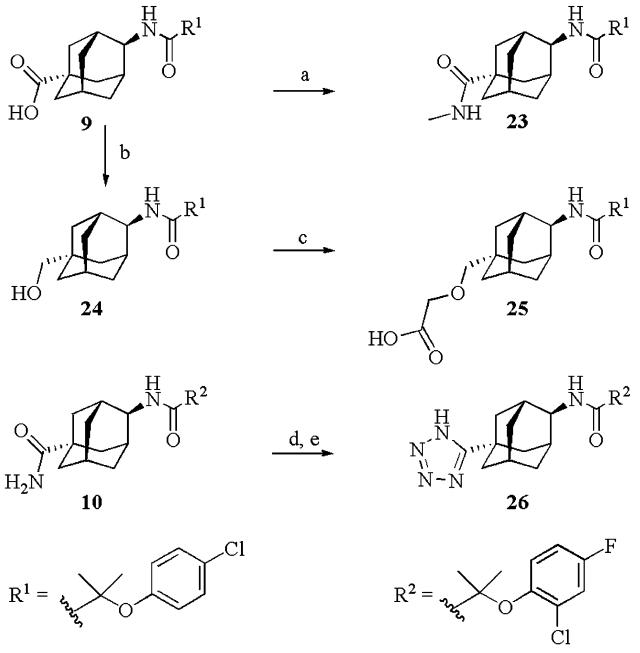


Compound	R^1	R^2	h-HSD-1 IC_{50}[a] (nM)	h-HSD-2 IC_{50}[a] (nM)	m-HSD-1 IC_{50}[a] (nM)	m-HSD-2 IC_{50}[a] (nM)	h-HSD-1 HEK IC_{50}[a] (nM)	Microsomal stability[b]
5	OH	H	39	17,000	119	1500	840	98
6	NH_2	H	5	23,000	4	40,000	24	78
7	OH	2-Cl	8	1800	8	140	59	94
8	OH	3-Cl	15	3500	51	540	190	100
9	OH	4-Cl	22	30,000	70	1700	220	89
10	NH_2	4-Cl	6	12,000	3	40,000	22	43
15	NH_2	4-OCH_3	6	18,000	4	55,000	21	57

[a] Values are means of at least two experiments.
[b] % remaining by HPLC analysis after a 30 min incubation with mouse liver microsomes.



Scheme 3. Reagents and conditions: (a) methyl 4-(aminomethyl)benzoate, TBTU, DIEA, DMF, rt, 84%; (b) NaOH, THF, EtOH, H_2O, rt, 80%; (c) methyl sulfonamide, DMAP, EDAC, DMF, rt, 53%; (d) 4-(aminomethyl)benzonitrile, TBTU, DIEA, DMF, rt, 80%; (e) NaN_3, NMP, $Et_3N{\cdot}HCl$, 150 °C to rt, 52%.



Scheme 4. Reagents and conditions: (a) CH_3NH_2, TBTU, DIEA, DMF, rt, 55%; (b) $BH_3{\cdot}THF$, THF, 65 °C, 20%; (c) ethyl 2-iodoacetate, KOH, DMSO, 70 °C, 16%; (d) $(CF_3CO)_2O$, pyridine, dioxane, rt, 58%; (e) NaN_3, Me_3SnCl, toluene, 120 °C, 59%.

azide. Compounds **27** and **28** were synthesized by procedures similar to acylsulfonamide **17**.

Inhibition of human and mouse 11β-HSD-1 and 11β-HSD-2 enzymatic activity was determined by scintillation proximity assay (SPA).[15] Cellular activity of the compounds was evaluated in a HEK293 HSD-1 FPIA assay and metabolic stability was determined using mouse liver microsomes.[15]

Table 1 shows the biological activity of the aryl ether adamantanes. In general, aliphatic or alicyclic ethers had comparable potency to aryl ethers but their metabolic stability was poor (data not shown). Aryl ethers with an acidic adamantane group (**5** and **7**–**9**) were generally less potent in the cellular assay and less selective over m-HSD-2. They did show excellent metabolic stability. Primary amide adamantanes (**6**, **10**, and **15**) had excellent potency and selectivity compared to the parent acids. However, they had lower metabolic stability. Compound **7**, with ortho substitution on the phenyl ring was more potent than the meta and para analogs but showed loss of selectivity over mouse HSD-2.

An X-ray crystal structure of human 11β-HSD1 with **15** was obtained (PDB code 2IRW).[16] Comparison with previously determined structures of h-11β-HSD-1 reveals that the inhibitor **15** is bound in the steroid-binding site neighboring the bound cofactor $NADP^+$.[17] The adamantyl moiety of **15** is located near the nicotinamide portion of the cofactor and the primary amide is positioned close to the pyrophosphates of the $NADP^+$. The central amide of **15** interacts with the active site residues, where the carbonyl is within 2.8 Å and 2.9 Å from the hydroxyl groups of Ser170 and Tyr183, respectively. The gem-dimethyl and ether-linked phenyl groups extend into the hydrophobic cavity of the steroid-binding site, where Tyr177 forms the base of the pocket. The close packing around the phenyl moiety of the inhibitor suggests the protein may adopt different conformations to accommodate compounds with substituents at different positions of the aromatic ring (Fig. 1).

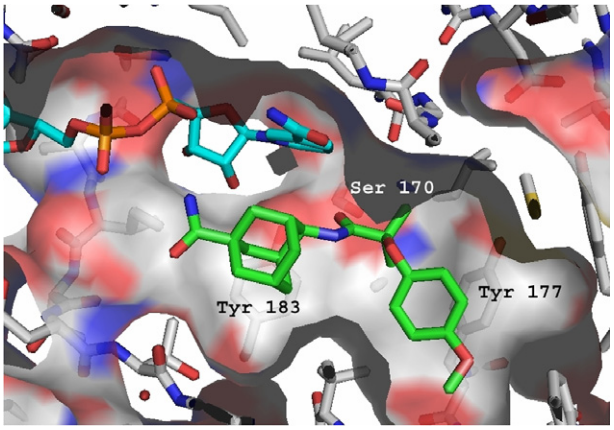
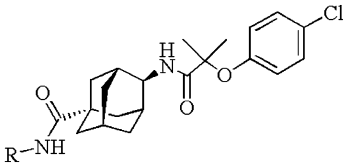


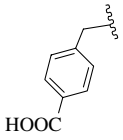
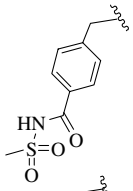
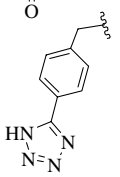
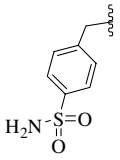
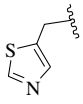
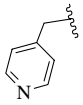
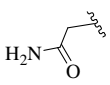
Figure 1. Crystal structure of h-11β-HSD-1 with compound **15**. Atoms are colored according to atom type and the components differ by carbon atom colors: the protein is gray, the NADP+ cofactor is cyan, and compound **15** is green. The protein surface is also colored according to atom color.

Plasma hydrolysis of the primary amide group at C-5 of the adamantane has been observed in the compounds similar to **15** (data not shown). We designed secondary amides (Table 2) to slow or halt the plasma hydrolysis. The crystal structure of **15** with the enzyme also suggests that extending off of the primary amide with aryl or heterocyclic groups could be accommodated.

Typically, secondary amides with a 1-carbon spacer between the terminal group and the amide were most promising. Acid **16** showed an excellent in vitro profile and microsomal stability, but is subject to phase II metabolism of the free carboxyl group. Therefore, compounds **17**–**19** with acid mimetic groups were prepared. However, they showed a decline in microsomal stability and cellular activity. Metabolic stability was significantly reduced in heterocycles such as **20** and **21**. Amide **22** showed excellent in vitro potency with a moderate decline in metabolic stability, while *N*-methylamide (**23**) showed decreased cellular activity.

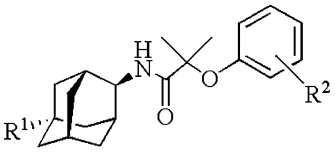
Table 2. Secondary amides: in vitro inhibition and metabolic stability data for **16**–**23**



Compound	R	h-HSD-1 IC_{50}[a] (nM)	h-HSD-2 IC_{50}[a] (nM)	m-HSD-1 IC_{50}[a] (nM)	m-HSD-2 IC_{50}[a] (nM)	h-HSD-1 HEK IC_{50}[a] (nM)	Microsomal stability[b]
16		15	20,000	12	5800	59	94
17		25	50,000	25	10,000	310	51
18		16	26,000	18	6200	690	51
19		51	>30,000	24	16,000	300	35
20		27	13,000	11	21,000	92	5
21		25	5300	14	19,000	91	16
22		12	20,000	4	90,000	120	78
23	CH_3NHCO	13	12,000	8	16,000	210	NT

[a] Values are means of at least two experiments.
[b] % remaining by HPLC analysis after a 30 min incubation with mouse liver microsomes (NT, not tested).

Table 3. Primary amide replacement: in vitro inhibition and metabolic stability data for **24**–**28**



Compound	R^1	R^2	h-HSD-1 IC_{50}[a] (nM)	h-HSD-2 IC_{50}[a] (nM)	m-HSD-1 IC_{50}[a] (nM)	m-HSD-2 IC_{50}[a] (nM)	h-HSD-1 HEK IC_{50}[a] (nM)	Microsomal stability[b]
24	CH_2OH	4-Cl	9	25,000	6	>100,000	53	19
25	$CH_2OCH_2CO_2H$	4-Cl	110	>100,000	210	45,000	670	100
26		2-Cl-4-F	11	550	10	1200	54	87
27	CH_3SO_2NHCO	2-Cl	96	580	28	1200	744	94
28	$PhSO_2NHCO$	2-Cl	500	NT	1000	NT	NT	NT

[a] Values are means of at least two experiments, (NT, not tested).
[b] % remaining after a 30 min incubation with mouse liver microsomes (NT, not tested).

Table 4. Ex vivo pharmacodynamic data for selected compounds

Compound	% inhibition in liver 1 h/7 h/16 h	% inhibition in fat 1 h/7 h/16 h	% inhibition in brain 1 h/7 h/16 h	Dose (mg/kg)
7	81/76/35	67/47/6	ND	30
16	99/93/77	37/38/36	ND	30
19	45/55/58	15/18/5	0/0/18	30

ND, not determined.

In an effort to improve overall profile of our compounds, we replaced the primary amide group on C-5 of the adamantane with extended acid, acid mimetics, and electron donating groups (Table 3). Compound **24** with the hydrogen donating hydroxymethyl group had comparable potency to the primary amide, but lacked metabolic stability. Compound **25** with a free carboxylic acid group was potent but had poor cellular activity. Acid mimetic groups like tetrazole and methylacylsulfonamide led to potent and metabolically stable compounds (**26** and **27**, respectively) with the loss of the selectivity over human HSD-2, while the phenylacylsulfonamide **28** showed a significant loss of HSD-1 activity. These data indicate that compounds like **10** with a primary amide group have the best overall profile.

In order to identify compounds for efficacy studies, selected compounds were advanced to ex vivo pharmacodynamic and PK studies (Tables 4 and 5). In the ex vivo pharmacodynamic assay, the compounds were administered as a single oral dose to *ob*/*ob* mice.[15,18] Inhibition of 11β-HSD-1 in liver, fat, and brain tissues was measured. We were looking for compounds with strong inhibition in the liver and fat at 7 and 16 h post-dose. Acids **7** and **16** exhibited moderate inhibition in liver and fat after 7 h. Sulfonamide **19**, with an acid mimetic group, had an interesting profile. It showed moderate inhibition in the liver but did not show significant inhibition in the fat or brain.

Table 5. Mouse PK data[a] for selected compounds

Compound	nAUC (μg h/mL)	CLp (L/h/kg)	$t_{1/2}$ (h)	F (%)
7	5.8	0.9	3.9	100
10	1.2	4.2	0.3	20
19	5.7	0.9	3.8	44

[a] Calculated from 5 mg/kg IV and 10 mg/kg oral dosing.

Compound **7** showed an excellent PK profile, which correlated its activity in ex vivo assay. Primary amide **10** had high clearance, short half-life, and low bioavailability. When the primary amide group in **10** was replaced with a secondary amide containing an acid mimetic group (**19**), bioavailability increased leading to an improved PK profile (Table 5, entry 3).

We have discovered adamantane ethers as potent and selective inhibitors of human and mouse 11β-HSD-1. Our SAR indicates that the primary amide group at the C-5 of adamantane is optimal. We have introduced secondary amides with large groups at C-5 of the adamantane to provide potent and selective inhibitors of human and mouse 11β-HSD-1. However, the resulting compounds have lower metabolic stability or cellular potency than the primary amides. We have been successful in aquiring the crystal structure of amide **15** bound to the active site of h-11β-HSD-1 enzyme, which will be helpful in the design of future analogs with the improved PK and PD profiles.

Acknowledgments

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constructs used in the crystallography experiments. We thank Dr. Lan Gao and Mr. Steve Cepa for the LC/MS measurement of cortisol in ex vivo activity assay. Robin Shapiro, Brian Droz, Tom Fey, Victoria Knourek-Segal, and Kelly Larson are thanked for their assistance with the ex vivo experiments. Dr. Dan Plata is acknowledged for process chemistry support.

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16. Recombinant protein was expressed as described in Ref. 17 and the protein was purified in the presence of inhibitor **15.** The protein-inhibitor complex was crystallized by the vapor diffusion method using 2.0 M ammonium sulfate, 0.1 M sodium citrate (pH 5.6), and 0.2 M K/Na tartrate. X-ray data were collected to 3.1 Å resolution, and molecular replacement with refinement revealed electron density for the cofactor NADP+ and compound.
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