Supporting Information

to

Validating the Vitality Strategy for Fighting Drug Resistance

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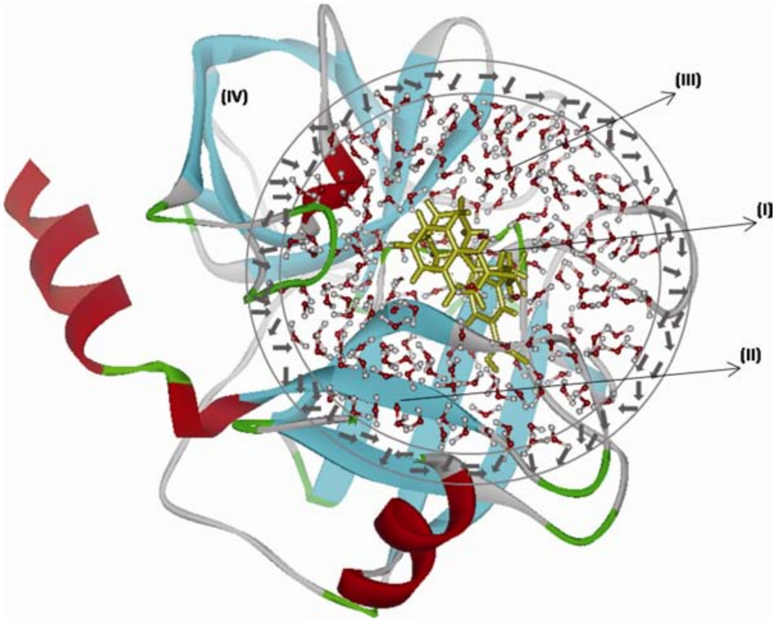

Figure S1. Using a complex of trypsin (flat ribbon) and an inhibitor (stick) to illustrate the construction of the explicit SCAAS simulation system. The enzyme substrate complex is solvated by a water sphere (ball and stick). The figure illustrates the typical boundary conditions in the PDLD/S-LRA/β calculations. In such calculations we confine to Region I the ‘‘inhibitor’’ or the group whose electrostatic energy is of interest, Region II includes all the protein residues within 18 Å cutoff radius from the center of Region I and Region III includes the explicit water molecules in and around regions I and II and is completed by a 2Å surface water region, which is subjected to polarization and radial constraints. This region is surrounded by bulk solvent (Region IV) with a high dielectric constant (ε = 80). The electrostatic effects of regions I, II, and III are treated explicitly whereas those of Region IV are treated by a macroscopic continuum formulation.

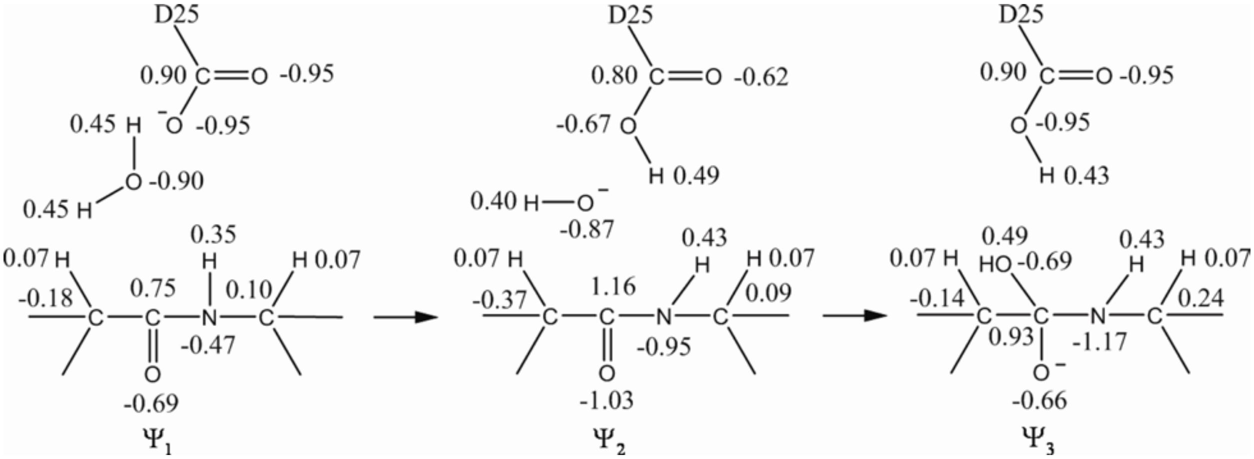

Figure S2. The *ab initio* charges used in EVB calculations. Ψ_1, Ψ_2 and Ψ_3 designates the reactant state (RS), the TS1 and the intermediate (Int) respectively (see Figure 1 in the main text).

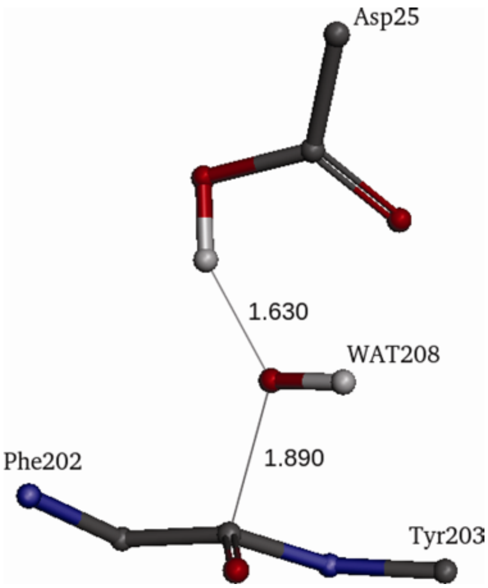

Figure S3. Illustrating the calculated geometry of TS1'. The depicted geometry is a snapshot from a EVB trajectory at the TS of the rate limiting step of the attack by an hydroxide ion on the carbonyl carbon of the peptide bond, during the formation of the oxyanion tetrahedral intermediate (the reaction step involved in moving from *TS1* to *Int*, see Figure 1 in the main text).

Table SI. Parameters used in the EVB calculations*.

Morse bond parameters: $\Delta M\left(b\right)=D_M\left(1-e^{-\mu\left(b-b_0\right)}\right)^2$

Bond type	D_M	b_0	μ
N-H_N	98.0	1.10	2.0
C-O (ψ_1,ψ_2)	93.0	1.43	2.0
C-O (ψ_3)	93.0	1.50	2.0
C_A-H_A	102.0	1.00	2.0
N-C_A	94.0	1.40	2.0
N-C (ψ_1,ψ_2)	92.0	1.47	2.0
N-C (ψ_3)	94.0	1.40	2.0
C-C_A (ψ_1,ψ_2)	96.0	1.54	2.0
C-C_A (ψ_3)	96.0	1.54	2.0
O_H-$H_{i=1,2}$ (water)	102.0	0.98	2.0
C_G-$O_{D1,D2}$ (aspartate)	93.0	1.43	2.0

Angle parameters: $V_\theta(\theta)=1/2\,k_\theta\left(\theta-\theta_0\right)^2$

Angle type	$1/2\ k_\theta$	θ_0
O_{D1}-C_G-O_{D2}	50.0	120.0
H_1-O_H-H_2	80.0	109.5
C-N_1-C_A	50.0	120.0
N-C_A-H_A	50.0	109.5
O-C-N	50.0	120.0

Torsion angle parameters: $V_\phi(\phi)=k_\phi\left(1+\cos\left(n\phi-\phi_0\right)\right)$

Angle type	k_ϕ	n	ϕ_0
H-C_A-C-O	2.0	3.0	0.0
C_A-C-N-C_A	15.0	2.0	180.0
H-O_{D1}-C_G-O_{D2}	15.0	2.0	180.0
C-N-C_A-H_A	2.0	3.0	0.0
H-O_H-C-O	2.0	3.0	0.0

Improper torsion angle parameters: $V_{\phi}(\phi) = k_{\phi}\left(1 + \cos\left(n\phi - \phi_0\right)\right)$

Angle type	k_{ϕ}	n	ϕ_0
C-N-O-C_A	15.0	2.0	180.0
N-H_N-C_A-C	30.0	2.0	180.0

Nonbonded parameters (repulsion function)[1]: $V_{nb} = Ce^{-\alpha r}$

Atom type	C	α
O_H-$H_{i=1,2}$	4000	4.0

Nonbonded parameters (van der Waals)[2]: $V_{nb} = \varepsilon^* \left[\left(r^*/r\right)^{12} - 2\left(r^*/r\right)^{6}\right]$

Atom type	r^*	ε^*
O_{D1}-O_{D2}	3.0	0.08
H-$H_{i=1,2,N,A}$	2.5	0.01

*Energies are in kcal/mol, distances in Å and angles in degrees.

[1] Nonbonded interactions, where only the repulsion term is considered for atoms, which are bonded in one of the VB structures.

[2] Nonbonded interactions for atoms, which are never bonded in any of the VB structures.

Table SII. Parameters used for the calibration of the EVB surface of the uncatalyzed reaction in water and later in the protein to reproduce the experimental trend.

Reaction Step	H_{ij}	$\Delta\alpha_{ij}$
$RS \rightarrow TS1$	20.0	43.0
$TS1 \rightarrow Int$	111.0	112.0

Table SIII. The calculated apparent pKa’s of the basic and acidic groups obtained using pKa-PDLD level of the MOLARIS program at dielectric constant ε = 4.0.

ionizable group	calculated apparent pKa
ARG8	13.2
ARG8’	12.2
ASP29	4.6
ASP 29’	5.5
ASP30	5.4
ASP30’	5.3
ARG87	13.6
ARG87’	13.2
ASP25’	10.2