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Computational Chemistry Calculation on Stavudine (D4T) and Its Derivatives Activity to predict a new compound with best drug potency

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ABSTRACT

Activity of stavudine and its derivatives as an anti-HIV drug were quantitatively analyzed in terms of molecular structure properties and topological Properties (Log s, Connolly Accessible Area, k_{Pgas}, Sum of Degrees, Sum of Valence Degrees and Shape Attribute). by regression analysis using GAMESS software, approximation quantum mechanical PM3 method and then a model quantitative structure activity relationships (QSARs) is obtained for each parameter from physicochemical properties in a general equation:-

Log $1/ic_{50}$ = -13.99562 + 0.008565888 (logs) + 0.00213801 (Connolly Accessible Area) + 0.806128614 (Henry's Law Constant) + 0.158223372(Sum of Valence Degrees) - 0.2776682 (Sum of Degrees) + 0.339053908 (Shape Attribute)

Keywords: QSARs, PM3, topological properties, GAMESS and HIV

INTRODUCTION

D4T (stavudine, Zerit) is an anti-HIV drug that reduces the amount of virus in the body. Anti-HIV drugs such as d4T slow down or prevent damage to the immune system, and reduce the risk developing AIDS-related illnesses. Stavudine belongs to a class of drugs known as nucleoside reverse transcriptase inhibitors (NRTIs). [1-3]

In May 1996, D4T was approved as a treatment for HIV in patients who had experienced failure of AZT (zidovudine, *Retrovir*) treatment or intolerance to AZT. It was approved in United States in 1994. In August 1997, it received full approval as an initial therapy for the treatment of HIV-infected adults and children over three months of age with progressive or advanced immune deficiency, when used in combination with other anti-HIV drugs. However, d4T has fallen out of favour as a drug for use in first-line therapy due to the increased risk of body fat side-effects. In June 2003, the British HIV Association recommended against the use of d4T in an initial anti-HIV drug regimen. In 2009, the World Health Organization recommended against the use of d4T because of its long-term, irreversible side effects [4, 5].

Mechanism of action

It belongs to Reverse-transcriptase inhibitors(RTIs) that inhibit activity of reverse transcriptase, a viral DNA polymerase that is required for replication of HIV and other retroviruses. Stavudine (D4T) is a pyrimidine nucleoside analogue that has significant activity against HIV-1 after intracellular conversion of the drug to a D4T-triphosphate, it differs in structure from thymidine by the replacement of the 3′-hydroxyl group with a hydrogen atom and a double bond in the 2′, 3′-posit ions on the deoxyribose ring, it decreases p24 antigen and raised CD4 cell counts. D4T is beneficial for patients where CD4 cell counts do not decrease less than 300 cells /mm^3 with ZDV and ddI. It is more effective than ZDV or ddC in treating patients by delaying the progression of HIV infection [6].

Quantitative Structure Activity Relation-Ships (QSARs):
QSARs represent predictive models derived from application of statistical tools correlating activity of chemicals with descriptors representative of molecular structure and/or properties. QSARs are being applied in many disciplines for example risk assessment, toxicity prediction, and regulatory decisions [7] also to drug discovery [8]

QSARs also a classification models used in the chemical and biological sciences relate a set of variables (X) to the activity of the properties variable (Y),.In QSAR modeling, the predictors consist of physicochemical properties or theoretical molecular geometric of chemical molecules; the QSAR response-variable could be activity of the chemical agents. QSAR models first summarize a supposed relationship between chemical structures and activity in a data-set of chemicals. Second, predict the activities of new chemicals [9]. QSAR has the form of a mathematical model:

Activity= f (physicochemical properties and or structural properties)+ constant [10] **.....1**

This work employs conventional PM3 calculation to introduce a system investigation for d4T and its new noval analogs.

MATERIALS AND METHODS

1-Computational Methods
A series of Stavudine derivatives tested for HIV activity were selected for the present study and the program of Windows Chem SW was adopted for molecular modeling studies. The molecules were generated and energy minimization was carried out by using Molecular Modeling Program, all calculations are carried out by General Atomic and Molecular Electronic Structure System (GAMESS) software [11], using approximation quantum mechanical Parameterized Model number 3 (PM3) methods[12]. After minimized energy, physicochemical properties were calculated for all studied molecules and the results are shown in table -I.

Selected Stavudine derivatives [13]**:**
A: tert-butyl (2S)-2-[[[(2S, 5R)-5-(5-methyl-2,4-dioxopyrimidin-1-yl)-2,5-dihydrofuran-2-yl] methoxy-phenoxy phosphoryl]amino]propanoate MIC: 0.85 µM
B: pentyl (2S)-2-[[[(2S,5R)-5-(5-methyl-2,4-dioxopyrimidin-1-yl)-2,5-dihydrofuran-2-yl] methoxy-phenoxy phosphoryl]amino]propanoate MIC:0.04 µM
C: 2,2-dimethylpropyl (2S)-2-[[[(2S, 5R)-5-(5-methyl-2,4-dioxopyrimidin-1-yl)-2,5-dihydrofuran-2-yl]methoxy-phenoxy phosphoryl]amino]propanoate MIC: 0.05 µM
D: hexyl (2S)-2-[[[(2S, 5R)-5-(5-methyl-2,4-dioxopyrimidin-1-yl)-2,5-dihydrofuran-2-yl]methoxy-phenoxy phosphoryl]amino]propanoate MIC: 0.06 µM
E: cyclohexyl (2S)-2-[[[(2S, 5R)-5-(5-methyl-2,4-dioxopyrimidin-1-yl)-2,5-dihydrofuran-2-yl]methoxy-phenoxy phosphoryl]amino]propanoate MIC: 0.06 µM
F: phenyl (2S)-2-[[[(2S, 5R)-5-(5-methyl-2,4-dioxopyrimidin-1-yl)-2,5-dihydrofuran-2-yl]methoxy-phenoxy phosphoryl]amino]propanoate MIC: 0.03 µM
G: cyclohexylmethyl (2S)-2-[[[(2S, 5R)-5-(5-methyl-2,4-dioxopyrimidin-1-yl)-2,5-dihydrofuran-2-yl]methoxy-phenoxy phosphoryl]amino]propanoate MIC: 0.04 µM

2-Mathmatical treatments
For each property; select a sharing percent to the activity depending on the slope (S) of properties linearity behavior to activity. By solving set of mathematical equations using *wolfram alpha program Wolframalpha.com, Matrixcalc.org, Google Calculator* to find the final activity equation {Activity = ∫ (properties) +constant}…….2

RESULTS AND DISCUSSION

Using GAMESS software approximation quantum mechanical PM3 method to minimized the total energy of each derivative and optimizes the equilibrium electronic structure of molecules which related to its physical properties, then calculation of molecular structure properties (topological properties) which found that proportionated to their activities ($Log1/ic_{50}$) with R^2 value more than 0.9, the results reported in figure -1

Figure1. Topological Properties of Stavudine derivatives proportionated to their activities (Log1/ic_{50})

Connolly Accessible Area: is the surface area of a biomolecule that is accessible to a solvent [14].
k_{Pgas}: Henry's Law Constant
Log s: Water solubility
Sum of Valence Degrees: the amount of power of an atom which is determined by the number of electrons the atom will be lose, gain or share when it forms compounds [15]
Sum of degrees: twice the number of edges (the number of edges touching the vertex) [16].
Shape attributes: the position and dimensions of the area together [17]
So can be conclude the relation-ship between activities and some molecular structure properties (topological properties), the results calculation were reported in table –I

Table -1 Molecular structure properties of compounds related to its activities

Compound	ic_{50}	$Log1/ic_{50}$	log s y = -6.6921x + 3.4967, R^2 = 0.9416	Connolly Accessible Area y = 0.0021x - 0.2819, R^2 = 0.9066	k_{Pgas} y = -0.1327x + 1.8334, R^2 = 0.9444	Sum of Valence Degrees y = 0.0131x - 0.3741, R^2 = 0.9396	Sum of Degrees y = 0.02x - 0.2296 , R^2 = 0.9098	Shape Attribute y = 0.0431x - 0.158, R^2 = 0.9071
F	0.03	1.5228	-5.70014	781.985	3.062	137.5556	80	35.02703
G	0.04	1.3974	-5.70014	842.365	3.8	133.5556	82	36.02632
B	0.04	1.3974	-6.02566	825.405	3.8	127.5556	76	34.02778
C	0.05	1.30102	-5.30519	777.432	3.8	127.5556	76	34.02778
E	0.06	1.2218	-5.03405	804.294	3.8	131.5556	80	35.02703
D	0.06	1.2218	-5.5792	694.749	3.8	129.5556	78	35.02703
Stavudine	0.36	0.44369	0.898644	369.057	10.551	62	34	14.0625

By applying the values of the calculated properties in QSAR equation -1

The above equation can be written in another expression suggested in this research as:
Activity= $Log1/ic_{50}$ (Y) = $a_o \pm \sum à_i X_i$ 3
Where $\sum$ ai= 1 (unity) ……...4
Xi: molecular structure property
a_i: property sharing factor in activity
a_o: constant
$à_i = a_i$*slope ……....5

$Log1/ic_{50}= a_0 \pm a_1$ * slope (logs) $\pm a_2$ * slope (Connolly Accessible Area) $\pm a_3$ * slope (Henry's Law Constant) $\pm a_4$ * slope (Sum of Valence Degrees) $\pm a_5$ * slope (Sum of Degrees) $\pm a_6$ * (Shape Attribute) ……...6
$Y=a_0 \pm a_1$*slope*$x_1 \pm a_2$*slope*$x_2 \pm a_3$*slope*$x_3 \pm a_4$*slope*$x_4 \pm a_5$*slope*$x_5 \pm a_6$*slope*x_6 ….7

Now there was7 equations with7 unknowns by using mathematical ways (converting them to matrix) and using websites (matrixcalc.org and wolframalpha.com) can be finding the values of a_i and found to be:

a_o= -13.99562, a_1=-0.00128, a_2=1.01810, a_3=-6.07482, a_4=12.07812, a_5=-13.88341, a_6=7.86668 ……..……8

Then can concluding the final equation:
$Log1/ic_{50}$ = -13.99562 + 0.0085659 X_1 + 0.00213801 X_2 + 0.806128614 X_3 + 0.158223372 X_4 - 0.2776682 X_5 + 0.339053908 X_6 ……..……9
Or
Log ($1/ic_{50}$) = -13.99562 + 0.0085659(logs) +0.00213801 (Connolly Accessible Area) + 0.806128614 ($k_{p\ gas}$) + 0.158223372(Sum of Valence Degrees) - 0.2776682 (Sum of Degrees)+0.339053908 (Shape Attribute..10

The solution for the studied derivatives is:
Comp. F: $log1/ic_{50}$=-13.99562+ 0.008566 (-5.70014) +0.00213801 (781.985) +0.806128614 (3.062) +0.158223372 (137.5556)-0.2776682 (80) +0.339053908 (35.02703) = 1.522……11
IC_{50} = 0.02999 µM ……12

Comp. G: log1/ic50= -13.99562 + 0.0085659 (-5.70014) +0.00213801 (842.365) +0.806128614 (3.8) + 0.158223372 (133.5556) - 0.2776682 (82) + 0.339053908 (36.02632) = 1.397516 ….....13 IC_{50} = 0.04004 µM ……14

Comp. B: log1/ic50= -13.99562 + 0.0085659 (-6.02566) +0.00213801 (825.405) + 0.806128614 (3.8) + 0.158223372(127.5556) - 0.2776682 (76) + 0.339053908 (34.02778) = 1.3975235…..15 IC_{50} = 0.04004 µM ……..……..16

Comp. C: log1/ic50= -13.99562 + 0.0085659 (-5.30519) +0.00213801 (777.432) + 0.806128614 (3.8) + 0.158223372(127.5556) - 0.2776682 (76) + 0.339053908 (34.02778) = 1.3011282 ….17 IC_{50} = 0.04999 µM ……18

Comp. E: log1/ic50= -13.99562 + 0.0085659 (-5.03405) +0.00213801 (804.294) + 0.806128614 (3.8) + 0.158223372(131.5556) - 0.2776682 (80) + 0.339053908 (35.02703) = 1.2219023….19 IC_{50} = 0.05999 µM

Comp. D: log1/ic50= -13.99562 + 0.0085659 (-5.5792) +0.00213801 (694.749) + 0.806128614 (3.8) + 0.158223372 (129.5556) - 0.2776682 (78) + 0.339053908 (35.02703) = 1.22191394……..….20 IC_{50} = 0.059991 µM ……..……..21

Stavudine: log1/ic50= -13.99562 0.0085659 (0.898644) +0.002138 (369.057) + 0.806128614 (10.551) + 0.158223372(62) - 0.27767 (34) + 0.339054 (14.0625) = 0.443664092 ……..…..……. 22
IC_{50} = 0.36003 µM ……23

From these results obtained, can be compered between theoretical and practical activity values as in figure -2, it show an excellent linear relation with R^2 and slope of unity.

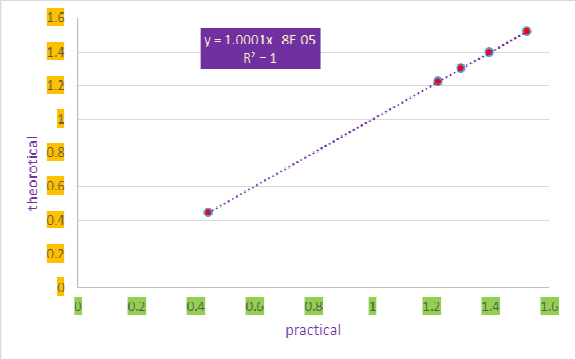


Figure2. Practical activities (Log 1/ic_{50}) as measured and theoretical activities as calculated

Since the statistical parameters obtained for the test set are comparable to those of training set. The obtained results, in agreement with a number of previously reported differently motivated analysis that physicochemical properties of compound are indeed very suitable descriptors for predicting its activity [18].

Another derivative but with unknown activity where found from the final equation can be calculated, the results tabled in table -II

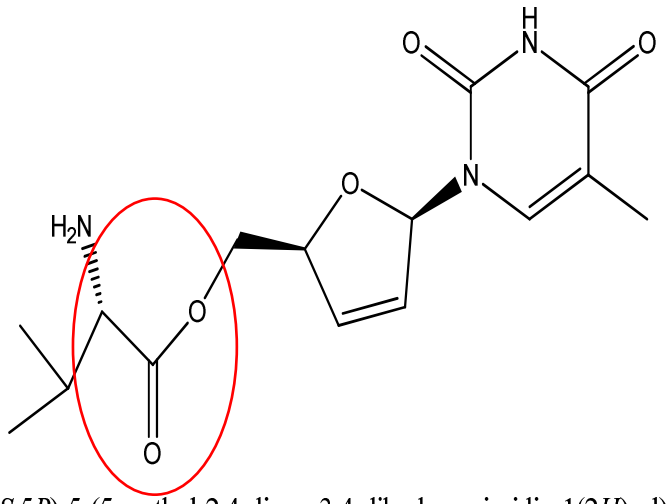
Table II. Molecular structure properties of unknown activities compounds

Compound	log s y = -6.6921x + 3.4967, R^2 = 0.9416	Connolly Accessible Area y = 0.0021x - 0.2819, R^2 = 0.9066	kPgas y = -0.1327x + 1.8334, R^2 = 0.9444	Sum of Valence Degrees y = 0.0131x - 0.3741, R^2 = 0.9396	Sum of Degrees y = 0.02x - 0.2296 , R^2 = 0.9098	Shape Attribute y = 0.0431x - 0.158 , R^2 = 0.9071
Stampidine	-4.68831	616.387	3.077	121.5556	70	31.0303
Ethynyl Stavudine	-1.07884	193.288	10.551	70	38	16.0556

For **Stampidine**:
log1/ic_{50}=-13.99562+0.008566 (-4.68831) +0.002138 (616.387) +0.806129 (3.077) +0.158223372(121.5556)-0.2776682(70) +0.33905391(31.030303) = 0.079621…..23
Ic_{50}= 0.8325 µM ……..……24

For **Ethynyl Stavudine**:
log1/ic_{50}=-13.99562+ 0.008566(-1.07884) +0.002138 (193.288) + 0.806128614 (10.551) +0.158223372(70)-0.2776682(38) +0.33905391 (16.055556)= 0.8817968 ....25 Ic_{50}= 0.1313 µM ……..……26

Now the suggestion of a new compound structure, as a prodrug by substitution of amino acid moiety, was shown in figure-3 to predict its activity.



(*S*)-((2*S*,5*R*)-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2,5-dihydrofuran-2-yl)methyl 2-amino-3-methylbutanoate

Figure3. Structure of suggested compound

Then the calculation of its molecular structure properties using PM3 calculation were found and reported in table - III, then predict its activity according to the predicted general equation.

Table III. Molecular structure properties of suggested compound

Compound	log s y = -6.6921x + 3.4967, R^2 = 0.9416	Connolly Accessible Area y = 440.81x + 192.25, R^2 = 0.9066	kPgas y = -7.1168x + 13.307, R^2 = 0.9444	Sum of Valence Degrees y = 71.734x + 34.167, R^2 = 0.9396	Sum of Degrees y = 45.522x + 16.97, R^2 = 0.9098	Shape Attribute y = 21.065x + 6.2928, R^2 = 0.9071
Sugested	-2.01822	507.88	10.551	84	48	21.04348

$Log1/ic_{50}$=-13.99562+0.008565888 (-2.01822) +0.00213801(507.88) +0.80613 (10.551) + 0.158223372(84)-0.2776682 (48)+0.33905391(21.0434783)=2.676 …..27

Ic_{50}= 0.00211 µM ……28

Consider this new derivative as prodrug by masking its polar OH group so its lipophilicity will increase and its absorption and cellular entrance will increase too, also increase activity, then IC_{50} will be decrease.

CONCLUSION

1- The activity of any stavudine derivative can be found by knowing its structural properties and apply them in the final equation. Also can add or remove moieties to the stavudine structure and form new anti HIV derivative with minimum active concentration and less host toxicity.

2- The suggested equation which used in this research (***Activity= Log1/ic$_{50}$ (Y) = a_o ± ∑ àiXi***) is perfect to predict a new activity.

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