

Supplementary Information

KnowMol: A Knowledge-Guided Multi-Agent Framework for Interpretable Drug-Target Interaction Prediction, Validated in PRMT3-Targeted NAFLD Therapy

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1 Supplementary Tables

Table S1 | Comparison results of the model performance on DrugBank

DrugBank	Accuracy (std)	Recall (std)	Precision (std)	MCC (std)	F1 score (std)	AUC (std)	AUPR (std)
RF	71.07 (1.34)	73.08 (0.95)	76.92 (1.42)	51.23 (1.54)	74.94 (0.92)	83.03 (0.65)	84.78 (0.67)
NB	52.90 (1.13)	<u>87.99 (1.77)</u>	51.71 (1.01)	42.34 (3.24)	65.13 (0.89)	60.76 (1.24)	59.37 (1.77)
SVM	78.02 (1.92)	<u>75.04 (2.93)</u>	73.86 (2.14)	53.87 (1.29)	74.39 (1.40)	82.02 (1.62)	82.85 (1.49)
DeepConv-DTI	79.50 (0.22)	80.45 (0.21)	79.30 (0.64)	57.91 (0.61)	79.87 (0.62)	86.69 (0.22)	86.28 (0.13)
GraphDTA	77.69 (0.11)	78.77 (1.13)	76.92 (1.05)	55.41 (0.63)	77.83 (1.18)	83.62 (0.25)	83.26 (0.18)
MolTrans	78.48 (0.17)	81.97 (0.23)	77.01 (0.35)	55.65 (0.62)	79.41 (0.73)	85.98 (0.64)	86.67 (0.12)
HyperAttention	80.85 (0.23)	88.16 (0.15)	77.09 (0.17)	62.32 (0.42)	82.26 (0.33)	89.94 (0.14)	88.95 (0.15)
TransformerCPI	79.01 (0.24)	76.26 (0.36)	80.47 (0.34)	58.09 (0.22)	78.31 (0.38)	84.62 (0.33)	84.23 (0.28)
GraphormerDTI	80.22 (1.07)	82.05 (1.23)	79.11 (0.91)	60.48 (2.16)	80.55 (1.02)	88.63 (1.02)	88.36 (0.99)
AIGO-DTI	81.88 (1.37)	82.28 (2.69)	81.26 (0.36)	63.80 (2.78)	81.74 (1.40)	88.62 (1.02)	88.44 (1.65)
DLM-DTI	<u>82.13 (0.27)</u>	82.54 (1.91)	81.68 (1.56)	<u>66.32 (0.55)</u>	81.08 (0.56)	<u>90.48 (0.48)</u>	<u>90.20 (0.60)</u>
EviDTI	82.02 (0.43)	82.28 (1.03)	81.90 (0.58)	64.29 (1.05)	82.09 (0.74)	88.87 (0.73)	88.45 (1.51)
KnowMol	87.33(0.53)	82.58(1.23)	90.80(0.42)	74.91(0.63)	86.50(0.59)	93.73(0.47)	94.60(0.83)

The best results are highlighted in bold, while the second-best results are underlined. Five independent replications of each method were performed ($n = 5$). Data are expressed as means (std).

Table S2 | Comparison results of the model performance on KIBA

KIBA	Accuracy (std)	Recall (std)	Precision (std)	MCC (std)	F1 score (std)	AUC (std)	AUPR (std)
RF	88.41 (0.34)	64.84 (2.48)	70.57 (2.30)	63.21 (1.67)	67.59 (1.37)	91.05 (0.38)	76.05 (1.04)
NB	52.92 (0.83)	71.72 (1.77)	24.22 (1.40)	24.56 (3.24)	36.21 (1.47)	65.92 (0.78)	35.51 (0.94)
SVM	81.72 (0.46)	3.87 (0.76)	66.40 (2.91)	5.24 (1.34)	7.32 (0.92)	73.27(0.56)	43.38 (1.60)
DeepConv-DTI	89.05 (0.32)	68.87 (0.43)	80.52 (0.34)	<u>70.21 (0.28)</u>	74.24 (0.63)	90.67 (0.17)	80.42 (0.62)
GraphDTA	88.92 (0.11)	59.42 (3.23)	77.53 (2.03)	67.51 (0.52)	71.24 (0.81)	91.41 (0.12)	77.61 (0.74)
MolTrans	88.91 (0.16)	73.53 (0.23)	70.42 (0.34)	67.62 (0.22)	71.94 (0.16)	92.32 (0.33)	79.49 (0.64)
HyperAttention	89.33 (0.12)	<u>79.63 (0.24)</u>	68.93 (0.18)	70.12 (0.22)	74.21 (0.35)	93.51 (0.17)	81.41 (0.23)
TransformerCPI	87.01 (0.18)	63.12 (0.32)	66.93 (0.34)	66.2 (0.26)	69.12 (0.23)	88.81 (0.18)	70.81 (0.16)
GraphormerDTI	86.54 (0.85)	85.40 (1.68)	60.63 (1.84)	64.03 (1.10)	70.87 (0.89)	92.58 (0.25)	81.95 (0.91)
AIGO-DTI	90.68 (0.32)	73.65 (0.77)	76.77 (1.12)	69.46 (0.97)	75.17 (0.77)	93.06 (0.26)	83.91 (0.77)
DLM-DTI	88.25 (0.25)	68.10 (2.15)	69.86 (0.90)	61.72 (0.78)	68.94 (0.87)	91.14 (0.39)	75.63 (0.41)
EviDTI	<u>91.27 (0.07)</u>	70.77 (1.69)	80.90 (1.32)	70.44 (0.78)	75.48 (0.83)	93.57 (0.35)	83.03 (0.98)
KnowMol	91.28(0.09)	68.45(0.61)	82.44(1.25)	70.01(0.40)	74.79(0.39)	94.81(0.27)	84.93(0.92)

The best results are highlighted in bold, while the second-best results are underlined. Five independent replications of each method were performed ($n = 5$). Data are expressed as means (std).

Table S3 | Comparison results of the model performance on Davis

Davis	Accuracy (std)	Recall (std)	Precision (std)	MCC (std)	F1 score (std)	AUC (std)	AUPR (std)
RF	84.48 (0.60)	65.01 (1.47)	80.70 (1.87)	64.12 (2.11)	72.01 (1.49)	89.64 (0.68)	83.04 (1.68)
NB	67.53 (0.92)	61.70 (1.82)	47.78 (1.95)	45.21 (1.68)	53.85 (1.72)	70.11 (1.39)	58.43 (2.09)
SVM	82.13 (0.59)	59.70 (1.57)	76.96 (2.19)	60.23 (1.45)	67.24 (1.61)	87.85 (0.78)	80.16 (1.65)
DeepConv-DTI	86.41 (0.27)	72.14 (0.33)	77.85 (0.44)	64.53 (0.35)	74.89 (0.64)	91.83 (0.20)	83.87 (0.62)
GraphDTA	81.72 (0.19)	53.01 (1.76)	74.33 (1.45)	62.42 (0.67)	71.83 (0.82)	85.92 (0.43)	74.31 (0.74)
MolTrans	83.61 (0.18)	76.31 (0.34)	68.87 (0.24)	62.91 (0.13)	72.40 (0.17)	89.84 (0.22)	80.26 (0.66)
HyperAttention	86.61 (0.14)	<u>78.01 (0.23)</u>	75.41 (0.16)	67.54 (0.28)	74.21 (0.22)	92.01 (0.14)	83.92 (0.13)
TransformerCPI	82.22 (0.16)	68.82 (0.38)	68.81 (0.37)	64.21 (0.24)	72.41 (0.25)	87.72 (0.16)	76.71 (0.18)
GraphormerDTI	84.81 (0.84)	83.78 (2.52)	68.43 (2.18)	65.22 (1.84)	75.28 (1.43)	91.24 (0.74)	84.31 (1.48)
AIGO-DTI	86.19 (0.79)	72.55 (2.94)	78.01 (2.11)	65.72 (1.96)	75.12 (1.52)	92.01 (0.97)	84.81 (1.10)
DLM-DTI	85.66 (0.47)	74.08 (2.50)	75.26 (1.92)	64.68 (1.27)	74.62 (1.03)	91.30 (0.35)	82.48 (0.86)
EviDTI	87.40 (1.08)	72.93 (1.93)	81.17 (2.94)	68.40 (2.78)	76.81 (2.03)	92.10 (0.78)	85.07 (2.12)
KnowMol	87.47(0.27)	71.01(0.67)	83.18(0.71)	68.53(0.68)	<u>76.61(0.45)</u>	92.97(0.58)	86.59(1.37)

The best results are highlighted in bold, while the second-best results are underlined. Five independent replications of each method were performed ($n = 5$). Data are expressed as means (std).

Table S4 | Natural compounds screened as PRMT3 candidates

No.	Compounds
1	Baicalin
2	Aescin
3	Geniposide
4	Icarin
5	Salvianolic acid B
6	Timosaponin
7	Psoralen
8	Salidroside
9	Agrimol B
10	Hanbaicalin
11	Parthenolide
12	Quercetin
13	Isoquercitroside
14	Echinoid
15	Senoside
16	Imperatorin
17	Hesperedin
18	Geniposide B
19	Dihydrocurcurbitacin B
20	Dihydromyricetin