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N-(Pyridin-2-yl) arylsulfonamide inhibitors of 11β-hydroxysteroid dehydrogenase type 1: Discovery of PF-915275

Michael Siu [a,*], Theodore O. Johnson [a], Yong Wang [a], Sajiv K. Nair [a], Wendy D. Taylor [a], Stephan J. Cripps [a], Jean J. Matthews [a], Martin P. Edwards [a], Thomas A. Pauly [b], Jacques Ermolieff [c], Arturo Castro [c], Natilie A. Hosea [d], Amy LaPaglia [d], Andrea N. Fanjul [e], Jennifer E. Vogel [e]

[a] *Discovery Chemistry, Pfizer Global Research and Development, 10770 Science Center Drive, San Diego, CA 92121, United States*
[b] *Structural and Computational Biology and Design, Pfizer Global Research and Development, 10770 Science Center Drive, San Diego, CA 92121, United States*
[c] *Biochemical Pharmacology, Pfizer Global Research and Development, 10770 Science Center Drive, San Diego, CA 92121, United States*
[d] *Pharmacokinetics, Dynamics, and Metabolism, Pfizer Global Research and Development, 10770 Science Center Drive, San Diego, CA 92121, United States*
[e] *Diabetes Biology, Pfizer Global Research and Development, 10770 Science Center Drive, San Diego, CA 92121, United States*

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ABSTRACT

N-(Pyridin-2-yl) arylsulfonamides are identified as inhibitors of 11β-hydroxysteroid dehydrogenase type 1 (11βHSD1), an enzyme that catalyzes the reduction of the glucocorticoid cortisone to cortisol. Dysregulation of glucocorticoids has been implicated in the pathogenesis of diabetes and the metabolic syndrome. In this Letter, we present the development of an initial lead to an efficient ligand with improved physiochemical properties using a deletion strategy. This strategy allowed for further optimization of potency leading to the discovery of the clinical candidate PF-915275.

11β-Hydroxysteroid dehydrogenase type 1 (11βHSD1), a short chain reductase expressed mainly in the adipose and the liver, catalyzes the reduction of the inactive glucocorticoid cortisone to the active glucocorticoid cortisol using the cofactor NADPH (Fig. 1). Dysregulation of glucocorticoids in the liver and adipose has been implicated in the pathogenesis of diabetes and the metabolic syndrome.[1] Cortisol is involved in metabolic and homeostatic pathways, one of which is gluconeogenesis in the liver. In non-insulin dependent diabetes mellitus, gluconeogenesis can contribute up to 90% of the increase in overall hepatic glucose production.[2] The type 2 isoform, 11β-hydroxysteroid dehydrogenase type 2 (11βHSD2), is expressed mainly in the kidney and catalyzes the reverse reaction (oxidation of cortisol to cortisone) to prevent activation of the mineralcorticoid receptor by cortisol. Interest in the inhibition of 11βHSD1 has emerged because of the potential to control cortisol concentrations in the liver and adipose without affecting systemic circulating concentrations. In 2002 Barf et al. reported 2-aminothiazole sulfonamides as the first selective 11βHSD1 inhibitors.[3] Subsequently, various potent inhibitors have been disclosed by others.[4,5] We present in this communication our efforts toward developing an efficient inhibitor of 11βHSD1 leading to the discovery of clinical candidate PF-915275.

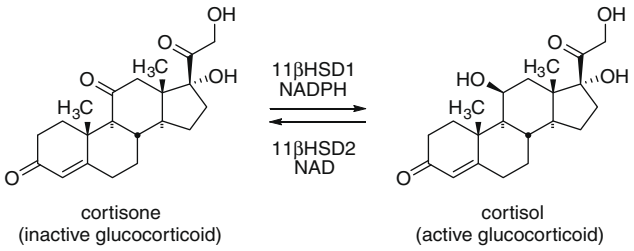
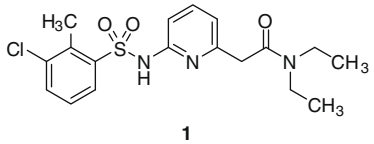


Figure 1. Interconversion between cortisone and cortisol mediated by 11βHSD1 and 11βHSD2.



1

K_i = 0.287 μM
HLM = high CL
Caco2 BA = 12 x 10^{-6} cm/s
Caco2 AB = 20 x 10^{-6} cm/s
ClogP = 2.91
Binding Efficiency
= 0.33 kcal/mol/atom

Figure 2. Initial lead.

* Corresponding author at present address: Genentech, Inc., 1 DNA Way, MS 18B, South San Francisco, CA 94080, United States. Tel.: +1 650 467 7764; fax: +1 650 467 8922.
E-mail address: siu.michael@gene.com (M. Siu).

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Our initial lead, *N*-(pyridin-2-yl) benzenesulfonamide **1**, has a K_i of 0.287 μM against 11βHSD1 (Fig. 2).[6] Although reasonably potent in our biochemical assay, the sulfonamide **1** has poor in vitro pharmacokinetic properties. In particular, sulfonamide **1** is categorized as a high clearance compound in our in vitro human liver microsome assay. Close-in analogs of amide **1**, shown in Table 1, did not have significantly improved potency.

In addition to potency, we sought to improve the physiochemical properties of sulfonamide **1**. Accordingly, a deletion strategy was employed to reduce molecular weight, hydrogen bond acceptors and rotatable bonds. Tactical implementation included removal of the amide functional group. A cocrystal structure of sulfonamide **1** bound to guinea pig 11βHSD1 with NADP shows the ethyl groups of the diethylamide substituent positioned in a polar region of the protein with several unsatisfied hydrogen bond donors and acceptors. This observation suggested that the diethyl amide may be too lipophilic for this region of the protein, and that truncation may not compromise potency (Fig. 3).[7]

Representative chemistry that enabled the synthesis of the amides in Table 1 is shown in Scheme 1.[8] Sulfonylation of aminopyridine **9**, derived from commercially available 2-amino-6-methylpyridine,[9] with 3-chloro-2-methylbenzenesulfonyl chloride in pyridine provided ester **10**. Direct amide formation occurred upon treatment of intermediate **10** with chloromethylaluminum morpholide (CH_2Cl_2, 0→24 °C) to afford amide **2**.[10]

In keeping with our deletion strategy, 2-amino-6-methylpyridine **11** was then synthesized.[11] Removal of the diethylamide resulted in a lower molecular weight compound with improved potency, ligand binding efficiency,[12] in vitro metabolic stability, and permeability (Fig. 4).

Although compound **11** revealed new structure–activity relationship findings at the pyridyl C-6 position and provided improved potency and stability compared to the initial lead (**1**), the potency was still below our laboratory objectives. With a view to further enhancing the potency of **11**, we investigated substitution

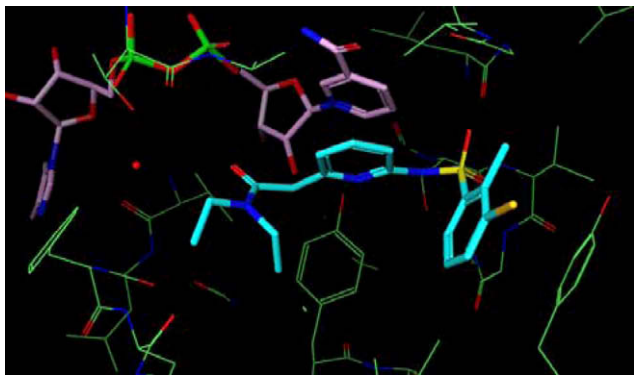
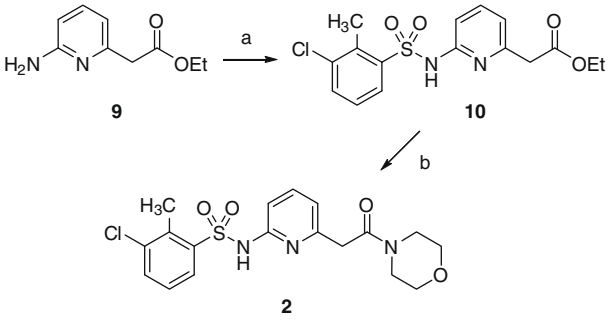
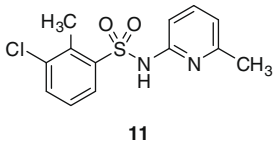


Figure 3. X-ray cocrystal structure of compound **1** (blue) and NADP (magenta) bound to guinea pig 11βHSD1 (green).



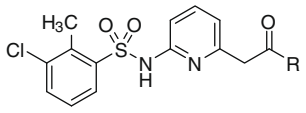
Scheme 1. Reagents and conditions: (a) 3-chloro-2-methylbenzenesulfonyl chloride, pyridine, 75%; (b) $(CH_3)_2AlCl$, morpholine, CH_2Cl_2, 0→24 °C, 96%.

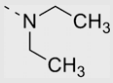
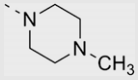
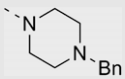


K_i = 0.169 uM
HLM = low CL
Caco2 AB = 36 x 10^{-6} cm/s
Caco2 BA = 46 x 10^{-6} cm/s
ClogP = 3.53
Binding Efficiency
= 0.44 kcal/mol/atom

Figure 4. Compound **11** properties.

Table 1

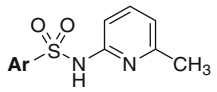


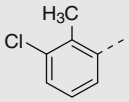
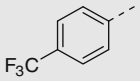
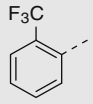
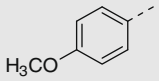
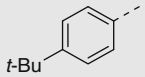
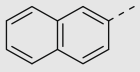
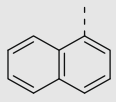
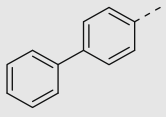
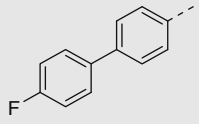
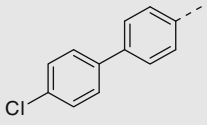
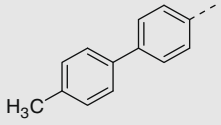
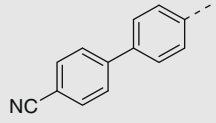
	R	11βHSD1 % inhib @ 0.1 μM	11βHSD1 K_i (nM)
1		–	287
2		6	–
3		55	169
4		8	–
5		39	–
6		22	–
7		11	–
8		25	–

on the phenylsulfonamide. A survey of aryl groups on the sulfonyl group (Table 2) showed that electron deficient aromatic groups that maximize pi–pi interaction to an adjacent tyrosine improved potency (see Fig. 3), although the substitution pattern was important (e.g., **12** vs **13**). The largest initial gain in enzymatic potency was obtained when a biphenyl substitution (**18**) was evaluated wherein the binding affinity improved to <50 nM. Biphenylsulfonamide **18** provided a fourfold enhancement in potency in comparison to **11** but lacked metabolic stability as expected due to the increased lipophilicity. Further evaluation of groups on the biaryl appendage showed that electron withdrawing groups such as fluoro and cyano at the 4′-position provided significant improvements in potency and metabolic stability with the 4′-cyanobiphenyl substitution (**22**) being the most optimal.

Further optimization of this series was achieved by maintaining the 4′-cyanobiphenyl group and varying the 6-position on the pyridine ring. We began this exploration by reviewing additional alkyl groups in place of the methyl group in **22**, such as the ethyl, cyclopropyl and *iso*-propyl groups (compounds **23**–**25**, Table 3). These alkyl substituents either retained or showed slight improvements in potency. In contrast, the introduction of an amino substitution (**26**, PF-915275) provided a considerable gain in activity while reducing lipophilicity (*Clog P* = 2.76) thus improving lipophilicity

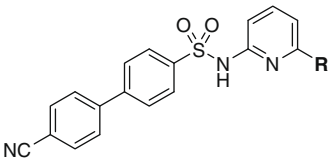
Table 2

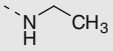


	Ar	11βHSD1 % inhib @ 0.1 μM	11βHSD1 K_i (nM)
11		–	169
12		–	108
13		1	–
14		23	–
15		32	–
16		46	84
17		10	–
18		52	48
19		87	20
20		96	5.8
21		84	62
22		99	4

efficiency. A review of alkylamino substitutions (compounds **27**–**29**) highlighted the importance of having an unsubstituted amino group for potency.

Table 3



	R	11βHSD1 K_i (nM)	11βHSD1 HEK293 EC_{50} (nM)
23		6.6	40
24		1.9	50
25		1.7	5
26		<1.0	5
27		9.8	184
28		4.8	10
29		ND	846

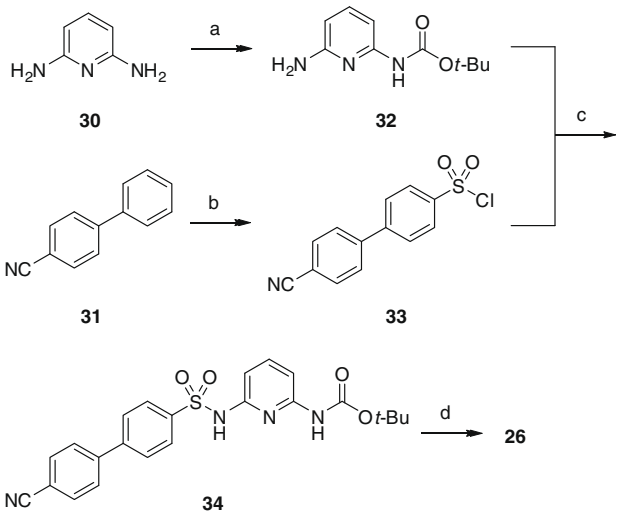
PF-915275 (**26**) maintains potency in our cellular assay against human 11βHSD1 (HEK293, EC_{50} = 5 nM) and is selective against human 11βHSD2 (HEK293, 1.5% inhibition @ 10 μM).[13] PF-915275, in general, displayed only weak affinity for the rodent choline transporter (K_i = 9.6 μM) and the hamster melatonin MT_3 receptor (K_i = 9.6 μM) in the Cerep Bioprint screening panel. PF-915275 (**26**) has good in vitro pharmacokinetic properties. In particular, **26** is categorized as a low clearance compound (liver microsome assays) with high permeability (Caco2 assay). As a prelude to in vivo studies with PF-915275 (**26**), the rat pharmacokinetic properties of this compound were determined. As shown in Table 4, PF-915275 (**26**) has an excellent pharmacokinetic profile characterized by low clearance, long half-life and good oral bioavailability.

The favorable potency and pharmacokinetic profile of PF-915275 (**26**) led us to progress this compound into an in vivo model to quantify the relationship between 11βHSD1 inhibition and exposure (PK/PD). As noted above, this sulfonamide is a selective and potent inhibitor of the human 11βHSD1 enzyme. On evaluating the cross-species potency of PF-915275 (**26**), it was found to be significantly less active against the mouse 11βHSD1 enzyme (K_i = 750 nM). The difference between human and rodent species was also observed in rat hepatoma cells (EC_{50} = 14,500 nM). Thus, PF-915275 (**26**)

Table 4

Compound	CLp (mL/min/kg)	Vss (L/kg)	$T_{1/2}$ (h)	AUC(oral) (h * μg/mL)	*F*
PF-915275 (**26**)	0.87	0.38	6.6	14.7	74%

IV = 0.1 mg/kg; 40% PEG200, 10% ethanol, 50% H_2O.
PO = 1 mg/kg; 0.5% methyl cellulose suspension.



Scheme 2. Reagents and conditions: (a) LiHMDS, BOC_2O, THF, 42%; (b) (i) $ClSO_3H$, CH_2Cl_2, 10 °C, (ii) NaOH, (iii) $POCl_3$, 106 °C, 40%; (c) pyridine; (d) HCl, dioxane, 70 °C, 54% (from **32**).

demonstrated species-dependent potency in both our biochemical and cellular assays, and its activity in primary hepatocytes can be rank ordered as human (EC_{50} = 20 nM) > monkey (EC_{50} = 100 nM) > dog (EC_{50} = 120 nM). The lack of rodent enzyme inhibitory activity presented a situation wherein PF-915275 (**26**) could not be used to demonstrate biomarker inhibition or efficacy in rodent models. To circumvent this issue, the in vivo target inhibition was demonstrated in primates using prednisone to prednisolone conversion, in the absence and presence of PF-915275 (**26**), as a biomarker for 11βHSD1 inhibition.[14] This pharmacodynamic approach was evaluated further in healthy human volunteers in Phase I studies which also assessed the safety, tolerability and pharmacokinetics of PF-915275 (**26**).[15]

PF-915275 (**26**) is synthesized in ~22% overall yield over four steps (longest linear sequence) as shown in Scheme 2. The synthetic route begins with commercially available 2,6-diaminopyridine (**30**) and 4-cyanobiphenyl (**31**). Monoprotection of the diaminopyridine **30** provides the *t*-butylcarbamate **32**. Chlorosulfonylation of the 4-cyanobiphenyl (**31**) afforded the 4′-cyanobiphenyl-4-sulfonyl chloride (**33**). Subsequent coupling of the aminopyridine **32** and sulfonyl chloride **33** furnished sulfonamide **34**, which was deprotected under acidic conditions to afford PF-915275 (**26**).

In conclusion, *N*-(pyridin-2-yl) arylsulfonamides are identified as inhibitors of 11βHSD1. Implementation of a deletion strategy arrived at efficient inhibitors with improved ligand efficiency and physiochemical properties. Further optimization furnished clinical candidate PF-915275 (**26**), a potent and selective inhibitor of human 11βHSD1 with good preclinical pharmacokinetic properties.

Acknowledgement

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8. *Ethyl [6-(3-chloro-2-methyl-benzenesulfonyl-amino)-pyridin-2-yl]-acetate* (**10**): 3-Chloro-2-methylbenzenesulfonyl chloride (3.4 g, 15 mmol, 1.5 equiv) was added in one portion to a solution of ethyl 2-(6-aminopyridin-2-yl)acetate (**9**) (1.8 g, 10 mmol, 1 equiv) in pyridine (75 mL) at 24 °C. After 16 h, the pyridine

was removed in vacuo (<1 mm Hg), and the resulting residue was dissolved in ethyl acetate (200 mL). The organic solution was washed sequentially with water (3 × 100 mL) and saturated aqueous sodium chloride solution (100 mL). The collected organic was dried over anhydrous sodium sulfate, filtered, and concentrated. Purification by high performance flash chromatography (0→5% methanol in dichloromethane) yielded product (2.76 g, 75%). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 8.02 (dd, J = 8.0, 1.1 Hz, 1H), 7.52 (dd, J = 8.5, 7.4 Hz, 2H), 7.22 (t, J = 8.0 Hz, 1H), 7.01 (d, J = 8.3 Hz, 1H), 6.80 (d, J = 7.3 Hz, 1H), 4.17 (q, J = 7.1 Hz, 2H), 3.68 (s, 2H), 2.73 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H); HRMS (ESI): Calcd for $C_{16}H_{18}ClN_2O_4S$ m/z 369.0676; Found: 369.0677.

3-Chloro-2-methyl-N-[6-(2-morpholin-4-yl-2-oxoethyl)-pyridin-2-yl]-benzenesulfonamide (**2**): Dimethylaluminum chloride (1.36 mL, 1.36 mmol, 5.0 equiv, 1.0 M in hexanes) was added dropwise to an ice-cooled solution of morpholine (0.119 mL, 1.36 mmol, 5.0 equiv) in dichloromethane (3 mL). The resulting solution was warmed to 24 °C for 1 h before the addition of a solution of ethyl [6-(3-chloro-2-methyl-benzenesulfonylamino)-pyridin-2-yl]-acetate (10) (0.100 g, 0.271 mmol, 1 equiv) in dichloromethane (2 mL). After 1 h, 20% sodium potassium tartrate aqueous solution (5 mL) was slowly added to the reaction mixture, and the resulting suspension was stirred vigorously for an additional hour. The resulting mixture was extracted with dichloromethane (2 × 25 mL). The collected organic was dried over anhydrous sodium sulfate, filtered, and concentrated. Purification by high performance flash chromatography (0→10% methanol in dichloromethane) yielded a light orange solid (0.107 g, 96%). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 8.01 (dd, J = 8.1, 1.0 Hz, 1H), 7.53 (t, J = 8.1 Hz, 2H), 7.23 (m, 1H), 7.03 (d, J = 8.3 Hz, 1H), 6.84 (d, J = 7.3 Hz, 1H), 3.77 (s, 2H), 3.63 (m, 4H), 3.56 (m, 2H). 3.48 (m, 2H), 2.73 (s, 3H); HRMS (ESI): Calcd for $C_{18}H_{21}ClN_3O_4S$ m/z: 410.0941; Found: 410.0936.

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