Available online at www.sciencedirect.com
ScienceDirect
European Journal of Medicinal Chemistry 43 (2008) 548–556
EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY
http://www.elsevier.com/locate/ejmech

Original article

QSAR study of heparanase inhibitors activity using artificial neural networks and Levenberg–Marquardt algorithm

M. Jalali-Heravi*, M. Asadollahi-Baboli, P. Shahbazikhah

Department of Chemistry, Sharif University of Technology, Azadi Avenue, P.O. Box 11365-9516, Tehran, Iran

Received 3 December 2006; received in revised form 14 March 2007; accepted 16 April 2007
Available online 18 May 2007

Abstract

A linear and non-linear quantitative structure–activity relationship (QSAR) study is presented for modeling and predicting heparanase inhibitors' activity. A data set that consisted of 92 derivatives of 2,3-dihydro-1,3-dioxo-1*H*-isoindole-5-carboxylic acid, furanyl-1,3-thiazol-2-yl and benzoxazol-5-yl acetic acids is used in this study. Among a large number of descriptors, four parameters classified as physico-chemical, topological and electronic indices are chosen using stepwise multiple regression technique. The artificial neural networks (ANNs) model shows superiority over the multiple linear regressions (MLR) by accounting 87.9% of the variances of antiviral potency of the heparanase inhibitors. This paper focuses on investigating the role of weight update functions in developing ANNs. Levenberg–Marquardt (L–M) algorithm shows a better performance compared with basic back propagation (BBP) and conjugate gradient (CG) algorithms. The accuracy of 4-3-1 L–M ANN model was illustrated using leave-one-out (LOO), leave-multiple-out (LMO) cross-validations and *Y*-randomization. The mean effect of descriptors and sensitivity analysis show that log *P* is the most important parameter affecting the inhibitory behavior of the molecules.
© 2007 Elsevier Masson SAS. All rights reserved.

Keywords: Quantitative structure–activity relationship; Artificial neural network; Heparanase; Inhibitors; Weight update function

1. Introduction

Heparan sulfate proteoglycans (HSPGs) play a key role in the self-assembly, insolubility and barrier properties of basement membranes and extracellular matrices [1]. The basic HSPG structure consists of a protein core to which several linear heparan sulfate (HS) chains are covalently O-linked. Hence, cleavage HS affects the integrity and functional state of tissues and thereby fundamental normal and pathological phenomena involving cell migration and response to changes in the extracellular microenvironment [2–4]. Heparanase enzyme cleaves heparan sulfate so heparanase may facilitate both tumor cell invasion and neovascularization in critical steps in cancer progression [1]. In addition, expression of heparanase has long been correlated with the metastatic potential of tumor cell [1,5–8]. In fact, treatment with heparanase inhibitors markedly reduces tumor growth, metastasis and autoimmune disorder in animal models [9]. Although these data indicate the importance of heparanase as a drug target, progress in this area has been limited by lack of small molecules acting as inhibitors. Parish et al. have developed phosphomannopentaose sulfate (PI-88) which is currently in phase 2 clinical trials [9]. However, it is shown that heparanase inhibition mode of action is complicated because of its large structure [10]. Therefore, the challenging problem is to find small, drug-like molecules with acceptable dystrophia myotonica-protein kinase (DMPK) properties for evaluation in animal models and to use them as therapeutic leads [11].

A systematic study of the various substituents on the activity of the analogues helps one to rationalize the finding and design compounds with enhanced activity. In addition, the growth of computational techniques has accelerated the drug design process. Many databases of inhibitors exist that are yet to be evaluated against heparanase. This demand enforces

* Corresponding author. Tel.: +98 21 66165315; fax: +98 21 66012983.
E-mail address: jalali@sharif.edu (M. Jalali-Heravi).

0223-5234/$ - see front matter © 2007 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmech.2007.04.014

us to develop more effective and reliable strategies for the 'virtual screening' of candidate inhibitors. Quantitative structure–activity relationship (QSAR) has been demonstrated as a capable tool for the investigation of bioactivity of various classes of compounds. Fernandez and Caballero have developed a non-linear model to predict HIV-1 protease inhibition of 55 cyclic urea derivatives [12]. These researchers have also presented linear and non-linear models for acetamide derivatives as matrix metalloproteinase inhibitors [13]. Doble and co-workers have developed a QSAR model to predict IC_{50} for paeonol analogues as inhibitors of platelet aggregation [14]. A large number of QSAR studies have been successfully applied to model activities of various kinds of agents [14–19]. Recently different derivatives of three series of molecules have been reported as heparanase inhibitors [10,11]. These are the derivatives of 2,3-dihydro-1,3-dioxo-1*H*-isoindole-5-carboxylic acid, furanyl-1,3-thiazol-2-yl and benzoxazol-5-yl acetic acids. In the present contribution, a quantitative structure–activity relationship (QSAR) study was carried out on these compounds. To the best of our knowledge, this is the first QSAR study using ANN for the prediction of pIC_{50} heparanase inhibitors. In developing ANN models, we have chosen different weight update functions and examined their influences on the reliability of the model. It is shown in this work that the weight update functions play an important role in reliability of the models using ANN. Therefore, selecting a suitable weight update function is essential for developing a good model.

2. Theory

2.1. Artificial neural network

An artificial neural network (ANN) with a layered structure is a mathematical system that stimulates biological neural network, consisting of computing units named neurons and connections between neurons named synapses [20–22]. Input or independent variables are considered as neurons of input layer, while dependent or output variables are considered as output neurons. Synapses connect input neurons to hidden neurons and hidden neurons to output neurons. The strength of the synapse from neuron i to neuron j is determined by means of a weight, W_{ij}. In addition, each neuron j from the hidden layer, and eventually the output neuron, are associated with a real value b_j, named the neuron's bias and with a non-linear function, named the transfer or activation function.

Because artificial neural networks (ANNs) are not restricted to linear correlations, they can be used for non-linear phenomena or curved manifold [20]. As biological phenomena may have non-linear characteristics, ANN techniques are required to discover the possible relationship between the input descriptors and output bioactivity, IC_{50}. Back propagation neural networks (BNNs) are most often used in analytical applications [21]. The back propagation network receives a set of inputs, which is multiplied by each node and then a non-linear transfer function is applied. The goal of training the network is to change the weights between the layers in a direction to minimize the output errors. The changes in the values of the weights can be obtained using Eq. (1):

$$\Delta W_{ij,n} = F_n + \alpha \Delta W_{ij,n-1} \tag{1}$$

where ΔW_{ij} is the change in the weight factor for each network node, α is the momentum factor, and F is a weight update function, which indicates how weights are changed during the learning process. There is no single best weight update function which can be applied for all non-linear optimizations. One needs to choose a weight update function based on the characteristics of the problem and the data set of interest. Various types of algorithms have been found to be effective for most practical purposes. However, three different weight update functions of basic back propagation algorithm (BBP), conjugate gradient algorithm (CG) and Levenberg–Marquardt (L–M) algorithm are the common ones which are discussed below.

2.1.1. Basic back propagation algorithm

The basic back propagation training algorithm, in which the weights are moved in the direction of the negative gradient to minimize an objective function (error function) is called gradient decent algorithm [23]. The most popular error function is the *sum of squares* that is given by Eq. (2) [24]:

$$E = \frac{1}{2}\sum_{p=1}^{P}\sum_{j}^{J}\left(t_{pj} - o_{pj}\right)^2 \tag{2}$$

where t_{pj} is the target value (desired output) and o_{pj} is the actual output.

In basic back propagation training algorithm the function F_n in Eq. (1) is defined by Eqs. (3) and (4) [25]:

$$g_n = \eta \frac{\partial E_n}{W_{ij,n}} \tag{3}$$

$$F_n = -g_n \tag{4}$$

where w_{ij} are the weights connected between neurons i and j, and η is learning rate.

2.1.2. Conjugate gradient algorithms

These techniques not only focus on the local gradient of the error function, but also make use of its second derivative. The first derivative measures the slope of the error surface at a point, while the second one measures the curvature of the error surface at the same point. This information is very important for determining the optimal update direction [25]. As these methods make use of the second derivatives of the function to be optimized, they are typically referred to as second-order methods. In particular, the conjugate gradient method is commonly used in training BP networks due to its speed and simplicity [26,27]. Over the years, a large number of conjugate gradient functions have been proposed [28]. One of these is

Download English Version:

https://daneshyari.com/en/article/1398157

Download Persian Version:

https://daneshyari.com/article/1398157

Daneshyari.com