

Communications

A Comparative Molecular Field Analysis of Phenylcyclohexylamine Derivatives

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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 phenylcyclohexylamine is given in Figure 1 and derivatives are shown in Figure 2.

Figure 1 shows that the gray lobe contours are positive

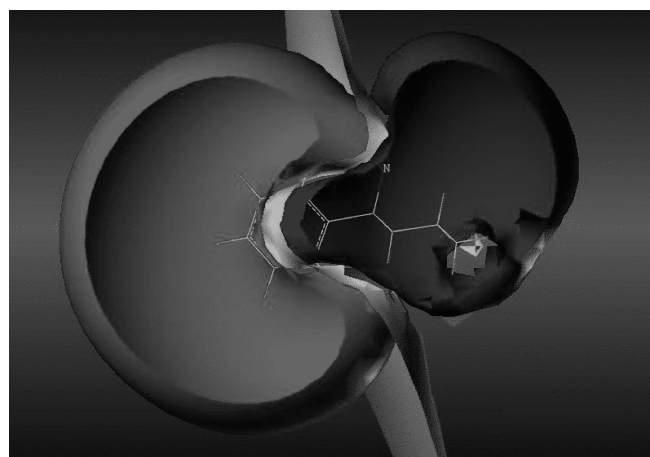


Figure 1. Gasteiger-Hückel electron density contour map for phenylcyclohexylamine.

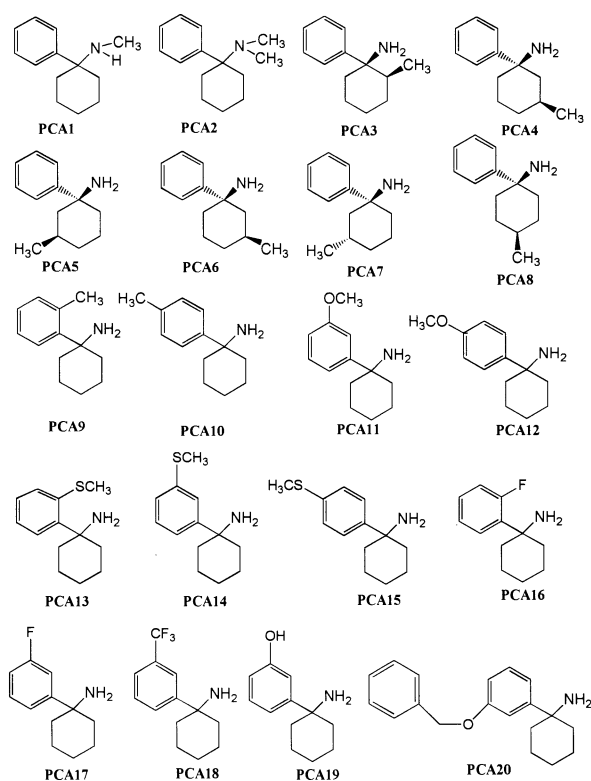


Figure 2. The PCA derivatives considered in this work.

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

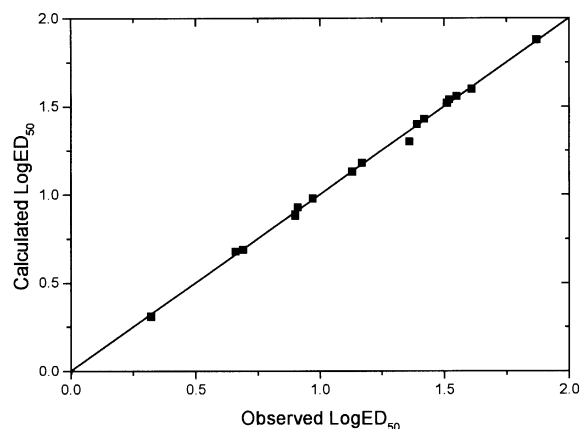
charge favored contribution, dark gray lobe contours represent the electrostatic features (negative charge increases bio-activity), and light gray plane exhibit neutral charge. The observed and calculated residual activities of all derivatives are listed in Table 1.

Among all derivatives, PCA-1 produced the highest activity (Log ED₅₀=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 ED₅₀ 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 LogED₅₀ for the CoMFA of PCA derivatives.

Figure 3 shows that the CoMFA indicates satisfactory agreement between observed and predicted LogED₅₀ values.

**Figure 3.** Predicted and measured Log ED₅₀ 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 cerebellum.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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