Cyclobutane Derivatives as Novel Non-peptidic Small Molecule Agonists of Glucagon-like Peptide-1 Receptor

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Type 2 diabetes is emerging as one of the largest health issues worldwide with an estimated 23.6 million children and adults (7.8% of the population) affected in the United States alone. Glucagon-like peptide-1 (GLP-1) has proven to be an efficacious agent to combat this serious and life-long disease. A novel cyclobutane class of non-peptidic GLP-1 receptor agonists, exemplified by Boc5, was identified using receptor binding and cAMP response element-driven reporter gene assays. The structures of Boc5 and its three isomers were elucidated by NMR, HRESIMS, and X-ray crystallography. A series of structural modifications were also made based on the core structure of Boc5 with different substitution groups at the west and east ends. *In vitro* characterization of these analogues demonstrated that the cyclobutane core and the two carboxylic groups were essential for the bioactivity and modifications such as decreasing the size of the ring and conversion of the acids to amide and ester led to the total loss of activity. The Boc and the 2-thiophenyl groups were well-tolerated with compound 13 as the optimum that consistently displayed more potent GLP-1 activities (than Boc5) both *in vitro* and *in vivo*. Preliminary structure-activity relationship studies suggested that the cyclobutane analogues may serve as a starting point for the development of new GLP-1 mimetics.

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