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Adamantane 11-β-HSD-1 inhibitors: Application of an isocyanide multicomponent reaction

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Abstract—A series of potent and selective adamantane aminoamide 11-β-HSD-1 inhibitors has been optimized. Chemically these studies were expedited by utilizing readily obtained amino acids as starting materials or an isocyanide multicomponent reaction. Structure–activity relationship studies resulted in the discovery of dual human and mouse 11-β-HSD-1 potent and selective inhibitors like adamantane **11** and related compounds with high metabolic stability and robust pharmacokinetic profiles.

Patients with Cushing's syndrome have elevated circulating glucocorticoid levels that cause a variety of abnormalities including central/visceral obesity, insulin resistance, hyperglycemia, and dyslipidemia amongst others. The similarity of these symptoms to those observed in patients with metabolic syndrome, diabetes, and obesity have led numerous investigators to target the glucocorticoid axis for research and potential therapy. Recent research has focused on 11-β-hydroxysteroid dehydrogenase 1 (11-β-HSD-1) which is found primarily in the liver, fat, and brain.[1] 11-β-HSD-1 catalyzes the reduction of the glucocorticoid receptor (GR) inactive 11-keto glucocorticoid cortisone to the corresponding active glucocorticoid cortisol. The prereceptor metabolism performed by this enzyme is responsible for increasing local glucocorticoid levels relative to circulating concentrations. Inhibitors of 11-β-HSD-1 are being examined as a potential treatment for metabolic syndrome, diabetes, obesity, and other indications and are currently under intense investigation. 11-β-HSD-2 is a related enzyme that catalyzes the reverse reaction. It is found primarily in mineralocorticoid sensitive tissues, like the kidney, where it lowers local glucocorticoid concentrations to prevent cortisol from activating mineralocorticoid receptors. Inhibition of this enzyme leads to high blood pressure and other deleterious consequences necessitating selectivity against this dehydrogenase.

Multiple classes of 11-β-HSD-1 inhibitors have been discovered (Fig. 1).[2] Many of the early examples are steroids like carbenoxolone (**1**), that are typically unselective and inhibit 11-β-HSD-2 as well.[3] In terms of 11-β-HSD-1 selective compounds, multiple nonsteroidal inhibitors have been discovered. This includes sulfonamides such as BVT.2733 (**2**),[4] triazoles like 544 (**3**),[5] and adamantanes such as **4**.[6] We have optimized a series of adamantane amides as 11-β-HSD-1 inhibitors.[6] During our initial studies we learned that the substituents R^2 and R^3 had a dramatic effect upon cross species potency, particularly in rodents. Therefore, we set out to explore the SAR at this position and to discover simple methods to prepare a diverse set of analogs. Two strategies in particular were explored. Building the central α-amino amide portion from amino acids and by a multicomponent reaction.

Keywords: 11-β-HSD-1 inhibitors; Adamantane; Multicomponent reaction; Metabolism; HSD1 inhibitor; Hydroxysteroid dehydrogenase type 1; Metabolic syndrome.
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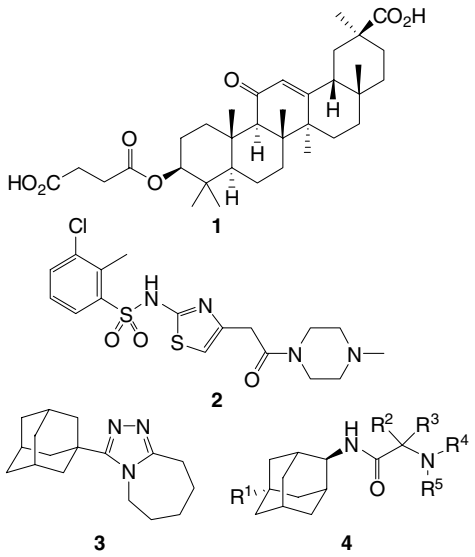
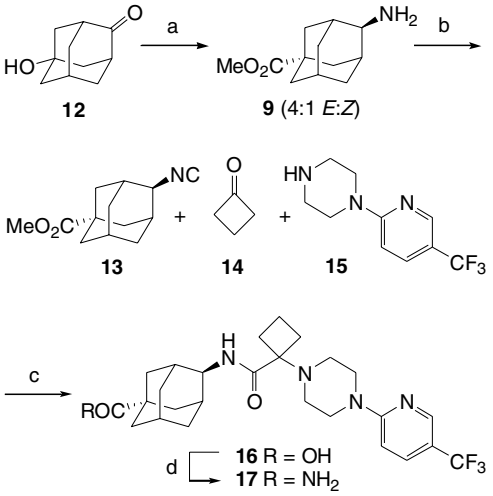


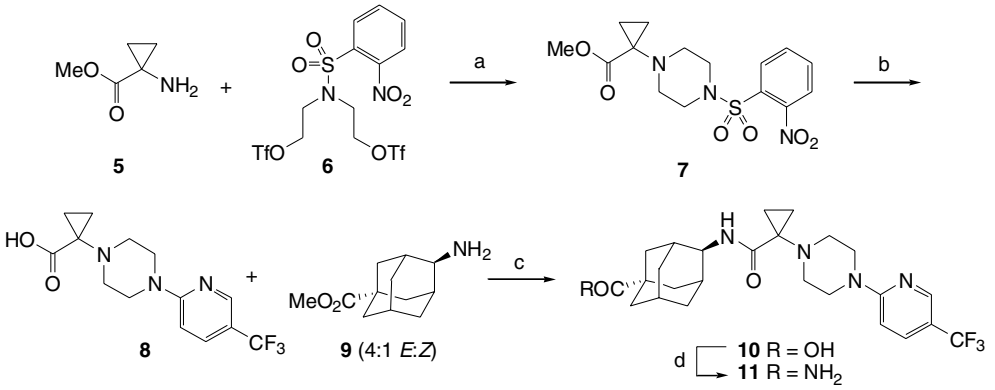
Figure 1. Inhibitors of 11-β-HSD1: carbenoxolone (**1**), BVT.2733 (**2**), Merck compound 544 (**3**), and adamantanes **4**.

In addition to the large number of commercially available amino acids, there are also numerous methods for preparing nonnatural relatives, often enantioselectively.[7] We sought to develop procedures to prepare analogs from these readily available starting materials. For instance, adamantanes **4**, wherein R^4 and R^5 combine to form a piperazine, can be prepared as shown in Scheme 1. Aminoester **5** can be treated with the previously reported bis-triflate **6**, according to a known procedure,[8] to efficiently provide piperazine **7**. The piperazine can then be deprotected with phenylthiolate under mildly basic conditions and arylated by several methods, including nucleophilic aromatic substitution with 2-bromo-5-trifluoromethyl-pyridine, to provide piperazine acids like **8** after ester hydrolysis. The acid **8** can then be coupled under standard amide formation conditions to a 4:1 *E*:*Z* 4-amino-adamantane-1-carboxylic acid methyl ester **9** (see Scheme 2 for its preparation). The resulting amides then can be separated by column chromatography and hydrolyzed to provide adamantane acids like **10**, which can be converted to primary amides like **11**.

In order to further increase the diversity of available analogs, a route to prepare these compounds in parallel was developed. Multicomponent reactions are a powerful tool allowing a diverse set of analogs to be prepared rapidly.[9] In order to take advantage of an isocyanide multicomponent reaction, similar to those originally discovered by Ugi[10] and McFarland,[11] isocyanide **13** was prepared. Commercially available hydroxyadamantanone **12** was converted to a 4:1 *E*:*Z* mixture of aminoadamantyl esters **9**, by carbomethoxylation followed by diastereoselective reductive amination. Acylation of the amine with methyl formate followed by dehydration with phosphorus oxychloride provided isocyanide **13** in moderate yield diastereomerically pure after removal of

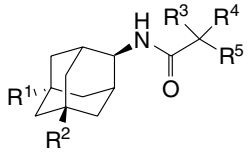


Scheme 2. Reagents and conditions: (a) 30% oleum, HCO_2H, 60 °C, 1.5 h; MeOH, 0 °C → rt, 2 h; NH_3, 4 Å molecular sieves, MeOH, 16 h; $NaBH_4$, 0 °C → rt, 2 h; (b) methyl formate; Et_3N, 50 °C, 12 h, 42% (4 steps); $POCl_3$, Et_3N, CH_2Cl_2, −10 °C → rt, 2 h, 79%; (c) 1-(5-trifluoromethyl-pyridin-2-yl)-piperazine, cyclobutanone, AcOH, MeOH, rt → 70 °C, 12 h, 22%; NaOH, THF, H_2O, MeOH, rt, 16 h, 100%; (d) EDCI, HOBt, DMF, rt, 2 h; NH_4OH, 12 h, 76%.

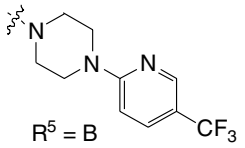


Scheme 1. Reagents and conditions: (a) Na_2CO_3, CH_3CN, 60 °C, 12 h, 80%; (b) PhSH, K_2CO_3, DMF, rt, 1 h; 2-bromo-5-trifluoromethyl-pyridine, K_2CO_3, DMSO, 80 °C, 12 h, 59% (2 steps); NaOH, THF, H_2O, MeOH, 60 °C, 16 h, 100%; (c) TBTU, *i*-Pr_2NEt, DMF, rt, 12 h, 75%; NaOH, THF, H_2O, MeOH, 60 °C, 12 h, 53% (+*Z*-isomer); (d) EDCI, HOBt, DMF, rt, 2 h; NH_4OH, 12 h, 78%.

Table 1. Human and mouse HSD1 and HSD2 inhibition for compounds **7**–**15**



R5 = A

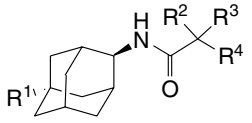


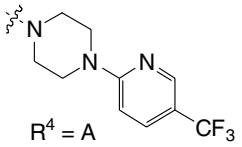
R5 = B

Compound	R^1	R^2	$R^{3,a}$	$R^{4,a}$	R^5	h-HSD1 K_i[b], nM	h-HSD2 IC_{50}[b], nM	m-HSD1 K_i[b], nM	m-HSD2 IC_{50}[b], nM	h-HSD1 HEK IC_{50}[b], nM	% Remaining MLM[c]
18	OH	H	Me	Me	A	13	3600	4	>100,000	28	19
19	OH	H	–CH_2–	–CH_2–	A	2	8300	2	26,000	7	ND
20	H	OH	–CH_2–	–CH_2–	A	6	>100,000	58	>100,000	390	ND
21	CO_2H	H	Me	Me	B	13	21,000	180	780	39	89
10	CO_2H	H	–CH_2–	–CH_2–	B	7	>10,000	500	3200	45	98
22	H	CO_2H	–CH_2–	–CH_2–	B	250	ND	1700	ND	1900	ND
23	CO_2NH_2	H	Me	Me	B	9	>10,000	5	3600	45	65
11	CO_2NH_2	H	–CH_2–	–CH_2–	B	8	>10,000	15	>100,000	22	70
24	H	CO_2NH_2	–CH_2–	–CH_2–	B	13	>100,000	1500	90,000	490	ND

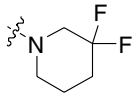
[a] When R^3 and R^4 are –CH_2– it represents a substituent where R^3 and R^4 are linked to form a cyclopropane.
[b] Values are means of two experiments (ND, not determined).
[c] Percent remaining after a 30 min incubation with mouse liver microsomes (MLM).

Table 2. Human and mouse HSD1 and HSD2 inhibition for compounds **7**, **8**, **12**, **13**, and **16**–**23**





R4 = A



R4 = B

Compound	R^1	R^2	R^3	R^4	h-HSD1 K_i[a], nM	h-HSD2 IC_{50}[a], nM	m-HSD1 K_i[a], nM	m-HSD2 IC_{50}[a], nM	h-HSD1 HEK IC_{50}[a], nM	% Remaining MLM[b]
21	CO_2H	Me	Me	A	12	>10,000	180	650	39	89
25	CO_2H	Et	H	A	120	65,000	700	5400	1800	ND
26	CO_2H	Cyclopropyl	H	A	18	24,000	580	2700	87	ND
16	CO_2H	CB[c]	CB[c]	A	17	27,000	270	1700	37	ND
27	CO_2H	CP[d]	CP[d]	A	22	15,000	580	1100	280	ND
23	CO_2NH_2	Me	Me	A	9	>10,000	5	3600	36	65
28	CO_2NH_2	Et	H	A	6	>100,000	15	>100,000	24	88
29	CO_2NH_2	Cyclopropyl	H	A	6	>100,000	5	>100,000	38	93
17	CO_2NH_2	CB[c]	CB[c]	A	7	34,000	3	8900	19	91
30	CO_2NH_2	CP[d]	CP[d]	A	42	50,000	26	14,000	29	ND
31	CO_2H	Et	H	B	73	100,000	1200	7700	640	ND
32	CO_2NH_2	Et	H	B	5	>10,000	3	>100,000	36	ND

[a] Values are means of two experiments (ND, not determined).
[b] Percent remaining after a 30 min incubation with mouse liver microsomes (MLM).
[c] When R^2 and R^3 are CB it represents a substituent where R^2 and R^3 are linked to form a cyclobutane.
[d] When R^2 and R^3 are CP it represents a substituent where R^2 and R^3 are linked to form a cyclopentane.

the *Z*-isomer by chromatography. Isocyanide **13** undergoes a multicomponent reaction with aldehydes and ketones, like cyclobutanone **14**, and an amine, like aryl piperazine **15**, to provide adamantane aminoamides, such as **16**, after ester hydrolysis.[11] The acids can then be converted to the corresponding amides by standard coupling procedures.

We set out to discover long-acting inhibitors that would potently inhibit 11-β-HSD-1 in the fat and liver. It was further hoped that compounds could be identified that either penetrated, or were excluded from, the central nervous system (CNS) to determine the role of inhibition of brain 11-β-HSD-1. To simplify preclinical compound evaluation, compounds with mouse 11-β-HSD-1 potency and selectivity over m-11-β-HSD-2 that matched their human potency and selectivity were sought. Dual species potent and selective compounds have been difficult to identify in other inhibitor series.[2,4] Identifying long-acting inhibitors against 11-β-HSD-1 is also challenging. The steroid binding site, where many classes of inhibitors bind, is lipophilic as are many of

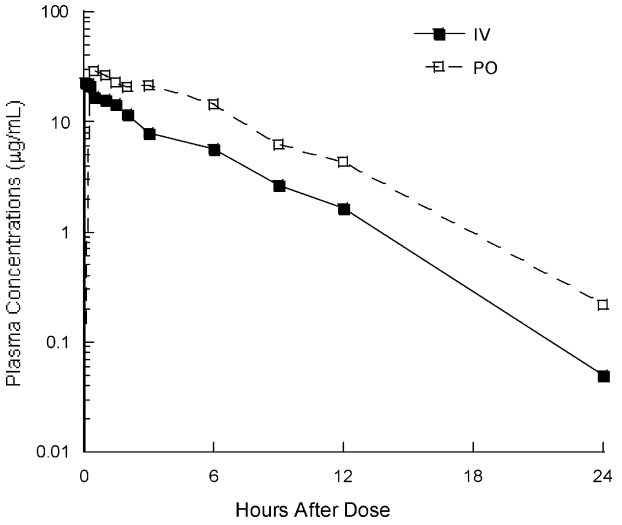
the inhibitors. The compound lipophilicity often leads to poor metabolic stability making identifying compounds with robust PK profiles difficult.

The potency of compounds was measured in assays that quantitated the inhibition of conversion of radiolabeled cortisone to cortisol (truncated h- and m-11-β-HSD-1) or disappearance of cortisol (h- and m-11-β-HSD-2). Radioactive cortisol concentrations were determined by a scintillation proximity assay (SPA) employing an anticortisol monoclonal antibody and SPA beads coated with anti-mouse antibodies. Cellular activity was measured in HEK293 cells that are stably transfected with h-11-β-HSD-1. Cortisone is added and inhibition of the formation of cortisol is measured by fluorescent polarization immuno-assay.

Piperidine substituted inhibitor **18** has an excellent biochemical profile with excellent h- and m-11-β-HSD-1 potency and good h- and m-11-β-HSD-2 selectivity with potent cellular activity (Table 1). However, it has poor metabolic stability as assessed in mouse liver microsomes. SAR of related compounds indicated the dimethyl substituents at R^3 and R^4 were important for m-11-β-HSD-1 activity. To mimic this group, the corresponding cyclopropanes **19** and **20** were prepared and they maintained a similar profile. In order to improve the metabolic stability, more polar substituents were incorporated at both ends of the compounds. The adamantane acid **21** has excellent h-11-β-HSD-1 potency and h-11-β-HSD-2 selectivity, moderate m-11-β-HSD-1 potency, and poor m-11-β-HSD-2 selectivity. It also has excellent metabolic stability. Examination of the corresponding cyclopropane **10** indicates it maintained the human HSD profile but unfortunately did not improve the rodent profile. The *Z*-adamantane **22** was dramatically less potent, as are many of the *Z*-substituted compounds like **20** and **24**. The corresponding amides **23**, **11**, and **24** are dual potent and selective.

The compounds shown in Table 2 were prepared via a multicomponent reaction and allowed for the assessment of a broad range of substituents for R^2 and R^3. Large (e.g., R^2 = Ph, R^3 = H) or polar substituents (e.g., R^2 = CH_2OH, R^3 = H) had poor activity and small nonpolar groups were potent (data not shown). For adamantane acids **16**, **21**, and **25**–**27**, human potent and selective compounds were obtained. However, varying the substituents did not dramatically improve the mouse potency or selectivity. The adamantane amides **17**, **23**, and **27**–**30** were all both human and mouse potent and selective with excellent cellular potency. Furthermore, these compounds have robust metabolic stability. Varying R^4 to a smaller more lipophilic group (difluoropiperidine) in compounds **31** and **32** resulted in an acid with poor potency and an amide with excellent potency and selectivity.

In order to get a sense of the pharmacokinetic profiles of this class of compounds, the mouse pharmacokinetic profile of the adamantane acid **10** was assessed (Scheme 3). The compound has excellent bioavailability (ca. 107%), high oral AUC (197 μg h/mL), moderate iv half-life (2.9 h), low iv clearance (0.1 L/h kg), and a low volume of distribution. The data indicate that this series of compounds can provide long-acting inhibitors for pharmacologic evaluation of 11-β-HSD-1 inhibition.



Scheme 3. Mouse pharmacokinetic data for adamantane acid **10**.

In summary, a potent series of adamantane 11-β-HSD-1 inhibitors was optimized by employing chemistry that relies upon amino acids as starting materials and a multicomponent reaction. Dual human and mouse 11-β-HSD-1 potent and selective amides like **11** were discovered that also have excellent cellular potency and metabolic stability. Adamantane acids, like arylpiperazine **10**, have an excellent human biochemical profile and a robust pharmacokinetic profile.

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References and notes

1. (a) Walker, B. R.; Seckl, J. R. *Expert Opin. Ther. Targets* **2003**, *7*, 771; (b) Draper, N.; Stewart, P. M. *J. Endocrinol.* **2005**, *186*, 251; (c) Thieringer, R.; Hermanowski-Vosatka, A. *Expert Rev. Cardiovasc. Ther.* **2005**, *3*, 911.
2. (a) Fotsch, C.; Askew, B. C.; Chen, J. J. *Expert Opin. Ther. Patents* **2005**, *15*, 289; (b) Barf, T.; Williams, M. *Drugs Future* **2006**, *31*, 231.
3. Sandeep, T. C.; Yau, J. L. W.; MacLullich, A. M. J.; Noble, J.; Dreary, I. J.; Walker, B. R. *PNAS* **2004**, *101*, 6734.
4. (a) Barf, T.; Vallgårda, J.; Emond, R.; Häggström, C.; Kurz, G.; Nygren, A.; Larwood, V.; Mosialou, E.; Axelsson, K.; Olsson, R.; Engblom, L.; Edling, N.; Rönquist-Nil, Y.; Öhman, B.; Alberts, P.; Abrahmsén, L. *J. Med. Chem.* **2002**, *45*, 3813; (b) Alberts, P.; Engblom, L.; Edling, N.; Forsgren, M.; Klingström, G.; Larsson, C.; Rönquist-Nii, Y.; Öhman, B.; Abrahmsèn, L. *Diabetologiz* **2002**, *45*, 1528;

(c) Alberts, P.; Nilsson, C.; Selén, G.; Engblom, L. O. M.; Edling, N. H. M.; Norling, S.; Klingström, G.; Larsson, C.; Forsgren, M.; Ashkzari, M.; Nilsson, C. E.; Fiedler, M.; Bergqvist, E.; Öhman, B.; Björkstrand, E.; Abrahmsén, L. B. *Endocrinology* **2003**, *144*, 4755.

5. (a) Olson, S.; Aster, S. D.; Brown, K.; Carbin, L.; Graham, D. W.; Hermanowski-Vosatka, A.; LiGrand, C. B.; Mundt, S. S.; Robbins, M. A.; Schaeffer, J. M.; Slossberg, L. H.; Szymonifka, M. J.; Thieringer, R.; Wright, S. D.; Balkovec, J. M. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4359; (b) Hermanowski-Vosatka, A.; Balkovec, J. M.; Cheng, K.; Chen, H. Y.; Hernandez, M.; Koo, G. C.; Le Grand, C. B.; Li, Z.; Metzger, J. M.; Mundt, S. S.; Noonan, H.; Nunes, C. N.; Olson, S. H.; Pikounis, B.; Ren, N.; Robertson, N.; Schaeffer, J. M.; Shah, K.; Springer, M. S.; Strack, A. M.; Strowski, M.; Wu, K.; Wu, T.; Xiao, J.; Zhang, B. B.; Wright, S. D.; Thieringer, R. *JEM* **2005**, *202*, 517.
6. Rohde, J. J.; Pliuschev, M. A.;Wodka, D.; Sorensen, B. K.; Yong, H.; Madar, D. J.; Shuai, Q.; Patel, J. R.; Jae, H.; Sarris, K. A.; Wang, J.; Fung, S.; Monzon, K.; Chiou, W.; Pan, L.; Deng, X.; Chovan, L. E.; Longenecker, K. L.; Judge, R. A.; Qin, W.; Wagaw, S. H.; Engstrom, K. M.; Kerdesky, F. A. J.; Stolarik, D. F.; Imade, H. M.; Marsh, K. C.; Beno, D. W. A.; Fey, T. A.; Droz, B. A.; Brune, M.; Camp, H.; Sham, H. L.; Frevert, E. U.; Jacobson, P.; Link, J. T. *J. Med. Chem.*, *manuscript in preparation.*.
7. Ma, J.-A. *Angew. Chem. Int. Ed.* **2003**, *42*, 4290.
8. Kozlowski, J. A.; Zhou, G.; Tagat, J. R.; Lin, S.-I.; McCombie, S. W.; Ruperto, V. B.; Duffy, R. A.; McQuade, R. A.; Crosby, G.; Taylor, L. A.; Billard, W.; Binch, H.; Lachowicz, J. E. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 791.
9. (a) Dömling, A.; Ugi, I. *Angew. Chem. Int. Ed.* **2000**, *39*, 3168; (b) Hulme, C.; Gore, V. *Curr. Med. Chem.* **2003**, *10*, 51.
10. Ugi, I; Steinbrückner, C. DE-B 1,103,337, 1959.
11. McFarland, J. W. *J. Org. Chem.* **1963**, *28*, 2180.