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Structure-activity relationships of 2-pyridinone derivatives for HIV-1- specific reverse transcriptase inhibitors: with ETM And ANNs

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Abstract

The aim of this study is to find the relationship between HIV-1 activity and chemical structure for 2-Pyridinone derivatives by using the Electron-Topological Method (ETM). Data for ETM were obtained quantum mechanical calculations. Quantum chemical calculations were performed after the conformational analysis. By using the data obtained from quantum chemical calculation results ETM were perfomed and pharmacophere and anti-pharmacophere fragments for the HIV-1-specific Reverse Transcriptase inhibitors were explained. Conformational analysis and quantum-chemical calculations of 2-pyridinone derivatives were carried out by using B3LYP method with basis set of the 6-311G(d,p) in order to determine molecular properties. The descriptors of HOMO, LUMO, HOMO-LUMO energy gap, chemical hardness, chemical softness, electro-negativity, chemical potential, dipole moment etc. were calculated and tabulated in order to employed in statistical analyses that are Linear Discriminant Analysis (LDA) and Artificial Neural Networks (ANNs). By doing so, the linear and non-linear sections of data structure are investigated and their corresponding descriptors having impact on dependent variable has been found.

We see from the fragment properties atoms found in benzoxazole groups give rise to activity of the molecules, and atoms in the naphthyl groups causes breaking the activity.

Introduction

The identification of human immunodeficiency virus type-1 (HIV-1) as a causal agent of acquired immunodeficiency syndrome (AIDS) has led to intense research efforts to find effective therapies for this disease. Although there are inhibitors targeting various stages of the life cycle of human immunodeficiency virus (HIV), but only reverse transcriptase (RT) and protease inhibitors are currently being used to treat this disease [1-3].

Reverse transcription means the passage of an RNA genome to a double-stranded DNA molecule. This process was first reported Temin and Mizutani [4] for RNA tumor viruses. Since all previously known transfers of genetic information are made from DNA to RNA, the synthesis of retro viral DNA from an RNA genome has been termed as "reverse" transcription, ie reverse transcription. All viruses that are dependent on their proliferation in the reverse transcript are grouped in the *Retroviridae* family.

Reverse transcriptase (RT) is an important target for AIDS antiviral drug therapies. This enzyme is blocked by nucleoside analogues that function as chain terminators during the replication of newly synthesized proviral DNA from viral RNA.

However, their usefulness has remained limited due to toxic side effects and emergence of resistant strains of HIV-1. Non-nucleoside RT inhibitors (NNRTIs) usually contain a class of potent antiviral agents that are non-competitive inhibiting and bind to a unique site on the structure of HIV-1 RT [5,6].

It was reported that TIBO (4,5,6,7-tetrahydro-5-methylimidazo[4,5,1-j,k] [1,4] benzodiazepin-2(1H)-one) derivatives inhibited HIV-1 replication. Electron-Topological Method (ETM) [7-11] were used to study structure-activity relationships for different series [7-11].

QSAR studies were performed by Garg, *et al.* [12] for the pyridinone analogues and suggested a positive role of hydrophobic 20 and 21 positions R-substituents. Electron-releasing R substituents that are marginal at best seem to favour activity, and there is detrimental

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steric effect of R substituents. The R-substituents at 22 and 23 positions have steric effects.

In this study, structure-activity relationships have been performed for 2-pyridinone series (Table 1). The series of compounds subjected to ETM calculations studies are given in Table 1 where the activity parameter IC_{50} is a measure of antiviral potency and refers to the molar concentration of the compound, required to reduce the concentration of HIV-1 reverse transcriptase. The ETM modelling is a method to elucidate fragments presenting activity and represents fragments breaking activity. ETM methods have been applied to drug design problems. Besides, two statistical models conducted for the determination of statistically significant descriptors for the linear and non-linear parts of the data set are Linear Discriminant Analysis (LDA) and Artificial Neural Networks (ANNs), respectively.

Materials and methods

Data set on the HIV-1-Specific Reverse Transcriptase Inhibitors

2-Pyridinone derivatives whose biological activity taken from the literature [13,14] were selected to determine pharmacophore properties causing activity or inactivity. The compounds investigated were divided into two common structure as shown in Figure 1.

78 Compounds in the series are divided into three groups according to their inhibition of human immunodeficiency virus type 1 reverse transcriptase as active molecules whose IC_{50} values between 0.0096 and 0.29 μM, low ones between 0.29 and 1.26 μM, inactive ones between 1.26 and 310 μM.

ETM [15] was applied to active compounds and inactive ones separately to reveal pharmacophore feature.

Brief description of the ET-method

The calculations under the Electronic-Topological approach are represented by a result of the following steps [16-20]:

a. Conformational analysis.

b. Quantum-chemical calculations.

c. **ETMC** formation

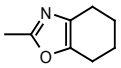
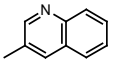
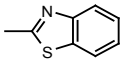
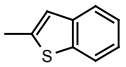
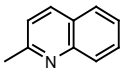
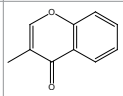
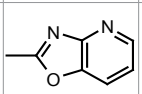
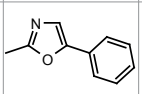
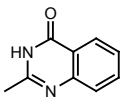
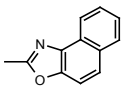
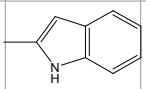
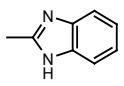
d. **ETMC** processing and search of the structural features of activity (pharmacophores-Ph) or inactivity (anti-pharmacophores-AP).

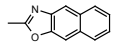
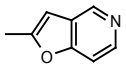
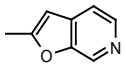
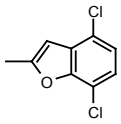
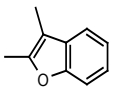
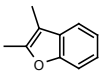
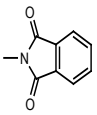
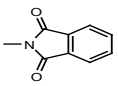
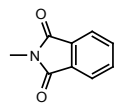
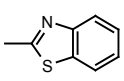
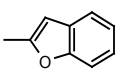
Computational details

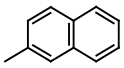
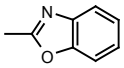
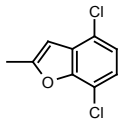
In this section of study, all calculations were carried out using DFT/B3LYP method with Gaussian program [21]. Optimization of molecules was performed with 6-311G (d,p) basis set. This basis set is known as one of the basis sets that gives more accurate results in terms of the determination of electronic and geometries properties for a wide range of organic compounds. Quantum chemical parameters, the energy of the highest occupied molecular orbital (E_{HOMO}), the energy of the lowest unoccupied molecular orbital (E_{LUMO}), HOMO-LUMO energy gap (ΔE), dipole moment (DM), molar volume (MV), total negative charge (TNC), chemical hardness (η) and softness (σ), electronegativity (), chemical potential (μ), global electrophilicity (ω), sum of the total negative charge (TNC) and sum of electronic and zero-point energies (SEZPE), were calculated by 6-311G (d,p) basis set of B3LYP method and discussed.

Molecular properties associated with related to the reactivity and selectivity of the compounds were estimated following the Koopmans's

Table 1. A list of molecules under investigation [13,14]. [a]2 naphthyl instead of benzoxazole.

Molecules	Skeleton	Ar/ Substituent	X	IC_{50}, μM
1	I		NH	0.280
2	I		NH	0.335
3	I		NH	0.35
4	I		NH	0.46
5	I		NH	0.50
6	I		NH	0.53
7	I		NH	1.10
8	I		NH	1.90
9	I		NH	2.10
10	I		NH	2.35
11	I		NH	2.50
12	I		NH	2.70
13	I		NH	4.40
14	I		NH	5.33
15	I		NH	7.58
16	I		NH	9.50

17	I		NH	10.0
18	I		NH	15.0
19	I		NH	22.5
20	I		NH	29.0
21	I		NH	32.3
22	I		NH	105
23	I		NH	145
24	I		NH	300
25	I		NH	0.057
26	I		NH	0.335
27	I		NH	1.95
28	I		NH	0.03
29	I		NH	0.33
30	I		CH_2	3.7
31	I		CH_2	0.37
32	I		CH_2	0.077

33	I		N-CH_3	0.440
34	I		N-CH_3	0.021
35	I		N-CH_3	1.05
36	II	5-Et, 6,20-Me_2	NH	0.12
37	II	5-Et, 6,22-Me_2	NH	1.25
38	II	5-Et, 6,23-Me_2	NH	1.65
39	II	5-Et, 6,21-Me_2	NH	0.055
40	II	5-Et, 6-Me, 21-Et	NH	0.26
41	II	5-Et, 6,20,21-Me_3	NH	0.020
42	II	5-Et, 6-Me, 20-Cl	NH	0.15
43	II	5-Et, 6-Me, 21-Cl	NH	0.065
44	II	5-Et, 6-Me, 20,21-Cl_2	NH	0.019
45	II	5-Et, 6-Me, 20-F	NH	0.11
46	II	5-Et, 6-Me, 22-F	NH	0.47
47	II	5-Et, 6-Me, 23-F	NH	1.25
48	II	5-Et, 6-Me, 21-F	NH	0.092
49	II	5-Et, 6-Me, 20–F, 21-Cl	NH	0.105
50	II	5-Et, 6-Me, 20,21-F_2	NH	0.070
51	II	5-Et, 6-Me, 20-OMe	NH	0.180
52	II	5-Et, 6-Me, 20-OH	NH	0.440
53	II	5-Et, 6-Me, 20-NO_2	NH	24.5
54	II	5-Et, 6-Me, 20-NH_2	NH	67
55	II	5-Et, 6-Me	NH	0.21
56	II	5-Et, 6-Me, 20,21-Cl_2	N-Me	0.058
57	II	5-Et, 6-Me, 20,21-Cl_2	N-Et	0.654
58	II	5-Et, 6,20,21-Me_3	N-Me	0.103
59	II	5-Et, 6,20,21-Me_3	CH_2	23
60	II	5-Et, 6-Me, 20,21-Cl_2	CH_2	9.6
61	II	5-Et, 6-Me	CH_2	0.022
62	II	5-CH=CH_2, 6-Me, 20,21-Cl_2	NH	0.023
63	II	5-S-Me, 6-Me, 20,21-Cl_2	NH	0.043
64	II	2-Thio, 5-Et, 6-Me, 20,21-Cl_2	NH	0.042
65	II	4,5-(CH_2), 6-Me, 20,21-Cl_2	NH	0.113
66	II	5-OMe, 6-Me, 20,21-Cl_2	NH	0.115
67	II	5-Acetyl, 6-Me, 20,21-Cl_2	NH	0.300

68	II	5-CH(OH)Me, 6-Me, 20,21-Cl_2	NH	1.05
69	II	4,6-Me_2, 20,21-Cl_2	NH	2.85
70	II	5-SMe, 6-Me	NH	0.19
71	II	5-SEt, 6-Me	NH	0.43
72	II	4,6-Me_2, 5Et	NH	0.60
73	II	5-SO_2Me, 6-Me	NH	1.15
74	II	5-CO_2Et, 6-Me	NH	1.75
75	II	5-S(O)Me, 6-Me	NH	31.5
76[a]	II	2-Thio, 5-Et, 6-Me	NH	0.30
77[a]	II	1,6-Me_2, 5-Et	NH	11
78[a]	II	5,6-benzo	NH	> 300

theorem relating the energy of the HOMO and the LUMO. Electronegativity is estimated using the following the equation:

$$\chi \cong -\frac{1}{2}(E_{HOMO} + E_{LUMO}) \quad (1)$$

Chemical hardness (η) measures the resistance of an atom to a charge transfer [22], it is calculated by using the equation:

$$\eta \cong -\frac{1}{2}(E_{HOMO} - E_{LUMO}) \quad (2)$$

Electron polarizability, called chemical softness (σ), describes the capacity of an atom or group of atoms to receive electrons [22] and is estimated by using equ. (3):

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

Chemical potential (μ) and electronegativity (χ) can be calculated with the help of the following equations [23].

$$\mu = -\chi \cong \frac{E_{HOMO} + E_{LUMO}}{2} \quad (4)$$

The global electrophilicity (ω) is a useful reactivity descriptor that can be used to compare the electron-donating abilities of molecules [24]. Global electrophilicity index is estimated by using the electronegativity and chemical hardness parameters with below equation:

$$\omega = \frac{\chi^2}{2\eta} \quad (5)$$

A high value of electrophilicity describes a good electrophile while a small value of electrophilicity describes a good nucleophile [25].

Results and discussion

All the conformational and quantum-chemical data for molecules under study were obtained by the MM2P method and the semi-empirical quantum-chemical method MM1 of molecular mechanics. We used to find out **ETM**-software for activity features' selection.

These are chemically bonded and chemically unbounded atomic pairs, respectively. Every active compound in the series. As using every active compound as a template to compare with the rest of **ETMC**s, Molecule **60** was chosen as template compound and we found pharmacophore Ph1 being found 20 in active compounds and only one inactive ones. Ph1 include atoms in the benzoxazole ring, and C_{12} as seen Figure 2a. The probability of realizing P_α in this class is nearly 0.90. Ph2 was obtained as taken molecule **61** template compound. Pharmacophore 2 includes 5 atoms belonging to four of them benzoxazole ring and one is C4. The distance between C4 and C22 is 8.95 Å as seen Figure 2b. This feature was found in 21 active and 1 inactive compounds.

78 and **24** compounds in inactive ones were taken as template compounds to determine anti-pharmacophores. As seen from Figure 3a. AP1 includes atoms in naphthyl group and C25 in benzo pyridine ring. This feature was seen in 23 inactive compounds; the probability is 0.97. AP2 consists of four atoms being C_4, C_5, C_{11}, C_{18}. (Figure 3b).

(Aminomethyl)phthalimide derivatives contain benzoxazole group in Figure 4. Introduction of NH_2, NO_2, phenyl groups into available positions on to benzoxazole ring decreases inhibitory potency. Thus, the compound 35 is active while the other compounds are inactivated.

As seen from Figure 5, both pharmacophores appear with high values of frequencies in the class of active compounds being practically absent in the class of inactive compounds. In a similar way, AP1 and AP2 are observed in maximal values for the in the class of inactive compounds while for the Ph1 and Ph2 the frequencies are almost close to zero. They are practically very low levels in the class of inactive compounds.

Similarly, maximum values for frequencies of AP1 and AP2 appearances in the class of inactive compounds are observed, but the frequencies for P1 and P2 are close to zero

Molecular structure

E_{HOMO}, E_{LUMO}, ΔE, DM, MV, TNC, η, σ, μ, χ, ω, SEZPE were calculated for 2-pyridinone derivatives (**1**-**78**) with the B3LYP/6-311G(d,p) method, as shown in Table 2.

E_{HOMO} and E_{LUMO} are associated with electron donating ability and electron accepting ability of a molecule, respectively. Higher E_{HOMO} is essential for molecular reaction with nucleophiles while lower E_{LUMO} reacts easily with electrophiles [26]. E_{HOMO} values for comparative molecules, **60** and **61**, of active molecules are found -5.96 and -5.86 eV, and comparative molecules, **24** and **78**, of active molecules are found, -5.31 and -5.58 eV, respectively (Table 2). According to these results, the electron donating trends for comparative molecules can be written as: **60>61** for active molecules and **78>24** for inactive molecules. Also, E_{HOMO} values of active molecules are greater than E_{HOMO} values of inactive molecules. E_{HOMO} and E_{LUMO} values of other molecules can be seen in Table 2. There is no significant change in the E_{HOMO} and E_{LUMO} values according to the position of phenyl ring (Figures 6 and 7).

ΔE, chemical hardness and softness are closely related to chemical properties of molecules. ΔE value is smaller when the basis set of atomic orbitals are magnified due to the changing of HOMO, usually to a more negative energy and decreasing in energy of LUMO [27]. More stable molecules have large ΔE value and less stable molecules have small ΔE value. ΔE values of active molecules **60** and **61** that they are more stable were found 4.65 and 4.66 eV, and ΔE values for inactive molecules **24** and **78** that they are less stable were found 4.32 and 4.14 eV, respectively (Table 2).

The chemical hardness and softness are common used in chemistry for explaining stability of compounds. According to Maximum Hardness Principle [26], chemical hardness is a measure of the stability of chemical species. The chemical hardness is just half the energy gap between the E_{HOMO} and E_{LUMO} (eq. 2). If a molecule has a large energy gap, it is called hard and other wise is called soft [28]. Softness is a measure of the polarizability and soft molecules give more easily electrons to an electron acceptor molecule or surface [23]. The calculated chemical hardness, softness and energy gap are given in Table 2.

The average values of the HOMO and LUMO energies have been defined as the chemical potential (μ). The negative of the

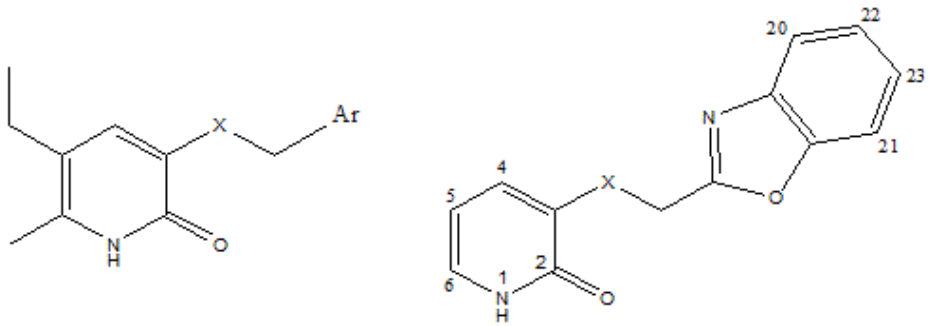
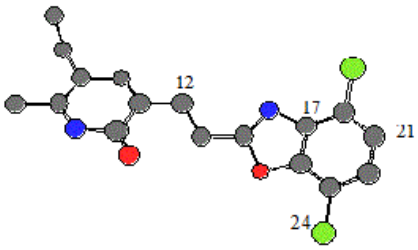


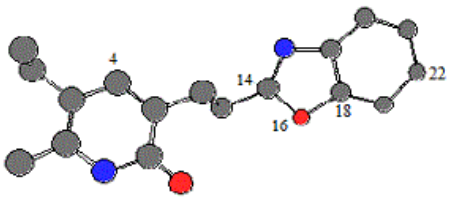
Figure 1. Skeletons of studied compounds.



60

C_{12}	C_{17}	C_{21}	C_{24}
0.05	4.27	6.58	6.52
	0.08	2.41	4.02
		-0.02	4.09
n1/n3=20/1, Pia=0.91			-0.15

a

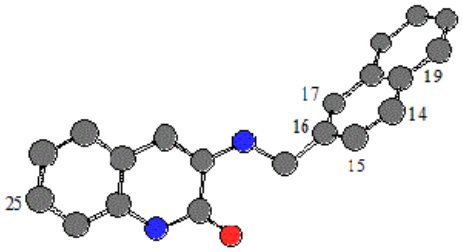


61

C_4	C_{14}	O_{16}	C_{18}	C_{22}
0.05	4.70	5.80	6.70	8.95
	0.24	1.05	2.11	4.48
		-0.20	1.03	3.73
δ1=0.06, δ2=0.16			0.09	2.43
n1/n3=21/3, Pia=0.85				-0.01

b

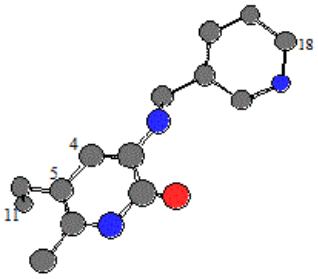
Figure 2. ETSC and corresponding structure of the pharmacophores Ph1 and Ph2 found relative to active compounds **60** and **61**, respectively.



78

C_{14}	C_{15}	C_{16}	C_{17}	C_{19}	C_{25}
0.00	1.52	2.43	2.79	1.34	8.36
	-0.01	1.35	2.42	2.43	7.56
		0.02	1.47	2.82	7.46
			0.03	2.43	8.18
δ1=0.04, δ2=0.13				0.03	9.02
n3/n1=23/2, Pia=0.97					-0.04

a



24

C_4	C_5	C_{11}	C_{18}
0.00	1.21	2.95	7.02
	-0.03	2.61	8.35
		-0.01	9.09
δ1=0.04, δ2=0.13			0.11
n1/n3=18/1, Pia=0.90			

b

Figure 3. ETSC and corresponding structure of the anti-pharmacophores AP1 and AP2 found relative to inactive compounds **78** and **24**, respectively.

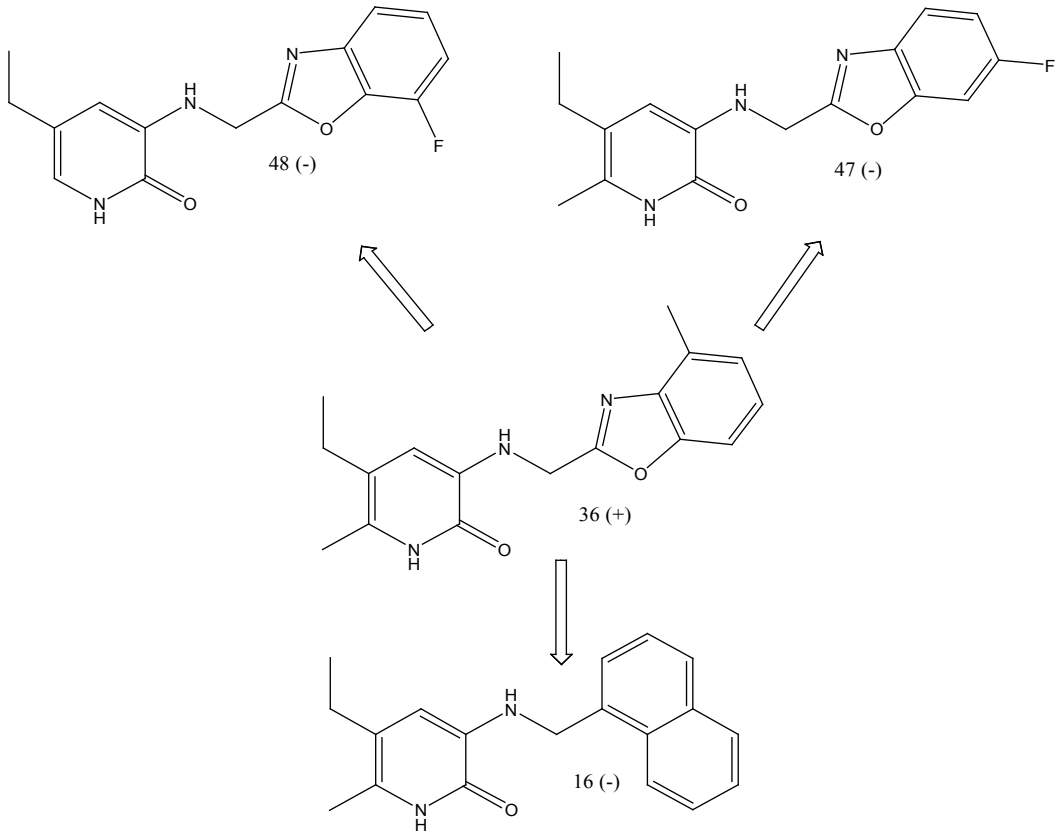


Figure 4. Comparison of pharmacophores.

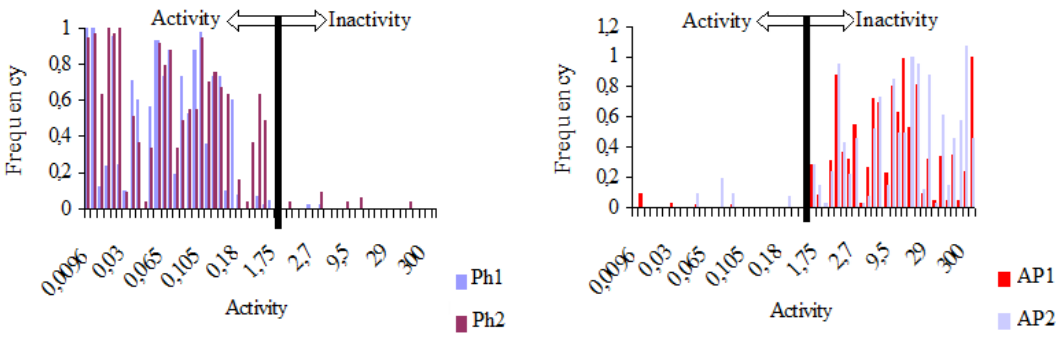


Figure 5. Frequency of the fragments' occurrences in the compounds studied: for pharmacophores Ph1and Ph2; and for antipharmacophores AP1 and AP2.

chemical potential was known as the electronegativity (χ) (eq. 3). The chemical potential, electronegativity and hardness are descriptors for the predictions about chemical properties of molecules [29]. Electronegativity that represents the power to attract the electrons of chemical species is a useful quantity in the prediction of inhibitive performance of molecules [23]. The electronegativity values of active molecules **60** and **61** are more than those of in active molecules **24** and **78** (Table 2).

The total electronic charge (TNC) values were calculated with the 6-311G(d,p) basis set of B3LYP method. TNC values of active molecules are found lower than those for inactive molecules (Table 2).

HOMOs and LUMOs shapes of inactive and active molecules for 2-pyridinone derivatives are also shown in Figure 6 for active template molecules and Figure 7 for inactive template molecules. As seen from the Figures 6 and 7 electron density is concentrated much more in the vicinity of oxygen atoms for active and inactive molecules.

Statistical analysis

The descriptor variables of 78 molecules which are called E_{HOMO}, E_{LUMO}, Energy Gap, Chemical Hardness, Softness, Chemical Potential, Dipole Moment, Total Negative Charge, Molecular Volume, SEZPE, Electro Negativity, Global Electrophilicity and dependent variable called IC_{50} are investigated in order to determine which descriptors have impact on dependent variable called IC_{50}. It is a fact that the data set has a characteristic of having both linearity and non-linearity among descriptors and between descriptors and dependent variable. Therefore, while Linear Discriminant Analysis (LDA) is conducted in order to determine which attributes have impact on dependent variable for the linear part, Artificial Neural Networks (ANNs) is run for the

Table 2. The calculated quantum chemical parameters for investigation compounds using B3LYP/6-311G(d,p) method.

Mol.	E_{HOMO} (eV)	E_{LUMO} (eV)	ΔE (eV)	DM (D)	MV (cm^3/mol)	TNC (e)	η (eV)	σ (eV^{-1})	χ (eV)	μ (eV)	ω (D^2/eV)	SEZPE (eV)
1	-5.07	-0.72	4.35	3.707	221.884	-3.992	2.173	0.460	2.894	-2.894	3.162	-25527.731
2	-5.32	-1.49	3.82	5.452	228.958	-3.333	1.912	0.523	3.405	-3.405	7.772	-25490.558
3	-5.06	-1.13	3.93	2.742	216.818	-3.295	1.965	0.509	3.097	-3.097	1.913	-34220.358
4	-5.19	-1.09	4.10	4.212	239.054	-3.071	2.049	0.488	3.141	-3.141	4.329	-25053.729
5	-5.29	-0.96	4.32	4.744	177.798	-3.234	2.162	0.463	3.125	-3.125	5.206	-33783.192
6	-4.81	-1.65	3.16	1.865	241.085	-3.274	1.579	0.633	3.229	-3.229	1.101	-25490.729
7	-5.25	-1.46	3.78	4.936	225.997	-3.807	1.892	0.529	3.355	-3.355	6.440	-28111.157
8	-5.28	-1.34	3.94	2.129	204.652	-3.521	1.971	0.507	3.308	-3.308	1.150	-25868.317
9	-5.09	-1.29	3.80	3.515	206.798	-3.075	1.900	0.526	3.190	-3.190	3.252	-25053.628
10	-5.04	-1.26	3.78	2.243	218.818	-3.463	1.890	0.529	3.153	-3.153	1.331	-27537.622
11	-5.14	-1.41	3.74	5.197	202.259	-4.011	1.868	0.535	3.277	-3.277	7.230	-27975.826
12	-5.23	-1.31	3.92	3.229	286.259	-3.570	1.960	0.510	3.274	-3.274	2.659	-29612.090
13	-5.21	-1.12	4.08	7.285	219.944	-3.550	2.042	0.490	3.166	-3.166	12.993	-24453.742
14	-5.16	-0.85	4.31	4.046	225.463	-2.890	2.157	0.464	3.006	-3.006	3.795	-20873.247
15	-5.02	-0.77	4.25	2.235	190.404	-3.511	2.125	0.470	2.896	-2.896	1.175	-24890.800
16	-5.02	-0.78	4.24	4.219	235.746	-3.579	2.120	0.472	2.903	-2.903	4.198	-25118.109
17	-5.26	-1.50	3.76	3.253	227.430	-3.568	1.881	0.532	3.380	-3.380	2.813	-29612.005
18	-4.84	-0.96	3.88	1.709	149.066	-2.999	1.942	0.515	2.898	-2.898	0.752	-21310.156
19	-4.98	-0.70	4.27	1.901	211.705	-3.402	2.137	0.468	2.842	-2.842	0.846	-24453.474
20	-5.12	-0.81	4.31	3.244	201.723	-2.931	2.153	0.465	2.964	-2.964	2.444	-20813.622
21	-5.31	-0.98	4.32	6.030	216.899	-3.479	2.162	0.463	3.143	-3.143	8.409	-25431.093
22	-5.32	-1.12	4.20	5.192	188.868	-3.248	2.098	0.477	3.220	-3.220	6.425	-25431.065
23	-5.19	-0.87	4.32	4.286	171.738	-2.952	2.159	0.463	3.026	-3.026	4.254	-20813.520
24	-5.31	-0.99	4.32	5.489	154.031	-3.102	2.162	0.463	3.151	-3.151	6.969	-21310.022
25	-5.31	-1.25	4.07	4.407	239.488	-3.420	2.034	0.492	3.281	-3.281	4.775	-50008.672
26	-5.23	-0.97	4.27	3.011	220.327	-3.373	2.133	0.469	3.102	-3.102	2.125	-37501.495
27	-5.23	-0.92	4.31	4.320	222.379	-3.498	2.157	0.464	3.072	-3.072	4.327	-26063.809
28	-5.18	-2.37	2.81	2.794	220.579	-3.931	1.406	0.711	3.774	-3.774	2.775	-28516.933
29	-5.18	-0.87	4.31	3.603	253.760	-3.227	2.156	0.464	3.026	-3.026	3.011	-24994.355
30	-5.80	-2.23	3.57	3.403	235.251	-3.987	1.783	0.561	4.014	-4.014	3.248	-28080.295
31	-5.87	-1.27	4.60	4.743	229.796	-3.440	2.299	0.435	3.568	-3.568	4.893	-33783.745
32	-5.77	-1.21	4.56	5.151	202.393	-3.196	2.282	0.438	3.487	-3.487	5.814	-24557.788
33	-5.76	-1.21	4.56	4.857	258.071	-3.171	2.279	0.439	3.484	-3.484	5.177	-26122.660
34	-5.85	-1.27	4.58	5.664	212.762	-3.635	2.291	0.436	3.561	-3.561	7.000	-26500.452
35	-5.93	-1.32	4.61	5.958	252.609	-3.575	2.305	0.434	3.629	-3.629	7.700	-49572.120
36	-5.23	-0.89	4.34	3.515	237.976	-3.643	2.169	0.461	3.058	-3.058	2.848	-26501.019
37	-5.21	-0.87	4.34	3.401	233.199	-3.637	2.169	0.461	3.042	-3.042	2.666	-26500.962
38	-5.21	-0.86	4.35	3.229	206.205	-3.641	2.175	0.460	3.031	-3.031	2.396	-26500.976
39	-5.22	-0.87	4.35	2.882	216.850	-3.652	2.177	0.459	3.045	-3.045	1.908	-26501.014
40	-5.23	-0.87	4.35	2.930	290.191	-3.895	2.177	0.459	3.051	-3.051	1.972	-27570.289
41	-5.21	-0.86	4.35	3.125	276.250	-3.882	2.174	0.460	3.039	-3.039	2.246	-27570.467
42	-5.29	-1.14	4.14	2.195	218.783	-3.537	2.072	0.483	3.213	-3.213	1.162	-37938.711
43	-5.32	-1.13	4.19	4.773	249.998	-3.526	2.093	0.478	3.224	-3.224	5.443	-37938.674
44	-5.36	-1.39	3.97	3.386	248.611	-3.657	1.984	0.504	3.373	-3.373	2.890	-50445.794
45	-5.27	-0.96	4.31	2.322	218.517	-3.580	2.155	0.464	3.117	-3.117	1.251	-28132.788
46	-5.30	-1.12	4.19	2.761	196.870	-3.594	2.093	0.478	3.210	-3.210	1.821	-28132.866
47	-5.30	-1.01	4.29	3.959	219.714	-3.590	2.143	0.467	3.156	-3.156	3.657	-28132.868
48	-5.30	-0.99	4.32	4.524	250.401	-3.557	2.159	0.463	3.144	-3.144	4.740	-28132.727
49	-5.35	-1.21	4.14	3.627	249.337	-3.706	2.072	0.483	3.279	-3.279	3.174	-40639.867
50	-5.34	-1.08	4.26	3.406	244.373	-3.734	2.132	0.469	3.208	-3.208	2.720	-30833.906
51	-5.28	-0.94	4.34	3.850	236.117	-3.837	2.172	0.460	3.111	-3.111	3.412	-28547.776
52	-5.17	-0.81	4.36	4.001	206.132	-3.715	2.180	0.459	2.992	-2.992	3.672	-27478.836
53	-5.36	-2.60	2.76	2.491	235.239	-3.770	1.380	0.724	3.976	-3.976	2.248	-30997.555
54	-5.22	-0.88	4.35	4.862	212.443	-3.836	2.173	0.460	3.050	-3.050	5.440	-26937.953
55	-5.24	-0.91	4.33	3.231	195.771	-3.407	2.165	0.462	3.070	-3.070	2.411	-25431.563
56	-5.96	-1.43	4.53	6.110	223.819	-3.888	2.266	0.441	3.691	-3.691	8.238	-51514.688
57	-5.31	-1.46	3.85	4.758	272.096	-4.027	1.925	0.519	3.387	-3.387	5.879	-52584.115
58	-5.83	-1.25	4.58	5.622	266.359	-4.107	2.288	0.437	3.541	-3.541	6.908	-28639.355
59	-5.84	-1.19	4.66	5.019	254.722	-3.994	2.328	0.430	3.516	-3.516	5.410	-27133.880

60	-5.96	-1.31	4.65	5.748	247.139	-3.774	2.326	0.430	3.638	-3.638	7.102	-50009.220
61	-5.86	-1.20	4.66	4.974	197.358	-3.521	2.328	0.430	3.532	-3.532	5.314	-24994.981
62	-5.30	-0.93	4.37	2.503	226.866	-3.659	2.186	0.457	3.117	-3.117	1.433	-27537.579
63	-5.46	-1.06	4.40	1.735	274.436	-4.012	2.201	0.454	3.262	-3.262	0.684	-37337.017
64	-5.20	-1.51	3.70	5.411	246.585	-3.642	1.849	0.541	3.355	-3.355	7.917	-36358.769
65	-5.13	-0.79	4.34	3.235	265.187	-3.808	2.169	0.461	2.960	-2.960	2.412	-27537.036
66	-5.23	-0.95	4.29	2.522	218.943	-3.588	2.143	0.467	3.089	-3.089	1.484	-28547.936
67	-5.64	-1.42	4.22	1.434	224.491	-4.022	2.108	0.474	3.527	-3.527	0.488	-29585.673
68	-5.24	-0.86	4.38	2.898	263.211	-4.049	2.188	0.457	3.052	-3.052	1.919	-29617.507
69	-5.18	-0.79	4.39	2.992	245.459	-3.642	2.194	0.456	2.982	-2.982	2.040	-26501.278
70	-5.46	-1.06	4.40	1.735	252.032	-4.012	2.201	0.454	3.262	-3.262	0.684	-37337.017
71	-5.44	-1.04	4.40	1.959	267.979	-4.245	2.199	0.455	3.243	-3.243	0.873	-38406.342
72	-5.09	-0.74	4.35	3.242	267.768	-4.244	2.176	0.460	2.913	-2.913	2.415	-28639.730
73	-5.76	-1.26	4.49	2.414	260.171	-5.440	2.247	0.445	3.509	-3.509	1.297	-42499.229
74	-5.42	-0.93	4.49	1.971	272.458	-4.648	2.245	0.445	3.178	-3.178	0.865	-33771.888
75	-5.57	-1.16	4.41	2.075	246.759	-4.141	2.206	0.453	3.364	-3.364	0.976	-39383.395
76	-5.22	-1.54	3.68	6.366	257.832	-2.846	1.842	0.543	3.380	-3.380	11.002	-33842.015
77	-5.12	-1.08	4.04	4.167	201.459	-3.304	2.021	0.495	3.098	-3.098	4.296	-26122.732
78	-5.58	-1.44	4.14	2.740	212.020	-2.571	2.070	0.483	3.514	-3.514	1.814	-26026.390

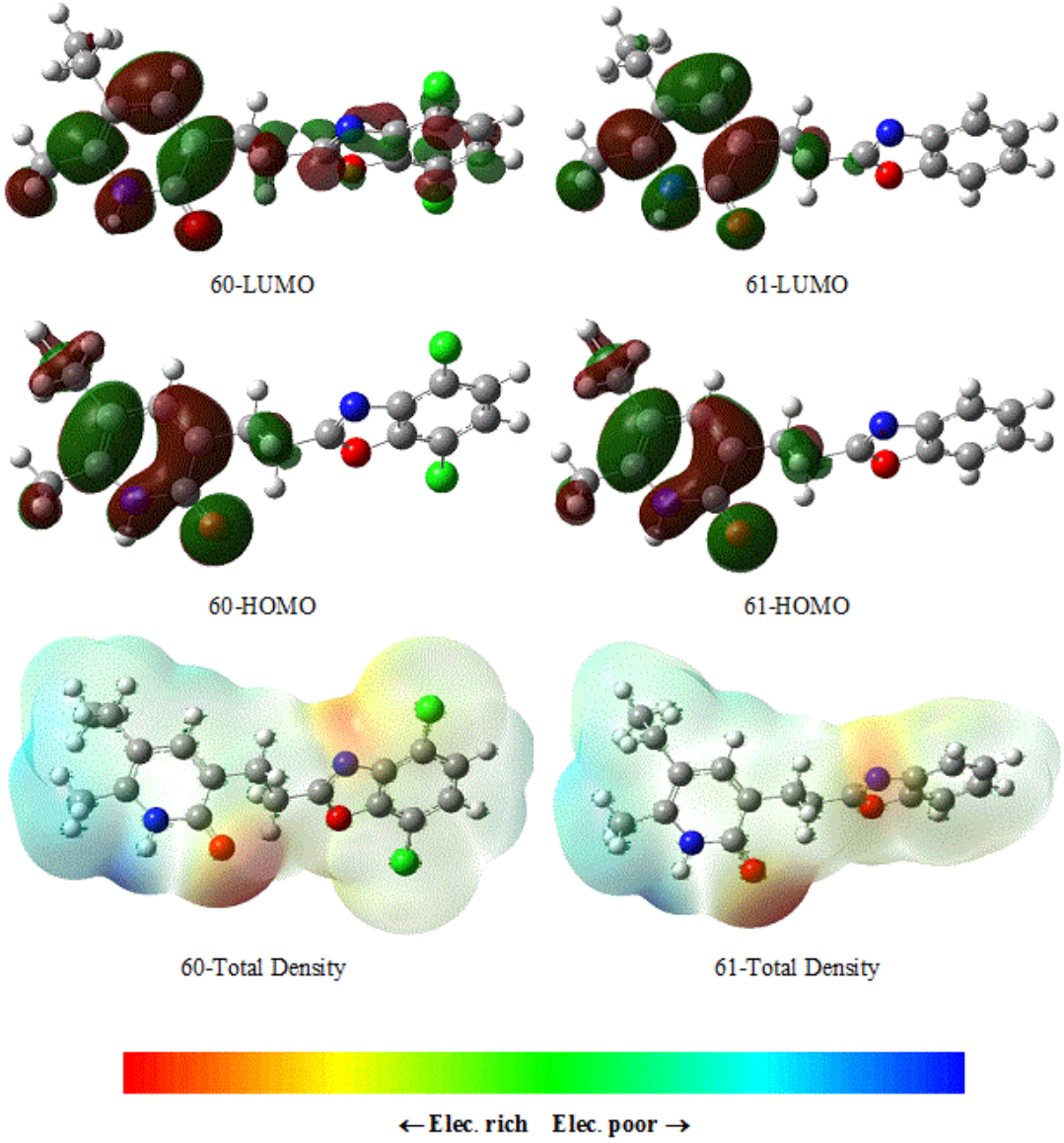


Figure 6. HOMO, LUMO and total density of the inactive molecules for 60 and 61 using DFT/B3LYP/6-311G(d,p) method.

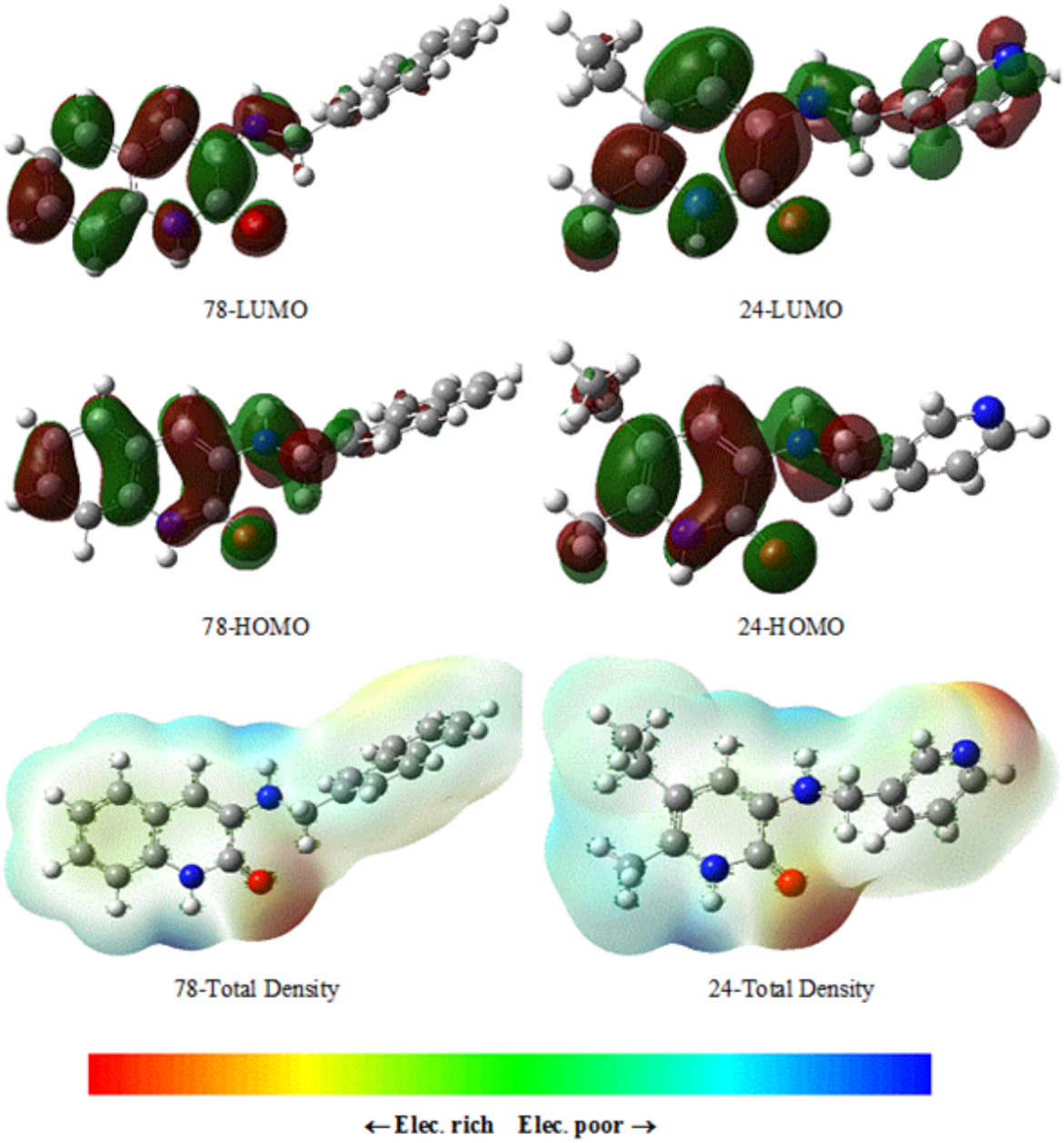


Figure 7. HOMO, LUMO and total density of the active molecules for 78 and 24 using DFT/B3LYP/6-311G(d,p) method.

non-linear part in order to determine which attributes have impact on it.

In order to run LDA, the dependent variable is split into two non-overlapping data sets. While the first group consists of 58 molecules whose values range between 0.019 and 2.850, the second group composes of 20 molecules whose values are relatively high values and alter between 3.7 and 300.00. Therefore, LDA calculated function which separates the first group from the second group is given in standardized coefficient form as follows:

$$0.958 * Molecular\ Volume - 0.252 * Global\ Electrophilicty + 0.152 * E_{LUMO}$$

The 39 percent of the total variance is explained by the linear discriminant function given above and its level of significance measured by Wilk's lamba is 0008<0.05 shows that the model is statistically significant. On the other hand, linear discriminant function calculated above has a low misclassification rate of 23 percent. Also, when cross-validated, its misclassification rate hits 25 percent, which means that when one of the data used for constructing modeling repeatedly is excluded, the correct classification rate of the constructed model for the excluded observation hits 75 percent. In other words, when a new molecule arrives in data set, it is possibly being classified with 75 percent accuracy. All computations are done using SPSS 20.0 version [30].

For the non-linear part, Artificial Neural Networks (ANNs) with multilayer perceptron using sigmoid activation function is conducted using SPSS 20.0 version. The descriptors except the ones used in LDA, namely, E_{HOMO}, Energy Gap, Softness, Hardness, Chemical Potential, Dipole Moment, Total Negative Charge, SEZPE, Electro Negativity are employed in order to predict which descriptors have impact on dependent variable IC50. The data set is split into two non-overlapping

sets. The first of which is called training set and the second one is called the test set whose partitions are 70 percent and 30 percent, respectively. Dipole Moment, Hardness, E_{HOMO} and Electro Negativity are determined as the most important descriptors with 0.64 coefficient of determination.

As a result, due to the complex structure of the data set, it requires the investigation to be conducted including both linearity and non-linearity analysis which are Linear Discriminant Analysis (LDA) and Artificial Neural Networks (ANNs), respectively. While Molecular Volume, Global Electrophilicity and E_{LUMO} are the most significant descriptors and have a power of correctly separating molecules with 77 percent for linear part, Dipole Moment, Hardness, Homo and Electro Negativity are descriptors having impact on dependent variable called IC_{50} for non-linear part.

Conclusions

In this study, we find the relationship between HIV-1 activity and chemical structure for 2-pyridinone derivatives by using ETM, and also we calculated and discussed quantum chemical parameters of 2-pyridinone derivatives such as the energy of the highest occupied molecular orbital, the energy of the lowest unoccupied molecular orbital, HOMO–LUMO energy gap, chemical hardness, softness, electronegativity, chemical potential, dipole moment, global electrophilicity, sum of the total negative charge (TNC) and sum of electronic and zero-point energies (SEZPE) quantum-mechanical calculations by using B3LYP method with basis set of the 6-311G(d,p) in order to find molecular properties.

Based on those calculations, two statistical models conducted for the determination of statistically significant descriptors for the linear and non-linear parts of the data set are Linear Discriminant Analysis (LDA) and Artificial Neural Networks (ANNs), respectively. Due to the complex structure of data set, linearly correlated and non-linearly correlated descriptors are separately used in order to find which attributes having impact on dependent variable. While Molecular Volume, E_{LUMO} and Electrophilicity are significant descriptors for linear part determined by LDA, Dipole Moment, Hardness, E_{HOMO} and Electro Negativity are significant descriptors for non-linear part of the data set.

References

1. de Clercq E (1996) Non-nucleoside reverse transcriptase inhibitors (NNRTIs) for the treatment of human immunodeficiency virus type 1 (HIV-1) infections: strategies to overcome drug resistance development. *Med Res Rev* 16: 125-157. [Crossref]
2. Debnath AS, Radigan L, Jiang S, Lindsley F (1999) Structure-based identification of small molecule antiviral compounds targeted to the gp41 core structure of the human immunodeficiency virus type 1. *J Med Chem* 42: 3203-3209.
3. De Clercq E (2000) Novel compounds in preclinical/early clinical development for the treatment of HIV infections. *Rev Med Virol* 10: 255-277.
4. Temin HM, Mizutani S (1970) RNA-dependent DNA polymerase in virion of rous sarcoma virus. *Nature* 226: 1211-1213.
5. Nouvel P (1994) The mammalian genome shaping activity of reverse transcriptase. *Genetica* 93: 191-201. [Crossref]
6. De Clercq E (1993) HIV-1 specific RT inhibitors: Highly selective inhibitors of human immunodeficiency virus type 1 that are specifically targeted at the viral reverse transcriptase. *Med Res Rev* 13: 229-258.
7. Dimoglo AS, Chumakov YM, Dobrova BN, Saracoglu M (1997). Electron-topological of the Structure-antitumor activity relationship of thiosemicarbazone derivatives. *Arzn-Forsch-Drug Res* 47: 415-419.
8. Kandemirli F, Saracoglu M, Kovalishyn V (2005). Human acetylcholinesterase inhibitors: Electronic-topological and neural network approaches to the structure-activity relationships study. *Mini-Rev Med Chem* 5: 479-487.
9. Dimoglo AS, Gorbachov MY, Lesnik TI, Saracoglu M, Güzel Y, et al. (1997) Investigation of the relationship between chemical structure and anti-HIV-1 activity in a class of nucleoside analogues: Electron topological approach. *Curr Med Chem* 4: 23-34.
10. Saracoglu M, Kandemirli SG, Basaran A, Sayiner H, Kandemirli F (2011) Investigation of structure-activity relationship between chemical structure and CCR5 antiHIV-1 activity in a class of 1-[N-(methyl)-N-(phenylsulfonyl) amino]-2-(phenyl)-4-[4-(substituted) piperidin-1-yl] butanes derivatives: The electronic-topological approach. *Curr HIV Res* 9: 300-312.
11. Kandemirli F, Kovalishyn V, Kandemirli SG (2007) Electron-topological method of the non-nucleoside HIV-1 RT inhibitors study: Structure-activity relationships. *Curr HIV Res* 5: 449-458.
12. Garg R, Gupta SP, Gao H, Babu MS, Debnath AS, et al. (1999) Comparative quantitative structure-activity relationship studies on anti-HIV drugs. *Chem Rev* 99: 3525-3601.
13. Saari WS, Wai JS, Fisher TE, Thomas CM, Hoffman JM, et al. (1992) Synthesis and evaluation of 2-pyridinone derivatives as HIV-1-specific reverse transcriptase inhibitors. 2. Analogues of 3-aAminopyridin-2(1H)-one. *J Med Chem* 35: 3792-3802.
14. Saari WS, Hoffman JM, Wai JS, Fisher TE, Rooney CS, et al. (1991) 2-Pyridinone derivatives: A new class of nonnucleoside, HIV-1- specific reverse transcriptase inhibitors. *J Med Chem* 34: 2922-2925.
15. Dimoglo AS (1985) Compositional approach to electronic structure description of chemical compounds, oriented on computer analysis of structure-activity relationships. *Khim-Pharm Zhurn* 4: 438-444.
16. Shvets NM (1993) Applied program system for the prognosys of biological activity of chemical compounds: Development and use. *Comp Sci J Moldova* 1: 101-110.
17. Shvets NM (1997) The study of data and control flows and the user interface organization in an applied system used in chemistry and medicine for the biological activities prediction. *Comp Sci J Moldova* 3: 301-311.
18. Dimoglo AS, Vlad PF, Shvets NM, Coltsa MN (2001) Structure-ambergris odour relationships investigation in a mixed series of decalin and non-decalin compounds the electronic-topological approach. *New J Chem* 25: 283-288.
19. Dimoglo AS, Shvets NM, Tetko IV, Livingstone DJ (2001) Electronic-topological investigation of the structure-acetylcholinesterase inhibitor activity relationship in the series of n-benzylpiperidine derivatives. *QSAR* 20: 31-45.
20. Kandemirli F, Tokay N, Shvets NM, Dimoglo AS (2003) Electronic-Topological Study of the Structure-Activity Relationships in a Series of Steroids with Mineralocorticoid Binding Affinity. *Arzneimittelforschung* 53: 133-138.
21. Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, et al. (2004) Gaussian Inc, Wallingford, CT.
22. Parr RG, Pearson RG (1983) Absolute hardness: companion parameter to absolute electronegativity. *J Am Chem Soc* 105: 7512-7516.
23. Kaya S, Kaya C, Guo L, Kandemirli F, Tüzün B, et al. (2016) Quantum chemical and molecular dynamics simulation studies on inhibition performances of some thiazole and thiadiazole derivatives against corrosion of iron. *J Mol Liquids* 219: 497-504.
24. Chattaraj PK, Sarkar U, Roy DR (2006) Electrophilicity index. *Chem Rev* 106: 2065-2091. [Crossref]
25. Ebenso EE, Kabanda MM, Arslan T, Saracoglu M, Kandemirli F, et al. (2012) Quantum chemical investigations on quinoline derivatives as effective corrosion inhibitors for mild steel in acidic medium. *Int J Electrochem Sci* 7: 5643-5676.
26. Rank A (2001) Orbital Interaction Theory of Organic Chemistry. (2nd Edn), Wiley & Sons: New York.
27. Pearson R (1993) The principle of maximum hardness. *Acc Chem Res* 26: 250-255.
28. Pearson RG (1986) Absolute electronegativity and hardness correlated with molecular orbital theory. *Proc Natl Acad Sci U S A* 83: 8440-8441. [Crossref]
29. Özalp A, Kökbudak Z, Saracoglu M, Kandemirli F, Ilhan IÖ, et al. (2015) Synthesis and theoretical study of the novel 2-oxopyrimidin-1(2H)-yl-amides derivatives. *Chem Sci Rev Lett* 4: 719-728.
30. IBM (2016) SPSS 200 Manual, USA.