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Bioorganic & Medicinal Chemistry Letters 18 (2008) 3168–3172
Bioorganic & Medicinal Chemistry Letters

Pyridine amides as potent and selective inhibitors of 11β-hydroxysteroid dehydrogenase type 1

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Received 8 March 2008; revised 18 April 2008; accepted 28 April 2008
Available online 1 May 2008

Abstract—Several series of pyridine amides were identified as selective and potent 11β-HSD1 inhibitors. The most potent inhibitors feature 2,6- or 3,5-disubstitution on the pyridine core. Various linkers (CH_2SO_2, CH_2S, CH_2O, S, O, N, bond) between the distal aryl and central pyridyl groups are tolerated, and lipophilic amide groups are generally favored. On the distal aryl group, a number of substitutions are well tolerated. A crystal structure was obtained for a complex between 11β-HSD1 and the most potent inhibitor in this series.

The enzyme 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) catalyzes the interconversion of inactive cortisone to the active steroid cortisol, which is the principal circulating glucocorticoid in humans.[1] This enzyme is expressed in several tissues, such as liver, adipose, and central nervous system.[2] Excess glucocorticoids account for increased glucose output in the liver, dampened glucose-dependent insulin sensitivity in the adipose tissue, and reduced insulin secretion from the pancreas. Due to the close relationship between glucocorticoids and metabolic disease risk factors, tissue specific 11β-HSD1 inhibition has gained attention as a potentially effective method for treating the metabolic syndrome, including type 2 diabetes.[3] This idea has been supported by several model studies in animals. For example, 11β-HSD1 knockout mice are resistant to diet induced obesity and glucose intolerance,[4] while transgenic mice that overexpress 11β-HSD1 in adipose exhibit a phenotype characterized by metabolic dysregulation, including obesity, insulin resistance, glucose intolerance, and hyperglycemia.[5]

A second isoform of this enzyme, 11β-HSD2, catalyzes the reverse reaction, the conversion of cortisol to its inactive keto form, cortisone. This enzyme is mainly expressed in kidney, gut, and placenta, where it acts to prevent cortisol from stimulating the mineralocorticoid receptor.[6] It is thus important that inhibitors of 11β-HSD1 do not significantly inhibit 11β-HSD2 in order to avoid undesirable sodium retention, hypokalemia, and hypertension.

Following the publication of arylsulfonamidothiazole 11β-HSD1 inhibitors,[7] several other series have appeared in the literature. [8] Herein we describe the synthesis and SAR of pyridine amides as potent and selective 11β-HSD1 inhibitors, using a homogeneous Scintillation Proximity Assay (SPA) for in vitro screening in a high-throughput 96-well plate format.[9]

Benzamide **1** (Fig. 1, human 11β-HSD1 IC_{50} = 235 nM) was first identified through directed screening of our

Keywords: 11β-Hydroxysteroid dehydrogenase type 1; 11β-HSD1; Pyridine amide.
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doi:10.1016/j.bmcl.2008.04.069

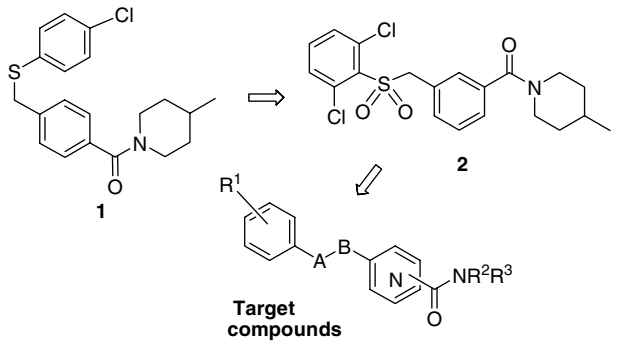
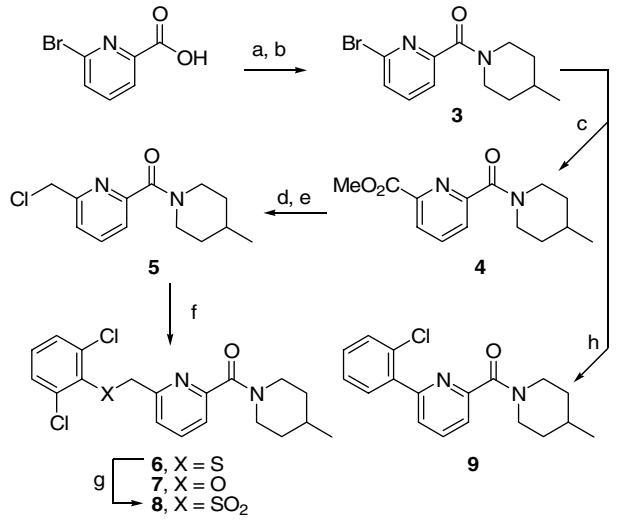


Fig. 1. Evolutionary path from screening lead **1** to pyridine amides.

internal compound collection. A quick survey of different linkers between the two aryl groups and various regioisomeric arrangements of **1** resulted in identification of sulfone **2** (IC_{50} = 13 nM), which exhibits an approximately 20-fold improvement in potency. To improve biological potency and increase structural diversity, analogues featuring pyridyl rings in place of the central phenyl ring and various linkers (A–B) between the two aryl groups were synthesized and evaluated.

The synthetic route to pyridine amide derivatives featuring a two-atom arene linker begins with conversion of the commercially available 6-bromopicolinic acid to the corresponding amide **3** via the acid chloride (Scheme 1). Subsequent catalytic carbonylation followed by $NaBH_4$ reduction yielded the alcohol, which was reacted with $SOCl_2$ to form intermediate chloride **5**. Alkylation with either thiophenoxide or phenoxide gave the corresponding thioether **6** or the ether analog **7**, respectively. The thioether **6** was then oxidized to the corresponding sulfone **8** using in situ generated *p*-toluenesulfonic peracid, a modified literature procedure, which does not affect the nitrogen of the pyridine ring.[10] The bisaryl analogue **9** was prepared through Suzuki coupling of 2-chlorophenylboronic acid and bromopyridine derivative **3**. The related regioisomers and analogues of compounds **6**–**9** were prepared by analogous routes.

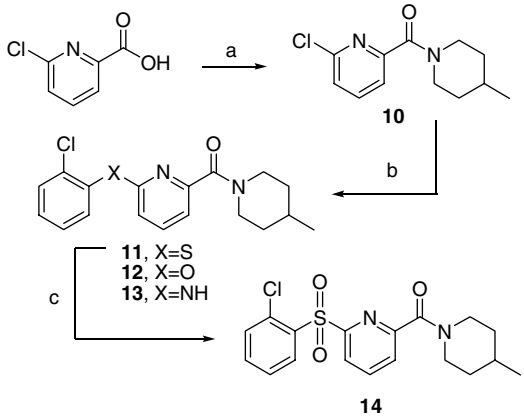


Scheme 1. Reagents and conditions: (a) $SOCl_2$; (b) 4-methlylpiperidine, rt, CH_2Cl_2, 2-step: 95%; (c) $Pd(OAc)_2$, DPPP, DBU, CO, MeOH/DMF, 85 °C, 91%; (d) $NaBH_4$, EtOH, rt, 59%; (e) $SOCl_2$, CH_2Cl_2, rt, quantitative; (f) Cs_2CO_3, DMF, 60 °C, X=S, 2,6-dichlorobenzenethiol, 98%; X=O, 2,6-dichlorophenol, 90%; (g) 1-tosyl-1*H*-imidazole, H_2O_2, NaOH, THF/MeOH/H_2O, rt, 94%; (h) 2-chlorophenylboronic acid, $Pd(PPh_3)_4$, Na_2CO_3, toluene/EtOH/H_2O, 80 °C, 49%.

Analogues **11**–**14**, which feature a one-atom linker, were accessed through 6-chloropicolinic amide **10**, which was reacted with sulfur, oxygen, or nitrogen nucleophiles under microwave irradiation to form the biaryl thioether **11**, ether **12**, or aniline **13**, respectively (Scheme 2). The biaryl sulfone analogue **14** was prepared via oxidation of thioether **11**.

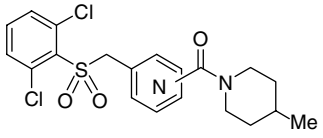
A systematic evaluation of arylsulfonylmethylpyridyl amides incorporating the 6 possible positional isomers **8**, **15**–**19** was undertaken (Table 1). Two of the four 'V-shaped' isomers (i.e., 2,6- and 3,5-di-substituted pyridyl amides **8** and **15**) exhibited the greatest potency, while the two linear isomers **18** and **19** exhibited the weakest in vitro potency in this set. This is consistent with the SAR in a benzamide series, where the *meta*-substituted regioisomers have greater potency than their corresponding *para*-substituted analogues (unpublished results).

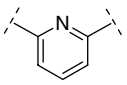
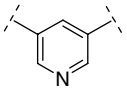
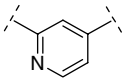
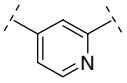
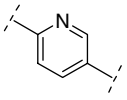
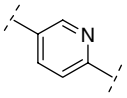
The effects of different amide groups on 11β-HSD1 activity were evaluated using a series of 3,5-disubstituted derivatives analogous to **15**, one of the two best templates from the initial SAR study. The pyrrolidine amide **20** was a significantly weaker inhibitor, though increasing the lipophilic bulk steadily improved potency (Table 2). The 9-membered ring analogue **23** is 800-fold more potent than pyrrolidine amide **20**. On the other hand, incorporating polar groups greatly decreased activity. Replacing the methyl group in **15** with a primary amide moiety as in **25** results in 100-fold loss in potency. The inhibitory effect of morpholine amide **26** is minimal.



Scheme 2. Reagents and conditions: (a) 4-methyl piperidine, HOAT, EDAC, DMAP, CH_2Cl_2, rt, 88%; (b) Cs_2CO_3, DMF, microwave, 200 °C, X=S, 2-chlorothiolphenol, 81%; X=O, 2-chlorophenol, 32%; X=N, 2-chloroaniline, 12%; (c) 1-tosyl-1*H*-imidazole, H_2O_2, NaOH, THF/MeOH/H_2O, 0 °C–rt, 36%.

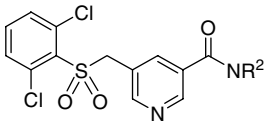
Table 1. SAR on the central pyridine core—regioisomers



Compound	Core	IC_{50}[a] (nM)
8		35
15		22
16		106
17		319
18		2050
19		2130

[a] IC_{50}'s refer to biochemical human 11β-HSD1 assay data.

Table 2. Variation of amides



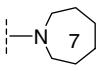
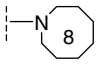
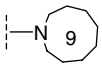
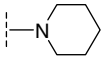
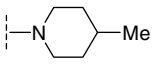
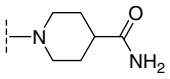
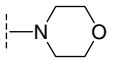
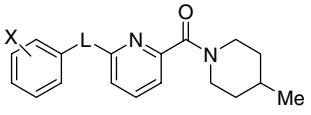
Compound	NR^2	IC_{50} (nM)
20		2140
21		21
22		11
23		2.5
24		220
15		22
25		2350
26		$>10^4$

Table 3. Variation of linkers



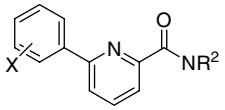
Compound	L	X	IC_{50} (nM)
6	SCH_2	2,6-di-Cl	7.2
8	SO_2CH_2	26-di-Cl	35
7	OCH_2	2,6-di-Cl	79
11	S	2-Cl	218
12	O	2-Cl	282
13	NH	2-Cl	381
14	SO_2	2-Cl	4670
9	bond	2-Cl	17

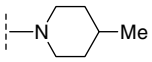
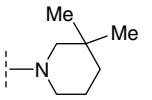
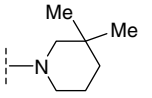
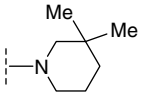
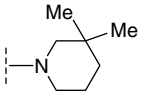
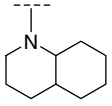
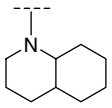
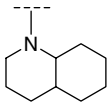
A study of the 11β-HSD1 inhibitory effects with respect to linkers was conducted in the 2,6-disubstituted pyridine manifold, which was another potent scaffold (Table 3). Thiomethyl ether **6** was 5-fold more potent than sulfonylmethyl analogue **8**, while the corresponding ether analogue **7** was slightly less active. Due to the relative ease of synthesis and similar potencies, the subsequent linker study focused on utilization of the 2-chlorophenyl group instead of the 2,6-dichlorophenyl group. Analogues with single heteroatom linkers (**11**–**13**) are only modestly active, while the strongly electron withdrawing sulfonyl linkage in **14** was detrimental to 11β-HSD1 potency. The biaryl analogue (**9**) exhibited potency comparable to the two-atom linked derivatives. Additional analogues featuring this linkage were prepared and evaluated (Table 4).

Consistent with previous observations, when 4-methylpiperidyl amide **9** was replaced with the more lipophilic 3,3-dimethylpiperidyl amide group (**27**), the potency increased 5-fold. Modifications on the distal aryl group yielded highly potent compounds, including several *para*-substituted analogues such as compounds **28**–**29**. The 3,4-disubstituted compound **30** was the most potent inhibitor in this series (IC_{50} = 0.1 nM). With a decahydroquinolinyl amide group, analogues bearing strongly electron deficient moieties such as 2-NO_2Ph (**31**) and 4-CF_3Ph (**32**) as well as the bulky biphenyl group (**33**) were prepared and tested. All these groups appeared to be well tolerated, exhibiting IC_{50}'s in the single digit nanomolar range.

A crystal structure of a complex between 11β-HSD1 and compound **30** was obtained (Fig. 2).[11] The crystal structure shows that the amide carbonyl oxygen is within hydrogen bonding distance to two active site residues, Ser170 and Tyr183. Compound **30** also forms a number of favorable hydrophobic interactions with the protein. The dimethylpiperidyl moiety is buried deep in the bind-

Table 4. Variation of aryl and amide groups



Compound	X	NR^2	IC_{50} (nM)
9	2-Cl		17
27	2-Cl		2.9
28	4-Cl		1.1
29	4-OCF_3		1.1
30	3-F,4-Me		0.1
31	2-NO_2		2.0
32	4-CF_3		3.6
33	2-Ph		4.7

ing pocket, and interacts with the side chains of Thr124 and several other amino acid residues.[11] The central pyridyl core interacts with both the side chain and backbone of Tyr177. The 3-fluoro-4-methylphenyl moiety is closest to the entrance to the pocket and it also interacts with the side chain of Tyr177, albeit from a different angle.

Novel 11β-HSD1 inhibitors with single digit nanomolar IC_{50}'s were identified in three distinct series: arylsulfonylmethyl pyridyl amides (e.g., **23**), arylthiomethyl pyridyl amides (e.g., **6**), and biaryl amides (e.g. **27**–**33**). However, further potency improvement was still desired for another series of interest, the arylbenzyl ethers. Several combinatorial libraries featuring ether linkages were prepared and tested, and some selected compounds from these efforts are listed in Table 5. Modifications on the aryl and amide groups led to a variety of active compounds featuring both 3,5- and 2,6-disubstituted pyridine analogues (**34**–**37**).

Through an extensive SAR study on various regions of the pyridine amide structure, a series of potent and selective 11β-HSD1 inhibitors that exhibit potency in the single digit nanomolar IC_{50} range have been identified. Among the various pyridyl regioisomers, 2,6- or 3,5-disubstituted analogues exhibit the greatest potency. Between the central pyridyl and distal aryl groups, multiple linkers appear well tolerated and lipophilic amide groups are favored. The results from further studies will be reported in due course.

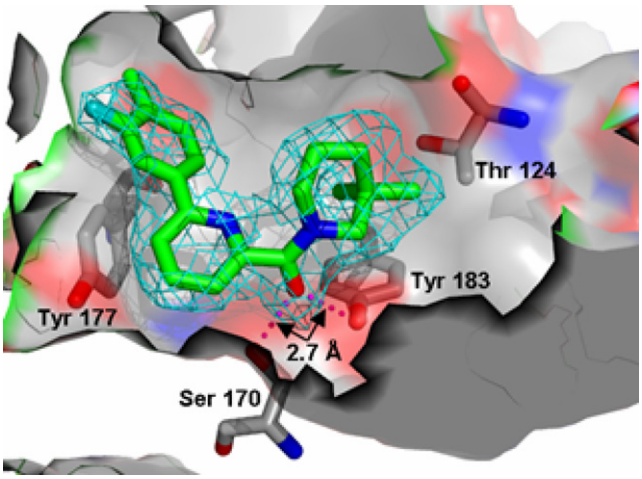
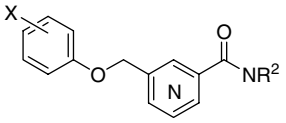
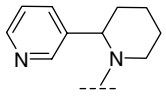
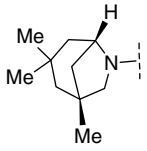
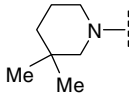
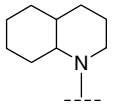


Fig. 2. Crystal structure of compound **30** complexed with human 11β-HSD1 and cofactor NADP. For clarity, the NADP has been omitted from this representation, and only a few of the surrounding residues are included in the figure, although the entire surface in the vicinity is included. Color-coding: carbon—gray (11β-HSD1); green (compound **30**), nitrogen—blue, oxygen—red, and fluorine—cyan. Initial Fo–Fc density contoured at 3σ is shown in cyan. Hydrogen bonds are shown as small magenta spheres. This crystal form contains four 11β-HSD1 monomers per asymmetric unit and in two of them the 3-fluoro-4-methylphenyl group is flipped 180° relative to the orientation shown here. This figure was created with PyMol.[12]

Table 5. Potent inhibitors in the arylbenzyl ether amide chemotype



Compound	X	py Core	NR^2	IC_{50} (nM)
34	2,6-di-Cl	3,5		2.0
35	2,6-di-Cl	3,5		1.7
36	2,4,6-tri-Cl	2,6		6.5
37	2,6-di-Cl	2,6		4.6

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9. (a) 11β-HSD1 microsomes isolated from HEK 293 cells over-expressing human 11β-HSD1 were incubated with the substrate cortisone and cofactor NADPH at room temperature. The reactions were terminated with the addition of a nonspecific 11β-HSD1 inhibitor (18β-glycyrrhetinic acid). The product cortisol was quantified in an immuno-competition SPA wherein the [^{3}H]-cortisol bound to anti-rabbit antibody Yitrium silicate SPA beads coated with polyclonal anti-cortisol antibody was competed by cortisol produced in the reaction, and the reaction mixture was read in a scintillation plate reader (TopCount). The amount of cortisol was determined from a cortisol standard curve; (b) To ensure that compounds were selective for 11β-HSD1 versus 11β-HSD2, all active inhibitors of interest (11β-HSD1 $IC_{50} < 100$ nM) were counter-screened in an in vitro 11β-HSD2 assay. Human in vitro 11β-HSD2 activity was assayed by incubating cortisol (100 nM) and NAD (1 μM) with human 11β-HSD2 microsomes and measuring the product cortisone formed in the reaction by LC/MS/MS analysis. None of the compounds in this series showed significant inhibition of 11β-HSD2 at 10 μM.
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11. PDB Deposition number is 3CH6. The dimethylpiperidinyl moiety also interacts with the side chains of Ile121, Tyr183, Val227, and the nicotinamide moiety of NADP. The central pyridinyl moiety interacts with Tyr177 side chain and the main chain in the vicinity of Gly216 and Leu217. Besides Tyr177, the 3-fluoro-4-methylphenyl moiety interacts with the side chains of Leu126, Met179, Val231, and Tyr284 from the other chain of the 11β-HSD1 dimer.
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