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4-Aryl-3-arylsulfonyl-quinolines as negative allosteric modulators of metabotropic GluR5 receptors: From HTS hit to development candidate

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ABSTRACT

High throughput screening of our corporate compound library followed by hit-to-lead development resulted in a 4-aryl-3-arylsulfonyl-quinoline derivative lead (**2**) with mGluR5 negative allosteric modulator activity. During the lead optimization process, our objective was to improve affinity and metabolic stability. Modifications at the three targeted regions of the lead structure resulted in compounds with nanomolar affinity and acceptable metabolic stability. One of the most promising compounds (**3**), showing excellent in vivo efficacy, was selected for preclinical development and subsequent phase I clinical studies.

Glutamate is the major excitatory neurotransmitter in the central nervous system (CNS). Its actions are mediated by two classes of receptors: ligand-gated ionotropic glutamate (iGlu) receptors and G-protein coupled (GPCR) metabotropic glutamate (mGlu) receptors. By activating iGlu receptors, represented by *N*-methyl-D-aspartate (NMDA) receptors, the α-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid (AMPA) receptors, and the kainic acid (KA) receptors, glutamate generates fast synaptic events that may produce long-lasting changes in synaptic excitability. By contrast, glutamate mediates slower modulatory neurotransmission via the activation of mGlu receptors. Eight subtypes of mGlu receptors have been identified and divided into three groups that act through different intracellular pathways. Group I (mGlu1 and mGlu5) are coupled to Gq proteins and activate phospholipase C (PLC), whereas group II (mGlu2 and mGlu3) and group III (mGlu4, mGlu6, mGlu7, and mGlu8) are coupled to Gi proteins and inhibit adenylate cyclase. mGlu5 receptors are found most abundantly throughout the cerebral cortex, hippocampus, caudate-putamen, nucleus accumbens, and lamina I–III of the spinal cord.[1]

Although multiple metabotropic glutamate receptor subtypes were cloned in the early 1990s, progress in the characterization of these receptors has been slow because of the absence of subtype-selective ligands and poor blood–brain penetration of the amino-acid derived ligands. Targeting the allosteric site of the mGluR5 receptor led to potent and selective compounds, but brought disadvantageous physicochemical properties, such as low solubility and high lipophilicity, which hinder producing developable drugs. However, recently several preclinical and some clinical experiments suggested that inhibition of mGluR5 receptors with allosteric ligands may have therapeutic value in the treatment of various CNS disorders, such as anxiety[2], pain[3], depression[4], epilepsy[5], neurodegeneration[6,7], Parkinson's disease[8], cocaine-dependence[9] and Fragile X syndrome.[10]

Above all, several lines of preclinical evidence suggested an involvement of mGluR5 antagonists in anxiolysis.[11] In addition, a double bind, placebo-controlled clinical trial of an old drug candidate, fenobam, (which did not reach the market) showed an efficacy and onset of action comparable with that of diazepam.[12] At the time of this clinical study the mechanism of action of fenobam was not known. However, more recently fenobam was shown to be an allosteric mGluR5 antagonist with a functional IC_{50} of 51–53 nM at rat and human mGluR5 and to have anxiolytic activity in several rodent models of anxiety at doses of 10–100 mg/kg, p.o.[13]

Several mGluR5 negative allosteric modulators (NAMs) have now entered human clinical trials. For example, clinical trials with

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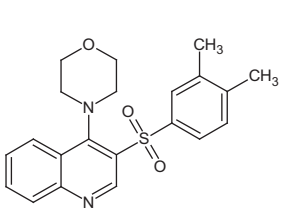
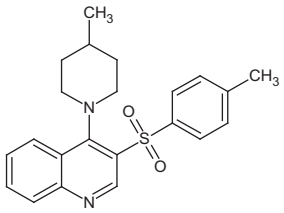


1

mGluR5 rKi: 68 nM; hKi: 52 nM

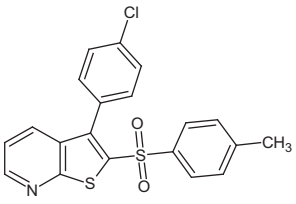
Cl_{int} (ml/min*g liver): r18.0 / h3.37



4

mGluR5 rKi: 22 nM

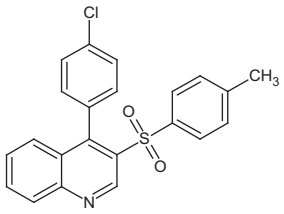
Cl_{int} (ml/min*g liver): r17.4 / h3.54



5

mGluR5 rKi: 15 nM

Cl_{int} (ml/min*g liver): r13.8 / h2.31



2

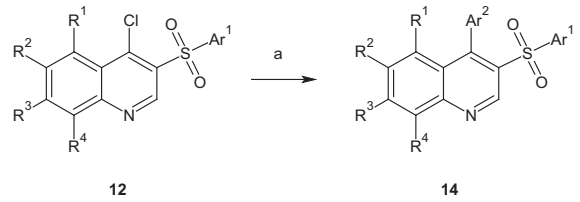
mGluR5 rKi: 9.5 nM; hKi: 17 nM

Cl_{int} (ml/min*g liver): r17.5 / h2.12

Figure 1. The hit-to-lead process.

Dipraglurant (Addex), Mavoglurant (Novartis), RG-7090 (Roche, Chugai) and STX-107 (Seaside, Merck, Roche) have been undertaken for indications such as fragile X syndrome, gastroesophageal reflux disease, Parkinson's disease, levodopa-induced dyskinesia, treatment-resistant depression and major depressive disorder.[14]

According to patent reviews[15], most mGluR5 NAM clinical candidates and in vivo tool compounds are alkyne chemotypes. This crowded intellectual property space subsequently led us to look for non-alkyne chemotypes for this molecular target.



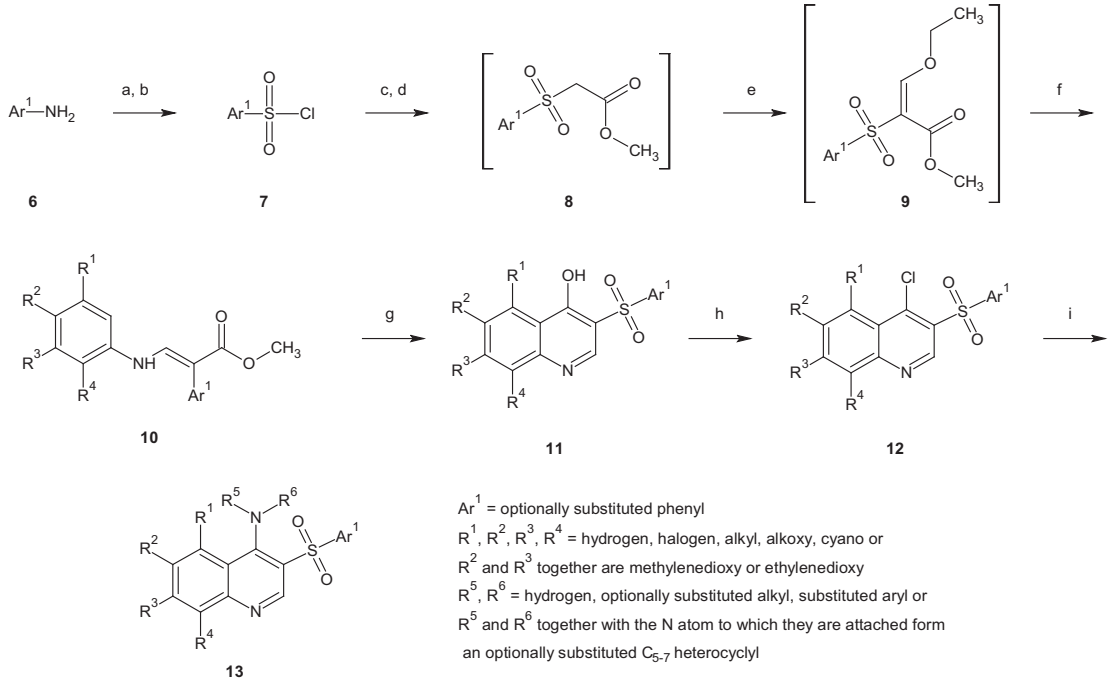
12 **14**

Scheme 2. Reagents and conditions: (a) $Ar^2B(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, 1,2-dimethoxyethane, water, 2–4 h, 65–90% yield.

High throughput screening (HTS) of our corporate compound collection resulted in several non-alkyne chemotype hits and hit clusters. Optimization of the three most interesting clusters resulted in potent mGluR5 NAM compounds, as reported in our previous communications.[16] This Letter describes the hit-to-lead development, and subsequent lead optimization, starting from an additional singleton hit (**1**) identified during our HTS campaign.

Compound **1** had been purchased from a vendor company and was found to be a potent negative allosteric modulator of rat and human mGlu5 receptors[17], but had poor metabolic stability.[18] Subsequently, 350 analogs of **1** were tested. Several similarly active derivatives were found in this series, with compound **4** being the most potent.

During the hit-to-lead process our aim was the full utilization of the accumulated experience previously gained in connection with other lead series.[16] Comparison of the structural characteristics of this compound family, represented by **1** and **4**, with those of thieno [2,3-*b*]pyridines described earlier[16d], (represented by compound **5**) suggested that replacement of the saturated heterocycles at position 4 in compounds **1** and **4** by aryl moieties might retain biological activity. In line with our expectations, substitution of the 4-methylpiperidinyl group in **4** for the 4-chlorophenyl group



Scheme 1. Reagents and conditions: (a) $NaNO_2$, HCl, water, 0–5 °C, 1 h; (b) $SOCl_2$, Cu(I)Cl, HCl, water, 0–5 °C, 2 h, 80% yield (two steps); (c) Na_2SO_3, $NaHCO_3$, water, 70–72 °C, 1.5 h; (d) $BrCH_2COOCH_3$, TBAB, water, 70–72 °C, 1 h; (e) $(CH_3CO)_2O$, $CH(OC_2H_5)_3$, 124–126 °C, 4.5 h; (f) optionally substituted aniline, TEA, 67–69 °C, 1.5 h, 30% yield (four steps); (g) $(C_6H_5)_2O$, reflux, 2.5 h, 95% yield; (h) $POCl_3$, DIPEA, CH_3CN, 76–78 °C, 5 h, 85% yield; HNR_5R_6, DBU, DMF, 80 °C, 1–6 h, 47–93% yield.