Development of HSD-016 and HSD-621 as potential agents for the treatment of type 2 diabetes

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Abstract

The glucocorticoid receptor (GR) signaling pathway has been linked to the pathophysiology of diabetes and metabolic syndrome. We developed a series of potent and selective 11β-HSD1 inhibitors. These compounds showed excellent potency against both human and mouse 11β-HSD1 enzymes and displayed good pharmacokinetics and ex vivo inhibition of the target in mice.Compounds HSD-016 and HSD-621 were ultimately selected as clinical development candidates. Both compounds have attractive overall pharmaceutical profiles and demonstrated good oral bioavailability in mouse, rat and dog. When orally dosed in C57/BL6 diet-induced-obesity (DIO) mice, HSD-016 and HSD-621 were efficacious and showed a significant reduction in both fed and fasting glucose and insulin levels. Furthermore, both compoundswere well tolerated in drug safety assessment studies.

Glucocorticoid hormones are key regulators of a wide range of biological processes such as the control of immune and stress responses as well as modulation of energy metabolism. Glucocorticoids (cortisol in humans and corticosterone in mice and rats) stimulate hepatic glucose production and suppress insulin-mediated glucose uptake in peripheral tissues (i.e., adipose and muscle). 11β-Hydroxysteroid dehydrogenase type I (11β-HSD1),1−1g a reduced β-nicotinamide adenine dinucleotide phosphate (NADPH)-dependent enzyme, predominantly acts as a reductase in vivo, converting inactive, nonreceptor binding cortisone to active, receptor-binding cortisol in tissues such as liver, adipose, vasculature, brain, and macrophages.2 The enzyme is a tetramer consisting of two dimers each with an independent active site.2 It has been proposed that 11β-HSD1 reductase activity exists predominantly in metabolic tissues because of the increased ratio of NADPH to β-nicotinamide adenine dinucleotide phosphate (NADP) within the endoplasmic reticulum (ER) lumen and/or through direct interactions with NADPH-generating hexose-6-phosphate dehydrogenase (H6PDH), an enzyme that has been associated with cortisone reductase deficiency in humans.3 Cortisone itself is generated by the action of 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) with cortisol using NADP as a cofactor. 11β-HSD1 levels are highest in liver and adipose tissues as well as in the central nervous system, whereas 11β-HSD2 is mainly expressed in the kidney and colon.4

The rationale for 11β-HSD1 as a therapeutic target for the treatment of diabetes and the metabolic syndrome is based on data from tissue-specific overexpression in transgenic mice5,5b and mice 11β-HSD knockout experiments.6,6b In addition, 11β-HSD1 activity in adipose tissue also correlates positively with body mass index (BMI), fat percentage, and fasting glucose and insulin levels in humans. Recent studies have demonstrated that whole-body 11β-HSD1 activity is elevated in obese men with type 2 diabetes, whereas liver 11β-HSD1 activity is relatively unchanged, suggesting that disease suppression via 11β-HSD1 inhibition is likely to be more effective in obese patients with type 2 diabetes.7

Several classes of potent and selective 11β-HSD1 inhibitors have been reported in the literature.8−8k Some inhibitors, including our own,8,8b have displayed in vivo efficacy in animal models related to diabetes.9−9e Data from phase II clinical trials for 11β-HSD1 inhibitor INCB-173910 showed improved hepatic and peripheral insulin sensitivity and a reduction in fasting plasma glucose and cholesterol observed after 28 days of treatment in type II diabetic patients. Decreased triglyceride levels and improvement in blood pressure were also reported.

We previously disclosed a series of compounds exemplified by 1 and 2, which displayed potent and selective inhibition against both human and rodent 11β-HSD1 in vitro. The compounds also showed oral efficacy in the cortisone-induced hyperinsulinemia rat model8 and in the diet-induced obesity (DIO) mouse model8b (Figure (Figure1).1). In the continuation of our 11β-HSD1 program, we are reporting on the discovery of our clinical development candidate 18a [HSD-621, (R)-3,3,3-trifluoro-2-(5-((R)-4-(4-fluoro-2-(trifluoromethyl)-phenyl)-2-methylpiperazin-1-ylsulfonyl)thiophen-2-yl)-2-hydroxypropanamide]. Selected characterization and preclinical data for HSD-621 will be disclosed.

On the basis of the profile of our earlier compounds,8,8b we imposed additional requirements when selecting compounds to move forward in our screening cascade.

Specifically, we were interested in compounds with the following profile: (i) potent cellular activity, (ii) good microsomal stability, and (iii) potent adipose ex vivo activity. Among these considerations, adipose ex vivo activity became the most significant driver in terms of compound selection for in vivo efficacy studies. This stemmed from the earlier observation of poor in vivo results from compounds possessing high liver ex vivo activity alone.8b This finding is in line with the report that liver-specific overexpression of 11β-HSD1 in transgenic mice causes insulin resistance without obesity,11 possibly indicating the importance of targeting 11β-HSD1 outside of the liver, particularly in the adipose.

Biography

Zhao Kui Wan received his Ph.D. degree from Boston University and conducted postdoctoral research at Harvard University where he discovered the sulfonamide-based ligand for asymmetric Nozaki-Hiyama-Kishi Reactions under the guidance of Prof. Yoshito Kishi. Also at Harvard, he developed a practical synthesis of a key fragment of Eribulin that is now approved for the treatment of breast cancer under the name of HalavenTM. As a medicinal chemist, his research has experience in the fields of metabolic and inflammatory diseases. He played a key role in the development of two clinical and pre-clinical candidates for Type II diabetes. He also developed a novel and efficient phosphonium-mediated and related bond forming reactions in heterocyclic systems arising from serendipitous observations. He has nearly has near 70 scientific publications in peer-reviewed journals, patents and meeting abstracts. He is an ad hoc reviewer for almost a dozen prestigious scientific journals and serves on the Editorial board for North American Journal of Medicine & Health. He was a co-founder of Chinese BioMedical Association (CABA) and served as the President (2009-2010). He was a Young Industrial Investigator (the American Chemistry Society, Division of Organic Chemistry and Diversion of Medicinal Chemistry, 2008).