Letters

Piperazine Sulfonamides as Potent, Selective, and Orally Available 11β-Hydroxysteroid Dehydrogenase Type 1 Inhibitors with Efficacy in the Rat Cortisone-Induced Hyperinsulinemia Model

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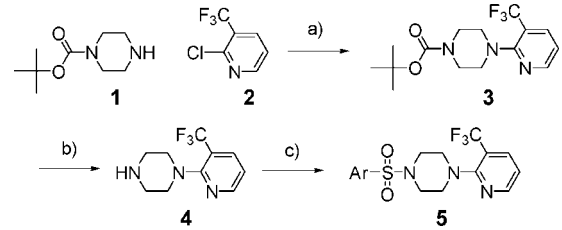
Abstract: 11β-Hydroxysteroid dehydrogenase type 1 (11β-HSD1) is the enzyme that converts cortisone to cortisol. Evidence suggests that selective inhibition of 11β-HSD1 could treat diabetes and metabolic syndrome. Presented herein are the synthesis, structure−activity relationship, and in vivo evaluation of piperazine sulfonamides as 11β-HSD1 inhibitors. Through modification of our initial lead **5a**, we have identified potent and selective 11β-HSD1 inhibitors such as **13q** and **13u** with good pharmacokinetic properties.

The dramatic increase in the prevalence of type 2 diabetes and obesity in recent years has led to an increased recognition of "metabolic syndrome", a collection of metabolic and cardiovascular abnormalities. Metabolic syndrome is characterized by abdominal obesity, impaired glucose tolerance, dyslipidemia, low levels of high density lipoprotein (HDL[a]), cholesterol, and hypertension.[1] Recent investigations have implicated aberrant glucocorticoid receptor (GR) signaling in the development of several phenotypes associated with metabolic syndrome. Glucocorticoid hormones are key metabolic regulators. The major activator of the GR in humans is cortisol, and the adrenal cortex is the major source of circulating cortisol. GR signaling depends not only on the circulating cortisol levels but also on the intracellular generation of cortisol through reduction of cortisone, the inactive glucocorticoid.[2] The reduction reaction is catalyzed by 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) with the concomitant oxidation of NADPH, while cortisone itself is generated by the action of 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) on cortisol using NADP as a cofactor.[2] These two enzymes have very different expression profiles: 11β-HSD1 is highest in liver, adipose, and the central nervous system, whereas 11β-HSD2, is expressed in kidney, colon, and other tissues.[2]

Scheme 1[a]



[a] Conditions: (a) Hunig's base, DMF, 85%; (b) TFA, CH_2Cl_2, 95%; (c) $ArSO_2Cl$, Hunig's base, CH_2Cl_2, 75−90%.

A potential role for 11β-HSD1 inhibitors in metabolic disease has been established using transgenic mice. Mice overexpressing 11β-HSD1 in adipose or liver show several features of metabolic syndrome.[3a,b] On the other hand, 11β-HSD1 knockout mice are resistant to diet-induced obesity and exhibit improved insulin sensitivity and lipid profiles.[3c] Administration of specific 11β-HSD1 inhibitors in mouse models of insulin resistance led to improved hyperglycemia and insulin sensitivity.[4,5] Recent studies with the nonspecific 11β-HSD1 inhibitor carbenoxolone also show improved hepatic insulin sensitivity and decreased glucose production in humans.[6] However, the 11β-HSD2 inhibitory activity of carbenoxolone is a limiting factor because it induces renal mineralocorticoid excess at higher doses.[6] Disruption or mutation in the 11β-HSD2 gene results in sodium retention, hypokalemia, and hypertension.[7] Therefore, while inhibition of 11β-HSD1 is an attractive strategy for the design of therapeutics for metabolic syndrome, it is ideal to have 11β-HSD1 inhibitors to be selective against 11β-HSD2.

Several publications reported potent and selective 11β-HSD1 inhibitors.[8] This report describes the SAR, PK, ex vivo activity, and in vivo efficacy of a series of piperazine sulfonamides. Early in our 11β-HSD1 program, piperazine sulfonamide **5a** was identified through HTS as a potent lead compound.[9] Our screening approach was to use a cell-based assay to assess all new analogues, thus increasing the chances that active compounds will also be cell permeable and potentially more druglike.

Pyridylpiperazine sulfonamides were prepared via the route shown in Scheme 1. Piperazine **3** was prepared by heating *tert*-butylpiperazine 1-carboxylate **1** and 2-chloro-3-trifluoromethylpyridine **2** in the presence of Hünig's base. Deprotection of the *tert*-butyl carbamate was carried out using TFA to provide the intermediate pyridylpiperazine **4**. Final products **5** were obtained in excellent yield by sulfonylation of the piperazine **4** with various arylsulfonyl chlorides. Phenylpiperazine sulfonamides were prepared via the route shown in Scheme 2. Intermediate phenylpiperazine **7** was prepared from 2-bromo-5-fluorobenzotrifluoride **6** and *tert*-butylpiperazine 1-carboxylate **1** via Buchwald amination. Removal of the carbamate and sulfonylation of the resulting piperazine provided final phenylpiperazine sulfonamide **9**. Preparation of phenyl 2-(*R*)-methylpiperazine sulfonamides is depicted in Scheme 3. In this case, unprotected 2-(*R*)-methylpiperazine **10** was used directly

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[a] Abbreviations: 11β-HSD1, 11β-hydroxysteroid dehydrogenase type 1; 11β-HSD2, 11β-hydroxysteroid dehydrogenase type 2; HDL, high density lipoprotein; GR, glucocorticoid receptor; HTS, high-throughput screening; SAR, structure−activity relationship; PK, pharmacokinetics; NADP, β-nicotinamide adenine dinucleotide phosphate; NADPH, β-nicotinamide adenine dinucleotide phosphate reduced form; CHO cell, Chinese hamster ovary cell; HLM, human liver microsomes; MLM, mouse liver microsomes.

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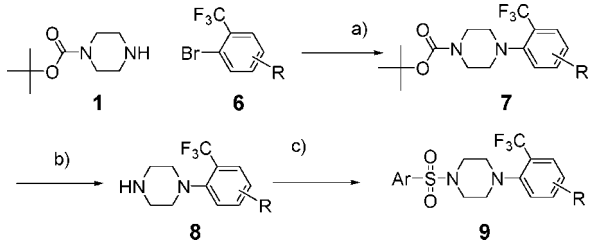
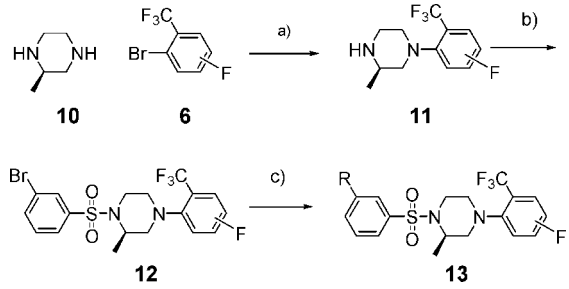
Scheme 2[a]



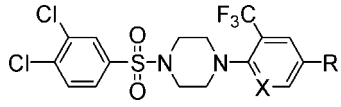
[a] Conditions: (a) $Pd_2(dba)_3$, BINAP, toluene, 80−85%; (b) TFA, CH_2Cl_2, 85−95%; (c) $ArSO_2Cl$, Hunig's base, CH_2Cl_2, 75−90%.

Scheme 3[a]



[a] Conditions: (a) $Pd_2(dba)_3$, BINAP, toluene, 65−85%; (b) $ArSO_2Cl$, Hunig's base, CH_2Cl_2, 75−90%; (c) $Pd_2(dba)_3$, BINAP, toluene, 45−75%.

Table 1. Biological Activities of Piperazine Sulfonamides **5** and **9**



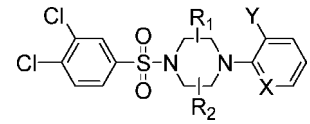
	X	R	IC$_{50}$ (μM) h-HSD1	IC$_{50}$ (μM) m-HSD1	$T_{1/2}$ (min) MLM	$T_{1/2}$ (min) HLM
5a	N	H	0.061	0.19	5	5
9a	C	H	0.052	0.42	3	4
9b	C	F	0.068	0.25	8	12[a]

[a] Assay run in duplicate.

in the Buchwald amination followed by sulfonylation. 3-Substituted analogues were obtained by derivatization of bromide **12** (Scheme 3).

The original hit **5a** is a potent inhibitor of human and mouse 11β-HSD1 in cell-based assays (Table 1). However, **5a** has low microsomal stability with a $T_{1/2}$ less than 5 min in human and mouse liver microsomes. Pharmacokinetic studies also suggest that **5a** has very high iv clearance (149 (mL/min)/kg at 2 mg/kg, mice) and low oral bioavailability (5% at 30 mg/kg, mice). Metabolite studies indicated that the pyridyl ring of the molecule is prone to oxidation. N-Dealkylation at the middle ring was also observed. To address the oxidation of the pyridyl ring, analogues with a phenyl ring were explored. It was very encouraging to see that replacement of the pyridyl ring by a phenyl ring retained activity against the enzyme. Compounds such as **9a** show potency comparable to that of the original hit **5a**. However, **9a** still suffers from low microsomal stability. We then introduced a fluoro group at the phenyl ring to see if we could block metabolic soft spots. Such analogues are easily accessible because several fluorine-substituted *o*-bromotrifluorobenzenes are commercially available. **9b** showed similar potency to **9a**, suggesting that the fluorine group is allowed at the para position. **9b** also showed improvement in microsomal stability ($T_{1/2}$ = 12 min in the human liver microsomes versus $T_{1/2}$ = 4 min for **9a**). Detailed SAR and microsomal stability

Table 2. Biological Activities of Piperazine Sulfonamides **5** and **9**



	X	Y	R_1,R_2	IC$_{50}$ (μM) h-HSD1	IC$_{50}$ (μM) m-HSD1	$T_{1/2}$ (min) MLM	$T_{1/2}$ (min) HLM
5b	N	Cl	2, 5-*trans*-di-Me	1.6	4.7	2	3
5c	N	Cl	2, 6-*cis*-di-Me	1.3	6.9	3	6
5d	N	CF_3	2-oxo	0.50	>10	6	2
5e	N	CF_3	3-oxo	9.9	>10	30	30
9c	C	CF_3	2-(*R*)-Me	0.010	0.010	3	5[a]

[a] Assay run in duplicate.

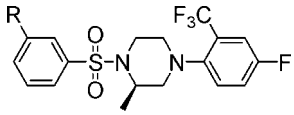
of analogues bearing various substitutions on the phenyl ring will be reported in due course.

Modification of the middle piperazine ring was then undertaken to evaluate the impact on potency and microsomal stability. Disubstituted piperazine derivatives were prepared. Compounds **5b** and **5c** showed a significant decrease in potency, while no improvement in terms of microsomal stability was observed (Table 2). Incorporation of a carbonyl group into middle ring led to piperazinone analogues such as **5d** and **5e**. Compound **5d** is a much weaker inhibitor of the enzyme, and no improvement in the microsomal stability was observed. Compound **5e** on the other hand has a significantly improved microsomal stability with $T_{1/2}$ > 30 min in the presence of mouse and human liver microsomes. Unfortunately, **5e** is also drastically less potent against human and mouse 11β-HSD1. Interestingly, analogues with monosubstitution such as 2-methyl showed excellent activity against human and mouse 11β-HSD1. For example, **9c** has an IC$_{50}$ of approximately 10 nM in cell-based assays, which represents about 5-fold improvement in potency against the human enzyme and 25-fold improvement against mouse enzyme when compared to the unsubstituted piperazine **9a**. Further comparison of the 2-(*R*) and the 2-(*S*)-methylpiperazine analogues indicated that the *R* series was significantly more potent in the ex vivo assay when compared to the *S* series, and we decided to focus our efforts on the *R* series (data not shown). Our detailed findings on the stereochemistry preference will be reported in due course.

On the basis of the preliminary SAR of the piperazine ring and the aryl substituent on the right-hand side of the molecule, we focused on analogues that incorporate the 2-(*R*)-methylpiperazine in the middle ring and 2-trifluoro-4-fluorophenyl of the right-hand side, as exemplified by **13**. Further optimization of the molecule was undertaken by focusing on the left side of the molecule. The remainder of this communication is focused on the meta position of the benzenesulfonamide. Analogues with substitution at other positions offered additional opportunities for improvement and will be published separately.

Compounds incorporating a *m*-piperidine (**13a**) or *m*-morpholine (**13b**) on the benzenesulfonamide are potent inhibitors of 11β-HSD1 with IC$_{50}$ values of about 10 nM against the human enzyme in cell-based assays. The potency of the N-substituted piperazine analogues varies depending on the size and the polarity of the substituents. Smaller substituents such as 4-methyl and 4-ethyl (**13c**, **13d**) are tolerated, while 4-isopropyl substitution led to a significant decrease in potency (**13e**). Carbamates and ureas such as the methylcarbamate **13f** and the ethylurea **13g** decreased dramatically the activity against human 11β-HSD1. Analogues containing a free amine such as **13h** is a much weaker human 11β-HSD1 inhibitor with IC$_{50}$ over 10 μM. We also investigated the size of the ring at the meta position

Table 3. Biological Activities of 2-Methylpiperazinesulfonamides **13a−u**



	R	IC$_{50}$ (μM) h-HSD1	m-HSD1	m-HSD1
13a	piperidine	0.015	0.010	0.067
13b	morpholine	0.013	0.011	0.056
13c	4-Me-piperazine	0.021	0.012	0.028
13d	4-Et-piperazine	0.030	0.029	0.045
13e	4-iPr-piperazine	0.49	0.15	0.25
13f	piperazine-4-methylcarbamate	0.33	0.011	0.22
13g	piperazine-4-methylurea	0.37	0.012	0.22
13h	piperazine	>10	0.16	0.19
13i	pyrrolidine	0.061	0.016	0.056
13j	pyrrolidine-3-ol	0.010	0.013	0.011
13k	pyrrolidine-3-ol (R)	0.010	0.012	0.013
13l	pyrrolidine-3-ol (S)	0.028	0.020	0.041
13m	pyrrolidine-3-carboxylate	0.011	0.010	0.055
13n	pyrrolidine-3-COOH	0.16	0.010	0.090
13o	pyrrolidine-3-CONH$_2$	0.032	0.011	0.014
13p	proline	0.069	0.027	0.032
13q	1,2,4-triazole	0.026	0.010	0.042
13r	1,3,4-triazole	0.12	0.23	0.12
13s	imidazole	0.074	0.011	0.073
13t	pyrazole	0.013	0.012	0.10
13u	OCMe$_2$COOH	0.30	0.037	0.13[a]

[a] Assay run in duplicate.

by making five-membered rings such as the pyrrolidines. Compound **13i** is a potent inhibitor with a human IC$_{50}$ of 60 nM and a mouse IC$_{50}$ of 16 nM. Further SAR studies around the pyrrolidine ring suggested that OH, CO$_2$Et, COOH, and amido groups are all tolerated at the 3-position (examples **13j**, **13k**, **13l**, **13m, 13n**, **13o**). Proline analogues such as **13p** are also very potent, suggesting polar groups at 2-position are tolerated. Other five-membered heterocycles such as triazole (**13q** and **13r**), imidazole (**13s**), and pyrazole (**13t**) are well tolerated, yielding potent compounds against human and mouse HSD1. These polar groups were designed to increase the aqueous solubility of the inhibitors. In addition to N-substituted analogues, oxygen linker analogues were also prepared. Compound **13u** carries a free carboxylic acid and is potent against the mouse enzyme with an IC$_{50}$ value of 37 nM. However, **13u** is weaker against the human enzyme with an IC$_{50}$ value of 300 nM. It is interesting to note that for the majority of the compounds listed in Table 3, the inhibition decreased only marginally in the presence of serum suggesting that protein binding of this series might not be an issue. We also note that of all the compounds from the piperazine sulfonamide class, none showed any activity against 11β-HSD2 at concentrations as high as 100 μM.

Potent compounds with a microsomal stability $T_{1/2}$ > 10 min were selected for pharmacokinetics studies. Compounds **13c**, **13j**, **13n**, **13q**, and **13u** have moderate iv clearance and reasonable oral bioavailability (Table 4). For **13c**, **13n**, and **13u**, the oral bioavailabilities are 79−100%. These five compounds were then tested in a mouse ex vivo assay. Compounds were dosed orally at 30 mg/kg. Mice were sacrificed 5 h after oral dosing. Liver samples were obtained, and the activity of 11β-HSD1 converting cortisone to cortisol was measured. Compounds **13c**, **13j**, and **13n** showed 36−47% inhibition at 30 mg/kg, while **13q** achieved 44% inhibition at 10 mg/kg. Despite its excellent oral bioavailability, **13u** showed modest ex vivo inhibition, which could be attributed to unfavorable tissue distribution.

Table 4. Mouse Microsomal Stability, PK, and ex Vivo Data

	MLM $T_{1/2}$ (min)	Cl ((mL/min)/kg)[a]	F[b] (%)	mouse ex vivo inhibition[c] (%)
13c	15	36	79	45
13j	11	54	9	47
13n	>30	55	100	36
13q	12	13	34	44 (10 mpk)
13u	>30	25	100	38

[a] Mouse iv PK at 2 mg/kg in DMSO/Tween. [b] Mouse po PK at 30 mg/kg in 0.5% methylcellulose/2% Tween. [c] 30 mg/kg po dose unless otherwise noted.

Table 5. Rat in Vitro, PK, and ex Vivo Data

	r-HSD1 IC$_{50}$ (μM)	C_{max} (ng/mL)[a]	AUC (ng·h/mL)[a]	rat ex vivo inhibition at 2 h (%)
13c	0.042	246	2285	32
13j	0.013	185	1043	62
13q	0.081	149	1041	59
13u	0.11	9183	51088	35

[a] Rat po PK dosed at 30 mg/kg in 0.5% methyl cellulose/2% Tween.

Table 6. Effects of 11β-HSD1 Inhibitors on Cortisone Induced Hyperinsulinemia in SD Rat

	dose[a] (mpk, b.i.d.)	insulin reduction at day 7 (%)
13q	60	34
13c	60	11
13j	60	19
13u	30	30

[a] Dosed po in 0.5% methyl cellulose/2% Tween.

The cortisone-induced hyperinsulinemia model in rats was one of numerous models we evaluated in the course of this program. The aim was to determine if our 11β-HSD1 inhibitors can prevent the cortisone induced hyperinsulinemia in Sprague−Dawley (SD) rats. Selected compounds were tested in CHO cell expressing rat 11β-HSD1 to confirm their potency against the rat enzyme. **13c**, **13j**, and **13q** were found to be potent inhibitors of rat 11β-HSD1 with IC$_{50}$ values below 100 nM (Table 5). PK studies were carried out to determine the plasma exposure in rat. All of these compounds displayed reasonable exposure with AUCs over 1000 ng·h/mL. The four compounds were examined in the rat ex vivo assay, and **13j** and **13q** were the most potent of the group tested, displaying ~60% inhibition in the liver.

On the basis of their favorable exposure and ex vivo inhibition, these four compounds were tested in the rat cortisone induced hyperinsulinemia model. Male SD rats were used for this study. Cortisone was administered in drinking water (2 mg/mL), and the inhibitors were dosed orally at 60 mg/kg, b.i.d. Body weight, food intake, liquid consumption, plasma glucose, and serum insulin were measured on day 7. After 7 days of treatment, rats receiving **13q** or **13u** displayed a ~30% decrease in serum insulin level (Table 6, Figure 1). There was no change in the glucose level in these animals. This finding is not unexpected, since the model above relates to the hyperinsulinemia model rather than hyperglycemia.

In summary, HTS led to the identification of piperazine sulfonamide **5a**, a lead with poor microsomal stability and high clearance. Optimization of the piperazine middle ring and the pyridyl ring led to the identification of numerous compounds with excellent potency, high selectivity against 11β-HSD2, and good exposure following oral dosing. Compounds such as **13c**, **13j**, **13q**, and **13u** showed activity in the mouse and rat ex vivo assays. We also evaluated our lead compounds in a cortisone-

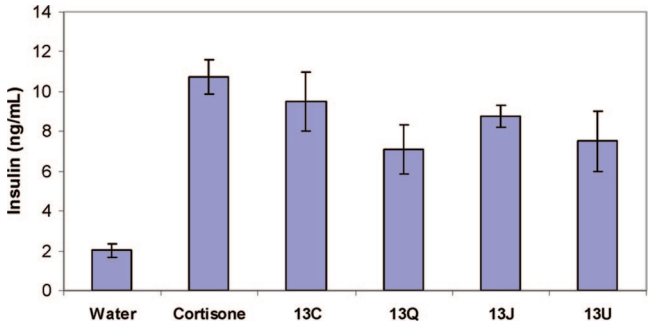


Figure 1. Serum insulin after 7 days of treatment.

induced hyperinsulinemia model. **13q** and **13u** led to decreased insulin levels after 7 days of treatment via oral administration.

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Supporting Information Available: Experimental details for the synthesis and characterization of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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