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Synthesis and optimization of novel 4,4-disubstituted cyclohexylbenzamide derivatives as potent 11β-HSD1 inhibitors

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ABSTRACT

The synthesis and SAR of a series of 4,4-disubstituted cyclohexylbenzamide inhibitors of 11β-HSD1 are described. Optimization rapidly led to potent, highly selective, and orally bioavailable inhibitors demonstrating efficacy in both rat and non-human primate ex vivo pharmacodynamic models.

11β-Hydroxysteroid dehydrogenase type 1 (11β-HSD1) is a key enzyme that acts as an NADPH-dependent reductase capable of converting inactive glucocorticoids such as cortisone into their active form (e.g., cortisol) in specific tissues, such as liver, adipose, and brain.[1–4] Conversely, 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), a structurally related isoenzyme of 11β-HSD1, catalyzes the conversion of cortisol to cortisone using $NADP^+$ as a cofactor. 11β-HSD2 is expressed in cells that contain the mineralocorticoid receptor (MR) and protects the MR by converting cortisol to cortisone.[5] Selective inhibition of 11β-HSD1 may be a viable therapeutic strategy for the treatment of metabolic syndrome and has attracted significant attention from the pharmaceutical research community.[6–29]

We previously described the design and optimization of substituted cyclohexylbenzamide 11β-HSD1 inhibitors.[30–32] During the course of that research, we noted that 4,4-disubstituted cyclohexylbenzamides, such as compound **1** (Fig. 1), exhibited significantly less potential for PXR transactivation relative to the corresponding 4-monosubstituted analogs. In addition, **1** showed excellent cross-species pharmacokinetics and in vivo inhibition of 11β-HSD1 in a rat ex vivo pharmacodynamic model. However, the potency of **1** made it unsuitable for further development in its present form. We felt that additional modifications of **1** at the 4-position of the cyclohexane ring would offer an opportunity to increase its potency while maintaining other properties (such as pharmacokinetics) which would provide a compound more suitable for development.

Compounds were synthesized via the routes outlined in Schemes 1–5.[33] 4,4-Disubstituted cyclohexyl benzamides **2**, **9**, **14**, **15**, and **16**, were prepared in a straightforward manner (Scheme 1). 4-Aryl/heteroaryl, 4-cyanocyclohexanones **19** were obtained by a

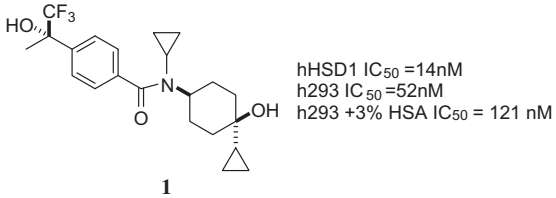

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Figure 1. An early 4,4-disubstituted cyclohexylbenzamide 11β-HSD1 inhibitor (**1**).

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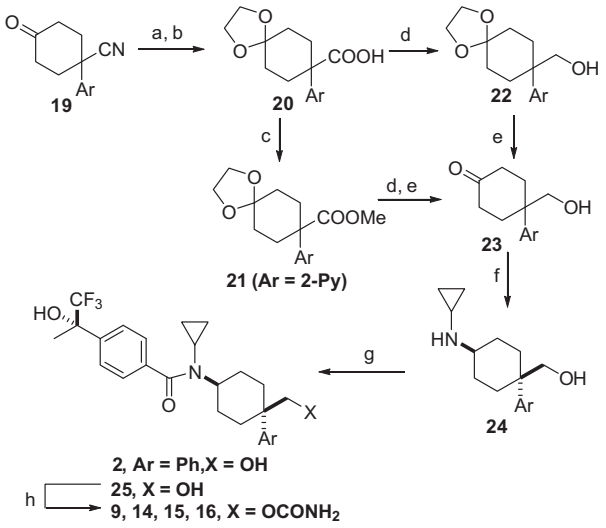
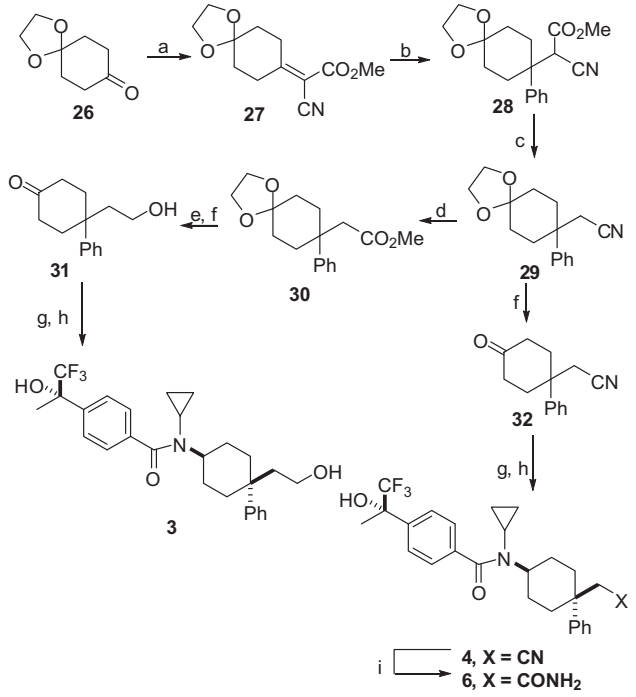
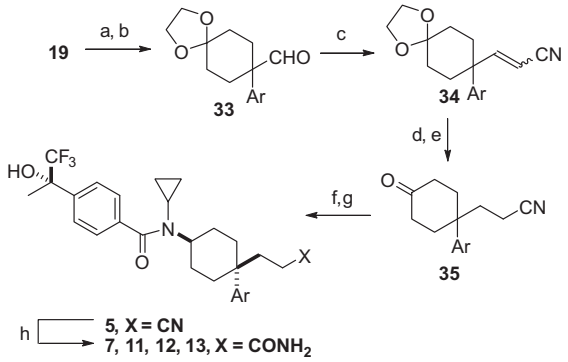


Scheme 1. Reagents and conditions: (a) ethylene glycol, *p*-toluenesulfonic acid, benzene, reflux, 45–92%; (b) ethylene glycol, KOH, 170 °C, 54–88%; (c) K_2CO_3, MeI, THF, 52–74%; (d) $LiAlH_4$, THF, reflux, 54–92%; (e) 3 N HCl, THF, 60–95%; (f) cyclopropylamine, $NaBH(OAc)_3$, acetic acid, dichloroethane, 8–24%; (g) EDC, HOAt, (*S*)-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzoic acid, DMF, 48–57%; (h) trichloroacetyl isocyanate, neutral Al_2O_3, $CHCl_3$, 84–95%.

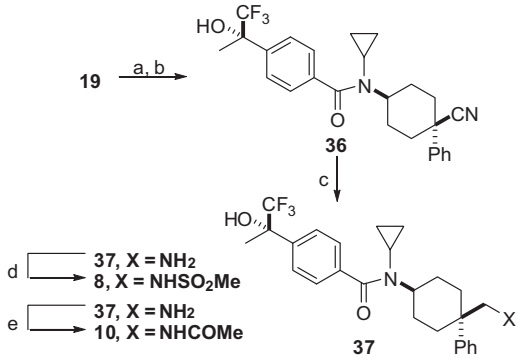


Scheme 2. Reagents and conditions: (a) ethyl cyanoacetate, acetic acid, NH_4OAc, toluene, reflux, 70%; (b) 2-bromobenzene, *n*-BuLi, CuI, *n*-Bu_2S, Et_2O, 49%; (c) DMSO, NaCl, H_2O, 80%; (d) (i) ethylene glycol, KOH, 170 °C, 54–92%; (ii) K_2CO_3, MeI, THF, 52–74%; (e) $LiAlH_4$, THF, 65–84%; (f) 3 N HCl, THF, 60–75%; (g) cyclopropylamine, $NaBH(OAc)_3$, acetic acid, dichloroethane, 21–35%; (h) EDC, HOAt, (*S*)-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzoic acid, DMF, 58–62%; (i) KOH, *t*-BuOH, 90 °C, 81%.

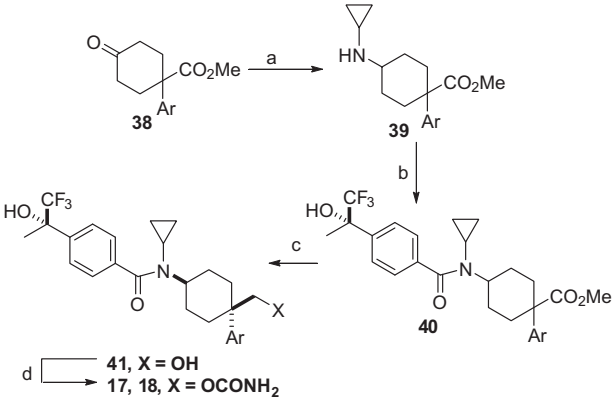
tandem one-pot double Michael addition–Dieckman condensation between methyl acrylate and the appropriate benzylic nitrile, followed by Krapcho decarboxylation.[34] Protection of **19** as its monoethylene ketal was followed by hydrolysis of the nitrile to produce acid **20**. Reduction of **20** with $LiAlH_4$ followed by removal of the ketal protecting group gave disubstituted cyclohexanones **23**.



Scheme 3. Reagents and conditions: (a) ethylene glycol, *p*-toluenesulfonic acid, benzene, reflux, 45–92%; (b) $LiAlH_4$ (0.5 equiv), THF, 80–98%; (c) NaH, diethyl (cyanomethyl) phosphonate, THF, 63–80%; (d) H_2, 10% Pd/C, EtOAc, 89–99%; (e) 3 N HCl, THF, 63–76%; (f) cyclopropylamine, $NaBH(OAc)_3$, acetic acid, dichloroethane, 33%; (g) EDC, HOAt, (*S*)-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzoic acid, DMF, 52%; (h) KOH, *t*-BuOH, 90 °C, 77%.



Scheme 4. Reagents and conditions: (a) cyclopropylamine, $NaBH(OAc)_3$, acetic acid, dichloroethane, 75–78%; (b) EDC, HOAt, (*S*)-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzoic acid, DMF, 49–57%; (c) H_2, Raney Ni, 28% NH_4OH, MeOH, 98%; (d) MsCl, Et_3N, 75%; (e) Hunig's base, acetyl chloride, DMF, 79%.



Scheme 5. Reagents and conditions: (a) cyclopropylamine, $NaBH(OAc)_3$, acetic acid, dichloroethane, 94%; (b) EDC, HOAt, (*S*)-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzoic acid, DMF, 74%; (c) $LiAlH_4$, THF, 21–31%; (d) trichloroacetyl isocyanate, neutral Al_2O_3, $CHCl_3$, 54%.

In a similar fashion, 2-pyridyl cyclohexanone **23** was prepared by conversion of **20** into ester **21** followed by reduction and deprotection. Reductive amination of **23** with cyclopropylamine resulted in a mixture of *cis*/*trans* cyclopropylamine products, and the desired