Electronic Supplementary Material (ESI) for Molecular Omics.

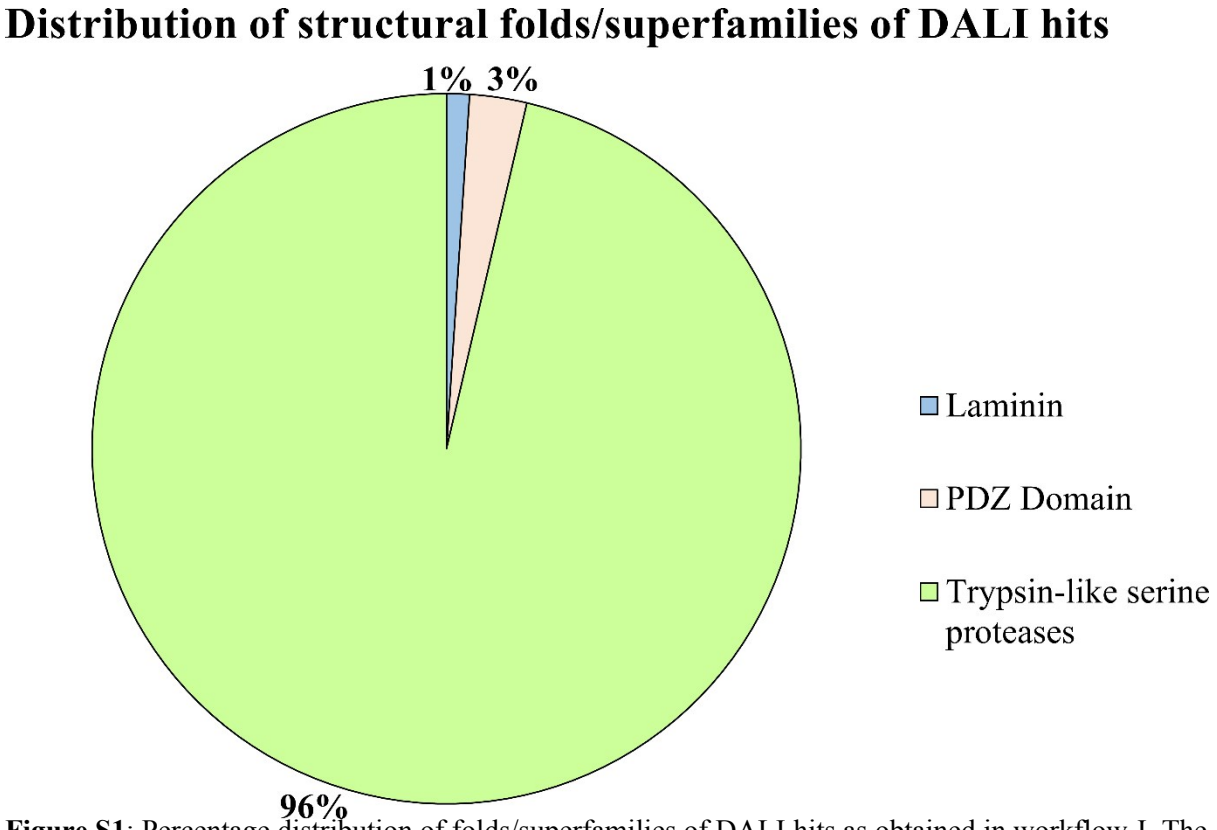

Figure S1: Percentage distribution of folds/superfamilies of DALI hits as obtained in workflow-I. The percentages are mentioned near the respective pie. As could be seen, majority of the hits belong to Trypsin-like serine proteases (superfamily/fold).

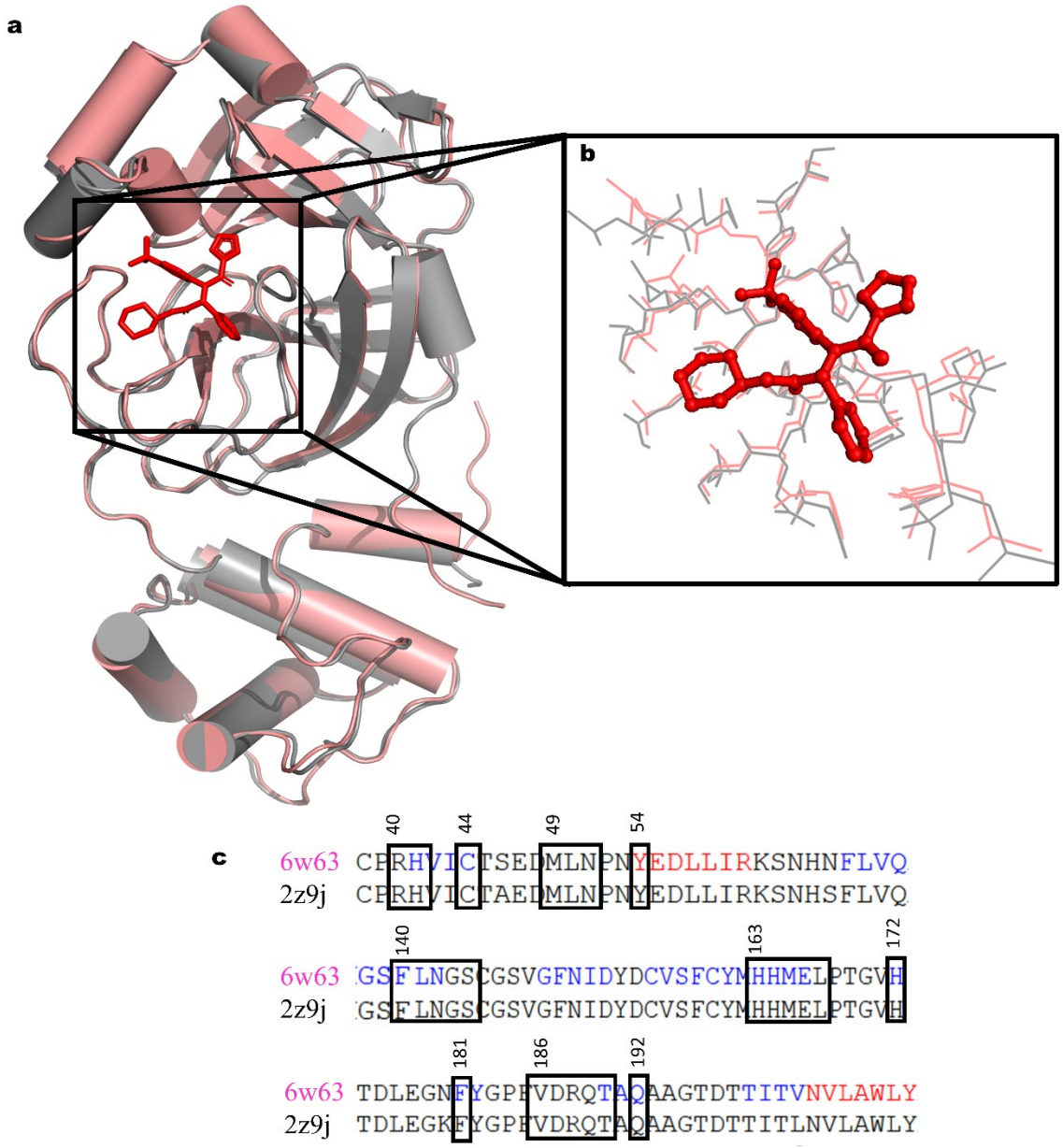

Figure S2: **Structural comparison of SARS-CoV (2Z9J, salmon red) and SARS-CoV-2 main protease (6W63, grey)**. (a) Overlay of the two proteins shows that the two proteins superimpose very well (the structural alignment has been done using DALI server; RMSD: 0.7Å). The protein backbones are shown in cartoon representation (helices: cylinder; beta-strands: arrows) The region within the box encloses the inhibitor binding site corresponding to X77 (red stick) in 6W63. (b) Zoomed-in view of the overlaid inhibitor binding site (X77 in 6W63, red stick). The binding site residues are shown in line representation. (c) The pairwise structure-guided sequence alignment of the two proteins as obtained from Promals3D. Only those alignment blocks are shown which contain the binding site residues and the concerned residues are enclosed within black rectangles. The numbers shown in black color above the blocks represent the residue position in SARS-CoV-2 main protease sequence. As could be seen the binding site of the two proteins have identical sequence. Details related to alignment format is explained elsewhere

(http://prodata.swmed.edu/promals3d/info/promals3d_help.html). The images of the protein-ligand complexes have been generated using PyMOL (Schrödinger, LLC) freely available for academic usage.

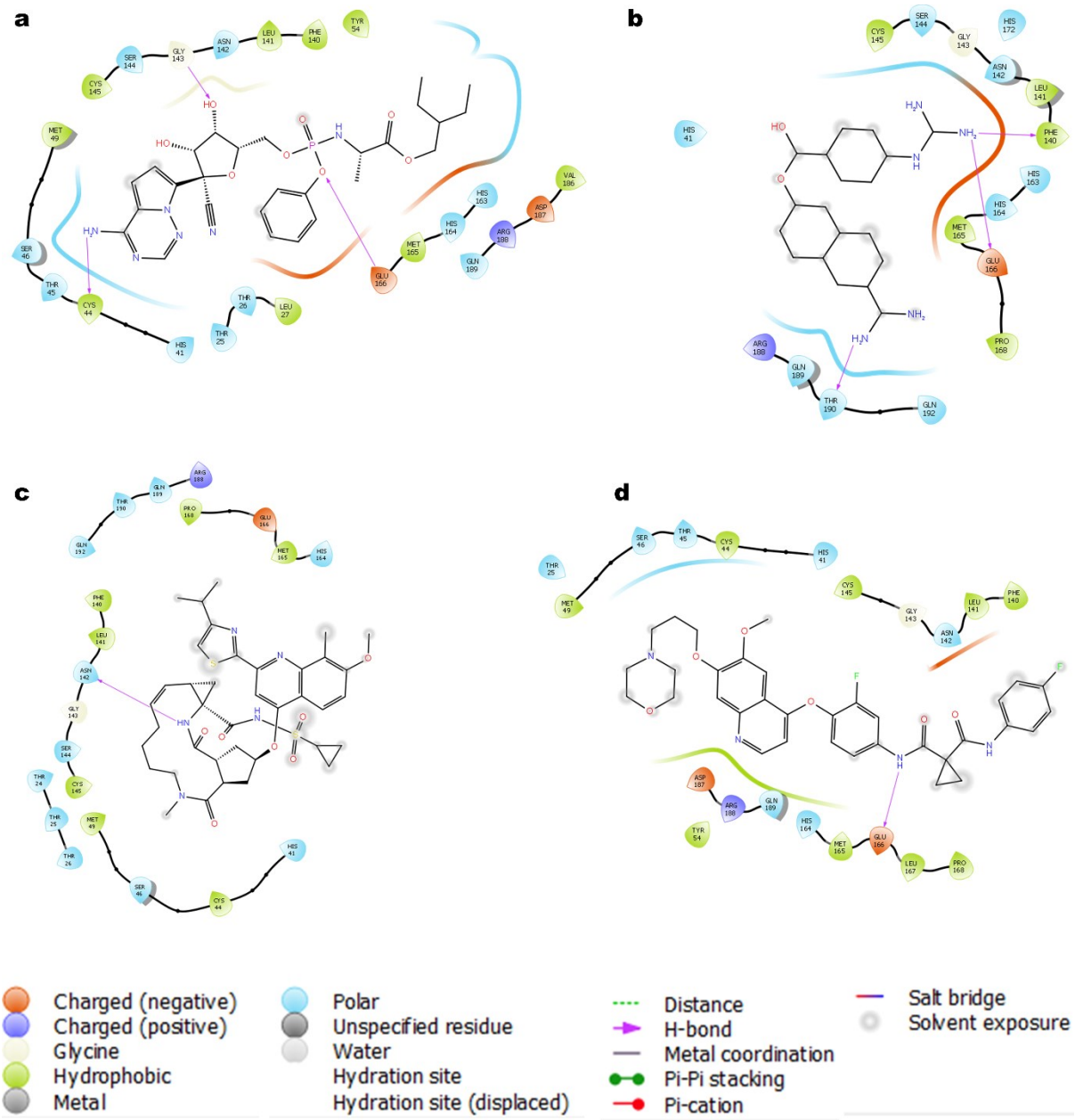

Figure S3: 2D interaction maps of representative prioritized molecules with SARS-CoV-2 main protease as obtained from workflow-I. (a) Remdesivir (b) Nafamostat (c) Simeprevir (d) Foretinib. The image has been generated using Maestro GUI (Schrödinger, LLC) freely available for academic usage.

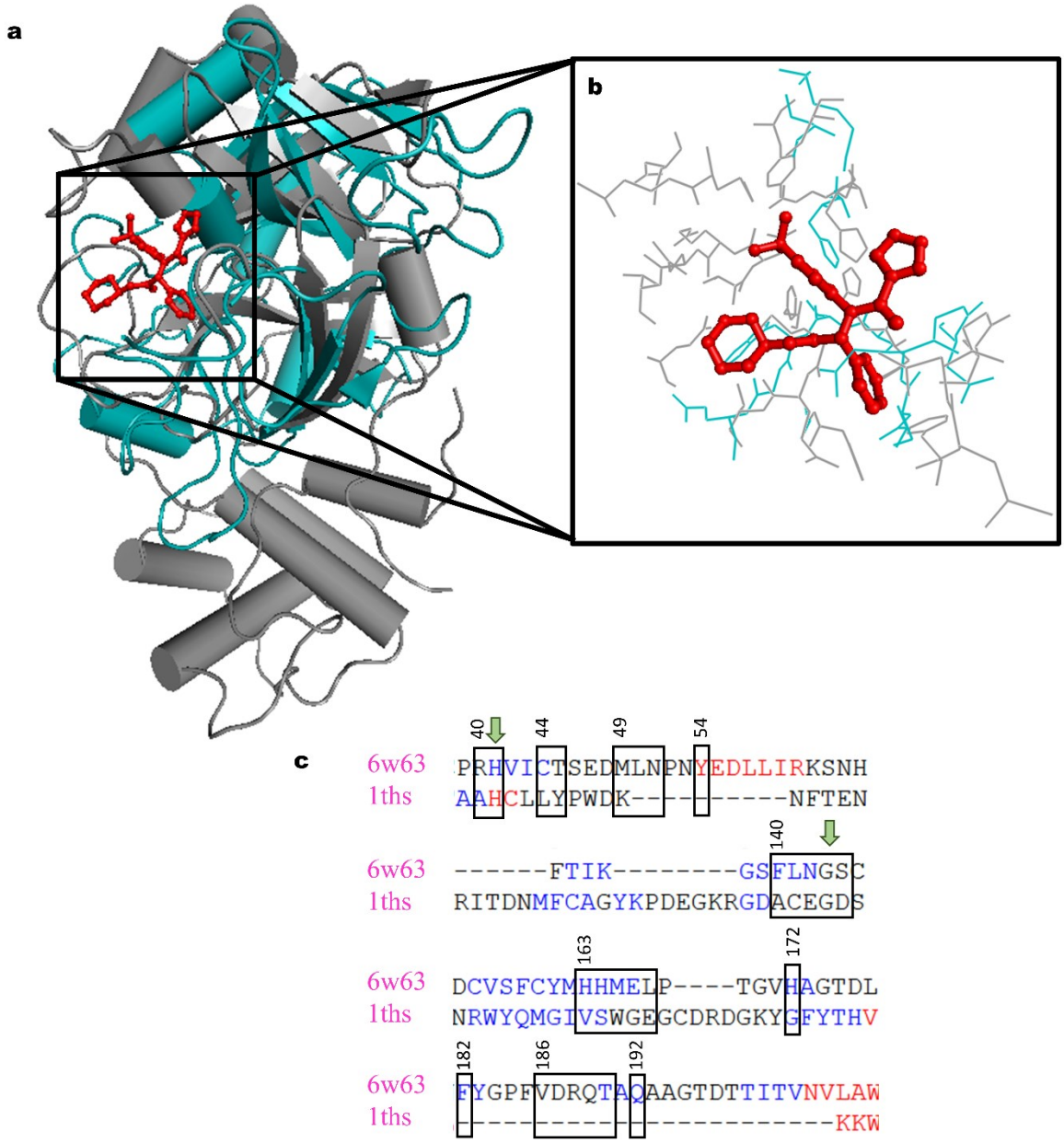

Figure S4: Structural comparison of SARS-CoV-2 main protease (6W63, grey) and human prothrombin (1THS, teal). (a) Overlay of the two proteins shows that the two proteins poorly superimpose on to each other (the structural alignment has been done using DALI server; RMSD: 2.9Å; sequence identity 11%). The protein backbones are shown in cartoon representation (helices: cylinder; beta-strands: arrows) The region within the box encloses the inhibitor binding site corresponding to X77 (red stick) in 6W63 which shows a gross resemblance of the protein backbone. (b) Zoomed-in view of the overlaid inhibitor binding site (X77 in 6W63, red stick). The binding site residues are shown in line representation. (c) The pairwise structure-guided sequence alignment of the two proteins as obtained from Promals3D. Only those alignment blocks are shown which contain the binding site residues and the concerned residues are enclosed within black rectangles. The green arrows indicate the positions with identical amino acid residue in the binding site. The numbers shown in black color above the blocks represent the residue position in SARS-CoV-2 main protease sequence. Details related to alignment format is explained elsewhere

(http://prodata.swmed.edu/promals3d/info/promals3d_help.html). The images of the protein-ligand complexes have been generated using PyMOL (Schrödinger, LLC) freely available for academic usage.

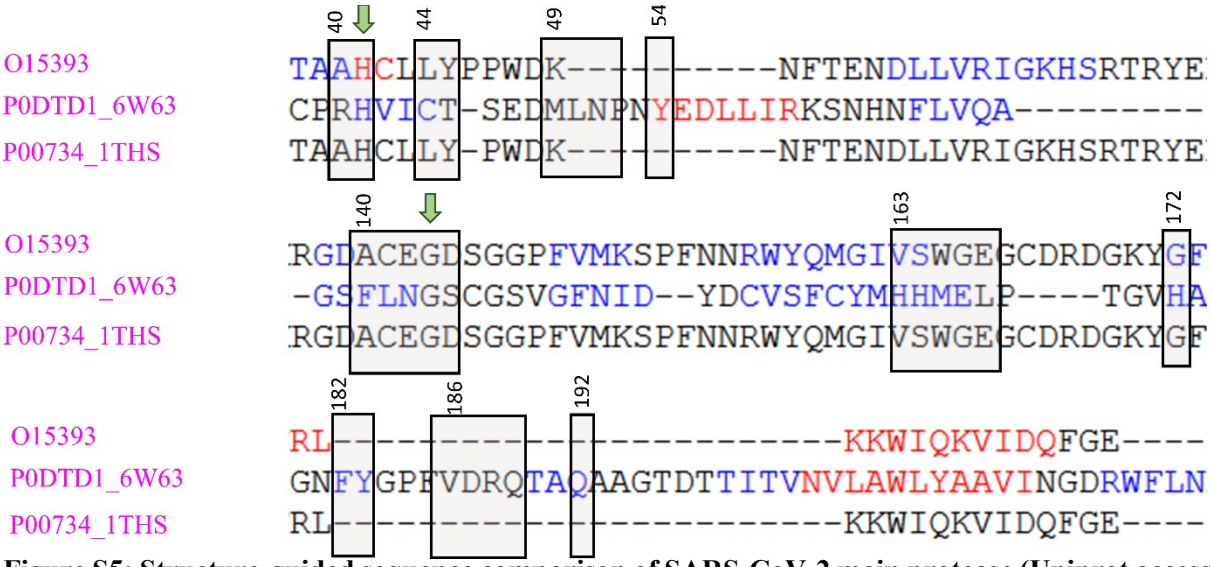

Figure S5: Structure-guided sequence comparison of SARS-CoV-2 main protease (Uniprot accession code: P0DTD1; PDB code: 6W63), human prothrombin (Uniprot accession code: P00734; PDB code: 1THS) and TMPRSS2 (Uniprot accession code: O15393; experimental structure is unavailable) binding site. Only the blocks containing the inhibitor binding site of X77 in 6W63 are shown. The corresponding binding site residues are shown inside the black rectangles. The green arrows indicate the positions with identical amino acid residue in the binding site. The numbers shown in black color above the blocks represent the residue position in SARS-CoV-2 main protease sequence. Details related to alignment format is explained elsewhere (http://prodata.swmed.edu/promals3d/info/promals3d_help.html).

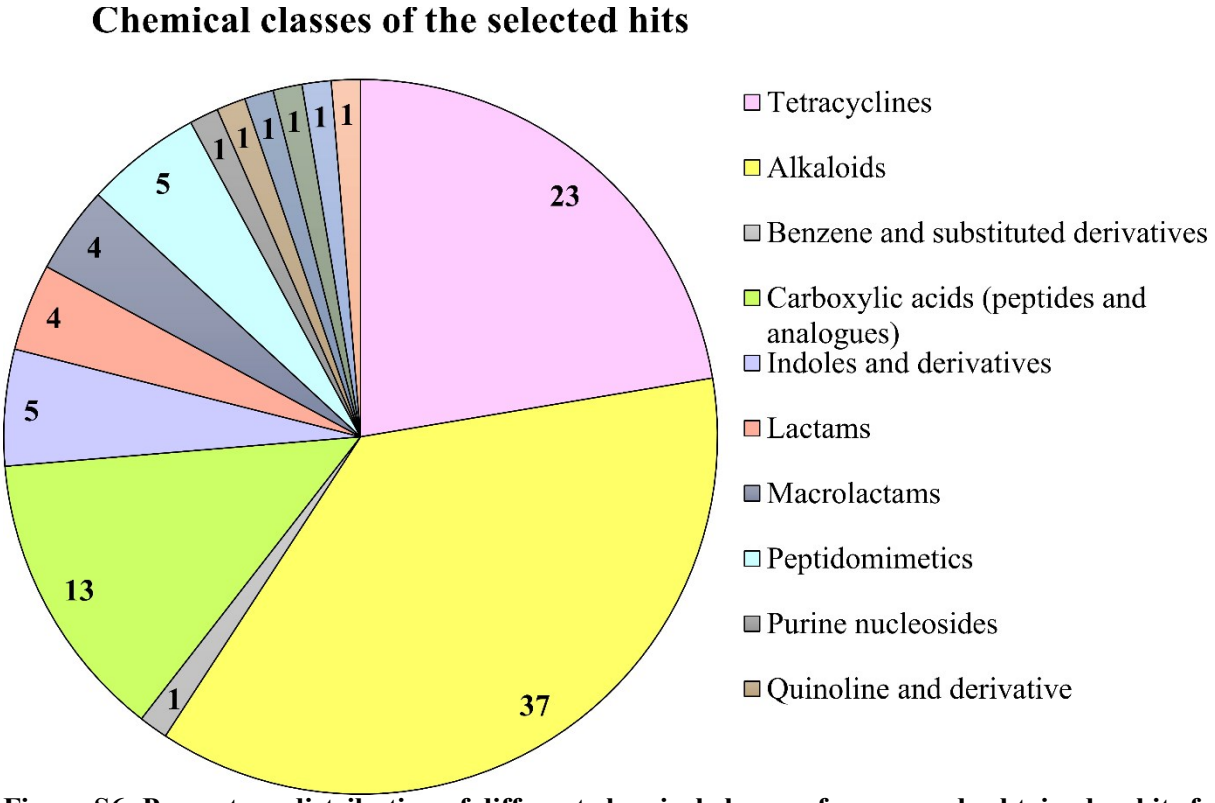

Figure S6: Percentage distribution of different chemical classes of compounds obtained as hits from workflow-II. The respective percentages are shown inside the pie-chart.

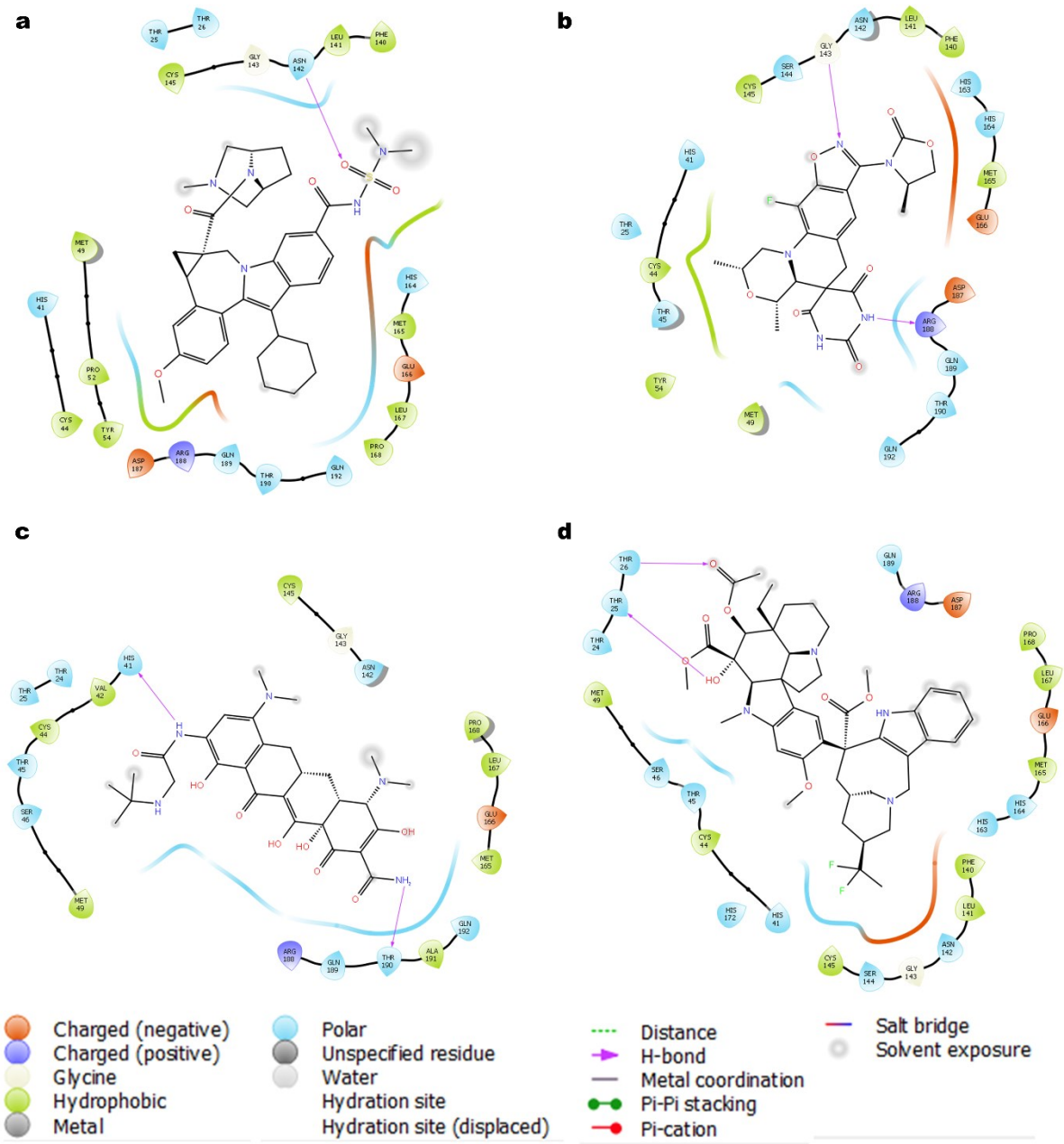

Figure S7: **2D interaction maps of representative molecules with SARS-CoV-2 main protease as shortlisted from workflow-II**. (a) Beclabuvir (b) Zoliflodacin (c) Tigecycline (d) Vinflunine. The image has been generated using Maestro GUI (Schrödinger, LLC) freely available for academic usage.