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Discovery of 4-heteroarylbicyclo[2.2.2]octyltriazoles as potent and selective inhibitors of 11β-HSD1: Novel therapeutic agents for the treatment of metabolic syndrome

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Abstract—Replacement of the pentyl chain on our original bicyclo[2.2.2]octyltriazole leads **1** and **2** has led to the discovery that heteroaryl substituted bicyclo[2.2.2]octyltriazoles are potent and selective 11β-hydroxysteroid dehydrogenase type I (11β-HSD1) inhibitors with excellent pharmacokinetic profiles.

Metabolic syndrome is a cluster of risk factors which includes visceral adiposity, diabetes, dyslipidemia, and hypertension. When they occur together, these risk factors greatly increase the incidence of cardiovascular disease.[1] There is a growing body of data suggesting that increased levels of intracellular cortisol can cause metabolic syndrome.[2] The enzyme 11β-HSD1 plays a central role in regulating intracellular concentrations of glucocorticoids by converting inactive cortisone to the metabolically active hormone cortisol. It has been hypothesized that inhibition of 11β-HSD1 would lower intracellular cortisol concentrations and thereby treat metabolic syndrome.[2,3] In support of this hypothesis, it has been shown that 11β-HSD1 knockout mice resist metabolic syndrome,[4] whereas overexpression of 11β-HSD1 in mouse adipose tissue leads to a metabolic syndrome-like phenotype.[5] A successful therapeutic agent[6] would have to be selective for 11β-HSD1 over the related enzyme 11β-HSD2, which protects the mineralocorticoid receptor from activation by cortisol.[3]

Unpublished work from our laboratories demonstrated that bicyclo[2.2.2]octyltriazoles with an alkyl tail are inhibitors of human 11β-HSD1. Compound **1** (Fig. 1) is very potent against the mouse and human 11β-HSD1 enzymes (m-HSD1 and h-HSD, respectively) and has reasonable in vivo activity in the pharmacodynamic (PD) assays.[7] The PD assay is an in vivo measurement of a compound's ability to inhibit 11β-HSD1 enzyme activity as assessed by the extent of the conversion of exogenously administered [^{3}H]cortisone, a substrate of this enzyme, to [^{3}H]cortisol. Optimization of the right side of the molecule led to a more potent and selective compound **2**, which inhibits cortisone to cortisol conversion almost completely 4 h after dosing. However, compound **2** still suffers from high clearance and low bioavailability in pharmacokinetic studies in the mouse. Liver microsomal studies indicated that hydroxylation of the 5-carbon alkyl chain is the major metabolic product.[8] This paper summarizes our efforts to prepare compounds showing greater metabolic stability by replacing the *n*-pentyl chain with heterocycles. The synthesis of heteroaryl substituted bicyclo[2.2.2]-octy-

Keywords: Metabolic syndrome; 11β-Hydroxysteroid dehydrogenase type I; 11β-HSD1; 11β-HSD2; Glucocorticoids; Cortisone; Cortisol; Bicyclo[2.2.2]octyltriazole; Heterocycle; Oxadiazole; Imidazole; Triazole; Pharmacokinectics; Pharmacodynamic assay.
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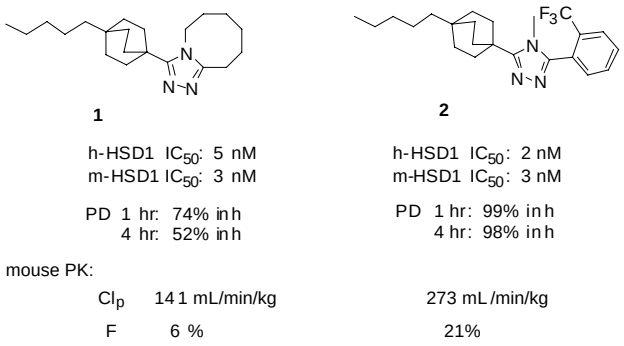
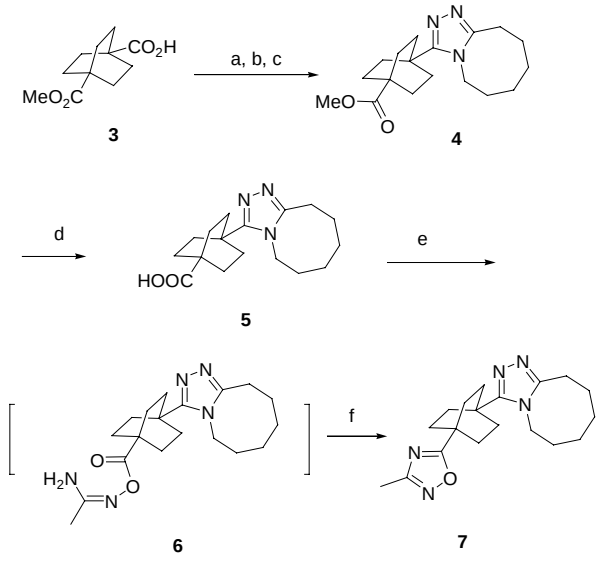


Figure 1. Bicyclo[2.2.2]octyltriazole leads.

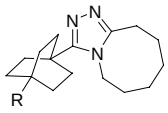
ltriazoles took advantage of the known monomethyl ester (**3**) of bicyclo[2.2.2]octane diacid.[9] In general, the acid group was first converted into the central triazole, after which the ester group was elaborated to a heterocycle. A representative example is shown in Scheme 1. Acid **3** was first converted to the corresponding hydrazide, which was then reacted with the imidate derived from 2-azacyclooctanone to give triazole **4**. The ester group in **4** was hydrolyzed and coupled with an amidoxime to give intermediate **6**, which was subsequently heated at reflux in toluene to afford oxadiazole **7**.[10]

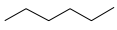
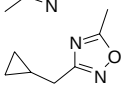
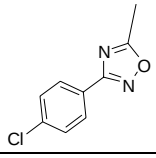
These compounds were tested against both human and mouse 11β-HSD1 and 11β-HSD2 enzymes.[7] Data for selected compounds are shown in Table 1. It was encouraging to find that replacing the pentyl chain with a simple methyl ester yielded a compound (**4**) that was still moderately active. This demonstrated that polar groups were tolerated at this site. An initial survey of oxadiazoles showed that small alkyl substituents produced compounds with only modest potency (**7** and **8**), but with greatly improved selectivity vs. 11β-HSD2. The potency seemed to increase with the lipophilicity of the substituents, and indeed the *para*-chlorophenyl



Scheme 1. Reagents and conditions: (a) Et_3N, TFFH, DMF, rt; (b) anhydrous NH_2NH_2; (c) imidate, DMF, 130 °C; (d) KOH, MeOH/H_2O, 60 °C; (e) CDI, $CH_3C(NH_2)$=NOH; (f) reflux in toluene.

Table 1. Inhibitory properties of selected compounds

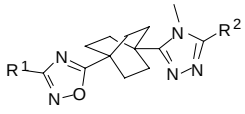


Compound	R	IC_{50} (nm)	
		h-HSD1/ h-HSD2	m-HSD1/ m-HSD2
1		5/183	3/2100
4	MeOOC-	110/>4000	68/>4000
7		289/>4000	136/>4000
8		170/61% at 4 μM	<3.9/>4000
9		13/228	17/4000

group brought both the human and mouse 11β-HSD1 IC_{50} down into the 10–20 nM range (**9**) but there was an erosion of selectivity. Nevertheless, the potency and HSD1/HSD2 selectivity of **9** essentially matched those of our lead compound **1**.

Compound **9** was followed up with a series of right hand variations known from previous analogs to give good potency, at the same time varying the substituents on the phenyl ring pendant to the oxadiazole (Table 2). All the compounds shown have good selectivity against 11β-HSD2 (IC_{50} >1 μM). The *para*-fluorophenyl analog **11** was quickly identified as very potent (2.2 nM against

Table 2. Inhibitory activities of selected compounds

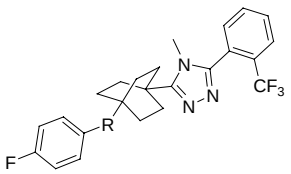


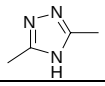
Compound	R^1	R^2	IC_{50} (nM)	
			h-HSD1	m-HSD1
10	4-Cl-Ph	2-CF_3-Ph	4	2
11	**4-F-Ph**	**2-CF_3-Ph**	**2.2**	**1.9**
12	2,4-di-F-Ph	2-CF_3-Ph	2.6	2.6
13	4-F-Ph	2-CH_3O-4-OH-Ph	8.6	2.3
14	4-F-Ph	2-CHF_2O-Ph	9.3	5.2
15	4-F-Ph	2-Cl-Ph	4.1	3.2
16	4-F-Ph	2-Cl-4-CH_3O-Ph	22	12
17	4-F-Ph	2-CH_3SO_2-Ph	9.8	29

Table 3. Pharmacokinetic properties of 11β-HSD1 inhibitor **11**

Species	nAUC (μM h)	Clp (mL/min/kg)	$t_{1/2}$ (h)	*F* (%)
Mouse	5.7	5.88	17.7	58
Rat	6.2	5.39	5.1	83
Dog	9.55	3.51	9.87	100

Table 4. Inhibitory activities of selected compounds



Compound	R	IC_{50} (nM)		% Inhibition at 4 h/16 h
		h-HSD1	m-HSD1	PD (10 mg/kg po)
11		2.2	1.9	86/74
18		7.2	5	85/79
19		2	<1	93/91
20		5.3	2.4	84/32
21		4.7	1.6	93/28

h-HSD1, 1.9 nM against m-HSD1) and selective (HSD1/HSD2 ~1800-fold). In the PD assay, it inhibited cortisone to cortisol conversion by 86% at 4 h and 74% at 16 h. Further, compound **11** had an excellent PK profile in mouse, rat, and dog with low clearance, long half life, and very high oral bioavailability (Table 3).

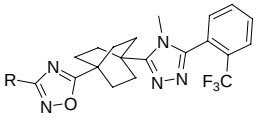
We also investigated other heterocyclic linkages, including the two other isomeric oxadiazoles. Table 4 summarizes some of the interesting data for these compounds, including IC_{50} values against human and mouse 11β-HSD1 enzymes and potency in PD assays.

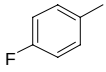
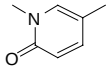
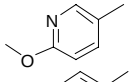
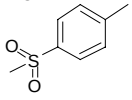
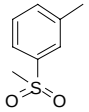
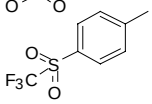
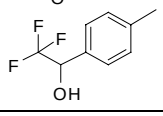
As shown in Table 4, replacing the 1,2,4-oxadiazole in **11** with a more polar 1,3,4-oxadiazole[11] (**18**) caused a slight loss of in vitro potency, while retaining similar PD activity. The isomeric 1,2,4-oxadiazole (**19**) showed further improved activity: 2 nM for h-HSD1 and <1 nM for mouse HSD1. The PD activity for compound **19** was excellent (93% at 4 h, 91% at 16 h). Imidazole[12] (**20**) and triazole (**21**) analogs also had good potency in vitro, though their activity in the PD diminished at 16 h.

One of the problems compound **11** had to suffer was poor water solubility. In order to improve its physical properties, we synthesized analogs of **11** incorporating polar groups on the phenyl ring (Table 5).

The pyridone analog **22** and pyridine analog **23** lost potency in vitro by 10- and 2-fold, respectively. They also lost potency in the PD assay at 16 h. The *para*-methyl sulfone analog **24** had better PD activity than the *meta*-methyl sulfone analog **25**. Substituting the methyl sulfone group with trifluoromethylsulfone (**26**) improved

Table 5. Inhibitory activities of selected compounds



Compound	R	IC_{50} (nM)		% Inhibition at 4 h/16 h
		h-HSD1	m-HSD1	PD (10 mg/kg po)
11		2.2	1.9	86/74
22		20	22	69/7
23		4.1	4.5	81/0
24		4.9	1.8	95/40
25		4.2	9.5	71/11
26		1.9	<0.98	76/71
27		1.4	<1.0	86/84

the in vitro potency and PD activity at 16 h compared to that of **24**. A trifluoromethyl carbinol replacement of the sulfone (**27**) had superior in vitro activity (1.4 nM for h-HSD1 and <1.0 nM for m-HSD1), and excellent in vivo activity (PD 86% at 4 h, 84% at 16 h).

In summary, replacement of the pentyl chain on our original bicyclo[2.2.2]octyltriazole lead has led to the discovery of heteroaryl substituted bicyclo[2.2.2]octyltriazoles as potent and selective HSD1 inhibitors, which have excellent pharmacokinetic profiles. Further studies on these compounds will be reported in due course.

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8. For mouse and rat liver microsomal studies, parent compound (2 μM) was incubated in liver microsomal suspension (1 mg protein/mL of 0.1 M phosphate buffer containing 1 mM EDTA at pH 7.4) containing 5 mM NADPH at 37 °C for 1 h. The major oxidative metabolite (hydroxylation of the ω-1 carbon on the 5-carbon alkyl chain) was biosynthesized via incubation of parent compound (2 mM) in recombinant rCYP-2C11 suspension (1 mg protein/mL) containing NADPH regenerating system at 37 °C for 24 h. LC/MS and NMR were used to identify the structure of the metabolite (unpublished results).
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