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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 analogs of aryl ether which were reported as mGluR5 NAMs. The study produced a statistically significant model with high correlation coefficient and good predictive abilities.

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The metabotropic glutamate receptors (mGlu receptors) have emerged as attractive therapeutic targets for several psychiatric and neurological problems.[1] mGlus 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. Todate, 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) (Fig. 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] HMGR inhibitors[18] using 3-D QSAR studies. In this study, CoMFA[19] 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 ethers[7] that encompasses compounds with structural diversity and wider range (pIC_{50} range: 4.5–8.13) of biological activity. The chemical structures and pIC_{50} values of the compounds used for the present study are given in Table 1. We used sybyl[20] software (X2.1.1) of Tripos Inc for molecular modeling and 3-D QSAR studies. Geometry optimization was done using Tripos force field, Powel method[21] 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

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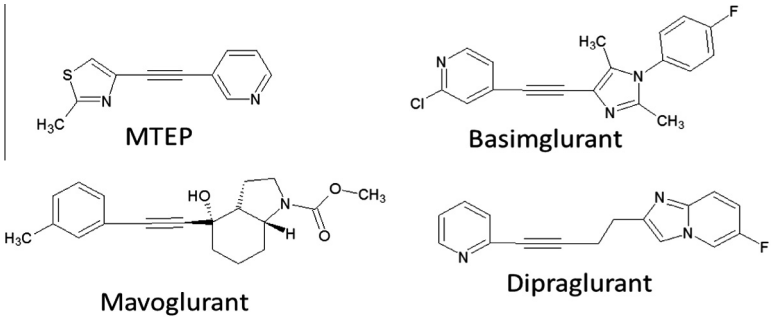
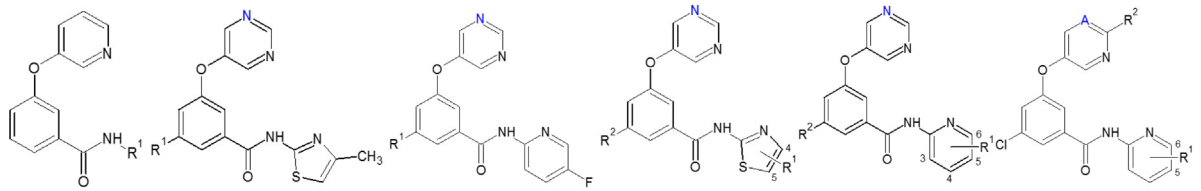
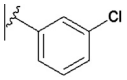
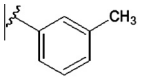
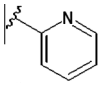
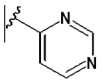
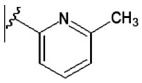
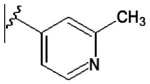
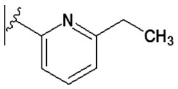
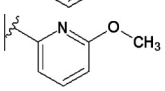
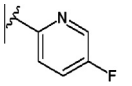
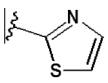
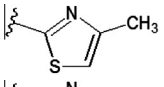
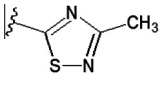


Figure 1. Structures of some known NAMs of mGluR5.

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
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

(*continued on next page*)