

Novel 3-aminochromans as potential pharmacological tools for the serotonin 5-HT₇ receptor

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Abstract—The synthesis of novel C6-aryl substituted derivatives of 3-(dimethylamino)chroman is described. The novel derivatives display 5-HT₇ 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-HT₇ activity relationship (SAR) studies.

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The most recent member of the serotonin (5-HT) receptor family is the 5-HT₇ receptor subtype. It has been identified in rat,^{1–4} mouse,⁵ human,⁶ and guinea pig⁷ independently by several groups. The human 5-HT₇ receptor consists of 445 amino acids and is positively linked to adenylyl cyclase. Two additional isoforms of the human 5-HT₇ 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-HT₇ 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-HT₇ receptor is a new interesting target for drug discovery.

Although several well-known compounds have high affinity for the 5-HT₇ receptor^{11,18} it was only recently that the first selective 5-HT₇ receptor antagonists, **1** and **2**, were published.^{19,20} Some nonselective 5-HT₇ agonists (**3–4**) have also recently been reported^{21,22} (Fig. 1).

In our search for compounds with selectivity for the 5-HT₇ receptor we recently identified **5** as a potent 5-HT₇ receptor agonist and **6** as a partial 5-HT₇ receptor

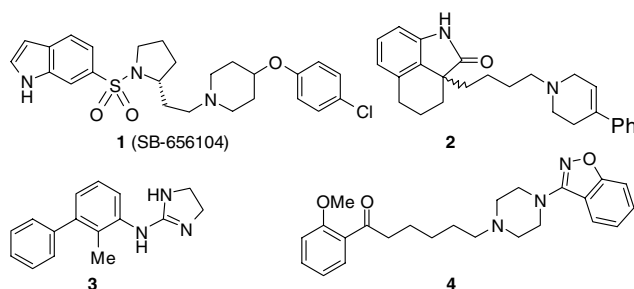


Figure 1. Serotonin 5-HT₇ receptor antagonists and agonists.

agonist.²³ The interaction of **5** and **6** with 5-HT₇ receptors was shown to be stereoselective, the (*R*)-isomer being the most potent isomer (Fig. 2).

In order to further study SAR of 5-HT₇ ligands we here present the synthesis of a new series of 6-arylated (*S*)-3-(dimethylamino)chromans. The new derivatives are

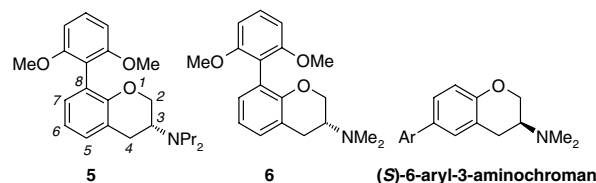


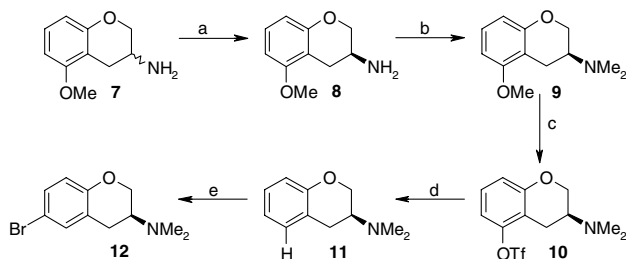
Figure 2. Based on the activities of 8-arylated **5** and **6** for the 5-HT₇ receptors (*S*)-6-aryl-3-aminochromans were suggested as structures with potential of generating high affinity ligands for the 5-HT₇ receptor.

Keywords: 3-Aminochromans; Serotonin 5-HT₇ receptor ligands; Pharmacological tools.

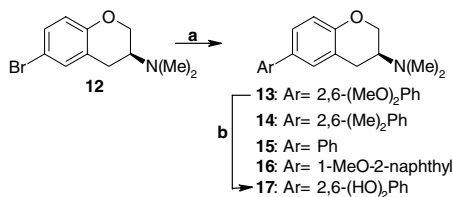
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regioisomers of **5** and **6** and were synthesized in order to study structural factors of importance for the generation of high affinity ligands at serotonin 5-HT₇ receptors. The affinity of the compounds for cloned rat 5-HT₇ receptors was evaluated in vitro. The novel derivatives display 5-HT₇ receptor affinities varying from nM to μ M, indicating that this small set of derivatives constitutes an interesting starting point for further structure-5-HT₇ 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 H₂O to give **8**.



Scheme 1. Reagents: (a) D-tartaric acid, H₂O (63%); (b) HCHO, NaBH₃CN, MeOH (93%); (c) (i) 48% aq HBr; (ii) Tf₂O, Et₃N, CH₂Cl₂ (81%); (d) HCOOH, Et₃N, (PPh₃)₂PdCl₂, dppf, DMF, (60%); (e) Br₂, HOAc (76%).



Scheme 2. Reagents: (a) ArB(OH)₂, (PPh₃)₄Pd, DME/EtOH/H₂O, Na₂CO₃, 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 NaBH₃CN 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 reactions²⁶ 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-dimethoxybenzene 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-HT₇ receptors was studied. The affinities of the compounds for cloned rat 5-HT₇ receptors expressed in Sf9-cells and labeled by [³H]5-HT as well as for cloned 5-HT_{1A} receptors expressed in CHO-cells and labeled by [³H]8-OH-DPAT were determined in vitro. Efficacy of **14** at the 5-HT₇ 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-HT₇ receptors, the corresponding 2,6-dimethyl-phenyl derivative **14** has high affinity for the 5-HT₇ receptor and is a highly efficacious 5-HT₇ receptor partial agon-

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

Compound	Ar	Yield (%)	Mp (°C)	[α] _D ²³ ^a	Anal. ^b	<i>K_i</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 ·HCl·1/4H ₂ O	75.1	367 ± 11	6	76 ± 11
14	2,6-DiMePh	57	220–223	–66	C ₁₉ H ₂₃ NO·HCl·1/4H ₂ O		13.4 ± 15		
15	Ph	71	232	–110	C ₁₇ H ₁₉ NO·HCl		>1000		
16	1-MeO-2-Naphthyl	73	192	–94	C ₂₂ H ₂₃ NO ₂ ·HCl·1/4H ₂ O		75.9 ± 15		
17	2,6-DiOHPh	69	310–306	–88	C ₁₇ H ₁₉ NO ₃ ·HCl·1/4H ₂ O	562	>1000	282	Antagonist
1 ^d							1.99		
5 ^e							174 ± 15		
6 ^e							6.44 ± 1.39		
						>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-HT₇ receptors.^{23,28} Changing the *ortho* substituents from dimethyl to dimethoxy as in compound **13**, decreases the affinity 27 times for the 5-HT₇ 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-HT₇ receptor. The 1-methoxy-2-naphthyl derivative **16** showed both some affinity and selectivity for 5-HT₇ 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*-dimethyl-amino 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-HT₇ 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-HT₇ receptors. The results indicate that bulky lipophilic substituents at C6 in 3-aminochromanes are accommo-

dated in the binding site of the serotonin 5-HT₇ receptor.

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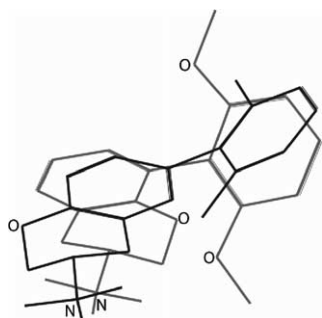


Figure 3. Best fit of the 5-HT₇ partial agonists **6** (gray) and **14** (black). Mean distance between fitted atoms (centroids in the two aromatic rings and the *N*-electron pairs) is 0.67 Å.

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