# 1,3-DIAZO-4-OXA-[3.3.1]-BICYCLIC DERIVATIVES, PROCESS FOR THEIR MANUFACTURE AND THEIR USE AS A MEDICAMENT, IN PARTICULAR FOR TREATING DIABETES

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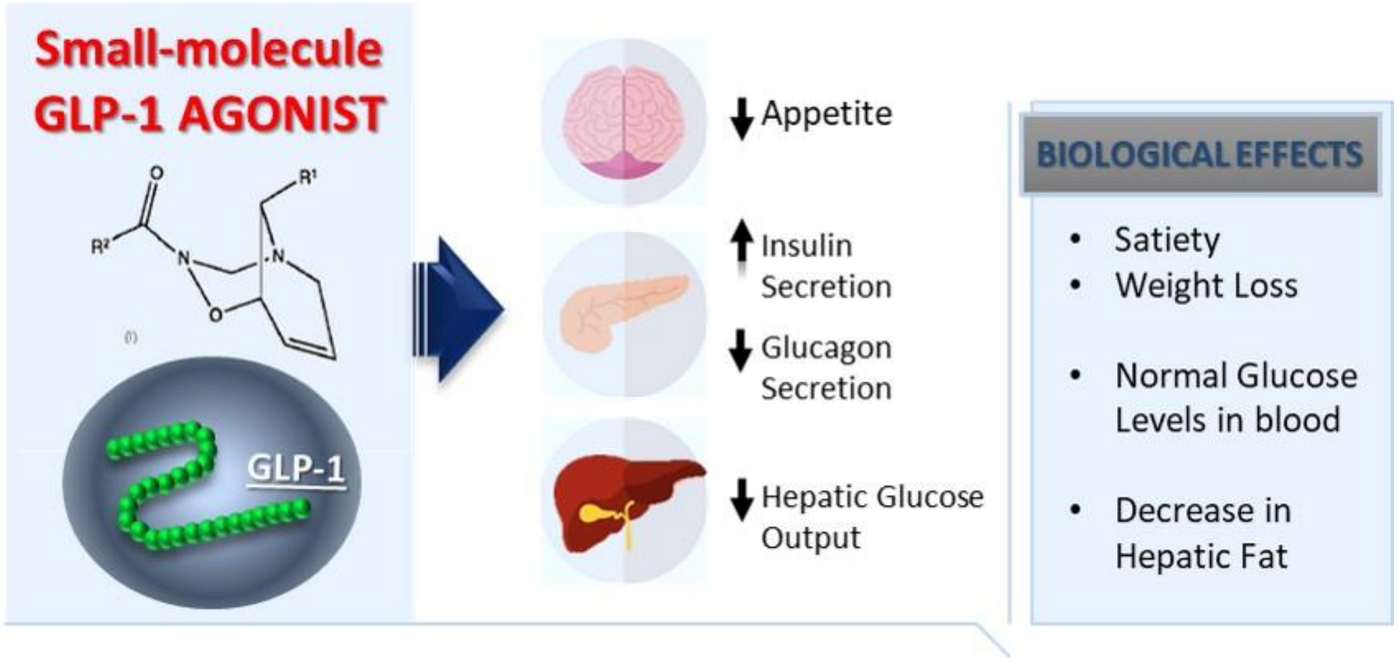
# Invention

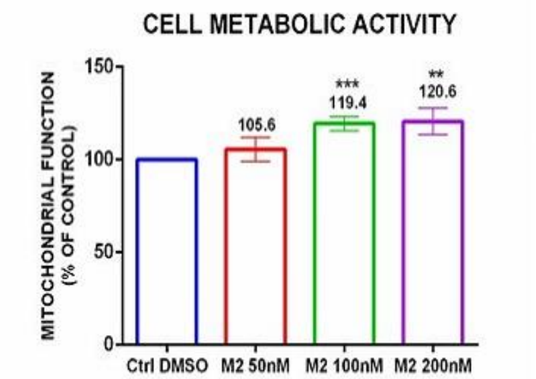
The present invention concerns the synthesis of small molecules, obtained by a totally innovative process, characterized by a stimulatory effect on the **secretion of GLP-1, a gastrointestinal hormone**. The compounds can be implicated in drug formulation for the development of innovative treatment for **diabesity and liver disease**.

GLP-1 is a gastrointestinal peptide hormone that enhances glucose-stimulated insulin secretion, decreases gastric emptying, and suppresses food intake. Activation of GLP-1 secretion has recently been shown to have a beneficial effect on liver diseases (fatty liver, NASH) and neurodegenerative diseases (Alzheimer, Parkinson).

The new synthetic compounds, stable in an aqueous medium, have **GLP-1 secretagogue activity**; they can, therefore, be conveniently exploited for the introduction of new orally active drugs into therapy for the treatment of type 2 diabetes, obesity, nonalcoholic fat loss disease (NAFLD) and neurodegenerative diseases (AD, PD).

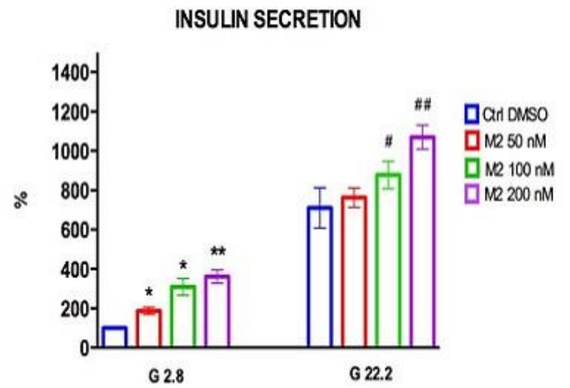
Drawings
& pictures




**Effect of M2 compound treatment on cell viability/metabolic activity in INS-1 cells.**

MTT assay in INS-1 cells exposed to M2 (50, 100 and 200 nM) after 1 h. Data are expressed as means ± standard error of 570 nM absorbance to % of control. ** $p < 0.002$, *** $p < 0.0002$ with respect to controls (t-test, n = 6).




**Effect of M2 compound treatment on glucose-induced insulin release in INS-1 cells.**

Acute glucose-induced insulin secretion in control cells and in cells exposed to 50, 100 or 200 nM of M2 compound for 1 h. *$P < 0.05$, **$P < 0.005$, vs. control at 2.8 mM glucose; #$P < 0.05$, ##$P < 0.005$ vs. control at 22.2 mM glucose; Student's t test (n = 4).

# Industrial applications

The purpose of this invention is to develop new pharmaceutical compositions, administered by os, for the **treatment of diabetes and obesity (diabesity), liver disease and related conditions**.

The development of an orally active antidiabetic drug may offer advantages in the management of type 2 diabetes care, **improving compliance** of patients, especially the elderly, and **reducing treatment costs**.

To date, there are no drugs with specific indication for the **treatment of NAFLD (Non-Alcoholic Fatty Liver Disease)**. Medical therapies used include drugs for the treatment of obesity, but these are burdened by possible side effects due to accumulation in the brain. An alternative is the use of GLP-1 analog drugs: to date commercially available compositions for the treatment of diabetes and obesity are Exenatide, Liraglutide, Semaglutide. Since these compounds are **peptide molecules**, they normally require parenteral and repeated administration, and give very pronounced side effects (nausea, vomiting, abdominal pain), thus demonstrating poor patient compliance along with very high costs to the health care system.

Our strategy is to introduce **new drugs able to increase GLP-1 secretion** based on small molecules that are stable, easy to prepare, and orally active.

## Possible developments

Heterobicyclic compounds, characterized by an innovative molecular scaffold, are able to increase GLP-1 secretion both *in vitro* and *in vivo*. *In vitro* experimental data and in silico prediction of ADME and toxicity are promising: some compounds resulted in increased GLP-1 levels in STC-1 cells, much greater than the reference compounds, oleoylethanolamide (OEA) and PMA. *In vivo* experiments on diabetic mice showed a significant increase in GLP-1 and insulin secretion.

Thanks to the preliminary SAR studies, structural modifications are being made to the original scaffold in order to obtain active molecules in the nanomolar range. At the same time, through collaboration with academic partners, studies on human astrocyte are being undertaken to evaluate the activity of the new small molecules on other types of targets.

The inventors are interested in future collaborations to increase the technological readiness level of the invention, considering licensing or possible transfer of the patented technology for development by interested pharmaceutical companies.

Take a look at the technology sheet and video: www.knowledge-share.eu/en/patent/new-bicyclic-compounds-for-diabetes-treatment/

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