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# Computational Investigation on Naphtoquinone Derivatives: Nuclear Magnetic Resonancs (NMR) and Quantum Mechanic

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## ABSTRACT

Naphthoquinones are natural aromatic compounds that can be discovered in various plant families. In recent times a diversity of biological activities of these compounds has been reported. In most cases, these pharmacological activities are related to redox and acid-base properties, which can be modulated synthetically by modifying the substituents attached to the 1, 4- naphthoquinone ring, in order to enhance their therapeutic actions. In the current study we used dipole moment and nuclear magnetic resonance (NMR) to depict these molecules properties. The density functional theory (DFT) calculations at the level of B3LYP/6-31G* have been applied to analyze the substituent effect on the electronic structural properties including thermochemical parameters of Naphtoquinone Derivatives in gas phase using Gaussian 98. Dipole moment (Debye), energy of structure formation (HF/Kcal/mol) and point group, NMR parameters such as isotropic shielding ($\sigma_{iso}$) and anisotropic shielding ($\sigma_{aniso}$), $\sigma_{11}$, $\sigma_{22}$, $\sigma_{33}$ obtained. Also thermodynamic properties and natural bond orbitals (NBO) were calculated. It dovetails our recent work of electron transfer pathways on Naphtoquinone Derivatives in different replacement is a fundamental step in constructing a knowledge base which will ultimately be of use in many cases.

**Keywords:** biological activities; dipole moment; thermodynamic properties; DFT; Debye.

## INTRODUCTION

Naphthoquinones are structurally related to naphthalene, are characterized by the presence of two carbonyl groups in the 1,4 position and 1,2 position with lower incidence, which are named as 1,4-naphthoquinones and 1,2-naphthoquinones respectively. Naturally present hydroxyl and methyl groups as substituents can be found in free form or condensed with oligosaccharides. Naphthoquinones are highly reactive organic compounds, traditionally used as natural or synthetic dyes whose colors range from yellow to red [1, 2].In the chemistry of natural and synthetic naphthoquinones redox and acid-base properties are important because they are directly related to the biological properties possessed by different compounds. The capacity to accept one or two electrons to form the corresponding radical- anion ($Q^{\cdot-}$) and hydroquinone radical anion($Q^{2-}$) shown in the fig. 1, can be modulated by the electro-donating and electro-withdrawing substituents attachment to naphthoquinone ring [3,4].

Naphthoquinone derivatives have attracted continuing interest over the years because of the use of its ring system as important core structure in many drug substances and reported to cover wide

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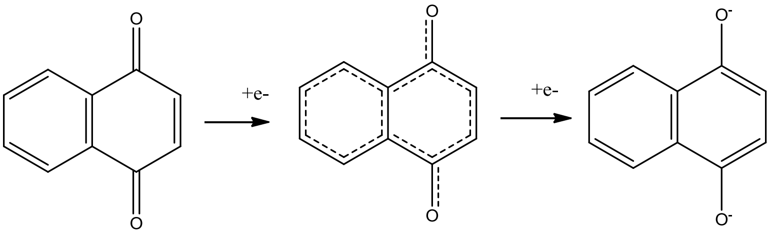
range of pharmacological applications[5, 6], furthermore, quinones, particularly 1,4-naphthoquinones are widely distributed phenolic compounds in nature such naphthoquinones are reported to exhibit diverse pharmacological properties like antibacterial [7], antifungal, antiviral, anti-inflammatory antipyretic properties and anticancer activity[8]. These quinones have the ability to induce oxidative stress which is responsible for initiation of tissue damage selectively in tumor cells and this seems to be a promising approach for targeting cancer cells [9]. Moreover many biological properties for 2-aminothiophene derivatives have been reported, such as A1 adenosine receptor allosteric enhancers [10, 11], antifungal [12], antibacterial [13], anti- inflammatory [14], antitumor and anti-HIV activates. In view of the above mention and as a part of our continuous efforts towards the development of more potent antioxidant agents [15-19], it was thought of interest to combine the above mentioned boilable rings together in a molecular framework to investigate the additive effect of these rings towards antioxidant activities



Q-

Q2-

**Fig.1.** Redox properties of naphthoquinone ring. Quinone produces the semiquinone radical (Q$^-$) and dianion hydroquinone (Q$^{2-}$) by a sequence of two electron reduction.

Their antimicrobial, anti-parasitic and cytotoxic activities emerge due to their ability to act as potent inhibitors of electron transport, as uncouples of oxidative phosphorylation, as intercalating agents in the DNA double helix, as bio reductive alkylating agents of bio-molecules, and as producers of reactive oxygen radicals by redox cycling under aerobic conditions. Naphthoquinones, especially juglone, are widely studied for allelopathic activity. Plants with naphthoquinone content are world-wide used in the traditional medicines of countries where they grow. Naphthoquinones are highly toxic. Moreover, 1, 4-naphthoquinone has been evaluated as a corrosion inhibitor in 0.5M NaCl solutions. This effect is a result of its adsorption on the metal surface and blocking the corrosion process [20].

In this paper, stabilities of three structures as potential candidates for high energy density materials have been investigated theoretically by using quantum chemical treatment. Geometric features, electronic structures of these naphthoquinone derivatives have been systematically studied using density functional theory (DFT, B3LYP) at the level of 6-31G*, These molecules properties were investigated at B3LYP/6-31G* level.

## COMPUTATIONAL METHODS

We have carried out quantum theoretical calculations of naphthoquinone derivatives using DFT (B3LYP) method with 6-31G* basis set by the Gaussian98 program. For further investigation of the substituent effects, the frequency calculations as well as their corresponding thermochemical parameters including Gibbs free energies of the derivatives of naphthoquinone have been performed. Then isotropic part $\sigma_{iso}$ of $\sigma$ was determined by averaging $\sigma$ over orientations in the magnetic field, that is, $\sigma_{iso}= (\sigma_{11}+ \sigma_{22}+\sigma_{33})/3$. The anisotropy is $\sigma_{aniso}=| \sigma_{33}- \sigma_{iso}|$, and the asymmetry is $\eta= (\sigma_{22}-\sigma_{33})/ \sigma_{aniso}$[21].

Nuclear magnetic resonance (NMR) calculations on derivatives of naphthoquinone using Hartree-Fock and density functional theory(DFT) reveal that methods including electron correlation show significant imorovements in the NMR shielding over results.

In contrast to empirical potentials, DFT calculation can be used in the study of biomolecules which are very important in understanding the many aspects of structure and function of these structures. We know computation can reveal all possible structures available at the applied level of theory. However, a theoretical method ignores a set of factors associated with the molecular environment. One of the most successful density functional applied to small molecules, B3LYP employs Becke's method of using Lee-Yang-Parr's gradient-corrected exchange-correlation density functionals, which include a hybrid of the Hartree-Fock exchange and the DFT exchange. Thus the B3LYP is semi-empirical to an extent [22].

Therefore, in this work, computer demands are moderate and comparable to naphthoquinone derivatives, and its different electronegative replacements. Also, the thermodynamics of naphthoquinone derivatives is an important subject which has received much attention theoretically. Such interactions have several specific aspects which complicate their study. In present work, we have calculated the lowest energy each locally geometrically stable structure, thermodynamic properties and NMR parameters in various replacement of electronegative elements. LUMO-HOMO band gap is a gap between LUMO (the lowest unoccupied molecular orbital and HOMO (the highest occupied molecular orbital) [23, 24].The band gap of naphthoquinone derivatives system as the relative differences in the energy of the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) have been calculated.

## RESULTS AND DISCUSSION

In this investigation, we have studied the stability energy, thermodynamic properties, and atomic charge and NMR parameters in various replacements of halogen atoms. The electronic structure of the complex has optimized at DFT/B3LYP/6-31G* level for each replaced structure that we investigate the possibility of forming.

Properties profile is generally wished for in the quantum chemical computations. As we have seen in this paper, the electronic structure is remarkably affected by in replacement of F, Cl and Br electronegative atoms, which means that reactions are strongly governed (and controlled) by the electron transfer as well.

A particularly important advance related to this work is the parameterization of electronic effects, which yielded results, such as stability energy, thermodynamic and NMR properties, charge distribution, total dipole moment and HOMO and the LUMO differences of derivatives of naphthoquinone structure (Fig.2.Table 1).

In particular, we tried to starting for thermochemical calculations of derivatives of naphthoquinone in replacement of F, Cl and Br electronegative atoms at DFT/B3LYP method using by 6-31G* basis set (Fig.3).

As a consequence, a relatively large set of starting structures has been generated and the geometry optimization procedure has been employed to verify whether the resulting converged structure correspond to global minima at B3LYP/6-31G* level via thermodynamic data (Fig.3).

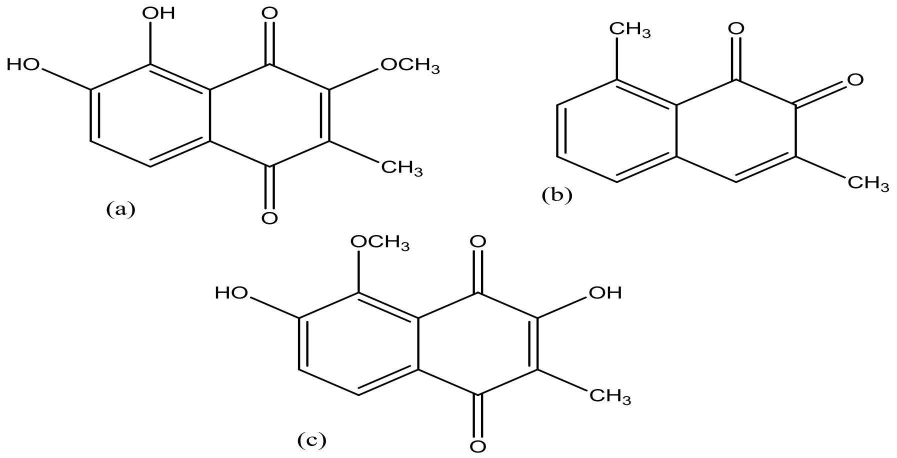


**Fig. 2**. a) 2-methyl-3-methoxy-5, 6-dihydroxy-1, 4-naphthoquinone b) 3, 8-dimethyl-1, 2-naphthoquinone c) 2-methyl -3, 6-dihydroxy-5-methoxy -1, 4-naphthoquinone.

**Table 1.** Calculated Parameters of Gibbs free energy, enthalpy, stability energy Dipole moment and Δ(HOMO-LUMO) LUMO-HOMO band gap for compound C different replacement of 6 atoms of F, Cl and Br at DFT/B3LYP / 6-31G* level

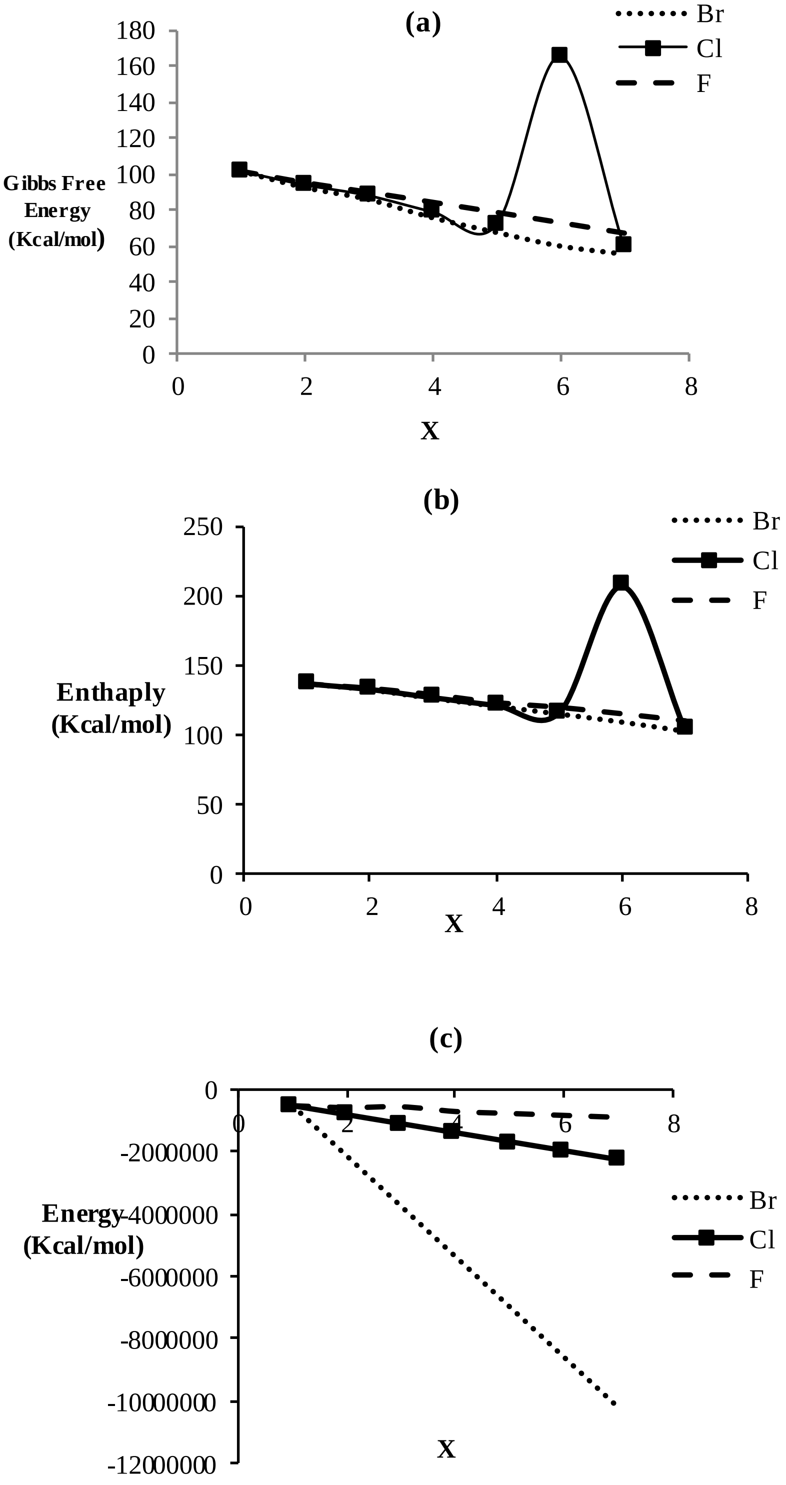
| COMPOUND | Dipole moment (Debye) | Energy (Kcal/mol) | Enthalpy (Kcal/mol) | Gibbs Free Energy (Kcal/mol) | (HOMO-LUMO) (Kcal/mol) |
|---|---|---|---|---|---|
| **C** | 3.214021988 | -526729.8025 | 137.2926434 | 100.5327202 | -0.12393 |
| **1F** | 4.462453576 | -588990.8878 | 133.4899576 | 95.50137793 | -0.12312 |
| **2F** | 5.83826095 | -651263.5909 | 128.8269613 | 90.03956658 | -0.12233 |
| **3F** | 6.27323344 | -713542.432 | 123.8734297 | 84.18995658 | -0.12213 |
| **4F** | 5.10879689 | -775815.5791 | 119.7469509 | 78.7890133 | -0.12382 |
| **5F** | 5.49247747 | -838092.4756 | 115.0852096 | 72.90551798 | -0.12729 |
| **6F** | 4.62784296 | -900369.7165 | 110.027512 | 66.83188837 | -0.12969 |
| **1Cl** | 4.85896679 | -815126.1606 | 132.5756815 | 94.14533768 | -0.12195 |
| **2 Cl** | 6.2953949 | -1103516.619 | 127.1502655 | 86.93717741 | -0.12056 |
| **3 Cl** | 6.57856675 | -1391897.422 | 121.0527907 | 78.93647718 | -0.12078 |
| **4 Cl** | 4.5873021 | -1680297.914 | 115.9543052 | 71.70196166 | -0.12082 |
| **5 Cl** | 3.6947056 | -1968690.462 | 110.3600901 | 64.13486802 | -0.12154 |
| **6 Cl** | 4.50203698 | -2257075.403 | 104.171627 | 56.59538463 | -0.12684 |
| **1Br** | 4.6984681 | -2140111.46 | 132.251261 | 92.8181627 | -0.12091 |
| **2 Br** | 5.94979209 | -3753487.73 | 126.5779801 | 84.81746248 | -0.11966 |
| **3 Br** | 6.23212437 | -5366855.317 | 120.4259123 | 75.53916024 | -0.11916 |
| **4 Br** | 4.32402227 | -6980240.774 | 114.9164105 | 67.12305111 | -0.11882 |
| **5 Br** | 4.560309 | -8593618.081 | 108.9783221 | 59.03450006 | -0.12125 |
| **6 Br** | 4.20814124 | -10206992 | 102.8005266 | 50.22557224 | -0.12172 |

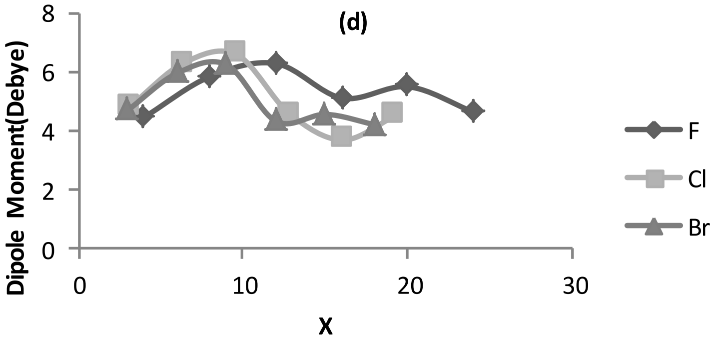
**Table 2.**Calculated NMR parameters of isotropic chemical (σiso) and anisotropic chemical shielding (σaiso) (ppm) for each atoms of compound C structure at DFT/B3LYP / 6-31G* level

| atom | charge | σiso | σaniso | η | Δδ | Ω |
|---|---|---|---|---|---|---|
| 1 C | 0.047586 | 71.9857 | 138.3466 | 0.266438327 | 138.34665 | 92.2311 |
| 2 C | 0.02129 | 69.8027 | 141.4853 | 0.574770868 | 141.4853 | 94.3235 |
| 3 C | 0.348461 | 13.1865 | 151.6326 | -2.44302196 | 12.34395 | 51.0609 |
| 4 C | 0.051821 | 75.7031 | 111.2217 | 0.8111623 | 111.22175 | 74.1478 |
| 5 C | 0.260837 | 43.4093 | 116.899 | 0.114021457 | 83.3346 | 77.9327 |
| 6 C | 0.370706 | 14.2561 | 149.7123 | -2.673145495 | 9.0351 | 46.5825 |
| 7 C | 0.23809 | 50.1823 | 102.1613 | 0.272596997 | 102.16125 | 68.1075 |
| 8 C | 0.346776 | 42.0226 | 132.973 | 6.787203277 | -50.0794 | -16.1135 |
| 9 C | -0.166937 | 75.5415 | 142.1844 | 0.570019285 | 142.18435 | 94.7896 |
| 10 C | -0.182501 | 68.6577 | 174.9517 | 0.177312888 | 153.7566 | 116.6345 |
| 11 O | -0.637472 | 227.2508 | 111.2973 | 0.511614462 | -196.4879 | -164.3253 |
| 12 O | -0.632255 | 222.4669 | 152.655 | 0.799715404 | -202.99 | -168.66 |
| 13 C | -0.513444 | 177.5826 | 9.5751 | 0.032320817 | -113.8542 | -109.2361 |
| 14 O | -0.521424 | -191.6733 | 893.866 | 0.434186028 | 264.60875 | 595.9107 |
| 15 O | -0.485893 | -260.9576 | 988.0968 | 0.356982939 | 207.4504 | 658.7312 |
| 16 O | -0.544555 | 273.6926 | 127.9875 | 0.553778296 | -211.28245 | -174.1883 |
| 17 C | -0.2263 | 132.3726 | 81.8593 | 0.609713747 | -144.8908 | -129.9272 |
| 18 H | 0.158923 | 25.183 | 5.3532 | 0.940461626 | -5.51745 | -3.6783 |
| 19 H | 0.173785 | 24.3551 | 5.7552 | 0.682674385 | -6.8405 | -4.5603 |
| 20 H | 0.425901 | 26.1839 | 12.515 | 0.630458361 | -15.35155 | -10.2343 |
| 21 H | 0.428839 | 25.2388 | 15.1316 | 0.998741839 | -15.1412 | -10.0941 |

**Table 3.**Calculated NMR parameters of isotropic chemical (σiso) and anisotropic chemical shielding (σaiso) (ppm) for each atoms of compound C structure and replacement with 6 Br at DFT/B3LYP / 6-31G* level

| atom | charge | σiso | σaniso | η | Δδ | Ω |
|---|---|---|---|---|---|---|
| 1 C | 0.085431 | 71.2568 | 140.3459 | 0.25092557 | 140.346 | 93.564 |
| 2 C | 0.01549 | 69.9579 | 139.6319 | 0.608809523 | 139.6319 | 93.0879 |
| 3 C | 0.39382 | 18.6381 | 139.0276 | -2.244139611 | 4.18675 | 45.6497 |
| 4 C | 0.057422 | 71.5699 | 94.3496 | 0.889212684 | 94.34965 | 62.8998 |
| 5 C | 0.28442 | 49.4732 | 109.6548 | 0.353515304 | 97.68255 | 73.1032 |
| 6 C | 0.377996 | 14.1366 | 148.4698 | -2.292206923 | 11.63435 | 51.5419 |
| 7 C | 0.213235 | 56.484 | 76.6529 | 0.76676014 | 76.65295 | 51.1019 |
| 8 C | 0.363765 | 42.4528 | 131.1534 | 5.690643281 | -52.0428 | -19.1798 |
| 9 C | -0.157882 | 68.9896 | 145.8579 | 0.598960701 | 145.85785 | 97.2386 |
| 10 C | -0.165968 | 64.4447 | 180.211 | 0.072821284 | 152.1289 | 120.1407 |
| 11 O | -0.63695 | 209.002 | 113.2753 | 0.595906509 | -185.9477 | -157.2985 |
| 12 O | -0.602338 | 197.7458 | 212.3571 | 0.976424617 | 262.3571 | 141.5714 |
| 13 O | -0.502875 | -205.2073 | 924.891 | 0.446298537 | 247.8824 | 616.594 |
| 14 O | -0.461314 | -286.3039 | 28.5543 | 0.455536793 | 220.24365 | 685.7029 |
| 15 O | -0.471794 | 134.7857 | 146.0374 | 0.615528019 | 146.03735 | 97.3582 |
| 16 C | 0.184218 | 41.5161 | 11.4306 | 0.898573653 | -12.04125 | -8.0275 |
| 20 C | -0.124169 | 69.5519 | 29.8342 | 0.327551971 | -44.9462 | -29.9641 |
| 24 H | 0.174427 | 24.9258 | 5.9382 | 0.988506618 | 5.93815 | 3.9588 |
| 25 H | 0.188793 | 24.0468 | 6.7925 | 0.825763532 | -7.4407 | -4.9605 |
| 26 H | 0.43449 | 25.6375 | 18.3402 | 0.793977165 | 18.3403 | 12.2268 |
| 27 H | 0.441758 | 24.1152 | 17.1018 | 0.896484581 | 17.1018 | 11.4012 |


(a)
Br
Cl
F
Gibbs Free Energy (Kcal/mol)
180
160
140
120
100
80
60
40
20
0
0
2
4
6
8
X
(b)
Br
Cl
F
Enthaply (Kcal/mol)
250
200
150
100
50
0
0
2
4
6
8
X
(c)
0
-2000000
-4000000
-6000000
-8000000
-10000000
-12000000
Energy (Kcal/mol)
0
2
4
6
8
Br
Cl
F
X



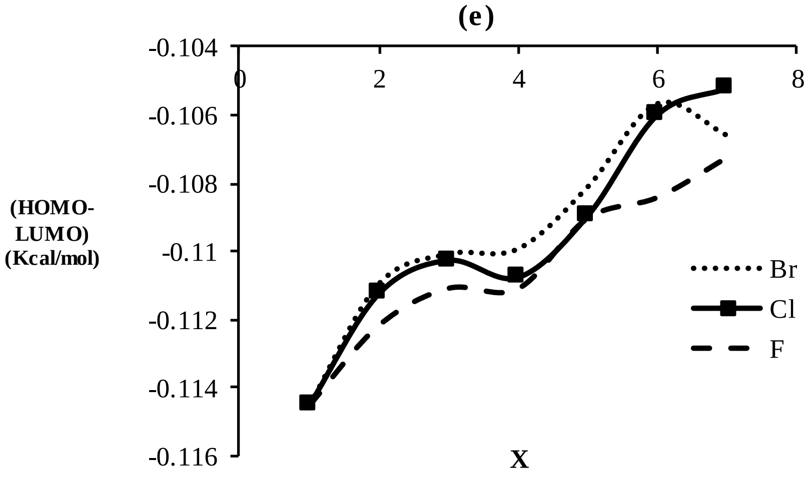
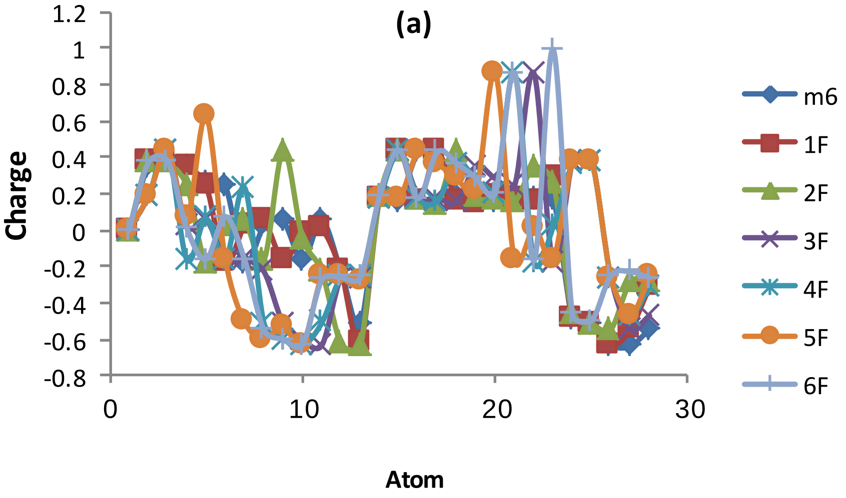
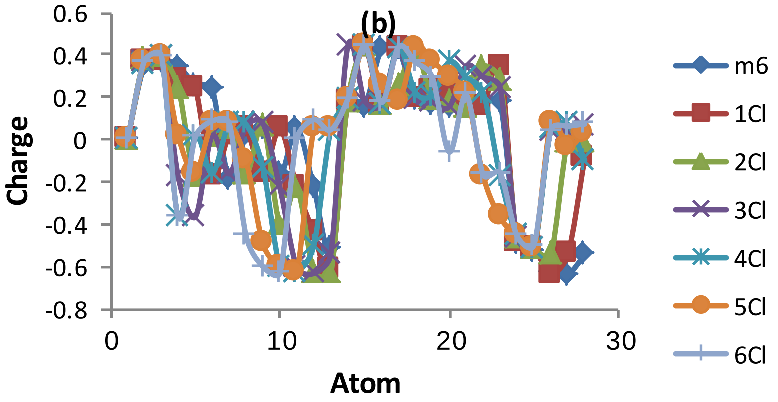


**Fig. 3.** Plotted of (a) Gibbs free energy (b) enthalpy (c) stability energy (d) Dipole moment and (e) (HOMO-LUMO) band gap for compound C structure and different replacement of 1-6 atoms of F, Cl and Br (X).





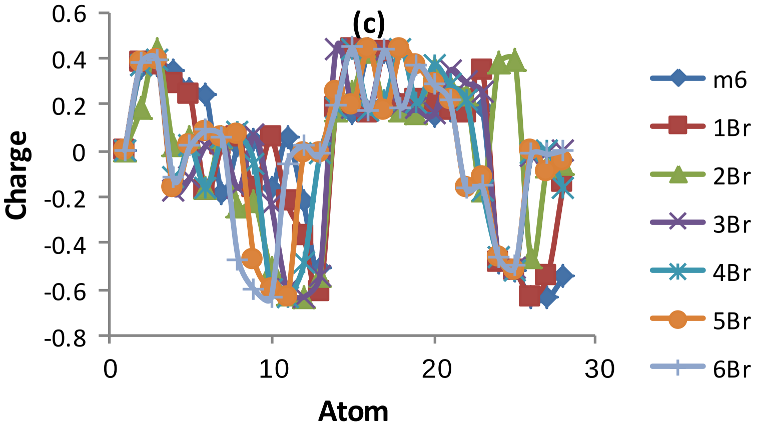
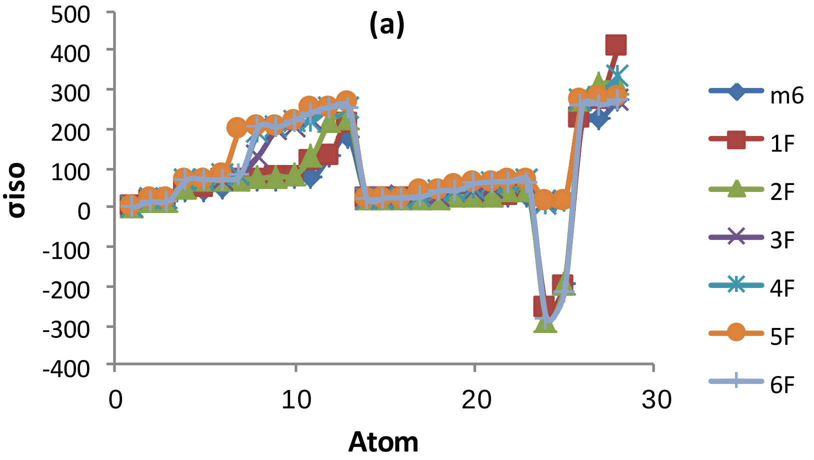
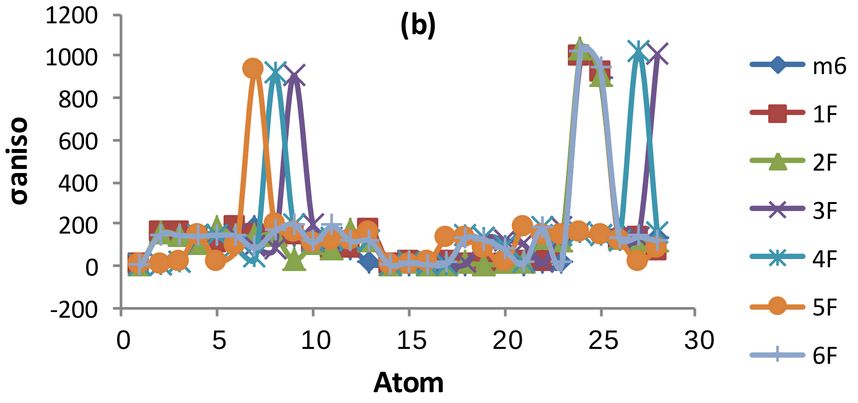
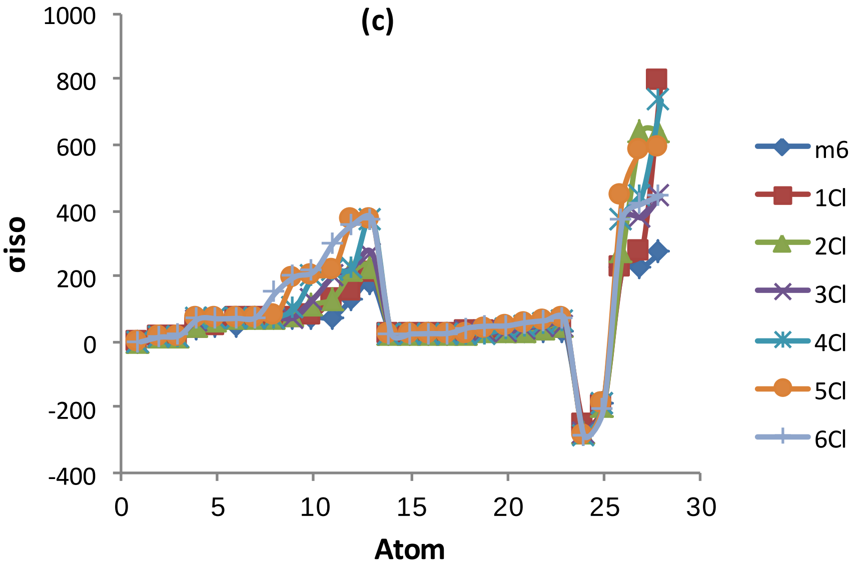


**Fig.4.** Calculated atomic charge each atoms of via compound C structure and different replacement of **(a)** F, **(b)** Cl and **(c)** Br electronegative atoms at DFT/B3LYP / 6-31G* level.




(b)
σaniso
1200
1000
800
600
400
200
0
-200
0
5
10
15
20
25
30
Atom
m6
1F
2F
3F
4F
5F
6F


(c)
σiso
1000
800
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400
200
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-400
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15
20
25
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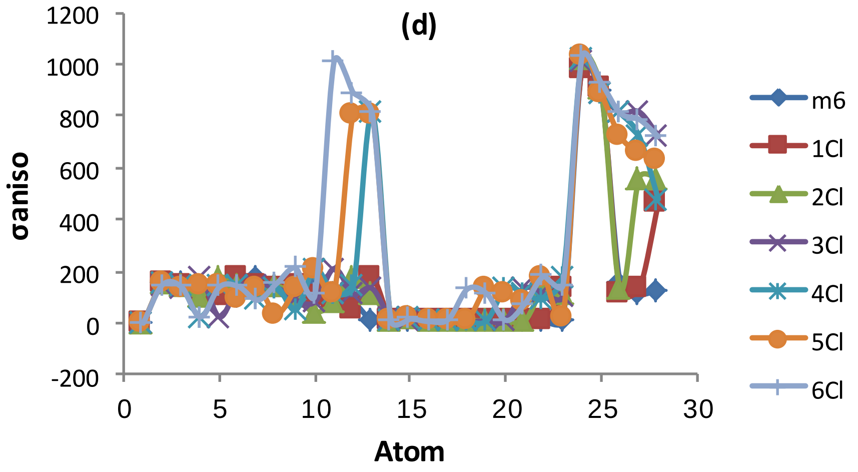
Atom
m6
1Cl
2Cl
3Cl
4Cl
5Cl
6Cl


(d)
σaniso
1200
1000
800
600
400
200
0
-200
0
5
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25
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Atom
m6
1Cl
2Cl
3Cl
4Cl
5Cl
6Cl

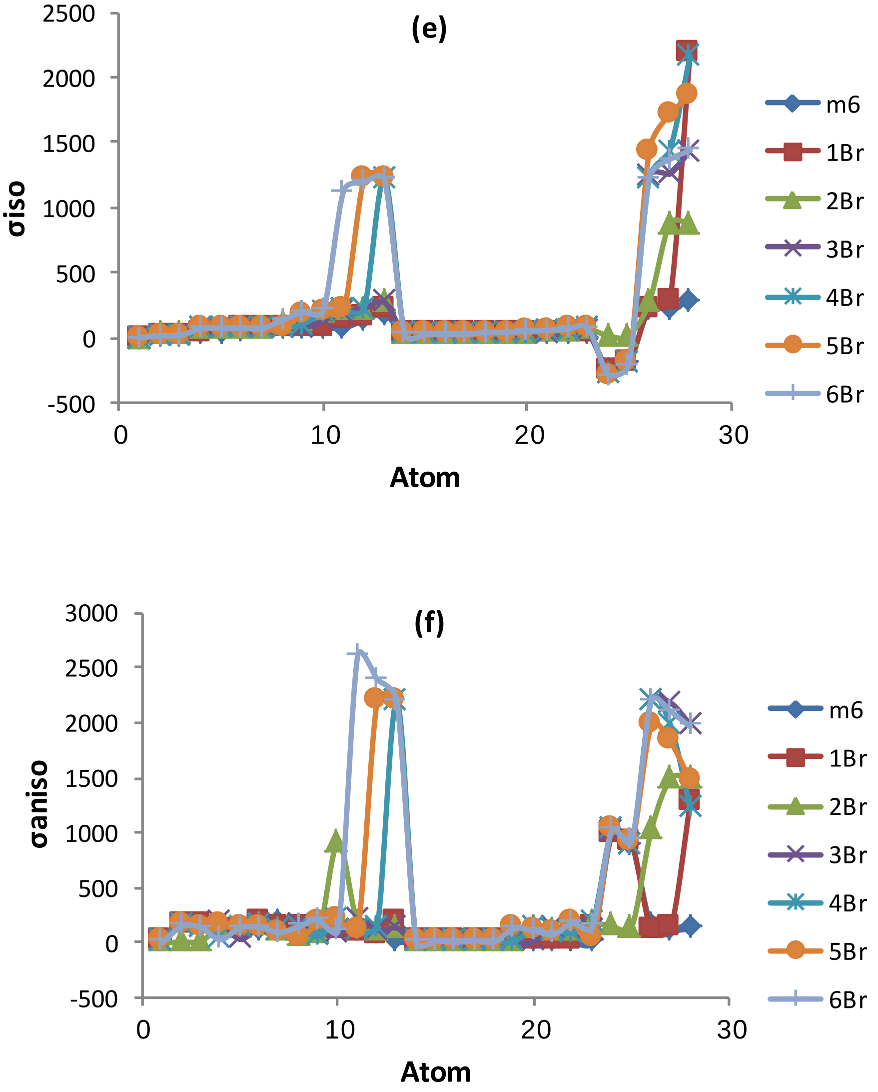

**Fig.5.**Calculated NMR parameters of isotropic chemical shielding (σiso) and anisotropic chemical shielding (σaiso) (ppm) for each atoms of compound C structure and different replacement of **(a,b)** F, **(c,d)** Cl and **(e,f)** Br electronegative atoms at DFT/B3LYP / 6-31G* level

The electrostatic component of the free energy, Enthalpy and Stability energy , due to the interaction with replacement of F, Cl and Br atoms are approximated to the gas phase energy. As a result, it has been shown that by increasing F Cl and Br atoms, the Gibbs free energy and Enthalpy and stability energy have been decreased and the system has been stabilized (Fig.3.a, b and c).

In this work, we have seen that the structure and reactivity pattern on derivatives of naphthoquinone are well reproduced by DFT quantum chemical method assuming with active binding assignment as center of electron transfer. The structure and reactivity properties appear to be dependent on the spin states of the complex, of which several close-lying states were identified.

Also, such a change in the electron distribution is reflected, among other properties, in an increase of the atomic charges and dipole moments in neutral polar molecules (Fig.3.d).

The results indicate that electronegative atoms enlarge the dipole moment by, which for molecule corresponds to an increase with regard to the number of F, Cl and Br atoms (Fig.3.d).

As a check on the quality of the calculated geometrical parameters and their stability with respect to the level of theory, the HOMO and the LUMO differences have been explored (Table 1 and Fig.3.e).

In other words, the obtained values for derivatives of naphthoquinone and different replacement of halogen atoms on methyl and methoxy groups, which had significant differences with electronegative effects have been studied.

In inspection amongst the highest HOMO- LUMO band gaps in all F,Cl and Br, it seems that in all three considered cases the highest Δ(HOMO-LUMO) values and then highest stability has been occurred by increasing the number from 1-6 (X=F,Cl,Br) (Fig.3.e).

As it has been noted above, electronegative effects react to generate a reaction field, which in turn interacts with the charge distribution. The magnitude of the polarization depends on the number and characteristics of the atom, especially its polarity and polarizability (Table 1, 2 and Fig.4).

As it has been shown, by increasing the electronegative atoms of F,Cl and Br (1-6 numbers) to derivatives of naphthoquinone ,changes of each pick has been increased and also we have seen the same behavior for halogens in this replacement (Fig.4 a,b and c).

NMR calculations on derivatives of naphthoquinone with different electronegative atoms replacement using DFT/B3LYP method reveal that methods including electron correlation show significant improvements in the NMR shielding over results (Table 2).

The NMR measurements were carried out using B3LYP/6-31G* in GIAO approximation of nuclear magnetoic resonance at theoretical concepts in different replacement of 6 halogen atoms (X=F,Cl and Br) (Table 2).

The results of table 2 have been shown in fig.5 , where we plot the isotropic chemical shielding (σiso) and anisotropic chemical shielding (σaiso) for each atoms of derivatives of naphthoquinone structure in different replacement (X=1-6 of F,Cl and Br). We have found that derivatives of naphthoquinone structure with 6F,6Cl and 6Br replacement denoted has maximal shift in theoretical level and other indicated replacement almost have the less shifts in different positions. Also, we have seen that by increasing charge transfer, value of chemical shift and chemical anisotropy has been increased (Fig.5 a-f).

## CONCLUSIONS

In this study, we investigated NMR parameters of naphthoquinone derivatives (2-methyl-3-methoxy-5, 6-dihydroxy-1,4-naphthoquinone and 3, 8-dimethyl-1, 2-naphthoquinone and 2-methyl -3, 6-dihydroxy-5-methoxy -1, 4-naphthoquinone). These molecules have effective role in anticancer properties. Quantum mechanic calculations were carried out with GAUSSIAN 98 program using DFT theory at the B3LYP/6-31G* basis set. Finally, on the basis of the obtained we have realized that naphthoquinone derivatives (2-methyl-3-methoxy-5, 6-dihydroxy-1, 4-naphthoquinone and 3, 8-dimethyl-1, 2-naphthoquinone and 2-methyl -3, 6-dihydroxy-5-methoxy -1, 4-naphthoquinone) with most Br replacement showed highly effects in DFT theoretical level with demonstrated some high comparable peaks. Also, these complexes correlated strongly with the total electron charge transfer and electronegative effect. All this may have direct effects on the antioxidant, anti-cancer and anti-inflammatory properties.

## ACKNOWLEDGMENT

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