Supporting Information

1. The Settings for the Docking Program

AutoDock Vina: The protein and ligand was prepared and outputted as PDBQT files by the AutoDock Tools with default parameters.[1] The binding pocket of protein was defined by the corresponding cocrystal ligands, where the docking grid box was set as 20 Å×20 Å×20 Å centering on the cocrystal ligand. During docking runs, the exhaustiveness was set to 32 while the energy range was kept as default. For each ligand, only the top-1 pose was retained.

PLANTS: SPORES program was used for structural preparation of protein and ligand under *complete* mode. The conformation was sampled under the *screen* mode on the basis of the ant colony optimization algorithm and then scored using the *CHEPLP* scoring functions, which contains additional term to account for hydrogen bonding and metal-acceptor interactions. The *search_speed* parameter was set to speed 1. The center of binding site was set as the center of cocrystal ligand, and the radius of binding sphere was set as 20 Å. Similarly, only the top-1 pose was retained.

Glide SP: Glide SP is empirical scoring function-based docking program that can define metal constraints. The protein structure was prepared by *Protein Preparation Wizard* module in Schrödinger, and ligand was prepared by *LigPrep* module. The INNERBOX was set as 10 Å×10 Å×10 Å and the OUTERBOX was set as 30 Å×30 Å×30 Å . The docking center was adopted from the cocrystal ligand center. Finally, the other docking and scoring parameters was kept default, only the top-1 scored pose was retained for analysis.

2. The Detailed Descriptions of Baselines

NNScore2.0: NNScore2.0 is one of the most popular scoring functions for protein-ligand complex. The protein-ligand complex in NNScore2.0 is characterized by five Vina energy terms (“gauss 1”, “gauss 2”, “repulsion”, “hydrophobic” and “hydrogen-bond”) and BINANA binding characteristics. For the descriptions of metallic interactions, the number counting of metal-ligand atom pairs and energy summation of the electrostatic interaction between metal and ligand atoms are considered in BINANA. The NNscore2.0 algorithm was implemented in the ODDT python package with default parameters.[2]

RosENet: As the variation of ResNet-101 architecture, RosENet encodes molecular descriptors and atom energies into its inputs. The descriptors used in RosENet is calculated by HTMD Python library, and a total of 11 descriptors including aromatic carbon, hydrogen bond acceptor, positive ionizable, negative ionizable, metal ion, attractive, repulsive, positive electrostatic, negative electrostatic, positive implicit solvation, and negative implicit solvation are provided. Here all the available descriptors were employed in this study to systematically describe the properties of complex. We trained RosENet using the Adam optimizer with the loss function of RMSE and learning rate of 10^{-4}, and the batch size was set as 128. Each 3D grid was augmented by 24 times for per protein-ligand complex to consider rotation translation and invariance. All the training scripts are based on https://github.com/DS3Lab/RosENet.[3]

Physics-based Methods: The scoring functions from PLANTS and Glide SP docking programs were used as baselines. And the MM/GBSA method was implemented by the *prime_mmgbsa* utility in Schrödinger, and two calculation procedures with different force fields (OPLS2005 or OPLS3) were tested in this study. All other parameters were kept default.

Reference

1. Morris, G. M.; Huey, R.; Lindstrom, W.; Sanner, M. F.; Belew, R. K.; Goodsell, D. S.; Olson, A. J., AutoDock4 and AutoDockTools4: Automated docking with selective receptor flexibility. *Journal of computational chemistry* **2009**, 30, 2785-2791.
2. Wójcikowski, M.; Zielenkiewicz, P.; Siedlecki, P., Open Drug Discovery Toolkit (ODDT): a new open-source player in the drug discovery field. *Journal of Cheminformatics* **2015**, 7, 26.
3. Hassan-Harrirou, H.; Zhang, C.; Lemmin, T., RosENet: Improving Binding Affinity Prediction by Leveraging Molecular Mechanics Energies with an Ensemble of 3D Convolutional Neural Networks. *Journal of Chemical Information and Modeling* **2020**, 60, 2791-2802.

Table S1. The detailed information of the independent test dataset containing about 25000 active ligands towards 22 metalloproteins.

UniProt_ID	Metal Ion Type	Protein Family	K_i Ligands	K_d Ligands
O43570	Zn	Adenosine deaminase domain	2691	228
P00492	Zn	Alpha carbonic anhydrase domain	99	0
P00742	Zn	Alpha carbonic anhydrase domain	2525	4
P00915	Zn	Alpha carbonic anhydrase domain	4431	268
P00918	Zn	Alpha carbonic anhydrase domain	4740	352
P03956	Zn	Alpha carbonic anhydrase domain	525	0
P08254	Zn	Alpha carbonic anhydrase domain	489	4
P09237	Zn	Alpha carbonic anhydrase domain	101	0
P22748	Zn	Alpha carbonic anhydrase domain	726	138
P22894	Zn	Bcl-2, Bcl-2 homology region 1-3	319	0
P24941	Mg	Gamma-carboxyglutamic acid-rich (GLA) domain	192	28
P25774	Zn	Hemopexin-like domain	187	47
P43166	Zn	Hemopexin-like domain	703	259
P45452	Zn	Hemopexin-like domain	194	0
P49841	Zn	Hemopexin-like domain	214	21
P56658	Zn	Peptidase C1A, papain C-terminal	240	0
P98170	Zn	Peptidase M10, metallopeptidase	117	49
P9WKE1	Mg	Phosphoribosyl transferase domain	137	0
Q07820	Mg	Protein kinase	641	19

		domain		
Q16790	Mn	Protein kinase domain	3377	172
Q8N1Q1	Mg	Thymidylate kinase-like domain	80	258
Q9ULX7	Zn	Zinc finger, RING-type	393	127

Table S2. The number of the training, validation and test complexes for different binding affinity models.

Model Type	Training	Validation	Test
Mixture Model	10212	3405	618
Finetuning Model	1845	616	618

Table S3. The detailed information of the training, validation and test targets used in the virtual screening power test of MetalProGNet.

Training and Validation Targets (DUD-E)	Test Targets (DEKOIS) Modify 'DEKOIS' as 'DEKOIS2.0'
ace, ada, cah2, def, fnta, hdac2, hdac8, lkha4, mp2k, pa2ga, comt	mmp2, adam17, pde5, sars-hcov, qpct, pde4b

Table S4. The training hyper-parameters used for MetalProGNet.

Hyperparameters	Explantion Modify 'Explantion' as 'Explanation'	Value
batch_size	the training batch_size	200
n_FC_layer	the number of hidden layers in MLP	2
d_FC_layer	the number of hidden layers in MLP	200
dis_threshold	the distance threshold for protein-ligand atom pair interaction	8
dropout	dropout ratio	0.25
epochs	the number of maximum epochs	500
graph_feat_size	the hidden state size of covalent AAIN	128
l2	L2 regularization	0
lr	learning rate	0.001
num_layers	the number of hidden layers in covalent AAIN	5

outdim_g3	the vertor length for molecular binding vector	200
patience	the training patience in early stopping	70

Table S5. Impacts of similarity on the MetalProGNet performance (finetuning model of crystal pose).[a]

No.	R_p	RMSE
618	0.680	1.321
587	0.664	1.331
556	0.649	1.340
525	0.649	1.348
494	0.648	1.356
463	0.642	1.367
432	0.637	1.385
401	0.636	1.399
370	0.636	1.366
339	0.616	1.389
308	0.605	1.407

[a]The similarity was measured by the Euclidean distance between two interaction fingerprints. For each complex in test set, the similarity was assigned by the minimum Euclidean distance (maximum similarity) with the 2461 training(validation) complexes. The test set complexes were ascendingly sorted according to the similarity, and each time 5 percent complexes (31 complexes or so) were removed from the test set and new metrics were calculated for the remaining unsimilar test complexes. The lower limit of the remaining unsimilar test complexes is set as 50 percent.

Modify 'CHEMBL' as 'ChEMBL'

Table S6. Comparison with other state-of-the-art baselines on the CHEMBL dataset.

UniProt_ID	Ki_Num	Kd_Num	MetalProGNet_Finetuning		MetalProGNet_Mixture		Rosenet_Mixture		Rosenet_Finetuning		NNScore2.0_Mixture		NNScore2.0_Finetuning	
			Ki_R_p	Kd_R_p	Ki_R_p	Kd_R_p	Ki_R_p	Kd_R_p	Ki_R_p	Kd_R_p	Ki_R_p	Kd_R_p	Ki_R_p	Kd_R_p
O43570	2691	228	0.345	0.249	0.298	0.064	0.128	0.366	0.151	0.409	0.286	0.328	0.312	0.065
P00492	99	0	0.246	—	0.311	—	0.188	—	0.107	—	0.094	—	0.195	—
P00742	2525	0	0.289	—	0.230	—	0.133	—	0.170	—	0.263	—	0.271	—
P00915	4431	268	0.170	0.364	0.177	0.316	0.093	-0.101	0.102	-0.131	0.197	0.032	0.196	0.338
P00918	4740	352	0.340	0.482	0.337	0.352	0.113	0.334	0.135	0.308	0.291	0.385	0.301	0.387
P03956	525	0	0.230	—	0.178	—	0.103	—	0.146	—	-0.150	—	-0.038	—
P08254	489	0	0.358	—	0.488	—	0.412	—	0.384	—	0.132	—	0.017	—
P09237	101	0	-0.023	—	0.274	—	0.257	—	0.168	—	0.117	—	0.121	—

Modify 'Rosenet' as 'RosENet'

P22748	726	138	0.286	0.217	0.237	0.038	0.209	0.109	0.237	0.163	0.195	0.072	0.230	0.170
P22894	319	0	0.375	—	0.458	—	0.268	—	0.284	—	0.251	—	0.254	—
P24941	192	28	0.334	0.569	0.261	0.718	0.185	0.630	0.238	0.611	0.269	0.628	0.299	0.662
P25774	187	47	0.205	-0.473	0.065	-0.207	0.067	0.226	0.037	0.395	0.120	-0.063	0.189	-0.045
P43166	703	259	0.411	0.221	0.407	-0.035	0.226	0.185	0.235	0.149	0.367	0.058	0.400	-0.054
P45452	194	0	0.105	—	0.201	—	0.116	—	0.163	—	-0.017	—	0.019	—
P49841	214	21	0.134	-0.038	0.068	0.193	0.207	0.341	0.283	0.577	0.257	-0.043	0.202	-0.422
P56658	240	0	0.255	—	0.213	—	0.321	—	0.306	—	0.279	—	0.396	—
P98170	117	49	-0.167	0.203	-0.104	0.341	-0.127	0.243	-0.125	0.270	-0.285	0.384	-0.297	0.306
P9WKE1	137	0	0.292	—	0.483	—	0.339	—	0.451	—	0.336	—	0.204	—
Q07820	641	19	0.357	0.419	0.547	0.488	0.508	0.359	0.480	0.419	0.551	0.150	0.326	0.125
Q16790	3377	172	0.314	0.023	0.283	0.042	0.069	0.265	0.089	0.230	0.210	0.160	0.200	0.002
Q8N1Q1	80	258	0.726	0.057	0.631	-0.080	0.083	0.001	0.116	-0.023	0.465	0.010	0.613	0.013
Q9ULX7	393	127	0.453	0.166	0.426	0.061	0.149	0.074	0.199	0.038	0.344	0.050	0.459	0.046

Table S7. The performance of the PLANTS scoring function and MM/GBSA on the CHEMBL dataset. Modify 'CHEMBL' as 'ChEMBL'

UniProt_ID	Ki_Num	Kd_Num	PLANTS		MM/GBSA (OPLS_2005)		MM/GBSA (OPLS3e)	
			Ki_R_p	Kd_R_p	Ki_R_p	Kd_R_p	Ki_R_p	Kd_R_p
O43570	2691	228	-0.145	0.113	0.009	0.497	0.094	0.354
P00492	99	0	0.485	—	0.358	—	0.294	—
P00742	2525	0	0.087	—	0.188	—	0.218	—
P00915	4431	268	-0.025	-0.046	0.042	-0.155	0.097	-0.024
P00918	4740	352	-0.071	-0.092	0.083	0.233	0.104	0.099
P03956	525	0	-0.240	—	-0.167	—	-0.094	—
P08254	489	0	0.243	—	0.145	—	-0.011	—
P09237	101	0	0.226	—	0.174	—	0.029	—
P22748	726	138	0.033	0.089	0.041	0.246	0.089	0.264
P22894	319	0	0.207	—	-0.011	—	-0.092	—
P24941	192	28	-0.332	0.319	0.155	0.247	0.147	0.065
P25774	187	47	-0.151	0.042	0.156	0.235	0.107	0.375
P43166	703	259	-0.080	-0.069	0.057	0.136	0.011	0.100
P45452	194	0	0.072	—	0.053	—	-0.017	—
P49841	214	21	0.153	0.123	0.354	0.024	0.395	-0.175
P56658	240	0	0.231	—	0.097	—	0.095	—
P98170	117	49	0.046	0.167	0.015	0.322	0.117	0.034
P9WKE1	137	0	0.097	—	-0.201	—	-0.258	—
Q07820	641	19	0.274	0.181	0.246	-0.352	0.053	-0.232
Q16790	3377	172	-0.089	-0.124	-0.073	0.076	-0.015	-0.042
Q8N1Q1	80	258	-0.405	-0.129	0.072	0.024	0.103	0.014

Q9ULX7	393	127	-0.097	-0.040	0.083	0.217	0.172	0.201