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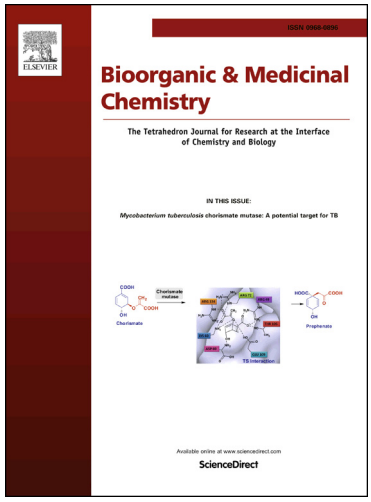

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Design, Synthesis and Structure–Activity Relationship Studies of Novel Free Fatty Acid Receptor 1 Agonists Bearing Amide Linker

Jianyong Yang[a,1], Zheng Li[a,1], Huilan Li[a], Chunxia Liu[a], Nasi Wang[a], Wei Shi[a], Chen Liao[a], Xingguang Cai[a], Wenlong Huang[a, b*], Hai Qian[a, b*]

[a] *Center of Drug Discovery, State Key Laboratory of Natural Medicines, China Pharmaceutical University, 24 Tongjiaxiang, Nanjing 210009, PR China.*

[b] *Jiangsu Key Laboratory of Drug Discovery for Metabolic Disease, China Pharmaceutical University, 24 Tongjiaxiang, Nanjing 210009, PR China.*

Abstract

The free fatty acid receptor 1 (FFA1/GPR40) has attracted extensive attention as a novel antidiabetic target. Aiming to explore the chemical space of FFA1 agonists, a new series of lead compounds with amide linker were designed and synthesized by combining the scaffolds of NIH screened lead compound **1** and GW9508. Among them, the optimal lead compound **17** exhibited a considerable agonistic activity (45.78 %) compared to the NIH screened compound **1** (15.32 %). During OGTT in normal mice, the compound **17** revealed a significant glucose-lowering effect (-23.7 %) at the dose of 50 mg/kg, proximity to the hypoglycemic effect (-27.8 %) of Metformin (200 mg/kg). In addition, the compound **17** (100 mg/kg) also exhibited a significant improvement in glucose tolerance with a 29.1 % reduction of glucose $AUC_{0\text{-}2h}$ in type 2 diabetic mice. All of these results indicated that compound **17** was considered to be a promising lead structure suitable for further optimization.

Keywords: Amide, FFA1 agonist, GPR40, Hybrid, Type 2 diabetes.

1. Introduction

* Co-corresponding authors: Wenlong Huang and Hai Qian, Centre of Drug Discovery, State Key Laboratory of Natural Medicines, China Pharmaceutical University, 24 Tongjiaxiang, Nanjing 210009, China.
Tel: +86-25-83271050; Fax: +86-25-83271050.
E-mail: ydhuangwenlong@126.com (W.l. Huang), qianhai24@163.com (H. Qian).
[1] These authors contributed equally to this work.