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Research article

# Quantitative structure property relationship (QSPR) studies for predicting renal clearance of cephalosporins

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## Abstract

ß-lactam antibiotics are of clinical importance for treatment of bacterial infections. Several penicillins and cephalosporins with broad spectra of activity and high stability against various β-lactamases have been developed and introduced in clinical practice. Due to increasing prevalence of antibiotic resistance, efforts to synthesize more compounds for better activity are still on. Traditionally, a combination of serendipity and empiricism has been the basis of new drug discovery. Trial and error synthesis of compounds and their random screening for activity have proved to be both time-consuming and uneconomical. Hence, predicting pharmacokinetic parameters, of a new molecule, in an early stage of drug design, is of as high importance as the activity of the compound. With rapid advances in computation power of machines and availability of experimental data, these ADME properties can now be better predicted by using suitable computational methods. In the present study, a quantitative structure-property relationship study of 32 cephalosporins to renal clearance was performed with descriptors of molecular structures. Good correlations of Renal Clearance were obtained with constitutional and electrostatic descriptors like Bond length between C-O, bond length between H-O bonds, maximum bond length between H-N bond, number of H-O bonds and charge of all C atoms. High values of $R^2$ (0.8397) and $Q^2$ (0.7746) were indicative of high predictive power of this correlation. Also, lower $R^2$ RAND value compared to $R^2$ indicates that the correlations obtained are not chance correlations and hence can be used for prediction purposes.

**Key words:** Cephalosporins, ADME, QSPR, renal clearance.

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## 1. Introduction

Infectious diseases are responsible for a significant proportion of deaths worldwide and according to the World Health Organization, antimicrobial agents are considered to be miracle drugs that are the leading weapons in the treatment of infectious diseases. Unfortunately, a number of the current clinically

efficacious antimicrobial agents are becoming less effective because of the development of microbial resistance. So, there is an urgent need for discovery or optimization of novel antimicrobial agents that are active against resistant microbial strains.

The pharmaceutical industry need to develop continuously new drugs in order to fight the development of resistance in pathogenic agents, and to cope with newly discovered types of infections [1]. Since ADME (absorption, distribution, metabolism and elimination) properties are important parameters in lead identification, the *in silico* methods to search for drug candidates with good ADME properties has attracted the pharmaceutical industry [2-4].

Various quantitative structure-activity/property relationship (QSAR/QSPR) approaches have been applied to find relationships between ADME parameters and molecular structure and properties. QSPRs are among the most widely used techniques in rational drug design, which find mathematical relationships between physicochemical properties of compounds and their experimentally determined values. Thus, these derived QSPR models can be subsequently used to predict pharmacokinetic properties of new derivatives.

Traditionally, a combination of serendipity and empiricism has been the basis of new drug discovery. Trial and error synthesis of compounds and their random screening for activity have proved to be both time-consuming and uneconomical. Further, therapeutic effects and hazards to health are assessed using a series of experimental and *in vivo* tests. However, usage of animal models is often subject to ethical (and financial) considerations. Therefore, alternative methods have been under development to reduce the requirement of animals in testing [5].

The structural formula of an organic compound, in principle, contains coded within it all the information which predetermines the chemical, biological, and physical properties of that compound. If we can understand how a molecular structure brings about a particular effect in a biological system, we have a key to unlocking the relationship and using that information to our advantage. Formal development of these relationships on this premise proved to be the foundation for the development of predictive models [6, 7].

Quantitative structure–property relationships (QSPRs) are mathematical models that attempt to relate the structure-derived features of a compound to its biological or physicochemical activity. Similarly, quantitative structure–toxicity relationship (QSTR) or quantitative structure–pharmacokinetic relationship (QSPR) is used when the modeling applies on toxicological or pharmacokinetic systems. QSAR (also QSPR, QSTR, and QSPR) works on the assumption that structurally similar compounds have similar activities. Therefore, these methods have predictive and diagnostic abilities. They can be used to predict the biological activity (e.g., $IC_{50}$) or class (e.g., inhibitor versus non-inhibitors) of compounds before the actual biological testing. They can also be used in the analysis of structural characteristics that can give rise to the properties of interest.

The explosive development of computer technology and methodologies to calculate molecular properties increasingly made it possible to use computer techniques to aid the drug discovery process. The use of computer techniques in this context is often called computer-aided drug design (CADD), but since the development of

drug involves a large number of steps in addition to the development of a high affinity ligand a more appropriate name computer-aided ligand design (CALD) has also been proposed [8].

## 2. Materials and Methods

The present study was undertaken with an objective to establish quantitative-structure pharmacokinetic relationships (QSPR) of prognostic relevance in the β-lactam series of drugs, specifically cephalosporins. The reason to select cephalosporins was because such correlations are developed for very few drugs. Further, very few reports on QSPR were available for this series of drugs and that too involving only small sets of drugs and few descriptors. Thus, an attempt was made to evaluate quantitative relationships between structural descriptors of cephalosporin molecules and renal clearance.

**The work was divided into three phases:**

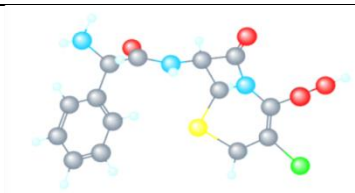
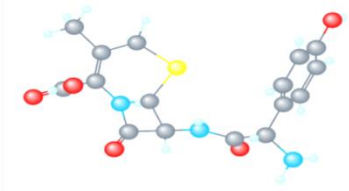
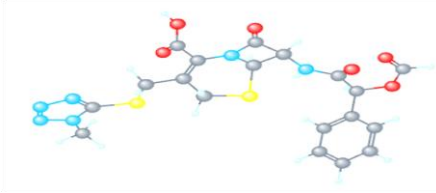
1. Computation of molecular descriptors
2. Compilation of pharmacokinetic data
3. Development of meaningful correlations

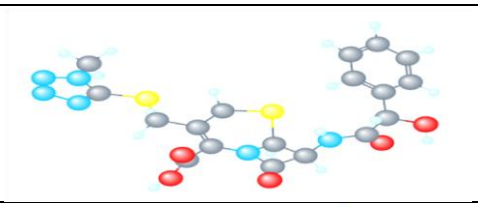
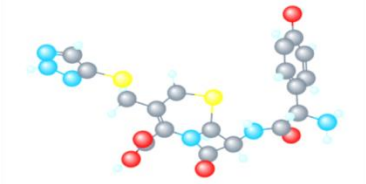
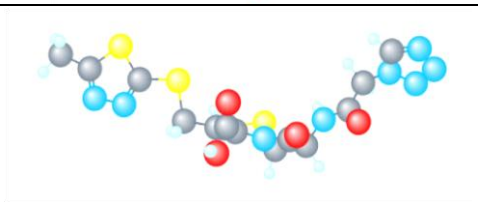
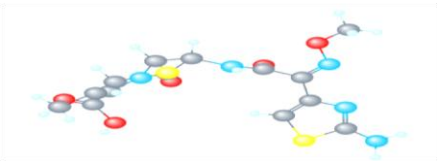
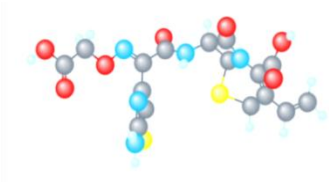
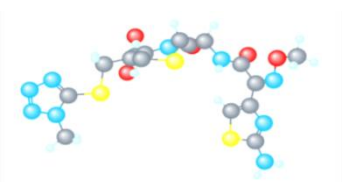
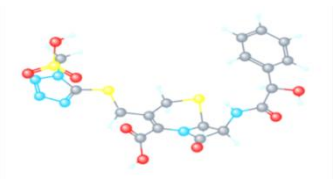
**Computation of molecular descriptors**

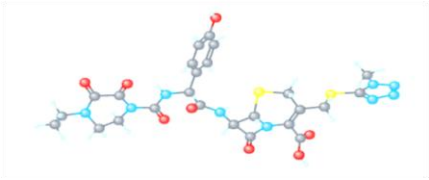
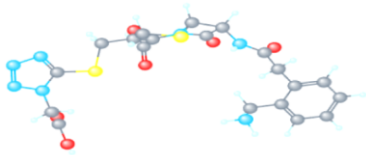
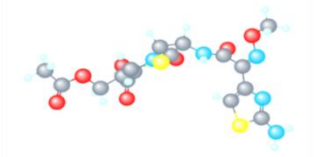
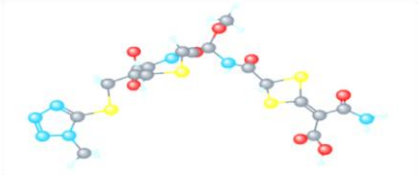
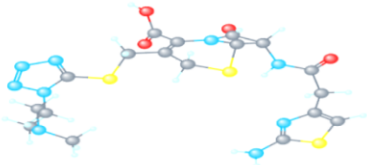
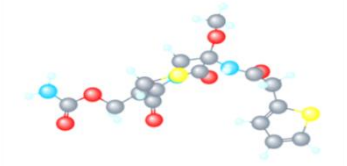
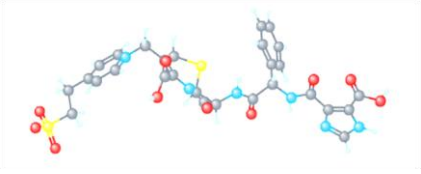
It is well known fact that the structure of drug molecules is expressed quantitatively in terms of its physicochemical descriptors, which are lipophilic, electronic and steric in nature. The physicochemical descriptors govern the biological activity of the compounds.

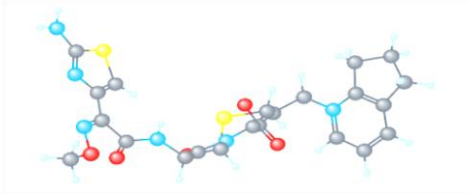
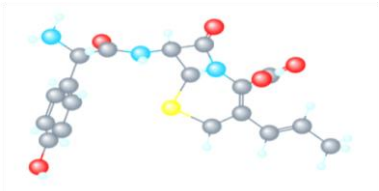
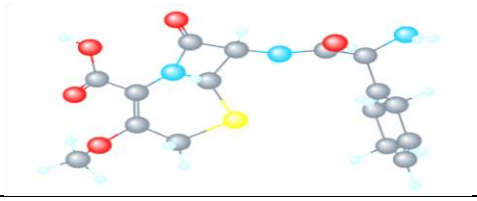
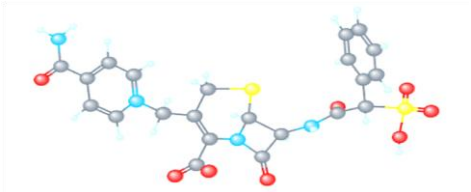
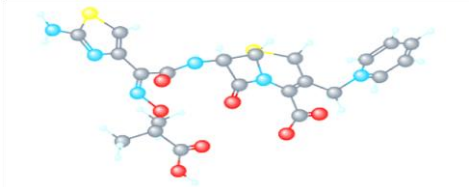
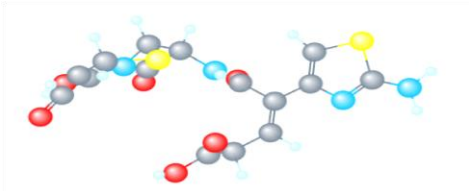
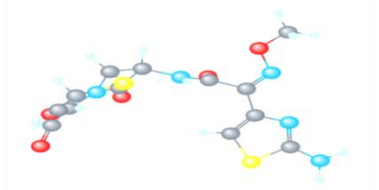
32 cephalosporins, for which experimental renal clearance values are available, were selected for the study. PUBCHEM database contains 2D and 3D minimized structures of large number of drugs and other molecules. 3D structures of selected cephalosporins were downloaded from the database and used as such for correlation studies. (Table 1) Structures of cephalosporins in molfile format were used as input for computation of descriptors.

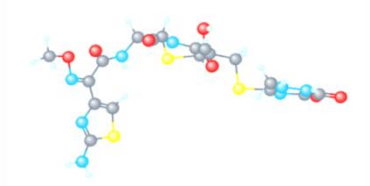
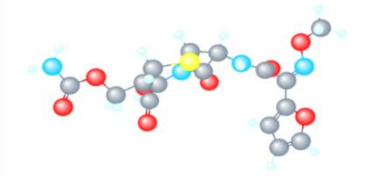
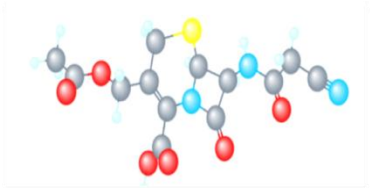
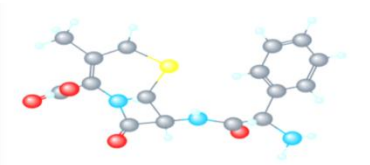
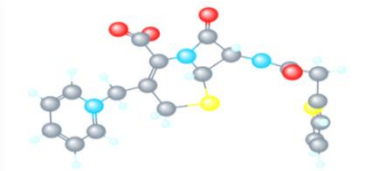
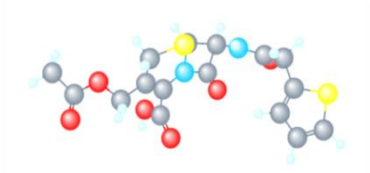
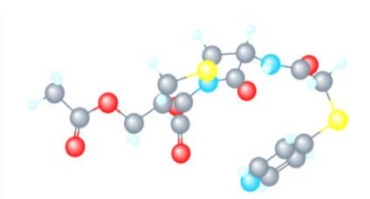
**Table 1. 3D structure of selected Cephalosporins used in study**

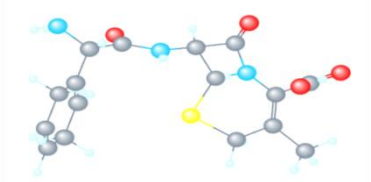
| S No. | Cephalosporin | 3 D Structure |
|---|---|---|
| 1 | Cefaclor |  |
| 2 | Cefadroxil |  |
| 3 | Cefamandole nafate |  |

| S No. | Cephalosporin | 3 D Structure |
|---|---|---|
| 4 | Cefamandole |  |
| 5 | Cefatrizine |  |
| 6 | Cefazolin |  |
| 7 | Cefetamet |  |
| 8 | Cefixime |  |
| 9 | Cefmenoxime |  |
| 10 | Cefonicid |  |

| S No. | Cephalosporin | 3 D Structure |
|---|---|---|
| 11 | Cefoperazone |  |
| 12 | Ceforanide |  |
| 13 | Cefotaxime |  |
| 14 | Cefotetan |  |
| 15 | Cefotiam |  |
| 16 | Cefoxitin |  |
| 17 | Cefpimizole |  |

| S No. | Cephalosporin | 3 D Structure |
|---|---|---|
| 18 | Cefpirome |  |
| 19 | Cefprozil |  |
| 20 | Cefroxadine |  |
| 21 | Cefsulodin |  |
| 22 | Ceftazidime |  |
| 23 | Ceftibuten |  |
| 24 | Ceftizoxime |  |

| S No. | Cephalosporin | 3 D Structure |
|---|---|---|
| 25 | Ceftriaxone |  |
| 26 | Cefuroxime |  |
| 27 | Cephacetrile |  |
| 28 | Cephalexin |  |
| 29 | Cephaloridine |  |
| 30 | Cephalothin |  |
| 31 | Cephapirin |  |

| S No. | Cephalosporin | 3 D Structure |
|---|---|---|
| 32 | Cephradine |  |

| | | | |
|---|---|---|---|
| = Hydrogen | = Carbon | = Oxygen | = Nitrogen |
| = Sulfur | = Chlorine | | |

Representative Molfile of one of the cephalosporin, i.e. Cefaclor used in the study is given below:

```
CEFACLOR 51039
 -OEChem-01232605283D

 38 40  0     1  0  0  0  0  0999 V2000
   4.3759   -2.8607    0.1803 Cl  0  0  0  0  0  0  0  0  0  0  0  0
   0.4211   -1.2636    1.0217 S   0  0  0  0  0  0  0  0  0  0  0  0
   2.3110    2.5640   -0.8543 O   0  0  0  0  0  0  0  0  0  0  0  0
  -2.1507    2.0851    1.5566 O   0  0  0  0  0  0  0  0  0  0  0  0
   5.3604    0.5101    0.0076 O   0  0  0  0  0  0  0  0  0  0  0  0
   4.3871    0.0327   -2.0061 O   0  0  0  0  0  0  0  0  0  0  0  0
   2.2714    0.5146    0.3114 N   0  0  0  0  0  0  0  0  0  0  0  0
  -0.6351    1.4084   -0.0623 N   0  0  0  0  0  0  0  0  0  0  0  0
  -4.0767    2.3920   -0.3999 N   0  0  0  0  0  0  0  0  0  0  0  0
   1.2515    0.3141    1.3270 C   0  0  1  0  0  0  0  0  0  0  0  0
   0.5689    1.5738    0.7510 C   0  0  1  0  0  0  0  0  0  0  0  0
   1.8682    1.7394   -0.0895 C   0  0  0  0  0  0  0  0  0  0  0  0
   3.2440   -0.3919    0.0343 C   0  0  0  0  0  0  0  0  0  0  0  0
   1.9540   -2.2411    1.2193 C   0  0  0  0  0  0  0  0  0  0  0  0
   3.1419   -1.6662    0.4708 C   0  0  0  0  0  0  0  0  0  0  0  0
  -1.9169    1.6830    0.4179 C   0  0  0  0  0  0  0  0  0  0  0  0
  -3.0082    1.4114   -0.6118 C   0  0  1  0  0  0  0  0  0  0  0  0
   4.3725    0.0641   -0.7926 C   0  0  0  0  0  0  0  0  0  0  0  0
  -3.5054   -0.0155   -0.5080 C   0  0  0  0  0  0  0  0  0  0  0  0
  -2.8881   -1.0009   -1.2576 C   0  0  0  0  0  0  0  0  0  0  0  0
  -4.5653   -0.3008    0.3343 C   0  0  0  0  0  0  0  0  0  0  0  0
  -3.3458   -2.3150   -1.1619 C   0  0  0  0  0  0  0  0  0  0  0  0
  -5.0228   -1.6150    0.4300 C   0  0  0  0  0  0  0  0  0  0  0  0
  -4.4130   -2.6221   -0.3182 C   0  0  0  0  0  0  0  0  0  0  0  0
   1.6341    0.4445    2.3464 H   0  0  0  0  0  0  0  0  0  0  0  0
   0.4597    2.3811    1.4859 H   0  0  0  0  0  0  0  0  0  0  0  0
  -0.5495    1.0672   -1.0168 H   0  0  0  0  0  0  0  0  0  0  0  0
   1.7232   -3.2486    0.8573 H   0  0  0  0  0  0  0  0  0  0  0  0
   2.1915   -2.3136    2.2862 H   0  0  0  0  0  0  0  0  0  0  0  0
  -2.6100    1.5863   -1.6194 H   0  0  0  0  0  0  0  0  0  0  0  0
  -4.7869    2.2823   -1.1235 H   0  0  0  0  0  0  0  0  0  0  0  0
  -3.7028    3.3332   -0.5191 H   0  0  0  0  0  0  0  0  0  0  0  0
  -2.0565   -0.7725   -1.9177 H   0  0  0  0  0  0  0  0  0  0  0  0
```

```
   -5.0487    0.4568    0.9434 H   0  0  0  0  0  0  0  0  0  0  0  0
    6.1360    0.8252   -0.5037 H   0  0  0  0  0  0  0  0  0  0  0  0
   -2.8705   -3.0993   -1.7438 H   0  0  0  0  0  0  0  0  0  0  0  0
   -5.8510   -1.8554    1.0903 H   0  0  0  0  0  0  0  0  0  0  0  0
   -4.7684   -3.6456   -0.2425 H   0  0  0  0  0  0  0  0  0  0  0  0
  1 15  1  0  0  0  0
  2 10  1  0  0  0  0
  2 14  1  0  0  0  0
  3 12  2  0  0  0  0
  4 16  2  0  0  0  0
  5 18  1  0  0  0  0
  5 35  1  0  0  0  0
  6 18  2  0  0  0  0
  7 10  1  0  0  0  0
  7 12  1  0  0  0  0
  7 13  1  0  0  0  0
  8 11  1  0  0  0  0
  8 16  1  0  0  0  0
  8 27  1  0  0  0  0
  9 17  1  0  0  0  0
  9 31  1  0  0  0  0
  9 32  1  0  0  0  0
 10 11  1  0  0  0  0
 10 25  1  0  0  0  0
 11 12  1  0  0  0  0
 11 26  1  0  0  0  0
 13 15  2  0  0  0  0
 13 18  1  0  0  0  0
 14 15  1  0  0  0  0
 14 28  1  0  0  0  0
 14 29  1  0  0  0  0
 16 17  1  0  0  0  0
 17 19  1  0  0  0  0
 17 30  1  0  0  0  0
 19 20  2  0  0  0  0
 19 21  1  0  0  0  0
 20 22  1  0  0  0  0
 20 33  1  0  0  0  0
 21 23  2  0  0  0  0
 21 34  1  0  0  0  0
 22 24  2  0  0  0  0
 22 36  1  0  0  0  0
 23 24  1  0  0  0  0
 23 37  1  0  0  0  0
 24 38  1  0  0  0  0
M  END
$$$$
```

Software used to calculate the descriptors were, QikProp and CODESSA (Comprehensive Descriptors for Structural and Statistical Analysis). One of the major advantages of CODESSA is its large pool of molecular descriptors, which are calculated for each chemical structure. Descriptors are automatically calculated for all structures

added to the storage. These programs were taken from Schrödinger and M/s Semichem, Kansas, USA respectively. These software were selected on the basis of literature reports where it was shown to possess most of the desired attributes in the development of quantitative structure property relationships.

Steps in QikProp software to calculate descriptors included:

- MOL files were used as input to the software by selecting the command Project→Import structures. All the molfiles were selected and imported into QikProp. Descriptors were calculated by using commands Application→QikProp and pressing run. QikProp calculates all the descriptors and creates a project table.

For developing better correlations, additional descriptors were calculated using CODESSA. Descriptors obtained in QikProp were saved as CSV file for integration into CODESSA. CODESSA has a facility to input files directly from a CSV or a text file format. To calculate codessa descriptors, command Descriptors→calculate was used.
CODESSA calculated additional descriptors for each of cephalosporin.

**Compilation of pharmacokinetic (Renal clearance) data**

For comparing the predicted values of renal clearance with actual values, reported values of renal clearance of cephalosporins in humans were taken from literature [9-13]. Different authors have reported variable values, all values were taken and a mean of value for each cephalosporin was calculated. Compiled values of renal clearance for all 32 cephalosporins used in study are given in Table 2.

**Table 2. Renal clearance values of selected Cephalosporins**

| # | Cephalosporin | $CL_R$ (mL/min) | # | Cephalosporin | $CL_R$ (mL/min) |
|---|---|---|---|---|---|
| 1. | Cefaclor | 289.5 | 2. | Cefotiam | 200 |
| 3. | Cefadroxil | 128.35 | 4. | Cefoxitin | 285.37 |
| 5. | Cefamandole | 162 | 6. | Cefpimizole | 94.5 |
| 7. | Cefamandole nafate | 225 | 8. | Cefpirome | 82.1 |
| 9. | Cefatrizine | 175 | 10. | Cefprozil | 171.5 |
| 11. | Cefazolin | 52.5 | 12. | Cefroxadine | 291.5 |
| 13. | Cefetamet | 130.3 | 14. | Cefsulodin | 85 |
| 15. | Cefixime | 21.8 | 16. | Ceftazidime | 90.87 |
| 17. | Cefmenoxime | 176 | 18. | Ceftibuten | 62.1 |
| 19. | Cefonicid | 22.26 | 20. | Ceftizoxime | 107.33 |
| 21. | Cefoperazone | 17.86 | 22. | Ceftriaxone | 7.87 |
| 23. | Ceforanide | 4.15 | 24. | Cefuroxime | 125 |
| 25. | Cefotaxime | 160.5 | 26. | Cephacetrile | 313 |
| 27. | Cefotetan | 26.5 | 28. | Cephalexin | 195 |
| 29. | Cephalothin | 252 | 30. | Cephaloridine | 130 |
| 31. | Cephapirin | 340 | 32. | Cephradine | 343 |

**Development of meaningful correlations**

One of several problems in design of QSPR models is the selection of the most relevant set of molecular descriptors for the property or activity that is intended to be modeled. Chemical structures are usually encoded by a variety of descriptor families such as functional groups, topological, constitutional, thermodynamic, quantum mechanical, etc. Descriptor selection is the process of identifying most relevant information rich descriptors from large set of available descriptors. . All the descriptors generated for each molecule are not significant in developing QSPR models. The use of all available descriptors in the model development process causes poor predictions because of over fitting. Only significant descriptors calculated by QikProp and CODESSA were taken in the correlation studies. Insignificant or intercorrelated descriptors were skipped. Correlation studies were carried out by "Best Multilinear Regression" sub routine in CODESSA.

Selection criteria and steps used for "Best Multilinear Regression" in CODESSA were:

- Maximum number of descriptors, started from 1 and then taken up to depending on the number of molecules selected. Drug molecules: Descriptor ratio was taken as 6:1, which implies that not more than one descriptor per 6 molecules in a series was used for developing correlations. For example, if there were 21 molecules for a particular property, maximum number of descriptors used for developing regression equations was kept at 3. Similarly for a series having 40 molecules, maximum number of descriptors was 6.
- Maximum number of correlations per number of descriptor were kept as 5
- Correlation improvement cut-off was kept as 0.01
- Maximum $r^2$ for orthogonal descriptor was kept as 0.5
- If missing property value, then the selection was made to skip structure

"Best Multilinear Regression" routine tests a large number of correlations as each descriptor type is analyzed for correlations individually for the selected pharmacokinetic property.

## 3. Results and discussion

Renal clearance data was available for 32 cephalosporins, thus, correlations were attempted keeping the number of maximum descriptors to 5 thereby limiting the drug: descriptor ration to 6:1. LOO and y-scramble tests were also performed. The best correlations obtained with renal clearance ($CL_R$) for cephalosporins are given in below Table 3. The table lists equations starting from 1 descriptor equation up to an equation with maximum number of descriptors (i.e. 5) that can be used as mentioned above.

With the probability of reporting a large number of such correlations for each property, it was considered necessary to change the format of these correlations into an equation format. The validity of the equation and the relative importance of the different parameters used can be judged by four statistical criteria; namely coefficient of determination $R^2$, Cross validated $R^2$ ($Q^2$), Fisher's F value, and $R^2$ Rand which is the maximum $R^2$ obtained after randomizing the property values and finding correlations with descriptors again. The larger value of *F* indicates higher probability of QSPR equation being significant. These methods provide correlation coefficient (*r*), standard deviation (*s*), and ratio between variance of calculated and observed activates (*F*). Depending upon the values of these statistical parameters, the significance of each equation was evaluated.

**Table 3. Correlations of renal clearance in the series of Cephalosporins**

| | Equation | M | N | $R^2$ | $Q^2$ | F-Value | $R^2$ RAND |
|---|---|---|---|---|---|---|---|
| 1. | $Cl_R$ = - 333.858*Average Information Content (Order 1) + 1570.007 | 1 | 32 | 0.4689 | 0.4089 | 26.4875 | 0.4021 |
| 2. | $Cl_R$ = 1898.612*Average Bond Length for a C-O Bond - 382.605*Average Information Content (Order 1) - 642.784 | 2 | 32 | 0.6054 | 0.5289 | 22.2454 | 0.4762 |
| 3. | $Cl_R$ = 3405.017*Average Bond Length for a C-O Bond - 647.698*Net Zefirov Charge of All C Atoms - 197.354*Uniform-Mass, Center of Mass, X - 3904.678 | 3 | 32 | 0.7476 | 0.6802 | 27.6409 | 0.5456 |
| 4. | $Cl_R$ = 3350.916*Average Bond Length for a C-O Bond + -618.266*Net Zefirov Charge of All C Atoms + - 177.44*Uniform-Mass, Center of Mass, X-33.616*Number of H-O Bonds-3804.09 | 4 | 32 | 0.7899 | 0.7128 | 25.3760 | 0.4818 |
| 5. | $Cl_R$ = 3208.327*Average Bond Length for a C-O Bond - 590.784*Net Zefirov Charge of All C Atoms - 205.246*Uniform-Mass, Center of Mass, X + 43161.077*Maximum Bond Length for a H-N Bond - 31.141*Fractional Minimum Zefirov Negative Charge Times ASASA - 47542.826 | 5 | 32 | 0.8397 | 0.7746 | 27.2366 | 0.5690 |

M = Number of molecular descriptors, N = Number of cephalosporins

Good correlations of Renal Clearance were obtained with constitutional and electrostatic descriptors. The descriptors that figured in the best correlation (Equation 5, Table 3) were Bond length between C-O, bond length between H-O bonds, maximum bond length between H-N bond, number of H-O bonds and charge of all C atoms. High values of $R^2$ (0.8397) and $Q^2$ (0.7746), obtained with equation 5, are indicative of high predictive power of this correlation equation. It is notable that the $R^2$ RAND value is lesser than the $R^2$, which indicates that the correlation equation obtained, is not chance correlations and hence can be used for prediction purposes.

As it would be too voluminous to give details of each of the equations obtained, details of only the best correlation is given. The correlation matrix of descriptors used in Equation 5 is given in the Table 4**.**

**Table 4. Correlation matrix for selected descriptors in Equation 5, Table 3**

| | Average Bond Length for a C-O Bond | Net Zefirov Charge of All C Atoms | Uniform-Mass, Center of Mass, X | Maximum Bond Length for a H-N Bond | Fractional Minimum Zefirov Negative Charge Times ASASA |
|---|---|---|---|---|---|
| Average Bond Length for a C-O Bond | 1.0000 | | | | |
| Net Zefirov Charge of All C Atoms | 0.4030 | 1.0000 | | | |
| Uniform-Mass, Center of Mass, X | 0.2481 | -0.1699 | 1.0000 | | |
| Maximum Bond Length for a H-N Bond | -0.3289 | -0.6175 | 0.2802 | 1.0000 | |
| Fractional Minimum Zefirov Negative Charge Times ASASA | -0.3428 | -0.4416 | 0.1628 | 0.7545 | 1.0000 |

*The correlation matrix* indicates that none of the descriptors used in the correlation are orthogonal with the other descriptors.

*The MLR regression coefficients* for individual descriptors used in best fit Equation 5 are given in Table 5.

*The plots of experimental versus predicted renal clearance values* obtained are given in Figure 1.

With all the correlations highly significant, and the $Q^2$ values reasonably high (all > 0.5), some excellent relationships are achieved which can be successfully used to assess the renal clearance of newer molecules.

**Table 5. MLR regression coefficients and t-values for $CL_R$ in cephalosporins**

| # | Desc. Name | Coeff. | t | p(t) | SE |
|---|---|---|---|---|---|
| 0 | Intercept | -47542.8256 | -3.3559 | 0.002442 | 14167.1347 |
| 1 | Average Bond Length for a C-O Bond | 3208.3268 | 6.8197 | 3.08E-07 | 470.4483 |
| 2 | Net Zefirov Charge of All C Atoms | -590.7837 | -7.7480 | 3.21E-08 | 76.2496 |
| 3 | Uniform-Mass, Center of Mass, X | -205.2464 | -7.0943 | 1.56E-07 | 28.9313 |
| 4 | Maximum Bond Length for a H-N Bond | 43161.0773 | 3.1112 | 0.004485 | 13872.5941 |
| 5 | Fractional Minimum Zefirov Negative Charge Times ASASA | -31.1406 | -3.7809 | 0.000826 | 8.2364 |

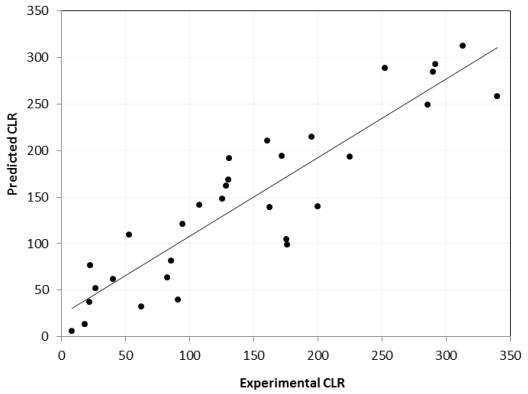



**Figure 1. Plot of experimental vs predicted renal clearance (CLR)**

## Conclusion

Good correlations of Renal Clearance were obtained with constitutional and electrostatic descriptors. The descriptors that figured in the best correlation were Bond length between C-O, bond length between H-O bonds, maximum bond length between H-N bond, number of H-O bonds and charge of all C atoms. High values of $R^2$ (0.8397) and $Q^2$ (0.7746), obtained with 5 descriptors are indicative of high predictive power of this correlation. Also, $R^2$ RAND values lesser than $R^2$ shows that these are not chance correlations.

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