Bioorganic & Medicinal Chemistry Letters 19 (2009) 1446–1450

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Optimization of novel di-substituted cyclohexylbenzamide derivatives as potent 11β-HSD1 inhibitors ☆

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ARTICLE INFO

Article history:
Received 11 November 2008
Revised 7 January 2009
Accepted 12 January 2009
Available online 15 January 2009

Keywords:
11β-HSD1
Diabetes
Metabolic syndrome
Hydroxysteroid dehydrogenase
Cardiovascular disease
Cyclohexylbenzamides

ABSTRACT

Novel 4,4-disubstituted cyclohexylbenzamide inhibitors of 11β-HSD1 were optimized to account for liabilities relating to in vitro pharmacokinetics, cytotoxicity and protein-related shifts in potency. A representative compound showing favorable in vivo pharmacokinetics was found to be an efficacious inhibitor of 11β-HSD1 in a rat pharmacodynamic model (ED_{50} = 10 mg/kg).

In humans, 11β-HSD1 catalyzes the reduction of the inactive glucocorticoid cortisone to its active form, cortisol.[2] Glucocorticoid balance is checked by the hypothalamic-pituitary-adrenal (HPA) axis[3] and reversion of cortisol to cortisone by isozyme 11β-HSD2.[4] Upon binding to the glucocorticoid receptor, cortisol positively regulates glucose production. Excessive hepatic glucose production and the functional antagonism of glucocorticoids towards insulin action contribute to the diabetic state. Therefore, augmented regulation of cortisol levels via inhibition of 11β-HSD1 may be a potential therapy for treatment of diabetes.[5] Inhibitors of 11β-HSD1 may also serve as treatment for 'metabolic syndrome.' Unregulated overexpression of cortisol is manifested in Cushing's disease. Symptoms associated with this disease are typical metabolic syndrome indicators (visceral obesity, reduced insulin sensitivity, dyslipidemia, and high blood pressure)[6] and are reversible upon surgical correction of glucocorticoid over-production.[7]

In addition to Cushing's disease, genetic evidence for the role of 11β-HSD1 in diabetes and obesity has been illustrated in separate experiments involving fat-specific 11β-HSD1 overexpression[8] and liver-specific 11β-HSD1 knock-out mice models.[9] Animals in the former experiment displayed increased levels of gluconeogenesis, visceral obesity, and triglyceride production coupled with impaired insulin sensitivity. In contrast, 11β-HSD1 knock-out mice showed improved glucose tolerance and insulin sensitivity. Moreover, studies utilizing fat-specific overexpression of 11β-HSD2 in mice demonstrate that such animals are resistant to diet-induced obesity. Interestingly, studies in monozygotic twins where one of the twins is obese suggest that relative overexpression of 11β-HSD1 in fat tissues of the obese twin may present as an acquired defect of endocrinology as opposed to a genetic dysfunction.[10] Inhibition of 11β-HSD1 may also retard the development of atherosclerosis.[11] Given their potential for treatment of metabolic syndrome, diabetes, and cardiovascular disease, inhibitors of 11β-HSD1 are of active interest to the pharmaceutical industry.[12]

We have previously disclosed optimization of potency and metabolic stability for a series of *trans*-4-substituted cyclohexylbenzamide-based 11β-HSD1 inhibitors (Table 1).[13] Some members of this series, such as compound **1**, showed moderate PXR activation in vitro.[14] This liability proved manageable by increasing polarity within the otherwise hydrophobic *trans*-4-substituent (compounds **2**, **4**, and **6**).[13a] Although **2**, **4**, and **6** elicited minimal PXR activation, it was recently discovered that these compounds exhibited appreciable cytotoxicity in vitro.[15] In contrast, *cis*-isomers of

☆ See Ref. 1.

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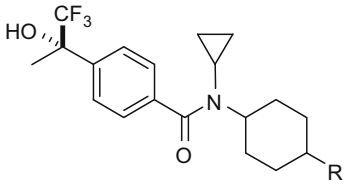
doi:10.1016/j.bmcl.2009.01.026

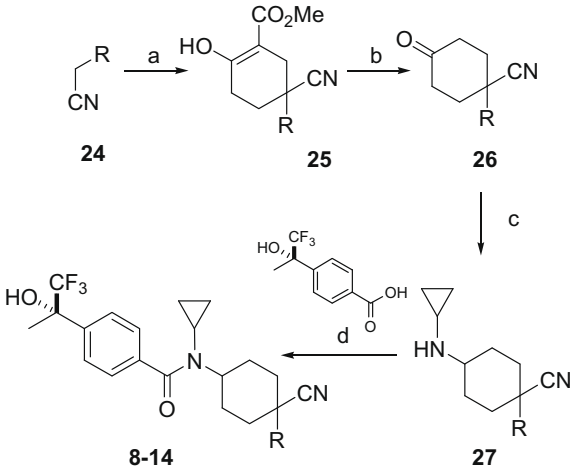
Table 1
4-Substituted cyclohexylbenzamides 11β-HSD1 inhibitors[19]



Compound	R	hHSD1 IC_{50} (nM)	% TO at 30 min HLM	PXR, % activ. at 2 μM	HeLa Cytotox IC_{50} (μM)
1	Phenyl (*trans*)	1.3	<5	31	>10
2	3-Pyridyl (*trans*)	1.7	<5	2.2	2.5
3	3-Pyridyl (*cis*)	1.6	94	38	>10
4	2-Pyridyl (*trans*)	1.6	<5	11	2.3
5	2-Pyridyl (*cis*)	1.6	87	66	>10
6	4-Cyanophenyl (*trans*)	0.76	<5	11	1.1
7	4-Cyanophenyl (*cis*)	4.9	33	75	>10

these compounds (**3**, **5**, and **7**) exhibited reduced in vitro cytotoxicity (IC_{50} > 10 μM). The mechanism leading to cytotoxicity for *trans*-substituted compounds is not fully understood. Unfortunately, the improved cytotoxicity profile for **3**, **5**, and **7** accompanied increases in the percent turnover in human liver microsomes (HLM) and re-introduction of PXR activation. We hypothesized that appropriately configured 4,4-disubstitution on the cyclohexylbenzamide ring would provide metabolically stable, non-cytotoxic 11β-HSD1 inhibitors. As *cis*-4-monosubstituted cyclohexylbenzamides had thus far enabled PXR activation, we investigated revealing the additional *cis*-substitution as size-minimized polar functionality represented by simple nitrile or hydroxyl substituents.

4-Aryl/heteroaryl, 4-nitrile substituted cyclohexylbenzamides were synthesized in straightforward fashion (Scheme 1). Using a tandem one-pot double Michael addition-Dieckmann condensation between methyl acrylate and aryl/heteroarylacetonitriles,[16] β-keto esters **25** were efficiently obtained. Krapcho decarboxylation[17] of **25** to the 4,4-disubstituted cyclohexanones **26** was followed by reductive amination with cyclopropylamine. Separation of stereoisomers by silica gel chromatography was performed following either this or the final step. Amide coupling to (*S*)-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzoic acid[13] provided compounds **8–14** (Table 2).



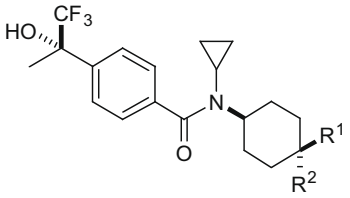
Scheme 1. Reagents and conditions: (a) methyl acrylate, KOtBu, THF, 63–87% (b) DMSO, NaCl, H_2O, 160 °C, 71-quant% (c) cyclopropylamine, $NaBH(OAc)_3$, DCE, AcOH, 35–98%; (d) EDC, HOAT, $NaHCO_3$, (*S*)-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzoic acid, DMF, 55 °C, 46–98% (syn/anti = 2/1–2.5/1).

Synthesis of 4-cyclopropyl, 4-nitrile cyclohexylbenzamide **15** proceeded through monoethyleneketal protected 4-cyclopropyl, 4-cyano-cyclohexanone (**30**, Scheme 2). Preparation of intermediate **30** relied upon nucleophilic trapping of the 1-cyclopropylcyclohexyl trifluoromethanesulfonate intermediate formed from treatment of the homoallylic alcohol **29** with triflic anhydride in the presence of hindered base.[18] Deprotection of the cyclohexanone was followed by reductive amination to afford the purified stereoisomer **31**. Amide coupling was performed as before to produce **15**.

4-Hydroxy substituted compounds were obtained by reaction of the appropriate carbon nucleophile with monoethylene ketal protected cyclohexadione to provide after deprotection 4,4-disubstituted cyclohexanones **33** (Scheme 3). Completion of the syntheses followed that of the nitriles with separation of stereoisomers after the final amide coupling.

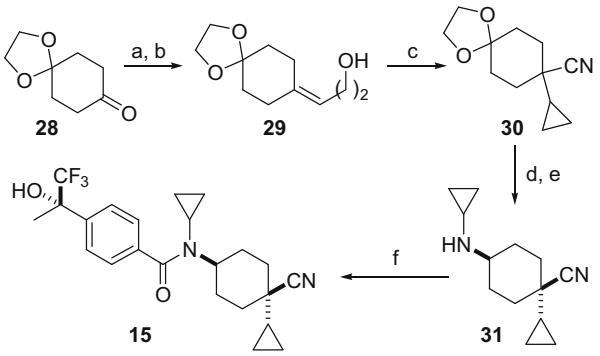
Geminal substituted cyclohexylbenzamide derivatives were evaluated for inhibition of 11β-HSD1 in biochemical assays and were assessed for relative protein-related potency shifts in cellular assays with and without 3% human serum albumin (Table 2).[19] PXR transactivation potential, HeLa cytotoxicity, and in vitro metabolic stability were evaluated. Regardless of *cis*/*trans* orientation, compounds **8–23** showed minimal PXR activation relative to their monosubstituted cognates. Moreover, with the exception of compounds **16** and **22**, HeLa IC_{50}s for most disubstituted compounds were improved to >10 μM. Interestingly, *trans*-4-hydroxy/nitrile, 4-aryl/pyridylcyclohexylbenzamides exhibited compromised metabolic stability in rat microsomal homogenates (RLM) relative to their direct (*cis*) analogues (**12**, **14**, **17**, vs **11**, **13**, **16,** respectively). Inhibition of 11β-HSD1 was also affected by *cis*/*trans* orientation with *cis*-stereoisomers, being more potent in the biochemical assay. Compounds with relatively polar 4-aryl/heteroaryl groups (**9, 10, 11, 18, 19**) appeared to be less potent in the biochemical assay. Methyl carbinol **20**, reflective of diminished hydrophobic surface area at the 4-position, also exhibited lower biochemical potency. These observations indicated that favorable interactions with the enzyme are dictated by a balance of polarity/hydrophobicity in features pendant from the 4-position. Within the nitrile sub-series, cyclohexylbenzamides with less polar 4-substituents showed considerable potency shifts in the cellular assay (**8**, **13**, **15**). The 4-cyclopropyl, 4-nitrile compound **15** showed a minimal protein-related shift in cellular potency and thus constituted the optimal nitrile containing compound. Of the more potent members of the hydroxyl sub-series, potencies for the phenyl and methylcyclopropyl analogs (**16**, **22**) were more protein shifted [ca ≥ 6×] than the smaller isopropyl (**21** [ca 3×]) and cyclopropyl (**23** [ca 2×]) compounds. Although quite potent in cellular assays, **21** showed com-

Table 2
4,4-Disubstituted cyclohexylbenzamide 11β-HSD1 inhibitors[19]

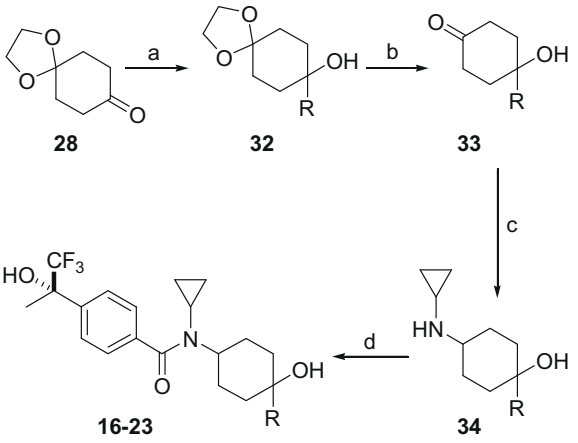


Compound	R^1	R^2	hHSD1 IC_{50} (nM)	h293 hHSD1 IC_{50} (nM)	h293 hHSD1 + 3% HSA IC_{50} (nM)	% TO at 30 min HLM	% TO at 30 min RLM	PXR,% of control at 2 μM[a]	HeLa Cytotox IC_{50} (μM)
8	CN	Phenyl	1.7	62	219	< 5	6	<5	>10
9	CN	4-CN-Phenyl	43	82	>300	6.8	<5	<5	>10
10	CN	3-Pyridyl	64	190	>300	<5	35	<5	>10
11	CN	2-Pyridyl	17	41	>300	<5	14	7.6	>10
12	2-Pyridyl	CN	22	39	>300	6.9	95	6.3	>10
13	CN	3-Fluoro, 6-pyridyl	3.3	48	>300	10	<10	<5	>10
14	3-Fluoro, 6-pyridyl	CN	11	96	>300	13	55	12	>10
15	CN	Cyclopropyl	1.5	36	64	<10	<10	<5	>10
16	OH	Phenyl	9	48	>300	<5	<5	<5	5.1
17	Phenyl	OH	150	>300	>300	15	>95	<5	>10
18	OH	3-Pyridyl	190	>300	>300	<5	<5	<5	>10
19	OH	2-Pyridyl	34	170	>300	<5	<5	6.1	>10
20	OH	CH_3	26	97	>300	<5	<5	<5	>10
21	OH	Isopropyl	5.8	26	69	10	69	<3.4	>10
22	OH	Methylcyclopropyl	4.2	27	154	10	43	5.9	2.8
23	OH	Cyclopropyl	14	52	121	<5	7.4	<5	>10

[a] Rifampin was used as a control.



Scheme 2. Reagents and conditions: (a) (3-benzyloxypropyl)triphenylphosphonium bromide, nBuLi, THF, 43%; (b) Na, EtOH, Et_2O, NH_3, 99%; (c) sym-collidine, Tf_2O, CH_2Cl_2, −78 °C, then Et_2AlCN, 42%; (d) TFA, H_2O, 99%; (e) cyclopropylamine, $NaBH(OAc)_3$, DCE, AcOH, 64% (syn/anti = 2.2/1); (f) EDC, HOAT, $NaHCO_3$, (*S*)-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzoic acid, DMF, 55 °C, 85%.



Scheme 3. Reagents and conditions: (a) RBr, tBuLi or RMgBr, Et_2O or THF, 45–79%; (b) 2 N HCl, THF, 71–99%; (c) cyclopropylamine, $NaBH(OAc)_3$, DCE, AcOH, 89–98%; (d) EDC, HOAt, (*S*)-4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzoic acid, DMF, 15–56% (syn/anti = 1.2/1–2.3/1).

promised in vitro rat metabolic stability. Being more metabolically stable, compound **23** proved to be the optimal 4-hydroxyl cyclohexylbenzamide.

A comparison of PK amongst animals with potential to serve as pharmacodynamic models indicated superior oral exposure for hydroxyl substituted cyclohexylbenzamide **23** relative to nitrile **15** (Table 3). Moreover, the hydroxyl cyclohexylbenzamide was 2.4× less protein bound in a human protein binding assay (separation by ultracentrifugation, fraction unbound = 0.12). Compound **23** inhibited the rat 11β-HSD1 enzyme (IC_{50} = 244 nM) more effectively than the cynomolgus monkey enzyme (IC_{50} = 640 nM). It was therefore decided to forward **23** to a pharmacodynamic model in the rat and assess the effect of oral administration towards inhibition of 11β-HSD1.[20]

Compound **23** was dosed orally in Sprague–Dawley rats at 1, 3, 10, and 30 mg/kg. Two hours post dose,[21] animals were sacrificed, epididymal fat was isolated and incubated in media containing [^{3}H] cortisone. Rat 11β-HSD1 activity was then measured by detection of tritiated cortisol. A dose dependent reduction in cortisol production was observed indicating an ED_{50} of ca. 10 mg/kg for inhibition of rat 11β-HSD1 (Fig. 1). Noting the superior inhibition

Table 3
Pharmacokinetic data for 4,4-di-substituted cyclohexylbenzamides

Compound	Species	CL, iv (L/h/kg)	Vdss (L/kg)	AUC, po (μg*h/L)	% F
23	Rat[a]	0.24	2.7	8900	76
15	Rat[b]	0.19	2.2	4100	40
23	Cyno[a]	0.11	1.5	4700	43
15	Cyno[a]	0.093	1.9	1000	5

[a] Dosed iv 0.5 mg/kg, po 2.0 mg/kg.
[b] Dosed iv 0.7 mg/kg, po 2.0 mg/kg.

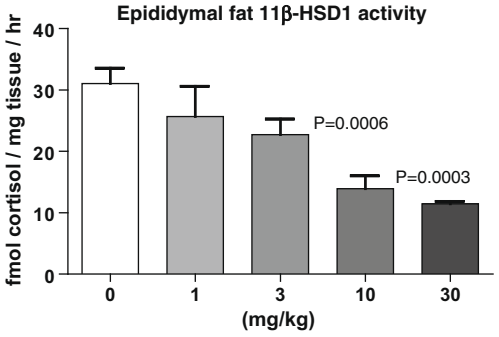


Figure. 1. Dose dependent inhibition of rat 11b-HSD1 and plasma exposure by oral administration of **23**.

by **23** of the human relative to the rat enzyme**,** the results of this experiment indicate a reasonable potential for compounds of this class to serve as effective orally bioavailable inhibitors of 11β-HSD1 in humans.

A 2.65 Å resolution X-ray co-crystal structure of **23** bound to human 11β-HSD1 containing NADP was acquired (Fig. 2).[22] Similar to previously obtained structures from this[13] and closely related compound classes,[12c] **23** binds in a V-shaped conformation in the active site of the enzyme (Fig. 2a). A H-bond from the carbonyl of the amide to Y183 disrupts the catalytic triad (Fig. 2b). Also, a potential VDW contact exists between the aminocyclopropyl group and Y177 (Fig. 2d). The cyclohexanol hydroxyl group makes a hydrogen bond to Y280 (Fig. 2c). The *trans*-isomer of **23** would likely fail to achieve this interaction with Y280 post-desolvation. Not surprisingly, the *trans*-isomer displays a compromised inhibition of the enzyme (hHSD1 IC_{50} = 90 nM).

In conclusion, 4,4-disubstituted cyclohexylbenzamide 11β-HSD1 inhibitors were optimized to eliminate in vitro cytotoxicity and PXR transactivation potential. Replacement of 4-aryl/heteroaryl features with a cyclopropyl group served to minimize protein-related shifts in potency resulting in an orally bioavailable compound capable of inhibiting 11β-HSD1 activity in animal tissues. These early developments suggest that additional effort within this sub-series is warranted. Efforts within this chemical archetype are ongoing.

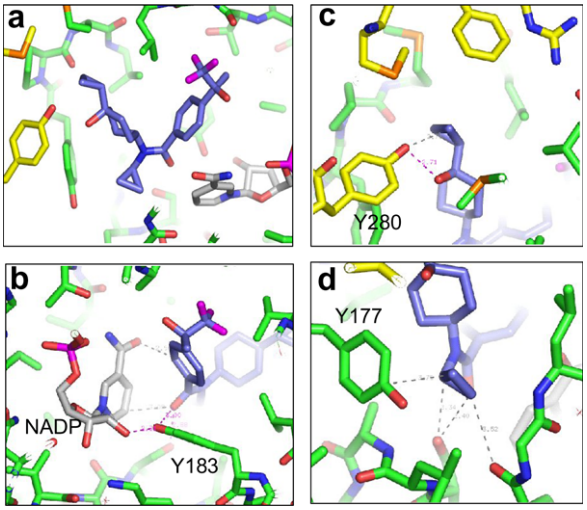


Figure. 2. Co-crystal structure of compound **23** in human 11β-HSD1. Compound carbons are color coded purple, NADP carbons are grey. Hydrogen bonds are shown as a dashed magneta line.

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19. All compounds were characterized by NMR and LCMS and found to be >95% purity. As described in reference 12c, 11β-HSD1 enzyme activity was determined by measuring the reduction of [3H]-cortisone to [3H]-cortisol.

[3H]-cortisol was captured by an anticortisol monoclonal antibody conjugated to scintillation proximity assay (SPA) beads and quantified by scintillation detection. Biochemical enzyme assays were performed with baculovirus-produced recombinant full-length human, rat, or cyno11β-HSD1 as the enzyme source and NADPH as cofactor. Cell-based enzyme assays employed HEK293 cells stably expressing recombinant human full-length 11β-HSD1 as the enzyme source without supplementation of NADPH. IC50 values for enzyme inhibition were calculated with a dose response curve fitting algorithm with at least duplicate sets of samples.

20. Details for an analogous experiment carried out in cynomolgus monkeys is described in Ref. 13.
21. Time point chosen to coincide with Tmax (ca. 2 h) of the compound upon oral administration.
22. PDB database deposition code 3FCO.