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4-Methyl-5-phenyl triazoles as selective inhibitors of 11β-hydroxysteroid dehydrogenase type I

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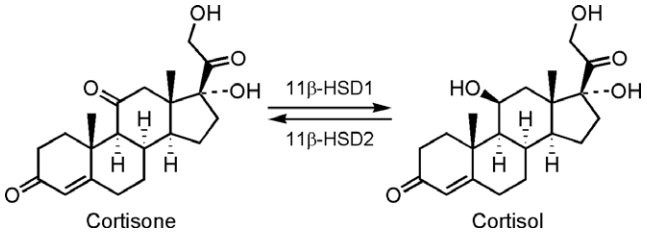
Abstract—4-Methyl-5-phenyl-(1,2,4)-triazoles were identified as selective inhibitors of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1). They were active in vitro and in an in vivo mouse pharmacodynamic (PD) model. The synthesis and structure activity relationships are presented.

11β-Hydroxysteroid dehydrogenase enzymes (11β-HSD) interconvert cortisol and cortisone in man, and corticosterone and 11-dehydrocorticosterone in rodents. The type I isoform (11β-HSD1), which is located in the membranes of the endoplasmic reticulum, converts 11-keto metabolites into active glucocorticoids in the presence of NADPH.[1] The type II isoform (11β-HSD2) utilizes NAD[2] to metabolize glucocorticoids to 11-keto compounds which possess low affinity for glucocorticoid and mineralocorticoid receptors[3] (Scheme 1).

Glucocorticoids are important regulators of glucose and lipid homeostasis, acting largely via intracellular glucocorticoid receptors in the liver, adipose tissue, and muscle. Glucocorticoid excess, epitomized by Cushing's syndrome in humans, leads to insulin resistance/type 2 diabetes, dyslipidemia and a redistribution of fat to visceral depots associated with increased cardiovascular risk.[4,5] Therefore, selective inhibition of the 11β-HSD1 enzyme may lead to an effective treatment for metabolic syndrome. The selectivity over 11β-HSD2 is very important since inhibition of 11β-HSD2 is known to result in sodium retention, hypokalemia, and hypertension.[6,7] The discovery and development of selective 11β-HSD1 inhibitors is an important area of academic and pharmaceutical research.[8]

Previously, we identified adamantyl triazole **1** 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 an SPA-based assay.[9] In a human 11β-HSD2 counterscreen, the compound had an IC_{50} of >3000 nM (>10,000 nM for mouse). We also described phenyl analog **2** which possesses similar hydrophobicity and mouse 11β-HSD1 activity (109 nM). The mouse pharmacodynamic activity of **2**, which measures the in vivo activity of the inhibitor,[9] is significantly improved, suggesting improved pharmacokinetics for this analog[10] (Table 1).



Scheme 1. Enzymatic interconversion of cortisone and cortisol.

Keywords: 11β-HSD1; 4-Methyl-5-phenyl triazole; Metabolic syndrome.
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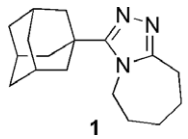
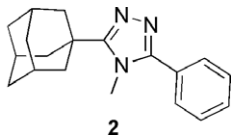
Table 1. SAR of *N*-alkyl-substituted adamantyl triazoles[10]

Compound	IC_{50} (nM)				Mouse pharmacodynamic assay (% inhibition)[a]	
	Human 11β-HSD1	Mouse 11β-HSD1	Human 11β-HSD2	Mouse 11β-HSD2	1 h (%)	4 h (%)
1	7.8	98	>3000	>10,000	31	21
2	37	109	>4000	>4000	85	47

[a] % Inhibition of the conversion of [^{3}H]-cortisone to [^{3}H]-cortisol after a single oral dose of compound at 10 mg/kg.

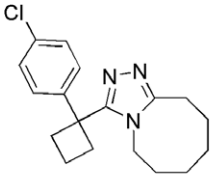


1

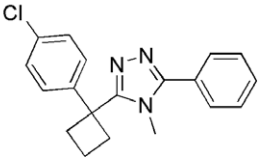


2

Through SAR studies that focused on the left side of triazole **1**, we identified phenyl cyclobutyl triazole **3** as a more potent inhibitor of 11β-HSD1 (IC_{50} vs human 11β-HSD1 1.3 nM; 13.5 nM for the mouse enzyme).[11] Compared to **3**, the 5-phenyl analog **4** had poorer pharmacodynamic activity which we believe resulted from its weaker mouse 11β-HSD1 activity (52 nM). Our previous studies in adamantyl triazoles series showed that the phenyl analog, which has comparable mouse 11β-HSD1 activity, also had a significantly improved pharmacodynamic activity.[10] Therefore in order to improve the in vivo pharmacodynamic activities in this series, we explored the SAR of the phenyl group on the right-hand side of the triazole (Table 2).



3



4

Table 2. SAR of phenyl cyclobutyl triazoles

Compound	11β-HSD1 IC_{50} [a] (nM)		Mouse pharmacodynamic assay [b]	
	Human	Mouse	1 h (%)	4 h (%)
3	1.3	13.5	91	77
4	1.7	52	47	29

[a] The human and mouse 11β-HSD2 IC_{50}s were >4000 nM for all compounds.

[b] % Inhibition of the conversion of [^{3}H]-cortisone to [^{3}H]-cortisol after oral dosing with compound at 10 mg/kg.

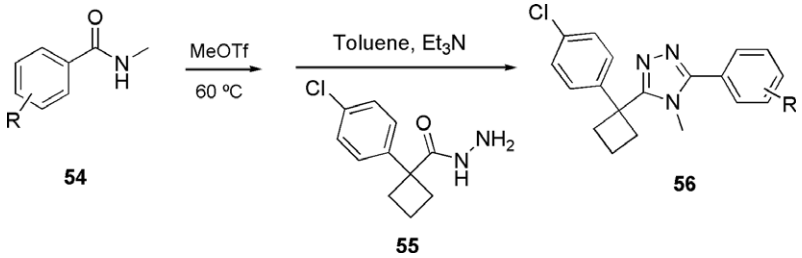
Triazole **4** and its analogs were prepared from the corresponding methyl amide (**54**) and acylhydrazide (**55**) in a one pot reaction. The amides were converted to methyl imino ethers with one equivalent of neat methyl triflate followed by addition of an acylhydrazide in the presence of base (Scheme 2). A number of phenyl substituents were prepared and evaluated (Table 3). For simple substitution, we found that –OH, $–OCF_3$, –Cl, and $–CF_3$ gave similar human 11β-HSD1 activity as triazole **4**, but the mouse 11β-HSD1 activity improved signifi-

Table 3. SAR of small substituent group substitutions of phenyl cyclobutyl triazoles

Compound	R =	11β-HSD1 IC_{50}[a] (nM)		Mouse pharmacodynamic assay (% inhibition)[b]	
		Human	Mouse		
5	*p*-OH	0.34	19	17	10
6	*o*-OH	1.8	17	−2	−2
7	*m*-OH	1	19	—	—
8	*p*-OCF_3	13	6.9	64	27
9	*o*-OCF_3	2.3	4.1	59	44
10	*m*-OCF_3	2.2	36	—	—
11	*p*-Cl	2.7	43	20	14
12	*o*-Cl	0.28	3.5	86	73
13	*m*-Cl	1	34	24	12
14	*p*-F	1.5	101	—	—
15	*o*-F	2	21	—	—
16	*m*-F	2.2	163	—	—
17	*p*-CF_3	9.3	26	—	—
18	*o*-CF_3	2	4	73	63
19	*p*-I	3.8	8.2	—	—
20	*o*-CH_3	5	21	9	1
21	*o*-OCH_3	2.7	7.8	28	12
22	2,4-di-Cl	1	13	—	—
23	3-F, 4-OH	2	61	3	6
24	3-F, 4-OCH_3	3	42	10	−1
25	4-Cyclopropyloxy	10	2.2	95	95

[a] The human and mouse 11β-HSD2 IC_{50}s were >4000 nM for all compounds.

[b] % Inhibition of the conversion of [^{3}H]-cortisone to [^{3}H]-cortisol after a single oral dose of the test compound at 10 mg/kg.



Scheme 2. Synthesis of phenyl cyclobutyl triazoles.

cantly. For the same substituent, the *ortho*-position gave the greatest potency in the mouse while *meta*-substitution proved to be the worst. The *o*-Cl and the 4-cyclopropyloxy analogs were found to be the most potent compounds in this series.

We also explored a number of biphenyl triazole analogs. For biphenyl substitution, mouse 11β-HSD1 activity increased, however, human 11β-HSD1 activity decreased. Among those substituents, the *p*-Ph analog gave the highest pharmacodynamic activity (86% at 1 h; 90% at 4 h) (Table 4).

The synthesis of compounds **26**–**27** and **29**–**31** was similar to that shown in Scheme 1. However, the same route did not apply to the synthesis of compound **28**. Analog **28** was obtained in 95% yield through Suzuki coupling [12] (Scheme 3).

Heterocyclic substitution on the phenyl triazole was accomplished via a copper mediated coupling of the aryl iodide. Using Cu (I) triflate as the catalyst gave a very good yield (79%) of imidazole analog **32** (Scheme 4).[13]

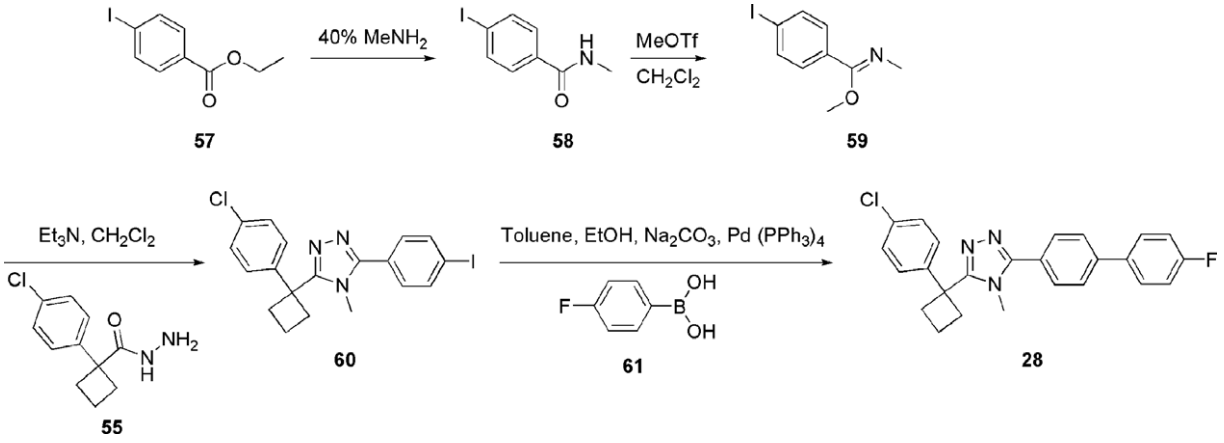
The SAR of heterocyclic substitution was also explored. The thiazole analog was very potent versus mouse 11β-HSD1 (IC_{50} 3.1 nM) although human 11β-HSD1 activity dropped to 44 nM. This analog also had good pharmacodynamic activity (92% at 1 h; 67% at 4 h). The pyrrole analog had excellent activity versus both human and mouse 11β-HSD1 (3 nM vs human, 5.4 nM vs mouse). Unfortunately, the pharmacodynamic activity of this analog was relatively poor (41% at 1 h, 28% at 4 h) (Table 5).

Since both *o*-Cl and *p*-Ph substitutions improved potency and pharmacodynamic activity, analog **35** which is the combination of *o*-Cl and *p*-Ph was prepared. This analog showed excellent potency versus both human and mouse 11β-HSD1 (1 nM for human, 1.4 nM for mouse). It is not surprising that we found the pharmacodynamic activity of **35** was much improved over the two precursors (99% at 4 h, 85% at 16 h). Unfortunately, this analog was a full and potent Pregnane X Receptor

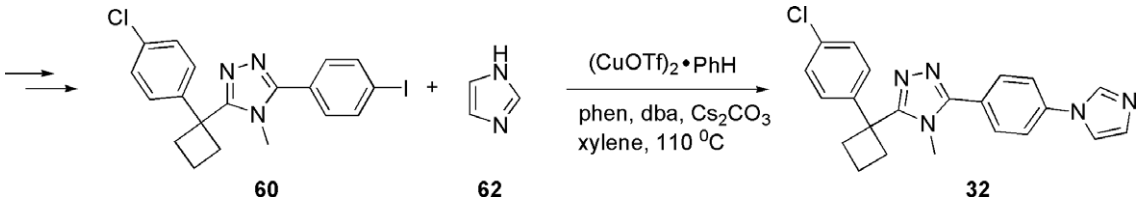
Table 4. SAR of large group substitutions on methyl phenyl cyclobutyl triazoles

Compound	R =	11β-HSD1 IC_{50}[a] (nM)		Mouse pharmacodynamic assay[b]	
		Human	Mouse	1 h (%)	4 h (%)
26	*p*-Ph	11	4	86	90
27	*m*-Ph	4.3	56	−2	−2
28	*p*-4-F-Ph	11	9.1	—	—
29	*p*-Bn	68	18	20	−4
30	*p*-*tert*-Butyl	14	1.8	—	—
31	*p*-OPh	26	3.7	—	—

[a] The human and mouse 11β-HSD2 IC_{50}s were >4000 nM for all compounds.
[b] % Inhibition of the conversion of [^{3}H]-cortisone to [^{3}H]-cortisol after oral dosing with compound at 10 mg/kg.

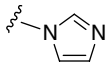
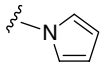
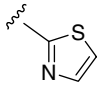


Scheme 3. Synthesis of **28**.



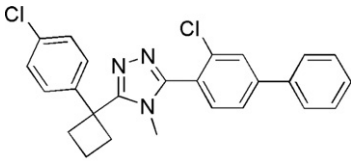
Scheme 4. Synthesis of **32**.

Table 5. SAR of heterocyclic substitution on methyl phenyl cyclobutyl triazoles

Compound	R =	11β-HSD1 IC_{50}[a] (nM)		Mouse pharmacodynamic assay[b]	
		Human	Mouse	1 h (%)	4 h (%)
32		3.5	46	79	44
33		3	5.4	41	28
34		44	3.1	92	67

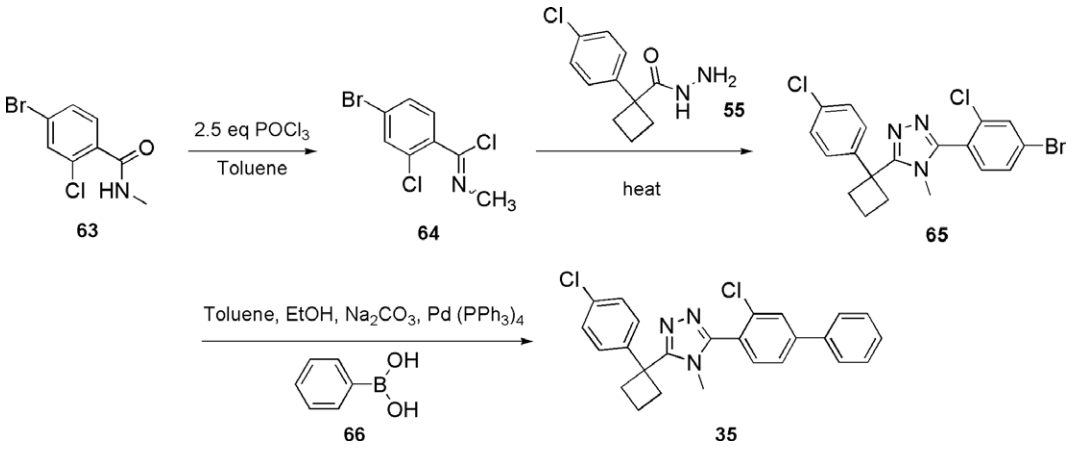
[a] The human and mouse 11β-HSD2 IC_{50}s were >4000 nM for all compounds.
[b] % Inhibition of the conversion of [^{3}H]-cortisone to [^{3}H]-cortisol after oral dosing with compound at 10 mg/kg.

(PXR) agonist (EC_{50} 1.7 μM) suggesting cytochrome P450 induction might be an issue at pharmacologically relevant exposures.

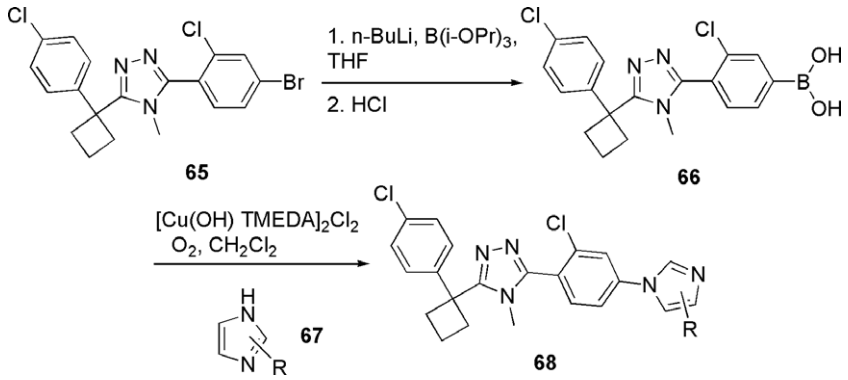


35

Molecular modeling suggested that introduction of polar groups at the end of the molecule could reduce human PXR activity by destabilizing interactions in the hydrophobic area of the ligand binding pocket.[14] Therefore, a series of analogs with heterocyclic substitution was prepared. The pyridine analogs of **35** were prepared as shown in Scheme 5. The imidazole analogs of **35** however, could not be synthesized utilizing the same chemistry. To solve this problem, we prepared the boronic acid



Scheme 5. Synthesis of **35**.



Scheme 6. Synthesis of heterocycle substituted methyl *o*-Cl phenyl cyclobutyl triazoles.

Table 6. SAR of heterocyclic substitution on methyl *ortho*-chlorophenyl cyclobutyl triazoles

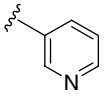
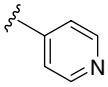
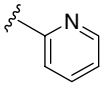
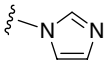
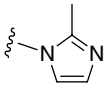
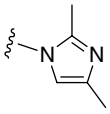
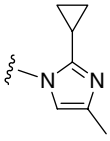
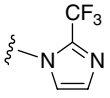
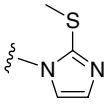
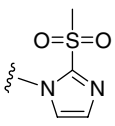
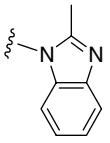
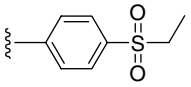
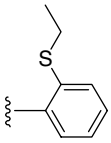
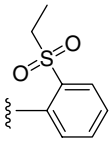
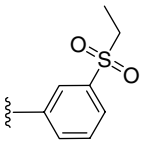
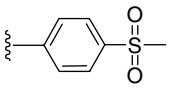
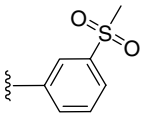
Compound	R =	11β-HSD1 IC_{50} (nM)		Mouse pharmacodynamic assay (% inhibition)		PXR activity	
		Human	Mouse	4 h (%)	16 h (%)	EC_{50} (μM)	% Activation at 10 μM
36		1	1.3	100	26	3.6	35%
37		1	2	39	8	7.7	42%
38		1	1.4	41	−5	2.4	98%
39		1	2.8	78	10	12	21%
40		2.6	9.6	—	—	>25	22%
41		6.9	7.2	—	—	—	—
42		9.8	6	60	7	1.3	13%
43		0.98	0.96	58	20	3.2	24%
44		3.9	3.9	—	—	—	—
45		14	9.4	—	—	7.9	23%
46		12	57	—	—	—	—

Table 7. SAR of sulfone analogs[b]

Compound	R =	IC_{50}[a] (nM)		Mouse pharmacodynamic assay (% inhibition)			PXR activity	
		Human 11β-HSD1	Mouse 11β-HSD1	Human 11β-HSD2	4 h (%)	16 h (%)	EC_{50} (μM)	% Activation at 10 μM
47		2.1	0.98	75% inh. at 4 μM	71	16	>25	−8%
48		11	4.7	54% inh. at 4 μM	51	1	1.7	48%
49		0.98	1.2	>4000	56	6	0.7	74%
50		0.98	0.98	59% inh. at 4 μM	93	29	25	−31%
51		1.7	1.2	>4000	20	−5	>25	2%
52		0.98	0.98	>4000	96	36	>25	−5%

[a] Mouse 11β-HSD2 IC_{50}s were >4000 nM for all compounds.
[b] Data also shown in Ref. 14.

intermediate[15] to couple with imidazole pieces using $[Cu(OH)TMEDA]_2Cl_2$ as catalyst.[16] (see Scheme 6).

The PXR assay data, in accordance with the modeling predictions, showed that substitution with a polar group can reduce the PXR activity. For the pyridine analog, nitrogen substitutions at the 3- or 4-position had lower PXR activity (35% and 42% activation at 10 μM) than the analog with a less exposed nitrogen (2-substitution) (98% activation at 10 μM). All the imidazole analogs decreased the PXR activation to less than 25% at 10 μM. The docking model suggested that the polarity of the imidazole and pyridine groups makes them unfavorable to the highly hydrophobic binding site, thereby reducing the receptor activation compared to their non-polar parent compound **35** (Table 6).

In our SAR studies, we also found that sulfone substitution helped to reduce PXR activity. The synthesis of these sulfone analogs was very similar to that shown in Scheme 5 (Table 7).

In conclusion, a novel class of potent and selective inhibitors of mouse and human 11β-HSD1 have been identified. These analogs showed potent in vivo 11β-HSD1 activity in a mouse pharmacodynamic model. It was found that small group substitutions at the *ortho*-position and larger group substitutions at the *para*-position increase in vivo activity. By introducing polar groups at the end of molecule, we successfully eliminated PXR activity while maintaining both in vitro and in vivo activity. Additional optimization of these lead compounds may eventually lead to a treatment strategy for metabolic syndrome.

References and notes

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