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The Pharma Innovation

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In silico quantitative structure pharmacokinetic relationships for elimination half life of antidiabetic agents

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Abstract
In silico quantitative structure pharmacokinetic relationships (QSPkR) 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 QSPkR for the prediction of elimination half-life (t1/2) in humans for congeneric series of antidiabetic drugs, using computer assisted Hansch approach. Analysis of several hundreds of QSPkR correlations developed in the current study on antidiabetic 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 t1/2.

Keywords: Antidiabetic drugs, Multi linear regression analysis, ADME, Pharmacokinetics, Descriptors, In silico

1. 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* QSPkR 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* QSPkR amongst various antidiabetic for t1/2. Antidiabetic were selected for QSPkR due to treatment of diabetes and have attracted much attention [4]. Also, this congeneric series consist of significant number of compounds (n = 23), thoroughly investigated for their pharmacokinetic performance particularly t1/2. 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. The t1/2 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, t1/2 of a drug is used to calculate the dosage regimen [5]

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

2.1 Dataset
23 antidiabetic with known human t1/2 values were selected from literature [6-11]. In order to ensure that experimental variations in determining t1/2 do not significantly affect the quality of present datasets, only t1/2 values obtained from healthy adult males after oral administration of drug were used for constructing the dataset.

2.2 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 1475 diverse descriptors, *viz.* constitutional, geometrical, topological, Whim3D, electronic, *etc.* were calculated. Molfiles were also transferred to CODESSA software (Semichem, Shawnee, USA) for calculation of 185 more molecular descriptors.

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2.3 Multivariate statistical analyses

Attempts were made to correlate various descriptors with the t1/2 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 t1/2 available for 23 antidiabetic 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 antidiabetic. A set of important descriptors found to significantly ascribe the variation of t1/2, 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 t1/2. 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 re derived 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 cross validated R^2, commonly called Q^2, is then computed analogous to the conventional R^2 according to eqn. 1:

$$Q^2 = 1 - \frac{\sum (ypred - yobs)^2}{\sum (yobs - ymean)^2}$$ (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:

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

3. Results and Discussion

Variable QSPkR results were obtained following application of multivariate statistical analysis on antidiabetic 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 23 antidiabetic showed significant dependence upon topological parameters and electronic parameters. The prominent descriptors explaining variation in t1/2 encompass (like X5v, C1C2, BIC2 *etc.*). The overall predictability was found to be quite high ($R^2 = 0.8812$, F = 20.74, $S^2 = 9.3262$, $Q^2 = 0.7404$, 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 t1/2 as reported in literature and those using multi-parameter QSPkR for a series of 24 antidiabetic as well as residual plots of t1/2 values showed better uniformity in scatter and randomization (Fig. 1).

Table I: Statistical Parameters for a series of 23 Antidiabetic 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	0.3082	7.79	32.9521	0.0967	0.005
t$_{1/2}$ = -16.976 + 1.342 KHI3 + 0.5231 WNSA-3	2	0.4154	8.66	29.7064	0.2190	0.005
t$_{1/2}$ = -32.785 + 1.897 KSI2 + 0.6720 WNSA-3 - 2.3276 SIC1	3	0.5318	10.28	24.7271	0.3261	0.005
t$_{1/2}$ = 76.416 + 3.419 KHI3 + 0.4307 HASA-1 - 68.764 BIC2 - 7.4626 AIC2	4	0.6128	12.24	21.1273	0.3874	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	0.7291	14.92	14.3456	0.4978	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	0.8159	18.01	11.5520	0.6192	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	0.8812	20.74	9.3262	0.7404	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.
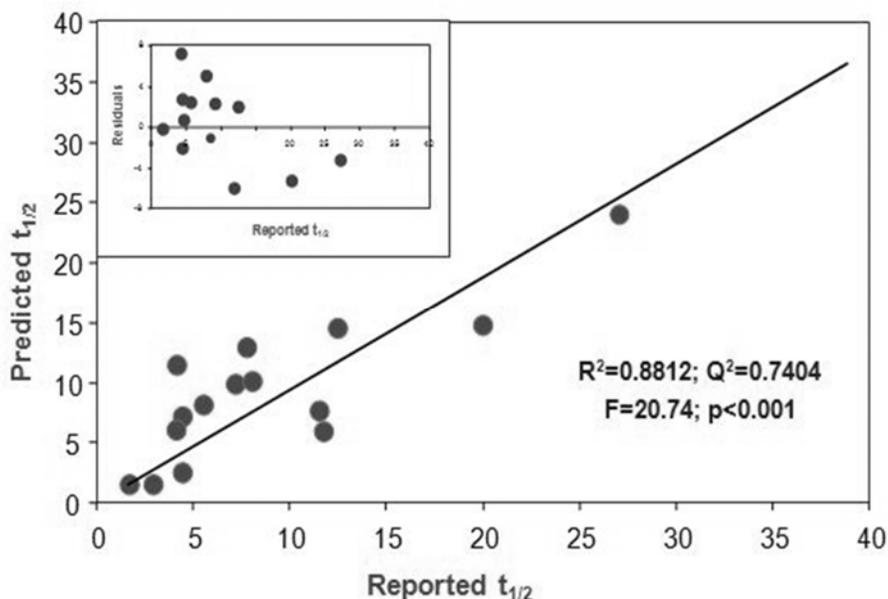
Fig 1: Linear correlation plot between the values of t1/2 as reported in literature and those predicted using multi-parameter QSPkR for a series of 23 antidiabetic. The inset shows the corresponding residual plot

4. Conclusion
In case of antidiabetic, topological and electronic parameters were found to primarily ascribe the variation in t1/2. Thus overall diffusional (rather than permeational) interactions seem to play a major role in attributing t1/2 of antidiabetic.

5. Acknowledgement

6. References
1. Hecht P. Curr. Drug Discov., 2002, 21.
2. Beresford AP, Segall M, Tabit MH. Curr. Opin. Drug Discov. Develop., 2004; 7:36.
3. Singh B, Dhake AS, Yashpaul. The Pharma Review, 2007; 29:93.
4. Clopman G, Fercu D, Renau TE, Jacols MR. Antimicrob. Agents Chemother. 1996; 40:2637.
5. Venkateswarlu V. Biopharmaceutics and Pharmacokinetics, Pharma Books Syndicates Hyderabad, Reprint, 2006, 170.
6. Lubasch A, Keller I, Borner K, Koeppe P, Lode H. Antimicrob. Agents Chemother. 2000; 44:2256.
7. Granneman GR, Carpentier P, Morrison PJ, Pernet AG. Antimicrob. Agents Chemother 1991; 35:436.
8. I. De. Lepeleire, Hecken AV, Verbesselt R, De. Schepper PJ. J Antimicro7b. Chemother. 1988; 22:197.
9. Xiao YH, Wang QN, Qian YS, Du JZ, He HX. Chonquing Yikedaxue Xuebao 1994; 19:177.
10. Hooper DC. Quinolone Antimicrobial Agents, American Society for Microbiology, Washington, DC 1993; 2:195.
11. Shargel L. Applied Biopharmaceutics and Pharmacokinetics, the McGraw-Hill Companies, Inc 2005; 5:259.