Hit-to-lead optimization of disubstituted oxadiazoles and tetrazoles as mGluR5 NAMs

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ABSTRACT

Here we report the discovery and early SAR of a series of mGluR5 negative allosteric modulators (NAMs). Starting from a moderately active HTS hit we synthesized 3,5-disubstituted-oxadiazoles and tetrazoles as mGluR5 NAMs. Based on the analysis of ligand efficiency and lipophilic efficiency metrics we identified a promising lead candidate as a starting point for further optimization.

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Glutamate is a major excitatory neurotransmitter in the mammalian central nervous system (CNS) and binds to neurons in the CNS, thereby activating cell surface receptors. These receptors can be divided into two major classes, ionotropic and metabotropic glutamate receptors, based on the structural features of the receptor proteins.

Metabotropic glutamate receptors are a family of eight G-protein coupled receptors which are classified into three groups according to their sequence homology, effector coupling and pharmacology. Group I mGlu receptors (mGluR1 and mGluR5) are positively coupled to phospholipase C; group II mGlu receptors (mGluR2 and mGluR3) and group III mGlu receptors (mGluR4, mGluR6, mGluR7 and mGluR8) are negatively coupled to adenylate cyclase.[1]

Activation of group I mGlu receptors leads to a transient increase in intracellular calcium via the production of inositol-tris-phosphate. Generally, it has been shown that activation of group I receptors enhances or facilitates the excitatory effects of glutamate by modulation of ion channel activity.[2] Although group I mGlu receptors are related phylogenetically, both mGlu1 and mGlu5 receptors have a distinct expression pattern in the brain, which clearly suggests their different roles in nervous system function. mGlu5 receptors are found most abundantly throughout the cerebral cortex, hippocampus, caudate-putamen, nucleus accumbens, and lamina I–III of the spinal cord.[3]

A large body of preclinical data were reported with mGluR5-antagonists and mGluR5 knock-out mice emphasising the mGlu5 receptor as a potentially important therapeutic target for several CNS disorders including anxiety,[4] pain,[5] depression,[6] epilepsy,[7] neurodegeneration,[8] Parkinson's disease[9] and cocaine-dependence.[10] There is a large unmet medical need for new anti-anxiety agents that relieve symptoms quickly and have no (benzodiazepine-like) side effects. Recent findings have suggested an important role for the mGlu5 receptor in anxiolysis.

According to the literature, the first selective non-competitive mGluR5 antagonist compound, 2-methyl-6-(phenylethynyl)pyridine (MPEP, **1**)[11] has a very broad and potent anxiolytic-like activity in rodent models of anxiety. It has a short onset of action and lacks the potential to induce sedation or psychotomimetic effects, in contrast to the benzodiazepines.[12] (Fig. 1) Before cloning of metabotropic glutamate receptor subtypes, the non-GABAergic

MPEP, **1**
hmGluR5 pK$_i$ = 7.44

Fenobam, **2**
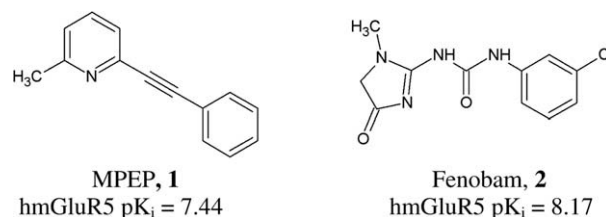hmGluR5 pK$_i$ = 8.17

Figure 1. Proof of concept mGluR5 antagonists.

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agent fenobam (**2**) was investigated in a double-blind placebo-controlled clinical trial and showed efficacy and onset of action comparable with diazepam.[13] In 2005 Roche reported that similar to MPEP, fenobam is a negative allosteric modulator of mGluR5[14] that provided clinical proof of principle for the mGluR5 approach in anxiety. Consequently, several pharmaceutical companies have initiated mGluR5 discovery programmes.[15]

The high throughput screening (HTS) of our corporate compound library resulted in several hits. This Letter describes the hit-to-lead optimization process of 3,5-disubstituted-oxadiazoles represented by compound **3**. (Fig. 2) Optimization of other clusters were reported in several patent applications.[16]

Multiple objectives were set for our hit-to-lead optimization, including the identification of the optimal central heterocycle, the cyclic secondary amide, the substitution pattern of the aromatic ring etc. In order to achieve these goals we utilized a parallel synthesis strategy, synthesizing both oxadiazoles and tetrazoles as racemates. The hit-to-lead process was monitored calculating size independent ligand efficiency (SILE)[19] and a lipophilic ligand efficiency metrics (LELP)[20] recently introduced by us. LELP was defined as the logP/LE ratio indicating the price of ligand efficiency paid in logP. Consequently, the higher the absolute value of LELP the less drug-like the lead compound.

Scheme 1 demonstrates the synthetic pathways leading to the oxadiazole series.[21] The synthesis of amines **8** was realized by preparing amidoximes **6** from suitable nitriles **5** refluxed in methanol with hydroxylamine, followed by acylation with Boc-protected pipecolic acid, nipecotic acid, proline or thioproline under mild conditions.[22] Cyclocondensation of O-acylamidoximes using tetrabutylammonium fluoride then provided the oxadiazoles ring[23] (**7**).
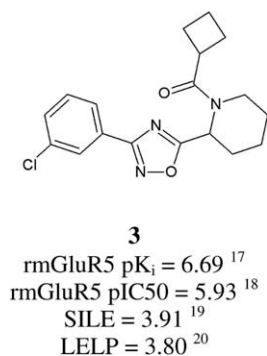
Finally, amines **8** were obtained by deprotection of **7**. In the last step we used parallel synthesis to prepare final products (**9**). Acylation of the secondary amines **8** can be accomplished with carboxylic acids (RCOOH) activated by EDC in the presence of a base (e.g. TEA). Various commercially available substituted or unsubstituted alkyl-, cycloalkyl-, aryl-, heteroaryl-carboxylic acids were used.

Final products (**9**) can be obtained in appropriate purity therefore after concentration of the solution. Biological experiments were carried out without further purification. All compounds were characterized by LC–MS.

Yields and purity data of the parallel synthetic step are summarized in Table 1. The purity of most oxadiazoles was greater than 95%, and yields were also sufficient.
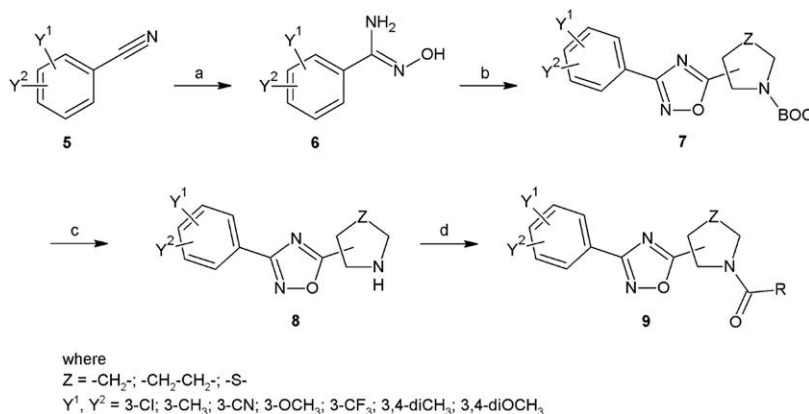
For the final acylation step, 15 amines and 61 acids were selected, 915 reactions were performed and 701 endproducts were isolated, 656 compounds fulfilled the purity criterion (>85%, LC–MS) and were tested. The K_i values of the compounds,[22] with only a couple of exceptions, were above 200 nM, Affinities and functional activities of the most active compounds are presented in Table 2.

The 2-piperidinyl, 2-pyrrolidinyl, and 4-thiazolidinyl derivatives were found to be the most active compounds, while 3-piperidinyl derivatives were generally inferior. The optimal acyl groups depended on the nature of the saturated heterocycles. The 2-piperidines with cycloalkylcarbonyl groups, (like cyclobutylcarbonyl (**9c**, **9e**) and cyclopentylcarbonyl) gave active compounds while 2-pyrrolidines acylated with 2-furoyl and 2-thiophenecarbonyl (**9b**, **9d**) groups had higher affinity towards the target. The

3
rmGluR5 pK_i = 6.69 [17]
rmGluR5 pIC50 = 5.93 [18]
SILE = 3.91 [19]
LELP = 3.80 [20]

Figure 2. The HTS hit served as starting point of hit-to-lead optimization.

Table 1
Purity and yield data of for the final products (**9**) obtained by parallel synthesis

Core	Cyclic sec. Amine (num. of subtypes)	Num. of compound	Purity (%)			Yield (%)		
			>95	85–95	<85	>60	30–60	<30
Oxa	3-Pip (8)	274	71.5	22.3	6.2	57.3	34.7	8
Oxa	2-Pip (4)	244	75	19.7	5.3	43.4	42.2	14.4
Oxa	2-Pyr (3)	183	69.4	22.4	8.2	32.2	48.1	19.7
Oxa	Sum	701	72.1	21.4	6.4	45.9	40.8	13.3
Tet	3-Pip (2)	57	89.5	10.5	0	15.8	63.2	21
Tet	2-Pip (10)	344	78.2	20	1.7	13.4	57.3	29.4
Tet	2-Pyr (9)	228	53.1	45.2	1.7	31.1	53.5	15.4
Tet	Sum	629	70.1	28.3	1.6	20	56.4	23.5
	Total	1330	71.2	24.7	4.1	33.7	48.2	18.1

Oxa, oxadiazoles; Tet, tetrazoles; pip, piperidines; pyr, pyrrolidines; num, number; comp, compounds.

where
Z = -CH$_2$-; -CH$_2$-CH$_2$-; -S-
Y^1, Y^2 = 3-Cl; 3-CH$_3$; 3-CN; 3-OCH$_3$; 3-CF$_3$; 3,4-diCH$_3$; 3,4-diOCH$_3$

Scheme 1. Reagents and conditions: (a) Hydroxylamine, K$_2$CO$_3$, MeOH, rt, 3 h, 90%; (b) Boc-pipecolic acid or Boc-nipecotic acid or Boc-proline or Boc-thioproline, i-butylchloroformate, N-Me-morpholine, DMF, 0 °C, 30 min, then tetrabutylammonium fluoride, 0 °C, 3 h, 60%; (c) HCl, EtOAc, rt, 3 h, 50–70%; (d) RCOOH, EDC, TEA, CH$_2$Cl$_2$, rt, overnight, parallel synthesis.