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DFT-based QSAR studies and Molecular Docking of 1-Phenylcyclohexylamine Analogues as anticonvulsant of NMDA Receptor

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Abstract: The phencyclidine (PCP) and their analogues have been reported to exhibit inhibitory activities toward the N-methyl-D-aspartate receptor (NMDAR). To discover the QSAR between structure of PCP derivatives and Ki activities we have used density functional theory (DFT) to generate quantum descriptors, multiple regression linear (MLR) method was applied to establish QSAR model, and an artificial neural network (ANN), considering the relevant descriptors obtained with the MLR method is explored, a correlation coefficient of R_{ANN} = 0.912 was obtained with 6-4-1 ANN model. This model is tested by using a cross-validation method with the LOO procedure (R_{CV} = 0.841). To study the configuration impact on activity, we proceed to the Molecular Docking of four configurations, two configurations of compound have (Ki = 502 nM) and two configurations of compound have (Ki = 1200nM). The phenyl group, when placed in an equatorial position in cis9e, a configuration of the less active compound, does not form π-sigma interaction. The superimposition of this configuration with trans7e reveals that the phenyl group of cis9e configuration is shifted from the binding site compared to trans7e which forms an interaction π-sigma throughout its phenyl group with ARG B: 894. So, we could claim that the cis9e is the configuration adopted by compound having (Ki = 502 nM).

Keywords: Inhibition activity; QSAR model; MLR; ANN; LOO; Docking.

1. Introduction

The NMDA receptor is involved in many neurological disease studies; which cause trouble in various types of learning and memory task b [1-5]. The NMDA receptor is a receptor-channels [6]; it is composed of two subunits NR1/NR2 or NR1/NR3 [2,6-9], which have a variety of binding sites of synthetic non-competitive antagonist drugs such as phencyclidine (PCP), thienylcyclohexylpiperidine (TCP) and (+)-10,11-Dihydro-5-methyl-5H dibenzo(a,d)cyclohepten-5,10-diyldiammonium maleate (MK801) [10,11].

Several attempts had been performed in the goal to understand the mechanism of the interaction mode of non-competitive antagonists with the NMDAR. Recently, a novel family of allosteric modulators was discovered and helped to distinguish between NMDARs depending upon their GluN2 subunit composition [12-16]. To date, however, the binding site and mechanisms of action of these compounds remain unknown. This is partly because of the lack of knowledge about the full-length NMDAR structure that is comprised of unique, multi-domain patterns of interaction, which was not elucidated until recently by X-ray crystallography. Previous studies of Costa and collaborators [13-15,17] demonstrate that the compounds are not channeled blockers, do not bind at the glutamate or glycine binding sites, and do not require the N-terminal domain (NTD) for their activity. Despite the low affinity exhibited by the modulators at this point, their novelty in activity pattern, chemical structure, and mechanism of action warrant further investigation of their binding site to contribute to the further development of high-affinity compounds. In an antecedent paper in which we have proposed an electrostatic and geometrical pharmacophore based on superimposition of PCP, ketamine dexoxadrol and other non-competitive antagonists with the two configurations of MK801, we had presented a description of interaction mode using molecular modeling techniques [18].

Always, to more understand about the mode of interaction and to improve the activity at this receptor, in this work we propose a predictive QSAR model based on data analysis methods (multiple linear regression-MLR-analysis and artificial neural network-ANN), which is validated with cross-validation method-CV. On the other hand, we have

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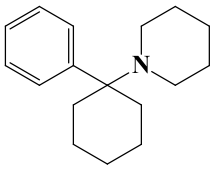
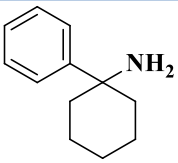
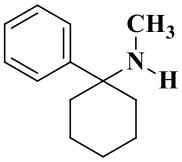
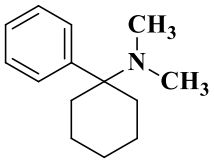
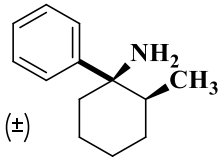
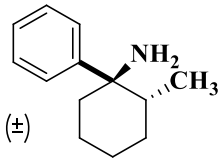
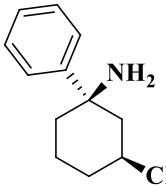
proceeded to molecular docking of some compounds with the NMDA receptor.

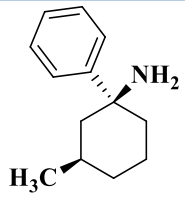
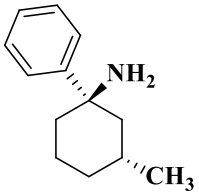
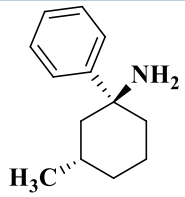
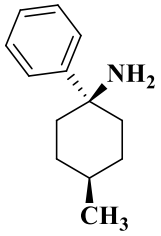
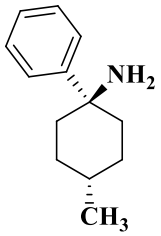
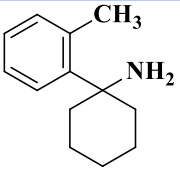
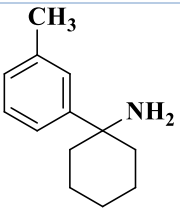
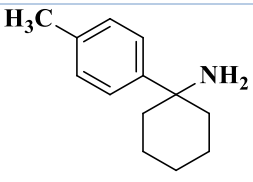
2. Methods and materials

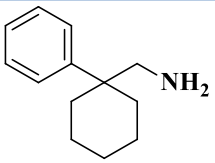
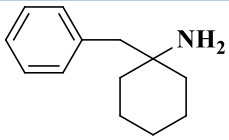
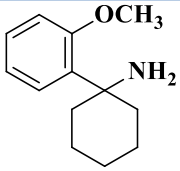
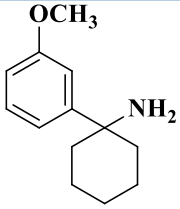
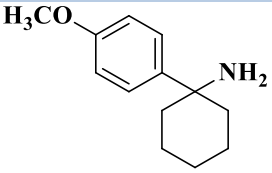
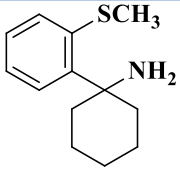
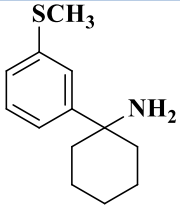
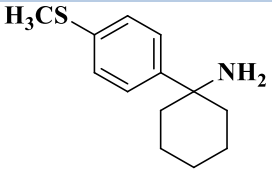
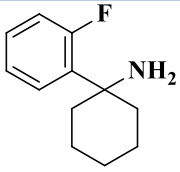
2.1. Multiple regression linear (MLR) and artificial neural network (NN)

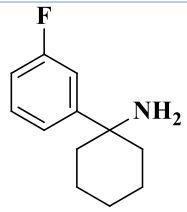
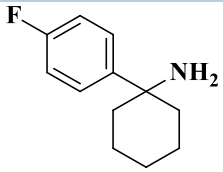
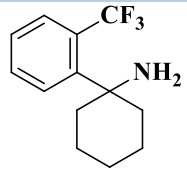
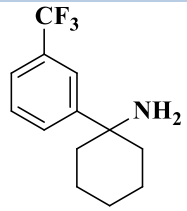
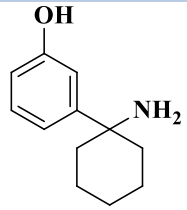
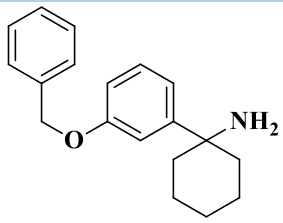
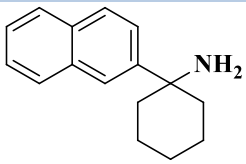
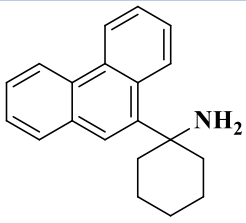
To establish a structure-activity relationship for non-competitive antagonists of the NMDA receptor, our study is realized in a series of 38 PCP derivatives that have been analyzed and tested for their binding affinities to the PCP binding sites in rat brain membranes labeled with [^{3}H] -1-[1-(2-thienyl)cyclohexyl]piperidine(^{3}H-TCP) [19]. In this work, the Ki activity is expressed in nM [19], and it is presented in a logarithmic scale (pKi). Table 1 shows the chemical structures of the studied compounds, their observed pKi values (pKi_{obs}) and the MLR, ANN and CV predicted ones, respectively pKi_{RLM}; pKi_{ANN} and pKi_{CV}.

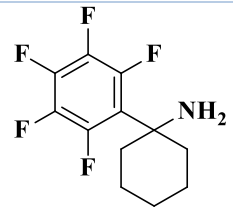
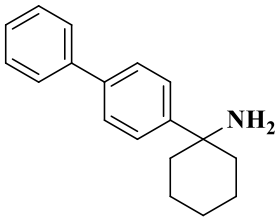
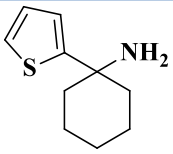
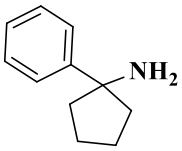
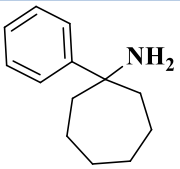
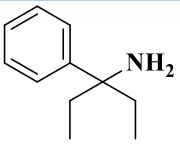
Table 1. The chemical structures of the 38 studied compounds. The observed pKi values (pKi_{obs}), and the predicted pKi (pKi_{RLM}; pKi_{ANN} and pKi_{CV}) calculated using the MLR, ANN and CV methods, respectively.

Compound	Structure	Ki.nM	pKi_{obs}	pKi_{MLR}	pKi_{ANN}	pKi_{CV}
1		**70**	**-1.8451**	**-1.97992**	**-1.8527**	**-1.784**
2		**527**	**-2.7218**	**-3.43975**	**-2.7863**	**-2.9897**
3		**347**	**-2.54033**	**-3.03868**	**-2.6528**	**-2.9897**
4		**722**	**-2.85854**	**-2.58646**	**-2.977**	**-2.4348**
5		**2000**	**-3.30103**	**-3.12298**	**-3.2767**	**-2.8896**
6		**1600**	**-3.20412**	**-3.07526**	**-3.5552**	**-3.1673**
7		**502**	**-2.7007**	**-3.20267**	**-3.0391**	**-3.2692**

8		**8000**	**-3.90309**	**-3.23717**	**-3.0269**	**-3.2492**
9		**1200**	**-3.07918**	**-3.19926**	**-3.0333**	**-3.2434**
10		**1640**	**-3.21484**	**-3.32307**	**-3.1648**	**-3.2281**
11		**1100**	**-3.04139**	**-3.70961**	**-3.4535**	**-3.3124**
12		**8400**	**-3.92428**	**-3.7066**	**-3.4467**	**-3.5441**
13		**7800**	**-3.89209**	**-3.27268**	**-3.5756**	**-3.7491**
14		**592**	**-2.77232**	**-3.38604**	**-2.8841**	**-3.3233**
15		**7300**	**-3.86332**	**-3.75796**	**-3.8471**	**-2.848**

16		**5100**	**-3.70757**	**-3.39257**	**-3.8161**	**-3.7828**
17		**16000**	**-4.20412**	**-3.63487**	**-4.2239**	**-4.38**
18		**850**	**-2.92942**	**-3.12253**	**-2.8956**	**-2.7987**
19		**563**	**-2.75051**	**-3.25981**	**-2.7652**	**-2.6874**
20		**121000**	**-5.08279**	**-4.34468**	**-5.079**	**-4.9799**
21		**820**	**-2.91381**	**-3.09145**	**-2.8396**	**-2.7267**
22		**2420**	**-3.38382**	**-3.20983**	**-3.3648**	**-3.3211**
23		**43000**	**-4.63347**	**-4.80873**	**-4.637**	**-4.5626**
24		**10700**	**-4.02938**	**-3.32105**	**-3.9359**	**-4.1859**

25		**675**	**-2.8293**	**-3.52462**	**-3.3078**	**-3.1247**
26		**923**	**-2.9652**	**-3.51709**	**-2.9675**	**-3.2495**
27		**12400**	**-4.09342**	**-3.61101**	**-4.2013**	**-4.1049**
28		**8400**	**-3.92428**	**-4.23672**	**-4.0651**	**-3.9131**
29		**222**	**-2.34635**	**-2.24451**	**-2.2977**	**-2.3233**
30		**10600**	**-4.02531**	**-3.76524**	**-4.0283**	**-3.9832**
31		**34000**	**-4.53148**	**-4.57381**	**-4.2906**	**-4.574**
32		**27500**	**-4.43933**	**-4.4627**	**-4.4878**	**-4.4391**

33		**10000**	**-4**	**-3.87262**	**-3.933**	**-3.8923**
34		**86000**	**-4.9345**	**-5.05234**	**-4.9434**	**-4.7608**
35		**145**	**-2.16137**	**-2.50103**	**-2.1866**	**-2.2262**
36		**10500**	**-4.02119**	**-3.21974**	**-3.8444**	**-4.1585**
37		**2600**	**-3.41497**	**-3.7995**	**-3.3866**	**-3.2321**
38		**6000**	**-3.77815**	**-3.35736**	**-3.8929**	**-3.6374**

The electronic descriptors were obtained from quantum chemical calculations. So, all compounds were fully optimized with the density functional theory (DFT)/B3LYP [20-22], combined with the 6-31G* basis set. All the calculations were performed using the Gaussian 03 software. The rest of the representative descriptors were calculated with the MM2 method using ChemBio3D Ultra (version 13.0) and ACD Lab [23]. The total descriptors chosen to construct the QSAR model are summarized in Table 2.

Table 2. The Computed descriptors, constituting the data table to construct the QSAR model.

Categoryof descriptors	**Description**	**Notation**	**Method**
Electronic	Dipole moment	μ	
	Electrophilicity Index	EI	
	Total energy	E	DFT
	Electronic affinity	A	
Thermodynamic	Dipole Length	DL	
	Index of refraction	Ω	MM2
	Polarisability	P	

	Molar refractivity	MR	
	Henry's law cte	H	MM2
Steric	Sum of Degrees	SD	
	Sum of valence degrees	SOV	
	Cluster Count	ClsC	MM2
	Diameter	D	
	Density	De	
	pKa	pKa	
	Ovality	O	
	Log P	LogP	

The different QSAR techniques and methods applied in this work are detailed in our previous paper [24,25].

2.2. Molecular Docking

Molecular docking is performed with AutoDockTools [26,27]. The native structure of the NMDA receptor was retrieved from the protein data bank (PDB code: 2HQW, resolution: 1.9Å [28]). Our ligands are built and optimized with chemBio3D Ultra 13.0 software, and the docked conformations were viewed using Discovery Studio 4.1 software package [29]. The docking process parameters are adjusted as follows: the Grid size set is 100×40×40 related to XYZ dimension, with grid spacing of 0.375Å, the center grid box is of 23Å, -25Å, 17Å, the number of Genetic Algorithm run = 5, the population size = 150, the maximum number of evaluations = 2.5 million, the maximum number of generations = 27000 parameters. The binding mode analysis is performed with the complex (ligand + receptor) having the lowest energy [30].

To study the configuration impact on activity, two molecules, compound 7 (Ki=502nM) and compound 9 (Ki=1200nM almost three-fold higher than that of compound 7) were submitted to molecular docking. Compounds 7 and 9, as it is shown in Figure 1, have the same chemical structure but have different configurations of asymmetric carbons 1 and 3.

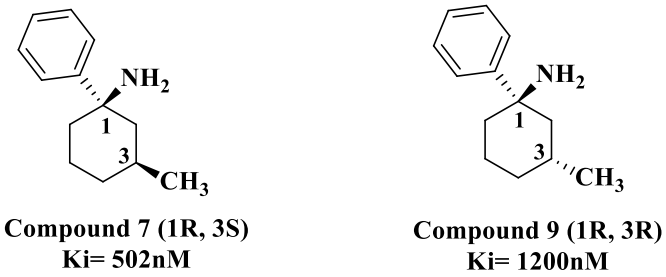


Figure 1. Chemical structures of compound 7 and 9

The configurational analysis of compounds 7 and 9 showed that each molecule is presented in two forms (Figure 2), so that the group phenyl could adopt an axial position (**trans7a**, **cis9a**) or an equatorial position (**trans7e**, **cis9e**).

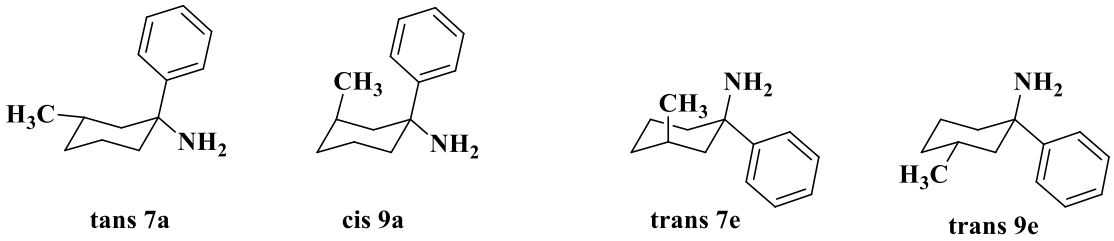


Figure 2. The 4 configurations of compounds 7 and 9

3. Results and Discussion

3.1. Multiple Regression Linear

To quantify the relationship of molecules structure of non-competitive antagonists of the NMDA receptor-related to their Ki activities, 38 PCP derivatives have been submitted to the MLR method. This method uses the correlation coefficient (R), the determination coefficient (R^2) and t-value values to select the best model. Good results are obtained with 6 descriptors: **Somme of degrees (SD), diameter (D), pKa, Dipole moment (µ), Density (De) and Electrofilicity index (Ei).**

The best model is represented by the following equation:

$$\boldsymbol{pKi = 13.281 + 0.167\,SD - 0.536\,D - 0.986\,pKa + 0.580\,\mu - 5.219\,De - 2.624\,Ei}$$

R = 0.825 R^2 = 0.681 S = 0.478

The selected descriptors related to their coefficients with their standard errors and the t-values are shown in Figure 2**.**

Table 2. the selected descriptors related to their coefficients with their standard errors and the t-values.

Descriptor	Coefficient	standard Error	t-values
SD	0.167	0.043	3.869
D	-0.536	0.124	-4.325
pKa	-0.986	0.345	-2.860
µ	0.580	0.240	2.421
De	-5.624	2.391	-2.183
Ei	-2.624	0.504	-5.209

The MLR model shows an important contribution to the electronic and topological descriptors. We note the high contribution of the **Dipole moment (µ), Electrofilicity index (Ei).**

The predicted activities values (pKi_{RLM}) calculated from the MLR model and those observed (pKi_{obs}) are presented in Table 1. The correlation between pKi_{RLM} and pKi_{obs} is illustrated in Figure 3.

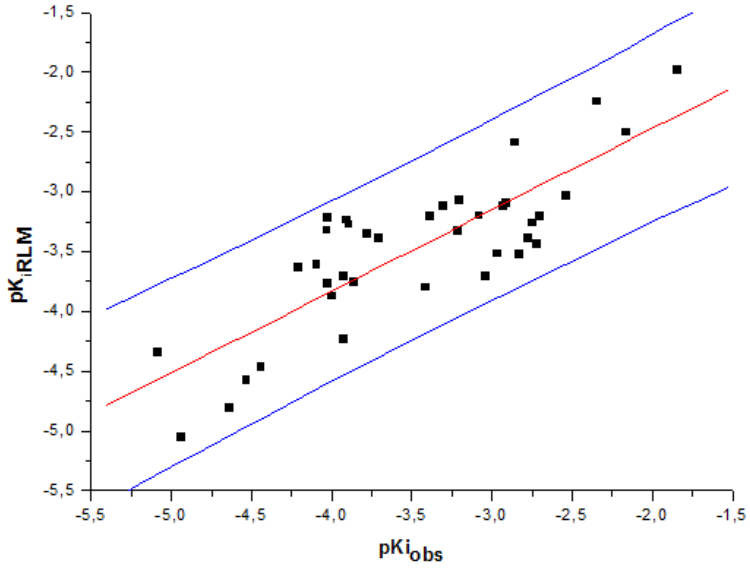


Figure 3. The correlation between pKi_{RLM} and pKi_{obs}

The selected descriptors by MLR are used as the input layer parameters in the Neural Network (NN).

3.2. Neural network (NN)

To improve the QSAR model, we have proceeded to a non-linear method, so the NN is a suitable technique to implement this task. The data table comprising the six descriptors selected by MLR is submitted to three layers ANN. So, the network input layer is composed of six neurons; the output layer is a linear neuron that represents the pKi_{obs} activity, the hidden layer has been defined by

$\rho = \frac{number\ of\ weight}{number\ of\ connection}$ which should have a value between 1 and 3 [31]. Therefore, for a network configuration (6-4-1) the number of weight is 38, so ρ = 1.15, which leads to an acceptable network.

The pKi_{ANN} values predicted by the neural network are shown in Table 1, and the correlation between pKi_{obs} and pKi_{ANN} is illustrated in Figure 4.

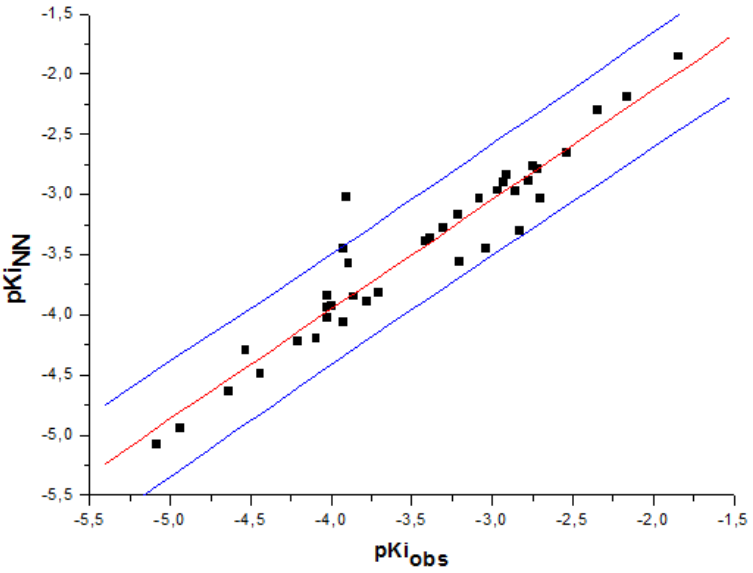


Figure 4. The correlation between pKi_{ANN} and pKi_{obs}
R = 0.955 R^2 = 0.912 S = 0.232

The excellent correlation obtained with the ANN model confirms that the selected descriptors by the MLR method are relevant, and the proposed model has a high power of predictability.

3.3. Cross-validation (CV)

To test the effectiveness of the proposed ANN model, we used the cross-validation method using "leave one out" procedure [32], keeping the same ANN architecture as used in the training set.

The predicted activities calculated by the CV method (pKi_{CV}) are given in Table 1. The correlation between pki_{CV} and pki_{obs} is shown in Figure 5.

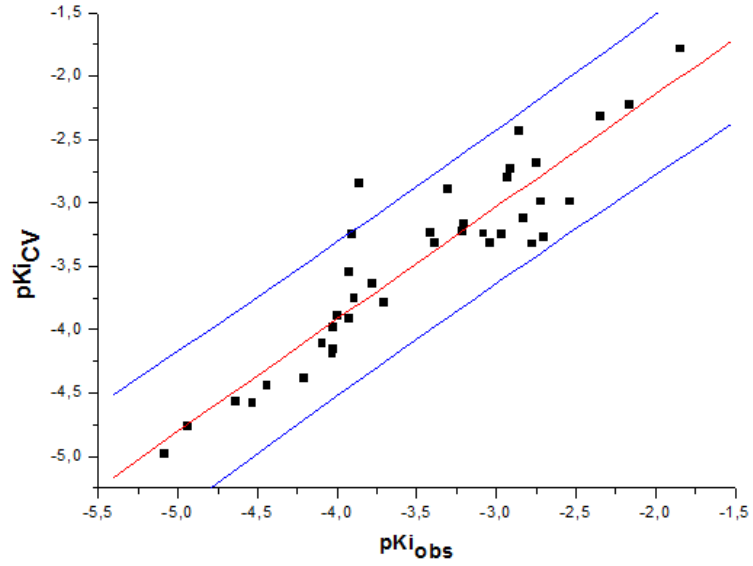


Figure 5. Correlation between pKi_{CV} and pKi_{obs}

R_{cv} = 0.921 R^2 = 0.849 S = 0.305

The CV predicted values show a good correlation with the observed activities, which confirms the predictive stability of the proposed model.

3.4. Molecular docking

To bring out the interactions of non-competitive antagonists of the NMDA receptor and to explore the geometric pharmacophore characteristics, in this part of the work we proceed to the molecular docking of the two configurations of compounds 7 and 9.

In the case of the axial position of phenyl, the analysis of interactions with the NMDA receptor for both compounds 7 and 9, shows a hydrogen bonding

interaction between the two hydrogen atoms of the NH_2 group and the amino-acid SER B:890 at a distance of 2.05159Å and 2.22661Å. On the other hand, a π-sigma interaction is produced between the phenyl and the amino acid ARG B:894 at a distance of 3.38849Å **(**Figures 6 and 7**).**

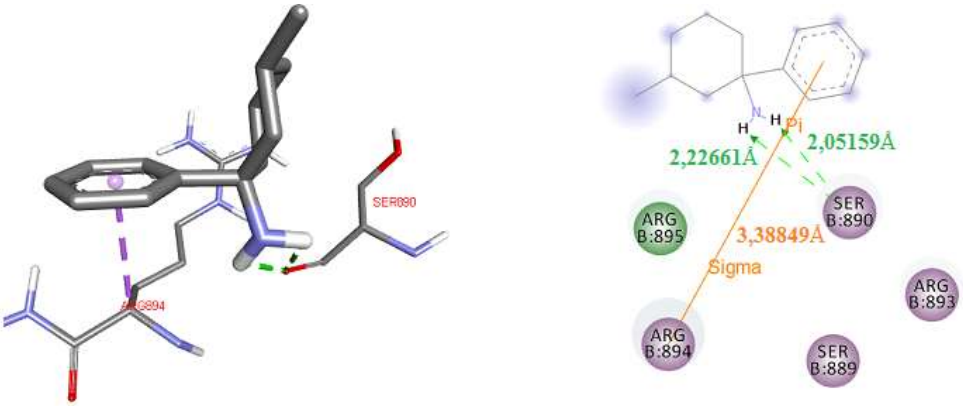


Figure 6. Molecular docking of trans7a with NMDA receptor in 3D and 2D

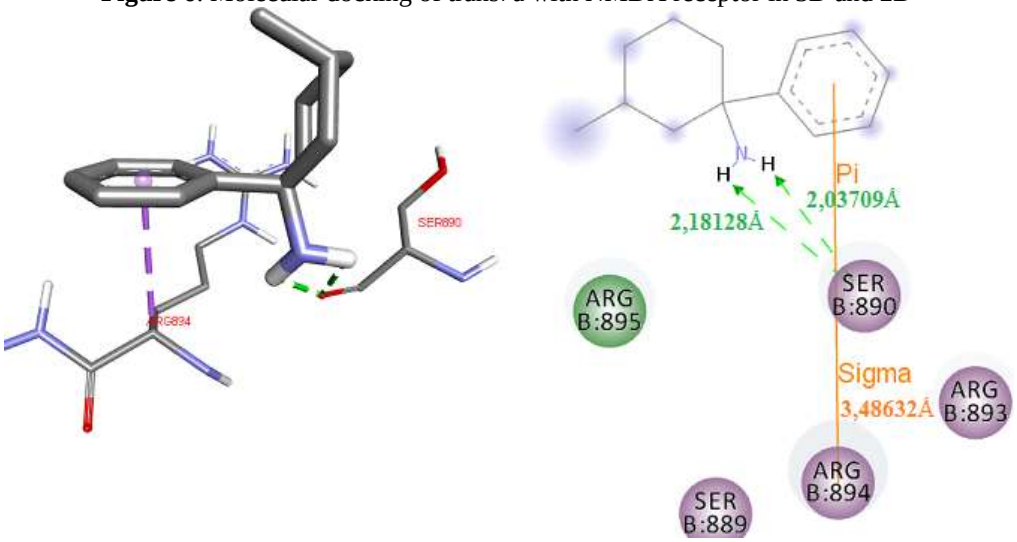


Figure 7. Molecular docking of cis9a with NMDA receptor in 3D and 2D

With the equatorial position of phenyl, the examined interactions of **trans7e** and **cis9e** show the same hydrogen bonding as with the case of axial position at almost the same distance. However, a π-sigma interaction between the phenyl and the ARG B: 894 amino-acid is shown with the **trans7e** configuration, at a distance of 3.54736 Å, but not for the **cis9e** configuration (Figures 8 and 9).

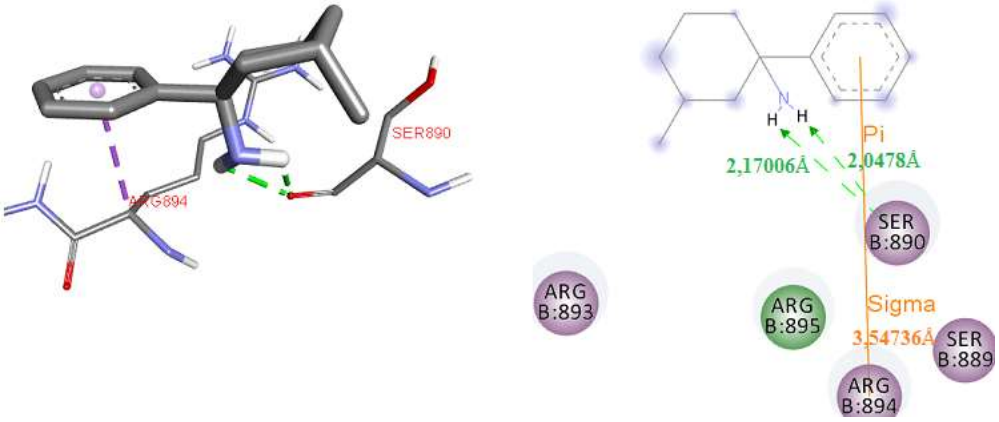


Figure 8. Molecular docking of trans7e with NMDA receptor in 3D and 2D

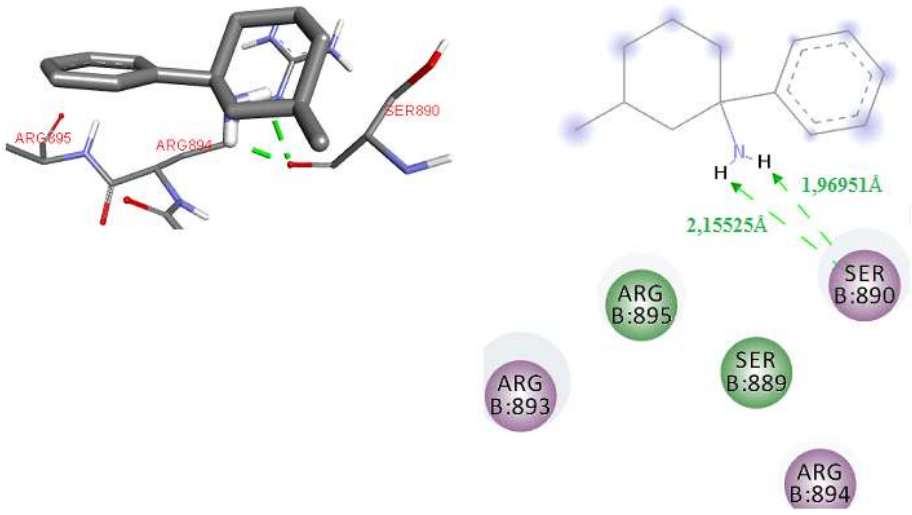


Figure 9. Molecular docking of cis9e with NMDA receptor in 3D and 2D

In summary the phenyl of the compound 9, having the lowest activity (ki=1200nM), doesn't form π-sigma interaction with the cis9e configuration when the phenyl adopts an equatorial position, however, it is formed for all others configurations, which let us think that it is probably to be active in the NMDA receptor, the phenyl has to adopt an axial position.

To more understand the non-interaction of phenyl adopting the equatorial position in cis9e configuration, we have proceeded to the superimposition of molecules **trans7e** and **cis9e** in the binding site of the NMDA receptor **(**Figure 10**)**.

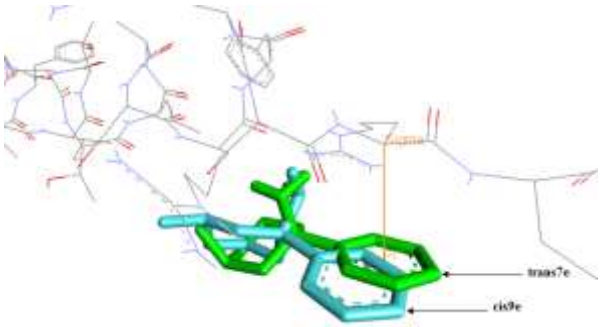


Figure 10. Superimposition of trans7e (green) and cis9e (cyan)

This superimposition reveals that the phenyl group of cis9e configuration is shifted from the binding site compared to the trans7e configuration which appears to be placed in a good position leading to the interaction of its phenyl group with ARG B:894. So we can claim that the configuration adopted by the compound 9 (cis9e) is the cause of the decrease in its activity.

Conclusion

The mathematical analysis combined to electronic computations of we have conducted to build a quantitative structure-activity relationship for non-competitive NMDA receptor antagonists suggests that the biological activity is closely related to the Density (De) and Electrophylicity Index (Ei). These descriptors selected automatically by the multiple linear regression analysis show a high correlation with the neural network model. The CV test of the performance of this model confirms that the descriptors selected by the MLR method are relevant, and the proposed model presents an excellent predictive power.

The configurational analysis of compounds 7 and 9 followed by molecular docking of their different configurations with NR1 binding site showed that the same interactions (π-sigma and hydrogen bonding) are formed for trans7a, trans7e, and cis9a. However, cis9e do not form π-sigma interaction. In attempt to explain why the phenyl group of compound 9 don't interact with NMDA receptor we have proceeded to the superimposition of cis9e to trans7e, so we observed that the phenyl group of cis9e configuration is shifted from the binding site compared to the trans7e configuration which appears to be placed in the excellent position leading to the interaction of its phenyl group with ARG B:894. So we could claim that the configuration adopted by the compound 9 (cis9e) is the cause of the decrease in its activity.

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