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Hungarian Academy of Sciences
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Review

Quantitative structure–(chromatographic) retention relationships

Károly Héberger *

Chemical Research Center, Hungarian Academy of Sciences, P.O. Box 17, H-1525 Budapest, Hungary

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Abstract

Since the pioneering works of Kaliszan (R. Kaliszan, Quantitative Structure–Chromatographic Retention Relationships, Wiley, New York, 1987; and R. Kaliszan, Structure and Retention in Chromatography. A Chemometric Approach, Harwood Academic, Amsterdam, 1997) no comprehensive summary is available in the field. Present review covers the period of 1996–August 2006. The sources are grouped according to the special properties of kinds of chromatography: Quantitative structure–retention relationship in gas chromatography, in planar chromatography, in column liquid chromatography, in micellar liquid chromatography, affinity chromatography and quantitative structure enantioselective retention relationships. General tendencies, misleading practice and conclusions, validation of the models, suggestions for future works are summarized for each sub-field. Some straightforward applications are emphasized but standard ones. The sources and the model compounds, descriptors, predicted retention data, modeling methods and indicators of their performance, validation of models, and stationary phases are collected in the tables. Some important conclusions are: Not all physicochemical descriptors correlate with the retention data strongly; the heat of formation is not related to the chromatographic retention. It is not appropriate to give the errors of Kovats indices in percentages. The apparently low values (1–3%) can disorient the reviewers and readers. Contemporary mean interlaboratory reproducibility of Kovats indices are about 5–10 i.u. for standard non polar phases and 10–25 i.u. for standard polar phases. The predictive performance of QSRR models deteriorates as the polarity of GC stationary phase increases. The correlation coefficient alone is not a particularly good indicator for the model performance. Residuals are more useful than plots of measured and calculated values. There is no need to give the retention data in a form of an equation if the numbers of compounds are small. The domain of model applicability of models should be given in all cases.

Keywords: QSRR; QRAR; QSERR; Gas chromatography; Column liquid chromatography; Planar chromatography; Micellar liquid chromatography; Affinity chromatography; Chemometrics; Modeling

Contents

* Tel.: +36 1 438 11 03; fax: +36 1 438 11 43.
E-mail address: heberger@chemres.hu.

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1. Introduction

Quantitative structure–retention relationships (QSRRs) represent a powerful tool in chromatography. What are QSRRs? The terminology is still used confusedly. Firstly, 'R' may mean 'reactivity' and not retention; secondly, quantitative structure–property relationships (QSPRs) or quantitative structure–activity relationships (QSAR) are often used instead: generally if the retention data are used as independent variables to predict properties of the molecules. Quantitative retention–activity relationship (QRAR) is also used instead of QSRR. The principal aim of QSRR is to predict retention data from the molecular structure. However, the same methodology can be used for prediction of physical properties e.g. for octanol/water partition coefficients ($\log P$ values) from retention data. The relationships are empirical, but a firm theoretical basis can be rendered to them using linear free energy relationships (LFERs), in these special cases linear solvation energy relationships (LSERs).

QSRR is a technique for relating the variations in one (or rarely several) response variables (***Y***-variables) to the variations of several descriptors (***X***-variables), with predictive or at least explanatory purposes. ***Y***-variables are often called dependent and ***X***-variables as independent variables. One of the ***Y***- or ***X***-variables should be related to (chromatographic) retention, the others should encode the molecular structure.

QSRRs allow the prediction of retention data of novel, not yet synthesized compounds, solely from their structural descriptors.

In many cases, the precision and accuracy of the QSRR models are not sufficient for identification purposes; still the models are useful to elucidate retention mechanisms, to optimize the separation of complex mixtures or to prepare experimental designs.

One of the crucial problems is how to represent molecular structure for QSRR. Generally, the descriptors encoding the molecular structure are classified as physicochemical, quantumchemical, topological, etc. descriptors. The advantage of physicochemical descriptors is that they are generally strongly related to the retention; i.e. they correlate the retention data strongly. However, they are often not available or with relatively large errors only. The advantage of quantumchemical descriptors is that they provide insights into the mechanism of chromatographic retention on a molecular level. Their correlation is, however, weak only and their calculation is tedious and time consuming. Topological descriptors are easy to be calculated with present computing facilities, but they are not necessarily related to the retention phenomena.

The second crucial problem is to select the most informative descriptors from among a large number of correlated descriptors. A lot of variable selection methods have been elaborated and the proper feature selection is a key to build successful QSRR models.

Since the pioneering reviews [1,2], a lot of interesting papers have appeared; new tendencies can be observed in the field. QSRR models can be used for successful classification of drugs of various compound classes and/or chromatographic columns (systems). Another interesting and increasing application of QSRRs is to test (compare) various chemometric methods. As the descriptors are highly correlated and numerous, to select a proper model is not a trivial task. Moreover, many laboratories use QSRR models to demonstrate the usefulness and advantages of recently developed chemometric techniques. Similarly, QSRR models demonstrate the applicability of novel topological descriptors many times.

Although the basic book of chromatography devotes only several pages to QSRR [3], the field achieved its 'riped' phase. Fig. 1 shows the steady and 'noisy' increase of papers dealing with QSRRs.

The search covers the period of 1996–August 2006 with extensive usage of 'Web of Science' and 'Scopus' data bases. The increase is not continuous; random factors also influence the number of papers dealing with structure and retention correlations.

Fig. 2 illustrates the dispersion law of spreading scientific information on this special example (QSRR). The distribution is much more peaked than the normal distribution. The core journals (disseminating 50% of scientific information) can be seen from Fig. 2: J. Chromatogr. A, Chromatographia, J. Liq.

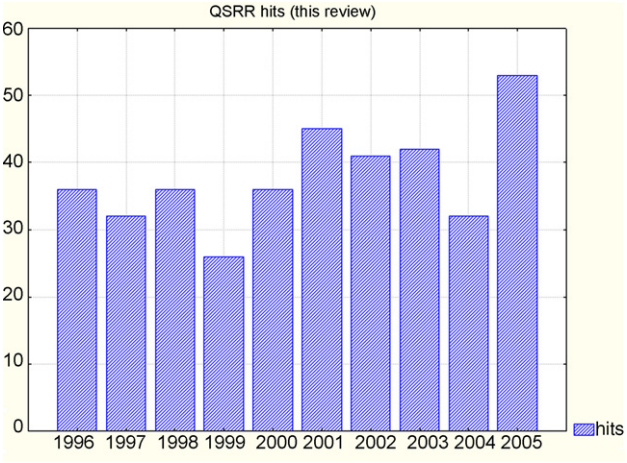

Fig. 1. Number of scientific papers dealing with QSRR within 1996–August 2006.

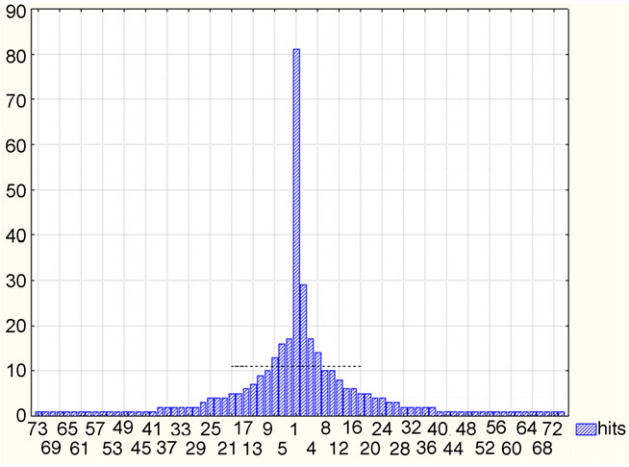

Fig. 2. Occurrence (frequency) of QSRR papers versus rank ordering of scientific journals within 1996–August 2006.

Chromatogr. Rel. Technol., Anal. Chim. Acta, Anal. Chem., Chemometrics Intell. Lab. Syst., J. Chem., Inf. Modeling (earlier J. Chem. Inf. Comput. Sci.).

The review is divided into seven parts: QSRR in gas chromatography, quantitative structure–enantioselective retention relationships (QSERR), QSRR in planar chromatography, QSRR in column liquid chromatography, QSRR in micellar chromatography, QSRR in affinity chromatography and QSRR in remaining fields.

2. Quantitative structure–retention relationships in gas chromatography

2.1. General tendencies

Alkanes, alkenes, alkylbenzenes, alcohols, ketones, aldehydes, volatile organic compounds (VOCs) and compounds of environmental reverence [polychlorinated biphenyls (PCBs), polychlorinated dibenzofurans (PCDFs), polybrominated diphenyl ethers (PBDEs), etc.] have often been used as model compounds (explanations for abbreviations can be found in the footnotes of tables). The Kovats retention index (I) is the most popular dependent variable in QSRR studies because of its reproducibility and accuracy. Relative retention times (RRTs) are also applied many times. In some cases response factors are also predicted from molecular structure.

Best models can be built using physical properties. There is a common statement in gas chromatography that boiling point governs the retention. In fact, the volatility governs, but the vapor pressure is of exponential function of the column temperature. Hence, normal boiling points are used as a well-defined and in many cases known quantity instead of vapor pressure. The retention index depends from the boiling points in a complicated nonlinear manner, which can be written in an exponential [4] or in a logarithmic form [5].

Multiple linear regression (MLR) is without doubt the most frequently applied technique in building QSRR models. The features and advantages of artificial neural networks (ANNs) fascinated numerous scientists. A lot of ANN studies are fairly descriptions how to apply ANN for model building than elaborations of predictive models.

2.2. Validation of the models

Perhaps the most sensitive problem is the validation. Validation was not required in the first, exploratory phase of QSRR investigations, when the most important approach was to unravel the potential usefulness of the method. Later, the validation became crucial. As the physical background is not unambiguous, chance correlations have to be avoided. Therefore, efforts should be done to prove that the found QSRR relationships are not fortuitous but applicable for future predictions. It is recommended to split the data into three sets if sufficient data are available: one is used for model selection, the second one for parameter estimation (calibration) and the third one for external validation (cross-validation is a poor alternative instead) [6].

The general practice is to split the data into training and testing sets. However, one single training set is not appropriate to make variable selection and parameter estimation (calibration) without bias. It is not (absolute) necessary to split the training set into two; resampling methods, cross-validation (CV) would also do. The cross-validation almost unbiasedly estimates the prediction error when no feature selection has been made [7], but it is heavily biased when a large amount of model selection is applied (i.e. sifting through thousands of models). In the latter case, the indicators of the fit are deceptively overoptimistic (inflation of the cross-validated correlation coefficient) [8].

Independently from the fact, whether the training set is split into two sets or a CV has been made, the test set should be independent from the model building and parameter estimation. The process is called then as external validation [9].

An instinctive (naïve) way is to estimate the performance of a model using randomly generated variables. The same number of variables should be simulated as was calculated for prediction of retention data. The same steps should be carried out as in the real case: variable selection, parameter estimation, prediction for ‘unknown’ compounds. The performance indicators (correlation coefficient, prediction errors) should be compared

with the same values of the real case. If the variables consisting of solely random numbers indicate approximately the same fit and prediction, the models are of little value even if physical significance can be found for its parameters.

Unfortunately, there is no agreed method how to split data set into training, calibration and test sets. Of course a lot of empirical experiences were accumulated, but they are also contradictory. Some algorithms ensure that no outliers or extrapolated values are placed in the test set. However, it provides an overoptimistic performance for prediction if future samples will not be gathered according to such algorithm.

Examination of the residua is often missing from QSRR studies, i.e. nonlinear relationships are overlooked in many cases.

2.3. Misleading practice and conclusions

The role of temperature is sometimes described with descriptors from the molecular structure. However, the temperature dependence of retention data is determined by thermodynamic relationships and cannot be derived from structural descriptors. Similarly, the polarity of stationary phases is related to the structure of stationary phase and not to that of solute molecules. The more polar a stationary phase is, the more difficult is its characterization. As the polarity of stationary phase increases, the goodness of fit (the correlation) deteriorates.

The fact that ANN (or support vector machine, SVM) provides less residual error leads to the conclusion that ANN (or SVM) is better than MLR. However, less residual errors can simply be the consequence of overfit. It is true; there are no accepted, correct, fair ways to compare various methods. The conclusions 'Root mean square errors (RMSEs) show the superiority of ANN over that of the MLR', or conversely 'the results of MLR equation are better than the neural network ones' do not say much about the power and usefulness of the methods. If the relation is nonlinear, ANN cannot be worse than MLR provided its proper usage. Even in the case of linear relationships ANN is at least as good as MLR. However, according to the principle of parsimony MLR models are recommended because of their simplicity and their physical relevance.

Considering variable selection an error is often committed in the literature. Namely, the variable selection is made linearly and then the linearly selected descriptors are used in a nonlinear model, i.e. for ANN. This is not simply an inconsequent but a malpractice. It has already been shown that it is expedient to use the same method (linear or nonlinear) for variable selection as for parameter estimation [10].

Some authors give errors in percentage for Kovats retention indices. The apparently low values (1–3%) can disorient the reviewers and readers. The interlaboratory reproducibility for Kovats indices is about 5–10 i.u. for standard non polar phases and 10–25 i.u. for standard polar phases i.e. 0.1–0.5% error should be achieved for a successful identification.

The domain of model applicability is rarely given for QSRR investigations though it would be essential, e.g. which boiling point range is covered, what is the retention time domain, how far can the models be used for extrapolation, which compounds can be included and which ones should be excluded, etc.

Quantumchemical packages provide the calculations of standard heat of formation values. As a consequence many authors try to find correlations between retention and heat of formation. However, contrary to the heat of solution (heat of vaporization), the heat of formation is not related to (chromatographic) retention; at least not better than molecular mass, carbon atom numbers, chain lengths and alike. Another problem with quantumchemical packages is that they are steadily corrected and updated, reparameterized, i.e. without giving the exact version numbers the results are not reproducible.

Many authors discover fortuitous relationships again and again, e.g. slope–intercept relations or the notorious compensation effect. It is easy to prove that such a relation is a consequence of random errors unavoidably present in the measurement process. However, such a relation can be useful that a certain phenomenon belongs to the same process. Just the physical significance is questionable.

2.4. Suggestions for future works

Apolar or medium polar phases are recommended for further studies. Use the most persistent ones: methyl- and phenylsilicones (OV-1, DB-5, etc.).

Alcohols are particularly recommended as model compounds because all major interactions can take place between alcohol molecules and molecules of the stationary phases. A possible association is concentration dependent. The alcohols participate in dispersive and polar (dipole) interactions and they exert to hydrogen bond donating and accepting abilities.

The correlation coefficient is not a particularly good indicator for the model performance. It should be emphasized that its value says nothing without the degrees of freedom ($r = 0.997$ is not significant at the 5% level if $n = 3$! On the other hand $r = 0.300$ is significant, i.e. the correlation is not due to random effects, if $n = 100$.) Therefore, phrases as 'satisfactory' or even 'excellent' correlation should be avoided. The readers should evaluate the performance and not the authors themselves.

Generally, simpler models are better according to the principle of parsimony.

Way of giving correlation equations should contain the predictive equation and indicators for the model performance (n, R, F, S) both for training and external test sets. The indicators are n – number of solutes involved, R – multiple correlation coefficient (adjusted R and cross-validated R are recommended), F – overall Fisher statistics, and S – the residual error or RMSE – root mean squared error. R and F are indeed linear indicators, but they can be calculated for the $\boldsymbol{Y}$(measured) versus $\boldsymbol{Y}$(calculated) linear relationship even if the calculated $\boldsymbol{Y}$ was derived from a nonlinear model (ANN, SVM, etc.), ($\boldsymbol{Y}$ can be any form of retention data, response factor, etc.). Residual analysis, too, is strongly recommended; residual plots are more useful than plots of measured and calculated values. If curvature, trend can be seen in the residua (against $\boldsymbol{Y}$(calculated)) the model is not adequate. Either further, nonlinear descriptors should be involved or a nonlinear relationship.

The domain of application should be given, within it the models are able to predict properly (compound classes, congener series, limits, polarity of columns, etc.).

2.5. Summary of papers on quantitative structure–retention relationships in gas chromatography

The QSRR papers in gas chromatography are gathered in Table 1 covering the period of 1996–August 2006.

'Isomer cluster(ing) phenomena' have been observed for a variety of monofunctional and some multi functional compounds, i.e. isomers containing the same carbon numbers are always located on parallel lines (different numbers of methylene groups are found on different lines) if the Kovats indices of homologous compounds are plotted on two stationary phases of different polarity [15].

Deviations from the linear boiling point correlations indicate host–guest interactions on cyclodextrin stationary phases [24,72]; e.g. bicyclic camphene is retained behind myrcene though its boiling point is appreciably smaller.

The elution orders and coelutions of all 209 PCB congeners can be predicted using a data base and structure retention correlations and congener substitution patterns [28].

Prediction of the retention indices of any organic compounds with known boiling points became possible using a three-parameter non linear equation:

$$\log I = a \log T_b + b(n_1 + \Sigma k_i n_i) + c \quad (1)$$

where n_1 is the serial number of homologue within corresponding series and n_i is the number of other structural fragments in the molecules. The coefficients k_i in this equation reflect the relative alterations of molecular polarizabilities and may be estimated as ratios of refractions $k_i = R(D)(X)/R(D)(CH_2)$, (X are variable structural fragments within a group of congeners, $R(D)(CH_2) = 4.647\ cm^3\ mol^{-1}$) [5].

Factor analysis (FA) was performed to interpret the meaning of the descriptors included in the models [26]. Hydrocarbons were successfully classified into paraffins (P), olefins (O), naphthenes (N) and aromatics (A) using FA [48]. Differentiation of ketones and aldehydes has been carried out by principal component analysis (PCA) [49]. PCA, a factorial design was applied for selecting 21 representative congeners, PBDEs. The spacing of these congeners in the physicochemical domain maximizes the coverage of key factors such as molecular size and substitution pattern [94].

Using the same QSRR methodology response factors can also be predicted [39].

Theoretical prediction of gas-chromatographic retention indices could be used as an additional method for the identification of organic substances during gas-chromatographic separation [40].

The thermodynamic interpretation was given to retention time–boiling point correlations using the Trouton's rule, i.e. physical significance can be attributed to empirical QSRR equations [32]. Later the physical significance could be extended using the Trouton–Hildebrand–Everett's (THE) rule [43]. Heats of vaporization, Gibbs free energies [33] and Gibbs free energy of vaporization of one methylene group (CH_2) of *n*-alkanes [46] can be calculated from QSRR equations (boiling point correlations of retention indices). A sophisticated relationship was elaborated between retention time and carbon atom number; the related thermodynamic quantities of solvation can be calculated [41].

The semiempirical topological index can help in the elucidation of the molecular structure [47,113].

Some data sets became standards for further QSRR investigations: for apolar interactions, methyl-alkanes [59], for polar interactions, oxo compounds [49].

Partition coefficients (K_p) in a heterogeneous system consisting of two immiscible organic solvents can be successfully used for a supplementary identification parameter in qualitative GC and GC–MS analysis of organic compounds including alkyl aromatic hydrocarbons and esters, group identification of components [72].

The correlations serve as a basis for physicochemical interpretation of the topological parameters of molecules as quantities proportional to the intramolecular vibrational and rotation energies [87].

If GC–MS library search 'hit list' matches the retention index of the unknown, there is a strong presumption that a correct identification can be made [119].

Quantitative prediction of normal boiling points for organic compounds is possible using chromatographic retention times on two columns of different polarity. Only hydrocarbons on nonpolar columns gave good results with a simple linear model [126].

The only review found concerning gas chromatography was in Chinese language [146].

3. Quantitative structure–enantioselective retention relationships

Enantiomer separations are difficult to predict. The present status of solution theories does not enable an unambiguous prediction. Nevertheless, enormous amount of empirical knowledge was gathered. Commercial data bases (CHIRBASE and CHIRSOURCE) contain more than 61,000 separations [3]. As a large number of chiral stationary phases is available, the success rate in enantiomer separations is quite high. The efforts to rationalize chiral separation using QSRR methodology have achieved limited success only. QSERR models provide some insights into the role of various interactions, but they are not able to recognize chiral selectors for a particular separation. One of the crucial problems is the selection of suitable molecular descriptors. The other problem is that the available congener series are small, the small number of compounds involved excludes the proper validation of models. Even the elution order (whether *R* or *S* enantiomer elutes first) is uncertain. A QSERR can be used as an alternative method to confirm the elution order of enantiomers. The prediction of elution order can be considered as a classification study from a chemometric point of view.

Table 1
QSRR in gas chromatography 1996–August 2006 (number of solutes and multiple correlation coefficients are in brackets)

Solutes	Descriptors	Model building	Stationary phase (SP)	Validation	Source
Linear alkylbenzene isomers with C_{10}–C_{14} linear alkyl chains	Balaban, Wiener, Electrotopological state and molecular shape indices	*I*, MLR	Apolar phases	No	[11]
Organosulfur compounds (37) (vesicants)	Quantumchemical MNDO, PM3, AM1	MLR	Three	No	[12]
Various examples	Homomorphic factors, topochemically equivalent increments	*I*, Additive schemes	OV-1, OV-101, OV-3, HP-5, OV-7, SE-30, SE-52, SE-54, CP Sil 5 SV, etc.	No	[13]
Alkyl groups	Internal molecular energies of reactants and products	*I*, increments	OV-101		[14]
Homologous series and their branched-chain isomers (1000)	Retention data on other SPs	*I*	Two various	'Relative higher accuracy'	[15]
Congener series of substituted benzenes, benzaldehydes and acetophenones	Different set of topological parameters	*I*, Correspondence factor analysis CFA	Six OV (Ohio Valley) i.e. (methyl–phenyl–siloxanes)		[16]
Polychlorinated biphenyls (PCBs)	Physicochemical descriptors (52): ultraviolet (UV) absorption spectra, semiempirical parameters (AM1): heat of formation, dipole moments, ionization potential and the barrier of internal rotation, GC retention times	PCA		No	[17]
N,*N*-Dialkylhydrazones	T_b, homomorphic factors, bond angle and electron density {I(oxo)}, volumes, van der Waals' surface	*I*, Simple linear	HP-1, HP-5	Visual	[18,19]
Isoalkanes (38), alkenes (24)	Various descriptors (49) T_b, log *P*, VDW, HOMO, LUMO, etc.	*I*, MLR	Squalane, citroflex, carbon black		[20]
Aromatic analytes, positional isomers of xylenes, ethyltoluenes and diethylbenzenes		RRT	Methylsilicone, Carbopack		[21]
PAHs (70)	T_b, vaporization enthalpy, molecular total energy	*I*, linear, nonlinear (Etot)	Methylsilicone	No	[22]
Anabolic steroids, stimulants and narcotics	T_b				[23]
Low-polarity solutes (9) e.g. camphene, α-terpinene, myrcene	T_b	RRT, linear (0.994)	Six different modified α-, β- and γ-cyclodextrin	No	[24]
Alkylbenzenes (150)	Topological (8), chemical (4)	*I*, CP–ANN	Carbowax 20 M	Training and test set, RMS < 43	[25]
Alkylbenzenes (150)	Topological, geometric, electronic	*I*, BP–ANN	DB-1, DB-wax	Training and test set	[26]
Compounds from Ylang–Ylang essential oil (48)	Topological, geometric, electronic	*I*, MLR, PCA	DB-1, DB-wax		[27]
Flavonoids (49: flavones, Flavonols, flavanones, a chalcone)	Topological, geometric, electronic	RI, MLR (0.975)	Apolar column	SD < 14	[28]
Alkenes (55)	Congener substitution pattern	*I*, MLR (0.9957–0.9987)	Graphitized carbon black	7 < SD < 13.6	[29]
All PCB congeners (209)	T_b				[30]
Allylic alcohols and unsaturated esters	T_b	*I*, biparameter linear	HP-5	Deviation < 3.00%	[31]

Allylic alcohols and unsaturated esters	T_b, reciprocal T_b	I, Additive schemes	Polar and non polar	$0.047 < SD < 0.42$	[32]
Alkylbenzenes (18)	T_b, reciprocal T_b	RI	Silicon oil 550, dinonylphtalate, PEG4000, Bentone 34	Theoretical, comparison of thermodynamic quantities	[33]
Alkylbenzenes (18)	T_b	I		Theoretical derivation	[34]
Aliphatic alcohols, aldehydes, acids and amines	Ortogonalized descriptors	PCA		No	[35]
Organic compounds, homologues, congeners	T_b, structural fragments, molecular polarizabilities	I, linear-logarithmic	PDMS	$I \sim 5/10$ i.u.	[5]
Acyclic and cyclic alkanes, alkenes, alcohols, esters, ketones and ethers (184)	Molar volume, T_b	I, BP–ANN	SE-52	Cross-validation and leave-20%-out	[37]
PAHs (100)	Pseudo-conjugated π-system surface (S(π)) and quasi-length of carbon chain (N')	I, bilinear (0.9968)	SE-52	$7.1 < S < 10.3$	[37]
PCBs	3D WHIM	RRT, solubility, log Kow, MLR, GA	SE-54	Leave-one-out, leave-multiple-out, SEC = SEP = 0.023	[38]
Various organic compounds	Total energy, relative effective mass and number of carbon atoms, minimum valency on H atoms, etc	RF (0.956), MLR, BP–ANN	HP-1	Two prediction sets, $5.0 < SEP < 7.1$	[39]
Acyclic, cyclic alkanes, alkenes, dienes, ketones aldehydes ethers, aromatic hydrocarbons C3–C11 O1–O2 (381)	Informational and topological structural descriptors (16)	I, MLR (0.987), BP–ANN (0.990), CP–ANN (0.969)	Squalene	LOO, 10 fold CV, average RMS: 19 (BP–ANN), 22.5 (MLR), 36.1 (CP–ANN)	[40]
n-Alkanes	Backbone carbon atom number	k, exponential	PDMS	Theoretical derivation	[41]
Alkylbenzenes (18)	T_b, $1/T_b$, T/T_b, $(T_b - T)$, $(1 - T_b/T)$, ${T_b}^2$, $(T_b - T)^2$, $(1 - T_b/T)^2$	I, linear (0.9692–0.9992)	Silicon oil 550, dinonylphtalate, PEG4000, Bentone 34	$4.3 < SD < 47.9$	[42]
Alkylbenzenes (18)	T_b, reciprocal T_b	RRT, exponential (0.9455–0.9977)	Silicon oil 550, dinonylphtalate, PEG4000, Bentone 34	$0.028 < SD < 0.079$	[43]
Polysubstituted alkylbenzene isomers	Indices of benzene, monsubstituted alkylbenzenes and disubstituted alkylbenzenes	I			[44]
Polychlorinated naphthalenes (62)	Number of chlorine substitutions, heat of formation, maximum value for atomic valence, the minimum value for electronic orbital population	RRT, MLR (0.9975)	DB-5	SE = 16.7	[45]
Aldehydes (16), ketones (19)	T_b, $\ln T_b$, $T_b \times \ln T_b$	I, linear, (0.9976–0.99994)	DB-210	$11.5 < SD < 12.1$	[46]
Alkanes (157), *cis*- and *trans*-*n*-alkene isomers (79)	Semiempirical topological index, increments	I, linear (0.9901), (0.99996)	Squalane	$2.35 < SD < 26.2$ cross-validation comparison with prediction by Wiener, Randic indices	[47]
Hydrocarbons (191)	Oblique factors	FA, varimax, promax rotations	DB-1, DB-5, SE-54, OV-1	GC/MS identification	[48]
Aldehydes (16), ketones (19)	T_b, M_w, V_m, R_m, log P, Ind	I, scores, PCA, MLR (0.99901)	HP-1, HP-50, DB-210, HP-Innowax	SD = 0.0491	[49]
Alkanes (156) oxygen-containing organic molecules (81)	Weighted fragments, spectral moments	Additive schemes	Squalane, OV-1	leave-one-out	[50]
Coumarins	Total surface area (AT), electrotopological state index, oxygen in position 1, HOMO	MLR	Low polarity phases	Cross-validation	[51]

Table 1 (*Continued*)

Solutes	Descriptors	Model building	Stationary phase (SP)	Validation	Source
Alkylbenzenes (32)	Boiling point, molar volume, stationary phase	*I*, BP–ANN	Squalane, SE- 30, PEG	Training and test sets, relative error 3%	[52]
Isoalkanes, dialkyl sulfates, and aliphatic amines and	T_b, NC, V_m, R_m, sum of internal rotational and vibrational energies	*I*, structural fragments	PDMS	Molecular dynamic caculations	[53]
Diverse chemical compounds (152)	CODESSA descriptors (296), linear selection	Retention time, RF, MLR, nonlinear models		Comparison with earlier results	[54]
Halocarbons C1–C4, hydrocarbons C4–C6 (17)	Retention time, R_m, μ	Virial coefficients Interaction energies (0.973, 0.982)	Carbopack C	Theoretical derivation	[55]
Trimethylsilyl ether derivatives of natural sterols (16)	Conventional, topological, quantum-chemical (60)	*I*, MLR (>0.9880)	SE-54, SE-52	Relative mean errors 2.88%,3.24%	[56]
Aldehydes (16), ketones (19)	T_b, M_w, V_m, R_m, log *P*, Ind	*I*, scores, PLS, (0.990–0.995)	HP-1, HP-50, DB-210, HP-Innowax	Cross-validation $0.975 < Q\hat{2} < 0.990$	[57]
Polychlorinated biphenyl (PCB) congeners	New QSRR descriptors for selectivity correction	Retention time	Various	SDs are 'within a chromatographic peak width'	[58]
Methylalkanes produced by insects (178)	Mainly topological descriptors	*I*, MLR	DB-1	Internal (LOO, leave-33%-out) and external (30) CV, SD = 4.6 (overall), SD = 4.3 (truncated)	[59]
Polychlorinated dibenzofurans (PCDFs)	Substitution pattern, positions	*I*, MLR (>0.9995)	DB-5	SD < 7 i.u.	[60]
Alkylbenzenes (129)	Molecular graph descriptors, sequential orthogonalization	*I*, MLR		Calibration and prediction sets	[61]
Diverse sets	Abraham type solvatochromic parameters (6)	Gas–liquid partition coefficient, *K*(L), MLR, BP–ANN, nonlinear function	EGAD, THPED, QBES, DEHBA, Ucon 50 HB 660	Residual analysis, training, prediction sets	[62]
Alkylphenols	Wiener, hyper-Wiener, minimum and maximum eigenvalue, Ivanciuc-Balaban, and information on distance operators	*I*, MLR	Not given	S = 37–38 i.u. (biparametric); S = 15–19 (4–5 parametric)	[63]
Alkanes (64)	Novel molecular distance-edge vector (10 elements)	*I*, MLR (0.9988 -0.9992)		CV, RMS (training) = 5.9, RMS(test) = 7.1	[64]
Alkanes, alcohols and polycyclic aromatic hydrocarbons	Electronegativity-distance vector (MEDV)	*I*, MLR			[65]
Amines	Topological indices Aml, Am2, Am3, gravitational index G1	*I*, MLR	Phase of various polarity (3)		[66]
Saturated and monounsaturated six-carbon aldehydes, alcohols and esters (35)	M_w	*I*	DB-5, DB- 1701, DB-Wax	No	[67]
Hydrocarbons and derivatives containing oxygen, nitrogen and halogens	Valence connectivity indices, $1(\chi)(\nu)$ Wiener, W, and Balaban, J, indices	log *V*(g), *I*, linear, non linear (0.9597–0.99999)	Various, PDMS, PEA, PBD, TFPS15, XF-1150	No	[68]
Alkanes, diverse compounds	LSER	Specific retention volumes, MLR	Eighteen polymers	No	[69]
Polychlorodibenzothiophenes PCDTs (19)	Structural features	MLR	DB-5 and DB-5 ms		[70]
Hydrocarbons, benzene derivatives, esters, alcohols, aldehydes, ketones and heterocyclics (110)	Molecular mass, number of vibrational modes of the molecule, molecular surface area and Balaban index	RF, MLR, BP–ANN	Not given	Mean absolute error = 0.02	[71]
Diverse C10 polar solutes from volatile oils	T_b	RRT, linear (>0.990)	Twelve modified cyclodextrin	SD < 5.5	[72]

PAHs (unsubstituted six-membered fused aromatic rings, 48)	Electronic, geometric, topological (e.g. electron affinity, the difference between electron affinity and ionization potential (GAP), Wiener, and connectivity indexes, volume, surface area, length-to-breadth ratio, enthalpy of formation	LC retention time index, T_b, PLS	Polymeric phase	CV, SEP	[73]
Aldehydes (16), ketones (19)	Quantum-chemical method: PM3. HOMO, LUMO, polarizability, dipole moment, solvent accessible surface area	*I*, MLR, (0.9930–0.9975) PCA, CA	OV-1, HP-50, DB-210 and HP-Innowax	$12 < SD < 19$	[74]
Polycyclic aromatic hydrocarbons (PAH)s (100)	Novel molecular distance–edge vector (six parameters)	*I*, linear (0.988), to the gas		Comparison with results of molecular polarizability index	[75]
Alkylbenzenes (129)	Molecular graph descriptors (5)	*I*, MLR		Calibration and prediction sets	[76]
Alkylbenzenes (46)	Simple set of six numeric codes McReynolds' constant of the different stationary phases, temperature	*I*, MLR, BP–ANN	Cit.A-4, SE-30 and Carbowax 20 M	$12.6 < SD < 26.1$ training, validation prediction sets	[77]
Hydrocarbons	Molecular structural	*I*, BP–ANN (0.9934)		Leave-10%-out, SD = 16.5	[78]
Polychlorinated dibenzofurans PCDFs	Molecular distance-edge vector	MLR, (>0.98)	DB-5, SE-54, OV-101	Cross-validation (0.97)	[79]
Hydrocarbons (150)	Numeric structural codes	*I*, MLR (0.9874–0.9901)		$20.2 < SD < 22.9$ leave-one-out cross-validation	[80]
Noncyclic and monocyclic terpenes (53)	One electronic, two geometric, two topological and one physicochemical descriptors	*I*, MLR, BP–ANN	Carbowax 20 M	Training and prediction (1.88%) sets, SD = 38	[81]
Alkyl aromatic hydrocarbons and esters (252)	Partition coefficients (K_p), group identification	*I*, linear	HP-5	Visual	[82]
Halogenated hydrocarbons (207)	CODESSA descriptors: Kier–Hall connectivity index, number of F atoms, gravitation index	*I*, MLR (0.994–0.993)	PDMS	LOO CV $0.991 < q < 0.992$	[83]
Amines (22)	Novel connectivity index, mQ	*I*, MLR (0.9734–0.9733)	OV-101, OV-225 and NGA	Modified Jackknife's test	[84]
Malodorous organic sulfur compounds, thiols and thioethers organic compounds (373)	Molar refractivity and connectivity index values	Second gas–solid virial coefficient *I*, (0.975–0.994)	Carbopack C	Visual	[85]
Linear, branched alcohols with hydroxyl group on a primary, secondary, or tertiary carbon atom	Molecular connectivity indices	*I*, MLR, BP–ANN	OV series columns	Cross-validation	[86]
Several groups of isomeric organic compounds	Topological (Wiener and Hosoya indices) and dynamic parameters	*I*, MLR	PDMS		[87]
Chlorinated alkylarenes	Molecular dynamic parameters	*I*, additivity schemes	Nonpolar		[88]
Various	Topological	Retention times, PCA	Various		[89]
Polycyclic aromatic hydrocarbons PAHs (94)	Molecular distance-edge vector (VMDE)	*I*, MLR (0.9928–0.9946)		$LOO\ CV\ 8.15 < RMS < 9.35$	[90]
Alkanes (48), alcohols (31)	Variable connectivity index $1\chi f$	*I*, MLR (0.9933)		SD = 14.2	[91]
Alkanes	Molecular distance edge vector (MDEV)-consisting of ten elements	*I*, Wavelet NN (0.9996) BP–ANN		SD = 5.06	[92]
Polychlorinated dibenzo-*p*-dioxins	Molecular descriptors: Randic index (order 3), the Kier shape index (order 3)	Retention time (0.9950)	DB-5	SD = 0.2550	[93]

Table 1 (*Continued*)

Solutes	Descriptors	Model building	Stationary phase (SP)	Validation	Source
Polybrominated diphenyl ethers PDBEs	Physicochemical descriptors (40) AM1 quantumchemical, molecular mechanics, ΔH_f, HOMO, LUMO, atomic charges, μ, $\log P$, molecular surface areas	RRT, PCA, PLS	CPSil-8, HP-1701, SP-2380, SB-Smectic	Test set (21)	[94]
Organic compounds with various functional groups	T_b, α, ΔH_f, density, various indices, inertia, HOMO, etc.	RF, MLR, BP–ANN	Not given	Training, prediction sets; residual analysis	[95]
Methylalkanes produced by insects (178)	Semi-empirical topological index	*I*, MLR (0.99999)	DB-1	SD = 3.20 External SD = 4.6	[96]
Branched alkenes	Semi-empirical topological index	*I*, MLR	Squalane, 1-octadecene, Apiezon-L, OV-1, DB-1	Cross-validation (0.9985)	[97]
Polychlorinated dibenzodioxins PCDDs	Molecular distance edge vector (VMDE)	MLR	DB-5, SP-2100, SE-54, OV-1701	Leave-one-out	[98]
Different classes of organic compounds (13)	Molecular density, Wiener number, T_b, polarizability and square of polarizability	RRT, MLR, BP–ANN	Rtx-5	Training, prediction sets	[99]
Polycyclic aromatic hydrocarbons PAHs (209)	Molecular electronegativity-distance vector (MEDV)	*I*, MLR (0.9812)	SE-52	RMS = 15.5	[100]
Esters, alcohols, aldehydes, ketones (107)	HOMO, molecular values, number of atoms, molecular shadow area on the xy plane	*I*, BP–ANN	OV-1, SE-54	Training, prediction sets; average percentage deviation 2.5–3.0%	[101]
Alkanes, alkenes, alcohols, esthers, ketones, ethers (184)	T_b, V_m	*I*, RBF-NN (0.9910)	Not given, as in [36]	Test set, RMS = 14.1	[102]
Saturated esters (98)	PM3 descriptors (Hyperchem 4.0), topological, degree of branching	*I*, MLR, PCA	SE-30, OV-7, DC-710, OV-25, 100% phenyl, DC-230 and DC-530	SE = 13.1–23.0	[103]
Oxo compounds (54)	Semiempirical topological index	*I*, linear (0.999)	HP-1, HP-50, DB-210, HP-Innowax	SD = 5.0	[104]
Chlorinated phenols		RRT, MLR (0.985)	DB-5	SD = 0.0472	[105]
Polychlorinated naphthalenes (62)	Molecular electronegativity distance vector	*I*, MLR (0.9912)		RMS = 31.4, LOO (0.9898) RMS = 33.8	[106]
Alkenes (383)	Class distance variable (information about the branch, position of the double bonds, the number of double bonds)	*I*, projection pursuit	Squalane	Training and prediction sets	[107]
Series of compounds (226)	Increments	ΔI, additivity scheme	PDMS, polyethylene glycol	Theoretical	[108]
Polychlorinated biphenyls, PCBs (30)	Topological parameters (Balaban index and electrotopological index	RRT, *I*, linear (0.78–0.99) nonlinear	PE-5 MS	Relative error = 2.8%-24.4%	[109]
Disulfides (50)	Semi-empirical quantum chemical (AM1) HYPERCHEM 4.0	*I*, MLR (0.976–0.995), RBF-NN	Apiezon M, OV-17, Triton X-305 and PEG-1000	Training and validation sets	[110]
Benzene, chlorobenzenes (12)	Mosaic and bond increments	*k*, *I*, additivity schemes	Agilent 6850, HP-5, HP-5890, HP-5840, SE-30, SPB-1, Wax-10	Training (6) test (8) absolute deviation = 1.7 i.u. relative errors = 0.9% 3.5%	[111]
Benzene, chlorobenzenes (12)	Topological indices (first-order connectivity index, Wiener's index and Balaban index) physico-chemical properties (freezing point, T_b, refraction index, μ, density, M_w, vapor pressure)	*I*, MLR (0.9976–0.9998), PCA	Various (7)		[112]

Aldehydes (16), ketones (19)	Xu index, atom-type-based AI topological indices (fragments)	*I*, MLR (> 0.995)	HP-1, HP-50, DB-210, HP-Innowax	Theoretical considerations	[113]
Alkanes, alkenes, esters, ketones, aldehydes, and alcohols (548)	Semi-empirical topological index, IET	*I*, MLR (1.0000)	Squalane, OV-1, DB-1, 1-octadecene, Apiezon-L	Test set (182), SD = 7.7	[114]
Alkoxyl silicon chlorides	Molecular topological index mXY	*I*			[115]
Alcohols (25)	Hydrogen connectivity index	*I*, MLR			[116]
Homologues	Number of carbon atoms *n*C, reciprocal T_b	Nonlinear			[117]
Branched alkanes	Class distance variable	projection pursuit (PP)			[118]
Various (20 chemical classes)	T_b	(Lee's scale) nonlinear *I*	Not given		[119]
Saturated alcohols	Semi-empirical topological index	*I*, linear (0.9978)	OV-1, SE-30, OV-3, OV-7, OV-11, OV-17, OV-25	SD = 9.54	[120]
Chlorinated polycyclic aromatic hydrocarbons, Cl-PAHs (18)	MNDO quantumchemical: total energy, dipole moment, net atomic charge on Cl	RRT (0.9968), Cl-atom position	HP-5 ms		[121]
Polychlorinated naphthalenes (62)	Structural parameters	*I*, MLR (0.9839- 0.9880)		Leave-one-out cross-validation	[122]
Trimethyl silyl derivatives of natural phenols and sterols	Descriptors generated with the HYPERCHEM 4.0, AMPAC 6.7 and CODESSA 2.3	RRT, MLR(>0.99)	SE-54 and SE-52	Relative errors: 0.01% 0.37%	[123]
Aldehydes (16), ketones (19)	Semi-empirical topological index, IET	*I*, MLR (>0.9995)	HP-1, HP-50, DB-210, HP-Innowax	SD = 5.5	[124]
n-alkanes, 1-alkenes, and 2-alkenes Homologous series	Hyperchem, MOPAC	ΔH_f, RT, MLR	DB-1	SD (ΔH) = 161 cal/mol; cross-validation	[125]
Organic compounds of diverse structures (271)	Retention data on two phases of different polarity	T_b, bilinear (0.9724)	DB1–60 W, DBWAX-30N	SD = 16.1 K	[126]
α-, β1-, and β2-agonists	Diverse connectivity and electrotopological indices	RRT, MLR, PCA, PLS	Crosslinked methylsilicone gum	Training and prediction set	[127]
CNS agents (benzodiazepines, barbiturates, phenytoin)	Calculated descriptors	*I*, MLR (0.983–0.988)	DB-5, DB-17	LOO CV (0.967) external prediction set (0.954)	[128]
O-, *N*-, and *S*-heterocyclic compounds	T_b, WHIM, GETAWAY, connectivity indices, 0D constitutive descriptors	*I*, MLR, PLS	Nonpolar PDMS	Cross-validation	[129]
Polycyclic aromatic hydrocarbons, PAHs	T_b, molecular mass and connectivity index	*I* (Lee's scale), linear, quadratic exponential	DB-5	SD = 1.9, external SD = 2.4; 3.3	[130]
Sulfides	Atomic structure parameters molecular connectivity index topological index	*I*, MLR (>0.97)	Different polarity		[131]
Mercaptans, sulfides, thiophenes (34)	Molecular descriptors (7,8)	RT, *I*, MLR		SD = 0.61 and 1.63	[132]
Methane, ethane, propane, $ClCH_3$, ClF_2CH, CH_3OCH_3, sulfur hexafluoride, (65)	R_m, connectivity index, surface area, surface energy contribution of the 65 different lnB2s *T*	Second gas-solid virial coefficient, B2s (0.9757)	Carboxen-1000 carbon molecular sieve		[133]
Polychlorinated hydroxybiphenyls (839)	Simpler structural analogues of target compounds	Additivity scheme arithmetical operations of *I*s	HP-5	External set, precalculation by varius ways	[134]
C3–C12 volatile organic compounds (149)	Total information index of atomic composition IAC, Wiener number, W, solvation connectivity index, Xlsol, number of substituted aromatic C(sp2), *n*CaR	PCA, MLR for variable selection BP–ANN	DB-1	LMO CV	[135]

Table 1 (*Continued*)

Solutes	Descriptors	Model building	Stationary phase (SP)	Validation	Source
Polychlorinated biphenyls, PCBs (118)	Ionization potential (molecules and molecular ions), topological indices, inertia	RF (ECD), MLR for variable selection, BP–ANN	DB-5	Training and prediction sets	[136]
Methylbenzenes, chlorobenzenes	Methyl/chlorine substitution pattern, number of substituents	*I*	HP-5, ZB-WAX	Comparison with literature data	[137]
Diverse organic compounds (146)	Dragon descriptors (529)	MLR, PLS	Apolar phases, HP1, OV-101	Training and prediction (SD = 80) sets	[138]
Polychlorinated dibenzofurans, PCDFs	Modified molecular distance-edge (MDE) vector	MLR (0.958–0.995)	DB-5, SE-54, OV-101, OV-1701, SP-2300	Leave-one out (0.834–0.992)	[139]
Alkoxyl silicon chlorides (22), sulfides (61) and alkanes (74)	Molecular structure information connectivity index mY	*I*, MLR		'Clear physical significance'	[140]
Saturated hydrocarbons, olefines and dienes	Quantum chemistry parameters HOMO, LUMO, ElcE, R_m	*I*, MLR	Various	'Good stability and prediction'	[141]
Polybrominated diphenyl ethers, PBDEs (126)	Congener substitution patterns	Elution order, nonlinear	DB-1, DB-5, HT-5, DB-17, DB-XLB, HT-8, CP-Sil19		[142]
Aliphatic alcohols	Hyperchem 4.0, Dragon descriptors (109)	*I*, PCA, MLR, RR, PLS (0.9712 – 0.9950)	OV-1	Leave-33%-out cross-validation (0.9052–0.9900)	[143]
Various molecules (10 series of compounds, 142)	Modified topological index (mT)	*I*, RRT, MLR			[144]
Alcohols	Quantum chemical descriptors AM1, Hartree–Fock (HF) Gaussian 98	*I*, MLR	Superox 20 M-diglycerol		[145]
Polyaromatics, polychlorobiphenyls		*I*			[146]
Aliphatic alcohols	Semi-empirical topological index (IET)	Linear (>0.98)		Cross-validation, LOO	[147]
Polycyclic aromatic sulfur heterocyclic compounds, PASHs	μ, Constitutional, geometric, topological, molecular walks	*I*, nonlinear	BPX5	Cross-validation	[148]
One hundred and thirty-six polychlorinated dibenzofurans, PCDFs	Number and position of chlorine substitutions, quantumchemical	*I*, (0.993–0.998)	DB-5	Cross-validation	[149]
Polychlorinated dibenzo-p-dioxins, PCDDs, dibenzofurans, PCDFs, (178)	*I*	Subcooled liquid vapor pressures (PL)			[150]
Methyl-substituted alkanes produced by insects	Total number of carbons in the backbone, the number of the multiple methyl groups attached to the carbon chain, their relative positions	*I*, BP–ANN	DB-1	Average relative error = 3.3%	[151]
Polychlorinated dibenzofurans, PCDFs	Molecular structure index, group modify index	*I*, RRT, MLR	DB-5, SE-54 and OV-101	Relative deviation = 1.09%	[152]
Organic sulfur compounds	Topological descriptors, temperature	*I*, MLR		Leave-one-out (0.978) leave-two-out (0.976)	[153]
Polychlorinated dibenzofurans, PCDFs (135) PCDFs	Molecular hologram	*I*, PLS (0.999)		Training and prediction set	[154]
Nitrogen-containing polycyclic aromatic compounds, N-PACs	Codessa descriptors (3)	*I*, MLR (0.9923)	SE-52	Cross-validation	[155]

Sulfides and mercaptans	Molecular polarizability effect index (MPEI), the effective topological steric effect index (ETSEI), the number of carbon (N), Wiener three-walk path (P3)	I, MLR (>0.98)	Various		[156]
Polycyclic aromatic hydrocarbons, PAHs	T_b, connectivity indices, M_w	I, BP–ANN		Test sets	[157]
Volatile organic compounds (VOCs), (149)	Five molecular descriptors (CODESSA)	RT, SVM	DB-1	Training and prediction set	[158]
Alkanes, organic compounds	Topological index based on distance matrix and branch vertex of the atoms	I, MLR (0.9919–0.9922)	Squalane, SE-30	SD = 13.7, 12.0	[159]
Polychlorinated naphthalenes PCNs	Quantumchemical (HF/6–31G− and B3LYP/6–31G* levels), relative position of chlorine substitution	I, MLR (0.9907–0.9978), 0.9983		Cross-validation (0.9885–0.9974) 0.9979	[160]
Aromatic imines	Topologic, topographic and quantum-chemical	I, MLR (0.987), BP–ANN (0.940)	DB-1	External set (0.911–0.985), LOO, LMO	[161]
Organophosphates (35)	Electrotopological state index for atom types, ETSI	I, MLR (>0.99)		Calibration, validation (0.98) sets	[162]
Polybrominated diphenyl ethers (209)	Wiener index, Randic index, polarity parameter	RRT, MLR (0.983–0.996)	DB-1 DB-5 MS, HT-5, DB-17, DB-XLB, HT-8, CP-Sil 19	Cross-validation (0.979–0.995)	[163]
Aliphatic alcohols (35)	Electrotopological state index (En) the molecule connectivity index (MCI)	I, MLR (0.994), PLS		Leave-one-out	[164]
Saturated esters (90)	Lu index, distance-based atom-type DAI topological indices	I, MLR	SE-30, OV-7, DC-710, OV-25, XE-60, OV-225, Silar-5CP	SD = 10–19.3 i.u.-(cross-validated)	[165]
Aliphatic carbonyl compounds, esters and alcohols	T_b, linear temperature programmed retention index	K_{fg}, bilinear	Carboxen/polydimethylsiloxane	No	[166]
PAHs	T_b, molecular mass, connectivity index, Schabron molecular size	I (Lee scale), BP–ANN (0.9381)	SE-52, DB-5	Validation and two testing sets (0.8939–0.9460)	[167]
Methylalkanes (insects), (177)	Molecular tightness index, MTI, polarizability effect index, PEI, number of carbon atoms in backbone, NC, number of the 2-methyl groups (N2-CH3) number of methyl groups attached to the carbon backbone (NCH3)	I, MLR (0.99999)	DB-1	Leave-one-out cross-validation, external data set, 3.7 < SD < 4.6	[168]
Fatty acid methyl esters (FAME)	Two-dimensional fatty acid retention index system, 2D-FAI	Equivalent chain lengths, ECL, MLR	BPX-70	Test sets 0.002 < RMS < 0.012 ECL units, CV	[169]
Methylene-interrupted polyunsaturated fatty acids	Chain length, number of double bonds, position of the double bond system	Retention indices as equivalent chain lengths (ECL)	Cyanopropyl column	RMS = 0.03 ECL units	[170]
Polycyclic aromatic sulfur heterocycles, PASH alkylated dibenzothiophenes (43)	Substitution pattern	I	Methylphenylsiloxane (5% and 50% phenyl groups): DB5 ms, DB17 ms	New synthesized compounds (external validation)	[171]

ANN: artificial neural network; α: polarizability; BP: back-propagation; CA: cluster analysis; CFA: correspondence factor analysis; CP: counter-propagation; DB-1: 100% dimethylpolysiloxane; CV: cross-validation; DB-5: 5% diphenyl and 95% dimethylpolysiloxane; DB-210: trifluoropropylmethyl polysiloxane; DB-wax: polyethyleneglycol; DEHPA: di(2-ethylhexyl)phosphoric acid; EGAD: polyethylene glycol adipate,; ECL: eqivalent chain length; FA: factor analysis; GA: genetic algorithm; ΔH_f: heat of formation; HOMO: highest occupied molecular orbital; HP-1: 100% dimethylpolysiloxane,; HP-5: 5% diphenyl and 95% dimethylpolysiloxane; HP-50:50% diphenyl and 50% dimethylpolysiloxane; HP-Innowax: polyethyleneglycol; I: Kovats retention index; k: retention coefficient, (capacity factor); K_{fg}: distribution coefficients between fiber coating and gas phase; LOO: leave-one-out (internal) cross-validation; LMO: leave-multiple-out (internal) cross-validation; LUMO: lowest occupied molecular orbital; μ: dipole moment; MLR: multiple linear regression; M_w: molecular mass; PAH: polycyclic aromatic hydrocarbon; PCA: principal component analysis; PCB: polychlorinated biphenyls; PCDF: polychlorinated dibenzofuran; PDMS: dimethylpolysiloxane; PP: projection pursuit; PPEG: poly(ethylene glycol); Ucon 50 HB 660: poly(alkylene glycols); QBES: tetra-n-butylammonium N,N-(bis-2-hydroxylethyl)-2-aminoethanesulfonate; RBF-NN: radial basis function neural network; RF: response factors; R_m: molar refraction; RMS, RMSE: root mean squared error; RR: ridge regression; RRT: relative retention time; RT: retention time; SD: standard deviation; SE, SEC, SEP, standard error, calibration, prediction; SOM: self-organizing map, (Kohonen network); T_b: boiling point; THPED: N,N,N',N'-tetrakis(2-hydroxypropyl) ethylenediamine; V_m: molar volume; VDW: van der Waals Volume.

3.1. General tendencies

Only one review is available in Chinese [172]. A common feature of QSERR investigations is that the authors attempt to use quantumchemical and 3D descriptors in linear regression. Chiral descriptors are rarely applied. The elution order of the enantiomers can be predicted from the interaction energy calculated by molecular mechanics.

3.2. Misleading practice and suggestions for future works

The prediction performance of models is questionable. There is no need to give the retention data in a form of an equation, if the numbers of compounds are small. The retention data, the selectivity for enatiomeric separation (α) can be used directly for identification, for determination of absolute conformation. The conclusion that e.g. 'molecular mechanics is suitable to study chiral separation' is either trivial or not true. The small number of compounds involved in the studies cannot make proper validations feasible. Hence, validation is missing from the contributions with several exceptions.

Any model providing elution order of enantiomers has an *a priori* success rate of 50%. Sign test and other test based on binomial distribution could show whether the predicted elution order is accidental or bear definite physiochemical relevance. As the number of compounds is generally small, careful internal validation (leave-one-out, leave-multiple-out) is recommended.

3.3. Summary of papers on quantitative structure–enantioselective retention relationships

Table 2 gathers the QSERR examinations covering the period of 1996–August 2006.

One example is emphasized, where hundreds of descriptors have encoded resolution for chiral separation successfully [195].

4. Quantitative structure - retention relationships in planar chromatography

4.1. General tendencies

Wang and Zhang have summarized the developments till 1999 [196]. Moreover, Cserhati and Forgacs have critically evaluated how to calculate quantitative relationships between molecular structure and retention data, and how to determine physicochemical parameters by TLC [197]. Only the sources not covered in these reviews are enumerated here.

Physicochemical parameters, topological indices, nonspecific parameters, and their combinations are used generally as descriptors. QSRRs in TLC are used for prediction of retention and determination of lipophilicity (and other physicochemical constants).

As TLC is a rapid, low-cost, simple method, the best TLC systems are routinely selected for determination of the octanol/water partition coefficient and thus the lipophilicity of the molecules.

4.2. Misleading practice and conclusions

The prediction performance of models has not been examined. Correlations can be found frequently by chance, especially if the number of descriptors is large. As the number of substances is limited on a plate the validation of models is often missing from the contributions. The conclusions such as 'correlations can be found between lipophilicity (hydrophobicity) and retention data' are trivial or at least well-known for a long time.

4.3. Suggestions for future works

The plates are of limited magnitudes; hence, QSRRs can be developed for a limited number of solutes. The mobile phases can be varied more extensively than in the case of HPLC. As the number of compounds is necessarily small careful internal validation (leave-one-out, leave-multiple-out) is recommended.

4.4. Summary of papers on quantitative structure–retention relationships in planar chromatography

Table 3 summarizes the solutes, methods and techniques for QSRR models in TLC.

5. Quantitative structure–retention relationships in column liquid chromatography

Despite the ever increasing usage of HPLC for the separation and analysis of various compounds, drugs, metabolites, etc., the selection of chromatographic conditions is still a tedious, time-consuming procedure mainly governed by trial and error approaches. *A priori* knowledge of the retention time of a given solute simplifies the selection of conditions. No wonder that the mainstream is to rationalize and to predict retention data using available and interpretable descriptors.

Although linear solvation energy relationships have similarly been defined for gas and liquid chromatography data, LSER has not gained general usage in gas chromatography, but in liquid chromatography, where LSER is used to predict retention data, to predict physical properties of solutes and classify chromatographic columns. The LSER equation for liquid chromatography is as follows [221]:

$$\text{Solute property} = c + eE + sS + aA + bB + vV \quad (2)$$

where solute property can be of any kind, e.g. $\log k'$, $\log P$, etc.; E is the excess molar refraction (R_2); S is the dipolarity/polarizability (π_2^H); A is the overall hydrogen bond acidity ($\Sigma\alpha_2^H$); B is the overall hydrogen bond basicity ($\Sigma\beta_2^H$); V is the McGowan volume (V_x in ($cm^3\ mol^{-3}$)); c is a constant (intercept, off-set, e.g. $\log k_{ref}$); e, s, a, b, v are regression coefficients of the multilinear model. Eq. (2) has been designed to deal with transfers from one condensed phase to another. In gas chromatography instead of the McGowan volume the gas–hexadecane partition coefficient is used: $\log(L_{16})$, which accounts for the transfers from the gas phase to a condensed phase.

Table 2
QSERR examinations between 1996–August 2006 (number of solutes and number of descriptors are in brackets)

Solutes	Descriptors	Model building	Stationary phase (SP)	Source
Chiral α-alkyl arylcarboxylic acids (28)	Hydrogen bonding ability and aromaticity	Retention data	AD-CSP	[173]
Mexiletine and a series of structurally related compounds	Presence or absence of secondary hydrogen-bonding group, nonempirical descriptors	Retention data, MLR	AD-CSP	[174]
Racemic 3-phenyl-4-(1-adamantyl)-5-X-phenyl-Δ^2-1,2,4-oxadiazolines	Aromatic ring substituents, electronic and bulk parameters or CoMFA descriptors	MLR, CoMFA	Pirkle-type *N*,*N*'-(S.S-dinitrobenzoyl)-1(R),2(R)-diaminocyclohexane	[175]
Chiral arylcarboxylic acids	Hydrophobicity and steric volume	MLR	Immobilized human serum albumin chiral stationary phase (HSA-CSP)	[176]
Aromatic acids (29)	Charge transfer, electrostatic, lipophilic, and dipole interactions	MLR, BP–ANN	Amylosic CSP	[177]
Enantiomeric amides	Chirality of the amylose backbone	Elution order	Amylosic CSP	[178]
Homologous series of 1,4-disubstituted piperazine	Carbon number of the alkyl substituent (max. C4–C5)	Nonlinear	Chiral cellulose tris(4-methylbenzoate)	[179]
Nonlinear data set for chiral separation	Mass (*m*/*z*)	PLS, ANN	Pirkle-type CSP	[180]
O-ethyl *O*-(substituted) phenyl *N*-isopropyl-phosphoroamidothioates (14)	Molecular descriptors (7) significant descriptors (4)	MLR		[181]
Chiral sulphoxides	Molecular connectivity indices, similarity and holistic descriptors (3D-WHIM)	RRT, MLR	Cellulose and amylose tris-phenylcarbamates coated onto 3-aminopropyl mesoporous silica	[182]
O-ethyl *O*-(substituted) phenyl *N*-isopropyl phosphoroamidothioate	LUMO, interaction of hydrogen bond, π–π interaction, log *P*	MLR	Pirkle-type CSPs, Sumichiral OA4700	[183]
Chiral arylalkylcarbinols (42)	2D and 3D molecular descriptors quantum chemical (LUMO) hydrophobicity	log α, MLR, ANN, CoMFA	Pirkle-type CSP	[184]
α-Aminophosphonates	Molecular parameters (4)	*k*, MLR, FA	Phenyl carbamate derivative β-cyclodextrin bonded	[185]
Diphenyl 1-(*N*-benzyloxycarbonyl)-aminoalkanephosphonates	log *P*, Angle, HOMO and LUMO	*k*, MLR, FA		[186]
Diphenyl 1-(*N*-benzyloxycarbonyl)-aminoalkanephosphonates	log *P*, Angle, loc*D* and TE	MLR	Pirkle-type	[187]
Various drugs, phenoxy propionic acid derivatives	Molecular descriptors (4)	MLR	Riboflavin Binding Protein (RfBP)	[188]
Diastereomers and enantiomers	Molecular dynamics	Addition of chiral substituents	Cyclodextrin derivatives	[189]
Aryl- and hetaryl-carbinols (22)	3D descriptors descriptor based on normal mode eigenvalues (EVA)	log α, CoMFA, CoMSIA, PLS, (0.97–0.99) validation (0.85–0.91)	(SS)-3,5-dinitrobenzoylated 1,2-diphenylethane-1,2-diamine	[190]
5-Arylhydantoins (50)	2D and 3D molecular descriptors, quantum chemical	MLR	Pirkle-type	[191]
Organophosponates	V_m, M_w, H-bond acceptor, dipole-Z	Elution order	*N*-(3,5-dinitrobenzoyl)-*S*-leucine	[192]
Hydroxy acids (8), amino acids (10)	Chiral topological indices	*I* (HP-TLC)		[193]
2-Aryloxy-2-arylacetic acids (1–3, 5–16), thioisostere derivative (4)	Polar, charge-transfer interactions, steric effects	*k*, Elution order, enantioseparation factors ($\alpha > 2$)	Penicillin G Acylase chiral stationary phase (PGA-CSP)	[194]
5-Arylhydantoins (50)	Dragon descriptors (557)	Selectivity, resolution, PCA, PP, UVE-PLS MLR, CART	3R, 4S-Welk-O-1	[195]

AD-CSP: amylose tris(3,5-dimethylphenylcarbamate); AR-CSP: amylose tris(R-phenylethyl-carbamate); AS-CSP: amylose tris(S-phenylethylcarbamate); ANN: artificial neural network; α: chiral separation factor; BP: back-propagation; CART: classification and regression trees; CoMFA: comparative molecular field analysis; CoMSIA: comparative molecular similarity indices analysis; CSP: chiral stationary phase.; FA- factor analysis; HSA-CSP: immobilized human serum albumin CSP; *k*: retention coefficient, (capacity factor); LOO: leave-one-out (internal) cross-validation; LUMO: energy of lowest unoccupied molecular orbital; M_w: molecular mass; MLR: multiple linear regression; PCA: principal component analysis; PGA-CSP: Penicillin G Acylase CSP; PLS: partial least squares; PP: projection pursuit; RfBP: riboflavin binding protein; UVE–PLS: uninformative variable elimination–PLS; V_m: molar volume.

Table 3
QSRR examinations in TLC between 1996– August 2006 (number of solutes in brackets)

Solutes	Descriptors	Model building	Method	Source
Antibiotics (29)	Hydrophobicity parameters, surface areas	Weak or no correlations	Impregnated silica and alumina supports	[198]
Estrone, equilin, equilenin, their 17α-diols, 17α-estradiol, 17α-dihydroequilin (DHEQ), 17α-dihydroequilenin	μ, Randic's connectivity indices, number of H atoms	PCA, NLM	TLC, RP-HPLC, capillary GC	[199]
Nonsteroidal anti-inflammatory drugs (18)	Lipophilicity and specific hydrophobic surface area	NLM	RP-TLC, methanol (acetic acid, sodium acetate, or sodium chloride)	[200]
Monotetrazolium and nine ditetrazolium salts (7)	Physicochemical parameters (hydrophobic, electronic, steric)	PLS, CCA	Alumina and reversed-phase (RP) alumina layers using *n*-hexane–1-propanol and water–1-propanol	[201]
Amino acids (15)	Topological indexes, physicochemical properties (15)	R_f, MLR	Silica gel layers	[202]
Aryloxyaminopropanol derivatives of 1,4-piperazine	Lipophilic Hansch's constants π, the number of carbon atoms in R1 substituent	R_m, linear, β-adrenolytic activity vs. $\log k$ is parabolic	TLC, HPLC	[203]
Mono- and nine ditetrazolium salts (7)	Steric and electronic parameters	PCA, NLM	TLC, HPLC	[204]
Dihydroxythiobenzanilides	Hydrophobicity, antimycotic activity, lipophilicity Hansch parameter	$\log k$, limited linear	RPTLC, acetone–water methanol–water	[205]
Flavonoids	Number of hydroxyl groups	Selectivities, sequences	Silica-diluent + polar modifier	[206]
O-alkyl, *O*-(1-methylthioethyl-ideneamino) phosphoramidates	Structural parameters (17): topologic indices, physicochemical	MLR	RPTLC	[207]
Ginsenosides (10)	Topologic indices, physicochemical properties, novel parameter 'E'	MLR	Silica gel layers (chloroform–ethyl acetate, methanol–water)	[208]
Homologous series of higher fatty acids, their methyl esters, higher alcohols	Topological indexes based on adjacency matrix, distance matrix	R_M, $\log P$ (Rekker), simple linear		[209]
Estradiol derivates	$\log P$	Various chromatographically obtained hydrophobicity parameters (R_{M0}, $\log k_w$ and φ_0)	HPTLC, HPLC, methanol–water and acetonitrile–water	[210]
Methyl laurate, -myristate, -palmitate, -isostearate, -stearate, -arachidate	Dipole moments of the mobile phases, percentage impregnation of SP, topological index	R_M, $\log P$ for methyl isostearate	Kieselguhr F254 impregnated with different amounts of paraffin oil	[211]
Biogenic amine neurotransmitters, their metabolites	Semi-empirical quantumchemical	Retention data, linear, CA	RP-18 plates	[212]
Meta- and para-alkoxyphenols	Topological indexes based on adjacency matrix, distance matrix, electrotopological states	R_M	Cellulose impregnated with ethyl oleate	[213]
Barbiturates (13)	Partition coefficients, μ, permittivities, topological indices	R_M, bilinear	Mobile phases (13)	[214]

Thiazole and benzothiazole derivatives	H -antihistamine 1 activity	Retention data, log P	Silica gel RP2 60F silanised precoated impregnated with amino acid mixtures	[215]
1,3-Oxazolidine derivatives	PC, Theoretical molecular descriptors (ALCHEMY 2000), lipophilicity	R_{M0}, PCA	C18 silica gel bonded, methanol	[216]
s-Triazines	Partition coefficients, Alog P, IAlog P, Clog P, Xlog P, log PKowin, and ACDlog P	Retention factors R_{M0}	Methanol–water, acetone–water, acetonitrile–water, 2-propanol–water, tetrahydrofuran–water	[217]
Nicotinic acid, its derivatives Alkyl nicotinates (MN), nicotinamide, N-methylnicotinamide	Measured and calculated partition coefficients, log Pexp, Alog Ps, IAlog P, Clog P, log PKowin, xlog P, topological indices	R_{M0}	RP18WF254, methanol–water	[218]
Benzimidazole and benztriazole derivatives	Molecular descriptors, scores	R_f and R_{M0}, PCA	Paraffin oil-impregnated silica gel plates, methanol–water	[219]
2,4-Dihydroxyphenylthioamide derivatives	Antifungal activity	R_{Mw} and log k_w, linear, parabolic	RPLC, TLC, methanol–water	[220]

CA: cluster analysis; FA: factor analysis; HPTLC: high-pressure TLC; k: retention coefficient, (capacity factor); μ: dipole moment; MLR: multiple linear regression; NLM: non linear mapping; PAH: polycyclic aromatic hydrocarbons; PC: principal components; PCA: principal component analysis; PLS: partial least squares; R_m, R_M: TLC retention parameter, $R_m = \log(1/R_f - 1)$; RPTLC: reversed phase TLC; TLC: thin layer chromatography.

LSER includes cavity formation/dispersive interactions (V), dipolarity/polarizability interactions (S), and hydrogen bonding interactions (A and B). The outcome of a LSER analysis is a set of regression coefficients which provide us with information about which solute–solvent interactions significantly affect the retention process. The coefficients (e, s, a, b, v) are related to the chemical nature of the mobile and stationary phases, and their values can be determined easily. It should be mentioned that the regression coefficients are interrelated (coupled) similarly to the Abraham descriptors (E, S, A, B, V or L) i.e. they do not carry independent information. Recent (unpublished) examinations on the data of [221] show that two to four (on average three) independent (orthogonal) coefficients would be sufficient to represent the retention phenomenon properly (depending on the method used for determination of independent parameters). This finding has been supported by separate examinations [222].

LSER models can be applied with very large variations in chromatographic conditions. Using a relatively small set of model compounds predictions can be made well outside of the model domain. This implies that LSER models are general and indeed the LSER explanation for partitioning is generally accepted. On the other hand LSER models are typically not accurate enough for prediction purposes. LSER models contribute mainly to the general understanding of partition processes and less to optimize separations.

Linear relationships were established for a set of compounds between logarithm of retention factor (k) and volume fraction of organic modifier (φ):

$$\log k = \log k_w - S\varphi \tag{3}$$

where S is the slope, and $\log k_w$ is the intercept. S versus $\log k_w$ correlations are chemically meaningful for a non homologous series of compounds.

The hydrophobic-subtraction model assumes that first the major contribution of hydrophobicity is subtracted from the retention in reversed-phase liquid chromatography (RP-HPLC). Such a way the remaining contributions to retention from other solute–column interactions can be established. The general formula for retention (k) and column selectivity (α) is given by Snyder et al. [223]:

$$\log \alpha \equiv \frac{\log k}{k_{ref}} = \eta' H - \sigma' S^* + \beta' A + \alpha' B + \kappa' C \tag{4}$$

where k_{ref} – non polar reference solute. The coefficients denote properties of the solute: η' – hydrophobicity; σ' – molecular 'bulkiness' or resistance to insertion of the solute into the stationary phase; β' – hydrogen-bond basicity; α' – hydrogen-bond acidity; κ' – approximate charge (either positive or negative) on the solute molecule whereas parameters denoted by capital letters are complementary properties of columns: H – hydrophobicity; S^* – steric resistance to insertion of bulky solute molecules into the stationary phase; A – column hydrogen-bond acidity, B – column hydrogen-bond basicity, C – column cation-exchange activity, (hence, C is pH dependent).

Snyder's parameters are tabulated for more than 300 columns [223]. Eq. (4) is suitable for prediction and optimization of RP-HPLC separations.

5.1. General tendencies

Linear solvation energy relationships (LSERs) are abundantly used for characterization of stationary phases (polymers). Another important aspect is to determine lipophilicity (hydrophobicity) parameters from retention data. The reference scale for lipophilicity (logarithm of partition coefficient denoted by log P and determined in the 1-octanol–water partition system) is accepted broadly. As the conventional determination of log P is tedious and lacks the acceptable interlaboratory reproducibility, alternative scales based on chromatographic retention have been defined to measure lipophilicity. The reversed-phase high-performance liquid chromatography, i.e. the partition of a solute between a polar, aqueous mobile phase and a nonpolar stationary phase appeared to be especially suitable for lipophilicity determinations. Rational drug design have profited a lot using fast screening HPLC methods.

Fundamental relationships between chromatographic parameters are reviewed from the point of view of convenient and reliable lipophilicity measurements [298].

As theoretical basis exists to rationalize the main effects of retention many colleagues do not feel to be bounded to validate QSRR models for liquid chromatography. Since the millennium the number of validated models has been increasing.

5.2. Misleading practice and conclusions

Statements as 'the model describes the retention of . . . compounds under . . .. conditions very well' do not say much about the achievements. The description is not inevitably necessary as the retention data for *these* compounds under *these* conditions are available in tabular form. A prediction of retention data for not yet measured compounds would be a real gain. However, this should be checked and proved by cross-validation or external validation. Other valuable aims could be the rationalization of measured data and classification of column/system properties, but we should not forget that such rationalizations for the same/similar compounds are available from renowned authors abundantly. Similarly, numerous classification schemes are available, but none of them achieved general usage.

The correlation coefficients are often given without the degrees of freedom; cross-validated correlation coefficients are also missing in many cases.

Concluding remarks as 'The predicted values are in very good agreement with the experimental values' say very little about the real prediction performance, they should be avoided.

There is some ambiguity in the usage of 'test analytes' and 'test sets'. Test analytes form the training set whereas new independent series of compounds serve for testing the prediction performance. The prediction set is often called as test set in chemometrics.

Statements as 'ANN predicts the retention data better than MLR method' have little relevance (see the text in Section 2).

5.3. Suggestions for future works

The domain of model applicability is rarely given for QSRR investigations in liquid chromatography, if at all. Although mobile phase concentrations are generally provided, it is missing which compounds can be included and which ones should be excluded from the investigations.

Properly validated models should be recommended for prediction purposes. The same performance indicators (adjusted correlation coefficients, cross-validated correlation coefficients, F values, standard errors, etc.) should be used for comparison.

Standardization of optimization strategies for chromatographic separation conditions would provide great benefit using QSRR equations.

5.4. Summary of papers on quantitative structure–retention relationships in column liquid chromatography

Table 4 summarizes the solutes, methods and techniques for QSRR models in column LC (correlation coefficients are in brackets).

The basicity of solutes has a larger effect on the retention of the PBD-zirconia phase than of conventional bonded phases. Strong hydrogen bases and highly dipolar solutes, when compared to nonpolar ones, are less strongly retained on PBD-zirconia than on conventional phases [224].

A (good) linear correlation was obtained between the gradient retention time values and the isocratically determined φ_0 values for 76 structurally unrelated compounds. The constants of this linear correlation can be used to calculate chromatographic hydrophobicity index, CHI [238].

The assignment of HPLC peaks to their corresponding compounds in libraries of single compounds can be made on the basis of the correlation of the retention times with the different substituents in the variable positions of the molecule. The correlation is performed automatically by a new algorithm which is part of the computer program LIBFINDER [244].

Lipopholicity parameters, CHI and log k_{50} are moderately correlated with log P (water/octanol), and both can be used as alternative measures of lipophilicity. Analysis using the general salvation equation of Abraham shows that the solute factors that influence CHI and log k_{50} are not entirely the same as those that influence log P, so that neither CHI nor log k_{50} can be used as a direct measure of log P and *vice versa*. However, the factors that influence CHI are the same qualitatively and quantitatively as those that influence log k_{50} [251].

Using three-dimensional descriptors variable-reduced models resulted in considerably better predictions, although these were not as good as for those models obtained by means of classical physical–chemical descriptors [257].

QSRR investigations may reveal non congeneric behavior of similar compounds [266], but the problem remains whether an extraordinary high lipophilicity will cause outlying biological activity or not.

Properly designed test series of analytes can be recommended for comparative studies of analytical columns. QSRRs once derived on a given column for model analytes can be used to predict the retention of other analytes of a defined structure. That in turn can facilitate the procedure of the rational optimization of chromatographic separations and can characterize

Table 4
QSRR examinations in column liquid chromatography between 1996–August 2006 (number of solutes and number of descriptors are in brackets)

Solutes	Descriptors	Models	Column, mobile phase	Source
Substituted aromatic hydrocarbons	S, A, B, V	LSER	Polybutadiene (PBD)-coated zirconia	[224]
Structurally diverse solutes (25)	E, S, A, B, V; and water accessible V_w, μ, atomic electron excess charge	LSER, $\log k'$	Polyethylene-coated silica (PECSiO(2)) polyethylene-coated zirconia (PECZrO(2))	[225]
Substituted benzenes	Substituent constant (π) and the total solubility parameter (δT)	MLR	Various columns in several different eluents	[226]
Quinolones	S_w, y-component of μ, MM + and AM1	MLR, CA of solutes	PRP-1 column and aqueous organic solvent system	[227]
Unsubstituted 3–6-ring PAHs (31)	Moment of inertia	CoMFA (0.973), cross-validated (0.930)	Polymeric C18 reversed-phase column	[228]
Small peptides	Sum of the hydrophobic contributions of respective amino acid residues	MLR, PLS, retention times	Ultrasphere Octyl, Ultrasphere ODS, Polymeric reversed phase PLRP-S Nova-pak C-18	[229]
Alkyl (1-phenylsulfonyl) cycloalkane-carboxylates (28)	Octanol/water partition coefficients	LSER	RP-HPLC	[230]
Carboxamides and oxadiazoles	MM+ and AM1 descriptors for intermolecular interaction, isomeric effect and substituent effect: S_w, x component of μ, $\log P$ and μ	MLR, Bilinear	RP-HPLC	[231]
LSER solutes (nitroalkanes, substituted benzenes)	LSER descriptors: E, S, A, B, V	$\log k'$ or $\log k$(w), $\log P$ (octanole or alkane)	Poly(styrene-divinylbenzene) and immobilized artificial membrane, PRP-1	[232]
Substituted biphenyls (25)	Solute volume (V) and hydrogen bond basicity (B)	S, $\log k_w$ (>0.99)	C18 column, methanol/water	[233]
Pesticides; triazines	MM+ and AM1 descriptors: solvation energy of specific site of solute, solvation energy and polarizability, S_w	t_R	RP, methanol–water acetonitrile–water	[234]
Series of xenobiotics, 83 drugs	Physicochemical parameters	LSER, classification, PCA, similarity analysis	Eight systems	[235]
PCBs and Chlorobenzenes, non ortho-substituted chlorobiphenyls	Polarizability, LUMO, third order valence path molecular connectivity index	$\log k$, linear (0.994), bilinear (0.992)	PGC: porous graphitic carbon PYE: 2-(1-pyrenyl)ethyldimethyl silica)	[236]
Substituted benzenes	S, δT, $\log P$ molecular structure parameters	$\log k_w$, linear, nonlinear, $\log P$	RP-HPLC	[237]
Structurally unrelated compounds (66)	CHI	$\log k_c$, t_R, $\log P$	Fast gradient RP-HPLC, acetonitrile–water	[238]
Test series of structurally diverse solutes	Structurally specific dipole–dipole and charge transfer interactions	MLR	C18 and AP (*N*-acylaminopropylsilica)	[239]
Barbituric acid derivatives (42)	Hydrophobicity parameters (e.g. hydrophobicity)	$\log k$, PCA, NLM	PGC porous graphitized carbon, water-acetonitrile	[240]
Heteroatom containing compounds	Quantumchemical, AM1 Hamiltonian, average molecular polarizability, net atomic charges on oxygen atoms that connect with the sulfur atoms, μ	$\log k$, LSER	Not given	[241]
Hydroxy compounds, glucuronides	Physico-chemical constants, Parent compound	$\log k$	Not given	[242]
Phenolic and nitrogen-containing aromatics	Quantumchemical, Hammett's constants	pK_a	Acetonitrile, water, sodium phosphate buffer	[243]
Library	Different substituents in various positions	RT	HPLC	[244]
Finasteride, *N*-methylfinasteride	Polar functionalities on the surface of adsorbent, $\log P$	$\log k_w$	Chemically-bonded-silica (SG-MIX), with hydroxyl (—OH), amino (—NH2), cyano (—CN), phenyl (—Ph), octyl (—C8) and octadecyl (— C18) groups	[245]

Table 4 (*Continued*)

Solutes	Descriptors	Models	Column, mobile phase	Source
Nonsteroidal anti-inflammatory drugs (20)	Physicochemical. parameters	PCA, NLM, CA	RP-HPLC	[246]
Substituted *N*-benzylidene anilines (70)	Solute polarity, Hammett's constants	CA, CFA	NP: heptane and three modifiers, tetrahydrofuran, 1-octanol and ethyl acetate	[247]
Disubstituted *N*-benzylidene anilines	μ, Hammett's constants, σ_X, σ_Y LSER descriptors	$\log k$	NP-HPLC	[248]
Selected phospholipid classes	Configurational + conformational descriptors	Nonlinear, ANN-PLS	RP-HPLC	[249]
Natural phenols in olive oils	Molecular descriptors (62): conventional, topological, and quantum-chemical	MLR (0.9825–0.9974)	RMSE 6.8–2.6%	[250]
Very diverse set of compounds (55)	CHI, $\log P$	$\log k_{50}$	ODS column and acetonitrile mobile phase	[251]
Compounds (29) were examined under conditions using automated fast gradient methods	CHI, LSER descriptors: *E*, *S*, *A*, *B*, *V*	$\log k_c$, t_R, $\log P$	Twenty different RP-HPLC, fast gradient	[252]
Homologous series	LSER descriptors	Hydrophobic selectivity and polar selectivities	Widely different RP-HPLC	[253]
Solutes of widely different type (34)	LSER descriptors	PCA	Nine prepacked narrow-pore and six wide-pore RP-HPLC various ligands (C18, C8, C4, CN)	[254]
Quinolones studied. At pH 3, was mainly affected by two descriptors	HOMO μ, MM+, AM1 semiempirical	$\log k'$	PRP-1 columns, MeOH, THF	[255]
2-Cyano-3-methylthio-3-substituted amino-acrylates (25)	Structural parameters (10)	$\log k'$, PCA, MLR	Not given	[256]
Steroids	3D field descriptors	RT, SOM, PLS calibration set, test set (0.65–0.89)	NP, RP	[257]
2,4-Dihydroxythiobenzanilides (fungicides)	φ	$\log k'$, $\log k_w$, linear, parabolic	RP, methanol–water or acetonitrile–water	[258]
Diverse analytes (58)	LSER descriptors, $\log P$	$\log k'$, $\log k_w$	Inertsil ODS3, symmetry C8, IAM.PC.C10/C3, methanol	[259]
Substituted indoles (18)	Molecular connectivity indices and quantum chemical descriptors	k'	RP-HPLC, C18 column	[260]
O-alkyl, *O*-(1- methylthio-ethylideneamino) phosphoramidate	Solute-related structural parameters	k', FA, CA, MLR	Not given	[261]
Structurally diverse analytes (25)	$\log P$, LSER descriptors, simple structural descriptors	$\log k_w$, Column classification	18 RP-HPLC	[262]
Perhydrogenated and Perfluorinated polyoxyethylene surfactants	Length of alkyl chain, the number of oxyethylene residues, the presence of an oxygen or sulfur atom in the molecule, Molecular electrostatic potential, molecular lipophilic potential, $\log P_{calc}$, V_m	$\log k$, $\log k_w$	RP-HPLC, methanol–water	[263]
Iridoid glucosides	Free rotation around σ-bonds		C18, normal diol SPs	[264]
Benzene and phenol derivatives, indazol, tiophene, caffeine, etc.	$\log P$, structural- and LSER descriptors	$\log k'$, chromatographic indices	SG-AP, Supelcosil ABZ + Plus C18 Symmetry-Shield RP8, Symmetry	[265]
2,4-Dihydroxythiobenzanilides	$\log P$	Outlier detection	RP-HPLC	[266]
Chalcones (17)	Molecular descriptors, LSER	PLS (0.976) test set (0.933)	RP-HPLC, methanol–water	[267]
Antimicrobial hydrazides	3D-fields	$\log k$, CoMFA	C-8, methanol–water	[268]
O-aryl, *O*-(1-methylthioethylidene-amino)phosphates (13)	Solute-related structural parameters (8)	k', FA, MLR	RP-HPLC	[269]

Very different compounds (233)	Structural descriptors (4), log P	Solute polarity parameter (p), MLR (0.977)	RP-HPLC	[270]
Ethynyl-substituted PAHs (20) and unsubstituted counterparts	Polarizability and subpolarity, AM1; PM3	RT (0.967–0.984)	C18, RP-HPLC, water/acetonitrile	[271]
Substances (25)	Structural descriptors	log k', ANN (MLP), PLS	Polyethylene–silica and polyethylene–alumina	[272]
Substances (25)	Structural descriptors	ANN (RBF), GRNN, PCR, polynomial PLS	Polyethylene–silica and polyethylene–alumina	[273]
Three test series of analytes	Reduced LSER, log P	RT	RP-HPLC	[274]
Substituted benzaldehydes (14)	Molecular connectivity indices, LSER and quantum chemical parameters	log k	C18, RP-HPLC, methanol–water	[275]
Alkylbenzenes, halobenzenes, xylenes, alkanes, isoalkanes	LSER, structural	α, log k	C8, C18, PBB, PYE	[276]
Steroids (24)	3D image	Pulse-coupled neural network: PCNN, PLS	RP-HPLC, cross-validation	[277]
Drugs (162)	Molecular similarity	log k, ANN (0.992–0.996)	RP-HPLC, cross-validation	[278]
Pyrethroid pesticides	log k'	log k, log P	RP-HPLC, LOO	[279]
Diverse compounds (86)	CHI(ACN, MeOH), hydrogen bond acidity	log P (0.943–0.970)	Fast gradient RP-HPLC	[280]
Hydantoin derivatives	CODESSA descriptors, AM1 main structural factors, LFER descriptors	Lipophilicity (S)	RP-HPLC RP-HPLC	[281] [282]
Xanthines and derivatives	Semiempirical quantumchemical	log k', MLR	Chromolith RP-18e	[283]
Barbituric acid derivatives (45)	φ, substituents steric parameters	log k, MLR, PCA, NLM	Amide embedded RP silica column (Discovery RP-AmideC16), water-acetonitrile	[284]
Barbituric acid derivatives (45)	φ, $-\varphi_0$, conventional and quantum chemical structural	log k, MLR, asymmetry factor (AF5) theoretical plate (N)	Amide embedded RP silica column (Discovery RP-AmideC16), methanol–water	[285]
Barbituric acid derivatives (45)	φ, $-\varphi_0$, conventional and quantum chemical structural	log k, MLR, six retention related parameters, PCA, NLM	Amide embedded RP silica column (Discovery RP-AmideC16), tetrahydrofuran–water	[286]
Barbituric acid derivatives (45)	φ, $-\varphi_0$, conventional and quantum chemical structural	log k, MLR, 6 retention related parameters, PCA, NLM	Amide embedded RP silica column (Discovery RP-AmideC16), dioxan–water	[287]
New α-branched phenylsulfonyl acetates (20)	Geometric and electronic descriptors, surface area (S), ovality (O), the charge of carboxyl group (Qoc), surface area	log k_w (0.981 adjusted)	Li Chrosorb RP-18 column	[288]
Selected amino acids (18), phenylthiocarbamyl (PTC) amino acid derivatives	Molecular descriptors (36), log P, molecular size, shape (topological indices)	RT, GA–ANN	ODS column	[289]
Basic compounds related to caproctamine, dibenzylamine-diamide (reversible inhibitor of acetylcholinesterase)	Hammett σ (electronic properties of the ortho-substituents)	pK_a	C18, C4, RP-HPLC, acetonitrile	[290]
Drugs and model compounds	Lipophilicity and acidity	RT, pK_a, log k_w	Inertsil ODS3, XTerra RP-18, Aluspher 100 RP-select B	[291]
Neutral, acidic and basic solutes (67)	LSER descriptors, and variants	k	Ten different C18 (alkylsilica) columns	[292]
Aromatic acids	log P, pK_a (partial charges of atoms)	k	RP-HPLC	[293]
Model series, 15 analytes	Total μ, electron excess charge of the most negatively charged atom water-accessible surface area	Rt, log k_w, S	Gradient RP-HPLC	[294]
Disubstituted benzenes (54)	Molecular descriptors (8), PM3 semiempirical	log k_w, MLR, RBF-ANN	RP-HPLC	[295]
Mainly substituted benzenes (25)	LSER descriptors, S_w	log k_w, MLR, PCA	Eight RP-HPLC, CE	[296]

Table 4 (*Continued*)

Solutes	Descriptors	Models	Column, mobile phase	Source
PAHs	Molecular connectivity, μ	RT, bilinear, MLR	Training, test sets, HPLC	[297]
Xenobiotics	Chromatographic parameters	log P, PCA	RP-HPLC	[298]
Phenols	pK_a, atomic partial charges by AM1 and PM3	RT	RP-HPLC	[299]
Diverse aromatics (training, 15) diverse compounds (test, 47)	log P, μ, S_w, electron excess charge on the most negatively charged atom	RT, MLR (0.8953–0.9870)	Supelcosil LP18	[300]
Structurally diverse drugs (83)	Descriptors (266), hydrophobicity (log P and Hy), the size (TPC) of the molecules	log k_w, CART	Unisphere PBD column isocratic elution	[301]
Diverse aromatics (training, 15)	log P, μ, S_w, electron excess charge on the most negatively charged atom	RT, MLR, ANN	RP-HPLC, methanol–water	[302]
Very different compounds (233)	Descriptors (4), log P, hydrogen bond acidity	Solute polarity parameter p, MLR, (0.977)	RP-HPLC	[303]
Para substituted anilides of 2,2-dimethylpropanoic, benzoic and α-phenylacetic acid	Physicochemical parameters, μ, ε, topological indexes, log P, log S, hydrogen-bond acceptor indicator (HA) and molecular mass	RT, MLR	RP-18 HPLC, methanol–water	[304]
Test solutes	LSER descriptors	MLR	C18, C8 columns methanol, acetonitrile, and tetrahydrofuran	[305]
PAHs	AM1: HOMO, LUMO, GAP hardness, polarizability, atomic charges, connectivity index, volume and surface area	T_b, log P, I, PCR, PLS (0.898–0.995)	RP-HPLC	[306]
L-amino acids (18)	Binding energy (Eb), log P, molecular refractivity (MR), polarizability (α), total energy (Et), water solubility (log S), connectivity index (χ) of different orders and Wiener index (W)	k, MLR (>0.9)	RP-HPLC	[307]
Phenols (16)	As above + hydrophilic-lipophilic balance (HLB)	k, MLR		[308]
PAHs, methyl substituted PAHs	Spatial and topological descriptors	PLS, structural differences, nonplanarity	Monomeric and polymeric C18 stationary phases	[309]
2-(2,4-dihydroxyphenyl) benzothiazoles	Specific hydrophobic surface area (S), and isocratic CHI (φ_0)	log k, log k_w, log P	RP-18, methanol–water	[310]
Solutes (neutral, acidic and basic), (60)	Retention from neutral components	RT, MLR	C18, RP-HPLC, RP-IPC, Acetonitrile–water	[311]
Solutes (neutral, acidic and basic), (60)	LSER descriptors extended by ionization and ion-pair terms	RT, MLR	C18, RP-HPLC, RP-IPC, Acetonitrile–water	[312]
Different compounds (200)	LSER descriptors, acidity	p, log k, log P	RP-HPLC, Acetonitrile–water, methanol–water	[313]
Acidic drugs (19)	Molecular mechanics, interaction energies	RT (0.878)	Pentyl bonded phase	[314]
Diverse	log P, various types of lipophilicity	Retention data	RP-HPLC, biomimetic stationary phases	[315]
Peptides (75)	CODESSA, Molecular descriptors (7)	log k, linear, nonlinear, SVM, prediction set (0.9801)	Carbonex microspherical carbon	[316]
Structurally diverse solutes	Molecular descriptors (1000)	RT, MLR (0.927), GA, prediction (0.79–0.87)	15 HPLC columns, 5 gradients	[317]
Aromatic compounds	Structural descriptors (9), log P	log k, PCA, CA, MLR	Polybutadiene coated titania SP (PBD-TiO2), HPLC, methanol–water	[318]
Xanthones, aglycones, glucosides	S	log k_w	Gradient HPLC	[319]
Benzoylphenylureas, Dihalogeno benzoylphenylureas (18)	μ, MR, log P	k, MLR	Polystyrene-octadecene-encapsulated zirconia, Kromasil-C18-SiO2	[320]

Peptides (101)	Sum of RTs of amino acids, log V_w, log P	RT, MLR	Gradient HPLC	[321]
Peptides (98)	Sum of RTs of amino acids, log V_w, log P	RT, MLR	Gradient HPLC	[322]
Series of test analytes	log P, μ, δ, S_w, hydrophobic subtraction LSER model	RT, classification	Nine representative RP-HPLC column	[323]
Steroid analogues		De novo mathematical model	RP-HPLC, methanol, acetonitrile, tetrahydrofuran	[324]
Triazine herbicides, metabolites	Descriptors (4)	k, MLR, ANN	Methanol – water, Spherisorb ODS2, precolumn LC 8	[325]
Unsaturated alkenes, phenols, acidic and basic drugs	Alkyl-chain length, atomic partial charge, pK_a	k	Graphitic carbon	[326]
Alkyl(1-phenylsulfonyl) cycloalkane carboxylates (28)	Ab initio quantum chemical, B3LYP/6–31G*, AM1	log k, bilinear, (0.9747, 0.9741)	LOO	[327]
Ricobendazole and albendazole sulfone	log P	log k_w, log k, Internal standard selection by QSRR	C-18 column, rapid HPLC	[328]
Aromatic acid derivatives	Interaction energies, MM, pK_a	log k	RP-HPLC	[329]
Benzoic acid derivatives	Interaction energies, MM, pK_a	log k	RP-HPLC	[330]
Model series of test analytes	Structural parameters of stationary phases	Retention data	NP, RP, CE	[331]
Purine nucleobases (33)	3D field descriptors	CoMFA (0.969) validation (0.832)	C18 column	[332]
Neutral and basic compounds	log P	log k_w, log k	Supelcosil ABZ + Plus, Discovery RP Amide C16, and Zorbax Extend C18	[333]
Antiprotozoal meso-ionic 1,3,4-thiadiazolium-3-aminides	VolSurf descriptors, hydrophobic (DRY), amide N-atom (N(1)) and carbonyl O-atom (O) probes	RT	Supelcosil ABZ + Plus column methanol–water acetonitrile–water	[334]
Basic drugs (83)	Molecular descriptors (1272)	CART, stochastic gradient boosting random forest, GA–MLR (0.964), UVE–PLS	Unisphere PBD column	[335]
Indole derivatives (17)	Ab initio B3LYP/6–311G**	log k, log k_w (0.9796), S (0.9874)		[336]
Nitrogen containing heterocycles (29)	Molecular connectivity, Wiener, Kier flexibility, Harary, Balaban, Zagreb indices	log k, simple linear (0.9–1.0)	LC	[337]
Nitrogen-containing heterocycles (24)	α, MR, log P, μ, Etot, ΔH_f, molecular surface area (SM), binding energy (Eb)	log k, Simple linear (0.8–1.0), multilinear (1.000)		[338]
Single- and multi-ring aromatic hydrocarbons (AH)	Substituent effect, electronic and geometric descriptors, IP, EA	RT, PLS, GA	[3-(2,4-Dinitroanilino)]propyl-silica column	[339]

ANN: artificial neural network; α: polarizability; CA: cluster analysis; CART: classification and regression tree; CE capillary electrophoresis; CFA: correspondence factor analysis; CHI: chromatographic hydrophobicity index; CoMFA: comparative molecular field analysis; δ: electron excess charge of the most negatively charged atom; ΔH_f: heat of formation; δT: total solubility parameter; EA: electron affinity; Etot: total energy; ε: permittivity; FA: factor analysis; φ: volume fraction of mobile phase; GA: genetic algorithm; GRNN: generalized regression neural networks; HOMO: energy of highest occupied molecular orbital; index of hydrophobicity $\varphi_0 = -\log k_w/S$; IP: ionization potential; IPC: ion pair chromatography; k, k': retention coefficient, (capacity factor); log k_w: intercept of the plot for log k' vs. φ (extrapolated to mobile phase without water); log P, log $k_{o/w}$: octanol/water partition coefficient; LOO: leave-one-out cross-validation; LUMO: energy of the lowest unoccupied molecular orbital; MLR: multiple linear regression; MLP: multilayer perceptron neural networks; MR: molar refraction; μ: dipole moment; NLM: non linear mapping; NP: normal phase; ODS: octadecil silica; p: solute polarity parameter (ref. [303]); PAH: polycyclic aromatic hydrocarbons; PCA: principal component analysis; PCR: principal components regression; pK_a: dissociation constant; PLS: partial least squares; RBF: radial basis function; RP: reversed phase; RT: retention time; S: slope of the plot for log k' vs. volume fraction of mobile phase (φ); SOM: self-organizing map, Kohonen network; SP: stationary phase; S_w: solvent-accessible surface area; T_b: boiling point; UVE–PLS: uninformative variable elimination–PLS; V_m: molar volume; V_w: van der Waals volume.

modern stationary phases (systems) in an objective, quantitative manner [274].

The linear solvent strength (LSS) model + QSRR approach have been demonstrated to provide approximate, yet otherwise unattainable, *a priori* predictions of gradient retention of analytes based solely on their chemical formulae [302].

Solute polarity descriptor (p) is useful to transfer retention data between solvents and/or columns. The retention for any chromatographic systems (mobile phase composition) can be predicted using the five solvation descriptors (Eq. (1)), if the polarity of the column has been characterized using a small training set. Alternatively, log P and hydrogen-bond acidity data can be used for these predictions [313].

Numerous correlations of retention data with an octanol–water partition coefficient have been reported. Valko has reviewed lipophilicity correlations and alternative lipophilicity measures [315].

A comparison of chemometric methods based on predictive performance indicated the most important variables and that, individually, genetic algorithm selected descriptors with multiple linear regression modeling outperformed all other models [335].

6. Quantitative structure–retention relationships in micellar chromatography

Micellar liquid chromatography, micellar electrokinetic chromatography, micellar electrokinetic capillary chromatography, biopartitioning micellar chromatography, liposome electrokinetic chromatography, and microemulsion electrokinetic chromatography are indexed under this heading. Although physicochemical principles of separation are different in case of electrokinetic and non electrokinetic methods, the two types were merged here. There is no use to fragment the review further.

The separation system in micellar electrokinetic chromatography (MEKC) consists of a homogeneous distribution of charged surfactant micelles in an electrolyte solution. Provided that the velocity of the micelles in a defined direction is different to the velocity of the bulk electrolyte solution in an electric field a separation of neutral solutes is possible.

6.1. General tendencies

Generally, correlations are searched between retention data in micellar liquid chromatoghraphy (MLC) and different measures for hydrophobicity (log P). Diverse chemical compounds, substituted benzenes, drugs, pesticides, etc. are frequently used as model compounds.

Pharmacodynamic quantities, toxicity values, bioconcentration factors can preferably be predicted with micellar chromatography. The retention often serves as independent ($\boldsymbol{X}$) variable; the method sometimes is called QRAR, i.e. quantitative retention–activity relationships.

6.2. Misleading practice and suggestions for future works

In this first phase of the research the potential of the new method is used to be revealed. Hence, chemometric methods, encoding the molecular structure and cross-validation, are rarely used. After the rationalization of measured data multivarate methods will be applied with proper validation in the near future.

6.3. Summary of papers on quantitative structure–retention relationships in micellar chromatography

Table 5 summarizes the solutes, methods and techniques for QSRR models in micellar chromatography (correlation coefficients are in brackets).

A migration index (MI) concept, a novel scale for measuring the hydrophobicity of neutral solutes, was extended to anionic solutes. The MI values of anionic solutes correlated very well with log P, whereas the RP-HPLC retention parameter (log k'_w), which is also used as a hydrophobicity scale, correlated very little with log P for the examined anionic solutes [341].

A measure of the hydrophobic character of such amphoteric compounds (as the studied sulfonamides), could be the values of the retention coefficient determined at pH of the isoelectric point [351].

Biopartitioning micellar chromatography (BMC) based models may be useful to screen new chemicals in the early stage of development and to select safer chemicals [356].

The retention of compounds in MLC using Brij 35 surfactant is able to describe and predict pharmacokinetic and pharmacodynamic parameters of non steroidal anti-inflammatory drugs. QRAR model is a model which can estimate the pharmacokinetic and pharmacodynamic parameters of new compounds in vitro [359].

The chromatographic retention of any molecule in BMC, independently of its family, can be adequately described by its hydrophobicity (expressed as log P) and its anionic and cationic total molar charge [363].

7. Quantitative structure–retention relationships in affinity chromatography

Affinity chromatography (AC) and immobilized artificial membrane (IAM) chromatography are indexed under this heading. Affinity chromatography where biomacromolecules form the stationary phase became an important tool in rational drug design. AC models the drug-receptor interactions. Structural requirements of specific binding sites on biomacromolecules are also revealed. Protein based stationary phases can be used for enantiomer separations (c.f. QSERR, Section 3) as all proteins are in fact chiral; AC can be applied to elucidate the molecular mechanism of enantioseparation on natural biopolymer stationary phases, hence rational selection of chiral columns for specific analytical separations is enhanced.

Affinity chromatography plays an important role in rational drug design because the efficiency of finding new drugs is enhanced. Moreover, it can reduce the tedious experiments of in vivo screenings. Strictly speaking refs. [377,385] do not belong to artificial membrane chromatography as no biomacromolecules form the stationary phases. However, receptor binding, affinity is modeled; hence these references are also included.

Table 5
QSRR examinations in micellar liquid chromatography between 1996–2006

Solutes	Descriptors	Models	Column, mobile phase, surfactant	Source
Congener series of steroid hormones	Topological i.e., connectivity indices, X, steric factors	RT, linear, multilinear	ODS column (RP-HPLC,) sodium dodecyl sulfate (SDS)-borate system and with a mixed micellar solution of SDS and sodium cholate	[340]
Anionic solutes	Migration index, $\log k_w$	$\log P$	Sodium dodecyl sulfate/1-butanol/heptane/buffer, CE	[341]
	$\log P$, $\log k_w$, LSER descriptors	I, linear	SDS surfactant no such a linear relationship with CTAB, DTAB	[342]
Catecholamines	Physico-chemical parameters	$\log k$, $\log P$, MLR, PLS		[343]
Local Anesthetics	Molar fraction of the charged form, $\log P$	$\log k$, MLR	Nonionic surfactant solution	[344]
Flavonoids	Structural descriptors (183), electrotopological state indices (Si) of skeletal carbons	Mobility, effective mobility CA, FA, $\log k$, migration	Thirty-eight buffer conditions, CZE, MEKC	[345]
Barbiturates	Hydrophobic and electrostatic ($\log P$, δ'), PCs	$\log k$, $\log k = a \log P + b\delta' + c$	C18, surfactant: Brij 35, SDS, CTAB	[346]
Catecholamines, local anesthetics, diuretics and *o*-phthalaldehyde-*N*-acetyl-L-cysteine amino acid derivatives	Hydrophobic and electrostatic forces	$\log k = a \log P + b\alpha' + c$	Brij35, SDS	[347]
	$\log P$, molecular structure parameters	$\log k'$, ANN, MLR (>0.998)	MECC	[348]
Basic pharmaceutical substances (21)	$-0.026 < \log P < 6.45$)	PCA, drug classification	MLC, MEKC, IMC, HPLC	[349]
Non steroidal anti-inflammatory drugs	Retention data	Biological activity, pharmacokinetic parameters	MLC, RP-HPLC, Brij35	[350]
Amphoteric sulfonamides (10)	$\log P$	$\log k$	MLC, SDS	[351]
Aromatic compounds (60) and corticosteroids (9)	$\log P$, LSER descriptors	$\log k'$	MEKC, SDS, SC, LiPFOS, C14TAB	[352]
β-Blocking agents (16)	$\log P$	$\log k$	MLC, SDS, *n*-propanol (organic modifier)	[353]
Phenoxy acid herbicides	Migration parameters	Toxicity	MLC, MEKC, Brij35	[354]
Antihistamine drugs	Hydrophobic, electronic and steric, k in BMC	Pharmacokinetic parameters	BMC, Brij35	[355]
Organic pollutants (66)	$\log k$, Structural parameters	Ecotoxicity parameters, $\log P$, PCA	BMC, cross-validation, calibration set	[356]
Neutral aromatic compounds, β-blockers, and other drugs	$\log P$, LSER descriptors	$\log k$, K_{lw}	LEKC, CE, liposomes are in a buffer solution (pseudostationary phase)	[357]
Basic pharmaceutical substances	pK_a, $\log D$	Fast $\log P$, PCA	MLC, monolithic silica	[358]
Non steroidal anti-inflammatory drugs	$\log P$, IC50 (concentration required to 50% inhibition), $t_{1/2}$ (half-life time)	V_d (volume of distribution), CL (clearance), $\log k$	MLC, Brij 35	[359]
Pesticides (85)	$\log k$	Acute toxicity pLC50	BMC	[360]
Pesticides (85)	$\log k$, $\log P$	BCF, $\log k$	BMC	[361]
β-Blockers (10), tricyclic antidepressants (7), steroids, sulfonamides (10)	$\log P$, $\log P_{apparent}$	$\log k$	RPLC acetonitrile, MLC	[362]

Table 5 (*Continued*)

Solutes	Descriptors	Models	Column, mobile phase, surfactant	Source
Structurally unrelated solutes (151)	log *P*, molecular size, hydrogen bonding properties, ionization degrees	log *k*, MLR	BMC, Brij35	[363]
Benzene derivatives, heterocyclic compounds	Molecular surface area, maximum value of electron density, path four connectivity index, M_w, sum of atomic polarizability	log *k*, MLR, ANN	MEKC, training set	[364]
Substituted benzenes	LSER, hydrophobic, H-bond, polar interactions	log K_{mw} (0.979) MLR	MEKC	[365]
Heterogeneous pesticides (79)	LSER descriptors	log *k*, MLR, SVM (0.9755)	BMC	[366]

ANN: artificial neural network; α: polarizability; α': molar total charge of compound at a given pH value; BMC: biopartitioning micellar chromatography; C14TAB: cationic surfactant; CA: cluster analysis; CART: classification and regression tree; CE capillary electrophoresis; CHI: chromatographic hydrophobicity index; CoMFA: comparative molecular field analysis; δ: electron excess charge of the most negatively charged atom; δ': molar fraction of the charged form of the compound; δT: total solubility parameter; EA: electron affinity; Etot: total energy; ε: permittivity; FA: factor analysis; φ: volume fraction of mobile phase; GA: genetic algorithm; GRNN: generalized regression neural networks index of hydrophobicity $\varphi_0 = -\log k_w/S$; IPC: ion pair chromatography; k, k': retention coefficient, (capacity factor); K_{mw}: micelle–water partition coefficient; K_{lw}: liposome–water partition coefficients; LiPFOS: lithium perfluorooctane sulfonate; LEKC: liposome electrokinetic chromatography; $\log k_w$: intercept of the plot for $\log k'$ vs. φ (extrapolated to mobile phase without water); log *P*, $\log k_{o/w}$: octanol/water partition coefficient; MLC: micellar liquid chromatography; MECC: micellar electrokinetic capillary chromatography; MEKC: micellar electrokinetic chromatography; MI: migration index, a general hydrophobicity scale; MLR: multiple linear regression; MLP: multilayer perceptron neural networks; MR: molar refraction; M_w: molecular mass; μ: dipole moment; NP: normal phase; ODS: octadecil silica; *p*: solute polarity parameter (Eq. (1)); PAH: polycyclic aromatic hydrocarbons; PC: principal components; PCA: principal component analysis; pK_a: dissociation constant; PLS: partial least squares; RP: reversed phase; RT: retention time; *S*: slope of the plot for $\log k'$ vs. volume fraction of mobile phase (φ); SC: sodium cholate; SDS: sodium dodecyl sulfate.

7.1. General tendencies

AC followed by chemometric data evaluation (searching QSRRs) provides information on both the solute molecules and the macromolecules forming the stationary phases. QSRR equations derived for selected solutes (often drugs) can be interpreted in terms of structural requirements of the specific binding sites on macromolecules. Multiple linear regression of affinity-chromatographic data increases the speed of search for new drugs. Specific high-performance affinity-chromatographic separations can be optimized by rational selection of chiral columns, the characteristics of which are provided by QSRR.

The main efforts concern to find lipohilicity measures from IAM chromatography, i.e. a lot of work is devoted to relate hydrophobicity parameters (log *P*) and retention date on AIM phases.

7.2. Misleading practice and suggestions for future works

Chemometric analysis is over and over again limited to linear regression, to search correlations. Although the way of giving correlation equations is appropriate, considerably more information could be extracted if multivariate methods were used.

Calculation of descriptors encoding of the molecular structure and cross-validation are rarely used. It is easy to foreseen that multivarate methods will be applied with proper validation in the near future.

7.3. Summary of papers on quantitative structure–retention relationship in affinity chromatography

Table 6 summarizes the solutes, methods and techniques for QSRR models in affinity chromatography.

Detailed reviews are available abundantly [370,374–376,383,384].

A good chromatographic model of skin permeability has been determined solely by a lipophilic property, log *k*, which was measured on an immobilized artificial membrane column [369].

Immobilized human serum albumin (HSA) could be used to estimate plasma protein binding [372].

The IAM-retention is governed by hydrophobicity factors for carboxylic compounds, followed by electronic effects due to polarizability in second place. Moreover, it can be concluded that the ratio of polarizability and hydrophobic effects is not the same toward IAM phases and biological membranes [381].

Negatively charged compounds bind more strongly to human serum albumin than it could be expected from the lipophilicity of the ionized species at certain pH values. Several compounds showed stronger HSA binding than it could be expected solely from their lipophilicity [382].

It is possible to classify potential drug molecules on the basis of QSRR analysis of retention data. Artificial neural network models utilize structural descriptors and predict pharmacological properties. Such a way it becomes possible to diminish the number of biological assays in the search for new drugs [385].

Table 6
QSRR examinations in affinity chromatography between 1996–August 2006

Solutes	Descriptors	Models	Column, protein	Source
Antihistamine drugs	$\log k$ (IAM), electron excess charge on thealiphatic N	$\log k$ (AGP)	α1-Acid glycoprotein (AGP), IAM	[367]
Acidic, basic and neutral drugs (56)	$\log k$ (IAM), $\log P$, ionization of acidic groups	Brain/blood concentration	Commercial IAM.PC.DD	[368]
Xenobiotics	M_w, μ, $\log P$, $\log k$ (IAM)	$\log k$ (keratin), $\log K_p$	IAM, physical immobilization of keratin on silica support	[369]
Test series of drug analytes	$\log P$, structural descriptors from molecular modeling	Drug-macromolecule binding	AGP, keratin, collagen, melanin	[370]
Test analytes (24)	$\log P$, LSER descriptors	$\log k$, $\log k_w$, MLR	Immobilized cholesterol on spherical silica gel, RP-HPLC, C18, IAM	[371]
Structurally unrelated drugs (40)	Percentage of binding	Retention	Immobilized human serum albumin (HSA)	[372]
Set of standards	LSER descriptors	$\log k$ (IAM), CHI, CHI(IAM)	Fast gradient, IAM	[373]
Drugs	$\log P$, $\log k$	$\log k$ (. . .)	HPLC, CE, biomacromolecules	[374]
Drugs, standards	QSRR descriptors	Retention	Macromolecules as SP	[375]
Appropriately designed sets	$\log k$ (AGP), $\log k_w$	$\log K_p$, $\log k$ (KER, COLL, MEL, etc.)	HAS, AGP, keratin, collagen, melanin, amylose Tris(3,5-dimethylphenylcarbamate) basic fatty acid binding protein	[376]
Series of analytes, new buspirones (65)		Diverse and mutually interrelated retention parameters, PCA	Carefully designed HPLC systems (9), 5-HT1A serotonin receptors	[377]
	$\log P$, molecular structural parameters	$\log k$	C18, C8, IAM, AGP, PBCA, PGC	[378]
Antihelmintic 6,7-diaryl-pteridine derivatives	$\log P$, $\log k$ (IAM)	$\log k$(IAM), IC50	ODS, IAM.PC.DD2	[379]
Arylpropionic acid derivatives (11)	$\log P$, $\log D$	$\log k_w$ (IAM), $\log k_w$ (ODS)	ODS, IAM.PC.MG	[380]
Structurally diverse drugs (32)	$\log P$, $\log D$, $\log P_{apparent}$	$\log k$ (IAM), MLR, PLS	Phospholipids, IAM	[381]
Drug molecules (68)	CHI (IAM), $\log P$, LSER	$\log K$ (HAS)	Fast gradient HPLC, HSA	[382]
Long fatty acids	$\log P$, total lipole	$\log k$	Immobilized liver basic FABP	[383]
			'Embedded' phases: aminopropylated silica gel, e.g. phospholipids and cholesterol, IAM's	[384]
Azapirone derivatives	Molecular structural	Retention parameters, BP–ANN	Rat brain serotonin 5-HT1A receptors, HPLC systems (14)	[385]

BP–ANN: back propagation artificial neural network; C18: bonded octadecil silica; C8: bonded octyl silica; CHI: chromatographic hydrophobicity index; φ: volume fraction of mobile phase; FABP: fatty acid binding protein; HSA: human serum albumin; index of hydrophobicity $\varphi_0 = -\log k_w/S$; IAM: immobilized artificial membrane; k, k': retention coefficient, (capacity factor); K_p: human skin permeation coefficient; $\log D$: $\log P$ for ionisable compounds; $\log k_w$: intercept of the plot for $\log k'$ vs. φ (extrapolated to mobile phase without water); $\log P$, $\log k_{o/w}$: octanol/water partition coefficient; LSER: linear solvation energy relationships; MLR: multiple linear regression; μ: dipole moment; NP: normal phase; ODS: octadecil silica, C18; PCA: principal component analysis; pK_a: dissociation constant; PBCA: polybutadiene-coated alumina; PGC: porous graphitic carbon; RP: reversed phase; S: slope of the plot for $\log k'$ vs. volume fraction of mobile phase (φ).

Table 7
Remaining QSRR examinations between 1996–August 2006

Solutes	Descriptors	Models	Column, method	Source
Series of sulfonamides		Electrophoretic mobility, MLR, BP–ANN	CZE, cross-validation	[386]
Beta-diketones (20)	Descriptors (6)	*I*, MLR, polynoms		[387]
Proteins	Descriptors, from protein structure	RT (0.969–0.952)	Ion exchange systems, cross and external validation	[388]
Probe molecules	Traditional and novel molecular property descriptors	GA, PLS	Ion-exchange chromatography (IEC)	[389]
Solutes (Ala, Gly, Lys, Phe, homopeptides, 19)	log *P* and specific hydrophobic surface area	PCA, NLM	TLC, impregnated alumina layers	[390]
o-Acetylphenyl esters	Topological	RT	Not given	[391]
1-Bromo-2-aryiloxyetanes and 3-aryloxypropiononitrile derivatives	Quantumchemical (5)	RT, polynoms	Not given	[392]
	Set of fragmental descriptors	I, T_b	GC	[393]
Proteins	Topological, subdivided surface area, TAE, electron-density-based descriptors	RT, SVM	Anion exchange chromatography, training and validation sets	[394]
Proteins	Molecular descriptors	RT, SVM (0.943–0.994) cross-validated	Anion exchange chromatography salt-in	[395]
Proteins		RT, SVM (0.919–0.980)	Cation-exchange systems, counterions	[396]
	Number of single bonds, of double bonds, hydrophilic factor	Retention factors, BP–ANN, MLR	SFC, cross-validation	[397]
Basic compounds (drugs)	Molecular interaction energies	Elution order	Ion-exchange chromatography	[398]
Proteins, human lactoferrin	New protein descriptors, ASP 1	RT	Ion-exchange chromatography	[399]
Set of model proteins	New hydrophobicity descriptors, S_w	RT, SVM	Hydrophobic interaction chromatography, four resins	[400]

ASP: average surface potential; BP–ANN: back propagation artificial neural network; CHI: chromatographic hydrophobicity index; CZE: capillary zone electrophoresis; FABP: fatty acid binding protein; GA: genetic algorithm; HSA: human serum albumin; *I*: Kovats retention index; IAM: immobilized artificial membrane; IEC: ion-exchange chromatography; LSER: linear solvation energy relationships; MLR: multiple linear regression; NLM: nonlinear mapping; ODS: octadecil silica, C18; PCA: principal component analysis; PLS: partial least squares; RT: retention time; SFC: supercritical fluid chromatography; SVM: support vector machines; S_w: solvent accessible surface area; TAE: transferable atom equivalent.

8. Remaining quantitative structure–(chromatographic) retention relationship studies

Mainly ion exchange systems are gathered under this heading. Other studies cannot be easily classified into the preceding groups: supercritical chromatography, fragmental approach, etc. Therefore, general tendencies, etc. have no relevance here. In ion exchange chromatography protein retention data are predicted in several cases with advanced chemometric methods e.g. with support vector machines. Whether simpler tools would do—remains unknown.

Table 7 summarizes the solutes, methods and techniques for QSRR studies, which cannot easily be categorized in the former groups.

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