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Synthesis and biological evaluation of fenobam analogs as mGlu5 receptor antagonists

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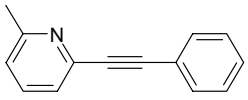
Abstract—Optimization of affinity and microsomal stability led to identification of the potent, metabolically stable fenobam analog **4l**. Robust in vivo efficacy of **4l** was demonstrated in four different models of anxiety. Additionally, a ligand based pharmacophore alignment of fenobam and MPEP is proposed.

L-Glutamate, the major excitatory amino acid neurotransmitter in the central nervous system, binds to and activates several classes of receptors, which are divided into two groups termed ionotropic (iGlu) and metabotropic glutamate receptors (mGlu).[1] The mGlu receptors are classified based on their homology, pharmacology, and second messengers in three groups.[2] The mGlu5 receptor belongs to group I mGlu receptors, which are coupled to phospholipase C leading to the activation of phosphoinositide (PI) hydrolysis and elevation of Ca^{2+} levels. The high expression of mGlu5 receptor in the limbic areas of the brain suggests a potential role of this receptor in psychiatric disorders, such as anxiety.



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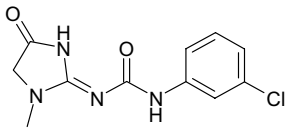

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MPEP (2-methyl-6-(phenylethynyl)-pyridine) **1** has been reported to be an mGlu5 receptor antagonist and acts via an allosteric binding site located in the transmembrane domain.[3] MPEP is active in a wide range of preclinical anxiety models such as the stress-induced hyperthermia, Vogel conflict and plus maze test.[4]

We have serendipitously discovered in a screening campaign that fenobam [*N*-(3-chlorophenyl)-*N*′-(4,5-dihydro-1-methyl-4-oxo-1*H*-imidazole-2-yl)urea] **2** is a potent, subtype-selective, and non-competitive mGlu5 receptor antagonist.[5] Fenobam entered clinical trials for anxiety in the late seventies and proved to be similarly active as benzodiazepines in a double blind placebo-controlled clinical trial, but did not show the same liabilities such as ethanol interaction and sedation.[6]

With studies using point mutated mGlu5 receptors and 3-D receptor pharmacophore-based modeling, we have demonstrated recently that the two structurally diverse allosteric antagonists MPEP and fenobam have similar contact sites on the mGlu5 receptor binding crevice.[7]

In this paper, we would like to report a SAR of fenobam analogs[8] and to propose a ligand based pharmacophore alignment of fenobam and MPEP. In addition, we describe the biological evaluation of fenobam analog **4l** with improved metabolic stability.

To establish a SAR, we decided to vary the 3-chlorophenyl substituent of fenobam. Synthesis was accomplished by either direct condensation of creatinin with the corresponding aniline in the presence of CDI or via a stepwise

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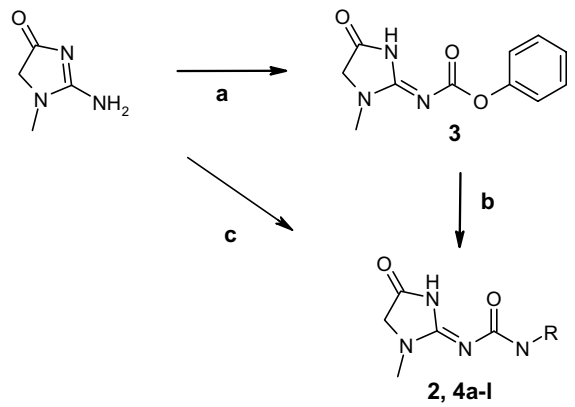


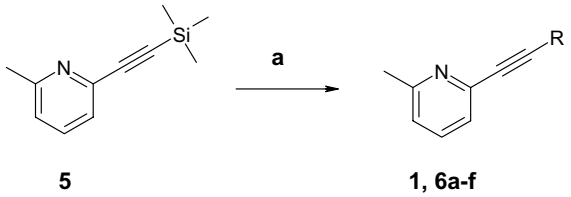
Scheme 1. Synthesis of fenobam analogs **2**, **4a**–**l**. Reagents and conditions: (a) phenylchloroformate, THF, reflux, 17%; (b) aniline, DMF, 50 °C, 30–70%; (c) aniline, CDI, DMF, 90 °C or reflux, 20–65%, 1% for **4b**.

procedure using the phenoxycarbamate intermediate **3** (Scheme 1).

To allow a direct comparison with the SAR of MPEP, we also synthesized a representative subset of MPEP analogs varying the phenyl substituent via Sonogashira coupling reaction using intermediate **5**[9] (Scheme 2).

The fenobam analogs show a steep structure–activity relationship. The 3-chloro substituent is of crucial importance and the unsubstituted phenyl analog is significantly less active. Shifting the chloro substituent to the ortho- and para-position also leads to a drop in affinity. The 2- and 4-pyridine derivatives maintain some activity, whereas the 3-pyridine derivative is inactive (Table 1). Hepatic stability (determined in vitro using rat and human liver microsomes) is low for fenobam, an observation that can be rationalized by assuming hydroxylation of the para-position on the phenyl.[10] The more polar pyridine derivatives **4d**–**f** show a higher microsomal stability (Table 1).

In the MPEP series modifications of the phenyl ring are much better tolerated at the mGlu5 receptor compared to fenobam analogs. In particular, the influence of the 3-chloro substituent is of lower importance than for fenobam and a chloro substituent in the 2-position is also tolerated (Table 2). Nevertheless, the SAR of the MPEP derivatives shows some qualitative overlap with fenobam analogs as, for example, the 3-chloro derivatives are most potent whereas the 4-chloro derivatives



Scheme 2. Synthesis of MPEP derivatives **1**, **6a**–**f**. Reagents and conditions: (a) ArI, CuI, Bu_4NF; $Pd(PPh_3)Cl_2$, PPh_3, triethylamine, THF, 50 °C, 36–80%.

Table 1. Binding affinity and functional activity of fenobam analogs **2**, **4a**–**f**

Compound	R	3H-MPEP (nM)	FLIPR (nM)	CL (r/h) (μl/min/mg prot)
4a	Ph	1360	3300	—
4b	2-Cl–Ph	2520	6800	—
2	3-Cl–Ph	61	38	44/100
4c	4-Cl–Ph	>5000	>5000	—
4d	2-Py	587	1100	22/47
4e	3-Py	>5000	>5000	5/20
4f	4-Py	1120	>5000	9/11

Table 2. Binding affinity and functional activity of MPEP analogs **1**, **6a**–**f**

Compound	R	3H-MPEP (nM)	FLIPR (nM)
1	Ph	4	29
6a	2-Cl–Ph	5	15
6b	3-Cl–Ph	3	7
6c	4-Cl–Ph	286	1020
6d	2-Py	39	400
6e	3-Py	10	66
6f	4-Py	26	213

are least potent in both series. Substitution of the phenyl ring by a pyridine in the MPEP series leads only to a moderate drop in affinity, which is less pronounced than substitution of the 3-Cl-phenyl ring by a pyridine in the fenobam series. We believe that the similarities in the SAR of fenobam and MPEP support the hypothesis that the phenyl ring of MPEP and the 3-chloro phenyl substituent of fenobam occupy a similar position in the allosteric mGlu5 binding site. A ligand based pharmacophore model supporting this hypothesis is proposed further below (see modeling section).

As mentioned above, a substituent in the meta-position clearly increases affinity in the fenobam series. We therefore investigated the influence of a chloro- or methyl-substituent in combination with ortho- or para-pyridine moieties (Table 3). Interestingly, the influence of the meta substituents is less pronounced than for the phenyl substituents, but in case of the ortho pyridine derivatives **4g** and **4i** compounds with improved potency were obtained. Microsomal clearance is medium to high for these compounds in both rat and human, and is higher than for the respective para pyridine derivatives **4h** and **4j**. This observation is again in line with a potential hydroxylation of the para-position for the ortho pyridine derivatives. To prove the theory of oxidative

Table 3. Binding affinity, functional activity, and microsomal stability of fenobam analogs **4g**–**l**

Compound	R	3H-MPEP (nM)	FLIPR (nM)	CL (r/h) (μl/min/mg prot)
4g	3-Cl-2-Py	166	—	53/42
4h	3-Cl-4-Py	663	—	31/15
4i	3-Me-2-Py	320	681	37/29
4j	3-Me-4-Py	2670	1600	14/2
4k	3-Thienyl	700	4016	–/–
4l	5-Cl-3-thienyl[11]	78	434	27/55