Table S1. The references of the data set.

NO.	Reference
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Table S2. Binding energy of the molecular docking.

No.	Binding energy kJ/mol	No.	Binding energy kJ/mol	No.	Binding energy kJ/mol	No.	Binding energy kJ/mol
1	-32.23	8	-35.04	15	-48.47	22	-35.41
2	-27.29	9	-34.07	16	-28.21	23	-27.50
3	-33.19	10	-33.19	17	-36.25	24	-37.88
4	-27.59	11	-32.40	18	-33.24	25	-32.86
5	-36.69	12	-28.84	19	-38.68	26	-38.26
6	-27.29	13	-31.48	20	-29.67	27	-30.10
7	-33.24	14	-29.43	21	-25.74	28	-32.27

28 compounds were selected to carry out molecular docking in Autodock4. Each molecule underwent 50 molecular docking sessions to find the best binding position. No.15 is the best docking result which shows the highest binding energy -48.47 kJ/mol. And No.5, No.19, No.24, No.26 follow closely behind. The binding energy of all selected compounds is up to -6 Kcal/mol which illustrates the upstanding interaction with EGFR protein.

Figure S1 The descriptors screened by Mutual information and Correlation are listed in Figure. S1. (A) 30 descriptors sorted from highest to lowest were selected by Mutual information. (B) 30 descriptors sorted from highest to lowest were selected by Correlation.

Figure. S2 The two-dimensional scatter plot of the fingerprint ECFP4. It can be observed that the data set distributed between -30 and 30 of ECFP4 of TNSE-1 and -40 and 40 of ECFP4 of TNSE-2 on the horizontal and vertical coordinates.

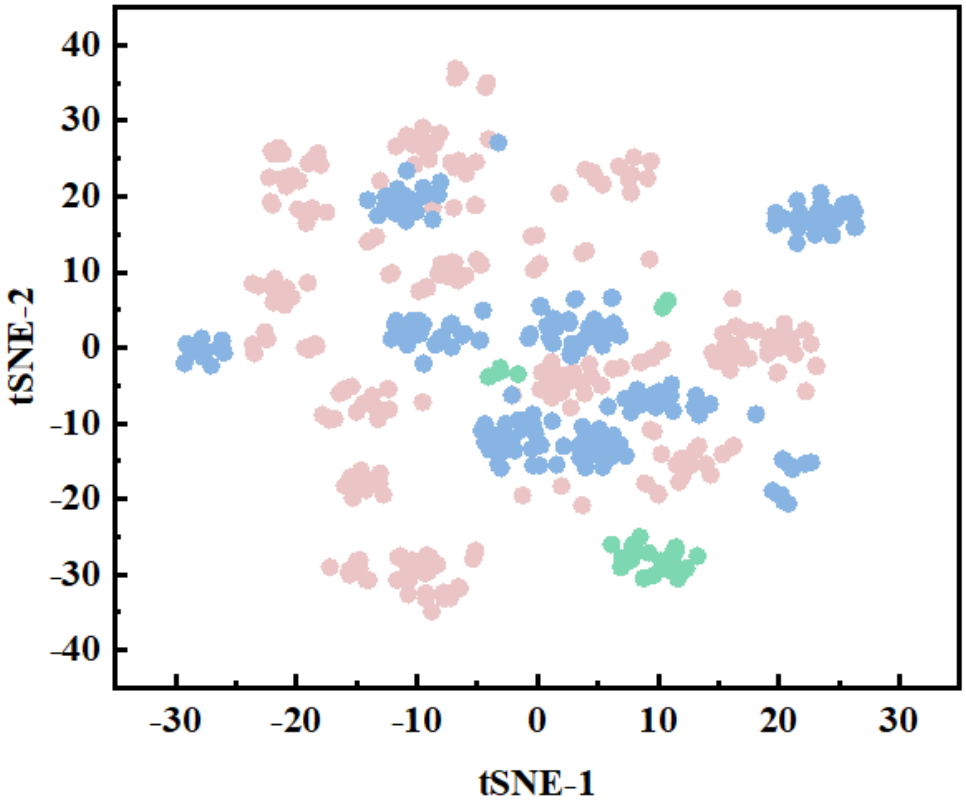

Figure. S3 The scatter plots of experimental pIC50 versus in silico prediction of the EGFR target by the SVM-GBDT and the SVM-DT. It can be observed that the points do not deviate too far from the regression line in figure s3, which shows the accuracy of the prediction.

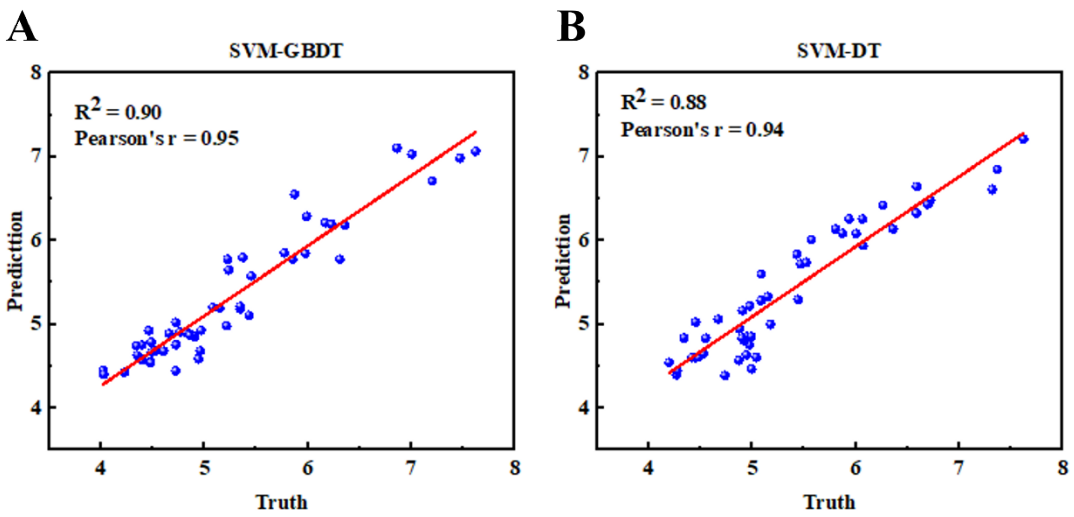

Figure. S4 Swarm plots of SHAP values. Shapley additive explanations (SHAP) analysis for the top 20 features in four machine-learning methods. The position of dots in the horizontal location represents whether the effect of that feature value contributed positively or negatively. The color of the dots from blue to pink represents the importance of features.

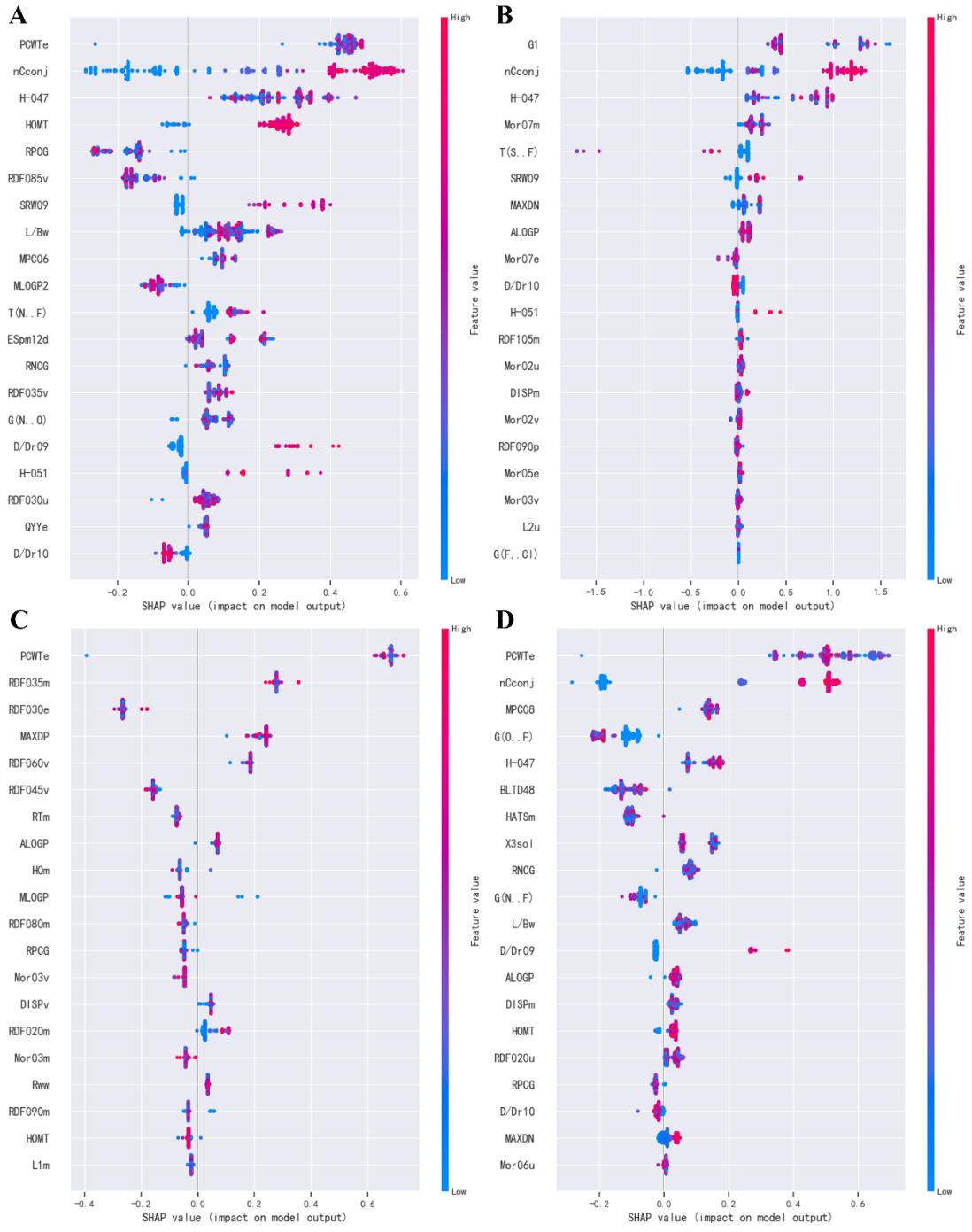

Figure. S5 The docking results of the four top-ranked exclude the highest. (A) (No.5) Four hydrogen bonding interactions with amino acid residues (LYS708, TYR915, LYS929, and GLU931) are shown. Five hydrophobic interactions with amino acid residues (TYR915, ASP916, ILE926, GLU931, and PRO934) are found. (B) (No.19) Five hydrogen bonding interactions with amino acid residues (LEU704, ILE706, TYR944, GLU931, GLN935) are shown. Five hydrophobic interactions with amino acid residues (ARG705, LEU707, TYR915, LEU933, PRO934) are found. (C) (No.24) Three hydrogen bonding interactions with amino acid residues (ILE706, ARG705, GLN935) are shown. Five hydrophobic interactions with amino acid residues (LEU703, PRO733, PRO934, GLN935) are found. (D) (No.26) Four hydrogen bonding interactions with amino acid residues (LEU718, ARG841, VAL843, THR854) are shown. Six hydrophobic interactions with amino acid residues (LEU718, VAL726, LEU792, LEU844, THR854) are found.