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A new series of pyridinyl-alkynes as antagonists of the metabotropic glutamate receptor 5 (mGluR5)

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Abstract—Synthesis and some structure–activity relationships for a new series of propargyl ethers as mGluR5 antagonists are reported.

The metabotropic glutamate receptors (mGluRs) are a family of G-protein coupled receptors.[1] Based on sequence homology, the mGluRs have until now been divided into eight subtypes, comprising 3 groups with mGluR1 and mGluR5 forming group I. mGluR2 and mGluR3 are forming group II, while group III includes mGluR4, mGluR6, mGluR7, and mGluR8. The sequence homology between the eight mGluRs is high, 40–50% between the groups, and more than 60% within a group. For group I the homology is 61%.[2]

The group I receptors work by stimulating phospholipase C which raises the intracellular inositol phosphates and Ca^{2+} levels.[3] Antagonism of mGluR5 has been related to the treatment of disease states such as pain,[4] depression,[5] and anxiety.[6] Another recently discovered potential indication for mGluR5 antagonists is gastro-esophageal reflux disease (GERD).[7]

An HTS campaign on the AstraZeneca substance collection against the cloned human mGluR5 receptor presented the pyridinyl-alkyne **1**[8] (Fig. 1) as a quite potent ligand (racemate; IC_{50} = 300 nM, FLIPR) with

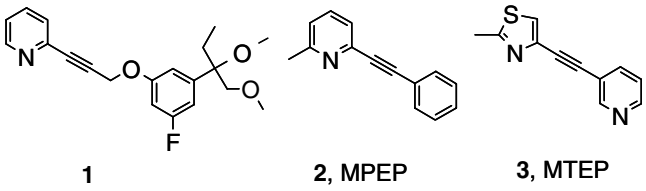

Figure 1. HTS-hit **1** and known mGluR5-antagonists MPEP (**2**) and MTEP (**3**).

selectivity over mGluR1 ($IC_{50} \geqslant$ 10,000 nM, FLIPR). Compound **1** belonged to a cluster of hits that are structurally related to the two known non-competitive mGluR5-selective antagonists[9] 2-methyl-6-(phenyl-ethynyl) pyridine (MPEP, **2**)[10] and 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine (MTEP, **3**)[11] that showed high potencies toward mGluR5 with IC_{50}s of 2 nM and 5 nM, respectively.[12] Various analogues of MPEP and MTEP have been reported.[13] A series of close analogues to **1** was synthesized by rather straightforward methodologies, as outlined in Scheme 1.

Thus, Sonogashira cross-coupling[14] of 2-bromo-6-methyl pyridine **4** with propargyl alcohol by route a[15] with subsequent mesylation by route b gave **5**. The mesylate **5** was then reacted with a selection of phenols in a parallel format by route c, forming a series of ethers **6**. Purification was done by reverse-phase

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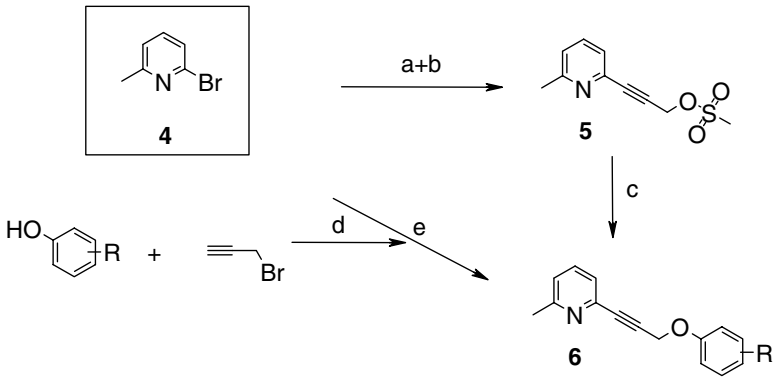


Scheme 1. Reagents and conditions: (a) HC≡CCH$_2$OH, (PPh$_3$)$_2$PdCl$_2$, CuI, NEt$_3$, 60 °C, 3.5–4 h (56%); (b) MsCl, NEt$_3$, DCM, −20 °C, 1 h (98%); (c) ArOH, K$_2$CO$_3$, acetone, 60 °C, 5 h (R = *p*-Cl: 40%) or ArOH, K$_2$CO$_3$, acetone, 60 °C, 20 h, then DMF, 60 °C, 20 h (R = *p*-Me: 28%) or ArOH, NaH, THF, rt, 18 h (R = *p*-OMe: 12%); (d) K$_2$CO$_3$, acetone, 60 °C, 17 h (R = H: 78%); (e) (PPh$_3$)$_2$PdCl$_2$, CuI, NEt$_3$, 60 °C, 2 h (R = H: 66%).

chromatography with focus on high purity of the screening compounds rather than on high yields. Thus, yields for step *c* varied from 11% to 85% with yields 25–45% being typical. For scale-up it proved useful first to form a propargyl ether by route d[16], followed by Sonogashira coupling by route e to give the final ether products **6**. Route e was also employed for reactions with other halogenoheterocycles than **4** in order to study structure–activity relationships (SAR) around the binding site of the pyridine ring.

Development of SAR was made around the two aromatic ring systems, Ar$_1$ and Ar$_2$ (Fig. 2). Synthesized compounds were tested in a FLIPR assay.[17] IC$_{50}$ values for active (IC$_{50}$ < 10,000 nM) compounds were determined as means of three measurements. MPEP and MTEP measured in this assay showed activities of 22 nM (SEM = 1.9) and 77 nM (SEM = 6.4), respectively.

Initially, variation of the aryl Ar$_1$ was investigated. A series (compounds **7**–**12**, Table 1) of methyl/methoxy pyridines illustrated the very tight SAR around the Ar$_1$ ring. 6-Methylation gave a fourfold increase in potency, while the 3-, 4-, and 5-monomethyl compounds were inactive. Likewise, an attempt to introduce alternative heterocycles (**13**–**15**) gave inactive compounds. Compounds **7** and **8** were also tested in a mGluR1 assay and found to be inactive (IC$_{50}$ > 10,000 nM). Having identified the 6-methyl-pyridinyl group as optimal for Ar$_1$, a SAR investigation was made for the aryl Ar$_2$ (Table 2). With the Ar$_2$ ring being phenyl no potency (IC$_{50}$ > 10,000 nM) was observed (**16**). A slight increase in potency was observed for compounds having simple substituents in the *o*-position (**17**). Remarkably, potency was significantly increased by having simple substituents in the *m*- and/or *p*-position (**18**–**25**) most pronounced for lipophilic groups (compare **18**–**20** with **8** and **22**–**23**) with basically no dependency on the electron donating/withdrawing ability of the substituents (compare **8** and **22**). Further branching was allowed in the *p*-position (**21**). Compounds with heterocycles (**26**–**29**) as the Ar$_2$ group showed at best medium potencies. In vitro metabolic stability of the most potent compound **24** in rat liver microsomes showed a CL$_{int}$ = 278 μL/min/mg.

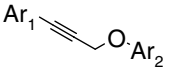
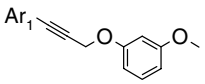


Figure 2.

Table 1. SAR around aryl Ar$_1$



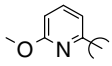
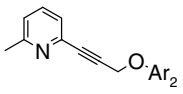
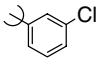
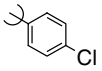
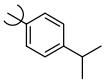
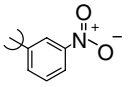
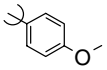
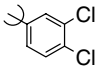
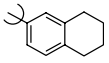
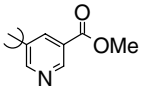
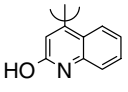
Compound	Ar$_1$	IC$_{50}$ (nM)	SEM
7		1540	559
8		397	78
9		7926	3593
10		>10,000	—
11		>10,000	—
12		>10,000	—
13		>10,000	—
14		>10,000	—
15		>10,000	—

Table 2. SAR around aryl Ar_2



Compound	Ar_2	IC_{50} (nM)	SEM
16		>10,000	—
17		>3000	—
18		101	0.6
19		102	10.9
20		115	7.9
21		83	6.5
22		416	96
23		455	156
24		15	3.0
25		36	2.9
26		>10,000	—
27		2490	508
28		1490	510
29		825	113

in MPEP. Having methoxy instead of methyl in the 6-position lowered the activity 80-fold in the case of MPEP and gave an inactive compound (**12**) in our series. Compound **9** had low activity in analogy to the corresponding 5-methyl MPEP-isomer being inactive. However, compounds **10** and **11** showed no activity, while the corresponding 4- (respectively 3-) methyl MPEP-isomers still had good activity. For Ar_2 the SAR is not obviously related to that for MPEP.

In summary, a new series of pyridinyl-alkynes was revealed to include potent antagonists of the cloned human metabotropic glutamate receptor 5.

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