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DISCOVERY OF NOVEL SIRT5 ACTIVATORS AS POTENTIAL ANTI-INFLAMMATORY AGENTS

Chaired by Dr. Alfredo Berzal-Herranz and Prof. Dr. Maria Emília Sousa

pharmaceuticals MDPI

Arianna Gelain[1,*], Matteo Mori[1], Giulia Cazzaniga[1], Fiorella Meneghetti[1], Vincent Wong[2], Li Jun Yang[2], Paolo Saul Coghi[3] and Stefania Villa[1]

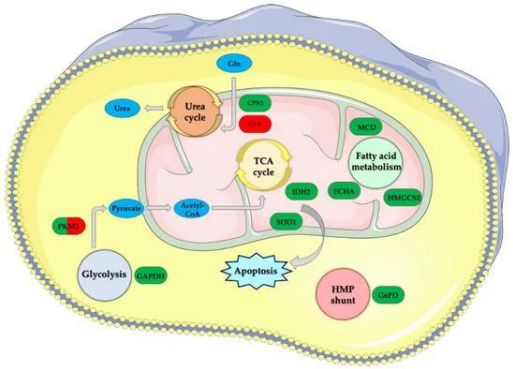
[1] University of Milan, Department of Pharmaceutical Sciences;
[2] Macau University Science and Technology, Dr. Neher's Biophysics Laboratory for Innovative Drug Discovery and State Key Laboratory of Quality Research in Chinese Medicine;
[3] Macau University Science and Technology, School of Pharmacy and State Key Laboratory of Quality Research in Chinese Medicine

* Corresponding author: arianna.gelain@unimi.it

DISCOVERY OF NOVEL SIRT5 ACTIVATORS AS POTENTIAL ANTI-INFLAMMATORY AGENTS

Graphical Abstract

SIRT5 →



→ STACs → ANTI-INFLAMMATORY ACTIVITY

Abstract:

NAD^+-dependent class-III histone deacetylases (HDACs), also known as sirtuins (SIRTs), comprise seven isoforms (SIRT1-7) that play key roles in maintaining cellular functions, regulating metabolic and homeostatic processes, and preventing oxidative stress damage. SIRT5 is located in the mitochondrial matrix (along with SIRT3, which shares some of its activities, and SIRT4). This isoform regulates the metabolism of ammonia, the tricarboxylic acid cycle (TCA), glycolysis, fatty acid oxidation, apoptosis, and the electron transport chain. Considering the potential of SIRT5 as a pharmacological target, several modulators, acting as both sirtuin-activating (STACs) and sirtuin-inhibiting compounds (STICs), have been published. SIRT5 deficiency is known to increase the severity of rheumatoid arthritis in rat model; so, its activation may exert an anti-inflammatory role. On this basis, we decided to focus our efforts on SIRT5 STACs, since only few selective SIRT5 activators have been reported in the literature so far.

In an attempt to identify novel anti-inflammatory agents, we considered the repositioning of several compounds belonging to our in-house library, also including some furan derivatives, active as antitubercular agents.

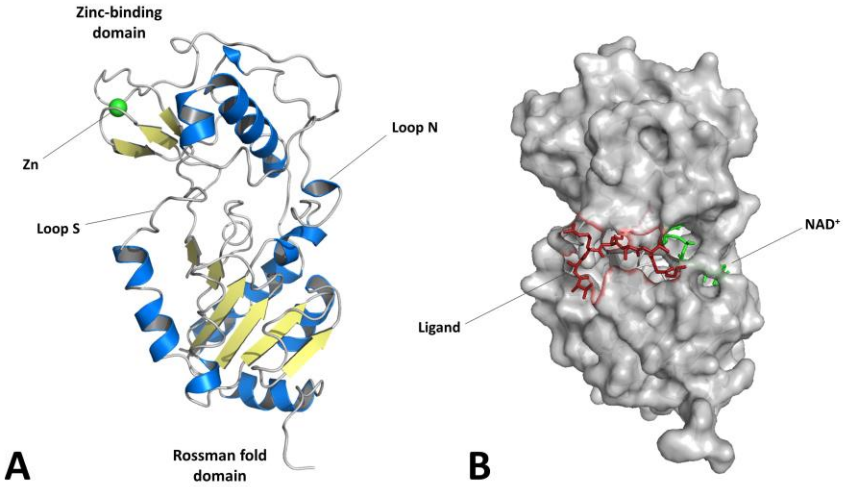
The compounds were screened by a SIRT5 promoter assay, and their SIRT5 desuccinylation activity was evaluated. Some of them showed interesting properties as SIRT5 activators and, most notably, no cytotoxic activity. The preliminary results of our ongoing studies will be presented.

Keywords: Sirtuins; SIRT5 activators; repositioning; furan derivatives.

Introduction

SIRT5

Sirtuins belong to HDACs, class III histone deacetylase and use NAD^+ as cofactor.
Seven type of sirtuins in mammals: SIRT1,2 (nucleus); SIRT3,4 (mitochondria);
SIRT5 (mitochondria and cytosol); SIRT6 and SIRT7 (nucleus).
SIRT5 is composed by fourteen α helices and nine β strands, organized in two domains: Zn^{2+} binding domain and Rossmann fold domain.

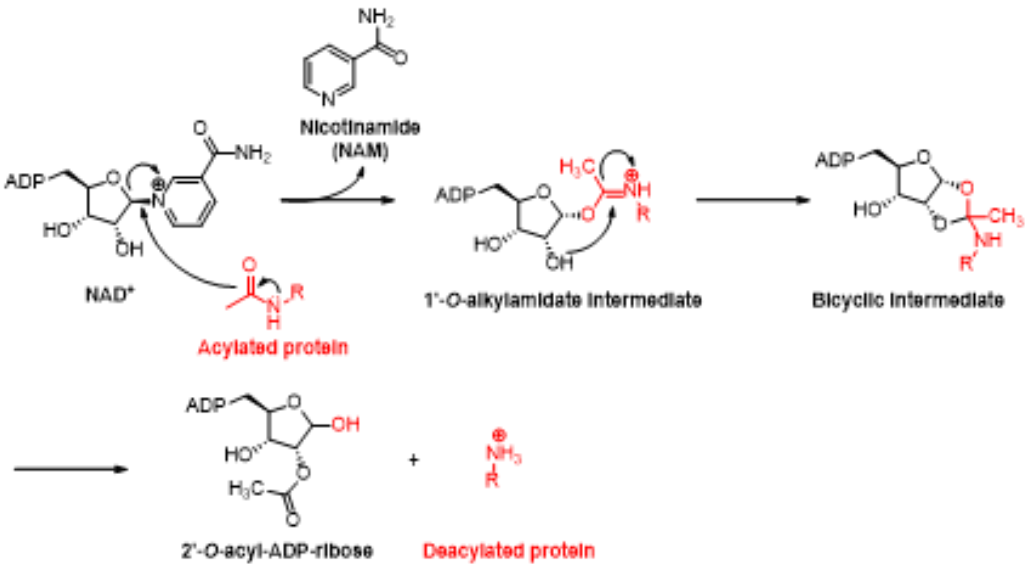


A) Ribbon diagram of SIRT5 (PDB code: 3RIY) evi idencing the two domains and the position of the zinc cofactor. α-Helices are colored blue, β-sheets are yellow, while undefined loops are gray.
B) Surface representation of SIRT5 (PDB code: 3RIY), highlighting the succinyl-lysine peptide substrate (Thr-Ala-Arg-SLL-Ser-Thr-Gly-Gly, red) and the NAD+ cofactor (green), bound in their respective pockets.

Mori, M. *et al.* , Molecules, **2022,** *17,* 4449.

SIRT5 ACTIVITY

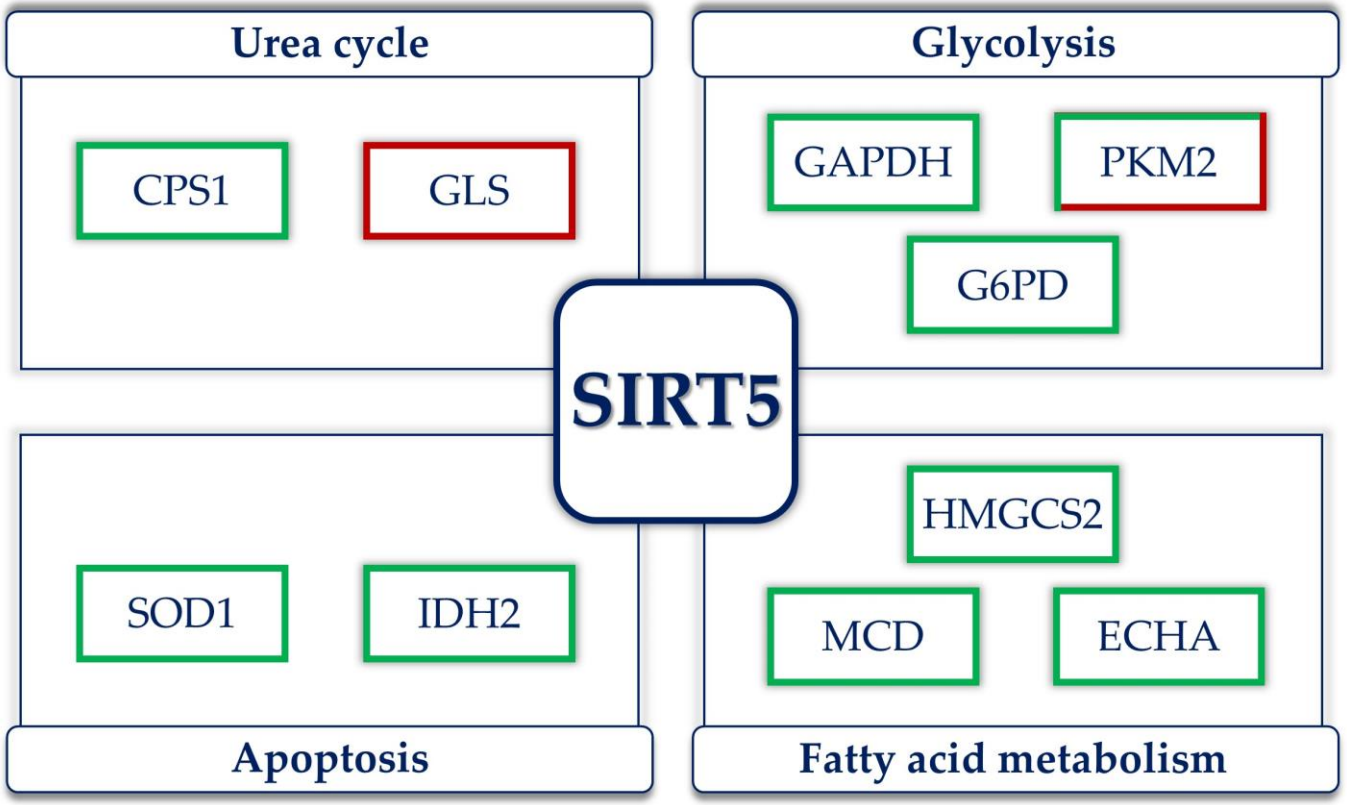
SIRT5 removes of acidic acyl groups (succinyl, malonyl and glutaryl) moieties from lysine residues.



Mechanism of the deacetylation reaction catalyzed by SIRTs

Mori, M. *et al.* , Molecules, **2022,** *17,* 4449.

SIRT5 ROLES



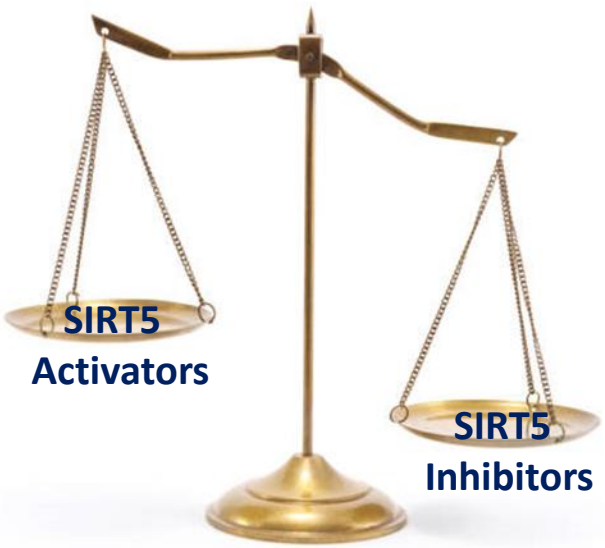
Graphical representation of the main metabolic pathways regulated by SIRT5. The activated targets are contained in green boxes, whereas inhibited proteins are in red.

Mori, M. *et al.* , Molecules, **2022,** *17,* 4449.

SIRT5 MODULATION

Considering the potential role of SIRT5 as a pharmacological target in cancer, diabetes, cardiovascular diseases, obesity, neurodegenerative disorders, and inflammation, many studies have been undertaken to identify new molecules acting as:

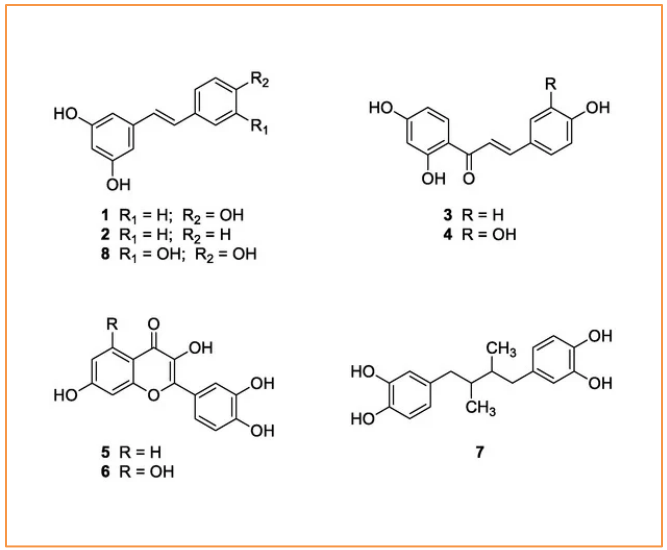
- SIRT5 activators (STACs)
- SIRT5 inhibitors (STICs)



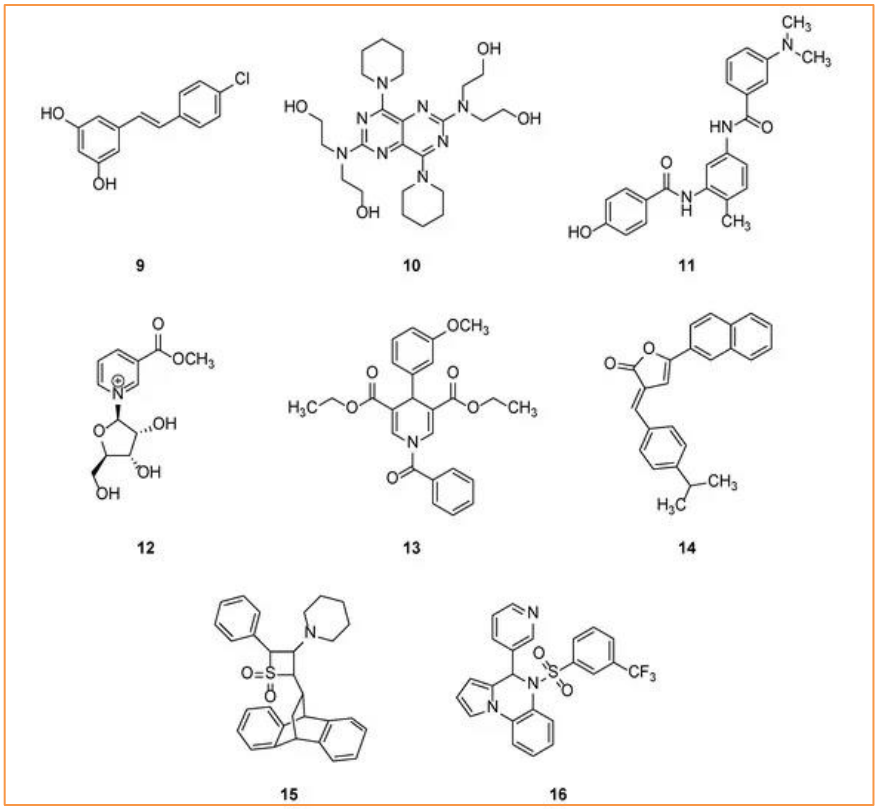
Mori, M. *et al.* , Molecules, **2022,** *17,* 4449.

OVERVIEW OF RECENT KNOWN STACs

STACs induce cellular and physiological effects amplified by downstream signaling pathways and they have been studied for the potential role in the treatment of type 2 diabetes, hyperlipidemia and hypercholesterolemia, various tumors, Alzheimer's disease and rheumatoid arthritis.



Chemical structures of the natural SIRT5 activators



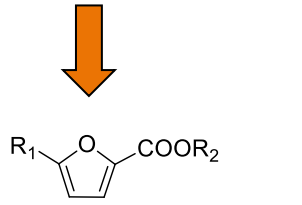
Chemical structures of the synthetic SIRT5 activators

Mori, M. *et al.* , Molecules, **2022,** *17,* 4449.

Results and discussion

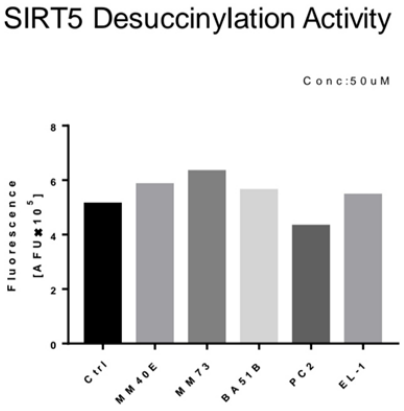
FURAN DERIVATIVES AS SIRT5 ACTIVATORS

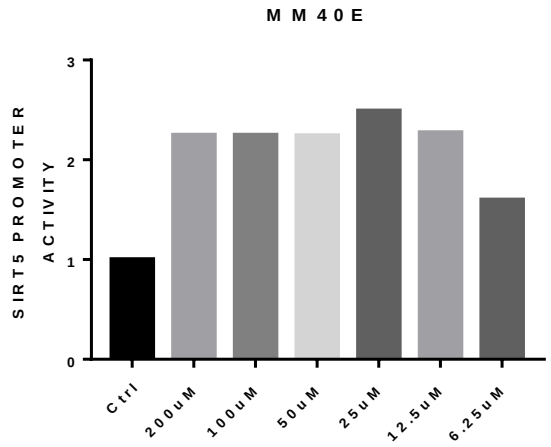
By repositioning of several compounds belonging to our in-house library

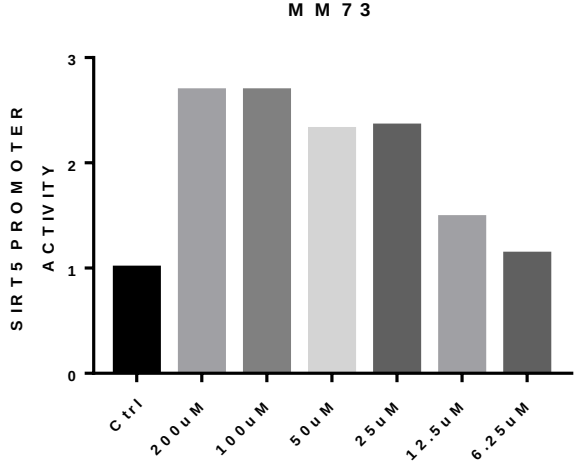


R_1= NO_2,  , etc.

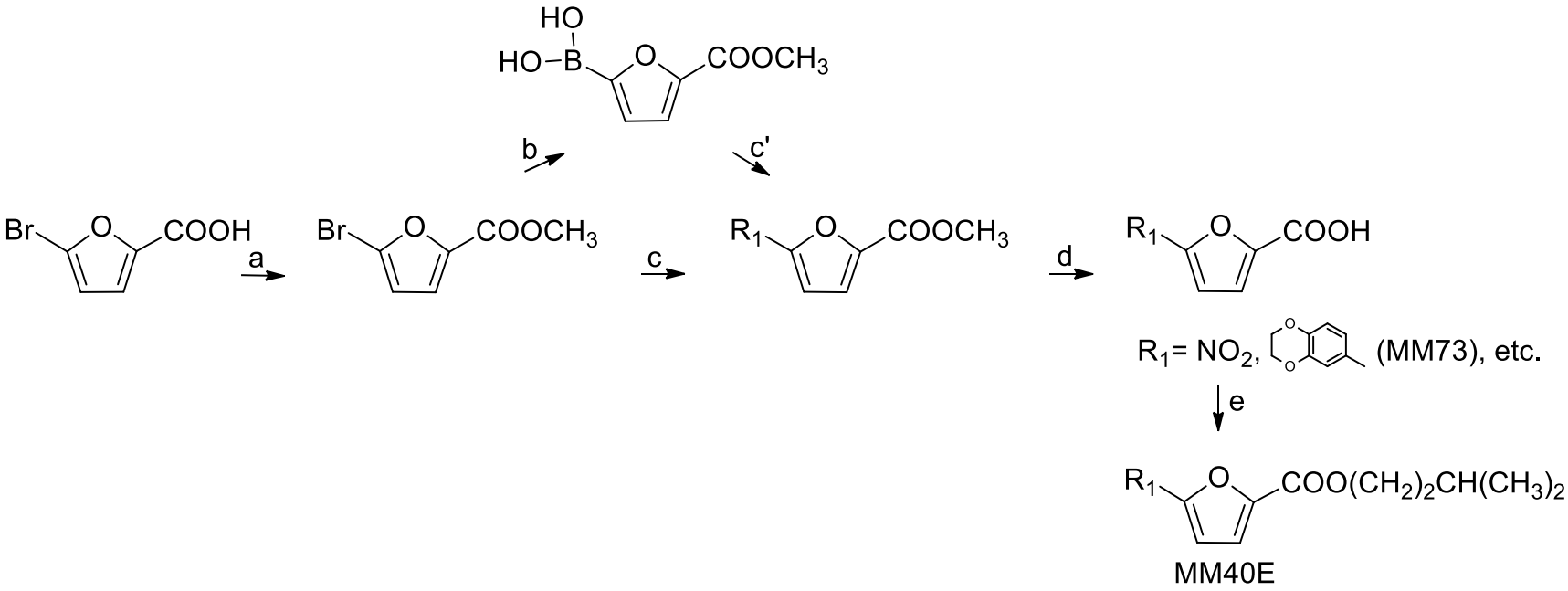
R_2= H, CH_3, $CH_2CH_2CH(CH_3)_2$, etc.





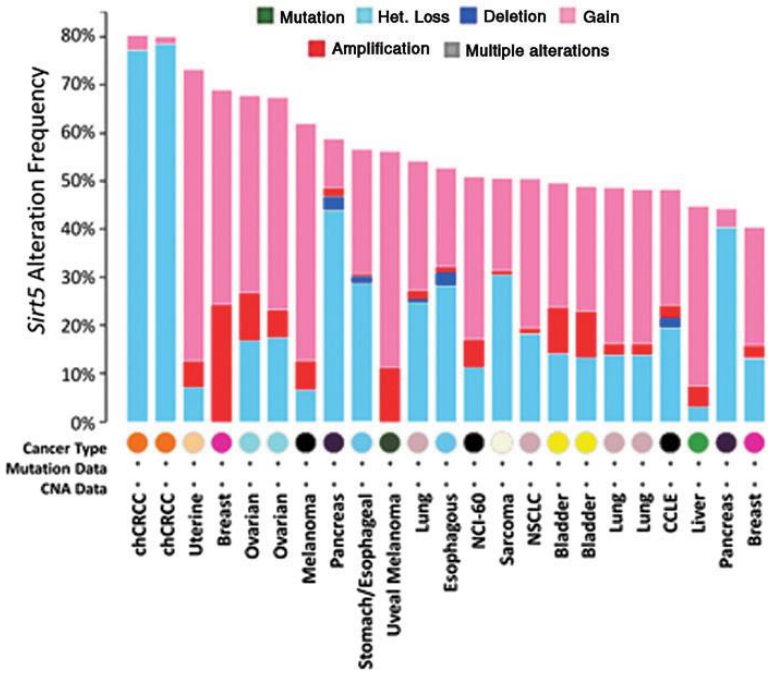


FURAN DERIVATIVES SYNTHESIS



Reagents and conditions: a) conc. H_2SO_4, CH_3OH, reflux, 24h; b) i-PrMgCl, *Bis* [2-(*N*,*N*-dimethylamino) ethyl] ether, $B(OCH_3)_3$,THF, 15°C, 20 min → 20°C, 30 min → 0°C, 10 min, N_2; c) suitable reagent ($R_1BO_2H_2$ or R_1Br), $Pd(PPh_3)_2Cl_2$, 2M Na_2CO_3, 1,4-dioxane, 90°C, overnight, N_2; d) 1M NaOH, CH_3CH_2OH/THF 1:1, reflux, 5h; e) conc. H_2SO_4, 3-methylbutan-1-ol, reflux, 24 h.

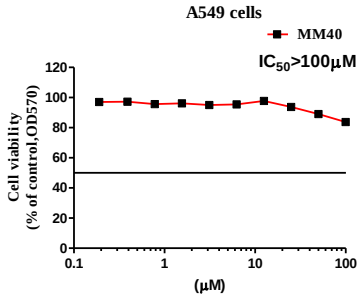
SIRT5 AND CANCER

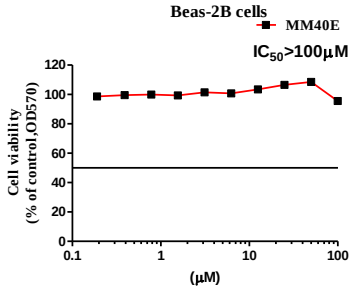


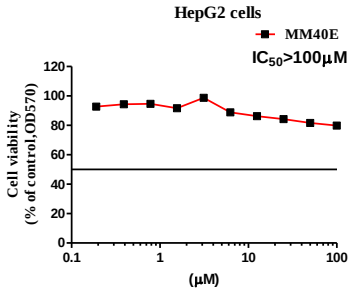
SIRT5 gene alterations are different in various cancer types.

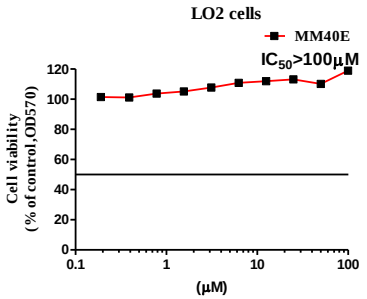
Bringman-Rodenbarger X. *et al.,* Antioxidants & Redox Signaling, **2018,** *28*, 680.

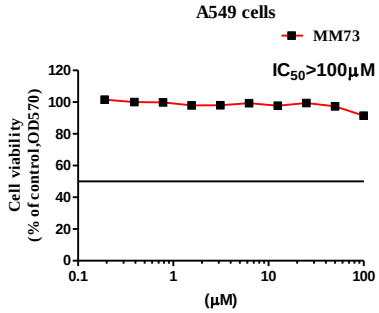
FURAN DERIVATIVES ANTIPROLIFERATIVE ACTIVITIES ASSAYS

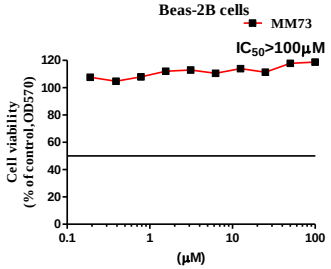


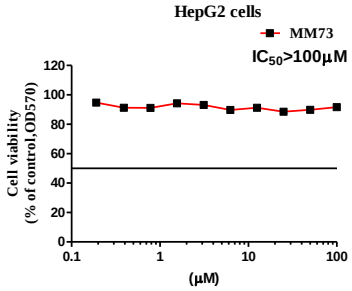


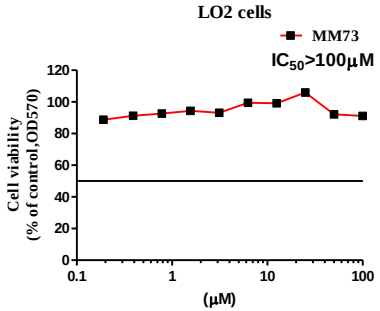












A549 cancer lung cell lines | Beas 2B Normal lung cells lines | HepG2 Cancer liver cells lines | LO2 Normal liver cells lines

Conclusions

FUTURE PERSPECTIVES

Work in progress:

- Tests evaluating the anti-inflammatory activity

- Selectivity assay *versus* SIRT3

- Computational studies to clarify the interactions of the furan derivatives with SIRT5

Acknowledgments

UNIVERSITÀ DEGLI STUDI DI MILANO
FACOLTÀ DI SCIENZE DEL FARMACO
DiSFarM Dipartimento di Scienze Farmaceutiche

School of Pharmacy
MACAU UNIVERSITY OF SCIENCE AND TECHNOLOGY

Thank you for your kind attention