IECC 2026 Conference
The 5th International Electronic Conference on Cancers
10–12 June 2026 | Online
MDPI

In Silico Pharmacokinetic Profiling And Molecular Docking Of Margolonone Against The Oncogenic Idh1-r132h Mutant

Charu Verma[1], Praveen Kumar Verma[2]
[1] Centre for Interdisciplinary Research in Basic Sciences (CIRBSC), Jamia Millia Islamia, New Delhi, India
[2] National Museum of Natural History, New Delhi, India

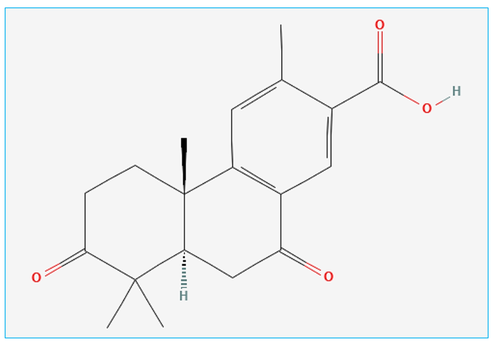
INTRODUCTION & AIM

Mutations in the isocitrate dehydrogenase 1 (IDH1) enzyme, specifically the R132H substitution, are primary drivers in several malignancies. This mutation confers a neomorphic ability to produce the oncometabolite D-2-hydroxyglutarate (D-2-HG), promoting tumorigenesis.

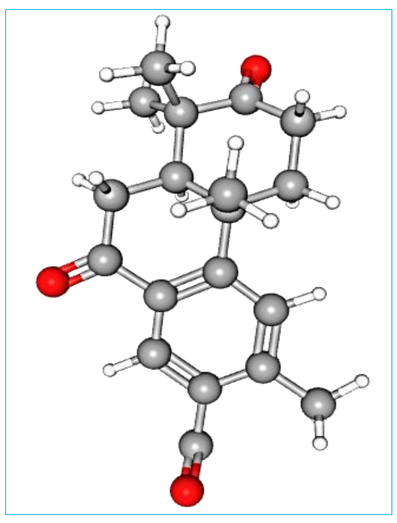
Targeting the altered catalytic pocket of IDH1-R132H remains a critical therapeutic strategy. This study investigates the biophysical viability of **Margolonone**, a novel phytochemical scaffold, as a potential selective inhibitor.

LIGAND STRUCTURE

Margolonone features a unique scaffold with oxygen-rich functional groups optimised for polar contacts in enzymatic active sites.



2D Structure



3D Ball-and-Stick

METHODOLOGY

- **Receptor:** IDH1-R132H mutant crystal structure (PDB ID: 6ADG). Co-crystallized ligands removed; polar hydrogens added.
- **Ligand:** Prepared in PDBQT format with Gasteiger charges.
- **Grid Box:** 20 × 20 × 20 Å search space centered on the mutated His132 residue.
- **Software:** (PDB ID: 6ADG), software (Webina, ChimeraX_daily for visualization), and web servers (SwissADME) .

BIOCHEMICAL PATHWAY

Margolonone acts as a roadblock, inhibiting the production of the D-2-HG oncometabolite.
By physically anchoring within the mutant catalytic pocket, it sterically hinders α-KG binding, effectively halting D-2-HG production and restoring balance.

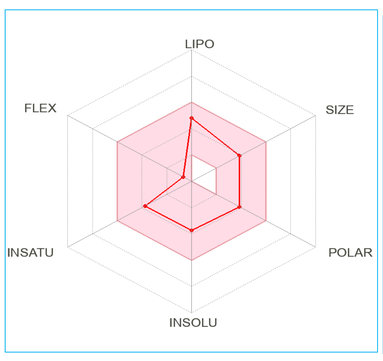
Mechanism of Action:

- **Wild-Type IDH1:** Catalyzes the oxidative decarboxylation of isocitrate to α-ketoglutarate (α-KG).
- **Oncogenic Mutation (R132H):** Confers a neomorphic activity, consuming NADPH to reduce α-KG into the oncometabolite D-2-hydroxyglutarate (D-2-HG).
- **Margolonone Intervention:** By selectively anchoring in the mutant catalytic pocket, Margolonone sterically blocks the α-KG binding site, arresting the oncogenic cascade and preventing D-2-HG accumulation.

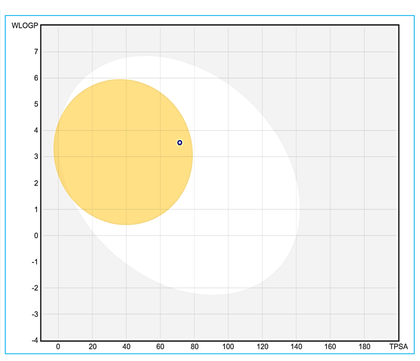
PHARMACOKINETICS (ADME)

Computational profiling was conducted via the SwissADME server to evaluate lead-likeness and physicochemical stability.

Parameter	Value
Molecular Weight	314.4 g/mol
Lipophilicity (XLogP3)	2.9
Lipinski Violations	0



Bioavailability Radar



BOILED-Egg Plot

Margolonone exhibits optimal molecular weight and lipophilicity, suggesting high permeability across cell membranes and gastrointestinal absorption.

MOLECULAR DOCKING RESULTS

Simulations revealed highly spontaneous and stable binding within the mutant catalytic pocket.

HIGHEST BINDING AFFINITY
ΔG = -6.224 kcal/mol

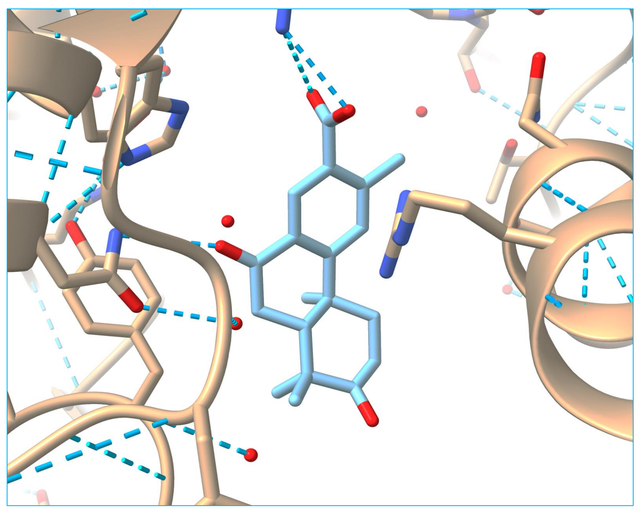


Figure 1: Hydrogen Bond (Showing ASN96 Interaction)

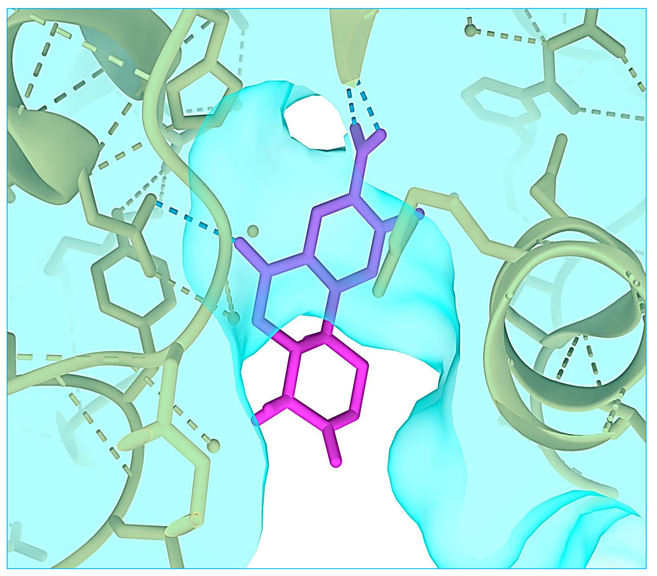


Figure 2: Surface Cavity (Frosted-Glass Effect)

Structural Analysis: Margolonone successfully penetrates the target pocket alongside the oncogenic His132. Stability is heavily anchored by strong, direct polar hydrogen bonding with the **ASN96** residue and hydrophobic packing against the surrounding alpha-helices.

CONCLUSION

The combination of optimal lipophilicity, zero structural violations, and a highly favorable binding thermodynamic energy indicates that Margolonone is a potent, stable ligand for the IDH1-R132H mutant. These findings present Margolonone as a highly viable pharmacokinetic scaffold, warranting immediate in vitro enzymatic validation.

References:
1. RCSB Protein Data Bank (PDB ID: 6ADG).
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3. Pettersen, E. F., et al. (2021). UCSF ChimeraX: Structure visualization for researchers, educators, and developers. *Protein Science*.
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Acknowledgments:
We gratefully acknowledge at the Centre for Interdisciplinary Research in Basic Science (CIRBSC), Jamia Millia Islamia, for providing the resources and support necessary for this computational study.