Available online at www.sciencedirect.com
ScienceDirect
Bioorganic & Medicinal Chemistry Letters 17 (2007) 6525–6528
Bioorganic & Medicinal Chemistry Letters

Synthesis and SAR comparison of regioisomeric aryl naphthyridines as potent mGlu5 receptor antagonists

Paul Galatsis,[a] Koji Yamagata,[a] John A. Wendt,[a,*] Cleo J. Connolly,[a] John W. Mickelson,[a] Jared B. J. Milbank,[a] Susan E. Bove,[b] Christopher S. Knauer,[b] Rachel M. Brooker,[b] Corinne E. Augelli-Szafran,[a] Roy D. Schwarz,[b] Jack J. Kinsora[b] and Kenneth S. Kilgore[b]

[a]*Department of Medicinal Chemistry, Pfizer Global Research & Development, 2800 Plymouth Road, Ann Arbor, MI 48105, USA*
[b]*Departments of CNS Biology and Inflammation, Pfizer Global Research & Development, 2800 Plymouth Road, Ann Arbor, MI 48105, USA*

Received 23 July 2007; revised 24 September 2007; accepted 25 September 2007
Available online 29 September 2007

Abstract—We describe three novel regioisomeric series of aryl naphthyridine analogs, which are potent antagonists of the Class III GPCR mGlu5 receptor. The synthesis and in vitro and in vivo pharmacological activities of these analogs are discussed.

Non-competitive metabotropic glutamate receptor 5 (mGluR5) antagonists are viewed as having promise against a number of CNS and peripheral diseases including the treatment of pain, anxiety, gastro-esophageal reflux disease (GERD), Fragile X syndrome, and Parkinson's disease.[1] The target has attracted much attention in the search for small non-competitive antagonists which can be useful in the treatment of these disease states.[2–13] We have recently disclosed two novel classes of potent mGlu5 receptor antagonists (Fig. 1) which utilize heterocyclic ring cores, namely quinoline **2** and pyrido[2,3-*d*]pyrimidine **3**, identified from a molecular overlay with MPEP (2-methyl-6-(2-phenylethynyl)pyridine) (**1**).[14,15]

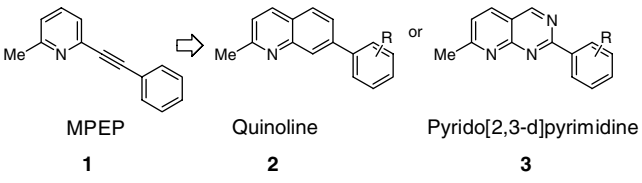


Figure 1.

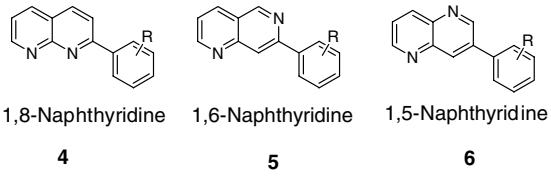


Figure 2.

In addition to **2** and **3**, we now disclose three additional novel classes of mGlu5 receptor antagonists all containing regioisomeric 1,8-, 1,6-, and 1,5-naphthyridine cores (**4**, **5**, and **6**, respectively) (Fig. 2).

It has become obvious, from previous reports, that very potent inhibitors can be prepared by focusing synthetic efforts to a particular portion of the molecule. Thus, our SAR exploration of these new scaffolds was primarily focused on the pendent aryl moiety of the naphthyridine core. In addition, select SAR investigation of the 2-methyl 1,8- and 1,6-naphthyridine derivatives was explored in analogy to **1**.

Assembly of these naphthyridine cores utilized three separate synthetic routes. The 1,8-naphthydrine core was constructed utilizing a Friedländer reaction.[16,17] The desired products **4** were readily prepared by a sim-

Keywords: mGlu5 receptor; Antagonist; 1,5-Naphthyridine; 1,6-Naphthyridine; 1,8-Naphthyridine; Rat; Osteoarthritis; Pain.
* Corresponding author. E-mail: john.a.wendt@pfizer.com

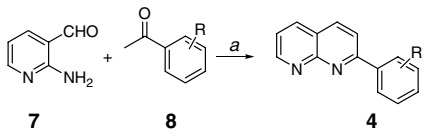
0960-894X/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2007.09.083

ple one step protocol from commercially available 2-aminonicotinaldehyde (**7**) and a diverse set of aryl acetophenones (**8**) (Scheme 1). Overall, the desired products were isolated in modest to good yields.

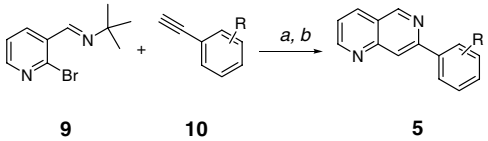
The 7-aryl 1,6-naphthydrines were constructed utilizing the procedure of Larock and Roesch.[18] Commercially available 2-bromonicotinaldehyde was converted to its *N*-^{t}Bu imine (**9**) which underwent a sequential Sonagashiro coupling with an aryl acetylene derivative[19] (**10**) (Scheme 2). The resulting crude intermediate was cyclized upon heating in DMF using CuI (1equiv) to the desired 7-aryl 1,6-naphthydrine (**5**). This overall route, while succinct, revealed variable yields (10–80%) which appeared to be highly dependent on the substitution on the aryl ring. For example, a 3-cyano moiety on the aryl ring afforded the desired 1,6-naphthydrine ring in only a 26% yield.

The 1,5-naphthydrine series was constructed utilizing a Suzuki cross coupling reaction. The desired products **6** were synthesized from a palladium catalyzed cross coupling of intermediate **11**[20] and an aryl boronic acid derivative[21] (**12**) (Scheme 3).

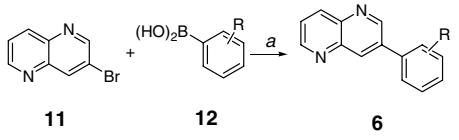
Additionally, 2-methyl-7-phenyl-1,8-naphthyridine analogs were constructed from 2-amino-6-methylnicotinaldehyde in a reasonable yield using the route from Scheme 1. Similarly, the 2-methyl 7-aryl 1,6-naphthyridine compounds were constructed from 2-bromo-6-methylnicotinaldehyde[22] using the Larock synthetic route from Scheme 2.



Scheme 1. Reagent: (a) L-proline, EtOH reflux.



Scheme 2. Reagents and conditions: (a) cat. $PdCl_2(PPh_3)_2$, TEA, cat CuI, 50 °C; (b) CuI, DMF, 100 °C.



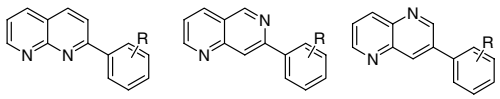
Scheme 3. Reagents: (a) cat. $Pd(Ph_3)_4$, $NaCO_3$ (aq), toluene reflux.

The compounds prepared (**13**–**29**) were assessed to compare the biological activity of all three regioisomeric naphthyridines to determine mGlu5 receptor antagonist functional activity. This data is presented in Table 1. While our SAR studies explored many aryl substitution patterns, we discovered that similar to the quinoline[14] (**2**) and the pyrido[2,3-*d*]pyrimidine[15] (**3**) series, the 3- and 3,5-aryl substitution pattern was generally the optimal substitution pattern for imparting antagonist activity to these new series. The lone exception was in the 1,8-naphthyridine series, where compound **17** (3,4-di-Me) was the most potent synthesized (IC_{50} = 45 nM).

In general, comparing the data for these three series (**4**, **5**, and **6**), reveals less antagonist potency relative to both the quinoline and the pyrido[2,3-*d*]pyrimidine series. In particular, compound **23** and **29** are 10-fold less potent than their respective pyrido[2,3-*d*]pyrimidine analogs.[15] The SAR between these regioisomeric naphthyridines seems to reveal that the 1,8-naphthyridine series (**4**) contains the most potency, highlighted by simple 3-aryl substitution (**14** and **15**) which is 10- to 100-fold more potent relative to comparable 1,5- and 1,6-analogs (**19**, **25**, and **26**).

Table 2 illustrates selected 2-methyl 1,8- and 1,6-naphthyridine derivatives (**32**–**44**) that were prepared and tested for mGlu5 receptor antagonist activity. These

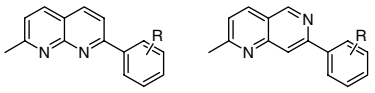
Table 1. Functional (FLIPR) activity for select 1,8-(**4**), 1,6-(**5**), and 1,5-(**6**) naphthyridine analogs



Compound	R	FLIPR IC_{50}[a] (nM)	Series
13	H	1840	4
14	3-CN	115	4
15	3-Me	225	4
16	3,5-diOMe	67	4
17	3,4-diMe	45	4
18	H	>30,000	5
19	3-Me	1270	5
20	3-Me-5-F	6570	5
21	3-CN-5-F	1590	5
22	3-CN-5-OCH_2OMe	468	5
23	3-CN-5-OMe	68	5
24	3,5-diOMe	6070	5
25	3-CN	18,600	6
26	3-Me	15,700	6
27	3,4-diMe	12,000	6
28	3,5-diMe	>30,000	6
29	3-CN-5-OMe	55	6

[a] Compounds were measured for potency to inhibit quisqualate stimulated calcium mobilization using FLIPR technology. The data shown were obtained using CHO cells stably expressing rat mGlu5 receptors. Values are geometric means of two or more experiments.

Table 2. Functional (FLIPR) activity for selected 2-methyl 1,8-(**30**) and 1,6-(**31**) naphthyridine analogs



30 **31**

Compound	R	FLIPR IC_{50}[a] (nM)	Series
32	H	664	30
33	3-CN	480	30
34	3-Me	277	30
35	3,5-diF	181	30
36	3,5-diOMe	51.7	30
37	3-Cl	177	30
38	3-Br	47.9	30
39	H	>30,000	31
40	3-Me	676	31
41	3-OMe	7900	31
42	3,5-diOMe	345	31
43	3-CN-5-OMe	6.19	31
44	3-Me-5-F	2930	31

[a] Compounds were measured for potency to inhibit quisqualate stimulated calcium mobilization using FLIPR technology. The data shown were obtained using CHO cells stably expressing rat mGlu5 receptors. Values are geometric means of two or more experiments.

analogs explore the role the methyl moiety has on potency for these two series.

From the limited SAR shown, it appears the 2-methyl moiety is beneficial to optimal potency in the 1,6-naphthyridine series with **43** being 10x more potent than **23**. Surprisingly, in the 1,8-naphthyridine series, it was revealed that the 2-methyl substitution appears not to improve the potency relative to the 2-desmethyl template. This is highlighted by the similar potencies between **16** and **36**.

The in vivo activity of compound **36** was evaluated (ip, 10 MPK) in the rat monosodium iodoacetate (MIA) model of osteoarthritis (OA) pain.[23,24] The results are presented in Figure 3. The time course results of a single dose intraperitoneal administration of **36** revealed a significant inhibition of change in hind paw weight distribution versus vehicle at the 2, 4, and 6 h post dose time points. This effect, although intraperitoneal, was quite robust which further supports the evidence of the mGlu5 receptor antagonists as possible agents to alleviate the signs and symptoms of arthritis.

In summary, synthetic routes of three regioisomeric aryl naphthyridine series possessing potent mGluR5 antagonist activity were developed. The overall SAR studies for these three series illustrate that the antagonist activity resides predominantly in the appropriate substitution of the C3-and C3,5-disubstituted position of the aryl ring. In general, the 3 regioisomeric naphthydrine series do not appear to be as potent as either the quinoline or the pyrido[2,3-*d*]pyrimidine series. The SAR of the 1,8-naphthyridine series appears to reveal that this regioisomer is more potent than the other two naphthyridine regioisomers. Additional 2-methyl substitution onto the 1,8- and 1,6-naphthyridine series revealed, unlike the quinoline and pyrido[2,3-*d*]pyrimidine series, a limited potency benefit. In vivo activity (ip) of compound **35** revealed a robust effect in the rat MIA model which validates the 7-aryl 1,8-naphthyridine series as another new class of promising mGlu5 receptor antagonists.

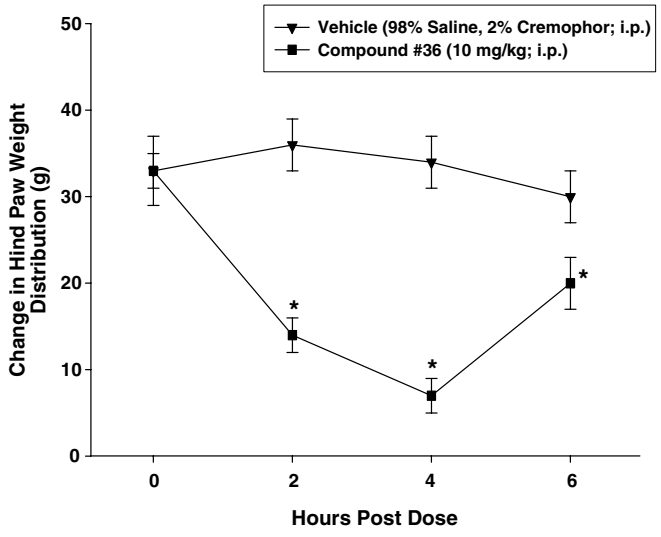


Figure 3. On day 14 post MIA injection, rats were assessed for change in hind paw weight distribution (0 h post dose). Rats were then administered compound **36** or vehicle (ip) and reassessed 2, 4, and 6 h later. Data are expressed as mean ± SEM. Statistically significant differences were determined using a one-way analysis of covariance adjusted for multiplicity of statistical testing by Hochberg's Procedure ($^{*}P < 0.05$ vs vehicle at same time point). $N = 18$ rats per group.

References and notes

1. Bach, P.; Isaac, M.; Slassi, A. *Expert Opin. Ther. Patents* **2007**, *17*, 371.
2. Augelli-Szafran, C.; Schwarz, R. *Ann. Rep. Med. Chem.* **2003**, *38*, 21.
3. Bach, P.; Nilsson, K.; Wallberg, A.; Bauer, U.; Hammerland, L. G.; Peterson, A.; Svensson, T.; Oesterlund, K.; Karis, D.; Boije, M.; Wensbo, D. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4792.
4. Bach, P.; Nilsson, K.; Svensson, T.; Bauer, U.; Hammerland, L. G.; Peterson, A.; Wallberg, A.; Oesterlund, K.; Karis, D.; Boije, M.; Wensbo, D. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4788.
5. Chua, P. C.; Nagasawa, J. Y.; Bleicher, L. S.; Munoz, B.; Schweiger, E. J.; Tehrani, L.; Anderson, J. J.; Cramer, M.; Chung, J.; Green, M. D.; King, C. D.; Reyes-Manalo, G.; Cosford, N. D. P. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4589.
6. Iso, Y.; Grajkowska, E.; Wroblewski, J. T.; Davis, J.; Goeders, N. E.; Johnson, K. M.; Sanker, S.; Roth, B. L.; Tueckmantel, W.; Kozikowski, A. P. *J. Med. Chem.* **2006**, *49*, 1080.
7. Alagille, D.; Baldwin, R. M.; Roth, B. L.; Wroblewski, J. T.; Grajkowska, E.; Tamagnan, G. D. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 945.
8. Alagille, D.; Baldwin, R. M.; Roth, B. L.; Wroblewski, J. T.; Grajkowska, E.; Tamagnan, G. D. *Bioorg. Med. Chem.* **2004**, *13*, 197.
9. Jaechke, G.; Porter, R.; Buettelmann, B.; Ceccarelli, S.; Guba, W.; Kuhn, B.; Kolczewski, S.; Huwyler, J.; Mutel, V.; Peters, J.-U.; Ballard, T.; Prinssen, E.; Vieira, E.; Wichmann, J.; Spooren, W. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1307.
10. Hammerland, L.; Johansson, M.; Malmstroem, J.; Mattsson, J.; Minidis, A.; Nilsson, K.; Peterson, A.; Wensbo, D.; Wallberg, A.; Oesterlund, K. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2467.
11. Tasler, S.; Kraus, J.; Pegoraro, S.; Aschenbrenner, A.; Poggesi, E.; Testa, R.; Motta, G.; Leonardi, A. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2876.
12. Bonnefous, C.; Vernier, J.-M.; Hutchinson, J.; Chung, J.; Reyes-Manalo, G.; Kamenecka, T. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1197.
13. Kulkarni, S.; Hauck Newman, A. *Bioorg. Med. Chem.* **2007**, *17*, 2987.
14. Milbank, J.; Knauer, C.; Augelli-Szafran, C.; Sakkab-Tan, A.; Lin, K.; Yamagata, K.; Hoffman, J.; Zhuang, N.; Thomas, J.; Galatsis, P.; Wendt, J.; Mickelson, J.; Schwarz, R.; Kinsora, J.; Lotarski, S.; Stakich, K.; Gillespie, K.; Lam, W.; Mutlib, M. *Bioorg. Med. Chem. Lett.* **2007**, *17(16)*.
15. Wendt, J.; Deeter, S.; Bove, S.; Knauer, C.; Brooker, R.; Augelli-Szafran, C.; Schwartz, R.; Kinsora, J.; Kilgore, K. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5396.
16. Reddy, K. V.; Mogilaiah, K.; Sreenivasulu, B. *J. Indian Chem. Soc.* **1986**, *63*, 443.
17. Piao, Ming-Zhu; Imafuku, Kimiaki *J. Heterocycl. Chem.* **1996**, *33*, 389.
18. Roesch, R.; Larock, R. *J. Org. Chem.* **2002**, *67*, 86.
19. The respective aryl acetylenes (**10**) were either commercially available or constructed via a Sonagashira coupling between trimethylsilylacetylene and an aryl halide or aryl triflate (0.02 equiv $PdCl_2(PPh_3)_2$, 4 equiv TEA, 0.04 equiv CuI, 50 °C), followed by removal of TMS group (0.1 M NaOH in THF).
20. Synthetic procedure **11**: a solution of 1,5-naphthiridine (55.6 g, 0.43 mol) in glacial acetic acid (550 ml) was treated with sodium acetate (70.0 g, 0.85 mol) and stirred at 85 °C while a solution of bromine (75.3 g, 0.470 mol) in 75 ml glacial acetic acid was added slowly. Stirring was continued for 2.5 h at this temperature. This mixture was cooled and concentrated and the residue was suspended in water (500 ml), made basic with 50% sodium hydroxide and stirred for 20 min. The precipitate was collected by filtration, washed (water), dried, and triturated with hot ethyl acetate (800 ml). After cooling the precipitate was collected by filtration and washed with ethyl acetate, yielding 3,7-dibromo-1,5-naphthyiridine (15 g). The remaining filtrate was purified by silica gel chromatography (CH_2Cl_2 followed by CH_2Cl_2/EtOAc, 8:2) to afford 3-bromo-1.5-naphthyridine **11** (44 g, 35.8%) as a white solid.
21. The aryl boronic acids were either commercially available or synthesized between dipinacolatoborane and an aryl halide under standard Suzuki type conditions.
22. Piao, M.-Z.; Imafuku, K. *J. Heterocycl. Chem.* **1996**, *33*, 389.
23. Bove, S.; Calcaterra, S.; Brooker, R.; Huber, C.; Guzman, R.; Juneau, P.; Schrier, D.; Kilgore, K. *Osteoarthritis Cartilage* **2003**, *11*, 821.
24. All experimental procedures were conducted in an AAALAC International-accredited facility in compliance with the United States Department of Agriculture Animal Welfare Act Regulations and the Guide for the Care and Use of Laboratory Animals and were approved by the PGRD Ann Arbor Institutional Animal Care and Use Committee prior to initiation of the studies.