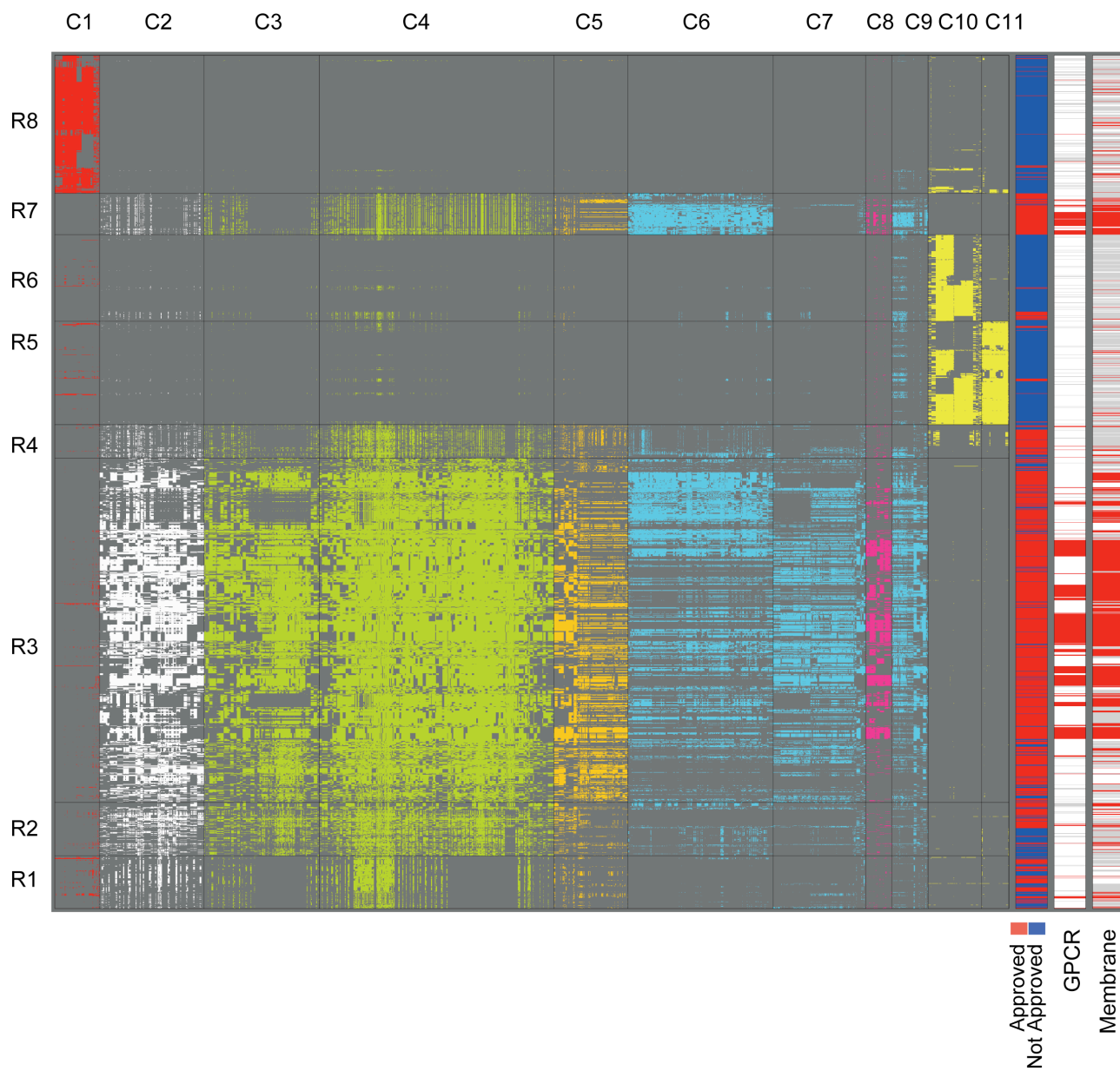
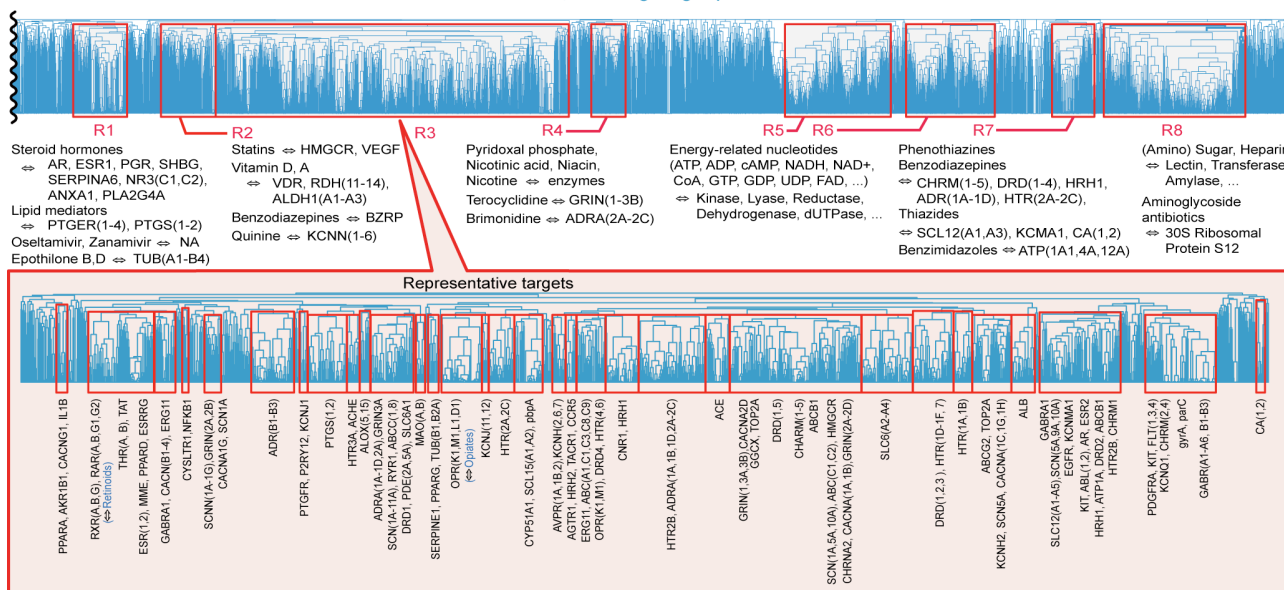


Supplementary Figures & Tables

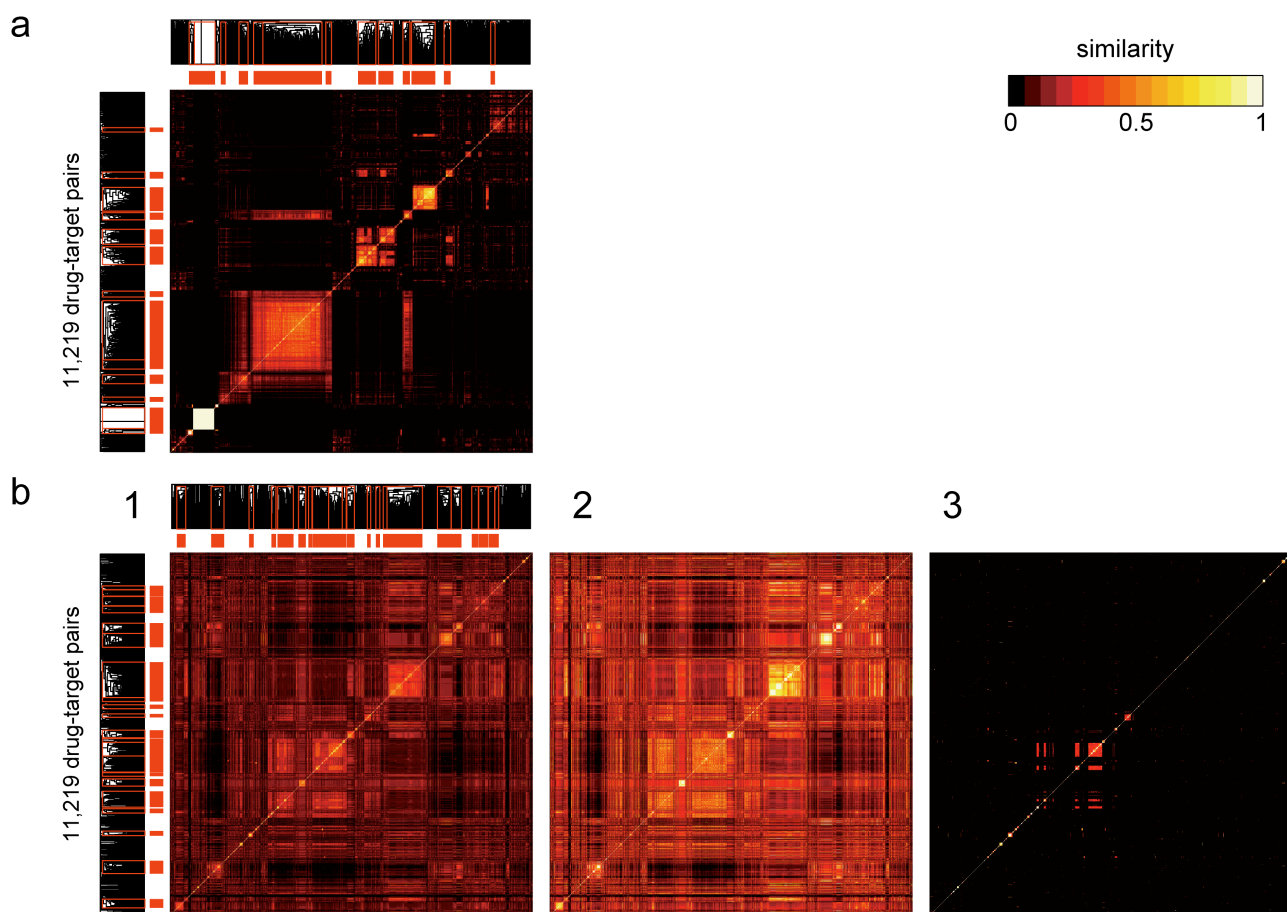


Supplementary Figure 1: An enlargement of the matrix of Fig.3, including all major clusters of both significant substructure pairs and drug-target pairs. From left to right on the three columns on the right-hand side of the matrix, in the first column, an element is colored red if the corresponding drug-target pair has an approved drug; otherwise blue. In the middle column, an element is colored red if the corresponding drug-target pair has GPCR; otherwise blue. In the right column, an element colored red if the target of the corresponding drug-target pair is a membrane protein; otherwise blue.

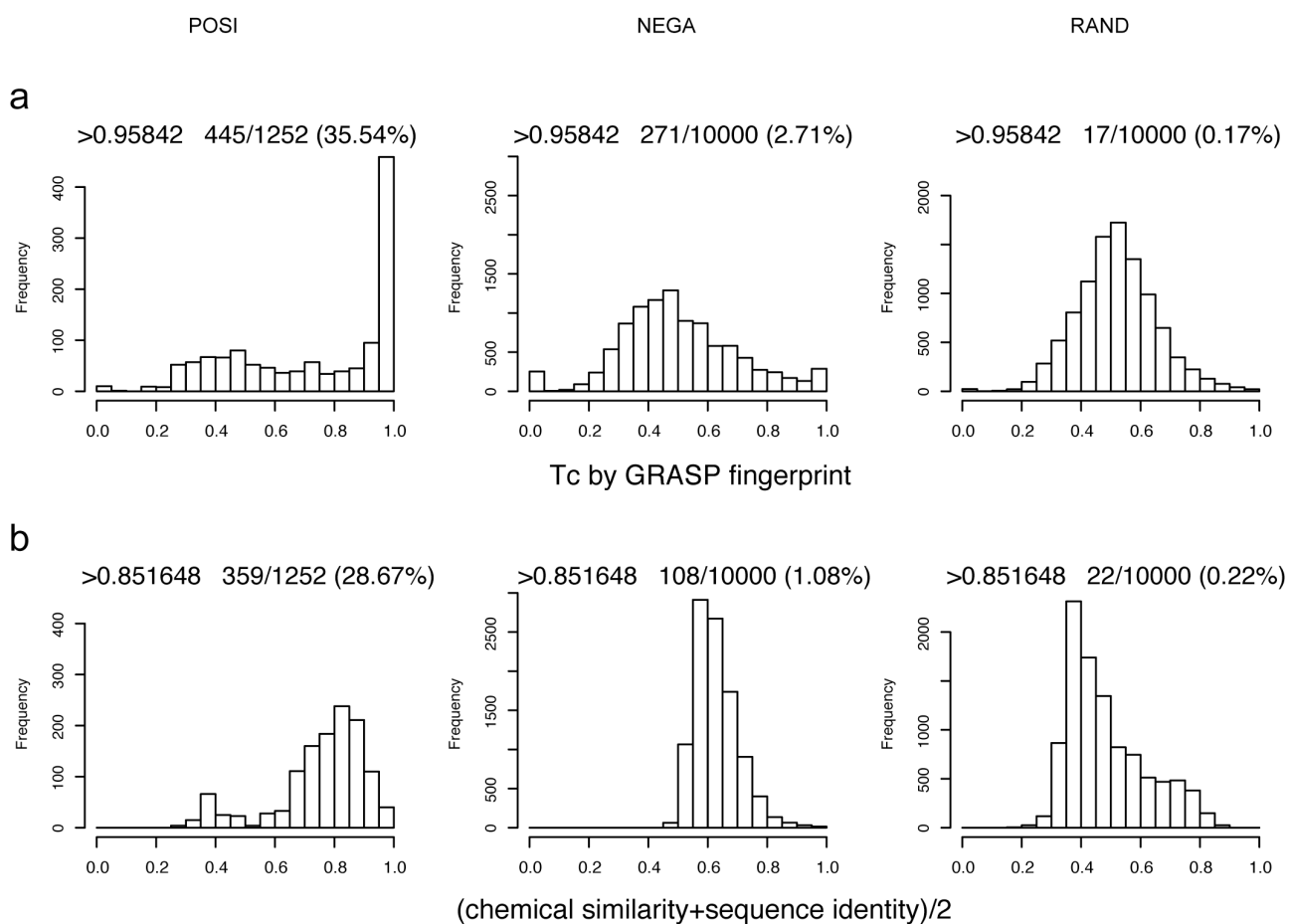
11,219 drug-target pairs



Supplementary Figure 2: Hierarchical clustering on drug-target pairs where R1 to R8 are specified with brief descriptions on representative drug-target pairs or targets.



Supplementary Figure 3: Symmetric heatmaps of similarities among 11,219 drug-target pairs in terms of (a) GRASP fingerprints, (b-1) compound similarity plus sequence identity, (b-2) compound similarity only and (b-3) sequence identity only, where a brighter dot shows a higher similarity. In (a) the order of drug-target pairs in rows follows that of Fig. 2 of the main text. In (b-1), the order of drug-target pairs in rows is arranged so that the most similar pair in terms of compound similarity plus sequence identity should be as nearest as possible. In (b-2) and (b-3), the order of drug-target pairs in rows follows that of (b-1).



Supplementary Figure 4: (a) Distributions of highest Tc of compound-protein pairs in POSI, NEGA and RAND, when the Tc was computed between the GRASP fingerprints of two pairs. (b) Distributions of highest similarities of compound-protein pairs in POSI, NEGA and RAND, when the similarity is given by compound similarity plus sequence identity.

Supplementary Table 1: For each of R1 to R8, (a) the number of drug-target pairs, (b) the number of drug-target pairs which gave the highest Tc of larger than 0.95 for pairs in POSI and (c) the number of drug-target pairs which gave the highest Tc of larger than 0.95 for pairs in MASS.

| | R1 | R2 | R3 | R4 | R5 | R6 | R7 | R8 | other | Total |
|--|------------------|-------------------|---------------------|-----------------|-----------------|-----------------|---------------------|-------------------|-------------------|---------------------|
| #drug-target pairs | 283 (2.52%) | 287 (2.56%) | 1,848 (16.47%) | 180 (1.60%) | 555 (4.95%) | 465 (4.14%) | 222 (1.98%) | 741 (6.60%) | 6,638 (59.17%) | 11,219 (100%) |
| #drug-target pairs with highest Tc > 0.95 for POSI | 17 (7.30%) | 6 (2.58%) | 3 (1.29%) | 2 (0.86%) | 7 (3.00%) | 11 (4.72%) | 0 (0%) | 40 (17.17%) | 147 (63.09%) | 233 (100%) |
| #drug-target pairs with highest Tc > 0.95 for MASS | 9,865 (0.85%) | 29,696 (2.56%) | 928,957 (79.97%) | 186 (0.016%) | 129 (0.011%) | 134 (0.012%) | 147,531 (12.70%) | 10,874 (0.93%) | 34,241 (2.95%) | 1,161,613 (100%) |

Supplementary Table 2: The number of drug-target pairs with the number of drugs and targets in each of R1 to R8.

| Cluster | R1 | R2 | R3 | R4 | R5 | R6 | R7 | R8 |
|---|----------------|----------------|-----------------|---------------|----------------|----------------|--------------|----------------|
| #pairs (#drugs, #targets) | 283 (154, 149) | 287 (136, 204) | 1848 (840, 540) | 180 (63, 146) | 555 (138, 406) | 465 (135, 333) | 222 (88,84) | 741 (219, 413) |
| #pairs (#drugs, #targets) of promiscuous drugs only | 205 (76, 111) | 216 (65, 178) | 1451 (443, 462) | 140 (23, 125) | 508 (91, 393) | 419 (89, 324) | 176 (42, 66) | 621 (99, 379) |

Supplementary Table 3: The most related 30 GO terms with each of R1 to R8. The most right column shows the value of the number of genes in both the corresponding cluster and the corresponding GO term divided by the number of genes in the corresponding GO term.

| R1 | | | | |
|--------------------|----------|---------------|--|-------------|
| | P value | GO | Description | Rate |
| molecular function | 1.17e-05 | 0004879 | ligand-dependent nuclear receptor activity | 11/30 |
| | 3.7e-05 | 0003707 | steroid hormone receptor activity | 10/28 |
| | 3.7e-05 | 0043565 | sequence-specific DNA binding | 11/35 |
| | 5.17e-05 | 0005496 | steroid binding | 9/23 |
| | 0.000433 | 0003700 | transcription factor activity | 11/46 |
| | 0.000433 | 0004872 | receptor activity | 27/257 |
| | 0.0016 | 0004957 | prostaglandin E receptor activity | 4/5 |
| | 0.0016 | 0004953 | icosanoid receptor activity | 5/9 |
| | 0.0016 | 0004954 | prostanoid receptor activity | 5/9 |
| | 0.00486 | 0003924 | GTPase activity | 7/25 |
| | 0.00486 | 0015926 | glucosidase activity | 3/3 |
| | 0.00486 | 0004558 | alpha-glucosidase activity | 3/3 |
| | 0.00535 | 0003677 | DNA binding | 13/86 |
| | 0.00585 | 0004955 | prostaglandin receptor activity | 4/7 |
| 0.00831 | 0008289 | lipid binding | 13/91 | |
| | P value | GO | Description | Rate |
| biological process | 2.62e-06 | 0007018 | microtubule-based movement | 8/11 |
| | 3.78e-06 | 0030705 | cytoskeleton-dependent intracellular transport | 8/12 |
| | 3.7e-05 | 0007017 | microtubule-based process | 8/16 |
| | 7.0e-05 | 0051258 | protein polymerization | 7/13 |
| | 0.00278 | 0008610 | lipid biosynthetic process | 13/79 |
| | 0.00535 | 0044255 | cellular lipid metabolic process | 19/175 |
| | 0.0058 | 0007010 | cytoskeleton organization and biogenesis | 9/44 |
| | 0.0101 | 0032774 | RNA biosynthetic process | 13/94 |
| | 0.0101 | 0006351 | transcription, DNA-dependent | 13/94 |
| | | P value | GO | Description |
| cellular component | 0.000157 | 0005874 | microtubule | 8/20 |
| | 0.0016 | 0044430 | cytoskeleton#cytoskeletal part | 9/36 |
| | 0.0016 | 0015630 | microtubule cytoskeleton | 8/28 |
| | 0.00452 | 0005856 | cytoskeleton | 11/61 |
| | 0.0085 | 0042598 | vesicular fraction | 9/47 |
| | 0.0085 | 0005792 | microsome | 9/47 |

| R2 | | | | | |
|--------------------|--------------------|--|--|---------------------------------------|------|
| | P value | GO | Description | Rate | |
| molecular function | 0.00258 | 0020037 | heme binding | 11/39 | |
| | 0.00258 | 0046906 | tetrapyrrole binding | 11/39 | |
| | 0.0134 | 0005506 | iron ion binding | 16/103 | |
| | 0.0307 | 0016709 | oxidoreductase activity, acting on paired donors, with incorporation or reduction of molecular oxygen, NADH or NADPH as one donor, and incorporation of one atom of oxygen | 5/10 | |
| | 0.0318 | 0004745 | retinol dehydrogenase activity | 4/6 | |
| | 0.0318 | 0005497 | androgen binding | 3/3 | |
| | 0.0413 | 0008236 | serine-type peptidase activity | 9/39 | |
| | 0.0413 | 0017171 | serine hydrolase activity | 9/40 | |
| | -0.0413 | 0016740 | transferase activity | 5/322 | |
| | -0.0503 | 0032555 | purine ribonucleotide binding | 4/285 | |
| | -0.0503 | 0032553 | ribonucleotide binding | 4/285 | |
| | 0.0523 | 0016705 | oxidoreductase activity, acting on paired donors, with incorporation or reduction of molecular oxygen | 10/53 | |
| | 0.0523 | 0004252 | serine-type endopeptidase activity | 8/36 | |
| | 0.0557 | 0008233 | peptidase activity | 13/90 | |
| | 0.0584 | 0004954 | prostanoid receptor activity | 4/9 | |
| | 0.0584 | 0004953 | icosanoid receptor activity | 4/9 | |
| | 0.0596 | 0004175 | endopeptidase activity | 11/66 | |
| | 0.0634 | 0004879 | ligand-dependent nuclear receptor activity | 7/30 | |
| | | P value | GO | Description | Rate |
| | biological process | 0.000159 | 0006775 | fat-soluble vitamin metabolic process | 8/13 |
| 0.00258 | | 0006776 | vitamin A metabolic process | 6/10 | |
| 0.0413 | | 0065008 | regulation of biological quality | 23/195 | |
| 0.0441 | | 0006766 | vitamin metabolic process | 9/41 | |
| 0.0469 | | 0050878 | regulation of body fluid levels | 9/42 | |
| 0.0469 | | 0050817 | coagulation | 8/34 | |
| 0.0469 | | 0007596 | blood coagulation | 8/34 | |
| 0.0523 | | 0007599 | hemostasis | 8/36 | |
| 0.0584 | | 0006720 | isoprenoid metabolic process | 4/9 | |
| 0.0584 | 0001763 | morphogenesis of a branching structure | 4/9 | | |
| | P value | GO | Description | Rate | |
| cellular component | 0.0318 | 0044421 | extracellular region#extracellular region part | 15/101 | |
| | 0.0523 | 0005615 | extracellular space | 13/89 | |

| R3 | | | | |
|--------------------|----------|----------|--|-------------|
| | P value | GO | Description | Rate |
| molecular function | 8.41e-26 | 0004872 | receptor activity | 139/257 |
| | 4.17e-25 | 0004871 | signal transducer activity | 158/313 |
| | 4.17e-25 | 0060089 | molecular transducer activity | 158/313 |
| | 1.52e-23 | 0001584 | rhodopsin-like receptor activity | 69/95 |
| | 1.76e-23 | 0004888 | transmembrane receptor activity | 109/188 |
| | 6.16e-21 | 0004930 | G-protein coupled receptor activity | 72/107 |
| | 4.38e-19 | 0008227 | amine receptor activity | 34/35 |
| | 8.27e-16 | 0022836 | gated channel activity | 62/97 |
| | 1.22e-14 | 0015075 | ion transmembrane transporter activity | 86/160 |
| | 5.37e-14 | 0046873 | metal ion transmembrane transporter activity | 52/79 |
| | 5.37e-14 | 0022803 | passive transmembrane transporter activity | 64/107 |
| | 5.37e-14 | 0015267 | channel activity | 64/107 |
| | 7.09e-14 | 0005216 | ion channel activity | 63/105 |
| | 1.43e-13 | 0022838 | substrate specific channel activity | 63/106 |
| | 2.86e-13 | 0005261 | cation channel activity | 48/72 |
| | 4.11e-13 | 0022843 | voltage-gated cation channel activity | 35/45 |
| | | P value | GO | Description |
| biological process | 2.87e-19 | 0007166 | cell surface receptor linked signal transduction | 128/254 |
| | 5.45e-19 | 0007186 | G-protein coupled receptor protein signaling pathway | 86/145 |
| | 1.03e-15 | 0007154 | cell communication | 208/523 |
| | 8.93e-15 | 0019932 | second-messenger-mediated signaling | 56/86 |
| | 9.75e-14 | 0007165 | signal transduction | 182/452 |
| | 7.25e-13 | 0006811 | ion transport | 85/165 |
| | | P value | GO | Description |
| cellular component | 1.44e-28 | 0005886 | plasma membrane | 212/453 |
| | 2.59e-28 | 0044459 | plasma membrane part | 179/357 |
| | 2.36e-27 | 0005887 | integral to plasma membrane | 149/278 |
| | 2.36e-27 | 0031226 | intrinsic to plasma membrane | 149/278 |
| | 3.24e-25 | 0016021 | integral to membrane | 223/509 |
| | 4.17e-25 | 0031224 | intrinsic to membrane | 223/510 |
| | 3.02e-18 | 0044425 | membrane#membrane part | 243/624 |
| 8.27e-16 | 0016020 | membrane | 275/760 | |

R4

| | P value | GO | Description | Rate |
|--------------------|----------|---------|---|--------|
| molecular function | 3.24e-57 | 0048037 | cofactor binding | 45/111 |
| | 3.12e-52 | 0030170 | pyridoxal phosphate binding | 42/44 |
| | 8.79e-32 | 0019842 | vitamin binding | 43/89 |
| | 9.89e-27 | 0016769 | transferase activity, transferring nitrogenous groups | 25/29 |
| | 5.57e-22 | 0008483 | transaminase activity | 20/22 |
| | 3.3e-09 | 0016829 | lyase activity | 21/69 |
| | 1.27e-07 | 0005231 | excitatory extracellular ligand-gated ion channel activity | 13/29 |
| | 2.88e-06 | 0004972 | N-methyl-D-aspartate selective glutamate receptor activity | 6/6 |
| | 2.88e-06 | 0004889 | nicotinic acetylcholine-activated cation-selective channel activity | 6/6 |
| | 3.05e-06 | 0016831 | carboxy-lyase activity | 9/16 |
| | 3.6e-06 | 0005230 | extracellular ligand-gated ion channel activity | 13/38 |
| | 1.03e-05 | 0016740 | transferase activity | 38/322 |
| | 2.15e-05 | 0043176 | amine binding | 10/25 |
| | 2.34e-05 | 0016830 | carbon-carbon lyase activity | 9/20 |
| | 3.81e-05 | 0022834 | ligand-gated channel activity | 13/47 |
| | 3.81e-05 | 0015276 | ligand-gated ion channel activity | 13/47 |
| | 9.28e-05 | 0016846 | carbon-sulfur lyase activity | 6/9 |
| | P value | GO | Description | Rate |
| biological process | 7.9e-07 | 0006519 | amino acid and derivative metabolic process | 29/195 |
| | 8.87e-06 | 0006807 | nitrogen compound metabolic process | 30/224 |
| | 2.34e-05 | 0009308 | amine metabolic process | 28/209 |
| | 6.27e-05 | 0009069 | serine family amino acid metabolic process | 8/17 |
| | 7.84e-05 | 0006520 | amino acid metabolic process | 23/163 |
| | 0.000237 | 0019752 | carboxylic acid metabolic process | 31/266 |
| | 0.000255 | 0006082 | organic acid metabolic process | 31/267 |
| | P value | GO | Description | Rate |
| cellular component | 2.88e-06 | 0044456 | synapse#synapse part | 15/50 |
| | 7.11e-06 | 0045211 | postsynaptic membrane | 14/47 |
| | 7.84e-05 | 0043235 | receptor complex | 9/23 |
| | 0.000142 | 0030054 | cell junction | 15/70 |
| | 0.00036 | 0008328 | integral to plasma membrane#ionotropic glutamate receptor complex | 4/4 |
| | 0.00036 | 0017146 | N-methyl-D-aspartate selective glutamate receptor complex | 4/4 |

R5

| | P value | GO | Description | Rate |
|--------------------|----------|---------|---|----------|
| molecular function | 1.9e-11 | 0000166 | nucleotide binding | 62/322 |
| | 5.6e-11 | 0030554 | adenyl nucleotide binding | 54/267 |
| | 8.88e-10 | 0017076 | purine nucleotide binding | 57/305 |
| | 2.06e-09 | 0032559 | adenyl ribonucleotide binding | 49/247 |
| | 2.65e-08 | 0032555 | purine ribonucleotide binding | 52/285 |
| | 2.65e-08 | 0032553 | ribonucleotide binding | 52/285 |
| | 3.71e-06 | 0005524 | ATP binding | 43/239 |
| | 6.99e-05 | 0016208 | AMP binding | 6/6 |
| | 0.000779 | 0016740 | transferase activity | 48/322 |
| | 0.00152 | 0009055 | electron carrier activity | 19/88 |
| | 0.00256 | 0016301 | kinase activity | 26/143 |
| | 0.00322 | 0016772 | transferase activity, transferring phosphorus-containing groups | 28/161 |
| | 0.006 | 0008146 | sulfotransferase activity | 5/7 |
| | 0.00903 | 0016773 | phosphotransferase activity, alcohol group as acceptor | 23/130 |
| | 0.0141 | 0030551 | cyclic nucleotide binding | 4/5 |
| | P value | GO | Description | Rate |
| biological process | 8.71e-05 | 0005975 | carbohydrate metabolic process | 27/132 |
| | 0.0008 | 0044262 | cellular carbohydrate metabolic process | 22/106 |
| | 0.00322 | 0055086 | nucleobase, nucleoside and nucleotide metabolic process | 16/71 |
| | 0.00322 | 0006164 | purine nucleotide biosynthetic process | 9/22 |
| | 0.00758 | 0006163 | purine nucleotide metabolic process | 9/25 |
| | 0.00758 | 0006091 | generation of precursor metabolites and energy | 29/178 |
| | 0.0103 | 0044237 | cellular metabolic process | 106/1011 |
| | 0.0154 | 0016310 | phosphorylation | 26/159 |
| | P value | GO | Description | Rate |
| cellular component | 0.000893 | 0005622 | intracellular | 110/1010 |
| | 0.00447 | 0044424 | intracellular#intracellular part | 106/990 |
| | -0.00581 | 0005887 | integral to plasma membrane | 6/278 |
| | -0.00581 | 0031226 | intrinsic to plasma membrane | 6/278 |
| | 0.00653 | 0044446 | intracellular organelle#intracellular organelle part | 48/350 |
| | 0.00758 | 0044422 | organelle#organelle part | 48/353 |
| | -0.0229 | 0044459 | plasma membrane part | 13/357 |

R6

| | P value | GO | Description | Rate |
|--------------------|-----------|--|---|--------|
| molecular function | 1.48e-14 | 0016614 | oxidoreductase activity, acting on CH-OH group of donors | 24/75 |
| | 2.42e-11 | 0016491 | oxidoreductase activity | 51/302 |
| | 2.14e-10 | 0050662 | coenzyme binding | 23/61 |
| | 6.91e-10 | 0016616 | oxidoreductase activity, acting on the CH-OH group of donors, NAD or NADP as acceptor | 24/71 |
| | 6.8e-08 | 0048037 | cofactor binding | 24/111 |
| | P value | GO | Description | Rate |
| biological process | 1.74e-11 | 0044262 | cellular carbohydrate metabolic process | 27/106 |
| | 2.42e-11 | 0019318 | hexose metabolic process | 24/60 |
| | 2.42e-11 | 0005996 | monosaccharide metabolic process | 24/61 |
| | 4.9e-10 | 0006066 | alcohol metabolic process | 26/110 |
| | 4.9e-10 | 0006096 | glycolysis | 15/25 |
| | 5.56e-09 | 0005975 | carbohydrate metabolic process | 28/132 |
| | 1.07e-08 | 0046365 | monosaccharide catabolic process | 15/30 |
| | 1.07e-08 | 0019320 | hexose catabolic process | 15/30 |
| | 1.07e-08 | 0006007 | glucose catabolic process | 15/30 |
| | 1.81e-08 | 0046164 | alcohol catabolic process | 15/31 |
| | 4.38e-07 | 0006006 | glucose metabolic process | 17/49 |
| | 6.19e-07 | 0009057 | macromolecule catabolic process | 18/75 |
| | 6.66e-07 | 0044275 | cellular carbohydrate catabolic process | 15/39 |
| | 9.57e-07 | 0016052 | carbohydrate catabolic process | 15/40 |
| 5.51e-06 | 0044265 | cellular macromolecule catabolic process | 16/51 | |
| 1.68e-05 | 0006091 | generation of precursor metabolites and energy | 29/178 | |
| | P value | GO | Description | Rate |
| cellular component | 1.31e-07 | 0043233 | organelle lumen | 25/121 |
| | 1.31e-07 | 0031974 | membrane-enclosed lumen | 25/121 |
| | 5.71e-06 | 0044446 | intracellular organelle#intracellular organelle part | 47/350 |
| | 7.84e-06 | 0044422 | organelle#organelle part | 47/353 |
| | 1.05e-05 | 0005737 | cytoplasm | 88/885 |
| | -1.33e-05 | 0031224 | intrinsic to membrane | 10/510 |
| | -1.36e-05 | 0016021 | integral to membrane | 10/509 |
| | 1.46e-05 | 0044429 | mitochondrial part | 27/159 |
| 1.9e-05 | 0044424 | intracellular#intracellular part | 94/990 | |

R7

| | P value | GO | Description | Rate |
|--------------------|----------|--|--|--------|
| molecular function | 2.38e-25 | 0008227 | amine receptor activity | 24/35 |
| | 9.94e-19 | 0004888 | transmembrane receptor activity | 31/188 |
| | 1.16e-16 | 0001584 | rhodopsin-like receptor activity | 27/95 |
| | 3.17e-15 | 0004930 | G-protein coupled receptor activity | 27/107 |
| | 1.49e-12 | 0004872 | receptor activity | 32/257 |
| | 9.85e-10 | 0042165 | neurotransmitter binding | 14/38 |
| | 1.04e-09 | 0004871 | signal transducer activity | 33/313 |
| | 1.04e-09 | 0060089 | molecular transducer activity | 33/313 |
| | 6.2e-09 | 0004935 | adrenoceptor activity | 8/10 |
| | 6.77e-08 | 0030594 | neurotransmitter receptor activity | 12/35 |
| | 1.12e-07 | 0004936 | alpha-adrenergic receptor activity | 6/6 |
| | 4.08e-07 | 0042166 | acetylcholine binding | 7/10 |
| | 2.68e-06 | 0004981 | muscarinic acetylcholine receptor activity | 5/5 |
| 6.99e-06 | 0015464 | acetylcholine receptor activity | 6/9 | |
| | P value | GO | Description | Rate |
| biological process | 1.12e-20 | 0007186 | G-protein coupled receptor protein signaling pathway | 28/145 |
| | 1.46e-10 | 0007166 | cell surface receptor linked signal transduction | 30/254 |
| | 9.85e-10 | 0003008 | system process | 30/266 |
| | 1.54e-06 | 0019932 | second-messenger-mediated signaling | 16/86 |
| | 7.59e-06 | 0007187 | G-protein signaling, coupled to cyclic nucleotide second messenger | 12/52 |
| | 9.2e-06 | 0019935 | cyclic-nucleotide-mediated signaling | 12/53 |
| 1.25e-05 | 0007188 | G-protein signaling, coupled to cAMP nucleotide second messenger | 10/36 | |
| | P value | GO | Description | Rate |
| cellular component | 1.12e-20 | 0005887 | integral to plasma membrane | 40/278 |
| | 1.12e-20 | 0031226 | intrinsic to plasma membrane | 40/278 |
| | 2.4e-18 | 0044459 | plasma membrane part | 44/357 |
| | 5.62e-15 | 0005886 | plasma membrane | 47/453 |
| | 6.96e-13 | 0016021 | integral to membrane | 48/509 |
| | 7.12e-13 | 0031224 | intrinsic to membrane | 48/510 |
| | 2.77e-12 | 0044425 | membrane#membrane part | 53/624 |
| | 3.12e-09 | 0016020 | membrane | 55/760 |
| 8.84e-07 | 0005624 | membrane fraction | 21/180 | |

R8

| | P value | GO | Description | Rate |
|--------------------|----------|---------|--|--------|
| molecular function | 2.71e-10 | 0030246 | carbohydrate binding | 22/50 |
| | 3.06e-06 | 0005529 | sugar binding | 13/27 |
| | 3.06e-06 | 0004553 | hydrolase activity, hydrolyzing O-glycosyl compounds | 12/23 |
| | 2.73e-05 | 0016798 | hydrolase activity, acting on glycosyl bonds | 12/28 |
| | 0.000175 | 0017171 | serine hydrolase activity | 13/40 |
| | 0.000193 | 0016758 | transferase activity, transferring hexosyl groups | 9/19 |
| | 0.00073 | 0008236 | serine-type peptidase activity | 12/39 |
| | 0.000816 | 0008378 | galactosyltransferase activity | 5/6 |
| | 0.000816 | 0035250 | UDP-galactosyltransferase activity | 5/6 |
| | 0.000889 | 0030247 | polysaccharide binding | 9/23 |
| | 0.000931 | 0016787 | hydrolase activity | 42/326 |
| | 0.00144 | 0008233 | peptidase activity | 17/90 |
| | 0.00144 | 0003945 | N-acetyllactosamine synthase activity | 4/4 |
| | 0.00144 | 0005537 | mannose binding | 4/4 |
| | 0.00157 | 0001871 | pattern binding | 9/25 |
| | P value | GO | Description | Rate |
| biological process | 1.53e-09 | 0005975 | carbohydrate metabolic process | 30/132 |
| | 6.31e-06 | 0006955 | immune response | 19/81 |
| | 6.31e-06 | 0002376 | immune system process | 23/110 |
| | 2.88e-05 | 0009611 | response to wounding | 23/117 |
| | 0.000103 | 0009605 | response to external stimulus | 28/166 |
| | 0.000298 | 0007599 | hemostasis | 12/36 |
| | 0.000816 | 0042060 | wound healing | 12/40 |
| | 0.000816 | 0050817 | coagulation | 11/34 |
| | 0.000816 | 0007596 | blood coagulation | 11/34 |
| | 0.00119 | 0050878 | regulation of body fluid levels | 12/42 |
| | P value | GO | Description | Rate |
| cellular component | 2.73e-05 | 0044421 | extracellular region#extracellular region part | 21/101 |
| | 5.11e-05 | 0005615 | extracellular space | 19/89 |
| | 0.000103 | 0005764 | lysosome | 13/38 |
| | 0.000103 | 0000323 | lytic vacuole | 13/38 |
| | 0.000135 | 0005773 | vacuole | 13/39 |

Supplementary Table 4: For each of R1 to R8, the average Tc of paired GRASP fingerprints over all drug-target pairs in the corresponding cluster, and that over 10^5 clusters, each having interactions randomly selected out of the original 11,219 drug-target pairs and keeping the cluster size the same as that of the corresponding cluster.

| Cluster | R1 | R2 | R3 | R4 | R5 | R6 | R7 | R8 |
|---|---------|---------|---------|---------|---------|---------|---------|---------|
| Average Tc of GRASP fingerprints | 0.3174 | 0.2590 | 0.3566 | 0.2426 | 0.3944 | 0.3474 | 0.3822 | 0.4765 |
| Average Tc of GRASP fingerprints over 10^5 random clusters (RC) | 0.03739 | 0.03741 | 0.03741 | 0.03742 | 0.03741 | 0.03742 | 0.03741 | 0.03741 |
| Standard deviation of RC | 0.00317 | 0.00316 | 0.00114 | 0.00402 | 0.00222 | 0.00245 | 0.00360 | 0.00191 |
| Maximum of RC | 0.05384 | 0.05503 | 0.04278 | 0.06011 | 0.04791 | 0.05117 | 0.05659 | 0.04716 |

Supplementary Table 5: For each of R1 to R8, the average Tc of paired GRASP fingerprints over drug-target pairs of all promiscuous drugs in the corresponding cluster, and that over 10^5 clusters, each having interactions randomly selected out of the original 8,475 promiscuous drug-target pairs and keeping the cluster size the same as that of the corresponding cluster.

| Cluster | R1 | R2 | R3 | R4 | R5 | R6 | R7 | R8 |
|---|---------|---------|---------|---------|---------|---------|---------|---------|
| Average Tc of GRASP fingerprints | 0.3384 | 0.2739 | 0.3627 | 0.2801 | 0.3998 | 0.3510 | 0.4113 | 0.4930 |
| Average Tc of GRASP fingerprints over 10^5 random clusters (RC) | 0.03938 | 0.03938 | 0.03938 | 0.03936 | 0.03938 | 0.03938 | 0.03939 | 0.03938 |
| Standard deviation of RC | 0.00408 | 0.00397 | 0.00141 | 0.00498 | 0.00252 | 0.00280 | 0.00444 | 0.00227 |
| Maximum of RC | 0.061 | 0.06227 | 0.0466 | 0.06966 | 0.05120 | 0.05320 | 0.06454 | 0.04962 |

Supplementary Table 6: In each of R1 to R8, given drugs and targets of drug-target pairs, the ratio of drug-target pairs which were in the corresponding cluster to all drug-target pairs between them, and the average over those of 10^5 clusters, each having drug-target pairs randomly selected out of the original 11,219 drug-target interactions and keeping the cluster size the same as that of the corresponding cluster.

| Cluster | R1 | R2 | R3 | R4 | R5 | R6 | R7 | R8 |
|--|-------------------|---------------------|-----------------------|---------------------|---------------------|---------------------|-------------------|---------------------|
| Ratio | 1.00 (283/283) | 0.9349 (287/307) | 0.9946 (1848/1858) | 0.9730 (180/185) | 0.9652 (555/575) | 0.9810 (465/474) | 1.00 (222/222) | 0.9933 (741/746) |
| Average ratio by 10^5 random clusters (RC) | 0.5663 | 0.5650 | 0.5327 | 0.6102 | 0.5234 | 0.5318 | 0.5882 | 0.5143 |
| Standard deviation of RC | 0.0227 | 0.0225 | 0.0658 | 0.0298 | 0.0150 | 0.0167 | 0.0262 | 0.0124 |
| Max of RC | 0.6612 | 0.6568 | 0.5627 | 0.7407 | 0.5873 | 0.6008 | 0.7231 | 0.5731 |

Supplementary Table 7: In each of R1 to R8, given drugs and targets of drug-target pairs (of promiscuous drugs), the ratio of drug-target pairs which were in the corresponding cluster to all drug-target pairs between them, and the average over those of 10^5 clusters, each having drug-target pairs (of promiscuous drugs) randomly selected out of the original 11,219 drug-target interactions and keeping the cluster size the same as that of the corresponding cluster.

| Cluster | R1 | R2 | R3 | R4 | R5 | R6 | R7 | R8 |
|--|-------------------|---------------------|-----------------------|---------------------|---------------------|---------------------|-------------------|---------------------|
| Ratio | 1.00 (205/205) | 0.9153 (216/236) | 0.9932 (1451/1461) | 0.9655 (140/145) | 0.9621 (508/528) | 0.9790 (419/428) | 1.00 (176/176) | 0.9920 (621/626) |
| Average ratio by 10^5 random clusters (RC) | 0.5679 | 0.5664 | 0.4986 | 0.6185 | 0.5127 | 0.5245 | 0.5938 | 0.4976 |
| Standard deviation of RC | 0.0536 | 0.0533 | 0.0146 | 0.0696 | 0.0349 | 0.0392 | 0.0617 | 0.0286 |
| Max of RC | 0.68 | 0.678 | 0.532 | 0.788 | 0.594 | 0.614 | 0.735 | 0.560 |

Supplementary Table 8: The number of drug-target pairs sharing the same drugs and the average sequence identity between targets (amino acid sequences) of these pairs

| Cluster | R1 | R2 | R3 | R4 | R5 | R6 | R7 | R8 | Average |
|---|--------|--------|--------|--------|--------|--------|--------|--------|---------|
| #pairs of drug-target pairs sharing the same drugs | 327 | 3,828 | 2,761 | 3,107 | 6,554 | 5,254 | 495 | 13,405 | |
| Average sequence identity between targets (drug-target pairs) sharing the same drug | 0.3128 | 0.0212 | 0.2371 | 0.0372 | 0.0127 | 0.0148 | 0.2784 | 0.0927 | 0.0311 |