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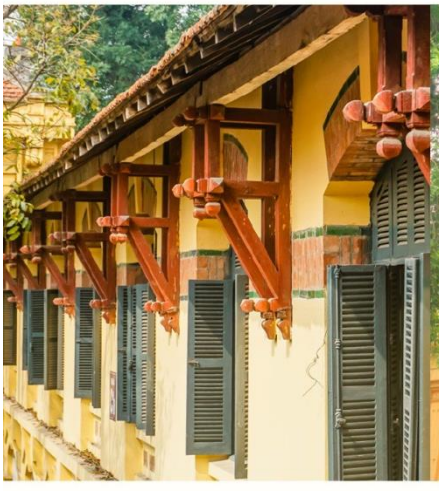

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Identification of novel inhibitors of interleukin-33 using 3D shape-based similarity approach

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Purpose Interleukin (IL)-33 is implicated in a variety of inflammatory and autoimmune diseases. Several IL-33 inhibitors have been reported, most notably the compound **7c**. Our objective was to leverage the 3D-shape of **7c** to identify more potent IL-33 inhibitors.

Methods The conformations set of **7c** was used to develop 3D-shape query using OpenEyes-vROCS software. The model was validated on a test-set of 13 active compounds and 100 decoys. The obtained model was used for screening through the EnaminePPI-Database. Compounds that satisfied the 3D-shape query were subsequently docked into IL-33 using AutodockVina program. Hit compounds were ranked based on their binding energy. The promising compounds were subjected to ADMET profiling (ADMETLab) and molecular dynamics simulations (MDs) to investigate the stability of their binding to IL-33 (GROMACS).

Results A 3D-shape query generated from **7c** was validated on the test-set, resulting in AUC-ROC = 0.987 and $EF_{1\%}$ = 73.8. The EnaminePPI-Database (40,640 compounds) was screened through the shape-based model. The top 500 hits with highest Tanimoto-Combo score were retained and entered into molecular docking, revealing 137 compounds with docking affinities surpassing that of **7c** (<−7.2 kcal·mol^{-1}). The top 20 ranked compounds with best docking energies were rescored using MM/GBSA. Finally, Z131345790 was the most potential compound with good ADMET properties, stable binding in MDs, and a binding free energy of -22.44 kcal·mol^{-1}.

Conclusions Ligand-shape-based approach is a simple yet effective strategy in new drug discovery. Application of this method to the initial inhibitor **7c** led to the identification of more promising IL-33 inhibitors.

KEYWORDS:interleukin-33, 3D-similarity, shape-based, molecular docking, dynamics simulations.

Graphical abstract