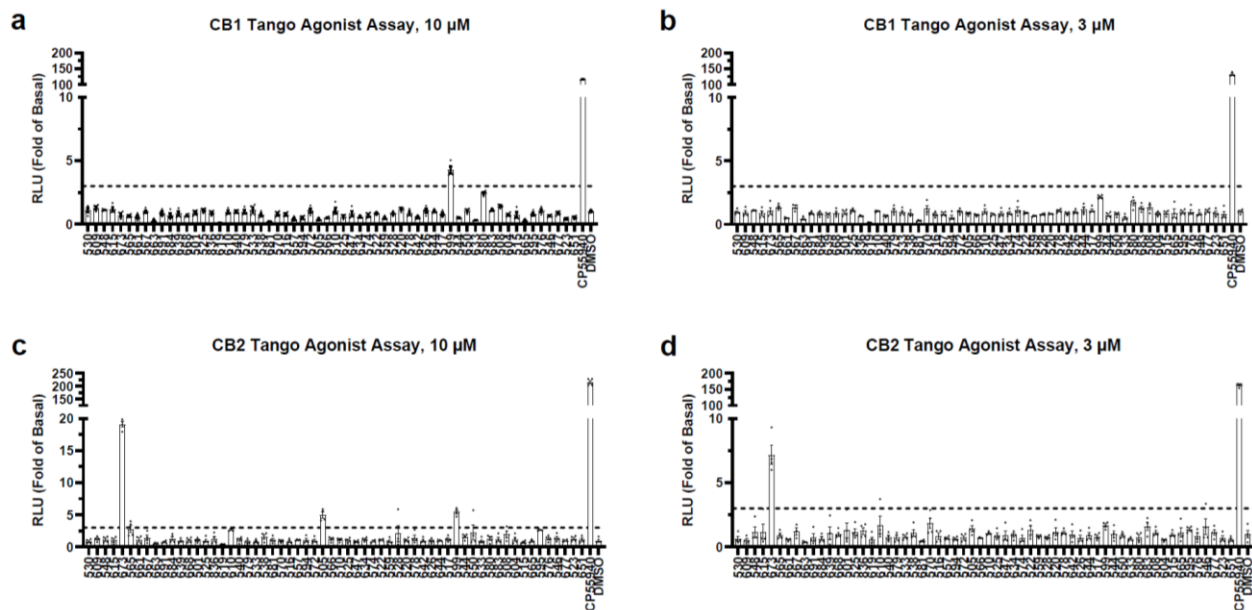
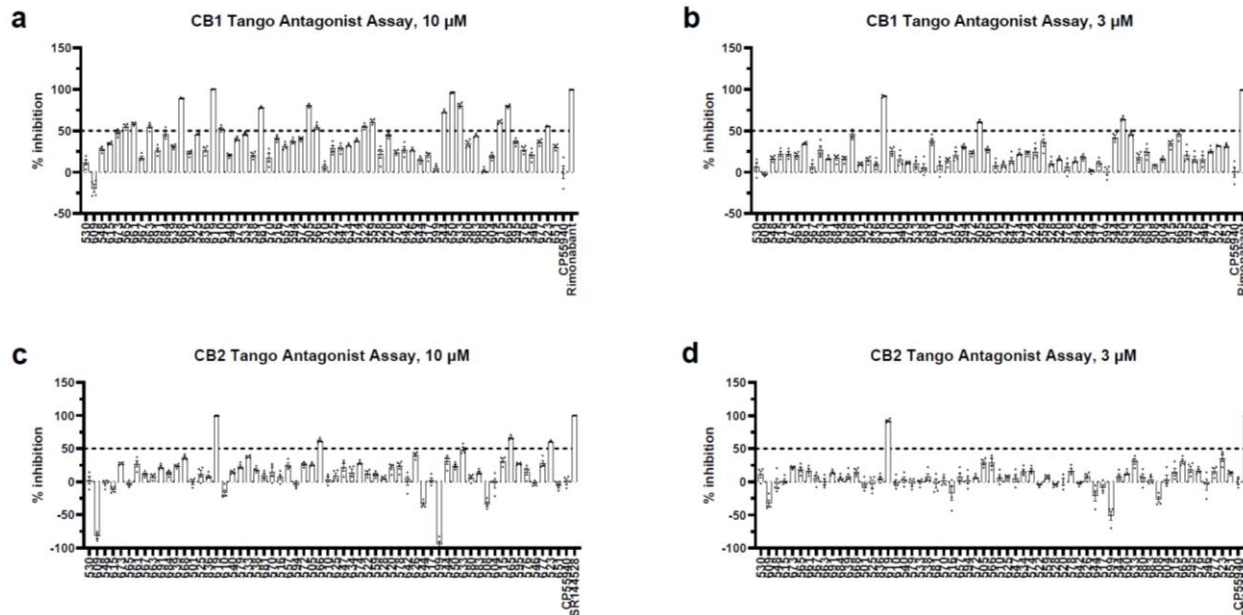


## Supplementary Information 1



**Figure S1.** Primary agonist screening of the compounds predicted by V-SYNTHES.

$\beta$ -arrestin recruitment Tango assays were performed to determine the relative agonist activity of CB<sub>1</sub> (a-b) and CB<sub>2</sub> (c-d) receptors. All the predicted compounds were tested at 10  $\mu$ M (a and c) and 3  $\mu$ M (b and d) concentrations. The dual CB<sub>1</sub>/CB<sub>2</sub> agonist CP55,940 at 1  $\mu$ M was used as a positive control, and DMSO was used as a negative control. The data were presented as mean  $\pm$  SEM ( $n=4$ ) and compounds with > 3 fold of basal activity were considered as significant hits.



**Figure S2. Primary antagonist screening of the compounds predicted by V-SYNTHES.**

The  $\beta$ -arrestin recruitment Tango assays were performed to determine the relative antagonist activity of  $\text{CB}_1$  (a-b) and  $\text{CB}_2$  (c-d) receptors. All the predicted compounds were tested at 10  $\mu\text{M}$  (a and c) and 3  $\mu\text{M}$  (b and d) concentrations. The assays were carried out in the presence of 100 nM ( $\text{EC}_{80}$ ) of the dual  $\text{CB}_1/\text{CB}_2$  agonist CP55,940. Antagonists rimonabant (a-b) or SR144528 (c-d) at 10  $\mu\text{M}$  was used as positive control, and DMSO served as the negative control. The data were presented as mean  $\pm$  SEM ( $n=4$ ) and compounds with inhibition  $> 50\%$  were considered as significant hits.

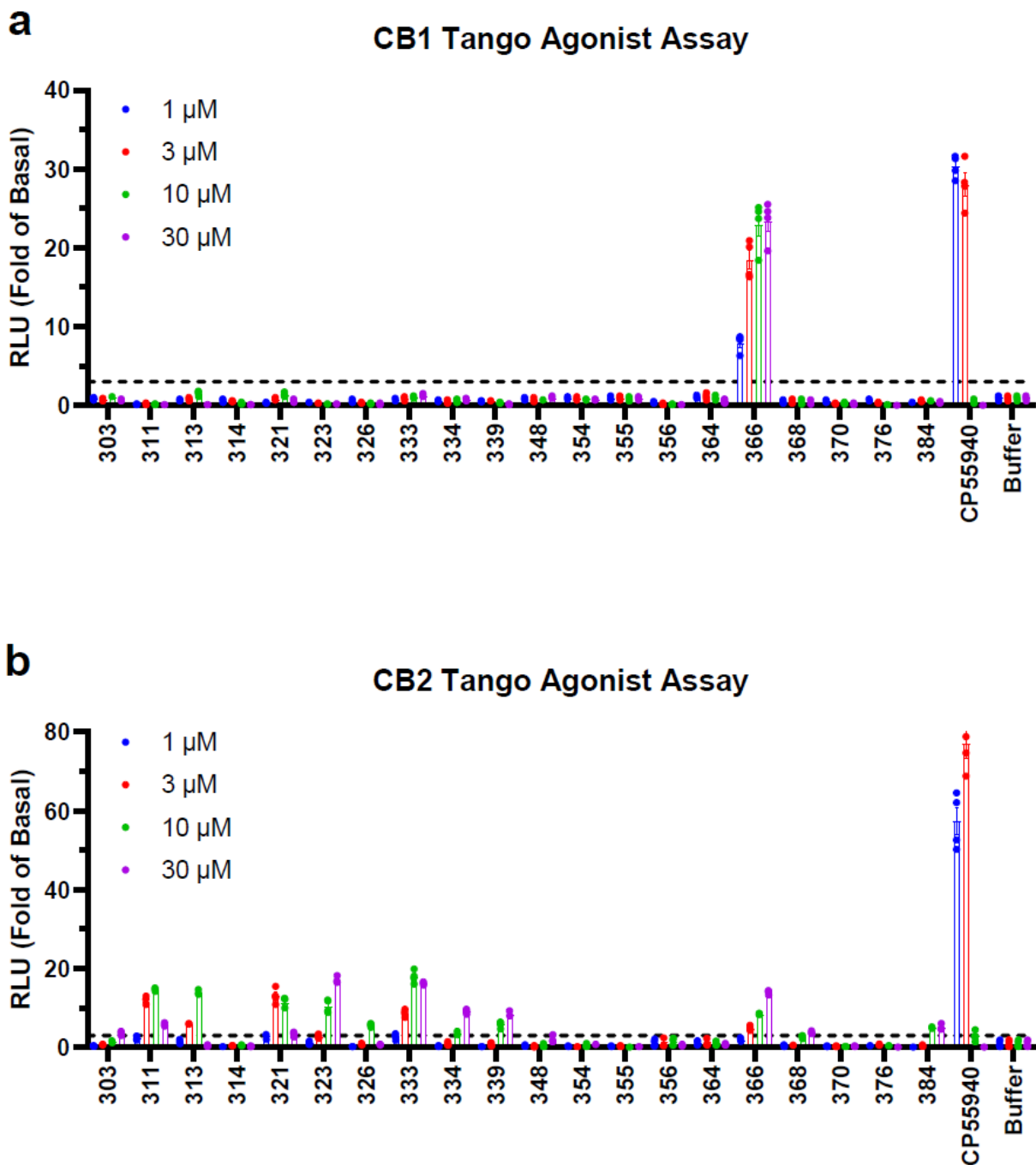
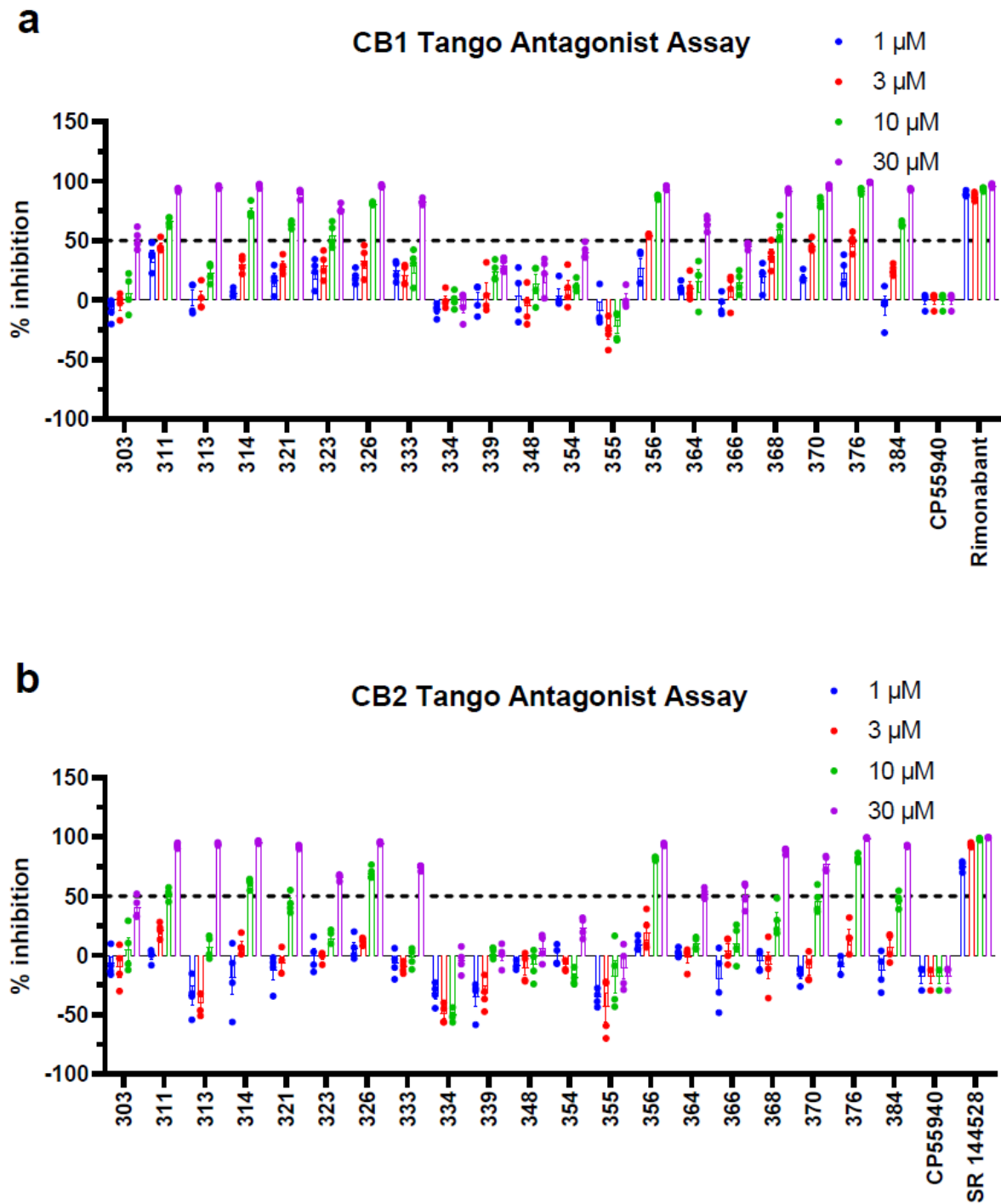


Figure S3. Agonist screening of the compounds predicted from standard VLS and showing receptor binding.

The  $\beta$ -arrestin recruitment Tango assays were performed to determine the relative agonist activity of CB<sub>1</sub> (a) and CB<sub>2</sub> (b) receptors. All the compounds were tested at 1, 3, 10, and 30  $\mu\text{M}$  concentrations. The dual CB<sub>1</sub>/CB<sub>2</sub> agonist CP55,940 was used as a positive control. The data were presented as mean  $\pm$  SEM ( $n=4$ ) and the compounds with  $>3$  fold of basal activity were considered as significant hits.



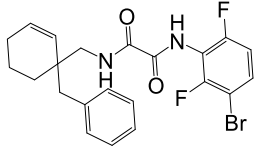
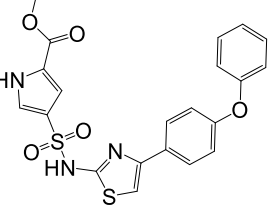
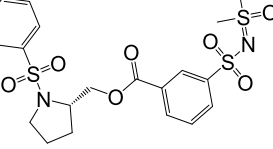
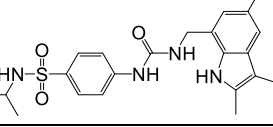
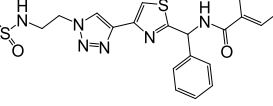
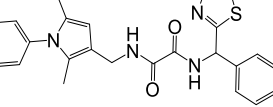
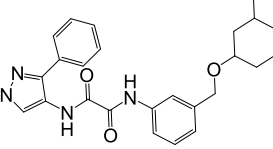
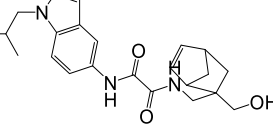
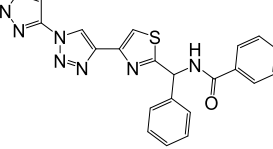
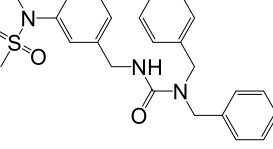
*Figure S4. Antagonist screening of the compounds predicted from standard VLS and showing receptor binding.*

*The  $\beta$ -arrestin recruitment Tango assays were performed to determine the relative antagonist activity of CB<sub>1</sub> (a) and CB<sub>2</sub> (b) receptors. The assays were carried out in the presence of 100 nM ( $EC_{30}$ ) of the dual CB<sub>1</sub>/CB<sub>2</sub> agonist CP55,940. All the compounds were tested at 1, 3, 10, and 30  $\mu$ M concentrations. Rimonabant (a) or SR144528 (b) at 10  $\mu$ M was used as a positive control. The data are presented as mean  $\pm$  SEM ( $n=4$ ) and the compounds with inhibition  $>50\%$  were considered as significant hits.*

Table S1. All compounds (60) selected by V-SYNTHES and synthesized for biochemical testing.

| BRI-ID    | ID  | Enamine ID  | Chemical Structure | MW    | Binding Score 4D Model | Model From 4D | Purity, % | Tanimoto distance, >0.3 | Closest ChEMbe ID |
|-----------|-----|-------------|--------------------|-------|------------------------|---------------|-----------|-------------------------|-------------------|
| BRI-13501 | 501 | Z4121492000 |                    | 442.2 | -47.0                  | 2             | 100       | 0.39                    | CHEMBL567297      |
| BRI-13505 | 505 | Z4121492004 |                    | 461.2 | -42.5                  | 2             | 100       | 0.38                    | CHEMBL602591      |
| BRI-13508 | 508 | Z4121492212 |                    | 423.2 | -42.0                  | 2             | 93        | 0.39                    | CHEMBL2338171     |
| BRI-13510 | 510 | Z4121492216 |                    | 469.2 | -41.3                  | 2             | 100       | 0.44                    | CHEMBL563400      |
| BRI-13515 | 515 | Z1200683193 |                    | 427.2 | -40.4                  | 2             | 100       | 0.39                    | CHEMBL2316403     |
| BRI-13516 | 516 | Z4121492248 |                    | 444.2 | -40.3                  | 2             | 97        | 0.45                    | CHEMBL247516      |
| BRI-13517 | 517 | Z3561064053 |                    | 388.2 | -40.3                  | 2             | 100       | 0.40                    | CHEMBL572860      |
| BRI-13520 | 520 | Z4121492251 |                    | 462.1 | -39.9                  | 3             | 98        | 0.40                    | CHEMBL1814323     |
| BRI-13522 | 522 | Z4121492019 |                    | 437.2 | -39.6                  | 2             | 93        | 0.41                    | CHEMBL406675      |
| BRI-13523 | 523 | Z4121492020 |                    | 495.2 | -39.5                  | 1             | 94        | 0.39                    | CHEMBL2336535     |

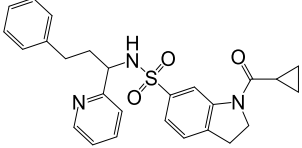
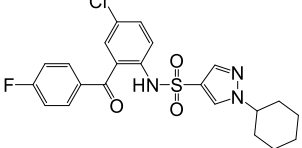
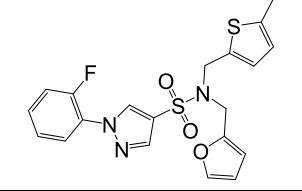
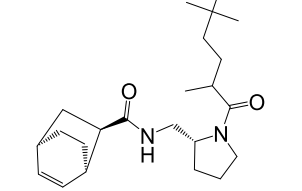
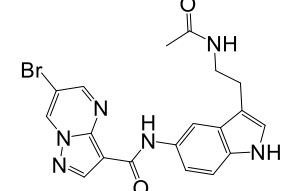
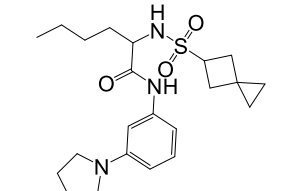
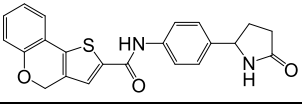
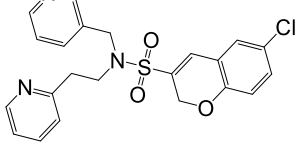
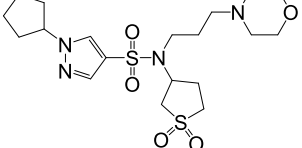
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|-----------|-----|-------------|--|-------|-------|---|-----|------|---------------|
| BRI-13525 | 525 | Z4121492022 |  | 441.1 | -39.4 | 1 | 98  | 0.36 | CHEMBL3912856 |
| BRI-13528 | 528 | Z4121492273 |  | 424.2 | -38.8 | 2 | 99  | 0.38 | CHEMBL584332  |
| BRI-13530 | 530 | Z4121492026 |  | 406.1 | -38.3 | 3 | 100 | 0.42 | CHEMBL1814323 |
| BRI-13533 | 533 | Z4121492029 |  | 400.2 | -38.3 | 2 | 100 | 0.39 | CHEMBL3899579 |
| BRI-13538 | 538 | Z1731969993 |  | 396.2 | -37.8 | 2 | 100 | 0.53 | CHEMBL2348061 |
| BRI-13540 | 540 | Z4121492289 |  | 403.2 | -37.6 | 2 | 100 | 0.44 | CHEMBL2030936 |
| BRI-13544 | 544 | Z4121492036 |  | 459.2 | -37.2 | 3 | 100 | 0.34 | CHEMBL602591  |
| BRI-13546 | 546 | Z4121492296 |  | 441.2 | -37.2 | 3 | 92  | 0.33 | CHEMBL2179727 |
| BRI-13548 | 548 | Z4121492040 |  | 402.2 | -37.0 | 2 | 98  | 0.44 | CHEMBL2057795 |
| BRI-13559 | 559 | Z4121492050 |  | 468.2 | -36.4 | 3 | 98  | 0.43 | CHEMBL406675  |
| BRI-13565 | 565 | Z4121492325 |  | 375.2 | -36.1 | 3 | 91  | 0.37 | CHEMBL560407  |

|           |     |             |   |       |       |   |     |      |               |
|-----------|-----|-------------|---|-------|-------|---|-----|------|---------------|
| BRI-13566 | 566 | Z4121492326 |    | 462.1 | -36.1 | 1 | 100 | 0.42 | CHEMBL3899579 |
| BRI-13567 | 567 | Z4121492058 |    | 455.1 | -36.1 | 2 | 93  | 0.49 | CHEMBL2336549 |
| BRI-13570 | 570 | Z4121492335 |    | 500.1 | -35.8 | 2 | 100 | 0.36 | CHEMBL246713  |
| BRI-13572 | 572 | Z975082230  |    | 428.2 | -35.7 | 2 | 90  | 0.45 | CHEMBL3920675 |
| BRI-13574 | 574 | Z4121534933 |   | 482.1 | -35.6 | 2 | 96  | 0.43 | CHEMBL1814318 |
| BRI-13576 | 576 | Z4121492339 |  | 444.2 | -35.6 | 3 | 90  | 0.30 | CHEMBL3901846 |
| BRI-13578 | 578 | Z4121492343 |  | 446.2 | -35.4 | 2 | 95  | 0.42 | CHEMBL35835   |
| BRI-13579 | 579 | Z4121492344 |  | 395.2 | -35.4 | 2 | 100 | 0.40 | CHEMBL4079817 |
| BRI-13580 | 580 | Z4121534245 |  | 441.1 | -35.4 | 3 | 94  | 0.36 | CHEMBL1814318 |
| BRI-13594 | 594 | Z4121492081 |  | 437.2 | -34.8 | 2 | 100 | 0.37 | CHEMBL2326298 |

|           |     |             |  |       |       |   |     |      |               |
|-----------|-----|-------------|--|-------|-------|---|-----|------|---------------|
| BRI-13595 | 595 | Z4121492388 |  | 449.2 | -34.8 | 1 | 100 | 0.34 | CHEMBL571323  |
| BRI-13599 | 599 | Z4121492409 |  | 475.2 | -34.6 | 2 | 100 | 0.34 | CHEMBL591795  |
| BRI-13604 | 604 | Z4121492418 |  | 412.2 | -34.4 | 2 | 90  | 0.50 | CHEMBL560886  |
| BRI-13609 | 609 | Z4121492096 |  | 409.2 | -34.1 | 3 | 100 | 0.40 | CHEMBL3410826 |
| BRI-13610 | 610 | Z1893460093 |  | 430.2 | -34.1 | 3 | 100 | 0.31 | CHEMBL567297  |
| BRI-13615 | 615 | Z4121492102 |  | 405.1 | -33.8 | 3 | 99  | 0.39 | CHEMBL2071066 |
| BRI-13619 | 619 | Z1565632280 |  | 447.2 | -33.8 | 2 | 100 | 0.42 | CHEMBL307887  |
| BRI-13625 | 625 | Z4121492512 |  | 441.2 | -33.5 | 3 | 98  | 0.37 | CHEMBL3410826 |
| BRI-13626 | 626 | Z813262444  |  | 421.2 | -33.4 | 1 | 100 | 0.43 | CHEMBL2336546 |
| BRI-13633 | 633 | Z4121492118 |  | 463.1 | -33.1 | 2 | 94  | 0.50 | CHEMBL555869  |



|           |     |             |  |       |       |   |     |      |               |
|-----------|-----|-------------|--|-------|-------|---|-----|------|---------------|
| BRI-13634 | 634 | Z4121641081 |  | 449.3 | -33.0 | 2 | 98  | 0.42 | CHEMBL255681  |
| BRI-13639 | 639 | Z1733682771 |  | 443.2 | -32.9 | 3 | 100 | 0.35 | CHEMBL3920675 |
| BRI-13642 | 642 | Z439615516  |  | 447.2 | -32.7 | 2 | 100 | 0.38 | CHEMBL3934815 |
| BRI-13644 | 644 | Z3561062829 |  | 372.2 | -32.6 | 2 | 100 | 0.39 | CHEMBL4097041 |
| BRI-13647 | 647 | Z4121640613 |  | 497.2 | -32.5 | 1 | 100 | 0.49 | CHEMBL3669113 |
| BRI-13650 | 650 | Z4121492133 |  | 423.0 | -32.4 | 3 | 91  | 0.48 | CHEMBL3935866 |
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| BRI-13657 | 657 | Z4121492608 |  | 413.1 | -32.2 | 1 | 95  | 0.54 | CHEMBL3909817 |
| BRI-13661 | 661 | Z4121492610 |  | 471.1 | -32.0 | 2 | 100 | 0.39 | CHEMBL180963  |

|           |     |             |   |       |       |   |     |      |               |
|-----------|-----|-------------|---|-------|-------|---|-----|------|---------------|
| BRI-13663 | 663 | Z4121492611 |    | 461.2 | -32.0 | 3 | 100 | 0.36 | CHEMBL3920675 |
| BRI-13665 | 665 | Z4121492147 |    | 461.1 | -31.9 | 3 | 97  | 0.47 | CHEMBL484014  |
| BRI-13668 | 668 | Z1270981281 |    | 431.1 | -31.8 | 3 | 100 | 0.40 | CHEMBL2336536 |
| BRI-13673 | 673 | Z4121493648 |    | 374.3 | -31.6 | 3 | 100 | 0.46 | CHEMBL122884  |
| BRI-13677 | 677 | Z4121492158 |   | 440.1 | -31.4 | 3 | 93  | 0.45 | CHEMBL1828806 |
| BRI-13681 | 681 | Z4121492674 |  | 419.2 | -31.3 | 3 | 96  | 0.42 | CHEMBL589985  |
| BRI-13683 | 683 | Z4121492676 |  | 390.1 | -31.2 | 3 | 91  | 0.43 | CHEMBL2064059 |
| BRI-13684 | 684 | Z4121492165 |  | 441.1 | -31.1 | 3 | 91  | 0.48 | CHEMBL259339  |
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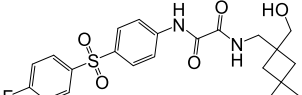
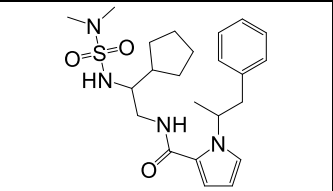
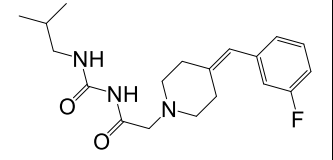
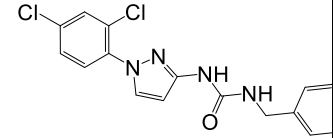
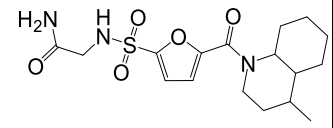
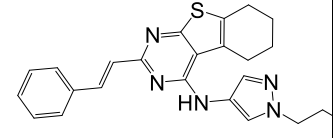
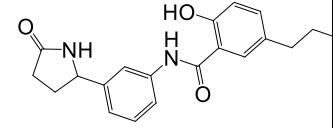
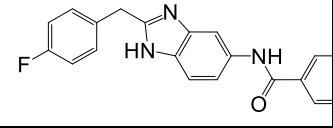
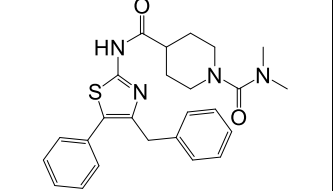
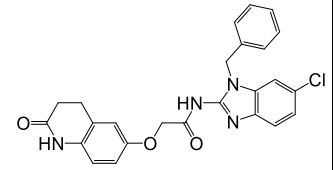
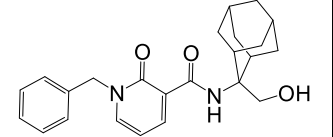
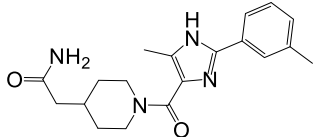
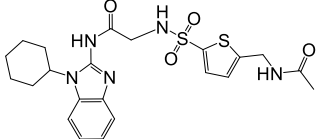
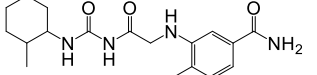
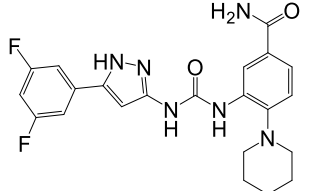
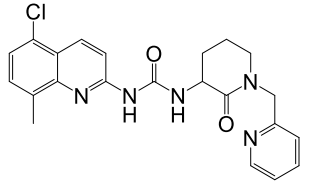
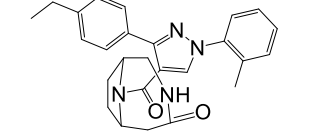
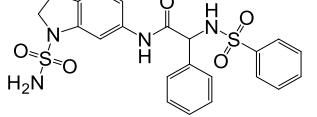
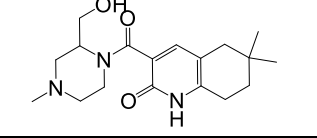
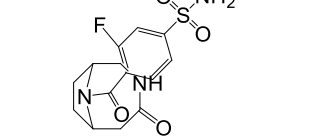
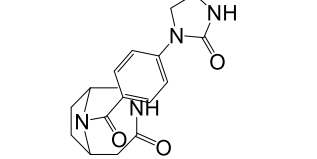
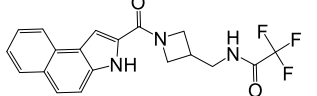
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|----------|-----|-------------|---|-------|-------|---|-----|------|--------------|
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|----------|-----|-------------|---|-------|-------|---|-----|------|--------------|

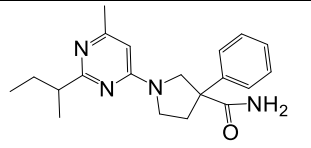
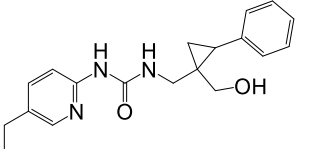
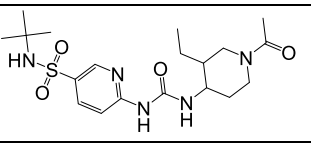
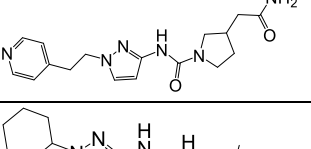
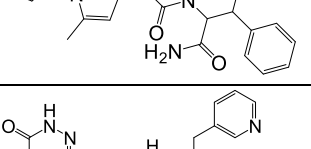
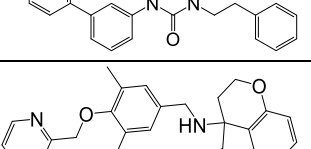
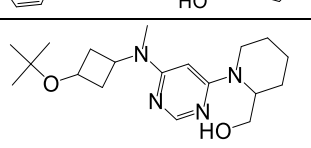
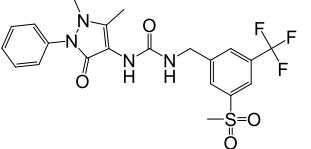
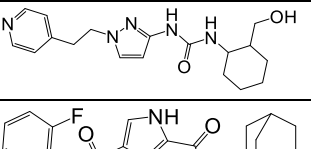
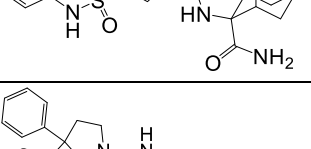
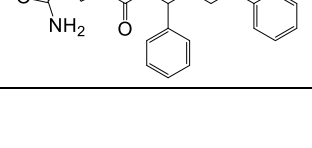

Table S2. All compounds (97) selected from the Standard VLS of 115M REAL diversity subset library and synthesized for biochemical testing.

| BRI-ID    | ID  | Enamine ID      | Chemical Structure | MW    | Binding Score | Model | Purity, % | Tanimoto distance >0.3 | Closest ChEMbl ID |
|-----------|-----|-----------------|--------------------|-------|---------------|-------|-----------|------------------------|-------------------|
| BRI-13301 | 301 | Z2961658334     |                    | 368.1 | -41.7         | 3     | 95        | 0.46                   | CHEMBL2326282     |
| BRI-13303 | 303 | PV-002596373138 |                    | 391.2 | -42.2         | 2     | 100       | 0.34                   | CHEMBL2326281     |
| BRI-13304 | 304 | Z3322177313     |                    | 322.1 | -41.2         | 2     | 100       | 0.45                   | CHEMBL566260      |
| BRI-13305 | 305 | Z2485334379     |                    | 348.1 | -35.6         | 3     | 100       | 0.44                   | CHEMBL2326293     |
| BRI-13306 | 306 | Z2234945970     |                    | 389.1 | -44.8         | 2     | 100       | 0.42                   | CHEMBL2348280     |
| BRI-13307 | 307 | Z2635933404     |                    | 338.1 | -43.6         | 2     | 95        | 0.49                   | CHEMBL511404      |
| BRI-13308 | 308 | PV-002197211605 |                    | 473.1 | -38.2         | 3     | 100       | 0.36                   | CHEMBL592264      |
| BRI-13309 | 309 | Z1068301846     |                    | 471.2 | -42.5         | 2     | 96        | 0.39                   | CHEMBL488032      |
| BRI-13310 | 310 | Z2110620860     |                    | 339.2 | -39.8         | 2     | 97        | 0.47                   | CHEMBL2316267     |

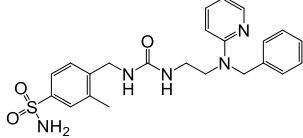
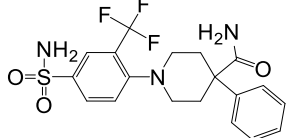
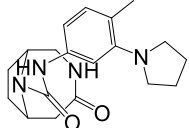
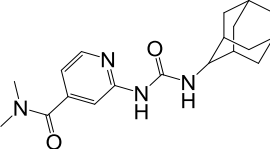
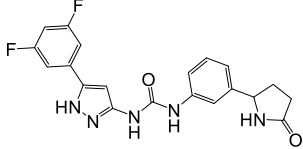
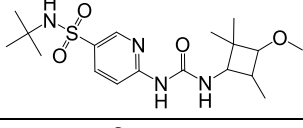
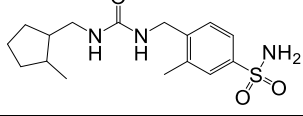
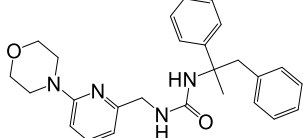
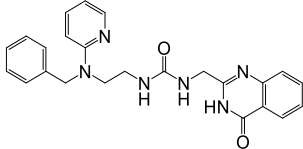
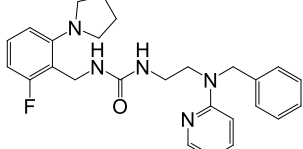
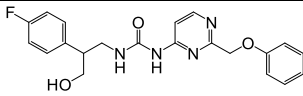
|           |     |                     |   |       |       |   |     |      |               |
|-----------|-----|---------------------|---|-------|-------|---|-----|------|---------------|
| BRI-13311 | 311 | PV-<br>001853441755 |    | 446.2 | -40.5 | 1 | 100 | 0.41 | CHEMBL3950265 |
| BRI-13312 | 312 | Z1317923243         |    | 347.2 | -39.6 | 1 | 100 | 0.46 | CHEMBL49407   |
| BRI-13314 | 314 | Z1581087524         |    | 433.1 | -46.9 | 2 | 94  | 0.36 | CHEMBL2022406 |
| BRI-13315 | 315 | Z1313061975         |    | 383.2 | -39.7 | 1 | 99  | 0.43 | CHEMBL3907911 |
| BRI-13316 | 316 | PV-<br>002306906593 |    | 417.2 | -40.7 | 3 | 100 | 0.51 | CHEMBL1223234 |
| BRI-13317 | 317 | PV-<br>001854381332 |   | 400.2 | -44.0 | 2 | 100 | 0.46 | CHEMBL3114182 |
| BRI-13318 | 318 | PV-<br>002257411096 |  | 466.1 | -45.4 | 2 | 98  | 0.50 | CHEMBL472506  |
| BRI-13319 | 319 | Z444667174          |  | 448.2 | -42.8 | 2 | 100 | 0.47 | CHEMBL1668505 |
| BRI-13320 | 320 | PV-<br>002475346314 |  | 460.1 | -43.7 | 2 | 100 | 0.40 | CHEMBL4079520 |
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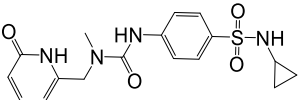
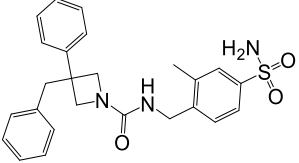
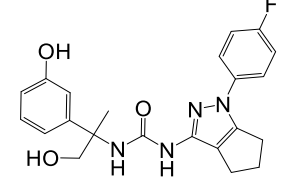
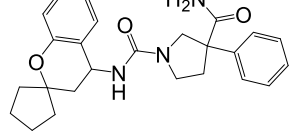
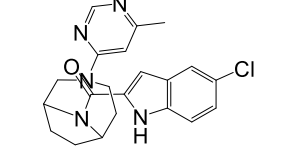
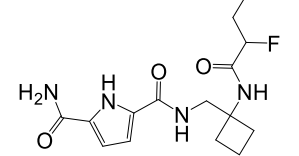
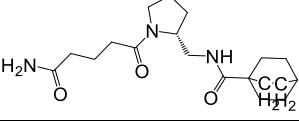
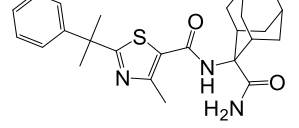
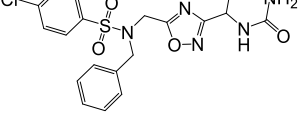
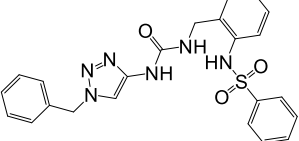
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|-----------|-----|-----------------|---|-------|-------|---|-----|------|---------------|
| BRI-13322 | 322 | Z1521776225     |    | 340.2 | -40.2 | 2 | 100 | 0.37 | CHEMBL173662  |
| BRI-13323 | 323 | PV-002260335185 |    | 489.2 | -40.3 | 2 | 100 | 0.39 | CHEMBL1950329 |
| BRI-13324 | 324 | Z928610054      |    | 346.2 | -40.5 | 1 | 100 | 0.39 | CHEMBL2179733 |
| BRI-13325 | 325 | PV-002310541667 |    | 440.2 | -43.0 | 1 | 100 | 0.42 | CHEMBL3341878 |
| BRI-13326 | 326 | PV-001945154150 |    | 423.1 | -41.8 | 2 | 91  | 0.43 | CHEMBL2316402 |
| BRI-13327 | 327 | Z1335418442     |  | 428.2 | -42.6 | 2 | 100 | 0.42 | CHEMBL3759440 |
| BRI-13328 | 328 | PV-002131347728 |  | 486.1 | -43.1 | 2 | 95  | 0.34 | CHEMBL560462  |
| BRI-13329 | 329 | Z2914926861     |  | 333.2 | -37.6 | 1 | 95  | 0.36 | CHEMBL2018657 |
| BRI-13330 | 330 | Z1574930403     |  | 341.1 | -38.0 | 2 | 100 | 0.50 | CHEMBL489450  |
| BRI-13331 | 331 | Z1335414856     |  | 328.2 | -38.2 | 2 | 100 | 0.51 | CHEMBL1086903 |
| BRI-13332 | 332 | Z2803805359     |  | 375.1 | -41.6 | 2 | 97  | 0.42 | CHEMBL2071071 |

|           |     |                 |  |       |       |   |     |      |               |
|-----------|-----|-----------------|--|-------|-------|---|-----|------|---------------|
| BRI-13334 | 334 | PV-002590000161 |  | 440.2 | -34.8 | 3 | 100 | 0.42 | CHEMBL3920675 |
| BRI-13335 | 335 | PV-001873928923 |  | 375.2 | -41.7 | 2 | 100 | 0.37 | CHEMBL2326281 |
| BRI-13336 | 336 | Z1367242541     |  | 441.2 | -41.0 | 1 | 96  | 0.34 | CHEMBL3920675 |
| BRI-13337 | 337 | Z1344761622     |  | 358.1 | -41.3 | 3 | 97  | 0.35 | CHEMBL3109780 |
| BRI-13338 | 338 | Z2634446262     |  | 346.1 | -35.2 | 1 | 100 | 0.41 | CHEMBL272139  |
| BRI-13339 | 339 | Z2295310789     |  | 337.2 | -40.9 | 1 | 100 | 0.43 | CHEMBL572097  |
| BRI-13341 | 341 | PV-002505268577 |  | 416.2 | -38.6 | 1 | 100 | 0.42 | CHEMBL2326032 |
| BRI-13342 | 342 | PV-001850966499 |  | 414.2 | -43.9 | 2 | 100 | 0.46 | CHEMBL3943735 |
| BRI-13343 | 343 | PV-001856728324 |  | 391.2 | -43.5 | 2 | 100 | 0.30 | CHEMBL217862  |
| BRI-13344 | 344 | Z1905189179     |  | 329.1 | -42.8 | 2 | 100 | 0.36 | CHEMBL427100  |
| BRI-13345 | 345 | Z1311789376     |  | 343.2 | -40.6 | 2 | 97  | 0.45 | CHEMBL2316410 |

|           |     |                 |   |       |       |   |     |      |               |
|-----------|-----|-----------------|---|-------|-------|---|-----|------|---------------|
| BRI-13346 | 346 | PV-002471788812 |    | 338.2 | -39.0 | 2 | 100 | 0.39 | CHEMBL560886  |
| BRI-13347 | 347 | Z2845727635     |    | 325.2 | -38.4 | 1 | 100 | 0.39 | CHEMBL570792  |
| BRI-13348 | 348 | Z1733663498     |    | 425.2 | -39.9 | 1 | 100 | 0.42 | CHEMBL603529  |
| BRI-13349 | 349 | Z2150824767     |    | 342.2 | -40.5 | 2 | 100 | 0.42 | CHEMBL2296779 |
| BRI-13350 | 350 | Z2294553207     |    | 383.2 | -43.0 | 3 | 94  | 0.44 | CHEMBL567297  |
| BRI-13351 | 351 | Z1160329459     |   | 425.2 | -43.6 | 2 | 95  | 0.45 | CHEMBL3758973 |
| BRI-13352 | 352 | Z1994352703     |  | 404.2 | -41.4 | 2 | 97  | 0.40 | CHEMBL2069427 |
| BRI-13354 | 354 | Z2370574710     |  | 348.3 | -37.5 | 2 | 97  | 0.49 | CHEMBL565023  |
| BRI-13355 | 355 | PV-002340081461 |  | 482.1 | -42.3 | 1 | 100 | 0.35 | CHEMBL1928337 |
| BRI-13357 | 357 | Z1331035983     |  | 343.2 | -38.7 | 1 | 100 | 0.47 | CHEMBL272754  |
| BRI-13358 | 358 | PV-002131209937 |  | 460.2 | -40.0 | 2 | 96  | 0.49 | CHEMBL256110  |
| BRI-13359 | 359 | PV-001954118798 |  | 441.2 | -41.5 | 2 | 100 | 0.31 | CHEMBL2179754 |



|           |     |                 |   |       |       |   |     |      |               |
|-----------|-----|-----------------|---|-------|-------|---|-----|------|---------------|
| BRI-13361 | 361 | PV-001961332629 |    | 453.2 | -46.1 | 1 | 100 | 0.42 | CHEMBL2179726 |
| BRI-13362 | 362 | Z1272404453     |    | 427.1 | -40.8 | 2 | 100 | 0.33 | CHEMBL3341900 |
| BRI-13363 | 363 | Z2845039443     |    | 342.2 | -35.7 | 1 | 100 | 0.52 | CHEMBL592703  |
| BRI-13364 | 364 | Z2057335502     |    | 342.2 | -36.7 | 2 | 100 | 0.44 | CHEMBL568564  |
| BRI-13365 | 365 | Z3291075268     |    | 397.1 | -46.9 | 2 | 96  | 0.41 | CHEMBL584332  |
| BRI-13366 | 366 | Z1733663560     |   | 398.2 | -40.0 | 1 | 100 | 0.46 | CHEMBL571323  |
| BRI-13367 | 367 | Z1984214773     |  | 339.2 | -38.4 | 1 | 100 | 0.40 | CHEMBL255681  |
| BRI-13368 | 368 | PV-001961067500 |  | 430.2 | -38.9 | 1 | 95  | 0.37 | CHEMBL2179755 |
| BRI-13369 | 369 | PV-002291621417 |  | 428.2 | -42.1 | 2 | 100 | 0.47 | CHEMBL3943326 |
| BRI-13370 | 370 | PV-001962076740 |  | 447.2 | -42.3 | 2 | 97  | 0.34 | CHEMBL3341878 |
| BRI-13371 | 371 | PV-002237735346 |  | 396.2 | -43.1 | 2 | 100 | 0.37 | CHEMBL551346  |

|           |     |                 |   |       |       |   |     |      |               |
|-----------|-----|-----------------|---|-------|-------|---|-----|------|---------------|
| BRI-13372 | 372 | PV-001943525291 |    | 376.1 | -46.4 | 2 | 100 | 0.42 | CHEMBL3912856 |
| BRI-13373 | 373 | PV-001961330897 |    | 449.2 | -40.2 | 1 | 100 | 0.40 | CHEMBL3086045 |
| BRI-13374 | 374 | PV-001948949294 |    | 410.2 | -40.0 | 1 | 100 | 0.40 | CHEMBL3928040 |
| BRI-13375 | 375 | PV-002301528868 |    | 419.2 | -39.7 | 2 | 100 | 0.46 | CHEMBL1085566 |
| BRI-13376 | 376 | PV-000027612529 |   | 395.2 | -35.9 | 3 | 100 | 0.44 | CHEMBL2071071 |
| BRI-13377 | 377 | PV-001744706024 |  | 324.2 | -35.1 | 3 | 94  | 0.43 | CHEMBL413775  |
| BRI-13378 | 378 | PV-001548699156 |  | 349.2 | -35.7 | 3 | 94  | 0.47 | CHEMBL568683  |
| BRI-13379 | 379 | PV-002313999485 |  | 437.2 | -40.1 | 1 | 90  | 0.43 | CHEMBL3933185 |
| BRI-13380 | 380 | Z2193904412     |  | 449.1 | -40.4 | 3 | 98  | 0.39 | CHEMBL508362  |
| BRI-13381 | 381 | Z3291011809     |  | 462.1 | -44.6 | 2 | 92  | 0.48 | CHEMBL2316380 |

|           |     |                 |  |       |       |   |     |      |               |
|-----------|-----|-----------------|--|-------|-------|---|-----|------|---------------|
| BRI-13382 | 382 | PV-002202560437 |  | 481.2 | -38.5 | 1 | 99  | 0.36 | CHEMBL255681  |
| BRI-13383 | 383 | PV-000394892590 |  | 339.2 | -38.2 | 1 | 100 | 0.48 | CHEMBL4079817 |
| BRI-13384 | 384 | PV-000002653403 |  | 392.2 | -36.4 | 3 | 99  | 0.40 | CHEMBL495528  |
| BRI-13385 | 385 | PV-000394893256 |  | 349.2 | -40.1 | 2 | 100 | 0.30 | CHEMBL4079817 |
| BRI-13386 | 386 | PV-001961486172 |  | 317.2 | -40.5 | 2 | 100 | 0.36 | CHEMBL3410730 |
| BRI-13387 | 387 | PV-000533613985 |  | 332.2 | -36.3 | 3 | 100 | 0.44 | CHEMBL3962321 |
| BRI-13388 | 388 | PV-001626138258 |  | 347.2 | -41.2 | 2 | 100 | 0.30 | CHEMBL2113257 |
| BRI-13390 | 390 | PV-000491819559 |  | 336.2 | -38.6 | 1 | 95  | 0.45 | CHEMBL373223  |
| BRI-13391 | 391 | PV-000920263702 |  | 383.2 | -38.6 | 3 | 95  | 0.45 | CHEMBL2071071 |
| BRI-13392 | 392 | PV-002634829747 |  | 340.2 | -40.5 | 3 | 91  | 0.52 | CHEMBL3109780 |
| BRI-13393 | 393 | Z1595398791     |  | 343.2 | -36.7 | 2 | 100 | 0.46 | CHEMBL2316410 |
| BRI-13394 | 394 | PV-000605863331 |  | 412.2 | -43.0 | 3 | 97  | 0.46 | CHEMBL2180222 |

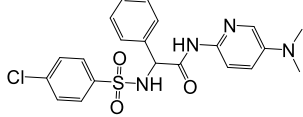
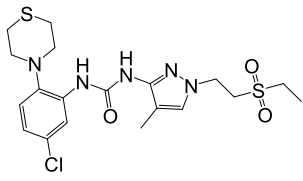
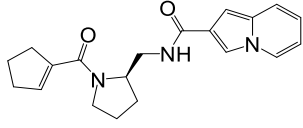
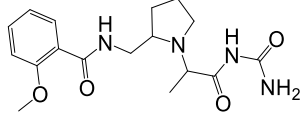
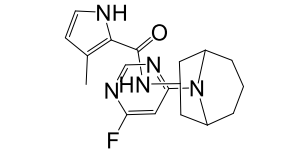
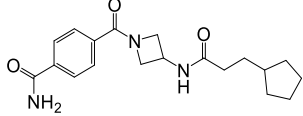
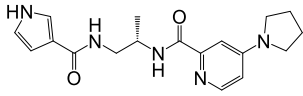
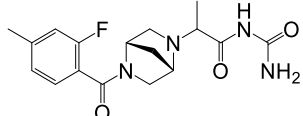
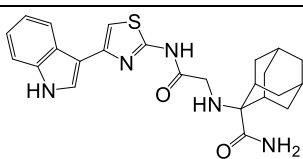
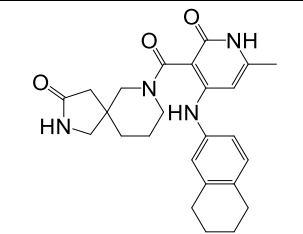
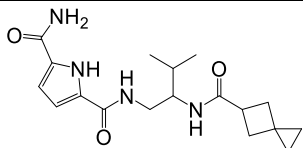
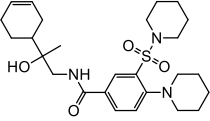
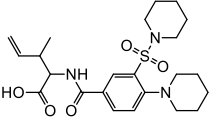
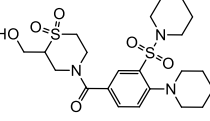
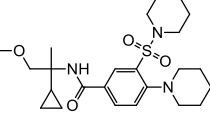
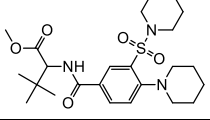
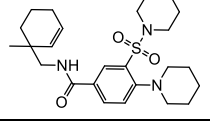
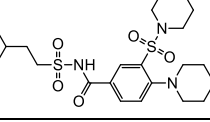
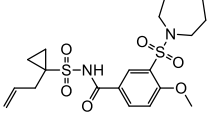
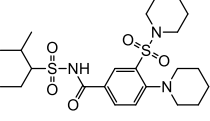
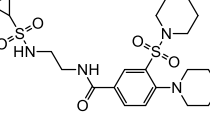
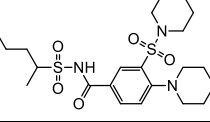
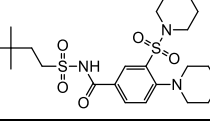
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|-----------|-----|---------------------|---|-------|-------|---|-----|------|---------------|
| BRI-13395 | 395 | PV-<br>002089418236 |    | 444.1 | -41.8 | 1 | 91  | 0.42 | CHEMBL395422  |
| BRI-13396 | 396 | PV-<br>002378036998 |    | 471.1 | -42.3 | 1 | 97  | 0.44 | CHEMBL2296779 |
| BRI-13397 | 397 | PV-<br>000520888167 |    | 337.2 | -35.4 | 3 | 100 | 0.51 | CHEMBL3919875 |
| BRI-13398 | 398 | PV-<br>000803663989 |    | 348.2 | -42.0 | 2 | 94  | 0.32 | CHEMBL3397445 |
| BRI-13399 | 399 | PV-<br>002652951344 |    | 343.2 | -40.8 | 3 | 98  | 0.48 | CHEMBL2071070 |
| BRI-13400 | 400 | PV-<br>001499049059 |   | 343.2 | -43.6 | 2 | 95  | 0.37 | CHEMBL488033  |
| BRI-13401 | 401 | PV-<br>001634150813 |  | 341.2 | -40.8 | 2 | 91  | 0.37 | CHEMBL4112489 |
| BRI-13402 | 402 | PV-<br>000831297441 |  | 348.2 | -38.2 | 3 | 91  | 0.46 | CHEMBL3956862 |
| BRI-13403 | 403 | PV-<br>002541052168 |  | 449.2 | -44.1 | 2 | 100 | 0.48 | CHEMBL2023583 |
| BRI-13404 | 404 | PV-<br>002593714190 |  | 434.2 | -43.6 | 2 | 91  | 0.41 | CHEMBL551462  |
| BRI-13405 | 405 | PV-<br>001583481983 |  | 346.2 | -33.9 | 3 | 100 | 0.44 | CHEMBL3962321 |



Table S3. Synthetized analogs (104) for V-SYNTHES hit compounds 523, 610, and 673.

| BRI_ID                   | ID  | Enamine_ID  | mol | MW    | Binding Score | Model | Purity, % | Tanimoto to |  | Closest ChEMbl ID |
|--------------------------|-----|-------------|-----|-------|---------------|-------|-----------|-------------|--|-------------------|
|                          |     |             |     |       |               |       |           | parent      | CB <sub>1</sub> /CB <sub>2</sub> ligands |                   |
| <b>BRI-13523 analogs</b> |     |             |     |       |               |       |           |             |  |                   |
| BRI-13701                | 701 | Z4886825499 |     | 499.6 | -32.9         | 1     | >95       | 0.14        | 0.42                                     | CHEMBL3906510     |
| BRI-13702                | 702 | Z4886825504 |     | 495.6 | -32.7         | 2     | >95       | 0.29        | 0.41                                     | CHEMBL248140      |
| BRI-13703                | 703 | Z4886825509 |     | 497.7 | -32.3         | 2     | >95       | 0.28        | 0.40                                     | CHEMBL248140      |
| BRI-13704                | 704 | Z4886924423 |     | 464.6 | -31.8         | 3     | >95       | 0.30        | 0.35                                     | CHEMBL2336535     |
| BRI-13705                | 705 | Z4886825517 |     | 479.6 | -31.6         | 1     | >95       | 0.11        | 0.40                                     | CHEMBL248140      |
| BRI-13706                | 706 | Z4886825521 |     | 500.6 | -31.2         | 2     | >95       | 0.15        | 0.36                                     | CHEMBL402137      |
| BRI-13707                | 707 | Z4886825525 |     | 491.6 | -30.6         | 2     | >95       | 0.18        | 0.30                                     | CHEMBL248140      |
| BRI-13729                | 729 | Z4886818373 |     | 475.6 | -40.5         | 2     | >95       | 0.25        | 0.33                                     | CHEMBL402137      |
| BRI-13730                | 730 | Z4886818380 |     | 499.6 | -39.8         | 1     | >95       | 0.30        | 0.40                                     | CHEMBL403628      |
| BRI-13731                | 731 | Z4886816116 |     | 483.6 | -39.3         | 2     | >95       | 0.04        | 0.38                                     | CHEMBL2336535     |

|           |     |             |  |       |       |   |      |      |      |               |
|-----------|-----|-------------|--|-------|-------|---|------|------|------|---------------|
| BRI-13732 | 732 | Z4886816119 |  | 495.6 | -37.7 | 2 | >95  | 0.30 | 0.37 | CHEMBL403628  |
| BRI-13733 | 733 | Z4886816121 |  | 469.7 | -36.7 | 1 | >95  | 0.26 | 0.35 | CHEMBL2336535 |
| BRI-13734 | 734 | Z4886818388 |  | 497.7 | -36.4 | 2 | >95  | 0.26 | 0.37 | CHEMBL403628  |
| BRI-13735 | 735 | Z4886816128 |  | 486.6 | -36.0 | 1 | >95  | 0.18 | 0.34 | CHEMBL248140  |
| BRI-13736 | 736 | Z4886816129 |  | 446.6 | -36.0 | 2 | >95  | 0.25 | 0.37 | CHEMBL2336547 |
| BRI-13737 | 737 | Z4886816131 |  | 456.6 | -35.4 | 2 | >95  | 0.23 | 0.37 | CHEMBL256749  |
| BRI-13738 | 738 | Z4886818395 |  | 447.6 | -35.4 | 1 | >95  | 0.25 | 0.30 | CHEMBL402137  |
| BRI-13739 | 739 | Z4886816147 |  | 484.6 | -35.0 | 1 | >95  | 0.18 | 0.34 | CHEMBL2336548 |
| BRI-13740 | 740 | Z4886818400 |  | 453.6 | -34.8 | 2 | >95  | 0.17 | 0.37 | CHEMBL2336535 |
| BRI-13741 | 741 | Z4886818402 |  | 477.6 | -34.7 | 1 | >95  | 0.30 | 0.36 | CHEMBL403628  |
| BRI-13742 | 742 | Z4886818404 |  | 446.6 | -34.6 | 3 | 90.3 | 0.29 | 0.37 | CHEMBL2336535 |
| BRI-13743 | 743 | Z4886816160 |  | 481.6 | -34.4 | 2 | >95  | 0.25 | 0.41 | CHEMBL2336535 |

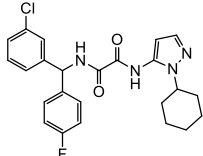
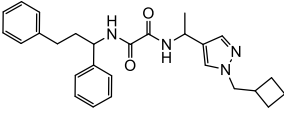
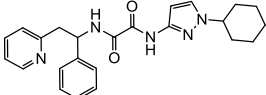
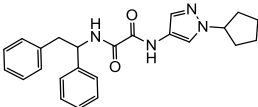
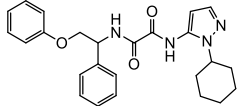
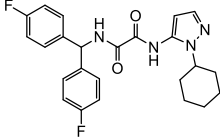
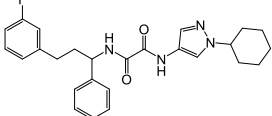
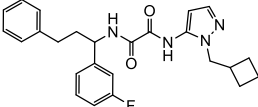
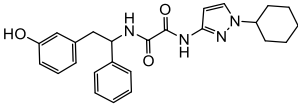
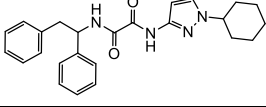
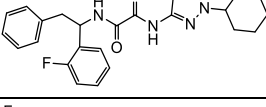
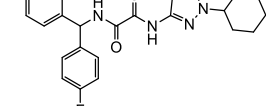
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|-----------|-----|-------------|---|-------|-------|---|------|------|------|---------------|
| BRI-13744 | 744 | Z4886818412 |    | 489.7 | -34.2 | 1 | 91.5 | 0.26 | 0.32 | CHEMBL403628  |
| BRI-13745 | 745 | Z4886818414 |    | 463.6 | -34.2 | 3 | >95  | 0.23 | 0.33 | CHEMBL403628  |
| BRI-13746 | 746 | Z4886818415 |    | 499.6 | -34.2 | 2 | 92.3 | 0.30 | 0.38 | CHEMBL2336535 |
| BRI-13747 | 747 | Z4886816179 |    | 463.6 | -34.1 | 2 | >95  | 0.28 | 0.33 | CHEMBL403628  |
| BRI-13748 | 748 | Z4886818417 |    | 479.6 | -33.8 | 2 | >95  | 0.30 | 0.35 | CHEMBL403628  |
| BRI-13749 | 749 | Z4886818418 |    | 459.6 | -33.7 | 2 | >95  | 0.21 | 0.30 | CHEMBL403628  |
| BRI-13750 | 750 | Z4886816202 |  | 485.7 | -33.2 | 2 | 93.5 | 0.07 | 0.36 | CHEMBL2336535 |
| BRI-13751 | 751 | Z4886816208 |  | 456.6 | -32.9 | 2 | >95  | 0.23 | 0.37 | CHEMBL256749  |
| BRI-13752 | 752 | Z4886818428 |  | 499.7 | -32.8 | 2 | >95  | 0.08 | 0.36 | CHEMBL2336535 |
| BRI-13753 | 753 | Z4886816220 |  | 498.7 | -32.5 | 2 | >95  | 0.19 | 0.39 | CHEMBL248140  |
| BRI-13754 | 754 | Z4886818436 |  | 485.7 | -32.5 | 2 | >95  | 0.08 | 0.36 | CHEMBL2336535 |
| BRI-13755 | 755 | Z4886816226 |  | 499.7 | -32.4 | 2 | >95  | 0.06 | 0.36 | CHEMBL2336535 |

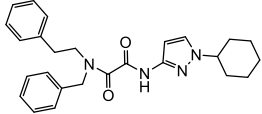
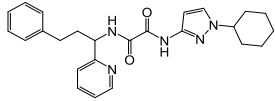
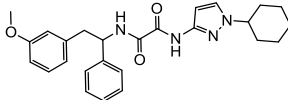
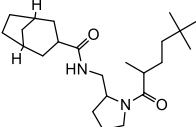
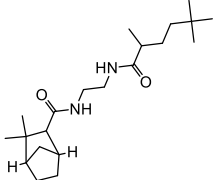
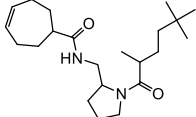
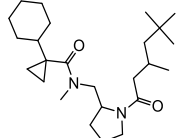
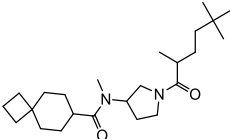
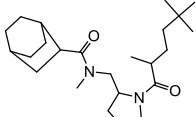
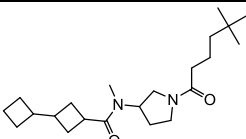
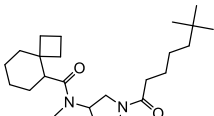


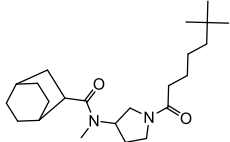
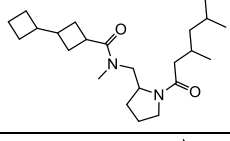
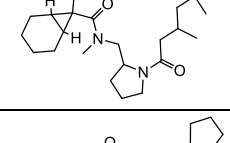
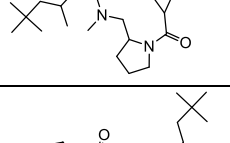
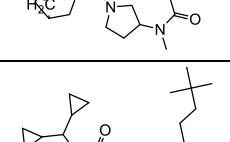
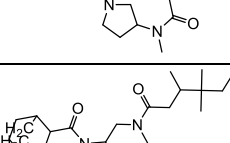
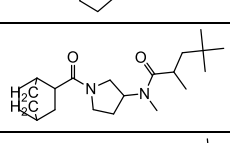
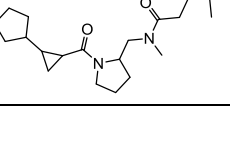

|           |     |             |  |       |       |   |      |      |      |               |
|-----------|-----|-------------|--|-------|-------|---|------|------|------|---------------|
| BRI-13756 | 756 | Z4886816234 |  | 454.6 | -32.3 | 2 | >95  | 0.19 | 0.32 | CHEMBL1668513 |
| BRI-13757 | 757 | Z4886816241 |  | 481.6 | -32.2 | 1 | >95  | 0.06 | 0.40 | CHEMBL248140  |
| BRI-13758 | 758 | Z4886816252 |  | 500.7 | -32.2 | 3 | >95  | 0.19 | 0.33 | CHEMBL402137  |
| BRI-13759 | 759 | Z4886818445 |  | 451.6 | -32.0 | 2 | 91.4 | 0.26 | 0.30 | CHEMBL402137  |
| BRI-13760 | 760 | Z649786252  |  | 483.6 | -31.1 | 2 | >95  | 0.25 | 0.36 | CHEMBL403628  |
| BRI-13761 | 761 | Z4886818449 |  | 467.6 | -30.9 | 2 | >95  | 0.17 | 0.36 | CHEMBL2336535 |
| BRI-13762 | 762 | Z4886818455 |  | 499.7 | -30.8 | 1 | >95  | 0.07 | 0.37 | CHEMBL2336535 |
| BRI-13763 | 763 | Z4886816294 |  | 453.6 | -30.6 | 2 | >95  | 0.17 | 0.37 | CHEMBL2336535 |
| BRI-13764 | 764 | Z4886816301 |  | 469.6 | -30.5 | 2 | >95  | 0.05 | 0.37 | CHEMBL248140  |
| BRI-13765 | 765 | Z4886816304 |  | 469.6 | -30.0 | 3 | >95  | 0.06 | 0.36 | CHEMBL248140  |
| BRI-13766 | 766 | Z2175374182 |  | 440.6 | -29.4 | 2 | >95  | 0.17 | 0.33 | CHEMBL403628  |
| BRI-13767 | 767 | Z2175373672 |  | 440.6 | -29.2 | 2 | >95  | 0.18 | 0.33 | CHEMBL403628  |

|                          |     |             |  |       |       |   |     |      |      |               |
|--------------------------|-----|-------------|--|-------|-------|---|-----|------|------|---------------|
| BRI-13768                | 768 | Z2175381372 |  | 440.6 | -29.0 | 1 | >95 | 0.19 | 0.36 | CHEMBL403628  |
| BRI-13769                | 769 | Z4886818480 |  | 481.6 | -28.7 | 2 | >95 | 0.19 | 0.39 | CHEMBL2336535 |
| BRI-13770                | 770 | Z2175381493 |  | 440.6 | -28.5 | 1 | >95 | 0.18 | 0.34 | CHEMBL403628  |
| <b>BRI-13610 analogs</b> |     |             |  |       |       |   |     |      |      |               |
| BRI-13708                | 708 | Z1538552259 |  | 438.5 | -36.5 | 3 | >95 | 0.26 | 0.31 | CHEMBL567297  |
| BRI-13709                | 709 | Z4121492321 |  | 466.6 | -36.3 | 3 | >95 | 0.26 | 0.40 | CHEMBL567297  |
| BRI-13710                | 710 | Z4121492356 |  | 445.5 | -35.0 | 3 | >95 | 0.25 | 0.41 | CHEMBL2316410 |
| BRI-13711                | 711 | Z4886924680 |  | 431.5 | -34.5 | 3 | >95 | 0.14 | 0.35 | CHEMBL567297  |
| BRI-13712                | 712 | Z4886924738 |  | 451.5 | -32.8 | 3 | >95 | 0.29 | 0.43 | CHEMBL567297  |
| BRI-13713                | 713 | Z1579740596 |  | 438.5 | -31.9 | 3 | >95 | 0.24 | 0.34 | CHEMBL567297  |
| BRI-13714                | 714 | Z4886924881 |  | 430.5 | -31.1 | 3 | >95 | 0.31 | 0.40 | CHEMBL567297  |
| BRI-13715                | 715 | Z4886924947 |  | 452.5 | -26.8 | 2 | >95 | 0.28 | 0.39 | CHEMBL3234698 |
| BRI-13716                | 716 | Z4886925010 |  | 416.5 | -25.5 | 3 | >95 | 0.20 | 0.39 | CHEMBL2316410 |
| BRI-13771                | 771 | Z2221890363 |  | 432.5 | -36.6 | 2 | >95 | 0.10 | 0.36 | CHEMBL567297  |

|           |     |             |  |       |       |   |     |      |      |               |
|-----------|-----|-------------|--|-------|-------|---|-----|------|------|---------------|
| BRI-13772 | 772 | Z4886816337 |  | 417.5 | -35.9 | 2 | >95 | 0.20 | 0.35 | CHEMBL567297  |
| BRI-13773 | 773 | Z1783021934 |  | 417.5 | -35.8 | 2 | >95 | 0.19 | 0.36 | CHEMBL567297  |
| BRI-13774 | 774 | Z1289963826 |  | 430.5 | -35.6 | 2 | >95 | 0.16 | 0.36 | CHEMBL567297  |
| BRI-13775 | 775 | Z2221889954 |  | 446.5 | -35.0 | 2 | >95 | 0.15 | 0.37 | CHEMBL567297  |
| BRI-13776 | 776 | Z4886818501 |  | 431.5 | -34.9 | 3 | >95 | 0.14 | 0.32 | CHEMBL567297  |
| BRI-13777 | 777 | Z4886818507 |  | 448.5 | -34.9 | 2 | >95 | 0.26 | 0.36 | CHEMBL4102128 |
| BRI-13780 | 780 | Z4886818523 |  | 434.5 | -33.7 | 2 | >95 | 0.23 | 0.40 | CHEMBL2316410 |
| BRI-13781 | 781 | Z4886816371 |  | 446.5 | -33.5 | 2 | >95 | 0.22 | 0.39 | CHEMBL567297  |
| BRI-13783 | 783 | Z2173483653 |  | 446.5 | -33.5 | 2 | >95 | 0.13 | 0.33 | CHEMBL567297  |
| BRI-13784 | 784 | Z1480332192 |  | 432.6 | -33.4 | 2 | >95 | 0.20 | 0.33 | CHEMBL567297  |
| BRI-13785 | 785 | Z1289888474 |  | 432.5 | -33.3 | 3 | >95 | 0.15 | 0.36 | CHEMBL567297  |
| BRI-13786 | 786 | Z4886818552 |  | 465.0 | -33.2 | 2 | >95 | 0.26 | 0.38 | CHEMBL4088509 |
| BRI-13787 | 787 | Z1289884410 |  | 416.5 | -33.0 | 3 | >95 | 0.11 | 0.31 | CHEMBL567297  |

|           |     |             |   |       |       |   |     |      |      |               |
|-----------|-----|-------------|---|-------|-------|---|-----|------|------|---------------|
| BRI-13788 | 788 | Z4886818555 |    | 454.9 | -32.9 | 3 | >95 | 0.16 | 0.32 | CHEMBL567297  |
| BRI-13789 | 789 | Z4886818558 |    | 444.6 | -32.8 | 2 | >95 | 0.24 | 0.35 | CHEMBL4098746 |
| BRI-13790 | 790 | Z1894264392 |    | 417.5 | -32.6 | 3 | >95 | 0.09 | 0.33 | CHEMBL567297  |
| BRI-13791 | 791 | Z4886818577 |    | 402.5 | -32.6 | 2 | >95 | 0.23 | 0.39 | CHEMBL2316410 |
| BRI-13792 | 792 | Z1290183067 |    | 432.5 | -32.5 | 2 | >95 | 0.20 | 0.39 | CHEMBL567297  |
| BRI-13793 | 793 | Z1290044889 |   | 438.5 | -32.4 | 3 | >95 | 0.13 | 0.32 | CHEMBL567297  |
| BRI-13794 | 794 | Z4886818591 |  | 448.5 | -32.2 | 2 | >95 | 0.23 | 0.40 | CHEMBL2316410 |
| BRI-13795 | 795 | Z4886818594 |  | 434.5 | -32.2 | 3 | >95 | 0.12 | 0.31 | CHEMBL567297  |
| BRI-13796 | 796 | Z1894516221 |  | 432.5 | -31.8 | 3 | >95 | 0.06 | 0.32 | CHEMBL567297  |
| BRI-13797 | 797 | Z1893268738 |  | 416.5 | -30.9 | 2 | >95 | 0.03 | 0.30 | CHEMBL567297  |
| BRI-13798 | 798 | Z1893860264 |  | 434.5 | -30.6 | 3 | >95 | 0.07 | 0.31 | CHEMBL567297  |
| BRI-13799 | 799 | Z1893499762 |  | 438.5 | -29.9 | 3 | >95 | 0.09 | 0.34 | CHEMBL567297  |

|                          |     |             |   |       |       |   |      |      |      |              |
|--------------------------|-----|-------------|---|-------|-------|---|------|------|------|--------------|
| BRI-13800                | 800 | Z1893379869 |    | 430.5 | -29.7 | 2 | >95  | 0.13 | 0.38 | CHEMBL567297 |
| BRI-13801                | 801 | Z4886818606 |    | 431.5 | -28.6 | 3 | >95  | 0.09 | 0.36 | CHEMBL567297 |
| BRI-13803                | 803 | Z1894051580 |    | 446.5 | -27.1 | 3 | >95  | 0.09 | 0.35 | CHEMBL567297 |
| <b>BRI-13673 analogs</b> |     |             |   |       |       |   |      |      |      |              |
| BRI-13723                | 723 | Z4886925912 |    | 376.6 | -30.4 | 3 | 93.4 | 0.21 | 0.48 | CHEMBL122884 |
| BRI-13726                | 726 | Z4886926284 |    | 350.5 | -27.1 | 3 | >95  | 0.23 | 0.44 | CHEMBL122884 |
| BRI-13728                | 728 | Z4886926555 |   | 362.5 | -24.2 | 2 | >95  | 0.25 | 0.30 | CHEMBL122884 |
| BRI-13804                | 804 | Z4886818613 |  | 404.6 | -26.0 | 2 | >95  | 0.40 | 0.39 |              |
| BRI-13806                | 806 | Z4886818620 |  | 390.6 | -25.2 | 2 | >95  | 0.43 | 0.43 | CHEMBL484392 |
| BRI-13808                | 808 | Z4886818622 |  | 390.6 | -24.3 | 1 | >95  | 0.19 | 0.49 | CHEMBL373223 |
| BRI-13809                | 809 | Z4886818625 |  | 362.5 | -24.3 | 1 | >95  | 0.43 | 0.41 | CHEMBL15948  |
| BRI-13811                | 811 | Z4886818632 |  | 390.6 | -24.2 | 1 | >95  | 0.38 | 0.44 | CHEMBL484392 |

|           |     |             |   |       |       |   |      |      |      |              |
|-----------|-----|-------------|---|-------|-------|---|------|------|------|--------------|
| BRI-13812 | 812 | Z4886818633 |    | 376.6 | -23.9 | 2 | >95  | 0.22 | 0.51 | CHEMBL373223 |
| BRI-13813 | 813 | Z4886818635 |    | 376.6 | -23.4 | 1 | 92   | 0.41 | 0.39 | CHEMBL15948  |
| BRI-13817 | 817 | Z4886818652 |    | 394.6 | -22.6 | 2 | >95  | 0.43 | 0.53 | CHEMBL484392 |
| BRI-13851 | 851 | Z4886818614 |    | 390.6 | -25.4 | 0 | >95  | 0.41 | 0.39 | CHEMBL15948  |
| BRI-13852 | 852 | Z4886818621 |    | 362.5 | -24.9 | 0 | >95  | 0.22 | 0.50 | CHEMBL373223 |
| BRI-13853 | 853 | Z4886818631 |  | 376.6 | -27.1 | 0 | >95  | 0.43 | 0.39 | CHEMBL140773 |
| BRI-13854 | 854 | Z4886818643 |  | 390.6 | -26.5 | 0 | >95  | 0.19 | 0.49 | CHEMBL373223 |
| BRI-13855 | 855 | Z4886818658 |  | 362.5 | -26.2 | 0 | 94.5 | 0.21 | 0.51 | CHEMBL373223 |
| BRI-13856 | 856 | Z4886818665 |  | 390.6 | -25.1 | 0 | >95  | 0.39 | 0.39 | CHEMBL15948  |

*Table S4. Assessment of antagonist potencies for series of analogs of V-SYNTHES hit antagonists 523 (except those shown in Extended Data Table 2), 610 and 673, which showed potency with  $K_i < 10\mu\text{M}$  in Tango antagonist assays.*

| #                                     | PDSP-ID | CB1 Antagonist potency |           | CB2 Antagonist potency |           | Tanimoto |                 |
|---------------------------------------|---------|------------------------|-----------|------------------------|-----------|----------|-----------------|
|                                       |         | Ki, nM                 | 95% CI    | Ki, nM                 | 95% CI    | Parent   | CB1/CB2 ligands |
| <b>523 analogs (see also Table 2)</b> |         |                        |           |                        |           |          |                 |
| 704                                   | 59013   | 858                    | 670-1094  | 1021                   | 808-1291  | 0.30     | 0.35            |
| 730                                   | 59027   | 6342                   | 5031-8122 | 5472                   | 4378-6898 | 0.30     | 0.40            |
| 744                                   | 59041   | 438                    | 367-522   | 925                    | 784-1093  | 0.26     | 0.32            |
| 748                                   | 59045   | 629                    | 526-750   | 648                    | 559-750   | 0.30     | 0.35            |
| 752                                   | 59049   | 5261                   | 4151-6771 | 4429                   | 3506-5646 | 0.08     | 0.36            |
| 757                                   | 59054   | 6257                   | 4618-8717 | N/D                    | N/D       | 0.06     | 0.40            |
| 758                                   | 59055   | 1678                   | 1362-2063 | 2569                   | 1960-3380 | 0.19     | 0.33            |
| <b>610 analogs</b>                    |         |                        |           |                        |           |          |                 |
| 708                                   | 59017   | 1183                   | 598-2517  | N/D                    | N/D       | 0.26     | 0.31            |
| 713                                   | 59020   | 331                    | 123-916   | N/D                    | N/D       | 0.24     | 0.34            |
| 772                                   | 59069   | 220                    | 138-354   | 167                    | 60.0-419  | 0.20     | 0.35            |
| 773                                   | 59070   | 208                    | 146-297   | 307                    | 147-637   | 0.19     | 0.36            |
| 774                                   | 59071   | 825                    | 706-963   | 3261                   | 2597-4125 | 0.16     | 0.36            |
| 777                                   | 59074   | 3185                   | 2515-4052 | N/D                    | N/D       | 0.26     | 0.36            |
| 781                                   | 59075   | 1521                   | 1233-1869 | 2372                   | 1683-3332 | 0.22     | 0.39            |
| 784                                   | 59077   | 637                    | 521-775   | 2571                   | 2115-3134 | 0.20     | 0.33            |
| 785                                   | 59167   | 204                    | 161-257   | 101                    | 39.5-254  | 0.15     | 0.36            |
| 786                                   | 59078   | 285                    | 135-599   | N/D                    | N/D       | 0.26     | 0.38            |
| 787                                   | 59079   | 202                    | 148-274   | 167                    | 72.2-388  | 0.11     | 0.31            |
| 788                                   | 59080   | 332                    | 226-485   | 1527                   | 819-2989  | 0.16     | 0.32            |
| 789                                   | 59081   | 494                    | 242-1059  | N/D                    | N/D       | 0.24     | 0.35            |
| 792                                   | 59082   | 673                    | 558-811   | 4050                   | 3171-5221 | 0.20     | 0.39            |
| 793                                   | 59083   | 45.5                   | 24.3-84.7 | N/D                    | N/D       | 0.13     | 0.32            |
| 794                                   | 59084   | 208                    | 89-456    | N/D                    | N/D       | 0.23     | 0.40            |
| 795                                   | 59085   | 1205                   | 908-1600  | 3279                   | 1455-9984 | 0.12     | 0.31            |
| 796                                   | 59170   | 286                    | 221-367   | 426                    | 294-610   | 0.06     | 0.32            |
| 797                                   | 59086   | 220                    | 132-362   | 71                     | 19.0-193  | 0.03     | 0.30            |
| 798                                   | 59087   | 589                    | 467-742   | 1160                   | 751-1818  | 0.07     | 0.31            |
| 799                                   | 59088   | 143                    | 105-194   | 149                    | 78.0-290  | 0.09     | 0.34            |
| 800                                   | 59089   | 838                    | 663-1063  | 2222                   | 1818-2724 | 0.13     | 0.38            |
| 801                                   | 59090   | 736                    | 576-935   | 2990                   | 1548-6440 | 0.09     | 0.36            |
| 803                                   | 59091   | 237                    | 105-556   | N/D                    | N/D       | 0.09     | 0.35            |
| <b>673 analogs</b>                    |         |                        |           |                        |           |          |                 |
| 723                                   | 59023   | 692                    | 566-843   | 2724                   | 2158-3449 | 0.21     | 0.48            |
| 726                                   | 59024   | 416                    | 344-503   | 1128                   | 937-1356  | 0.23     | 0.44            |

|     |       |      |           |      |           |      |      |
|-----|-------|------|-----------|------|-----------|------|------|
| 728 | 59025 | 1522 | 1168-1978 | 6100 | 4687-8057 | 0.25 | 0.30 |
| 804 | 59171 | 585  | 486-702   | 2259 | 1817-2816 | 0.40 | 0.39 |
| 806 | 59092 | 429  | 365-503   | 1522 | 1296-1787 | 0.43 | 0.43 |
| 809 | 59094 | 1209 | 1004-1453 | 2102 | 1633-2707 | 0.43 | 0.41 |
| 811 | 59095 | 559  | 468-666   | 1400 | 1068-1837 | 0.38 | 0.44 |
| 812 | 59096 | 1043 | 854-1273  | 1825 | 1376-2423 | 0.22 | 0.51 |
| 813 | 59097 | 432  | 360-518   | 742  | 577-952   | 0.41 | 0.39 |
| 817 | 59098 | 749  | 598-937   | 1489 | 1199-1849 | 0.43 | 0.53 |
| 851 | 59128 | 371  | 307-446   | 933  | 743-1171  | 0.41 | 0.39 |
| 852 | 59129 | 972  | 791-1190  | 3001 | 2322-3906 | 0.22 | 0.50 |
| 853 | 59130 | 1407 | 1148-1722 | 5155 | 3845-7036 | 0.43 | 0.39 |
| 854 | 59131 | 417  | 343-506   | 1410 | 1108-1796 | 0.19 | 0.49 |
| 855 | 59132 | 2020 | 1627-2509 | N/D  | N/D       | 0.21 | 0.51 |
| 856 | 59133 | 378  | 311-457   | 884  | 707-1106  | 0.39 | 0.39 |