SUPPLEMENTARY DATA

Integrative Machine Learning-Guided *In-silico* and *In-vitro* Approach Reveals Selective Small Molecule Inhibitors Targeting Mutant IDH1

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Files

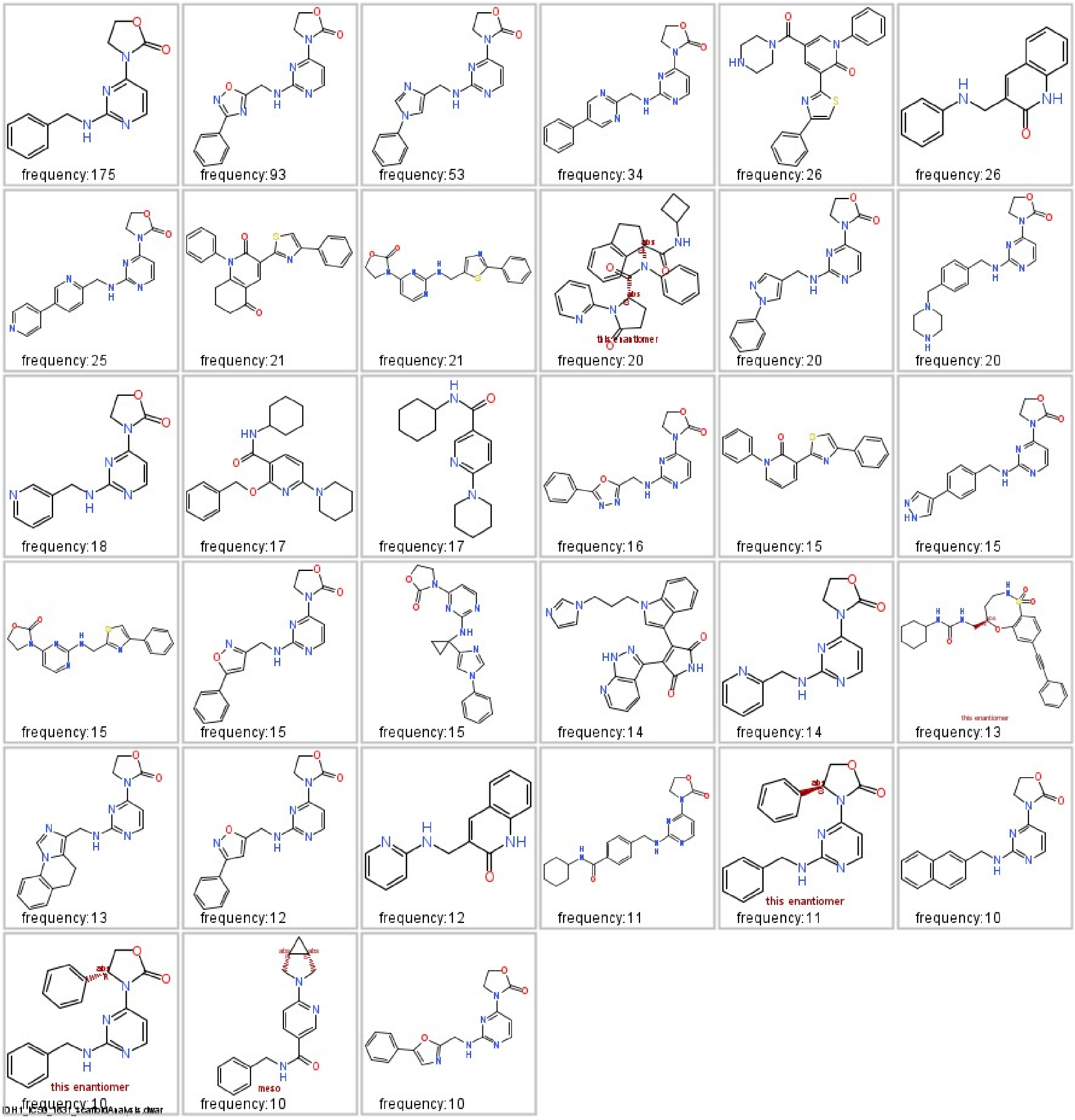
Supplementary File S1: Curated dataset of 1631 compounds used for model building and validation with descriptor data and pIC50 values

Supplementary File S2: Final dataset of 1342 structurally diverse compounds curated after applying Tanimoto similarity filter (< 0.85) randomly split in an 80:20 ratio into training and test sets.

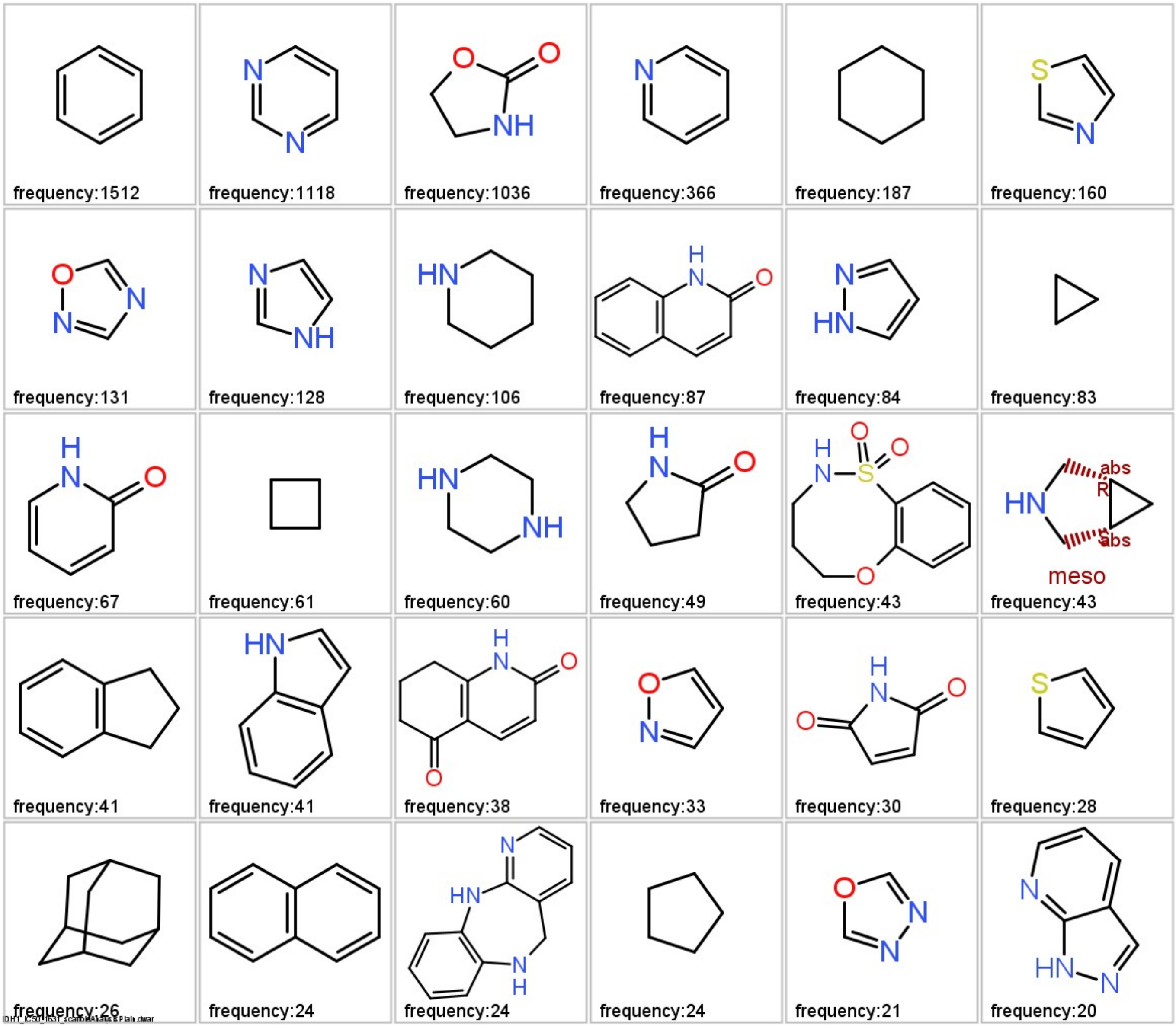
Supplementary File S3: The actual and predicted pIC50 values of 1631 compounds using selected features on Random Forest model highlighting robustness and potential of this model for the prediction of biological activity of unknown compounds.

Figures

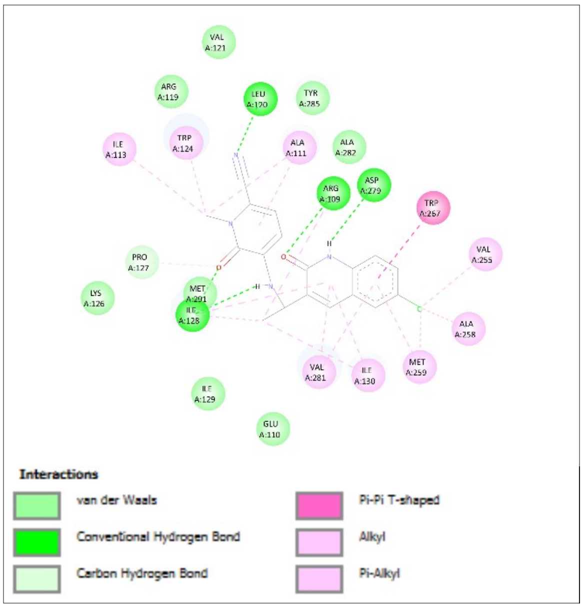
Supplementary Figure S1: The figure represents most frequent Murcko scaffolds identified for the ML dataset of bioactive compounds against IDH1. Each structure represents a distinct core framework, with the count indicating corresponding frequencies of occurrence. These scaffolds highlight key structural backbones and the recurring chemotypes within the dataset.



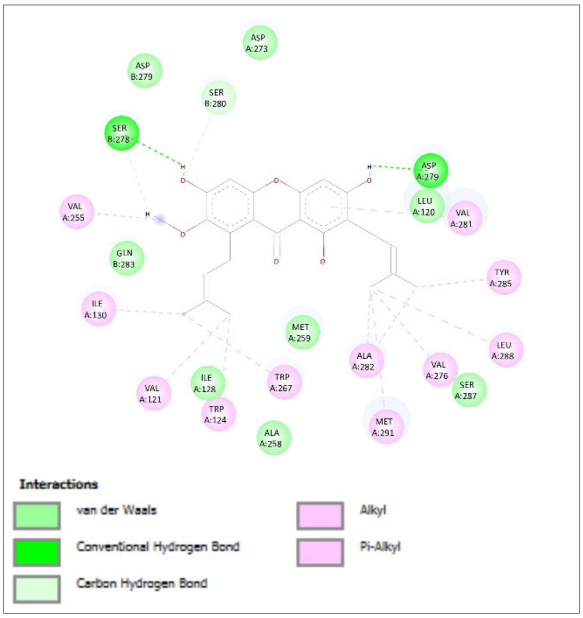
Supplementary Figure S2: This figure illustrates the most common plain ring scaffolds found in a dataset of bioactive compounds. Each structure represents a simple, unbranched ring system without side chains or complex substitutions. The associated frequency indicates how often each ring appears across the dataset. These core ring motifs form the foundational elements of many drug-like molecules and are essential for understanding recurring chemical patterns in medicinal chemistry.



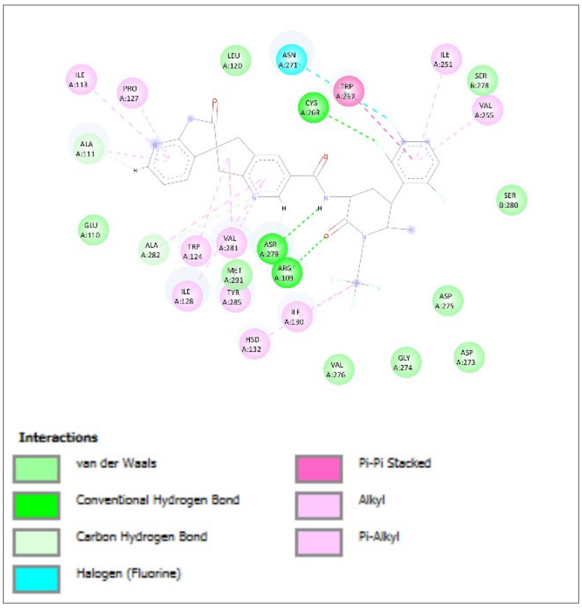
Supplementary Figure S3: The 2D interaction diagrams for each compound against MT-IDH1 depicting the interactions ***A)*** *Olutasidenib,* ***B)*** *α-Mangostin,* ***C)*** *Atogepant,* ***D)*** *Dacomitinib,* ***E)*** *Duvelisib,* ***F)*** *Idelalisib,* ***G)*** *Vandetanib* ***H)*** *Temozolomide.*



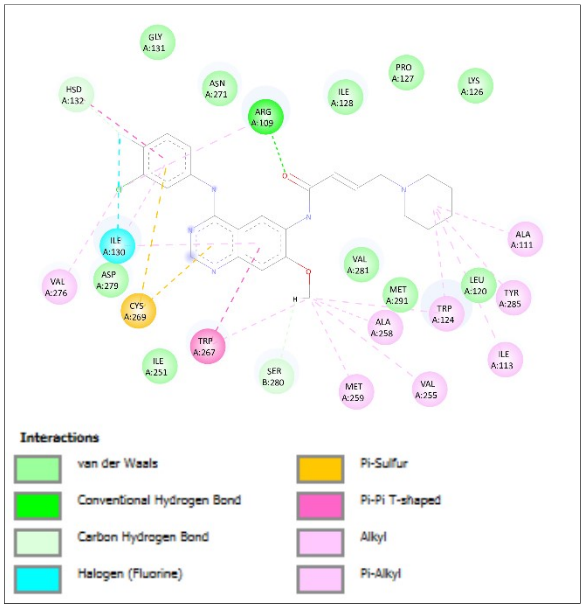
A)



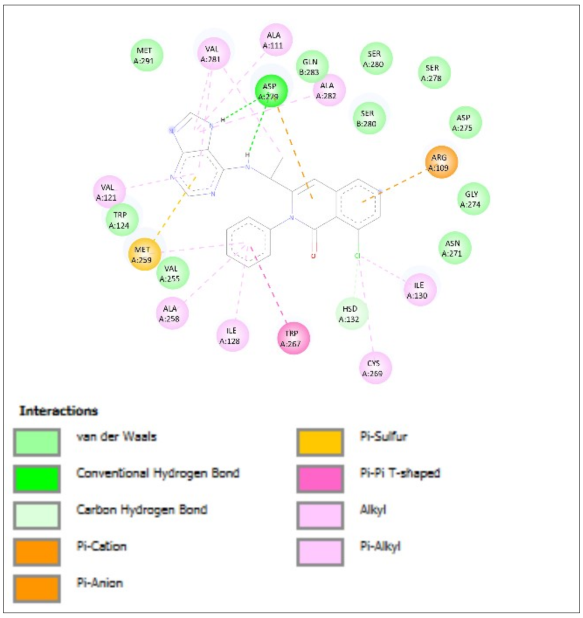
B)



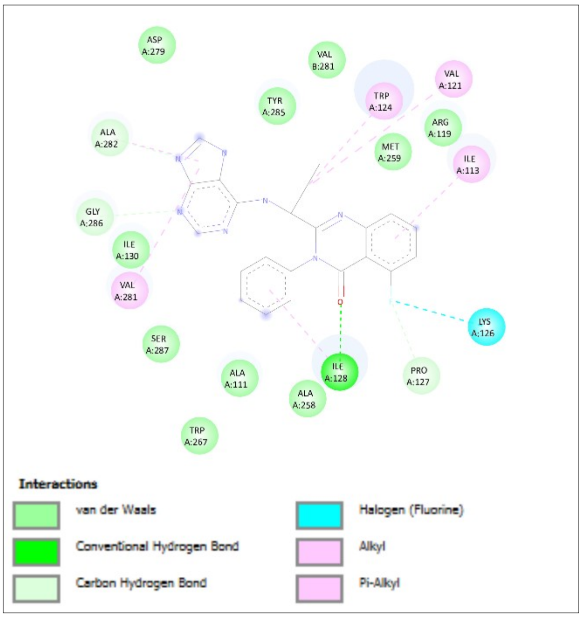
C)



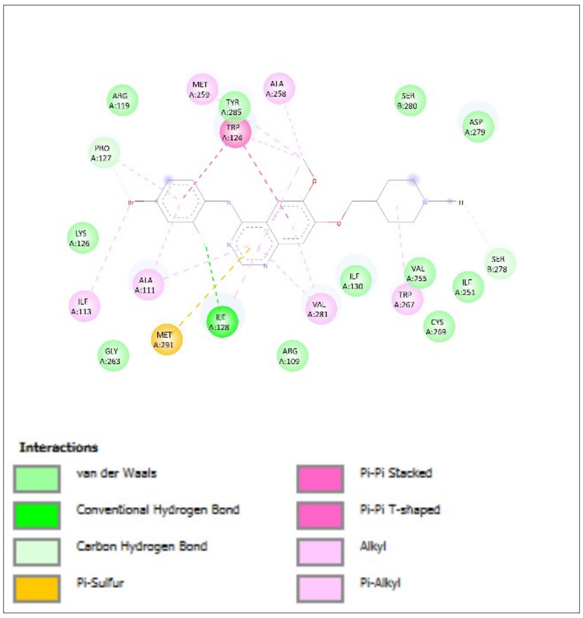
D)


Interactions
van der Waals
Conventional Hydrogen Bond
Carbon Hydrogen Bond
Pi-Cation
Pi-Anion
Pi-Sulfur
Pi-Pi T-shaped
Alkyl
Pi-Alkyl

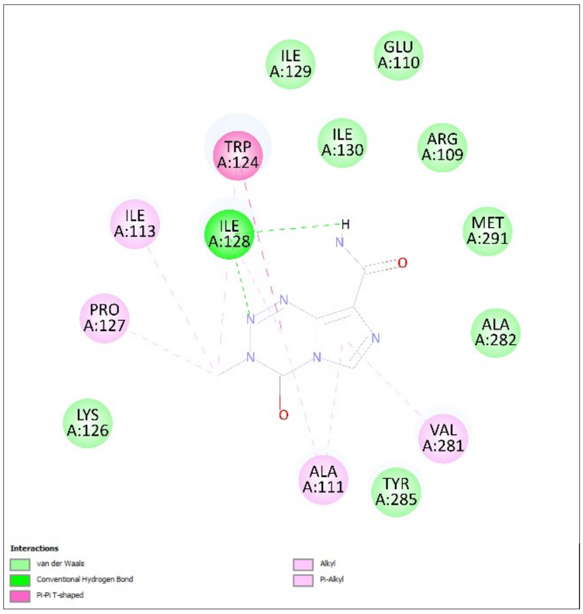
E)


Interactions
van der Waals
Conventional Hydrogen Bond
Carbon Hydrogen Bond
Halogen (Fluorine)
Alkyl
Pi-Alkyl

F)


Interactions
van der Waals
Conventional Hydrogen Bond
Carbon Hydrogen Bond
Pi-Sulfur
Pi-Pi Stacked
Pi-Pi T-shaped
Alkyl
Pi-Alkyl

G)


ILE
A:129
GLU
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TRP
A:124
ILE
A:130
ARG
A:109
ILE
A:113
ILE
A:128
MET
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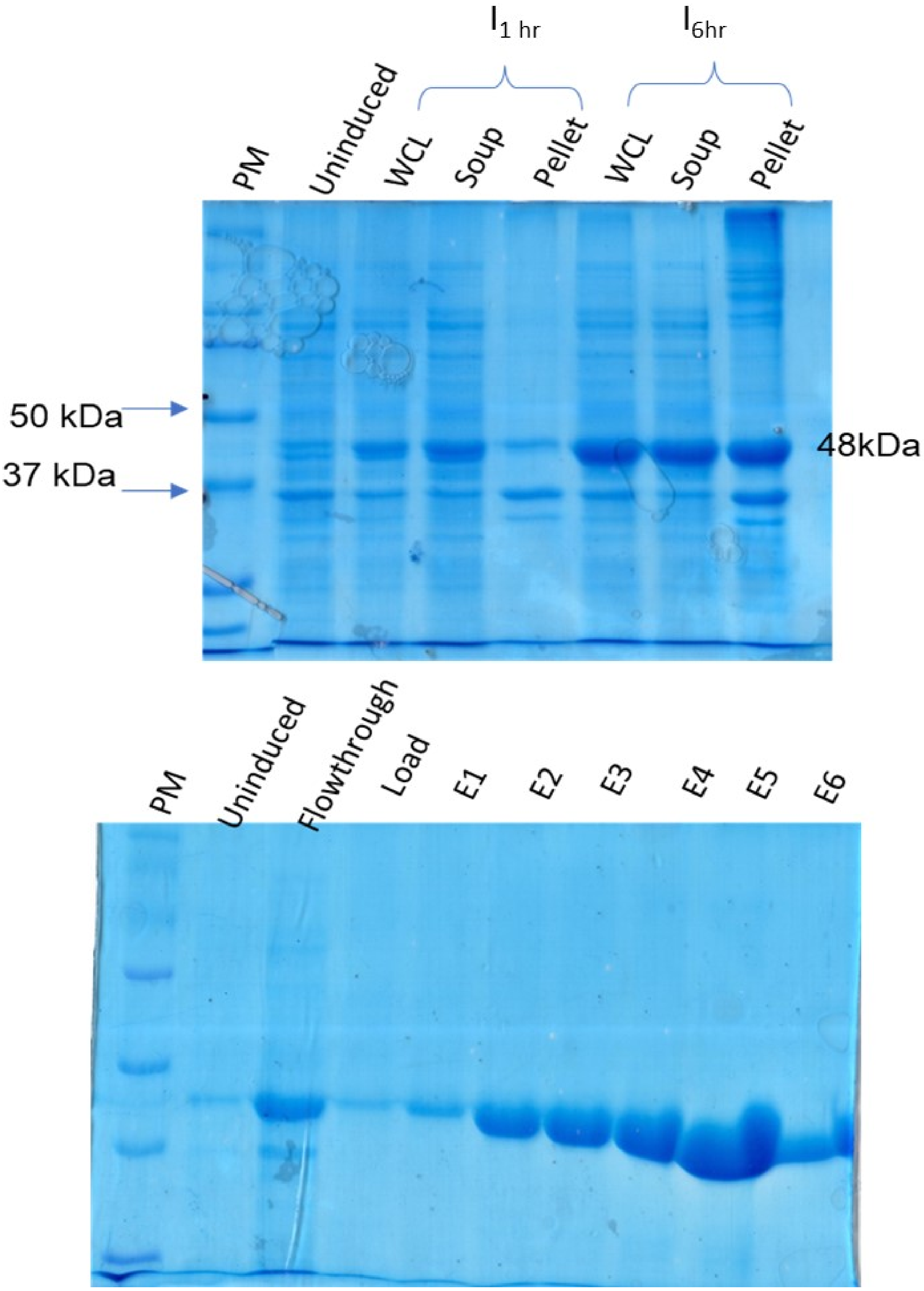
PRO
A:127
ALA
A:282
LYS
A:126
VAL
A:281
ALA
A:111
TYR
A:285
Interactions
van der Waals
Conventional Hydrogen Bond
Pi-Pi T-shaped
Alkyl
Pi-Alkyl

H)

Supplementary Figure S4: SDS-PAGE analysis for recombinantly purified mutant IDH1.



Supplementary Figure S5: Calculation of kinetic parameters, Km and Vmax for purified MT-IDH1 protein for α-KG and NADPH substrates.