Bioorganic & Medicinal Chemistry Letters 19 (2009) 4563–4565

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

The discovery of azepane sulfonamides as potent 11β-HSD1 inhibitors

Santhosh F. Neelamkavil *, Craig D. Boyle, Samuel Chackalamannil, William J. Greenlee, Lili Zhang, Giuseppe Terracina

Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033, USA

ARTICLE INFO

Article history:
Received 6 March 2009
Revised 23 June 2009
Accepted 2 July 2009
Available online 8 July 2009

Keywords:
11β-HSD1
11β-HSD2
Diabetes
Obesity
Cortisol
Cortisone
Azepine sulfonamides

ABSTRACT

Discovery of a series of azepine sulfonamides as potent inhibitors of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) is described. SAR studies at the 4-position of the azepane ring have resulted in the discovery of a very potent compound **30** which has an 11β-HSD1 IC_{50} of 3.0 nM.

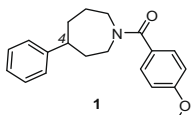
Glucocorticoids are involved in many physiological functions from fetal development to carbohydrate metabolism and anti-inflammatory responses.[1] Cortisol is the most prevalent glucocorticoid in human, and in rodent, the equivalent of cortisol is corticosterone.[2] Under physiologic conditions, 11β-HSD1 (11β-hydroxysteroid dehydrogenase type 1) functions as a reductase that converts inactive cortisone to active cortisol.[3] 11β-HSD2,[4] on the other hand, catalyzes the dehydrogenase reaction of converting cortisol to cortisone, a process essential for protecting mineralocorticoid receptors from excess cortisol. Although 11β-HSD1 and 11β-HSD2 are isozymes in terms of their biologic functions, they share only 16% sequence homology.[5] This structural diversity should provide potential to develop 11β-HSD1 selective inhibitors.

11β-HSD1 is a 288 amino acid single transmembrane domain protein which localizes to the endoplasmic reticulum.[6] It has been shown that genetic deletion of 11β-HSD1 lowers plasma glucose levels in mice fed on high-fat diets and attenuates the activation of enzymes involved in hepatic gluconeogenesis,[7] suggesting that inhibitors of this enzyme may be of therapeutic use in various metabolic disorders such as diabetes, obesity and hypertension.[8]

In the last several years, considerable interest has been generated by the pharmaceutical industry on 11β-HSD1 as a therapeutic target for diabetes and obesity.[9] This can be witnessed by a multitude of patents that have been published recently in this area.[10] In this Letter we describe our efforts to develop potent and selective 11β-HSD1 inhibitors for the treatment of diabetes, obesity and other metabolic disorders.

Our efforts in this program started with the identification of compound **1** (human 11β-HSD1 IC_{50} = 111 nM) from a high throughput screening of our internal compound collection. This was an attractive lead, and other laboratories have also explored related benzamides as 11β-HSD1 inhibitors.[11] Thus we decided to investigate the potential of sulfonamides as possible amide surrogates with the azepane core of lead **1** (Fig. 1). We also introduced a double bond at the 4-position to examine whether reduced rotation of the phenyl group would improve upon activity. The synthesis of this series of targets is summarized in Scheme 1.

The reaction of commercially available ethyl 4-oxopiperidine-1-carboxylate (**2**) with $BF_3{\cdot}Et_2O$ and ethyl diazoacetate resulted in a facile ring expansion to provide the azepane ring β-keto ester (**3**).[12] This was then decarboxylated under standard conditions followed by the addition of phenyl lithium at −78 °C to give the tertiary alcohol **5**. The ethyl carbamate protecting group was



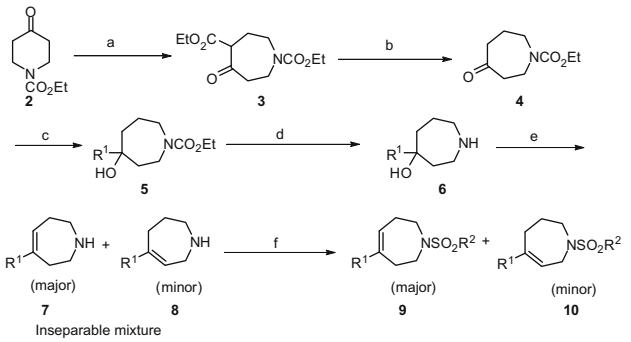
1

h 11β-HSD1 IC_{50} = 111 nM
m 11β-HSD1 IC_{50} = 9 μM

Figure 1. Lead compound 4-phenylazepane amide **1**.

* Corresponding author. Tel.: +1 908 740 3717; fax: +1 908 740 7164.
E-mail address: santhosh.neelamkavil@spcorp.com (S.F. Neelamkavil).

0960-894X/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2009.07.003



Scheme 1. Synthesis of phenyl-tetrahydroazepine sulfonamides. Reagents and conditions: (a) $N_2CH_2CO_2Et$, $BF_3{\cdot}Et_2O$, Et_2O, −25 °C to rt, 82%; (b) 4 N KOH, EtOH, 56%; (c) R^1Li, THF, −78 °C to rt; (d) N_2H_4, 50% KOH, EtOH, reflux; (e) AcOH, concd HCl, 120 °C, 4 h; (f) R^2SO_2Cl, DIEA, CH_2Cl_2, rt.

reductively removed by refluxing with hydrazine in the presence of 50% KOH to provide the free amine **6**.[13] It was observed that excess phenyl lithium could also result in the removal of the ethyl carbamate.

Compound **6** was then subjected to refluxing conditions with concentrated HCl and glacial acetic acid to provide olefins **7** and **8** as an inseparable mixture. This mixture of olefins was taken directly and treated with various *para*-substituted aryl sulfonamides to give **9** (major isomer) and **10** (minor isomer). Gratifyingly the major and minor isomers could be separated after this reaction.[14] The SAR of the promising sulfonamides obtained are shown in Tables 1 and 2.

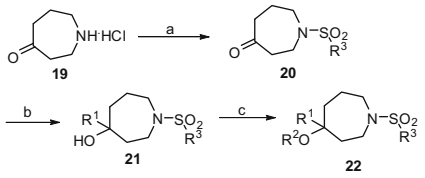
Compound **11** with a 4-methoxyphenyl sulfonamide was the best inhibitor in this series and was twofold more potent than the azepane lead **1**. However the mouse IC_{50} of this compound was ~32-fold lower. The *p*-(*t*-butyl)-phenylsulfonamide **12** had improved affinity for the human 11β-HSD1 receptor with comparatively less separation of affinity for the mouse receptor (~13-fold). We also noticed that sulfonamides derived from the major olefin isomer **9** were more active than those from the minor isomer **10** (**13** vs **16**, **11** vs **17**, **12** vs **18**; Tables 1 and 2).

It is to be noted that the difference between human and mouse IC_{50} values for our compounds is consistent with the fact that the mouse shares only ~80% homology with the human enzyme.[5,16] Another key issue that we encountered in the above series was a lack of good solubility. This was a major concern in getting reliable pharmacokinetic data on these compounds.

To address the solubility concerns we decided to explore compounds with a hydroxy group at the 4-position of the azepane ring which were precursors to the olefins described above. Thus azepan-4-one **19** was treated with the appropriate sulfonyl chloride in the presence of base, followed by the addition of alkyl or aryl lithium at −78 °C to provide the tertiary alcohols **21** (Scheme 2).

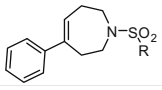
The effects of aryl substitution in the sulfonamide region of the 4-hydroxy azepine compounds are shown in Table 3. We had observed previously that *para*-substitution was optimal and thus confined our SAR efforts in this series to several *para*-substituted aryl sulfonamides. Limited examples from this SAR study are shown in Table 3. *p*-(*t*-Butyl)-phenylsulfonamide (**23**) was the best substituent in this series and was found to be a preferred group in all other series.

Next we explored substituent effects at the 4-position of azepan-4-ol *p*-(*t*-butyl)-phenylsulfonamides (Table 4). Towards this



Scheme 2. Synthesis of 4-alkoxy substituted azepane sulfonamides. Reagents and conditions: (a) R^3SO_2Cl, DIEA, CH_2Cl_2, rt; (b) R^1Li, THF, 0 °C to rt; (c) NaH, R^2I, DMF, rt.

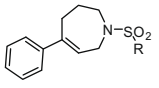
Table 1
11β-HSD1 inhibition for 4-phenyl-tetrahydroazepine sulfonamides



Compounds	R	11β-HSD1 hIC_{50}[a] (nM)	11β-HSD1 mIC_{50}[a] (nM)
11	4-MeO–Ph	58	1876
12	4-*t*-Bu–Ph	68	905
13	4-Me–Ph	76	1551
14	4-Et–Ph	97	1242
15	2,4-Dichloro-Ph	994	1277

[a] hIC_{50} = human IC_{50}, mIC_{50} = mouse IC_{50}.[15]

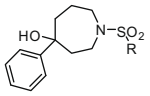
Table 2
11β-HSD1 inhibition for 5-phenyl-tetrahydroazepine sulfonamides



Compounds	R	11β-HSD1 hIC_{50}[a] (nM)	11β-HSD1 mIC_{50}[a] (nM)
16	4-Me–Ph	124	1511
17	4-MeO–Ph	178	1553
18	4-*t*-Bu–Ph	358	1648

[a] hIC_{50} = human IC_{50}, mIC_{50} = mouse IC_{50}.[15]

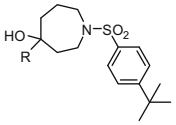
Table 3
11β-HSD1 inhibition for 4-phenylazepan-4-ol sulfonamides



Compounds	R	11β-HSD1 hIC_{50}[a] (nM)	11β-HSD1 mIC_{50}[a] (nM)
23	4-*t*-Bu–Ph	307	860
24	4-Et–Ph	493	1406
25	4-Cl–Ph	1069	2721
26	4-MeO–Ph	1315	1981

[a] hIC_{50} = human IC_{50}, mIC_{50} = mouse IC_{50}.[15]

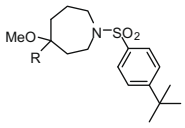
Table 4
11β-HSD1 inhibition for azepan-4-ol sulfonamides



Compounds	R	11β-HSD1 hIC_{50}[a] (nM)	11β-HSD1 mIC_{50}[a] (nM)
27	Me	5	35
28	Cyclopropyl	12	115
23	Ph	307	860
29	H	466	629

[a] hIC_{50} = human IC_{50}, mIC_{50} = mouse IC_{50}.[15]

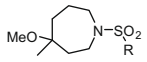
Table 5
11β-HSD1 inhibition for 4-methoxyazepane sulfonamides

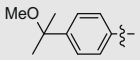
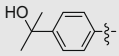


Compounds	R	11β-HSD1 hIC_{50}[a] (nM)	11β-HSD1 mIC_{50}[a] (nM)
30	Me	3	57
31	H	7	165
32	Cyclopropyl	43	328
33	Ph	110	210

[a] hIC_{50} = human IC_{50}, mIC_{50} = mouse IC_{50}.[15]

Table 6
11β-HSD1 inhibition for 4-methoxy-4-methylazepane sulfonamides



Compounds	R	11β-HSD1 hIC_{50}[a] (nM)	11β-HSD1 mIC_{50}[a] (nM)
30	4-*t*-Bu–Ph	3	57
34		20	229
35		113	656

[a] hIC_{50} = human IC_{50}, mIC_{50} = mouse IC_{50}.[15]

end, we introduced different alkyl and aryl groups at the 4-position of the azepane ring.

We were very pleased to identify compound **27** which had a human 11β-HSD1 IC_{50} of 5 nM (Table 4).[17] We quickly realized that there was only a very small window for the R group in this structure, as simple H (**29**) or a bulkier phenyl group (**23**) resulted in significant loss in potency. A small change from methyl (**27**) to cyclopropyl (**28**) led to a twofold loss in potency.

To further examine the contribution from the hydroxy group to potency, we alkylated the tertiary alcohol at the 4-position with methyl iodide and several R groups were again explored. As shown in Table 5 the SAR data showed that the free (**27**) as well as methylated (**30**) tertiary hydroxy groups had comparable potency, which seems to indicate the absence of a hydrogen bond donation to binding. It is also interesting to note that methylating the secondary hydroxyl compound **29** resulted in compound **31** which had a significantly increased potency.

We were pleased that our SAR efforts at the 4-position resulted in the discovery of a compound **30** which was ~35 times more potent than our initial lead **1**. Importantly the compounds shown in Tables 4 and 5 also were 10–20 times more soluble than our earlier compounds (Tables 1 and 2) based on kinetic solubility measurements.[18] Finally, to incorporate additional solubility elements on **30**, we introduced hydroxy groups at the *t*-butyl site and synthesized compounds **34** and **35**. However this resulted in a significant loss in potency as shown in Table 6.

In conclusion, SAR studies of several novel azepane sulfonamides have resulted in the identification of several potent inhibitors of 11β-HSD1. The most potent compound **30** has a human IC_{50} of 3 nM. *p*-(*t*-Butyl)-phenylsulfonamide has been found to be a preferred group in a wide array of compounds. We believe that these compounds which are more potent and have increased solubility compared to our initial series have the potential for good pharmacokinetics and in vivo activity in 11β-HSD1 models. Further optimization of this series and SAR of structurally related compounds will be reported in due course.

Acknowledgements

We thank Drs. John Piwinski, Michael Graziano and Catherine Strader for helpful discussions. We thank Dr. Pradip Das for obtaining analytical data. We also thank Dr. Charles McNemar, Ashwin Ranchod and Dr. William Windsor for solubility measurements.

References and notes

1. Brian, R. W. *Eur. J. Endocrinol.* **2007**, *157*, 545.
2. Chrousos, G. P. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 6329.
3. Boyle, C. D.; Kowalski, T. J.; Zhang, L. *Annu. Rep. Med. Chem.* **2006**, *41*, 127.
4. Morton, N. M.; Paterson, J. M.; Masuzaki, H.; Holmes, M. C.; Staels, B.; Fievet, C.; Walker, B. R.; Flier, J. S.; Mullins, J. J.; Seckl, J. R. *Diabetes* **2004**, *53*, 931.
5. Barf, T. *Mini-Rev. Med. Chem.* **2004**, *4*, 897.
6. Seckl, J. R. *Curr. Opin. Pharm.* **2004**, *4*, 597.
7. Kotelevtsev, Y.; Holmes, M. C.; Burchell, A.; Houston, P. M.; Schmoll, D.; Jamieson, P. M.; Best, R.; Brown, R.; Edwards, C. R. W.; Seckl, J. R.; Mullins, J. J. *Proc. Natl. Acad. Sci. U.S.A.* **1997**, *94*, 14924.
8. Putignano, P.; Giraldi, F. P.; Cavagnini, F. *J. Endocrinol. Invest.* **2004**, *27*, 969.
9. Boyle, C. D. *Curr. Opin. Drug Discovery Dev.* **2008**, *11*, 495.
10. Webster, S. P.; Pallin, T. D. *Expert Opin. Ther. Pat.* **2007**, *17*, 1407.
11. Richards, S.; Sorensen, B.; Jae, H. S.; Winn, M.; Chen, Y.; Wang, J.; Fung, S.; Monzon, K.; Frevert, E. U.; Jacobson, P.; Sham, H.; Link, J. T. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 6241. and references cited therein.
12. Finney, Z. G.; Riley, T. N. *J. Med. Chem.* **1980**, *23*, 895.
13. Lyles-Eggleston, M.; Altundas, R.; Xia, J.; Sikazwe, D. M. N.; Fan, P.; Yang, Q.; Li, S.; Zhang, W.; Zhu, X.; Schmidt, A. W.; Vanase-Frawley, M.; Shrihkande, A.; Villalobos, A.; Borne, R. F.; Ablordeppey, S. Y. *J. Med. Chem.* **2004**, *47*, 497.
14. Isomers **9** and **10** were separated by silica gel chromatography with 40% hexanes/ethyl acetate as the eluent system.
15. The following are the conditions used for the 11β-HSD1 binding assays: (a) *Preparation of 11β-HSD1 membranes*. Human 11β-HSD1 with N-terminal myc tag 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*. 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 anti-mouse 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 TopCount scintillation counter.
16. The lower activity in the mouse assay as compared to human makes it challenging to predict human efficacy based on a rodent in vivo model.
17. Representative compounds **27** and **31** showed <10% inhibition in an 11β-HSD2 assay at a concentration of 50 μM implying that these compounds are highly selective inhibitors of 11β-HSD1.
18. *Kinetic solubility of selected compounds*: (**12** = 10 μM, **27** = 200 μM, **23** = 100 μM, **31** = 100 μM). The nephelometric (light scattering) method was used to determine the kinetic solubility of compounds. The test compound (1.0 mg) was dissolved in DMSO at 25 mM. A serial dilution into DMSO was performed and 3 μl of the compound in DMSO at various concentrations was added to the buffer (10 mM phosphate, pH 7.4). Presence of precipitate was detected by nephelometry. Solubility was defined as the highest concentration of material that did not scatter light. Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. *Adv. Drug Delivery Rev.* **2001**, *46*, 3.