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Bis-aryl triazoles as selective inhibitors of 11β-hydroxysteroid dehydrogenase type 1

Susan D. Aster,[a,*] Donald W. Graham,[a] Divya Kharbanda,[a] Gool Patel,[a] Mitree Ponpipom,[a] Gina M. Santorelli,[a] Michael J. Szymonifka,[a] Steven S. Mundt,[b] Kashmira Shah,[b] Marty S. Springer,[b] Rolf Thieringer,[b] Anne Hermanowski-Vosatka,[b] Samuel D. Wright,[b] Jianying Xiao,[b] Hratch Zokian[b] and James M. Balkovec[a]

[a]*Department of Medicinal Chemistry, Merck & Co., Inc., PO Box 2000, Rahway, NJ 07065, USA*
[b]*Department of Cardiovascular Disease, Merck & Co., Inc., PO Box 2000, Rahway, NJ 07065, USA*

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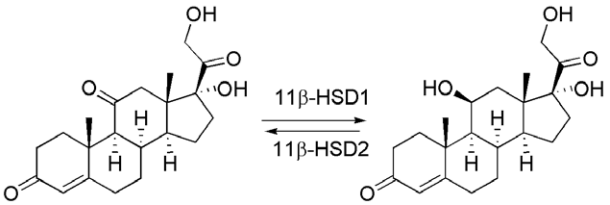
Abstract—3-Aryl-5-phenyl-(1,2,4)-triazoles were identified as selective inhibitors of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1). They are active in both in vitro and an in vivo mouse pharmacodynamic (PD) model. The synthesis and structure activity relationships are presented.

11β-Hydroxysteroid dehydrogenase type 1 (11β-HSD1) resides in the endoplasmic reticulum and catalyzes the conversion of cortisone to the metabolically active glucocorticoid cortisol[1] (Scheme 1).

Elevated levels of cortisol can cause visceral adiposity, diabetes, dyslipidemia and hypertension collectively known as Metabolic Syndrome which can greatly increase the incidence of cardiovascular disease.[2] The structurally related enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) protects the mineralocorticoid receptor from activation by cortisol by catalyzing the reverse reaction of cortisol to cortisone.[3] It has been shown that 11β-HSD1 knockout mice resist metabolic syndrome, while overexpression of 11β-HSD1 in mouse adipose tissue leads to a metabolic syndrome-like phenotype.[4] Since inhibition of 11β-HSD2 is known to result in hypokalemia, sodium retention and hypertension[5] the discovery of a selective 11β-HSD1 inhibitor could lead to an effective treatment for metabolic syndrome.[6]



Scheme 1. Interconversion of cortisone and cortisol.

Published work from our laboratories identified adamantyl triazole **1** (Fig. 1) as a potent and selective inhibitor of both mouse and human 11β-HSD1 enzymes[7]; pharmacodynamic (PD) assays indicated good in vivo activity as well.[8]

m11β-HSD1 IC_{50}:	37 nM	m11β-HSD2 IC_{50}:	>4000 nM
h11β-HSD1 IC_{50}:	109 nM	h11β-HSD2 IC_{50}:	>4000 nM
PD	1hr	85% inh	
	4hr	47% inh	

Further investigation in our laboratory led us to explore the SAR of relatively simple, substituted bis-phenyl triazoles. Schemes 2–4 below show the three different methods that were used to prepare these triazoles.

Keywords: 11β-Hydroxysteroid dehydrogenase; Metabolic syndrome ; Bis-aryl triazoles.
* Corresponding author. Tel.: +732 +1 732 594 5337; fax: +732 +1 732 594 3007; e-mail: susan_aster@merck.com

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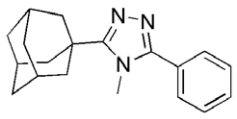


1

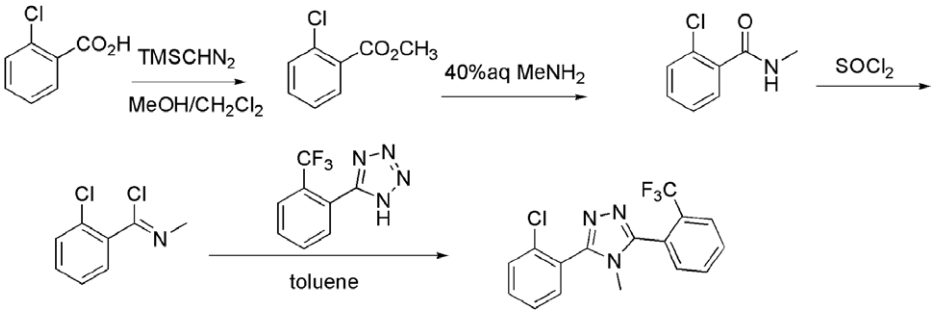
Figure 1. Adamantyl-phenyl triazole.

Data for selected compounds are shown in Table 1. These compounds were tested against both human and mouse 11β-HSD1 and 11β-HSD2 and the table includes data from PD assays as well. IC_{50} values for the mouse and human 11β-HSD2 counterscreen were >4000 nM for all compounds.

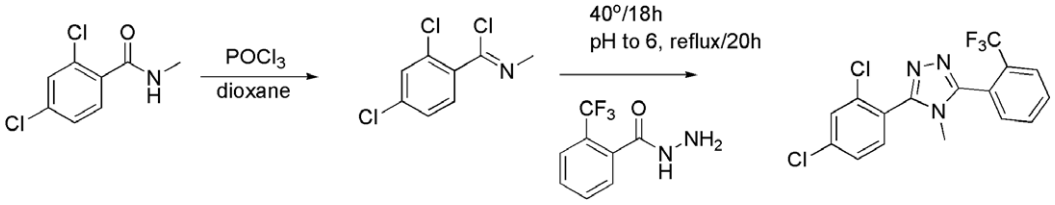
SAR data from compounds **1**–**11** show that *ortho*-Cl, -Br and -CF_3 in both rings is needed for good activity. Comparison of compounds **3** and **12** reveals that *ortho*-F appears to lower the potency. This is seen again with compounds **13**–**15**. Halogen substitution in the *meta* or *para* position (compounds **19**–**21**) also lowers activity. The poor potency of compounds lacking any substituents in ring 2 (**16**–**18**) suggests that perhaps *ortho*-substitution forces the phenyl out of the plane of the triazole and helps it to more efficiently fill a hydrophobic pocket in the enzyme active site.

We next explored the effect of including non-halogens in ring 2 of the bis-aryl triazoles. Data for these compounds are shown in Table 2.

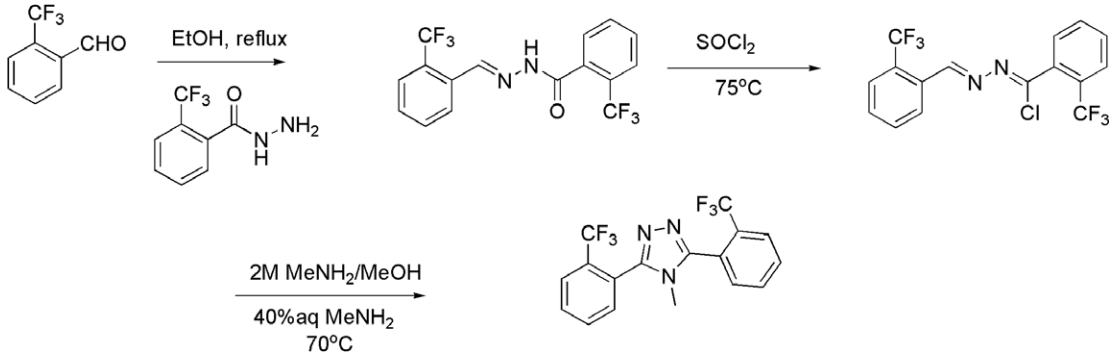
SAR data from compounds **22**–**25** indicate that good potency is maintained when the ring 2 phenyl is substituted at the *para* position with a 4 or 5 carbon chain, with or without a sulfonyl group, and the *ortho* position is occupied by a methyl or chloro group. Compound **26** shows that potency in the PD assay begins to drop when the 5-carbon chain is combined with a lack of substitution at the *ortho* position. A further dropoff in activity is observed (**28** and **29**), when there is no substitution on ring 1. Finally, **30**–**32** show that the strongly electron-withdrawing nitro and methylsulfonyl groups in the *ortho* or *para* position substantially lower activity in the mouse.



Scheme 2. Method A for the preparation of bis-phenyl triazoles.

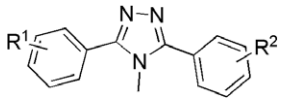


Scheme 3. Method B for the preparation of bis-phenyl triazoles.



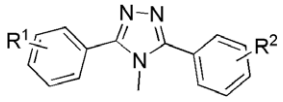
Scheme 4. Method C for the preparation of bis-phenyl triazoles.

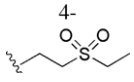
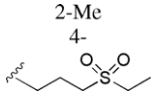
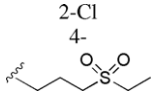
Table 1. SAR of halogen and CF_3-substituted bis-phenyl triazoles

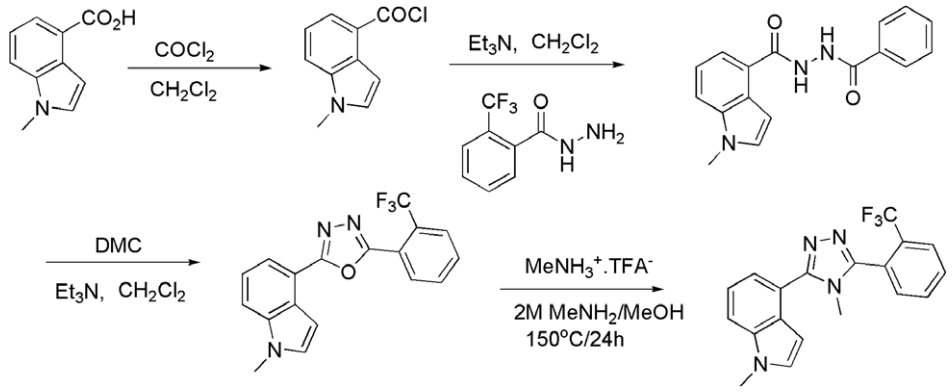


Compound	R^1	R^2	IC_{50} (nM)		PD (% inhibition)	
			hHSD1	mHSD1	4 h	16 h
1	*o*-CF_3	*o*-OCF_3	1.3	4.5	79	2
2	*o*-CF_3	*o*-Cl	3.1	8.6	70	4
3	*o*-CF_3	*o*-Cl, *p*-F	2.6	42	70	5
4	*o*-Cl	*o*-Br	2	12	67	−1
5	*o*-Cl	*o*-Cl	2.9	22	67	−6
6	2,4-di-Cl	2,4-di-Cl	21	89	65	0
7	*o*-CF_3	*o*-Br	1	8	56	0
8	*o*-CF_3	*o*-CF_3	.98	7.1	46	3
9	*o*-CF_3	2,4-di-Cl	1.3	11	43	0
10	*o*-Cl	*o*-Cl,*p*-F	5.8	71	34	2
11	*o*-CF_3	2,3-di-CF_3	3.6	22	27	0
12	*o*-CF_3	*o*-F,*p*-Cl	15	100	—	—
13	2,4-di-Cl	*o*-F	20	180	—	—
14	*o*-CF_3	2,3-di-F	32	260	—	—
15	*o*-Cl	2-F, 4-CF_3	88	140	—	—
16	*o*-CF_3	H	27	120	11	4
17	*o*-Cl	H	43	190	−3	—
18	2,4-di-Cl	H	90	850	—	—
19	*o*-CF_3	3,5-di-Cl	89	1300	—	—
20	*o*-Cl	3,4-di-Cl	200	410	—	—
21	2,4-di-Cl	*p*-Cl	630	1500	—	—

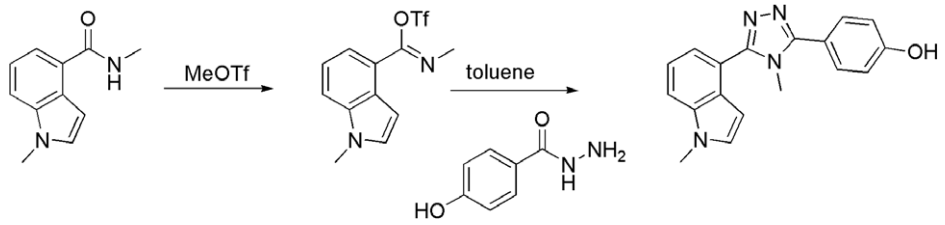
Table 2. SAR of non-halogen (ring 2) with halogen and CF_3-substituted (ring 1) bis-phenyl triazoles



Compound	R^1	R^2	IC_{50} (nM)		PD (% inhibition)	
			hHSD1	mHSD1	4 h	16 h
22	*o*-CF_3	2-Me; 4- 	28	6.4	86	15
23	*o*-CF_3	2-Me 4- 	34	11	76	3
24	*o*-CF_3	2-Cl 4- 	28	8.4	73	11
25	*o*-CF_3	2-Me; 4-*n*-C_4H_9	<1	<1	76	−5
26	*o*-CF_3	4-*n*-C_5H_{11}	5.2	2.9	53	5
27	*o*-Cl	4-*n*-C_5H_{11}	7.7	10	38	3
28	H	4-*n*-C_4H_9	260	68	25	—
29	H	4-*n*-C_5H_{11}	250	54	9	—
30	2,4-di-Cl	*o*-NO_2	13	140	—	—
31	*o*-Cl	*o*-SO_2Me	38	1500	—	—
32	*o*-Cl	*p*-SO_2Me	50	3000	—	—

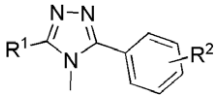


Scheme 5. Method D for the preparation of indole-phenyl triazoles.



Scheme 6. Method E for the preparation of indole-phenyl triazoles.

Table 3. SAR of indole-phenyl triazoles



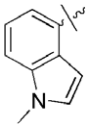
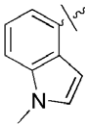
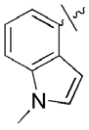
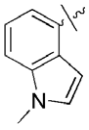
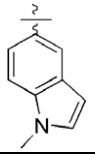
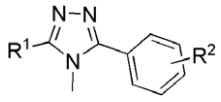
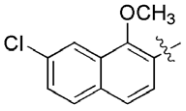
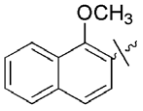
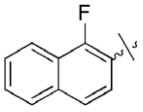
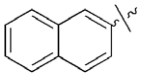
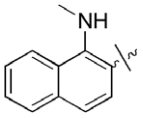
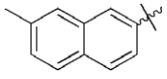
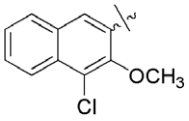
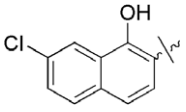
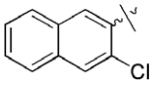
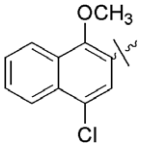
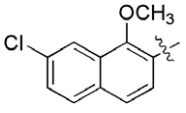
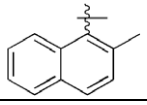
Compound	R^1	R^2	IC_{50} (nM)		PD (% inhibition)	
			hHSD1	mHSD1	4 h	16 h
33		*p*-OH	3.9	6.6	75	−8
34		*o*-Cl	.98	1.2	66	4
35		*o*-CF_3	.98	1.3	52	8
36		H	12	91	9	0
37		H	963	346	—	—

Table 4. SAR of naphthyl-phenyl triazoles



Compound	R^1	R^2	IC_{50} (nM)		PD (% inhibition)	
			hHSD1	mHSD1	4 h	16 h
38		*o*-CF_3	<1	<1	70	74
39		*o*-CF_3	<1	<1	77	31
40		*o*-CF_3	4.3	2.8	37	0
41		*o*-CF_3	26	15	35	5
42		*o*-CF_3	1.4	2.3	24	5
43		*o*-CF_3	9	10	15	−4
44		*o*-CF_3	2.7	20	14	3
45		*o*-CF_3	89	19	14	0
46		*o*-CF_3	2.9	9.8	13	4
47		*o*-CF_3	2.3	2.3	10	−5
48		*o*-SO_2Me	1.9	1.9	7	0
49		*o*-CF_3	4.6	46	0	—

We also investigated the effect of substituting indole for phenyl on the western side of the triazole. These compounds were prepared by Method D (Scheme 5) or Method E, (Scheme 6). Data for compounds in this series are presented in Table 3.

The *N*-methyl indole series (**33**–**35** compared with **36**–**37**) reiterates what was observed with the bis-phenyl compounds in that substitution on the phenyl ring is needed for potency. The indoles differ in that a *para* substituent (*p*-OH in **33**) rather than just the *ortho*, confers very good activity, a phenomenon which was observed with an earlier set of analogs we examined. In addition, the potency is substantially lowered if connection to the triazole is on C5 of the indole (**37**).

The final area that we explored was replacing the indole group with a naphthylene. These triazoles were prepared using Methods A, B and C (Schemes 2–4). Table 4 displays the observed SAR for these compounds.

The potency of compound **38**, the 7-chloro-1-methoxy naphthyl triazole surpasses all the others in the bis-aryl series with its good PD activity extending out to 16 h but seems to have rather specific requirements for maintaining this activity. The 16 h potency is reduced somewhat (**39**) when the chloro substituent is absent. A much larger drop in mouse PD activity is seen with the chloro at the 4-position (**47**), when *o*-SO_2Me replaces the *o*-CF_3 on the phenyl ring (**48**) or when the methoxy is replaced by a hydroxyl group (**45**); human potency is also lower with (**45**). PD potency is generally lower when just a single substituent (1-fluoro, 1-*N*-methylamino, 7-methyl or 3-chloro) is present on the naphthyl ring. Finally, mouse activity drops significantly and is reflected in poor PD as well if the connection to the triazole is on C1 of the naphthyl (**49**).

In summary, we have identified several new classes of potent and selective mouse and human 11β-HSD1 inhibitors. Potency of relatively simple bis-phenyl triazoles has been enhanced by the inclusion of various *o*-halogens and the *o*-CF_3 group. Potency can be maintained by incorporating a 4- or 5-carbon chain in the 4-position. Good activity is observed with an *N*-methyl indole replacing one of phenyls and *para* substitution on the 2nd phenyl ring is well tolerated. Finally, extended PD potency out to 16 h is seen with a 7-chloro-1-methoxy naphthyl group replacing one of the phenyls.

References and notes

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8. For details of enzymatic assays see Ref. 6. The pharmacodynamic (PD) assay was performed as follows. The test compound was dosed orally at 10 mg/kg, and after a prescribed time interval, ^{3}H-cortisone was injected intravenously via the tail vein. After 2 min, blood was collected by cardiac puncture. Steroids were extracted from the serum and analyzed by HPLC. The relative levels of ^{3}H-cortisone and ^{3}H-cortisol were measured and a percent inhibition was calculated.