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In Silico Quantitative Structure Pharmacokinetic Relationships for Elimination Half Life of Fluoroquinolones

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In silico quantitative structure pharmacokinetic relationships (QSPR) enables the drug designer to predict the pharmacokinetic properties of compounds, before their actual synthesis and hence leads to a rational design of new drug. The current study was conducted to develop QSPR for the prediction of elimination half-life ($t_{1/2}$) in humans for congeneric series of fluoroquinolones, using computer assisted Hansch approach. Analysis of several hundreds of QSPR correlations developed in the current study on fluoroquinolones drugs revealed extremely high degree of cross-validated coefficients (Q^2) using leave-one-out (LOO) method ($p < 0.001$). Topological and electronic parameters were found to primarily ascribe the variation in $t_{1/2}$.

Key Words: Fluoroquinolones, Multi linear regression analysis, ADME, Pharmacokinetics, Descriptors.

INTRODUCTION

Drug discovery has always been a competitive industry and now the stakes are even higher than ever. A combination of technologies including *in silico* (computational) models can offer great advantages in improving the odds of success in a discovery programme[1]. Therefore, the use of *in silico* QSPR models in the prognosis of ADME properties is growing rapidly in drug discovery, as they provide immense benefits in throughput and early application of drug design[2,3]. The key objective of this study was to investigate *in silico* QSPR amongst various fluoroquinolones for $t_{1/2}$. Fluoroquinolones were selected for QSPR as, among the different types of antibacterial agents, the effects of fluoroquinolones are better and have attracted much attention[4]. Also, this congeneric series consist of significant number of compounds (n = 24), thoroughly investigated for their pharmacokinetic performance particularly $t_{1/2}$. Further, important descriptors like experimental log P, melting point, molecular weight, *etc.* of these drugs are known and are available in standard texts or in research journals.

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The $t_{1/2}$ value of a drug is an important pharmacokinetic parameter because it determines the residence time of the drug in the body and is useful to find out the time at which the drug levels fall below the therapeutic levels. Also, $t_{1/2}$ of a drug is used to calculate the dosage regimen[5].

EXPERIMENTAL

Quantitative structure pharmacokinetic relationships was carried out amongst various fluoroquinolone drugs employing extra-thermodynamic Multi Linear Regression Analysis (MLRA) approach (Hansch approach).

Dataset: 24 Fluoroquinolones with known human $t_{1/2}$ values were selected from literature[6-11]. In order to ensure that experimental variations in determining $t_{1/2}$ do not significantly affect the quality of present datasets, only $t_{1/2}$ values obtained from healthy adult males after oral administration of drug were used for constructing the dataset.

Molecular structure and descriptors: Chemical structures were drawn using suitable templates under Chem3D software pro v.3.5. (Cambridge Soft Corporation, Cambridge, MA) and HyperChem software. 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 software (Semichem, Shawnee, USA) for calculation of 165 more molecular descriptors.

Multivariate statistical analyses: Attempts were made to correlate various descriptors with the $t_{1/2}$ values. The initial regression analysis was carried out using heuristic analysis followed by best MLRA (RGMS) options of CODESSA software. 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 and multiple parameter correlation equations for each descriptor were calculated.

Data of pharmacokinetic parameters of $t_{1/2}$ available for 24 fluoroquinolones 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 fluoroquinolones. A set of important descriptors found to significantly ascribe the variation of $t_{1/2}$, 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 $t_{1/2}$. 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.

Validation of testing set: The predictability of the final models was tested by cross validation using the "leave-one-out method". Briefly, the descriptors of one compound are removed, the model is rederived and the target properties of the removed compound are predicted. This process is repeated until all target properties have been predicted once for each drug. A value of crossvalidated R^2, commonly called Q^2, is then computed analogous to the conventional R^2 according to eqn. 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.

RESULTS AND DISCUSSION

Variable QSPR results were obtained following application of multivariate statistical analysis on fluoroquinolone drugs. Thousands of such correlation and regression analysis were attempted choosing all the possible combination of available descriptors, each yielding an elaborate output. 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 have been taken into consideration.

As is vivid from Table-1, elimination of half-life for a set of 24 fluoroquinolones showed significant dependence upon topological parameters and electronic parameters. The prominent descriptors explaining variation in $t_{1/2}$ encompass (like X5v, C1C2, BIC2 *etc.*). The overall predictability was found to be quite high ($R^2 = 0.8243$, $F = 16.42$, $S^2 = 13.7009$, $Q^2 = 0.5779$, $P < 0.001$). As lipophilic parameters were not observed to be considerably significant, the diffusional interactions tend to outweigh the permeational ones. The linear correlation plot between the values of $t_{1/2}$ as reported in literature and those using multi-parameter QSPR for a series of 24 fluoroquinolones as well as residual plots of $t_{1/2}$ values showed better uniformity in scatter and randomization (Fig. 1).

Conclusion

In case of fluoroquinolones, topological and electronic parameters were found to primarily ascribe the variation in $t_{1/2}$. Thus overall diffusional (rather than permeational) interactions seem to play a major role in attributing $t_{1/2}$ of fluoroquinolones.

TABLE-1
SIGNIFICANT LINEAR QSPR POLYNOMIAL EQUATIONS ALONG WITH THE STATISTICAL PARAMETERS FOR A SERIES OF 24 FLUOROQUINOLONES USING BIOLOGICAL HALF-LIFE AS THE PHARMACOKINETIC PARAMETER

Equations	m	R^2	F	S^2	Q^2	p<
$t_{1/2}$ = - 5.1519 + 5.4543 X5v	1	0.1689	5.28	52.3377	0.0142	0.05
$t_{1/2}$ = - 2.0051 + 11.762 CIC2	1	0.1288	3.84	54.8637	0.0240	0.1
$t_{1/2}$ = 183.29 - 127.69 BIC2 - 355.76 MSD	2	0.3564	6.92	42.1502	0.2122	0.05
$t_{1/2}$ = - 52.452 + 853.55 PW5 - 496.88 Orel	2	0.3360	6.33	43.4846	0.1550	0.05
$t_{1/2}$ = 56.562 - 95.454 BIC2 + 0.06304 piPC05	2	0.3098	5.61	45.2045	0.1595	0.05
$t_{1/2}$ = 212.12 - 123.92 BIC2 - 514.63 MSD + 12.999 Sn	3	0.5704	10.62	29.3085	0.2985	0.005
$t_{1/2}$ = 259.01 - 182.46 BIC2 - 700.93 MSD + 320.85 HASA-1/TMSA + 7132.4 Xt	4	0.6904	12.82	22.0403	0.3558	0.005
$t_{1/2}$ = - 39.796 + 1118.2 PW5 - 659.86 Orel + 18.070 Sn - 1297.6 MIA - 0.074392 D/Dr06	5	0.7484	13.09	18.7226	0.4258	0.001
$t_{1/2}$ = 1026.3 - 892.13 BIC2 - 811.43 MSD - 109.03 CIC2 + 21.258 X5v - 67.693 AROM - 7.6861 X5sol	6	0.8243	16.42	13.7009	0.5779	0.001

m = no. of descriptors; X5v = average valence connectivity index chi-5; CIC2 = Complementary information content (neighborhood symmetry of 2-order); BIC2 = Bond information content (neighborhood symmetry of 2-order); MSD = Mean square distance index (Balaban); PW5 = Path/walk 5-Randic shape index; Orel = Relative no. of O atoms; PiPC05 = Molecular multiple path of order 05; Sn = No. of sulphur atoms; Xt = Total structure connectivity index; MIA = Moment of inertia A; D/Dr06 = Distance/detour ring index of order 6; AROM = Aromatic city (trial); X5sol = Solvation connectivity index chi-5.

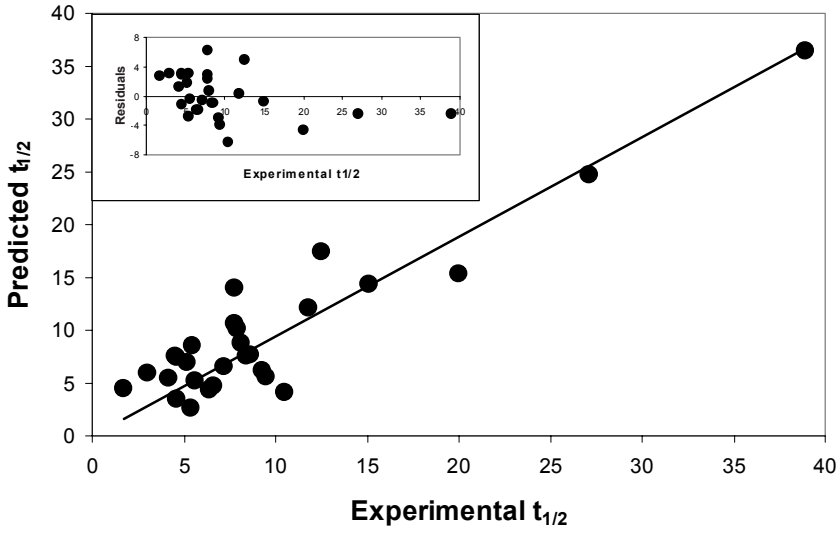

Fig. 1. Linear correlation plot between the values of $t_{1/2}$ as reported in literature and those predicted using multi-parameter QSPR for a series of 24 fluoroquinolones. The inset shows the corresponding residual plot

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