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The discovery of 2-anilinothiazolones as 11β-HSD1 inhibitors

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Abstract—A series of 2-anilinothiazolones were prepared as inhibitors of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1). The most potent compounds contained a 2-chloro or 2-fluoro group on the aniline ring with an isopropyl substituent on the 5-position of the thiazolone ring (compounds **2** and **3**, respectively). The binding mode was determined through the X-ray co-crystal structure of the enzyme with compound **3**. This compound was also ~70-fold selective over 11β-HSD2 and was orally bioavailable in rat pharmacokinetic studies. However, compound **3** was >580-fold less active in the 11β-HSD1 cell assay when tested in the presence of 3% human serum albumin.

The metabolic syndrome is a cluster of cardiovascular risk factors including visceral obesity, insulin resistance, dyslipidemia, and hypertension.[1] Features of metabolic syndrome are also seen in patients with increased circulating glucocorticoids, such as Cushing's syndrome,[2] suggesting that glucocorticoid action may play a role in the development of metabolic syndrome. The enzyme that increases tissue concentrations of glucocorticoids is 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1). Expressed mainly in liver, adipose, and the brain, 11β-HSD1 catalyzes the conversion of inactive cortisone to the active glucocorticoid cortisol. Elevation in tissue cortisol levels increases glucocorticoid action.[3] Although there is no concrete evidence that patients with metabolic syndrome exhibit increased circulating glucocorticoid levels, elevated adipose 11β-HSD1 activity has been observed in obese humans,[4] suggesting that there is increased tissue-specific glucocorticoid action in obesity. Its isoform, 11β-HSD2, is mainly expressed in the kidney and acts as a dehydrogenase to generate cortisone from cortisol.[5] Inhibition of this enzyme might lead to sodium retention, hypokalemia, and hypertension,[5] so inhibition of 11β-HSD2 should be avoided.

The connection between metabolic syndrome and glucocorticoid action was demonstrated in mouse genetic models. Animals with elevated adipose 11β-HSD1 expression developed metabolic syndrome-like phenotypes such as central obesity and insulin resistance.[6] Moreover, mice deficient in 11β-HSD1 are resistant to diet-induced obesity and insulin resistance.[7–9] Adipose-specific expression of 11β-HSD2 in mice, a condition that emulates adipose-specific inhibition of 11β-HSD1, improved insulin sensitivity, reduced adiposity, and increased energy expenditure.[10] Pharmacologic inhibition of 11β-HSD1 in animal models of type 2 diabetes also improved insulin sensitivity.[11] These data indicate that suppression of local glucocorticoid action in tissues through inhibition of 11β-HSD1 may be a viable treatment for the metabolic syndrome and type 2 diabetes. In the last several years, 11β-HSD1 as a therapeutic target for type 2 diabetes has stimulated a lot of interest in the pharmaceutical industry. Mounting evidence

Keywords: 11β-Hydroxysteroid dehydrogenase type 1; 11β-HSD1; Metabolic syndrome; Thiazolone.
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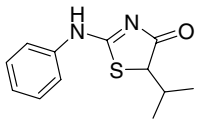


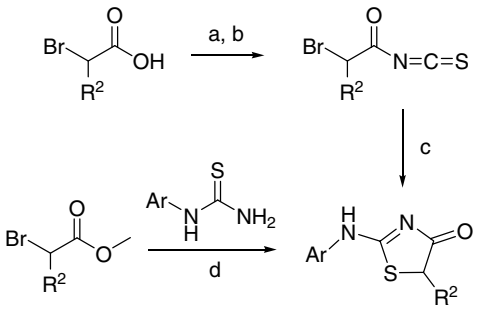
1
11β-HSD1 Ki = 110 nM

Figure 1. 2-Anilinothiazolone compound **1**.

obtained from preclinical studies supports the concept that inhibiting 11β-HSD1 may have a therapeutic benefit by lowering hepatic glucose output and increasing insulin sensitivity.[12,13] Many patent applications and studies on 11β-HSD1 inhibitors illustrate the intense interest in this field.[14–27] In this publication, we describe some of our efforts to identify potent, selective, and bioavailable inhibitors of 11β-HSD1.

Compound **1**, with a K_i = 110 nM, was identified from the high-throughput screening of our internal compound collection (Fig. 1). This compound represented a new class of 11β-HSD1 inhibitors with an unknown binding mode at that time. Initial structure–activity relationship (SAR) exploration included modification of the phenyl moiety to include substituted phenyl and heteroaromatic rings. The isopropyl group of **1** was then replaced with various lipophilic groups. Our synthetic strategy entailed two approaches allowing for rapid modification of either region of the molecule.[27] The first route used the reaction between 2-bromoalkanoyl isothiocyanates and anilines to form thiazolones under basic conditions (Scheme 1, step c). The 2-bromoalkanoyl isothiocyanates were prepared from the corresponding 2-bromoalkanoyl acid chlorides and potassium thiocyanate (Scheme 1, step b). The second route involved the cyclization between a thiourea and 2-alkyl-2-bromoacetate in presence of *N*,*N*′-diisopropylethylamine under microwave irradiation at 120 °C (Scheme 1, step d). The compounds were prepared and tested as racemates unless mentioned otherwise.

Inhibition of 11β-HSD1 and 11β-HSD2 enzymatic activity was determined using a scintillation proximity assay (SPA).[14,28] Cell-based activity was measured by monitoring the conversion of cortisone to cortisol in Chinese hamster ovary cells stably transfected with human 11β-HSD1.[29] Results are reported as the average of at least two independent experiments with at least two replicates at each concentration. The variance in the measurements is expressed as the standard error of the mean (SEM).

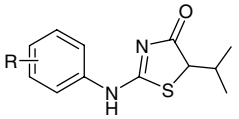


Scheme 1. Reagents and conditions: (a) oxalyl chloride, CH_2Cl_2, rt; (b) KSCN, acetone, rt; (c) $ArNH_2$, triethylamine, CH_2Cl_2; (d) *N*,*N*′-diisopropylethylamine, EtOH, microwave, 120 °C.

In general, compounds with small groups on the 2-position of the phenyl ring were more potent than the parent compound **1**. For example, compounds containing the 2-chloro, 2-fluoro, 2-methyl or 2-trifluoromethyl groups were all potent with K_i values of <40 nM (see compounds **2**–**5**, Table 1). The analog with the larger 2-methoxyl group, compound **6**, was >25-fold less potent than compounds **2**–**5**. The 4-fluoro analog, compound **7**, was 20-fold less potent than its *ortho*-substituted analog **2**. Other analogs containing groups at the 4-position (e.g., phenoxyl and cyclohexyl substituted compounds **8** and **9**) were also significantly less potent than the parent compound **1**. Additional analogs were prepared where the 2-chloro or 2-fluoro groups were retained and an additional group was added to the aromatic ring (see compounds **10**–**13**, Table 1). For all of these analogs, the potency was within twofold of the potency observed for the mono-substituted compounds **2** and **3**. Generally, the cellular potencies for this set of compounds were within two- to threefold of the potency obtained in the biochemical assay, indicating that these compounds had good cell permeability and could readily access the active site of the enzyme in the lumen of the endoplasmic reticulum.

We then replaced the aryl ring with various heteroaromatic groups (see Table 2). Replacing the phenyl group with either 2- or 4-pyridinyl ring (compounds **14** and **15**) resulted in a 23- and 45-fold loss in potency, respectively (compared to analog **1**). Three 5,6-membered ring heterocycles were prepared (see compounds **16**–**18**). The most potent in this set was the 1*H*-indol-4-yl analog

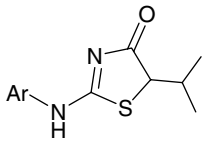
Table 1. SAR of the phenyl ring on compound **1**

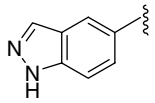
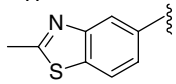
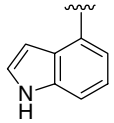
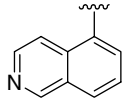


Compound	R	11β-HSD1 K_i (SPA) (nM)[a]	11β-HSD1 IC_{50} (cell) (nM)[a]
1	H	110 ± 10	310 ± 90
2	2-Cl	7.2 ± 2.2	10 ± 2
3	2-F	17 ± 1	50 ± 31
4	2-Me	27 ± 5	120 ± 60
5	2-CF_3	23 ± 3	28 ± 11
6	2-OMe	1000 ± 200	1500 ± 270
7	4-F	340 ± 100	230 ± 70
8	4-OPh	220 ± 13	
9	4-Cyclohexyl	660 ± 190	3300 ± 1800
10	2-Cl, 4-Cl	18 ± 9	40 ± 18
11	2-Cl, 6-Cl	13 ± 2	21 ± 7
12	2-F, 5-F	12 ± 1	28 ± 10
13	2-F, 4-F	26 ± 3	45 ± 16

[a] Values are reported as the avg. ± SEM. For assay details, see Refs. 28,29.

Table 2. SAR of heteroaromatic rings in place of the phenyl ring on compound **1**



Compound	Ar	11β-HSD1 K_i (SPA) (nM)[a]	11β-HSD1 IC_{50} (cell) (nM)[a]
14	Pyridin-2-yl	4900 ± 300	1400 ± 400
15	Pyridin-4-yl	2500 ± 900	
16		1000 ± 150	1500 ± 400
17		510 ± 10	
18		210 ± 14	360 ± 130
19		32 ± 9	200 ± 70

[a] Values are reported as the avg. ± SEM. For assay details, see Refs. 28,29.

which had a $K_i = 210$ nM. The most potent heteroaromatic compound prepared was the 5-isoquinolinyl analog **19**, which had a $K_i = 32$ nM. However, compound **19** had a cell IC_{50} sixfold less potent than the SPA K_i, which may indicate that this compound did not penetrate the cell as well as other analogs in this series.

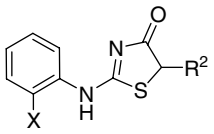
Having found that the 2-chloro and 2-fluoro groups on the phenyl ring improved potency, we kept this group constant while exploring the SAR of the C-5 substituent (see Table 3). In the 2-chlorophenyl series, the C-5 methyl analog **20** was 49-fold less potent than the C-5 isopropyl analog **2**. Analogs in the 2-chlorophenyl series with a larger C-5 group, that is, cyclohexyl or cyclopentyl analogs **21** and **22**, had potencies very similar to the isopropyl analog **2** (K_is from 6 to 11 nM). For the 2-fluorophenyl series, the cyclohexyl or cyclopentyl analogs **23** and **24** showed a slight improvement in potency over the isopropyl analog **3**. Interestingly, the 2-chlorophenyl analogs **21** and **22** were more selective for 11β-HSD1 over 11β-HSD2 than the 2-fluorophenyl analogs, **23** and **24** (420- and 710-fold for 2-chloro analogs **21** and **22**, respectively, vs. ~70-fold for 2-fluorophenyl analogs, **23** and **24**).

To better understand the interactions between the lead compounds with the active site of 11β-HSD1, the ternary X-ray co-crystal structure of compound **3**, NADPH, and human 11β-HSD1 was determined using conditions previously described.[30] The overall fold and other structural features of the dimeric, crystallized 11β-HSD1 protein have been previously discussed.[30] Compound *R*-**3** interacts with a single monomer of the dimeric 11β-HSD1 and forms several key interactions with the amino acids located in the active site (Fig. 2). Only the *R*-enantiomer of compound **3** formed a complex with the enzyme, which is consistent with the activities of the separated isomers of **3**, where *R*-**3** was found to be 20-fold more potent than *S*-**3** (see Table 4). The isopropyl function of *R*-**3** occupies a large hydrophobic pocket comprised primarily of Thr124, Leu126, Tyr183, and Ala223 (some residues not shown for clarity). The isopropyl-bearing methine carbon of *R*-**3** is 3.79 Å from the pendant amide carbonyl carbon of NADPH in the co-crystal structure. If the stereoisomer *S*-**3** were to bind, a steric clash with the NADPH cofactor would occur, which may be why *S*-**3** is less potent than *R*-**3**.

Table 4. Activity of compound **3** and its separated enantiomers[36]

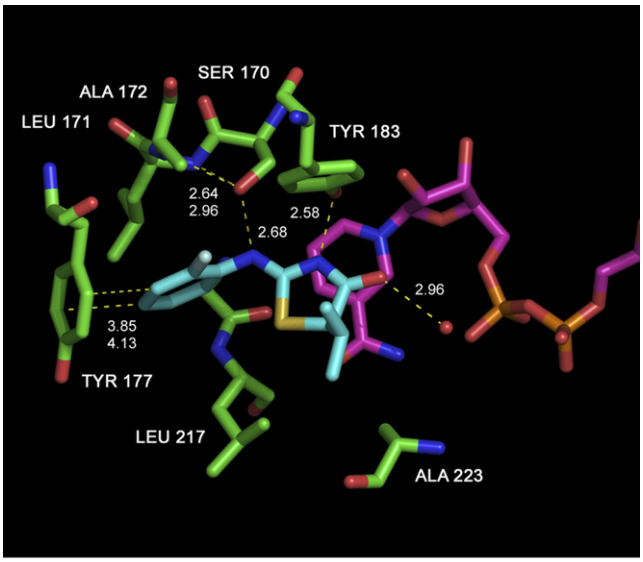
Compound	11β-HSD1 K_i (SPA) (nM)[a]	11β-HSD1 IC_{50} (cell) (nM)[a]
3	17 ± 12	50 ± 31
R-**3**	7 ± 1	15 ± 4
S-**3**	140 ± 30	97 ± 42

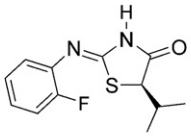
Table 3. SAR of 5-alkyl groups on compounds **2** and **3**



Compound	X	R^2	11β-HSD1 K_i (SPA) (nM)[a]	11β-HSD1 IC_{50} (cell) (nM)[a]	11β-HSD2 IC_{50} (SPA)(nM)[a]
20	Cl	Me	350 ± 70		
2	Cl	Isopropyl	7.2 ± 2.2	10 ± 2	2510 ± 600
21	Cl	Cyclohexyl	11 ± 5	33 ± 9	4600 ± 3400
22	Cl	Cyclopentyl	6.3 ± 2.7	17 ± 7	4500 ± 3500
3	F	Isopropyl	17 ± 1	50 ± 31	
23	F	Cyclohexyl	7.2 ± 2.3	43 ± 10	530 ± 310
24	F	Cyclopentyl	5.3 ± 1.2	19 ± 11	380 ± 190

[a] Values are reported as the avg. ± SEM. For assay details, see Refs. 28,29.





R-**3**, exo tautomer

Figure 2. Key binding interactions of compound **3** (cyan) with human 11β-HSD1. Active site residues are depicted in green, NADPH in purple. Bound active site water is depicted in red.

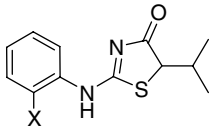
From the hydrogen bonding interactions of the OH groups on Ser170 and Tyr183 with *R*-**3**, it is apparent that *R*-**3** *existed as the exo-tautomer* (see Fig. 2).[31] In the X-ray structure, the CH_2OH side chain of Ser170 is oriented *syn* to residues Leu171 and Ala172, with the side chain oxygen atom located at a distance of 2.64 and 2.96 Å from the respective backbone NH nitrogen atoms of these residues (see Fig. 2.) In this orientation, the lone pairs of the side chain oxygen of Ser170 function as acceptors to the Leu171 and Ala172 backbone NH protons, leaving the Ser170 OH proton to interact with the imine-like nitrogen of the exocyclic double bond tautomer of *R*-**3**.[32] Compound *R*-**3** forms a hydrogen bond between the endocyclic NH and the side chain oxygen on Tyr183. The hydrogen on the side chain hydroxyl of Tyr183 may interact with either a ribose OH oxygen of NADPH and/or solvent waters.

Turning to the other regions of the molecule, the carbonyl group of *R*-**3** interacts (2.96 Å) with a bound water molecule near the solvent exposed region of the protein. Additionally, the phenyl ring is perpendicular to the plane of the thiazolone core, maximizing conjugation with the exocyclic nitrogen lone pair and forming an edge-to-face (T-shaped) aromatic stacking interaction[33] (ca. 4 Å) with the phenyl moiety of Tyr177. The 2-fluoro substituent is thought to aid in potency through both enhanced van der Waals contacts within the active site, as well as enhancement of the interaction between the adjacent, *meta* aryl C–H and the electron-rich π-face of Tyr177.[34] Through site-directed mutagenesis studies, we have previously shown that Tyr177 is also an important residue for binding the licorice derived inhibitor, glycyrrhetinic acid.[35]

To test whether these compounds could be used for in vivo studies, the rat pharmacokinetics for some of our most potent compounds were determined (see Table 5). For compounds **3**–**5**, the in vivo clearance (CL) was well below liver blood flow, and for compounds **4** and **5**, the oral bioavailability was >70%.[37] The volume of distribution (V_{ss}) was less than the CL for all three of these compounds which resulted in half-lives of less than 1 h. The plasma protein binding (PPB) for compounds **4** and **5** was >99%, which might explain the low V_{ss}. To assess the impact of PPB on potency for this set of compounds, the cellular assay was run in the presence of 3% human serum albumin (HSA) to mimic the in vivo concentration of albumin. In all three cases, the whole cell IC_{50}s in the presence of 3% HSA were >1 μM, which represents a 10–580-fold loss in activity. The high protein binding and its effect on potency and half-life may limit the in vivo efficacy of these compounds in rats.

In summary, from the lead 2-anilinothiazolone **1**, we identified several compounds that have K_is < 10 nM. The most potent compounds in this series had IC_{50}s < 50 nM in a whole cell assay and were at least 70-fold more selective for 11β-HSD1 over 11β-HSD2. As revealed through an X-ray structure of lead compound **3** with 11β-HSD1, this molecule binds as the *exo* tautomer, forms hydrogen bonding interactions with Ser170 and Tyr183, and forms a hydrophobic, edge-to-face stacking interaction with Tyr177 within

Table 5. Rat pharmacokinetics, protein binding, and protein shift of selected 2-anilinothiazolones



Compound	X	CL (L/h/kg)[a]	V_{ss} (L/kg)[a]	$t_{1/2}$ (h)[a]	%F[b]	%PPB[c]	Cell IC_{50} with 0% HSA (nM)	Cell IC_{50} with 3% HSA (μM)
3	F	0.30	0.16	0.84	nd	nd	50	>10
4	Me	1.30	0.42	1.23	87	99.6	120	1.3
5	CF_3	0.76	0.54	1.35	73	99.8	28	2.0

[a] Dosed IV (0.5 mg kg^{-1}) in DMSO.
[b] Dosed PO (2.0 mg kg^{-1}) in 0.5% CMC/0.1% Tween 80 in water.
[c] Human plasma protein binding measured by equilibrium dialysis.

the active site. The rat pharmacokinetic profile for some of these compounds had moderate to low clearance and oral bioavailability >70%. However, there was a 10–580-fold loss in activity when the whole cell assay was run in the presence of 3% HSA for compounds **3**–**5**. The data reported here on the 2-anilinothiazolones complement the SAR we previously reported on benzyl thiazolone analogs.[14] Additional SAR on the thiazolone core structure will be reported in due course.

Supporting information: X-ray data have been deposited in the RCSB Protein Data Bank (www.rcsb.org). PDB ID: 2RBE.

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31. B3LYP/6-31G* + SCRF solvation calculations also predict the exocyclic double bond tautomer of **3** to be the dominant species in aqueous solution.[32]
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36. Compound **3** was separated using preparative supercritical fluid chromatography (SFC). Eluant: 55:45 CO_2(l)/CH_3OH; column: Chiralpak AD-H (250 × 21 mm, 5 μm); flow rate: 65 mL/min; column temp: 40 °C.
37. Compounds **3**–**5** are racemates and it is possible that the single enantiomers may have different PK. However, the protein shift was not significantly different for the separated enantiomers.