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Synthesis and structure–activity relationship of novel lactam-fused chroman derivatives having dual affinity at the 5-HT$_{1A}$ receptor and the serotonin transporter

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ABSTRACT

The structure–activity relationship (SAR) for three series of lactam-fused chroman derivatives possessing 3-amino substituents was evaluated. Many compounds exhibited affinities for both the 5-HT$_{1A}$ receptor and the 5-HT transporter. Compounds **45** and **53** demonstrated 5-HT$_{1A}$ antagonist activities in the in vitro cAMP turnover model.

Selective serotonin reuptake inhibitors (SSRIs) have been implicated in disorders of the central nervous system and have become of particular interest for their roles in the autoregulation of the brain 5-HT system and in the treatment of depression.[1] Because of the improved therapeutic index of SSRIs compared to traditional tricyclic antidepressants,[2] attention has been increasingly focused on overcoming their drawbacks.[3] SSRIs display latency in the onset of clinic antidepressant effects for more than three weeks as well as non-consistent responses in some refractory patients.[4] Other notable side effects include sexual dysfunction, anxiety and gastrointestinal intolerance. The discovery of better antidepressants with less adverse events continues to be an area of significant research. One strategy to accelerate the onset of action of SSRIs involves co-administering a 5-HT$_{1A}$ antagonist to block the initial reduced rate of neuronal firing until neuronal accommodation occurs.[5] Additionally, 5-HT$_{1A}$ antagonists may lessen the sexual dysfunction liabilities seen with SSRIs.[6] Support for this approach comes from animal studies in which 5-HT$_{1A}$ antagonists decreased the amount of time required to see antidepressant effects with SSRIs.[7] Additionally, some clinical studies demonstrate the potential for similar effect in humans, although the clinical tool compounds used in these studies were not optimal.[8]

An alternative to administering two pharmaceutical agents is to design molecules that possess both desired pharmacological activities. To this end, significant amounts of effort have been focused on a synthetic strategy developing molecules containing a nitrogen-containing template and a 5-HT$_{1A}$ antagonist moiety (**1**, Fig. 1) with a serotonin transporter group (**2**, Fig. 1). This strategy has led to compounds that demonstrate desirable binding affinities for both the 5-HT$_{1A}$ receptor and the 5-HT transporter. As part of an ongoing effort to identify single molecules with dual activity to inhibit both the 5-HT$_{1A}$ and 5-HT reuptake sites, we reported on a series of analogs containing a chroman-based 5-HT$_{1A}$ antagonist pharmacophore inherent in robalzotan (NAD-299)[9,10] and indolealkylamine fragments such as **2**.[11] The SAR showed that 5-carboxamide-8-fluoro derivatives and 5-carboxamide-8-des-fluoro analogs with the proper *N*-alkyls displayed good affinities for the 5-HT$_{1A}$ receptor and the 5-HT reuptake site in the GTPγS assay.[12] That work culminated in the identification of (3*R*)-3-{cyclobutyl[3-(5-fluoro-1*H*-indol-3-yl) propyl] amino}-8-fluorochroman-5-carboxamide **3**, which possessed both potent 5-HT$_{1A}$ receptor antagonist and SSRI activities (see data in Fig. 1). In a micro dialysis study (30 mg/kg po), compound **3** induced acute increases in serotonin levels in the rat frontal cortex that were

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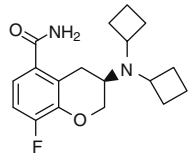
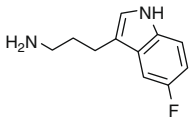


1. NAD-299



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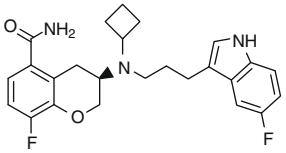
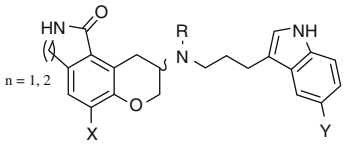


3. Lead Compound
Ki = 1.2 nM, IC_{50} = 27 nM in cAMP, Emax = 0% ($5\text{-}HT_{1A}$ receptor)
Ki= 1.5 nM, IC_{50} = 18.7 nM in functional assay (5-HT Transporter)

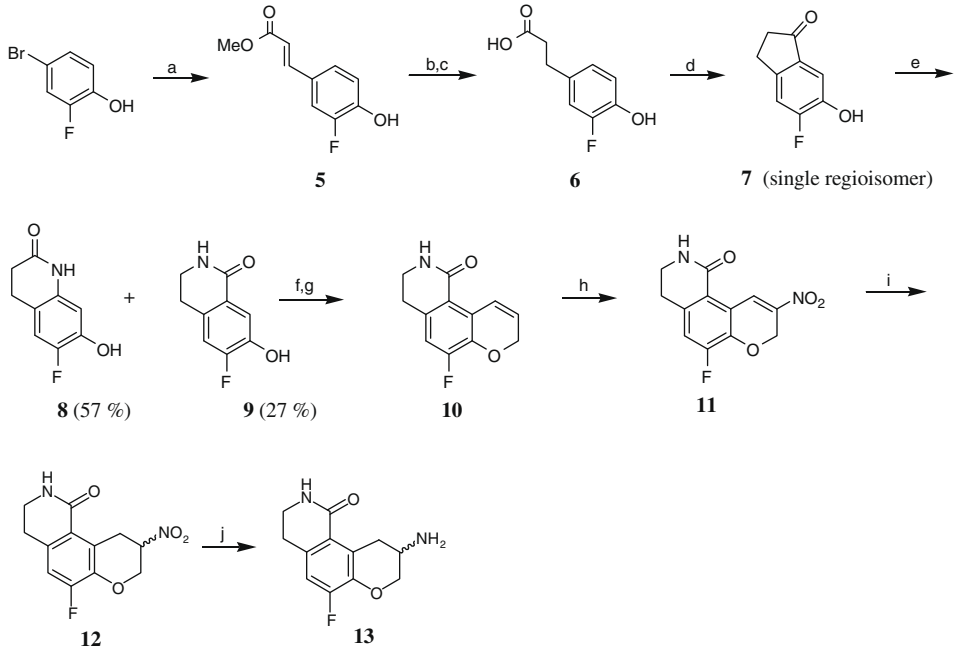


4A. n = 1, X = H, Y = F, CN
4B. n = 2, X = H, Y = F
4C. n = 2, X = F, Y = F

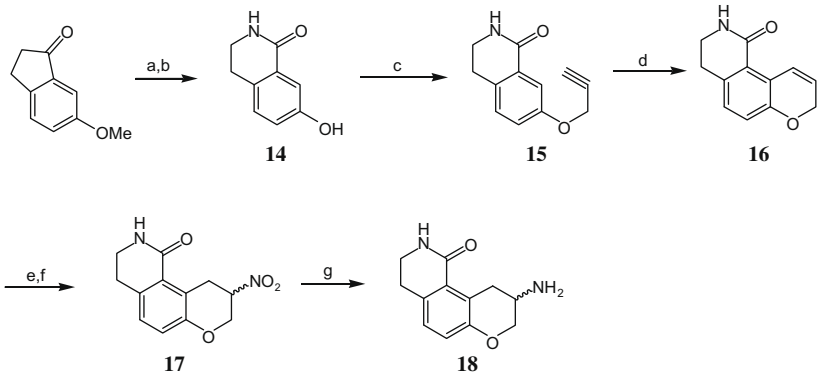
Figure 1. Design strategy.

similar to those achieved only with chronic (14 days) dosing of an SSRI alone. To continue the SAR effort around compound **3** in Figure 1, we designed and prepared a series of lactam-fused chroman amine derivatives (**4**, Fig. 1). The present manuscript describes the synthesis and pharmacological evaluation of those fused chroman analogs.

Due to the difficulties in the synthesis of five-membered lactam-fused chromans with 9-fluoro and 3-amino substituents, we initially focused on the synthesis of key intermediate **13** (Scheme 1). The formation of the lactam-fused chroman relies on the presence of a carboxylic acid moiety either in the *para* or *meta* position of 2-fluorophenol. We began the synthesis by introducing an α,β unsaturated propionate at the *para* position. This was achieved in 56% yield by reacting 4-bromo-2-fluorophenol with methylacrylate under Heck conditions. Subsequent double bond reduction, ester hydrolysis and intramolecular cyclization yielded substituted indanone **7** as a single regioisomer, which was purified by chromatography. The six-membered lactams **8** and **9** were obtained in the respective ratio of 2:1 at room temperature by Schmidt reaction. These two isomers were easily purified by chromatography. It should be noted that higher reaction temperatures favored the formation of the undesirable isomer **8**. Compound **10** was synthesized from **9** in two steps via a sequence that involved alkylation with propargyl bromide followed by cyclization. We modified the reported nitration procedure for the conversion of **10** to **11** by replacing the THF/pyridine solvent system with *N*-methylpyrrolidine for easy handling of the material during the work up of the reaction. Reduction of the double bond in pyran derivative **11** followed by Raney nickel catalyzed reduction of the nitro group in intermediate **12** yielded the desired six-membered lactam-fused chroman amine **13**. The enantiomers of **13** were not separated at this stage of the synthesis.



Scheme 1. Synthesis of six-membered lactam chroman amine. Reagents and conditions: (a) methyl acrylate, $Pd(OAc)_2$, tri-*o*-tolylphosphine, Et_3N, DMF, 80 °C, 84%; (b) H_2, Pd/C, MeOH, 95%; (c) LiOH, MeOH/THF/H_2O, 90%; (d) $AlCl_3$, NaCl, 180 °C, 30 min; 78%; (e) MsOH, NaN_3, $CHCl_3$, 57% and 27%; (f) propargyl bromide, K_2CO_3, acetone, reflux, 90%; (g) diethylaniline, 210 °C, 70%; (h) $NaNO_2$, I_2, NMP, 73%; (i) $NaBH_4$, SiO_2, $CHCl_3$, 60%; (j) NH_2NH_2, Raney Ni, EtOH, 50 °C, 72%.

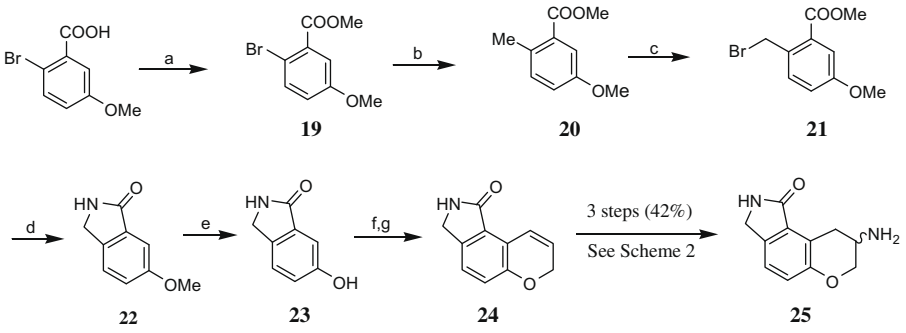


Scheme 2. Synthesis of the des-fluoro six-membered lactam-fused chroman amine. Reagents and conditions: (a) MsOH, NaN_3, $CHCl_3$, 0 °C, 87%; (b) BBr_3 (1 M in hexane), CH_2Cl_2, 77%; (c) propargyl bromide, K_2CO_3, acetone, reflux, 89%; (d) diethylaniline, 210 °C, 55%; (e) $NaNO_2$, I_2, NMP, 71%; (f) $NaBH_4$, SiO_2, $CHCl_3$, 83%; (g) NH_2NH_2, Raney Ni, EtOH, 50 °C, 61%.

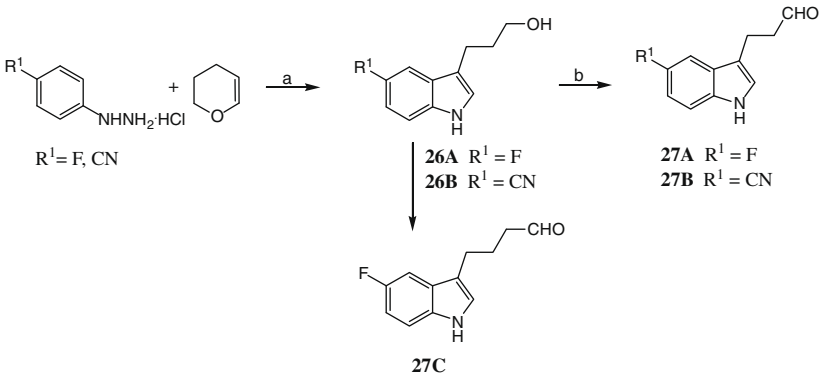
We then turned our attention to the synthesis of the des-fluoro six-membered lactam **18** (Scheme 2). Commercially available 6-methoxy-1-indanone was used as starting material to obtain **14** in two steps. We were concerned that the cyclization of propargyl ether **15** could yield two conceivable regioisomers. To our surprise, compound **16** was the exclusive product obtained from the reaction. Compound **18** was then prepared using analogous methods to those shown in Scheme 1.

The synthesis of the des-fluoro five-membered lactam-fused chroman amine **25** (Scheme 3), required an efficient route to intermediate **22**. The most significant reaction in this scheme was the transformation of the aryl halide **19** to the toluene derivative **20**. Transition metal catalyzed cross coupling of an aryl bromide with alkyl zinc is a known approach.[13] The reaction of **19** with dimethylzinc in DMF at 50 °C was catalyzed by bis-(triphenylphosphine) palladium(II) dichloride to produce **20**. The formation of **20** provided the eventual synthesis of the five-membered lactam **22**,[14] which was elaborated to **25** as an exclusive regioselective isomer using standard synthetic methodology.

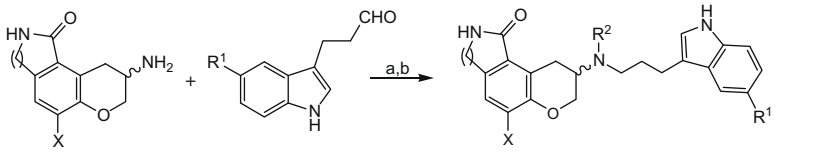
Since we envisioned preparing the desired final compounds using a reductive amination approach, the synthesis of indole alkyl aldehyde intermediates was required. The preparation of these compounds (**27A** and **27B**) is shown in Scheme 4. Compounds **26** were synthesized by Fisher indole synthesis, and then converted to aldehyde derivatives. The four-carbon homolog **27C** was prepared from **26A** via a four-step sequence that involved bromina-



Scheme 3. Synthesis of des-fluoro five-membered lactam-fused chroman amine. Reagents and conditions: (a) MeI, DBU, MeCN, reflux,73%; (b) Me_2Zn, $Cl_2Ni(PPh_3)_2$, DMF, 55 °C, 82%; (c) NBS, AIBN, benzene, reflux, 88%; (d) NH_3/MeOH, 130 °C, 92%; (e) BBr_3, CH_2Cl_2, 65%; (f) propargyl bromide, K_2CO_3, acetone, reflux, 92%; (g) diethylaniline, 210 °C, 58%.



Scheme 4. Synthesis of indole-substituted alkyl aldehydes. Reagents and conditions: (a) dioxane/water, 90 °C, 95%; (b) PCC, Et_3N, DMSO, 71–80%.



Scheme 5. Target synthesis. Reagents and conditions: (a) $NaBH_3CN$, AcOH, MeOH, 80–90%; (b) aldehyde or cyclobutanone, $NaBH_3CN$, AcOH, MeOH.

tion, cyanation, hydrolysis and then reduction (not shown) in 45% overall yield.

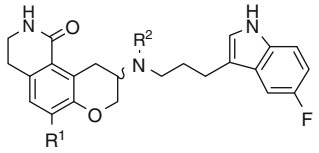
With intermediates in hand, the final products **28–56** were synthesized through a two-step sequence (Scheme 5). Reductive amination of the three different lactam-fused chroman amines (**13**, **18** and **25**) with indole-substituted aldehydes **27** generated penultimate secondary amine derivatives. A second reductive amination reaction with alkyl aldehydes, aryl aldehydes or cyclobutanone installed the R^2 group to give the final targets, as shown in Scheme 5.

We investigated the effect of three lactam-fused chroman amines linked to a known serotonin transporter pharmacophore as potential dual-acting 5-HT_{1A} antagonist/SSRIs. The 5-HT_{1A} receptor affinity, serotonin transporter affinity, and in vitro 5-HT_{1A} intrinsic activity are summarized in Tables 1–3. 5-HT_{1A} functional activity was measured in CHO cells stably transfected with the human 5-HT_{1A} receptor by assessing test compound's ability to inhibit the agonist-induced decrease in adenylate cyclase activity. Intrinsic activity is expressed as the percentage (E_{max} %) of the full response of the agonist 8-OH-DPAT (E_{max} % = 100). Based on early SAR studies for 8-fluoro-5-carboxamide-3-aminochroman derivatives, we limited R^2 to small alkyl groups (methyl, ethyl, cyclopropylmethyl, cyclobutyl, etc).

Table 1 summarizes data for six-membered lactam chroman containing an indole-3-propylamine moiety. The resulting final products were obtained and evaluated as racemic mixtures. When the 10-fluoro substituent was present (R^1 = F), small substituents were tolerated on the basic amine by both the 5-HT_{1A} receptor and the 5-HT transporter (e.g., compounds **28** and **29**). Affinities for both binding sites decreased when somewhat larger R^2 groups were incorporated, such as the cyclopropylmethyl moiety in compound **30**. A similar trend was seen when the 10-fluoro substituent was removed (compounds **31–40**), with R^2 = ethyl being the optimal substitution pattern for both fluoro and des-fluoro derivatives. Similar results were obtained when the 10-fluoro group was replaced with a cyano moiety (unpublished data). These results are similar to those seen in the 5-carboxamido analogs,[11] although that system better tolerated somewhat larger groups in the R^2 position at both the 5-HT_{1A} receptor and the 5-HT transporter. Interestingly, all of the racemic six-membered lactams tested displayed agonist or partial agonist activity in the functional assay, although previous evidence suggested that the two enantiomers might display different functional characteristics.[11]

We then turned our attention to five-membered ring lactam derivatives (Table 2). Both the fluoro and the cyano substituent at indole moiety were examined. Similar to the six-membered ring lactams, substituents up to and including cyclopropylmethyl were tolerated in the R^2 position, with some loss in both 5-HT_{1A} and 5-HT transporter affinity seen with larger groups such as cyclobutyl (compound **47**). Five-membered lactam derivatives displayed somewhat greater affinity for both binding sites compared to analogs six-membered ring lactams (e.g., compounds **43** and **44** compared to compounds **29** and **30**, respectively). Because the racemic mixtures **44** and **52** displayed antagonist profiles in the in vitro functional assay, we separated and evaluated the enantio-

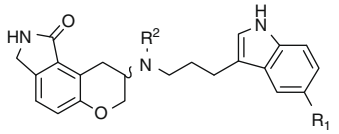
Table 1
Data for substituted six-membered lactams



Compound	R^1	R^2	Stereo	5-HT_{1A} K_i[a] (nM)	5-HT-T K_i[b] (nM)	cAMP[c] EC_{50} (nM)	E_{max}[d] (%)
28	F	H	rac	6	27	4	98
29	F	Et	rac	4	15	10	92
30	F	(CH_2)*c*Pr	rac	50	112	101	62
31	H	H	rac	44	10	25	87
32	H	Me	rac	23	17	26	99
33	H	Et	rac	6	30	9	97
34	H	*n*-Pr	rac	13	61	34	100
35	H	*i*-Pr	rac	129	8	252	94
36	H	(CH_2)*c*Pr	rac	19	26	36	91
47	H	*i*-Bu	rac	927	184	NT	NT
38	H	*c*Bu	rac	95	28	54	77
39	H	$(CH_2)_2CF_3$	rac	966	340	NT	NT
40	H	Bz	rac	1220	671	NT	NT

[a] Binding affinity at 5-HT_{1A} receptor in CHO cells labeled with [^{3}H]-OH-DPAP (n >2).
[b] Binding affinity for 5HT transporter labeled with paroxetine (n >2).
[c] Maximal agonist effect relative to 5-HT in inhibiting forskolin-stimulated adenylate cyclase activity.
[d] Maximal response of the compound as a result of 5-HT_{1A} receptor-mediated stimulation of b(^{35}S)GTPγ binding.

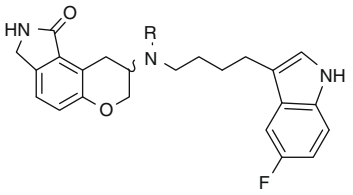
Table 2
Data for des-fluoro five-membered lactams[a]



Compound	R^1	R^2	Stereo	5-HT_{1A} K_i (nM)	5-HT-T K_i (nM)	cAMP EC_{50} (nM)	E_{max} (%)
41	F	H	rac	24	8	62	100
42	F	Me	rac	22	9	75	80
43	F	Et	rac	2	8	28	78
44	F	(CH_2)cPr	rac	6	15	223 (IC_{50})	0
45	F	(CH_2)cPr	(−)[b]	8	6	320 (IC_{50})	0
46	F	(CH_2)cPr	(+)[b]	3	5	24	84
47	F	*c*Bu	rac	101	63	350	NT
48	F	*i*-Bu	rac	NT	617	NT	NT
49	F	(CH_2)cHex	rac	NT	1242	NT	NT
50	F	Bz	rac	85	31	436	96
51	CN	H	rac	36	13	22	91
52	CN	(CH_2)cPr	rac	4	25	63 (IC_{50})	0
53	CN	(CH_2)cPr	(−)[a]	10	17	203 (IC_{50})	0
54	CN	(CH2)cPr	(+)[a]	31	12	19	100

[a] See notes in Table 1.
[b] As determined by optical rotation.

Table 3
Data for compounds possessing a 4-carbon spacer[a]



Compound	R	Stereo	5-HT_{1A} K_i (nM)	5-HT-T K_i (nM)	cAMP EC_{50} (nM)	E_{max} (%)
55	H	rac	22	20	284	96
56	(CH_2)cPr	rac	19	139	49	87

[a] See notes in Table 1.

mers. As was seen in the amide series,[11] one enantiomer (compounds **45** and **53**) carried the antagonist activity while the other (compounds **46** and **54**) profiled as a partial or full agonist. However, the EC_{50} values of both compounds **45** and **53** in the functional assay (IC_{50} values = 320 nM and 203 nM, respectively) were much higher than that obtained with compound **3** (IC_{50} = 27 nM).

Finally, we examined the effect of the length of the carbon 'spacer' between the chroman group and the indole moiety by preparing compounds **55** and **56** (Table 3). The potency of compound **55** for both the 5-HT_{1A} receptor and the 5-HT transporter was comparable to that seen with the propyl analogs, but compound **56** displayed some loss in affinity relative to its propyl counterparts. Because the SAR of the present series correlated with that of the previously reported carboxamides,[11] the ethyl 'spacer' group was not examined.

In the present Letter, we have expanded the SAR of a previously reported series of chroman indole alkylamine analogs that possess both 5-HT_{1A} and 5-HT transporter affinity. The results suggested that cyclopropylmethyl played a fairly important role in the antagonistic properties of the molecules along with the stereochemistry at the 3-position of the chroman. When compounds contained a propyl chain linker, the five-membered lactam chroman analogs displayed slightly greater affinity for both binding sites compared to their six-membered ring lactam counterparts. The rank order of potency for substituents on the basic amine was similar for both systems. Like the previously reported carboxamides, one enantiomer appears to possess 5-HT_{1A} antagonist functional activity while the other profiles as an agonist, at least in vitro. However, the functional potency of the two optimal compounds from this series, **45** and **53**, was significantly lower than that seen with the corresponding carboxamides. We believe that the constrained conformation of the lactam group has a subtle effect on the shift from antagonist to almost full agonist. It provides a novel alternative to the freely rotating primary carboxamide moiety in compounds such as **3** and yields potent dual 5-HT_{1A}/5-HT transporter ligands that can display 5-HT_{1A} antagonist activity. However, in these series, either the constrained amide conformation inherent in the lactam group or the differences in electronics or hydrogen bonding properties induced by moving from a primary to a secondary amide result in less potent 5-HT_{1A} antagonist activity.

Acknowledgments

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