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New Theoretical Model for the Study of New β-Secretase Inhibitors

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Abstract: Alzheimer's disease (AD) is the most prevalent form of dementia, and current indications show that twenty-nine million people live with AD worldwide, a figure expected rise exponentially over the coming decades. AD is characterize with several pathologies this disease, amyloid plaques, composed of the β-amyloid peptide and γ-amyloid peptide are hallmark neuropathological lesions in Alzheimer's disease brain. Indeed, a wealth of evidence suggests that β-amyloid is central to the pathophysiology of AD and is likely to play an early role in this intractable neurodegenerative disorder. For this reason, we developed a new QSAR (QSAR) model to discover new drugs. A public database ChEMBL contain Big Data sets of inhibitors of *β*-secretase. We revised QSAR studies using method of Artificial Neural Network (ANN) in order to understand the essential structural requirement for binding with receptor for *β*-secretase inhibitors.

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Keywords: QSAR; *β*-secretase inhibitors; Alzheimer's disease (AD).

1. Introduction

Alzheimer´s disease (AD) (1) is a serious and degenerative disorder that causes a the gradual loss of neurons, and in spite of the efforts realized by the big pharmaceutical companies of the world, the origen of this pathology is still not very clear. We can see in this paper that the development of theoretical and QSAR models to study γ-secretase inhibitors are usually not many

achieved so far, and most of these works present docking studies. Watching this situation we need to develop QSAR models with γ-secretase inhibitors. In this sense, quantitative structure-activity relationships (QSAR) could play an important role in studying these γ-secretase inhibitors; QSARs can be used as predictive tools for the development of molecules (2, 3). Computer-aided drug design techniques based on Quantitative Structure-Activity Relationships (QSAR) could play an important role in drug discovery programs. The QSAR approach involves the development of models that relate the structure of drugs with their biological activity against different targets (4, 5). In principle, there are currently more than 1600 molecular descriptors that may be generalized and used to solve the problem outlined above (6). Numerous different molecular descriptors have been reported to encode chemical structures in QSAR studies. Furthermore, there are multiple chemometric approaches that can, in principle, be selected for this step. Multiple linear regression (MLR), linear discriminant analysis (LDA) (7), partial least squares (PLS) and different kinds of artificial neural networks (ANN) can be used to relate molecular structure (represented by molecular descriptors) with biological properties. The ANNs are particularly useful in QSAR studies in which the linear models fit poorly due to high data complexity [17; 18;], an example was the work of Prado-Prado *et. al*. In which four types of artificial neural networks (ANN) were developing for γ-secretase inhibitors, ANNs was constructing from more than 15 000 cases with more than 1 500 different molecules inhibitors of γ-secretase obtained from ChEMBL database http://www.ebi.ac.uk/ChEMBLdb/index.php. We used spectral moments molecular descriptors calculated with Modeslab software (8).

2. METHOD

2.1. Data set

The data set used in this article was obtained from ChEMBL database. It has more than 30 000 cases and more than 1 500 different compounds inhibitors of γ-secretase. In total we used more than 10 000 different molecules to develop the QSAR models obtained in ChEMBL. This is a database of bioactive drug-like small molecules, it contains 2D structures, calculated properties (e.g. logP, Molecular Weight, Lipinski Parameters, etc.) and abstracted bioactivities (e.g. binding constants, pharmacology and ADMET data). ChEMBL normalises the bioactivities into a uniform set of end-points and units where possible, and also tags the links between a molecular target and a published assay with a set of varying confidence levels. The data is abstracted and curated from the primary scientific literature, and covers a significant fraction of the SAR and discovery of modern drugs..

1.2.ANN models

The ANN models are non-linear models useful to predict the biological activity of a large datasets of molecules. This technique is an alternative to linear methods such as LDA. **Figure 1** depicts the networks maps for some of the ANN models. In general, at least one ANN of every types tested was statically significant. However, one must note that the profiles of each network indicate that these are highly nonlinear and complicated models.

There are several different kinds of ANN and these include multilayer perceptron (MLP), radial basis functions (RBF) and PNNs; the latter ANN is a variant of RBF systems. In particular, PNN is a type of neural network that uses a

kernel-based approximation to form an estimate of the probability density functions of classes in a classification problem (9).

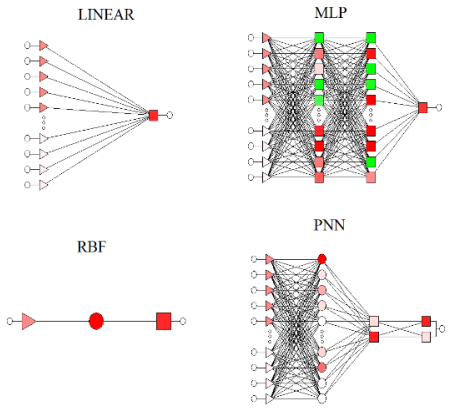

Figure 1. Topology of some ANN models trained in this work.

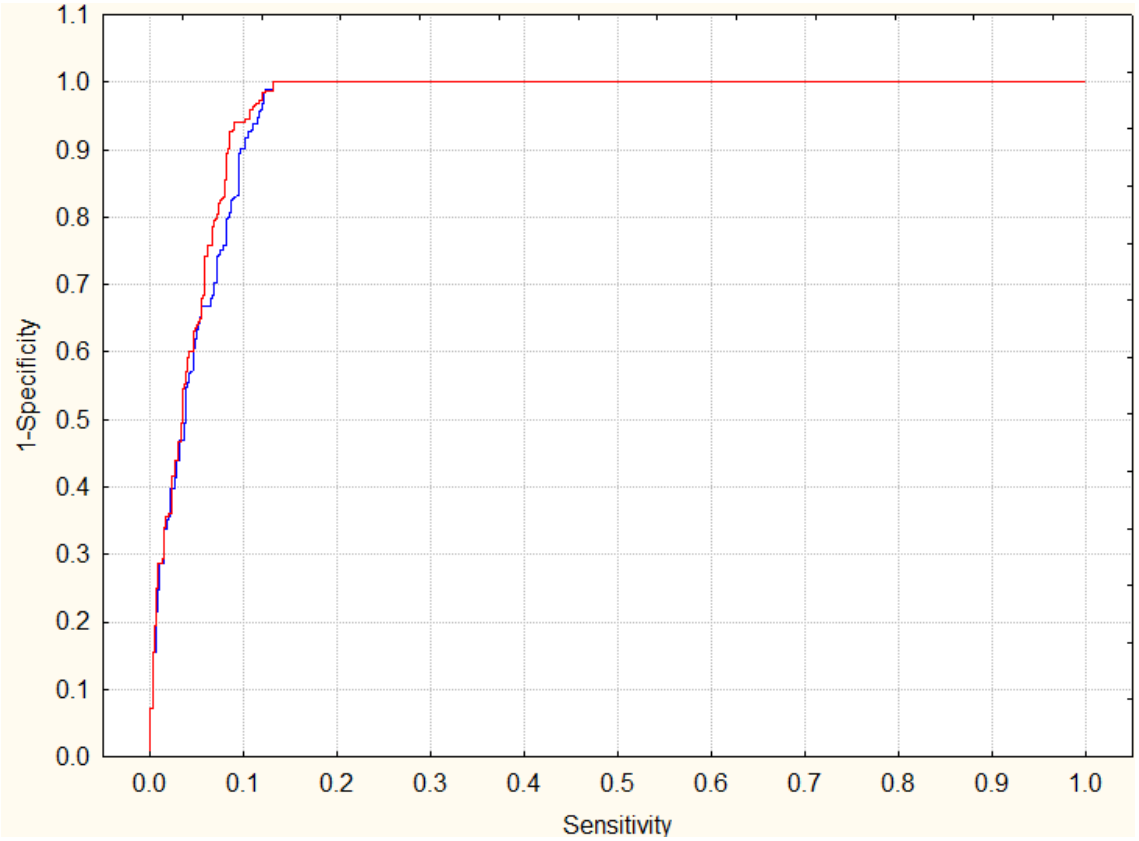

Figure 2. ROC Curve for classifier.

Model profile	Train			Stat. Par.	Validation		
	active	Non-active	%		active	Non-active	%
LNN	983	129	88.40	Sn	475	81	85.43
14:14-1:1	2943	22415	88.39	Sp	1545	11187	87.87
			88.39	Ac			87.76

PNN	0	1112	0	Sn	0	556	0
14:14-26470-2-2:1	0	25358	100	Sp	0	12732	100
			95.80	Ac			95.82
MLP	781	331	70.23	Sn	396	160	71.22
15:15-9-1:1	7610	17748	69.99	Sp	3879	8853	69.53
			70.00	Ac			69.60
RBF	482	74	86.69	Sn	964	148	86.69
15:15-691-1:1	0	12697	100	Sp	0	25393	100
			99.44	Ac			99.44

Table 1. Comparison of different ANNs classification models.

3. RESULTS AND DISCUSSION

The network found was RBF and it showed training performance higher than 99%. We compare different types of networks to obtain a better model; **Table 1** shows the classification matrix of the different networks. 15:15-691-1:1 was taken as the main network because it presented a wider range of variables, 15 inputs in the first layer and 15 neurons in second layer, and two sets of cases (Training and Validation). Another tested networks found were MLP 15:15-9-1:1, LNN 14:14-1:1 presented low accuracy and PNN 14:14-26470-2-2:1 had a very low percentage of non-active leading to possible errors in the model although its accuracy very good, see **Table 1.** In **Figure 2**, we depict the ROC-curve (10) for LNN tested (ROC=0.96). Notably, almost model presented and an area under curve higher than 0.5 (the value for a random classifier). The vitality of this type of procedures developing ANN-QSAR models has been demonstrated before(11); see, for instance, the work of Fernandez and Caballero (12). The same is true about the ANNs tested, where is illustrated ROC-curve of ANN LNN with an area higher than 0.93. To show how important is this result, we compared the present model with other model used to address the same problem. We processed our data with Artificial Neural Networks (ANNs) looking for a better model. In general, the ANN RBF tested was statically significant.

4. CONCLUSIONS

Theoretical studies such as QSAR models have become a very useful tool in this context substantially reduce time and resources consuming experiments. The functions of γ-secretase and its implication in Alzheimer's disease have triggered an active search for potent and selective γ-secretase inhibitors. In this sense, QSAR could play an important role in studying these γ-secretase inhibitors. QSARs can be use as predictive tools for the development of molecules. In this work, we developed a new ANN RBF model using the ModesLab descriptors, based on a large database using about 10,000 different drugs obtained from the ChEMBL server. A very good model obtained, and it predict near to 99% γ-secretase inhibitors. This model could be a goal to discover new drugs to treat AD.

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