N-(5-(3-Methoxybenzyl/pyrimidin-2-yl-methyl)-1,3,4-oxadiazol-2-yl)-2-(arylthio)acetamide Derivatives as SIRT2 Inhibitors

Ahmet Bugra AKSEL[1], Yesim OZKAN[2], Gokcen EREN[1]
[1]SIRTeam Group, Faculty of Pharmacy, Department of Pharmaceutical Chemistry, Gazi University, 06330, Ankara, Turkey
[2]Faculty of Pharmacy, Department of Biochemistry, Gazi University, 06330, Ankara, Turkey

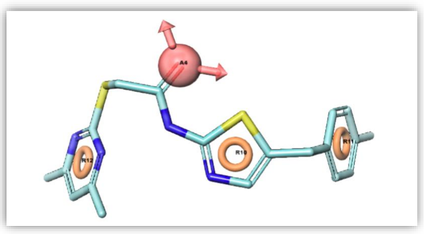
ABSTRACT

The SIRT family is known as NAD^+-dependent class III histone deacetylase enzymes. Mammalian sirtuins consist of seven isoforms (SIRT1-7), which show different subcellular localizations and enzymatic functions [1]. Accordingly, inhibition of SIRT2 activity has been associated with cancer, diabetes, inflammation, and neurodegeneration pathogenesis [2]. Herein, we reported the synthesis, characterization, and SIRT2 inhibition profiles of *N*-(5-(3-methoxybenzyl)-1,3,4-oxadiazol-2-yl)-2-(arylthio)acetamide and *N*-(5-(pyrimidin-2-yl-methyl)-1,3,4-oxadiazol-2-yl)-2-(arylthio)acetamide derivatives which were designed based on the key interactions in SIRT2 active site.

DESIGN

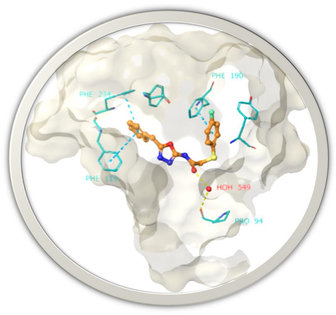
In our previous study [3], a pharmacophore-based virtual screening campaign was performed by a strategy combining ligand- and structure-based features.

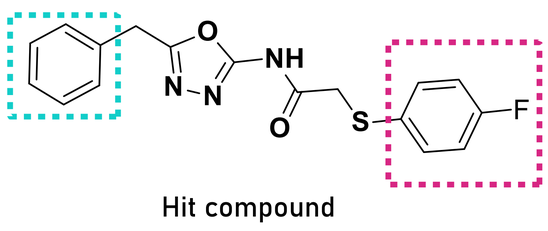
Ligand- and structure-based pharmacophore



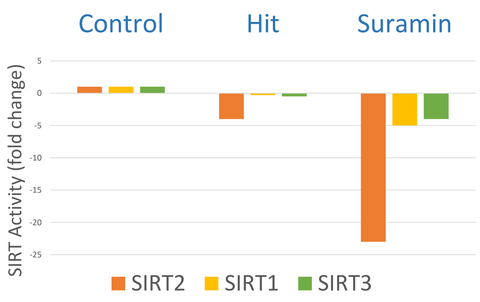
Virtual screening

Molecular docking



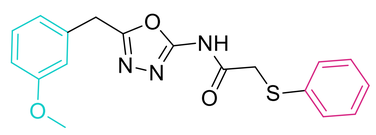


Hit compound

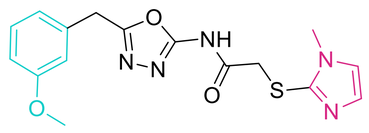


H2L

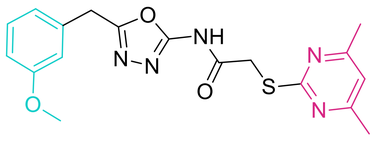
1



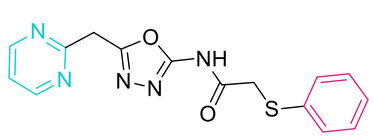
2



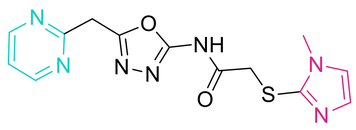
3



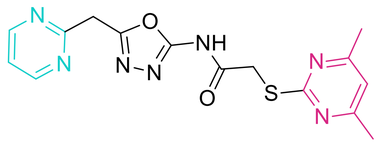
4



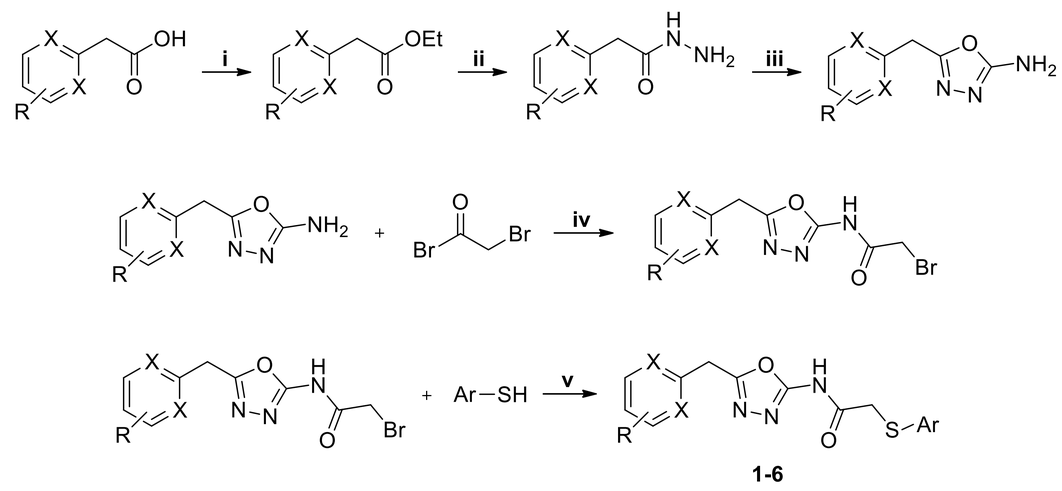
5



6



SYNTHESIS



i. H_2SO_4, EtOH, reflux, 6h, **ii.** hydrazine hydrate, EtOH, reflux, 6h, **iii.** cyanogen bromide, MeOH, reflux, 6-8h, **iv.** TEA/pyridine, DCM, rt, 2-4h, **v.** NaOH, EtOH:H_2O, rt, 4-6h

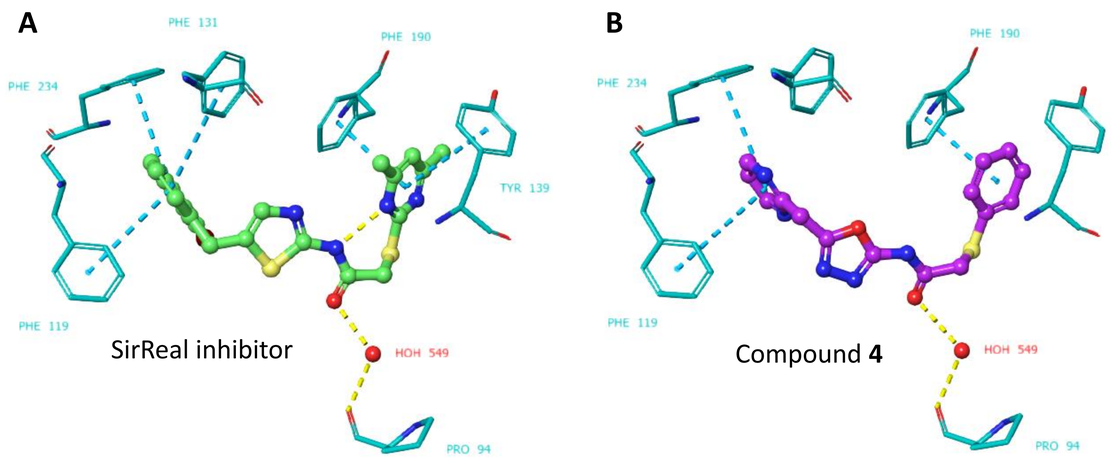
BIOLOGICAL DATA

The synthesized compounds were evaluated in a fluorescence-based assay using Fluor de Lys SIRT2 Fluorometric Drug Discovery Kit (BML-AK556-0001), according to the supplier's protocol (Enzo Life Sciences).

Compound ID	SIRT2 Inhibition(%) @ 100 uM
1	n.i.
2	21.24±4.71
3	n.i.
4	60.40±0.47
5	35.30±0.14
6	49.41±8.38
Suramin	98.37±0.25

MOLECULAR DOCKING

It has been reported that π-π contacts with Tyr139 and Phe190 in selectivity pocket, H-bonding with Pro94 via water-bridged, and π-π contacts with Phe119, Phe131, Phe234 located at the entrance of substrate channel required for selective SIRT2 inhibition [4]. Compound 4 made π-π interactions with Phe119, Phe190, Phe234 and H-bonding with Pro94 via water-bridge.



PDB: 5DY4

REFERENCES

[1] Wątroba, M., Dudek, I., Skoda, M., Stangret, A., Rzodkiewicz, P., & Szukiewicz, D. Sirtuins, epigenetics and longevity. Ageing research reviews, 40, 11–19 (2017).
[2] Aventaggiato, M., Vernucci, E., Barreca, F., Russo, M. A., & Tafani, M. Sirtuins' control of autophagy and mitophagy in cancer. Pharmacology & therapeutics, 221, 107748 (2021).
[3] Eren G., Bruno A., Guntekin-Ergun S., Cetin-Atalay R., Ozgencil F., Ozkan Y., Gozelle M., Kaya SG., Costantino G. Pharmacophore modeling and virtual screening studies to identify novel selective SIRT2 inhibitors. J. Mol. Graph. Model. 89, 60 (2019).
[4] Schiedel, M., Rumpf, T., Karaman, B., Lehotzky, A., Oláh, J., Gerhardt, S., Ovádi, J., Sippl, W., Einsle, O., & Jung, M. Aminothiazoles as Potent and Selective Sirt2 Inhibitors: A Structure-Activity Relationship Study. Journal of medicinal chemistry, 59(4), 1599–1612 (2016).

This study was supported by the Scientific and Technological Research Council of Turkey (TUBITAK SBAG 118S673).