2-(*S*)-Phenethylaminothiazolones as Potent, Orally Efficacious Inhibitors of 11β-Hydroxysteriod Dehydrogenase Type 1

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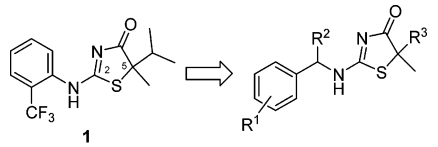
Abstract: 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) is the enzyme that converts cortisone to cortisol. A growing body of evidence suggests that selective inhibition of 11β-HSD1 could potentially treat metabolic syndrome as well as type 2 diabetes. Through modification of our initial lead **1**, we have discovered trifluoromethyl thiazolone **17**. This compound had a K_i of 22 nM, possessed low in vivo clearance, and showed a 91% inhibition of adipose 11β-HSD1 enzymatic activity in a mouse ex vivo pharmacodynamic model.

Glucocorticoid excess, like that observed in Cushing's syndrome,[1] leads to central obesity, insulin resistance, dyslipidemia, and hypertension; a cluster of disorders resembling metabolic syndrome.[2] Correction of glucocorticoid excess in patients with Cushing's syndrome by surgery reverses the features of metabolic syndrome.[3] This observation suggests that glucocorticoid excess may play a role in the development of metabolic syndrome and that suppression of glucocorticoid action could be a potential therapy for insulin resistance and other disorders in type 2 diabetic patients. In addition to biosynthesis in the adrenal gland, cortisol in human (corticosterone in rodents) is regenerated by 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1[a]) at the tissue level.[4] 11β-HSD1 (primarily expressed in liver, adipose, and brain) acts as a reductase in vivo to convert cortisone to the active glucocorticoid cortisol. Its isoform 11β-HSD2 is mainly expressed in the kidney and acts as a dehydrogenase to generate cortisone from cortisol. Although no systemic glucocorticoid excess is observed in patients with metabolic syndrome, 11β-HSD1 expression is increased in the adipose tissue of obese subjects,[5,6] suggesting that there is tissue-specific glucocorticoid excess. Animals with elevated adipose 11β-HSD1 expression developed metabolic syndrome-like phenotypes such as central obesity and insulin resistance.[7] Consistent with these findings, mice deficient in 11β-HSD1 are resistant to diet-induced obesity and insulin resistance.[8,9] Both genetic and pharmacologic studies have demonstrated that tissue-specific reduction of glucocorticoids results in beneficial metabolic effects.[10−12] Adipose-specific expression of 11β-HSD2 in mice, a condition that resembles adipose-specific inhibition of 11β-HSD1, improved insulin sensitivity, reduced adiposity, and increased energy expenditure.[10] In addition, 11β-HSD1 appears to slow the progression of atherosclerosis.[12] These data suggest that 11β-HSD1 could be a drug target for the treatment of metabolic syndrome as well as type 2 diabetes. Recently, a number of small molecule inhibitors of 11β-HSD1 have been disclosed.[13−20]

Early in our 11β-HSD1 program, racemic thiazolone **1** was identified as a potential lead (SPA K_i = 503 nM, Figure 1).[21] Unfortunately, compounds within this series were plagued by high clearances in rats (≥2000 mL/h/kg).[22] To improve the potency and pharmacokinetic properties, we were interested in discovering a suitable replacement for the 2-anilino functionality appended at C-2. This report describes the structure−activity relationship (SAR) and pharmacokinetics (PK) profiles of analogs that substitute a benzyl amine for the 2-anilino moiety present in **1**.



1
h11β -HSD1
SPA K_i = 503 nM

Figure 1. 2-anilino and 2-benzyl thiazolones.

The 2-benzylamino thiazolone core was constructed via the two different methods shown in Scheme 1. The first route involved the reaction of a benzyl amine with 2-bromo-3-methylbutanoyl isothiocyanate. Alternatively, the starting benzyl amine was converted to the intermediate thiourea via a two-step protocol (benzoyl isothiocyanate then KOH/MeOH). Reaction of the thiourea with 2-bromo-3-methylbutanoic acid in refluxing EtOH provided the desired thiazolone. This cyclization could also be conducted in the microwave (ethyl 2-bromo-3-methylbutanoate, diisopropylethyl amine (DIEA), EtOH), which reduced the reaction time.

For our scintillation proximity assay (SPA), compounds were tested against recombinant human 11β-HSD1 using ^{3}H-cortisone as the substrate.[23] Our whole cell assay measured the conversion of cortisone to cortisol in a CHO cell line stably overexpressing human 11β-HSD1 (Table 1).[23] Substitution of the 2-(2-trifluoromethyl)anilino functionality present in **1** with phenylmethylamine resulted in a 10-fold increase in potency (**2**, K_i = 65 nM). Further investigation of this scaffold revealed that potency of **2** was unchanged with the incorporation of (*S*)-phenethylamine at C-2 (**3**, K_i = 50 nM); however, the potency decreased with the corresponding *R*-epimer (**4**, K_i = 130 nM). Although the biochemical potencies of **2** and **3** were similar, the whole cell activity of **3** (IC_{50} = 20 nM) was higher when compared to **2** (IC_{50} = 53 nM). Due to more potent cellular activity, we focused our efforts on constructing analogues of thiazolone **3**.

Incorporation of a trifluoromethyl group at the 3- or 4-position (**5** and **6**, Table 2) of the phenyl ring resulted in no statistically significant change in biochemical potency relative to thiazolone **3** (K_i = 87 and 45 nM, respectively). However, the 2-CF_3 analog displayed a notable increase in potency (**7**, K_i = 18 nM). The activity was further improved with the addition of a fluorine atom at the 2-position (**8**, K_i = 3 nM). Incorporation of other

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[a] Abbreviations: 11β-HSD1, 11β-hydroxysteroid dehydrogenase type 1; 11β-HSD2, 11β-hydroxysteroid dehydrogenase type 2; SAR, structure−activity relationship; PK, pharmacokinetics; SPA, scintillation proximity assay; PD, pharmacodynamic.

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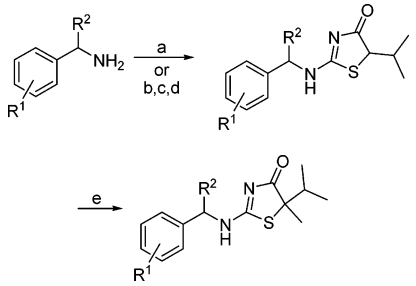
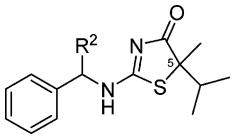
Scheme 1. General Preparation of 2-Benzylaminothiazolones[a]



[a] Reagents and conditions: (a) 2-bromo-3-methylbutanoyl isothiocyanate, NEt_3, CH_2Cl_2, 0 °C to rt; (b) benzoyl isothiocyanate, CH_2Cl_2, 0 °C to rt; (c) KOH, MeOH, rt; (d) 2-bromo-3-methylbutanoic acid, NaOAc, EtOH, 90 °C, 24 h or ethyl 2-bromo-3-methylbutanoate, DIEA, EtOH, MW, 150 °C, 1 h; (e) 4 equiv LDA, 8 equiv MeI, THF, −78 °C.

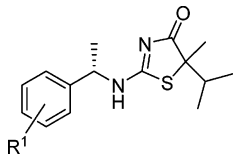
Table 1. SAR of the 2-Benzylamine



cmpd[a]	R^2	h11β-HSD1 SPA K_i[b] (nM)	whole cell IC_{50}[b] (nM)
2	H	65 ± 19	53 ± 10
3	*S*-Me	50 ± 22	20 ± 9
4	*R*-Me	130 ± 13	268 ± 98

[a] A 1:1 mixture of epimers at C-5. [b] Potency data is reported as an average of at least three runs ± the SEM.

Table 2. SAR of the 2-(*S*)-Phenethylamine



cmpd[a]	R^1	h11β-HSD1 SPA K_i[b] (nM)	whole cell IC_{50}[b] (nM)
5	4-CF_3	87 ± 22	170 ± 52
6	3-CF_3	45 ± 9	40 ± 16
7	2-CF_3	18 ± 5	41 ± 2
8	2-F	3 ± 1	18 ± 5
9	2-Cl	8 ± 2	10 ± 4
10	2-Br	7 ± 2	18 ± 4
11[c]	2-F	4 ± 1	4 ± 0.5
12[d]	2-F	9 ± 4	18 ± 8

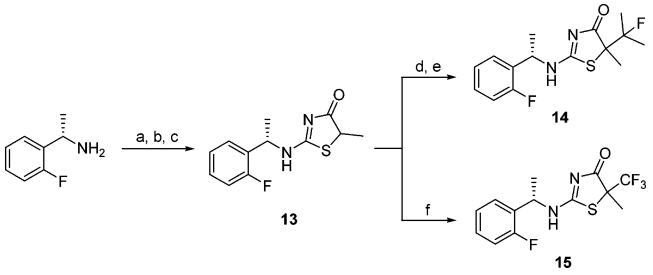
[a] A 1:1 mixture of epimers at C-5 unless otherwise noted. [b] Potency data is reported as an average of at least 3 runs ± the SEM. [c] Single isomer with *S*-configuration at C-5. [d] Single isomer with *R*-configuration at C-5.

halogens (i.e., **9**, **10)** in the 2-position did not further improve the potency. Separation of the C-5 epimers of 2-fluorobenzyl derivative **8** revealed that the more active isomer (**11**) had a K_i and whole cell IC_{50} of 4 nM.[23] X-ray crystallographic analysis of **11** confirmed the *S*-configuration at C-5.[23]

Although thiazolone **11** showed excellent potency in our 11β-HSD1 SPA and whole cell assays, this molecule exhibited high clearance in rats (CL = 2570 mL/h/kg, Table 3). In an analogous series of compounds, metabolite identification revealed that the isopropyl group appended at C-5 was prone to oxidative metabolism. Therefore, we hypothesized that replacing this functionality with a metabolically stable surrogate would reduce the clearance.

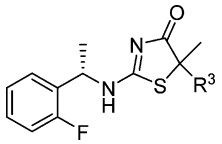
To this end, two fluorinated derivates (**14** and **15**) were synthesized from intermediate **13**, which was obtained via the three-step sequence described in Scheme 2. 5-Methylthiazolone **13** underwent a lithium diisopropylamide (LDA)-mediated aldol reaction with acetone. The resulting tertiary alcohol was converted to the desired fluoride **14** upon treatment with diethylaminosulfur trifluoride (DAST). For the synthesis of **15**, attempts to directly trifluoromethylate the enolate of compound **13** proved problematic. However, it was discovered that the trimethylsilyl enolether of **13** underwent smooth trifluoromethylation when exposed to *S*-(trifluoromethyl)dibenzothiophenium-3-sulfonate in MeCN.[24]

Scheme 2. Synthesis of Fluorinated Analogs **14** and **15**[a]



[a] Reagents and conditions: (a) benzoyl isothiocyanate, CH_2Cl_2; (b) KOH, MeOH, rt; (c) 2-bromopropanoic acid, NaOAc, EtOH, 90 °C; (d) LDA, acetone, −78 °C; (e) DAST, CH_2Cl_2, −78 °C to rt; (f) (i) NaHMDS, THF, −20 °C; (ii) TMSCl, −20 °C; (iii) *S*-(trifluoromethyl)dibenzothiophenium-3-sulfonate, MeCN, rt.

Table 3. Potency Data and PK Profiles for **11**, **14**, **15**, **16**, and **17** in Male Sprague−Dawley Rats



cmpd[a]	R^1	h11β-HSD1 SPA K_i[b] (nM)	whole cell IC_{50}[b] (nM)	C_{max}[c] (ng/mL)	V_{SS}[d] (mL/kg)	CL[d] (mL/h/kg)	%F[c]
11[e]	*i*-Pr	4 ± 1	4 ± 0.5	176	5733	2570	20
14	$CF(CH_3)_2$	18 ± 2	18 ± 2	1079	1662	890	47
15	CF_3	20 ± 3	56 ± 6	1044	2976	501	55
16[f]	CF_3	48 ± 4	96 ± 35	1227	1661[g]	576[g]	50
17[e]	CF_3	22 ± 2	33 ± 7	4628	1201	188	75

[a] A 1:1 mixture of epimers at C-5 unless otherwise noted. [b] Potency data is reported as an average of at least 3 runs ± the SEM. [c] 10 mg/kg oral dose (0.1% Tween 80, 0.5% CMC, 99.4% water). [d] 2 mg/kg intravenous dose (100% solution in DMSO). [e] Single isomer with *S*-configuration at C-5. [f] Single isomer with *R*-configuration at C-5. [g] 2 mg/kg intravenous dose (1% Tween 80 in OraPlus).

Fluorinated analog **14** showed good potency and exhibited dramatically improved in vivo clearance (CL = 890 mL/h/kg) relative to thiazolone **11** (Table 3). Epimeric mixture **15** also showed good potency (K_i = 20 nM, whole cell IC_{50} = 56 nM) and exhibited even lower clearance (501 mL/h/kg). Separation of individual epimers of **15** revealed that the more potent isomer, **17**, displayed both low clearance and high bioavailability in rats (188 mL/h/kg and 75%, respectively). In addition to good potency and rat PK, **17** was found to be a selective inhibitor of 11β-HSD1. Thiazolone **17** had weak activity against both human 11β-HSD2 (IC_{50} > 10 μM) and glucocorticoid receptor (IC_{50} > 50 μM). Because thiazolone **17** also displayed acceptable potency for murine 11β-HSD1 (K_i = 130 nM), this molecule was chosen to be tested in a mouse ex vivo pharmacodynamic (PD) assay.[25]

In this PD study, male C57/Bl6 mice were dosed orally with 30 mg/kg of thiazolone **17**. At 2 and 6 h post-dose, the animals were sacrificed and the inguinal fat pads were removed and

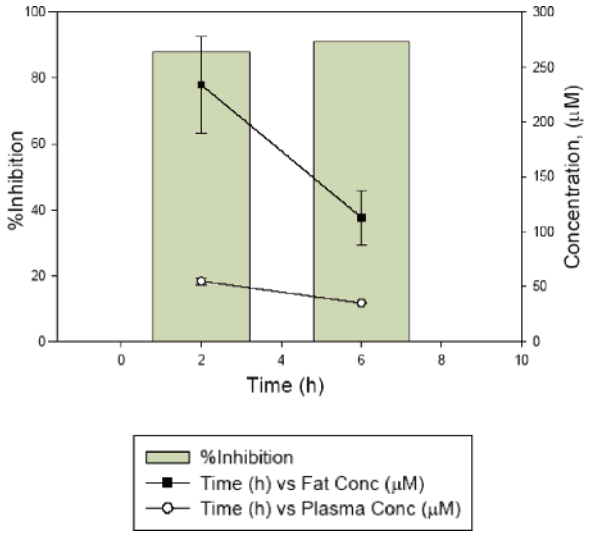


Figure 2. Acute effects of thiazolone **17** as assessed by ex vivo cortisone to cortisol turnover. Percent inhibition of adipose tissue enzyme activity (solid bars) is compared to adipose (solid squares) and plasma (open circles) concentration levels of **17**. Adipose and plasma drug levels are expressed as mean ± SEM of $n = 3$.

assayed for 11β-HSD1 activity. As shown in Figure 2, adipose 11β-HSD1 enzymatic activity was substantially reduced. Relative to vehicle controls, 11β-HSD1 activity in animals treated with **17** was reduced by 88% 2 h after dosing and remained reduced by 91% 6 h post-dose. Absolute levels of **17** were measured in plasma and adipose of these same animals. Levels in adipose ranged from 234 μM at 2 h to 113 μM at 6 h, while plasma levels were 55 μM at 2 h to 35 μM at 6 h.

In summary, through modifications of our original lead **1**, we discovered the potent 11β-HSD1 inhibitor **11** (SPA K_i and whole cell $IC_{50} = 4$ nM). Although potent, thiazolone **11** displayed high in vivo clearance in rats. By replacing the metabolically labile isopropyl moiety at C-5, we were able to overcome this liability. Trifluoromethyl derivative **17** not only possessed a desirable rat PK profile but also exhibited good potency (SPA $K_i = 22$ nM). Furthermore, we have demonstrated that thiazolone **17** can substantially inhibit adipose 11β-HSD1 enzymatic activity in a mouse ex vivo PD model.

Acknowledgment. We thank Dr. Rashid Syed and Dr. Richard J. Staples for determining the X-ray structures of **11** and **17**.

Supporting Information Available: Experimental details for the synthesis and characterization of all compounds as well as the X-ray crystal data for **11** and **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(25) Value determined using an in vitro SPA assay with purified recombinant mouse 11β-HSD1. See Supporting Information.

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