CHEMISTRY
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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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Supporting Information Contents

Section S1. DeNovo ALGORITHM

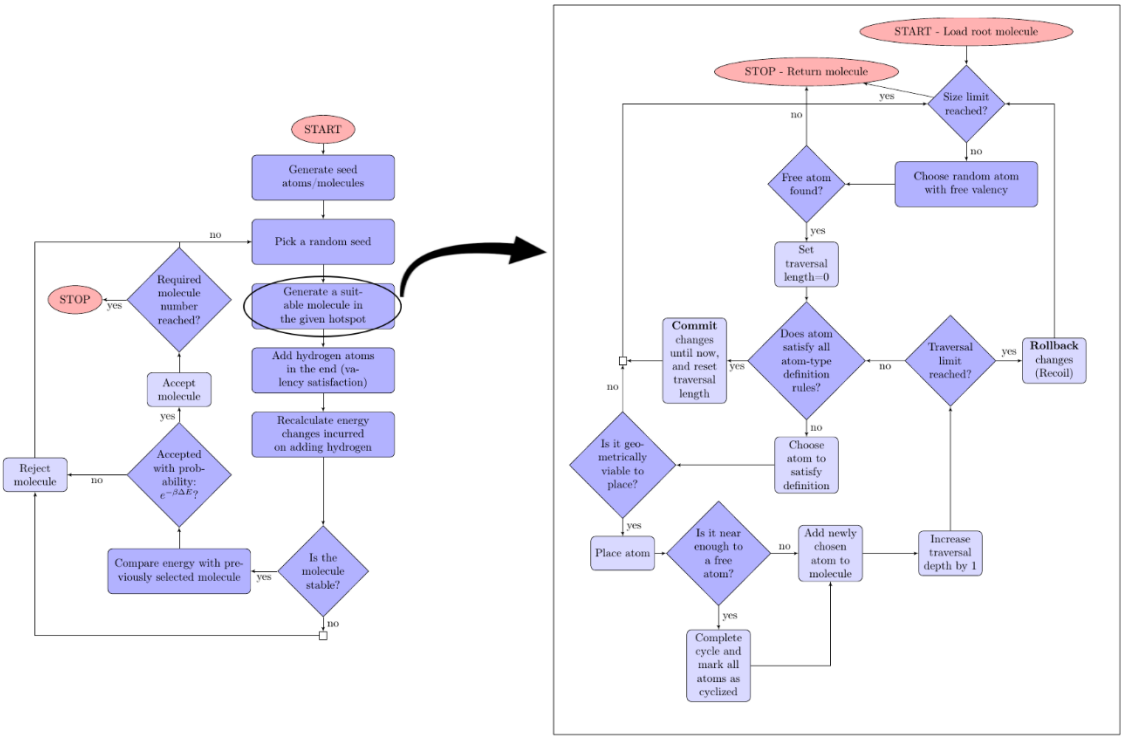


Figure S1. The algorithmic flowchart of DeNovo drug generation protocol.

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 the 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 valencies 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.

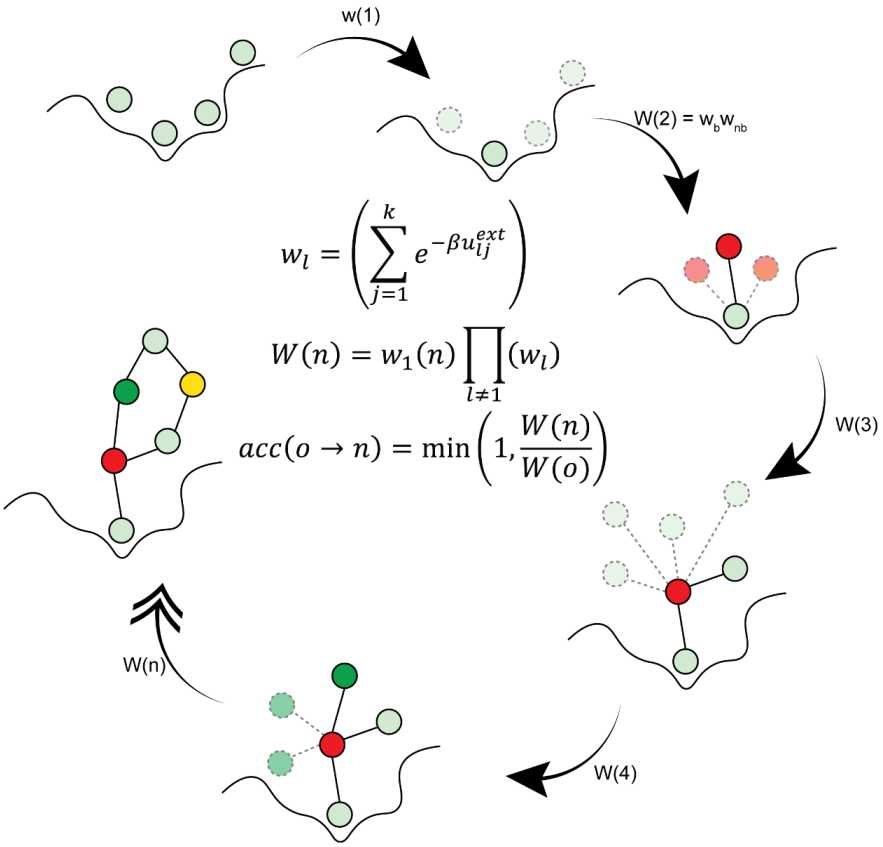
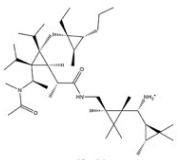


Figure S2. Visual step-by-step schematic of the generation algorithm broadly covering the underlying probabilistic model used.



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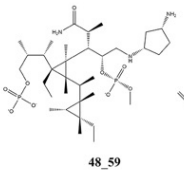

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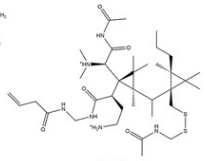

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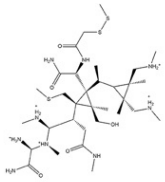

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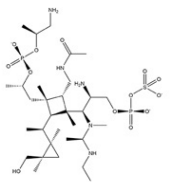

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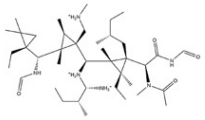

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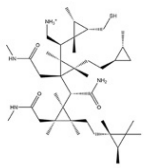

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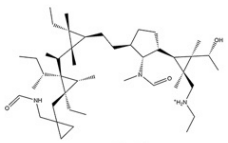

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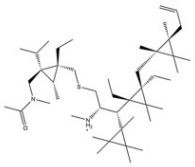

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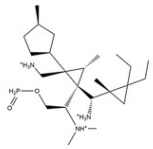

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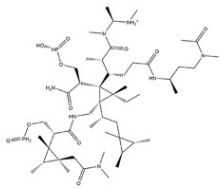

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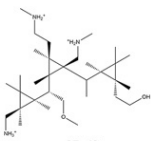

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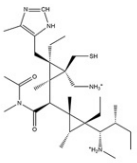

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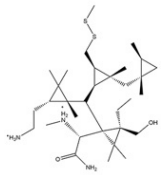

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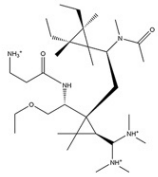

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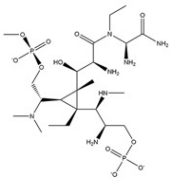

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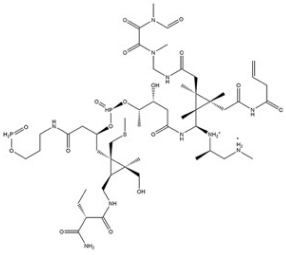

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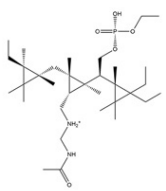

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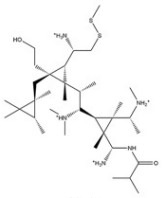

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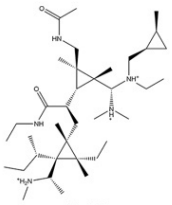

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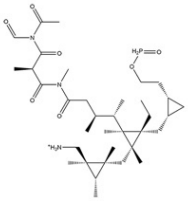

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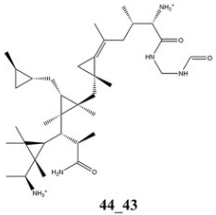

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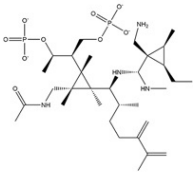

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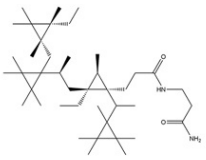

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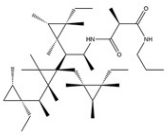

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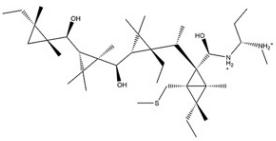

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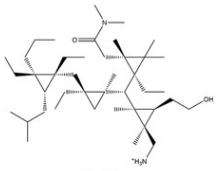

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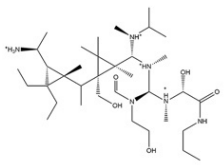

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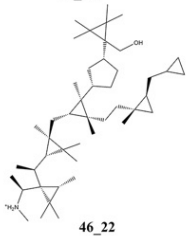

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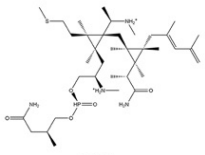

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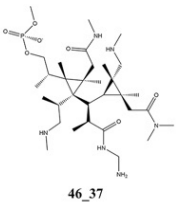

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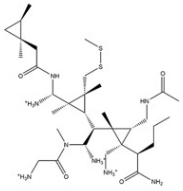

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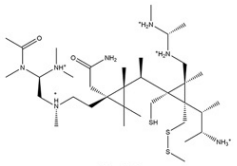

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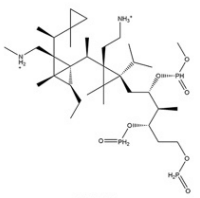

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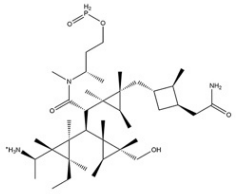


47_68

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),

		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), DB00117(0.404), DB09102(0.403), DB06645(0.403), DB14955(0.402), DB09290(0.4)
5	39_57	DB06335(0.546,-5.9), DB12795(0.471,-6.4), DB11860(0.462,-7.4), 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(0.429), DB05541(0.424,-5.5), DB02691(0.42), DB06127(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)
6	40_35	DB00790(0.593,-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), DB06614(0.514,-5.6), DB00178(0.512,-6.8), DB08965(0.507), DB00519(0.506,-6.7), DB13288(0.504), DB00479(0.5,-6.1), 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), DB11762(0.467,-6.2), 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)
7	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),

		DB12791(0.465,-6.5), DB06497(0.46,-8.1), DB00790(0.456,-6.2), DB08889(0.455,-7.5), DB12613(0.455,-6.7), DB14911(0.452,-7.5), DB00141(0.452), DB12536(0.452), DB11784(0.451,-6.7), DB12730(0.45,-6.8), DB11762(0.449,-6.2), DB06335(0.449,-5.9), DB15412(0.448,-5.8), DB06045(0.448), DB12615(0.448), DB11879(0.445), DB06573(0.444,-6.1), DB12704(0.441), DB09291(0.438), DB11890(0.435,-6.7), DB00207(0.435,-7), DB11471(0.434), DB00479(0.431,-6.1), DB05645(0.431,-6.5), DB12416(0.43,-7.3), DB13034(0.43,-7.3), DB14932(0.43,-6.5), DB00337(0.43,-8.7), DB00178(0.428,-6.8), DB06696(0.427), DB15188(0.427,-6.6), DB15205(0.425), DB00519(0.424,-6.7), DB01082(0.423), DB11938(0.422,-7.5), DB04876(0.422,-6.5), DB14941(0.422), DB11929(0.421,-8.2), DB12538(0.421,-8.7), DB01590(0.42), DB06641(0.42,-6), DB00864(0.419), DB13067(0.418), DB00877(0.418,-7.9), DB11797(0.418), DB00558(0.416) DB12508(0.416,-8.4), DB12279(0.416), DB06233(0.415,-7.6), DB11273(0.415), DB11274(0.415,-7.4), DB11275(0.415,-7.8), DB06478(0.412), DB05633(0.412), DB13345(0.411), DB00224(0.411,-7.5), DB14760(0.411,-8.4), DB11781(0.411), DB11586(0.411,-7.3), DB00305(0.409), DB12989(0.407), DB05541(0.407,-5.5), DB00320(0.407), DB12232(0.406,-6.1), DB11512(0.406), DB08818(0.405), DB11682(0.405,-6.6), DB09271(0.405), DB01319(0.404), DB11996(0.404), DB15251(0.404), DB01601(0.403,-7.7), DB12069(0.403,-8), DB04878(0.402,-5.6), DB09059(0.402), DB11709(0.402), DB00955(0.402), DB06419(0.401), DB15601(0.401), DB11783(0.401), DB11779(0.401,-9), DB01232(0.40,-8.7)
8	41_37	DB01190(0.483,-6), DB08873(0.48,-6.1), DB01627(0.478,-5.9), DB06573(0.478,-6.1), DB00760(0.471,-6.2), DB06293(0.463,-5.8), DB06211(0.451,-6.5), DB11586(0.45,-7.3), DB12791(0.45,-6.5), DB09297(0.45,-9.1), DB12791(0.449,-6.5), DB06233(0.443,-7.6), DB11929(0.443,-8.2), DB00303(0.441,-7.4), DB12876(0.439,-8.7), DB00503(0.438,-8), DB15249(0.438,-8), DB06827(0.437,-8.2), DB08993(0.437,-8.2), DB11779(0.436,-9), DB11273(0.436), DB11274(0.436,-7.4), DB11275(0.436,-7.8), DB11575(0.435,-7.5), DB12069(0.434,-8), DB12037(0.433,-7.9), DB00248(0.432,-6.2), DB13345(0.432), DB01598(0.432,-5.4), DB12730(0.431,-6.8), DB06335(0.431,-5.9), DB13028(0.428,-6.1), DB12587(0.428,-6.5), DB05868(0.427,-8.1), DB11808(0.426,-7.3), DB11682(0.426,-6.6), DB01601(0.425,-7.7), DB00790(0.425,-6.2), DB00320(0.424), DB00696(0.423,-8.7), DB01200(0.423,-7.9), DB13034(0.422,-7.3), DB12538(0.42,-8.7), DB00739(0.42), DB14911(0.42,-7.5), DB06614(0.419,-5.6), DB12677(0.419,-6), DB06124(0.418,-6.4), DB00337(0.418,-8.7), DB09065(0.418), DB05434(0.418,-7), DB01180(0.418), DB01992(0.418), DB01764(0.417,-7.2), DB00319(0.417,-7.2), DB14932(0.417,-6.5), DB00948(0.416,-7.5), DB00224(0.416,-7.5), DB14760(0.416,-8.4), DB05796(0.416), DB08889(0.416,-7.5), DB13879(0.416,-8.3), DB12026(0.416,-7.2),

		DB01590(0.415), DB00786(0.415,-6.5), DB09308(0.415,-9), DB12785(0.415), DB01301(0.413), DB12416(0.413,-7.3), DB00877(0.412,-7.9), DB15284(0.412), DB11961(0.412), DB15040(0.411), DB06497(0.411,-8.1), DB12279(0.41), DB00256(0.41), DB04845(0.41,-7.1), DB12228(0.41,-8.3), DB15188(0.41,-6.6), DB06290(0.409,-8.3), DB12691(0.409), DB00864(0.409), DB06604(0.409), DB12615(0.408), DB00206(0.408), DB11691(0.408), DB11762(0.407,-6.2), DB01089(0.407), DB12190(0.407), DB12190(0.407), DB12939(0.406), DB15205(0.404), DB12486(0.404), DB11783(0.402), DB12329(0.402), DB12795(0.402,-6.4), DB00558(0.401), DB00541(0.401), DB01061(0.4), DB01346(0.4), DB05521(0.4,-7.9), DB13253(0.4), DB01232(0.4,-8.7)
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	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)
11	44_16	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), DB01107(0.52), 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)
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),

		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), DB01437(0.429), DB01783(0.429), DB05645(0.426,-6.5), DB13087(0.425), DB11190(0.423), DB04348(0.42,-8.3), DB08834(0.42), DB06274(0.419), DB09026(0.419,-6.5), DB12712(0.418), DB05814(0.415), DB15412(0.412,-5.8), DB01197(0.411), DB12951(0.41), DB12613(0.408,-6.7), DB11938(0.407,-7.5), DB12677(0.405,-6), DB01216(0.403), DB00561(0.403), DB13288(0.402), DB11879(0.402), DB12184(0.4), DB15199(0.4,-6.4)
13	44_43	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)
14	44_81	DB06614(0.509,-5.6), DB11860(0.459,-7.4), DB15286(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)
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),

		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), DB13087(0.417), DB15199(0.416,-6.4), DB00790(0.415,-6.2), DB12839(0.412), DB12833(0.412,-8), DB00141(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)
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), DB00230(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), DB00786(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), DB15286(0.409), DB13288(0.409), DB15412(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,-5.6), DB12032(0.484), DB11860(0.483,-7.4), DB00478(0.471), DB04926(0.469), DB05513(0.46), DB11924(0.455), DB15264(0.452), DB00915(0.451), DB01043(0.451), DB12449(0.446), DB00302(0.443), DB06333(0.43,-6.3), DB06461(0.43,-6.6),

		DB11684(0.422), DB00996(0.422), DB01337(0.422), DB01339(0.422), DB00230(0.419), DB04545(0.419,-4.5), DB13288(0.412), DB00149(0.41), DB12493(0.405), DB01637(0.404), DB01245(0.4), DB01718(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), DB09123(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), DB06573(0.468,-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),

		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(0.419,-7.9), 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)
27	48_44	DB05541(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),

		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)
28	48_59	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), DB06293(0.44,-5.8), DB00728(0.44,-6.8), DB11693(0.439), DB00091(0.438), DB12139(0.438), DB13068(0.438), DB15259(0.438), DB14631(0.437,-7.4), DB04933(0.433), DB11882(0.431), DB14542(0.43,-7.6), DB02691(0.429), DB04878(0.426,-5.6), DB06614(0.425,-5.6), DB09114(0.423), DB11283(0.423), DB14099(0.423), DB14829(0.423), DB00479(0.422,-6.1), DB05456(0.42), DB00786(0.42,-6.5), DB06087(0.419), DB00207(0.419,-7), DB06696(0.418), DB15286(0.418), DB04834(0.417,-6), DB15412(0.416,-5.8), DB01337(0.416), DB01339(0.416), DB11471(0.413), DB00517(0.412), DB01111(0.411), DB14669(0.411), DB06447(0.41), DB09026(0.407,-6.5), DB11797(0.405), DB04660(0.405), DB00141(0.404), DB12536(0.404), DB11762(0.403,-6.2), DB11332(0.403), DB12655(0.402), DB05814(0.401), DB12232(0.401,-6.1), DB01627(0.401,-5.9), DB00790(0.4,-6.2), DB11813(0.4)
29	49_24	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), DB01351(0.442), 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(0.41,-5.9), DB12184(0.41), DB05521(0.409,-7.9), DB15205(0.407), DB06127(0.406), DB09421(0.404,-7.6), DB00143(0.403), DB12279(0.403), DB09060(0.402), DB09291(0.402)
30	49_38	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,-

		6.5), DB05541(0.461,-5.5), DB06127(0.458), DB04876(0.456,-6.5), DB11879(0.455), DB00143(0.451), DB15412(0.449,-5.8), DB06045(0.449), DB01282(0.448), DB12279(0.447), DB14911(0.447,-7.5), DB15188(0.446,-6.6), DB12795(0.446,-6.4), DB05434(0.443,-7), DB06211(0.441,-6.5), DB12730(0.439,-6.8), DB09059(0.439), DB13018(0.438), DB00760(0.436,-6.2), DB06827(0.435,-8.2), DB11890(0.43,-6.7), DB00143(0.427), DB11762(0.426,-6.2), DB00178(0.423,-6.8), DB06604(0.42), DB05446(0.42), DB06293(0.42,-5.8), DB00519(0.419,-6.7), DB06497(0.418,-8.1), DB00303(0.417,-7.4), DB15297(0.416), DB00886(0.414), DB05633(0.414), DB01598(0.413,-5.4), DB05796(0.412), DB11938(0.41,-7.5), DB04898(0.41), DB12380(0.409), DB11929(0.408,-8.2), DB15299(0.408), DB13028(0.408,-6.1), DB05521(0.406,-7.9), DB01000(0.406), DB09291(0.405), DB12292(0.404), DB12541(0.403), DB15601(0.403), DB01348(0.403), DB08889(0.4,-7.5)
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), DB06827(0.42,-8.2), DB12791(0.42,-6.5), DB15286(0.413), DB11586(0.411,-7.3), DB06641(0.41,-6), DB01346(0.409), DB14941(0.409), DB12730(0.406,-6.8), DB06124(0.405,-6.4), DB14911(0.402,-7.5), DB01190(0.401,-6)
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), 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),

		DB08958(0.426), DB12199(0.425,-7.9), DB00241(0.424), DB00599(0.424), DB12128(0.423), DB12239(0.42), DB09210(0.42), DB09421(0.42,-7.6), DB01154(0.417), DB00731(0.414), DB09059(0.413), DB13090(0.413), DB00143(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), DB08889(0.402,-7.5), DB01000(0.402), 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)
33	50_23	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)
34	50_76	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)
35	50_82	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)

Section S3. DOCKING RELATED INFORMATION

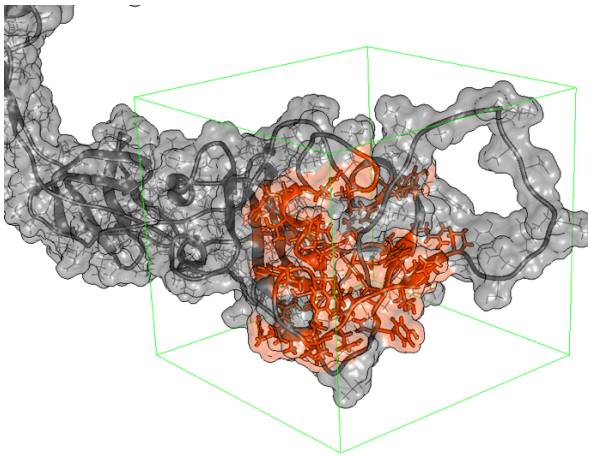


Figure S4. The docking region with the hotspot on SARS-CoV-2 spike RBD that binds to the hACE2 peptidase domain.

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	Telcagepant	-8.3
DB00696	Ergotamine	-8.7	DB13879	Glecaprevir	-8.3
DB01232	Saquinavir	-8.7	DB06827	Viomycin	-8.2
DB12538	Nepadutant	-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	Aplaviroc	-8.1

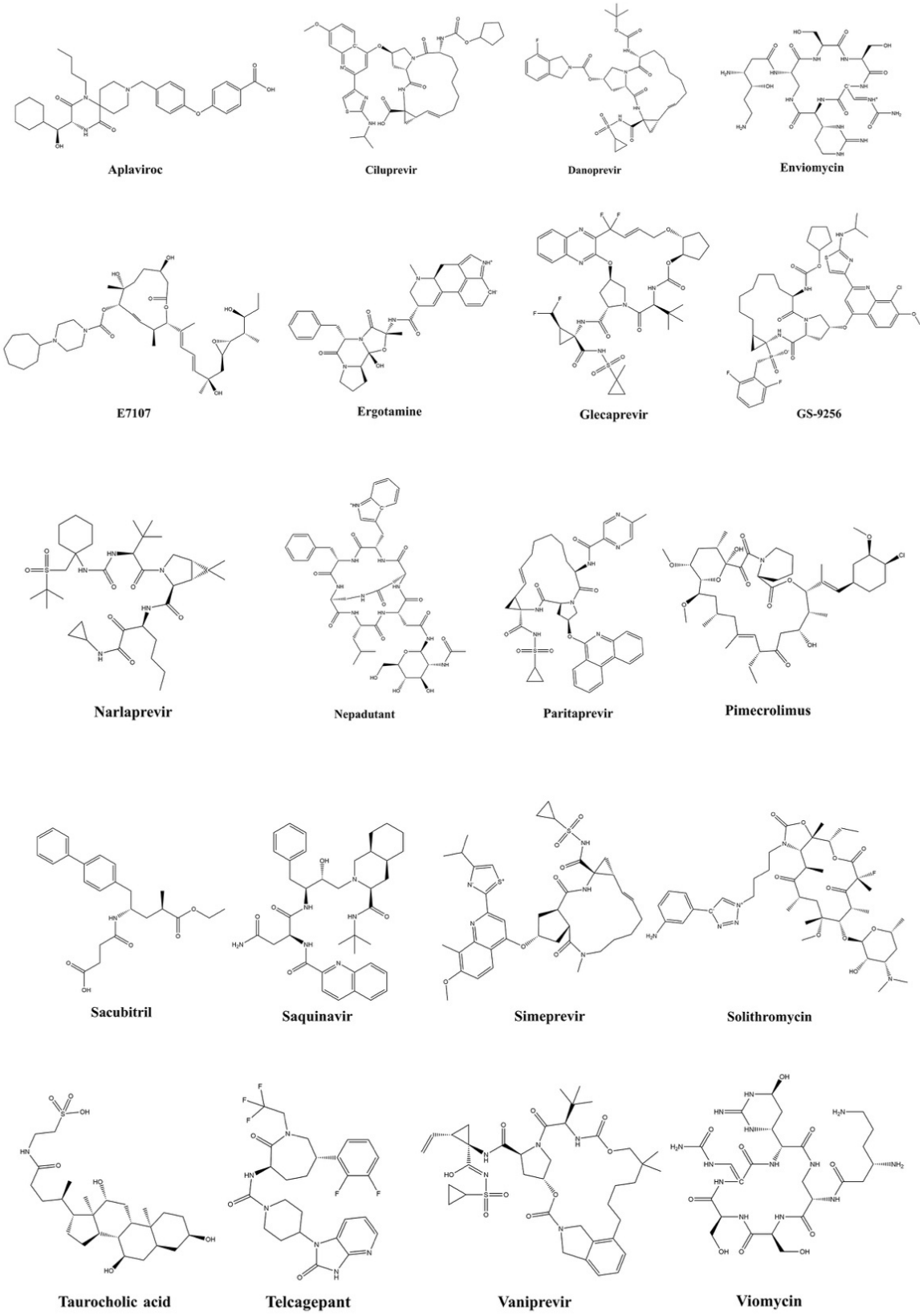


Figure S5. The chemical structures of the drug molecules selected based on the criteria mentioned in the manuscript. Binding free energy of all these molecules were calculated using all-atom explicit water simulations using well-tempered metadynamics.

Section S4. FREE ENERGY RELATED INFORMATION

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 define as, $X = \hat{b}.\vec{d}$, Figure S6 shows a schematic diagram of DISTVEC. Similarly, the angle θ is defined as, $\theta = \cos^{-1}(\hat{b}.\vec{d}/|d|)$.

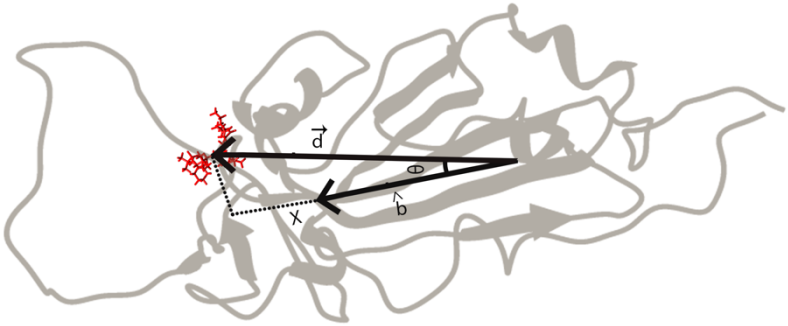


Figure S6. The collective variable DISTVEC ($X = \hat{b}.\vec{d}$) and its components are defined in the picture. The protein is shown in grey and ligand is shown in red.

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,

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

where, s_{ij} given by,

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

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 Å and d_0=0 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 gB. 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. gA (ligand) is shown in orange and gB (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".

Syste m	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 (run2)	381	86305	Danoprevir	99	114053
37_42 (run 1	41	86337	Solithromyci n	149	114129
37_42 (run2)	64	86337	Solithromyci n	157	114129
45_23 (run 1)	115	114066	Saquinavir	44	86314

45_23 (run 2)	126	114066	Saquinavir (run 2)	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.

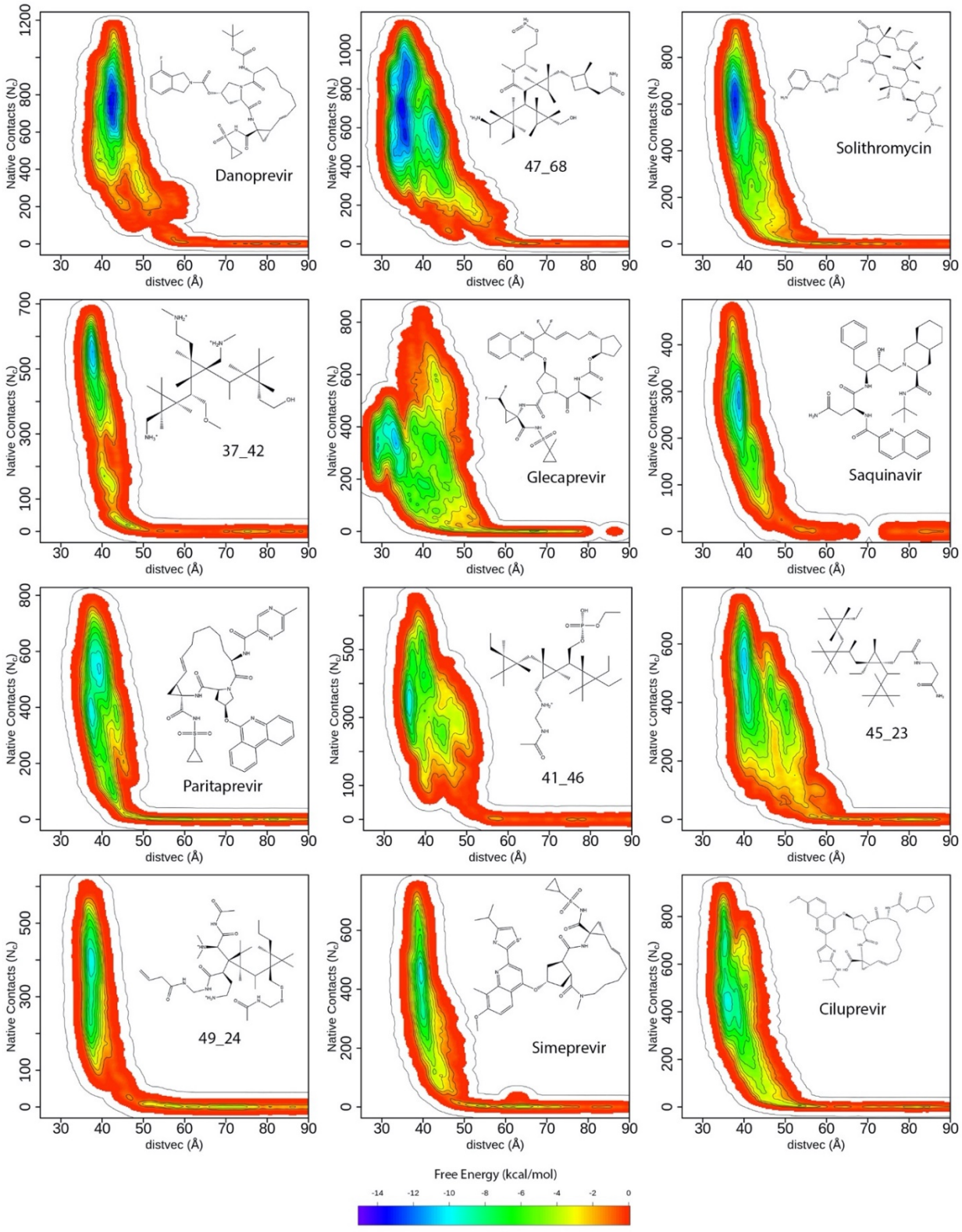


Figure S8. Free Energy surfaces of de novo and drug molecules with free energy stability between -14.4 kcal/mol and -9.9 kcal/mol. The chemical structure of the molecule is shown in the inset of the respective plot. Free energy color bar for this plot is shown.

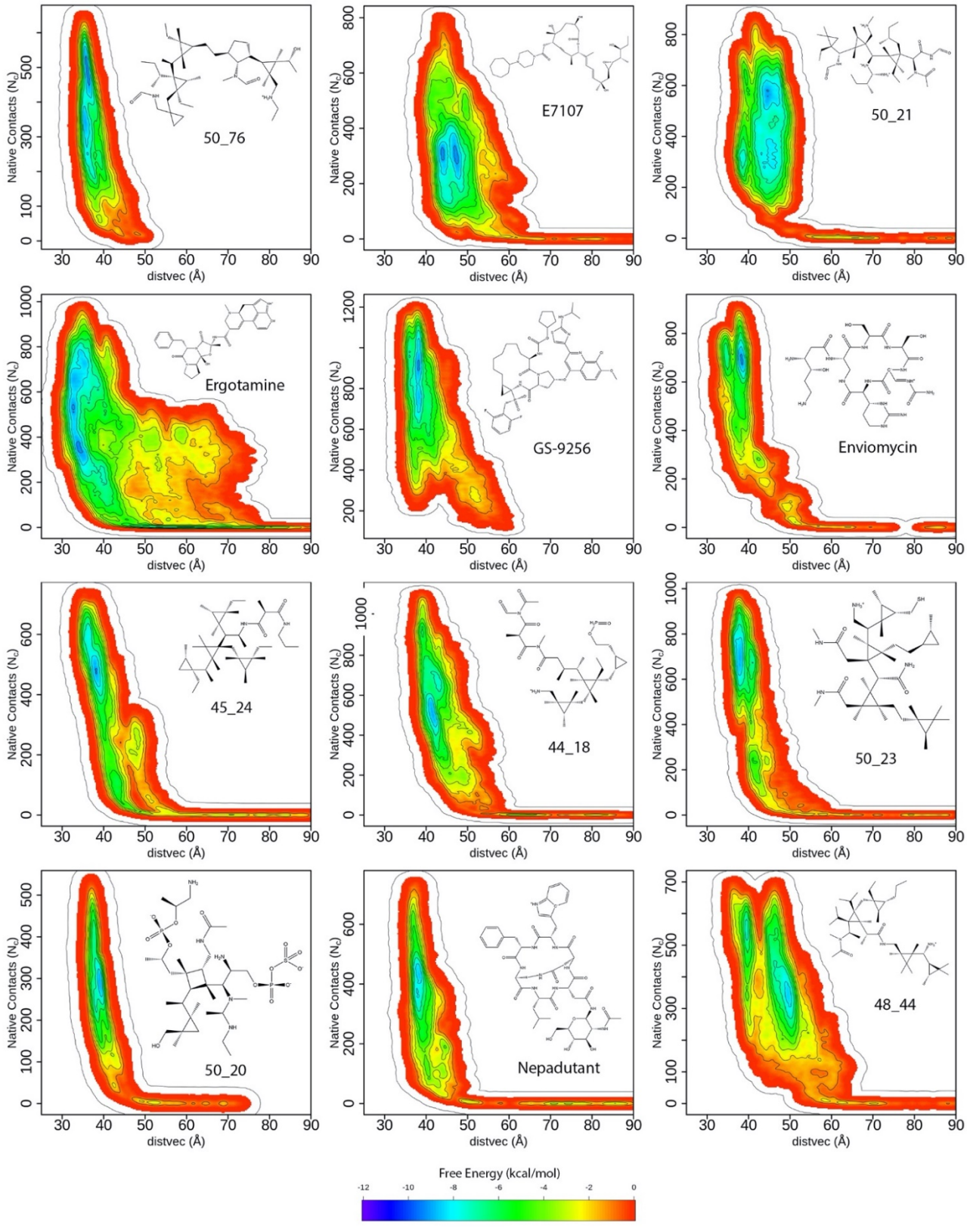


Figure S9. Free Energy surfaces of de novo and drug molecules with free energy stability between -9.8 kcal/mol and -8.7 kcal/mol. The chemical structure of the molecule is shown in the inset of the respective plot. Free energy color bar for this plot is shown.

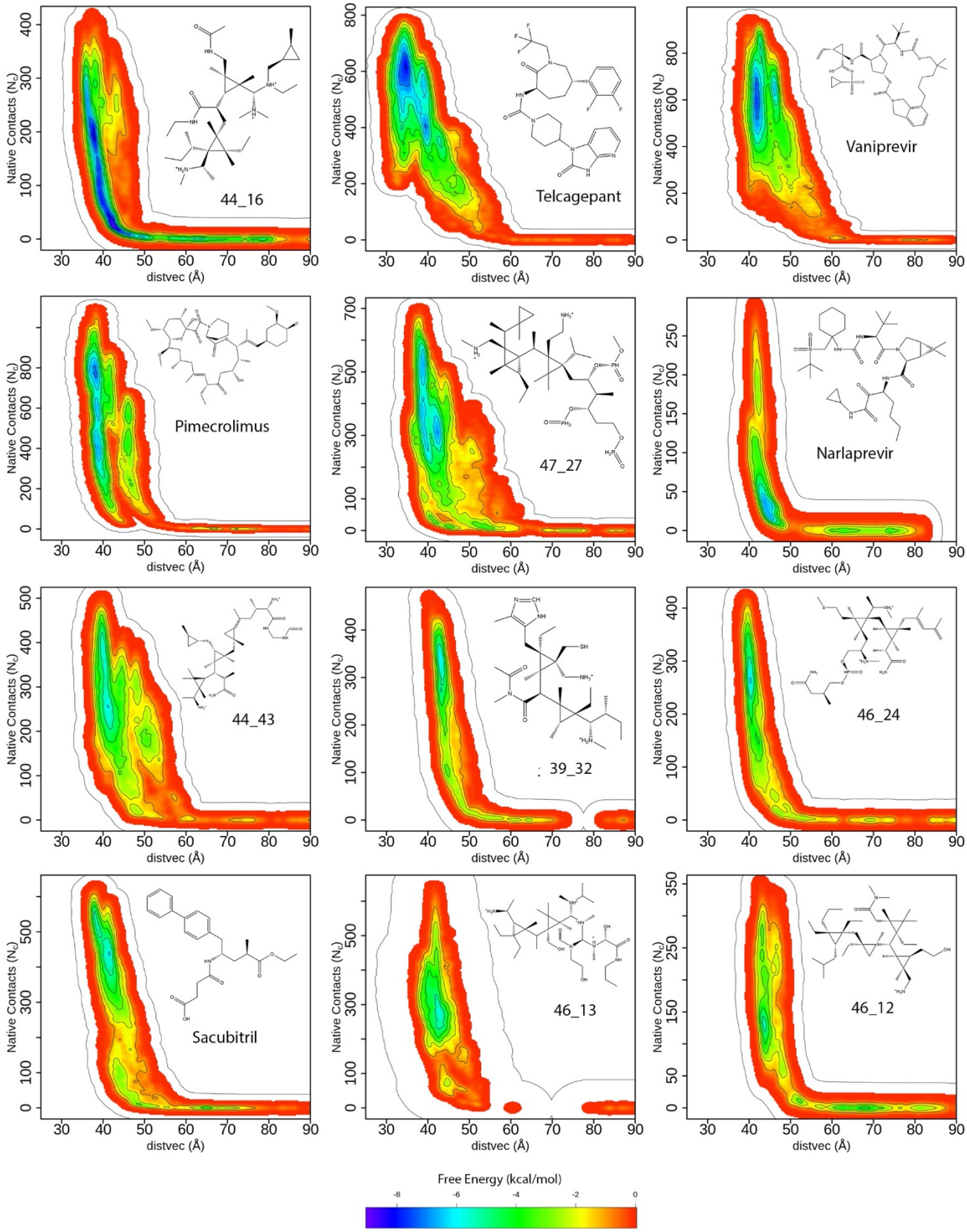


Figure S10. Free Energy surfaces of de novo and drug molecules with free energy stability between -8.6 kcal/mol and -5.6 kcal/mol (both ends are included). The chemical structure of the molecule is shown in the inset of the respective plot. Free energy color bar for this plot is shown.

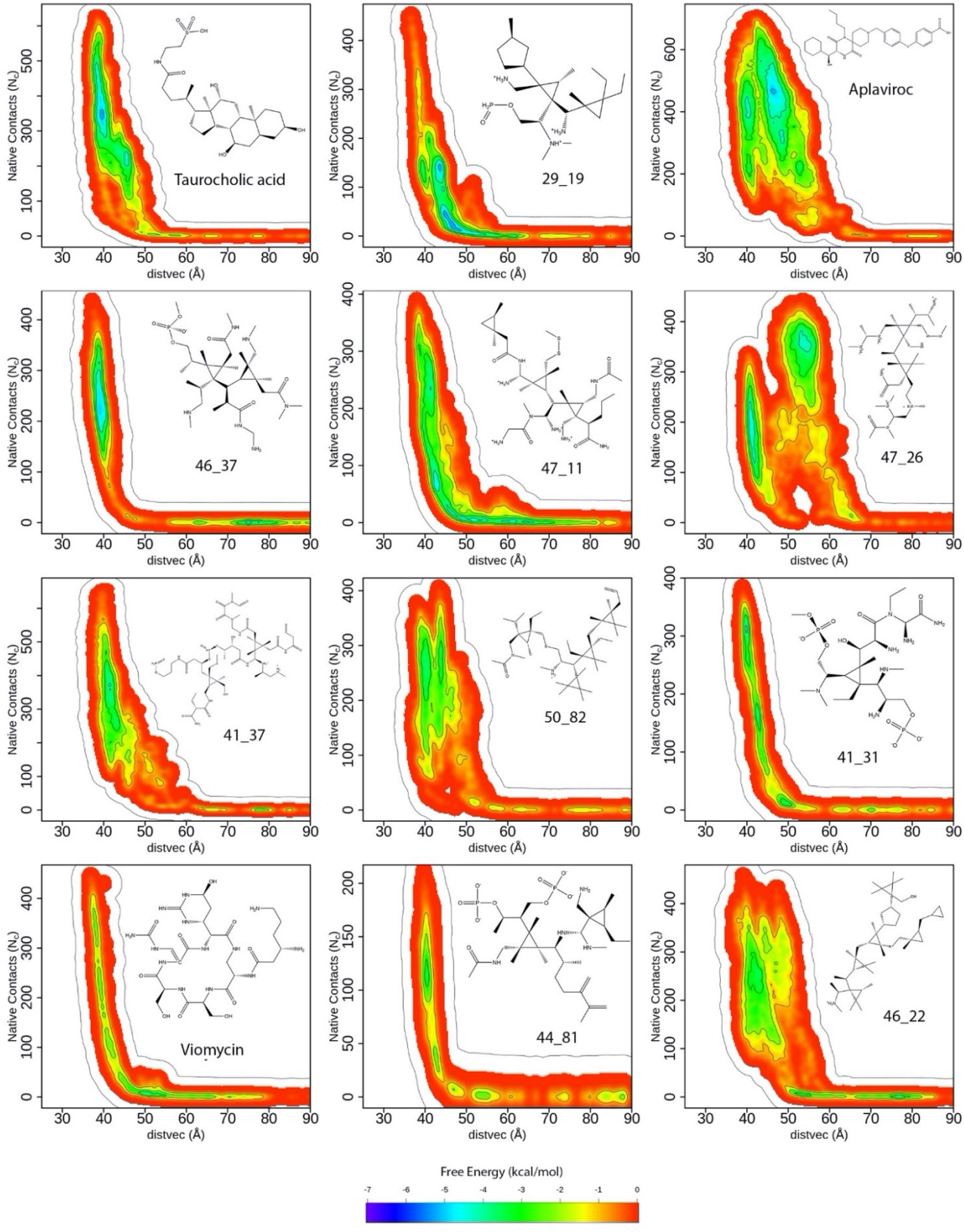
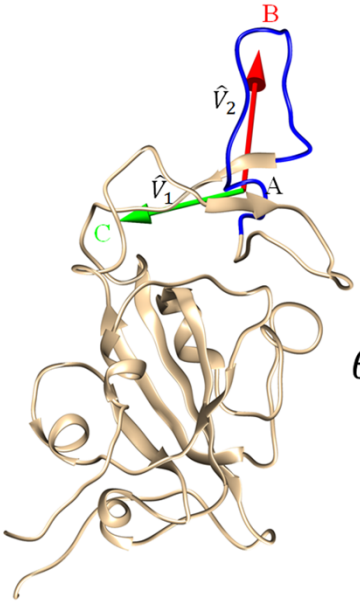


Figure S11. Free Energy surfaces of de novo and drug molecules with free energy stability between -5.5 kcal/mol and -3.4 kcal/mol (both ends are included). The chemical structure of the molecule is shown in the inset of the respective plot. Free energy color bar for this plot is shown.



$$\theta = cos^{-1}(\hat{V}_1 \cdot \hat{V}_2)$$

Figure S12. Representation of angle θ between vectors $\hat{V}_1$ and $\hat{V}_2$. $\hat{V}_1$ is a vector from the point A to point C, whereas $\hat{V}_2$ 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.

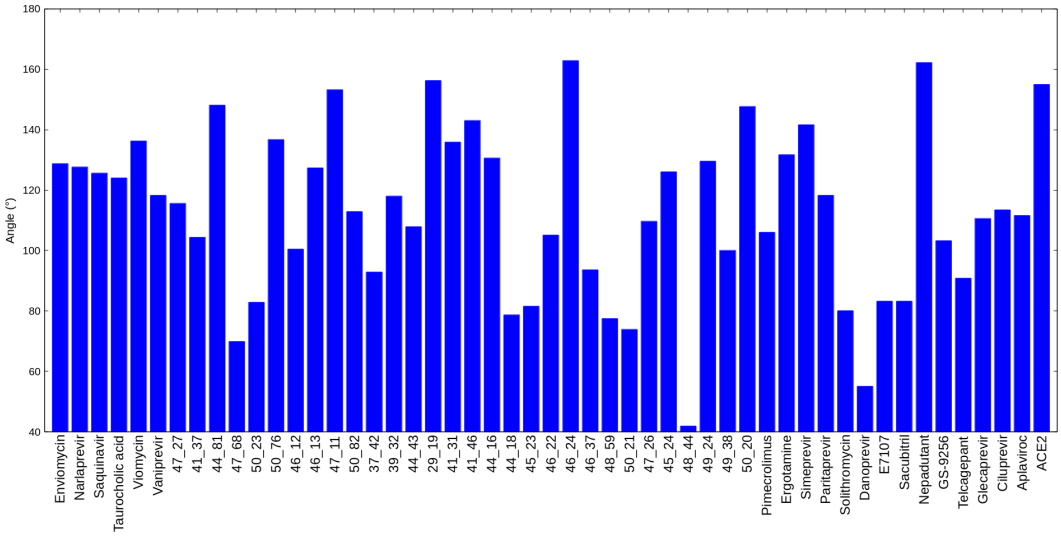


Figure S13. The values of θ for the most stable ligand bound RBD configurations for all the 35 de novo molecules and 20 drugs. Note that, although the θ is low for 48_44, the molecule is not encapsulated by the loop.