New Generation Dopaminergic Agents. 1. Discovery of a Novel Scaffold Which Embraces the D_2 Agonist Pharmacophore. Structure−Activity Relationships of a Series of 2-(Aminomethyl)chromans

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A series of 2-(aminomethyl)chromans (2-AMCs) was synthesized and evaluated for their affinity and selectivity for both the high- and low-affinity agonist states (D_2^{High} and D_2^{Low}, respectively) of the dopamine (DA) D_2 receptor. The 7-hydroxy-2-(aminomethyl)chroman moiety was observed to be the primary D_2 agonist pharmacophore. The 2-methylchroman moiety was discovered to be an entirely novel scaffold which could be used to access the D_2 agonist pharmacophore. Attaching various simple alkyl and arylalkyl side chains to the 7-hydroxy 2-AMC nucleus had significant effects on selectivity for the D_2^{High} receptor vs the $5HT_{1A}$ and α_1 receptors. A novel DA partial agonist, (*R*)-(−)-2-(benzylamino)methyl)chroman-7-ol [*R*-(−)-**35c**], was identified as having the highest affinity and best selectivity for the D_2^{High} receptor vs the α_1 and $5HT_{1A}$ receptors. Several regions of the 2-AMC nucleus were modified and recognized as potential sites to modulate the level of intrinsic activity. The global minimum conformer of the 7-hydroxy-2-AMC moiety was identified as fulfilling the McDermed model D_2 agonist pharmacophoric criteria and was proposed as the D_2 receptor-bound conformation. Structure−activity relationships gained from these studies have aided in the synthesis of D_2 partial agonists of varying intrinsic activity levels. These agents should be of therapeutic value in treating disorders resulting from hypo- and hyperdopaminergic activity, without the side effects associated with complete D_2 agonism or antagonism.

Introduction

The discovery of more effective side effect free therapy for the treatment of both the positive and negative symptoms of schizophrenia remains a challenging research problem. The positive symptoms are believed to be associated with hyperactive dopaminergic transmission in the mesolimbic brain region, whereas the negative symptoms are associated with a hypoactive prefrontal cortex.[1,2] Although traditional D_2 antagonist antipsychotics are efficacious for the positive symptoms, they are also responsible for extrapyramidal side effects (EPS) which occur as a result of excessive attenuation of brain dopamine (DA) neuronal activity due to the blockade of postsynaptic DA receptors. One theory which has gained renewed attention in recent years is based on the potential normalization of dopaminergic activity using a DA D_2 partial agonist.[3] A successful D_2 partial agonist would be effective in treating the positive symptoms by selectively activating the inhibitory presynaptic D_2 autoreceptors located on the cell bodies and terminals of DA neurons to inhibit DA neuronal firing, synthesis, and release of DA via a feedback mechanism which decreases neuronal activity.[4] Though there is no evidence for a structural difference between the DA D_2 pre- and postsynaptic receptors,[5] it has been postulated that the autoreceptors are much more sensitive due to a large DA receptor reserve available on DA neurons while far fewer spare DA receptors are available on postsynaptic cells.[6] In a hyperactive dopaminergic system, a D_2 partial agonist should reduce the overstimulation of the D_2 postsynaptic receptors by competing with dopamine and in principle normalize dopaminergic transmission. In a hypoactive situation, commonly associated with both a dysfunctional prefrontal cortex and the negative symptoms, the supersensitive D_2 postsynaptic receptors may be sufficiently stimulated by a D_2 partial agonist. As such, a D_2 partial agonist may provide a viable approach toward influencing dopaminergic activity both pre- and postsynaptically and therefore be a successful means of treating the positive and negative symptoms of schizophrenia with low liability for producing EPS.[7] D_2 partial agonists could also be of value in hyperprolactinemia, Parkinson's disease, Tourette's syndrome, and potentially any disorder in which DA function is abnormal.

Numerous DA agonists with various levels of intrinsic activity have been prepared and concomitantly used to explore the pharmacophoric and topographical requirements of the DA D_2 receptor.[8] As a result of this research, the discovery of several D_2 agonists have emerged which can be categorized into two general classes (Chart 1). The first class has a close resemblance with respect to the pharmacophoric elements of DA [i.e. (*S*)-3-PPP (**1**),[9] talipexole (**2**),[10] U-68553 (**3**),[11] pramipexole (**4**),[12] PD 128483 (**5**),[13] SDZ-208-911 (**6**),[14] SDZ-208-912 (**7**)[14]] and a second class whose structural elements do not mimic DA and whose pharmacophore is less well understood [i.e. roxindole (**8**),[15] PD 120700

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Chart 1. Several Dopamine D_2 Partial Agonists

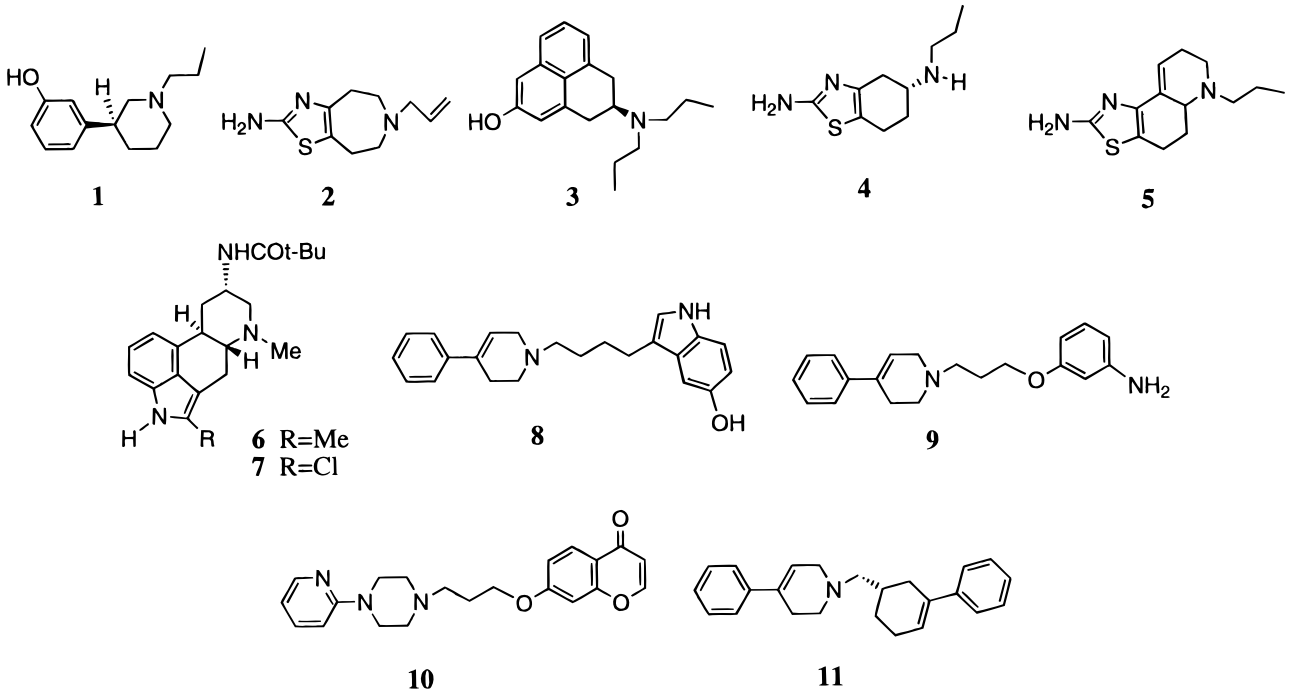
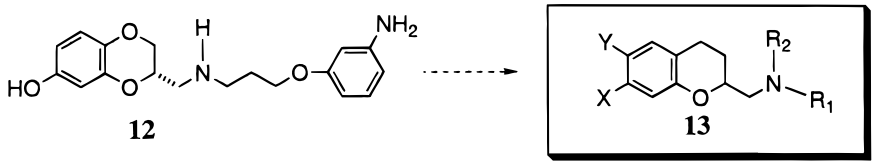


Chart 2. WAY 124486 and Its 2-Aminomethyl Chroman Analogue Variations



(**9**),[16] PD 119819 (**10**),[17] and CI-1007 (**11**)[18]]. Recently it has been suggested that there may be alternative modes of agonist binding other than those represented by the McDermed DA D_2 concept.[19]

Clinically, compounds such as talipexole (**2**) and pramipexole (**4**) appear to possess too much intrinsic activity, as evidenced by the appearance of hallucinations in some patients.[20] Pramipexole (**4**) is currently being marketed for Parkinson's disease.[21] Compounds such as SDZ-208-911(**6**) and SDZ-208-912 (**7**) have shown efficacy with respect to the positive symptoms; however, due to their low intrinsic activity, they can produce an unacceptable level of EPS.[22] Other agents either lack specificity, have a pharmacokinetic profile that hinders therapeutic ability, or are currently being evaluated.

Our interests in the discovery of a D_2 partial agonist emerged with the recent identification of the 2-(aminomethyl)benzodioxan (2-AMB) WAY 124486 (**12**, Chart 2).[23] Previously reported structure−activity relationship (SAR) studies of the AMB derivatives revealed the 7-hydroxyl group and *S* configuration were essential requirements to achieve high affinity for the D_2 receptor [K_i (D_2^{High}) = 0.3 nM vs [^{3}H]quinpirole, Table 1]. Despite the poor bioavailability and rather low selectivity vs the 5-HT_{1A} and α_1 receptors, **12** provided an opportunistic chemical lead to evolve toward other more selective compounds with improved pharmacokinetic properties.

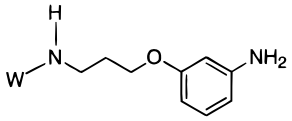
In this report will be discussed several potential avenues for D_2, $5HT_{1A}$, and α_1 receptor profile modulation within a related series of 2-(aminomethyl)chromans (2-AMCs; i.e., **13,** Chart 2).[24,25] Structural modifications were systematically carried out to evaluate (a) the importance of the dioxan ring of **12**, (b) the importance of the anilino moiety, (c) the optimal length of the side chain spacer, (d) the D_2 primary pharmacophoric elements, and (e) how intrinsic activity may be influenced through molecular modifications. Our ultimate goal was to establish SAR directed at identifying a highly selective and potent D_2 partial agonist with low intrinsic activity. Although 5-HT_{1A} agonism has been shown to reverse D_2 antagonist-induced catalepsy in rodent,[26] it was felt that a suitable D_2 partial agonist candidate would not need this additional property to be of therapeutic value.

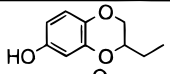
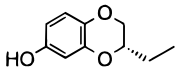
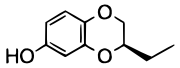
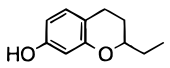
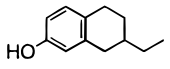
As a consequence of our study, we identified that the 2-AMC and 2-AMB moieties were found to be entirely novel scaffolds which could be used to access the D_2 agonist pharmacophore. A conformational analysis and proposed receptor-bound conformation will also be discussed.

Results

Chemical Synthesis. The general synthetic routes for the syntheses of the 2-AMCs (**22-60**) are shown in Schemes 1−3 For detailed transformations, see the Experimental Section. In all cases, the chromones (**15a,b,e**) were synthesized from their respective known 2-hydroxyacetophenones (**14**) using the method of Kostanecki (Scheme 1).[27] Hydrogenation in acetic acid afforded the chromans (**16a,b**, R = OMe or OBn). Benzyl-protected chroman (**15b**) was prepared as previous described from **14b**.[28] Reduction of esters **16a,b,e** using $LiBH_4$ furnished the alcohols (**17a,b,e**). Alcohols **17a,b,e** were converted in a straightforward manner to

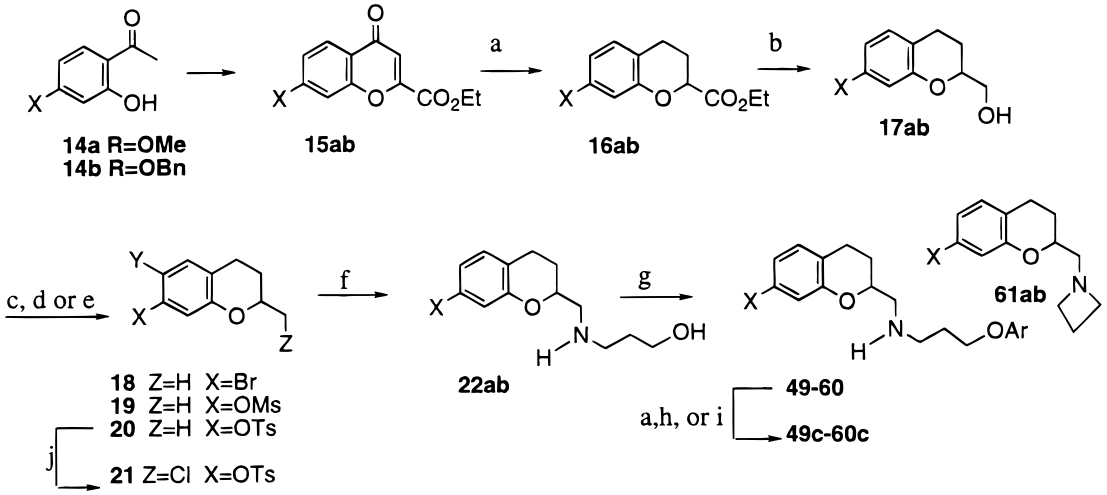
Table 1. Affinity of Benzo-Fused Ring Variations Derivatives



compd[c]	W	K_i (nM)[a,b] $D2^{High}$	$D2^{Low}$	5-HT1A	α1	Ratio ($D2^{Low}/D2^{High}$)
(±)-12[d]		1.0 ± 0.2	24.1 ± 2.2	6.2 ± 2.7	17.0 ± 9.2	24
S-(-)-12[d]		0.3 ± 0.2	17.8 ± 4.7	6.8 ± 0.8	3	59
R-(+)-12[d]		13.1 ± 2.2	278 ± 107	36.0	38	21
49c		0.9 ± 0.2	15.9 ± 6.7	2.6 ± 1.4	38.0 ± 10.5	18
70		22.3 ± 3.3	546 ± 180	50 ± 31	145 ± 24	24
1		21.4 ± 1.2	702 ± 16	*	*	33
2		5.8 ± 1.1	2700 ± 130	*	*	466
6		0.9 ± 0.2	1.0 ± 0.2	*	*	1.1

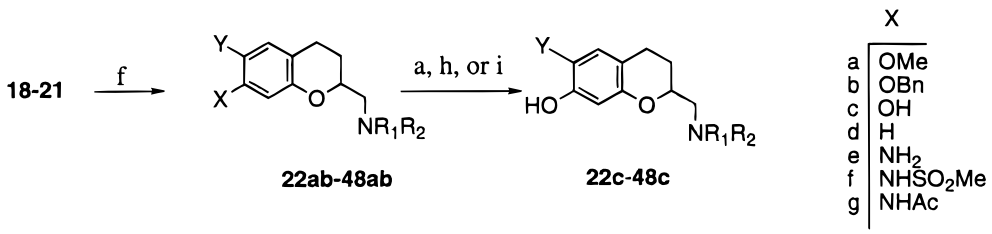
[a] K_i values are the means of at least two experiments ± SEM (performed in triplicate determined from nine concentrations). Values without SEM are for a single determination only. [b] The radioligands used were [^{3}H] quinpirole (D_2^{High}),[^{3}H]spiperone + GTP (D_2^{Low}), [^{3}H] 8-OH-DPAT (5-HT_{1A}), and [^{3}H]prazosin (α_1). [c] All compounds were prepared in racemic form unless otherwise noted. [d] Reference 23. *Not determined.

Scheme 1[a]



[a] Reagents and conditions: (a) H_2, Pd/C; (b) $LiBH_4$, THF; (c) CBr_4, PPh_3, CH_2Cl_2; (d) MsCl, NEt_3; (e) TsCl, pyridine; (f) NH_2R_1, method A or B; (g) DIAD, PPh_3, HOAr; (h) 40% HBr; (i) Ph_2PH, *n*-BuLi, THF; (j) NCS, THF, rt; (k) $(CO_2Et)_2$, NaOEt.

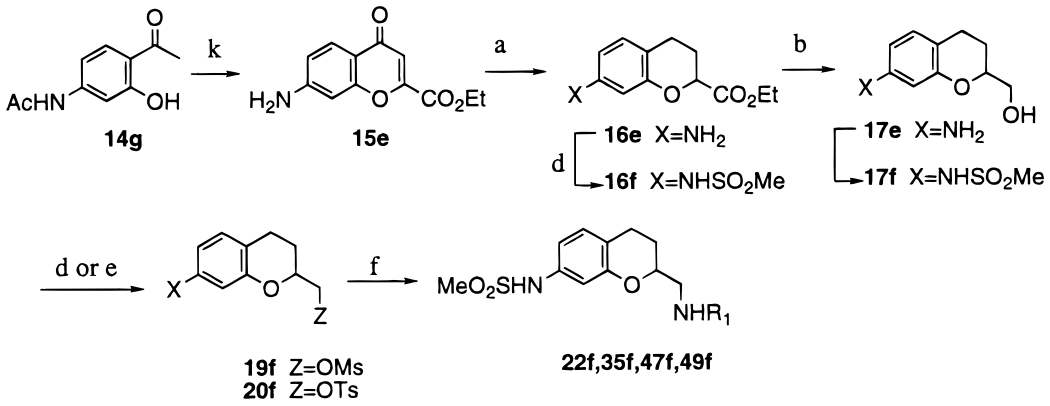
Scheme 2[a]



[a] Reagents and conditions: (a) H_2, Pd/C; (b) $LiBH_4$, THF; (c) CBr_4, PPh_3, CH_2Cl_2; (d) MsCl, NEt_3; (e) TsCl, pyridine; (f) NR_1R_2, method A or B; (g) DIAD, PPh_3, HOAr; (h) 40% HBr; (i) Ph_2PH, *n*-BuLi, THF; (j) NCS, THF, rt; (k) $(CO_2Et)_2$, NaOEt.

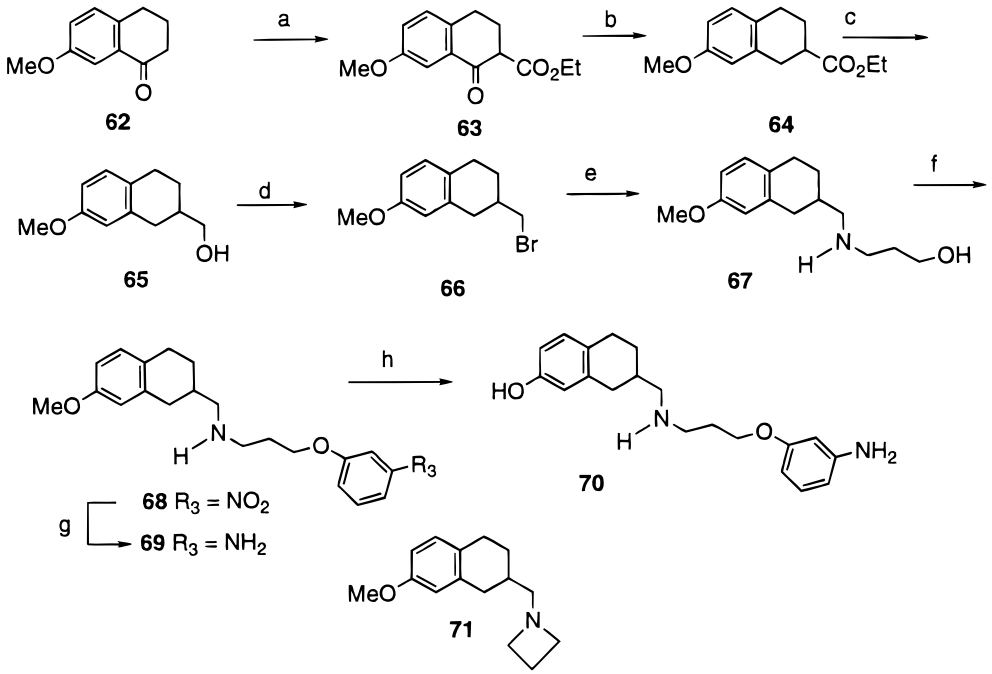
their corresponding bromides, mesylates or tosylates (**18**−**20**) using standard protocol. Chlorination of **20** with NCS led exclusively to **21**. Treatment of **18**−**21** with an excess of the appropriately substituted amines provided the 2-AMCs (**22**−**48**) (method A or B). The amino alcohols (**22a,b**) were coupled to a variety of phenol derivatives using the Mitsunobu protocol (method C).[29] The formation of azetidine **61ab** was observed as a byproduct in cases when the intermediate phenoxide anion was relatively nonnucleophilic. The phenol moi-

Scheme 3[a]



[a] Reagents and conditions: (a) H_2, Pd/C; (b) $LiBH_4$, THF; (c) CBr_4, PPh_3, CH_2Cl_2; (d) MsCl, NEt_3; (e) TsCl, pyridine; (f) NH_2R_1, method A or B; (g) DIAD, PPh_3, HOAr; (h) 40% HBr; (i) Ph_2PH, *n*-BuLi, THF; (j) NCS, THF, rt; (k) $(CO_2Et)_2$, NaOEt.

Scheme 4[a]



[a] Reagents and conditions: (a) NaH, EtOCOOEt, THF; (b) Et_3SiH, TFA, CH_2Cl_2; (c) $LiBH_4$, THF; (d) CBr_4, PPh_3, CH_2Cl_2; (e) $NH_2(CH_2)OH$; (f) DEAD, PPh_3, 3-nitrophenol; (g) H_2, Pd/C; (h) HBr.

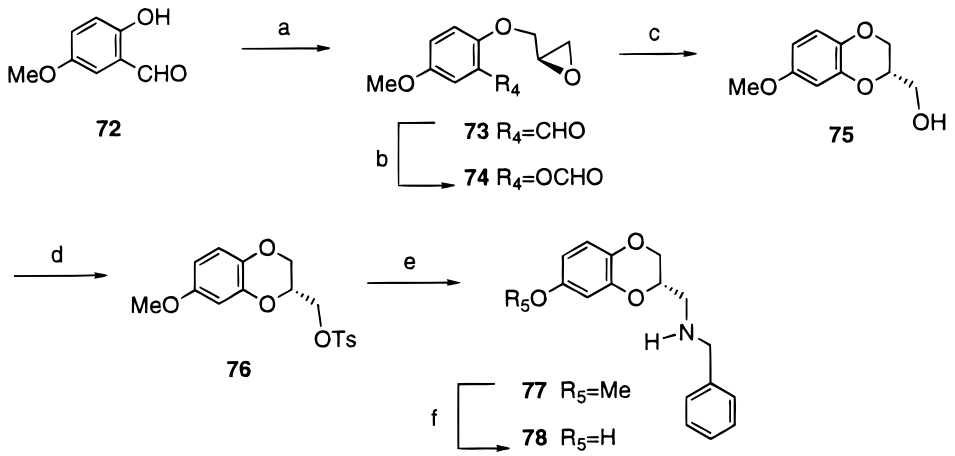
eties were liberated by using either 48% HBr (method D) for the methoxy derivatives or hydrogenolysis (method F) of the benzoxy derivatives to afford compounds **22c**−**60c**. Reduction of quinoline **50c** using $NaBH_4$−$NiCl_2$[30] afforded the tetrahydroquinoline **51c** (method E). Methanesulfonamides (**22f**, **35f**, **47f**, **49f**) were prepared using a similar route beginning with **14g**[31] (Scheme 3).

Synthesis of the tetralin **70** began with commercially available 7-methoxy-1-tetralone (**62**) (Scheme 4). The *β*-keto ester **63** was prepared from **62** using diethyl carbonate and sodium hydride. Subsequent treatment with triethylsilane afforded ester **64**.[32] Conversion to the corresponding bromide (**66**) followed by treatment with 1-aminopropanol afforded the 2-(aminomethyl)-tetralin (**67**). Coupling of 3-nitrophenol to **67** using Mitsunobu methodology provided the bis(arylalkyl)-amine (**68**). A significant amount of azetidine (**71**) was isolated during the Mitsunobu reaction. Presumably the increased nucleophilicity of the nitrogen of **67** (next to a tetralin ring vs a chroman ring) allows for the intramolecular reaction to compete effectively. Reduction of the nitro group of **68**, followed by treatment with 48% HBr, furnished tetralin (**70**).

The 2-AMB (**78**) was prepared in six steps as depicted in Scheme 5. Commercially available **72** was reacted with (2*R*)-(−)-gylcidyl 3-nitrobenzenesulfonate to afford epoxide **73**. Treatment with *m*-chloroperbenzoic acid followed by base hydrolysis and cyclization gave benzodioxan **75**. Tosylation followed by reaction with excess benzylamine provided **77**, which was subsequently demethylated with 48% HBr to afford **78**.

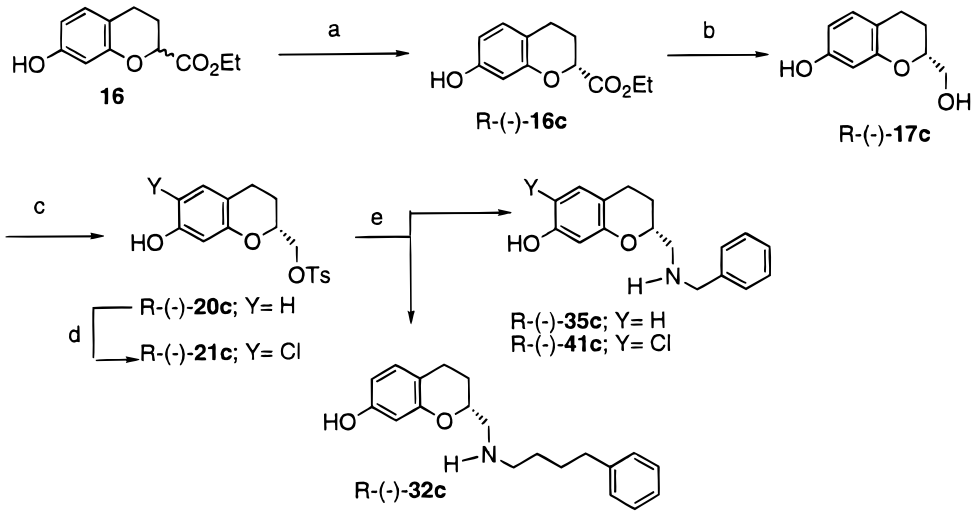
Resolution and Determination of Absolute Configuration. Racemic **35c**, **41c,** and **48c** were resolved using a Diacel Chiralcel OJ 1 in. × 25 cm (10 mkm) preparative column. The optical purities of (−)-**35c** and (+)-**35c** was determined to be 99.0% ee and 99.8% ee, respectively, using a Chiralcel OD-R (0.46 × 25 cm, acetonitrile−1 M sodium perchlorate, 1:1, 0.5 mL/min, 280 nM). The optical purities of (−)-**41c**, (+)-**41c,** (−)-**48c**, and (+)-**48c** were determined to be 100% ee, 99.5% ee, 100% ee, and 96.6% ee, respectively. The absolute stereochemistry of the eutomers [(−)-**35c** and (−)-**41c**]

Scheme 5[a]



[a] Reagents and conditions: (a) NaH, (2*R*)-(−)-glycidyl 3-nitrobenzenesulfonate; (b) mCBPA; (c) K_2CO_3/MeOH; (d) TsCl, pyridine; (e) $BnNH_2$, DMSO, 80 °C; (f) HBr.

Scheme 6[a]



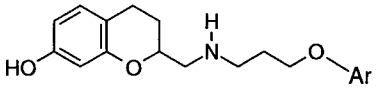
[a] Reagents and conditions: (a) Lipase PS-30, (b) $LiBH_4$; (c) TsCl, pyr; (d) NCS; (e) RNH_2, DMSO.

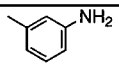
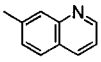
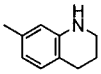
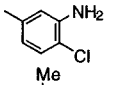
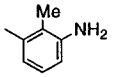
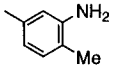
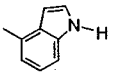
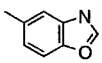
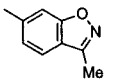
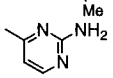
was determined to be of the *R* configuration when both were prepared from a known intermediate [i.e. *R*-(−)-**16c**[33]] through an alternative route depicted in Scheme 6. The corresponding phenylbutyl derivative [i.e. *R*-(−)-**32c**] was similarly prepared from *R*-(−)-**16c**.

Pharmacology

All compounds were evaluated for their in vitro binding affinity to rat striatal DA D_2 receptors using the agonist [^{3}H]quinpirole to label the high affinity state (D_2^{High}) and the antagonist [^{3}H]spiperone plus GTP to label the low-affinity state (D_2^{Low}). Ketanserin (30 nM) was present in all assays with [^{3}H]spiperone to preclude binding of spiperone to 5-HT_2 receptors. Although [^{3}H]-quinpirole possesses high affinity for D_3 receptors, it appears to be labeling predominantly the D_2 high-affinity state in striatal tissue, and may be the ligand of choice for assessing D_2 agonist binding.[34,35] Additionally, the majority of quinipirole binding (>80%) appears to be very sensitive to inhibition by guanylylimidodiphosphate (unpublished results). Compounds were also evaluated for their affinity for the 5-HT_{1A} and α_1 receptors using [^{3}H]-8-OH-DPAT and [^{3}H]prazosin, respectively. Selected compounds were further evaluated for their binding affinity for the human D_{2s}, D_3, and $D_{4.4}$ receptors, each expressed in CHO cells using the antagonist ligand [^{3}H]spiperone. The affinities were expressed as K_i values using the Cheng−Prussoff equation.[36] The compound's intrinsic activity was predicted upon the preferential antagonism of agonist vs antagonist radioligand binding, based upon a similar method previously reported by Lahti et al.[37] The displacement of the antagonist, [^{3}H]spiperone, in the presence of high concentrations of GTP measures the ability of the ligand to bind to the D_2^{Low} receptor, while displacement of an agonist, [^{3}H]quinpirole, in the absence of GTP measures the ligand's ability to bind to the D_2^{High} receptor [$K_i^L = K_i(D_2^{Low})$; $K_i^H = K_i(D_2^{High})$]. The ratio [i.e. (K_i^L/K_i^H)] was shown to be a reliable estimate with the ligand's intrinsic activity as determined by other assays. Selected compounds which displayed impressive affinity, selectivity, and a ratio predictive of intrinsic activity between talipexole (**2**) [(K_i^L/K_i^H) = 466, Table 1] and SDZ-208−911 (**6**) [(K_i^L/K_i^H) = 1.1, Table 1] were subsequently evaluated in vivo by utilizing the well-established phenomenon of receptor-mediated feedback inhibition of the presynaptic neuron.[38] Activity at DA autoreceptors was established by their ability to reverse γ-butyrolactone (GBL)-induced increase in DA synthesis as measured by the rate of dihydroxyphenylalanine (DOPA) formation in the rat corpus striatum. Effects in mouse exploratory locomotor activity (LMA)

Table 2. Affinities of Bis(arylalkyl)Amines: Side Chain Variations of 7-Hydroxy-2-AMCs



compd[c]	Ar	K_i (nM)[a,b] D_2^{High}	D_2^{Low}	5-HT1A	α_1	Ratio (D_2^{Low}/D_2^{High})
49c		0.9 ± 0.2	15.9 ± 6.7	2.6 ± 1.4	38.0 ± 10.5	18
50c		0.5 ± 0.1	12.0 ± 3.6	6.5	13	24
51c		0.7 ± 0.1	13.4 ± 3.0	0.8	25	19
52c		0.3 ± 0.1	16.2 ± 2.8	1.90	18	54
53c		1.2 ± 0.4	19.4 ± 0.2	0.60	9.5	16
54c		0.5 ± 0.1	6.7 ± 0.4	1.4	9.0	13
55c		2.3 ± 1.6	26.9 ± 8.2	1.0	18	12
56c		0.7 ± 0.01	13.0 ± 3.5	0.6	6.0	19
57c		0.5 ± 0.2	14.6 ± 3.1	2.0	28	29
58c		0.4 ± 0.03	11.4 ± 3.8	0.19	13	28
59c		0.3 ± 0.03	10.3 ± 0.3	0.3 ± 0.1	42	34
60c		0.5 ± 0.04	18.4 ± 5.9	77 ± 21	35	37

[a-c] See footnotes of Table 1

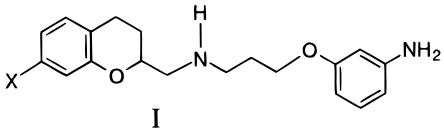
were used as a behavioral index of DA autoreceptor activation/postsynaptic DA agonism; selective activation of DA autoreceptors results in the inhibition of LMA, while postsynaptic DA stimulation increases LMA. The pharmacological test models are described in detail in the Experimental Section.

Results and Discussion

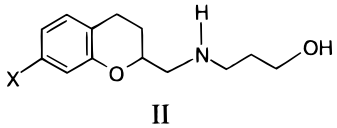
Structure−Affinity Relationships (SAR). Binding affinities for the D_2^{High}, D_2^{Low}, $5HT_{1A}$, and α_1 receptors are reported in Tables 1−8 along with relevant reference compounds. As indicated in Table 1, ring variations of 2-AMB (±)-**12** revealed that the D_2^{High} receptor was very sensitive to structural modification in this region of the molecule. The 7-OH-2-AMB (±)-**12** (K_i^H = 1.0 nM) and 7-OH-AMC (**49c**, K_i^H = 0.90 nM) had almost identical affinities for the D_2^{High} receptor, whereas, in the case of the tetralin (**70**), replacement of both oxygens led to a 25-fold loss in affinity (K_i^H = 22.3 nM).

Our initial focus was the modification or replacement of the anilino moiety of **49c** to attempt to control affinity and selectivity (Table 2). Surprisingly, the bis(arylalkyl)amines (**49c−60c**) all had affinities of <3 nM for the D_2^{High}, indicating a large tolerance of the D_2^{High} receptor toward structural variation in this region of the molecule. Interestingly, every molecule in Table 2, with the exception of **60c**, had affinities of similar magnitude (<7 nM) at the $5HT_{1A}$ receptor. The aminopyrimidine (**60c**) was identified as the most selective compound of the bis(arylalkyl)amine shown in Table 2 [K_i(5-HT_{1A})/K_i^H = 154; $K_i(\alpha_1)/K_i^H$ = 70]. The SAR suggests that the flexible arylalkyl side chain moiety may be playing an auxiliary role in the ligand's ability to bind to the D_2 receptor. In fact, as shown in Table 3, when the aryl moiety was completely removed (i.e. **22c**), high affinity for the D_2^{High} receptor was retained (K_i^H = 3.4 nM), indicating that the primary pharmacophore was the 7-OH-2-AMC nucleus. Apparently the D_2 receptor can withstand the complete removal of the side chain aryl group with only a slight loss in affinity (**22c**; K_i^H = 3.4 nM vs **49c**; K_i^H = 0.90 nM). However, a more significant loss in affinity was observed for $5HT_{1A}$ and α_1 receptors (**49c−60c** vs **22c**), which suggests these receptors may be more dependent on hydrophobic interactions than on complementary receptor−ligand interactions. Further investigation of the simple alkyl side chains (Table 4) revealed that elongation of the alkyl group to a hexyl group (i.e. **26c**) resulted in maximum affinity for D_2 and $5HT_{1A}$ receptors. The butyl derivative (**24c**) had the best selectivity for the D_2^{High} receptor vs the 5-HT_{1A} [K_i(5HT_{1A})/K_i^H = 112] receptor when compared to the simple alkyl derivatives. Branched alkyl group side chains (i.e. **27c−31c**) had lower affinity for the D_2^{High} receptor than their corresponding isomeric straight chain analogues. However, when these branched alkyl derivatives were compared to their respective alkyl groups of the same length, little difference in affinity was observed (**23c** vs **28c**; **25c** vs **29c**). In general, the arylalkylamines shown in Table 4 retained excellent selectivity for the D_2^{High} receptor vs the α_1 receptor, and were overall superior in selectiv-

Table 3. 7-Position Substitutent Effects of Simple Alkyl Side Chains vs Arylalkyl Side Chain Derivatives



I

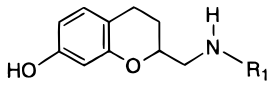


II

compd[c]	X	series	K_i (nM)[a,b] D_2^{High}	K_i (nM)[a,b] D_2^{Low}	K_i (nM)[a,b] 5-HT_{1A}	K_i (nM)[a,b] α_1	ratio (D_2^{Low}/D_2^{High})
49a	OMe	I	222 35	1132	*	*	5
49c	OH	I	0.9 ± 0.2	15.9 ± 6.7	2.6 ± 1.4	38 ± 10	18
49d	H	I	34 ± 19	472 ± 197	2.8	11	14
49f	$NHSO_2Me$	I	16 ± 1	102 ± 58	3	35	6
22a	OMe	II	1300 ± 93	20,861	*	*	16
22c	OH	II	3.4 ± 0.5	177 ± 62	86	307 ± 20	52
22d	H	II	294 ± 70	2763 ± 493	*	*	9
22f	$NHSO_2Me$	II	102 ± 36	662 ± 93	56	500	6

[a–c] See footnotes of Table 1. *Not determined.

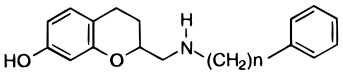
Table 4. Simple Alkyl-Substituted 2-(Aminomethyl)chroman Analogues



compd[c]	R_1	K_i (nM)[a,b] D_2^{High}	K_i (nM)[a,b] D_2^{Low}	K_i (nM)[a,b] 5-HT_{1A}	K_i (nM)[a,b] α_1	ratio (D_2^{Low}/D_2^{High})
22c	$(CH_2)_3OH$	3.4 ± 0.5	156 ± 67	86	307 ± 20	46
23c	$(CH_2)_2CH_3$	6.9 ± 1.5	96 ± 4	177 ± 24	582	14
24c	$(CH_2)_3CH_3$	2.4 ± 0.6	62 ± 30	268	177	26
25c	$(CH_2)_4CH_3$	1.2 ± 0.2	44 ± 14	13	160	37
26c	$(CH_2)_5CH_3$	0.7 ± 0.05	17 ± 1	2.9	111	24
27c	$CH(CH_3)_2$	58 ± 7	515 ± 112	*	*	9
28c	$CH_2CH(CH_3)_2$	7.9	372 ± 212	308	452	47
29c	$CH_2CH_2CH(CH_3)_2$	1.6 ± 0.1	36 ± 1.5	67	375	22
30c	$CH(CH_2CH_3)_2$	40 ± 16	413 ± 183	*	*	10
31c	cyclohexyl	22 ± 2	230 ± 132	330	1268	10

[a–c] See footnotes of Table 1. *Not determined.

Table 5. Phenyl Group Tether Study of 7-Hydroxy-2-AMCs (**32c**-**35c**)



compd[c]	*n*	K_i (nM)[a,b] D_2^{High}	K_i (nM)[a,b] D_2^{Low}	K_i (nM)[a,b] 5-HT_{1A}	K_i (nM)[a,b] α_1	ratio (D_2^{Low}/D_2^{High})
RS-(±)-**32c**	4	0.6 ± 0.1	4.0 ± 0.8	1.4	40.0	7
R-(−)-**32c**	4	0.2 ± 0.1	2.8 ± 0.7	0.40	9.5	14
33c	3	0.4 ± 0.1	13.5 ± 2.7	3.60	63.5	34
34c	2	0.8 ± 0.2	26.4 ± 6.7	7.0	43.0	33
35c	1	0.2 ± 0.1	8.4 ± 1.2	52.0	572.5	42

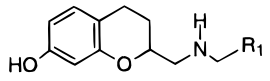
[a–c] See footnotes of Table 1.

ity when compared to the bis(aryl)alkylamine derivatives shown in Table 2. The anomalous selective bis(arylalkyl) amine (i.e. **60c**) suggests that an aryl group side chain having hydrophilic properties may not be complementary to the 5-HT_{1A} and α_1 receptor binding sites. Instead, **60c** may be recognized by 5-HT_{1A} and α_1 receptors as having hydrophobic properties not unlike the simple alkyl-substituted 2-AMCs (**22c**−**31c**).

The significance of having a hydrogen bond donating group in the 7 position is nicely unveiled in Table 3. A 38-fold loss in affinity was manifested when the 7-hydroxyl group was replaced by a hydrogen (i.e. **49c** vs **49d**), while incorporation of a methoxy group (i.e. **49a**) resulted in a 247-fold loss in affinity vs **49c**. An attempt to identify a hydroxy group replacement proved disappointing with the methanesulfonamido group (i.e. **49f**), which led to a 18-fold loss in affinity when compared to **49c**. Though the methanesulfonamide moiety is known to be a popular bioisosteric replacement for phenol,[39] its decreased D_2^{High} affinity may arise from differences in both steric effects and their preferred hydrogen-bond directionality capabilities. While the deshydroxy AMC (**22d**) resulted in a 86-fold loss in affinity, the methanesulfonamide (**22f**) lost only 30-fold affinity when compared to the 7-hydroxy analogue (**22c**), again exemplifying the inefficient hydrogen bonding interaction of the sulfonamido group with the D_2^{High} receptor.

Table 5 depicts an investigation of the spacer unit utilized between a phenyl group and the 7-OH-AMC nucleus. Interestingly, when the oxygen of the four-atom linkage of **54c** (Table 2) was replaced with a methylene (i.e. **32c**), improved selectivity was discovered for the D_2^{High} receptor over the α_1 receptor [**32c**, $K_i(\alpha_1)/K_i^H = 67$ vs **54c**, $K_i(\alpha_1)/K_i^H = 18$], as was also observed for the 2- and 3-atom linkages (i.e. **33c** and **34c**). However, rather low selectivity was observed with

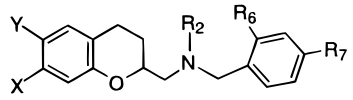
Table 6. Ring Variation Analogues of AMC **35c**



compd[c]	R_1	K_i (nM)[a,b] D_2^{High}	D_2^{Low}	5-HT_{1A}	α_1	ratio (D_2^{Low}/D_2^{High})
35c	Ph	0.2 ± 0.1	8.4 ± 1.2	52.0	572	42
36c	2-thienyl	0.6 ± 0.1	2.8 ± 0.7	42.5	514	5
37c	2-furanyl	1.1 ± 0.4	42 ± 29	208	1710	38
38c	cyclohexyl	0.9 ± 0.3	7.2 ± 1.6	26.5	414	8
39c	1-naphthyl	1.1 ± 0.4	3.8 ± 1.7	6.0	36	3
40c	4-pyridinyl	1.1 ± 0.2	115 ± 18	57.5	1002	104

[a−c] See footnotes of Table 1.

Table 7. Analogues of AMC **35c:** Substituent Effects



compd[c]	Y	X	R_2	R_6	R_7	K_i (nM)[a,b] D_2^{High}	D_2^{Low}	5-HT_{1A}	α_1	ratio (D_2^{Low}/D_2^{High})
35c	H	OH	H	H	H	0.2 ± 0.1	8.4 ± 1.2	52.0	572	42
35d	H	H	H	H	H	51 ± 19	*	59.5	315	*
35f	H	$NHSO_2Me$	H	H	H	8.8 ± 0.01	46.3 ± 17.0	52.0	1136	5
41c	Cl	OH	H	H	H	1.0 ± 0.3	7.1 ± 1	387	69	7
42c	H	OH	Me	H	H	4.8 ± 0.3	61.1 ± 3.6	192	811	13
43d	H	H	H	H	F	73.7 ± 3.5	*	46.0	641	*
44c	H	OH	H	H	F	0.8 ± 0.1	68.9 ± 4.7	71.5	1442	86
45c	H	OH	H	H	Cl	0.3 ± 0.02	32.4 ± 10.3	43.5	624	108
46c	H	OH	H	H	OH	0.6 ± 0.2	16.2 ± 1.6	31.5	504	27
47f	H	$NHSO_2Me$	H	H	Me	7.1 ± 1.7	25.4 ± 7.1	10.5	579	4
48c	H	OH	$(CH_2)_2$		H	0.6 ± 0.2	3.2 ± 1.3	*	160	5

[a−c] See footnotes of Table 1. *Not determined.

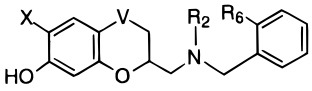
respect to the 5-HT_{1A} receptor when the tethering unit was a two-, three-, or four-atom linkage. Remarkably, the benzyl-substituted 2-AMC (**35c**) was observed to have excellent affinity (K_i^{High} = 0.2 nM) and impressive selectivity for the D_2^{High} receptor [K_i(5-HT_{1A})/K_i^H = 260; $K_i(\alpha_1)/K_i^H$ = 2862)]. Maintaining the one atom spacer, a limited study of ring variation analogues of **35c** (Table 6) afforded several compounds (**36c**−**40c**) having high affinity and impressive selectivity for the D_2^{High} receptor vs the α_1 receptor and the $5HT_{1A}$ receptor. A π electron interaction with the D_2^{High} receptor does not appear to be operative for the aryl side chain of **35c** when considering the cyclohexyl derivative (**38c**) had similar affinity to that of **35c**, suggesting lipophilicity may be playing a role in affinity.

Unexpectedly, when the hydroxyl group of **35c** was removed (i.e. **35d**), a 255-fold loss in affinity was observed for the D_2^{High} receptor (Table 7). Previous examples of hydroxyl removal revealed only a 38-fold (**49c** vs **49d**) and a 86-fold (**22c** vs **22d**) loss in affinity. To make valid arguments with respect to receptor topography and SAR, knowledge of whether a class of ligands is consistently binding with a common alignment rule needs to be assessed. In the case of the deshydroxy and hydroxy analogues, parallel modifications led to nonparallel effects on affinity, suggesting a common orientation at the D_2^{High} receptor was not being maintained. The observation that the anilino analogue (**49d**) decreased affinity by 38-fold for the D_2^{High} receptor vs its 7-hydroxy analogue (**49c**) and the benzyl analogue (**35d**) decreased affinity 255-fold vs its 7-hydroxy analogue (**35c)** implies that **49d** has a different mode of binding not available to **35d**. In the same light, the methanesulfonamides (**22f**, **35f**, and **49f**) were all observed to have near parallel losses in affinity (20−40-fold) when compared to their respective hydroxy analogues (i.e. **22c**, **35c**, and **49c**), suggesting that the 7-methanesulfonamido and 7-OH-AMCs were aligning themselves in a similar orientation in the D_2^{High} receptor cavity.

Substituting a chlorine atom for hydrogen in the 6 position of **35c** (i.e. **41c**) led to a 5- and 7-fold loss in affinity for D_2^{High} and $5HT_{1A}$ receptors, respectively. However, **41c** increased affinity for D_2^{Low} and α_1 receptors vs **35c**. A limited study on the substituent effects at the 4-position of the benzyl side chain of **35c** and **35f** (i.e. **44c**-**46c, 47f**) revealed little change in affinity for the D_2^{High} receptor occurred when replacing a hydrogen with either a fluorine, chlorine, or a hydroxyl group. Interestingly, converting the secondary amine (**35c**) to its methylamino analogue (i.e. **42c**) led to a 24-fold loss in affinity for the D_2^{High} receptor. However, incorporating the methyl group of **42c** within a six-membered ring (i.e. **48c**) led to a 8-fold increase in affinity for the D_2^{High} receptor (**42c**; K_i^H = 4.8 nM vs **48c**; K_i^H = 0.6 nM).

Enantioselectivity. Upon resolution of (±)-**35c**, it was determined that *R*-(−)-**35c** had 60-fold higher affinity for the D_2^{High} receptor than *S*-(+)-**35c** (Table 8). All three receptors recognized *R*-(−)-**35c** as the eutomer; however, *R*-(−)-**35c** was much more enantioselective for the D_2^{High} receptor, having eudismic ratios of 60, 44, and 8 for the D_2^{High}, $5HT_{1A}$, and α_1 receptors, respectively. Interestingly, although 60 times less potent, the distomer [*S*-(+)-**35c**] maintained significant affinity (K_i^H = 12 nM) and selectivity for the D_2^{High} receptor. Resolution of (±)-**41c** again revealed the eutomer to have

Table 8. Affinities of **35c**, **41c**, ***S*-78**, and **48c**



compd[c]	Y	V	R_2	R_6	K_i (nM)[a,b] D_2^{High}	D_2^{Low}	5-HT_{1A}	α_1	ratio (D_2^{Low}/D_2^{High})
RS-(±)-**35c**	H	CH_2	H	H	0.2 ± 0.1	8.4 ± 1.2	52.0	572	42
R-(−)-**35c**	H	CH_2	H	H	0.2 ± 0.1	3.3 ± 0.8	22.5	212	16
S-(+)-**35c**	H	CH_2	H	H	12 ± 2.4	110 ± 21	990	1624	9
RS-(±)-**41c**	Cl	CH_2	H	H	1.0 ± 0.3	7.1 ± 1	387	69	7
R-(−)-**41c**	Cl	CH_2	H	H	0.6 ± 0.1	2.2 ± 0.5	214	487	4
S-(+)-**41c**	Cl	CH_2	H	H	32 ± 10	28.1 ± 17.7	4961 ± 1109	285	0.9
S-(−)-**78**	H	O	H	H	0.4 ± 0.2	5.7 ± 3.7	156	254	14
(±)−**48c**	H	CH_2	$(CH_2)_2$		0.6 ± 0.1	3.2 ± 1.3	110	160	5
(−)-**48c**	H	CH_2	$(CH_2)_2$		0.6 ± 0.2	3.8 ± 0.1	35.5	120	6
(+)-**48c**	H	CH_2	$(CH_2)_2$		40 ± 2	110 ± 33	635 ± 164	98	3

[a−c] See footnotes of Table 1.

Table 9. Affinities of **35c**, **41c**, ***S*-78**, and **48c**

compd[c]	K_i (nM)[a] hD_2	hD_3	hD_4	LMA (ED_{50}, mg/kg, sc)	DOPA (% inhib at 10 mg/kg, sc)
RS-(±)−**35c**	9.7 ± 2.4	8.4 ± 1.3	192 ± 7.5	0.01 (0.006−0.018)	*
R−(−)−35c	10.4 ± 0.2	2.4 ± 0.1	116 ± 15	0.0014 (0.0006−0.0032)	66%
S-(+)-**35c**	228 ± 4.5	27.6 ± 1.2	256 ± 4	0.22 (0.11−0.45)	43%
RS-(+)-**41c**	5.2 ± 0.2	5.0 ± 0.1	4.9 ± 1.0	0.18 (0.08−0.43)	*
R-(−)-**41c**	7.0 ± 0.6	3.4 ± 0.0	8.7 ± 0.5	0.20 (0.08−0.60)	*
S-(+)-**41c**	77 ± 5	19.7 ± 1.9	73.0 ± 1.0	NSE	*
RS-(±)-**48c**	4.3 ± 0.9	0.5 ± 0.1	396 ± 102	0.04 (0.02−0.07)	*
(−)-**48c**	2.5 ± 0.6	0.2 ± 0.1	529 ± 136	0.02 (0.01−0.03)	*
(+)-**48c**	73.9 ± 6.5	1.0 ± 0.4	292 ± 44	NSE	*
S-(−)-**78**	7.2 ± 0.5	1.1 ± 0.02	16.6 ± 0.2	*	*

[a,b] See footnotes of Table 1. *Not determined. NSE = no significant effect.

the *R* configuration with an eudismic ratio of 53 for the D_2^{High} receptor. The absolute configuration of *R*-(−)-**35c** and *R*-(−)-**41c** corresponded to the previously observed *S* configuration of (−)-**12** (benzodioxan), indicating that the D_2^{High} receptor recognized the analogous levorotary enantiomer as the eutomer in both series. Resolution of (±)-**48c** revealed that the levorotary isomer [i.e. (−)-**48c**] was again found to be the eutomer (K^H_i = 0.6 nM), with an eudismic ratio of 67. The corresponding benzodioxan analogue of *R*-(−)-**35c** [i.e. *S*-(−)-**78**)] was observed to have similar affinity for D_2^{High} and α_1 receptors.

The affinities of **35c**, **41c**, **48c**, and **78** for the human D_{2s}, D_3, and $D_{4.4}$ receptors are disclosed in Table 9. *R*-(−)-**35c**, *R*-(−)-**41c**, and (−)-**48c** were recognized as the eutomers at all three receptors, with the hD_{2s} receptor demonstrating the highest enantioselectivity. Although *R*-(−)-**35c** was observed to be selective for the hD_{2s} and hD_3 vs the $hD_{4.4}$ receptor, *R*-(−)-**41c** demonstrated virtually no selectivity for D_2-like receptors. The only noticeable difference between *R*-(−)-**35c** and *S*-(−)-**78** for D_2-like receptors was the 7-fold increase in affinity for the $hD_{4.4}$ receptor observed for *S*-(−)-**78**. Interestingly, (−)-**48c** and (+)-**48c** were both found to have high affinity and selectivity for the hD_3 receptor vs hD_{2s} and $D_{4.4}$ receptors.

Intrinsic Activity and in Vivo Studies. An initial assessment of intrinsic activity was estimated based on the ability of the compounds of this study to bind to the D_2^{High} and D_2^{Low} affinity states of the D_2 receptor. A comparison of the results obtained with the six standards using the current methodology[40] agrees well with that reported by Lahti et al.[37] According to this method, a reliable prediction of intrinsic activity between the range of 100% and 10% can be made based on a compound's affinity ratio {i.e. [$K_i(D_2^{Low})/K_i(D_2^{High})$]}. Conversion of the AMB **12** (WAY 124486) to its chroman analogue (**49c**) resulted in very similar ratios. As indicated in Table 2, the bis(arylalkyl)amine derivative **52c** had the highest ratio (54) predicting high intrinsic activity. Compounds **54c** and **55c** had the lowest ratios (13 and 12, respectively) of the bis(arylalkyl)amine derivatives shown in Table 2. By replacing the phenyl group of **49c** by a hydrogen (i.e. **22c**) resulted in a high ratio again (52, Table 3).

As indicated in Table 5, tethering the phenyl ring from the basic nitrogen resulted in ratios of 42, 33, and 34 for the benzyl, phenylethyl, and phenylpropyl side chain derivatives, suggesting similar intrinsic activities. Interestingly, incorporating a four carbon spacer between the phenyl ring and nitrogen (i.e. *RS*-(±)-**32c**) resulted in one of the lower ratios [i.e. (K_i^L/K_i^H) = 7] observed in this study and parallels a similar observation made in Table 2 for compound **54c** [i.e. (K_i^L/K_i^H) = 13]; both compounds have four-atom tethers and an unsubstituted phenyl ring. *R*-(−)-**32c** was prepared to again verify that the active component in this class of 2-(aminomethyl)chromans resided in the *R* enantiomer, which was observed to have a ratio of 14. Restricting the benzyl side chain, exemplified by (±)-**48c**, resulted in another means for lowering the ratio [i.e. (K_i^L/K_i^H) = 5]. (−)-**48c** was predicted to have slightly higher intrinsic activity [i.e. (K_i^L/K_i^H) = 6] than its distomer, (+)-**48c** [i.e. (K_i^L/K_i^H) = 3] (Table 8). By substituting other ring systems for the phenyl ring of **35c** (Table 6), the ratio was observed to vary from as low as 3 (**39c**) to as high as 104 (**40c**). Though the thiophene analogue (**36c**) had similar affinity for the for the D_2^{High} receptor as **35c**, their ratios were quite different **35c** [i.e. (K_i^L/K_i^H) = 42 vs (K_i^L/K_i^H) = 5], which suggests **36c** to have

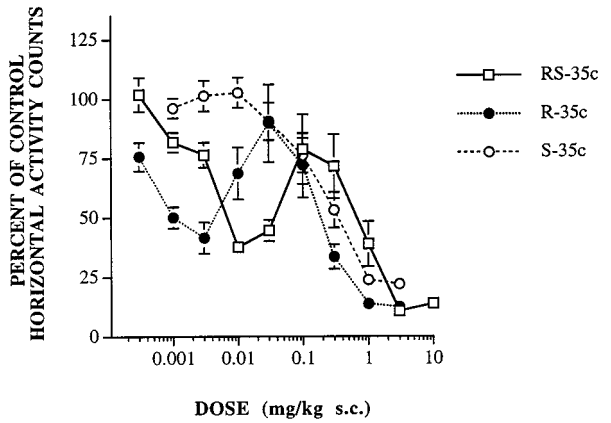


Figure 1. Dose−response curves for inhibition of spontaneous locomotor activity for *RS*-**35c**, *R*-**35c**, and *S*-**35c**.

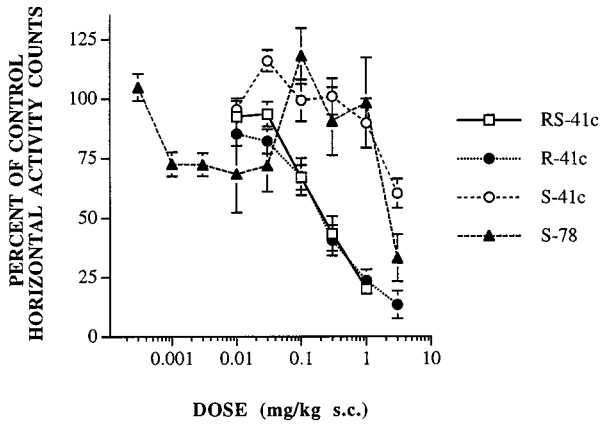


Figure 2. Dose−response curves for inhibition of spontaneous locomotor activity for *RS*-**41c**, *R*-**41c**, *S*-**41c**, and *S*-**78**.

a lower intrinsic activity. As indicated in Table 7, substituent effects on the benzyl side chain only played a minor role in varying the ratio (i.e. **44c**−**46c** vs **35c)**. Replacement of the hydroxy group of **35c** with a methanesulfonamide (i.e. **35f**) achieved a very low intrinsic activity [i.e. $(K_i^L/K_i^H) = 5$], verifying a similar trend observed in Table 3 (i.e. **49c** and **22c** vs **49f** and **22f**). Interestingly, when a chlorine was attached to the 6 position [i.e. *RS*-(±)-**41c**], a significant decrease in the predicted intrinsic activity ratio was observed when compared to **35c** [i.e. $(K_i^L/K_i^H) = 42$ vs $(K_i^L/K_i^H) = 7$]. As depicted in Table 8, the ratios of the enantiomers of *RS*-(±)-**35c** predicted that the eutomer [*R*-(−)-**35c**] to have slightly greater intrinsic activity than the distomer [*S*-(+)-**35c**] [i.e. $(K_i^L/K_i^H) = 16$ vs $(K_i^L/K_i^H) = 9$].

Further in vivo neurochemical and behavioral evaluations were performed on *RS*-(±)-**35c**, *R*-(−)-**35c**, *S*-(+)-**35c**, *RS*-(±)-**41c**, *R*-(−)-**41c**, *S*-(+)-**41c** (±)-**48c**, (−)-**48c**, (+)-**48c**, and *S*-(−)-**78**. *R*-(−)-**35c** inhibited dopamine synthesis (Table 9), indicating in vivo presynaptic dopamine D_2 agonism. All compounds, except *S*-(+)-**41c** and (+)-**48c**, produced significant reductions in locomotor activity (LMA) (Figures 1−3; Table 9). These actions are most readily explained by either a presynaptic agonist or postsynaptic antagonist effect of each active compound on dopamine D_2 receptors in vivo.[41] With respect to their racemates, potencies for the hypolocomotor effects of *R*-(−)-**35c**, *R*-(−)-**41c,** and (−)-**48c** were shifted to the left or remained the same. No significant effects were observed over the same dose range for *S*-(+)-**35c**, *S*-(+)-**41c**, and (+)-**48c**. These results confirm that *R*-(−)-**35c**, *R*-(−)-**41c**, and (−)-**48c** are recognized as the eutomers in vivo.

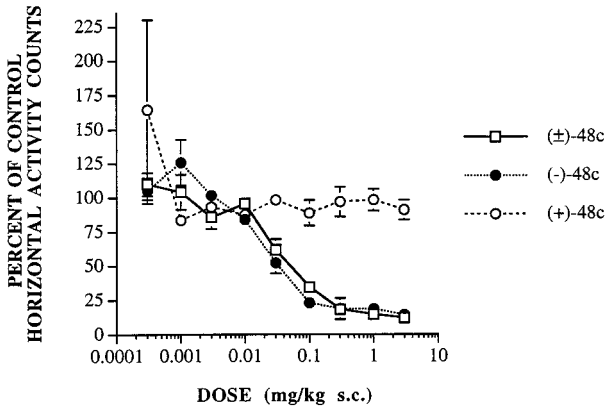
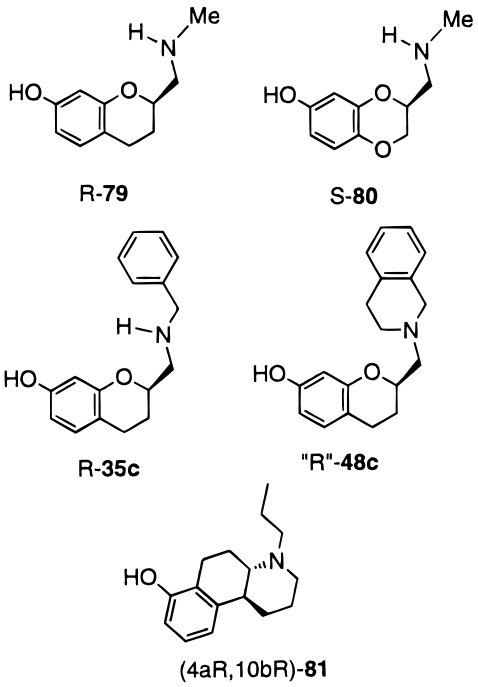


Figure 3. Dose−response curves for inhibition of spontaneous locomotor activity for *RS*-**48c**, (+)-**48c**, and (−)-**48c**.

Evidence for postsynaptic receptor stimulation was seen in the locomotor studies as the dose−response curves for *RS*-(±)-**35c**, *R*-(−)-**35c**, and *S*-(−)-**78** are U-shaped with low doses, presumably stimulating presynaptic receptors, thereby reducing locomotor activity, and at higher doses, presumably stimulating postsynaptic receptors, having less of an effect. Since these three agents are also known to possess D_3 affinity (Table 9), and since the D_3 agonist PD 128907 has been reported to produce hypolocomotor activity at low doses and hyperlocomotor activity at high doses,[42,43] a potential role for D_3 receptors in this response cannot be excluded. The decreased locomotor activity at the highest doses is not clearly understood but could be due to factors such as excessive autoreceptor agonism, postsynaptic dopamine receptor antagonism and/or potential sedative properties of these agents. *RS*-(±)-**41c**, *R*-(−)-**41c**, (±)-**48c**, and (−)-**48c** did not produce U-shaped dose−response curves, suggesting that these compounds do not have sufficient intrinsic activity to stimulate postsynaptic dopamine D_2 receptors. These data confirm the low estimated intrinsic activity ratios (K_i^L/K_i^H) of *RS*-(±)-**41c**, *R*-(−)-**41c**, (±)-**48c**, and (−)-**48c** from in vitro studies compared with the higher ratios of *RS*-(±)-**35c**, *R*-(−)-**35c,** and *S*-(−)-**78** (Table 8). Moreover, *R*-(−)-**35c** (Figure 1) and *S*-(−)-**78** (Figure 2) had similar LMA profiles as was estimated by their intrinsic activity ratios. As no compound produced sufficient postsynaptic agonism to result in hyperactivity, these compounds are presumably partial agonists at dopamine D_2 receptors. *RS*-(±)-**35c** and *R*-(−)-**35c** functioned as partial agonists at postsynaptic dopamine D_2 receptors in vivo showing both postsynaptic agonist and antagonist effects. *RS*-(±)-**35c** and *R*-(−)-**35c** reversed apomorphine-induced stereotypy and climbing behavior. *RS*-(±)-**35c** produced significant antagonism of apomorphine-induced stereotypy at 3 and 10 mg/kg sc and the ED_{50} vs apomorphine-induced climbing was 1.8 mg/kg sc. *R*-(−)-**35c** antagonized apomorphine-induced stereotypy with an ED_{50} of 1.5 mg/kg sc and apomorphine-induced climbing with an ED_{50} of 0.4 mg/kg sc. *RS*-(±)-**35c** and *R*-(−)-**35c** also stimulated postsynaptic dopamine D_2 receptors. *RS*-(±)-**35c** produced apomorphine-like stereotypy (0.3−10 mg/kg sc) in reserpinized mice whereas *R*-(−)-**35c** produced both stereotypy (ED_{50} = 0.3 mg/kg sc) and climbing (ED_{50} = 5.7 mg/kg sc) in reserpinized mice. *RS*-(±)-**35c** produced no significant effects in mice treated with a D_1 agonist, whereas *R*-(−)-**35c** induced significant stereotypy only (0.3−10 mg/kg sc). These results suggest that *RS*-(±)-**35c** and

Chart 3. Molecules Discussed in Molecular Modeling Studies



R-(−)-**35c** stimulate presynaptic dopamine D_2 receptors at low doses and stimulate supersensitive postsynaptic dopamine D_2 receptors at high doses.

Molecular Modeling Studies

The immense amount of interest in the D_2 receptor has led to a prolific amount of SAR directed at discerning the D_2 receptor pharmacophore and topography. The D_2 dopamine agonists which have been most helpful at formulating the D_2 receptor topography have been the dopamine-like and ergot-like structures.[44−50] To discern whether the 7-OH-AMCs had access to low energy conformations which adhered to the D_2 pharmacophore as represented by the McDermed model,[44] an initial simplified conformational analysis was performed on the methyl analogue of *R*-**35c** (i.e. *R*-**79**, Chart 3). A random search was performed using Sybyl on the unprotonated amine *R*-**79**, which led to the identification of thirty conformations of which 20 conformers were within 4 kcal of the global minimum. Eight of these conformations had a basic nitrogen to oxygen distance ranging between 6.4 and 7.8 Å, a criteria abided by potent D_2 agonists. However, only one of the eight conformers adhered to the nitrogen lone pair directionality requirements represented by the McDermed model. This conformation, depicted in Figure 4, was also observed to be the global minimum and was discerned as the most plausible D_2 receptor-bound conformation. A Grid Search in Sybyl about the aminomethyl side chain of *R*-**79** again identified this exact conformation. The aminomethyl side chain is in a pseudoequatorial position with the nitrogen atom located syn to the oxygen of the pyran ring. The N−O distance of 7.3 Å and the lone pair electrons of the nitrogen are nearly orthogonal to the plane of the phenyl ring, as stipulated by the McDermed D_2 model. Using the known D_2 agonist (4a*R*,10b*R*)-**81** as a template, with its *N*-propyl group oriented as previously rationalized and directed toward the large *N*-alkyl binding site in the D_2 receptor,[50b] an overlay of *R*-**79** is shown in Figure 4. A root-mean-square value of 0.3 was observed when the hydroxyl groups, basic nitrogens, and centroids were used as fitting points, and as revealed in Figure 4 the crucial pharmacophoric groups (7-OH and nitrogen) could be fitted over each other in extremely close proximity, with the lone pair electrons directed at a similar region of space. A random search performed on the corresponding benzodioxan *S*-**80** identified an analogous low-energy conformer to that found for the global minimum of *R*-**79**, which again fulfilled the McDermed model criteria very closely (Figure 5).

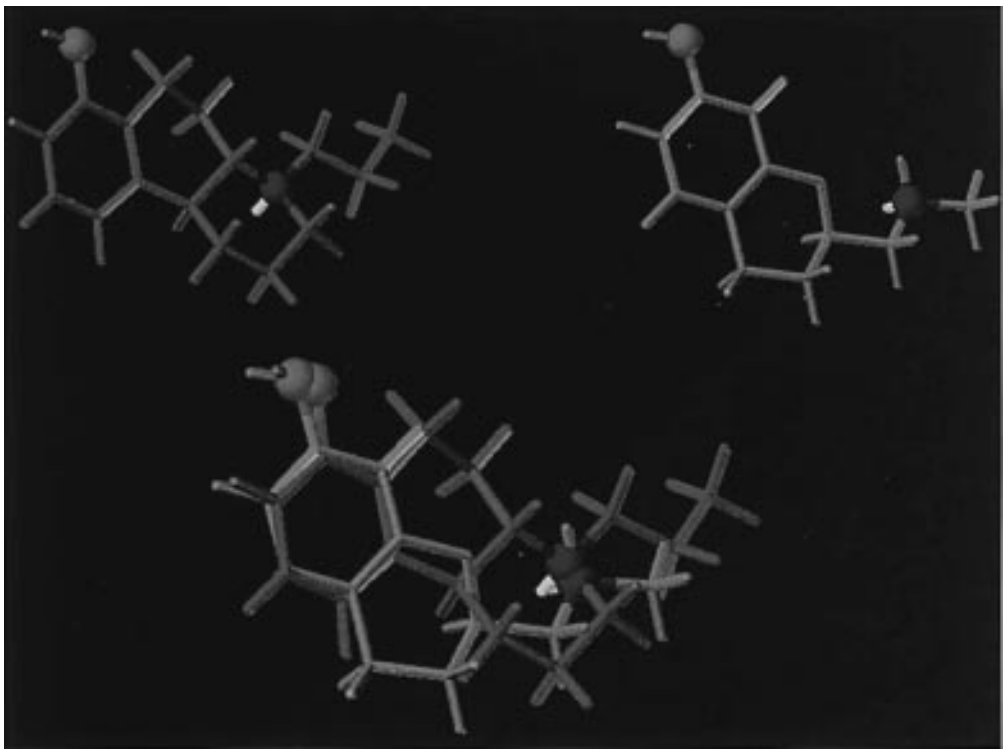


Figure 4. (4a*R*,10b*R*)-**81** (green) and *R*-**79** (blue) in their D_2 agonist "Pharm" conformations and superimposed.

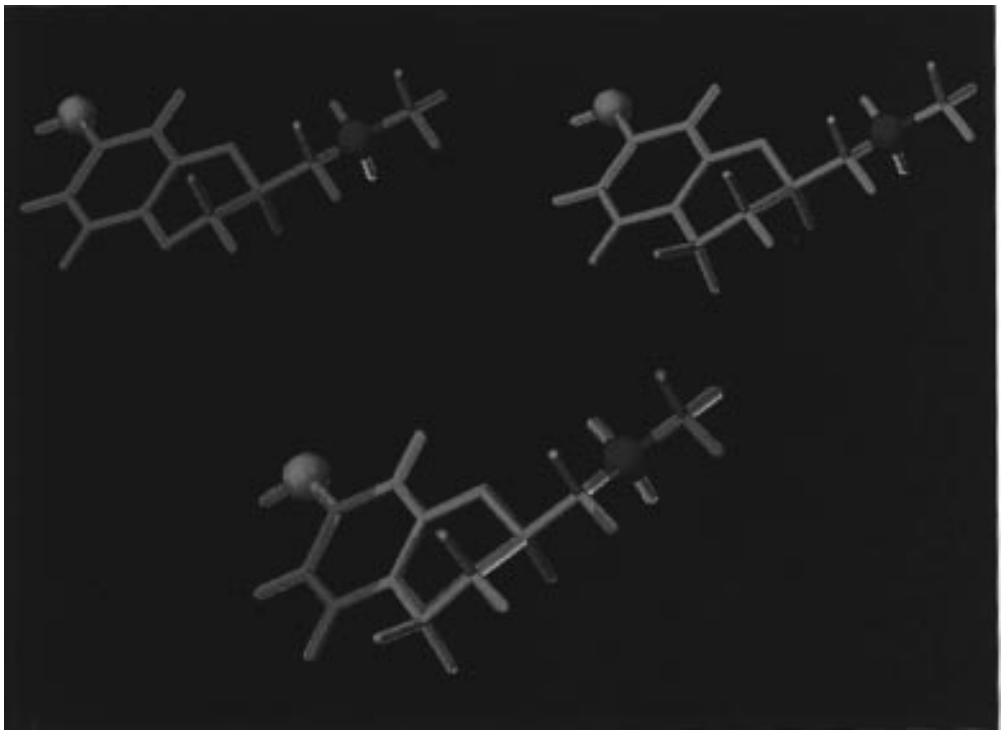


Figure 5. Superimposition of *S*-**80** (green) and *R*-**79** (blue) in their D_2 agonist "Pharm" conformations and superimposed.

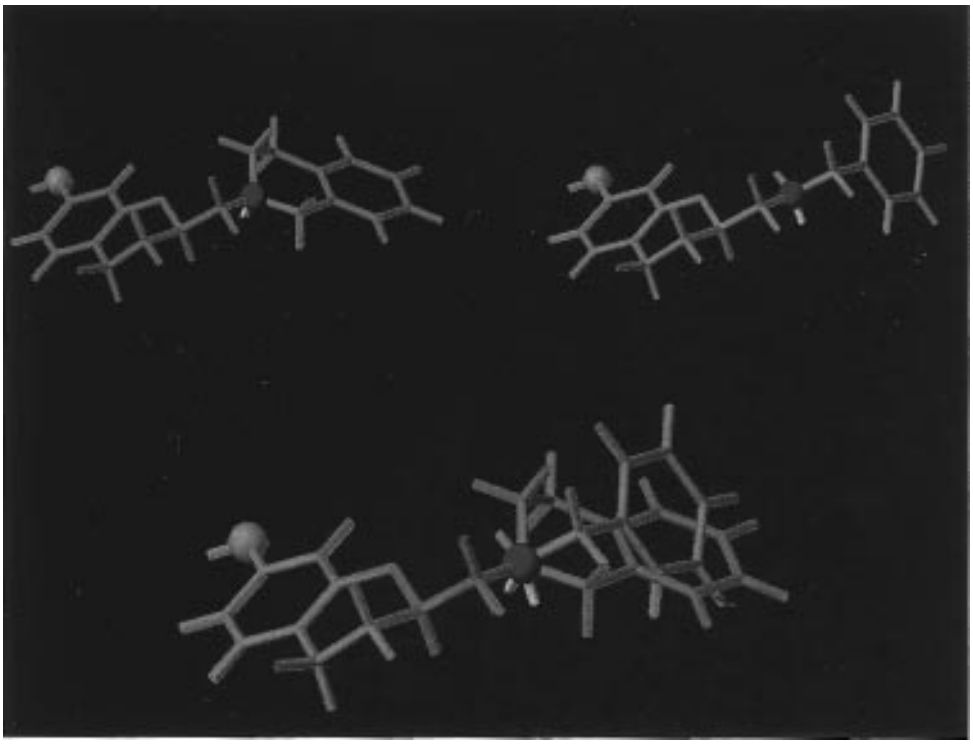


Figure 6. Superimposition of *R*-**48c** (green) and *R*-**35c** (blue) in their low-energy D_2 agonist "Pharm" conformations and superimposed.

A systematic search was performed on the benzyl side chain of *R*-(−)-**35c** and revealed no apparent conformational preference in terms of energy. Although conformational ambiguities appear to exist for the benzyl side chain, comparison of the high affinities for the D_2^{High} receptor of *R*-(−)-**35c** with that of (−)-**48c** (i.e. $K_i = 0.2$ nM vs 0.6 nM) strongly suggests that the phenyl ring of the benzyl and dihydroisoquinoline groups, as well as the chroman rings, can access similar spacial regions in the D_2 receptor cavity. Although the stereochemistry of (−)-**48c** was not unambiguously established, the *R*/levorotary enantiomers were consistently observed to be the eutomers in the AMC class. In light of this observation, modeling studies performed on (−)-**48c**, assumed, by analogy, the (−)-eutomer to be of the putative "*R*" configuration. Shown in Figure 6 is a low-energy pharmacophore conformer ("pharm") of *R*-(−)-**35c**, identified from a random search, overlayed onto a minimized "pharm" conformer of "*R*"-(−)-**48c**. This superimposition suggests that the benzylamine of *R*-(−)-**35c** and the dihydroisoquinoline group of "*R*"-(−)-**48c** may access similar spacial requirements in their receptor-bound conformations. Also worthmentioning, are the orientation of the side chains of *R*-**79**,

S-**80**, and "*R*"-**48c**, of which all are pointed toward the large *N*-alkyl binding site and not interfering with the sterically encumbered "propyl cleft" known to exist in the D_2 receptor.[50a]

To rationalize the 24-fold loss in affinity when the pyranyl oxygen was replaced by a methylene (i.e. **49c** vs **70**), the oxygen atom of the proposed receptor bound conformer of *R*-**79** was replaced by a methylene and subsequently minimized. Consequently two major differences between the chroman ring system and the tetralin ring system were revealed: (1) the critical nitrogen to oxygen distance increased from 7.3 to 7.8 Å and (2) this particular conformer was approximately 1 kcal/mol higher in energy than the global minimum. The combination of these two differences may be playing a significant role in D_2^{High} receptor affinity. Interestingly, Seeman reports the highest potencies for D_2 agonists were those compounds wherein the distance between the hydroxyl group and nitrogen atom was 7.3 Å or less.[45]

One of the major differences with the receptor-bound conformation of *R*-**79** and the postulated D_2 pharmacophore based on the McDermed model was the observation that the nitrogen was 0.92 Å below the plane of the phenyl ring. In general, all known rigid D_2 agonists were observed to have their nitrogen atoms nearly coplanar with the phenyl ring (approximately 0.2−0.6 Å from the plane of the aromatic ring).[45] Though the side chain of *R*-**79** containing the basic nitrogen is flexible, any conformations involving the nitrogen adjusting to a position closer to the plane of the phenyl ring also required a large amount of energy. Since it is known that the D_2 receptor can tolerate a range of N−O distances (preferably 7.3 Å or less), it is not unreasonable to assume that it may also tolerate a range of distances from the plane of the aromatic ring as well. Our results suggests that the previously proposed positional criteria of the phenyl ring with respect to the basic nitrogen may simply be a consequence of having the D_2 pharmacophoric elements deduced based on rigid dopamine-like structure which utilized the phenethylamine scaffold. As such, certain topographical criteria of the currently known D_2 models may need to be expanded to incorporate structures which no longer embrace the phenethylamine backbone. Apparently, structures exploiting the 7-OH-AMC and 7-OH-AMB moieties exemplify that this particular characteristic does not need to be adhered to for the pharmacophoric groups to be recognized by the D_2 receptor.

Interestingly, our proposed D_2 receptor-bound conformation of the 7-OH-AMC and 7-OH-AMB moieties are related to Hibert's putative $5HT_{1A}$ pharmacophore model,[51] with respect to the phenyl rings and basic nitrogens. The 7-OH-AMC and 7-OH-AMB moieties access the D_2^{High} and 5-HT_{1A} pharmacophoric elements simultaneously through the global minimum of the AMC and AMB moieties. In fact, recently 2-(aminomethyl)chroman derivatives have been reported in the patent literature to have 5-HT_{1A} and D_2 activity.[52] Worth mentioning is the observation that the AMCs in this study appear to have remarkably parallel SAR for the $5HT_{1A}$ receptor as another series of heterobicylic phenylpiperazines published by van Steen et al.[53] In both series the simple alkyl side chain affinities were observed to be maximum for the *n*-hexyl derivatives, with the benzyl side chain derivatives having the lowest affinities for the 5-HT_{1A} receptor. Also, Kuipers et al.[54] recently reported a series of N^4-substituted N^1-arylpiperazines which prefer apolar aromatic rings tethered to the N^1-arylpiperazine nucleus in order to bind with high affinity to both D_2 and 5-HT_{1A} receptors. Taken together, these observations strongly suggest that N^4-substituted N^1-arylpiperazines, as well as their respective side chains, may be capable of aligning and interacting in a similar fashion to AMCs and AMBs within both the D_2 and $5HT_{1A}$ receptor cavities.

Conclusion

We have identified a series of 7-OH-AMCs which have high affinity for the D_2^{High} receptor. Both the AMC and AMB moieties represent entirely novel scaffolds which have access to the D_2 agonist pharmacophore as represented by the McDermed D_2 model. Side chains attached to the 7-OH-2-AMC moiety had a secondary binding interaction which could influence affinity and selectivity at other receptors ($5HT_{1A}$, α_1, and D_2^{Low}). As revealed in this study, the bis(arylalkyl)amines were among some of the largest dopamine agonists reported to date to bind to the D_2^{High} receptor as depicted in the McDermed D_2 pharmacophore model. However, they were also found to be, in general, the least selective derivatives of this class of D_2 ligands. The most selective derivatives contained side chains with a one atom tether between the 7-OH-AMC moiety and another ring system. The most potent and selective member of this series for the D_2^{High} receptor was observed to be the benzyl derivative *RS*-(±)-**35c**. The *R* isomer [i.e. *R*-(−)-**35c**] was identified as the eutomer, having a 60-fold higher affinity than its distomer. Modeling studies identified low-energy conformations of the 7-OH-AMC and 7-OH-AMB moieties which closely adhered to the McDermed D_2 model. The combination of modeling studies and SAR studies strongly suggested a low energy conformation of *R*-(−)-**35c** which was at least topographically complementary to the D_2^{High} receptor. A conformationally restricted analogue of *R*-(−)-**35c** [i.e. (−)-**48c**] suggested that in both structures the aryl rings may exist in a similar spacial environment in their receptor-bound conformations. In vivo studies of *RS*-(±)-**35c** and *R*-(−)-**35c** are indicative of a highly potent agonist in the LMA and DOPA accumulation assay. Lower intrinsic activity could be achieved by replacing the benzyl side chain with other types of side chains with the caveat of attaining less selectivity. However, lower intrinsic activity could also be achieved with little loss in selectivity by either maintaining the benzyl side chain and attaching a chlorine atom at the 6 position of the AMC ring (i.e. **41c**) or by conformationally restricting the benzyl group as in **48c**.

The 7-OH-2-AMC and 7-OH-2-AMB moieties represent prototypic reference templates for the future design of a new generation of dopaminergic agents currently being investigated in our laboratories. These two novel templates no longer use the phenethyl scaffold (based on dopamine) but instead exploit the 2-methylchroman and 2-methylbenzodioxan moieties as scaffolds which can be used to access the D_2 agonist pharmacophore.

Experimental Section

Chemistry. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian Unity Plus 400, Varian

VXR-300, or Varian XL-200 instrument. Chemical shifts are reported in δ values (parts per million, ppm) relative to an internal standard of tetramethylsilane in $CDCl_3$ or DMSO-d_6. Infrared (IR) spectra were recorded on a Mattson Galaxy Series FT-IR 3000 spectrophotometer and are reported in reciprocal centimeters (cm^{-1}). Microanalyses were obtained on a Perkin-Elmer 2400 elemental analyzer. The mass spectra were determined on a LKB-9000S, Kratos MS 50, or Finnigan 8230 mass spectrometer. Optical rotation were performed on a Perkin-Elmer 241MC polarimeter. Analytical thin-layer chromatography (TLC) was carried out on precoated plates (silica gel, 60 F-254), and spots were visualized with UV light and stained either with an alcohol solution of phosphomolybdic acid or in an iodine chamber. Where analyses in the tables are indicated by symbols of the elements, analytical results obtained for those elements were ±0.4% of the theoretical values. Solvents and reagents were used as purchased.

7-Methoxychroman-2-carboxylic Acid Ethyl Ester (16a). A solution of **15a**[28] in AcOH (200 mL) was hydrogenated over 10% palladium on carbon at room temperature at 50 psi for 5 days. The reaction mixture was filtered through Celite, and the solvent was removed under vacuum. The product was crystallized and washed with 1:1 EtOAc−hexane to afford 20 g (72% yield) of product: mp 63−64 °C; MS (EI) *m/e* 236 (M^+). Anal. ($C_{13}H_{16}O_4$) C, H.

(7-Methoxychroman-2-yl)methanol (17a). To a solution of **16a** (20.0 g, 84.7 mmol) in THF (215 mL) was added a 2.0 M solution of $LiBH_4$ (100 mL, 0.20 mol) over 0.5 h. After 2 h the reaction was complete and the excess $LiBH_4$ was destroyed by the cautious addition of MeOH. The reaction mixture was then diluted with EtOAc and washed with water. The organic layer was separated and dried over $MgSO_4$ and the solvent removed under vacuum to afford 16 g (97% yield) of a clear oil: IR ($CDCl_3$) 3600, 3450, 2920, 1620, 1585, and 1510 cm^{-1}; MS (EI) *m/e* 194 (M^+); ^{1}H NMR ($CDCl_3$) δ 1.75−1.94 (2H, m), 2.08 (1H, bs), 2.67−2.84 (2H, m), 3.74−3.86 (2H, m), 3.76 (3H, s), 4.09 (1H, m), 6.40 (1H, d, J = 2.6 Hz), 6.46 (1H, dd, J =8.35, 2.64 Hz), 6.94 (1H, d, J = 8.35 Hz).

(7-(Benzyloxy)chroman-2-yl)methanol (17b). This compound was prepared from **16b**[28] by the procedure described to prepare **17a** in 98% yield as a clear oil: MS (EI) *m/e* 270 (M^+); ^{1}H NMR (DMSO-d_6) δ 1.57−1.67 (1H, m), 1.92−1.98 (1H, m), 2.48−2.73 (2H, m), 3.51−3.61 (2H, m), 4.74 (1H, t, J = 5.71 Hz), 5.02 (2H, s), 6.36 (1H, d, J = 2.64 Hz), 6.46 (1H, dd, J = 8.35, 2.64 Hz), 6.92 (1H, d, J = 8.35 Hz), 7.28−7.41 (5H, m).

2-(Bromomethyl)-7-methoxychroman (18a). To a solution of **17a** (3.14 g, 16.2 mmol) and CBr_4 (9.13 g, 28 mmol) in of CH_2Cl_2 (50 mL) was slowly added a solution of triphenylphosphine (7.21 g, 27.5 mmol) in CH_2Cl_2 (50 mL) at 0 °C. The reaction was allowed to warm to room temperature, stirred for 12 h, then poured into water (150 mL), extracted with CH_2Cl_2 (300 mL), dried over $MgSO_4$, and filtered and the solvent evaporated. Purification by chromatography (15% EtOAc−hexanes) afforded 3.2 g (75% yield) of a clear oil: IR (film) 2920, 1620, 1580, 1505, 1440, and 1160 cm^{-1}; MS (EI) *m/e* 256/258 (M^+); ^{1}H NMR ($CDCl_3$) δ 1.84−1.93 (1H, m), 2.11−2.18 (1H, m), 2.72−2.80 (2H, m), 3.52 (1H, dd, J = 10.54, 5.93 Hz), 3.59 (1H, dd, J = 10.54, 5.49 Hz), 3.75 (3H, s), 4.18−4.24 (1H, m), 6.40 (1H, d, J = 2.42 Hz), 6.45 (1H, dd, J = 8.35, 2.64 Hz), 6.94 (1H, d, J = 8.35 Hz).

7-(Benzyloxy)-2-(bromomethyl)chroman (18b). This compound was prepared similarly to **18a** starting with **17b** in 60% yield as a white solid, mp 76−78 °C. Anal. ($C_{17}H_{17}BrO_2$) C, H.

Toluene-4-sulfonic Acid, (7-Methoxychroman-2-yl)-methyl Ester (20a). To a solution of **17a** (23.0 g, 0.12 mol) in anhydrous pyridine (500 mL) was added *p*-toluenesulfonyl chloride (33.9 g, 0.78 mol). The reaction mixture was allowed to stir for 2 days under nitrogen at room temperature, and then the solution was concentrated under vacuum. The crude product was diluted with CH_2Cl_2 (1 L) and washed with 1 M H_2SO_4 (2 × 500 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (1 L) and brine (500 mL). The organic layer dried over $MgSO_4$, filtered, and concentrated under vacuum to afford 34 g (92% yield) of a white solid: mp 67−69 °C; MS (EI) *m/e* 348 (M^+); ^{1}H NMR (DMSO-d_6) δ 1.51−1.65 (1H, m), 1.84−1.90 (1H, m), 2.41 (3H, s), 2.53−2.70 (2H, m), 3.66 (3H, s), 4.16 (1H, m), 4.26 (1H, m), 6.18 (1H, d, J = 2.42 Hz), 6.38 (1H, dd, J = 8.35, 2.64 Hz), 6.90 (1H, d, J = 8.35 Hz), 7.48 (2H, d, J = 8.57 Hz), 7.82 (2H, d, J = 8.35 Hz). Anal. ($C_{18}H_{20}O_5S$).

Toluene-4-sulfonic Acid, (6-Chloro-7-methoxychroman-2-yl)methyl Ester (21a). A solution of **20a** (1.32 g, 3.79 mmol) and *N*-chlorosuccinimide (607 mg, 4.54 mmol) in anhydrous THF (12 mL) was allowed to stir at room temperature for 40 h and then poured into ether (200 mL). The organic layer was washed with water (100 mL), dried over $MgSO_4$, and filtered, and the solvent was removed under vacuum. Purification by chromatography (10% EtOAc−hexanes) afforded 1.37 g (94%) of a white solid. Recrystallization from EtOAc provided an analytical sample: mp 114−115 °C; ^{1}H NMR ($CDCl_3$) δ 1.76 (m, 1H), 1.93−1.99 (1H, m), 2.45 (3H, s), 2.64−2.73 (2H, m), 3.81 (3H, s), 4.15−4.21 (3H, m), 6.31 (1H, s), 6.99 (1H, s), 7.35 (2H, d, J = 8.06 Hz), 7.82 (2H, d, J = 8.35 Hz); MS (EI) *m/e* 382/384 (M^+). Anal. ($C_{18}H_{19}ClO_5S$) C, H.

Method A. 3-[[(7-Methoxychroman-2-yl)methyl]amino]propan-1-ol (22a). A mixture of **18a** (12.8 g, 49 mmol) and 1-amino-3-propanol (10 equiv) was heated to 100 °C for 2 h. The reaction mixture was poured into water (750 mL) and extracted with CH_2Cl_2 (3 × 500 mL). The organic layer was dried over $MgSO_4$ and filtered and the solvent evaporated to afford 11.3 g (92%) of desired product: ^{1}H NMR ($CDCl_3$) δ 1.80−1.96 (3H, m), 2.69−2.79 (2H, m), 2.89−3.00 (2H, m), 3.05 (2H, t, J = 5.60 Hz), 3.76 (3H, s), 4.22 (1H, m), 6.40 (1H, d, J = 2.42 Hz), 6.45 (1H, d, J = 8.24, 2.42 Hz), 6.92 (1H, d, J = 8.34 Hz): MS (EI) *m/e* 251 (M^+). The oxalate salt was prepared from MeOH, mp 180−190 °C. Anal. ($C_{14}H_{21}NO_3 \cdot C_2H_2O_4$) C, H, N.

Using the above procedure, compounds **23a**, **24a**, **25a**, **28a**, **29a**, **32a**, **33a**, **34a**, and **35a** were prepared in yields ranging from 90 to 99%, by replacing 1-amino-3-propanol with the appropriate amine. **22d** was prepared by replacing **18a** with 2-(bromomethyl)chroman.[56]

***N*-[(7-Methoxychroman-2-yl)methyl]-*N*-propylamine (23a)**: yield 98%; MS (EI) *m/e* 235 (M^+).

***N*-Butyl-*N*-[(7-methoxychroman-2-yl)methyl]amine oxalate (24a)**: yield 99%; mp 210−212 °C; MS (EI) *m/e* 249 (M^+). Anal. ($C_{15}H_{23}NO_2 \cdot C_2H_2O_4$) C, H, N.

***N*-[(7-Methoxychroman-2-yl)methyl]-*N*-pentylamine (25a)**: yield 90%; MS (EI) *m/e* 263 (M^+).

***N*-[(7-Methoxychroman-2-yl)methyl]-*N*-(2-methylpropyl)amine (28a)**: yield 91%; MS (EI) *m/e* 235 (M^+).

***N*-[(7-Methoxychroman-2-yl)methyl]-*N*-(3-methylbutyl)amine oxalate (29a)**: yield 97%; mp 221−222 °C; MS (EI) *m/e* 263 (M^+). Anal. ($C_{16}H_{25}NO_2 \cdot C_2H_2O_4 \cdot 0.25H_2O$) C, H, N.

***N*-[(7-Methoxychroman-2-yl)methyl]-*N*-(4-phenylbutyl)amine oxalate (32a)**: yield 90%; mp 217−218 °C. Anal. ($C_{21}H_{27}NO_2 \cdot C_2H_2O_4$) C, H, N.

***N*-[(7-Methoxychroman-2-yl)methyl]-*N*-(3-phenylpropyl)amine oxalate (33a)**: yield 99%; mp 219−220 °C; MS (EI) *m/e* 311 (M^+). Anal. ($C_{20}H_{25}NO_2 \cdot C_2H_2O_4 \cdot 0.25H_2O$) C, H, N.

***N*-[(7-Methoxychroman-2-yl)methyl]-*N*-phenethylamine oxalate (34a)**: yield 93%; mp 223−224 °C; MS (EI) *m/e* 297 (M^+). Anal. ($C_{19}H_{23}NO_2 \cdot C_2H_2O_4$) C, H, N.

***N*-Benzyl-*N*-[(7-methoxychroman-2-yl)methyl]amine oxalate (35a)**: yield 95%; mp 223−224 °C; MS (EI) *m/e* 283 (M^+). Anal. ($C_{18}H_{21}NO_2 \cdot C_2H_2O_4 \cdot 0.25H_2O$) C, H, N.

3-[(Chroman-2-ylmethyl)amino]propan-1-ol (22d): yield 37%; mp 173−174 °C. Anal. ($C_{13}H_{19}NO_2 \cdot HCl \cdot 0.25H_2O$) C, H, N.

3-[[[7-(Benzyloxy)chroman-2-yl]methyl]amino]propan-1-ol (22b). This compound was prepared from **18b** and 1-amino-3-propanol according to method A in 98% yield as a pale yellow solid, mp 54−55 °C; MS (EI) *m/e* 327 (M^+). Anal. ($C_{20}H_{25}NO_3$) C, H, N.

Using method A and replacing 3-amino-1-propanol with the appropriate amines afforded compounds **26b**, **27b**, **30b**, **31b**, **37b**, **38b**, and **39b**.

***N*-[[7-(Benzyloxy)chroman-2-yl]methyl]-*N*-hexylamine (26b)**: yield 100%; ^{1}H NMR (DMSO-d_6) δ 0.86 (3H, t, J = 3.4 Hz), 1.16−1.30 (6H, m), 1.42 (2H, m), 1.61 (1H, m),

1.98 (1H, m), 2.58−2.84 (6H, m), 3.34 (1H, bs, NH), 4.04 (1H, m), 5.75 (2H, s), 6.37 (1H, d, J = 2.64 Hz), 6.47 (1H, dd, J = 8.46, 2.42 Hz), 6.93 (1H, d, J = 8.35 Hz), 7.28−7.41 (5H, m); MS (EI) *m/e* 353 (M^+).

***N*-[[7-(Benzyloxy)chroman-2-yl]methyl]-*N*-isopropylamine (27b)**: yield 77%; MS (EI) *m/e* 311 (M^+).

***N*-[[7-(Benzyloxy)chroman-2-yl]methyl]-*N*-(2-pentyl)amine (30b)**: yield 60%; MS (EI) *m/e* 339 (M^+).

***N*-[[7-(Benzyloxy)chroman-2-yl]methyl]-*N*-cyclohexylamine (31b)**: yield 87%; MS (EI) 351 *m/e* (M^+).

***N*-[[7-(Benzyloxy)chroman-2-yl]methyl]-*N*-(furan-2-ylmethyl)amine (37b)**: yield 97%; ^{1}H NMR ($CDCl_3$) δ 1.74−1.98 (4H, m), 2.69−2.94 (2H, m), 3.86 (2H, s), 4.13 (1H, m), 5.01 (2H, s), 6.21 (1H, d, J = 3.2 Hz), 6.33 (1H, dd, J = 3.2, 1.9 Hz), 6.47−6.53 (2H, m), 6.93 (1H, d, J = 8.35 Hz), 7.31−7.44 (6H, m); MS (EI) *m/e* 349 (M^+).

***N*-[[7-(Benzyloxychroman-2-yl]methyl]-*N*-cyclohexylmethylamine (38b)**: yield 98%; ^{1}H NMR ($CDCl_3$) δ 1.51 (1H, m), 1.64−1.99 (10H, m), 2.48−2.57 (2H, m), 4.14 (1H, m), 5.01 (2H, s), 6.47 (1H, s), 6.51 (1H, d, J = 8.35, 2.64 Hz), 6.93 (1H, d, J = 8.35 Hz), 7.29−7.43 (5H, m). MS (FAB) *m/e* 366 (M + H^+).

***N*-[[7-(Benzyloxy)chroman-2-yl]methyl]-*N*-(naphthyl-1-ylmethyl)amine (39a)**: yield 67%; MS (EI) *m/e* 409 (M^+).

Method B. *N*-[(7-Methoxychroman-2-yl)methyl]-*N*-(4-pyridinyl)amine (40a). A solution of **20a** (2.0 g, 6.4 mmol) and 4-(aminomethyl)pyridine (1.29 g, 11.9 mmol) in anhydrous DMSO (30 mL) was heated at 100 °C for 6 h and then poured into water (200 mL) and extracted with CH_2Cl_2 (2 × 150 mL). The combined organic layers were dried over $MgSO_4$ and filtered and the solvent removed under vacuum. Purification by flash chromatography (5% MeOH−CH_2Cl_2) afforded 1.2 g (69% yield) of a thick oil: ^{1}H NMR (DMSO) δ 1.71−1.97 (2H, m), 2.70−2.89 (4H, m), 3.75 (3H, s), 3.92 (2H, s), 4.19 (1H, m), 6.38 (1H, d, J = 2.42 Hz), 6.44 (1H, dd, J = 8.35, 2.63 Hz), 6.93 (1H, d, J = 8.35 Hz), 7.34 (2H, d, J = 5.47 Hz), 8.56 (2H, d, J = 0.88 Hz); MS (EI) *m/e* 284 (M^+).

Replacing 4-(aminomethyl)pyridine with the appropriate amines afforded compounds **36a**, **42a**, **44a**, **45a**, **46a**, and **48a**.

***N*-[(7-Methoxychroman-2-yl)methyl]-*N*-(thiophend-2-ylmethyl)amine (36a)**: yield 71%; MS (EI) *m/e* 289 (M^+).

***N*-Benzyl-*N*-[(7-methoxychroman-2-yl)methyl]-*N*-methylamine (42a)**: yield 34%; MS (EI) *m/e* 297 (M^+).

***N*-(4-Fluorobenzyl)-*N*-[(7-methoxychroman-2-yl)methyl]-amine (44a)**: yield 41%; MS (EI) *m/e* 301 (M^+).

***N*-(4-Chlorobenzyl)-*N*-[(7-methoxychroman-2-yl)methyl]-amine (45a)**: yield 59%; ^{1}H NMR ($CDCl_3$) δ 1.75−1.83 (1H, m), 1.91−1.97 (1H, m), 2.61 (1H, s, NH), 2.65−2.91 (4H, m), 3.75 (3H, s), 3.85 (2H, s), 6.37 (1H, d, J = 2.64 Hz), 6.44 (1H, dd, J = 8.35, 2.64 Hz), 6.92 (1H, d, J = 8.35 Hz), 7.30 (4H, s); MS (EI) *m/e* 317/319 (M^+).

***N*-(4-Methoxybenzyl)-*N*-[(7-methoxychroman-2-yl)-methyl]amine (46a)**: yield 88%; mp 68−70 °C; MS (EI) *m/e* 313 (M^+). Anal. ($C_{19}H_{23}NO_3$) C, H, N.

(3,4-Dihydro-1*H*-isoquinolinyl)[(7-methoxychroman-2-yl)methyl]amine (48a): yield 89%; MS (EI) *m/e* 385 (M^+).

***N*-Benzyl-*N*-[(6-chloro-7-methoxychroman-2-yl)-methyl]amine (41a).** A solution of **21a** (1.97 g, 5.15 mmol) in dry DMSO (12 mL) containing benzylamine (3 equiv) was reacted according to method B to afford 1.48 g (90%) of a clear oil: ^{1}H NMR ($CDCl_3$) δ 1.72−1.80 (3H, m), 1.92−1.98 (1H, m), 2.62−2.92 (4H, m), 3.82 (3H, s), 3.87 (2H, s), 4.14 (1H, m), 6.41 (1H, s), 7.01 (1H, s), 7.25−7.38 (5H, m); MS (EI) *m/e* 317 (M^+); HRMS calcd for $C_{18}H_{20}NO_2Cl$ 317.118 26, observed 317.1101.

2-[(Benzylamino)methyl]-6-chlorochroman-7-ol (41c). Treatment of **41a** (1.41 g, 4.43 mmol) with HBr according to method D afforded 1.20 g (89%) of yellow solid: mp 151−152 °C. Anal. ($C_{17}H_{18}NO_2Cl$) C, H, N. The fumarate salt was prepared in 2-propanol: mp 216−217 °C; MS (EI) *m/e* 303/305 (M^+); ^{1}H NMR (DMSO-d_6) δ 1.60 (1H, m), 1.94−1.97 (1H, m), 2.58−2.65 (2H, m), 2.84−2.86 (2H, m), 3.91 (2H, s), 4.11 (1H, m), 6.38 (1H, s), 6.55 (2H, d, J = 2.42 Hz), 6.98 (1H, s), 7.26−7.41 (5H, m). Anal. ($C_{17}H18NO_2Cl·C_4H_4O_4$) C, H, N.

Method C. General Procedure for Mitsunobu Coupling. *N*-[(7-Methoxy-chroman-2-yl)methyl]-*N*-[3-(quinolin-7-yloxy)propyl]amine (50a). To a solution of **22a** (3.07 g, 13 mmol), 7-hydroxyquinoline (1.88 g, 13 mmol), and triphenylphosphine (3.67 g, 14 mmol) in anhydrous THF (50 mL) was slowly added a solution of DEAD (2.44 g, 14 mmol) in THF (10 mL). The reaction was allowed to stir for 3 h and then quenched with water, extracted with CH_2Cl_2 (150 mL), dried over $MgSO_4$, and filtered and the solvent removed under vacuum. Chromatography (2.5% MeOH−CH_2Cl_2) afforded 2.72 g of product (55% yield): MS (EI) *m/e* 378 (M^+). The maleate salt was prepared from THF, mp 132−134 °C. Anal. ($C_{23}H_{26}N_2O_3·2.0C_4H_4O_4·1.0H_2O$) C, H, N. The more polar azetidine byproduct (**61a**) was isolated and converted to its oxalate salt in THF: mp 176−177 °C. Anal. ($C_{14}H_{19}NO_2·C_2H_2O_4$) C, H, N.

Using method C and replacing 7-hydroxyquinoline with 3-nitrophenol, 4-chloro-3-nitrophenol, 2-methyl-3-nitrophenol, phenol, 4-methyl-3-nitrophenol, and 4-hydroxyindole afforded the corresponding bis(arylalkyl)amine derivatives.

***N*-[(7-Methoxychroman-2-yl)methyl]-*N*-[3-(3-nitrophenoxy)propyl]amine oxalate (49a-nitro)**: yield 52%; MS (EI) *m/e* 372 (M^+).

***N*-[3-(4-Chloro-3-nitrophenoxy)propyl]-*N*-[(7-methoxychroman-2-yl)methyl]amine oxalate (52a-nitro)**: yield 18%; mp 215−216 °C; MS (EI) *m/e* 406/408 (M^+). Anal. ($C_{20}H_{23}ClN_2O_5·C_2H_2O_4$) C, H, N.

***N*-[(7-Methoxychroman-2-yl)methyl]-*N*-[3-(2-methyl-3-nitrophenoxy)propyl]amine oxalate (53a-nitro)**: yield 40%; mp 221−223 °C; MS (EI) *m/e* 386 (M^+). Anal. ($C_{21}H_{26}N_2O_5·C_2H_2O_4·0.25H_2O$) C, H, N.

***N*-[(7-Methoxychroman-2-yl)methyl]-*N*-(3-phenoxypropyl)amine oxalate (54a)**: yield 63%; mp 204−205 °C; MS (EI) *m/e* 327 (M^+). Anal. ($C_{20}H_{25}NO_3·C_4H_4O_4$) C, H, N.

***N*-[(7-Methoxychroman-2-yl)methyl]-*N*-[3-(4-methyl-3-nitrophenoxy)propyl]amine oxalate (55a-nitro)**: yield 49%; MS (EI) *m/e* 386 (M^+).

***N*-[3-(1H-Indol-4-yloxy)propyl]-*N*-[(7-methoxychroman-2-yl)methyl]amine oxalate (56a)**: yield 67%; mp 206−207.5 °C. Anal. ($C_{22}H_{26}N_2O_3·C_4H_4O_4·0.33H_2O$) C, H, N.

***N*-[3-(Benzoxazol-6-yloxy)propyl]-*N*-[[(7-(benzyloxy)-chroman-2-yl]methyl]amine (57b).** This compound was prepared from **22b** and 6-hydroxybenzoxazole using method C in 95% yield and converted to the hydrogen oxalate salt, mp 127−128 °C. Anal. ($C_{27}H_{28}N_2O_4·1.5C_2H_2O_4·0.75H_2O$) C, H, N.

In an analogous fashion replacing 6-hydroxybenzoxazole with 5-hydroxybenzoxazole, 3-methyl-6-hydroxybenzisoxazole and isocytosine afforded compounds **58b** (78%), **59b** (77%), and **60b** (51%), respectively.

Method D. General Procedure for Demethylation. 2-[[[3-Quinolin-7-yloxy)propyl]amino]methyl]chroman-7-ol (50c). A solution of **50a** (2.19 g, 5.7 mmol) in 48% aqueous HBr (30 mL) was heated to reflux for 3 h. The reaction mixture was then allowed to cool to room temperature and basified with 1 N NaOH until pH 12. The basic reaction mixture was extracted with EtOAc (2 × 100 mL), dried over $MgSO_4$, and filtered and the solvent removed under vacuum. Chromatography (7% MeOH−CH_2Cl_2 containing 1% NH_4OH) afforded 1.34 g (63%) of product. The corresponding hydrogen oxalate salt was prepared in ethanol, mp 195.5−196.5 °C. Anal. ($C_{22}H_{24}N_2O_3·2C_2H_2O_4$) C, H, N.

Using this general procedure, phenols **23c**−**25c**, **28c**, **29c**, **32c**, ***R*-32c**, **33c**−**36c**, **40c**−**42c**, **44c**−**46c**, **48c**−**50c**, **52c**−**55c**, **70**, and **78** were prepared. See Table 10 for physical data.

Method E.[30] **2-[[[3-(1,2,3,4-Tetrahydroquinolin-5-yloxy)propyl]amino]methyl]chroman-7-ol (51c).** A mixture of **50c** (1.1 g, 3.0 mmol) and $NiCl_2·6H_2O$ (6 mmol) was dissolved in MeOH (30 mL), and $NaBH_4$ (0.14 mol) was added in portions with stirring under cooling for 30 min and then allowed to warm to room temperature for 0.5 h. After removal of MeOH, the black precipitate was dissolved in 1 N HCl, and the acidic solution was basified by the addition of concentrated NH_4OH and extracted with ether. The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed under vacuum. Chromatography (10% MeOH−CH_2Cl_2) afforded 350 mg (29%) of a brown oil: MS (EI) *m/e* 368 (M^+). The oxalate salt was prepared from MeOH, mp 136−139 °C. Anal. ($C_{22}H_{28}N_2O_3·2.0\ C_2H_2O_4·0.5H_2O$) C, H, N.

Method F. 2-[[[3-[(3-Methylbenzo[*d*]isoxazol-6-yl)oxy]-propyl]amino]methyl]chroman-7-ol (59c). A solution of

Table 10. Physical Data

compd	formula[a]	mp, °C	recyr solvent	method	% yield[b]
22a	$C_{14}H_{21}NO_3 \cdot C_2H_2O_4$	180−190	MeOH	A	92
22c	$C_{13}H_{19}NO_3 \cdot C_2H_2O_4$	163−165	MeOH	F	71
22d	$C_{13}H_{19}NO_2 \cdot HCl$[e]	173−174	Et_2O/EtOH	A	37
22f	$C_{14}H_{22}N_2O_4S \cdot C_2H_2O_4$	164−165	IPA	A	63
23c	$C_{13}H_{19}NO_2 \cdot 0.5C_2H_2O_4$	216−219	THF	D	25
24c	$C_{14}H_{21}NO_2 \cdot C_2H_2O_4$[c]	175−178	THF	D	55
25c	$C_{15}H_{23}NO_2 \cdot C_2H_2O_4$	169−170	THF	D	39
26c	$C_{16}H_{25}NO_2 \cdot C_2H_2O_4$	171−173	IPA	F	81
27c	$C_{13}H_{19}NO_2 \cdot C_2H_2O_4$	195−196	IPA	F	63
28c	$C_{14}H_{21}NO_2 \cdot C_2H_2O_4$	158−160	IPA	D	48
29c	$C_{15}H_{23}NO_2 \cdot C_2H_2O_4$[e]	185−186	IPA	D	66
30c	$C_{15}H_{23}NO_2 \cdot 0.5C_2H_2O_4$[d]	165−166	IPA	F	67
31c	$C_{16}H_{22}NO_2 \cdot C_2H_2O_4$	190−191	IPA	F	81
32c	$C_{20}H_{25}NO_2 \cdot 0.5C_2H_2O_4$	227−228	IPA	D	47
***R*−32c**	$C_{20}H_{25}NO_2 \cdot C_4H_4O_4$	148−149	IPA	D	32
33c	$C_{19}H_{23}NO_2 \cdot 0.5C_2H_2O_4$[d]	270−290 dec	IPA	D	61
34c	$C_{18}H_{21}NO_2 \cdot C_2H_2O_4$[e]	194−195	IPA	D	46
35c	$C_{17}H_{19}NO_2 \cdot C_2H_2O_4$[c]	176−177	IPA	D	33
***R*-35c**	$C_{17}H_{19}NO_2 \cdot C_2H_2O_4$	212−213	THF	K	52
***S*-35c**	$C_{17}H_{19}NO_2 \cdot C_2H_2O_4$	212−213	THF	K	87
35d	$C_{17}H_{19}NO \cdot C_2H_2O_4$	231.5−232.5	THF	J	31
35f	$C_{19}H_{24}N_2O_3S \cdot C_2H_2O_4$	247−248.5	THF	B	34
36c	$C_{15}H_{15}NO_4S \cdot C_2H_2O_4$[h]	203−205	THF	D	47
37c	$C_{15}H_{17}NO_3 \cdot C_2H_2O_4$[g]	169−170	IPA	F	47
38c	$C_{17}H_{25}NO_2 \cdot C_2H_2O_4$	160−161	IPA	F	50
39c	$C_{21}H_{21}NO_2 \cdot C_2H_2O_4$	113−114	IPA	F	41
40c	$C_{16}H_{18}N_2O_6 \cdot C_2H_2O_4$[e]	210−211	IPA	D	42
41c	$C_{17}H_{18}NO_2Cl \cdot C_4H_4O_4$	216−217	IPA	D	89
***R*-41c**	$C_{17}H_{18}NO_2Cl \cdot C_4H_4O_4$	214−215	IPA	K	87
***S*-41c**	$C_{17}H_{18}NO_2Cl \cdot C_4H_4O_4$	211−212.5	IPA	K	87
42c	$C_{18}H_{21}NO_2 \cdot C_2H_2O_4$	179−180	THF	D	86
43d	$C_{17}H_{18}NOF \cdot C_2H_2O_4$	231−232	THF	J	29
44c	$C_{17}H_{18}NF \cdot C_2H_2O_4$	165−166	IPA	D	54
45c	$C_{17}H_{18}NO_2Cl \cdot C_2H_2O_4$	179−180	IPA	D	34
46c	$C_{18}H_{21}NO_3 \cdot C_2H_2O_4$[e]	188−189	IPA	D	35
47f	$C_{19}H_{24}N_2O_3S \cdot C_2H_2O_4$	247−248.5	THF	B	33
48c	$C_{19}H_{21}NO_2 \cdot C_2H_2O_4$	177−178.5	EtOH	D	83
(−)-48c	$C_{19}H_{21}NO_2 \cdot C_2H_2O_4$[e]	198−199	EtOH	K	87
(+)-48c	$C_{19}H_{21}NO_2 \cdot C_2H_2O_4$[e]	195−196	EtOH	K	85
49a	$C_{20}H_{26}N_2O_3 \cdot 2HCl$	214−216	EtOH	F	75
49c	$C_{19}H_{24}N_2O_3 \cdot 2.0HCl$	163−170	EtOH	D	66
49d	$C_{19}H_{24}N_2O_2 \cdot C_4H_4O_4$[e]	136−137	IPA	F	91
49f	$C_{20}H_{27}N_3O_4S \cdot 2.0C_2H_2O_4$[c]	183−185	THF	G	70
50c	$C_{22}H_{24}N_2O_3 \cdot 2.0C_2H_2O_4$	195.5−196.5	EtOH	D	63
51c	$C_{22}H_{28}N_2O_3 \cdot 2.0C_2H_2O_4$[c]	136−139	MeOH	E	29
52a	$C_{19}H_{23}N_2O_3Cl \cdot C_4H_4O_4$	219−220	THF	G	87
52c	$C_{20}H_{25}N_2O_3Cl \cdot C_4H_4O_4$[f]	153−154	THF	D	72
53c	$C_{20}H_{26}N_2O_3 \cdot C_2H_2O_4$[c]	196−198	MeOH	D	46
54c	$C_{19}H_{23}NO_3 \cdot C_2H_2O_4$[c]	165−166	MeOH	D	52
55c	$C_{20}H_{23}N_2O_3 \cdot 2.0C_2H_2O_4$[f]	186−187	MeOH	D	38
56c	$C_{21}H_{24}N_2O_3 \cdot C_2H_2O_4$[f]	199−201	THF	H	39
57c	$C_{20}H_{22}N_2O_4 \cdot C_2H_2O_4$[c]	193−195	IPA	F	66
58c	$C_{20}H_{22}N_2O_4 \cdot C_2H_2O_4$[e]	162−175	IPA	F	48
59c	$C_{21}H_{24}N_2O_4 \cdot C_2H_2O_4$	233−235	MeOH	F	69
60c	$C_{17}H_{22}N_4O_3 \cdot 1.5C_2H_2O_4$[c]	193−196	MeOH	F	63
61a	$C_{14}H_{19}NO_2 \cdot C_2H_2O_4$	176−177	THF	C	26
70	$C_{20}H_{26}N_2O_2 \cdot C_2H_2O_4$	211−212	MeOH	D	62
S-78	$C_{16}H_{17}NO_3 \cdot C_2H_2O_4$	209−219	IPA	D	95

[a] $C_2H_2O_4$ and $C_4H_4O_4$ represent oxalic acid and fumaric acid, respectively. All new compounds analyzed correctly (±0.4%) for C, H, N. [b] See the Experimental Section. [c] Hemihydrate. [d] Hydrate. [e] Quarterhydrate. [f] $0.33H_2O$. [g] $0.75H_2O$. [h] $0.3C_4H_8O$.

59b (2.72 g, 5.9 mmol) in MeOH (120 mL) containing 10% palladium on carbon (530 mg) was hydrogenated at 50 psi for 12 h. The mixture was filtered through Celite and washed with MeOH, and the solvent was evaporated. Chromatography (3% MeOH/CH_2Cl_2) afforded 1.5 g (69%) of a tan foam. The oxalate was prepared from MeOH to afford 1.23 g of an off-white solid: mp 233−235 °C. Anal. ($C_{21}H_{24}N_2O_4 \cdot C_2H_2O_4$) C, H, N.

Using this procedure phenols **22c**, **26c**, **27c**, **30c**, **31c**, **37c**−**39c**, **49a**, **49d**, and **57c**−**60c** were prepared. See Table 10 for physical data.

Method G. 2-Chloro-5-[3-[(7-methoxychroman-2-yl)-methyl]amino]propoxy]phenylamine (52a). To a mixture of [3-(4-chloro-3-nitro-phenoxy)propyl](7-methoxychroman-2-yl)methyl]amine (**52a**-nitro) (990 mg, 2.43 mmol) and hydrazine (156 mg, 4.87 mmol) in EtOH at 5 °C was added Raney nickel (400 mg). After 0.5 h another portion of Raney nickel (300 mg) was added, and the reaction was heated to reflux for 1 h. The catalyst was filtered and the solvent removed to afford 800 mg (87%) of the title compound. The oxalate salt was prepared in THF, mp 219−220 °C. Anal. ($C_{20}H_{25}N_2O_3Cl \cdot C_2H_2O_4$) C, H, N.

Compounds **49a**, **53a**, and **55a** were prepared in a similar fashion from their respective nitro derivatives.

5-[3-[[(7-Methoxychroman-2-yl)methyl]amino]propoxy]-phenylamine oxalate (**49a**): yield 71%; mp 214−216 °C. Anal. ($C_{20}H_{26}N_2O_3 \cdot 2.0HCl$) C, H, N.

5-[3-[[(7-Methoxychroman-2-yl)methyl]amino]propoxy]-2-methylphenylamine (**53a**): yield 75%.

5-[3-[[(7-Methoxychroman-2-yl)methyl]amino]propoxy]-4-methylphenylamine oxalate (**55a**): yield 65%; mp 209−

213 °C; MS (EI) *m/e* 356 (M^+). Anal. ($C_{21}H_{28}N_2O_3 \cdot C_2H_2O_4 \cdot 0.25H_2O$) C, H, N.

Method H. 2-[[[3-(1*H*-Indol-4-yloxy)propyl]amino]-methyl]chroman-7-ol (56c). To a solution of diphenylphosphine in anhydrous THF (25 mL) at 5 °C was added *n*-butyllithium (3.5 mL, 2.5 M). After 10 min a solution of **56a** in THF (10 mL) was added, and the mixture was allowed to stir for 2.5 days. The reaction was quenched with water and poured into ether (100 mL). The organic layer was separated and dried over $MgSO_4$ and the solvent evaporated under vacuum. Chromatography (5% MeOH−CH_2Cl_2 containing 1% NH_4OH) afforded 280 mg (39.1%) a white foam. The oxalate salt was prepared from THF, mp 199−201 °C. Anal. ($C_{21}H_{24}N_2O_3 \cdot C_2H_2O_4 \cdot 0.33H_2O$) C, H, N.

7-Amino-4-oxo-4*H*-1-chromene-2-carboxylic Acid Ethyl Ester (15e). A mixture of **14g**[31] (24.1 g, 0.125 mol) and diethyl oxalate (47.5 g, 0.33 mol) in absolute EtOH (200 mL) was added to a solution of sodium ethoxide (14 g sodium in 300 mL absolute EtOH). The reaction was heated to reflux for 2 h, allowed to cool to room temperature, and then poured into water (500 mL) and CH_2Cl_2 (1500 mL). The aqueous layer was made slightly acidic using 6 N HCl, the organic layer was separated, and the aqueous layer was washed again using CH_2Cl_2 (500 mL). The combined organic layers were dried, and the solvent was removed under vacuum. The solid material (35.8 g) was dissolved in EtOH (350 mL), and concentrated HCl (6 mL) was added. The solution was heated to reflux for 1 day, removed from heat, and allowed to stand for 2 days. The orange solid was filtered to afford 17 g of product. The mother liquor was concentrated to afford another 4.94 g (76%) of desired product: ^{1}H NMR (DMSO-d_6) δ 1.32 (3H, t, J = 7.25 Hz), 4.34 (2H, q, J = 7.03 Hz), 6.50 (2H, bs), 6.53 (1H, d, J = 1.98 Hz), 6.69 (1H, dd, J = 8.78, 1.98 Hz), 6.71 (1H, s), 7.68 (1H, d, J = 8.78 Hz); MS (EI) *m/e* 233 (M^+).

7-Amino-4-chroman-2-carboxylic Acid Ethyl Ester (16e). To a solution of **15e** (2.4 g, 10.3 mmol) in acetic acid (40 mL) was added 10% palladium on carbon, and the mixture was hydrogenated on a Parr hydrogenator at 50 psi for 5 days. The catalyst was filtered through Celite and the acetic acid removed under high vacuum. The crude product was chromatographed (30% EtOAc−hexanes) to afford 1.27 g (56%) of desired product as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.28 (3H, 3H, t, J = 7.14 Hz), 2.07−2.26 (2H, m), 2.59−2.74 (2H, m), 3.50 (2H, bs), 4.23 (1H, q, J = 7.03 Hz), 4.66 (1H, m), 6.25 (1H, dd, J = 8.02, 2.42 Hz), 6.28 (1H, d, J = 2.42 Hz), 6.79 (1H, d, J = 7.91 Hz); IR (film) 3400, 2930, 1750, and 1630 cm^{-1}; MS (EI) *m/e* 221 (M^+).

7-[(Methylsulfonyl)amino]chroman-2-carboxylic Acid Ethyl Ester (16f). To a solution of **16e** (2.5 g, 11.2 mmol) in CH_2Cl_2 (20 mL) containing pyridine (6 mL) at 5 °C was added methanesulfonyl chloride (1.3 g, 13.6 mmol). The reaction mixture was allowed to stir for 20 min then poured in water (80 mL) and washed with 1 N aqueous HCl (2 × 100 mL), followed by water (100 mL). The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed under vacuum. Purification by chromatography (30% EtOAc−hexanes) afforded 3.21 g (95%) of a clear oil: MS (EI) *m/e* 299 (M^+); IR (film) 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.29 (3H, t, J = 7.24 Hz), 2.15−2.27 (2H, m), 2.68−2.79 (2H, m), 2.96 (3H, s), 4.26 (2H, q, J = 7.25 Hz), 4.72 (1H, dd, J = 7.14, 3.52 Hz), 6.77−6.82 (2H, m), 6.98 (1H, d, J = 8.57 Hz).

(7-Aminochroman-2-yl)methanol (17e). To a solution of **16e** (1.47 g, 6.64 mmol) in THF (25 mL) at 0 °C was added 2.0 M $LiBH_4$ (7 mL), and the mixture was allowed to warm to room temperature. The reaction was quenched after 1.5 h by the cautious addition of MeOH (5 mL), and the reaction mixture was stirred for another 2 h. The reaction mixture was diluted with EtOAc (300 mL) and washed with water (2 × 60 mL). The aqueous layer was washed again with EtOAc (100 mL), the combined layers were dried over $MgSO_4$ and filtered, and the solvent was removed under vacuum. Purification by chromatography (50% EtOAc−hexane) afforded 892 mg (82%) of desired product as a white solid: mp 89−90 °C; ^{1}H NMR ($CDCl_3$) δ 1.73−1.95 (2H, m), 2.61−2.83 (3H, m), 3.72−3.84 (2H, m), 4.04−4.12 (1H, m), 6.18 (1H, d, J = 2.34 Hz), 6.24 (1H, dd, J = 8.06, 2.34), 6.83 (1H,d, J = 7.91). Anal. ($C_{10}H_{13}NO_2$) C, H, N.

***N*-[2-(Hydroxymethyl)chroman-7-yl]methanesulfonamide (17f).** To a solution of **16f** (3.2 g, 10.7 mmol) in anhydrous THF (30 mL) was added 2.0 M $LiBH_4$ (10.1 mL). The reaction mixture was allowed to stir at room temperature for 18 h then quenched by the slow addition of MeOH. After 2 h water was slowly added (100 mL) and the reaction mixture extracted with ether (2 × 100 mL). The organic layer was separated, dried over $MgSO_4$, and filtered and the solvent removed under vacuum to afford a clear oil: MS (EI) *m/e* 257 (M^+); ^{1}H NMR ($CDCl_3$) δ 1.77−1.99 (2H, m), 2.71−2.85 (2H, m), 3.00 (3H, s), 3.73−3.87 (2H, m), 4.10 (1H, m), 6.62−6.74 (2H, m), 7.00 (1H, J = 7.91 Hz).

Toluene-4-sulfonic Acid, [7-[(methylsulfonyl)amino]-chroman-2-yl]methyl Ester (20f). A solution of **17f** (2.1 g, 8.16 mmol) and *p*-toluenesulfonyl chloride (2.33 g, 12.2 mmol) in anhydrous pyridine (20 mL) was allowed to stir for 24 h and then poured into 1 N aqueous HCl (100 mL). The reaction was then extracted with CH_2Cl_2 (350 mL) and the organic layer washed with 1N HCl (100 mL) followed by water (100 mL). The organic layer was dried over $MgSO_4$ and filtered, and the solvent removed under vacuum to afford a solid. Trituration with ether (30 mL) afforded 2.87 g (85.5%) of a white solid: mp 170−171 °C; MS (EI) *m/e* 411 (M^+); ^{1}H NMR (DMSO-d_6) δ 1.60 (1H, m), 1.86 (1H, m), 2.42 (3H, s), 2.55−2.72 (2H, m), 2.92 (3H, s), 4.13−4.28 (3H, m), 6.60 (1H, d, J = 2.05 Hz), 6.68 (1H, dd, J = 8.20, 2.05 Hz), 6.97 (1H, d, J = 8.20 Hz), 7.48 (2H, d, J = 8.06 Hz), 7.81 (2H, d, J = 8.35 Hz), 9.58 (1H, s).

Methanesulfonic Acid, [7-[(methylsulfonyl)amino]-chroman-2-yl]methyl Ester (19f). To a solution of **17e** (810 mg, 4.96 mmol) in dry CH_2Cl_2 (20 mL) containing pyridine (4 equiv) at 0 °C was added methanesulfonyl chloride (1.42 g, 12.4 mmol), and the mixture was allowed to stir for 1.5 h while gradually warming to room temperature. The reaction mixture was poured into 1 N HCl (100 mL) and extracted with CH_2Cl_2 (2 × 100 mL). The organic layer was washed with 1 N HCl (50 mL) and water (50 mL), dried over $MgSO_4$, and filtered, and the solvent was removed under vacuum. Purification by chromatography (50% EtOAc−hexanes) afforded 1.48 g (90%) of desired product as a white foam: IR (film) 3290, 3050, 2950, 1630, and 1600 cm^{-1}; MS (EI) *m/e* 335 (M^+); ^{1}H NMR ($CDCl_3$) δ 1.82−1.94 (2H, m), 2.03−2.08 (2H, m), 2.79−2.86 (2H, m), 3.00 (3H, s), 3.12 (3H, s), 4.29−4.45 (3H, m), 6.64 (1H, bs), 6.72−6.75 (3H, m), 7.02 (1H, d, J = 8.56 Hz).

Method I. *N*-[2-[[[3-(3-Aminophenoxy)propyl]amino]-methyl]chroman-7-yl]methanesulfonamide (49f). A mixture of **19f** (128 mg, 0.38 mmol), 3-(3-nitrophenoxy)-1-aminopropane (374 mg, 1.91 mmol), K_2CO_3 (132 mg, 2.5 mmol), and 20 mg of NaI in dry DMF (20 mL) was heated to 80 °C for 16 h. The reaction mixture was poured into ether (150 mL), extracted with water (2 × 100 mL), washed with brine, dried over $MgSO_4$, and filtered, and the solvent was removed under vacuum. Chromatography (3% MeOH−CH_2Cl_2) afforded 68 mg of desired product [i.e. *N*-[2-[[[3-(3-nitrophenoxy)propyl]-amino]methyl]chroman-7-yl]methanesulfonamide] (41%): MS (EI) *m/e* 436 (M^+).

To a mixture of the above product (250 mg, 0.618 mmol) and Raney nickel (1 g) in EtOH (40 mL) was added hydrazine (1.5 g). The reaction mixture was heated to reflux for 1 h and allowed to cool to room temperature. The catalyst was filtered through Celite and the solvent removed under vacuum. Purification by chromatography (10% MeOH−CH_2Cl_2 containing 1% NH_4OH) afforded 175 mg (70%) of a foam. The oxalate salt was prepared from THF and triturated with MeOH: mp 183−185 °C; MS (EI) *m/e* 405 (M^+). Anal. ($C_{20}H_{27}N_3O_4S \cdot 2C_2H_2O_4 \cdot 0.5H_2O$) C, H, N.

***N*-[2-[[(3-Hydroxypropyl)amino]methyl]chroman-7-yl]-methanesulfonamide (22f).** This compound was prepared according to method A by reacting **19f** with 3-aminopropanol to afford the product in 62.8% yield. The oxalate salt was prepared from 2-propanol: mp 164−165 °C. Anal. ($C_{14}H_{22}N_2O_4S \cdot C_2H_2O_4$) C, H, N.

***N*-[2-[(Benzylamino)methyl]chroman-7-yl]methanesulfonamide (35f).** A mixture of **20f** (900 mg, 2.19 mmol), benzylamine (469 mg, 4.37 mmol), and triethylamine (221 mg, 2.19 mmol) was reacted according to method B to afford 496 mg (65%) of a clear thick oil. The oxalate salt was prepared

in THF: mp 232−233 °C; ^{1}H NMR (DMSO-d_6) δ 1.62−1.67 (1H, m), 1.97−2.01 (1H, m), 2.62−2.76 (2H, m), 2.92 (3H, s), 3.07−3.19 (2H, m), 4.19 (2H, s), 4.32 (1H, m), 6.68 (1H, dd, J = 8.13, 1.98 Hz), 6.74 (1H, d, J = 1.98 Hz), 7.01 (1H, d, J = 8.13 Hz), 7.37−7.47 (3H, m), 7.51−7.53 (2H, m). Anal. ($C_{18}H_{22}N_2SO_3 \cdot C_2H_2O_4$) C, H, N..

***N*-[2-[[(4-Methylbenzyl)amino]methyl]chroman-7-yl]-methanesulfonamide (47f).** Utilizing **20f** and 4-methylbenzylamine according to method B afforded **47f**. The oxalate salt was prepared in THF: mp 247−248.5 °C. Anal. ($C_{19}H_{24}N_2O_3S \cdot C_2H_2O_4$) C, H, N.

7-Methoxy-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylic Acid Ethyl Ester (63). To a solution of **62** (25 g, 0.142 mol) in anhydrous THF (300 mL) was added NaH (60% oil dispersion, 21 g, 0.525 mol), and the mixture was heated to reflux for 2.5 h. The reaction was quenched with AcOH (35 mL) and allowed to stir overnight at room temperature. The solvent was removed, and benzene was added and evaporated to remove any remaining AcOH. The residue was partitioned between EtOAc (300 mL) and water (300 mL). The aqueous layer was washed with EtOAc (3 × 400 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$, and filtered, and the solvent was evaporated. Purification by chromatography (5% EtOAc−hexanes) afforded 33.3 g (94%) of product: mp 47−48 °C; MS (EI) *m/e* 248 (M^+); IR (KBr) 1750, 1740 cm^{-1}. Anal. ($C_{14}H_{16}O_4$) C, H.

7-Methoxy-1,2,3,4-tetrahydronaphthalene-2-carboxylic Acid Ethyl Ester (64). To a solution of **63** (10.0 g, 40 mmol) and triethylsilane (9.4 g, 80 mmol) in CH_2Cl_2 (50 mL) at 0 °C was slowly added trifluoroacetic acid (30 mL) over 0.5 h. The reaction mixture was allowed to stir for 16 h and then quenched with aqueous $NaHCO_3$ (200 mL). The mixture was extracted with EtOAc (3 × 100 mL), dried over $MgSO_4$, and filtered and the solvent removed under vacuum. Chromatography (2% EtOAc−hexanes) afforded 5.5 g (59%) of **64**[55] as a clear oil: IR (film) 2900, 1730, 1610, and 1500 cm^{-1}; MS (EI) *m/e* 234 (M^+).

(7-Methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)methanol (65). According to the procedure used to prepare **17**, ester **64** (5.92 g, 25.3 mmol) was reacted with 2 M $LiBH_4$ in THF (50 mL) to afford 4.6 g (95%) of the title compound as a clear oil: ^{1}H NMR ($CDCl_3$) δ 1.36−1.48 (1H, m), 1.90−2.04 (2H, m), 2.50 (1H, dd, J = 16.48, 10.54 Hz), 2.69−2.89 (3H, m), 3.63 (2H, dd, J = 6.37, 1.32 Hz), 3.77 (3H, s), 6.63 (1H, d, J = 8.35, 2.63 Hz), 6.99 (1H, d, J = 8.35 Hz); IR (film) 3300, 2910, 1610, 1502, and 1400 cm^{-1}; MS (EI) *m/e* 192 (M^+).

2-(Bromomethyl)-7-methoxy-1,2,3,4-tetrahydronaphthalene (66). The title compound was prepared from **64** according to the procedure used to prepared **18** and isolated in 95% yield as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.48−1.58 (1H, m), 2.01−2.18 (2H, m), 2.57 (1H, dd, J = 16.47, 10.54 Hz), 2.75−2.80 (2H, m), 2.96 (1H, dd, J = 16.36, 4.39 Hz), 3.44 (2H, d, J = 6.37, 2.20 Hz), 3.77 (3H, s), 6.63 (1H, d, J = 2.64 Hz), 6.70 (1H, dd, J = 8.46, 2.64 Hz), 7.00 (1H, d, J = 8.35 Hz) MS (EI) *m/e* 254, 256 (M^+).

3-[[(7-Methoxy-1,2,3,4-tetrahydronaphthalenyl-2-yl)-methyl]amino]propan-1-ol (67). This compound was prepared from **66** and 1-amino-3-propanol according to method A to afford 3.3 g (49%) of the title compound as an orange solid. The oxalate salt was prepared in MeOH: mp 165−170 °C. Anal. ($C_{15}H_{23}NO_2 \cdot 0.5C_2H_2O_4 \cdot 0.33H_2O$) C, H, N.

7-[[[3-(3-Aminophenoxy)propyl]amino]methyl]-5,6,7,8-tetrahydronaphthalen-2-ol (69). Alcohol **67** (2.9 g, 11.6 mmol) was coupled to 3-nitrophenol according to method C to afford 2.35 g (55%) of [(7-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)methyl]-[3-(3-nitrophenoxy)propyl]amine **(68)** as a yellow semisolid: MS (EI) *m/e* 370 (M^+). The more polar azetidine **71** (1.29 g, 48%) was also isolated; MS (EI) *m/e* 231 (M^+). The corresponding oxalate salt of **71** was prepared in MeOH as a white crystalline solid: mp 165−166 °C. Anal. ($C_{15}H_{21}NO \cdot C_2H_2O_4$) C, H, N.

Hydrogenation of **68** according to method F afforded the title compound in 78% yield, which was analyzed as its bisoxalate salt: mp 185−186 °C; MS (EI) *m/e* 340 (M^+). Anal. ($C_{21}H_{28}N_2O_2 \cdot 2C_2H_2O_4$) C, H, N.

7-[[[3-(3-Aminophenoxy)propyl]amino]methyl]-5,6,7,8-tetrahydronaphthalen-2-ol (70). Aniline **69** was treated with HBr according to method D to afford 1.1 g (62%) of **70** as an oil. The oxalate salt was prepared in MeOH, mp 211−212 °C. Anal. ($C_{20}H_{26}N_2O_2 \cdot C_2H_2O_4$) C, H, N.

(2*R*)-5-Methoxy-2-(oxiranylmethoxy)benzaldehyde (73). To a suspension of 60% NaH (2.4 g, 60.3 mmol) in anhydrous DMF (60 mL) at room temperature was slowly added a solution of **72** (7.34 g, 48.2 mmol) in DMF (5 mL). After 1 h (2*R*)-(−)-glycidyl 3-nitrobenzenesulfonate (10.0 g, 38.6 mmol) was added, and the solids were rinsed into the flask with another 5 mL of DMF. The reaction was heated to 70 °C and allowed to stir for 6 h. Upon cooling to ambient temperature, the reaction was poured into CH_2Cl_2 (400 mL) and washed consecutively with 2 N HCl (2 × 150 mL), saturated Na_2CO_3 (80 mL), and brine (80 mL). The solution was dried over $MgSO_4$ and filtered, and the solvent was removed under vacuum. Purification by chromatography (20−50% EtOAc−hexanes) afforded 3.18 g (32%) of a yellow oil: ^{1}H NMR ($CDCl_3$) δ 2.76 (1H, dd, J = 4.83, 2.64 Hz), 2.91 (1H, app t, J = 4.47 Hz), 3.34−3.39 (1H, m), 3.78 (3H, s), 3.98 (1H, dd, J = 11.20, 5.78 Hz), 4.32 (1H, dd, J = 11.13, 2.78 Hz), 6.94 (1H, dd, J = 8.93, 5.86 Hz), 7.10 (1H, dd, J = 9.00, 3.00 Hz), 7.28 (1H, d, J = 3.37 Hz), 10.46 (1H, s); MS (EI) *m/e* 208 (M^+); HRMS calcd for $C_{11}H_{12}O_4$ 208.073 560, observed 208.065 12.

((*S*)-7-Methoxy-2,3-dihydrobenzo[1,4]dioxin-2-yl)methanol (75). To a solution of **73** (3.2 g, 15.4 mmol) in CH_2Cl_2 (50 mL) at room temperature was added mCPBA (2.91 g, 16.9 mmol). After 1 h the solids were filtered, and the solvent was removed and dissolved in ether (80 mL). The solution was washed with sodium thiosulfite, followed by 50% aqueous Na_2CO_3 (2 × 100 mL), followed by brine (80 mL), dried over $MgSO_4$, and filtered. Evaporation of the solvent afforded 3 g of the formate ester (**74**) which was dissolved in methanol (80 mL), and 4 g of Na_2CO_3 was added. After 0.5 h the mixture was filtered and partitioned between CH_2Cl_2 (100 mL) and water (50 mL). The organic layer was dried over $MgSO_4$ and filtered, and the solvent was evaporated. Chromatography (20% EtOAc−hexanes) afforded 2.3 g (76%) of desired product as a clear oil: $[\alpha]^{25}_D$ −31.4° (c = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.13 (1H, bt, O*H*), 3.74 (3H, s), 3.78−3.95 (2H, m), 4.10−4.11 (1H, m), 4.21−4.31 (2H, m), 6.42 (1H, dd, J = 8.79. 2.93 Hz)), 6.48 (1H, d, J = 2.93 Hz), 6.78 (1H, d, J = 8.79 Hz); MS (EI) *m/e* 196 (M^+); HRMS calcd for $C_{10}H_{12}O_4$ 196.0356, observed 196.0650.

Toluene-4-sulfonic Acid, (7-Methoxy-2,3-dihydrobenzo-[1,4]dioxin-2(*S*)-yl)methyl Ester (76). A solution of **75** (2.27 g, 11.6 mmol) and tosyl chloride (4.59, 24.1 mmol) in dry pyridine (40 mL) at room temperature was allowed to stir for 4 h. The reaction was poured into 3 N aqueous HCl (250 mL) and extracted with CH_2Cl_2 (2 × 150 mL). The organic layer was washed with 3 N HCl (80 mL), followed by saturated aqueous $NaHCO_3$ (100 mL), dried over $MgSO_4$, and filtered and the solvent evaporated to afford a solid. Trituration with ether (70 mL) afforded 2.78 g (69%) of a white solid: mp 102−103 °C; $[\alpha]^{25}_D$ −3.98° (c = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.46 (3H, s), 3.72 (3H, s), 4.00 (1H, m), 4.15−4.23 (3H, m), 4.38 (1H, m), 6.35−6.42 (2H, m), 6.74 (1H, d, J = 8.79 Hz), 7.36 (2H, d, J = 8.06 Hz), 7.80 (2H, d, J = 8.20 Hz); MS (EI) *m/e* 301 (M^+); HRMS calcd for $C_{17}H_{18}O_6S$ 350.082 413, observed 350.078 93. Anal. ($C_{17}H_{18}O_6S$).

***N*-(*S*)-Benzyl-*N*-[(7-methoxy-2,3-dihydrobenzo[1,4]-dioxin-2-yl)methyl]amine (77).** A solution of **76** (2.76 g, 7.85 mmol) and benzylamine (3.36 g, 31.4 mmol) in dry DMSO (10 mL) was heated to 80 °C for 15 h. The reaction mixture was poured into a dilute solution of 10% $NaHCO_3$ (200 mL) and extracted with CH_2Cl_2 (2 × 200 mL). The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed under vacuum. Purification by chromatography (40% EtOAc/hexanes) afforded 2.05 g (92%) of a clear oil: $[\alpha]^{25}_D$ −36.92 ° (c = 1.01, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.86−2.95 (2H, m), 3.74 (3H, s), 3.86 (2H, m), 4.00 (1H, m), 4.22 (1H, d, J = 11.31, 2.20 Hz), 4.29 (1H, m), 6.42 (1H, d, J = 8.79, 2.86 Hz), 6.47 (1H, d, J = 2.86 Hz), 6.78 (1H, d, J = 8.79 Hz), 7.28 (1H, m), 7.34 (3H, app s); MS (EI) *m/e* 285 (M^+); HRMS calcd for $C_{17}H_{19}NO_3$ 285.136 494, observed 285.1328.

(*S*)-3-[(Benzylamino)methyl]-2,3-dihydrobenzo[1,4]-dioxin-7-ol (78). A mixture of **77** (1.90 g, 6.66 mmol) and aqueous HBr (35 mL) was reacted according to method D to

give a light yellow oil: $[\alpha]^{25}_D$ −47.5° (*c* = 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.79−2.87 (2H, m), 3.81−3.86 (2H, m), 3.94 (1H, d, *J* = 12.96 Hz), 4.13 (1H, dd, *J* = 11.20, 2.20 Hz), 4.25 (1H, m), 6.32 (1H, dd, *J* = 8.79, 2.86 Hz), 6.40 (1H, d, *J* = 2.86 Hz), 6.66 (1H, d, *J* = 8.79 Hz), 7.28−7.38 (5H, m), (3H, s); MS (EI) *m/e* 271 (M^+). The oxalate salt was prepared in 2-propanol: mp 209−210 °C; $[\alpha]^{25}_D$ −39.4° (*c* 1.00, DMSO). Anal. ($C_{16}H_{17}NO_3 \cdot C_2H_2O_4$).

(*R*)-2-(Hydroxymethyl)chroman-7-ol (*R*-17c). A solution of **16c**[29a] (1.5 g, 6.8 mmol) in THF (100 mL) was reacted with 2.0 M $LiBH_4$ as described above for **17a**. After 2 h the reaction was diluted with ether (50 mL), poured into a 1:1 solution of water/brine (100 mL), acidified to pH 2 with 2 N HCl, and then extracted with ether (2 × 150 mL). The organic layer was dried over $MgSO_4$ and the solvent removed under vacuum. Purification by chromotagraphy (50% EtOAc−hexanes) afforded 1.1 g (91%) of a white crystalline solid: mp 88−90 °C; MS(EI) *m/e* 180 (M^+); $[\alpha]^{25}_D$ −114.3° (*c* = 1.01, DMSO); ^{1}H NMR (DMSO-d_6) δ 1.53−1.63 (1H, m), 1.88−1.95 (1H, m), 2.63−2.69 (2H, m), 3.47−3.56 (2H, m), 3.86−3.92 (1H, m), 4.82 (1H, t, *J* = 5.7 Hz), 6.12 (1H, d, *J* = 2.42 Hz), 6.22 (1H, dd, *J* = 8.24, 2.42 Hz), 6.79 (1H, d, *J* = 8.13 Hz), 9.07 (1H, s). Anal. ($C_{10}H_{12}O_3$).

(*R*)-(−)-2-[(Benzylamino)methyl]chroman-7-ol [*R*-(−)-35c]. To a solution of *R*-(−)-**17c** (400 mg, 2.22 mmol) in anhydrous pyridine was added *p*-toluenesulfonyl chloride (444 mg, 2.33 mmol). The reaction mixture was stirred for 4 h at 5 °C then poured into 2 N HCl (50 mL) and extracted with CH_2Cl_2 (2 × 100 mL). The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed under vacuum. The product mixture was purified by flash chromatography (30% EtOAc−hexanes) to afford 697 mg of *R*-**20c** as a clear oil which ^{1}H NMR and mass spectroscopy [(EI) *m/e* 344 (M^+) and (EI) *m/e* 488 (M^+)] identified a 85:15 mixture of the desired tosylate and the ditosylate. The mixture was dissolved in anhydrous DMSO (10 mL) containing benzylamine (703 mg, 6.56 mmol). The reaction mixture was heated to 100 °C for 10 h whereby the reaction mixture was poured into water (50 mL) and extracted with EtOAc (2 × 150 mL). The organic layer dried over $MgSO_4$ and filtered, and the solvent was removed under vacuum. Purification by flash chromatography (3% MeOH−CH_2Cl_2) afforded 311 mg (52%) of a thick clear oil: $[\alpha]^{25}_D$ −110.0° (*c* = 1.04, $CHCl_3$). The free base was converted to the oxalate salt in THF: mp 213−214 °C; $[\alpha]^{25}_D$ −77.5° (*c* = 1.1, DMSO). The optical purity determined to be 99% ee using the chiral method described below in method K.

(*R*)-(−)-2-[[(4-Phenylbutyl)amino]methyl]chroman-7-ol [*R*-(−)-32c]. The title compound was prepared in 32% yield in a similar fashion as that described above for *R*-(−)-**35c** by replacing benzylamine with phenylbutylamine; $[\alpha]^{25}_D$ −98.0° (*c* = 1.4, $CHCl_3$, free base); MS (EI) *m/e* 311 (M^+). The fumarate salt was prepared from 2-propanol: mp 148−149 °C; $[\alpha]^{25}_D$ −62.5° (*c* = 1.0, DMSO). Anal. ($C_{20}H_{25}NO_2 \cdot C_4H_4O_4$) C, H, N.

(*R*)-(−)-2-[(Benzylamino)methyl]chroman-6-chloro-7-ol [*R*-(−)-41c]. To a solution of R-**20c** (930 mg) in THF (30 mL) was added *N*-chlorosuccinimide (375 mg) and the reaction allowed to stir at room temperature for 18 h. The reaction mixture was poured into water (100 mL) and extracted with CH_2Cl_2 (2 × 150 mL). The combined organic layers were dried over $MgSO_4$ and filtered, and the solvent was removed. Purification by chromatography (25% EtOAc−hexanes) afforded 677 mg of *R*-(−)-**21c** (contaminated with a small amount of dichlorinated product): MS (EI) *m/e* 368/370 (M^+); $[\alpha]^{25}_D$ −54.2° (*c* = 1.0, $CHCl_3$).

A solution of *R*-(−)-**21c** (638 mg, 1.73 mmol) and benzylamine (740 mg, 6.92 mmol) in dry DMSO (7 mL) was reacted according to method B to afford 363 mg (62%) of title product: mp 117.5−118.5 °C; $[\alpha]^{25}_D$ −123.4 (*c* = 1.0, $CHCl_3$).

Method J. *N*-Benzyl-*N*-(chroman-2-ylmethyl)amine (35d). To a suspension of chroman-2-ylmethylamine hydrochloride[56] (300 mg, 1.5 mmol) and K_2CO_3 (519 mg, 4.5 mmol) in dry DMF (5 mL) was added benzyl chloride (190 mg, 1.5 mmol), and the mixture was allowed to stir at 55 °C for 2 h. The reaction mixture was poured into water (25 mL) and extracted with ether (2 × 40 mL). The organic layer was separated, dried over $MgSO_4$, and filtered, and the solvent was evaporated. Purification by chromatography (5% MeOH−CH_2Cl_2) afforded 119 mg (31%) of product as a clear oil. The oxalate was prepared from THF: mp 231.5−232.5 °C. Anal. ($C_{17}H_{19}NO \cdot C_2H_2O_4$) C, H, N.

***N*-(4-Fluorobenzyl)-*N*-(chroman-2-ylmethyl)amine (43d).** Compound **43d** was prepared according to the above procedure (method J) using 4-fluorobenzyl chloride in 29% yield. The oxalate salt was prepared in THF: mp 231−232 °C. Anal. ($C_{17}H_{18}FNO \cdot C_2H_2O_4$) C, H, N.

3-[3-[(Chroman-2-ylmethyl)amino]propoxy]phenylamine (49d). Treatment of chroman-2-ylmethylamine hydrochloride[56] with 3-(nitrophenoxy)propyl bromide according to the above procedure (method J) gave [3-(3-nitrophenoxy)propyl](chroman-2-ylmethyl)amine, followed by hydrogenation according to method F afforded the title compound (Table 10). The fumarate salt was prepared in 2-propanol: mp 136−137 °C. Anal. ($C_{19}H_{24}N_2O_2 \cdot C_4H_4O_4 \cdot 0.25H_2O$) C, H, N.

Method K. Resolution of (+)-2-[(Benzylamino)methyl]-chroman-7-ol (35c). (±)-2-[(Benzylamino)methyl]chroman-7-ol (**35c**) (400 mg) was submitted to semipreparative HPLC containing a Chiralcel OJ column and eluted (10 mL/min, pressure 430 psi, detection at 280 nm) with a hexane/EtOH (1:1) mixture. The first peak at 8.7 min was collected to afford *R*-(−)-**35c** (103 mg) as a clear thick oil (99.0% ee): $[\alpha]^{25}_D$ −107° (*c* = 1.01, $CHCl_3$). The (−)-free base was treated with excess oxalic acid in THF to afford 118 mg of oxalate salt: mp 212−213 °C; $[\alpha]^{25}_D$ −76° (*c* = 1.03, DMSO). Anal. ($C_{17}H_{19}NO_2 \cdot C_2H_2O_4$) C, H, N. Optical purity observed to be 99.0% ee by HPLC (acetonitrile−1 M sodium perchlorate, 1:1, 0.5 mL/min, 280 nM). The second peak isolated with a retention time of 10.15 min was collected to afford the *S*-(+)-**35c** (174 mg) as a clear thick oil: $[\alpha]^{25}_D$ +104 ° (*c* = 1.15, $CHCl_3$). Optical purity observed to be 100% ee (acetonitrile−1 M $NaClO_4$, 1:1, 0.5 mL/min, 280 nM). The (+)-free base was treated with excess oxalic acid in THF to afford 175 mg of oxalate salt: mp 212−213 °C; $[\alpha]^{25}_D$ +82° (*c* = 1.0, DMSO). Anal. ($C_{17}H_{19}NO_2 \cdot C_2H_2O_4$) C, H, N.

Resolution of (+)-2-[(Benzylamino)methyl]-6-chloro-chroman-7-ol. *RS*-(±)-**41c** (731 mg) was resolved on a Chiralcel OJ column (10 mL/min, pressure 430 psi, detection at 290 nm) in a similar fashion as described for **35c** (method K) by collecting fractions from 40 separate runs using approximately 18 mg per injection to initially afford *R*-(−)-**41c** (322 mg, 8.9 min) as a light tan solid (optical purity determined to be 100% ee): mp 118−119 °C; $[\alpha]^{25}_D$ −124.0° (*c* = 1.0, $CHCl_3$). The (−)-free base was converted to its fumarate salt in 2-propanol to afford a white crystalline solid: mp 214−215 °C; $[\alpha]^{25}_D$ −69.0° (*c* = 1.0, DMSO). Chemical purity determined to be 97.6% pure by HPLC, and optical purity was determined to be 99.6% ee. Anal. ($C_{17}H_{18}ClNO_2 \cdot C_4H_4O_4$) C, H, N.

The second peak isolated having a retention time of 10.9 min was collected to afford *S*-(+)-**41c** (321 mg) as a light pinkish solid (optical purity determined to be 99.4% ee): mp 116−118 °C; $[\alpha]^{25}_D$ +120.0° (*c* = 1.0, $CHCl_3$). The fumarate salt was prepared in 2-propanol to afford white crystalline solid: mp 211−212.5 °C; $[\alpha]^{25}_D$ +68.1 (*c* = 1.0, DMSO). Chemical purity was determined to be 100.0% and optical purity found to be 99.0% ee. Anal. ($C_{17}H_{18}ClNO_2 \cdot C_4H_4O_4$) C, H, N.

Resolution of (+)-2-(3,4-Dihydro-1*H*-isoquinolin-2-ylmethyl)chroman-7-ol [*RS*-(+)-48c]. (±)-2-(3,4-Dihydro-1*H*-isoquinolin-2-ylmethyl)chroman-7-ol [(±)-**48c**] (610 mg) was resolved in a similar fashion as described in method K by dissolving in EtOH and submitting to semipreparative HPLC containing a Chiralcel OJ column and eluted (0.8 mL/min, pressure 430 psi, detection at 254 nm) with a hexane/2-propanol (4:1) mixture. The first peak at 8.1 min was collected to afford (−)-**48c** (265 mg) as a yellow glass (100% ee), $[\alpha]^{25}_D$ −105° (*c* = 1.1, $CHCl_3$). The (−)-free base (240 mg) was treated with excess oxalic acid in EtOH to afford 160 mg of oxalate salt: mp 198−199 °C; $[\alpha]^{25}_D$ −75°, (*c* = 1.0, DMSO). Anal. ($C_{19}H_{21}NO_2 \cdot C_2H_2O_4 \cdot 0.25H_2O$) C, H, N. The second peak isolated with a retention time of 11.1 min was collected to afford the (+)-**48c** (260 mg) as a yellow glass: $[\alpha]^{25}_D$ +103° (*c* = 1.0, $CHCl_3$). Optical purity observed to be 96.6% ee (acetonitrile−1 M $NaClO_4$, 1:1, 0.5 mL/min, 280 nM). The (+)-

free base (240 mg) was treated with excess oxalic acid in EtOH to afford 223 mg of oxalate salt: mp 195−196 °C, $[\alpha]^{25}_D$ +74° (c = 1.1, DMSO). Anal. ($C_{19}H_{21}NO_2 \cdot C_2H_2O_4 \cdot 0.25H_2O$) C, H, N.

Molecular Modeling. All computation were performed using Sybyl software package version 6.3 (Tripos Associates, St. Louis, MO) and a Silicon Graphic workstation. For Maximin calculations (Tripos force field), the Powell method was chosen (default values).

Cell Culture and Preparation of hD_2, hD_3, and hD_4 Receptor Membranes. Chinese hamster ovary cells (CHO) expressing the human dopamine D_{2S} and D_3 receptors were cultured in suspension by expansion, in serum free media (CHO−SFM) to which was added 5% fetal calf serum. The culture was expanded in a 1:5 split every 3−4 days. NS-0 cells semiattached from a cell line, expressing the human dopamine $D_{4.4}$ receptor, were cultured in roller bottles, in DMEM media supplied with 10% dialyzed fetal calf serum, and split in the same ratio ratio as the CHO. Upon reaching a density of approximately 7.5×10^5 cells per mL of suspension, the cells were harvested by low speed centrifugation (900g) for 10 min. The pellet was resuspended in half volume of 1× Dulbecco phosphate-buffered saline solution (PBS) without calcium chloride or magnesium chloride, at pH 7.4. The suspension was recentrifuged as to remove traces of the culture media. The cell pellet was immediately resuspended in 50 mM of Tris·HCl buffer, pH 7.4, containing 1.5 mM $CaCl_2$, 5.0 mM EDTA, 5.0 mM KCl, 120 mM NaCl, 1.0 mM PMSF, and 1.0 mg % leupeptin. The cells are homogenized in a glass/Teflon homogenizer with zero clearance, with 20 up and down strokes. The homogenate was centrifuged at 900g for 10 min and the supernatant saved. The pellet was resuspended in fresh buffer (approximately 10 mL), rehomogenized and recentrifuged as before. The supernatant fluid was combined with the previous one and centrifuged at 40000g for 30 min. This operation was repeated once with the resulting pellet. The final pellet was resuspended in a small volume of 50 mM Tris HCl, pH 7.4. An aliquot (10−50 μL) of the final suspension was withdrawn for protein determination, by the method of Lowry.[57] The suspension was then finally diluted with 50 mM Tris·HCl to give a protein concentration of 125 μg/mL of membrane suspension and stored at −80 °C until used in receptor binding assays.

Receptor Binding Assays: hD_{2s}, hD_3, and $hD_{4.4}$ Dopamine Receptors. [^{3}H]Spiperone (SA 80−100 Ci/mmol) was used as a ligand for binding to all three human dopamine receptor subtypes. Cell membrane preparation was incubated with [^{3}H]ligand in a final volume of 200 μL. Briefly, 100 μL of incubation buffer was added to the wells of a 96-well microtiter plate. Wells for nonspecific binding (NSB) assessment or test compounds received 80 μL of incubation buffer. [^{3}H]Spiperone was added at 0.5 nM in 20 μL volume to all wells, followed by the addition of displacer for NSB determination: D-butaclamol (1 μM) for D_{2s} receptors, 7-OH-DPAT (1 μM) for D_3 receptors, and clozapine (10 μM) for $D_{4.4}$ receptors, all in 20 μL volume. The reaction was initiated by the addition of 80 μL of appropriate tissue membranes. The mixture was incubated at room temperature for 120 min. Following incubation, the wells were harvested onto Glass fiber filter (GF/B), presoaked in 0.1% polyethylimine (PEI), using a Brandell harvester. The filter disks were washed three times with 5.0 mL of cold 50 mM Tris·HCl buffer, pH 7.4. The filter mat was dried in an oven and sealed in an envelope with melted multilex, for scintillation counting in a Wallac 1205 BetaPlate Counter. The data obtained were analyzed with the help of a computer-assisted software program by Lundon Software Inc. (OH). In competition experiments, apparent K_i values were calculated from IC_{50} values by the method of Cheng and Prusoff,[36] using nine concentrations of the drug, in triplicate.

Receptor Binding Assays: Dopamine D_2 High- and Low-Affinity States. The affinity of dopaminergic agents for the high- and low-affinity states of the D_2 receptor was determined using conventional in vitro receptor binding methodology. Affinity for the high-affinity state was determined by measuring the ability of various drugs to inhibit [^{3}H]-quinpirole (4 nM) binding to striatal membranes (approximately 0.3 mg of protein). Incubation buffer was 50 mM Tris, pH 7.4, containing 1 mM EDTA, 5 mM KCl, 1.5 mM $CaCl_2$, and 4 mM $MgCl_2$ (NaCl was omitted to promote high-affinity agonist binding). Incubation was at 25 °C for 1 h. Sulpiride (10 μM) was used to define specific binding. Affinity for the low-affinity state of the D_2 receptor was determined by measuring the ability of various drugs to inhibit [^{3}H]spiperone (1 nM) binding to striatal membranes (approximately 0.3 mg protein). Incubation buffer was 50 mM Tris, pH 7.4, containing 125 mM NaCl, 5 mM KCl, 1 mM $CaCl_2$, and 1 mM $MgCl_2$; 1 mM GppNHp was present in all tubes to shift binding to the low-affinity state. and 30 nM ketanserin was present in all tubes to exclude binding to 5-HT_2 receptors. Incubation was at 37 °C for 5 min. All incubations were terminated by adding cold buffer followed by rapid filtration using a TomTec 96 cell harvester. Bound radioactivity was counted using a Wallac 1205 BetaPlate Counter. K_i values were calculated from IC_{50} values by the method of Cheng and Prusoff,[36] using nine concentrations of the drug, in triplicate.

Receptor Binding Assays: 5-HT_{1A} and α_1 Receptors. The 5-HT_{1A} and α_1 receptor binding assays are modifications of those used by Hall et al.[58] and Morrow et al.,[59] respectively. Compounds were evaluated for their affinity at 5-HT_{1A} receptors using rat hippocampal homogenates labeled with [^{3}H]-8-OH-DPAT (1.8 nM). Samples were incubated for 10 min at 37 °C and incubations terminated by adding cold buffer (50 mM Tris, pH 7.7). Affinity at the α_1 receptors was determined using rat cortical homogenates labeled with [^{3}H]prazosin (0.2 nM). Samples were incubated at 25 °C for 30 min. Incubations were then terminated by the addition of cold buffer (50 mM Tris, pH 7.4) followed by rapid filtration using a TomTec 96-cell harvester. Bound radioactivity was counted as above. Test compounds were run in triplicate, using at least eight concentrations. All analyses were done using nonlinear regression. In competition experiments, apparent K_i values were calculated from IC_{50} values by the method of Cheng and Prusoff.[36]

Mouse Hypolocomotion.[41] Spontaneous locomotor activity effects were tested in mice (25−30 g, Charles River CF-1). Test compounds, dissolved in 0.25% Tween 80 were administered at several dose levels (10−12 mice/dose) immediately prior to testing. Horizontal activity counts were collected 10−20 min after dosing using infrared monitors (Omnitech Digiscan) surrounding an open field (8 × 8 in.) in a darkened room. Data were analyzed by one-way ANOVA followed by Dunnett's comparison to control post-hoc analyses and by nonlinear regression analysis followed by inverse prediction to obtain potency estimates.

Induction or Antagonism of Stereotypy and Climbing.[60,61] Induction of apomorphine-like stereotypy and climbing behaviors were tested in mice (20−30 g, Charles River CF-1) treated with the D_1 agonist SKF-38393 (10 mg/kg ip) immediately prior to drug or reserpine (5 mg/kg sc) 20−24 h prior to drug. Tests for antagonism of apomorphine-induced stereotypy and climbing behavior were conducted in mice treated with apomorphine (1 mg/kg sc) 30 min after drug. Drug, dissolved in 0.25% Tween 80, was administered subcutaneously at five dose levels (six mice/dose) for each test. After the final injection, mice were scored for stereotypy (2-point scale) and climbing (3-point scale) every 5 min for a total of 30 min. Accumulated scores were analyzed by one-way ANOVA followed by Dunnett's comparison to control test and by nonlinear regression analysis followed by inverse prediction to obtain potency estimates.

Inhibition of Dopa Accumulation.[62] Male Sprague−Dawley rats (225−300 g, Charles River) were given test drugs at a dose of 10 mg/kg, sc (t = 0 min). Ten minutes later (t = 10) rats were administered γ-butyrolactone (GBL) (750 mg/kg, ip) to inhibit neuronal impulse flow. Twenty minutes later (t = 20) rats were administered the dopa decarboxylase inhibitor NSD-1015 (100 mg/kg, ip) to permit an accumulation of dopa levels. Thirty minutes following NSD-1015 (t = 50) administration, animals were killed and striatal tissue was removed, placed in perchloric acid, and frozen at −80 °C until subsequent analysis of dopa levels using HPLC analysis with

electrochemical detection. Compounds possessing agonism at D_2 autoreceptors are known to inhibit dopa accumulation in this model.

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