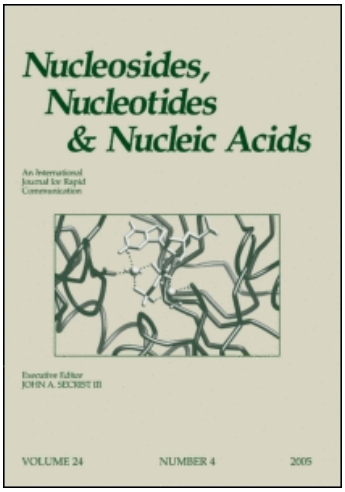



**Nucleosides, Nucleotides and Nucleic Acids**
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

# QSAR Analysis for ADA upon Interaction with a Series of Adenine Derivatives as Inhibitors

A. A. Moosavi-Movahedi[a]; S. Safarian[ab]; G. H. Hakimelahi[c]; G. Ataei[ad]; D. Ajloo[ae]; S. Panjehpour[a]; S. Riahi[f]; M. F. Mousavi[f]; S. Mardanyan[g]; N. Soltani[h]; A. Khalafi-Nezhad[h]; H. Sharghi[h]; H. Moghadamnia[h]; A. A. Saboury[a]
[a] Institute of Biochemistry and Biophysics, University of Tehran, Tehran, Iran [b] Department of Biology, Faculty of Science, University of Tehran, Tehran, Iran [c] Institute of Chemistry, Academia Sinica Taipei, Taipei, Taiwan, ROC [d] Department of Chemistry, Faculty of Paramedical Science, Shahid Beheshti University of Medical Science, Tehran, Iran [e] Department of Chemistry, University of Damghan, Damghan, Iran [f] Department of Chemistry, Faculty of Science, Tarbiat-Modares University, Tehran, Iran [g] H.Ch. Buniatyan Institute of Biochemistry of the Armenia, Yerevan, Armenia [h] Department of Chemistry, Faculty of Science, University of Shiraz, Shiraz, Iran

Online publication date: 03 December 2004

**To cite this Article** Moosavi-Movahedi, A. A. , Safarian, S. , Hakimelahi, G. H. , Ataei, G. , Ajloo, D. , Panjehpour, S. , Riahi, S. , Mousavi, M. F. , Mardanyan, S. , Soltani, N. , Khalafi-Nezhad, A. , Sharghi, H. , Moghadamnia, H. and Saboury, A. A.(2004) 'QSAR Analysis for ADA upon Interaction with a Series of Adenine Derivatives as Inhibitors', Nucleosides, Nucleotides and Nucleic Acids, 23: 3, 613 — 624
**To link to this Article: DOI:** 10.1081/NCN-120030719
**URL:** http://dx.doi.org/10.1081/NCN-120030719

NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS
Vol. 23, No. 3, pp. 613–624, 2004

# QSAR Analysis for ADA upon Interaction with a Series of Adenine Derivatives as Inhibitors

**A. A. Moosavi-Movahedi,[1,*] S. Safarian,[1,2] G. H. Hakimelahi,[3] G. Ataei,[1,4] D. Ajloo,[1,5] S. Panjehpour,[1] S. Riahi,[6] M. F. Mousavi,[6] S. Mardanyan,[7] N. Soltani,[8] A. Khalafi-Nezhad,[8] H. Sharghi,[8] H. Moghadamnia,[4] and A. A. Saboury[1]**

[1]Institute of Biochemistry and Biophysics, and [2]Department of Biology, Faculty of Science, University of Tehran, Tehran, Iran
[3]Institute of Chemistry, Academia Sinica Taipei, Taipei, Taiwan, ROC
[4]Department of Chemistry, Faculty of Paramedical Science, Shahid Beheshti University of Medical Science, Tehran, Iran
[5]Department of Chemistry, University of Damghan, Damghan, Iran
[6]Department of Chemistry, Faculty of Science, Tarbiat-Modares University, Tehran, Iran
[7]H.Ch. Buniatyan Institute of Biochemistry of the Armenia, Yerevan, Armenia
[8]Department of Chemistry, Faculty of Science, University of Shiraz, Shiraz, Iran



## ABSTRACT

The kinetic parameters of adenosine deaminase such as $K_m$ and $K_i$ were determined in the absence and presence of adenine derivatives ($R_1-R_{24}$) in sodium phosphate buffer (50 mM; pH 7.5) solution at 27°C. These kinetic parameters were used for QSAR analysis. As such, we found some theoretical descriptors to which the binding affinity of adenosine deaminase (ADA) towards several adenine nucleosides as inhibitors is correlated. QSAR analysis has revealed that binding affinity of the adenine nucleosides upon interaction with ADA depends on the molecular volume, dipole

*Correspondence: A. A. Moosavi-Movahedi, Institute of Biochemistry and Biophysics, University of Tehran, Tehran, Iran; Fax: +9821-6404680; E-mail: moosavi@ibb.ut.ac.ir.



DOI: 10.1081/NCN-120030719
1525-7770 (Print); 1532-2335 (Online)

moment of the molecule, electric charge around the N1 atom, and the highest of positive charge for the related molecules.

*Key Words:* Adenosine deaminase; Adenine nucleosides; QSAR analysis; Cyclic and acyclic adenosine derivatives.

## INTRODUCTION

Adenosine deaminase (ADA EC 3.5.4.4) is an important enzyme of the purine salvage pathway catalyzes the irreversible hydrolytic deamination of adenosine or deoxyadenosine to their respective inosine product and ammonia. It is present in virtually all mammalian cells and has a central role in maintaining immune competence. Lack of the enzyme is associated with severe combined immunodeficiency disease (SCID) that is a genetically inherited disease fatal to newly born children if not properly diagnosed and treated.[1,2] Higher levels of ADA in the alimentary tract and decidual cells of developing fetal–maternal interface put ADA among those enzyme performing a unique role in the growth rate of cells, embryo implantation, and undetermined functions.[3,4]

Understanding the interaction of ADA with its inhibitors and substrates at the molecular level will be important in the development of the next generation of pharmaceutical agents that act as inhibitors or substrates.[5] Computer simulations can examine these interactions at the molecular level and describe features important for ADA–substrate and ADA–inhibitor recognition.[5–8] For example, molecular dynamics and free energy simulations of coformycin and deoxycoformycin (two potent inhibitors of adenosine deaminase) and their complexes with ADA can be used to obtain structural and dynamic insights into the behavior of these molecules, which help to understand the differences in the strength of binding of these inhibitors.[5] On the other hand, performing the analysis of quantitative structure activity relationship (QSAR analysis as a potent computational method) for several series of drugs, enzymes and biologically active compounds is now well appreciated. The basic assumption of QSAR is that there are some quantitative relationships between the microscopic (molecular structure) and the macroscopic (empirical) properties (particularly biological activity) of a molecule.[9] The term structure does not necessarily mean the spatial arrangement of atoms in a molecule itself, but rather the chemical and physicochemical properties inherent in that arrangement. In fact, the first logic confirming QSAR based predictions is that the physicochemical properties of a chemical compound can be attributed to the molecular structure via the mathematical functions. As such, we can write *molecular properties* = *f*(*structure*). Most of the QSAR studies have frequently used empirical parameters, i.e., lipophilicity (expressed by logarithm of partition coefficient or log P), solubility, cavity surface area (CSA) and Hammetts constant.[10–13] But, it will be quite meaningful to seek the other theoretical parameters, which may replace the common experimental parameters. In the biological world, such empirical parameters may be found through ascertaining some kinetic parameters of the enzymes (such as $K_m$ and $K_i$) to elucidate the amount of enzyme's affinity for binding to the substrate or inhibitor molecules.





MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

Our main objectives in the present study are to find some theoretical descriptors to which the binding affinity of adenosine deaminase (ADA) for attachment of several adenine nucleoside inhibitors is well correlated. Then, it would be possible to determine those molecular characteristics, which are necessary for increasing the binding affinity of the adenine nucleoside molecules to inhibit ADA.

## MATERIALS AND METHODS

### Materials

Adenosine deaminase from calf intestinal mucosa (type IV) and adenosine were obtained from Sigma. Reagents were of analytical grade and buffer solutions were made in double distilled water.



### Methods

#### Enzyme Assay and Kinetic Analysis

Enzymatic activities were assayed on a Shimadzu UV-3100 spectrophotometer by a measuring the rate of ADA-dependent decrease of adenosine absorption was measured at 265 nm at 27°C using an extinction coefficient of 8.4 $mM^{-1}$ $cm^{-1}$. One unit of ADA activity is defined as the amount of enzyme that produces 1 mole of inosine per minute. Cuvettes of 1 cm path length were used. Assays were carried out in 50 mM sodium phosphate buffer, pH 7.5. Activities were measured over at least seven different concentrations of adenosine and the assays were repeated at least three times. Adenosine concentration range is between 0.5 to 3.5 $K_m$. The concentration of enzyme in the assay mixture was 1.0 nM. $K_m$ was determined by Lineweaver–Burk plots with a fourth power weighting function using the enzyme kinetics (Trinity Software) program. For measuring $K_i$ using mixture of substrate and inhibitor prior addition of enzyme. The quantity of $K_i$ was ascertained regarding to the reciprocal plot of the apparent $K_m$ values plotted against the different inhibitor concentrations.[14] $K_i$ or $K_m$ were measured for ADA in the presence of nucleosides $R_2$–$R_{10}$ in our laboratory.

#### Data Set and Computational Methods

Data set was made for the literature selected compounds. This set was divided into two groups, the cyclic and acyclic nucleosides. QSAR analysis was performed on the two cited groups regarding to the following steps: 1) entry of the molecular structures into the adequate software to perform the structural optimization, 2) generation of the molecular descriptors, 3) statistical analysis through the multiple linear regression method (MLR), 4) defining of the model validation. In the first step, molecular structure of each adenosine derivative was constructed in the Hyperchem-5.0 medium and the three-dimensional optimized structure was generated using molecular modeling calculations. The MOPAC-7.0 was also utilized to generate the final three-dimensional coordinates. At the second step, quantum mechanical descriptors were generated using



MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

the MOPAC program. These obtained numerical descriptors encode the structural features (e.g. topological, geometrical, physicochemical and electronic properties) for each adenosine derivatives. For example, geometrical descriptors (which were calculated through the optimized Cartesian as well as van der Waals radii of each participating atom in the molecule) encode valuable information about the three-dimensional features (such as molecular size and shape) for the related molecules. Electronic descriptors are another types of informative descriptors, which contained partial atomic charge, electron density and dipole moment. In the third step, our main goal was checking each descriptor to eliminate those descriptors which had not shown any desirable correlation upper than R = 0.931. This selection of descriptors was performed by MLR method based on the construction of a linear mathematical model regarding to the observed binding affinities of the nucleosides (which has been quantified by the $K_m$ and $K_i$ values) with the numerical descriptors. The final linear equation was formed by stepwise deletion of terms (backward procedure). In the fourth step, model validation was defined through randomly dividing of the data-set into two groups, a training set and a prediction set. The training set was used for model



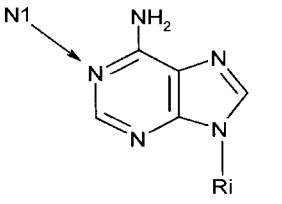
***Table 1.*** Quantitative values for the experimental ($K_m$ and $K_i$) and calculated parameters (molecular volume, *Vol*; electronic charge around the N1 atom, *ECN1*, dipole moment of the molecule, *DIPM*; the highest of positive charge on the molecule, *HPOST*).

| Compound | *log* (*Km* or *Ki*) (μM) | *Vol* | *ECN1* | *DIPM* | *HPOST* | Ref. |
|---|---|---|---|---|---|---|
| R1 | 1.9494 | 708 | −0.2245 | 2.213 | 0.2001 | [22,23] |
| R2 | 1.1139 | 986 | −0.2254 | 5.372 | 0.4112 | [19] |
| R3 | 0.5051 | 1231 | −0.2254 | 7.14 | 0.4381 | [20] |
| R4 | 1.8921 | 754 | −0.2244 | 3.839 | 0.2036 | [18,19] |
| R5 | 1.9395 | 689 | −0.2236 | 3.349 | 0.2057 | [20] |
| R6 | 2.2148 | 704 | −0.2249 | 4.558 | 0.2223 | [18] |
| R7 | 2.2788 | 672 | −0.2249 | 4.337 | 0.1990 | [19] |
| R8 | 0.5051 | 729 | −0.2252 | 1.945 | 0.1861 | [22,23] |
| R9 | 1.3979 | 794 | −0.2240 | 3.930 | 0.2170 | [22,23] |
| R10 | 1.3222 | 711 | −0.2241 | 4.068 | 0.2177 | [22,23] |
| R11 | 1.1139 | 986 | −0.2254 | 5.372 | 0.4112 | [21] |
| R12 | 0.5051 | 1231 | −0.2254 | 7.140 | 0.4381 | [21] |
| R13 | 2.2148 | 704 | −0.2249 | 4.558 | 0.2223 | [20] |
| R14 | 2.2788 | 672 | −0.2249 | 4.337 | 0.1990 | [20] |
| R15 | − 0.7423 | 843 | −0.2233 | 1.487 | 0.2149 | [21] |
| R16 | 2.3424 | 824 | −0.2244 | 1.140 | 1.3189 | [20] |
| R17 | 1.8751 | 896 | −0.2239 | 2.732 | 1.3227 | [20] |
| R18 | 1.6532 | 966 | −0.2242 | 2.320 | 1.3438 | [20] |
| R19 | 2.1139 | 705 | −0.2283 | 1.053 | 0.2378 | [20] |
| R20 | − 0.8539 | 1292 | −0.2226 | 7.378 | 0.4543 | [20] |
| R21 | 1.0792 | 975 | −0.2242 | 5.284 | 0.4130 | [20] |
| R22 | 1.1471 | 706 | −0.2257 | 1.667 | 0.1847 | [20] |
| R23 | 1.5563 | 936 | −0.2254 | 2.661 | 0.4455 | [20] |
| R24 | 2.1461 | 775 | −0.2257 | 2.156 | 0.3941 | [20] |

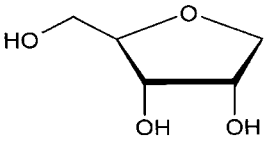
The $R_2$–$R_{10}$ compounds are synthesized in our lab or their kinetic parameters have been ascertained directly by us. Kinetic information of the other compounds is obtained from the literature.



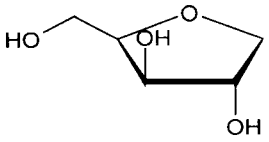
Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016



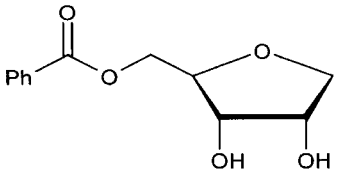

i =1,2,3,…,24



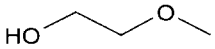

**R1**



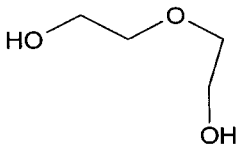

**R2**



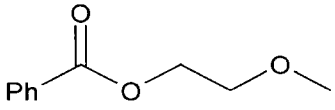

**R3**



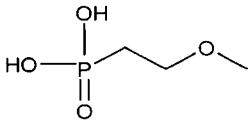

**R4**



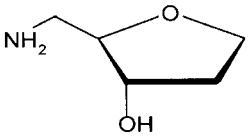

**R5**



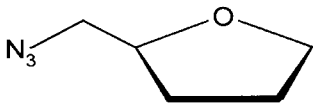

**R6**

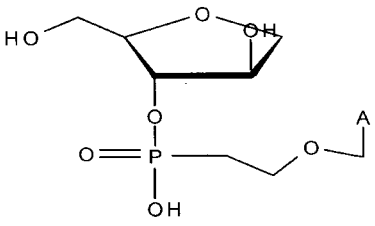



**R7**




**R8**



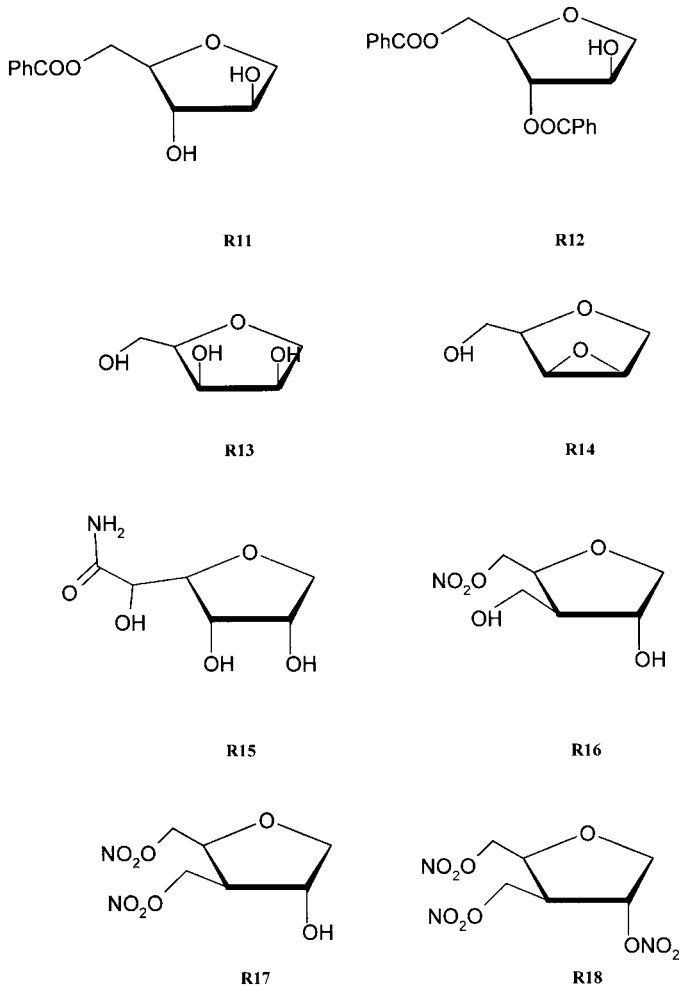

**R9** **R10**

***Scheme 1.*** Molecular structures of adenine derivatives.





MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016



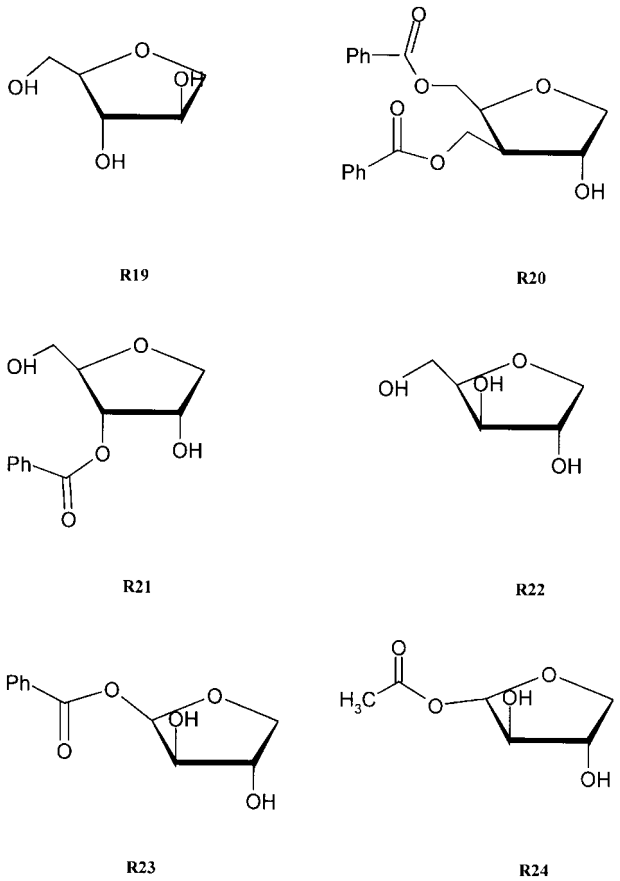

***Scheme 2.*** Molecular structures of adenine derivatives.

generation and prediction set used for evaluation of the model. Generally, the good linear agreement between the predicted and experimental values can be used as an adequate parameter for testing the validity of the model. It should be noted here that, in our statistical analysis the total number of selected compounds is equal to 24. In the literature, there are many QSAR reports in which a lower set of compounds is utilized for statistical studies.[15–17] So, it can be deduced that here, an acceptable accuracy is existed for the accomplished statistical work. In the QSAR analysis it has been commonly accepted that the data set should be contained of five times as many compounds as descriptors. The reason for this is that too few compounds relative to the number of descriptors will give a falsely high correlation. This subject has been also considered in our QSAR study.





Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016




***Scheme 3.*** Molecular structures of adenine derivatives.

## RESULTS AND DISCUSSION

To gain insight into the structure–activity relationship of the nucleoside compounds, QSAR analysis has been performed through ascertaining of several suitable descriptors that is followed by defining of any linear correlation between the cited descriptors and the parameters of binding affinity for the enzyme. Thus, a number of molecular descriptors have been primarily determined for a set of cyclic as well as acyclic adenine–nucleoside derivatives. The interested common feature in some nucleosides was the presence of adenine base as a consensus part of the molecules and the availability of the kinetic parameters in the same environmental condition (especially $K_m$ and $K_i$ values) for the selected nucleosides among the interaction with ADA. Fortunately, in the literature,[18–23] there were several adenine nucleosides which their kinetic parameters were reported during their interactions with ADA at those environmental conditions that is similar to the exerted conditions of our studies. Among





Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016

*Table 2.* Specification of the multiple linear regression model for cyclic and acylic nucleosides.

| Descriptor | Coefficient | Mean effect |
|---|---|---|
| Dipole moment | 1.869 (± 0.369) | 0.893 |
| Volume | − 15.557 (± 1.446) | 43.298 |
| The highest positive of charge | − 0.560 (± 0.068) | 1.973 |
| Charge of N1 | 13.165 (± 3.508) | 55.743 |
| Constant | 106.421 (± 16.156) | |

R = 0.931; F = 34.302; n = the total number of nucleoside compounds (n = 24).

the total studied nucleosides, herein, the numerical information of $R_2$–$R_{10}$ are tabulated in the first part of the Table 1 because all of these compounds were synthesized in our laboratory or their kinetic parameters were obtained directly through our kinetic investigations (see also Schemes 1–3). It should be mentioned that utilizing of the

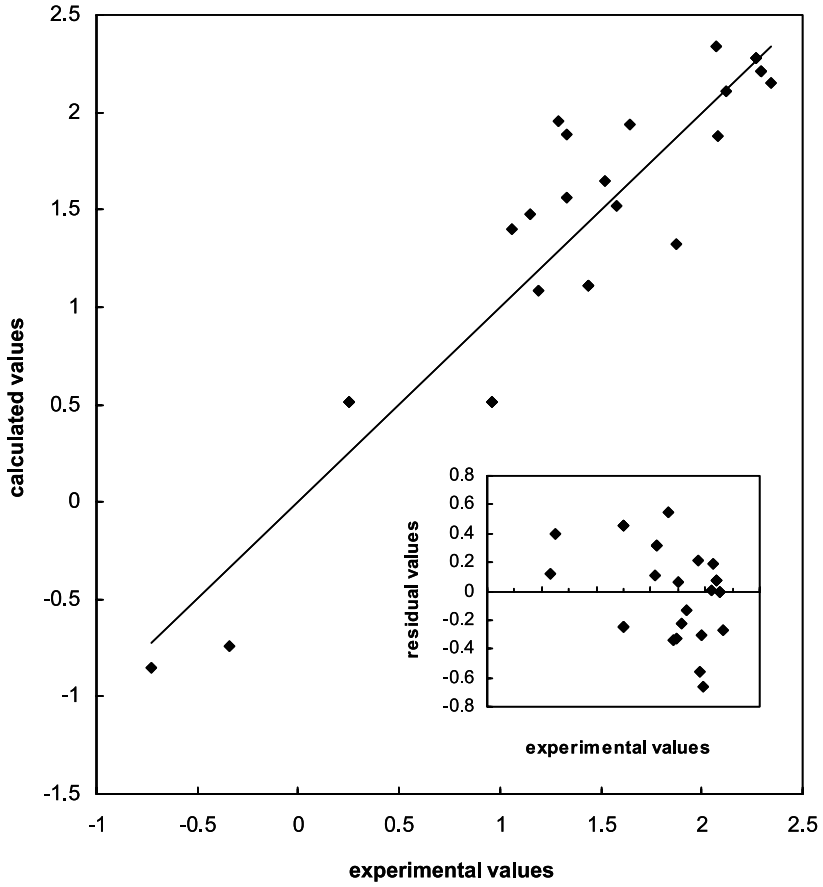



*Figure 1.* The good linear correlation between the empirical values of $K_m$ or $K_i$ and the related values of the prediction set (r = 0.931). Inset: Symmetrical distribution of the residual values confirming the goodness of the performed calculations.





Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016

kinetic parameters of $K_m$ and $K_i$ as the quantified amounts for quantifying the enzyme's binding affinity is permissive because, these both parameters are dissociation constants with the identical thermodynamic dimension of mole/liter. Interestingly, regarding to the kinetic studies all of the selected nucleosides manifested the similar type of inhibition which was the competitive inhibition. Therefore, it can be concluded that the specific binding site for settling of the total nucleoside derivatives should be the enzyme's catalytic site.

In pharmacology ascertaining of the molecular properties of the chemical compounds that is interfered with the molecular binding affinity is very important because, the obtained data can be finally used for improving the general insight for designing the new potent drug inhibitors to suppress the over activated enzymes. Here, the QSAR analysis has revealed that binding affinity (*BA*) of the adenine nucleosides in interaction with ADA depends on the molecular volume (*Vol*), dipole moment of the molecule (*Dipm*), electric charge around the N1 atom (*ECN1*) and the highest of positive charge (*HPOST*), see Eq. 1.

$$log(BA) = -15.557\ log(Vol) + 13.165(ECN1)^{-1} + 1.69\ log(Dipm) - 0.560(HPOST)^{-1} + 106.42 \quad (1)$$

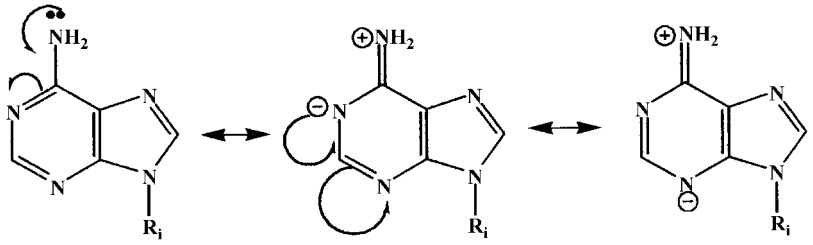
Generally in the QSAR studies the algebraic sign before each term of the resulted equation elucidates the essence of the existent correlation between each of the related descriptor and the mathematical function, e.g. *log*(*BA*). For example when the algebraic sign before the first term of Eq. 1 is negative it means that a negative correlation between the molecular volume of the adenine nucleosides and the enzyme's binding affinity should be existed. Therefore, whatever the molecular volume of the adenine nucleosides are largely growing the affinity for settling into the ADA catalytic site will be decreased. Consequently, regarding to the cited logic, binding affinity of the adenine nucleosides will be increased if the molecular volume as well as electric charge around the N1 atom are both diminished. It should be mentioned here that *log*(*BA*) is related with the reciprocal amounts of *ECN1* so, the positive sign before the second term of Eq. 1 shows the positive correlation of *log*(*BA*) with $(ECN1)^{-1}$. Therefore, it can be deduced that increasing of $(ECN1)^{-1}$ (or decreasing of *ECN1*) will be followed by increment of the enzyme's affinity. Subsequently increment of dipole moment for the adenine nucleosides will be resulted the increment of the binding affinity for the ADA catalytic site. The highest of positive charge (*HPOST*) is the last descriptor which shown acceptable linear correlation with *log*(*BA*) but, regarding to its delocalized position in the molecular structure of the adenine nucleosides this descriptor is not an informative parameter and is set aside in our presented discussion. If we want to compare the degree of importance of the cited descriptors for evaluation of the enzyme's binding affinity it would be better to utilize the statistical factor of the mean effect. Regarding to this valuable parameter the validity order of (*Vol*), (*ECN1*), (*Dipm*) is distinguished (Table 2). Figure 1 shows the good linear correlation between the empirical values of $K_m$ or $K_i$ and the related values of the prediction set (r = 0.931). The inset of the figure indicates the symmetrical distribution of the residual values confirming the goodness of our performed calculations.

In conclusion, there is no doubt that N1 atom must contain the higher negative charge density this was due to delocalization of electron (resonance effect) through the





MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016



I II III

electron demanding pyrimidine structure (see the following scheme). In state (I) the electron is injected to highly electron-withdrawal pyrimidine ring which bring the electrons on the N1 atom (state II). On the other hand, the sequence of electron motion in this manner will bring electron to N3 (state III). The state II must have lower energy with regard that it posses of minimum charge separation respect to the other allowed representative states (states I or III). Here, using quantum mechanic calculations it has been shown that for the optimized geometry related to the nucleoside structures there is considerable electron density around the N1 atom (see Table 1). But, it is also determined here that whenever the electronic charge around the N1 atom is decreased then the binding affinity for the catalytic site of ADA will be increased. In fact, regarding to the state III and the possibility for repletion of electron around the N3 atom (decrement of electron density around N1), establishment of hydrogen bond between N3 and one of the free hydroxyl groups in the sugar moiety is probable. In this manner, it can be deduced that however the strength of the established secondary binding (hydrogen bond) is increased then formation of the state III as a suitable enzyme-bound structure (with a low electron density around N1) will be more probable. Evidently, in this structure (state III) the N1 atom is free and it can better interacted to the enzyme's surface.

## ACKNOWLEDGMENT

Financial support of the Research Council of the University of Tehran is gratefully appreciated.

## REFERENCES

1. Trotta, P.P.; Smithwick, E.M.; Balis, M.E. A normal level of adenosine deaminase activity in the red cell lysates of carriers and patients with severe combined immunodeficiency disease. Proc. Natl. Acad. Sci. U. S. A. **1976**, 73, 104–108.
2. Kredich, N.M.; Hershfield, M. *The Metabolic Basis of Inherited Disease*; Scriver, C.R., Beaudet, A.L., Sly, W.S., Valle, D., Eds.; Mc Graw-Hill: New York, 1989; 1045–1075.

3. Lee, P.C. Developmental changes of adenosine deaminase, xanthine oxidase, and uricase in mouse tissues. Dev. Biol. **1973**, 31, 227–233.
4. Chinsky, J.M.; Ramamurthy, V.; Fanslow, W.C.; Ingolia, D.E.; Blackburn, M.R.; Shaffer, K.T.; Higley, H.R.; Trentin, J.J.; Rudolph, F.B.; Knudsen, T.B. Developmental expression of adenosine deaminase in the upper alimentary tract of mice. Differentiation **1990**, 42, 172–183.
5. Marrone, T.J.; Straatsma, T.P.; Briggs, J.M.; Wilson, D.K.; Quiocho, F.A.; McCammon, J.A. Theoretical study of inhibition of adenosine deaminase by (8R)-coformycin and (8R)-deoxycoformycin. J. Med. Chem. **1996**, 39, 277–284.
6. Schaeffer, H.J.; Johnson, R.N.; Odin, E.; Hansch, C. Structure–activity relationships. Adenosine deaminase inhibitors. J. Med. Chem. **1970**, 13, 452–455.
7. Kasibhatla, S.R.; Bookser, B.C.; Probst, G.; Appleman, J.R.; Erion, M.D. AMP deaminase inhibitors. 3. SAR of 3-(carboxyarylalkyl)coformycin aglycon analogues. J. Med. Chem. **2000**, 43, 1508–1518.
8. Kasibhatla, S.R.; Bookser, B.C.; Xiao, W.; Erion, M.D. AMP deaminase inhibitors. 5. Design, synthesis, and SAR of a highly potent inhibitor series. J. Med. Chem. **2001**, 4, 613–618.
9. Hansch, C. Quantitative structure–activity relationships in drug design. In *Drug Design*; Ariens, E.J., Ed.; Academic Press: New York, 1971; 271–342.
10. Herman, R.B. Theory of hydrophobic bonding. II. The correlation of hydrocarbon solubility in water with solvent cavity surface area. J. Phys. Chem. **1972**, 76, 2754–2759.
11. Herman, R.B. Theory of hydrophobic bonding. III. A method for the calculation of the hydrophobic interaction based on liquid state perturbation theory and a simple liquid model. J. Phys. Chem. **1975**, 79, 163–169.
12. Kauzmann, W. Some factors in the interpretation of protein denaturation. Adv. Protein Chem. **1959**, 14, 1–63.
13. Fujita, T.; Iwasa, J.; Hansch, C. A new substituent, π, derived from partition coeficients. J. Am. Chem. Soc. **1964**, 86, 5175–5180.
14. Segel, I.H. *Enzyme Kinetics*; John Wiley & Sons: New York, 1975.
15. Gupta, S.P. Quantitative structure–activity relationship studies on local anesthetics. Chem. Rev. **1991**, 91, 1109–1118.
16. Hadjipavlou-Litina, D.; Hansch, C. Quantitative structure–activity relationships of the benzodiazepines. Chem. Rev. **1994**, 94, 1483–1505.
17. Zhang, L.; Gao, H.; Hansch, C.; Selassie, C.D. Molecular orbital parameters and comparative QSAR in the analysis of phenol toxicity to leukemia cells. J. Chem. Soc., Perkin Trans. 2 **1998**, (11), 2553–2556.
18. Moosavi-Movahedi, A.A.; Rahmani, Y.; Hakimelahi, G.H. Thermodynamic and kinetic studies of competitive inhibition of adenosine deaminase by ring opened analogues of adenine nucleoside. Int. J. Biol. Macromol. **1993**, 15, 125–129.
19. Hakimelahi, G.H.; Moosavi-Movahedi, A.A.; Sadeghi, M.M.; Tsay, S.; Hwu, J. Design, synthesis, and structure–activity relationship of novel dinucleotide analogs as agents against herpes and human immunodeficiency viruses. J. Med. Chem. **1995**, 38, 4648–4659.
20. Maury, G.; Daiboun, T.; Elalaoui, A.; Cenu-Dellac, C.; Perigaud, C.; Bergogne, C.; Gosselin, G.; Imbach, J.L. Inhibition and substrate specificity of adenosine






MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

deaminase interaction with 2′-3′- and 5′-substituted adenine nucleoside derivatives. Nucleosides Nucleotides **1991**, 10, 1677–1692.
21. Hampton, A.; Harper, P.J.; Sasaki, T. Evidence for the conformation of enzyme-bound adenosine 5′-phosphate. Substrate and inhibitor properties of 8,5′-cyclo-adenosine 5′-phosphate with adenylate kinase, adenylate aminohydrolase, adenylo-succinate lyase, and 5′-nucleotidase. Biochemistry **1972**, 11, 4965–4969.
22. Hakimelahi, G.H.; Zarrinehzad, M.; Jarrahpour, A.A.; Sharghi, H. 26. Ring-open analogues of adenine nucleoside. Aminoacyl derivatives of cyclo- and acyclo-nucleosides. Helv. Chim. Acta **1987**, 70, 219–221.
23. Khorshidi, A. Doctoral thesis; Faculty of Pharmacy, Isfahan University, Iran.

Received March 13, 2003
Accepted November 26, 2003

# Request Permission or Order Reprints Instantly!