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Synthesis and structural activity relationship of 11β-HSD1 inhibitors with novel adamantane replacements

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Abstract—A series of structurally novel and metabolically stable bridged bicyclic carbocycle and heterocycle adamantane replacements have been synthesized and biologically evaluated. Several of these compounds exhibit excellent human and mouse 11β-HSD1 potency and 11β-HSD2 selectivity.

In the preceding communication, the synthesis and biological evaluation of heterocycle-containing adamantane-based 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) inhibitors were described.[1] A number of modifications were made on adamantane amide lead structure **1** (Fig. 1) which led to compounds with significant improvements in pharmacokinetic (PK) profiles. One structural commonality with the described inhibitors is the adamantane head group. Adamantane-based 11β-HSD1 inhibitors have also been reported by several groups working in this area (Fig. 1).[2] Due to its hydrophobic nature, the unsubstituted adamantane group is metabolically unstable in vivo. We have improved the metabolic stability issue by placing a polar group such as a primary carboxamide at the 1 position of the adamantane. We are intrigued by the possibility of introducing other ring systems in our structural activity studies based on **1**. In this communication, we describe our efforts in discovering a number of potent and metabolically stable 11β-HSD1 inhibitors with structurally novel adamantane replacements.

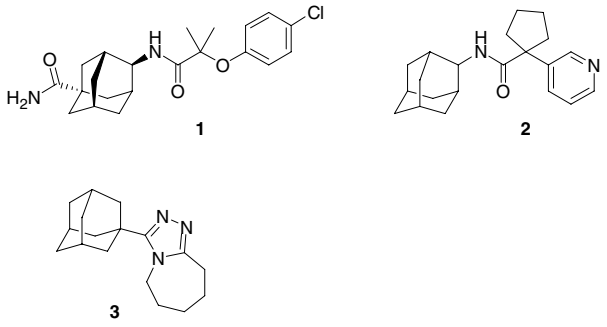

Figure 1. Adamantane-based 11β-HSD1 inhibitors.

Our strategy is to synthesize a number of carbocycles and heterocycles of various ring shapes and sizes to explore the hydrophobic binding pocket of the enzyme. These carbocycles and heterocycles are substituted with a polar group at different positions and spatial orientations on the ring to stabilize the hydrophobic ring from metabolism, to increase water solubility and increase potency by polar interactions with the enzyme.

We designed these rings with C_2 symmetry to simplify stereochemical issues. We explored the structures of these rings in increasing complexity going from monocyclic to bicyclic to bridged bicyclic.

We initially targeted a mono-cyclic eight-membered ring which was synthesized from commercially available diol **4**. Mono-protection of **4**, followed by oxidation of the alcohol, gave ketone **5** which was converted into nitrile **6** by TOSMIC homologation[3] followed by deprotection. The alcohol **6** was then transformed into the amine **7** by oxidation followed by reductive amination (Scheme 1).

Keywords: 11β-HSD1; Adamantane replacements; Metabolic stability.
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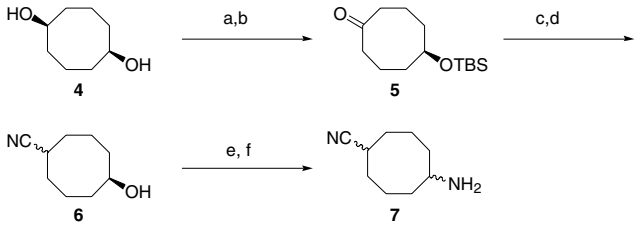
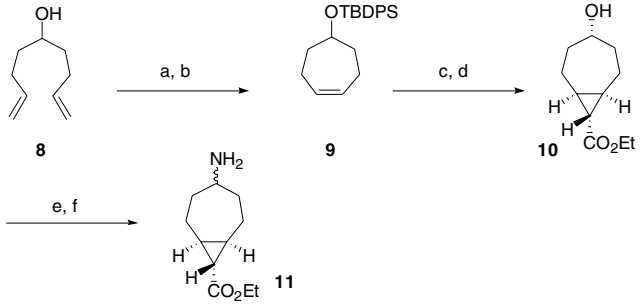


Scheme 1. Reagents and conditions: (a) i—NaH, THF, rt, 3 h; ii—TBSCl, 0 °C to rt, 5 h, 90%; (b) TPAP (5 mol%), NMO, molecular sieves, CH_2Cl_2, rt, 3 h, 80%; (c) TOSMIC, KO-*t*-Bu, DME, MeOH, 50 °C, 3 h, 74%; (d) TBAF, THF, rt, 2 h, 90%; (e) TPAP (5 mol%), NMO, molecular sieves, CH_2Cl_2, rt, 3 h, 75%; (f) NH_4OAc, $NaCNBH_3$, MeOH, rt, 12 h, 90%.

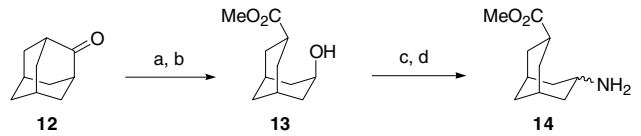
Amine **7** was isolated and used as a mixture of two *syn* and *anti* isomers.

A bicyclo[5.1.0]octane ring system was synthesized from known diene **8** (Scheme 2).[4] Ring closing metathesis, using first generation Grubb's catalyst[5] gave a good yield of the desired seven-membered ring **9**. Rh (I)-catalyzed[6] [2 + 1] cyclopropanation gave the bicyclo[5.1.0]octane ring, and after removal of the protecting group, the isomers were separated. The major isomer is the all trans isomer shown (**10**) as determined by NOE studies. Alcohol **10** was then converted into amine **11** as a near 1:1 mixture of isomers from unselective reductive amination.

The bicyclo[3.3.1]nonane system was synthesized from adamantan-2-one **12** (Scheme 3). Bayer–Villeger oxidation[7] followed by methanolysis gave ester **13** which



Scheme 2. Reagents and conditions: (a) $Cl_2(PCy_3)_2Ru{=}CHPh$ (5 mol%), CH_2Cl_2, 45 °C, 5 h, 80%; (b) TBDPSCl, imidazole, THF, rt, 5 h, 90%; (c) ethyl diazoacetate (syringe pump), $Rh_2(OAc)_4$, CH_2Cl_2, rt, 6 h, 75%; (d) TBAF, THF, 2 h, 85%; (e) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to rt, (Swern oxidation), 83%; (f) NH_4OAc, $NaCNBH_3$, MeOH, rt, 12 h, 90%.



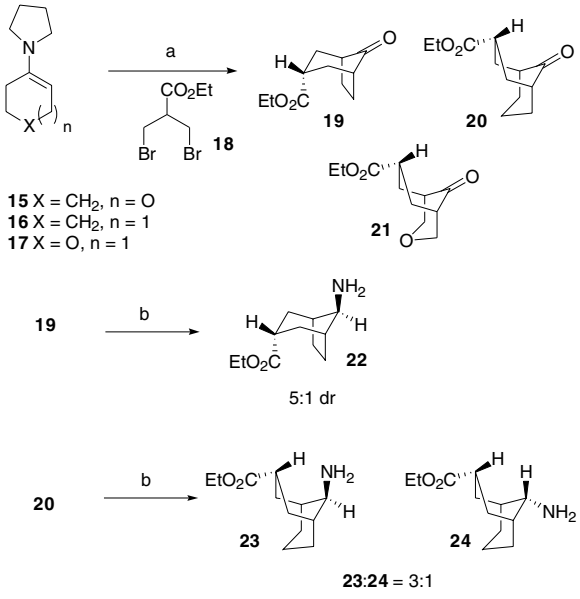
Scheme 3. Reagents and conditions: (a) MCPBA, CH_2Cl_2, rt, 5 h; (b) NaOMe, MeOH, rt, 72%, two steps; (c) Swern oxidation; (d) NH_4OAc, $NaCNBH_3$, MeOH, rt, 85%, two steps.

was then converted into a mixture of syn and anti isomers of amine **14** using standard conditions.

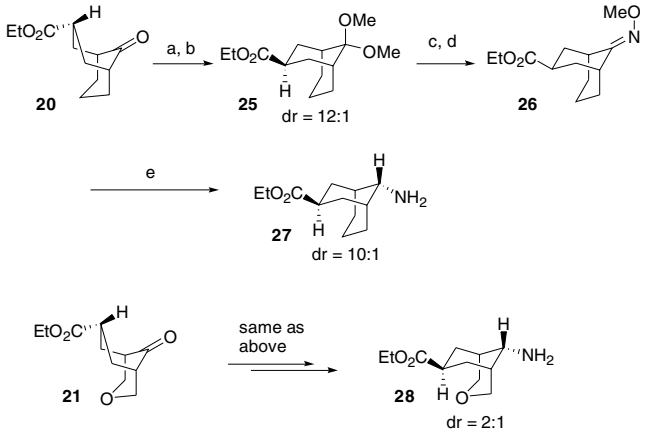
With the above ring systems in hand, we then set to synthesize several 1,4-disubstituted bridged bicyclic six-membered rings which more closely resemble the adamantane carboxamide lead **1** in terms of the distance between the polar head group and the acyl side chain. We utilized an efficient double annulation reaction of enamines with dibromide **18** to synthesize the following three bridged bicycles (Scheme 4). The bicyclo[3.2.1]-octane system was derived from enamine **15** to give the endo ketoester **19**.[8] Ketone **19** was converted into amine **22** via reductive amination which gave a 5:1 mixture of isomers favoring the shown anti isomer.

In a similar fashion, the bicyclo[3.3.1]nonane **20** was obtained from enamine **16** in good yields.[9] Reductive amination of ketone **20** gave a 3:1 mixture of amines **23** and **24** favoring the *syn* isomer **23**. The 3-oxa-bicyclo[3.3.1]nonane **21** was synthesized following the same strategy.[10] Enamine **17** was found to be substantially less stable than the carbocyclic counterparts **15** and **16**, hence affecting the yield of **21**.

Scheme 5 shows the conversion of bridged bicyclic ketones **20** and **21** into *anti*-substituted amines **27** and **28**. Ketone **20** was protected as a dimethyl ketal and the ester group was epimerized under basic condition to give the exo isomer **25** (Scheme 5). After deprotection and imine formation, the trans amine was installed via a highly selective hydrogenation of methoxy imine **26** using Raney nickel to give **27** in good overall yields. Ketone **21** was epimerized and converted to amine **28** following the same reaction sequence as shown for amine **27**. The selectivity in the methoxy imine hydrogenation step was noticeably lower than the carbocylic



Scheme 4. Reagents and conditions: (a) i—Et_3N, CH_3CN, reflux, 12 h; ii—AcOH, water, reflux, 1 h, 75% for **19** and **20**, 55% for **21**; (b) NH_4OAc (10 equiv), $NaCNBH_3$ (4 equiv), MeOH, rt, 92%.



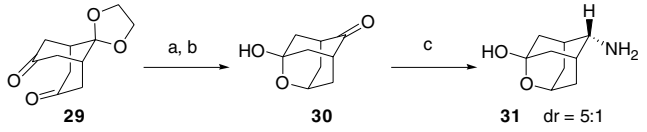
Scheme 5. Reagents and conditions: (a) MeOH, $HC(OMe)_3$, Amberlyst 15, reflux, 3 h; (b) NaOEt, EtOH, reflux, 12 h, 70%, two steps; (c) acetone, Amberlyst 15, reflux, 3 h: (d) $MeONH_3Cl$, Et_3N, EtOH, (90%, two steps); (e) Raney nickel, H_2 (1 atm), EtOH, 92%.

analog giving a ratio of only 2:1 favoring the trans isomer.

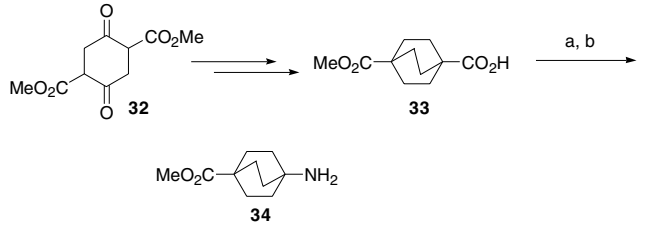
The oxa-adamantane was synthesized from the known di-ketone **29** (Scheme 6).[11] Reduction of **29** followed by acid catalyzed removal of dioxolane gave a stable hemiketal **30** which was converted into amine through hydrogenation of in situ generated imine giving amine **31** in 5:1 ratio.

The known bicyclo[2.2.2]octane acid **33** was synthesized from commercially available **32** following literature procedures.[12] Curtius rearrangement followed by debenzylation gave amine **34** in good overall yield (Scheme 7).

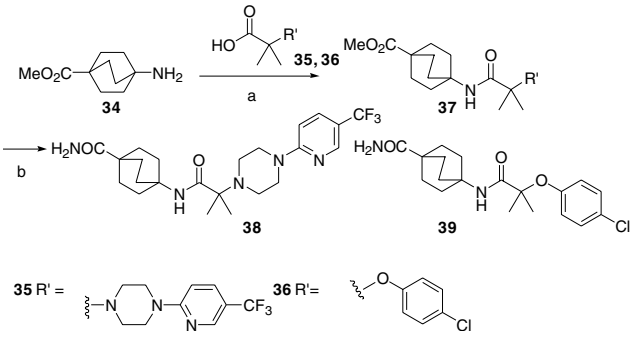
Scheme 8 shows the reaction sequence that was used for the completion of the 11β-HSD1 inhibitors. Amine **34** was acylated with aryl piperazine acid **35**[13] to give an intermediate ester **37**. The ester was hydrolyzed to the



Scheme 6. Reagents and conditions: (a) $NaBH_4$, MeOH, rt, 3 h, 71%; (b) 6 N HCl, dioxane, 70 °C, 48 h, 57%; (c) H_2, 7 N NH_3/MeOH, 5% Pd/C, 12 h, 98%.



Scheme 7. Reagents and conditions: (a) DPPA, Et_3N, BnOH, tol, reflux, 12 h, 80%; (b) H_2, $Pd(OH)_2/C$, MeOH, 3 h, 99%.



Scheme 8. Reagents and conditions: (a) HATU, *i*-Pr_2NEt, **35** or **36**, CH_2Cl_2, rt, 6 h, 70–85%; (b) i—LiOH, MeOH, H_2O, 12 h; ii—EDCI, HOBT, Et_3N, CH_2Cl_2, 3 h, then add 2 M NH_3 in *i*-PrOH, 3 h, 80–90%.

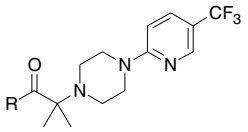
corresponding acid and then converted into the primary amide **38** to give the aryl piperazine series of inhibitors. Similarly, amine **34** can was also acylated with aryl ether acid **36** and further converted into primary amide **39** to give the aryl ether series of inhibitors.

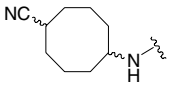
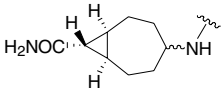
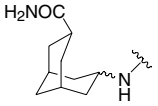
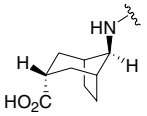
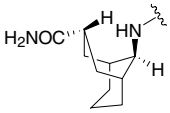
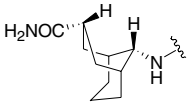
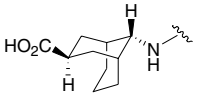
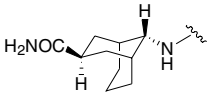
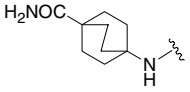
Both series of inhibitors were evaluated in both human and mouse 11β-HSD1 and 11β-HSD2 enzymatic assays.[14] Cellular 11β-HSD1 inhibition was measured in human embryonic kidney (HEK) cells that overexpress the enzyme.[14] The in vitro metabolic stability of these compounds was determined in mouse liver microsome incubation assays. The data for the aryl piperazines **38**–**47** are summarized in Table 1.

Several general observations can be made upon examination of the data. Nearly all of the carbocyclic adamantane replacements gave potent and selective aryl piperazine inhibitors against human 11β-HSD1 with compounds **38** and **41** reaching 20 nM IC_{50} (Table 1). In addition, a few of these compounds are very metabolically stable (**43**, **45**–**47**). With these potent inhibitors featuring structurally different carbocycle head groups, we are able to expand our understanding of human 11β-HSD1 SAR. Moreover, the metabolically stable compounds can be used in vivo studies. Contrary to the human enzyme, it was much more difficult to obtain active molecules against mouse 11β-HSD1. For example, the cyclooctane compound **40** and bicyclo[5.1.0]octane amide **41** are both potent against the human enzyme but much weaker against the mouse enzyme. Compound **40** is metabolically unstable. Both acid (**43** and **46**) or primary amide polar head groups are tolerated by the human enzyme, but the mouse enzyme prefers primary amides over acid groups (**46** vs **47**). It is interesting to note that the geometrical isomers **44** and **45** not only differ in enzymatic activities, but they also showed significant differences in metabolic stability. The mouse 11β-HSD1 active compound **47** has a [3.3.1] carbocyclic group that closely mimics the topology and polar group orientations of the original adamantane carboxamide lead **1**.

The in vitro biological data for the aryl ether series of inhibitors are presented in Table 2. Unlike the aryl piperazine inhibitors, several compounds in Table 2

Table 1. In vitro inhibition and metabolic stability data for aryl piperazine inhibitors **38**–**47**

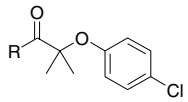


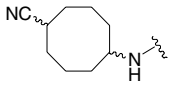
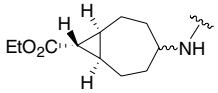
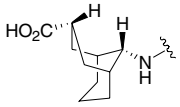
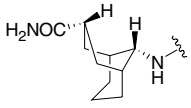
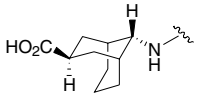
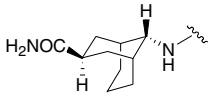
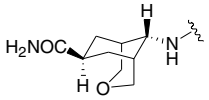
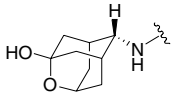
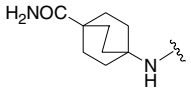
Compound	R	IC_{50}[a] (nM)			Microsomal stability (% remaining)[b]
		h-HSD1/h-HSD2	m-HSD1/m-HSD2	h-HSD1 HEK	
40		66/>30,000	4780/>100,000	219	8
41		24/>30,000	119/>100,000	185	ND[c]
42		269/ND	>10,000/ND	ND	ND
43		97/>30,000	>10,000/>10,000	75	97
44		164/>30,000	10,000/>30,000	1000	17
45		88/>30,000	4000/>30,000	73	75
46		44/>100,000	1150/15,000	606	91
47		62/>100,000	62/85,000	65	85
38		23/90,000	2000/>100,000	442	ND

[a] Values are means of two experiments.
[b] % remaining after a 30-min incubation with mouse liver microsomes.
[c] Not determined.

achieved excellent potency and selectivity for both human and mouse 11β-HSD1 enzymes. Compounds **39**, **51**, **53**, and **55** are highlighted for their potency with compound **53** reaching IC_{50} of 5 nM. A number of compounds in Table 2 also feature excellent metabolic stability. In this series, acid head group is well tolerated in both species (**50** and **52**). **50** is also highly metabolically stable and it might offer different in vivo profiles than the primary carboxamides. Bicyclo[3.3.1]nonane **51** is particularly interesting since it is both potent and metabolically stable, and it contains a more polar heteroaryl side chain (described in the preceding communication)[1] that might offer other desirable characteristics such as increased water solubility. Oxabicyclic inhibitors such as **54** and **55** are also very potent and selective. Moreover, oxygen substitution in the bridge ring provided significant improvement in metabolic stability as compared to the all carbon analog (**53** vs **54**). Compound **39**, which features a rigid bicycle[2.2.2]octane head group, also shows excellent potency and metabolic stability. It is interesting to note that although compounds such as **53** and **39** do not differ significantly in physical properties, they showed large differences in their cellular activities (HEK, 8 nM vs 450 nM) and metabolic stabilities (21% vs 85% remaining). We examined compounds **55** and **39** in our pharmacodynamic assay (Table 3).[14] The inhibition of 11β-HSD1 was measured ex vivo in liver, epididymal fat pad, and brain of DIO mice at 1,

Table 2. In vitro inhibition and metabolic stability data for aryl ether inhibitors **39**, **48**–**55**



Compound	R	IC_{50}[a] (nM)			Microsomal stability (% remaining)[b]
		h-HSD1/h-HSD2	m-HSD1/m-HSD2	h-HSD1 HEK	
48		54/>100,000	255/>100,000	637	0.1
49		587/ND	>10,000/ND	ND	ND
50		22/16,000	32/1820	80	90
51[c]		11/>100,000	28/>100,000	22	89
52		149/ND	164/ND	ND	ND
53		5/>100,000	3/100,000	8	21
54		25/>100,000	23/>100,000	2400	88
55		15/70,000	24/>100,000	199	98
39		13/100,000	28/>100,000	450	85

[a] Values are means of two experiments.
[b] % remaining after a 30-min incubation with mouse liver microsomes.
[c] Compound **51** has the following acyl side chain.

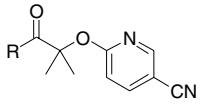


Table 3. Ex vivo pharmacodynamic data[a]

Compound	% inhibition in liver 7 h/16 h	% inhibition in fat 7 h/16 h	% inhibition in brain 7 h/16 h
55	43/0	ND	ND
39	80/70	40/20	60/72

[a] See Ref. 1 for assay details.

7 and 16 h postdose. We hypothesize that long acting compounds would allow sufficient coverage in BID dosing scheme in long-term efficacy studies. Therefore, Table 3 highlights the data for the longer time points. The inhibition of 11β-HSD1 was measured in brain to help us establish the effect of the ability of these compounds to cross the blood–brain barrier. Compound **55** displayed 43% inhibition of the target enzyme in liver at 7 h and none at 16 h. Compound **39** showed robust inhibition in liver and brain at 16 h with weaker activity in fat.

In conclusion, a number of structurally novel and metabolically stable adamantane replacements have been indentified. Several of these bridged carbocycles and heterocycles showed good potency against both human and mouse 11β-HSD1 and excellent selectivity against 11β-HSD2 in both species in the aryl ether inhibitor series.

Compound **39** showed significant 11β-HSD1 inhibition in liver, fat, and brain in ex vivo assay.

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