“Unveiling the antiviral mechanism of *Forsythia suspense*: A comprehensive analysis of screening targets and components

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List of Supporting Information

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Table S1 The PDB ID, Resolution, and ligand of key antiviral target proteins

Protein name	PDB ID	Resolution	ligand
AkT1	1H10	1.40 Å	4IP
TP53	3ZME	1.35 Å	QC5
CASP3	2CNO	1.95 Å	M60
CASP8	4PS1	1.73 Å	DTT
PTGS2	1CX2	2.50 Å	S58
PTEN	5BZZ	2.20 Å	TLA
MMP9	1GKC	2.50 Å	NFH
TNF	6M95	2.10 Å	J8S
VEGFA	4KZN	1.71 Å	PGE
MYC	6C4U	2.60 Å	GOL

Table S2 Molecular docking results of compounds **1**–**11** and 4IP with AKT1

Compound	Total score	D score	PMF score	G score	Chem score
1	4.76	-539.250	18.277	-287.207	-47.703
2	4.47	-65.459	-63.570	-35.246	-15.732
3	4.16	-69.908	-66.274	-38.203	-10.228
4	3.31	-77.864	-62.248	-95.841	-10.530
5	7.73	-115.758	-70.813	-233.988	-16.562
6	5.56	-88.842	-81.789	-172.355	-14.905
7	4.60	-116.315	-110.970	-191.858	-21.197
8	3.13	-100.424	-66.886	-193.587	-20.471
9	4.31	-70.220	-28.728	-158.919	-11.832
10	0.49	-44.325	-41.230	-133.917	-9.732
11	4.00	-76.847	-69.690	-143.446	-11.234
4IP	5.98	-48.012	-143.012	-194.068	-13.498

Table S3 Molecular docking results of compounds **1**–**11** and QC5 with TP53

Compound	Total score	D score	PMF score	G score	Chem score
1	5.52	-101.950	-11.731	-153.339	-23.724
2	6.43	-105.662	-8.428	-122.874	-23.156
3	3.81	-99.934	-13.185	-101.335	-21.349
4	4.72	-101.211	-17.566	-167.587	-24.269
5	5.25	-136.099	-5.170	-218.426	-24.885
6	7.11	-136.165	-11.946	-249.175	-29.480
7	5.93	-132.545	-7.269	-208.247	-10.726
8	5.06	-136.726	5.063	-247.932	-30.655
9	2.33	-105.225	4.440	-251.042	-26.938
10	0.39	-49.689	-11.987	-113.396	-12.119
11	3.46	-90.485	6.026	-175.535	-15.816
QC5	6.91	-123.036	-16.421	-219.765	-24.264

Table S4 Molecular docking results of compounds **1**–**11** and M60 with CASP3

Compound	Total score	D score	PMF score	G score	Chem score
1	4.73	-97.340	-64.962	-121.263	-28.088
2	5.10	-115.341	-65.170	-99.297	-29.065
3	5.18	-78.668	-43.816	-82.560	-23.661
4	4.14	-93.562	-47.440	-136.037	-20.857
5	5.64	-109.236	-64.160	-161.841	-26.550
6	7.19	-122.751	-68.932	-186.468	-28.675
7	4.69	-120.831	-86.228	-166.663	-22.026
8	8.10	-133.383	-74.075	-202.190	-35.315
9	5.07	-91.810	-32.259	-204.277	-21.164
10	3.15	-76.387	-46.466	-181.601	-16.730
11	3.27	-89.973	-71.169	-173.770	-18.993
M60	8.37	-210.733	-84.552	-347.428	-33.402

Table S5 Molecular docking results of compounds **1**–**11** and DTT with CASP8

Compound	Total score	D score	PMF score	G score	Chem score
1	3.02	-62.550	-17.116	-84.455	-17.290
2	3.66	-73.055	-43.156	-62.559	-23.484
3	3.23	-69.478	-12.597	-64.170	-20.553
4	3.69	-81.756	-51.274	-118.451	-24.155
5	3.22	-96.306	-20.710	-160.741	-20.182
6	1.81	-121.318	-4.152	-200.293	-23.317
7	2.97	-133.037	-34.791	-216.628	-15.708
8	5.09	-103.572	-5.038	-168.501	-20.258
9	6.69	-124.596	3.986	-283.839	-28.953
10	4.99	-104.824	-18.930	-230.702	-23.606
11	4.14	-96.230	-78.750	-159.189	-20.623
4PS1	1.93	-57.092	-17.272	-104.746	-12.684

Table S6 Molecular docking results of compounds **1**–**11** and S58 with PTGS2

Compound	Total score	D score	PMF score	G score	Chem score
1	7.14	-124.049	-30.759	-213.958	-28.747
2	6.51	-126.972	-38.119	-175.606	-28.378
3	5.56	-131.585	-48.040	-163.655	-31.372
4	7.16	-120.514	-36.894	-200.990	-30.187
5	6.36	-162.476	-55.395	-304.896	-37.268
6	2.03	-191.461	-49.804	-355.462	-38.769
7	4.88	-265.534	-53.945	-467.499	-47.648
8	-6.63	-172.680	-2.417	-339.060	-42.688
9	-15.52	-206.538	14.668	-478.891	-55.417
10	-58.38	-253.971	94.158	-516.284	-55.348
11	-3.98	-172.784	-25.414	-334.745	-35.151
S58	10.47	-155.733	-42.851	-269.959	-40.039

Table S7 Molecular docking results of compounds **1**–**11** and TLA with PTEN

Compound	Total score	D score	PMF score	G score	Chem score
1	3.56	-85.030	-71.733	-127.821	-28.999
2	3.47	-90.905	-72.368	-103.494	-25.076
3	3.95	-91.625	-80.074	-119.539	-25.309
4	5.54	-101.829	-69.835	-152.786	-28.044
5	3.65	-103.499	-75.713	-166.087	-20.349
6	5.41	-123.493	-74.103	-204.576	-27.050
7	2.36	-148.520	-130.413	-244.518	-25.417
8	3.50	-102.171	-50.931	-147.761	-21.114
9	1.06	-65.940	-51.789	-136.168	-16.248
10	-0.32	-92.498	-45.342	-210.185	-22.317
11	3.64	-78.863	-63.378	-154.860	-20.149
TLA	4.80	-62.005	-52.972	-97.174	-13.469

Table S8 Molecular docking results of compounds **1**–**11** and NFH with MMP9

Compound	Total score	D score	PMF score	G score	Chem score
1	5.24	-132.769	-58.981	-218.892	-27.756
2	5.89	-138.530	-60.298	-181.768	-32.436
3	4.00	-79.778	-39.810	-76.365	-21.265
4	3.45	-90.164	-28.243	-122.820	-21.466
5	7.60	-144.540	-67.692	-221.301	-34.147
6	6.72	-166.618	-2.179	-305.128	-33.576
7	7.08	-169.843	-2.628	-293.462	-32.381
8	6.64	-167.323	-32.083	-265.460	-29.958
9	6.41	-179.890	-24.672	-359.780	-37.178
10	1.70	-98.924	-4.715	-204.240	-21.361
11	2.45	-106.599	-64.339	-192.751	-18.190
NFH	5.36	-113.448	-36.600	-214.200	-20.966

Table S9 Molecular docking results of compounds **1**–**11** and J8S with TNF

Compound	Total score	D score	PMF score	G score	Chem score
1	5.24	-123.097	-33.232	-183.370	-27.605
2	5.05	-113.157	-11.229	-129.713	-23.101
3	5.49	-118.746	-42.496	-147.039	-26.232
4	7.20	-117.122	-10.024	-199.729	-29.306
5	1.14	-167.490	-31.996	-275.667	-34.854
6	6.81	-173.365	-33.675	-261.540	-36.718
7	-5.43	-252.960	31.840	-469.661	-33.634
8	9.43	-167.271	-31.928	-282.853	-33.831
9	2.91	-198.303	30.110	-426.330	-48.343
10	-12.19	-177.827	33.807	-394.443	-40.960
11	2.99	-79.249	10.196	-156.702	-11.261
J8S	13.20	-163.854	5.571	-301.363	-41.942

Table S10 Molecular docking results of compounds **1**–**11** and PGE with VEGFA

Compound	Total score	D score	PMF score	G score	Chem score
1	2.60	-59.519	21.998	-77.977	-13.814
2	1.98	-50.617	17.193	-12.642	-15.797
3	2.05	-62.790	-3.478	-76.492	-15.286
4	2.19	-42.975	-26.726	-62.856	-18.089
5	3.26	-75.420	-2.107	-129.928	-19.906
6	4.46	-71.212	-12.166	-105.488	-17.785
7	3.02	-92.991	-28.908	-184.017	-13.689
8	1.98	-59.119	-25.212	-102.984	-14.574
9	3.27	-66.963	9.358	-152.777	-14.814
10	2.77	-65.266	-12.664	-168.994	-17.196
11	1.89	-48.074	-18.777	-116.572	-14.682
PGE	2.87	-57.025	10.183	-81.044	-6.108

Table S11 Molecular docking results of compounds **1**–**11** and GOL with MYC

Compound	Total score	D score	PMF score	G score	Chem score
1	2.58	-68.986	-9.986	-100.145	-21.601
2	2.95	-82.134	-4.173	-42.953	-20.236
3	3.95	-77.736	-16.227	-45.616	-23.217
4	3.58	-60.370	-10.275	-86.202	-18.773
5	4.52	-92.220	11.325	-151.966	-17.548
6	3.44	-96.183	-6.918	-170.588	-22.777
7	6.48	-138.721	-3.509	-207.983	-27.701
8	5.31	-109.491	-11.505	-173.752	-20.534
9	3.06	-72.921	5.995	-184.435	-15.966
10	0.64	-103.716	44.593	-248.958	-25.270
11	2.71	-95.111	21.306	-200.680	-16.541
GOL	3.52	-38.295	-1.433	-65.774	-11.792

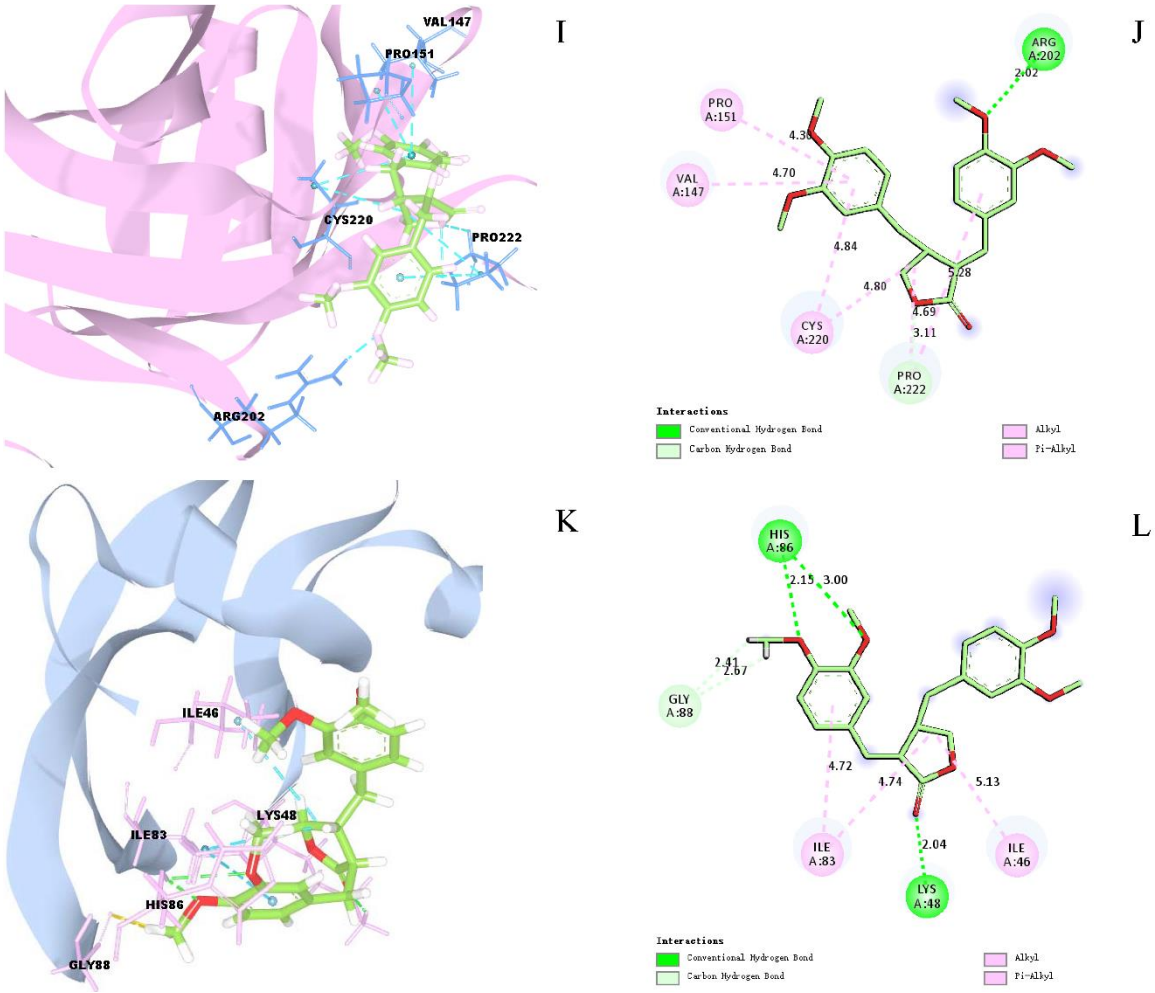

Fig S1 **I**. Docking and binding pattern of compound **6** (green) into TP53 active site **J**. 2D interaction diagram of compound **6** (green) with amino acid residues of TP53 **K**. Docking and binding pattern of compound **6** (green) into VEGFA active site **L**. 2D interaction diagram of compound **6** (green) with amino acid residues of VEGFA.

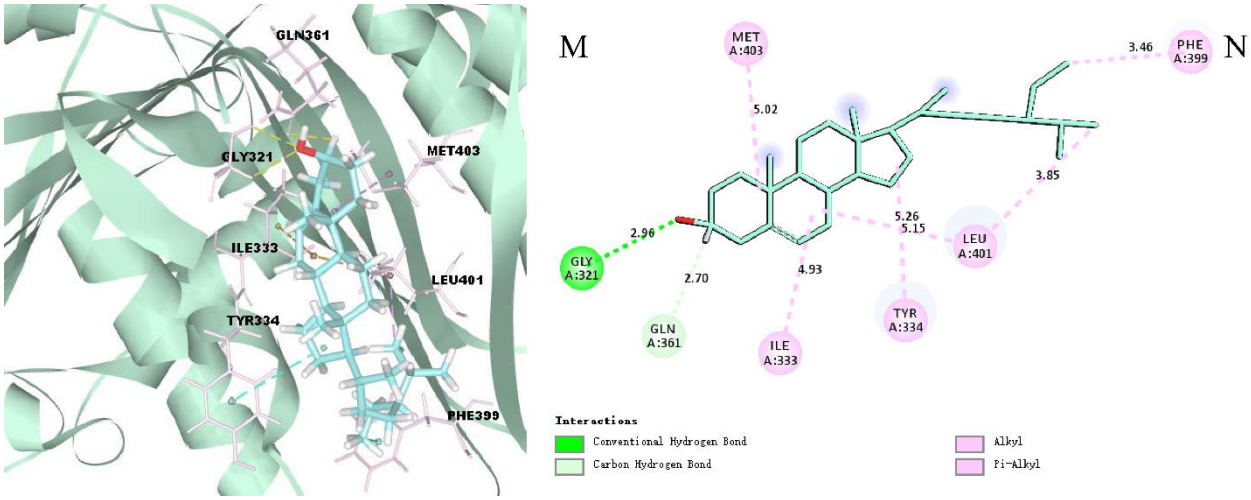

Fig S2 **M**. Docking and binding pattern of compound **9** (blue) into CASP8 active site **N**. 2D interaction diagram of compound **9** (blue) with amino acid residues of CASP8.

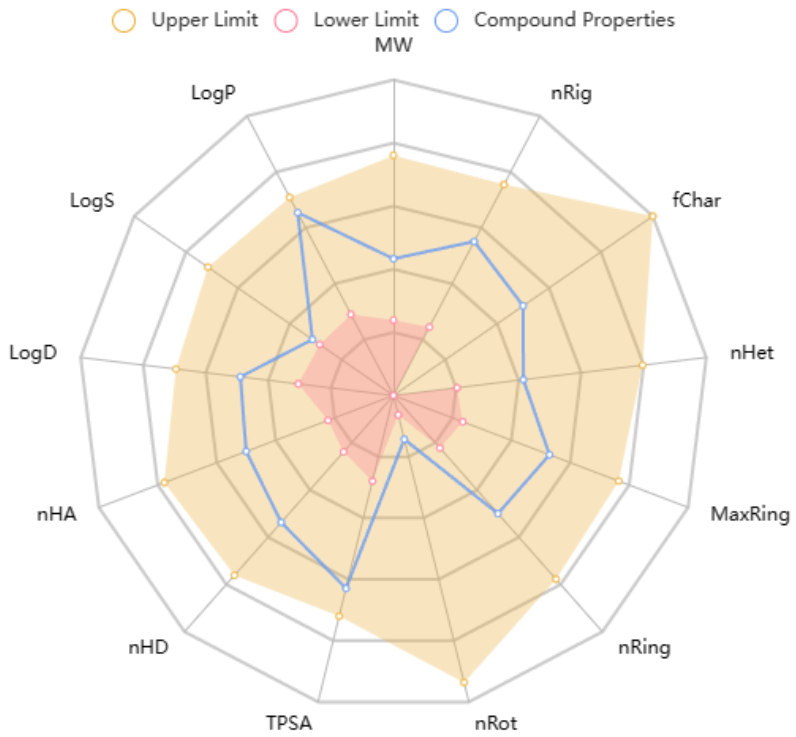

Fig S3 Physicochemical property of compound **1**.

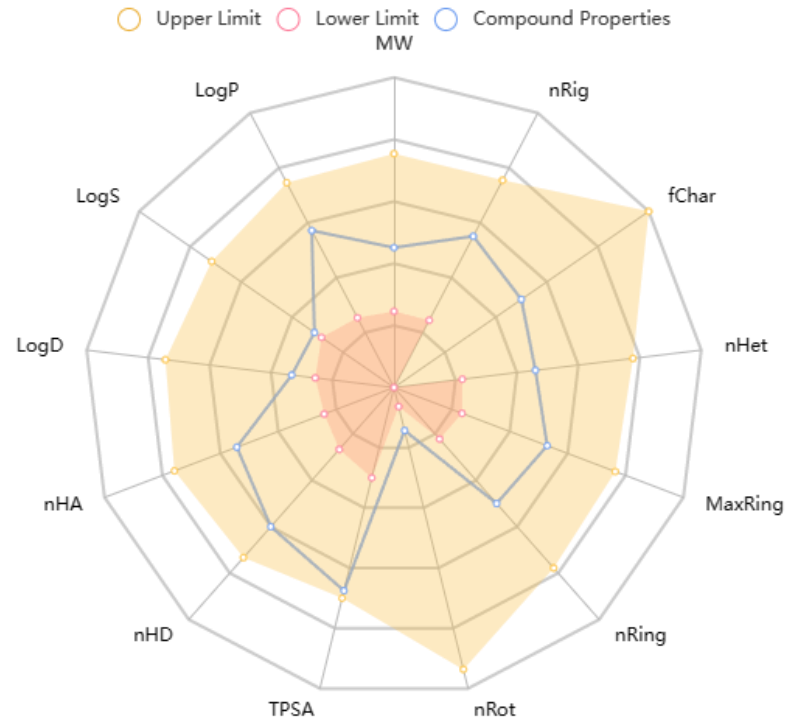

Fig S4 Physicochemical property of compound **2**.

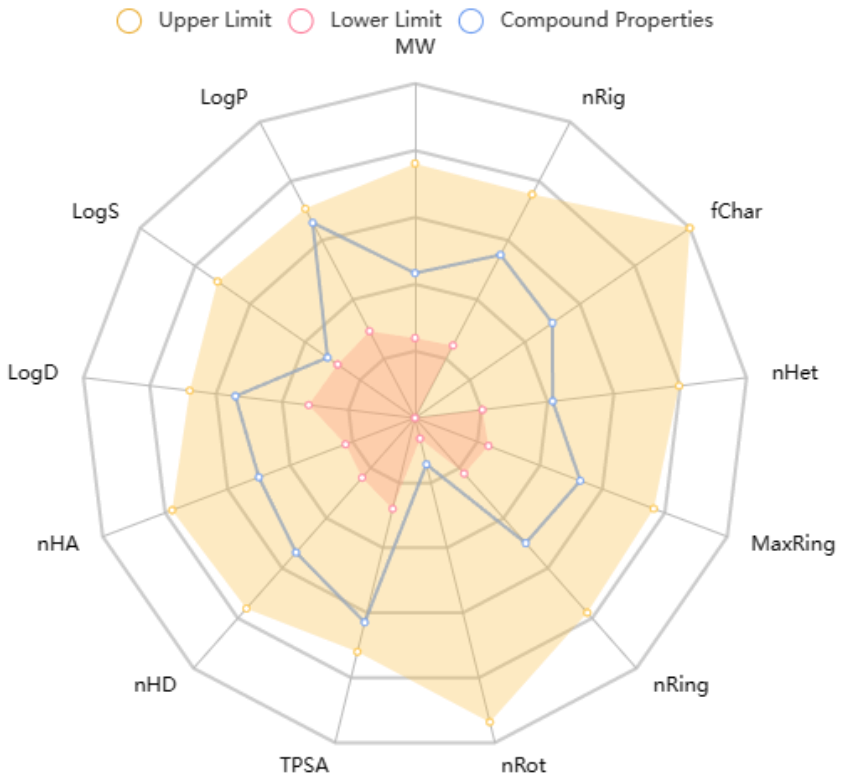

Fig S5 Physicochemical property of compound **3**.

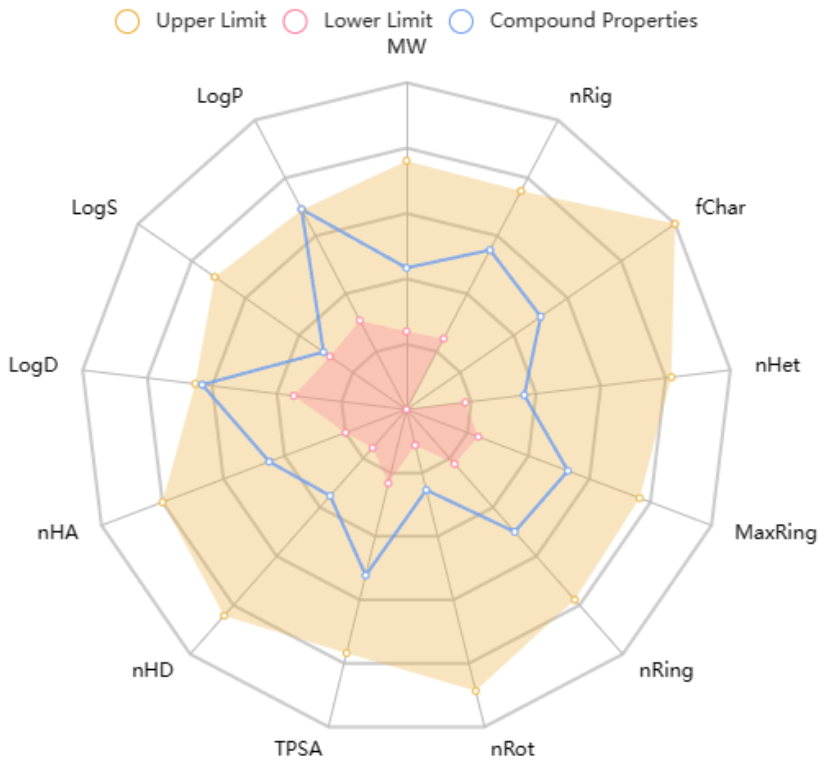

Fig S6 Physicochemical property of compound **4**.

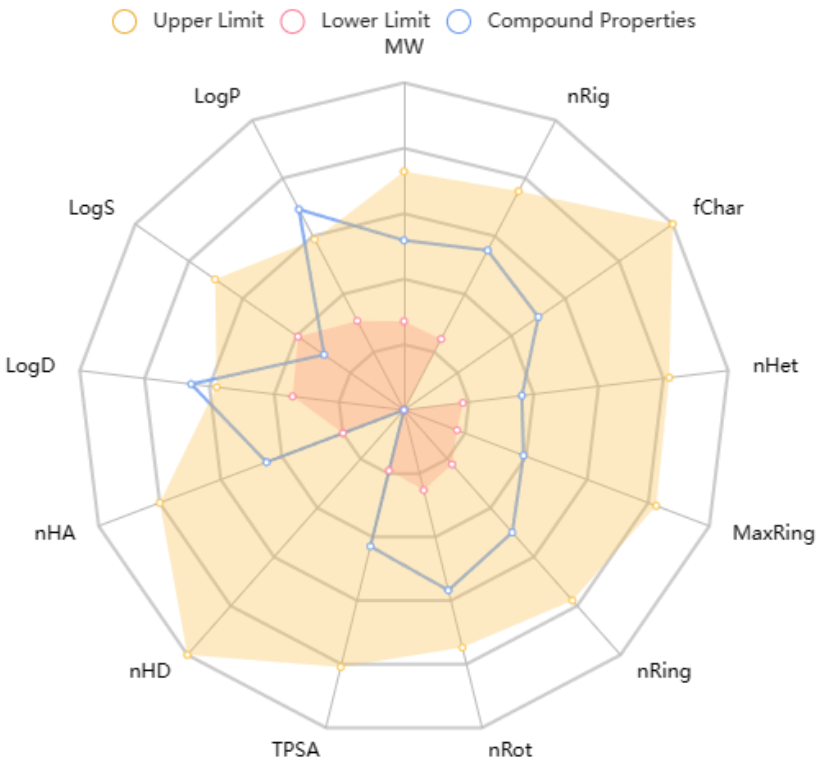

Fig S7 Physicochemical property of compound **6**.

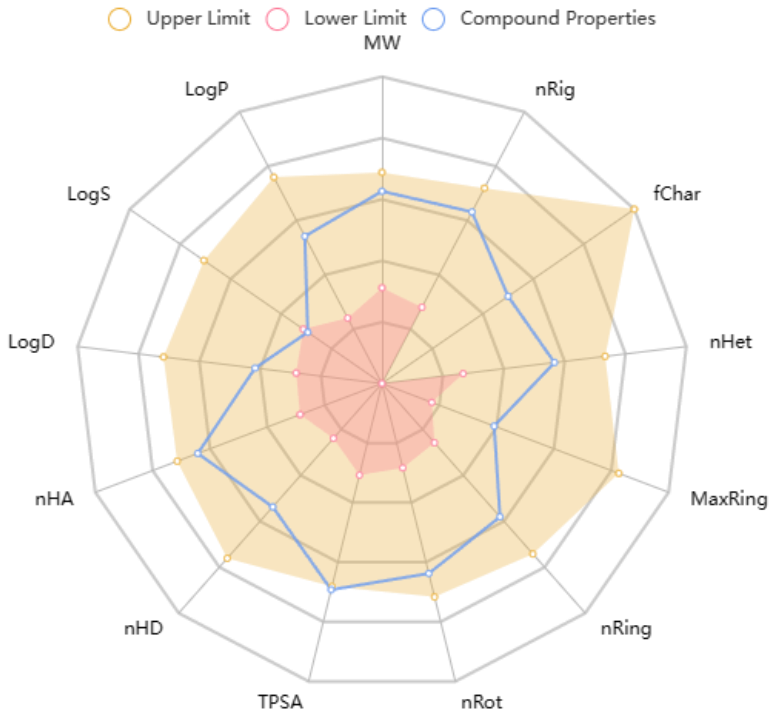

Fig S8 Physicochemical property of compound **7**.

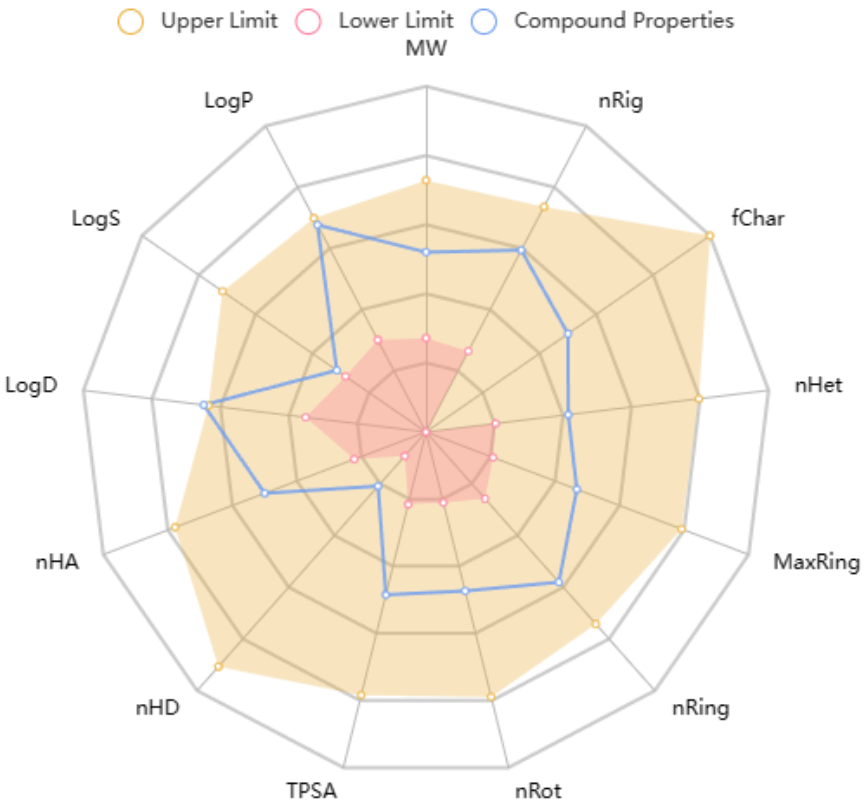

Fig S9 Physicochemical property of compound **8**.

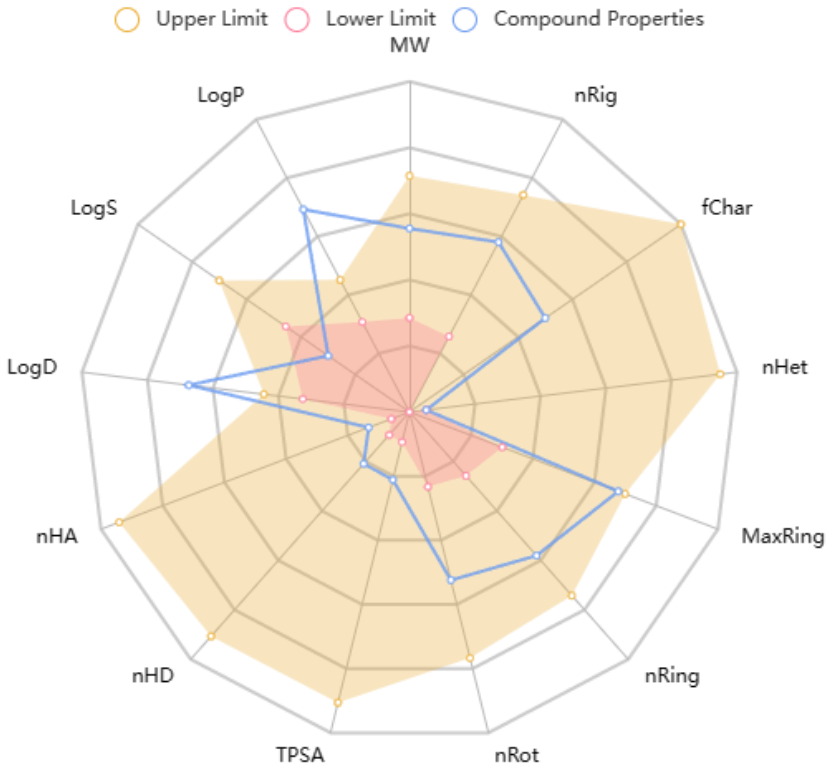

Fig S10 Physicochemical property of compound **9**.

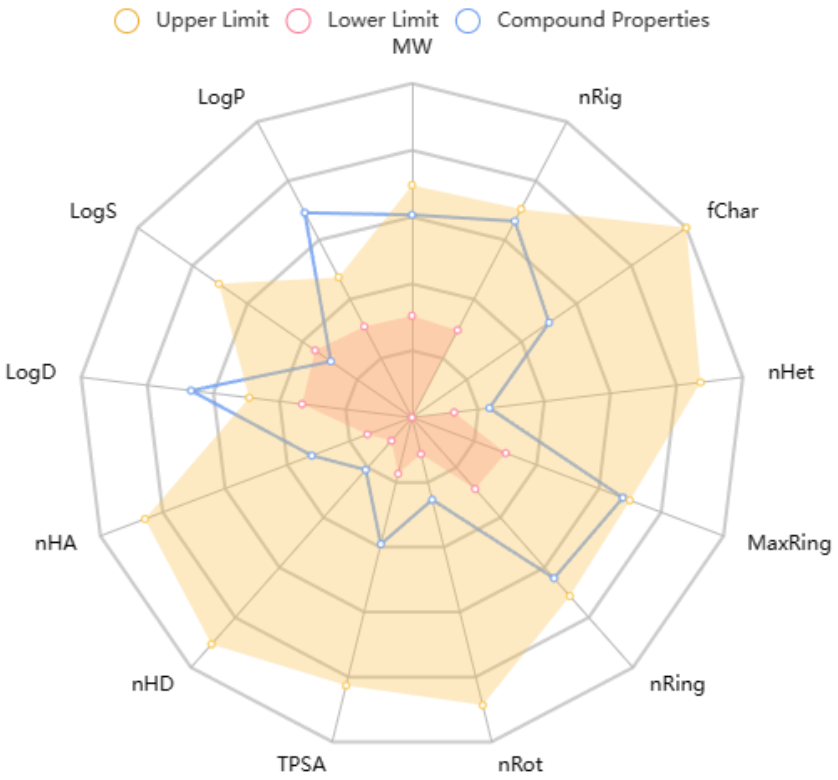

Fig S11 Physicochemical property of compound **10**.

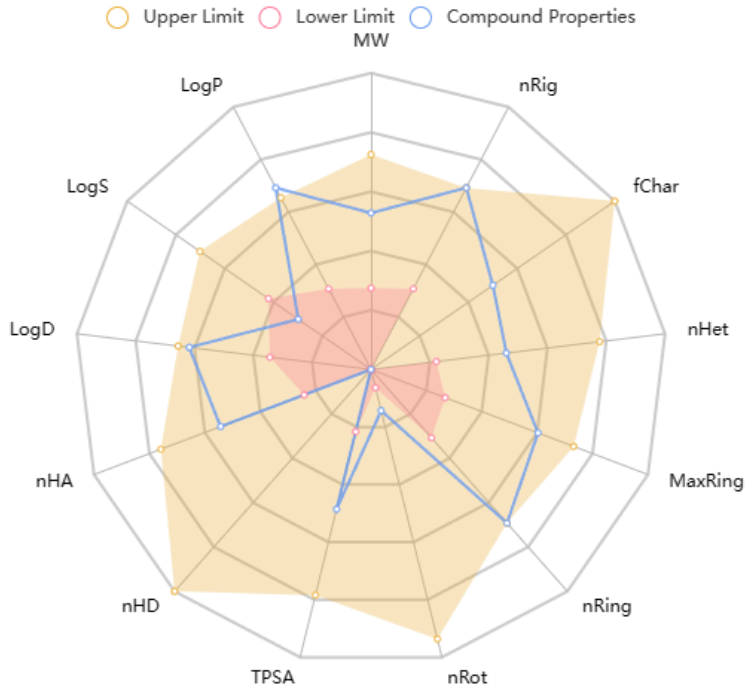

Fig S12 Physicochemical property of compound **11**.

Explanation of ADMET parameters

1. Physicochemical property

1.1 Molecular Weight

Contain hydrogen atoms. Optimal:100~600, based on Drug-Like Soft rule.

1.2 Volume

Van der Waals volume.

1.3 Density

Density = MW / Volume

1.4 nHA

Number of hydrogen bond acceptors. Sum of all O and N. Optimal: 0~12, based on Drug-Like Soft rule.

1.5 nHD

Number of hydrogen bond donors. Sum of all OHs and NHs. Optimal:0~7, based on Drug-Like Soft rule.

1.6 nRot

Number of rotatable bonds. In some situation Amide C-N bonds are not considered because of their high rotational energy barrier. Optimal:0~11, based on Drug-Like Soft rule.

1.7 nRing

Number of rings. Smallest set of smallest rings. Optimal:0~6, based on Drug-Like Soft rule.

1.8 MaxRing

Number of atoms in the biggest ring. Number of atoms involved in the biggest system ring. Optimal:0~18, based on Drug-Like Soft rule.

1.9 nHet

Number of heteroatoms. Number of non-carbon atoms (hydrogens included). Optimal:1~15, based on Drug-Like Soft rule.

1.10 fChar

Formal charge. Optimal:-4 ~4, based on Drug-Like Soft rule

1.11 nRig

Number of rigid bonds. Number of non-flexible bonds, in opposite to rotatable bonds. Optimal:0~30, based on Drug-Like Soft rule.

1.12 Flexibility

Flexibility = nRot / nRig

1.13 Stereo Centers

Number of stereocenters. Optimal: ≤ 2, based on Lead-Like Soft rule.

1.14 TPSA

Topological polar surface area. Sum of tabulated surface contributions of polar fragments. Optimal:0~140, based on Veber rule.

1.15 logS

The predicted solubility of a compound is given as the logarithm of the molar concentration (log mol/L). Compounds in the range from -4 to 0.5 log mol/L will be considered proper.

1.16 logP

The predicted logP of a compound is given as the logarithm of the molar concentration (log mol/L). Compounds in the range from 0 to 3 log mol/L will be considered proper.

1.17 logD7.4

The predicted logD7.4 of a compound is given as the logarithm of the molar concentration (log mol/L). Compounds in the range from 1 to 3 log mol/L will be considered proper.

2. Absorption

2.1 Caco-2 Permeability

The predicted Caco-2 permeability of a given compound is given as the log cm/s. A compound is considered to have a proper Cao-2 permeability if it has predicted value > -5.15log cm/s.

2.2 MDCK Permeability

The unit of predicted MDCK permeability is cm/s. A compound is considered to have a high passive MDCK permeability for a $P_{app} > 20\times10^{-6}$ cm/s, medium permeability for $2\text{-}20\times10^{-6}$ cm/s, low permeability for $< 2\times10^{-6}$ cm/s.

2.3 $F_{20\%}$

Molecules with a bioavailability ≥ 20% were classified as $F_{20\%}$- (Category 0), while molecules with a bioavailability < 20% were classified as $F_{20\%}$+ (Category 1). The output value is the probability

of being $F_{20\%}$+, within the range of 0 to 1. Empirical decision: 0-0.3: excellent; 0.3-0.7: medium; 0.7-1.0: poor.

3. Distribution

3.1 PPB

A compound is considered to have a proper PPB if it has predicted value < 90%, and drugs with high protein-bound may have a low therapeutic index. Empirical decision: ≤ 90%: excellent; otherwise: poor.

3.2 BBB Penetration

The unit of BBB penetration is cm/s. Molecules with logBB > -1 were classified as BBB+ (Category 1), while molecules with logBB ≤ -1 were classified as BBB- (Category 0). The output value is the probability of being BBB+, within the range of 0 to 1. Empirical decision: 0-0.3: excellent; 0.3-0.7: medium; 0.7-1.0: poor.

4. Metabolism

4.1 CYP1A2 / 2C19 / 2C9 / 2D6 / 3A4 inhibitor, CYP1A2 / 2C19 /2C9 / 2D6 / 3A4 substrate

Based on the chemical nature of biotransformation, the process of drug metabolism reactions can be divided into two broad categories: phase I (oxidative reactions) and phase II (conjugative reactions). The human cytochrome P450 family (phase I enzymes) contains 57 isozymes and these isozymes metabolize approximately two-thirds of known drugs in human with 80% of this attribute to five isozymes—1A2, 3A4, 2C9, 2C19 and 2D6. Most of these CYPs responsible for phase I reactions are concentrated in the liver.

Category 0: Non-substrate / Non-inhibitor; Category 1: substrate / inhibitor. The output value is the probability of being substrate / inhibitor, within the range of 0 to 1.

5. Excretion

5.1 CL

The unit of predicted CL penetration is ml/min/kg. >15 ml/min/kg: high clearance; 5-15 ml/min/kg: moderate clearance; <5 ml/min/kg: low clearance. Empirical decision: ≥ 5: excellent; < 5: poor.

5.2 $T_{1/2}$

Molecules with $T_{1/2} > 3$ were classified as $T_{1/2}$ - (Category 0), while molecules with $T_{1/2} \leq 3$ were classified as $T_{1/2}$ + (Category 1). The output value is the probability of being $T_{1/2}$+, within the range of 0 to 1. Empirical decision: 0-0.3: excellent; 0.3-0.7: medium; 0.7-1.0: poor.

6. Toxicology

6.1 H-HT

The human hepatotoxicity. Category 0: H-HT negative (-); Category 1: H-HT positive (+). The output value is the probability of being toxic, within the range of 0 to 1. Empirical decision: 0-0.3: excellent; 0.3-0.7: medium; 0.7-1.0: poor.

6.2 DILI

The drug-induced liver injury. Category 0: DILI negative (-); Category 1: DILI positive (+). The output value is the probability of being toxic, within the range of 0 to 1. Empirical decision: 0-0.3: excellent; 0.3-0.7: medium; 0.7-1.0: poor.

6.3 AMES Toxicity

The Ames test for mutagenicity. Category 0: AMES negative (-); Category 1: AMES positive (+). The output value is the probability of being toxic, within the range of 0 to 1. Empirical decision: 0-0.3: excellent; 0.3-0.7: medium; 0.7-1.0: poor.

6.4 Rat Oral Acute Toxicity

Determination of acute toxicity in mammals (rat). Category 0: low-toxicity, > 500 mg/kg; Category 1: high-toxicity; < 500 mg/kg. The output value is the probability of being toxic, within the range of 0 to 1. Empirical decision: 0-0.3: excellent; 0.3-0.7: medium; 0.7-1.0: poor.