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Substitution of Carbonyl Group of Ellagic Acid with Silanediol Group for Better Inhibition of VEGFR-2 Kinase Enzyme

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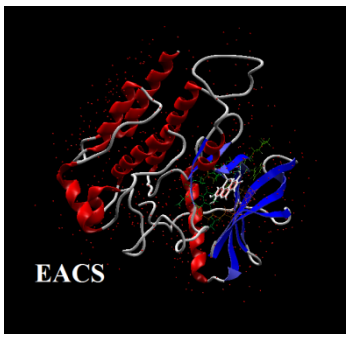

Keywords:
Ellagic Acid;
In silico;
Molecular docking;
Molecular simulation;
VEGFR-2 Kinase enzyme.

ABSTRACT

Evaluating structural and medicinal properties of novel silicon containing molecules of Ellagic acid (EADC) is the main purpose of this work. Density functional theory (DFT) methods as implemented in the Gaussian 03 program and molecular modeling methods using the Molegro Virtual Docker (MVD) program and SwissADME web server have been employed to achieve the purpose. Here, the molecular structures of original EADC and modified EACS and EADS were optimized at the B3LYP/6-311++G(d,p) level of theory. The reactivity and stability properties of the investigated molecules were evaluated via global reactivity indices using frontier molecular orbitals (FMOs) energies; showing the stability order of the molecules as EADS > EACS > EADC. On the other hand, obtained data from performed molecular docking analyses indicated that the steric interactions play dominant role of molecular binding to VEGFR-2 Kinase enzyme. Furthermore, EACS has been viewed as the strongest interacting molecule with other biomacromolecules. And finally, the evaluated ADME properties indicated that the oral bioavailability for the investigated compounds is low.

Introduction

One of the major causes of human death worldwide is cancer. Surgery, chemotherapeutic agents and radiation, which are available cancer therapy protocols, have not been so much efficient to reduce cancer occurrence and raising the cancer patient survival rate [1, 2]. Uncontrolled growth of abnormal cells that are able to be spread to other cells in the vicinity and organs is one of the characteristics of cancer.

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Unfortunately, cancer stands for a main scared disease in the world despite the accessibility of impressive chemotherapy and efficient drugs affecting one-third of the world population without any effective medicine [3]. Although considerable progresses have been devoted to develop therapeutic strategies and molecular statements, the details of problems such as breast disaffections, reversion and metastasis are not yet understood too much [4, 5]. Anticancers from plant resources are seen as a realistic outlook leading to possible achievements on new anticancer medicines [6, 7]. The plant-derived anticancer compounds have received significant attention recently because of low toxicities, low costs, and low side effects. Punica granatum (pomegranate) possess phytochemicals with antioxidant characteristics, which has been seen with the function of the major polyphenol in pomegranate; Ellagic Acid (EADC). Natural phenolic component of grapes and lots of berries including strawberries, raspberries, and cranberries have high concentrations of EADC. Hereby, EADC derivatives belonging to the group of bioactive polyphenols with promising role of anticancer have been studied in this work. . These compounds show antioxidant, antiproliferative, chemopreventive, and antiatherogenic properties in a variety of tissues and cells, such as liver, lung and breast cancer [8]. The Angiogenesis effect of the investigated natural compound is due to inhibiting the VEGFR-2 Kinase enzyme [9].

Computational analysis of chemical and also phytochemical compounds could help to develop new potential molecules against the cancer targets [10]. Molecular docking, as a computational method, is among the versatile methods for predicting the small molecule bioactive component orientation against the protein target [11-15]. Density functional theory (DFT), as a fundamental theory for small molecule drug design, is also another popular method for accurate explanation of biologically molecular systems at almost suitable computational costs and reliable results [16-20]. In this study, novel silicon-derived compounds of EADC (Fig. 1) have been designed by substituting carbonyl functional groups with silanediol groups. After optimizing the designed molecular structures, their activity as anti-angiogenesis have been evaluated using molecular docking analysis. Further related pharmaceutical information for the investigated compounds have been also obtained from the SwissADME web server.

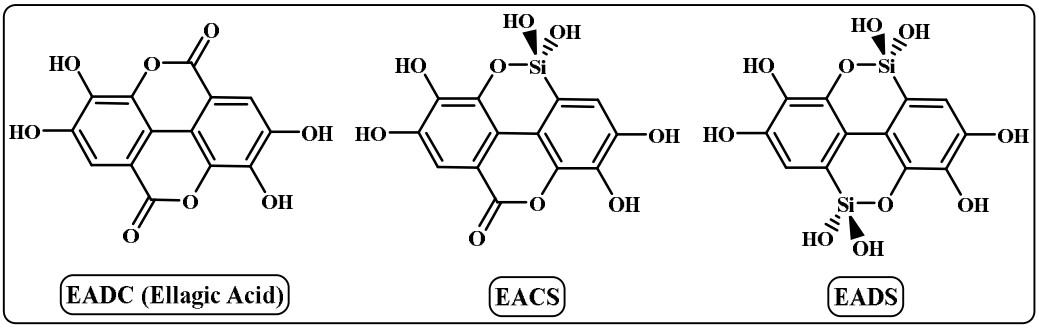

Fig. 1. The molecular structures of EADC, EACS and EADS.

Materials and Methods

Computer-aided drug design and discovery (CADDD) is a new field of medicinal chemistry relating to the study of physicochemical and pharmaceutical properties of novel chemical derivatives to introduce new drugs [21-23]. Within this work, new information about the novel derivatives of EADC (Fig. 1) have been obtained by the benefit of CADDD methodology. In the first step, geometries of the investigated molecular

structures have been optimized using the Gaussian 03 software employing the B3LYP/6-311++G(d,p) level of theory [24-26]. Reactivity and stability properties of the optimized molecular structure have been obtained by the frontier molecular orbitals (FMOs) theory. The global reactivity indices and molecular electrostatic potential (MEP) graphs have been calculated for this purpose. On the other hand, anti-angiogenesis effects have been examined for the optimized molecules through their interactions with VEGFR-2 Kinase enzyme. Embedding the optimized molecular structures into the VEGFR-2 Kinase enzyme has been carried out by the Molegro Virtual Docker (MVD) software. Predicting the physicochemical and pharmaceutical properties of the designed molecules have been done using the SwissADME web server (www.swissadme.ch).

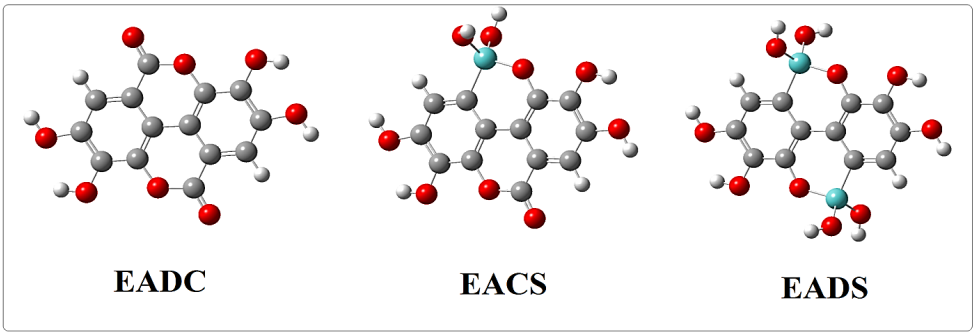

Fig. 2. The optimized molecular structures of EADC, EACS and EADS.

Results and Discussion

Reactivity and Stability Properties

As mentioned above, EADC (Ellagic Acid) is a natural polyphenol antioxidant found in numerous fruits and vegetables as the dilactone of hexahydroxydiphenic acid. The investigated molecules (Fig. 1) are silicon derivatives of EADC, in which one carbonyl functional group of EADC has been substituted with one silanediol group; named EACS, and two carbonyl functional groups have been substituted with two silanediol groups; named EADS. First, the molecular structures of each of EADC, EACS and EADS compounds were optimized using the quantum mechanical computations at the B3LYP/6-311++G(d,p) level of theory in gas phase (Fig. 2). The oxygen atom of the carbonyl groups acts as a hydrogen bond acceptor whereas the hydroxyl functional groups of the silanediol groups play both roles of hydrogen bond acceptor and donor. On the other hand, the Si-O and Si-C bond lengths are longer than the C=O and C-C bond lengths causing the disruption of the planarity of the structures. Calculating the global reactivity indices yields the stability and reactivity properties of a chemical compound [27-31]. The global reactivity descriptors (Table 1) such as energy gap (*Eg*), ionization potential (*IP*), electron affinity (*EA*), chemical hardness (η), chemical softness (S), electronegativity (χ), chemical potential (μ) and electrophilicity index (ω) were obtained from the frontier orbitals energies using eqs. (1-8) [32].

$$E_g = E_{LUMO} - E_{HOMO} \quad (1)$$

$$IP = -E_{HOMO} \quad (2)$$

$$EA = -E_{LUMO} \quad (3)$$

$$\eta = \frac{(\varepsilon_{LUMO} - \varepsilon_{HOMO})}{2} \quad (4)$$

$$\chi = \frac{-(\varepsilon_{LUMO} + \varepsilon_{HOMO})}{2} \quad (5)$$

$$\mu = \frac{(\varepsilon_{LUMO} + \varepsilon_{HOMO})}{2} \quad (6)$$

$$\omega = \frac{\mu^2}{2\eta} \quad (7)$$

$$S = \frac{1}{\eta} \quad (8)$$

Molecular electrostatic potential (MEP) graph is a good computational technique to discover the charge distribution model on the elements of a compound [33]. The MEP graphs of EADC, EACS and EADS are shown in Fig. 2, in which the negative, zero and positive charges on the atoms have been indicated by red, green and blue colors, respectively. The MEP graphs show that only the hydrogen atoms of the hydroxyl groups have positive charges. In contrast, the negative charges are relating to the oxygen atoms showing more reactivity of these atoms than other ones. Information of Table 1 show that the ionization potential order of compounds is EADC > EACS > EADS. This order shows the silicon contained analogues have more resistance in reactions with oxidizing agents. On the other hand, the electron affinity order (EADC > EACS > EADS) indicates that the silicon contained compounds hardly accept electron from the reducer agents.

Table 1: Global reactivity indices of EADC, EACS and EADS

	Energy Value (eV)		
Indices	**EADC**	**EACS**	**EADS**
HOMO	-8.75	-8.32	-7.92
LUMO	1.36	2.03	2.72
Ionization Potential (*IP*)	8.75	8.32	7.92
Electron Affinity (*EA*)	-1.36	-2.03	-2.72
Energy Gap (*Eg*)	10.11	10.35	10.64
Electronegativity (χ)	3.70	3.15	2.60
Chemical Potential (μ)	-3.70	-3.15	-2.60
Chemical Hardness (η)	5.06	5.18	5.32
Chemical Softness (*S*)	0.19	0.19	0.18
Electrophilicity index (ω)	1.36	0.95	0.63

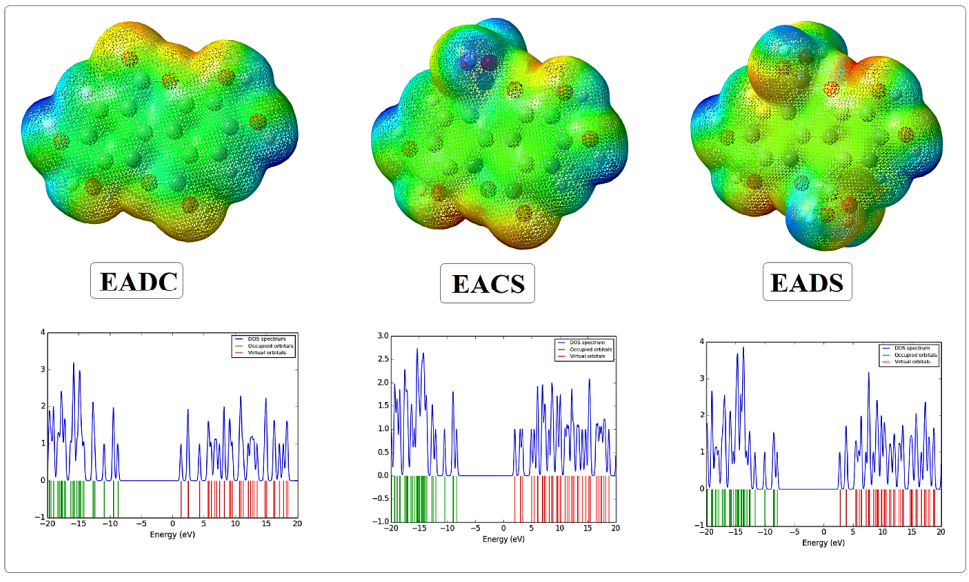

Fig. 3. The MEP and DOS graphs of EADC, EACS and EADS.

The Eg values of the frontier molecular orbitals (HOMO and LUMO), stating the stability for the compounds, show that EADS compound has the most stability among the investigated molecules (the stability order: EADS > EACS > EADC). Fig. 3 exhibits the distribution patterns of HOMO/LUMO

and Eg revealing high chemical hardness and low chemical softness regarding the global reactivity indices for all three molecules. Hence, the investigated molecules are shown to be stable and the silanediol-contained molecules are the most stable compounds regarding the obtained low reactivity and low electrophilicity molecular properties.

Molecular Docking Analysis

Recent studies indicated that EADC inhibits VEGFR-2 Kinase enzyme [34]. Here, complex formations of the EADC, EACS and EADS with VEGFR-2 Kinase have been studied via molecular docking analysis. The Molegro Virtual Docker (MVD) program was used to evaluate docking analyses of the interacting ligand-enzyme complex formation. The crystal structure of human VEGFR-2 Kinase domain (PDB 3VHE) has been chosen as the biomolecular target to interact with the small molecules [35]. Fig. 4 indicates the investigated compounds embedded in the active site of the VEGFR-2 Kinase. The MolDock score data of the complexes of the designed molecules with VEGFR-2 Kinase are listed in Table 2. The total interactions data show that the EACS has the strongest interaction with the biomolecular target.

EADC-Enzyme complex: The total interaction MolDock score is -104.013 and the steric interactions (score = -112.52) play main role in the complex formation of the small molecules with VEGFR-2 Kinase. Val899, Cys1045, Asp1046, Cys919, Glu917, Lys868, Phe1047, Val848, Ala1050, Gly841, Phe918, Lys920, Leu1035, Leu840, Gly922, Ala866 and Val916 residues of enzyme participate in steric interactions. On the other hand, only Cys919 makes hydrogen bond with the EADC molecule (score = -4.51).

Table 2: The interactions of EADC, EACS and EADS with the VEGFR-2 Kinase enzyme

Interactions		MolDock Score		
		EADC	**EACS**	**EADS**
External Ligand Interactions	**Steric (by PLP)**	-112.52	-108.48	-96.63
	Hydrogen bonds	-4.51	-10.64	-12.28
	Electrostatic (short range)	0.00	0.00	0.00
	Electrostatic (long range)	0.00	0.00	0.00
	Water-Ligand Interactions	-11.31	-10.69	-3.26
	Total External Interactions	-128.33	-129.81	-112.17
Internal Ligand Interactions	**Torsional Strain**	0.00	0.00	0.00
	Steric (by PLP)	24.32	16.57	8.25
	Hydrogen Bonds	0.00	0.00	0.00
	Electrostatic	0.00	0.00	0.00
	Total Internal Interactions	24.32	16.57	8.25
Total Interactions		-104.01	-113.24	-103.92

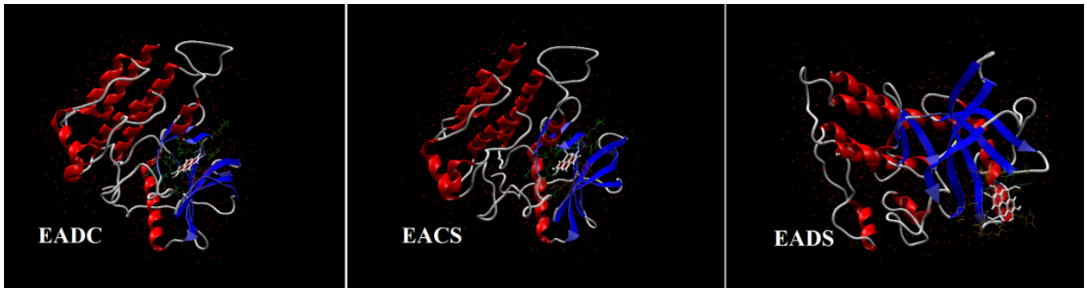

Fig. 4. The docking of EADC, EACS and EADS into the VEGFR-2 Kinase enzyme.

EACS-Enzyme complex: The total interaction MolDock score is -113.24 and the steric interactions (score = -108.48) play main role in the complex formation of the said molecule with VEGFR-2 Kinase. As same as the EADS-Enzyme complex, the VEGFR-2 Kinase residues Phe1047, Leu840, Lys920, Gly922, Phe918, Ala866, Glu917, Cys919, Val899, Val848, Val916, Asp1046, Cys1045, Lys868, Leu1035, Ala1050 and Gly841 participate in steric interactions. On the other hand, Cys919 and Glu917 residues make hydrogen bond with the EADC molecule (score = -10.64).

EADS-Enzyme complex: The total interaction MolDock score is -103.92 and the steric interactions (score = -96.63) play main role in the complex formation of the investigated molecule with VEGFR-2 Kinase. As same as the EADS-Enzyme complex, the VEGFR-2 Kinase residues Lys871, Met869, Pro911, Gly910, His879, Leu912, Leu882, Leu870, His876, Thr875, Glu872, Gly873 and Ala874 participate in steric interactions. On the other hand, His879, Leu870, Gly873, Lys871, Ala874 and Glu872 residues make hydrogen bond with the EADC molecule (score = -12.28).

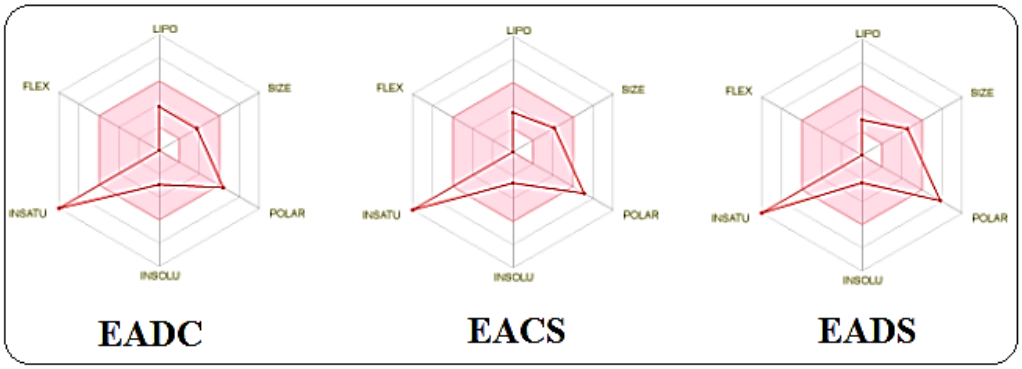

Fig. 5. Physicochemical properties graphs of the designed compounds.

Physicochemical Descriptors and ADME Parameters

In medicinal chemistry, ADME is the abbreviation for the absorption, distribution, metabolism and excretion, as the key factors to predict the pharmaceutical activity of a medicinal compound [36]. Herein, ADME properties of the designed molecules (EADC, EACS and EADS) have been evaluated using the SwissADME web server, which are presented in Fig. 5. The oral bioavailability of a medicinal compound is identified via six key parameters: lipophilicity (-0.7 < XLOGP3 < +5.0), size (150 g/mol < M < 500 g/mol), polarity (20 $Å^2$ < TPSA < 130 $Å^2$), insolubility (0 < ESOL < 6), insaturation (0.25 < Fraction Csp3 < 1) and flexibility (0 < number of rotatable bonds < 9). The colored zone in this graph shows the suitable physicochemical space for oral bioavailability of a compound [37]. Insaturation and polarity properties of all compounds are seen to be out of acceptable ranges revealing low oral bioavailability of the compounds. Evaluating the compounds properties shows the lipophilicity (LogPO/W) of 1.10, 0.48 and -0.15 for EADC, EACS and EADS, respectively. TPSA factors of the EADC, EACS and EADS are 141.34 $Å^2$, 160.84 $Å^2$ and 180.30 $Å^2$, respectively. ESOL factors of the EADC, EACS and EADS are -2.94, -2.68 and -2.41, respectively. So, all investigated molecules are soluble. The fraction Csp3 of the EADC, EACS and EADS are zero. The molecules under study show the bioavailability score of 0.55. So, all three molecules have drug-likeness property (based on Lipinski rules). On the other hand, the investigated molecules do not have any activity as an inhibitor of the cytochrome P450 subunits. Fig. 6 shows the boiled egg graphs of the designed compounds. The yellow-colored zone of the graph shows the

permeation of the molecules through the blood-brain barrier (BBB). In contrast, the white-colored zone of the boiled egg graph relates to the absorbed molecules by the gastrointestinal tract. The boiled egg graphs indicate that EADC is absorbed by gastrointestinal tract, but the EACS and EADS are not absorbed by gastrointestinal tract or permeated through the BBB. Moreover, as indicated by in the Fig. 6, the red color of the molecules in these graphs shows that they are not effluated from the central nervous system (CNS) by the P-glycoprotein.

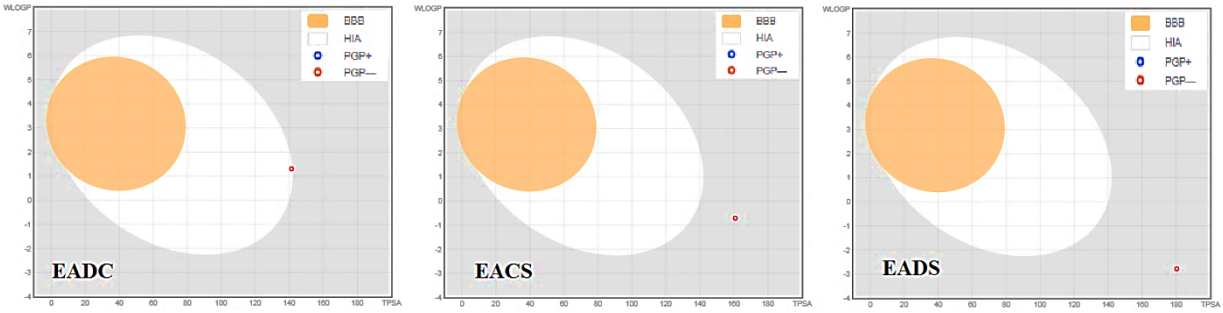

Fig. 6. Boiled egg graphs of the designed molecules.

Conclusion

Analyses of physicochemical, structural and electronic properties of Ellagic Acid (EADC) and its silicon containing analogues (EACS and EADS) were the main objective of the present research work. Electronic properties prediction of the molecules were performed using the quantum mechanical (QM) computations. The molecular structures were optimized at the B3LYP/6-311++G(d,p) level of theory. The HOMO/LUMO energies gap showed all molecules are stable against the oxidizing agents in the cell and the silicon contained analogues have more resistance in reactions with oxidizing agents. Calculating the reactivity indices using frontier molecular orbitals (FMOs) energies showed EADS > EACS > EADC. Order for the stability molecule On the other hand, the obtained docking analyses information indicated that the steric interactions play dominant role in molecular binding to VEGFR-2 Kinase. The total interactions data showed the strongest interaction for EACS with the biomolecular target. Furthermore, the obtained ADME properties showed low oral bioavailability for the compounds. Based on the obtained results from electronic, docking and ADME analyses, it could be concluded that EACS could be considered as a proper inhibitor for the VEGFR-2 Kinase enzyme.

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