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Quantum Chemical Studies on Some Thiosemicarbazone Derivatives as Ribonucleotide Reductase Inhibitor

Mustafa Lawar[1,2*], Safia Badwe[3,4], Ismail Yalçin[5], Kayhan Bolelli[5], Hakan Sezgin Sayiner[6] and Fatma Kandemirli[7]

[1]Higher Instiute of Medical Proffessionals, Absalim, Tripoli, Libya.
[2]Department of Genetic and Bioengineering, Kastamonu University, Kastamonu, Turkey.
[3]Department of Statistics, Faculty of Science, Tripoli University, Tripoli, Libya.
[4]Modes and Design Engineering System Department, School of Natural and Applied Science, Atilim University, Ankara, Turkey.
[5]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Ankara University, Ankara, Turkey.
[6]Department of Infectious Diseases, Faculty of Medicine, Adiyaman University, Adiyaman, Turkey.
[7]Department of Biomedical Engineering, Faculty of Engineering and Architecture, Kastamonu University, Kastamonu, Turkey.

Authors' contributions

"This work was carried out in collaboration between all authors. Authors ML, HSS and FK designed the study, wrote the protocol and wrote the first draft of the manuscript. Author SB performed the statistical analysis. Authors IY and KB managed the analyses of the study. Authors FK and ML managed the literature searches. All authors read and approved the final manuscript.

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**Corresponding author: E-mail: alawermustafa@gmail.com;*

ABSTRACT

QSAR analysis of thiosemicarbazone derivatives exposing RNR inhibitory activities [1] was performed for 21 compounds. Among these compounds, 13 of them were reported with inhibitory concentration (IC_{50}) in the I M range. The inhibitory concentration of those compounds was converted into -logIC_{50} before being correlated with the structural features.
The quantum chemical calculations have been carried out at the B3LYP at Complete Basis set (CBS) level of theory using Gaussian-09 series of program package. The density functional theory (DFT), Becke's three parameter exchange function along with the Lee–Yang–Parr correlation function (B3LYP) were considered to calculate the quantum chemical descriptors such as HOMO, LUMO, Energy gap, Hardness, Softness, Chemical potential and Dipole moment of the investigated molecules. The variables make a unique statistically significant contribution ($p < 0.05$). According to their beta values, electronegativity showed the biggest beta coefficient (–13.225). It has been revealed that variable has a unique contribution to a stronger explanation of dependent variables. Beta values for the electrofugality was slightly lower (8.350) , showing least contribution for rest of the elements. Other variables (Energy gap, chemical potential, nucleofugality) measured for this model was statistically significant.

Keywords: Ribonucleotide reductase (RNR); thiosemicarbazones derivatives; RNR inhibitory activities; methoxy group (OCH_3).

1. INTRODUCTION

Thiosemicarbazones can be obtained by the condensation of an aldehyde, or ketones with thiosemicarbazide. The compounds are considerably important because of their chemical properties as well as potentially beneficial for biological activities [2-4]. According to the International Union of Pure and Applied Chemistry (IUPAC) nomenclature [5], these compounds, named so by adding the class name "thiosemicarbazone" after the name of the condensed aldehyde or ketone. In the same way, bis (thiosemicarbazones) are derived from dicarbonyl compounds and two thiosemicarbazide moieties.

Thiosemicarbazones are efficient on specific biological mechanisms because of their chelating ability towards trace metal ions. After the chemotherapeutic effective platin complexes of thiosemicarbazide derivatives were synthesized [6], these chemicals have raised considerable interest due to their pharmacological properties. In addition to the antitumor effect of transition metal complexes of thiosemicarbazones [7-9], it is well known that the compounds have antiviral as well asanti-HIV properties [8,10-13]. Numerous thiosemicarbazones, especially their Cu (II) [14] complexes, have been studied substantially for their antibacterial and antifungal properties [15-17]. Furthermore, it is worthwhile to mentioned that the thiosemicarbazones have anticonvulsant [18], *anti-malarial* [13], antiamoebic [19,20] and antioxidant properties [21] with other biological activities.

Ribonucleotide reductase, also known as ribonucleoside diphosphate reductase (RNR, E.C. 1.17.4.1), catalysis the reduction of ribonucleotides to their corresponding deoxyribonucleotides, which are the building blocks for DNA in almost all the living cells [20]. Furthermore, RNR plays a significant role in regulating the total rate of DNA synthesis, so that DNA to cell mass could be maintained at a constant ratio during cell division and DNA repairing [22]. Ribonucleotide reductase (RNR) catalysis the de-novo synthesis of dNTPs. Catalysis of ribonucleoside 5'-diphosphates (NDPs) involves a reduction at the 2'- carbon of ribose 5-phosphate to form the 2'-deoxy derivative-reduced 2'-deoxyribonucleoside 5'-diphosphates (dNDPs). This reduction is initiated with the generation of a free radical. Following a single reduction, RNR requires electrons donated from the dithiol groups of the protein thioredoxin. Regeneration of thioredoxin occured when nicotinamide adenine dinucleotide phosphate (NADPH) provides two hydrogen atoms that are used to reduce the disulfide groups of thioredoxin.

Ribonucleotide reductases have been grouped into three classes based on their primary radical. Class I ribonucleotide reductase, reported in eukaryotes, prokaryotes, and viruses is a 1:1 protein complex. Class II ribonucleotide reductase exists mainly in bacteria, contains a

transient 5′-deoxyadenosyl radical. Class III ribonucleotide reductase harbors a stable glycyl radical in anaerobic bacteria [9]. In this study, QSAR analysis on thiosemicarbazone derivatives was carried out to reveal RNR inhibitory activities.

A series of thiosemicarbazone derivatives was considered to perform the QSAR. Among 21 compounds, 13 compounds were reported with inhibitory concentration (IC_{50}) in the l M range. The inhibitory concentration of those compounds were converted into -logIC_{50} before being correlated with the structural features.

Quantitative structure-activity relationship (QSAR) is a method for building statistically ... relationships between the molecular structure and biological activities [23-27]. The objective of QSAR is to explore new molecules with required properties by using chemical intuition and changed into a mathematically quantified and computerized form. Formerly, a correlation is recognized and the structure of any number of compounds with preferred properties can be predicted. Therefore, QSAR methodology saves resources and accelerates the process of development of new molecules and drugs [28]. Success of QSAR for development of new drug molecules and prediction of toxicity of molecules is highly significant [23-27]. Quantum chemical descriptors have been extensively used in QSAR studies in biochemistry. Recently the use of quantum chemical descriptors for the development of QSAR, have received attention due to reliability and versatility of prediction by these descriptors. In particular, net atomic charges, HOMO–LUMO energies, frontier orbital electron densities and superdelocalizabilities have been used to correlate with various biological activities [27].

2. METHODOLOGY

These calculations have been carried out at the B3LYP CBS level of theory by using Gaussian-09 series of program package [29]. The calculations were based on 6-311G (d,p) basis set. The method has been widely implemented to study the relationship between inhibitory activation efficiency of the molecules and their electronic properties [30]. In order to set up correlation between experimental activity, structural and electronic characteristics of the investigated inhibitors, geometry of the molecules were optimized by the density functional theory (DFT) [31], the Becke's three parameter exchange function [32] along with the Lee Yang Parr correlation function (B3LYP) [33]. To examine the relationships between quantum chemical parameters obtained with the DFT calculations for thiosemicarbazone derivatives and the enzymatic activity, SPSS statistical software has been used.

3. RESULTS AND DISCUSSION

The studied molecules and their activity has been given in Table 1 [33,34], andclassified into seven groups for further comparisons and discussion. These groups were:

Group 1 was red colored, include inactive molecules (1,2,5-10).

Group 2 was black coloured, contain one molecule (3) without any functional group.

Group 3 was green coloured, include molecules (4,11,12) which contains Cl atom in positions 2,3 and 4.

Group 4 was violet coloured, include molecules (13-15) which contain methyl group.

Group 5 was dark green, include molecule (16) which contain methoxy group.

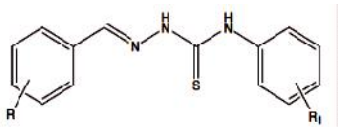
Group 6 was brown coloured, include molecules (17, 18) which contain nitro group.

Group 7 was blue coloured, include molecules (19,20,21) which contains hydroxyl group.

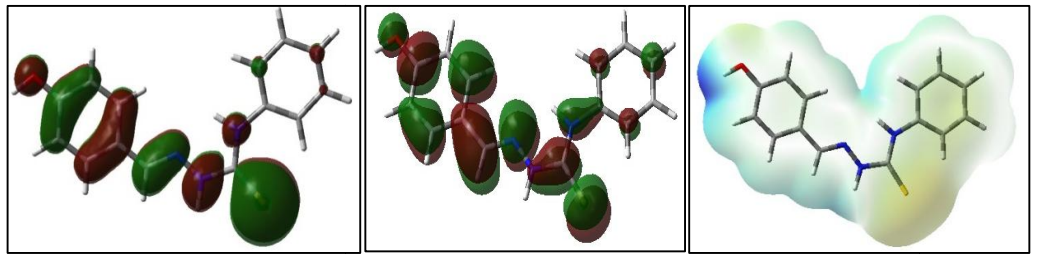
The degree of activity of the molecules could be differentiated through groups; each group have its own activity; related to its composition; for example, when R is hydroxy group (OH) in the position 4, the molecules were active as in the molecules (3, 4, 11-21), but when the hydroxy group was in position 2, the molecules were inactive as in the compounds (1 and 2). Additionally, the presence of other group like methoxy group (OCH_3), or hydroxyl group (OH) in the position 4 as in the molecules (5 and 6), that were inactive, a similar kind of positional activity for molecule (7 and 8) and (9 and 10), contains furyl and thiophenyl respectively, the R1 group type and its position indicates the amount of activity.

Tables 2 and 3 delineates the calculated parameters of the 21 thiosemicarazone derivative molecules using B3LYP/6-311g (d,p) method.

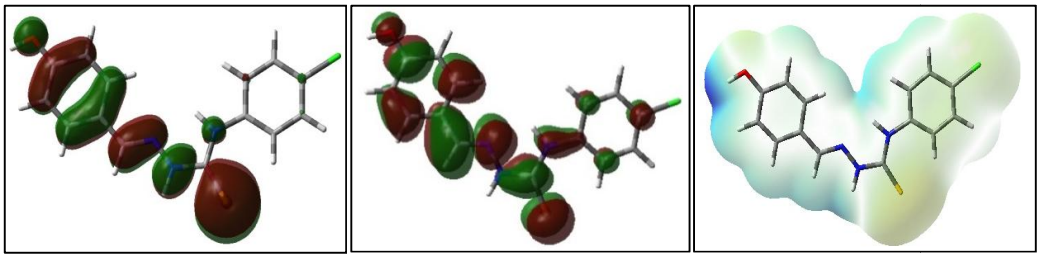
Table 1. Studied molecules with their activity

Mol. No	Molecule	R	R-1	Activity
1		2-OH	H	NA
2		2-OH	4-Cl	NA
3		4-OH	H	3.616
4		4-OH	4-Cl	3.542
5		3-OCH3-4-OH	H	NA
6		3-OCH3-4-OH	4-Cl	NA
7		2-Furyl	H	NA
8		2-Furyl	4-Cl	NA
9		2-Thiophenyl	H	NA
10		2-Thiophenyl	4-Cl	NA
11		4-OH	2-Cl	4.330
12		4-OH	3-Cl	4.533
13		4-OH	2-CH3	4.438
14		4-OH	3-CH3	4.517
15		4-OH	4-CH3	4.848
16		4-OH	2-OCH3	4.381
17		4-OH	2-NO2	4.406
18		4-OH	4-NO2	4.346
19		4-OH	2-OH	4.533
20		4-OH	3-OH	4.544
21		4-OH	4-OH	4.364

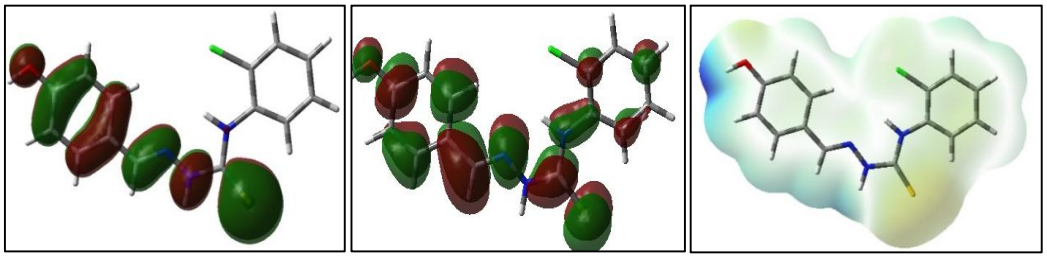
HOMO and LUMO orbitals of 21 molecules were obtained from the quantum chemical calculation by the DFT by using B3LYP/6-311G (d,p), depicted in Fig. 1 [29,35]. It is known that HOMO is often associated with the ability of a molecule for electron donating capacity, although high value of HOMO is likely to indicate the tendency of the molecule to donate electrons to appropriate acceptor molecules with lower energy LUMO [1,8,36].



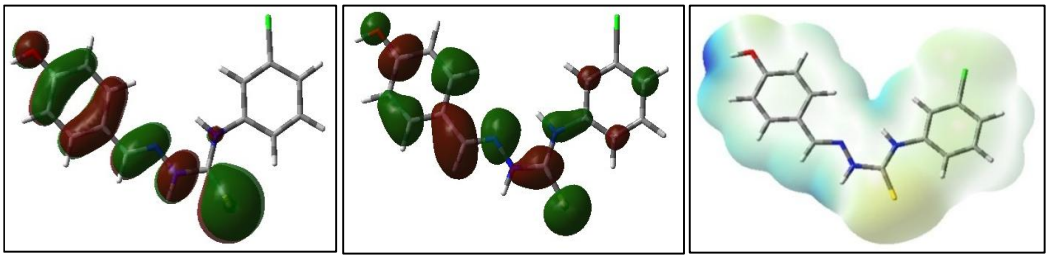
Molecule 3-HO **Molecule 3-LUMO** **Molecule 3-ESP**



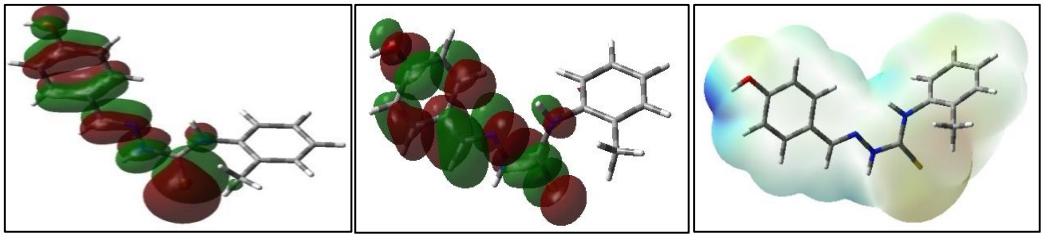
Molecule 4-HOMO **Molecule 4-LUMO** **Molecule 4-ESP**



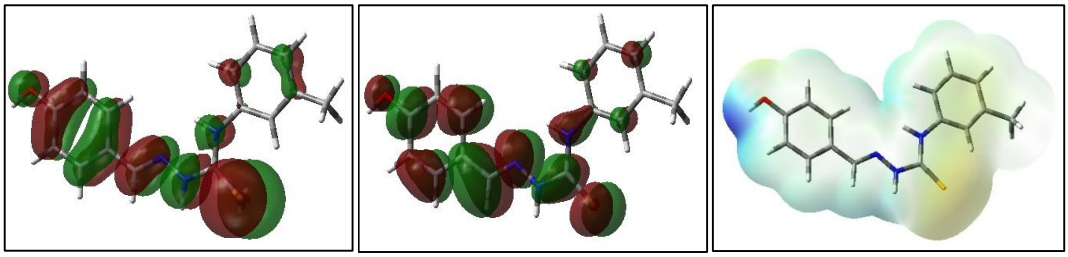
Molecule 11-HOMO | Molecule 11-LUMO | Molecule 11-ESP



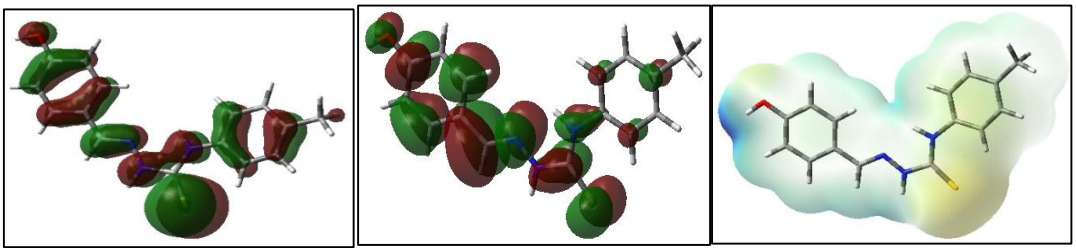
Molecule 12-HOMO | Molecule 12-LUMO | Molecule 12-ESP



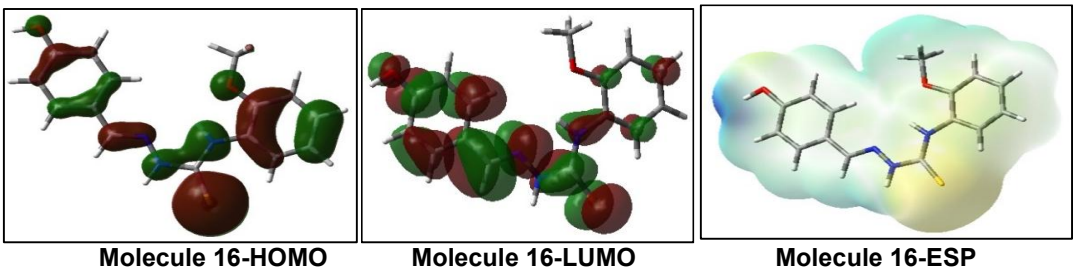
Molecule 13-HOMO | Molecule 13-LUMO | Molecule 13-ESP



Molecule 14-HOMO | Molecule 14-LUMO | Molecule 14-ESP



Molecule 15-HOMO | Molecule 15-LUMO | Molecule 15-ESP



Molecule 16-HOMO | Molecule 16-LUMO | Molecule 16-ESP

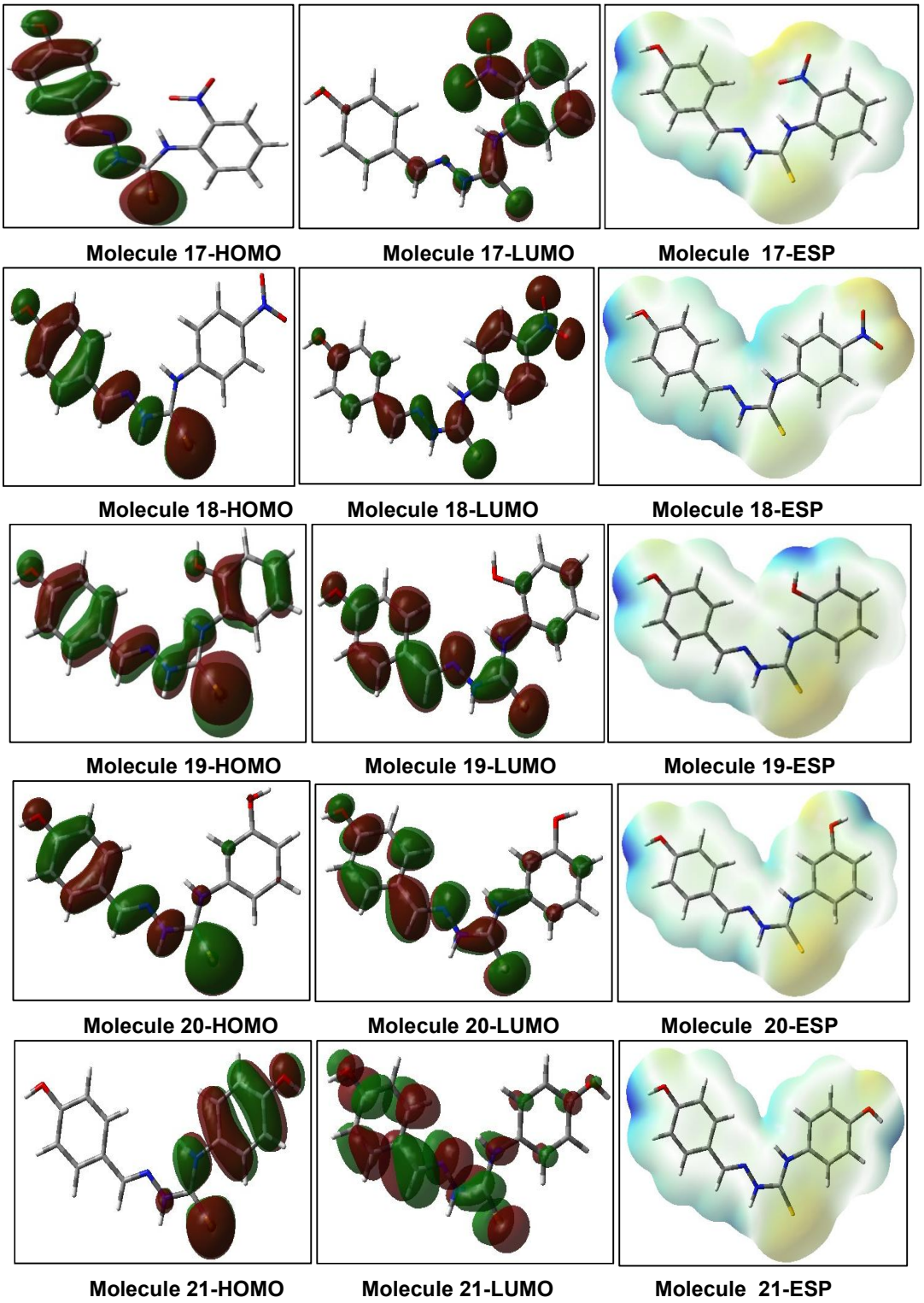


Fig. 1. HOMO, LUMO & ESP of the active molecules

Table 2. The calculated parameters by B3LYP/6-311G (d,p): HOMO, LUMO, energy gap, hardness, softness, chemical potential, electrophilicity index (ω) & electronegativity

Mole. no.	HOMO (eV)	LUMO (eV)	Energy gap (eV)	Hardness	Softness	Electronegativity	Chemical potential (J)	Electrophilicity index (eV)
1	-5.93485	-2.15026	3.784589	0.817164	0.408582	8.085111	-8.08511	26.70861
2	-7.06658	-2.25258	4.814004	1.280714	0.640357	9.319157	-9.31916	55.61288
3	-5.89675	-2.01502	3.881735	0.933358	0.466679	7.911773	-7.91177	29.2123
4	-6.01349	-2.12142	3.892075	0.885329	0.442665	8.134908	-8.13491	29.2941
5	-6.80018	-1.96903	4.831147	1.431058	0.715529	8.76921	-8.76921	55.0235
6	-5.89539	-2.07461	3.820781	0.873084	0.436542	7.970006	-7.97001	27.72959
7	-5.98791	-2.17257	3.815338	0.821382	0.410691	8.160487	-8.16049	27.34937
8	-6.1539	-2.27271	3.881191	0.804239	0.402119	8.426616	-8.42662	28.55364
9	-5.95009	-2.16278	3.78731	0.812266	0.406133	8.112866	-8.11287	26.73111
10	-6.2018	-2.25666	3.945138	0.84424	0.42212	8.458454	-8.45845	30.20076
11	-5.93975	-2.0308	3.908946	0.939072	0.469536	7.97055	-7.97055	29.82947
12	-6.30302	-2.25992	4.0431	0.891588	0.445794	8.562946	-8.56295	32.68742
13	-5.77621	-1.91189	3.864319	0.976216	0.488108	7.688093	-7.68809	28.8505
14	-5.91825	-2.13965	3.778603	0.819477	0.409739	8.057899	-8.0579	26.60422
15	-5.87961	-2.12468	3.754929	0.815123	0.407562	8.004292	-8.00429	26.11195
16	-5.76587	-1.90644	3.859421	0.976488	0.488244	7.672311	-7.67231	28.74017
17	-5.9841	-3.01532	2.968786	-0.02327	-0.01163	8.99942	-8.99942	-0.94215
18	-6.29241	-2.74184	3.55057	0.404364	0.202182	9.034251	-9.03425	16.50164
19	-5.79825	-1.90944	3.88881	0.989686	0.494843	7.707686	-7.70769	29.39784
20	-5.90682	-2.14672	3.760099	0.806688	0.403344	8.053545	-8.05355	26.16072
21	-5.76641	-2.1255	3.640912	0.757707	0.378854	7.891908	-7.89191	23.59584

The E_{HOMO} among the 13 active molecules were -5.76587 eV, -5.76641 eV ,-5.77621 eV, -5.79825 eV, -5.87961 eV, -5.89675 eV, -5.90682 eV, -5.91825 eV, -5.93975 eV, -5.9841 eV, -6.01349 eV, -6.29241 eV and -6.30302 eV. These results were observed in the molecules 16, 19, 13, 3, 11, 4, 15, 21, 14, 20, 12, 18 and 17 respectively. The E_{LUMO} of these molecules were -1.90644 eV, -1.90944 eV, -1.91189 eV, -2.01502 eV, -2.0308 eV, -2.12142 eV, -2.12468 eV, -2.1255 eV, -2.13965 eV, -2.14672 eV, -2.25992 eV, -2.74184 eV and -3.01532 eV for the molecules 16, 19, 13, 3, 11, 4, 15, 21, 14, 20, 12, 18 and 17 respectively. The energy gap among the 13 active molecules results were 2.968786 eV, 3.55057 eV, 3.640912 eV, 3.754929 eV, 3.760099 eV, 3.778603 eV, 3.859421 eV, 3.864319 eV, 3.881735 eV, 3.88881 eV, 3.892075 eV, 3.908946 eV and 4.0431 eV for the molecules 17, 18, 21, 15, 20, 14, 16, 13, 3, 19, 4, 11 and 12 respectively. It is worthwhile to mention from the results of energy gap calculated by B3LYP/6-311G (d,p) method and the interpretation of Figs. (1, 2-a, 2-b and 3), that the molecules with smaller E_{HOMO}-E_{LUMO} energy gap lead to lower kinetic stability and higher chemical reactivity [1]. Therefore, molecules with the highest reactivity, also have most inhibitory activities for molecule 17.

Nucleofugality is defined as the propensity of an atom or group of them to depart bearing the bonding electron pair in a heterolytic cleavage process [8,37,38], the highest nucleofugality of 21 molecules as demonstrated in Table 3 was: 87.90 eV, 81.65 eV, 80.99 eV, 78.36 eV, 73.68 eV, 71.85 eV, 71.27 eV, 66.87 eV, 66.52 eV, 66.09 eV, 65.64 eV, 65.20 eV, 65.12 eV, 64.34 eV, 63.94 eV, 63.85 eV, 63.00 eV, 62.5 eV, 59.89 eV, 59.57 eV and 59.33 eV these results were for the molecules: 2, 18, 17, 5, 12, 10, 8, 7, 4, 9, 1, 14, 20, 15, 11, 6, 3, 21, 19, 13 and 16 respectively. According to these results, the molecules that have more inhibitory activity of the RNR enzyme of the above-mentioned group of molecules were as stated above. Statistical analyses for studied molecules showed that Nucleofugality has a significant correlation with the activity.

3.1 Statistical Analysis

To find out the amount of total variance spelled out by the variables of interest (HOMO, LUMO, Energy gap, hardness, softness, electronegativity, chemical potential, electrophilicity, nucleofugality, electrofugality), R-square values should be considered. The output has been displayed in Table 4 in the summary

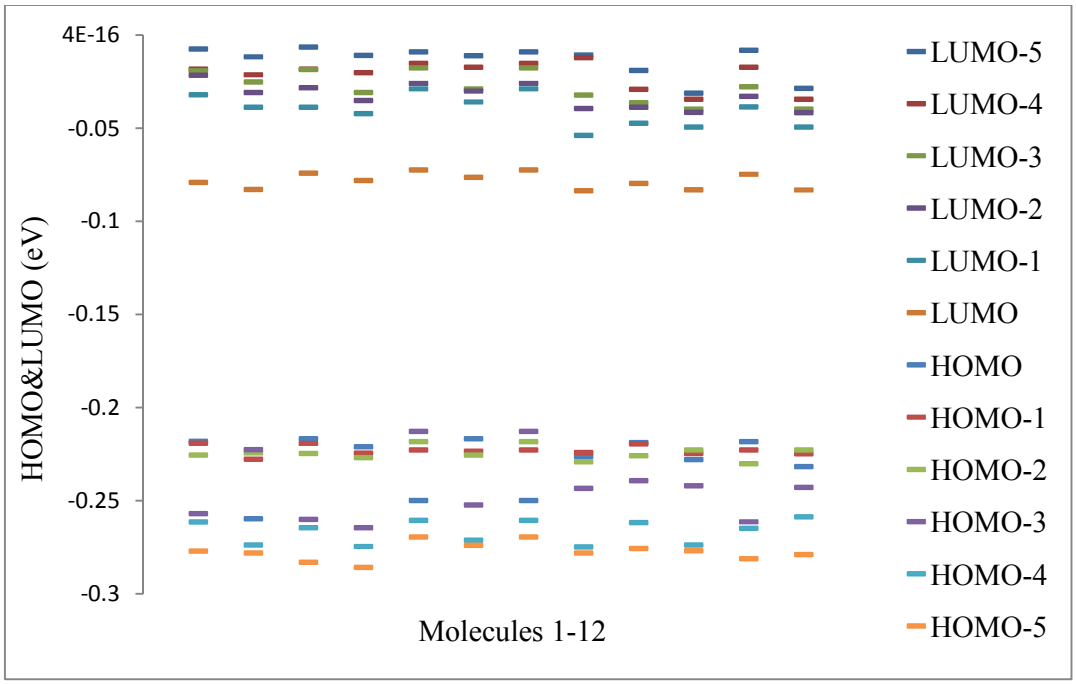


Fig. 2-a. HOMO & LUMO molecules 1-12 at B3LYP/6-311G(d,p)

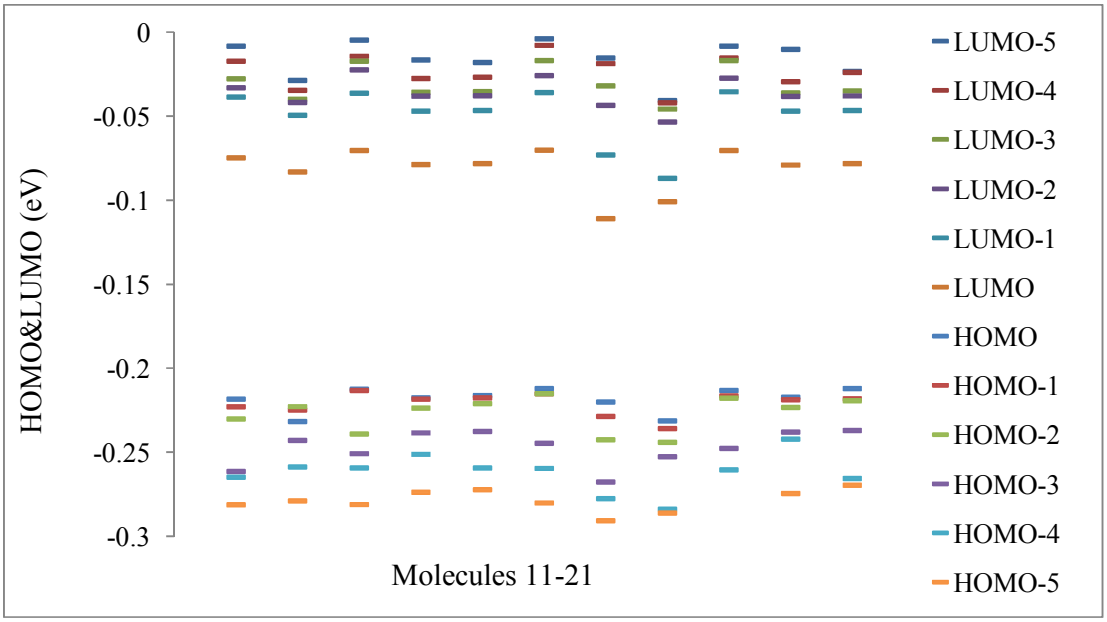


Fig. 2-b. HOMO & LUMO of molecules 11-21 at B3LYP/6-311G (d,p)

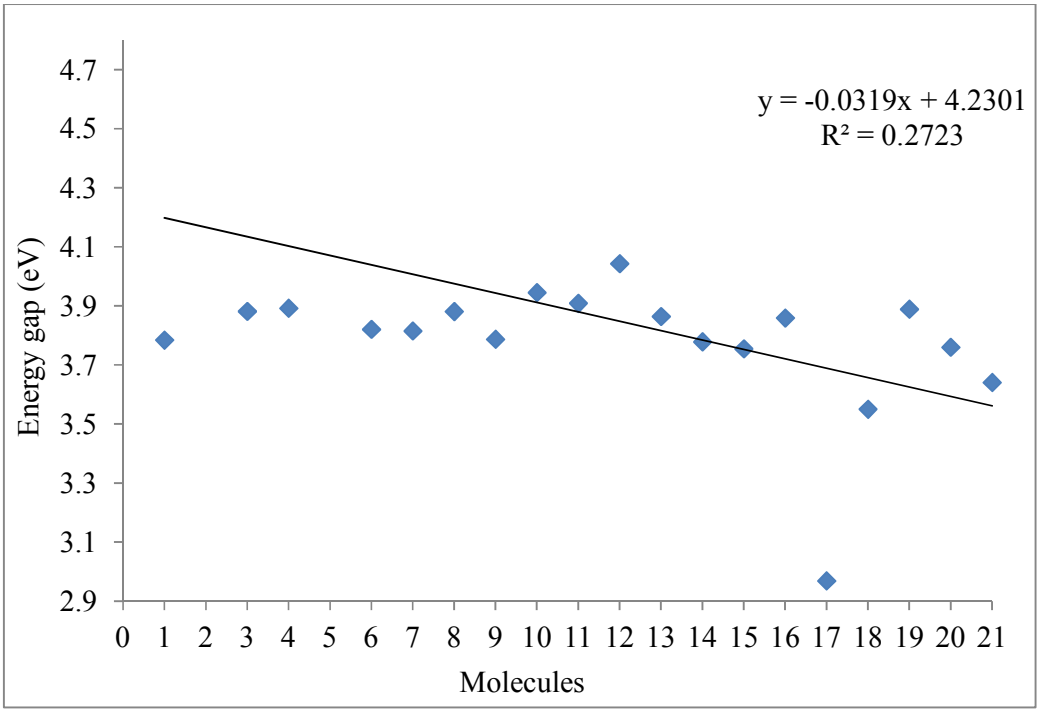


Fig. 3. The energy gap relation to the molecules

model; the R^2 value is 0.386. This is a statistically significant contribution. In other words, all of the above factors seem to represent 0.39% variance of observed activity, even when their effect on activity is statistically controlled.

Table 3. The calculated parameters by B3LYP/6-311G(d,p): Sum of electronic and zero-point energies, sum of electronic and thermal energies, sum of electronic and thermal enthalpies, sum of electronic and thermal free energies, Polarisability, Nucleofugality, Electrofugality & Activity

Mole no.	Sum of electronic and zero-point energies	Sum of electronic and thermal energies	Sum of electronic and thermal enthalpies	Sum of electronic and thermal free energies	Polarisability	Nucleofugality	Electrofugality	Activity
1	-1179	-1179	-1179	-1179	261	65.64185	65.09618	NA
2	-1638.6	-1638.6	-1638.6	-1638.7	280	87.89701	85.79635	NA
3	-1179	-1179	-1179	-1179	264	63.0027	62.1896	3.616
4	-1638.6	-1638.6	-1638.6	-1638.7	283	66.52369	65.82976	3.542
5	-1293.5	-1293.5	-1293.5	-1293.6	285	78.3644	75.4337	NA
6	-1753.2	-1753.1	-1753.1	-1753.2	304	63.85375	63.18822	NA
7	-1293.5	-1293.5	-1293.5	-1293.6	313	66.87062	66.31646	NA
8	-1792.2	-1792.2	-1792.2	-1792.3	332	71.26795	70.74777	NA
9	-1733	-1733	-1733	-1733	362	66.08656	65.55064	NA
10	-2192.6	-2192.6	-2192.6	-2192.7	381	71.8463	71.24458	NA
11	-1638.6	-1638.6	-1638.6	-1638.7	276	63.94373	63.1156	4.33
12	-2192.6	-2192.6	-2192.6	-2192.7	378	73.67842	72.96967	4.533
13	-1218.3	-1218.3	-1218.3	-1218.3	269	59.57195	58.64161	4.438
14	-1772.3	-1772.3	-1772.3	-1772.4	376	65.20489	64.65458	4.517
15	-1772.3	-1772.3	-1772.3	-1772.4	379	64.33949	63.7979	4.848
16	-1293.5	-1293.5	-1293.5	-1293.6	281	59.32991	58.3988	4.381
17	-1383.6	-1383.5	-1383.5	-1383.6	287	80.98956	80.98957	4.406
18	-1937.6	-1937.5	-1937.5	-1937.6	392	81.65075	81.58464	4.346
19	-1254.2	-1254.2	-1254.2	-1254.3	268	59.89311	58.92373	4.533
20	-1808.2	-1808.2	-1808.2	-1808.3	368	65.12206	64.59712	4.544
21	-1808.2	-1808.2	-1808.2	-1808.3	370	62.49972	62.06471	4.364

Table 4. The model summary[b]

Model	R	R square	Adjusted R square	Std. error of the estimate	Change statistics				
					R square change	F change	df1	df2	Sig. F change
1	.621[a]	.386	.181	1.97020	.386	1.884	5	15	.157

a. Predictors: (Constant), electrofugality, electrophilicity, Energy gap, nucleofugality, chemical potential

b. Dependent Variable: Activity

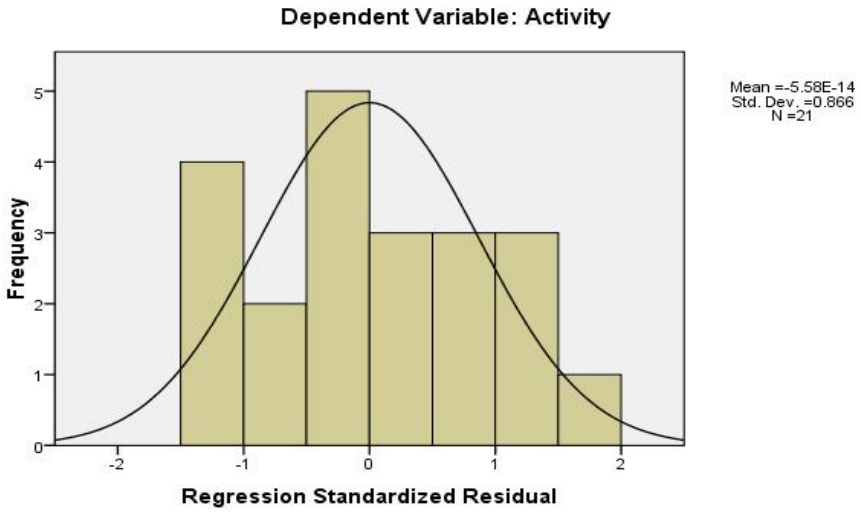


Fig. 4. The normal distribution of the variables

The results of ANOVA revealed that the model as a whole (contains both blocks of variables) is significantly correlated [F (5, 15) =1,884, p < 0.0005]. The coefficient table represents the results of all variables introduced in the equation with the objective of highlighting the statistical significance indicates where dependent variables is inconsequential.

The beta values revealed a unique contribution of some variables included in the equation, some of the other variables were eliminated merely because those variables had no statistically significant effect on activity. In different equations, with a diverse set of independent variables or with a different sample, these values would change subsequently. Therefore, the use of beta values by observing the beta column to find the highest beta value (excluding any negative signs) was conducted. There are variables which make a statistical contribution of unique significance (<0.05). In order of importance, the most significant beta coefficient was reported for electronegativity (beta= -13.225) in reference to the beta values of other factors. This means that the electronegativity variable has a unique contribution as it indicates a stronger explanation of dependent variables. The beta values for electrofugalitywas slightly lower (8.350). The least contribution was indicated to the rest of the elements**.** In addition, other variables measured (Energy gap, chemical potential, nucleofugality) in the model were statistically significant.

The prediction of a variable can be reported by its significant contribution when the value is less than 0.05. The results were more than 0.05 as delineated in the significance column of the coefficient table, suggesting that the interpretation of the prediction could be difficult.

The equation from the Coefficients table is:

$yi= \beta_0+ \beta_1 x_{i1} + \beta_2 x_{i2}+ \ldots..+ \beta_n x_{in}$ i= 1,2,3….m

Activity = 216.535 + 20.313 enargy gap - 62.061 electronegativity -.731 electrophilicity +1.186 nucleofugality +2.341 electrofugality.

Finally, the following variables: HOMO, LUMO, hardness, and softness were excluded in the regression equation because the studied variables did not show a derivation effect.

4. SUMMARY AND CONCLUSION

The present study aimed to examine the descriptors of 21 molecules that may inhibit the activity of RNR. The study revealed that there is a significant relationship between the activity inhibition of the enzyme and the studied descriptors. The results of calculated energy gap and the interpretation of Figs. 1, 2 and 3, demonstrate that the molecules with smaller E_{HOMO}-E_{LUMO} energy gap lead to lower kinetic stability and higher chemical reactivity [1]. Therefore, the molecules with the highest reactivity illustrate that the molecule 17 has most inhibitory activity. The most significant descriptors for the linear part were Energy gap, chemical potential, nucleofugality. Most significant beta coefficient goes for electronegativity (beta = -13.225) the study also

revealed that electronegativity variable has a unique contribution as it indicates a stronger explanation of dependent variables.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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