***Supporting Information***

**MeLAD: an integrated resource for metalloenzyme-ligand associations**

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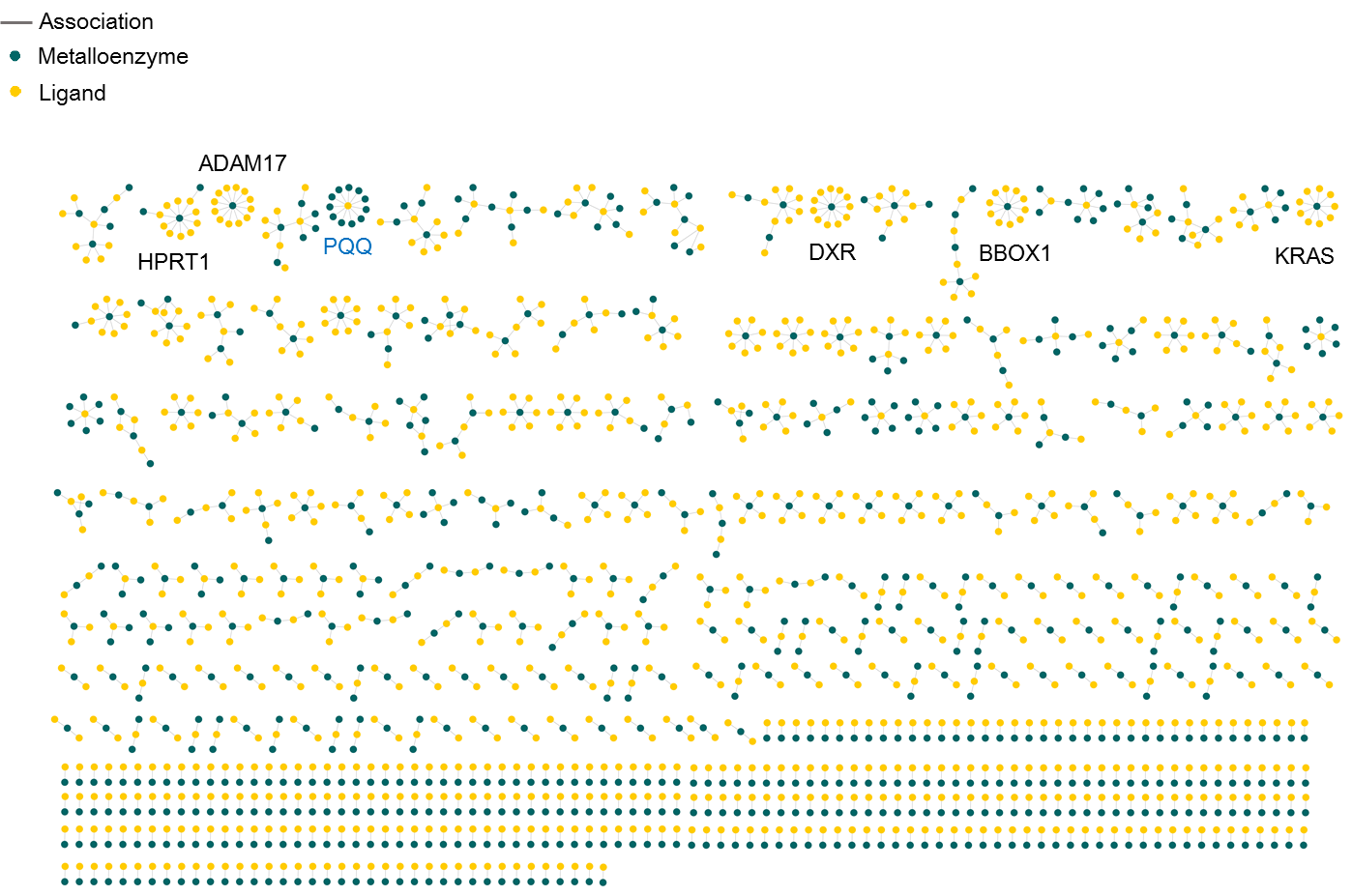
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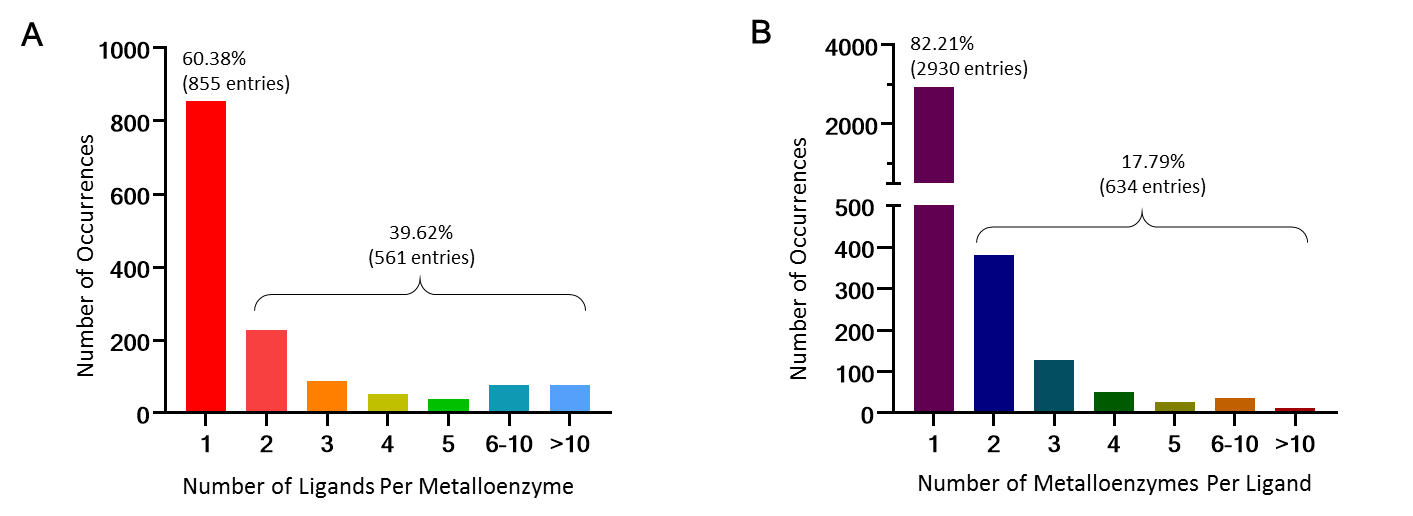
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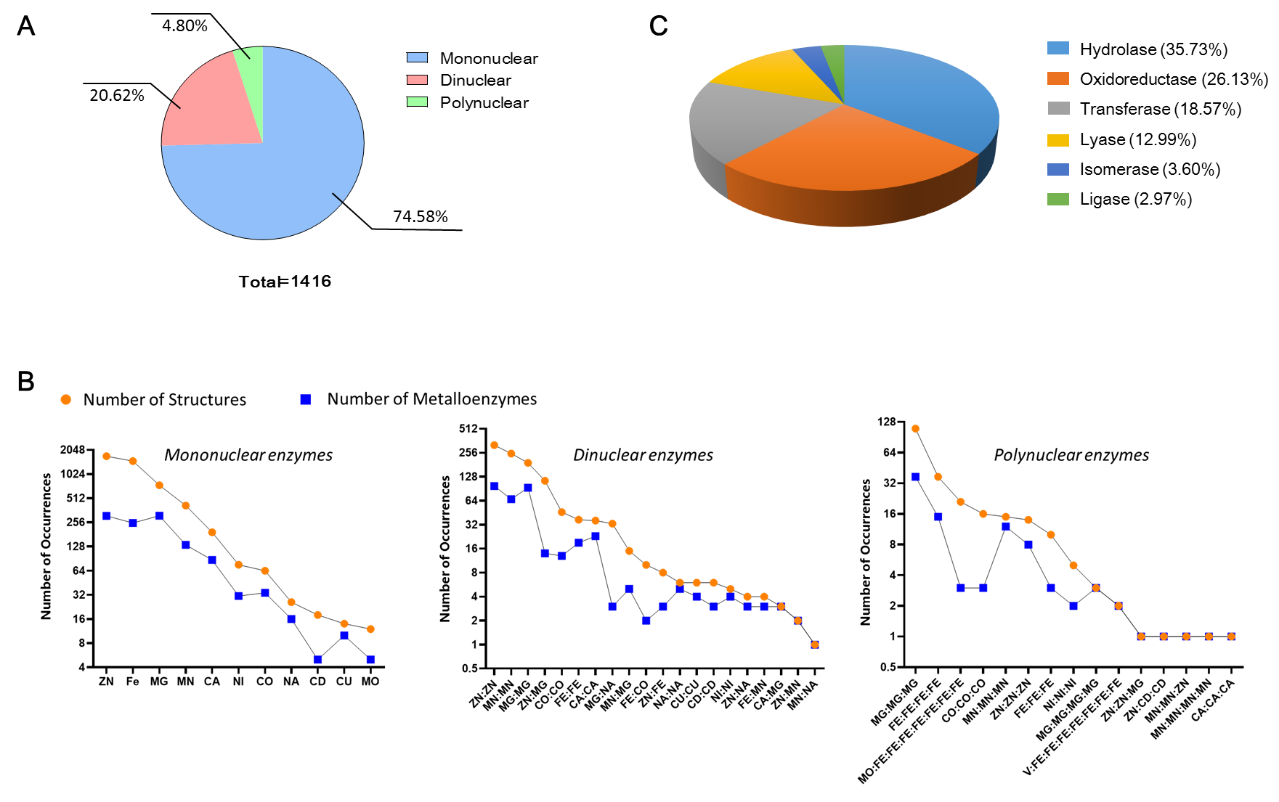
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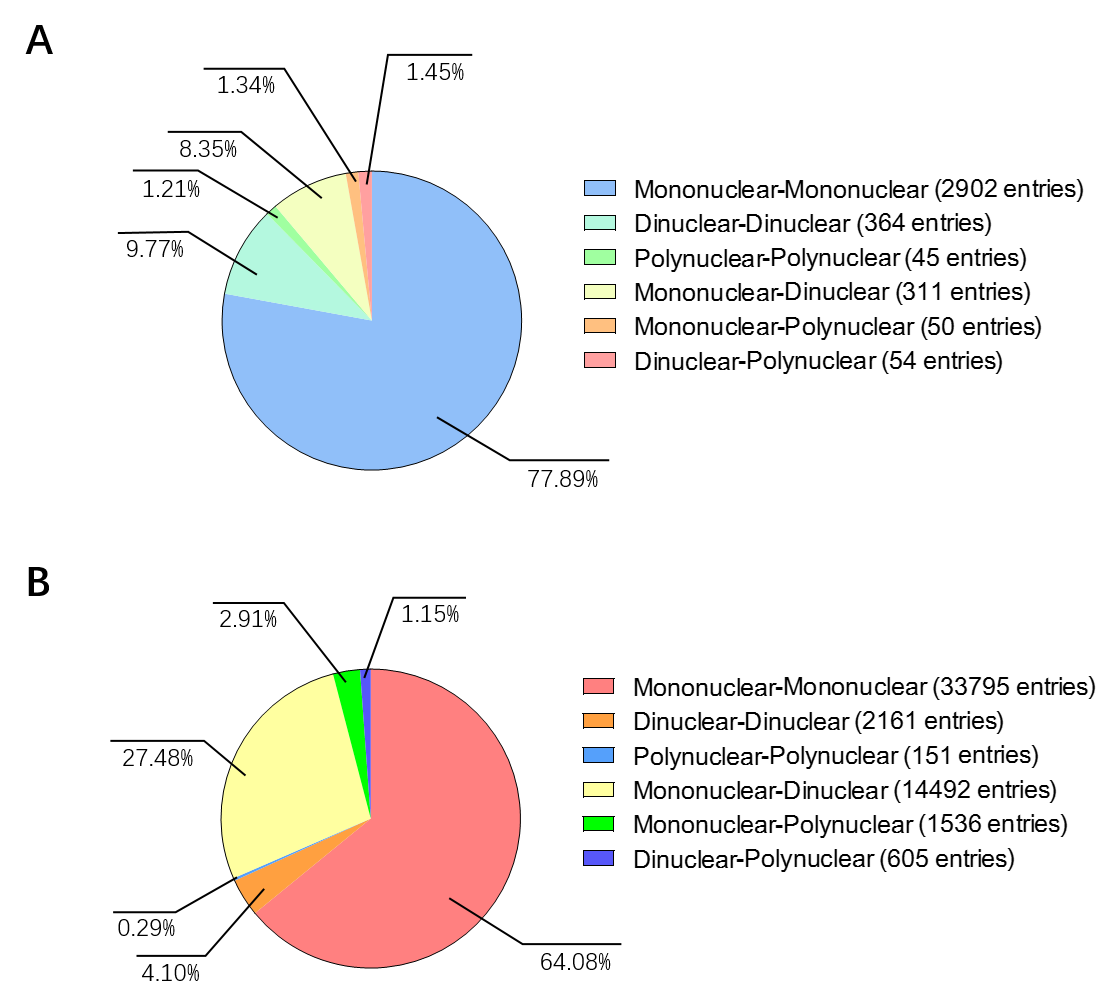
## Figure S1. Complementary metalloenzyme-ligand associations to Figure 1.

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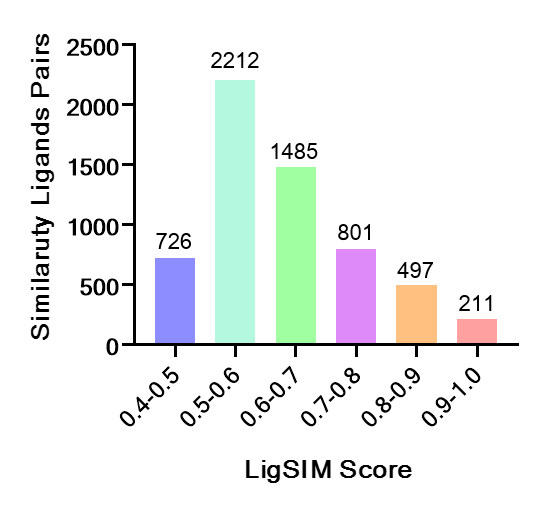
## Figure S2. Database statistics. (A) Each bar represents the number of metalloenzymes for which there have a certain number of binding ligands in MeLAD. (B) Each bar shows the number of ligands for which there have a certain number of associated metalloenzymes in the database.

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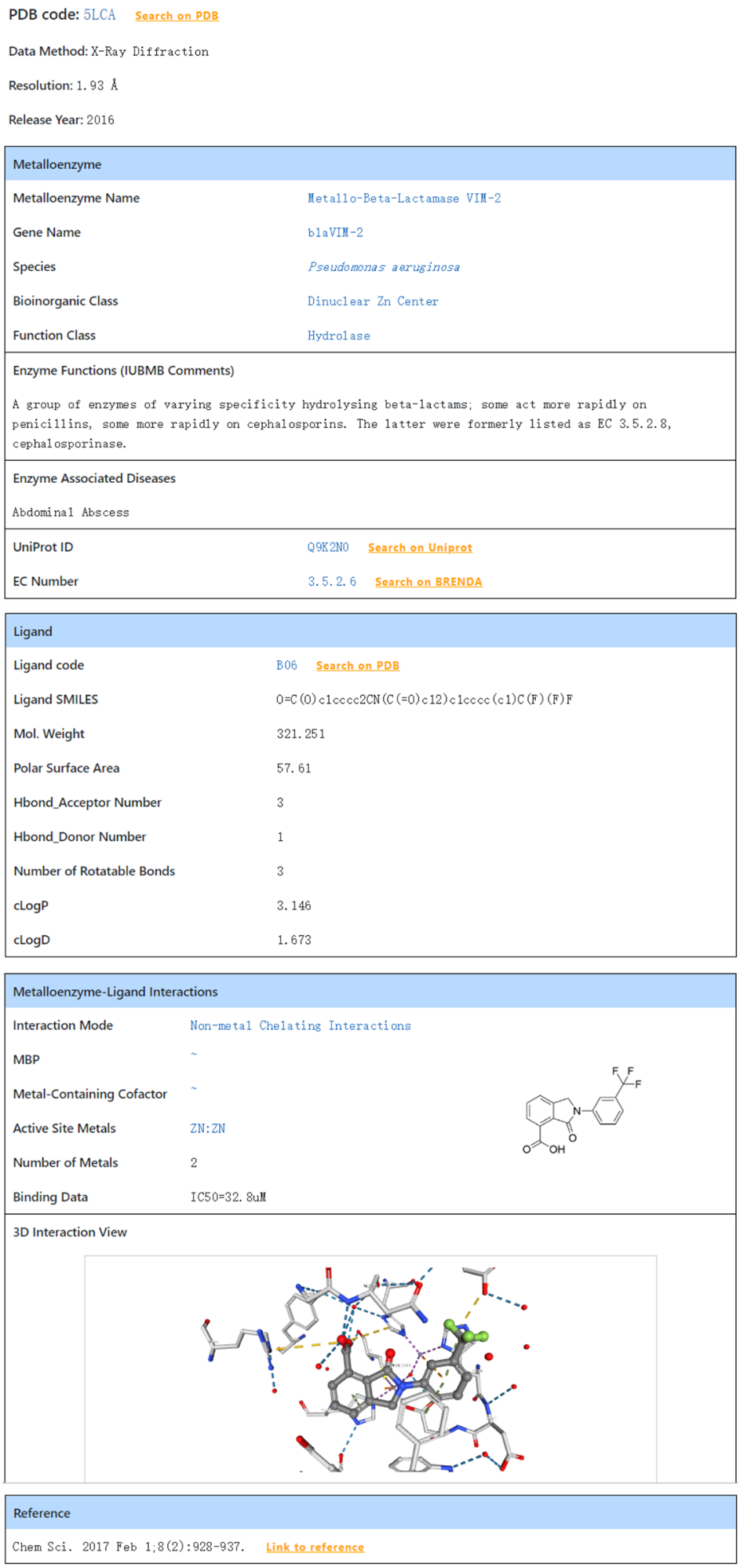
## Figure S3. Statistic data for metalloenzymes. (A) Distribution of metalloenzymes according to mono-, bi-, and poly-nuclear classification. (B) Number of metalloenzyme or structure entries corresponding to active site metal ions. (C) Distribution of metalloenzymes according to the EC classes, *i.e.* hydrolase, oxidoreductase, transferase, lyase, isomerase, and ligase.

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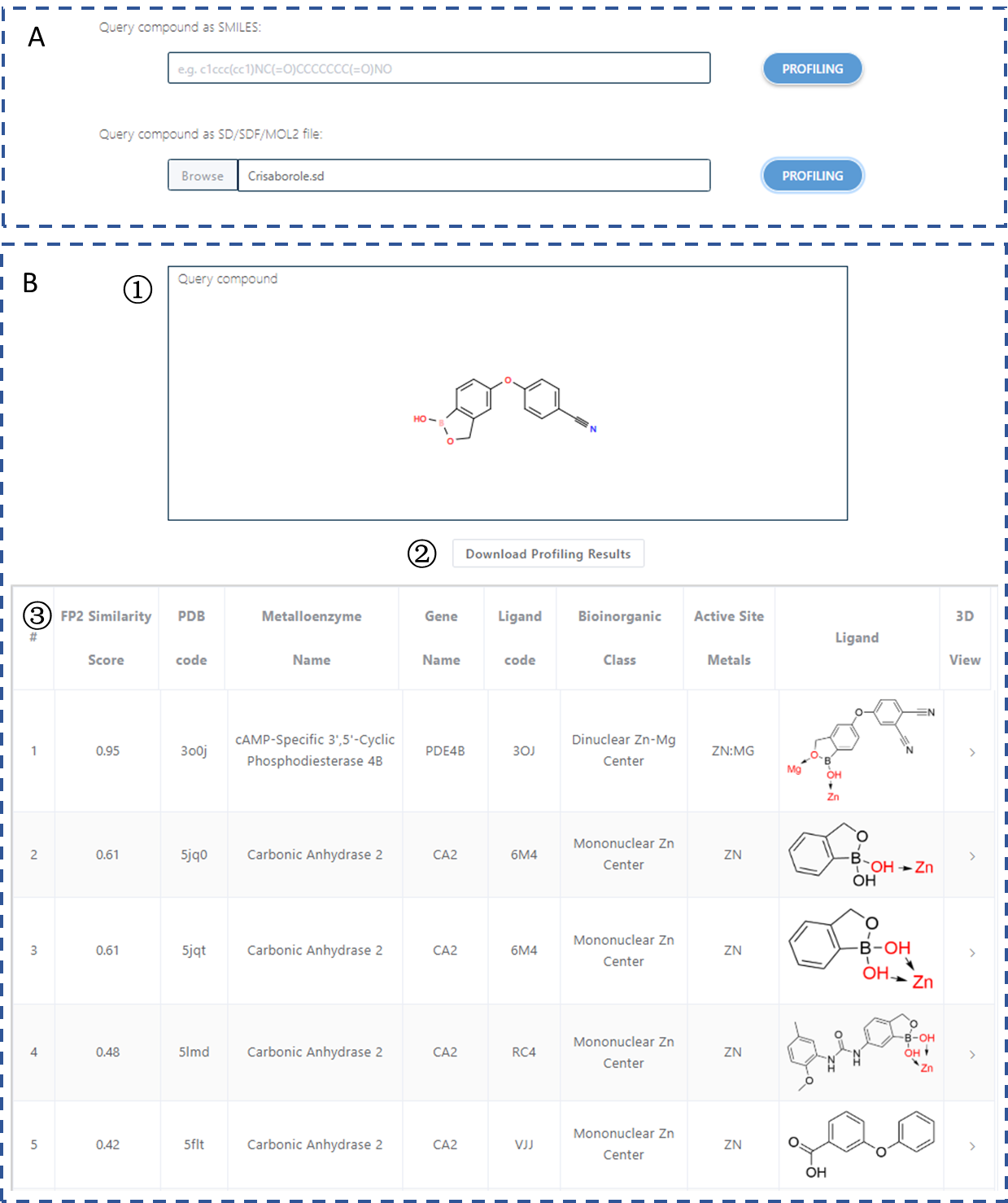
## Figure S4. Statistic data for MeSIM and LigSIM results. (A) Distribution of structurally metalloenzyme related associations between/cross mono-, bi-, and poly-nuclear enzymes. (B) Distribution of ligand similarity related associations for mono-, bi-, and poly-nuclear enzymes.



## Figure S5. Distribution of similar ligand pairs to LigSIM scores.

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## Figure S6. The detailed information page for an example.

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## Figure S7. An example of metalloenzyme profiling for Crisaborole ([Li, et al., 2018](#_ENREF_1); [Paton, 2017](#_ENREF_2)). (A) User interface. Users can query a molecule using canonical SMILES strings or sd/sdf/mol2 files. Once a molecule is uploaded, clicking ‘PROFILING’ tab will yield metalloenzyme profiling results. (B) The profiling results. ① The chemical structure of the query compound. ② The link to download the profiling results. ③ The information of resulted metalloenzymes ranked by FP2 fingerprint similarity; user can directly compare chemical similarity, MBP chemotypes, coordination modes, and binding modes.

# Additional Tables

## Table S1. The metal-involving cofactor identifiers in PDB database.

|  |  |  |
| --- | --- | --- |
| **Metal ion** | **Records in the given PDB file** | **Ligand codes in PDB database** |
| Magnesium (Mg) | MG | MD9, BCL, CLA, BCB, CHL, CL0, PMR, HEG, CL7, 68G, AOH, GB0, GBF |
| Vanadium (V) | V | VN4, VVO, 8P8, D6N |
| Manganese (Mn) | MN, MN3 | MNH, MH2, 76R,OEX, OEC, MNR, HNN |
| Iron (Fe) | FE, FE2 | SF4, FCO, FEO, ICS, NFU, FNE, FSO, CFO, FSX, FEA, NTE, FE9, OFO, HC1, VER, YOM, OFE, NWN, 402, 6CQ, 4HE, CCH, DDH, HC0, CN1, CNB, CNF, YOK, YOL, HCN, BTF, WPC, 0KA, ISW, FS5, ICE, ICG, ICH, 4WV, 4WW, 4WX, 82N, 6CO, FFE, 9SQ, HEM, FES, HEC, F3S, HEA, FCO, FEO, SRM, HDD, HAS, CLF, DHE, NFV, SF3, CFM, HEB, F4S, HDE, WCC, XCC, FDE, 9S8, CFN, FEC, NFS, MH0, 1CL, HEV, FSF, FMI, HKL, S3F, SFS, 6ML, FEL, CLP, NFE, NFC, NFO, FDD, 6HE, 7HE, VEA, 8JU, CUV, HE6, HIF, HDM, HCO, HFM, 2FH, 1FH, FS2, NFR, CLN, POR, HME, CZL, UFE, OBV, N7H, 522, 6WF, HP5, Q46, 8P8, 83L, WUP, WXP, WYP, WVP, 89R, FS0, BF8, BJ8, D6N, ER2 |
| Cobalt (Co) | CO, 3CO | J1R, J1S, SIR, B12, COH, BVQ, CNC, CBY, COB, COY, DEU, I2A, B1Z, OBL, PC3, B1M, B13, HCB, 9QQ |
| Nickel (Ni) | NI, 3NI | NFU, FNE, NWN, PNI, 82N, F43, NFV, HNI, WCC, XCC, NFS, NFE, NFC, NFO, CUV, NFR, M43, BF8 |
| Copper (Cu) | CU, CU1, CUA | CUZ, MP1, CUL, C2O, C1O, CUM, CUN, CUB, C2C, PCU |
| Zinc (Zn) | ZN | DTZ, HE5, 2GO, ZND, HES, BAZ, BOZ, DOZ, DAZ, 7BU, 9D7, ZNH, ZEM |
| Molybdenum (Mo) | MO, 6MO, 4MO | MOS, ICS, 2MO, MOM, SMO, MOW, RMO, ICE, ICG, ICH, CFM, CFN, CUM, 4SM |
| Tungsten (W) | W | 6WO |

## Table S2. Statistic data for MBP chemotypes.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| MBP ID | MBP Chemical Structure | Number of Metalloenzymes / Structures | MBP ID | MBP Chemical Structure | Number of Metalloenzymes / Structures |
| 1-1-1 |  | 43/71 | 1-2-107 |  | 1/1 |
| 1-1-2 |  | 3/3 | 1-2-108 |  | 1/2 |
| 1-1-3 |  | 1/1 | 1-3-1 |  | 45/108 |
| 1-1-4 |  | 1/1 | 1-3-2 |  | 1/1 |
| 1-1-5 |  | 3/4 | 1-3-3 |  | 1/3 |
| 1-1-6 |  | 7/13 | 1-3-4 |  | 2/4 |
| 1-1-7 |  | 2/3 | 1-3-5 |  | 1/1 |
| 1-1-8 |  | 5/9 | 1-3-6 |  | 2/2 |
| 1-1-9 |  | 3/3 | 1-3-7 |  | 2/5 |
| 1-1-10 |  | 3/3 | 1-3-8 |  | 1/1 |
| 1-1-11 |  | 3/5 | 1-3-9 |  | 1/1 |
| 1-1-12 |  | 4/21 | 1-3-10 |  | 1/1 |
| 1-1-13 |  | 12/18 | 1-3-11 |  | 1/2 |
| 1-1-14 |  | 2/7 | 1-3-12 |  | 2/2 |
| 1-1-15 |  | 2/4 | 1-3-13 |  | 1/1 |
| 1-1-16 |  | 1/2 | 1-3-14 |  | 1/4 |
| 1-1-17 |  | 6/8 | 1-3-15 |  | 1/1 |
| 1-1-18 |  | 1/2 | 1-3-16 |  | 2/3 |
| 1-1-19 |  | 33/42 | 1-3-17 |  | 1/1 |
| 1-1-20 |  | 1/1 | 1-3-18 |  | 1/3 |
| 1-1-21 |  | 3/4 | 1-3-19 |  | 1/1 |
| 1-1-22 |  | 7/8 | 1-4-1 |  | 1/1 |
| 1-1-23 |  | 7/12 | 1-4-2 |  | 1/1 |
| 1-1-24 |  | 7/9 | 1-4-3 |  | 1/1 |
| 1-1-25 |  | 3/4 | 1-4-4 |  | 1/1 |
| 1-1-26 |  | 33/71 | 1-4-5 |  | 1/1 |
| 1-1-27 |  | 1/1 | 1-5-1 |  | 1/2 |
| 1-1-28 |  | 4/4 | 1-6-1 |  | 3/4 |
| 1-1-29 |  | 3/5 | 2-1-1 |  | 12/16 |
| 1-1-30 |  | 1/3 | 2-1-2 |  | 1/1 |
| 1-1-31 |  | 1/1 | 2-1-3 |  | 22/38 |
| 1-1-32 |  | 4/8 | 2-1-4 |  | 12/28 |
| 1-1-33 |  | 6/9 | 2-1-5 |  | 14/27 |
| 1-1-34 |  | 18/24 | 2-1-6 |  | 58/127 |
| 1-1-35 |  | 3/3 | 2-1-7 |  | 6/16 |
| 1-1-36 |  | 137/228 | 2-1-8 |  | 5/7 |
| 1-1-37 |  | 35/65 | 2-1-9 |  | 101/315 |
| 1-1-38 |  | 21/42 | 2-1-10 |  | 1/1 |
| 1-1-39 |  | 10/20 | 2-1-11 |  | 7/19 |
| 1-1-40 |  | 6/21 | 2-1-12 |  | 6/6 |
| 1-1-41 |  | 1/2 | 2-1-13 |  | 1/1 |
| 1-1-42 |  | 8/9 | 2-1-14 |  | 1/2 |
| 1-1-43 |  | 1/1 | 2-1-15 |  | 4/4 |
| 1-1-44 |  | 6/9 | 2-1-16 |  | 1/1 |
| 1-1-45 |  | 2/2 | 2-1-17 |  | 2/4 |
| 1-1-46 |  | 1/1 | 2-1-18 |  | 3/6 |
| 1-1-47 |  | 6/37 | 2-1-19 |  | 2/5 |
| 1-1-48 |  | 1/1 | 2-1-20 |  | 2/2 |
| 1-1-49 |  | 1/1 | 2-1-21 |  | 3/8 |
| 1-1-50 |  | 1/1 | 2-1-22 |  | 6/12 |
| 1-1-51 |  | 1/2 | 2-1-23 |  | 2/2 |
| 1-1-52 |  | 1/1 | 2-1-24 |  | 1/1 |
| 1-1-53 |  | 1/2 | 2-1-25 |  | 1/1 |
| 1-1-54 |  | 1/1 | 2-1-26 |  | 1/1 |
| 1-1-55 |  | 1/1 | 2-1-27 |  | 136/317 |
| 1-1-56 |  | 2/9 | 2-1-28 |  | 2/2 |
| 1-1-57 |  | 1/1 | 2-1-29 |  | 4/4 |
| 1-1-58 |  | 1/1 | 2-1-30 |  | 21/24 |
| 1-1-59 |  | 4/4 | 2-1-31 |  | 13/16 |
| 1-1-60 |  | 1/1 | 2-1-32 |  | 16/86 |
| 1-1-61 |  | 1/2 | 2-1-33 |  | 1/2 |
| 1-1-62 |  | 1/1 | 2-1-34 |  | 6/8 |
| 1-1-63 |  | 1/1 | 2-1-35 |  | 1/2 |
| 1-1-64 |  | 1/2 | 2-1-36 |  | 1/1 |
| 1-1-65 |  | 4/5 | 2-1-37 |  | 1/3 |
| 1-1-66 |  | 2/2 | 2-1-38 |  | 2/2 |
| 1-1-67 |  | 5/6 | 2-1-39 |  | 3/11 |
| 1-1-68 |  | 2/4 | 2-1-40 |  | 2/2 |
| 1-1-69 |  | 2/2 | 2-1-41 |  | 6/13 |
| 1-1-70 |  | 1/2 | 2-1-42 |  | 2/2 |
| 1-1-71 |  | 1/2 | 2-1-43 |  | 3/4 |
| 1-1-72 |  | 1/1 | 2-1-44 |  | 1/2 |
| 1-1-73 |  | 1/1 | 2-1-45 |  | 1/2 |
| 1-1-74 |  | 11/19 | 2-1-46 |  | 1/4 |
| 1-1-75 |  | 4/9 | 2-1-47 |  | 1/5 |
| 1-1-76 |  | 3/5 | 2-1-48 |  | 7/14 |
| 1-1-77 |  | 8/16 | 2-1-49 |  | 11/20 |
| 1-1-78 |  | 1/1 | 2-1-50 |  | 2/2 |
| 1-1-79 |  | 2/7 | 2-1-51 |  | 1/1 |
| 1-1-80 |  | 1/1 | 2-1-52 |  | 1/1 |
| 1-1-81 |  | 1/1 | 2-1-53 |  | 1/1 |
| 1-1-82 |  | 2/3 | 2-1-54 |  | 1/2 |
| 1-1-83 |  | 2/2 | 2-1-55 |  | 1/1 |
| 1-1-84 |  | 1/1 | 2-1-56 |  | 1/1 |
| 1-1-85 |  | 1/1 | 2-1-57 |  | 1/1 |
| 1-1-86 |  | 2/2 | 2-1-58 |  | 1/1 |
| 1-1-87 |  | 9/15 | 2-1-59 |  | 5/10 |
| 1-1-88 |  | 1/5 | 2-1-60 |  | 4/6 |
| 1-1-89 |  | 1/4 | 2-1-61 |  | 21/91 |
| 1-1-90 |  | 1/1 | 2-1-62 |  | 2/4 |
| 1-1-91 |  | 2/2 | 2-1-63 |  | 10/28 |
| 1-1-92 |  | 1/1 | 2-1-64 |  | 3/4 |
| 1-1-93 |  | 1/1 | 2-1-65 |  | 2/4 |
| 1-1-94 |  | 1/1 | 2-1-66 |  | 1/1 |
| 1-1-95 |  | 1/3 | 2-1-67 |  | 1/1 |
| 1-1-96 |  | 1/1 | 2-1-68 |  | 1/2 |
| 1-1-97 |  | 1/1 | 2-1-69 |  | 1/1 |
| 1-1-98 |  | 1/1 | 2-1-70 |  | 1/1 |
| 1-1-99 |  | 2/5 | 2-1-71 |  | 2/3 |
| 1-1-100 |  | 1/1 | 2-1-72 |  | 10/22 |
| 1-1-101 |  | 3/4 | 2-1-73 |  | 1/2 |
| 1-1-102 |  | 2/3 | 2-1-74 |  | 1/1 |
| 1-1-103 |  | 1/1 | 2-1-75 |  | 1/1 |
| 1-1-104 |  | 2/2 | 2-1-76 |  | 1/1 |
| 1-1-105 |  | 2/2 | 2-1-77 |  | 1/1 |
| 1-1-106 |  | 1/1 | 2-1-78 |  | 2/3 |
| 1-1-107 |  | 5/11 | 2-1-79 |  | 2/2 |
| 1-1-108 |  | 1/1 | 2-1-80 |  | 2/4 |
| 1-1-109 |  | 2/2 | 2-1-81 |  | 1/2 |
| 1-1-110 |  | 1/1 | 2-1-82 |  | 2/2 |
| 1-1-111 |  | 1/1 | 2-1-83 |  | 2/2 |
| 1-1-112 |  | 1/1 | 2-1-84 |  | 4/8 |
| 1-1-113 |  | 1/1 | 2-1-85 |  | 2/23 |
| 1-1-114 |  | 1/2 | 2-1-86 |  | 2/2 |
| 1-1-115 |  | 3/3 | 2-1-87 |  | 2/3 |
| 1-1-116 |  | 1/1 | 2-1-88 |  | 3/5 |
| 1-1-117 |  | 1/1 | 2-1-89 |  | 1/1 |
| 1-1-118 |  | 1/1 | 2-1-90 |  | 1/1 |
| 1-1-119 |  | 2/4 | 2-1-91 |  | 1/1 |
| 1-1-120 |  | 1/1 | 2-1-92 |  | 1/1 |
| 1-1-121 |  | 1/2 | 2-1-93 |  | 1/1 |
| 1-1-122 |  | 1/2 | 2-1-94 |  | 2/5 |
| 1-1-123 |  | 1/1 | 2-1-95 |  | 1/1 |
| 1-1-124 |  | 1/2 | 2-1-96 |  | 1/1 |
| 1-1-125 |  | 2/4 | 2-1-97 |  | 1/1 |
| 1-1-126 |  | 1/1 | 2-1-98 |  | 1/1 |
| 1-1-127 |  | 5/7 | 2-1-99 |  | 2/9 |
| 1-1-128 |  | 1/2 | 2-1-100 |  | 2/2 |
| 1-1-129 |  | 1/2 | 2-1-101 |  | 1/1 |
| 1-2-1 |  | 9/15 | 2-1-102 |  | 3/3 |
| 1-2-2 |  | 1/1 | 2-1-103 |  | 3/4 |
| 1-2-3 |  | 1/1 | 2-1-104 |  | 1/3 |
| 1-2-4 |  | 1/2 | 2-1-105 |  | 1/1 |
| 1-2-5 |  | 1/1 | 2-1-106 |  | 1/1 |
| 1-2-6 |  | 1/1 | 2-1-107 |  | 2/3 |
| 1-2-7 |  | 1/1 | 2-1-108 |  | 1/2 |
| 1-2-8 |  | 2/2 | 2-2-1 |  | 5/14 |
| 1-2-9 |  | 2/2 | 2-2-2 |  | 6/7 |
| 1-2-10 |  | 2/3 | 2-2-3 |  | 1/1 |
| 1-2-11 |  | 1/1 | 2-2-4 |  | 1/1 |
| 1-2-12 |  | 1/1 | 2-2-5 |  | 1/1 |
| 1-2-13 |  | 5/9 | 2-2-6 |  | 1/1 |
| 1-2-14 |  | 1/1 | 2-2-7 |  | 6/20 |
| 1-2-15 |  | 2/3 | 2-2-8 |  | 2/2 |
| 1-2-16 |  | 23/61 | 2-2-9 |  | 1/1 |
| 1-2-17 |  | 1/2 | 2-2-10 |  | 1/1 |
| 1-2-18 |  | 2/2 | 2-2-11 |  | 6/13 |
| 1-2-19 |  | 1/1 | 2-2-12 |  | 11/14 |
| 1-2-20 |  | 1/1 | 2-2-13 |  | 1/1 |
| 1-2-21 |  | 1/1 | 2-2-14 |  | 1/2 |
| 1-2-22 |  | 1/1 | 2-2-15 |  | 3/8 |
| 1-2-23 |  | 1/1 | 2-2-16 |  | 1/1 |
| 1-2-24 |  | 1/6 | 2-2-17 |  | 1/1 |
| 1-2-25 |  | 1/1 | 2-2-18 |  | 1/1 |
| 1-2-26 |  | 31/70 | 2-2-19 |  | 1/1 |
| 1-2-27 |  | 1/1 | 2-2-20 |  | 1/1 |
| 1-2-28 |  | 23/32 | 2-2-21 |  | 1/2 |
| 1-2-29 |  | 1/5 | 2-2-22 |  | 2/14 |
| 1-2-30 |  | 4/4 | 2-2-23 |  | 1/3 |
| 1-2-31 |  | 1/1 | 2-2-24 |  | 1/1 |
| 1-2-32 |  | 1/4 | 2-2-25 |  | 1/1 |
| 1-2-33 |  | 1/1 | 2-2-26 |  | 1/1 |
| 1-2-34 |  | 1/1 | 2-2-27 |  | 17/19 |
| 1-2-35 |  | 9/33 | 2-2-28 |  | 3/5 |
| 1-2-36 |  | 1/1 | 2-2-29 |  | 1/1 |
| 1-2-37 |  | 1/1 | 2-2-30 |  | 1/1 |
| 1-2-38 |  | 2/7 | 2-2-31 |  | 1/2 |
| 1-2-39 |  | 2/2 | 2-2-32 |  | 1/1 |
| 1-2-40 |  | 4/6 | 2-2-33 |  | 1/1 |
| 1-2-41 |  | 1/1 | 2-2-34 |  | 1/1 |
| 1-2-42 |  | 2/2 | 2-2-35 |  | 1/12 |
| 1-2-43 |  | 5/9 | 2-2-36 |  | 7/12 |
| 1-2-44 |  | 1/4 | 2-2-37 |  | 1/1 |
| 1-2-45 |  | 1/1 | 2-2-38 |  | 1/7 |
| 1-2-46 |  | 1/2 | 2-2-39 |  | 1/1 |
| 1-2-47 |  | 1/2 | 2-2-40 |  | 1/1 |
| 1-2-48 |  | 1/1 | 2-2-41 |  | 2/2 |
| 1-2-49 |  | 1/1 | 2-2-42 |  | 1/1 |
| 1-2-50 |  | 4/4 | 2-2-43 |  | 2/17 |
| 1-2-51 |  | 1/2 | 2-2-44 |  | 1/1 |
| 1-2-52 |  | 1/2 | 2-3-1 |  | 3/7 |
| 1-2-53 |  | 3/4 | 2-3-2 |  | 3/5 |
| 1-2-54 |  | 3/3 | 2-3-3 |  | 1/1 |
| 1-2-55 |  | 3/3 | 2-3-4 |  | 1/1 |
| 1-2-56 |  | 1/1 | 2-3-5 |  | 1/1 |
| 1-2-57 |  | 2/2 | 2-3-6 |  | 1/2 |
| 1-2-58 |  | 1/1 | 2-3-7 |  | 1/8 |
| 1-2-59 |  | 1/1 | 2-3-8 |  | 1/3 |
| 1-2-60 |  | 1/9 | 2-3-9 |  | 1/1 |
| 1-2-61 |  | 1/1 | 2-3-10 |  | 1/2 |
| 1-2-62 |  | 1/2 | 2-3-11 |  | 2/2 |
| 1-2-63 |  | 2/2 | 2-3-12 |  | 1/1 |
| 1-2-64 |  | 1/1 | 2-3-13 |  | 1/1 |
| 1-2-65 |  | 1/3 | 2-4-1 |  | 1/1 |
| 1-2-66 |  | 1/1 | 2-4-2 |  | 2/2 |
| 1-2-67 |  | 1/1 | 2-4-3 |  | 6/8 |
| 1-2-68 |  | 1/1 | 2-4-4 |  | 1/2 |
| 1-2-69 |  | 3/8 | 2-4-5 |  | 1/1 |
| 1-2-70 |  | 1/1 | 2-4-6 |  | 1/1 |
| 1-2-71 |  | 2/3 | 2-4-7 |  | 2/2 |
| 1-2-72 |  | 1/1 | 2-4-8 |  | 1/1 |
| 1-2-73 |  | 1/1 | 2-4-9 |  | 1/1 |
| 1-2-74 |  | 1/5 | 2-4-10 |  | 3/3 |
| 1-2-75 |  | 2/2 | 2-4-11 |  | 6/15 |
| 1-2-76 |  | 1/1 | 2-4-12 |  | 1/1 |
| 1-2-77 |  | 1/1 | 2-4-13 |  | 1/1 |
| 1-2-78 |  | 1/1 | 2-4-14 |  | 1/1 |
| 1-2-79 |  | 1/1 | 2-4-15 |  | 1/1 |
| 1-2-80 |  | 6/35 | 2-4-16 |  | 1/1 |
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| 1-2-82 |  | 2/8 | 2-4-18 |  | 1/1 |
| 1-2-83 |  | 2/2 | 2-4-19 |  | 1/1 |
| 1-2-84 |  | 1/1 | 2-4-20 |  | 2/13 |
| 1-2-85 |  | 3/12 | 2-5-1 |  | 1/6 |
| 1-2-86 |  | 16/40 | 2-6-1 |  | 1/1 |
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| 1-2-88 |  | 10/285 | 2-8-1 |  | 1/1 |
| 1-2-89 |  | 1/2 | 2-8-2 |  | 2/4 |
| 1-2-90 |  | 1/1 | 2-8-3 |  | 2/2 |
| 1-2-91 |  | 1/2 | 3-1-1 |  | 15/35 |
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| 1-2-99 |  | 1/1 | 3-2-1 |  | 1/1 |
| 1-2-100 |  | 1/1 | 3-2-2 |  | 2/2 |
| 1-2-101 |  | 1/2 | 3-2-3 |  | 2/2 |
| 1-2-102 |  | 1/1 | 3-2-4 |  | 1/1 |
| 1-2-103 |  | 1/1 | 3-2-5 |  | 1/1 |
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| 1-2-105 |  | 1/1 | 3-2-7 |  | 1/1 |
| 1-2-106 |  | 1/1 |  |  |  |

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