Electronic Supplementary Material (ESI) for RSC Advances

Supporting Information

Interaction of pyrazinamide drug functionalized carbon and boron nitride nanotubes with pncA protein: a molecular dynamics and density functional approach

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Contents:

1. Computational Details

DFT:

The *ab initio* spin polarized DFT calculation is adopted using SIESTA[1] code. The generalized gradient approximation (GGA) within the Perdew Burke Ernzerhof (PBE) is used to describe the exchange correlation energy. [2] As it is well known that LDA produces electronic densities more homogeneous than the exact ones which leads to overestimation of binding energy values (predominant in case of weakly bound systems), it is believed that for molecular systems, GGA significantly improves the binding (adsorption) energy values. Although conventional DFT methods like LDA and GGA cannot account for dispersive interactions like π–π stacking and van der Waals interaction yet we can get a qualitative generalized overview towards the noncovalent functionalization of organic therapeutic molecules of varying chirality indices and diameter. Troullier Martins type pseudopotentials[3] in the Kleinman–Bylander[4] form and double zeta with polarization function (DZP) basis set are used to describe the valence state wavefunction and the reciprocal space within the real-space integration performed on a regular grid corresponding to a plane – wave cutoff of 300Ry. The radial part of the basis function is described using the zeta function. To sample the Brillouin Zone (BZ) a set of 60 Monkhorst–Pack[5] special k-points are used along the nanotube axis with a vacuum separation of about 20 Å to avoid the lateral interactions between the replicating periodic supercell images. The conjugate gradient (CG)

method is employed to perform the geometry optimization and the system is relaxed until the residual forces of all the atoms are converged below 0.03 eV/Å.

To investigate the interaction of PZA molecule with CNTs, nanotubes of varying chirality namely, armchair (5,5) comprising of 5 unit cells (100 atoms) and zigzag (8,0) CNT comprising of 3 unit cells (96 atoms), respectively are adopted in the simulation. For PZA adsorbed onto BBNT, (5,5) BNNT comprising of 5 unit cells (isoelectronic with (5,5) SWCNT) is considered for the study. The adsorption onto the two different CNTs are studied for three basic adsorption sites: (a) hollow, (b) bridge, and (c) top sites, the pictorial description of which is given in Fig. 1(a), likewise for PZA adsorption onto (5,5) BNNT the following sites are considered: (a) hollow, (b) bridge, (c) B top and (d) N top sites as depicted in Fig. 1(b). The band structure, density of states (DOS), projected density of states (PDOS) and wavefunction of the isosurface corresponding to highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) are calculated.

The adsorption energy is defined as

$$E_{ads} = E_{(complex)} - E_{(CNT/BNNT)} - E_{(PZA)}, \quad (1)$$

where $E_{(complex)}$ is the total energy of the system (CNT/BNNT+PZA). By definition, a more negative E_{ads} denotes a more favourable interaction between the drug-nanotube systems.

Molecular docking:

For docking studies the structure of the wild type pncA protein is retrieved from protein data bank (PDB: 3PL1). The structures of PZA, and PZA functionalized (5,5) SWCNT, (8,0) SWCNT and (5,5) BNNT are taken from the optimized DFT calculations. The docking simulations are performed using Molegro Virtual Docker for active binding of the SWNT functionalized with PZA onto the protein. The detection active binding site within the enzyme is performed for drug binding utilizing MolDock function which is based on the evolutionary algorithm, which combines differential evolution with cavity prediction algorithm. The docking scoring function is an extension of the piecewise linear potential (PLP) which includes the H–bonding and the electrostatic terms. The search algorithm selected is the Moldock SE and docking simulation was performed for 100 runs with maximum iterations of 1500, population size of 50 and energy threshold of 100. From the docking simulation the best pose (best docked conformer) is generated and sorted based on the re-rank score which uses the weighed combination of terms like the steric (LJ12–6) term and identifies the most promising docking solution from the solutions obtained by the docking algorithm.

Molecular Dynamics:

The molecular dynamics simulation has been performed to probe the interaction of (5,5) SWCNT, PZA drug and PZA/(5,5) SWCNT with pncA protein. The MD simulation has been performed only for (5,5) SWCNT taken as the model nanotube system to get the essence of interaction between the complex (PZA/SWCNT) and pncA protein. We have not performed the MD simulation of BNNT system as we could not derive the force field parameter for BNNT. Three set of MD simulation has been carried out: (a) PZA with protein, (b) (5,5)

SWCNT with pncA and (c) PZA/CNT with pncA. These simulations have been done using GROMACS 4.0.4 simulation package with OPLSA force field. [6] The starting geometries were centered in a cubic periodic box of TIP3P water molecules. [7] The distance between the surface atom of the complexes and walls of the box is kept greater than 12Å in all considered systems. Before performing the MD simulation, energy minimization is performed using the conjugant gradient (CG) algorithm for all the three investigated systems for 10ns at 298 K temperature and 1 bar pressure. In the modelling of the system, periodic boundary condition is assumed. The energy minimization was finally followed by equilibration and 20ns MD simulation without any position restraints in the NVT ensemble at 298 K with a time step of 2fs. The visualization and analysis of the configurations are performed with the help of VMD[8] and PyMOL[9] packages.

(1) P. Ordejón, E. Artacho, J. M. Soler, *Phys. Rev. B*, 1996, **53**, 10441.

(2) J. P. Pewdew, K. Burke, M. Ernzerhof, *Phys. Rev. Lett*., 1996, **77**, 3865.

(3) N. Troullier, J.L. Martins, *Phys Rev B*, 1991, **43**, 1993.

(4) L. Kleinman, D.M. Bylander, *Phys. Rev. Lett.*, 1982, **48**, 1425.

(5) H.J. Monkhorst, J.D. Pack, *Phys Rev B*, 1976, **13**, 5188.

(6) D. van der Spoel, E. Lindahl, B. Hess, G. Groenhof, A.E. Mark, H.J.C. Berendsen, *J. Comput. Chem*. 2005, **26**, 1701.

(7) H.J.C. Berendsen, J.R. Grigera, T.P. Straatsma, *J. Phys. Chem*. 1987, **91**, 6269.

(8) W. Humphrey, A. Dalke, K. Schulten, *J. Mol. Graphics* 1996, **14**, 33–38.

(9) The PyMOL Molecular Graphics System, Version 1.5.0.4 Schrödinger, LLC.

2. Supplementary Tables

Table S1. Summary of calculated distances (R) from the aromatic ring of PZA molecule onto (5,5), (8,0) CNTs and (5,5) BNNT surfaces, adsorption energies (*E*ads) of PZA onto nanotubes, Fermi energy, energy difference at the first van Hove singularity for pristine and functionalized PZA/nanotube systems.

System	Optimum distance (Å)	*E*ads (eV)	Fermi Energy (eV)	Energy difference (eV)
PZA	–	–	–3.201	2.821
(5,5) CNT	–	–	–3.411	2.275
PZA/(5,5) CNT hollow	3.06	–1.395	–3.440	2.122
PZA/(5,5) CNT bridge	3.11	-1.432	–3.434	2.201
PZA/(5,5) CNT top	2.98	-1.431	–3.428	2.159
(8,0) CNT	–	–	–3.667	0.547
PZA/(8,0) CNT hollow	3.23	–0.905	–3.682	0.538
PZA/(8,0) CNT bridge	3.01	–0.937	–3.697	0.543
PZA/(8,0) CNT top	3.17	–0.946	–3.688	0.541
(5,5) BNNT	–	–	–3.344	4.932
PZA/(5,5) BNNT hollow	3.20	–0.854	–4.718	2.800
PZA/(5,5) BNNT bridge	3.28	–0.858	–4.725	2.833
PZA/(5,5) BNNT N top	3.27	–0.867	–4.581	2.836
PZA/(5,5) BNNT B top	3.16	–0.813	–4.594	2.792

Table S2. The MolDock score, re-rank score, H bond score for bare PZA drug and PZA functionalized onto (5,5) SWCNT, (8,0) SWCNT and (5,5) BNNT. All the parameters are in arbitrary units.

Parameters	Bare PZA docked onto pncA	PZA/(5,5) SWCNT–pncA	PZA/(8,0) SWCNT–pncA	PZA/(5,5) BNNT–pncA
MolDock score PZA (au)	–54.644	–55.119	–56.099	–57.387
Re-rank score PZA (au)	–46.609	–47.024	–47.486	–48.363
MolDock score SWCNT/BNNT (au)	–	–119.676	–135.71	– 121.121
Re-rank score SWCNT/BNNT (au)	–	4.012	–31.126	–87.963
H bond score PZA (au)	– 5.007	–4.901	–4.968	–6.074
H bond score SWCNT/BNNT (au)	–	–	–	–1.649

3. Supplementary Figures

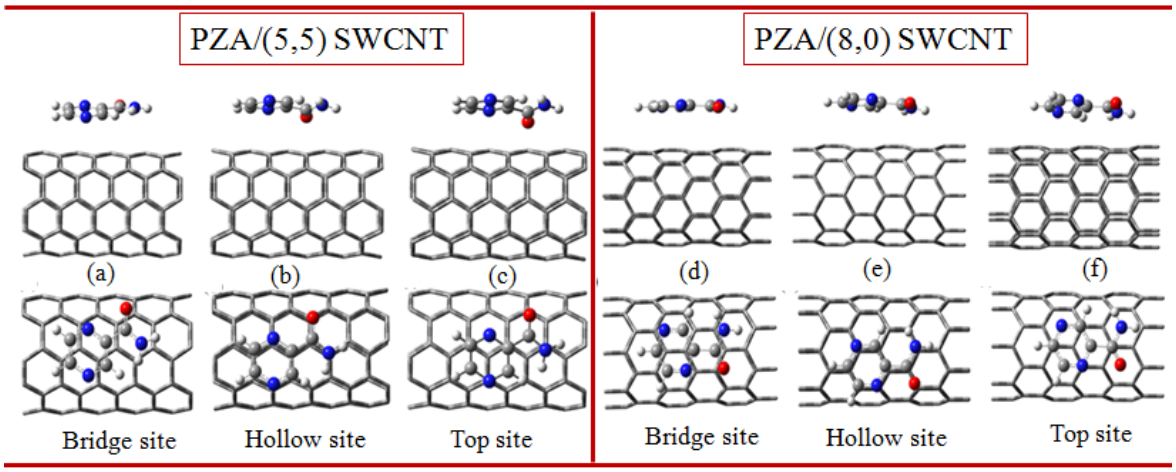

Figure S1. The optimized geometry of PZA functionalized onto (5,5) SWCNT at (a) bridge, (b) hollow, (c) top sites; PZA functionalized onto (8,0) SWCNT at (d) bridge, (e) hollow, and (f) top sites.

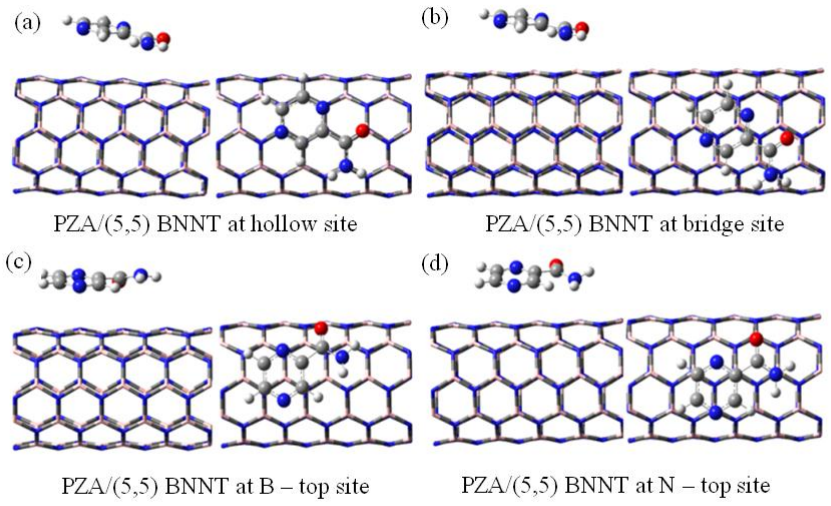

Figure S2. The optimized geometry of PZA functionalized onto (5,5) BNNT at (a) hollow, (b) bridge, (c) B-top and (d) N-top sites.

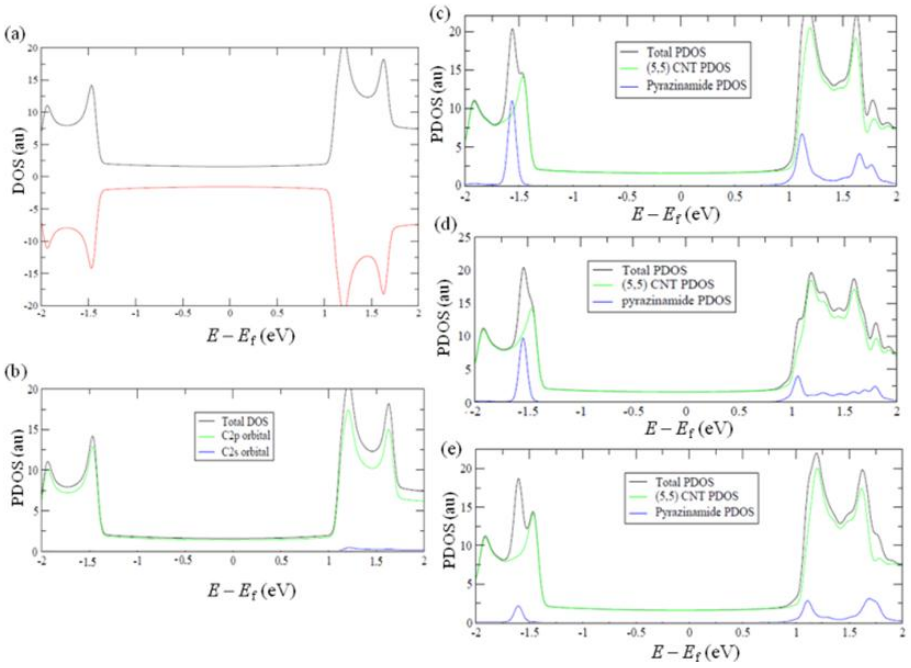

Figure S3. (a) The calculated DOS vs. Energy plot of pristine (5,5) CNT, (b) total PDOS of pristine (5,5) CNT, combined total PDOS of PZA functionalized onto (5,5) CNT at (c) bridge site, (d) hollow site and (e) top sites. The Fermi level is set to 0 eV and the energy has been scaled with respect to the Fermi energy.

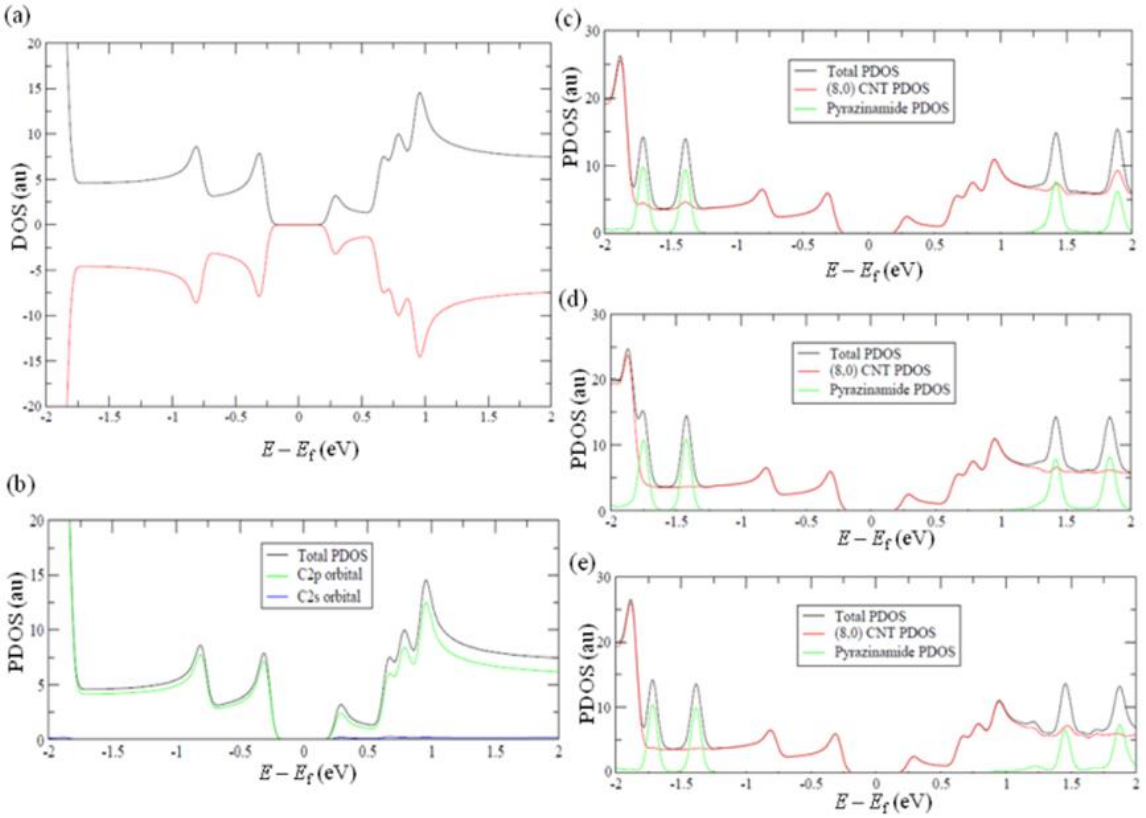

Figure S4. The DOS vs. Energy plot of pristine (8,0) CNT, (b) PDOS of pristine (8,0) CNT, combined total PDOS of PZA functionalized onto (8,0) CNT at (c) bridge site, (d) hollow and (e) top sites. The Fermi level is set to 0 eV and the energy has been scaled with respect to the Fermi energy.

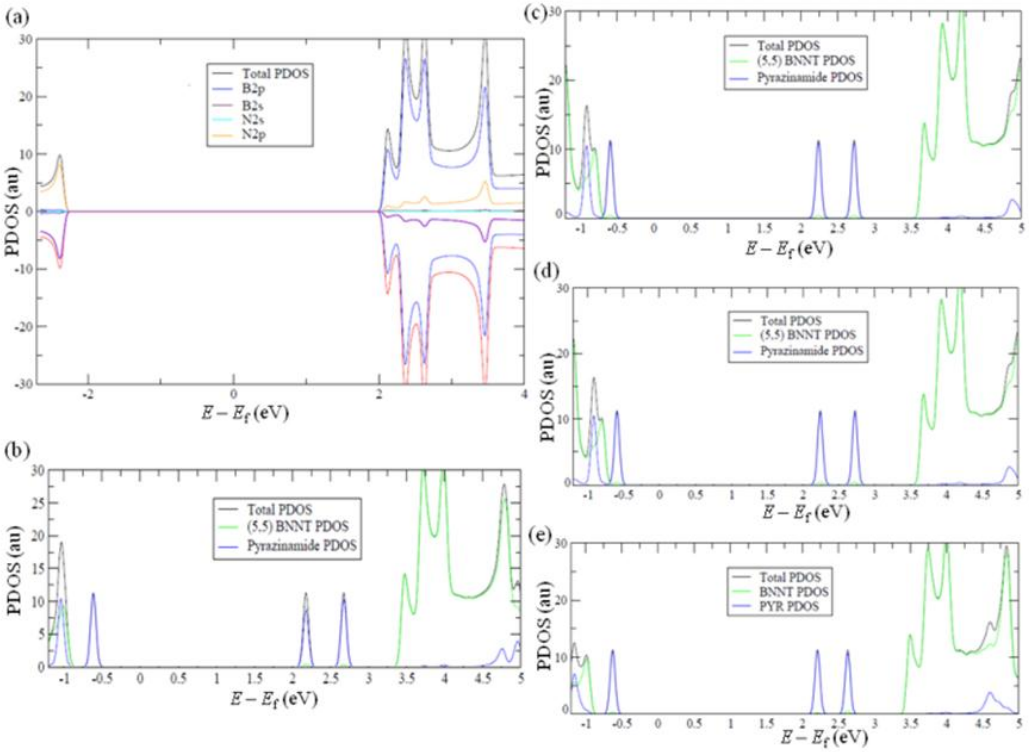

Figure S5. The total PDOS vs. Energy plot of (a) pristine (5,5) BNNT, combined total PDOS of PZA functionalized onto (5,5) BNNT at (b) B top, (c) bridge site, (d) hollow site and (e) N top sites. The Fermi level is set to 0 eV and the energy has been scaled with respect to the Fermi energy.

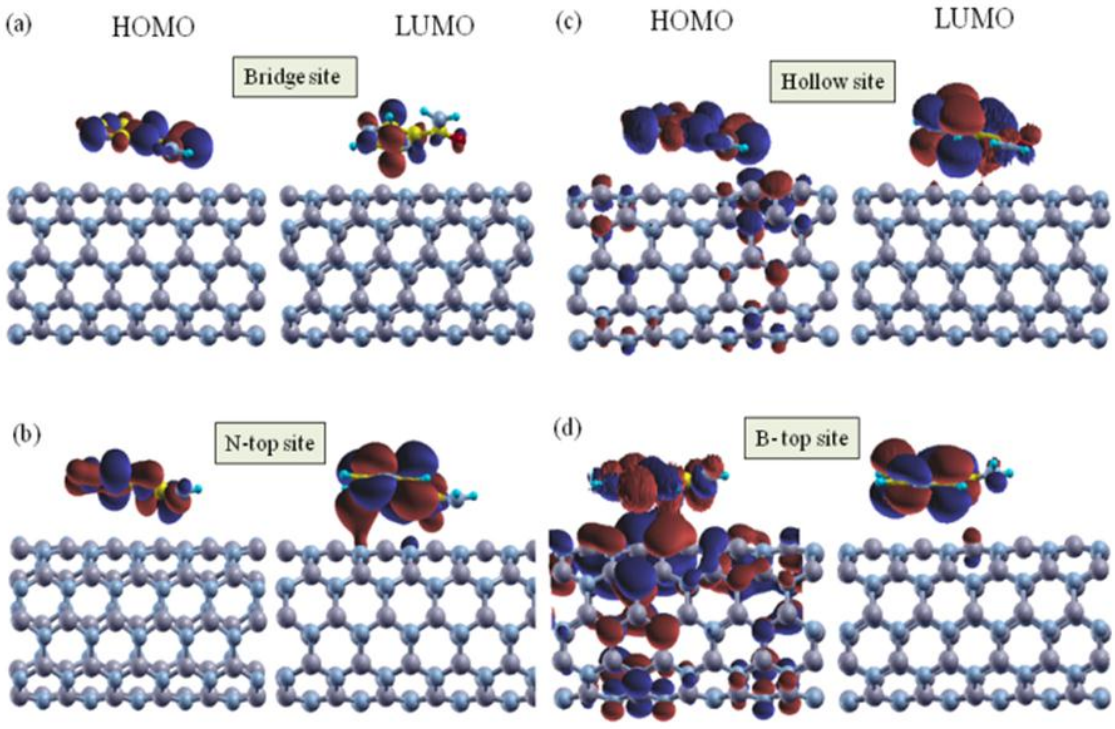

Figure S6. Isosurface corresponding to the HOMO and LUMO for PZA adsorbed onto (5,5) BNNT at (a) bridge, (b) N top, (c) hollow and (d) B top sites.

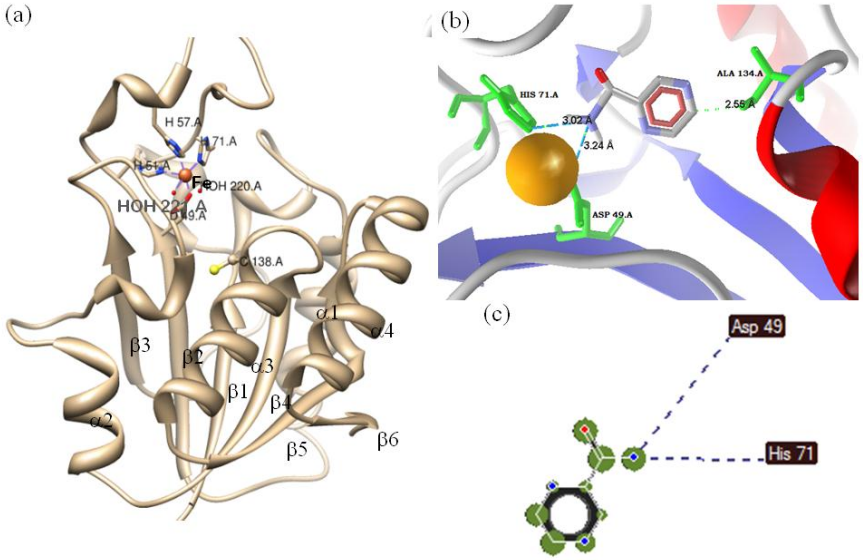

Figure S7. (a)The optimized structure of pncA protein depicting the active binding residues and the Fe2+ cofactor, (b) hydrogen bond interaction between PZA and His71 and Asp49 (lines shown in blue) and non-bonded interaction between PZA and Ala134 (lines shown in green) of the pncA protein. The Fe+2 co–factor is depicted in orange circle, (e) depiction of the hydrogen bonded interaction between PZA/Asp49 and PZA/His71 residues.

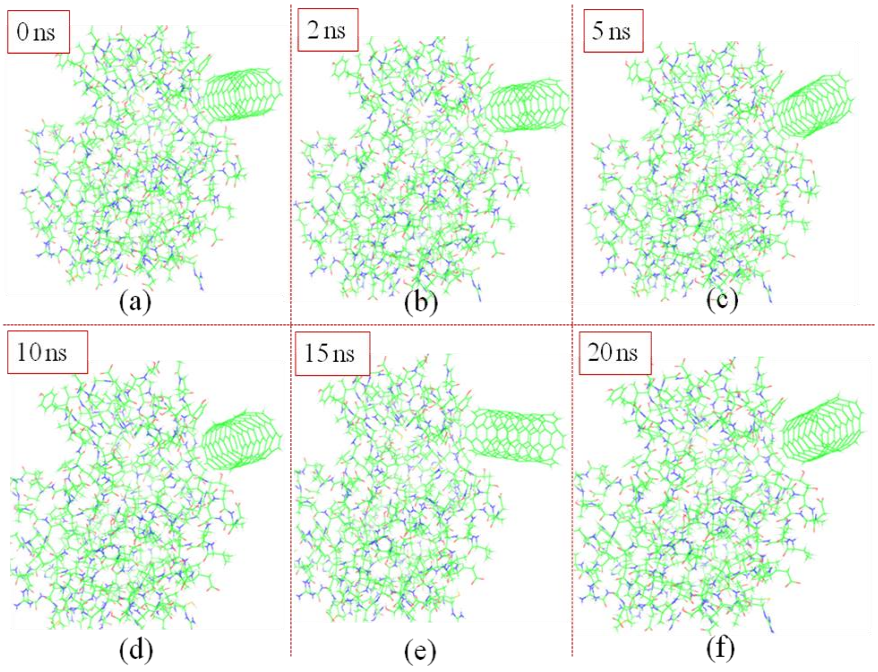

Figure S8 Representative snapshots at various times for the interaction of (5,5) SWCNT with pncA protein, (a) 0ns, (b) 2 ns, (c) 5 ns, (d) 10 ns, (e) 15 ns and (f) 20 ns.

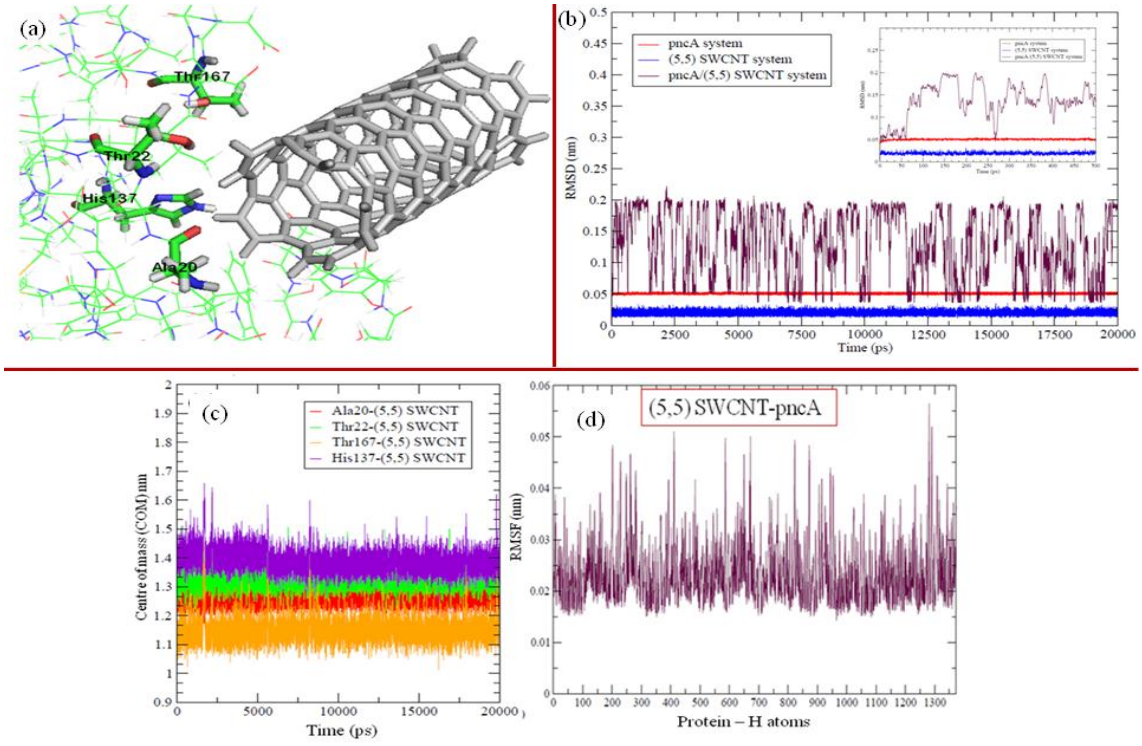

Figure S9 (a) Selective amino acid residues namely Ala20, Thr22, His137, and Thr167 in close proximity to (5,5) SWCNT, (b) RMSD) of (5,5) SWCNT, pncA protein and (5,5) SWCNT-pncA combined. The inset picture illustrates zoom in of the RMSD up to 500 ps, (c) distance between (5,5) SWCNT and key residues of pncA, (d) RMSF of pncA protein without the hydrogen atoms and ligand.

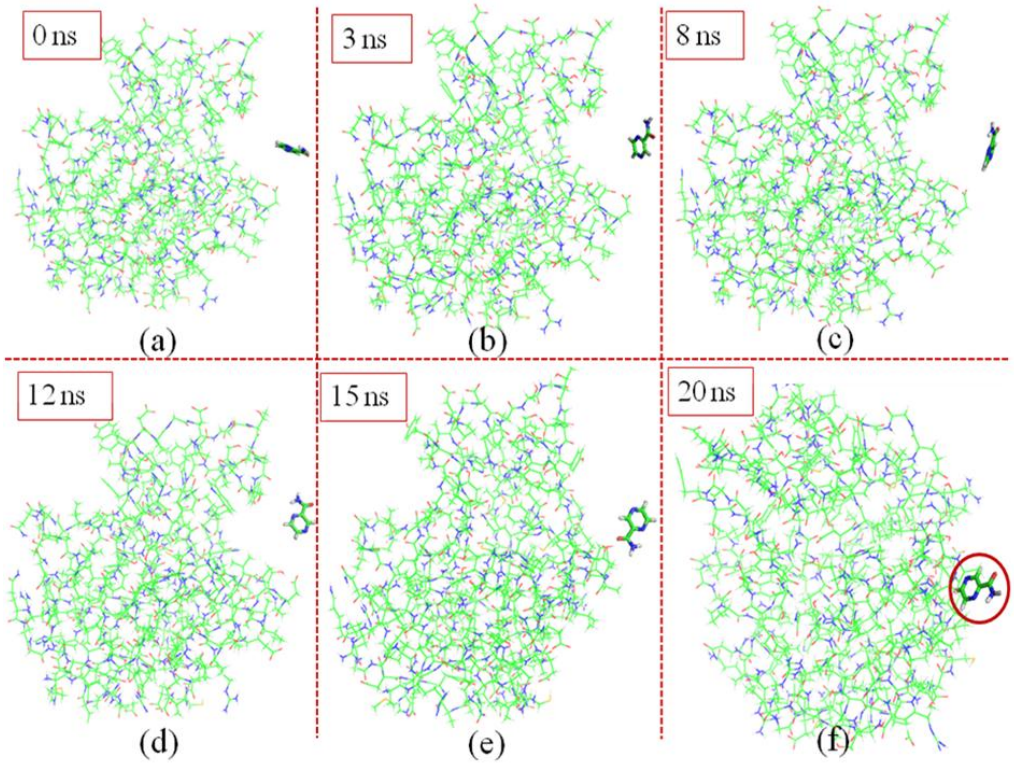

Figure S10. Representative snapshots at various times for the interaction of PZA drug with pncA protein, (a) 0ns, (b) 3 ns, (c) 8 ns, (d) 12 ns, (e) 15 ns and (f) 20 ns.

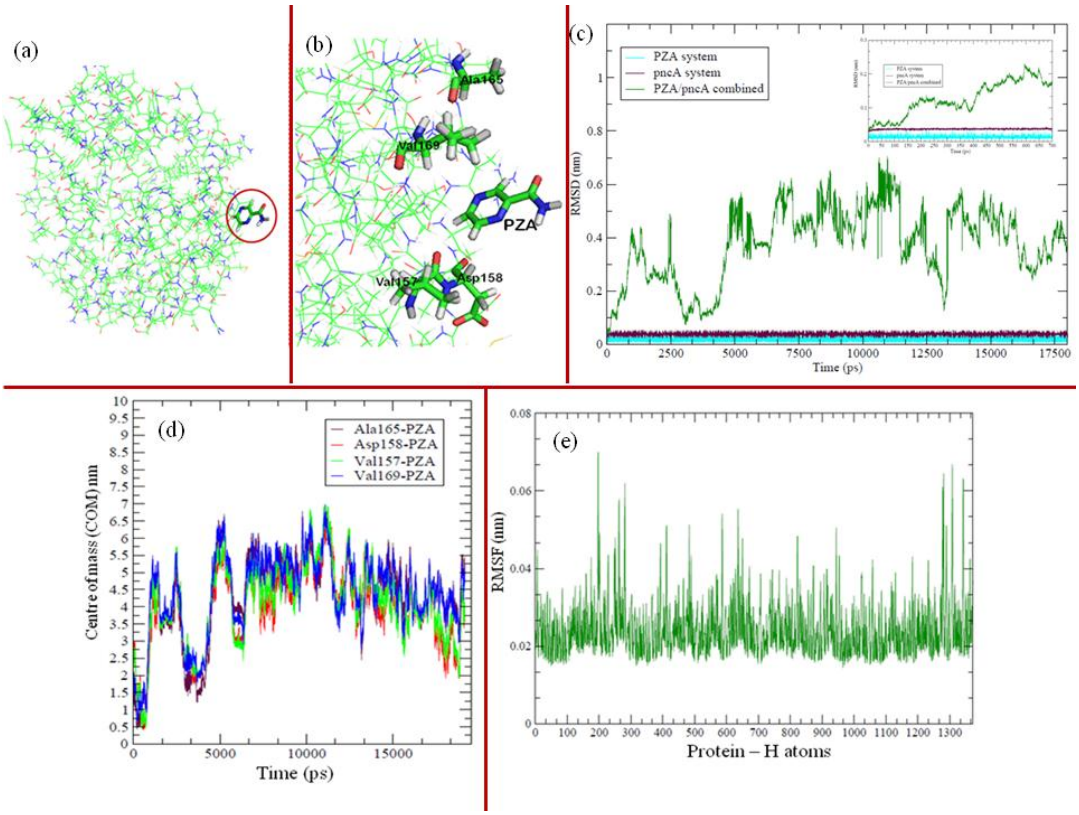

Figure S11. (a) The representative snapshot of PZA (circled in red) with pncA protein at 20ns simulation time, (b) the nearest interacting residues Val157, Asp158, Ala165, and Val169 in close proximity of PZA drug, (c) Root mean square deviation (RMSD) with respect to time (ps) of PZA, pncA protein and PZA-pncA protein combined. The inset picture illustrates zoom in of the RMSD up to 700 ps, (d) distance between the PZA drug and key residues of pncA as a function of time (ps), (e) the root mean square fluctuations (RMSF) of protein without the hydrogen atoms in PZA/pncA system.