Further Studies with the 2-Amino-1,3-thiazol-4(5*H*)-one Class of 11β-Hydroxysteroid Dehydrogenase Type 1 Inhibitors: Reducing Pregnane X Receptor Activity and Exploring Activity in a Monkey Pharmacodynamic Model

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A series of compounds containing the 2-amino-1,3-thiazol-4(5*H*)-one core were found to be potent inhibitors of the enzyme 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1). One of our lead compounds from this series activated the human nuclear xenobiotic receptor, pregnane X receptor (PXR). To try and mitigate the PXR activity, we prepared analogues of our lead series that contained polar groups on the right-hand side of the thiazolone. Several analogues containing amides or alcohols appended to the C-5 position of the thiazolone showed a significant reduction in PXR activity. Through these structure−activity efforts, a compound containing a *tert*-alcohol group off the C-5 position, analogue (*S*)-**33a**, was found to have an 11β-HSD1 K_i = 35 nM and negligible PXR activity. Compound (*S*)-**33a** was advanced into a pharmacodynamic model in cynomolgus monkeys, where it inhibited adipose 11β-HSD1 activity after being orally administered.

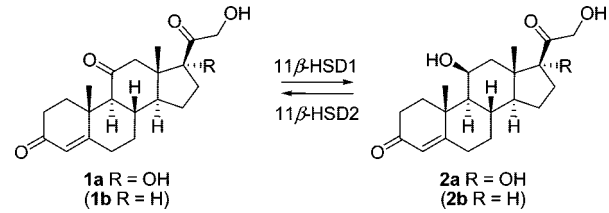
Introduction

An estimated 171 million people worldwide suffered from diabetes in the year 2000.[1] By the year 2030, the number of people afflicted with diabetes could more than double.[1] The majority of these cases are defined as type II diabetes mellitus (T2DM), a condition characterized by an abnormally high fasting blood glucose (>126 mg/dL) and insulin resistance. Left untreated, T2DM can lead to debilitating sequelae such as retinopathy, neuropathy, coronary artery disease, and ischemic stroke. While many therapies are currently available for managing the symptoms associated with T2DM (e.g., insulin secretagogues, insulin sensitizers, and modulators of glucose uptake and production), improved therapies are being sought that target novel biological pathways involved in this disease. One target that has piqued the interest of many pharmaceutical companies is the enzyme 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1[a]).[2−5]

Expressed mainly in liver, adipose, and brain, 11β-HSD1 is an NADPH-dependent enzyme that primarily acts as a reductase to convert the inactive glucocorticoid cortisone (**1a**) to the active form, cortisol (**2a**) (Scheme 1). In rodents, 11β-HSD1 converts dehydrocorticosterone (**1b**) to the active form, corticosterone (**2b**). The isozyme of 11β-HSD1, 11β-HSD2, is mainly expressed in the kidney and acts as a dehydrogenase to convert cortisol (**2a**) to cortisone (**1a**) (Scheme 1). In adipose and liver, cortisol activates the glucocorticoid receptor (GR), which upregulates the expression of genes involved in energy homeostasis, that is, genes that regulate gluconeogenesis,[6] adipogenesis, and lipolysis.[7] Because 11β-HSD1 is the enzyme that controls the tissue levels of the GR ligand, cortisol, excessive activity of 11β-HSD1 is thought to play a role in the development of hyperglycemia, insulin resistance, and lipid disorders. Evidence supporting this hypothesis was obtained in mice that have genetically altered 11β-HSD1 expression. Mice that overexpress 11β-HSD1 in adipose tissue developed central obesity, insulin resistance, and dyslipidemia.[8] Conversely, mice deficient in 11β-HSD1 were resistant to diet-induced obesity and insulin resistance.[9−11] In addition, orally available 11β-HSD1 inhibitors have been shown to improve glucose tolerance and insulin resistance in mouse models of type II diabetes [12,13] (see Chart 1 for examples of 11β-HSD1 inhibitors[14−18]). Although there is no concrete evidence that patients with diabetes exhibit increased circulating glucocorticoid levels, elevated adipose 11β-HSD1 activity has been correlated with obesity in humans, suggesting that there is increased tissue-specific GR activity in obesity.[19,20] The weight of evidence suggests that inhibition of 11β-HSD1 is an attractive strategy to lower GR activity, which could be useful for treating type II diabetes.

We have previously described a class of 11β-HSD1 inhibitors containing the 1,3-thiazol-4(5*H*)-one core (referred to as thiazolone).[21,22] In our publications,[21,23] compound **3** was shown to be a potent and selective inhibitor of 11β-HSD1, which

Scheme 1. Interconversion of Cortisone, **1a** (Dehydrocorticosterone, **1b**), to Cortisol, **2a** (Corticosterone, **2b**)



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[a] Abbreviations: 11β-HSD1, 11β-hydroxysteroid dehydrogenase; CYP, cytochrome P450; PXR, pregnane X receptor; thiazolone, 1,3-thiazol-4(5*H*)-one; AUC, area under the curve; POC, percent of control.

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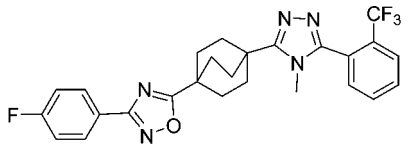
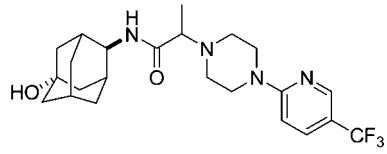
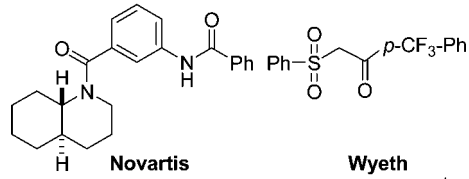
Chart 1. Examples of 11β-HSD1 Inhibitors



Merck
IC_{50} = 2.2 nM[a]

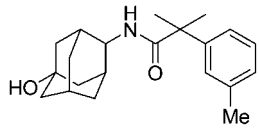


Abbott
K_i = 5 nM[b]



Novartis
IC_{50} = 14 nM[c]

Wyeth
IC_{50} = 190 nM[d]



Janssen
IC_{50} = 5 nM[e]

[a] Ref 14. [b] Ref 15. [c] Ref 16. [d] Ref 17. [e] Ref 18.

inhibited adipose 11β-HSD1 activity in vivo and was efficacious in rodent models of diabetes.[24] After further profiling in drug metabolism studies, compound **3** was found to activate the human pregnane X receptor (PXR), a nuclear receptor that upregulates genes involved in drug metabolism [e.g., cytochrome P450 (CYP) 3A4 and multidrug resistance proteins]. By activating PXR, the efficacy of a compound may be reduced since PXR upregulates proteins that may increase the clearance of a drug.[25] Our strategy to reduce the PXR activation of compound **3** was to replace the CF_3 group at the 5-position with polar groups to decrease the logP, a strategy that is known to lower PXR activity.[26] Also, the X-ray data[27] and a homology model[28] of PXR suggest that its binding site is very hydrophobic, so adding polar groups to our compounds might make binding to this site unfavorable. Because we knew from our previous work that the left-hand α-methyl benzylamine group of **3** was important for 11β-HSD1 activity and metabolic stability,[21] we kept this group in the analogues prepared in this paper. Herein, we describe the structure−activity relationship (SAR) of 2-aminobenzyl thiazolone analogues that contain amides, carboxylic acids, and alcohols appended to the 5-position, and we describe how some of these changes affected PXR activity.

Chemistry

Compounds containing an aryl group at the 5-position of the thiazolone were prepared using the methods outlined in Schemes 3 and 4. Thiourea **5** was prepared in two steps from the commercially available amine **4** by first treating the amine with benzoyl isothiocyanate followed by basic hydrolysis. Thiourea **5** was treated with α-bromo carboxylates **7** to give thiazolones, which were then methylated at the 5-position of the thiazolone ring to give compounds **8** and **9**. The aryl bromide on compound **9** was converted to a carboxymethyl group through a palladium-mediated carbonylation reaction to provide intermediate **10**. This intermediate was converted to the carboxylic acid **11**, which was then converted to amide derivatives **12a**−**e** and **13**. Alternatively, the ester **10** was converted to alcohol **14**, which was then converted in a three-step process to amide **15**.

The thiourea **5** was also treated with methyl 2-bromopropanoate to give 5-methyl thiazolone **16** as a key intermediate, which was used for the preparation of the final compounds shown in Scheme 4. Amide **18** was prepared from thiazolone **16** by first alkylating the 5-position with 4-(bromomethyl)benzonitrile and then hydrolyzing the nitrile with KOH. To introduce an aromatic ring directly onto the 5-position of the thiazolone, aryl bromide **19** was cross-coupled with intermediate **16** using LiHMDS, $Pd_2(dba)_3$, and BINAP. The nitrile was then hydrolyzed as before to provide amide compound **20**. The cross-coupling procedure used to prepare **20** was also used in the preparation of analogues **23**, **26**, and **29**. Amide analogue **30** was prepared from alcohol **29** through commonly used functional group interconversions.

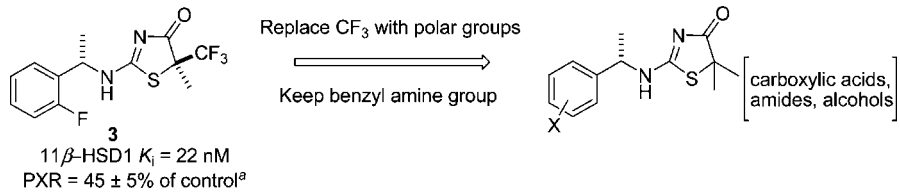
Compounds containing tertiary alcohols off the 5-position of the thiazolone were prepared as outlined in Scheme 5. The thioureas for these compounds were prepared from commercially available benzyl amines using the procedure described above. To prepare 5-methyl thiazolones **32**, thioureas **31** were heated with 2-bromoproprionic acid and NaOAc (Compound **16** was prepared by this alternate procedure in addition to being prepared by the method illustrated in Scheme 4. See the Experimental Section). Tertiary alcohol derivatives **33** were prepared from thiazolone **32** using LDA and the appropriate ketone. Analogue **35** was prepared from 5-methyl thiazolone **16** by alkylating the 5-position with 2-methyloxirane to give intermediate **34**. Oxidation of **34** and subsequent addition of methyl Grignard afforded the desired tertiary alcohol **35**.

Results and Discussion

Inhibition of 11β-HSD1 and 11β-HSD2 enzymatic activity was measured using a scintillation proximity assay (SPA).[21,29] Cell-based activity was measured by monitoring the conversion of cortisone to cortisol in Chinese hamster ovary (CHO) 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).

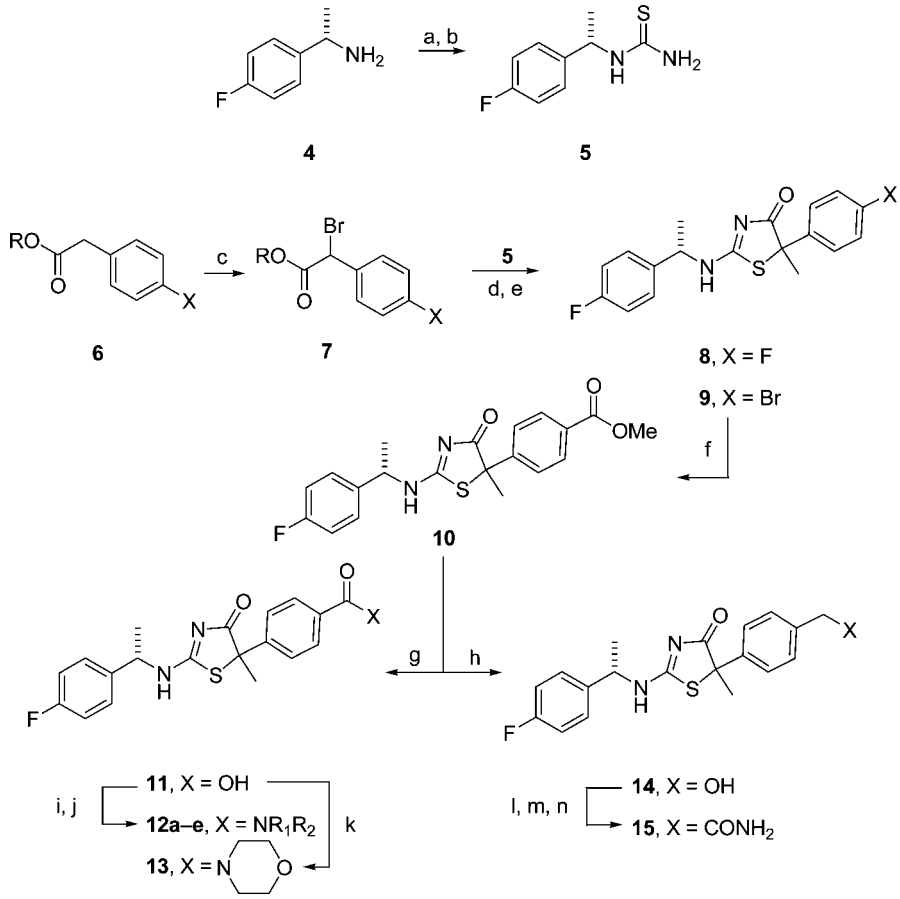
During the expansion of the SAR for lead compound **3**, analogue **8**, containing a 4-fluoro phenyl group at the 5-position of the thiazolone, was found to have 11β-HSD1 activity similar to our lead compound **3** (both have K_i values = 22 nM, see Table 1). Rather than trying to substitute polar groups off the CF_3 group of **3**, we felt that the C-5 phenyl group on **8** was an easier platform to append polar groups. Table 1 summarizes the analogues of **8** that we prepared that contained polar groups on the C-5 aromatic ring. The first attempt at incorporating a polar group led to carboxylate analogue **11**, which had a K_i = 3.5 μM. We were able to quickly improve the activity of this compound with ester and primary amide derivatives, **10** and **12a**, which were ≥80-fold more potent than carboxylate analogue **11**. Keeping the primary amide in place, and extending the aromatic ring by one methylene group, gave compound **18**, which was ~40-fold less potent than the amide analogue **12a**. Because activity decreased with the addition of a methylene

Scheme 2. Strategy To Address the Issue of PXR Activation



[a] PXR activity with a 20 μM concentration of **3** (100% of control is equivalent to the activity achieved with 12.5 μM rifampin).

Scheme 3[a]

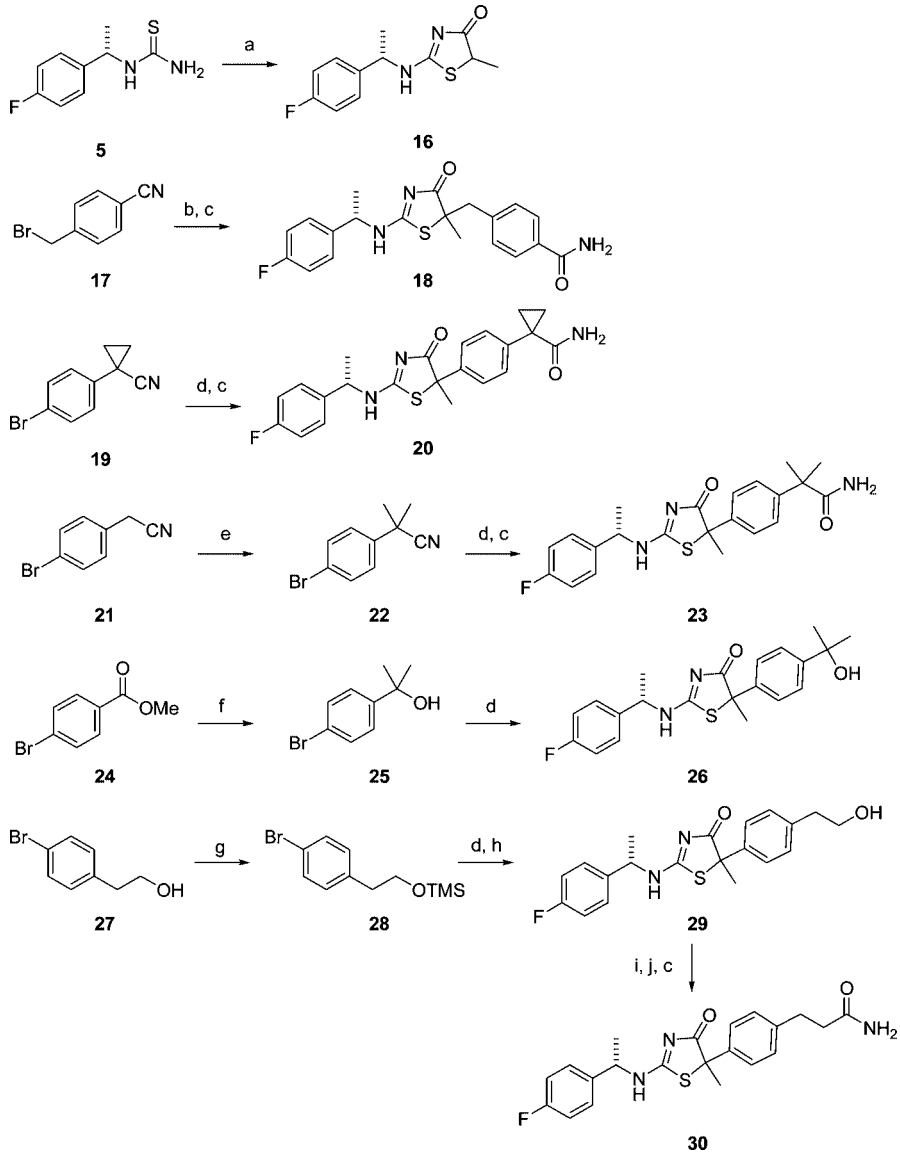


[a] Reagents and conditions: (a) Benzoyl isothiocyanate, CH_2Cl_2. (b) K_2CO_3, THF/methanol/H_2O, 98% for two steps. (c) NBS, AIBN, CCl_4, 80 °C (X = F, R = H, 86%; X = Br, R = Et, 96%). (d) X = F, NaOAc, ethanol, reflux, 48%; X = Br, NEt(*i*-Pr)$_2$, ethanol, reflux, 71%. (e) LDA, CH_3I, THF, −78 °C, (X = F, 68%, X = Br, 97%). (f) CO, PPh_3, $Pd(OAc)_2$, KOAc, methanol, DMF, 100 °C, 99%. (g) LiOH, H_2O, THF, methanol, reflux, 62%. (h) $LiAlH_4$, THF, 0 °C, 70%. (i) $SOCl_2$, CH_2Cl_2, room temperature, 100%. (j) HNR_1R_2, THF, 0 °C, 8−79%. (k) Morpholine, HOBT, dicyclohexanecarbodiimide, CH_2Cl_2, room temperature, 91%. (l) $SOCl_2$, dioxane, room temperature, 100%. (m) Bu_4NCN, CH_2Cl_2, reflux, 63%. (n) KOH, *t*-BuOH, 100 °C, 17%.

spacer, subsequent analogues in this series contained an aromatic ring directly attached to 5-position of the thiazolone ring. Tertiary and secondary amide analogues, **12b**−**12d** and **13**, were all less potent (K_i values = 76−330 nM) than the primary amide analogue **12a**, but the pyrrolidine amide analogue **12e** was slightly more potent than **12a**. Four other primary amide analogues were also prepared. Analogue **15**, containing a methylene spacer between the amide and the aryl ring, was ∼2-fold less potent than amide analogue **12a**. An analogue containing geminal methyl groups at the benzylic position (analog **23**) and an analogue with a two-carbon spacer (**30**) were also less potent than primary amide **12a**. However, the analogue containing a cyclopropyl ring at the benzylic position, compound **20**, was slightly more potent than the primary amide **12a** (cf. K_i = 30 vs 44 nM). Analogues containing alcohols were also tested in this series of compounds. As observed in the SAR of the primary amides, the alcohol containing geminal methyl groups at the benzylic position (compound **26**) and the alcohol with a two-carbon spacer (compound **29**) were less potent that analogue containing the primary alcohol (compound **14**, K_i = 46 nM).

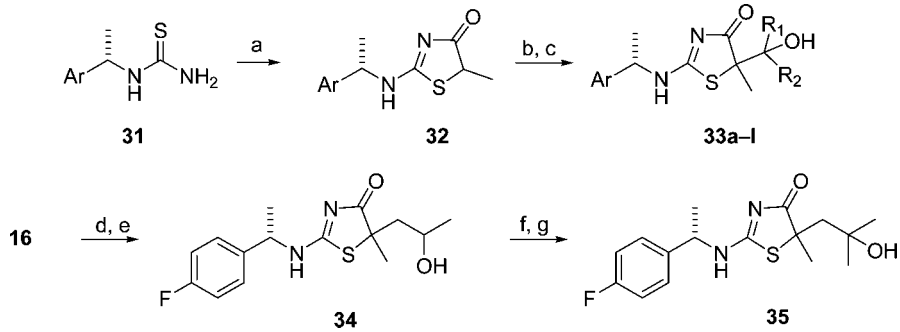
The most potent compounds from Table 1 were then tested in the PXR reporter gene assay. Analogue **8** had PXR activity of ca. 65% of control when tested at both 2 and 20 μM. At a test concentration of 2 μM, however, analogues with polar groups off the right-hand phenyl ring, compounds **12a**,**e**, **20**, and **14**, showed little activation of PXR (Table 2). Raising the test concentration to 20 μM, pyrrolidine amide **12e** and cyclopropyl analogue **20** activated PXR at 35 and 97% of control, respectively. On the other hand, the primary amide **12a** and alcohol **14**, at a test concentration of 20 μM, activated PXR by only 9.3 and 25%, respectively, which was significantly lower than our lead compound **3** (PXR = 45% of control). While these results were encouraging, amide analogue **12a** was found to be

Scheme 4[a]



[a] Reagents and conditions: (a) Methyl 2-bromopropanoate, Et_3N, ethanol, 100 °C, microwave, 88%. (b) Compound **16**, LDA, THF, −78 to 0 °C, 87%. (c) KOH, *t*-BuOH, 85−100 °C, 66−86%. (d) Compound **16**, LiHMDS, $Pd_2(dba)_3$, BINAP, toluene, 95 °C, 26−37%. (e) *t*-BuOK, 18-crown-6, CH_3I, THF, −78 °C to room temperature, 99%. (f) CH_3MgBr, THF, 0 °C to room temperature, 74%. (g) TMSCl, $NEt(i\text{-}Pr)_2$, K_2CO_3, CH_2Cl_2, 0 °C to room temperature, 84%. (h) K_2CO_3, methanol, room temperature, 93%. (i) Imidazole, iodine, PPh_3, CH_2Cl_2, room temperature, 82%. (j) Bu_4NCN, CH_2Cl_2, reflux, 65%.

Scheme 5[a]

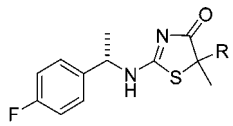


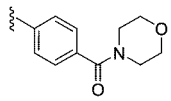
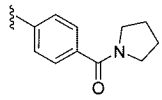
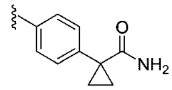
[a] Reagents and conditions: (a) 2-Bromopropanoic acid, NaOAc, ethanol, reflux, 88−100%. (b) LDA, THF, −78 °C. (c) $R_1R_2C{=}O$, THF, −78−0 °C, 17−100%. (d) Lithium bis(trimethylsilyl)amide, THF, 0 °C. (e) 2-Methyloxirane, $LiClO_4$, THF, 0 °C to room temperature, 71%. (f) Dess−Martin periodinane, CH_2Cl_2, 83%. (g) CH_3MgBr, THF, 0 °C, 61%.

an efflux substrate in CACO-2 cells (efflux ratio = 10). Therefore, we focused on expanding the SAR of derivatives containing alcohols to maintain low PXR activation.

In the next set of analogues, we added hydroxyl groups to aliphatic chains on the C-5 position (Table 3). An analogue containing the 2-methyl-propan-2-ol side chain, compound **35**,

Table 1. SAR of Thiazolones Substituted with Polar Aryl Rings

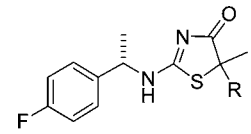


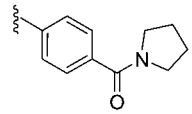
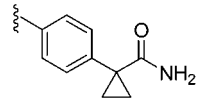
#	R =	hu11β-HSD1 SPA[a] $K_i \pm$ SEM[c] (nM)	hu11β-HSD1 cell[b] $IC_{50} \pm$ SEM[c] (nM)
8	phenyl-4-F	22 ± 6	53[d]
11	phenyl-4-COOH	3500 ± 1200	
10	phenyl-4-$COOCH_3$	26 ± 6	
12a	phenyl-4-$CONH_2$	44 ± 4	79 ± 3
18	CH_2-(phenyl-4-$CONH_2$)	1800 ± 600	
13		330± 20	
12b	phenyl-4-CONH-*cyclo*-Pr	240 ± 60	
12c	phenyl-4-CONH-*cyclo*-Pn	120 ± 20	
12d	phenyl-4-$CONHCH_3$	76 ± 13	
12e		28 ± 8	
15	phenyl-4-CH_2CONH_2	84 ± 33	
23	phenyl-4-$C(CH_3)_2CONH_2$	83 ± 14	
30	phenyl-4-$CH_2CH_2CONH_2$	60 ± 14	680 ± 110
20		30 ± 3	110 ± 40
26	phenyl-4-$C(CH_3)_2OH$	220 ± 10	
29	phenyl-4-CH_2CH_2OH	79 ± 32	130 ± 70
14	phenyl-4-CH_2OH	46 ± 1	110[d]

[a] K_i was derived from a SPA using human 11β-HSD1 expressed in *E. coli* cells and ^{3}H-cortisone as the substrate. [b] IC_{50} was determined from a whole cell assay using CHO cells overexpressing human 11β-HSD1. [c] SEM for at least two independent determinations. [d] $n = 1$.

was 6-fold less potent than the benzyl alcohol analogue **14** but had similar PXR activity. Shortening the side chain further gave tertiary alcohol **33a**, which was nearly as potent as benzyl alcohol analogue **14** in the biochemical assay, but showed a significant decrease in PXR transactivation [10% (not significant) of control at a test concentration of 20 μM]. Encouraged by the lower PXR activity, more analogues were prepared that contained the tertiary alcohol directly attached to the C-5 position of the thiazolone. The biochemical and cell-based potency of such analogues improved with tertiary alcohol analogues containing the cyclobutyl and cylcopentyl groups (analogues **33b** and **33c**). However, in both cases, PXR activity increased (26 and 61% of control). Therefore, we kept the dimethyl tertiary alcohol in place and tried to improve potency by modifying the left-hand side of the molecule. Analogues

Table 2. Transactivation of PXR[a]



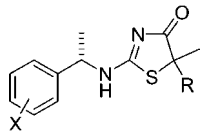
#	R =	2 μM (% of control)[b]	20 μM (% of control)[b]
8	Phenyl-4-F	64 ± 15	65 ± 7
12a	phenyl-4-$CONH_2$	0.8 ± 2.8	9.3 ± 1.3
12e		4.1 ± 1.0	35 ± 7
20		6.7 ± 1.6	97 ± 8
14	phenyl-4-CH_2OH	2.3 ± 2.0	25 ± 2

[a] PXR luciferase reporter gene assay. [b] Data were expressed as a percent of control (POC) where 100% of control is equivalent to the activity achieved with 12.5 μM rifampin. Compounds were run in triplicate and have been reported with the SEM.

containing groups larger than a fluorine atom at the *para*-position, analogues **33d**−**f**, or the analogue without a substituent on the phenyl ring, analogue **33h**, were less potent than analogue **33a**. Moving the fluoro to the *meta*-position gave analogue **33i**, which was ∼3-fold less potent than *para*-fluoro analogue **33a**. The *ortho*-fluoro analogue **33j**, on the other hand, was 2-fold more potent than **33a**. Other analogues with electron-withdrawing groups at the *ortho*-position, for example, **33k** and **33l**, were also more potent than *para*-fluoro analogue **33a**. However, all three of these *ortho*-substituted analogues, **33j**−**l**, were also more potent in the PXR assay than the *para*-fluoro substituted analogue **33a**. From this last set of results, PXR transactivation seems to be affected by subtle changes made to the phenyl ring on **33**. For example, the slight change of moving the fluoro from the *para*-position to the *ortho*-position led to a statistically significant increase in PXR transactivation (cf. the PXR values for **33a** and **33j**). Even more surprising is the PXR activity of the unsubstituted analogue **33h**, which had a PXR activity nearly 7-fold higher than the *para*-fluoro analogue **33a**. Because the goal of this work was to mitigate PXR transactivation, we only measured PXR functional activity and not PXR binding. We cannot, therefore, exclude the possibility that **33a** may bind to PXR and not activate the receptor.[30] Nevertheless, compound **33a** seemed to strike the right balance between 11β-HSD1 potency and low PXR activity, so we subjected compound **33a** to further in vitro and in vivo testing.

Before running additional studies with compound **33a**, the two diastereomers were separated using supercritical fluid chromatography. The C-5 (*S*)-isomer,[31] compound (*S*)-**33a**, had a K_i and cell IC_{50} of ∼35 nM, while the corresponding (*R*)-isomer was 6−8-fold less potent (Table 4). Compound (*S*)-**33a** was cocrystallized with human 11β-HSD1 (Figure 1) and occupied the catalytic binding pocket of the enzyme. As we observed with a related thiazolone inhibitor,[32] the OH of Tyr183

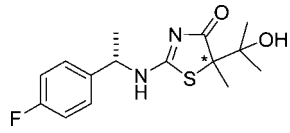
Table 3. SAR of Thiazolones Substituted with Aliphatic Alcohols



#	X=	R =	hu11β-HSD1[g] SPA[a] $K_i \pm$ SEM[c] (nM)	hu11β-HSD1[g] cell[b] $IC_{50} \pm$ SEM[c] (nM)	PXR[e] @ 20 μM (% of control) $\pm$ SEM[f]
14	4-F	phenyl-4-CH_2OH	46 ± 1	110[d]	25 ± 2
35	4-F	$CH_2C(CH_3)_2OH$	290 ± 40	310 ± 140	28 ± 8
33a	4-F	$C(CH_3)_2OH$	65 ± 10	51 ± 45	10 ± 2
33b	4-F		49 ± 5	32 ± 7	26 ± 3
33c	4-F		25 ± 3	11 ± 3	61 ± 5
33d	4-CN	$C(CH_3)_2OH$	6500 ± 1300		
33e	4-Br	$C(CH_3)_2OH$	210 ± 70		
33f	4-CH_3	$C(CH_3)_2OH$	130 ± 80		
33g	4-Cl	$C(CH_3)_2OH$	110 ± 20	78 ± 42	
33h	4-H	$C(CH_3)_2OH$	100 ± 30		68 ± 5
33i	3-F	$C(CH_3)_2OH$	220 ± 30	180 ± 80	
33j	2-F	$C(CH_3)_2OH$	34 ± 11	70 ± 28	19 ± 3
33k	2-Cl	$C(CH_3)_2OH$	26 ± 6	18 ± 6	63 ± 8
33l	2-CF_3	$C(CH_3)_2OH$	25 ± 1	43 ± 5	43 ± 7

[a] K_i was derived from a SPA using human 11β-HSD1 expressed in *E. coli* cells and ^{3}H-cortisone as the substrate. [b] IC_{50} was determined from a whole cell assay using CHO cells overexpressing human 11β-HSD1. [c] SEM for at least two independent determinations. [d] $n = 1$. [e] PXR luciferase reporter gene assay. [f] Data were expressed as a POC where 100% of control is equivalent to the activity achieved with 12.5 μM rifampin. Compounds were run in triplicate and have been reported with the SEM. [g] Compounds **33a**−**c** and **33j**−**l** had IC_{50} values > 10000 nM in the human 11β-HSD2 assay.

Table 4



#	hu11β-HSD1 activity SPA[a] $K_i \pm$ SEM[c]	hu11β-HSD1 activity cell[b] $IC_{50} \pm$ SEM[c]
(*R*)-**33a**	210 ± 38	300 ± 80
(*S*)-**33a**	35 ± 1	34 ± 3

[a] K_i was derived from a SPA using the human 11β-HSD1 expressed in *E. coli* cells and ^{3}H-cortisone as the substrate. [b] IC_{50} was determined from a whole cell assay using CHO cells overexpressing the human 11β-HSD1. [c] SEM for at least two independent determinations.

formed a hydrogen bond with the C-2 NH of (*S*)-**33a**, and the backbone NH of Ala172 formed a hydrogen bond with the carbonyl group of thiazolone (*S*)-**33a**. The Ser170 OH formed a hydrogen bond with the side chain oxygen of Tyr183, which was also observed in our previously reported structure.[32] The phenyl ring of (*S*)-**33a** formed an edge-to-face π-stacking interaction with Tyr183, which was likely enhanced by the

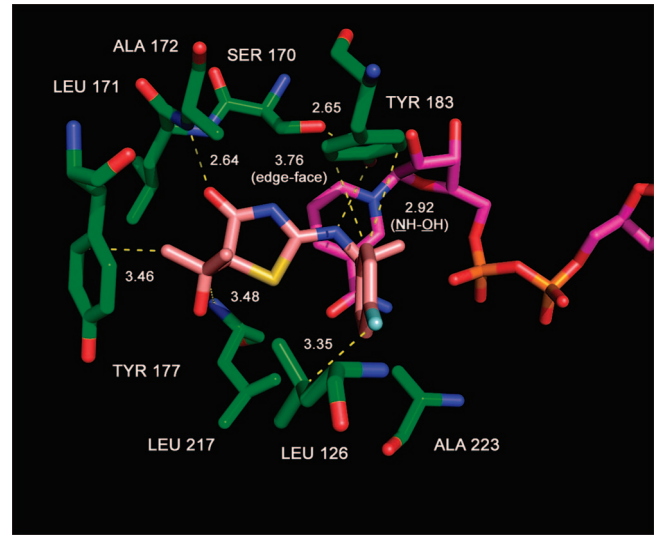


Figure 1. X-ray structure of human 11β-HSD1−(*S*)-**33a** complex.

presence of the *para*-fluoro substituent.[33] The fluorophenyl ring also formed hydrophobic contacts with the side chain of Leu126 and other nearby residues. The "rearward" methyl group at the chiral C-5 position of (*S*)-**33a** formed a van der Waals contact with the backbone nitrogen atom of Leu217. The proximity of the C-5 substituent to Leu217 may explain why (*R*)-**33a** is less potent than (*S*)-**33a** in the human 11β-HSD1 assay, since the bulkier tertiary alcohol group at the C-5 of (*R*)-**33a** would suffer a steric clash with Leu217. The tertiary alcohol group of (*S*)-**33a** formed a hydrophobic contact with the side chain of Tyr177, but the hydroxyl group did not appear to form a direct H-bond contact with the protein. Instead, the hydroxyl may have interacted with solvent molecules. From prior crystallographic studies, water molecules have been observed in the 11β-HSD1 active site.[22,32]

In the PXR assay, the POCs at 20 μM of compound (*S*)-**33a** and its diastereomer (*R*)-**33a** were 6 and 11, respectively. The result for (*S*)-**33a** represented a greater than 7-fold improvement over the PXR value obtained for compound **3**. To determine how PXR activation correlated with induction of CYP3A4, we measured the mRNA expression and enzyme activity of CYP3A4 in cryopreserved human hepatocytes.[34−36] Using hepatocytes from two different donors, compound **3** at a test concentration of 20 μM showed an increase in both CYP3A4 mRNA and enzyme activity (67−110 and 56−64% of control, respectively). Compound (*S*)-**33a**, on the other hand, only showed a modest increase in CYP3A4 mRNA expression and enzyme activity (13−45 and 10−17% of control, respectively). The CYP3A4 activities for compounds **3** and (*S*)-**33a** are consistent with the results from the PXR reporter gene assay; that is, increased PXR transactivation led to higher levels of CYP3A4 mRNA expression and enzyme activity.

Encouraged by the PXR results, we next assessed (*S*)-**33a** for nonhuman 11β-HSD1 activity and in vivo pharmacokinetics (PK) to determine which species might be most appropriate for in vivo assessment (Table 6). In mouse, rat, dog, and monkey, the in vivo pharmacokinetics showed that compound (*S*)-**33a** had moderate to low clearance and oral bioavailabilities between 56 and 100%. In the 11β-HSD1 biochemical and cell-based assays, (*S*)-**33a** was less potent in the rodent assays ($K_i = 100$ and 300 nM for mouse and rat, respectively) than in the nonrodent assays ($K_i = 12$ and 48 nM for dog and monkey, respectively). Because compound (*S*)-**33a** was less potent in the rat assay than in the monkey assay, we chose to run the in vivo

Table 5. Human PXR Activity and CYP3A4 Activity in Cryopreserved Hepatocytes

		activity in cryopreserved human hepatocytes			
		CYP3A4 mRNA (% of control)[b] ± SD		CYP3A4 activity[c] (% of control)[b] ± SD	
	PXR activity (% of control) ± SEM[a]	donor DJV	donor NPV	donor DJV	donor NPV
rifampin	100 ± 10	100 ± 9	100 ± 5	100 ± 2	100 ± 3
3	45 ± 5	110 ± 10	67 ± 4	64 ± 10	56 ± 5
(*S*)-**33a**	6 ± 2	45 ± 4	13 ± 1	17 ± 1	10 ± 1

[a] PXR luciferase reporter gene assay. Data are expressed as a POC where 100% of control is equivalent to the activity achieved with 12.5 μM rifampin. Compounds were run in triplicate and have been reported with the SEM. [b] Data are expressed as a POC where 100% of control is equivalent to the activity achieved with 20 μM rifampin. Compounds were run twice and have been reported with the SD. [c] Enzyme activity was determined by measuring the conversion of midazolam to 1′-hydroxy midazolam. For details, see the Experimental Section.

Table 6. Potency and Pharmacokinetics of Compound (*S*)-**33a** in Four Different Species

	11β-HSD1 activity		in vivo pharmacokinetics[d]				
species	SPA[a] K_i ± SEM[c]	cell[b] IC_{50} ± SEM[c]	CL (L $h^{-1}kg^{-1}$)	V_{ss} (L kg^{-1})	$t_{1/2}$ (i.v., h)	AUC_{oral}[e] (ng h mL^{-1})	F_{oral} (%)
mouse	100 ± 18	140 ± 60	1.6	1.4	3.3	6500	100
rat	300 ± 70	340 ± 80	0.31	2.5	5.6	9200	56
dog	12 ± 2	45 ± 22	0.085	0.88	7.3	54000	91
monkey	48 ± 13	42 ± 6	1.2	1.9	2.2	5700	65

[a] K_i was derived from a SPA using the species 11β-HSD1 expressed in *E. coli* cells and ^{3}H-cortisone as the substrate. [b] IC_{50} was determined from a whole cell assay using CHO cells overexpressing the species 11β-HSD1. [c] SEM for at least two independent determinations. [d] Mouse dosed i.v., 2 mg kg^{-1} in 10% dimethylacetamide, 23% water, 67% PEG 400; p.o. 10 mg kg^{-1} in 0.1% Tween 80, 0.5% CMC, 99.4% water. Rat dosed i.v., 2 mg kg^{-1} in DMSO; dosed p.o., 5 mg kg^{-1} in 0.1% Tween 80, 0.5% CMC, 99.4% water. Dog dosed i.v., 2 mg kg^{-1} in 10% dimethylacetamide, 23% water, 67% PEG 400; dosed p.o., 5 mg kg^{-1} in 1% Tween 80, 47.5% OraPlus, 51.5% water. Monkey dosed i.v., 2 mg kg^{-1} in 10% dimethylacetamide, 40% water, 50% PEG 400; dosed p.o., 10 mg kg^{-1} in 10% dimethylacetamide, 40% water, 50% PEG 400. [e] AUC_{oral} = oral area under the curve (AUC) for time 0−∞.

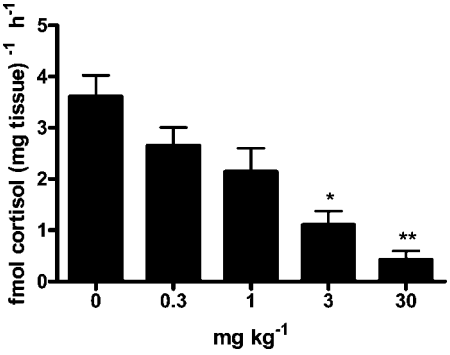


Figure 2. Inhibition of 11β-HSD1 activity with (*S*)-**33a** (dosed PO) in the mesenteric fat of cynomolgus monkeys. *p = 0.0048, **p = 0.0007, and $n \geq 4$. Statistical analyses were carried out using a two-tailed Student's t-test.

pharmacodynamic assay in monkeys. In addition, performing such a study in monkeys would lay the groundwork for additional studies in diabetic models with nonhuman primates.

To measure the pharmacodynamic effects of (*S*)-**33a** in cynomolgus monkeys, we measured the activity of 11β-HSD1 in a fat tissue explant 2 h after the compound was given orally to the animals. The enzyme activity was measured by incubating the mesenteric fat with ^{3}H-cortisone and monitoring for the conversion to ^{3}H-cortisol. At the same time, blood was collected from the animals so that the plasma concentrations of (*S*)-**33a** could be determined. Statistically significant inhibition of 11β-HSD1 activity was observed at 3 and 30 mg kg^{-1} (Figure 2). Plasma concentrations of (*S*)-**33a** at 3 and 30 mg kg^{-1} were 4.9 and 26 μM, respectively. Running a linear regression analysis on the data from the plasma concentrations vs the percent enzyme inhibition gave a plasma IC_{50} = 910 nM. Adjusting for plasma protein binding (monkey $f_{unbound}$ = 10.8%), the unbound IC_{50} was calculated as 98 nM, which was slightly greater than the monkey cell IC_{50} (42 nM). These data indicate that, when given orally, compound (*S*)-**33a** is able to penetrate the fat and inhibit 11β-HSD1 in the target tissue at plasma concentrations that are near the cellular IC_{50}, when corrected for fraction unbound.

In summary, while our strategy to lower PXR activity by adding polar groups worked for some analogues, in other cases, the functionality on other parts of the inhibitors also affected PXR activity. Reducing steric bulk on the right-hand side of the molecule often helped reduce PXR activity. In addition, the substituents on the left-hand aromatic ring also influenced the PXR activity. The right balance of low PXR activity, biochemical potency, and cell-based activity was achieved with a compound that had a 4-fluorophenyl group on the left-hand side of the molecule and a dimethyl tertiary alcohol group at the C-5 position (compound **33a**). The C-5 (*S*)-enantiomer of this compound had biochemical and cell-based hu11β-HSD1 activity of ∼35 nM. In cryopreserved human hepatocytes, the CYP3A4 mRNA and enzyme activity for (*S*)-**33a** was significantly lower than the lead compound **3**. The X-ray cocrystal structure of (*S*)-**33a** with human 11β-HSD1 indicated that the compound formed hydrogen bonds and hydrophobic interactions with the amino acid residues in the catalytic pocket of the enzyme. Compound (*S*)-**33a** also had good pharmacokinetics across four different species. In a monkey pharmacodynamic model, compound (*S*)-**33a** showed significant inhibition of 11β-HSD1 activity in the mesenteric fat of monkeys at both 3 and 30 mg kg^{-1}. With these results, compound (*S*)-**33a** may be used to further understand the biological effects of inhibiting 11β-HSD1 in nonhuman primates.

Experimental Section

General. Unless otherwise noted, all materials were obtained from commercial sources and used without further purification. Preparative flash chromatography was carried out on Merck silica gel 60 (230−400 mesh) or prepacked silica gel cartridges (Biotage or Isco). ^{1}H NMR spectra were recorded on Bruker 400 MHz instrument. All spectra were recorded using the residual solvent proton resonance or tetramethylsilane (TMS) as an internal standard. Chemical shifts are reported in parts per million (ppm, δ units). For products containing a thiazolone, the ^{1}H NMR spectra were complex due to the presence of two diastereomers and the two tautomeric forms of the thiazolone. In many instances, the ^{1}H NMR spectra could be simplified by adding one drop of trifluoroacetic acid, which shifted the equilibrium of thiazolone tautomers to one form. In instances where the compound was a mixture of diaster-

eomers, a pair of signals was observed for many of the protons in the spectra. The chemical shifts for the other diastereomer are reported parenthetically. Mass spectrometry (MS) was performed using an electrospray Agilent 1100 Series liquid chromatograph/mass selective detector (MSD) to give the molecular $[M + H]^+$ ion of the target molecules. The purity of final compounds was determined by either elemental analysis (performed by Atlantic Microlab, Inc., Norcross, GA) or by analytical reverse-phase high-performance liquid chromatography (HPLC) using two separate signals (215 and 254 nm) on two separate instruments (see the Supporting Information for details).

(*S*)-1-[1-(4-Fluorophenyl)ethyl]thiourea (5). A solution of (*S*)-1-(4-fluorophenyl)ethanamine (**4**) (5.0 g, 36 mmol) and benzoyl isothiocyanate (4.8 mL, 36 mmol) in CH_2Cl_2 was stirred at ambient temperature in a round-bottomed flask overnight. The solvent was removed in vacuo, and the crude product was dissolved in THF/MeOH/H_2O (30, 30, and 30 mL, respectively). K_2CO_3 (20 g, 140 mmol) was added, and the mixture was stirred at ambient temperature in a round-bottomed flask. After 4 h, the solvent was removed under reduced pressure, and the crude reaction mixture was diluted with water (60 mL) and extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine, filtered, and concentrated in vacuo. Purification by flash column chromatography (silica gel, 0−5% MeOH in CH_2Cl_2) afforded the title compound **5** (7 g, 98%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.33−7.20 (m, 2H), 7.10−7.05 (m, 2H), 6.48 (br s, 1H), 5.60 (br s, 2H), 4.56 (m, 1H), 1.52 (d, 3H, J = 4 Hz). MS (ESI, pos. ion) *m*/*z*: 199 (M + H).

2-Bromo-2-(4-fluorophenyl)acetic Acid (7, X = F). To a round-bottomed flask containing a solution of 2-(4-fluorophenyl)acetic acid (**6**, X = F) (2.0 g, 13 mmol) in CCl_4 (30 mL) were added *N*-bromosuccinimide (2.5 g, 14 mmol) and AIBN (0.32 g, 2.0 mmol). The mixture was gradually heated to reflux, and after 2.5 h, the heating was stopped and the mixture was stirred overnight at room temperature. The liquid was filtered and concentrated in vacuo. Purification by flash column chromatography (silica gel, 20−50% EtOAc in hexane) afforded the title compound as yellow oil (2.6 g, 86%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.56 (dd, 2H, J = 4, 8 Hz), 7.08 (t, 2H, J = 8 Hz), 5.35 (s, 1H). MS (ESI, pos. ion) *m*/*z*: 231, 233 (M + H).

5-(4-Fluorophenyl)-2-[(*S*)-1-(4-fluorophenyl)ethylamino]thiazol-4(5*H*)-one. To a round-bottomed flask with (*S*)-1-[1-(4-fluorophenyl)ethyl]thiourea (**5**) (0.12 g, 0.62 mmol) and 2-bromo-2-(4-fluorophenyl)acetic acid (**7**, X = F) (0.16 g, 0.68 mmol) in ethanol (2 mL) was added sodium acetate (0.10 g, 1.2 mmol), and the mixture was heated to reflux overnight. A 10% solution of Na_2CO_3 was then added to the reaction mixture, and the mixture was extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash column chromatography (silica gel, 0−5% MeOH in CH_2Cl_2) afforded the title compound as a white solid (0.10 g, 48%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.42−7.48 (m, 2H), 7.32−7.36 (m, 1H), 7.18−7.22 (m, 1H), 6.96−7.09 (m, 4H), 5.20 (tautomer 5.12) (s, 1H), 4.63 (q, 1H, J = 8 Hz), 1.83 (tautomer 1.80) (d, 3H, J = 8 Hz). MS (ESI, pos. ion) *m*/*z*: 333 (M + H).

5-(4-Fluorophenyl)-2-[(*S*)-1-(4-fluorophenyl)ethylamino]-5-methylthiazol-4(5*H*)-one (8). To a round-bottomed flask, cooled to −78 °C, containing a solution of 5-(4-fluorophenyl)-2-[(*S*)-1-(4-fluorophenyl)ethylamino]thiazol-4(5*H*)-one (0.10 g, 0.30 mmol) in 2 mL of THF, was added LDA (0.90 mL of a 2.0 M solution in heptane/THF/ethylbenzene, 1.8 mmol). After 1 h, iodomethane (0.11 mL, 1.8 mmol) was added, and the reaction mixture was gradually warmed to −40 °C and quenched with 10 mL of saturated NH_4Cl. The aqueous phase was extracted with ethyl acetate (3×), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification of the crude material by flash column chromatography (silica gel, 0−5% MeOH−CH_2Cl_2) afforded the title compound as a white solid (71 mg, 68%). ^{1}H NMR ($CDCl_3$ + one drop of TFA, 400 MHz): δ 7.39−7.42 (m, 1H), 7.27−7.33 (m, 3H), 7.02−7.14 (m, 4H), 4.54−4.61 (m, 1H), 2.14 (2.04) (s, 3H), 1.77 (1.75) (d, 3H, J = 6 Hz). MS (ESI, pos. ion) *m*/*z*: 347 (M + H). Anal. ($C_{18}H_{16}F_2N_2OS$) C, H, N.

Ethyl 2-Bromo-2-(4-bromophenyl)acetate (7, X = Br). According to the procedure described for **7**, X = F, the title compound was prepared from ethyl 2-(4-bromophenyl)acetate (**6**, X = Br) (3.0 g, 12 mmol), *N*-bromosuccinimide (2.4 g, 14 mmol), and AIBN (0.20 g, 1.2 mmol). After purification by silica gel chromatography (7% EtOAc in hexane), the desired product was isolated as a colorless oil (3.8 g, 96%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.50 (d, 2H, J = 8 Hz), 7.43 (d, 2H, J = 8 Hz), 5.28 (s, 1H), 4.24 (m, 2H), 1.28 (m, 3H).

5-(4-Bromophenyl)-2-[(*S*)-1-(4-fluorophenyl)ethylamino]thiazol-4(5*H*)-one. According to the procedure described for 5-(4-fluorophenyl)-2-[(*S*)-1-(4-fluorophenyl)ethylamino]thiazol-4(5*H*)-one, the title compound was prepared from (*S*)-1-[1-(4-fluorophenyl)-ethyl]thiourea (**5**) (1.0 g, 5.0 mmol), ethyl 2-bromo-2-(4-bromophenyl)acetate (**7**, X = Br) (2.0 g, 6.1 mmol), and di-*iso*-propylethylamine (1.05 mL, 6.05 mmol). After purification (silica gel chromatography: 34% EtOAc in hexane and then 40% EtOAc in hexane), the desired product was isolated as a white solid (1.4 g, 71%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.53−7.34 (m, 4H), 7.24−6.99 (m, 4H), 5.17 (5.09) (s, 1H), 4.62 (q, 1H, J = 8 Hz), 1.80 (1.77) (d, 3H, J = 8 Hz). MS (ESI, pos. ion) *m*/*z*: 393, 395 (M + H).

5-(4-Bromophenyl)-2-[(*S*)-1-(4-fluorophenyl)ethylamino]-5-methylthiazol-4(5*H*)-one (9). According to the procedure described for **8**, the title compound was prepared from 5-(4-bromophenyl)-2-[(*S*)-1-(4-fluorophenyl)ethylamino]thiazol-4(5*H*)-one (1.3 g, 3.2 mmol), LDA (9.6 mL of a 2.0 M solution in heptane/THF/ethylbenzene, 19 mmol), and iodomethane (1.2 mL, 19 mmol). After purification (silica gel chromatography, 1.5% MeOH in CH_2Cl_2, and then 3% MeOH in CH_2Cl_2), the product was isolated as a light yellow solid (1.27 g, 97%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.50−7.35 (m, 5H), 7.19 (d, 1H, J = 8 Hz), 7.10−6.96 (m, 3H), 4.57 (m, 1H), 2.06 (1.98) (s, 3H), 1.78 (1.76) (d, 3H, J = 8 Hz). MS (ESI, pos. ion) *m*/*z*: 407, 409 (M + H).

Methyl 4-{2-[(*S*)-1-(4-fluorophenyl)ethylamino]-5-methyl-4-oxo-4,5-dihydrothiazol-5-yl}benzoate (10). A round-bottomed flask with a mixture of 5-(4-bromophenyl)-2-[(*S*)-1-(4-fluorophenyl)ethylamino]-5-methylthiazol-4(5*H*)-one (**9**) (0.79 g, 1.9 mmol), triphenylphosphine (0.15 g, 0.58 mmol), and palladium acetate (0.11 g, 0.48 mmol) in MeOH/DMF (3 mL/3 mL) was pressurized with CO(g), purged twice with CO(g), and then heated to 100 °C overnight at 40−50 psi of CO(g). The reaction mixture was cooled to room temperature, and the mixture was filtered through Celite. The Celite pad was washed with CH_2Cl_2, and the filtrate was washed with water (3×). The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash column chromatography (silica gel, 2−3.6% MeOH in CH_2Cl_2) afforded the title compound as a light yellow solid (0.74 g, 99%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 11.42 (br s, 1H), 7.94−8.04 (m, 2H), 7.39−7.67 (m, 4H), 6.63−7.01 (m, 2H), 4.56 (q, 1H, J = 8 Hz), 3.92 (s, 3H), 2.11 (2.02) (s, 3H), 1.82 (1.80) (d, 3H, J = 8 Hz). MS (ESI, pos. ion) *m*/*z*: 387 (M + H).

4-{2-[(*S*)-1-(4-Fluorophenyl)ethylamino]-5-methyl-4-oxo-4,5-dihydrothiazol-5-yl}benzoic Acid (11). In a round-bottomed flask was added a mixture of methyl 4-{2-[(*S*)-1-(4-fluorophenyl)ethylamino]-5-methyl-4-oxo-4,5-dihydrothiazol-5-yl}benzoate (**10**) (1.2 g, 3.1 mmol), THF (6 mL), MeOH (2 mL), H_2O (2 mL), and lithium hydroxide hydrate (0.26 g, 6.2 mmol). The mixture was heated to reflux for 2 h, then neutralized with 1 N HCl, and extracted with CH_2Cl_2 (5×). The organic solution was dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash column chromatography (silica gel, 3.6−10% MeOH in CH_2Cl_2) afforded the title compound as a light brown solid (0.72 g, 62%). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.85 (d, 1H, J = 8 Hz), 7.83−7.93 (m, 2H), 7.40−7.65 (m, 4H), 7.17−7.24 (m, 2H), 5.28 (qn, 1H, J = 8 Hz), 1.90 (1.95) (s, 3H), 1.50 (d, 3H, J = 8 Hz). MS (ESI, pos. ion) *m*/*z*: 373 (M + H).

4-{2-[(*S*)-1-(4-Fluorophenyl)ethylamino]-5-methyl-4-oxo-4,5-dihydrothiazol-5-yl}benzamide (12a). To a solution of 4-{2-[(*S*)-1-(4-fluorophenyl)ethylamino]-5-methyl-4-oxo-4,5-dihydrothiazol-5-yl}benzoic acid (**11**) (0.25 g, 0.67 mmol) in CH_2Cl_2 (2 mL) were added thionyl chloride (0.10 mL, 1.3 mmol) and two drops of DMF. After the reaction mixture was stirred overnight at room temperature, the mixture was concentrated in vacuo. The crude product was dissolved in THF (2.5 mL), and then, ammonium hydroxide (37% solution in H_2O, 0.6 mL) was added to the solution at 0 °C. After 1 h, the mixture was diluted with water (5 mL) and extracted with CH_2Cl_2 (3×). The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash column chromatography (silica gel, 4−10% MeOH in CH_2Cl_2) gave the product as a white solid (0.20 g, 79%). Analytical data for single diastereomer: ^{1}H NMR ($CDCl_3$ + 1 drop of TFA, 400 MHz): δ 7.87 (br s, 1H), 7.82 (d, 2H, J = 8 Hz), 7.45 (d, 2H, J = 8 Hz), 7.30−7.33 (m, 2H), 7.08−7.12 (m, 2H), 6.51 (br s, 1H), 4.62 (q, 1H, J = 8 Hz), 2.19 (s, 3H), 1.78 (d, 3H, J = 8 Hz). MS (ESI, pos. ion) *m*/*z*: 372 (M + H). Anal. ($C_{19}H_{18}FN_3O_2S\cdot0.3H_2O$) C, H, N.

***N*-Cyclopropyl-4-{2-[(*S*)-1-(4-fluorophenyl)ethylamino]-5-methyl-4-oxo-4,5-dihydrothiazol-5-yl}benzamide (12b).** The title compound was prepared according to the procedure of example **12a** using 4-{2-[(*S*)-1-(4-fluorophenyl)ethylamino]-5-methyl-4-oxo-4,5-dihydrothiazol-5-yl}benzoyl chloride (0.080 g, 0.20 mmol) and cyclopropylamine (0.20 mL, 2.9 mmol). After purification (preparative TLC, 5% MeOH in CH_2Cl_2), the product was obtained as a white solid (6.7 mg, 8%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.72−7.63 (m, 2H), 7.51−7.34 (m, 4H), 7.06−6.90 (m, 2H), 6.49 (6.63) (br s, 1H), 4.56 (q, 1H, J = 8 Hz), 2.88 (m, 1H), 2.09 (2.00) (s, 3H), 1.79 (1.77) (d, 3H, J = 8 Hz), 0.89−0.80 (m, 2H), 0.61 (m, 2H). MS (ESI, pos. ion) *m*/*z*: 412 (M + H). HPLC purity at 215 and 254 nm: 98 and 100% in system C; 96 and 99% in system A.

***N*-Cyclopentyl-4-{2-[(*S*)-1-(4-fluorophenyl)ethylamino]-5-methyl-4-oxo-4,5-dihydrothiazol-5-yl}benzamide (12c).** The title compound was prepared according to the procedure described for example **12a** using 4-{2-[(*S*)-1-(4-fluorophenyl)ethylamino]-5-methyl-4-oxo-4,5-dihydrothiazol-5-yl}benzoyl chloride (0.10 g, 0.30 mmol) and cyclopentylamine (0.2 mL, 2.0 mmol). After purification (preparative TLC, 5% MeOH in CH_2Cl_2, and then 50% EtOAc in hexane), the product was isolated as a white solid (44 mg, 49%). ^{1}H NMR ($CDCl_3$ + 1 drop of TFA, 400 MHz): δ 7.76 (7.69) (d, 2H, J = 8 Hz), 7.51 (7.39) (d, 2H, J = 8 Hz), 7.29−7.34 (m, 2H), 7.07−7.14 (m, 2H), 6.255 (6.21) (d, 1H, J = 8 Hz), 4.55−4.62 (m, 1H), 4.36−4.43 (m, 1H), 2.16 (2.05) (s, 3H), 2.08−2.13 (m, 2H), 1.75 (1.77) (d, 3H, J = 8 Hz), 1.46−1.73 (m, 6H). MS (ESI, pos. ion) *m*/*z*: 440 (M + H). Anal. ($C_{24}H_{26}FN_3O_2S\cdot0.2H_2O$) C, H, N.

4-{2-[(*S*)-1-(4-Fluorophenyl)ethylamino]-5-methyl-4-oxo-4,5-dihydrothiazol-5-yl}-*N*-methylbenzamide (12d). The title compound was prepared according to the procedure of example **12a** using 4-{2-[(*S*)-1-(4-fluorophenyl)ethylamino]-5-methyl-4-oxo-4,5-dihydrothiazol-5-yl}benzoyl chloride (0.10 g, 0.26 mmol) and methylamine (1.0 mL of a 2 M solution in THF, 2.0 mmol). After purification (preparative TLC, 5% MeOH in CH_2Cl_2), the product was obtained as a white solid (10 mg, 10%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.75−7.66 (m, 2H), 7.53−7.36 (m, 4H), 7.09−6.92 (m, 2H), 6.63 (6.18) (m, 1H), 4.56 (q, 1H, J = 8 Hz), 3.02−2.96 (m, 3H), 2.09 (2.05) (s, 3H), 1.79 (1.77) (d, 3H, J = 8 Hz). MS (ESI, pos. ion) *m*/*z*: 386 (M + H). HPLC purity at 215 and 254 nm: 97 and 100% in system C; 98 and 99% in system A.

2-[(*S*)-1-(4-Fluorophenyl)ethylamino]-5-methyl-5-[4-(pyrrolidine-1-carbonyl)phenyl]thiazol-4(5*H*)-one (12e). The title compound was prepared according to the procedure of example **12a** using 4-{2-[(*S*)-1-(4-fluorophenyl)ethylamino]-5-methyl-4-oxo-4,5-dihydrothiazol-5-yl}benzoyl chloride (0.10 g, 0.26 mmol) and pyrrolidine (0.063 mL, 0.77 mmol). After purification (preparative TLC, 5% MeOH in CH_2Cl_2, and then 100% EtOAc), the product was obtained as a white solid (67 mg, 61%). ^{1}H NMR ($CDCl_3$ + one drop of TFA, 400 MHz): δ 7.58−7.30 (m, 6H), 7.15−7.08 (m, 2H), 4.64−4.57 (m, 1H), 3.73−3.67 (m, 2H), 3.46−3.40 (m, 2H), 2.17 (2.07) (s, 3H), 2.06−1.92 (m, 4H), 1.76 (1.78) (d, 3H, J = 8 Hz). MS (ESI, pos. ion) *m*/*z*: 426 (M + H). Anal. ($C_{23}H_{24}FN_3O_2S\cdot0.4H_2O$) C, H, N.

2-[(*S*)-1-(4-Fluorophenyl)ethylamino]-5-methyl-5-[4-(morpholine-4-carbonyl)phenyl]thiazol-4(5*H*)-one (13). Into a round-bottomed flask was added 4-{2-[(*S*)-1-(4-fluorophenyl)ethylamino]-5-methyl-4-oxo-4,5-dihydrothiazol-5-yl}benzoic acid (89 mg, 0.24 mmol), dicyclohexanecarbodiimide (74 mg, 0.36 mmol), 1-hydroxybenzotriazole (29 mg, 0.22 mmol), and morpholine (0.042 mL, 0.48 mmol) in CH_2Cl_2 (2 mL). After the mixture was stirred overnight at room temperature, the reaction mixture was diluted with 10% Na_2CO_3 (15 mL) and extracted with CH_2Cl_2 (3×). The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo. After purification (preparative TLC, 10% MeOH in CH_2Cl_2), the desired product was isolated as a white solid (97 mg, 91%). ^{1}H NMR ($CDCl_3$ + 1 drop of TFA, 400 MHz): δ 7.53−7.30 (m, 6H), 7.15−7.08 (m, 2H), 4.64−4.57 (m, 1H), 3.87 (m, 4H), 3.69 (m, 2H), 3.46 (m, 2H), 2.18 (2.08) (s, 3H), 1.78 (1.76) (d, 3H, J = 8 Hz). MS (ESI, pos. ion) *m*/*z*: 442 (M + H). Anal. ($C_{23}H_{24}FN_3O_3S$) C, H, N.

2-[(*S*)-1-(4-Fluorophenyl)ethylamino]-5-[4-(hydroxymethyl)phenyl]-5-methylthiazol-4(5*H*)-one (14). Into a round-bottomed flask was added methyl 4-{2-[(*S*)-1-(4-fluorophenyl)ethylamino]-5-methyl-4-oxo-4,5-dihydrothiazol-5-yl}benzoate (23 mg, 0.060 mmol) in THF (1 mL) and lithium aluminum hydride (1.0 M solution in THF, 0.089 mL, 0.089 mmol) at 0 °C. The reaction was quenched by adding sodium sulfate decahydrate. The solid was filtered and washed with CH_2Cl_2 (3×). The filtrate was dried over Na_2SO_4, filtered, and concentrated in vacuo. After purification (preparative TLC 8% MeOH in CH_2Cl_2), the desired product was isolated as a white solid (15 mg, 70%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.47−7.31 (m, 6H), 7.00−6.91 (m, 2H), 4.67 (m, 2H), 4.55 (m, 1H), 2.09 (2.00) (s, 3H), 1.81 (1.79) (d, 3H, J = 8 Hz). MS (ESI, pos. ion) *m*/*z*: 359 (M + H). HPLC purity at 215 and 254 nm: 99 and 100% in system C; 98 and 96% in system A.

5-[4-(Chloromethyl)phenyl]-2-[(*S*)-1-(4-fluorophenyl)ethylamino]-5-methylthiazol-4(5*H*)-one. Into a round-bottomed flask was added 2-[(*S*)-1-(4-fluorophenyl)ethylamino]-5-[4-(hydroxymethyl)phenyl]-5-methylthiazol-4(5*H*)-one (0.17 g, 0.47 mmol) in 1,4-dioxane (5 mL) and thionyl chloride (0.14 mL, 1.9 mmol). After 45 min of stirring at room temperature, the reaction mixture was concentrated in vacuo. The white solid was used in the next step without purification. MS (ESI, pos. ion) *m*/*z*: 377 (M + H).

2-(4-{2-[(*S*)-1-(4-Fluorophenyl)ethylamino]-5-methyl-4-oxo-4,5-dihydrothiazol-5-yl}phenyl)acetonitrile (Intermediate B). Into a round-bottomed flask was added a solution of 5-[4-(chloromethyl)phenyl]-2-[(*S*)-1-(4-fluorophenyl)ethylamino]-5-methylthiazol-4(5*H*)-one (0.18 g, 0.48 mmol) in CH_2Cl_2 (3.5 mL) and tetrabutylammonium cyanide (0.26 g, 0.95 mmol). The reaction mixture was heated to reflux for 4 h, and then, the mixture was concentrated in vacuo. After purification by flash column chromatography (silica gel, 30−50% EtOAc in hexane), the desired product was isolated as a white solid (0.11 g, 63%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 11.33 (br s, 1H), 7.50−7.28 (m, 6H), 6.99−6.92 (m, 2H), 4.56 (m, 1H), 3.73 (m, 2H), 2.09 (2.00) (s, 3H), 1.82 (1.80) (d, 3H, J = 8 Hz). MS (ESI, pos. ion) *m*/*z*: 368 (M + H).

2-(4-{2-[(*S*)-1-(4-Fluorophenyl)ethylamino]-5-methyl-4-oxo-4,5-dihydrothiazol-5-yl}phenyl)acetamide (15). Into a round-bottomed flask were added 2-(4-{2-[(*S*)-1-(4-fluorophenyl)ethylamino]-5-methyl-4-oxo-4,5-dihydrothiazol-5-yl}phenyl)acetonitrile (60 mg, 0.16 mmol), potassium hydroxide (0.12 g, 2.1 mmol), and *t*-BuOH (2 mL). The mixture was gradually heated to 100 °C, and after 2 h, the reaction mixture was cooled to room temperature and concentrated in vacuo. The residue was neutralized with 2 N HCl until the pH was 5−6, and then, the aqueous layer was extracted with CH_2Cl_2 (3×). The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo. After purification (preparative TLC, 10% MeOH in CH_2Cl_2), the title compound was isolated as a white solid (11 mg, 17%). ^{1}H NMR (CD_3OD, 400 MHz): δ 7.42−7.23 (m, 6H), 7.12−7.07 (m, 2H), 5.34 (q, 1H, J = 8 Hz), 3.47−3.51 (m, 2H), 2.02−1.92 (m, 3H), 1.62−1.57 (m, 3H). MS

(ESI, pos. ion) *m/z*: 386 (M + H). HPLC purity at 215 and 254 nm: 98 and 99% in system C; 99 and 100% in system A.

2-[(*S*)-1-(4-Fluorophenyl)ethylamino]-5-methylthiazol-4(5*H*)-one (16). A mixture of (*S*)-1-[1-(4-fluorophenyl)ethyl]thiourea (**5**) (3.5 g, 18 mmol), methyl 2-bromopropanoate (2.2 mL, 19 mmol), and triethylamine (2.7 mL, 19 mmol) in ethanol (10 mL) was heated in a sealed vessel at 100 °C in a microwave reactor (Personal Chemistry). After 1 h, the reaction vessel was cooled to room temperature, and the solvent was removed in vacuo. The crude mixture was diluted with water (100 mL) and extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash column chromatography (silica gel, 0−50% EtOAc in hexane) afforded the title compound **16** (4.0 g, 88%) as a white solid. ^{1}H NMR ($CDCl_3$ + 1 drop of TFA, 400 MHz): δ 7.36−7.32 (m, 2H), 7.13−7.08 (m, 2 H), 4.57 (4.566) (q, 1H, J = 8 Hz), 4.21 (4.13) (q, 1H, J = 8 Hz), 1.76 (1.75) (d, 3H, J = 8 Hz), 1.72 (1.66) (d, 3H, J = 8 Hz)). MS (ESI, pos. ion) *m/z*: 253 (M + H).

2-[(*S*)-1-(4-Fluorophenyl)ethylamino]-5-methylthiazol-4(5*H*)-one (16) (Alternative Procedure). Into a round-bottomed flask equipped with stirring was added a mixture of (*S*)-1-[1-(4-fluorophenyl)ethyl]thiourea (**5**) (60 g, 30 mmol), 2-bromopropanoic acid (30 mL, 340 mmol), and sodium acetate (36 g, 440 mmol) in ethanol (220 mL), which was heated overnight at reflux. The reaction mixture was then cooled to room temperature, and then, water (500 mL) and saturated Na_2CO_3 (50 mL) were added. The mixture was extracted with ethyl acetate (3 × 500 mL), and the combined organic layers were washed with saturated Na_2CO_3, water (3 × 400 mL), and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to give 70 g of the desired product (91% yield).

4-({2-[(*S*)-1-(4-Fluorophenyl)ethylamino]-5-methyl-4-oxo-4,5-dihydrothiazol-5-yl}methyl)benzonitrile. Into a round-bottomed flask was added a solution of 2-[(*S*)-1-(4-fluorophenyl)ethylamino]-5-methylthiazol-4(5*H*)-one (**16**) (0.30 g, 1.2 mmol) in THF (3 mL), and LDA (2.0 M solution in heptane/tetrahydrofuran/ethylbenzene, 2.4 mL, 4.8 mmol) was added at −78 °C. After 1 h, a solution of 4-(bromomethyl)benzonitrile (**17**) (0.70 g, 3.6 mmol) in THF (3 mL) was added at −78 °C. The mixture was gradually warmed to 0 °C, and then, saturated NH_4Cl (4 mL) was added to quench the reaction. The mixture was extracted with EtOAc (3×), and the combined organic fractions were dried over Na_2SO_4, filtered, and concentrated in vacuo. After purification by flash column chromatography (silica gel, 17−50% EtOAc in hexane), the desired product was isolated as a white solid (0.38 g, 87%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.48−7.62 (m, 1H), 7.27−7.39 (m, 3H), 7.00−7.20 (m, 4H), 4.44 (m, 1H), 2.32−3.36 (m, 1H), 2.94−3.10 (m, 1H), 1.61−1.74 (m, 6H). MS (ESI, pos. ion) *m/z*: 368 (M + H).

4-({2-[(*S*)-1-(4-Fluorophenyl)ethylamino]-5-methyl-4-oxo-4,5-dihydrothiazol-5-yl}methyl)benzamide (18). Into a round-bottomed flask was added 4-({2-[(*S*)-1-(4-fluorophenyl)ethylamino]-5-methyl-4-oxo-4,5-dihydrothiazol-5-yl}methyl)benzonitrile (70 mg, 0.19 mmol), potassium hydroxide (0.14 g, 2.5 mmol), and *t*-BuOH (2 mL). The mixture was gradually heated to 85 °C, and after 2 h, the reaction was concentrated in vacuo. A 2 N solution of HCl was added until the pH was 7−8. The mixture was then extracted with CH_2Cl_2 (3×), and the organic phases were dried over Na_2SO_4, filtered, and concentrated in vacuo. After purification by flash column chromatography (silica gel, 0−10% MeOH in CH_2Cl_2), the title compound was isolated as a white solid (54 mg, 74%). ^{1}H NMR ($CDCl_3$ + 1 drop of TFA, 400 MHz): δ 7.83 (d, 1H, J = 8 Hz), 7.77 (7.71) (br s, 1H), 7.61 (d, 1H, J = 8 Hz), 7.33 (d, 1H, J = 8 Hz), 7.23−7.26 (m, 1H), 7.04−7.11 (m, 4H), 6.64 (6.57) (br s, 1H), 4.46 (q, 1H, J = 8 Hz), 3.01−3.45 (m, 2H), 1.82 (1.73) (s, 3H), 1.66 (1.63) (d, 3H, J = 8 Hz). MS (ESI, pos. ion) *m/z*: 386 (M + H). Anal. ($C_{20}H_{20}FN_3O_2S \cdot 0.2H_2O$) C, H, N.

1-(4-{2-[(*S*)-1-(4-Fluorophenyl)ethylamino]-5-methyl-4-oxo-4,5-dihydrothiazol-5-yl}phenyl)cyclopropanecarbonitrile (Intermediate A). To a round-bottomed flask was added 2-[(*S*)-1-(4-fluorophenyl)ethylamino]-5-methylthiazol-4(5*H*)-one (**16**) (0.20 g, 0.79 mmol), 1-(4-bromophenyl)cyclopropanecarbonitrile (**19**) (0.35 g, 1.6 mmol), $Pd_2(dba)_3$ (51 mg, 0.055 mmol), BINAP (0.099 g, 0.16 mmol), and LiHMDS (0.33 g, 2.0 mmol) in toluene (8 mL). The mixture was heated to 95 °C and stirred overnight. Saturated NH_4Cl (5 mL) was then added, and the mixture was extracted with EtOAc (30 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo. After purification (preparative TLC, 50% EtOAc in hexane), the desired product was isolated as a light yellow solid (0.12 g, 37%). ^{1}H NMR (CD_3OD, 400 MHz): δ 7.44−7.26 (m, 6H), 7.10 (7.08) (d, 2H, J = 8 Hz), 5.33 (q, 1H, J = 8 Hz), 2.02−1.91 (m, 3H), 1.73−1.67 (m, 2H), 1.61−1.56 (m, 3H), 1.49−1.43 (m, 2H). MS (ESI, pos. ion) *m/z*: 394 (M + H).

1-(4-{2-[(*S*)-1-(4-Fluorophenyl)ethylamino]-5-methyl-4-oxo-4,5-dihydrothiazol-5-yl}phenyl)cyclopropanecarboxamide (20). The title compound was prepared according to the procedure of example **18** using 1-(4-{2-[(*S*)-1-(4-fluorophenyl)ethylamino]-5-methyl-4-oxo-4,5-dihydrothiazol-5-yl}phenyl)cyclopropanecarbonitrile (0.073 g, 0.19 mmol), KOH (0.13 g, 2.4 mmol), and *t*-BuOH (2 mL). After purification (preparative TLC, 10% MeOH in CH_2Cl_2, then 50% EtOAc in hexane), the title compound was isolated as a white solid (50 mg, 66%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.91 (br s, 1H), 7.47−7.31 (m, 6H), 7.03−6.97 (m, 2H), 5.57 (5.32) (m, 2H), 4.57 (m, 1H), 2.10 (2.00) (s, 3H), 1.79 (1.77) (d, 3H, J = 8 Hz), 1.64−1.60 (m, 2H), 1.08−1.04 (m, 2H). MS (ESI, pos. ion) *m/z*: 412 (M + H). HPLC purity at 215 and 254 nm: 97 and 99% in system C; 100 and 100% in system A.

2-(4-Bromophenyl)-2-methylpropanenitrile (22). Into a round-bottomed flask was added 2-(4-bromophenyl)acetonitrile (**21**) (1.0 g, 5.1 mmol), 18-crown-6 (0.34 g, 1.3 mmol), iodomethane (0.70 mL, 11 mmol), and THF (50 mL). After the reaction flask was cooled to −78 °C, potassium *tert*-butoxide (1.3 g, 11 mmol) was added. The mixture was stirred at −78 °C for 2 h, then warmed to room temperature, and stirred overnight. Saturated NH_4Cl was then added, and the reaction mixture was extracted with EtOAc (3×). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated in vacuo. After purification by flash column chromatography (silica gel, 0−50% EtOAc in hexane), the desired product was isolated as an orange oil (1.1 g, 99%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.52 (d, 2H, J = 8 Hz), 7.35 (d, 2H, J = 8 Hz), 1.71 (s, 6H).

2-(4-{2-[(*S*)-1-(4-Fluorophenyl)ethylamino]-5-methyl-4-oxo-4,5-dihydrothiazol-5-yl}phenyl)-2-methylpropanamide (23). This compound was prepared according to the procedure described for **20**. ^{1}H NMR ($CDCl_3$ + 1 drop of TFA, 400 MHz): δ 7.46−7.29 (m, 6H), 7.15−7.09 (m, 2H), 4.62 (m, 1H), 2.17 (2.07) (s, 3H), 1.77 (1.75) (d, 3H, J = 8 Hz), 1.63 (1.60) (s, 6H). MS (ESI, pos. ion) *m/z*: 414 (M + H). Anal. ($C_{22}H_{24}FN_3O_2S \cdot 0.3H_2O$) C, H, N.

2-(4-Bromophenyl)propan-2-ol (25). To a round-bottomed flask containing a solution of methyl 4-bromobenzoate (**24**) (1.0 g, 4.7 mmol) in THF (30 mL) cooled to 0 °C was added methylmagnesium bromide (4.7 mL of a 3.0 M solution in diethyl ether, 14 mmol). After the addition, the reaction mixture was warmed to room temperature and stirred for 2 h. Saturated NH_4Cl (10 mL) was added, and the reaction mixture was extracted with EtOAc (3×). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated in vacuo. After purification by flash column chromatography (silica gel, 9−14% EtOAc in hexane), the title compound was isolated as a colorless oil (0.74 g, 74%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.45 (d, 2H, J = 8 Hz), 7.36 (d, 2H, J = 8 Hz), 1.56 (s, 6H). MS (ESI, pos. ion) *m/z*: 197, 199 [(M + H) − H_2O].

2-[(*S*)-1-(4-Fluorophenyl)ethylamino]-5-[4-(2-hydroxypropan-2-yl)phenyl]-5-methylthiazol-4(5*H*)-one (26). Using the cross-coupling procedure used for the preparation of intermediate A, the title compound was prepared from 2-[(*S*)-1-(4-fluorophenyl)ethylamino]-5-methylthiazol-4(5*H*)-one (**16**) (0.10 g, 0.40 mmol), 2-(4-bromophenyl)propan-2-ol (**25**) (0.17 g, 0.79 mmol), $Pd_2(dba)_3$ (0.025 g, 0.028 mmol), (*S*)-BINAP (0.049 g, 0.079 mmol), and $LiN(TMS)_2$ (0.33 g, 2.0 mmol). After purification (preparative TLC, 50% EtOAc in hexane), the desired product was isolated as an off-white solid (45 mg, 30%). ^{1}H NMR ($CDCl_3$ + 1 drop of TFA, 400 MHz): δ

7.53−7.28 (m, 6H), 7.14−7.08 (m, 2H), 4.60 (m, 1H), 2.16 (2.06) (s, 3H), 1.77 (1.75) (d, 3H, J = 8 Hz), 1.63 (1.59) (s, 6H). MS (ESI, pos. ion) m/z: 387 (M + H). Anal. ($C_{21}H_{23}FN_2O_2S \cdot H_2O$) C, H, N.

(4-Bromophenethoxy)trimethylsilane (28). To a round-bottomed flask with a solution of 2-(4-bromophenyl)ethanol (**27**) (3.0 g, 15 mmol) and diisopropylethylamine (3.9 mL, 22 mmol) in CH_2Cl_2 (30 mL) cooled to 0 °C was added chlorotrimethylsilane (2.8 mL, 22 mmol). The mixture was warmed to room temperature and stirred overnight. K_2CO_3 (1.1 g, 8.0 mmol) was then added, and the reaction mixture was stirred for an additional 3 h at room temperature. The solids were then filtered off, and the filtrate was concentrated in vacuo. After purification by flash column chromatography (silica gel, 15% EtOAc in hexane), the title compound was isolated as a colorless oil (3.4 g, 84%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.40 (d, 2H, J = 8 Hz), 7.08 (d, 2H, J = 8 Hz), 3.75 (t, 2H, J = 8 Hz), 2.77 (t, 2H, J = 8 Hz), 0.06 (s, 9H).

2-[(*S*)-1-(4-Fluorophenyl)ethylamino]-5-methyl-5-{4-[2-(trimethylsilyloxy)ethyl]phenyl}thiazol-4(5*H*)-one. Using the cross-coupling procedure used for the preparation of intermediate A, the title compound was prepared using 2-[(*S*)-1-(4-fluorophenyl)ethylamino]-5-methylthiazol-4(5*H*)-one (**16**) (0.80 g, 3.2 mmol), (4-bromophenethoxy)trimethylsilane (**28**) (1.7 g, 6.3 mmol), $Pd_2(dba)_3$ (0.20 g, 0.22 mmol), (*S*)-BINAP (0.40 g, 0.63 mmol), and $LiN(TMS)_2$ (1.6 g, 9.5 mmol). After purification (silica gel, 23% EtOAc in hexane, then 39% EtOAc in hexane), the title compound was isolated as a light yellow solid (0.43 g, 31%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.44−7.13 (m, 6H), 7.02−6.94 (m, 2H), 4.56 (m, 1H), 3.75 (m, 2H), 2.82 (m, 2H), 2.07 (1.98) (s, 3H), 1.79 (1.76) (d, 3H, J = 8 Hz), 0.08 (0.07) (s, 9H). MS (ESI, pos. ion) m/z: 373 [(M + H) − $Si(CH_3)_3$].

2-{(*S*)-[1-(4-fluorophenyl)ethyl]amino}-5-[4-(2-hydroxyethyl)phenyl]-5-methyl-1,3-thiazol-4(5*H*)-one (29). Into a round-bottomed flask was added 2-[(*S*)-1-(4-fluorophenyl)ethylamino]-5-methyl-5-{4-[2-(trimethylsilyloxy)ethyl]phenyl}thiazol-4(5*H*)-one (0.41 g, 0.92 mmol), K_2CO_3 (0.64 g, 4.6 mmol), and MeOH (1.5 mL). After the mixture was stirred at room temperature for 1 h, the solids were filtered off, and the filtrate was concentrated in vacuo. Purification by flash column chromatography (silica gel, 0−6% MeOH in CH_2Cl_2) gave the desired product as a white solid (0.32 g, 93%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.42−7.17 (m, 6H), 7.04−6.96 (m, 2H), 4.57 (m, 1H), 3.85 (m, 2H), 2.86 (m, 2H), 2.09 (2.00) (s, 3H), 1.78 (1.75) (d, 3H, J = 8 Hz). MS (ESI, pos. ion) m/z: 373 (M + H). HPLC purity at 215 and 254 nm: 100 and 100% in systems C and A.

2-[(*S*)-1-(4-Fluorophenyl)ethylamino]-5-[4-(2-iodoethyl)phenyl]-5-methylthiazol-4(5*H*)-one. Into a round bottomed flask was added 2-[(*S*)-1-(4-fluorophenyl)ethylamino]-5-[4-(2-hydroxyethyl)phenyl]-5-methylthiazol-4(5*H*)-one (**29**) (0.29 g, 0.79 mmol), triphenylphosphine (0.25 g, 0.94 mmol), imidazole (64 mg, 0.94 mmol), and iodine (0.22 g, 0.86 mmol) in CH_2Cl_2 (2 mL). After the mixture was stirred at room temperature for 2 h, the mixture was filtered, and the filtrate was concentrated in vacuo. Purification of the crude product by flash column chromatography (silica gel, 43% EtOAc in hexane) afforded the title compound as a white solid (0.31 g, 82%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.43−7.26 (m, 4H), 7.20−6.95 (m, 4H), 4.57 (m, 1H), 3.32 (m, 2H), 3.17 (m, 2H), 2.09 (2.00) (s, 3H), 1.78 (1.76) (d, 3H, J = 8 Hz). MS (ESI, pos. ion) m/z: 483 (M + H).

3-(4-{2-[(*S*)-1-(4-Fluorophenyl)ethylamino]-5-methyl-4-oxo-4,5-dihydrothiazol-5-yl}phenyl)propanenitrile. Using the cyanide displacement reaction used in the synthesis intermediate B, the title compound was prepared from 2-[(*S*)-1-(4-fluorophenyl)ethylamino]-5-[4-(2-iodoethyl)phenyl]-5-methylthiazol-4(5*H*)-one (0.31 g, 0.64 mmol) and tetrabutylammonium cyanide (0.86 g, 3.2 mmol). After purification (silica gel, 55% EtOAc in hexane), the desired product was isolated as a white solid (0.16 g, 65%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.45−7.40 (m, 2H), 7.31−7.17 (m, 4H), 7.02−6.95 (m, 2H), 4.57 (m, 1H), 2.94 (m, 2H), 2.61 (m, 2H), 2.08 (2.00) (s, 3H), 1.80 (1.77) (d, 3H, J = 8 Hz). MS (ESI, pos. ion) m/z: 382 (M + H).

3-(4-{2-[(*S*)-1-(4-Fluorophenyl)ethylamino]-5-methyl-4-oxo-4,5-dihydrothiazol-5-yl}phenyl)propanamide (30). According to the procedure of example **18**, the title compound was prepared from 3-(4-{2-[(*S*)-1-(4-fluorophenyl)ethylamino]-5-methyl-4-oxo-4,5-dihydrothiazol-5-yl}phenyl)propanenitrile (70 mg, 0.18 mmol) and KOH (51 mg, 0.92 mmol). After purification (preparative TLC, 10% MeOH in CH_2Cl_2), the title compound was isolated as a white solid (63 mg, 86%). ^{1}H NMR ($CDCl_3$ + 1 drop of TFA, 400 MHz): δ 7.35−7.29 (m, 2H), 7.27−7.18 (m, 4H), 7.14−7.07 (m, 2H), 4.60 (m, 1H), 2.98 (m, 2H), 2.60 (m, 2H), 2.15 (2.05) (s, 3H), 1.77 (1.75) (d, 3H, J = 8 Hz). MS (ESI, pos. ion) m/z: 400 (M + H). Anal. ($C_{21}H_{22}FN_3O_2S \cdot 0.2H_2O$) C, H, N.

(*S*)-2-[1-(4-Fluorophenyl)ethylamino]-5-(2-hydroxypropan-2-yl)-5-methylthiazol-4(5*H*)-one [(*S*)-33a, (*R*)-33a]. According to the general procedure described for **33d**, **33a** was synthesized from 2-[(*S*)-1-(4-fluorophenyl)ethylamino]-5-methylthiazol-4(5*H*)-one (**16**) (330 mg, 1.3 mmol), LDA (3.5 mL of a 1.5 M solution in THF/cyclohexane, 5.3 mmol), and acetone (0.29 mL, 3.9 mmol). After purification of the crude reaction mixture (silica gel, 0−50% EtOAc in hexanes), a colorless film was obtained as the mixture of diastereomers (300 mg, 73%). The isomers were separated using a Berger Multigram II supercritical fluid chromatography system. The column was Chiralpak ASH (21 mm × 250 mm, 5 μm) using CO_2(l) with 25% methanol as the eluant with a flow rate of 60 mL/min. The column temperature was 40 °C, and the outlet pressure was 100 bar.

(*S*)-2-[(*S*)-1-(4-Fluorophenyl)ethylamino]-5-(2-hydroxypropan-2-yl)-5-methylthiazol-4(5*H*)-one [(*S*)-33a]. Yield: 57 mg, white solid (14%). ^{1}H NMR ($CDCl_3$ + 1 drop of TFA, 400 MHz): δ 7.35−7.30 (m, 2H), 7.14−7.08 (m, 2 H), 4.59 (q, 1H, J = 8 Hz), 1.81 (s, 3H), 1.75 (d, 3H, J = 8 Hz), 1.31 (s, 3 H), 1.26 (s, 3H). MS (ESI, pos. ion) m/z: 311 (M + H). Anal. ($C_{15}H_{19}FN_2O_2S$) C, H, N.

(*R*)-2-[(*S*)-1-(4-Fluorophenyl)ethylamino]-5-(2-hydroxypropan-2-yl)-5-methylthiazol-4(5*H*)-one [(*R*)-33a]. Yield: 50 mg, white solid (12%). ^{1}H NMR ($CDCl_3$ + 1 drop of TFA, 400 MHz): δ 7.35−7.30 (m, 2H), 7.14−7.09 (m, 2H), 4.62 (q, 1H, J = 8 Hz), 1.76 (d, 3H, J = 7 Hz), 1.72 (s, 3H), 1.46 (s, 3H), 1.43 (s, 3H). MS (ESI, pos. ion) m/z: 311 (M + H). Anal. ($C_{15}H_{19}FN_2O_2S$) C, H, N.

2-[(*S*)-1-(4-Fluorophenyl)ethylamino]-5-(1-hydroxycyclobutyl)-5-methylthiazol-4(5*H*)-one (33b). According to the procedure described **33d**, this compound was prepared from 2-[(*S*)-1-(4-fluorophenyl)ethylamino]-5-methylthiazol-4(5*H*)-one (**16**) (0.20, 0.79 mmol), LDA (1.6 mL of a 2 M solution in THF, 0.32 mmol), and cyclobutanone (0.33 g, 4.8 mmol). After purification (silica gel, 2−5% methanol/CH_2Cl_2), the title compound was isolated as a white solid (65 mg, 25%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.67−7.47 (m, 2H), 7.11−6.97 (m, 2H), 6.01−5.96 (tautomer 3.95−3.79) (br s, 1H), 5.53−5.42 (tautomer 4.66−4.52) (m, 1H), 2.45−1.39 (m, 13H). MS (ESI, pos. ion) m/z: 323.2 (M + H). HPLC purity at 215 and 254 nm: 99 and 100% in systems B and C.

2-[(*S*)-1-(4-Fluorophenyl)ethylamino]-5-(1-hydroxycyclopentyl)-5-methylthiazol-4(5*H*)-one (33c). According to the general procedure described for **33d**, this compound was synthesized from 2-[(*S*)-1-(4-fluorophenyl)ethylamino]-5-methylthiazol-4(5*H*)-one (**16**) (0.25 g, 1.0 mmol), LDA (2.5 mL of a 2 M solution in THF, 2.5 mL, 5 mmol), and cyclopentanone (0.27 mL, 3.0 mmol). After purification of the crude product (silica gel, 4:1 hexanes/ethyl acetate to 1:1 hexanes/ethyl acetate), the title compound was isolated as a white solid (230 mg, 67%). ^{1}H NMR ($CDCl_3$ + 1 drop of TFA, 400 MHz): δ 7.31 (7.30) (d, 2H, J = 8 Hz); 7.11 (app t, 2H, J = 8 Hz), 4.69 (q, 1H, J = 8 Hz), 1.93−1.58 (m, 14H). MS (ESI, pos. ion) m/z: 337 (M + H). Anal. ($C_{17}H_{21}FN_2O_2S$) C, H, N.

4-{(*S*)-1-[5-(2-Hydroxypropan-2-yl)-5-methyl-4-oxo-4,5-dihydrothiazol-2-ylamino]ethyl}benzonitrile (33d). To a round-bottomed flask equipped with magnetic stirring and nitrogen purge was added a solution of 4-[(*S*)-1-(5-methyl-4-oxo-4,5-dihydrothiazol-2-ylamino)ethyl]benzonitrile[37] (0.21 g, 0.81 mmol) in THF (10 mL). After the reaction flask was cooled to −78 °C, LDA (1.8 mL of a 1.8 M solution in heptane/THF/ethylbenzene, 3.2 mmol) was added. The reaction mixture was stirred at −78 °C for 30 min, and then, acetone (0.24 g, 4.0 mmol) was added. After the mixture was stirred for

1.5 h at −78 °C, the reaction mixture was quenched with a saturated solution of NH_4Cl. The reaction mixture was then extracted with EtOAc (3 × 100 mL), and the combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash column chromatography (silica gel, 0−3% MeOH-CH_2Cl_2) afforded the title compound (116 mg, 45%) as a tan solid. ^{1}H NMR ($CDCl_3$ + 1 drop of TFA, 400 MHz): δ 7.74 (d, 2H, J = 8 Hz), 7.48 (d, 2H, J = 8 Hz), 4.66 (4.65) (q, 1H, J = 8 Hz), 1.78 (d, 3H, J = 8 Hz), 1.71 (1.82) (s, 1H), 1.46 (1.34) (s, 3H), 1.42 (1.26) (s, 3H). MS (ESI, pos. ion) m/z: 318 (M + H). Anal. ($C_{16}H_{19}N_3O_2S \cdot 0.6H_2O$) C, H, N.

2-[(*S*)-1-(4-Bromophenyl)ethylamino]-5-(2-hydroxypropan-2-yl)-5-methylthiazol-4(5*H*)-one (33e). Compound **33e** was prepared according to the general procedure described **33d** using 2-[(*S*)-1-(4-bromophenyl)ethylamino]-5-methylthiazol-4(5*H*)-one[37] (0.70 g, 2.2 mmol), LDA (5 mL of a 1.8 M solution in heptane/THF/ethylbenzene, 8.9 mmol), and acetone (0.65 g, 11 mmol). After purification of the crude product (silica gel, 0−3% CH_3OH in CH_2Cl_2), the product was isolated as a white solid (700 mg, 84%). ^{1}H NMR ($CDCl_3$ + 1 drop of TFA, 400 MHz): δ 7.57 (d, 2H, J = 8 Hz), 7.22 (d, 2H, J = 8 Hz), 4.615 (q, 1H, J = 8 Hz), 1.83 (1.73) (s, 3H), 1.75 (1.46) (d, 3H, J = 8 Hz), 1.37 (1.35) (s, 3H), 1.31 (1.27) (s, 3H). MS (ESI, pos. ion) m/z: 371, 373 (M + H). Anal. ($C_{15}H_{19}BrN_2O_2S$) C, H, N.

5-(2-Hydroxypropan-2-yl)-5-methyl-2-[(*S*)-1-*p*-tolylethylamino]thiazol-4(5*H*)-one (33f). Compound **33f** was prepared according to the general procedure described **33d** using 5-methyl-2-[(*S*)-1-*p*-tolylethylamino]thiazol-4(5*H*)-one[37] (0.60 g, 2.4 mmol), LDA (5.4 mL of a 1.8 M solution in heptane/THF/ethylbenzene, 9.7 mmol), and acetone (0.70 g, 12 mmol). After purification of the crude product (silica gel, 0−3% CH_3OH in CH_2Cl_2), the product was isolated as a colorless thin film (670 mg, 90%). ^{1}H NMR ($CDCl_3$ + 1 drop of TFA, 400 MHz): δ 7.21 (m, 4H), 4.615 (m, 1H), 2.38 (s, 3H), 1.82 (1.76) (s, 3H), 1.445 (1.75) (d, 3H, J = 8 Hz), 1.28 (1.35) (s, 3H). MS (ESI, pos. ion) m/z: 307 (M + H). Anal. ($C_{16}H_{22}N_2O_2S \cdot 0.2H_2O$) C, H, N.

2-[(*S*)-1-(4-Chlorophenyl)ethylamino]-5-(3-hydroxypropan-2-yl)-5-methylthiazol-4(5*H*)-one (33g). According to the procedure described for **33d**, this compound was synthesized from 2-[(*S*)-1-(4-chlorophenyl)ethylamino]-5-methylthiazol-4(5*H*)-one[37] (0.30 g, 1.1 mmol), LDA (2.2 mL of a 2.0 M solution in THF, 4.4 mmol), and acetone (0.52 g, 8.9 mmol). After purification (silica gel, 30−70% ethyl acetate/hexane), the title compound was isolated as a white foam (0.17 g, 47%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.41−7.28 (m, 4H), 4.62−4.51 (m, 1H), 3.96−3.83 (br s, 1H), 2.61 (s, 1H), 1.83−1.58 (m, 5H), 1.37−1.14 (m, 7H). MS (ESI, pos. ion) m/z: 327.1 (M + H). HPLC purity at 215 and 254 nm: 100 and 100% in system B; 99 and 97% in system C.

5-(2-Hydroxypropan-2-yl)-5-methyl-2-[(*S*)-1-phenylethylamino]thiazol-4(5*H*)-one (33h). Compound **33h** was prepared according to procedure described for **33d** using 5-methyl-2-[(*S*)-1-phenylethylamino]thiazol-4(5*H*)-one[37] (0.51 g, 2.2 mmol), LDA (4.8 mL of a 1.8 M solution in heptane/THF/ethylbenzene, 8.7 mmol), and acetone (0.63 g, 11 mmol). The crude material was purified by flash column chromatography (silica gel, 0−3% MeOH−CH_2Cl_2) to afford the title compound as a white solid (600 mg, 94%). ^{1}H NMR ($CDCl_3$ + 1 drop of TFA, 400 MHz,): δ 7.45−7.37 (m, 3H), 7.34−7.31 (m, 2H) 4.645 (q, 1H, J = 7 Hz), 1.82 (1.71) (s, 3H), 1.775 (1.45) (d, 3H, J = 7 Hz), 1.27 (1.33) (s, 6H). MS (ESI, pos. ion) m/z: 293(M + H). Anal. ($C_{15}H_{20}N_2O_2S \cdot 0.2H_2O$) C, H, N.

2-[(*S*)-1-(3-Fluorophenyl)ethylamino]-5-(2-hydroxypropan-2-yl)-5-methylthiazol-4(5*H*)-one (33i). A 100 mL round-bottomed flask was charged with 2-[(*S*)-1-(3-fluorophenyl)ethylamino]-5-methylthiazol-4(5*H*)-one[37] (0.66 g, 2.6 mmol) and 10 mL of THF. After the mixture was cooled to −78 °C, LDA (6.5 mL of a 2 M solution in THF, 13 mmol) was added, and the solution was stirred for 1 h at −78 °C. After that time, acetone (1.7 mL, 24 mmol) was added, and the mixture was stirred at −78 °C for 2.5 h. The reaction was quenched with a saturated solution of NH_4Cl. The mixture was extracted with EtOAc, dried with $MgSO_4$, and concentrated to give an oil, which was purified by silica gel chromatography (30−70% ethyl acetate/hexanes) to give the title compound as a white foam (0.55 g, 68%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35−6.94 (m, 4H), 4.63−4.53 (m, 1H), 2.64 (s, 1H), 1.85−1.58 (m, 6H), 1.36−1.13 (m, 6H). MS (ESI, pos. ion) m/z: 311.2 (M + H). HPLC purity at 215 and 254 nm: 98 and 98% in system B; 98 and 96% in system C.

2-[(*S*)-1-(2-Fluorophenyl)ethylamino]-5-(2-hydroxypropan-2-yl)-5-methylthiazol-4(5*H*)-one (33j). According to the general procedure described for **33d**, this compound was synthesized from 2-[(*S*)-1-(2-fluorophenyl)ethylamino]-5-methylthiazol-4(5*H*)-one[37] (0.75 g, 3.0 mmol), LDA (6.0 mL of a 2 M solution in THF, 12 mmol), and acetone (0.47 mL, 6.0 mmol). After purification of the crude product (silica gel, 4:1 hexanes/ethyl acetate), the title compound was isolated as a white solid (160 mg, 17%). ^{1}H NMR ($CDCl_3$ + 1 drop of TFA, 400 MHz): δ 7.40−7.33 (m, 2H); 7.23 (t, 1H, J = 8 Hz), 7.13 (dd, 1H, J = 8 Hz, 12 Hz), 5.01 (m, 1H), 1.84 (1.73) (3H, s), 1.78 (d, 3H, J = 4 Hz), 1.48(1.38) (s, 3H), 1.48(1.34) (s, 3H). MS (ESI, pos. ion) m/z: 311 (M + H). Anal. ($C_{15}H_{19}FN_2O_2S$) C, H, N.

2-[(*S*)-1-(2-Chlorophenyl)ethylamino]-5-(2-hydroxypropan-2-yl)-5-methylthiazol-4(5*H*)-one (33k). According to the procedure described **33d**, this compound was prepared from 2-[(*S*)-1-(2-chlorophenyl)ethylamino]-5-methylthiazol-4(5*H*)-one[37] (1.3 g, 4.8 mmol), LDA (9.7 mL of a 2 M solution in THF, 19 mmol), and acetone (2.2 g, 39 mmol). After purification (silica gel, 10−50% ethyl acetate/hexane), the title compound was isolated as a light yellow foam (1.2 g, 76%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.62−7.16 (m, 4H), 5.15−5.01 (m, 1H), 3.99 (tautomer 3.48) (s, 1H), 2.62 (s, 1H), 1.80−1.58 (m, 6H), 1.36−1.07 (m, 6H). MS (ESI, pos. ion) m/z: 327.1 (M + H). HPLC purity at 215 and 254 nm: 100 and 100% in system B; 98 and 97% in system C.

(*S*)-5-(2-Hydroxypropan-2-yl)-5-methyl-2-{1-[2-(trifluoromethyl)-phenyl]ethylamino}thiazol-4(5*H*)-one (33l). According to the procedure described for **33d**, this compound was prepared from 5-methyl-2-[(*S*)-1-(2-(trifluoromethyl)phenyl]ethylamino)thiazol-4(5*H*)-one[37] (0.50 g, 1.7 mmol), LDA·THF (4.4 mL of a 1.5 M solution in cyclohexane, 6.6 mmol), and acetone (0.49 mL, 6.6 mmol). After purification (silica gel, 0−4% MeOH in CH_2Cl_2), the desired product was isolated as a white solid (530 mg, 89%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.81 (dd, 1H, J = 8.0, 16.5 Hz), 7.67 (d, 1H, J = 8.0 Hz), 7.60−7.53 (m, 1H), 7.40 (m, 1H), 5.04−5.00 (m, 1H), 3.91 (m, 1H), 1.81−1.64 (m, 6 H), 1.34−1.12 (m, 6H). MS (ESI, pos. ion) m/z: 361 (M + H). HPLC purity at 215 and 254 nm: 100 and 100% in system A; 98 and 100% in system D.

2-[(*S*)-1-(4-Fluorophenyl)ethylamino]-5-(2-hydroxypropyl)-5-methylthiazol-4(5*H*)-one (34). To a round-bottomed flask equipped with stirring was added 2-[(*S*)-1-(4-fluorophenyl)ethylamino]-5-methylthiazol-4(5*H*)-one **16** (0.34 g, 1.4 mmol) in THF (3 mL) under nitrogen at 0 °C. Lithium bis(trimethylsilyl)amide (5.4 mL of a 1 M solution in THF, 5.4 mmol) was added, and the reaction mixture was stirred at 0 °C for 1 h. A solution of 2-methyloxirane (0.38 mL, 5.4 mmol) and lithium perchlorate (0.29 g, 2.7 mmol) in THF (4 mL) was added, and the reaction mixture was stirred at 0 °C for 2 h and then warmed to ambient temperature overnight. The reaction mixture was quenched with a saturated solution of NH_4Cl and extracted with EtOAc (3×). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash column chromatography (silica gel, 0−7% MeOH in CH_2Cl_2) afforded the title compound **34** (310 mg, 71%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.45−7.30 (m, 2H), 7.03−6.98 (m, 2H), 4.59−4.51 (m, 1 H), 4.06−3.91 (m, 1H), 2.15−1.98 (m, 2 H), 1.82−1.48 (m, 6H), 1.27−1.14 (m, 3H). MS (ESI, pos. ion) m/z: 311 (M + H).

2-[(*S*)-1-(4-Fluorophenyl)ethylamino]-5-methyl-5-(2-oxopropyl)-thiazol-4(5*H*)-one. To a round-bottomed flask equipped with stirring was added 2-[(*S*)-1-(4-fluorophenyl)ethylamino]-5-(2-hydroxypropyl)-5-methylthiazol-4(5*H*)-one (**34**) (0.28 g, 0.90 mmol) and Dess−Martin periodinane (0.54 g, 1.3 mmol) in CH_2Cl_2 (8 mL). After the mixture was stirred at ambient temperature overnight, $Na_2S_2O_3$ (1.5 g) and a saturated solution of $NaHCO_3$ (5 mL) were added, and the mixture was stirred at ambient temperature for 30

min. The reaction mixture was extracted with CH_2Cl_2 (3 × 60 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash column (silica gel, 0−3% MeOH in CH_2Cl_2) afforded the title compound (230 mg, 83%) as a white solid. ^{1}H NMR ($CDCl_3$ + 1 drop of TFA, 400 MHz): δ 7.35−7.29 (m, 2H), 7.14−7.05 (m, 2H), 4.58 (4.53) (q, 1H, J = 8 Hz), 3.31 (3.30) (d, 1H, J = 20 Hz), 3.05 (2.91) (d, 1H, J = 20 Hz), 2.25 (2.19) (s, 3H), 1.74, 1.725 (2d, 3H, J = 8 Hz), 1.72 (1.63) (s, 3H). MS (ESI, pos. ion) *m/z*: 309 (M + H).

2-[(*S*)-1-(4-Fluorophenyl)ethylamino]-5-(2-hydroxy-2-methylpropyl)-5-methylthiazol-4(5*H*)-one (35). In a round-bottomed flask equipped with stirring was added methylmagnesium bromide (0.42 mL of a 3 M solution in diethyl ether, 1.3 mmol) to a solution of 2-[(*S*)-1-(4-fluorophenyl)ethylamino]-5-methyl-5-(2-oxopropyl)thiazol-4(5*H*)-one (98 mg, 0.32 mmol) in THF at 0 °C under nitrogen. The resulting reaction mixture was stirred at 0 °C for 5 h, and then, additional methylmagnesium bromide (0.42 mL of a 3 M solution in diethyl ether, 1.3 mmol) was added. The reaction mixture was stirred at 0 °C for 1 h, and again, methylmagnesium bromide (0.42 mL of a 3 M solution in diethyl ether, 1.3 mmol) was added. After the reaction mixture was stirred to ambient temperature for 1 h, the mixture was quenched with a saturated solution of NH_4Cl and extracted with EtOAc (3 × 60 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash column (silica gel, 0−3% MeOH in CH_2Cl_2) afforded the title compound (63 mg, 61%) as a white solid. ^{1}H NMR ($CDCl_3$ 400 MHz): δ 7.47−7.30 (m, 2 H), 7.07−6.95 (m, 2H), 4.62−4.60 (m, 1H), 2.28−2.11 (m, 2H, m), 1.77 (m, 3H), 1.70−1.63 (m, 3H), 1.33−1.12 (m, 6H). MS (ESI, pos. ion) *m/z*: 325 (M + H). Anal. ($C_{16}H_{21}FN_2O_2S \cdot 0.3H_2O$) C, H, N.

11β-HSD1 SPA Assay. Enzyme assays were performed using purified recombinant 11β-HSD1 that was expressed in *E. coli*. Assays were run in a total volume of 100 μL, including 40 μL of purified enzyme, 10 μL of compound dilutions, 10 μL of [^{3}H]cortisone (100 nM final), 10 μL of NADPH (200 μM final), and 30 μL of assay buffer (50 mM Tris-HCl, 1 mM EDTA, pH 7.2). The assay was initiated by the addition of purified enzyme preparation. The final concentrations of enzyme varied for different species. For human, rat, and dog 11β-HSD1, the final concentration of enzyme was 20 nM. For mouse and monkey 11β-HSD1, the final concentration of enzyme was 5 and 10 nM, respectively. Assay plates were incubated on an orbital shaker for 1 h at room temperature. The reaction was stopped by the addition of 10 μL of buffer containing 100 μM 18 β-glycyrrhetinic acid (GE). At the same time, 10 μL of a 1:50 dilution of anticortisol and 100 μL of 15 mg mL^{-1} antimouse SPA beads were added to the wells. Plates were incubated on an orbital shaker for another 30 min at room temperature. Radiometric quantitation was determined on a TopCount NXT instrument (Perkin-Elmer, Downers Grove, IL).

11β-HSD2 SPA Assay. Enzyme assays were performed using human 11β-HSD2 enzyme expressed in CHO cells. Assays were run in a total volume of 100 μL, including 40 μL of enzyme, 10 μL of compound dilutions, 10 μL of [^{3}H]cortisol (3 nM final), 10 μL of NAD^+ (300 μM final), and 30 μL of assay buffer (0.1 M sodium phosphate buffer, pH 7.6). The assay was initiated by the addition of 40 μL of enzyme preparation. Assay plates were incubated on an orbital shaker for 1 h at room temperature. The reaction was stopped by the addition of 10 μL of buffer containing 100 μM 18 β-glycyrrhetinic acid (GE). At the same time, 10 μL of a 1:70 dilution of anticortisol and 100 μL of 10 mg mL^{-1} antimouse SPA beads were added to the wells. Plates were incubated on an orbital shaker for another 30 min at room temperature. Radiometric quantitation was determined on a TopCount NXT instrument (Perkin-Elmer).

Measurement of 11β-HSD1 Activity in Whole Cells. Cell-based activity was measured by monitoring the conversion of cortisone to cortisol in CHO cell lines stably overexpressing 11β-HSD1. Cells were maintained in Dulbecco's modified Eagle's medium supplemented with 10% dialyzed serum, penicillin/streptomycin/glutamine, nonessential amino acids, and sodium pyruvate. Assay plates were prepared 1 day prior to the addition of the compound. Cells were seeded at a density of 30000 cells per well in 100 mL of maintenance medium. The assay was initiated by removing the medium and rinsing cells twice with glucose buffer (50 mM HEPES containing 120 mM NaCl, 1.85 mM $CaCl_2$, 1.3 mM $MgSO_4$, and 4.8 mM KCl, pH 7.4), followed by the addition of 80 mL of glucose buffer containing 0.1% DMSO. The compound was added to achieve a final concentration of 0.1 nM to 10 μM. The plates were incubated for 60 min at 37 °C. Following the incubation, cortisone was added to each well to achieve a final concentration of 100 nM. The plates were then incubated at 37 °C. The incubation time for human 11β-HSD1 was 40 min; for mouse 11β-HSD1, 45 min; for dog 11β-HSD1, 1.5 h; and for rat and monkey 11β-HSD1, 2 h. Cortisol formed from cortisone was quantitated using a cortisol enzyme-linked immunosorbent assay kit.

PXR Reporter Gene Assay. This assay was conducted at Indigo Biosciences (State College, PA).[38]

Human Hepatocyte Culture and Experimental Procedure. Fresh human hepatocytes from two donors were purchased from Cellz-Direct. Donor 1 was a 60 year old Caucasian male (lot DJV) with no adverse medical history or history of substance or alcohol abuse, and donor 2 was a 40 year old Caucasian female (lot NPV) with a history of tobacco usage and substance usage (cocaine and marijuana). On day 1, fresh hepatocytes were received and suspended in plating medium (0.8×10^6 cells mL^{-1}). Hepatocytes were counted and plated in collagen-coated 24 well plates (BD Biosciences, Bedford, MA) with 0.4×10^6 cells per well. The hepatocytes were placed in a 37 °C incubator (Steri-Cult CO_2 Incubator, model 3310, Thermo Electron Corp., Waltham, MA) under an atmosphere of 95% air/5% CO_2 and 90% relative humidity and allowed a 3−5 h attachment period. Following the attachment period, the plating medium and unattached cells were aspirated, sandwich medium was applied (0.5 mL per well), and the cells were incubated overnight. On day 2, the sandwich medium was aspirated, and culture medium (0.5 mL per well) was applied for an overnight acclimation period. On days 3 and 4, culture medium containing either DMSO (0.1%) or rifampin (0.05−5 μM) was applied on each day (0.5 mL per well). The test articles were prepared in DMSO stock solutions resulting in final incubation concentrations of 0.1% DMSO. Compound treatment was maintained for a total of 48 h. On day 5, hepatocytes were gently washed with Krebs−Henseleit buffer (KHB) (2 × 0.5 mL per well; ∼37 °C) and allowed to acclimate for an additional 10 min. Subsequently, CYP enzyme activities were determined by the addition of the marker substrate midazolam (10 μM; CYP3A4) dissolved in KHB (0.5 mL per well; ∼37 °C). Following a 10 min incubation time period, the supernatant was removed and stored at −80 °C until analyzed. Hepatocytes designated for mRNA analysis were washed once with PBS (0.5 mL per well) containing calcium and magnesium and aspirated. To each well was added 0.5 mL of 33% lysis mixture (Panomics, Inc., Fremont, CA) and then stored at −80 °C until assay.

mRNA Analysis. The CYP3A4 mRNA content was determined with branched DNA (bDNA) signal amplification technology using the Panomics Discover XL Kit (Panomics, Inc.) with assays performed according to the manufacturer's instructions. bDNA probe sets, containing capture extender, label extender, and blocking probes for human CYP3A4 (catalog no. PA-10909) and GAPDH (catalog no. PA-10382) were also purchased from Panomics, Inc. Plate washing steps were performed on an Elx405 automated microplate washer (BIO-TEK, Winooski, VT), and luminescence was analyzed on a Luminoskan Ascent microplate luminometer (Thermo Labsystems, Helsinki, Finland). CYP mRNA levels were normalized to the mRNA levels of the housekeeping gene GAPDH.

Enzyme Activity. Following the induction treatment period, cell cultures were assayed for the metabolism of the CYP3A4 marker substrate, midazolam. Analysis and quantification of 1′-OH-midazolam, the major midazolam metabolite in hepatocyte cultures, were performed by LC-MS/MS on a system comprising a reverse phase HPLC (Shimadzu, Kyoto, Japan) and a triple quadrupole mass

spectrometer (Applied Biosystems API 5000, Foster City, CA) using Turbo Ionspray (Applied Biosystems) via multiple reaction monitoring. Samples (25 μL) were loaded on a C18 column (Phenomenex Onyx Monolithic C18, 100 mm × 3.0 mm, P/no. CHO-8158) eluted with a linear gradient of mobile phase A (H_2O with 0.1% acetic acid and 5% methanol) to B (H_2O with 0.1% acetic acid and 95% methanol). The flow rate was 1 mL/min. Metabolites were quantitated by a peak area ratio of metabolite to internal standard (prazosin).

X-ray Structure Determination. The X-ray cocrystal structure of (*S*)-**33a** with human 11β-HSD1 was collected using the procedure described in ref 32.

In Vivo Pharmacodynamics in Monkeys. Male cynomolgus monkeys were assigned based on their body weight to treatment groups [0, 0.3, 1, 3, and 30 mg kg^{-1} of compound (*S*)-**31a**] with at least four animals per group. The animals were dosed via the nasal−gastric route once with compound of target dosage in dosing vehicle (1% Tween 80, 47.5% Ora-Plus, and 51.5% water). At 2 h postdosing, plasma and tissue samples were collected, snap-frozen in liquid nitrogen, and stored either in dry ice or at −80 °C. Approximately 50 mg of mesenteric fat tissues was cut in triplicate into a 24 well plate on dry ice. The tissues were then incubated with 600 μL of warm Krebs Ringer Phosphate (KRP) buffer (0.9% NaCl, 1.15% KCl, 1.8% $MgSO_4$, and 0.1 M Na_2HPO_4 at pH 7.4) containing ^{3}H-cortisone (Amersham, GE Healthcare) at 37 °C on a shaker for 1 h. After the incubation, 150 μL of media was collected into a 96 well plate. To measure ^{3}H-cortisol by SPA, 40 μL of SPA PVT beads (Amersham, GE Healthcare) mix containing cortisol monoclonal antibody (5.4 μg mL^{-1}) (East Coast Biologics, MA) was added to all wells. The plates were incubated at room temperature on a shaker for 15 min, followed by centrifugation at 2500 RPM for 5 min. After the supernatant was removed, 100 μL of PBS/0.1% BSA was added for further incubation at room temperature on a shaker, followed by another round of centrifugation. The beads were resuspended in 150 μL of PBS/0.1% BSA and transferred to a 96 well Opti-Plate white assay plates (PerkinElmer, Waltham, MA) to be read on a TopCount plate reader (PerkinElmer). The DPM readout from TopCount was converted to the absolute amount of cortisol produced, which was then normalized by the amount of fat tissue used and the assay incubation time. The unit of ex vivo activity was expressed as fmol cortisol produced per mg of fat tissue used per hour (fmol cortisol/mg tissue/h).

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Supporting Information Available: Analytical data for final compounds and X-ray structure coordinates for (*S*)-**33a** and (*S*)-**33a** with human 11β-HSD1 (PDB ID: 3EY4). This material is available free of charge via the Internet at http://pubs.acs.org.

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