Discovery of Clinical Candidate BMS-823778 as an Inhibitor of Human 11 β -Hydroxysteroid Dehydrogenase Type 1 (11 β -HSD-1)

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Supporting Information

ABSTRACT: BMS-823778 (2), a 1,2,4-triazolopyridinyl-methanol derived analog, was identified as a potent and selective inhibitor of human 11 β -hydroxysteroid dehydrogenase type 1 (11 β -HSD-1) enzyme (IC_{50} = 2.3 nM) with >10,000-fold selectivity over 11 β -HSD-2. Compound 2 exhibits robust acute pharmacodynamic effects in cynomolgus monkeys (ED_{50} = 0.6 mg/kg) and in diet-induced obese (DIO) mice (ED_{50} = 34 mg/kg). Compound 2 also showed excellent inhibition in an *ex vivo* adipose DIO mouse model (ED_{50} = 5.2 mg/kg). Oral bioavailability ranges from 44% to 100% in preclinical species. Its favorable development properties, pharmacokinetics, high adipose-to-plasma concentration ratio, and preclinical pharmacology profile have prompted the evaluation of 2 for the treatment of type 2 diabetes and metabolic syndrome in phase 2 clinical trials.

KEYWORDS: Enzyme inhibitors, human 11 β -hydroxysteroid dehydrogenase-type 1, 11 β -HSD-1, triazolopyridine, 1,2,4-triazolopyridinyl-methanol, BMS-823778, high adipose selectivity, type 2 diabetes, cortisol, cortisone

Diabetes continues to be a worldwide epidemic disease. A World Health Organization (WHO) report issued in 2015 showed that globally 8.5% of adults had diabetes in 2014 with type 2 diabetes making up about 90% of the cases, and the death of people caused by diabetes rose to 1.5 million in 2012.¹ Type 2 diabetes is a long-term metabolic disorder, typically associated with high blood sugar, insulin deficiency in some cases, and insulin resistance. While several existing options for diabetic treatment are available, current clinical evidence advocates that a better control of blood sugar level is desired and that combination therapy is usually more effective in achieving the target glycemic level, thereby discovery and development of new diabetic drugs with novel mechanisms of action to medically manage type 2 diabetes are greatly needed.

The active glucocorticoid, cortisol, in human regulates a wide range of processes throughout the body, including metabolism, inflammatory, and immune response. High salivary cortisol levels was found to be associated with components of metabolic syndrome and glucose level,² thus a potential therapeutic treatment for metabolic syndrome and diabetes can be realized through regulating or reducing the cortisol level in the human body. 11 β -Hydroxysteroid dehydrogenase type 1 (11 β -HSD-1), an enzyme mainly expressed in liver and adipose tissue, converts inactive cortisone to the active cortisol.³ Numerous preclinical studies regarding the role of 11 β -HSD-1 have been reported.^{4–8} These preclinical results suggested that inhibition of 11 β -HSD-1 activity in

humans may help the treatment of metabolic syndrome and diabetes.⁵ As a result, significant efforts to discover inhibitors of 11 β -HSD-1 have been reported.^{8–15}

We have previously reported a novel inhibitor of 11 β -HSD-1 compound 1 (Figure 1), which was derived from a 1,2,4-

Figure 1. Lead compound 1.

triazolopyridine (TZP) core structure.¹³ Compound 1 showed excellent human 11 β -HSD-1 enzyme inhibitory activity (IC_{50} = 1.6 nM) and low Pregnane-X receptor (PXR) transactivation (EC_{50} > 50 μ M), a major off-target liability for this class of compounds. However, the murine enzyme activity of 1 was much weaker (m-11 β -HSD-1 IC_{50} = 241 nM). Compound 1

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also demonstrated limited aqueous solubility (219 $\mu\text{g/mL}$ at pH 7), which made high dose *in vivo* evaluation difficult. In addition, a potential Cytochromes P450 (CYP) inhibition liability (2C19 $\text{IC}_{50} = 1.9 \mu\text{M}$) was present, which may raise potential drug–drug interaction issues in clinical development. Ultimately, the failure to prompt a robust response *in vivo* in a standard 11-dehydrocorticosterone (DHC) challenging assay in mice made it difficult to further evaluate the potential of **1**. Thus, a better and more optimized compound was sought.

Compound **1** proved to be an excellent starting point for modifications of this chemotype due to its excellent activity with minimal PXR liability. We decided to concentrate on variations of the small alkyl group on the left side of the molecule, a “sweet-spot” for SAR changes, where it was shown that variation at this position can maintain the potency with the benefit of attenuation of PXR activity.¹³ With this focus in mind, we sought to further improve ADME profiles such as solubility and CYP inhibition by incorporating polar functionalities with a primary focus on hydroxyl groups. Simply replacing the cyclopropyl group with a hydroxymethyl group (**3a**) resulted in a ~ 10 -fold loss of potency. Two hydroxyl groups (**3b**) further decreased potency indicating that a balance of polarity is needed at this position. Thus, reinstallation of small hydrophobic alkyl groups was explored. Adding a cyclopropyl group to **3a**, which resulted in **3c**, improved human 11 β -HSD-1 inhibitory potency but further reduced activity versus the mouse enzyme. However, attempting to increase alkyl chain length by inserting an ethyl group between the TZP core and the hydroxymethyl group (**3d**) only slightly improved the potency over **3a**.

Adding more lipophilicity (**3e**) by introduction of a terminal *gem*-dimethyl group on **3d** was found to diminish potency and increase the unwanted PXR activity. Moving the *gem*-dimethyl group to the benzylic position (**3f**) significantly increased the potency but enhanced the PXR liability. Optimally it was found that reducing the chain length of **3f**, resulting in **2**, afforded a compound with potent human 11 β -HSD-1 inhibition ($\text{IC}_{50} = 2.3 \text{ nM}$), remarkable aqueous solubility (Table S5, Supporting Information), and negligible PXR activity, although mouse 11 β -HSD-1 inhibition ($\text{IC}_{50} = 600 \text{ nM}$) was still moderate. Interestingly, although cLogP generally correlated with human 11 β -HSD-1 potency within the triazolopyridinyl-methanol chemotype, it did not show a similar trend for PXR activity. Other polar functionalities such as a carboxylic acid group (**3g**) were also explored, which resulted in a significant loss of potency (Table 1).

A full enzyme kinetic analysis of the microsomal form of human 11 β -HSD-1 at the biologically relevant temperature of 37 °C was performed on **2** and yielded a K_i value of 0.9 nM (Table S2, Supporting Information). The K_i values for the cynomolgus monkey and mouse enzymes were 7 and 380 nM, respectively. In addition, no 11 β -HSD-2 inhibition up to 30 μM versus the human enzyme and up to 20 μM versus the corresponding mouse, rat, and monkey enzymes were found for **2**.

Inhibition of 11 β -HSD-1 *in vivo* was accomplished using a pharmacodynamic (PD) protocol in mice and cynomolgus monkeys (Table S3, Supporting Information). The test compound was administered orally prior to initiation of a challenge with DHC. Plasma samples were isolated at various time points thereafter and the concentration of product generated *in vivo* by 11 β -HSD-1, in this case corticosterone, was measured by immunoassay. Inhibition of 11 β -HSD-1 was

Table 1. SAR Results of 3-[1-(4-Chlorophenyl)cyclopropyl]-8-aryloxy-TZP Analogs **3a–3d** and **2** ^{α}

Compd	R	h- IC_{50}^{α} (nM)	m- IC_{50}^{α} (nM)	PXR EC_{50} (μM)	cLogP ^{β}
3a		17	3800	25	2.7
3b		71	>10000	>50	1.3
3c		5.9	8060	48	3.0
3d		11	5700	25	2.8
3e		43	>10000	3.6	3.5
3f		0.5	1150	1.3	3.6
2		2.3	600	>50	2.3
3g		1280	>10000	>50	3.2

^{α} IC_{50} and PXR values refer to average of at least two duplicates.
 ^{β} cLogP calculated by Chemdraw professional, version 16.0.1.4, PerkinElmer Informatics, Inc.

observed as a measure of decrease in the plasma concentration of corticosterone. Drug plasma concentrations were measured concurrently. The ED_{50} value of **2** was found to be 34 mg/kg in mice and 0.6 mg/kg in cynomolgus monkeys. The difference between the ED_{50} values for these two species (~ 57 -fold) is consistent with the difference of their intrinsic potencies (~ 55 -fold based on K_i value).

While the pharmacodynamic models described above are useful for assessing the activity of compounds in an intact animal, it did not allow for a discrete assessment of drug activity in specific tissues of interest. Adipose is believed to be a key target organ for inhibitors of 11 β -HSD-1.^{4,16} Thus, a DIO mouse based *ex vivo* model was used to further evaluate **2**. Male DIO mice were treated with various doses of **2** via oral gavage. Three hours later, the animals were sacrificed, the adipose tissue was harvested and incubated with exogenous DHC, and the conversion of DHC to corticosterone was evaluated. The ED_{50} value of **2** for inhibition of 11 β -HSD-1 in this *ex vivo* adipose model was determined to be 5.2 mg/kg. As compared to the ED_{50} value obtained from the pharmacody-

namic model, this *ex vivo* value was approximately 6.5-fold more potent. This result was qualitatively consistent with the preference of **2** to distribute to the adipose tissue (adipose/plasma ratio of **2** is ~ 2.5 in DIO mice).

The pharmacokinetic (PK) studies of **2** were performed in mouse and cynomolgus monkeys. Compound **2** distributed extra vascularity in both species, with a steady-state volume of distribution (V_{ss}) of 1.2 and 2.3 L/kg in mouse and monkey, respectively. The clearance of **2** was low in both species (mouse, 2.3 mL/min/kg; cynomolgus monkey, 1.2 mL/min/kg). Oral bioavailability from a homogenized suspension was 44% and $\sim 100\%$ in mouse and monkey, respectively. Permeability of **2** in the parallel artificial membrane permeability assay (PAMPA) was high (>500 nm/s), suggesting that the compound is likely to be well absorbed in humans. In the Caco-2 cells permeability assay, **2** exhibited a B-A/A-B efflux ratio of less than 2, indicating it is unlikely to be a substrate for efflux transporters like permeability glycoprotein (P-gp). For plasma protein binding (PPB), **2** was 85% bound to human serum proteins and 84 to 87% bound to the serum proteins of the animal species studied (Table S5, Supporting Information). These encouraging pharmacokinetic results including acceptable bioavailability and favorable half-life in different animal species indicated that once a day (QD) oral administration should be feasible in human clinical trials.

Compound **2** also showed desirable development properties. For example, no significant activity ($IC_{50} > 30 \mu M$) against five major human liver cytochrome P450 isoform enzymes (CYP3A4, CYP2C9, CYP2C19, CYP2D6, and CYP1A2) was observed, indicating a reduced potential for drug–drug interactions. Glutathione (GSH) conjugative adducts were not detected when **2** was incubated with liver microsomes of human, monkey, dog, rat, and mouse in the presence of nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) and GSH, suggesting that reactive metabolites may not be an issue. In mice, **2** showed excellent adipose selectivity with an adipose-to-plasma concentration ratio of 2.5 and a liver-to-plasma concentration ratio of 3.5. The excellent partitioning of drug in adipose tissue is particularly interesting since preclinical studies suggest that 11 β -HSD-1 activity within the adipose is critical to the development of the adverse metabolic profile related with circulating excess endogenous glucocorticoids.¹⁶

The HCl salt of **2** exhibited good intrinsic aqueous solubility (0.50 mg/mL at pH 6.5 and 220 mg/mL at pH 1); it showed good solid-state and oxidative solution stability as well as hydrolytic solution stability under accelerated degradation conditions. The compound was stable in aqueous buffers ranging from pH 1.1 to pH 7.4 for at least 1 week at 40 °C with no degradation observed. The crystalline solid HCl salt was found to be physically and chemically stable for at least 12 weeks under stress conditions, e.g., 50 °C and in the presence of high intensity light/ultraviolet (HIL/UV). Compound **2** also showed favorable *in vitro* metabolic stability in isolated microsomes testing, 96–100% of parent compound was preserved after 30 min of incubation for all tested species including human, mouse, cynic, and rat.

Whole-cell patch-clamp was used to directly measure human ether-a-go-go-related gene (hERG) potassium channel activity, **2** exhibited a slight inhibition of the hERG ion channel currents (19.8 and 31.2% inhibition at 10 and 30 μM , respectively), predicting minimal likelihood for QT prolonga-

tion *in vivo*. PXR transactivation activity was minimal with an $EC_{50} > 50 \mu M$. Both SOS chromotest (SOS test) and salmonella plate incorporation test (Ames test) were negative. Single dose toxicology studies in mice and cynomolgus monkeys at oral doses up to 100 mg/kg were well tolerated except for mild emesis observed in the monkeys.

Human dose projections were based on preclinical data from PK studies with **2** in DIO mice. Compound **2** exhibits an *in vitro* K_i of 380 nM against the mouse 11 β -HSD-1 enzyme and 0.9 nM against the human enzyme. Correcting for the species differences in intrinsic activity and free fraction in plasma, the predicted human plasma concentrations that will lead to 50% and 90% inhibition in adipose (EC_{50} and EC_{90}) are 16 and 146 nM, respectively. The human efficacious dose calculations were based on maintaining the steady-state concentration of 16 nM (EC_{50}) or 146 nM (EC_{90}) at 24 h, and with the projected human PK parameters (using an anticipated half-life of 32 h with an accumulation ratio in humans upon repeat daily dosing of ~ 2), we concluded that doses of 1 to 21 mg QD may be sufficient to maintain the target exposures at steady state for a 70 kg human subject.

An optimized discovery synthesis of **2** is illustrated in Scheme 1. The commercially available 3-bromo-2-chloropyr-

Scheme 1. Synthesis of Compound **2**

idine **4** was treated with hydrazine in EtOH to afford 3-bromo-2-hydrazinylpyridine-1-(4-chlorophenyl) **5** in 91% yield. Coupling aryl hydrazine **5** with cyclopropane-1-carboxylic acid **6** afforded acyl hydrazide **7**, which underwent aqueous work up and was used directly in the next step without further purification. The crude compound **7** was treated with $PEt_3/CCl_4/i-Pr_2NEt$ initially at 0 °C and then slowly warmed to room temperature over 3 h to give the desired cyclodehydration product 8-bromo-3-(1-(4-chlorophenyl)-cyclopropyl)-[1,2,4]triazolo[4,3-a]pyridine **8** in good yield (90%). Compound **8** was treated with *n*-BuLi at -78 °C in THF for 15 min to form the aryllithium intermediate. Subsequent addition of anhydrous acetone afforded **2** in modest but acceptable yields (30–50%).

X-ray crystal structures for both human and mouse 11 β -HSD-1 complex with **2** were obtained at 2.45 and 2.65 Å resolution, respectively, as shown in Figure 2 (human) and Figure 3 (mouse).^{17,18} The binding pose in the mouse enzyme is rotated $\sim 180^\circ$ relative to the binding pose in the human enzyme. The bulk of the differences in activity and binding pose between the human and mouse enzymes are believed to be due to residue 177, which is a Tyr in human and a Gln in

Figure 2. X-ray crystallographic binding position of **2** in human 11 β -HSD1. The refined structure in the vicinity of **2** with omit mFo–DFc electron density contoured at 2.5 rmsd (cyan) and 8 rmsd (orange), which indicates the location of the chlorine atom. Atom color coding carbon in 11 β -HSD1, green; **2**, gray; nitrogen, blue; oxygen, red; phosphate, orange; chlorine, split pea green. Two-dimensional diagram below shows the orientation of **2**.

Figure 3. X-ray crystallographic binding position for **2** in mouse 11 β -HSD1. The refined structure in the vicinity of **2** with omit mFo–DFc electron density contoured at 2 rmsd (cyan). Atom color coding carbon 11 β -HSD1, green; **2**, gray; nitrogen, blue; oxygen, red; phosphate, orange; chlorine, split pea green. Two-dimensional diagram below shows the orientation of **2**.

mouse, although other residues, e.g., 231 (Val in human and Ile in mouse) and 233 (Met in human and Ala in mouse) also play a role.

In summary, compound **2** was identified as a novel, potent, and selective inhibitor of human 11 β -HSD-1 enzyme with an excellent ADME profile, a desired adipose-to-plasma ratio in conjunction with its acceptable safety attributes. Its overall favorable development properties warranted advancement of **2**

into clinical Phase 1 and subsequently Phase 2 trials for the treatment of type 2 diabetes and metabolic syndrome.¹⁹ The preliminary human clinical trials indicated that **2** was safe and well tolerated in healthy subjects after single and multiple oral doses with different doses. The systemic clearance of **2** was found to be directly correlated with the genetic polymorphism of CYP2C19.²⁰

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmchemlett.8b00307.

In vitro and *in vivo* potencies of **2**; single-dose pharmacokinetic parameters and physical properties of **2**; experimental methods for the preparation of compounds, *in vitro* and *in vivo* assays, analytical and spectroscopic data for compounds **2** and **3a–3g**; and X-ray crystallographic data of compound **2** complexed with 11 β -HSD-1 (PDF)

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

11 β -HSD-1, 11 β -hydroxysteroid dehydrogenase type 1; DHC, dehydrocorticosterone; TZP, triazolopyridines; NMM, N-methylmorpholine; PK, pharmacokinetic; CYPs, Cytochromes P450; PXR, Pregnane-X receptor; ADME, absorption, distribution, metabolism, and excretion; DIO, diet-induced obesity model; P-gp, permeability glycoprotein; NADPH, nicotinamide adenine dinucleotide phosphate hydrogen; GSH, glutathione; hERG, human ether-a-go-go-related gene; SOS test, SOS chromotest; Ames test, salmonella plate incorporation test

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