List of Supporting Information

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

Protein name	PDB ID	Resolution	ligand
AKT1	1H10	1.40 Å	4IP
HMOX1	1N3U	2.58 Å	HEM
IL1B	6Y8I	1.46 Å	OGE
TP53	3ZME	1.35 Å	QC5
PPARG	4F9M	1.90 Å	FCM
CASP3	2CNO	1.95 Å	M60
PTGS2	1CX2	2.50 Å	S58
MMP9	1GKC	2.50 Å	NFH
IL6	4CNI	2.20 Å	TAM
TNF	6M95	2.10 Å	J8S
VEGFA	4KZN	1.71 Å	PGE

Table S2 Molecular docking results of compounds **1**–**8** and 4IP with AKT1

Compound	Total score	D score	PMF score	G score	Chem score
1	3.44	-74.053	-71.159	-112.147	-13.443
2	3.64	-70.650	-63.846	-70.530	-13.779
3	3.98	-65.762	-58.895	-91.343	-16.205
4	4.66	-85.889	-86.186	-106.026	-12.966
5	3.51	-13.189	-56.705	-60.669	-9.099
6	3.28	-78.261	-39.557	-194.694	-16.571
7	4.32	-61.079	-32.208	-179.342	-10.646
8	4.62	-87.836	-36.382	-260.459	-17.918
4IP	5.98	-48.012	-143.012	-194.068	-13.498

Table S3 Molecular docking results of compounds **1**–**8** and HEM with HMOX1

Compound	Total score	D score	PMF score	G score	Chem score
1	4.03	-68.122	-39.851	-105.929	-22.720
2	4.06	-60.460	-85.007	-66.168	-24.324
3	3.75	-84.772	-64.966	-68.313	-23.863
4	4.03	-95.782	-5.389	-82.090	-16.303
5	4.48	-83.601	-85.627	-109.933	-28.416
6	5.40	-137.510	-36.002	-278.728	-32.859
7	5.86	-128.771	-33.895	-289.629	-29.490
8	7.49	-145.967	-34.850	-270.829	-31.043
HEM	8.27	-86.281	-98.644	-277.994	-32.101

Table S4 Molecular docking results of compounds **1**–**8** and OGE with IL1B

Compound	Total score	D score	PMF score	G score	Chem score
1	2.44	-37.858	-4.850	-38.409	-17.731
2	2.53	-73.397	-10.047	-42.211	-16.718
3	2.50	-82.995	4.465	-94.224	-17.021
4	2.33	-61.975	12.163	-14.360	-12.317
5	2.81	-49.081	-0.611	-63.809	-16.957
6	4.59	-88.232	-2.073	-187.598	-19.785
7	3.76	-81.894	22.197	-189.869	-18.316
8	2.85	-81.706	25.221	-211.133	-18.405
OGE	2.00	-47.576	-0.576	-99.549	-14.355

Table S5 Molecular docking results of compounds **1**–**8** and QC5 with TP53

Compound	Total score	D score	PMF score	G score	Chem score
1	5.65	-95.392	-10.846	-144.441	-24.458
2	4.96	-110.224	-10.457	-126.099	-23.774
3	4.73	-104.131	-22.832	-111.218	-23.918
4	4.53	-88.282	15.579	-88.097	-27.063
5	7.12	-18.759	-11.411	-161.403	-29.133
6	4.20	-99.367	-3.999	-232.905	-27.059
7	3.77	-107.117	-2.787	-249.463	-29.379
8	2.84	-137.566	30.816	-327.175	-34.674
QC5	6.67	-124.784	-14.885	-226.399	-25.582

Table S6 Molecular docking results of compounds **1**–**8** and FCM with PPARG

Compound	Total score	D score	PMF score	G score	Chem score
1	6.00	-87.502	-38.172	-168.580	-17.283
2	5.41	-95.390	-33.089	-146.513	-13.040
3	4.96	-81.465	-27.739	-117.609	-15.130
4	5.78	-97.250	-26.639	-91.229	-12.635
5	5.36	-102.315	-31.963	-181.459	-10.470
6	6.08	-142.011	-21.708	-296.967	-29.151
7	6.40	-136.066	-0.108	-297.624	-29.631
8	2.97	-130.456	-11.265	-297.539	-27.475
FCM	3.01	-65.667	-11.102	-120.571	-5.491

Table S7 Molecular docking results of compounds **1**–**8** and M60 with CASP3

Compound	Total score	D score	PMF score	G score	Chem score
1	5.18	-104.625	-54.078	-162.852	-27.096
2	4.05	-94.283	-51.990	-76.712	-22.200
3	4.93	-84.487	-51.125	-73.216	-23.400
4	4.17	-79.798	-57.424	-49.724	-22.652
5	3.44	-83.626	-41.796	-96.562	-22.305
6	4.62	-108.880	-25.860	-240.709	-22.901
7	5.51	-109.110	-34.816	-227.409	-26.529
8	6.44	-114.898	-38.129	-244.968	-26.743
M60	8.59	-146.063	-60.820	-220.227	-23.630

Table S8 Molecular docking results of compounds **1**–**8** and S58 with PTGS2

Compound	Total score	D score	PMF score	G score	Chem score
1	7.82	-125.209	-58.629	-160.359	-39.568
2	7.39	-129.593	-29.479	-184.334	-27.885
3	5.81	-115.115	-54.928	-124.993	-32.835
4	7.16	-132.958	-38.810	-169.767	-30.726
5	8.22	-124.114	-24.931	-211.148	-30.091
6	-15.62	-219.671	10.172	-472.648	-53.117
7	-16.71	-220.209	22.418	-504.628	-57.175
8	-17.77	-223.336	27.920	-509.312	-54.334
S58	10.75	-153.753	-45.251	-272.545	-39.578

Table S9 Molecular docking results of compounds **1**–**8** and NFH with MMP9

Compound	Total score	D score	PMF score	G score	Chem score
1	5.71	-127.202	-46.410	-185.087	-29.568
2	6.00	-133.343	-58.431	-69.460	-31.362
3	4.92	-88.556	-22.494	-103.205	-26.737
4	5.23	-91.010	-36.383	-97.464	-30.403
5	6.64	-146.615	-79.150	-202.252	-28.303
6	7.29	-156.627	-34.718	-312.573	-34.838
7	6.72	-160.340	-36.958	-328.195	-36.106
8	8.35	-155.041	19.425	-338.679	-35.076
NFH	6.88	-124.640	-39.648	-242.251	-28.888

Table S10 Molecular docking results of compounds **1**–**8** and TAM with IL6

Compound	Total score	D score	PMF score	G score	Chem score
1	3.96	-83.381	-71.012	-135.144	-23.229
2	3.31	-185.122	-75.774	-52.178	-20.020
3	3.42	-79.299	-70.680	-29.576	-24.519
4	3.77	-85.207	-47.734	-109.807	-28.898
5	3.59	-78.878	-60.724	-96.696	-27.763
6	4.85	-98.020	-51.367	-204.518	-26.413
7	4.94	-108.777	-40.211	-241.678	-27.594
8	4.79	-101.125	-39.533	-203.667	-25.808
TAM	4.78	-58.236	-13.254	-71.158	-13.693

Table S11 Molecular docking results of compounds **1**–**8** and J8S with TNF

Compound	Total score	D score	PMF score	G score	Chem score
1	6.62	-113.372	-47.326	-186.038	-27.315
2	7.47	-124.730	-37.670	-140.382	-28.165
3	5.76	-125.129	-36.957	-134.548	-24.091
4	5.12	-114.498	-24.947	-107.169	-23.315
5	5.82	-123.609	-34.001	-175.624	-27.016
6	0.14	-187.952	14.163	-423.263	-46.017
7	2.73	-190.575	26.669	-434.088	-44.872
8	0.53	-187.790	18.590	-457.151	-47.409
J8S	12.16	-165.413	6.652	-310.906	-41.635

Table S12 Molecular docking results of compounds **1**–**8** and PGE with VEGFA

Compound	Total score	D score	PMF score	G score	Chem score
1	2.22	-58.808	24.333	-56.055	-13.675
2	2.07	-57.233	21.622	-5.160	-15.178
3	1.56	-51.860	-17.601	7.712	-17.387
4	1.96	-71.346	-22.110	-41.604	-17.094
5	2.62	-56.975	17.058	-37.584	-17.856
6	2.40	-68.018	2.006	-170.650	-16.690
7	2.57	-68.226	18.405	-174.744	-16.246
8	2.88	-74.133	2.522	-181.525	-17.857
PGE	3.19	-59.453	8.716	-67.605	-7.587

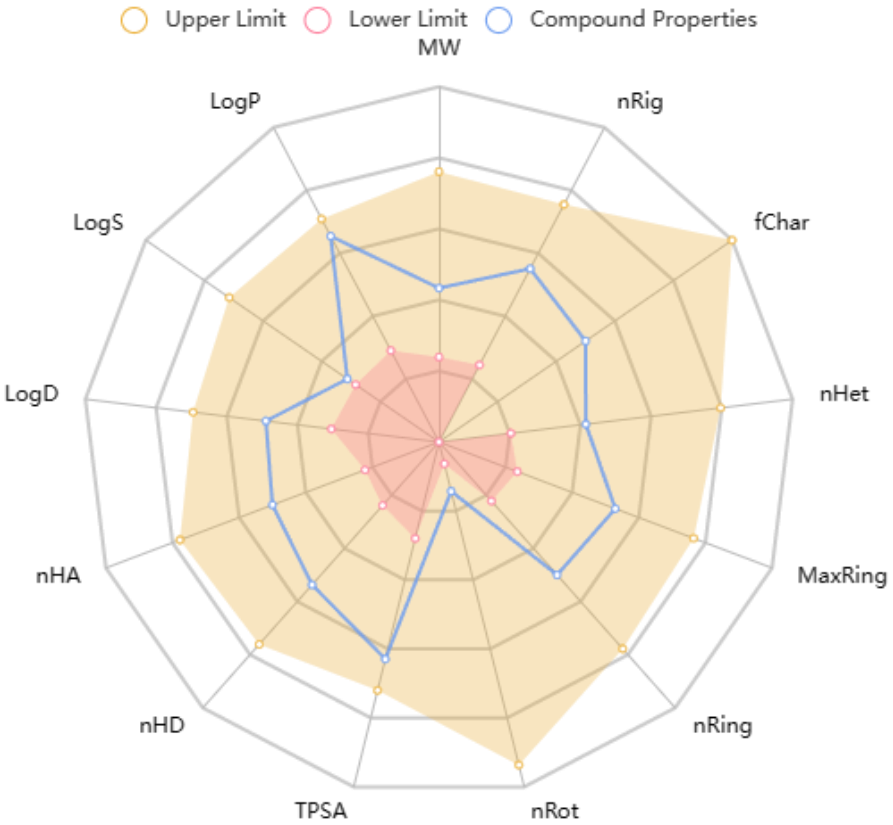

Figure S1 Physicochemical property of compound **1**.

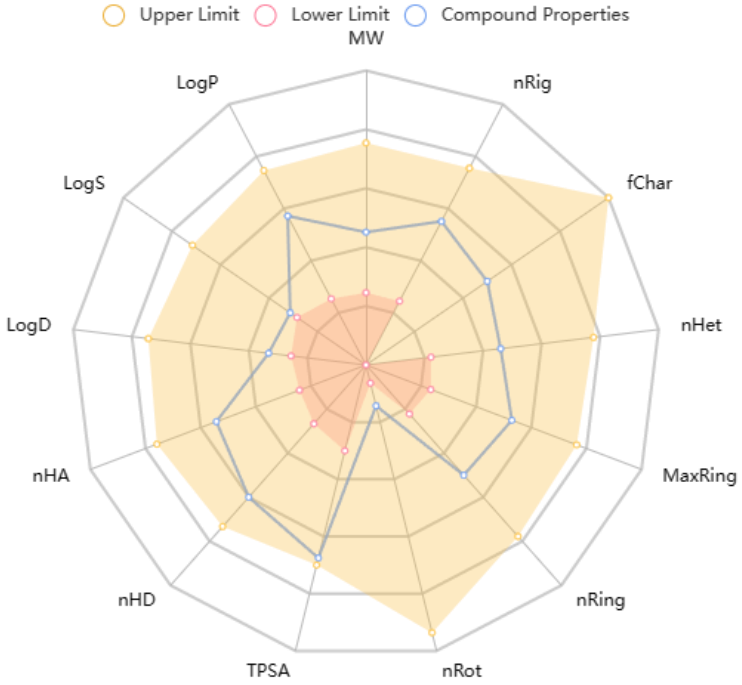

Figure S2 Physicochemical property of compound **2**.

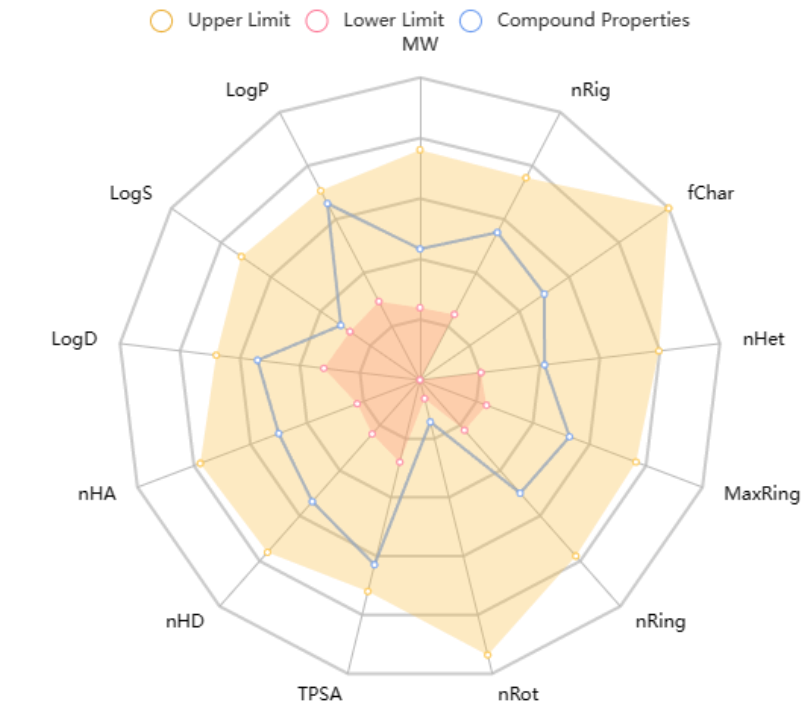

Figure S3 Physicochemical property of compound **3**.

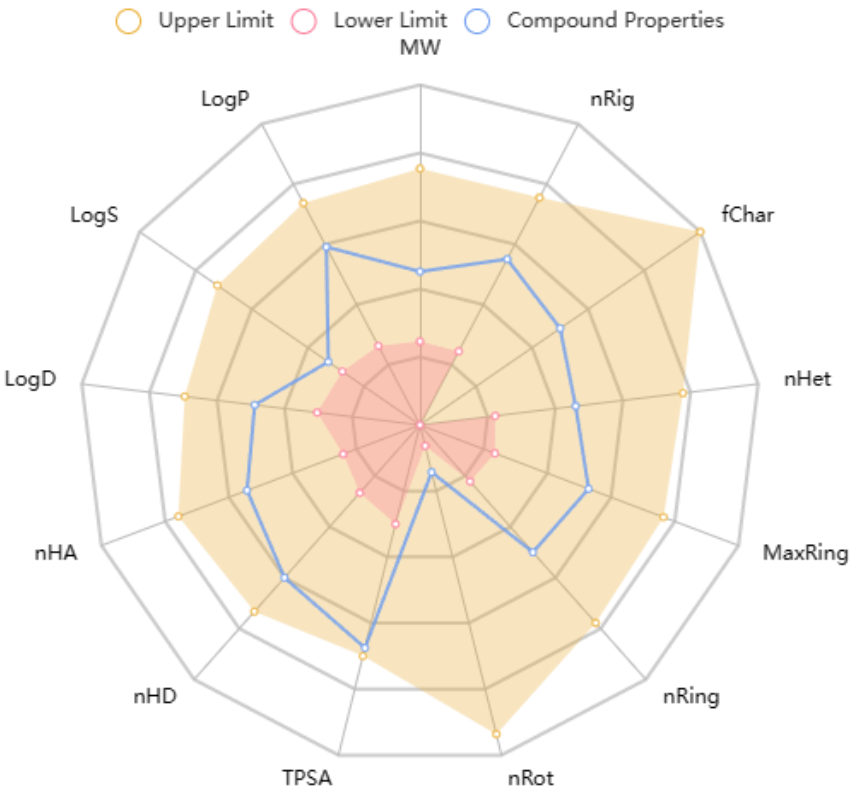

Figure S4 Physicochemical property of compound **4**.

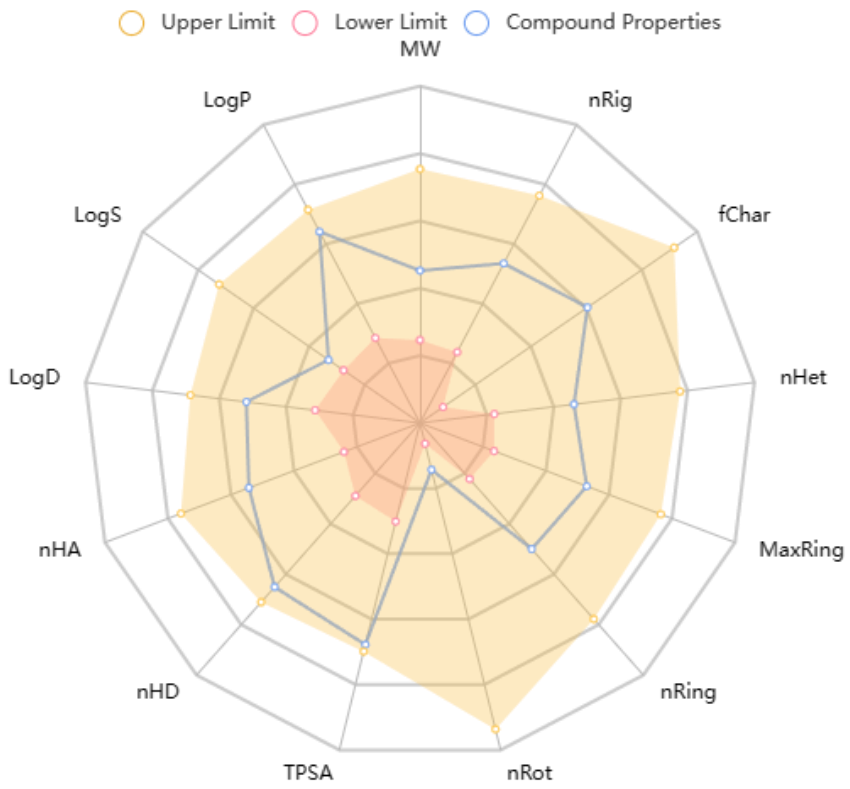

Figure S5 Physicochemical property of compound **5**.

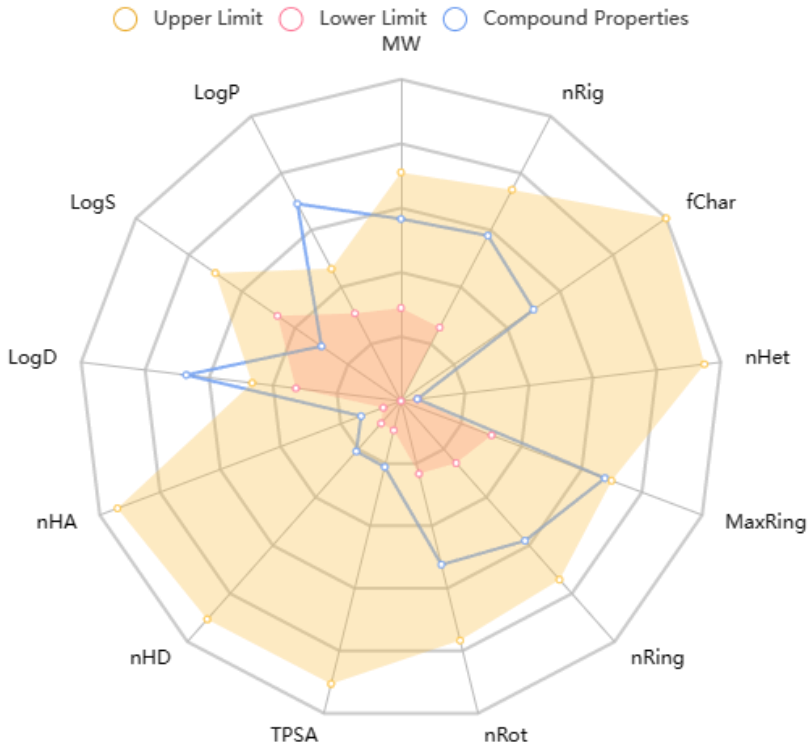

Figure S6 Physicochemical property of compound **6**.

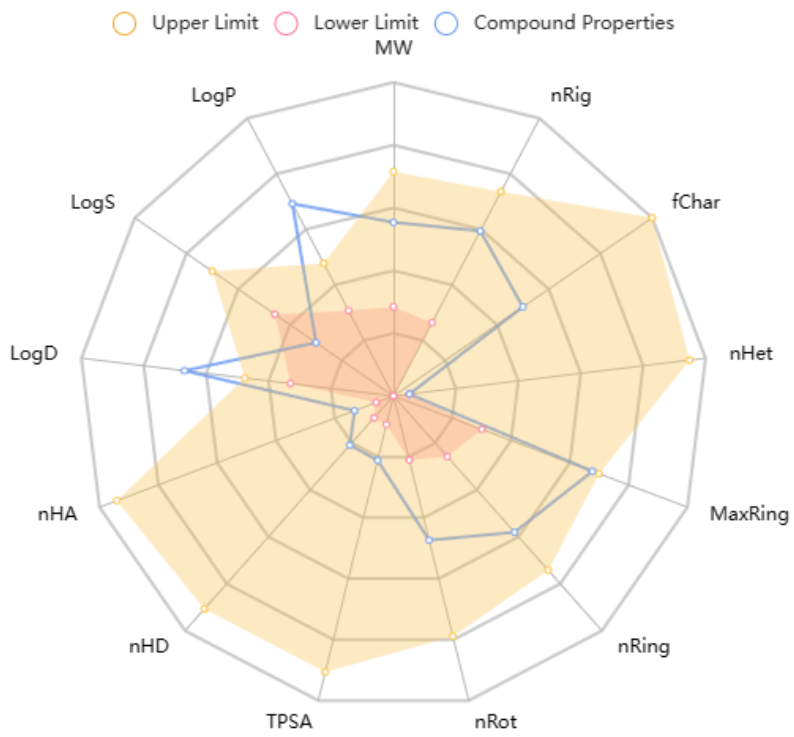

Figure S7 Physicochemical property of compound **7**.

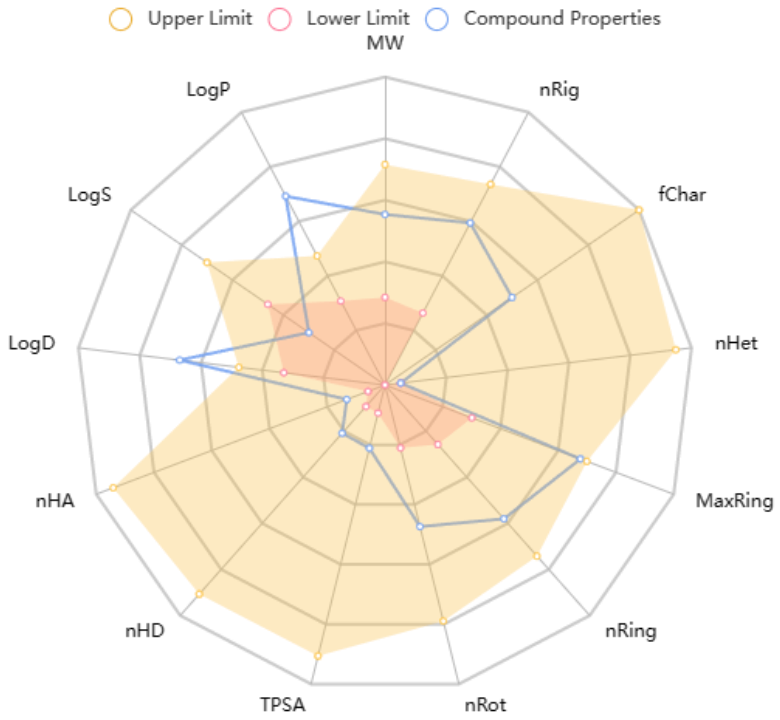

Figure S8 Physicochemical property of compound **8**.

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.