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# The theoretical investigation of global reactivity descriptors, NLO behaviours and bioactivity scores of some norbornadiene derivatives

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## ABSTRACT

In this study, global reactivity descriptors such as ionization potential, electron affinity, electronegativity, chemical hardness, softness and electrophilicity index of norbornadiene derivatives which include some halogen atoms and atom groups, have been investigated with DFT/BPV86/B3LYP/B3PW91 methods with 6-31G(d,p) basis set. To determine the non-linear optical behaviours of the structures; the total dipole moment, mean polarizability and first-order hyperpolarizability values have been examined at the same theoretical level. It has been found that thiol-bonded groups in comparison with others have a much better NLO material property. In addition, the potentials being drug-active compounds of the structures have been examined with Lipinski's rule of 5 and bioactivity scores. Thiol and hydroxyl-bonded groups have a good drug-likeness and bioactivity score relative to the others.

**Keywords:** Global reactivity descriptors, NLO, DFT, Lipinski's rule of 5, bioactivity score

## 1. INTRODUCTION

Quantum mechanically based approaches provide very effective results in the process of understanding the physical and chemical properties of molecular structures. Day by day developing software technology, along with the mathematical background foresee of these approaches provides positive contribution at the effects of the theoretical analyses. Density Functional Theory (DFT) is one of the quantum mechanical approaches that are quite successful in elucidating the electronic structures of substances and giving results which are consistent with experimental data at the same time [1-4].

Global reactivity descriptors such as ionization potential, electron affinity, electronegativity, chemical softness-hardness, chemical potential, electrophilic index, are used to explain the reactivity and stability properties of over the entire molecular structure. In determining these identifiers in DFT-based calculations, the frontier molecular orbital energy values are considered as a starting point and some of them are obtained from derivative of the energy respect to electron density for the molecular structures [5-7].

The design of molecules exhibiting a non-linear optical behaviour is a current research topic in modern communication technology, optical data storage, transmission of optical signals, signal processing and in many optoelectronic applications areas [8-11]. The delocalization of π electrons that increased by conjugation, and the high polarization, are effective factors in displaying the non-linear optical character of molecular structures [12].

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Norbornadiene which is used in the synthesis of complex polycyclic hydrocarbons is a significant organic compound. The structural properties of the compounds which is synthesized by 1,3-dipolar mono-domino cycloaddition reactions and having norbornadiene skeleton, isoxazole moiety, the aromatic groups were examined with spectroscopic and theoretical methods by our working group [13,14].

In the present paper, global reactivity descriptors and non-linear optical properties at the theoretical level have been examined of new derivatives obtained by connecting some atoms (*-F*, *-Cl*, *-Br*) and atom groups (*-OH*, *-SH*,- *tert*-Butyl) in *para*-position to the aromatic groups of the two compounds. Theoretical analyses were carried out with DFT method at 6-31G(d,p) basis set and three different functionals, such as BPV86, B3LYP, B3PW91 to examine the effects of functional selections on reactivity parameters and NLO behaviour of molecular structures.

Furthermore, the potential drug-active compound properties and some bioactivity scores have been examined as theoretical for the obtained derivatives.

## 2. COMPUTATIONAL DETAILS

The derivatives of compounds **1** and **2** having the norbornadiene skeleton have been obtained with halogens like fluorine, chlorine, bromine and also atomic groups such as hydroxyl, thiol, tert-butyl, and molecular structures are shown in Figure 1.

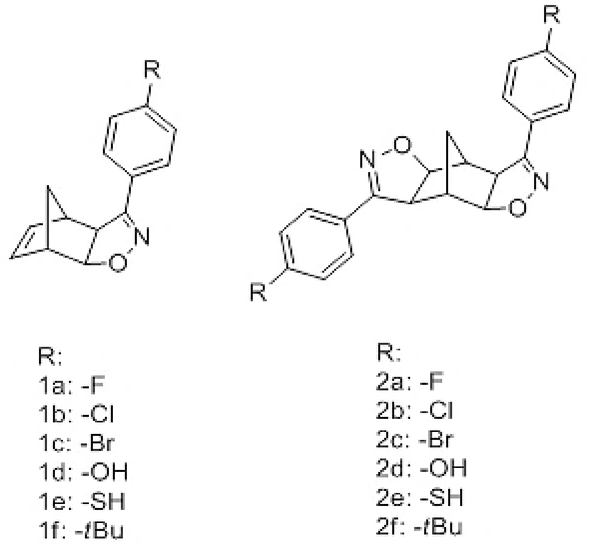

Figure 1. The chemical structures of the compound **1** and **2**

The geometric optimization of the obtained structures were realized with DFT using the BPV86, Burke and Perdew's 1986 functional with correlation replaced by Vosko et al [15], B3LYP, Becke's Three-Parameter Hybrid Functional using the Lee, Yang and Parr correlation [16], and B3PW91, Becke's Three- Parameter Hybrid Method Functional with Perdew/Wang 91 [16-c,17] functionals with 6-31G(d,p) basis set in ground state. In this process, the theoretical analyses were carried out with Gaussian 09, Revision C.01 [18] electronic structure and GaussView 5.0.9 [19] graphical interface programmes. All theoretical analyses were performed on optimized structures. The optimized molecular geometries of compounds **1** and **2** are shown in Figure 2 and 3. In these figures a ... f are defined as (a)*p*-F, (b)*p*-Cl, (c)*p*-Br, (d)*p*-OH, (e)*p*-SH, (f)*p*-*tert*-Butyl.

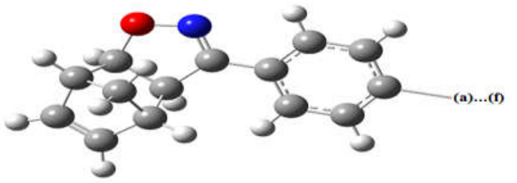

Figure 2. The optimized geometry of the compound **1**

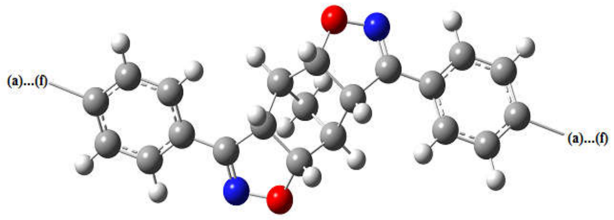

Figure 3. The optimized geometry of the compound **2**

The ionization potential (*I*) and electron affinity (*A*) according to Koopmans' Theory can be stated as [20],

$$I = -E_{HOMO} \quad \text{and} \quad A = -E_{LUMO} \qquad (1)$$

The electronegativity ($\chi$), global chemical hardness ($\eta$) and electronic chemical potential ($\mu$) are defined as [7,21];

$$\mu = \left(\frac{\partial E}{\partial N}\right)_{\nu(r)} = -\chi \qquad (2)$$

$$\eta = \frac{1}{2}\left(\frac{\partial \mu}{\alpha N}\right)_{\nu(\vec{r})} = \frac{1}{2}\left(\frac{\partial^2 E}{\partial N^2}\right)_{\nu(\vec{r})} \qquad (3)$$

in here, E; is the energy, N; is the number of electrons, $\nu(\vec{r})$; is the external potential of the molecular system under consideration.
Also, these concepts are expressed using *I* and *A* values as follows, respectively [22-25];

$$\chi = (I+A)/2, \quad \eta = (I-A)/2, \quad \text{and} \quad \mu = -(I+A)/2 \qquad (4)$$

Global chemical softness (*S*) and electrophilicity index ($\omega$) values are defined as follows [26-27];

$$S=1/2\eta \text{ and } \omega=\mu^2/2\eta \qquad (5)$$

To have knowledge about NLO behaviours of the obtained structures were analysed total electric dipole moment, $\mu_{tot}$, mean polarizability,<α>, total first-order hyperpolarizability, $\beta_{tot}$, values with the x,y,z components and can be computable with the following equations [28-30];

$$\mu_{tot} = \left(\mu_x^2 + \mu_y^2 + \mu_z^2\right)^{1/2} \qquad (6)$$

$$< \alpha >= \frac{(\alpha_{xx}+\alpha_{yy+}\alpha_{zz})}{3} \qquad (7)$$

$$\beta_{tot} = \left[(\beta_{xxx} + \beta_{xyy} + \beta_{xzz})^2 + (\beta_{yyy} + \beta_{yzz} + \beta_{yxx})^2 + (\beta_{zzz} + \beta_{zxx} + \beta_{zyy})^2\right]^{1/2} \qquad (8)$$

In order to determine the biological activity properties of the compounds, it has been investigated whether Lipinski's 5 rules [31,32] are provided for all the structures obtained. Also, a number of bioactivity scores such as GPCR ligand, ion channel modulator, nuclear receptor ligand, kinase inhibitor, protease inhibitor and enzyme inhibitor were examined at the theoretical level using Molinspiration Cheminformatics software [33-35].

## 3. RESULTS AND DISCUSSION

### 3.1. Global Reactivity Descriptors

The global reactivity descriptors such as ionization potential (*I*), electron affinity (*A*), electronegativity ($\chi$), chemical hardness ($\eta$), chemical softness (*S*), chemical potential ($\mu$) and electrophilicity index ($\omega$) values were examined with DFT/BPV86/B3LYP/B3PW91/6-31G(d,p) level in gas phase to have information about the chemical stability of the compounds having norbornadiene skeleton. Reactivity parameters defined by the equations (1), (4), (5) and obtained results are given in Table 1.

When the ionization potential (*I*) values, which is the minimum energy required to remove an electron from the molecule in the gas phase [36] were examined; compounds **1d** and **2d** have a lower *I* value than the others with respect to used methods. As can be seen in Table 1, compounds **1c** and **2b**, **2c** have a higher (*A*) value than others, according to electron affinity values which are the amount of energy that is increased when an electron has added the molecule [37]. According to these results, it can be said that hydroxyl-bonded groups with lower *I* values have better electron donating and the bromine and chlorine-bonded groups having a high *A* values have better electron accepting characteristics.

As regards the electronegativity values ($\chi$) chlorine and bromine-bounded groups (**1b**,**c** and **2b**,**c**) can be said to have the character which attracts bond electrons more than the others. When the global chemical hardness-softness ($\eta$,*S*) values considered as a measure of the inhibition of intramolecular charge transfer were examined, it was observed that the structures **1e** and **2e** have lower chemical hardness, higher chemical softness value for both compounds. It can be considered that thiol-bonded groups with soft molecular structure are more reactive, they can give the easier electron to acceptor group and thus more likely to transfer of charge. The chemical potential ($\mu$) and electrophilic index ($\omega$) indicate the tendency of structures to accept electrons. High chemical potential and electrophilicity index values are associated with a good electrophilic character [38]. For this reason, the chlorine and bromine-bonded structures have a better electrophilic character than the others.

Table 1. Global reactivity descriptors of the structures

| Struc. | $E_H$ (eV) | $E_L$ (eV) | I (eV) | A (eV) | χ (eV) | η (eV) | S ($eV^{-1}$) | μ (eV) | ω (eV) |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | BPV86 | | | | |
| *1a* | -5.09 | -1.94 | 5.09 | 1.94 | 3.51 | 1.57 | 0.31 | -3.51 | 3.93 |
| *1b* | -5.21 | -2.15 | 5.21 | 2.15 | 3.68 | 1.53 | 0.32 | -3.68 | 4.43 |
| *1c* | -5.21 | -2.17 | 5.21 | 2.17 | 3.69 | 1.51 | 0.32 | -3.69 | 4.48 |
| *1d* | -4.78 | -1.68 | 4.78 | 1.68 | 3.23 | 1.54 | 0.32 | -3.23 | 3.38 |
| *1e* | -4.91 | -1.96 | 4.91 | 1.96 | 3.44 | 1.47 | 0.33 | -3.44 | 4.01 |
| *1f* | -4.96 | -1.83 | 4.96 | 1.83 | 3.39 | 1.56 | 0.31 | -3.39 | 3.68 |
| *2a* | -5.14 | -2.32 | 5.14 | 2.32 | 3.73 | 1.40 | 0.35 | -3.73 | 4.95 |
| *2b* | -5.34 | -2.46 | 5.34 | 2.46 | 3.90 | 1.44 | 0.34 | -3.90 | 5.29 |
| *2c* | -5.33 | -2.46 | 5.33 | 2.46 | 3.90 | 1.43 | 0.34 | -3.93 | 5.31 |
| *2d* | -4.82 | -1.92 | 4.82 | 1.92 | 3.37 | 1.45 | 0.34 | -3.37 | 3.92 |
| *2e* | -5.00 | -2.22 | 5.00 | 2.22 | 3.61 | 1.38 | 0.35 | -3.61 | 4.70 |
| *2f* | -5.01 | -2.07 | 5.01 | 2.07 | 3.54 | 1.47 | 0.34 | -3.54 | 4.27 |
| | | | | | B3LYP | | | | |
| *1a* | -5.91 | -1.12 | 5.91 | 1.12 | 3.51 | 2.39 | 0.20 | -3.51 | 2.58 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| ***1b*** | -6.02 | -1.34 | 6.02 | 1.34 | 3.68 | 2.33 | 0.21 | -3.68 | 2.90 |
| ***1c*** | -6.00 | -1.35 | 6.00 | 1.35 | 3.67 | 2.32 | 0.21 | -3.67 | 2.91 |
| ***1d*** | -5.57 | -0.85 | 5.57 | 0.85 | 3.21 | 2.35 | 0.21 | -3.21 | 2.19 |
| ***1e*** | -5.66 | -1.16 | 5.66 | 1.16 | 3.41 | 2.25 | 0.22 | -3.41 | 2.59 |
| ***1f*** | -5.75 | -1.00 | 5.75 | 1.00 | 3.37 | 2.37 | 0.21 | -3.37 | 2.39 |
| ***2a*** | -6.04 | -1.40 | 6.04 | 1.40 | 3.72 | 2.32 | 0.21 | -3.72 | 2.98 |
| ***2b*** | -6.16 | -1.63 | 6.16 | 1.63 | 3.90 | 2.26 | 0.22 | -3.90 | 3.36 |
| ***2c*** | -6.14 | -1.64 | 6.14 | 1.64 | 3.89 | 2.25 | 0.22 | -3.89 | 3.36 |
| ***2d*** | -5.62 | -1.08 | 5.62 | 1.08 | 3.35 | 2.27 | 0.22 | -3.35 | 2.47 |
| ***2e*** | -5.76 | -1.40 | 5.76 | 1.40 | 3.58 | 2.18 | 0.22 | -3.58 | 2.95 |
| ***2f*** | -5.81 | -1.21 | 5.81 | 1.21 | 3.51 | 2.29 | 0.21 | -3.51 | 2.68 |
| **B3PW91** | | | | | | | | | |
| ***1a*** | -5.96 | -1.16 | 5.96 | 1.16 | 3.56 | 2.40 | 0.20 | -3.56 | 2.64 |
| ***1b*** | -6.07 | -1.40 | 6.07 | 1.40 | 3.73 | 2.33 | 0.21 | -3.73 | 2.99 |
| ***1c*** | -6.06 | -1.42 | 6.06 | 1.42 | 3.74 | 2.31 | 0.21 | -3.74 | 3.02 |
| ***1d*** | -5.62 | -0.90 | 5.62 | 0.90 | 3.26 | 2.35 | 0.21 | -3.26 | 2.26 |
| ***1e*** | -5.73 | -1.22 | 5.73 | 1.22 | 3.47 | 2.25 | 0.22 | -3.47 | 2.68 |
| ***1f*** | -5.80 | -1.05 | 5.80 | 1.05 | 3.43 | 2.37 | 0.21 | -3.43 | 2.47 |
| ***2a*** | -6.02 | -1.5 | 6.02 | 1.56 | 3.79 | 2.23 | 0.22 | -3.79 | 3.22 |
| ***2b*** | -6.21 | -1.71 | 6.21 | 1.71 | 3.96 | 2.25 | 0.22 | -3.96 | 3.48 |
| ***2c*** | -6.19 | -1.72 | 6.19 | 1.72 | 3.95 | 2.23 | 0.22 | -3.95 | 3.50 |
| ***2d*** | -5.68 | -1.15 | 5.68 | 1.15 | 3.41 | 2.26 | 0.22 | -3.41 | 2.57 |
| ***2e*** | -5.83 | -1.48 | 5.83 | 1.48 | 3.65 | 2.17 | 0.23 | -3.65 | 3.08 |
| ***2f*** | -5.87 | -1.29 | 5.87 | 1.29 | 3.58 | 2.28 | 0.21 | -3.58 | 2.80 |

The variation of ionization potential ($I$), electron affinity ($A$), global chemical softness ($S$) and electrophilicity index ($\omega$) values at different level for the structures are shown in Figure 1-8.

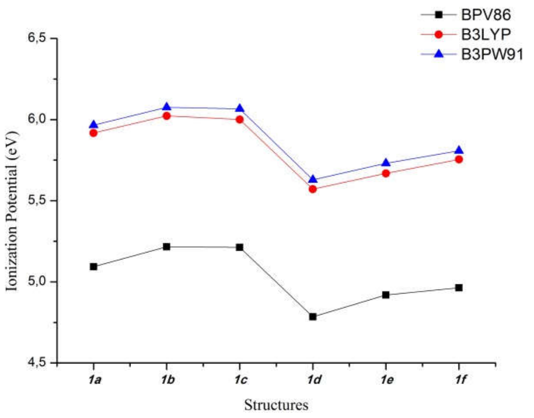

Figure 1. The variation of ionization potential for the compound **1**

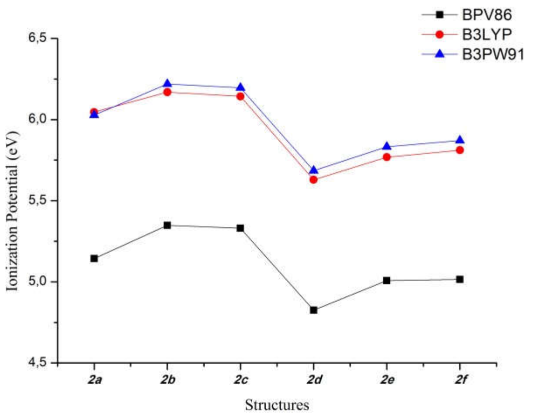

Figure 2. The variation of ionization potential for the compound **2**

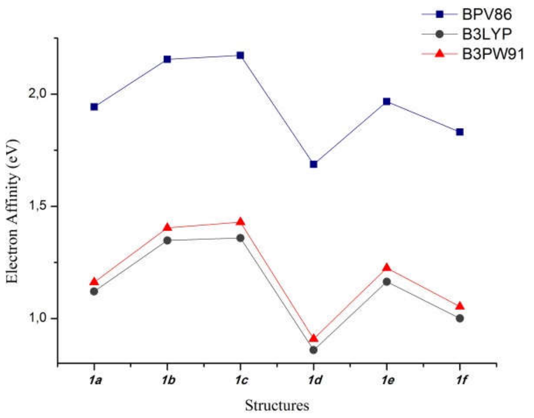

Figure 3. The variation of electron affinity for the compound **1**

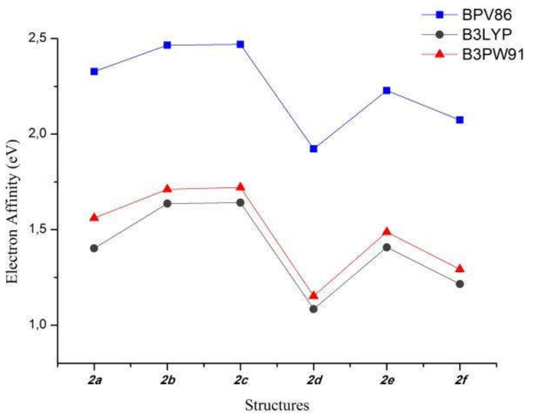

Figure 4. The variation of electron affinity for the compound **2**

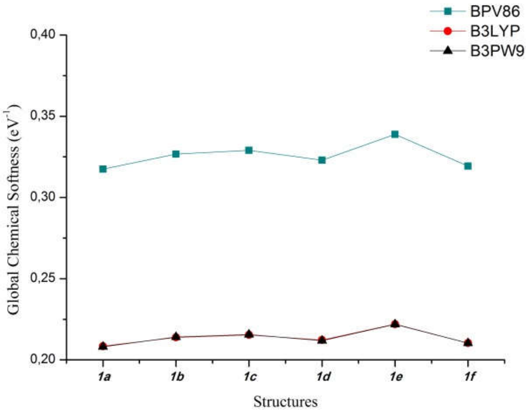

Figure 5. The variation of global chemical softness for the compound **1**

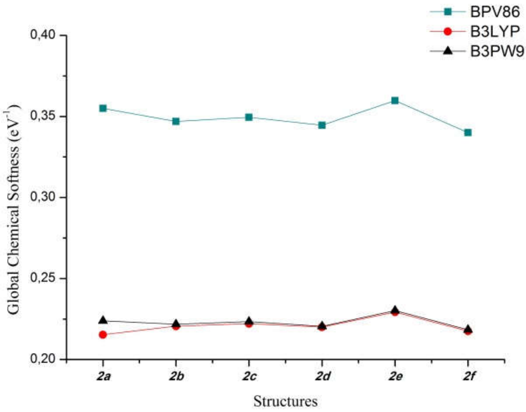

Figure 6. The variation of global chemical softness for the compound **2**

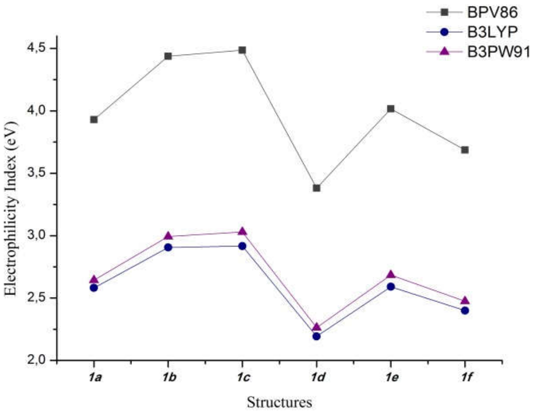

Figure 7. The variation of electrophilicity index for the compound **1**

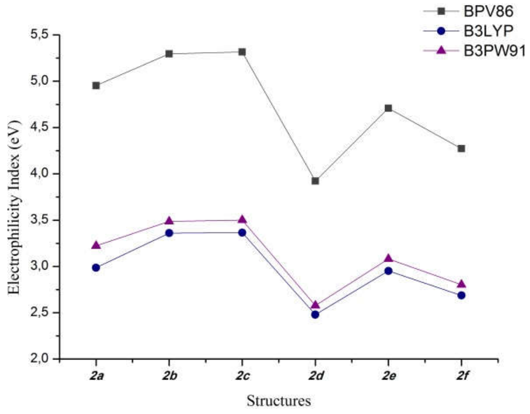

Figure 8. The variation of electrophilicity index for the compound **2**

## 3.2. Non-Linear Optical (NLO) Behaviour

On behalf of determining the NLO behaviours of the derivatives of compounds **1** and **2**, total electric dipole moment ($\mu_{tot}$), mean polarizability (<α>), total first-order hyperpolarizability ( $\beta_{tot}$) values were examined using the equations described with (6), (7), (8) at DFT/BPV86 B3LYP/B3PW91/6-31G(d, p) level.

The same parameters were examined for the urea molecule, which is considered as a threshold value in such analyses, to determine the possibility of being NLO materials of the obtained derivatives for the compounds **1** and **2**. The calculated <α>, $\beta_{tot}$, values for urea are, 4.0725x$10^{-24}$ esu, 579.46 x$10^{-33}$ esu for the BPV86 functional, 3.8734x$10^{-24}$ esu, 378.73 x$10^{-33}$ esu for the B3LYP functional, 3.8455x$10^{-24}$ esu, 383.51x$10^{-33}$esu for the B3PW91 functional. When a comparison is made to $\beta_{tot}$values, it can be said that especially the thiol-bonded groups have a higher possibility of being NLO material. Namely, $\beta_{tot}$ value is of the compound **1e**, 14.46 times, compound **2e**, 5.31 times for the BPV86, the compound **1e**, 18.03 times, compound **2e**, 6.39 times for the B3LYP, the compound **1e**, 17.33 times, compound **2e**, 6.61 times for the B3PW91 greater from the value of urea. The obtained results are tabulated in Table 2. In table, mean polarizability's unit was converted into esu (electrostatic unit), (1 a.u=0.1482×$10^{-24}$ esu) and first-order hyperpolarizability's unit was converted into esu, (1 a.u=8.6393×$10^{-33}$ esu) [39].

Table 2. The total dipole moment, mean polarizability and first-order hyperpolarizability values of the structures

| Structures | $\mu_{tot}$ (Debye) | $<\alpha>$ ($x10^{-24}$ esu) | $\beta_{tot}$ ($x10^{-33}$ esu) |
|---|---|---|---|
| **BPV86** | | | |
| ***1a*** | 3.1169 | 22.9014 | 1478.86 |
| ***1b*** | 3.1072 | 25.2135 | 721.93 |
| ***1c*** | 3.4026 | 26.5592 | 1101.86 |
| ***1d*** | 4.4131 | 23.9046 | 2670.14 |
| ***1e*** | 3.8795 | 26.9375 | 8381.64 |
| ***1f*** | 3.1638 | 30.7047 | 4164.08 |
| ***2a*** | 1.9502 | 37.1056 | 818.53 |
| ***2b*** | 2.1069 | 42.0626 | 1345.84 |
| ***2c*** | 2.0818 | 44.8897 | 1672.22 |
| ***2d*** | 0.2941 | 39.3484 | 1212.25 |
| ***2e*** | 0.9840 | 45.8642 | 3081.69 |
| ***2f*** | 1.5567 | 53.2837 | 207.24 |
| **B3LYP** | | | |
| ***1a*** | 3.2125 | 21.6641 | 884.37 |
| ***1b*** | 3.4698 | 23.8012 | 1006.99 |
| ***1c*** | 3.8182 | 25.0684 | 1285.78 |
| ***1d*** | 4.1198 | 22.5645 | 3063.83 |
| ***1e*** | 3.9902 | 25.3133 | 6831.49 |
| ***1f*** | 3.3436 | 29.0320 | 2231.58 |
| ***2a*** | 2.0290 | 34.7829 | 832.35 |
| ***2b*** | 2.1642 | 39.3022 | 1204.31 |
| ***2c*** | 2.1325 | 41.9448 | 1333.12 |
| ***2d*** | 0.3520 | 36.7529 | 1167.50 |
| ***2e*** | 1.0404 | 42.5736 | 2422.27 |
| ***2f*** | 1.7902 | 49.9637 | 492.51 |
| **B3PW91** | | | |
| ***1a*** | 3.2285 | 21.5051 | 878.85 |
| ***1b*** | 3.4801 | 23.7604 | 920.42 |
| ***1c*** | 3.4461 | 25.0298 | 1126.37 |
| ***1d*** | 4.5461 | 22.5209 | 2897.96 |
| ***1e*** | 4.1770 | 25.2955 | 6647.83 |
| ***1f*** | 3.3052 | 29.0074 | 2517.00 |
| ***2a*** | 2.0353 | 34.6991 | 924.64 |
| ***2b*** | 2.1741 | 39.2195 | 1193.24 |
| ***2c*** | 2.1506 | 41.8605 | 1350.64 |
| ***2d*** | 0.3112 | 36.6649 | 1477.00 |
| ***2e*** | 1.0138 | 42.5424 | 2538.06 |
| ***2f*** | 1.5845 | 49.9040 | 284.77 |

### 3.3. Lipinski's Rule of 5 and Bioactivity Scores

Lipinski's rule of 5, which is considered as a starting point in the design optimization process of small molecules having the potential to be drug-active compound, was studied for all structures. And, these rules are as follows [31,32];

- Molecular mass less than 500 Dalton,
- Less than 5 hydrogen bond donors,
- Less than 10 hydrogen bond acceptors,
- High lipophilicity (expressed as LogP) less than 5,
- Molar refractivity should be between 40-130.

The results obtained for all structures are given in Table 3.

Table 3. The analysis "Lipinski's rule of 5" for the structures

| Structures | MW | HBD | HBA | LogP | MR |
|---|---|---|---|---|---|
| ***1a*** | 229 | 0 | 2 | 2.75 | 62.03 |
| ***1b*** | 225 | 0 | 2 | 2.92 | 66.81 |
| ***1c*** | 291 | 0 | 2 | 2.22 | 63.41 |
| ***1d*** | 227 | 1 | 3 | 2.31 | 63.74 |
| ***1e*** | 243 | 0 | 2 | 2.90 | 69.33 |
| ***1f*** | 267 | 0 | 2 | 3.90 | 80.77 |
| ***2a*** | 366 | 0 | 4 | 3.75 | 94.19 |
| ***2b*** | 358 | 0 | 4 | 4.09 | 103.75 |

| | | | | | |
|---|---|---|---|---|---|
| *2c* | 490 | 0 | 4 | 2.70 | 96.96 |
| *2d* | 362 | 2 | 6 | 2.88 | 97.61 |
| *2e* | 394 | 0 | 4 | 4.05 | 108.78 |
| *2f* | 442 | 0 | 4 | 6.06 | 131.68 |

**MW:** Molecular mass, **HBD:** Hydrogen bond donors, **HBA:** Hydrogen bond acceptors, **LogP:** Lipophilicity coefficient, **MR** :Molar refractivity.

According to these results; except for the fact that the *tert*-butyl derivative of the compound **2** (2f) has a slightly higher of the lipophilicity coefficient and the molar refractivity values, all the other structures are within the foreseen limits.

The activity scores of the GPCR ligand, ion channel modulator, nuclear receptor legend, kinase inhibitor, protease inhibitor, enzyme inhibitor were examined for all the structures.

The bioactivity scores of derivatives of the compound **1** and **2** were computed through Molinspiration software [33-35] accessed online and results are shown in Table 4.

Table 4. Bioactivity scores of the compound **1** and **2**

| | GPCR | ICM | KI | NRL | PI | EI |
|---|---|---|---|---|---|---|
| *1a* | -0.34 | -0.70 | -1.40 | -0.41 | -0.81 | -0.41 |
| *1b* | -0.36 | -0.69 | -1.47 | -0.47 | -0.83 | -0.44 |
| *1c* | -0.50 | -0.79 | -1.51 | -0.61 | -0.94 | -0.49 |
| *1d* | -0.11 | -0.49 | -1.08 | -0.08 | -0.50 | -0.26 |
| *1e* | -0.37 | -0.21 | -1.41 | -0.44 | -0.84 | -0.04 |
| *1f* | -0.42 | -0.89 | -1.63 | -0.64 | -0.67 | -0.33 |
| *2a* | -0.02 | -0.39 | -0.40 | -0.07 | -0.13 | -0.17 |
| *2b* | -0.03 | -0.39 | -0.45 | -0.11 | -0.15 | -0.19 |
| *2c* | -0.12 | -0.45 | -0.47 | -0.20 | -0.21 | -0.23 |
| *2d* | 0.01 | -0.27 | -0.35 | 0.01 | -0.09 | -0.12 |
| *2e* | 0.01 | -0.34 | -0.39 | 0.04 | -0.10 | -0.11 |
| *2f* | -0.07 | -0.51 | -0.54 | -0.22 | -0.04 | -0.12 |
| *Acivicin* | -0.03 | -0.03 | -1.17 | -0.77 | -0.30 | -0.04 |

**GPCR**:GPCR ligand, **ICM**:ion channel modulator, **KI** :kinase inhibitör, **NRL:** nuclear receptor legend, **PI:** protease inhibitor, **EI**:enzyme inhibitör.

For organic molecules, if these bioactivity scores are >0, they are active, (-5.0-0.0) are moderately active, and <-5.0 are interpreted as inactive [40].

When the values of these parameters especially which are effective in cholesterol, heart, vascular diseases and cancer-derived diseases, were examined, it can be said that the derivatives of the compound **1** and **2** are moderately active. These parameters were also examined for the Acivicin molecule, which is used as an antitumor antibiotic and contains the isoxazole group, just like the compound **1** and **2** examined. According to the results obtained for bioinformatics purposes, hydroxyl- and thiol-bonded for compound **1**, hydroxyl-bonded groups for compound **2**, appear to be more likely drug-precursor compounds.

## 4. CONCLUSION

In this paper, the global reactivity properties of fluorine, chlorine, bromine, hydroxyl, thiol, *tert*-butyl-bonded derivatives of compounds having the norbornadiene skeleton were examined by the DFT/BPV86/B3LYP/B3PW91 methods with 6-31G(d,p) basis set. Chemical reactivity parameters such as ionization potential ($I$), electron affinity ($A$), electronegativity ($\chi$), chemical hardness ($\eta$), chemical softness ($S$), chemical potential ($\mu$) and electrophilicity index ($\omega$) values were examined for all the structures. This analysis shows that the structures **1d** and **2d** have lower value of $I$, structures **1c** and **2b**, **2c** have higher value of $A$, more electronegativity of structures **1b**, **c** and **2b**, **c** structures, **1e**, **2e** have more soft molecule structure, structure **1b**, **c** and **2b**, **c** have more electrophilic character than the others. As can be seen in Figure 1-8, the B3LYP and B3PW91 functionals have given more similar results with respect to BPV86 functional. The parameters required to determine the non-linear optical behaviours of the structures were calculated at the theoretical level indicated. It has been observed that compounds **1e** and **2e**, i.e., thiol-bonded groups, have the potential to be a higher NLO material than others for every three functionals. In addition, the potentials of all the structures to be a drug-active compound was evaluated with the Lipinski's rule of 5 and some bioactivity scores. It can be said that the compounds have drug-likeness properties that they provide the five rules of Lipinski and exhibit moderate bioactive properties. As it is well known, molecular structures exhibiting high NLO behaviour, have electron motions between donor-acceptor groups through the π-conjugated system. Aromatic-thiol-bonded structures with electron donor character having high first-order hyperpolarizability value and the smaller HOMO-LUMO gap ($\Delta E$=4.50 eV for 1e, $\Delta E$=4.36 eV for 2e) than others, with possible intramolecular charge transfer effect also given remarkable results in bioactivity scores values.

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