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Identification of Novel Benzimidazole-Based NS5B Polymerase Inhibitors of Hepatitis C Virus Using Molecular Docking, Atom-Based 3D-QSAR Model, and ADMET Prediction

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INTRODUCTION & AIM

The Hepatitis C Virus (HCV) remains a worldwide health emergency, infecting tens of millions and inducing severe hepatic complications (cirrhosis, hepatocellular carcinoma) [1]. Although the arrival of direct-acting antivirals (DAAs) has revolutionized the treatment, the challenges of viral resistance generation and the need for less expensive therapies, particularly in low-income countries, justify the continued quest for new drugs [2].

The NS5B RNA polymerase is the key HCV replication enzyme and remains the foremost and approved target for inhibitor design, i.e., Sofosbuvir [3].

In this context, our study utilized a virtual screening and rational design approach, involving the utilization of molecular docking, a robust 3D-QSAR model, and ADMET prediction to:

Establish the molecular descriptors that determine the binding of benzimidazole derivatives with the active site of NS5B.

Develop and characterize new benzimidazole derivatives as new potential NS5B inhibitors [4].

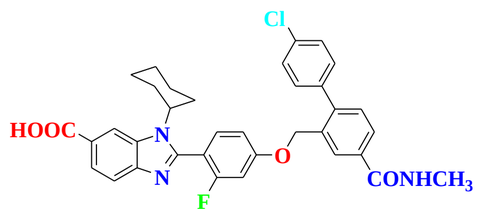

*Fig.1: **Benzimidazole compound 29. (IC50=0.012µM).***

METHOD

- A dataset of 53 benzimidazole derivatives reported as NS5B polymerase inhibitors was collected from the literature. The structure was prepared using the LigPrep.
- The crystal structure of HCV NS5B RNA polymerase (PDB ID:2DXS) was downloaded from the Protein Data Bank (PDB).
- Prepared ligands were docked into the active site using the Glide module in extra precision (XP) docking for the top-ranked compounds.
- Atom-based 3D-QSAR model was performed using PHASE (Schrödinger). Model performance was evaluated by internal and external validation.
- Predicted pharmacokinetic and drug-likeness properties were evaluated using QikProp (Schrödinger).

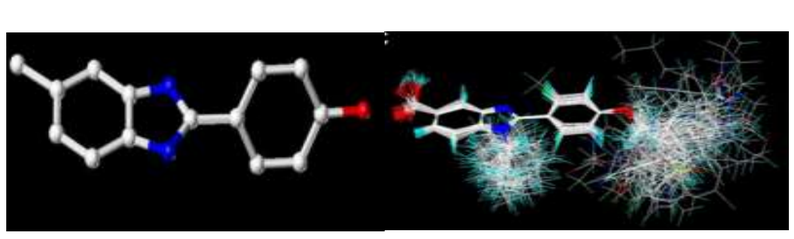

*Fig.2:**Template used for molecular alignment , Structural alignment of the dataset***

RESULTS & DISCUSSION

1- 3D QSAR Analysis

Table 1: **PLS statistic of the atom-based 3D-QSAR model.**

Factors	SD	R^2	F	P	RMSE	Q^2	Pearson-r
1	0.32	0.88	110.5	1.46e-14	0.64	0.58	0.48
2	0.22	0.93	203.7	2.9e-20	0.62	0.62	0.92
3	**0.18**	**0.95**	**941.2**	**4.09e-29**	**0.57**	**0.79**	**0.92**

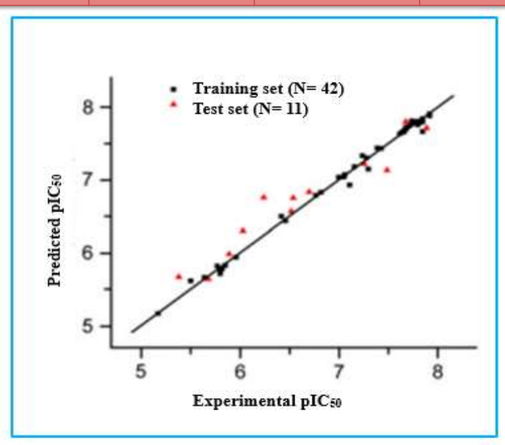

*Fig.3: **Correlation between actual and predicted activity pIC50 of training and test set.***

2- Molecular Docking

Table 2: ***Docking results of two compounds with the predicted activity (pIC_{50}).***

Compounds	XPScore	Glide Emodel	pIC_{50}
N1	**-9.51**	**-65.82**	**8.64**
N2	**-9.06**	**-56.51**	**7.42**
Compound 29	**-8.92**	**-70.15**	**7.22**

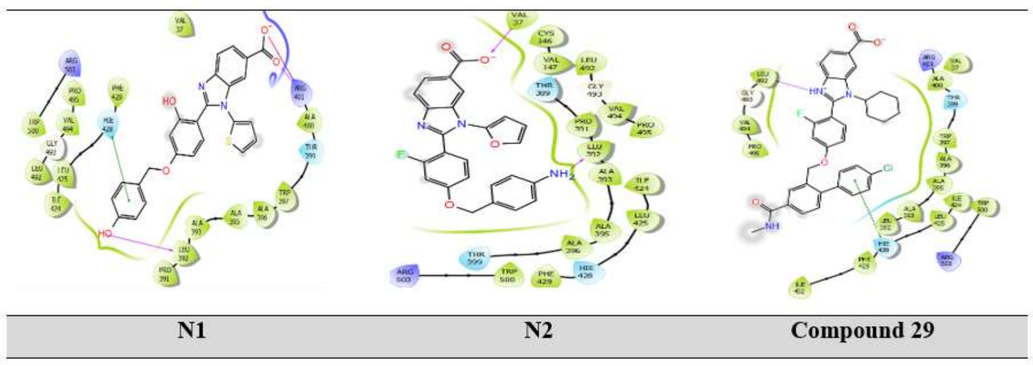

*Fig. 4: **Molecular docking and interaction analysis of NS5B polymerase inhibitors Compound 29 and proposed molecules N1–N2.***

CONCLUSION

- This study successfully used computational modeling (docking, 3D-QSAR, ADMET) to rationally design novel benzimidazole derivatives targeting HCV NS5B.
- The 3D-QSAR models revealed key molecular features for strong binding.
- We identified promising new inhibitors with optimal binding affinities and favorable ADMET profiles.
- These molecules are excellent drug candidates for the next generation of affordable NS5B inhibitors and require urgent experimental validation.

FUTURE WORK / REFERENCES

[1] Gish, R. G. W. The Global Burden of Hepatitis C Virus Infection: A Public Health Perspective. *J. Hepatol.* **2015**, *63*(1), 3–10.

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[3] Gane, E. J. Sofosbuvir, a NS5B Polymerase Inhibitor in the Treatment of Hepatitis C: A Review of Its Clinical Potential. *Hepatic Med. Evid. Res.* **2014**, *6*, 21–30.

[4] Dhar, T. K.; Saha, A.; Jha, S. S.; Bandyopadhyay, S. 3D QSAR and Molecular Docking Studies of Benzimidazole Derivatives as Hepatitis C Virus NS5B Polymerase Inhibitors. *J. Chem. Inf. Model.* **2008**, *48*(12), 2307–2316.