OMICS Group Conferences
Accelerating Scientific Discovery

4th World Congress on
Diabetes & Metabolism

August 14-16, 2013 Holiday Inn Chicago-North Shore, IL, USA

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

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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.

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).

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