Supporting Information

Atomistic De-novo Inhibitor Generation-Guided Drug Repurposing for SARS-CoV-2 Spike Protein with Free-Energy Validation by Well-Tempered Metadynamics

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Section S1. DeNovo ALGORITHM
Figure S1. The algorithmic flowchart of DeNovo drug generation protocol.

The de novo molecule generation flowchart is shown in Fig. S1. Figure S2 gives a visual description of the algorithm with the configurational bias Monte Carlo (CBMC) method. The generation proceeds as follows:

1. Define the “hotspot” of the given protein or any receptor. For this, the residue numbers of the proteins constituting the hotspot is supplied.
2. Then, the centre of mass (COM) of these residues is calculated, and seed atoms (C, N, O, P, or S atoms, picked randomly) are placed at random points close to this COMs.
3. For each of the positions, interaction energy between the ligand and the receptor is calculated, denoted as $W(i)$ [where $i$ is the atom number], in Fig. S2.
4. Then the second atom, again chosen randomly, is placed near the first one [shown in “red” color in Fig. S2]. While placing a second atom certain requirements need to be met. The second atom should be in bonding sphere of the first one and it should make an appropriate bonds based on both atoms valences.
5. Then the third atom is trialled, again chosen randomly, within the bonding sphere of the second atom while maintaining the angle between the first-second-third, i.e., $[i, (i + 1), (i + 2)]$, within a small range of the equilibrium bond angle. Similarly for the fourth atom, the equilibrium bond length with the third, angle with the second, third, and the fourth atom and dihedral for all the four atoms are kept within a small range of the equilibrium value.
6. The equilibrium values of all the parameters are taken from classical force-fields. Here we used CHARMM27 [MacKerell et al., Biopolymers 56, 257-265 (2001)] force filed for bonding, nonbonding, and charge parameters.
7. All the subsequent atom placements follow the above rules of molecule construction.
8. If after a certain length of additions, the growth is hindered due to unmatched valency and bond formation, the growth is recoiled to the previous stage and attempted to start again.
9. The growth continues till the required length (number of heavy atoms) is reached, or until there are no free valences left.
10. At this point, the growth part terminates. In case the program terminates due to reaching full length, it is possible that some valences would be left unsatisfied. In this case, these valences are completed by adding hydrogen atoms (called the reduction step).
11. Finally, the total energy of the molecule (after adding the hydrogen atoms) is compared to the previously generated molecule as shown in the acceptance formula in Fig. S2.

Therefore, our generation of drug molecules follow CBMC algorithm except for two things:
(a) The length of the old and new molecules are not exactly fixed
(b) The constituents of the old and new molecule are not fixed.

Therefore, this algorithm will not maintain the equilibrium of generation. However, we think it will make the generation better than just random sampling.

Figure S2. Visual step-by-step schematic of the generation algorithm broadly covering the underlying probabilistic model used.
Figure S3. The 35 de novo molecules that made the energy cut-off criteria discussed in the method. Binding free energy of all these molecules were calculated using all-atom explicit water simulations using metadynamics.

Section S2. SIMILARITY BASED REPURPOSING

Table S1. List of similar drug molecules retrieved from DrugBank based on Tanimoto coefficient cutoff of 0.4 for each of the chosen de novo molecules. All narcotics, anesthetics, illicit substances, anti-depressants, schizophrenia/Alzheimer’s/Parkinson’s related hyper specific molecules, contrasting agents, neuromuscular blocking agents, immune-depressants, and pain relievers have been discarded due to their biochemical and pharmacological irrelevance to this problem. These rejects have been marked in red, all others that were acceptable were passed on to docking to RBD and are marked in blue. The docking score and similarity score to the respective de novo molecules are shown in bracket. For the rejected molecules, only similarity score is shown.

| SR. No. | DeNovo Id | Similar Drugs with DrugBank Id with similarity and docking scores |
|---------|-----------|------------------------------------------------------------------|
| 1       | 29_19     | DB06200(0.456,-6), DB04878(0.449,-5.6), DB09031(0.444,-5.5),  |
|         |           | DB01337(0.432), DB01339(0.432), DB00657(0.422),  |
|         |           | DB11807(0.422), DB00728(0.418,-6.8), DB05513(0.416),  |
|         |           | DB11860(0.407,-7.4), DB00419(0.402), DB14872(0.402),  |
|         |           | DB04834(0.401,-6)                                               |
| 2       | 32_26     | DB06614(0.557,-5.6), DB11682(0.522,-6.6), DB15286(0.5),  |
|         |           | DB00312(0.489), DB08873(0.483,-6.1), DB11860(0.479,-7.4),  |
|         |           | DB00786(0.478,-6.5), DB06345(0.478,-7.6), DB06293(0.471,-5.8),  |
|         |           | DB01351(0.468), DB01353(0.468), DB06335(0.463,-5.9),  |
|         |           | DB00418(0.463), DB00237(0.46), DB00790(0.446,-6.2),  |
|         |           | DB00599(0.445), DB13253(0.442), DB06573(0.441,-6.1),  |
|         |           | DB06827(0.437,-8.2), DB00306(0.436), DB11762(0.433,-6.2),  |
|         |           | DB01154(0.429), DB06124(0.429,-6.4), DB00241(0.426),  |
|         |           | DB00248(0.419,-6.2), DB14932(0.419,-6.5), DB12613(0.419,-6.7),  |
|         |           | DB05541(0.418,-5.5), DB00474(0.417), DB11879(0.414),  |
|         |           | DB05434(0.413,-7), DB06641(0.413,-6), DB01627(0.412,-5.9),  |
|         |           | DB11938(0.41,-7.5), DB00178(0.409,-6.8), DB12416(0.407,-7.3),  |
|         |           | DB01216(0.406), DB15412(0.406,-5.8), DB00519(0.405,-6.7),  |
|         |           | DB04845(0.404,-7.1), DB06127(0.401), DB01190(0.401,-6)       |
| 3       | 37_42     | DB00657(0.5), DB11807(0.5), DB06200(0.47,-6),  |
|         |           | DB12493(0.465), DB06714(0.463), DB13012(0.463,-6.2),  |
|         |           | DB15264(0.452), DB00302(0.443), DB04545(0.438,-4.5),  |
|         |           | DB12032(0.438), DB01074(0.426), DB04878(0.424,-5.6),  |
|         |           | DB00996(0.422), DB00230(0.419), DB05513(0.415),  |
|         |           | DB12105(0.409), DB01337(0.408), DB01339(0.408),  |
|         |           | DB11684(0.407), DB01637(0.404), DB11860(0.404,-7.4)       |
| 4       | 39_32     | DB09421(0.536,-7.6), DB12370(0.507,-7), DB11944(0.503),  |
|         |           | DB15188(0.5,-6.6), DB11695(0.47), DB12199(0.461,-7.9),  |
|         |           | DB06763(0.457,-7.4), DB12631(0.45,-7.5), DB12099(0.448),  |
|         |           | DB01085(0.447), DB04896(0.446), DB08918(0.446),  |
|         |           | DB11720(0.437), DB05521(0.436,-7.9), DB01437(0.433), }
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|---|---|---|
| 5 | 39_57 | DB12833(0.433,-8), DB00357(0.43), DB06471(0.429), DB15299(0.429), DB14870(0.428), DB06335(0.425,-5.9), DB15091(0.421), DB00561(0.418), DB00490(0.418), DB00248(0.417,-6.2), DB06448(0.416), DB14813(0.408), DB01618(0.406), DB04872(0.406), DB14854(0.406), DB05796(0.404), DB01117(0.404), DB09102(0.403), DB06645(0.403), DB14955(0.402), DB09290(0.4) |
|   | 40_35 | DB06335(0.546,-5.9), DB12795(0.471,-6.4), DB00786(0.453,-6.5), DB04878(0.442,-5.6), DB04348(0.438,-8.3), DB08834(0.438), DB00790(0.436,-6.2), DB04876(0.432,-6.5), DB15286(0.411), DB06614(0.408,-5.6), DB15412(0.408,-5.8), DB06657(0.408), DB11684(0.405), DB00141(0.403), DB12536(0.403), DB01338(0.403,-7.3), DB12677(0.401,-6), DB01627(0.4,-5.9) |
|   | 41_31 | DB06705(0.52), DB06293(0.503,-5.8), DB06124(0.497,-6.4), DB12677(0.495,-6), DB06614(0.489,-5.6), DB05434(0.489,-7), DB00786(0.486,-6.5), DB06827(0.484,-8.2), DB08993(0.48,-8.2), DB01627(0.48,-5.9), DB01190(0.479,-6), DB08873(0.474,-6.1), DB15286(0.473), DB11801(0.47), DB12791(0.47,-6.5), DB01338(0.436,-6.2), DB01337(0.557), DB01339(0.557), DB06124(0.54,-6.4), DB04834(0.539,-6), DB01338(0.536,-7.3), DB11860(0.528,-7.4), DB00728(0.525,-6.8), DB06335(0.514,-5.9), DB00178(0.512,-6.8), DB08965(0.507), DB00519(0.506,-6.7), DB06696(0.485), DB11684(0.484), DB03567(0.483), DB01197(0.481), DB12232(0.481,-6.1), DB11682(0.476,-6.6), DB13087(0.476), DB12677(0.474,-6), DB05645(0.472,-6.5), DB12613(0.47,-6.7), DB14932(0.47,-6.5), DB01627(0.466,-5.9), DB12839(0.463), DB06345(0.456,-7.6), DB15286(0.455), DB06045(0.453), DB05814(0.453), DB01083(0.452), DB00786(0.45,-6.5), DB11879(0.449), DB01190(0.444,-6), DB06580(0.442), DB12655(0.441), DB04876(0.441,-6.5), DB09291(0.44), DB06472(0.437), DB05434(0.435,-7), DB05541(0.434,-5.5), DB12416(0.431,-7.3), DB13106(0.43), DB08873(0.43,-6.1), DB11929(0.43,-8.2), DB12287(0.43), DB04878(0.429,-5.6), DB06127(0.429), DB12704(0.428), DB00141(0.425), DB12536(0.425), DB06354(0.425,-7.9), DB08818(0.424), DB09271(0.424), DB00584(0.423), DB11876(0.422), DB11781(0.422), DB00899(0.421), DB02691(0.42), DB12615(0.417), DB15412(0.417,-5.8), DB11797(0.415), DB00517(0.413), DB09292(0.412,-8.4), DB00207(0.412,-7), DB01340(0.411), DB05633(0.408), DB09026(0.408,-6.5), DB00198(0.407), DB01232(0.407,-8.7), DB06293(0.407,-5.8), DB11801(0.407), DB06497(0.407,-8.1), DB13262(0.406), DB06573(0.406,-6.1), DB00708(0.404), DB14783(0.403), DB12795(0.403,-6.4), DB00747(0.401), DB09300(0.401), DB11315(0.401), DB12086(0.401), DB12178(0.401,-8), DB04863(0.4) |
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|---|---|
| 9 | 41_46 |
|   | DB06641(0.482,-6), DB09031(0.467,-5.5), DB00312(0.449), DB01351(0.436), DB01353(0.436), DB00599(0.434), DB00418(0.433), DB13253(0.432), DB00237(0.427), DB01154(0.426), DB00306(0.413), DB00241(0.411) |
| 10 | 44_15 |
|   | DB06345(0.557,-7.6), DB00312(0.556), DB08873(0.542,-6.1), DB11879(0.538), DB01351(0.528), DB01353(0.528), DB05541(0.527,-5.5), DB06614(0.522,-5.6), DB00237(0.519), DB00418(0.517), DB11682(0.515,-6.6), DB11860(0.513,-7.4), DB05645(0.5,-6.5), DB06335(0.5,-5.9), DB00599(0.496), DB15199(0.495,-6.4), DB00593(0.49), DB15286(0.489), DB00306(0.483), DB00786(0.474,-6.5), DB01154(0.472), DB00241(0.47), DB15601(0.469), DB08958(0.465), DB06573(0.459,-6.1), DB05434(0.457,-7), DB12833(0.455,-8), DB12839(0.455), DB12613(0.454,-6.7), DB06657(0.45), DB00490(0.448), DB00790(0.446,-6.2), DB12692(0.444), DB12991(0.444), DB13087(0.444), DB13018(0.44), DB01216(0.439), DB06045(0.435), DB13288(0.434), DB05814(0.433), DB06200(0.433,-6), DB00474(0.432), DB13253(0.431), DB01197(0.429), DB01252(0.427,-7.9), DB01437(0.424), DB13221(0.421), DB04896(0.419), DB08918(0.419), DB12444(0.419), DB12951(0.418), DB06124(0.417,-6.4), DB12184(0.417), DB09026(0.407,-6.5), DB11801(0.406), DB11890(0.405,-6.7), DB00155(0.404), DB00746(0.404), DB11938(0.404,-7.5), DB00357(0.401), DB11876(0.4) |
| 11 | 44_16 |
|   | DB00312(0.56), DB01107(0.556), DB01351(0.532), DB01353(0.532), DB00237(0.523), DB00418(0.521), DB15286(0.514), DB00593(0.51), DB11860(0.504,-7.4), DB06335(0.493,-5.9), DB13253(0.492), DB05541(0.491,-5.5), DB00786(0.489,-6.5), DB00306(0.487), DB00241(0.475), DB11682(0.474,-6.6), DB02691(0.462), DB06200(0.454,-6), DB06614(0.451,-5.6), DB00599(0.45), DB06293(0.449,-5.8), DB00490(0.448), DB00790(0.446,-6.2), DB12692(0.444), DB12991(0.444), DB13087(0.444), DB13018(0.44), DB01216(0.439), DB06045(0.435), DB13288(0.434), DB05814(0.433), DB06200(0.433,-6), DB00474(0.432), DB13253(0.431), DB01197(0.429), DB01252(0.427,-7.9), DB01437(0.424), DB13221(0.421), DB04896(0.419), DB08918(0.419), DB12444(0.419), DB12951(0.418), DB06124(0.417,-6.4), DB12184(0.417), DB09026(0.407,-6.5), DB11801(0.406), DB11890(0.405,-6.7), DB00155(0.404), DB00746(0.404), DB11938(0.404,-7.5), DB00357(0.401), DB11876(0.4) |
| 12 | 44_18 |
|   | DB00312(0.56), DB01107(0.556), DB01351(0.532), DB01353(0.532), DB00237(0.523), DB00418(0.521), DB15286(0.514), DB00593(0.51), DB11860(0.504,-7.4), DB06335(0.493,-5.9), DB13253(0.492), DB05541(0.491,-5.5), DB00786(0.489,-6.5), DB00306(0.487), DB00241(0.475), DB11682(0.474,-6.6), DB02691(0.462), DB06200(0.454,-6), DB06614(0.451,-5.6), DB00599(0.45), DB06293(0.449,-5.8), DB00490(0.448), DB00790(0.446,-6.2), DB12692(0.444), DB12991(0.444), DB13087(0.444), DB13018(0.44), DB01216(0.439), DB06045(0.435), DB13288(0.434), DB05814(0.433), DB06200(0.433,-6), DB00474(0.432), DB13253(0.431), DB01197(0.429), DB01252(0.427,-7.9), DB01437(0.424), DB13221(0.421), DB04896(0.419), DB08918(0.419), DB12444(0.419), DB12951(0.418), DB06124(0.417,-6.4), DB12184(0.417), DB09026(0.407,-6.5), DB11801(0.406), DB11890(0.405,-6.7), DB00155(0.404), DB00746(0.404), DB11938(0.404,-7.5), DB00357(0.401), DB11876(0.4) |
| 13 | 44_43 |
|-----|-------|
| DB12833(0.448,-8), DB12839(0.446), DB06657(0.441), DB06345(0.44,-7.6), DB00474(0.436), DB08873(0.435,-6.1), DB05513(0.432), DB00490(0.431), DB01252(0.431,-7.9), DB00790(0.43,-6.2), DB01154(0.43), DB12677(0.405,-6), DB01216(0.403), DB00561(0.403), DB13288(0.402), DB11879(0.402), DB12184(0.4), DB15199(0.4,-6.4) |
| 14 | 44_81 |
| DB01154(0.563), DB00418(0.546), DB00599(0.526), DB00306(0.513), DB00312(0.491), DB00241(0.487), DB11825(0.469), DB01351(0.466), DB01353(0.466), DB08873(0.464,-6.1), DB00237(0.457), DB13253(0.447), DB12513(0.438), DB01216(0.434), DB13221(0.427), DB12020(0.416), DB15601(0.409), DB00786(0.407,-6.5), DB05541(0.407,-5.5), DB06657(0.402) |
| 15 | 45_23 |
| DB01107(0.7), DB06657(0.6), DB01351(0.59), DB01353(0.59), DB00593(0.571), DB00312(0.57), DB00237(0.523), DB00418(0.521), DB05541(0.517,-5.5), DB11860(0.516,-7.4), DB00241(0.511), DB02691(0.495), DB00306(0.479), DB00599(0.479), DB12839(0.477), DB12692(0.475), DB12991(0.475), DB06200(0.472,-6), DB12951(0.472), DB01783(0.471), DB00746(0.468), DB06345(0.467,-7.6), DB15199(0.462,-6.4), DB01154(0.451), DB13288(0.449), DB01437(0.449), DB12521(0.446), DB13253(0.443), DB11190(0.443), DB05513(0.443), DB13099(0.433,-5.1), DB09357(0.432), DB13087(0.432), DB08873(0.431,-6.1), DB00490(0.425), DB04348(0.425,-8.3), DB08834(0.425), DB06335(0.424,-5.9), DB15601(0.422), DB00786(0.419,-6.5), DB15286(0.416), DB12444(0.415), DB01074(0.412), DB09210(0.41), DB01202(0.41), DB11868(0.41), DB00357(0.407), DB01216(0.403), DB11879(0.402), DB12833(0.4,-8) |
| 16 | 45_24 |
| DB01107(0.633), DB06345(0.56,-7.6), DB05541(0.559,-5.5), DB11860(0.541,-7.4), DB00593(0.538), DB01074(0.536), DB13288(0.527), DB00312(0.526), DB06200(0.526,-6), DB01351(0.511), DB01353(0.511), DB06657(0.506), DB00237(0.5), DB05513(0.5), DB11682(0.5,-6.6), DB06614(0.509,-5.6), DB11860(0.459,-7.4), DB12586(0.448), DB06345(0.447,-7.6), DB06293(0.445,-5.8), DB00786(0.442,-6.5), DB08873(0.441,-6.1), DB06335(0.437,-5.9), DB11762(0.433,-6.2), DB11682(0.431,-6.6), DB13253(0.424), DB00479(0.42,-6.1), DB14542(0.419,-7.6), DB14631(0.417,-7.4), DB12704(0.416), DB00418(0.416), DB06696(0.408), DB12416(0.407,-7.3), DB06124(0.406,-6.4), DB09026(0.405,-6.5), DB11471(0.405), DB04878(0.403,-5.6), DB06641(0.403,-6) |
|   |   |   |
|---|---|---|
| 17 | 45_74 | DB04878(0.4,-5.6) |
| 18 | 46_12 | DB11860(0.554,-7.4), DB15264(0.53), DB02691(0.516), DB12032(0.515), DB000230(0.5), DB00996(0.5), DB13099(0.492,-5.1), DB06335(0.491,-5.9), DB12105(0.486), DB00302(0.478), DB04348(0.471,-8.3), DB08834(0.471), DB06200(0.459,-6), DB01107(0.458), DB00312(0.457), DB05541(0.457,-5.5), DB12444(0.457), DB12493(0.456), DB00593(0.455), DB00599(0.454), DB04878(0.451,-5.6), DB06657(0.443), DB13087(0.438), DB12839(0.433), DB05513(0.431), DB11825(0.429), DB00149(0.426), DB14187(0.426), DB01351(0.426), DB01353(0.426), DB000786(0.424,-6.5), DB11684(0.418), DB00657(0.418), DB11807(0.418), DB01154(0.415), DB00237(0.415), DB00513(0.413), DB00167(0.412), DB12521(0.412), DB05814(0.411), DB04876(0.411,-6.5), DB00418(0.41), DB12032(0.409), DB15264(0.409), DB00790(0.409), DB06124(0.408,-5.8), DB06714(0.406), DB01337(0.405), DB01339(0.405), DB09357(0.405), DB00130(0.4) |
| 19 | 46_13 | DB08873(0.492,-6.1), DB06573(0.443,-6.1), DB14941(0.441), DB11682(0.434,-6.6), DB14075(0.429), DB15286(0.426), DB00790(0.425,-6.2), DB06124(0.424,-6.4), DB06045(0.423), DB12613(0.422,-6.7), DB14173(0.422), DB04876(0.42,-6.5), DB06293(0.416,-5.8), DB00786(0.412,-6.5), DB12416(0.41,-7.3), DB06614(0.41,-5.6), DB13018(0.409), DB06335(0.408,-5.9), DB15251(0.408), DB06827(0.407,-8.2), DB01601(0.407,-7.7), DB05645(0.405,-6.5), DB11783(0.405), DB13034(0.4,-7.3) |
| 20 | 46_22 | DB00657(0.714), DB11807(0.714), DB06714(0.612), DB01074(0.554), DB06200(0.516,-6), DB13012(0.508,-6.2), DB12105(0.5), DB04878(0.494,-6.4), DB12032(0.484), DB11860(0.483,-7.4), DB00478(0.471), DB04926(0.469), DB05513(0.46), DB11924(0.455), DB15264(0.452), DB09915(0.451), DB01043(0.451), DB12449(0.446), DB00302(0.443), DB06333(0.43,-6.3), DB06461(0.43,-6.6), DB00786(0.492,-6.5), DB01216(0.487), DB00418(0.486), DB06614(0.484,-5.6), DB06335(0.483,-5.9), DB00657(0.471), DB11807(0.471), DB11879(0.468), DB08873(0.463,-6.1), DB00306(0.462), DB15286(0.461), DB00241(0.461), DB15601(0.46), DB05645(0.457,-6.5), DB12951(0.45), DB00599(0.447), DB06714(0.441), DB01437(0.435), DB05832(0.432,-7.1), DB04876(0.431,-6.5), DB00746(0.43), DB01197(0.427), DB01202(0.427), DB11868(0.427), DB01154(0.423), DB12513(0.423), DB12712(0.422), DB01783(0.421), DB08958(0.42), DB00306(0.462), DB15286(0.461), DB00241(0.461), DB15601(0.46), DB05645(0.457,-6.5), DB12951(0.45), DB00599(0.447), DB06714(0.441), DB01437(0.435), DB05832(0.432,-7.1), DB04876(0.431,-6.5), DB00746(0.43), DB01197(0.427), DB01202(0.427), DB11868(0.427), DB01154(0.423), DB12513(0.423), DB12712(0.422), DB01783(0.421), DB08958(0.42), DB13087(0.417), DB15199(0.416,-6.4), DB00790(0.415,-6.2), DB12839(0.412), DB12833(0.412,-8), DB00514(0.411), DB12536(0.411), DB01255(0.409), DB05814(0.407), DB05434(0.403,-7), DB13221(0.402), DB11801(0.402), DB05885(0.402), DB04878(0.4,-5.6), DB09357(0.4), DB12613(0.4,-6.7), DB06045(0.4) |
| 21  | 46_24                  |
|-----|------------------------|
|     | DB14631(0.451,-7.4), DB14542(0.444,-7.6), DB05456(0.434), DB11471(0.425), DB12655(0.422), DB09031(0.419,-5.5), DB01256(0.417), DB14669(0.417), DB091123(0.413), DB06705(0.409), DB14096(0.407), DB01627(0.406,-5.9), DB06293(0.406,-5.8), DB09091(0.405), DB11921(0.404), DB11762(0.402,-6.2), DB01190(0.402,-6), DB01590(0.4) |

| 22  | 46_37                  |
|-----|------------------------|
|     | DB06641(0.487,-6), DB00312(0.467), DB09031(0.459,-5.5), DB00599(0.452), DB06293(0.45,-5.8), DB00418(0.45), DB01154(0.443), DB01351(0.442), DB01353(0.442), DB13253(0.437), DB15286(0.434), DB00237(0.433), DB06614(0.424,-5.6), DB11860(0.422,-7.4), DB14542(0.42,-7.6), DB00306(0.419), DB14631(0.409,-7.4), DB00241(0.406), DB15412(0.405,-5.8), DB11848(0.403), DB06335(0.403,-5.9) |

| 23  | 47_11                  |
|-----|------------------------|
|     | DB05541(0.508,-5.5), DB06335(0.497,-5.9), DB11879(0.496), DB05645(0.486,-6.5), DB06673(0.486,-6.1), DB12833(0.465,-8), DB13018(0.464), DB08873(0.461,-6.1), DB00786(0.455,-6.5), DB15286(0.451), DB05434(0.449,-7), DB12692(0.448), DB12991(0.448), DB15199(0.447,-6.4), DB12613(0.447,-6.7), DB00490(0.441), DB00790(0.44,-6.2), DB06124(0.438,-6.4), DB00312(0.43), DB15601(0.43), DB06657(0.429), DB06127(0.425), DB15412(0.423,-5.8), DB12677(0.422,-6), DB11709(0.418), DB12795(0.417,-6.4), DB01107(0.416), DB06614(0.415,-5.6), DB12184(0.413), DB00593(0.412), DB01351(0.407), DB01353(0.407), DB00418(0.407), DB06045(0.403), DB01597(0.402), DB00237(0.4) |

| 24  | 47_26                  |
|-----|------------------------|
|     | DB08873(0.506,-6.1), DB06573(0.477,-6.1), DB11879(0.465), DB00599(0.46), DB06335(0.459,-5.9), DB15412(0.458,-5.8), DB00312(0.452), DB01154(0.451), DB13018(0.444), DB15601(0.44), DB00418(0.438), DB00790(0.432,-6.2), DB05541(0.431,-5.5), DB01351(0.43), DB01353(0.43), DB05645(0.429,-6.5), DB00474(0.428), DB12795(0.427,-6.4), DB11682(0.425,-6.6), DB00237(0.422), DB06127(0.418), DB15286(0.417), DB15199(0.416,-6.4), DB06124(0.415,-6.4), DB05434(0.415,-7), DB00786(0.41,-6.5), DB00306(0.41), DB12613(0.404,-6.7), DB04876(0.4,-6.5), DB12692(0.4), DB01627(0.4,-5.9), DB12991(0.4) |

| 25  | 47_27                  |
|-----|------------------------|
|     | DB06641(0.515,-6), DB14981(0.48,-5.1), DB14542(0.445,-7.6), DB14631(0.433,-7.4), DB09031(0.426,-5.5), DB04878(0.418,-5.6), DB11848(0.407) |

| 26  | 47_68                  |
|-----|------------------------|
|     | DB11860(0.579,-7.4), DB06335(0.533,-5.9), DB00786(0.53,-6.5), DB15286(0.521), DB06614(0.511,-5.6), DB05541(0.5,-5.5), DB01107(0.477), DB06293(0.476,-5.8), DB00141(0.475), DB12536(0.475), DB13087(0.471), DB04878(0.47,-5.6), DB05814(0.469), DB00790(0.467,-6.2), DB04876(0.466,-6.5), DB00786(0.455,-5.6), DB12833(0.448), DB06614(0.445,-6.5), DB11848(0.44,-5.9), DB12991(0.4) |
|   |   |
|---|---|
| 27 | 48.44 |
| DB05141(0.641,-5.5), DB01107(0.627), DB00593(0.595), DB11860(0.57,-7.4), DB11879(0.566), DB05645(0.563,-6.5), DB06335(0.559,-5.9), DB00786(0.529,-6.5), DB15601(0.527), DB13288(0.526), DB06657(0.524), DB08873(0.519,-6.1), DB01216(0.512), DB06345(0.51,-7.6), DB00312(0.51), DB06200(0.506,-6), DB15199(0.505,-6.4), DB13087(0.505), DB05434(0.496,-7), DB12833(0.492,-8), DB12613(0.492,-6.7), DB00490(0.487), DB01437(0.487), DB05814(0.486), DB00746(0.483), DB01197(0.482), DB01351(0.48), DB01353(0.48), DB04896(0.479), DB08918(0.479), DB12839(0.474), DB01074(0.474), DB15286(0.473), DB06614(0.473,-5.6), DB00418(0.473), DB00790(0.47,-6.2), DB00237(0.47), DB11801(0.468), DB05513(0.462), DB06045(0.46), DB12184(0.453), DB12444(0.451), DB01255(0.45), DB00599(0.449), DB01202(0.446), DB11868(0.446), DB05832(0.445,-7.1), DB00357(0.444), DB11682(0.441,-6.6), DB05885(0.441), DB01252(0.438,-7.9), DB00561(0.438), DB00306(0.436), DB11876(0.436), DB12951(0.435), DB12712(0.435), DB00657(0.434), DB11807(0.434), DB04876(0.433,-6.5), DB12521(0.429), DB00141(0.427), DB12536(0.427), DB01154(0.426), DB12513(0.425), DB01783(0.424), DB06573(0.423,-6.1), DB12692(0.422), DB12991(0.422), DB00241(0.422), DB00731(0.421), DB02691(0.421), DB09357(0.419), DB12677(0.418,-6), DB11684(0.417), DB13099(0.417,-5.1), DB08873(0.461,-6.1), DB02691(0.458), DB00517(0.458), DB06641(0.457,-6), DB12839(0.456), DB11684(0.455), DB01197(0.453), DB12677(0.453,-6), DB09357(0.449), DB13288(0.448), DB12232(0.448,-6.1), DB12704(0.447), DB05645(0.445,-6.5), DB12613(0.445,-6.7), DB00731(0.442), DB11801(0.442), DB14932(0.441,-6.5), DB01216(0.441), DB00419(0.439), DB01783(0.439), DB14872(0.439), DB05434(0.438,-7), DB11797(0.438), DB15412(0.438,-5.8), DB06345(0.437,-7.6), DB00593(0.433), DB00491(0.43), DB04348(0.429,-8.3), DB08834(0.429), DB06045(0.427), DB11784(0.425,-6.7), DB05805(0.425), DB11938(0.423,-7.5), DB06156(0.423), DB09292(0.423,-8.4), DB00178(0.422,-6.8), DB11879(0.421), DB11682(0.421,-6.6), DB01252(0.421,-6.9), DB11762(0.418,-6.2), DB06354(0.417,-7.9), DB00519(0.417,-6.7), DB03424(0.417), DB15601(0.416), DB00312(0.415), DB00207(0.414,-7), DB06127(0.414), DB00907(0.413), DB04896(0.411), DB08918(0.411), DB06657(0.411), DB12013(0.411), DB00422(0.409), DB06701(0.409), DB09026(0.409,-6.5), DB01337(0.409), DB01339(0.409), DB06497(0.408,-8.1), DB08824(0.407), DB12712(0.407), DB01437(0.406), DB05137(0.406), DB01255(0.405), DB06124(0.402,-6.4), DB01627(0.402,-5.9), DB00418(0.402), DB04834(0.401,-6), DB00479(0.401,-6.1), DB09271(0.401), DB13004(0.401), DB08889(0.401,-7.5), DB04947(0.4), DB06472(0.4), DB04947(0.4)
|   | 48_59 | 49_24 | 49_38 |
|---|---|---|---|
| DB09026(0.415, -6.5), DB11938(0.412, -7.5), DB13221(0.406), DB05521(0.406, -7.9), DB06714(0.405), DB11784(0.405, -6.7), DB11797(0.403), DB00178(0.403, -6.8) | DB06705(0.489), DB06641(0.481, -6), DB09031(0.48, -5.5), DB11860(0.475, -7.4), DB13615(0.472), DB14932(0.443, -6.5), DB00803(0.442), DB06335(0.441, -5.9), DB09031(0.44, -5.8), DB00728(0.44, -6.8), DB11938(0.437, -6.5), DB13615(0.433), DB14932(0.431), DB14542(0.43, -7.6), DB06614(0.425, -5.6), DB11283(0.423), DB14099(0.423), DB14829(0.422, -6.1), DB05456(0.42), DB00786(0.42, -6.5), DB11860(0.42, -6.7), DB06614(0.42, -5.6), DB09114(0.423), DB11283(0.423), DB00803(0.422, -6.8), DB11938(0.422, -7.5), DB13615(0.422, -7.5), DB11890(0.422, -6.7), DB06614(0.421, -5.6), DB15259(0.421, -7.4), DB00803(0.421, -6.5), DB00091(0.421, -5.8), DB00786(0.421, -6.5), DB11860(0.421, -7.4), DB13615(0.421, -6.7), DB14932(0.421, -6.5), DB06614(0.421, -5.6), DB11283(0.421, -5.6), DB14099(0.421, -5.6), DB14829(0.421, -5.6), DB05456(0.421, -6.5), DB00786(0.421, -6.5), DB11860(0.421, -7.4), DB13615(0.421, -6.7), DB14932(0.421, -6.5), DB06614(0.421, -5.6), DB11283(0.421, -5.6), DB14099(0.421, -5.6), DB14829(0.421, -5.6), DB05456(0.421, -6.5), DB00786(0.421, -6.5), DB11860(0.421, -7.4), DB13615(0.421, -6.7), DB14932(0.421, -6.5), DB06614(0.421, -5.6), DB11283(0.421, -5.6), DB14099(0.421, -5.6), DB14829(0.421, -5.6), DB05456(0.421, -6.5), DB00786(0.421, -6.5), DB11860(0.421, -7.4), DB13615(0.421, -6.7), DB14932(0.421, -6.5), DB06614(0.421, -5.6), DB11283(0.421, -5.6), DB14099(0.421, -5.6), DB14829(0.421, -5.6), DB05456(0.421, -6.5), DB00786(0.421, -6.5) | DB06573(0.586, -6.1), DB08873(0.52, -6.1), DB05645(0.513, -6.5), DB11879(0.503), DB05541(0.483, -5.5), DB12613(0.482, -6.7), DB15601(0.478), DB00786(0.473, -6.5), DB12795(0.471, -6.4), DB05434(0.468, -7), DB06124(0.463, -6.4), DB00312(0.463), DB12677(0.462, -6), DB06045(0.458), DB13018(0.455), DB11682(0.453, -6.6), DB12833(0.449, -8), DB00418(0.449), DB15286(0.444), DB11709(0.443), DB01353(0.442), DB06335(0.442, -5.9), DB15188(0.439, -6.6), DB13090(0.437), DB00237(0.435), DB01282(0.435), DB00490(0.435), DB00790(0.434, -6.2), DB00599(0.431), DB12692(0.431), DB12991(0.431), DB15199(0.43, -6.4), DB06497(0.429, -8.1), DB11801(0.428), DB04898(0.427), DB09059(0.425), DB01154(0.425), DB00306(0.423), DB00474(0.422), DB11938(0.422, -7.5), DB11890(0.422, -6.7), DB06614(0.419, -5.6), DB15412(0.418, -5.8), DB05885(0.418), DB04842(0.417), DB11784(0.416, -6.7), DB13034(0.415, -7.3), DB01601(0.414, -7.7), DB14911(0.413, -7.5), DB01058(0.413), DB11749(0.413), DB00241(0.413), DB12377(0.413), DB05633(0.411), DB01041(0.411), DB01627(0.411, -5.9), DB12184(0.41), DB05521(0.409, -7.9), DB15205(0.407), DB01627(0.404, -7.6), DB00143(0.403), DB12279(0.403), DB09060(0.402), DB09291(0.402) | DB06335(0.548, -5.9), DB06573(0.51, -6.1), DB06124(0.498, -6.4), DB11709(0.493), DB01190(0.492, -6), DB08873(0.49, -6.1), DB13034(0.488, -7.3), DB01627(0.487, -5.9), DB12613(0.487, -6.7), DB12677(0.481, -6), DB00786(0.478, -6.5), DB15286(0.474), DB06614(0.474, -5.6), DB00790(0.464, -6.2), DB05645(0.464, -6.2) |
|   |   |
|---|---|
| 31 | 50_20 |
| DB06705(0.459), DB12416(0.429,-7.3), DB12791(0.429,-6.5), DB08873(0.429,-6.1), DB12704(0.427), DB06614(0.426,-5.6), DB06627(0.42,-8.2), DB12791(0.42,-6.5), DB11586(0.411,-7.3), DB06641(0.410,-6.1), DB12692(0.406), DB09291(0.405), DB12292(0.404), DB12541(0.403), DB15601(0.403), DB01348(0.403), DB08889(0.40,-7.5) |
| 32 | 50_21 |
| DB11879(0.716), DB08873(0.655,-6.1), DB05645(0.651,-6.5), DB05541(0.643,-5.5), DB15601(0.606), DB12613(0.59,-6.7), DB05434(0.583,-7), DB15199(0.583,-6.4), DB00786(0.581,-6.5), DB06573(0.561,-6.1), DB06045(0.551), DB12692(0.547), DB12991(0.547), DB00790(0.544,-6.2), DB11801(0.543), DB06335(0.539,-5.9), DB15286(0.537), DB11682(0.532,-6.6), DB06614(0.527,-5.6), DB06124(0.525,-6.4), DB11890(0.524,-6.7), DB00490(0.522), DB12833(0.514,-8), DB11938(0.513,-7.5), DB05633(0.504), DB05832(0.503,-7.1), DB13018(0.496), DB06345(0.496,-7.6), DB05521(0.495,-7.9), DB05885(0.493), DB12184(0.493), DB06657(0.491), DB12677(0.486,-6), DB11860(0.484,-7.4), DB00312(0.484), DB01202(0.482), DB11868(0.482), DB15251(0.48), DB13087(0.48), DB14940(0.477), DB11784(0.476,-6.7), DB04876(0.475,-6.5), DB11981(0.474), DB11709(0.473), DB00178(0.471,-6.8), DB13247(0.469), DB06497(0.468,-8.1), DB00418(0.466), DB00519(0.466,-6.7), DB11702(0.465), DB01197(0.463), DB04898(0.461), DB01351(0.46), DB01353(0.46), DB14911(0.459,-7.5), DB11876(0.458), DB05814(0.456), DB00722(0.456), DB05155(0.455), DB01058(0.454), DB00237(0.452), DB12795(0.451,-6.4), DB15188(0.45,-6.6), DB01216(0.45), DB01107(0.448), DB00143(0.448), DB06293(0.446,-5.8), DB12501(0.446), DB11996(0.446), DB13034(0.441,-7.3), DB06127(0.44), DB14941(0.439), DB01282(0.438), DB06827(0.437,-8.2), DB00306(0.436), DB00593(0.432), DB15412(0.429,-5.8), DB01601(0.428,-7.7), DB12377(0.428), DB01255(0.426), DB01601(0.428,-7.7), DB12377(0.428), DB01255(0.426) |
|   |   |
|---|---|
|   | DB08958(0.426), DB12199(0.425,-7.9), DB00241(0.424), DB00599(0.424), DB12128(0.423), DB12239(0.42), DB09210(0.42), DB09059(0.413), DB13090(0.413), DB00143(0.411), DB00584(0.411), DB01041(0.411), DB05446(0.41), DB08382(0.409), DB12839(0.408), DB09210(0.42), DB09421(0.42,-7.6), DB01154(0.417), DB00731(0.414), DB09059(0.424), DB12128(0.423), DB01154(0.411), DB00584(0.411), DB01041(0.411), DB05446(0.41), DB08382(0.409), DB12839(0.408), DB15205(0.407), DB12122(0.407), DB11821(0.406), DB05426(0.406), DB00380(0.405), DB12013(0.403), DB01627(0.403,-5.9), DB06645(0.403), DB13067(0.402), DB09026(0.402,-6.5), DB12054(0.402), DB13288(0.402), DB12492(0.401), DB09060(0.401), DB00895(0.401), DB09291(0.401), DB01232(0.4,-8.7), DB03424(0.4), DB09286(0.4), DB15460(0.4), DB13099(0.508,-5.1), DB01107(0.488), DB00312(0.484), DB00599(0.479), DB06657(0.474), DB00593(0.468), DB01351(0.452), DB01353(0.452), DB00237(0.441), DB01154(0.438), DB00418(0.433), DB06335(0.425,-5.9), DB05541(0.408,-5.5), DB04348(0.4,-8.3), DB08834(0.4), DB11860(0.592,-7.4), DB06335(0.564,-5.9), DB04878(0.543,-5.6), DB06614(0.524,-5.6), DB04876(0.513,-6.5), DB06200(0.513,-6), DB01337(0.482), DB01339(0.482), DB00657(0.479), DB11807(0.479), DB13288(0.469), DB12287(0.468), DB02691(0.466), DB04545(0.466,-4.5), DB00491(0.463), DB01338(0.463,-7.3), DB00419(0.458), DB14872(0.458), DB13012(0.452,-6.2), DB05513(0.45), DB00786(0.448,-6.5), DB00141(0.444), DB04834(0.444,-6), DB12536(0.444), DB15286(0.444), DB04348(0.443,-8.3), DB08834(0.443), DB05541(0.442,-5.5), DB01074(0.442), DB06345(0.441,-7.6), DB00728(0.44,-6.8), DB06333(0.44,-6.3), DB06461(0.44,-6.6), DB12449(0.44), DB11684(0.434), DB13004(0.428), DB03206(0.426), DB05018(0.426), DB13262(0.422), DB00790(0.42,-6.2), DB00517(0.415), DB12704(0.414), DB00942(0.414), DB13087(0.411), DB06714(0.411), DB15412(0.41,-5.8), DB01197(0.409), DB00387(0.407), DB11797(0.407), DB12839(0.406), DB06787(0.405), DB00593(0.404), DB01227(0.403), DB00376(0.402), DB06335(0.496,-5.9), DB04876(0.473,-6.5), DB13288(0.431), DB05541(0.421,-5.5), DB06345(0.408,-7.6), DB15601(0.401) |
Figure S4. The docking region with the hotspot on SARS-CoV-2 spike RBD that binds to the hACE2 peptidase domain.

Table S2. Docking scores for the final list of drugs.

| DrugBank ID | Drug Name       | Docking Score (kcal/mol) | DrugBank ID | Drug Name       | Docking Score (kcal/mol) |
|-------------|-----------------|--------------------------|-------------|-----------------|--------------------------|
| DB09297     | Paritaprevir    | -9.1                     | DB14760     | Narlaprevir     | -8.4                     |
| DB09308     | Solithromycin   | -9.0                     | DB04348     | Taurocholic acid| -8.3                     |
| DB11779     | Danoprevir      | -9.0                     | DB06290     | Simeprevir      | -8.3                     |
| DB00337     | Pimecrolimus    | -8.7                     | DB12228     | Telcapeptin     | -8.3                     |
| DB00696     | Ergotamine      | -8.7                     | DB13879     | Glecaprevir     | -8.3                     |
| DB01232     | Saquinavir      | -8.7                     | DB06827     | Viomycin        | -8.2                     |
| DB12538     | Nepadutan       | -8.7                     | DB08993     | Enviomycin      | -8.2                     |
| DB12876     | GS-9256         | -8.7                     | DB11929     | Vaniprevir      | -8.2                     |
| DB09292     | Sacubitril      | -8.4                     | DB05868     | Ciluprevir      | -8.1                     |
| DB12508     | E7107           | -8.4                     | DB06497     | Aplavirin       | -8.1                     |
Figure S5. The chemical structures of the drug molecules selected based on the criteria mentioned in the manuscript. Binding free energy of all these molecules were calculated using all-atom explicit water simulations using well-tempered metadynamics.
Definition of Collective Variables

We used two collective variables DISTVEC (displacement along the body-fixed vector) and native contact for the well-tempered metadynamics simulations. We discuss the construction of each of the variables below.

a. Reaction coordinate DISTVEC $(X)$: It is the projection of $\vec{d}$ on the body-fixed unit vector $\hat{b}$. While $\hat{b}$ is a vector from the COM of residues ARG331, VAL369, TYR370, ALA371, LEU487, SER488, GLU490 to the COM of residues SER323, VAL324, TYR325, VAL375, ILE376, ARG377, GLY378, ASP379, GLU380, VAL381, ARG382, GLN383, GLY390, LYS391, ILE392, TYR395, ASN396, SER412, ASN413, ASN414, LEU415, ASP416, SER417, TYR423, ASN424, TYR425, LEU426, TYR427, ARG428, PRO465, LEU466, GLN467, SER468, TYR469, GLY470, PHE471, GLN472, PRO473, THR474, VAL477, GLY478, TYR479, GLN480, PRO481, TYR482 that lie more toward the hotspot region. $\vec{d}$ is the vector from the COM of ARG331, VAL369, TYR370, ALA371, LEU487, SER488, GLU490 to the COM of drug molecule. DISTVEC is defined as, $X = \hat{b} \cdot \vec{d}$. Figure S6 shows a schematic diagram of DISTVEC. Similarly, the angle $\theta$ is defined as, $\theta = \cos^{-1}(\hat{b} \cdot \vec{d} / |\vec{d}|)$.

b. The Native contact $(N_c)$ is defined by the spatial proximity of groups of atoms in the native state. The native contact between one group $(gA)$ of atoms to the other group $(gB)$ of atoms is defined as,

$$N_c = \sum_{i \in gA} \sum_{j \in gB} s_{ij},$$

where, $s_{ij}$ given by,

$$s_{ij} = \begin{cases} 1 & \forall r_{ij} \leq 0 \\ \frac{1 - \left(\frac{r_{ij}}{r_0}\right)^n}{\left(1 - \left(\frac{r_{ij}}{r_0}\right)^m\right)} & \forall r_{ij} > 0 \end{cases}$$

and $r_{ij} = |r_i - r_j| - d_0$. The user-defined parameters were chosen to be $n = 6$, $m = 12$, $r_0 = 5.5 \text{ Å}$ and $d_0 = 0 \text{ Å}$. Above equation ensures the variation of $s_{ij}$ is continuous and differentiable. Also, the cut off value being large allows $N_c$ to be higher than in the native state if more atoms come close. The heavy atoms of the ligand constitute $gA$ while the heavy atoms of part of the protein (residues 376-377, 379, 382-
383,389-392,394-396, 427-430, 440-470, 475, 477, 479) constitute $g_B$. We have chosen the residues of the protein that either belong to the loop (residues 442 to 468) or reside within 5.5Å from the ligand in the bound state. Figure S7 shows the protein's hotspot region in yellow and the ligand in orange.

Figure S7. The collective variable native contact is shown. $g_A$ (ligand) is shown in orange and $g_B$ (part of the protein) is shown in yellow.

**Simulation runtime parameters**

Table S3. The system size and simulation lengths for the metadynamics simulation for all the systems. A general optimization, heating and 5 ns normal molecular dynamics simulations are applied to all the systems. The metadynamics simulations were not carried out for the unstable system and runtime is denoted for them as “NA”.

| System     | Runtim e (ns) | System Size (numbe r of atoms) | System     | Runtim e (ns) | System Size (numbe r of atoms) |
|------------|---------------|-------------------------------|------------|---------------|-------------------------------|
| hACE2 (run 1) | 234           | 236699                        | hACE2 (run 2) | 51            | 236699                        |
| 47_68 (run 1) | 154           | 86305                         | Danoprevir | 236           | 114053                        |
| 47_68 (run 2) | 381           | 86305                         | Danoprevir | 99            | 114053                        |
| 37_42 (run 1) | 41            | 86337                         | Solithromycin | 149         | 114129                        |
| 37_42 (run 2) | 64            | 86337                         | Solithromycin | 157         | 114129                        |
| 45_23 (run 1) | 115           | 114066                        | Saquinavir | 44            | 86314                         |
| Run | Species | Accession | Concentration | End Point | Description |
|-----|---------|-----------|---------------|-----------|-------------|
| 45_23 | (run 2) | 126 | 114066 | Saquinavir | 104 | 86314 |
| 41_46 | (run 1) | 64 | 114089 | Glecaprevir | 166 | 86308 |
| 41_46 | (run 2) | 67 | 114089 | Paritaprevir | 106 | 114087 |
| 49_24 | | 48 | 86318 | Ciluprevir | 118 | 86330 |
| 50_76 | | 88 | 86329 | Simeprevir | 56 | 114028 |
| 50_21 | | 156 | 114066 | Paritaprevir | 48 | 114087 |
| 45_24 | | 72 | 86323 | E7107 | 124 | 114121 |
| 44_18 | | 109 | 114091 | Ergotamine | 240 | 114037 |
| 50_23 | | 75 | 86324 | GS-9256 | 156 | 86284 |
| 50_20 | | 30 | 86318 | Enviomycin | 62.9 | 86351 |
| 48_44 | | 92 | 86318 | Nepadutant | 53 | 86294 |
| 44_16 | | 20 | 114068 | Vaniprevir (run 1) | 97 | 86309 |
| 47_27 | | 63 | 114028 | Vaniprevir (run 2) | 151 | 86309 |
| 44_43 | | 37 | 99557 | Telcagepant | 88 | 86316 |
| 46_24 | | 16 | 114066 | Pimecrolimus | 73 | 114056 |
| 39_32 | | 14 | 86356 | Narlaprevir | 10.4 | 86376 |
| 46_13 | | 24 | 86310 | Sacubitril | 29 | 86338 |
| 46_12 | | 13 | 86310 | Taurocholic acid | 24 | 86352 |
| 29_19 | | 14 | 114079 | Aplaviroc | 52 | 86307 |
| 46_37 | | 11 | 114066 | Viomycin | 6 | 86309 |
| 47_11 | | 18 | 86318 | 49_38 | NA | 86318 |
| 47_26 | | 23 | 86305 | 45_74 | NA | 114074 |
| 41_37 | | 16 | 86283 | 44_15 (run 1) | NA | 86298 |
| 50_82 | | 14 | 86316 | 44_15 (run 2) | NA | 86298 |
| 41_31 | | 8 | 114039 | 39_57 | NA | 86330 |
| 44_81 | | 3 | 86293 | 32_26 | NA | 86300 |
| 46_22 | | 18 | 114066 | 40_35 | NA | 86327 |
| 48_59 | | 7 | 114066 | | | |
**All Free Energy Surfaces**

The two-dimensional free energy surfaces of binding of all stable the de novo and drug molecules are shown, except some of the least stable ones.
Figure S8. Free Energy surfaces of de novo and drug molecules with free energy stability between -14.4 kcal/mol and -9.9 kcal/mol. The chemical structure of the molecule is shown in the inset of the respective plot. Free energy color bar for this plot is shown.
Figure S9. Free Energy surfaces of de novo and drug molecules with free energy stability between -9.8 kcal/mol and -8.7 kcal/mol. The chemical structure of the molecule is shown in the inset of the respective plot. Free energy color bar for this plot is shown.
Figure S10. Free Energy surfaces of de novo and drug molecules with free energy stability between -8.6 kcal/mol and -5.6 kcal/mol (both ends are included). The chemical structure of the molecule is shown in the inset of the respective plot. Free energy color bar for this plot is shown.
Figure S11. Free Energy surfaces of de novo and drug molecules with free energy stability between -5.5 kcal/mol and -3.4 kcal/mol (both ends are included). The chemical structure of the molecule is shown in the inset of the respective plot. Free energy color bar for this plot is shown.

\[
\theta = \cos^{-1}(\mathbf{V}_1 \cdot \mathbf{V}_2)
\]

Figure S12. Representation of angle \(\theta\) between vectors \(\mathbf{V}_1\) and \(\mathbf{V}_2\). \(\mathbf{V}_1\) is a vector from the point A to point C, whereas \(\mathbf{V}_2\) goes from point A to point B. The point A is the center of mass (COM) of residues 423 to 429 and 465 to 470. The point C is the COM of residues 415 to 422 and 470 to 479. The point B is the COM of residues 454 to 459. Only carbon, nitrogen and oxygen atoms were used to calculate COM calculation.

Figure S13. The values of \(\theta\) for the most stable ligand bound RBD configurations for all the 35 de novo molecules and 20 drugs. Note that, although the \(\theta\) is low for 48_44, the molecule is not encapsulated by the loop.