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Adamantyl triazoles as selective inhibitors of 11β-hydroxysteroid dehydrogenase type 1

Steven Olson,[a,*] Susan D. Aster,[a] Kai Brown,[b] Linda Carbin,[b] Donald W. Graham,[a] Anne Hermanowski-Vosatka,[b] Cheryl B. LeGrand,[b] Steven S. Mundt,[b] Michael A. Robbins,[a] James M. Schaeffer,[b] Llnon H. Slossberg,[a] Michael J. Szymonifka,[a] Rolf Thieringer,[b] Samuel D. Wright[b] and James M. Balkovec[a]

[a]*Department of Medicinal Chemistry, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065, USA*
[b]*Department of Atherosclerosis and Endocrinology, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065, USA*

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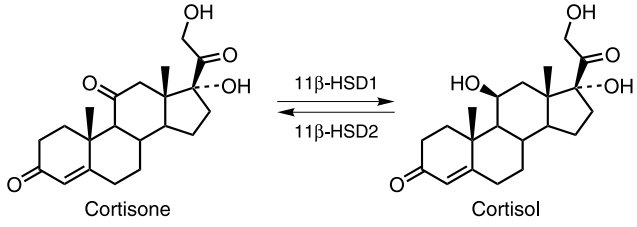
Abstract—Adamantyl triazoles were identified as selective inhibitors of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1). They are active both in in vitro and in in vivo pharmacodynamic models. The synthesis and structure–activity relationships of these inhibitors are presented.

11β-Hydroxysteroid dehydrogenase type 1 (11β-HSD1) is an endoplasmic reticulum-associated enzyme that acts as an NADPH-dependent reductase and converts inactive cortisone to the active glucocorticoid cortisol.[1] As such, it is a regulator of intracellular cortisol concentration and has been implicated in a number of metabolic sequela of increased glucocorticoid tone: visceral adiposity, high blood pressure, elevated fasting glucose, and dyslipidemia.[1,2]

The complement of 11β-HSD1 is the structurally related 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), an NAD-dependent dehydrogenase that catalyzes the inactivation of cortisol by conversion to cortisone (Scheme 1).[1,3] 11β-HSD2 is expressed in cells that contain the mineralocorticoid receptor (MR) and protects the MR from illicit occupation by cortisol.[4]

Carbenoxolone is a drug developed in the 1960s for the treatment of digestive tract ulcers, but it has recently found attention as a potent but nonspecific inhibitor[4c,5] of both 11β-HSD1 and 11β-HSD2. In the past few years, it has been shown that carbenoxolone can improve insulin sensitivity in men with type 2 diabetes[6]



Scheme 1. Interconversion of cortisone and cortisol.

and enhance cognitive function in both healthy elderly men and type 2 diabetics.[7] Since inhibition of 11β-HSD2 is known to result in hypokalemia, sodium retention, and hypertension,[3,4] the invention of selective 11β-HSD1 inhibitors is an important area of academic and pharmaceutical research.[8]

Adamantyl triazole **1** was identified as a potent and selective inhibitor of 11β-HSD1 by high-throughput screening. It was determined to have an IC_{50} versus human 11β-HSD1 of 7.8 nM (98 nM for mouse) using a SPA-based assay.[9] In the human 11β-HSD2 counterscreen, the compound had an IC_{50} of >3000 nM (>10,000 nM for mouse).

A pharmacodynamic mouse model of 11β-HSD1 inhibition was developed to measure the in vivo activity of the inhibitors. In this model, a test compound is

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* Corresponding author. Tel.: +1 732 594 4831; fax: +1 732 594 9545; e-mail: steven_olson@merck.com

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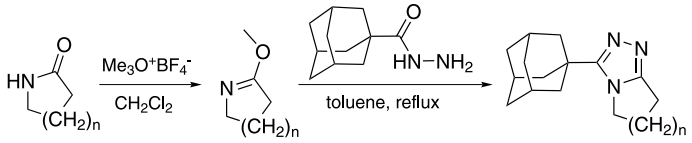
dosed orally (10 mg/kg), and after a prescribed time interval, [^{3}H]cortisone is injected intravenously via the tail vein. After 2 min, blood is collected by cardiac puncture. Steroids are then extracted from the serum and analyzed by HPLC. The relative levels of [^{3}H]cortisone and [^{3}H]cortisol are measured, and a percent inhibition is calculated. In the case of **1**, the compound inhibited 59% of [^{3}H]cortisone conversion 1 h after dosing and 17% of conversion 4 h after dosing relative to untreated control animals. This powerful assay of 11β-HSD1 activity was an important driver of the SAR. Moreover, **1** has been shown to have positive therapeutic effects in mouse models of obesity, diabetes, and atherosclerosis, showing that the pharmacodynamic activity may play a role in the etiology of metabolic syndrome.[10]

Triazole **1** was prepared in 80% yield by the condensation of adamantyl-1-carbohydrazide and the imino ether of caprolactam,[11] and analogs were readily prepared by this method, starting with lactams of varying ring size (Scheme 2). The imino ether was formed using Meerwein's salt and then coupled to the adamantyl-substituted acyl hydrazide. The in vitro activity of this series (Table 1) showed a strong correlation to the number of methylenes in the starting lactam with **7** ($n = 7$) being the most potent inhibitor. The 12-membered ring compound **8** ($n = 8$) shows a slight drop-off in activity, but it is still an excellent inhibitor. It appears that the active site is quite accommodating to large hydrophobic substituents. The murine pharmacodynamic activity, on the other hand, initially increases with the size of the ring, but plateaus with **4** and slowly decreases for the largest compounds. The implication is that the compounds with larger rings suffer from poor pharmacokinetics, and their intrinsic potency becomes less relevant.

Substitution on the adamantane fragment was explored using a similar synthetic method (Scheme 3).[12] Interestingly, the 2-substitued adamantyl triazole **9**[13] had similar activity as the corresponding 1-substituted analog, **1**, suggesting that the active site can accommodate considerable differences in the orientation the adamantane. Unfortunately, additional substituents on the adamantane led, generally, to poorer activity. The most polar compound in the series, 3-hydroxyadamantyl triazole **14**, was a particularly poor inhibitor with a 100-fold loss in activity relative to the unsubstituted adamantyl triazole **1** (see Table 2).

The lack of a clear SAR for the adamantyl fragment contrasted with the clear relationship between ring size and activity on the eastern half. It was postulated that this trend toward improved potency may be due to the increased hydrophobicity found in the larger rings rather than an intrinsic preference for a specific ring size. To that end, a series of acyclic analogs was synthesized which kept the overall hydrophobicity constant while varying the attached groups (**18**–**21**). For acyclic amides, methyl triflate was the reagent of choice for the formation of the methyl imino ethers. Disappointingly, the reaction of these imino ethers with adamantane-1-carbohydrazide using the previously optimized conditions gave significant amounts of oxadiazole as an unwanted byproduct (Scheme 4).

Improving the selectivity of this reaction proved difficult. However, it was found that the oxadiazole could be directly converted to the triazole in the presence of excess amine.[16] To take advantage of this reaction, the synthetic sequence was redesigned (Scheme 5). Adamantane-1-carbohydrazide was acylated with an

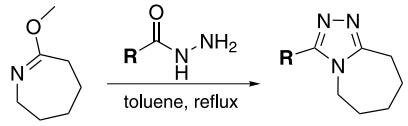


Scheme 2. Synthesis of adamantyl triazoles.

Table 1. Activity of adamantyl triazoles by ring size

Compound	n	IC_{50} (nM)[a]				Mouse pharmacodynamic assay (% inhibition[b])	
		Human 11β-HSD1	Mouse 11β-HSD1	Human 11β-HSD2	Mouse 11β-HSD2	1 h	4 h
2	1	2180	6820	2000	10,000	0	0
3	2	278	1112	>3000	>10,000	—	—
1	3	7.8	98	>3000	>4000	59	17
4	4	2.2	16	787	~10,000	83	24
5	5	4	8	30	4563	43	44
6	6	2.5	4.6	25	~4000	69	31
7	7	1.4	2.2	8.7	11,650	45	29
8	8	3.6	9.2	358	>4000	17	3

[a] Most values were determined by a single seven point titration with 4-fold dilutions. To establish the reliability of the data, compound **1** was tested >30 times. Its human and mouse 11β-HSD1 values and standard deviation were 7.8 ± 2.7 and 98 ± 28 nM, respectively.
[b] Relative to control.



Scheme 3. Synthesis of triazoles with substituted adamantanes.

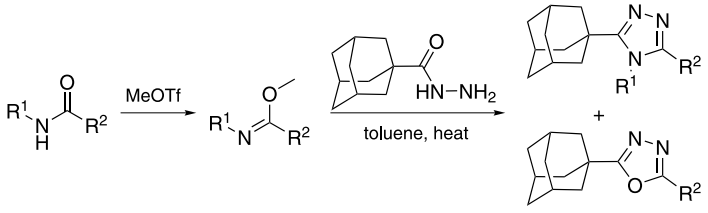
acid chloride in the presence of triethylamine to give an *N*-acetyl hydrazide. This intermediate was converted to the imidoyl chloride and cyclized to give the oxadiazole. Finally, the oxadiazole was heated in a sealed tube with the trifluoroacetate salt of a primary amine to provide the desired triazole.

The activities for this series of isomeric inhibitors (**18**–**21**) are shown in Table 3. The IC_{50}s vary moderately with no clearly evident trend, and it seems that the enzyme is relatively undiscerning for small alkyl substituents of equal polarity. Given their similarity to **1**, it is not surprising that these compounds have comparable pharmacodynamic activity. In this series, the *N*-propyl analog, **20**, is the most potent with 37% inhibition at the 4 h timepoint, whereas the *N*-ethyl compound, **19**, performs quite poorly in the PD assay. In an attempt to improve the metabolic stability of the eastern half of the molecule, two phenyl-containing analogs were prepared using the route shown in Scheme 4. The benzyl analog **22** has a hydrophobicity similar to that of the eight-membered ring analog **4**. As predicted from the SAR, the IC_{50} of **22** is also similar to **4**. Unfortunately, the pharmacodynamic activity of **22** was not improved, possibly because the benzylic methylene is a metabolic liability. The phenyl analog **23** possesses a hydrophobicity and mouse 11β-HSD1 activity comparable to **1**, but its pharmacodynamic activity is significantly improved, suggesting improved pharmacokinetics for this analog. Further optimization studies will be reported in due course.

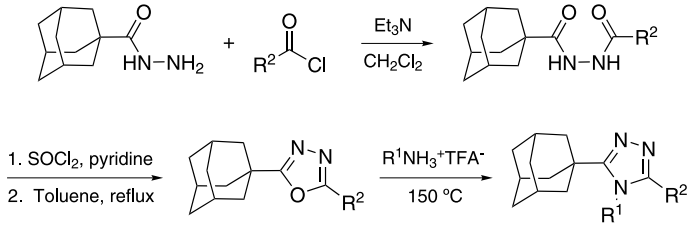
In summary, a novel class of potent and selective inhibitors of mouse and human 11β-HSD1 has been identified. In addition, in vivo 11β-HSD1 inhibitory activity in a mouse pharmacodynamic model has been demonstrated. The initial pharmacological results imply that increasing the hydrophobicity of the inhibitors generally results in a corresponding improvement of 11β-HSD1 inhibition, but this progression is often counterbalanced by poor performance in the pharmacodynamic assay.

Table 2. SAR of substituted adamantyl triazoles

Compound	R	IC_{50} (nM)				Mouse pharmacodynamic assay (% inhibition)	
		Human 11β-HSD1	Mouse 11β-HSD1	Human 11β-HSD2	Mouse 11β-HSD2	1 h	4 h
9	2-Adamantyl	7.7	35	>4000	>4000	42	24
10	3,5-Dimethyladamantyl	13	104	2550	>10,000	—	—
11	3,5,7-Trimethyladamantyl	180	118	>4000	>4000	—	—
12	3-Phenyladamantyl	2.3	365	23	>4000	7	0
13	3-Bromoadamantyl	23	292	>4000	>4000	—	—
14	3-Hydroxyadamantyl	739	1674	>4000	>4000	—	—
15[14]	3-Fluoroadamantyl	37	417	>4000	>4000	—	—
16	Adamantylmethyl	74	587	>4000	>4000	0	7
17[15]	3,5-Dimethyladmantylmethyl	36	50	17,600	>2000	—	—



Scheme 4. Initial synthesis of triazoles from acyclic imino ethers.



Scheme 5. Improved synthesis of triazoles from acyclic imino ethers.

Table 3. SAR of *n*-alkyl-substituted adamantyl triazoles

Compound	R^1	R^2	IC_{50} (nM)				Mouse pharmacodynamic assay (% inhibition)	
			Human 11β-HSD1	Mouse 11β-HSD1	Human 11β-HSD2	Mouse 11β-HSD2	1 h	4 h
18	Methyl	Butyl	11	91	2840	>4000	31	21
19	Ethyl	Propyl	52	50	<4000	>4000	24	5
20	Propyl	Ethyl	11	23	>4000	50	55	37
21	Butyl	Methyl	72	270	>4000	>4000	—	—
22	Methyl	Benzyl	3	14	92	>4000	48	23
23	Methyl	Phenyl	37	109	>4000	>4000	85	47

Replacing the alkyl substituents on the eastern half of the molecule with a phenyl group, as in **23**, enhances pharmacodynamic activity without changing the overall polarity of the inhibitor. Additional optimization of these lead compounds may eventually lead to a treatment strategy for metabolic syndrome.

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