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Multialgorithm-based docking reveals Imidazolidinyl urea as a multitargeted inhibitor for Lung Cancer

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Preprocessing Preparations

Glide- Grid+ Docking

ADMET Optimisation Fingerprinting

Molecular

Molecular **Dynamics Simulation**

In-vitro validation



PREPARATION

Proteins were prepared with PPW, and ligand with LigPrep tool to fill the missing loops, residues and optimized Hbonds, minimised with OPLS4.

QUALITY CHECK

QikProp tool was used for the ADMET computations and Jaguar program was used to optimise the ligand molecule to check the relative energy.

SIMULATIONS

All five complexes of proteins-Imidurea was kept for production run with MD simulated in neutralisd state in water for 100ns at 300K. RMSD, RMSF and intermolecular interactions were analysed.



PROTEIN + DRUG

The important proteins participating in lung cancer were identified (5PDBs) from literatures and downloaded from the rcsb database while the complete Drug Bank library was collected.

MOLECULAR DOCKING

Grids were generated on active site (native ligand) and on complete protein. Multisampling algorithm-based HTVS, SP, XP docking performed followed by MM\GBSA, and the complete pathway helped us to identify the *Imidurea* as a multitargeted inhibitor for Lung Cancer

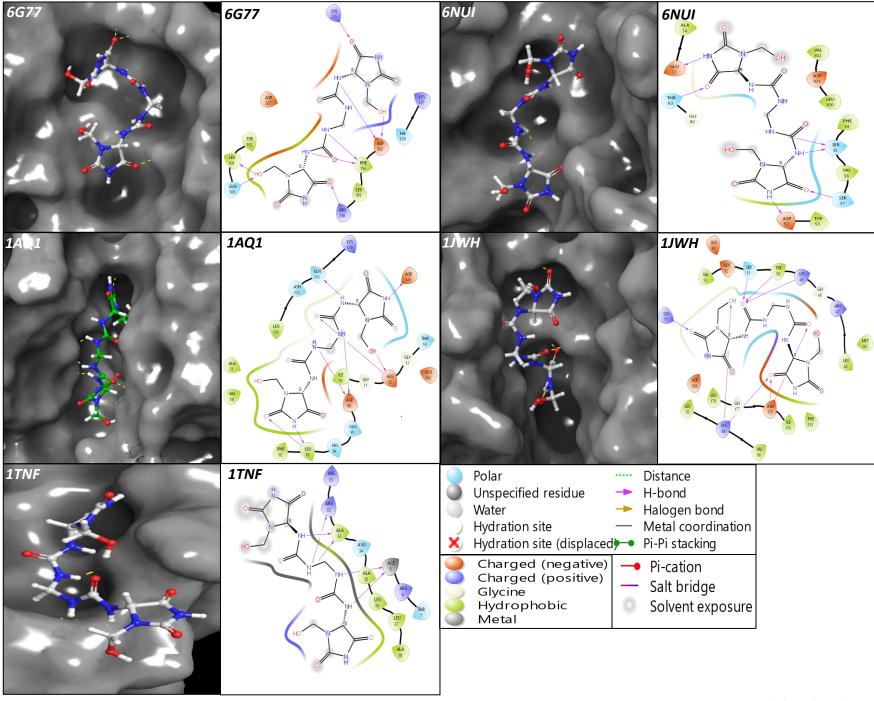
PATTERNS

The interaction pattern were generated with interaction fingerprint tool against the docking score and analysed for the count of residue and count of atoms interactions.

EXPERIMENTAL

The identified compound Imidurea was validated by following- Cell culture, treatment, Morphological imaging, Annexin V/PI FACS assay, ROS levels, MMP, Caspase 3/7 activity assay and analysis.

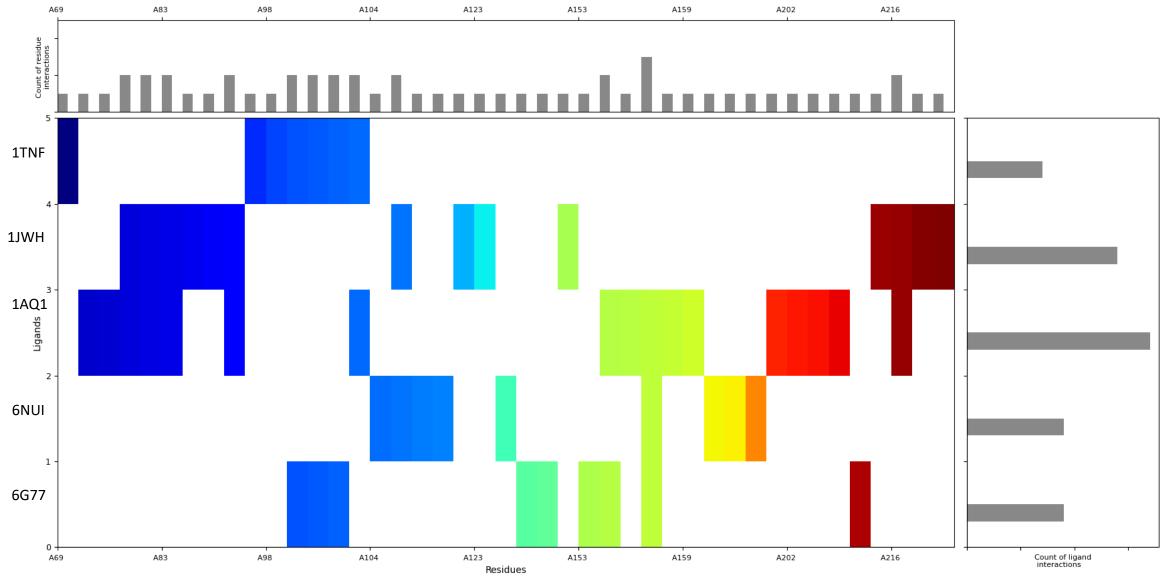






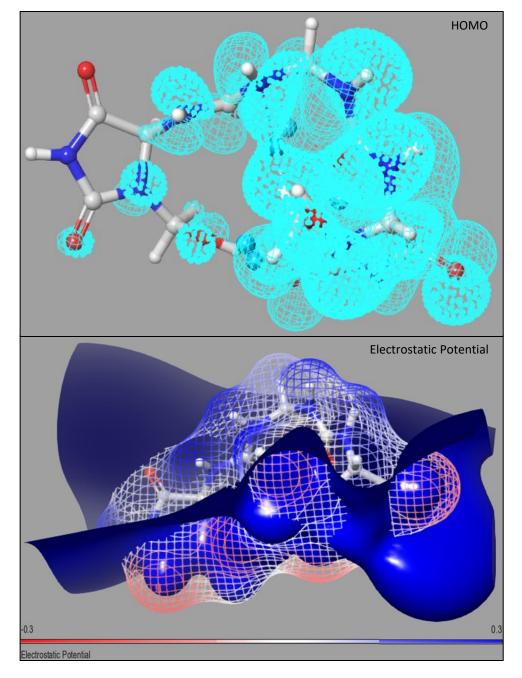






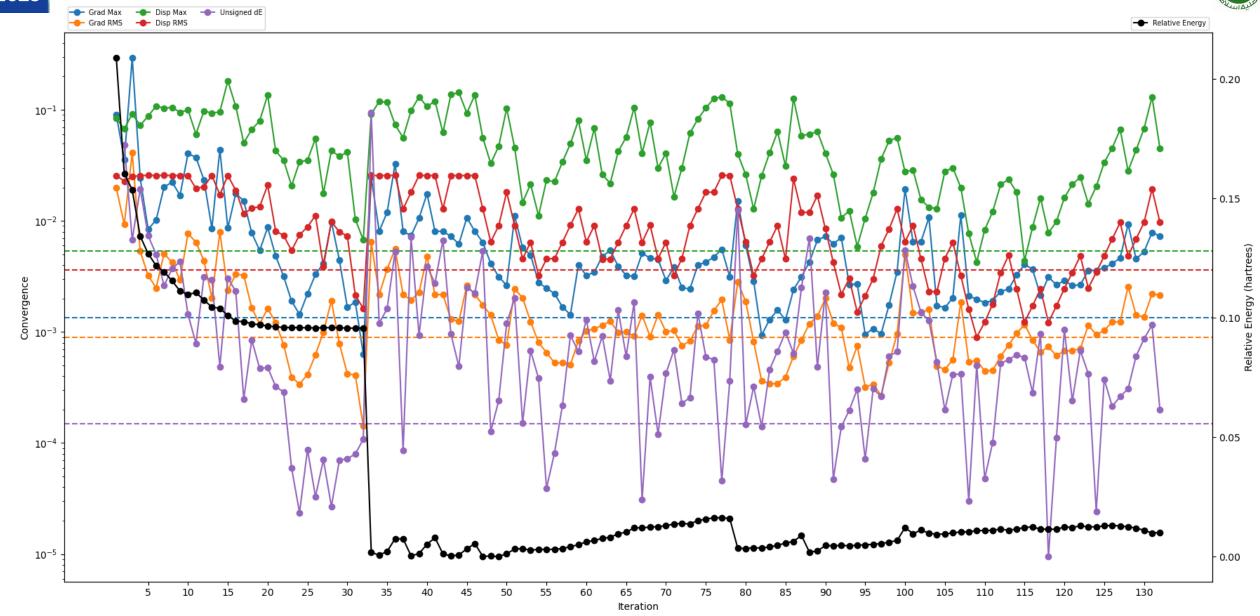






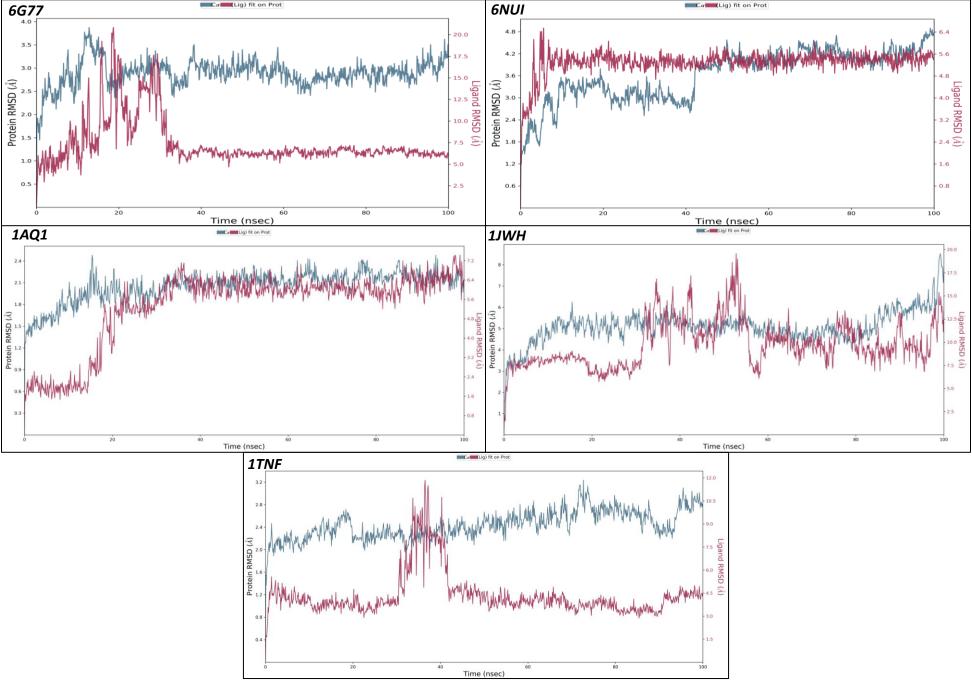






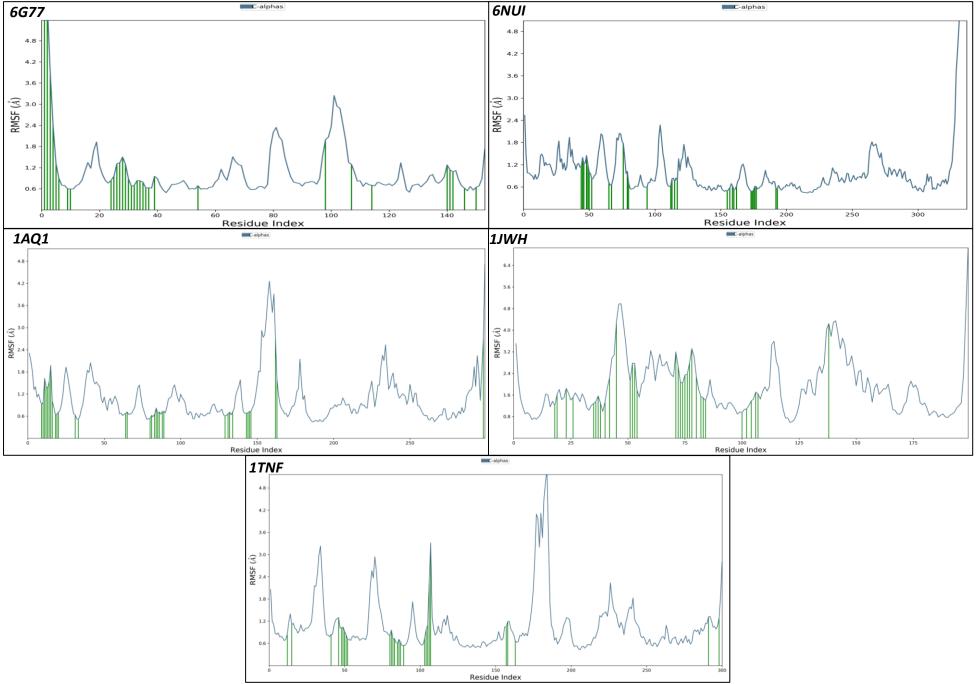




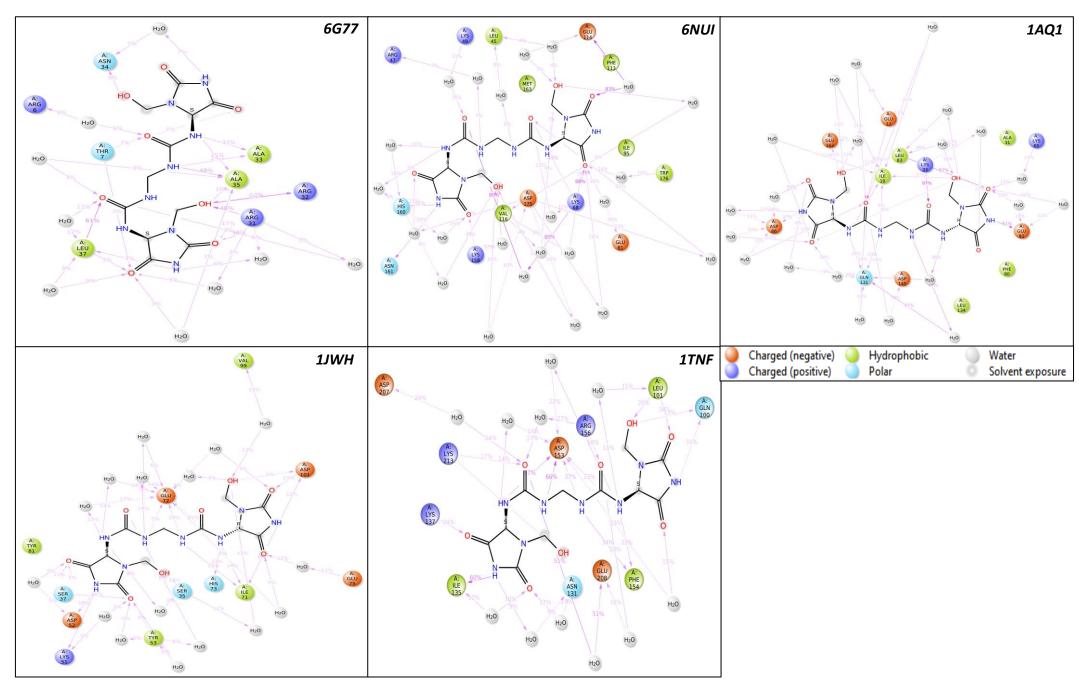








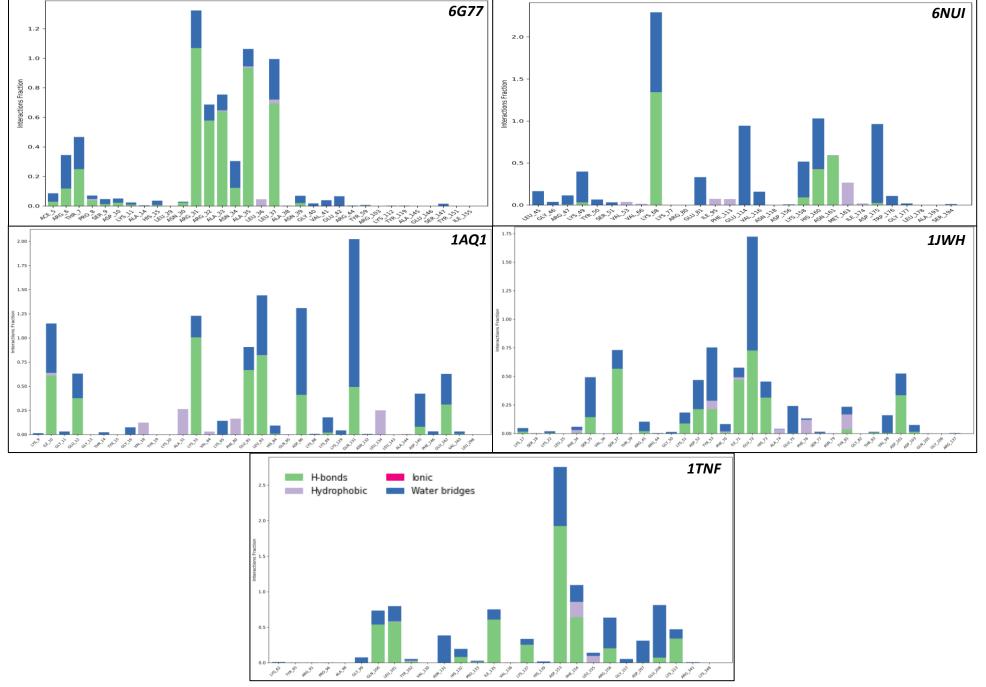


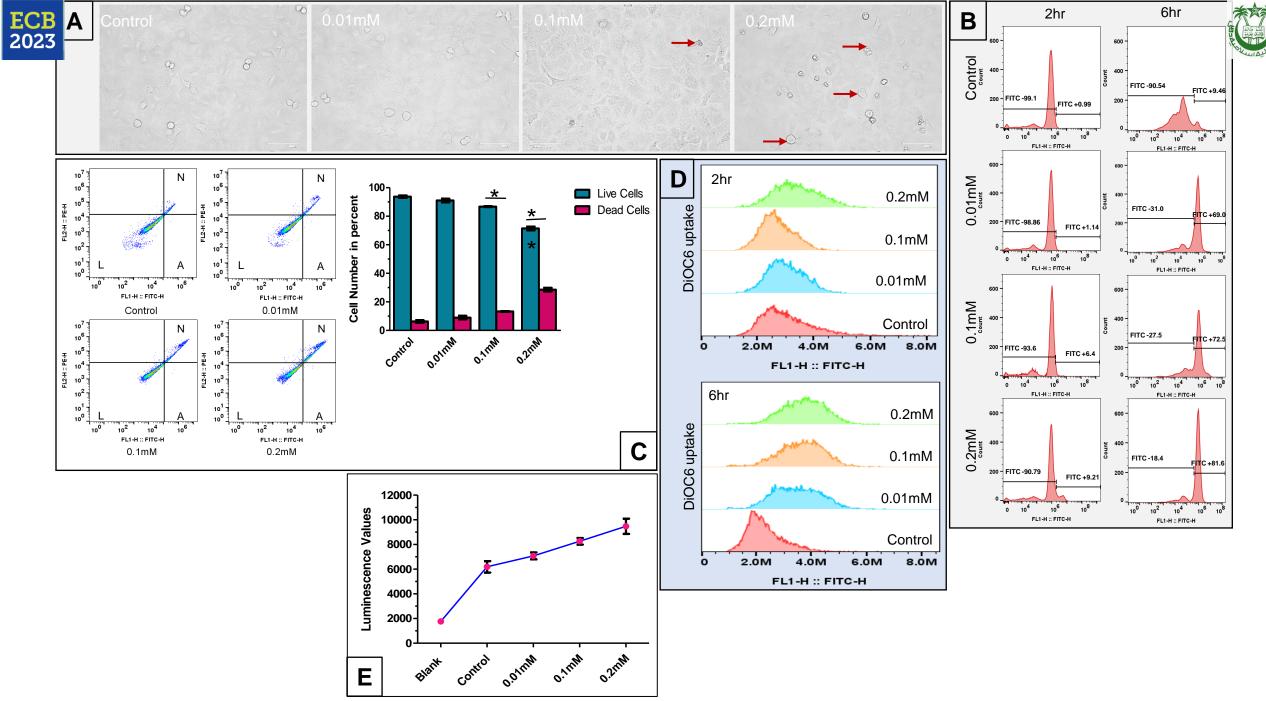
















Conclusion

- The food and drug administration has approved almost 100 drugs against SCLC and NSCLC, which are being used actively. However, this is unfortunate; even after so much expenditure, the world frequently faces the drug resistance problem and needs a new drug.
- This study includes multisampling algorithms based on screening, ADMET analysis, interaction
 pattern analysis and MD simulation for 100ns in the SPC water medium has produced a promising
 results.
- In this study, we have identified Imidazolidinyl urea as a multitargeted inhibitor against lung cancer, validated with computational methods, and proven as a prominent candidate.
- The identified compound Imidazolidinyl urea has less chance to develop resistance, or it might take a more extended period. It can be experimentally validated and used for the welfare of humankind.
- This study also set an example of how to proceed with multitargeted drug designing or repurposing to cure any prevalent disease and developing resistance.

