**Supplementary file 1A**

**Table 1.** Cryo-EM structures used in the PCA analysis.

“Form” is determined by the number of chains which take Down form of RBD in S-protein (3: Down, 2: 1UP, 1: 2UP, 0: 3Up, respectively). The ‘Down’ or ‘Up’ form of protomer is determined from PCA of protomers. “Different protein” means whether there are protein chain(s) other than S-protein (uniprot: P0DTC2) in Cryo-EM or X-ray structures.

|  |  |  |
| --- | --- | --- |
| **PDB** | **Form** | **Different protein** |
| 7DWX | 1UP, 1UP | Yes |
| 7JJJ | Down, Down | No |
| 6VXX | Down | No |
| 6WPS | Down | Yes |
| 6X29 | Down | No |
| 6X2C | Down | No |
| 6X6P | Down | No |
| 6X79 | Down | No |
| 6XEY | Down | Yes |
| 6XF5 | Down | No |
| 6XLU | Down | No |
| 6XM5 | Down | No |
| 6XR8 | Down | No |
| 6ZB4 | Down | No |
| 6ZB5 | Down | No |
| 6ZGE | Down | No |
| 6ZGI | Down | No |
| 6ZOX | Down | No |
| 6ZOY | Down | No |
| 6ZOZ | Down | No |
| 6ZP0 | Down | No |
| 6ZP1 | Down | No |
| 6ZP2 | Down | No |
| 6ZWV | Down | No |
| 7A4N | Down | No |
| 7BNM | Down | No |
| 7CAB | Down | No |
| 7DDD | Down | No |
| 7DF3 | Down | No |
| 7DWY | Down | No |
| 7E7B | Down | No |
| 7E7D | Down | No |
| 7JJI | Down | No |
| 7JV6 | Down | Yes |
| 7JWY | Down | No |
| 7K43 | Down | Yes |
| 7K8S | Down | Yes |
| 7K90 | Down | Yes |
| 7KDG | Down | No |
| 7KDI | Down | No |
| 7KDK | Down | No |
| 7KE4 | Down | No |
| 7KE6 | Down | No |
| 7KE7 | Down | No |
| 7KE8 | Down | No |
| 7KKK | Down | Yes |
| 7KKL | Down | Yes |
| 7KRQ | Down | No |
| 7L02 | Down | Yes |
| 7L06 | Down | Yes |
| 7L09 | Down | Yes |
| 7L2D | Down | Yes |
| 7L2E | Down | Yes |
| 7L2F | Down | Yes |
| 7L56 | Down | Yes |
| 7L57 | Down | Yes |
| 7L7K | Down | No |
| 7LAB | Down | Yes |
| 7LCN | Down | Yes |
| 7LS9 | Down | Yes |
| 7LWI | Down | No |
| 7LWJ | Down | No |
| 7LWK | Down | No |
| 7LWL | Down | No |
| 7LWS | Down | No |
| 7LXY | Down | Yes |
| 7LXZ | Down | Yes |
| 7LY2 | Down | Yes |
| 7LYL | Down | No |
| 7LYM | Down | No |
| 7M0J | Down | No |
| 7M6E | Down | Yes |
| 7MKL | Down | Yes |
| 7N01 | Down | Yes |
| 7N1T | Down | No |
| 7N1U | Down | No |
| 7N8H | Down | Yes |
| 7ND7 | Down | Yes |
| 7ND8 | Down | Yes |
| 7NDA | Down | Yes |
| 7NDC | Down | Yes |
| 7NT9 | Down | No |
| 7OAN | Down | Yes |
| 7R8N | Down | Yes |
| 7R8O | Down | Yes |
| 7RW2 | Down | Yes |
| 6VSB | 1UP | No |
| 6VYB | 1UP | No |
| 6WPT | 1UP | Yes |
| 6X2A | 1UP | No |
| 6XF6 | 1UP | No |
| 6XKL | 1UP | No |
| 6XM0 | 1UP | No |
| 6XM3 | 1UP | No |
| 6XM4 | 1UP | No |
| 6Z43 | 1UP | Yes |
| 6Z97 | 1UP | No |
| 6ZGG | 1UP | No |
| 6ZHD | 1UP | Yes |
| 6ZP7 | 1UP | No |
| 6ZXN | 1UP | Yes |
| 7A25 | 1UP | Yes |
| 7A94 | 1UP | Yes |
| 7AD1 | 1UP | No |
| 7AKD | 1UP | Yes |
| 7BNN | 1UP | No |
| 7BYR | 1UP | Yes |
| 7C2L | 1UP | Yes |
| 7CAC | 1UP | Yes |
| 7CHH | 1UP | Yes |
| 7CN9 | 1UP | No |
| 7CWM | 1UP | Yes |
| 7CZX | 1UP | Yes |
| 7D03 | 1UP | Yes |
| 7D0B | 1UP | Yes |
| 7DD8 | 1UP | Yes |
| 7DDN | 1UP | No |
| 7DF4 | 1UP | Yes |
| 7DK3 | 1UP | No |
| 7DK5 | 1UP | Yes |
| 7DWZ | 1UP | No |
| 7DX0 | 1UP | No |
| 7DX1 | 1UP | No |
| 7DX2 | 1UP | No |
| 7DX3 | 1UP | No |
| 7DX5 | 1UP | Yes |
| 7DX7 | 1UP | Yes |
| 7DZW | 1UP | No |
| 7DZX | 1UP | Yes |
| 7DZY | 1UP | Yes |
| 7EAZ | 1UP | No |
| 7EB0 | 1UP | No |
| 7EB3 | 1UP | No |
| 7EDF | 1UP | No |
| 7EDG | 1UP | No |
| 7JV4 | 1UP | Yes |
| 7K8T | 1UP | Yes |
| 7K8V | 1UP | Yes |
| 7K8W | 1UP | Yes |
| 7K8X | 1UP | Yes |
| 7K8Z | 1UP | Yes |
| 7KDH | 1UP | No |
| 7KDJ | 1UP | No |
| 7KDL | 1UP | No |
| 7KE9 | 1UP | No |
| 7KEA | 1UP | No |
| 7KEB | 1UP | No |
| 7KEC | 1UP | No |
| 7KJ2 | 1UP | Yes |
| 7KJ5 | 1UP | No |
| 7KNB | 1UP | Yes |
| 7KNE | 1UP | Yes |
| 7KRR | 1UP | No |
| 7KRS | 1UP | No |
| 7KS9 | 1UP | Yes |
| 7L58 | 1UP | Yes |
| 7LJR | 1UP | Yes |
| 7LQV | 1UP | Yes |
| 7LQW | 1UP | Yes |
| 7LWM | 1UP | No |
| 7LWN | 1UP | No |
| 7LWO | 1UP | No |
| 7LWT | 1UP | No |
| 7LWU | 1UP | No |
| 7LWV | 1UP | No |
| 7LWW | 1UP | No |
| 7LYN | 1UP | No |
| 7LYO | 1UP | No |
| 7LYP | 1UP | No |
| 7LYQ | 1UP | No |
| 7M6G | 1UP | Yes |
| 7M6H | 1UP | Yes |
| 7M6I | 1UP | Yes |
| 7M8K | 1UP | No |
| 7MJG | 1UP | No |
| 7MJH | 1UP | Yes |
| 7N0G | 1UP | Yes |
| 7N1Q | 1UP | No |
| 7N1V | 1UP | No |
| 7N1W | 1UP | No |
| 7N1X | 1UP | No |
| 7N9B | 1UP | Yes |
| 7ND3 | 1UP | Yes |
| 7ND5 | 1UP | Yes |
| 7ND6 | 1UP | Yes |
| 7ND9 | 1UP | Yes |
| 7NDB | 1UP | Yes |
| 7NDD | 1UP | Yes |
| 7NTA | 1UP | No |
| 7NTC | 1UP | Yes |
| 7P7B | 1UP | No |
| 7R8M | 1UP | Yes |
| 6X2B | 2UP | No |
| 6XCM | 2UP | Yes |
| 7A29 | 2UP | Yes |
| 7A93 | 2UP | No |
| 7A95 | 2UP | Yes |
| 7A96 | 2UP | Yes |
| 7A97 | 2UP | Yes |
| 7BNO | 2UP | No |
| 7CAI | 2UP | Yes |
| 7CWL | 2UP | Yes |
| 7CWT | 2UP | Yes |
| 7CYP | 2UP | Yes |
| 7CZP | 2UP | Yes |
| 7CZQ | 2UP | Yes |
| 7CZR | 2UP | Yes |
| 7CZT | 2UP | Yes |
| 7CZU | 2UP | Yes |
| 7CZW | 2UP | Yes |
| 7CZY | 2UP | Yes |
| 7D00 | 2UP | Yes |
| 7D0C | 2UP | Yes |
| 7D0D | 2UP | Yes |
| 7DD2 | 2UP | Yes |
| 7DK4 | 2UP | Yes |
| 7DK6 | 2UP | Yes |
| 7DX6 | 2UP | Yes |
| 7DX8 | 2UP | Yes |
| 7EB4 | 2UP | No |
| 7EB5 | 2UP | No |
| 7EDI | 2UP | No |
| 7JWB | 2UP | Yes |
| 7JZL | 2UP | Yes |
| 7JZN | 2UP | Yes |
| 7K8U | 2UP | Yes |
| 7K8Y | 2UP | Yes |
| 7KJ3 | 2UP | Yes |
| 7KL9 | 2UP | Yes |
| 7KMK | 2UP | Yes |
| 7KMZ | 2UP | Yes |
| 7KNH | 2UP | Yes |
| 7KQB | 2UP | Yes |
| 7KXK | 2UP | Yes |
| 7LWP | 2UP | No |
| 7LYK | 2UP | No |
| 7MJJ | 2UP | Yes |
| 7MJM | 2UP | Yes |
| 7MM0 | 2UP | Yes |
| 7MY3 | 2UP | Yes |
| 7N0H | 2UP | Yes |
| 7N1Y | 2UP | No |
| 7P78 | 2UP | Yes |
| 7P79 | 2UP | Yes |
| 6XCN | 3UP | Yes |
| 6ZDH | 3UP | Yes |
| 7A98 | 3UP | Yes |
| 7B18 | 3UP | Yes |
| 7CAK | 3UP | Yes |
| 7CT5 | 3UP | Yes |
| 7CWN | 3UP | Yes |
| 7CWS | 3UP | Yes |
| 7CWU | 3UP | Yes |
| 7CZS | 3UP | Yes |
| 7CZV | 3UP | Yes |
| 7CZZ | 3UP | Yes |
| 7DCC | 3UP | Yes |
| 7DCX | 3UP | Yes |
| 7DK7 | 3UP | Yes |
| 7DX9 | 3UP | Yes |
| 7E3K | 3UP | Yes |
| 7E3L | 3UP | Yes |
| 7E8C | 3UP | Yes |
| 7EDJ | 3UP | Yes |
| 7EH5 | 3UP | Yes |
| 7EJ4 | 3UP | Yes |
| 7EJ5 | 3UP | Yes |
| 7JVC | 3UP | Yes |
| 7JW0 | 3UP | Yes |
| 7K4N | 3UP | Yes |
| 7KJ4 | 3UP | Yes |
| 7KML | 3UP | Yes |
| 7KMS | 3UP | Yes |
| 7KNI | 3UP | Yes |
| 7KQE | 3UP | Yes |
| 7KSG | 3UP | Yes |
| 7KXJ | 3UP | Yes |
| 7LD1 | 3UP | Yes |
| 7LRT | 3UP | Yes |
| 7M6F | 3UP | Yes |
| 7MJK | 3UP | Yes |
| 7MY2 | 3UP | Yes |
| 7N9T | 3UP | Yes |
| 7ND4 | 3UP | Yes |
| 7P77 | 3UP | Yes |
| 7RA8 | 3UP | Yes |
| 7RKV | 3UP | Yes |
| 6ZGH | 2 chains | No |
| 6ZOW | 2 chains | No |
| 6ZP5 | 2 chains | No |
| 7EDH | 2 chains | No |
| 7L3N | 2 chains | Yes |
| 7LWQ | 2 chains | No |
| 7MTC | 2 chains | No |
| 7MTE | 2 chains | No |
| 7N9C | 2 chains | Yes |
| 7N9E | 2 chains | Yes |
| 7P7A | 2 chains | Yes |
| 7LAA | 1 chain | Yes |
| 7LSS | 1 chain | Yes |

**Supplementary file 1B**

**Table 2.** Definition of protomer coarse-grained particles representing rigid domains for PCA.

|  |  |
| --- | --- |
| **Rigid domains** | **Residue numbers** |
| NTD | 27-43, 54-271 |
| NTD-b | 116-129, 169-172 |
| RBD | 330-443, 503-528 |
| RBD-h | 403-410 |
| NTD’ | 44-53,272-293 |
| SD1 | 323-329, 529-590 |
| SD2 | 294-322, 591-696 |
| S2-b | 717-727, 1047-1071 |
| CD | 711-716, 1072-1122 |

**Supplementary file 1C**

**Table 3.** List of clusters for gREST\_Down, gREST\_Up and gREST\_Down w/o glycan simulations.

|  |  |  |  |
| --- | --- | --- | --- |
| **Initial clusters** | **Refined clusters** | **Cluster name** | **Macro clusters** |
| **gREST\_Down** | | | |
| C1 | C1 | D1asym | DownLike (DownAsym) |
| C2 | C2 | I1a | DownLike (Int1) |
| C3 | C3 | D1Sym | DownSym |
| C4 | C4(1) | I2a | Int2 |
| C5 | C5(1) | I1b | DownLike (Int1) |
| C6 | C6 | I3b | Int3 |
| C7 | C7(1) | D2asym | DownLike (DownAsym) |
| C8 | C8 | D2Sym | DownSym |
|  | C4(2) | I3a | Int3 |
|  | C5(2) | I1c | DownLike (Int1) |
|  | C7(2) | I2b | Int2 |
|  | C7(3) | I2c | Int2 |
|  | C7(4) | 1UL | 1Up |
| **gREST\_Up** | | | |
| C1 | C1 | 1UO | 1Up |
| C2 | C2 | 1Ub | 1Up (1U) |
| C3 | C3(1) | 1Ue | 1Up (1U) |
| C4 | C4(1) | 1Uc | 1Up (1U) |
| C5 | C5(1) | 2UaL | 1Up (2UL) |
| C6 | C6 | 1Uf | 1Up (1U) |
| C7 | C7(1) | 1Uh | 1Up (1U) |
| C8 | C8 | 1Ua | 1Up (1U) |
|  | C3(2) | 1Ud | 1Up (1U) |
|  | C4(2) | 1Ug | 1Up (1U) |
|  | C5(2) | 2UbL | 1Up (2UL) |
|  | C7(2) | 1Uj | 1Up (1U) |
|  | C7(3) | 1Ui | 1Up (1U) |
| **gREST\_Down w/o glycan** | | | |
| C1 | C1(1) | 1Ua |  |
| C2 | C2 | I1b |  |
| C3 | C3(1) | I2a |  |
| C4 | C4(1) | D3 |  |
| C5 | C5 | D1 |  |
| C6 | C6 | I1a |  |
| C7 | C7 | D4 |  |
| C8 | C8(1) | D2 |  |
|  | C1(2) | 1Ub |  |
|  | C3(2) | I2b |  |
|  | C4(2) | 2UbL |  |
|  | C8(2) | 2UaL |  |

**Supplementary file 1D**

**Table 4.** The RBD interface cryptic pockets predicted by P2Rank30.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Intermediate** | **Rank** | **Score** | **Probability** | **Residue ids** |
| **I2a** | 3  (Pocket\_1) | 113.9 | 0.994 | A\_403 A\_405 A\_406 A\_408 A\_409 A\_414 A\_415 A\_416 A\_417 A\_420 A\_421 A\_424 A\_455 A\_456 A\_460 A\_473 A\_474 A\_475 A\_476 A\_477 A\_478 A\_479 A\_489 B\_335 B\_336 B\_338 B\_339 B\_342 B\_344 B\_345 B\_367 B\_368 B\_372 B\_373 B\_374 B\_375 B\_376 B\_378 B\_380 B\_403 B\_404 B\_405 B\_406 B\_407 B\_408 B\_409 B\_410 B\_411 B\_414 B\_415 B\_416 B\_417 B\_420 B\_421 B\_433 B\_435 B\_436 B\_437 B\_438 B\_439 B\_440 B\_441 B\_449 B\_453 B\_455 B\_493 B\_494 B\_495 B\_496 B\_498 B\_499 B\_500 B\_501 B\_502 B\_503 B\_504 B\_505 B\_506 B\_508 B\_509 C\_368 C\_369 C\_371 C\_372 C\_374 C\_375 C\_376 C\_377 C\_378 C\_379 C\_380 C\_382 C\_384 C\_403 C\_404 C\_405 C\_407 C\_408 C\_411 C\_414 C\_437 C\_501 C\_502 C\_503 C\_504 C\_505 C\_506 C\_508 |
| 8  (Pocket\_2) | 37.0 | 0.896 | A\_375 A\_376 A\_378 A\_380 A\_404 A\_405 A\_407 A\_408 A\_411 A\_412 A\_414 A\_503 A\_504 A\_508 C\_403 C\_406 C\_409 C\_416 C\_417 C\_418 C\_453 C\_455 C\_493 C\_494 C\_495 C\_496 C\_498 C\_500 C\_501 C\_505 |
| **I3a** | 8  (Pocket\_1) | 49.6 | 0.942 | A\_403 A\_405 A\_406 A\_408 A\_409 A\_413 A\_414 A\_415 A\_416 A\_417 A\_418 A\_420 A\_421 A\_424 A\_427 A\_453 A\_455 A\_456 A\_459 A\_460 A\_461 A\_463 A\_505 B\_375 B\_376 B\_377 B\_403 B\_404 B\_405 B\_406 B\_407 B\_408 B\_500 B\_501 B\_502 B\_503 B\_504 B\_505 B\_508 C\_375 C\_376 C\_404 C\_405 C\_408 C\_502 C\_503 C\_504 C\_505 C\_508 |
| 9  (Pocket\_2) | 38.7 | 0.908 | A\_375 A\_376 A\_378 A\_380 A\_404 A\_405 A\_407 A\_408 A\_411 A\_412 A\_414 A\_502 A\_503 A\_504 A\_505 A\_508 C\_403 C\_406 C\_409 C\_415 C\_416 C\_417 C\_418 C\_449 C\_453 C\_455 C\_493 C\_494 C\_495 C\_496 C\_498 C\_500 C\_501 C\_505 |
| **I3b** | 5  (Pocket\_2) | 37.8 | 0.904 | A\_371 A\_374 A\_375 A\_376 A\_377 A\_378 A\_379 A\_380 A\_381 A\_404 A\_405 A\_407 A\_408 A\_409 A\_411 A\_412 A\_414 A\_433 A\_437 A\_439 A\_499 A\_501 A\_502 A\_503 A\_506 A\_508 C\_403 C\_405 C\_406 C\_408 C\_409 C\_414 C\_417 C\_453 C\_455 C\_493 C\_494 C\_495 C\_496 C\_498 C\_500 C\_501 C\_503 C\_504 C\_505 |
| 12  (Pocket\_1) | 26.2 | 0.815 | A\_420 A\_421 A\_455 A\_456 A\_457 A\_460 A\_473 A\_475 A\_476 A\_487 A\_489 B\_375 B\_376 B\_378 B\_407 B\_408 B\_433 B\_437 B\_438 B\_439 B\_441 B\_502 B\_504 B\_505 B\_506 B\_508 |
| 16 | 21.6 | 0.747 | B\_415 B\_416 B\_417 B\_420 B\_421 B\_455 B\_456 B\_457 B\_458 B\_460 B\_473 B\_474 B\_475 B\_476 B\_477 B\_478 B\_487 B\_489 B\_490 B\_493 C\_367 C\_369 C\_370 C\_371 C\_372 C\_373 C\_374 C\_375 C\_376 C\_377 C\_384 |

**Supplementary file 1E**

**Table 5.** List of the top ranked molecules from the virtual screening of 2115 FDA approved drugs to RBD interface in I2a, I3a and I3b intermediate structures.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Rank** | **ZINC ID** | **Name** | **I2a\*** | **I3a\*** | **I3b\*** |
| 1 | ZINC000001612996 | Irinotecan | **−**11.9 | **−**9.5 | **−**9.4 |
| 2 | ZINC000052955754 | Ergotamine | **−**11.3 | **−**9.1 | **−**9.3 |
| 3 | ZINC000003978005 | Dihydroergotamine | **−**11.1 | **−**9.9 | **−**9.4 |
| 4 | ZINC000169289767 | Trypan Blue | **−**11.1 | **−**10.0 | **−**10.1 |
| **5** | **ZINC000006716957** | Nilotinib | **−10.9** | **−9.6** | **−9.5** |
| **6** | **ZINC000006716957** | Nilotinib | **−10.8** | **−10.0** | **−9.4** |
| 7 | ZINC000003978005 | Dihydroergotamine | **−**10.8 | **−**9.8 | **−**9.8 |
| 8 | ZINC000003932831 | Avodart | **−**10.8 | **−**9.3 | **−**9.1 |
| 9 | ZINC000003978005 | Dihydroergotamine | **−**10.7 | **−**10.4 | **−**10.4 |
| 10 | ZINC000052955754 | Ergotamine | **−**10.6 | **−**9.8 | **−**9.7 |
| 11 | ZINC000052955754 | Ergotamine | **−**10.5 | **−**9.7 | **−**9.7 |
| 12 | ZINC000053683151 | Bromocriptine | **−**10.4 | **−**9.8 | **−**9.0 |
| 13 | ZINC000064033452 | Lumacaftor | **−**10.4 | **−**9.9 | **−**9.3 |
| 14 | ZINC000011679756 | Eltrombopag | **−**10.3 | **−**9.2 | **−**10.0 |
| 15 | ZINC000036701290 | Ponatinib | **−**10.3 | **−**9.6 | **−**9.5 |
| 16 | ZINC000084668739 | Lifitegrast | **−**10.2 | **−**10.1 | **−**9.3 |
| 17 | ZINC000003927822 | Lurasidone | **−**10.1 | **−**9.0 | **−**9.4 |
| 19 | ZINC000164528615 | Glecaprevir | **−**10.1 | **−**9.6 | **−**9.0 |
| 20 | ZINC000100378061 | Naldemedine | **−**10.0 | **−**9.8 | **−**9.0 |

Molecules are ranked based on binding energy to I2a while binding energy to other intermediates (I3a and I3b) are also shown.

\* Binding energy in kcal mol-1.

Rank 5 and 6, shown in bold, represent Nilotinib.

**Supplementary file 1F**

**Table 6.** Nilotinib binding energy to I2a, I3a and I3b intermediates.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **I2a** | **I3a** | **I3b** |
| **Mode** | **Affinity (kcal mol-1)** | | |
| **1** | **−**10.9 | **−**9.6 | **−**9.5 |
| **2** | **−**10.9 | **−**9.6 | **−**9.4 |
| **3** | **−**10.8 | **−**9.5 | **−**9.3 |
| **4** | **−**10.8 | **−**9.4 | **−**9.2 |
| **5** | **−**10.6 | **−**9.3 | **−**9.2 |
| **6** | **−**10.5 | **−**9.2 | **−**9.2 |
| **7** | **−**10.4 | **−**9.0 | **−**9.2 |
| **8** | **−**10.4 | **−**8.8 | **−**9.1 |
| **9** | **−**10.3 | **−**8.7 | **−**9.1 |