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Design, synthesis, and SAR studies of novel polycyclic acids as potent and selective inhibitors of human 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD-1)

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ABSTRACT

Starting from high throughput screening hit 2-adamantyl acetic acid **3**, a series of polycyclic acids have been designed and synthesized as novel, potent, and selective inhibitors of human 11β-HSD1. Structure–activity relationships of two different regions of the chemotype (polycyclic ring and substituents on quaternary carbon) are discussed.

According to the World Health Organization, the number of type 2 diabetes patients had reached 154 million in 2000, and is growing rapidly with the projection of over 330 million diabetics worldwide by 2030.[1] This chronic progressive disease, characterized by elevation in plasma glycosylated hemoglobin (HbA1c), is driven in part by insulin resistance exacerbated by abdominal obesity and insulin deficiency due to progressive deterioration of pancreatic beta-cell function. Metabolic syndrome, a cluster of metabolic abnormalities (insulin resistance, obesity, dyslipidemia, hyperglycemia and hypertension) is increasingly recognized as a major cause of cardiovascular diseases and type 2 diabetes. Selective inhibition of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD-1) represents a promising approach for the potential treatment of type 2 diabetes and metabolic syndrome and as such has received intensive attention from both academia and the pharmaceutical industry.[2] 11β-HSD-1 catalyzes the inter-conversion of inactive cortisone to the active steroid cortisol, a principle circulating glucocorticoid in humans. Excess glucocorticoids are implicated in increased glucose output in the liver, dampened glucose-dependent insulin sensitivity in adipose tissue, and reduced insulin secretion from the pancreas. The concept of selective inhibition of 11β-HSD-1 as a viable strategy for treating type 2 diabetes and metabolic syndrome is supported by genetic and pharmacological studies in various animal models, as well as preliminary clinical studies in type 2 diabetic (T2D) patients. For example, 11β-HSD-1 knockout mice are resistant to developing diet induced obesity and hyperglycemia,[3] while transgenic mice that overexpress 11β-HSD-1 in adipose exhibit a phenotype characterized by a variety of metabolic disorders, including obesity, insulin resistance, glucose intolerance, and hyperglycemia.[4] Several papers have reported that adipose tissue from obese individuals exhibits elevated 11β-HSD-1 activity. Chronic administration of inhibitors in animal models of diabetes has demonstrated positive effects on glucose, body weight, and plasma lipids.[5] Furthermore, Incyte has recently demonstrated that the selective 11β-HSD-1 inhibitor INCB-13739 improves hepatic and peripheral insulin sensitivity and lipid profiles in T2D patients after 1–3 months of treatment.[6]

Over the past few years, several classes of non-steroidal 11β-HSD-1 inhibitors have been reported in the literature.[7,8] These include sulfonamides and sulfones, amides and lactams, triazoles,

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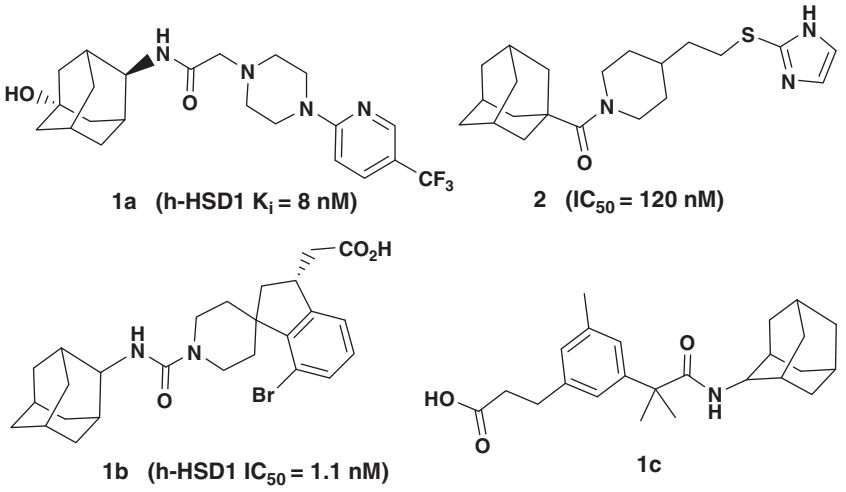


Figure 1. 2-Adamantamine and 1-adamantyl carboxylic acid based 11β-HSD-1 inhibitors.

thiazolones, and others inhibitors. Within the amide/lactam category, researchers from Abbott and several other organizations have incorporated 2-adamantamine into their chemotypes, as exemplified by compounds **1a–c**.[9a] Researchers from Novo Nordisk have disclosed amides derived from 1-adamantyl carboxylic acid, as exemplified by compound **2** (Fig. 1).[9b] In both cases, the amido functionalities are presumed to interact with the catalytic Ser170 and Tyr183 residues in the active site of the enzyme. In this Letter, we wish to report the discovery of novel adamantyl/polycyclic carboxylic acids as potent and selective inhibitors of human 11β-HSD-1. While several teams have reported inhibitors which contain a carboxylic acid group (e.g., compounds **1b** and **1c**),[10] other functional moieties present in the molecule (ureas, amides, etc.) are presumed to serve as the hydrogen-bonding pharmacophore with the Ser170 and Tyr183 residues. To the best of our knowledge, the compounds represented by structures **4**, **5** and **6** are the first in which a carboxylic acid functionality is proposed to serve as the *primary* pharmacophore to the enzyme's catalytic binding site.[11]

Our initial lead, 2-adamantyl acetic acid **3** (Fig. 2), was identified via high throughput screening and exhibited moderate inhibitory activity against human 11β-HSD-1 (IC_{50} = 860 nM). Molecular docking[12] of **3** using a published crystal structure of human 11β-HSD-1[13] showed a key hydrogen bond interaction of the carboxylic group of the ligand with the catalytic residues Ser170 and Tyr183 on the enzyme. The adamantyl moiety positions well in the enzyme's hydrophobic pocket (Fig. 3). Based on this docking model, we speculated that additional of a lipophilic substituent (e.g., aryl) at the C-2 position of adamantyl should further enhance the potency by more optimally filling the proximal hydrophobic binding site. This was supported by the identification of the highly potent C-2 4-F-phenyl derivative **4a** in the screening deck. The finding demonstrated that the hydrophobic groups at C-2 position were not only well tolerated, but dramatically enhanced potency. In contrast, we found that introducing a polar substituent (such as –CN in **4b**) in the C-2 position significantly decreased inhibitory potency.

Using **4a** as a starting point for our SAR program, we subsequently varied the linker length between the carboxylate group and the adamantane ring to find that the acetic acid based analog (n = 1) was optimal (compare compound **4a** with **5a** and **5b**). These initial findings set the stage for subsequent optimization studies in

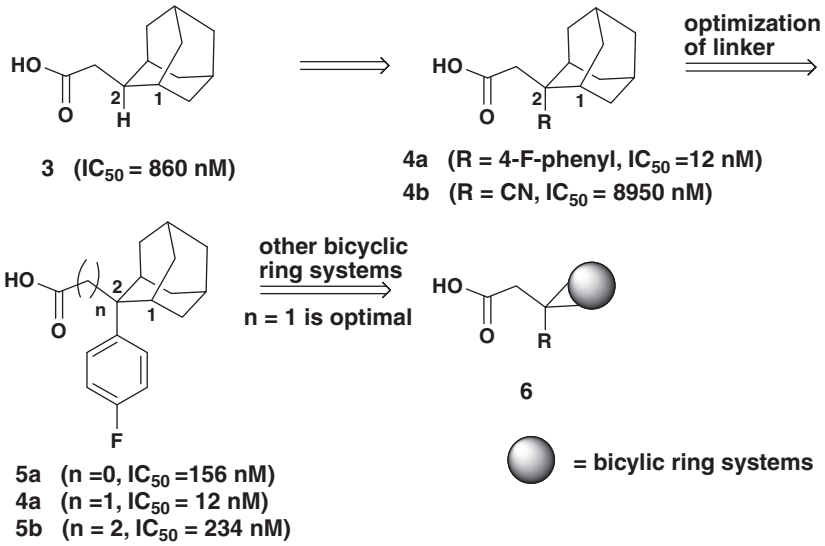


Figure 2. HTS hit and the evolution of bicyclic carboxylic acids as novel 11β-HSD-1 inhibitors.

this series. In addition to variation of the adamantyl group, we also examined other bicyclic ring systems and substituents on the rings with the aim to enhance metabolic stability and in vitro potency of the series. As a result, we synthesized a series of bicyclic carboxylic acids with the general structure shown as **6** in Figure 2.

We developed a general route to access polycyclic acids **6** as described in Scheme 1. Knoevenagel condensation of polycyclic ketones **7** (commercially available or obtained via literature procedures) and Meldrum's acid was carried out in anhydrous pyridine in the presence of catalytic piperidine to afford the disubstituted alkylidene **8**.[14] 1,4-Conjugate addition of nucleophiles such alkyl or aryl Grignard (RMgX) or other organometallic (RLi) reagents to **8** was carried out in the presence of Cu^{+} salts (such as CuBr, CuCN, etc.) at room temperature or at 40 °C to afford **9**.[15] The isopropylidene malonate **9** was converted to **6** in generally high yields via hydrolysis and subsequent decarboxylation in wet organic solvent at 110 °C.[16] This general scheme allowed variation of the R group as well as the polycyclic ring system for rapid SAR elucidation.

Overall, compound **4a** represented an excellent starting point for the chemical program. Based on the presence of the polar carboxylic acid, the lead exhibited favorable in vitro properties that have been typically problematic with known/reported inhibitors. In addition to good intrinsic potency versus human 11β-HSD-1

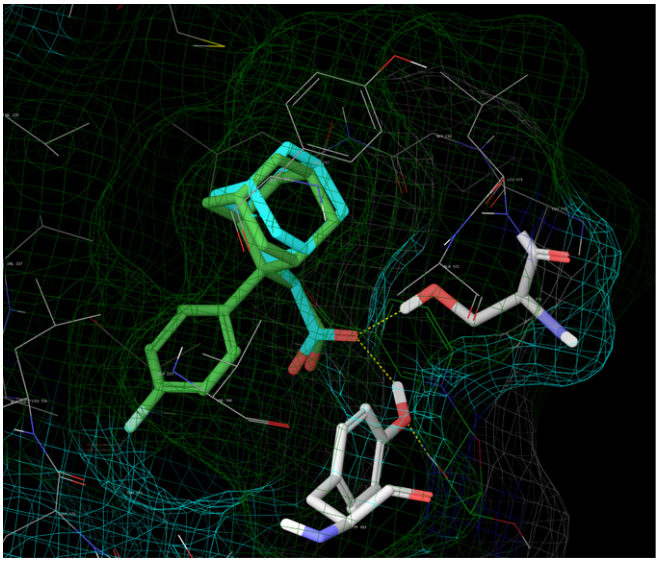
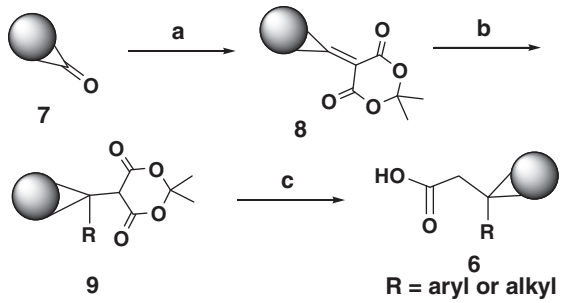
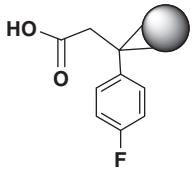


Figure 3. Docking model of compounds **3** (blue) and **4a** (green) with human 11β-HSD-1.[12] The enzyme's hydrophobic pocket is shown in green wire mesh, while the hydrophilic pocket is shown in blue wire mesh.

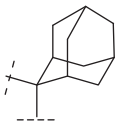
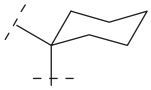
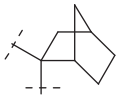
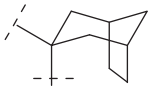
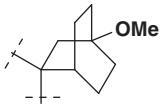
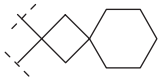
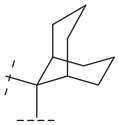
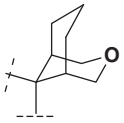
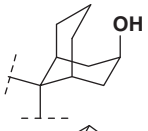
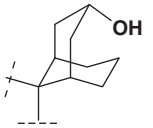
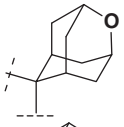
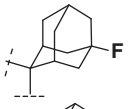
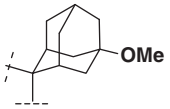


Scheme 1. Synthesis of bicyclic carboxylic acids **6**. Reagents and conditions: (a) Meldrum's acid, anhydrous pyridine, cat. piperidine, room temperature, 5 days (50–90%); (b) RLi or RMgX, CuBr, THF, −20 °C to room temperature (or to 40 °C), 6 h (30–85%); (c) NaCl (saturated, aqueous), DMSO, 110 °C, 12 h (~90%).

Table 1
SAR of polycyclic carboxylic acids[18]

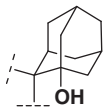
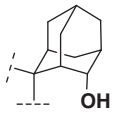
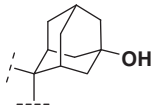
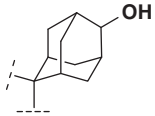
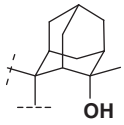


6

Compd		IC_{50}[a] (nM)		% Remaining[b]	
		Hu	Mu	Hu	Mu
4a		12	120	78	48
6a		694	9545	NT[c]	NT
6b		193	2621	83	81
6c		63	2381	100	100
6d		594	>10K	NT	NT
6e		153	1016	87	50
6f		3	184	100	73
6g		204	3954	NT	NT
6h		174	6849	NT	NT
6i		127	354	NT	NT
6j		2203	6508	NT	100
6k		13	1616	87	94
6l		21	4570	100	100

(*continued on next page*)

Table 1 (*continued*)

Compd		IC_{50}[a] (nM)		% Remaining[b]	
		Hu	Mu	Hu	Mu
6m		4705	NT	100	89
6n		189	>10K	100	100
6o		425	>10K	NT	NT
6p		160	776	NT	NT
6q		48	4446	100	100

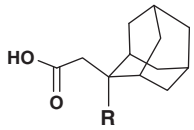
[a] IC_{50} refers to biochemical assay versus the human or mouse 11β-HSD-1 enzyme.
[b] Represents percentage of compound remaining after incubation in human or mouse microsomes after a 10-minute incubation period.
[c] NT = not tested.

(IC_{50} = 12 nM) and selectivity versus human 11β-HSD-2 (<50% inhibition at 10 μM), compound **4a** also exhibited reasonable aqueous solubility, good permeability, weak CYP450 inhibition (1A2, 2C9, 2C19, 2D6, 3A4) and hERG inhibition, as well as negligible PXR transactivation (EC_{50} > 50 μM). Unfortunately, microsomal stability (assessed using isolated liver microsomes) was marginal and mouse enzymatic inhibitory activity was weak, preventing evaluation of the lead in our in vivo pharmacodynamic and efficacy models. Thus, attention was primarily directed towards optimization of potency and metabolic stability in this chemotype.

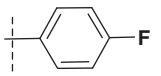
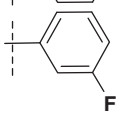
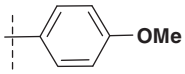
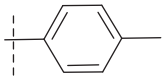
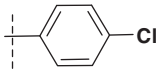
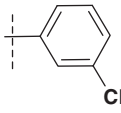
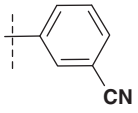
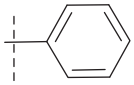
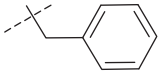
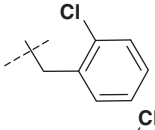
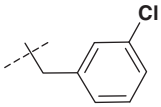
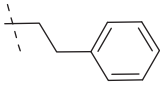
The known propensity of the adamantyl ring system to undergo microsomal oxidation prompted us to first examine the effect of different polycyclic ring systems on potency and metabolic stability. Table 1 summarizes the inhibitory activity of these compounds tested against both human and mouse 11β-HSD-1. In vitro stability in the presence of human and mouse liver microsomes is reported when available. The simple cyclohexyl derivative **6a** exhibits only moderate activity against human 11β-HSD-1, while the carboxylic acids bearing more sophisticated polycyclic rings such as [2,2,1]-bicycloheptane and [3,2,1]-bicyclooctane (**6b** and **6c**) enhance potency 3–10-fold, highlighting the critical need for hydrophobic space-filling at this position of the molecule. Notably, the inhibitor bearing a [3,3,0]-bicyclooctane ring motif (**6f**) was the most potent among this set of compounds, exhibiting single digit nanomolar activity versus the human enzyme, but only modest potency versus the mouse.[17] Metabolic stability was also enhanced relative to **4a**. Attempts to modify **6f** by either incorporating a polar hydroxyl functional group (**6h** and **6i**) or building an oxygen into the ring as an ether linker (**6g** and **6j**) resulted in a substantial loss of potency. In order to directly block putative metabolic oxidation of the adamantyl ring, we also incorporated a fluorine or methoxy group at the bridgehead position (**6k** and **6l**). Both compounds maintained in vitro potency for the human enzyme while exhibiting enhanced metabolic stability in liver microsomes. Finally, additional attempts to incorporate a polar hydroxyl (**6m**–**6q**) directly to the adamantyl ring, while routinely enhancing metabolic stability, often led to a diminution in potency versus the human enzyme and a near abolishment of potency versus the mouse.

Table 2 highlights a limited SAR set directed towards variation of the hydrophobic R group in structure **6**. Not surprisingly, when R is unsubstituted phenyl (**6x**), the inhibitory activities against both human and mouse enzymes decrease slightly compared to its 4-fluoro phenyl analog **4a**. In general, substituents (whether po-

Table 2
SAR of adamantyl carboxylic acids[18]



6

Compd	R	IC_{50}[a] (nM)		% Remaining[b]	
		Hu	Mu	Hu	Mu
4a		12	120	78	48
6r		7	334	83	47
6s		16	134	NT	NT
6t		5	103	NT	NT
6u		4	105	NT	NT
6v		4	111	NT	NT
6w[19]		12	216	87	100
6x		20	172	NT	NT
6y		24	113	100	100
6z		4.9	155	66	7.4
6aa		14	82	55	43
6bb		2.2	54	98	5

NT = not tested.
[a] IC_{50} refers to biochemical assay in human or mouse 11β-HSD-1 enzyme.
[b] Represents percentage of compound remaining after incubation in human or mouse microsomes after a 10-minute incubation.

Table 3
Coarse mouse pharmacokinetic studies and in vitro glucuronidation half-lives of representative bicyclic acids

Compound	C_{max} (μM)	AUC[a] (0–8 h) (μM∗h)	UGT $T_{1/2}$[b] (human/mouse) (min)
4a	0.48	2	NT
6y	1.4	4.1	1.9/2.1
6w	0.07	0.3	4.2/0.8
6k	0.04	0.22	NT
6l	<LLQ	<LLQ	8.7/2.2
6o	<LLQ	<LLQ	35/8.8
6f	0.06	0.3	NT
6q	0.04	0.244	11/2.8

NT = not tested.

[a] Pharmacokinetic studies were performed in mice using 0.5% methocel, and 0.1% tween 80 in water as vehicle. The dose used was 10 μmole/kg (30 μmole/kg for **4a**). Plasma concentration was measured at 1, 4, and 8 h time points. AUC (0–8 h) was calculated based on the concentrations measured at these time points.

[b] Glucuronidation half-lives were measured by incubating substrate (10 μM) with either human or mouse liver microsomes (1 mg/mL) in the presence of UDGPA (5 mM) over a 0, 5, 15, and 30 min period. The incubation mixture was quenched at each time point and analyzed by LC–MS to obtain the percentage of substrate remaining for each time point. UGT $T_{1/2}$ was obtained from the curve plotted from the above data.

lar or non-polar group) in either the 3-position or 4-position of phenyl ring appeared to be neutral or slightly increase potency (**6r–6v**). The inhibitory activity of benzyl analog **6y** decreased slightly versus **4a** but was similar to the unsubstituted phenyl **6x**. Clearly substitution at this position is well tolerated with the enzyme's ability to accommodate a variety of diverse hydrophobic groups. For reasons that are unclear, the metabolic stability of the benzyl analog **6y** appears to be enhanced versus the 4-F-phenyl (**4a**) and other substituted benzyl derivatives (**6z** and **6aa**). The most potent inhibitor in this comparison is the phenethyl analog **6bb**, which exhibits superior inhibitory activity against both human (IC_{50} = 2.2 nM) and mouse (IC_{50} = 54 nM) 11β-HSD-1, although its metabolic stability in mouse liver microsomes is quite poor.

Select compounds from Tables 1 and 2 were tested for enzymatic assay in a HEK cell line expressed with human 11β-HSD-1 and were found to exhibit reasonable potency.[20] The result suggests that this class of compounds have ability to penetrate cells and reach the target enzyme in the mitochondria.

Despite the marginal mouse potency generally observed for this chemotype, several compounds having reasonable human in vitro potency and good human/mouse metabolic stability were assessed in a coarse mouse pharmacokinetic model and the results are summarized in Table 3. Unfortunately all compounds exhibited low plasma exposure in mice, despite their reasonably good PAMPA permeability, solubility, and in vitro microsomal metabolic stability profiles (shown in Tables 1 and 2). To rationalize these results, we looked to see if phase 2 metabolism could be contributing to the low exposure and rapid clearance, particularly since the presence of the carboxyl groups enable glucuronidation as a route of elimination. While glucuronidation rates varied in the human in vitro assay, half-lives in the mouse assay were quite short, suggesting that rapid glucuronidation (perhaps coupled with some oxidative metabolism) was responsible for the poor pharmacokinetic exposures of these compounds upon oral dosing.

In summary, we have designed and synthesized a series of polycyclic carboxylic acids as potent and selective[21] 11β-HSD-1 inhibitors. These compounds were generally potent against the human enzyme, but less potent against the mouse (better analogs exhibited IC_{50} values in the 100–300 nM range). Though not fully reported, the chemotype in general exhibited favorable development attributes such as good metabolic stability, weak inhibition of CYP450 enzymes, no PXR activation and weak ion channel activities.[22] Unfortunately, the propensity of these compounds to undergo glucuronidation represented a significant hurdle for pharmacokinetic optimization of this chemotype. As a result, additional efforts were subsequently directed to the identification of suitable replacements for the carboxylic acid functionality, including tetrazoles, sulfonamides and amide based functionalities. These efforts will be the topic of future disclosures.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2011.09.055.

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11. Though the attempts to grow co-crystal structure of ligands **4**–**6** with human 11β-HSD-1 failed, we did obtain several co-crystal structures of their corresponding amide derivatives bound to human 11β-HSD-1. The conformation of adamantyl moiety and carbonyl group in co-crystal

structures are superimposed to those shown in docking model (Fig. 3). The results will be reported elsewhere.
12. The software used for docking is Glide-SP implemented in Maestro version 9.0; http://www.schrodinger.com.
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17. In general, the higher potency of the inhibitors for the human enzyme versus the mouse can be attributed to the higher lipophilic nature of the binding pocket of human 11β-HSD-1. Significant differences in the binding pocket include, A226 and Y177 in human versus E226 and Q177 in mouse. The docking model (Fig. 3) shows the adamantyl group pointing towards Y177 in human, but Q177 in mouse, and the 4-F-phenyl group pointing towards A226 in human, but E226 in mouse. In both cases, the interaction of the ligand with the human enzyme is more favored than with the mouse enzyme. This difference can be especially dependent upon the chemotype. For example, see our recent publication in Ref. 7a.
18. In general, compounds in Tables 1 and 2 were generated via the reaction sequences in Scheme 1 using different ketones **7** as the starting material and appropriate RMgX or RLi as the nucleophile. Some acids in Table 1 require additional steps for functional group transformation. For typical experimental procedure, see Supplementary data.
19. Compound **6w** was synthesized from compound **6v**. See Supplementary data for details.
20. In general, the cellular assay IC_{50} values were 5–10-fold less potent than the corresponding IC_{50} values in the biochemical assay.
21. Though not reported, all inhibitors tested exhibited little/no inhibition (<50% at 10 μM) versus human 11β-HSD-2.
22. The lipophilic nature of these carboxylic acids resulted in a concern for PPAR activity. We tested several compounds from this class, including **4a**, and no PPAR activity across α, γ, δ subtypes was detected up to a concentration of 30 μM.