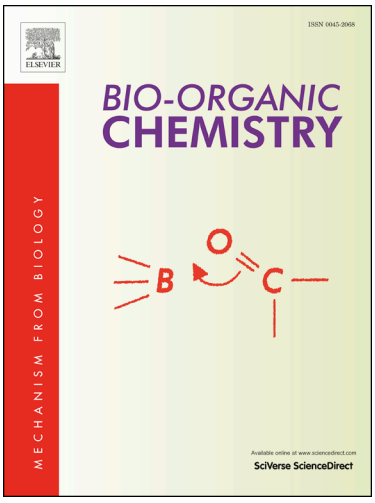

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Abstract

The free fatty acid receptor 1 (FFA1) is a potential target due to its function in enhancement of glucose-stimulated insulin secretion. Takeda's compound **1** has robustly *in vitro* activity for FFA1, but it has been suffered from poor pharmacokinetic (PK) profiles because the phenylpropanoic acid is vulnerable to β-oxidation. To identify orally available agonists, we tried to interdict the metabolically labile group by incorporating two deuterium atoms at the α-position of phenylpropionic acid. Interestingly, the differences of physicochemical properties between hydrogen and deuterium are quite small, but there are many differences in the structure-activity

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