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Bioorganic & Medicinal Chemistry Letters 15 (2005) 747–750
Bioorganic & Medicinal Chemistry Letters

# Novel 3-aminochromans as potential pharmacological tools for the serotonin 5-HT$_7$ receptor

Pär Holmberg,[a] Lars Tedenborg,[a] Susanne Rosqvist[b] and Anette M. Johansson[a,c,*]

[a]*Organic Pharmaceutical Chemistry, Uppsala University, PO Box 574, SE-751 23 Uppsala, Sweden*
[b]*Department of Lead Generation, AstraZeneca R&D Södertälje, SE 151-85 Södertälje, Sweden*
[c]*Discovery Chemistry Research & Technologies, Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN 46285, USA*

Received 1 September 2004; revised 3 November 2004; accepted 4 November 2004
Available online 26 November 2004

**Abstract**—The synthesis of novel C6–aryl substituted derivatives of 3-(dimethylamino)chroman is described. The novel derivatives display 5-HT$_7$ receptor affinities that varies from nM to μM, indicating that this small set of derivatives constitute a novel and interesting starting point for further structure-serotonin 5-HT$_7$ activity relationship (SAR) studies.


The most recent member of the serotonin (5-HT) receptor family is the 5-HT$_7$ receptor subtype. It has been identified in rat,[1–4] mouse,[5] human,[6] and guinea pig[7] independently by several groups. The human 5-HT$_7$ receptor consists of 445 amino acids and is positively linked to adenylyl cyclase. Two additional isoforms of the human 5-HT$_7$ receptor, 5-HT$_{7b}$, and 5-HT$_{7d}$, which have different C-terminal tails due to alternative splicing, have also been identified.[8–10] The discrete expression of 5-HT$_7$ receptor mRNA in the central and peripheral nervous systems (CNS and PNS) suggests that it is involved in psychosis,[11] in the regulation of the circadian rhythm[2,12–14] and that it mediates relaxation of blood vessels.[15–17] Therefore, the 5-HT$_7$ receptor is a new interesting target for drug discovery.

Although several well-known compounds have high affinity for the 5-HT$_7$ receptor[11,18] it was only recently that the first selective 5-HT$_7$ receptor antagonists, **1** and **2**, were published.[19,20] Some nonselective 5-HT$_7$ agonists (**3**-**4**) have also recently been reported[21,22] (Fig. 1).

In our search for compounds with selectivity for the 5-HT$_7$ receptor we recently identified **5** as a potent 5-HT$_7$ receptor agonist and **6** as a partial 5-HT$_7$ receptor agonist.[23] The interaction of **5** and **6** with 5-HT$_7$ receptors was shown to be stereoselective, the (*R*)-isomer being the most potent isomer (Fig. 2).

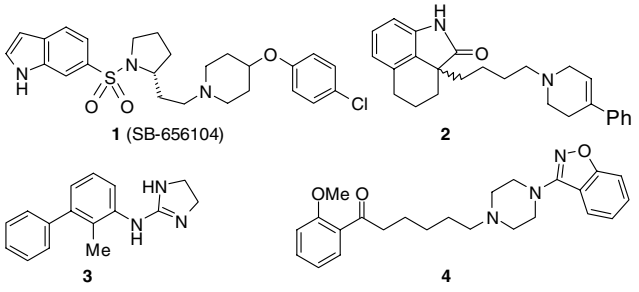


**Figure 1.** Serotonin 5-HT$_7$ receptor antagonists and agonists.

In order to further study SAR of 5-HT$_7$ ligands we here present the synthesis of a new series of 6-arylated (*S*)-3-(dimethylamino)chromans. The new derivatives are

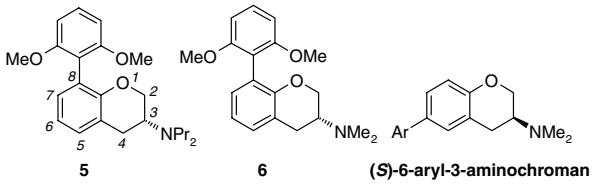


**Figure 2.** Based on the activities of 8-arylated **5** and **6** for the 5-HT$_7$ receptors (*S*)-6-aryl-3-aminochromans were suggested as structures with potential of generating high affinity ligands for the 5-HT$_7$ receptor.

*Keywords*: 3-Aminochromans; Serotonin 5-HT$_7$ receptor ligands; Pharmacological tools.
* Corresponding author. Fax: +1 317 279 5431; e-mail: johansson_anette@lilly.com

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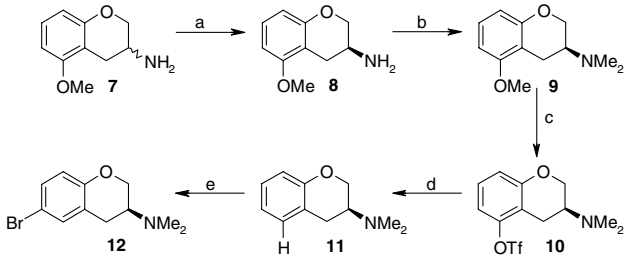
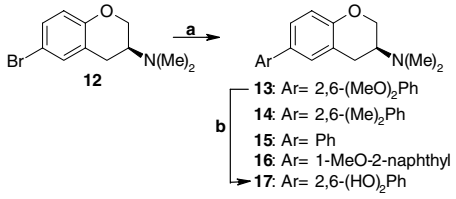
doi:10.1016/j.bmcl.2004.11.013

regioisomers of **5** and **6** and were synthesized in order to study structural factors of importance for the generation of high affinity ligands at serotonin 5-$HT_7$ receptors. The affinity of the compounds for cloned rat 5-$HT_7$ receptors was evaluated in vitro. The novel derivatives display 5-$HT_7$ receptor affinities varying from nM to μM, indicating that this small set of derivatives constitutes an interesting starting point for further structure-5-$HT_7$ receptor activity relationship (SAR) studies.

The synthesis of the novel compounds **12**–**17** is outlined in Schemes 1 and 2. The starting material **7**[24] contained about 10% of the (*R*)-isomer and was further resolved by recrystallization of the D-(−)-tartrate in $H_2O$ to give **8**.




**Scheme 1.** Reagents: (a) D-tartaric acid, $H_2O$ (63%); (b) HCHO, $NaBH_3CN$, MeOH (93%); (c) (i) 48% aq HBr; (ii) $Tf_2O$, $Et_3N$, $CH_2Cl_2$ (81%); (d) HCOOH, $Et_3N$, $(PPh_3)_2PdCl_2$, dppf, DMF, (60%); (e) $Br_2$, HOAc (76%).




**Scheme 2.** Reagents: (a) $ArB(OH)_2$, $(PPh_3)_4Pd$, DME/EtOH/$H_2O$, $Na_2CO_3$, 45 W; (b) 48% aq HBr.

The enantiomeric purity of **8** was indirectly determined on the corresponding diastereomeric (*S*)-Mosher amides of **8** to be >99% ee as analyzed by HPLC. Reductive alkylation of **8** by formaldehyde and $NaBH_3CN$ gave **9**. Demethylation of **9** gave the phenol, which was treated with triflic anhydride to give triflate **10**. The hydrogen analogue **11**[25] was obtained by a palladium catalyzed reduction of **10**. Bromination of **11** afforded the key intermediate **12**.

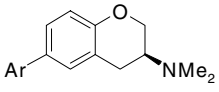
The novel derivatives **13**–**16** were synthesized from **12** using palladium mediated Suzuki-coupling reactions[26] with various arylboronic acids facilitated by microwave irradiation.[27] The dimethyl ether **13** was converted to the resorcinol derivative **17** by treatment with HBr.

2,6-Dimethylphenyl-, 2,6-dimethoxyphenyl- and 1-methoxy-2-naphthylboronic acids were prepared from 2-bromo-1,3-dimethylbenzene, 2,6-dimethoxy-benzene and 1-methoxy-naphthalene, respectively. The arenes were lithiated with BuLi and then treated with trimethylborate followed by acid hydrolysis to yield the corresponding boronic acids.

The ability of the novel compounds to bind to serotonin 5-$HT_7$ receptors was studied. The affinities of the compounds for cloned rat 5-$HT_7$ receptors expressed in Sf9-cells and labeled by [$^3$H]5-HT as well as for cloned 5-$HT_{1A}$ receptors expressed in CHO-cells and labeled by [$^3$H]8-OH-DPAT were determined in vitro. Efficacy of **14** at the 5-$HT_7$ receptor was determined by measuring its effect on cAMP production in CHO cells in relation to the effect elicited by 5-HT.[28] The results are presented in Table 1 and compounds **1**, **5**, and **6** are included for comparative purposes.

Whereas the C6–phenyl derivative **15** does not bind to 5-$HT_7$ receptors, the corresponding 2,6-dimethyl-phenyl derivative **14** has high affinity for the 5-$HT_7$ receptor and is a highly efficacious 5-$HT_7$ receptor partial agon-

**Table 1.** Physical and biological data of the novel derivatives **13**–**17**




| Compound | Ar | Yield (%) | Mp (°C) | $[\alpha]_D^{23}$ [a] | Anal.[b] | $K_i$ (nM)[c] | | Ratio 5-$HT_{1A}$/5-$HT_7$ | Efficacy (%) |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | [$^3$H]8-OH-DPAT (5-$HT_{1A}$) | [$^3$H]5-HT (5-$HT_7$) | | |
| **13** | 2,6-DiMeOPh | 76 | 220–222 | −72 | $C_{19}H_{23}NO_3 \cdot HCl \cdot 1/4H_2O$ | | 367 ± 11 | | |
| **14** | 2,6-DiMePh | 57 | 220–223 | −66 | $C_{19}H_{23}NO \cdot HCl \cdot 1/4H_2O$ | 75.1 | 13.4 ± 15 | 6 | 76 ± 11 |
| **15** | Ph | 71 | 232 | −110 | $C_{17}H_{19}NO \cdot HCl$ | | >1000 | | |
| **16** | 1-MeO-2-Naphthyl | 73 | 192 | −94 | $C_{22}H_{23}NO_2 \cdot HCl \cdot 1/4H_2O$ | 594 | 75.9 ± 15 | 8 | |
| **17** | 2,6-DiOHPh | 69 | 310–306 | −88 | $C_{17}H_{19}NO_3 \cdot HCl \cdot 1/4H_2O$ | | >1000 | | |
| **1**[d] | | | | | | 562 | 1.99 | 282 | Antagonist |
| **5**[e] | | | | | | 174 ± 15 | 6.44 ± 1.39 | 27 | 154 ± 11 |
| **6**[e] | | | | | | >1000 | 5.29 ± 0.09 | >189 | 28 ± 3 |

[a] (*c* 1.0, MeOH).
[b] The compounds were analyzed for C, H, and N and the results were within 0.4% of the theoretical value.
[c] For experimental conditions see Ref. 28.
[d] See Ref. 19.
[e] See Ref. 23.

ist. Introduction of *diortho* substituents into a phenyl ring has previously been shown to affect both the affinity and selectivity for 5-$HT_7$ receptors.[23,28] Changing the *ortho* substituents from dimethyl to dimethoxy as in compound **13**, decreases the affinity 27 times for the 5-$HT_7$ receptor. This is in contrast to the 8-aryl-3-aminochroman series where the dimethoxy derivatives were identified as having high affinity for the receptor.[23] The corresponding resorcinol derivative **17** is devoid of or has low affinity to the 5-$HT_7$ receptor. The 1-methoxy-2-naphthyl derivative **16** showed both some affinity and selectivity for 5-$HT_7$ receptors.

A requisite for agonism in the 8-aryl-3-aminochroman series appears to be dipropyl substitution at the nitrogen as in compound **5**, while the dimethylsubstituted **6** is a weak partial agonist. In this series, the *N*,*N*-dimethylamino derivative **14** is a highly efficacious partial agonist.

To rationalize the difference in stereoselectivity and activity between **6** (the (*R*)-isomer) and **14** (the (*S*)-isomer) the two regioisomers can be overlayed as shown in Figure 3. We performed a Monte Carlo search in Macromodel using the MM2 force field to identify low-energy conformations of the selective 5-$HT_7$ ligands **6** (partial agonist) and **14** (partial agonist). The lowest energy conformations of **6** and the second lowest energy conformation of **14** were used to compare the two structures. In this fit the 8-aryl and 6-aryl substituents overlap. The nitrogen and the nitrogen lone-pair also overlaps and can interact with the same hypothetical binding points in the receptor. However, the position of the oxygen in the chroman ring is different between the two isomers and may to a certain extent explain the differences observed between the 8- and 6-aryl series. There are other options to overlay these structures. However, the present overlay rationalizes the difference in stereochemistry as well as having the common bulk of the compounds in the same region.

The present series of compounds, although limited, seems to constitute an interesting starting point for further structure–activity relationship (SAR) studies at 5-$HT_7$ receptors. The results indicate that bulky lipophilic substituents at C6 in 3-aminochromanes are accommodated in the binding site of the serotonin 5-$HT_7$ receptor.

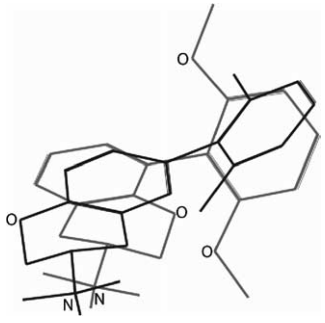



**Figure 3.** Best fit of the 5-$HT_7$ partial agonists **6** (gray) and **14** (black). Mean distance between fitted atoms (centroids in the two aromatic rings and the *N*-electron pairs) is 0.67 Å.

## Acknowledgements

Financial support was obtained from AstraZeneca R&D Södertälje, Sweden. We are grateful to Personal Chemistry for providing the Smith Microwave Synthesizers and to Dr. A. Karlen for the computational chemistry.

## References and notes

1. Shen, Y.; Monsma, F. J.; Metcalf, M. A.; Jose, P. A.; Hamblin, M. W.; Sibley, D. R. *J. Biol. Chem.* **1993**, *268*, 18200–18204.
2. Lovenberg, T. W.; Baron, B. M.; Lecea, L.; de Miller, J. O.; Prosser, R. A.; Rea, M. A.; Foye, P. E.; Rucke, M.; Slone, A. L.; Siegel, B. W.; Danielsson, P. E.; Sutcliffe, J. G.; Erlander, M. G. *Neuron* **1993**, *11*, 449–458.
3. Ruat, M.; Traiffort, E.; Leurs, R.; Tardivel-Lacombe, J.; Diaz, J.; Arrang, J.-M.; Schwartz, J.-C. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 8547–8551.
4. Meyerhof, W.; Obermüller, F.; Fehr, S.; Richter, D. *DNA Cell Biol.* **1993**, *12*, 401–409.
5. Plassat, J.-L.; Amlaiky, N.; Hen, R. *Mol. Pharmacol.* **1993**, *44*, 229–236.
6. Bard, J. A.; Zgombick, J.; Adham, N.; Vaysse, P.; Branchek, T. A.; Weinshank, R. L. *J. Biol. Chem.* **1993**, *268*, 23422–23426.
7. Tsou, A.-P.; Kosaka, A.; Bach, C.; Zuppan, P.; Yee, C.; Tom, L.; Alvarez, R.; Ramsey, S.; Bonhaus, D. W.; Stefanich, E.; Jakeman, L.; Eglen, R. M.; Chan, H. W. *J. Neurochem.* **1994**, *63*, 456–464.
8. Heidman, D. E. A.; Metcalf, M. A.; Kohen, R.; Hamblin, M. W. *J. Neurochem.* **1997**, *413*, 489–494.
9. Stam, N. J.; Roesnik, C.; Dijcks, F.; Garritsen, A.; van Herpen, A.; Olijve, W. *FEBS Lett.* **1997**, *413*, 489–494.
10. Jasper, J. R.; Kosaka, A.; To, Z. P.; Chang, D. J.; Eglen, R. M. *Br. J. Pharmacol.* **1997**, *122*, 126–132.
11. Roth, B.; Craigo, S. C.; Choudhary, M. S.; Uluer, A.; Monsma, F. J., Jr.; Shen, Y.; Meltzer, H. Y.; Sibley, D. R. *J. Pharmacol. Exp. Ther.* **1994**, *268*, 1403–1410.
12. Sumova, A.; Maywod, E. S.; Selvage, D.; Ebling, F. J. P.; Hastings, M. H. *Brain Res.* **1996**, *709*, 88–96.
13. Ying, S.-W.; Rusak, B. *Brain Res.* **1997**, *755*, 246–254.
14. Schwartz, W. J. *Adv. Int. Med.* **1993**, *38*, 81–106.
15. Leung, E.; Walsh, L. K. M.; Pulido-Rios, M. T.; Eglen, R. M. *Br. J. Pharmacol.* **1996**, *117*, 926–930.
16. Cushing, D. J.; Zgombick, J. M.; Nelson, D. L.; Cohen, M. L. *J. Pharmacol. Exp. Ther.* **1996**, *277*, 1560–1566.
17. Martin, G. R.; Wilson, R. J. *Br. J. Pharmacol.* **1995**, *114*, 383, Suppl S.
18. Sleight, A. J.; Boess, F. G.; Bourson, A.; Sibley, D. R.; Monsma, F., Jr. *J. Drug News Perspect.* **1997**, *10*, 214–224.
19. Forbes, I. T.; Douglas, S.; Gribble, A. D.; Ife, R. J.; King, F. D.; Lightfoot, A. P.; Garner, A. E.; Riley, G. J.; Jeffrey, P.; Stevens, A. J.; Stean, T. O.; Thomas, D. R. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3341–3344.
20. Kikuchi, C.; Nagaso, H.; Hiranuma, T.; Koyama, M. *J. Med. Chem.* **1999**, *42*, 533–535.

21. Parikh, V.; Welch, W. M.; Schmidt, A. W. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 269–271.
22. Perrone, R.; Berardi, F.; Colabufo, N. A.; Lacicita, E.; Leopoldo, M.; Tortorella, V. *J. Med. Chem.* **2003**, *46*, 646–649.
23. Holmberg, P.; Sohn, D.; Leideborg, R.; Caldirola, P.; Zlatoidsky, P.; Hanson, S.; Mohell, N.; Rosqvist, S.; Nordvall, G.; Johansson, A. M.; Johansson, R. *J. Med. Chem.* **2004**, *47*, 3927–3930.
24. A gift from AstraZeneca R&D, Södertälje.
25. Brisander, M.; Caldirola, P.; Johansson, A. M.; Hacksell, U. *J. Org. Chem.* **1998**, *63*, 5362–5367.
26. Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483.
27. The microwave heating was performed with a single-mode cavity in sealed heavy walled Pyrex tubes. See, for example: Larhed, M.; Lindeberg, G.; Hallberg, A. *Tetrahedron Lett.* **1996**, *37*, 8219–8222.
28. Linnanen, T.; Brisander, M.; Unelius, L.; Rosqvist, S.; Nordvall, G.; Hacksell, U.; Johansson, A. M. *J. Med. Chem.* **2001**, *44*, 1337–1340.