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Extended Abstract

New Diarylureas as Activators of the Heme-Regulated EIF2α Kinase for the Treatment of Type 2 Diabetes Mellitus †

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Type 2 diabetes mellitus (T2DM) has reached epidemic proportions. Unfortunately, current therapies for T2DM are suboptimal, and thus, there is an urgent need to develop more effective treatments. Fibroblast growth factor 21 (FGF21) has recently emerged as a therapeutic strategy for treating T2DM due to its antidiabetic effects, and this has led to the development of FGF21 long-acting analogs [1]. However, these compounds require subcutaneous injection and have shown some serious side effects, mainly due to their prolonged pharmacodynamic effect compared with native FGF21. Therefore, there is a need for orally available approaches to enhance FGF21 native production.

We have lately demonstrated that activation of the heme-regulated eIF2α kinase (HRI) by intraperitoneal administration of some already known *N,N'*-diarylureas increases FGF21 levels in liver, leading to an improvement of glucose intolerance and hepatic steatosis in mice fed a high-fat diet [2].

Encouraged by our findings, we aimed to design and synthesize new *N,N'*-diarylureas suitable for oral administration. Thus, a large series of compounds have been developed and evaluated in a human hepatocyte cell line in culture [3]. Further in vitro profiling (mice and rat microsomal stability, solubility, cytotoxicity) and pharmacokinetics have allowed us to select a candidate for in vivo efficacy studies. Proof-of-concept studies have demonstrated that oral administration of our lead compound improves glucose intolerance, hepatic steatosis, and hypertriglyceridemia in mice fed a high-fat diet [4].

Overall, the results presented herein suggest that orally bioavailable HRI activators induce FGF21 production and may be of clinical interest for the treatment of T2DM and other metabolic disorders.

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