Advances toward New Antidepressants with Dual Serotonin Transporter and 5-HT$_{1A}$ Receptor Affinity within a Class of 3-Aminochroman Derivatives. Part 2

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Novel compounds combining a 5-HT$_{1A}$ moiety (3-aminochroman scaffold) and a 5-HT transporter (indole analogues) linked through a common basic nitrogen via an alkyl chain attached at the 1- or 3-position of the indole were evaluated for dual affinity at both the 5-HT reuptake site and the 5-HT$_{1A}$ receptor. Compounds of most interest were found to have a 5-carbamoyl-8-fluoro-3-amino-3,4-dihydro-2*H*-1-benzopyran linked to a 3-alkylindole (straight chain), more specifically substituted with a 5-fluoro ((*R*)-(−)-**35c**), 5-cyano ((−)-**52a**), or 5,7-difluoro ((−)-**52g**). Several factors contributed to 5-HT$_{1A}$ affinity, serotonin rat transporter affinity, and functional antagonism in vitro. Although most of our analogues showed good to excellent affinities at both targets, specific features such as cyclobutyl substitution on the basic nitrogen and stereochemistry at the 3-position of the chroman moiety seemed necessary for antagonism at the 5-HT$_{1A}$ receptor. Branched linkers seemed to impart antagonism even as racemates; however, the potency of these analogues in the functional assay was not desirable enough to further pursue these compounds.

Introduction

Depression can have devastating effects and can lead to suicide. Affected individuals lack the energy and motivation to perform everyday activities, which results in a poor quality of life. Although depression is one of the most frequently diagnosed psychiatric disorder, current therapies have several drawbacks.[1,2] The discovery and development of new antidepressants remain an active area of research. Several undesired side effects have been associated with the traditional tricyclic antidepressants (TCAs[a]),[3,4] but the discovery and development of selective serotonin reuptake inhibitors (SSRIs) have resulted in improved drugs for the treatment of depression and related illnesses.[4] SSRIs such as fluoxetine, sertraline, paroxetine, and citalopram are the most prescribed drugs since the 1980s. Although SSRIs are devoid of anticholinergic and cardiovascular side effects, they are generally effective in less than two-thirds of patients. Additionally, like the TCAs, their delayed onset of action (2−6 weeks) in therapeutic efficacy[5] is less than desirable in the treatment of depression. This delay of action may be attributed to the nonselective stimulation of serotonergic sites such as somatodendritic 5-HT$_{1A}$ autoreceptors, which reduce cell-firing activity, thus limiting the amount of synaptic 5-HT in desired brain regions. Eventually, following chronic antidepressant treatment, desensitization of the somatodendritic 5-HT$_{1A}$ autoreceptors occurs, resulting in less autoregulatory feedback inhibition and a more pronounced increase in serotonergic activity compared to acute treatment.[6] Antagonism of the 5-HT$_{1A}$ autoreceptor blocks the reduced rate of neuronal firing, thus presumably allowing the effects of the SSRI to be seen more rapidly.[7] More recently, drugs targeting multiple sites associated with depression have been discovered.[8,9] For example, venlafaxine[10,11] and duloxetine[12] have been developed as serotonin and norepinephrine reuptake inhibitors (SNRIs). Several studies have shown that antidepressant effects of an SSRI can be accelerated by the coadministration of a 5-HT$_{1A}$ antagonist.[13−15] This effect has not been seen by all investigators.[13,16] It should be noted that while pindolol is the only clinically available 5-HT$_{1A}$ antagonist, it is also a β-adrenoreceptor antagonist that has 5-HT$_{1A}$ partial agonist properties in rats.[17] Animal models have shown that the 5-HT$_{1A}$ antagonist **1** (WAY-100635) can potentiate the antidepressant effects of several SSRIs when given in combination.[14,18] There is currently an unfilled need for a single agent with a dual mechanism of antidepressant action (5-HT uptake inhibition plus 5-HT$_{1A}$ antagonism). Therefore, the concept of combining 5-HT$_{1A}$ antagonism and selective serotonin reuptake inhibition (SSRI) in one molecule to reduce the latency period to efficacy has been proposed for the discovery of a new generation of antidepressant drugs. Several reports have appeared in the literature by researchers trying to create such a molecular entity.[19,20] In our own laboratories, there has been an ongoing effort to discover compounds with dual 5-HT$_{1A}$ receptor and serotonin transporter affinity through utilization of a common basic nitrogen linking the 5-HT$_{1A}$ and SSRI moieties.[21] This generic strategy was previously termed "the overlapping type approach".[22]

Several years ago, 5-methoxy-3-(di-*n*-propylamino)chroman (5-OMe-DPAC, **2**) was discovered as a selective 5-HT$_{1A}$ ligand vs other 5-HT and D$_2$ sites in rat brain membranes.[23] Subsequently, different 3-amino-3,4-dihydro-2*H*-1-benzopyran derivatives were explored and developed as 5-HT$_{1A}$ agonists.[24] The discovery of robalzotan (**3**, NAD-299) as a potent 5-HT$_{1A}$

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[a] Abbreviations: TCAs, tricyclic antidepressants; SSRIs, selective serotonin reuptake inhibitors; SNRIs, selective norepinephrine reuptake inhibitors; 8-OH-DPAT, 8-hydroxydipropylaminotetralin; EDC, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; cPr, cyclopropyl; cBu, cyclobutyl; cHexyl, cyclohexyl; MecPr, methylcyclopropyl; RA, reductive amination; VCD, vibrational circular dichroism; SFC, supercritical fluid chromatography.

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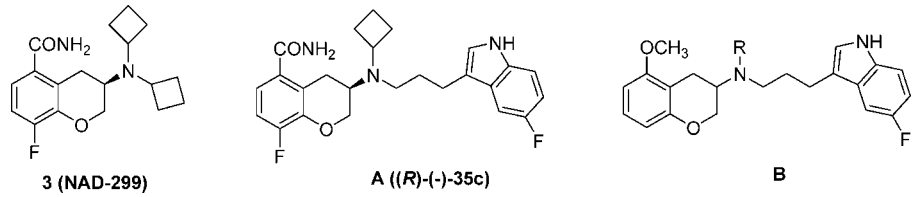


Figure 1. Structures of **3** and 3-aminochroman analogues **A** and **B**.

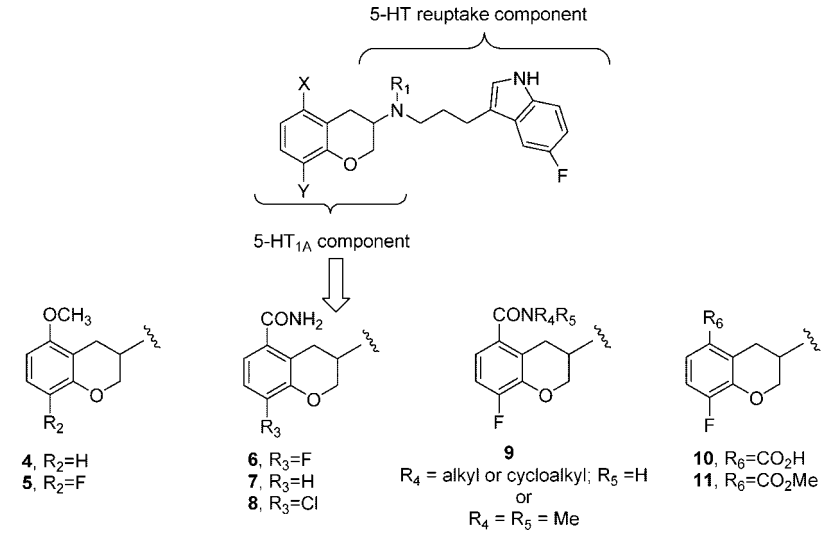


Figure 2. Design strategy and different 5-HT_{1A} scaffolds.

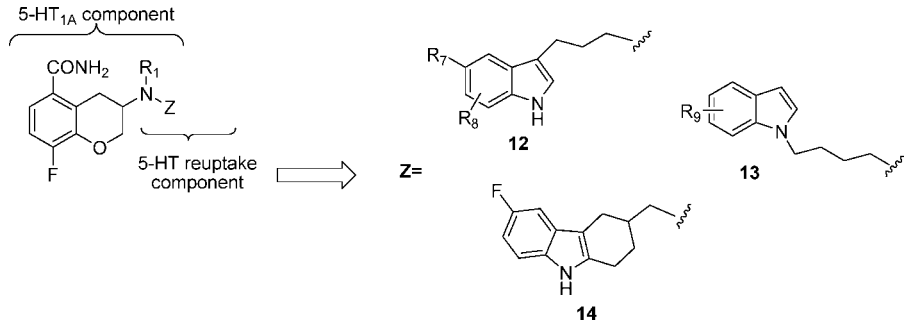


Figure 3. Design strategy and different indole scaffolds.

receptor antagonist for the treatment of depression and anxiety by other researchers[25] (Figure 1) led us to the finding of novel compounds that possess dual affinity at both the 5-HT_{1A} receptor and the 5-HT reuptake site. We recently reported[26] on the discovery of derivatives that contain a 5-carbamoyl-8-fluoro-3-amino-3,4-dihydro-2*H*-1-benzopyran (or 3-amino-3,4-dihydro-2*H*-1-benzopyran) and a straight chain aminoalkyl indole moiety linked through a common basic nitrogen. Interestingly, compound **A** (Figure 1) was shown to possess neurochemical activity in vivo by producing acute and rapid increases in 5-HT in the rat frontal cortex as measured by microdialysis.[26] We also found that similar analogues of structure **B** (Figure 1) showed dual affinities at both 5-HT_{1A} receptor and serotonin transporter but they lacked 5-HT_{1A} antagonism in preliminary structure−activity relationship (SAR) studies.

These results prompted us to investigate further the SAR around the 5-HT_{1A} moiety and the stereochemistry at the C-3 of the chroman ring of the dual acting molecule using the 3-aminoalkyl-5-fluoro indole as the SSRI entity.

In this report, we look at several chroman scaffolds (summarized in Figure 2) and discuss the synthesis and structure−activity relationship (SAR) of these derivatives by looking at

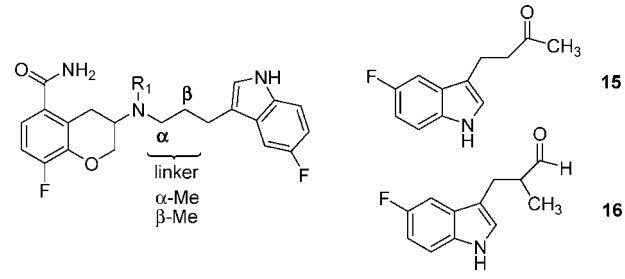
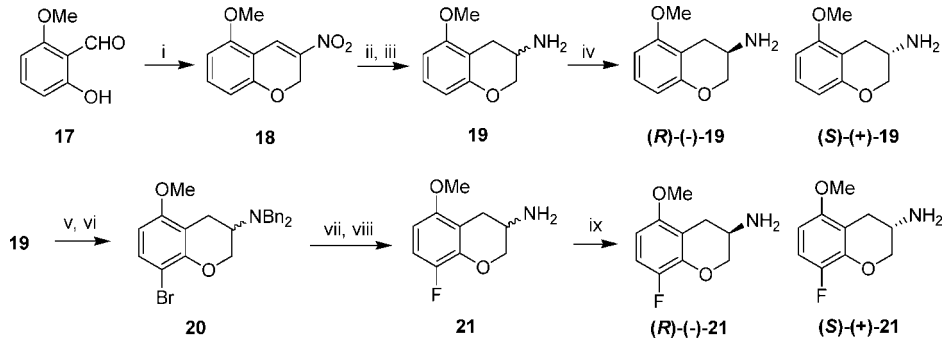


Figure 4. Design strategy and substitution on linker.

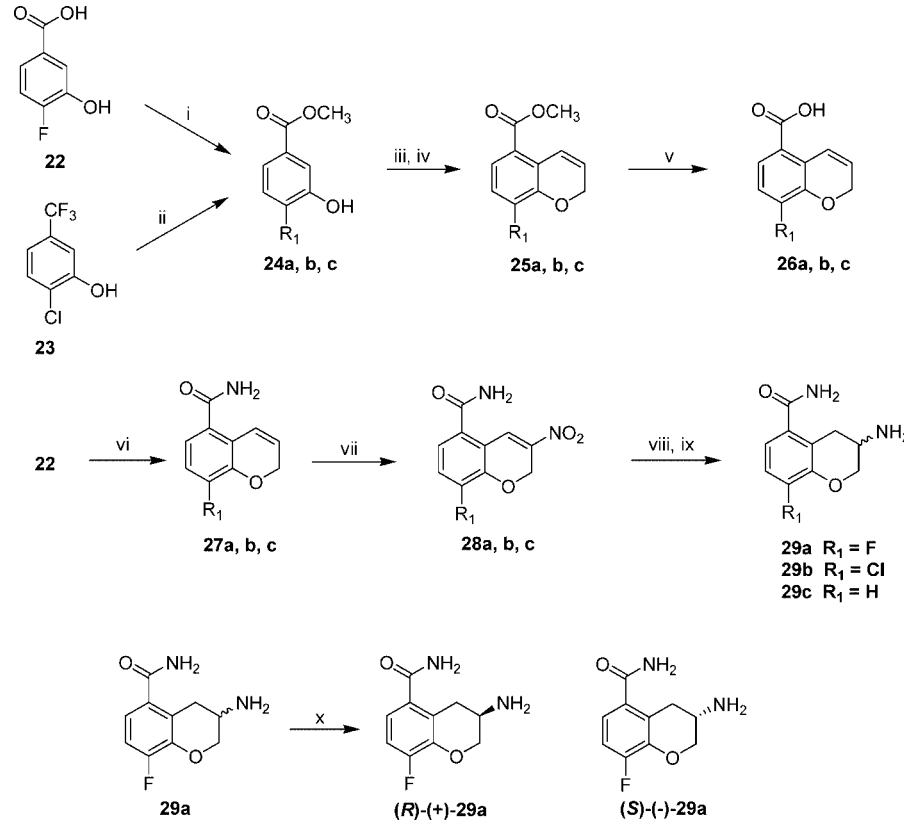
the effects of substitution on the basic nitrogen (more specifically R_1 = Pr or cBu) and the nature of the substituents on the aromatic ring of the chroman, on the binding affinities at the 5-HT_{1A} receptor and 5-HT reuptake site. We also elaborate on what features of these novel derivatives might be responsible for their agonist or antagonist properties at the 5-HT_{1A} receptor. In addition, we address the effect of varying the 5-HT reuptake component of the dual-acting molecule on the binding affinities at 5-HT_{1A} and transporter receptors using the 5-carboxamide 8-fluoro 3-aminochroman as the 5-HT_{1A} moiety. Several

Scheme 1[a]



[a] Reagents: (i) nitroethanol, $Bu_2NH \cdot HCl$, isoamylacetate; (ii) $NaBH_4$, SiO_2, $CHCl_3$, ^iPrOH; (iii) $NH_2NH_2 \cdot H_2O$, Raney Ni, EtOH; (iv) chiral HPLC; (v) BnBr, K_2CO_3, DMF; (vi) NBS, CH_3CN; (vii) *N*-fluorobenzenesulfonimide, *n*-BuLi/hexane, THF; (viii) ammonium formate, Pd/C, MeOH−THF; (ix) chiral resolution with L-(+)-tartaric acid followed by base treatment.

Scheme 2[a]



[a] Reagents: (i) trimethylorthoformate, H_2SO_4, MeOH; (ii) H_2SO_4, MeOH; (iii) propargyl bromide, K_2CO_3, acetone; (iv) *N*,*N*-diethylaniline; (v) NaOH, EtOH−H_2O; (vi) CDI, THF followed by NH_3(g); (vii) 18-crown-6, KNO_2, I_2, THF−pyridine, sonication; or ethylene glycol, THF, $NaNO_2$, I_2; (viii) $NaBH_4$, SiO_2, $CHCl_3$−^iPrOH; or $NaBH_4$, MeOH; (ix) $NH_2NH_2 \cdot H_2O$, Raney Ni, EtOH−THF; (x) chiral resolution with L-(+)-tartaric acid.

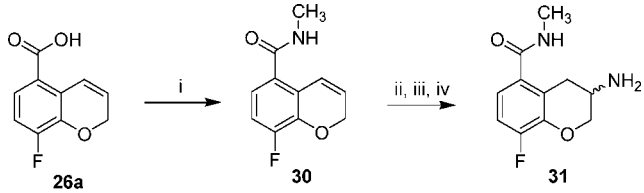
substituted indole scaffolds were investigated as summarized in Figure 3. Finally, we look at substitution on the linker tethering the 5-HT_{1A} and SSRI moieties as illustrated in Figure 4.

Chemistry

Intermediates **19** and **21**, needed for the synthesis of final targets in series **4** and **5**, respectively, were synthesized as racemates from the benzaldehyde **17** as previously described (Scheme 1).[26,27] The stereochemistry of the enantiomers of **19** had been determined earlier by other researchers through resolution with L-(+)-tartaric acid.[28] We separated these enantiomers by chiral HPLC, and the *R*/*S* stereochemistry was determined by comparing the optical rotation of each enantiomer with published data.[24] Intermediate **21** was prepared from racemic **19**, and the enantiomers were separated by chiral resolution with L-(+)-tartaric acid. The *R*/*S* stereochemistry was assigned by matching their optical rotations with literature data.[29]

For compounds in series **6**, **7**, and **8**, the required moieties **29a** (3-amino-8-fluorochromane-5-carboxamide), **29b** (3-amino-8-chlorochromane-5-carboxamide), and **29c** (3-aminochroman-5-carboxamide) were prepared as illustrated in Scheme 2. Their syntheses were carried out as previously described[26,30,31] using commercially available 4-fluoro-3-hydroxybenzoic acid **22**, 2-chloro-5-trifluoromethylphenol **23**, and methyl 3-hydroxybenzoate **24c** (R_1 = H) as starting materials, respectively. The trifluoromethyl derivative **23** was converted to the methyl ester

Scheme 3[a]



[a] Reagents: (i) CH_3NH_2, EDC, HOBt, THF; (ii) 18-crown-6, KNO_2, I_2, THF−pyridine, sonication; (iii) $NaBH_4$, SiO_2, $CHCl_3$−^{i}PrOH; (iv) $NH_2NH_2 \cdot H_2O$, Raney Ni, EtOH−THF.

by heating with sulfuric acid at 100 °C for 1 h followed by treatment with methanol to generate **24b** (R_1 = Cl). The chloro intermediate **29b** and the des-fluoro analogue **29c** were prepared using a slightly modified protocol published earlier for the fluoro compound **29a**.[26] The enantiomers of **29a** were separated by chiral resolution with L-(+)-tartaric acid, and the stereochemistry was confirmed by NMR studies and VCD experiments. The stereochemistry was further elucidated by X-ray crystallography of one of the final targets. The enantiomers of **29b** and **29c** were not separated at this step, and the racemates were carried through to the secondary amines **33d** and **33e**.

Several routes can be used for the synthesis of the substituted carboxamide derivatives **9**. For example, the *N*-methyl analogue **33f** was prepared using intermediate **31** where the chroman moiety is already N-methylated as shown in Scheme 3. The acid **26a** was reacted with methylamine in the presence of EDC and HOBt to generate a quantitative yield of **30**, which was then converted to the amine **31** using chemistry described in Scheme 2.

Final targets **34a**−**c**,**e**,**f** and **35a**,**c**−**f** were synthesized using the route illustrated in Scheme 4. Following coupling of the chroman amine template with the alkylindole moiety **32a** or **32b** (prepared using chemistry already published[26]) through alkylation or reductive amination, the desired targets were obtained by reductive amination of the secondary amines **33a**−**f** with the desired aldehyde or cyclobutanone in the presence of sodium cyanoborohydride and acetic acid in methanol. The enantiomers of intermediates **33b**−**e** were separated by chiral HPLC, but only the stereochemistry of **33c** was further confirmed as *R*/*S*. The absolute configuration of all other intermediates was not determined, and it is identified as (+) and (−). The secondary amine intermediates **33a** and **33f** were not chirally separated at this step.

Most of the final targets with mono- or bis-substitution of the carboxamide functionality (series **9**, compounds **35f** and **40a**−**h**) were prepared using a more convergent synthetic pathway amenable to combinatorial chemistry and summarized in Scheme 5. Intermediate **36** was prepared from derivative **25a** using the chemistry elaborated earlier in Scheme 2. Coupling of **36** with indole aldehyde **32a** under reductive amination conditions generated desired product **37**, which was then reacted with cyclobutanone to yield compound **38** (series **11**). The ester **38** was converted to the acid derivative **39** (series **10**), which was then subjected to standard coupling conditions with desired amine (EDC and HOBt) to generate the substituted carboxamide targets **35f** and **40a**−**h**. Since this synthetic route generated both methyl ester **38** and carboxylic acid **39**, these were also tested in the in vitro biological assays. A different route[32] was investigated for the synthesis of substituted carboxamide derivatives (more specifically, the (*R*)-*N*-Me enantiomer) from the primary carboxamide as summarized in Scheme 6 (route A). Compound (*R*)-**41** was prepared from (*R*)-**33c** through reductive amination with propionaldehyde followed by triple Boc protection with *tert*-butyl dicarbonate. Treatment of (*R*)-**41** with methylamine in tetrahydrofuran yielded a mixture of two compounds, the desired methylated carboxamide (*R*)-(−)-**42** (30%) and a di-Boc derivative (*R*)-(−)-**43** (62%). Compound (*R*)-(−)-**43** was reacted with iodomethane in the presence of sodium hydride in THF to generate the di-Boc methylated derivative (*R*)-**44** in good yield. Finally upon treatment of (*R*)-(−)-**42** and (*R*)-**44** with HCl in ethanol, a quantitative yield of the desired N-methylated carboxamide derivative (*R*)-(−)-**34f** was obtained. An alternative route B was also looked at where (*R*)-**33c** was converted to the methyl ester under acidic conditions followed by reductive amination with cyclobutanone to generate (*R*)-**38**. The methyl ester was then converted to the acid, which was coupled with methylamine in THF in the presence of EDC and HOBt to generate the desired target (*R*)-(−)-**35f**.

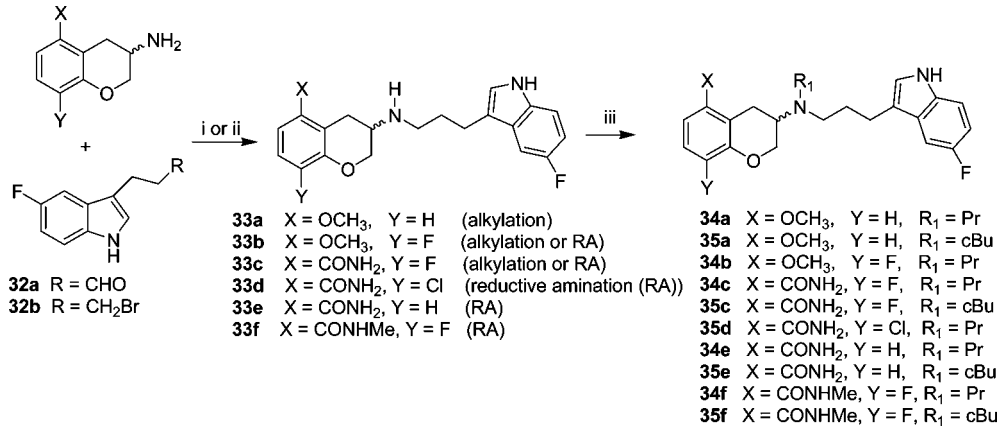
The synthesis of the 5-HT reuptake scaffolds of general structure **12** is shown in Scheme 7. They were all prepared using a Fischer indole synthesis, followed by conversion of the generated alcohol intermediates **45** or **47** to either the bromo derivatives **32a**,**c**,**d** using carbon tetrabromide and triphenylphosphine or the aldehydes **32b**,**e**−**i** under modified Swern conditions. Only the 5-cyanoindole alcohol **47** was prepared from the 5-bromo compound **46** by treatment with copper(I) cyanide in DMF. Most alkylindoles were converted to the aldehyde except for 5-methoxyindole, which turned out to be unstable under the oxidation conditions, and the 5-cyanoindole. In these instances, the bromides **32c** and **32d** were then prepared and alkylation reaction conditions were used for synthesis of the final targets.

The synthesis of scaffold **13** was carried out in one step by alkylation of the appropriately substituted indole with 1,4-dibromobutane to generate the desired intermediate **48** as illustrated in Scheme 8.

Scaffold **14** was prepared as summarized in Scheme 9 according to a literature procedure.[33] Commercially available (4-fluorophenyl)hydrazine hydrochloride and 4-oxocyclohexanecarboxylic acid ethyl ester were combined in the presence of ethanol under reflux to yield **49**. Intermediate **49** was reduced with lithium aluminum hydride followed by Dess−Martin oxidation to generate the aldehyde **50**.

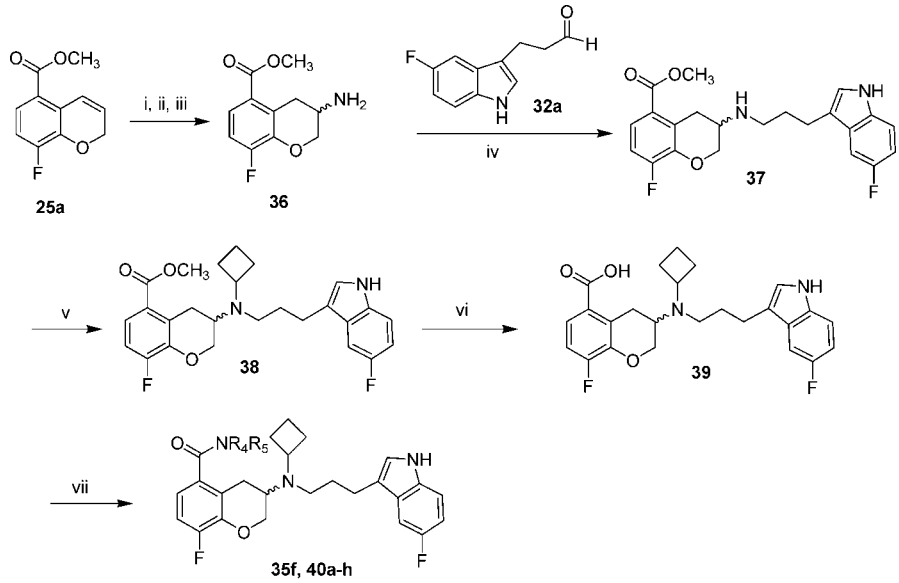
Final targets **52a**−**g** were synthesized using route 1 as illustrated in Scheme 10. After the 5-carboxamide 8-fluoro-3-aminochroman template **29a** was coupled with the alkylindole moieties (**32a**−**i**) through alkylation or reductive amination to generate the secondary amines **51a**−**g**, the final products were obtained by reductive amination with cyclobutanone or an aldehyde. Only the enantiomers of **51g** and the final target **52a** were separated by chiral HPLC. However, their stereochemistry was not determined and these compounds are identified as (+) and (−) based on their optical rotation. Novel compounds **54a**−**d**, **55a**−**d**, and **56a**−**d** linked at the indole nitrogen were prepared as racemates under alkylation conditions, generating the secondary amines **53a**−**d** as shown in Scheme 10 (route 2). Introduction of alkyl groups on the basic nitrogen was carried out under reductive amination conditions. Finally, targets **57**−**59** were synthesized by coupling (*R*)-(+)-**29a** with intermediate **50** under reductive amination conditions followed by introduction of different R_1 groups on the basic nitrogen as illustrated in Scheme 10 (route 3) to generate one pair of enantiomers. Target **60** was synthesized using racemic **29a** to provide two diastereomeric pair of enantiomers of undetermined stereochemistry.

Scheme 4[a]



[a] Reagents: (i) **32b**, TEA, DMSO; (ii) **32a**, $NaBH_3CN$, HOAc, MeOH; or $NaBH(OAc)_3$, HOAc, 1,2-dichloroethane; (iii) aldehyde or cyclobutanone, $NaBH_3CN$, HOAc, MeOH.

Scheme 5[a]



[a] Reagents: (i) 18-crown-6, KNO_2, I_2, THF−pyridine, sonication; (ii) $NaBH_4$, SiO_2, $CHCl_3$−^{i}PrOH; (iii) $NH_2NH_2 \cdot H_2O$, Raney Ni, EtOH−THF; (iv) $NaBH_3CN$, HOAc, MeOH; (v) cyclobutanone, $NaBH_3CN$, HOAc, MeOH; (vi) NaOH, EtOH−H_2O; (vii) R_4R_5NH, EDC, HOBt, THF.

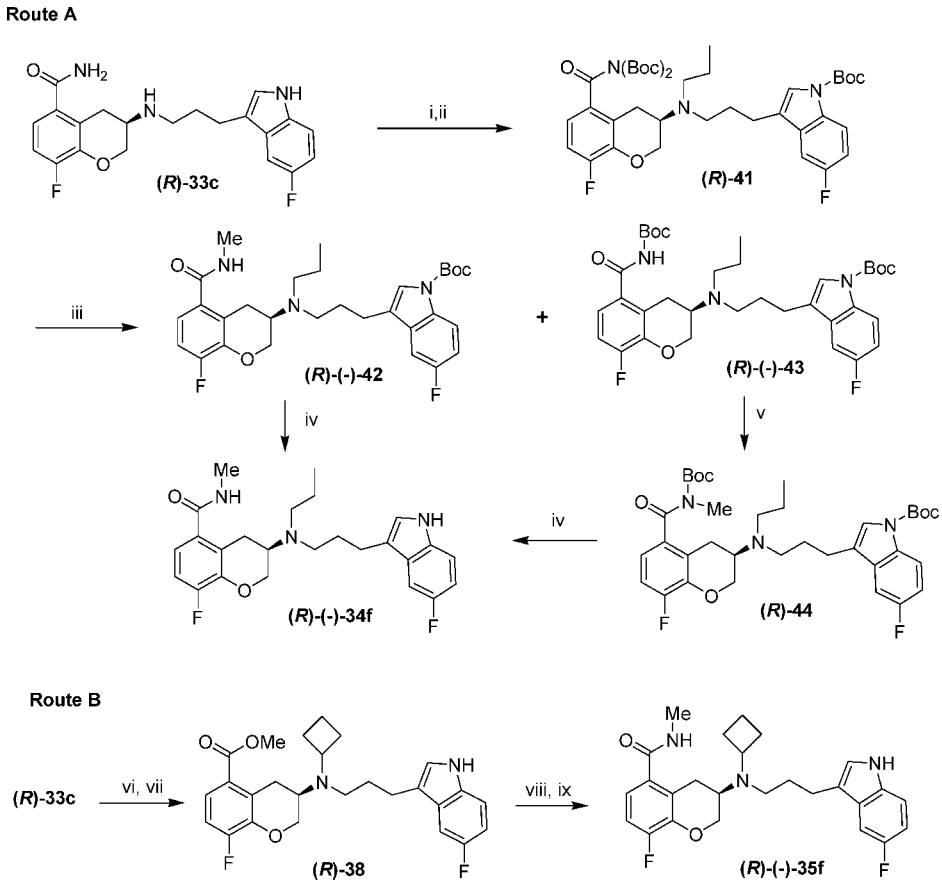
The α-methylalkylindole scaffold **15** (compound **61**) was prepared in one step as summarized in Scheme 11 using 5-fluoroindole as starting material. The *β*-methylindole derivative **16** (compound **65**) was synthesized using the racemic route illustrated in Scheme 12. 5-Fluorogramine **62** prepared from 5-fluoroindole using a well-known procedure[34] was reacted with diethyl methyl malonate in the presence of tributylphosphine to generate intermediate **63**, which upon treatment with base followed by decarboxylation yielded derivative **64**.[35] Finally, reduction with lithium aluminum hydride and oxidation of the resulting alcohol to the aldehyde generated starting material **65**.

Targets **67**, **68**, and **70** were synthesized as shown in Scheme 13 under reductive amination conditions. The secondary amines **66** and **69** were then converted to tertiary amines by reaction with the appropriately substituted alkylaldehyde or ketone. The diastereomers of the secondary amine **66** were separated by HPLC, followed by SFC separation of the enantiomers. On the basis of in vitro biological data for compounds **67a**−**d** (see Table 7), only two enantiomers of **66** were chosen for preparation of **68a**,**b**. In the synthesis of target **70**, (*R*)-(+)-**29a** was used. The stereochemistry at the second chiral center was not determined.

Discussion

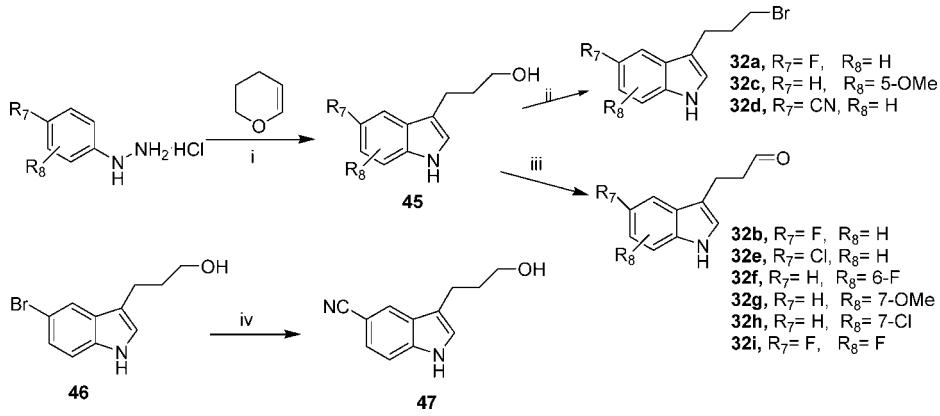
1. Effect of Chroman Moiety for *N*-Propyl Derivatives. We recently published some SAR on the effect of substitution on the basic nitrogen in the methoxy and carboxamide series.[26] As observed earlier,[26] a secondary amine is far from optimal in terms of affinity for the 5-HT_{1A} receptor. Propyl, methylcyclopropyl, and cyclobutyl were favored substituents for desired dual activity at both 5-HT_{1A} receptor and 5-HT reuptake site. Further studies were carried out investigating the 5-HT_{1A} moiety in the *N*-propyl series, and the in vitro biological data are summarized in Table 1. Using racemic compounds, we found that the 5-carboxamide-8-fluoro derivative (**34c**), the 5-*N*-methylcarboxamide-8-fluoro analogue (**34f**), and the 5-carboxamide-8-des-fluoro analogue (**34e**) have the best affinities for the 5-HT_{1A} receptor. Furthermore, derivatives **34c** and **34f** had excellent affinities at the 5-HT reuptake site while the des-fluoro analogue

Scheme 6[a]



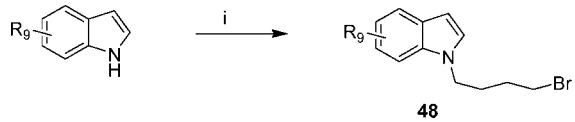
[a] Reagents: (i) propionaldehyde, $NaBH_3CN$, AcOH, MeOH; (ii) $(Boc)_2O$, DMAP, CH_2Cl_2; (iii) $MeNH_2$, THF; (iv) HCl/EtOH; (v) CH_3I, NaH, THF; (vi) H_2SO_4, MeOH; (vii) cyclobutanone, $NaBH_3CN$, AcOH, MeOH; (viii) $LiOH/H_2O$, THF−MeOH; (ix) $MeNH_2$/THF, EDC, HOBt.

Scheme 7[a]



[a] Reagents: (i) acid, dioxane, reflux; (ii) CBr_4, PPh_3, CH_2Cl_2; (iii) TFA, pyridine, DMSO−benzene, DCC; (iv) Cu(I)CN, DMF.

Scheme 8[a]

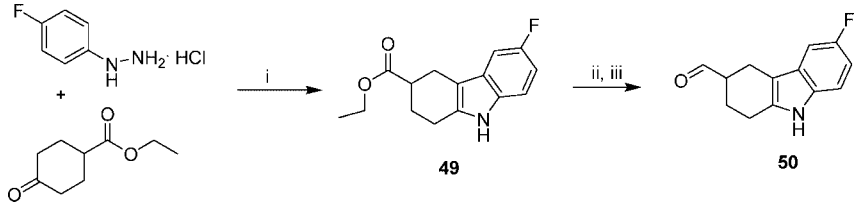


[a] Reagents: (i) 1,4-dibromobutane, NaH, DMF.

34e had a slightly weaker affinity. The 5-methoxy (**34a**) and 5-methoxy-8-fluoro (**34b**) analogues had moderate affinity at both the 5-HT_{1A} receptor and SSRI site. In general, the 5-carboxamide derivatives (8-F or 8-des-F) have better affinities at the 5-HT_{1A} receptor and the 5-HT reuptake site than their 5-methoxy counterparts.

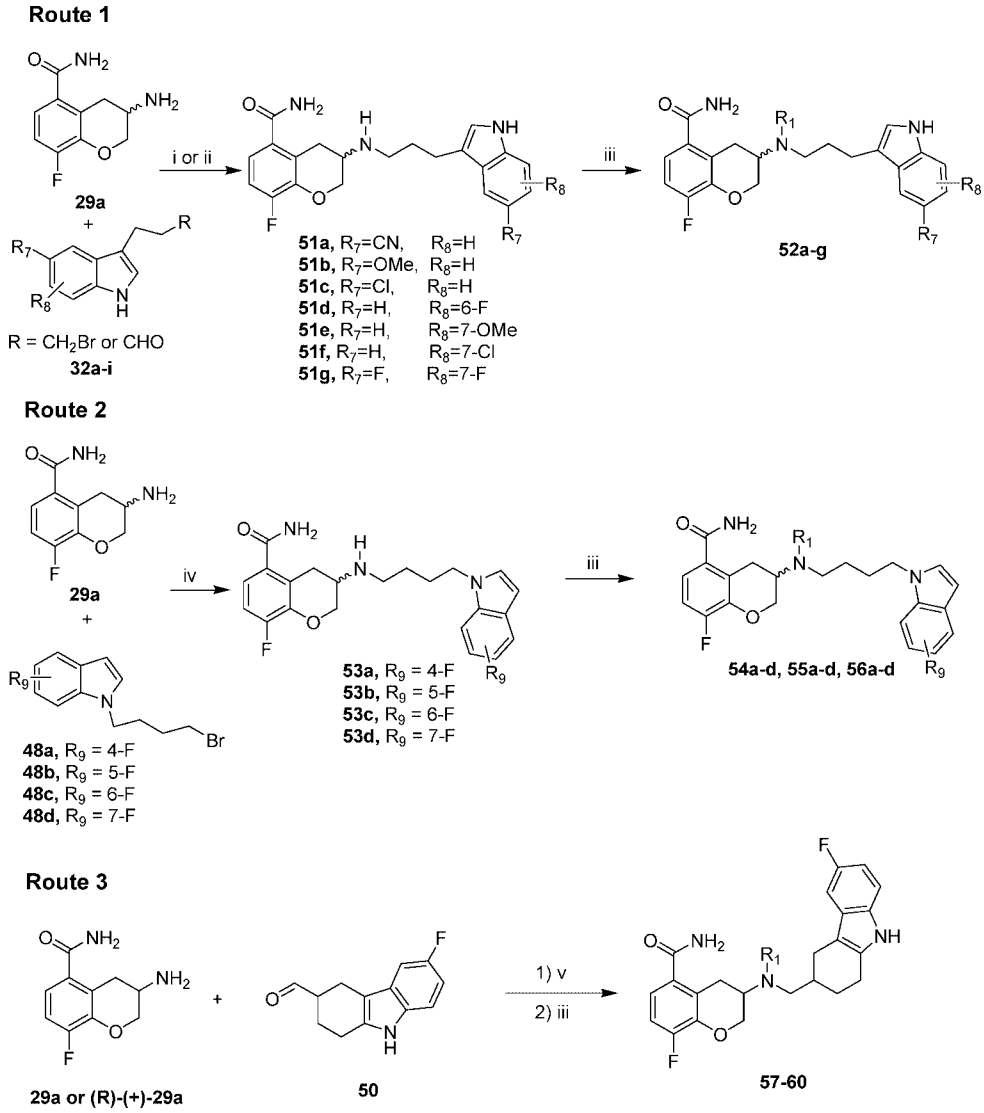
The 5-carboxamide-8-fluoro (**34c**) and 5-methoxy-8-fluoro (**34b**) chromans were directly compared with respect to intrinsic functional activity at the 5-HT_{1A} receptor in a GTPγS assay. The racemates of **34c** and **34b** were separated into their enantiomers (*R*)-(−)-**34c**, (*S*)-(+)-**34c** and (*R*)-(−)-**34b**, (*S*)-(+)-**34b**, respectively. Interestingly, we found that (*R*)-(−)-**34c** was a 5-HT_{1A} antagonist in the assay while (*S*)-(+)-**34c** was a partial agonist with excellent affinities at both 5-HT_{1A} receptor and 5-HT reuptake site. In contrast, the enantiomers of **34b** ((*R*)-(−)-**34b** and (*S*)-(+)-**34b**) were both partial agonists at the

Scheme 9[a]



[a] Reagents: (i) EtOH, reflux; (ii) $LiAlH_4$, THF; (iii) Dess−Martin periodinane, CH_3CN.

Scheme 10[a]



[a] Reagents: (i) **32a**,**c**,**d**, TEA, DMSO; (ii) **32b**,**e**−**i**, $NaBH_3CN$, HOAc, MeOH; or $NaBH(OAc)_3$, HOAc, 1,2-dichloroethane; (iii) aldehyde or cyclobutanone, $NaBH_3CN$, HOAc, MeOH; (iv) DMSO, Hünig's base, 85 °C; (v) **29a** or (*R*)-(+)-**29a**, $NaBH_3CN$, HOAc, MeOH.

5-HT_{1A} receptor with moderate SSRI and 5-HT_{1A} affinities. Introduction of a methyl on the carboxamide functionality generated a racemate (**34f**) with partial agonist activity in the GTPγS assay (48% E_{max}), while the *R*-enantiomer ((*R*)-(−)-**34f**) was an antagonist at the 5-HT_{1A} receptor (0% E_{max}). Although it is known that the stereochemistry at the 3-position of the chroman ring plays a role in the agonist/antagonist properties of these dual acting molecules, the above results suggest that the carboxamide (or substituted carboxamide) may also have some influence on this intrinsic functional activity at the 5-HT_{1A} receptor (cf. (*R*)-(−)-**34c**, (*S*)-(+)-**34c**, and (*R*)-(−)-**34f** vs (*R*)-(−)-**34b**, (*S*)-(+)-**34b**).

2. Effect of Chroman Moiety for *N*-Cyclobutyl Derivatives. Similar to the *N*-propyl series, the 5-carboxamide-8-fluoro (**35c**) and 8-chloro (**35d**) derivatives, the 5-*N*-methylcarboxamide-8-fluoro analogue (**35f**), and the 5-carboxamide-8-des-fluoro compound (**35e**) all had excellent to good affinities at both the 5-HT_{1A} receptor and the 5-HT reuptake site as summarized in Table 2. Additionally, the 5-methoxy derivative **35a** had relatively good affinity at both the 5-HT_{1A} receptor and the 5-HT reuptake site, although slightly weaker than the carboxamide derivatives. Interestingly, as racemates, most of the cyclobutyl substituted compounds were either antago-

nists or partial agonists at 5-HT_{1A} in the GTPγS assay both in 5-carboxamide and in 5-methoxy series. Furthermore, when the enantiomers of compounds **35a**, **35c**, **35d**, **35e**, and **35f** were separated, (*R*)-(−)-**35a**, (*R*)-(−)-**35c**, (−)-**35d**, and (*R*)-(−)-**35f** were 5-HT_{1A} antagonists except for the 5-carboxamide-8-des-fluorochroman analogue (−)-**35e**, where partial agonism was observed. Even more interesting was the 5-HT_{1A} antagonism of the 5-methoxy-8-des-fluoro derivative (*R*)-(−)-**35a**, although with a drop-off in potency at the transporter (K_i of 41 nM vs 13 nM for racemate). In comparison with the data observed for the *N*-propyl derivatives (see Table 1), these results suggest that the cyclobutyl seems to play a fairly important role in the antagonistic properties of these molecules along with the stereochemistry at the 3-position of the chroman. In general, the other enantiomers (data not shown) were found to have decreased affinity along with partial agonism at the 5-HT_{1A} receptor. We also found that the 5-carboxamide-8-des-fluoro derivative **35e** (partial agonist as a racemate), once separated into its enantiomers, resulted in two partial agonists, (−)-**35e** and (+)-**35e**. Moreover, one of the enantiomers of the 5-carboxamide-8-chloro analogue ((−)-**35d**) was relatively potent at both receptors and an antagonist. This suggests that substitution at the 8-position might also be important for agonism/antagonism of these molecules at the 5-HT_{1A} receptor.

The substitution of a methyl ester (**38**) or carboxylic acid (**39**) for a primary carboxamide resulted in a significant decrease in affinity at both 5-HT_{1A} receptor and 5-HT reuptake site for these molecules (see Table 2). To further understand this SAR, we decided to investigate the effect of substitution on the carboxamide functionality.

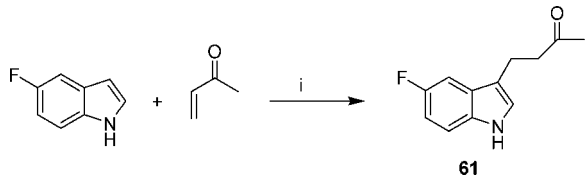
3. Substitution on the Carboxamide Functionality. The structure−activity relationship studies carried out so far have shown that the most preferred compound is a 5-carboxamide-8-fluoro substituted chroman, with a cyclobutyl substitution on the basic nitrogen and a 3-alkyl-5-fluoroindole as the SSRI moiety (compound **35c**). The in vitro biological results summarized in Table 3 show the effect of substitution on the carboxamide functionality. The substituent on the secondary amide has minimal effect on the SSRI affinity. However, the various substituents investigated did have an effect on the binding affinity at the 5-HT_{1A} receptor. Methyl (**35f**), ethyl (**40a**), and cyclopropyl (**40d**) groups were well tolerated with 5-HT_{1A} affinities similar to the primary carboxamide. However, their potency in the GTPγS was weaker than that of the unsubstituted carboxamide. An isopropyl (**40c**) substituent resulted in a 4-fold drop in affinity at the 5-HT_{1A} receptor compared to **35c**. Finally, all other groups investigated (propyl, cyclobutyl, cyclohexyl, and methylcyclopropyl, **40b**,**e**−**g**) generated compounds with lower binding affinity at the 5-HT_{1A} receptor. Moreover, disubstitution (e.g., dimethyl, **40h**) also resulted in lower binding affinity at the 5-HT_{1A} receptor with moderate affinity at the 5-HT reuptake site. Having a secondary or tertiary carboxamide did not affect the intrinsic functional activity of these racemic compounds resulting in antagonism at the 5-HT_{1A} receptor. However, their potency was decreased as shown by their IC_{50} values in the GTPγS assay. Therefore, a primary carboxamide, secondary carboxamide (with relatively small substituents), or methoxy functionalities are necessary for good 5-HT_{1A} affinity.

In keeping with the SAR of this chroman series, all these compounds demonstrated acceptable binding selectivity over the α_1 receptor.

4. Effect of Substitution on Indole Moiety. All the SAR studies were so far focused on the use of a 3-alkyl-5-fluoroindole as the SSRI moiety. Cyclobutyl substitution on the basic nitrogen was also favored, especially for antagonism at the 5-HT_{1A} receptor. We then decided to investigate further the SAR around the indole functionality as summarized in Table 4. The replacement of 5-fluoro (**35c**) by 5-cyano ((−)-**52a**), 5-methoxy (**52b**), and 5-chloro (**52c**) did not affect the binding affinity at the 5-HT_{1A} receptor. Although the affinity at the 5-HT reuptake site was very good for the 5-cyano derivative (−)-**52a**, a 25-fold drop in affinity was observed for the 5-chloro analogue **52c** while the 5-methoxy compound **52b** was rather weak. Both derivatives **52b** and **52c** showed weaker functional activity at both 5-HT_{1A} and 5-HT reuptake sites. Furthermore, as racemates, the 5-methoxy analogue (**52b**) was found to be a partial agonist at 5-HT_{1A} in GTPγS assay and the 5-chloro compound (**52c**) was found to be an antagonist. Interestingly, both enantiomers of the 5-cyano analogue ((−)-**52a** and (+)-**52a**) were antagonists at the 5-HT_{1A} receptor, the best one being (−)-**52a** although its IC_{50} (195 nM) is weaker than its 5-fluoro counterpart (*R*)-(−)-**35c** (48 nM). The 6-fluoroindole analogue **52d** did show an 80-fold decrease in affinity at the 5-HT reuptake site (K_i of 237 nM vs 3 nM for **35c**) without any significant effect on the binding affinity at the 5-HT_{1A} receptor. Methoxy (**52e**) and chloro (**52f**) substitution at the 7-position of the indole generated compounds with relatively good binding affinity at the 5-HT_{1A} receptor. However, the 7-methoxy derivative **52e** lost significant affinity at the 5-HT reuptake site with the 7-chloro (**52f**) showing a 20-fold decrease in affinity (K_i of 66 nM vs 3 nM for **35c**). We decided to investigate a 5,7-difluoroindole as an SSRI moiety in order to block a potential site of metabolism of (*R*)-(−)-(**35c**). As shown in Table 4, the 5,7-difluoro analogue (−)-**52g** showed comparable affinities to the 5-fluoroindole derivative (*R*)-(−)-**35c** at both 5-HT_{1A} and 5-HT reuptake sites. However, no improvement in microsomal metabolic stability was observed. Regardless of the substitution on the indole moiety, most of these compounds were antagonists at the 5-HT_{1A} receptor as racemates, suggesting that agonism or antagonism is mainly affected by the changes on the 5-HT_{1A} moiety or substitution at the basic nitrogen, as discussed earlier.

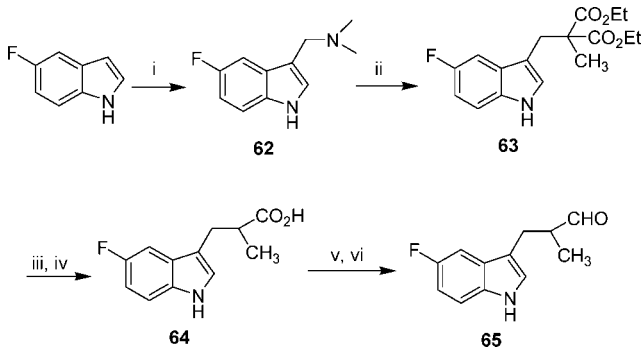
5. Chroman−Indole Nitrogen Linker. One potential site of metabolism for all compounds discussed is the indole nitrogen, thus leading us to investigate derivatives where the chroman is tethered to this nitrogen through an alkyl chain. Several such analogues were prepared with fluoro substitution at the 4-, 5-, 6-, and 7-position of the indole as summarized in Table 5. Furthermore, substitution on the basic nitrogen was also looked at for each analogue. In terms of affinity at the 5-HT_{1A} receptor, propyl (**54a**−**c**), methylcyclopropyl (**55a**−**c**), and cyclobutyl (**56a**−**c**) were all well tolerated. In all cases, the 7-fluoroanalogues (**54d**, **55d**, and **56d**) showed slightly weaker affinity at the 5-HT_{1A} receptor. Although all compounds (**54a**−**d**, **55a**−**d**, **56a**−**d**) had good to excellent affinity at the 5-HT_{1A} receptor (K_i = 3.25−39.95 nM), the position of the fluoro on the indole moiety affected the binding affinity at the 5-HT reuptake site. The 7-fluoro analogues had the best binding affinities at the 5-HT reuptake site except for analogue **55c**, which with methylcyclopropyl on the basic nitrogen and 6-fluoro substitution on the indole had the best profile. However, derivative **55c** lacks intrinsic functional activity at the transporter site. When a propyl group is present on the basic nitrogen, partial agonism was observed at the 5-HT_{1A} receptor for **54c** and **54d** racemates. For the

Scheme 11[a]



[a] Reagents: (i) $BF_3 \cdot Et_2O$/EtOH, CH_3NO_2, −20 °C.

Scheme 12[a]



[a] Reagents: (i) Eschenmoser's salt, HOAc, CH_3CN; (ii) diethylmethylmalonate, $P(Bu)_3$, CH_3CN, reflux; (iii) NaOH/EtOH; (iv) bromobenzene, reflux; (v) $LiAlH_4$, THF; (vi) TFA, pyridine, DMSO−toluene, DCC.

methylcyclopropyl (**55a** and **55c**) and cyclobutyl (**56b**−**d**) derivatives, antagonism was shown by most of the compounds. However, all these targets were characterized by weaker IC_{50} values in the GTPγS assay, notwithstanding their good binding affinity at both receptors.

6. Tetrahydrocarbazole as Transporter Moiety. Earlier work in our laboratories had shown that a tetrahydrocarbazole imparts binding affinity at the 5-HT reuptake site when linked to different ligands (unpublished results). We can view this tricyclic moiety as a constrained propylindole. Although it introduces another chiral center, it may also impart more microsomal metabolic stability to the targets. We decided to look at its effect when linked through the basic nitrogen of the 5-carboxamide-8-fluoro-3-aminochroman scaffold on dual affinity at both receptors. The in vitro biological data are summarized in Table 6. The binding affinity at the 5-HT_{1A} receptor was very much dependent on the stereochemistry at both chiral centers. One diastereomer is preferred over all others for each substituent on the basic nitrogen: propyl (**58b**), methylcyclopropyl (**59b**), and cyclobutyl (**60b**). All the diastereomers were separated by HPLC, and we know that the *R*-stereochemistry at the C-3 position of the chroman is present in compounds **57a**,**b**, **58a**,**b**, and **59a**,**b**, since they were synthesized from (*R*)-(+)-**29a**. Regardless of the substitution on the basic nitrogen, all these compounds are antagonists at the 5-HT_{1A} receptor. In the case of cyclobutyl substitution, the compound with the best binding affinity at 5-HT_{1A} (**60b**) did show some partial agonism in the GTPγS assay. Unlike the 5-fluoroindole analogues, the best affinity at the 5-HT reuptake site was obtained with the unsubstituted derivatives (R_1 = H). The intrinsic functional activity at the transporter was weaker for all the compounds, and a slight increase in metabolic stability in rat microsomes was observed. In summary, this novel series of compounds did show good dual activity at both receptors but did not have the potency needed for further evaluation.

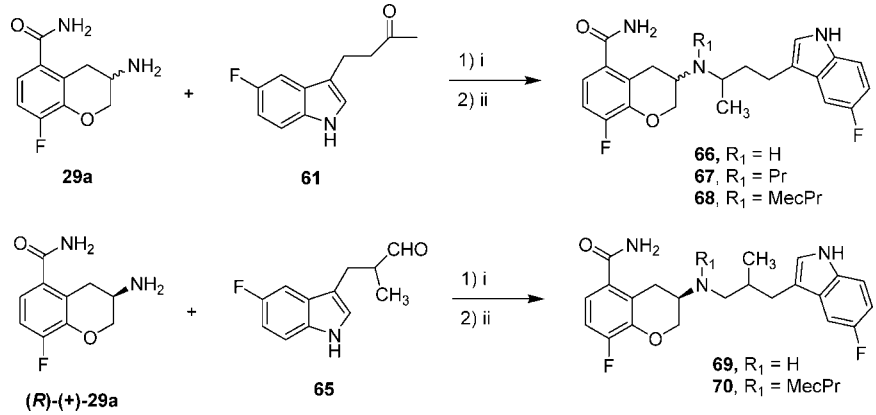
7. Substitution on Linker. α-Substitution to the basic nitrogen was investigated in order to potentially slow down dealkylation as one of the metabolic pathway for novel compound (*R*)-(−)-**35c**. Interestingly, only one diastereomer (**67a** and **68a**) shows excellent binding affinity at both receptors, with the methylcyclopropyl derivative **68a** having the best profile. This compound possesses the *R*-stereochemistry at the C-3 of the chroman amine, since it was synthesized from (*R*)-(+)-**29a**, but the stereochemistry at the α-methyl position has not been determined. The introduction of a β-methyl group on the chain generated targets **70a** and **70b**, with **70a** having excellent binding affinity at the 5-HT_{1A} receptor and reasonable affinity at the 5-HT reuptake site. However, it is a little weaker in intrinsic functional activity at the 5-HT_{1A} receptor. The substitution on the linker did not impart greater microsomal metabolic stability to these derivatives. Antagonism at the 5-HT_{1A} receptor was observed for most of the compounds regardless of the substitution on the basic nitrogen. Unlike the tetrahydrocarbazole derivatives, which are analogues of the β-methyl derivatives, these compounds are showing better affinities at the 5-HT_{1A} receptor and SSRI site (cf. **67a** vs **58b** and **68a** vs **59b**).

All compounds generated in the course of investigating the various SSRI moieties demonstrated acceptable binding selectivity over the α_1 receptor.

Conclusion

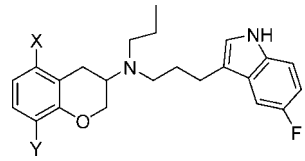
The combination of a 5-HT_{1A} scaffold and a transporter moiety (indole analogue) sharing a common basic nitrogen resulted in compounds with desirable affinities at the serotonin reuptake site and 5-HT_{1A} receptor. A detailed structure−activity relationship investigation of this series has shown that several factors influence the binding affinity and functional agonism or antagonism of these compounds. First, the 5-HT_{1A} affinity seems to be dependent on (1) the substitution on the basic nitrogen with cyclobutyl, propyl, and methylcyclopropyl as favored substituents, (2) the substitution on the carboxamide functionality with unsubstituted or nonbulky substitution (methyl or ethyl) preferred, (3) a carboxamide at the 5-position of the chroman moiety favored over a methoxy, carboxylic acid, or methyl ester, and (4) the SSRI moiety with straight chain alkyl linked to the 3-position or nitrogen of the indole as preferred over substitution on the alkyl linker or a more constrained alkylindole such as a tetrahydrocarbazole. Interestingly, in the tetrahydrocarbazole series, only one of the diastereomers was favored in terms of affinity at the 5-HT_{1A} receptor. Second, the SSRI affinity was mostly influenced by (1) the substitution on the basic nitrogen with propyl, cyclobutyl, and methylcyclopropyl as favored substituents, (2) the presence of a methoxy, primary carboxamide, or secondary carboxamides (such as methyl or ethyl) at the 5-position of the aromatic portion of the chroman, and (3) the substitution on the indole with fluoro or cyano at the 5-position or 5,7-difluoro as favored for the straight chain alkyl derivatives. The fluoro at the 6- or 7-position of the indole was preferred in N-linked analogues. Any substitution on the alkyl chain did lower the affinity for the 5-HT reuptake site. Third, the agonist or antagonist properties of these dual-acting compounds seem to be mostly influenced by the stereochemistry at the 3-position of the chroman moiety with one enantiomer (*R* for compounds where stereochemistry is known) usually preferred. Another critical observation seems to be the presence of a cyclobutyl on the basic nitrogen for the straight chain alkylindoles or N-linked derivatives. Even as racemates, many of these compounds are antagonists at the 5-HT_{1A} receptor. However, antagonism was not an issue when

Scheme 13[a]



[a] Reagents: (i) $NaBH(OAc)_3$, HOAc, 1,2-dichloroethane or $NaBH_3CN$, HOAc, MeOH; (ii) aldehyde or cyclobutanone, $NaBH_3CN$, HOAc, MeOH.

Table 1. *N*-Propyl Analogues with Different Chroman Moieties[a]



			5-HT transporter		5-HT_{1A} receptor		
compd	X	Y	affinity[b] K_i (SEM), nM	function[c] IC_{50} (SEM), nM	affinity[d] K_i (SEM), nM	GTPγS[e] E_{max}, % (IC_{50}, nM)	α_1 receptor[g] K_i, nM
34a[h]	OMe	H	9.0 (3.0)	386 (153)	15.8 (1.5)	100	820
34b	OMe	F	12.5 (2.5)	442 (9.5)	19.4 (1.06)	79.5	1059
(*R*)-(−)-**34b**	OMe	F	17.5 (1.5)	379	10.9 (4.4)	88	50%
(*S*)-(+)-**34b**	OMe	F	13.5 (5.5)	452 (61)	12.6 (0.51)	94	345
34c[h]	$CONH_2$	F	7.1 (1.7)	128 (44)	3.5 (0.9)	78	nd
(*R*)-(−)-**34c**[h]	$CONH_2$	F	8.0 (0.9)	181 (22)	1.5 (0.1)	0 (405)	1150
(*S*)-(+)-**34c**[h]	$CONH_2$	F	4.7 (0.7)	59.9 (14.3)	3.2 (1.0)	60	46%
34f	CONHMe	F	2.40 (0.5)	24.3 (11.3)	0.81 (0.05)	48 (617)	476
(*R*)-(−)-**34f**	CONHMe	F	11.3 (4.9)	47 (1.6)	2.64 (0.27)	0 (752)	39%
34e	$CONH_2$	H	23.4 (2.7)	146 (87)	0.93 (0.31)	74	31%
fluoxetine			3.9 (0.35)	39.4 (3.1)			
1					0.96 (0.21)	0 (4.04)	
8-OH-DPAT					3.0 (0.1)	100 (26)[f]	

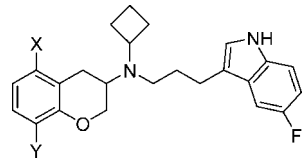
[a] K_i and IC_{50} values are the mean of at least two experiments ± SEM (performed in singlet, determined from 11 concentrations for 5-HT_{1A} binding and function; 5-HT transporter binding and function were performed in triplicate, determined from eight concentrations). Values without SEM are for a single determination only. nd: not determined. Percentages represent inhibition of binding at 1 μM. [b] Binding affinity for the 5-HT transporter was determined by displacement of [^{3}H]-paroxetine from rat cortical membranes.[36] K_i values were calculated from IC_{50} values using the method of Cheng and Prusoff.[37] [c] Inhibition of [^{3}H]-5-HT uptake by human 5-HT transporter in Jar cells.[38] [d] Binding affinity at human 5-HT_{1A} receptor in CHO cells labeled with [^{3}H]-8-OH-DPAT.[39] [e] Stimulation of GTPγS binding in CHO cells expressing 5-HT_{1A} receptors.[40] E_{max} refers to maximal agonist effect relative to DPAT. [f] Reported as an EC_{50} of 26 nM for 8-OH-DPAT. [g] Binding affinity at rat cortical α_1 adrenergic receptor labeled with [^{3}H]-prazosin.[41] [h] Data for these compounds were published in a previous paper.[26]

substitution was introduced on the alkyl chain. This holds true especially for the tetrahydrocarbazole compounds regardless of the substitution on the basic nitrogen as long as *R*-stereochemistry is present at the 3-amino position of the chroman. These substituted derivatives did lack potency in the functional assay. In summary, a combination of several factors seems to contribute to the agonist or antagonist properties of these derivatives. From this SAR study, compound (*R*)-(−)-**35c** was found to have the best profile, and a more complete in vivo profiling will be the subject of future publications.

Experimental Section

Chemistry. Melting points were determined on a MEL-TEMP apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian Unity Plus 400 spectrometer or a Unity INOVA Varian 500 MHz spectrometer. Chemical shifts δ are reported in ppm relative to DMSO-d_6 at 2.49 ppm or MeOH-d_4 at 3.31 ppm as an internal standard. Mass spectra were recorded on a Micromass LCT spectrometer. CHN combustion analyses were determined on a Perkin-Elmer 2400 analyzer or were performed by Robertson Microlit (Madison, NJ). All analyzed compounds are within ±0.4% of the theoretical value unless otherwise indicated. Optical rotations were measured using a Jasco P-1020 polarimeter. Solvents and reagents were used as purchased. All final targets were converted to the HCl salt by dissolution in ethyl acetate and addition of 1 M HCl/Et_2O, followed by filtration unless otherwise indicated. Chiral HPLC screens were carried out on two Agilent 1100 series HPLC equipped with quaternary pumps (model G13411A), autosamplers (model G1367A), diode-array detectors (model G1315B) from Agilent Technologies (CA), and LC Spiderling Deluxe automated column selection systems (Chiralizer Services, Newton, PA). Preparative supercritical fluid chromatography (SFC) separations were carried out on a Berger Multigram III SFC equipped with two SD-1 Varian pumps, a Knauer K-2501 spectrophotometer, 6-ton

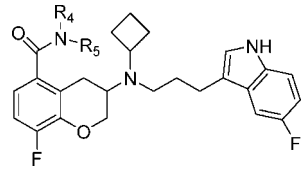
Table 2. *N*-Cyclobutyl Analogues with Different Chroman Moieties[a]



			5-HT transporter		5-HT$_{1A}$ receptor		
compd	X	Y	affinity[b] K_i (SEM), nM	function[c] IC_{50} (SEM), nM	affinity[d] K_i (SEM), nM	GTPγS[e] E_{max}, % (IC_{50}, nM)	α_1 receptor[g] K_i, nM
35a[h]	OMe	H	13 (4.0)	400 (169)	15.6 (0.2)	8.5 (>2000)	15%
(*R*)-(−)-**35a**[h]	OMe	H	41.4	732	2.14 (1.1)	0 (488)	15%
35c[h]	$CONH_2$	F	3.0 (0.5)	25.2 (8.3)	9.3 (2.1)	0 (202)	16%
(*R*)-(−)-**35c**[h]	$CONH_2$	F	1.5 (0.04)	18.7 (1.8)	1.2 (0.35)	0 (48)	21%
35d	$CONH_2$	Cl	3.74 (0.6)	56.5 (7.1)	6.21 (1.06)	0 (>1000)	567
(−)-**35d**	$CONH_2$	Cl	1.98 (1.1)	61.4 (19)	10.9 (0)	0 (125)	22%
35e	$CONH_2$	H	9.55 (0.4)	114 (61)	1.75 (0.43)	28 (184.5)	500
(−)-**35e**	$CONH_2$	H	5.9 (2.4)	109	0.66 (0.09)	30 (66)	10%
(+)-**35e**	$CONH_2$	H	7.2	28.3	29.6	71	6%
35f	CONHMe	F	8.3 (1.9)	15 (9.0)	5.35 (0.17)	0 (812)	27%
(*R*)-(−)-**35f**	CONHMe	F	10.2 (5.7)	147	1.32 (0.09)	0 (262)	0%
38	COOMe	F	161	1860	73.8 (3.8)	nd	6000
39	COOH	F	498.5	1026	4%	0 (>2000)	8%
fluoxetine			3.9 (0.35)	39.4 (3.1)			
1					0.96 (0.21)	0 (4.04)	
8-OH-DPAT					3.0 (0.1)	100 (26)[f]	

[a] K_i and IC_{50} values are the mean of at least two experiments ± SEM (performed in singlet, determined from 11 concentrations for 5-HT$_{1A}$ binding and function; 5-HT transporter binding and function were performed in triplicate, determined from 8 concentrations). Values without SEM are for a single determination only. nd: not determined. Percentages represent inhibition of binding at 1 μM. [b] Binding affinity for the 5-HT transporter was determined by displacement of [^{3}H]-paroxetine from rat cortical membranes.[36] K_i values were calculated from IC_{50} values using the method of Cheng and Prusoff.[37] [c] Inhibition of [^{3}H]-5-HT uptake by human 5-HT transporter in Jar cells.[38] [d] Binding affinity at human 5-HT$_{1A}$ receptor in CHO cells labeled with [^{3}H]-8-OH-DPAT.[39] [e] Stimulation of GTPγS binding in CHO cells expressing 5-HT$_{1A}$ receptors.[40] E_{max} refers to maximal agonist effect relative to DPAT. [f] Reported as an EC_{50} of 26 nM for 8-OH-DPAT. [g] Binding affinity at rat cortical α_1 adrenergic receptor labeled with [^{3}H]-prazosin.[41] [h] Data for these compounds were published in a previous paper.[26]

Table 3. Substituted Carboxamide Chroman Analogues[a]

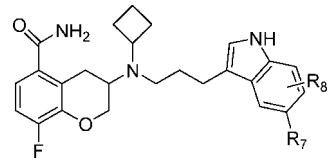


			5-HT transporter		5-HT$_{1A}$ receptor		
compd	R_4	R_5	affinity[b] K_i (SEM), nM	function[c] IC_{50} (SEM), nM	affinity[d] K_i (SEM), nM	GTPγS[e] E_{max}, % (IC_{50}, nM)	α_1 receptor[g] K_i, nM
35c[h]	H	H	3.0 (0.5)	25.2 (8.3)	9.3 (2.1)	0 (202)	16%
35f	Me	H	8.3 (1.9)	15 (9.0)	5.35 (0.17)	0 (812)	27%
40a	Et	H	9.47 (2.9)	27.9	17.8 (2.09)	0 (>1000)	12%
40b	Pr	H	7.96 (3.1)	32.7	196 (1.06)	0 (800)	21%
40c	^{i}Pr	H	11.28 (3.8)	44.7	46.1 (7.5)	0 (>2000)	4%
40d	cPr	H	8.05 (1.8)	69.6	19.2 (1.66)	0 (395)	12%
40e	cBu	H	7.26 (2.6)	70.6	213.5 (26.5)	0 (91.5)	12%
40f	cHexyl	H	19.8	144	44%	0 (>1000)	21%
40g	MecPr	H	6.91 (1.2)	43.6	160.5 (11.6)	0 (>1000)	31%
40h	Me	Me	28.8	218	372 (8.49)	0 (>2000)	55.5
fluoxetine			3.9 (0.35)	39.4 (3.1)			
1					0.96 (0.21)	0 (4.04)	
8-OH-DPAT					3.0 (0.1)	100 (26)[f]	

[a] K_i and IC_{50} values are the mean of at least two experiments ± SEM (performed in singlet, determined from 11 concentrations for 5-HT$_{1A}$ binding and function; 5-HT transporter binding and function were performed in triplicate, determined from 8 concentrations). Values without SEM are for a single determination only. nd: not determined. Percentages represent inhibition of binding at 1 μM. [b] Binding affinity for the 5-HT transporter was determined by displacement of [^{3}H]-paroxetine from rat cortical membranes.[36] K_i values were calculated from IC_{50} values using the method of Cheng and Prusoff.[37] [c] Inhibition of [^{3}H]-5-HT uptake by human 5-HT transporter in Jar cells.[38] [d] Binding affinity at human 5-HT$_{1A}$ receptor in CHO cells labeled with [^{3}H]-8-OH-DPAT.[39] [e] Stimulation of GTPγS binding in CHO cells expressing 5-HT$_{1A}$ receptors.[40] E_{max} refers to maximal agonist effect relative to DPAT. [f] Reported as an EC_{50} of 26 nM for 8-OH-DPAT. [g] Binding affinity at rat cortical α_1 adrenergic receptor labeled with [^{3}H]-prazosin.[41] [h] Data for this compound were published in a previous paper.[26]

bulk CO_2 tank with built-in chiller and heater, and G700 compressor (Mettler-Toledo, Newark, DE). Columns and conditions used for HPLC were as specified for each compound. Analytical thin-layer chromatography (TLC) was carried out on precoated plates (silica

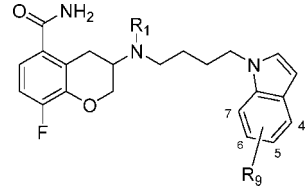
Table 4. Substituted Indole Analogues[a]



			5-HT transporter		5-HT$_{1A}$ receptor		
compd	R_7	R_8	affinity[b] K_i (SEM), nM	function[c] IC_{50} (SEM), nM	affinity[d] K_i (SEM), nM	GTPγS[e] E_{max}, % (IC_{50}, nM)	α_1 receptor[g] K_i, nM
35c[h]	F	H	3.0 (0.5)	25.2 (8.3)	9.3 (2.1)	0 (202)	16%
(*R*)-(−)-**35c**[h]	F	H	1.5 (0.04)	18.7 (1.8)	1.2 (0.35)	0 (48)	21%
(*S*)-(+)-**35c**[h]	F	H	5.3 (0.3)	17.4 (10)	253 (31)	0 (>1000)	nd
(−)-**52a**	CN	H	2.44	24.1 (1.55)	1.98 (0.78)	0 (195)	19%
(+)-**52a**	CN	H	9.05	10.1 (0.43)	258 (21.9)	0 (>1000)	27%
52b	OMe	H	>1000	834	1.19 (0.15)	84 (419)	659
52c	Cl	H	75.5	612 (18.5)	3.98 (0.8)	0 (735)	20%
52d	H	6-F	237.5	899	5.02 (2.43)	0 (512)	30%
52e	H	7-OMe	>1000	>1000	3.22 (0.39)	0 (557)	15%
52f	H	7-Cl	66	>1000	26.1 (1.66)	0 (>1000)	29%
(−)-**52g**	F	7-F	3.34 (0.19)	71.6 (2.8)	1.73 (0.49)	0 (206)	788
(+)-**52g**	F	7-F	12.15	225	68.9 (0.71)	0 (>1000)	5%
fluoxetine			3.9 (0.35)	39.4 (3.1)			
1					0.96 (0.21)	0 (4.04)	
8-OH-DPAT					3.0 (0.1)	100 (26)[f]	

[a] K_i and IC_{50} values are the mean of at least two experiments ± SEM (performed in singlet, determined from 11 concentrations for 5-HT$_{1A}$ binding and function; 5-HT transporter binding and function were performed in triplicate, determined from 8 concentrations). Values without SEM are for a single determination only. nd: not determined. Percentages represent inhibition of binding at 1 μM. [b] Binding affinity for the 5-HT transporter was determined by displacement of [^{3}H]-paroxetine from rat cortical membranes.[36] K_i values were calculated from IC_{50} values using the method of Cheng and Prusoff.[37] [c] Inhibition of [^{3}H]-5-HT uptake by human 5-HT transporter in Jar cells.[38] [d] Binding affinity at human 5-HT$_{1A}$ receptor in CHO cells labeled with [^{3}H]-8-OH-DPAT.[39] [e] Stimulation of GTPγS binding in CHO cells expressing 5-HT$_{1A}$ receptors.[40] E_{max} refers to maximal agonist effect relative to DPAT. [f] Reported as an EC_{50} of 26 nM for 8-OH-DPAT. [g] Binding affinity at rat cortical α_1 adrenergic receptor labeled with [^{3}H]-prazosin.[41] [h] Data for these compounds were published in a previous paper.[26]

Table 5. Linkage of Chroman Moiety to the Indole Nitrogen[a]



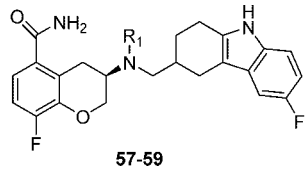
			5-HT transporter		5-HT$_{1A}$ receptor		
compd	R_1	R_9	affinity[b] K_i (SEM), nM	function[c] IC_{50} (SEM), nM	affinity[d] K_i (SEM), nM	GTPγS[e] E_{max}, % (IC_{50}, nM)	α_1 receptor[g] K_i, nM
54a	Pr	4-F	210.5	>1000	14 (1.63)	nd	23%
54b	Pr	5-F	114	>1000	6.54 (0.48)	nd	655
54c	Pr	6-F	70	776 (182)	10.6 (0.18)	40	15%
54d	Pr	7-F	32.9	435 (246)	16.6 (0.85)	39	39%
55a	MecPr	4-F	160	>1000	9.64 (2.8)	0 (>1000)	18%
55b	MecPr	5-F	77	>1000	5.44 (0.89)	nd	387
55c	MecPr	6-F	9.96 (5.99)	>1000	3.25 (0.29)	0 (371)	898
55d	MecPr	7-F	38.7	138	19.25 (0.74)	31 (204)	27%
56a	cBu	4-F	288.5	103	17.35 (2.51)	nd	5%
56b	cBu	5-F	241.5	>1000	10.78 (0.87)	0 (>1000)	670
56c	cBu	6-F	123.5	>1000	12.83 (2.25)	0 (428)	7%
56d	cBu	7-F	39.3	>1000	39.95 (0.32)	0 (>1000)	14%
fluoxetine			3.9 (0.35)	39.4 (3.1)			
1					0.96 (0.21)	0 (4.04)	
8-OH-DPAT					3.0 (0.1)	100 (26)[f]	

[a] K_i and IC_{50} values are the mean of at least two experiments ± SEM (performed in singlet, determined from 11 concentrations for 5-HT$_{1A}$ binding and function; 5-HT transporter binding and function were performed in triplicate, determined from 8 concentrations). Values without SEM are for a single determination only. nd: not determined. Percentages represent inhibition of binding at 1 μM. [b] Binding affinity for the 5-HT transporter was determined by displacement of [^{3}H]-paroxetine from rat cortical membranes.[36] K_i values were calculated from IC_{50} values using the method of Cheng and Prusoff.[37] [c] Inhibition of [^{3}H]-5-HT uptake by human 5-HT transporter in Jar cells.[38] [d] Binding affinity at human 5-HT$_{1A}$ receptor in CHO cells labeled with [^{3}H]-8-OH-DPAT.[39] [e] Stimulation of GTPγS binding in CHO cells expressing 5-HT$_{1A}$ receptors.[40] E_{max} refers to maximal agonist effect relative to DPAT. [f] Reported as an EC_{50} of 26 nM for 8-OH-DPAT. [g] Binding affinity at rat cortical α_1 adrenergic receptor labeled with [^{3}H]-prazosin.[41]

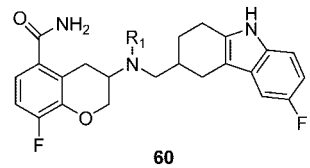
gel, 60 F-254), and spots were visualized with UV light and stained in iodine chamber.

Intermediates **18**−**21** were prepared according to literature procedures.[27,29] Intermediates **24a**−**27a** were prepared according

Table 6. Tetrahydrocarbazole as Transporter Moiety[a]



57-59

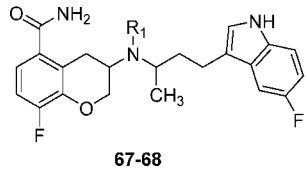


60

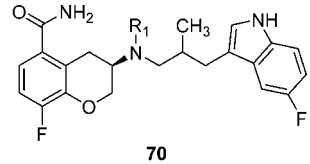
			5-HT transporter		5-HT$_{1A}$ receptor		
compd	R_1	optical rotation[h]	affinity[b] K_i (SEM), nM	function[c] IC_{50} (SEM), nM	affinity[d] K_i (SEM), nM	GTPγS[e] E_{max}, % (IC_{50}, nM)	α_1 receptor[g] K_i, nM
57a	H	−52.8	20.9	291	38.05(0.25)	0 (429)	23%
57b	H	59.8	47.6	>1000	31.4 (11.8)	0 (174)	250
58a	Pr	−90.8	>1000	>1000	60.3 (7.35)	0 (>1000)	5%
58b	Pr	12.4	180.5	>1000	7.34 (1.35)	0 (181)	15%
59a	MecPr	−89	347	>1000	117.5(8.84)	0 (>1000)	3%
59b	MecPr	10	116	>1000	9.48 (1.15)	0 (611)	22%
60a	cBu	−26.2	855	>1000	49%@1 μM	0 (>1000)	9%
60b	cBu	27.4	192	>1000	0.85 (0.11)	25 (>1000)	5%
60c	cBu	50.2	>1000	>1000	185 (14.1)	55 (978)	1%
60d	cBu	−50.2	322	>1000	73.3 (10.5)	0 (>1000)	0%
fluoxetine			3.9 (0.35)	39.4 (3.1)			
1					0.96 (0.21)	0 (4.04)	
8-OH-DPAT					3.0 (0.1)	100 (26)[f]	

[a] K_i and IC_{50} values are the mean of at least two experiments ± SEM (performed in singlet, determined from 11 concentrations for 5-HT$_{1A}$ binding and function; 5-HT transporter binding and function was performed in triplicate, determined from 8 concentrations). Values without SEM are for a single determination only. nd: not determined. Percentages represent inhibition of binding at 1 μM. [b] Binding affinity for the 5-HT transporter was determined by displacement of [^{3}H]-paroxetine from rat cortical membranes.[36] K_i values were calculated from IC_{50} values using the method of Cheng and Prusoff.[37] [c] Inhibition of [^{3}H]-5-HT uptake by human 5-HT transporter in Jar cells.[38] [d] Binding affinity at human 5-HT$_{1A}$ receptor in CHO cells labeled with [^{3}H]-8-OH-DPAT.[39] [e] Stimulation of GTPγS binding in CHO cells expressing 5-HT$_{1A}$ receptors.[40] E_{max} refers to maximal agonist effect relative to DPAT. [f] Reported as an EC_{50} of 26 nM for 8-OH-DPAT. [g] Binding affinity at rat cortical α_1 adrenergic receptor labeled with [^{3}H]-prazosin.[41] [h] Optical rotations of compounds **57**−**59** were recorded in DMSO and **60** in MeOH.

Table 7. Substitution on the Linker[a]



67-68



70

			5-HT transporter		5-HT$_{1A}$ receptor		
compd	R_1	optical rotation[h]	affinity[b] K_i (SEM), nM	function[c] IC_{50} (SEM), nM	affinity[d] K_i (SEM), nM	GTPγS[e] E_{max}, % (IC_{50}, nM)	α_1 receptor[g] K_i, nM
67a	Pr	−22.1	22.0 (7.07)	330 (75)	3.19 (0.71)	0 (323)	48%
67b	Pr	23.4	50	>1000	19.39 (5.48)	73.5	5%
67c	Pr	−67.4	121	>1000	48.77 (0.48)	0 (>1000)	14%
67d	Pr	61.4	152	>1000	44%	7 (>1000)	nd
68a	MecPr	−17	10.2	193	1.88 (0.57)	0 (333)	15%
68b	MecPr	15.4	46.7	162	31.65 (1.59)	32	7%
70a	MecPr	−22.2	48.8	498	4.16 (0.35)	0 (151)	24%
70b	MecPr	−59.6	144.5	>1000	127.5 (6.01)	nd	16%
fluoxetine			3.9 (0.35)	39.4 (3.1)			
1					0.96 (0.21)	0 (4.04)	
8-OH-DPAT					3.0 (0.1)	100 (26)[f]	

[a] K_i and IC_{50} values are the mean of at least two experiments ± SEM (performed in singlet, determined from 11 concentrations for 5-HT$_{1A}$ binding and function; 5-HT transporter binding and function was performed in triplicate, determined from 8 concentrations). Values without SEM are for a single determination only. nd: not determined. Percentages represent inhibition of binding at 1 μM. [b] Binding affinity for the 5-HT transporter was determined by displacement of [^{3}H]-paroxetine from rat cortical membranes.[36] K_i values were calculated from IC_{50} values using the method of Cheng and Prusoff.[37] [c] Inhibition of [^{3}H]-5-HT uptake by human 5-HT transporter in Jar cells.[38] [d] Binding affinity at human 5-HT$_{1A}$ receptor in CHO cells labeled with [^{3}H]-8-OH-DPAT.[39] [e] Stimulation of GTPγS binding in CHO cells expressing 5-HT$_{1A}$ receptors.[40] E_{max} refers to maximal agonist effect relative to DPAT. [f] Reported as an EC_{50} of 26 nM for 8-OH-DPAT. [g] Binding affinity at rat cortical α_1 adrenergic receptor labeled with [^{3}H]-prazosin.[41] [h] All optical rotations were recorded in DMSO.

to procedures elaborated in U.S. Patent No. 6,197,978, and intermediates **28a**,**29a** were prepared as we recently described.[26] New intermediates **24c**, **25b**,**c**, **26b**,**c**, and **27b**,**c** were synthesized using the same procedure as for **24a**−**27a**. New intermediate **28b** was prepared as described for **28a**,[26] while **28c** was synthesized using the procedure published in U.S. Patent No. 6,197,978. Intermediates **32a**,**b** were prepared according to procedures elaborated in U.S. Patent No. 6,121,307.

Methyl 4-Chloro-3-hydroxybenzoate (24b). 2-Chloro-5-trifluoromethylphenol **23** (5 g, 25 mmol) was added to concentrated sulfuric acid (37 g, 375 mmol) under exclusion of moisture and heated under stirring to 100 °C. The reaction mixture was stirred

at this temperature for 1 h, then cooled to ambient temperature and poured slowly into anhydrous MeOH (300 mL). The obtained solution was refluxed for 3 h, followed by stirring at ambient temperature overnight. The solvent was removed in vacuo to a final volume of ~150 mL and then poured carefully into 10% aqueous Na_2CO_3 (300 mL). The product was extracted with Et_2O (3×), and the combined organic layers were washed with brine (100 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated. The 4.2 g (90.5%) of **24b** was isolated as an off-white solid: mp 100−101 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.83 (s, 3H), 7.35−7.41 (m, 1H), 7.48 (d, J = 8.1 Hz, 1H), 7.55 (d, J = 2.0 Hz, 1H,) 10.65 (br s, 1H); MS (APCI) m/z 187 ([M + H]$^+$).

3-Amino-8-fluorochromane-5-carboxamide (29a). To **28a** (3.73 g, 15.7 mmol) in $CHCl_3$ (340 mL)−^{i}PrOH (125 mL), under nitrogen at room temperature, was added silica gel (11 g). To the slurry was slowly added over a 15 min period $NaBH_4$ (1.48 g, 39.2 mmol). After 30 min, the reaction mixture was quenched with acetic acid (28 mL) and stirred for another 30 min. The reaction mixture was then filtered and the silica gel washed thoroughly with CH_2Cl_2. The filtrate was concentrated and the residue taken up in EtOAc/H_2O. The organic layer was separated, treated with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The 3.65 g (97%) of 8-fluoro-3-nitrochromane-5-carboxamide was isolated as an off-white solid: mp 184−185.5 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.41−3.53 (m, 1H), 3.52−3.67 (m, 1H), 4.33−4.52 (m, 1H), 4.74−4.92 (m, 1H), 5.42 (s, 1H), 6.98−7.24 (m, 2H), 7.43 (s, 1H), 7.84 (s, 1H); MS (ESI) m/z 239 ([M − H]$^-$). Anal. ($C_{10}H_9FN_2O_4$) C, H, N.

To 8-fluoro-3-nitrochromane-5-carboxamide (2 g, 8.3 mmol) in absolute EtOH (90 mL) was added THF (15 mL). The mixture was heated to 60 °C to help solubilize the starting material and cooled down to 45 °C. Wet Raney Ni was added followed by, over a 30 min period, a solution of hydrazine hydrate (4.7 mL) in absolute EtOH (12 mL). The reaction mixture was kept at 45 °C for 1 h. While still warm, the mixture was filtered over Celite and the Raney Ni washed thoroughly with hot EtOH. The filtrate was concentrated under vacuum. Chromatography (4:1 CH_2Cl_2−MeOH (1% NH_4OH)) afforded 1.06 g (61%) of **29a** as an off-white solid: mp 229 °C/dec; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.96−3.15 (m, 1H), 3.23−3.43 (m, 1H), 3.67−3.89 (m, 1H), 4.15−4.37 (m, 2H), 7.03−7.23 (m, 2H), 7.43 (s, 1H), 7.80 (s, 1H), 8.40 (s, 3H); MS (ESI) m/z 211 ([M + H]$^+$). Anal. ($C_{10}H_{11}FN_2O_2\cdot$1HCl) C, H, N.

The enantiomers of **29a** were separated by chiral resolution with L-(+)-tartaric acid to generate (*R*)-(+)-**29a** as a tartrate salt: $[\alpha]_D^{25}$ +71.0° (*c* 1.0, H_2O).

3-Amino-8-chlorochromane-5-carboxamide (29b). This intermediate was prepared as described above for **29a**, generating 1.28 g (85%) of 8-chloro-3-nitrochromane-5-carboxamide as a light-beige solid: mp 193−4 °C; MS (ESI) m/z 255/257 ([M − H]$^-$). Reduction in the presence of Raney Ni and hydrazine hydrate followed by chromatography (1:4 MeOH−$CHCl_3$ (1% NH_4OH)) afforded 0.78 g (83%) of **29b** as an off-white solid: mp 231−6 °C; MS (ES) m/z 225 ([M − H]$^-$). It was then converted to the HCl salt by dissolving the free base in methanol, adding ethereal HCl, and evaporating the solution in vacuo. The residue was crystallized from methanol/ether, affording the mono-HCl salt of **29b** as off-white microcrystals: mp >250 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.97−3.12 (m, 1H), 3.21−3.41 (m, 1H), 3.74−3.86 (m, 1H), 4.20−4.35 (m, 2H), 7.02−7.15 (m, 1H), 7.33−7.44 (m, 1H), 7.46−7.54 (m, 1H), 7.79−7.91 (m, 1H), 8.21−8.40 (m, 3H); MS (ES) m/z 225.0 ([M − H]$^-$).

3-Aminochromane-5-carboxamide (29c). This intermediate was prepared as described above for **29a**, generating 2 g (95%) of 3-nitrochromane-5-carboxamide as off-white microcrystals; mp 200−202 °C. MS (ES) m/z 223.0. Reduction in the presence of Raney Ni and hydrazine hydrate afforded 1.75 g (~100%) of **29c** as waxy faintly green solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.10−2.40 (m, 2H), 2.55−3.20 (m, 2H), 3.40−3.60 (m, 1H), 3.90−4.20 (m, 2H), 6.75 (d, 1H), 6.85 (d, 1H), 7.02 (t, 1H), 7.30 (s, 1H), 7.60 (s, 1H); MS (ES) m/z 193.1 ([M + H]$^+$).

8-Fluoro-*N*-methyl-2*H*-chromene-5-carboxamide (30). To **26a** (3.5 g, 0.018 mol) in anhydrous THF (100 mL), under nitrogen at room temperature, was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC, 6.9 g, 0.036 mol), 1-hydroxybenzotriazole hydrate (HOBt, 4.86 g, 0.036 mol), and methylamine (2 M/THF, 36 mL, 0.072 mol). The mixture was stirred at room temperature overnight. It was concentrated and the residue taken up in CH_2Cl_2/H_2O. The aqueous layer was extracted one more time with CH_2Cl_2, and the organic extracts were treated with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. Chromatography (3:1 EtOAc−hexanes) afforded 3.69 g (99%) of **30** as a white solid: mp 150−153 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.73 (d, J = 4.6 Hz, 3H), 4.74−4.90 (m, 2H), 5.94−6.08 (m, 1H), 6.70−6.83 (m, 1H), 6.90−7.02 (m, 1H), 7.04−7.18 (m, 1H), 8.19−8.33 (m, 1H); MS (ES) m/z 206.1 ([M − H]$^-$).

3-Amino-8-fluoro-*N*-methylchromane-5-carboxamide (31). Nitration of **30** was carried out using the procedure described in U.S. Patent No. 6,197,978. Reduction with $NaBH_4$ was carried out as described above for **29a**, generating 2.54 g (98%) of 8-fluoro-*N*-methyl-3-nitrochromane-5-carboxamide: ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.65−2.80 (d, 3H), 3.40−3.50 (m, 2H), 4.38−4.48 (m, 1H), 4.75−4.90 (m, 1H), 5.35−5.45 (m, 1H), 6.97−7.08 (m, 1H), 7.08−7.20 (m, 1H), 8.20−8.40 (m, 1H). Reduction of the nitro to the amine using Raney Ni and hydrazine hydrate was carried out as described above for **29a**, affording 1.35 g (60%) of **31** as an off-white solid which was converted to the monohydrochloride salt: mp 131 °C/dec; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.73 (d, J = 4.6 Hz, 3H), 2.93−3.06 (m, 1H), 3.20−3.42 (m, 1H), 3.55−3.66 (m, 1H), 3.71−3.84 (m, 1H), 4.15−4.35 (m, 2H), 7.01−7.08 (m, 1H), 7.13−7.21 (m, 1H), 8.15−8.38 (m, 3H); MS (ES) m/z 225.1 ([M + H]$^+$). Anal. ($C_{11}H_{13}FN_2O_2\cdot$1HCl$\cdot$0.5H_2O) C, H, N.

Methyl 3-Amino-8-fluorochromane-5-carboxylate (36). Nitration of **25a** was carried out using the procedure already published.[26] Reduction with $NaBH_4$ was carried out as described above for **29a**, generating 1.72 g (84%) of methyl 8-fluoro-3-nitrochromane-5-carboxylate: ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.45−3.60 (m, 1H), 3.75−3.90 (m, 4H), 4.38−4.50 (m, 1H), 4.78−4.90 (m, 1H), 5.40−5.50 (m, 1H), 7.18−7.30 (m, 1H), 7.50−7.60 (m, 1H). Reduction of the nitro to the amine using Raney Ni and hydrazine hydrate was carried out as described above for **29a**, affording 1.46 g (55%) of **36** as a thick orange liquid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.60−2.00 (m, 2H), 2.62−2.78 (m, 1H), 3.05−3.28 (m, 2H), 3.62−3.74 (m, 1H), 3.78 (s, 3H), 4.08−4.20 (m, 1H), 7.05−7.20 (m, 1H), 7.32−7.45 (m, 1H).

1-(4-Bromobutyl)-4-fluoro-1*H*-indole (48a). To a solution of the appropriate indole (1 g) in 20 mL of DMF was added sodium hydride (60% in mineral oil, 8.14 mmol). The solution was stirred for 1−2 h and then treated with 1,4-dibromobutane (2.66 mL, 22 mmol). The mixture was stirred for 45 min to 2 h, quenched with 20 mL of H_2O, and extracted with EtOAc. The combined extracts were dried over anhydrous $MgSO_4$ and concentrated. Purification carried out by flash chromatography using a Biotage Quad 12/25 (Dyax Corp) with KP Sil 32−63 mM, 60 Å cartridge, and a gradient of 100% Hex to 2% EtOAc/Hex generated a 72% yield of **48a** as a clear oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.67−1.79 (m, 2H), 1.86 (q, 2H), 3.52 (t, J = 6.6 Hz, 2H), 4.23 (t, J = 6.8 Hz, 2H), 6.48 (d, J = 2.9 Hz, 1H), 6.78 (t, J = 9.3 Hz, 1H), 7.10 (dd, J = 16.1, 5.4 Hz, 1H), 7.34 (d, J = 8.3 Hz, 1H), 7.42 (d, 1H); MS (ESI) m/z 269.1, 271.1([M + H]$^+$).

1-(4-Bromobutyl)-5-fluoro-1*H*-indole (48b). 48b was obtained according to the procedure for **48a**, and a 69% yield of **48b** was isolated as a clear oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.62−1.76 (m, 2H), 1.76−1.90 (m, 2H), 3.42−3.52 (m, 2H), 4.10−4.22 (m, 2H), 6.34−6.40 (m, 1H), 6.88−6.98 (m, 1H), 7.20−7.30 (m, 1H), 7.38−7.42 (m, 1H), 7.42−7.50 (m, 2H); MS (ESI) m/z 269.1, 271.1 ([M + H]$^+$).

1-(4-Bromobutyl)-6-fluoro-1*H*-indole (48c). 48c was obtained according to the procedure for **48a**, and a 68% yield of **48c** was isolated as a clear oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.69−1.78 (m, 2H), 1.79−1.88 (m, 2H), 3.47−3.58 (m, 2H), 4.09−4.23 (m,

2H), 6.40−6.48 (m, 1H), 6.78−6.92 (m, 1H), 7.31−7.41 (m, 2H), 7.45−7.56 (m, 1H); MS (ESI) *m/z* 269.0, 271.1 ([M + H]$^+$).

1-(4-Bromobutyl)-7-fluoro-1*H*-indole (48d). 48d was obtained according to the procedure for **48a**, and a 44% yield of **48d** was isolated as a clear oil by preparative HPLC (Primesphere Silica, 5 cm × 25 cm column, flow rate 95 mL/min, sample dissolved in hexane, mobile phase of 5% ethyl acetate in hexane). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.64−1.79 (m, 2H), 1.79−1.93 (m, 2H), 3.51 (t, J = 6.7 Hz, 2H), 4.30 (t, J = 6.7 Hz, 2H), 6.48 (s, 1H), 6.83−6.99 (m, 2H), 7.28−7.43 (m, 2H); MS (ESI) *m/z* 270.0, 272.0 ([M + H]$^+$).

Ethyl 6-Fluoro-2,3,4,9-tetrahydro-1*H*-carbazole-3-carboxylate (49). 4-Cyclohexanonecarboxylic acid ethyl ester (25 g, 0.14 mol) and 4-fluorophenyhydrazine hydrochloride (22.5 g, 0.13 mol) were dissolved in EtOH (450 mL) and heated under reflux for 16 h. After the mixture was cooled, the white solid was filtered off and the filtrate concentrated. The residue was taken up in EtOAc, washed with H_2O, dried over anhydrous $MgSO_4$, and concentrated to generate 35.5 g (93%) of **49** which was recrystallized from heptane: mp 115−117 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.21 (t, J = 7.1 Hz, 3H), 1.78−1.93 (m, 1H), 2.11−2.24 (m, 1H), 2.64−2.93 (m, 5H), 4.02−4.18 (m, 2H), 6.75−6.85 (m, 1H), 7.06−7.13 (m, 1H), 7.16−7.23 (m, 1H), 10.78 (s, 1H); MS (ES) *m/z* 262 ([M + H]$^+$).

6-Fluoro-2,3,4,9-tetrahydro-1*H*-carbazole-3-carbaldehyde (50). Lithium aluminum hydride (800 mg) was added portionwise to a solution of **49** (5.77 g, 22.1 mmol) in dry THF (100 mL). The mixture was stirred at ambient temperature under nitrogen for 16 h, followed by quenching with the addition of an aqueous Rochelle salt solution. The mixture was diluted with Et_2O, and the aqueous phase was extracted once more with Et_2O. The organic extracts were pooled, dried over anhydrous $MgSO_4$, and concentrated. Chromatography ((2:1) Hex−EtOAc) afforded 3.90 g (80%) of (6-fluoro-2,3,4,9-tetrahydro-1*H*-carbazol-3-yl)methanol: mp 107−109 °C; MS (ES) *m/z* 218.1 ([M − H]$^-$).

Dess−Martin periodinane (7.37 g 17.4 mmol) was added portionwise to a stirred solution/suspension of (6-fluoro-2,3,4,9-tetrahydro-1*H*-carbazol-3-yl)methanol (2.64 g, 11.8 mmole) in CH_2Cl_2 (120 mL). The alcohol completely dissolved after the Dess−Martin reagent was added. The mixture was stirred at ambient temperature for 30 min and quenched with EtOH. The mixture was diluted with Et_2O, washed with saturated aqueous $NaHCO_3$ (2×) followed by 5% sodium thiosulfate pentahydrate, treated with brine, dried over anhydrous $MgSO_4$, and concentrated. Chromatography ((4:1) Hex−EtOAc) afforded 1.2 g (47%) of **50**: mp 96−98 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.78−1.94 (m, 1H), 2.12−2.23 (m, 1H), 2.76 (t, J = 11.6 Hz, 5H), 6.75−6.85 (m, 1H), 7.07−7.15 (m, 1H), 7.15−7.24 (m, 1H), 9.73 (s, 1H), 10.78 (br s, 1H); MS (ES) *m/z* 216.1 ([M − H]$^-$).

4-(5-Fluoro-1*H*-indol-3-yl)butan-2-one (61). To 5-fluoroindole (5 g, 37mmol) in nitromethane (150 mL) was added methyl vinyl ketone (3.7 mL, 44 mmol). The mixture was cooled to −20 °C, and a mixture of $BF_3 \cdot Et_2O$ (0.94 mL, 7.4 mmol) and EtOH (4 mL) was added dropwise. The mixture was stirred at −20 °C for 45 min. It was quenched with 1 N NaOH, diluted with EtOAc, extracted with H_2O (2×), treated with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. Chromatography ((2:1) Hex−EtOAc)) afforded 6.23 g (81%) of **61**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.08 (s, 3H), 2.72−2.86 (m, 4H), 6.84−6.92 (m, 1H), 7.14−7.18 (m, 1H), 7.22−7.32 (m, 2H), 10.85 (br s, 1H).

Diethyl [(5-Fluoro-1*H*-indol-3-yl)methyl](methyl)malonate (63). A solution of 5-fluorogramine **62** (15.5 g, 80.6 mmol) in CH_3CN (450 mL) was treated with diethyl methylmalonate (20.8 mL, 121 mmol) and tributylphosphine at reflux for 17 h. The cooled reaction was concentrated, dissolved in EtOAc, washed with 1 N aqueous HCl, treated with brine, dried over anhydrous $MgSO_4$, and concentrated. Chromatography ((3:1) hexane−EtOAc) afforded 16.5 g (64%) of **63** as an oil which solidified on standing to a white solid: mp 76−77 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.15 (t, J = 7.1 Hz, 6H), 1.27 (s, 3H), 3.21 (s, 2H), 3.98−4.17 (m, 4H), 6.82−6.93 (m, 1H), 7.08−7.14 (m, 1H), 7.15−7.21 (m, 1H), 7.24−7.36 (m, 1H), 10.97−11.09 (m, 1H).

3-(5-Fluoro-1*H*-indol-3-yl)-2-methylpropanoic Acid (64). A solution of **63** (15.7 g, 48.9 mmol) in EtOH (160 mL) was treated with 2.5 N aqueous NaOH (80 mL, 200 mmol) and refluxed for 1.5 h. The cooled solution was concentrated to remove EtOH. The residue was acidified with concentrated HCl and extracted with EtOAc (3×). The combined organic extracts were treated with brine, dried over anhydrous $MgSO_4$, and concentrated. The residue was triturated with CH_2Cl_2/hexane and dried under vacuum to afford 12.1 g (93%) of [(5-fluoro-1*H*-indol-3-yl)methyl](methyl)malonic acid as a pinkish-white solid: mp 135−137 °C/dec.

A suspension of [(5-fluoro-1*H*-indol-3-yl)methyl](methyl)malonic acid (12.3 g, 46.4 mmol) in bromobenzene (50 mL) was refluxed for 1.5 h and then concentrated. The residue was triturated with CH_2Cl_2/hexane. Air drying afforded 8.86 g (86%) of **64** as a tan solid: mp 112−113 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.99−1.11 (m, 3H), 2.58−2.76 (m, 2H), 2.87−3.01 (m, 1H), 6.81−6.92 (m, 1H), 7.14−7.19 (m, 1H), 7.20−7.34 (m, 2H), 10.89 (br s, 1H), 11.88−12.20 (m, 1H); MS (ES) *m/z* 220.1 ([M − H]$^-$).

3-(5-Fluoro-1*H*-indol-3-yl)-2-methylpropanal (65). A solution of **64** (9.24 g, 41.8 mmol) in anhydrous THF (30 mL) was chilled to 0 °C and treated with 1 N $LiAlH_4$/THF (50 mL, 50 mmol) at room temperature for 3 h. Additional 1 N $LiAlH_4$/THF (34 mL, 34 mmol) was added and the mixture stirred for an additional 2 h. The reaction was quenched with ice−water, diluted with saturated aqueous potassium sodium tartrate, and extracted with EtOAc (3×). The combined organic extracts were treated with brine, dried over anhydrous $MgSO_4$, and concentrated to afford 7.74 g (89%) of (5-fluoro-1*H*-indol-3-yl)-2-methylpropan-1-ol as a viscous orange oil.

A solution of pyridine (8.3 mL, 100 mmol) in anhydrous toluene (100 mL) was chilled to 0 °C and treated sequentially with TFA (4.0 mL, 51 mmol), anhydrous DMSO (100 mL), (5-fluoro-1*H*-indol-3-yl)-2-methylpropan-1-ol (7.06 g, 34.1 mmol), and dicyclohexylcarbodiimide (21.1 g, 102 mmol). It was stirred at room temperature for 5 h. The reaction was quenched with ice−water and stirred for 1 h. A white precipitate was filtered out and the resulting solution extracted with EtOAc (3×). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrated. Chromatography ((85:15) hexane−EtOAc) afforded 5.45 g (78%) of **65** as a tan solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.95 (d, 3H), 2.62−2.80 (m, 2H), 2.96−3.08 (m, 1H), 6.80−6.90 (m, 2H), 7.12−7.32 (m, 3H), 9.63 (s, 1H), 10.90 (s, 1H).

General Procedure A (Alkylation Reaction). *N*-[3-(5-Fluoro-1*H*-indol-3-yl)propyl]-5-methoxychroman-3-amine (33a) and (3*R*)-*N*-[3-(5-fluoro-1*H*-indol-3-yl)propyl]-5-methoxychroman-3-amine ((*R*)-33a). A solution of **19** (0.20 g, 1.12 mmol), **32b** (0.19 g, 0.75 mmol), and triethylamine (0.21 mL, 1.5 mmol) in anhydrous DMSO (6 mL) was stirred at 90 °C for 9 h. The mixture was cooled to room temperature, diluted with EtOAc, and washed with H_2O (2×). The organic layer was treated with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. Chromatography (6:3:1 hexanes/EtOAc/MeOH (1% NH_4OH)) afforded 0.16 g (60%) of **33a** as a dark-yellow solid. Conversion to the oxalate salt using oxalic acid in isopropanol generated a white solid: mp 133−136 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.89−2.06 (m, 2H), 2.65−2.83 (m, 3H), 2.92−3.20 (m, 3H), 3.68−3.87 (m, 5H), 4.15−4.30 (m, 2H), 6.45−6.52 (m, 1H), 6.56−6.65 (m, 1H), 6.85−6.97 (m, 1H), 7.07−7.16 (m, 1H), 7.21−7.27 (m, 1H), 7.27−7.40 (m, 2H), 10.94 (s, 1H); MS (ESI) *m/z* 355 ([M + H]$^+$). Anal. ($C_{21}H_{23}FN_2O_2 \cdot C_2H_2O_4$) C, H, N. Similarly, (*R*)-(−)-**19** was reacted with **32b** followed by chromatography (6:3:1 hexanes/EtOAc/MeOH (1% NH_4OH)) to afford 0.2 g (71%) of (*R*)-**33a** as an orange gum.

3-{[3-(5-Cyano-1*H*-indol-3-yl)propyl]amino}-8-fluorochromane-5-carboxamide (51a). Using general procedure A, **29a** was reacted with **32d** as described above for **33a** followed by chromatography ((96:4) CH_2Cl_2−MeOH (5% NH_4OH)) to generate 0.677 g (47%) of **51a** as an off-white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.65−1.80 (m, 2H), 2.52−2.78 (m, 4H), 2.85−3.10 (m, 2H),

3.20−3.32 (m, 2H), 3.68−3.85 (m, 1H), 4.12−4.25 (m, 1H), 6.80−7.10 (m, 2H), 7.20−7.50 (m, 4H), 7.58−7.70 (m, 1H), 8.04 (s, 1H).

8-Fluoro-3-{[3-(5-methoxy-1*H*-indol-3-yl)propyl]amino}chromane-5-carboxamide (51b). Using general procedure A, **29a** was reacted with **32c** as described above for **33a** followed by chromatography ((95:5) CH_2Cl_2−methanol(5% NH_4OH) to generate 0.75 g (62%) of **51b** which was converted to the mono-HCl salt as a reddish-white solid: mp 171−176 °C (melts with decomposition); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.95−2.08 (m, 2H), 2.69−2.81 (m, 2H), 2.99−3.45 (m, 4H), 3.72−3.85 (m, 4H), 4.29−4.45 (m, 2H), 6.66−6.77 (m, 1H), 6.97−7.05 (m, 1H), 7.07−7.26 (m, 4H), 7.37−7.48 (m, 1H), 7.75−7.85 (m, 1H), 8.98−9.11 (m, 2H), 10.63−10.72 (m, 1H); MS (ES) *m*/*z* 398.1 ([M + H]$^+$). Anal. ($C_{22}H_{24}FN_3O_3\cdot$HCl$\cdot$0.30H_2O) C, H, N (N calcd 9.56, found 8.55).

8-Fluoro-3-[4-(4-fluoroindol-1-yl)butylamino]chroman-5-carboxylic Acid Amide (53a). Using general procedure A, **29a** was reacted with **48a** as described above for **33a**. Purification was carried out using a Biotage Quad 12/25 (Dyax Corp) with KP Sil 32−63 mM, 60 Å cartridges, and a gradient from 100% CH_2Cl_2 to 4% methanolic ammonia/CH_2Cl_2), generating **53a** (63%) as a pale-yellow foam: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.23−1.39 (m, 2H), 1.66−1.82 (m, 3H), 2.51−2.69 (m, 4H), 2.82−2.94 (m, 1H), 2.94−3.06 (m, 1H), 3.67−3.78 (m, 1H), 4.07−4.24 (m, 3H), 6.38−6.47 (m, 1H), 6.67−6.78 (m, 1H), 6.83−6.93 (m, 1H), 6.95−7.10 (m, 2H), 7.24−7.31 (m, 2H), 7.33−7.39 (m, 2H), 7.63 (br s, 1H); MS (ESI), *m*/*z* 400.17 [M + H]$^+$, MS (ESI) *m*/*z* 398.2 [M − H]$^-$.

8-Fluoro-3-[4-(5-fluoroindol-1-yl)butylamino]chroman-5-carboxylic Acid Amide (53b). Using general procedure A, **29a** was reacted with **48b** as described above for **53a**, generating **53b** (58%) as a pale-yellow foam: ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.28−1.39 (m, 2H), 1.70−1.81 (m, 3H), 2.55−2.69 (m, 3H), 2.85−2.96 (m, 1H), 2.98−3.08 (m, 1H), 3.71−3.81 (m, 1H), 4.08−4.25 (m, 3H), 6.36−6.42 (m, 1H), 6.88−6.98 (m, 2H), 6.99−7.07 (m, 1H), 7.22−7.35 (m, 2H), 7.39−7.49 (m, 2H), 7.66 (s, 1H); MS (ESI) *m*/*z* 400.2 [M + H]$^+$, MS (ESI) *m*/*z* 398.2 [M − H]$^-$.

8-Fluoro-3-[4-(6-fluoroindol-1-yl)butylamino]chroman-5-carboxylic Acid Amide (53c). Using general procedure A, **29a** was reacted with **48c** as described above for **53a**, generating **53c** (60%) as a white solid: mp 146−148 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.29−1.41 (m, 2H), 1.67−1.83 (m, 3H), 2.53−2.69 (m, 3H), 2.86−2.96 (m, 1H), 2.97−3.09 (m, 1H), 3.69−3.81 (m, 1H), 4.07−4.25 (m, 3H), 6.38−6.45 (m, 1H), 6.78−6.96 (m, 2H), 6.96−7.09 (m, 1H), 7.25−7.39 (m, 3H), 7.44−7.54 (m, 1H), 7.66 (br s, 1 H); MS (ESI) *m*/*z* 400.2 [M + H]$^+$, MS (ESI) *m*/*z* 398.2 [M − H]$^-$.

8-Fluoro-3-{[4-(7-fluoro-1*H*-indol-1-yl)butyl]amino}chromane-5-carboxamide (53d). Using general procedure A, **29a** was reacted with **48d** as described above for **53a**, generating **53d** as a white solid: mp 166−168 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.26−1.40 (m, 2H), 1.68−1.84 (m, 3H), 2.53−2.70 (m, 3H), 2.84−2.95 (m, 1H), 2.95−3.09 (m, 1H), 3.68−3.79 (m, 1H), 4.13−4.34 (m, 3H), 6.41−6.51 (m, 1H), 6.82−6.97 (m, 3H), 6.98−7.09 (m, 1H), 7.24−7.42 (m, 3H), 7.66 (br s, 1H); MS (ESI) *m*/*z* 400.2 [M + H]$^+$, MS (ESI) *m*/*z* 398.2 [M − H]$^-$.

General Procedure B (Reductive Amination). 8-Fluoro-*N*-[3-(5-fluoro-1*H*-indol-3-yl)propyl]-5-methoxychroman-3-amine (33b), (3*R*)-8-Fluoro-*N*-[3-(5-fluoro-1*H*-indol-3-yl)propyl]-5-methoxychroman-3-amine ((*R*)-33b), and (3*S*)-8-Fluoro-*N*-[3-(5-fluoro-1*H*-indol-3-yl)propyl]-5-methoxychroman-3-amine ((*S*)-33b). To **21** (0.24 g, 1.22 mmol) in anhydrous MeOH (18 mL) was added **32a** (0.198 g, 1.04 mmol), acetic acid (0.15 mL, 2.92 mmol), and sodium cyanoborohydride (0.115 g, 1.83 mmol). The mixture was stirred at room temperature overnight, quenched with 1 N NaOH/H_2O, and concentrated. The residue was taken up in EtOAc/H_2O and extracted with EtOAc (2×). The organic extracts were treated with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. Chromatography (2:1 EtOAc−hexanes) afforded 0.34 g (87%) of **33b** as a gum. Conversion to the mono-HCl salt generated a beige solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.95−2.08 (m, 2H), 2.71−2.79 (m, 2H), 2.80−2.91 (m, 1H), 2.98−3.15 (m, 3H), 3.73−3.84 (m, 4H), 4.26−4.41 (m, 2H), 6.49−6.57 (m, 1H), 6.87−6.96 (m, 1H), 7.03−7.12 (m, 1H), 7.24−7.28 (m, 1H), 7.29−7.37 (m, 2H), 8.88−9.31 (m, 2H), 10.97 (s, 1H); MS (ESI) *m*/*z* 373 ([M + H]$^+$). Anal. ($C_{21}H_{22}F_2N_2O_2\cdot$1HCl$\cdot$0.25$H_2O$) C, H, N.

(*R*)-**33b** and (*S*)-**33b** were prepared according to general procedure A using (*R*)-(−)-**21** and (*S*)-(+)-**21**, respectively, as starting material. Both products were found to be >99% ee by chiral HPLC using either Chiralcel OJ column (20 mm × 250 mm) with 100%EtOH or a Chiralpak AS column (4.6 mm × 250 mm) with 50% EtOH/hexane.

8-Fluoro-3-{[3-(5-fluoro-1*H*-indol-3-yl)propyl]amino}chromane-5-carboxamide (33c), (3*R*)-8-Fluoro-3-{[3-(5-fluoro-1*H*-indol-3-yl)propyl]amino}chromane-5-carboxamide ((*R*)-33c), and (3*S*)-8-Fluoro-3-{[3-(5-fluoro-1*H*-indol-3-yl)propyl]amino}chromane-5-carboxamide ((*S*)-33c). Using general procedure A, **29a** was reacted with **32b** as described above for **33a** followed by chromatography (5:4:1 EtOAc−hexanes−MeOH (1% NH_4OH)) to generate 0.48 g (60%) of **33c** as a peach solid which was converted to the mono-HCl salt, yielding an off-white solid: mp 122 °C/dec; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.90−2.08 (m, 2H), 2.68−2.82 (m, 2H), 2.98−3.25 (m, 3H), 3.27−3.45 (m, 2H), 3.71−3.88 (m, 1H), 4.27−4.46 (m, 2H), 6.82−6.98 (m, 1H), 7.08−7.21 (m, 2H), 7.22−7.27 (m, 1H), 7.27−7.37 (m, 2H), 7.43 (s, 1H), 7.81 (s, 1H), 9.00 (s, 1H), 10.95 (s, 1H); MS (ESI) *m*/*z* 384([M − H]$^-$). Anal. ($C_{21}H_{21}F_2N_3O_2\cdot$1.20HCl) C, H, N.

It was also prepared using general procedure B where **29a** is reacted with **32a** as described above for **33b**, generating 2.17 g (92%) of **33c** as a white foamy solid which was then subjected to chiral separation of the enantiomers by SFC on a Chiralcel AS column (2 cm × 25 cm) using 40% MeOH in CO_2 (100 bar). The enantiomers were isolated and characterized as mono-HCl salts.[26] In some instances, enantiomers were prepared from (*R*)-(+)-**29a** and (*S*)-(−)-**29a**, respectively, as specified in each experimental of the final targets.

8-Chloro-3-{[3-(5-fluoro-1*H*-indol-3-yl)propyl]amino}chromane-5-carboxamide (33d). Using general procedure B, **29b** was reacted with **32a** as described above for **33b**, generating 0.37 g (54%) of **33d** as a dense white foam: mp 65−67 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.68−1.81 (m, 2H), 1.87 (br s, 1H), 2.67 (d, J = 7.1 Hz, 4H), 2.91−3.12 (m, 2H), 3.24−3.38 (m, 1H), 3.78−3.90 (m, 1H), 4.23−4.33 (m, 1H), 6.82−6.97 (m, 2H), 7.17 (br s, 1H), 7.21−7.35 (m, 3H), 7.41 (br s, 1H), 7.74 (br s, 1H), 10.83 (s, 1H); MS (ES) *m*/*z* 402.1 ([M + H]$^+$).

The enantiomers of **33d** were separated by chiral HPLC using a Chiralpak AS column (2 cm × 25 cm) with (3:7) hexanes−EtOH as mobile phase to generate each enantiomer which were both isolated and characterized as free bases.

3-{[3-(5-Fluoro-1*H*-indol-3-yl)propyl]amino}chromane-5-carboxamide (33e). Using general procedure B, **29c** was reacted with **32a** as described above for **33b**, generating 1.37 g (42%) of **33e** as a white amorphous powder: mp 153−155 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.70−1.85 (m, 2H), 2.57−2.75 (m, 5H), 2.90−3.13 (m, 2H), 3.32 (br s, 1H), 3.65−3.80 (m, 1H), 4.12−4.25 (m, 1H), 6.78−6.84 (m, 1H), 6.88 (td, J = 9.2, 2.4 Hz, 2H), 7.05−7.14 (m, 1H), 7.15−7.21 (m, 1H), 7.21−7.39 (m, 3H), 7.68 (s, 1H), 10.83 (s, 1H); MS (ES) *m*/*z* 368.2 ([M + H]$^+$).

The enantiomers of **33e** were separated by chiral HPLC using a Chiracel AS column (2 cm × 25 cm) with 75% EtOH/Hex as mobile phase to generate each enantiomer which were both isolated and characterized as free bases.

8-Fluoro-3-{[3-(5-fluoro-1*H*-indol-3-yl)propyl]amino}-*N*-methylchromane-5-carboxamide (33f). Using general procedure B, **31** was reacted with **32a** as described above for **33b**, generating 0.52 g (87%) of **33f** as a white solid which was converted to the HCl salt: mp 148 °C/dec; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.88−2.09 (m, 2H), 2.66−2.82 (m, 5H), 2.96−3.23 (m, 3H), 3.25−3.43 (m, 1H), 3.71−3.89 (m, 1H), 4.29−4.45 (m, 2H), 6.85−6.96 (m, 1H), 7.01−7.10 (m, 1H), 7.13−7.22 (m, 1H), 7.22−7.27 (m, 1H),

7.28−7.38 (m, 2H), 8.27 (s, 1H), 8.87−9.12 (m, 2H), 10.95 (s, 1H); MS (ES) *m/z* 400.2 ([M + H]$^+$). Anal. ($C_{22}H_{23}F_2N_3O_2\cdot$ 1HCl$\cdot$0.5H_2O) C, H, N.

3-{[3-(5-Chloro-1*H*-indol-3-yl)propyl]amino}-8-fluorochromane-5-carboxamide (51c). Using general procedure B, **29a** was reacted with **32e** as described above for **33b**, generating 0.60 g (64%) of **51c** which was converted to the mono-HCl salt and isolated as a white solid: mp 218−221 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.92−2.07 (m, 2H), 2.67−2.81 (m, 2H), 2.97−3.45 (m, 4H), 3.74−3.86 (m, 1H), 4.28−4.46 (m, 2H), 7.00−7.28 (m, 4H), 7.30−7.45 (m, 2H), 7.55−7.63 (m, 1H), 7.75−7.84 (m, 1H), 8.92−9.09 (m, 2H), 11.00−11.10 (m, 1H); MS (ES) *m/z* 402.1 ([M + H]$^+$). Anal. ($C_{21}H_{21}ClFN_3O_2\cdot$HCl) C, H, N.

8-Fluoro-3-{[3-(6-fluoro-1*H*-indol-3-yl)propyl]amino}chromane-5-carboxamide (51d). Using general procedure B, **29a** was reacted with **32f** as described above for **33b**, generating 0.24 g (67%) of **51d**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.88−2.10 (m, 2H), 2.67−2.85 (m, 2H), 2.97−3.48 (m, 4H), 3.69−3.88 (m, 1H), 4.23−4.47 (m, 2H), 6.74−6.92 (m, 1H), 7.00−7.24 (m, 4H), 7.35−7.59 (m, 2H), 7.80 (br s, 1H), 9.01 (br s, 2H), 10.91 (br s, 1H); MS (ES) *m/z* 384.2 ([M − H]$^-$).

8-Fluoro-3-{[3-(7-methoxy-1*H*-indol-3-yl)propyl]amino}chromane-5-carboxamide (51e). Using general procedure B, **29a** was reacted with **32g** as described above for **33b**, generating 0.28 g (68%) of **51e** which was converted to the mono-HCl salt and isolated as a white solid: mp 196−198 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.93−2.08 (m, 2 H), 2.69−2.81 (m, 2 H), 2.97−3.44 (m, 4 H), 3.74−3.84 (m, 1 H), 3.88 (s, 3 H), 4.27−4.45 (m, 2 H), 6.56−6.68 (m, 1 H), 6.84−6.96 (m, 1 H), 7.00−7.24 (m, 4 H), 7.35−7.48 (m, 1 H), 7.74−7.86 (m, 1 H), 8.95−9.11 (m, 2 H), 10.84−10.94 (m, 1 H); MS (ES) *m/z* 398.1 ([M + H]$^+$). Anal. ($C_{22}H_{24}FN_3O_3\cdot$HCl$\cdot$0.30H_2O) C, H, N.

3-{[3-(7-Chloro-1*H*-indol-3-yl)propyl]amino}-8-fluorochromane-5-carboxamide (51f). Using general procedure B, **29a** was reacted with **32h** as described above for **33b**, generating 0.73 g (79%) of **51f** which was converted to the mono-HCl salt and isolated as a white solid: mp 222−224 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.92−2.08 (m, 2H), 2.73−2.84 (m, 2H), 2.99−3.42 (m, 4H), 3.73−3.86 (m, 1H), 4.28−4.45 (m, 2H), 6.94−7.05 (m, 1H), 7.07−7.29 (m, 4H), 7.36−7.47 (m, 1H), 7.49−7.58 (m, 1H), 7.73−7.86 (m, 1H), 8.94−9.11 (m, 2H), 11.16−11.26 (m, 1H); MS (ES) *m/z* 402.1 ([M + H]$^+$). Anal. ($C_{21}H_{21}ClFN_3O_2\cdot$HCl) C, H, N.

3-[3-(5,7-Difluoro-1*H*-indol-3-yl)propylamino]-8-fluorochroman-5-carboxylic Acid Amide (51g). Using general procedure B, **29a** was reacted with **32i** as described above for **33b**, generating 0.70 g (99%) of racemic **51g** as an off-white foam. ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.66−1.82 (m, 2H), 2.59−2.76 (m, 6H), 2.93−3.14 (m, 2H), 3.74−3.89 (m, 1H), 4.19−4.28 (m, 1H), 6.83−6.98 (m, 2H), 7.00−7.19 (m, 2H), 7.20−7.39 (m, 2H), 7.63−7.75 (m, 1H), 11.29−11.39 (m, 1H); MS (ES) *m/z* 404.1 ([M + H]$^+$). The enantiomers were separated by SFC using a Chiralpak AS column (25 cm × 2 cm) and 40% MeOH (0.1% DEA)/CO_2 (100 bar) as mobile phase. Both enantiomers were isolated as white foam: (+)-**51g**, MS (ES) *m/z* 404.2 ([M + H]$^+$), $[\alpha]_D^{25}$ +19.8° (*c* 1.0, DMSO); (−)-**51g**, MS (ES) *m/z* 402.3 ([M − H]$^-$), $[\alpha]_D^{25}$ −21.8° (*c* 1.0, DMSO).

(3*R*)-(−)-8-Fluoro-3-{[(6-fluoro-2,3,4,9-tetrahydro-1*H*-carbazol-3-yl)methyl]amino}chromane-5-carboxamide (57a) and (3*R*)-(+)-8-Fluoro-3-{[(6-fluoro-2,3,4,9-tetrahydro-1*H*-carbazol-3-yl)methyl]amino}chromane-5-carboxamide (57b). Using general procedure B, **57a** and **57b** were prepared by reaction of (*R*)-(+)-**29a** with **50**. The diastereomers were separated by chiral HPLC using a Chiracel AD column (2 cm × 25 cm) and 30% Hex/EtOH as mobile phase, isolated as free base, and converted to the mono-HCl salt to generate **57a** and **57b** as white solids. **57a**: mp 197−202 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.51−1.68 (m, 1H), 2.04−2.43 (m, 3H), 2.63−2.94 (m, 3H), 3.01−3.51 (m, 4H), 3.75−3.90 (m, 1H), 4.35−4.53 (m, 2H), 6.74−6.86 (m, 1H), 6.97−7.07 (m, 1H), 7.08−7.27 (m, 3H), 7.38−7.48 (m, 1H), 7.76−7.88 (m, 1H), 9.01−9.27 (m, 2H), 10.83 (s, 1H); MS (ES) *m/z* 412.1 ([M + H]$^+$); $[\alpha]_D^{25}$ −52.8° (*c* 1.0, DMSO). **57b**: mp 198−202 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.54−1.68 (m, 1H), 2.02−2.44 (m, 3H), 2.63−2.93 (m, 3H), 3.07−3.21 (m, 2H), 3.23−3.50 (m, 2H), 3.80−3.90 (m, 1H), 4.35−4.50 (m, 2H), 6.76−6.87 (m, 1H), 6.94−7.06 (m, 1H), 7.08−7.26 (m, 3H), 7.37−7.48 (m, 1H), 7.76−7.87 (m, 1H), 8.98−9.15 (m, 2H), 10.83 (s, 1H); MS (ES) *m/z* 412.1 ([M + H]$^+$); $[\alpha]_D^{25}$ +59.8° (*c* 1.0, DMSO).

General Procedure C (Reductive Amination with Cyclobutanone). 3-{Cyclobutyl[3-(5-fluoro-1*H*-indol-3-yl)propyl]amino}-8-fluorochromane-5-carboxamide (35c). To **33c** (0.14 g, 0.35 mmol) in anhydrous MeOH (6 mL), under nitrogen at room temperature, was added cyclobutanone (0.070 mL, 0.876 mmol), acetic acid (0.050 mL, 0.84 mmol), and sodium cyanoborohydride (0.044 g, 0.70 mmol). The reaction mixture was stirred at room temperature overnight. More cyclobutanone (0.026 mL), acetic acid (0.21 mL), and sodium cyanoborohydride (0.22 g) were added after 24 and 48 h, at which time the reaction went to completion. Workup was the same as for procedure B. Chromatography ((5:4:1) EtOAc−hexane−MeOH (1% NH_4OH)) afforded 0.12 g (78%) of **35c** as a sticky gum. Conversion to the mono-HCl salt generated an off-white solid: mp 109 °C/dec; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.51−1.75 (m, 2H), 1.85−2.57 (m, 7H), 2.59−2.76 (m, 2H), 3.06−3.48 (m, 3H), 3.88−4.14 (m, 2H), 4.31−4.43 (m, 1H), 4.45−4.59 (m, 1H), 6.84−6.95 (m, 1H), 7.10−7.25 (m, 3H), 7.26−7.35 (m, 2H), 7.38−7.49 (m, 1H), 7.72−7.89 (m, 1H), 10.11−10.42 (m, 1H), 10.93 (s, 1H); MS (ES) *m/z* 438.2 ([M − H]$^-$). Anal. ($C_{25}H_{27}F_2N_3O_2\cdot$1.10 HCl$\cdot$0.50$H_2O$) C, H, N.

(3*R*)-(−)-3-{Cyclobutyl[3-(5-fluoro-1*H*-indol-3-yl)propyl]amino}-8-fluorochromane-5-carboxamide ((*R*)-(−)-35c). The enantiomers of **35c** were separated by chiral HPLC using a Chiralcel AD column (2 cm × 25 cm) and 16% IPA in hexane/DEA as mobile phase. They were isolated and characterized as mono-HCl salts. (*R*)-(−)-**35c** (white solid): mp 129 °C/dec; MS (ES) *m/z* 440.1 ([M + H]$^+$); $[\alpha]_D^{25}$ −26.76° (*c* 1.0, DMSO); 99.5% ee by chiral HPLC. Anal. ($C_{25}H_{27}F_2N_3O_2\cdot$1HCl$\cdot$0.40$H_2O$) C, H, N. (*S*)-(+)-**35c** (white solid): mp 129 °C/dec; MS (ES) *m/z* 438.2([M − H]$^-$); $[\alpha]_D^{25}$ +27.56° (*c* 1.0, DMSO); 95% ee by chiral HPLC. Anal. ($C_{25}H_{27}F_2N_3O_2\cdot$1 HCl$\cdot$0.50$H_2O$) C, H, N.

(*R*)-(−)-**35c** was also prepared according to procedures B and C using (*R*)-(+)-**29a** as starting material, and X-ray analysis further confirmed the stereochemistry of this final target.

General Procedure D (Amide Functionalization). 3-{Cyclobutyl[3-(5-fluoro-1*H*-indol-3-yl)propyl]amino}-8-fluoro-*N*-methylchromane-5-carboxamide (35f). To **39** (0.1 g, 0.227 mmol) in anhydrous THF (8 mL) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC, 0.087 g, 0.454 mmol), 1-hydroxybenzotriazole hydrate (HOBt, 0.061 g, 0.454 mmol), and methylamine (2 M/THF, 0.45 mL, 0.908 mmol). The mixture was stirred at room temperature overnight. It was concentrated and the residue taken up in CH_2Cl_2/H_2O. The aqueous layer was extracted one more time with CH_2Cl_2, and the organic extracts were treated with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. Chromatography (6:3:1 hexanes−EtOAc−MeOH (1% NH_4OH) afforded 0.1 g (97%) of **35f**. Conversion to the mono-HCl salt generated a white solid: mp 132 °C/dec; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.49−1.78 (m, 2H), 1.91−2.44 (m, 5H), 2.63−2.81 (m, 5H), 3.05−3.23 (m, 2H), 3.32 (s, 3H), 3.85−4.16 (m, 2H), 4.30−4.44 (m, 1H), 4.49−4.64 (m, 1H), 6.85−6.95 (m, 1H), 7.03−7.12 (m, 1H), 7.15−7.27 (m, 2H), 7.28−7.37 (m, 2H), 8.21−8.37 (m, 1H), 10.29−10.60 (m, 1H), 10.93 (s, 1H); MS (ES) *m/z* 454.2 ([M + H]$^+$). Anal. ($C_{26}H_{29}F_2N_3O_2\cdot$1.2HCl$\cdot$0.25$H_2O$) C, H, N.

Final Targets. *N*-[3-(5-Fluoro-1*H*-indol-3-yl)propyl]-5-methoxy-*N*-propylchroman-3-amine (34a). 34a was obtained according to procedure B using **33a** and propionaldehyde. Chromatography (2% MeOH/CH_2Cl_2) afforded 0.44 g (100%) of **34a** as a yellow oil. Conversion to the mono-HCl salt generated an off-white solid: mp 117−120 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.81−0.94 (m, 3H), 1.58−1.79 (m, 2H), 1.97−2.16 (m, 2H), 2.63−2.77 (m, 2H), 2.82−2.95 (m, 1H), 2.95−3.45 (m, 5H), 3.79 (s, 3H), 3.84−3.95

(m, 1H), 4.16−4.29 (m, 1H), 4.38−4.57 (m, 1H), 6.45−6.52 (m, 1H), 6.56−6.65 (m, 1H), 6.86−6.96 (m, 1H), 7.07−7.17 (m, 1H), 7.20−7.39 (m, 3H), 10.39−10.57 (m, 1H), 10.96 (s, 1H); MS (ESI) *m/z* 397 ([M + H]$^+$). Anal. ($C_{24}H_{29}FN_2O_2 \cdot HCl \cdot 0.50H_2O$) C, H, N (N calcd 6.34, found 5.89).

***N*-Cyclobutyl-*N*-[3-(5-fluoro-1*H*-indol-3-yl)propyl]-5-methoxychroman-3-amine (35a). 35a** was obtained according to procedure C using **33a** and cyclobutanone. Chromatography (9:1:1 hexanes−EtOAc−MeOH (1% NH_4OH)) afforded 0.17 g (65%) of **35a**. Conversion to the mono-HCl salt generated an off-white solid: mp 70.5 °C/dec; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.51−1.79 (m, 2H), 1.92−2.24 (m, 4H), 2.26−2.48 (m, 2H), 2.58−2.76 (m, 2H), 2.75−3.24 (m, 4H), 3.67−3.91 (m, 4H), 3.97−4.27 (m, 2H), 4.33−4.47 (m, 1H), 6.43−6.51 (m, 1H), 6.57−6.65 (m, 1H), 6.85−6.96 (m, 1H), 7.08−7.15 (m, 1H), 7.16−7.25 (m, 1H), 7.26−7.36 (m, 2H), 10.44−10.62 (m, 1H), 10.92 (s, 1H); MS (ESI) *m/z* 407 ([M − H]$^-$). Anal.($C_{25}H_{29}FN_2O_2 \cdot 1.20\ HCl \cdot 0.40C_4H_8O_2$) C, H, N.

(3*R*)-(−)-*N*-Cyclobutyl-*N*-[3-(5-fluoro-1*H*-indol-3-yl)propyl]-5-methoxychroman-3-amine ((*R*)-(−)-35a). (*R*)-(−)-**35a** was obtained according to procedure C using (*R*)-**33a** (synthesized from (*R*)-(−)-**19**) and cyclobutanone. Chromatography (1:1 hexanes−EtOAc) afforded 0.15 g (69%) of (*R*)-(−)-**35a**. Conversion to the mono-HCl salt generated an off-white solid: mp 115 °C/dec; $[\alpha]_D^{25}$ −33.02° (*c* 1.0, DMSO); ^{1}H NMR (500 MHz, DMSO-d_6) δ1.52−1.79 (m, 2H), 1.91−2.45 (m, 6H), 2.58−2.76 (m, 2H), 2.78−3.23 (m, 4H), 3.68−3.90 (m, 4H), 3.98−4.26 (m, 2H), 4.32−4.48 (m, 1H), 6.44−6.51 (m, 1H), 6.57−6.65 (m, 1H), 6.86−6.94 (m, 1H), 7.09−7.16 (m, 1H), 7.17−7.25 (m, 1H), 7.26−7.36 (m, 2H), 10.43−10.58 (m, 1H), 10.94 (s, 1H); MS (ES) *m/z* 409.2 ([M + H]$^+$). Anal. ($C_{25}H_{29}FN_2O_2 \cdot HCl \cdot 0.50H_2O$) C, H, N.

8-Fluoro-*N*-[3-(5-fluoro-1*H*-indol-3-yl)propyl]-5-methoxy-*N*-propylchroman-3-amine (34b). 34b was obtained according to procedure B using **33b** and propionaldehyde. Chromatography (4:1) EtOAc−hexanes afforded 0.16 g (96%) of **34b**. Conversion to the mono-HCl salt generated a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.87 (t, J = 7.1 Hz, 3H), 1.60−1.77 (m, 2H), 2.02−2.16 (m, 2H), 2.65−2.78 (m, 2H), 2.88−3.00 (m, 1H), 3.01−3.31 (m, 5H), 3.77 (s, 3H), 3.87−4.00 (m, 1H), 4.26−4.39 (m, 1H), 4.52−4.66 (m, 1H), 6.48−6.59 (m, 1H), 6.84−6.96 (m, 1H), 7.02−7.13 (m, 1H), 7.21−7.29 (m, 1H), 7.29−7.39 (m, 2H), 10.59−10.81 (m, 1H), 10.97 (s, 1H); MS (ESI) *m/z* 415 ([M + H]$^+$). Anal. ($C_{24}H_{28}F_2N_2O_2 \cdot 1HCl \cdot 0.75H_2O$) C, H, N.

(3*R*)-(−)-8-Fluoro-*N*-[3-(5-fluoro-1*H*-indol-3-yl)propyl]-5-methoxy-*N*-propylchroman-3-amine ((*R*)-(−)-34b). (*R*)-(−)-**34b** was obtained according to procedure B using (*R*)-**33b**. Chromatography (4:1) EtOAc−hexanes afforded 0.026 g (78%) of (*R*)-(−)-**34b**. Conversion to the mono-HCl salt generated a white solid: MS (APCI) *m/z* 415 ([M + H]$^+$); $[\alpha]_D^{25}$ −30.2° (*c* 1.0, DMSO). Anal. ($C_{24}H_{28}F_2N_2O_2 \cdot 1HCl$) C, H, N.

(3*S*)-(+)-8-Fluoro-*N*-[3-(5-fluoro-1*H*-indol-3-yl)propyl]-5-methoxy-*N*-propylchroman-3-amine ((*S*)-(+)-34b). (*S*)-(+)-**34b** was obtained according to procedure B using (*S*)-**33b**. Chromatography (4:1) EtOAc−hexanes afforded 0.12 g (94%) of (*S*)-(+)-**34b**. Conversion to the mono-HCl salt generated a white solid: $[\alpha]_D^{25}$ +32.2° (*c* 1.0, DMSO). Anal. ($C_{24}H_{28}F_2N_2O_2 \cdot 1HCl$) C, H, N.

8-Fluoro-3-{[3-(5-fluoro-1*H*-indol-3-yl)propyl](propyl)amino}chromane-5-carboxamide (34c). 34c was obtained according to procedure B using **33c** and propionaldehyde. Chromatography (5:4:1 EtOAc−hexanes−MeOH (1% NH_4OH)) afforded 0.12 g (90%) of **34c** as a sticky gum. Conversion to the mono-HCl salt generated a pale-yellow solid: mp 125 °C/dec; ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.75−0.95 (m, 3H), 1.56−1.72 (m, 2H), 1.96−2.16 (m, 2H), 2.66−2.78 (m, 2H), 3.00−3.53 (m, 6H), 3.92−4.04 (m, 1H), 4.34−4.49 (m, 1H), 4.50−4.68 (m, 1H), 6.82−6.96 (m, 1H), 7.09−7.38 (m, 5H), 7.39−7.51 (m, 1H), 7.75−7.98 (m, 1H), 10.11 (s, 1H), 10.95 (s, 1H); MS (ESI) *m/z* 426 ([M − H]$^-$). Anal. ($C_{24}H_{27}F_2N_3O_2 \cdot 1HCl \cdot 0.20H_2O$) C, H, N.

(3*R*)-(−)-8-Fluoro-3-{[3-(5-fluoro-1*H*-indol-3-yl)propyl](propyl)amino}chromane-5-carboxamide ((*R*)-(−)-34c) and (3*S*)-(+)-8-Fluoro-3-{[3-(5-fluoro-1*H*-indol-3-yl)propyl](propyl)amino}-chromane-5-carboxamide ((*S*)-(+)-34c). The enantiomers of **34c** were separated by chiral HPLC on a Chiralpak AS column (2 cm × 25 cm) using (1:1) hexane−EtOH as mobile phase. They were isolated and characterized as mono-HCl salts. (*R*)-(−)-**34c** (white solid): mp 126 °C/dec; ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.77−0.94 (m, 3H), 1.56−1.76 (m, 2H), 1.97−2.19 (m, 2H), 2.66−2.80 (m, 2H), 3.00−3.56 (m, 6H), 3.90−4.04 (m, 1H), 4.35−4.49 (m, 1H), 4.50−4.63 (m, 1H), 6.79−7.00 (m, 1H), 7.11−7.28 (m, 3H), 7.29−7.36 (m, 2H), 7.39−7.53 (m, 1H), 7.77−7.94 (m, 1H), 10.03 (s, 1H), 10.94 (s, 1H); MS (ESI) *m/z* 428 ([M + H]$^+$); $[\alpha]_D^{25}$ −31.49° (*c* 1.0, DMSO); >99.9% ee by chiral HPLC. Anal. ($C_{24}H_{27}F_2N_3O_2 \cdot 1.20HCl \cdot 0.25H_2O$) C, H, N. (*S*)-(+)-**34c** (white solid): mp 126 °C/dec; ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.80−0.96 (m, 3H), 1.58−1.73 (m, 2H), 2.01−2.16 (m, 2H), 2.65−2.77 (m, 2H), 3.03−3.50 (m, 6H), 3.91−4.08 (m, 1H), 4.33−4.49 (m, 1H), 4.51−4.68 (m, 1H), 6.85−6.97 (m, 1H), 7.11−7.27 (m, 3H), 7.28−7.38 (m, 2H), 7.41−7.50 (m, 1H), 7.76−7.96 (m, 1H), 10.12 (s, 1H), 10.95 (s, 1H); MS (ESI) *m/z* 426 ([M − H]$^-$); $[\alpha]_D^{25}$ +30.67° (*c* 1.0, DMSO); >99.9% ee by chiral HPLC. Anal. ($C_{24}H_{27}F_2N_3O_2 \cdot 1.20HCl \cdot 0.20H_2O$) C, H, N.

8-Fluoro-3-{[3-(5-fluoro-1*H*-indol-3-yl)propyl](propyl)amino}-*N*-methylchromane-5-carboxamide (34f). 34f was obtained according to procedure B using **33f** and propionaldehyde. Chromatography (6:3:1 hexanes−EtOAc−MeOH (1% NH_4OH)) afforded 0.097 g (89%) of **34f**. Conversion to the mono-HCl salt generated a white solid: mp 123 °C/dec; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.78−0.96 (m, 3H), 1.57−1.73 (m, 2H), 1.98−2.13 (m, 2H), 2.64−2.82 (m, 5H), 3.01−3.45 (m, 6H), 3.91−4.04 (m, 1H), 4.38−4.48 (m, 1H), 4.51−4.66 (m, 1H), 6.85−6.96 (m, 1H), 7.04−7.13 (m, 1H), 7.15−7.27 (m, 2H), 7.29−7.38 (m, 2H), 8.24−8.36 (m, 1H), 9.87−10.03 (m, 1H), 10.94 (s, 1H); MS (ES) *m/z* 440.2 ([M − H]$^-$). Anal. ($C_{25}H_{29}F_2N_3O_2 \cdot 1HCl \cdot 0.25H_2O$) C, H, N.

3-{[3-(5-Fluoro-1*H*-indol-3-yl)propyl](propyl)amino}chromane-5-carboxamide (34e). 34e was obtained according to procedure B using **33e** and propionaldehyde. Without further purification, it was converted to the mono-HCl salt, generating **34e** as a colorless oil: ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.87 (t, J = 7.2 Hz, 3H), 1.64−1.75 (m, 2H), 1.99−2.15 (m, 2H), 2.64−2.77 (m, 2H), 3.01−3.51 (m, 6H), 3.86−3.99 (m, 1H), 4.28−4.37 (m, 1H), 4.45−4.56 (m, 1H), 6.85−7.01 (m, 2H), 7.07−7.16 (m, 1H), 7.17−7.28 (m, 2H), 7.29−7.37 (m, 2H), 7.38−7.47 (m, 1H), 7.77−7.88 (m, 1H), 10.16−10.30 (m, 1H), 10.95 (s, 1H); MS (ES) *m/z* 410.2 ([M + H]$^+$).

8-Chloro-3-{cyclobutyl[3-(5-fluoro-1*H*-indol-3-yl)propyl]amino}-chromane-5-carboxamide (35d). 35d was obtained according to procedure C using **33d** and cyclobutanone. Chromatography (5% MeOH in EtOAc) afforded 0.13 g (89%) of **35d** as a colorless oil: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.45−1.60 (m, 2H), 1.66−1.77 (m, 2H), 1.78−1.97 (m, 3H), 2.55−2.69 (m, 4H), 2.81−3.02 (m, 2H), 3.04−3.16 (m, 1H), 3.26−3.43 (m, 1H), 3.85−3.96 (m, 1H), 3.98−4.08 (m, 1H), 4.24−4.35 (m, 1H), 6.82−6.98 (m, 2H), 7.15−7.34 (m, 4H), 7.37−7.46 (m, 1H), 7.66−7.82 (m, 1H), 10.82 (s, 1H); MS (ES) *m/z* 456.1 ([M + H]$^+$).

(−)-8-Chloro-3-{cyclobutyl[3-(5-fluoro-1*H*-indol-3-yl)propyl]-amino}chromane-5-carboxamide ((−)-35d) and (+)-8-Chloro-3-{cyclobutyl[3-(5-fluoro-1*H*-indol-3-yl)propyl]amino}chromane-5-carboxamide ((+)-35d). The compounds were prepared according to procedure C using each enantiomer of **33d** separately and cyclobutanone, generating (−)-**35d** and (+)-**35d**. (−)-**35d**: mp 104−107 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.53−1.75 (m, 2H), 1.93−2.25 (m, 2H), 2.29−2.50 (m, 3H), 2.62−2.74 (m, 2H), 3.05−3.25 (m, 2H), 3.27−3.50 (m, 3H), 3.86−4.12 (m, 2H), 4.31−4.50 (m, 1H), 4.57−4.73 (m, 1H), 6.86−6.94 (m, 1H), 7.07−7.13 (m, 1H), 7.20−7.27 (m, 1H), 7.28−7.36 (m, 2H), 7.36−7.42 (m, 1H), 7.47−7.54 (m, 1H), 7.82−7.94 (m, 1H), 10.96 (s, 1H); MS (ES) *m/z* 456.2 ([M + H]$^+$); $[\alpha]_D^{25}$ −37.8° (*c* 1.0, DMSO). (+)-**35d**: mp 190−194 °C; MS (ES) *m/z* 456.2 ([M + H]$^+$); $[\alpha]_D^{25}$ +37.2° (*c* 1.0, DMSO).

3-{Cyclobutyl[3-(5-fluoro-1*H*-indol-3-yl)propyl]amino}chromane-5-carboxamide (35e). 35e was obtained according to procedure C using **33e** and cyclobutanone to generate **35e**: mp 102−5 °C; ^{1}H

NMR (400 MHz, DMSO-d_6) δ 1.87−2.46 (m, 6H), 2.59−2.76 (m, 2H), 3.01−3.46 (m, 6H), 3.79−3.92 (m, 1H), 3.95−4.11 (m, 1H), 4.21−4.35 (m, 1H), 4.37−4.49 (m, 1H), 6.85−6.97 (m, 2H), 7.08−7.15 (m, 1H), 7.17−7.25 (m, 2H), 7.26−7.36 (m, 2H), 7.40−7.48 (m, 1H), 7.75−7.85 (m, 1H), 9.94−10.27 (m, 1H), 10.93 (s, 1H); MS (ES) *m/z* 422.3 ([M + H]$^+$).

(−)-3-{Cyclobutyl[3-(5-fluoro-1*H*-indol-3-yl)propyl]amino}chromane-5-carboxamide ((−)-35e) and (+)-3-{Cyclobutyl[3-(5-fluoro-1*H*-indol-3-yl)propyl]amino}chromane-5-carboxamide ((+)-35e). The compounds weres obtained according to procedure C using either (−)-**33e** or (+)-**33e** and cyclobutanone to generate (−)-**35e** and (+)-**35e**. (−)-**35e**: MS (ES) *m/z* 422.2 ([M + H]$^+$); $[\alpha]_D^{25}$ −68.4° (*c* 1.0, DMSO). (+)-**35e**: MS (ES) *m/z* 422.2 ([M + H]$^+$); $[\alpha]_D^{25}$ +69.4° (*c* 1.0, DMSO).

Methyl (3*R*)-3-{Cyclobutyl[3-(5-fluoro-1*H*-indol-3-yl)propyl]amino}-8-fluorochromane-5-carboxylate ((*R*)-38). To (*R*)-**33c** (maleate salt) (0.85 g, 1.69 mmol) in MeOH (20 mL) was added concentrated sulfuric acid (0.5 mL). The mixture was stirred under reflux overnight. It was cooled to room temperature and extracted with CH_2Cl_2 from 2.5 N NaOH. The organic extracts were dried over anhydrous sodium sulfate and concentrated. It was purified by chromatography (0−10% MeOH−CH_2Cl_2) to generate 0.45 g (66%) of methyl (3*R*)-8-fluoro-3-{[3-(5-fluoro-1*H*-indol-3-yl)propyl]amino}chromane-5-carboxylate as a white solid. To this methyl ester (0.45 g, 1.12 mmol) in MeOH (10 mL) was added acetic acid (0.3 mL), cyclobutanone, and sodium cyanoborohydride (0.16 g, 2.54 mmol). The mixture was stirred at room temperature over the weekend. The mixture was diluted with CH_2Cl_2, extracted from saturated $NaHCO_3$/NaOH (pH 10), dried over anhydrous sodium sulfate, and concentrated. It was purified by chromatography (0−15% MeOH−CH_2Cl_2) to afford 0.55 g (100%) of (*R*)-**38** as a colorless oil.

(3*R*)-(−)-3-{Cyclobutyl[3-(5-fluoro-1*H*-indol-3-yl)propyl]amino}-8-fluoro-*N*-methylchromane-5-carboxamide ((*R*)-(−)-35f). To (*R*)-**38** (0.1 g, 0.22 mmol) in MeOH (1 mL)−THF (3 mL) was added 1 M LiOH/H_2O (1 mmol, 1 mL), and the mixture was stirred at room temperature for 2 days. It was concentrated to afford crude (3*R*)-3-{cyclobutyl[3-(5-fluoro-1*H*-indol-3-yl)propyl]amino}-8-fluorochromane-5-carboxylic acid (0.12 g). This crude acid was dissolved in THF (10 mL) and treated with EDC (0.15 g, 0.78 mmol) and HOBt (0.156 g, 1.15 mmol) followed by addition of 2 M $MeNH_2$/THF (0.5 mL, 1 mmol). The mixture was stirred at room temperature for 5 days. The mixture was then diluted with EtOAc, extracted from brine, dried over anhydrous sodium sulfate, and concentrated. Preparative HPLC on a Luna 5 μm C_{18} column (150 mm × 21.2 mm) using a gradient (5−50% CH_3CN/H_2O (0.075% TFA)) afforded (*R*)-(−)-**35f** which was then converted to the mono-HCl salt: ^{1}H NMR (400 MHz, MeOH-d_4) δ 2.09−2.31 (m, 2H), 2.42−2.84 (m, 7H), 3.15−3.29 (m, 2H), 3.56−3.70 (m, 2H), 3.71−3.89 (m, 5H), 4.33−4.57 (m, 2H), 4.70−4.93 (m, 2H), 7.24−7.36 (m, 1H), 7.44−7.57 (m, 3H), 7.60−7.68 (m, 1H), 7.69−7.76 (m, 1H); MS (APPI) *m/z* 400.0 ([M + H]$^+$); $[\alpha]_D^{25}$ −21.6° (*c* 1.0, DMSO).

Methyl 8-Fluoro-3-{[3-(5-fluoro-1*H*-indol-3-yl)propyl]amino}-chromane-5-carboxylate (37). Using general procedure B, **36** was reacted with **32a** in the presence of acetic acid and $NaBH_3CN$. Chromatography (6:3:1 hexanes−EtOAc−MeOH (1% NH_4OH)) afforded 0.46 g (91%) of **37** as a white solid which was converted to the mono-HCl salt: mp 219 °C/dec; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.94−2.06 (m, 2H), 2.70−2.80 (m, 2H), 3.06−3.16 (m, 2H), 3.29−3.37 (m, 1H), 3.44−3.55 (m, 1H), 3.77−3.90 (m, 4H), 4.31−4.39 (m, 1H), 4.42−4.53 (m, 1H), 6.83−6.98 (m, 1H), 7.18−7.38 (m, 4H), 7.50−7.62 (m, 1H), 8.86−9.08 (m, 2H), 10.95 (s, 1H); MS (ES) *m/z* 401.2 ([M + H]$^+$). Anal. ($C_{22}H_{22}F_2N_2O_3$·1HCl) C, H, N.

Methyl 3-{Cyclobutyl[3-(5-fluoro-1*H*-indol-3-yl)propyl]amino}-8-fluorochromane-5-carboxylate (38). Using general procedure C, **37** was reacted with cyclobutanone in the presence of acetic acid and $NaBH_3CN$. Chromatography (2:1 hexanes−EtOAc) afforded 0.33 g (81%) of **38** as a white solid which was converted to the mono-HCl salt: mp 110 °C/dec; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.54−1.76 (m, 2H), 1.92−2.25 (m, 3H), 2.25−2.46 (m, 2H), 2.59−2.76 (m, 2H), 3.05−3.28 (m, 3H), 3.36−3.60 (m, 2H), 3.78−3.87 (m, 3H), 3.89−4.14 (m, 2H), 4.33−4.45 (m, 1H), 4.49−4.63 (m, 1H), 6.84−6.97 (m, 1H), 7.15−7.39 (m, 4H), 7.49−7.62 (m, 1H), 10.36−10.60 (m, 1H), 10.85−11.00 (m, 1H); MS (ES) *m/z* 455.2 ([M + H]$^+$). Anal. ($C_{26}H_{28}F_2N_2O_3$·HCl) C, H, N.

3-{Cyclobutyl[3-(5-fluoro-1*H*-indol-3-yl)propyl]amino}-8-fluorochromane-5-carboxylic Acid (39). To **38** (0.25 g, 0.558 mmol) in absolute EtOH (3.5 mL) was added 2.5 N NaOH/H_2O (0.3 mL, 0.781 mmol). The mixture was brought to reflux and kept under reflux for 50 min. It was concentrated, and the residue was taken up in CH_2Cl_2/H_2O. The organic layer was separated and the aqueous layer made acidic with 2 N HCl/H_2O. The aqueous layer was then extracted with CH_2Cl_2 (3×) followed by EtOAc (1×). The organic extracts were pooled, dried over anhydrous $MgSO_4$, filtered, and concentrated to generate 0.216 g (88%) of **39** as an off-white solid which was converted to a di-HCl salt: mp 140 °C/dec; MS (ES) *m/z* 441.3 ([M + H]$^+$). Anal. ($C_{25}H_{26}F_2N_2O_3$·2HCl·1.5H_2O) C, H, N.

***tert*-Butyl 3-{3-[{(3*R*)-5-[Bis(*tert*-butoxycarbonyl)carbamoyl]-8-fluoro-3,4-dihydro-2*H*-chromen-3-yl}(propyl)amino]propyl}-5-fluoro-1*H*-indole-1-carboxylate ((*R*)-41).** To (*R*)-**34c** (which was synthesized from (*R*)-**33c**) (0.77 g, 1.8 mmol) in anhydrous CH_2Cl_2 (10 mL), under nitrogen at room temperature, was added *N*,*N*-dimethylaminopyridine (DMAP, 0.22 g, 1.8 mmol) and di-*tert*-butyl dicarbonate (1.45 mL, 6.3 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred at room temperature for 1.5 h. It was concentrated and purified by chromatography (7:1 hexanes−EtOAc) to generate 1.17 g (89%) of (*R*)-**41** as a foamy white solid: LC−MS *m/z* 728.25 ([M + H]$^+$); ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.78−0.88 (t, 3H), 1.28 (s, 18H), 1.30−1.40 (m, 2H), 1.40−1.48 (m, 1H), 1.58 (s, 9H), 1.65−1.80 (m, 2H), 2.55−2.68 (m, 4H), 2.75−3.15 (m, 4H), 3.89−4.05 (m, 1H), 4.30−4.40 (m, 1H), 7.00−7.25 (m, 3H), 7.30−7.40 (m, 1H), 7.47 (s, 1H), 7.92−8.05 (m, 1H).

***tert*-Butyl 5-Fluoro-3-(3-{[(3*R*)-8-fluoro-5-(methylcarbamoyl)-3,4-dihydro-2*H*-chromen-3-yl](propyl)amino}propyl)-1*H*-indole-1-carboxylate ((*R*)-(−)-42) and *tert*-Butyl 3-{3-[{(3*R*)-5-[(*tert*-Butoxycarbonyl)carbamoyl]-8-fluoro-3,4-dihydro-2*H*-chromen-3-yl}(propyl)amino]propyl}-5-fluoro-1*H*-indole-1-carboxylate ((*R*)-(−)-43).** To (*R*)-**41** (1.16 g, 1.59 mmol) in anhydrous THF (15 mL), under nitrogen at room temperature, was added 2 M $MeNH_2$/THF (0.95 mL, 1.9 mmol). The mixture was stirred at room temperature overnight. It was concentrated and purified by chromatography (3:1 hexanes−EtOAc to EtOAc) to generate 0.62 g (62%) of (*R*)-(−)-**43** as a white foamy solid: mp 58−63 °C; $[\alpha]_D^{25}$ −46.6° (*c* 1.0, DMSO); ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.76−0.89 (m, 3H), 1.38 (s, 11H), 1.61 (s, 9H), 1.67−1.79 (m, 2H), 2.56−2.69 (m, 4H), 2.79−2.94 (m, 2H), 3.03−3.14 (m, 1H), 3.27−3.37 (m, 2H), 3.88−4.00 (m, 1H), 4.26−4.37 (m, 1H), 6.90−7.01 (m, 1H), 7.02−7.20 (m, 2H), 7.35−7.43 (m, 1H), 7.46−7.53 (m, 1H), 7.95−8.07 (m, 1H), 10.58−10.69 (m, 1H); MS (ES) *m/z* 628.3 ([M + H]$^+$). Also generated was 0.26 g (30%) of (*R*)-(−)-**42** as a white foamy solid: mp 58−63 °C; $[\alpha]_D^{25}$ −42.8° (*c* 1.0, DMSO); ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.77−0.89 (m, 3H), 1.30−1.45 (m, 2H), 1.61 (s, 9H), 1.68−1.80 (m, 2H), 2.56−2.67 (m, 4H), 2.72 (d, J = 4.4 Hz, 3H), 2.85−2.97 (m, 2H), 3.00−3.14 (m, 1H), 3.25−3.38 (m, 2H), 3.88−4.00 (m, 1H), 4.24−4.36 (m, 1H), 6.85−6.94 (m, 1H), 7.02−7.11 (m, 1H), 7.11−7.20 (m, 1H), 7.37−7.44 (m, 1H), 7.48−7.52 (m, 1H), 7.97−8.07 (m, 1H), 8.10−8.19 (m, 1H); MS (ES) *m/z* 542.2 ([M + H]$^+$).

***tert*-Butyl 3-{3-[{(3*R*)-5-[(*tert*-Butoxycarbonyl)(methyl)carbamoyl]-8-fluoro-3,4-dihydro-2*H*-chromen-3-yl}(propyl)amino]propyl}-5-fluoro-1*H*-indole-1-carboxylate ((*R*)-44).** To NaH (60% suspension in oil, 9.6 mg, 0.24 mmol) in anhydrous THF (3 mL), under nitrogen at room temperature, was added (*R*)-(−)-**43** (0.1 g, 0.16 mmol) in anhydrous THF (3 mL). The mixture was stirred at room temperature for 30 min. Iodomethane (0.012 mL, 0.19 mmol) was added and the mixture stirred at room temperature overnight. It was quenched with H_2O and concentrated and the residue taken up in EtOAc/H_2O. The aqueous layer was extracted once more with

EtOAc, and the organic extracts werre pooled, treated with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. Chromatography (4:1 hexanes−EtOAc) afforded 61 mg (60%) of (*R*)-**44** as a white gummy solid: MS (ES) *m*/*z* 642 ([M + H]$^+$); ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.75−0.88 (t, 3H), 1.04 (s, 9H), 1.28−1.45 (m, 2H), 1.69 (s, 9H), 1.65−1.80 (m, 2H), 2.53−2.80 (m, 6H), 2.88−3.10 (m, 2H), 3.14 (s, 3H), 3.28−3.38 (m, 1H), 3.80−3.97 (m, 1H), 4.28−4.40 (m, 1H), 6.70−6.82 (m, 1H), 7.00−7.20 (m, 2H), 7.30−7.42 (m, 1H), 7.47 (s, 1H), 7.92−8.05 (m, 1H).

(3*R*)-(−)-8-Fluoro-3-{[3-(5-fluoro-1*H*-indol-3-yl)propyl](propyl)amino}-*N*-methylchromane-5-carboxamide ((*R*)-(−)-34f). To either (*R*)-(−)-**42** or (*R*)-**44** was added 1.25 N HCl/EtOH (25 equiv), and the mixture was stirred at 60 °C for 4 h. It was concentrated to generate (*R*)-(−)-**34f** (quantitative yield) as the HCl salt: mp 142 °C, dec; $[\alpha]_D^{25}$ −25.8° (*c* 1.0, DMSO); ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.87 (t, J = 7.3 Hz, 3H), 1.58−1.77 (m, 2H), 2.00−2.18 (m, 2H), 2.66−2.80 (m, 6H), 3.01−3.44 (m, 5H), 3.91−4.02 (m, 1H), 4.37−4.49 (m, 1H), 4.55−4.69 (m, 1H), 6.86−6.94 (m, 1H), 7.04−7.11 (m, 1H), 7.14−7.28 (m, 2H), 7.30−7.37 (m, 2H), 8.25−8.38 (m, 1H), 10.41−10.56 (m, 1H), 10.96 (s, 1H); MS (ES) *m*/*z* 442.2 ([M + H]$^+$). Anal. ($C_{25}H_{29}F_2N_3O_2\cdot$1HCl$\cdot$0.8H$_2$O) C, H, N.

3-{Cyclobutyl[3-(5-fluoro-1*H*-indol-3-yl)propyl]amino}-*N*-ethyl-8-fluorochromane-5-carboxamide (40a). 40a was obtained according to procedure D using **39** and ethylamine. Chromatography (6:3:1 hexanes−EtOAc−MeOH (1% NH_4OH)) afforded 0.092 g (86%) of **40a**. Conversion to the mono-HCl salt generated a white powder: mp 130 °C/dec; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.04−1.17 (m, 3H), 1.52−1.78 (m, 2H), 1.89−2.47 (m, 6H), 2.59−2.76 (m, 2H), 3.02−3.43 (m, 6H), 3.83−4.17 (m, 2H), 4.31−4.45 (m, 1H), 4.46−4.62 (m, 1H), 6.85−6.96 (m, 1H), 7.02−7.11 (m, 1H), 7.15−7.27 (m, 2H), 7.28−7.37 (m, 2H), 8.24−8.46 (m, 1H), 10.13−10.51 (m, 1H), 10.92 (s, 1H); MS (ES) *m*/*z* 468.2 ([M + H]$^+$). Anal. ($C_{27}H_{31}F_2N_3O_2\cdot$1.1HCl$\cdot$0.25H$_2$O) C, H, N.

3-{Cyclobutyl[3-(5-fluoro-1*H*-indol-3-yl)propyl]amino}-8-fluoro-*N*-propylchromane-5-carboxamide (40b). 40b was obtained according to procedure D using **39** and propylamine. Chromatography (6:3:1 hexanes−EtOAc−MeOH (1% NH_4OH)) afforded 0.084 g (77%) of **40b**. Conversion to the mono-HCl salt generated an off-white solid: mp 67 °C/dec; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.74−0.97 (m, 3H), 1.42−1.74 (m, 4H), 1.85−2.44 (m, 6H), 2.62−2.76 (m, 2H), 3.07−3.23 (m, 4H), 3.23−3.43 (m, 2H), 3.88−4.15 (m, 2H), 4.32−4.45 (m, 1H), 4.45−4.62 (m, 1H), 6.85−6.95 (m, 1H), 7.03−7.10 (m, 1H), 7.14−7.26 (m, 2H), 7.27−7.36 (m, 2H), 8.27−8.41 (m, 1H), 10.18−10.48 (m, 1H), 10.94 (s, 1H); MS (ES) *m*/*z* 482.2 ([M + H]$^+$). Anal. ($C_{28}H_{33}F_2N_3O_2\cdot$1.2HCl$\cdot$0.25H$_2$O) C, H, N.

3-{Cyclobutyl[3-(5-fluoro-1*H*-indol-3-yl)propyl]amino}-8-fluoro-*N*-isopropylchromane-5-carboxamide (40c). 40c was obtained according to procedure D using **39** and isopropylamine. Chromatography (6:3:1 hexanes−EtOAc−MeOH (1% NH_4OH)) afforded 0.10 g (93%) of **40c**. Conversion to the mono-HCl salt generated a white solid: mp 127 °C/dec; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.05−1.19 (m, 6H), 1.52−1.77 (m, 2H), 1.88−2.47 (m, 6H), 2.60−2.77 (m, 2H), 3.06−3.24 (m, 2H), 3.24−3.44 (m, 2H), 3.87−4.16 (m, 3H), 4.32−4.45 (m, 1H), 4.47−4.63 (m, 1H), 6.85−6.95 (m, 1H), 7.00−7.09 (m, 1H), 7.14−7.27 (m, 2H), 7.28−7.38 (m, 2H), 8.12−8.25 (m, 1H), 10.24−10.59 (m, 1H), 10.94 (s, 1H); MS (ES) *m*/*z* 482.2 ([M + H]$^+$). Anal. ($C_{28}H_{33}F_2N_3O_2\cdot$1HCl$\cdot$0.5H$_2$O) C, H, N.

3-{Cyclobutyl[3-(5-fluoro-1*H*-indol-3-yl)propyl]amino}-*N*-cyclopropyl-8-fluorochromane-5-carboxamide (40d). 40d was obtained according to procedure D using **39** and cyclopropylamine. Chromatography (6:3:1 hexanes−EtOAc−MeOH (1% NH_4OH)) afforded 0.092 g (85%) of **40d**. Conversion to the mono-HCl salt generated a white solid: mp 134 °C/dec; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.48−0.59 (m, 2H), 0.63−0.74 (m, 2H), 1.51−1.77 (m, 2H), 1.89−2.47 (m, 6H), 2.61−2.75 (m, 2H), 2.76−2.89 (m, 1H), 3.03−3.23 (m, 2H), 3.24−3.41 (m, 2H), 3.84−4.16 (m, 2H), 4.30−4.44 (m, 1H), 4.48−4.62 (m, 1H), 6.86−6.95 (m, 1H), 6.99−7.08 (m, 1H), 7.13−7.27 (m, 2H), 7.28−7.37 (m, 2H), 8.34−8.46 (m, 1H), 10.30−10.61 (m, 1H), 10.95 (s, 1H); MS (ES) *m*/*z* 480.2 ([M + H]$^+$). Anal. ($C_{28}H_{31}F_2N_3O_2\cdot$1HCl$\cdot$0.75H$_2$O) C, H, N.

***N*-Cyclobutyl-3-{cyclobutyl[3-(5-fluoro-1*H*-indol-3-yl)propyl]amino}-8-fluorochromane-5-carboxamide (40e). 40e** was obtained according to procedure D using **39** and cyclobutylamine. Chromatography (6:3:1 hexanes−EtOAc−MeOH (1% NH_4OH)) afforded 0.092 g (82%) of **40e**. Conversion to the mono-HCl salt generated a white solid: mp 135 °C/dec; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.52−1.77 (m, 4H), 1.87−2.45 (m, 10H), 2.61−2.73 (m, 2H), 3.06−3.23 (m, 2H), 3.22−3.40 (m, 2H), 3.86−4.15 (m, 2H), 4.28−4.43 (m, 2H), 4.46−4.61 (m, 1H), 6.84−6.96 (m, 1H), 7.03−7.12 (m, 1H), 7.14−7.26 (m, 2H), 7.27−7.38 (m, 2H), 8.52−8.64 (m, 1H), 10.16−10.48 (m, 1H), 10.95 (s, 1H); MS (ES) *m*/*z* 494.2 ([M + H]$^+$). Anal. ($C_{29}H_{33}F_2N_3O_2\cdot$1HCl$\cdot$0.5H$_2$O) C, H, N.

3-{Cyclobutyl[3-(5-fluoro-1*H*-indol-3-yl)propyl]amino}-*N*-cyclopentyl-8-fluorochromane-5-carboxamide (40f). 40f was obtained according to procedure D using **39** and cyclohexylamine. Chromatography (6:3:1 hexanes−EtOAc−MeOH (1% NH_4OH)) afforded 0.09 g (76%) of **40f**. Conversion to the mono-HCl salt generated a white solid: mp 134 °C/dec; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.02−1.39 (m, 5H), 1.50−1.88 (m, 7H), 1.88−2.48 (m, 6H), 2.61−2.76 (m, 2H), 3.04−3.24 (m, 2H), 3.25−3.46 (m, 2H), 3.62−3.78 (m, 1H), 3.84−4.14 (m, 2H), 4.30−4.44 (m, 1H), 4.47−4.63 (m, 1H), 6.84−6.97 (m, 1H), 6.98−7.08 (m, 1H), 7.13−7.27 (m, 2H), 7.28−7.39 (m, 2H), 8.12−8.24 (m, 1H), 10.27−10.62 (m, 1H), 10.95 (s, 1H); MS (ES) *m*/*z* 522.2 ([M + H]$^+$). Anal. ($C_{31}H_{37}F_2N_3O_2\cdot$1.2HCl$\cdot$0.25H$_2$O) C, H, N.

3-{Cyclobutyl[3-(5-fluoro-1*H*-indol-3-yl)propyl]amino}-*N*-(cyclopropylmethyl)-8-fluorochromane-5-carboxamide (40g). 40g was obtained according to procedure D using **39** and methylcyclopropylamine. Chromatography (6:3:1 hexanes−EtOAc−MeOH (1% NH_4OH)) afforded 0.10 g (92%) of **40g**. Conversion to the mono-HCl salt generated a white solid: mp 114 °C/dec; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.15−0.27 (m, 2H), 0.32−0.49 (m, 2H), 0.93−1.08 (m, 1H), 1.50−1.76 (m, 2H), 1.86−2.46 (m, 7H), 2.60−2.76 (m, 2H), 3.00−3.23 (m, 4H), 3.24−3.46 (m, 1H), 3.86−4.14 (m, 2H), 4.31−4.46 (m, 1H), 4.47−4.63 (m, 1H), 6.83−6.96 (m, 1H), 7.01−7.12 (m, 1H), 7.14−7.27 (m, 2H), 7.26−7.36 (m, 2H), 8.38−8.52 (m, 1H), 10.25−10.60 (m, 1H), 10.94 (s, 1H); MS (ES) *m*/*z* 494.2 ([M + H]$^+$). Anal. ($C_{29}H_{33}F_2N_3O_2\cdot$1HCl$\cdot$0.5H$_2$O) C, H, N.

3-{Cyclobutyl[3-(5-fluoro-1*H*-indol-3-yl)propyl]amino}-8-fluoro-*N*,*N*-dimethylchromane-5-carboxamide (40h). 40h was obtained according to procedure D using **39** and dimethylamine. Chromatography (6:3:1 hexanes−EtOAc−MeOH (1% NH_4OH)) afforded 0.116 g (86%) of **40h**. Conversion to the mono-HCl salt generated an off-white solid: mp 126 °C/dec; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.52−1.78 (m, 2H), 1.88−2.24 (m, 3H), 2.23−2.47 (m, 2H), 2.58−2.81 (m, 5H), 2.87−3.24 (m, 7H), 3.26−3.45 (m, 1H), 3.90−4.15 (m, 2H), 4.35−4.62 (m, 2H), 6.81−6.87 (m, 1H), 6.87−6.94 (m, 1H), 7.13−7.25 (m, 2H), 7.26−7.36 (m, 2H), 10.42−10.57 (m, 1H), 10.88−11.01 (m, 1H); MS (ES) *m*/*z* 466.2 ([M − H]$^-$). Anal. ($C_{27}H_{31}F_2N_3O_2\cdot$1HCl$\cdot$1H$_2$O) C, H, N.

(−)-3-[[3-(5-Cyano-1*H*-indol-3-yl)propyl](cyclobutyl)amino]-8-fluorochromane-5-carboxamide ((−)-52a) and (+)-3-[[3-(5-Cyano-1*H*-indol-3-yl)propyl](cyclobutyl) amino]-8-fluorochromane-5-carboxamide ((+)-52a). The compounds were obtained according to procedure C using **51a** and cyclobutanone. Chromatography ((96:4) CH_2Cl_2−MeOH (5%NH_4OH)) afforded 0.381 g (84%) of racemic **52a** as a white solid. The enantiomers were separated by chiral HPLC using a Whelk O column (2 cm × 25 cm) and 52% EtOH−DEA/Hex−DEA as mobile phase, isolated, and characterized as mono-HCl salts. (−)-**52a** (white solid): mp 166−171 °C/dec; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.49−1.77 (m, 2H), 1.86−2.21 (m, 4H), 2.23−2.38 (m, 1H), 2.65−2.81 (m, 2H), 3.03−3.22 (m, 2H), 3.22−3.49 (m, 3H), 3.84−4.13 (m, 2H), 4.31−4.62 (m, 2H), 7.07−7.25 (m, 2H), 7.28−7.55 (m, 4H), 7.76−7.88 (m, 1H), 8.09−8.17 (m, 1H), 10.38−10.67 (m, 1H),

11.41−11.51 (m, 1H); MS (ES) *m/z* 445.2 ([M − H]$^-$); $[\alpha]_D^{25}$ −27.8° (*c* 1.0, DMSO); 99.4% ee by chiral HPLC. Anal. ($C_{26}H_{27}FN_4O_2 \cdot HCl \cdot 1.3H_2O$) C, H, N. (+)-**52a** (white solid): mp 170−177 °C/dec; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.53−1.76 (m, 2H), 2.00−2.22 (m, 4H), 2.25−2.43 (m, 2H), 2.68−2.81 (m, 2H), 3.06−3.24 (m, 2H), 3.29−3.45 (m, 2H), 3.85−4.12 (m, 2H), 4.31−4.62 (m, 2H), 7.07−7.23 (m, 2H), 7.29−7.55 (m, 4H), 7.76−7.89 (m, 1H), 8.12 (s, 1H), 10.47−10.76 (m, 1H), 11.40−11.52 (m, 1H); MS (ES) *m/z* 445.2 ([M − H]$^-$); $[\alpha]_D^{25}$ +19.0° (*c* 1.0, DMSO); 99.5% ee by chiral HPLC. Anal. ($C_{26}H_{27}FN_4O_2 \cdot HCl \cdot 0.80H_2O$) C, H, N.

3-{Cyclobutyl[3-(5-methoxy-1*H*-indol-3-yl)propyl]amino}-8-fluorochromane-5-carboxamide (52b). 52b was obtained according to procedure C using **51b** and cyclobutanone, generating after chromatography 0.13 g (93%) of **52b** which was converted to the mono-HCl salt: mp 151−158 °C/dec; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.48−1.78 (m, 2H), 1. 86−2.44 (m, 6H), 2.59−2.75 (m, 2H), 3.04−3.21 (m, 2H), 3.31 (s, 2H), 3.75 (s, 3H), 3.85−4.14 (m, 2H), 4.28−4.44 (m, 1H), 4.47−4.62 (m, 1H), 6.67−6.74 (m, 1H), 6.97−7.03 (m, 1H), 7.04−7.26 (m, 4H), 7.35−7.51 (m, 1H), 7.71−7.93 (m, 1H), 10.32−10.76 (m, 2H); MS (ES) *m/z* 452.3 ([M + H]$^+$).

3-[[3-(5-Chloro-1*H*-indol-3-yl)propyl](cyclobutyl)amino]-8-fluorochromane-5-carboxamide (52c). 52c was obtained according to procedure C using **51c** and cyclobutanone, generating 0.135 g (96%) of **52c** which was converted to the mono-HCl salt and isolated as a white solid: mp 152−160 °C/dec; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.50−1.77 (m, 2H), 1.84−2.43 (m, 6H), 2.61−2.79 (m, 2H), 3.05−3.24 (m, 2H), 3.26−3.47 (m, 2H), 3.83−4.15 (m, 2H), 4.28−4.45 (m, 1H), 4.47−4.63 (m, 1H), 7.01−7.08 (m, 1H), 7.09−7.27 (m, 3H), 7.31−7.37 (m, 1H), 7.38−7.47 (m, 1H), 7.59 (s, 1H), 7.74−7.91 (m, 1H), 10.34−10.72 (m, 1H), 10.95−11.12 (m, 1H); MS (ES) *m/z* 454.1 ([M − H]$^-$).

3-{Cyclobutyl[3-(6-fluoro-1*H*-indol-3-yl)propyl]amino}-8-fluorochromane-5-carboxamide (52d). 52d was obtained according to procedure C using **51d** and cyclobutanone, generating 0.16 g (99%) of **52d** which was converted to the mono-HCl salt and isolated as a white solid: mp 126 °C/dec; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.49−1.76 (m, 2H), 1.89−2.44 (m, 6H), 2.60−2.76 (m, 2H), 3.03−3.22 (m, 2H), 3.26−3.46 (m, 2H), 3.85−4.13 (m, 2H), 4.30−4.44 (m, 1H), 4.45−4.61 (m, 1H), 6.77−6.88 (m, 1H), 7.02−7.25 (m, 4H), 7.35−7.56 (m, 2H), 7.75−7.88 (m, 1H), 10.32−10.60 (m, 1H), 10.90 (s, 1H); MS (ES) *m/z* 440.2 ([M + H]$^+$). Anal. ($C_{25}H_{27}F_2N_3O_2 \cdot 1.10\ HCl \cdot H_2O$) C, H, N.

3-{Cyclobutyl[3-(7-methoxy-1*H*-indol-3-yl)propyl]amino}-8-fluorochromane-5-carboxamide (52e). 52e was obtained according to procedure C using **51e** and cyclobutanone, generating 0.11 g (81%) of **52e** which was converted to the mono-HCl salt and isolated as a white solid: mp 156−162 °C/dec; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.50−1.76 (m, 2H), 1.89−2.46 (m, 6H), 2.62−2.77 (m, 2H), 3.02−3.22 (m, 2H), 3.25−3.48 (m, 2H), 3.88 (s, 3H), 3.92−4.13 (m, 2H), 4.27−4.43 (m, 1H), 4.46−4.62 (m, 1H), 6.56−6.69 (m, 1H), 6.83−6.96 (m, 1H), 6.97−7.27 (m, 4H), 7.36−7.50 (m, 1H), 7.73−7.90 (m, 1H), 10.41−10.71 (m, 1H), 10.90 (s, 1H); MS (ES) *m/z* 452.2 ([M + H]$^+$).

3-[[3-(7-Chloro-1*H*-indol-3-yl)propyl](cyclobutyl)amino]-8-fluorochromane-5-carboxamide (52f). 52f was obtained according to procedure C using **51f** and cyclobutanone, generating 0.133 g (97%) of **52f** which was converted to the mono-HCl salt and isolated as a white solid: mp 154−163 °C/dec; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.50−1.77 (m, 2 H), 1.87−2.46 (m, 6 H), 2.61−2.79 (m, 2 H), 3.03−3.22 (m, 2 H), 3.31 (s, 2 H), 3.85−4.14 (m, 2 H), 4.29−4.44 (m, 1 H), 4.46−4.61 (m, 1 H), 6.92−7.04 (m, 1 H), 7.07−7.29 (m, 4 H), 7.37−7.57 (m, 2 H), 7.74−7.88 (m, 1 H), 10.27−10.55 (m, 1 H), 11.20 (s, 1 H); MS *m/z* 455.2.

(−)-3-{Cyclobutyl[3-(5,7-difluoro-1*H*-indol-3-yl)propyl]amino}-8-fluorochromane-5-carboxamide ((−)-52g) and (+)-3-{Cyclobutyl[3-(5,7-difluoro-1*H*-indol-3-yl)propyl]amino}-8-fluorochromane-5-carboxamide ((+)-52g). The compounds were obtained according to procedure C using each enantiomer of **51g** and cyclobutanone, generating a 70% yield of each enantiomer. (−)-**52g**: mp 59−61 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.42−1.59 (m, 2H), 1.62−1.76 (m, 2H), 1.76−1.97 (m, 4H), 2.54−2.70 (m, 4H), 2.82−3.00 (m, 2H), 3.03−3.15 (m, 1H), 3.24−3.42 (m, 1H), 3.78−3.93 (m, 1H), 4.17−4.29 (m, 1H), 6.83−7.16 (m, 4H), 7.21−7.36 (m, 2H), 7.68 (s, 1H), 11.33 (s, 1H); MS (ES) *m/z* 458.2 ([M + H]$^+$). (+)-**52g**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.42−1.57 (m, 2H), 1.63−1.75 (m, 2H), 1.76−1.96 (m, 4H), 2.55−2.69 (m, 4H), 2.82−3.00 (m, 2H), 3.03−3.14 (m, 1H), 3.27−3.40 (m, 1H), 3.80−3.92 (m, 1H), 4.17−4.30 (m, 1H), 6.83−7.17 (m, 4H), 7.21−7.37 (m, 2H), 7.69 (s, 1H), 11.33 (s, 1H); MS (ES) *m/z* 458.2 ([M + H]$^+$); $[\alpha]_D^{25}$ +51.0° (*c* 1.0, DMSO).

8-Fluoro-3-[[4-(4-fluoro-1*H*-indol-1-yl)butyl](propyl)amino]chromane-5-carboxamide (54a). 54a was obtained according to procedure B using **53a** and propionaldehyde, generating **54a** (69%) as a glassy foam which was converted to the mono-HCl salt to afford a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.76 (t, J = 7.3 Hz, 3H), 1.24−1.39 (m, 4H), 1.68−1.81 (m, 2H), 2.33−2.43 (m, 2H), 2.45−2.57 (m, 2H), 2.85−3.05 (m, 3H), 3.84−3.94 (m, 1H), 4.10−4.29 (m, 3H), 6.43−6.49 (m, 1H), 6.69−6.80 (m, 1H), 6.90−6.98 (m, 1H), 6.99−7.13 (m, 2H), 7.27−7.43 (m, 3H), 7.68 (br s, 1H); MS (ESI) *m/z* 442.2 ([M + H]$^+$); MS (ESI) *m/z* 440.3 ([M − H]$^-$).

8-Fluoro-3-[[4-(5-fluoro-1*H*-indol-1-yl)butyl](propyl)amino]chromane-5-carboxamide (54b). 54b was obtained according to procedure B using **53b** and propionaldehyde, generating **54b** (63%) as a glassy foam which was converted to the mono-HCl salt to afford an off-white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.70−0.81 (m, 3H), 1.24−1.38 (m, 4H), 1.67−1.78 (m, 2H), 2.33−2.44 (m, 2H), 2.44−2.54 (m, 2H), 2.84−3.05 (m, 3H), 3.83−3.94 (m, 1H), 4.09−4.27 (m, 3H), 6.39 (s, 1H), 6.86−6.98 (m, 2H), 7.00−7.10 (m, 1H), 7.21−7.36 (m, 2H), 7.38−7.50 (m, 2H), 7.65−7.73 (m, 1H); MS (ESI) *m/z* 442.2 ([M + H]$^+$); MS (ESI) *m/z* 440.2 ([M − H]$^-$).

8-Fluoro-3-[[4-(6-fluoro-1*H*-indol-1-yl)butyl](propyl)amino]chromane-5-carboxamide (54c). 54c was obtained according to procedure B using **53c** and propionaldehyde, generating **54c** (73%) as a glassy foam which was converted to the mono-HCl salt to afford an off-white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.71−0.82 (m, 3H), 1.24−1.37 (m, 4H), 1.65−1.78 (m, 2H), 2.33−2.45 (m, 2H), 2.43−2.54 (m, 2H), 2.82−3.06 (m, 3H), 3.82−3.93 (m, 1H), 4.06−4.16 (m, 2H), 4.17−4.29 (m, 1H), 6.41 (s, 1H), 6.78−6.88 (m, 1H), 6.90−6.97 (m, 1H), 6.99−7.10 (m, 1H), 7.26−7.38 (m, 3H), 7.45−7.55 (m, 1H), 7.67 (br s, 1H); MS (ESI) *m/z* 442.2 ([M + H]$^+$); MS (ESI) *m/z* 440.2 ([M − H]$^-$).

8-Fluoro-3-[[4-(7-fluoro-1*H*-indol-1-yl)butyl](propyl)amino]chromane-5-carboxamide (54d). 54d was obtained according to procedure B using **53d** and propionaldehyde, generating a quantitative yield of **54d** as a colorless glass which was converted to the mono-HCl salt to afford a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.69−0.80 (m, 3H), 1.21−1.36 (m, 4H), 1.68−1.81 (m, 2H), 2.32−2.44 (m, 2H), 2.43−2.53 (m, 2H), 2.82−3.03 (m, 3H), 3.79−3.92 (m, 1H), 4.17−4.31 (m, 3H), 6.43−6.50 (m, 1H), 6.82−6.96 (m, 3H), 6.98−7.08 (m, 1H), 7.28−7.41 (m, 3H), 7.68 (s, 1H); MS (ESI) *m/z* 442.2 ([M + H]$^+$); MS (ESI) *m/z* 440.2 ([M − H]$^-$).

3-{(Cyclopropylmethyl)[4-(4-fluoro-1*H*-indol-1-yl)butyl]amino}-8-fluorochromane-5-carboxamide (55a). 55a was obtained according to procedure B using **53a** and cyclopropane carboxaldehyde, generating **55a** (73%) as a glassy foam which was converted to the mono-HCl salt to afford an off-white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ −0.05 to 0.08 (m, 2H), 0.31−0.42 (m, 2H), 0.66−0.81 (m, 1H), 1.30−1.43 (m, 2H), 1.69−1.82 (m, 2H), 2.31−2.42 (m, 2H), 2.53−2.64 (m, 2H), 2.85−2.98 (m, 2H), 3.06−3.20 (m, 1H), 3.84−3.94 (m, 1H), 4.12−4.30 (m, 3H), 6.46 (d, J = 2.9 Hz, 1H), 6.69−6.82 (m, 1H), 6.89−6.98 (m, 1H), 6.99−7.14 (m, 2H), 7.26−7.44 (m, 3H), 7.68 (br s, 1H); MS (ESI) *m/z* 454.3 ([M + H]$^+$); MS (ESI) *m/z* 452.3 ([M − H]$^-$).

3-{(Cyclopropylmethyl)[4-(5-fluoro-1*H*-indol-1-yl)butyl]amino}-8-fluorochromane-5-carboxamide (55b). 55b was obtained according to procedure B using **53b** and cyclopropane carboxaldehyde, generating **55b** (71%) as a glassy foam which was converted to the mono-HCl salt to afford an off-white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ −0.06−0.07 (m, 2H), 0.32−0.42 (m, 2H), 0.68−0.78 (m, 1H), 1.29−1.41 (m, 2H), 1.67−1.79 (m, 2H), 2.31−2.41 (m, 2H), 2.53−2.63 (m, 2H), 2.84−2.97 (m, 2H), 3.07−3.19 (m, 1H), 3.81−3.95 (m, 1H), 4.09−4.31 (m, 3H), 6.35−6.44 (m, 1H), 6.88−7.10 (m, 3H), 7.22−7.35 (m, 2H), 7.38−7.51 (m, 2H), 7.68 (br s, 1H); MS (ESI) *m/z* 454.2 ([M + H]$^+$); MS (ESI) *m/z* 452.2 ([M − H]$^-$).

3-{(Cyclopropylmethyl)[4-(6-fluoro-1*H*-indol-1-yl)butyl]amino}-8-fluorochromane-5-carboxamide (55c). 55c was obtained according to procedure B using **53c** and cyclopropane carboxaldehyde, generating **55c** (81%) as a glassy foam which was converted to the mono-HCl salt to afford an off-white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ −0.04−0.08 (m, 2H), 0.33−0.42 (m, 2H), 0.68−0.79 (m, 1H), 1.30−1.42 (m, 2H), 1.67−1.79 (m, 2H), 2.31−2.43 (m, 2H), 2.52−2.62 (m, 2H), 2.86−2.97 (m, 2H), 3.08−3.19 (m, 1H), 3.83−3.95 (m, 1H), 4.08−4.17 (m, 2H), 4.20−4.31 (m, 1H), 6.38−6.45 (m, 1H), 6.77−6.88 (m, 1H), 6.89−6.98 (m, 1H), 6.99−7.11 (m, 1H), 7.28−7.38 (m, 3H), 7.46−7.54 (m, 1H), 7.68 (br s, 1H); MS (ESI) *m/z* 454.2 ([M + H]$^+$); MS (ESI) *m/z* 452.2 ([M − H]$^-$).

3-{(Cyclopropylmethyl)[4-(7-fluoro-1*H*-indol-1-yl)butyl]amino}-8-fluorochromane-5-carboxamide (55d). 55d was obtained according to procedure B using **53d** and cyclopropane carboxaldehyde, generating **55d** (97%) as a colorless glass which was converted to the mono-HCl salt to afford a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ −0.04 to 0.06 (m, 2H), 0.31−0.40 (m, 2H), 0.66−0.76 (m, 1H), 1.28−1.40 (m, 2H), 1.70−1.82 (m, 2H), 2.31−2.41 (m, 2H), 2.53−2.62 (m, 2H), 2.84−2.97 (m, 2H), 3.04−3.18 (m, 1H), 3.81−3.92 (m, 1H), 4.18−4.32 (m, 3H), 6.42−6.49 (m, 1H), 6.83−7.10 (m, 4H), 7.28−7.42 (m, 3H), 7.68 (br s, 1H); MS (ESI) *m/z* 454.2 ([M + H]$^+$); MS (ESI) *m/z* 452.2 ([M − H]$^-$).

3-{Cyclobutyl[4-(4-fluoro-1*H*-indol-1-yl)butyl]amino}-8-fluorochromane-5-carboxamide (56a). 56a was obtained according to procedure C using **53a** and cyclobutanone, generating **56a** (68%) as a glassy foam which was converted to the mono-HCl salt to afford an off-white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.26−1.39 (m, 2H), 1.40−1.56 (m, 2H), 1.64−1.95 (m, 6H), 2.39−2.55 (m, 3H), 2.76−3.06 (m, 3H), 3.78−3.90 (m, 1H), 4.11−4.23 (m, 3H), 6.43−6.48 (m, 1H), 6.71−6.80 (m, 1H), 6.89−6.98 (m, 1H), 7.00−7.12 (m, 2H), 7.27−7.43 (m, 3H), 7.68 (br s, 1H); MS (ESI) *m/z* 454.2 ([M + H]$^+$); MS (ESI) *m/z* 452.3 ([M − H]$^-$).

3-{Cyclobutyl[4-(5-fluoro-1*H*-indol-1-yl)butyl]amino}-8-fluorochromane-5-carboxamide (56b). 56b was obtained according to procedure C using **53b** and cyclobutanone, generating **56b** (71%) as a glassy foam which was converted to the mono-HCl salt to afford an off-white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.25−1.38 (m, 2H), 1.38−1.55 (m, 2H), 1.61−1.92 (m, 6H), 2.40−2.57 (m, 3H), 2.73−3.08 (m, 3H), 3.75−3.89 (m, 1H), 4.08−4.22 (m, 3H), 6.35−6.42 (m, 1H), 6.88−6.98 (m, 2H), 7.00−7.10 (m, 1H), 7.22−7.36 (m, 2H), 7.39−7.51 (m, 2H), 7.68 (br s, 1H); MS (ESI) *m/z* 454.2 ([M + H]$^+$); MS (ESI) *m/z* 452.2 ([M − H]$^-$).

3-{Cyclobutyl[4-(6-fluoro-1*H*-indol-1-yl)butyl]amino}-8-fluorochromane-5-carboxamide (56c). 56c was obtained according to procedure C using **53c** and cyclobutanone, generating **56c** (75%) as a glassy foam which was converted to the mono-HCl salt to afford an off-white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.25−1.38 (m, 2H), 1.39−1.56 (m, 2H), 1.62−1.94 (m, 6H), 2.40−2.59 (m, 3H), 2.74−3.07 (m, 3H), 3.77−3.89 (m, 1H), 4.05−4.21 (m, 3H), 6.38−6.43 (m, 1H), 6.78−6.87 (m, 1H), 6.88−6.98 (m, 1H), 6.99−7.10 (m, 1H), 7.28−7.38 (m, 3H), 7.44−7.54 (m, 1H), 7.68 (br s, 1 H); MS (ESI) *m/z* 454.2 ([M + H]$^+$); MS (ESI) *m/z* 452.2 ([M − H]$^-$).

3-{Cyclobutyl[4-(7-fluoro-1*H*-indol-1-yl)butyl]amino}-8-fluorochromane-5-carboxamide (56d). 56d was obtained according to procedure C using **53d** and cyclobutanone, generating **56d** (93%) as a colorless glass which was converted to the mono-HCl salt to afford a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.24−1.37 (m, 2H), 1.39−1.55 (m, 2H), 1.65−1.94 (m, 6H), 2.42−2.53 (m, 3H), 2.74−3.06 (m, 3H), 3.76−3.86 (m, 1H), 4.12−4.20 (m, 1H), 4.21−4.33 (m, 2H), 6.43−6.50 (m, 1H), 6.83−6.98 (m, 3H), 7.00−7.11 (m, 1H), 7.28−7.42 (m, 3H), 7.68 (br s, 1H); MS (ESI) *m/z* 454.2 ([M + H]$^+$); MS (ESI) *m/z* 452.2 ([M − H]$^-$).

(3*R*)-(−)-8-Fluoro-3-[{[6-fluoro-2,3,4,9-tetrahydro-1*H*-carbazol-3-yl]methyl}(propyl)amino]chromane-5-carboxamide (58a) and (3*R*)-(+)-8-Fluoro-3-[{[6-fluoro-2,3,4,9-tetrahydro-1*H*-carbazol-3-yl]methyl}(propyl)amino]chromane-5-carboxamide (58b). The compounds were obtained according to procedure B using **57a** and propionaldehyde, generating 0.085 g (96%) of **58a** which was converted to the mono-HCl salt to afford a white solid: mp 174−180 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.81−1.00 (m, 3H), 1.49−1.66 (m, 1H), 1.70−1.91 (m, 2H), 2.09−2.39 (m, 3H), 2.67−2.81 (m, 2H), 2.83−3.04 (m, 1H), 3.06−3.57 (m, 6H), 3.96−4.09 (m, 1H), 4.32−4.53 (m, 1H), 4.63−4.77 (m, 1H), 6.74−6.87 (m, 1H), 6.99−7.27 (m, 4H), 7.40−7.51 (m, 1H), 7.80−7.91 (m, 1H), 9.93−10.07 (m, 1H), 10.82 (s, 1H); MS (ES) *m/z* 454.2 ([M + H]$^+$); $[\alpha]_D^{25}$ −90.8° (*c* 1.0, DMSO). Similarly, **57b** was reacted with propionaldehyde to generate 0.072 g (82%) of **58b** which was converted to the mono-HCl salt to afford a white solid: mp 173−178 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.92 (t, 3H), 1.52−1.69 (m, 1H), 1.69−1.91 (m, 2H), 2.02−2.39 (m, 3H), 2.61−2.83 (m, 2H), 2.84−3.05 (m, 1H), 3.08−3.59 (m, 5H), 3.93−4.12 (m, 1H), 4.36−4.55 (m, 1H), 4.59−4.76 (m, 1H), 6.71−6.86 (m, 1H), 6.97−7.27 (m, 4H), 7.39−7.49 (m, 1H), 7.77−7.91 (m, 1H), 9.77−9.96 (m, 1H), 10.83 (s, 1H); MS (ES) *m/z* 454.2 ([M + H]$^+$); $[\alpha]_D^{25}$ +12.4° (*c* 1.0, DMSO).

(3*R*)-(−)-3-((Cyclopropylmethyl){[6-fluoro-2,3,4,9-tetrahydro-1*H*-carbazol-3-yl]methyl}amino)-8-fluorochromane-5-carboxamide (59a) and (3*R*)-(+)-3-((Cyclopropylmethyl){[6-fluoro-2,3,4,9-tetrahydro-1*H*-carbazol-3-yl]methyl}amino)-8-fluorochromane-5-carboxamide (59b). The compounds were obtained according to procedure B using **57a** and cyclopropanecarboxaldehyde, generating 0.071 g (79%) of **59a** which was converted to the mono-HCl salt to afford a white solid: mp 175−179 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.37−0.55 (m, 2H), 0.60−0.76 (m, 2H), 1.17−1.32 (m, 2H), 1.51−1.66 (m, 1H), 2.05−2.39 (m, 3H), 2.68−2.83 (m, 2H), 2.83−3.20 (m, 2H), 3.21−3.55 (m, 4H), 4.03−4.18 (m, 1H), 4.35−4.52 (m, 1H), 4.63−4.76 (m, 1H), 6.74−6.87 (m, 1H), 6.99−7.26 (m, 4H), 7.39−7.52 (m, 1H), 7.79−7.91 (m, 1H), 9.90−10.05 (m, 1H), 10.82 (s, 1H); MS (ES) *m/z* 466.2 ([M + H]$^+$); $[\alpha]_D^{25}$ −89.0° (*c* 1.0, DMSO). Similarly, **57b** was reacted with cyclopropanecarboxaldehyde, generating 0.083 g (92%) of **59b** which was converted to the mono-HCl salt to afford a white solid: mp 174−178 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.34−0.55 (m, 2H), 0.57−0.74 (m, 2H), 1.14−1.33 (m, 2H), 1.52−1.69 (m, 1H), 2.02−2.41 (m, 3H), 2.68−2.84 (m, 2H), 2.85−3.07 (m, 1H), 3.07−3.62 (m, 4H), 4.01−4.17 (m, 1H), 4.39−4.52 (m, 1H), 4.61−4.76 (m, 1H), 6.73−6.87 (m, 1H), 6.99−7.26 (m, 4H), 7.40−7.52 (m, 1H), 7.78−7.90 (m, 1H), 9.84−9.99 (m, 1H), 10.83 (s, 1H); MS (ES) *m/z* 466.2 ([M + H]$^+$); $[\alpha]_D^{25}$ +10.0° (*c* 1.0, DMSO).

3-{Cyclobutyl[(6-fluoro-2,3,4,9-tetrahydro-1*H*-carbazol-3-yl)-methyl]amino}-8-fluorochromane-5-carboxamide (60a−d). 60a−d were obtained according to procedure C using **57** and cyclobutanone to give a residue which was purified by chiral HPLC [column, Chiralcel AD, 0.46 cm × 25 cm; mobile phase, 1:1 hexane/ethanol], generating the four diastereoisomers below as the free bases, which were then converted to the mono-HCl salts to afford **60a−d**. **60a**: mp 192 °C; MS (ES) *m/z* 466.2 ([M + H]$^+$); $[\alpha]_D^{25}$ −26.2° (*c* 1.0, MeOH). **60b**: mp 218 °C; MS (ES) *m/z* 464.2 ([M − H]$^-$); $[\alpha]_D^{25}$ +27.4° (*c* 1.0, MeOH). **60c**: mp 227 °C; MS (ES) *m/z* 464.2 ([M − H]$^-$); $[\alpha]_D^{25}$ +50.2° (*c* 1.0, MeOH). **60d**: mp 210 °C; MS (ES) *m/z* 464.2 ([M − H]$^-$); $[\alpha]_D^{25}$ −50.2° (*c* 1.0, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) (for

60a−d) δ 1.45−1.83 (m, 3H), 2.04−2.37 (m, 6H), 2.36−2.62 (m, 3H), 2.68−2.82 (m, 2H), 2.85−3.20 (m, 2H), 3.28−3.53 (m, 1H), 3.86−4.21 (m, 2H), 4.34−4.50 (m, 1H), 4.59−4.72 (m, 1H), 6.75−6.86 (m, 1H), 6.99−7.26 (m, 4H), 7.39−7.49 (m, 1H), 7.74−7.90 (m, 1H), 10.19−10.40 (m, 1H), 10.77−10.86 (m, 1H).

8-Fluoro-3-[[3-(5-fluoro-1*H*-indol-3-yl)-1-methylpropyl]amino]chromane-5-carboxamide (66). To a slurry of **29a** (0.59 g, 2.79 mmol) in anhydrous 1,2-dichloroethane (25 mL), under nitrogen at room temperature, was added **61** (0.57 g, 2.79 mmol), acetic acid (0.29 mL, 5.58 mmol), and sodium triacetoxyborohydride (0.83 g, 3.91 mmol). The mixture was stirred at room temperature overnight. Workup was the same as described in procedure B. Chromatography ((14:1) CH_2Cl_2−MeOH (1% NH_4OH)) afforded 0.82 g (74%) of **66**: MS (ESI) *m*/*z* 400 ([M + H]$^+$). The diastereomers were first separated by normal phase HPLC using a Luna SIL column (5 cm × 25 cm) and 3% MeOH (5% H_2O) in CH_2Cl_2 as mobile phase. The enantiomers were then separated by SFC using a Chiralpak AS column (2 cm × 25 cm) and 50% MeOH (0.1% DEA) in CO_2 as mobile phase and isolated. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.95−1.10 (d, 3H), 1.45−1.85 (m, 3H), 2.52−2.70 (m, 3H), 2.70−2.88 (m, 1H), 2.98−3.10 (m, 2H), 3.62−3.80 (m, 1H), 4.10−4.28 (m, 1H), 6.78−6.97 (m, 2H), 6.97−7.10 (m, 1H), 7.10−7.40 (m, 4H), 7.67 (s, 1H), 10.75 −10.82 (m, 1H).

8-Fluoro-3-[[3-(5-fluoro-1*H*-indol-3-yl)-1-methylpropyl](propyl)amino]-3,4-dihydro-2*H*-chromene-5-carboxamide (67a−d). Each isomer of compound **66** was converted to the desired products **67a−d** by reaction of **66** with propionaldehyde according to procedure B, generating the following desired products as white solids which were converted to their mono-HCl salts. **67a**, 0.114 g (100%): mp 133 °C/dec; MS (ESI) *m*/*z* 442 ([M + H]$^+$); $[\alpha]_D^{25}$ −22.1° (*c* 1.0, DMSO). Anal. ($C_{25}H_{29}F_2N_3O_2 \cdot HCl \cdot 0.60H_2O$) C, H, N. **67b**, 0.11 g (96%): mp 133 °C/dec; MS (ESI) *m*/*z* 442 ([M + H]$^+$); $[\alpha]_D^{25}$ +23.4° (*c* 1.0, DMSO). Anal. ($C_{25}H_{29}F_2N_3O_2 \cdot HCl \cdot 0.60H_2O$) C, H, N. **67c**, 0.093 g (94%): mp 133 °C/dec; MS (ESI) *m*/*z* 442 ([M + H]$^+$); $[\alpha]_D^{25}$ −67.4° (*c* 1.0, DMSO). Anal. ($C_{25}H_{29}F_2N_3O_2 \cdot HCl \cdot 0.60H_2O$) C, H, N. **67d**, 0.095 g (95%): mp 133 °C/dec; MS (ESI) *m*/*z* 442 ([M + H]$^+$); $[\alpha]_D^{25}$ +61.4° (*c* 1.0, DMSO). Anal. ($C_{25}H_{29}F_2N_3O_2 \cdot HCl \cdot 0.60H_2O$) C, H, N. ^{1}H NMR (400 MHz, DMSO-d_6) (for **67a−d**) δ 0.75−0.94 (m, 3H), 1.31−1.56 (m, 3H), 1.57−1.79 (m, 1H), 1.81−2.37 (m, 1H), 2.58−2.88 (m, 4H), 3.06−3.63 (m, 5H), 3.89−4.13 (m, 1H), 4.22−4.39 (m, 1H), 4.41−4.73 (m, 1H), 6.84−6.97 (m, 1H), 7.09−7.24 (m, 2H), 7.25−7.47 (m, 4H), 7.78−7.90 (m, 1H), 9.55−9.73 (m, 1H), 10.90−11.00 (m, 1H).

(−)-3-{(Cyclopropylmethyl)[3-(5-fluoro-1*H*-indol-3-yl)-1-methylpropyl]amino}-8-fluorochromane-5-carboxamide (68a) and (+)-3-{(Cyclopropylmethyl)[3-(5-fluoro-1*H*-indol-3-yl)-1-methylpropyl]amino}-8-fluorochromane-5-carboxamide (68b). Two isomers of compound **66** were converted to the desired products **68a**,**b** by reaction of **66** with cyclopropanecarboxaldehyde according to procedure B, generating the following desired products as white solids which were converted to their mono-HCl salts. **68a**, 0.08 g (90%): mp 135 °C/dec; MS (ES) *m*/*z* 454.2 ([M + H]$^+$); $[\alpha]_D^{25}$ −17.0° (*c* 1.0, DMSO). Anal. ($C_{26}H_{29}F_2N_3O_2 \cdot HCl$) C, H, N. **68b**, 0.075 g (90%): mp 135 °C/dec; MS (ES) *m*/*z* 452.2 ([M − H]$^-$); $[\alpha]_D^{25}$ +15.4° (*c* 1.0, DMSO). Anal. ($C_{26}H_{29}F_2N_3O_2 \cdot HCl \cdot 0.60H_2O$) C, H, N. ^{1}H NMR (500 MHz, DMSO-d_6) (for **68a**,**b**) δ 0.25−0.69 (m, 4H), 0.92−1.28 (m, 1H), 1.36−1.53 (m, 3H), 1.78−1.99 (m, 1H), 2.10−2.40 (m, 1H), 2.55−3.11 (m, 3H), 3.14−3.45 (m, 2H), 3.47−3.81 (m, 2H), 3.98−4.72 (m, 3H), 6.83−6.97 (m, 1H), 7.08−7.49 (m, 6H), 7.80−7.91 (m, 1H), 9.49−9.72 (m, 1H), 10.89−11.00 (m, 1H).

(3*R*)-8-Fluoro-3-{[3-(5-fluoro-1*H*-indol-3-yl)-2-methylpropyl]amino}chromane-5-carboxamide (69). 69 was obtained according to procedure B by reacting (*R*)-**29** with **65** to generate 1.07 g (80%) of **69** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.93 (d, *J* = 6.6 Hz, 3H), 2.16−2.30 (m, 1H), 2.82−2.98 (m, 2H), 3.07−3.17 (m, 1H), 3.21−3.48 (m, 3H), 3.71−3.85 (m, 1H), 4.32−4.52 (m, 2H), 6.83−6.95 (m, 1H), 7.04−7.48 (m, 6H), 7.81 (br s, 1H), 8.92−9.22 (m, 2H), 10.97 (br s, 1H).

(3*R*)-3-{(Cyclopropylmethyl)[3-(5-fluoro-1*H*-indol-3-yl)-2-methylpropyl]amino}-8-fluorochromane-5-carboxamide (70a,b). 70a,**b** were obtained according to procedure B using **69** and cyclopropanecarboxaldehyde to generate 0.214 g (94%) of racemic **70** as a white solid. The diastereomers were separated by HPLC using a Whelk O column (2 cm × 25 cm) and 40% EtOH/Hex as mobile phase, isolated, and converted to the mono-HCl salt to afford the following products as white solids. **70a**: mp 155−159 °C/dec; MS (ES) *m*/*z* 454.2 ([M + H]$^+$); $[\alpha]_D^{25}$ −22.2° (*c* 1.0, DMSO); 99.9% ee by chiral HPLC. **70b**: mp 155−160 °C/dec; MS (ES) *m*/*z* 454.2 ([M + H]$^+$); $[\alpha]_D^{25}$ −59.6° (*c* 1.0, DMSO); 99.9% ee by chiral HPLC. ^{1}H NMR (400 MHz, DMSO-d_6) (for **70a**,**b**) δ 0.16−0.69 (m, 4H), 0.92−1.24 (m, 5H), 2.21−2.37 (m, 1H), 2.54−2.80 (m, 1H), 2.88−3.30 (m, 4H), 3.29−3.58 (m, 2H), 3.94−4.10 (m, 1H), 4.29−4.73 (m, 2H), 6.82−6.98 (m, 1H), 7.06−7.51 (m, 6H), 7.84 (br s, 1H), 9.68−10.12 (m, 1H), 10.99 (br s, 1H).

Biological Assays. 5-HT$_{1A}$ Binding Affinity Assay. The affinity of compounds for the 5-HT$_{1A}$ receptor was performed using a standard [^{3}H]-8-OH-DPAT binding assay using human 5-HT$_{1A}$ receptors stably cloned in CHO cells.[42]

^{3}H-Paroxetine Binding To Assess Affinity of Drugs for the Serotonin Transporter. A protocol similar to that used by Cheetham et al.[36] was used to determine the affinity of compounds for the serotonin transporter. Briefly, frontal cortical membranes prepared from male Sprague−Dawley rats were incubated with ^{3}H-paroxetine (0.1 nM) for 60 min at 25 °C. All tubes also contained vehicle, test compound (one to eight concentrations), or a saturating concentration of fluoxetine (10 μM) to define specific binding. All reactions are terminated by the addition of ice cold Tris buffer followed by rapid filtration using a Tom Tech filtration device to separate bound from free ^{3}H-paroxetine. Bound radioactivity was quantitated using a Wallac 1205 Beta Plate counter. Nonlinear regression analysis was used to determine IC_{50} values which were converted to K_i values using the method of Cheng and Prusoff;[37] $K_i = IC_{50}/[(\text{radioligand concn})/(1 + KD)]$.

Inhibition of ^{3}H-5-HT Uptake by Cells Possessing the Human 5-HT Transporter. A human carcinoma cell line (Jar cells) possessing low endogenous levels of the 5-HT transporter were seeded into 96-well plates and treated with staurosporine at least 18 h prior to assay. [Staurosporine greatly increases the expression of the 5-HT transporter.] On the day of assay, vehicle, excess of fluoxetine, or test compound was added to various wells on the plate. All wells then received ^{3}H-5-HT and were incubated at 37 °C for 5 min. The wells are then washed with ice cold 50 mM Tris HCl (pH 7.4) buffer and aspirated to remove free ^{3}H-5-HT. An amount of 25 μL of 0.25 M NaOH is then added to each well to lyse the cells and 75 μL scintillation cocktail (Microscint 20) added prior to quantitation on a Packard TopCount machine. Tubes with vehicle represent total possible uptake, and radioactivity counted in tubes with fluoxetine represent nonspecific binding/uptake and is subtracted from the total possible uptake to give total possible specific uptake. This nonspecific binding (usual low in number) is then subtracted from the counts obtained in wells with various test compounds (or different concentrations of test drug) to give specific uptake in the presence of drug. Specific uptake is then expressed as a % of control values and is analyzed using nonlinear regression analysis (Prizm) to determine IC_{50} values. If the compound is active at inhibiting 5-HT uptake, its counts will be close to that obtained with fluoxetine.

Assessment of Agonism/Antagonism at the 5-HT$_{1A}$ Receptor Using [^{35}S]-GTPγS Binding to Cloned Human 5-HT$_{1A}$ Receptors. The [^{35}S]-GTPγS binding assay was similar to that used by Larenzo and Birdsall.[40] Briefly, 5-HT$_{1A}$ cloned receptor membrane fragments (as used for 5-HT$_{1A}$ receptor binding assays) were stored at −70 °C until needed. These membranes were then incubated for 30 min at 37 °C with [^{35}S]-GTPγS (1

nM) in the presence of vehicle, test compound (11 concentrations), or excess 8-OH-DPAT to define maximum agonist response. All reactions were terminated by the addition of ice cold Tris buffer (50 mM Tris, 3 mM $MgCl_2$; 100 mM NaCl, pH 8.0) followed by rapid filtration using a Brandel filtration device to separate bound from free [^{35}S]-GTPγS. Agonists produce an increase in the amount of [^{35}S]-GTPγS bound, whereas antagonists produce no increase in binding. Bound radioactivity was counted and analyzed as above.

^{3}H-Prazosin Binding To Assess Affinity of Drugs for the α_1 Receptor. Briefly, cortical membranes prepared from male Sprague−Dawley rats were incubated with ^{3}H-prazosin (0.2nM) for 30 min at 25 °C. All tubes also contained vehicle, test compound (one to eight concentrations), or a saturating concentration of phentolamine (10 μM) to define specific binding. All reactions are terminated by the addition of ice cold Tris buffer followed by rapid filtration using a Tom Tech filtration device to separate bound from free ^{3}H-prazosin. Bound radioactivity was quantitated using a Wallac 1205 β plate counter. Nonlinear regression analysis was used to determine IC_{50} values, which were converted to K_i values using the method of Cheng and Prusoff;[37] $K_i = IC_{50}/[(\text{radioligand concn})/(1 + KD)]$.

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Supporting Information Available: Synthesis and analytical data of some intermediates and elemental analysis data for most final targets. This material is available free of charge via the Internet at http://pubs.acs.org.

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