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Accepted Article

Title: Structure guided synthesis and evaluation of small molecule inhibitors targeting protein-protein interactions of BRCA1 tBRCT domain

Authors: Vadiraj Kurdekar, Saranya Giridharan, Jasti Subbarao, Mamatha B Nijaguna, Jayaprakash Periasamy, Sanjana Boggaram, Amol V Shivange, Gayathri Sadasivam, Muralidhara Padigaru, Vijay Potluri, Ashok R Venkitaraman, and Kavitha Bharatham

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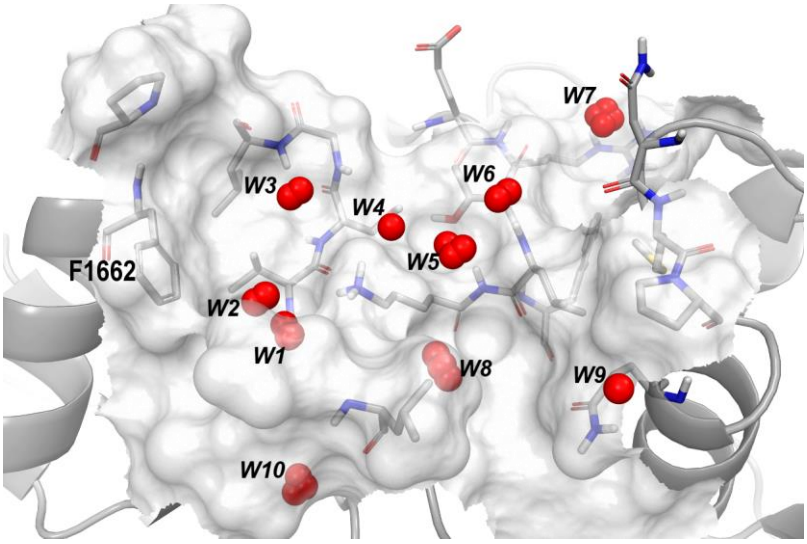
Supplementary data

Table S1. Thermodynamic properties of most stable water molecules observed by GIST analysis



Water grouping (red sphere) based on high density and with greater free energy change.

ID	ΔE_{sw}	ΔE_{ww}	ΔE_{total}	$T\Delta S^{trans}$	$T\Delta S^{orient}$	$T\Delta S_{total}$	ΔG
w1	-14.28	-2.33	-16.61	-2.540	-2.290	-4.830	-11.779
w2	-1.105	-1.071	-2.176	-0.284	-0.183	-0.467	-1.708
w3	-2.473	-1.113	-3.586	-0.580	-0.304	-0.884	-2.702
w4	-0.959	-0.616	-1.575	-0.185	-0.122	-0.306	-1.269
w5	-3.828	-4.034	-7.862	-1.600	-0.924	-2.524	-5.338
w6	-2.880	-1.610	-4.490	-0.559	-0.303	-0.862	-3.629
w7	-5.997	-2.463	-8.460	-1.029	-0.605	-1.634	-6.827
w8	-3.622	-1.515	-5.137	-0.689	-0.548	-1.236	-3.901
w9	-1.392	-0.287	-1.679	-0.166	-0.131	-0.298	-1.382
w10	-11.373	-1.346	-12.719	-1.757	-1.601	-3.359	-9.361

All values are in Kcal/mol unit

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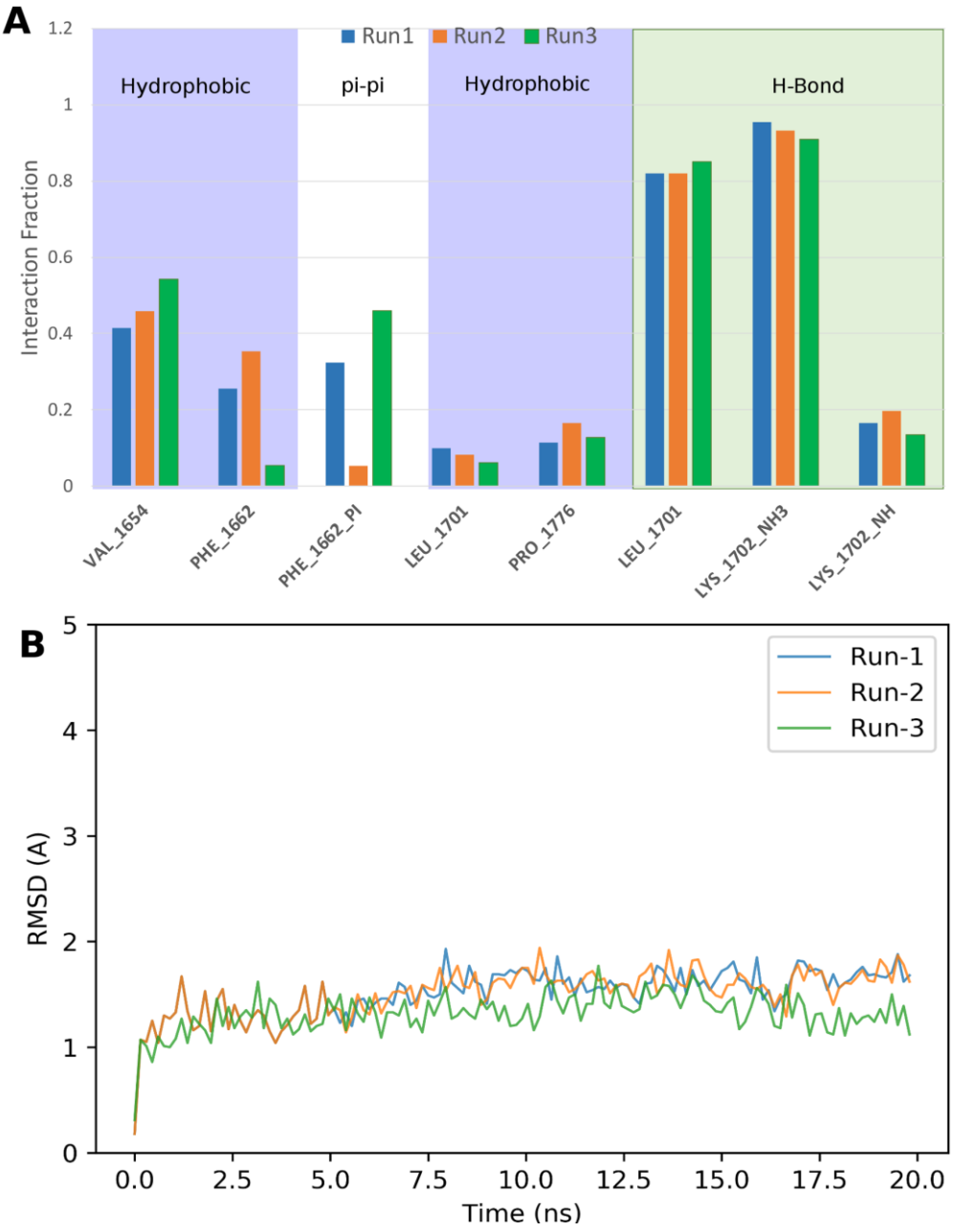

Figure S1. Stability of Bractoppin's Binding mode evaluated in three 20 ns MD simulations: **A**) The histogram shows the fraction of protein- ligand contacts between Bractoppin and BRCA1 pocket residues plotted on X-axis tBRCT during MD simulations, and the interaction fraction plotted on Y-axis for the three repeats. **B)** Calpha atom Root Mean Square Deviation (RMSD) of BRCA1 tBRCT domain residues.

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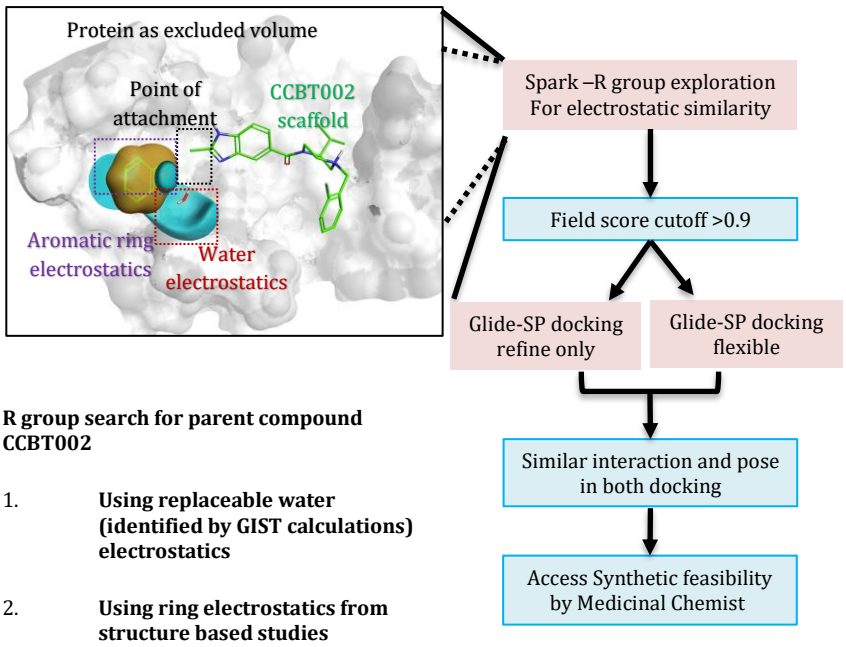

Figure S2: Work-flow for R group search using Spark-cresset tools. Required electrostatic field point of R group to attach on CCBT002 scaffold were identified by water thermodynamic analysis and structural analysis. New Spark suggestions were further filtered by docking and finally shortlisted based on synthetic feasibility while accounting for time, cost and novelty involved in synthesis.