

# Supplementary Figures and Tables: A comprehensive comparison of deep learning-based compound-target interaction prediction models to unveil guiding design principles

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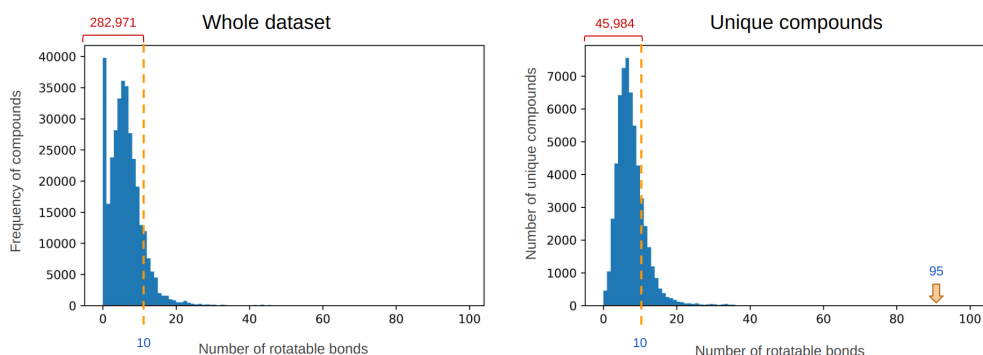
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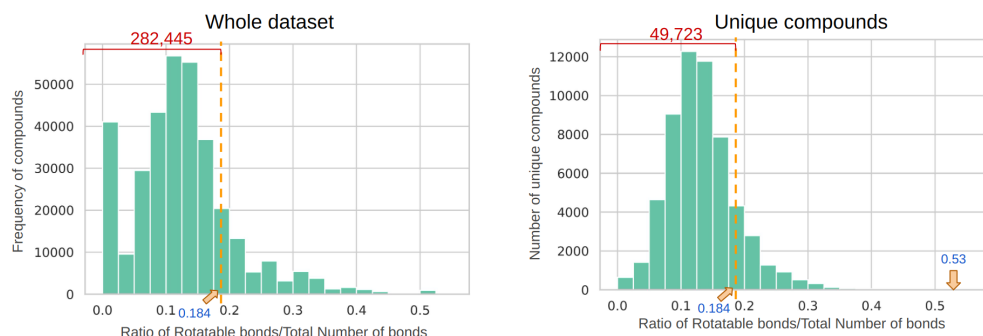
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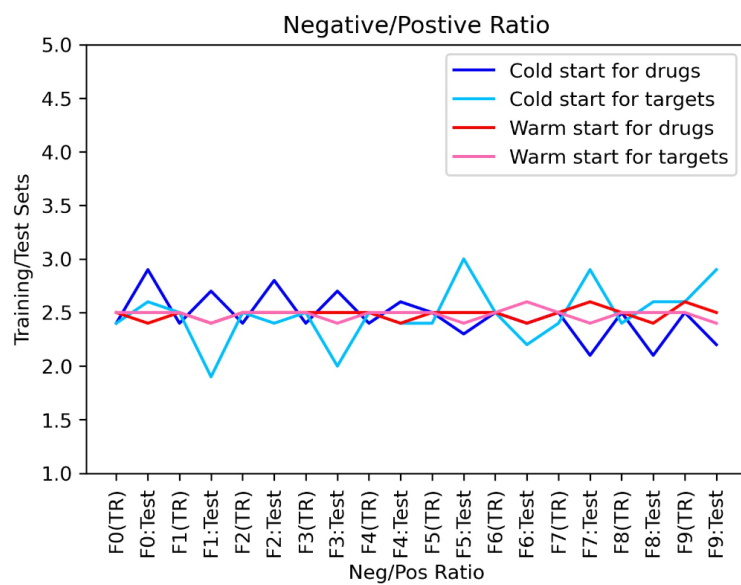
<sup>†</sup>These authors contributed equally to this work.



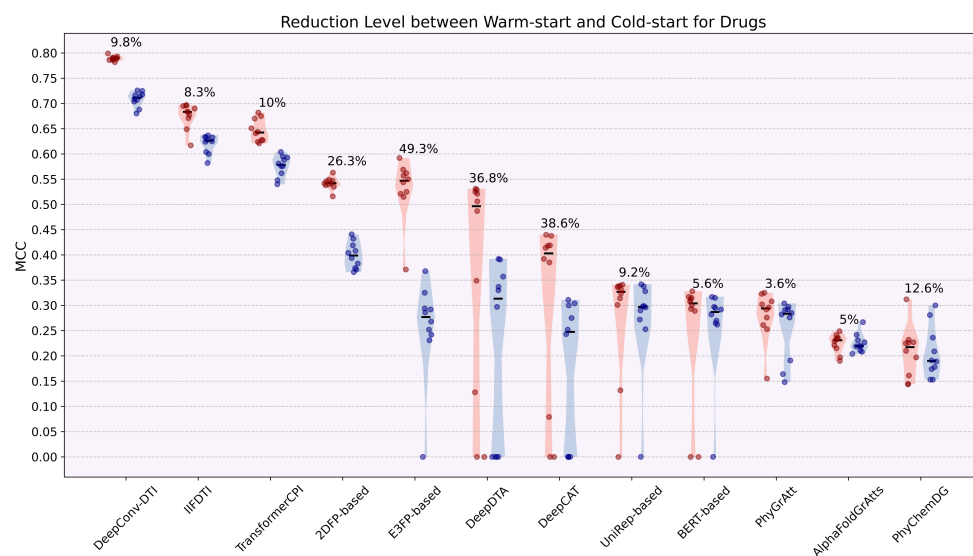
Supplementary Figure 1: The frequency distribution of compounds based on their number of rotatable bonds. The number of rotatable bonds in the compounds within the large aggregated dataset ranges from 0 to 95. The Limited-Rotatable-Bonds (LRB) dataset is created by retaining compounds with fewer than 10 rotatable bonds. As a result, 282,971 compound-target samples out of 337,526 meet this criterion. The LRB dataset includes 45,984 unique compounds, representing approximately 79% of the compounds in the main dataset. Additionally, there are 460 compounds without any rotatable bonds, which are associated with 39,796 compound-target interaction samples in the main dataset. There are approximately 400 compounds with zero rotational bonds. The entire dataset comprises over 37,000 positive and negative CTIs involving these compounds. On average, each compound with zero rotational bonds appears 92 times across the dataset.



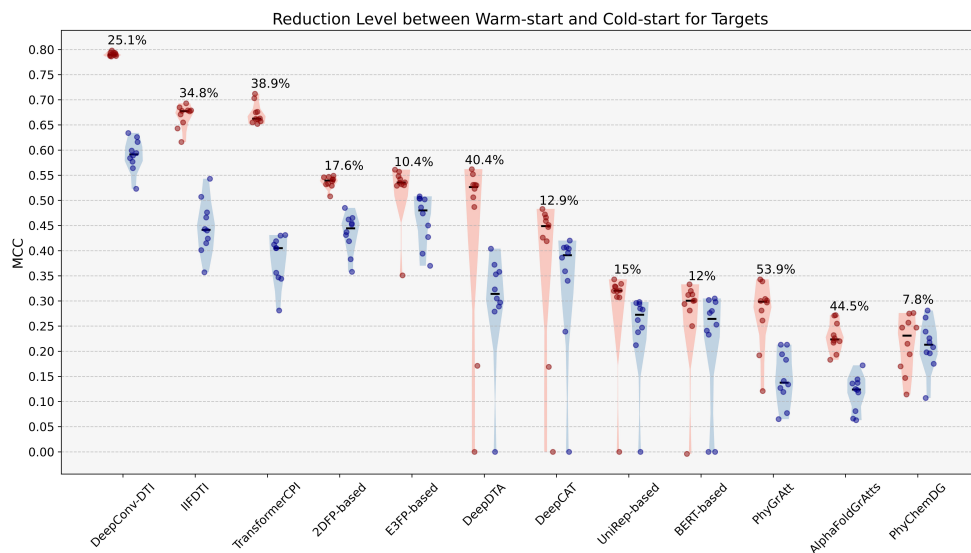
Supplementary Figure 2: The frequency distribution of compounds based on the ratio of the number of rotatable bonds over the total number of bonds. The ratio is referred to as the Rotatable Bond Fraction (RBF), and the Ratio-based Rotatable Bonds (RRB) dataset is created by retaining compounds with an RBF of less than 0.184. The RRB dataset includes 49,723 unique compounds, representing approximately 85% of the compounds in the large aggregated dataset.



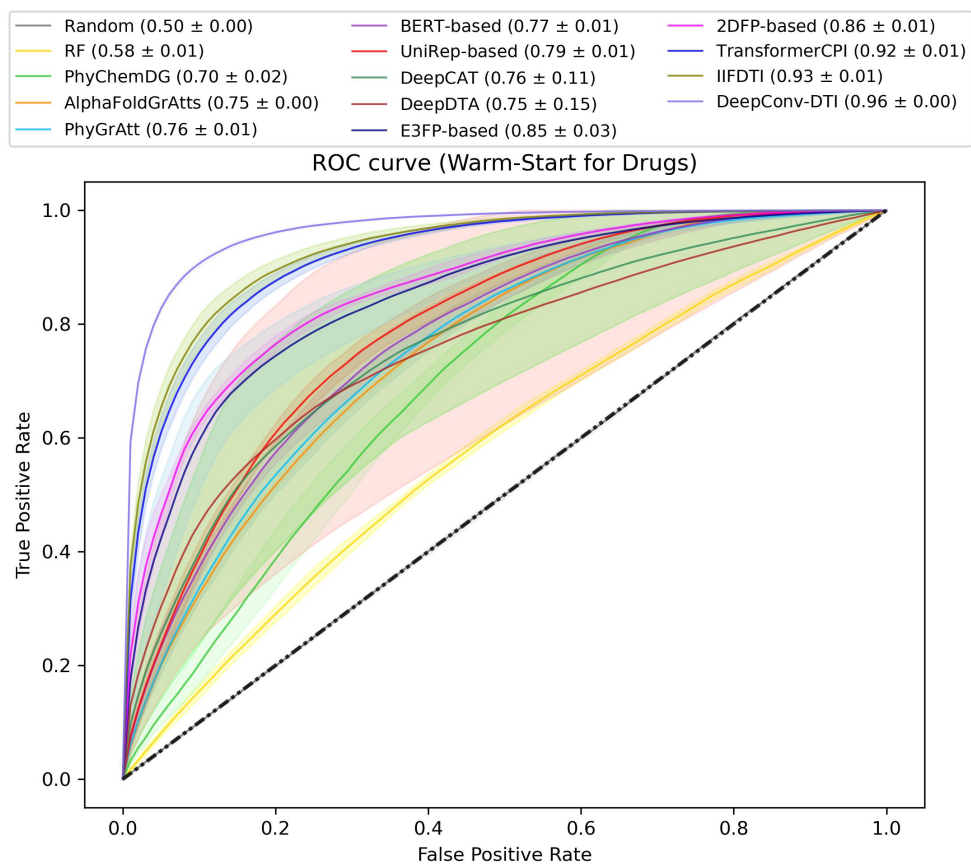
Supplementary Figure 3: The ratio of negative samples to positive samples varies across different folds. 'F0(TR)' represents the combination of all folds except fold 0, while 'F0: Test' represents fold 0 itself.



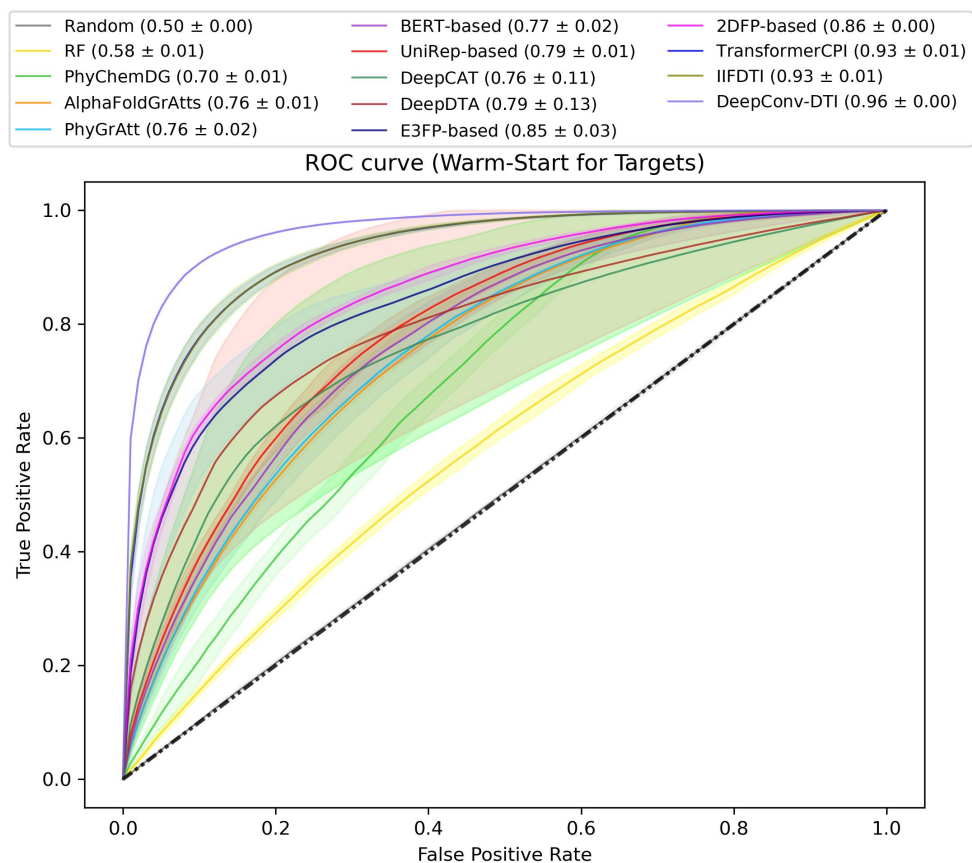
Supplementary Figure 4: The reduction disparity between warm-start and cold-start for compounds. The reduction level in performance for compound-based models, such as 2DF-based and E3FP-based models, is quite significant due to their reliance on the compounds' 2D or 3D structures.



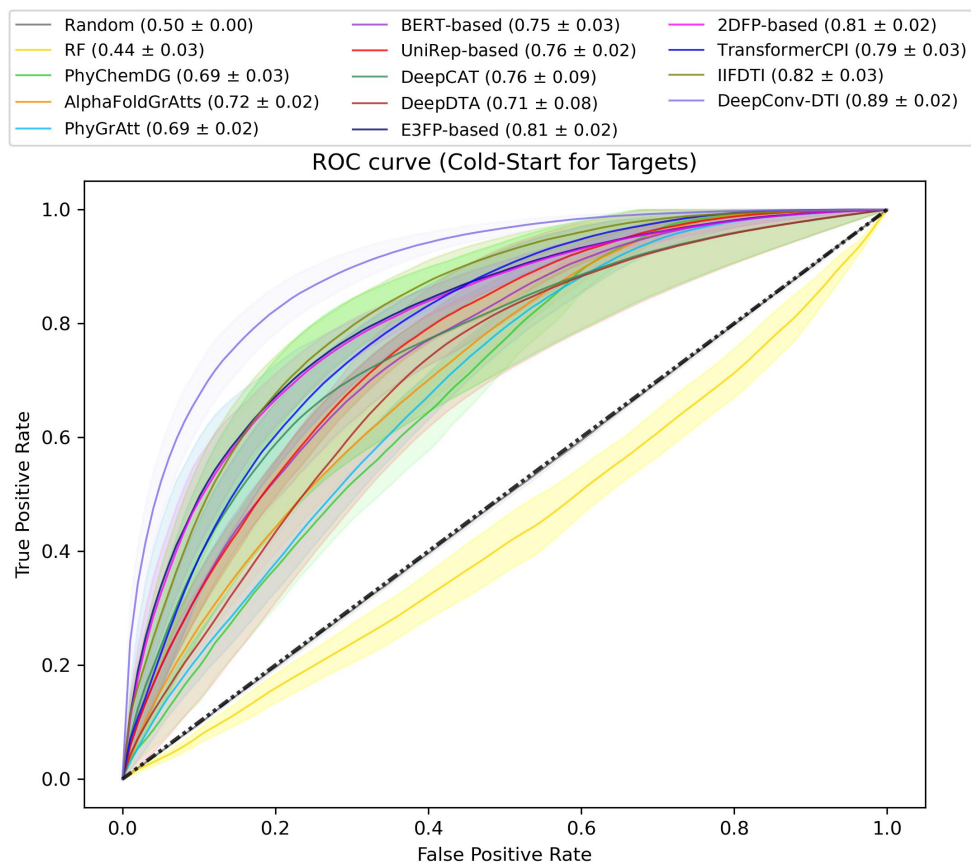
Supplementary Figure 5: The reduction disparity between warm-start and cold-start for targets. The reduction level in performance for protein structure-based models, such as AlphaFoldGrAtts and PhyGrAtt, is quite significant due to their reliance on the proteins' structures.



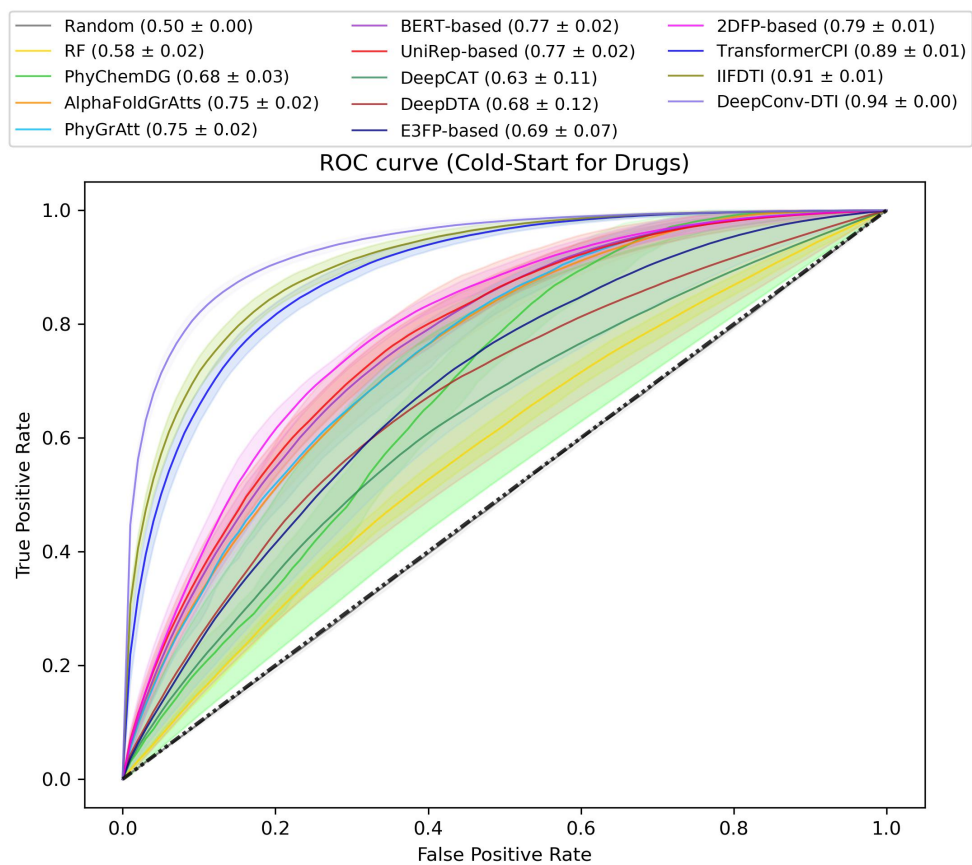
Supplementary Figure 6: Comparison of ROC curves for various models on the large aggregated dataset, split using the warm-start splitting scenarios for compounds.



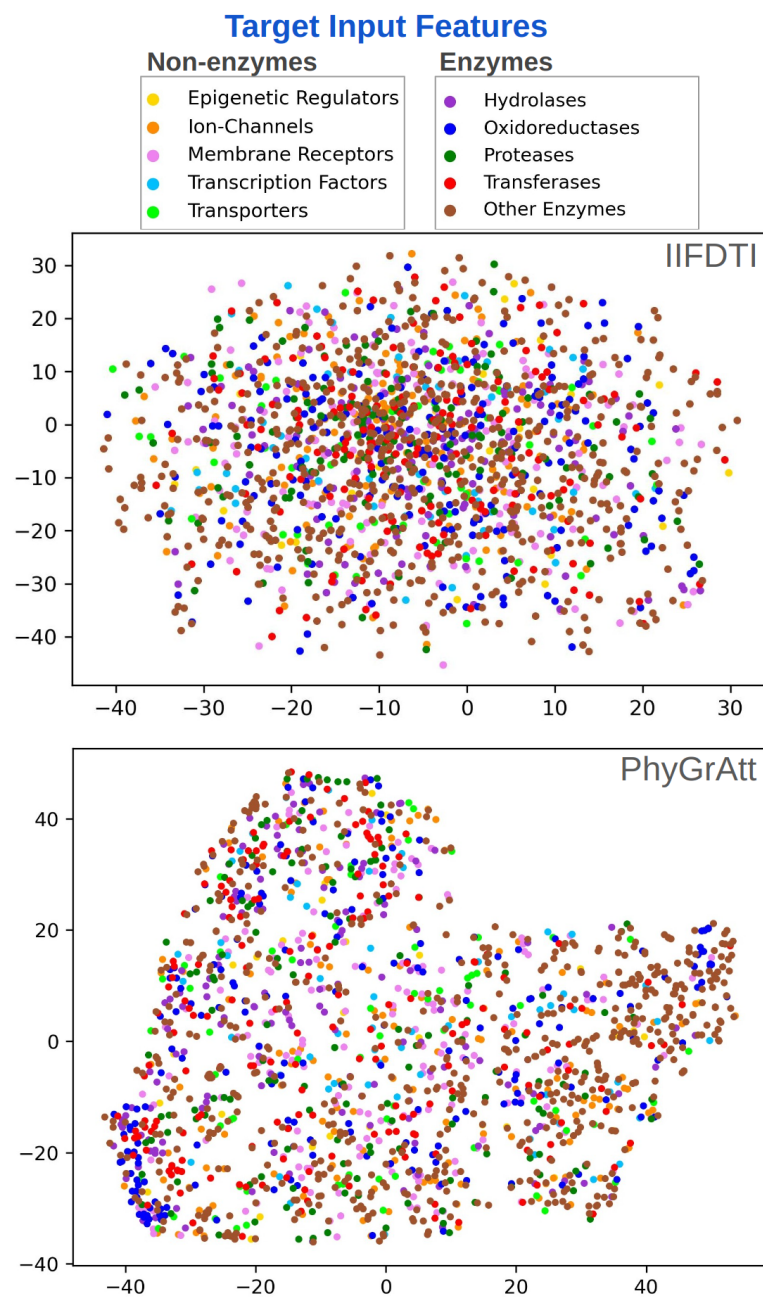
Supplementary Figure 7: Comparison of ROC curves for various models on the large aggregated dataset, split using the warm-start splitting scenarios for targets.



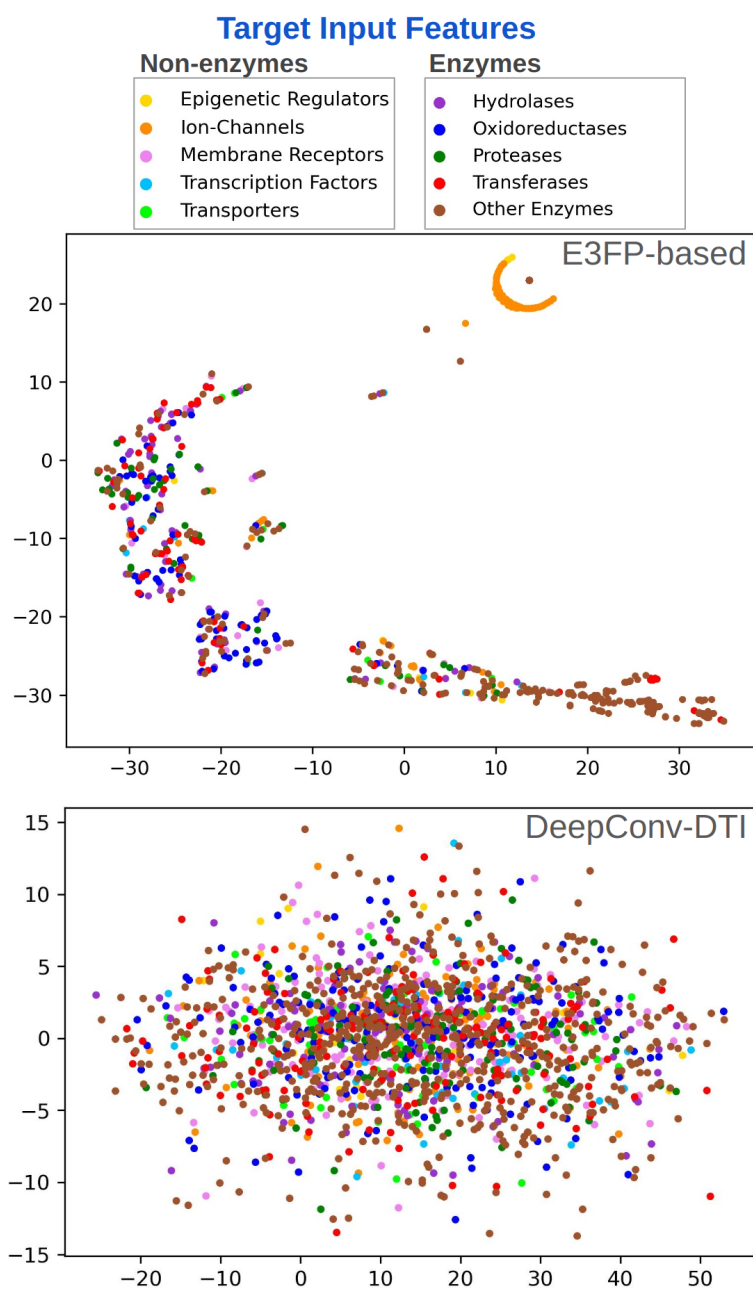
Supplementary Figure 8: Comparison of ROC curves for various models on the large aggregated dataset, split using the cold-start splitting scenarios for targets.



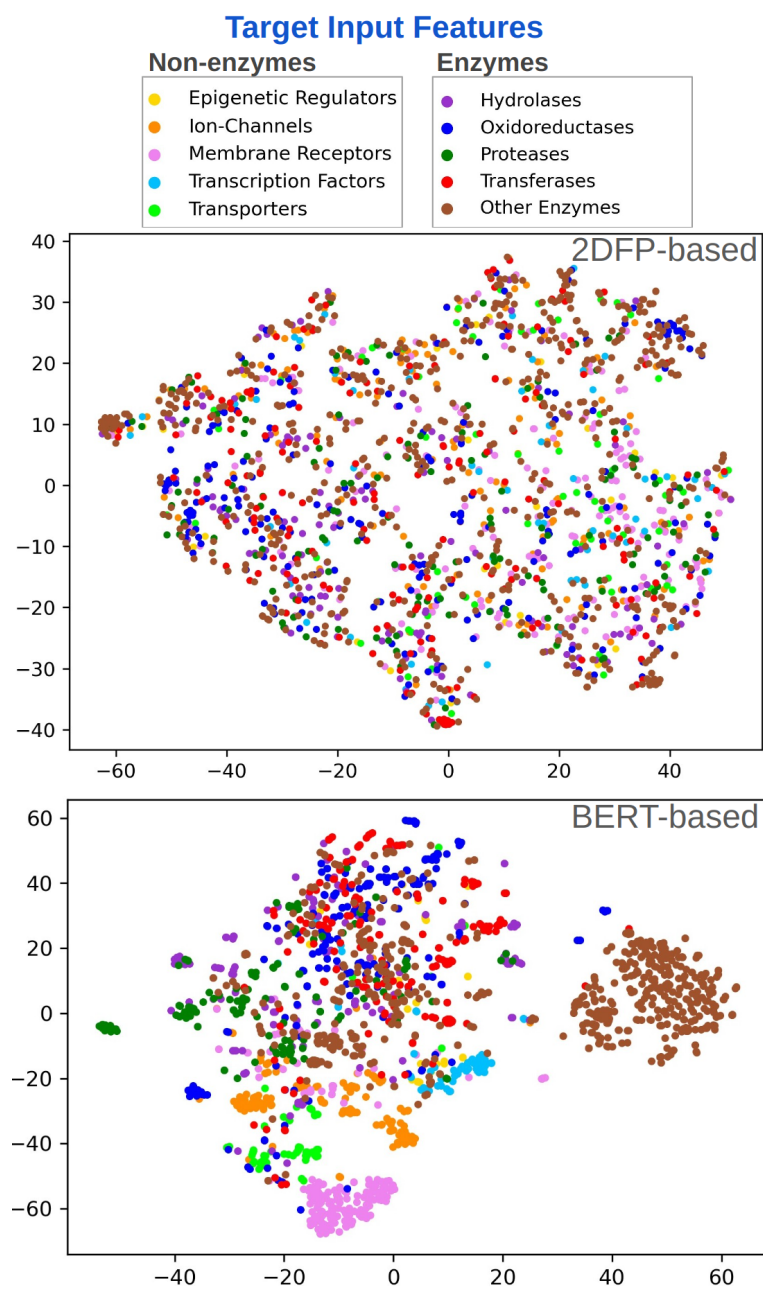
Supplementary Figure 9: Comparison of ROC curves for various models on the large aggregated dataset, split using the cold-start splitting scenarios for compounds.



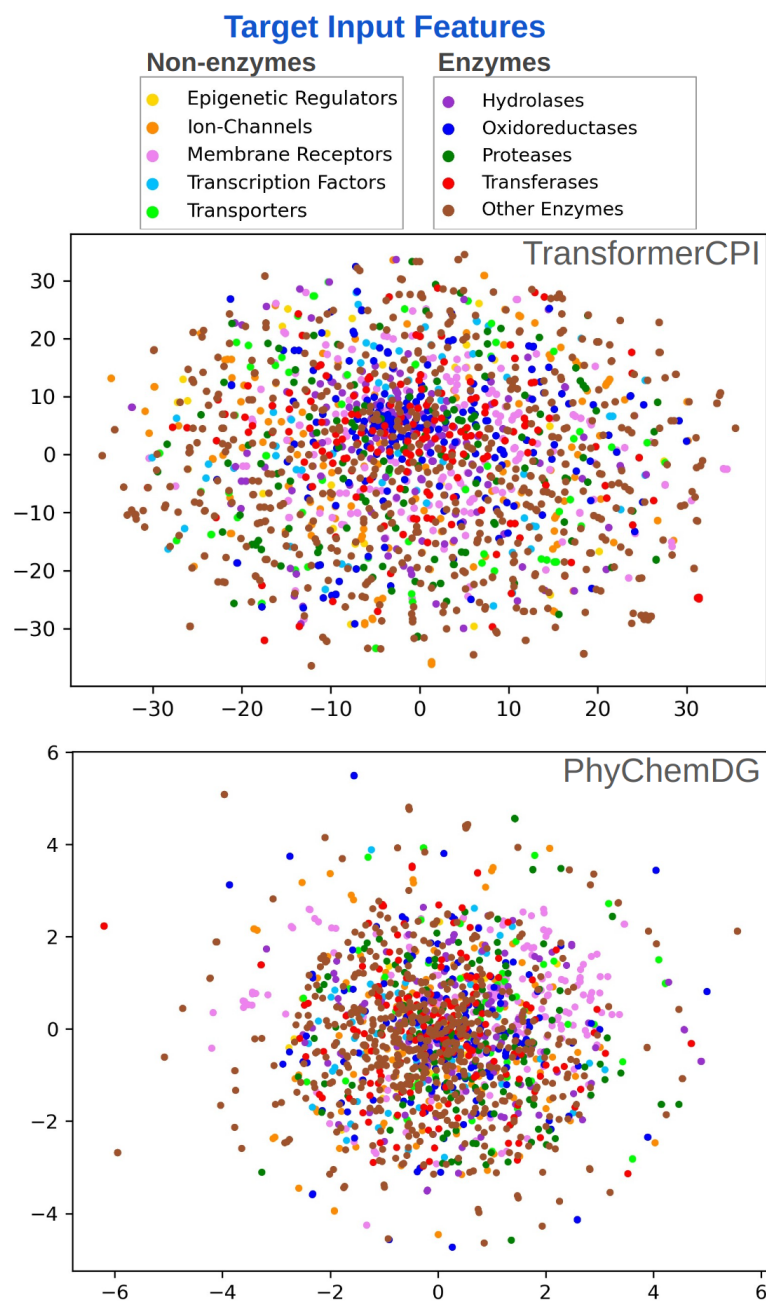
Supplementary Figure 10: The t-SNE plots of the target representative vectors obtained from the IIFDTI and PhyGrAtt models after training across the large aggregated dataset.



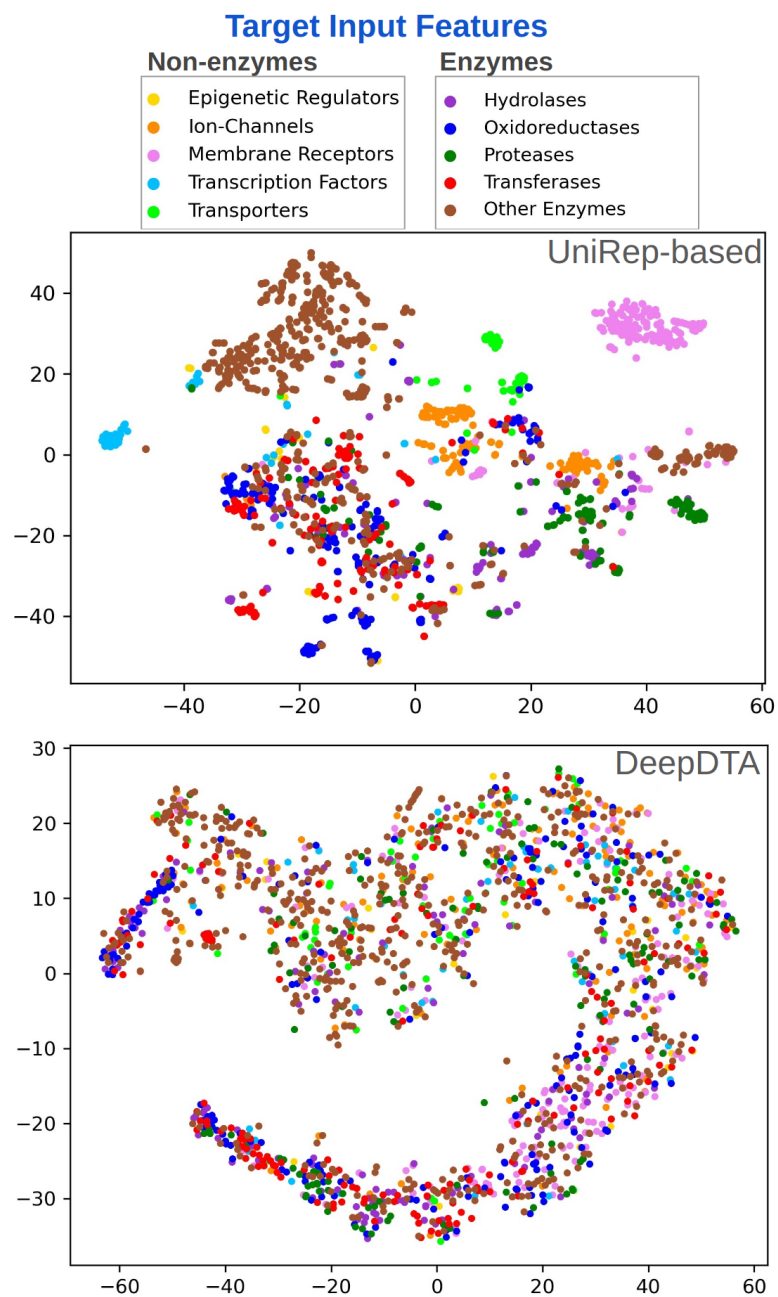
Supplementary Figure 11: The t-SNE plots of the target representative vectors obtained from the E3FP-based and DeepConv-DTI models after training across the large aggregated dataset.



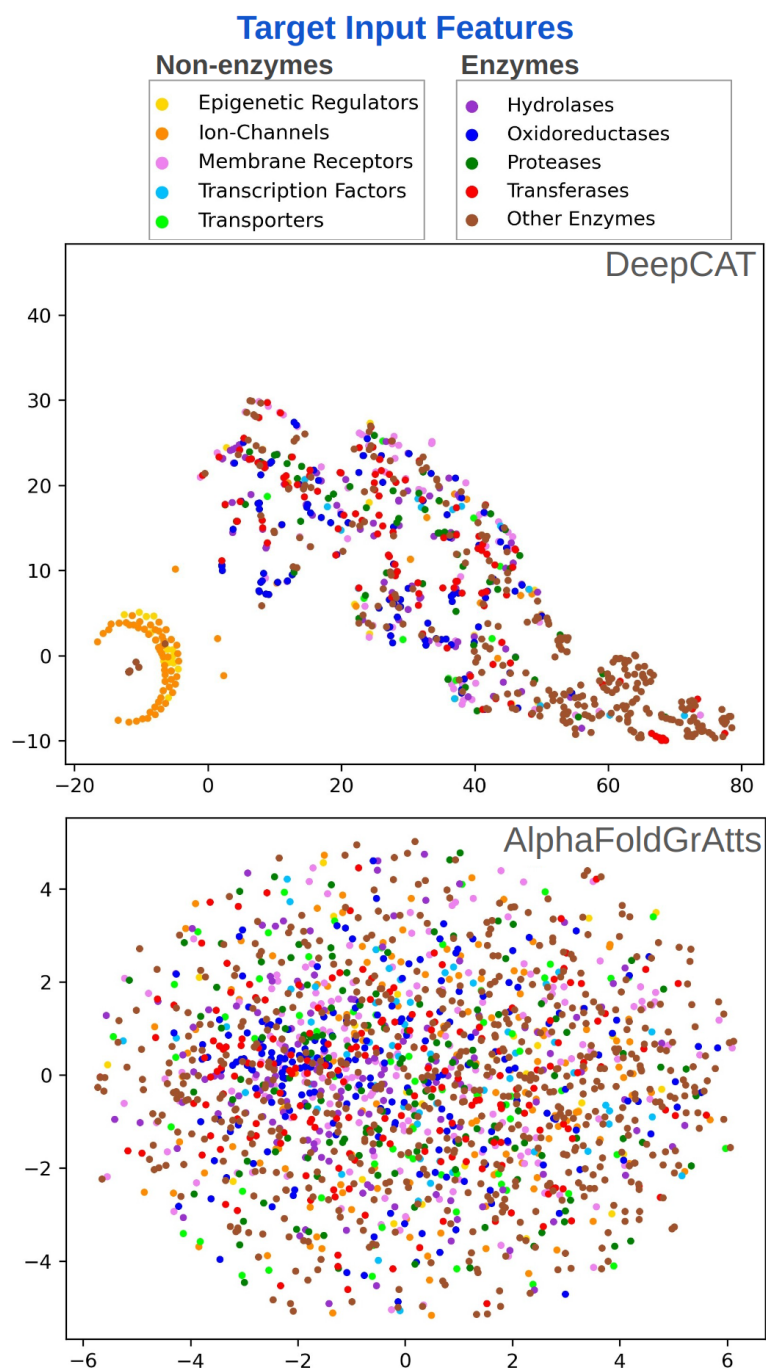
Supplementary Figure 12: The t-SNE plots of the target representative vectors obtained from the 2DFP-based and BERT-based models after training across the large aggregated dataset.



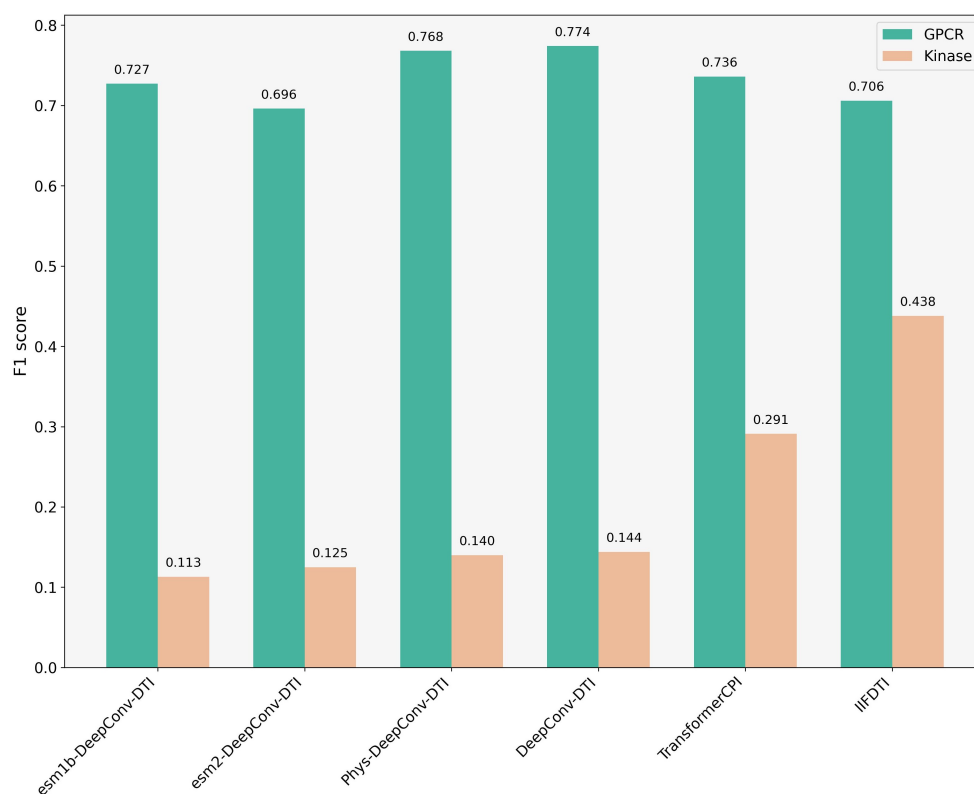
Supplementary Figure 13: The t-SNE plots of the target representative vectors obtained from the TransformerCPI and PhyChemDG models after training across the large aggregated dataset.



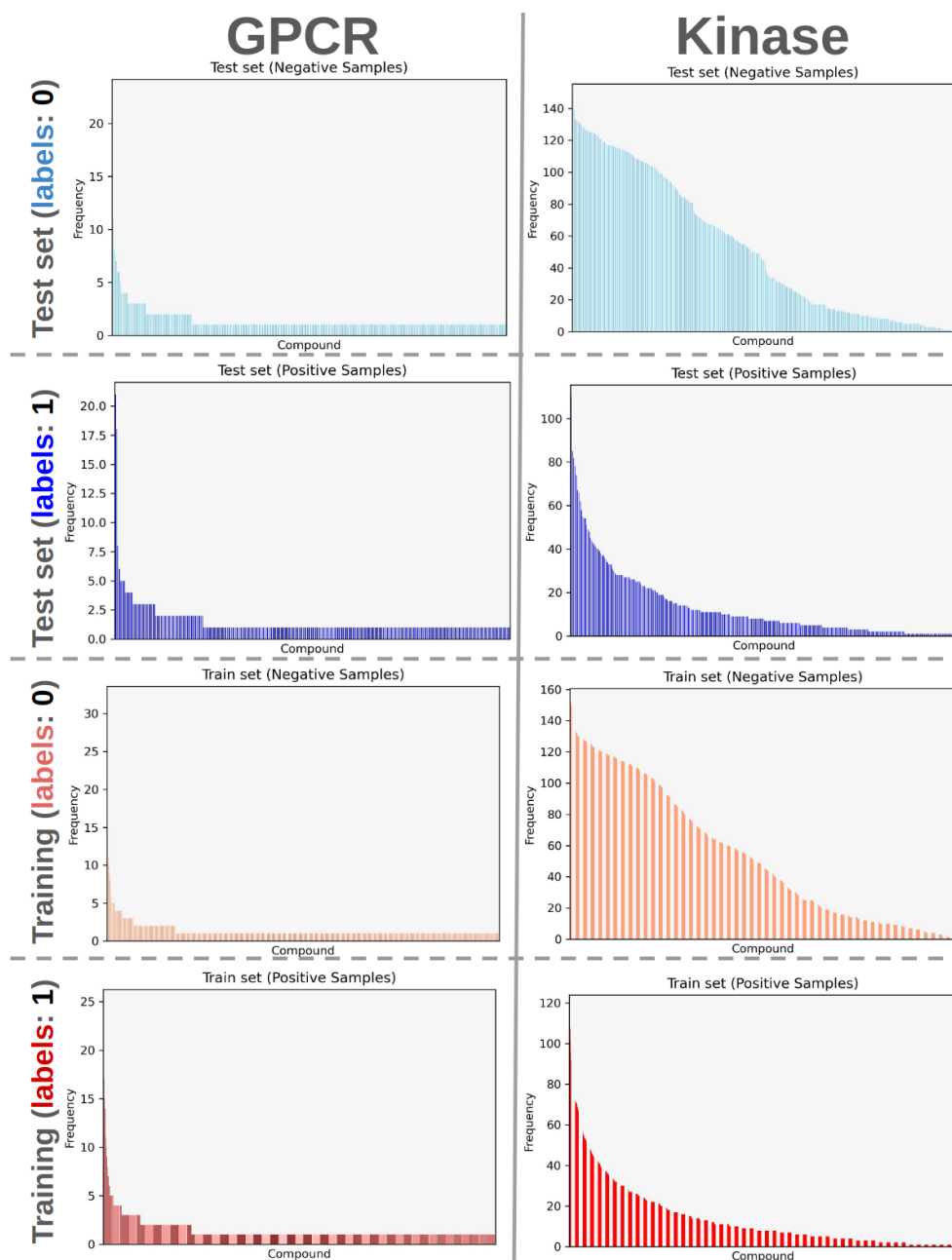
Supplementary Figure 14: The t-SNE plots of the target representative vectors obtained from the UniRep-based and DeepDTA models after training across the large aggregated dataset.



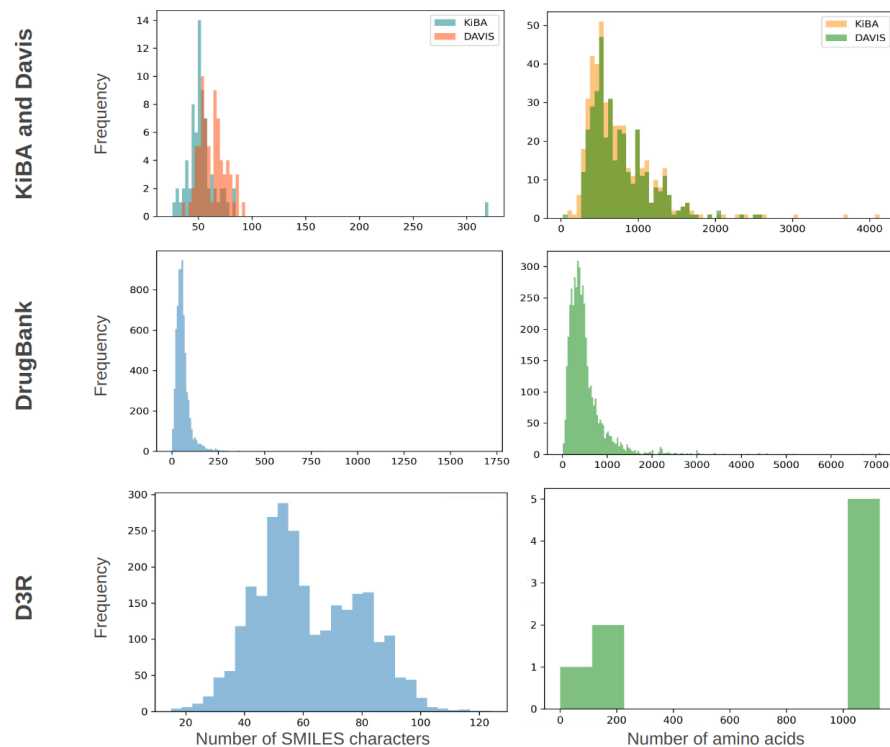
Supplementary Figure 15: The t-SNE plots of the target representative vectors obtained from the DeepCAT and AlphaFoldGrAtts models after training across the large aggregated dataset.



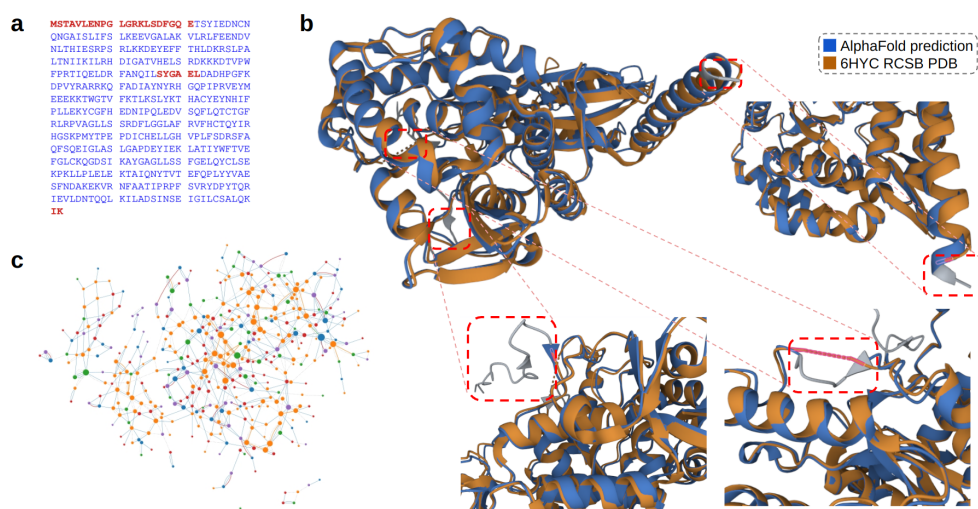
Supplementary Figure 16: Comparison of models across the label reversal dataset in terms of F1 score.



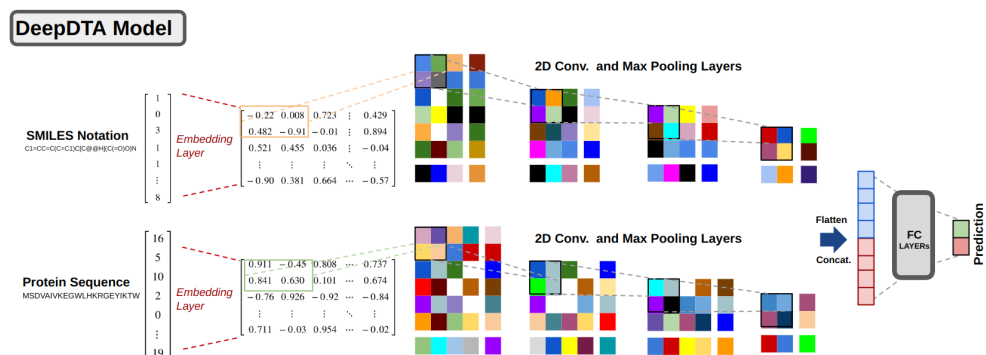
Supplementary Figure 17: Distribution of compound frequencies contributing to negative and positive CTIs in the GPCR and Kinase label reversal training and test sets.



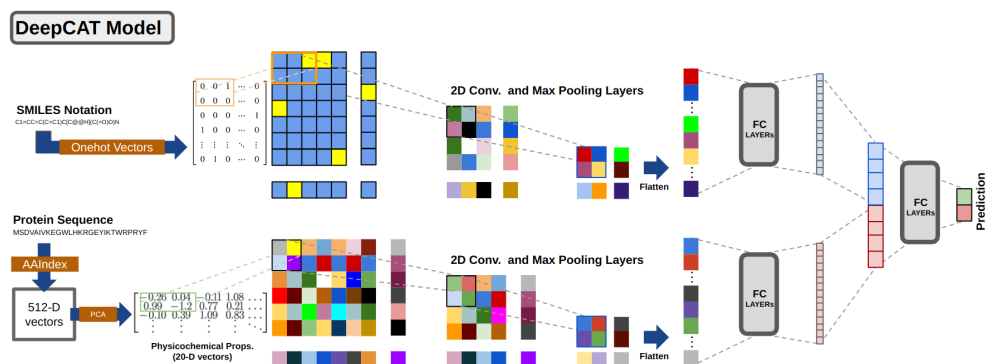
Supplementary Figure 18: The frequency distribution of compounds and targets in different datasets based on the number of SMILES characters and the number of amino acids, respectively.



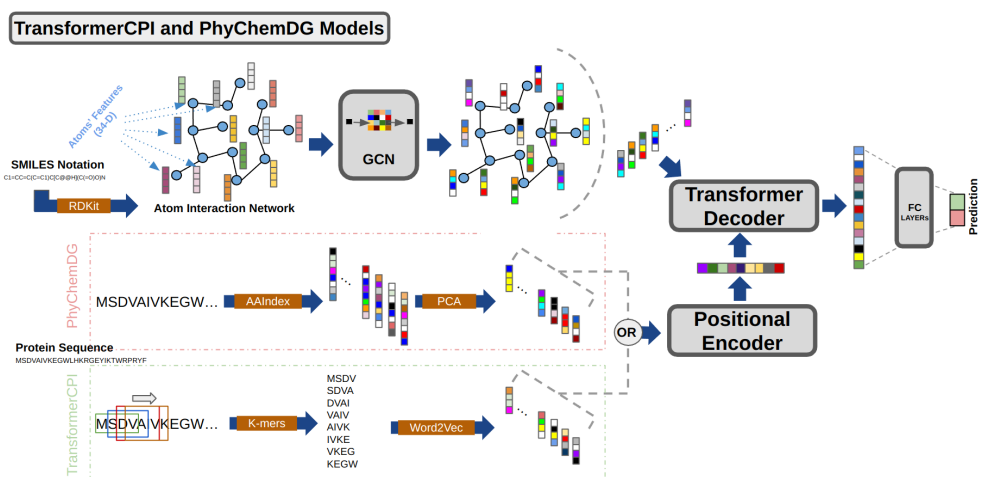
Supplementary Figure 19: (a) The amino acid sequence of the PH4H protein. Amino acids that do not appear in the 6HYC PDB file are highlighted in red. (b) The real (orange) and AlphaFold-predicted (blue) 3D structure of the PH4H protein. Missing amino acids, predicted by AlphaFold, are shown in gray. (c) The residue interaction network of the PH4H protein extracted using RINGv3.0.



Supplementary Figure 20: DeepDTA: Utilizing learnable embeddings (targets and compounds).

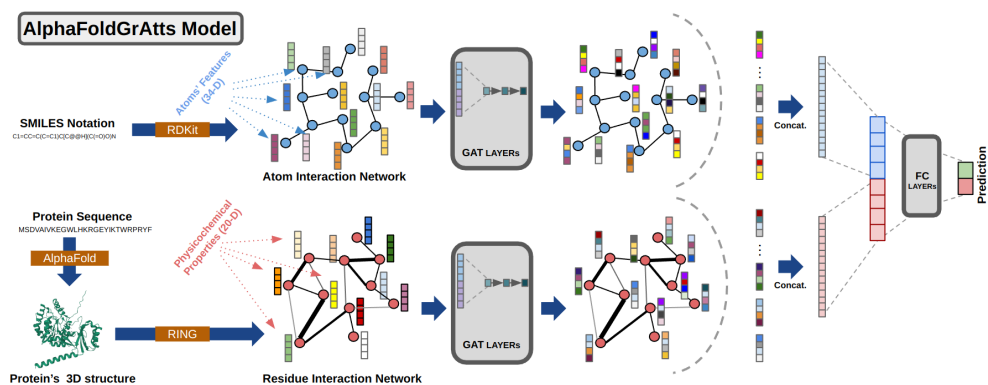


Supplementary Figure 21: DeepCAT: Utilizing physicochemical properties (targets) and onehot vectors (compounds).

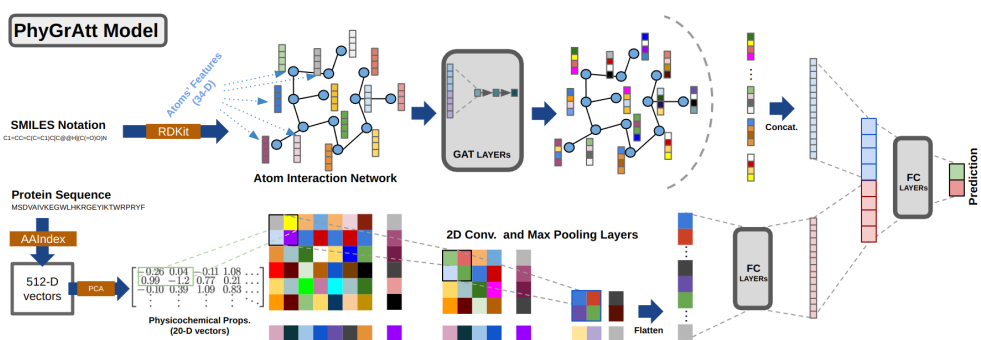


Supplementary Figure 22: TransformerCPI: Utilizing k-mers and Word2Vec (targets) and atoms' interaction network (compounds). PhyChemDG: Utilizing physicochemical properties (target) and atoms' interaction network (compounds)

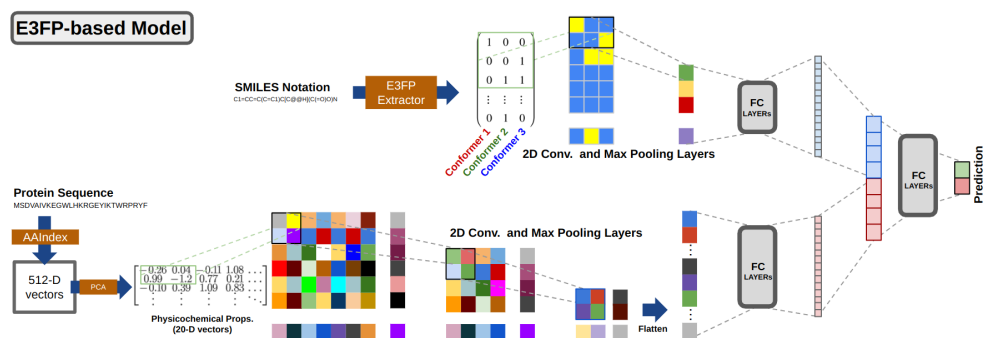




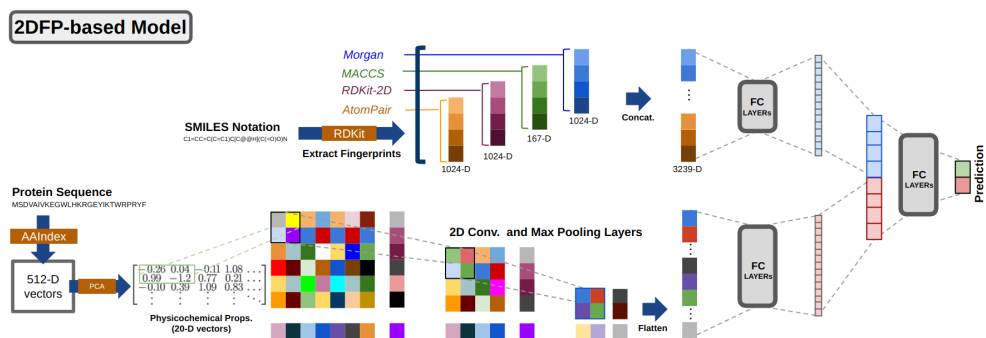
Supplementary Figure 25: AlphaFoldGrAtts: Utilizing residue interaction network (targets) and atoms' interaction network (compounds)



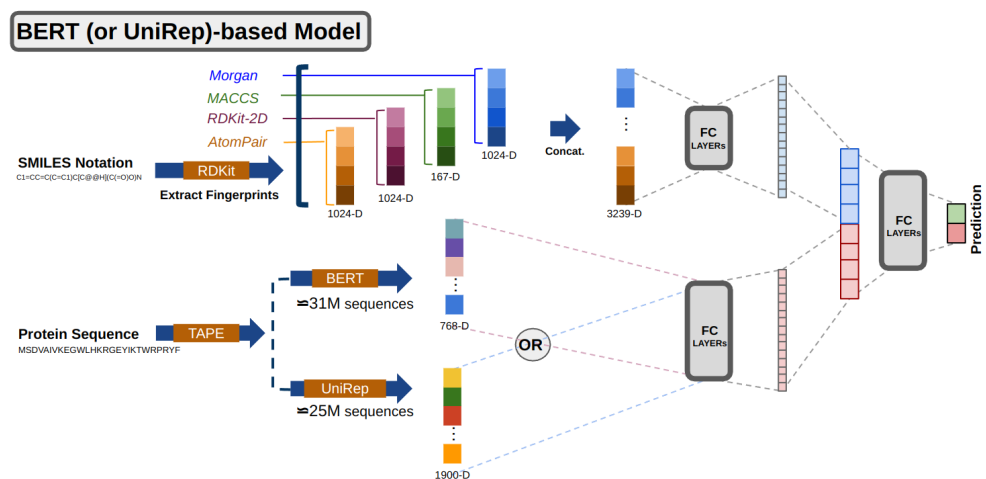
Supplementary Figure 26: PhyGrAtt: Utilizing physicochemical properties (targets) and atoms' interaction network (compounds)



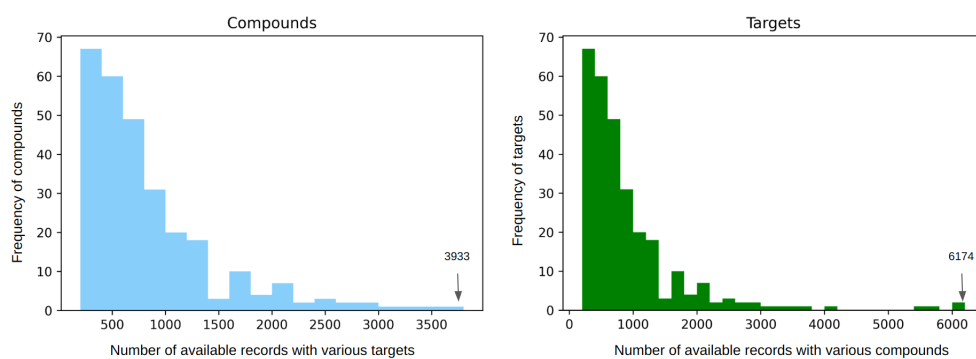
Supplementary Figure 27: The E3FP-based model: Utilizing physicochemical properties (targets) and 3D drug fingerprints (compounds)



Supplementary Figure 28: The 2DFP-based model: Utilizing physicochemical properties (targets) and 2D drug fingerprints (compounds)



Supplementary Figure 29: The BERT (and UniRep)-based models: Utilizing learned, BERT-based or UniRep-based, embeddings (targets) and 2D drug fingerprints (compounds)



Supplementary Figure 30: The frequency distribution of compounds and target in the large aggregated dataset.

Supplementary Table 1: Warm-start for compounds splitting

| Folds         | Dataset      | Negative | Positive | Ratio N/P | Avg No. Rot. bonds |
|---------------|--------------|----------|----------|-----------|--------------------|
| <b>Fold 0</b> | Training Set | 216274   | 87499    | 2.5       | 7.2                |
|               | Test Set     | 23781    | 9972     | 2.4       | 7.1                |
| <b>Fold 1</b> | Training Set | 216200   | 87573    | 2.5       | 7.2                |
|               | Test Set     | 23855    | 9898     | 2.4       | 7.0                |
| <b>Fold 2</b> | Training Set | 215997   | 87776    | 2.5       | 7.2                |
|               | Test Set     | 24058    | 9695     | 2.5       | 7.1                |
| <b>Fold 3</b> | Training Set | 215880   | 87893    | 2.5       | 7.2                |
|               | Test Set     | 24175    | 9578     | 2.5       | 7.1                |
| <b>Fold 4</b> | Training Set | 216145   | 87628    | 2.5       | 7.2                |
|               | Test Set     | 23910    | 9843     | 2.4       | 7.1                |
| <b>Fold 5</b> | Training Set | 215908   | 87865    | 2.5       | 7.2                |
|               | Test Set     | 24147    | 9606     | 2.5       | 7.1                |
| <b>Fold 6</b> | Training Set | 216306   | 87468    | 2.5       | 7.2                |
|               | Test Set     | 23749    | 10003    | 2.4       | 7.1                |
| <b>Fold 7</b> | Training Set | 215741   | 88033    | 2.5       | 7.2                |
|               | Test Set     | 24314    | 9438     | 2.6       | 7.1                |
| <b>Fold 8</b> | Training Set | 216093   | 87681    | 2.5       | 7.2                |
|               | Test Set     | 23962    | 9790     | 2.4       | 7.1                |
| <b>Fold 9</b> | Training Set | 215951   | 87823    | 2.6       | 7.2                |
|               | Test Set     | 24104    | 9648     | 2.5       | 7.1                |

Supplementary Table 2: Warm-start for targets splitting

| Folds         | Dataset      | Negative | Positive | Ratio N/P | Avg No. Rot. bonds |
|---------------|--------------|----------|----------|-----------|--------------------|
| <b>Fold 0</b> | Training Set | 215967   | 87806    | 2.5       | 7.2                |
|               | Test Set     | 24088    | 9665     | 2.5       | 7.1                |
| <b>Fold 1</b> | Training Set | 216279   | 87494    | 2.5       | 7.2                |
|               | Test Set     | 23776    | 9977     | 2.4       | 7.1                |
| <b>Fold 2</b> | Training Set | 215951   | 87822    | 2.5       | 7.2                |
|               | Test Set     | 24104    | 9649     | 2.5       | 7.0                |
| <b>Fold 3</b> | Training Set | 216259   | 87514    | 2.5       | 7.2                |
|               | Test Set     | 23796    | 9957     | 2.4       | 7.1                |
| <b>Fold 4</b> | Training Set | 215812   | 87961    | 2.5       | 7.2                |
|               | Test Set     | 24243    | 9510     | 2.5       | 7.0                |
| <b>Fold 5</b> | Training Set | 216116   | 87657    | 2.5       | 7.2                |
|               | Test Set     | 23939    | 9814     | 2.4       | 7.0                |
| <b>Fold 6</b> | Training Set | 215808   | 87966    | 2.5       | 7.2                |
|               | Test Set     | 24247    | 9505     | 2.6       | 7.1                |
| <b>Fold 7</b> | Training Set | 216146   | 87628    | 2.5       | 7.2                |
|               | Test Set     | 23909    | 9843     | 2.4       | 7.1                |
| <b>Fold 8</b> | Training Set | 215859   | 87915    | 2.5       | 7.2                |
|               | Test Set     | 24196    | 9556     | 2.5       | 7.1                |
| <b>Fold 9</b> | Training Set | 216298   | 87476    | 2.5       | 7.2                |
|               | Test Set     | 23757    | 9995     | 2.4       | 7.1                |

Supplementary Table 3: Cold-start for compounds splitting

| Folds         | Dataset      | Negative | Positive | Ratio N/P | Avg No. Rot. bonds |
|---------------|--------------|----------|----------|-----------|--------------------|
| <b>Fold 0</b> | Training Set | 214805   | 88968    | 2.4       | 7.2                |
|               | Test Set     | 25250    | 8503     | 2.9       | 7.6                |
| <b>Fold 1</b> | Training Set | 215316   | 88457    | 2.4       | 7.2                |
|               | Test Set     | 24739    | 9014     | 2.7       | 7.8                |
| <b>Fold 2</b> | Training Set | 215139   | 88634    | 2.4       | 7.2                |
|               | Test Set     | 24916    | 8837     | 2.8       | 7.7                |
| <b>Fold 3</b> | Training Set | 215452   | 88321    | 2.4       | 7.2                |
|               | Test Set     | 24603    | 9150     | 2.7       | 7.6                |
| <b>Fold 4</b> | Training Set | 215689   | 88084    | 2.4       | 7.2                |
|               | Test Set     | 24366    | 9387     | 2.6       | 7.5                |
| <b>Fold 5</b> | Training Set | 216459   | 87314    | 2.5       | 7.2                |
|               | Test Set     | 23596    | 10157    | 2.3       | 7.2                |
| <b>Fold 6</b> | Training Set | 216354   | 87419    | 2.5       | 7.2                |
|               | Test Set     | 23701    | 10052    | 2.4       | 7.0                |
| <b>Fold 7</b> | Training Set | 217028   | 86745    | 2.5       | 7.3                |
|               | Test Set     | 23027    | 10726    | 2.1       | 7.0                |
| <b>Fold 8</b> | Training Set | 217270   | 86503    | 2.5       | 7.3                |
|               | Test Set     | 22785    | 10968    | 2.1       | 6.9                |
| <b>Fold 9</b> | Training Set | 216983   | 86794    | 2.5       | 7.3                |
|               | Test Set     | 23072    | 10677    | 2.2       | 6.7                |

Supplementary Table 4: Cold-start for targets splitting

| Folds         | Dataset      | Negative | Positive | Ratio N/P | Avg No. Rot. bonds |
|---------------|--------------|----------|----------|-----------|--------------------|
| <b>Fold 0</b> | Training Set | 215564   | 88209    | 2.4       | 7.3                |
|               | Test Set     | 24491    | 9262     | 2.6       | 6.9                |
| <b>Fold 1</b> | Training Set | 217813   | 85960    | 2.5       | 7.3                |
|               | Test Set     | 22242    | 11511    | 1.9       | 6.9                |
| <b>Fold 2</b> | Training Set | 216296   | 87477    | 2.5       | 7.2                |
|               | Test Set     | 23759    | 9994     | 2.4       | 6.9                |
| <b>Fold 3</b> | Training Set | 217464   | 86309    | 2.5       | 7.3                |
|               | Test Set     | 22591    | 11162    | 2.0       | 6.9                |
| <b>Fold 4</b> | Training Set | 216258   | 87515    | 2.5       | 7.1                |
|               | Test Set     | 23797    | 9956     | 2.4       | 7.4                |
| <b>Fold 5</b> | Training Set | 214611   | 89162    | 2.4       | 7.2                |
|               | Test Set     | 25444    | 8309     | 3.0       | 7.3                |
| <b>Fold 6</b> | Training Set | 216959   | 86814    | 2.5       | 7.2                |
|               | Test Set     | 23096    | 10657    | 2.2       | 7.1                |
| <b>Fold 7</b> | Training Set | 214874   | 88899    | 2.4       | 7.1                |
|               | Test Set     | 25181    | 8572     | 2.9       | 7.8                |
| <b>Fold 8</b> | Training Set | 215640   | 88133    | 2.4       | 7.3                |
|               | Test Set     | 24415    | 9338     | 2.6       | 6.7                |
| <b>Fold 9</b> | Training Set | 215016   | 88761    | 2.6       | 7.2                |
|               | Test Set     | 25039    | 8710     | 2.9       | 7.0                |

Supplementary Table 5: Warm-start for compounds: performance details in various folds

| <b>Fold-0</b>   | Accuracy | AUC ROC | AUC PR | F1 score | MCC    |
|-----------------|----------|---------|--------|----------|--------|
| TransformerCPI  | 0.862    | 0.928   | 0.849  | 0.780    | 0.682  |
| RF              | 0.658    | 0.581   | 0.351  | 0.292    | 0.084  |
| Random          | 0.501    | 0.501   | 0.284  | 0.362    | 0.002  |
| PhyChemDG       | 0.597    | 0.709   | 0.447  | 0.552    | 0.312  |
| PhyGrAtt        | 0.740    | 0.775   | 0.554  | 0.481    | 0.325  |
| AlphaFoldGrAtts | 0.727    | 0.757   | 0.527  | 0.330    | 0.234  |
| E3FP-based      | 0.751    | 0.772   | 0.522  | 0.541    | 0.371  |
| 2DFP-based      | 0.827    | 0.866   | 0.757  | 0.647    | 0.547  |
| DeepCAT         | 0.772    | 0.813   | 0.616  | 0.510    | 0.385  |
| DeepDTA         | 0.723    | 0.581   | 0.393  | 0.128    | 0.128  |
| BERT-based      | 0.744    | 0.749   | 0.561  | 0.390    | 0.300  |
| UniRep-based    | 0.753    | 0.797   | 0.598  | 0.453    | 0.339  |
| DeepConv-DTI    | 0.914    | 0.967   | 0.933  | 0.850    | 0.791  |
| IIFDTI          | 0.876    | 0.937   | 0.869  | 0.781    | 0.695  |
| <b>Fold-1</b>   | Accuracy | AUC ROC | AUC PR | F1 score | MCC    |
| TransformerCPI  | 0.856    | 0.930   | 0.859  | 0.775    | 0.675  |
| RF              | 0.654    | 0.583   | 0.350  | 0.322    | 0.099  |
| PhyChemDG       | 0.609    | 0.659   | 0.394  | 0.502    | 0.232  |
| Random          | 0.497    | 0.497   | 0.265  | 0.347    | -0.003 |
| PhyGrAtt        | 0.729    | 0.757   | 0.528  | 0.371    | 0.253  |
| E3FP-based      | 0.838    | 0.883   | 0.756  | 0.703    | 0.592  |
| 2DFP-based      | 0.830    | 0.858   | 0.725  | 0.641    | 0.540  |
| DeepCAT         | 0.780    | 0.829   | 0.617  | 0.520    | 0.392  |
| DeepDTA         | 0.814    | 0.859   | 0.705  | 0.589    | 0.487  |
| AlphaFoldGrAtts | 0.731    | 0.754   | 0.535  | 0.281    | 0.229  |
| UniRep-based    | 0.707    | 0.790   | 0.547  | 0.000    | 0.000  |
| BERT-based      | 0.742    | 0.770   | 0.568  | 0.387    | 0.289  |
| DeepConv-DTI    | 0.912    | 0.965   | 0.929  | 0.847    | 0.786  |
| IIFDTI          | 0.875    | 0.934   | 0.866  | 0.783    | 0.696  |
| <b>Fold-2</b>   | Accuracy | AUC ROC | AUC PR | F1 score | MCC    |
| TransformerCPI  | 0.832    | 0.915   | 0.817  | 0.740    | 0.627  |
| RF              | 0.660    | 0.587   | 0.345  | 0.305    | 0.091  |
| PhyChemDG       | 0.660    | 0.680   | 0.409  | 0.376    | 0.144  |
| Random          | 0.497    | 0.498   | 0.288  | 0.361    | -0.007 |
| PhyGrAtt        | 0.738    | 0.760   | 0.536  | 0.361    | 0.261  |
| E3FP-based      | 0.829    | 0.857   | 0.741  | 0.678    | 0.569  |
| 2DFP-based      | 0.819    | 0.851   | 0.677  | 0.673    | 0.549  |
| DeepCAT         | 0.784    | 0.818   | 0.665  | 0.514    | 0.419  |
| DeepDTA         | 0.763    | 0.794   | 0.607  | 0.434    | 0.349  |

|                 |          |         |        |          |        |
|-----------------|----------|---------|--------|----------|--------|
| AlphaFoldGrAtts | 0.737    | 0.755   | 0.522  | 0.315    | 0.241  |
| BERT-based      | 0.752    | 0.784   | 0.575  | 0.425    | 0.317  |
| UniRep-based    | 0.746    | 0.796   | 0.568  | 0.422    | 0.301  |
| DeepConv-DTI    | 0.914    | 0.967   | 0.929  | 0.848    | 0.788  |
| IIFDTI          | 0.869    | 0.929   | 0.853  | 0.767    | 0.677  |
| <b>Fold-3</b>   | Accuracy | AUC ROC | AUC PR | F1 score | MCC    |
| TransformerCPI  | 0.850    | 0.918   | 0.817  | 0.755    | 0.651  |
| RF              | 0.659    | 0.576   | 0.339  | 0.308    | 0.091  |
| PhyChemDG       | 0.675    | 0.710   | 0.431  | 0.457    | 0.227  |
| Random          | 0.497    | 0.498   | 0.269  | 0.350    | -0.004 |
| PhyGrAtt        | 0.742    | 0.765   | 0.530  | 0.449    | 0.302  |
| E3FP-based      | 0.819    | 0.854   | 0.716  | 0.630    | 0.525  |
| 2DFP-based      | 0.823    | 0.859   | 0.716  | 0.654    | 0.538  |
| DeepCAT         | 0.795    | 0.820   | 0.647  | 0.555    | 0.438  |
| DeepDTA         | 0.815    | 0.859   | 0.710  | 0.623    | 0.506  |
| AlphaFoldGrAtts | 0.734    | 0.743   | 0.503  | 0.277    | 0.215  |
| UniRep-based    | 0.758    | 0.787   | 0.586  | 0.440    | 0.330  |
| BERT-based      | 0.749    | 0.765   | 0.553  | 0.391    | 0.293  |
| DeepConv-DTI    | 0.914    | 0.965   | 0.926  | 0.849    | 0.789  |
| IIFDTI          | 0.860    | 0.920   | 0.838  | 0.743    | 0.649  |
| <b>Fold-4</b>   | Accuracy | AUC ROC | AUC PR | F1 score | MCC    |
| TransformerCPI  | 0.859    | 0.925   | 0.842  | 0.770    | 0.670  |
| RF              | 0.663    | 0.589   | 0.351  | 0.306    | 0.099  |
| PhyChemDG       | 0.713    | 0.732   | 0.473  | 0.387    | 0.226  |
| Random          | 0.500    | 0.505   | 0.300  | 0.375    | 0.004  |
| PhyGrAtt        | 0.737    | 0.765   | 0.552  | 0.389    | 0.276  |
| E3FP-based      | 0.825    | 0.864   | 0.759  | 0.658    | 0.557  |
| 2DFP-based      | 0.825    | 0.867   | 0.756  | 0.677    | 0.563  |
| DeepCAT         | 0.784    | 0.826   | 0.674  | 0.559    | 0.440  |
| AlphaFoldGrAtts | 0.731    | 0.752   | 0.524  | 0.316    | 0.233  |
| BERT-based      | 0.748    | 0.781   | 0.582  | 0.401    | 0.308  |
| UniRep-based    | 0.752    | 0.804   | 0.591  | 0.467    | 0.336  |
| DeepDTA         | 0.704    | 0.500   | 0.296  | 0.000    | 0.000  |
| DeepConv-DTI    | 0.916    | 0.966   | 0.931  | 0.852    | 0.793  |
| IIFDTI          | 0.871    | 0.934   | 0.863  | 0.781    | 0.690  |
| <b>Fold-5</b>   | Accuracy | AUC ROC | AUC PR | F1 score | MCC    |
| TransformerCPI  | 0.845    | 0.912   | 0.809  | 0.737    | 0.628  |
| RF              | 0.659    | 0.587   | 0.343  | 0.307    | 0.090  |
| PhyChemDG       | 0.714    | 0.723   | 0.468  | 0.341    | 0.197  |
| Random          | 0.503    | 0.502   | 0.272  | 0.355    | 0.007  |
| PhyGrAtt        | 0.726    | 0.721   | 0.476  | 0.147    | 0.155  |
| E3FP-based      | 0.827    | 0.866   | 0.724  | 0.680    | 0.562  |
| 2DFP-based      | 0.819    | 0.853   | 0.709  | 0.627    | 0.516  |

|                 |          |         |        |          |        |
|-----------------|----------|---------|--------|----------|--------|
| AlphaFoldGrAtts | 0.740    | 0.757   | 0.528  | 0.277    | 0.236  |
| UniRep-based    | 0.761    | 0.780   | 0.582  | 0.448    | 0.341  |
| BERT-based      | 0.753    | 0.788   | 0.566  | 0.429    | 0.315  |
| DeepCAT         | 0.729    | 0.500   | 0.271  | 0.000    | 0.000  |
| DeepDTA         | 0.729    | 0.503   | 0.272  | 0.000    | 0.000  |
| DeepConv-DTI    | 0.915    | 0.966   | 0.928  | 0.849    | 0.790  |
| IIFDTI          | 0.847    | 0.908   | 0.808  | 0.722    | 0.617  |
| <b>Fold-6</b>   | Accuracy | AUC ROC | AUC PR | F1 score | MCC    |
| TransformerCPI  | 0.831    | 0.913   | 0.825  | 0.742    | 0.624  |
| RF              | 0.655    | 0.581   | 0.356  | 0.309    | 0.093  |
| PhyChemDG       | 0.687    | 0.697   | 0.442  | 0.315    | 0.144  |
| Random          | 0.503    | 0.502   | 0.285  | 0.365    | 0.006  |
| PhyGrAtt        | 0.741    | 0.769   | 0.561  | 0.475    | 0.323  |
| E3FP-based      | 0.824    | 0.862   | 0.750  | 0.654    | 0.550  |
| 2DFP-based      | 0.824    | 0.867   | 0.751  | 0.644    | 0.542  |
| DeepCAT         | 0.784    | 0.837   | 0.674  | 0.528    | 0.418  |
| DeepDTA         | 0.820    | 0.870   | 0.746  | 0.632    | 0.529  |
| AlphaFoldGrAtts | 0.727    | 0.755   | 0.535  | 0.265    | 0.221  |
| BERT-based      | 0.704    | 0.788   | 0.546  | 0.000    | 0.000  |
| UniRep-based    | 0.753    | 0.795   | 0.607  | 0.442    | 0.338  |
| DeepConv-DTI    | 0.917    | 0.969   | 0.935  | 0.857    | 0.799  |
| IIFDTI          | 0.870    | 0.933   | 0.864  | 0.774    | 0.684  |
| <b>Fold-7</b>   | Accuracy | AUC ROC | AUC PR | F1 score | MCC    |
| TransformerCPI  | 0.851    | 0.916   | 0.818  | 0.745    | 0.641  |
| RF              | 0.672    | 0.586   | 0.349  | 0.328    | 0.119  |
| PhyChemDG       | 0.700    | 0.709   | 0.432  | 0.330    | 0.161  |
| Random          | 0.502    | 0.502   | 0.267  | 0.350    | 0.004  |
| PhyGrAtt        | 0.737    | 0.752   | 0.516  | 0.477    | 0.308  |
| E3FP-based      | 0.815    | 0.843   | 0.706  | 0.631    | 0.521  |
| 2DFP-based      | 0.827    | 0.863   | 0.716  | 0.661    | 0.546  |
| DeepCAT         | 0.735    | 0.657   | 0.391  | 0.059    | 0.079  |
| DeepDTA         | 0.806    | 0.848   | 0.618  | 0.654    | 0.521  |
| AlphaFoldGrAtts | 0.735    | 0.754   | 0.505  | 0.224    | 0.190  |
| UniRep-based    | 0.726    | 0.782   | 0.520  | 0.138    | 0.132  |
| BERT-based      | 0.757    | 0.771   | 0.556  | 0.411    | 0.312  |
| DeepConv-DTI    | 0.912    | 0.964   | 0.922  | 0.843    | 0.782  |
| IIFDTI          | 0.874    | 0.934   | 0.857  | 0.769    | 0.683  |
| <b>Fold-8</b>   | Accuracy | AUC ROC | AUC PR | F1 score | MCC    |
| TransformerCPI  | 0.839    | 0.922   | 0.839  | 0.753    | 0.644  |
| RF              | 0.663    | 0.591   | 0.357  | 0.322    | 0.109  |
| PhyChemDG       | 0.682    | 0.710   | 0.443  | 0.429    | 0.210  |
| Random          | 0.495    | 0.496   | 0.287  | 0.362    | -0.009 |
| PhyGrAtt        | 0.740    | 0.762   | 0.539  | 0.423    | 0.292  |

|                 |                 |                |               |                 |            |
|-----------------|-----------------|----------------|---------------|-----------------|------------|
| E3FP-based      | 0.812           | 0.839          | 0.709         | 0.619           | 0.515      |
| 2DFP-based      | 0.822           | 0.866          | 0.760         | 0.643           | 0.542      |
| DeepDTA         | 0.816           | 0.867          | 0.747         | 0.630           | 0.525      |
| AlphaFoldGrAtts | 0.736           | 0.752          | 0.519         | 0.325           | 0.249      |
| BERT-based      | 0.755           | 0.768          | 0.574         | 0.426           | 0.328      |
| UniRep-based    | 0.753           | 0.787          | 0.585         | 0.430           | 0.324      |
| DeepCAT         | 0.710           | 0.652          | 0.395         | 0.000           | 0.000      |
| DeepConv-DTI    | 0.914           | 0.967          | 0.931         | 0.849           | 0.790      |
| IIFDTI          | 0.877           | 0.935          | 0.861         | 0.783           | 0.697      |
| <b>Fold-9</b>   | <b>Accuracy</b> | <b>AUC ROC</b> | <b>AUC PR</b> | <b>F1 score</b> | <b>MCC</b> |
| TransformerCPI  | 0.829           | 0.911          | 0.818         | 0.736           | 0.621      |
| RF              | 0.653           | 0.569          | 0.327         | 0.278           | 0.062      |
| PhyChemDG       | 0.675           | 0.707          | 0.430         | 0.456           | 0.225      |
| Random          | 0.498           | 0.499          | 0.275         | 0.352           | -0.004     |
| PhyGrAtt        | 0.737           | 0.754          | 0.521         | 0.450           | 0.296      |
| E3FP-based      | 0.810           | 0.835          | 0.628         | 0.678           | 0.544      |
| 2DFP-based      | 0.824           | 0.858          | 0.726         | 0.644           | 0.535      |
| DeepDTA         | 0.821           | 0.866          | 0.724         | 0.647           | 0.531      |
| DeepCAT         | 0.787           | 0.837          | 0.657         | 0.529           | 0.414      |
| AlphaFoldGrAtts | 0.731           | 0.753          | 0.516         | 0.235           | 0.197      |
| UniRep-based    | 0.752           | 0.791          | 0.575         | 0.427           | 0.314      |
| BERT-based      | 0.714           | 0.777          | 0.516         | 0.000           | 0.000      |
| DeepConv-DTI    | 0.914           | 0.966          | 0.927         | 0.846           | 0.786      |
| IIFDTI          | 0.868           | 0.928          | 0.851         | 0.762           | 0.671      |

Supplementary Table 6: Average performance of the models using warm-start splitting scenario for compounds.

| MODELS                 | Accuracy | AUC ROC | AUC PR | F1 score | MCC   |
|------------------------|----------|---------|--------|----------|-------|
| <b>UniRep-based</b>    | 0.746    | 0.791   | 0.576  | 0.367    | 0.276 |
| <b>DeepConv-DTI</b>    | 0.914    | 0.966   | 0.929  | 0.849    | 0.789 |
| <b>IIFDTI</b>          | 0.869    | 0.929   | 0.853  | 0.766    | 0.676 |
| <b>TransformerCPI</b>  | 0.845    | 0.919   | 0.829  | 0.753    | 0.646 |
| <b>BERT-based</b>      | 0.742    | 0.774   | 0.560  | 0.326    | 0.246 |
| <b>AlphaFoldGrAtts</b> | 0.733    | 0.753   | 0.521  | 0.285    | 0.225 |
| <b>PhyGrAtt</b>        | 0.737    | 0.758   | 0.531  | 0.402    | 0.279 |
| <b>E3FP-based</b>      | 0.815    | 0.847   | 0.701  | 0.647    | 0.531 |
| <b>2DFP-based</b>      | 0.824    | 0.861   | 0.729  | 0.651    | 0.542 |
| <b>DeepCAT</b>         | 0.766    | 0.759   | 0.561  | 0.377    | 0.298 |
| <b>DeepDTA</b>         | 0.781    | 0.755   | 0.582  | 0.434    | 0.358 |
| <b>Random</b>          | 0.500    | 0.500   | 0.279  | 0.358    | 0.000 |
| <b>RF</b>              | 0.660    | 0.583   | 0.347  | 0.308    | 0.094 |
| <b>PhyChemDG</b>       | 0.671    | 0.704   | 0.437  | 0.415    | 0.208 |

Supplementary Table 7: Warm-start for targets: performance details in various folds

| <b>Fold-0</b>   | Accuracy | AUC ROC | AUC PR | F1 score | MCC    |
|-----------------|----------|---------|--------|----------|--------|
| TransformerCPI  | 0.878    | 0.937   | 0.868  | 0.789    | 0.703  |
| RF              | 0.672    | 0.580   | 0.345  | 0.289    | 0.096  |
| Random          | 0.500    | 0.503   | 0.291  | 0.368    | 0.004  |
| PhyChemDG       | 0.666    | 0.680   | 0.393  | 0.325    | 0.114  |
| PhyGrAtt        | 0.744    | 0.776   | 0.549  | 0.511    | 0.343  |
| E3FP-based      | 0.820    | 0.853   | 0.732  | 0.635    | 0.535  |
| 2DFP-based      | 0.812    | 0.848   | 0.723  | 0.609    | 0.508  |
| DeepDTA         | 0.821    | 0.868   | 0.733  | 0.687    | 0.562  |
| DeepCAT         | 0.784    | 0.815   | 0.583  | 0.623    | 0.472  |
| AlphaFoldGrAtts | 0.735    | 0.763   | 0.532  | 0.256    | 0.220  |
| UniRep-based    | 0.754    | 0.800   | 0.583  | 0.449    | 0.329  |
| BERT-based      | 0.756    | 0.787   | 0.585  | 0.449    | 0.333  |
| DeepConv-DTI    | 0.916    | 0.967   | 0.931  | 0.853    | 0.794  |
| IIFDTI          | 0.868    | 0.931   | 0.851  | 0.770    | 0.677  |
| <b>Fold-1</b>   | Accuracy | AUC ROC | AUC PR | F1 score | MCC    |
| TransformerCPI  | 0.880    | 0.940   | 0.881  | 0.797    | 0.712  |
| RF              | 0.657    | 0.569   | 0.340  | 0.282    | 0.076  |
| PhyChemDG       | 0.673    | 0.682   | 0.448  | 0.420    | 0.194  |
| Random          | 0.503    | 0.506   | 0.274  | 0.354    | 0.005  |
| PhyGrAtt        | 0.738    | 0.766   | 0.545  | 0.438    | 0.300  |
| E3FP-based      | 0.825    | 0.858   | 0.732  | 0.642    | 0.542  |
| 2DFP-based      | 0.830    | 0.861   | 0.728  | 0.656    | 0.549  |
| DeepDTA         | 0.821    | 0.866   | 0.709  | 0.675    | 0.552  |
| DeepCAT         | 0.785    | 0.805   | 0.551  | 0.631    | 0.483  |
| AlphaFoldGrAtts | 0.727    | 0.754   | 0.528  | 0.290    | 0.226  |
| UniRep-based    | 0.753    | 0.789   | 0.604  | 0.437    | 0.334  |
| BERT-based      | 0.704    | 0.770   | 0.511  | 0.000    | -0.004 |
| DeepConv-DTI    | 0.914    | 0.967   | 0.934  | 0.855    | 0.794  |
| IIFDTI          | 0.873    | 0.936   | 0.873  | 0.782    | 0.693  |
| <b>Fold-2</b>   | Accuracy | AUC ROC | AUC PR | F1 score | MCC    |
| TransformerCPI  | 0.858    | 0.924   | 0.841  | 0.757    | 0.657  |
| RF              | 0.655    | 0.588   | 0.347  | 0.325    | 0.099  |
| PhyChemDG       | 0.687    | 0.715   | 0.444  | 0.430    | 0.215  |
| Random          | 0.503    | 0.508   | 0.291  | 0.369    | 0.010  |
| PhyGrAtt        | 0.744    | 0.774   | 0.544  | 0.444    | 0.304  |
| E3FP-based      | 0.821    | 0.860   | 0.743  | 0.657    | 0.548  |
| 2DFP-based      | 0.821    | 0.859   | 0.739  | 0.639    | 0.532  |
| DeepDTA         | 0.716    | 0.500   | 0.284  | 0.000    | 0.000  |
| DeepCAT         | 0.784    | 0.836   | 0.670  | 0.534    | 0.419  |
| AlphaFoldGrAtts | 0.730    | 0.759   | 0.521  | 0.186    | 0.183  |

|                 |          |         |        |          |        |
|-----------------|----------|---------|--------|----------|--------|
| UniRep-based    | 0.759    | 0.805   | 0.603  | 0.463    | 0.343  |
| BERT-based      | 0.738    | 0.756   | 0.518  | 0.335    | 0.250  |
| DeepConv-DTI    | 0.918    | 0.967   | 0.932  | 0.855    | 0.798  |
| IIFDTI          | 0.848    | 0.910   | 0.816  | 0.717    | 0.616  |
| <b>Fold-3</b>   | Accuracy | AUC ROC | AUC PR | F1 score | MCC    |
| TransformerCPI  | 0.864    | 0.926   | 0.847  | 0.772    | 0.675  |
| RF              | 0.656    | 0.579   | 0.354  | 0.308    | 0.092  |
| PhyChemDG       | 0.656    | 0.704   | 0.453  | 0.496    | 0.247  |
| Random          | 0.502    | 0.503   | 0.274  | 0.354    | 0.005  |
| PhyGrAtt        | 0.737    | 0.757   | 0.550  | 0.432    | 0.297  |
| E3FP-based      | 0.827    | 0.865   | 0.729  | 0.677    | 0.561  |
| 2DFP-based      | 0.824    | 0.863   | 0.718  | 0.658    | 0.541  |
| DeepDTA         | 0.814    | 0.858   | 0.707  | 0.624    | 0.506  |
| DeepCAT         | 0.801    | 0.839   | 0.677  | 0.543    | 0.447  |
| AlphaFoldGrAtts | 0.727    | 0.748   | 0.524  | 0.274    | 0.217  |
| UniRep-based    | 0.747    | 0.795   | 0.590  | 0.435    | 0.319  |
| BERT-based      | 0.747    | 0.737   | 0.559  | 0.406    | 0.312  |
| DeepConv-DTI    | 0.914    | 0.966   | 0.932  | 0.850    | 0.790  |
| IIFDTI          | 0.871    | 0.932   | 0.864  | 0.776    | 0.685  |
| <b>Fold-4</b>   | Accuracy | AUC ROC | AUC PR | F1 score | MCC    |
| TransformerCPI  | 0.859    | 0.922   | 0.829  | 0.750    | 0.652  |
| RF              | 0.670    | 0.601   | 0.352  | 0.319    | 0.111  |
| PhyChemDG       | 0.528    | 0.686   | 0.407  | 0.518    | 0.276  |
| Random          | 0.499    | 0.498   | 0.284  | 0.361    | -0.002 |
| PhyGrAtt        | 0.733    | 0.731   | 0.493  | 0.211    | 0.192  |
| E3FP-based      | 0.826    | 0.858   | 0.752  | 0.655    | 0.557  |
| 2DFP-based      | 0.818    | 0.854   | 0.679  | 0.666    | 0.542  |
| DeepDTA         | 0.810    | 0.858   | 0.719  | 0.653    | 0.523  |
| DeepCAT         | 0.717    | 0.500   | 0.283  | 0.000    | 0.000  |
| AlphaFoldGrAtts | 0.743    | 0.759   | 0.525  | 0.384    | 0.272  |
| UniRep-based    | 0.759    | 0.780   | 0.578  | 0.433    | 0.328  |
| BERT-based      | 0.753    | 0.786   | 0.562  | 0.429    | 0.313  |
| DeepConv-DTI    | 0.915    | 0.965   | 0.926  | 0.844    | 0.786  |
| IIFDTI          | 0.870    | 0.929   | 0.852  | 0.769    | 0.678  |
| <b>Fold-5</b>   | Accuracy | AUC ROC | AUC PR | F1 score | MCC    |
| TransformerCPI  | 0.862    | 0.925   | 0.842  | 0.759    | 0.663  |
| RF              | 0.653    | 0.575   | 0.350  | 0.333    | 0.104  |
| PhyChemDG       | 0.687    | 0.696   | 0.422  | 0.364    | 0.170  |
| Random          | 0.500    | 0.498   | 0.269  | 0.350    | -0.001 |
| PhyGrAtt        | 0.737    | 0.758   | 0.540  | 0.347    | 0.261  |
| E3FP-based      | 0.821    | 0.844   | 0.720  | 0.632    | 0.530  |
| 2DFP-based      | 0.825    | 0.865   | 0.731  | 0.632    | 0.529  |
| DeepDTA         | 0.813    | 0.857   | 0.691  | 0.658    | 0.530  |

|                 |          |         |        |          |        |
|-----------------|----------|---------|--------|----------|--------|
| DeepCAT         | 0.799    | 0.824   | 0.641  | 0.582    | 0.459  |
| AlphaFoldGrAtts | 0.733    | 0.755   | 0.527  | 0.292    | 0.232  |
| UniRep-based    | 0.747    | 0.786   | 0.565  | 0.420    | 0.307  |
| BERT-based      | 0.746    | 0.761   | 0.559  | 0.400    | 0.300  |
| DeepConv-DTI    | 0.915    | 0.967   | 0.931  | 0.852    | 0.793  |
| IIFDTI          | 0.864    | 0.926   | 0.850  | 0.766    | 0.671  |
| <b>Fold-6</b>   | Accuracy | AUC ROC | AUC PR | F1 score | MCC    |
| TransformerCPI  | 0.862    | 0.926   | 0.843  | 0.758    | 0.661  |
| RF              | 0.666    | 0.593   | 0.343  | 0.321    | 0.107  |
| PhyChemDG       | 0.600    | 0.689   | 0.414  | 0.504    | 0.247  |
| Random          | 0.498    | 0.497   | 0.284  | 0.364    | -0.002 |
| PhyGrAtt        | 0.756    | 0.782   | 0.553  | 0.478    | 0.339  |
| E3FP-based      | 0.749    | 0.771   | 0.531  | 0.510    | 0.351  |
| 2DFP-based      | 0.822    | 0.860   | 0.737  | 0.664    | 0.547  |
| DeepDTA         | 0.816    | 0.859   | 0.729  | 0.650    | 0.531  |
| DeepCAT         | 0.790    | 0.794   | 0.638  | 0.577    | 0.451  |
| AlphaFoldGrAtts | 0.738    | 0.764   | 0.521  | 0.274    | 0.221  |
| UniRep-based    | 0.757    | 0.776   | 0.562  | 0.428    | 0.321  |
| BERT-based      | 0.755    | 0.787   | 0.561  | 0.437    | 0.320  |
| DeepConv-DTI    | 0.915    | 0.965   | 0.926  | 0.848    | 0.789  |
| IIFDTI          | 0.873    | 0.933   | 0.856  | 0.765    | 0.679  |
| <b>Fold-7</b>   | Accuracy | AUC ROC | AUC PR | F1 score | MCC    |
| TransformerCPI  | 0.866    | 0.928   | 0.848  | 0.771    | 0.676  |
| RF              | 0.668    | 0.580   | 0.351  | 0.298    | 0.101  |
| PhyChemDG       | 0.644    | 0.717   | 0.466  | 0.509    | 0.257  |
| Random          | 0.501    | 0.500   | 0.277  | 0.357    | 0.004  |
| PhyGrAtt        | 0.735    | 0.762   | 0.521  | 0.417    | 0.281  |
| E3FP-based      | 0.822    | 0.851   | 0.717  | 0.634    | 0.532  |
| 2DFP-based      | 0.825    | 0.861   | 0.727  | 0.635    | 0.533  |
| DeepDTA         | 0.733    | 0.582   | 0.387  | 0.218    | 0.171  |
| DeepCAT         | 0.731    | 0.576   | 0.339  | 0.234    | 0.169  |
| AlphaFoldGrAtts | 0.735    | 0.755   | 0.529  | 0.350    | 0.255  |
| UniRep-based    | 0.751    | 0.781   | 0.587  | 0.422    | 0.320  |
| BERT-based      | 0.741    | 0.789   | 0.559  | 0.416    | 0.294  |
| DeepConv-DTI    | 0.914    | 0.966   | 0.930  | 0.850    | 0.789  |
| IIFDTI          | 0.861    | 0.926   | 0.851  | 0.748    | 0.655  |
| <b>Fold-8</b>   | Accuracy | AUC ROC | AUC PR | F1 score | MCC    |
| TransformerCPI  | 0.862    | 0.923   | 0.832  | 0.759    | 0.662  |
| RF              | 0.662    | 0.594   | 0.345  | 0.308    | 0.093  |
| PhyChemDG       | 0.648    | 0.717   | 0.448  | 0.515    | 0.275  |
| Random          | 0.504    | 0.505   | 0.289  | 0.371    | 0.010  |
| PhyGrAtt        | 0.746    | 0.777   | 0.545  | 0.435    | 0.301  |
| E3FP-based      | 0.815    | 0.845   | 0.720  | 0.645    | 0.529  |

| 2DFP-based      | 0.824    | 0.864   | 0.750  | 0.650    | 0.546 |
|-----------------|----------|---------|--------|----------|-------|
| DeepDTA         | 0.801    | 0.825   | 0.673  | 0.612    | 0.487 |
| DeepCAT         | 0.794    | 0.825   | 0.668  | 0.590    | 0.466 |
| AlphaFoldGrAtts | 0.743    | 0.764   | 0.526  | 0.379    | 0.271 |
| UniRep-based    | 0.750    | 0.800   | 0.564  | 0.430    | 0.308 |
| BERT-based      | 0.745    | 0.781   | 0.551  | 0.388    | 0.281 |
| DeepConv-DTI    | 0.915    | 0.967   | 0.928  | 0.844    | 0.787 |
| IIFDTI          | 0.859    | 0.923   | 0.838  | 0.738    | 0.643 |
| <b>Fold-9</b>   | Accuracy | AUC ROC | AUC PR | F1 score | MCC   |
| TransformerCPI  | 0.858    | 0.922   | 0.843  | 0.756    | 0.655 |
| RF              | 0.651    | 0.568   | 0.344  | 0.300    | 0.080 |
| PhyChemDG       | 0.686    | 0.708   | 0.441  | 0.319    | 0.147 |
| Random          | 0.501    | 0.505   | 0.280  | 0.355    | 0.000 |
| PhyGrAtt        | 0.711    | 0.713   | 0.478  | 0.099    | 0.121 |
| E3FP-based      | 0.824    | 0.850   | 0.721  | 0.638    | 0.536 |
| 2DFP-based      | 0.823    | 0.859   | 0.722  | 0.653    | 0.538 |
| DeepDTA         | 0.825    | 0.876   | 0.750  | 0.630    | 0.531 |
| DeepCAT         | 0.789    | 0.818   | 0.648  | 0.547    | 0.426 |
| AlphaFoldGrAtts | 0.722    | 0.751   | 0.530  | 0.213    | 0.193 |
| UniRep-based    | 0.704    | 0.780   | 0.531  | 0.000    | 0.000 |
| BERT-based      | 0.743    | 0.783   | 0.574  | 0.400    | 0.301 |
| DeepConv-DTI    | 0.912    | 0.966   | 0.930  | 0.849    | 0.787 |
| IIFDTI          | 0.866    | 0.929   | 0.861  | 0.774    | 0.679 |

Supplementary Table 8: Average performance of the models using warm-start splitting scenario for targets.

| <b>MODELS</b>   | <b>Accuracy</b> | <b>AUC ROC</b> | <b>AUC PR</b> | <b>F1 score</b> | <b>MCC</b> |
|-----------------|-----------------|----------------|---------------|-----------------|------------|
| UniRep-based    | 0.748           | 0.789          | 0.577         | 0.392           | 0.291      |
| DeepConv-DTI    | 0.915           | 0.966          | 0.930         | 0.850           | 0.791      |
| IIFDTI          | 0.865           | 0.928          | 0.851         | 0.760           | 0.668      |
| TransformerCPI  | 0.865           | 0.927          | 0.847         | 0.767           | 0.672      |
| BERT-based      | 0.743           | 0.774          | 0.554         | 0.366           | 0.270      |
| AlphaFoldGrAtts | 0.733           | 0.757          | 0.526         | 0.290           | 0.229      |
| PhyGrAtt        | 0.738           | 0.760          | 0.532         | 0.381           | 0.274      |
| E3FP-based      | 0.815           | 0.845          | 0.710         | 0.632           | 0.522      |
| 2DFP-based      | 0.822           | 0.859          | 0.725         | 0.646           | 0.537      |
| DeepCAT         | 0.777           | 0.763          | 0.570         | 0.486           | 0.379      |
| DeepDTA         | 0.797           | 0.795          | 0.638         | 0.541           | 0.439      |
| Random          | 0.501           | 0.502          | 0.281         | 0.360           | 0.003      |
| RF              | 0.661           | 0.583          | 0.347         | 0.308           | 0.096      |
| PhyChemDG       | 0.648           | 0.699          | 0.434         | 0.440           | 0.214      |

Supplementary Table 9: Cold-start for targets: performance details in various folds

| <b>Fold-0</b>   | Accuracy | AUC ROC | AUC PR | F1 score | MCC    |
|-----------------|----------|---------|--------|----------|--------|
| TransformerCPI  | 0.732    | 0.766   | 0.502  | 0.531    | 0.344  |
| RF              | 0.535    | 0.429   | 0.241  | 0.239    | -0.091 |
| Random          | 0.505    | 0.501   | 0.277  | 0.358    | 0.005  |
| PhyChemDG       | 0.649    | 0.645   | 0.362  | 0.347    | 0.107  |
| PhyGrAtt        | 0.707    | 0.699   | 0.419  | 0.400    | 0.213  |
| DeepCAT         | 0.720    | 0.728   | 0.455  | 0.536    | 0.340  |
| DeepDTA         | 0.723    | 0.500   | 0.277  | 0.000    | 0.000  |
| 2DFP-based      | 0.771    | 0.773   | 0.598  | 0.521    | 0.383  |
| E3FP-based      | 0.782    | 0.798   | 0.641  | 0.594    | 0.450  |
| AlphaFoldGrAtts | 0.728    | 0.704   | 0.439  | 0.153    | 0.125  |
| BERT-based      | 0.738    | 0.736   | 0.483  | 0.385    | 0.253  |
| UniRep-based    | 0.750    | 0.758   | 0.509  | 0.424    | 0.296  |
| DeepConv-DTI    | 0.821    | 0.878   | 0.762  | 0.688    | 0.564  |
| IIFDTI          | 0.788    | 0.816   | 0.644  | 0.581    | 0.443  |
| <b>Fold-1</b>   | Accuracy | AUC ROC | AUC PR | F1 score | MCC    |
| TransformerCPI  | 0.729    | 0.787   | 0.606  | 0.613    | 0.405  |
| RF              | 0.494    | 0.401   | 0.292  | 0.273    | -0.115 |
| PhyChemDG       | 0.628    | 0.675   | 0.447  | 0.511    | 0.218  |
| Random          | 0.498    | 0.498   | 0.323  | 0.393    | -0.003 |
| PhyGrAtt        | 0.659    | 0.669   | 0.461  | 0.288    | 0.134  |
| DeepCAT         | 0.734    | 0.784   | 0.571  | 0.532    | 0.359  |
| DeepDTA         | 0.659    | 0.732   | 0.507  | 0.596    | 0.353  |
| 2DFP-based      | 0.759    | 0.805   | 0.638  | 0.567    | 0.419  |
| E3FP-based      | 0.776    | 0.807   | 0.687  | 0.615    | 0.474  |
| AlphaFoldGrAtts | 0.662    | 0.722   | 0.538  | 0.040    | 0.066  |
| UniRep-based    | 0.699    | 0.756   | 0.573  | 0.401    | 0.262  |
| BERT-based      | 0.659    | 0.747   | 0.545  | 0.000    | 0.000  |
| DeepConv-DTI    | 0.809    | 0.884   | 0.772  | 0.722    | 0.577  |
| IIFDTI          | 0.743    | 0.808   | 0.631  | 0.603    | 0.415  |
| <b>Fold-2</b>   | Accuracy | AUC ROC | AUC PR | F1 score | MCC    |
| TransformerCPI  | 0.720    | 0.739   | 0.489  | 0.460    | 0.281  |
| RF              | 0.544    | 0.441   | 0.269  | 0.240    | -0.086 |
| PhyChemDG       | 0.647    | 0.693   | 0.409  | 0.494    | 0.239  |
| Random          | 0.495    | 0.492   | 0.275  | 0.354    | -0.010 |
| PhyGrAtt        | 0.678    | 0.655   | 0.396  | 0.225    | 0.077  |
| DeepCAT         | 0.703    | 0.711   | 0.424  | 0.439    | 0.239  |
| DeepDTA         | 0.632    | 0.698   | 0.417  | 0.535    | 0.305  |
| 2DFP-based      | 0.738    | 0.766   | 0.495  | 0.541    | 0.358  |
| E3FP-based      | 0.741    | 0.778   | 0.541  | 0.582    | 0.394  |
| AlphaFoldGrAtts | 0.706    | 0.668   | 0.423  | 0.161    | 0.118  |

|                 |          |         |        |          |        |
|-----------------|----------|---------|--------|----------|--------|
| BERT-based      | 0.726    | 0.740   | 0.518  | 0.349    | 0.241  |
| UniRep-based    | 0.726    | 0.749   | 0.524  | 0.368    | 0.247  |
| DeepConv-DTI    | 0.829    | 0.891   | 0.754  | 0.703    | 0.584  |
| IIFDTI          | 0.742    | 0.779   | 0.563  | 0.532    | 0.357  |
| <b>Fold-3</b>   | Accuracy | AUC ROC | AUC PR | F1 score | MCC    |
| TransformerCPI  | 0.708    | 0.761   | 0.528  | 0.567    | 0.347  |
| RF              | 0.548    | 0.395   | 0.284  | 0.202    | -0.104 |
| PhyChemDG       | 0.580    | 0.650   | 0.414  | 0.535    | 0.226  |
| Random          | 0.495    | 0.496   | 0.336  | 0.397    | -0.013 |
| PhyGrAtt        | 0.672    | 0.700   | 0.490  | 0.373    | 0.183  |
| DeepCAT         | 0.660    | 0.510   | 0.353  | 0.000    | 0.000  |
| DeepDTA         | 0.630    | 0.705   | 0.482  | 0.592    | 0.323  |
| 2DFP-based      | 0.759    | 0.810   | 0.676  | 0.573    | 0.431  |
| E3FP-based      | 0.791    | 0.833   | 0.734  | 0.623    | 0.502  |
| AlphaFoldGrAtts | 0.677    | 0.747   | 0.541  | 0.053    | 0.081  |
| UniRep-based    | 0.699    | 0.729   | 0.546  | 0.368    | 0.238  |
| BERT-based      | 0.700    | 0.688   | 0.526  | 0.330    | 0.233  |
| DeepConv-DTI    | 0.785    | 0.857   | 0.737  | 0.685    | 0.523  |
| IIFDTI          | 0.735    | 0.787   | 0.603  | 0.599    | 0.401  |
| <b>Fold-4</b>   | Accuracy | AUC ROC | AUC PR | F1 score | MCC    |
| TransformerCPI  | 0.763    | 0.802   | 0.607  | 0.583    | 0.419  |
| RF              | 0.533    | 0.411   | 0.250  | 0.229    | -0.106 |
| PhyChemDG       | 0.686    | 0.708   | 0.455  | 0.405    | 0.198  |
| Random          | 0.497    | 0.496   | 0.271  | 0.351    | -0.005 |
| PhyGrAtt        | 0.695    | 0.669   | 0.425  | 0.240    | 0.119  |
| DeepCAT         | 0.780    | 0.791   | 0.577  | 0.521    | 0.396  |
| DeepDTA         | 0.653    | 0.703   | 0.396  | 0.517    | 0.289  |
| 2DFP-based      | 0.787    | 0.811   | 0.592  | 0.599    | 0.454  |
| E3FP-based      | 0.718    | 0.772   | 0.478  | 0.552    | 0.370  |
| AlphaFoldGrAtts | 0.710    | 0.706   | 0.454  | 0.146    | 0.123  |
| BERT-based      | 0.736    | 0.769   | 0.549  | 0.384    | 0.276  |
| UniRep-based    | 0.725    | 0.778   | 0.538  | 0.259    | 0.212  |
| DeepConv-DTI    | 0.837    | 0.894   | 0.801  | 0.702    | 0.594  |
| IIFDTI          | 0.770    | 0.814   | 0.625  | 0.579    | 0.424  |
| <b>Fold-5</b>   | Accuracy | AUC ROC | AUC PR | F1 score | MCC    |
| TransformerCPI  | 0.780    | 0.812   | 0.540  | 0.550    | 0.405  |
| RF              | 0.554    | 0.467   | 0.231  | 0.279    | -0.026 |
| PhyChemDG       | 0.541    | 0.662   | 0.379  | 0.435    | 0.175  |
| Random          | 0.499    | 0.498   | 0.266  | 0.346    | -0.003 |
| PhyGrAtt        | 0.685    | 0.672   | 0.361  | 0.332    | 0.127  |
| DeepCAT         | 0.785    | 0.806   | 0.613  | 0.534    | 0.407  |
| DeepDTA         | 0.776    | 0.798   | 0.611  | 0.551    | 0.404  |
| 2DFP-based      | 0.804    | 0.829   | 0.659  | 0.575    | 0.462  |

|                 |          |         |        |          |        |
|-----------------|----------|---------|--------|----------|--------|
| E3FP-based      | 0.776    | 0.804   | 0.563  | 0.579    | 0.427  |
| AlphaFoldGrAtts | 0.757    | 0.723   | 0.422  | 0.222    | 0.172  |
| UniRep-based    | 0.771    | 0.770   | 0.505  | 0.384    | 0.283  |
| BERT-based      | 0.773    | 0.777   | 0.516  | 0.405    | 0.298  |
| DeepConv-DTI    | 0.864    | 0.918   | 0.801  | 0.714    | 0.626  |
| IIFDTI          | 0.830    | 0.876   | 0.676  | 0.657    | 0.543  |
| <b>Fold-6</b>   | Accuracy | AUC ROC | AUC PR | F1 score | MCC    |
| TransformerCPI  | 0.736    | 0.791   | 0.609  | 0.531    | 0.356  |
| RF              | 0.561    | 0.422   | 0.278  | 0.224    | -0.077 |
| PhyChemDG       | 0.573    | 0.658   | 0.415  | 0.506    | 0.196  |
| Random          | 0.502    | 0.497   | 0.270  | 0.352    | 0.000  |
| PhyGrAtt        | 0.688    | 0.721   | 0.467  | 0.232    | 0.141  |
| DeepCAT         | 0.787    | 0.807   | 0.616  | 0.507    | 0.406  |
| DeepDTA         | 0.694    | 0.736   | 0.471  | 0.493    | 0.279  |
| 2DFP-based      | 0.801    | 0.823   | 0.656  | 0.584    | 0.465  |
| E3FP-based      | 0.809    | 0.835   | 0.695  | 0.598    | 0.503  |
| AlphaFoldGrAtts | 0.693    | 0.705   | 0.447  | 0.070    | 0.063  |
| BERT-based      | 0.723    | 0.772   | 0.580  | 0.390    | 0.280  |
| UniRep-based    | 0.684    | 0.753   | 0.504  | 0.000    | 0.000  |
| DeepConv-DTI    | 0.820    | 0.891   | 0.788  | 0.722    | 0.589  |
| IIFDTI          | 0.747    | 0.822   | 0.634  | 0.627    | 0.440  |
| <b>Fold-7</b>   | Accuracy | AUC ROC | AUC PR | F1 score | MCC    |
| TransformerCPI  | 0.782    | 0.824   | 0.589  | 0.577    | 0.430  |
| RF              | 0.524    | 0.494   | 0.255  | 0.321    | -0.004 |
| PhyChemDG       | 0.698    | 0.707   | 0.426  | 0.412    | 0.208  |
| Random          | 0.495    | 0.494   | 0.221  | 0.305    | -0.009 |
| PhyGrAtt        | 0.726    | 0.706   | 0.432  | 0.381    | 0.213  |
| DeepCAT         | 0.806    | 0.801   | 0.542  | 0.492    | 0.386  |
| DeepDTA         | 0.773    | 0.785   | 0.496  | 0.520    | 0.372  |
| 2DFP-based      | 0.811    | 0.821   | 0.583  | 0.556    | 0.437  |
| E3FP-based      | 0.807    | 0.823   | 0.638  | 0.615    | 0.486  |
| AlphaFoldGrAtts | 0.748    | 0.731   | 0.444  | 0.155    | 0.136  |
| UniRep-based    | 0.763    | 0.770   | 0.508  | 0.418    | 0.294  |
| BERT-based      | 0.767    | 0.766   | 0.517  | 0.419    | 0.302  |
| DeepConv-DTI    | 0.860    | 0.910   | 0.787  | 0.729    | 0.634  |
| IIFDTI          | 0.807    | 0.831   | 0.640  | 0.588    | 0.466  |
| <b>Fold-8</b>   | Accuracy | AUC ROC | AUC PR | F1 score | MCC    |
| TransformerCPI  | 0.765    | 0.822   | 0.619  | 0.596    | 0.431  |
| RF              | 0.532    | 0.435   | 0.250  | 0.251    | -0.085 |
| PhyChemDG       | 0.692    | 0.742   | 0.484  | 0.497    | 0.281  |
| Random          | 0.500    | 0.502   | 0.261  | 0.345    | 0.003  |
| PhyGrAtt        | 0.735    | 0.734   | 0.484  | 0.243    | 0.194  |
| DeepCAT         | 0.800    | 0.828   | 0.623  | 0.507    | 0.420  |

|                 |                 |                |               |                 |            |
|-----------------|-----------------|----------------|---------------|-----------------|------------|
| DeepDTA         | 0.709           | 0.756          | 0.437         | 0.548           | 0.358      |
| 2DFP-based      | 0.808           | 0.839          | 0.640         | 0.550           | 0.452      |
| E3FP-based      | 0.818           | 0.830          | 0.661         | 0.616           | 0.504      |
| AlphaFoldGrAtts | 0.731           | 0.745          | 0.492         | 0.134           | 0.144      |
| BERT-based      | 0.755           | 0.764          | 0.544         | 0.415           | 0.305      |
| UniRep-based    | 0.749           | 0.768          | 0.541         | 0.398           | 0.285      |
| DeepConv-DTI    | 0.842           | 0.901          | 0.790         | 0.707           | 0.599      |
| IIFDTI          | 0.805           | 0.855          | 0.671         | 0.639           | 0.507      |
| <b>Fold-9</b>   | <b>Accuracy</b> | <b>AUC ROC</b> | <b>AUC PR</b> | <b>F1 score</b> | <b>MCC</b> |
| TransformerCPI  | 0.777           | 0.822          | 0.609         | 0.561           | 0.412      |
| RF              | 0.579           | 0.470          | 0.248         | 0.284           | -0.008     |
| PhyChemDG       | 0.692           | 0.732          | 0.455         | 0.476           | 0.267      |
| Random          | 0.496           | 0.497          | 0.267         | 0.345           | -0.008     |
| PhyGrAtt        | 0.723           | 0.697          | 0.373         | 0.152           | 0.065      |
| DeepCAT         | 0.785           | 0.822          | 0.611         | 0.524           | 0.404      |
| DeepDTA         | 0.638           | 0.707          | 0.401         | 0.520           | 0.297      |
| 2DFP-based      | 0.811           | 0.820          | 0.636         | 0.596           | 0.485      |
| E3FP-based      | 0.823           | 0.852          | 0.678         | 0.612           | 0.508      |
| AlphaFoldGrAtts | 0.748           | 0.722          | 0.452         | 0.109           | 0.137      |
| UniRep-based    | 0.761           | 0.784          | 0.527         | 0.421           | 0.298      |
| BERT-based      | 0.742           | 0.768          | 0.461         | 0.000           | 0.000      |
| DeepConv-DTI    | 0.856           | 0.916          | 0.801         | 0.711           | 0.616      |
| IIFDTI          | 0.801           | 0.851          | 0.657         | 0.609           | 0.476      |

Supplementary Table 10: Average performance of the models using cold-start splitting scenario for targets.

| MODELS          | Accuracy | AUC ROC | AUC PR | F1 score | MCC    |
|-----------------|----------|---------|--------|----------|--------|
| UniRep-based    | 0.733    | 0.762   | 0.527  | 0.344    | 0.241  |
| DeepConv-DTI    | 0.832    | 0.894   | 0.779  | 0.708    | 0.591  |
| IIFDTI          | 0.777    | 0.824   | 0.634  | 0.601    | 0.447  |
| TransformerCPI  | 0.749    | 0.792   | 0.570  | 0.557    | 0.383  |
| BERT-based      | 0.732    | 0.753   | 0.524  | 0.308    | 0.219  |
| AlphaFoldGrAtts | 0.716    | 0.717   | 0.465  | 0.124    | 0.116  |
| PhyGrAtt        | 0.697    | 0.692   | 0.431  | 0.286    | 0.147  |
| E3FP-based      | 0.784    | 0.813   | 0.632  | 0.599    | 0.462  |
| 2DFP-based      | 0.785    | 0.810   | 0.617  | 0.566    | 0.435  |
| DeepCAT         | 0.756    | 0.759   | 0.539  | 0.459    | 0.336  |
| DeepDTA         | 0.689    | 0.712   | 0.450  | 0.487    | 0.298  |
| Random          | 0.498    | 0.497   | 0.277  | 0.355    | -0.004 |
| RF              | 0.540    | 0.436   | 0.260  | 0.254    | -0.070 |
| PhyChemDG       | 0.638    | 0.687   | 0.425  | 0.462    | 0.211  |

Supplementary Table 11: Cold-start for compounds: performance details in various folds

| <b>Fold-0</b>   | Accuracy | AUC ROC | AUC PR | F1 score | MCC    |
|-----------------|----------|---------|--------|----------|--------|
| TransformerCPI  | 0.841    | 0.904   | 0.784  | 0.710    | 0.604  |
| RF              | 0.683    | 0.595   | 0.310  | 0.276    | 0.080  |
| Random          | 0.496    | 0.493   | 0.255  | 0.336    | -0.009 |
| PhyChemDG       | 0.634    | 0.689   | 0.358  | 0.467    | 0.236  |
| PhyGrAtt        | 0.765    | 0.772   | 0.507  | 0.377    | 0.276  |
| E3FP-based      | 0.663    | 0.717   | 0.391  | 0.502    | 0.294  |
| 2DFP-based      | 0.754    | 0.774   | 0.485  | 0.533    | 0.366  |
| DeepCAT         | 0.718    | 0.741   | 0.462  | 0.496    | 0.304  |
| DeepDTA         | 0.741    | 0.500   | 0.259  | 0.000    | 0.000  |
| AlphaFoldGrAtts | 0.763    | 0.765   | 0.492  | 0.277    | 0.227  |
| UniRep-based    | 0.775    | 0.788   | 0.532  | 0.440    | 0.328  |
| BERT-based      | 0.772    | 0.776   | 0.523  | 0.434    | 0.317  |
| DeepConv-DTI    | 0.891    | 0.943   | 0.865  | 0.782    | 0.709  |
| IIFDTI          | 0.859    | 0.912   | 0.791  | 0.722    | 0.628  |
| <b>Fold-1</b>   | Accuracy | AUC ROC | AUC PR | F1 score | MCC    |
| TransformerCPI  | 0.820    | 0.896   | 0.754  | 0.705    | 0.588  |
| RF              | 0.671    | 0.602   | 0.335  | 0.316    | 0.104  |
| PhyChemDG       | 0.580    | 0.697   | 0.382  | 0.519    | 0.300  |
| Random          | 0.499    | 0.497   | 0.259  | 0.340    | -0.004 |
| PhyGrAtt        | 0.742    | 0.729   | 0.462  | 0.178    | 0.164  |
| E3FP-based      | 0.745    | 0.500   | 0.255  | 0.000    | 0.000  |
| 2DFP-based      | 0.741    | 0.785   | 0.542  | 0.558    | 0.383  |
| DeepCAT         | 0.740    | 0.500   | 0.261  | 0.000    | 0.000  |
| DeepDTA         | 0.740    | 0.500   | 0.260  | 0.000    | 0.000  |
| AlphaFoldGrAtts | 0.749    | 0.748   | 0.492  | 0.251    | 0.211  |
| BERT-based      | 0.756    | 0.771   | 0.525  | 0.410    | 0.292  |
| UniRep-based    | 0.758    | 0.772   | 0.532  | 0.397    | 0.290  |
| DeepConv-DTI    | 0.874    | 0.933   | 0.853  | 0.767    | 0.680  |
| IIFDTI          | 0.845    | 0.902   | 0.790  | 0.710    | 0.604  |
| <b>Fold-2</b>   | Accuracy | AUC ROC | AUC PR | F1 score | MCC    |
| TransformerCPI  | 0.808    | 0.896   | 0.762  | 0.694    | 0.576  |
| RF              | 0.683    | 0.599   | 0.327  | 0.288    | 0.095  |
| PhyChemDG       | 0.717    | 0.732   | 0.431  | 0.360    | 0.191  |
| Random          | 0.499    | 0.497   | 0.260  | 0.343    | -0.003 |
| PhyGrAtt        | 0.755    | 0.767   | 0.501  | 0.425    | 0.291  |
| E3FP-based      | 0.684    | 0.726   | 0.436  | 0.500    | 0.292  |
| 2DFP-based      | 0.723    | 0.779   | 0.514  | 0.556    | 0.371  |
| DeepCAT         | 0.737    | 0.500   | 0.263  | 0.000    | 0.000  |
| DeepDTA         | 0.737    | 0.500   | 0.263  | 0.000    | 0.000  |

|                 |          |         |        |          |        |
|-----------------|----------|---------|--------|----------|--------|
| AlphaFoldGrAtts | 0.754    | 0.770   | 0.497  | 0.301    | 0.231  |
| UniRep-based    | 0.771    | 0.788   | 0.552  | 0.454    | 0.338  |
| BERT-based      | 0.763    | 0.766   | 0.518  | 0.401    | 0.295  |
| DeepConv-DTI    | 0.895    | 0.939   | 0.876  | 0.795    | 0.725  |
| IIFDTI          | 0.857    | 0.914   | 0.815  | 0.730    | 0.633  |
| <b>Fold-3</b>   | Accuracy | AUC ROC | AUC PR | F1 score | MCC    |
| TransformerCPI  | 0.819    | 0.901   | 0.782  | 0.710    | 0.593  |
| RF              | 0.675    | 0.593   | 0.332  | 0.322    | 0.115  |
| PhyChemDG       | 0.589    | 0.668   | 0.388  | 0.449    | 0.174  |
| Random          | 0.495    | 0.500   | 0.253  | 0.333    | -0.005 |
| PhyGrAtt        | 0.754    | 0.779   | 0.529  | 0.433    | 0.304  |
| E3FP-based      | 0.703    | 0.746   | 0.512  | 0.538    | 0.325  |
| 2DFP-based      | 0.731    | 0.782   | 0.480  | 0.549    | 0.374  |
| DeepCAT         | 0.748    | 0.500   | 0.252  | 0.000    | 0.000  |
| DeepDTA         | 0.746    | 0.793   | 0.541  | 0.559    | 0.391  |
| AlphaFoldGrAtts | 0.747    | 0.759   | 0.504  | 0.261    | 0.219  |
| BERT-based      | 0.759    | 0.786   | 0.539  | 0.436    | 0.315  |
| UniRep-based    | 0.757    | 0.764   | 0.530  | 0.407    | 0.298  |
| DeepConv-DTI    | 0.885    | 0.940   | 0.874  | 0.786    | 0.707  |
| IIFDTI          | 0.854    | 0.912   | 0.814  | 0.721    | 0.624  |
| <b>Fold-4</b>   | Accuracy | AUC ROC | AUC PR | F1 score | MCC    |
| TransformerCPI  | 0.814    | 0.893   | 0.752  | 0.705    | 0.581  |
| RF              | 0.673    | 0.587   | 0.337  | 0.303    | 0.102  |
| PhyChemDG       | 0.585    | 0.683   | 0.395  | 0.521    | 0.281  |
| Random          | 0.500    | 0.503   | 0.274  | 0.356    | 0.003  |
| PhyGrAtt        | 0.736    | 0.743   | 0.494  | 0.217    | 0.191  |
| E3FP-based      | 0.666    | 0.700   | 0.470  | 0.471    | 0.231  |
| 2DFP-based      | 0.758    | 0.806   | 0.582  | 0.576    | 0.408  |
| DeepCAT         | 0.726    | 0.737   | 0.491  | 0.454    | 0.275  |
| DeepDTA         | 0.726    | 0.676   | 0.414  | 0.000    | 0.000  |
| AlphaFoldGrAtts | 0.749    | 0.775   | 0.538  | 0.343    | 0.267  |
| UniRep-based    | 0.761    | 0.803   | 0.572  | 0.471    | 0.342  |
| BERT-based      | 0.751    | 0.776   | 0.540  | 0.413    | 0.297  |
| DeepConv-DTI    | 0.885    | 0.935   | 0.875  | 0.798    | 0.718  |
| IIFDTI          | 0.852    | 0.916   | 0.815  | 0.738    | 0.634  |
| <b>Fold-5</b>   | Accuracy | AUC ROC | AUC PR | F1 score | MCC    |
| TransformerCPI  | 0.804    | 0.886   | 0.779  | 0.712    | 0.576  |
| RF              | 0.654    | 0.583   | 0.357  | 0.314    | 0.098  |
| PhyChemDG       | 0.686    | 0.723   | 0.472  | 0.418    | 0.209  |
| Random          | 0.501    | 0.503   | 0.290  | 0.367    | 0.003  |
| PhyGrAtt        | 0.732    | 0.773   | 0.555  | 0.402    | 0.282  |
| E3FP-based      | 0.669    | 0.702   | 0.478  | 0.531    | 0.286  |
| 2DFP-based      | 0.763    | 0.807   | 0.612  | 0.585    | 0.419  |

|                 |          |         |        |          |        |
|-----------------|----------|---------|--------|----------|--------|
| DeepCAT         | 0.676    | 0.717   | 0.484  | 0.475    | 0.243  |
| DeepDTA         | 0.738    | 0.772   | 0.562  | 0.540    | 0.357  |
| AlphaFoldGrAtts | 0.722    | 0.753   | 0.527  | 0.288    | 0.219  |
| BERT-based      | 0.733    | 0.791   | 0.557  | 0.397    | 0.282  |
| UniRep-based    | 0.738    | 0.779   | 0.582  | 0.407    | 0.299  |
| DeepConv-DTI    | 0.884    | 0.941   | 0.884  | 0.809    | 0.726  |
| IIFDTI          | 0.853    | 0.916   | 0.817  | 0.757    | 0.652  |
| <b>Fold-6</b>   | Accuracy | AUC ROC | AUC PR | F1 score | MCC    |
| TransformerCPI  | 0.776    | 0.874   | 0.748  | 0.687    | 0.540  |
| RF              | 0.651    | 0.593   | 0.364  | 0.348    | 0.116  |
| PhyChemDG       | 0.649    | 0.688   | 0.465  | 0.401    | 0.153  |
| Random          | 0.503    | 0.498   | 0.291  | 0.369    | 0.003  |
| PhyGrAtt        | 0.713    | 0.709   | 0.476  | 0.134    | 0.148  |
| E3FP-based      | 0.749    | 0.767   | 0.525  | 0.538    | 0.368  |
| 2DFP-based      | 0.758    | 0.797   | 0.587  | 0.571    | 0.404  |
| DeepCAT         | 0.642    | 0.669   | 0.406  | 0.540    | 0.300  |
| DeepDTA         | 0.723    | 0.768   | 0.545  | 0.534    | 0.337  |
| AlphaFoldGrAtts | 0.729    | 0.751   | 0.531  | 0.323    | 0.242  |
| UniRep-based    | 0.702    | 0.755   | 0.500  | 0.000    | 0.000  |
| BERT-based      | 0.730    | 0.761   | 0.545  | 0.370    | 0.262  |
| DeepConv-DTI    | 0.876    | 0.935   | 0.883  | 0.792    | 0.704  |
| IIFDTI          | 0.827    | 0.886   | 0.792  | 0.703    | 0.582  |
| <b>Fold-7</b>   | Accuracy | AUC ROC | AUC PR | F1 score | MCC    |
| TransformerCPI  | 0.805    | 0.894   | 0.803  | 0.732    | 0.595  |
| RF              | 0.632    | 0.564   | 0.368  | 0.316    | 0.078  |
| PhyChemDG       | 0.653    | 0.679   | 0.450  | 0.388    | 0.153  |
| Random          | 0.498    | 0.492   | 0.295  | 0.370    | -0.007 |
| PhyGrAtt        | 0.720    | 0.755   | 0.560  | 0.426    | 0.285  |
| E3FP-based      | 0.605    | 0.671   | 0.410  | 0.534    | 0.268  |
| 2DFP-based      | 0.749    | 0.776   | 0.596  | 0.571    | 0.394  |
| DeepCAT         | 0.700    | 0.725   | 0.490  | 0.454    | 0.252  |
| DeepDTA         | 0.717    | 0.749   | 0.501  | 0.533    | 0.330  |
| AlphaFoldGrAtts | 0.705    | 0.725   | 0.521  | 0.281    | 0.204  |
| BERT-based      | 0.719    | 0.753   | 0.563  | 0.382    | 0.270  |
| UniRep-based    | 0.720    | 0.747   | 0.569  | 0.373    | 0.272  |
| DeepConv-DTI    | 0.875    | 0.932   | 0.886  | 0.805    | 0.714  |
| IIFDTI          | 0.841    | 0.905   | 0.834  | 0.754    | 0.637  |
| <b>Fold-8</b>   | Accuracy | AUC ROC | AUC PR | F1 score | MCC    |
| TransformerCPI  | 0.789    | 0.873   | 0.750  | 0.715    | 0.562  |
| RF              | 0.629    | 0.559   | 0.366  | 0.317    | 0.078  |
| PhyChemDG       | 0.608    | 0.646   | 0.409  | 0.489    | 0.189  |
| Random          | 0.493    | 0.490   | 0.302  | 0.374    | -0.014 |
| PhyGrAtt        | 0.709    | 0.742   | 0.549  | 0.479    | 0.292  |

|                 |                 |                |               |                 |            |
|-----------------|-----------------|----------------|---------------|-----------------|------------|
| E3FP-based      | 0.635           | 0.684          | 0.459         | 0.508           | 0.242      |
| 2DFP-based      | 0.761           | 0.794          | 0.603         | 0.614           | 0.441      |
| DeepCAT         | 0.712           | 0.736          | 0.557         | 0.515           | 0.311      |
| DeepDTA         | 0.706           | 0.731          | 0.543         | 0.506           | 0.297      |
| AlphaFoldGrAtts | 0.704           | 0.726          | 0.544         | 0.282           | 0.220      |
| UniRep-based    | 0.710           | 0.748          | 0.568         | 0.348           | 0.253      |
| BERT-based      | 0.714           | 0.742          | 0.569         | 0.363           | 0.265      |
| DeepConv-DTI    | 0.874           | 0.938          | 0.890         | 0.810           | 0.716      |
| IIFDTI          | 0.836           | 0.906          | 0.831         | 0.756           | 0.633      |
| <b>Fold-9</b>   | <b>Accuracy</b> | <b>AUC ROC</b> | <b>AUC PR</b> | <b>F1 score</b> | <b>MCC</b> |
| TransformerCPI  | 0.779           | 0.879          | 0.781         | 0.703           | 0.548      |
| RF              | 0.624           | 0.558          | 0.357         | 0.336           | 0.080      |
| PhyChemDG       | 0.504           | 0.635          | 0.418         | 0.510           | 0.178      |
| Random          | 0.501           | 0.499          | 0.296         | 0.371           | 0.002      |
| PhyGrAtt        | 0.722           | 0.747          | 0.559         | 0.453           | 0.297      |
| E3FP-based      | 0.647           | 0.691          | 0.503         | 0.519           | 0.252      |
| 2DFP-based      | 0.756           | 0.797          | 0.566         | 0.607           | 0.432      |
| DeepCAT         | 0.706           | 0.500          | 0.294         | 0.000           | 0.000      |
| DeepDTA         | 0.707           | 0.767          | 0.507         | 0.593           | 0.392      |
| AlphaFoldGrAtts | 0.707           | 0.725          | 0.526         | 0.278           | 0.208      |
| BERT-based      | 0.684           | 0.732          | 0.496         | 0.000           | 0.000      |
| UniRep-based    | 0.726           | 0.758          | 0.570         | 0.426           | 0.296      |
| DeepConv-DTI    | 0.864           | 0.927          | 0.871         | 0.788           | 0.688      |
| IIFDTI          | 0.820           | 0.894          | 0.802         | 0.732           | 0.600      |

Supplementary Table 12: Average performance of the models using cold-start splitting scenario for compounds.

| MODELS                 | Accuracy | AUC ROC | AUC PR | F1 score | MCC    |
|------------------------|----------|---------|--------|----------|--------|
| <b>UniRep-based</b>    | 0.742    | 0.770   | 0.551  | 0.372    | 0.271  |
| <b>DeepConv-DTI</b>    | 0.880    | 0.936   | 0.876  | 0.793    | 0.709  |
| <b>IIFDTI</b>          | 0.844    | 0.906   | 0.810  | 0.732    | 0.623  |
| <b>TransformerCPI</b>  | 0.805    | 0.890   | 0.769  | 0.707    | 0.576  |
| <b>BERT-based</b>      | 0.738    | 0.765   | 0.537  | 0.361    | 0.260  |
| <b>AlphaFoldGrAtts</b> | 0.733    | 0.750   | 0.517  | 0.288    | 0.225  |
| <b>PhyGrAtt</b>        | 0.735    | 0.752   | 0.519  | 0.352    | 0.253  |
| <b>E3FP-based</b>      | 0.677    | 0.690   | 0.444  | 0.464    | 0.256  |
| <b>2DFP-based</b>      | 0.749    | 0.790   | 0.557  | 0.572    | 0.399  |
| <b>DeepCAT</b>         | 0.710    | 0.632   | 0.396  | 0.293    | 0.168  |
| <b>DeepDTA</b>         | 0.728    | 0.676   | 0.440  | 0.326    | 0.210  |
| <b>Random</b>          | 0.499    | 0.497   | 0.277  | 0.356    | -0.003 |
| <b>RF</b>              | 0.657    | 0.583   | 0.345  | 0.314    | 0.094  |
| <b>PhyChemDG</b>       | 0.621    | 0.684   | 0.417  | 0.452    | 0.206  |

Supplementary Table 13: Datasets

| <b>Davis</b>    | Positive Samples | Negative Samples | Neg/Pos | Size    |
|-----------------|------------------|------------------|---------|---------|
| Test Set        | 847              | 2,759            | 3.25    | 3,606   |
| Training Set    | 5975             | 19,285           | 3.22    | 25,260  |
| Dataset         | 6,822            | 22,044           | 3.23    | 28,866  |
| <b>DrugBank</b> | Positive Samples | Negative Samples | Neg/Pos | Size    |
| Test Set        | 2,168            | 10,778           | 4.97    | 12,946  |
| Training Set    | 15,039           | 75,895           | 5.04    | 90,934  |
| Dataset         | 17,207           | 86,673           | 5.03    | 103,880 |
| <b>KiBA</b>     | Positive Samples | Negative Samples | Neg/Pos | Size    |
| Test Set        | 9,718            | 19,430           | 1.99    | 29,148  |
| Training Set    | 66,898           | 137,865          | 2.06    | 204,763 |
| Dataset         | 76,616           | 157,295          | 2.05    | 233,911 |
| <b>WT-Mut</b>   | Positive Samples | Negative Samples | Neg/Pos | Size    |
| Test Set        | 1,995            | 3,824            | 1.91    | 5,819   |
| Training Set    | 95,518           | 163,599          | 1.71    | 259,117 |
| Dataset         | 97,513           | 167,423          | 1.71    | 264,936 |

Supplementary Table 14: Large-sized Dataset: KiBA

| <b>KiBA: Without Limitation</b>      |          |         |        |          |        |
|--------------------------------------|----------|---------|--------|----------|--------|
| Model                                | Accuracy | AUC ROC | AUC PR | F1 score | MCC    |
| TransformerCPI                       | 0.724    | 0.797   | 0.655  | 0.635    | 0.426  |
| PhyChemDG                            | 0.604    | 0.543   | 0.346  | 0.231    | -0.005 |
| PhyGrAtt                             | 0.706    | 0.735   | 0.558  | 0.431    | 0.275  |
| RF                                   | 0.572    | 0.596   | 0.406  | 0.474    | 0.139  |
| BERT-based                           | 0.682    | 0.677   | 0.495  | 0.242    | 0.166  |
| DeepDTA                              | 0.667    | 0.501   | 0.332  | 0.000    | 0.000  |
| DeepCAT                              | 0.667    | 0.703   | 0.499  | 0.000    | -0.004 |
| 2DFP-based                           | 0.668    | 0.584   | 0.399  | 0.046    | 0.053  |
| E3FP-based                           | 0.666    | 0.692   | 0.477  | 0.000    | -0.003 |
| AlphaFoldGrAtts                      | 0.695    | 0.710   | 0.533  | 0.291    | 0.216  |
| UniRep-based                         | 0.667    | 0.682   | 0.479  | 0.000    | -0.006 |
| DeepConv-DTI                         | 0.772    | 0.853   | 0.760  | 0.690    | 0.518  |
| IIFDTI                               | 0.743    | 0.795   | 0.662  | 0.621    | 0.426  |
| <b>KiBA: Limited Rotatable Bonds</b> |          |         |        |          |        |
| Model                                | Accuracy | AUC ROC | AUC PR | F1 score | MCC    |
| TransformerCPI                       | 0.738    | 0.802   | 0.662  | 0.637    | 0.439  |
| PhyGrAtt                             | 0.659    | 0.604   | 0.385  | 0.154    | 0.051  |
| BERT-based                           | 0.684    | 0.659   | 0.473  | 0.338    | 0.188  |
| 2DFP-based                           | 0.671    | 0.597   | 0.410  | 0.149    | 0.084  |
| E3FP-based                           | 0.683    | 0.636   | 0.477  | 0.138    | 0.134  |
| AlphaFoldGrAtts                      | 0.703    | 0.704   | 0.519  | 0.373    | 0.243  |
| DeepConv-DTI                         | 0.788    | 0.862   | 0.772  | 0.700    | 0.542  |
| IIFDTI                               | 0.769    | 0.825   | 0.709  | 0.642    | 0.471  |
| <b>KiBA: Ratio LRB</b>               |          |         |        |          |        |
| Model                                | Accuracy | AUC ROC | AUC PR | F1 score | MCC    |
| TransformerCPI                       | 0.726    | 0.803   | 0.670  | 0.638    | 0.432  |
| PhyGrAtt                             | 0.677    | 0.661   | 0.483  | 0.214    | 0.141  |
| E3FP-based                           | 0.668    | 0.703   | 0.492  | 0.000    | 0.000  |
| 2DFP-based                           | 0.659    | 0.597   | 0.418  | 0.272    | 0.114  |
| AlphaFoldGrAtts                      | 0.702    | 0.710   | 0.532  | 0.436    | 0.267  |
| BERT-based                           | 0.679    | 0.667   | 0.482  | 0.297    | 0.171  |
| DeepConv-DTI                         | 0.785    | 0.852   | 0.763  | 0.686    | 0.523  |
| IIFDTI                               | 0.743    | 0.803   | 0.669  | 0.608    | 0.417  |

Supplementary Table 15: Medium-sized Dataset: DrugBank

| <b>DrugBank: Without Limitation</b>      |          |         |        |          |        |
|------------------------------------------|----------|---------|--------|----------|--------|
| Model                                    | Accuracy | AUC ROC | AUC PR | F1 score | MCC    |
| TransformerCPI                           | 0.950    | 0.950   | 0.904  | 0.846    | 0.817  |
| PhyChemDG                                | 0.400    | 0.418   | 0.135  | 0.208    | -0.108 |
| PhyGrAtt                                 | 0.827    | 0.768   | 0.379  | 0.341    | 0.262  |
| RF                                       | 0.760    | 0.452   | 0.146  | 0.062    | -0.066 |
| BERT-based                               | 0.868    | 0.867   | 0.594  | 0.547    | 0.480  |
| DeepDTA                                  | 0.833    | 0.494   | 0.165  | 0.000    | 0.000  |
| DeepCAT                                  | 0.833    | 0.498   | 0.167  | 0.000    | 0.000  |
| 2DFP-based                               | 0.833    | 0.784   | 0.331  | 0.000    | 0.000  |
| E3FP-based                               | 0.833    | 0.653   | 0.221  | 0.000    | 0.000  |
| AlphaFoldGrAtts                          | 0.813    | 0.771   | 0.357  | 0.344    | 0.244  |
| UniRep-based                             | 0.866    | 0.878   | 0.610  | 0.558    | 0.483  |
| IIFDTI                                   | 0.967    | 0.984   | 0.958  | 0.901    | 0.881  |
| DeepConv-DTI                             | 0.956    | 0.969   | 0.927  | 0.868    | 0.842  |
| <b>DrugBank: Limited Rotatable Bonds</b> |          |         |        |          |        |
| Model                                    | Accuracy | AUC ROC | AUC PR | F1 score | MCC    |
| TransformerCPI                           | 0.951    | 0.955   | 0.907  | 0.849    | 0.821  |
| PhyGrAtt                                 | 0.844    | 0.819   | 0.452  | 0.254    | 0.247  |
| BERT-based                               | 0.837    | 0.879   | 0.565  | 0.000    | 0.000  |
| AlphaFoldGrAtts                          | 0.839    | 0.824   | 0.479  | 0.088    | 0.133  |
| 2DFP-based                               | 0.871    | 0.803   | 0.562  | 0.435    | 0.428  |
| E3FP-based                               | 0.836    | 0.477   | 0.156  | 0.001    | 0.000  |
| DeepConv-DTI                             | 0.925    | 0.965   | 0.920  | 0.798    | 0.761  |
| IIFDTI                                   | 0.969    | 0.979   | 0.946  | 0.901    | 0.883  |
| <b>DrugBank: Ratio LRB</b>               |          |         |        |          |        |
| Model                                    | Accuracy | AUC ROC | AUC PR | F1 score | MCC    |
| TransformerCPI                           | 0.952    | 0.960   | 0.904  | 0.841    | 0.813  |
| PhyGrAtt                                 | 0.835    | 0.798   | 0.420  | 0.446    | 0.350  |
| BERT-based                               | 0.849    | 0.872   | 0.560  | 0.120    | 0.194  |
| AlphaFoldGrAtts                          | 0.850    | 0.826   | 0.439  | 0.255    | 0.253  |
| E3FP-based                               | 0.842    | 0.525   | 0.173  | 0.000    | 0.000  |
| 2DFP-based                               | 0.842    | 0.883   | 0.557  | 0.000    | 0.000  |
| DeepConv-DTI                             | 0.957    | 0.967   | 0.927  | 0.865    | 0.840  |
| IIFDTI                                   | 0.963    | 0.977   | 0.943  | 0.879    | 0.859  |

Supplementary Table 16: Small-sized Dataset: Davis

| Model           | Accuracy | AUC ROC | AUC PR | F1 score | MCC    |
|-----------------|----------|---------|--------|----------|--------|
| TransformerCPI  | 0.704    | 0.674   | 0.370  | 0.416    | 0.221  |
| PhyChemDG       | 0.765    | 0.689   | 0.414  | 0.000    | 0.000  |
| PhyGrAtt        | 0.626    | 0.591   | 0.400  | 0.406    | 0.169  |
| RF              | 0.638    | 0.489   | 0.229  | 0.224    | -0.012 |
| BERT-based      | 0.765    | 0.557   | 0.256  | 0.000    | 0.000  |
| DeepDTA         | 0.765    | 0.479   | 0.223  | 0.000    | 0.000  |
| DeepCAT         | 0.762    | 0.588   | 0.272  | 0.009    | -0.002 |
| 2DFP-based      | 0.765    | 0.486   | 0.229  | 0.000    | 0.000  |
| E3FP-based      | 0.765    | 0.500   | 0.235  | 0.000    | 0.000  |
| AlphaFoldGrAtts | 0.353    | 0.577   | 0.333  | 0.395    | 0.098  |
| UniRep-based    | 0.765    | 0.538   | 0.254  | 0.000    | 0.000  |
| IIFDTI          | 0.736    | 0.732   | 0.495  | 0.476    | 0.302  |
| DeepConv-DTI    | 0.721    | 0.784   | 0.599  | 0.545    | 0.381  |

Supplementary Table 17: Training on Compound-Wildtype Target interactions and test on Compound-Mutated Target interactions

| Model           | Accuracy | AUC ROC | AUC PR | F1 score | MCC   |
|-----------------|----------|---------|--------|----------|-------|
| TransformerCPI  | 0.795    | 0.833   | 0.790  | 0.691    | 0.538 |
| PhyChemDG       | 0.661    | 0.649   | 0.506  | 0.330    | 0.157 |
| PhyGrAtt        | 0.686    | 0.766   | 0.670  | 0.621    | 0.382 |
| RF              | 0.619    | 0.571   | 0.418  | 0.188    | 0.004 |
| 2DFP-based      | 0.683    | 0.666   | 0.520  | 0.258    | 0.198 |
| AlphaFoldGrAtts | 0.651    | 0.670   | 0.434  | 0.502    | 0.257 |
| BERT-based      | 0.728    | 0.703   | 0.638  | 0.463    | 0.348 |
| DeepCAT         | 0.656    | 0.683   | 0.469  | 0.586    | 0.321 |
| DeepDTA         | 0.657    | 0.509   | 0.344  | 0.000    | 0.000 |
| E3FP-based      | 0.596    | 0.629   | 0.400  | 0.547    | 0.236 |
| UniRep-based    | 0.669    | 0.634   | 0.514  | 0.456    | 0.228 |
| DeepConv-DTI    | 0.816    | 0.831   | 0.800  | 0.654    | 0.587 |
| IIFDTI          | 0.776    | 0.709   | 0.688  | 0.567    | 0.481 |