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3D QSAR Studies on New Piperazine Derivatives with Antihistamine and Antibradykinin Effects

Hea-Young Park Choo and Bum-Jun Chung

School of Pharmacy, Ewha Womans University, Seoul, 120-750, Korea

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Three dimensional QSAR studies for antihistamine and antibradykinin effects of new piperazine derivatives were conducted using the comparative molecular field analysis. Electrostatic and steric factors, but not hydrophobic factor, of the synthesized compounds were correlated with the antagonistic effect.

Key words: 3D QSAR, Piperazine derivatives, Antihistamine, Antibradykinin

INTRODUCTION

H_1-Antagonists are used in the treatment of allergic diseases due to a major role the histamine plays in allergic response. Similarly the nonapeptide bradykinin is an autocoid which acts locally to produce pain, vasodilation, increased vascular permeability and the release of prostagrandin (Regoli *et al.*, 1980; Dray *et al.*, 1993). Therefore antagonists of the bradykinin B2 receptor also has the potential to become a drug for allergy and inflammation. Most of the bradykinin B_2 antagonists developed so far are bradykinin-derived peptides and their therapeutic use is limited. Non-peptide bradykinin antagonists such as FR 173657 and Win 64338 are reported only in very recent years(Salvino *et al.*, 1993; Abe *et al.*, 1998; Dziadulewicz *et al.*, 2000; Hritsch *et al.*, 1999; Dziadulewicz *et al.*, 1999). In our study of non-peptide bradykinin B_2 antagonists, we have reported the synthesis and antihistamine/antibradykinin activities of piperazine derivatives which were structurally related to a second generation antihistamine drug, cetirizine (Choo *et al.*, 1999). However, the structure activity relationship for non-peptide B_2 antagonists has not been studied yet. In this paper, we describe the three dimensional quantitative structure-activity relationship (3D QSAR) of the piperazine derivatives we prepared.

The disclosure of the relationship between physicochemical properties of compounds and their biological activities will minimize the number of compounds synthesized. Especially CoMFA (comparative molecular field analysis) has rapidly become one of the most powerful tools for 3D QSAR studies. CoMFA methodology is based on the assumption that the changes in the biological activities of sample compounds with same pharmacophore correlate with changes in the steric and electrostatic fields of these compounds. In CoMFA, all molecules under investigation are aligned in grid lattice point and the results of the molecular field evaluation are analyzed to correlate with the biological activities. Therefore, the most stable conformation (3D structure) of each compound in the biological pH where the compound reacts is calculated using molecular mechanics. The common pharmacophore of the each compound is aligned on a rectangular grid and the steric and electrostatic fields around them are sampled with the probe atoms, usually sp^3 carbon with +1 charge.

Correspondence to: Hae-Young Park Choo, *School of Pharmacy, Ewha Womans University, Seoul, 120-750, Korea*
E-mail: hypark@mm.ewha.ac.kr

MATERIALS AND METHODS

Molecular modeling

SYBYL 6.5 molecular modeling software (Tripos Inc.) and Silicon Graphics Indy workstation (IRIX 6.2) were used for structure generation and CoMFA. The 2D structure of each compound was built using SYBYL Build program with the default SYBYL settings. The 2D structure was converted to 3D structure using Concord 4.0 program. The structural energy minimization was performed using the SYBYL energy minimizer (Tripos Force Field) and Gasteiger-Huckel charge, with a 0.005 kcal/mol.Å. energy gradient convergence criterion. Low energy conformation was searched by geometry optimization after rotating every 30° of single bond from 1° to 330° of tortional angle. All of the structures generated were aligned into lattice box by fitting with chlorophenyl-

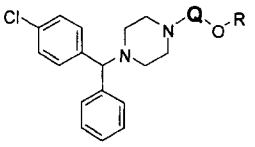
phenylmethylpiperazine group as a common structure.

CoMFA parameters

Conventional CoMFA was performed with the QSAR option of SYBYL. The steric and electrostatic field energies were calculated using sp^3 carbon probe atoms with +1 charge. Maximum energy cutoff for steric and electrostatic energies was 30 kcal/mol. The CoMFA grid spacing was 2.0Å in all three dimensions within the defined region. The partial least squares (PLS) method was used for fitting the 3D structural features and their biological activities. The optimum number of components in the final PLS model was determined by the q^2 value, obtained from the leave-one-out cross validation technique.

RESULTS AND DISCUSSION

Table I. Structures and hydrophobicity(logP) of piperazine deritives



Compound	Q	R	logP
Cetirizine	$-CH_2CH_2-$	$-CH_2COOH$	4.37
1	$-CH_2CH_2-$	$-CH_2CH_2COOH$	4.90
2	$-CH_2CH_2-$	$-CHCOOH$ (with CH_2CH_3)	5.21
3	$-CH_2CH_2-$	$-H_2C-C_6H_4-CH_2COOH$	7.00
4	$-CH_2CH_2-$	$-CHCOOH$ (with phenyl)	6.13
5	$-CH_2CH_2CH_2-$	$-CH_2COOH$	3.89
6	$-CH_2CHCH_2-$ (CH_3)	$-CH_2COOH$	4.38
7	$-CH_2C(CH_3)_2CH_2-$	$-CH_2COOH$	4.78
8	$-CH_2CH_2CH-$ (phenyl)	$-CH_2COOH$	5.87
9	$-CH_2CH-$ (naphthyl)	$-CH_2COOH$	7.31
10	$-CH_2C(CH_3)-$ (phenyl)	$-CH_2COOH$	6.53

QSAR of antihistamine effects

The structure and logP values of synthesized compounds are shown in Table I. The results of the CoMFA analysis of training set composed of 19 compounds prepared and cetirizine are summerized in Table II. The CoMFA field was used as descriptor and the inhibition(%) of histamine-induced contractions of isolated guinia-pig ileum (Choo et al, 1999) as a dependent column. Among the statistical results obtained after CoMFA analysis, a cross validated value q^2 served as a quantitative measure of the predictability of the CoMFA model and q^2 value greater than 0.4 is considered significant (Cho, *et al.*, 1995). For this system good cross validate q^2 (0.532) and conventional r^2 (0.962) were obtained as shown in Table II. This indicates the method was considerably reliable to predict the antihistamine activities of piperazine analogs. However the cross validated q^2 could be higher if the compounds were synthesized enantioselectively. The compounds having stereocenter were synthesized as racemic mixture, but when the structures were generated in computer, the common pharmacophore, chlorophenylphenylmethyl piperazine was assigned as S form. For the compounds which have another stereocenter in the molecule both isomers, R-form and S-form, were generated. But for both isomers only one biological data is available and some error between the stereoisomers is expected.

The contributions of steric and electrostatic fields were 52.3% and 47.7% respectively. However lipophilicity of the compounds (logP) did not show any relationship to activity and excluded from QSAR analysis.

The actual and predicted activities of the training set are reported in Table III and plotted in Fig. 1. The major steric and electrostatic features of the 3D QSAR derived from CoMFA study are illustrated in Fig. 2 as three dimensional solid surfaces. Steric model (Fig. 2a) contours indicate the location of steric bulk that enhances (green) or diminished (yellow) antihistamine activity in this series of compounds. Electrostatic contours model (Fig. 2b) the location of more positive charge (blue) or more negative charge (red) is correlated with higher antihistamine activity. The examples of the terminal bulky group which enhances the antihistamine activity can be found in

Table II . Summary of CoMFA-PLS results of the training set

	Histamine Inhibition Activity	Bradykinin Inhibition Activity
Opt No of Components	4	5
Cross-validated q^2	0.532	0.539
Standard error	5.057	1.263
Conventional r^2	0.962	0.998
F values	101.654	598.693
Steric contribution	52.3%	45.2%
Electronic contribution	47.7%	54.8%

Table III. Actual and Predicted Activites of Training Set for antihistamine effect

No.	CoMFA	Histamine antagonistic effect (% inhibition)		
		Actual	Predicted	Residue
Cetirzine	162	50.7	44.0551	6.6449
1	170	16.7	16.6836	0.0614
2-R	180	10.2	18.0649	-7.8649
2-S	178	10.2	11.102	-0.902
3	202	28.4	25.4492	2.9508
4-R	188	43.7	40.4663	3.2337
4-S	194	43.7	49.0962	-5.3962
6-S	182	14.3	12.0616	2.2384
7	188	42.9	39.6762	3.2238
8-R	194	52.7	52.0769	0.6231
9-R	210	57.0	61.8845	-4.8845
9-S	208	57.0	59.2164	-2.2164
10-R	202	12.5	16.2693	-3.7693
10-S	198	12.5	11.8761	0.6239
12-R	194	62.5	64.488	-1.988
13	202	20.0	13.4939	6.5061
14	200	10.0	18.0914	-8.0914
15	204	77.5	70.4791	7.0209
16	194	78.5	82.4587	-3.9587
18	208	63.0	60.3606	2.6394
19	206	26.4	23.05	3.35

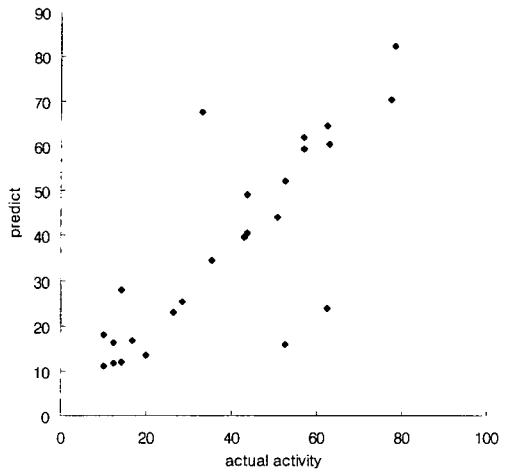


Fig. 1. Experimental *vs* predicted antihistamine activities.

compound 15-18. In a similar case other second generation antihistamines, Terfenadine and Ebastine have the *p-tert*-butylphenyl group in the terminal.

The CoMFA analysis of the test set composed of 6

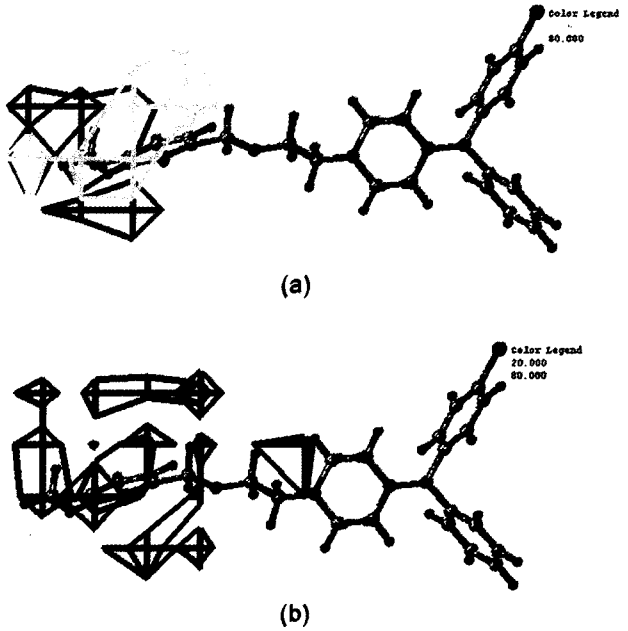


Fig. 2. CoMFA contour plots of antihistamin activity data for piperazine derivatives. (a) Steric model contours indicate the location of steric bulk that enhances (green) or detracts (yellow) the inhibitory activity. (b) Electrostatic model contours indicate the location of electronegative (red) and electropositive (blue) character that enhances the antihistamine activity. Molecule displayed is **15**.

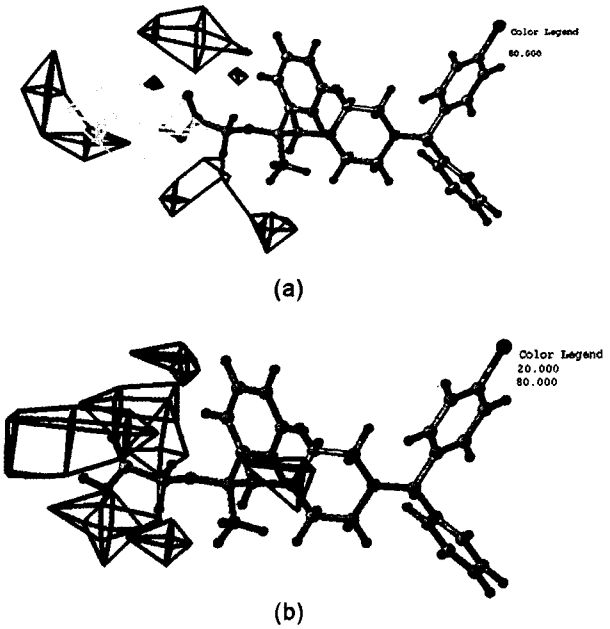


Fig. 4. CoMFA contour plots of antibradykinin activity data for piperazine derivatives. (a) Steric model contours indicate the location of steric bulk that enhances (green) or detracts (yellow) the inhibitory activity. (b) Electrostatic model contours indicate the location of electronegative (red) and electropositive (blue) character that enhances the antibradykinin activity. Molecule displayed is **10.**

Table IV. Actual and Predicted Activities of Test Set for antihistamine effect

No.	CoMFA	Histamine antagonistic effect (% inhibition)		
		Actual	Predicted	Residue
5	166	35.4	34.7379	0.6621
6-R	178	14.3	28.1962	-13.8962
8-S	200	52.7	15.9836	36.7164
12-S	190	62.5	23.9484	38.5516
17	192	33.0	67.5775	-34.5775

piperazine derivatives is reported in Table IV. The compound **5** showed good agreement between actual and predicted values but other compounds revealed considerable gap. The compounds with stereocenter, such as **8** and **12**, showed big difference in predicted values between two stereoisomers and only one isomer was close to actual value. Separate synthesis and activity evaluation of each stereoisomer would have unveiled better fit in this QSAR study. It is well known some but not all chiral antihistamine drugs show stereoselective activity (Cooper *et al.*, 1990) which indicate that specific molecular interactions must occur between drug and receptor.

QSAR of antibradykinin effects

From the results of the CoMFA analysis of training set composed of 20 compounds synthesized, which are summerized in Table II, it could be readly noticed that there are good cross validate q^2 (0.539) and conventional r^2 (0.995) values. This might suggest that this method be considerably reliable to predict the antibradykinin activities of piperazine analogs. The contributions of steric and electrostatic fields were 45.2% and 54.8% respectively. In this case the electrostatic field was the more contributing factor for their activities. However lipophilicity of the compounds (logP) did not show any relationship to activity, thus excluded from QSAR analysis. The actual inhibition(%) of bradykinin-induced contractions of isolated rat ileum (Choo *et al.*,1999) and predicted activities of the training set are reported in Table V and plotted in Fig. 3. The major steric and electrostatic features of the 3D QSAR derived from CoMFA study are illustrated in Fig. 4 as three dimensional solid surfaces. The CoMFA analysis of the test set composed of 8 compounds is reported in Table VI. Compounds **4S, 12S, 13, 18, 19,** and cetirizine showed good agreement in actual and predicted values but compounds **3, 10R** showed some differences.

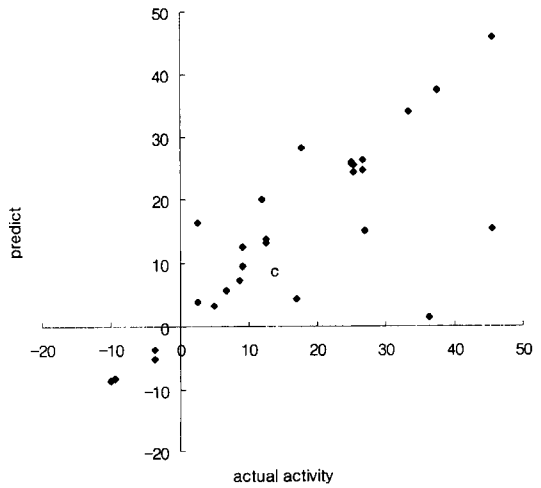


Fig. 3. Experimental *vs* predicted antibradykinin activities

3D QSAR analysis result shown in the Fig. 4 indicates the location of steric bulk (green) and next to piperazine ring as well as the location of electronegative (red) character in the terminal carboxylic acid region enhances antibradykinin activity in this series of compounds. The bulky group next to piperazine ring mimics the phenylalanine 8 of bradykinin (Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg) and hydrophobic pocket in bradykinin B_2 receptor which interacts with bulky group is expected. The non-peptide B_2 antagonist Win 64338 has naphthyl group to mimic

Table V. Actual and Predicted Activities of Training Set for antibradykinin effect

No.	CoMFA	Bradykinin antagonistic effect (% inhibition)		
		Actual	Predicted	Residue
1	170	6.7	5.610	1.09
2-R	180	12.6	13.848	-1.248
2-S	178	12.6	13.097	-0.497
4-R	188	9.1	9.411	-0.311
5	166	37.5	37.528	-0.028
6-R	178	25	25.744	-0.744
6-S	182	25	25.945	-0.945
7	188	33.4	34.082	-0.682
8-R	194	25.4	25.614	-0.214
8-S	200	25.4	24.388	1.012
9-R	210	26.6	24.76	1.84
9-S	208	26.6	26.409	0.191
10-S	198	45.6	45.776	-0.176
11-R	202	-3.7	-3.806	0.106
11-S	206	-3.7	-5.130	1.43
12-R	194	2.6	3.870	-1.27
14	200	-9.5	-8.198	-1.302
15	204	5	3.241	1.759
16	194	8.7	7.218	1.482
17	192	-10	-8.517	-1.483

Table VI. Actual and Predicted Activities of Test Set for antibradykinin effect

No.	CoMFA	Bradykinin antagonistic effect (% inhibition)		
		Actual	Predicted	Residue
Cetirizine	162	27	15.139	11.861
3	202	36.3	1.434	34.866
4-S	194	9.1	12.430	-3.33
10-R	202	45.6	15.371	30.229
12-S	190	2.6	16.406	-13.806
13	202	17	4.337	12.663
18	208	11.9	20.131	-8.231
19	206	17.7	28.202	-10.502

the phenyl group of phenylalanine 8 of bradykinin. The terminal carboxyl group can be compared with the terminal arginine of bradykinin even though the charge was opposite. The distance between the two arginine positive charges separated in bradykinin was reported to be 10 (Salvino *et al.*, 1993) and in Win 64338, the distance between guanine and phosphonium ion is reported to be ca 10. However recently reported strong B_2 antagonist FR 173657 does not carry positive charge in the terminal position. Therefore the terminal charge can be considered to only enhance the activity but not necessary for the activity.

Since only a few non-peptide antagonists are disclosed to date and the structure activity relationship for non-peptide antagonists has not been studied much yet, the 3D QSAR analysis of piperazine derivatives may provide useful informations in the design of new bradykinin antagonists.

CONCLUSION

The CoMFA method has been successfully applied to a set of recently described piperazine derivatives with antihistamine and antibradykinin activities. The resulting 3D QSAR models provide significant correlation of steric and electrostatic fields with the biological activities.

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