Figure caption

Figure 1. The (a) HuperzineA-AChE complex showing the Connolly surface of the active site of AChE and (b) the interactions of huperzineA with the neighbouring amino acid residues in the active site of AChE.

Figure 2. The structure of HuperzineA molecule (a) in gas phase and (b) in the active site of AChE with atom numbering scheme.

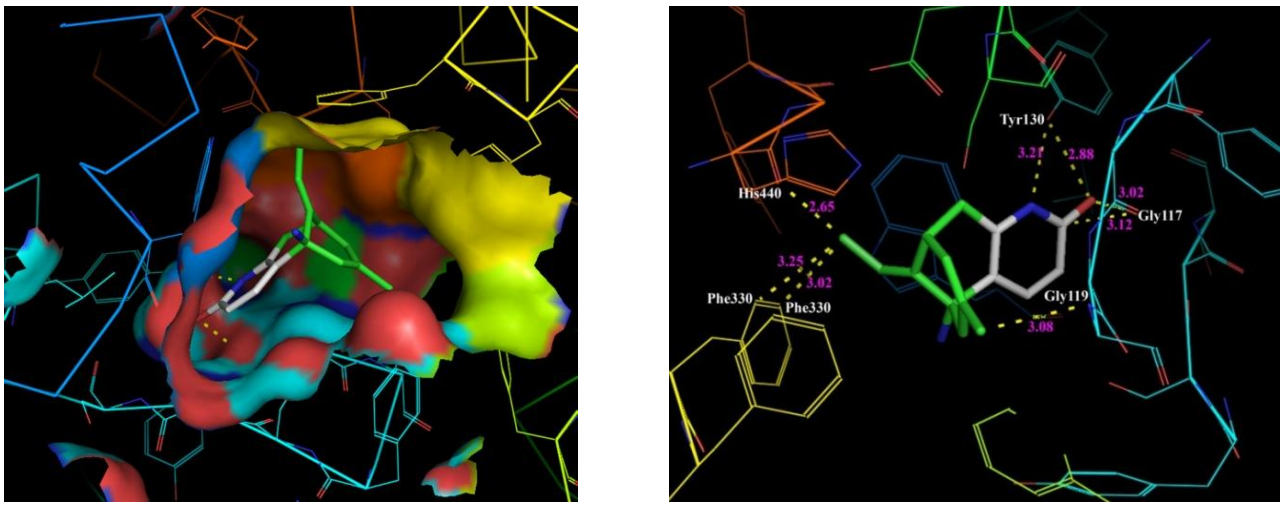
Figure 3. Deformation density map of HuperzineA molecule drawn in various planes in (a) gas phase (I) and (b) for the same molecule lifted from the active site of AChE (II). The contour lines represent positive (solid lines), negative (dotted lines) and the zero contours (dashed line). The contours are drawn at 0.05 $e\text{Å}^{-3}$ intervals.

Figure 4. The difference of (a) electron density $\rho_{bcp}(r)$ and (b) the Laplacian of electron density $\nabla^2\rho_{bcp}(r)$ of huperzineA in the gas phase (I) and the same molecule lifted from the active site (II) of AChE.

Figure 5. The orientation of dipole moment vectors of huperzineA molecule in gas phase (I) [blue] and the same lifted from the active site (II) [pink]. The origin is at the centre of mass of the molecule.

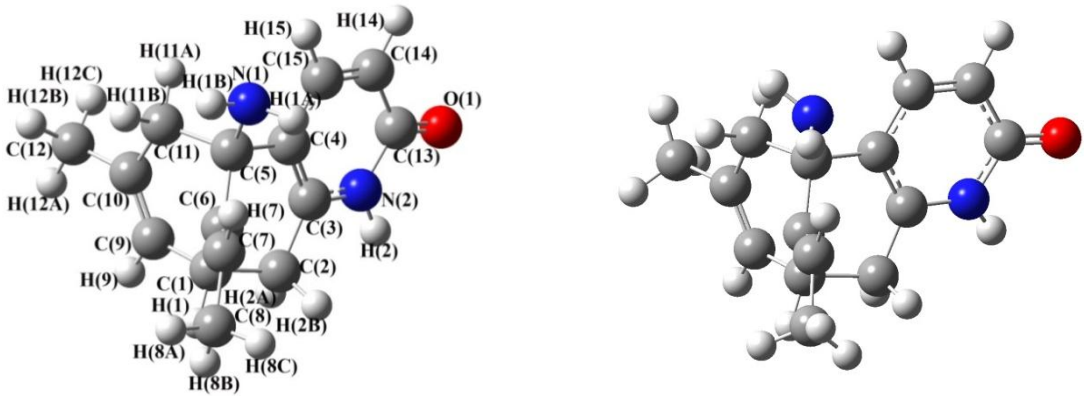
Figure 6. Isosurface of the molecular electrostatic potential of huperzineA (a) in gas phase and (b) the same lifted from the active site of AChE. The pictorial representation of contacts in (b) showing the intermolecular interactions. Blue: positive potential (+0.3 $e\text{Å}^{-1}$), red: negative potential (−0.03 $e\text{Å}^{-1}$).

Figure 1



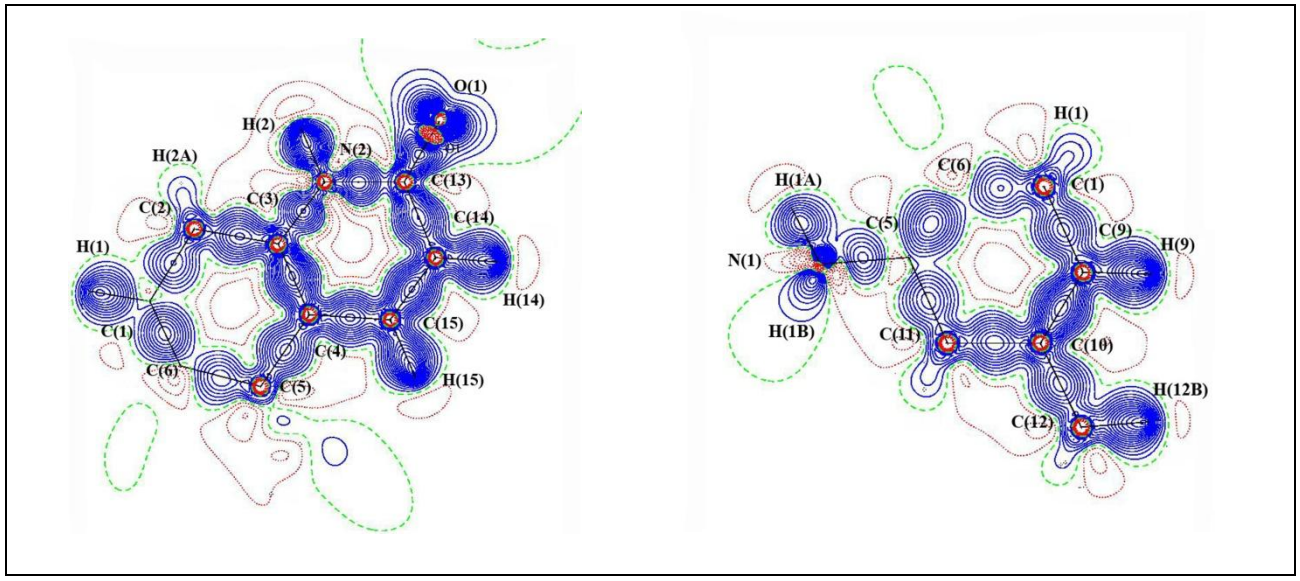
(a) (b)

Figure 2



(a) (b)

Figure 3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H(2)
N(2)
H(2A)
C(13)
C(3)
C(2)
C(14)
H(1)
H(14)
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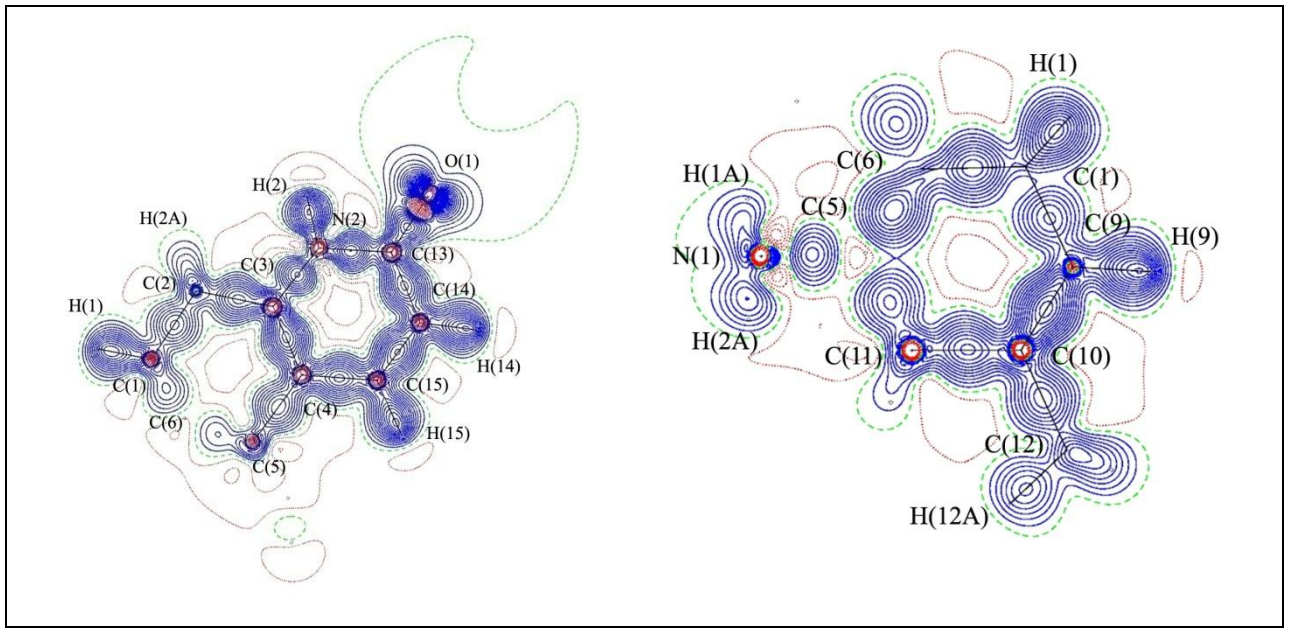
C(1)
C(4)
C(6)
C(5)
H(15)
H(1)
C(6)
C(1)
H(1A)
C(5)
C(9)
H(9)
N(1)
H(1B)
C(11)
C(10)
H(12B)
C(12)

(a)


O(1)
H(2)
N(2)
H(2A)
C(13)
C(3)
C(2)
C(14)
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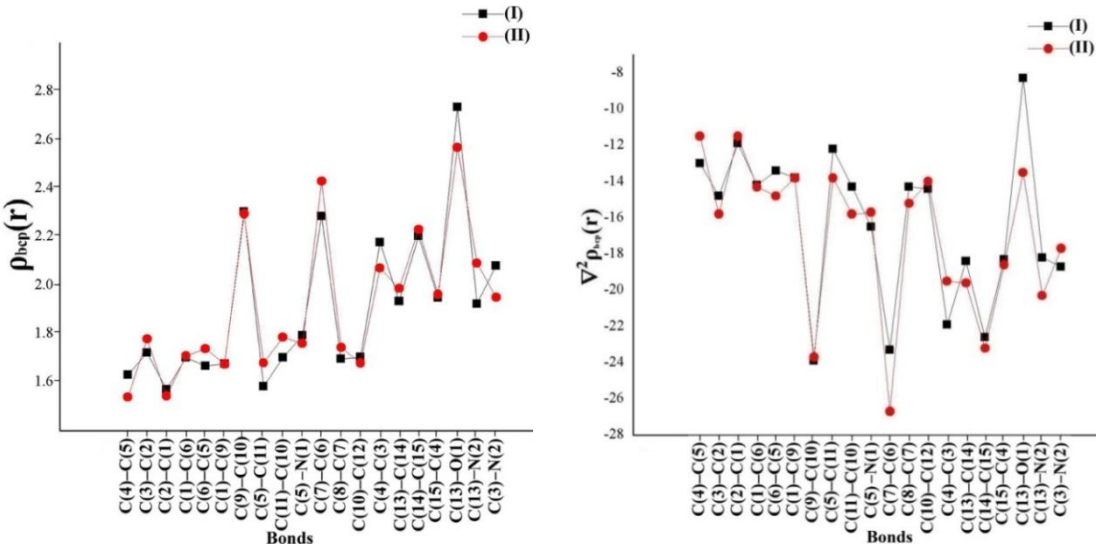
C(1)
C(4)
C(6)
H(15)
C(5)
H(1)
C(6)
C(1)
H(1A)
C(5)
C(9)
H(9)
N(1)
H(2A)
C(11)
C(10)
C(12)
H(12A)

(b)

Figure 4



(a) (b)

Figure 5

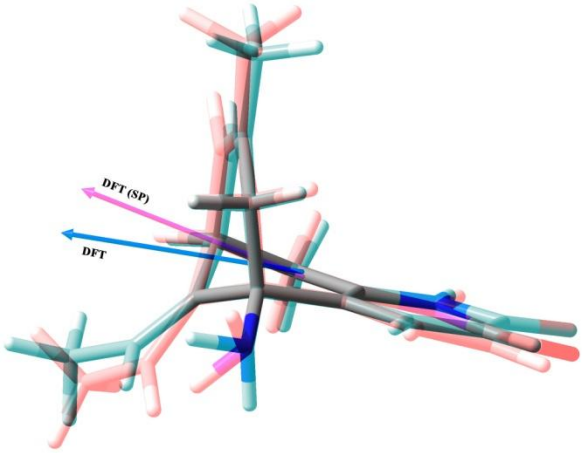
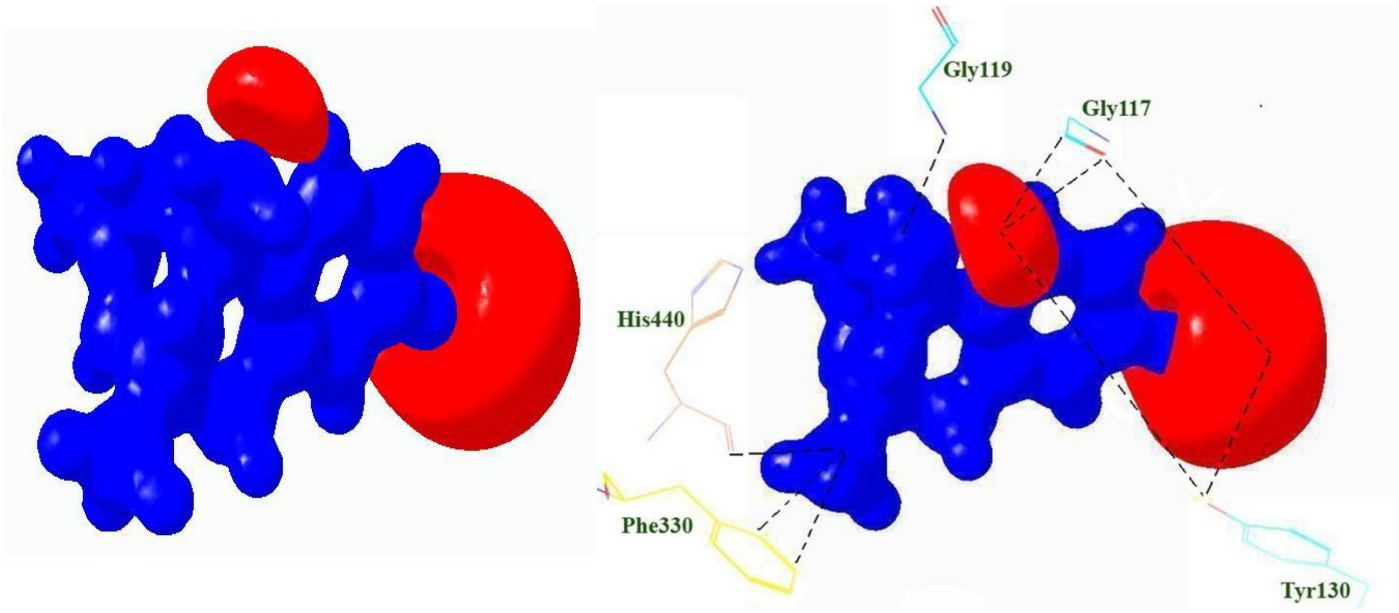


Figure 6



(a) (b)

Table 1. Nearest neighbours and the short intermolecular contact distances (Å) of huperzineA molecule in the active site of AChE.

Ligand atom···Amino acid and residue identifier	Distance
O(1)···Gly117/O	3.02
Tyr130/OH	2.88
Gly123/CA	3.49
C(13)···Gly113/O	3.12
Tyr130/OH	3.39
N(2)···Tyr130/OH	3.21
Gly117/O	3.44
Gly117/C	3.39
C(8)···His440/O	2.65
Phe330/CD2	3.25
Phe330/CE2	3.02
C(12)···Gly119/N	3.08

Table 2. Topological properties of electron density of gas phase (I) and the active site (II) forms of huperzineA molecule (First line indicates HF/6-311G**, second line B3LYP/6-311G** and third line single point energy calculation of B3LYP/6-311G** for the molecule lifted from the active site).

Bonds	$\rho_{bcp}(r)^a$	$\nabla^2\rho_{bcp}(r)^b$	ε	$\lambda_1{}^b$	$\lambda_2{}^b$	$\lambda_3{}^b$	$d_1{}^c$	$d_2{}^c$	D^c
Ring 1,1′									
C(4)–C(5)	1.721	-16.4	0.08	-12.1	-11.2	6.9	0.779	0.754	1.533
	1.630	-13.0	0.07	-11.2	-10.5	8.7	0.774	0.763	1.536
	1.539	-11.5	0.07	-10.4	-9.7	8.7	0.796	0.771	1.567
C(3)–C(2)	1.812	-18.5	0.05	-12.8	-12.2	6.6	0.797	0.707	1.505
	1.722	-14.8	0.05	-12.0	-11.4	8.6	0.778	0.728	1.506
	1.778	-15.8	0.05	-12.4	-11.9	8.5	0.773	0.715	1.489
C(2)–C(1)	1.684	-15.7	0.00	-11.3	-11.3	6.9	0.787	0.752	1.539
	1.569	-11.9	0.00	-10.3	-10.2	8.6	0.786	0.763	1.549
	1.543	-11.5	0.01	-10.1	-10.0	8.6	0.784	0.772	1.556
C(2)–H(2A)	1.924	-24.8	0.01	-17.3	-17.2	9.7	0.681	0.391	1.072
	1.848	-21.8	0.01	-17.0	-16.9	12.0	0.697	0.386	1.083
	1.952	-24.3	0.00	-18.4	-18.3	12.5	0.680	0.376	1.056
C(2)–H(2B)	1.920	-24.7	0.01	-17.4	-17.2	9.9	0.684	0.388	1.073
	1.844	-21.7	0.01	-17.0	-16.9	12.1	0.699	0.384	1.083
	1.951	-24.3	0.01	-18.4	-18.2	12.3	0.679	0.377	1.056
C(1)–C(6)	1.788	-17.6	0.02	-12.4	-12.1	6.8	0.746	0.765	1.511
	1.701	-14.2	0.02	-11.6	-11.3	8.7	0.752	0.759	1.512

	1.709	-14.3	0.02	-11.6	-11.4	8.6	0.750	0.758	1.508
C(1)–H(1)	1.969	-25.8	0.00	-17.9	-17.8	9.9	0.676	0.390	1.066
	1.881	-22.5	0.00	-17.4	-17.4	12.3	0.694	0.385	1.078
	1.970	-24.6	0.00	-18.5	-18.5	12.4	0.676	0.379	1.056
C(6)–C(5)	1.768	-17.2	0.06	-12.5	-11.8	7.1	0.776	0.752	1.528
	1.666	-13.4	0.06	-11.5	-10.9	9.0	0.770	0.762	1.532
	1.738	-14.8	0.05	-12.2	-11.5	8.9	0.752	0.756	1.508
C(1)–C(9)	1.760	-17.1	0.04	-12.2	-11.7	6.8	0.753	0.762	1.516
	1.676	-13.8	0.04	-11.4	-11.0	8.6	0.757	0.759	1.516
	1.675	-13.8	0.04	-11.4	-10.9	8.6	0.755	0.760	1.516
C(9)–H(9)	1.948	-25.5	0.03	-18.0	-17.4	9.9	0.677	0.386	1.063
	1.874	-22.5	0.03	-17.5	-17.1	12.1	0.691	0.383	1.074
	1.941	-24.0	0.03	-18.3	-17.8	12.1	0.676	0.379	1.056
C(9)–C(10)	2.424	-28.1	0.48	-19.3	-13.0	4.2	0.648	0.673	1.321
	2.304	-23.9	0.38	-17.8	-12.9	6.8	0.661	0.674	1.335
	2.295	-23.7	0.38	-17.7	-12.8	6.8	0.659	0.678	1.337
C(5)–C(11)	1.705	-16.1	0.03	-11.8	-11.4	7.1	0.778	0.766	1.544
	1.583	-12.2	0.03	-10.7	-10.4	8.8	0.782	0.772	1.554
	1.679	-13.8	0.02	-11.5	-11.2	8.9	0.770	0.754	1.524
C(11)–C(10)	1.785	-17.7	0.04	-12.5	-12.0	6.8	0.743	0.767	1.510
	1.701	-14.3	0.04	-11.7	-11.2	8.6	0.750	0.760	1.510
	1.786	-15.8	0.04	-12.5	-12.0	8.6	0.736	0.749	1.485
C(11)–H(11A)	1.930	-24.9	0.01	-17.4	-17.3	9.8	0.681	0.390	1.071
	1.855	-21.9	0.01	-17.1	-17.0	12.2	0.698	0.384	1.082
	1.944	-24.0	0.01	-18.1	-18.0	12.1	0.675	0.381	1.056
C(11)–H(11B)	1.903	-24.3	0.01	-16.9	-16.8	9.5	0.680	0.395	1.075
	1.826	-21.3	0.01	-16.6	-16.5	11.8	0.697	0.389	1.086
	1.948	-24.1	0.01	-18.3	-18.0	12.2	0.677	0.379	1.056
C(5)–N(1)	1.872	-21.2	0.04	-13.3	-12.8	5.0	0.919	0.535	1.454
	1.792	-16.5	0.06	-12.9	-12.2	8.6	0.857	0.609	1.465
	1.760	-15.7	0.04	-12.5	-12.0	8.8	0.856	0.621	1.477
N(1)–H(1A)	2.399	-42.6	0.05	-31.9	-30.3	19.6	0.734	0.246	0.980
	2.273	-35.5	0.05	-29.5	-28.1	22.0	0.735	0.263	0.998
	2.360	-38.2	0.05	-31.2	-29.6	22.5	0.724	0.257	0.982
N(1)–H(1B)	2.406	-42.6	0.06	-32.0	-30.3	19.7	0.732	0.246	0.978
	2.278	-35.5	0.05	-29.5	-28.1	22.1	0.733	0.263	0.997
	2.362	-38.6	0.05	-31.4	-29.8	22.6	0.727	0.255	0.981
C(7)–C(6)	2.395	-27.3	0.48	-18.8	-12.7	4.3	0.650	0.672	1.321
	2.285	-23.3	0.38	-17.4	-12.7	6.8	0.662	0.673	1.334
	2.430	-26.7	0.36	-18.9	-13.9	6.1	0.647	0.660	1.306
C(7)–H(7)	1.968	-25.9	0.02	-18.2	-17.8	10.0	0.676	0.385	1.061

	1.884	-22.7	0.02	-17.7	-17.2	12.3	0.692	0.382	1.074
	1.950	-24.0	0.03	-18.3	-17.8	12.1	0.672	0.384	1.056
C(8)–C(7)	1.767	-17.5	0.04	-12.3	-11.8	6.7	0.738	0.767	1.505
	1.696	-14.3	0.04	-11.6	-11.2	8.4	0.744	0.758	1.502
	1.743	-15.2	0.03	-12.0	-11.6	8.4	0.734	0.754	1.488
C(8)–H(8A)	1.933	-25.1	0.01	-17.5	-17.3	9.6	0.675	0.391	1.066
	1.859	-22.1	0.01	-17.1	-17.0	12.0	0.691	0.385	1.077
	1.930	-23.7	0.01	-17.9	-17.8	12.0	0.674	0.382	1.056
C(8)–H(8B)	1.905	-24.4	0.01	-17.1	-16.9	9.6	0.680	0.391	1.072
	1.832	-21.5	0.01	-16.8	-16.6	11.9	0.695	0.387	1.082
	1.932	-23.8	0.01	-18.0	-17.9	12.1	0.676	0.380	1.056
C(8)–H(8C)	1.905	-24.4	0.01	-17.1	-16.9	9.6	0.680	0.392	1.072
	1.831	-21.5	0.01	-16.8	-16.6	11.9	0.695	0.387	1.082
	1.944	-24.1	0.01	-18.2	-18.1	12.2	0.676	0.380	1.056
C(10)–C(12)	1.785	-17.8	0.04	-12.5	-12.0	6.7	0.770	0.736	1.506
	1.703	-14.4	0.04	-11.7	-11.3	8.5	0.761	0.744	1.505
	1.678	-14.0	0.03	-11.4	-11.1	8.5	0.767	0.746	1.513
C(12)–H(12A)	1.901	-24.3	0.01	-17.0	-16.8	9.5	0.680	0.393	1.072
	1.829	-21.4	0.01	-16.7	-16.5	11.8	0.695	0.387	1.083
	1.933	-23.8	0.01	-18.1	-17.9	12.2	0.676	0.379	1.056
C(12)–H(12B)	1.927	-25.0	0.01	-17.4	-17.3	9.7	0.679	0.389	1.068
	1.857	-22.1	0.01	-17.1	-17.0	12.1	0.693	0.384	1.078
	1.930	-23.8	0.01	-18.0	-17.9	12.2	0.676	0.379	1.056
C(12)–H(12C)	1.905	-24.4	0.01	-17.1	-16.9	9.6	0.681	0.391	1.072
	1.832	-21.5	0.01	-16.8	-16.6	11.9	0.696	0.386	1.082
	1.943	-24.0	0.01	-18.1	-18.0	12.1	0.675	0.381	1.056
Ring 2									
C(4)–C(3)	2.336	-27.0	0.46	-18.4	-12.6	4.0	0.597	0.748	1.345
	2.177	-21.9	0.33	-16.6	-12.5	7.3	0.649	0.721	1.370
	2.071	-19.5	0.33	-15.5	-11.6	7.7	0.663	0.732	1.395
C(13)–C(14)	2.013	-22.4	0.16	-15.4	-13.4	6.4	0.764	0.689	1.453
	1.934	-18.4	0.16	-14.5	-12.5	8.5	0.744	0.704	1.448
	1.987	-19.6	0.16	-15.0	-13.0	8.4	0.735	0.699	1.434
C(14)–C(15)	2.354	-27.5	0.35	-18.4	-13.6	4.6	0.643	0.698	1.341
	2.202	-22.6	0.26	-16.7	-13.2	7.2	0.672	0.690	1.362
	2.230	-23.2	0.26	-17.0	-13.4	7.2	0.665	0.691	1.357
C(15)–C(4)	1.978	-20.9	0.14	-14.5	-12.7	6.3	0.738	0.705	1.444
	1.948	-18.3	0.15	-14.1	-12.3	8.2	0.719	0.712	1.430
	1.962	-18.6	0.14	-14.3	-12.5	8.1	0.715	0.712	1.427
C(13)–O(1)	2.893	-0.9	0.06	-29.4	-27.8	56.3	0.401	0.798	1.199
	2.735	-8.3	0.09	-25.0	-23.0	39.7	0.421	0.801	1.223

	2.569	-13.5	0.08	-22.2	-20.5	29.1	0.438	0.819	1.256
C(13)–N(2)	2.059	-16.0	0.04	-16.1	-15.5	15.6	0.920	0.460	1.381
	1.923	-18.2	0.08	-14.0	-12.9	8.7	0.883	0.528	1.411
	2.091	-20.3	0.08	-15.8	-14.6	10.1	0.872	0.502	1.374
C(3)–N(2)	2.093	7.5	0.00	-15.3	-15.3	16.6	0.913	0.455	1.368
	2.081	-18.7	0.10	-15.0	-13.7	10.0	0.873	0.495	1.368
	1.950	-17.7	0.10	-13.6	-12.3	8.3	0.884	0.513	1.397
N(2)–H(2)	2.417	-48.2	0.05	-34.3	-32.6	18.6	0.747	0.226	0.973
	2.292	-39.7	0.05	-31.2	-29.8	21.4	0.745	0.248	0.993
	2.344	-42.9	0.04	-32.7	-31.4	21.2	0.742	0.238	0.980
C(14)–H(14)	1.981	-26.3	0.03	-18.8	-18.2	10.7	0.685	0.371	1.056
	1.906	-23.4	0.03	-18.3	-17.8	12.7	0.695	0.372	1.067
	1.956	-24.6	0.03	-19.0	-18.5	12.8	0.686	0.369	1.055
C(15)–H(15)	2.019	-27.5	0.00	-19.4	-19.4	11.3	0.693	0.364	1.057
	1.925	-24.0	0.01	-18.6	-18.5	13.1	0.702	0.367	1.069
	1.976	-25.2	0.01	-19.2	-19.1	13.1	0.687	0.368	1.055

[(a)]in eÅ^{-3}, [(b)] in eÅ^{-5}, [(c)]in Å.

Table 3. Molecular dipole moment (Debye) of huperzineA (I & II) † Single point energy DFT calculation

Form	Method	μ_x	μ_y	μ_z	μ
I	HF	-6.221	-0.363	-0.306	6.24
I	DFT	-5.878	-0.389	-0.438	5.91
II	DFT(SP)†	-6.827	0.283	-0.526	6.85

Table 4. The calculated global reactivity properties of huperzine A molecule.

Global Reactivity Descriptors	**DFT**	**DFT(SP)**
	Energy (eV)	
Band Gap	-4.68	-4.52
HOMO Energy	-5.72	-562

LUMO Energy	-1.04	-1.1
Ionization Potential $I= -E_{HOMO}$	5.72	5.62
Electron Affinity $A= -E_{LUMO}$	1.04	1.1
Global Hardness $\eta= (I-A)/2$	2.34	2.26
Electronegativity $\chi= (I+A)/2$	3.38	3.36
Electrophilicity $\omega=\mu^2/2\eta$, $\mu= -\chi$	2.44	2.49

Supplementry Table.

Table S1. Lowest docked energy (kcal/mol) of 10 different conformers of HuperzineA-AChE complex.

Conformation	Lowest docked energy
1	-8.46
2	-8.45
3	-8.44
4	-8.44
5	-8.43
6	-8.42
7	-8.40
8	-7.09
9	-6.90
10	-6.06

Table S2. Geometrical parameters of gas phase (I) and the active site (II) forms of huperzineA molecule.

		(I)		(II)†
	Bonds	HF/ 6-311G**	B3LYP/ 6-311G**	B3LYP/ 6-311G**
Bond lengths (Å)				
Ring 1,1′	C(2)–C(1)	1.538	1.549	1.556
	C(3)–C(2)	1.504	1.506	1.489
	C(4)–C(3)	1.345	1.370	1.395
	C(4)–C(5)	1.533	1.536	1.567
	C(6)–C(5)	1.528	1.532	1.507
	C(1)–C(6)	1.511	1.512	1.508
	C(1)–C(9)	1.515	1.516	1.515
	C(7)–C(6)	1.321	1.334	1.306
	C(8)–C(7)	1.505	1.502	1.488
	C(9)–C(10)	1.321	1.335	1.337
	C(5)–C(11)	1.544	1.554	1.524
	C(11)–C(10)	1.510	1.510	1.485
	C(10)–C(12)	1.506	1.505	1.513
	C(5)–N(1)	1.453	1.465	1.476
	N(1)–H(1A)	1.001	1.016	1.070
	N(1)–H(1B)	0.999	1.015	1.070
	C(1)–H(1)	1.081	1.092	1.070
	C(2)–H(2A)	1.088	1.096	1.070

	C(2)–H(2B)	1.088	1.097	1.070
	C(7)–H(7)	1.077	1.088	1.070
	C(8)–H(8A)	1.082	1.091	1.070
	C(8)–H(8B)	1.087	1.096	1.070
	C(8)–H(8C)	1.087	1.096	1.070
	C(9)–H(9)	1.079	1.088	1.070
	C(11)–H(11A)	1.087	1.095	1.070
	C(11)–H(11B)	1.090	1.100	1.070
	C(12)–H(12A)	1.088	1.096	1.070
	C(12)–H(12B)	1.084	1.092	1.070
	C(12)–H(12C)	1.087	1.096	1.070
Ring 2	C(15)–C(4)	1.444	1.430	1.427
	C(13)–C(14)	1.453	1.448	1.433
	C(14)–C(15)	1.341	1.362	1.357
	C(13)–O(1)	1.199	1.223	1.256
	N(2)–H(2)	0.996	1.012	1.000
	C(13)–N(2)	1.381	1.411	1.313
	C(3)–N(2)	1.368	1.368	1.397
	C(14)–H(14)	1.073	1.082	1.070
	C(15)–H(15)	1.074	1.084	1.070
Bond angles (°)				
Ring 1,1′	C(4)–C(3)–C(2)	123.9	123.9	124.0
	C(3)–C(2)–C(1)	110.9	110.8	111.0
	C(2)–C(1)–C(9)	111.1	110.9	113.0
	C(2)–C(1)–C(6)	108.2	108.2	107.6
	C(9)–C(1)–C(6)	110.2	110.5	110.2
	C(1)–C(9)–C(10)	124.0	123.9	123.3
	C(8)–C(7)–C(6)	128.6	128.2	126.7
	C(1)–C(6)–C(7)	125.9	125.8	125.4
	C(1)–C(6)–C(5)	110.1	110.5	110.7
	C(7)–C(6)–C(5)	124.0	123.7	121.6
	C(4)–C(5)–C(6)	108.4	108.7	107.0
	C(4)–C(5)–C(11)	110.1	109.8	110.8
	C(6)–C(5)–C(11)	107.2	107.1	109.3
	C(5)–C(11)–C(10)	113.7	113.9	114.5
	C(9)–C(10)–C(11)	121.5	121.3	121.7
	C(9)–C(10)–C(12)	122.6	122.5	123.8
	C(11)–C(10)–C(12)	115.9	116.2	114.4
	N(1)–C(5)–C(4)	107.9	107.9	110.3
	N(1)–C(5)–C(6)	115.9	116.3	112.3

	N(1)–C(5)–C(11)	107.3	107.0	107.1
	H(1A)–N(1)–H(1B)	108.1	107.6	109.5
	H(1A)–N(1)–C(5)	111.1	110.5	109.5
	H(1B)–N(1)–C(5)	111.2	110.6	109.5
	C(3)–C(2)–H(2A)	109.2	109.6	106.4
	C(3)–C(2)–H(2B)	109.0	109.4	106.4
	C(1)–C(2)–H(2A)	110.3	110.2	106.4
	C(1)–C(2)–H(2B)	110.1	109.8	106.5
	C(2)–C(1)–H(1)	108.1	107.8	108.6
	C(9)–C(1)–H(1)	108.2	108.6	106.0
	C(6)–C(1)–H(1)	111.0	110.9	111.5
	C(1)–C(9)–H(9)	116.2	116.4	118.3
	C(7)–C(8)–H(8A)	113.6	113.4	109.5
	C(7)–C(8)–H(8B)	110.2	110.7	109.5
	C(7)–C(8)–H(8C)	110.2	110.7	109.5
	C(8)–C(7)–H(7)	113.7	114.3	116.7
	C(6)–C(7)–H(7)	117.8	117.4	116.7
	C(10)–C(9)–H(9)	119.7	119.7	118.3
	C(5)–C(11)–H(11A)	109.1	108.8	105.7
	C(5)–C(11)–H(11B)	109.0	108.7	105.7
	C(10)–C(11)–H(11A)	109.8	110.1	105.7
	C(10)–C(11)–H(11B)	108.7	109.0	105.7
	C(10)–C(12)–H(12A)	110.7	111.0	109.5
	C(10)–C(12)–H(12B)	111.6	111.7	109.5
	C(10)–C(12)–H(12C)	110.6	110.9	109.5
	H(2A)–C(2)–H(2B)	107.3	107.0	120.0
	H(8A)–C(8)–H(8B)	107.8	107.7	109.5
	H(8A)–C(8)–H(8C)	107.8	107.7	109.5
	H(8B)–C(8)–H(8C)	106.9	106.5	109.5
	H(11A)–C(11)–H(11B)	106.4	106.1	120.0
	H(12A)–C(12)–H(12B)	108.3	108.1	109.5
	H(12A)–C(12)–H(12C)	107.1	106.7	109.5
	H(12B)–C(12)–H(12C)	108.4	108.3	109.5
Ring 2	C(13)–C(14)–C(15)	120.9	121.5	120.7
	C(14)–C(15)–C(4)	122.5	122.5	122.7
	C(15)–C(4)–C(3)	116.9	117.4	116.9
	C(3)–C(4)–C(5)	122.6	122.1	121.1
	C(14)–C(13)–O(1)	126.2	127.6	124.0
	N(2)–C(13)–O(1)	120.6	120.0	120.3
	C(13)–N(2)–C(3)	126.2	126.8	124.6

	N(2)–C(13)–C(14)	113.3	112.4	115.8
	N(2)–C(3)–C(4)	120.2	119.4	119.2
	H(2)–N(2)–C(13)	114.5	113.8	106.0
	H(2)–N(2)–C(3)	119.3	119.4	128.6
	C(13)–C(14)–H(14)	116.7	116.4	119.6
	C(15)–C(14)–H(14)	122.4	122.1	119.6
	C(14)–C(15)–H(15)	119.8	120.1	118.7
	C(4)–C(15)–H(15)	117.8	117.4	118.7
Interlinking	C(15)–C(4)–C(5)	120.5	120.6	122.0
Bonds	N(2)–C(3)–C(2)	115.8	116.7	116.6
Torsion angles (°)				
Ring 1,1′	C(5)–C(4)–C(3)–C(2)	0.0	-0.8	-0.6
	C(3)–C(4)–C(5)–C(6)	18.9	19.0	21.4
	C(3)–C(4)–C(5)–C(11)	-98.1	-97.8	-97.8
	C(4)–C(3)–C(2)–C(1)	14.3	15.2	13.4
	C(3)–C(2)–C(1)–C(9)	73.9	73.6	75.4
	C(3)–C(2)–C(1)–C(6)	-47.2	-47.7	6.7
	C(2)–C(1)–C(9)–C(10)	-100.7	-100.9	-100.2
	C(6)–C(1)–C(9)–C(10)	19.2	19.0	20.2
	C(2)–C(1)–C(6)–C(7)	-110.6	-110.7	-90.5
	C(2)–C(1)–C(6)–C(5)	69.5	69.6	72.4
	C(9)–C(1)–C(6)–C(7)	127.8	127.8	145.9
	C(9)–C(1)–C(6)–C(5)	-52.2	-52.0	-51.2
	C(1)–C(9)–C(10)–C(11)	0.0	-0.1	-0.3
	C(1)–C(9)–C(10)–C(12)	-179.7	-179.9	-175.7
	C(8)–C(7)–C(6)–C(1)	-0.6	-0.5	-16.4
	C(8)–C(7)–C(6)–C(5)	179.4	179.2	-177.5
	C(1)–C(6)–C(5)–C(4)	-53.1	-53.1	-57.0
	C(1)–C(6)–C(5)–C(11)	65.7	65.4	63.1
	C(7)–C(6)–C(5)–C(4)	127.0	127.1	106.6
	C(7)–C(6)–C(5)–C(11)	-114.2	-114.3	-133.3
	C(4)–C(5)–C(11)–C(10)	72.4	72.5	75.6
	C(5)–C(11)–C(10)–C(9)	14.0	14.2	11.6
	C(5)–C(11)–C(10)–C(12)	-166.3	-166.0	-172.6
	C(3)–C(4)–C(5)–N(1)	145.1	145.9	143.8
	C(1)–C(6)–C(5)–N(1)	-174.5	-175.1	-178.2
	C(7)–C(6)–C(5)–N(1)	5.5	5.2	-14.6
	N(1)–C(5)–C(11)–C(10)	-170.5	-170.6	-164.0
	N(1)–C(5)–C(11)–H(11A)	66.6	66.2	-48.1

N(1)–C(5)–C(11)–H(11B)	-49.1	-48.9	80.1
H(1A)–N(1)–C(5)–C(4)	-63.3	-64.3	-116.9
H(1A)–N(1)–C(5)–C(6)	58.5	58.0	2.4
H(1A)–N(1)–C(5)–C(11)	178.2	177.6	122.4
H(1B)–N(1)–C(5)–C(4)	176.2	176.7	123.1
H(1B)–N(1)–C(5)–C(6)	-62.0	-61.0	-117.6
H(1B)–N(1)–C(5)–C(11)	57.7	58.6	122.4
C(3)–C(2)–C(1)–H(1)	-167.6	-167.7	-167.4
C(4)–C(3)–C(2)–H(2A)	136.1	137.0	-102.1
C(4)–C(3)–C(2)–H(2B)	-107.0	-106.0	128.8
H(2A)–C(2)–C(1)–C(9)	-47.2	-47.9	169.2
H(2A)–C(2)–C(1)–C(6)	-168.3	-169.1	-51.9
H(2A)–C(2)–C(1)–H(1)	71.3	70.9	-51.9
H(2B)–C(2)–C(1)–C(9)	-165.4	-165.5	-40.1
H(2B)–C(2)–C(1)–C(6)	73.4	73.3	-162.0
H(2B)–C(2)–C(1)–H(1)	-46.9	-46.7	77.2
C(2)–C(1)–C(9)–H(9)	78.6	78.2	79.7
C(6)–C(1)–C(9)–H(9)	-161.5	-161.9	-159.8
H(1)–C(1)–C(9)–H(9)	-39.9	-40.1	-39.1
H(1)–C(1)–C(9)–C(10)	140.8	140.8	140.9
H(1)–C(1)–C(6)–C(7)	7.9	7.4	28.5
H(1)–C(1)–C(6)–C(5)	-172.1	-172.4	-168.6
H(9)–C(9)–C(10)–C(11)	-179.3	-179.2	179.7
H(9)–C(9)–C(10)–C(12)	1.0	1.0	4.3
H(8A)–C(8)–C(7)–H(7)	-179.4	180.0	0.0
H(8A)–C(8)–C(7)–C(6)	0.5	-0.1	-180.0
H(8B)–C(8)–C(7)–H(7)	59.5	58.9	120.0
H(8B)–C(8)–C(7)–C(6)	-120.6	-121.2	-60.0
H(8C)–C(8)–C(7)–H(7)	-58.3	-58.9	-120.0
H(8C)–C(8)–C(7)–C(6)	121.6	121.0	60.0
H(7)–C(7)–C(6)–C(1)	179.3	179.4	163.6
H(7)–C(7)–C(6)–C(5)	-0.7	-0.9	2.5
C(4)–C(5)–C(11)–H(11A)	-50.5	-50.7	-168.5
C(4)–C(5)–C(11)–H(11B)	-166.2	-165.8	-40.3
C(6)–C(5)–C(11)–C(10)	-45.3	-45.3	-42.1
C(6)–C(5)–C(11)–H(11A)	-168.2	-168.5	73.8
C(6)–C(5)–C(11)–H(11B)	76.1	76.5	-158.0
H(11A)–C(11)–C(10)–C(9)	136.5	136.7	-104.3
H(11A)–C(11)–C(10)–C(12)	-43.8	-43.5	71.5
H(11B)–C(11)–C(10)–C(9)	-107.6	-107.3	127.5
H(11B)–C(11)–C(10)–C(12)	72.1	72.5	-56.7

	C(9)–C(10)–C(12)–H(12A)	123.5	123.2	175.7
	C(9)–C(10)–C(12)–H(12B)	2.8	2.4	55.7
	C(9)–C(10)–C(12)–H(12C)	-118.0	-118.5	-64.3
	C(11)–C(10)–C(12)–H(12A)	-56.2	-56.6	0.0
	C(11)–C(10)–C(12)–H(12B)	-176.9	-177.4	-120.0
	C(11)–C(10)–C(12)–H(12C)	62.3	61.8	120.0
Ring 2	C(3)–N(2)–C(13)–C(14)	-0.6	-0.5	-2.3
	C(13)–C(14)–C(15)–C(4)	0.2	0.2	0.5
	C(14)–C(15)–C(4)–C(3)	-1.2	-0.9	-2.5
	C(14)–C(15)–C(4)–C(5)	-179.7	-179.4	175.4
	O(1)–C(13)–C(14)–C(15)	-179.6	-179.9	-179.5
	C(13)–N(2)–C(3)–C(4)	-0.4	-0.2	0.3
	N(2)–C(13)–C(14)–C(15)	0.7	0.4	1.9
	C(3)–N(2)–C(13)–O(1)	179.7	179.8	179.0
	C(15)–C(4)–C(3)–N(2)	1.3	0.8	2.1
	H(2)–N(2)–C(13)–O(1)	-0.8	-0.7	-10.9
	O(1)–C(13)–C(14)–H(14)	0.4	0.1	0.5
	H(2)–N(2)–C(13)–C(14)	178.9	179.0	167.8
	H(2)–N(2)–C(3)–C(4)	-179.9	-179.6	-167.5
	N(2)–C(13)–C(14)–H(14)	-179.3	-179.6	-178.1
	C(13)–C(14)–C(15)–H(15)	179.5	179.2	-179.5
	H(14)–C(14)–C(15)–C(4)	-179.8	-179.8	-179.5
	H(14)–C(14)–C(15)–H(15)	-0.4	-0.7	0.5
	H(15)–C(15)–C(4)–C(3)	179.4	-179.9	177.5
	H(15)–C(15)–C(4)–C(5)	0.9	1.5	-4.6
Interlinking Bonds	C(15)–C(4)–C(5)–C(11)	80.3	80.7	84.4
	C(15)–C(4)–C(5)–C(6)	-162.8	-162.5	-156.5
	C(15)–C(4)–C(3)–C(2)	-178.4	-179.3	177.3
	C(13)–N(2)–C(3)–C(2)	179.3	179.9	-175.3
	C(5)–C(4)–C(3)–N(2)	179.7	179.3	-175.8
	C(15)–C(4)–C(5)–N(1)	-36.5	-35.6	-34.0
	N(2)–C(3)–C(2)–C(1)	-165.4	-164.9	-171.3
	N(2)–C(3)–C(2)–H(2A)	-43.6	-43.1	73.2
	H(2)–N(2)–C(3)–C(2)	-0.2	0.5	17.0
	N(2)–C(3)–C(2)–H(2B)	73.2	73.9	-55.9

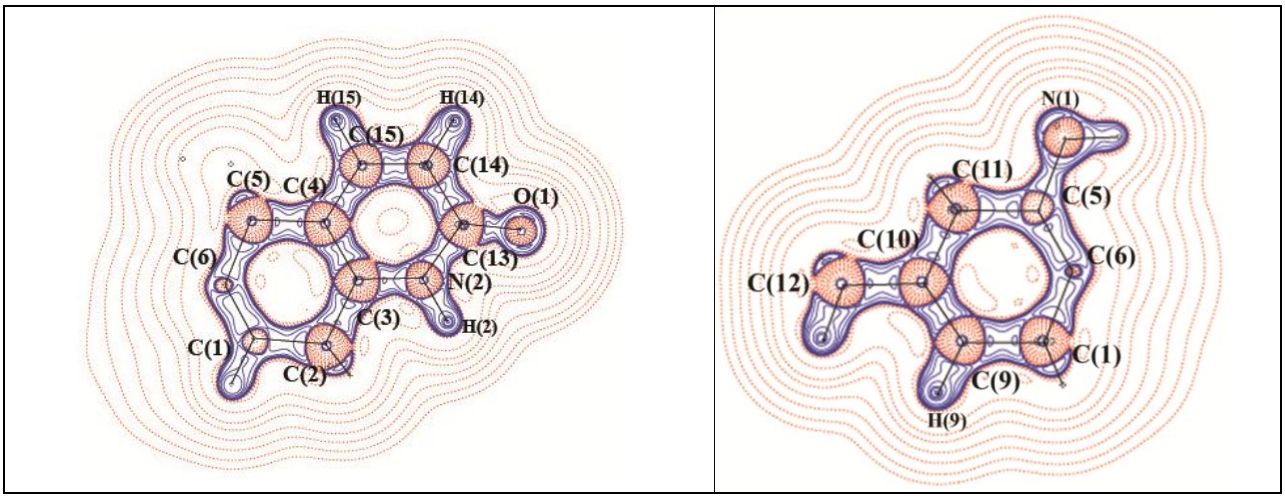
† single point energy DFT calculation.

Table S3. Atomic charges (e) of (I) and (II) forms of huperzineA molecule. (First line indicates HF/ 6-311G**, second line B3LYP/6-311G** and third line the single point energy calculation of B3LYP/6-311G** for the molecule lifted from the active site).

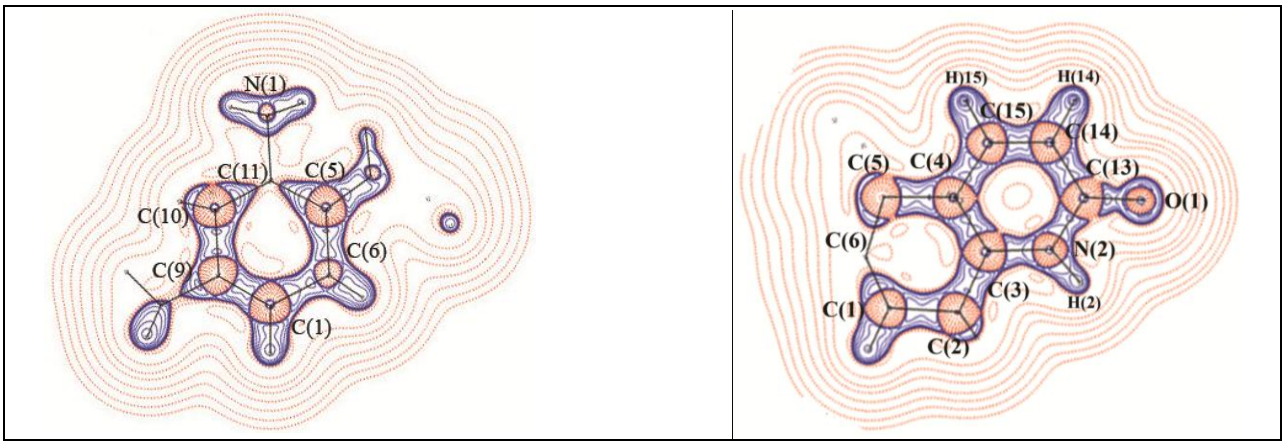
Atoms	MPA	NPA	AIM	Atoms	MPA	NPA	AIM
C(1)	-0.20	-0.20	0.13	H(1)	0.12	0.19	-0.04
	-0.20	-0.30	0.06		0.13	0.21	0.00
	-0.22	-0.24	0.07		0.13	0.21	-0.01
C(2)	-0.10	-0.30	0.14	H(1A)	0.20	0.34	0.36
	-0.10	-0.40	0.04		0.20	0.35	0.33
	-0.10	-0.40	0.07		0.20	0.34	0.34
C(3)	0.40	0.33	0.44	H(1B)	0.19	0.34	0.35
	0.30	0.26	0.41		0.19	0.35	0.32
	0.25	0.26	0.36		0.19	0.35	0.33
C(4)	-0.30	-0.20	0.06	H(2)	0.25	0.40	0.44
	-0.20	-0.10	-0.01		0.23	0.40	0.39
	-0.10	-0.11	-0.02		0.23	0.41	0.41
C(5)	0.00	0.19	0.54	H(2A)	0.11	0.18	-0.04
	-0.10	0.16	0.37		0.12	0.21	0.00
	-0.18	0.16	0.35		0.14	0.22	0.01
C(6)	-0.10	0.00	-0.09	H(2B)	0.13	0.19	-0.02
	0.00	0.00	-0.05		0.14	0.21	0.01
	-0.02	-0.01	-0.04		0.13	0.21	0.02
C(7)	-0.10	-0.20	0.01	H(7)	0.07	0.17	-0.04
	-0.10	-0.20	-0.03		0.06	0.18	-0.01
	-0.14	-0.17	-0.01		0.08	0.16	-0.03
C(8)	-0.20	-0.50	0.16	H(8A)	0.09	0.17	-0.04
	-0.30	-0.60	0.03		0.10	0.19	-0.01
	-0.27	-0.59	0.06		0.12	0.20	-0.01
C(9)	-0.10	-0.20	-0.01	H(8B)	0.10	0.18	-0.03
	-0.10	-0.20	-0.05		0.12	0.21	0.01
	-0.06	-0.22	-0.04		0.13	0.21	0.00
C(10)	-0.20	0.04	-0.04	H(8C)	0.10	0.18	-0.04
	-0.10	0.02	-0.01		0.12	0.20	0.00
	-0.15	0.05	-0.02		0.11	0.20	-0.01
C(11)	0.00	-0.40	0.13	H(9)	0.09	0.18	-0.03
	-0.10	-0.40	0.03		0.08	0.19	0.00
	-0.08	-0.43	0.05		0.08	0.19	-0.01
C(12)	-0.20	-0.50	0.15	H(11A)	0.12	0.19	-0.03
	-0.30	-0.60	0.02		0.13	0.21	0.01
	-0.26	-0.59	0.05		0.12	0.21	0.00

C(13)	0.60	0.79	1.69	H(11B)	0.11	0.18	-0.05
	0.40	0.63	1.31		0.11	0.20	-0.01
	0.37	0.62	1.28		0.13	0.21	-0.01
C(14)	-0.30	-0.30	0.02	H(12A)	0.10	0.18	-0.04
	-0.30	-0.30	-0.04		0.11	0.20	0.00
	-0.24	-0.28	-0.01		0.13	0.21	0.00
C(15)	0.20	-0.10	-0.02	H(12B)	0.09	0.18	-0.03
	0.10	-0.10	-0.02		0.11	0.20	0.00
	0.11	-0.14	0.00		0.13	0.21	-0.01
N(1)	-0.50	-0.90	-1.15	H(12C)	0.11	0.18	-0.03
	-0.40	-0.90	-0.96		0.12	0.21	0.01
	-0.41	-0.83	-0.97		0.11	0.20	0.00
N(2)	-0.60	-0.70	-1.51	H(14)	0.12	0.20	0.02
	-0.50	-0.60	-1.13		0.11	0.22	0.04
	-0.44	-0.58	-1.15		0.11	0.21	0.04
O(1)	-0.50	-0.70	-1.36	H(15)	0.12	0.21	0.04
	-0.40	-0.60	-1.15		0.11	0.23	0.06
	-0.42	-0.67	-1.12		0.09	0.21	0.03

Figure S1



(a)



(b)

Figure 4. The Laplacian of electron density of HuperzineA molecule (a,b) in the gas phase (I) and (c,d) the same lifted from the active site (II). Contours are drawn in logarithmic scale, $3x2^N$ $eÅ^{-5}$, where N=2,4 and $8x10^n$, n=-2,-1,0,1,2. Solid lines are positive contours, dotted lines are negative contours.