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Structure–activity relationship of thiopyrimidines as mGluR5 antagonists

Lance G. Hammerland,[a] Martin Johansson,[b] Jonas Malmström,[b] Jan P. Mattsson,[c] Alexander B. E. Minidis,[b,*] Karolina Nilsson,[c] Alecia Peterson,[a] David Wensbo,[b] Andreas Wållberg[c,*] and Krister Österlund[c]

[a]*NPS-Pharmaceuticals, 383 Colorow Drive, Salt Lake City, UT 84108, USA*
[b]*Medicinal Chemistry, Local Discovery CNS & Pain Control, Astra Zeneca R&D Södertälje, SE-151 85 Södertälje, Sweden*
[c]*Medicinal Chemistry, AstraZeneca R&D Mölndal, SE-43183 Mölndal, Sweden*

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Abstract—Structure–activity relationship investigations of the thiopyrimidine (**1**), an HTS hit with micromolar activity as a metabotropic glutamate receptor 5 (mGluR5) antagonist, led to compounds with sub-micromolar activity.

The metabotropic glutamate receptors (mGluRs) are G-protein-coupled receptors which have important roles in modulating neuronal signaling in the central nervous system.[1] The mGluRs belong to family C of G-protein-coupled receptors, of which there are eight subtypes identified, divided into three major groups: Group I includes mGluR1 and mGluR5, Group II mGluR2 and mGluR3, and Group III mGluR4, as well as mGluR6–8.[2]

There are preclinical data supporting the use of metabotropic glutamate receptor 5 (mGluR5) antagonists in the treatment of several CNS diseases and disorders[3] like inflammatory and neuropathic pain,[4] anxiety and depression[5] or drug addiction and drug withdrawal.[6] Recent evidence also indicates mGluR5 as a potential target for the treatment of gastroesophageal reflux disease, showing that mGluR5 antagonists inhibit transient lower esophageal sphincter relaxations, the main mechanism behind gastroesophageal reflux.[7]

Our interest in thiopyrimidines as mGluR5 antagonists started with the discovery of **1** (Fig. 1) as a weak antagonist (IC_{50} 1250 nM) in a high-throughput screening campaign targeting mGluR5, and a followup program was initiated to investigate SAR around this novel mGluR5 antagonist structure.

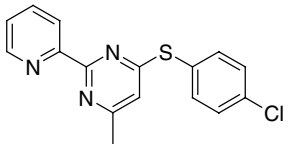

Figure 1. Thiopyrimidine (**1**), a weak mGluR5 antagonist HTS hit.

For this purpose, easy access to a variety of linker and thioaryl groups was obtained by synthesizing scaffold **5** in two steps (Scheme 1) according to a literature procedure.[8]

Elaboration of the thioaryl moiety (**6**–**13**) was achieved by treating **5** with an array of commercially available thiols in DMF, running the reaction overnight, followed by removal of volatiles and chromatographic purification. Amine as well as ether pyrimidine compounds was obtained similarly to the thioethers by treatment of **5** with the appropriate amine and alcohol, respectively.

For synthesis of the bipyridyl core as illustrated by **23**, a regioselective Negishi cross-coupling, followed by reaction with a thiol nucleophile, was employed (Scheme 2). Compound **24** was synthesized in a similar fashion.[9]

Keywords: Thiopyrimidine; Metabotropic glutamate receptor; mGluR5.
*Corresponding authors. Tel.: +46 31 7762788 (A.W.); e-mail: andreas.wallberg@astrazeneca.com

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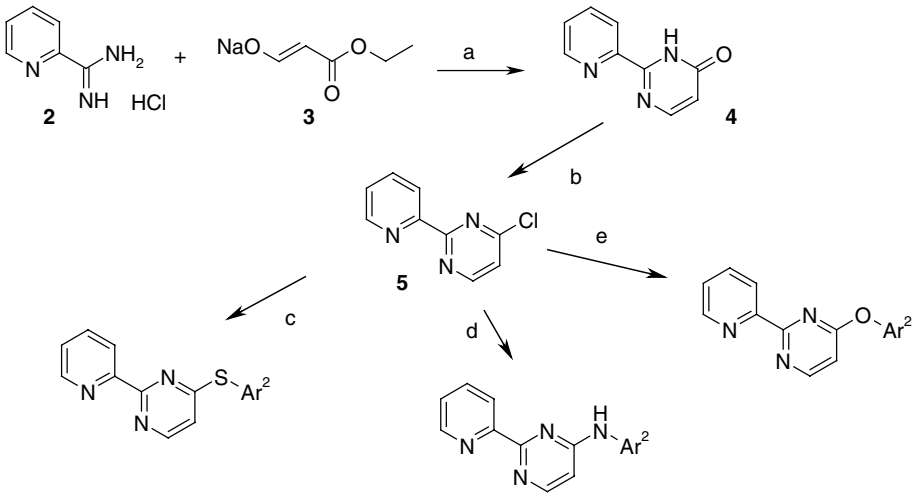
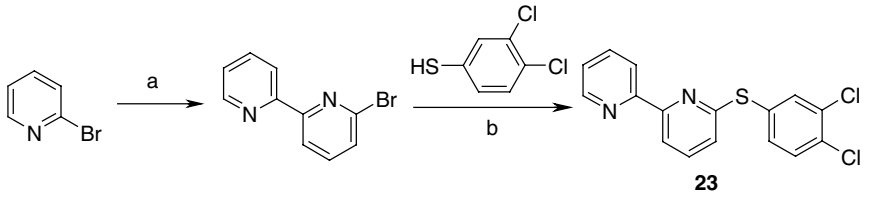
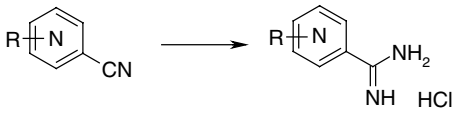


Scheme 1. Versatile intermediate **5**. Reagents and conditions: See Ref. 8c for compounds **2** and **3**. (a) NaOEt, EtOH, reflux, 18 h; filter and wash: 54%. (b) $POCl_3$, DCE, reflux; 93%. (c) Appropriate thiol, DMF, rt, o/n 2–90%. (d) Appropriate aniline, NEt_3, THF, reflux, 8–48%. (e) Appropriate phenol, *t*-BuOK, DME, 23–48%.



Scheme 2. Synthesis of **23**. Reagents: (a) 1—*n*-BuLi; 2—$ZnCl_2$; 3—$Pd(PPh_3)_4$, 2,6-dibromopyridine, 34%. (b) NaH, DMF, 16%.

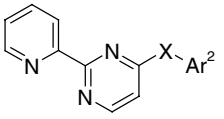


Scheme 3. Reagents and conditions: MeOH, cat. NaOEt, microwave 150 °C, 10 min; add NH_4Cl to mixture, microwave 80 °C, 12 min, 78%.

Variation of the lefthand pyridyl could be achieved by synthesis of appropriate amidine derivatives (Scheme 3), followed by the sequences shown in Scheme 1. We found it advantageous to conduct the amidine synthesis in a microwave reactor, thus decreasing reaction times from 1 to 2 days to less than half an hour.

Removal of the methyl group from the hit **1** gave compound **6** (Table 1), which was already fourfold more potent (IC_{50} 320 nM) compared to **1**. On this basis, we further investigated the SAR of the substitution pattern on the phenyl group (Ar^2), while keeping the remaining parts of the molecule constant (Entries **7**–**13**). Substituents in the meta position that gave compounds with a potency better than 1 μM were chloro (**7**) (IC_{50} 620 nM) and trifluoro methyl (**9**) (IC_{50} 550 nM). Likewise, substituents in the para position such as trifluoro methyl (**11**) (IC_{50} 210 nM) lead to compounds in the same potency range as **6**. Disubstitution on the 3 and 4 positions gave compounds **12** (difluoro, IC_{50} 1520 nM) and **13**[10] (dichloro, IC_{50} 90 nM). Next, we turned our efforts to replacement of the sulfur atom, since we anticipated metabolic oxidation at this position. Unfortunately, oxygen, nitrogen, *N*-acetyl, methylene, and hydroxymethylene analogues (**14**–**18**) were all inactive. Altering the position of the nitrogen in the pyridine ring (**19**–**20**) (Table 2) was not tolerated, whereas introduction of small substituents on the pyridine gave **21** (6-methyl-2-

Table 1. In vitro potencies of thiopyrimidine mGluR5 antagonists varying Ar^2

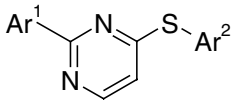


Compound	X	Ar^2	FLIPR IC_{50}[a] nM	*n*	SEM
6	S	4-Cl-Ph	320	3	53
7	S	3-Cl-Ph	620	1	
8	S	3-Br-Ph	2860	3	145
9	S	3-CF_3-Ph	550	3	66
10	S	3-Me-Ph	2300	3	706
11	S	4-CF_3-Ph	210	3	8
12	S	3,4-Di-F-Ph	1520	3	742
13	S	3,4-Di-Cl-Ph	90	3	7
14	O	4-Cl-Ph	>10,000	1	
15	NH	4-Cl-Ph	>10,000	1	
16	NAc	4-Cl-Ph	>10,000	1	
17	CHOH	4-Cl-Ph	>3000	3	0
18	CH2	4-Cl-Ph	>10,000	1	
MPEP[b], for comparison			22	3	2

[a] Effect on glutamate-induced $[Ca^{2+}]_i$ in a cell line expressing human mGluR5d (splice variant of mGluR5 with a truncated C-terminal domain) using a fluorescence imaging plate reader (FLIPR).

[b] 2-Methyl-6-(phenylethynyl)pyridine, see Ref. 12.

Table 2. In vitro potencies of thiopyrimidine mGluR5 antagonists varying Ar^1 and linker, using preferred Ar^2



Compound	Ar^1	Ar^2	FLIPR IC_{50}[a] nM	*n*	SEM
19	3-Pyridyl	4-Cl-Ph	>10,000	1	
20	4-Pyridyl	4-Cl-Ph	>10,000	1	
21	6-Me-2-Pyridyl	3,4-Di-Cl-Ph	390	3	63
22	5-F-2-Pyridyl	3,4-Di-Cl-Ph	80	3	14

[a] Effect on glutamate-induced $[Ca^{2+}]_i$ in a cell line expressing human mGluR5d (splice variant of mGluR5 with a truncated C-terminal domain) using a fluorescence imaging plate reader (FLIPR).

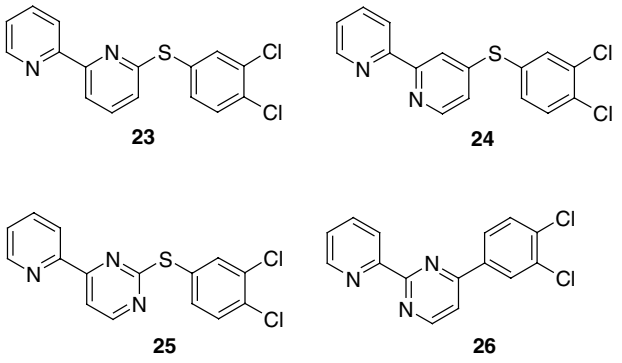


Figure 2. Variation of core and linker. Only **24** showed modest mGluR5 antagonist activity (FLIPR IC_{50} 2370 nM, $n = 3$, SEM 628).

pyridyl) (IC_{50} 390 nM) and **22**[11] (5-fluoro-2-pyridyl) (IC_{50} 80 nM). Replacement of the central pyrimidine moiety with the two isomers of pyridine (Fig. 2) gave one inactive compound (**23**) and one with micromolar activity (**24**, IC_{50} 2370 nM), while the reversed pyrimidine **25** was inactive. Absence of a linker atom gave an inactive compound (**26**). In conclusion, all three nitrogen atoms in the pyridine and pyrimidine rings and the sulfur linker appear to be crucial for effecting potency, which can be reinforced by introducing lipophilic substituents on the 3 and 4 positions of the phenyl group.

Compounds **21** and **22** were tested for selectivity, both as positive modulators and as antagonists, on the other mGluRs (**1**–**4** and **6**–**8**) exhibiting complete selectivity in all assays (>25 μM).

Compounds **13** and **22** both have rather high in vitro clearance (**13** 90 and 120 μL/min/mg in human and rat liver microsomes, respectively, and **22** 140 and 90 μL/min/mg in human and rat liver microsomes, respectively). Attempts to synthesize the presumed metabolites, the corresponding sulfoxides and sulfones, failed because of chemical instability of these species.

In summary, we have identified a novel structural class of mGluR5 antagonists, the thiopyrimidines, with mGluR5 potency better than 100 nM. We have shown that a 4-thiopyrimidine as a core-linker system is crucial for activity. Further optimisation is necessary to increase potency, for example, by variation of the substituents on the 2-pyridine ring (Ar^1) and replacement of the sulfur linker atom, since the latter is most likely the main cause of low metabolic stability. The SAR we have developed for thiopyrimidines could be of interest for other projects concerning mGluR5 antagonists and possibly applicable to other lead series.

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9. Intermediate for regioisomer **24** was synthesized according to Araki, K.; Mutai, T.; Shigemitsu, Y.; Yamada, M.; Nakajima, T.; Kuroda, S.; Shimao, I. J. *Chem. Soc. Perkin Trans. 2* **1996**, 613.
10. Analytical data for **13**: ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.1 (d, *J*=5.4 Hz, 1 H) 7.5 (m, 1 H) 7.7 (dd, *J*=8.4, 2.1 Hz, 1 H) 7.8 (d, *J*=8.4 Hz, 1 H) 7.9 (dt, *J*=7.7, 1.8 Hz, 1 H) 8.1 (d, *J*=2.1 Hz, 1 H) 8.2 (d, *J*=7.8 Hz, 1 H) 8.7 (d, *J*=5.4 Hz, 1 H) 8.7 (m, 1H). HRMS calcd for $C_{15}H_{10}N_3Cl_2S$ (M+H) 333.9972. Found 333.9981.
11. Analytical data for **22**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.89 (d, *J* = 5.30 Hz, 1 H), 7.48–7.52 (m, 1 H), 7.54 (m, 1 H), 7.60 (d, *J* = 8.34 Hz, 1 H), 7.81 (d, *J* = 2.02 Hz, 1 H), 8.35 (m, 1 H), 8.60 (d, *J* = 5.30 Hz, 1 H), 8.66 (d, *J* = 2.78 Hz, 1 H). HRMS calcd for $C_{15}H_9N_3Cl_2SF$ (M+H) 351.9878. Found 351.9868.
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