SUPPLEMENTARY DATA

Evaluation of *Taraxacum officinale* phytoconstituents as potential JNK1 inhibitors: perspectives from ADMET, molecular docking, molecular dynamics, and Density Functional Theory

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1. Flavonol backbone positions

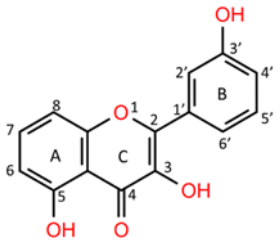

Figure S1: Flavonol backbone atom position numbering

2. Native ligand alignment

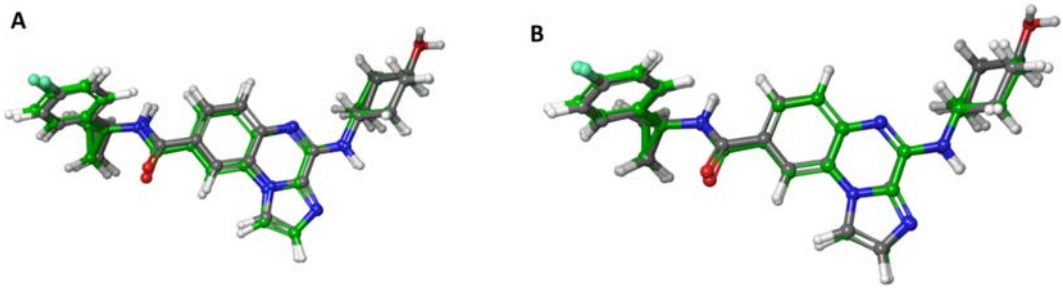

Figure S2: AX13587 ligand alignments (undocked ligand grey) A) Glide XP, B) QPLD

3. Detailed hydrophobic interactions in SP.

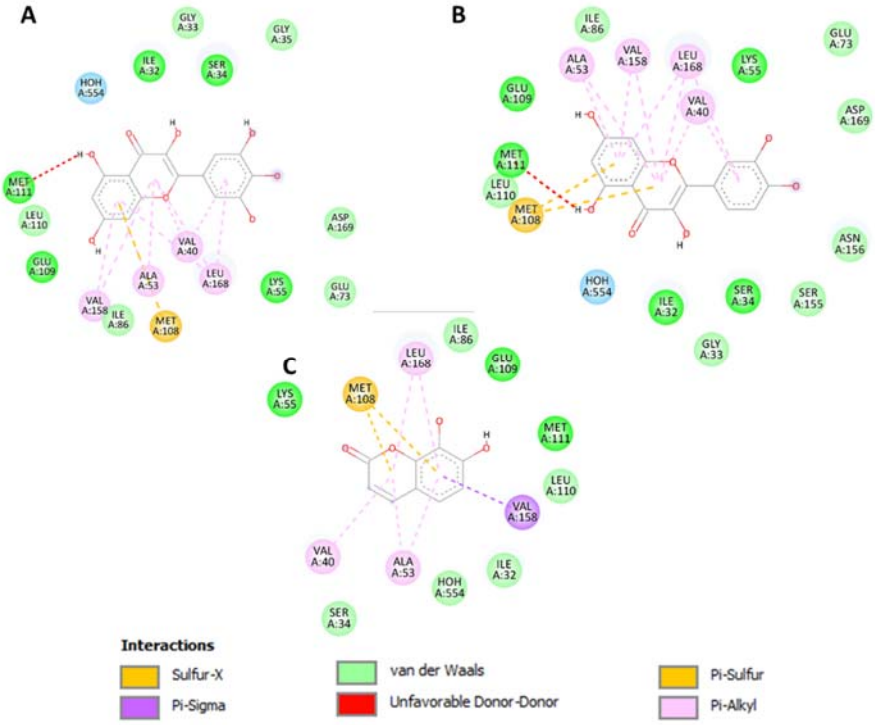

Figure S3: Hydrophobic and charge-charge interactions in SP

4. Detailed hydrophobic interactions in XP.

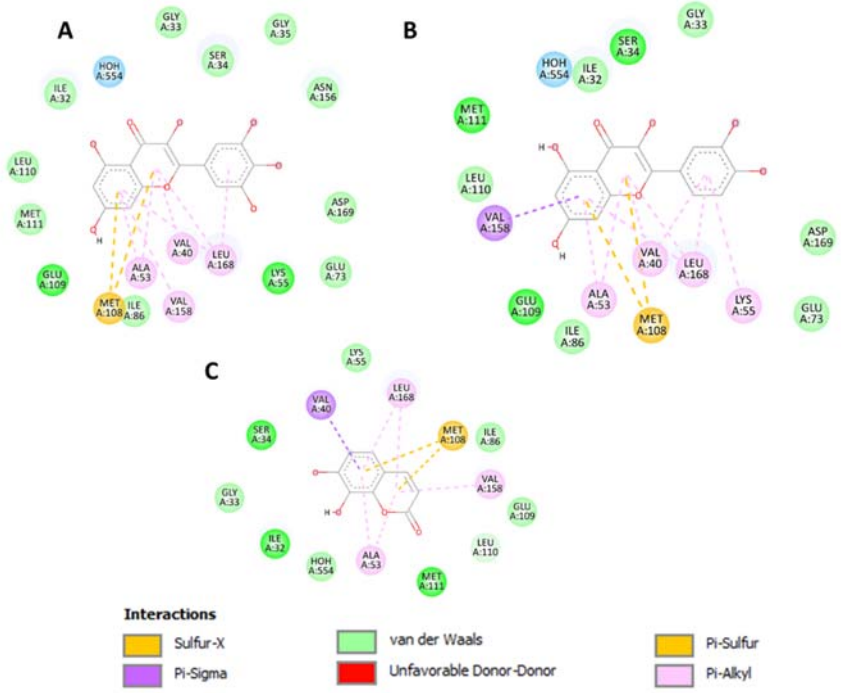

Figure S4: Hydrophobic and charge-charge interactions in XP

5. Detailed hydrophobic interactions in QPLD

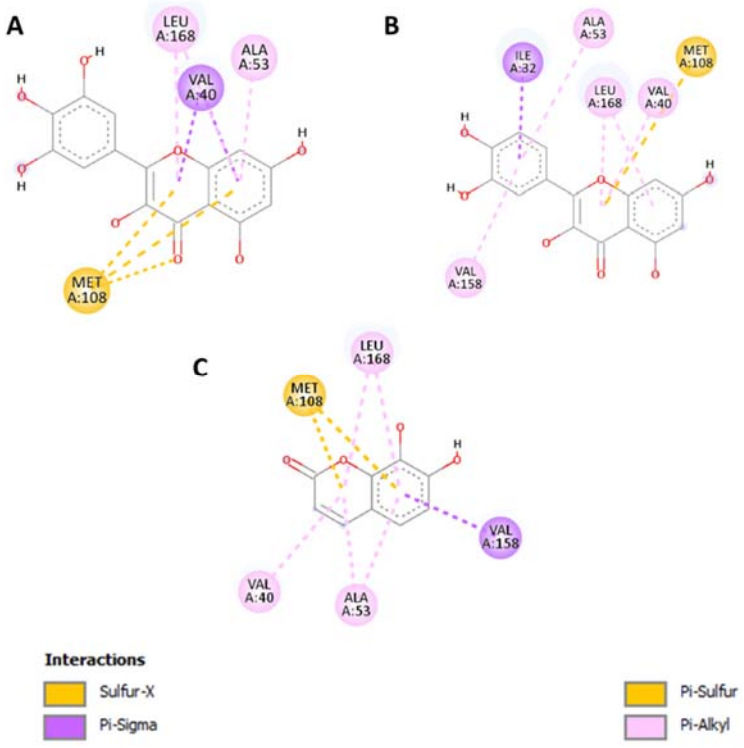

Figure S5: Hydrophobic and charge-charge interactions in QPLD

6. RMSD calculations for Glide XP and QPLD docking.

Table S1: Docking RMSD of AX13587 co-crystalized ligand.

Docking	**Glide XP**	**QPLD**
Schrodinger RMSD	0.281	0.1597
DockRMSD v1.1	0.283	0.171
Total # of Possible Mappings	6912	6912
	F 1 -> F 4 *	F 1 -> F 4 *
	C 2 -> C 3 *	C 2 -> C 3 *
	C 3 -> C 5 *	C 3 -> C 5 *
	C 4 -> C 6 *	C 4 -> C 6 *
	C 5 -> C 2 *	C 5 -> C 2 *
	C 6 -> C 1 *	C 6 -> C 1 *
	C 7 -> C 7	C 7 -> C 7
	C 8 -> C 8	C 8 -> C 8
	C 9 -> C 9	C 9 -> C 10 *
	C 10 -> C 10	C 10 -> C 9 *
	N 11 -> N 11	N 11 -> N 11
	C 12 -> C 12	C 12 -> C 12
	O 13 -> O 13	O 13 -> O 13
	C 14 -> C 14	C 14 -> C 14
	C 15 -> C 16 *	C 15 -> C 16 *
	C 16 -> C 17 *	C 16 -> C 17 *
	C 17 -> C 15 *	C 17 -> C 15 *
	C 18 -> C 19 *	C 18 -> C 19 *
	N 19 -> N 20 *	N 19 -> N 20 *
	C 20 -> C 21 *	C 20 -> C 21 *
	N 21 -> N 24 *	N 21 -> N 24 *
	C 22 -> C 23 *	C 22 -> C 23 *
	C 23 -> C 22 *	C 23 -> C 22 *
	C 24 -> C 26 *	C 24 -> C 26 *
	N 25 -> N 25	N 25 -> N 25
	C 26 -> C 18 *	C 26 -> C 18 *
	N 27 -> N 27	N 27 -> N 27
	C 28 -> C 28	C 28 -> C 28
	C 29 -> C 29	C 29 -> C 29
	C 30 -> C 30	C 30 -> C 30
	C 31 -> C 34 *	C 31 -> C 34 *
	C 32 -> C 33 *	C 32 -> C 33 *
	C 33 -> C 31 *	C 33 -> C 31 *
	O 34 -> O 32 *	O 34 -> O 32 *

Optimal mapping (First file -> Second file, * indicates correspondence is not one-to-one)

7. MMGSA energies for Glide XP and QPLD.

Table S2: Binding free-energy calculation of identified top hit molecules against 4L7F.

CID	Binding free energy(kcal/mol) (Glide XP)							Binding free energy(kcal/mol) (Glide QPLD)						
	ΔG_{Bind}	$\Delta G_{Coul.}$	$\Delta G_{Cov.}$	ΔG_{Hbond}	ΔG_{Lipo}	ΔG_{SolvGB}	ΔG_{vdW}	ΔG_{Bind}	$\Delta G_{Coul.}$	$\Delta G_{Cov.}$	ΔG_{Hbond}	ΔG_{Lipo}	ΔG_{SolvGB}	ΔG_{vdW}
5281672	-31.00	-20.78	3.74	-2.77	-7.77	30.42	-32.78	-39.58	-27.24	4.97	-3.79	-3.05	24.70	-34.39
5280343	-40.88	-27.60	2.20	-3.04	-10.30	24.16	-24.98	-44.65	-28.75	3.01	-2.99	-11.72	24.22	-27.44
5280569	-39.77	-9.97	0.43	-1.93	-13.31	7.78	-22.78	-35.62	-10.84	-0.23	-1.20	-6.62	10.59	-27.33
6508	-9.37	-7.09	0.58	-2.08	-3.12	27.54	-25.20	-6.57	-24.97	2.86	-2.71	-1.08	40.81	-21.48
525	11.20	62.74	1.73	-1.62	-3.34	-36.51	-11.79	0.33	38.93	2.31	-1.38	-1.74	-14.88	-29.91
4091*	-17.07	-44.09	1.89	-1.49	-3.80	47.54	-17.11	-18.88	-29.41	1.65	-1.05	-2.32	32.52	-20.26

*Metformin

8. Corrected metformin MD per-residue protein contacts

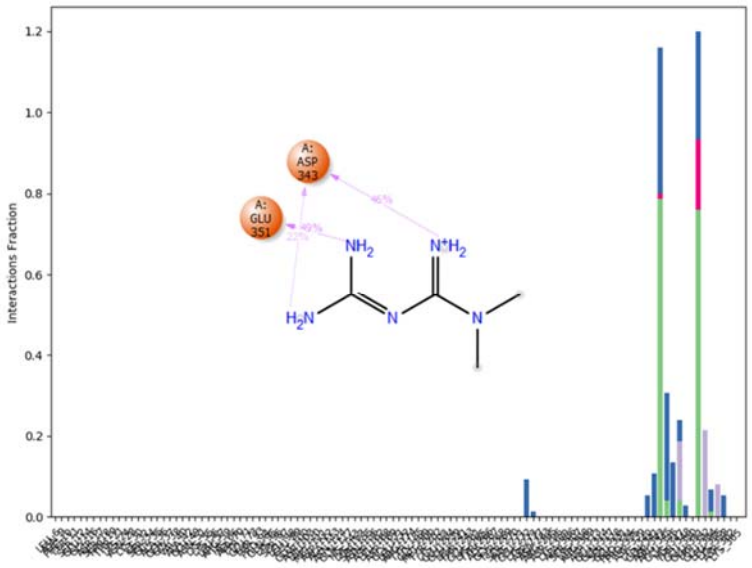

Figure S6: Metformin MD for 10ns (frames 900 to 1001).

9. Binding pockets and crevices data

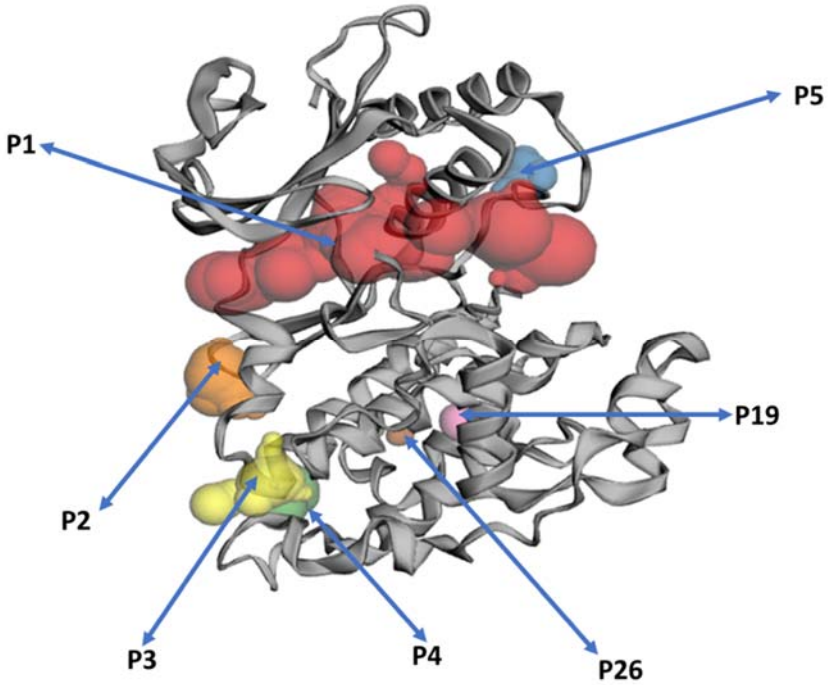

Figure S7: 4L7F significant five pockets and two minor pockets.

Table S3: Richards surface areas and volumes for selected 4L7F pockets and crevices.

Pocket	Size (Å)	Volume (Å^3)
1	659.344	468.079
2	53.497	27.114
3	65.192	23.751
4	46.469	22.120
5	37.763	10.410
19	9.570	1.055
26	3.152	0.267

10. Geometric parameters of myricetin (CID 5281672)

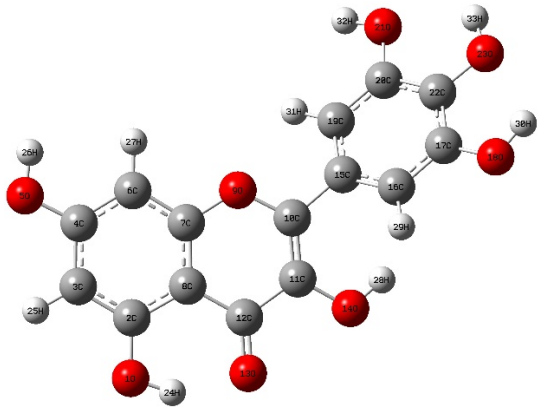

Figure S8: Optimized geometry of myricetin (CID 5281672)

Table S4 Optimized properties of myricetin (CID 5281672) structure

Atoms	Bond Length (Å)	Atoms	Angle (°)	Atoms	Dihedral (°)
C(8)C(7)	1.399	C(2)C(8)C(7)	117.914	C(12)C(8)C(2)C(7)	120.398
C(2)C(8)	1.421	C(12)C(8)C(2)	121.678	C(11)C(12)C(8)C(2)	179.214
C(12)C(8)	1.447	C(11)C(12)C(8)	115.189	C(6)C(7)C(8)C(2)	0.243
C(11)C(12)	1.457	C(6)C(7)C(8)	122.637	O(9)C(7)C(6)C(8)	120.652
C(6)C(7)	1.388	O(9)C(7)C(6)	116.709	C(4)C(6)C(7)C(8)	-0.122
O(9)C(7)	1.353	C(4)C(6)C(7)	117.672	C(3)C(2)C(8)C(7)	-0.26
C(4)C(6)	1.39	C(3)C(2)C(8)	120.373	C(10)O(9)C(7)C(6)	179.803
C(3)C(2)	1.381	C(10)O(9)C(7)	120.989	C(15)C(10)O(9)C(11)	125.193
C(10)O(9)	1.358	C(15)C(10)O(9)	112.573	C(16)C(15)C(10)O(9)	138.273
C(15)C(10)	1.472	C(16)C(15)C(10)	120.179	C(19)C(15)C(10)C(16)	120.685
C(16)C(15)	1.396	C(19)C(15)C(10)	119.135	C(17)C(16)C(15)C(10)	179.681
C(19)C(15)	1.398	C(17)C(16)C(15)	119.529	C(20)C(19)C(15)C(10)	-179.606
C(17)C(16)	1.39	C(20)C(19)C(15)	119.179	C(22)C(17)C(16)C(15)	0.117
C(20)C(19)	1.386	C(22)C(17)C(16)	120.076	O(1)C(2)C(3)C(8)	120.428
C(22)C(17)	1.392	O(1)C(2)C(3)	119.199	O(5)C(4)C(3)C(6)	121.892
O(1)C(2)	1.341	O(5)C(4)C(3)	116.222	O(13)C(12)C(8)C(11)	121.806
O(5)C(4)	1.35	O(13)C(12)C(8)	123.001	O(14)C(11)C(10)C(12)	114.894
O(13)C(12)	1.239	O(14)C(11)C(10)	124.585	O(18)C(17)C(16)C(22)	120.205
O(14)C(11)	1.356	O(18)C(17)C(16)	119.715	O(21)C(20)C(19)C(22)	114.561
O(18)C(17)	1.355	O(21)C(20)C(19)	124.947	O(23)C(22)C(17)C(20)	122.394
O(21)C(20)	1.36	O(23)C(22)C(17)	117.572	H(25)C(3)C(2)C(4)	120.124
O(23)C(22)	1.357	H(25)C(3)C(2)	120.359	H(27)C(6)C(4)C(7)	120.183
H(25)C(3)	1.082	H(27)C(6)C(4)	122.145	H(29)C(16)C(15)C(17)	118.694
H(27)C(6)	1.082	H(29)C(16)C(15)	121.713	H(31)C(19)C(15)C(20)	120.235
H(29)C(16)	1.084	H(31)C(19)C(15)	120.584	H(24)O(1)C(2)C(3)	179.231
H(31)C(19)	1.083	H(24)O(1)C(2)	107.648	H(26)O(5)C(4)C(3)	-179.611

H(24)O(1)	0.983	H(26)O(5)C(4)	110.689	H(28)O(14)C(11)C(10)	-12.258
H(26)O(5)	0.964	H(28)O(14)C(11)	110.223	H(30)O(18)C(17)C(16)	-178.531
H(28)O(14)	0.966	H(30)O(18)C(17)	109.171	H(32)O(21)C(20)C(19)	0.011
H(30)O(18)	0.966	H(32)O(21)C(20)	111.277	H(33)O(23)C(22)C(17)	-178.274
H(32)O(21)	0.963	H(33)O(23)C(22)	109.637		
H(33)O(23)	0.966				

Table S5: Fukui indices and NPA charges of myricetin (CID 5281672)

Atom	NPA N0	NPA N+1	NPA N-1	f^-	f^+	f^0	$f^{(2)}$
O1	0.7069	-0.7431	-0.6853	0.0216	0.0362	0.0289	0.0146
C2	0.4052	0.3466	0.4225	0.0173	0.0586	0.0379	0.0413
C3	-0.345	-0.3627	-0.3322	0.0128	0.0177	0.0153	0.0049
C4	0.3847	0.3327	0.4008	0.0161	0.052	0.0341	0.0359
O5	-0.6845	-0.7061	-0.6705	0.014	0.0216	0.0178	0.0076
C6	-0.367	-0.3863	-0.3344	0.0326	0.0193	0.026	-0.0132
C7	0.4006	0.3752	0.3952	-0.0054	0.0254	0.01	0.02
C8	-0.2845	-0.2555	-0.2773	0.0072	-0.029	0.0109	0.0218
O9	-0.4946	-0.5438	-0.4704	0.0242	0.0492	0.0367	0.025
C10	0.3184	0.1648	0.3379	0.0195	0.1536	0.0865	0.1341
C11	0.1865	0.1927	0.3196	0.1331	-0.0063	0.0634	-0.1268
C12	0.4967	0.2997	0.4852	-0.0115	0.197	0.0927	0.1855
O13	-0.6772	-0.8207	-0.624	0.0532	0.1435	0.0983	0.0903
O14	-0.6908	-0.7133	-0.6079	0.0829	0.0226	0.0527	-0.0604
C15	-0.1029	-0.0843	-0.017	0.0859	-0.0186	0.0336	-0.0673
C16	-0.2709	-0.3136	-0.2551	0.0158	0.0427	0.0292	0.0268
C17	0.2924	0.2914	0.3267	0.0342	0.001	0.0176	-0.0332
O18	-0.6948	-0.7047	-0.6532	0.0416	0.0098	0.0257	-0.0318
C19	-0.2584	-0.3005	-0.2199	0.0385	0.042	0.0403	0.0035
C20	0.2822	0.2806	0.3047	0.0225	0.0017	0.0121	-0.0208
O21	-0.7126	-0.7216	-0.6845	0.028	0.009	0.0185	-0.019
C22	0.2246	0.1748	0.3489	0.1243	0.0499	0.0871	-0.0744
O23	-0.7121	-0.727	-0.6328	0.0793	0.0149	0.0471	-0.0644
H24	0.5183	0.5175	0.5199	0.0016	0.0008	0.0012	-0.0008
H25	0.2437	0.2278	0.2515	0.0078	0.0158	0.0118	0.008
H26	0.4975	0.4895	0.5013	0.0038	0.008	0.0059	0.0042
H27	0.2453	0.2298	0.2539	0.0086	0.0155	0.012	0.007
H28	0.5011	0.4908	0.5145	0.0134	0.0103	0.0118	-0.0031
H29	0.2403	0.2291	0.2595	0.0193	0.0111	0.0152	-0.0081
H30	0.5035	0.4997	0.5115	0.0081	0.0037	0.0059	-0.0043
H31	0.2391	0.2278	0.2597	0.0205	0.0113	0.0159	-0.0092
H32	0.508	0.5038	0.5203	0.0123	0.0042	0.0082	-0.0081
H33	0.5144	0.5092	0.5315	0.017	0.0053	0.0112	-0.0117

Table S6: NBO analysis of myricetin (CID 5281672)

Donor(i)	ED(i)	Acceptor(j)	ED(j)	E^2 (kcal/mol)	E_j-E_i (a.u.)	F(i,j) (a.u.)
η_2 (O_1)	1.8446	π^* C_2-C_3	0.3374	48.12	0.44	0.130
η_2 (O_5)	1.8673	π^* C_4-C_6	0.3882	44.01	0.45	0.126
η_2 (O_9)	1.7636	π^* C_7-C_8	0.4636	41.79	0.45	0.123
η_2 (O_9)	1.7636	π^* C_{10}-C_{11}	0.2493	36.71	0.48	0.118
η_2 (O_{13})	1.8827	σ^* O_1-H_{24}	0.0455	18.47	0.85	0.112
η_2 (O_{13})	1.8827	σ^* C_8-C_{12}	0.0508	16.60	0.90	0.109
η_2 (O_{13})	1.8827	σ^* C_{11}-C_{12}	0.0609	22.08	0.88	0.124
η_2 (O_{14})	1.8971	π^* C_{10}-C_{11}	0.2493	34.58	0.46	0.113
η_2 (O_{18})	1.8838	π^* C_{17}-C_{22}	0.4140	38.62	0.45	0.117
η_2 (O_{21})	1.8927	π^* C_{19}-C_{20}	0.3930	36.84	0.46	0.116
η_2 (O_{23})	1.8922	π^* C_{17}-C_{22}	0.4140	33.80	0.45	0.111
π C_2-C_3	1.6985	π^* C_4-C_6	0.3882	39.54	0.35	0.106
π C_2-C_3	1.6985	π^* C_7-C_8	0.4636	18.18	0.34	0.070
π C_4-C_6	1.6756	π^* C_2-C_3	0.3374	16.04	0.36	0.068
π C_4-C_6	1.6756	π^* C_7-C_8	0.4636	44.71	0.34	0.110
π C_7-C_8	1.6511	π^* C_2-C_3	0.3374	31.21	0.37	0.096
π C_7-C_8	1.6511	π^* C_4-C_6	0.3882	15.67	0.36	0.067
π C_7-C_8	1.6511	π^* C_{12}-O_{13}	0.3360	39.37	0.35	0.105
π C_{10}-C_{11}	1.8160	π^* C_{12}-O_{13}	0.3360	30.65	0.39	0.097
π C_{15}-C_{16}	1.7131	π^* C_{10}-C_{11}	0.2493	10.64	0.37	0.056
π C_{15}-C_{16}	1.7131	π^* C_{17}-C_{22}	0.4140	29.29	0.36	0.091
π C_{15}-C_{16}	1.7131	π^* C_{19}-C_{20}	0.3930	22.84	0.36	0.081
π C_{17}-C_{22}	1.6274	π^* C_{15}-C_{16}	0.4313	27.20	0.36	0.089
π C_{17}-C_{22}	1.6274	π^* C_{19}-C_{20}	0.3930	31.60	0.36	0.096
π C_{19}-C_{20}	1.6801	π^* C_{15}-C_{16}	0.4313	32.41	0.36	0.096
π C_{19}-C_{20}	1.6801	π^* C_{17}-C_{22}	0.4140	24.86	0.36	0.084

11. Geometric parameters of quercetin (CID 5280343)

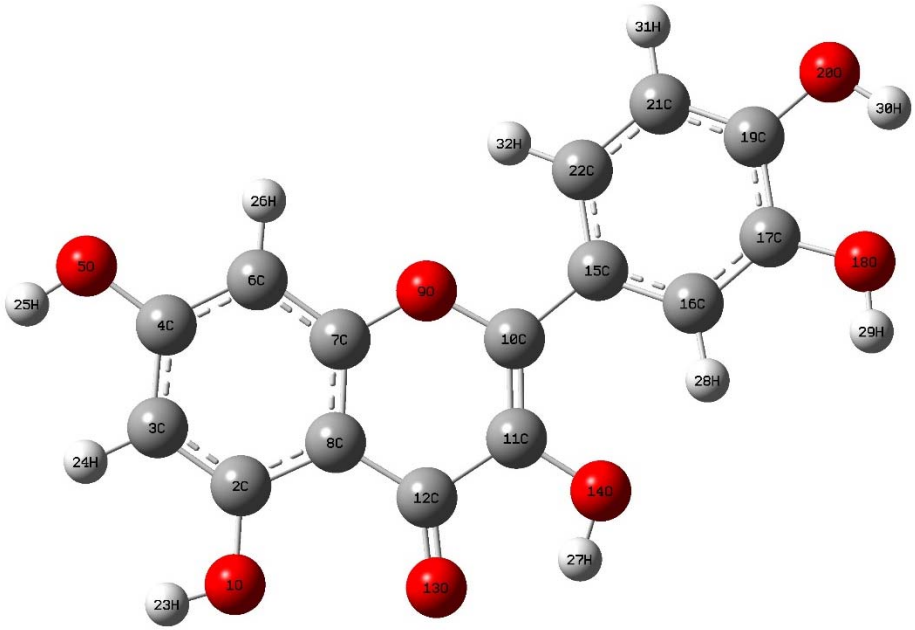

Figure S9: Optimized geometry of quercetin (CID 5280343)

Table S7: Optimized properties of quercetin (CID 5280343) structure

Atoms	Bond Length (Å)	Atoms	Angle (°)	Atoms	Dihedral (°)
C(8)C(7)	1.405	C(2)C(8)C(7)	117.035	C(12)C(8)C(2)C(7)	118.476
C(2)C(8)	1.418	C(12)C(8)C(2)	124.488	C(6)C(7)C(8)C(2)	-0.403
C(12)C(8)	1.452	C(6)C(7)C(8)	123.018	O(9)C(7)C(6)C(8)	121.686
C(6)C(7)	1.389	O(9)C(7)C(6)	115.296	C(3)C(2)C(8)C(7)	0.442
O(9)C(7)	1.35	C(3)C(2)C(8)	120.747	C(4)C(6)C(7)C(8)	0.061
C(3)C(2)	1.383	C(4)C(6)C(7)	118.066	C(10)O(9)C(7)C(6)	-179.702
C(4)C(6)	1.385	C(10)O(9)C(7)	122.42	C(11)C(12)C(8)C(2)	-179.772
C(10)O(9)	1.363	C(11)C(12)C(8)	115.56	C(15)C(10)O(9)C(11)	128.148
C(11)C(12)	1.465	C(15)C(10)O(9)	112.271	C(16)C(15)C(10)O(9)	167.908
C(15)C(10)	1.468	C(16)C(15)C(10)	121.422	C(22)C(15)C(10)C(16)	118.984
C(16)C(15)	1.405	C(22)C(15)C(10)	119.592	C(17)C(16)C(15)C(10)	-179.745
C(22)C(15)	1.399	C(17)C(16)C(15)	119.943	C(19)C(17)C(16)C(15)	0.02
C(17)C(16)	1.382	C(19)C(17)C(16)	120.788	C(21)C(22)C(15)C(10)	179.86
C(19)C(17)	1.401	C(21)C(22)C(15)	120.669	O(1)C(2)C(3)C(8)	117.899
C(21)C(22)	1.389	O(1)C(2)C(3)	121.355	O(5)C(4)C(3)C(6)	117.194
O(1)C(2)	1.347	O(5)C(4)C(3)	121.596	O(14)C(11)C(10)C(12)	114.631
O(5)C(4)	1.35	O(14)C(11)C(10)	123.092	O(18)C(17)C(16)C(19)	114.797
O(14)C(11)	1.352	O(18)C(17)C(16)	124.414	O(20)C(19)C(17)C(21)	120.192
O(18)C(17)	1.365	O(20)C(19)C(17)	120.404	O(13)C(12)C(8)C(11)	117.413
O(20)C(19)	1.355	O(13)C(12)C(8)	127.025	H(24)C(3)C(2)C(4)	120.168

O(13)C(12)	1.231	H(24)C(3)C(2)	119.909	H(26)C(6)C(4)C(7)	120.58
H(24)C(3)	1.085	H(26)C(6)C(4)	121.354	H(28)C(16)C(15)C(17)	119.214
H(26)C(6)	1.081	H(28)C(16)C(15)	120.841	H(31)C(21)C(19)C(22)	120.924
H(28)C(16)	1.082	H(31)C(21)C(19)	118.866	H(32)C(22)C(15)C(21)	119.38
H(31)C(21)	1.083	H(32)C(22)C(15)	119.95	H(23)O(1)C(2)C(3)	-0.019
H(32)C(22)	1.081	H(23)O(1)C(2)	109.731	H(25)O(5)C(4)C(3)	-0.269
H(23)O(1)	0.964	H(25)O(5)C(4)	110.862	H(27)O(14)C(11)C(10)	-179.381
H(25)O(5)	0.964	H(27)O(14)C(11)	105.01	H(29)O(18)C(17)C(16)	0.771
H(27)O(14)	0.974	H(29)O(18)C(17)	111.169	H(30)O(20)C(19)C(17)	0.061
H(29)O(18)	0.963	H(30)O(20)C(19)	108.838		
H(30)O(20)	0.966				

Table S8: Fukui indices and NPA charges of optimized quercetin (CID 5280343) structure.

Atom	NPA N0	NPA N+1	NPA N-1	f^-	f^+	f^0	$f^{(2)}$
O1	-0.6684	-0.6867	-0.6575	0.0109	0.0183	0.0146	0.0074
C2	0.4196	0.3542	0.4369	0.0174	0.0654	0.0414	0.048
C3	-0.3839	-0.4014	-0.3729	0.011	0.0175	0.0143	0.0065
C4	0.3826	0.333	0.402	0.0193	0.0496	0.0345	0.0303
O5	-0.6834	-0.7042	-0.6706	0.0127	0.0208	0.0168	0.0081
C6	-0.3435	-0.3651	-0.3217	0.0218	0.0216	0.0217	-0.0002
C7	0.4052	0.3839	0.402	-0.0032	0.0213	0.0091	0.0181
C8	-0.2859	-0.2567	-0.2824	0.0035	-0.0292	0.0129	0.0257
O9	-0.5015	-0.5427	-0.4828	0.0187	0.0412	0.03	0.0225
C10	0.3184	0.1807	0.3526	0.0342	0.1377	0.086	0.1035
C11	0.18	0.1858	0.3233	0.1433	-0.0058	0.0688	-0.1375
C12	0.4957	0.3138	0.4891	-0.0066	0.1819	0.0876	0.1752
O13	-0.662	-0.8057	-0.597	0.065	0.1437	0.1043	0.0787
O14	-0.7082	-0.7348	-0.6186	0.0896	0.0266	0.0581	-0.063
C15	-0.1158	-0.1012	-0.0356	0.0802	-0.0146	0.0328	-0.0656
C16	-0.2391	-0.2893	-0.2247	0.0144	0.0502	0.0323	0.0358
C17	0.2573	0.2578	0.2967	0.0394	-0.0005	0.0194	-0.0388
O18	-0.7219	-0.7312	-0.6912	0.0307	0.0093	0.02	-0.0214
C19	0.2898	0.2264	0.3961	0.1064	0.0633	0.0849	-0.0431
O20	-0.6975	-0.717	-0.6246	0.0729	0.0195	0.0462	-0.0534
C21	-0.2514	-0.2522	-0.2344	0.017	0.0008	0.0089	-0.0163
C22	-0.1985	-0.2608	-0.122	0.0765	0.0623	0.0694	-0.0142
H23	0.4948	0.4835	0.5004	0.0056	0.0113	0.0084	0.0057
H24	0.235	0.2201	0.2422	0.0073	0.0148	0.011	0.0076
H25	0.4978	0.4904	0.5021	0.0043	0.0074	0.0058	0.0031
H26	0.2486	0.233	0.2569	0.0084	0.0156	0.012	0.0072
H27	0.5109	0.5044	0.5285	0.0176	0.0065	0.0121	-0.011
H28	0.2485	0.2387	0.2623	0.0138	0.0098	0.0118	-0.004
H29	0.5058	0.5011	0.5181	0.0122	0.0047	0.0085	-0.0075
H30	0.5035	0.4974	0.5181	0.0146	0.0061	0.0104	-0.0085
H31	0.2332	0.2211	0.2558	0.0226	0.0121	0.0174	-0.0104
H32	0.2346	0.224	0.2533	0.0187	0.0106	0.0146	-0.0081

Table S9: NBO analysis of optimized quercetin (CID 5280343) structure

Donor(i)	ED(i)	Acceptor(j)	ED(j)	E^2 (kcal/mol)	E_j-E_i (a.u.)	F(i,j) (a.u.)
η_2 (O_1)	1.8606	π^* C_2-C_3	0.3469	45.47	0.45	0.128
η_2 (O_5)	1.8678	π^* C_4-C_6	0.3761	42.77	0.45	0.124
η_2 (O_9)	1.7728	π^* C_7-C_8	0.4605	43.02	0.45	0.124
η_2 (O_9)	1.7728	π^* C_{10}-C_{11}	0.2688	34.55	0.48	0.115
η_1 (O_{13})	1.9825	π C_{12}	0.0054	10.09	1.80	0.120
η_2 (O_{13})	1.8896	σ^* C_8-C_{12}	0.0551	21.80	0.87	0.123
η_2 (O_{13})	1.8896	σ^* C_{11}-C_{12}	0.0668	21.53	0.85	0.121
η_2 (O_{14})	1.8858	π^* C_{10}-C_{11}	0.2688	37.64	0.46	0.118
η_2 (O_{18})	1.8995	π^* C_{16}-C_{17}	0.3613	34.37	0.47	0.113
η_2 (O_{20})	1.8799	π^* C_{19}-C_{21}	0.3762	37.96	0.46	0.117
π C_2-C_3	1.9754	π^* C_4-C_6	0.3761	37.62	0.37	0.105
π C_2-C_3	1.9754	π^* C_7-C_8	0.4605	16.93	0.35	0.069
π C_4-C_6	1.6711	π^* C_2-C_3	0.3469	17.35	0.35	0.070
π C_4-C_6	1.6711	π^* C_7-C_8	0.4605	44.48	0.34	0.110
π C_7-C_8	1.6501	π^* C_2-C_3	0.3469	33.29	0.36	0.098
π C_7-C_8	1.6501	π^* C_4-C_6	0.3761	16.06	0.36	0.068
π C_7-C_8	1.6501	π^* C_{12}-O_{13}	0.3193	37.54	0.36	0.104
π C_{10}-C_{11}	1.8054	π^* C_{12}-O_{13}	0.3193	28.90	0.39	0.095
π C_{10}-C_{11}	1.8054	π^* C_{15}-C_{22}	0.4085	13.58	0.40	0.066
π C_{15}-C_{22}	1.6672	π^* C_{10}-C_{11}	0.2688	20.82	0.36	0.077
π C_{15}-C_{22}	1.6672	π^* C_{16}-C_{17}	0.3613	27.37	0.35	0.087
π C_{15}-C_{22}	1.6672	π^* C_{19}-C_{21}	0.3762	26.40	0.35	0.086
π C_{16}-C_{17}	1.6947	π^* C_{15}-C_{22}	0.4085	26.59	0.37	0.088
π C_{16}-C_{17}	1.6947	π^* C_{19}-C_{21}	0.3762	27.08	0.37	0.089
π C_{19}-C_{21}	1.6518	π^* C_{15}-C_{22}	0.4085	32.02	0.36	0.096
π C_{19}-C_{21}	1.6518	π^* C_{16}-C_{17}	0.3613	26.55	0.36	0.087

12. Geometric parameters of daphnetin (CID 5280569)

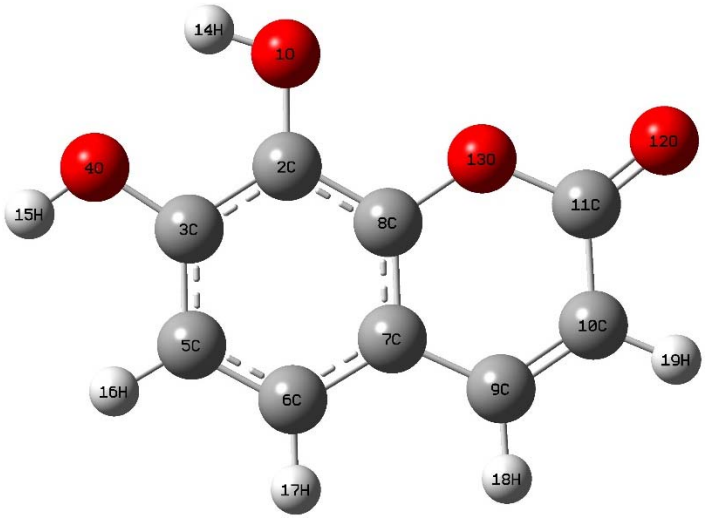

Figure S10: Optimized geometry of daphnetin (CID 5280569)

Table S10: Optimized structural properties of daphnetin (CID 5280569)

Atoms	Bond Length (Å)	Atoms	Angle (°)	Atoms	Dihedral (°)
C(8)C(7)	1.399	C(2)C(8)C(7)	121.328	O(13)C(8)C(2)C(7)	121.847
C(2)C(8)	1.39	O(13)C(8)C(7)	116.825	C(6)C(7)C(8)C(2)	0
O(13)C(8)	1.362	C(6)C(7)C(2)	119.111	C(9)C(7)C(6)C(8)	116.941
C(6)C(7)	1.4	C(9)C(7)C(8)	123.948	C(3)C(2)C(8)C(7)	0
C(9)C(7)	1.44	C(3)C(2)C(7)	118.356	C(5)C(6)C(7)C(8)	0
C(3)C(2)	1.395	C(5)C(6)C(8)	120.332	C(10)C(9)C(7)C(6)	180
C(5)C(6)	1.383	C(10)C(9)C(6)	120.815	C(11)O(13)C(8)C(2)	-179.995
C(10)C(9)	1.346	C(11)O(13)C(2)	122.369	O(1)C(2)C(3)C(8)	119.925
C(11)O(13)	1.372	O(1)C(2)C(8)	121.719	O(4)C(3)C(2)C(5)	124.399
O(1)C(2)	1.353	O(4)C(3)C(5)	114.378	O(12)C(11)C(10)O(13)	117.243
O(4)C(3)	1.357	O(12)C(11)O(13)	125.797	H(16)C(5)C(3)C(6)	120.904
O(12)C(11)	1.206	H(16)C(5)C(6)	119.446	H(17)C(6)C(5)C(7)	119.271
H(16)C(5)	1.084	H(17)C(6)C(7)	120.397	H(18)C(9)C(7)C(10)	120.58
H(17)C(6)	1.083	H(18)C(9)C(10)	118.605	H(19)C(10)C(9)C(11)	116.031
H(18)C(9)	1.085	H(19)C(10)C(11)	122.901	H(14)O(1)C(2)C(3)	-0.019
H(19)C(10)	1.081	H(14)O(1)C(3)	108.521	H(15)O(4)C(3)C(2)	179.949
H(14)O(1)	0.966	H(15)O(4)C(2)	111.351		
H(15)O(4)	0.963				

Table S11: Fukui indices and NPA charges of optimized daphnetin (CID 5280569)

Atom	NPA N0	NPA N+1	NPA N-1	f^-	f^+	f^0	$f^{(2)}$
O1	-0.7211	-0.7373	-0.6012	0.1199	0.0162	0.0681	-0.1037
C2	0.2499	0.2365	0.3833	0.1334	0.0133	0.0734	-0.1201
C3	0.2763	0.2012	0.4073	0.131	0.0751	0.1031	-0.0559
O4	-0.7376	-0.7619	-0.6373	0.1003	0.0242	0.0623	-0.076
C5	-0.3073	-0.3182	-0.3135	-0.0062	0.0109	0.0023	0.0046
C6	-0.2028	-0.2788	-0.0682	0.1346	0.0761	0.1053	-0.0585
C7	-0.1664	-0.1376	-0.066	0.1003	-0.0288	0.0358	-0.0716
C8	0.3002	0.2482	0.2904	-0.0098	0.0519	0.0211	0.0421
C9	-0.1249	-0.353	-0.1533	-0.0284	0.2281	0.0998	0.1996
C10	-0.3659	-0.5035	-0.2503	0.1155	0.1376	0.1266	0.0221
C11	0.8018	0.7249	0.7944	-0.0074	0.077	0.0348	0.0696
O12	-0.6425	-0.7647	-0.5936	0.0489	0.1222	0.0855	0.0734
O13	-0.5206	-0.5776	-0.4976	0.023	0.057	0.04	0.034
H14	0.5404	0.5334	0.5599	0.0195	0.0069	0.0132	-0.0126
H15	0.5446	0.535	0.5699	0.0253	0.0096	0.0175	-0.0156
H16	0.2673	0.2484	0.2993	0.0321	0.0189	0.0255	-0.0132
H17	0.2645	0.2418	0.2937	0.0292	0.0227	0.0259	-0.0065
H18	0.2698	0.2266	0.2904	0.0206	0.0432	0.0319	0.0225
H19	0.2745	0.2364	0.2928	0.0182	0.0381	0.0282	0.0199

Table S12: NBO analysis of optimized daphnetin (CID 5280569)

Donor(i)	ED(i)	Acceptor(j)	ED(j)	E^2 (kcal/mol)	E_j-E_i (a.u.)	F(i,j) (a.u.)
η_2 (O_1)	1.886	π^* C_2-C_3	0.4172	37.32	0.44	0.098
η_2 (O_4)	1.8858	π^* C_2-C_3	0.4172	36.62	0.45	0.065
η_1 (O_{12})	1.9794	σ C_{11}	0.0150	12.77	1.54	0.081
η_2 (O_{12})	1.8564	σ^* C_{10}-C_{11}	0.0541	19.71	0.85	0.089
η_2 (O_{12})	1.8564	σ^* C_{11}-O_{13}	0.1081	45.25	0.74	0.083
η_2 (O_{13})	1.7556	π^* C_7-C_8	0.4684	37.07	0.45	0.084
η_2 (O_{13})	1.7556	π^* C_{11}-O_{12}	0.2892	50.63	0.45	0.092
π C_2-C_3	1.6245	π^* C_5-C_6	0.3329	24.73	0.37	0.098
π C_2-C_3	1.6245	π^* C_7-C_8	0.4684	33.48	0.36	0.086
π C_5-C_6	1.7238	π^* C_2-C_3	0.4172	30.78	0.35	0.135
π C_5-C_6	1.7238	π^* C_7-C_8	0.4684	25.62	0.35	0.115
π C_7-C_8	1.6316	π^* C_2-C_3	0.4172	24.36	0.35	0.163
π C_7-C_8	1.6316	π^* C_5-C_6	0.3329	26.98	0.37	0.116
π C_7-C_8	1.6316	$\pi^*$$C_9$-$C_{10}$	0.1272	21.64	0.38	0.125
π C_9-C_{10}	1.8344	π^* C_7-C_8	0.4684	14.35	0.37	0.115
π C_9-C_{10}	1.8344	π^* C_{11}-O_{12}	0.2892	31.69	0.38	0.115

13. Geometric parameters of metformin (CID 4091)

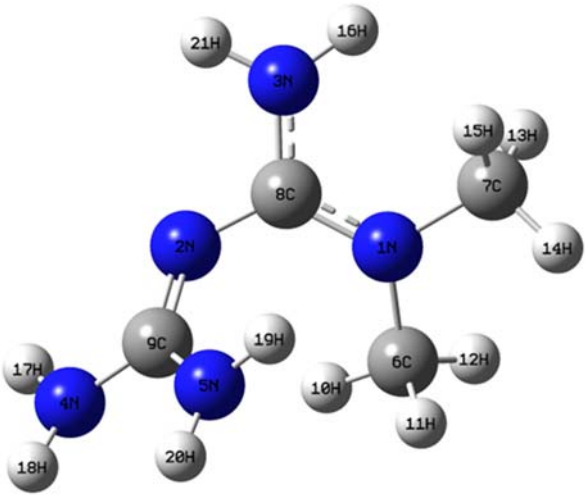

Figure S11: Optimized geometry of metformin (CID 4091)

Table S13: Optimized properties of Metformin (CID 4091)

Atoms	Bond Length (Å)	Atoms	Angle (°)	Atoms	Dihedral (°)
C(8)N(2)	1.343	N(3)C(8)N(2)	116.875	N(1)C(8)N(2)N(3)	118.849
N(3)C(8)	1.34	N(1)C(8)N(2)	124.242	C(9)N(2)C(8)N(1)	46.735
N(1)C(8)	1.338	C(9)N(2)C(8)	122.273	N(4)C(9)N(2)C(8)	-163.845
C(9)N(2)	1.322	N(4)C(9)N(2)	117.593	N(5)C(9)N(2)N(4)	117.704
N(4)C(9)	1.341	N(5)C(9)N(2)	124.697	C(6)N(1)C(8)N(2)	15.331
N(5)C(9)	1.343	C(6)N(1)C(8)	122.419	C(7)N(1)C(6)C(8)	120.803
C(6)N(1)	1.462	C(7)N(1)C(6)	115.882	H(16)N(3)C(8)N(1)	18.502
C(7)N(1)	1.462	H(16)N(3)C(8)	122.5	H(21)N(3)C(8)H(16)	118.025
H(16)N(3)	1.008	H(21)N(3)C(8)	117.171	H(10)C(6)N(1)C(7)	-159.237
H(21)N(3)	1.008	H(10)C(6)N(1)	110.402	H(11)C(6)N(1)H(10)	109.62
H(10)C(6)	1.087	H(11)C(6)N(1)	110.624	H(12)C(6)N(1)H(10)	108.638
H(11)C(6)	1.091	H(12)C(6)N(1)	108.154	H(13)C(7)N(1)C(6)	90.105
H(12)C(6)	1.09	H(13)C(7)N(1)	111.216	H(14)C(7)N(1)H(13)	108.821
H(13)C(7)	1.094	H(14)C(7)N(1)	108.028	H(15)C(7)N(1)H(13)	110.1
H(14)C(7)	1.088	H(15)C(7)N(1)	110.295	H(17)N(4)C(9)N(2)	-2.253
H(15)C(7)	1.09	H(17)N(4)C(9)	117.792	H(18)N(4)C(9)H(17)	118.406
H(17)N(4)	1.007	H(18)N(4)C(9)	121.918	H(19)N(5)C(9)N(2)	6.102
H(18)N(4)	1.007	H(19)N(5)C(9)	120.499	H(20)N(5)C(9)H(19)	117.393
H(19)N(5)	1.008	H(20)N(5)C(9)	121.263		
H(20)N(5)	1.008				

Table S14: Fukui indices and NPA charges of optimized metformin (CID 4091)

Atom	NPA N0	NPA N+1	NPA N-1	f^-	f^+	f^0	$f^{(2)}$
N1	-0.546	-0.5488	-0.4791	0.0669	0.0028	0.0348	-0.0641
N2	-0.732	-0.7343	-0.6916	0.0404	0.0023	0.0214	-0.0381
N3	-0.8536	-0.8468	-0.766	0.0876	-0.0068	0.0404	-0.0808
N4	-0.852	-0.8632	-0.7776	0.0744	0.0112	0.0428	-0.0632
N5	-0.8631	-1.063	-0.7955	0.0676	0.1999	0.1338	0.1323
C6	-0.3526	-0.3617	-0.3596	-0.007	0.0091	0.001	0.0021
C7	-0.3659	-0.3737	-0.3768	-0.0109	0.0078	0.0016	-0.0031
C8	0.4771	0.5031	0.7073	0.2302	-0.026	0.1021	-0.2043
C9	0.505	0.4763	0.6763	0.1713	0.0287	0.1	-0.1426
H10	0.2127	0.2082	0.22	0.0073	0.0046	0.0059	-0.0027
H11	0.1941	0.1584	0.2138	0.0197	0.0357	0.0277	0.016
H12	0.1898	0.187	0.2162	0.0264	0.0028	0.0146	-0.0236
H13	0.1847	0.183	0.2124	0.0277	0.0017	0.0147	-0.026
H14	0.2054	0.2047	0.2266	0.0213	0.0007	0.011	-0.0206
H15	0.2036	0.2001	0.2191	0.0155	0.0035	0.0095	-0.0121
H16	0.3878	0.3895	0.4229	0.0352	-0.0018	0.0167	-0.0334
H17	0.401	0.3943	0.4278	0.0268	0.0067	0.0167	-0.0201
H18	0.396	0.3792	0.4205	0.0245	0.0169	0.0207	-0.0076
H19	0.4086	-0.0063	0.4256	0.0169	0.4149	0.2159	0.398
H20	0.4044	0.1282	0.4268	0.0225	0.2762	0.1493	0.2538
H21	0.3951	0.3859	0.4309	0.0358	0.0092	0.0225	-0.0266

Table S15: NBO analysis of optimized metformin (CID 4091) structure

Donor(i)	ED(i)	Acceptor(j)	ED(j)	E^2 (kcal/mol)	E_j-E_i (a.u.)	F(i,j) (a.u.)
η_1 (N_2)	1.8415	σ^* N_1-C_8	0.0532	10.15	0.91	0.086
η_1 (N_2)	1.8415	π^* N1-C_8	0.4976	17.06	0.35	0.069
η_1 (N_2)	1.8415	σ^* N_5-C_9	0.0395	14.42	0.90	0.102
η_1 (N_3)	1.7184	π^* N1-C_8	0.4976	97.98	0.31	0.156
η_1 (N_4)	1.7400	π^* N_2-C_9	0.4921	92.37	0.34	0.157
η_1 (N_5)	1.7433	π^* N_2-C_9	0.4921	91.05	0.34	0.157
π N_2-C_9	1.8326	π^* N_1-C_8	0.4976	45.41	0.36	0.114

14. Perspective and numbering for LOL.

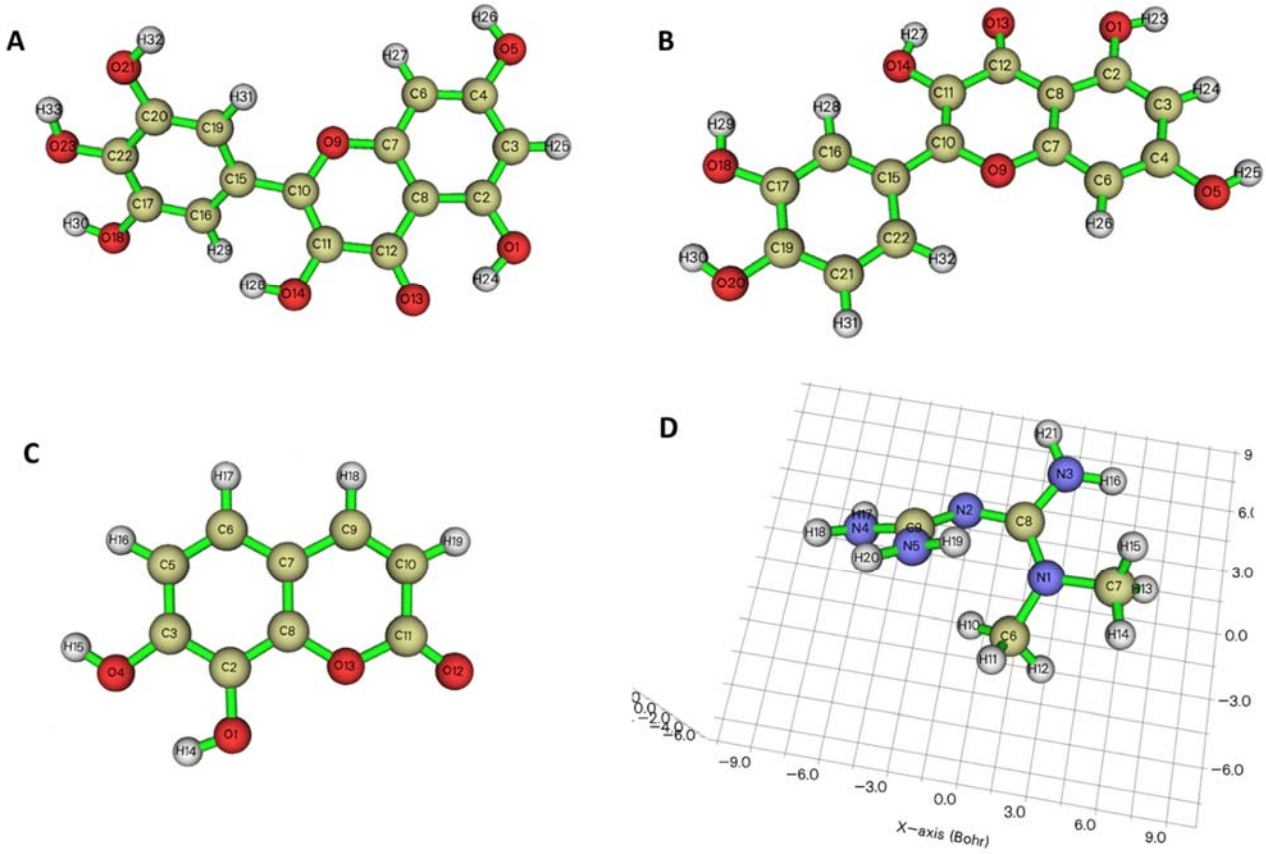

Figure S12: Perspective and numbering for LOL

15. Radical Fukui functions.

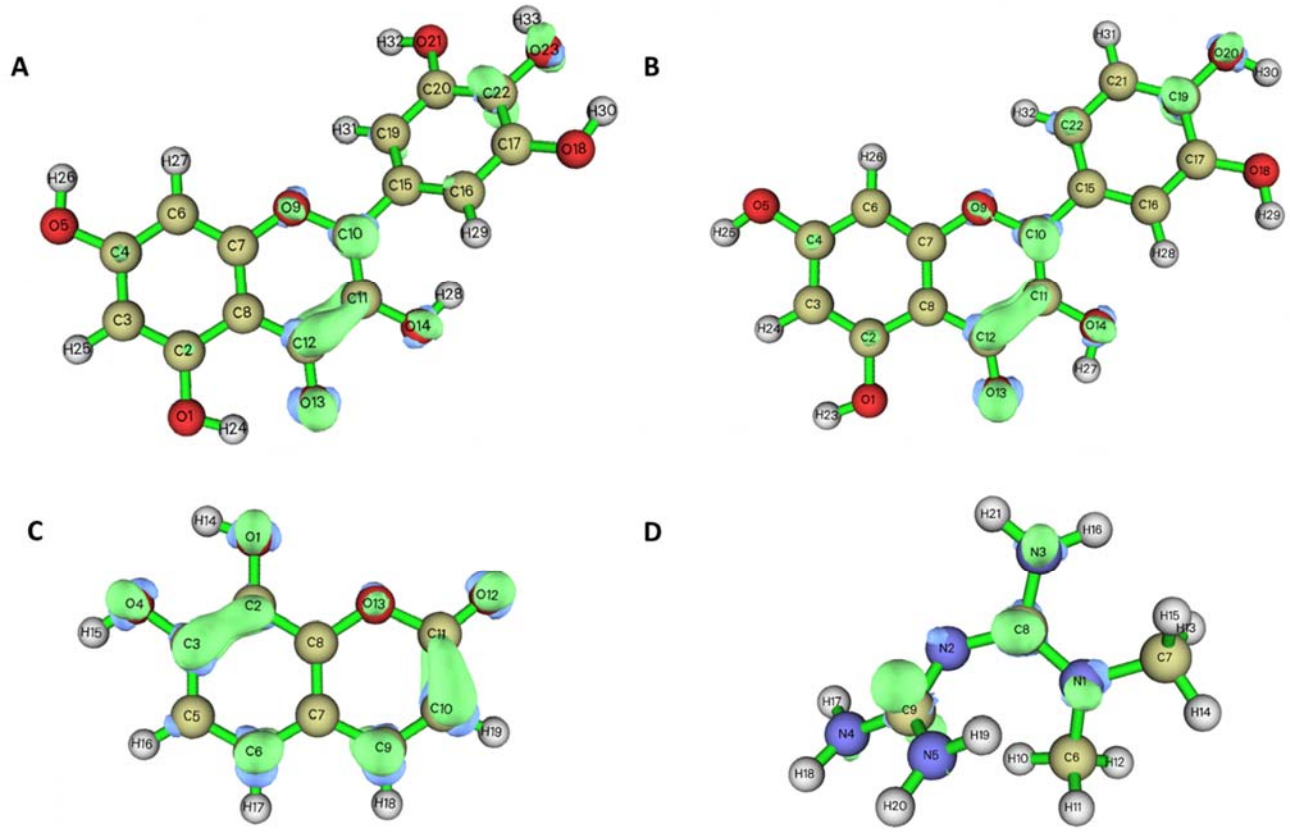

Figure S13: Radical Fukui contours

16. Spin density dual descriptor Fukui functions estimated in two states (N+1 and N-1)

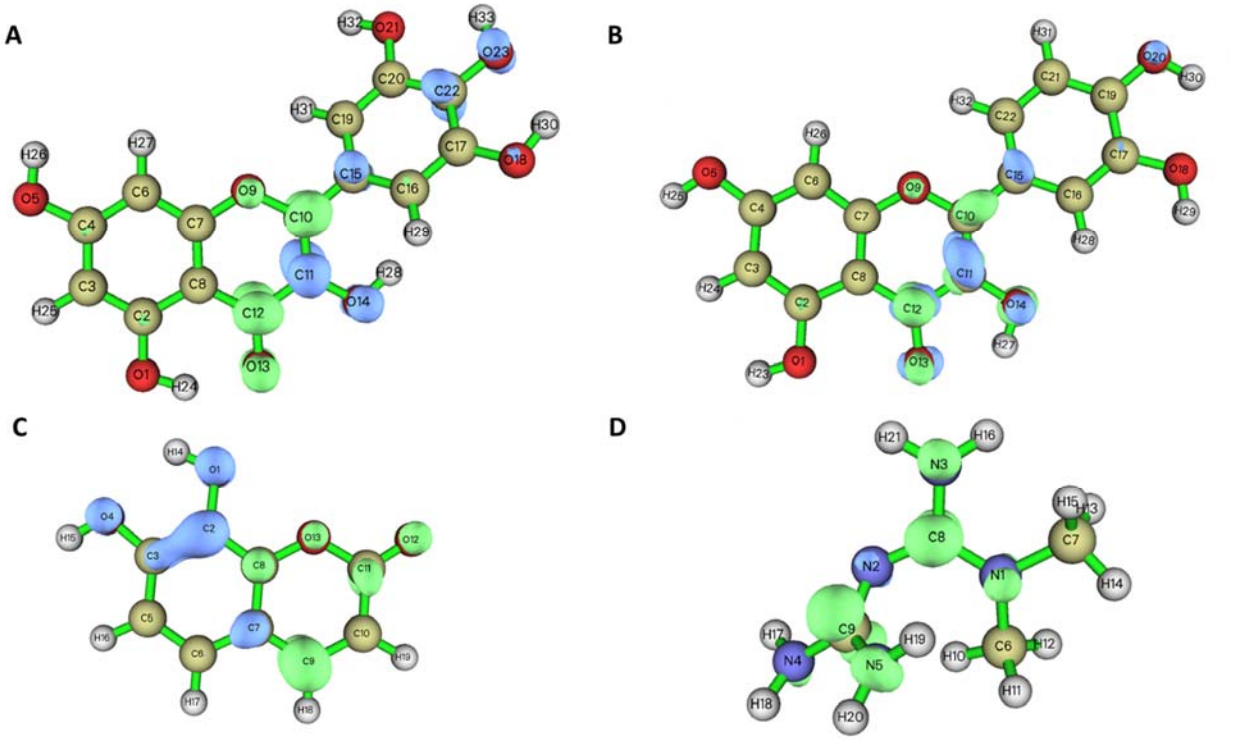

Figure S14: Spin density-based dual descriptors

17. MMGBSA per residue decomposition

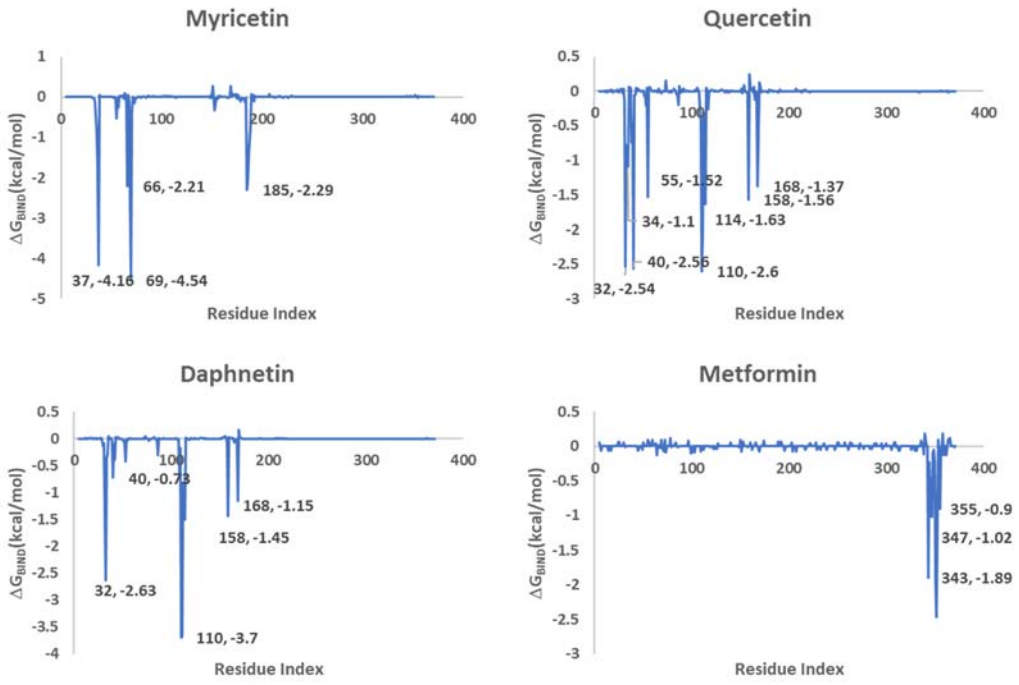

Figure S15: Per residue ΔG decomposition.