

**Table S2.** Energies for the top-ranked compounds (small molecules) against each indicated target.

|              | Molecule            | Binding Energy (kcal/mol) |
|--------------|---------------------|---------------------------|
| <b>Mpro</b>  | OSW1                | -108.79                   |
|              | Dispergo            | -103.79                   |
|              | MG-132              | -99.44                    |
|              | Geraniin            | -97.13                    |
|              | Proanthocyanidin-A2 | -89.11                    |
|              | Prodelphinidin-B3   | -83.42                    |
|              | PIK93               | -80.85                    |
| <b>PLPro</b> | Grandinin*          | -82.87                    |
|              | Silibin_A           | -66.24                    |
|              | Itraconazole        | -65.92                    |
|              | PIK93               | -65.06                    |
| <b>NPC1</b>  | Itraconazole        | -92.48                    |
|              | beta-Sitosterol     | -88.98                    |
|              | U18666A             | -85.69                    |
|              | Reserpine           | -82.24                    |
|              | Arbidol             | -80.62                    |
|              | Wortmannin          | -77.72                    |
|              | Phytol              | -77.27                    |
| <b>Spike</b> | Rapamycin           | -62.18                    |
|              | Dispergo            | -61.82                    |
|              | OSW1                | -59.33                    |
|              | Curcumin            | -58.67                    |
|              | Camostat mesylate   | -58.51                    |
| <b>NSP16</b> | PIK93               | -50.04                    |
|              | Taxifolin           | -47.83                    |
|              | Silibin A           | -46.60                    |
|              | Myrcetin            | -45.91                    |
|              | Quercetin           | -44.64                    |

(\*) Grandinin does not fit into the pocket but interacts with the external surface of the target.