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N-(Pyridin-2-yl) arylsulfonamide inhibitors of 11β-hydroxysteroid dehydrogenase type 1: Strategies to eliminate reactive metabolites

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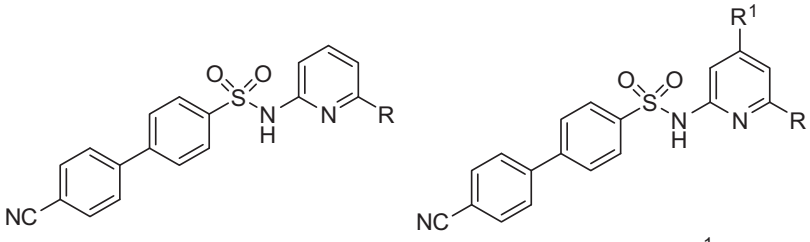
ABSTRACT

N-(Pyridin-2-yl) arylsulfonamides **1** and **2** (PF-915275) were identified as potent inhibitors of 11β-hydroxysteroid dehydrogenase type 1. A screen for bioactivation revealed that these compounds formed glutathione conjugates. This communication presents the results of a risk benefit analysis carried out to progress **2** (PF-915275) to a clinical study and the strategies used to eliminate reactive metabolites in this series of inhibitors. Based on the proposed mechanism of bioactivation and structure–activity relationships, design efforts led to *N*-(pyridin-2-yl) arylsulfonamides such as **18** and **20** that maintained potent 11β-hydroxysteroid dehydrogenase type 1 activity, showed exquisite pharmacokinetic profiles, and were negative in the reactive metabolite assay.



1: R = CH_3
2: R = NH_2 (PF-915275)

18: R = NH_2, R^1 = CH_3
20: R = CH_2OH, R^1 = H

Dysregulation of glucocorticoids has been associated with the pathogenesis of diabetes, metabolic syndrome and age-related cognitive dysfunction.[1] 11β-Hydroxysteroid dehydrogenase isozymes (11β-HSD 1 and 2) are microsomal enzymes that mediate the intracellular metabolism of glucocorticoids. 11β-Hydroxysteroid dehydrogenase type 1 (11β-HSD1) is expressed mainly in the adipose tissue, liver, and in the central nervous system and it catalyzes the reduction of the inactive glucocorticoid cortisone using the cofactor NADPH. The type 2 isoform, 11β-HSD2, is expressed mainly in the kidney and catalyzes the oxidation of the active glucocorticoid cortisol to cortisone to prevent activation of the mineralocorticoid receptor by cortisol.[2] 11β-HSD1 mediates the prereceptor activation of cortisone and thus its inhibition provides

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the ability to control cortisol concentrations at the desired tissues without affecting systemic circulating concentrations.[3] Inhibition of 11β-HSD1 offers a potential therapy to treat type 2 diabetes[4] and numerous 11β-HSD1 inhibitors have been reported in recent literature.[5]

As a part of our efforts to discover novel inhibitors of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1), we identified the *N*-(pyridin-2-yl) arylsulfonamides **1** and **2** (PF-915275) as potential clinical candidates (Fig. 1).[6] These compounds were selective and potent inhibitors of the human 11β-HSD1 (**1**, HEK293 EC_{50} = 53 nM, **2**, HEK293 EC_{50} = 5 nM) and showed good selectivity against 11β-HSD2 (**2**, 1.5% inhibition at 10 μM).

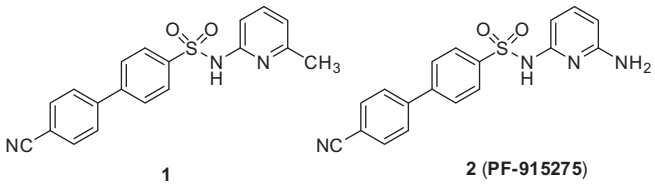

Figure 1. Lead *N*-(pyridin-2-yl) arylsulfonamides.

Table 1
Rat pharmacokinetic data for **1** and **2**

	Cl (mL/min/kg)	V_{ss} (L/kg)	$T_{1/2}$ (h)	*F* (%)
1	0.06	0.15	28	89
2	0.87	0.38	5	73[a]

Dosed at 0.1 mg/kg iv and 0.5 mg/kg p.o.
[a] 60% When dosed as suspension in 0.5% methylcellulose.

Both compounds also exhibited excellent pharmacokinetic profiles in rat, characterized by very low clearance, long half-lives and good oral bioavailability (Table 1) and were stable towards oxidative metabolism when incubated with human liver microsomes containing NADPH. However, surprisingly despite their good ADME properties both **1** and **2** showed a potential to form electrophilic intermediates which was assessed by their ability to form glutathione (GSH) adducts when incubated with GSH and NADPH fortified liver microsomes (see Supplementary data for LC–MS/MS data of adducts).

Metabolic activation of drugs to electrophilic reactive intermediates that covalently bind to macromolecules has been implicated in idiosyncratic adverse drug reactions. Such drug entities are usually characterized by the presence of 'structural alerts' or toxicophores, structural motifs that undergo biotransformation and give rise to the causative reactive species.[7] The element of surprise in the data obtained from the GSH assay arose from the perceived absence of such structural alerts in compounds **1** and **2**. Based on the favorable physicochemical properties and cell based potency, **2** was selected as our lead compound for further advancement into in vivo pharmacodynamic studies.[8] Given the need for an exquisite safety profile for diabetes therapeutics, we deemed it necessary to assess the risks posed by their metabolic activation. This communication presents the results of the risk benefit analysis[9] of the reactive metabolite formation and the design efforts undertaken to circumvent this issue in this class of 11β-HSD1 inhibitors.

As part of our risk benefit analysis for sulfonamide **2**, a number of studies were carried out to assess the impact of the reactive metabolite findings. In vitro covalent binding studies with ^{14}C-labeled **2** (^{14}C-label on nitrile group) showed that non-specific binding to proteins was reduced to near background levels when ^{14}C-labeled **2** was incubated with subcellular fractions (liver S9 and microsomes) of various species in a mixture containing co-factors

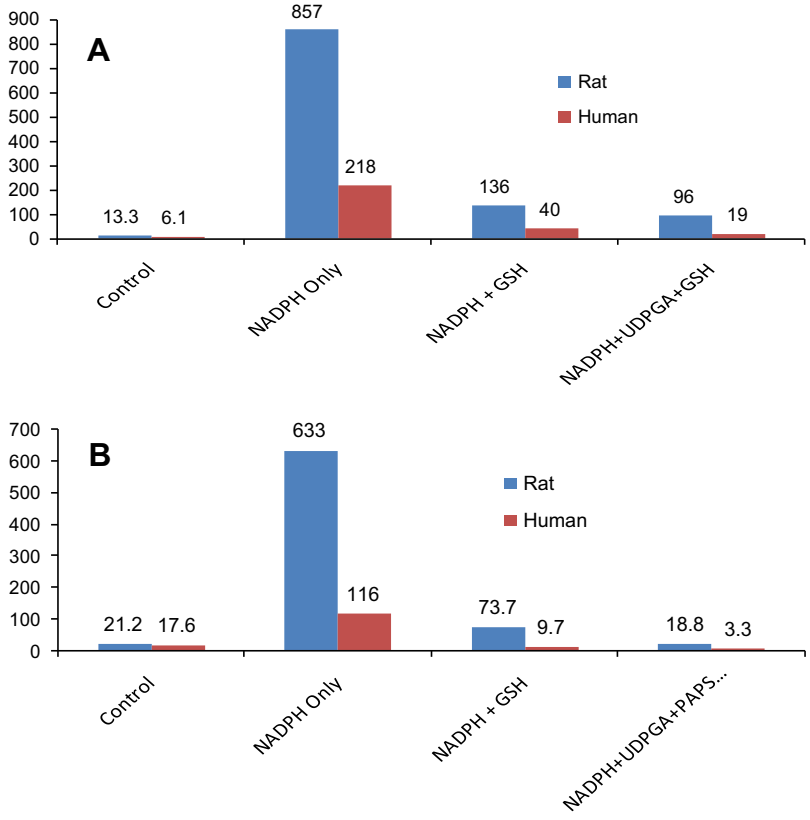

Figure 2. Covalent binding of radiolabeled **2** to proteins in rat and human liver microsomal (A) and S9 fractions (B) with and without co-factors.