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CHEMICAL REACTIVITY DESCRIPTORS FROM THEORETICAL METHODS FOR STRUCTURE-PROPERTY EVALUATION OF CERTAIN MEDICINAL IMPORTANT NAPHTHOQUINONE DERIVATIVES

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Abstract

A synthesized a series of heterocyclic benzylpyrazolyl naphthoquinone derivatives (5a-5p). The synthesized sixteen benzylpyrazolyl naphthoquinone molecule deals with some aspects of molecular reactivity descriptors based on density functional theory. Global and local reactivity descriptors have been generated using semi-empirical, ab-initio and DFT methods at the optimum basis sets for a about three classes of compounds. The descriptors include Fukui function, chemical potential, hardness, softness, electrophilicity, log P, pKa, surface volume, surface area etc. The descriptors were then used to treat the molecules in a semi-quantitative way. To establish the credibility to the studied works docking studies were performed apart from structure-property and structure activity analyses.

Introduction

Naphthoquinone represents an important class of biologically active molecules that are widespread in nature [1, 2]. It is also established that these compounds also exhibit a wide range of biological activities due to its abundance in medicinal scaffolds namely (α-Lapachone, β-Lapachone, Lapachol, Atovaquone. Many nature and synthetic naphthoquinones are known to be potent antitumor [3, 4], antimycobacterial [5], anticoagulant [6] and anticancer activities agents [7, 8]. Pyrazolones are also important structural cores in many pharmaceutical industries in view of their medicinal fields [9, 10]. Heterocyclic nucleus containing pyrazolones (phenazone, propyphenazone, ampyrome and metamizole) are useful antipyretic and analgesic drugs [11], whilst edaravone (MCI-186) has been used for treating brain [12] and myocardial ischemia [13] and is also used for treating diseases related these enzymes, such as bone loss, cancer and other proliferative diseases like antimicrobial [14], antibacterial [15], anti-inflammatory [16, 17], anti-cancer [18].

Among the theoretical methods available, the density functional theory (DFT) calculations provided good accuracy for the computation of molecular structure, vibrational frequencies and energies of chemical reactions [19-22]. DFT provides an efficient method to include correlation energy in electronic calculations [23]. Beside total electronic energies(E), the highest occupied molecule orbital (HOMO), the lowest unoccupied molecule orbital (LUMO), gap energy difference between E_{HOMO} and E_{LUMO} (E gap), dipole moments, polarizability, global chemical reactivity description such as electronic chemical potentials(μ) [24], chemical hardness(η) [25], electrophilicity [26], weight molecules (MW), surface molecules(S), volume molecules (Mv), octanol-waterm partition coefficient (log p) dipolemoment are calculated.

Theoretical calculations were performed by the density functional theory (DFT) method at the B3LYP/6-31G level of theory in the Gaussian 03 package of programs [27]. According to the frontier molecular orbital theory, (HOMO) has the priority to provide electrons while LUMO can accept electrons first are the most important factors that affect the bioactivity [28**].**

Hence, it is very important to know the parameters that represent the molecular structure and reactivity and the most appropriate representatives of a given molecule allowing the molecules to undergo a certain class of reactions. In the present work, special attention is given on the developments of the recently proposed density-based descriptors, such as chemical potential, hardness, softness and their derivatives. An attempt is also made to investigate the reactivity of molecular systems in a semi quantitative way using these concepts.

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Materials and methods

All of the chemicals used in the synthesis were purchased from Sigma-Aldrich and were used as received. Melting points were measured in open capillary tubes and are uncorrected.

Equipment and analytical instruments

The ^{1}H-NMR, ^{13}C-NMR were recorded on a Bruker (Avance) 300 MHz NMR instrument using TMS as an internal standard and DMSO as a solvent. Standard Bruker software was used throughout. Chemical shifts are given in parts per million (δ-scale) and the coupling constants are given in Hertz. Silica gel-G plates (Merck) were used for TLC analysis with a mixture of petroleum ether (60-80ºC) and ethyl acetate as the eluent. Elemental analyses were performed on a Perkin-Elmer 2400 Series II Elemental CHNS analyzer. ESI mass was recorded using a Thermo Fleet-LC mass instrument.

General Procedure for the synthesis of benzylpyrazolyl naphthoquinone (5a-5p)

To a mixture of 10 mol% p-TSA and 5ml water, 2-hydroxy naphthoquinone, **1** (1 mmol), P-hydroxybenzaldehyde **2** (1 mmol), ethyl acetoacetate **3** (1 mmol) and hydrazine **4** (1 mmol) were added and heated to reflux at 70ºC. The resulting clear solution that gradually became turbid, was stirred for the stipulated time 20 minutes. After completion of the reaction (indicated by TLC), the free-flowing solid was filtered and washed with ethanol (10ml) to afford the desired products.

Density Functional Theory

Theoretical calculations were performed by the density functional theory (DFT) method at the B3LYP/ 6-31G level of theory in the Gaussian 03 package of programs. According to the frontier molecular orbital theory, (HOMO) has the priority to provide electrons while LUMO can accept electrons first are the most important factors that affect the bioactivity [29, 30**].** Higher HOMO energy and lower LUMO energy in the drug molecule result in larger stabilizing interactions and hence, binding with the receptor. We also obtained a plot of the HOMO and LUMO of the molecules of each group to analyze the main atomic contributions for these orbital. The importance of observing these plots was to determine which atoms were located at the possible sites of electronic transfer between the molecule under study and its biological target. The results illustrate that HOMO lobes are spread mainly over only on carbonyl oxygen of quinone and pyrazol ring but compounds 5m and 5p electron density only located phenyl substituted small groups. In contrast, the LUMO lobes are almost homogeneously spread over naphthoquinone moiety as well as pyrazol ring **(Fig.1a and b).**

An important parameter to measure reactivity of the molecules is the energy gap, ΔE ($\Delta E = E_{LUMO} - E_{HOMO}$). Decreasing in ΔE of the molecule leads to decrease the required energy to remove an electron from the last occupied orbital. A molecule with a low energy gap is usually more polarisable with high chemical activity, low kinetic stability and high softness value [31]. The orbital energies of both HOMO and LUMO and their gaps were calculated for all the molecules and are reported in **(Table.1. and Fig.1).** The energy gap of compounds 5a, 5b, 5g, 5i, 5m, 5o have low energy gap and thus will exhibit the highest cytotoxic activity but expect compounds 5m and 5o very low activity due to LUMO electron cloud presence only in small groups as compared to all other compounds.

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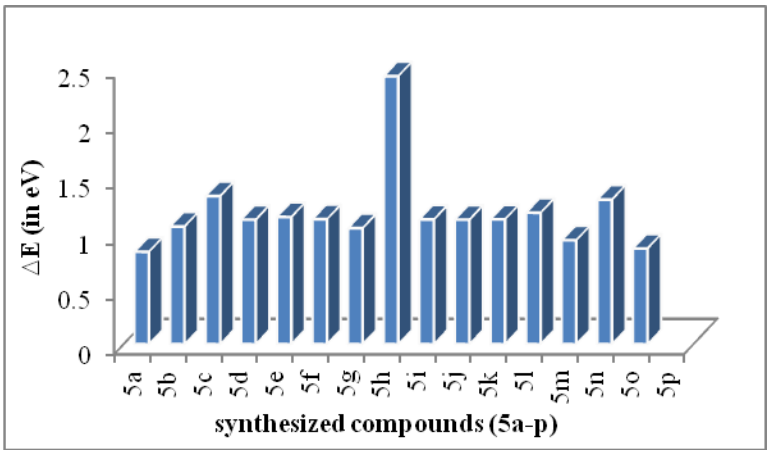

Fig.1. The energy gap of synthesized compounds (5a-p)

To describe reliably the reactive behavior of the studied compounds, global reactivity descriptors were computed within the DFT framework. The HOMO and LUMO energies, the ionization potential (I), the electron affinity (A), the absolute electronegativity (χ), the absolute hardness (η) and softness (S) are proposed for understanding various aspects of pharmacological sciences including drug design and possible eco-toxicological characteristics of the drugs [32**]** The above mentioned global reactivity descriptors were computed in the context of the finite difference method employing Koopmans' theorem. The descriptors were calculated according to the following equations.

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

$$EA = -E_{LUMO} \quad (2)$$

$$\chi = \frac{IP + EA}{2} = -\frac{E_{HOMO} + E_{LUMO}}{2} \quad (3)$$

$$\eta = \frac{IP - EA}{2} = \frac{E_{LUMO} - E_{HOMO}}{2} \quad (4)$$

$$S = \frac{1}{2\eta} \quad (5)$$

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Table.2.2. Important set of descriptors accounting for Cytotoxicity activity of synthesized compounds (5a-p)

Comp.	$E_{total\ (kcal)}$ E_{HF}	$\mu_{(Debye)}$	E_{HOMO}	E_{LUMO}	ΔE	χ	n	S
5a	-1909.808	5.1710	-3.7919	-2.9595	0.8323	3.3757	0.4162	1.201
5b	-1905.0524	3.1804	-3.7587	-2.6969	1.0617	3.2278	0.5309	0.941
5c	-1449.4496	6.0659	-4.1660	-2.8294	1.3366	3.4977	0.6683	0.748
5d	-1564.5213	3.8110	-4.0487	-2.9252	1.1232	3.4869	0.5596	0.893
5e	-1489.3908	3.3908	-3.9861	-2.8389	1.1472	3.4125	0.5736	0.871
5f	-1561.1899	3.0479	-4.2653	-3.1374	1.1279	3.7013	0.5639	0.886
5g	-1654.7526	6.8974	-4.3072	-3.2610	1.0462	3.7400	0.5672	0.881
5h	-1655.1102	5.0543	-5.7326	-3.3102	2.4223	4.5214	0.4985	1.003
5i	-1549.5568	2.8454	-4.0781	-2.9540	1.1241	3.5160	0.5620	0.889
5j	-1525.5302	3.0282	-4.0087	-2.8849	1.1238	3.4468	0.5619	0.889
5k	-4021.3171	3.1507	-4.1072	-2.9804	1.1260	3.5438	0.5616	0.890
5l	-1542.5172	5.8947	-4.3064	-3.1200	1.1864	3.6853	0.5932	0.842
5m	-1793.1380	3.9714	-3.6016	-2.6642	0.9374	3.3329	0.2687	1.860
5n	-1678.6050	9.1886	-4.2691	-2.9644	1.3047	3.6167	0.6612	0.756
5o	-1681.9279	1.4509	-3.3772	-2.5144	0.8628	3.1457	0.2314	2.164
5p	-1317.2800	10.320	-5.2120	-4.0585	1.1534	4.6352	0.5767	0.8673

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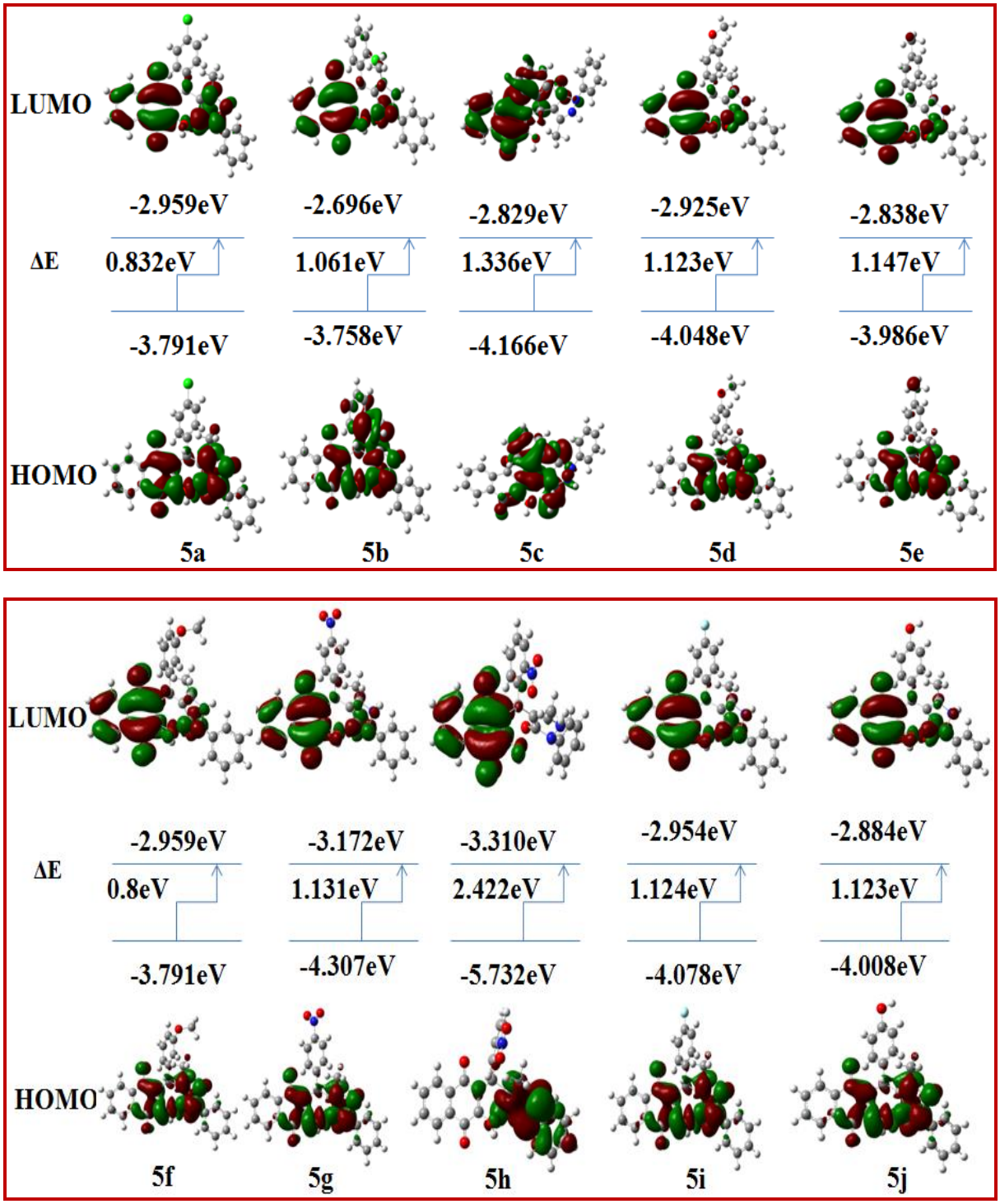

Fig.1.a. Schematic representation of HOMO and LUMO coefficient distribution of (5a- 5j) derivatives

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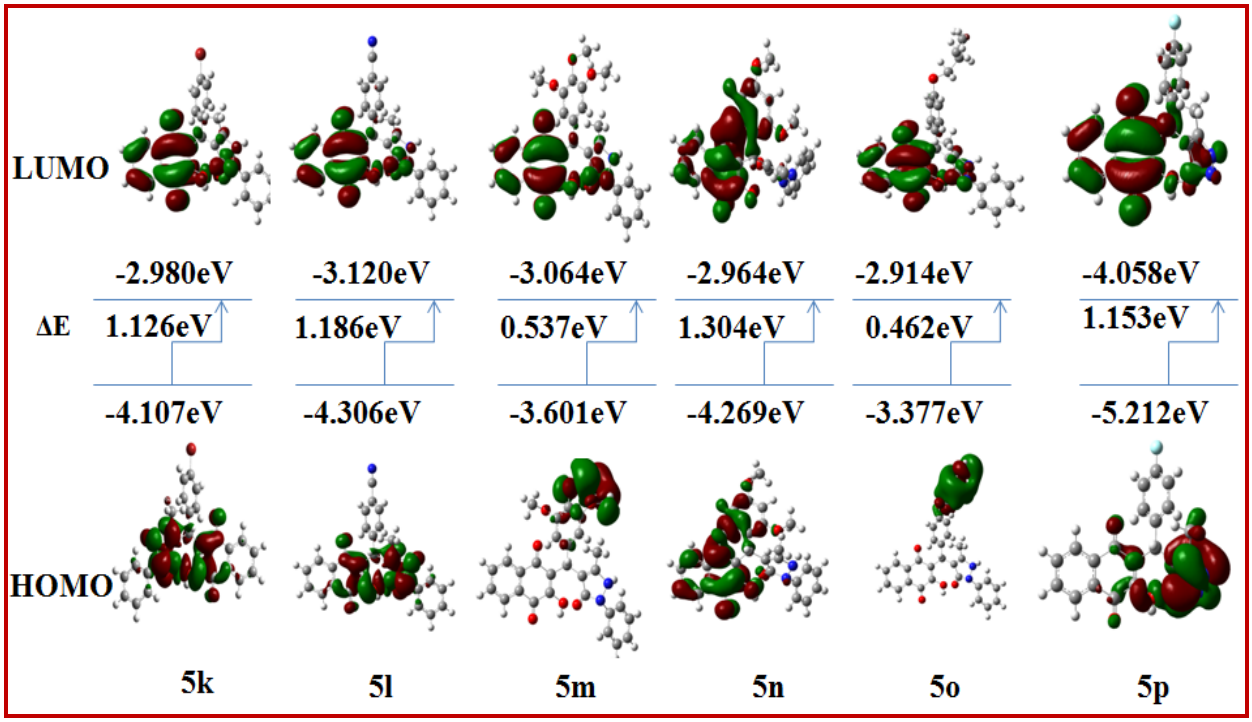

Fig.1b. Schematic representation of HOMO and LUMO coefficient distribution of (5k- 5p) derivatives

Molecular electrostatic potential (MEP)

Electrostatic potential surfaces [33] are valuable in computer-aided drug design because they help in optimization of electrostatic interactions between the protein and the ligand. These surfaces can be used to compare different inhibitors with substrates or transition states of the reaction. Electrostatic potential surfaces can be either displayed as isocontour surfaces or mapped onto the molecular electron density. The latter are more widely used because they retain the sense of underlying chemical structure better than isocontour plots. MESP maps for polar molecules reveal well sites that are most electron-rich and most electron-poor. True electrostatic potential maps of polar molecules generally do an excellent job predicting the possibility of charge-dipole, dipole-dipole and quadrupole-dipole interactions.

A molecular of electrostatic potential map of synthesized compounds provides information about the electron acceptor and electron donor regions. The different values of the MEP at the surface are represented by different colors, red represents regions of most electro negative electrostatic potential, oxygen of quinine ring and nitrogen of pyrazole atoms have more negative charges. Most likely this region as recognized the docking results oxygen and nitrogen atoms have some interaction with the hydrogen bond target receptor. The blue represents regions of most positive electrostatic potential were mainly distributed over the aromatic group which result hydrophobic interaction. The color code of these maps is in the range from -0.0315 a.u. (red) to +0.0315 a.u. (blue) for B3LYP/6-31G **(Fig.2.17).**

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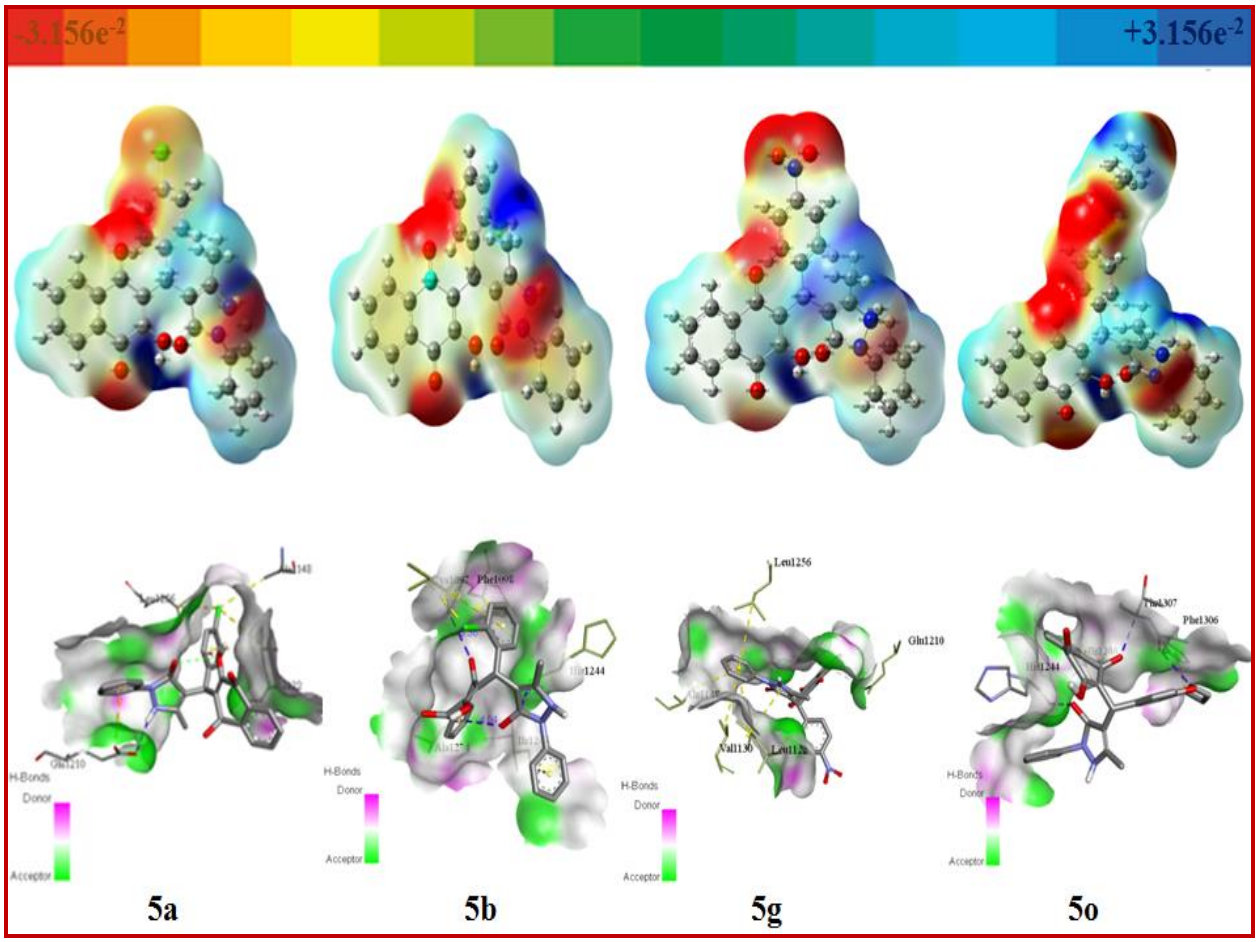

Fig.2.17. Molecular electrostatic potential and docking interaction

Conclusion

In summary, we synthesized a series of heterocyclic benzylpyrazolyl naphthoquinone derivatives **(5a-5p).** To gain a better insight into SAR, some electronic parameters including energies and plots of HOMO and LUMO as well as plots of MEP have been obtained by quantum chemical calculation. The HOMO-LUMO analysis in different molecules (pyridine and naphthalene derivatives) predicted that the HOMO→LUMO transition implies an electron density transfer. Moreover, lower in the HOMO and LUMO energy gap explains the eventual charge transfer interactions taking place within the molecule. The substitution pattern of the phenyl ring seems to be important in terms of biological activity.

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