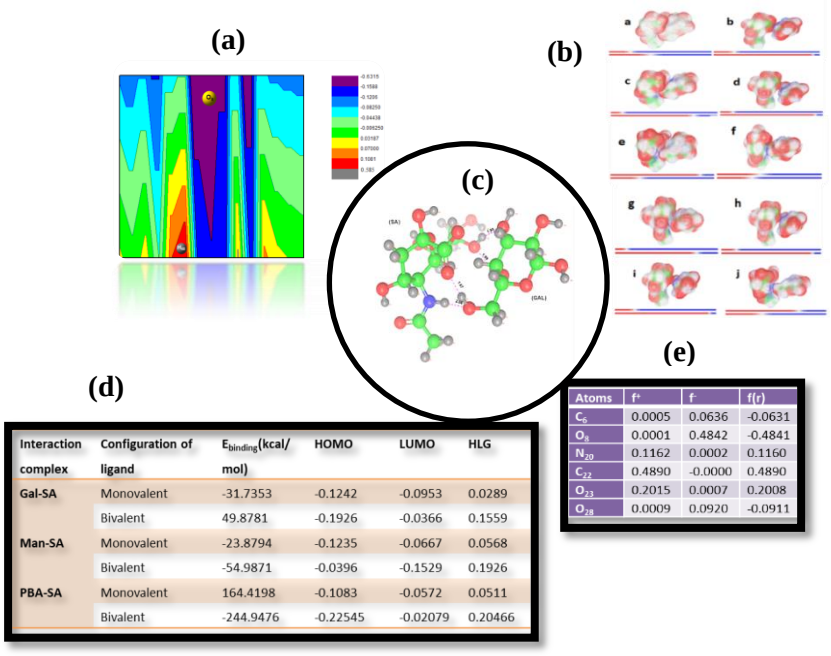
Chapter-6

Summary and Future scope

In first chapter, the main achievements of the thesis research work are summarized. This chapter provides a brief introduction of cancer, it's global impact and the role of various in-silico techniques in the design of anti-cancer drugs. There are numbers of types of cancers as the types of organ we have. To cure the disease, cancer therapies include four major types: (1) immunotherapy, (2) surgery, (3) radiotherapy and (4) chemotherapy. Further, by inspired of our study we have talked about the Principle of chemotherapy, classification of chemotherapy, types of chemotherapy agents, drug resistance as well as Resistance to chemotherapeutic agents. Most of the farmers in rural area in nigeria depend solely on wild animals and their by-products (hooves, tusks bones, feathers, skins) for their daily animal protein supply and preparation of traditional medicine such as fats of the lion (Panthera leo) and hyena (crocuta) are used topically to alleviate abdominal pains [1]. Curcumin [2], Rhizome [3] and several others can be included in herbal drugs. These compounds can inhibit specific targeted protein based on their structures. Finally the objectives conclude the chapter to understand and identify the malignant cells during glycosylation. The present thesis contains six chapters including summery and future scope. The first two chapters present introduction of the proposed problems with motivation and adopted computational methods. This is followed by three chapters which discuss the development of the anticancer drugs and drug delivery system based on carbon nano tube. In this we briefly describe the outcome of all chapters. In chapter two, we have discussed the computational methods such as density functional theory for quantum based properties (DFT) and molecular dynamics simulation (MDS) for classical mechanics based properties.

The aim of the thesis work presented in chapter three was to provide the new set of guiding principles to identify the efficient-stringent anticancer drug hypotheses that can be utilized in physical environment and give the best interaction with

target molecule. We have first of all employed first principle based density functional theory based (DFT) atomic study and analysed the best interacting molecule towards the target molecule. This theory as a quantum mechanical tool has emerged as an all-in-one solution to many electron problems and is famous for providing better prediction of the ground state properties of materials. To get the lead molecule from considered sachharide ligand molecules and the best binding side (Pocket side) we employed the B3LYP functional method and 631G basis set. Furthermore, the investigations were extended for actule conditions of chemotherapy by applying the physical environment to the selected complex. Physical environment carries the pH and temperature where we have varied the pH from 5.0 to 7.0 with 0.5 differences and consider various temperatures such as body temperature (37˚ C) and chemo- therapeutical temperature (42˚ C). To pursue this and retrieve the all focused dataset, deep assessment of all parameters such as vibrational modes, partial charge in the form of Mulliken charge and Fukui indices configurations, orbital properties and binding affinity have been performed. Moreover, to avoid the basis set overlapping errors boys and bernardi counterpoise correction method applied.



Interaction complex	Configuration of ligand	$E_{binding}$(kcal/mol)	HOMO	LUMO	HLG
Gal-SA	Monovalent	-31.7353	-0.1242	-0.0953	0.0289
	Bivalent	49.8781	-0.1926	-0.0366	0.1559
Man-SA	Monovalent	-23.8794	-0.1235	-0.0667	0.0568
	Bivalent	-54.9871	-0.0396	-0.1529	0.1926
PBA-SA	Monovalent	164.4198	-0.1083	-0.0572	0.0511
	Bivalent	-244.9476	-0.22545	-0.02079	0.20466

Atoms	f^+	f^-	$f(r)$
C_5	0.0005	0.0636	-0.0631
O_1	0.0001	0.4842	-0.4841
N_{20}	0.1162	0.0002	0.1160
C_{22}	0.4890	-0.0000	0.4890
O_{23}	0.2015	0.0007	0.2008
O_{28}	0.0009	0.0920	-0.0911

Figure 6.1: Analysed Electronic properties (a) Mulliken charge (b) molecular electrostatic potential (MEP), (c) molecular structure of galactose and sialic acid (d) orbital data in tabular form (e) fukui indices data base of chapter 3.

Figure 6.1 (a) displays the charge distribution of complex in the range of -0.6315 to 0.585 a.u with involved atom in interaction. Highly neucleofilic is shown in purple and electrofilic carries in grey color. In figure 6.1 (b), we have include the different values of electrostatic potential on the surfaces represented with different colors. Potential increases in the order red < orange < yellow < green < blue where, blue indicates the highest electrostatic potential energy and red indicates the lowest electrostatic potential energy. Where, (c) shows the distance between target and ligand molecules, (d) depicts the orbital properties of saccharide with SA molecule and (e) compare the resultant series for the SA-GAL complex molecule for different acceptable point charge sizes showed , C_6, O_8, and O_{28} acted as primary nucleophilic whereas C_{22}, N_{20}, and O_{23} were primary electrophilic attack sites. Result

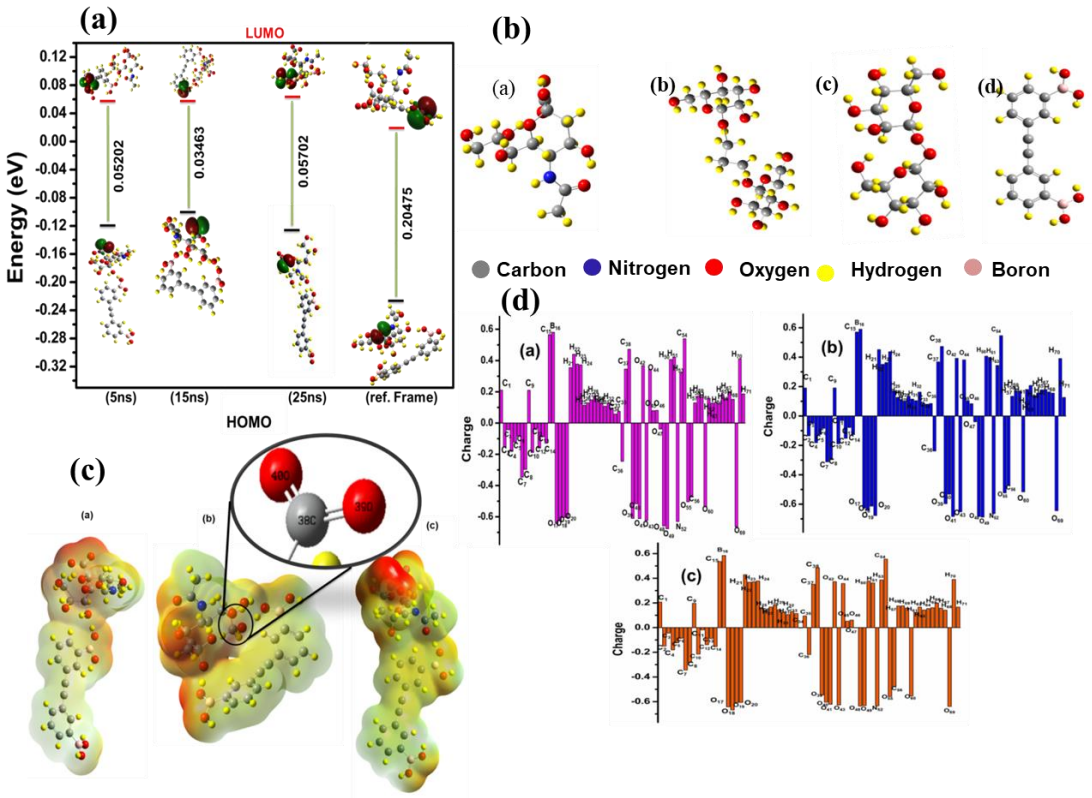


Figure 6.2: these figures depict the (a) Orbital properties, (b) Molecular structure, (c) Electrophilicity and nucleophilicity and (d) shows the mulliken charge.

conclude that the, 6.0pH and 42˚ C temperature are appropriate for the drug delivery with highest binding affinity and vibrations for amide group where it comes in contact with GAL [4].

Inspired by this finding, in chapter four in silico studies were conducted on bi- antennary saccharides. There are some known antifolates drugs vis. single and bi-antennary saccharides and mimics including galactose, mannose and phenyl boronic acid to the SA targeted molecule. However, addition of the SA significantly reduced the therapeutic potential of these antofolates. Therefore, to overcome, the mutation problem, in the present work, DFT calculations have been carried out for all bi-antennary saccharides with targeted molecule and the outcome of present work reveals that the 2PBA, the mimic of bi-antennary saccharide is pursuing best binding pose, which could be used as initial lead molecule to be a drug. Moreover, to full-fill all the physical environment we have employed the molecular dynamics simulation (MDs) calculation with different time slots such as 5ns, 15ns and 25ns for selected complexes. From the MD studies, it was observed that the entire complexes show stable dynamic behaviour throughout the simulation. The flexible nature of target was seen via RMSD studies which confirmed the ligand binding is corresponding to the stabilization of the system. Interacting nature is highest at 15ns. Moreover regarding that nature related properties such as HOMO-LUMO gap is low and distance between molecules is less as well. Further, the hardness and softness are 0.0173 eV and 28.9017 eV, which is very less and high respectively [5] (Figure 6.2). Thereafter, partial charge in the form of Mulliken's charge has been carried out to investigate the inductive effect and based on that electron density has also been explored using molecular electrostatic potential (MESP). Vibrational properties and respective modes at ground state level have been described. The famous commercial DESMOND and MAESTRO (visualized tool) package of SCHRODINGER and relevant plug-in packages were utilized for computation of dynamic calculations and the proposed

properties. To estimate the forces between atoms within molecules OPLS force field parameters were utilized. Quantum calculations have been performed by well-known GAUSSIAN09 package.

In chapter 5, *in silico* studies were conducted on paclitaxel (PTX) enclosed various sized single walled carbon nanotubes (SWCNT). In this investigation first we have first investigated the PTX enclosed (12, 12), (13, 13) and (15, 15) sized SWCNTs. (12, 12) and (13, 13) nanotubes encapsulated PTX geometry got disturbed in the relaxation process (fig. 6.2) and in (15, 15) with 22.7 Å diameter PTX gets adsorbed inside the CNT without dissociation of morphology (fig 6.3).

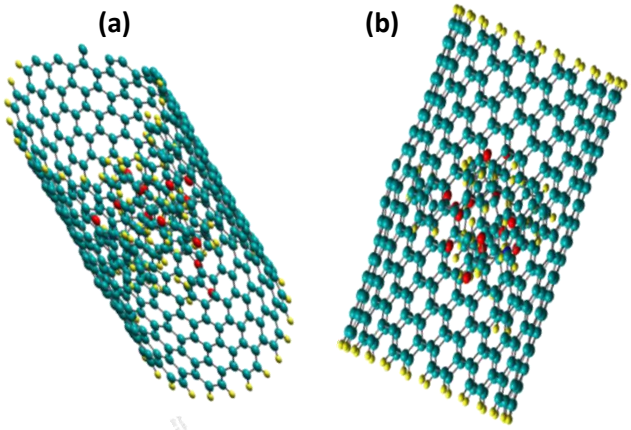


Figure 6.3: Minimized distorted (a) (12, 12) and (13, 13) nanotube encapsulated PTX.

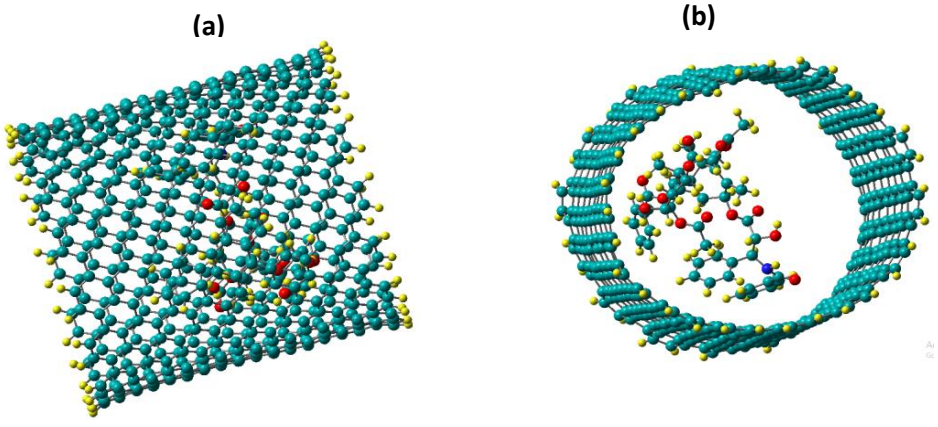


Figure 6.4: Minimized (15, 15) (a) side view (b) Front view of nanotube encapsulated PTX.

To take the better advantage already approved drug were analysed in the presence of the physical environment and various temperature includes 310.15 K (body temperature) and

315.15 K (chemotherapeutical temperature). The cutoff distance used for both the Coulombic and van der Waals interactions was 1.2 nm and the simulations were performed for 100ps for canonical ensemble. Where, to control the pressure, isothermal ensemble simulation was performed for 10ns. All the calculations were obtained using GROMACS free version with inbuilt GROMOS parameters. Calculations conclude that encapsulation is observed at 315.15 K temperature owing the higher absolute magnitude of the stronger interaction energy. Further, O-H/C-H..π and C=O.....π bonding and 20.53 Å diameter are optimal for proper encapsulation of the PTX with drug delivery time of 440 ps at chemotherapeutic temperature. O_{14}, O_5, and N_1 atoms are showing high amplitudes between 0.2 nm to 2.2 nm with parabolic nature due to inter-layer correlation with PTX structure in RDF analysis. The physiochemical nature SASA is showing almost constant nature in both temperature conditions. At elevated temperature the R_g concentration is observed to be insignificant below time 400 ps, with noticeable hike within the time range 400-1750 ps followed by a sudden fall in the magnitude above 1750 ps. This observation is in accordance with the computed radial distribution function and interaction energy profiles, at 310.10 K temperature, the SWCNT takes too long time to deliver the drug to diseased as compared to the 315.15 K temperature.

Future scope

The present study is developing the new drug to cure or identify the malignant cell and methodology fabricate new trend to generate the novel drugs. This technique indicates that the great need of evolution to design the multi-saccharides as a novel drug. We can perform and analyse the targeted therapy through the multi antennary saccharide with different physiological conditions, with different solvent as well. Also we can perform this calculation with various drug delivery system such as boron nitride nanotube (BNNT) and Functionalized BNNT. Where, BNNT is bio compatible and non-toxic nature. As the most

stable form of BNs, hexagonal boron nitrides (hBNs) have strong covalent bonds between B-N atoms with a graphene-like structure. The 2D BN layers can hold together through van der Waals interactions. Further recent trends to drug deliver using halloysite nanotubes (HNTs) in analytical sciences and preparation of magnetic HNTs also the best way to cure the disease. Apart from the technique development, the either way is to design novel drugs; within just a span of a decade, researchers and engineers have developed high throughput methods to screen the target form the database and design unique drugs utilizing artificial intelligence assisted tools. My future scope shall be a connection between my present knowledge of methods for studying drug properties with my future contributions to biological science using pre-existing and advanced theoretical techniques together with the relevant computational tools

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