1,2,4-OXADIAZOLE DERIVATIVES AS POTENTIAL ALLOSTERIC MODULATORS OF THE mGluR4

Anna Stankiewicz[a], Ryszard Bugno[a], Piotr Brański[b], Andrzej J. Bojarski[a]

[a]Department of Medicinal Chemistry, [b]Department of Neurobiology
Institute of Pharmacology Polish Academy of Sciences,
12 Smętna Street, 31-343 Cracow, Poland

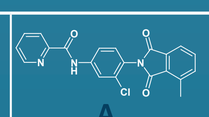
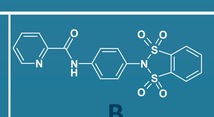
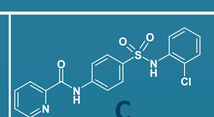
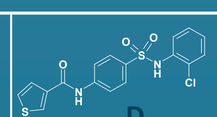
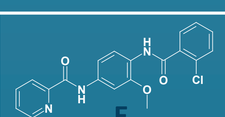
INTRODUCTION

Metabotropic glutamate receptors (mGluRs) are members of the group C family of G-protein-coupled receptors (GPCR) and play important roles in a broad range of central nervous system functions having therapeutic potential in a variety of neurological and psychiatric disorders such as Alzheimer's disease, Parkinson's disease, anxiety, depression, and schizophrenia [1]. MGluR's are cathegorized into three families based on their receptor structure and physiological activity. Metabotropic glutamate receptor 4 (mGluR4) is a member of the group III family negatively coupled to adenylate cyclase [2]. Until 2009 a very few positive allosteric modulators (PAM's) of mGluR4 (e.g. (-)-PHCCC and VU0155041) have been extensively studied [3]. Recently a significant progress has been made in determining the allosteric ligands that can modulate mGluR4 activity [4].

PHARMACOPHORE MODELS

Among known mGluR4 potentiators five representative compounds were chosen as a training set for pharmacophore model generation. Selection was made based on their structure similarity in functional group alignment combined with high declared activity (11nM – 269nM) [4]. After geometry optimization in Generate Conformations protocol (energy threshold - 20 kcal/mol) a set of ten five-point pharmacophore models was calculated in Common Feature Pharmacophore Generation protocol (Accelrys Discovery Studio) (Table 1).

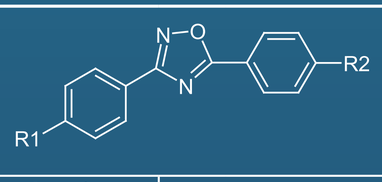
Table 1. Structures of model compounds combined with fitting values for all generated pharmacophore models.

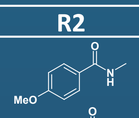
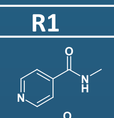
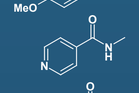
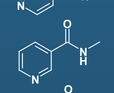
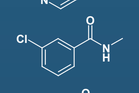
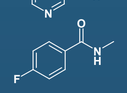
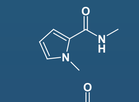
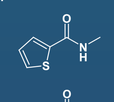
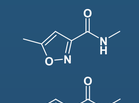
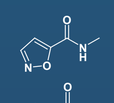
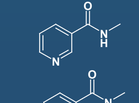
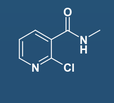
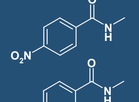
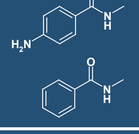
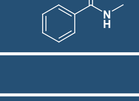
	 A 11 nM 19 conformers	 B 35 nM 11 conformers	 C 27 nM 101 conformers	 D 269 nM 91 conformers	 E 100 nM 49 conformers
Model No.	**Fit Values (Max fit = 5)** Generated features: HB DONOR – 2, RING AROMATIC – 3				
1	2.748	3.372	5.000	3.973	3.482
2	4.274	3.155	5.000	3.866	4.008
3	2.606	3.609	5.000	3.945	3.353
4	3.378	3.785	5.000	3.949	3.271
5	4.329	3.977	5.000	3.908	4.568
6	4.246	3.734	5.000	3.942	4.078
7	4.276	4.633	4.694	5.000	3.854
8	4.050	4.642	4.691	5.000	4.358
9	2.841	4.726	4.726	5.000	3.824
10	3.046	4.499	4.680	5.000	3.513

NEW STRUCTURES

A new series of potential mGluR4 PAM's was designed. 1,2,4-oxadiazole ring was used as a bioisoster of amide and sulphonyl bond (Table 2). All compounds were examined in Ligand Pharmacophore Mapping protocol (Accelrys Discovery Studio) with implementation of chosen pharmacophore model 8 which was characterized by the highest fit values for all leading structures A-E (FV = 4.050 – 5.000).

Table 2. Structures of designed compounds with results of fitting to pharmacophore model 8.



	R1	R2	Fit Value		R1	R2	Fit Value
1	H		0.9810	**10**		MeO	0.9847
2	H		0.9861	**11**		MeO	0.9845
3	H		0.9851	**12**		MeO	0.9853
4	H		0.9859	**13**		MeO	0.9859
5	H		0.9851	**14**		F	0.9836
6	H		0.9863	**15**		F	0.9858
7	H		0.9864				
8	H		0.9855				
9	H		0.9856				

REFERENCES

[1] (a) J.P. Pin et al. *Pharmacol. Ther.* **2003**, *98*, 325-354, (b) C.M. Niswender et al. *Curr. Top. Med. Chem*. **2005**, *5*, 847-857, (c) C.M. Niswender, J.P. Conn, *Ann. Rev. Pharmacol. Toxicol.* **2010**, *50*, 295-322, (d) S. Urwyler *Pharmacol. Rev*. **2011**, *63*, 59-126, [2] P.J. Conn, J.P. Pin, Annu. *Rev. Pharmacol. Toxicol.* **1997**, *37*, 205–237, [3] (a) M. Maj, P.J. Flor et al. *Neuropharmacology* **2003**, *45*, 895, (b) P.J. Conn et al. *Proc. Natl. Acad. Sci.* **2003**, *100*, 13668, (c) P.J. Conn et al. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4967–4970, [4] (a) C.M. Nieswander et al. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 962–966, (b) S.P. East, Gerlach et al. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 4901–4905, (c) C.M. Niswender et al. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5175–5178, (d) P.J. Conn, C.M. Niswender et al. *J. Med. Chem.,* **2011**, *54*, 1106–1110, (e) Merck & co. Inc. **WO2010/33349A1**.

Figure 1a. Pharmacophore model 8 aligned with structure of model compound C (FitValue = 0.9938).

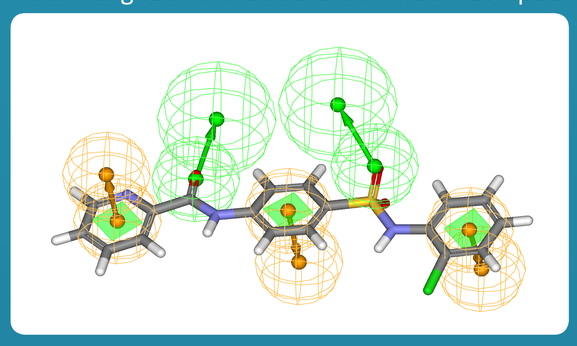
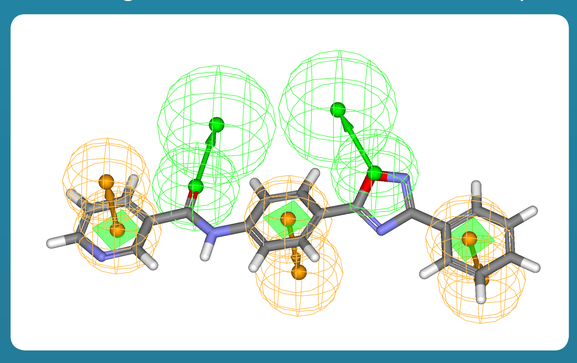


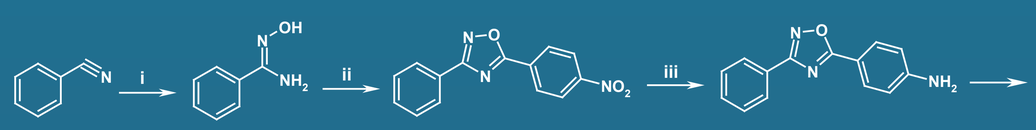
Figure 1b. Pharmacophore model 8 aligned with structure of model compound 6 (FitValue = 0.9863).

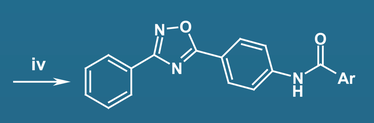


SYNTHESIS

Synthesis of all compounds was performed according to two synthetic pathways outlined in Scheme 1 (compounds 1-9) and Scheme 2 (compounds 10-15). In both methods in the first step an appropriate aminoxime was formed, followed by condensation with aromatic acid chloride to obtain corresponding substituted 1,2,4-oxadiazole. Further reduction of nitro group to primary amine and finally amide formation gave expected products.

Scheme 1. Conditions: i) $NH_2OH{\cdot}HCl$, NaOHaq, EtOH, 1.5h, reflux, 80%; ii) p-NO_2-benzoyl chloride, K_2CO_3, toluene, MW, 170^{0}C, 10 min, 80%; iii) Fe, CH_3COOH 90%, EtOH, 60^{0}C, 2h, 65%; iv) ArCOCl, py, RT, 12h; v) Fe, CH_3COOH 90%, EtOH, 60^{0}C, 2h, 74%.

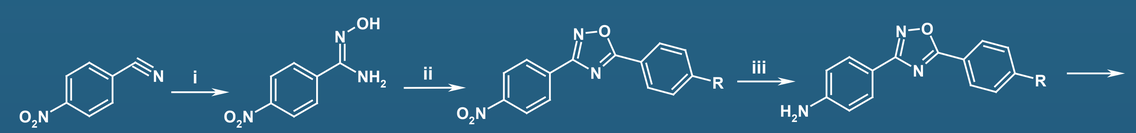


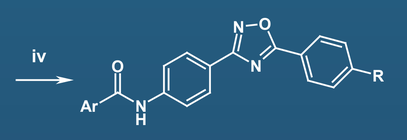


	Ar
1	4-MeO-C_6H_4, 97%
2	4-pirydyl, 90%
3	3-Cl-C_6H_4, 92%
4	N-methyl-1-pyrrol-2-yl, 76%
5	5-methyl-1,2-oxazol-3-yl, 99%
6	3-pirydyl, 90%
7	4-NO_2-C_6H_4, 97%
8	4-NH_2-C_6H_4, 74%
9	C_6H_5, 94%

v

Scheme 2. Conditions: i) $NH_2OH{\cdot}HCl$, NaOHaq, EtOH, 1h, reflux, 76%; ii) RC_6H_4COCl, K_2CO_3, toluene, MW, 1700C, 10 min; iii) Fe, CH_3COOH 90%, EtOH, 60^{0}C, 1h; iv) ArCOCl, py, RT, 12h.





	R	Ar
10	MeO	4-pirydyl, 93%
11	MeO	3-pirydyl, 89%
12	MeO	4-F-C_6H_4, 73%
13	MeO	2-thienyl, 71%
14	F	1,2-oxazol-5-yl, 70%
15	F	2-Cl-3-pirydyl, 71%

PHARMACOLOGYCAL ACTIVITY

All synthesized compounds are tested toward mGluR4 potentiation activity. Results of these studies are under development.

CONCLUSIONS

Based on selected known mGluR4 potentiators a set of five-point pharmacophore models was generated. Model with the highest fitting coefficients was applied to design a group of new compounds bearing 1,2,4-oxadiazole moiety. Finally synthesis of all invented structures was carried out. Testing for activity of presented compounds as an mGlur4 PAMs is currently in progress.

ACKNOWLEDGEMENTS

This study is supported by project UDA-POIG.01.03.010-12-100/08-00 "*Allosteric modulation – new strategy in pharmacotherapy. Identification of psychotropic properties of glutamatergic receptor ligands group III*" co-financed by European Union from the European Fund of Regional Development (EFRD).

ModAll

INNOWACYJNA GOSPODARKA
NARODOWA STRATEGIA SPÓJNOŚCI

UNIA EUROPEJSKA
EUROPEJSKI FUNDUSZ ROZWOJU REGIONALNEGO