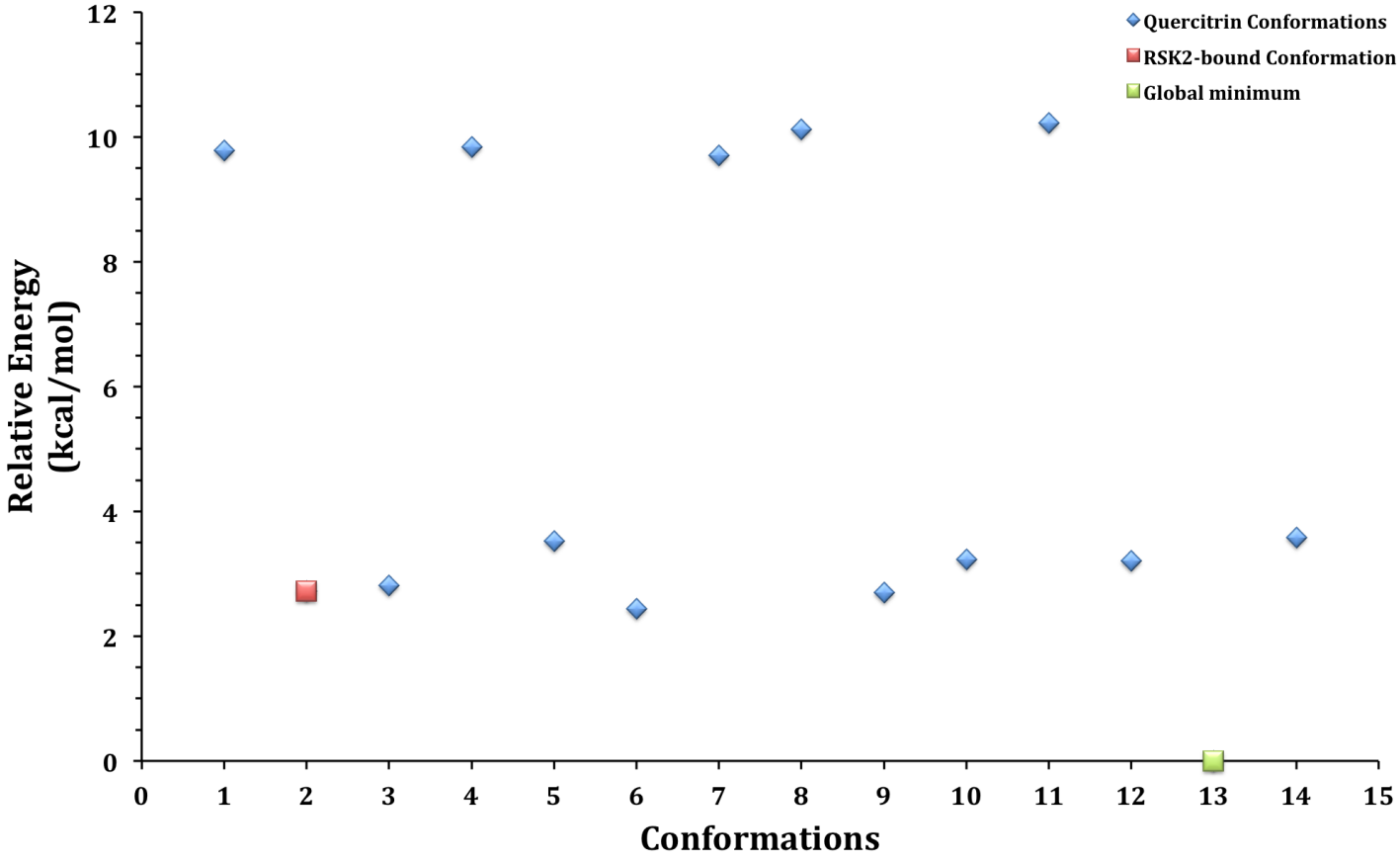
Supplementary Material

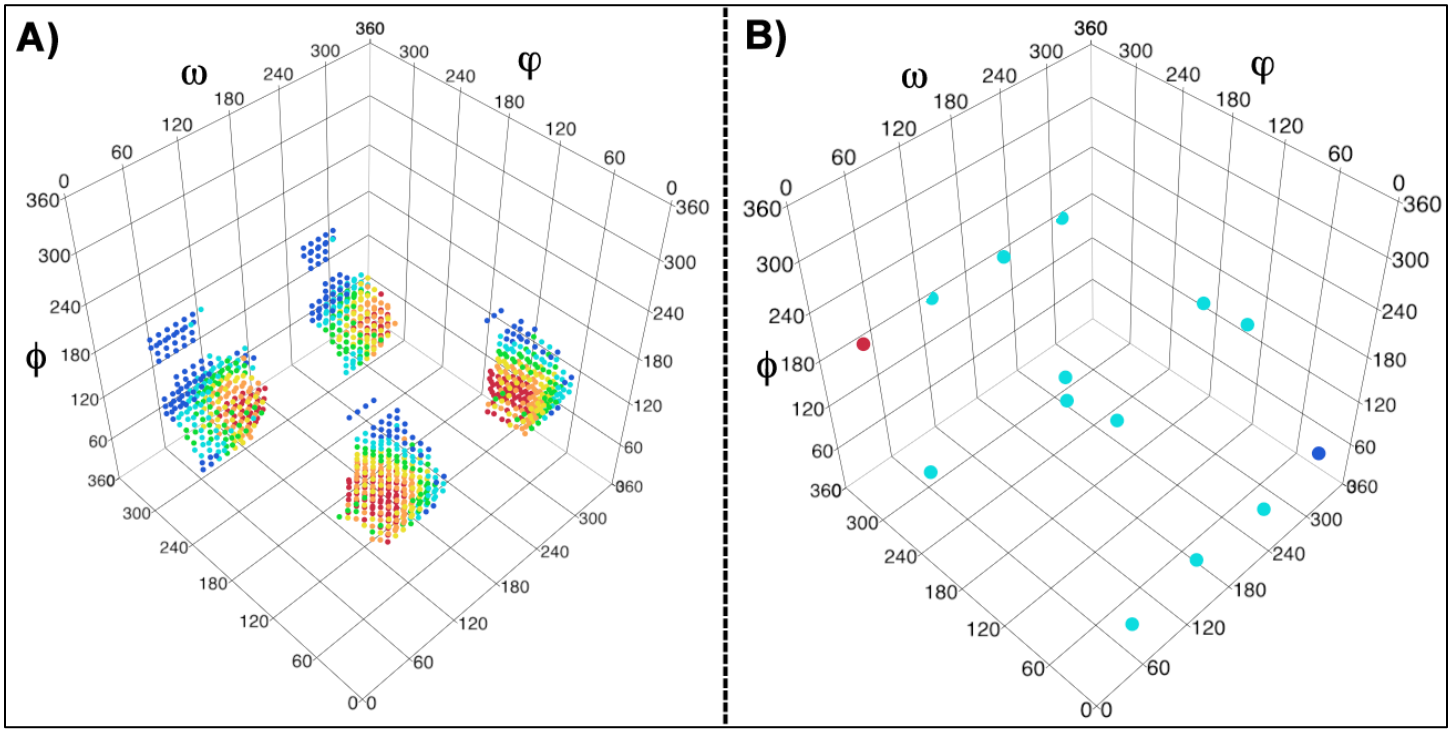


Supplementary Fig. S1. Unique energy minimized conformations of quercitin are shown as blue diamonds. The global minimum conformation is shown as green box, while the bound quercitrin conformation is shown as red box. The values in parentheses are the (ω, φ, ψ) torsion angles for each conformation.

Supplementary Table S1 – Quercitrin conformations

Conformation	**ω**	φ	ψ	**ENERGY** (kcal/mol)	**Relative Energy** (kcal/mol, strain with respect to CNF 13)
CNF1	35.2	256.7	78.3	32.183	9.786
CNF2	40.6	345.5	184.2	25.124	2.727
CNF3	45.2	1.2	76.9	25.212	2.815
CNF4	112.5	146.5	198.7	32.242	9.845
CNF5	133.1	357.1	176	25.917	3.520
CNF6	140	10.4	69.7	24.834	2.437
CNF7	143.4	114.7	173.5	32.104	9.707
CNF8	216	256.8	77.5	32.523	10.126
CNF9	219.4	346	183.8	25.092	2.695
CNF10	224	1.3	76.3	25.625	3.228
CNF11	292.8	144.7	199.6	32.627	10.230
CNF12	311.5	356.7	176	25.605	3.208
CNF13	**320.4**	**10.4**	**70**	**22.397**	**0.000**
CNF14	323.5	113.5	172.1	25.979	3.582
Unbound, crystal[a]	330.7	114.6	168.0	<53.825>	--
Bound, RSK2, crystal[b]	20.3	303.8	185.8	<56.315>	--
Bound, RSK2, optimized[c]	27.1	322.5	180.9	33.316	10.919

[a]Energy of quercitrin structure in free state as reported in crystal structure (Jiang *et al.*, 2009), which includes crystal packing forces, etc.; after vacuum minimization, this structure converges to CNF14. [b]Energy of quercitrin structure in bound state of RSK2 (this work); after vacuum minimization, the structure converges to CNF2. [c]Energy of quercitrin structure after optimization in binding site, i.e., constrained by pocket environment.



Supplementary Fig. S2

A – A 3D-scatter plot of all quercitrin conformers generated by a Systematic Search. X,Y,Z axis are the three rotatable bonds of quercitrin. The points are color-coded based on their energies, with high-energy conformers colored red and low energy conformers colored blue. The color ranges from red-orange-yellow-green-cyan-blue.

B – A 3D-scatter plot of 14 local minima structures of quercitrin, obtained after energy minimization. The global minima structure (lowest energy structure) is shown as a dark blue point while the quercitrin conformer in the bound state converged to the point shown in red (2.727 kcal/mol energy higher than the global minima)