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Computer-Aided Design of Negative Allosteric Modulators of Metabotropic Glutamate Receptor 5 (mGluR5): Comparative Molecular Field Analysis of Aryl Ether Derivatives

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Abstract

The metabotropic glutamate receptors (mGlu receptors) have emerged as attractive targets for number of neurological and psychiatric disorders. Recently, mGluR5 negative allosteric modulators (NAMs) have gained considerable attention in pharmacological research. Comparative Molecular Field Analysis (CoMFA) was performed on 73 analogues of aryl ether which were reported as mGluR5 NAMs. The study produced a statistically significant model with high correlation coefficient and good predictive abilities.

Graphical abstract

Keywords

mGluR5; Negative Allosteric Modulators; Aryl ethers; CoMFA; 3-D QSAR

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The metabotropic glutamate receptors (mGlu receptors) have emerged as attractive therapeutic targets for several psychiatric and neurological problems.¹ mGlu are family of eight G-protein-coupled receptors (GPCRs) that are clustered into group 1, group 2 and group 3.² Glutamate (L-glutamic acid) is the major excitatory neurotransmitter in the central nervous system. It binds to the orthosteric binding site of mGluR which are highly conserved. Thus, designing selective compounds targeting the orthosteric binding sites is highly challenging. To overcome the selectivity problems associated with the ligands binding to orthosteric binding sites, allosteric modulators are being developed.^{3,4}

Recently, mGluR5 negative allosteric modulators (NAMs) have gained considerable attention in pharmacological research. To date, numerous acetylenic and non-acetylenic NAMs have been identified.^{1,5-10} The recent revelation of the crystal structures of mGluR5 bound with NAMs explains the crucial interactions.^{10,11} Previous study provided structure activity relationship on many mGluR5 NAMs. mGluR5 negative allosteric modulators (NAMs) have now entered human clinical trials. Mavoglurant (Novartis) has completed phase III trial and basimglurant (Roche) (Figure 1) has completed phase II trial.^{12,13} Clinical trials with Dipraglurant (Addex), is ongoing. Despite the huge amount of work, there is no comprehensive report on quantitative structure activity relationship study of mGluR5 NAMs in the literature.

Our aim was to develop predictive QSAR models using comparative molecular field analysis (CoMFA).

We have been involved in the design of COX-2 inhibitors,¹⁴⁻¹⁷ HMGCR inhibitors¹⁸ using 3-D QSAR studies. In this study, CoMFA¹⁹ was applied to a series of mGluR5 NAMs belong to aryl ethers. The predictive ability of the models was validated by using external test set of molecules.

To develop 3-D QSAR models for mGluR5 NAMs, we selected a series of aryl ethers⁷ that encompasses compounds with structural diversity and wider range (pIC₅₀ range: 4.5-8.13) of biological activity. The chemical structures and pIC₅₀ values of the compounds used for the present study are given in Table 1. We used sybyl²⁰ software (X2.1.1) of Tripos Inc for molecular modeling and 3-D QSAR studies. Tripos force field, Powell method including Geometry optimization was done using Tripos force field, Powell method²¹ including Gasteiger-Hückel method. Out of 73 molecules, training set was constructed by taking 58 molecules and the remaining molecules were used as test compounds. We used “random” option during the CoMFA in order to select test set of molecules and many such trials were attempted till we get statistically significant models. We finally ensured that the selected molecules for test set have enough structural diversity and wider range of pIC₅₀ values. One of the most active molecules (**78**) was subjected to conformational analysis. The lowest energy conformation was used as a template. All other compounds were built by incorporating appropriate structural modifications on the template followed by minimization using Tripos force field.

Molecular alignment was performed using database alignment method by taking the most active molecule **78**. Molecular alignment was done by taking the common fragment shown

in figure 2a and the alignment is shown in figure 2b. Standard procedures were followed to generate the CoMFA fields.¹⁹ The partial least square (PLS) algorithm with leave-one-out method was used to find out the cross validated r^2 (Q^2). The statistical metrics are given in table 2. The cross validated r^2 (Q^2) was found to be 0.628 and the conventional R^2 value was found to be 0.925.

The abilities to predict the molecules that were not included in training the models were assessed by predicting the biological activities of test set molecules. Predictive r^2 was calculated using the following formula.¹⁴

$$r^2_{\text{predictive}} = \frac{SD - \text{PRESS}}{SD}$$

The CoMFA method generated the contour plots of steric and electrostatic interactions which are depicted in Figure 3. Green- and yellow-colored contours represent the steric interactions. Bulky substituents in the regions shaded green are likely to enhance biological activity. A green contour near the meta position of the phenyl core characterizes the regions where bulky substituents would increase the activity. The predicted activities from the CoMFA model for the molecules with substitutions on phenyl ring at meta position, **24-31**, are in reasonable agreement with the actual activity. Green-shaded regions located near the amino aryl/heteroaryl rings indicate that substituents (6th position, series V, VI and 4th position of series IV) on this ring would enhance the biological activity. The predicted activities from the model for compounds having substituents on pyridyl ring (next to amide) at 6th position, **64-70, 76, 78, 80** and for compounds having substituents on thiazole ring at 4th position, **33, 35, 38** and **40** are in reasonable agreement with the actual activity. Model failed to predict the activities of three compounds, namely, **44, 56**, and **60**. These three molecules can be treated as outliers. **44** and **56** are the only two compounds in the selected data set having substituent in 3rd position of the pyridyl ring that may be the reason for the incorrect predictions.

The electrostatic fields based on PLS analyses are represented by blue and red contours (Figure 3). Red-shaded region near the meta position of the ether linked pyridyl ring suggest that the electronegative substituents are likely to enhance biological activity. The predicted activities of compounds with fluorine and nitrile substituents, **77-80**, are good. Electropositive substituents in the regions shaded blue are likely to boost biological activity. Blue-shaded regions near the amide pyridyl ring indicate that the electropositive substituents are likely to enhance biological activity. The predicted activities from the model for the molecules **33, 46, 59, 66, 76, 78** and **80** are in reasonable agreement with the actual activity. Similarly, another blue contour near the meta position of the amide phenyl ring characterizes the region where electropositive substituents would increase the activity. The predicted activity of compound **29** is good. Figure 4 shows a plot between actual and predicted activities of all the molecules.

In summary, CoMFA of 73 analogues of aryl ethers produced good model with high predictive ability. The resulted contour maps highlight the structural features pertinent to

biological activities. The information gathered from this study might be useful to expand the design and development of novel mGluR5 NAMs. The current study is purely of ligand based approach, understanding the active site interactions and prediction of binding mode are currently undergoing that will be published in near future.

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Figure 1.
Structures of some known NAMs of mGluR5

Figure 2.
(a) Common fragment used for alignment (b) Aligned molecules.

Figure 3. CoMFA steric and electrostatic contour plots (STDEV*COEFF). Molecule **78** is displayed in the background for reference

Figure 4.
Plot between actual and predicted inhibitory activities (pIC₅₀) for all the molecules

Table 1

The structures and actual and predicted inhibitory activities

No	Series	R1	R2	A	Actual pIC ₅₀	Pred pIC ₅₀	Residual	Set
3	I				5.71	5.73	-0.02	TR
9	I				5.66	5.23	0.43	TR
10	I				6.07	5.82	0.25	TR
11	I				<5.0	5.25	-0.25	TR
12	I				6.45	6.23	0.22	TS
13	I				<5.0	4.70	0.30	TR

No	Series	R1	R2	A	Actual pIC ₅₀	Pred pIC ₅₀	Residual	Set
14	I				5.73	5.67	0.06	TR
15	I				5.44	5.41	0.03	TR
16	I				5.17	5.35	-0.18	TR
17	I				<5.0	5.06	-0.06	TR
18	I				6.11	6.32	-0.21	TR
19	I				<4.5	4.19	0.31	TR
20	I				<4.5	4.63	-0.13	TR
21	I				<4.5	4.47	0.03	TR

No	Series	R1	R2	A	Actual pIC ₅₀	Pred pIC ₅₀	Residual	Set
22	I				<4.5	5.06	-0.56	TS
23	II	H			6.69	7.22	-0.53	TR
24	II	F			7.62	7.43	0.19	TR
25	II	Cl			7.94	7.99	-0.05	TR
26	II	CF ₃			6.55	6.50	0.05	TR
27	III	F			6.52	6.42	0.10	TR
28	III	Cl			7.49	6.97	0.52	TR
29	III	CH ₃			7.72	7.57	0.15	TS
30	III	CF ₃			5.26	5.48	-0.22	TR
31	III	CN			6.50	6.35	0.15	TR
32	IV	H	F		5.75	6.21	-0.46	TR
33	IV	4-(C ₃ H ₅)	F		6.62	5.78	0.84	TS
34	IV	4-CH ₃ , 5-F	F		7.27	7.17	0.10	TR
35	IV	4-CH ₂ F	F		6.66	6.75	-0.09	TR
36	IV	4-CHF ₂	F		5.66	5.82	-0.16	TS
37	IV	4-CF ₃	F		5.49	5.77	-0.28	TS
38	IV	4-(C ₃ H ₅)	Cl		7.09	6.35	0.74	TS
39	IV	4-CH ₃ , 5-F	Cl		7.44	7.72	-0.28	TS
40	IV	4-CH ₂ F	Cl		7.01	7.31	-0.30	TS
41	IV	4-CHF ₂	Cl		6.51	6.37	0.14	TR
42	IV	4-CF ₃	Cl		6.68	6.34	0.34	TR
43	V	H	F		7.02	6.94	0.08	TR
44	V	3-F	F		<5.0	6.90	-1.90	Outlier
45	V	4-Cl	F		7.38	6.77	0.61	TR
46	V	4-CH ₃	F		6.67	6.34	0.33	TR
47	V	4-CF ₃	F		5.98	5.49	0.49	TR
48	V	5-Cl	F		5.97	6.33	-0.36	TS

No	Series	R1	R2	A	Actual pIC ₅₀	Pred pIC ₅₀	Residual	Set
49	V	5-CN	F		<4.5	4.60	-0.10	TR
50	V	6-F	F		6.59	7.13	-0.54	TR
51	V	6-Cl	F		7.35	7.15	0.20	TR
52	V	6-OCH ₃	F		6.18	6.17	0.01	TR
53	V	6-CHF ₂	F		6.83	6.68	0.15	TR
54	V	6-CF ₃	F		5.64	5.99	-0.35	TR
55	V	H	Cl		7.77	7.46	0.31	TR
56	V	3-F	Cl		<5.0	7.41	-2.41	Outlier
57	V	4-F	Cl		6.47	6.55	-0.08	TR
58	V	4-Cl	Cl		6.77	7.33	-0.56	TR
59	V	4-CH ₃	Cl		6.85	6.84	0.01	TR
60	V	4-CH ₂ CH ₃	Cl		5.35	7.05	-1.70	Outlier
61	V	4-CF ₃	Cl		5.36	5.92	-0.56	TR
62	V	5-Cl	Cl		6.99	6.85	0.14	TR
63	V	5-CF ₃	Cl		<4.5	4.59	-0.09	TR
64	V	6-F	Cl		8.00	7.66	0.34	TR
65	V	6-Cl	Cl		7.86	7.67	0.19	TR
66	V	6-CH ₃	Cl		7.75	7.71	0.04	TR
67	V	6-CH ₂ F	Cl		7.74	7.62	0.12	TR
68	V	6-CHF ₂	Cl		7.44	7.16	0.28	TR
69	V	6-CF ₃	Cl		6.51	6.55	-0.04	TR
70	V	6-OCH ₃	Cl		7.27	7.28	-0.01	TS
71	V	4-CH ₃ , 5-F	Cl		5.49	6.19	-0.70	TR
72	V	5-F, 6-CH ₃	Cl		7.30	7.28	0.02	TR
73	V	5-F, 6-CH ₂ F	Cl		6.84	6.76	0.08	TR
74	V	5-F, 6-CHF ₂	Cl		6.30	6.78	-0.48	TR
75	VI	5-F	CH ₃	N	5.35	6.08	-0.73	TS
76	VI	6-CH ₃	CH ₃	N	7.02	6.87	0.15	TR
77	VI	5-F	H	CF	7.61	7.44	0.17	TR
78	VI	6-CH ₃	H	CF	8.13	8.45	-0.32	TR

No	Series	R1	R2	A	Actual pIC ₅₀	Pred pIC ₅₀	Residual	Set
79	VI	5-F	H	CCN	7.57	7.51	0.06	TR
80	VI	6-CH ₃	H	CCN	7.99	8.30	-0.31	TR

Table 2

The summary of the results of CoMFA

	CoMFA
r ² _{cv}	0.628
NOC	8
r ² _{Conv}	0.925
SEE	0.311
r ² Pred	0.762