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Quantitative structure retention relationship modeling in liquid chromatography method for separation of candesartan cilexetil and its degradation products

Jelena B. Golubović, Ana D. Protić [1], Mira L. Zečević, Biljana M. Otašević

University of Belgrade-Faculty of Pharmacy Department of Drug Analysis, Vojvode Stepe 450 11 152 Belgrade , Serbia

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ABSTRACT

Artificial neural network (ANN) is a learning system based on a computation technique, which was employed for building of the quantitative structure-retention relationship (QSRR) model for candesartan cilexetil and its degradation products. Candesartan cilexetil has been exposed to forced degradation conditions and degradation products have been subsequently identified with the assistance of HPLC-MS technique. Molecular descriptors have been computed for all compounds and were optimized together with significant chromatographic parameters employing developed QSRR models. In this way, QSRR has been used in development of HPLC stability-indicating method, optimal conditions toward various outputs have been established and high prediction potential of the created QSRR models has been proved.

1. Introduction

Candesartan cilexetil (Fig. 1a) belongs to the class of angiotensin receptor antagonists and acts by binding selectively and non-competitively to angiotensin II receptor type 1, thus preventing actions of angiotensin II. The drug finds most significant clinical use in the treatment of hypertension of all grades. Chemically, candesartan cilexetil is an ester pro-drug of its active metabolite candesartan, to which it owes its therapeutic effect [1].

Quantitative structure–retention relationships (QSRRs) represent a powerful technique for relating the chromatographic retention parameters of groups of analytes to their descriptors, which are quantities encoding the structural characteristics [2,3]. In that way, QSRR can significantly contribute in prediction of chromatographic behavior and separation of complex mixtures for many compound classes and further in clarifying molecular mechanism of chromatographic retention [4,5]. QSRR models have been used only few times in predicting retention behavior and separation of active pharmaceutical substance and its process-related impurities [6,7]. To the best of our knowledge, no paper applying QSRR model based on artificial neural networks for separation of an active pharmaceutical substance and its degradation products arising during stability studies was published.

The QSRR model has been built employing an artificial neural network (ANN). An important advantage of ANN compared with classical statistical methods is that it does not require preliminary knowledge of the mathematical relationship between the variables. Also, ANNs work best if they are dealing with non-linear dependence between the inputs and outputs [8–11]. ANN has been chosen as it shows better results in retention prediction than other techniques such as multilinear regression (MLR) [12–14].

ANN topologies or architecture were formed by organizing nodes into layers and linking these layers of neurons with modifiable weighted interconnections [14]. Among the different kinds of ANNs, multi-layer feed-forward network is most often used in the structure–property relationship analysis. A network should be applicable on the cases-ability of generalization. At some moment, generalization ability progressively deteriorates as a consequence of overfitting. To avoid this, the predictive power of the network is evaluated after each weight adjustment on unknown data (validation set). The minimum of the validation error is taken as a suitable criterion to define the optimal duration of learning for a given network, or to select among alternative trained networks the one with the expected best predictive capability. After optimization, the actual predictive performance of the trained network was evaluated using an external validation data set [4].

Several previous papers were dealing with stability of candesartan cilexetil. Candesartan cilexetil was found to undergo basic hydrolysis in plasma to candesartan (Fig. 1b) [15]. Subba Rao et al. [16] conducted forced degradation studies, whereby obtaining three degradation products: DPI, DPII, and DPV (Fig. 1b, c, f). Yet drug substance was overstressed under acidic and basic hydrolysis, while understressed under other stress conditions. Mohan et al. performed accelerated and

E-mail address: anna@pharmacy.bg.ac.rs (A.D. Protić).
[1] Tel.: +38 1642233834; fax:+38 1113972840.

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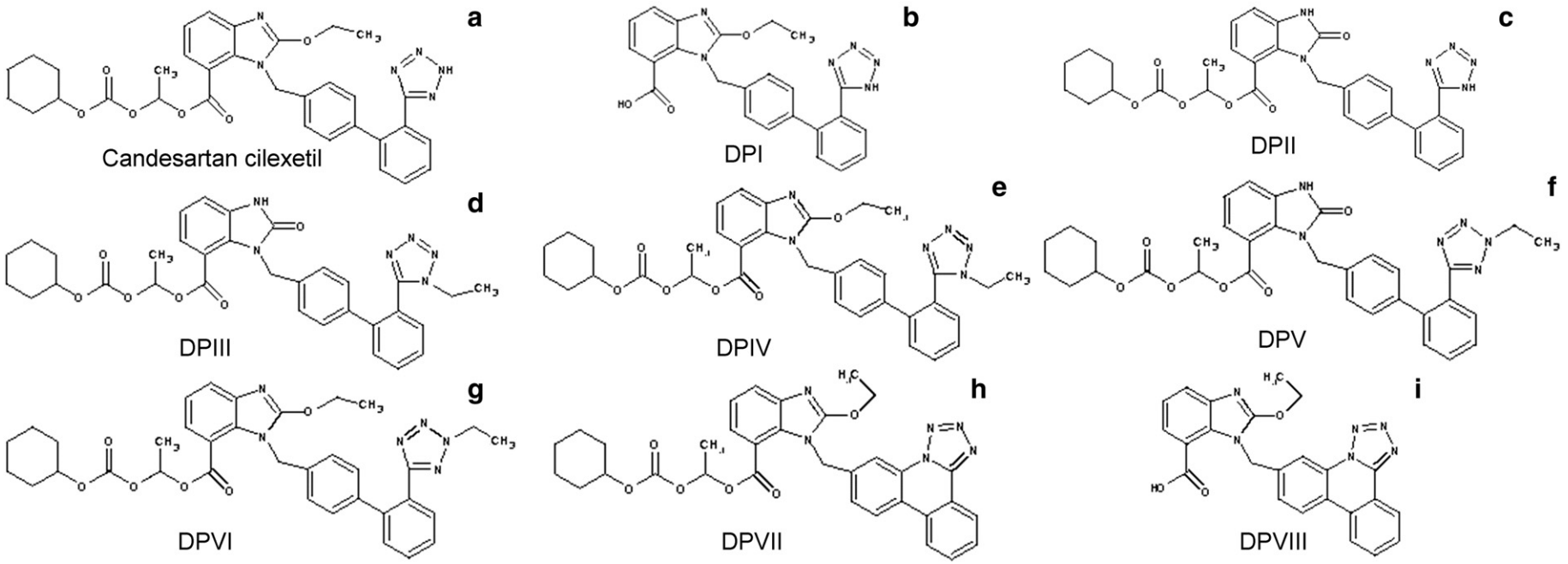

Fig. 1. Structures of candesartan cilexetil (a) and its degradation products, DPI-DPVIII (b–i).