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Discovery of orally active butyrolactam 11β-HSD1 inhibitors

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Abstract—A series of metabolically stable butyrolactam 11β-HSD1 inhibitors have been synthesized and biologically evaluated. These compounds exhibit excellent HSD1 potency and HSD2 selectivity, pharmacokinetic, and pharmacodynamic profiles.

Metabolic syndrome is a cluster of factors associated with an increased risk of atherosclerotic cardiovascular disease and diabetes. The characteristics of the metabolic syndrome include abdominal obesity, impaired glucose tolerance, dyslipidemia, and hypertension.[1] 11β-Hydroxysteroid dehydrogenase type 1 (11β-HSD1) has attracted significant attention from the pharmaceutical research community as a target for the treatment of metabolic syndrome.[2] This enzyme converts the glucocorticoid receptor (GR) inactive cortisone (dehydrocorticosterone in rodents) into the GR active hormone cortisol (corticosterone in rodents).[3] In the liver, cortisol stimulates gluconeogenesis through up-regulation of the enzymes phosphoenolpyruvate carboxykinase and glucose 6-phosphatase, and in adipose tissue, cortisol promotes adipogenesis and lipolysis. A related enzyme, 11β-HSD2, catalyzes the reverse reaction which, in tissues like kidney, protects the mineralocorticoid receptor (MR) from activation by cortisol.[4] 11β-HSD1 is mainly expressed in the liver, adipose, and brain, whereas 11β-HSD2 is expressed in kidney and other tissues where MR signaling is important. The current hypothesis presumes a small molecule that selectively targets 11β-HSD1 over 11β-HSD2 can be a viable therapeutic strategy for the treatment of metabolic syndrome.

Multiple structural classes of 11β-HSD1 inhibitors have been disclosed by us[5] and others.[2] High-throughput screening identified lactam **1** (Fig. 1) as a viable hit. Lactam **1** has a 11β-HSD1 inhibition IC_{50} of 107 nM (728 nM for mouse) and about 100-fold selectivity over 11β-HSD2 for both species.

In this communication, we describe our medicinal chemistry efforts based on lactam **1** and the structural evolutions that took place which led us to discover a series of butyrolactams that are orally efficacious in rodent models of metabolic syndrome.

Figure 1 shows the structure–activity relationship of our initial analogs based on **1**. The synthetic route that we used to obtain these lactams is shown in Scheme 1.

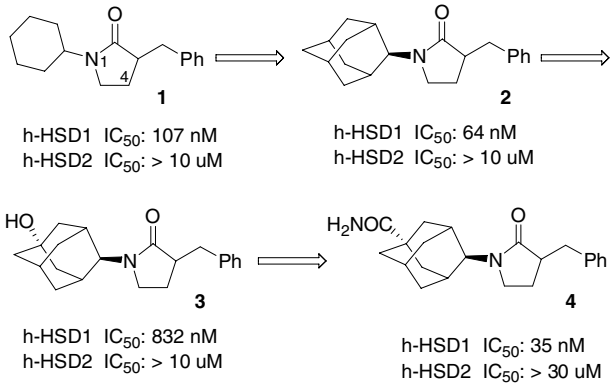

Figure 1. First-generation butyrolactam 11β-HSD1 inhibitors.

Keywords: 11b-HSD1 inhibitors; Butyrolactams; Pharmacokinetic; Pharmacodynamic.
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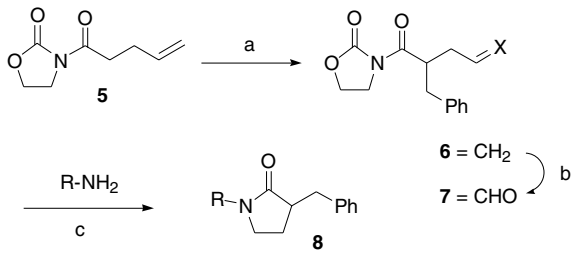
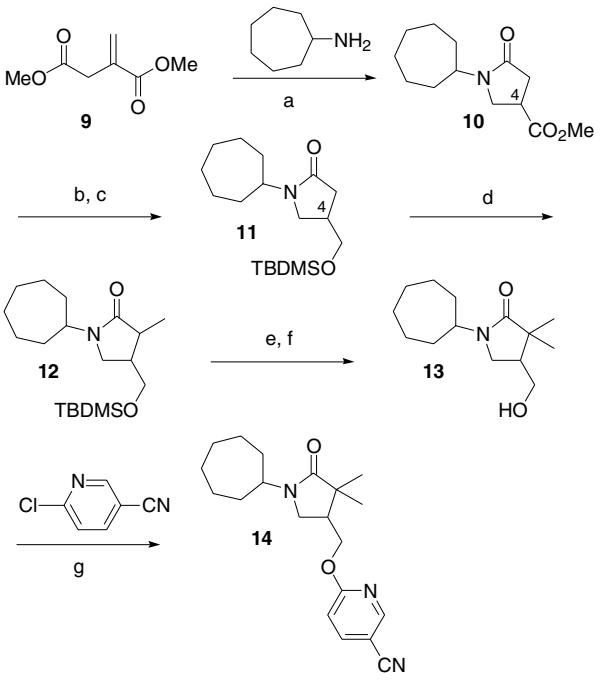


Scheme 1. Reagents and conditions: (a) NaHMDS, THF, −78 °C, 30 min; BnBr, −78 °C to rt, 2 h, 85%; (b) i—O_3, CH_2Cl_2, MeOH, −78 °C, 30 min; ii—Me_2S, rt, 5 h, 80%; (c) $NaHB(OAc)_3$, THF, rt, 12 h; 60 °C, 4 h, 50–80%.

Alkylation of oxazolidinone imide **5** followed by ozonolysis of the terminal olefin gave aldehyde **7**. Tandem reductive amination/cyclization of aldehyde **7** with various amines gave lactam products with different N-substitutions. We found that the in vitro potency can be significantly improved when the nitrogen of the lactam is substituted with a large hydrophobic group such as an adamantane, as seen in lactam **2**. Based on our experience with adamantane-based inhibitors,[5] unsubstituted adamantanes are rapidly metabolized in vivo, and the placement of a polar group such as a carboxamide on the adamantane (e.g., lactam **4**) significantly improves metabolic stability. Lactam **4**, however, lacked the desirable potency in our cellular 11β-HSD1 assay and acceptable pharmacokinetic (PK) properties. Modifications on the benzyl group did not improve the properties significantly. In addition, most of the analogs from this structural series were much weaker in potency against the



Scheme 2. Reagents and conditions: (a) MeOH, reflux, 5 h, 90%; (b) $LiAlH_4$, THF, 0 °C, 1 h, 85%; (c) TBDMSCl, imidazole, THF, rt, 99%; (d) LiHMDS, THF, −78 °C, 30 min; MeI, 1 h, 80%; (e) $LiNEt_2$, THF, 0 °C, 30 min; MeI, DMPU, 0 °C to rt; 4 h, 75%; (f) HCl, THF, rt, 3 h, 100%; (g) NaH, DMF, 0 °C to rt, 89%.

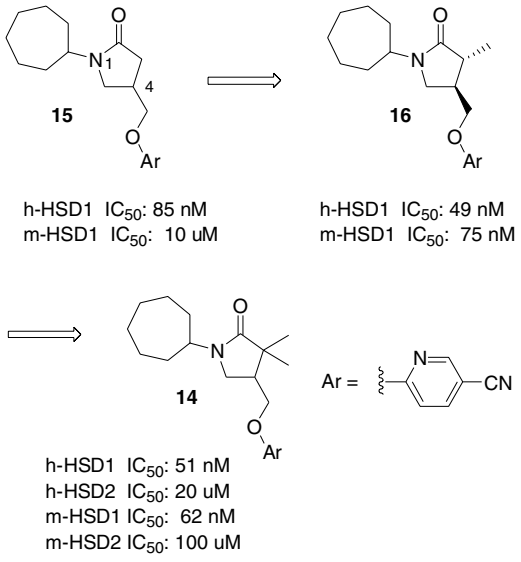
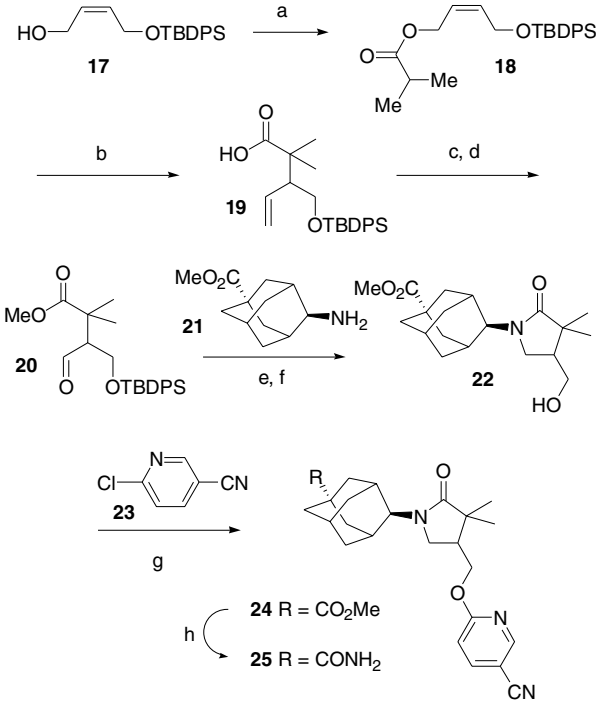


Figure 2. In vitro potency of second-generation lactam 11β-HSD1 inhibitors. Compounds are chiral racemic mixtures.

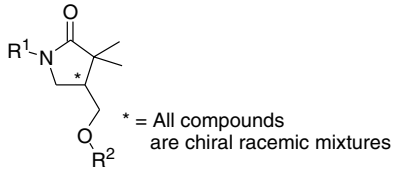


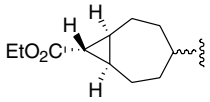
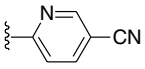
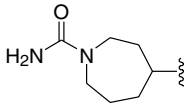
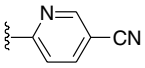
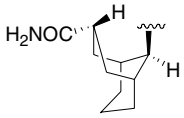
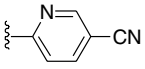
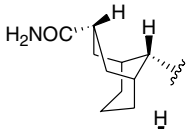
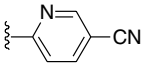
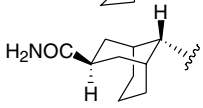
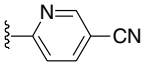
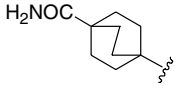
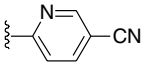
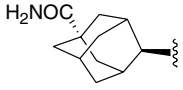
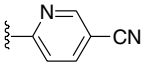
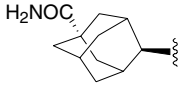
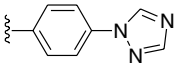
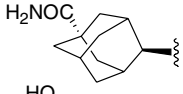
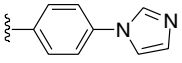
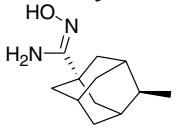
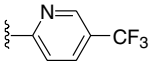
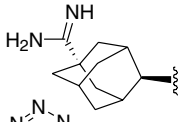
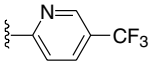
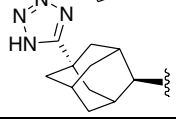
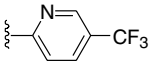
Scheme 3. Reagents and conditions: (a) isobutyryl chloride, Et_3N, DMAP, 0 °C to rt, 5 h, 90%; (b) i—KHMDS, −78 °C, tol, 1 h; TMSCl, −78 °C to rt, 1 h; ii—80 °C, 5 h, 90%; (c) TMS-diazomethane, tol, MeOH, rt, 3 h; (d) O_3, $NaHCO_3$, CH_2Cl_2, MeOH, −78 °C, 45 min; Me_2S, −78 °C to rt, 5 h, 85%; (e) i—**20**, **21**, 4 Å MS, THF, rt, 5 h; ii—$NaHB(OAc)_3$, THF, rt, 12 h; iii—tol, 80 °C, 2 h; 85%; (f) TBAF, THF, rt, 2 h, 92%; (g) compound **23**, NaH, THF, DMPU, 0 °C to rt, 5 h, 85%; (h) i—KOTMS, THF, rt, 10 h; ii—EDCI, HOBT, *i*-Pr_2NEt, CH_2Cl_2, 2 h; NH_3 in *i*-PrOH, 3 h, 91%.

mouse 11β-HSD1 which precluded us from studying these compounds in mouse models.

Faced with these drawbacks of our first-generation lactam inhibitor, we decided to explore the SAR of lactams

Table 1. In vitro inhibition and metabolic stability data for **25–37**

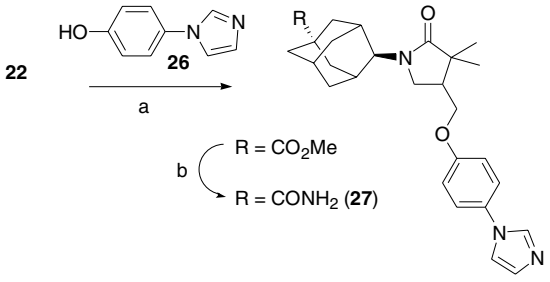


Compound	R^1	R^2	IC_{50}[a] (nM)			Microsomal stability (% remaining)[b]
			h-HSD1/h-HSD2	m-HSD1/m-HSD2	h-HSD1 HEK	
28			50*/>30,000	260*/>100,000	518	ND[c]
29[d]			190*/ND	250*/ND	ND	ND
30			29*/>100,000	17*/>100,000	510	12
31			7/15,000	3/>50,000	39	88
32			5/22,000	9/100,000	46	92
33			15/17,000	10/100,000	500	91
25			3/23,000	2/10,000	45	97
34			41/1,600	32/8,000	43	ND
27			76/1,800	41/14,000	28	28
35			19/14,000	14/60,000	260	67
36			51/90,000	110/>100,000	>10,000	100
37			310/630	430/1,600	230	ND

[a] Values are means of two experiments. *$K_i$values.
[b] % remaining after a 30-min incubation with mouse liver microsome.
[c] ND, not determined.
[d] mixture of diastereomers.

with substituents on position 4 of the ring. The first-generation synthesis of these lactams is shown in Scheme 2.

Tandem Michael addition and cyclization between cycloheptylamine and ester **9** gave lactam **10**[6] which was reduced and protected as silylether **11**. Position 3 of the lactam was then sequentially alkylated, and after removal of silyl group, a pyridyl group was appended on the hydroxymethylene of **13** to give inhibitor **14**. A brief summary of the SAR is shown in Figure 2. Substitution on the 4 position of lactam gave an inhibitor (**15**) with good potency against the human enzyme, but no activity for the mouse enzyme. A dramatic increase in potency for the mouse enzyme was observed when position 3 of the lactam is alkylated with a methyl group (**15** to **16**). Additional α-alkylation gave lactam **14** which showed good potency and excellent selectivity for the target enzyme in both species. Since lactam **14** is stereochemically simpler than **16**, the core structure of **14** was selected for further SAR optimization.



Scheme 4. Reagents and conditions: (a) DIAD, Ph_3P, THF rt to 60 °C, 5 h, 90%; (b) i—KOTMS, THF, rt, 10 h; ii—EDCI, HOBT, *i*-Pr_2NEt, CH_2Cl_2, 2 h; NH_3 in *i*-PrOH, 3 h, 85%.

Table 2. Ex vivo pharmacodynamic data[a]

Compound	% inhibition in liver 1 h/7 h/16 h	% inhibition in fat 1 h/7 h/16 h
31	73/33/14	68/30/17
25	99/94/67	ND[b]/71/46

[a] See Ref. 5b for a description of the assay.
[b] Not determined.

Table 3. Mouse PK data[a]

Compound	po nAUC (μg h/ml)	CLp (L/h/kg)	$t_{1/2}$ (h)	*F* (%)
31	4.4	1.4	1.3	63.9
25	3.7	2.0	1.3	76.6

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

An efficient synthetic route was developed to allow modifications on the nitrogen and oxygen substituents[7] and a representative synthesis is shown in Scheme 3. Acylation of alcohol **17** with isobutyryl chloride gave ester **18**. Ireland–Claisen rearrangement of **18** gave acid **19** which has both the required α-gem dimethyl group, and the β-alkoxymethylene group of the lactam core.

Acid **19** was then converted into aldehyde **20** by ester formation followed by ozonolysis of the olefin. The lactam ring was formed by a tandem reductive amination and ring cyclization sequence between aldehyde **20** and adamantane amine **21** which, after the removal of the silyl-protecting group, gave lactam alcohol **22** in good yields. The pyridyl group was attached via nucelophilic aromatic substitution reaction between alcohol **22** and a chloropyridine such as **23** to give **24**. Final ester to amide functional group conversion completed the synthesis of a representative butyrolactam lactam inhibitor **25**.

This reaction sequence allowed us to build lactams with various groups on the nitrogen by reacting aldehyde **20** with a series of structurally diverse functionalized bridged bicyclic amines[5c] to give inhibitors such as **31** and **33** as shown in Table 1.

Alcohol **22** served as a common intermediate for the exploration of the *O*-aryl appendage SAR. For example, Mitsunobu reaction between alcohol **22** and imidazole-substituted phenol **26** gave an ester intermediate which was converted into inhibitor **27** (Scheme 4).

These compounds were tested against both human and mouse 11β-HSD1 and 11β-HSD2 enzymes, as well as a cell-based assay with 11β-HSD1 overexpressed in human embryonic kidney cells (HEK).[5] In addition, metabolic stability of these compounds was determined using mouse liver microsomal incubation studies. The results are summarized in Table 1.

Several of the compounds in Table 1 exhibited excellent potency and selectivity for both human and mouse 11β-HSD1. For example, lactams **25**, **31**, and **32** all reached single digit nM range in terms of potency and greater

Table 4. In vivo efficacy of compound **25**, RU-486, and rosiglitazone in a 2-week DIO mouse study[a]

Compound	Body weight[b] (g)	Plasma insulin[b,c] (ng/ml)	Plasma glucose[b,c] (mg/dL)	Plasma triglyceride[b,c] (mg/dL)
LF[d]	29.4(0.7)	0.53(0.04)	133.9(3.1)	32.8(2.6)
HF[e]	41.9(0.7)	1.93(0.06)	174.0(5.8)	64.9(5.3)
RU-486	39.5(0.75)	1.5(0.25)	147.5(4.2)	43.2(3.7)
rosiglitazone	41.6(0.7)	0.97(0.1)	143.4(4.3)	50.8(3.4)
25	40.7(0.7)	1.31(0.18)	164.7(6.4)	33.3(2.5)

[a] Lactam **25** and RU-486 were dosed at 30 mg/kg and rosiglitazone was dosed at 5 mg/kg po, bid.
[b] p value <0.05 by Dunnett's test.
[c] Measured after 4 h fasting.
[d] Low-fat diet control group.
[e] High-fat diet control group.

than 7000-fold selectivity over 11β-HSD2. These three inhibitors also showed excellent metabolic stability in the microsome assay. Most of the lactams with non-adamantane N-substituents (**28**–**33**) are potent inhibitors. Lactams **30**–**32** are stereoisomers that differ in the orientations of the substituents on the bicyclo[3.3.1]nonane group.[5c] Although they are similar in their IC_{50} values, compounds **30** and **31** differ dramatically in their metabolic stability. The bicyclo[2.2.2]octane-substituted lactam **33** is particularly interesting. This rigid bicycle has been utilized by us in a different series of 11β-HSD1 inhibitors with good potency, selectivity, and metabolic stability.[5c] In addition, it has also been incorporated in a triazole class of inhibitors for the same enzyme with good success.[2d] Lactams with non-bridged structures such as **28** and **29** showed less potency, particularly for the mouse enzyme. We found that the SAR of the *O*-aryl portion of the molecule is quite flexible. A number of aromatic heterocycles, or carbocycles, could be used to obtain potent inhibitors (structures not shown) which allowed us to fine-tune PK properties of these molecules. Two examples (**34** and **27**) are shown. These lactams feature more polar aromatic substituents which can lead to improved water solubility (calculated clog *P* for **27** is 2.46 vs 2.67 for lactam **25**). Likewise, the polar substituents on the bridged bicycle head group can also be varied albeit with less flexibility. The primary caboxamide can be replaced with a hydroxyamidine group as in **35** with good potency and stability. However, replacement with a basic amidine group (**36**) abolished cellular activity and conversion to an acidic tetrazole (**37**) led to a loss in selectivity.

Selected compounds from Table 1 were examined in mouse ex vivo pharmacodynamic (PD)[5] and PK studies. The results for lactams **31** and **25** are summarized in Tables 2 and 3. For the PD experiments, the compounds were dosed in diet-induced obese (DIO) mice at 30 mpk and the inhibitions of 11β-HSD1 were measured ex vivo at 1, 7, and 16 h post-dose.

Overall, both compounds exhibited good PD profiles. The adamantane lactam **25** showed greater inhibition of the target enzyme at later time points in both liver and fat than the related bicyclo[3.3.1]nonane lactam **31**. The mouse PK profiles of these two compounds are very similar. Both lactams showed good systemic exposure and oral bioavailability with acceptable clearance and half-life.

Based on the favorable results shown above, lactam **25** was selected for in vivo efficacy evaluation in diet-induced obesity (DIO) mice as a metabolic syndrome animal model.[8]

Lactam **25** was dosed orally at 30 mg/kg BID for 14 days. Several metabolic parameters were measured including body weight, plasma insulin, plasma glucose, and plasma triglyceride levels. RU-486[9] and rosiglitazone[10] were used as positive controls. As shown in Table 4, lactam **25** induced significant efficacy in weight loss and lowering of plasma insulin levels. Blood glucose levels were also lowered, albeit not to the same level as the other two agents. Remarkably, plasma triglyceride levels were normalized after treatment with this 11β-HSD1 inhibitor.

In summary, a series of potent, selective, and metabolically stable butyrolactam 11β-HSD1 inhibitors have been identified. Based on its in vitro and pharmacokinetic profiles, adamantane-based lactam **25** was evaluated in DIO mice and showed efficacy in a number of metabolic parameters.

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