



Quantitative structure-(chromatographic) retention relationship models for dissociating compounds



Łukasz Kubik, Paweł Wiczling*

Department of Biopharmaceutics and Pharmacodynamics, Medical University of Gdańsk, Gen. J. Hallera 107, 80-416 Gdańsk, Poland

ARTICLE INFO

Article history:

Received 30 November 2015
Received in revised form 19 January 2016
Accepted 28 February 2016
Available online 2 March 2016

Keywords:

QSRR
RP HPLC
Dissociation
Hydrophobicity
Acidity

ABSTRACT

The aim of this work was to develop mathematical models relating the hydrophobicity and dissociation constant of an analyte with its structure, which would be useful in predicting analyte retention times in reversed-phase liquid chromatography. For that purpose a large and diverse group of 115 drugs was used to build three QSRR models combining retention-related parameters ($\log k_w$ —chromatographic measure of hydrophobicity, S —slope factor from Snyder-Soczewinski equation, and pK_a) with structural descriptors calculated by means of molecular modeling for both dissociated and nondissociated forms of analytes. Lasso, Stepwise and PLS regressions were used to build statistical models. Moreover a simple QSRR equations based on lipophilicity and dissociation constant parameters calculated in the ACD/Labs software were proposed and compared with quantum chemistry-based QSRR equations. The obtained relationships were further used to predict chromatographic retention times. The predictive performances of the obtained models were assessed using 10-fold cross-validation and external validation. The QSRR equations developed were simple and were characterized by satisfactory predictive performance. Application of quantum chemistry-based and ACD-based descriptors leads to similar accuracy of retention times' prediction.

© 2016 Elsevier B.V. All rights reserved.

1. Introduction

The relationship between molecular structure of chemical compounds and their chromatographic retention has been of great interest since the beginnings of chromatography. The first publication on the quantitative relationship between molecular structure and retention (QSRR) authored by R. Kaliszan appeared in 1977 [1–4]. Since that time, this research topic has been constantly developed [5,6].

So far, a number of structural parameters has been established to explain analyte retention in reversed-phase high performance liquid chromatography (RP HPLC) technique, e.g. number of carbon atoms in the molecule, molar mass, the total potential energy, dissociation constant, lipophilicity or partition coefficient [7]. When QSRR models are derived, the classical thermodynamic (physical) approach is used less often, in favor of approximate but realistically achievable extra-thermodynamic approach [8]. To date, the process of dissociation virtually has not been taken into account in QSRR research, except several reports [9]. However, most of the currently used drugs belong to a group of compounds which dissociate under

physiological conditions [10]. It is therefore important to develop mathematical models which would reliably describe the retention of the particular forms of analyte present in different pH of the mobile phase based on their chemical structure. Such models when combined with preliminary experiments might greatly improve the accuracy of retention time predictions and consequently facilitate the process of method development as recently shown in the literature [11].

In this work a quantum chemistry-based and simple, ACD-based, descriptors were calculated for a large set of 115 compounds (neutral and ionic forms). For both approaches QSRR equations were developed, allowing for the calculation of $\log k_w$, S , pK_a parameters followed by retention times' prediction. For this purpose, three different regression techniques (Lasso, combined Lasso/Stepwise and PLS) were applied. The purpose of this work was to calculate, evaluate and compare QSRR equations obtained by different approaches and methodologies.

2. Theory/calculation

2.1. Chromatographic related parameters

The gradient reversed-phase high performance liquid chromatography coupled with time-of-flight mass spectrometry allows

* Corresponding author.

E-mail address: wiczling@gumed.edu.pl (P. Wiczling).

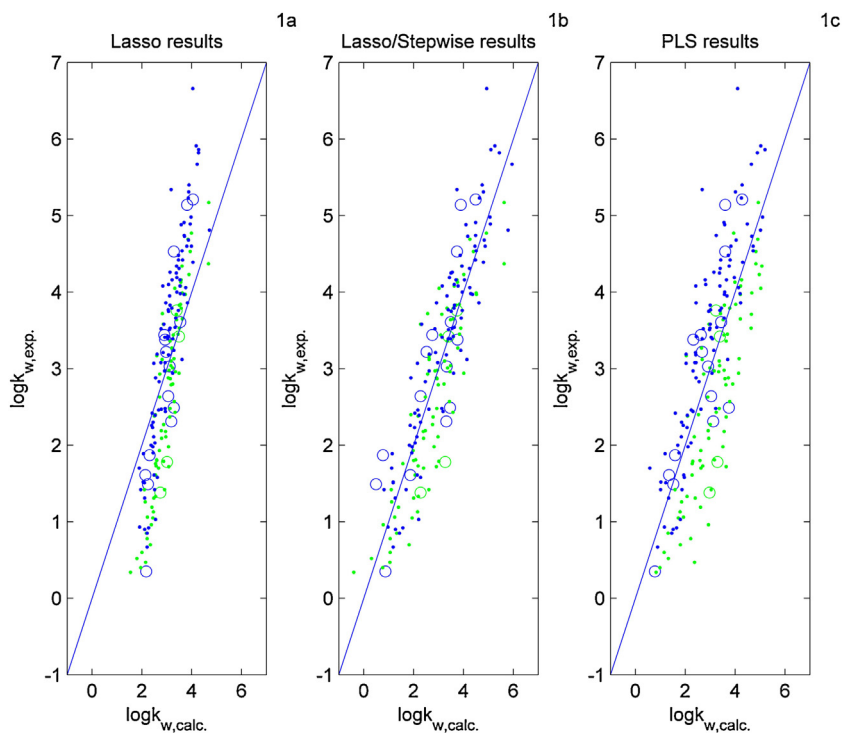


Fig. 1. Correlation plots relating the calculated ($\log k_{w,calc.}$) and experimental values ($\log k_{w,exp.}$) of $\log k_w$. Dots indicate the training set and circles indicate the test set compounds. Blue color indicates neutral and green color indicates ionic forms. The line of identity is shown in each subplot. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

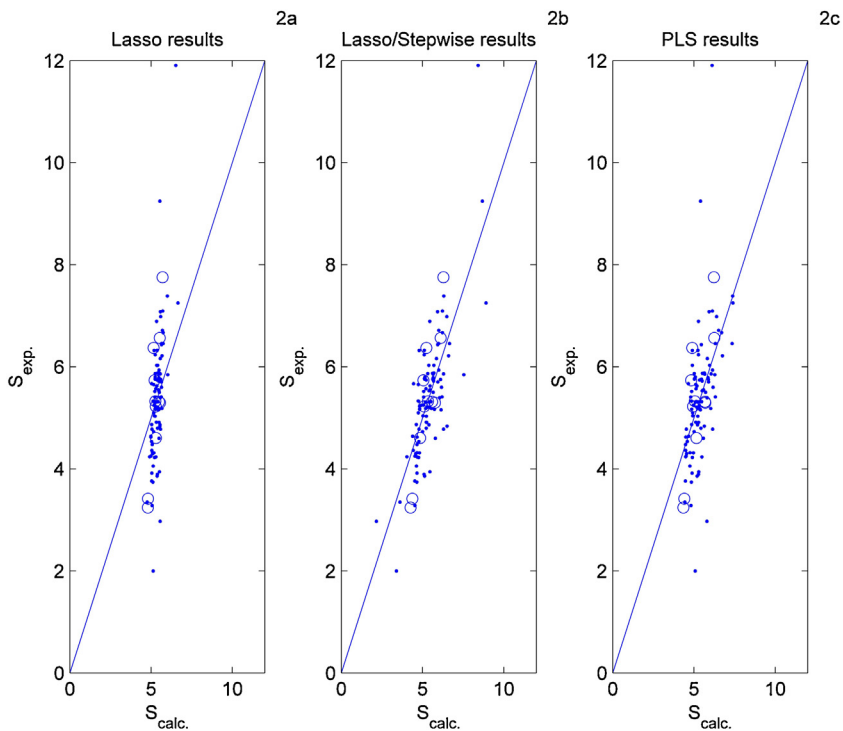


Fig. 2. Correlation plots relating the calculated ($S_{calc.}$) and experimental values ($S_{exp.}$) of slope parameter in Snyder-Soczewiński equation. Dots indicate the training set and circles indicate the test set compounds. The line of identity is shown in each subplot.

Download English Version:

<https://daneshyari.com/en/article/1220926>

Download Persian Version:

<https://daneshyari.com/article/1220926>

[Daneshyari.com](https://daneshyari.com)