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# Quantitative Structure-Pharmacokinetic Relationship Modelling on Quinolone Drugs: Serum Protein Binding

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This study was conducted to investigate quantitative structure pharmacokinetic relationships (QSPR) for serum protein binding (% SPB) in humans amongst 28 quinolone drugs employing extra thermodynamic multilinear regressions analysis (MLRA) approaches. The overall predictability was found to be quite high ($R^2$ = 0.8699, F = 19.10, $S^2$ = 93.79, $Q^2$ = 0.6675, $p < 0.001$).

**Key Words: QSPR, ADME, Pharmacokinetics, Descriptors.**

## INTRODUCTION

Quantitative structure pharmacokinetic relationships (QSPR) have increasingly been used for the prediction of pharmacokinetic properties of the drug leads. The primary aim of QSPR studies is to enable the drug designer to modify the chemical structure of a pharmacodynamically active drug in such a manner as to alter its pharmacokinetic properties without compromising its pharmacodynamic potential[1]. For more rational drug design, the derivation of QSPR is thus a necessary pre-condition[2].

In the current QSPR investigation, a series of quinolones were chosen due to the availability of % serum protein binding (% SPB) values for a large number of congeners (n = 28). This category of drugs has extensively been used as antimicrobial agents in the treatment of serious infections. Binding to plasma proteins is of fundamental importance in pharmacokinetics, since it affects volume of distribution[3] degree of metabolism[4] and rate of elimination[5].

Traditionally, the % SPB value of a drug candidate is obtained via *in vivo* studies, which tends to be time-consuming and expensive. Therefore, a computational QSPR modeling has been explored to predict % SPB value of drug candidates, as this modeling not only saves considerable amount of time, money, animal life and involvement of normally, healthy human volunteers required for conducting experimental pharmacokinetic studies, but also the expertise of pharmacokinetists and drug designers[6].

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## EXPERIMENTAL

**Molecules:** All 28 compounds used in this study are analogues of the quinolone antibacterials.

**Pharmacokinetic data:** Compounds with known human % SPB values of the quinolone drugs were selected from literature[7-11]. Only % SPB values obtained from healthy adult males after oral administration were used for constructing the dataset % SPB values of these compounds were also log transformed (log % SPB and inverse transformed 1 % SPB) to normalize the data and to reduce unequal error variance.

**Molecular descriptors:** The 3D structures of each compound was constructed by Chem3D software pro v.3.5 (Cambridge Soft Corporation, Cambridge, MA) and HyperChem 8.0.5 software (Hypercube Inc. USA). Energy minimization was carried out using MM2 force field routine(s) and the files were saved as MDL *molfiles*. *Molfiles* generated by Chem3D were exported to DRAGON software and as many as 1497 diverse descriptors, *viz.*, constitutional, geometrical, topological, Whim3D, electronic, *etc*. were calculated. *Molfiles* were also transferred to CODESSA (Semichem, Shawnee, USA) software for calculation of more molecular descriptors.

**QSPR Calculation:** Attempts were made to correlate various descriptors with the % SPB values of quinolone drugs. The initial regression analysis was carried out using heuristic analysis followed by best MLRA (RGMS) options of CODESSA software. In case of the heuristic method, a pre-selection of descriptors was accomplished. All the descriptors were checked to ensure that value of each descriptor was available for each structure and there is a significant variation in these values. Descriptors for which values were not available for every structure in the data in question were discarded. Thereafter, the one-parameter correlation equations for each descriptor were calculated. The number of descriptors in the starting set was further reduced by discarding them if: (a) The F value for one-parameter correlation with the descriptor is < 1.00. (b) The $r^2$ value of one-parameter equation is less than assigned value of $r^2_{min}$ (usually 0.10). (c) The one-parameter t-value is less than the assigned value (usually 1.50). (d) The multi-parameter t-value is less than the assigned value (usually 1.95). (e) Descriptors are highly inter-correlated with another descriptor ($r^2 > 0.65$).

Data of pharmacokinetic parameters of % SPB available for 28 quinolones were analyzed, limiting the ratio of descriptors: drug to 1:4.

As a final result, the heuristic method yields a list of the best 10 correlations each with the highest $r^2$ and F-values. Many such attempts were carried out to obtain significant correlations for quinolones. A set of important descriptors found to significantly ascribe the variation of % SPB, was constructed. Further, a search for the multi-parameter regression with the maximum predicting ability was performed. A number of sets of descriptors were thus made and MLRA performed with %

SPB. Regression plots of each correlation thus attempted were examined. Residual plots were also examined for absence of randomization and distinct patterns to eliminate chance correlations. Logarithmic and inverse transformations of % SPB were also carried out in order to screen the correlation with improved values of $R^2$ and/or F ratio.

**Validation of testing set:** The statistical significance of each correlation was determined on the basis of the value of F-criterion and the magnitude of cross-validated $R^2$, commonly referred to as $Q^2$, calculated according to eqn. no. 1.

$$Q^2 = 1 - \frac{\sum (y_{pred} - y_{obs})^2}{\sum (y_{obs} - y_{mean})^2} \quad (1)$$

A model with good predictive performance has a $Q^2$ value close to 1, models that do not predict better than merely chance alone can have negative values.

The F-values were computed according to eqn. 2:

$$F = \frac{S_1^2}{S_2^2} \quad (2)$$

where, $S_1$ is variance between samples and $S_2$ variance within samples.

The values of computed F-ratio were compared with the critical values tabulated in statistical texts and levels of significance discerned. The correlations found to be statistically significant were compiled from CODESSA software. The names of descriptors were conveniently coded using a WS-Macro program and the files converted to appropriate ASCII formats through in-house built program source codes. These ASCII files were further converted into tabular formats in MS-Word.

## RESULTS AND DISCUSSION

Variable QSPR results were obtained following application of multivariate statistical analysis on quinolone drugs. Table-1 enlists the concise results of only those correlations which were found to be statistical significant, usually at 5 % level or less and/or with important applications. As is vivid from Table-1, % SPB shows positive linear dependence on topological and steric parameters like CIC1, Mv, Mp, G3p, *etc*.

Both logarithmic transformation ($R^2$ = 0.8075, F = 11.79, $S^2$ = 0.0217, $Q^2$ = 0.6582, $p < 0.005$) and inverse transformation ($R^2$ = 0.8028, F = 11.63, $S^2$ = 0.0002, $Q^2$ = 0.5932, $p < 0.005$) of % SPB do not tend to improve the degree of correlations *vis-à-vis* untransformed % SPB ($R^2$ = 0.8699, F = 19.10, $S^2$ = 93.79, $Q^2$ = 0.6675, $p < 0.001$). However, the values of $S^2$ remarkably decreased from values ranging between 93.8 and 227.8 for untransformed to 0.0002-0.0007 for inverse transformed predictions. The residuals were more regulated around the zero-axis for logarithmic transformed values.

TABLE-1
SIGNIFICANT LINEAR, LOGARITHMIC AND INVERSE QSPR POLYNOMIAL EQUATIONS ALONG WITH THE STATISTICAL PARAMETERS FOR A SERIES OF 28 QUINOLONES USING % SPB AS THE PHARMACOKINETIC PARAMETER

| Equations | m | $R^2$ | F | $S^2$ | $Q^2$ | p < |
|---|---|---|---|---|---|---|
| %SPB = 165.85 - 304.88 Hrel | 1 | 0.3209 | 12.29 | 227.76 | 0.2299 | 0.005 |
| %SPB = - 175.66 + 1067.4 G3p + 0.03016 piPC08 | 2 | 0.7008 | 29.28 | 89.22 | 0.6474 | 0.001 |
| %SPB = - 243.65 + 1385.8 G3p + 0.00141 Wap + 9.0720 L2u | 3 | 0.6701 | 16.25 | 198.11 | 0.4223 | 0.001 |
| %SPB = - 514.32 + 605.24 G3p + 1.1104 piPC03 + 93.347 PJ12 + 1404.3 Gu | 4 | 0.7511 | 17.35 | 155.98 | 0.6143 | 0.001 |
| %SPB = - 74.787 + 786.18 G3p + 1.1410 piPC03 + 108.01 PJ12 + 1728.2 Gu - 547.28 FDI | 5 | 0.8040 | 18.04 | 128.44 | 0.5853 | 0.001 |
| %SPB = - 16.259 + 957.13 G3p + 1.2047 piPC03 + 98.908 PJ12 + 1882.8 Gu - 647.82 FDI - 3.4138 DBn | 6 | 0.8271 | 16.75 | 118.64 | 0.5828 | 0.001 |
| %SPB = - 268.09 + 1168.5 Gm + 0.001421 Wap + 708.65 Orel + 647.61 G3u + 7.4999 IAC - 40.406 BIC0 + 544.29 Nrel | 7 | 0.8699 | 19.10 | 93.79 | 0.6675 | 0.001 |
| Log %SPB = - 0.39012 + 4.7173 Crel | 1 | 0.1914 | 6.15 | 0.0700 | 0.0958 | 0.05 |
| Log %SPB = - 8.5029 - 14.722 Dp + 0.0149 piPC03 + 1.8902 PJ13 + 3.4188 L3p + 21.119 Gu 10.074 SPH - 0.67219 AIC2 | 7 | 0.8075 | 11.99 | 0.0217 | 0.6562 | 0.005 |
| 1/ %SPB = 0.034632 + 2.1729 Clrel | 1 | 0.1921 | 6.18 | 0.0007 | 0.0674 | 0.05 |
| 1/ %SPB = 0.97438 + 0.00032651 TIE - 0.0022819 piPC05 - 1.1538 G3p + 0.00034273 piPC08 + 0.47776 P2s - 0.041872 L2u - 0.073213 AIC1 | 7 | 0.8028 | 11.63 | 0.0002 | 0.5932 | 0.005 |

m (no. of descriptors); Hrel, Nrel, Orel, Crel, Clrel (relative number of H atoms, N atoms, O atoms, C atoms, Cl atoms respectively); G3p (3st component symmetry directional WHIM index/weighted by atomic polarizabilities); piPC03, piPC05, piPC08 (Molecular multiple path of order 03, 05 & 08 respectively); Wap (all path wiener index); L2u (2nd component size directional WHIM index/unweighted); PJ12, PJ13 (2D & 3D petitjean shape index respectively); Gu (G total symmetry index/unweighted); FDI (Folding degree Index); DBn (Number of double bonds); Gm (G total symmetry index/weighted by atomic mases); G3u(3st component symmetry directional WHIM index/unweighted); IAC (Total information index of atomic composition); BIC0 (bond information content neighborhood symmetry of 0 order); Dp (D total accessibility index/weighted by atomic polarizabilities); L3p ( 3rd component size directional WHIM index/weighted by atomic polarizabilities); SPH (spherosity); AIC1 & AIC2 (Average information content order 1 & 2 respectively); TIE (E-state topological parameter) P2s (2nd component shape directional WHIM index/weighted by atomic electrotopological states).

## Conclusion

The joint dependence of % SPB values of quinolones on topological and steric parameters indicates that hydrogen and van der Waal's interactions are likely to play a stellar role in governing serum protein binding, which is further fortified by its dependence on constitutional parameters like On, Hrel, Crel, *etc*. % SPB does not seem to have any dependence on lipophilic and electrostatic parameters indicating that hydrophobic and ionic bonding of quinolones is negligible.

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