SUPPLEMENTARY MATERIAL FOR

Potential Cancer and Alzheimer's Disease Targeting Phosphodiesterase Inhibitors from *Uvaria alba*: Insights from *In Vitro* and Consensus Virtual Screening

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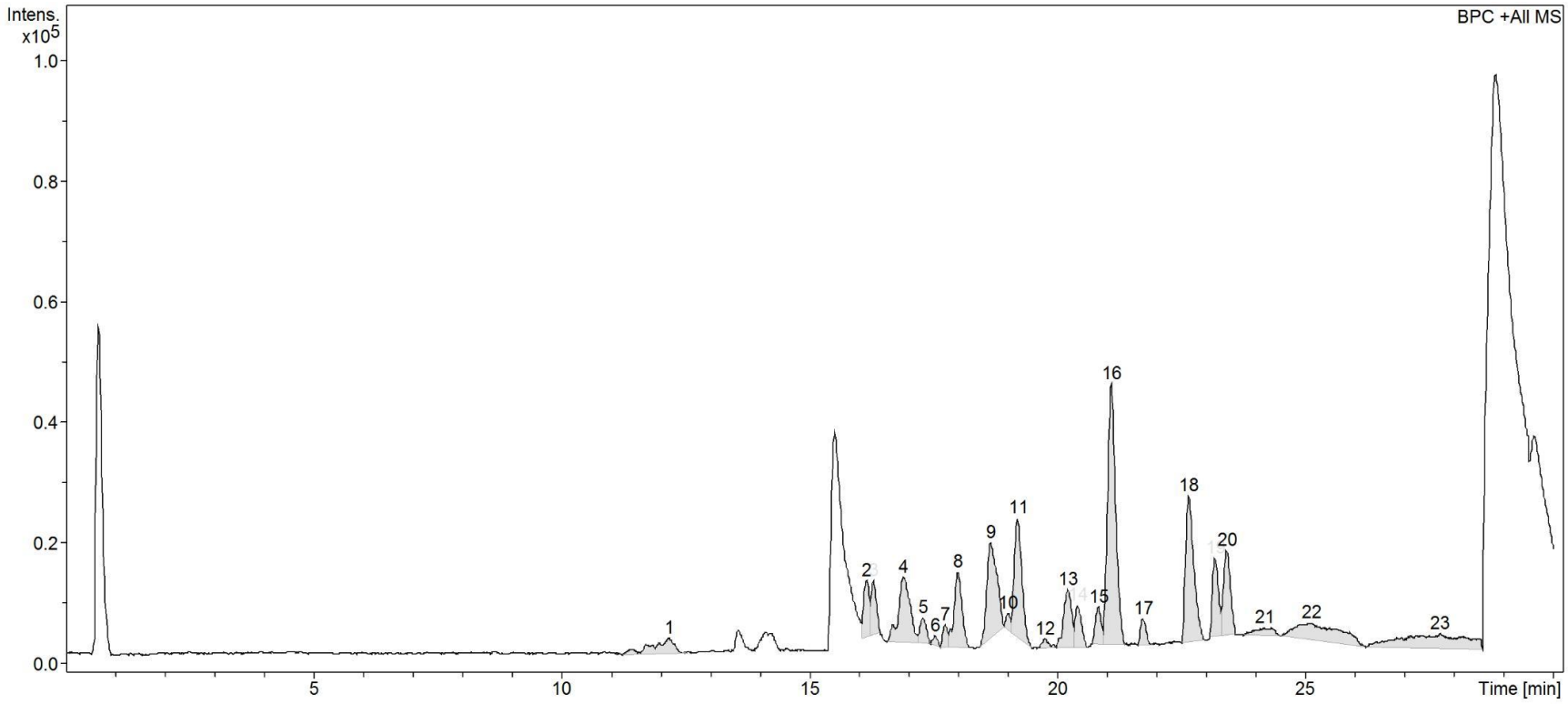


Figure S1. LC chemical profile of *Uvaria alba* DCM sub-extract (positive-ion mode MS detection).

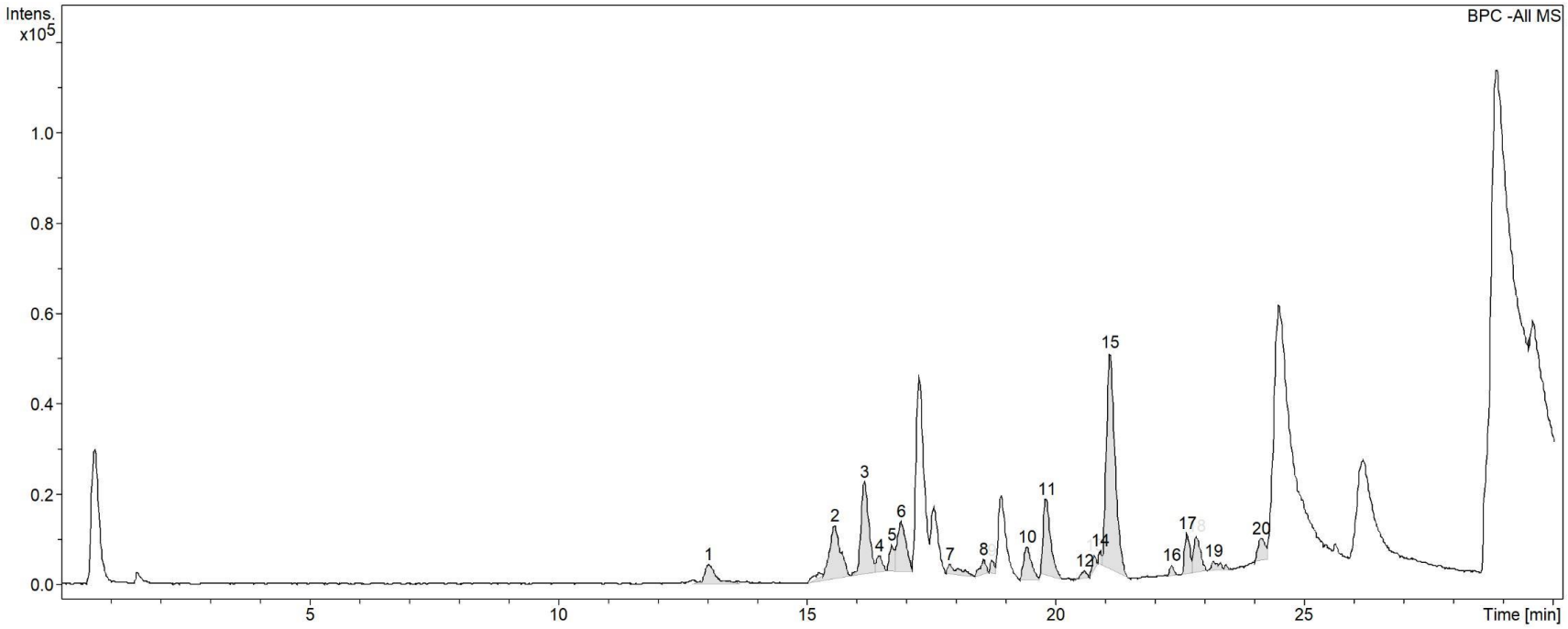


Figure S2. LC chemical profile of *Uvaria alba* DCM sub-extract (negative-ion mode MS detection).

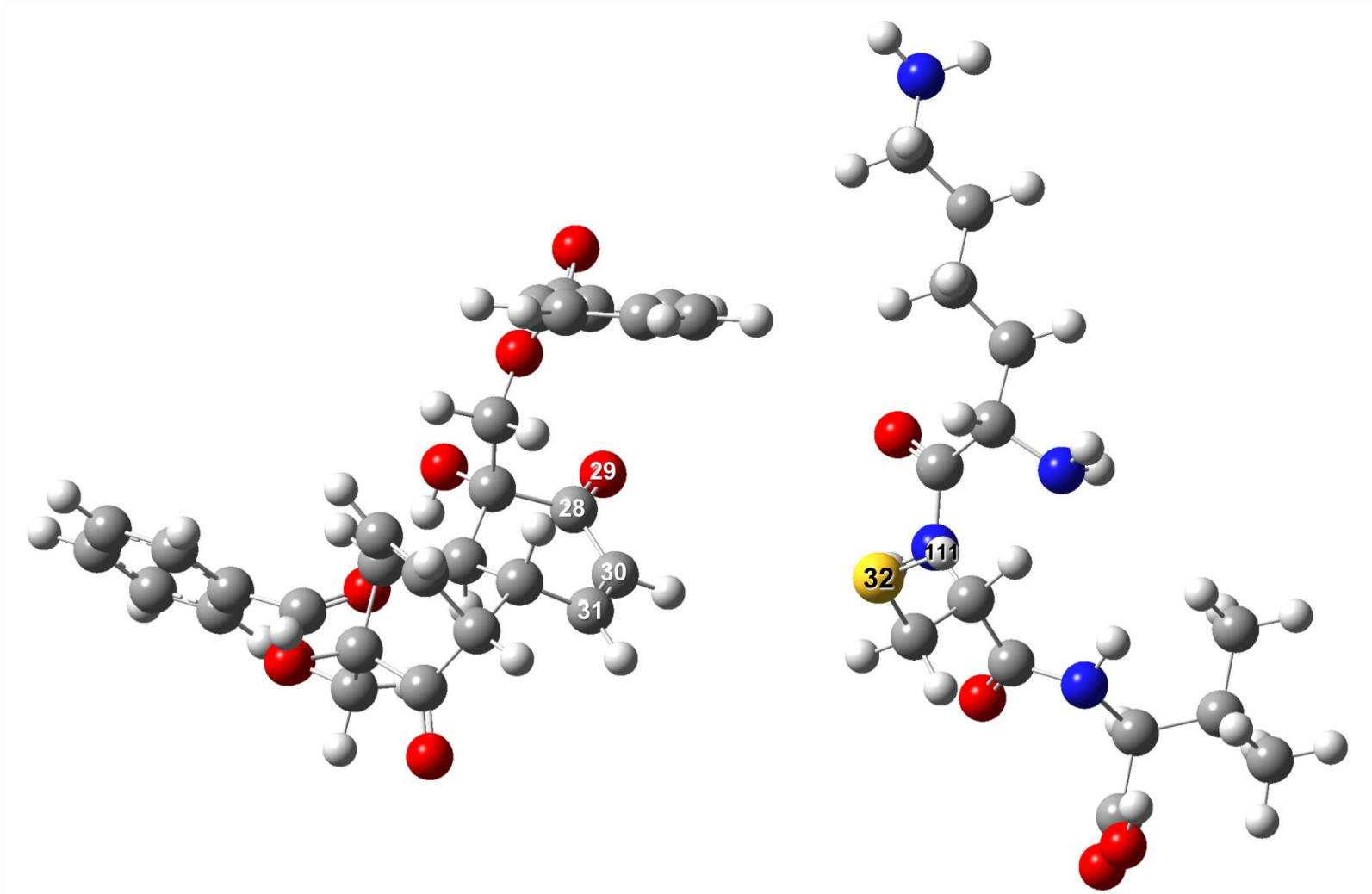


Figure S3. Optimized geometries of the reactants (grandifloracin (**15**) and Cys151 tripeptide (**19**)).

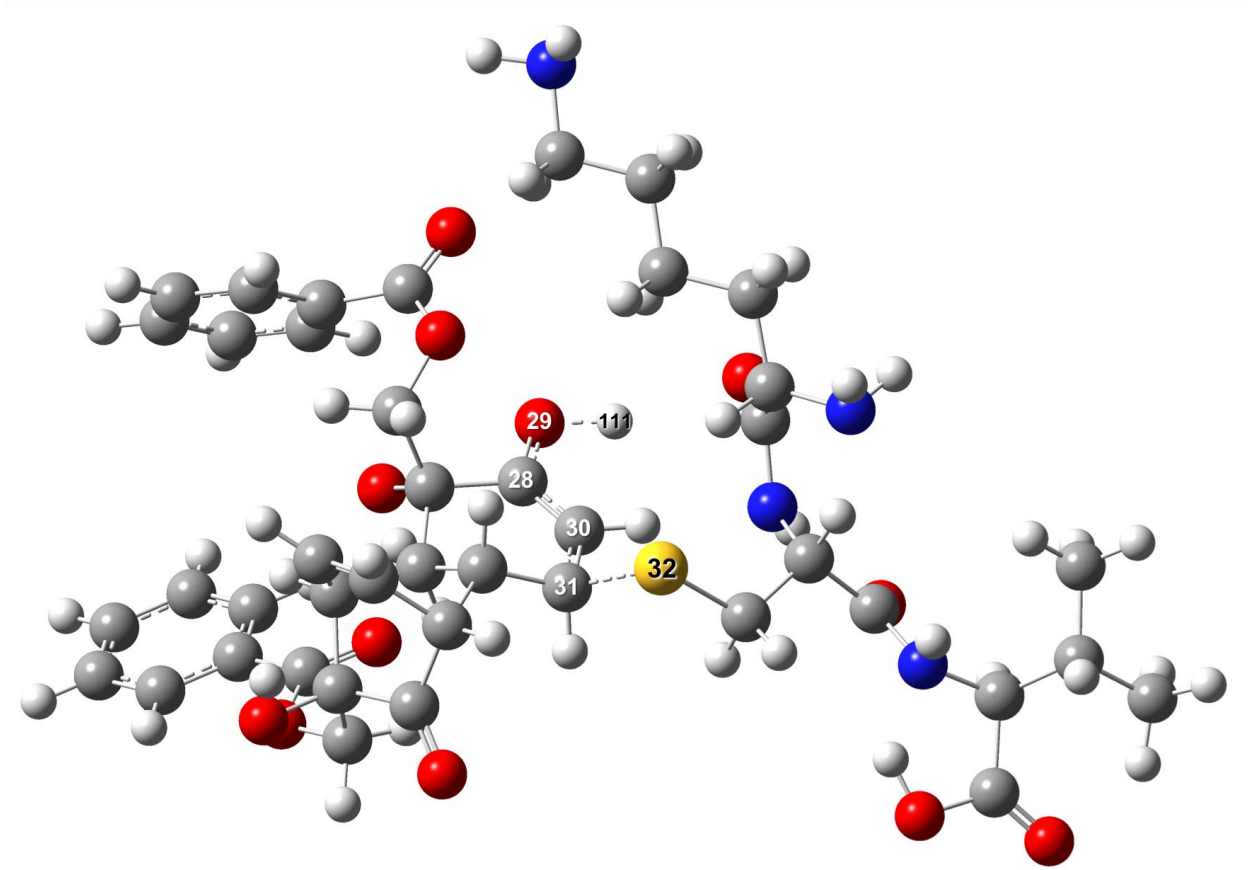


Figure S4. Optimized geometry of TS1.

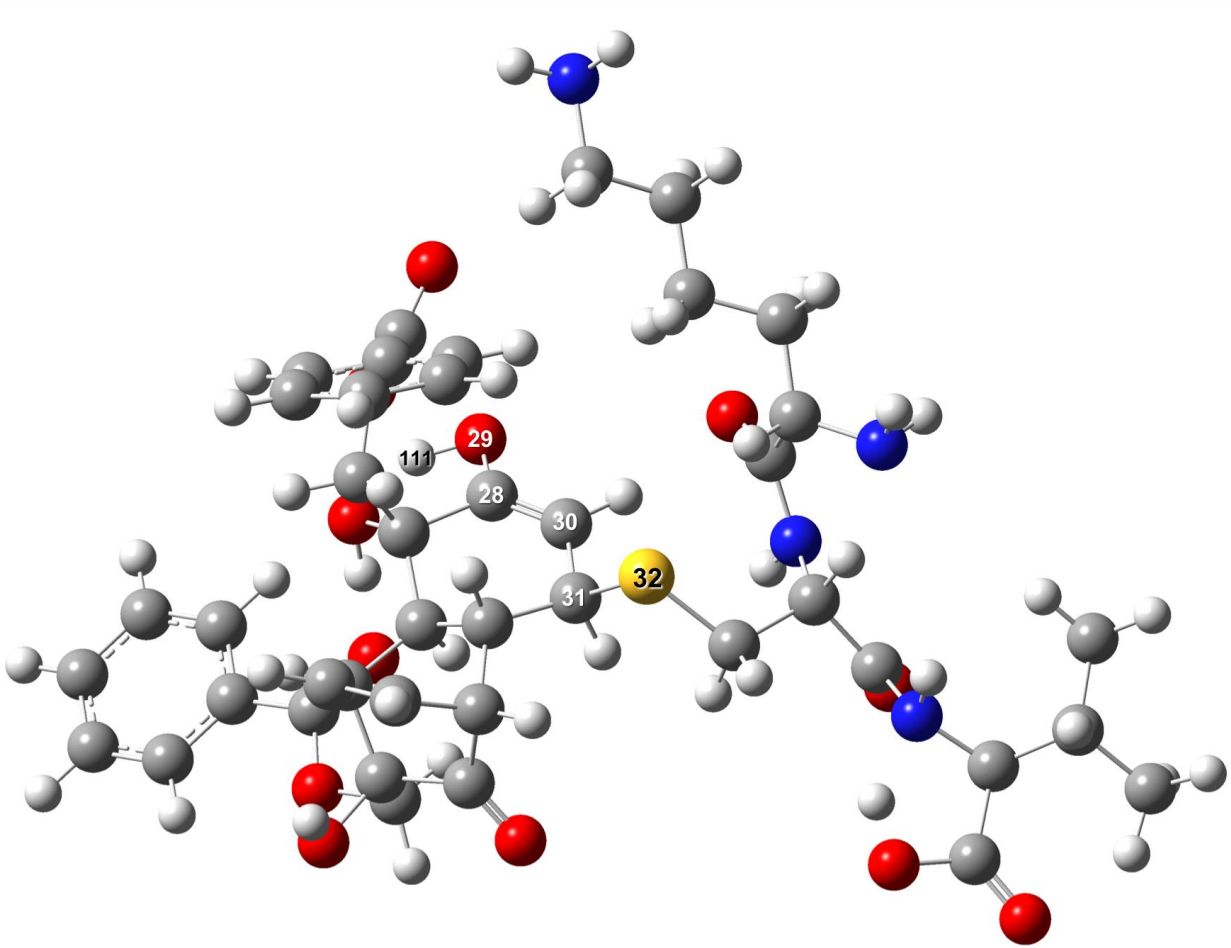


Figure S5. Optimized geometry of grandifloracin (**15**)-Cys151 enol adduct (**20**).

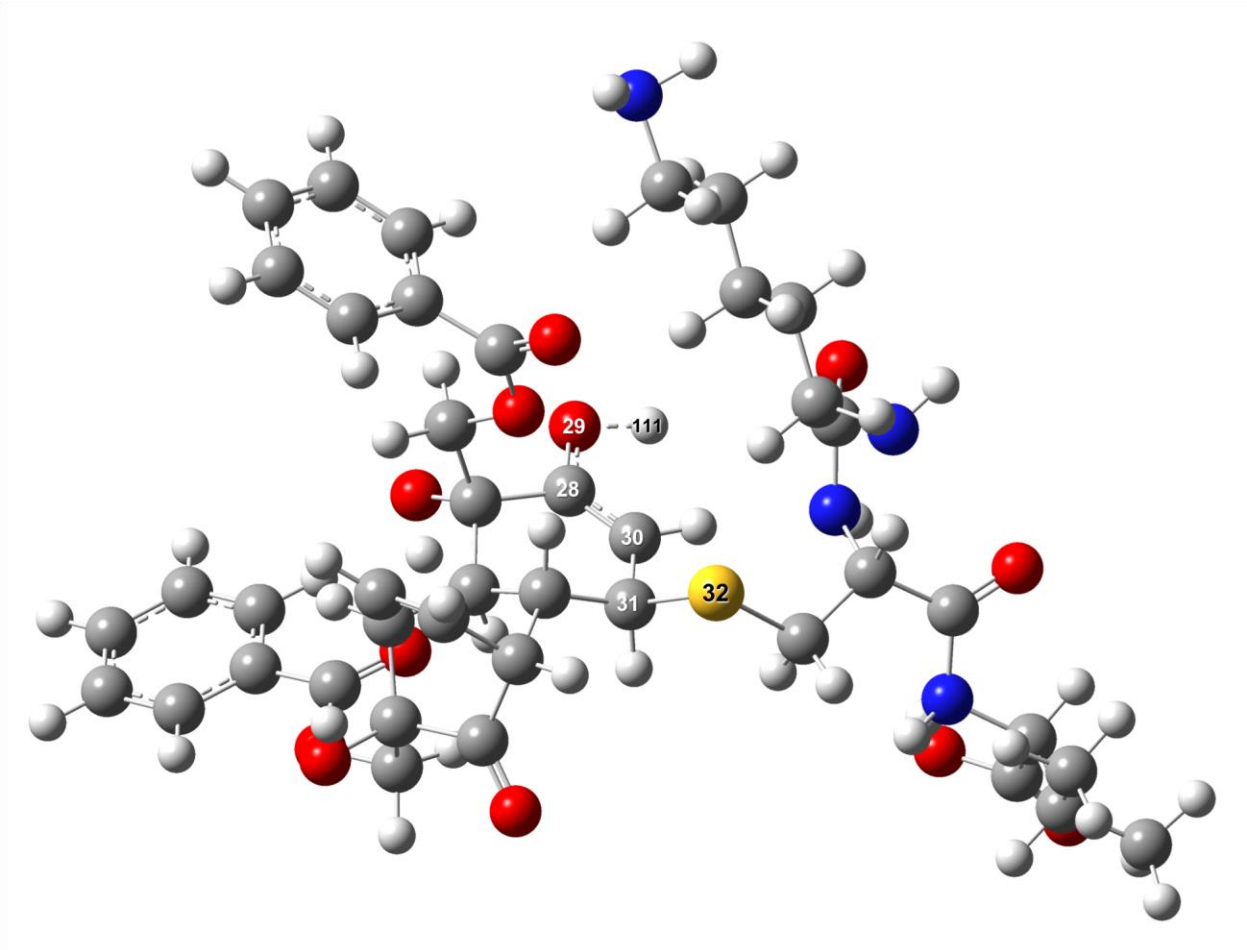


Figure S6. Optimized geometry of TS2.

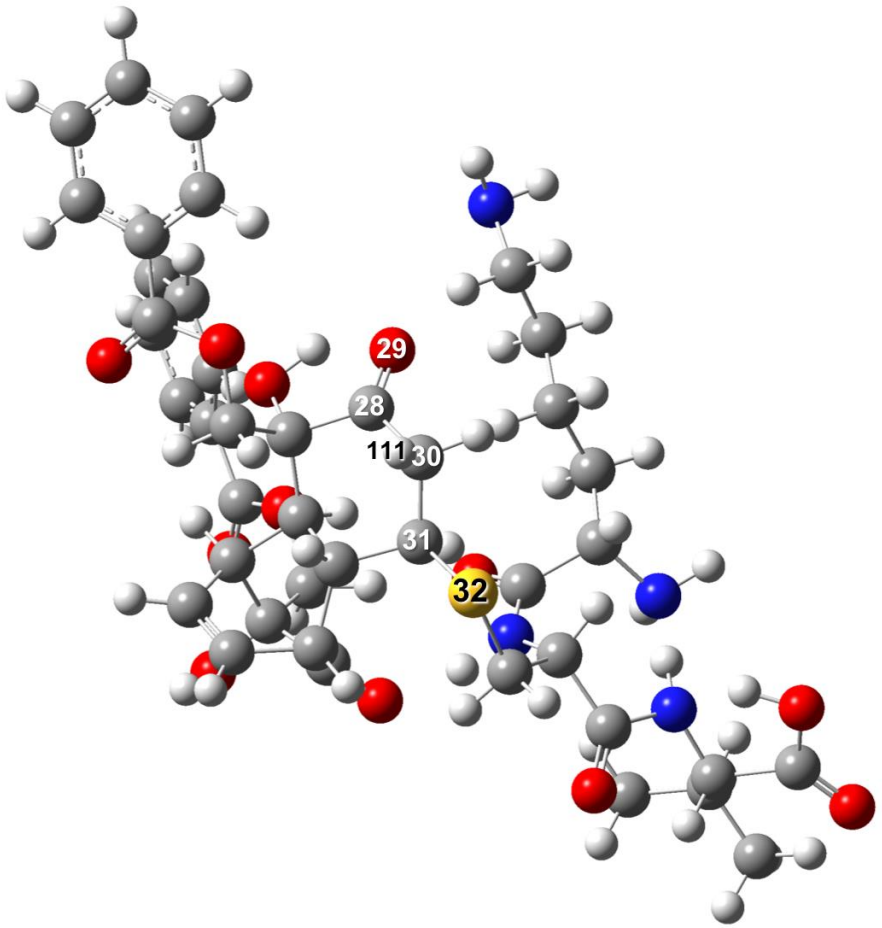


Figure S7. Optimized geometry of grandifloracin (**15**)-Cys151 keto adduct (**21**).

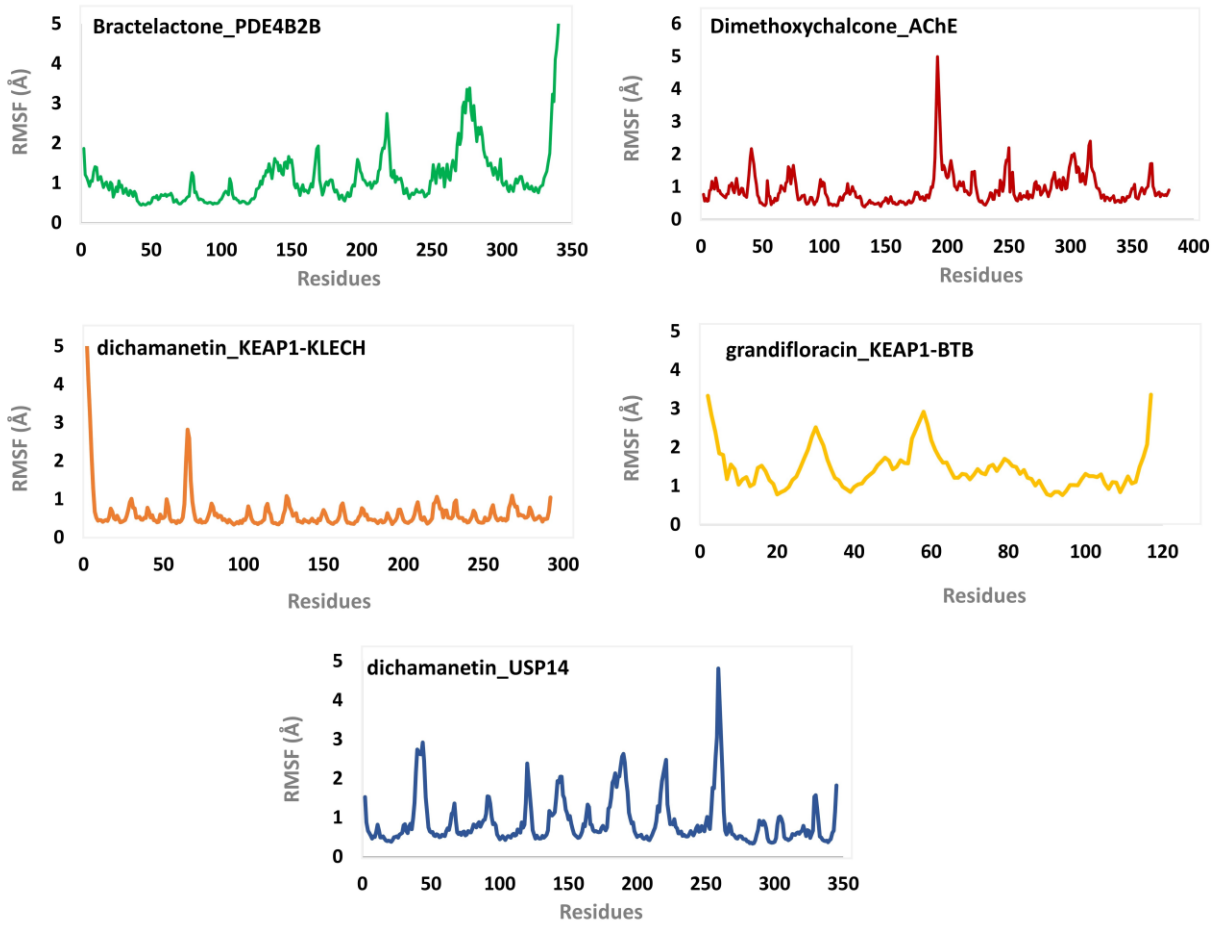


Figure S8. Root mean square fluctuation (RMSF) of selected top-scoring protein-ligand complexes. The x-axis shows the total residues while RMSF value in Å is given on y-axis.

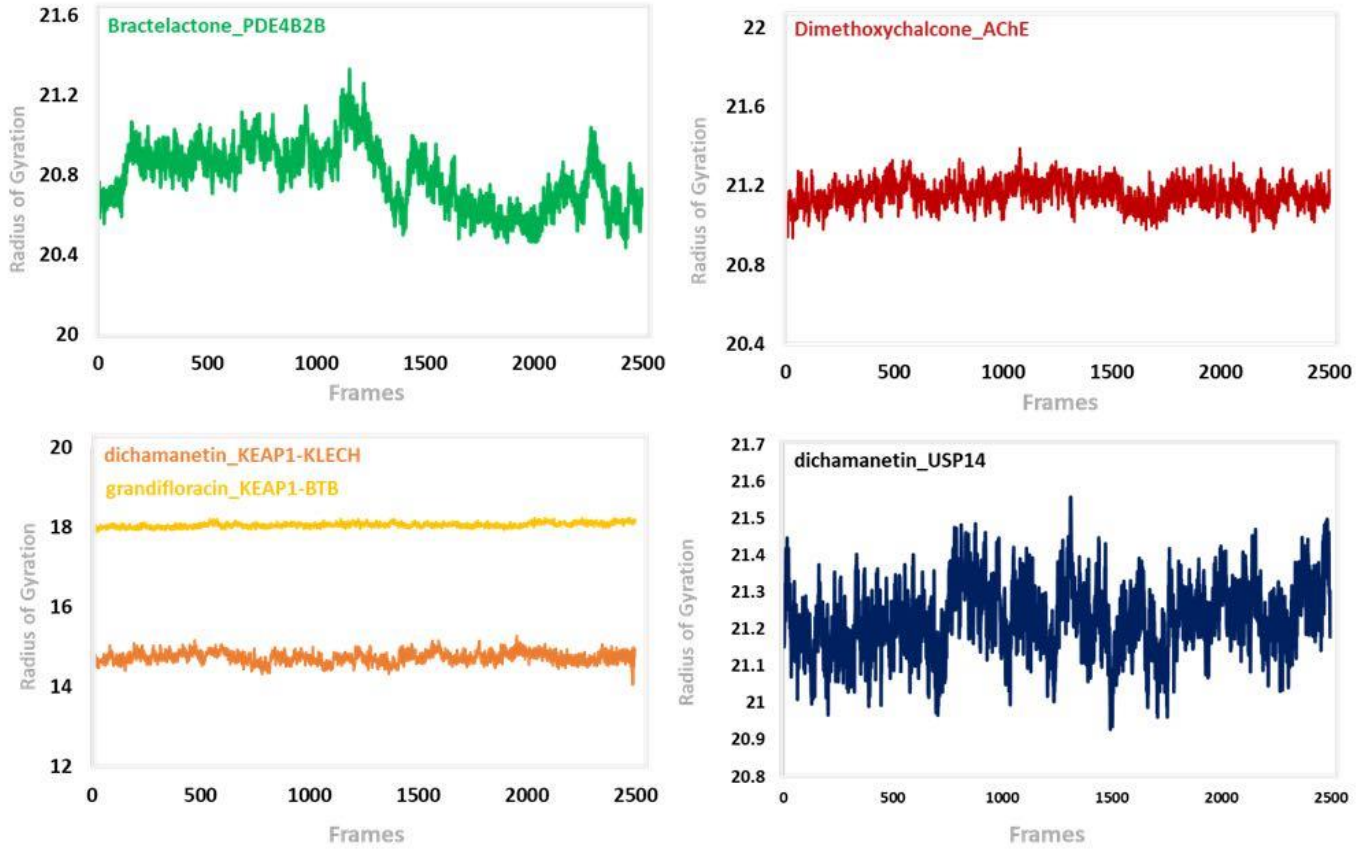


Figure S9. Radius of gyration of all the four ligands bound to different receptors. The y-axis shows the Rg value in Å while the x-axis shows the frames.

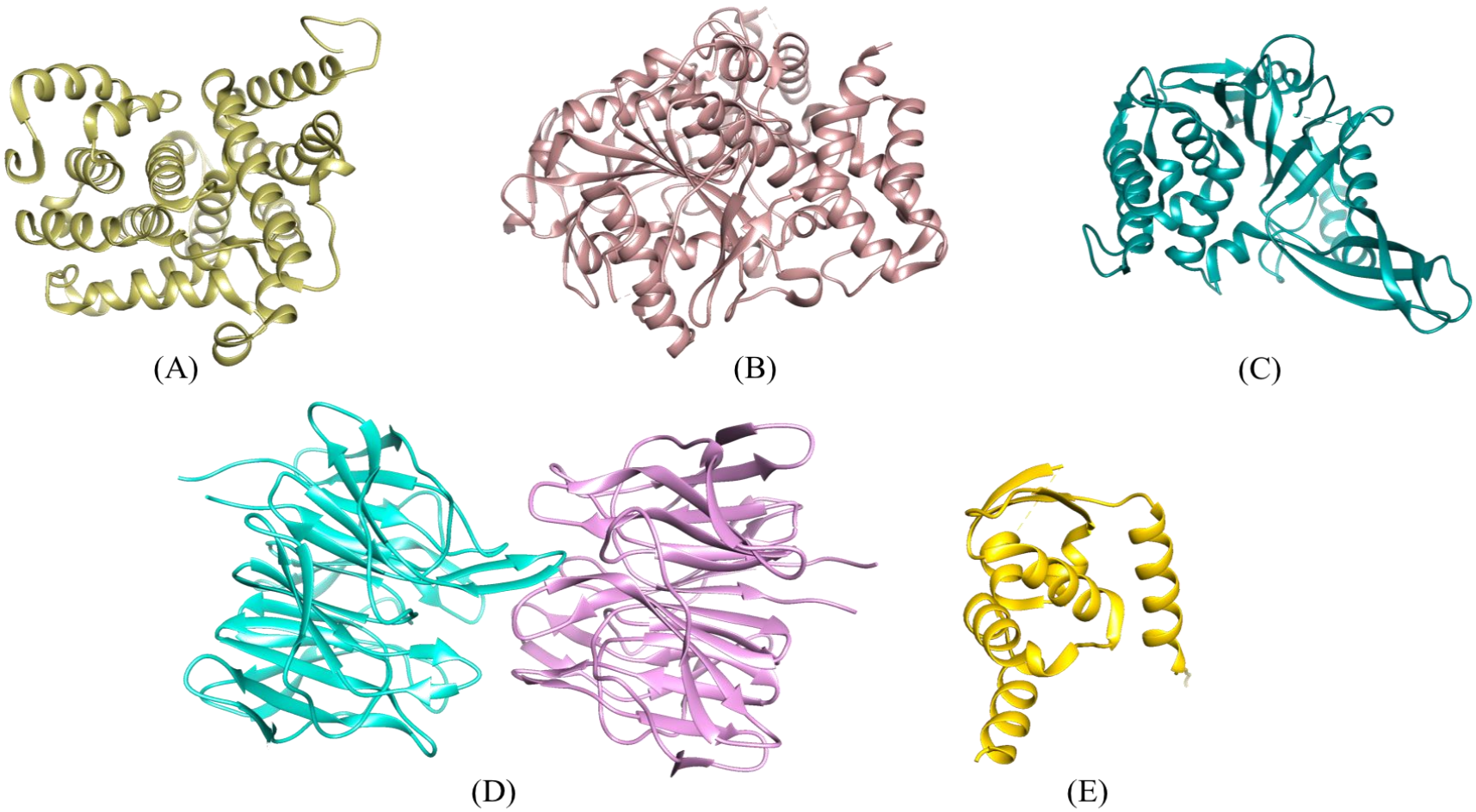


Figure S10. Structures of target proteins: (A) phosphodiesterase 4 B2B, PDE4 B2B, (B) acetylcholinesterase, AChE, (C) ubiquitin specific peptidase 14, USP14, (D) KEAP-1 Kelch domain, and (E) KEAP-1 BTB domain.

Table S1. Putative compounds **1**–**18** identified from the DCM sub-extract and their associated biological activities.

Compound	Retention Time (t_R, min)	Molecular ion (*m/z*)	Calculated Mass	Molecular Formula	Compound Identity	Reported Biological Activity
1	13.0	265.0483 $[M-H]^-$	265.2482	$C_{16}H_{10}O_4$	7-Benzoyloxy-2*H*-1-benzopyran-2-one	No reported activity
2	16.2	409.1246 $[M+H]^+$	408.4007	$C_{23}H_{20}O_7$	Uvaridapoxide A	Antiausterity and cytotoxic activities in human pancreatic cancer PANC-1[1]
3	16.4	385.1295 $[M-H]^-$	386.3952	$C_{21}H_{22}O_7$	Microcarpin A	No reported activity
4	16.5	385.1294 $[M-H]^-$	386.3952	$C_{21}H_{22}O_7$	Microcarpin B	No reported activity
5	16.7	325.0679 $[M+Na]^+$	325.0691	$C_{16}H_{14}O_6Na$	Grandiuvarone	Antitubercular activity; antiproliferative and cytotoxic activities in HeLa and KB-562[2,3]
6	17.5	311.1852 $[M+H]^+$	311.1283	$C_{19}H_{19}O_4$	Uvaridacane A	Antiausterity and cytotoxic activities in human pancreatic cancer PANC-1[1]
7	18.6	435.1462 $[M-H]^-$	435.4539	$C_{25}H_{24}O_7$	Valderramenol A	Antitubercular activity[2]
8	18.7	437.1243 $[M-H]^-$	437.4267	$C_{24}H_{22}O_8$	3-(3,4-Dihydroxy benzyl)-3',4',6-trihydroxy-2,4-dimethoxychalcone	No reported activity
9	19.0	469.1025 $[M+Na]^+$	469.8673	$C_{23}H_{23}ClO_7Na$	Albanol A	Antitubercular activity; antiproliferative

						and cytotoxic activities in HeLa and KB-562[3]
10	19.2	315.1225 $[M+H]^+$	315.3325	$C_{18}H_{18}O_5$	Tepanone	Cytotoxic activity in triple-negative breast cancer cells and human promyelocytic leukemia HL-60[4,5]
11	19.4	421.1301 $[M-H]^-$	421.4273	$C_{24}H_{22}O_7$	Valderramenol B	No reported activity
12	19.8	377.1378 $[M+H]^+$	377.4019	$C_{23}H_{21}O_5$	5-*O*-Methylchamanetin	No reported activity
13	19.8	527.1720 $[M-H]^-$	527.5492	$C_{31}H_{28}O_8$	Cyathosthemine	No reported activity
14	20.2	417.1309 $[M+H]^+$	417.4227	$C_{25}H_{20}O_6$	Bractelactone	Anti-inflammatory[6]
15	20.4	511.1725 $[M+Na]^+$	511.13687	$C_{28}H_{24}O_8Na$	Grandifloracin	Antiausterity activity against human pancreatic cancer PANC-[7]
16	20.8	469.1642 $[M+H]^+$	469.4973	$C_{29}H_{24}O_6$	Dichamanetin	Cytotoxic against the cancer cells HT-29 (colon), DU145 (prostate), and MDA-MB-231 (breast cancer)[8,9]
17	21.1	405.1327 $[M+H]^+$	405.8488	$C_{21}H_{22}ClO_6$	Albanol B	Antitubercular activity; antiproliferative and cytotoxic activities in HeLa and KB-562[3]
18	21.1	435.1454 $[M-H]^-$	435.4538	$C_{25}H_{24}O_7$	Cyathoviridine	Cytotoxic in KB cells[10]

Table S2. Molecular docking scores and binding site interactions of *U. alba* metabolites **1**–**18** against PDE4 B2B (PDB:1RO6).

Cpd	Binding Energy (kcal/mol)	Interacting Amino Acids (non-van der Waals)
1	-8.7	Ile336, Gln369, Phe372, Ile376
2	-7.9	His160, Asp201, Met273, Ile336, Phe372
3	-8.5	Tyr159, His160, His164, Met273, Pro322, Ile336, Phe340, Met 357, Phe372
4	-8.7	His160, Pro322, Ile336, Phe340, Phe372,
5	-7.8	Tyr159, Ile336, Phe372
6	-8.7	His234, Leu303, Glu304, Met347, Asp392, Leu393, Asn395, Ile401, Phe414, Phe446
7	-9.7	Tyr159, Ser208, Ile336, Phe340, Cys358, Phe372
8	-9.5	His160, Asp201, Ser208, Met273, Asn321, Ile336, Phe340, Gln369, Phe372
9	-8.4	Tyr159, Ser208, Ile336, Phe340, Gln343, Phe372
10	-8.1	Tyr159, Met273, Asp318, Leu319, Pro322, Tyr329, Ile336, Phe340, Phe372
11	-9.3	Ile336, Phe340, Pro356, Cys358
12	-9.7	Asp318, Leu319, Pro322, Ile336, Phe340, Met357, Gln369, Phe372
13	-9.9	Tyr159, His160, Met273, Asn209, Ser208, Ile336, Phe340, Gln343, Ser355, Phe372
14	-10.1	Met273, His276, Leu319, Ile336, Phe340, Met357, Phe372, Ile376
15	-10.2	Tyr233, His234, His278, Asn283, Glu304, Met347, Ile410, Phe446
16	-10.2	Tyr159, Met273, Pro322, Ile336, Met337, Phe340, Met357, Cys158, Phe372
17	-8.1	Tyr159, Asp201, His204, Glu230, Met273, Ile336, Phe372
18	-8.3	Tyr159, His204, Leu229, Glu230, His233, Met273, Ile336, Phe372

Table S3. Molecular docking scores and binding site interactions of *U. alba* metabolites **1**–**18** against acetylcholinesterase (PDB:4EY6).

Cpd	Binding Energy (kcal/mol)	Interacting Amino Acids (non-van der Waals)
1	-9.5	Trp289, Tyr337
2	-9.4	Trp86, Gly121, Tyr124, Glu202, Tyr341
3	-9.5	Asp74, Trp86, Tyr124, Trp286, Tyr337
4	-9.6	Trp86, Gly122, Ser203, Trp286, Phe297, Tyr337, Tyr341
5	-9.0	Ser125, Trp286, Tyr337, Phe338
6	-9.4	Trp86, Tyr124, Trp286, Tyr337, Phe338
7	-5.9	Gly82, Trp86, Gly121, Trp286, Tyr337, Trp439, His447, Tyr449
8	-9.8	Trp86, Tyr124, Trp286, Ser293, Arg296, Tyr337, His447, Gly448
9	-9.6	Trp86, Gly122, Try124, Trp286, Val294, Phe295, Phe297, Tyr337, Phe338, Tyr341, His447
10	-8.9	Gly121, Glu202, Trp286, Tyr337, Phe338
11	-6.0	Trp86, Gly122, Glu202, Trp286, Tyr337, Tyr341, Trp439, Pro446, His447, Tyr449
12	-9.2	Tyr72, Trp86, Asn87, Ser125, Tyr124, Gly126, Tyr337
13	-7.0	Asp74, Tyr72, Trp86, Ser125, Tyr133, Trp286, Tyr341
14	-9.7	Gln71, Asp74, Trp86, Tyr124, Trp286, Tyr337, Tyr341, His447
15	-7.8	Trp86, Gly122, Tyr124, Ser125, Glu202, Ser203, Trp286, Tyr341, His447
16	-9.5	Trp86, Tyr124, Trp286, Tyr337, His447, Gly448
17	-9.4	Asp74, Trp86, Ser125, Trp286, Tyr337
18	-7.0	Gly121, Ser125, Tyr124, Trp286, Phe297, Tyr337, Tyr341, His447

Table S4. Molecular docking scores and binding site interactions of *U. alba* metabolites **1**–**18** against USP14 (PDB:6IIM).

Cpd	Binding Energy (kcal/mol)	Interacting Amino Acids (non-van der Waals)
1	-8.3	Asp199, Arg330, Phe331, Lys342, His426, Tyr436
2	-8.4	Gln198, Phe331, Asn340, Lys342, Ser 431, Ser432
3	-8.0	Gln198, Arg330, Phe331, Asn340, Lys342, His426, Ser431
4	-7.7	Arg330, Phe331, Asn340, Lys342, His426, Ser431
5	-7.7	Arg330, Phe331, Lys342, His426, Ser431, Tyr436
6	-7.5	Arg330, Phe331, Lys342, Ser431
7	-7.8	Phe331, Asn340, Lys342, Tyr476
8	-8.4	Glu188, Gln198, Asn340, Lys342, Ser431, Tyr476
9	-8.0	Asp199, Arg330, Phe331, Lys342, His426, Ser431
10	-7.0	Asp199, Arg330, Phe331, Lys342, Tyr436
11	-7.9	Asp199, Phe331, Asn340, Lys342
12	-9.4	Gln197, Gln198, Phe331, Asn340, Lys342, Tyr476
13	-8.8	Asp199, Arg330, Phe331, Asn340, Lys342
14	-8.0	Gln198, Asn340, Tyr436, Tyr476
15	-9.0	Gln198, Asp199, Glu202, Phe331, Asn340, Lys342, Ser431
16	-9.8	Gln198, Asp199, Arg330, Lys342, Tyr476
17	-7.9	Asp199, Arg330, Phe331, Asn340, Lys342, His426, Ser431
18	-7.4	Gln198, Lys342, Ser431, Tyr476

Table S5. Molecular docking scores and binding site interactions of *U. alba* metabolites **1**–**18** against KEAP-1 Kelch domain (PDB:4L7B).

Cpd	Binding Energy (kcal/mol)	Interacting Amino Acids (non-van der Waals)
1	-8.7	Tyr334, Arg415, Ala556
2	-8.9	Tyr334, Ala556, Tyr572
3	-8.7	Tyr334, Arg415, Arg483, Tyr525, Tyr572, Ser602
4	-7.9	Arg415, Arg483, Tyr525, Tyr572
5	-8.1	Ser363, Tyr572, Ser602
6	-8.3	Tyr334, Ser363, Tyr572
7	-8.6	Asn387, Arg415, Ala556
8	-10.1	Tyr334, ASn387, Ala556, Tyr572
9	-9.3	Ser363, Arg415, Arg483, Tyr525, Tyr572, Ser602
10	-8.0	Tyr334, Arg415, Ile461, Ala556
11	-8.8	Asn382, Asn387, Ala556, Tyr572
12	-9.7	Arg415, Tyr525, Ala556, Tyr572
13	-10.6	Tyr334, Asn382, Arg415, Tyr525, Ala556, Tyr572, Ser602
14	-8.6	Ser383, Asn387, Arg415, Tyr525, Ala556, Tyr572
15	-10.2	Tyr334, Ser363, Arg380, Asn414, Arg415, Tyr525, Gln530, Ser555, Ala556, Tyr572
16	-11.1	Asn414, Arg415, Ile416, Gly462, Ala556, Tyr572, Gly603
17	-8.6	Tyr334, Ser555, Tyr572, Ser602, Gly603
18	-8.9	Ser363, Asn414, Arg415, Ala556, Tyr572, Ser602

Table S6. Molecular docking scores and binding site interactions of *U. alba* metabolites **1**–**18** against KEAP1-1 BTB domain (PDB:5DAD).

Cpd	Binding Energy (kcal/mol)	Interacting Amino Acids (non-van der Waals)
1	-6.8	His129, Lys131, Arg135, Cys151, His154
2	-6.4	Ala88, His129, Pro130, Lys131, Arg135, Lys150, Cys151
3	-5.8	Tyr85, Lys131, Arg135, Lys150, Cys151
4	-5.8	Tyr85, Lys131, Arg135, Cys151, His154
5	-6.0	His129, Lys131, Lys150, Cys151
6	-5.9	His129, Lys131, Arg135, Gly148, Cys151
7	-7.1	Ala88, His129, Lys131, Arg135, Cys151, His154
8	-7.1	Tyr85, Ala88, His129, Lys131, Arg135, Gly148, Cys151, His154
9	-6.4	His129, Lys131, Arg135, Cys151
10	-5.9	His129, Lys131, Arg135, Ser146, Cys151, His154
11	-6.9	Ala88, His129, Lys131, Arg135, Cys151
12	-6.8	His129, Lys131, Arg135, Cys151
13	-6.6	Tyr85, Ala88, His129, Lys131, Arg135, Cys151, His154
14	-6.8	Lys131, Arg135, Ser146, Gly148, Lys150, Cys151, His154
15	-7.3	Ala88, Pro89, His129, Pro130, Lys131, Cys151, His154
16	-6.7	Tyr85, Ala88, Pro89, His129, Lys131, Cys151
17	-5.9	Gln86, Asp87, Ala88, Lys131, Arg135, Cys151
18	-6.6	Ala88, Lys131, Val132, Cys151

Table S7. Summary of energies of HOMO, LUMO, electronic chemical potential **μ**, hardness **η** and global electrophilicity **ω** of the electrophilic *U. alba* secondary metabolites.

Compound	HOMO (Ha)	LUMO (Ha)	hardness, η (eV)	chemical potential,μ (eV)	electrophilicity index, ω (eV)
1	-0.315	-0.049	7.244	-4.960	1.698
5	-0.326	-0.044	7.673	-5.021	1.643
7	-0.291	-0.052	6.491	-4.661	1.674
8	-0.271	-0.045	6.140	-4.302	1.507
10	-0.280	-0.040	6.541	-4.347	1.444
11	-0.291	-0.052	6.516	-4.670	1.673
14	-0.271	-0.054	5.901	-4.412	1.650
15	-0.367	-0.037	8.965	-5.499	1.686
18	-0.293	-0.047	6.689	-4.618	1.594

Table S8. Energetics of the reaction species calculated at the B3LYP/6-31G** level of theory with the PCM water solvation model.

Reaction species	Energy, Ha	Relative Energy[a], kcal/mol
reactants	-3151.815138	-
TS1	-3151.766098	30.77
enol intermediate	-3151.770008	28.32
TS2	-3151.766007	30.83
keto product	-3151.801912	8.30
$\Delta E^{\ddagger}(E^{\ddagger}_{TS1} - E^{\circ}_{reactants})$		30.77
$\Delta E^{\ddagger}_{keto-enol}(E^{\circ}_{keto\ prod} - E^{\circ}_{enol\ intermediate})$		-20.02
$\Delta E^{\circ}_{reaction}(E^{\circ}_{keto\ prod} - E^{\circ}_{reactants})$		8.30

[a]relative to the reactants (grandifloracin (**15**) + Cys151 tripeptide).

Table S9. Cartesian coordinates of the optimized structure of grandifloracin (**15**) calculated at B3LYP/6-31G**(d,p).

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	8	0	5.244695	-0.560319	-0.672532
2	6	0	4.516187	0.211453	-0.001913
3	8	0	3.368649	-0.216528	0.746164
4	6	0	3.137949	-1.668265	0.558406
5	6	0	1.844967	-1.900512	-0.320716
6	8	0	2.156732	-1.236562	-1.592468
7	6	0	0.538744	-1.342651	0.417198
8	1	0	0.618168	-0.252396	0.572137
9	6	0	0.392637	-2.107766	1.740561
10	6	0	0.272331	-3.438040	1.616277
11	6	0	0.248887	-3.942631	0.166399
12	1	0	0.140766	-5.038317	0.088457
13	6	0	-0.954074	-3.207065	-0.589612
14	1	0	-0.933845	-3.530172	-1.648667
15	6	0	-0.707302	-1.641674	-0.510432
16	1	0	-0.461095	-1.281585	-1.527219
17	6	0	-1.978463	-0.824434	-0.054129
18	6	0	-2.938513	-0.548324	-1.305625
19	8	0	-2.392652	0.597855	-2.045983
20	6	0	-2.389886	1.808570	-1.228050
21	6	0	-3.735038	2.204498	-0.547105
22	6	0	-4.973424	1.988445	-1.199180
23	6	0	-6.171857	2.448760	-0.619941
24	6	0	-6.145404	3.131317	0.613090
25	6	0	-4.914649	3.363127	1.261202
26	6	0	-3.715265	2.908306	0.681051
27	8	0	-1.441574	2.616093	-1.379780
28	8	0	-1.648620	0.476099	0.517376
29	6	0	-2.789527	-1.565781	1.077901
30	6	0	-3.071962	-3.016015	0.852832
31	6	0	-2.261385	-3.723888	0.036448
32	8	0	-3.135733	-0.827397	2.051724
33	6	0	1.603414	-3.475581	-0.512098
34	8	0	2.379677	-4.231788	-1.135048
35	6	0	4.717968	1.721611	0.167721
36	6	0	3.834676	2.514141	0.940203
37	6	0	4.059606	3.897783	1.068421
38	6	0	5.164337	4.497505	0.427936
39	6	0	6.047072	3.712325	-0.343283
40	6	0	5.825015	2.329237	-0.473319
41	1	0	3.006796	-2.124105	1.560649

42	1	0	4.020206	-2.105683	0.042419
43	1	0	1.362069	-1.492312	-2.188998
44	1	0	0.412189	-1.573129	2.698933
45	1	0	0.174761	-4.142507	2.452222
46	1	0	-2.944046	-1.407939	-2.005185
47	1	0	-3.974389	-0.365293	-0.949177
48	1	0	-4.994878	1.469297	-2.167399
49	1	0	-7.127888	2.277181	-1.133396
50	1	0	-7.081161	3.487379	1.065165
51	1	0	-4.890009	3.901803	2.218401
52	1	0	-2.753558	3.096488	1.178496
53	1	0	-2.262949	0.395580	1.373141
54	1	0	-3.931605	-3.476247	1.359719
55	1	0	-2.468673	-4.791031	-0.147030
56	1	0	2.977688	2.036161	1.434098
57	1	0	3.373152	4.510943	1.668220
58	1	0	5.337328	5.577858	0.529795
59	1	0	6.907004	4.180107	-0.841827
60	1	0	6.502334	1.701593	-1.070052

Table S10. Cartesian coordinates of the optimized structure of Cys151 tripeptide (Lys150-Cys151-Val152) calculated at B3LYP/6-31G**(d,p).

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	7	0	2.361111	0.868023	1.268858
2	1	0	1.737003	0.011434	1.240928
3	6	0	1.373003	2.012693	0.967453
4	1	0	1.587561	2.852129	1.664499
5	6	0	1.481889	2.578131	-0.494324
6	6	0	-0.110017	1.476856	1.280106
7	1	0	2.561425	2.755486	-0.676392
8	1	0	1.138045	1.810312	-1.210880
9	16	0	0.498532	4.121111	-0.668202
10	8	0	-0.964151	2.188826	1.889927
11	1	0	0.966725	4.395032	-1.917097
12	6	0	3.488541	0.650127	0.349012
13	6	0	3.408449	-0.408497	-0.833282
14	8	0	4.193782	1.805101	-0.033247
15	7	0	4.243083	0.252130	-1.943675
16	1	0	2.366796	-0.550971	-1.190697
17	6	0	4.024614	-1.808205	-0.466955
18	1	0	4.505670	1.436889	-0.989412
19	1	0	3.639216	0.376324	-2.797153
20	1	0	5.007006	-0.409770	-2.240196
21	1	0	4.171270	-2.390032	-1.395565
22	1	0	5.020708	-1.636629	-0.022100
23	6	0	3.156981	-2.660345	0.525147
24	1	0	2.821307	-1.999071	1.346536
25	6	0	1.901718	-3.275338	-0.173120
26	6	0	4.037653	-3.789658	1.153005
27	1	0	2.217448	-3.894580	-1.026893
28	1	0	1.372945	-3.929197	0.537642
29	1	0	1.182262	-2.498787	-0.531573
30	1	0	4.900566	-3.361607	1.686274
31	1	0	3.448373	-4.384774	1.867600
32	1	0	4.415254	-4.465893	0.370454
33	7	0	-0.219205	0.138613	0.856504
34	1	0	0.171125	-0.430239	-0.182460
35	6	0	-1.541478	-0.558172	0.840606
36	1	0	-1.705644	-1.168579	1.757350
37	6	0	-2.830058	0.308245	0.601532
38	6	0	-1.321360	-1.552562	-0.441379
39	1	0	-2.940336	1.051941	1.410747
40	1	0	-2.721936	0.866197	-0.345051

41	6	0	-4.060390	-0.648410	0.502666
42	8	0	-0.102481	-1.308460	-0.995929
43	1	0	-3.723491	-1.504280	-0.131133
44	1	0	-4.310238	-1.035441	1.505373
45	6	0	-5.313463	0.056059	-0.101917
46	1	0	-5.609977	0.917421	0.523115
47	1	0	-5.085792	0.427549	-1.116564
48	6	0	-6.501267	-0.941430	-0.182070
49	1	0	-6.292034	-1.798266	-0.850783
50	1	0	-6.815024	-1.307570	0.814162
51	7	0	-7.758089	-0.245486	-0.781319
52	1	0	-7.567872	0.117243	-1.758970
53	1	0	-8.578494	-0.913805	-0.842461
54	1	0	-8.061179	0.579655	-0.189229
55	8	0	-2.311073	-2.475349	-0.903797
56	1	0	-1.881010	-3.266765	-1.235923

Table S11. Cartesian coordinates of the optimized structure of TS1 calculated at B3LYP/6-31G**(d,p).

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	8	0	-2.754592	-2.534959	-1.339143
2	6	0	-3.777586	-3.195930	-0.990625
3	8	0	-3.807572	-4.047511	0.147586
4	6	0	-2.505565	-4.049816	0.863247
5	6	0	-2.530788	-3.143255	2.157265
6	8	0	-3.488387	-3.807580	3.054150
7	6	0	-2.893815	-1.600293	1.915125
8	1	0	-3.853575	-1.507533	1.376184
9	6	0	-2.954738	-0.984524	3.328238
10	6	0	-1.819942	-1.084302	4.041631
11	6	0	-0.623768	-1.689190	3.278792
12	1	0	0.300252	-1.728426	3.881550
13	6	0	-0.460636	-0.755464	2.010110
14	6	0	-1.698551	-0.994779	1.079921
15	1	0	-1.414756	-1.770959	0.349024
16	6	0	-1.967519	0.281788	0.174730
17	6	0	-2.531830	1.504851	1.026712
18	8	0	-2.133654	2.822634	0.484042
19	6	0	-3.010314	3.417805	-0.472574
20	6	0	-4.457160	2.888805	-0.663407
21	6	0	-4.854290	2.386268	-1.925634
22	6	0	-6.191084	2.001445	-2.146001
23	6	0	-7.143015	2.126228	-1.113590
24	6	0	-6.756559	2.640383	0.140568
25	6	0	-5.419872	3.022598	0.367072
26	8	0	-2.574293	4.428423	-1.083258
27	8	0	-2.979014	0.040833	-0.854563
28	6	0	-0.558246	0.598645	-0.469726
29	8	0	-0.663382	1.521372	-1.542284
30	6	0	0.600393	-0.012971	-0.127625
31	6	0	0.820316	-0.880631	1.122195
32	16	0	2.318219	-0.306759	2.068699
33	6	0	3.635472	-0.944662	0.953041
34	6	0	4.332096	0.128926	0.016646
35	1	0	4.824092	0.956547	0.605060
36	7	0	3.373039	0.790905	-0.934595
37	6	0	3.034325	2.198708	-0.842005
38	6	0	3.321977	2.868365	0.572536
39	1	0	2.797135	2.248784	1.333903
40	6	0	2.795753	4.345990	0.605286
41	6	0	1.239943	4.448147	0.641090

42	6	0	0.758723	5.932683	0.605725
43	6	0	-0.786093	6.056761	0.787525
44	7	0	-1.209326	7.515252	0.631697
45	7	0	4.813114	2.754981	0.892401
46	8	0	2.412153	2.769380	-1.776348
47	6	0	5.359207	-0.575740	-0.947995
48	7	0	6.464159	-1.295785	-0.293804
49	6	0	7.640780	-1.652316	-1.187820
50	1	0	7.285220	-1.487295	-2.227583
51	6	0	8.935688	-0.804253	-0.914797
52	6	0	10.067214	-1.292835	-1.873737
53	6	0	8.671223	0.725312	-1.081280
54	6	0	7.869004	-3.235424	-0.960635
55	8	0	6.848675	-3.778613	-0.179005
56	8	0	8.823991	-3.908979	-1.421098
57	8	0	5.188079	-0.591777	-2.192832
58	6	0	-1.052371	-3.141641	2.811784
59	8	0	-0.363996	-4.172065	2.975784
60	6	0	-5.122520	-3.214339	-1.713292
61	6	0	-5.257824	-2.471243	-2.911959
62	6	0	-6.482228	-2.467237	-3.604498
63	6	0	-7.576828	-3.203938	-3.104113
64	6	0	-7.446602	-3.945660	-1.910584
65	6	0	-6.223746	-3.953369	-1.214446
66	1	0	-1.700470	-3.738443	0.167456
67	1	0	-2.333095	-5.097221	1.186385
68	1	0	-3.537576	-3.136854	3.831693
69	1	0	-3.883669	-0.537221	3.705158
70	1	0	-1.697278	-0.725772	5.072392
71	1	0	-0.487352	0.281700	2.390133
72	1	0	-3.632826	1.398208	1.090001
73	1	0	-2.108958	1.482351	2.051053
74	1	0	-4.113923	2.295058	-2.732386
75	1	0	-6.491167	1.606984	-3.126433
76	1	0	-8.185816	1.827760	-1.287843
77	1	0	-7.497822	2.746859	0.944421
78	1	0	-5.125583	3.433057	1.343065
79	1	0	-2.771558	-0.925415	-1.178944
80	1	0	1.525544	0.209592	-0.682951
81	1	0	0.980344	-1.943718	0.842647
82	1	0	3.226218	-1.759134	0.330197
83	1	0	4.428021	-1.382303	1.586609
84	1	0	3.614294	0.455803	-1.912808
85	1	0	3.179756	4.878169	-0.282726
86	1	0	3.212484	4.843496	1.499588
87	1	0	0.864411	3.958816	1.556677

88	1	0	0.823005	3.905733	-0.224471
89	1	0	1.265130	6.500967	1.406594
90	1	0	1.049977	6.389656	-0.355838
91	1	0	-1.063930	5.636728	1.778293
92	1	0	-1.319019	5.461721	0.011274
93	1	0	-0.812867	7.997294	1.492229
94	1	0	-2.247520	7.507429	0.859114
95	1	0	4.931818	3.228203	1.833153
96	1	0	5.303810	3.420033	0.229337
97	1	0	6.761664	-0.819655	0.596456
98	1	0	9.250253	-0.996906	0.129418
99	1	0	9.864004	-0.961297	-2.903140
100	1	0	10.090045	-2.396984	-1.852524
101	1	0	11.039177	-0.886559	-1.557571
102	1	0	8.335029	0.948953	-2.105354
103	1	0	9.598932	1.285553	-0.889713
104	1	0	7.904335	1.079398	-0.375768
105	1	0	6.314016	-2.887578	0.007855
106	1	0	-4.394661	-1.904063	-3.288678
107	1	0	-6.585121	-1.891306	-4.534288
108	1	0	-8.533333	-3.200386	-3.645327
109	1	0	-8.300587	-4.518131	-1.523406
110	1	0	-6.109394	-4.526515	-0.284051
111	1	0	0.318665	1.686839	-1.805817

Table S12. Cartesian coordinates of the optimized structure of grandifloracin (**15**)-Cys151 enol adduct (**20**) calculated at B3LYP/6-31G**(d,p).

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	8	0	-2.754592	-2.534959	-1.339143
2	6	0	-3.777586	-3.195930	-0.990625
3	8	0	-3.807572	-4.047511	0.147586
4	6	0	-2.505565	-4.049816	0.863247
5	6	0	-2.530788	-3.143255	2.157265
6	8	0	-3.488387	-3.807580	3.054150
7	6	0	-2.893815	-1.600293	1.915125
8	1	0	-3.853575	-1.507533	1.376184
9	6	0	-2.954738	-0.984524	3.328238
10	6	0	-1.819942	-1.084302	4.041631
11	6	0	-0.623768	-1.689190	3.278792
12	1	0	0.300252	-1.728426	3.881550
13	6	0	-0.460636	-0.755464	2.010110
14	6	0	-1.698551	-0.994779	1.079921
15	1	0	-1.414756	-1.770959	0.349024
16	6	0	-1.967519	0.281788	0.174730
17	6	0	-2.531830	1.504851	1.026712
18	8	0	-2.133654	2.822634	0.484042
19	6	0	-3.010314	3.417805	-0.472574
20	6	0	-4.457160	2.888805	-0.663407
21	6	0	-4.854290	2.386268	-1.925634
22	6	0	-6.191084	2.001445	-2.146001
23	6	0	-7.143015	2.126228	-1.113590
24	6	0	-6.756559	2.640383	0.140568
25	6	0	-5.419872	3.022598	0.367072
26	8	0	-2.574293	4.428423	-1.083258
27	8	0	-2.979014	0.040833	-0.854563
28	6	0	-0.558246	0.598645	-0.469726
29	8	0	-0.663382	1.521372	-1.542284
30	6	0	0.600393	-0.012971	-0.127625
31	6	0	0.820316	-0.880631	1.122195
32	16	0	2.318219	-0.306759	2.068699
33	6	0	3.635472	-0.944662	0.953041
34	6	0	4.332096	0.128926	0.016646
35	1	0	4.824092	0.956547	0.605060
36	7	0	3.373039	0.790905	-0.934595
37	6	0	3.034325	2.198708	-0.842005
38	6	0	3.321977	2.868365	0.572536
39	1	0	2.797135	2.248784	1.333903
40	6	0	2.795753	4.345990	0.605286
41	6	0	1.239943	4.448147	0.641090

42	6	0	0.758723	5.932683	0.605725
43	6	0	-0.786093	6.056761	0.787525
44	7	0	-1.209326	7.515252	0.631697
45	7	0	4.813114	2.754981	0.892401
46	8	0	2.412153	2.769380	-1.776348
47	6	0	5.359207	-0.575740	-0.947995
48	7	0	6.464159	-1.295785	-0.293804
49	6	0	7.640780	-1.652316	-1.187820
50	1	0	7.285220	-1.487295	-2.227583
51	6	0	8.935688	-0.804253	-0.914797
52	6	0	10.067214	-1.292835	-1.873737
53	6	0	8.671223	0.725312	-1.081280
54	6	0	7.869004	-3.235424	-0.960635
55	8	0	6.848675	-3.778613	-0.179005
56	8	0	8.823991	-3.908979	-1.421098
57	8	0	5.188079	-0.591777	-2.192832
58	6	0	-1.052371	-3.141641	2.811784
59	8	0	-0.363996	-4.172065	2.975784
60	6	0	-5.122520	-3.214339	-1.713292
61	6	0	-5.257824	-2.471243	-2.911959
62	6	0	-6.482228	-2.467237	-3.604498
63	6	0	-7.576828	-3.203938	-3.104113
64	6	0	-7.446602	-3.945660	-1.910584
65	6	0	-6.223746	-3.953369	-1.214446
66	1	0	-1.700470	-3.738443	0.167456
67	1	0	-2.333095	-5.097221	1.186385
68	1	0	-3.537576	-3.136854	3.831693
69	1	0	-3.883669	-0.537221	3.705158
70	1	0	-1.697278	-0.725772	5.072392
71	1	0	-0.487352	0.281700	2.390133
72	1	0	-3.632826	1.398208	1.090001
73	1	0	-2.108958	1.482351	2.051053
74	1	0	-4.113923	2.295058	-2.732386
75	1	0	-6.491167	1.606984	-3.126433
76	1	0	-8.185816	1.827760	-1.287843
77	1	0	-7.497822	2.746859	0.944421
78	1	0	-5.125583	3.433057	1.343065
79	1	0	-2.771558	-0.925415	-1.178944
80	1	0	1.525544	0.209592	-0.682951
81	1	0	0.980344	-1.943718	0.842647
82	1	0	3.226218	-1.759134	0.330197
83	1	0	4.428021	-1.382303	1.586609
84	1	0	3.614294	0.455803	-1.912808
85	1	0	3.179756	4.878169	-0.282726
86	1	0	3.212484	4.843496	1.499588
87	1	0	0.864411	3.958816	1.556677

88	1	0	0.823005	3.905733	-0.224471
89	1	0	1.265130	6.500967	1.406594
90	1	0	1.049977	6.389656	-0.355838
91	1	0	-1.063930	5.636728	1.778293
92	1	0	-1.319019	5.461721	0.011274
93	1	0	-0.812867	7.997294	1.492229
94	1	0	-2.247520	7.507429	0.859114
95	1	0	4.931818	3.228203	1.833153
96	1	0	5.303810	3.420033	0.229337
97	1	0	6.761664	-0.819655	0.596456
98	1	0	9.250253	-0.996906	0.129418
99	1	0	9.864004	-0.961297	-2.903140
100	1	0	10.090045	-2.396984	-1.852524
101	1	0	11.039177	-0.886559	-1.557571
102	1	0	8.335029	0.948953	-2.105354
103	1	0	9.598932	1.285553	-0.889713
104	1	0	7.904335	1.079398	-0.375768
105	1	0	6.314016	-2.887578	0.007855
106	1	0	-4.394661	-1.904063	-3.288678
107	1	0	-6.585121	-1.891306	-4.534288
108	1	0	-8.533333	-3.200386	-3.645327
109	1	0	-8.300587	-4.518131	-1.523406
110	1	0	-6.109394	-4.526515	-0.284051
111	1	0	0.318665	1.686839	-1.805817

Table S13. Cartesian coordinates of the optimized structure of TS2 calculated at B3LYP/6-31G**(d,p).

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	8	0	-2.698756	-3.444787	-1.116319
2	6	0	-3.675015	-4.035815	-0.566334
3	8	0	-3.682644	-4.423316	0.801051
4	6	0	-2.427132	-4.026888	1.491220
5	6	0	-2.606478	-2.702545	2.334163
6	8	0	-3.573585	-3.062406	3.381926
7	6	0	-3.063359	-1.413972	1.496674
8	1	0	-3.976930	-1.629914	0.914733
9	6	0	-3.295746	-0.320440	2.559234
10	6	0	-2.224018	-0.025145	3.315022
11	6	0	-0.921786	-0.738511	2.899565
12	1	0	-0.052065	-0.450214	3.515313
13	6	0	-0.730811	-0.334454	1.380913
14	6	0	-1.845554	-1.055833	0.556749
15	1	0	-1.439858	-2.017538	0.198658
16	6	0	-2.125166	-0.240879	-0.767423
17	6	0	-2.784395	1.182314	-0.522636
18	8	0	-1.769558	2.082490	0.082912
19	6	0	-2.262725	3.365728	0.490429
20	6	0	-3.736333	3.742073	0.183292
21	6	0	-4.122185	4.140350	-1.119477
22	6	0	-5.445693	4.552606	-1.368444
23	6	0	-6.390745	4.570654	-0.322403
24	6	0	-6.008789	4.181862	0.977444
25	6	0	-4.684925	3.773638	1.233090
26	8	0	-1.451442	4.123053	1.078717
27	8	0	-3.071369	-0.902388	-1.665722
28	6	0	-0.701252	-0.062585	-1.434115
29	8	0	-0.838287	0.313367	-2.792432
30	6	0	0.484409	-0.282200	-0.814676
31	6	0	0.641389	-0.611450	0.684442
32	16	0	1.943537	0.430073	1.499787
33	6	0	3.456939	-0.418023	0.880595
34	6	0	4.277440	0.445585	-0.147763
35	1	0	4.444571	1.486170	0.257703
36	7	0	3.508828	0.665627	-1.439863
37	6	0	3.214409	2.023373	-1.881077
38	6	0	2.858253	3.002553	-0.683588
39	1	0	2.200997	2.425647	0.006999
40	6	0	2.117667	4.277844	-1.218938
41	6	0	1.355165	5.049386	-0.097807

42	6	0	0.657328	6.335878	-0.640469
43	6	0	-0.243212	6.992210	0.452214
44	7	0	-1.026831	8.160587	-0.137486
45	7	0	4.132437	3.285381	0.110352
46	8	0	3.114513	2.309108	-3.099190
47	6	0	5.698375	-0.138154	-0.530643
48	7	0	5.919843	-1.576350	-0.203169
49	6	0	7.358258	-2.045904	-0.336447
50	1	0	7.881982	-1.227849	-0.877536
51	6	0	8.078797	-2.345621	1.027681
52	6	0	9.524786	-2.854817	0.729201
53	6	0	8.101463	-1.093782	1.960439
54	6	0	7.272859	-3.342166	-1.297742
55	8	0	5.980266	-3.503606	-1.793214
56	8	0	8.227772	-4.109944	-1.577244
57	8	0	6.556509	0.497502	-1.184105
58	6	0	-1.186357	-2.299692	2.995505
59	8	0	-0.425153	-3.116121	3.558086
60	6	0	-4.976281	-4.446563	-1.251497
61	6	0	-5.120014	-4.197051	-2.638820
62	6	0	-6.305147	-4.564167	-3.301716
63	6	0	-7.351621	-5.181317	-2.583834
64	6	0	-7.212793	-5.431761	-1.201912
65	6	0	-6.029223	-5.066616	-0.534248
66	1	0	-1.610444	-3.927174	0.748252
67	1	0	-2.191171	-4.851362	2.195150
68	1	0	-3.727307	-2.152798	3.835593
69	1	0	-4.287658	0.131086	2.690790
70	1	0	-2.221496	0.704205	4.136122
71	1	0	-0.916391	0.755016	1.302539
72	1	0	-3.120702	1.576316	-1.505445
73	1	0	-3.670235	1.078771	0.138889
74	1	0	-3.387401	4.133229	-1.936568
75	1	0	-5.739237	4.861453	-2.381119
76	1	0	-7.422983	4.890850	-0.519666
77	1	0	-6.742115	4.198900	1.795350
78	1	0	-4.387413	3.476551	2.248400
79	1	0	-2.834618	-1.910846	-1.563564
80	1	0	1.429853	-0.145355	-1.364041
81	1	0	0.923992	-1.677569	0.817926
82	1	0	3.184333	-1.390461	0.436727
83	1	0	4.106475	-0.612942	1.753803
84	1	0	3.852449	0.074771	-2.239516
85	1	0	1.401303	3.961949	-1.997008
86	1	0	2.853074	4.944093	-1.704836
87	1	0	2.055443	5.330512	0.708707

88	1	0	0.580378	4.394474	0.344765
89	1	0	1.416000	7.059936	-0.986815
90	1	0	0.028192	6.074027	-1.508708
91	1	0	0.388131	7.289379	1.317313
92	1	0	-0.969427	6.234307	0.810344
93	1	0	-0.286477	8.897433	-0.334286
94	1	0	-1.524422	8.585735	0.699981
95	1	0	3.836878	3.925489	0.901197
96	1	0	4.723243	3.918735	-0.500301
97	1	0	5.499010	-1.841117	0.723028
98	1	0	7.518303	-3.154581	1.535630
99	1	0	10.158347	-2.023166	0.385877
100	1	0	9.468227	-3.613738	-0.071694
101	1	0	9.973315	-3.289386	1.634604
102	1	0	8.630717	-0.260385	1.473579
103	1	0	8.624611	-1.337757	2.897504
104	1	0	7.083436	-0.761160	2.213257
105	1	0	5.529271	-2.690692	-1.282759
106	1	0	-4.294426	-3.717048	-3.183562
107	1	0	-6.414887	-4.370633	-4.377508
108	1	0	-8.277308	-5.467944	-3.102296
109	1	0	-8.029346	-5.912152	-0.645677
110	1	0	-5.908479	-5.255647	0.541317
111	1	0	0.132906	0.390690	-3.113500

Table S14. Cartesian coordinates of the optimized structure of grandifloracin (**15**)-Cys151 keto adduct (**21**) calculated at B3LYP/6-31G**(d,p).

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	8	0	-1.355818	4.827134	-1.451461
2	6	0	-1.902443	3.873882	-0.843009
3	8	0	-1.333704	2.562921	-0.738491
4	6	0	-0.086257	2.458609	-1.531554
5	6	0	-0.296487	1.486466	-2.771963
6	8	0	-0.356671	2.360009	-3.950481
7	6	0	-1.583774	0.537982	-2.631054
8	1	0	-2.478749	1.141893	-2.404430
9	6	0	-1.684617	-0.207642	-3.974702
10	6	0	-0.603317	-0.936510	-4.298872
11	6	0	0.480726	-1.011099	-3.204397
12	1	0	1.336305	-1.642356	-3.496681
13	6	0	-0.284346	-1.589554	-1.939585
14	6	0	-1.239642	-0.442593	-1.437049
15	1	0	-0.675273	0.165996	-0.707300
16	6	0	-2.429693	-1.053364	-0.596350
17	6	0	-3.380104	-2.007927	-1.440382
18	8	0	-4.506513	-2.451505	-0.589035
19	6	0	-5.678017	-1.669084	-0.865535
20	6	0	-6.813055	-2.074139	0.082228
21	6	0	-8.076318	-1.454039	-0.076706
22	6	0	-9.144522	-1.794623	0.773009
23	6	0	-8.957290	-2.756821	1.787760
24	6	0	-7.700933	-3.377318	1.951358
25	6	0	-6.630125	-3.038543	1.102745
26	8	0	-5.748537	-0.810023	-1.777873
27	8	0	-3.253316	-0.053085	0.076488
28	6	0	-1.684070	-1.817671	0.597827
29	8	0	-2.061398	-1.474934	1.753138
30	6	0	-0.493888	-2.773331	0.290666
31	6	0	0.544862	-2.137684	-0.719016
32	16	0	1.784179	-3.454407	-1.100487
33	6	0	3.297582	-2.483226	-1.474128
34	6	0	3.851960	-1.511023	-0.365005
35	1	0	3.770360	-1.975110	0.637728
36	7	0	3.066698	-0.238022	-0.388055
37	6	0	2.690187	0.615688	0.683507
38	6	0	3.181256	0.192997	2.133675
39	1	0	3.141100	-0.907282	2.248960
40	6	0	2.281353	0.868982	3.222646
41	6	0	0.962950	0.063953	3.438800

42	6	0	-0.008023	0.756607	4.443335
43	6	0	-1.262733	-0.130253	4.720246
44	7	0	-2.283250	0.643404	5.548377
45	7	0	4.657587	0.577105	2.239570
46	8	0	2.003217	1.659431	0.486353
47	6	0	5.402392	-1.220179	-0.661793
48	7	0	6.120051	-0.753737	0.520817
49	6	0	7.509365	-0.226626	0.228209
50	1	0	7.727772	-0.489464	-0.829769
51	6	0	7.693119	1.320939	0.437399
52	6	0	9.187238	1.691545	0.171869
53	6	0	6.732069	2.143296	-0.477651
54	6	0	8.470756	-1.101960	1.191019
55	8	0	7.736675	-2.116309	1.791686
56	8	0	9.701586	-0.912880	1.378579
57	8	0	5.947613	-1.417368	-1.774430
58	6	0	0.938296	0.465474	-2.869445
59	8	0	2.126935	0.809314	-2.641245
60	6	0	-3.237585	3.921610	-0.091852
61	6	0	-3.810182	5.193204	0.159744
62	6	0	-5.038169	5.297633	0.836333
63	6	0	-5.703704	4.128524	1.260617
64	6	0	-5.138869	2.862458	1.002779
65	6	0	-3.906768	2.744010	0.327489
66	1	0	0.731203	2.098952	-0.849829
67	1	0	0.164742	3.468579	-1.923563
68	1	0	-0.586779	1.690021	-4.696432
69	1	0	-2.565778	-0.089258	-4.618760
70	1	0	-0.484056	-1.504798	-5.230685
71	1	0	-0.886811	-2.429854	-2.325660
72	1	0	-3.781327	-1.443188	-2.309082
73	1	0	-2.851940	-2.919424	-1.783155
74	1	0	-8.203320	-0.706506	-0.872861
75	1	0	-10.123083	-1.311665	0.646399
76	1	0	-9.791123	-3.023089	2.452050
77	1	0	-7.557103	-4.125784	2.742608
78	1	0	-5.647123	-3.514425	1.221460
79	1	0	-3.057212	-0.353634	1.061676
80	1	0	0.001453	-3.040352	1.240130
81	1	0	1.065968	-1.296623	-0.227907
82	1	0	3.196087	-1.900673	-2.407048
83	1	0	4.073926	-3.244508	-1.663944
84	1	0	2.830450	0.134315	-1.357887
85	1	0	2.048251	1.895274	2.888050
86	1	0	2.840017	0.928806	4.173289
87	1	0	1.215750	-0.944874	3.809773

88	1	0	0.448338	-0.060226	2.470415
89	1	0	0.518121	0.953961	5.394014
90	1	0	-0.332838	1.728766	4.034329
91	1	0	-0.936594	-1.074018	5.208473
92	1	0	-1.741515	-0.405720	3.759846
93	1	0	-1.818469	0.751890	6.498000
94	1	0	-3.035735	-0.074879	5.765888
95	1	0	4.968694	0.350619	3.223690
96	1	0	4.717016	1.630227	2.182509
97	1	0	5.500655	-0.142027	1.246585
98	1	0	7.457772	1.552963	1.493928
99	1	0	9.403618	1.654470	-0.906428
100	1	0	9.821305	0.947300	0.688461
101	1	0	9.407838	2.704329	0.540156
102	1	0	6.943599	1.938711	-1.538401
103	1	0	6.869003	3.220816	-0.298392
104	1	0	5.680098	1.889580	-0.278557
105	1	0	6.781765	-1.839372	1.375439
106	1	0	-3.276944	6.091920	-0.181825
107	1	0	-5.476959	6.285211	1.032922
108	1	0	-6.664156	4.205524	1.788963
109	1	0	-5.666952	1.956271	1.330316
110	1	0	-3.486415	1.728963	0.122802
111	1	0	-0.905036	-3.700521	-0.152544

Table S15. Binding energy (kcal/mol) results of the top scoring compounds **8, 14, 15** and **16**.

Complex Name	MMGBSA				
	ΔvdW	Δelec	Δps	ΔSASA	ΔG Total
3-(3,4-dihydroxy benzyl)-3',4',6-trihydroxy-2,4-di methoxychalcone (8)-AChE	-62.35	-15.12	40.45	-34.69	-77.46
bractelactone (14)-PDE4 B2B	-54.83	-11.80	12.27	-31.03	-66.64
grandifloracin (15)-KEAP1 (BTB)	-54.37	-8.21	22.24	-29.14	-48.41
dichamanetin (16)-KEAP1 (Kelch)	-50.57	-5.19	30.02	-27.68	-55.76
dichamanetin (16)-USP14	-66.60	-17.38	37.30	-31.94	-83.98

vdW = van der Waals energy; **elec**= electrostatic energy; **ps** = polar solvation energy; **SASA** = solvent-accessible surface area energy; **G Total** = total binding free energy; **MMGBSA** = molecular mechanics generalized Born solvent accessibility

Table S16. Input parameters for molecular dynamics simulation used in this study.

Minimization 1 Initial minimization of MMP3 (MMMM): solvent molecules and added ions &cntrl imin = 1, maxcyc = 6000, ncyc = 3000, ntb = 1, ntr = 1, cut = 12.0, /	**Minimization 2** Full minimization of MMP3 (MMMM): protein, ligand, solvent molecules and added ions &cntrl imin = 1, maxcyc = 3000, ncyc = 1000, ntb = 1, ntr = 0, cut = 12.0, Drms = 0.0001, / END	**Heating** Heating Step of MMP3 (MMMM): stage-5 &cntrl imin= 0, irest=1, NTX=1, ntb= 1, NTPR=500, NTWX=500, NTWR=500, ntr=1, Tempi=0.0, Temp0=300.0, NTT=3, gamma_ln=1.0, NTC=2, NTF=2, cut= 12.0, nstlim=10000, dt=0.002, /
Equilibration Equilibration Step of MMP3 (MMMM): stage-1 &cntrl imin= 0, irest=1, NTX=7, ntb=2, ntp=1, PRES0=1.0, TAUP=2.0, NTPR=500, NTWX=500, ntr=0, Tempi=300.0, Temp0=300.0, NTT=3, gamma_ln=1.0, NTC=2, NTF=2, cut=12.0, nstlim=250000, dt=0.002 /	**Production** Equilibration Step of MMP3 (MMMM): stage-1 &cntrl imin= 0, irest=0, ig=-1, NTX=7, ntxo=2, ioutfm=1, ntb=2, ntp=1, PRES0=1.0, TAUP=2.0, NTPR=500, NTWX=500, ntr=0, Tempi=300.0, Temp0=300.0, NTT=3, gamma_ln=1.0, NTC=2, NTF=2, cut=12.0, nstlim=2500000, dt=0.002 /	

Table S17. The hydrogen bonding occupancy of the key residues during the course of simulation. Each residue bonding is given in percentage trajectories.

Complex name	Residues & H-Bonding lifetime					
Bractelactone_PDE4B2B	**Tyr233**	**His238**	**His274**	**Asn283**	**Met347**	*******
	0.89	0.82	0.47	0.62	0.77	***
Dimethoxychalcone_AChE	**Asp74**	**Tyr124**	**Glu202**	**Ser293**	**Arg296**	*******
	0.69	0.33	0.82	0.92	0.69	*******
Dichamanetin_KEAP1-KELCH	**Ser363**	**Asn414**	**Arg415**	**Tyr436**	***	***
	0.26	0.56	0.54	0.94	***	***
Grandifloracin_KEAP1-BTB	**Ala88**	**His129**	**Pro130**	**Lys131**	**Arg135**	***
	0.28	0.66	0.70	0.83	0.52	***
Dichamanetin_USP14	**Arg415**	**Ile416**	**His426**	***	***	***
	0.67	0.73	0.52	***	***	***

Table S18. Lipinski's rule of five for ADME analysis of compounds **1–18.**

Compound	Lipinski's Rule of Five					Drug-likeness
	Molecular weight (g/mol)	Lipophilicity (MLogP)	H-bond donors	H-bond acceptors	Rule violations	
	< 500	< 5	< 5	< 10	< 2	
1	266.25	2.88	0	4	0	yes
2	408.40	2.62	0	7	0	yes
3	386.40	1.84	3	7	0	yes
4	386.40	1.84	3	7	0	yes
5	302.28	0.89	0	6	0	yes
6	310.34	3.83	0	4	0	yes
7	436.45	1.00	1	7	0	yes
8	438.43	1.26	5	8	1	yes
9	446.88	3.22	1	7	0	yes
10	314.33	1.75	1	5	0	yes
11	422.43	0.80	2	7	0	yes
12	376.40	2.33	2	5	0	yes
13	528.55	3.75	0	8	1	yes
14	416.42	2.60	2	6	0	yes
15	488.49	1.89	2	8	0	yes
16	468.50	2.79	4	6	0	yes
17	390.86	2.66	2	5	0	yes
18	436.45	1.00	1	7	0	yes

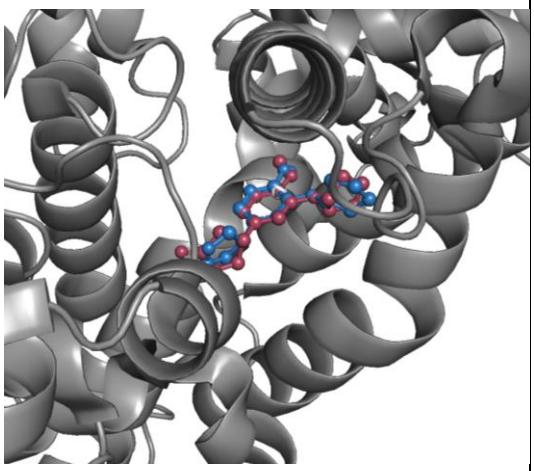
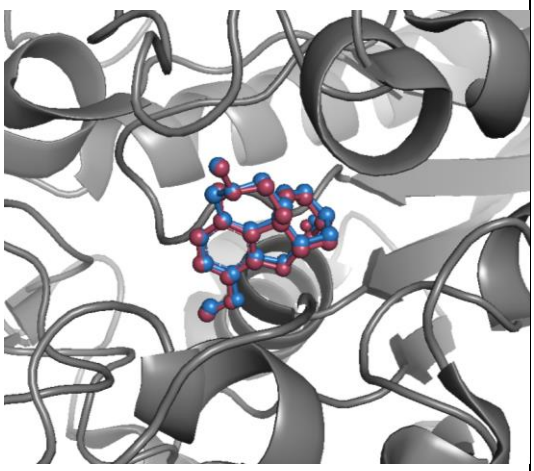
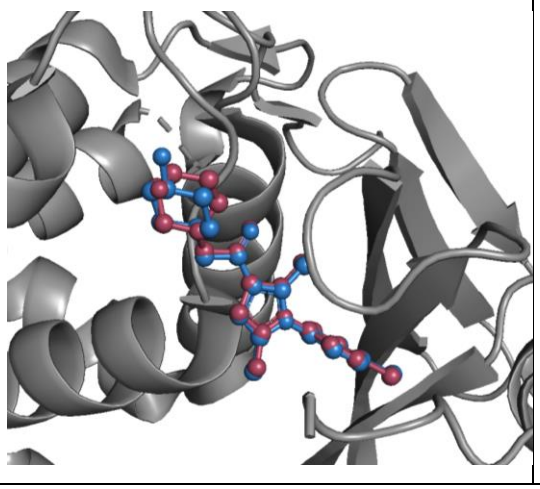
Table S19. Predicted toxicity parameters of compounds **1–18**.

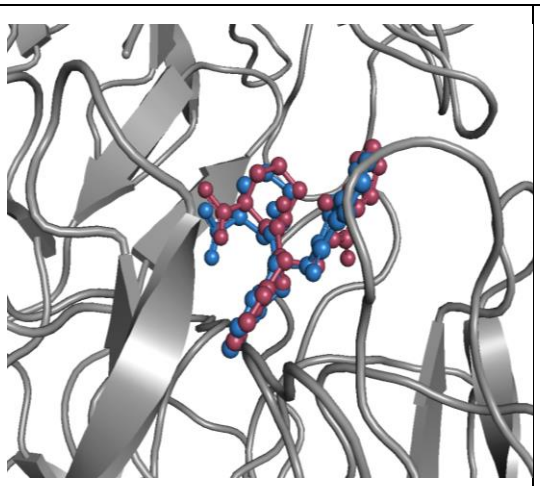
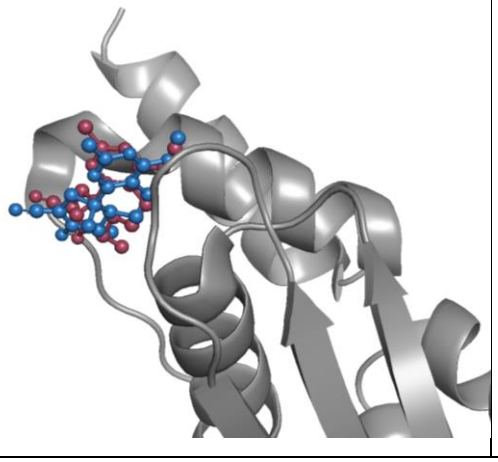
Compound	Mutagenicity	Tumorigenicity	Irritant Effect	Reproductive Toxicity
1	None	None	None	High Risk
2	None	None	None	High Risk
3	None	None	High Risk	Medium Risk
4	None	None	High Risk	Medium Risk
5	None	None	High Risk	None
6	None	None	High Risk	None
7	None	None	None	None
8	None	None	None	None
9	None	None	High Risk	High Risk
10	None	None	None	None
11	None	None	None	None
12	None	Medium Risk	None	Medium Risk
13	None	None	High Risk	None
14	None	None	None	High Risk
15	None	None	High Risk	Medium Risk
16	None	Medium Risk	None	Medium Risk
17	None	None	High Risk	High Risk
18	None	None	None	None

Table S20. Docking grid coordinates and active residues of the protein binding site.

Enzyme (PDB ID)	Coordinates			Active Residues
	x	y	z	
PDE4B (1RO6)	33.0	75.0	23.0	Tyr 233, His234, His238, His274, Asp275, Asp392, Ans395, Tyr403, Ile410, Glu413, Gln443,
AChE (4EY6)	-10.0	-43.0	30.0	Trp86, Glu202, Ser203, Gly120, Gly121, Gly122, Phe295, Phe297, Tyr337, His447
USP14 (6IIM)	-18.0	18.0	-4.0	His426, Tyr436, and Tyr476
KEAP1-Kelch (4L7B)	-2.0	5.0	-29.0	Tyr334, Ser 363, Arg380, Asn414, Arg415, Ser 508, Ser555, Tyr572, Ser602
KEAP1-BTB (5DAD)	-25.0	-5.0	10.0	His129, Lys131, Arg135, His154, Cys151

Table S21. RMSD analysis of co-crystallized ligand and its re-docked structure.

Enzyme (PDB ID)	Co-cystallized Ligand		Superimposition of Co-crystal (blue) and Re-docked (red) Structures	RMSD (Å)
	Code	Name		
PDE4B (1RO6)	ROL	Rolipram		0.839
AChE (4EY6)	GNT	(-)-Galantamine		0.157
USP14 (6IIM)	A8L	1-[1-(4-chlorophenyl)-2,5-dimethyl-1H-pyrrol-3-yl]-2-(4-hydroxypiperidin-1-yl)ethan-1-one		0.495

KEAP1 -Kelch (4L7B)	1VV	(1S,2R)-2-{[(1S)-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl) methyl]-3,4-dihydroisoquinolin-2(1H)yl]carbonyl}cyclo hexanecarboxylic acid		1.511
KEAP1 -BTB (5DAD)	TX6	(6aS,7S,10aS)-8-hydroxy-4-methoxy-2,7,10a-trimethyl-5,6,6a,7,10,10a-hexahydrobenzo[h] quinazoline-9-carbonitrile		0.473

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