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MDPI

THREE-DIMENSIONAL SHAPE SIMILARITY APPROACH FOR THE DISCOVERY OF IL-1R1 RECEPTOR INHIBITORS

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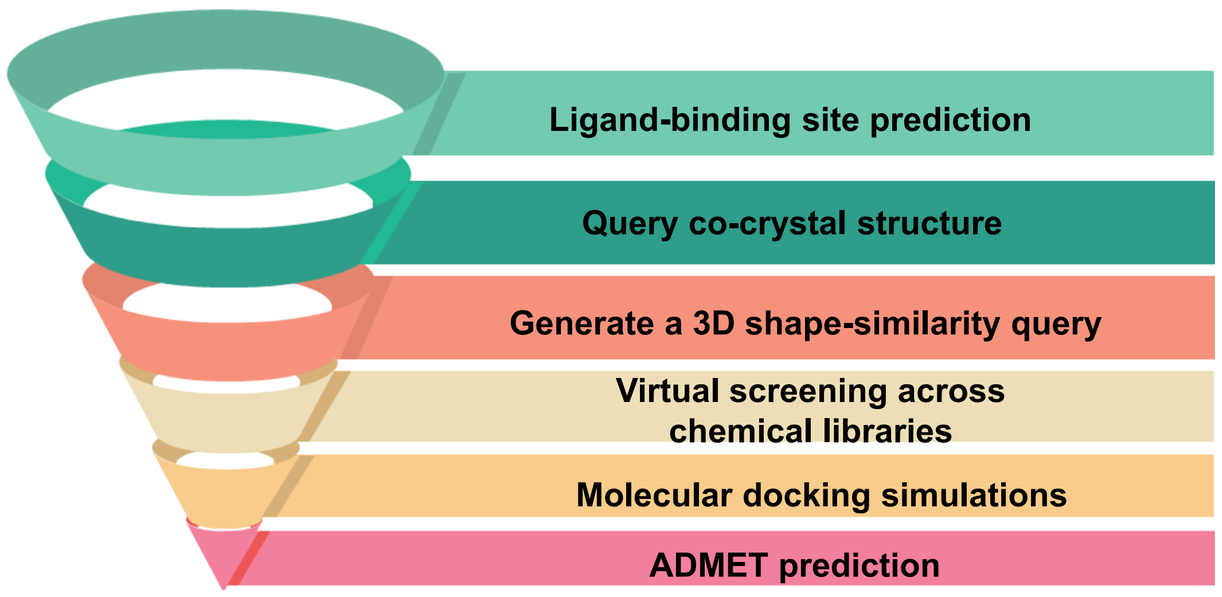
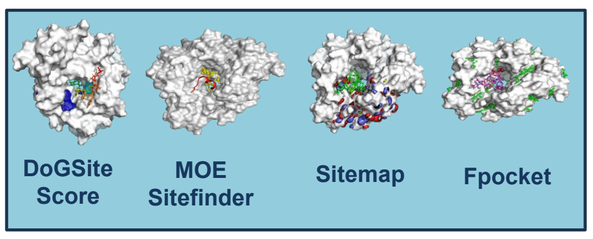
INTRODUCTION & AIM

Interleukin-1β (IL-1β) is a prototypical cytokine of the IL-1 family that regulates innate and adaptive immunity. Its cognate receptor, interleukin-1 receptor type 1 (IL-1R1), is therefore a tractable target for anti-inflammatory drug discovery. The peptide antagonist AF10847 binds IL-1R1 and disrupts the IL-1β/IL-1R1 protein–protein interface, validating the receptor's druggability. However, its peptidic nature entails poor oral bioavailability and unfavorable developability. This study aimed to discover non-peptidic small molecules capable of inhibiting IL-1R1 using a 3D shape-similarity strategy anchored on AF10847. The IL-1R1/AF10847 co-crystal structure was prepared for modeling, and the binding pocket was delineated using FPocket, DoGSiteScorer, and DeepSite. *In silico* alanine scanning of the complex identified interaction "hot spots" at the protein-protein interface. Following comprehensive conformer enumeration of AF10847, a ROCS query capturing its molecular envelope and salient pharmacophoric features was constructed and deployed to virtually screen large purchasable libraries (Enamine, ChemDiv, Asinex and NCI Open Database). Candidates were ranked by Tanimoto similarity score and lightly filtered for drug-likeness prior to structure-based triage. Top-ranked molecules underwent ensemble molecular docking into multiple IL-1R1 conformations to accommodate receptor flexibility, with poses assessed by consensus scoring and interaction-fingerprint analysis for consistency with the AF10847 recognition pattern. Short all-atom molecular-dynamics simulations were then performed to evaluate pose stability via heavy-atom RMSD and hydrogen-bond occupancy and to obtain qualitative affinity estimates using trajectory-averaged metrics. This computational cascade identified several chemically diverse small-molecule candidates predicted to engage IL-1R1 in persistent, well-packed poses with favorable interaction networks. These *in silico* hits constitute tractable starting points for experimental validation, including biochemical binding assays and cellular readouts of IL-1β signaling, orthogonal selectivity counterscreens early ADMET profiling to guide medicinal-chemistry optimization toward orally available IL-1R1 modulators.

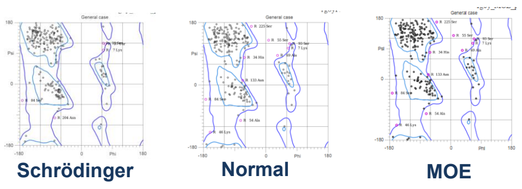
METHOD



LIGAND-BIDING SITE PREDICTION



MOLPROBITY CLEANFH-RAMA



88.1% of all residues were in favored
98.5% of all residues were in allowed

86.2% of all residues were in favored
96.0% of all residues were in allowed

86.3% of all residues were in favored
96.0% of all residues were in allowed

BUDE ALANINE SCAN

Constellation	Constellation ΔΔG (kJ/mol)	Summed Individual ΔΔGs (kJ/mol)	Cooperativity (kJ/mol)
I12_I13_I6	69.8	61.6	8.1
I13_I15_I6	67.6	61.8	5.8
I13_I4_I6	67.4	57	10.4
I12_I13_I15	66	46.4	19.6
I12_I13_I4	65.8	41.6	24.2

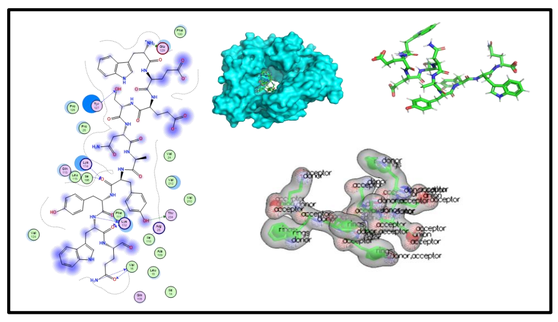
Chain	Residue	Amino acid	ΔΔG (kJ/mol)	Std Dev
I	6	TRP	27.5	0
I	13	TYR	22.1	0
I	17	TYR	12.7	0
I	15	GLN	12.3	0
I	12	TYR	12.1	0

RESULTS & DISCUSSION

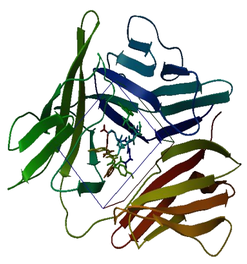
ROCS SCREEN

Database	Result
Chemdiv	38
NCI	9823
Asinex	365
Enamine	620

AF10847 PEPTIDE-IL-1R1 CO-CRYSTAL STRUCTURE



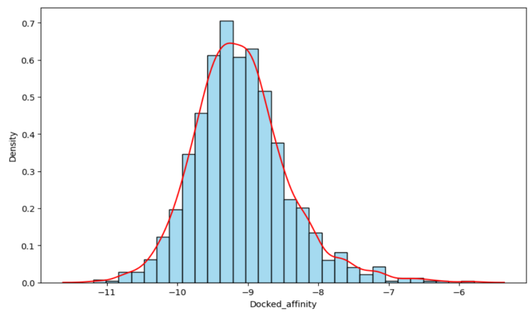
DOCKING PARAMETER



Scoring function: Vina
Exhaustiveness: 8
Spacing: 0.375

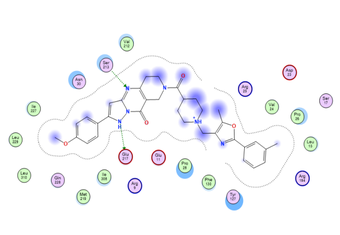
Search box size:
size_x = 44
size_y = 52
size_z = 54

Search box center:
center_x = 24.832
center_y = 9.696
center_z = 147.886

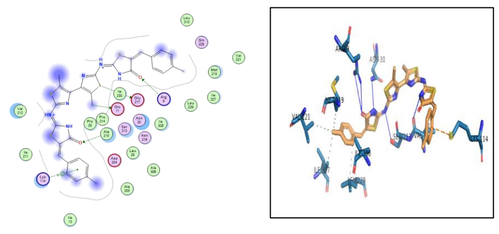


Distribution of Docking Scores

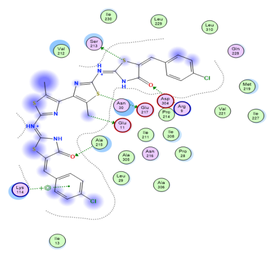
TOP DOCKING SCORES



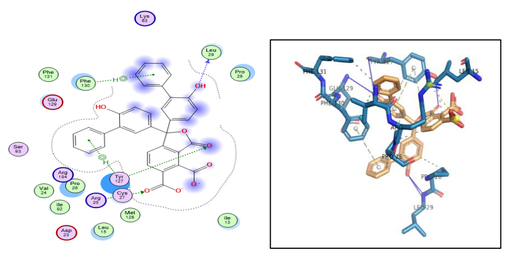
s022-1832
Docking affinity -11.119



130ebb702a6250fd_ficus_01_55
Docking affinity -11.194

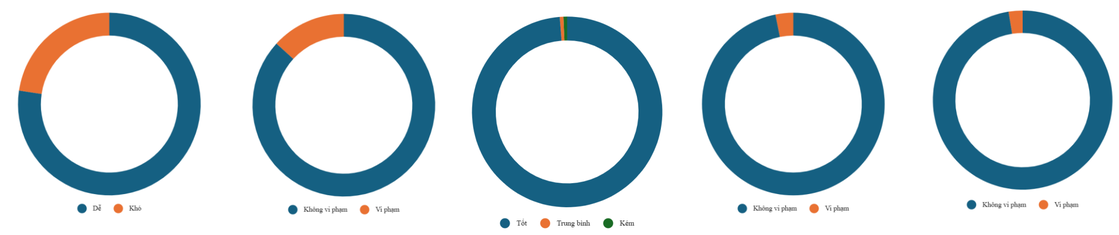


f9f13771b56b4eac_ficus_01_7b
Docking affinity -11.058



1f9e861369ce9413_ficus_01_56
Docking affinity -10.763

ADMET PREDICTION



Synthetic accessibility | Lipinski's Rule of Five | Intestinal absorption | PAINS | Pfizer rule

CONCLUSION

Compounds with the highest overall Tanimoto similarity scores were selected to evaluate IL-1R1 binding via molecular docking and molecular dynamics simulations. Using these computational approaches, several small molecules predicted to bind IL-1R1 *in silico* were identified and can be advanced to *in vitro* testing.

REFERENCES

(1) Vigers GP et al. X-ray crystal structure of a small antagonist peptide bound to interleukin-1 receptor type 1. J Biol Chem. 2000;275(47):36927–36933.
(2) Lee JY et al. Identification of new IL-7Rα small-molecule agonists: a multi-computational approach. SAR QSAR Environ Res. 2021;32(9):719–729.

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