Pyridoxine dipharmacophore derivatives as potent glucokinase activators for the treatment of type 2 diabetes mellitus

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Glucokinase is one of the promising targets for glucose-lowering agents, and the development of GK activators are now considered as one of the most promising strategies for the treatment of type 2 diabetes mellitus. In this work, a series of novel symmetric molecular constructs, in which two pyridoxine moieties are connected via sulfur-containing linkers, have been synthesized and tested in vitro for glucokinase activation potential. The enzyme activation rates by two most active compounds at 100 ?M (~150% and 130%) were comparable to that of the reference agent PF-04937319 (~154%). Both leading compounds demonstrated low cytotoxicity and excellent safety profile in acute toxicity experiment in rats after oral administration with LD50 exceeding 2000 mg/kg of body weight. Binding mode of the active compounds in comparison with the reference agent was studied using molecular docking. The leading compounds represent viable preclinical candidates for the treatment of type 2 diabetes mellitus, as well as a promising starting point for the design of structural analogs with improved activity.