Discovery of Novel, Potent Benzamide Inhibitors of 11β-Hydroxysteroid Dehydrogenase Type 1 (11β-HSD1) Exhibiting Oral Activity in an Enzyme Inhibition ex Vivo Model[▽]

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We report the discovery of potent benzamide inhibitors of 11β-hydroxysteroid dehydrogenase (11β-HSD1). The optimization and correlation of in vitro and in vivo metabolic stability will be described. Through modifications to our initial lead **2**, we discovered pyridyl compound **13**. This compound has a favorable pharmacokinetic profile across three species and showed a dose-dependent decrease in adipose 11β-HSD1 activity in a monkey ex vivo pharmacodynamic model.

Introduction

Glucocorticoids regulate glucose and lipid homeostasis, acting through intracellular glucocorticoid receptors in the liver, adipose, and brain tissues.[1] Elevated levels of glucocorticoids can result in insulin resistance by impairment of insulin dependent glucose uptake, enhanced hepatic gluconeogenesis, increased lipolysis, and the inhibition of insulin secretion from pancreatic β-cells.[2] As a result of sustained glucocorticoid excess, like that observed in Cushing's syndrome, patients can develop dyslipidemia, visceral obesity, and other symptoms of metabolic syndrome.[3]

The 11β-hydroxysteroid dehydrogenase type I (11β-HSD1[a]) enzyme catalyzes the conversion of cortisone to the active glucocorticoid hormone cortisol, thus regulating the local activation of glucocorticosteroid receptors (Figure 1).[1] Its counterpart, 11β-HSD2, catalyzes the reverse reaction of cortisol to cortisone. Evidence supporting the therapeutic potential of selectively inhibiting 11β-HSD1 for the treatment of type II diabetes and obesity has been obtained from mouse genetic models. Fat-specific 11β-HSD1 transgenic mice developed symptoms of metabolic syndrome (i.e., increased levels of glucose, insulin, triglycerides, and visceral fat accumulation).[4] Conversely, 11β-HSD1 knockout mice showed impaired induction of gluconeogenetic enzymes, improved glucose tolerance and insulin sensitivity, and resistance to obesity when fed a high fat diet.[5] These data, coupled with the increasing incidence of obesity and diabetes today, have generated significant interest from the pharmaceutical industry toward the development of an 11β-HSD1 inhibitor.[6]

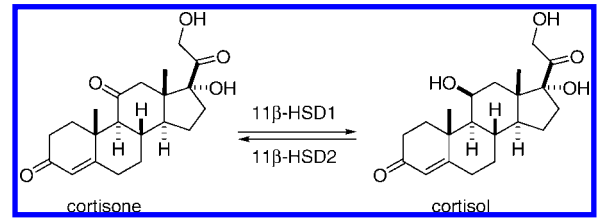

Figure 1. Interconversion of cortisone and cortisol catalyzed by 11β-HSD.

As part of our drug discovery effort to develop small molecule inhibitors of 11β-HSD1, we aimed to identify a novel chemical series based in part on the structure−activity relationships (SARs) derived from our previously reported sulfonamide analogues (e.g., **1**, Figure 2).[6c] Specifically, we envisioned that an amide moiety could serve as a suitable isosteric replacement of the sulfonamide core present in compound **1**. Indeed, we discovered that benzamide compound **2** demonstrated potent activity toward full length recombinant human 11β-HSD1 (IC_{50} = 1.3 nM).[7] While the potency of compound **2** was satisfactory at this stage, the molecule demonstrated poor in vitro metabolic stability, which translated into poor in vivo rodent pharmacokinetics. Improvement of the unfavorable metabolic profile was our initial objective in progressing this new series. In addition to the necessary improvements in the pharmacokinetics of these benzamide 11β-HSD1 inhibitors, our paradigm for compound advancement required the demonstration of 11β-HSD1 activity in an ex vivo model. This report describes the evolution of benzamide compound **2** toward 11β-HSD1 inhibitors that exhibit improved pharmacokinetics and significant primate ex vivo activity.

Chemistry

Generally, benzamide inhibitors were prepared in two steps from the corresponding cyclohexanone intermediate as shown in Scheme 1. The incorporation of ethyl, cyclopropylmethyl, and cyclopropyl substituents on nitrogen was accomplished by reductive amination of cyclohexanone **3** (R^1 = H) with the appropriate amine. The cyclohexylamines **4** were then coupled to optically pure (*S*)-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)-benzoic acid **17**, prepared from 4-acetylbenzonitrile **16**, using

[▽] Coordinates of the new structures have been deposited with the RCSB Protein Data Bank (http://www.rcsb.org/pdb) with codes 3D3E (**13**-HSD1 complex) and 3D4N (**20**-HSD1 complex).

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[a] Abbreviations: 11β-HSD1, 11β-hydroxysteroid dehydrogenase type 1; 11β-HSD2, 11β-hydroxysteroid dehydrogenase type 2; SPA, scintillation proximity assay; HLM, human liver microsomes; RLM, rat liver microsomes; h293, human embryonic kidney 293 cells; HSA, human serum albumin; NADP, nicotinamide adenine dinucleotide phosphate; Cp, cyclopropyl.

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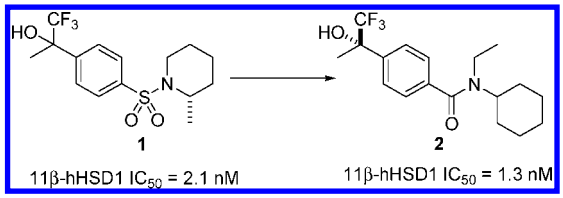
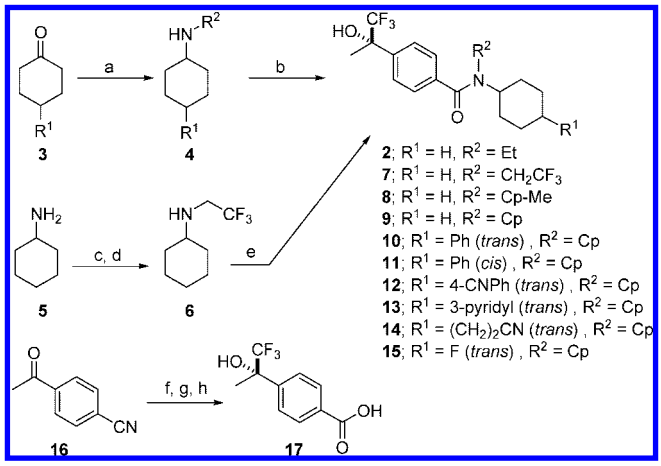


Figure 2. An initial benzamide compound.

Scheme 1. General Synthesis of Benzamide 11β-HSD1 Inhibitors[a]



[a] Reagents and conditions: (a) NH_2R^2, $NaBH(OAc)_3$, dichloroethane (16−99%); (b) **17**, EDCI, HOAt, $NaHCO_3$, DMF (10−63%); (c) $(CF_3CO)_2O$, pyridine (88%); (d) BH_3, THF; (e) **17**, $SOCl_2$, THF, 80 °C, then amine (29%, two steps); (f) $TMSCF_3$, TBAF, THF; (g) 5 M NaOH, 75 °C (78%, two steps); (h) recrystallization with chinconidine, optical purity >99% ee (24% from racemic material).

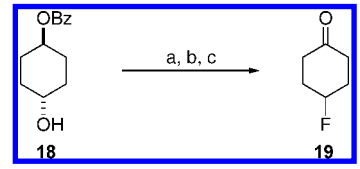
standard amide coupling conditions to afford the targeted analogues **2**, **8**, and **9**. Compound **7** was prepared via a different synthetic route starting from cyclohexylamine **5**. Acylation of cyclohexylamine with trifluoroacetic anhydride, followed by reduction of the resultant amide carbonyl with borane, gave the *N*-(2,2,2-trifluoroethyl)cyclohexylamine **6**, which was coupled to (*S*)-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzoic acid **17** through intermediate formation of the more reactive acid chloride.

The synthesis of 4-substituted cyclohexane benzamides was accomplished in a straightforward manner, starting with the appropriate 4-substituted cyclohexanone **3** ($R^1 \neq H$) (Scheme 1). For compounds **10**−**12**, the commercially available 4-phenyl- and 4-(4-cyano)phenylcyclohexanones (**3**, R^1 = Ph and 4-CNPh, respectively) were elaborated to the corresponding benzamides in two steps via reductive amination with cyclopropylamine followed by amide bond formation.[8] For analogues **13** and **14**, the 4-substituted cyclohexanone intermediates (**3**, R^1 = 3-pyridyl and CH_2CH_2CN, respectively) were prepared according to literature prodecures.[9,10] The preparation of 4-fluorocyclohexanone **19**, a precursor to derivative **15**, was achieved in three steps from known 4-hydroxycyclohexyl benzoate **18** as detailed in Scheme 2.[11]

Results and Discussion

All compounds were screened for 11β-HSD1 enzyme activity in a scintillation proximity assay (SPA).[7] Select compounds were then tested for cellular activity in human embryonic kidney 293 cells (HEK 293 or h293) that stably express recombinant full-length human 11β-HSD1 and nontransfected human fat stromal cells (adipocytes) expressing endogenous levels of 11β-HSD1.[12]

Scheme 2. Synthesis of 4-Fluorocyclohexanone **19**[a]



[a] Reagents and conditions: (a) diethylaminosulfur trifluoride (DAST), CH_2Cl_2, −78 °C to room temp (19%); (b) LiOH, MeOH, THF (93%); (c) PCC, CH_2Cl_2 (71%).

In the cellular assays, inhibitors were tested in the presence and absence of human serum albumin (HSA) to measure the impact of protein binding. The 11β-hydroxysteroid dehydrogenase selectivity profile of compounds was determined by measuring 11β-HSD2 activity using the SPA assay and comparing the results to 11β-HSD1 enzyme activity.

Initial characterization of compound **2** revealed that it was rapidly metabolized in vitro, showing nearly complete consumption in both human and rat liver microsomes after a 30 min incubation period.[12] In vivo pharmacokinetic data also showed compound **2** to be rapidly cleared in rats (CL = 3.1 L/h/kg). The identification and quantification of metabolites formed from human and rat liver microsomes (HLM and RLM, respectively) showed three major routes of oxidative metabolism: *N*-dealkylation (**2a**) and oxidation of both the *N*-ethyl (**2b**) and *N*-cyclohexyl (**2c**) substituents (Figure 3). Furthermore, the metabolite identification data revealed significant species differences. Specifically, *N*-dealkylation was primarily observed in humans, shown from quantification of **2a** (26% from HLM and <1% from RLM). The amount of *N*-ethyl oxidation was comparable in both species (i.e., **2b**); however, oxidation of the cyclohexyl ring occurred more extensively in rat, (**2c**, 62% from RLM vs 44% from HLM). With these data in hand, we sought to improve the metabolic stability of compound **2** via modifications to the ethyl and cyclohexyl substituents. We planned to use our in vitro assay to measure initial improvements in metabolic stability of synthesized compounds. Promising analogues would then be advanced to rodent pharmacokinetic studies.

Analogues containing *N*-ethyl replacements were initially explored, and it was found that the different nitrogen substituents were generally tolerated in regard to potency (Table 1). Compound **8** showed a slight reduction in potency, especially in the cellular assays; however, this compound was tested as a racemic mixture. On the basis of our metabolite identification studies described above, we expected improvements in stability to be greater in human liver microsomes over rat liver microsomes. Indeed, compounds **7**−**9** all showed improvements in HLM stability, while no stability gains were observed when evaluated in the rat microsome assay. Compound **9**, containing the *N*-cyclopropyl substituent, was found to be optimal in the HLM stability assay (81% remaining after 30 min). In addition to improved microsomal stability, the cyclopropyl-substituted analogue **9** showed a slight increase in potency (11β-HSD1 IC_{50} = 0.8 nM) compared to the parent compound **2**.

Having improved the in vitro stability in human liver microsomes, we then turned our attention to the optimization of metabolic stability in rats. The *N*-cyclopropyl group was maintained in subsequent analogues, which was predicted to have an additive effect with any improvements made in rat microsomal stability. It was found that, in general, substitution at the 4-position on the cyclohexane ring resulted in significant improvements in microsomal stability. The stereochemistry of this substituent was determined to be important because only

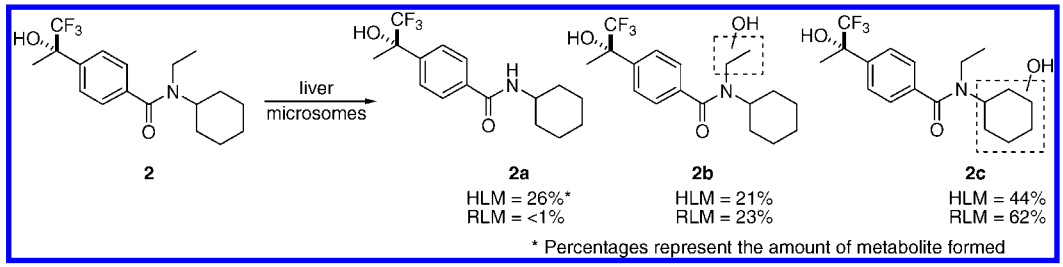
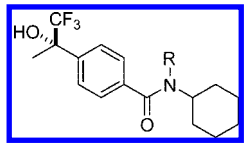


Figure 3. Major metabolites of compound **2**.

Table 1. Effect of *N*-Ethyl Modifications on in Vitro Metabolic Stability and Potency



Compound	R =	h11β-HSD1[a] IC_{50} (nM)[b]	h293[c] (cell) IC_{50} (nM)	h293[c] (cell + 3% HSA[d]) IC_{50} (nM)	%remaining @ 30 min HLM	RLM
2	CH_2CH_3	1.7	3.2	25	5	<5
7	CH_2CF_3	2.6	24	163	17	<5
8[e]		9.0	38	849	23	<5
9		0.8	2.4	38	81	<5

[a] IC_{50} values determind by scintillation proximity assay (SPA). [b] All potency data are reported as the average of at least two determinations. [c] h293 = HEK 293 cells stably transfected with full length human 11β-HSD1. [d] HSA = human serum albumin. [e] Racemic mixture; synthesized from racemic **17**.

the trans isomers showed improved microsomal stability. For example, the 4-phenyl trans derivative **10** was stable in both human and rat liver microsomes (>90% remaining after 30 min), while the corresponding cis analogue **11** was rapidly consumed (9% and <5% remaining in HLM and RLM after 30 min, respectively, Table 2). These results demonstrated that concomitant modifications to the *N*-ethyl and *N*-cyclohexane groups led to highly improved stability in the in vitro microsomal clearance assay in humans and rats, as predicted from the metabolic identification studies of parent compound **2**.

In addition to significant improvements measured in the microsomal stability assay, compounds containing a substituent at the 4-cyclohexane position were highly potent. It was found that trans aryl (**10**, **12**), heteroaryl (**13**), alkyl (**14**), and fluorine (**15**) substituents were tolerated. The 4-phenyl cis analogue **11** showed slightly diminished 11 β-HSD1 activity (~5-fold) relative to the corresponding trans derivative **10** in the noncellular assay, and this result exemplified the general SAR trend for the cis and trans stereoisomers. A shift in potency was observed in h293 cells for all compounds tested, ranging from 2-fold to 17-fold. The cellular potency was further lowered in the presence of HSA, ranging from 4-fold to 21-fold. The potency profile of pyridyl compound **13** exemplified the general trend: 11β-HSD1 (SPA) IC_{50} = 1.4 nM, h293 11β-HSD1 IC_{50} = 5.8 nM (4-fold shift), and h293 (+3% HSA) 11β-HSD1 IC_{50} = 124 nM (21-fold shift).

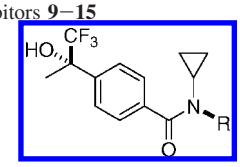
11β-HSD1 enzyme inhibition in the adipose tissue is believed to be important for achieving efficacy in vivo.[4] Thus, we measured the ability for compounds to inhibit 11β-HSD1 activity in human adipocytes (Table 2). The β-cyanoethyl analogue **14** showed exquisite potency across all assays, including in the adipocyte assay where subnanomolar potency of 0.2 nM was measured. Typically, IC_{50} values measured in adipocytes were comparable to the noncellular biochemical potency data. The trans-4-substituted cyclohexane benzamides were also tested against the 11β-HSD2 enzyme in the SPA assay to determine 11β-HSD selectivity. In all cases, the compounds were inactive (>10 μM).

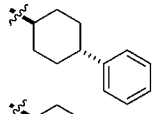
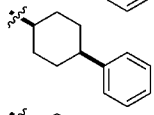
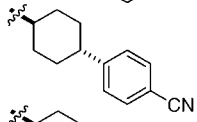
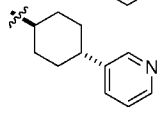
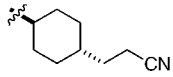
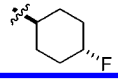
Since compounds **12**−**14** demonstrated satisfactory in vitro metabolic stability, these compounds were examined in rodent pharmacokinetic experiments (Table 3). It was found that in vivo results exhibited a correlation to the in vitro microsomal stability data. For example, the 4-(4-cyano)phenyl derivative **12** was found to have a very low clearance in rats (CL = 0.11 L/h/kg) as predicted from the rat liver microsome data (>90% remaining after 30 min). Analogues **13** and **14** were found to have moderate clearance in rats (CL = 1.0 and 1.28 L/h/kg, respectively), also reflected in the in vitro data (Table 2). Further pharmacokinetic evaluation of compound **13** was carried out in two separate species, cynomolgus monkey and dog. The measured clearance of **13** in cynomolgus monkey and dog (CL = 0.50 and 0.60 L/h/kg, respectively) was found to be about 2-fold lower than the rat clearance, which resulted in a low predicted clearance in humans based on allometric scaling.[13] Pyridine analogue **13** had excellent oral bioavailability in rats (F = 72%) and cynomolgus monkeys (F = 64%), but the bioavailability in dogs was poor (4%).[14] Overall, molecules **12** and **13** showed the most promising pharmacokinetic profiles, characterized by low clearances, long half-lives, and high exposures.

In addition to the excellent potency and pharmacokinetic profile, compound **13** had suitable activity in a recombinant cynomolgus monkey 11β-HSD1 enzyme assay (IC_{50} = 39 nM). We selected compound **13** for further evaluation in our cynomolgus ex vivo pharmacodymanic model in which we measured, in vitro, the 11β-HSD1 enzyme activity in intact fat tissues collected from animals dosed with the molecule. This ex vivo model is useful in that it can quantify the 11β-HSD1 activity not only in the tissue of choice but also at a time point of choice.

In the ex vivo study, cynomolgus monkeys were dosed orally with 2 and 10 mg/kg of inhibitor **13**. At 2 h postdose, the animals were sacrificed and the mesenteric fat tissue was removed. Following incubation of these tissues in media containing [^{3}H]cortisone, 11β-HSD1 activity was measured through detection of tritiated cortisol levels using a scintillation proximity assay. Relative to controls, both dose groups showed a decrease in [^{3}H]cortisol production in mesenteric fat, corresponding to an ED_{50} in cynomolgus monkey of 2 mg/kg[12] (Figure 4). Compound exposure levels were measured to be approximately 2.5 times greater in the adipose (levels ranged from 1510 to 2890 ng/g) than in the plasma, which showed that the compound effectively distributed to the target fat tissue. These results demonstrated that inhibitor **13** was effective in

Table 2. SAR of 4-Substituted Cyclohexane Benzamide Inhibitors **9**−**15**



Compound	R =	h11β-HSD1[a] IC_{50} (nM)[b]	h293[c] (cell) IC_{50} (nM)	h293[c] (cell + 3% HSA[d]) IC_{50} (nM)	human adipocyte IC_{50} (nM)	h11β-HSD2[a] IC_{50} (nM)	%remaining @ 30 min HLM	%remaining @ 30 min RLM
9		0.8	2.4	38	ND[e]	>10,000	81	<5
10		1.3	16	155	9.8	>10,000	>90	>90
11		6.1	18	123	ND	>10,000	9	<5
12		0.7	12	161	3.4	>10,000	>90	>90
13		1.4	5.8	124	3.0	>10,000	>90	51
14		0.7	1.3	11	0.2	>10,000	>90	42
15		6.6	36	140	4.1	>10,000	81	16

[a] IC_{50} values determind by scintillation proximity assay (SPA). [b] All potency data are reported as the average of at least two determinations. [c] h293 = HEK 293 cells stably transfected with full length human 11β-HSD1. [d] HSA = human serum albumin. [e] ND = not determined.

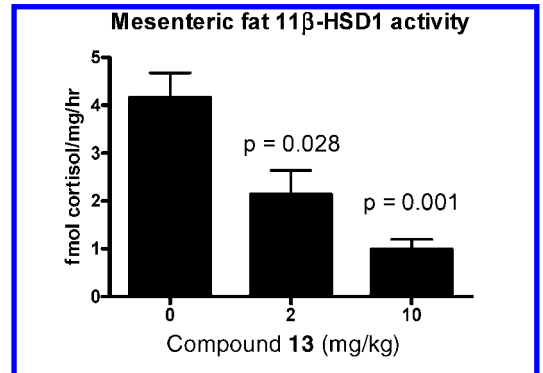
Table 3. Pharmacokinetic Profiles of Compounds **12**−**14**

compd	species	CL (iv, L/h/kg)	$t_{1/2}$ (iv, h)	V_{dss} (iv, L/kg)	AUC (iv, mg•h/L	*F* (po, %)
12	rat[a]	0.11	15.7	2.5	1590	29
13	rat[b]	1.0	4.5	6.7	481	72
13	cyno[b]	0.50	11.2	8.1	1010	64
13	dog[b]	0.60	9.3	3.5	915	4
14	rat[a]	1.28	0.5	0.91	393	83

[a] Dosed iv 0.17 mg/kg, po 2.0 mg/kg. [b] Dosed iv 0.5 mg/kg, po 2.0 mg/kg.

lowering 11β-HSD1 adipose activity in cynomolgus monkeys when administered orally.

Insight into the binding mode of the benzamide class of 11β-HSD1 inhibitors was obtained by X-ray crystallography, and the data were compared to our previously studied sulfonamide inhibitors (e.g., compound **20**, Figure 5d).[6c,15] Specifically, an X-ray cocrystal structure of compound **13** with human 11β-HSD1 enzyme containing NADP cofactor was generated (Figure 5). Benzamide **13** binds in a V-shaped conformation in the steroid substrate binding pocket with the amide carbonyl forming a central hydrogen bond interaction with hydroxyl of S170 (Figure 5a), one of the three residues that define the catalytic triad for 11β-HSD1 activity.[16] The rest of the molecule forms a number of van der Waals (VDWs) contacts with the enzyme as well as the cofactor NADP. The pyridine ring is positioned toward the solvent exposed area of the dimer interface region of the protein and does not make any specific interactions, which may explain the tolerability of polar groups at this position (Figure 5b). The cyclopropyl moiety forms close van der Waals interactions with the side chains of L171 and Y177 and the backbone of L215, and the trifluoromethyl tertiary alcohol positions toward the cofactor NADP with the trifluoromethyl group in close VDWs contacts with T124, S125, L126, and A226.



PO Dose	n	[**13**] (ng/mL) Plasma	[**13**] (ng/g) Mesenteric Fat
Vehicle	6	-----	-----
2 mg/kg	4	604 ± 315	1510 ± 639
10 mg/kg	4	1211 ± 517	2890 ± 1303

Figure 4. Exposure and activity of compound **13** as measured in a cynomolgus monkey enzyme inhibition ex vivo assay.

In comparison to the benzamide compound, our previously reported sulfonamide inhibitor **20** also binds in the active site with a similar V-shape binding mode.[15] The cyclopropane carboxamide group points toward the dimer interface region,

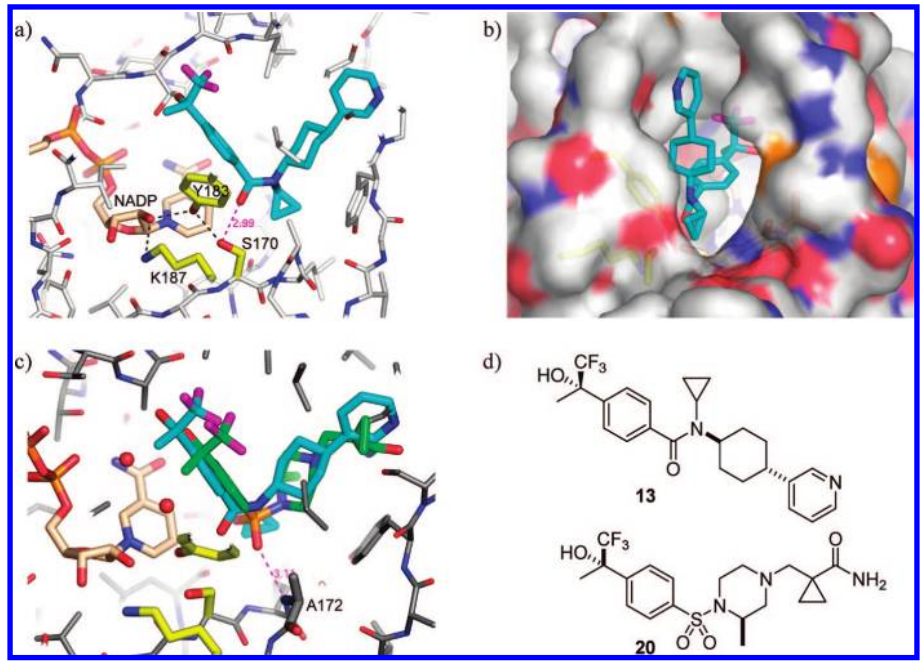


Figure 5. X-ray cocrystal structures of benzamide **13** and sulfonamide **20** with human 11β-HSD1. (a) Binding mode of inhibitor **13** in the active site of 11β-HSD1. The key hydrogen bonding interaction of **13** to the enzyme is shown with the magenta dashed line. The color scheme is red for oxygen atoms, blue for nitrogen atoms, orange for sulfur atoms, magenta for fluorine atoms. Carbon atoms are in gray for the enzyme, beige for NADP, and cyan for the inhibitor. The key residues in the catalytic triad are highlighted in yellow sticks, with hydrogen bond interactions indicated by gray dashed lines. (b) Molecular surface representation of a side view of **13** in the active site. (c) Binding mode of inhibitor **20** to the enzyme with inhibitor **13** overlaid on it. The key hydrogen bonding interaction of **20** to the enzyme is shown with the magenta dashed line. The carbon atoms are in green for inhibitor **20**. The water molecules in the active site are shown in red spheres. (d) Chemical structures of pyridine **13** and sulfonamide **20**.

similar to the area occupied by the pyridyl ring in **13** (Figure 5c). However, the isosteric sulfonamide core moiety does not form any direct hydrogen bond interactions to the catalytic triad residues, as observed in the cocrystal structure of inhibitor **13**. Instead, the sulfonamide oxygen forms a hydrogen bond with the backbone amide of A172, which represents a notable difference in the key binding interactions of the benzamide and sulfonamide inhibitors.

Conclusion

In summary, we have identified a novel class of 11β-HSD1 inhibitors containing a benzamide core structure. Our initial lead compound **2**, in the benzamide series, was highly potent, but showed poor metabolic stability. Significant improvements in metabolic stability were achieved by identifying the primary metabolites of compound **2** and utilizing these data to systematically modify the proposed structural liabilities. Modification of the parent compound **2**, which included incorporation of an *N*-cyclopropyl group and a trans-disposed substituent at the 4-position on the *N*-cyclohexyl ring, resulted in dramatically improved metabolic stability, as exemplified by compound **13**. In vitro microsomal stability data were predictive of pharmacokinetics and were used as a tool to select compounds for in vivo experiments. Pyridyl compound **13** possessed a desirable pharmacokinetic profile in three different species (rat, cynomolgus monkey, and dog) and was demonstrated to be orally efficacious in lowering adipose 11β-HSD1 activity in a monkey ex vivo model. Finally, X-ray cocrystallographic data of compound **13** with 11β-HSD1 revealed key interactions important for inhibitor binding.

Experimental Section

Unless otherwise noted, all materials were obtained from commercial suppliers and used without purification. Dry organic solvents (DriSolv) were purchased from EMD Chemicals and packaged under nitrogen in Sure Seal bottles. Reactions were monitered using thin-layer chromatography on 250 μm plates or using Agilent 1100 series LCMS with UV detection at 254 nm and a low resonance electrospray mode (ESI). Purification of title compounds was accomplished by flash column chromatography using silica gel 60 (particle size 0.04−0.063 mm, 230−400 mesh) or medium pressure liquid chromatography on a CombiFlash Companion (Teledyne Isco) with RediSep normal phase silica gel. ^{1}H NMR spectra were recorded on a Bruker spectrometer (400 or 500 MHz) at ambient temperature, with the exception of compounds **2**, **7**, and **8**, which were recorded at 120 °C. Compounds **2**, **7**, and **8** exist as a mixture of amide rotamers, which results in broad peaks at ambient temperature. Chemical shifts are reported in ppm relative to $CDCl_3$ or DMSO and coupling constants (*J*) are reported in hertz (Hz).

2-(*S*)-2-Methyl-1-(4-(2,2,2-trifluoro-1-hydroxy-1-methylethyl)phenylsulfonyl)piperidine (1). To a solution of 2-(*S*)-2-methylpiperidine[17] (1.69 g, 17.1 mmol) and triethylamine (10 mL, 71.9 mmol) in CH_2Cl_2 (35 mL) was added 4-acetylbenzenesulfonyl chloride (4.0 g, 18.3 mmol). After being stirred for 14 h, the reaction mixture was diluted with saturated aqueous $NaHCO_3$, extracted with CH_2Cl_2 (×2), dried with Na_2SO_4, and concentrated under reduced pressure. Purification of the crude material by flash column chromatography (SiO_2, 1% MeOH/CH_2Cl_2) gave the product (3.27 g, 68%) as a white solid.

The 4-acetylbenzenesulfonamide prepared above (1.60 g, 5.69 mmol) was dissolved in THF (30 mL) followed by the addition of $TMSCF_3$ (22.7 mL, 0.5 M solution in THF). After 30 min, tetrabutylammonium fluoride hydrate (6.3 mL, 1 M in THF) was added. After being stirred for 3 h, the reaction mixture was diluted with saturated aqueous $NaHCO_3$, extracted with EtOAc (×2), dried with $MgSO_4$, and concentrated under reduced pressure. Purification of this material by flash column chromatography (SiO_2, 0.5% MeOH/CH_2Cl_2) gave the product (902 mg, 45%) as a viscous yellow oil: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.80 (d, J = 9.0 Hz, 2 H), 7.79 (d, J = 9.0 Hz, 2 H), 6.85 (s, 1 H), 4.10 (m, 1 H), 3.59

(m, 1 H), 2.96 (ddd, J = 13.2, 13.2, 2.6 Hz, 1 H), 1.71 (s, 3 H), 1.45 (m, 5 H), 1.20 (m, 1 H), 0.99 (d, J = 6.9 Hz, 3 H). Anal. Calcd for $C_{15}H_{20}F_3NO_3S$: C, 51.27; H, 5.74; N, 3.99. Found: C, 51.37; H, 5.75; N, 4.05.

(*S*)-*N*-Cyclohexyl-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)-*N*-ethylbenzamide (2). To a solution of cyclohexanone **3** (R^1 = H) (200 mg, 2.04 mmol) in dichloroethane (6 mL) was added ethylamine hydrochloride (249 mg, 3.06 mmol), AcOH (114 μL, 2.04 mmol), and $NaBH(OAc)_3$ (648 mg, 3.06 mmol). After being stirred for 12 h, the reaction mixture was quenched with 2 N NaOH and extracted with CH_2Cl_2 (×1). The combined organic layers were washed with brine (×1), dried with $MgSO_4$, and concentrated in vacuo to afford the crude amine, which was used without purification in the following reaction.

To a mixture of crude *N*-cyclopropylcyclohexylamine (60 mg, 0.47 mmol), (*S*)-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzoic acid **17** (121 mg, 0.52 mmol), HOAt (95 mg, 0.70 mmol), EDCI (134 mg, 0.70 mmol), and $NaHCO_3$ (78 mg, 0.94 mmol) was added DMF (1.5 mL). After the mixture was stirred for 12 h, the reaction was quenched with water and the mixture was diluted with EtOAc. The aqueous layer was extracted with EtOAc (×1), and the combined organic layers were washed with water (×3) and brine (×1), dried with $MgSO_4$, and concentrated in vacuo. The crude material was purified by flash column chromatography (SiO_2, 50% EtOAc/hexanes) to afford 71 mg of **2** (44%) as a white solid: ^{1}H NMR (DMSO-d_6, 500 MHz, 120 °C) δ 7.65 (d, J = 8.1 H, 2 H), 7.34 (d, J = 8.1 Hz, 2 H), 6.24 (s, 1 H), 3.65 (m, 1 H), 3.28 (q, J = 6.8 H, 2 H), 1.75 (m, 4 H), 1.74 (s, 3 H), 1.61 (m, 3 H), 1.12 (t, J = 6.8 Hz, 3 H), 1.12 (m, 3 H). Anal. Calcd for $C_{18}H_{24}F_3NO_2$: C, 62.96; H, 7.04; N, 4.08. Found: C, 62.59; H, 7.08; N, 4.07.

(*S*)-*N*-Cyclohexyl-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)-*N*-(2,2,2-trifluoroethyl)benzamide (7). To a solution of cyclohexylamine **5** (324 mg, 3.27 mmol), pyridine (400 μL, 4.90 mmol), and CH_2Cl_2 (15 mL) at 0 °C was added trifluoroacetic anhydride (549 μL, 3.92 mmol) dropwise. The ice bath was removed, and the reaction mixture was stirred at ambient temperature for 12 h. The reaction mixture was quenched with water and extracted with CH_2Cl_2 (×1). The combined organics were washed with brine (×1), dried with $MgSO_4$, and concentrated in vacuo to afford the crude *N*-cyclohexyl-2,2,2-trifluoroacetamide, which was used without purification in the following reaction.

To a solution of *N*-cyclohexyl-2,2,2-trifluoroacetamide in THF (2 mL) at 0 °C was slowly added BH_3·THF (8.0 mL, 1 M in THF). The ice bath was removed, and the reaction mixture was refluxed for 12 h. The reaction mixture was then cooled to 0 °C, treated with MeOH (2.5 mL), and refluxed for an additional 5 h. After cooling to room temperature, the mixture was poured into water, acidified to pH 2 with 2 N HCl, and extracted with CH_2Cl_2 (×2). The organic layers were discarded, and the aqueous layer was basified with 2 M NaOH. Following extraction of the aqueous layer with CH_2Cl_2 (×2), the combined organics were washed with brine (×1), dried with $MgSO_4$, and carefully concentrated in vacuo to afford 520 mg of the volatile *N*-(2,2,2-trifluoroethyl)cyclohexylamine **6**, which was used without purification in the following reaction.

To a solution of (*S*)-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)-benzoic acid **17** (400 mg, 1.71 mmol), pyridine (279 μL, 3.42 mmol), and THF (4 mL) was added $SOCl_2$ (137 μL, 1.88 mmol). After being stirred at 80 °C for 2 h, the reaction mixture was cooled to room temperature and *N*-(2,2,2-trifluoroethyl)cyclohexylamine **6** was added. After being stirred for an additional 12 h, the reaction mixture was quenched with water. The aqueous layer was extracted with EtOAc (×1), and the combined organic layers were washed with water (×3) and brine (×1), dried with $MgSO_4$, and concentrated in vacuo. The crude material was purified by flash column chromatography (SiO_2, 20−33% EtOAc/hexanes, gradient elution) to afford 200 mg of **7** (29%) as a white solid: ^{1}H NMR (DMSO-d_6, 400 MHz, 120 °C) δ 7.65 (d, 8.1 Hz, 2 H), 7.40 (dt, J = 8.5, 1.9 Hz, 2 H), 6.27 (s, 1 H), 4.21 (q, J = 9.4 Hz, 2 H), 3.60 (tt, J = 11.9, 3.3 Hz, 1 H), 1.74 (m, 4 H), 1.74 (s, 3 H), 1.58 (m, 3 H), 1.06 (m, 3 H). Anal. Calcd for $C_{18}H_{21}F_6NO_2$: C, 54.41; H, 5.33; N, 3.52. Found: C, 54.56; H, 5.37; N, 3.48.

(*S*)-*N*-Cyclohexyl-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)-*N*-cyclopropylmethylbenzamide (8). Compound **8** was prepared in 41% yield (two steps) according to the procedure used for **2**, substituting cyclopropylmethylamine for ethylamine hydrochloride. ^{1}H NMR (DMSO-d_6, 500 MHz, 120 °C) δ 7.65 (d, J = 8.1 Hz, 2 H), 7.34 (d, J = 8.1 Hz, 2 H), 6.24 (s, 1 H), 3.65 (m, 1 H), 3.21 (m, 2 H), 1.74 (s, 3 H), 1.72 (m, 6 H), 1.58 (m, 1 H), 1.13 (m, 3 H), 1.01 (m, 1 H), 0.47 (m, 2 H), 0.17 (m, 2 H). Anal. Calcd for $C_{20}H_{26}F_3NO_2$: C, 65.02; H, 7.09; N, 3.79. Found: C, 64.58; H, 7.16; N, 3.74.

(*S*)-*N*-Cyclohexyl-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)-*N*-cyclopropylbenzamide (9). Compound **9** was prepared in 45% yield (two steps) according to the procedure used for **2**, substituting cyclopropylamine for ethylamine hydrochloride. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.58 (d, J = 9.0 Hz, 2 H), 7.47 (d, J = 9.0 Hz, 2 H), 4.09 (m, 1 H), 2.83 (s, 1 H), 2.56 (m, 1 H), 1.96 (m, 1 H), 1.85 (m, 4 H), 1.85 (s, 3 H), 1.71 (m, 2 H), 1.39 (m, 2 H), 1.18 (m, 1 H), 0.56 (m, 2 H), 0.45 (m, 2 H). Anal. ($C_{19}H_{24}F_3NO_2$) C, H, N.

(*S*)-*N*-(*trans*-4-Phenyl)cyclohexyl-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)-*N*-cyclopropylbenzamide (10) and (*S*)-*N*-(*cis*-4-Phenyl)cyclohexyl-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)-*N*-cyclopropylbenzamide (11). A solution of 4-phenylcyclohexanone **3** (R^1 = Ph) (500 mg, 2.87 mmol) in 1,2-dichloroethane (16 mL) was treated at 0 °C with cyclopropylamine (298 μL, 4.31 mmol), acetic acid (329 μL, 5.74 mmol), and $NaBH(OAc)_3$ (1.22 g, 5.74 mmol). After being stirred at 25 °C for 12 h, the reaction mixture was diluted (EtOAc) and washed with 1 M NaOH (×1) and brine (×1). The organics were dried with Na_2SO_4 and concentrated in vacuo to provide 610 mg of the product as a colorless oil (2.83 mmol, 99%). The product was used in the next step without further purification.

A solution of *N*-cyclopropyl-4-phenylcyclohexylamine (81 mg, 0.38 mmol) and (*S*)-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzoic acid **17** (80 mg, 0.34 mmol) in DMF (1.7 mL) was treated at 0 °C with EDCI (85 mg, 0.44 mmol), HOAt (60 mg, 0.44 mmol), and $NaHCO_3$ (57 mg, 0.68 mmol). After being stirred at 25 °C for 12 h, the reaction mixture was diluted (EtOAc), washed 10% aqueous citric acid (×1), saturated aqueous $NaHCO_3$ (×1), and brine (×1). The organics were dried with Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (SiO_2, 20% EtOAc/hexanes) gave 37 mg of the trans product **10** as a white solid (25%): ^{1}H NMR ($CDCl_3$, 500 MHz, trans isomer) δ 7.59 (d, J = 8.1 Hz, 2 H), 7.49 (d, J = 8.0 Hz, 2 H), 7.25 (m, 5 H), 4.23 (m, 1 H), 2.70 (m, 3 H), 2.04 (m, 6 H), 1.79 (s, 3 H), 1.64 (m, 2 H), 0.59 (m, 2 H), 0.51 (m, 2 H). Anal. Calcd for $C_{25}H_{28}F_3NO_2$: C, 69.59; H, 6.54; N, 3.25. Found: C, 69.57; H, 6.63; N, 3.26.

Further elution using more polar solvent (SiO_2, 25% EtOAc/hexanes) afforded 39 mg of the cis isomer **11** as a white solid (27%): ^{1}H NMR ($CDCl_3$ 500 MHz) 7.57 (d, J = 8.5 Hz, 2 H), 7.46 (d, J = 8.1 Hz, 2 H), 7.41 (m, 2 H), 7.34 (m, 2 H), 7.21 (m, 1 H), 4.33 (m, 1 H), 3.11 (m, 1 H), 2.76 (m, 1 H), 2.50 (m, 1 H), 2.30 (m, 1 H), 2.08 (m, 2 H) 1.95 (m, 2 H), 1.80 (m, 2 H), 1.78 (s, 3 H), 0.45 (m, 2 H), 0.35 (m, 2 H). Anal. Calcd for $C_{25}H_{28}F_3NO_2$: C, 69.59; H, 6.54; N, 3.25. Found: C, 69.38; H, 6.64; N, 3.24.

(*S*)-*N*-[*trans*-4-(4-Cyanophenyl)cyclohexyl]-4-[1,1,1-trifluoro-2-hydroxypropan-2-yl]-*N*-cyclopropylbenzamide (12). A solution of crude 4-(4-cyanophenyl)cyclohexanone **3** (R^1 = 4-CNPh) (7.3 g, 36.6 mmol) in 1,2-dichloroethane (170 mL) was treated at 0 °C with cyclopropylamine (3.80 mL, 54.7 mmol), acetic acid (4.19 mL, 73.2 mmol), and $NaBH(OAc)_3$ (15.5 g, 73.2 mmol). After being stirred at 25 °C for 12 h, the reaction mixture was diluted (EtOAc), washed with 1 M NaOH (×1) and brine (×1), dried with Na_2SO_4, and concentrated in vacuo. Flash chromatography (SiO_2, 20−30% EtOAc/hexanes containing 2.5% of TEA, gradient elution) gave the cis amine (13.8 mmol, 37%). Further elution using more polar solvent (30−50% EtOAc/hexanes containing 2.5% of TEA, gradient elution) afforded 2.20 g (25%) of the trans amine as a pale-yellow solid.

A solution of *trans*-*N*-cyclopropyl-4-(4-cyano)phenylcyclohexylamine (6.30 g, 26.2 mmol) and (*S*)-4-(1,1,1-trifluoro-2-hydrox-

ypropan-2-yl)benzoic acid **17** (6.14 g, 26.2 mmol) in DMF (66 mL) was treated at 0 °C with EDCI (6.53 g, 34.1 mmol), HOAt (4.64 g, 34.1 mmol), and $NaHCO_3$ (4.40 g, 52.4 mmol). After being stirred at 25 °C for 12 h, the reaction mixture was diluted (EtOAc), washed with 1 N HCl (×2), 1 N NaOH (×2), and brine (×1), dried with Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by recrystallization (3 × 50% EtOAc/hexanes) afforded 6.70 g of the product **12** as a white solid (56%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.59 (d, J = 8.1 Hz, 2 H), 7.59 (d, J = 8.1 Hz, 2 H), 7.49 (d, J = 8.2 Hz, 2 H), 7.32 (d, J = 8.1 Hz, 2 H), 4.25−4.15 (m, 1 H), 2.75−2.57 (m, 3 H), 1.96 (m, 6 H), 1.80 (s, 3 H), 1.64 (m, 2 H), 0.59 (m, 2 H), 0.51 (m, 2 H). Anal. ($C_{26}H_{27}F_3NO_2$) C, H, N.

(*S*)-*N*-(*trans*-4-(Pyridin-3-yl))cyclohexyl-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)-*N*-cyclopropylbenzamide (13). Compound **13** was prepared according to the procedure used for **12**, substituting 4-(pyridin-3-yl)cyclohexanone **3** (R^1 = 3-pyridyl) for 4-(4-cyanophenyl)cyclohexanone. The crude mixture of cis and trans amines was purified by flash column chromatography (SiO_2, 40−70% EtOAc/hexanes containing 2.5% TEA to 10% MeOH/CH_2Cl_2 containing 2.5% TEA, gradient elution) to provide *trans*-*N*-cyclopropyl-4-(pyridine-3-yl)cyclohexylamine in 31% yield. After the amide coupling reaction, compound **13** was purified by flash column chromatography (SiO_2, 3−10% MeOH/CH_2Cl_2, gradient elution) to afford the title compound (63%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.49 (s, 1 H), 8.46 (d, J = 3.6 Hz, 1 H), 7.61 (d, J = 8.1 Hz, 2 H), 7.58 (d, J = 7.7 Hz, 1 H), 7.50 (d, J = 8.3 Hz, 2 H), 7.24 (dd, 1 H, overlapping with $CDCl_3$), 4.23 (m, 1 H), 2.80 (m, 1 H), 2.62 (m, 2 H), 2.05 (m, 6 H), 1.80 (s, 3 H), 1.65 (m, 2 H), 0.60 (d, J = 4.8 Hz, 2 H). 0.49 (m, 2H). Anal. Calcd for $C_{24}H_{27}F_3NO_2$: C, 66.64; H, 6.29; N, 6.48. Found: C, 66.65; H, 6.26; N, 6.43.

(*S*)-*N*-(*trans*-4-(2-Cyanoethyl)cyclohexyl)-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)-*N*-cyclopropylbenzamide (14). Compound **14** was prepared according to the procedure used for **12**, substituting 4-(2-cyanoethyl)cyclohexanone **3** (R^1 = CH_2CH_2CN) for 4-(4-cyanophenyl)cyclohexanone. The crude mixture of cis and trans amines was purified by flash column chromatography (SiO_2, 30% EtOAc/hexanes containing 2.5% TEA) to provide *trans*-*N*-cyclopropyl-4-(2-cyanoethyl)cyclohexylamine in 16% yield. After the amide coupling reaction, the crude material was purified by flash column chromatography (SiO_2, 50−75% EtOAc/hexanes, gradient elution) to afford the title compound **14**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.59 (d, J = 8.2 Hz, 2H), 7.49 (dt, J = 8.6, 2.0 Hz, 2H), 4.13 (m, 1H), 2.58 (s, 1H), 2.57 (m, 1H), 2.40 (t, J = 7.0 Hz, 2H), 1.92 (m, 6H), 1.80 (s, 3H), 1.61 (q, J = 7.0 Hz, 2H), 1.49 (m, 1H), 1.14 (m, 2H), 0.56 (m, 2H), 0.45 (m, 2H). Anal. Calcd for $C_{22}H_{27}F_3NO_2$: C, 64.69; H, 6.66; N, 6.86. Found: C, 64.72; H, 6.69; N, 6.76.

(*S*)-*N*-(*trans*-4-Fluorocyclohexyl)-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)-*N*-cyclopropylbenzamide (15). A solution of *trans*-4-hydroxycyclohexyl benzoate **18** (5.26 g, 23.9 mmol) in CH_2Cl_2 (120 mL) at −78 °C was treated with a solution of DAST (2.0 mL, 15.4 mmol) in CH_2Cl_2 (120 mL). After being stirred at −78 °C for 10 min, 0 °C for 1 h, and 25 °C for 2 h, the reaction mixture was diluted with CH_2Cl_2, washed with brine (×1), dried with Na_2SO_4, and concentrated in vacuo. The crude material was purified by flash column chromatography (SiO_2, 5% MTBE/hexanes) to afford 1.01 g of the product as a white solid.

To a solution of *cis*-4-fluorocyclohexyl benzoate (300 mg, 1.35 mmol) in 1:1 THF/MeOH (5.4 mL) was added LiOH (1.4 mL, 1.2 M in H_2O). After being stirred for 5 h, the reaction mixture was diluted with water, extracted with 10% MeOH/CH_2Cl_2 (×5), dried with Na_2SO_4, and concentrated in vacuo to provide 150 mg of the alcohol as a yellow solid. This material was used in the subsequent step without further purification.

To a mixture of PCC (437 mg, 2.03 mmol) and 4 Å molecular sieves in CH_2Cl_2 (10 mL) was added a solution of 4-fluorocyclohexanol (150 mg, 1.26 mmol). After being stirred for 1 h, the reaction mixture was diluted with ether, filtered through silica gel, and concentrated under reduced pressure to provide 103 mg of 4-fluorocyclohexanone **19** as a yellow oil.

4-Fluorocyclohexanone **19** was converted to compound **15** following the amide coupling procedure described for compound **10**. After the amide coupling reaction, the crude material was purified by flash chromatography (SiO_2, 20−35% EtOAc/hexanes, gradient elution) to afford the title compound in 10% yield (three steps), along with 14% of the cis isomer. Data for the trans isomer: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.57 (d, J = 8.2 Hz, 2 H), 7.45 (d, J = 8.2 Hz, 2 H), 4.52 (m, 1 H), 4.09 (m, 1 H), 2.76 (m, 1 H), 2.56 (m, 1 H), 2.21 (m, 2 H), 1.95 (m, 4 H), 1.79 (s, 3 H), 1.64 (m, 2 H), 0.55 (m, 2 H), 0.43 (m, 2 H). Anal. Calcd for $C_{19}H_{23}F_4NO_2$: C, 61.12; H, 6.21; N, 3.75. Found: C, 61.37; H, 6.31; N, 3.68.

(*S*)-4-(1,1,1-Trifluoro-2-hydroxypropan-2-yl)benzoic Acid (17). To a solution of 4-acetylbenzonitrile **16** (1,293 g, 8.907 mol) in THF (6297 mL) at 20 °C was added TBAF (1.0 M in THF, 160.9 g). $TMSCF_3$ (1712 mL, 11.58 mol) was charged dropwise over 4 h. HCl (5 N, 9440 mL) was then added to the reaction mixture over 1 h. After the mixture was stirred for an additional 4.5 h, the phases were separated, the lower aqueous phase was extracted with EtOAc (×2), and the combined organic phases were concentrated to dryness in vacuo. The yellow-brown solid was triturated with heptane/ethyl acetate (4:1, 6465 mL), filtered, and washed with heptane/ethyl acetate (4:1, 647 mL). The filtrate was then concentrated to dryness in vacuo, then slurried in heptane/ethyl acetate (4:1, 1131 mL) at 20 °C for 30−60 min. The second crop was filtered, washed with heptane/ethyl acetate (4:1, 200 mL), and combined with the first crop. The combined solids were triturated with toluene (3200 mL) at 20 °C for 30−60 min, then filtered, washed with toluene (200 mL), and dried overnight (45 °C/27 in. Hg) to afford 1574.8 g (82% yield) the trifluoromethyl alcohol.

The product (597.5 g, 2.777 mmol) was dissolved in methanol (600 mL) at 50 °C. Aqueous sodium hydroxide (2790 mL, 5 N) was added in one portion and heated to reflux with subsurface nitrogen purge. After being stirred for 3 h, the reaction mixture was cooled to 0 °C and charged HCl (5 N, 2790 mL) dropwise. The mixture was polish filtered (0.45 μm PTFE) and rinsed with 600 mL of methanol. Cinchonidine (654 g, 2.222 mol) was added to the filtrate, followed by addition of methanol (4380 mL). The mixture was refluxed for 1−3 h, then cooled to 20 °C and vacuum filtered. The filter cake was washed with methanol/water (1:2, 600 mL) and the product was dried overnight (40 °C/27 in. Hg) to afford 601 g of the chinconidine salt (88.9% with respect to acid, 84.6% de).

The material could be further enriched by recrystallization with cinchonidine: The crude salt (10.0 g, 18.92 mmol) was dissolved in acetonitrile/water (1:1, 385 mL) at reflux. After the mixture was cooled to 65 °C, it was seeded with the enantiomerically pure material (0.100 g, 0.1892 mmol), held at 65 °C for 1 h, then cooled to 0 °C at 20 °C/min and held for 1 h. The mixture was filtered, washed with acetonitrile/water (1:2, 20 mL), and dried overnight (40 °C/27 in. Hg) to afford 5.458 g pure (*S*)-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzoic acid **17** (24.2% with respect to acid, 99% de). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 13.00 (br s, 1H), 7.96 (d, J = 8.6 Hz, 2H), 7.71 (d, J = 8.6 Hz, 2H), 6.75 (s, 1H), 1.70 (s, 3H). Anal. ($C_{10}H_9F_3O_3$) C, H.

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Supporting Information Available: Elemental analysis data and experimental details for the biological assays and cocrystallization. This material is available free of charge via the Internet at http://pubs.acs.org.

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