

QSAR STUDY ON THIOSEMICARBAZONE DERIVATIVES AS RIBONUCLEOTIDE REDUCTASE INHIBITORS

Abstract

QSAR analysis on thiosemicarbazone derivatives exposing RNR inhibitory activities [1] were performed. In this series of 21 compounds, 13 of them were reported with inhibitory concentration (IC_{50}) in the 1 M range. The inhibitory concentration of those compounds were converted into $-\log IC_{50}$ before being correlated with the structural features.

The quantum chemical calculations have been carried out at the B3LYP level of theory using Gaussian-09 series of program package. The density functional theory (DFT), with the Becke's three parameter exchange functional along with the Lee– Yang–Parr correlation functional (B3LYP) were performed in order to calculate the quantum chemical descriptors such as HOMO, LUMO, Energy gap, Hardness, Softness, Chemical potential and Dipole moment of the investigated molecules. There are variables which make a unique statistically significant contribution (less than .05). In order of importance (according to their beta values), In this case the biggest beta coefficient is ($\beta = -13.225$), which is for electronegativity. This means that variable has a unique contribution to a stronger explanation of dependents variable. The beta value for the next variable was slightly lower (8.350) which was for electrofugality, the least contribution is to the rest of the elements indicating. In the model, also the other variable measures were statistically significant (Energy gap, chemical potential, nucleofugality).

Key words: Ribonucleotide reductase (RNR), Thiosemicarbazones derivatives, RNR inhibitory activities, methoxy group (OCH_3).

Introduction:

Thiosemicarbazones are compounds that can be obtained by the condensation of an aldehyde, or a ketones with thiosemicarbazide. They are compounds of considerable interest because of their important chemical properties and potentially beneficial

biological activities [15,32,39]. According to the IUPAC nomenclature [34], 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 certain biological mechanisms because of their chelating ability towards trace metal ions. After the chemotherapeutic effective platinum complexes of thiosemicarbazide derivatives were synthesized [27], these kinds of chemicals have raised considerable interest due to their pharmacological properties. In addition to antitumor effect of transition metal complexes of thiosemicarbazones [2,28,35], it is well known that they are also antiviral, even anti-HIV chemicals [3,12,17, 28, 38]. Numerous thiosemicarbazones, especially their Cu(II) complexes, have been studied for their antibacterial and antifungal properties [7,22,26]. Further, it can be mentioned that the thiosemicarbazones have anticonvulsant [33], anti-malarial [38], antiamoebic [4,37] and antioxidant properties [20] as other biological activities.

Ribonucleotide reductase, also known as ribonucleoside diphosphate reductase (RNR, E.C. 1.17.4.1), it catalyzes 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 critical role in regulating the total rate of DNA synthesis so that DNA to cell mass is maintained at a constant ratio during cell division and DNA repair(18). The enzyme ribonucleotide reductase (RNR) catalyzes 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 occurs 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, found in eukaryotes, prokaryotes, and viruses, is a 1:1 protein complex. Class II ribonucleotide reductase, existing mainly in bacteria, contains a transient 5'-deoxyadenosyl radical. Class III ribonucleotide reductase harbors a stable glycy radical in anaerobic bacteria [35]. In this study, we have performed QSAR analysis on thiosemicarbazone derivatives reveal RNR inhibitory activities.

A series of thiosemicarbazone derivatives was considered to perform the QSAR. In this series of 21 compounds, 13 of them were reported with inhibitory concentration (IC_{50}) in the 10^{-6} to 10^{-4} M range. The inhibitory concentration of those compounds were converted into $-logIC_{50}$ before being correlated with the structural features.

The quantitative structure activity relationship (QSAR) is a mathematical demonstration of biological activity in terms of structural descriptors of a series of homologue molecules [11,13,14,16,21]. The objective of QSAR is to explore new molecules with required properties using chemical intuition and experience changed into a mathematically quantified and computerized form. Formerly a correlation is recognized, the structure of any number of compounds with preferred properties can be predicted. Therefore QSAR methodology saves resources and accelerate the process of development of new molecules and drugs [8]. Success of QSAR in the development of new drug molecules and prediction of toxicity of molecules is highly significant [11,13,14,16,21]. Quantum chemical descriptors have been extensively used in QSAR studies in biochemistry. Recently the uses of quantum chemical descriptors in 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 [21].

Methodology:

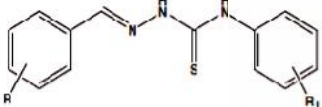
These calculation have been carried out at the B3LYP level of theory using Gaussian-09 series of program package [9]. The calculations were based on 6-311G (d,p) basis set. The method which has been widely implemented to study the relationship between inhibitory activation efficiency of the molecules and their electronic properties [41]. In order to set up correlation between experimental activity and structural and electronic characteristics of the investigated inhibitors, the geometry of the molecules were optimized by the density functional theory (DFT)[19],with the Becke's three parameter exchange functional [5] along with the Lee– Yang–Parr correlation functional (B3LYP) [24]. The optimized structure of the investigated inhibitors.

Results and discussion:

The studied molecules and their activity were given in the table 1[24, 29]. Molecules had been classified to seven groups for further comparisons and discussion. The first group which was red

colored in the table (1). include (1,2,5-10) the inactive compounds. The second group contain molecule (3) with black color which haven't any group. The third group with the green color include (4,11,12) molecules which contain Cl atom in positions 2,3 and 4. The fourth violet group include molecules (13-15) which contain methyl group. Fifth group (16) dark green compound which contain methoxy group. Sixth group contain two compounds colored with brown color, these compounds contain nitrogen dioxide. And the seventh group which in blue color and include (19,20,21) molecules which contain hydroxide.

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

The degree of the activity is differentiate through groups , each group had an own activity, which is related to its composition, for instance when R1is hydroxyl group (OH) as in the molecules (3,4 and 11-21) but in the position 2 the molecule is not active as in the (1 and 2) or any other group like methoxy (OCH3) even if it is with (OH) in the position 4 molecules (5and 6) or furyl and thiophenyl group as in the molecules (7 and 8) and (9 and 10) respectively, but when this group (OH) is in the position 4 the molecule will be active, and the R2 group type and its position will decide 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.

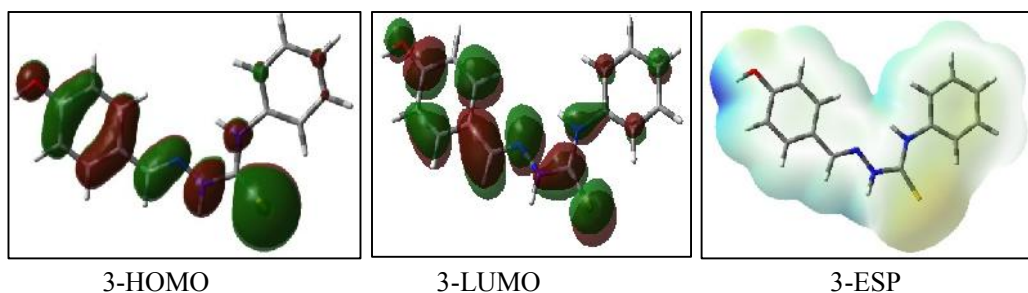
Table 2: The calculated parameters by B3LYP/6-311G(d,p) : HOMO, LUMO, Energy gap, Hardness, Softness, Electronegativity, Chemical potential, Electrophilicity index(ω) & Electronegativity.

Mole. no.	HOMO	LUMO	Energy gap	Hardness	Softness	Electron egativity	Chemical Potential	Electrophilicity index	Electronegativity
1	-5.93485	-2.15026	3.784589	0.817164	0.408582	8.085111	-8.08511	26.70861	-0.06293471
2	-7.06658	-2.25258	4.814004	1.280714	0.640357	9.319157	-9.31916	55.61288	-0.09223057
3	-5.89675	-2.01502	3.881735	0.933358	0.466679	7.911773	-7.91177	29.2123	-0.07522886
4	-6.01349	-2.12142	3.892075	0.885329	0.442665	8.134908	-8.13491	29.2941	-0.06624229
5	-6.80018	-1.96903	4.831147	1.431058	0.715529	8.76921	-8.76921	55.0235	-0.08850542
6	-5.89539	-2.07461	3.820781	0.873084	0.436542	7.970006	-7.97001	27.72959	-0.07288916
7	-5.98791	-2.17257	3.815338	0.821382	0.410691	8.160487	-8.16049	27.34937	-0.07087169
8	-6.1539	-2.27271	3.881191	0.804239	0.402119	8.426616	-8.42662	28.55364	-0.07830663
9	-5.95009	-2.16278	3.78731	0.812266	0.406133	8.112866	-8.11287	26.73111	-0.06953674
10	-6.2018	-2.25666	3.945138	0.84424	0.42212	8.458454	-8.45845	30.20076	-0.07958652
11	-5.93975	-2.0308	3.908946	0.939072	0.469536	7.97055	-7.97055	29.82947	-0.06873696
12	-6.30302	-2.25992	4.0431	0.891588	0.445794	8.562946	-8.56295	32.68742	-0.08080608
13	-5.77621	-1.91189	3.864319	0.976216	0.488108	7.688093	-7.68809	28.8505	-0.07001783
14	-5.91825	-2.13965	3.778603	0.819477	0.409739	8.057899	-8.0579	26.60422	-0.07223434
15	-5.87961	-2.12468	3.754929	0.815123	0.407562	8.004292	-8.00429	26.11195	-0.07302133
16	-5.76587	-1.90644	3.859421	0.976488	0.488244	7.672311	-7.67231	28.74017	-0.07002734
17	-5.9841	-3.01532	2.968786	-0.02327	-0.01163	8.99942	-8.99942	-0.94215	-0.07183531
18	-6.29241	-2.74184	3.55057	0.404364	0.202182	9.034251	-9.03425	16.50164	-0.07623938
19	-5.79825	-1.90944	3.88881	0.989686	0.494843	7.707686	-7.70769	29.39784	-0.07876125
20	-5.90682	-2.14672	3.760099	0.806688	0.403344	8.053545	-8.05355	26.16072	-0.0555575
21	-5.76641	-2.1255	3.640912	0.757707	0.378854	7.891908	-7.89191	23.59584	-0.105955

121

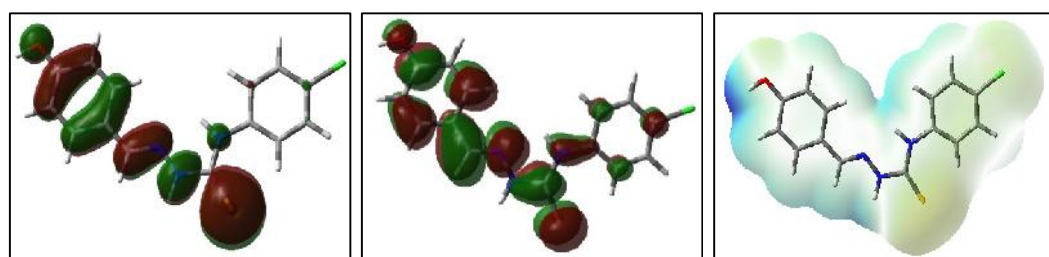
122 HOMO and LUMO orbitals of the 21 molecules were obtained from the quantum chemical
 123 calculation by the DFT using B3LYP/6-311G(d,p), as shown in figure 1 below [9,10]. It is
 124 known that HOMO is often associated with the electron donating ability of a molecule, high
 125 value of HOMO is likely to indicate the tendency of the molecule to donate electrons to
 126 appropriate acceptor molecules with lower energy MO [1, 23, 28].

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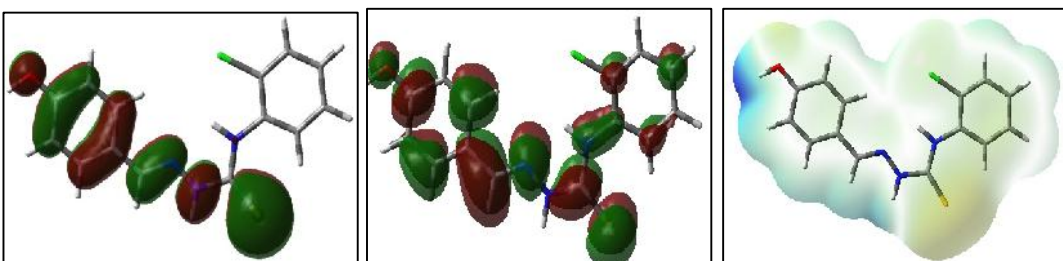
129



4-HOMO

4-LUMO

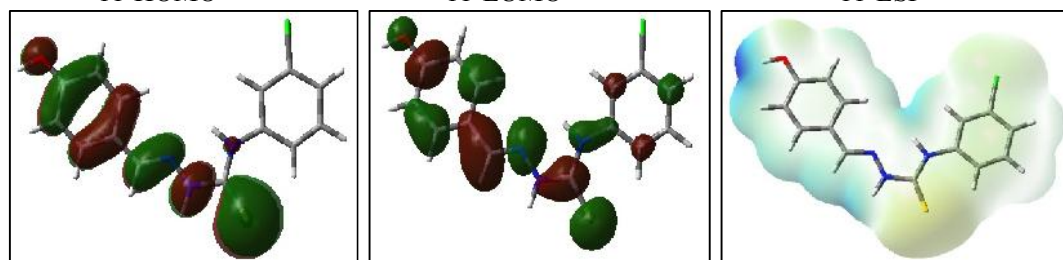
4-ESP



11-HOMO

11-LUMO

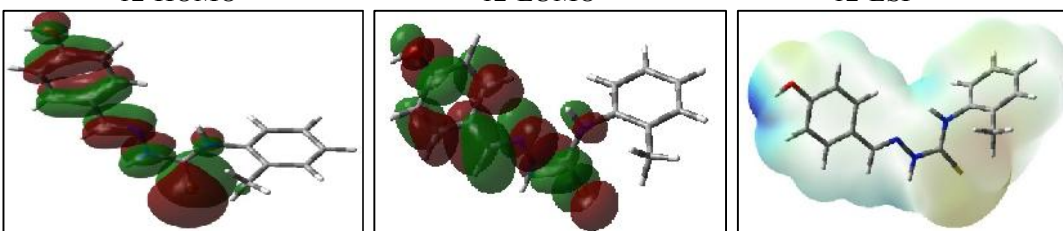
11-ESP



12-HOMO

12-LUMO

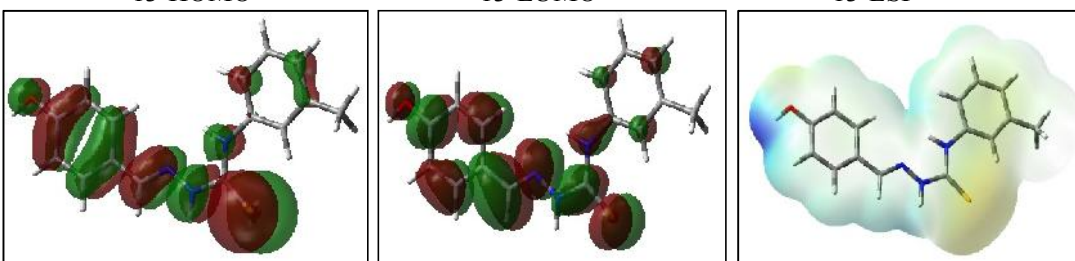
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13-HOMO

13-LUMO

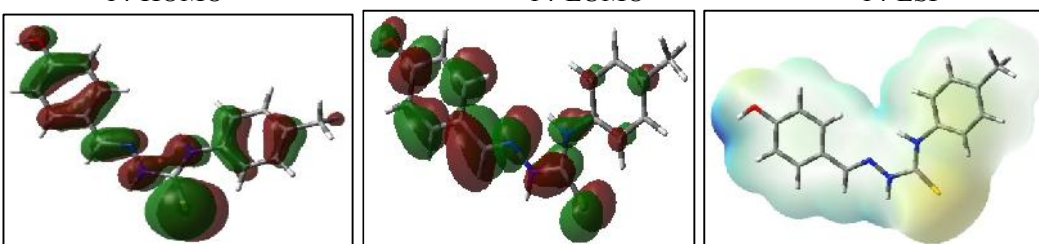
13-ESP



14-HOMO

14-LUMO

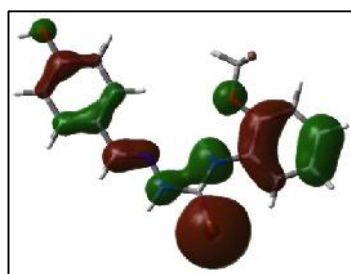
14-ESP



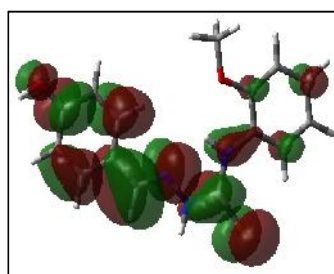
15-HOMO

15-LUMO

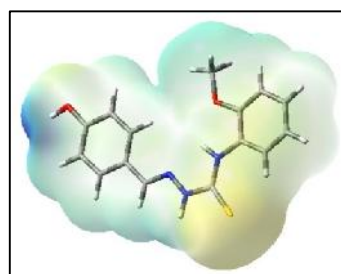
15-ESP



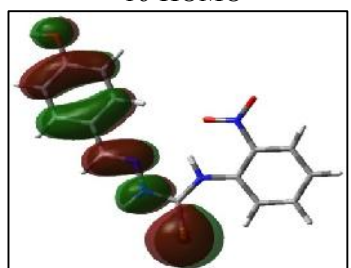
16-HOMO



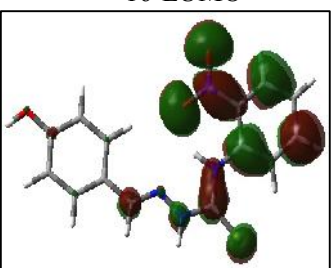
16-LUMO



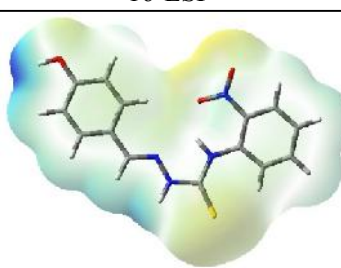
16-ESP



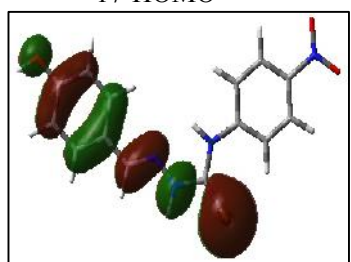
17-HOMO



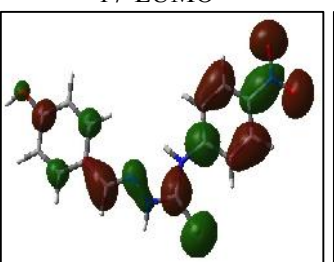
17-LUMO



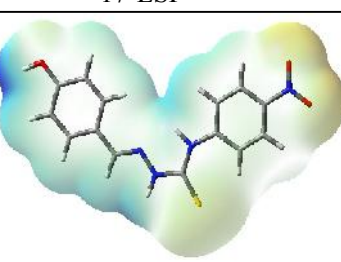
17-ESP



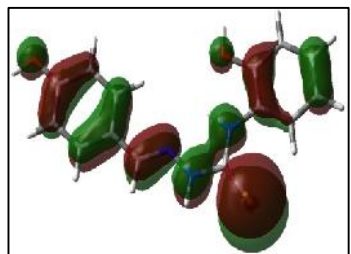
18-HOMO



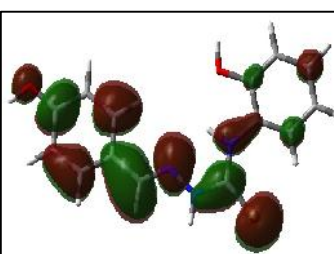
18-LUMO



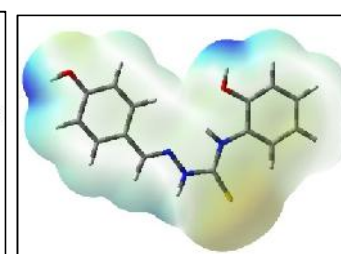
18-ESP



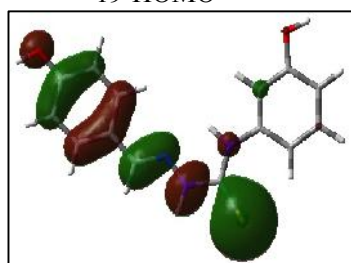
19-HOMO



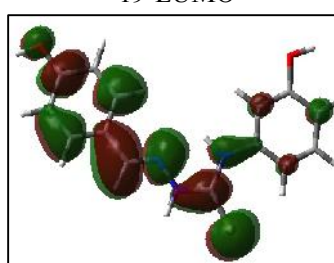
19-LUMO



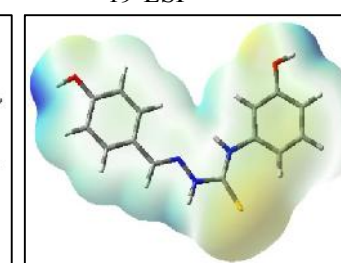
19-ESP



20-HOMO



20-LUMO



20-ESP

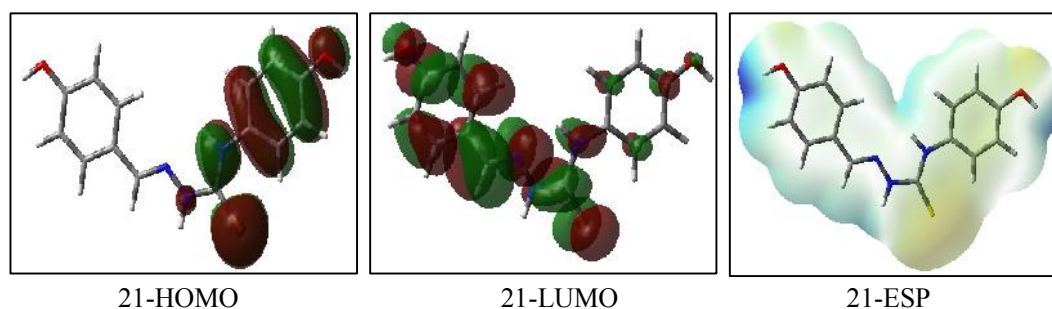
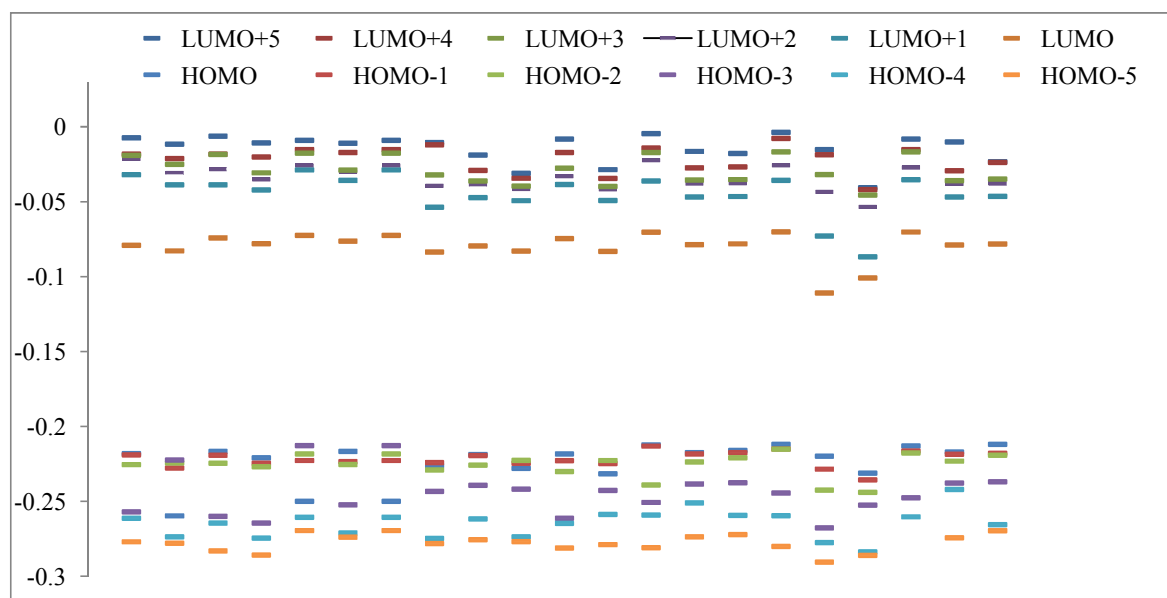
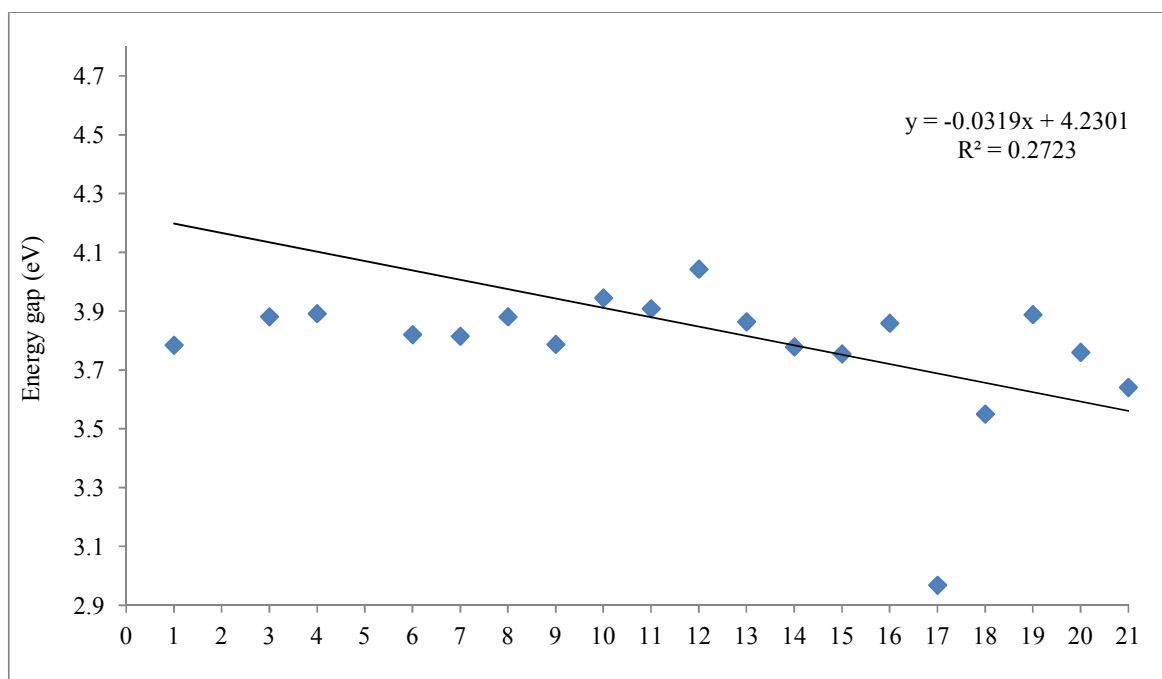


Fig. 1: HOMO, LUMO & ESP of the active molecules.

The highest E_{HOMO} among the 13 active molecules were -5.76587, -5.76641, -5.77621, -5.79825, -5.87961, -5.89675, -5.90682, -5.91825, -5.93975, -5.9841, -6.01349, -6.29241 and -6.30302. 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, -1.90944, -1.91189, -2.01502, -2.0308, -2.12142, -2.12468, -2.1255, -2.13965, -2.14672, -2.25992, -2.74184 and -3.01532 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, 3.55057, 3.640912, 3.754929, 3.760099, 3.778603, 3.859421, 3.864319, 3.881735, 3.88881, 3.892075, 3.908946 and 4.0431 for the molecules 17, 18, 21, 15, 20, 14, 16, 13, 3, 19, 4, 11 and 12 respectively. As we know that the results of energy gap calculated by B3LYP/6-311G(d,p) method and the interpretation of figures (1, 2 and 3), we can understand that the molecules with smaller $E_{\text{HOMO}}-E_{\text{LUMO}}$ energy gap lead to lower kinetic stability and higher chemical reactivity [1]. Therefore, the molecules with the highest reactivity are as mentioned above, which illustrate that the molecule 17 is the most molecule that have inhibitory activity.



171 Fig.2: HOMO & LUMO at B3LYP/6-311G(d,p)
172



173

174 Fig 3: The relation between the energy gap and the activity.

175 Nucleofugality is: defined as the propensity of an atom or group of them to depart bearing the
176 bonding electron pair in a heterolytic cleavage process [6, 28], the highest nucleofugality of
177 the 21 molecules as demonstrated in table 2 below was: 87.90, 81.65, 80.99, 78.36, 73.68,
178 71.85, 71.27, 66.87, 66.52, 66.09, 65.64, 65.20, 65.12, 64.34, 63.94, 63.85, 63.00, 62.5,
179 59.89, 59.57 and 59.33 these results were for the molecules: 2, 18, 17, 5, 12, 10, 8, 7, 4, 9, 1,
180 14, 20, 15, 11, 6, 3, 21, 19, 13 and 16 respectively. According to these results, the molecules
181 that have inhibitory activity of the RNR enzyme of the above-mentioned group of molecules.
182 In the statistical analysis followed show that this parameter show a good correlation with the
183 activity.

184

185 Table 3: The calculated parameters by B3LYP/6-311G(d,p) : Sum of electronic and zero-point energies, Sum of
186 electronic and thermal Energies, Sum of electronic and thermal Enthalpies, Sum of electronic and thermal Free Energies,
187 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

188

189 Statistical analysis

190 To find out the amount of the total variance spelled out by the variables of interest (HOMO,
191 LUMO, Energy gap, hardness, softness, electronegativity, chemical potential,
192 electrophilicity, nucleofugality, electrofugality), we have to closely at the column, R Square.

193 The output displayed in the summary table of the model, the R square value is 0.386. This is a
194 statistically significant contribution. In other words, all of the above factors seem to represent
195 0.39% variance of observed activity, even when their effect on activity is statistically
196 controlled..

197 The ANOVA table indicates that the model as a whole (which contains both blocks of
198 variables) is significant ($F(5, 15) = 1,884, p < .0005$). A closer look into the coefficient table
199 which represents the results of all variables introduced in the equation with the objective of
200 highlighting the statistical significance indicates that attention to the dependent variables is
201 inconsequential.

202 Owing to the fact that beta values revealed a unique contribution of some variables included
203 in the equation, some of the other variables were eliminated simply because those variables
204 had no statistically significant effect on activity. In different equations, with a different set of
205 independent variables or with a different sample, these values would change. Therefore, we
206 will use the beta values by observing the beta column to find the highest beta value

(excluding any negative signs). There are variables which make a statistical contribution of unique significance (less than .05). In order of importance, the biggest beta coefficient goes for electronegativity (beta = -13.225) with respect to the beta values of the other factors. This means that the electronegativity variable has a unique contribution as it indicates a stronger explanation of dependent variables. The beta value for the next variable, electrofugality, was slightly lower (8.350). The least contribution was to the rest of the elements indicated. In addition, the other variable measures in the model were statistically significant (Energy gap, chemical potential, nucleofugality). Nonetheless, measures of the other variables were statistically significant (Energy gap, chemical potential, nucleofugality).

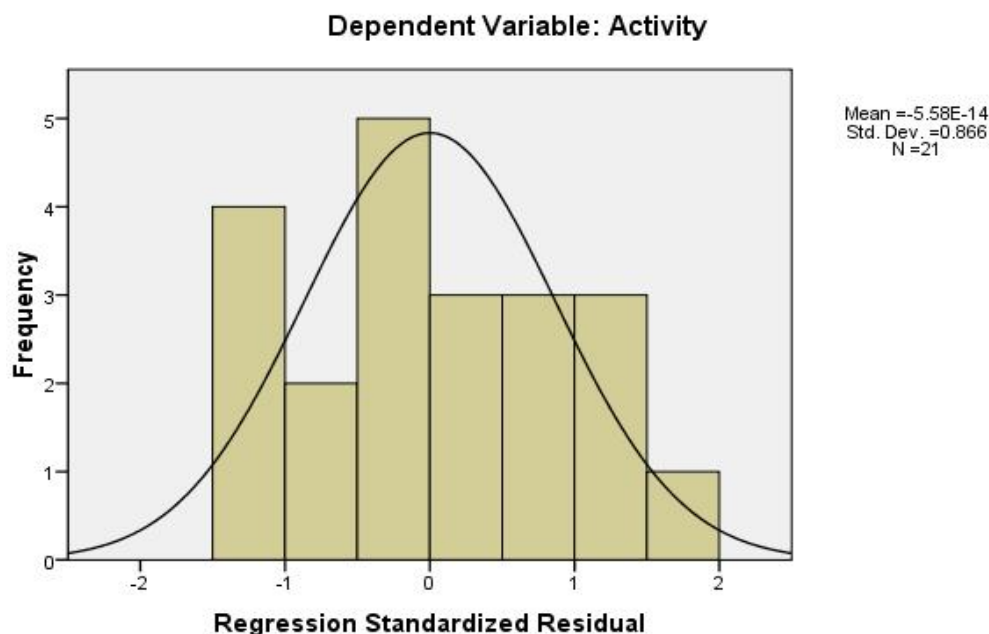
Table 4: The model summary^b

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

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



226 *Fig 4: The normal distribution of the variables.*

227 The equation from the Coefficients table is :-

$$228 \quad y_i = \beta_0 + \beta_1 x_{i1} + \beta_2 x_{i2} + \dots + \beta_n x_{in} \quad i = 1, 2, 3, \dots, m$$

229 Activity = 216.535 + 20.313 energy gap - 62.061 electronegativity - 7.31 electrophilicity
230 + 1.186 nucleofugality + 2.341 electrofugality.

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

233 **Summery Conclusion**

234 The purpose of this paper was to examine the descriptors of the 21 above-mentioned
235 molecules that may inhibit the activity of RNR. The results of the study reveal that there is a
236 relationships between the activity inhibition of the enzyme and the studied descriptors. The
237 results of calculated energy gap and the interpretation of figures (1, 2 and 3), demonstrate that
238 the molecules with smaller $E_{\text{HOMO}}-E_{\text{LUMO}}$ energy gap lead to lower kinetic stability and
239 higher chemical reactivity (1). Therefore, the molecules with the highest reactivity are as
240 mentioned above, which illustrate that the molecule 17 is the most molecule that have
241 inhibitory activity. In order to examine the relationships, (SPSS) software was used for the
242 linear data set. The most significant descriptors for the linear part were Energy gap, chemical
243 potential, nucleofugality. In order of importance, the biggest beta coefficient goes for
244 electronegativity (beta = -13.225) with respect to the beta values of the other factors. This
245 means that the electronegativity variable has a unique contribution as it indicates a stronger
246 explanation of dependent variables.

247

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