

# Supplementary materials of “D3I-COMCF: dissimilarity-driven dual-interaction via co-occurrence motifs and complementary fragments for drugdrug interaction prediction”

## I. EVALUATION METRICS

ACC, AUC, F1-score and AP are defined as follows:

$$\begin{aligned}
 ACC &= \frac{TP + TN}{TP + FP + FN + TN}, \\
 AUC &= \frac{1}{|\mathcal{P}| \cdot |\mathcal{N}|} \sum_{p \in \mathcal{P}} \sum_{n \in \mathcal{N}} \mathbb{I}(\text{score}(p) > \text{score}(n)) + \frac{1}{2|\mathcal{P}| \cdot |\mathcal{N}|} \sum_{p \in \mathcal{P}} \sum_{n \in \mathcal{N}} \mathbb{I}(\text{score}(p) = \text{score}(n)), \\
 F1 - score &= \frac{2TP}{FN + FP + 2TP}, \\
 AP &= \sum_{k=1}^z (R_k - R_{k-1}) \cdot P_k,
 \end{aligned} \tag{1}$$

where  $TP$  indicates the number of positive samples predicted as positive;  $FP$  is the number of negative samples predicted as positive;  $FN$  is the number of positive samples predicted as negative;  $TN$  represents the number of negative samples predicted as negative;  $p$  indicates an arbitrary positive sample in the positive sample set  $\mathcal{P}$ ;  $n$  represents an arbitrary negative sample in the negative sample set  $\mathcal{N}$ ;  $\mathbb{I}(\cdot)$  is the indicator function, takes value 1 if the condition inside holds, 0 otherwise;  $\text{score}(p)$  and  $\text{score}(n)$  represent model prediction score of positive sample  $p$  and negative sample  $n$ , respectively;  $z$  is the total number of samples;  $k$  is the sorting threshold index, corresponding to the top  $k$  samples sorted by prediction score (descending);  $R_k$  indicates the Recall at the  $k$ -th sorting threshold (ratio of true positives in top  $k$  samples to total true positives);  $P_k$  indicates the Precision at the  $k$ -th sorting threshold (ratio of true positives in top  $k$  samples to the number of top  $k$  samples)

## II. SUPPLEMENTARY DATA

### A. Supplementary table

TABLE S1: Summary of no-MCS cases in four datasets

Dataset	Number of drug pairs in the training and validation sets (deduplicated by drug pair)	Number of drug pairs with no MCS found (or MCS timeout)	Proportion
DB	153,187	1,332	0.0087
Twosides	63,443	1,308	0.0206
DeepDDI	115,044	1,028	0.0089
ZhangDDI	36,006	51	0.0014

TABLE S2: Details of CMMIG for four datasets

Information \ Dataset	DB	Twosides	DeepDDI	ZhangDDI
Node counts	2,311	1,028	2,306	847
Edge counts	8,495	3,201	8,509	2,681
Molecule node counts	1,706	645	1,704	544
Motif node counts	605	383	602	303
Connected component counts	25	10	25	3

TABLE S3: When randomly shuffling test labels while keeping predicted scores unchanged, the AUC values (%) obtained by S1 and S2 under the Train-only protocol

Inductive Fold	S1	S2
fold1	50.98	50.03
fold2	50.29	50.12
fold3	50.35	49.94

TABLE S4: When randomly shuffling test labels while keeping predicted scores unchanged, the AP values (%) obtained by S1 and S2 under the Train-only protocol

Inductive Fold	S1	S2
fold1	50.87	50.00
fold2	50.23	50.10
fold3	50.43	50.06

## B. Supplementary figure

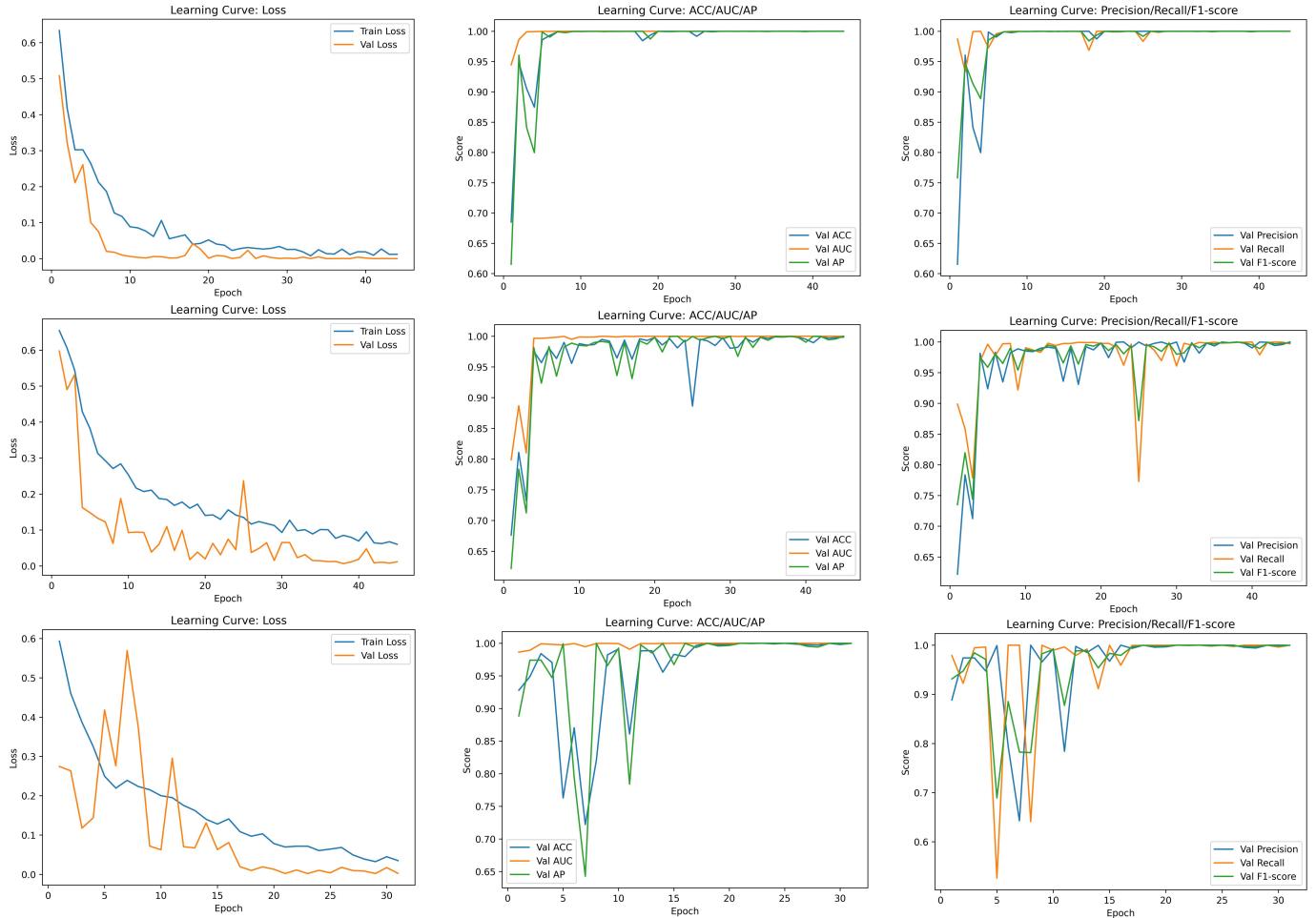


Fig. S1: Training/validation learning curves (loss, AP, ACC, AUC, F1, Precision, and Recall) on the DB dataset for three folds.

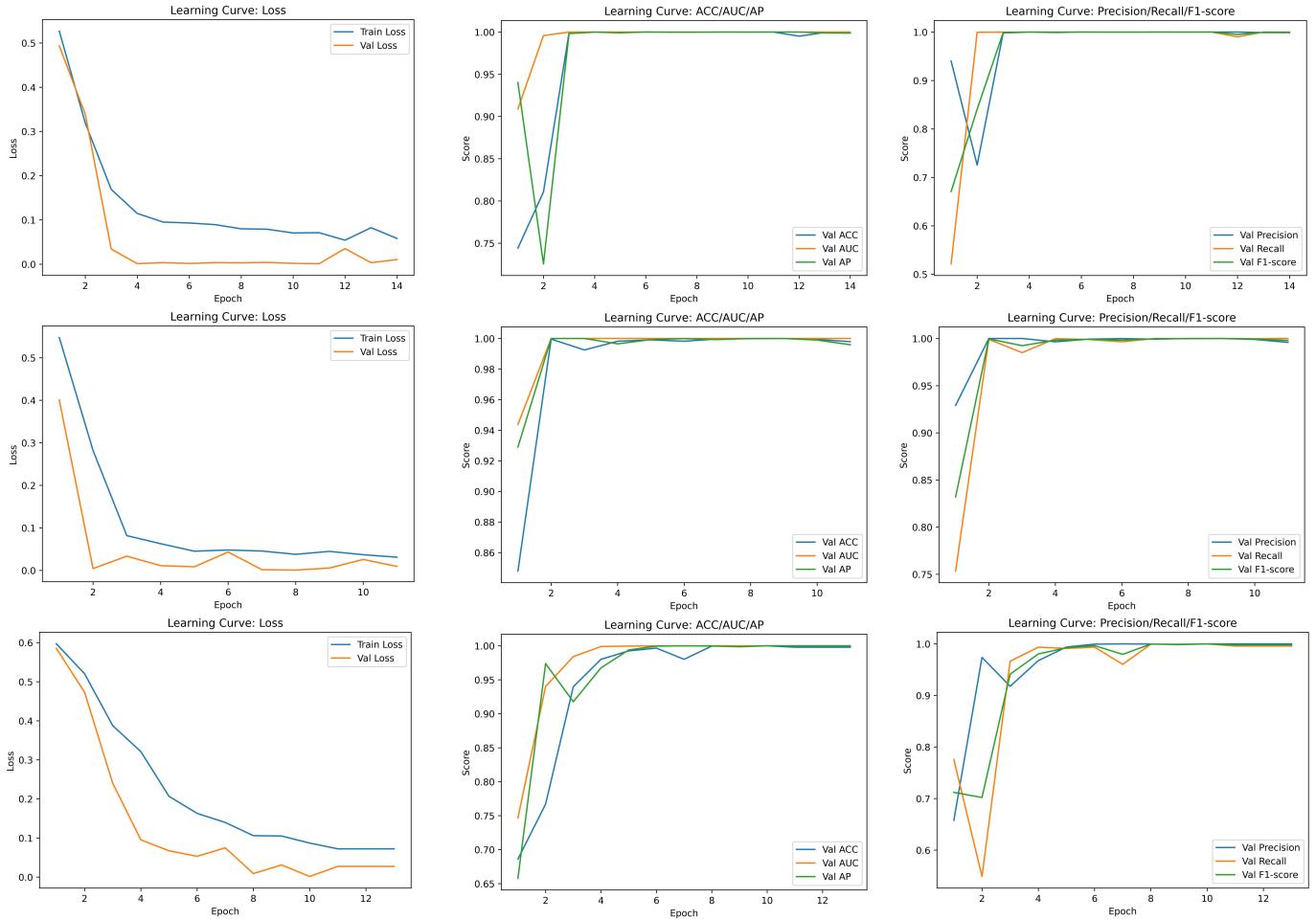


Fig. S2: Training/validation learning curves (loss, AP, ACC, AUC, F1, Precision, and Recall) on the Twosides dataset for three folds.

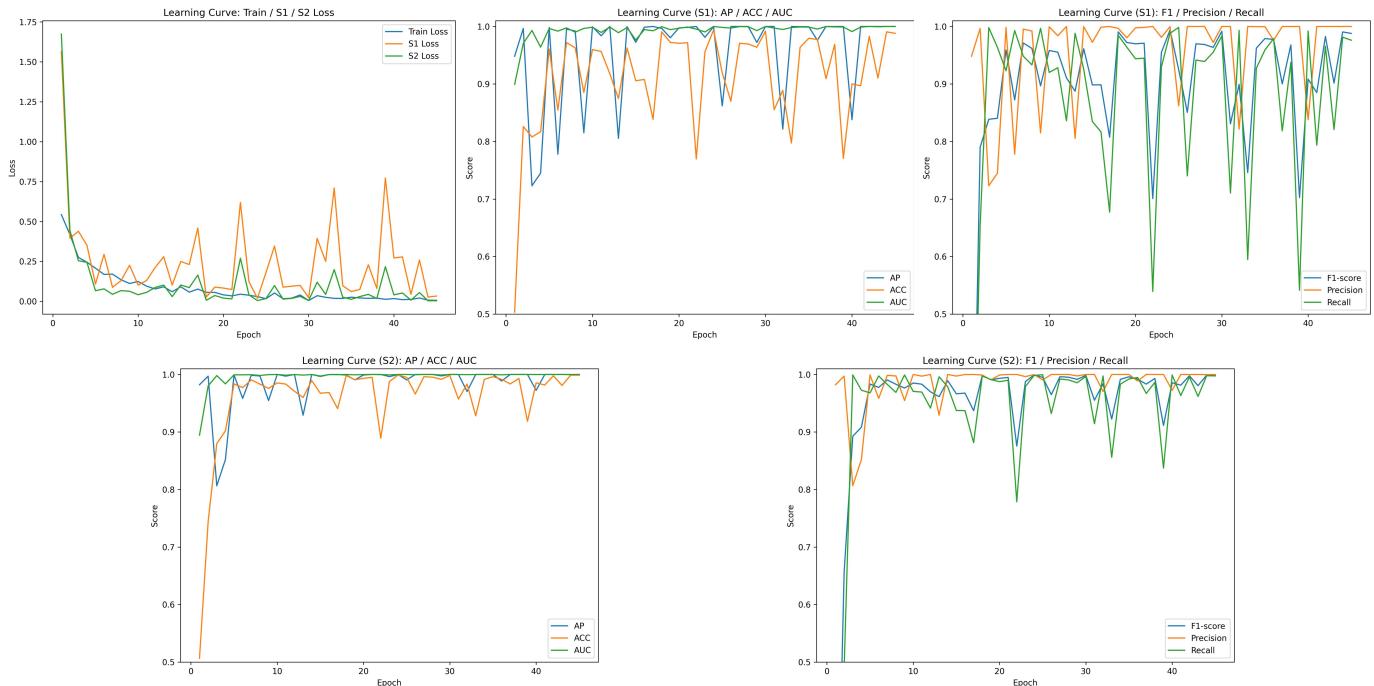


Fig. S3: Training/test learning curves (loss, AP, ACC, AUC, F1, Precision, and Recall) under the Global-CMMIG protocol (cold-start scenario) for fold 1.

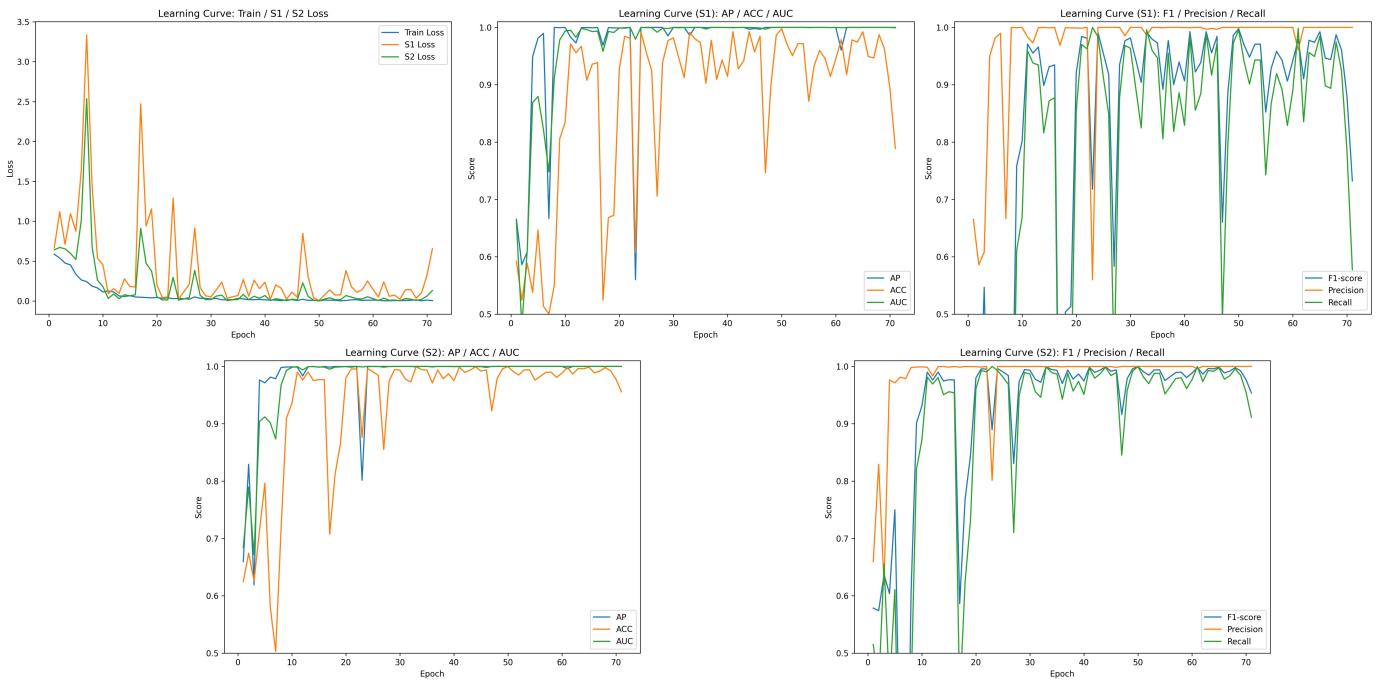


Fig. S4: Training/test learning curves (loss, AP, ACC, AUC, F1, Precision, and Recall) under the Global-CMMIG protocol (cold-start scenario) for fold 2.

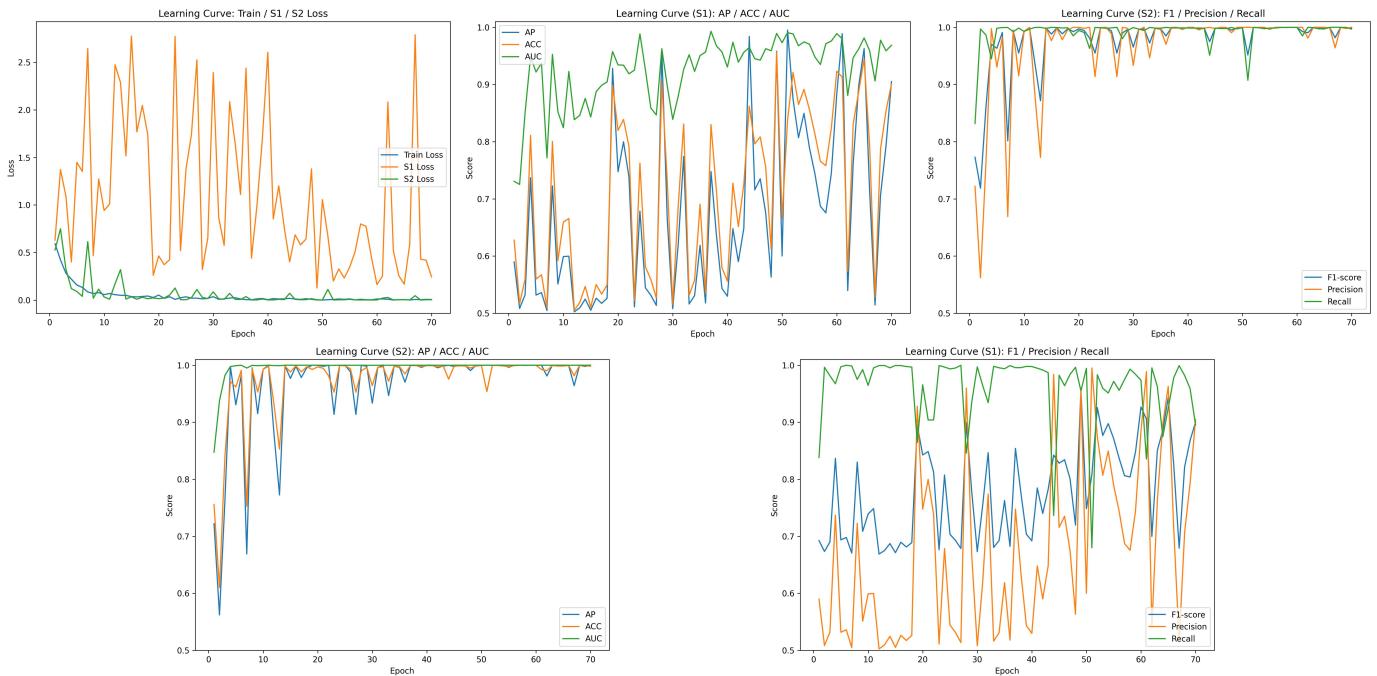


Fig. S5: Training/test learning curves (loss, AP, ACC, AUC, F1, Precision, and Recall) under the Global-CMMIG protocol (cold-start scenario) for fold 3.

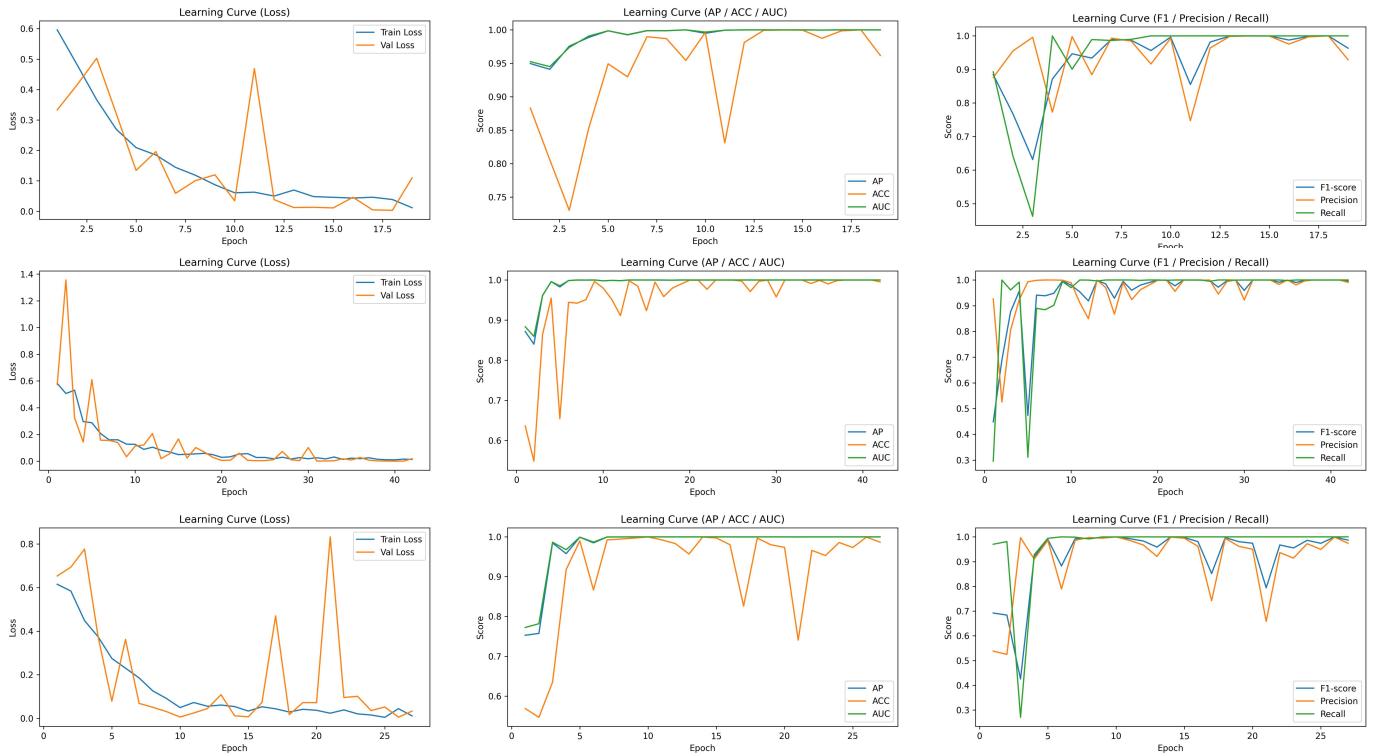


Fig. S6: Training/validation learning curves (loss, AP, ACC, AUC, F1, Precision, and Recall) under the Train-only protocol (cold-start scenario) for three folds.

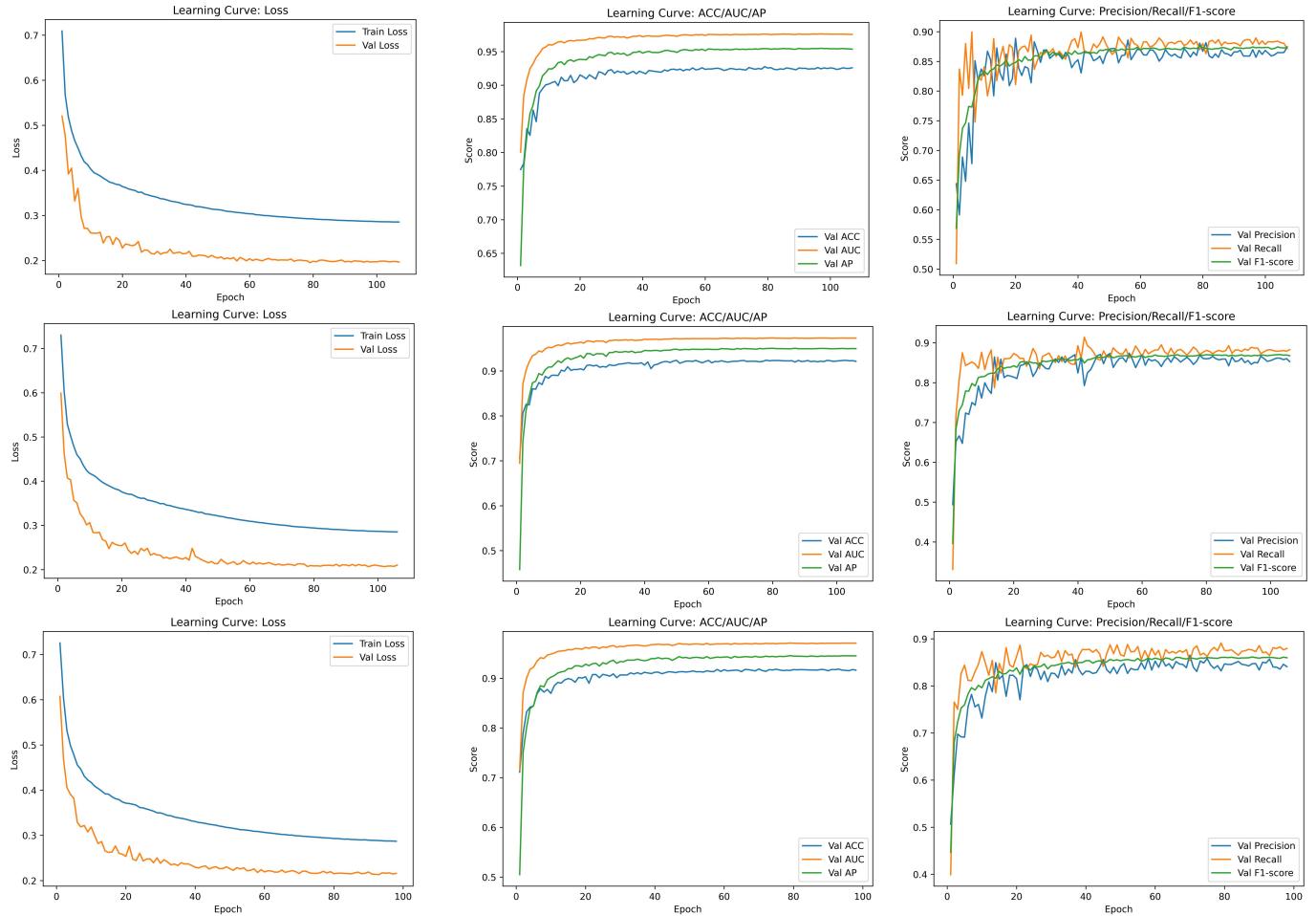


Fig. S7: Training/validation learning curves (loss, AP, ACC, AUC, F1, Precision, and Recall) on the ZhangDDI dataset for three folds.

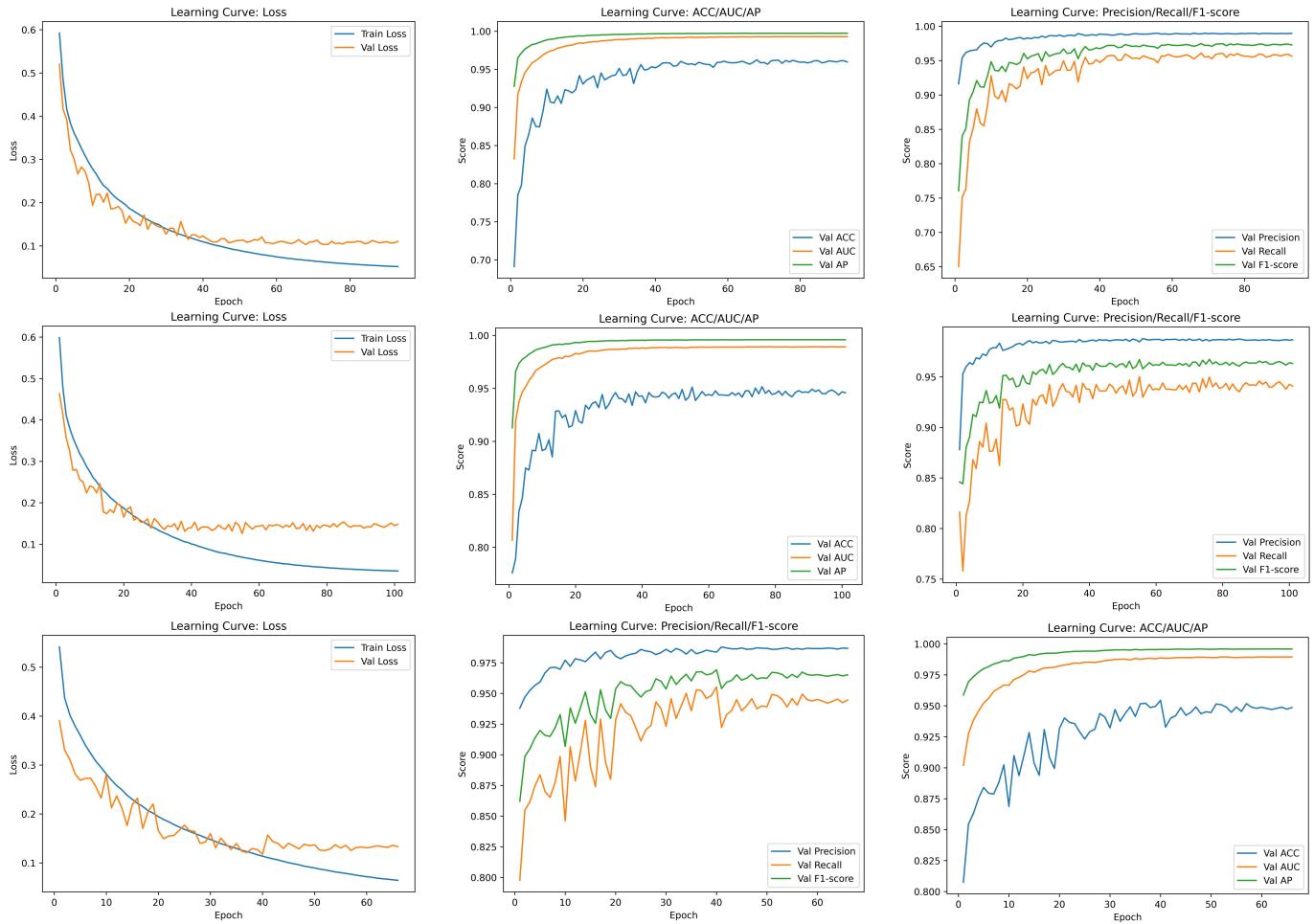


Fig. S8: Training/validation learning curves (loss, AP, ACC, AUC, F1, Precision, and Recall) on the DeepDDI dataset for three folds.

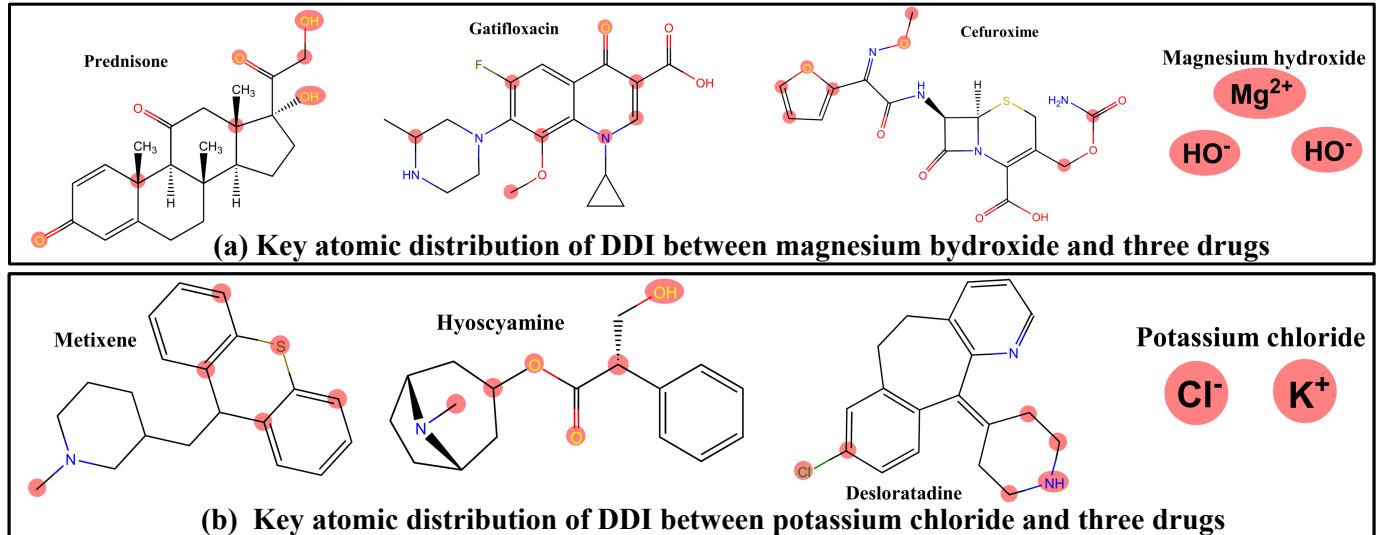


Fig. S9: Atom-level DDI interpretation for representative drugs that cannot be decomposed into motifs by BRICS. (a) Key atomic distributions for magnesium hydroxide paired with prednisone, gatifloxacin, and cefuroxime (DDI types: the bioavailability decrease, the absorption decrease, and the serum concentration decrease, respectively). (b) Key atomic distributions for potassium chloride paired with metixene, hyoscyamine, and desloratadine (all with the DDI type: the ulcerogenic activities Chloride increase).