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Azabicyclic sulfonamides as potent 11β-HSD1 inhibitors ☆

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ABSTRACT

Inhibition of 11β-HSD1 has demonstrated potential in the treatment of various components of metabolic syndrome. We wish to report herein the discovery of novel azabicyclic sulfonamide based 11β-HSD1 inhibitors. Highly potent compounds exhibiting inhibitory activities at both human and mouse 11β-HSD1 were identified. Several compounds demonstrated significant in vivo activity in the mouse cortisone challenge assay.

Glucocorticoids are steroid hormones that regulate glucose metabolism, cardiovascular homeostasis, CNS modulation, inflammation, and immune function.[1] Elevated glucocorticoid levels are associated with obesity, diabetes, hypertension, dyslipidemia, mood disorders, memory impairment, and increased cardiovascular risks.[2,3] Cortisol is an important human glucocorticoid, which upon binding to the glucocorticoid receptor regulates several physiological events.[4] 11β-Hydroxysteroid dehydrogenase (11β-HSD) catalyzes the interconversion of active cortisol and inert cortisone (Fig. 1), thereby protecting the glucocorticoid receptor from glucocorticoid excess.[2] Two isozymes of 11β-HSD have been isolated, each of which influence intracellular glucocorticoid levels.[5] 11β-HSD2 inactivates cortisol (by converting it to inactive cortisone), thereby protecting key tissues. By contrast, 11β-HSD1 regenerates the active cortisol, resulting in enhanced glucocorticoid effects. Consequently, inhibition of 11β-HSD1 is a potential therapeutic target for glucocorticoid-associated metabolic and CNS disorders.[2,6,7] Here we wish to report the discovery of potent 11β-HSD1 inhibitors for the treatment of diabetes, obesity, and related metabolic disorders.

Several classes of 11β-HSD1 inhibitors have been described in the literature for the treatment of metabolic syndrome and other indications.[6,7] Selectivity over 11β-HSD2 is usually not an issue since the amino acid sequence of 11β-HSD1 is approximately 14% identical to that of 11β-HSD2.[8] However, there is a difference in the sequence homology between the human and rodent 11β-HSD1 enzyme, which has presented some difficulties in identifying compounds that are equipotent towards human and rodent 11β-

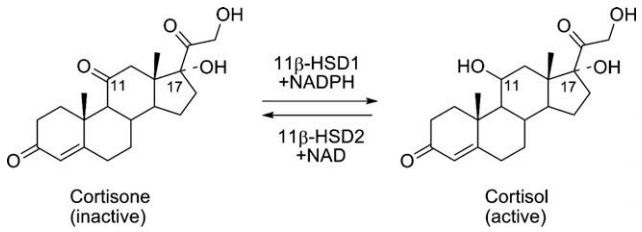

Figure 1. Interconversion of cortisone and cortisol via 11β-HSD1 and 11β-HSD2.

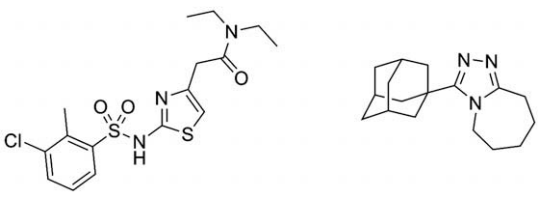

Figure 2. Early prototypical 11β-HSD1 inhibitors.

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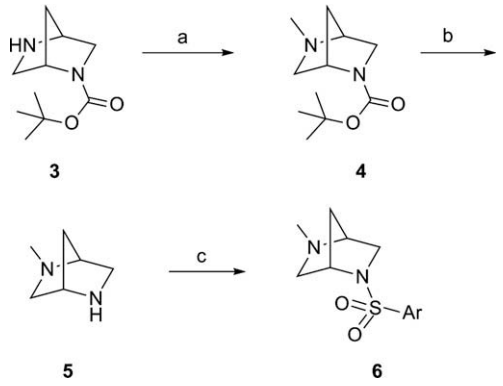
HSD1.[9] Some of the earlier reported 11β-HSD1 inhibitors were thiazole analogs containing an appropriately substituted sulfonamide moiety (e.g., **1**, Fig. 2).[10] Another striking structural feature in several published potent and selective 11β-HSD1 inhibitors was the presence of a lipophilic carbocycle, such as an adamantane group (e.g., **2**, Fig. 2).[7,11] Our plan was to combine these two structural features in a single molecule and towards this rationale we decided to explore azabicyclic sulfonamides containing lipophilic substituents as potential 11β-HSD1 inhibitors.

Our SAR efforts began with the exploration of substituted 2,5-diaza-bicyclo[2.2.1]heptane analogs prepared as shown in Scheme 1. N-Methylation of (1*S*,4*S*)-*tert*-butyl-2,5-diazabicyclo-[2.2.1]heptane-2-carboxylate (**3**) with sodium hydride and iodomethane, followed by deprotection of the *tert*-butylcarbamate group provided the free amine intermediate **5**. Treatment of this intermediate with commercially available arylsulfonyl chlorides in the presence of Hünig's base provided the corresponding 2,5-diaza-bicyclo[2.2.1]heptane based aryl-sulfonamide derivatives. The in vitro human and mouse 11β-HSD1 inhibitory activities are summarized in Table 1.[12] Our earlier SAR from a structurally related series had shown *para*-substitution on the aryl ring to be preferred and the *tert*-butyl group was identified as an optimal group at this position.[13] Incorporating this finding in the 2,5-diaza-bicyclo[2.2.1]heptane series resulted in **7**, which was close to satisfying our criteria of human 11β-HSD1 IC_{50} < 100 nM (**7**: hIC_{50} = 109 nM). This compound also demonstrated promising mouse 11β-HSD1 inhibition in vitro. Replacement of the *tert*-butyl group with other alkyl groups (**8**, **9**) resulted in diminished activity and alkoxy or halogen substitution rendered the compounds (**10**, **11**) close to inactive against 11β-HSD1.

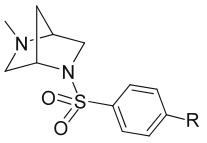
The 4-*tert*-butyl-phenylsulfonyl group was retained as the preferred sulfonamide moiety and further SAR was conducted by exploring substitution at the opposite nitrogen as shown in Scheme 2. Treatment of (1*S*,4*S*)-*tert*-butyl-2,5-diazabicyclo[2.2.1]-heptane-2-carboxylate (**3**) with 4-*tert*-butylbenzene-1-sulfonyl chloride in the presence of Hünig's base provided intermediate **12**. Interestingly, the *tert*-butyl carbamate functionality was tolerated, however the compound was about threefold less potent at human 11β-HSD1 compared to the initial lead **7** (Table 2). Removal of the Boc group resulted in the free amine **13**, which demonstrated a substantial loss in the human 11β-HSD1 activity. To further expand upon our initial plan to incorporate lipophilicity we explored cycloalkyl substituents at this amino position. Reductive alkylation of **13** with cycloalkanones in the presence of sodium triacetoxyborohydride afforded the corresponding 2,5-diazabicyclo[2.2.1]heptane analogs (**14**).

The nor-camphor derived analogs **15** and **16** (stereochemistry not established) demonstrated human and mouse 11β-HSD1

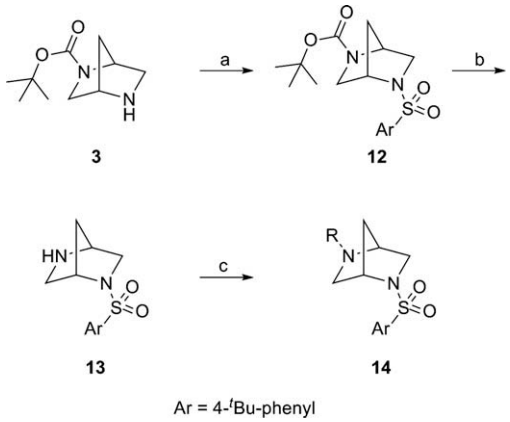


Scheme 1. Synthesis of *N*-methyl-2,5-diaza-bicyclo[2.2.1]heptane based aryl-sulfonamide analogs. Reagents and conditions: (a) 60% NaH, MeI, THF; (b) TFA, CH_2Cl_2; (c) $ArSO_2Cl$, DIPEA, CH_2Cl_2.

Table 1
SAR of *N*-methyl-2,5-diaza-bicyclo[2.2.1]heptane based aryl-sulfonamide analogs as 11β-HSD1 inhibitors

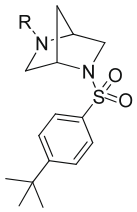


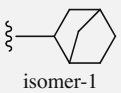
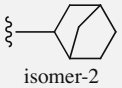
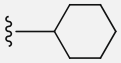
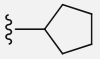
Compound #	R	11β-HSD1 hIC_{50} (μM)	11β-HSD1 mIC_{50} (μM)
7	^{t}Bu	0.11	0.36
8	Neopentyl	0.33	0.26
9	Et	3.30	3.09
10	OMe	16.1	8.88
11	Cl	11.3	12.1



Scheme 2. Synthesis of 2,5-diaza-bicyclo[2.2.1]heptane based sulfonamide analogs containing N-cycloalkyl substituents. Reagents and conditions: (a) $ArSO_2Cl$, DIPEA, CH_2Cl_2, where Ar = 4-^{t}Bu-phenyl; (b) TFA, CH_2Cl_2; (c) sodium triacetoxyborohydride, ketones, dichloroethane, 100 °C.

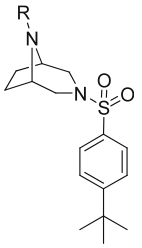
Table 2
SAR of 2,5-diaza-bicyclo[2.2.1]heptane based sulfonamide analogs



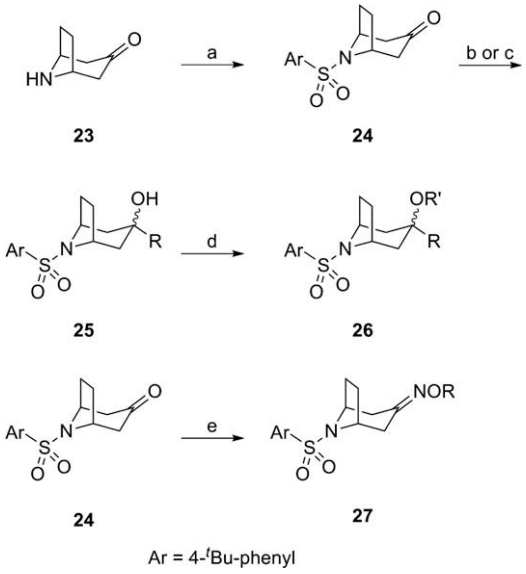
Compound #	–R	11β-HSD1 hIC_{50} (nM)	11β-HSD1 mIC_{50} (nM)
12	COO^{t}Bu	361	772
13	–H	4402	156
15	 isomer-1	75	31
16	 isomer-2	77	8
17		118	79
18		40	1

IC_{50} < 100 nM. While the cyclohexyl analog **17** was somewhat less active, the corresponding cyclopentyl analog **18** was the most promising compound in this series (hIC_{50} = 40 nM, mIC_{50} = 1 nM)

Table 3
SAR of 3,8-diaza-bicyclo[3.2.1]octane based sulfonamide analogs



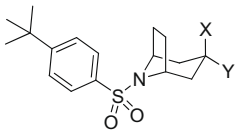
Compound #	–R	11β-HSD1 hIC$_{50}$ (nM)	11β-HSD1 mIC$_{50}$ (nM)
19	–H	547	54
20	–Boc	309	692
21	–Me	478	117
22		137	3



Scheme 3. Synthesis of 8-aza-bicyclo[3.2.1]octane derivatives. Reagents and conditions: (a) $ArSO_2Cl$, DIPEA, CH_2Cl_2, where Ar = 4-^{t}Bu-phenyl; (b) sodium borohydride, methanol; (c) RMgBr, THF or CF_3·TMS, TBAF, THF, 0 °C to rt; (d) NaH, R′I, DMF; (e) NH_2OR·HCl, pyridine.

and was studied in vivo. The in vivo assay was a mouse cortisone challenge in which the animals were orally dosed with a solution of dexamethasone and either the test agent or the vehicle (20% HPβCD). One hour later cortisone was administered (1 mg/kg, sc) and plasma cortisol levels were determined one hour subsequently.[14,15] Unfortunately, the cyclopentyl analog **18** failed to demonstrate in vivo activity, presumably due in part to the susceptibility of unsubstituted cycloalkyl groups to undergo oxidative metabolism.

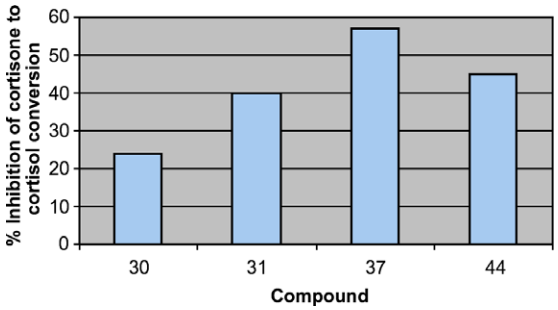
Table 4
SAR of C3 substituted 8-(4-^{t}butylphenylsulfonyl)-8-azabicyclo[3.2.1]octane analogs

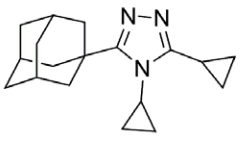


Compound #	–X	–Y	11β-HSD1 hIC$_{50}$ (nM)	11β-HSD1 mIC$_{50}$ (nM)
28	OH (or Ph)	Ph (or OH)	1623	138
29	OH (or Bn)	Bn (or OH)	740	114
30	OH	H	30	28
31	OMe	H	69	8
32	OH	Me	19	41
33	OMe	Me	14	13
34	OH	CF_3	276	3
35	OMe	CF_3	356	32
36	H	OH	970	5
37	H	OMe	37	5
38	H	OEt	114	2
39	CF_3	OH	32	206
40	CF_3	OMe	48	43

Simultaneously we explored 3,8-diaza-bicyclo[3.2.1]octane analogs, which were synthesized in a similar manner as their bicyclo[2.2.1]heptane counterparts. The 4-*tert*-butylphenyl sulfonamide motif was retained and SAR at the opposite nitrogen (Table 3) demonstrated the cyclopentyl group to be the optimal aza-substituent. Although compound **22** exhibited a single digit mIC$_{50}$, the criteria of hIC$_{50}$ < 100 nM was not achieved and hence it was not tested further.

8-Aza-bicyclo[3.2.1]octane analogs were prepared next as shown in Scheme 3. Base mediated sulfonylation of the commercially available (1*R*,5*S*)-8-azabicyclo[3.2.1]octan-3-one with 4-*tert*-butylbenzene-1-sulfonyl chloride provided the sulfonamide intermediate **24**. Using the 4-*tert*-butylphenyl sulfone as the N-capping group, several modifications at the C3 position were explored. The ketone functionality in **24** was subjected to nucleophilic attack resulting in the desired hydroxyl analogs (**25**). Alkylation of **25** in the presence of sodium hydride furnished the corresponding alkoxy derivatives (**26**). Although a clear SAR-trend could not be established (Table 4), it was clear that larger substituents were not tolerated in this region (**28**, **29**). Substitution at this position with a smaller substituent such as a hydroxyl, alkyl, or

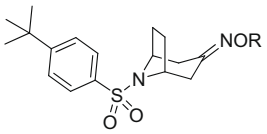




44

Figure 3. Activities of selected 11β-HSD1 inhibitors in an in vivo mouse cortisone challenge assay. Compound **44**, a known 11β-HSD1 inhibitor, was used for comparison.[14,15b]

Table 5
8-(4-^{t}Butylphenylsulfonyl)-8-azabicyclo[3.2.1]octane series: SAR of C3 oxime analogs



Compound #	R	11β-HSD1 hIC_{50} (nM)	11β-HSD1 mIC_{50} (nM)
41	Bn	159	989
42	Me	860	103
43	H	270	47

alkoxy group was found to be more favorable. Several compounds with hIC_{50} < 50 nM and mIC_{50} < 10 nM were identified and a selected few were evaluated in vivo (Fig. 3). The hydroxyl analog **30** demonstrated equipotent human and mouse 11β-HSD1 inhibition in vitro, and showed modest activity in the mouse cortisone challenge assay (24%I @ 30 mpk).[14,15] On the other hand, compounds **31** and **37**, which possessed single digit mIC_{50}, demonstrated better mouse efficacy (40% and 57%I @ 30 mpk, respectively). We also explored selected C3 oxime analogs (**27**, Scheme 3), which demonstrated somewhat diminished 11β-HSD1 inhibition (Table 5).

In summary, potent 11β-HSD1 inhibitors were identified in three azabicyclic sulfonamide series. Several compounds demonstrated significant activity in the mouse cortisone challenge assay. In the bridged piperazine series, **18** was the most promising analog having mouse IC_{50} = 1 nM and human IC_{50} = 40 nM. In the 8-aza-bicyclo[3.2.1]octane series, **37** was the lead compound (hIC_{50} = 37 nM, mIC_{50} = 5 nM), which demonstrated good 11β-HSD1 inhibition in vivo (57%I @ 30 mpk). Further evaluation of these and other related analogs along with additional SAR exploration will be reported in due course.

Acknowledgments

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12. *The in vitro assays were performed under the following conditions:* (a) *Preparation of 11β-HSD1 membranes.* Human and mouse 11β-HSD1 with N-terminal myctag was expressed in Sf9 cells using baculovirus Bac-to-Bac expression system (Invitrogen) according to manufacturer's instructions. Cells were harvested three days after infection and washed in PBS before frozen. To make membranes, the cells were resuspended in buffer A (20 mM Tris–HCl, pH 7.4, 100 mM NaCl, 2 mM EDTA, 2 mM EGTA and Complete™ protease inhibitor tablets (Roche Molecular Biochemicals), and lysed in a nitrogen bomb at 900 psi. The cell lysate was centrifuged at 600 *g* for 10 min to remove nuclei and large cell debris. The supernatant was centrifuged at 100,000 *g* for 1 h. The membrane pellet was resuspended in buffer A, flash-frozen in liquid nitrogen and stored at −70 °C before use. (b) *Measurement of 11β-HSD1 activity*. Human and mouse 11β-HSD1 enzymatic activity was measured in a 50 μL reaction containing 20 mM $NaPO_4$ pH 7.5, 0.1 mM $MgCl_2$, 3 mM NADPH (prepared fresh daily), 125 nM ^{3}H-cortisone (American Radiochemicals) and 0.5 μg membrane. The reaction was incubated at room temperature for 1 h before it was stopped by addition of 50 μM buffer containing 20 mM $NaPO_4$ pH 7.5, 30 μM 18β-glycyrrhetinic acid, 1 μg/ml monoclonal anti-cortisol antibody (Biosource) and 2 mg/ml antimouse antibody coated scintillation proximity assay (SPA) beads (Amersham Bioscience). The mixture was incubated at room temperature for 2 h with vigorous shaking and analyzed on a Top Count scintillation counter.
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