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A Comparative Molecular Field Analysis of Phenylcyclohexylamine Derivatives

Ja Hong Kim,* Sung Ho Sohn, and Sung Wan Hong†

*Department of Chemistry Education, Chonbuk National University, Chonju 561-756, Korea
†Department of Chemistry, Woosuk University, Wanju 565-701, Korea

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Quantitative structure activity analysis is the foundation for understanding structural features of both the ligands and the target receptors responsible for biological activity and helps to design more effective drugs.[1,2]

The effectiveness of phenylcyclohexylamine (PCA) as an anticonvulsant agent has been largely overshadowed by its notoriety as a drug of abuse. Nevertheless, PCA is protective in the maximal electroshock, pentylenetetrazol, and audiogenic seizure models.[3-5]

In our previous reports,[6,7] it has been shown that a set of 19 analogues of phenylcyclohexylamine was chosen for the study using a selection procedure aimed at minimizing the interparameter correlations, while ensuring that the frontier orbital covered the maximum possible range of LogP. Herein we describe a comparative molecular field analysis of phenylcyclohexylamine derivatives.

The computational calculations were performed using the molecular modeling software Sybyl 6.4.2 version on a Silicon Graphics with the standard bond lengths and angles.[8] The initial structures were optimized using a molecular mechanics method with Tripos force field and atomic charges were calculated by Gasteiger-Hückel method.[9,10]

The geometry of skeleton of phenylclohexylamine is given in Figure 1 and derivatives are shown in Figure 2.

Figure 1 shows that the gray lobe contours are positive

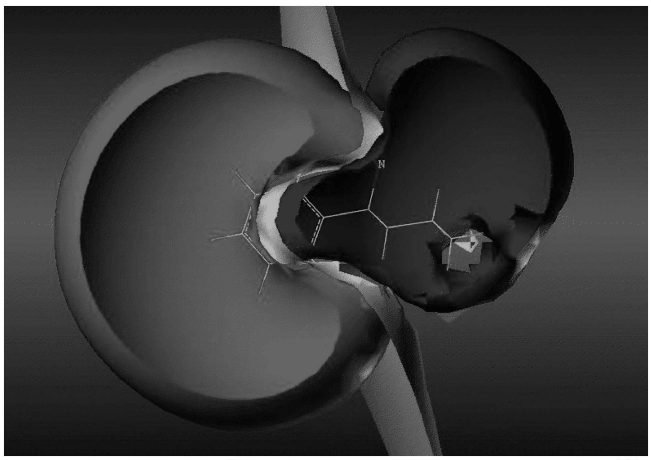

Figure 1. Gasteiger-Hückel electron density contour map for phenylcyclohexylamine.

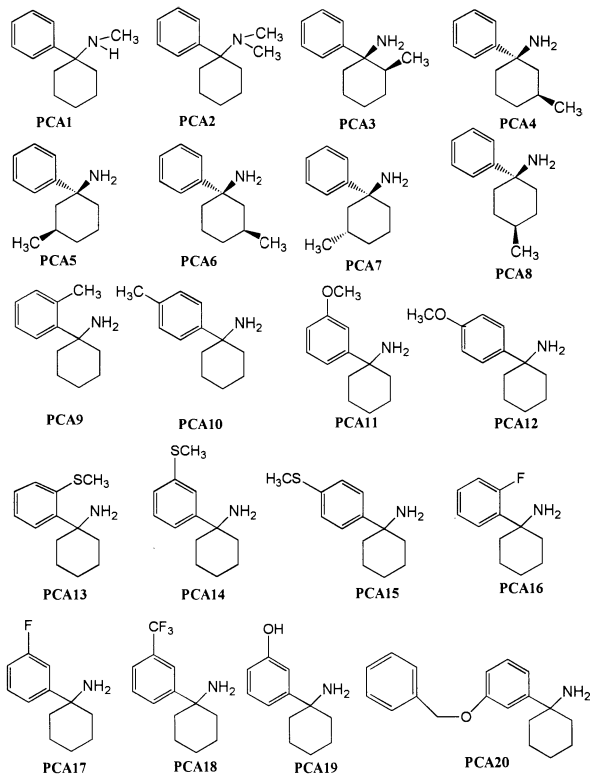

Figure 2. The PCA derivatives considered in this work.

Table 1. Observed and calculated biological activity of PCA derivatives

Analogues	Activity (Log ED_{50})		Residual
	Observed	Calculated	
PCA1	0.66	0.68	-0.02
PCA2	0.69	0.69	-0.00045
PCA3	0.90	0.88	0.02
PCA4	1.42	1.43	-0.01
PCA5	1.90	0.93	-0.02
PCA6	1.32	1.31	0.01
PCA7	0.90	0.89	0.01
PCA8	1.13	1.13	-0.0048
PCA9	0.69	0.69	-0.0017
PCA10	1.87	1.88	-0.01
PCA11	1.17	1.18	-0.01
PCA12	1.51	1.52	-0.01
PCA13	1.42	1.43	-0.01
PCA14	1.52	1.54	-0.02
PCA15	1.61	1.60	0.01
PCA16	1.36	1.30	0.06
PCA17	0.97	0.98	-0.01
PCA18	1.39	1.40	-0.01
PCA19	1.55	1.56	-0.01
PCA20	1.47	1.45	0.02

charge favored contribution, dark gray lobe contours represent the electrostatic features (negative charge increases bioactivity), and light gray plane exhibit neutral charge. The observed and calculated residual activities of all derivatives are listed in Table 1.

Among all derivatives, PCA-1 produced the highest activity (Log ED_{50}–0.68) in Table 1. It has been proposed that one might expect PCA-1 should be enough to explain the results in an available CoMFA study. The Log ED_{50} value was introduced as an additional independent variable for the hydrophobicity. The PCA derivatives produced good cross-validated results and conventional value (r^2–0.997, standard error of estimate–0.021) with the optimum components as shown in Table 1. For the set of 20 derivatives, the values of r^2 are quite good, being above 0.6 in all cases. The most important is the predictive or cross-validated r^2 value. Cross-validation evaluates a model not by how well it fits data but by how well it predict data.

The partial least-squares (PLS) model was performed to calculate the activity of each derivative, and this was compared with the actual value in Figure 3.

Figure 3. Predicted and measured LogED_{50} for the CoMFA of PCA derivatives.

Figure 3 shows that the CoMFA indicates satisfactory agreement between observed and predicted LogED_{50} values.

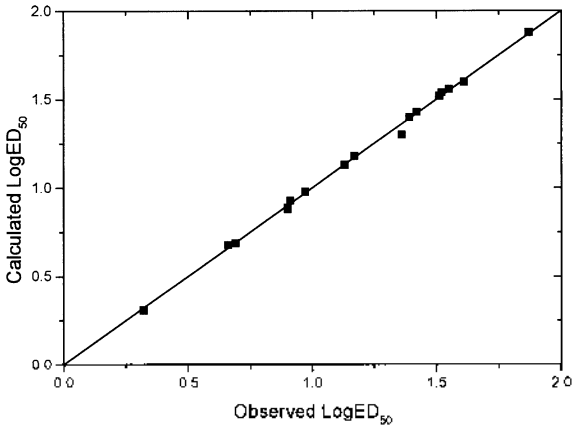

Figure 3. Predicted and measured Log ED_{50} for the CoMFA of PCA derivatives.

It suggests that the CoMFA sampling of the steric and electrostatic interactions of PCA derivatives may be capable of providing useful information about ligand-receptor interactions. Drug affinities for PCA binding sites in rat brain membranes were determined by a tissue homogenate preparation of whole rat brain minus carebellum.[11]

In conclusion, the results of CoMFA derived models was much more successful in correlation of the structural features of the PCA derivatives with their binding affinity.

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