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Research Article

QSAR study of acetylcholinesterase inhibitors for Alzheimer's disease

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ABSTRACT

Alzheimer's disease (AD) is an incapacitating neurodegenerative disease that slowly destroys brain cells. This disease progressively compromises both memory and cognition, culminating in a state of full dependence and dementia. Currently, AD is the main cause of dementia in the elderly and its prevalence in the developed world is increasing rapidly. Classic drugs, such as acetylcholinesterase inhibitors (AChEIs), fail to decline disease progression and display several side effects that reduce patient's adhesion to pharmacotherapy. The past decade has witnessed an increasing focus on the search for novel AChEIs and new putative enzymatic targets for AD, like β –and γ -secretases, sirtuins, caspase proteins and glycogen syntheses kinase-3 (GSK-3). Genetic algorithm (GA), artificial neural network (ANN), Imperialist Competitive Algorithm (ICA), multiple linear regression (MLR), was used to create QSAR models. According to the obtained results, GA-ANN model was the most favorable method toward the other statistical methods. For this purpose, ab initio geometry optimization was performed at B3LYP level with a known basis set at 6-31G(d). R and R^2 values of the GA-stepwise MLR model were obtained as 0.89 and 0.80.

Keywords: Alzheimer's disease, Acetylcholinesterase and Genetic algorithm

INTRODUCTION:

Although the specific cause of AD is unknown, analyzing the risk factors, age and family history in a first-degree are arguably the most important for developing dementia (Aliev and Obrenovich. 2008). However, the mentioned risk factors alone cannot be responsible for all documented cases of Alzheimer disease. Some detected cases, particularly with early onset (EOAD), are familial and inherited as autosomal dominant disorder. Familial AD risk is markedly genetic and, so far, four genes have been associated with AD pathology: the APP (amyloid protein precursor), preselinin 1 (PSEN-1), preselinin2 (PSEN-2) and the ε 4 allele of the apolipo protein E gene (APOE4)(Wollmer, 2010).Classic features found in the brains of AD patients include neuronal loss in regions associated with memory and cognition, particularly of cholinergic neurons, neurotransmitter depletion(mainly acetylcholine, ACh) and synaptic dysfunction . Microscopically, the most common findings are abnormal protein deposits, including senile neuritic plaques (SNP) and neurofibrillary tangles (NFT) . Senile plaques are the result of the extracellular accumulation of insoluble aggregates of β -amyloid protein (A β) while NFT occur intracellular and are composed of paired helical filaments of hyper phosphorylated tau protein (tau-P). These abnormalities lead to the activation of neurotoxin cascades and to cytoskeleton changes that eventually cause

synaptic dysfunction and neuronal death. Protein miss folding and abnormal aggregation both play a critical role in AD pathology, leading to the formation of insoluble pathological conformers that cause neuronal degeneration and cellular death (Sadqi and Hernandez. 2002).

Multiple linear regression (MLR) was utilized to establish the first type of QSAR models. Using minimum RMSE of TSET as a benchmark, subsets of descriptors were examined for establishing the best linear QSAR. The size of descriptor subset used for model establishment was increased until no improvement was seen. After model development with TSET members, the best model was further examined by the PSET compounds.

The best subset of descriptors selected in MLR-MLR was fed into neural networks to develop MLR-ANN. The neural networks used in this study were all three-layered fully-connected feed-forward networks

Computational Details

The structure and biological data of 20 molecules were obtained from literature. The 3D structures of the molecules were generated using the built optimum option of Chemoffice. The structures were then fully optimized based on the *ab initio* method using the DFT level of theory (Fig. 1). Dragon (version 5.5) was employed to calculate the molecular descriptors. All calculations were performed using the Gaussian 09W program series. Geometric optimization of compounds was carried out using the B3LYP method employing a 6–31G (d) basis set (Fig.1).

The independent variables were molecular descriptors and the dependent variables were the actual half-maximal inhibitory concentration (IC_{50}) values. More than 3226 theoretical descriptors were selected and calculated. For each compound in the training sets, a correlation equation was derived using the same descriptors. The equation was then used to predict log ($1/IC_{50}$) values for the compounds from the corresponding test sets.

Stepwise MLR and GA were used to select the most appropriate descriptor from all descriptors. GA(Tables 2,4) , ANN, ICA (Table 3) and MLR (Fig.2) were used to create the QSAR models.

RESULTS AND DISCUSSION

QSAR between bioavailability of some drugs and their molecular structural descriptors were investigated by using linear and nonlinear techniques. After calculations of descriptors, the different methods were performed on the remaining descriptors to select the most important of them.

The descriptors selected using the methods described above were used to construct linear and nonlinear models using GA-MLR (Table 1) and MLR(Fig.2). A value of 0 indicated that the corresponding feature was not selected and a value of 1 indicated that the feature was selected.

The efficiency of the QSAR model for predicting log (IC_{50}) was estimated using the internal cross-validation method which resulted a prediction for log ($1/IC_{50}$) using MLR. Considering experimental error, the overall prediction for log ($1/IC_{50}$) was satisfactory.

The most significant descriptors selected are JGI1، MATS5m ، RDF020v (Table 1).

Radial distribution function, atomic van der Waals volumes, topological charge index and atomic van der Waals volumes were important descriptors in this study. The efficiency of the QSAR model for predicting log (IC_{50}) was estimated using the internal cross-validation method which resulted a prediction for log ($1/IC_{50}$) using jack-knife method.

CONCLUSION

In the present study, MLR, GA and GA-MLR were used as linear and nonlinear models to their calculated molecular descriptors. The calculated statistical parameters of these models revealed that GA-ANN was better than others which mean that there are some linear and nonlinear relations between selected molecular descriptors and their structures ANN and MLR were successfully used to develop a QSAR model for acetylcholinesterase inhibitors that provided the best results in comparison with other methods.

Conflict of Interest: The authors have no conflict of interest.

ACKNOWLEDGMENTS

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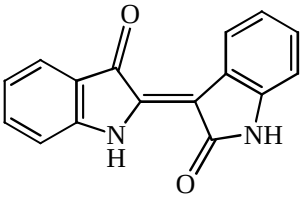

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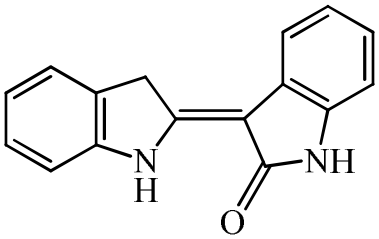

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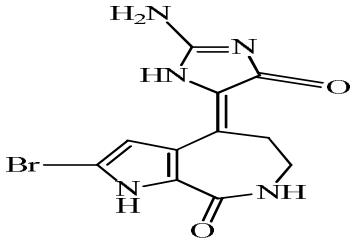

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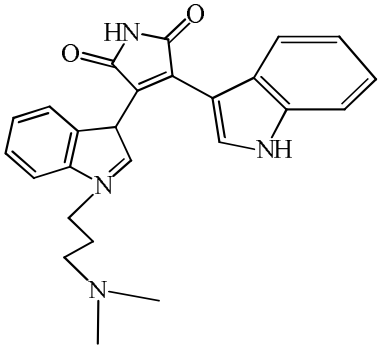

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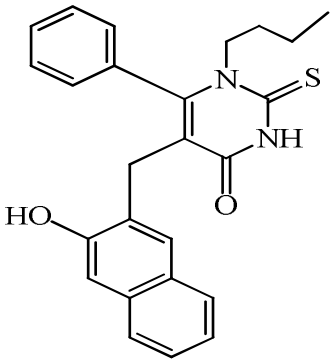

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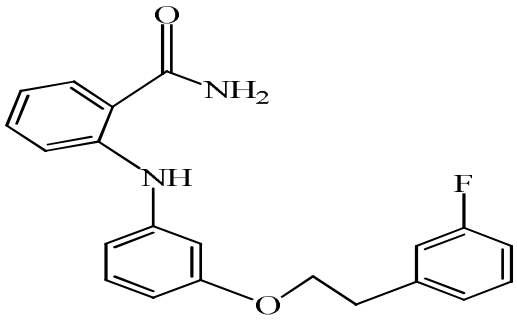

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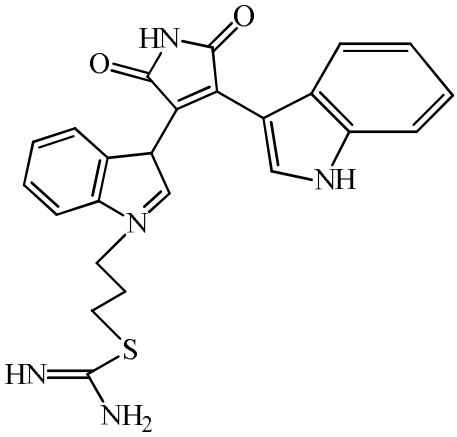

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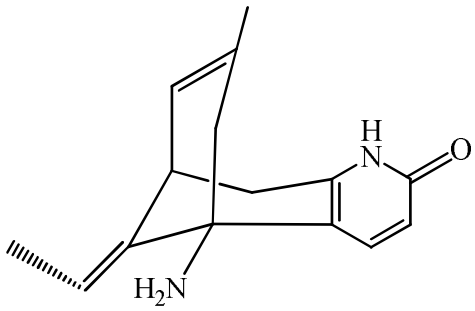

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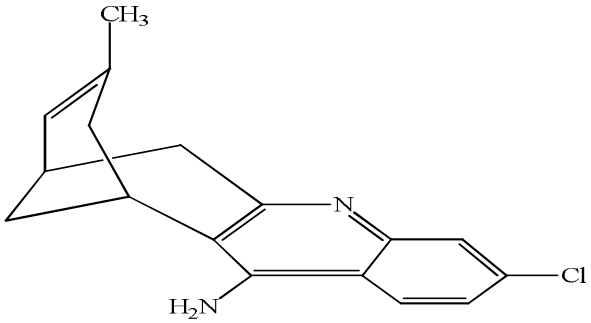

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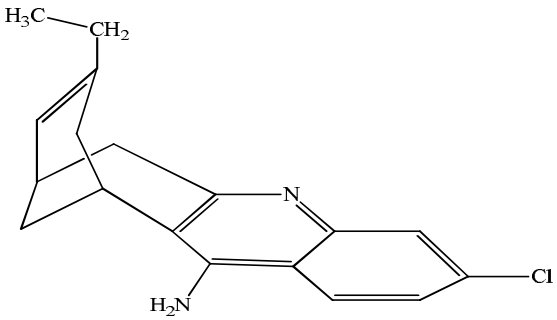

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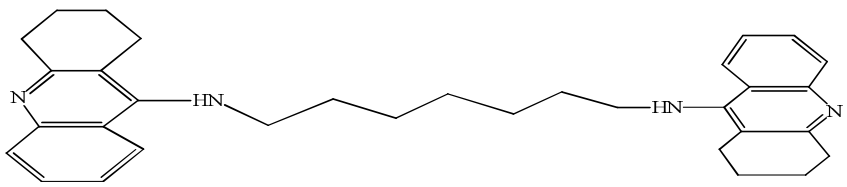

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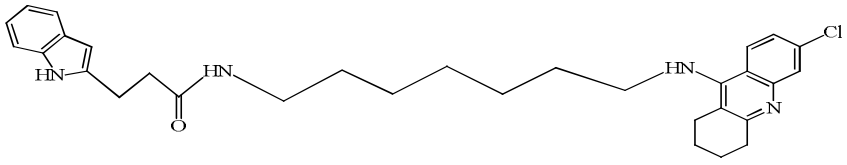

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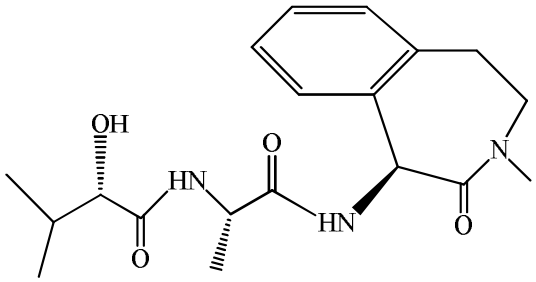

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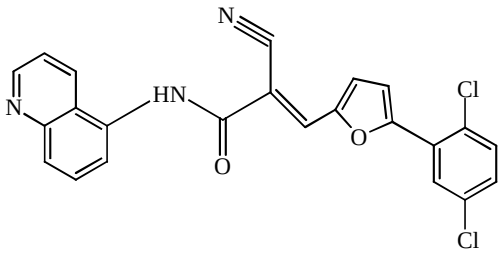

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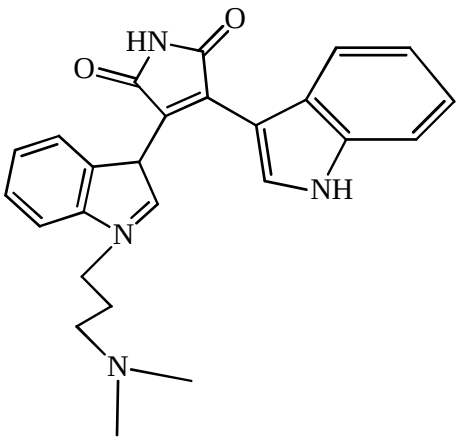

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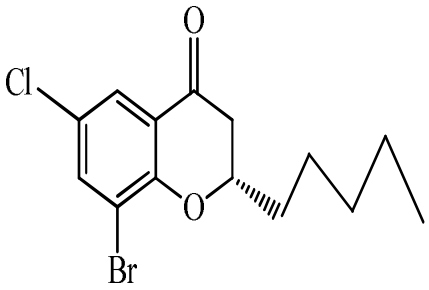

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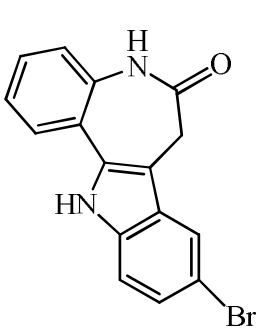

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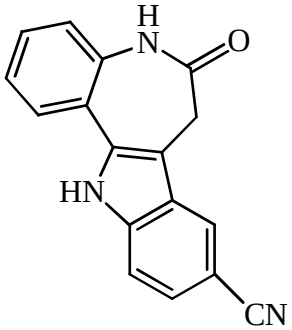

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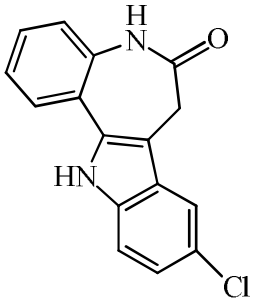

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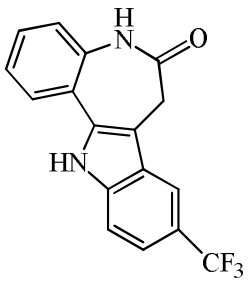

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Fig. 1 The molecular structure of molecules

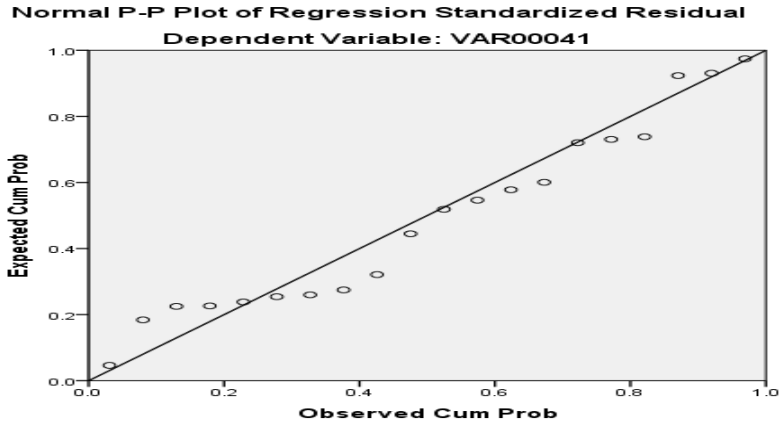

Fig.2. Plot of expected versus target data using MLR method.

Table 1. Descriptors values by MLR method.

Molecules	JGI1	MATS5m	RDF020v
1	0.275	-0.131	2.170
2	0.217	-0.088	1.405
3	0.217	-0.054	1.549
4	0.20	-0.042	1.516
5	0.08	-0.051	3.567
6	0.222	0.145	2.447
7	0.182	0.317	4.167
8	0.149	-0.040	6.425
9	0.143	-0.008	6.400
10	0.152	-0.108	2.780
11	0.179	-0.103	3.002
12	0.211	-0.124	1.360
13	0.174	-0.056	1.955
14	0.167	-0.042	1.678
15	0.174	-0.046	1.675
16	0.231	-0.145	3.059
17	0.130	0.079	3.343
18	0.125	-0.242	3.474
19	0.214	-0.092	4.968
20	0.134	-0.031	4.304

Table2. The Genetic algorithm results

RMSE train	RMSE test	Layer
0.1406	0.6710	(2-1)
0.1380	0.6936	(3-1)
0.1405	0.8270	(4-1)
0.1402	0.8511	(5-1)
0.1388	0.8419	(6-1)
0.1398	0.3909	(7-1)
0.1378	0.8913	(8-1)
0.1373	0.8193	(9-1)
0.1379	0.7136	(10-1)
0.1388	0.8746	(11-1)
0.1390	0.8686	(12-1)

Table3. The imperialist competitive algorithm results

RMSE train	RMSE test	Layer
0.1737	1.3623	(2-1)
0.2633	1.3429	(3-1)
0.2914	1.2185	(4-1)
0.2914	1.2185	(5-1)
0.2560	1.2815	(6-1)
0.2560	1.2815	(7-1)
0.2560	1.2815	(8-1)
0.2560	1.2815	(9-1)
0.1737	1.3623	(10-1)
0.2614	1.2185	(11-1)
0.2092	1.3181	(12-1)

Table4. The Results of Jack-knife method

Predicted	Observed
-2.83	-2.41
-0.54	-0.66
-0.04	0.11
0.74	0.12
0.09	0.09
-0.59	-1.18
-0.67	-0.54
0.19	0.10
-0.75	-0.86
0.08	0.001
0.38	0.24
-0.31	-0.18
-1.44	-1.36
-1.09	-1.00
-1.34	-1.38
-1.77	-1.48
-1.82	-2.78
-0.78	-0.70
-2.13	-2.00
1.61	1.70