N-(5-ARYLMETHYL-1,3,4-OXADIAZOLE-2-YL)-2-(ARYLTHIO)ACETAMIDE AS NEW SCAFFOLD FOR DEVELOPING SMALL-MOLECULE SIRT INHIBITORS

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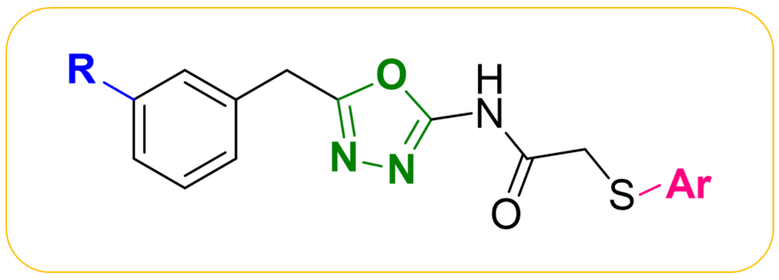
SIRTs

- Histone deacetylase deregulation causes silencing of tumor suppressor genes and overexpression of oncogenes. The **SIRT** family is known as NAD+ dependent **Class III histone deacetylase enzymes**.
- There are seven sirtuin isoforms (SIRT 1-7) that diverse in cellular localization, regulation, and substrate selectivity in mammals.
- Among this SIRT isoforms, **SIRT2** activity has been found associated with variety of cancers, neurodegenerative disorders.

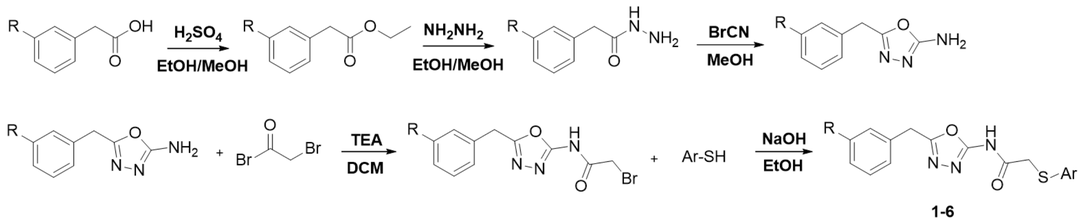
DESIGN



R: -H
-CN

Ar: -phenyl
-1-methyl-*1H*-imidazole-2-yl
-4,6-dimethylpyrimidine-2-yl

SYNTHETIC ROUTE

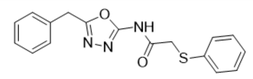
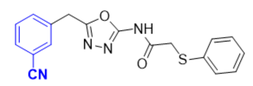
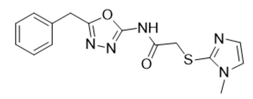
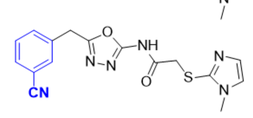
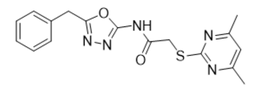
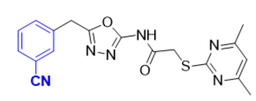


1-6

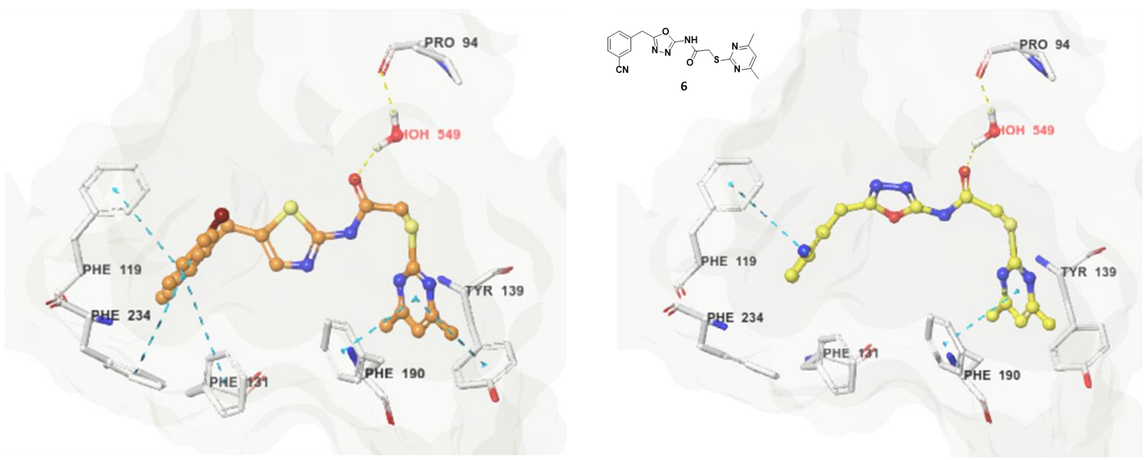
R: -H
-CN

Ar: -phenyl
-1-methyl-*1H*-imidazole-2-yl
-4,6-dimethylpyrimidine-2-yl

BIOLOGICAL DATA

ID	Structure	SIRT2 Inhibition% (@100 uM)
1		n.i.
2		22.91±2.14
3		n.i.
4		38.45±7.26
5		n.i.
6		**47.12±4.71**
Suramin		**94.52±0.92**

MOLECULAR DOCKING



Active site of **SIRT2** (PDB: 5DY4). **(A)** Binding conformation of SirReal inhibitor in the x-ray structure. **(B)** Predicted binding conformation of the compound **6.**

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