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In Silico Quantitative Structure Pharmacokinetic Relationship Modeling for Quinolone Drugs: Biological Half-Life

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The use of *in silico* approaches for successful prediction of pharmacokinetic properties of compounds during new drug discovery has been increasing exponentially. These *in silico* models, for the prognosis of absorption, distribution, metabolism and excretion (ADME) are invariably based upon the implementation of quantitative structure pharmacokinetic relationship (QSPkR) techniques. This study was conducted to investigate QSPkR for biological half-life ($t_{1/2}$) in humans for 28 quinolone drugs employing extra-thermodynamic multi-linear regression analysis (MLRA) approach. The overall predictability was found to be high (R^2 = 0.8752, F = 20.24, S^2 = 9.3212, Q^2 = 0.7384, $p < 0.001$). Topological, steric and electrostatic parameters were found to primarily ascribe the variation in $t_{1/2}$. Logarithmic transformations of $t_{1/2}$ tend to improve the degree of correlations during one-parameter and two-parameter studies. However, the inverse transformations of $t_{1/2}$ remarkably enhance the degree of correlations (both R^2 and Q^2). Maximum predictability for quinolones was found to be 94.16 %.

Key Words: *In silico* absorption, distribution, metabolism and excretion, QSPkR, Quinolones, Biological hal-life.

INTRODUCTION

Of late, it has been recognized that undesirable absorption, distribution, metabolism and excretion (ADME) of new drug candidates are the major cause(s) of many clinical trial failures. Accordingly, it has been an endeavour of the pharmaceutical scientists to design new drug molecules realistically predicting their pharmacokinetic and pharmacodynamic characteristics prior to their synthesis. Drug discovery and development using the traditional approaches of random screening, in this regard, have proved to be quite time consuming and expensive[1]. This has resulted in a paradigm shift to identify such problems early during the drug discovery process[2]. Apart from the scientific interest, there are economic considerations as well, as out of numerous compounds synthesized, only a few eventually reach the market as a new drug. A sizable proportion of drug candidates fail during clinical trials because

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of poor pharmacokinetic properties. This is an economic disaster, as the failed drugs have been in pipeline for several years, with the large amounts of effort and money invested in their development. Hence, the focus of drug development has widely expanded to include procedures aimed at identifying potential failures as well as successes[3].

The *in vitro* approaches are widely practiced to investigate the ADME properties of new chemical entities[2]. More recently, *in silico* modeling has been investigated as a tool to optimize selection of the most suitable drug candidates for development. Being able to predict ADME properties quickly using computational means is of great importance, as experimental ADME testing is both expensive and arduous, yielding low productivity. Use of computational models in the prediction of ADME properties has been growing rapidly in drug discovery, as they provide immense benefits in throughput and early application of drug design[4].

Biological half-life ($t_{1/2}$), a vital pharmacokinetic parameter, is helpful in designing an optimal dosage regimen. This is related with duration of clinical effects and frequency of dosing. Traditionally, the determination of $t_{1/2}$ value of a drug candidate, obtained *via in vivo* pharmacokinetic study, tends to be quite arduous, time-consuming and expensive. Therefore, in an endeavour to predict the ADME characteristic of $t_{1/2}$ values of quinolone drug candidates in fast and cost-effective manner, the *in silico* procedures of quantitative structure pharmacokinetic relationship (QSPkR) modeling have been explored[5]. The primary aim of QSPkR studies is to enable the drug designer to modify the chemical structure of drug in such a manner as to alter its pharmacokinetic properties without diminishing its pharmacodynamic potential[6,7]. The major advantage of QSPkR lies in the fact that once such a relationship is ascertained with adequate statistical degree of confidence, it can be a valuable assistance in the prognosis of the behaviour of new molecules, even before they are actually synthesized[8].

The key objective of current study is to investigate *in silico* QSPkR amongst various quinolone drugs for $t_{1/2}$. Quinolones were chosen for QSPkR, as this category of drugs has been extensively used as antimicrobial agents in the treatment of serious infections. Also, the quinolones consist of significant number of compounds (n = 28) thoroughly investigated for their pharmacokinetic performance, particularly $t_{1/2}$. Further, the congeners in this class have many common pharmacokinetic characteristics, including the mechanism and degree of affinity with body tissues. Moreover, descriptors like experimental values of log P, melting point, *etc*., of these drugs are known to be available in the standard texts or journals.

Construction of a typical QSPkR study consists of estimation or collection of pharmacokinetic parameters, structural descriptors and the subsequent statistical analysis, as shown in Fig. 1[9].

EXPERIMENTAL

Methods: QSPkR was conducted amongst quinolone drugs employing extra-thermodynamic multi-linear regression analysis (MLRA) approach. The general

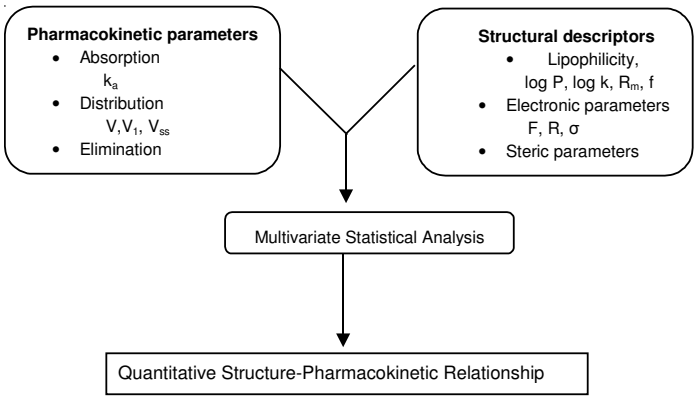

Fig. 1. Quantitative structure-pharmacokinetic relationship (QSPkR): A multidisciplinary endeavour

steps for developing QSPkR model include data set selection, chemical structure entry, 3D structure generation, descriptor calculation and model construction that involves selection of descriptors and validation of testing set using a pentium dual core microprocessor (Intel, USA) desktop (IBM, India) with 2GB RAM and 160 GB Hard Disk Drive. The computer peripherals included HP Laser 1020 series printer and HP Scanjet 2400 scanner.

Dataset selection: The reported values of $t_{1/2}$ of the quinolone drugs in humans were taken from various literature sources[10-14], as shown in Table-1. In order to ensure that experimental variation in determining $t_{1/2}$ does not significantly affect the quality of our datasets, only $t_{1/2}$ values obtained from healthy adult males after oral administration were employed for constructing the dataset. A total of 28 quinolone drugs were selected and used as the dataset for this study. The $t_{1/2}$ value of each of these compounds was also log-transformed (log $t_{1/2}$) and inverse transformed ($1/t_{1/2}$) to normalize the data and to reduce unequal error variance, respectively.

TABLE-1
REPORTED VALUES OF $t_{1/2}$ FOR VARIOUS QUINOLONE DRUGS
EMPLOYED DURING FOR THE CURRENT QSPkR STUDIES

Drug	$t_{1/2}$ (h)	Drug	$t_{1/2}$ (h)	Drug	$t_{1/2}$ (h)
Amifloxacin	4.14	Gatifloxacin	7.46	Oxolinic acid	5.50
Balofloxacin	7.80	Gemifloxacin	6.65	Pefloxacin	10.50
Cinoxacin	1.80	Grepafloxacin	5.20	Pipemidic acid	2.30
Clinafloxacin	5.65	Levofloxacin	7.40	Rosoxacin	6.50
Ciprofloxacin	4.60	Lomefloxacin	6.35	Sitafloxacin	4.60
Difloxacin	27.10	Moxifloxacin	11.80	Sparfloxacin	20.00
Enoxacin	6.20	Nalidixic acid	1.75	Temafloxacin	7.90
Fleroxacin	10.80	Norfloxacin	5.32	Tosufloxacin	4.02
Flosequinan	1.45	Ofloxacin	5.48	Trovafloxacin	7.80
Flumequin	9.50	–	–	–	–

Molecular structure and descriptors: Various structural parameters were computed theoretically employing diverse computer software.

Descriptors calculated by Pallas 2.0: The values of structural descriptors, like log P, pK_a, log D of various quinolones, were calculated using the software Pallas 2.0 (CompuDrug International, Inc., USA). The structures of drugs were graphically drawn on the monitor with the help of a mouse. Suitable templates/ rings were chosen, bonds were drawn and different heteroatoms were chosen from the periodic table provided in the software and incorporated into the structure. The rough graphical sketch representing the structural formula of the compound was transformed to its least energy configuration. The name of the compound was entered to let the structure of drug be stored under its assigned name in the software database. For the estimation of the log P and log D, compounds from the database were selected, the software run for the estimation of the desired descriptors and the results were stored as MDL molfiles.

Descriptors calculated by ChemDraw: Three-dimensional structures of the molecules were drawn in ChemDraw software environment. Structures of drugs were graphically drawn on the monitor with the help of a mouse. Various steps involved were: (**i**) Suitable templates/rings were chosen from the given set of these in the software. (**ii**) Bonds were drawn to represent the skeleton of the substituents attached. (**iii**) Different heteroatoms were chosen from the periodic table provided in the software and were incorporated into the structure. (**iv**) The rough graphical sketch representing the structural formula of the compound was arranged into its least energy configuration. (**v**) The name of the compound was entered to let the structure of drug under its assigned name be stored in the software database. (**vi**) For the estimation of various descriptors, compounds from the database were selected, the software run for estimation of the desired descriptors and the results were stored in the output file the name to which was previously assigned. (**vii**) Each compound from the database was selected and exported to the corresponding molfile after energy minimization is accomplished using Chem3D software.

Parameters calculated by DRAGON: The molfiles generated by Chem 3D software pro v.3.5. (Cambridge Soft Corporation, Cambridge, MA) were imported to Dragon 5.5 (Talete Srl, Milano, Italy). As many as 1497 diverse descriptors, *viz.*, constitutional, geometrical, topological, steric, electrostatic *etc*., were calculated with the help of Dragon software.

Parameters calculated by CODESSA: A large number of molecular descriptors were calculated with the help of CODESSA 2.0 software (Semichem, Shawnee, USA) also. First of all, a worksheet was made in MS-Excel environment to load various molfiles into the software. Each file was saved as a non-document ASCII text file. The said text file consisted of number of columns separated by blanks, each column containing data of one type, *e.g*., structure names, property values, file names, *etc*. Each line contained the same number of columns. The program then scanned the file in order to determine number of columns and provided columns

dialog box, where the type of data in each column and other parameters were specified. Before calculating the descriptors, each loaded structure was checked and necessary corrections were made. "Structure dialog box" was used to enter or change structure name as well as name and type of file associated with every structure. Various classes of descriptors, *viz*., constitutional, topological, geometrical and electrostatic descriptors were selected for calculation using the "calculate descriptor" dialog box. Initially, the descriptors were computed for all the structures loaded into the software. Further, as and when any information was available about new congeners, those particular compounds were also selected for computation of descriptors.

Multivariate statistical analysis: Attempts were made to correlate all the descriptors of quinolone drugs with their respective $t_{1/2}$ values. The initial regression analysis was carried out using HEURISTIC analysis, followed by the best multi-linear regression (BESREGMS) option of CODESSA software. In case of the HEURISTIC method, a pre-selection of descriptors was accomplished. All the descriptors were checked to ensure that the value of each descriptor was available for each structure and there is significant variation in these values. Descriptors, for which the values were not available for every drug structure in the data, were discarded. A hard copy showing the descriptors discarded in this manner was obtained. Thereafter, the one-parameter correlation equations for each descriptor were calculated. The number of descriptors in the starting set was further reduced by discarding these if: (**i**) The F value for the one-parameter correlation with the descriptor is below 1.00. (**ii**) The r^2 value of one-parameter equation is less than assigned value of r^2_{min} (usually 0.10). (**iii**) The one-parameter t-value is less than the assigned value (usually 1.50). (**iv**) The multi-parameter t-value is less than the assigned value (usually 1.95). (**v**) The descriptors are highly inter-correlated with another descriptor ($r^2 > 0.65$).

The maximum number of descriptors involved in a correlation was chosen in accordance with the ratio of number of compounds to number of descriptors as 4:1. The HEURISTIC methods tended to yield the best ten correlations each yielding highest values of r^2 and F ratio. Choosing these descriptors, many such attempts were carried out to obtain the significant correlation(s). A set of important descriptors found to significantly contribute to the variation of $t_{1/2}$ was constructed. Further, a search for the multi-parameter regression with the maximum predicting ability was performed. Regression plots of each correlation thus attempted were examined. Residual plots were also examined for absence of randomization and distinct patterns in order to eliminate chance correlations. Logarithmic and inverse transformations of various pharmacokinetic properties were also carried out in order to screen the correlation with improved values or R^2 and/or F ratio. Graphs were made using MS-Excel software.

The validity of the equation and the relative importance of the different parameters used were judged by four statistical criteria; *viz*., multiple correlation coefficient R, Fisher's F-value, Student's t values and the standard deviation. Depending upon the

values of these statistical parameters, the statistical significance of each correlation was determined on the basis of the F-criterion and the magnitudes of cross-validated R^2, commonly represented as Q^2, were calculated according to eqn. 1.

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

A model with good predictive performance had a Q^2 value close to 1. Models that did not predict better than merely chance alone could have negative values. The F-values were computed from the ratio of variances, according to eqn. 2:

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

where, S_1 and S_2 are the standard deviations between samples and within samples, respectively.

The values of computed F-ratio were compared with that of the critical values tabulated in statistical texts and the levels of significance discerned. The QSPkR correlations found to be statistically significant were compiled using CODESSA software and stored as respective files, under the extension of COD. The names of descriptors were conveniently coded using a WS-Macro program and the files converted to appropriate ASCII format using an in-house developed program code. These ASCII files were further converted into tabular formats in MS-Word milieu.

Therefore, to check for chance correlation, two different approaches were adopted. The first was to limit the drug: descriptor ratio to 4:1. This approach reduced the probability of getting a chance correlation[15,16]. The second was the calculation of the cross-validated R^2 employing the leave-one-out (LOO) method[17]. The bar diagram of the maximum values of the per cent explained (or predicted) variance (*i.e.*, R^2* 100) of untransformed $t^{1/2}$ of 3-D QSPkR studies constructed in comparison to that of the log-transformed and inverse transformed values of $t_{1/2}$ of various quinolones.

RESULTS AND DISCUSSION

Biological half-life ($t_{1/2}$) expresses the period of time required for the amount or the concentration of a drug in body fluids to get reduced by one-half of its original[9]. Biological half-life (or elimination half-life) is a complex parameter obtained from the terminal linear elimination phase. The $t_{1/2}$ values were available for 28 quinolone drugs. Therefore, correlations were attempted keeping the number of maximum descriptors to 7, thereby limiting the drug: descriptor ratio to 4:1.

As mentioned in Table-2, the magnitude of $t_{1/2}$ was found to significantly depend upon the topological, steric and electrostatic parameters. The prominent topological parameters influencing $t_{1/2}$ encompassed Kier shape indices, Kier Hall indices, *etc*. steric parameters included molar refractivity, molecular surface area, *etc*. and electrostatic parameters encompassed HASA, WNSA, *etc*. as is vivid from Table-2.

TABLE-2
SIGNIFICANT LINEAR, LOGARITHMIC AND INVERSE QSPkR EQUATIONS FOR A SERIES OF 28 QUINOLONES USING BIOLOGICAL HALF-LIFE AS THE PHARMACOKINETIC PARAMETER

Equations	m	R^2	F	S^2	Q^2	p <
$t_{1/2}$ = - 9.687 + 2.432 RMW	1	0.3032	7.29	32.9491	0.0917	0.050
$t_{1/2}$ = -16.976 + 1.342 KHI3 + 0.5231 WNSA-3	2	0.4104	8.16	29.7014	0.2140	0.050
$t_{1/2}$ = -32.785 + 1.897 KSI2 + 0.6720 WNSA-3 - 2.3276 SIC1	3	0.5268	9.78	24.7221	0.3211	0.005
$t_{1/2}$ = 76.416 + 3.419 KHI3 + 0.4307 HASA-1 - 68.764 BIC2 - 7.4626 AIC2	4	0.6378	11.74	21.1223	0.3824	0.005
$t_{1/2}$ = 109.762 + 2.9354 KHI3 + 0.3292 HASA-1 - 53.473 BIC2 + 16.473 HASA-2/ TMSA - 1.4372 SIC1	5	0.7241	14.42	14.3406	0.4928	0.005
$t_{1/2}$ = 148.974 + 1.9214 KHI3 + 0.4329 WNSA-3 - 109.871 BIC2 + 28.691 HASA-2/TMSA - 5.3292 AIC1 – 0.1329 Es	6	0.8109	17.51	11.5470	0.6142	0.001
$t_{1/2}$ = 223.647 + 1.6721 KHI3 + 0.3932 WNSA-3 – 152.462 BIC2 + 24.692 HASA-2/TMSA + 0.19814 HASA-1 + 1.431 KSI2 – 0.01134 Es	7	0.8752	20.24	9.3212	0.7384	0.001
log $t_{1/2}$ = -0.4692 + 0.0044 CIC0	1	0.3842	18.90	0.0624	0.2144	0.001
log $t_{1/2}$ = -0.6284 + 0.0642 KSI1 – 3.1243 BIC2	2	0.4869	15.46	0.0548	0.3310	0.001
log $t_{1/2}$ = -1.6992 – 9.688 MSA + 0.00214 piPC05 + 0.004138 HASA-1	3	0.5816	14.78	0.0421	0.4214	0.001
log $t_{1/2}$ = -2.3042 – 13.127 MSA + 0.00109 piPC05 – 2.9321 BIC2 + 0.006291 HASA-1	4	0.6754	15.25	0.0324	0.5153	0.001
log $t_{1/2}$ = 0.5422 - 3.1421 BIC2 + 0.002011 HASA-1 + 0.1204 KHI3 + 0.0024 WNSA-2 + 0.0104 MR	5	0.7670	16.23	0.0278	0.6278	0.001
log $t_{1/2}$ = -0.9321 - 1.9821 BIC2 + 0.001904 HASA-1 + 0.0998 KHI3 – 10.519 MSA + 0.0014 WNSA-2 + 0.0113 MR	6	0.8250	17.28	0.0198	0.6904	0.001
log $t_{1/2}$ = 4.7401 - 2.9048 BIC2 - 16.471 MSA + 0.014011 HASA-1 + 0.08188 KHI3 + 0.0019 WNSA-2 + 2.5761 HASA-1/TMSA + 0.00914 MR	7	0.8814	19.76	0.0106	0.7436	0.001
$1/t_{1/2}$ = -0.61013 + 0.34182 DECC	1	0.4704	34.46	0.0125	0.3104	0.001
$1/t_{1/2}$ = 0.04091 - 3.9614 PW5 + 0.002176 D/Dr05	2	0.6109	29.16	0.0104	0.4417	0.001
$1/t_{1/2}$ = 0.14123 - 5.7642 PW5 + 6.708 MR + 0.11321 KHI3	3	0.6875	27.42	0.0097	0.559	0.001
$1/t_{1/2}$ = 0.50137 + 114.76 Xt – 7.3214 PW5 – 0.47291 HASA-2/SQRT (TMSA) + 0.16923 KHI3	4	0.7712	30.54	0.0068	0.6140	0.004
$1/t_{1/2}$ = -0.67714 + 123.98 Xt + 4.716 MR + 0.1931 KHI3 - 4.9142 PW5 + 0.001140 D/Dr05	5	0.8108	25.24	0.0044	0.7706	0.001
$1/t_{1/2}$ = 0.09127 + 154.74 Xt + 8.721 MR + 0.1114 KHI3 – 3.1974 PW5 + 0.00124 D/Dr05 – 2.9176 HASA-2/SQRT (TMSA)	6	0.8846	24.96	0.0027	0.8508	0.001
$1/t_{1/2}$ = 0.48718 + 163.94 Xt – 10.336 PW5 + 9.135 MR + 0.00302 D/Dr05 – 0.021314 HASA-2 + 0.20113 KHI3 + 0.23412 DECC	7	0.9416	20.78	0.0013	0.8217	0.001

m = number of descriptors employed in the MLRA equation. **RMW** = Relative molecular weight; **KHI3** = Kier and Hall index (order 3); **WNSA-3** = WNSA-3 weighted PNSA (PNSA3* TMSA/1000) [Zefirov's PC); **KSI2** = Kier Shape index (order 2); **SIC1** = Structural information content (neighborhood symmetry of 1-order); **HASA-1** = Hydrogen acceptors dependent HASA-1 [Zefirov's PC]; **BIC2** = Bonding Information Content (order 2); **AIC2** = Average Information Content (order 2); **HASA-2/TMSA** = Hydrogen acceptors dependent HASA-2/TMSA [Zefirov's PC]; **AIC1** = Average Information Content (order 1); **Es** = Taft steric parameter; **CIC0** = Complimentary Information Content (order 0); **KSI2** = Kier Shape index (order 2); **KSI1** = Kier Shape index (order 1); **MSA** = Molecular surface area; **PiPC05** = Molecular multiple path count of order 05; **WNSA-2** = WNSA-2 weighted PNSA (PNSA2* TMSA/1000) [Zefirov's PC); **MR** = Molar refractivity; **DECC** = eccentric; **PW5** = Path/walk5-Randic shape index; **D/Dr05** = distance/detour ring index of orders5; **Xt** = Total structure connectivity index; **HASA-2/SQRT (TMSA)** = Hydrogen acceptors dependent HASA-2/SQRT (TMSA) [Zefirov's PC]; **HASA-2** = Hydrogen acceptors dependent HASA-2 [Zefirov's PC].

Logarithmic transformations of biological half-life tend to improve degree of correlations during one-parameter and two-parameter studies. The inverse transforms of biological half-life remarkably enhanced the degree of correlations for both R^2 and Q^2. There was quite significant reduction in S^2 values, attributable to reduction in the magnitude of the property values.

The values were found to be highly predictable ($p < 0.001$) during the current QSPkR studies. As lipophilic parameters were not observed to be considerably significant, the diffusional interactions tend to outweigh the permeational ones. Dependence of biological half-life on the topological descriptors has also been reported in literature[18,19]. However, dependence of half-life has also been reported on lipophilic parameters[20-22], the difference in inference ascribable to lesser number of descriptors (primarily lipophilic) in those studies.

Fig. 2 shows the linear and residual plots between the reported values of $t_{1/2}$ and those predicted using multi-parameter QSPkR studies for a series of 28 quinolones.

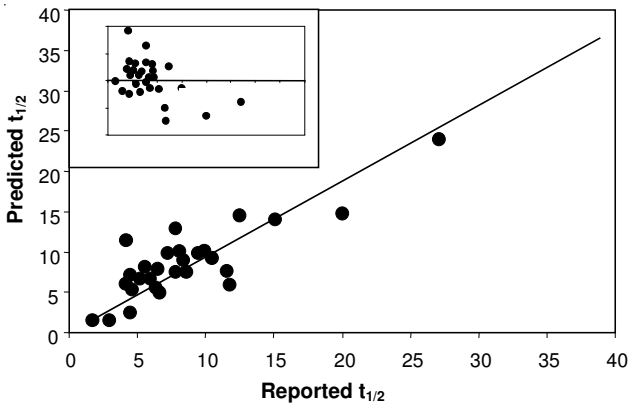

Fig. 2. Plot between the predicted and reported values of $t_{1/2}$ for QSPkR of quinolones. The inset shows the corresponding residual plot

Figs. 3 and 4 depict the corresponding plots for log-transform of $t_{1/2}$ and inverse transform of $t_{1/2}$, respectively. The study of residual plots in case of inverse transform of $t_{1/2}$ shows that $t_{1/2}$ values tend to be clustered. However, in the residual plots of $t_{1/2}$ and log transform of $t_{1/2}$, the cluster tends to be partially dispersed and the plots seems to be more regulated *vis a vis* plots of inverse transform of $t_{1/2}$. Fig. 5 depicts the bar diagram of the maximum values of the per cent explained (predicted) variance of untransformed $t_{1/2}$ of 3-D QSPkR studies in comparison to log transformed and inverse transformed $t_{1/2}$ values of various quinolones. Thus, the current *in silico* QSPkR studies yielded high degree of fruition in the ADME prognosis of $t_{1/2}$ property parameter of quinolone drugs.

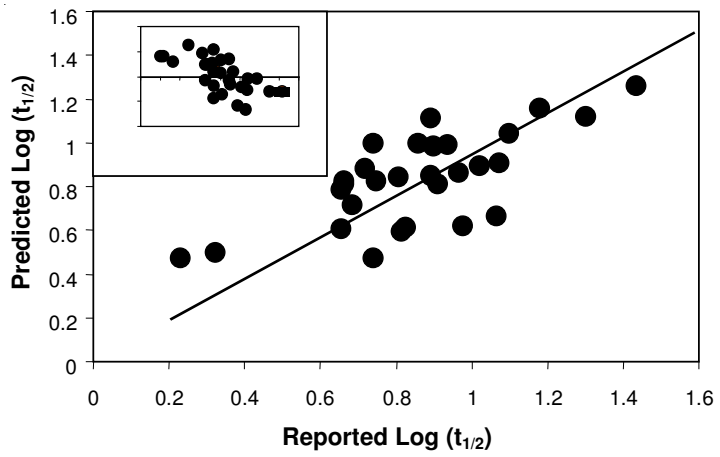

Fig. 3. Plot between the predicted and reported values of log $t_{1/2}$ for QSPkR of quinolones. The inset shows the corresponding residual plot

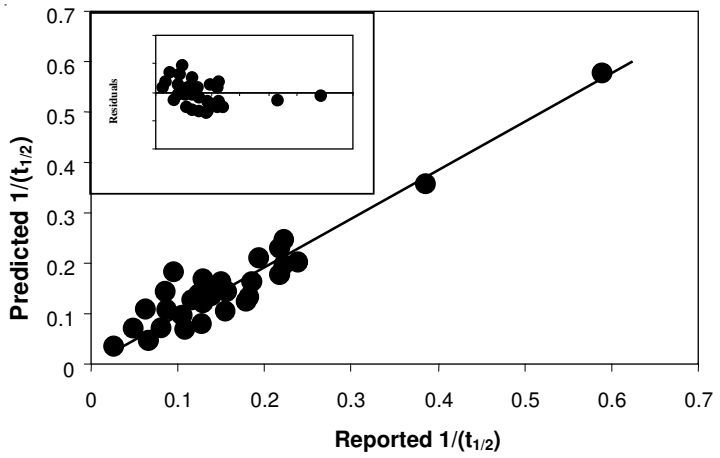

Fig. 4. Plot between the predicted and reported values of $1/t_{1/2}$ for QSPkR of quinolones. The inset shows the corresponding residual plot

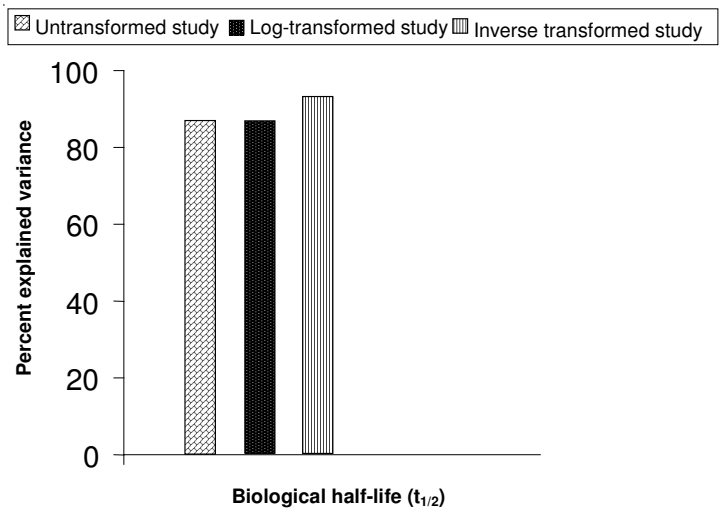

Fig. 5. Bar diagram depicting per cent explained variance of untransformed $t_{1/2}$ of 3-D QSPkR studies in comparison to log-transformed and inverse transformed $t_{1/2}$ of quinolones

Conclusion

Highly significant results on *in silico* prognosis of $t_{1/2}$ ($p < 0.001$), attributed major variation to topological, steric and electrostatic descriptors vouching the dependence on the diffusional interactions. Plausibility of any chance correlations was discarded in the light of high magnitudes of Q^2 obtained in the current QSPkR studies. Maximum predictability for quinolones was found to be 94.16 %. the pharmacokinetic performance of a drug is also known to be not merely a function of its physicochemical nature, but also of the biological system(s) too like somatic, psychological, pathological, environmental, nutritional, genetic, hereditary and diurnal status of the human subjects. This causes a great deal of plausible variation in pharmacokinetic profiles amongst the human volunteers undergoing study. The literature values of the pharmacokinetic parameters taken up in the present investigations, pertain to diverse subject populations hailing from different age groups, genders, races, nutritional and physical attributes, *etc*., studied in different geographical regions under different weather conditions. Considering these potentially high inter-subject and intra-subject variations amongst the pharmacokinetic parameters, the currently established relationships assume much higher credibility *in silico*.

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