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# Quantitative structure-activity relationship of matrix metalloproteinase inhibitors based on quantum chemical descriptors

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## ABSTRACT

*Quantitative structure-activity relationship of nineteen matrix metalloproteinase inhibitors based on quantum chemical descriptors, heat of formation; steric energy; total energy; energy of highest occupied molecular orbital; energy of lowest unoccupied molecular orbital; absolute hardness and electronegativity, has been studied. For QSAR prediction, the 3D structures of the inhibitors have been drawn and their geometries have been optimized with the help of CAChe software by using PM3 hamiltonian. The purpose of the study is to test the suitability of the above quantum chemical parameters as possible biological activity descriptor in the development of QSAR. Results emanated from the study show that heat of formation, steric energy, total energy and energy of lowest unoccupied molecular orbital can be used as descriptors of biological activity. On the basis of the derived models one can build up a theoretical basis to access the biological activity of the inhibitors of the same series.*

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## INTRODUCTION

Quantitative structure-activity relationship (QSAR) (sometimes QSPR: quantitative structure-property relationship) is the process by which chemical structure is quantitatively correlated with a well defined process, such as biological activity or chemical reactivity[1-10]. For example, biological activity can be expressed quantitatively as in the concentration of a substance required to give a certain biological response. Additionally, when physicochemical properties or structures are expressed by numbers, one can form a mathematical relationship, or quantitative structure-activity relationship, between the two. The mathematical expression can then be used to predict the biological response of other chemical structures. In this research work, we present the QSAR study of MMP inhibitors using quantum chemical descriptors. Quantum chemical methods and molecular modeling techniques[11] enable the definition of a large number of molecular and local quantities characterizing the reactivity, shape and binding properties of a complete molecule as well as of molecular fragments and substituents. Because of the large well-defined physical information content encoded in many theoretical descriptors, their use in the design of a training set in a QSAR study presents two main advantages: (a) the compounds and their various fragments and substituents can be directly characterized on the basis of their

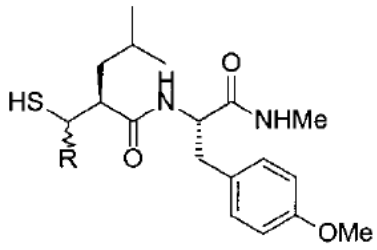
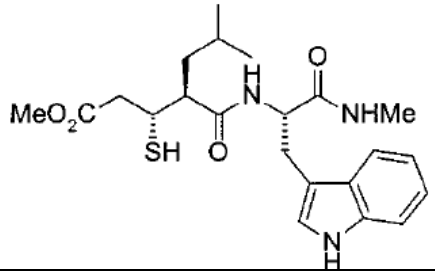
molecular structure only; and (b) the proposed mechanism of action can be directly accounted for in terms of the chemical reactivity of the compounds under study. Consequently, the derived QSAR models will include information regarding the nature of the intermolecular forces involved in determining the biological or other activity of the compounds in question. Quantum-chemically derived descriptors are fundamentally different from experimentally measured quantities, although there is some natural overlap [11]. Unlike experimental measurements there is no statistical error in quantum-chemical calculations. There is inherent error however, associated with the assumptions required to facilitate the calculations. In most cases the direction but not the magnitude of the error is known. In using quantum chemistry-based descriptors with a series of related compounds, the computational error is considered to be approximated constant throughout the series. The survey of the literatures[12-28] also indicates that no QSAR model for prediction of activity of matrix metalloproteinase (MMP) inhibitors under study has been made with the following quantum mechanical parameters:

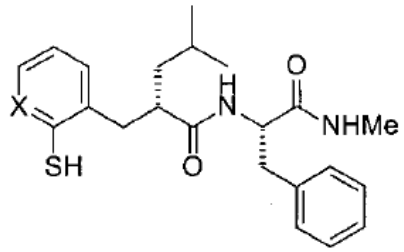
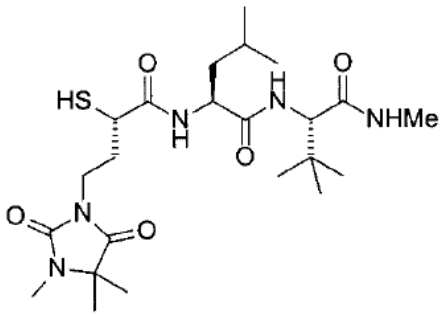
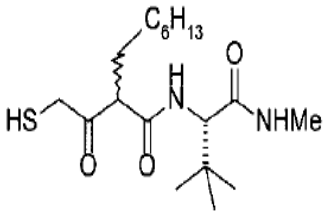
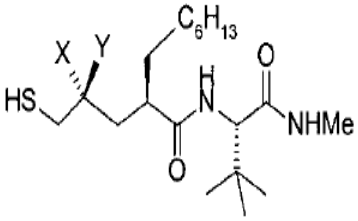
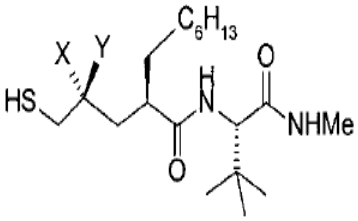
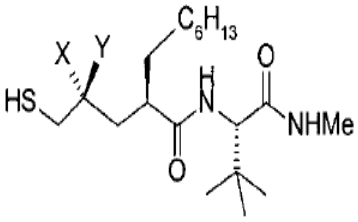
1. Heat of formation ($\Delta H_f^\circ$)[29]
2. Steric Energy (SE)[30]
3. Total energy (TE)[31]
4. HOMO energy ($\in$HOMO)[32]
5. LUMO energy ($\in$LUMO)[32]
6. Absolute Hardness ($\eta$)[33]
7. Electronegativity ($\chi$)[34]

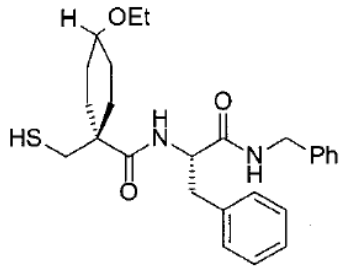
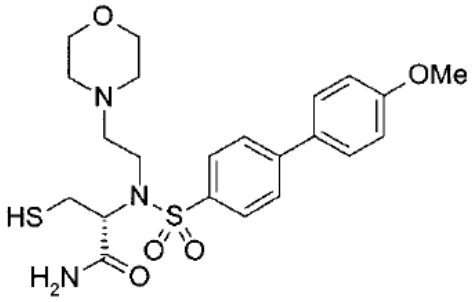
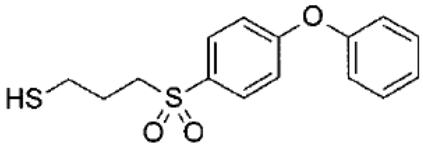
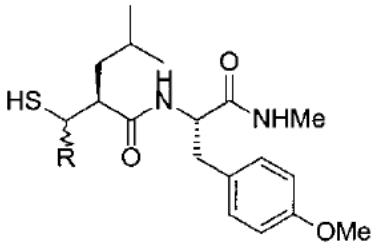
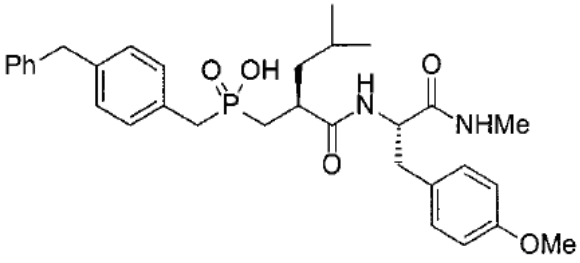
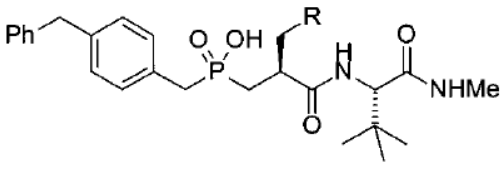
## MATERIALS AND METHODS

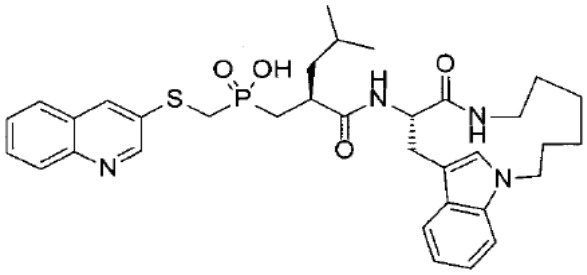
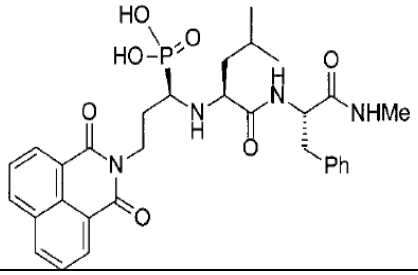
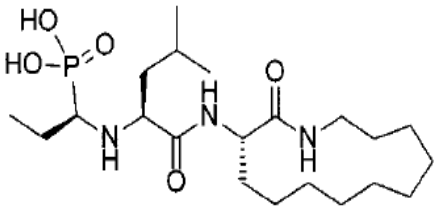
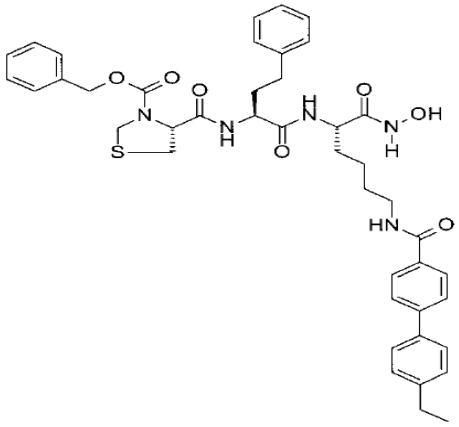
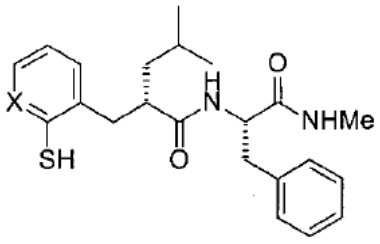
The study materials of this paper are MMP inhibitors [28] and are presented in Table-1. For QSAR prediction, the structures of all the above compounds have been drawn and their geometries[35] have been optimized with the help of CAChe software using PM3 hamiltonian[36-38].

**Table 1. List of compounds with their observed biological activity (OBA)**

| No. | Compound | $IC_{50}$ |
|---|---|---|
| 1 |  R=H | 360 |
| 2 |  | 2.5 |

| | | |
|---|---|---|
| 3 |  X=CH | 30 |
| 4 |  | 25 |
| 5 |  | 15 |
| 6 |  X, Y =O | 10 |
| 7 |  X=OH, Y=H | 140 |
| 8 |  X=H, Y=OH | 5 |

| | | |
|---|---|---|
| 9 |  | 823 |
| 10 |  | 70 |
| 11 |  | 1500 |
| 12 |  R=Me | 3000 |
| 13 |  | 270 |
| 14 |  R=PhCH$_2$ | 690 |

| | | |
|---|---|---|
| 15 |  | 5 |
| 16 |  | 20 |
| 17 |  | 180 |
| 18 |  | 40 |
| 19 |  X=N | 100 |

The values of selected descriptors have been obtained from the software by solving the equations given below and the results are included in Table 2.

The heat of formation[29] is defined as

$$\Delta H_f^o = E_{elect} + E_{nuc} - E_{isol} + E_{atom} \qquad \text{Eq.I}$$

where $E_{elect}$ is the electronic energy, $E_{nuc}$ is the nuclear-nuclear repulsion energy, $E_{isol}$ is the energy required to strip all the valence electrons of all the atoms in the system and $E_{atom}$ is the total heat of atomization of all the atoms in the system.

The steric energy (SE) of a molecule is the sum of the bonded and nonbonded terms (Van der Waals energy, and the electrostatic energy). The lowest energy conformation is the set of bond lengths and angles that gives the smallest steric energy[30].

Total energy (TE) of a molecular system is the sum of the total electronic energy, $E_{ee}$ and the energy of internuclear repulsion, $E_{nr}$. The total electronic energy of the system is given by[31]

$$E = \frac{P(H+F)}{2} \qquad \text{Eq.II}$$

where P is the density matrix and H is the one-electron matrix

Parr et al.[34] defined electronegativity as the negative of chemical potential:

$$\chi = -\mu = -\left(\frac{\delta E}{\delta N}\right)_{V(r)} \qquad \text{Eq.III}$$

The absolute hardness (η)[33] is defined as

$$\eta = \frac{1}{2}\left(\frac{\delta E}{\delta N}\right)_{V(r)}$$

$$\eta = \frac{1}{2}\left(\frac{\delta^2 E_T}{\delta N^2}\right)_{V(r)} \qquad \text{Eq.IV}$$

where $E_T$ is the total energy, N the number of electrons of the chemical species and v(r) the external potential.

The operational definition of absolute hardness and electronegativity[33, 34] is defined as

$$\eta = \frac{(IP - EA)}{2} \qquad \text{Eq.V}$$

$$\chi = -\mu = \frac{(IP + EA)}{2} \qquad \text{Eq.VI}$$

where IP and EA are the ionization potential and electron affinity respectively, of the chemical species. According to the Koopman's theorem[32], the IP is simply the eigen value of the HOMO with change of sign and the EA is the eigen value of the LUMO with change of sign hence the Eq.V and VI can be written as

$$\eta = \frac{(\varepsilon LUMO - \varepsilon HOMO)}{2} \qquad \text{Eq.VII}$$

$$\chi = \frac{(\varepsilon LUMO + \varepsilon HOMO)}{2} \qquad \text{Eq.VIII}$$

## RESULTS AND DISCUSSION

Based on above quantum chemical descriptors, the QSAR model of nineteen MMP inhibitors has been presented in this research work. The purpose of the study is to test the suitability of the above quantum chemical parameters as possible biological activity descriptor in the development of QSAR. In developing QSAR models, quantum chemical descriptors used as independent variables and the observed biological activity in term of $IC_{50}$ values as dependent variable. We have considered 90 QSAR models using MLR analysis[39-41] with the help of various combinations of the descriptors as shown in Table-3. The quantities of descriptors have been taken from Table-2. In order to explore the reliability of the proposed model we have used regression coefficient (r^2) and cross-validation coefficient (rCV^2). Out of above 90 QSAR models only 76 models have predictive powers as these have higher values (»0.5) of both rCV^2 and r^2 coefficients, while the rest have either the value of rCV^2 («0.2) or r^2 («0.5) or both much lower than their optimum values.

**Table 2. Calculation of various quantum chemical descriptors of the compounds with OBA**

| No. | $\Delta H_f^\circ$ (kcal/mole) | SE (kcal/mole) | TE (Hartree) | ∈HOMO (eV) | ∈LUMO (eV) | η | χ | OBA ($IC_{50}$) |
|---|---|---|---|---|---|---|---|---|
| 1 | -168.648 | -23.999 | -0.324 | -8.941 | -0.272 | 4.335 | 4.607 | 360.000 |
| 2 | -168.627 | -12.315 | -0.272 | -8.948 | -0.314 | 4.317 | 4.631 | 2.500 |
| 3 | -168.634 | -2.619 | -0.126 | -8.943 | -0.312 | 4.316 | 4.628 | 30.000 |
| 4 | -168.638 | 3.648 | -0.452 | -8.950 | -0.314 | 4.318 | 4.632 | 25.000 |
| 5 | -168.631 | -9.247 | -0.316 | -8.941 | -0.314 | 4.314 | 4.628 | 15.000 |
| 6 | -168.620 | 2.271 | -0.266 | -8.944 | -0.318 | 4.313 | 4.631 | 10.000 |
| 7 | -168.637 | 6.316 | -0.334 | -8.966 | -0.298 | 4.334 | 4.632 | 140.000 |
| 8 | -168.629 | 7.641 | -0.336 | -8.943 | -0.315 | 4.314 | 4.629 | 5.000 |
| 9 | -168.676 | 5.385 | -0.175 | -8.948 | -0.214 | 4.367 | 4.581 | 823.000 |
| 10 | -168.638 | 10.454 | -0.282 | -8.943 | -0.311 | 4.316 | 4.627 | 70.000 |
| 11 | -168.718 | -12.716 | -0.131 | -8.939 | -0.129 | 4.405 | 4.534 | 1500.000 |
| 12 | -168.799 | -18.569 | -0.320 | -8.936 | 0.058 | 4.497 | 4.439 | 3000.000 |
| 13 | -168.646 | -0.203 | -0.469 | -8.949 | -0.282 | 4.333 | 4.615 | 270.000 |
| 14 | -168.661 | 4.006 | -0.416 | -8.942 | -0.229 | 4.356 | 4.585 | 690.000 |
| 15 | -168.622 | 13.807 | -0.278 | -8.943 | -0.311 | 4.316 | 4.627 | 5.000 |
| 16 | -168.630 | -39.543 | -0.552 | -8.943 | -0.312 | 4.316 | 4.628 | 20.000 |
| 17 | -168.634 | 31.978 | -0.615 | -8.943 | -0.291 | 4.326 | 4.617 | 180.000 |
| 18 | -168.639 | -53.991 | -0.341 | -8.943 | -0.309 | 4.317 | 4.626 | 40.000 |
| 19 | -168.630 | 2.982 | -0.014 | -8.943 | -0.302 | 4.321 | 4.623 | 100.000 |

*$\Delta H_f^\circ$ is heat of formation, SE is steric energy, TE is total energy, ∈HOMO is energy of highest occupied molecular orbital, ∈LUMO is energy of lowest unoccupied molecular orbital, η is absolute hardness and χ is electronegativity*

**Table 3. Combination of descriptors for MLR analysis**

| Predicted Activity | First descriptor | Second descriptor | Third descriptor | Fourth descriptor | rCV^2 | r^2 |
|---|---|---|---|---|---|---|
| PAM1 | Heat of Formation | Steric Energy | — | — | 0.98578 | 0.98914 |
| PAM2 | Heat of Formation | Total Energy | — | — | 0.98147 | 0.98703 |
| PAM3 | Heat of Formation | HOMO Energy | — | — | 0.97907 | 0.98740 |
| PAM4 | Heat of Formation | LUMO Energy | — | — | 0.99953 | 0.99966 |
| PAM5 | Heat of Formation | Absolute Hardness | — | — | 0.99382 | 0.99663 |
| PAM6 | Heat of Formation | Electronegativity | — | — | 0.99601 | 0.99743 |
| PAM7 | Steric Energy | Total Energy | — | — | -1.26086 | 0.03790 |
| PAM8 | Steric Energy | HOMO Energy | — | — | -0.99994 | 0.16006 |
| PAM9 | Steric Energy | LUMO Energy | — | — | 0.99939 | 0.99960 |
| PAM10 | Steric Energy | Absolute Hardness | — | — | 0.99458 | 0.99581 |
| PAM11 | Steric Energy | Electronegativity | — | — | 0.99522 | 0.99609 |
| PAM12 | Total Energy | HOMO Energy | — | — | -0.84905 | 0.16384 |
| PAM13 | Total Energy | LUMO Energy | — | — | 0.99937 | 0.99961 |
| PAM14 | Total Energy | Absolute Hardness | — | — | 0.99467 | 0.99572 |
| PAM15 | Total Energy | Electronegativity | — | — | 0.99523 | 0.99596 |
| PAM16 | HOMO Energy | LUMO Energy | — | — | 0.99944 | 0.99960 |
| PAM17 | HOMO Energy | Absolute Hardness | — | — | 0.99944 | 0.99960 |
| PAM18 | HOMO Energy | Electronegativity | — | — | 0.99944 | 0.99960 |
| PAM19 | LUMO Energy | Absolute Hardness | — | — | 0.99944 | 0.99960 |
| PAM20 | LUMO Energy | Electronegativity | — | — | 0.99944 | 0.99960 |
| PAM21 | Absolute Hardness | Electronegativity | — | — | 0.99944 | 0.99960 |
| PAM22 | Heat of Formation | Steric Energy | Total Energy | — | 0.98553 | 0.98914 |
| PAM23 | Heat of Formation | Steric Energy | HOMO Energy | — | 0.98207 | 0.98990 |

| | | | | | | |
|---|---|---|---|---|---|---|
| PAM24 | Heat of Formation | Steric Energy | LUMO Energy | — | 0.99953 | 0.99968 |
| PAM25 | Heat of Formation | Steric Energy | Absolute Hardness | — | 0.99305 | 0.99664 |
| PAM26 | Heat of Formation | Steric Energy | Electronegativity | — | 0.99507 | 0.99793 |
| PAM27 | Steric Energy | Total Energy | HOMO Energy | — | -1.61221 | 0.16754 |
| PAM28 | Steric Energy | Total Energy | LUMO Energy | — | 0.99935 | 0.99961 |
| PAM29 | Steric Energy | Total Energy | Absolute Hardness | — | 0.99253 | 0.99586 |
| PAM30 | Steric Energy | Total Energy | Electronegativity | — | 0.99320 | 0.99609 |
| PAM31 | Total Energy | HOMO Energy | LUMO Energy | — | 0.99937 | 0.99961 |
| PAM32 | Total Energy | HOMO Energy | Absolute Hardness | — | 0.99937 | 0.99961 |
| PAM33 | Total Energy | HOMO Energy | Electronegativity | — | 0.99937 | 0.99961 |
| PAM34 | HOMO Energy | LUMO Energy | Absolute Hardness | — | 0.95001 | 0.00000 |
| PAM35 | HOMO Energy | LUMO Energy | Electronegativity | — | 0.00000 | 0.74517 |
| PAM36 | LUMO Energy | Absolute Hardness | Electronegativity | — | 0.49131 | -7.92753 |
| PAM37 | Steric Energy | HOMO Energy | LUMO Energy | — | 0.99938 | 0.99960 |
| PAM38 | Steric Energy | HOMO Energy | Absolute Hardness | — | 0.99938 | 0.99960 |
| PAM39 | Steric Energy | HOMO Energy | Electronegativity | — | 0.99938 | 0.99960 |
| PAM40 | Steric Energy | LUMO Energy | Absolute Hardness | — | 0.99938 | 0.99960 |
| PAM41 | Steric Energy | LUMO Energy | Electronegativity | — | 0.99938 | 0.99960 |
| PAM42 | Steric Energy | Absolute Hardness | Electronegativity | — | 0.99938 | 0.99960 |
| PAM43 | Total Energy | LUMO Energy | Absolute Hardness | — | 0.99937 | 0.99961 |
| PAM44 | Total Energy | LUMO Energy | Electronegativity | — | 0.99937 | 0.99961 |
| PAM45 | Total Energy | Absolute Hardness | Electronegativity | — | 0.99937 | 0.99961 |
| PAM46 | Heat of Formation | Total Energy | HOMO Energy | — | 0.97627 | 0.98740 |
| PAM47 | Heat of Formation | Total Energy | LUMO Energy | — | 0.99950 | 0.99967 |
| PAM48 | Heat of Formation | Total Energy | Absolute Hardness | — | 0.99281 | 0.99666 |

| | | | | | | |
|---|---|---|---|---|---|---|
| PAM49 | Heat of Formation | Total Energy | Electronegativity | — | 0.99562 | 0.99743 |
| PAM50 | Heat of Formation | HOMO Energy | LUMO Energy | — | 0.99951 | 0.99966 |
| PAM51 | Heat of Formation | HOMO Energy | Absolute Hardness | — | 0.99951 | 0.99966 |
| PAM52 | Heat of Formation | Total Energy | HOMO Energy | Electronegativity | 0.99948 | 0.99967 |
| PAM53 | Heat of Formation | LUMO Energy | Absolute Hardness | — | 0.99951 | 0.99966 |
| PAM54 | Heat of Formation | LUMO Energy | Electronegativity | — | 0.99951 | 0.99966 |
| PAM55 | Heat of Formation | Absolute Hardness | Electronegativity | — | 0.99951 | 0.99966 |
| PAM56 | HOMO Energy | Absolute Hardness | Electronegativity | — | 0.03361 | -0.73302 |
| PAM57 | Heat of Formation | Steric Energy | Total Energy | HOMO Energy | 0.98244 | 0.98990 |
| PAM58 | Heat of Formation | Steric Energy | Total Energy | LUMO Energy | 0.99952 | 0.99969 |
| PAM59 | Heat of Formation | Steric Energy | Total Energy | Absolute Hardness | 0.99252 | 0.99667 |
| PAM60 | Heat of Formation | Steric Energy | Total Energy | Electronegativity | 0.99488 | 0.99793 |
| PAM61 | Heat of Formation | Steric Energy | HOMO Energy | LUMO Energy | 0.99952 | 0.99968 |
| PAM62 | Heat of Formation | Steric Energy | HOMO Energy | Absolute Hardness | 0.99952 | 0.99968 |
| PAM63 | Heat of Formation | Steric Energy | HOMO Energy | Electronegativity | | |
| PAM64 | Heat of Formation | Steric Energy | LUMO Energy | Absolute Hardness | 0.99952 | 0.99968 |
| PAM65 | Heat of Formation | Steric Energy | LUMO Energy | Electronegativity | 0.99952 | 0.99968 |
| PAM66 | Heat of Formation | Steric Energy | Absolute Hardness | Electronegativity | 0.99952 | 0.99968 |
| PAM67 | Steric Energy | Total Energy | HOMO Energy | LUMO Energy | 0.99952 | 0.99968 |
| PAM68 | Steric Energy | Total Energy | HOMO Energy | Absolute Hardness | 0.99935 | 0.99961 |
| PAM69 | Steric Energy | Total Energy | HOMO Energy | Electronegativity | 0.99935 | 0.99961 |
| PAM70 | Steric Energy | Total Energy | LUMO Energy | Absolute Hardness | 0.99935 | 0.99961 |
| PAM71 | Steric Energy | Total Energy | LUMO Energy | Electronegativity | 0.99935 | 0.99961 |
| PAM72 | Steric Energy | Total Energy | Absolute Hardness | Electronegativity | 0.99935 | 0.99961 |
| PAM73 | Steric Energy | Total Energy | LUMO Energy | Absolute Hardness | 0.99935 | 0.99961 |

| | | | | | | |
|---|---|---|---|---|---|---|
| PAM74 | Steric Energy | Total Energy | LUMO Energy | Electronegativity | 0.76091 | 0.00079 |
| PAM75 | Total Energy | HOMO Energy | Absolute Hardness | Electronegativity | 0.59352 | 0.00079 |
| PAM76 | HOMO Energy | LUMO Energy | Absolute Hardness | Electronegativity | -1.30062 | 0.99332 |
| PAM77 | Heat of Formation | Total Energy | HOMO Energy | LUMO Energy | 0.94063 | 0.93225 |
| PAM78 | Heat of Formation | Total Energy | HOMO Energy | Absolute Hardness | 0.99948 | 0.99967 |
| PAM79 | Heat of Formation | Total Energy | HOMO Energy | Electronegativity | 0.99948 | 0.99967 |
| PAM80 | Heat of Formation | Total Energy | LUMO Energy | Absolute Hardness | -0.23329 | 0.24258 |
| PAM81 | Heat of Formation | Total Energy | LUMO Energy | Electronegativity | 0.99948 | 0.99967 |
| PAM82 | Heat of Formation | HOMO Energy | LUMO Energy | Absolute Hardness | 0.99948 | 0.99967 |
| PAM83 | Heat of Formation | HOMO Energy | LUMO Energy | Electronegativity | 0.98675 | 0.99237 |
| PAM84 | Heat of Formation | — | — | — | 0.82856 | 0.64527 |
| PAM85 | Steric Energy | — | — | — | 0.98394 | 0.98703 |
| PAM86 | Total Energy | — | — | — | -0.64568 | 0.02235 |
| PAM87 | HOMO Energy | — | — | — | -0.23137 | 0.01595 |
| PAM88 | LUMO Energy | — | — | — | -0.64039 | 0.15650 |
| PAM89 | Absolute Hardness | — | — | — | 0.99944 | 0.99960 |
| PAM90 | Electronegativity | — | — | — | 0.99502 | 0.99567 |

Out of 76 models the top five models are as below:

**I. Top First QSAR model:** The top first QSAR model is obtained when multi linear regression analysis is done by taking heat of formation as first descriptor, steric energy as second descriptor, total energy as third descriptor and LUMO energy as fourth descriptor. The regression equation is given below:

$PAM58=-1390.64\times\Delta H_f^{\circ}+0.172747\times SE+14.6851\times TE+7398.62\times\in LUMO-232162$
rCV^2=0.999519
r^2=0.999689 Eq.IX

The values of the predicted activity PAM58 of all the compounds are listed in the Table-4.

**II. Top Second QSAR model:** The top second QSAR model is obtained when multi linear regression analysis is done by taking heat of formation as first descriptor, steric energy as second

descriptor, HOMO energy as third descriptor and LUMO energy as fourth descriptor. The regression equation is given below:

$PAM61=-1457.11\times\Delta H_f^{\circ}+0.192461\times SE+216.259\times\in HOMO+7366\times\in LUMO-241450$
rCV^2=0.999518
r^2=0.999683 Eq.X

The values of the predicted activity PAM61 of all the compounds are listed in the Table-4.

**III. Top Third QSAR model:** The top third QSAR model is obtained when multi linear regression analysis is done by taking heat of formation as first descriptor, steric energy as second descriptor, HOMO energy as third descriptor and absolute hardness as fourth descriptor. The regression equation is given below:

$PAM62=-1457.11\times\Delta H_f^{\circ}+0.192461\times SE+7582.26\times\in HOMO+14732\times\eta-241450$
rCV^2=0.999518
r^2=0.999683 Eq.XI

The values of the predicted activity PAM62 of all the compounds are listed in the Table-4.

**IV. Top Fourth QSAR model:** The top fourth QSAR model is obtained when multi linear regression analysis is done by taking heat of formation as first descriptor, steric energy as second descriptor, HOMO energy as third descriptor and electronegativity as fourth descriptor. The regression equation is given below:

$PAM63=-1457.11\times\Delta H_f^{\circ}+0.192461\times SE-7149.74\times\in HOMO-14732\times\chi-241450$
rCV^2=0.999518

**Table 4. Predicted activities of compounds as obtained by Eq.IX to Eq.XIII**

| No. | PAM58 | PAM61 | PAM62 | PAM63 | PAM64 | OBA |
|---|---|---|---|---|---|---|
| 1 | 346.222 | 346.713 | 346.713 | 346.713 | 346.713 | 360.000 |
| 2 | 8.508 | 6.931 | 6.931 | 6.931 | 6.931 | 2.500 |
| 3 | 37.400 | 35.297 | 35.297 | 35.297 | 35.297 | 30.000 |
| 4 | 24.465 | 26.144 | 26.144 | 26.144 | 26.144 | 25.000 |
| 5 | 14.504 | 15.409 | 15.409 | 15.409 | 15.409 | 15.000 |
| 6 | -27.674 | -28.515 | -28.515 | -28.515 | -28.515 | 10.000 |
| 7 | 143.431 | 139.370 | 139.370 | 139.370 | 139.370 | 140.000 |
| 8 | 7.224 | 8.164 | 8.164 | 8.164 | 8.164 | 5.000 |
| 9 | 820.877 | 818.190 | 818.190 | 818.190 | 818.190 | 823.000 |
| 10 | 50.326 | 51.030 | 51.030 | 51.030 | 51.030 | 70.000 |
| 11 | 1506.350 | 1504.559 | 1504.559 | 1504.559 | 1504.559 | 1500.000 |
| 12 | 2998.488 | 2999.483 | 2999.483 | 2999.483 | 2999.483 | 3000.000 |
| 13 | 271.434 | 272.988 | 272.988 | 272.988 | 272.988 | 270.000 |
| 14 | 683.961 | 685.719 | 685.719 | 685.719 | 685.719 | 690.000 |
| 15 | 28.716 | 28.325 | 28.325 | 28.325 | 28.325 | 5.000 |
| 16 | 20.387 | 23.564 | 23.564 | 23.564 | 23.564 | 20.000 |
| 17 | 191.574 | 196.726 | 196.726 | 196.726 | 196.726 | 180.000 |
| 18 | 51.209 | 51.499 | 51.499 | 51.499 | 51.499 | 40.000 |
| 19 | 108.099 | 103.904 | 103.904 | 103.904 | 103.904 | 100.000 |

r^2=0.999683 Eq.XII

The values of the predicted activity PAM63 of all the compounds are listed in the Table-4.

**V. Top Fifth QSAR model:** The top fifth QSAR model is obtained when multi linear regression analysis is done by taking heat of formation as first descriptor, steric energy as second descriptor, LUMO energy as third descriptor and absolute hardness as fourth descriptor. The regression equation is given below:

PAM64=-1457.11×$\Delta H_f^\circ$+0.192461×SE+7582.26×∈LUMO-432.519×η-241450
rCV^2=0.999518
r^2=0.999683 Eq.XIII

The values of the predicted activity PAM64 of all the compounds are listed in the Table-4
In order to explore the reliability of the above five model we have used regression coefficient (r^2) and cross-validation coefficient (rCV^2). The regression summary of these models is as shown below

| QSAR | rCV^2 | r^2 | Variable Used | Variable Count |
|---|---|---|---|---|
| PAM58 | 0.999519 | 0.999689 | $\Delta H_f^\circ$, SE, TE, ∈LUMO | 4 |
| PAM61 | 0.999518 | 0.999683 | $\Delta H_f^\circ$, SE, ∈HOMO, ∈LUMO | 4 |
| PAM62 | 0.999518 | 0.999683 | $\Delta H_f^\circ$, SE, ∈HOMO, η | 4 |
| PAM63 | 0.999518 | 0.999683 | $\Delta H_f^\circ$, SE, ∈HOMO, χ | 4 |
| PAM64 | 0.999518 | 0.999683 | $\Delta H_f^\circ$, SE, ∈LUMO, η | 4 |

From the above study it is clear that the QSAR model no. 1 i.e., PAM58 has highest predictive powers as it has highest values of rCV^2 (0.999519) and r^2 (0.999689) among the five QSAR models.

## CONCLUSION

Results emanated from the study show that these quantum chemical descriptors ($\Delta H_f^\circ$, SE, TE and ∈LUMO) can be used as descriptors of biological activity. On the basis of the derived models one can build up a theoretical basis to access the biological activity of the inhibitors of the same series.

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