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Quantitative structure–retention relationships applied to development of liquid chromatography gradient-elution method for the separation of sartans

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ABSTRACT

QSRR are mathematically derived relationships between the chromatographic parameters determined for a representative series of analytes in given separation systems and the molecular descriptors accounting for the structural differences among the investigated analytes. Artificial neural network is a technique of data analysis, which sets out to emulate the human brain's way of working. The aim of the present work was to optimize separation of six angiotensin receptor antagonists, so-called sartans: losartan, valsartan, irbesartan, telmisartan, candesartan cilexetil and eprosartan in a gradient-elution HPLC method. For this purpose, ANN as a mathematical tool was used for establishing a QSRR model based on molecular descriptors of sartans and varied instrumental conditions. The optimized model can be further used for prediction of an external congener of sartans and analysis of the influence of the analyte structure, represented through molecular descriptors, on retention behaviour. Molecular descriptors included in modelling were electrostatic, geometrical and quantum-chemical descriptors: connolly solvent excluded volume non-1,4 van der Waals energy, octanol/water distribution coefficient, polarizability, number of proton-donor sites and number of proton-acceptor sites. Varied instrumental conditions were gradient time, buffer pH and buffer molarity. High prediction ability of the optimized network enabled complete separation of the analytes within the run time of 15.5 min under following conditions: gradient time of 12.5 min, buffer pH of 3.95 and buffer molarity of 25 mM. Applied methodology showed the potential to predict retention behaviour of an external analyte with the properties within the training space. Connolly solvent excluded volume, polarizability and number of proton-acceptor sites appeared to be most influential paramateres on retention behaviour of the sartans.

1. Introduction

Idea of predicting chromatographic behaviour from molecular structure of solutes resulted in concept of quantitative structure–retention relationships (QSRR) methodology. QSRR are mathematically derived relationships between the chromatographic parameters determined for a representative series of analytes in the given separation systems and the molecular descriptors accounting for the structural differences among the investigated analytes. Such relationships include an algorithm that connects molecular descriptors and retention parameters and may provide insight into the molecular mechanism of separation in a given chromatographic system, generate knowledge about the various interactions taking place between the solute and the stationary phase, evaluate physicochemical properties of analytes, identify the most informative structural descriptors and predict retention for a new analyte [1].

Couple of QSRR concepts can be found in literature. The oldest type of QSRR correlated retention factors with the logarithms of *n*-octanol–water partition coefficients (log *P*) [2]. The second type of QSRR is based on the so-called linear solvation energy relationships (LSERs) [3–5]. The third and most applied type of QSRR employs large number of descriptors (quantities that characterize the molecular structure of the analytes [6–9]. Miller et al. [8] pointed out some drawbacks of LSER modelling, in favour of third QSRR approach.

QSRRs are most commonly derived by multiple linear regression (MLR) analysis [10]. MLR is successful in QSRR modelling for prediction of gradient-elution retention behaviour if only molecular descriptors are included in the model [11,12]. But, the commonly used MLR will probably fail to develop an appropriate QSPR model when the nonlinear phenomenon is significant to some extent within the data investigated; which is the case with QSRR combining molecular descriptors and instrumental conditions.

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Therefore nonlinear modelling techniques such as artificial neural networks (ANN) are necessary in order to build an accurate and reliable QSRR model. An artificial neural network is a technique of data analysis, which sets out to emulate the human brain's way of working. [13]. A detailed description of the theory behind a neural network has been adequately described elsewhere [14–16].

ANN were applied as a mathematical tool for prediction of gradient-elution HPLC behaviour of different types of analytes based on their physical-chemical properties transferred to molecular descriptors [1,8–13,17]. Yet, this methodology can not be used for retention prediction under different gradient conditions. D'Archivio et al. developed QSRR model which combined structure of the analytes, through molecular descriptors, and gradient conditions but only for prediction of retention factors without separation [6–7]. There are couple of papers that applied ANN in order to optimize separation in a gradient-elution HPLC method but without employing analyte properties [18–20]. Lack of information about structures could possibly be the reasons for complete separation failure in the paper published by Webb et al. [18]. But, retention of a new congener can not be predicted by means of this approach. Further, no information about relationships between molecular properties and retention behaviour can be obtained.

The aim of the present work was to optimize separation of six angiotensin receptor antagonists, so-called sartans (Fig. 1) in a gradient-elution HPLC method by QSRR-ANN model. For this purpose, ANN as a mathematical tool was used for establishing a QSRR model based on molecular descriptors of sartans and varied instrumental conditions. The optimized model can be further used for prediction of an external congener of sartans and analysis of the influence of the analyte structure, represented through molecular descriptors, on retention behaviour. As far as we know, limited number of papers concerning application of QSRR-ANN model in gradient-elution mode were published [6,7] and none of them investigated separation of the analytes.

Couple of papers that dealt with separation of sartans (up to five) were found in literature. Run times of the optimized methods were 18–25 min [21–26]. Yet, separation of six sartans for less than 18 min has never been achieved so far and would be quit challengeable. Above explained methodology can be used for this purpose. The developed method can be applied for complex mixtures analysis and as a good starting point for bioanalytical method development.

2. Experimental

2.1. Solvents, chemicals and instrumentation

Reference substances of telmisartan (TEL) and candesartan cilexetil (CAN) were purchased from *Sigma Aldrich Chemie GmbH*, Taufkirchen, Germany. Eprosartan mesylate reference substance (EPR) was kindly donated by *Solvay*, Brussels, Belgium, while the reference substance of valsartan (VAL) was obtained from *Pharmanova*, Belgrade, Serbia. Irbesartan (IRB) reference substance was kindly donated by *Krka*, Novo mesto, Slovenia. Finally, reference substance of losartan (LOS) was kindly donated by *Alkaloid*, Skopje, Macedonia. HPLC grade acetonitrile was purchased from J.T.Baker, Deventer, USA. Purified water, obtained from a *Simplicity 185* purification system, *Millipore* (Billerica, MA, USA) was used for preparation of the sample solutions and mobile phase. Ammonium acetate, acetic acid, ammonium format, formic acid and ammonium hydroxide used for preparing buffers were purchased from *Sigma Aldrich Chemie GmbH*, Taufkirchen, Germany. pH of buffer

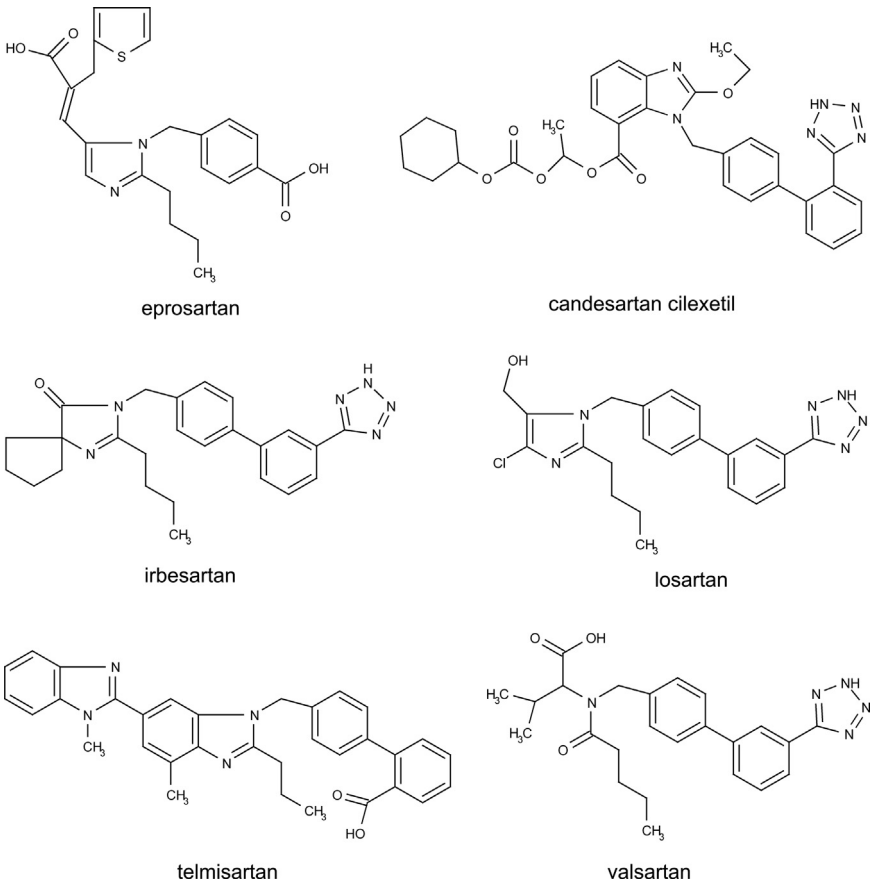

Fig. 1. Structural formulas of the investigated sartans.