

Synergistic acceleration of prostate-specific antigen ligand design and synthesis via machine learning and molecular docking.

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Table of Content

1. Maximum common substructures selected by K-means clustering	3
2. Synthetic routes of the synthesized ligands.....	3
3. Nuclear magnetic resonance (NMR) spectra of the synthesized ligands.	3
4. Circular dichroism (CD) experiments illustrating the impact of compound addition on protein structure through titration.....	4
5. The 2D structures of the published compounds	4
6. Free energy landscape diagrams for the synthesized molecules.....	5
7. The results of the virtual screening of the ZINC database.....	6

1. Maximum common substructures selected by K-means clustering.



Fig. S1 Maximum common substructures selected by K-means clustering.

2. Synthetic routes of the synthesized ligands.

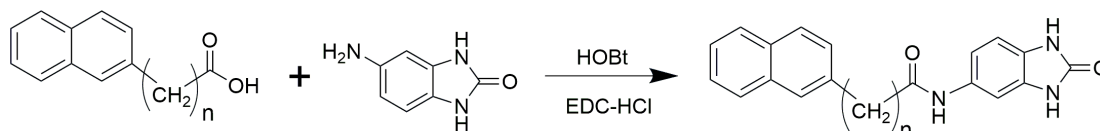


Fig. S2 Synthetic route of compounds, where $n=1$ for the synthesis of ligand 1, and $n=2$ for the synthesis of ligand 2.

3. Nuclear magnetic resonance (NMR) spectra of the synthesized ligands.

Synthesis of ligand 1: 2-(Naphthalen-2-yl)acetic acid (0.50 g, 2.68 mmol) was dissolved in DMF (30.0 mL). EDC-HCl (0.51 g, 2.68 mmol) and HOBT (0.36 g, 38.0 mmol) were added, and the mixture was stirred for 1 h. 5-amino-2-benzimidazolinone (0.40 g, 2.68 mmol) and triethylamine (0.45g, 4.50 mmol) were added, and the mixture was stirred at room temperature for 12 hour. The resulting suspension was separated by filtration and washed several times with water to give the compound (0.62g, 72.9%) as a white solid. $^1\text{H NMR}$ (400 MHz, DMSO- d_6) δ 10.55 (s, 1H), 10.49 (s, 1H), 10.11 (s, 1H), 7.88-7.82 (m, 4H), 7.51-7.48 (m, 4H), 7.05 (d, 1H, $J = 8.04$ Hz), 6.84 (d, 1H, $J = 8.24$ Hz), 3.78 (s, 2H).

Synthesis of ligand 2: To a solution of 5-amino-2-benzimidazolinone (0.55 g, 3.69 mmol) and 3-(naphthalen-2-yl)propanoic acid (0.74 g, 3.69 mmol) in DMF (30.0 mL) at 0°C was added HOBT (0.59 g, 4.43 mmol), EDC-HCl (0.87 g, 4.43 mmol) and triethylamine (0.45g, 4.50 mmol). The mixture was kept at room temperature and magnetically stirred for 12 h. Then the solution was diluted with water. The resulting suspension was separated by filtration and washed several times with water to give the compound (0.85g, 66.4%) as a white solid. $^1\text{H NMR}$ (400 MHz, DMSO- d_6) δ 10.52 (s, 1H), 10.45 (s, 1H), 9.78 (s, 1H), 7.85-7.80 (m, 3H), 7.73 (s, 1H), 7.47-7.41 (m, 4H), 6.97 (dd, 1H, $J_1 = 1.68$ Hz, $J_2 = 8.36$ Hz), 6.80 (d, 1H, $J = 8.32$ Hz), 3.08 (t, 2H, $J = 7.4$ Hz), 2.69 (t, 2H, $J = 7.88$ Hz).

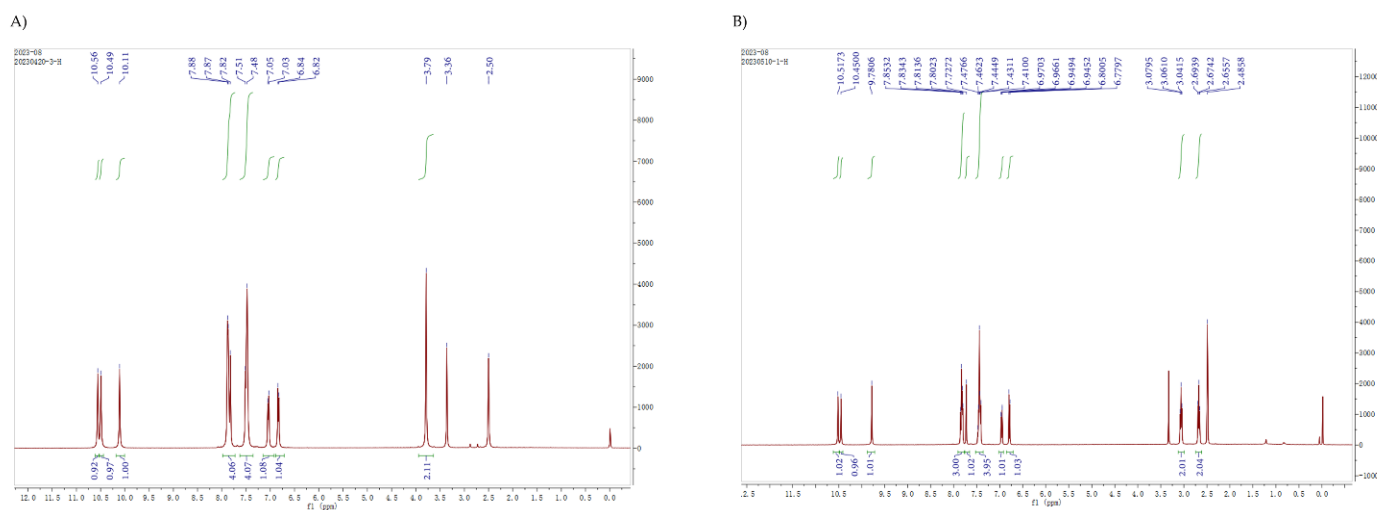


Fig. S3 Nuclear magnetic resonance (NMR) spectra of the synthesized ligands. (A) NMR spectrum of Ligand 1. (B) NMR spectrum of Ligand 2

4. Circular dichroism (CD) experiments illustrating the impact of compound addition on protein structure through titration.

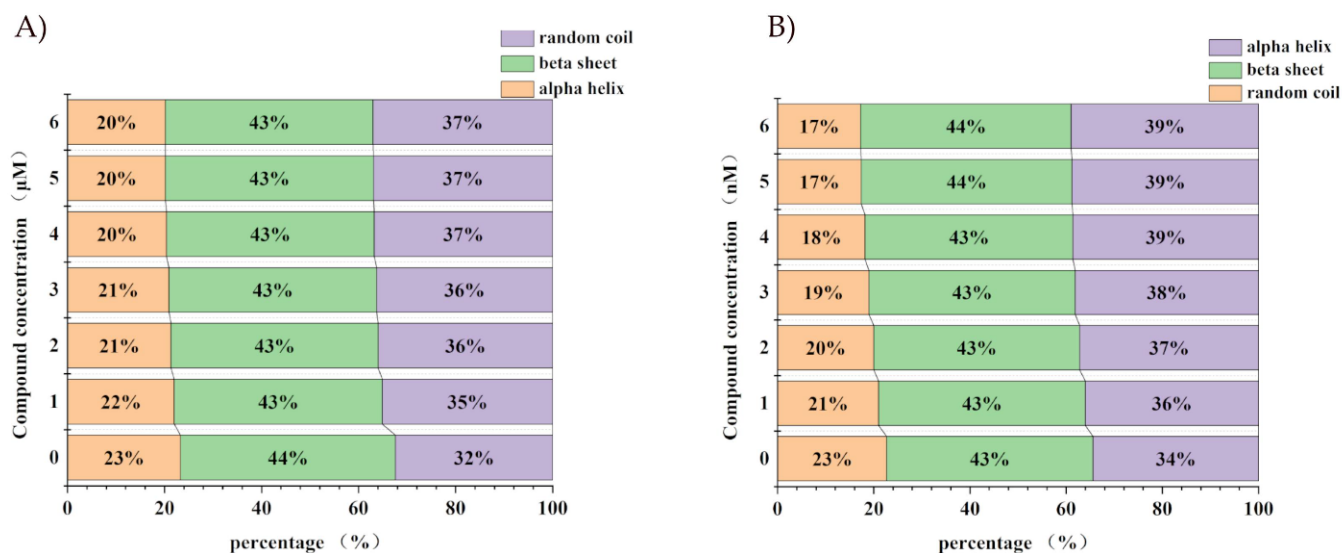


Fig. S4 Circular dichroism (CD) experiments illustrating the impact of compound addition on protein structure through titration. The x-axis denotes the protein structure content, while the y-axis represents the compound concentration. At a 6 nM compound concentration, the PSA protein:compound ratio is 1:3. (A) Titration results for ligand 1. (B) Titration results for ligand 2

5. The 2D structures of the published compounds

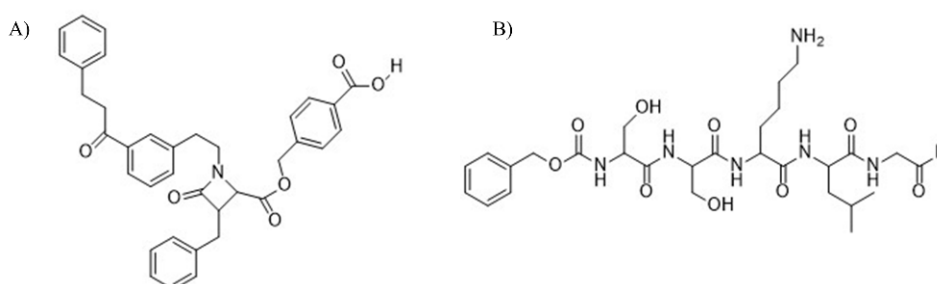


Fig. S5 The 2D structures of published compounds, where A) represents the 2D structure of Drug 1, and B) represents the 2D structure of Drug 2

6. Free energy landscape diagrams for the synthesized molecules.

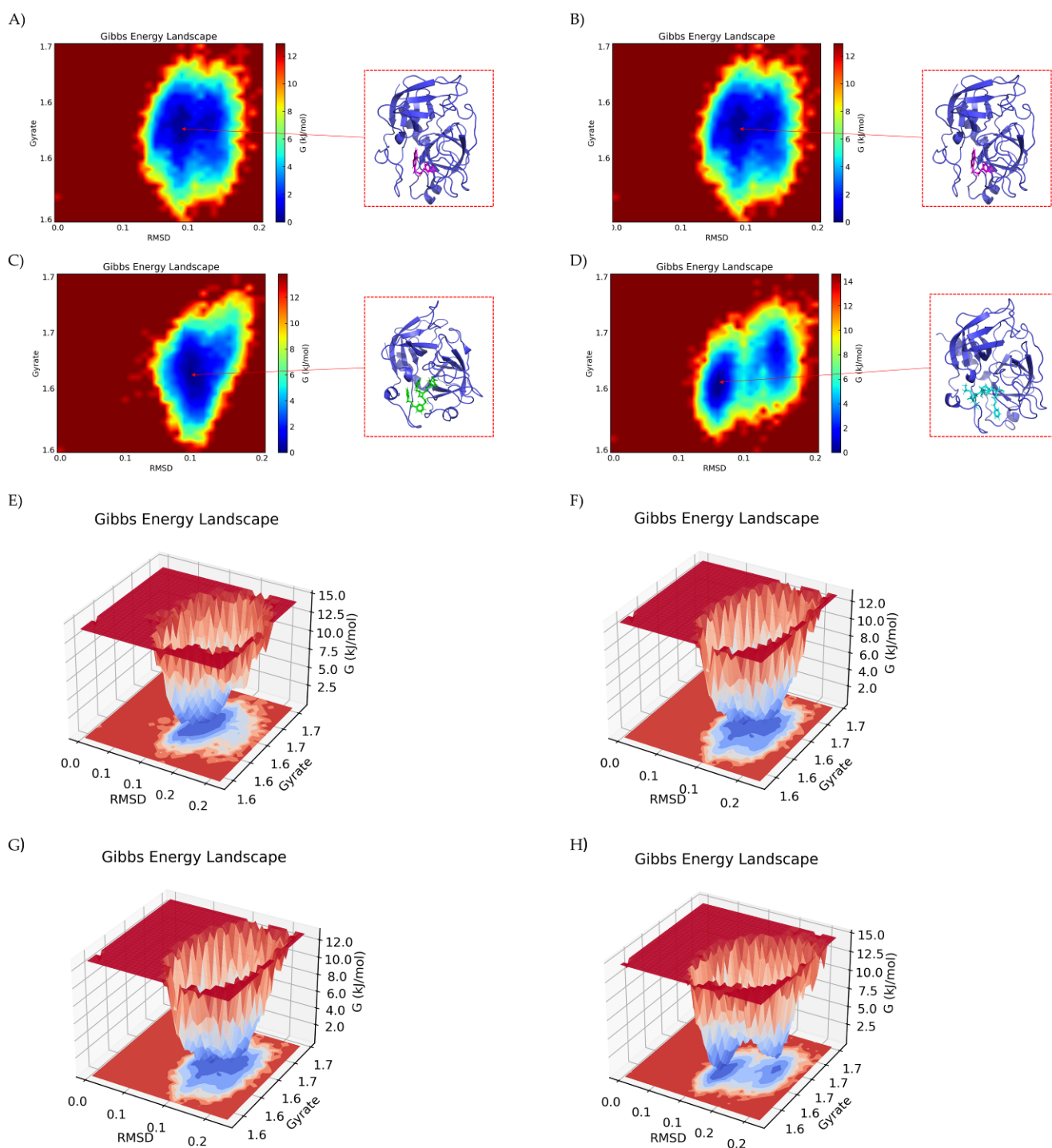


Fig. S6 Free energy landscape diagrams for the synthesized molecules. (A-D) 2D free energy landscapes of Ligand 1, Ligand 2, Drug1, and Drug2, respectively. (E-H) 3D free energy landscapes of Ligand 1, Ligand 2, Drug1, and Drug2, respectively.

7. The results of the virtual screening of the ZINC database

Table S1. ZINC IDs and Docking Scores for Compounds Selected by Energy-Based Molecular Docking Ranking

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