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DRUG LIKNESS FILTERS AND QSAR ANALYSIS OF CAMPHOR-BASED DIIMINES DERIVATIVES AS ANTIVIRAL AGENTS

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ABSTRACT

In the present study, Quantitative structure–activity relationship (QSAR) study has been applied on twenty-five molecules of camphor-based symmetric diimines. A Multiple Linear Regression (MLR) procedure was used to correlate the relationships between molecular descriptors and the biological activity of camphor-based symmetric diimine derivatives. The predictivity of the model was estimated by cross-validation with the leave-one-out method. Our results suggest a QSAR model based on the following descriptors: MW, HE, Pol, MR, MV, HBA, NRB, PSA, μ and E_{total}, for the influenza virus reproduction inhibition to confirm the predictive power of the models. High correlation between experimental and predicted activities was observed, indicating good quality of the QSAR model.

Keywords: Camphor, diimines derivatives, influenza virus, MLR, QSAR.

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1. INTRODUCTION

Influenza is a serious public health problem that results in serious illness in high-risk populations [1,2]. Influenza A virus is a respiratory pathogen that affects human health worldwide [3] .Two forms of drugs have been used for influenza therapy, M2 ion channel inhibitors (amantadine and rimantadine) and NA (neuraminidase) inhibitors (oseltamivir and zanamivir) [4,5] .

The development of new drugs for the treatment of viral infections is one of the most important promising leads in medicinal chemistry. Outbreaks of avian influenza H5N1 (1997–2006) followed by pandemic of ‘swine flu’Ain California/07/09 (H1N1) pdm09.

The recent introduction of avian virus of H7N9 subtype to the human population makes it necessary to revise the problem of searching for and developing novel antivirals [4].

In addition, the presence of specific antivirals also serves as a particular factor resulting in fast emergence of drug-resistant virus strains. These processes lead the screening of viral variants that are capable both of escaping the immune inactivation by neutralizing antibodies and of overcoming the suppressive action of antiviral drugs [5].

Camphor derives naturally from the bark of the Cinnammomum camphora tree, and is a major essential oil in many aromatic plants; camphor may be synthesized, using turpentine as a starting material [5,6] . Camphor has been used medicinally since ancient times in Asia and since the middle ages in Europe. Currently, camphor is used as an antimicrobial, antiviral, and analgesic agent. Camphor is also found in many cosmetics. Moreover, camphor derivatives exhibit several biological activities. Camphor derivatives of various types may be useful both from the viewpoint of their practical application and as key intermediates in fine organic synthesis, including enantioselective transformations. The significance of camphor is also determined by the fact that it is a natural renewable substance. Amino camphor derivatives were found to be effective inhibitors of M2 ion channels of influenza A [7]. The new imino-derivatives of camphor demonstrate high antiviral activity together with low toxicity [8].

Drug-likeness is a qualitative concept used in drug design, which is estimated from the molecular structure before the substance is even synthesized or after synthesis. The theoretical

calculation of certain properties of a molecule can inform the parameters necessary to demonstrate a certain biological activity. Lipinski's rule of five (ROF) is a rule of thumb to evaluate drug-likeness with a certain pharmacological or biological activity that would make it a likely orally active drug in humans [9,10].

QSAR study is indubitably of great importance in modern chemistry and biochemistry [11,12]. It is a mathematical model that was used to evaluate the toxicity of a compound from its physiochemical properties of electronic structures. To obtain a significant correlation, it is essential that appropriate descriptors are employed, whether they are theoretical or empirical [13,14].

The process of drug development is time-consuming and cost-intensive. Several years are required for led identification, optimization [15-17], in vitro [18-29] and in vivo [30-34] testing before starting the first clinical trials [35].

Multiple linear regressions (MLR) is a mathematical tool that quantifies the relationship between a dependent variable and one or more independent variables, it was used to develop QSAR models [36,37] and all the variables that have been included in the model are significant [38].

Our present research aimed to describe the structure-activity relationships study on camphor-based symmetric diimines derivatives and developed a QSAR model on these compounds.

2. MATERIAL AND METHODS

2.1. Biological Data

The activity parameter as evaluated in California/07/09 (H1N1) pdm09, sensitive cell line was used: A= ED50compound, µM [39,40].

A represent concentration of drug effective in inhibiting the cell-growth rate by 50% (ED50), dose-response curves were thus produced and used to determine this concentration [41].

Sokolova et al transformed the values of biological parameter to logarithmic scale; the inverse values of ED50 (pED50) were used to obtain higher values for the more active compounds [39].

2.2. Descriptors Generation

Firstly, the twenty-five investigated molecules were pre-optimized by means of the Molecular Mechanics Force Field (MM+) included in HyperChem release 8.08 [42]. After that, the resulted minimized structures were further refined using the semi empirical PM3 Hamiltonian implemented also in HyperChem. We chose a gradient norm limit of 0.01 kcal/Å for the geometry optimization. Then, these structures were re-optimized by using Gaussian 09 program package [43], with DFT/B3LYP/6- 311G+ (d, p), this theory was used to calculate a number of electronic descriptors: total energy (Et), dipole moment (μ), energy of frontier orbital's, EHOMO and ELUMO.

The QSAR properties module from HyperChem 8.08 was used to calculate: molar polarizability (Pol), the molar refractivity (MR), partition coefficient octanol/water (log P), hydration energy (HE), molecular volume (MV), Surface area grid (SAG), and molecular weight (MW) [44-47].

Molinspiration, web based software was used to obtain parameter such as PSA (polar surface area), NRB (number of rotatable bonds), HBA, HBD and drug likeness [48].

2.3. Regression Analysis

Multiple linear regression analysis of molecular descriptors was carried out using the stepwise strategy in SPSS version 19 for Windows [49].

3. RESULTS AND DISCUSSION

3.1. Equilibrium geometry and electrostatic

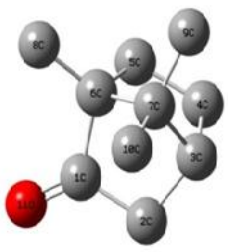


Fig.1. 3D structure of camphor

Table 1. Bond lengths and valence angles of Camphor

Comp.	Exp.[50]	Ab-initio/HF			DFT/ B3LYP		
		6-311G+ (d,p)	6- 311G (d)	6-311G	6-311G+(d,p)	6- 311G (d)	6- 311G
Bond length (angstrom)							
C1-C2	1.511	1.527	1.528	1.517	1.535	1.537	1.532
C1-C6	1.525	1.526	1.526	1.519	1.534	1.536	1.532
C1-O11	1.180	1.185	1.184	1.214	1.207	1.205	1.235
C2-C3	1.564	1.538	1.538	1.540	1.542	1.541	1.548
C3-C4	1.532	1.540	1.540	1.544	1.547	1.546	1.554
C3-C7	1.590	1.556	1.556	1.562	1.566	1.566	1.574
C4-C5	1.554	1.554	1.553	1.554	1.559	1.558	1.563
C5-C6	1.551	1.557	1.556	1.562	1.567	1.566	1.575
C6-C7	1.580	1.562	1.561	1.568	1.573	1.572	1.582
C6-C8	1.536	1.517	1.516	1.515	1.517	1.515	1.518
C7-C9	1.517	1.534	1.533	1.534	1.536	1.535	1.539
C7-C10	1.516	1.538	1.537	1.538	1.539	1.539	1.542
Valence angle (degree)							
C2-C1-C6	106.000	106.681	106.584	107.406	106.533	106.382	107.129
C2-C1-O11	126.000	126.285	126.417	126.039	126.484	126.694	126.322
C6-C1-O11	128.000	127.032	126.998	126.550	126.979	126.921	126.540
C1-C2-C3	104.000	101.708	101.747	101.633	101.962	101.996	101.872
C2-C3-C4	108.000	106.564	106.515	106.484	106.574	106.551	106.562
C2-C3-C7	099.000	102.614	102.617	102.484	102.661	102.684	102.569
C4-C3-C7	104.000	102.833	102.794	102.734	102.749	102.714	102.639
C3-C4-C5	103.000	102.668	102.686	102.809	102.738	102.769	102.900
C4-C5-C6	105.000	104.315	104.304	104.288	104.448	104.429	104.377
C1-C6-C5	102.000	103.184	103.243	103.225	102.931	102.996	103.086
C1-C6-C7	100.000	100.311	100.389	100.219	100.475	100.544	100.399
C1-C6-C8	112.000	114.256	114.076	114.545	114.537	114.205	114.684
C5-C6-C7	103.000	102.191	102.167	101.974	101.924	101.940	101.723
C5-C6-C8	117.000	114.892	114.908	114.975	114.993	115.036	115.059
C7-C6-C8	119.000	119.658	119.726	119.520	119.571	119.730	119.472
C3-C7-C6	093.000	093.846	093.875	093.683	093.813	093.825	093.654
C3-C7-C9	114.000	113.716	113.676	113.732	113.656	113.622	113.680
C3-C7-C10	109.000	113.876	113.852	113.771	114.114	114.059	113.974
C6-C7-C9	115.000	114.581	114.622	114.501	114.269	114.363	114.219
C6-C7-C10	112.000	113.693	113.619	113.500	113.368	113.391	113.2632
C9-C7-C10	112.000	107.083	107.066	107.438	107.414	107.386	107.768

The optimized geometrical parameters of camphor (Fig.1) were obtained using ab initio/HF and DFT/B3lYP methods with 6-311G+ (d,p), 6- 311G (d) and 6-311G basis, listed in Table 1

with the experimental results [50] which are approximately similar to the theoretical results, regarding bond length and valence angle values. We also note that the DFT/B3LYP method with 6-311G+ (d,p) base is more appropriate for further study on camphor (Table 1).

The molecular electrostatic potential surface MESP is a piece of electrostatic potential mapped onto the iso-electron density surface [51], the importance of the MESP lies in the fact that at the same time it shows the molecular size and form whether positive, negative and neutral electrostatic potential areas in terms of the electrostatic surface, which illustrate the investigation of the molecular structure with its physicochemical properties [52-54].

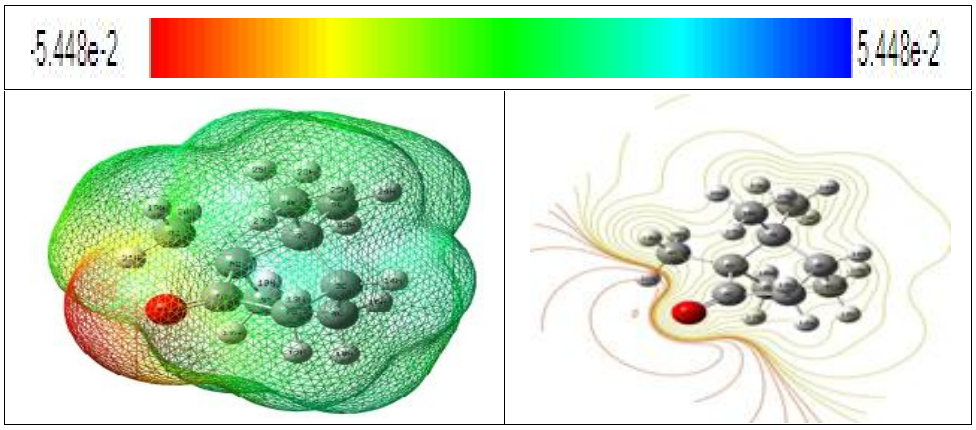


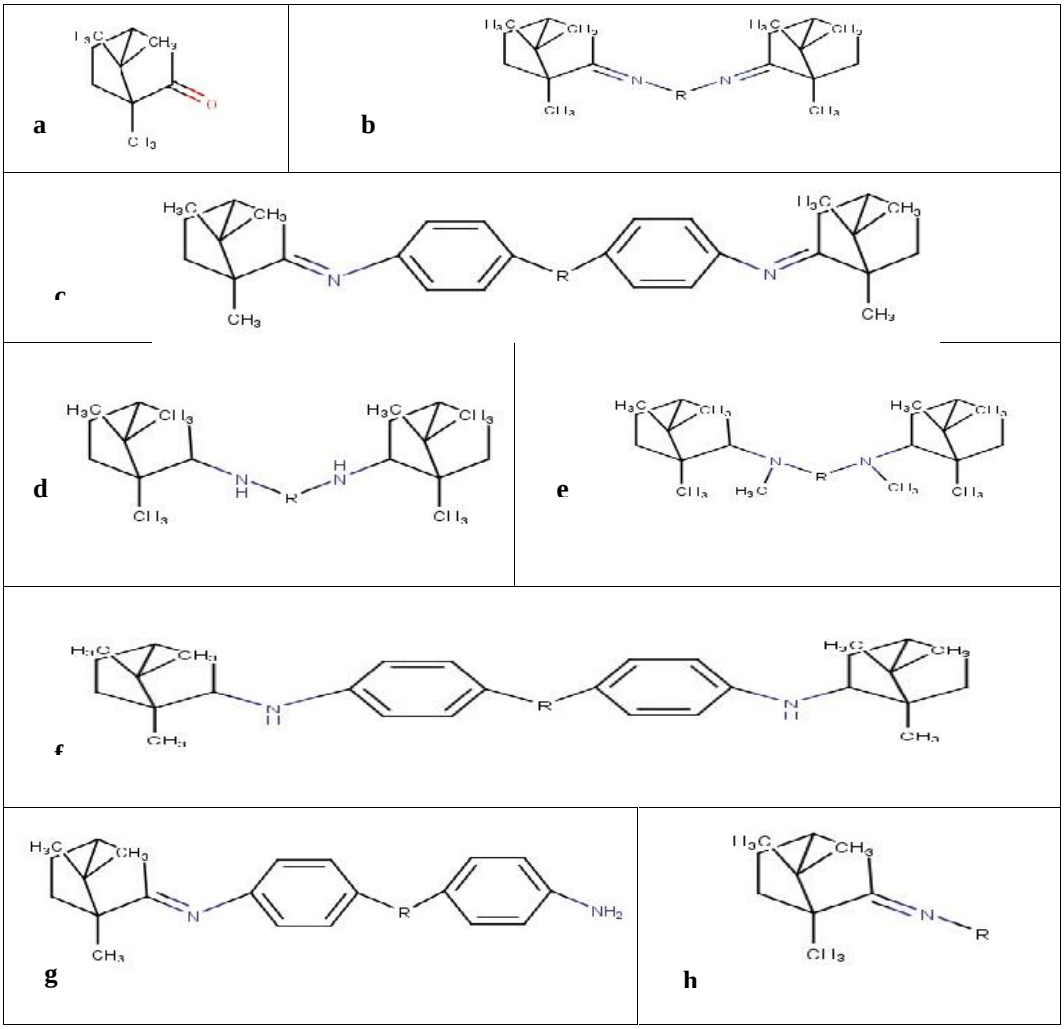
Fig.2. 3D MESP surface map and 2D MESP contour map for Camphor

3.2. Structure activity relationship (SAR)

3.2.1. Drug likeness filters of camphor-based symmetric diimines Derivatives

In this part, we have applied rules of thumb on twenty-five derivatives of camphor-based symmetric diimines with respect to their antiviral activity [33, 34] (Fig.3 and Table 2).

The properties involved are: partition coefficient octanol/water (logP), molecular weight (MW), hydrogen bond donors (HBD), hydrogen bond acceptors (HBA), number of rotatable bonds (NRB), polar surface area (PSA). The results using HyperChem 8.0.8 and MarvinSketch6.8.31 [55] and Molinspiration online database [42], are shown in Table 3.



These structures were designed by MarvinSketch 15.8.31 software[55]

Fig.3. 2D structures of camphor-based symmetric diimines derivatives

The empirical conditions to satisfy Lipinski's rule and manifest a good oral bioavailability involve a balance between the aqueous solubility of a compound and its ability to diffuse passively through the different biological barriers [56,57]. These parameters allow ascertaining oral absorption or membrane permeability that occurs when the evaluated molecule follows Lipinski's rule of five since molecular weight (MW) ≤ 500 Da, an octanol water partition coefficient log P ≤ 5, H-bond donors, nitrogen or oxygen atoms with one or more hydrogen atoms (HBD) ≤ 5 and H-bond acceptors, nitrogen or oxygen atoms (HBA) ≤ 10 [58].

For an ideal oral bioavailability, there are two other descriptors identified by Veber et al [59].

(1) Rotatable bonds are under 10.

(2) Polar surface area is under 140 $Å^2$.

Table 2.Chemical structures, experimental and predicted activities of the studied molecules

N°	R	pED_{50}exp.[39,40]	pED_{50}pred.	pED_{50}resid.
1a	/	-3.216	-3.345	0.129
2b	C_6H_{12}	-1.179	-1.019	-0.160
3b	C_8H_{16}	-1.384	-1.136	-0.248
4b	$C_{12}H_{24}$	-1.653	-1.540	-0.113
5c	CH_2	-2.545	-2.512	-0.034
6c	O	-2.572	-2.914	0.342
7d	C_6H_{12}	0.113	0.021	0.092
8d	C_7H_{14}	-0.506	-0.733	0.228
9d	$C_{12}H_{24}$	-0.643	-0.832	0.189
10e	CH_2	-3.022	-2.797	-0.225
11e	O	-2.317	-2.291	-0.026
12f	C_6H_{12}	-2.041	-2.131	0.089
13f	C_7H_{14}	-1.607	-1.505	-0.102
14g	CH_2	-1.176	-1.433	0.257
15g	O	-0.623	-0.321	-0.302
16h	C_3H_7	-1.294	-1.200	-0.094
17h	C_4H_9	-0.886	-1.263	0.376
18h	C_5H_{11}	-0.886	-0.924	0.038
19h	C_6H_{13}	-1.414	-1.312	-0.103
20h	C_8H_{17}	-1.810	-1.861	0.051
21h	$C_{10}H_{21}$	-1.235	-1.357	0.122
22h	$C_{12}H_{25}$	-1.195	-1.150	-0.046
23h	$C_{18}H_{37}$	-2.871	-2.774	-0.098
24h	cyclopropyl	-2.772	-2.227	-0.545
25h	cyclohexyl	-1.743	-1.927	0.184

The rules are based on a strong physicochemical rationale. Hydrogen bonds increase solubility in water and help the water soluble of low molecular weight to pass through the aqueous pores of biological membranes with molecules passive diffusion [60].

Table 3 shows that all the studied derivatives are compatible with Lipinski rules. Molecular weight (MW) is related to the size of the molecule, with its increasing, a larger cavity should be formed in water to solubilize the compound [61]. We have all series compounds of camphor derivatives with molecular weights less than 500 Da, so they are probably soluble and easily pass through cell membranes.

Log P is used to predict the solubility of oral drug; this is done by partitioning the molecule

between water and the hydrophobic solvent n-octanol, and determining the log P value as the ratio of the concentration of the compound in n-octanol and to that in water [62].

The number of rotatable bonds (NRB) was defined as any single bond, not in a ring, bound to a heavy atom (non-hydrogen). Excluded from the count the amide bonds (C–N), because of their high rotational energy barrier [59]. The low number of rotatable bonds (reduced flexibility) in the studied series indicates that these ligands upon binding to a protein change their conformation only slightly. On the other hand, the polar surface area (PSA) is formed by polar atoms of a molecule.

It is a descriptor that shows good correlation with passive good oral bioavailability and an optimal biological activity [63].Molecules with PSA values of 140 Å2 or more are expected to exhibit poor intestinal absorption[64], PSA Values of camphor-based symmetric diimines are below the 140 $Å^2$ belong to the compounds with reduced absorption (Table 3).

Table 3. Pharmacological activities and properties involved in MPO methods for camphor camphor-based symmetric diimines derivatives

Comp.	MW (a.m.u)	log *p*	HBD	HBA	Lipinski score of 4	NRB	PSA
1a	152.24	2.95	0	1	4	0	17.07
2b	384.65	7.85	0	2	3	7	24.73
3b	412.70	8.65	0	2	3	9	24.73
4b	468.81	10.23	0	2	3	13	24.73
5c	480.74	7.52	0	2	3	4	24.73
6c	468.68	5.62	0	3	3	4	33.96
7d	388.68	6.08	2	2	3	9	24.05
8d	402.71	6.48	2	2	3	10	24.05
9d	472.84	8.46	2	2	3	15	24.05
10f	470.74	5.36	2	2	3	6	24.05
11f	472.71	3.85	2	3	4	6	33.29
12e	416.73	6.81	0	2	3	9	6.48
13e	430.76	7.20	0	2	3	10	6.48
14g	332.49	3.14	2	2	4	3	38.39
15g	334.46	1.64	2	3	4	3	47.62
16h	193.33	4.18	0	1	4	2	12.36
17h	207.36	4.57	0	1	4	3	12.36
18h	221.39	4.97	0	1	4	4	12.36
19h	235.41	5.37	0	1	3	5	12.36
20h	263.47	6.16	0	1	3	7	12.36
21h	291.52	6.95	0	1	3	9	12.36
22h	319.57	7.75	0	1	3	11	12.36
23h	403.74	10.12	0	1	3	17	12.36
24h	191.32	3.76	0	1	4	1	12.36
25h	233.40	4.95	0	1	4	1	12.36

3.2.2. Structure Activity/Property Relationship for camphor-based symmetric diimines derivatives

In the first part of our studies, we have studied seven physical chemical proprieties of series of twenty five camphor-based symmetric diimines derivatives using HyperChem software (Tables 3 and 4).QSAR proprieties such as: MV, log P, MR, Pol, HE, MV and MW were investigated. The properties involved are: dipole moment (μ), Energy of frontier orbital's E_{HOMO} and E_{LUMO} and total Energy (Et)

Molecular polarizability of a molecule characterizes the capability of its electronic system to be distorted by the external field, and it plays an important role in modeling many molecular properties and biological activities [65,67]. The molar refractivity (MR) is important criterion to measure the steric factor. It is usually designated as a simple measure of the volume occupied either by an individual atom or a cluster (group) of atoms [68].

From the results obtained in Tables4, we observe that polarizability data are generally proportional to refractivity, molecular volume and molecular weight. This explains the accordance of our results with Lorentz- Lorenz expression [69, 70] for example, the compound 5c has great values of polarizability (59,24 Å3) and molar refractivity (158,83 Å3). In contrast, the compound 1a is the small molecule in the series of studied camphor-based symmetric diimines, which has a small value of polarizability (17,66 Å3), and of molar refractivity (44,49 Å3).Compound 23h indicates the maximum absolute value of hydration energy (8,84Kcal/mol). Regarding to compound 10f, it shows the minimum absolute value (0,07Kcal/mol). In fact, hydrophobic molecule of camphor-based symmetric diimines derivatives leads to the decrease of the hydration energy.

We noticed that the compound 23hdoes not have HBD (number of hydrogen bond donors) and he has one HBA (Number of hydrogen bond acceptors) lead to the increase of the hydration energy. For good oral bioavailability, the log P must be greater than zero and less than three ($0 < \log P < 3$). A drug with higher log P has low solubility whereas drugs with lower log P have difficulty in penetrating the lipid membranes [71].

The results obtained by calculating of logP of camphor-based symmetric diimines derivatives, show that compounds 1a and 15g have optimal values ($0 < \log P < 3$) which explain the good

oral bioavailability for these compounds.

On the other hand, a positive value for log P indicates that the compound is too lipophilic. So it has a good permeability through biological membrane, a better binding to plasma proteins, elimination by metabolism but a poor solubility and gastric tolerance [72,73].

Table 4. Values of quantum and physicochemical descriptors used in the regression analysis

N°	LogP	MR ($Å^3$)	MV ($Å^3$)	HE (kcal/mol)	Pol ($Å^3$)	SAG ($Å^2$)	E_t (a.u)	μ(D)	E_{HOMO} (a.u)	E_{LUMO} (a.u)
1a	2.95	44.49	520.82	1.38	17.66	325.87	-466.0434	3.3901	-0.24672	-0.3330
2b	7.85	119.63	1145.34	3.61	47.26	597.86	-1127.0195	3.1129	-0.22248	-0.00481
3b	8.65	128.84	1361.59	5.46	50.93	761.97	-1205.6634	3.4493	-0.22461	-0.01169
4b	10.23	147.24	1594.79	7.34	58.27	892.23	-1362.9688	3.2654	-0.22547	-0.01161
5c	7.52	158.83	1411.81	2.21	59.24	745.24	-1431.8980	3.9153	-0.20408	-0.03771
6c	5.62	152.07	1400.15	-0.87	56.20	772.48	-1428.5438	5.3524	-0.20224	-0.03199
7d	6.08	120.23	1292.86	3.68	48.09	728.52	-1129.4523	1.3787	-0.21900	-0.00380
8d	6.48	124.84	1291.63	3.41	49.93	704.84	-1168.7645	1.5065	-0.21941	-0.00717
9d	8.46	147.84	1565.27	5.21	59.10	857.02	-1365.3837	0.8267	-0.21812	-0.00397
10f	5.36	154.83	1414.52	-0.07	58.24	766.28	-1395.0397	2.2760	-0.19925	-0.02162
11f	3.85	152.67	1410.50	-2.93	57.4	773.91	-1430.9595	2.9314	-0.19318	-0.01778
12e	6.81	130.82	1263.88	5.28	51.76	653.03	-1208.0319	0.9786	-0.20508	-0.00453
13e	7.20	135.42	1355.26	5.89	53.60	712.27	-1247.3559	0.1475	-0.20552	-0.00588
14g	3.14	112.70	1036.89	-5.82	41.02	591.82	-1003.0586	2.5446	-0.20173	-0.02558
15g	1.64	110.54	1031.80	-8.51	39.82	601.09	-1038.9743	2.8630	-0.20159	-0.02644
16h	4.18	60.72	707.14	3.26	24.01	423.86	-564.12522	1.8748	-0.23452	-0.00956
17h	4.57	65.32	745.97	3.46	25.85	447.34	-603.43840	2.0333	-0.22634	-0.01253
18h	4.97	69.92	808.23	4.08	27.68	486.34	-642.77271	1.8544	-0.23395	-0.00929
19h	5.37	74.52	851.61	4.24	29.52	511.13	-682.08766	2.0908	-0.22562	-0.01404
20h	6.16	83.72	958.13	4.95	33.19	563.87	-760.73330	2.0169	-0.22591	-0.01227
21h	6.95	92.93	1067.49	5.71	36.86	643.09	-839.38229	2.0864	-0.22546	-0.01406
22h	7.75	102.13	1184.59	6.65	42.53	699.09	-918.03843	1.9134	-0.23350	-0.00896
23h	10.12	129.73	1506.49	8.84	51.54	880.66	-1153.9803	1.9125	-0.23348	-0.00889
24h	3.76	58.66	659.05	2.37	23.24	394.82	-562.8666	2.1336	-0.21890	-0.01824
25h	4.95	72.46	790.66	3.33	28.75	456.39	-680.8882	1.7928	-0.22906	-0.01035

E_t, μ ,E_{HOMO} and E_{LUMO} calculated by DFT/B3LYP /6-311G+(d,p) (Gaussian 09)

3.3. Quantitative Structure-Activity Relationships Studies (QSAR)

In the present study, twenty-five derivatives of camphor-based symmetric diimines were evaluated for their inhibitory activities of viral (Influenza virus) inhibitors (Table 2 and Fig.3).

In order to determine the role of structural features, we use QSAR studies, these compounds were used for multiple linear regressions (MLR) model generation. Different physicochemical descriptors such as steric, electronic and molecular structure were used as independent variables and were correlated with biological activity [74,76].

Developing a QSAR model requires a diverse set of data, and, thereby a large number of descriptors have to be considered. Descriptors are numerical values that encode different structural features of the molecules. Selection of a set of appropriate descriptors from a large number of them requires a method, which is able to discriminate between the parameters. Pearson's correlation matrix has been performed on all descriptors by using SPSS statistics 19 Software. The analysis of the matrix revealed ten descriptors for the development of MLR model. The values of descriptors selected for MLR model is presented in Table 5. The correlation between the biological activity (A) and descriptors expressed by the following relation:

$$\mathbf{pED50 = -3.081 - 0.051\,MW - 0.054\,MV + 1.063\,HE + 0.344MR + 0.397\,Pol + 0.253\,PSA + 3.785\,HBA - 0.109\,NRB + 0.035\,Et - 1.275\,\mu}$$

n = 25; r = 0.970;r^2=0.940; s = 0.277; F = 22.053; Q=4.273

where, "n" is the number of compounds, "r" is the correlation coefficient, "r^2" is the squared correlation coefficient, S is the standard error of estimate and F – Fischer statistics.

The values of fraction variance may vary between 0 and 1.

QSAR model having $r^2 > 0.6$ will only be considered for validation. For example, the value r = 0.970and r^2 = 0.940 allowed us to indicate firmly the correlation between different parameters (independent variables) with pED_{50} of the compounds. The F-value has found to be statistically significant at 95% level, since the calculated F value is higher as compared to tabulated value. The positive value of quality factor (Q) for this QSAR model suggests its high predictive power and lack of over fitting.

In the equation of $pED_{50}$the negative coefficients of MW, NRB, MV and μ explain that any

increase in molecular weight, number of rotatable bonds, molecular volume or dipole moment of the compounds cause a decrease in the biological activity.

Also the positive coefficient of HE indicates that any increase in hydration energy causes an increase in biological activity. From this parameter it may be concluded that hydrophilic molecules are more important for Influenza virus.

In order to test the validity of the predictive power of selected MLR model (eq.pED_{50}), the leave-one-out technique (LOO technique) was used. The developed model was validated by calculation of the following statistical parameters: predicted residual sum of squares (PRESS), total sum of squares deviation (SSY) and cross-validated correlation coefficient (r^2_{adj}) (Table 5).

PRESS is an important cross-validation parameter as it is a good approximation of the real predictive error of the model. Its value being less than SSY points out that model predicts better than chance and can be considered statically significant. The smaller PRESS value means the better of the model predictability. From the results depicted in Table 5, the model is statistically significant. Also, for reasonable QSAR model, the PREES/SSY ratio should be lower than 0.4 [77].The data presented in Table 5 indicate that for the developed model this ratio is 0.060. Our result of r^2_{cv} for this QSAR model has been to be 0.940. The high value of r^2_{cv} and r^2adj are essential criteria for the best qualification of the QSAR model.

The predictive error of the coefficient of correlation PE is yet another parameter used to evaluate the predictive power of the proposed model [78]. We have calculated the PE value of the proposed model and this is reported in Table 5. It is argued that if

If $r < PE$, then correlation is not significant;

if $r > PE$, several times (at least three times), then correlation is indicated;

if $r > 6$ PE, then the correlation is definitely good.

For the model developed the condition $r > 6$ PE is satisfied and hence it can be said to have a good predictive power.

However, the only way to estimate the true predictive power of developed model is to predict the by calculation of pED_{50} values of the investigated camphor-based symmetric diimines derivatives using this model (Fig.3 and table 2).

Table 5. Cross-validation parameters

Model	PRESS	SSY	PRESS/SSY	S_{PRESS}	r^2_{cv}	r^2_{adj}	PE	6PE
1	1.079	18,083	0.060	0.208	0.940	0.898	0.008	0.048

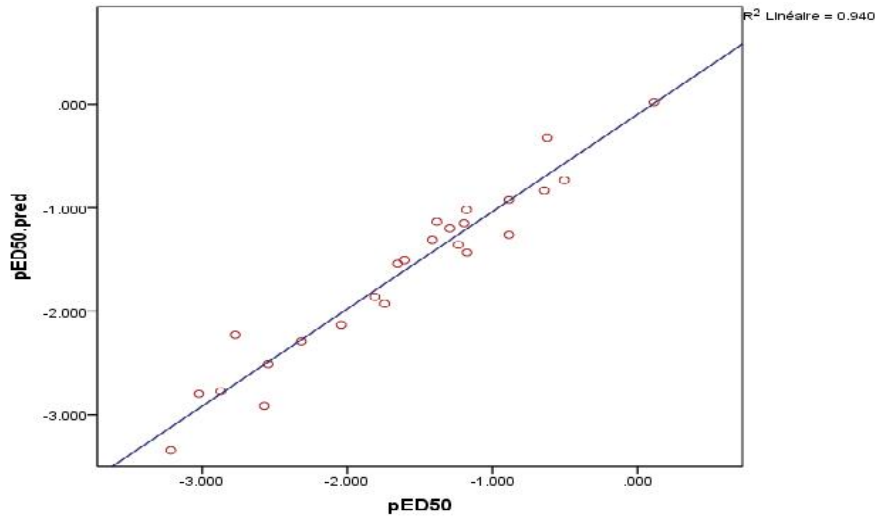


Fig.3. Predicted plot versus experimental observed $pED_{50}$of camphor-based diimines

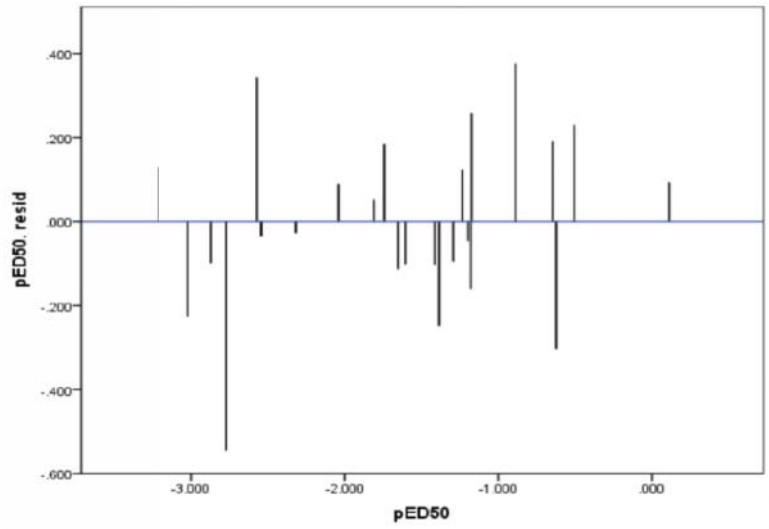


Fig.4. Plot of the residual values against the experimentally observed pED_{50}

Figure 3 shows the plots of linear regression predicted versus experimental value of the biological activity of camphor-based symmetric diimines derivatives outlined above. The

plots for this model show to be more convenient with $r^2 = 0.940$. It indicates that the model can be successfully applied to predict the antiviral activities of these compounds.

To investigate the presence of a systematic error in developing the QSAR model, the residuals of predicted values of the biological activity pED_{50} were plotted against the experimental values, as shows in Fig.4.The propagation of the residuals on both sides of zero indicates that no systemic error exists [79], as suggested by Jalali-Heravi and Kyani [80].

4. CONCLUSION

In the present work, the application of Lipinski rules and Veber rules on the studied camphor-based symmetric diimines derivatives shows that most of these compounds, theoretically, will not have problems with oral bioavailability.

QSAR study of the camphor-based symmetric diimines derivatives has been performed. A significant regression equation was obtained by the MLR method with respect to their experimental biological activities. The best equation of regression was obtained contains these descriptors: MW, HE, MR, MV, Pol, PSA, HBA, NRB, E and µ. QSAR model indicates that these descriptors have significant relationships with observed bioactivities.

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