Electronic Supplementary Material (ESI) for MedChemComm.

Structural Insights and Binding Analysis for Determining the Molecular Bases for Programmed Cell Death Protein Ligand-1 Inhibition

Rita C. Acúrcio[a], Carlota Leonardo-Sousa[a], Alfonso T. García-Sosa[b], Jorge A. Salvador[c], Helena F. Florindo[a]*, Rita C. Guedes[a]*

[a] Research Institute for Medicines (iMed.ULisboa), Faculty of Pharmacy, Universidade de Lisboa, 1649-003 Lisbon, Portugal

[b] Institute of Chemistry, University of Tartu, Ravila 14a, 50411 Tartu, Estonia ORCiD 0000-0003-0542-4446

[c] Center for Neurosciences and Cell Biology, Universidade de Coimbra, Coimbra, Portugal

*Corresponding authors:

Helena F. Florindo, hflorindo@ff.ulisboa.pt

Rita C. Guedes, rguedes@ff.ulisboa.pt

Supplementary Material

Figure 1 - RMSD analysis of 15 PD-L1 structures from the PDB. Structures of PD-L1 in complex with small-molecule inhibitors are highlighted in the black box. PD-L1 in complex with peptide-based inhibitors highlighted in the grey box. Similar average RMSD values in each cluster. For small-molecule inhibitors and 0.4 Å for peptide-based inhibitors 0.7 Å.

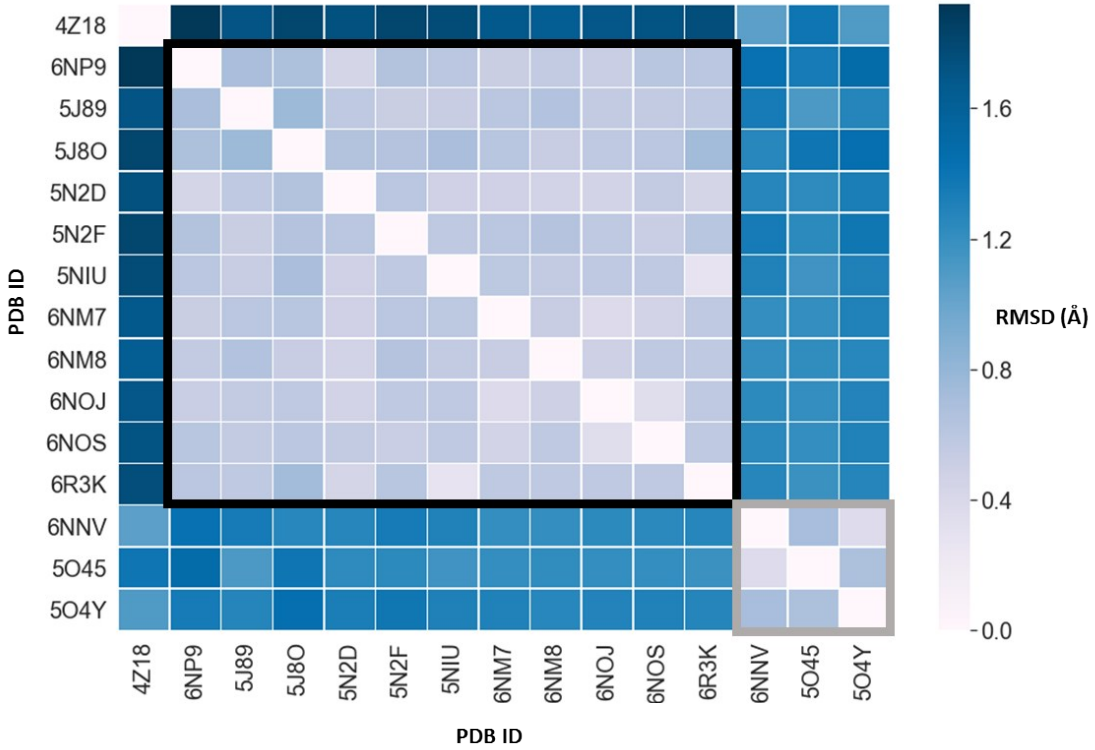

Figure 2 - Ribbon representation of two molecules of PD-L1 (silver) bridged by a small-molecule inhibitor **2** (yellow) (PDBID 5J89). Close-up view of hydrophobic cavity. Receptor-ligand interactions are displayed in dashes. Hydrophobic contacts (yellow), π-staking (green) and H-bond and salt bridges (red).

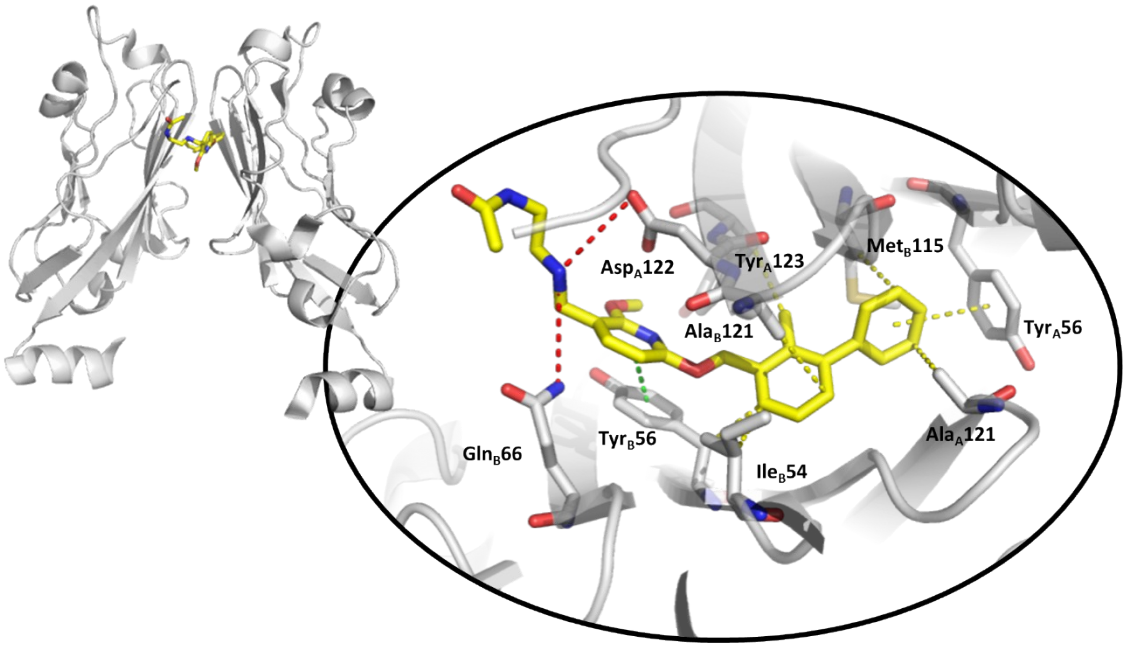

Figure 3 – Tyr_B56 movement

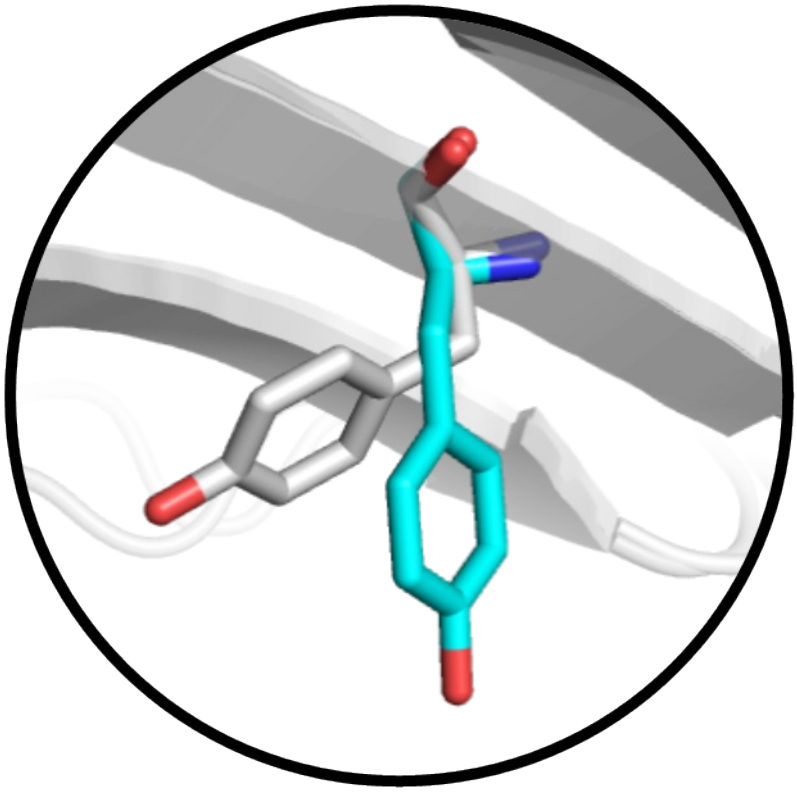

Figure 4 – Interaction between the ligand and the receptor. Each row represents the type of interaction and the columns represent the residues. Blue represent the residues in which there are a ligand/receptor interaction and white represents absence. (A) ligand 5J8O, (B) ligand 5J89 (C) ligand 5N2D (D) ligand 5N2F (E) ligand 5NIU and (F) ligand 6R3K.

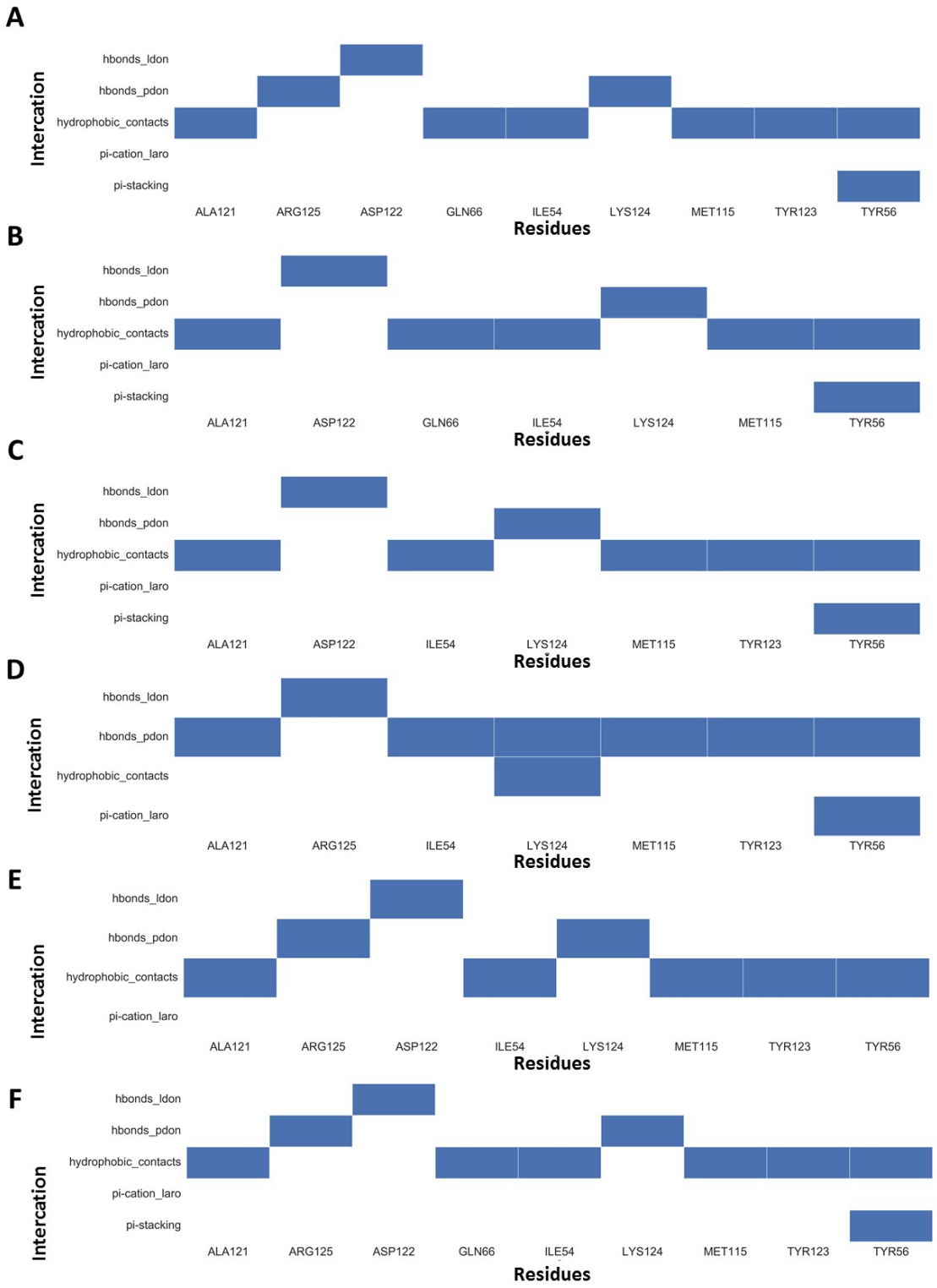

Figure 5 – Heat map of residues involved in PD-L1 homodimer stabilization among PD-L1 complex structures. (A) GoldScore, (B) ChemPLP, and (C) Chemscore.

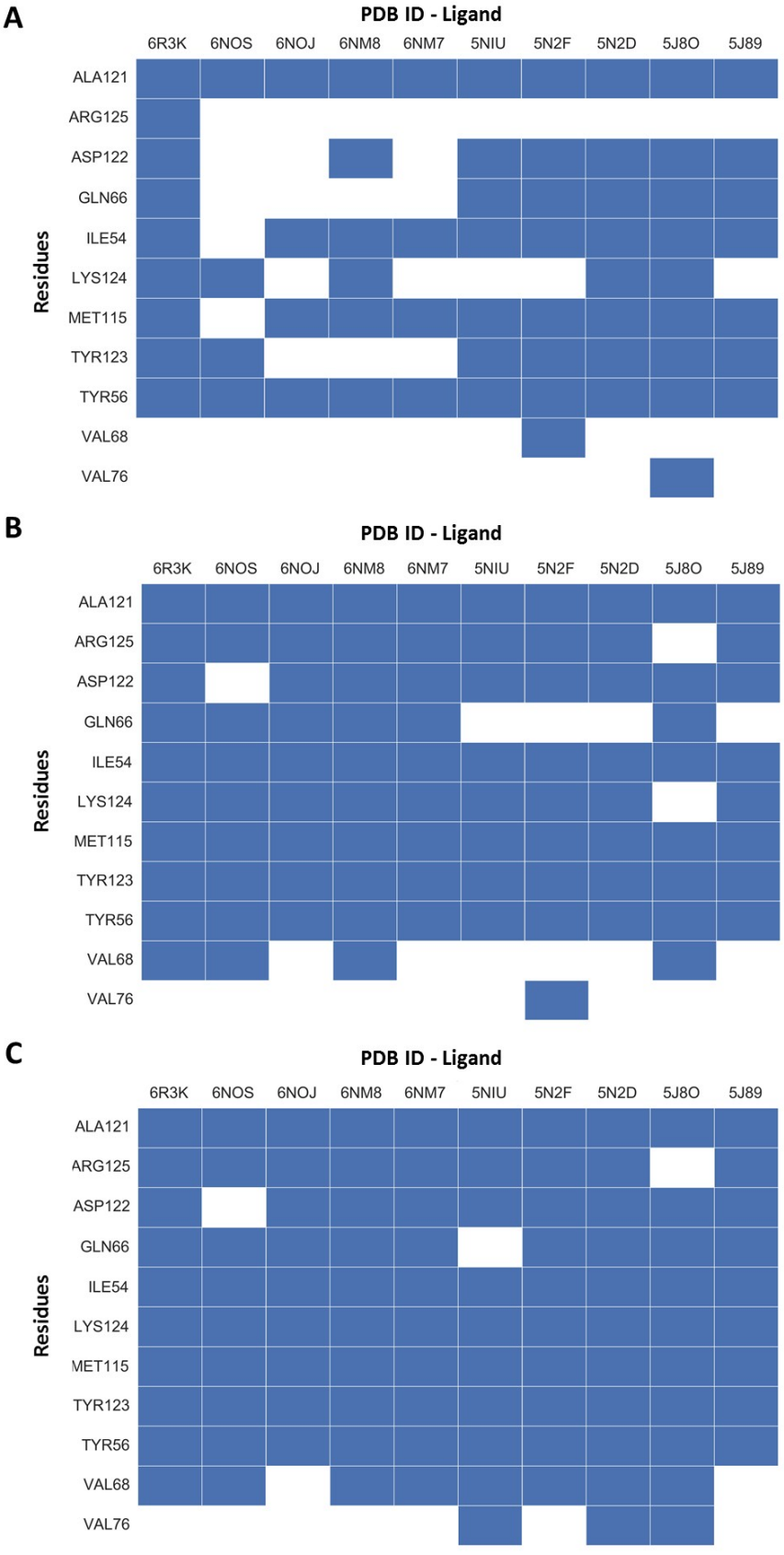

Figure 6 – Racking power of 5J89 and 6R3K for the best combination achieved (GOLD as docking program and GoldScore as scoring function). Score retrieved from docking solutions plotted against known IC50 values.

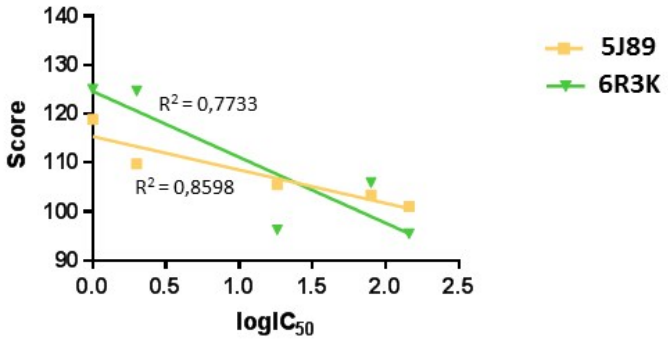

Figure 7 – 15 Å radius sphere around Tyr_B56.