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Substituted phenyl triazoles as selective inhibitors of 11β-Hydroxysteroid Dehydrogenase Type 1

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ABSTRACT

3-(Phenylcyclobutyl)-1,2,4-triazoles were identified as inhibitors of 11β-Hydroxysteroid Dehydrogenase Type 1 (HSD1). They were shown to be active in the mouse in vivo pharmacodynamic model (PD) for HSD1 but exhibited a potent off-target activation of the Pregnane X Receptor (PXR). SAR studies and synthesis of analogs that led to the discovery of a selective HSD1 inhibitor are described in detail.

Glucocorticoids are hormones that play key roles in lipid and glucose metabolism. At the tissue level, glucocorticoid activity is regulated by 11β-Hydroxysteroid Dehydrogenase Type 1 (HSD1), which in vivo converts the inactive glucocorticoid cortisone to the active glucocorticoid cortisol.[1] It has been proposed that an intracellular excess of glucocorticoids in metabolically active tissues such as liver and adipose causes Metabolic Syndrome, a cluster of health problems including hypertension, obesity, visceral adiposity, diabetes, and dyslipidemia.[2] Therefore, inhibition of HSD1 might lower the concentration of glucocorticoids in liver and adipose and thereby lead to a novel treatment for Metabolic Syndrome. Genetic validation for this target comes from the Seckl laboratories, where it was shown that 11β-HSD1 knockout mice resist Metabolic Syndrome,[3] whereas overexpression of HSD1 in mouse adipose tissue leads to a Metabolic Syndrome-like phenotype.[4]

A structurally related enzyme, 11β-Hydroxysteroid Dehydrogenase Type 2 (HSD2), plays a key protective role in the kidney. This enzyme, an NADPH-dependent dehydrogenase that converts cortisol to cortisone, prevents activation of the mineralocoticoid receptor by cortisol.[5] Therefore selectivity for HSD1 inhibition over inhibition of HSD2 is necessary for a novel and effective treatment for Metabolic Syndrome.

Our research lab has previously identified a series of triazole analogs **1**–**4** (Fig. 1 and Table 1) as potent and selective inhibitors of HSD1. Progression of the HTS hit **1** to more tractable leads **2**–**4** has been previously described.[6,7] Analog **4** was of particular interest to us since it shows an IC_{50} for human HSD1 of 11 nM (4 nM for mouse) using a SPA-based assay and excellent in vivo mouse activity (86% inhibition at 1 h; 90% inhibition at 4 h) in the pharmacodynamic (PD) assay.[8] However, it is a potent Pregnane X Receptor (PXR) agonist (EC_{50} 1.7 μM, 90% activation @ 10 μM),[9] raising concerns that at pharmacologically relevant exposures, this compound might cause induction of Cyp3A4. A detailed SAR paper describing some of our previous efforts to eliminate this off-target activity in the biphenyl series has been previously published in this journal.[7] In this Letter we further explore the SAR of the substituted phenyl class of analogs in order to optimize the potency for 11β-HSD1, improve the PK profile, and reduce PXR activation.

The analogs described in this Letter were prepared from common intermediates **A** or **B** (Scheme 1). The triazole was formed by cyclization of the activated methyl thioamide with the appropriate benzhydrazide to give **A** or **B**. Bromo intermediates **A** were converted into benzoic acids (**5**, **14**) under standard conditions and then further elaborated to amide analogs **6**–**13** and **15** (Table 2). Anilines (**16**, **22**) and amide derivatives (**17**–**24**) were prepared by reduction of nitro group of intermediate **B**, followed by treatment with the corresponding acid chloride (Table 3). Finally, the biaryl analogs **25**–**44** (Table 4) were prepared by Suzuki couplings of boronic acid (made from **A**) with the corresponding commercially available bromides.

Docking studies of HSD1 inhibitors with PXR[9] suggested that adding polar groups in place of the distal phenyl ring in **4** would

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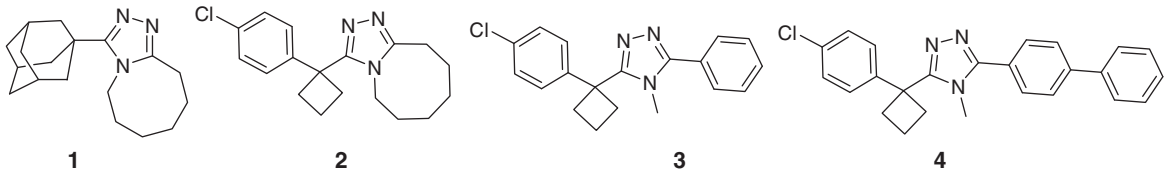


Figure 1. Triazole leads.

reduce PXR activity. Our first set of analogs with increased polarity included benzoic acids and their derivatives (Table 2). As predicted, most of these analogs exhibited very low activation of PXR, but generally, HSD1 affinities also decreased. Carboxamides (**6**, **15**) were more potent HSD1 inhibitors than the corresponding benzoic acids (**5**, **14**) in vitro. Larger amides were generally less potent than the smaller ones. As reported previously for similar triazole analogs,[7] *ortho*-chloro substitution boosted both in vitro and in vivo HSD1 activity. Despite the excellent in vitro activity and selectivity over PXR of analog **15**, the compound had very low PD activity at 4 h (10% inhibition) compared to **4** (90% inhibition), due to its unfavorable PK (po AUCN: 0.02 μM h kg/mg).

Next, we explored a series of the reversed amides (Table 3). Since anilines **16** and **22** had better HSD1 activities than carboxamides **6** and **15**, we expected this potency advantage to carry over into the amides. Indeed, the reversed amides were generally more potent, both in vitro and in vivo, but the PXR activation was also increased with these analogs. Several heterocyclic amide analogs (**20**, **24**) reached desirable activities in vivo with relatively low PXR activation. Zhu previously reported several pyridyl analogs[7] being potent HSD1 inhibitors but with high PXR activation. We continued our efforts on exploring other heterocyclic substitutions (Table 4).

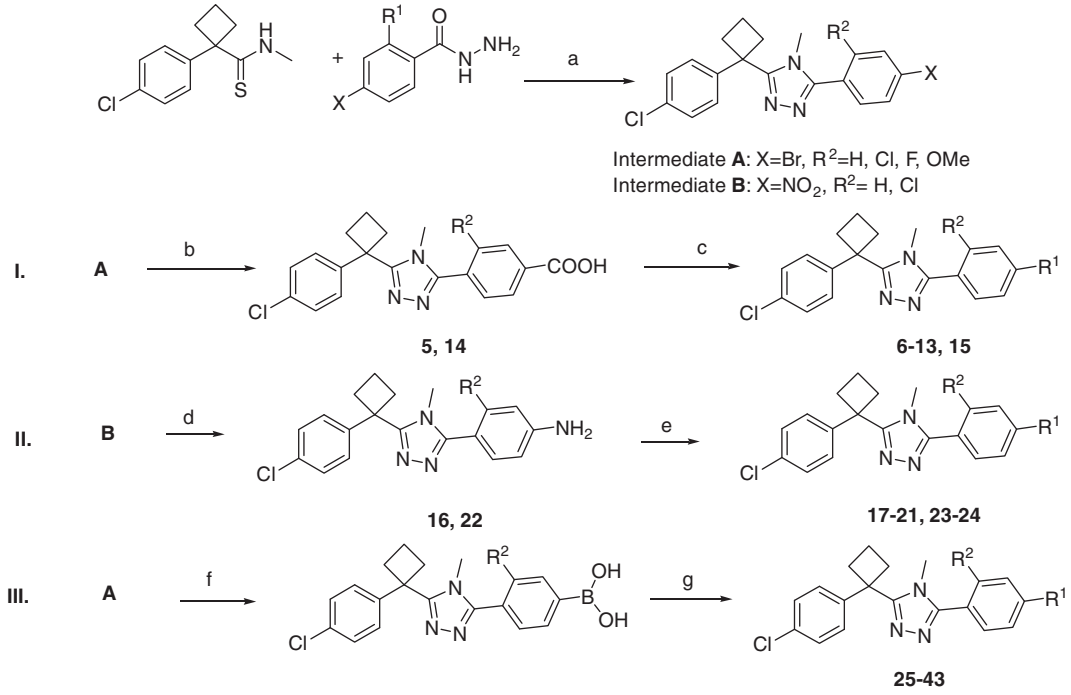
These heterocyclic analogs in Table 4 showed good in vitro potencies, but PD activities were generally low, with the exception of analogs **29**, **35**, and **36**. Thiophene **36** was very active in vitro and in vivo but showed high PXR activation (78% @ 10 μM). Pyrazine **29** and oxazole **35** maintained the desirable in vitro and in vivo profiles and exhibited lower PXR activation (23% and 35% @ 10 μM, respectively).

Next, we studied the effect of varying the *ortho* substituent in the biaryl series on HSD1 and PXR activity (Table 5). Difluoromethoxy group in **42** was prepared from the corresponding phenol intermediate using the reaction conditions reported by Frey.[11] Compound **44** was prepared by cyanoation of 4-bromo-2-chloro intermediate **A** followed by hydrolysis with $NaBO_3$.[12] We have pre-

Table 1
SAR of triazole leads

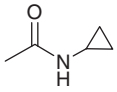
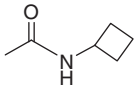
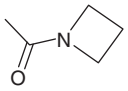
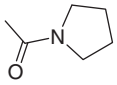
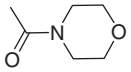
Compd	IC_{50}[a] (nM)		Mouse PD assay		PXR activation	
	Human	Mouse	(%inhibition)		EC_{50}	%activation
	11β-HSD1	11β-HSD1	1 h	4 h	(μM)	@10 μM
1	7.8	98	31	21	–	–
2	1.3	14	91	77	1.6	100
3	1.7	52	47	29	–	–
4	11	4	86	90	1.7	92

[a] Most of the IC_{50} values reported in this Letter are single determinations. For compounds where multiple determinations were obtained (compound **1**), standard error of the mean (SEM) was ±5%.



Scheme 1. Reagents and conditions: (a) TMSOTf, AgOTf, toluene, 100 °C; (b) *n*-BuLi, CO_2, THF, −78 °C; (c) RNH_2, EDC, HOBt, DIPEA, CH_2Cl_2, rt; (d) 10% Pd–C, H_2, MeOH, EtOAc; (e) RCOCl, Py, CH_2Cl_2; (f) triisopropyl borate, *n*-BuLi, THF, −78 °C to rt; (g) heteroaryl halide, $Pd(PPh_3)_4$ or $Cl_2Pd(dppf)$, Na_2CO_3, toluene, EtOH, water, 100 °C.

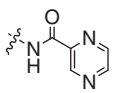
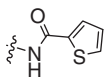
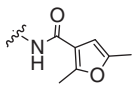
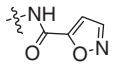
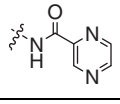
Table 2
SAR of carboxylic acid and amide substitution of phenyl triazole

Compd	R^1 =	R^2 =	IC_{50}[a] (nM)		Mouse PD assay[b]		PXR activation	
			Human	Mouse	(%inhibition)		EC_{50}	%activation
			11β-HSD1	11β-HSD1	4 h	16 h	(μM)	@10 μM (%)
5	COOH	H	76	87	10	−8	>30	−1
6	$CONH_2$	H	1	26	35	4	>30	21
7	CONHEt	H	69	7.8	71	0	>30	18
8	CONH*t*-Bu	H	540	3	71	5	>30	11
9		H	300	11	–	–	>30	14
10		H	470	6.6	–	–	>30	4
11		H	250	62	–	–	>30	10
12		H	650	130	24	0	>30	10
13		H	560	200	–	–	>30	16
14	COOH	Cl	11	19	90	38	18	28
15	$CONH_2$	Cl	<1	1	57	12	>30	16

[a] The human and mouse 11β-HSD2 IC_{50} were >4000 nM for all compounds in this Letter except where otherwise mentioned.
[b] %inhibition of the conversion of [^{3}H]-cortisone to [^{3}H]-cotisol after oral dosing with compound at 10 mg/kg.

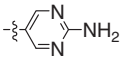
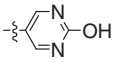
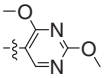
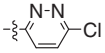
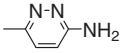
viously reported that *ortho* substitution has a profound effect on HSD1 activity, but the effect on PXR activation had not been studied.[7] As seen in Table 5, none of the analogs showed a better overall profile than the *ortho*-chloro analogs. Fluoro and methoxy derivatives were equipotent, but exhibited worse PXR activities, while hydroxy and carboxamide analogs, in turn, showed an improvement in terms of PXR activation, but suffered from poor HSD1 activities.

Table 3
SAR of amino and its amide derivative substitution of phenyl triazole

Compd	R^1 =	R^2 =	IC_{50} (nM)		Mouse PD assay		PXR activation	
			Human	Mouse	(%inhibition)		EC_{50}	%activation
			11β-HSD1	11β-HSD1	4 h	16 h	(μM)	@10 μM (%)
16	H	H	<1[a]	15	77	12	>30	22
17		H	5.8	9.1	59	10	>30	21
18		H	69	11	67	5	>30	−2.5
19		H	8.7	1	63	2	8.7	55
20		H	9.5	<1	91	81	>30	18
21		H	8	2.8	69	11	>30	21
22	H	Cl	<1[a]	<1	90	38	>30	35
23		Cl	<1	<1	79	27	>30	34
24		Cl	2.6	1.9	82	46	>30	33

[a] The human 11β-HSD2 IC_{50} of **16** was 3100 nM and **22** was 2300 nM.

Table 4
SAR of heterocyclic substitution of chlorophenyl triazoles

Compd	R^1 =	R^2 =	IC_{50} (nM)		Mouse PD assay (%inhibition)		PXR activation	
			Human 11β-HSD1	Mouse 11β-HSD1	4 h	16 h	EC_{50} (μM)	%activation @10 μM (%)
25		Cl	1.5	2.6	46	−4	>30	7
26		Cl	2.2	2.2	34	−5	>30	3
27		Cl	1.2	2.9	–	–	>30	9
28		Cl	14	2	59	10	>30	35
29		Cl	2.3	<1	93	79	>30	23
30		Cl	8.8	2.8	26	14	>30	15
31		Cl	1.5	1.5	40	−7	>30	14
32		Cl	4.8	1.1	–	–	>30	12
33		Cl	1.1	4.1	–	–	23	29
34		Cl	4.8	3.4	63	9	>30	26
35		Cl	11	6	95	67	>30	35
36		Cl	1.1[a]	<1	81	33	3	78

[a] The human 11β-HSD2 IC_{50} of **36** is 1300 nM.

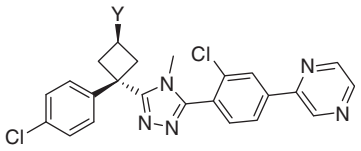
Table 5
SAR of *ortho* substitution of phenyl triazole

Compd	R^1 =	R^2 =	IC_{50} (nM)		Mouse PD assay (%inhibition)		PXR activation	
			Human 11β-HSD1	Mouse 11β-HSD1	4 h	16 h	EC_{50} (μM)	%activation @10 μM (%)
37		Cl	1	1.3	100	26	3.6	35
38		F	1.8	1.6	86	15	>30	43
39		OMe	1.5	0.75	82	21	4.6	65
40		OH	38	1	59	10	>30	45
29		Cl	2.3	<1	93	79	>30	23
41		F	2.8	1.7	91	81	4.8	74
42		$OCHF_2$	3.7	1	88	14	>30	45
43		$CONH_2$	120	68	–	–	>30	4
15	$CONH_2$	Cl	<1	1	57	12	>30	16
44		$CONH_2$	2.2	150	−11	0	>30	−7

Heterocyclic analog **29** had the best overall profile in our SAR studies thus far. However, in rodent PK, **29** exhibited high clearance and a short half life. Previously, we found that fluoro substitution on the cyclobutyl ring reduced metabolism of the cyclobutane group and improved PK,[10] so by analogy we applied the same modification here. The preparation of **45** (Table 6) was the same as that of **29** with the corresponding F-substituted thioamide starting material.[10] Analog **45** has excellent HSD1 inhibitory activity with low PXR activation, greatly improved systemic exposure and low CYP inhibition.

In conclusion, we have described the SAR of substituted phenyl triazole analogs as HSD1 inhibitors and identified an optimized inhibitor **45** with low PXR activation, a favorable CYP inhibition profile, and an excellent PK profile. Results on the study of these HSD1 inhibitors in animal models of metabolic disease will be reported in separate communications from our laboratories.

Table 6
SAR of heterocyclic phenyl triazoles with PK and CYP profile



Compd	Y	IC_{50} (nM)		Mouse PD		PXR activation		PK in C57B6 mice				CYP 3A4	CYP 2C9	CYP 2D6
		Human	Mouse	(%inh.)		EC_{50}	%act.	Cl[a]	$T_{1/2}$	AUCN (po)	*F*	IC_{50}	IC_{50}	IC_{50}
		11β-HSD1	11β-HSD1	4 h	16 h	μM	@10 μM (%)	(ml/min/kg)	(h)	(μM h kg/mg)	(%)	(μM)	(μM)	(μM)
29	H	2.3	<1	93	79	>30	23	54	0.7	0.21	30	10	13	16
45	F	5.5	2.3	95	80	>30	23	5	6.8	7.6	96	36	26	25

[a] Blood clearance.

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