Novel 2-Aminotetralin and 3-AminoChroman Derivatives as Selective Serotonin 5-HT$_7$ Receptor Agonists and Antagonists

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Abstract: The understanding of the physiological role of the G-protein coupled serotonin 5-HT$_7$ receptor is largely rudimentary. Therefore, selective and potent pharmacological tools will add to the understanding of serotonergic effects mediated through this receptor. In this report, we describe two compound classes, chromans and tetralins, encompassing compounds with nanomolar affinity for the 5-HT$_7$ receptor and with good selectivity. Within theses classes, we have discovered both agonists and antagonists that can be used for further understanding of the pharmacology of the 5-HT$_7$ receptor.

The functional significance of the serotonin 5-HT$_7$ receptor is largely unknown. However, the distribution pattern of the 5-HT$_7$ receptor mRNA in both the central nervous system and in the periphery has led to a number of suggestions of the physiological role of this G-protein coupled receptor. The presence of mRNA in the thalamus and hypothalamus combined with the high affinity of antipsychotic drugs for the 5-HT$_7$ receptor have implicated the importance of this subtype in psychiatric disorders.[1] Expression of 5-HT$_7$ receptors has also been reported in limbic and cortical areas of rodent brains where it is localized on glutamatergic neurons,[2a−c] and therefore signaling of the receptor has been linked to memory and learning processes. Furthermore, the receptor has been associated with central functions such as circadian time keeping,[1] epilepsy,[2b] pain perception,[3] and migraine.[4] A role for peripherally located 5-HT$_7$ receptors in gastrointestinal function[5] has been suggested.

The lack of further insight into the pharmacology of the 5-HT$_7$ receptor has been hampered by the absence of chemical tools. In recent time, antagonists such as **1**−**4**[6−9] with nanomolar affinity and selectivity toward selected receptors have appeared. Still, no potent and selective 5-HT$_7$ receptor agonists have emerged even though some nonselective 5-HT$_7$ agonists (**5**−**6**)[10,11] are reported. In this letter, we communicate the biochemical features of a number of 8-substituted-3-aminochromans (3,4-dihydro-*2H-1*-benzopyrans) and 5-substituted-2-aminotetralins with high affinity and good selectivity for the 5-HT$_7$ receptor. These novel structures have efficacies ranging from antagonists to full agonists, making them useful tools for disclosing the intricacies of this the most recently described serotonergic receptor.The tetralin derivatives were obtained from commercially available (*S*)-5-methoxy-2-aminotetralin (Scheme 1). Reductive alkylation with propanal and NaBH$_3$CN

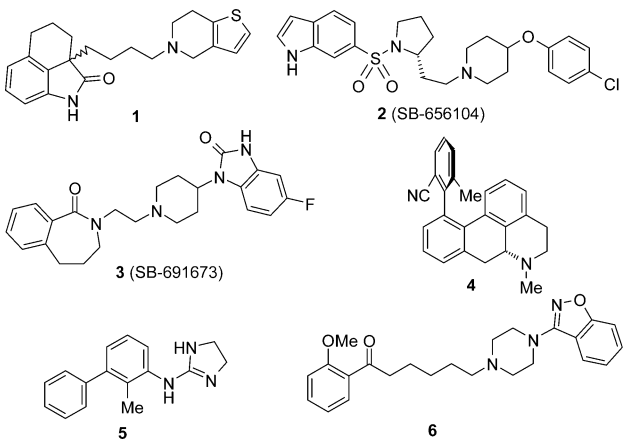
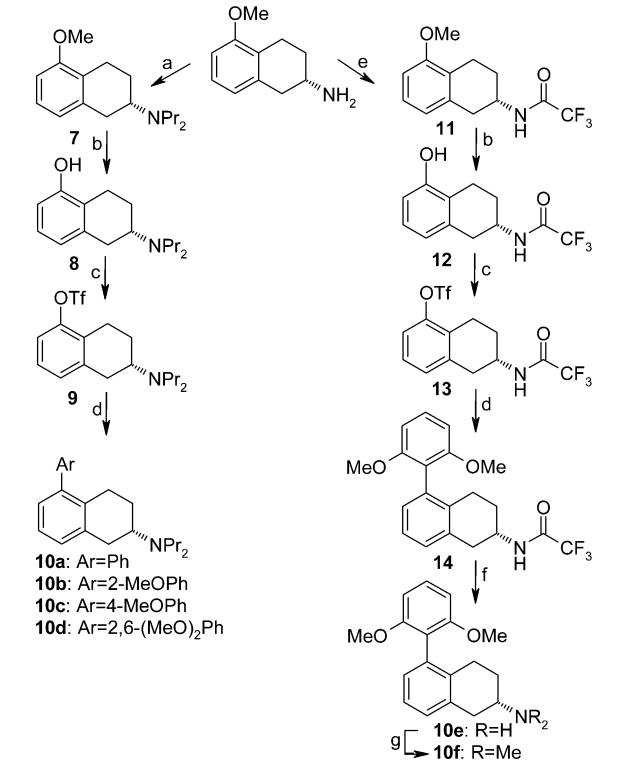


Figure 1. 5-HT$_7$ antagonists and agonists.

Scheme 1[a]



[a] Reagents: (a) EtCHO, NaBH$_3$CN, MeOH; (b) BBr$_3$, CH$_2$Cl$_2$; (c) (CF$_3$SO$_3$)$_2$O, Et$_3$N, CH$_2$Cl$_2$; (d) ArB(OH)$_2$, (PPh$_3$)$_4$Pd, Na$_2$CO$_3$, PhMe, EtOH; (e) TFAA, Et$_3$N, CH$_2$Cl$_2$; (f) AcOH, HCl, Δ; (g) HCHO, NaBH$_3$CN, MeOH.

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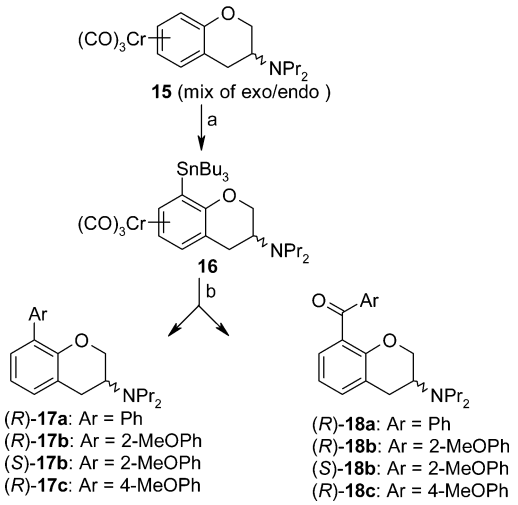
Scheme 2[a]



[a] Reagents: (a) *n*-BuLi, TMEDA, THF, Bu_3SnCl; (b) i. $(dba)_3Pd_2$, Ph_3As, CuI, ArI, DMF. ii. *hν*. iii. separation by chromatography.

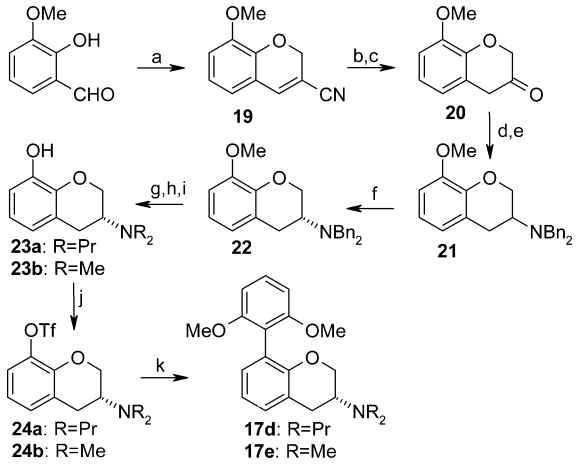
afforded (*S*)-5-methoxy-2-(dipropylamino)tetralin (**7**), which was demethylated by BBr_3 in CH_2Cl_2 at low temperature to give **8**.

Phenol **8** was converted to the triflate (trifluoromethanesulfonic acid) by reaction with triflic anhydride. The triflate was subjected to Suzuki cross-coupling reactions to afford the target (*S*)-5-aryl-2-(dipropylamino)tetralins, **10a**−**d**. To allow for the *N*-group(s) to be varied at a later stage, a slightly different route was also developed. (*S*)-5-Methoxy-2-aminotetralin was converted into the trifluoroacetamide **11**, followed by demethylation to phenol **12** and a subsequent triflation afforded **13**. The 5-aryl substituent was introduced, as above, using the Suzuki coupling reaction. Acidic hydrolysis of the *N*-trifluoroacetmide gave primary amine **10e**, which was reductively alkylated to afford the desired (*S*)-5-aryl-2-(dimethylamino)tetralin.

The C8-substituted (*R*)- or (*S*)-3-(dipropylamino)-chromans were prepared by two different routes. In the first route, the (*R*)- or (*S*)-enantiomer of a mixture of *endo* and *exo*-[η^6-3-(dipropylamino)chroman]-Cr$(CrO)_3$[12] (**15**) was reacted with *n*-butyllithium and tributyltin chloride to give the corresponding 8-tributylstannane **16** (Scheme 2). The 8-aryl substituent was then introduced by Stille coupling reactions with the appropriate iodoarene followed by photolytic cleavage of the chromium complex to give a mixture of the 8-aryl (**17a**−**c**) and the 8-aroyl (**18a**−**c)** derivatives. The target 8-aryl compounds were obtained by flash chromatography.

The second route starts with a base-catalyzed Michael addition of 2-hydroxy-3-methoxybenzaldehyde to acrylonitrile, followed by a ring-closing condensation to afford the unsaturated nitrile **19**. The nitrile was hydrolyzed to the carboxylic acid followed by a Curtius rearrangement to give ketone **20**. Reductive amination and *N*-alkylation gave the *N*,*N*-dibenzyl derivative **21**, which after fractional crystallization as the L-dibenzoyltartrate gave the (*R*)-enantiomer **22** in an enantiomeric purity of 99% ee. Pd-catalyzed *N*,*N*-debenzylation followed by reductive alkylation and demethylation gave phenols **23a**−**b**, which were treated with triflic anhydride to give triflates **24a**−**b**. The target compounds **17d** and **17e**

Scheme 3[a]



[a] Reagents: (a) CH_2═CHCN, 1,4-diazabicyclo[2.2.2]-octane; (b) NaOH (10% in H_2O); (c) $(PhO)_2P(O)N_3$, Et_3N, HCl; (d) $BnNH_2$, $NaBH_3CN$, AcOH; (e) BnBr, KI, K_2CO_3; (f) L-dibenzoyltartaric acid, H_2O/1,2-dichloro-ethane (1:2); (g) $HCOONH_4$, Pd(C); (h) EtCHO or HCHO, $NaBH_3CN$, Montmorillonite K-10; (i) Me_2SBF_3; (j) $(CF_3SO_2)_2O$, Et_3N; (k) $(PPh_3)_4Pd$, (2,6-$(MeO)_2$PhB$(OH)_2$.

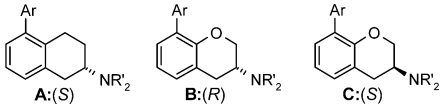
were obtained by Suzuki coupling of triflates **24a** and **24b** with (2,6-dimethoxyphenyl)boronic acid, respectively.

The novel compounds were evaluated for their affinity to the 5-HT_7, 5-HT_{1A}, and D_{2A} receptors, respectively, according to methods previously described,[9,13,15−19] and the results are summarized in Table 1. Selected compounds were also tested for affinities to a larger number of receptors and ion channels (Table 2).[14] In brief, the compounds were tested for their ability to displace [^{3}H]-raclopride from mouse fibroblast (Ltk$^-$) cells expressing the human D_{2A} receptor. Affinity for the 5-HT_{1A} receptor was determined in CHO cells expressing the human receptor or in rat hippocampal cells, using [^{3}H]-8-OH-DPAT as the ligand. The affinity of the compounds for the rat 5-HT_7 receptor was measured in CHO- or Sf9-cells using [^{3}H]-5-HT as the ligand. Efficacy at the rat 5-HT_7 receptor was obtained by measuring the effect of cAMP production in CHO cells in relation to the effect elicited by 5-HT.[9] Compounds **1**−**4** and the corresponding literature data are included for comparison (Table 1).

The biological results of the present series of compounds show that the dimethylaminotetralins and the dipropylaminotetralins as well as the corresponding chromans, gave ligands with high affinity for the 5-HT_7 receptor, whereas the primary amines are of lower potency.

The interaction of the novel ligands with the 5-HT_7 receptor is stereospecific favoring the (*R*)-chromans ((*S*)-tetralins), giving eudismic ratios of approximately 130 (**(*S*)-17b** vs. **(*R*)-17b**). Selectivity toward the 5-HT_{1A} receptor was accomplished by subtle changes of the 5-aryl substituent (8-aryl in the chromans). The introduction of a single *ortho* methoxy substituent reduces the affinity for the 5-HT_{1A} receptor 8−13 times, while the affinity for the 5-HT_7 receptors is unchanged (compare tetralins **10a** and **10b** and chromans **17a** and **17b)**. Further introduction of a second *ortho* methoxy substituent (**10d** and **17d**) substantially reduces the affinity for the 5-HT_{1A} receptor while only marginally affecting the binding to the 5-HT_7 receptor. It thus seems as the *ortho* substituents by forcing the 5- (or 8-)-

Table 1. In Vitro Binding Affinities of the Novel Derivatives to 5-HT_7, 5-HT_{1A}, and D_{2A} Receptors Labeled by [^{3}H]5-HT, [^{3}H]8-OH-DPAT, and [^{3}H]Raclopride and Effects on 5-HT_7-Mediated Stimulation of cAMP Production in CHO Cells Expressing Rat 5-HT_7 Receptors



				K_i (nM)[a]				
compd	Ar	R′	struct	5-HT_7	5-HT_{1A}	D_{2A}	K_i ratio 5-HT_{1A}/5-HT_7	efficacy[b](%)
10a	Ph	Pr	A	3.38 ± 0.53	0.87 ± 0.28	NT[c]	0.26	100
10b	2-MeOPh	Pr	A	1.73 ± 0.28	11.7 ± 1.7	NT	6.8	100
10c	4-MeOPh	Pr	A	12.4 ± 0.6	1.49 ± 0.36	NT	0.12	
10d	2,6-$(MeO)_2$Ph	Pr	A	7.9 ± 0.42	347 ± 198	1210 ± 10	44	100
10e	2,6-$(MeO)_2$Ph	H	A	78.7 ± 5.1	>1000	NT	>12.7	
10f	2,6-$(MeO)_2$Ph	Me	A	2.55 ± 0.45	1420 ± 210	241 ± 46	257	<10
17a	Ph	Pr	B	2.92 ± 1.11	1.23 ± 0.05	106 ± 11	0.42	100
(*R*)-17b	2-MeOPh	Pr	B	2.7 ± 0.35	10.3 ± 1.6	512 ± 110	3.8	100
(*S*)-17b	2-MeOPh	Pr	C	364 ± 37	680 ± 110	2110 ± 440	1.9	
17c	4-MeOPh	Pr	B	12.6 ± 2.3	1.31 ± 0.15	741 ± 200	0.10	91
17d	2,6-$(MeO)_2$Ph	Pr	B	6.44 ± 1.39	174 ± 15	NT	27	154 ± 11
17e	2,6-$(MeO)_2$Ph	Me	B	5.29 ± 0.09	>1000	NT	>189	28 ± 3
1[d]				6.46	513		79	antag
2[e]				1.99	562		282	antag
3[f]				2.24	479	234	214	antag
4[g]				3.79	142	498	37	antag

[a] The K_i-values are means ± standard errors of 2−3 experiments. The binding studies were performed essentially as described in Johansson et al.[19] [b] *c*AMP production in CHO-cells in % of 5-HT stimulated production. Antag = antagonist. [c] NT = not tested. [d] See ref 6. [e] See ref 7. [f] See ref 8. [g] See ref 9.

Table 2. Receptor Binding Profile of **10d** and **10f**

			K_i (nM)	
receptor	ligand	tissue or cell	**10d**	**10f**
$5HT_7$	[^{3}H]5-HT	CHOr$5HT_7$	7.9	2.55
$5HT_{1A}$	[^{3}H]8-OH-DPAT	CHOh$5HT_{1A}$	347	1420
$5HT_{2A}$	[^{3}H]Ketanserin	rat cortex	1450	1340
$5HT_3$	[^{3}H]GR-65630	rabbit ileum muscularis		>1000[a]
$5HT_4$	[^{3}H]GR-113808	guinea pig striatum		>1000[a,b]
$5HT_5$	[^{3}H]LSD	CHO cells		65[b]
$5HT_6$	[^{3}H]5-HT	CHOr$5HT_6$	>900	>1000[a,b]
D_1	[^{3}H]SCH23390	rat striatum	>1000	>1000
D_{2A}	[^{3}H]Raclopride	LtkhD$_{2A}$	1210	241
α_1	[^{3}H]Prazosin	rat cortex	>1000	3670
α_2	[^{3}H]RX821002	rat cortex	2090	188
β	[^{3}H]DHA	rat cortex	>1000	>1000
muscarinic	[^{3}H]QNB	rat cortex	>1000	>1000

[a] IC_{50} nM. [b] The binding studies were performed by MDS Pharma according to their standard protocols.

aryl group out of the plane of the tetralin (or chroman) reduces favorable interactions with the 5-HT_{1A} receptor. The 4-methoxyphenyl (**10c** and **17c**) and phenyl (**10a** and **17a**) derivatives are equipotent at the 5-HT_{1A} receptors, while their affinity for 5-HT_7 receptors is reduced 4 times. Thus, the ligand binding site of the 5-HT_7 receptor appears to be more restricted for substituents in the *para* position of the 5- (or 8-)-aryl group than the corresponding site in the 5-HT_{1A} receptor.

Interestingly, decreasing the size of the *N*-alkyl-substituents from propyl to methyl increases the selectivity for the 5-HT_7 receptor 6−7-fold. This increase is at least for the chromans and to some extent also for the tetralins, due to the drop in affinity for the 5-HT_{1A} receptor supporting earlier studies suggesting the existence of a propyl pocket at this receptor.[15] Not only is the selectivity affected by varying the alkyl substitution of the nitrogen group, but also the signal transduction seems to be influenced by the choice of *N*-alkyl groups. While the 2,6-dimethoxyphenyl substituted 2-(dipropylamino)-tetralin (**10d**) and 3-(dipropylamino)chroman (**17d**) are full agonists (100 and 154% of the effect of 5-HT, respectively) at the 5-HT_7 receptor, the corresponding dimethylamino substituted derivatives **10f** and **17e** are antagonist or weak partial agonist, respectively. The chroman derivatives appear to have a higher efficacy than the corresponding tetralins. The dipropylamino derivatives are all full agonists, whereas compounds with a dimethylamino group show significantly lower efficacy. The increase in volume and lipophilicity of the *N*-substituents induces a dramatic change in intrinsic activity without affecting affinity, indicating that occupation of a propyl pocket is needed for G-protein activation of the 5-HT_7 receptor.

Two compounds, the agonist **10d** and antagonist **10f**, showing high selectivity for the 5-HT_7 receptor over 5-HT_{1A} and D_2 receptors, were profiled against 32 other receptors and nine ion channels. The results show that this structural class seems to be highly selective toward other receptors and ion channels (K_i or IC50 > 1000 nM) except for a few targets shown in Table 2. It is noteworthy that the selectivity of **10d** and **10f** toward the other 5-HT receptors tested is high with the exception of a moderate selectivity for **10f** over the 5-HT_5 receptor (24-fold).

The results presented herein show that structural modifications of (*S*)-2-aminotetralin and (*R*)-3-aminochroman give 5-HT_7 ligands ranging from full agonists to antagonists. Further, **10d** has been identified as a selective 5-HT_7 receptor agonist and as such may be used in future studies of the pharmacology/physiology of this subtype of the serotonin family of receptors. A full account of the SAR within these series will be published in due course.

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Supporting Information Available: Experimental details for the binding and functional assays and the synthetic

procedures for the final compounds. This material is available free of charge via the Internet http://pubs.acs.org.

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