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Bicyclo[2.2.2]octyltriazole inhibitors of 11β-hydoxysteroid dehydrogenase type 1. Pharmacological agents for the treatment of metabolic syndrome

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ABSTRACT

Following the discovery of a metabolic 'soft-spot' on a bicyclo[2.2.2]octyltriazole lead, an extensive effort was undertaken to block the oxidative metabolism and improve PK of this potent HSD1 lead. In this communication, SAR survey focusing on various alkyl chain replacements will be detailed. This effort culminated in the discovery of a potent ethyl sulfone inhibitor with an improved PK profile across species and improved physical properties.

That there is a link between metabolic risk factors and cardiovascular disease (CVD) has been known for decades. However, it was not until the late 1980s that the term Metabolic Syndrome (or Syndrome X) was coined to describe a condition in which a set of metabolic risk factors, such as abdominal obesity, insulin resistance, atherogenic dyslipidemia and elevated blood pressure presented together in a single patient. Patients diagnosed with Metabolic Syndrome are at a threefold higher risk of developing CVD and a fivefold higher risk of developing type 2 diabetes.[1] Current treatment for Metabolic Syndrome consists of a combination of one or more agents for each of the individual risk factors. In recent years, a search for potential therapeutic targets that simultaneously treat multiple components of Metabolic Syndrome has become an active area of pharmaceutical and academic research.

11β-Hydroxysteroid Dehydrogenase Type 1 (HSD1), which regulates intracellular glucocorticoid levels in liver, adipose, brain and other tissues by converting cortisone to the active hormone cortisol, may be such a target.[2] In the liver and adipose, binding of cortisol to the Glucocorticoid Receptor (GR) leads to gluconeogenesis and adipogenesis, respectively. It has been postulated that inhibition of cortisol production in these key tissues, by inhibition of the HSD1 enzyme, would tone down the pathways leading to lipid and glucose elevation, while leaving the circulating glucocorticoid levels intact. A successful HSD1 small molecule inhibitor would need to exhibit a high level of selectivity for this enzyme over a structurally related dehydrogenase, 11β-Hydroxysteroid Dehydrogenase Type 2 (HSD2), expressed mainly in the kidney, which protects the Mineralocorticoid Receptor (MR) from excessive activation by cortisol which could cause electrolyte imbalances.

Previous work from our laboratories described the discovery of a [2.2.2]bicyclooctyltriazole lead **1** and its optimization to a more potent 3-*ortho*-trifluoromethylphenyl-4-methyl-1,2,4-triazole analog **3**.[3] This potent and selective HSD1 inhibitor served as the starting point for our work. It showed robust in vivo efficacy in the mouse pharmacodynamic model (PD),[4] expressed as percent inhibition of conversion of exogenously administered ^{3}H-cortisone to ^{3}H-cortisol, following a PO dose of the compound, despite the poor PK profile (Table 1). The unexpectedly good in vivo efficacy 4 h after compound dose suggested formation of an active metabolite, which was confirmed by microsomal stability studies of **1**. The primary site of metabolism was shown to be on the 4 position of the pentyl chain to generate alcohol **2**, also a potent inhibitor of HSD1. Identifying the metabolic 'soft-spot' allowed us to design analogs with improved PK[5] and also indicated that substitution on the alkyl chain of **3** was tolerated in terms of HSD1 inhibitory activity. In this paper we describe a series of analogs of **3** with alkyl chain modifications. Summary of related work from our laboratories describing heterocyclic replacements of the pentyl chain was previously published in this journal.[6]

Initially, a set of close analogs of **3** were prepared in an effort to alter or block the metabolism of the alkyl chain (Table 2). These

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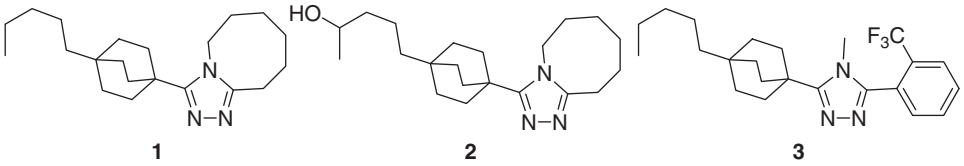
Table 1

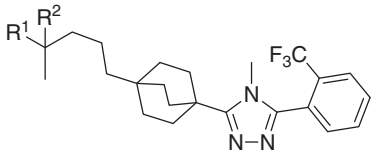


1 **2** **3**

Compound	IC$_{50}$ (nM)[a]				PD (10 mg/kg PO) % inhibition		Mouse pharmacokinetics[c]		
	Human HSD1	Mouse HSD1	Human HSD2	Mouse HSD2	1 h[b]	4 h[b]	PO AUCN (μM h kg/mg)	Cl (mL/min/kg)	%*F*
1	4	3	180	2100	71	51	0.022	141	6
2	35	19	290	190	67	41	—	—	—
3	1.8	3	1300	>4000	—	98	0.034	273	20

[a] IC$_{50}$ was determined using a SPA assay. The values are an average of two determinations.[4]
[b] Indicates time of compound dose prior to tail vein injection of ^{3}H-cortisone.
[c] Based on 2 mg/kg IV and 10 mg/kg dose;[5] PO AUCN is the normalized AUC; Cl is the IV dose blood clearance; %*F* is bioavailability.

Table 2

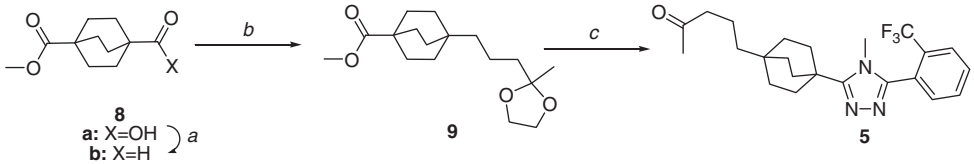


Compound	R^1, R^2	IC $_{50}$ (nM)				PD (10 mg/kg PO) % inhibition		Mouse pharmacokinetics		
		Human 11β-HSD1	Mouse 11β-HSD1	Human 11β-HSD2	Mouse 11β-HSD2	4 h	16 h	PO AUCN (μM h kg/mg)	Cl (mL/min/kg)	F%
3	H, H	1.8	3	1300	>4000	98	—	0.034	273	20
4	H, OH	<1	1.7	>1000	>4000	97	—	0.10	88	21
5	=O	1.2	1.3	4000	>4000	90	32	0.47	21	25
6	H, F	<1	<1	1300	>4000	96	51	—	—	—
7	F, F	<1	<1	>4000	>4000	99	94	1.1	14	36

analogs were prepared from a common [2.2.2] acid/ester intermediate **8a** as shown in Scheme 1. The acid was reduced to aldehyde **8b** in a two-step procedure, then further elaborated to the Wittig product **9** in high yield. Triazole **5** was prepared by cyclizing the methyl chloroimidate analog of **9** with *o*-trifluorophenyl tetrazole.[7] This triazole forming reaction was the method of choice for preparing *ortho*-substituted 3-phenyl 1,2,4-triazoles due to the competing 1,2,4-oxadiazole formation when coupling a hydrazide. Although the yields were somewhat variable, the reaction generally gave >30% desired triazole product for a wide range of substrates. Ketone **5** was reduced with sodium borohydride to yield alcohol **4**, which was in turn treated with diethylaminosulfur trifluoride (DAST) to yield **6**. Difluoro analog **7** was prepared by treating ketone **5** with DAST.

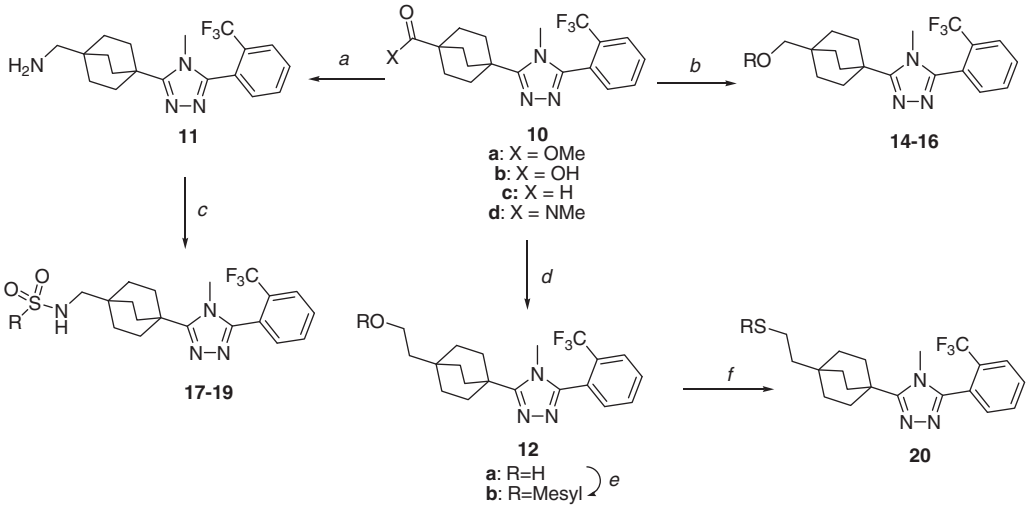
Among our first set of analogs of **3**, compounds **4** and **5** had a better blood clearance profile in the mouse, but the difluoro-substituted analog **7** showed an excellent overall PK profile and robust activity in PD at 16 h (94% inhibition). This was not surprising since fluorination completely blocked a known site of metabolism. Upon further evaluation of this compound, we discovered that it induced CYP3A4 in human liver hepatocytes. This off-target activity was traced to the activation of Pregnane X receptor (PXR), a known liability of related 1,2,4-triazoles.[8] Since modeling studies of the receptor binding pocket[9] suggested that introducing polar groups into the alkyl side chain would diminish this off-target activity, our later SAR focused on exploring compounds with hydrophylic side-chains.

In order to quickly access substituted analogs, we reworked the synthetic scheme into the more convergent Scheme 2 by first preparing the [2.2.2]bicyclooctane-1,2,4-triazole core **10a**.[10] The analogs were then synthesized by simple transformations of this common intermediate. Ethers **14–16** were synthesized by alkylating alcohol **10b**. Partial reduction to aldehyde **10c** gave access to Wittig products. Homologated alcohol **12a** was prepared by



8
a: X=OH
b: X=H
9
5

Scheme 1. Reagents and conditions: (a) BH_3, THF; TPAP, NMO, CH_2Cl_2, 82% two-steps; (b) [2-(2-methyl-1,3-dioxolan-2-yl)ethyl]triphenylphosphonium bromide, KHMDS, THF; H_2, Pd/C, 78% two-steps; (c) KOH, MeOH; CH_3NH_2, EDC, HOBt; oxalyl chloride, CH_2Cl_2, then *o*-trifluoromethylphenyltetrazole, 120 °C, 18 h. 42%.



Scheme 2. Reagents and conditions: (a) compound **10d**, $LiAlH_4$; (b) **10b**, BH_3, THF; RBr, NaH or MsCl, CH_2Cl_2, followed by ArOH, Cs_2CO_3; (c) RSO_2Cl, Et_3N, CH_2Cl_2; (d) **10c**, KHMDS, methyltriphenylphosphonium bromide; BH_3, THF; H_2O_2, KOH; (e) MsCl, CH2Cl2; (f) RSH, NaH, DMF.

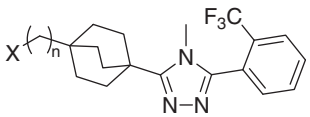
hydroboration of the vinyl intermediate. Methane sulfonylated alcohol **12b** was used for the synthesis of sulfides and sulfones (**20–30**). Sulfonamides (**17**–**19**) were prepared by sulfonylation of the methylamine derivative **11**, obtained, in turn, by reducing the carboxamide **10d**.

Table 3 shows selected examples of more polar analogs: ethers, sulfonamides and sulfones. Despite excellent potency of ethers, they generally had low PD activities due to poor PK. The most efficacious ether analog **15**, had decreased selectivity over HSD2 and showed other off-target activities. Sulfonamides lost human HSD1 activity, but in vitro potency seemed to improve as more lipophilic groups were introduced. However, introducing the larger substituents diminished the 16 h PD activity. Sulfide, sulfoxide and sulfone **20**–**22** had comparable activities for HSD1 in vitro and in vivo and the best off-target profile. Since the sulfone metabolite was present when the corresponding sulfide and sulfoxide were dosed, we focused on developing the SAR around the sulfone substitution.

Our initial set of sulfone examples is shown in Table 4. While all these analogs had similar in vitro potencies, a clear SAR trend emerged in the PD assay: increase in size and lipophilicity of the sulfone substituent was inversely proportional to the in vivo efficacy. So, the more lipophilic analogs had a higher potential for metabolism and lost efficacy in the 4 and 16 h PD assay. The most potent sulfone analogs, ethyl and trifloromethyl (**22** and **29**) also had excellent extended efficacies (76% and 78% inhibition at 16 h, respectively).

Next, we varied the length of the alkyl chain between the sulfone group and the [2.2.2] core (Table 5) and found that lengthening the chain resulted in increased in vitro potency but decreased 16 h PD activity. While more lipophilic analogs (longer alkyl chain analogs) had improved intrinsic potencies in vitro, this did not translate into improved extended PD efficacies, possibly due to increased oxidative metabolism on the longer alkyl chain.[11] Based on the extended PD efficacy data and overall off-target profile, the optimal alkyl chain length connecting sulfone group to the [2.2.2]

Table 3



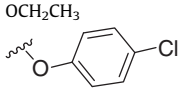
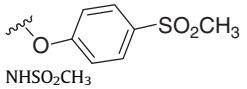
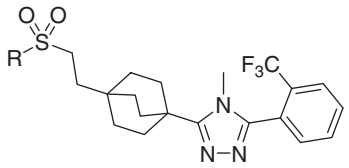
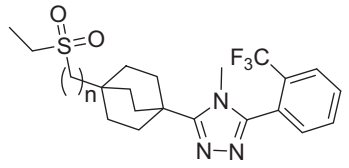
Compound	*n*	X	IC 50 (nM)				PD (10 mg/kg PO) % inhibition	
			Human 11β-HSD1	Mouse 11β-HSD1	Human 11β-HSD2	Mouse 11β-HSD2	4 h	16 h
13	4	OCH_3	2	2	4000	>4000	76	1
14	1	OCH_2CH_3	4	2	>4000	>4000	44	3
15	1		1.1	1.5	460	>4000	98	77
16	1		1	2	>4000	>4000	79	28
17	1	$NHSO_2CH_3$	30	4	>4000	>4000	73	27
18	1	$NHSO_2CH_2CH_3$	20	2.9	>4000	>4000	95	50
19	1	$NHSO_2(CH_2)_2CH_3$	8.1	1	>4000	>4000	93	7
20	2	SCH_2CH_3	3.3	3.9	>4000	>4000	79	72
21	2	$SOCH_2CH_3$	4.1	10	>4000	>4000	90	72
22	2	$SO_2CH_2CH_3$	7	9.7	>4000	>4000	89	76

Table 4



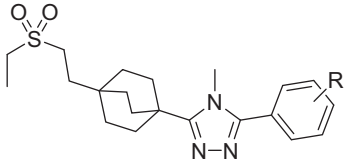
Compound	R	IC $_{50}$ (nM)				PD (10 mg/kg po) % inhibition	
		Human 11β-HSD1	Mouse 11β-HSD1	Human 11β-HSD2	Mouse 11β-HSD2	4 h	16 h
23	Methyl	11	4.1	>4000	>4000	96	63
24	Propyl	5.1	6.7	>4000	>4000	89	47
25	Isopropyl	4.1	3.6	>4000	>4000	88	59
26	*t*-Butyl	5.4	6.3	>4000	>4000	65	10
27	Phenyl	4.4	1.6	>4000	>4000	69	6
28	4-Florophenyl	5.5	1.8	>4000	>4000	63	2
29	CF_3	6.1	2.2	>4000	>4000	81	78
30	CH_2CF_3	3.7	1.5	1600	>4000	74	67

Table 5



Compound	*n*	IC $_{50}$ (nM)				PD (10 mg/kg po)%inhibition	
		Human 11β-HSD1	Mouse 11β-HSD1	Human 11β-HSD2	Mouse 11β-HSD2	4 h	16 h
31	1	25	4	>4000	>4000	94	80
22	2	7	9.7	>4000	>4000	89	76
32	3	3.2	2.4	>4000	>4000	92	63
33	4	1.6	1.8	>4000	>4000	90	58

Table 6

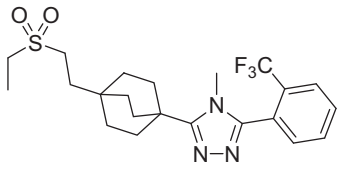


Compound	R	IC $_{50}$ (nM)				PD (10 mg/kg po)%inhibition	
		Human 11β-HSD1	Mouse 11β-HSD1	Human 11β-HSD2	Mouse 11β-HSD2	4 h	16 h
34	*o*-Cl	7.5	11	>4000	>4000	87	74
35	*m*-Cl	900	1100	>4000	>4000	—	—
36	*p*-Cl	2800	>4000	>4000	>4000	—	—
37	*o*-Cl, *p*-OH	2.8	3	>4000	>4000	26	14
38	*o*-Br	10	16	>4000	>4000	86	65
49	*o*-Me	20	21	>4000	>4000	86	30
40	*o*-F	140	170	>4000	>4000	—	—

core had 2 and 3 carbons (compound **22** and **32**). Adding sulfone group into the alkyl chain (as shown in Tables 4 and 5) improved metabolic stability and physical properties of this class of HSD1 inhibitors.

The optimized sulfone-containing Western end was then combined with a varied set of phenyl 1,2,4-triazoles (Table 6). Based on related work from our laboratories,[3] we considered *ortho*-trifluoromethyl substitution as optimal. Here, we confirmed that this substituent gave the best in vivo efficacy. Additionally, we found *ortho*-chloro analog **34** to be equipotent, while *meta*- and *para*-chloro analogs **35** and **36** were 10–30-fold less potent. We also observed that *para*-phenol **37** was quite active in vitro but had low PD

Table 7[5]



22

Species[a]	Dose IV/PO (mg/kg)	PO AUCN (μM h kg/mg)	Cl (mL/min/kg)	Vd (L/kg)	$t_{1/2}$ (h)	C_{max}N (μM kg/mg)	T_{max} (h)	*F* (%)
Mouse	2/10	4.6	2.1	0.72	4.8	0.47	5	24
Rat	1/4	13.0	2.9	1.1	4.9	1.22	2	87
Dog	0.5/2	14.2	1.9	1.7	12.2	1.06	2	59
Rhesus	0.5/2	8.3	4.0	1.6	6.5	1.35	2	89

[a] PK was determined in male C57 mice, male Sprague–Dawley rats, and Beagle dogs.

efficacy. Finally, several other *ortho*-substituted analogs were also prepared (**38**–**40**), but did not provide an advantage with respect to in vitro or in vivo potency over analog **22**.

Based on these SAR studies, we determined that the optimized sulfone analog **22** had superior in vitro and in vivo HSD1 potency. The compound also had a desirable physical property profile, exhibiting water solubility of >1 mg/ml and a relatively low HPLC log *D* of 2.2. Evaluation of pharmacokinetic properties of this compound in four species indicated an excellent profile with a slow rate of clearance, moderate half-life and good bioavailability across species (Table 7) Additionally, compound **22** was evaluated in human liver microsomes for Cyp induction potential and was shown not to be an inducer (with human PXR activation at 10 μM <10%). The compound was further tested in several rodent models of metabolic disease. It showed efficacies in the Diet Induced Obesity mouse model (DIO), apo-E knockout mouse model of atherosclerosis and Oral Glucose Tolerance Test (OGTT) in B6-Ay mouse. Detailed efficacy studies on this compound are still in progress and will be published elsewhere.[12]

In summary, we described the synthesis and SAR studies of a set of alkyl substituted [2.2.2]bicyclooctane triazole inhibitors of HSD1. We showed the progression from an active pentyl chain analog **3** with poor physical and pharmacokinetic properties to a highly selective and efficacious sulfone analog **22**. With this compound we showed a significant improvement in the pharmacokinetic profile over the initial lead. Finally, we used this compound to demonstrate efficacy in three different rodent metabolic disease models. Further studies of compound **22** and analogs are ongoing and will be subject of additional reports from our laboratories.

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12. Unpublished results; (a) Maletic, M.; Leeman, A.; Mundt, S.; Zokian, H.; Shah, K.; Dragovic, J.; Lyons, K.; Tan, E.; Thieringer, R.; Vosatka, A.; Springer, M.; Balkovec, J.; Waddell, S. T. '*Bicyclo[2.2.2]octyltriazole inhibitors of 11β-HSD type 1: Pharmacological agents for the treatment of metabolic syndrome*' Metabolic Syndrome and Cardiovascular Risk Keystone Symposium, Steamboat Springs, CO, Mar 28–Apr 1, 2007; Poster 224; (b) Maletic, M.; Leeman, A.; Waddell, S. T.; Balkovec, J. '*Bicyclo[2.2.2]octyltriazole inhibitors of 11β-HSD type 1: Pharmacological agents for the treatment of metabolic syndrome*' 231st ACS National Meeting, Atlanta, GA, Mar 26–30, 2006; MEDI-196.