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RESEARCH ARTICLE

MOLECULAR DOCKING AND ANTICANCER ACTIVITY STUDIES OF ANTHRACENE DERIVATIVES

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ABSTRACT

Computational Chemistry plays an important role in the research of new possible medicines. In this work, anti cancer activity and molecular docking analysis was carried out to study the effects of anthracene derivatives namely 9-Chloroanthracene and 2,6-Dimethoxyanthracene on effect of anticancer. The binding interactions in the targets active sites were reported**.** Results show that 9-Chloroanthracene and 2,6-Dimethoxyanthracene are promising leads, so the study of these compounds is recommended.

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INTRODUCTION

Anthracene is also called as paranaphthalene or green oil, which is a solid polycyclic aromatic hydrocarbon (PAH) having three benzene rings. Anthracene was first discovered in coal tar by Jean B.A. Dumas and Auguste Laurent in 1832. Anthracene is an important moiety in supramolecular chemistry due to its size and shape and photophysical properties. It is an ideal organic fluorophore due to its fluorescence property, well-resolved absorption and emission bands, and high fluorescence quantum yield and nanosecond lifetime. PAHs are carcinogens and have been associated with the increased risk of skin, respiratory tract, bladder, stomach, and kidney cancers. They may also cause reproductive effects and depress the immune system (ATSDR, 1995). Some of the most common applications of anthracene include use as a preservative in wood and lumber and use as an insecticide for crops. By all above applications, we studied molecular docking and anti cancer activity of anthracene derivatives for the first time.

Computational Details: The AutoDock-Vina software (http://autodock.scripps.edu/resources/ references.) and Auto Docking Tools (ADT) were used for molecular docking calculations.

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The polar hydrogens and Kollaman atomic charges were added to the target enzyme by used ADT graphical. Water molecules were removed and the partial charges added by Geistener method before the docking calculations. The active site of the enzyme was assign with the grid size of 60 × 60 × 60 Å to includes residues of protein. Receptor-ligand interactions were illustrated with PyMol and Discover Studio Visualizer 4.0 software (Diego, 2013).

RESULTS AND DISCUSSION

In vitro anticancer activity:

9-Chloroanthracene: The *in vitro* anticancer activity of the compound 9CA was screened against three human cancer cell lines such as MCF-7 (Brest), HepG-2 (liver) and IMR-32 (neuroblastoma) using MTT assay (Konakanchi *et al*., 2018). All the cell lines were cultured and maintained in Dulbecco's Modified Eagle's medium (DMEM) which contained 10% Fetal bovine serum (FBS) along with antibiotics (penicillin and streptomycin). 2×10^4 cells/well were plated in 96 well plates and incubated with humidified condition at 37 °C with 5% CO_2. The cells were treated with different concentration of the complexes (0-100 μM) and incubated for 24 h. After treatment, cells were washed twice with Phosphate-buffered saline (PBS) and incubated with MTT diluted fresh media for 3-4 h.

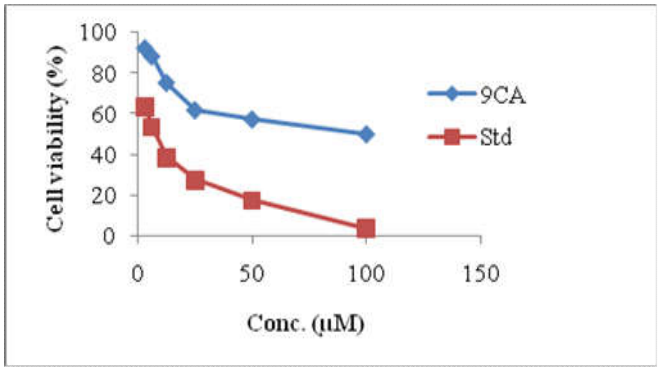

Fig. 1. Survival curves of cell lines MCF-7

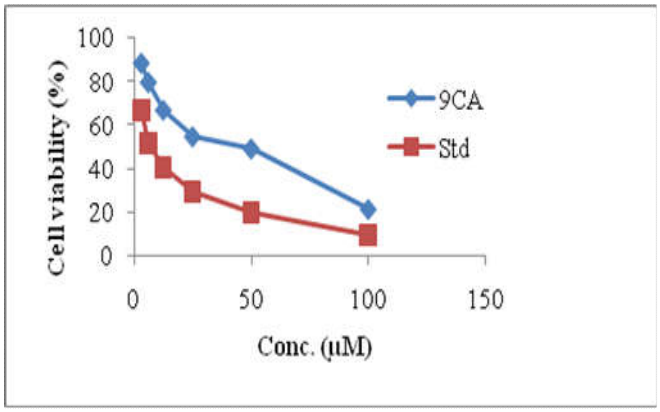

Fig. 2. Survival curves of cell lines HepG-2

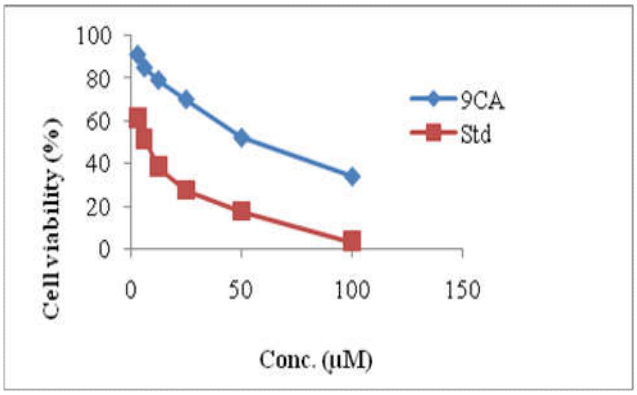

Fig. 3. Survival curves of cell lines CoLO-205

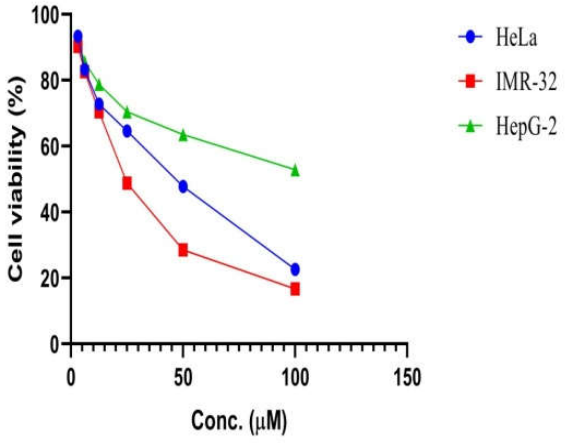

Fig. 4 Survival curves of cell lines HeLa, IMR-32 and HepG-2

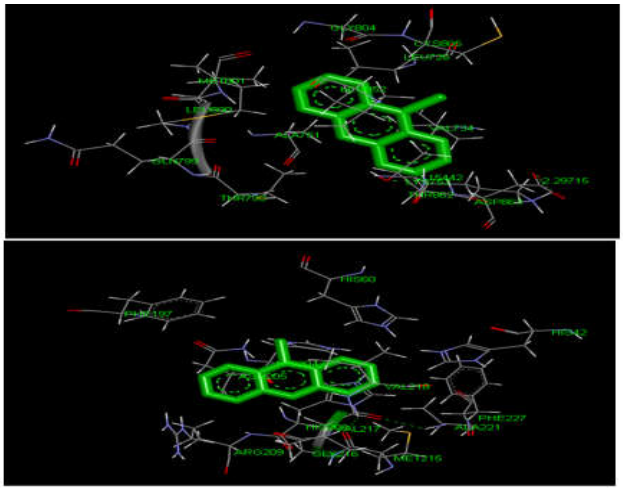

Fig. 5 Shows the binding poses and interactions of 9CA compound to the binding sites of HER2 receptor (top, PDB ID: 3PP0) and Tyrosinase receptor (bottom, PDB ID: 3NM8)

The absorbance was recorded at 570 nm. Then, percentage of inhibition was calculated using the formula (A–B/A) × 100 (A = absorbance of control group and B = absorbance of treated group). The anticancer activity results revealed that the compound 9CA was observed moderate activity against HepG-2 with IC_{50} value 46.17 ± 0.18 µM when compared with standard drug Doxorubicin with IC_{50} value 4.51 ± 0.25 µM. The compound was active against MCF-7 and COLO-205 with IC_{50} values 81.02 ± 0.11 µM and 62.79 ± 0.19 µM, respectively, on the comparing the IC_{50} values of positive control is 3.45 ± 0.31 µM and 1.25 ± 0.13 µM, respectively. The results represents in Fig 1-3

2,6-Dimethoxyanthracene: The in vitro anticancer activity of the compound 2,6-DA was screened against different human cancer cell lines i.e. HeLa, HepG-2, and IMR-32 using MTT assay (Ramaiah *et al*., 2004). All the cell lines were cultured and maintained in Dulbecco's Modified Eagle's medium (DMEM) which contained 10% Fetal bovine serum (FBS) along with antibiotics (penicillin and streptomycin). 2 × 104 cells/well were plated in 96 well plates and incubated with humidified condition at 37 °C with 5% CO2. The cells were treated with various concentrations of the compounds (0-100 µM) and incubated for 48 h. After treatment, cells were washed twice with Phosphate-buffered saline (PBS) and incubated with MTT diluted fresh media for 3- 4 h. The absorbance was recorded at 570 nm. Then, the percentage of inhibition was calculated using B/A) × 100 (A = absorbance of the control group and B = absorbance of the treated–the formula (A group). The anticancer activity results compared to reference drug Doxorubicin. From the results the compound 2,6-DA showed moderate activity to poor activity observed for three cell lines HeLa, IMR-32 and HepG-2 with IC50 values of 62.74 ± 0.11µM (HeLa), 45.04 ± 0.18 µM (IMR-32) and 97.81 ±0.19 µM (HepG-2), respectively when compared with standard drug Doxorubicin with IC50 values of 8.21 ± 0.31µM, 4.69± 0.25 µM and 16.33 ± 0.13 µM, respectively for HeLa, IMR-32 and HepG-2 cancer cells. The results represents in Fig. 4.

Molecular docking studies

9-Chloroanthracene: Nowadays cancer is an enormous global health problem, touching every region and socioeconomic groups in spite of a major aspire of research and development

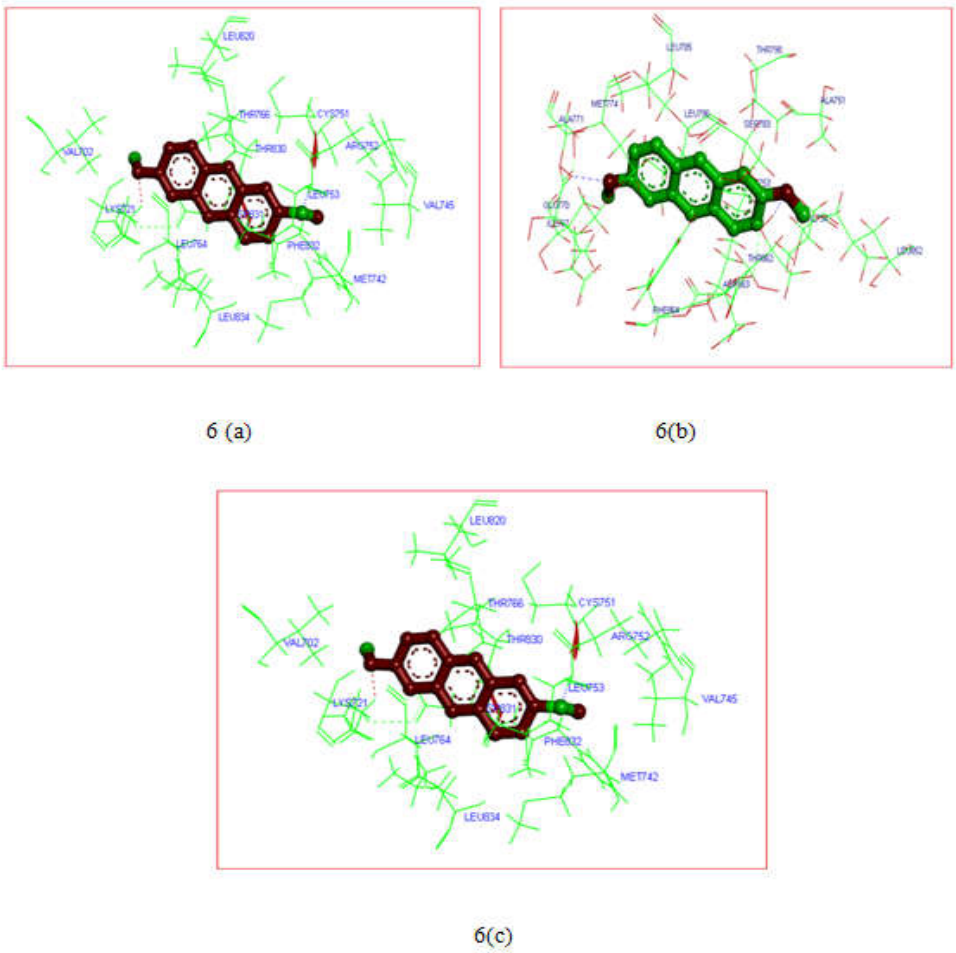

Fig. 6. (a-c) Showing the binding poses and interactions of 2,6-DA to binding sites of target protein: (a) *EGFR* (PDB ID: 4HJ0), (b) *HER2* (PDB ID: 3PP0) and (c) Tyrosinase (PDB ID: 3NM8)

in academia and pharmaceutical industry to pastime for new anticancer agents. In addition to anticancer agents, antioxidants are also appealing much interest of the researcher working in this filed. In principle, an anti-oxidant is a scaffold, which has the capability to inhibit the oxidation of other molecules and thus control the oxidative stress, damage or killing of cells which occur due to the low level of anti-oxidants or inhibition of antioxidant enzyme. The proteins HER2 and Tyrosinase an attractive targets for the development of anticancer agents (Herbst, 2004). In addition, HER2 is an excellent cell-surface receptor for epidermal growth factor family and stimulated by binding of its specific ligands. It also plays a crucial role in the growth of ductal system of the mammary glands (Sebastian, 1998). The crystallographic 3D structure ofHER2 and tyrosinase proteins were extracted from RCSB Protein Data Bank (www.rscb.org) with PDBID: 3PP0, 3NM8 for HER2 and tyrosinase, respectively. The previously associated ligands and water molecules of the downloaded proteins were eliminated using the UCSF chimera 1.10.1 software followed by the energy minimization. The molecular docking studies have been carried out by using Auto Dock Tools (ADT) (http://mgltools.scripps.edu) version 1.5.6 and Auto Dock 4.2package suite. The docking process was performed in between rigid protein receptor HER2 and tyrosinase with the 9CA. The Auto dock Tools 1.5.6 program was employed to merge non-polar hydrogens into related carbon atoms of the receptor HER2 and tyrosinase. Non-polar hydrogen, Gasteiger charges and torsions degrees of freedom were also assigned by ADT program.

The distance between donor and acceptor atoms showing the hydrogen bonding interactions was fixed to be 1.9 Å. Moreover, 10 docked conformations were generated for each analogue during the docking protocol and their structures were saved in PDBQT format. The energy calculations were done by using genetic algorithms (Ramaiah *et al*., 2004; Ramachary *et al*., 2018). A cubic grid box was also built with dimensions of 60 × 60 × 60 $Å^3$ on the receptor HER2 and tyrosinase with the aid of Auto Dock Tools 1.5.6 program with grid point spacing of 0.3750 Å. In this docking protocol, population size, 150 and maximum number of evaluations, 2.5 × 106 were used to optimized the binding mode of ligands. The output results were graphically analyzed by Discovery Studio 4.1.0 software. The output of the docking studies of 9CA including binding energies of receptor–ligand complex are illustrated in Table 1 and fig 4. As shown in Table 1 the compound under investigation shows strong binding behaviour against receptors HER2 and tyrosinase as inferred by their minimum binding energies –6.93 and –7.39 kcal mol^{-1} with HER2 and tyrosinase in 9CA.

6-Dimethoxyanthracene: The proteins EGFR, HER2 and Tyrosinase are good-looking targets for the evaluation of anticancer agents. It also plays a crucial role in the growth of the ductal system of the mammary glands. The 3D crystal structure of protein receptors was taken from RCSB Protein Data Bank with PDBID: 4HJO, 3PP0 and 3NM8 for EGFR, HER2 and Tyrosinase, respectively. The water molecules are eliminated using the UCSF chimera 1.10.1 software.

The docking process was executed in between rigid protein receptor and 9CA. Employing ADT program gasteiger, Non-polar hydrogens and torsions degrees of freedom were assigned. The hydrogen bonding interactions between donor and acceptor atoms was fixed to be 1.9 Å. The energy calculations were performed by genetic algorithms. A cubic grid box was also built with dimensions of 60 × 60 × 60 Å3 on the receptor HER2 and tyrosinase with the aid of Auto Dock Tools 1.5.6 program with grid point spacing of 0.3750 Å. The output of the docking studies of 9CA including binding energies of receptor–ligand complex are illustrated in Fig. 6 (a-c). From the Figure 6, the compound 2,6-DA under investigation shows interesting binding behaviour against receptors EGFR, HER2 and Tyrosinase as inferred by their minimum binding energies -8.32, -7.82 and -8.39 kcal mol^{-1} , respectively. Molecular docking results reveal that in 2,6-DA the ligand-receptor (EGFR) complex exhibits two hydrogen bonds, these bonds between C-O methoxy groups and Leu753 amino acid residue with bond distance 2.04293 Å and the other bond with Lys721 amino acid residue with bond distance 2.4169 Å.

Two hydrogen bonds are formed with ligand-receptor (HER2) in 2,6-DA, two hydrogen bonds are formed between C-O of two methoxy groups and Ala771 and Thr 862 amino acid residue with bond distances 2.1634 and 2.10018 Å. The ligand-receptor with Tyrosinase displays four hydrogen bonds. Two bonds are formed between the C-O of one methoxy oxygen atom with His60 and His42 amino acid residue at 2.28991 and 1.8694 Å bond distances. The remaining two hydrogen bonds between C-O of another oxygen atom of methoxy group with Arg209 amino acid residue at 2.17995 and 1.76901 Å bond distances. The hydrophobic interactions of amino acid residues are represented in Fig 6. Here the molecular docking results show the EGFR, HER2 and Tyrosinase are good target receptors of 2,6-DA, this shows that the molecules under investigation are good inhibitors of anti-cancer and anti-oxidant activities. PDB ID: 4HJ0), (b) HER2 (PDB ID: 3PP0) and (c) Tyrosinase (PDB ID: 3NM8)

Conclusions

The Molecular docking and activity Investigations of Anthracene derivatives 9-Chloroanthracene and 2,6-Dimethoxyanthracene shows good Anticancer activity computationally.

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