

# Supporting Information

## Property-unmatched decoys in docking benchmarks

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**Methods S1.** Python code for calculating adjusted logAUC.

This is provided as a pdf, **MethodsS1.pdf**.

**Table S1.** Enrichments from Parameter Scanning on DUD-E

This is provided as an Excel file, TableS1.xlsx

**Table S2.** Enrichments for all Targets

This is provided as an Excel file, TableS2.xlsx

**Table S3.** Properties of DUDE-Z Ligands and Decoys

This is provided as an Excel file, TableS3.xlsx

**Table S4.** Properties of Extrema Sets

This is provided as an Excel file, TableS4.xlsx

**Table S5.** Properties of Goldilocks Set

This is provided as an Excel file, TableS5.xlsx

**Table S6.** Charge-Matched DUD-E with full ligand set

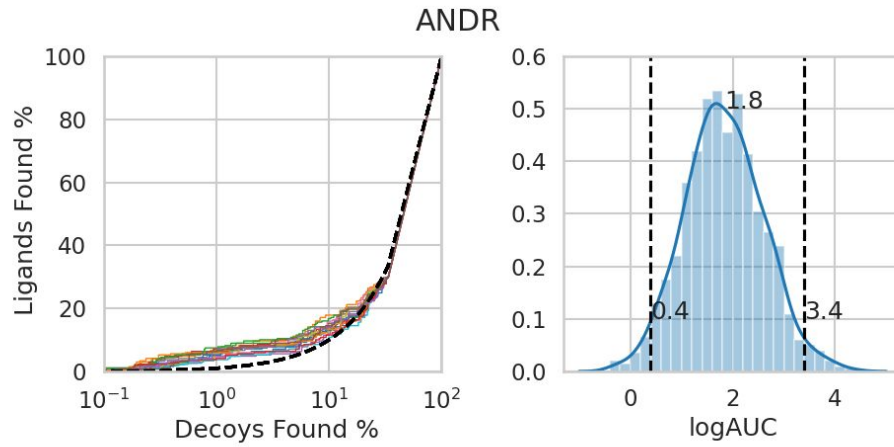
This is provided as an Excel file, TableS6.xlsx



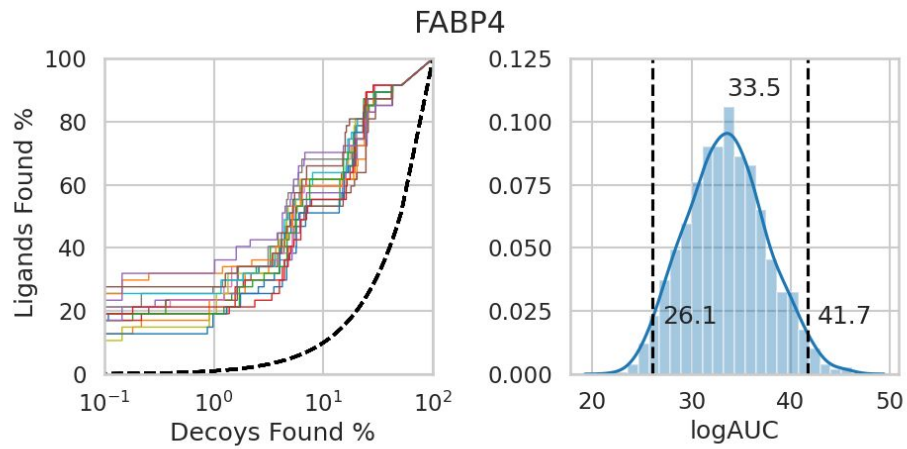
**Table S7.** Comparison of enrichments for unoptimized and optimized AmpC, DRD4, and MT1 docking setups.

This is provided as an Excel file, TableS7.xlsx

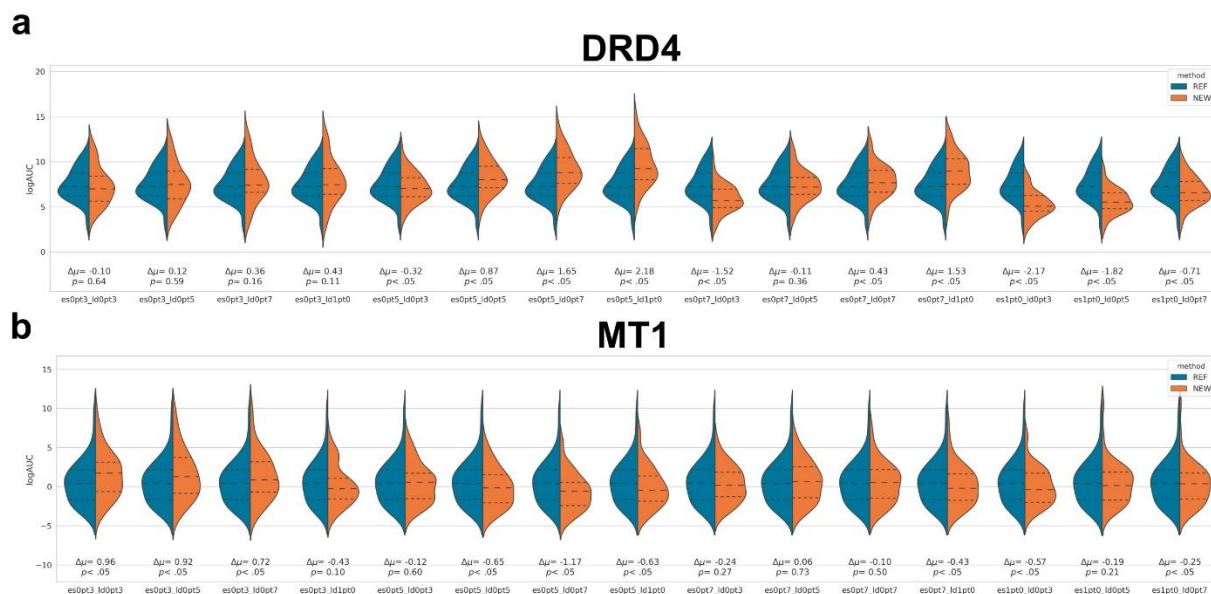
(a)



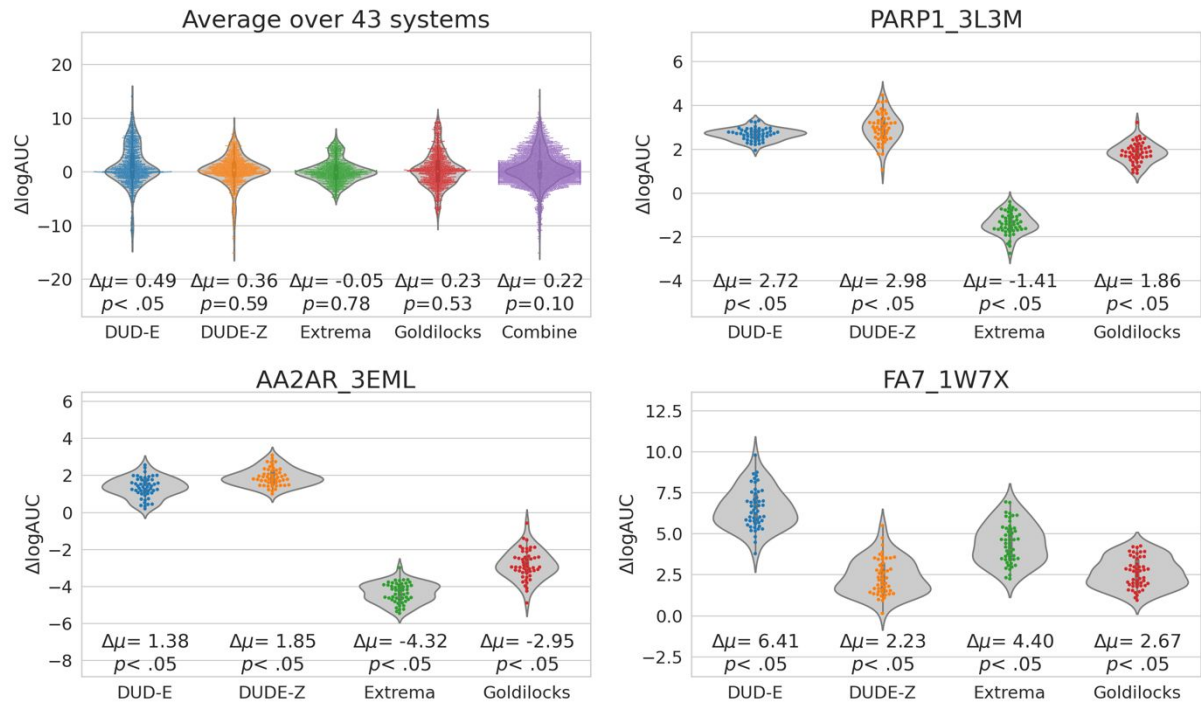
(b)



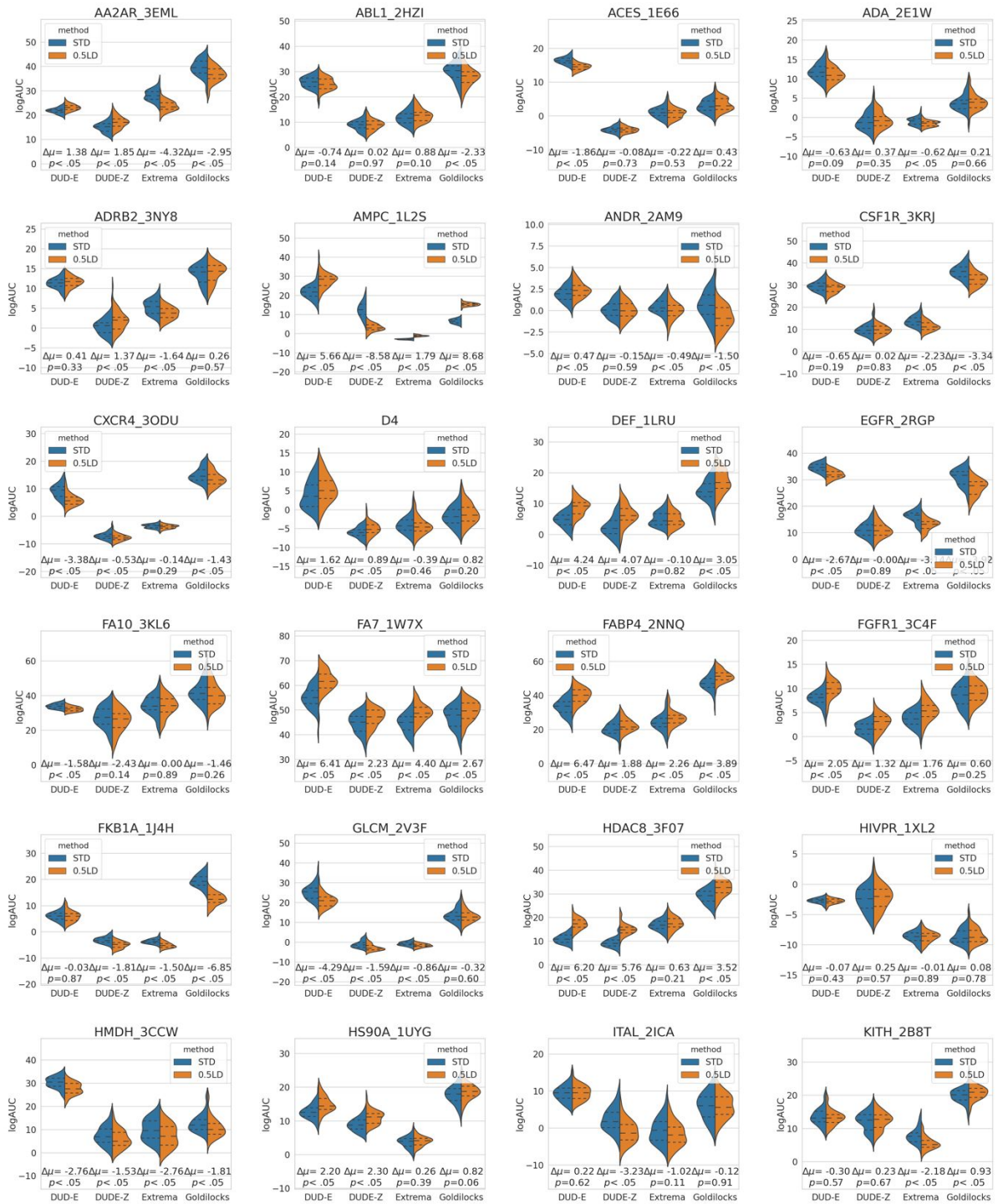
**Figure S1.** Examples of bootstrapping enrichment distribution with 95% confidence interval indicated. ROC curves with 15 bootstrap replicas are shown on the left. Tight distribution for Androgen Receptor (ANDR, **a**) where 95% confidence interval is 3 adjusted log AUC units. Wider distribution for Fatty acid binding protein adipocyte (FABP4, **b**) with 95% confidence interval of 15.6 adjusted log AUC units.



**Figure S2.** Bootstrapping enrichment distributions of all scoring function coefficient combinations for binders and nonbinders for D4 dopamine (84 binders, 468 nonbinders) and MT1 melatonin (105 binders, 65 nonbinders) receptors. The left panels (REF, blue) are different bootstrapping enrichment distributions of the standard scoring function whereas the right panels (NEW, orange) represent the bootstrapped enrichment distribution of the scoring function coefficient combination labeled. Mean log AUC differences and p-values are reported below.



**Figure S3.** Examples of bootstrapping enrichment distribution where the difference for each the pairs of log AUC is calculated and then the distribution is plotted, and the z-test performed comparing to the distribution about zero.



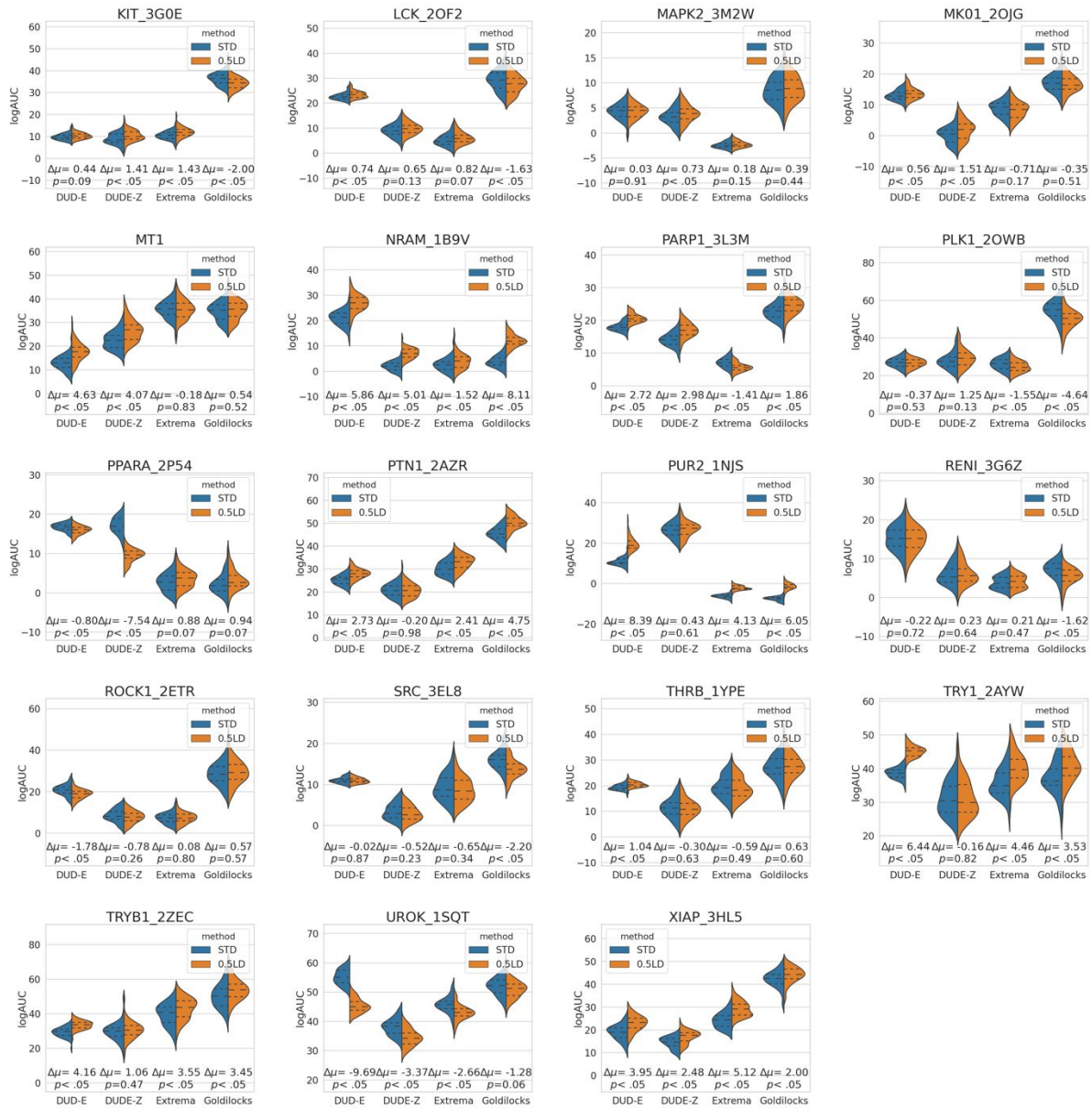
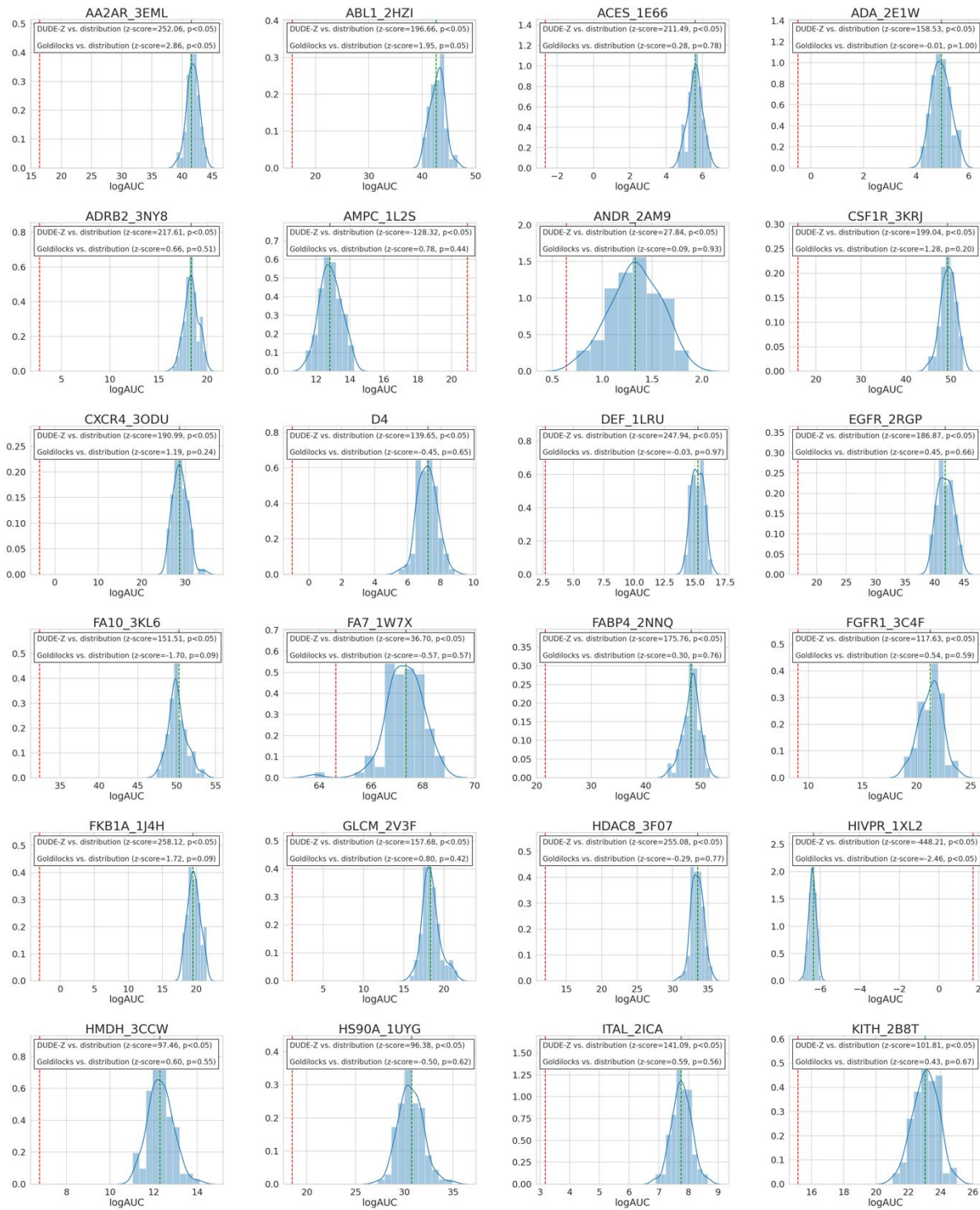
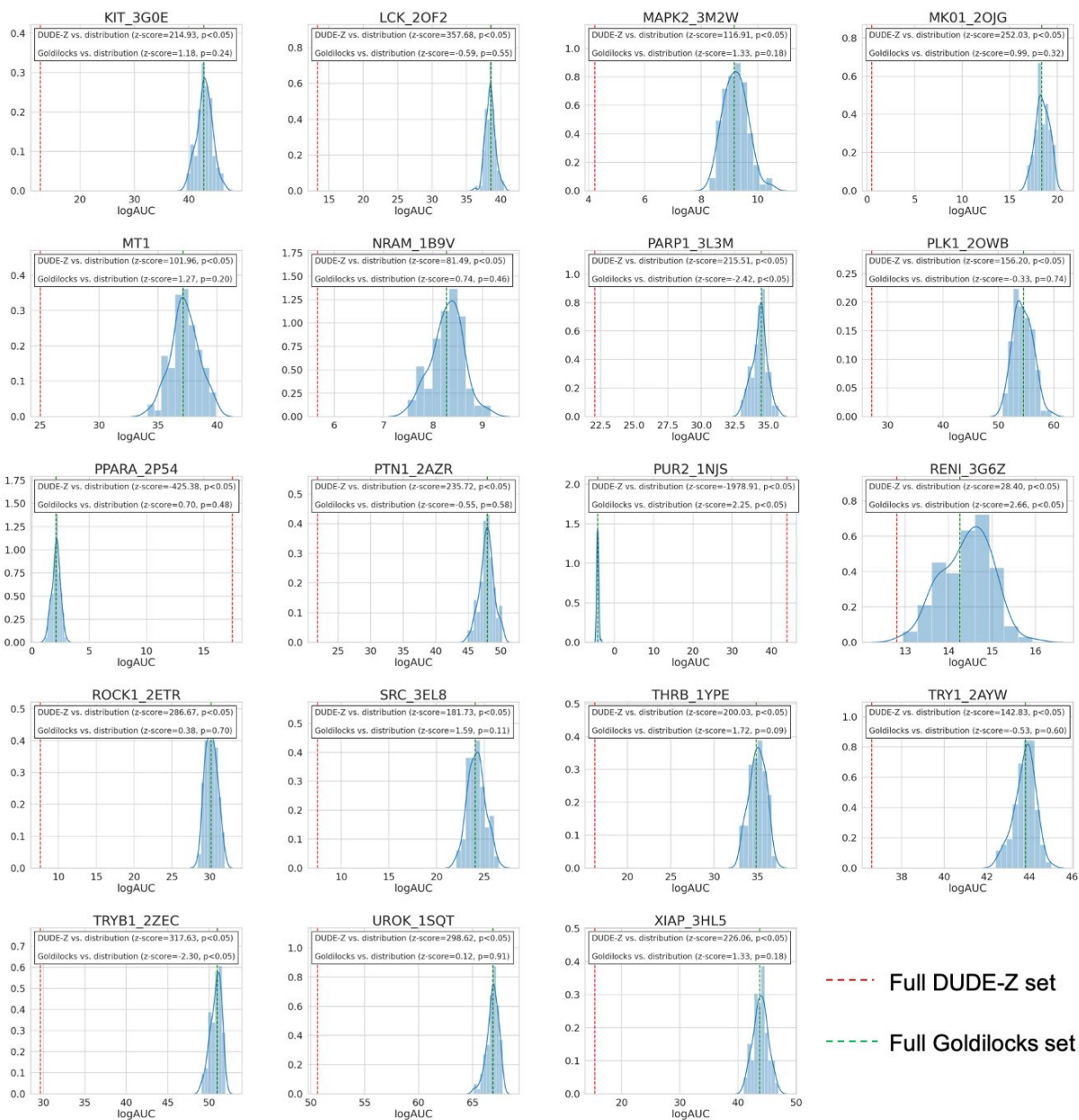


Figure S4. Bootstrapping statistics for 43 individual systems.



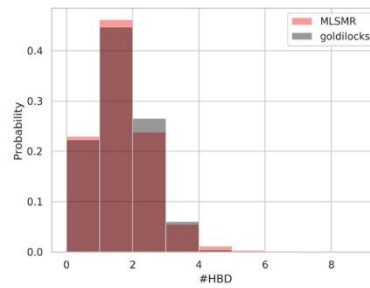
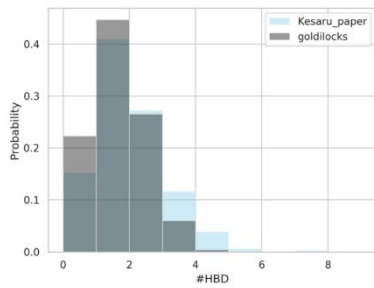
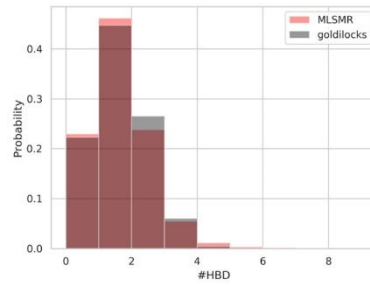
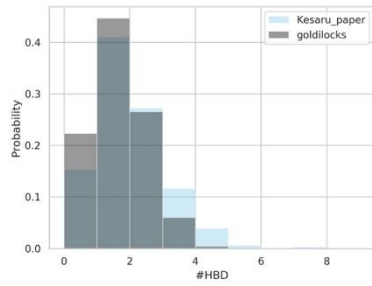
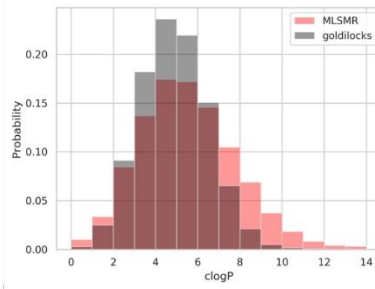
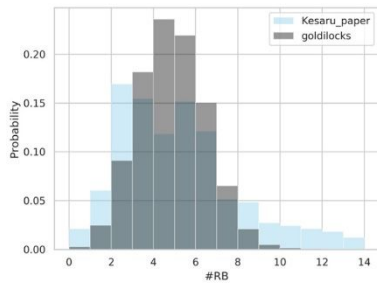
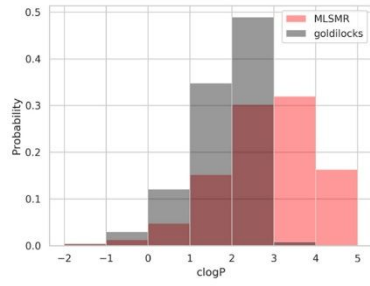
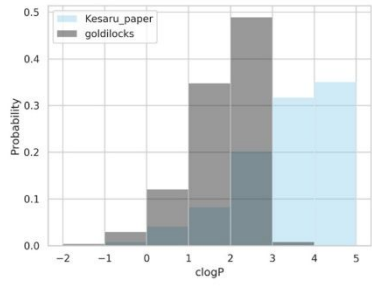
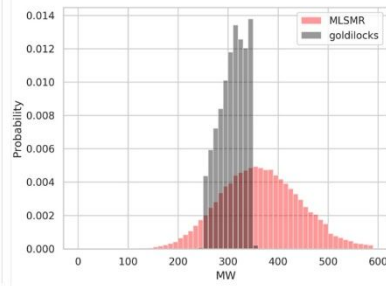
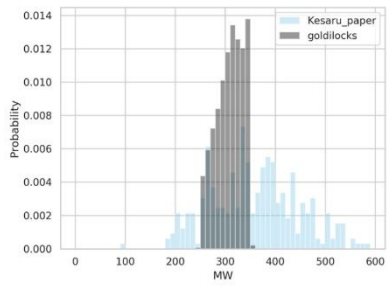


**Figure S5.** Comparison between a distribution of adjusted log AUC from randomly sampled Goldilocks set to the logAUC of full DUDE-Z set and full Goldilocks set.

For each system, a distribution of adjusted log AUC was obtained by randomly sampled decoys from the Goldilocks set. With the same ligand set, decoys were sub-sampled from the Goldilocks set with 1:50 ligands to decoys ratio for 100 times. The distribution is then



compared to the adjusted log AUC value from the DUDE-Z property-matched decoys set (red dashed line) and the full Goldilocks decoys set (green dashed line). Z-score and p-value for such comparison are calculated indicating the statistical significance of the difference.



**Figure S6.** Comparison of molecular properties (molecular weight, cLogP, number of rotatable bonds, and number of hydrogen bond donors and acceptors) from Goldilocks set and the hits from Kesaru et al., 2009 and the 400K Molecular Libraries Small Molecule Repository.