nature protocols

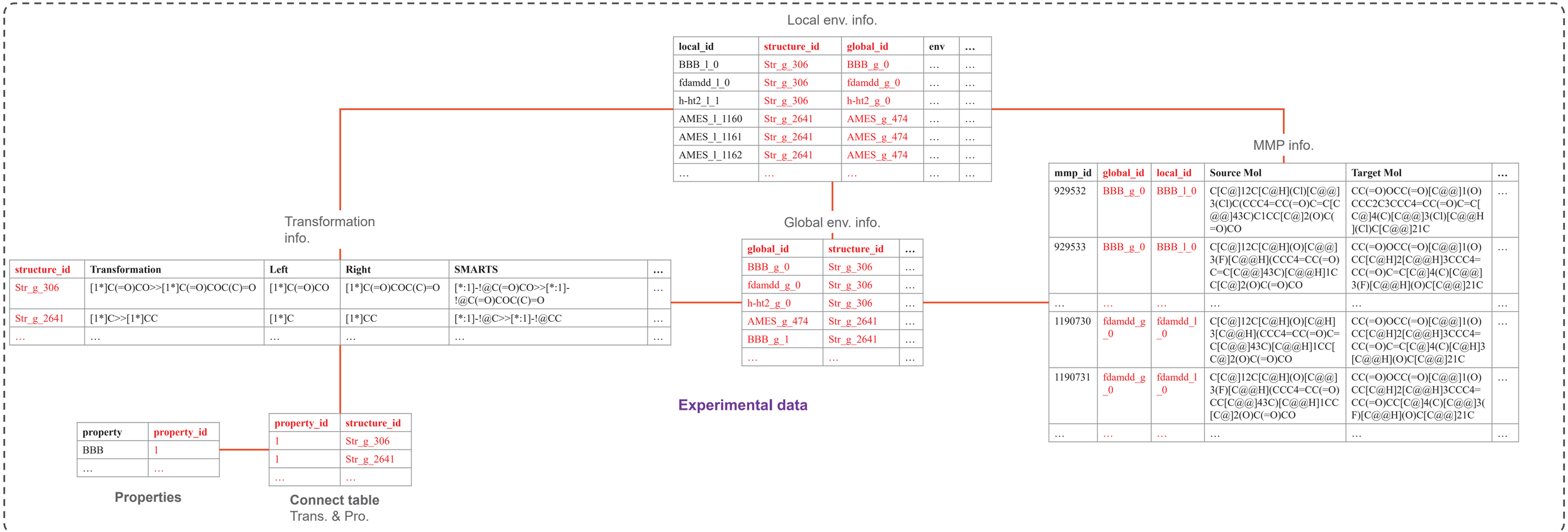
https://doi.org/10.1038/s41596-023-00942-4

Protocol

Check for updates

OptADMET: a web-based tool for substructure modifications to improve ADMET properties of lead compounds

In the format provided by the authors and unedited



Local env. info.

local_id	structure_id	global_id	env	…
BBB_l_0	Str_g_306	BBB_g_0	…	…
fdamdd_l_0	Str_g_306	fdamdd_g_0	…	…
h-ht2_l_1	Str_g_306	h-ht2_g_0	…	…
AMES_l_1160	Str_g_2641	AMES_g_474	…	…
AMES_l_1161	Str_g_2641	AMES_g_474	…	…
AMES_l_1162	Str_g_2641	AMES_g_474	…	…
…	…	…	…	…

Transformation info.

structure_id	Transformation	Left	Right	SMARTS	…
Str_g_306	[1*]C(=O)CO>>[1*]C(=O)COC(C)=O	[1*]C(=O)CO	[1*]C(=O)COC(C)=O	[*:1]-!@C(=O)CO>>[*:1]-!@C(=O)COC(C)=O	…
Str_g_2641	[1*]C>>[1*]CC	[1*]C	[1*]CC	[*:1]-!@C>>[*:1]-!@CC	…
…	…	…	…	…	…

Global env. info.

global_id	structure_id	…
BBB_g_0	Str_g_306	…
fdamdd_g_0	Str_g_306	…
h-ht2_g_0	Str_g_306	…
AMES_g_474	Str_g_2641	…
BBB_g_1	Str_g_2641	…
…	…	…

MMP info.

mmp_id	global_id	local_id	Source Mol	Target Mol	…
929532	BBB_g_0	BBB_l_0	C[C@]12C[C@H](Cl)[C@@]3(Cl)C(CCC4=CC(=O)C=C[C@@]43C)C1CC[C@]2(O)C(=O)CO	CC(=O)OCC(=O)[C@@]1(O)CCC2C3CCC4=CC(=O)C=C[C@]4(C)[C@@]3(Cl)[C@@H](Cl)C[C@@]21C	…
929533	BBB_g_0	BBB_l_0	C[C@]12C[C@H](O)[C@@]3(F)[C@@H](CCC4=CC(=O)C=C[C@@]43C)[C@@H]1CC[C@]2(O)C(=O)CO	CC(=O)OCC(=O)[C@@]1(O)CC[C@H]2[C@@H]3CCC4=CC(=O)C=C[C@]4(C)[C@@]3(F)[C@@H](O)C[C@@]21C	…
…	…	…	…	…	…
1190730	fdamdd_g_0	fdamdd_l_0	C[C@]12C[C@H](O)[C@H]3[C@@H](CCC4=CC(=O)C=C[C@@]43C)[C@@H]1CC[C@]2(O)C(=O)CO	CC(=O)OCC(=O)[C@@]1(O)CC[C@H]2[C@@H]3CCC4=CC(=O)C=C[C@]4(C)[C@H]3[C@@H](O)C[C@@]21C	…
1190731	fdamdd_g_0	fdamdd_l_0	C[C@]12C[C@H](O)[C@@]3(F)[C@@H](CCC4=CC(=O)CC[C@@]43C)[C@@H]1CC[C@@]2(O)C(=O)CO	CC(=O)OCC(=O)[C@@]1(O)CC[C@H]2[C@@H]3CCC4=CC(=O)CC[C@]4(C)[C@@]3(F)[C@@H](O)C[C@@]21C	…
…	…	…	…	…	…

Properties

property	property_id
BBB	1
…	…

Connect table
Trans. & Pro.

property_id	structure_id
1	Str_g_306
1	Str_g_2641
…	…

Fig. S1

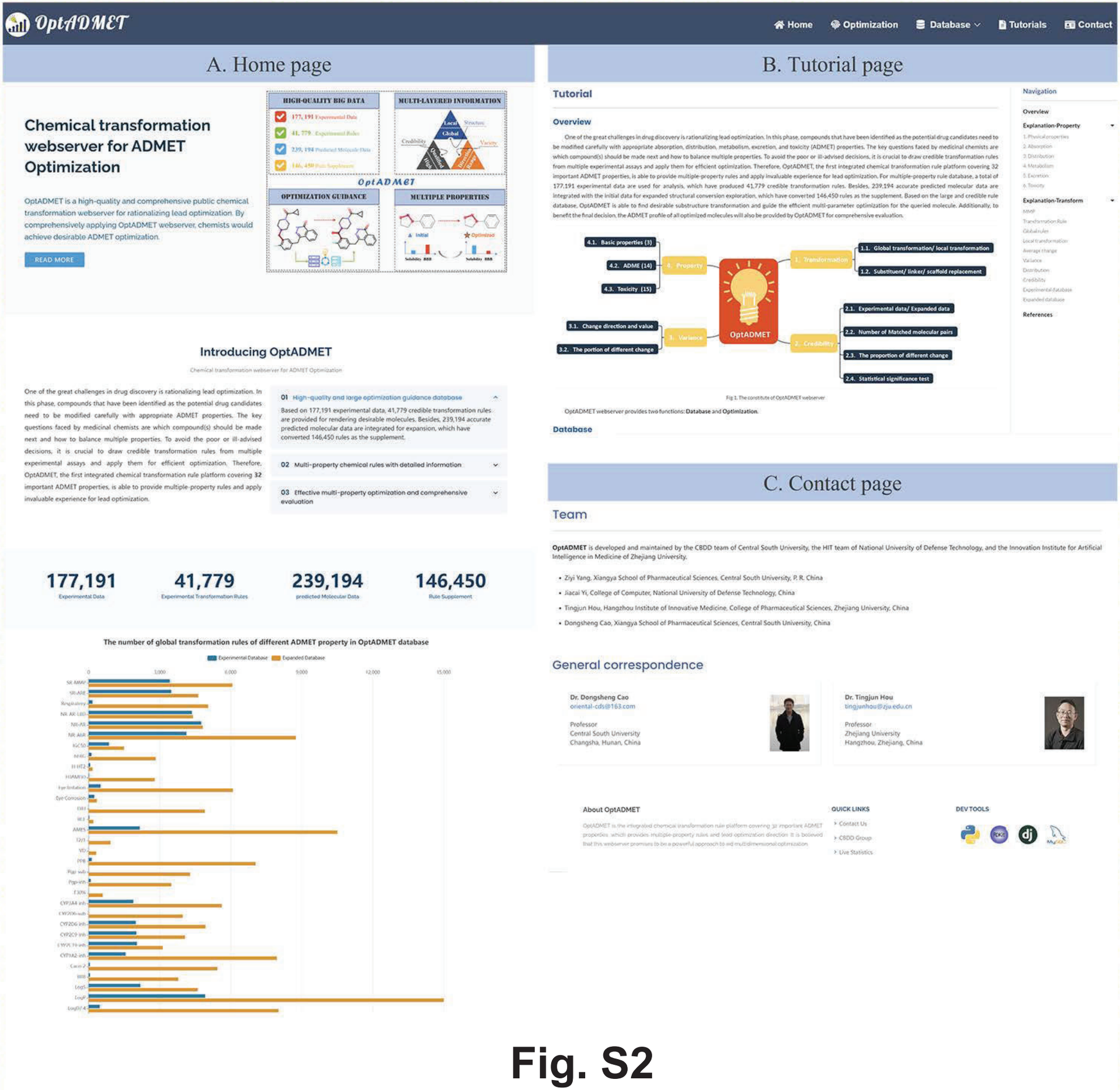

OptADMET
Home
Optimization
Database
Tutorials
Contact
A. Home page
Chemical transformation webserver for ADMET Optimization
OptADMET is a high-quality and comprehensive public chemical transformation webserver for rationalizing lead optimization. By comprehensively applying OptADMET webserver, chemists would achieve desirable ADMET optimization.
READ MORE
HIGH-QUALITY BIG DATA
177, 191 Experimental Data
41, 779 Experimental Rules
239, 194 Predicted Molecule Data
146, 450 Rule Supplement
MULTI-LAYERED INFORMATION
Local
Global
Structure
Variety
Credibility
Qualified
Intensive power
Weak
OptADMET
OPTIMIZATION GUIDANCE
MULTIPLE PROPERTIES
Initial
Optimized
Introducing OptADMET
Chemical transformation webserver for ADMET Optimization
One of the great challenges in drug discovery is rationalizing lead optimization. In this phase, compounds that have been identified as the potential drug candidates need to be modified carefully with appropriate ADMET properties. The key questions faced by medicinal chemists are which compound(s) should be made next and how to balance multiple properties. To avoid the poor or ill-advised decisions, it is crucial to draw credible transformation rules from multiple experimental assays and apply them for efficient optimization. Therefore, OptADMET, the first integrated chemical transformation rule platform covering 32 important ADMET properties, is able to provide multiple-property rules and apply invaluable experience for lead optimization.
01 High-quality and large optimization guidance database
Based on 177,191 experimental data, 41,779 credible transformation rules are provided for rendering desirable molecules. Besides, 239,194 accurate predicted molecular data are integrated for expansion, which have converted 146,450 rules as the supplement.
02 Multi-property chemical rules with detailed information
03 Effective multi-property optimization and comprehensive evaluation
177,191
Experimental Data
41,779
Experimental Transformation Rules
239,194
predicted Molecular Data
146,450
Rule Supplement
The number of global transformation rules of different ADMET property in OptADMET database
Experimental Database
Expanded Database
0
3,000
6,000
9,000
12,000
15,000
SR-MMP
SR-ARE
Respiratory
NR-AR-LBD
NR-AR
NR-AhR
IGC50
NHRC
H-HT2
HAMWS
Eye-Irritation
Eye-Corrosion
DILI
BCF
AMES
D2/1
VD
PPB
Pgp-sub
Pgp-inh
F30%
CYP3A4-inh
CYP2D6-sub
CYP2D6-inh
CYP2C9-inh
CYP2C19-inh
CYP1A2-inh
Caco-2
BBB
LogS
LogP
LogD7.4
B. Tutorial page
Tutorial
Overview
One of the great challenges in drug discovery is rationalizing lead optimization. In this phase, compounds that have been identified as the potential drug candidates need to be modified carefully with appropriate absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties. The key questions faced by medicinal chemists are which compound(s) should be made next and how to balance multiple properties. To avoid the poor or ill-advised decisions, it is crucial to draw credible transformation rules from multiple experimental assays and apply them for efficient optimization. Therefore, OptADMET, the first integrated chemical transformation rule platform covering 32 important ADMET properties, is able to provide multiple-property rules and apply invaluable experience for lead optimization. For multiple-property rule database, a total of 177,191 experimental data are used for analysis, which have produced 41,779 credible transformation rules. Besides, 239,194 accurate predicted molecular data are integrated with the initial data for expanded structural conversion exploration, which have converted 146,450 rules as the supplement. Based on the large and credible rule database, OptADMET is able to find desirable substructure transformation and guide the efficient multi-parameter optimization for the queried molecule. Additionally, to benefit the final decision, the ADMET profile of all optimized molecules will also be provided by OptADMET for comprehensive evaluation.
4.1. Basic properties (3)
4.2. ADME (14)
4.3. Toxicity (15)
4. Property
1. Transformation
1.1. Global transformation/ local transformation
1.2. Substituent/ linker/ scaffold replacement
OptADMET
3.1. Change direction and value
3.2. The portion of different change
3. Variance
2. Credibility
2.1. Experimental data/ Expanded data
2.2. Number of Matched molecular pairs
2.3. The proportion of different change
2.4. Statistical significance test
Fig 1. The constitute of OptADMET webserver
OptADMET webserver provides two functions: Database and Optimization.
Database
Navigation
Overview
Explanation-Property
1. Physical properties
2. Absorption
3. Distribution
4. Metabolism
5. Excretion
6. Toxicity
Explanation-Transform
MMP
Transformation Rule
Global rules
Local transformation
Average change
Variance
Distribution
Credibility
Experimental database
Expanded database
References
C. Contact page
Team
OptADMET is developed and maintained by the CBDD team of Central South University, the HIT team of National University of Defense Technology, and the Innovation Institute for Artificial Intelligence in Medicine of Zhejiang University.
Ziyi Yang, Xiangya School of Pharmaceutical Sciences, Central South University, P. R. China
Jiacai Yi, College of Computer, National University of Defense Technology, China
Tingjun Hou, Hangzhou Institute of Innovative Medicine, College of Pharmaceutical Sciences, Zhejiang University, China
Dongsheng Cao, Xiangya School of Pharmaceutical Sciences, Central South University, China
General correspondence
Dr. Dongsheng Cao
oriental-cds@163.com
Professor
Central South University
Changsha, Hunan, China
Dr. Tingjun Hou
tingjunhou@zju.edu.cn
Professor
Zhejiang University
Hangzhou, Zhejiang, China
About OptADMET
OptADMET is the integrated chemical transformation rule platform covering 32 important ADMET properties, which provides multiple-property rules and lead optimization direction. It is believed that this webserver promises to be a powerful approach to aid multi-dimensional optimization.
QUICK LINKS
Contact Us
CBDD Group
Live Statistics
DEV TOOLS

Fig. S2


A. Input molecule and condition
B. Generated molecules result view
C. A PDF file of all the results
OptADMET
Summary Information
1. Original molecular profile
D. A PDF file of one transformation result
OptADMET
1. Transformation information
Original Molecule
Transformation
Generated Molecule
2. Property information
E. A CSV file of all the results
F. Detail information
TRANSFORMATION INFORMATION
PROPERTY INFORMATION

Fig. S3

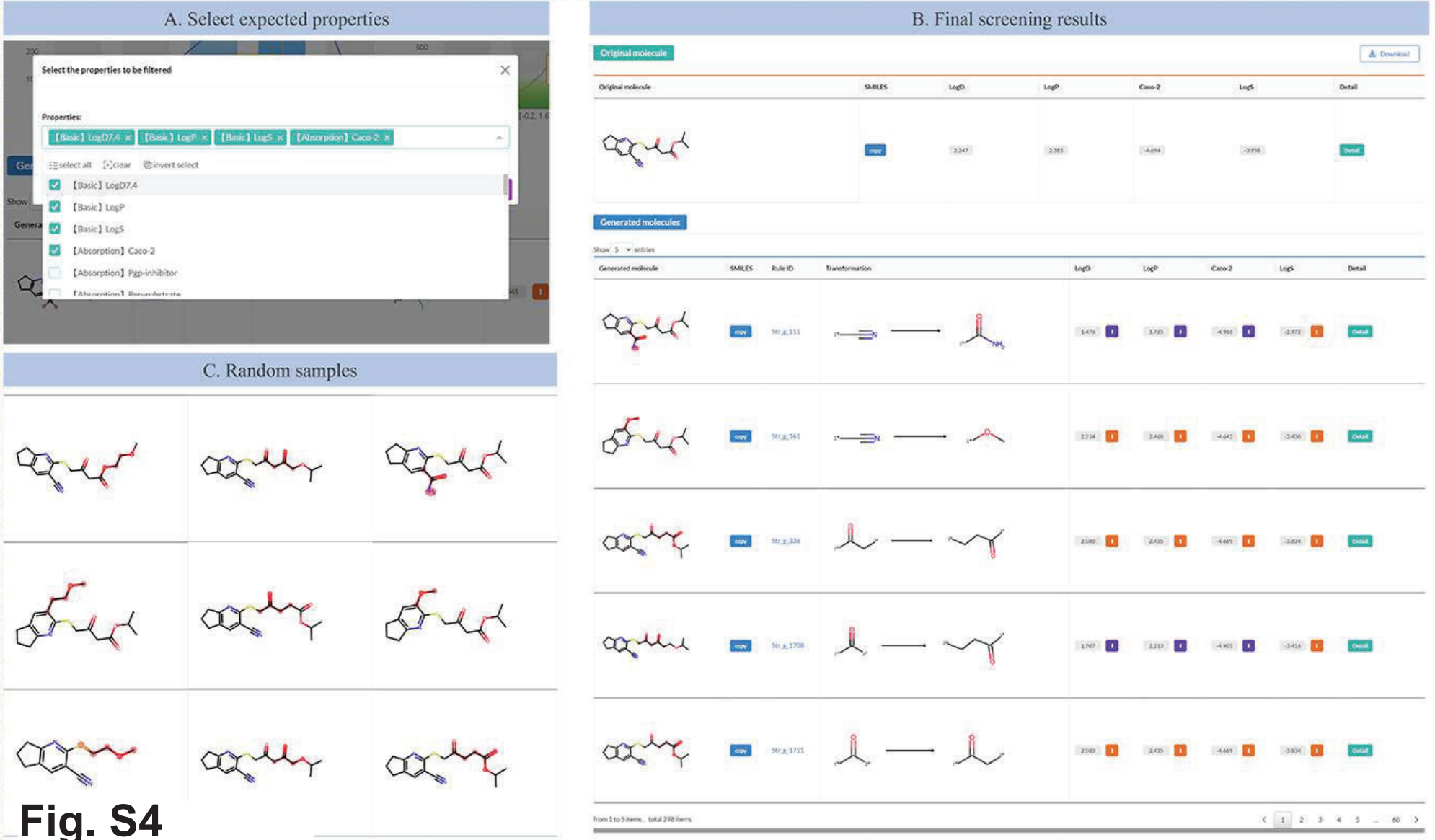

A. Select expected properties
Select the properties to be filtered
Properties:
【Basic】LogD7.4
【Basic】LogP
【Basic】LogS
【Absorption】Caco-2
select all
clear
invert select
【Basic】LogD7.4
【Basic】LogP
【Basic】LogS
【Absorption】Caco-2
【Absorption】Pgp-inhibitor
B. Final screening results
Original molecule
Download
Original molecule
SMILES
LogD
LogP
Caco-2
LogS
Detail
Generated molecules
Generated molecule
SMILES
Rule ID
Transformation
LogD
LogP
Caco-2
LogS
Detail
C. Random samples

Fig. S4

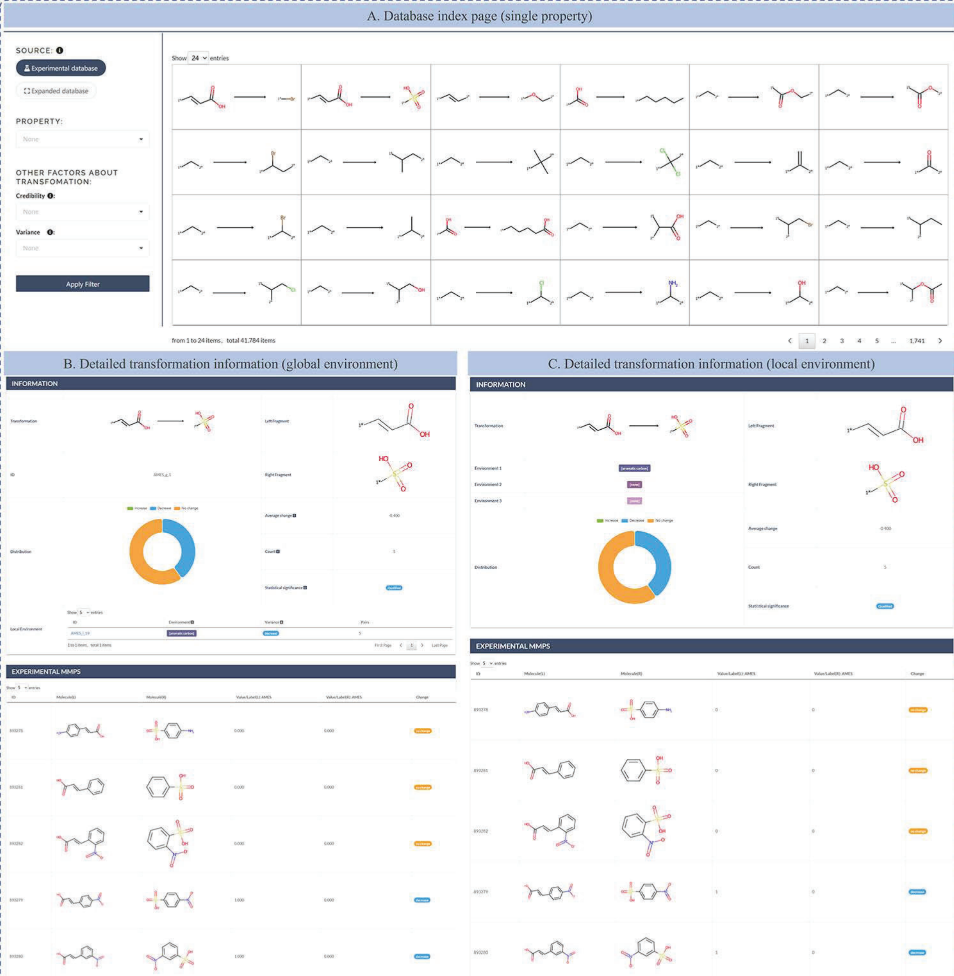

A. Database index page (single property)
SOURCE:
Experimental database
Expanded database
PROPERTY:
None
OTHER FACTORS ABOUT TRANSFOMATION:
Credibility
None
Variance
None
Apply Filter
Show 24 entries
from 1 to 24 items, total 41,784 items
1 2 3 4 5 ... 1,741
B. Detailed transformation information (global environment)
INFORMATION
Transformation
Left Fragment
ID
Right Fragment
Distribution
Average change
Count
Statistical significance
Local Environment
EXPERIMENTAL MMPS
C. Detailed transformation information (local environment)
INFORMATION
Transformation
Left Fragment
Environment 1
Environment 2
Environment 3
Right Fragment
Average change
Distribution
Count
Statistical significance
EXPERIMENTAL MMPS

Fig. S5

Table S1. Performance of the ADMET classification prediction models on the test set.

Category	Models	AUC	ACC	F-measure	Specificity	Sensitivity
Absorption	Pgp-inhibitor	0.936	0.877	0.843	0.825	0.991
	Pgp-substrate	0.915	0.828	0.830	0.835	0.821
	$F_{30\%}$	0.774	0.747	0.572	0.871	0.501
Distribution	BBB Penetration	0.924	0.843	0.863	0.803	0.873
Metabolism	CYP1A2 inhibitor	0.933	0.859	0.847	0.844	0.871
	CYP2C19 inhibitor	0.883	0.814	0.799	0.811	0.817
	CYP2C9 inhibitor	0.875	0.810	0.715	0.719	0.855
	CYP2D6 inhibitor	0.882	0.882	0.647	0.557	0.98
	CYP2D6 substrate	0.821	0.748	0.748	0.756	0.741
	CYP3A4 inhibitor	0.899	0.818	0.778	0.775	0.848
Excretion	$T_{1/2}$	0.801	0.727	0.478	0.658	0.827
Toxicity	hERG Blockers	0.943	0.889	0.778	0.869	0.909
	H-HT-2	0.776	0.706	0.752	0.614	0.776
	DILI	0.912	0.835	0.833	0.822	0.847
	AMES Toxicity	0.914	0.841	0.860	0.807	0.868
	FDAMDD	0.843	0.760	0.749	0.762	0.757
	Skin Sensitization	0.707	0.775	0.462	0.539	0.889
	Eye Corrosion	0.990	0.952	0.961	0.948	0.958
	Eye Irritation	0.978	0.942	0.961	0.850	0.973
	Respiratory Toxicity	0.828	0.764	0.514	0.732	0.786
	NR-AR	0.886	0.890	0.348	0.896	0.731
	NR-AR-LBD	0.915	0.936	0.472	0.942	0.783
	NR-AhR	0.943	0.862	0.573	0.858	0.896
	SR-ARE	0.863	0.827	0.469	0.850	0.701
	SR-MMP	0.927	0.897	0.660	0.908	0.835

Table S2. Performance of the ADMET regression prediction models on the test sets.

Category	Properties	R^2	RMSE	MAE
Physicochemical property	LogS	0.863	0.812	0.552
	LogD7.4	0.836	0.559	0.427
	LogP	0.957	0.357	0.256
Absorption	Caco-2 Permeability	0.733	0.364	0.256
Distribution	PPB	0.734	0.135	0.834
	VDss	0.819	0.637	0.371
Toxicity	IGC_{50}	0.784	0.489	0.347
	BCF	0.775	0.648	0.471

Table S3. The data information about the OptADMET webserver.

Property	Experimental Database				Expanded Database			
	Molecule	MMP	Global[1]	Local[2]	Molecule	MMP	Global[1]	Local[2]
LogD7.4	10372	14155	471	1736	22640	201761	8025	18029
LogP	12549	154009	4926	13750	22210	379642	15102	37423
LogS	4880	56878	2185	4485	10485	117674	4609	10466
BBB Penetration	2905	759	59	149	14200	53252	3787	6885
Caco-2 Permeability	1272	1571	56	119	9384	113986	5443	9555
CYP1A2 inhibitor	12659	41682	1556	2170	21530	119169	7953	12340
CYP2C19 inhibitor	12688	52446	2040	2713	21866	71783	3132	5121
CYP2C9 inhibitor	12105	50518	2019	2665	20631	86467	4073	7255
CYP2D6 inhibitor	13150	46398	1996	2779	23455	98430	4943	9206
CYP2D6 substrate	883	109	8	25	9744	58009	3977	7321
CYP3A4 inhibitor	12405	41033	1890	2576	23214	102599	5624	10366
F30%	1006	48	5	13	6750	8812	600	1078
Pgp inhibitor	2255	1703	93	205	12168	45847	3494	6715
Pgp substrate	1248	28	3	8	10148	45420	4285	6796
PPB	4789	3325	131	334	17235	164071	7054	14381
VD	1117	40	2	5	4056	6683	317	755
T2/1	1284	48	4	10	6630	10112	924	1536
AMES Toxicity	7670	36544	2160	5141	16823	134709	10510	21091
Bioconcentration Factor	676	684	29	60	2954	5055	198	471
DILI	472	16	2	6	8716	58061	4910	7636
Eye Corrosion	2298	6273	240	695	4068	8249	351	970
Eye Irritation	5220	19613	503	1459	15185	91146	6097	10204
FDAMDD	1215	221	20	44	9783	34357	2790	5431
H-HT2	2395	775	69	157	4607	2920	170	407
hERG Blockers	13844	2994	121	380	25200	45593	2832	6278
IGC50	1787	30017	860	2223	5819	48720	1498	4153
NR-AhR	6679	68190	4127	8436	16099	122700	8762	14926

NR-AR	7391	76762	4756	9510	7739	77762	4824	9742
NR-AR-LBD	6928	70903	4360	8960	7201	71526	4409	9094
Respiratory Toxicity	1398	2164	165	446	12165	78378	5049	9941
SR-ARE	5666	56341	3492	7126	8448	71660	4629	9609
SR-MMP	5985	56692	3431	7075	15232	92840	6079	12797

Note: 1,2: Global rules and local transformations

Table S4. The development environment of OptADMET.

Third party library	Version
RDKit	2019.03.1
Django	2.2.0
DGL	0.5.2
DGL-LifeSci	0.2.5
PyTorch	1.6.0
TorchVision	0.7.0
PyCharts	1.8.1
MySQL	8.0
Nginx	1.6.2

Table S5. The development environment of OptADMET.

Type	Endpoint	Property interval	Unit
Basic	LogD7.4	1≤value≤3	log mol/L
Basic	LogP	0≤value≤3	log mol/L
Basic	LogS	-4≤value≤0.5	log mol/L
Absorption	Caco-2	-5.15≤value	log cm/s
Absorption	Pgp-inhibitor	0≤value≤0.3	probability
Absorption	Pgp-substrate	0≤value≤0.3	probability
Absorption	F (30%)	0≤value≤0.3	probability
Distribution	PPB	value<0.9	probability
Distribution	BBB	0≤value≤0.3	probability
Distribution	vdss	0.04≤value≤20	L/kg
Metabolism	CYP 1A2-inhibitor	value≤0.5	probability
Metabolism	CYP 2C19-inhibitor	value≤0.5	probability
Metabolism	CYP 2C9-inhibitor	value≤0.5	probability
Metabolism	CYP 2D6-inhibitor	value≤0.5	probability
Metabolism	CYP 2d6-substrate	value≤0.5	probability
Metabolism	CYP 3A4-inhibitor	value≤0.5	probability
Excretion	T1/2	value≤0.5	probability
Toxicity	Ames	value≤0.5	probability
Toxicity	BCF	value≤0.5	probability
Toxicity	DILI	value≤0.5	probability
Toxicity	EC	value≤0.5	probability
Toxicity	EI	value≤0.5	probability
Toxicity	FDAMDD	value≤0.5	probability
Toxicity	H-HT-2	value≤0.5	probability
Toxicity	hERG	value≤0.5	probability
Toxicity	IGC50	value≤0.5	probability
Toxicity	NR-AhR	value≤0.5	probability
Toxicity	NR-AR	value≤0.5	probability
Toxicity	NR-AR-LBD	value≤0.5	probability
Toxicity	Respiratory	value≤0.5	probability
Toxicity	SR-ARE	value≤0.5	probability
Toxicity	SR-MMP	value≤0.5	probability