NEW HETEROCYCLIC DERIVATIVES AS POTENTIAL ALLOSTERIC MODULATORS OF GROUP III METABOTROPIC GLUTAMATE RECEPTORS

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Introduction

Allosteric modulation of metabotropic glutamate receptors is new and attractive approach in research of safer treatments for central nervous system diseases. Main advantages of allosteric mechanism, over traditional orthosteric agonists/antagonists, is that they exert their effects only in the presence of the endogenous ligand, and provides the possibility for more selective interaction with different subtypes of mGluR family[1]. In group III of mGluR, mGluR4 is belived to be the most interesting drug target for the treatments of Parkinson's disease.[2] Our research focuses on finding new potential allosteric modulators of mGluR4 based on heterocyclic core.

Pharmacophore modelling

Exploration of potential allosteric modulators of mGluR4 was initiated by creating a database of known group III mGluR ligands. From among more than 500 active compounds six leading structures (**A-F**)[3] with the highest activity for mGluR4 were selected.

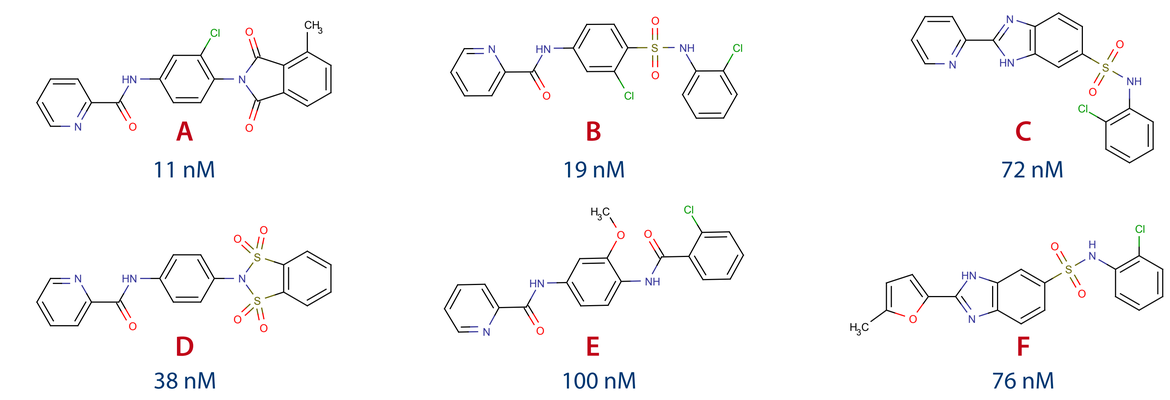
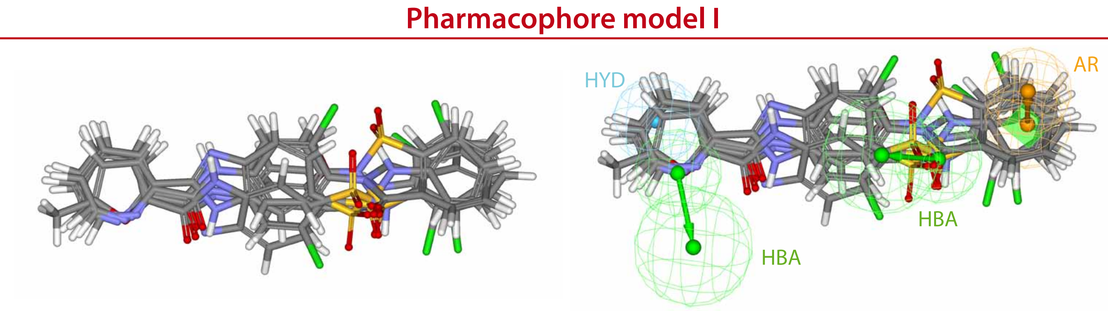


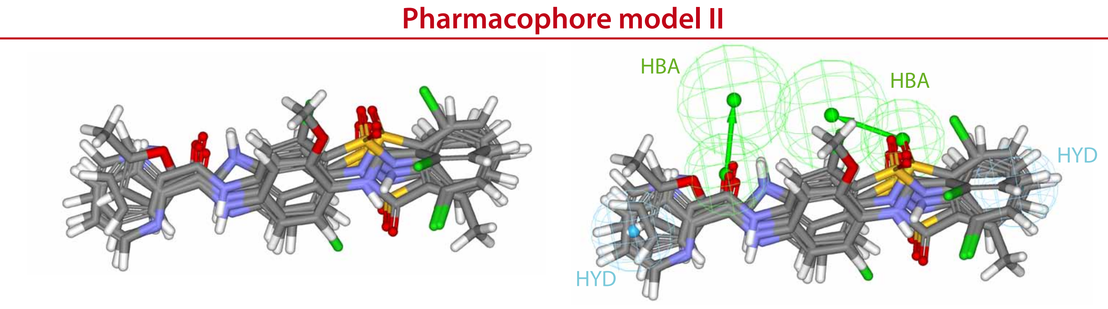
Figure 1. Structure and activity of selected mGluR4 ligands used in pharmacophore generation protocol

Using *Common Feature Pharmacophore Generation* protocol in Accelrys Discovery Studio 2.5 software three sets of pharmacophore models based on leading compounds **A-F** were generated.

Pharmacophore model I



Pharmacophore model II



Pharmacophore model III

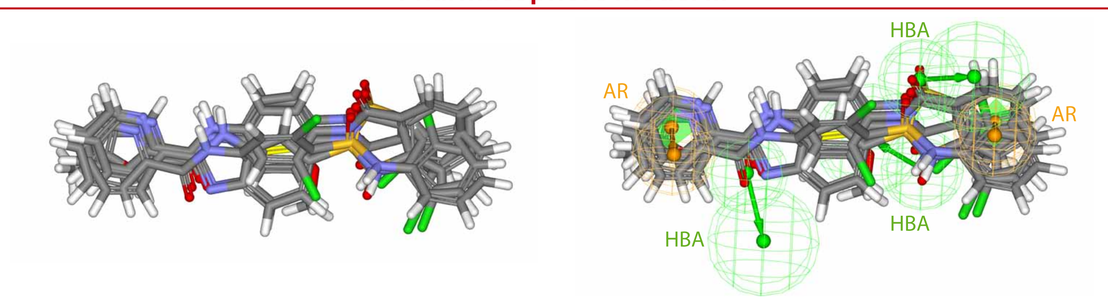
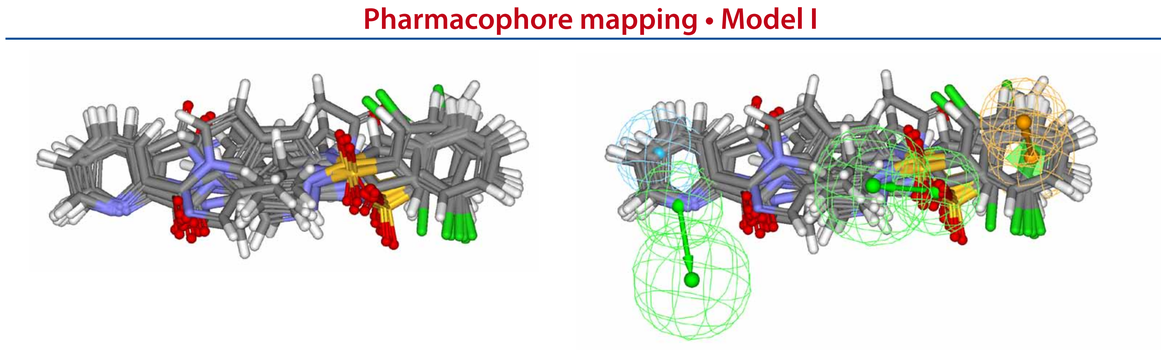


Figure 2. Pharmacophore models based on mGluR4 allosteric modulators A-F.
AR - *aromatic*, HBA - *hydrogen bond acceptor*, HYD - *hydrophobic* feature.

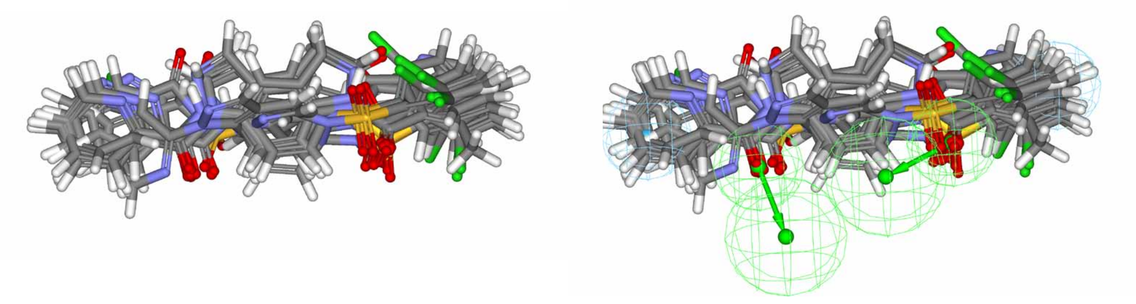
Ligand pharmacophore mapping

Designed heterocyclic derivatives have been mapped independently to the mGluR4 models I-III (Figure 3.) and the results of mapped conformers and FitValue are summarized in Table 1.

Pharmacophore mapping • Model I



Pharmacophore mapping • Model II



Pharmacophore mapping • Model III

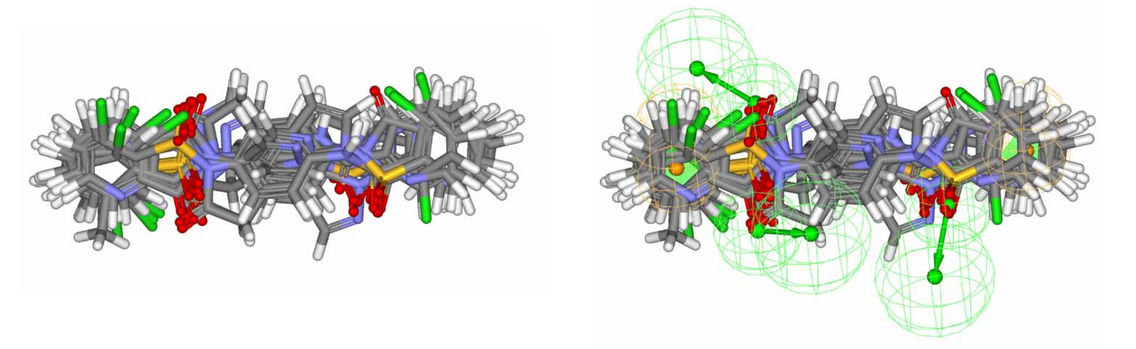


Figure 3. Series of 14 designed compounds mapped to generated pharmacophore models

Compound [total conformers]	Model I		Model II		Model III	
	mapped conformers	FitValue [%]	mapped conformers	FitValue [%]	mapped conformers	FitValue [%]
1 [156]	93	0.99	121	0.99	60	0.92
2 [134]	102	0.98	28	0.99	6	0.80
3 [136]	90	0.99	62	0.99	42	0.81
4 [113]	86	0.98	91	0.99	52	0.98
5 [55]	21	0.98	37	0.99	24	0.91
6 [102]	70	0.99	9	0.99	92	0.79
7 [60]	38	0.98	16	0.99	25	0.79
8 [85]	61	0.99	17	0.99	25	0.98
9 [58]	35	0.99	39	0.98	39	0.98
10 [86]	54	0.93	32	0.94	32	0.94
11 [71]	67	0.84	8	0.70	63	0.56
12 [47]	42	0.84	34	0.66	42	0.80
13 [47]	35	0.82	29	0.73	24	0.61
14 [105]	99	0.96	105	0.90	99	0.89

Table 1. FitValue for designed compounds

Conclusions

Designed heterocyclic compounds were mapped into three pharmacophore models of mGlur4 active modulators and showed high level of FitValue. The compounds with the highest number of mapped conformers and best FitValues will be synthesised and tested for activity toward mGlu4 receptor.

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References

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