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Novel pyridyl-fused 3-amino chroman derivatives with dual action at serotonin transporter and 5-HT$_{1A}$ receptor

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Abstract—Structural modifications of the initial lead, 3-aminochroman (**4**), led to the identification of a novel series of pyridyl-fused amino chroman derivatives (**5**–**8**) and the structural isomers (**9**–**12**). The compounds described were evaluated for dual 5-HT transporter inhibitory and 5-HT$_{1A}$ receptor activities. The design strategy, synthesis, and in vitro biological characterization for these novel compounds are described.

Selective serotonin reuptake inhibitors (SSRIs) are effective antidepressants with fewer side effects than the older tricyclics. SSRIs work by blocking the neuronal reuptake of serotonin, thereby increasing the concentration of serotonin in the synaptic space, and thus increasing the activation of postsynaptic serotonin receptors. However, long-term treatment is required before clinical efficacy is achieved.[1,2] It has been suggested that the SSRIs increase the serotonin levels in the vicinity of the serotonergic cell bodies and that excess serotonin activates somatodendritic 5-HT$_{1A}$ autoreceptors that decrease neuron firing to release serotonin in the forebrain. A 5-HT$_{1A}$ antagonist would limit the negative feedback and should improve the efficacy of the serotonin reuptake mechanism. Co-administration of a 5-HT$_{1A}$ receptor antagonist and a SSRI has been shown to accelerate antidepressant effects.[3,4] Therefore, the concept of developing a dual-acting agent blocking both the 5-HT$_{1A}$ receptor and 5-HT reuptake site in one molecule has been proposed. Several groups have already reported their efforts and design strategies toward constructing new agents with 5-HT$_{1A}$ receptor antagonist and 5-HT reuptake inhibitor properties.[5–9]

Previous reports from our laboratories have revealed a dual-ligand approach to incorporate both a 5-HT transporter and 5-HT$_{1A}$ receptor pharmacophore within a single molecule. Amalgamation of a 5-fluoroindole alkyl amine (**1**)[5] and a 3-aminochroman (**2**)[10] through the common basic nitrogen (Fig. 1) provided racemic *N*-(3-(5-fluoro-1*H*-indol-3-yl)propyl)-5-methoxy-*N*-propylchroman-3-amine (**4**) as an initial lead.[11] As a continuation of this effort, structural modifications were focused on the 3-aminochroman ring present in **4**, with the aim of improving affinity for the 5-HT$_{1A}$ receptor and 5-HT transporter while reducing intrinsic activity at the 5-HT$_{1A}$ receptor. Herein, we report our design strategy, the synthesis, and corresponding biological activities of compounds represented by the 2,3-dihydro-1*H*-pyrano[3,2-*f*]-quinolin-2-amine core **5**–**8** and the constitutionally isomeric 3,4-dihydro-2*H*-pyrano[2,3-*f*]quinolin-3-amine core **9**–**12**.

Inspired by our previous results with heterocycle-fused benzodioxane analogs that demonstrated potent dual activity as both 5-HT transporter inhibitors and 5-HT$_{1A}$ receptor antagonists,[12] we elected to replace the pendant methoxy group on the 3-aminochroman in **4** with a fused pyridine ring. We envisioned this modification would serve a dual role; that the nitrogen in the pyridine would serve as a conformationally constrained hydrogen bond acceptor, a recognized feature of the 5-HT$_{1A}$ pharmacophore,[13] and that the tricyclic ring scaffold would reduce the intrinsic activity at the 5-HT$_{1A}$ receptor.

Keywords: Serotonin transporter; 5-HT$_{1A}$ receptor.
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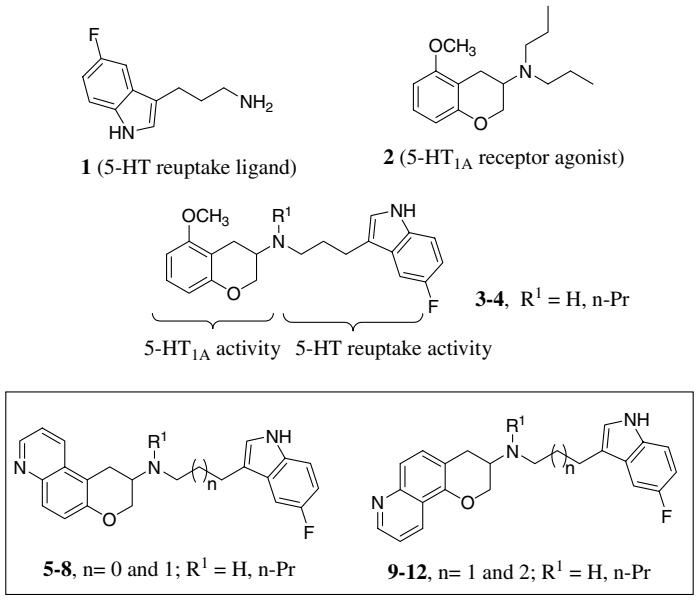
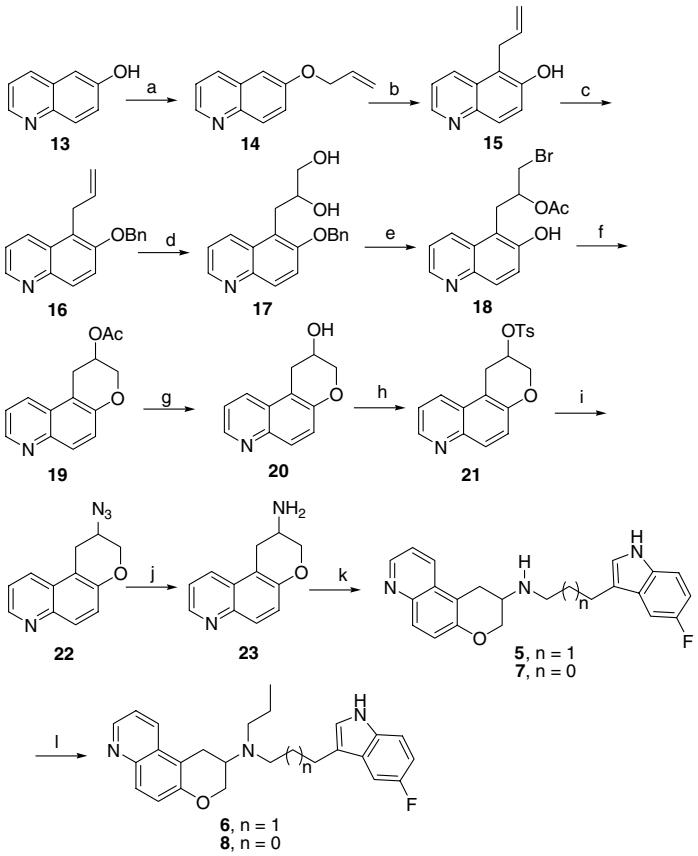
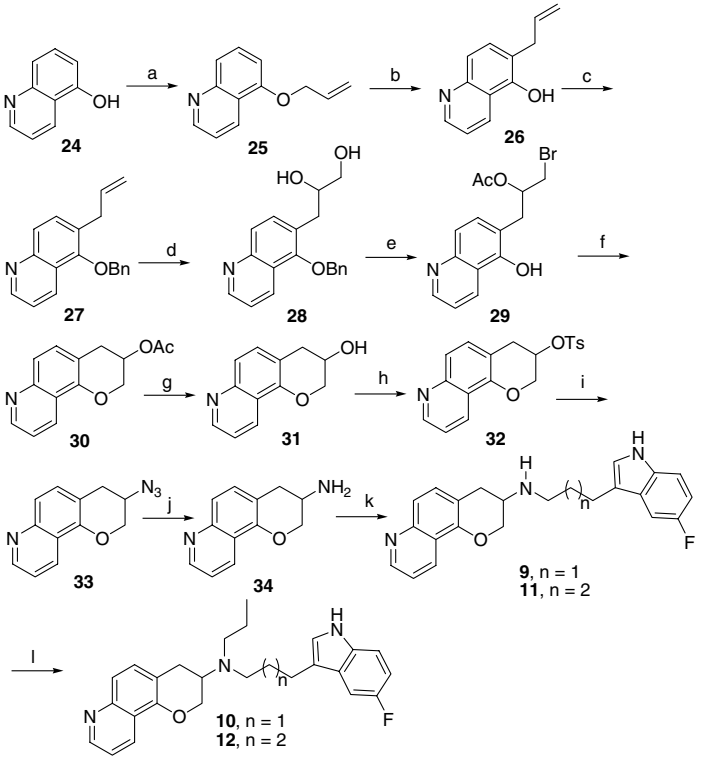


Figure 1. Design strategy.



Scheme 1. Reagents and conditions: (a) allyl bromide/NaH, rt, 89%; (b) *p*-xylene, reflux, 72%; (c) BnCl/NaH, rt, 92%; (d) AD-mix-α/*t*-BuOH · H_2O, rt, 88%; (e) 33% HBr/HOAc, 60 °C, 65%; (f) NaH/DMF, 61%; (g) K_2CO_3/MeOH, rt, 91%; (h) TsCl/Py, rt, 93%; (i) NaN_3/DMF, 60 °C, 77%; (j) Ph_3P/THF–H_2O, rt, 70%; (k) 5-fluoro-3-indolepropyl-bromide or 5-fluoro-3-indoleethyl bromide/Et_3N/DMSO, 90 °C, 38–64%; (l) CH_3CH_2CHO/$NaCNBH_3$/HOAc/MeOH, rt, 45–77%.

The synthesis of compounds **5**–**8** (Scheme 1) began with the formation of 6-allyloxy-quinoline (**14**) from commercially available 6-hydroxyquinoline (**13**). Subsequent Claisen rearrangement produced 5-allyl-quinolin-6-ol (**15**). Following benzyl protection of the phenol present in **15**, Sharpless catalytic dihydroxylation[14] afforded



Scheme 2. Reagents and conditions: (a) allyl bromide/NaH, rt, 85%; (b) *p*-xylene, reflux, 48%; (c) BnCl/NaH, rt, 100%; (d) AD-mix-α/*t*-BuOH · H_2O, rt, 94%; (e) 30% HBr/HOAc, 60 °C, 66%; (f) NaH/DMF, 67%; (g) K_2CO_3/MeOH, rt, 81%; (h) TsCl/Py, rt, 59%; (i) NaN_3/DMF, 60 °C, 68%; (j) Ph_3P/THF–H_2O, rt, 68%; (k) 5-fluoro-3-indolepropyl-bromide or 5-fluoro-3-indolebutyl chloride/Et_3N/DMSO, 90 °C; 18–74%; (l) CH_3CH_2CHO/$NaCNBH_3$/HOAc/MeOH, rt, 36–90%.

3-(6-benzyloxy-quinolin-5-yl)-propane-1,2-diol **17**. Treatment of **17** with 33% hydrogen bromide in acetic acid provided the acetoxy bromide (**18**). Ring closure was carried out in DMF using sodium hydride to generate the chroman **19**. Removal of the acetyl group under the basic condition produced 2,3-dihydro-1*H*-pyrano[3,2-*f*]quinolin-2-ol (**20**). Formation of the tosylate **21** was followed by conversion to azide **22**. Reduction of the azide (**22**) to the amine **23** using triphenylphosphine in THF–H_2O followed by coupling with an appropriate indole alkyl bromide afforded the secondary amines (±)-**5** and (±)-**7**. The corresponding *N*-propyl derivatives (±)-**6** and (±)-**8** were generated by reductive amination with propionaldehyde. Utilizing chiral HPLC, resolution of (±)-**5** provided the corresponding enantiomers in 99% ee. In a similar fashion to that described for the racemates, reductive amination of (+)-**5** and (−)-**5** provided (+)-**6** and (−)-**6** in optically pure form.

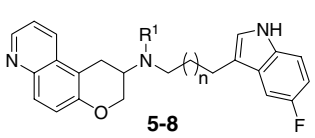
Utilizing 5-hydroxyquinoline (**24**) and following the same general synthetic sequence described above, the desired products (±)-**9** and (±)-**10** were isolated (Scheme 2). Resolution of (±)-**9** into its respective enantiomers using chiral HPLC provided (+)-**9** and (−)-**9** in 99% ee, respectively. The intermediate **34** was also coupled to indole butyl chloride to afford the secondary amine (±)-**11**. The corresponding *N*-propyl derivative (±)-**12** was generated by reductive amination with propionaldehyde.

Compounds were evaluated in vitro to determine affinity for both the serotonin transporter (r-5-HT-T) and 5-HT_{1A} receptor (h-5-HT_{1A}) as well as 5-HT_{1A} receptor intrinsic activity ([^{35}S]-GTPγS E_{max}). Additionally, since the receptor binding pharmacology for the 5-HT_{1A} receptor exhibits significant overlap with the α_1 receptor,[15] the α_1 receptor affinity for compounds **3**–**12** was also determined.

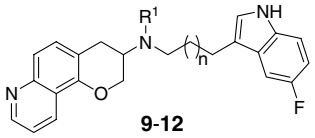
Comparison of 5-methoxy-3,4-dihydro-2*H*-1-benzopyran analog (±)-**3** and 2,3-dihydro-1*H*-pyrano[3,2-*f*]quinolin-2-amine (±)-**5** demonstrated a 4-fold improvement in 5-HT-T affinity, while the affinity at the 5-HT_{1A} receptor remained the same (Table 1). Resolution of (±)-**5** identified the (+)-enantiomer as the eutomer with respect to both 5-HT_{1A} receptor and 5-HT-T affinity; (+)-**5** exhibited a 13-fold increase in affinity for the 5-HT_{1A} receptor and 4-fold increase in affinity for the 5-HT transporter when compared to its corresponding enantiomer. However, the α_1 affinity appeared to reside in the (−)-enantiomer as (+)-**5** was observed to be more selective over the α_1 receptor. Unfortunately, the introduction of additional substitution (*n*-propyl) on the basic nitrogen of (±)-**5** led to a decrease in 5-HT transporter affinity [(±)-**6** vs. (±)-**5**] albeit without a corresponding decrease in 5-HT_{1A} receptor binding.

Shortening the length of the aminoalkyl tether between the indole and chroman resulted in decreased affinity for both the 5-HT_{1A} receptor and 5-HT transporter [(±)-**7** vs. (±)-**5**]. As previously observed, alkylation of the basic nitrogen present in (±)-**7** resulted in a further decrease in affinity [(±)-**8**].

Table 1. Binding affinities at 5-HT transporter, 5-HT_{1A} receptor, and α_1-adrenoceptor for compounds **3**–**12**[a]



5-8



9-12

Compound	R^1	*n*	r-5-HT-T K_i[b] (nM)	h-5-HT_{1A} K_i[c] (nM)	r-α_1 K_i[d] (nM)
(±)-**3**	H	1	9.2	70.4	772.5
(±)-**4**	*n*-Pr	1	9	15.8	820
(±)-**5**	H	1	2.4	62.6	324.2
(+)-**5**	H	1	1.3	23.9	590.8
(−)-**5**	H	1	5.1	313.8	221
(±)-**6**	*n*-Pr	1	16.9	63.5	18% at 1 μM
(−)-**6**	*n*-Pr	1	8.8	209.6	31% at 1 μM
(+)-**6**	*n*-Pr	1	19.8	58	38% at 1 μM
(±)-**7**	H	0	30.5	10% at 1 μM	1078.7
(±)-**8**	*n*-Pr	0	62.8	477.8	711.2
(±)-**9**	H	1	2.6	105.1	489.5
(+)-**9**	H	1	3	392	623.7
(−)-**9**	H	1	1.2	67.8	387.7
(±)-**10**	*n*-Pr	1	12.4	46% at 1 μM	1234.3
(±)-**11**	H	2	1.5	47% at 1 μM	33% at 1 μM
(±)-**12**	*n*-Pr	2	12	21% at 1 μM	19% at 1 μM

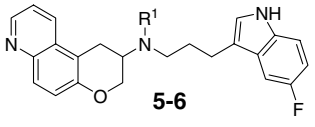
[a] K_i values are means of at least two experiments ± SEM (performed in triplicate, determined from nine concentrations) and all K_i values were calculated from IC_{50} values using the method of Cheng and Prusoff.[16]
[b] Binding affinity at rat cortical 5-HT reuptake sites labeled with [^{3}H]-paroxetine.[17]
[c] Binding affinity at human 5-HT_{1A} receptors in CHO cells labeled with [^{3}H]-8-OH-DPAT.[18]
[d] Binding affinity at rat cortical α_1 adrenergic receptors labeled with [^{3}H]-prazosin.[19]

The constitutional isomer (±)-**9** also demonstrated an improvement in affinity for the 5-HT_{1A} receptor (5-fold) and 5-HT-T (3-fold) when compared to the incipient chroman analog (±)-**3**. Extending the aminoalkyl tether [(±)-**11**] resulted in small improvement in 5-HT-T affinity. However, the four-carbon tether compound showed a significant decrease in 5-HT_{1A} receptor affinity [(±)-**11** vs. (±)-**9**]. Unlike the improvement in 5-HT-T affinity exhibited by (±)-**4** upon alkylation of the secondary amine present in (±)-**3**, the introduction of an *n*-propyl substituent to secondary amines (±)-**9** and (±)-**11** resulted in decreased affinity for the 5-HT_{1A} receptor [(±)-**10** vs. (±)-**9** and (±)-**12** vs. (±)-**11**]. In general, all the compounds demonstrated good selectivity over the α_1 receptor.

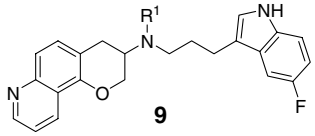
The 5-HT_{1A} receptor functional activity was obtained for the enantiomeric pairs of **5**, **6**, and **9** (Table 2). For the enantiomers of the secondary amines **5** and **9** there was little, if any, separation of the intrinsic activity elicited at the 5-HT_{1A} receptor. However, the influence of the stereogenic center present in **6** had a significant impact on function with (−)-**6** demonstrating partial agonist (55%) activity at the 5-HT_{1A} receptor. Unfortunately, the affinity for the 5-HT_{1A} receptor resided with (+)-**6**.

In conclusion, the secondary amine analogs demonstrated greater affinity for both the serotonin transporter and the 5-HT_{1A} receptor than their corresponding tertiary amine analogs. A three-carbon tether between the indole and aminochroman was optimal for affinity. As observed with compound (−)-**6**, contrary to the effect on binding, the presence of a tertiary amine appeared critical for the ability to modulate function. Our continued efforts are focused on developing our understanding of how to resolve this dichotomy in the design of novel molecules with dual 5-HT_{1A} receptor antagonism and 5-HT reuptake inhibitory activity.

Table 2. Functional activity at 5-HT_{1A} receptor



5-6



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Compound	R^1	h-5-HT_{1A} GTPγS E_{max} (EC_{50}[a] nM)
(+)-**5**	H	100 (181.8)
(−)-**5**	H	86 (116.2)
(−)-**6**	*n*-Pr	55 (628.6)
(+)-**6**	*n*-Pr	100 (301.2)
(+)-**9**	H	75 (332.4)
(−)-**9**	H	100 (171.60)

[a] Stimulation of GTPγS^{35} binding in CHO cells expressing 5-HT_{1A} receptor;[20] E_{max} refers to maximal agonist effect relative to 5-HT.

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