CHAPTER 6

QUANTITATIVE STRUCTURE ACTIVITY
RELATIONSHIP (QSAR) ANALYSIS

6.1 INTRODUCTION

The purpose of this study is to gain insight into structural features related to the anticancer, antioxidant, and antifungal activities of the compounds from the triazole-thiadiazole series by applying the QSAR methodology and also to suggest new substituents that enhance this activity. The QSAR study is a useful tool for a retinal search of bioactive compounds and also it describes a definite role in quantitative terms of structural features in molecules with a definite contribution to the activity of a particular physiochemical property of the structural feature. Thus QSAR provides a deeper insight into the mechanism of drug-receptor interactions.

The QSAR paradigm is based on the assumption that there is an underlying relationship between the molecular structure and biological activity. On this assumption QSAR attempts to establish a correlation between various molecular properties of a set of molecules with their experimentally known biological activity. Determination of QSAR [126] generally proceeds as follows:

a) Biological activity: For QSAR analysis, a dataset of a series of synthesized molecules tested for its desired biological activity is required. For a QSAR to be valid and reliable, the activity of all the chemicals covered
must be elicited by a common mechanism. The quality of the model is totally dependent on the quality of the experimental data used for building the model.

Biological activity can be of two types:

- Continuous Response: MEC, IC\(_{50}\), ED\(_{50}\), % inhibition
- Categorical Response: Active/Inactive

b) Molecular descriptors: Molecular descriptors can be defined as a numerical representation of chemical information encoded within a molecular structure via mathematical procedure.

c) Selection of training and test set: QSAR models are used increasingly to screen chemical databases and/or virtual chemical libraries for potentially bioactive molecules. These developments emphasize the importance of rigorous model validation to ensure that the models have both the ability to explain the variance in the biological activity (internal validation) and also the acceptable predictive power (external validation).

For model validation the dataset is required to be divided into training set (for building the QSAR model) and test set (for examining its predictive ability). Following are the methods for division of the dataset into training and test set:

- Manual Selection: This is done by visualizing the variation in the chemical and biological space of the given dataset.
- Random Selection: This method creates training and test set by random distribution.
- Sphere Exclusion Method: This is a rational method for creation of training and test set. It ensures that the points in
both sets are uniformly distributed with respect to chemical and biological space.


d) **Variable selection methods**: There are hundreds of molecular descriptors available for building a QSAR model. Not all of the molecular descriptors are important in determining the biological activity and hence to find the optimal subset of the descriptors which plays an important role in determining activity, a variable selection method is required. The variable selection method could be divided mainly into two categories:

  - **Systematic variable selection**: This method adds and/or deletes a descriptor in steps one-by-one in a model.

  - **Stochastic variable selection**: This method is based on simulation of various physical or biological processes. These methods create a model starting from randomly generated model(s) and later modifying these model(s) by using different process operator(s) (e.g. perturbation, crossover etc.) to get better model(s).

e) **Statistical methods**: A suitable statistical method coupled with a variable selection method allows analyses of this data in order to establish a QSAR model with the subset of descriptors that are most statistically significant in determining the biological activity.

f) **Validate the equation**: There is no single method that works better for predictiveness, interpretability and computational efficiency. Cross Validation Technique is used to evaluate the validity of a model by how well
it will predict data rather than how well it will fit data. The analysis uses Leave-One-Out (LOO) scheme.

g) **Predict the biological activity**: From the developed QSAR model the biological activity of proposed compounds can be calculated.

6.2 **QSAR STUDIES ON BIOLOGICAL ACTIVITIES**

QSAR studies were performed on the synthesized compounds 4a-o and 5a-o for tubercular activity against *Mycobacterium tuberculosis*, antioxidant activity by DPPH and Nitric oxide scavenging methods.

The lead moiety selected for the present study is

![Chemical structure](image)

a) **Biological activity**: The *in vitro* antitubercular activity data MIC values were determined against *Mycobacterium tuberculosis* and antioxidant activities by DPPH and Nitric oxide scavenging methods of synthesized compounds 4a-o and 5a-o were converted to pIC\(_{50}\).

b) **Molecular descriptors**: Molecular modelling studies were performed using Chem Office12 version 8.0 (Cambridge Soft). All the molecules were constructed using Chem Draw Ultra version 8.0 and it was saved as template structure. For every compound, the template structure was suitably changed considering its structural feature, copied on 3D model and finally the model was cleaned up and subjected to energy minimization using Molecular Mechanics (MM\(_2\)).
The minimization was executed until the Root Mean Square (RMS) gradient value reaches a value smaller than 0.1Kcal / mol. The minimized molecules were subjected to reoptimization via Austin model-1 method until RMS gradient attains a value smaller than 0.0001 Kcal / mol. A° using MOPAC. The geometry optimization of the lowest energy structure was carried out using Eigenvector Following (EF) routine. The descriptor values for all the molecules were calculated using “compute properties” module of program. Descriptors used in present QSAR study is given in Table 6.2.

c) Selection of training and test set: The compounds were divided into training and test sets by random selection. The training set was used for the model development and the test set was used for cross validation of QSAR model developed by the training set. The compounds 4a, 4c, 4f, 4g, 4i, 4k, 4l, 4n, 4o, 5a, 5c, 5d, 5g, 5i, 5j, 5l and 5m were used for training set. The remaining compounds 4b, 4d, 4e, 4h, 4j, 4m, 5b, 5e, 5f, 5h, 5k, 5n and 5o were used as test set.

d) Statistical methods: The data obtained was transferred to the statistical program in order to establish a correlation between physicochemical parameters as independent variable and pIC$_{50}$ as dependent variable employing multiple regression analysis method. The multiple regression analysis using a computer programme VALSTAT was carried out for building QSAR model [127]. All the possible combination of parameters was considered for the QSAR study.
Table 6.1  Dependent data used for QSAR study for antioxidant and antitubercular activities

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<th>Compound code</th>
<th>Antioxidant (pIC_{50})</th>
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Table 6.2 Descriptors used in QSAR study

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<td>Thermodynamic</td>
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<td>LogP</td>
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<td>PC</td>
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<td>Stberg</td>
<td>Thermodynamic</td>
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<td>Thermodynamic</td>
<td>Torison energy (kcal/mol)</td>
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<td>Connolly solvent – exclude surface area (Å)</td>
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<tr>
<td>11</td>
<td>Csev</td>
<td>Steric</td>
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6.2.1 QSAR model for antitubercular activity

All the 30 compounds were subjected to QSAR studies. 17 compounds were selected as training set and remaining 13 compounds were selected as test compounds. The following compounds used for training set 4a, 4c, 4f, 4g, 4i, 4k, 4l, 4n, 4o, 5a, 5c, 5d, 5g, 5i, 5j, 5l and 5m. Compounds used for test set includes 4b, 4d, 4e, 4h, 4j, 4m, 5b, 5e, 5f, 5h, 5k, 5n and 5o. The descriptors used in this study were given along with values in the Table 6.3. The best was selected from the various statistically significant equations on the basis of the observed squared correlation coefficient ($r^2$), standard error of estimate (Std), sequential Fischer test ($F$) cross validated squared correlation coefficient using leave-one-out procedure ($q^2$).
QSAR Model 1

\[ BA= [1.54 (\pm 0.35)] + Csev [-0.0002 (\pm 0.0001)] + PMI-X [-0.0003(\pm 0.0001)] \\
+ Tse [-0.0003(\pm 0.0001)] \]

\[ n = 17, r = 0.87, r^2 = 0.76, \text{variance} = 0.1439, \text{std} = 0.3794, F = 13.35. \]

\[ Q^2 = 0.9788, \quad \text{Spress} = 0.8352, \quad \text{SDEP} = 0.2527 \] \hspace{1cm} (6.1)

QSAR Model 2

\[ BA= [0.93 (\pm 0.39)] + PMI-X [-0.0002 (\pm 0.0002)] + Stberg [0.0002 (\pm 0.0002)] \\
+ Tse [-0.0002 (\pm 0.0001)] \]

\[ n = 17, r = 0.73, r^2 = 0.54, \text{variance} = 0.2866, \text{std} = 0.5353, F = 5.23. \]

\[ Q^2 = 0.9347, \quad \text{Spress} = 0.8461, \quad \text{SDEP} = 0.2516 \] \hspace{1cm} (6.2)

QSAR Model 3

\[ BA= [0.17 (\pm 0.41)] + Hf [0.0003 (\pm 0.0003)] + Stberg [0.0002 (\pm 0.0002)] + \\
Vdw [0.0001 (\pm 0.0001)] \]

\[ n = 17, r = 0.73, r^2 = 0.54, \text{variance} = 0.29, \text{std} = 0.5387, F = 5.11 \]

\[ Q^2 = 0.9283, \quad \text{Spress} = 0.8228, \quad \text{SDEP} = 0.2569 \] \hspace{1cm} (6.3)

QSAR Model 4

\[ BA= [1.32 (\pm 0.46)] + Csev [-0.0002(\pm 0.0002)] + PMI-X [-0.0002 \\
(\pm 0.0002)] + Tse [-0.0002(\pm 0.0001)] \]

\[ n = 17, r = 0.73, r^2 = 0.53, \text{variance} = 0.29, \text{std} = 0.5434, F = 4.95. \]

\[ Q^2 = 0.9419, \quad \text{Spress} = 0.8334, \quad \text{SDEP} = 0.2513 \] \hspace{1cm} (6.4)

QSAR Model 5

\[ BA= [0.87(\pm 0.43)] + PMI-X[-0.0002 (\pm 0.0002)] + Tse [-0.0002(\pm 0.0001)] + \\
Vdw [0.0001 (\pm 0.0001)] \]

\[ n = 17, r = 0.73, r^2 = 0.53, \text{variance} = 0.29, \text{std} = 0.5436, F = 4.94. \]

\[ Q^2 = 0.9579, \quad \text{Spress} = 0.8321, \quad \text{SDEP} = 0.2507 \] \hspace{1cm} (6.5)
Table 6.3  Descriptors used for QSAR study of antitubercular activity

<table>
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<tr>
<th>Code</th>
<th>PMI-X</th>
<th>Tse</th>
<th>Stberg</th>
<th>Vdw</th>
<th>Hf</th>
<th>Csev</th>
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6.2.2 QSAR equations for antioxidant activity by Nitric oxide method

All the 30 compounds were subjected to QSAR studies. 17 compounds were selected as training set and remaining 13 compounds were selected as test compounds. The best model was selected from the various statistically significant equations. The descriptors used in this study were given along with values in the Table 6.4.

QSAR Model 1
\[
BA = [-2.77 (± 0.02)] + Csev [1.87 (± 7.26)] + PMI-Y [5.45 (± 2.02)] + PC [4.41 (± 1.41)]
\]
\(n = 17, r = 0.93, r^2 = 0.87, \text{variance} = 0.001, \text{std} = 0.0384, F = 32.7\)
\(Q^2 = 0.9991, Spress = 0.0439, SDEP = 0.8226\) (6.6)

QSAR Model 2
\[
BA = [-2.76 (± 0.03)] + Csev [1.76 (± 1.18)] + PMI-Y [5.14(±3.30)] + PC [4.20 (± 2.31)]
\]
\(n = 17, r = 0.82, r^2 = 0.68, \text{variance} = 0.003, \text{std} = 0.0631, F = 10.9,\)
\(Q^2 = 0.9367, Spress = 0.0449, SDEP = 0.8236\) (6.7)

QSAR Model 3
\[
BA = [-2.77 (± 0.03)] + CAE [3.64 (± 2.61)] + Csev [1.88 (± 1.96)] + PC [4.25 (± 2.42)]
\]
\(n = 17, r = 0.81, r^2 = 0.65, \text{variance} = 0.004, \text{std} = 0.0661, F = 9.56\)
\(Q^2 = 0.9336, Spress = 0.0423, SDEP = 0.8251\) (6.8)

QSAR Model 4
\[
BA = [-2.78 (± 0.03)] + CAE [3.52 (± 1.97)] + Csev [1.97 (± 9.41)] + PC [4.42 (± 1.82)]
\]
\(n = 17, r = 0.89, r^2 = 0.79, \text{variance} = 0.002, \text{std} = 0.0494, F = 17.88\)
\(Q^2 = 0.9289, Spress = 0.0456, SDEP = 0.8281\) (6.9)

QSAR Model 5
\[
BA = [-2.76 (± 0.03)] + PMI-Y [5.14 (± 3.46)] + PC [4.19 (± 2.42)] + NVDW [3.70(± 2.83)]
\]
\(n = 17, r = 0.80, r^2 = 0.65, \text{variance} = 0.004, \text{std} = 0.0663, F = 9.44\)
\(Q^2 = 0.9380, Spress = 0.0442, SDEP = 0.8218\) (6.10)
Table 6.4  Descriptors used for QSAR study of antioxidant activities by Nitric oxide method

<table>
<thead>
<tr>
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<th>CAE</th>
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<td>505.696</td>
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<td>-10.317</td>
<td>286.646</td>
<td>503.129</td>
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</table>
6.2.3 QSAR equations for antioxidant activity by DPPH method

A set of 30 compounds were selected from the reports obtained from the antioxidant activity by DPPH method and divided as training set and test set each consisting of 17 and 13 compounds respectively by random selection. The descriptors used in this study were given along with values in the Table 6.5.

QSAR Model 1

\[
BA = [-2.75(\pm 0.03)] + \text{PMI-Z} [3.75(\pm 2.65)] + \text{PC} [2.13(\pm 2.22)] + \text{NVDW} [4.23(\pm 2.59)] \\
n = 17, r = 0.77, r^2 = 0.60, \text{variance} = 0.003, \text{std} = 0.0607, F = 7.68. \\
Q^2 = 0.9401, \text{Spress} = 0.8386, \text{SDEP} = 0.9526 \quad (6.11)
\]

QSAR Model 2

\[
BA = [-2.75 (\pm 0.03)] + \text{PMI-Z} [3.73 (\pm 2.69)] + \text{V} [-2.22(\pm 2.69)] + \text{NVDW} [4.21 (\pm 2.63)] \\
n = 17, r = 0.77, r^2 = 0.59, \text{variance} = 0.003, \text{std} = 0.0616, F = 7.32. \\
Q^2 = 0.9371, \text{Spress} = 0.8167, \text{SDEP} = 0.9254 \quad (6.12)
\]

QSAR Model 3

\[
BA = [-2.76(\pm 0.03)] + \text{CT} [5.20(\pm 5.87)] + \text{PMI-Z} [3.87(\pm 2.71)] + \text{NVDW} [4.41 (\pm 2.66)] \\
n = 17, r = 0.77, r^2 = 0.59, \text{variance} = 0.003, \text{std} = 0.0617, F = 7.28. \\
Q^2 = 0.9231, \text{Spress} = 0.8672, \text{SDEP} = 0.9112 \quad (6.13)
\]

QSAR Model 4

\[
BA = [-2.73(\pm 0.03)] + \text{V} [-2.22(\pm 2.69)] + \text{PMI-Z} [3.45 (\pm 2.73)] + \text{NVDW} [3.95( \pm 2.67)] \\
n = 17, r = 0.76, r^2 = 0.58, \text{variance} = 0.003, \text{std} = 0.0625, F = 6.95. \\
Q^2 = 0.9100, \text{Spress} = 0.8218, \text{SDEP} = 0.9052 \quad (6.14)
\]

QSAR Model 5

\[
BA = [-2.77 (\pm 0.04)] + \text{CT} [6.51 (\pm 6.27)] + \text{MW} [8.29 (\pm 5.39)] + \text{PMI-Z} [4.13 (\pm 2.82)] \\
n = 17, r = 0.75, r^2 = 0.56, \text{variance} = 0.004, \text{std} = 0.0638, F = 6.47482. \\
Q^2 = 0.9004, \text{Spress} = 0.8166, \text{SDEP} = 0.9021 \quad (6.15)
\]
Table 6.5  Descriptors used for QSAR study of antioxidant activities by DPPH method

<table>
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<tr>
<th>Code</th>
<th>PMI-Z</th>
<th>NVDW</th>
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