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Supporting Information for: Prediction of Binding Pose and Affinity of Nelfinavir, a SARS-CoV-2 Main Protease Repositioned Drug by Combining Docking, Molecular Dynamics, and Fragment Molecular Orbital Calculations

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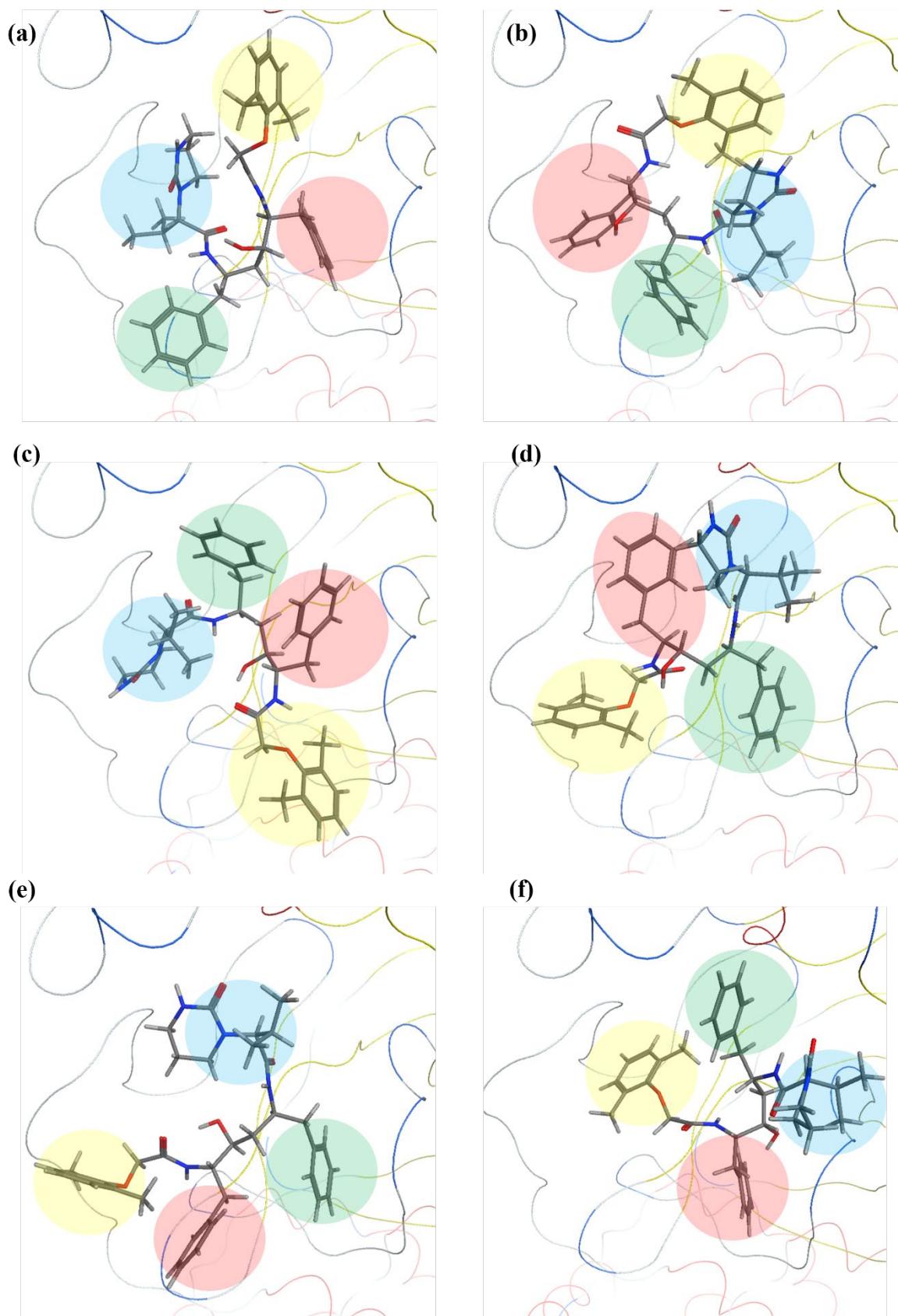


Figure S1 Six structures of Mpro and lopinavir selected based on docking and FMO scoring.

(a) Pose 1, (b) Pose 2, (c) Pose 3, (d) Pose 4, (e) Pose 5, (f) Pose6.

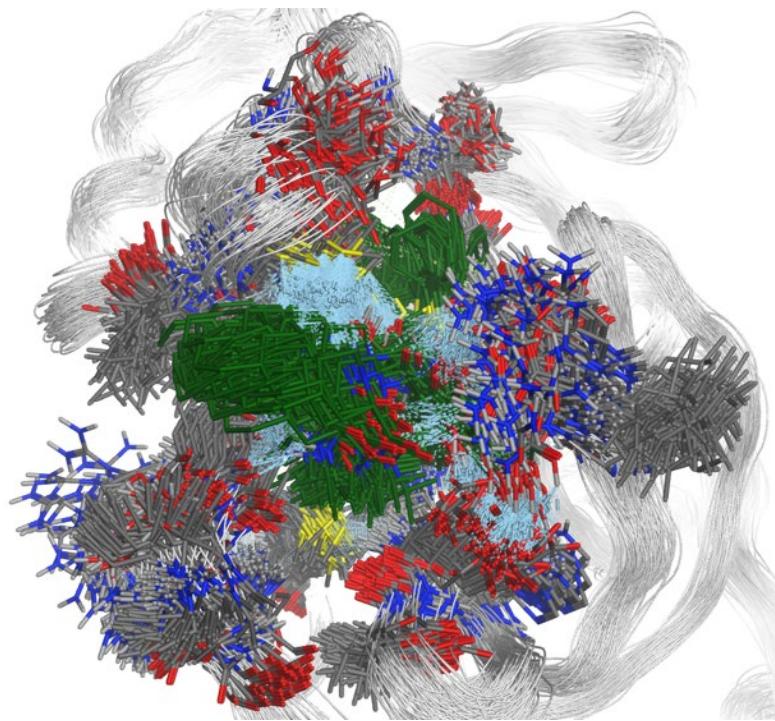


Figure S2 Amino acids for which desolvation energies are calculated: THR25, THR26, LEU27, HIS41, SER46, MET49, LEU50, LEU141, ASN142, GLY143, SER144, CYS145, HIS163, HIS164, MET165, GLU166, LEU167, HIS172, PHE181, ASP187, ARG188, GLN189, THR190, ALA191, GLN192. The figure shows the superposition structure for 50-100 ns in Pose3. (Green; NLF)

Table S1 FMO calculation results for 30 structures of Mpro-Nelfinavir complex obtained by docking (in kcal/mol), sorted by FMO score ($\Delta E^{int(static)}$). The four structures with the top FMO scores were selected as Poses 1-4.

| docking structure number | docking score | ES | EX | CT + mix | DI | $\Delta E^{int(static)}$ (Total IFIE) |
|--------------------------|---------------|--------|-------|----------|--------|--|
| No.7 (Pose 3) | -9.07 | -139.5 | 63.2 | -33.1 | -83.1 | -192.6 |
| No.1 (Pose 1) | -9.70 | -150.4 | 105.1 | -35.0 | -103.5 | -183.7 |
| No.11 (Pose 4) | -9.00 | -145.9 | 89.9 | -33.4 | -84.9 | -174.3 |
| No.2 (Pose 2) | -9.63 | -135.1 | 118.1 | -24.4 | -105.6 | -147.1 |
| No.8 | -9.07 | -113.0 | 82.0 | -30.3 | -84.7 | -146.0 |
| No.3 | -9.58 | -116.6 | 96.0 | -32.8 | -91.2 | -144.6 |
| No.4 | -9.40 | -118.1 | 92.2 | -28.0 | -90.1 | -144.0 |
| No.5 | -9.35 | -108.9 | 82.1 | -27.9 | -88.3 | -142.9 |
| No.6 | -9.24 | -101.0 | 72.7 | -27.5 | -81.9 | -137.6 |
| No.19 | -8.76 | -98.4 | 59.9 | -25.4 | -64.5 | -128.4 |
| No.10 | -9.01 | -96.5 | 67.3 | -24.7 | -74.4 | -128.3 |
| No.9 | -9.03 | -97.3 | 70.1 | -25.1 | -75.3 | -127.6 |
| No.17 | -8.79 | -91.2 | 58.8 | -24.9 | -69.9 | -127.2 |
| No.15 | -8.86 | -95.0 | 60.7 | -24.3 | -66.4 | -125.1 |
| No.23 | -8.65 | -92.3 | 57.3 | -21.1 | -66.2 | -122.3 |
| No.14 | -8.91 | -91.5 | 58.4 | -22.1 | -66.5 | -121.7 |
| No.12 | -8.94 | -90.3 | 60.2 | -21.3 | -69.1 | -120.4 |
| No.18 | -8.78 | -90.1 | 57.1 | -22.1 | -64.9 | -120.1 |
| No.22 | -8.65 | -89.3 | 55.4 | -20.8 | -62.6 | -117.3 |
| No.13 | -8.92 | -87.1 | 57.3 | -20.2 | -67.2 | -117.2 |
| No.20 | -8.75 | -86.3 | 53.0 | -19.2 | -60.7 | -113.3 |
| No.24 | -8.59 | -84.6 | 52.5 | -19.5 | -60.9 | -112.6 |
| No.21 | -8.67 | -84.8 | 53.2 | -19.1 | -60.1 | -111.8 |
| No.16 | -8.79 | -84.8 | 51.6 | -18.6 | -59.0 | -110.8 |
| No.26 | -8.52 | -84.1 | 50.8 | -15.9 | -60.9 | -110.1 |
| No.25 | -8.58 | -83.8 | 51.6 | -16.7 | -60.9 | -109.8 |
| No.28 | -8.47 | -78.8 | 44.2 | -14.3 | -59.9 | -108.8 |
| No.27 | -8.49 | -79.6 | 47.1 | -17.1 | -58.9 | -108.6 |
| No.29 | -8.46 | -78.9 | 45.2 | -15.4 | -57.8 | -106.9 |
| No.30 | -8.46 | -77.8 | 43.2 | -14.0 | -57.2 | -105.8 |

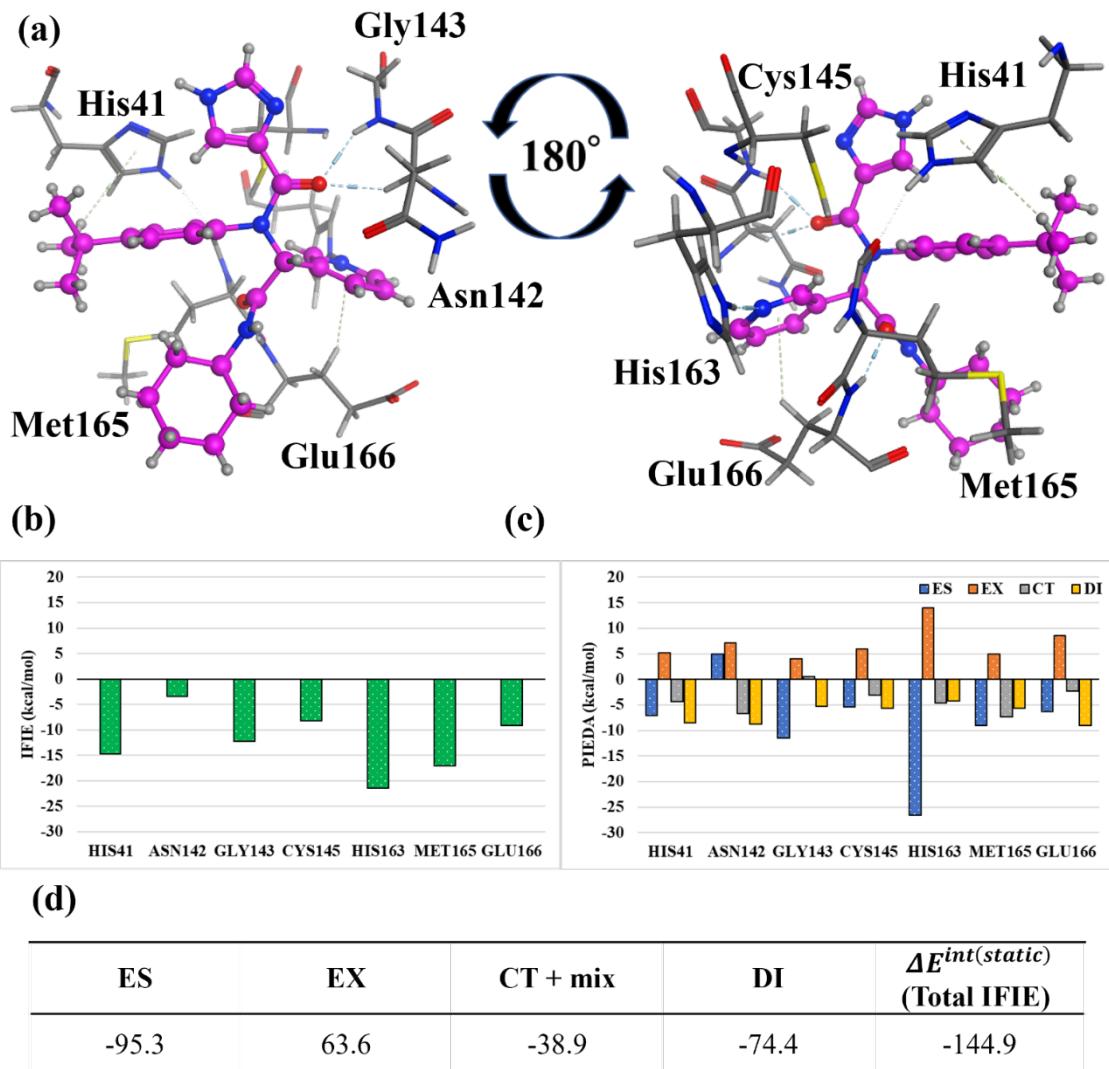


Figure S3 Interaction analysis of NLF-like compounds and Mpro by FMO. (a) Amino acid residues of Main Protease interacting with NLF-like compounds (PDBID: 6w63). (b)(c) Interaction energies between each amino acid residue and NLF-like compounds; (b) IFIE and (c) PIEDA energies. (d) Total IFIE (Sum of interaction energy) and each PIEDA energy (in kcal/mol).

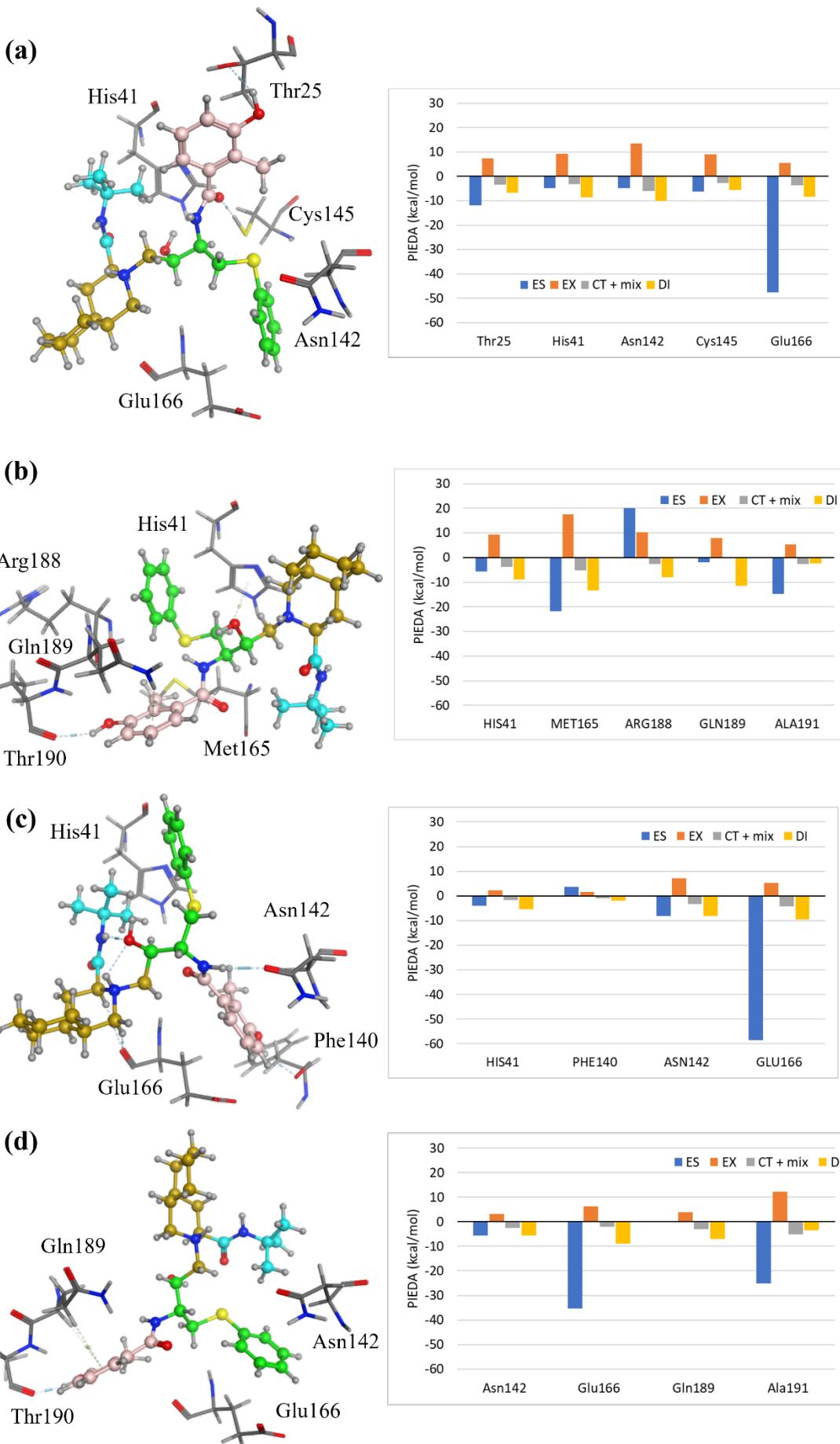


Figure S4 PIEA for four docking poses. (a)Pose1 (b)Pose2 (c)Pose3 (d)Pose4

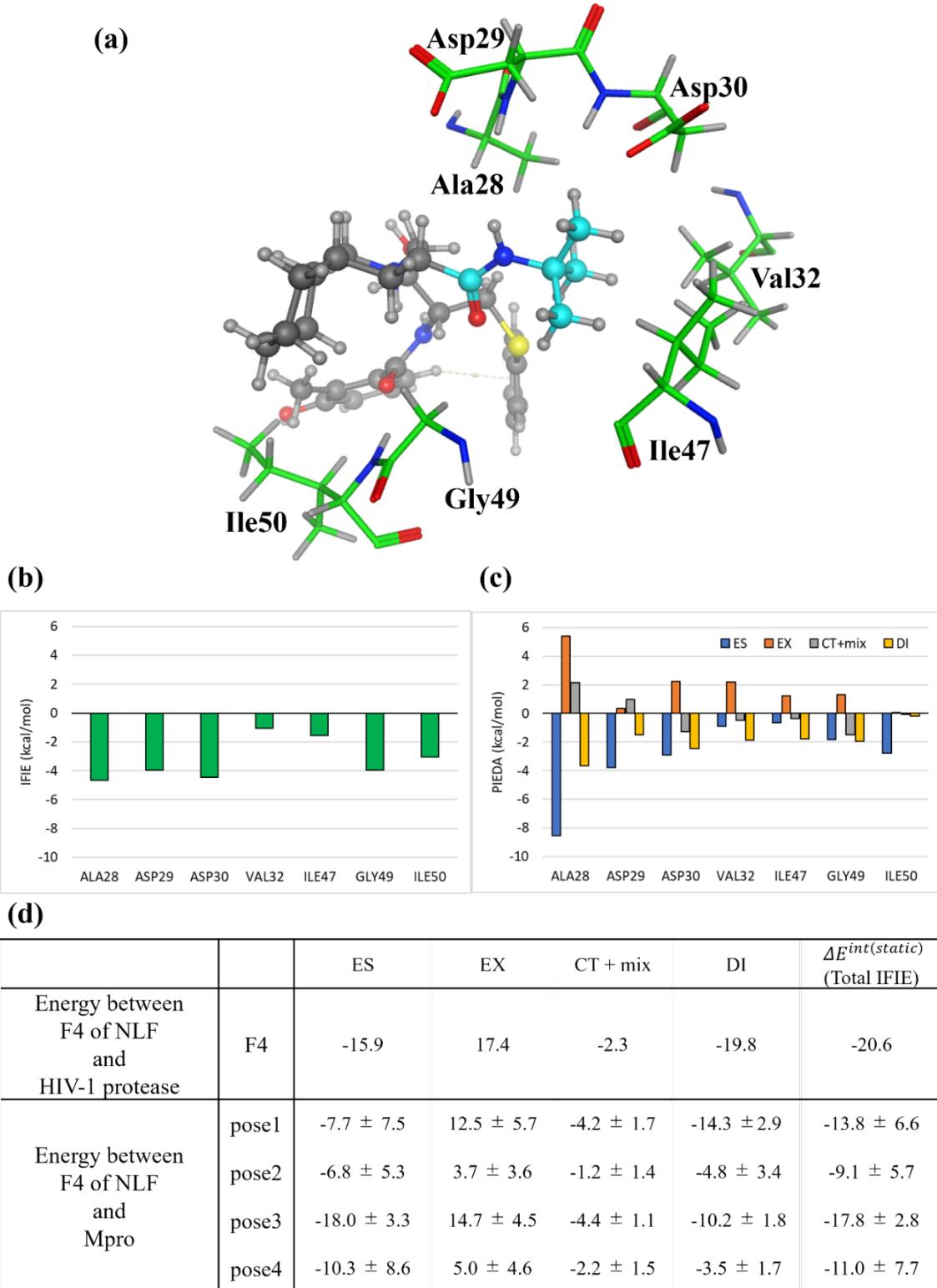


Figure S5 The interaction involving the tert-butyl group of NLF. (a) Amino acid residues of HIV-1 protease interacting with the tert-butyl group of NLF (PDBID: 3el5). (b)(c) Interaction energy of each amino acid residue indicated by (a); (b) IFIE and (c) PIEDA energies. (d) Total IFIE and PIEDA of fragment containing tert-butyl groups (F4) (in kcal/mol).

Table S2 FMO calculation results for 15 structures of Mpro- Lopinavir complex obtained by docking (in kcal/mol), sorted by FMO score ($\Delta E^{int(static)}$). The six structures with the top FMO scores (excluding conformational overlap) were selected as Poses 1-6.

| docking structure number | docking score | ES | EX | CT + mix | DI | $\Delta E^{int(static)}$ (Total IFIE) |
|--------------------------|---------------|-------|------|----------|-------|--|
| No.2 (Pose2) | -9.12 | -91.0 | 93.0 | -37.4 | -93.5 | -128.9 |
| No.4 (Pose4) | -8.88 | -60.0 | 78.1 | -40.7 | -94.7 | -117.3 |
| No.5 (Pose5) | -8.87 | -62.6 | 64.8 | -34.9 | -84.3 | -117.0 |
| No.1 (Pose1) | -9.14 | -65.4 | 84.8 | -36.9 | -93.9 | -111.4 |
| No.9 | -8.49 | -65.6 | 79.4 | -28.9 | -90.6 | -105.7 |
| No.10 (Pose6) | -8.45 | -64.1 | 89.9 | -34.7 | -93.7 | -102.7 |
| No.3 (Pose3) | -8.96 | -65.4 | 83.4 | -30.8 | -89.0 | -101.8 |
| No.14 | -8.43 | -45.4 | 53.1 | -27.8 | -79.4 | -99.5 |
| No.8 | -8.54 | -54.7 | 68.1 | -29.6 | -81.4 | -97.7 |
| No.6 | -8.63 | -35.8 | 58.5 | -30.9 | -81.9 | -90.1 |
| No.13 | -8.43 | -52.1 | 72.1 | -25.8 | -83.9 | -89.8 |
| No.11 | -8.44 | -46.1 | 70.2 | -28.2 | -83.4 | -87.5 |
| No.12 | -8.43 | -36.5 | 72.6 | -30.6 | -88.7 | -83.2 |
| No.7 | -8.63 | -37.5 | 72.6 | -26.2 | -88.1 | -79.2 |
| No.15 | -8.41 | -36.7 | 72.1 | -27.0 | -83.0 | -74.7 |

Table S3 Interaction energies of each docking pose in Lopinavir (in kcal/mol)

| | Pose 1 | Pose 2 | Pose 3 | Pose 4 | Pose 5 | Pose 6 |
|-------------------------------|------------------|------------------|------------------|------------------|------------------|------------------|
| ES | -53.7 ± 11.4 | -76.8 ± 15.1 | -37.1 ± 14.2 | -45.4 ± 24.7 | -46.0 ± 17.6 | -43.5 ± 16.6 |
| EX | 55.7 ± 11.4 | 60.9 ± 16.0 | 38.5 ± 10.5 | 52.3 ± 18.6 | 51.0 ± 13.9 | 57.5 ± 15.6 |
| CT + mix | -23.0 ± 3.5 | -27.6 ± 4.8 | -17.9 ± 3.8 | -22.7 ± 6.4 | -21.9 ± 4.3 | -24.5 ± 6.7 |
| DI | -56.4 ± 6.7 | -56.1 ± 7.6 | -47.4 ± 8.1 | -57.4 ± 12.5 | -52.6 ± 7.8 | -70.3 ± 13.4 |
| ΔE^{int} (Total IFIE) | -77.4 ± 11.1 | -99.6 ± 12.0 | -63.9 ± 15.1 | -73.2 ± 25.7 | -69.5 ± 15.6 | -80.1 ± 23.1 |

Table S4 Energies (ΔE^{int}) between NFV and amino acid residues important for binding that are common to all binding poses and distances between their nearest neighboring atoms.

| | | Glu47 | Asp48 | Glu166 | Asp187 | Gln189 |
|-------|-----------------------------|------------------|-----------------|------------------|-----------------|--|
| Pose1 | Distance (Å) | 4.4 ± 1.7 | 6.7 ± 1.9 | 3.0 ± 0.9 | 3.0 ± 0.7 | F3: 2.4 ± 0.2 F4: 2.8 ± 0.8 |
| | ΔE^{int} (kcal/mol) | -31.1 ± 12.3 | -20.6 ± 2.4 | -10.7 ± 6.2 | -26.4 ± 2.7 | -14.7 ± 16.3 |
| Pose2 | Distance (Å) | 4.0 ± 1.0 | 6.4 ± 1.1 | 4.3 ± 1.8 | 2.6 ± 0.4 | F1: 2.6 ± 0.7 F2: 2.4 ± 0.3 |
| | ΔE^{int} (kcal/mol) | -39.6 ± 9.4 | -26.0 ± 5.7 | -26.1 ± 6.7 | -29.9 ± 3.2 | -18.8 ± 10.5 |
| Pose3 | Distance (Å) | 4.3 ± 1.1 | 4.3 ± 1.3 | 1.9 ± 0.7 | 6.5 ± 0.8 | F3: 1.9 ± 0.1 F4: 1.9 ± 0.1 |
| | ΔE^{int} (kcal/mol) | -33.1 ± 8.0 | -39.4 ± 7.1 | -49.6 ± 10.9 | -34.4 ± 3.4 | -45.2 ± 4.6 |
| Pose4 | Distance (Å) | 3.5 ± 0.3 | 5.2 ± 0.4 | 2.5 ± 0.2 | 3.0 ± 0.4 | F1: 2.1 ± 0.3 |
| | ΔE^{int} (kcal/mol) | -23.2 ± 3.4 | -25.3 ± 1.6 | -25.0 ± 3.4 | -33.5 ± 1.8 | -25.9 ± 6.6 |

Table S5. List of FMODB IDs of FMO calculation results for each MD sampling structure.

| Time step (ps) | FMODBID Pose1 | FMODBID Pose2 | FMODBID Pose3 | FMODBID Pose4 |
|----------------|------------------|------------------|------------------|------------------|
| 50100 | 398KL | 8544Y | V5JM1 | 4953N |
| 50600 | JL749 | G6ZZ1 | YZJ32 | K9J33 |
| 51100 | N9JZQ | 1788Z | 528MZ | QYZ1Y |
| 51600 | 854GY | V5JJ1 | 4987N | R9658 |
| 52100 | G6Z81 | YZJJ2 | K9MN3 | Z6KYN |
| 52600 | 1785Z | 5284Z | QYJQY | 6NK6Z |
| 53100 | V5JV1 | 4985N | R9VR8 | 2J92R |
| 53600 | YZJ92 | K9MJ3 | Z613N | 72QGK |
| 54100 | 528YZ | QYJZY | 6N89Z | MV43Z |
| 54600 | 4986N | R9V68 | 2J86R | 94ZG2 |
| 55100 | K9M83 | Z61KN | 725LK | LZYJ9 |
| 55600 | QYJMY | 6N8KZ | MVJGZ | 39LQL |
| 56100 | R9VM8 | 2J89R | 94KJ2 | JLN39 |
| 56600 | Z61LN | 725QK | LZ989 | N9K1Q |
| 57100 | 6N87Z | MVJ4Z | 398YL | 85R2Y |
| 57600 | 2J8RR | 94KZ2 | JL7J9 | G6JN1 |
| 58100 | 725NK | LZ9Y9 | N9J5Q | 17M4Z |
| 58600 | MVJ8Z | 398LL | 8543Y | V59R1 |
| 59100 | 94K72 | JL7N9 | G6Z91 | YZ4Y2 |
| 59600 | LZ9G9 | N9JKQ | 178ZZ | 5242Z |
| 60100 | 398ZL | 854RY | V5J71 | 4959N |
| 60600 | JL7Y9 | G6ZJ1 | YZJL2 | K9J93 |
| 61100 | N9J8Q | 178MZ | 528KZ | QYZYY |
| 61600 | 8547Y | V5J91 | 4984N | R9698 |
| 62100 | G6ZR1 | YZJ42 | K9M63 | Z6K6N |
| 62600 | 178YZ | 528VZ | QYJ3Y | 6NKNZ |
| 63100 | V5JN1 | 498VN | R9VJ8 | 2J9JR |
| 63600 | YZJ12 | K9ML3 | Z61QN | 72Q2K |
| 64100 | 5285Z | QYJGY | 6N8QZ | MV4VZ |
| 64600 | 498YN | R9VG8 | 2J81R | 94Z42 |
| 65100 | K9MV3 | Z615N | 725RK | LZYZ9 |
| 65600 | QYJLY | 6N8VZ | MVJ7Z | 39L9L |
| 66100 | R9VL8 | 2J83R | 94K62 | JLNL9 |
| 66600 | Z61ZN | 725VK | LZ929 | N9K9Q |
| 67100 | 6N84Z | MVJ1Z | 3985L | 85R5Y |
| 67600 | 2J8MR | 94KV2 | JL7Z9 | G6J61 |
| 68100 | 725KK | LZ939 | N9JMQ | 17M7Z |
| 68600 | MVJLZ | 398VL | 854ZY | V5951 |
| 69100 | 94KR2 | JL799 | G6ZK1 | YZ4Z2 |
| 69600 | LZ9V9 | N9JGQ | 178GZ | 524JZ |
| 70100 | 398ML | 854VY | V5J11 | 495JN |
| 70600 | JL7V9 | G6Z21 | YZJK2 | K9JG3 |
| 71100 | N9JLQ | 178LZ | 528LZ | QYZVY |
| 71600 | 854QY | V5JG1 | 498MN | R9688 |
| 72100 | G6ZV1 | YZJG2 | K9M13 | Z6KVN |
| 72600 | 1789Z | 5286Z | QYJ9Y | 6NKYZ |
| 73100 | V5JY1 | 498ZN | R9V38 | 2J9NR |
| 73600 | YZJR2 | K9M53 | Z61MN | 72Q6K |
| 74100 | 528GZ | QYJ6Y | 6N8JZ | MV4NZ |
| 74600 | 498GN | R9V28 | 2J8ZR | 94Z82 |
| 75100 | K9MQ3 | Z618N | 7258K | LZYN9 |
| 75600 | QYJ5Y | 6N82Z | MVJKZ | 39LJL |
| 76100 | R9V48 | 2J8QR | 94K52 | JLNQ9 |
| 76600 | Z619N | 7257K | LZ959 | N9KNQ |
| 77100 | 6N85Z | MVJYZ | 3982L | 85R9Y |
| 77600 | 2J8GR | 94K92 | JL789 | G6J51 |
| 78100 | 7254K | LZ949 | N9JRQ | 17MNZ |

| | | | | |
|--------|-------|-------|-------|-------|
| 78600 | MVJZZ | 398RL | 8541Y | V59Q1 |
| 79100 | 94KQ2 | JL7G9 | G6ZM1 | YZ4V2 |
| 79600 | LZ9R9 | N9JQQ | 178QZ | 524NZ |
| 80100 | 398GL | 854MY | V5J41 | 495LN |
| 80600 | JL7K9 | G6ZG1 | YZJ22 | K9J23 |
| 81100 | N9J6Q | 178KZ | 524ZZ | QYZNY |
| 81600 | 854KY | V5JL1 | 495RN | R96Y8 |
| 82100 | G6Z71 | YZJ82 | K9J73 | Z6KNN |
| 82600 | 178VZ | 5281Z | QYZ7Y | 6NKGZ |
| 83100 | V5JZ1 | 4981N | R96N8 | 2J9LR |
| 83600 | YZJ72 | K9M43 | Z6KRN | 72QMK |
| 84100 | 528QZ | QYJ2Y | 6NKLZ | MV49Z |
| 84600 | 498KN | R9V78 | 2J97R | 94ZM2 |
| 85100 | K9MZ3 | Z614N | 72Q3K | LZY79 |
| 85600 | QYJ4Y | 6N81Z | MV46Z | 39L7L |
| 86100 | R9VK8 | 2J8VR | 94ZN2 | JLN29 |
| 86600 | Z61GN | 7251K | LZYM9 | N9K2Q |
| 87100 | 6N8RZ | MVJQZ | 39L3L | 85RNY |
| 87600 | 2J85R | 94K12 | JLN69 | G6JY1 |
| 88100 | 725ZK | LZ9K9 | N9KVQ | 17M6Z |
| 88600 | MVJ2Z | 3981L | 85R8Y | V59K1 |
| 89100 | 94K22 | JL759 | G6JL1 | YZ4N2 |
| 89600 | LZ969 | N9JYQ | 17M2Z | 524RZ |
| 90100 | 3984L | 854YY | V5981 | 495QN |
| 90600 | JL7R9 | G6Z31 | YZ462 | K9JK3 |
| 91100 | N9J7Q | 1781Z | 5249Z | QYZKY |
| 91600 | 8546Y | V5J31 | 495NN | R96Q8 |
| 92100 | G6Z41 | YZJ52 | K9JR3 | Z6K7N |
| 92600 | 1783Z | 5287Z | QYZ8Y | 6NKZZ |
| 93100 | V5J61 | 4982N | R9618 | 2J94R |
| 93600 | YZJM2 | K9MY3 | Z6K2N | 72QYK |
| 94100 | 5288Z | QYJRY | 6NK3Z | MV4RZ |
| 94600 | 4988N | R9VZ8 | 2J9KR | 94ZL2 |
| 95100 | K9MM3 | Z61JN | 72QJK | LZYQ9 |
| 95600 | QYJJY | 6N8MZ | MV4MZ | 39LKL |
| 96100 | R9VV8 | 2J8YR | 94ZY2 | JLN49 |
| 96600 | Z611N | 7259K | LZYL9 | N9KZQ |
| 97100 | 6N88Z | MVJ5Z | 39LNL | 85RGY |
| 97600 | 2J88R | 94K32 | JLNM9 | G6J81 |
| 98100 | 7255K | LZ919 | N9K3Q | 17M5Z |
| 98600 | MVJJZ | 3986L | 85RJY | V59V1 |
| 99100 | 94KK2 | JL719 | G6JQ1 | YZ492 |
| 99600 | LZ999 | N9J4Q | 17MJZ | 524YZ |
| 100100 | MVJRZ | 3988L | 854LY | V5921 |
| 100600 | 94KL2 | JL779 | G6Z11 | YZ4Q2 |
| 101100 | LZ9Q9 | N9JJQ | 178RZ | 5243Z |