NEW ACTIVATORS OF SIRT1 ENZYME FOR THE TREATMENT OF CARDIOVASCULAR AND CARDIOMETABOLIC PATHOLOGIES

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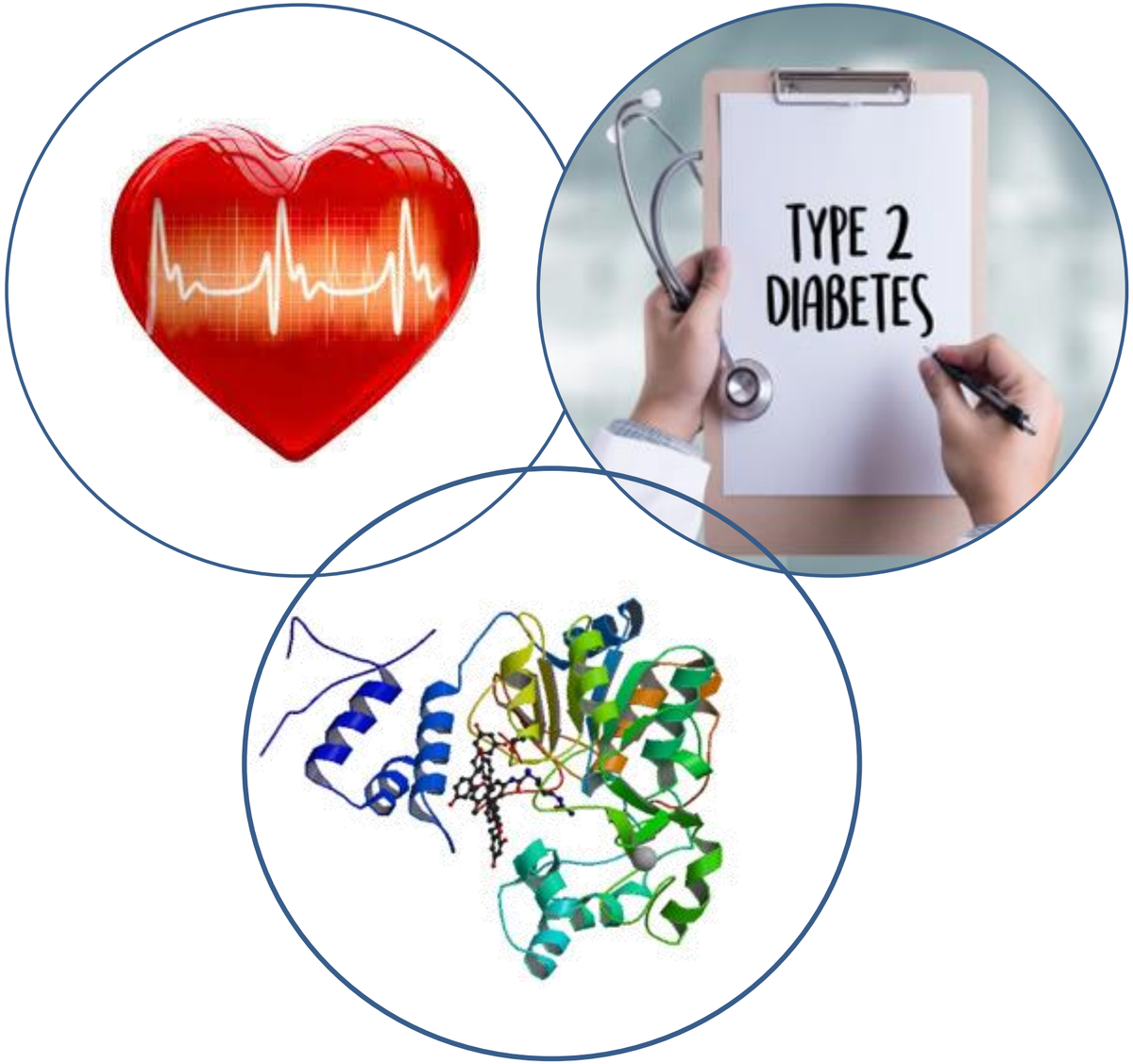
Invention

The present invention targets a class of **compounds able to activate the enzyme SIRT1 in humans** by regulating numerous metabolic functions. The appropriately designed compounds could be used in pharmaceutical formulations, preferably in the treatment or prevention of cardiometabolic diseases, including diabetes, and cardiovascular diseases, including coronary artery disease, heart failure, acute myocardial infarction, and atherosclerosis.

Sirtuins constitute a family of deacetylase enzymes deeply involved in metabolic regulation. To date, seven types of enzymes have been described, classified from SIRT1 to SIRT7 on the basis of different cellular localization. SIRT1 is biosynthesized at the nuclear level and transferred, depending on cellular needs, to the cytosolic level, where it is able to affect mitochondrial and whole-cell metabolic activity by modulating various transcriptional cofactors critical for maintaining homeostasis.

The reduction in its expression and/or activity that is also observed in mammals with advancing age may be a key to explaining the worsening of age-related cellular function, which is also a cause of various cardiovascular and noncardiovascular diseases. Recent studies show that the enzyme is less functional in patients with heart failure and coronary artery disease and, in preclinical studies, its activity is reduced following ischemia-reperfusion protocols; finally, SIRT1 is involved in insulin resistance, suggesting that it could be an interesting target in the management of type II diabetes mellitus.

Drawings
& pictures



Industrial applications

The research aims to demonstrate **antidiabetic efficacy resulting from SIRT 1 enzyme activation from new chemical entities** synthesized in a research laboratory.

The molecules, acting as SIRT1-activators, could exert an anti-aging action, opening up a considerable range of therapeutic possibilities for the treatment of diseases where aging, inflammaging and oxidative stress processes are involved.

Cardiovascular disease is still the leading cause of disease and death in Western countries. One of the main risk factors is precisely age, which contributes significantly to the increased likelihood of morbidity and death.

Further field of application of patented molecules concerns kidney diseases associated with various conditions (e.g., diabetic nephropathy, age-associated nephropathies), which do not currently have gold standard therapies.

Some patents on SIRT1-activating compounds have been produced (Graziadio, et al. Med chem 2016, 6:6). However, to the best of our knowledge, there are to date no SIRT1-activators in development as antidiabetics, and none of the patents on SIRT1-modulators claims pharmacological activities for kidney disease.

Possible developments

The patent compounds were developed with the aim of improving activity, selectivity, and bioavailability of the SIRT1 activators discovered so far, and preliminary studies confirm their full potential. Indeed, the newly synthesized molecules showed **interesting SIRT1 activation properties**, in many cases higher than the reference compounds (e.g. resveratrol). Selected compounds also showed interesting **cardioprotective properties** in the acute myocardial infarction model. The molecules have demonstrated *in vitro* abilities to **enhance glucose uptake** by human liver cells (HepG2 line).

More recent data obtained in the experimental development of the project have also identified a possible and highly advantageous use of these molecules in other therapeutic areas, in parallel with the cardiovascular and metabolic fields.

Future studies could focus in the field of renal diseases associated with different conditions (e.g., diabetic nephropathy, aging-associated nephropathies), as these diseases do not have a gold standard to date.

The research was developed within the Department of Pharmacy (University of Pisa) by an experienced team in Pharmaceutical Chemistry and Pharmacology. The inventors are interested in future collaborations to increase the technological readiness level of the invention and develop innovative products in the pharmaceutical field.

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