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TETRAHEDRON

New Generation Dopaminergic Agents 4. Exploiting the 2-Methyl Chroman Scaffold. Synthesis and Evaluation of Two Novel Series of 2-(Aminomethyl)-3,4,7,9-tetrahydro-2H-pyrano[2,3-e]indole and Indol-8-one Derivatives†

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Abstract. The rational design, synthesis, and evaluation of two novel series of 2-(aminomethyl)-3,4,7,9-tetrahydro-2H-pyrano[2,3-e]indole and indolone derivatives are disclosed, based on the recently discovered D_2 agonist phenolic template prototype [i.e. the 7-OH-2-(aminomethyl)chroman nucleus]. The indolones were observed to have higher affinity and intrinsic activity than the corresponding indoles.

INTRODUCTION

The search for more potent and selective dopamine (DA) D_2 agonists continues to attract considerable attention due to their implication in several psychiatric and neurological illnesses such as schizophrenia, Parkinson's disease and drug addiction [1,2]. The design of D_2 agonists has revolved predominately around the modification and rigidification of DA, and more specifically, analogs embracing the '3-OH-phenethylamine'

†*Dedicated to our colleague and friend Professor Madeleine M. Joullié in celebration of 40 years of distinguished teaching and research at the University of Pennsylvania*

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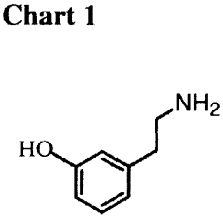
DA pharmacophore (i.e. **1**) [3]. By embedding the 3-OH-phenethylamine moiety in either its α- or β-rotameric conformations, medicinal chemists have systematically explored the conformational and topographical requirements of the D_2 receptor pharmacophore. A thorough understanding of the D_2 receptor has been achieved through the development of indirect D_2 receptor models by the work of McDermed [4,5], Cannon [6,7], Seiler [8,9], Liljefors [10,11], Wikstrom [10,11], and others [3]. More recent efforts have focused on identifying second generation dopaminergic agents with improved oral bioavailability and duration of action [12].

Chart 1



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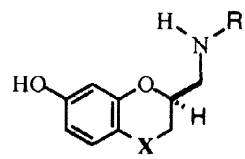
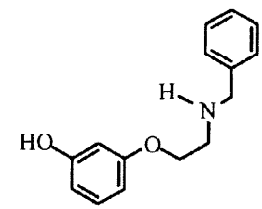


2a X=CH_2 R=Bzl
2b X=CH_2 R=Me
3 X=O R=Bzl
4 X=NH R=Bzl



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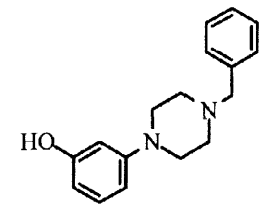

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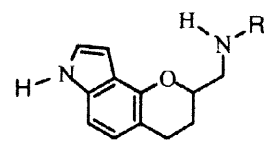
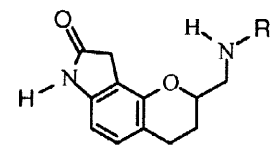


7a R=Bzl
7b R= Me



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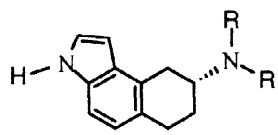
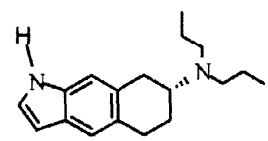


9a R=*n*-Pr
9b R=H



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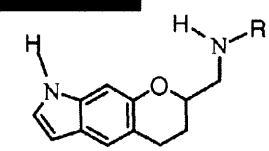


11a R=Bzl
11b R=Me

Recently, our laboratories discovered several novel phenolic templates (**2-6**, Chart 1) which were recognized as embracing novel scaffolds having ready access to the D_2 agonist pharmacophore. This discovery opened new and promising opportunities toward expanding our knowledge of the D_2 agonist pharmacophore and the design of a new generation of D_2 agonists and partial agonists [13-15]. Modeling studies performed on the 7-OH-2-(aminomethyl)chromans (7-OH-AMC, **2ab**) [13], 7-OH-2-(aminomethyl)benzodioxan (**3**) [13] and 7-OH-(aminomethyl)benzoxazine (**4**) [15] identified low energy conformations which closely adhered to

the McDermed D_2 model [4,5], and were proposed as the receptor-bound conformations. Through a systematic structure-activity relationship (SAR) study, the benzyl group of **2a** was found to impart impressive selectivity over the $5HT_{1A}$ and α_1 adrenergic receptors (Table 1). The *R*-isomer was discovered to be the eutomer, exhibiting 60-fold higher affinity than its distomer. Not surprisingly, **2a** was not orally bioavailable, presumably due to its rapid metabolism via conjugation of the C-7 phenolic hydroxyl group with glucoronic acid.

In order to exploit this potent and highly selective prototypic agonist (i.e. **2a**), our next challenge was to overcome the problem of oral bioavailablity by replacing the metabolically labile phenol moiety with more stable bioisosteres. Though there is much precedent in the dopamine area demonstrating the use of indoles [16-19] and more recently indolones [20-22] as bioisosteric replacements for the phenol moiety, the directionality of the hydrogen bond donating group of the 7-OH-2-AMC (**2a**) template was not immediately apparent. In this report is described the synthesis and SAR of two novel congeneric series of dopaminergic agents (i.e. **7** and **8**), based on the newly discovered 7-OH-AMC D_2 agonist template (i.e. **2a**).

Molecular Modeling/Design Strategy

Unlike the rotationally promiscuous hydroxyl group of the phenol, indoles and indolones contain 'fixed geometry' hydrogen bonding groups, due to their rigid colinear N-H bond. Previous studies, demonstrating the D_2 receptor's sensitivity toward the ligand's hydrogen bond directionality capabilities, revealed the angular indole (**9a**) to be active, while the linear indole (**10**) was found to be inactive [23]. Consequently, superposition of the 7-OH-AMC moiety of **2a** in its putative receptor-bound conformation, onto the pharmacophoric elements of the active angular indole (**9a**), should allow for the identification of the H-bond directionality of the phenol. A similar analysis could also be used to evaluate which of the regioisomeric indoles (**7a** or **11a**) would be our target series. In order to simplify our modeling studies, which focused on the pharmacophoric groups, the flexible side chains were removed. As disclosed in our earlier study of **2a**, the *N*-methyl analog (**2b**) was instead relied upon to identify the putative pharmacophoric conformation of **2a**. The structure of **9a** was obtained from the Cambridge database, however, the propyl groups were removed to provide a simplified template (i.e. **9b**). Superposition of **2b** onto the indole template **9b**, followed by alignment of the hydrogen of the hydroxyl group of **2b** onto the N-H of the indole moiety of **9b**, allowed for excellent overlap and common directionality of both hydrogen bond donating groups (Figure 1). In order to determine which N-H bond of the potential target indoles, **7a** and **11a**, best aligned with the N-H vector directionality of **9b**, the corresponding 2-AMC moiety of the indoles was first manipulated and minimized to an analogous conformation to that of the previously postulated receptor-bound conformation of **2b**. Subsequently, using **9b** as a template, superposition of the *N*-methyl analogs of **7b** and **11b**, again using the

centroids, basic nitrogens and indole nitrogens as fitting points, revealed that the H-bond directionality of **7b** and **9b** coincided very closely (Figure 2). In contrast, the H-bond directionality of indole **11b** was observed to

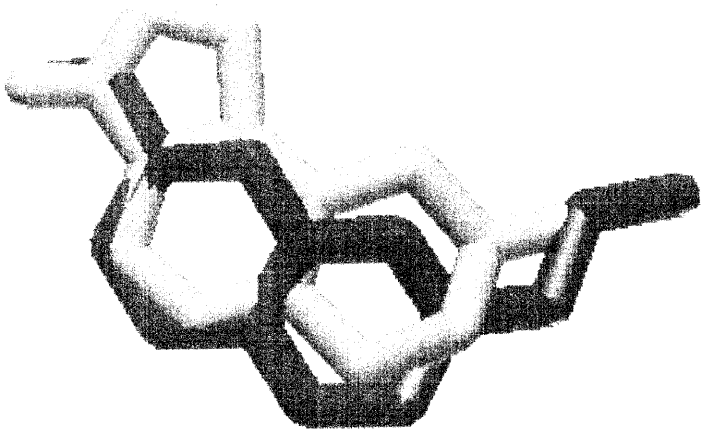


Figure 1. Pharmacophoric groups of **2b** (black) overlayed onto indole template **9b** (gray).

be nearly orthogonal to the indole N-H of template **9b** (Figure 3). Shown in Figure 4 is an overlay of **2b** with its corresponding angular indole analog (**7b**). On the basis of these overlaps, the proper N-H directionality requirements were identified and the angular tricyclic ring systems [i.e. **7a** and its indolone analog (**8a**)] were considered high priority targets which should potentially fulfill the D_2 pharmacophoric criteria.

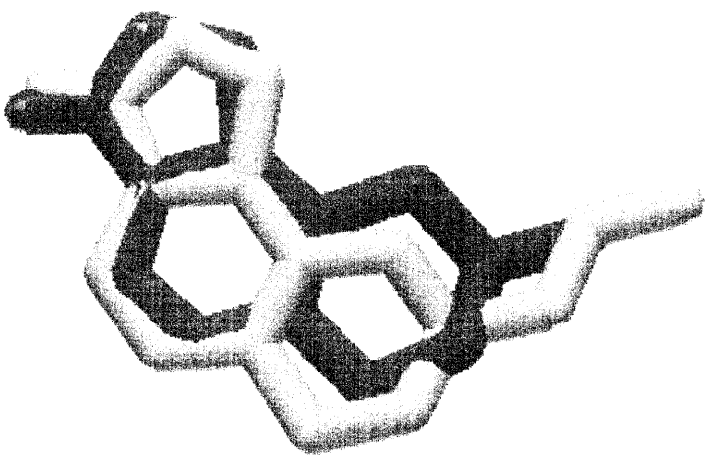


Figure 2. Superposition of angular indole **7b** (gray) onto indole template **9b** (black).

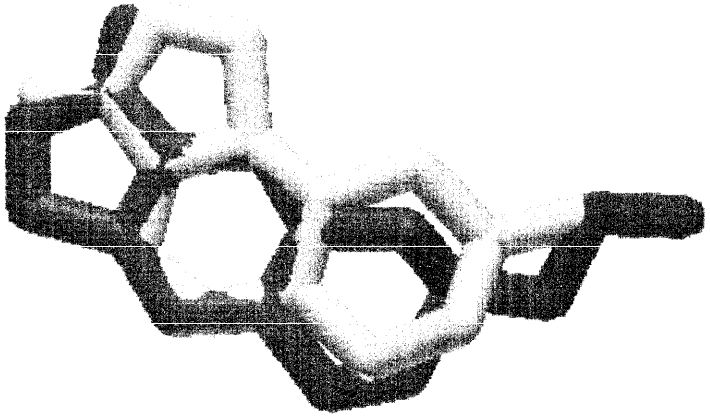


Figure 3. Superposition of linear indole **11b** (black) onto indole template **9b** (gray).

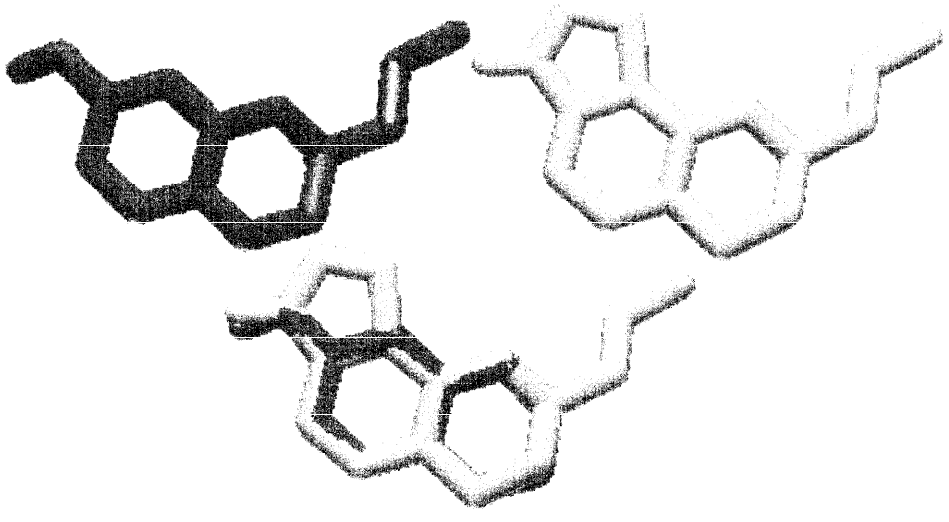
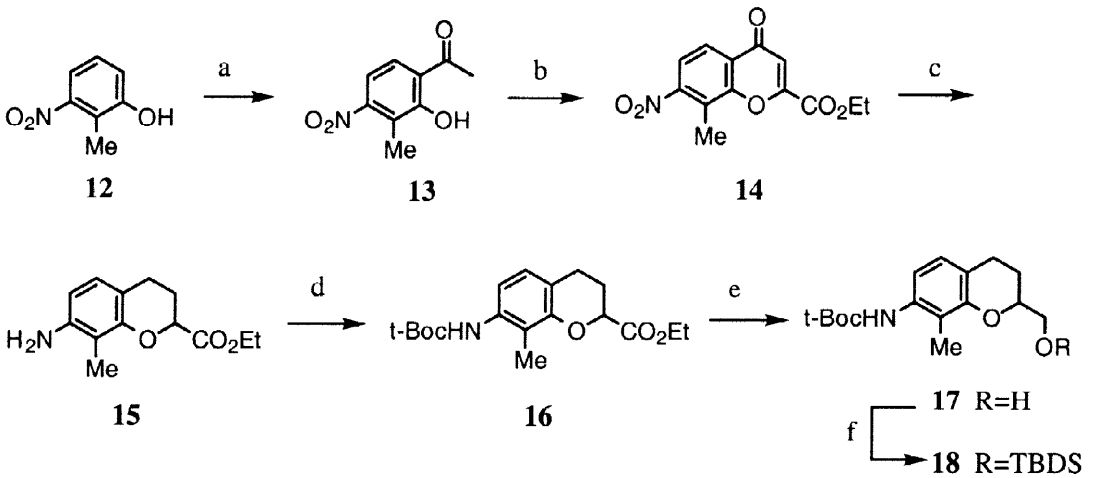


Figure 4. Superposition of **2b** (black) onto angular indole **7b** (gray).

CHEMISTRY

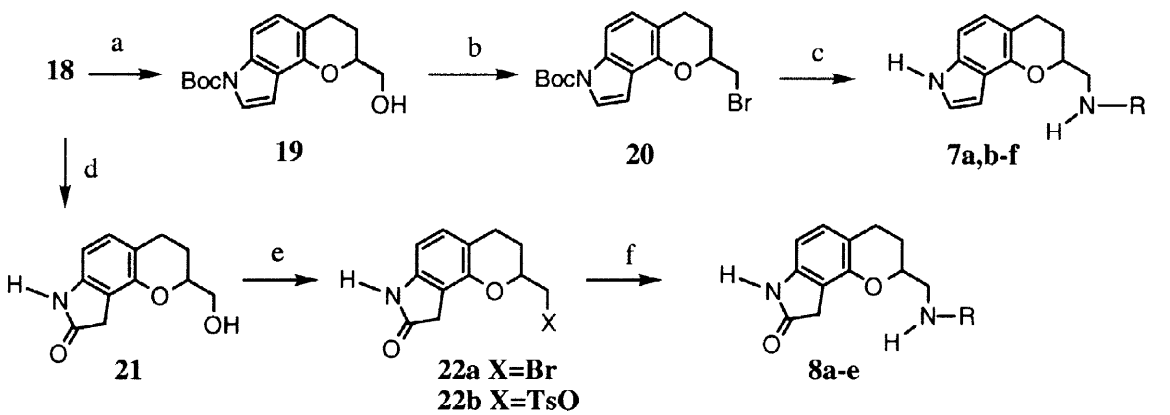
The synthesis of angular indoles (**7a, c-f**) and angular indolones (**8a-f**) could be achieved through the common key intermediate **18** whose preparation is shown in Scheme 1. Commercially available **12** was treated with acetyl chloride and $AlCl_3$ to afford **13** in yields ranging from 40-70%. Chromone **14** could be prepared in a one-pot reaction by treating **13** with NaOEt and ethyl oxalate followed by the *in situ* cyclization elimination sequence using concentrated sulfuric acid. Hydrogenation in acetic acid afforded **15**. Treatment with di-tert-butyl dicarbonate followed by reduction with $LiBH_4$ gave **17** in excellent yield. Protection of **17** with t-butyl-

Scheme 1[a]



[a]**Reagents** (a) $AlCl_3$/ CH_3COCl (b) (1) NaOEt, $(CO_2Et)_2$; (2) H_2SO_4/EtOH (c) H_2, Pd/C (d) $(t\text{-Boc})_2O$ (e) $LiBH_4$ (f) t-$BuMe_2SiCl$, imidazole, DMF

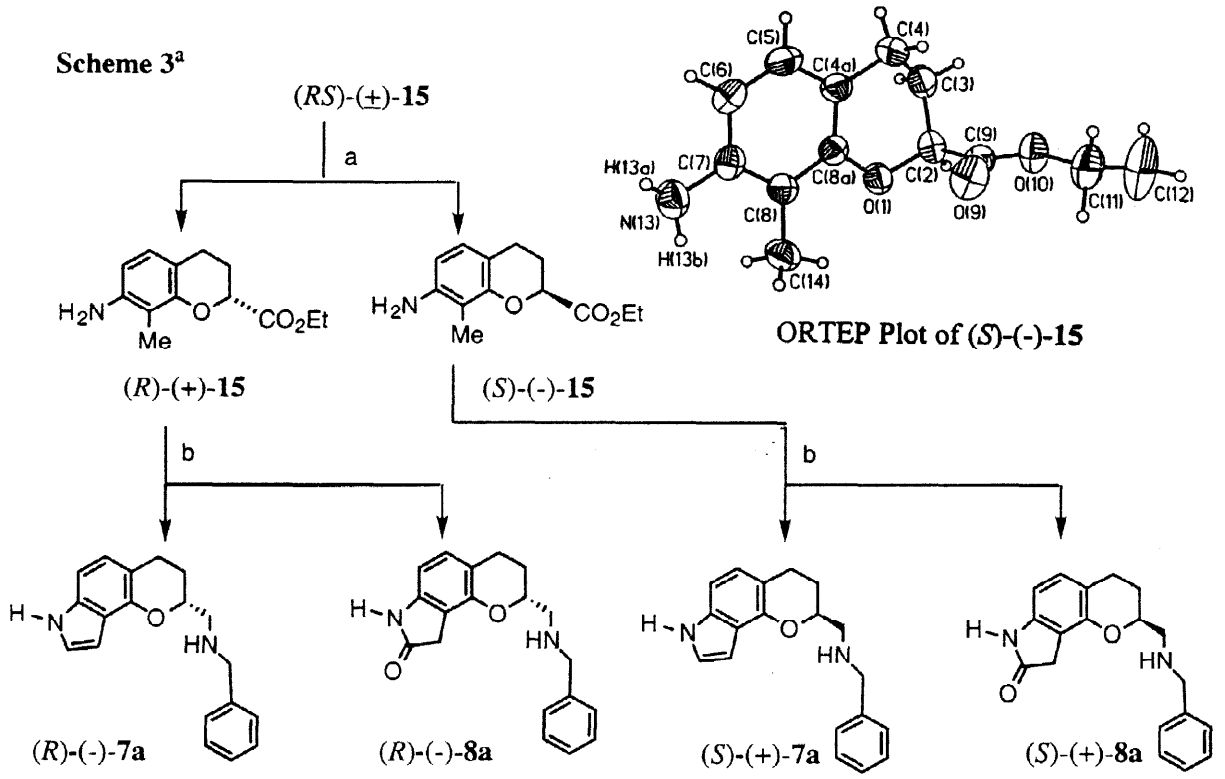
Scheme 2[a]



[a]**Reagents** (a) (i) s-BuLi; (ii) DMF; (iii) HCl/THF (b) CBr_4, PPh_3 (c) RNH_2, DMSO (d) (i) s-BuLi (ii) CO_2 (iii) H_2SO_4, MeOH (e) TsCl, C_5H_5N (f) RNH_2, DMSO

dimethylsilylchloride afforded the pivotal intermediate **18**. Shown in Scheme 2 is the route used to convert **18** to the angular indoles (**7a, c-f**). Deprotonation of **18** using s-butyllithium afforded the corresponding dianion which was quenched with DMF and treated with sulfuric acid to give indole **19**. The corresponding bromide (**20**), prepared using triphenylphosphine and carbon tetrabromide, was reacted with the appropriate amines, which concomitantly deprotected the t-Boc group to afford the desired target indoles (**7a, c-f**). The congeneric indolones were prepared (Scheme 2) by quenching the corresponding dianion of **18** with carbon dioxide. Concomitant deprotection of the t-Boc and silyl groups, followed by esterification and cyclization in the

Scheme 3[a]



ORTEP Plot of (*S*)-(-)-**15**

[a]**Reagents** (a) (i) Dibenzoyl tartaric acid (ii) K_2CO_3-H_2O (b) See methods in Schemes 1 & 2.

same reaction vessel, using aqueous HCl in methanol, afforded **21**. In contrast to the indole synthesis, only small amounts of bromide **22a** were isolated using carbon tetrabromide and triphenylphosphine. Instead, tosylate **22b** was prepared in good yield and subsequently treated with the appropriately substituted amines to afford the target angular indolones (**8a-f**).

Chromatographic resolution using a Chiralcel AS column (see experimental section) allowed for the separation of the (+) and (-)-isomers of **7a**. A classical resolution of intermediate **15** (Scheme 3) using dibenzoyl tartaric acid afforded both (+) and (-) enantiomers in 99.9% optical purity. Assignment of the absolute stereochemistry of (-)-**15** was established by a X-ray crystallographic analysis and found to be of the *S*-configuration. No racemization was observed thoughout the entire synthetic route as observed by chiral HPLC. Both (*S*)- and (*R*)-**15** were converted to their corresponding indoles and indolones (Scheme 3) according to those methods used for the racemates to reveal that the *S*- configuration belonged to both (+)-**7a** and (+)-**8a**, whereas the *R* configuration corresponded to (-)-**7a** and (-)-**8a** .

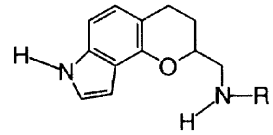
PHARMACOLOGY

All compounds were evaluated for their *in vitro* binding affinity for 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}) of the receptor. Ketanserin (30 nM) was present in all assays with [^{3}H]-spiperone to preclude binding of spiperone to 5-HT_2 receptors. Compounds were also evaluated for their affinity for 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 compound's intrinsic activity was predicted based upon the preferential antagonism of agonist versus antagonist radioligand binding, based upon a similar method previously reported by Lahti et al. [24]. 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 [(K_i^L/K_i^H)=466] [13] and SDZ-208-911 [(K_i^L/K_i^H)= 1.1] [13] were subsequently evaluated in vivo. Further details of the pharmacological assays and test models can be found in our earlier report [13].

RESULTS AND DISCUSSION

As shown in Table 1 (*R*)-**7a** was observed to lose 10-fold affinity (K_i=1.9 nM) for the D_2^{High} when compared to the analogous phenol [i.e. (*R*)-**2**; K_i=0.2 nM)]. As in the case of the 7-OH-AMC series, the eutomer was revealed to have the *R* stereochemistry. In order to determine whether a common alignment binding mode at the D_2 receptor was occurring with respect to the indolic and 7-OH-AMC series, several analogs (i.e. **7c-f**) were prepared with previously explored side chains from our earlier study and tested to reveal very similar losses in affinity in both series. The observation that parallel modifications resulted in parallel affinity changes strongly suggests that both the 7-OH-AMCs and the indole analogs are aligning themselves in a very similar orientation in the D_2 receptor cavity. In fact, the indoles (**7a**, **c-f**) were consistently observed to bind to the D_2^{High} receptor with approximately 10-12 fold lower affinity than their analogous 7-OH- AMCs. The side-chain variations of the indoles had an enormous influence on affinity and selectivity. Though indoles **7c-e** had only modest affinity for the D_2^{High}, attaching the 2-thienyl-methylamine

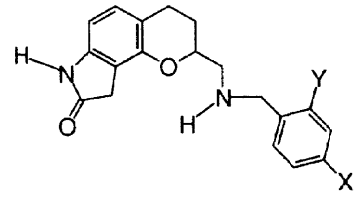
Table 1. Indole Derivatives



compd[c]	R	Ki (nM)[a,b] D_2^{High}	D_2^{Low}	5-HT_{1A}	α_1	Ratio (D_2^{Low}/D_2^{High})	LMA [ED_{50}, mg/kg, po,(sc)]	DOPA % Inhibition (10 mg/kg, sc)
***(RS)*-(±)-7a**	Bzl	2.5 ± 0.1	47.4 ± 14	1.5 ± 0.1	140	19	0.55 (0.17)	83 %
***(R)*-(-)-7a**	Bzl	1.9 ± 0.8	35.9 ± 4.7	0.4	24	18	*	*
***(S)*-(+)-7a**	Bzl	59.5 ± 8.8	245 ± 23	8.5	93.5	4	*	*
7c	n-Pr	40.1 ± 10.4	468 ± 20	7.5 ± 6	29.5 ± 3	11	*	*
7d	$(CH_2)_3OH$	34.3 ± 5.5	514.4	1.2	37.5	15	*	*
7e	Furanyl-2-methyl	23.8 ± 0.8	543 ± 50	3.7	178	23	*	*
7f	Thiophen-2-yl-methyl	6.1 ± 0.4	95.2 ± 2.0	1.1 ± 0.7	72 ± 13	16	12.4 (< 0.3)	*
***(RS)*-(±)-2[d]**		0.2 ± 0.1	8.4 ± 1.2	52.0	572	42	(0.01)	66 %
***(R)*-(-)-2[d]**		0.2 ± 0.1	3.3 ± 0.8	22.5	212	16	(0.0014)	
***(S)*-(+)-2[d]**		12 ± 2.4	110 ± 21	990	1624	6	(0.22)	

[a]K_i values are the means of at least two experiments ± SEM (performed in triplicate using 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 (a_1). [c]All compounds were prepared in racemic form unless otherwise noted. [d]Reference 13. *Not determined.

Table 2. N-Benzyl Indolone Derivatives



			Ki (nM) [a,b]					
compd[c]	X	Y	D_2^{High}	D_2^{Low}	5-HT_{1A}	α_1	Ratio (D_2^{Low} /D_2^{High})	LMA (ED_{50}, mg/kg, sc)
***(RS)*-(±)-8a**	H	H	0.37 ± 0.05	12.0 ± 0.9	17 ± 4.5	122 ± 10	32	0.21
***(R)*-(-)-(8a)**	H	H	0.14 ± 0.01	5.9 ± 0.3	8.5 ± 4	165 ± 21	42	0.0015
***(S)*-(+)-(8a)**	H	H	8.2 ± 3.5	94.6 ± 37.1	165 ± 20	260 ± 18	12	0.15
8b	OMe	H	0.43 ± 0.06	23.1 ± 2.7	19	129	54	*
8c	Me	H	0.23 ± 0.02	8.1 ± 1.3	5	97	35	*
8d	F	H	0.41 ± 0.05	24.3 ± 2.4	8	176	59	*
8e	Cl	H	0.32 ± 0.01	11.6	3.8	92	36	*
8f	Me	Me	1.3 ± 0.17	30.7	7.5	40.5	24	*

[a-c]See footnotes of Table 1.

Table 3. Affinities of **7a** and **8a** for hD_2-like receptors.

	K_i (nM)		
compd	hD_{2S}	hD_3	$hD_{4.4}$
***(RS)*-(±)-7a**	100.1 ± 3.9	48.4 ± 0.55	1139
***(R)*-(-)-7a**	107 ± 19	34 ± 3	2174 ±15
***(S)*-(+)-7a**	287 ± 30	379 ± 10	2306 ± 214
***(RS)*-(±)-8a**	15.4 ± 2.0	10.2 ± 4.6	406 ± 75
***(R)*-(-)-8a**	9.3 ± 0.1	2.4 ± 1.0	359
***(S)*-(+)-8a**	47.6 ± 0.9	21.8 ± 1.7	2535

and benzylamine side chains (i.e. **7a** and **7f**, respectively) resulted in a significant increase in affinity for the D_2^{High} and a loss in affinity for the a_1 receptor. The entire series of indoles (**7a**, **c-f**) had excellent affinity for the $5HT_{1A}$ receptor. Worth mentioning is a related series of indolodioxan derivatives prepared by Ennis et al. [25] which was discovered to have excellent affinity for the $5HT_{1A}$ receptor. Though these indolodioxans were also identified as having significant affinity for the D_2 receptor, the embedded D_2 pharmacophore was not reported as being recognized. The loss in affinity when replacing the phenolic moiety with an indole was a common trend observed when comparing the analogous compounds prepared in this study with the 7-OH-AMC derivatives of our earlier investigation [13] and suggested that the decreased affinity may be attributed to the ligand's ability to effectively act as a hydrogen bond donor with the D_2 receptor.

Interestingly, the D_2^{High} affinity state was much more enantioselective for (*R*)- and (*S*)-**7a** than the D_2^{Low} affinity state, indicating that (*R*)-**7a** was more optimized for the agonist state of the D_2 receptor. The eudismic ratios of **7a** for D_2^{High} and the $5HT_{1A}$ receptors were of similar magnitude (31 vs 21). Though **7a** had good D_2 selectivity versus α_1 receptors, its inability to differentiate between D_2 and $5HT_{1A}$ receptors prompted our search for another bioisosteric replacement for the indole moiety. Even though **7a** was found to have good oral activity (see Table 1, LMA, po), its observed short half-life in rat microsomes was another concern which needed to be addressed. These two deficiencies of **7a** provided a further impetus to continue the modification of the core structure of indole **2a**.

In order to optimize the ability of **7a** to donate a hydrogen bond through its N-H bond more effectively, the indole nucleus was replaced by the indolone moiety. Indolone **8a** was observed to bind to the D_2^{High} receptor with a 7-fold increase in affinity and a 11-fold decrease in affinity for the $5HT_{1A}$ receptor when compared to indole **7a**. Affinity for α_1 receptors remained unaffected and consequently indolone **8a** was observed to have a 46-fold and 330-fold selectivity for the D_2^{High} versus $5HT_{1A}$ and α_1 receptors, respectively. Initially a chromatographic chiral resolution of (*RS*)-**8a** revealed that the eutomer, which was subsequently determined to have the *R* configuration, had similar affinity to the corresponding phenolic analog (*R*)-**2a** with respect to D_2^{High} [0.2 nM vs 0.14 nM] and α_1 receptors (212 nM vs 165 nM) and was slightly less selective versus $5HT_{1A}$ receptors (22.5 nM vs 8.5 nM). This observation demonstrates that the the DA D_2^{High} receptor recognizes the indolone and the phenol moieties as bioisosteric surrogates, as well as the *R*-configuration as being the eutomeric series. Substituent effects on the benzyl ring led to slight increases in affinity for the 4-chloro and 4-methyl groups. However, the 2,4-dimethyl derivative led to a loss of 4-fold affinity for the D_2^{High} receptor, suggesting the 2-methyl group was having a detrimental effect. Parallel SAR modifications in the indole and indolone series discovered in this study were observed to have parallel effects

in affinity as the previously reported 7-OH-2-AMCs, strongly suggesting that all three series were aligning in a common orientation within the high affinity (agonist) state of the D_2 receptor.

Throughout the racemic indole series the intrinsic activity ratios were much lower (K_i^L/K_i^H= 4-18) than the corresponding indolones (K_i^L/K_i^H=12-48]). This suggests that the indole pharmacophoric group is less optimized for the D_2^{High} receptor than the indolones, which apparently have superior hydrogen bonding capabilities necessary for binding to the agonist state of the D_2 receptor. The higher intrinsic activity ratios of the indolones predicts that these compounds would have good to excellent intrinsic activity. This prediction was confirmed in the DOPA accumulation, and locomotor activity assays. The ratio of (*S*)-**8a** (K_i^L/K_i^H=12) suggests that it would have a lower intrinsic activity level. Unfortunately, not only did (*S*)-**8a** have 59-fold lower affinity than its eutomer [(*R*)-**8a**], it also had unimpressive selectivity versus $5HT_{1A}$ and α_1 receptors.

We have previously reported the effects of the phenolic analog (*R*)-**2a** and its enantiomers on locomotor activity in mice [13]. Multiphasic dose response curves were produced by these compounds. Specifically, low doses resulted in reductions of locomotor activity; intermediate doses produced less of a reduction and sometimes baseline levels of locomotor activity; high doses resulted in reductions in locomotor activity. It was observed that other compounds produced only reductions in locomotor activity and that there was a correlation between the estimate of intrinsic activity and the locomotor activity profile. That is, compounds with higher estimates of intrinsic activity had multiphasic dose response curves, while compounds with lower estimates of intrinsic activity did not. This relationship is also observed in the locomotor activity profiles of (*RS*)-**7a** and (*RS*)-**8a** (Figures 5 and 6). The indolone (*RS*)-**8a** and its eutomer (*R*)-**8a** had intrinsic activity ratios >20 and were observed to produced multiphasic dose response curves. The potency of (*R*)-**8a** was shifted left relative to (*RS*)-**8a** consistent with its higher affinity for the D_2^{High} receptor. The distomer (*S*)-**8a** did not produce any significant effect on mouse locomotor activity in this same dose range. In contrast, (*RS*)-**7a**, and its eutomer (*R*)-**7a** as well as the distomer (*S*)-**7a** produced locomotor activity dose response curves with only a single phase. This is consistent with their lower intrinsic activity ratios compared with (*RS*)-**8a**. Moreover, the left shift of the dose response curves for (*R*)-**7a** relative to (*RS*)-**7a** was consistent with its higher affinity for D_2^{High} receptor.

Correlation also exists between the estimates of intrinsic activity and the degree of rotational behavior elicited by some of these compounds in 6-OHDA lesioned rats. The higher the affinity and degree of intrinsic activity, the greater degree of contralateral rotation elicited. Mean contralateral rotations (±SEM) collected for 60 min following administration (0.3 mg/kg s.c.) of (*R*)-**8a**, (*S*)-**8a** and (*R*)-**7a** were 401.37 ± 49.74, 5.00 ± 2.94 and 205.25 ± 81.68, respectively. The eutomer (*R*)-**8a** also produced significant contralateral rotation at 0.1 mg/kg s.c. (mean = 347.62 ± 67.07). Due to its lower affinity, the distomer (*S*)-**8a** was tested at a higher dose of 3 mg/kg s.c. Again it failed to elicit significant contralateral rotation (mean = 27.75 ±17.21). These results

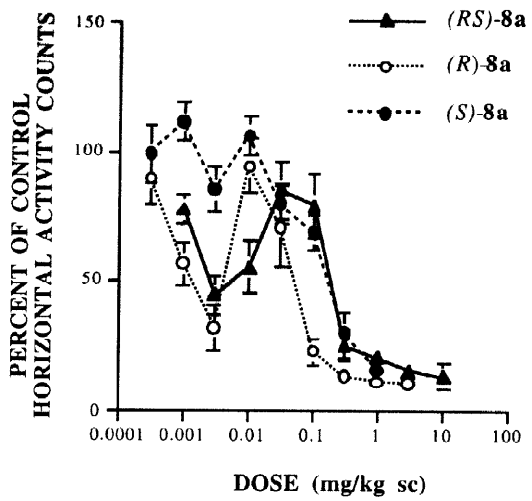


Figure 5. Dose-response curve for inhibition of spontaneous locomotor activity for (*RS*)-**8a**, (*R*)-**8a** and (*S*)-**8a**.

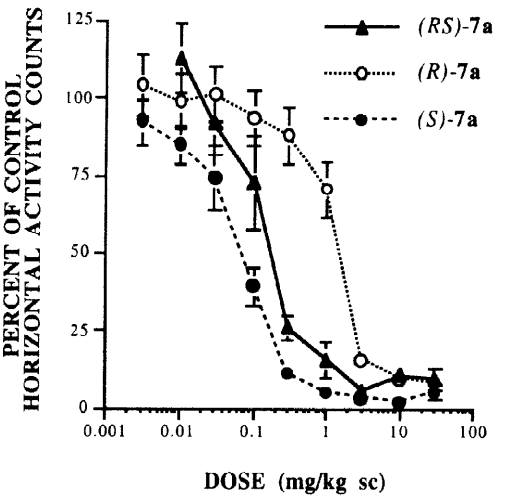


Figure 6. Dose-response curve for inhibition of spontaneous locomotor activity for (*RS*)-**7a**, (*R*)-**7a** and (*S*)-**7a**.

support the characterization of the indolones as more potent and efficacious D_2 agonists when compared with the indole congeners.

CONCLUSIONS

We have designed and prepared two novel series of indoles and indolones which have high affinity for the D_2^{High} receptor based on our the recently discovered 7-OH-AMC D_2 agonist pharmacophore template. The indolone ring was found to be an excellent bioisostere for the phenol moiety and as revealed in our previous study, the benzyl group was optimized for the D_2^{High} receptor. Excellent selectivity over the $5HT_{1A}$ and α_1 receptors was achieved in the indolone series. The SAR revealed in this investigation suggests that these two novel classes of indoles and indolones have a common orientation at the agonist (high affinity) state of the D_2 receptor, analogous to the previously reported 7-OH-AMCs [13]. The indoles demonstrated activity when administered both orally and subcutaneously. Both series demonstrated D_2 agonism in vivo.

Currently our laboratories are continuing to investigate SAR related to the modulation of potency, intrinsic activity, and selectivity within this new generation of dopaminergic agents.

EXPERIMENTAL

Materials

Melting points were detemined on a Thomas-Hoover melting point apparatus and are uncorrected. ^1H NMR spectra were recorded on a Varian Unity Plus 400, Varian VXR-300 or Varian XL-200 instrument. Chemical shifts are reported in d 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 with either an alcohol solution of phosphomolybdic acid or in an iodine chamber. Solvents and reagents were used as purchased.

Methods

2-Hydroxy-3-methyl-4-nitro-acetophenone (13). To a 5 L round-bottom flask equipped with a mechanical stirrer, nitrogen inlet and temperature controlled heating mantle was added 2-methyl-3-nitrophenol

(210 g, 1.37 mol), nitrobenzene (1680 mL), and acetyl chloride (127 mL, 1.79 mol). The reaction was warmed up to 45 °C and a small amount of aluminum chloride was added and the reaction was stirred at 45 °C for 1 hour. After the addition of another portion of aluminum chloride (183 g, 1.37 mol), the temperature rose to 60 °C and the reaction mixture was slowly heated to 120 °C and allowed to stirred for another 16 hours. The reaction mixture was cooled in an ice bath to 15 °C and a saturated aqueous solution of sodium chloride (2 L) was added slowly, keeping the temperature below 25 °C. The organic layer was separated and was diluted with toluene, filtered over Solka Floc to remove tar impurities, and washed with water. More tar impurties precipitated and the mixture was again filtered over Solka Floc. The organic layer was separated and washed with 0.5 N sodium hydroxide (4 x 1 L). The combined aqueous layers were filtered over Solka Floc, and acidified by slow addition of concentrated hydrochloric acid (240 ml). The product was extracted in CH_2Cl_2, dried over anhydrous $MgSO_4$, treated with decolorizing carbon, filtered and the solvent removed to afford 193 g (72 %) of a thick oil which solidified upon standing: mp 40-41 °C; IR (KBr) 1650 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.22 (3H, s), 2.70 (3H, s), 7.40 (1H, d, J=8.8 Hz), 8.02 (1H, d, J=8.8 Hz) 12.84 (1H, s, OH); MS EI *m/e* 195 (M^+). Anal. calcd. for $C_9H_9NO_4$: C, 55.39; H, 4.65; N, 7.18; found: C, 55.30; H, 4.53; N, 7.06.

8-Methyl-7-nitro-4-oxo-4H-chromene-carboxylic acid ethyl ester (14). To a 5 L 3-neck round-bottom flask, equipped with a mechanical stirrer and nitrogen inlet was added diethyl oxalate (167 mL, 1.23 mol) and 21 % sodium ethoxide in ethanol (840 mL, 2.25 mol). After cooling the mixture in an ice water bath for 10 min, a solution of **13** (192.8 g, 0.99 mol) in ethanol (775 mL) was added under vigorous stirring. The solution became thick, solidified, and the temperature was increased to 50 °C for 3 h while the mixture was stirred. A solution of concentrated sulfuric acid (80 mL) in ethanol (280 mL) was added slowly, and the reaction mixture was heated to reflux for 1.5 hours, then stirred overnight at room temperature. Sodium acetate (77 g) was added and the mixture was stirred for 20 min, followed by the dropwise addition of water (280 mL). After stirring for 20 min, the solid was collected on a filter and washed with a solution of ethanol-water (60/40). The solid was triturated in water for 1 h, collected by filtration, washed with water and dried in a vacuum oven to afford 193 g (70 %) of desired product. This product was taken on to the next step without further purification: mp 119-5-120 °C; IR (KBr) 1780, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.46 (3H, t, J=7.2 Hz), 2.71 (3H, s), 4.49 (2H, q, J=7.2 Hz), 7.15 (1H, s), 7.82 (1H, d, J=8.8 Hz), 8.16 (1H, dd, J=8.6, 0.7 Hz); MS EI *m/e* 277 (M^+). Anal. calcd. for $C_{13}H_{11}NO_6$: C, 56.32; H, 4.00; N, 5.05; found: C, 56.36; H, 3.86; N, 4.88.

(*RS*)-7-Amino-8-methyl-chroman-2-carboxylic acid ethyl ester (15). A mixture of **14** (42.2 g, 0.152 mol) and palladium on carbon (4.7 g) in glacial acetic acid was hydrogenated at 50 psi for 48 hr. The

catalyst was removed by filtration of the mixture through celite and the solvent removed under high vacuum. The crude product was chromatographed (25 % EtOAc-hexanes) to afford 24.5 g (68.4%) of an orange oil which solidifies upon standing: mp 82-85 °C; IR (film) 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (3H, t, J=7.0 Hz), 2.12 (3H, s), 2.12-2.15 (2H, m), 4.20-4.26 (2H, m), 4.22 (2H, q, 7.0 Hz), 4.70 (1H, dd, J=7.5, 3.7 Hz), 6.19 (2H, bs, NH_2), 6.82 (1H, d, J=8.1 Hz), 7.26 (1H, d, J=8.3 Hz); MS EI *m/e* 235 (M^+). Anal. calcd. for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95; found: C, 66.26; H, 7.26; N, 5.88.

Resolution of (*RS*)-7-amino-8-methyl-chroman-2-carboxylic acid ethyl ester [(*RS*)-**15**]. To a solution of (*RS*)-**15** (36.0 g, 0.15 mol) in EtOAc (100 mL) was added a solution of (-)-dibenzoyl-L-tartaric acid (28.0 g, 0.075 mol) in ethanol (60 mL) while stirring. The solution was allowed to stand overnight and the crystals were filtered and recrystallized three times from a mixture of EtOAc: ethanol (80 mL:20 mL) to afford 11.6 g of the (*R*)-(-)-dibenzoyl-tartrate salt, mp 145-146°C; $[\alpha]^{25}_D$ -87.21 (c=0.91, MeOH). The free base was prepared by dissolving the salt in a minimum amount of water and basified with solid K_2CO_3. Extraction with EtOAc (5x100 mL) and recrystallizing from EtOAc afforded a white crystalline solid: mp 105-107 °C; $[\alpha]^{25}_D$ -46.9 (c=1.0, MeOH). The product was determined to be >99.9 e.e. by a chiral column. Anal. calcd. for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95; found: C, 66.26; H, 7.26; N, 5.88.

The (+) isomer was resolved in an identical fashion by using (+)-dibenzoyl tartaric acid to afford a crystalline salt: $[\alpha]^{25}_D$ +83.0 (c=1.0, MeOH). The free base was prepared similarly; mp 105-107 °C; $[\alpha]^{25}_D$ +48.0 (c=1.0, MeOH). Anal. calcd. for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95; found: C, 66.52; H, 7.37; N, 5.94.

(*RS*)-7-tert-Butoxycarbonylamino-8-methyl-chroman-2-carboxylic acid ethyl ester (16). To a solution of **15** (7.4 g, 31.5 mmol) in anhydrous THF (40 mL) at 0 °C was added a solution of di-t-butyl-dicarbonate (7.21g, 33.0 mmol) in anhydrous THF (30 mL). The reaction was allowed to warm to ambient temperature and stirred for an additional 24 h. The reaction mixture was diluted with ether (150 mL) and washed with water (80mL), brine (50 mL), dried over anhydrous $MgSO_4$, filtered, and the solvent removed. Purification by chromatography (15 % EtOAc-hexane) afforded 9.5 g (90 %) of white solid: mp 121.5-123 °C; ^1H NMR ($CDCl_3$) δ 1.22-1.30 (3H, m), 1.38-1.45 (9H, m), 2.01-2.28 (5H, m), 2.71-2.84 (2H, m), 4.17-4.27 (2H, m), 4.67-4.72 (1H, m), 6.68-6.91 (2H, m); IR (KBr) 3250, 2985, 1760, 1690 cm^{-1}; MS EI *m/e* 335 (M^+). Anal. calcd. for $C_{18}H_{25}NO_5$: C, 64.46; H, 7.51; N, 4.18; found: C, 64.55; H, 7.56; N, 4.05.

(*S*)-7-tert-Butoxycarbonylamino-8-methyl-chroman-2-carboxylic acid ethyl ester [(*S*-)**16**]. Following the same procedure described above using (*S*)-**15** afforded (*S*)-**16** in 95 % yield: mp 131-132 °C; $[\alpha]^{25}_D$ -24.8 ° (c=1.0, $CHCl_3$). Optical purity determined to be 99.9%. Anal. calcd. for $C_{18}H_{25}NO_5$: C, 64.46; H, 7.51; N, 4.18; found: C, 64.46; H, 7.56; N, 4.05.

(*R*)-7-tert-Butoxycarbonylamino-8-methyl-chroman-2-carboxylic acid ethyl ester [(*R*)-**16**]. Following the same procedure described above using (*R*)-**15** afforded (*R*)-**16** in 96 % yield: mp 130.5-131 °C; $[\alpha]^{25}_D$ +25.0 ° (c=1.0, $CHCl_3$). Optical purity determined to be 99.1%. Anal. calcd. for $C_{18}H_{25}NO_5$: C, 64.46; H, 7.51; N, 4.18; found: C, 64.31; H, 7.45; N, 4.04.

(*RS*)-7-(tert-Butoxycarbonylamino-8-methyl-chroman-2-yl)-methanol (17). To a solution of **16** (9.4 g, 28.0 mmol) in anhydrous THF (70 mL) was slowly added a 2.0 M solution of lithium borohydride (33.6 mL, 67.3 mmol) in THF. The reaction was allowed to stir for 24 h then quenched by the cautious addition of MeOH (15 mL). The reaction mixture was allowed to stir another 1 h, upon which time water (250 mL) was added and the mixture extracted with ether (2 x 400 mL). The organic layer was separated, dried over anhydrous $MgSO_4$, filtered, and the solvent removed. Purification by flash chromatography (50 % EtOAc-hexanes) afforded 12.3 g (99 %) a thick oil: ^1H NMR ($CDCl_3$) δ 1.28 (3H, t, J=7.0 Hz), 1.51 (9H, s), 2.13 (3H, s), 2.10-2.26 (2H, m), 2.68-2.81 (2H, m), 4.23 (2H, q, J=7.0 Hz), 4.71 (1H, dd, J=7.6, 3.7 Hz), 6.22 (1H, s), 6.85 (1H, d, J=8.4 Hz), 7.28 (1H, bd, J=8.4 Hz); IR (film) 3350, 2960, 2920, 1710, 1690 cm^{-1}; MS EI *m/e* 293 (M^+).

(*S*)-7-(tert-Butoxycarbonylamino-8-methyl-chroman-2-yl)-methanol [(*S*)-**17**)]. Following the same procedure described above using (*S*)-**16** afforded (*S*)-**17** in 98 % yield: mp 112-113 °C (CH_2Cl_2); $[\alpha]^{25}_D$ +70.81 (c=1.0, $CHCl_3$); IR (KBr) 3400, 3200, 1700, 1670 cm^{-1}. Optical purity determined to be 99.9%. Anal. calcd. for $C_{16}H_{23}NO_4$: C, 65.51; H, 7.90; N, 4.78; found: C, 65.12; H, 7.93; N, 4.79.

(*R*)-7-(tert-Butoxycarbonylamino-8-methyl-chroman-2-yl)-methanol [(*R*-)-**17**]. Following the same procedure described above using (*R*)-**16** afforded (*R*)-**17** in 99 % yield: mp 111-112 °C (CH_2Cl_2); $[\alpha]^{25}_D$ -70.8 (c= 1.0, $CHCl_3$); IR (KBr) 3400, 3200, 1700, 1670 cm^{-1}. Anal. calcd. for $C_{16}H_{23}NO_4$: C, 65.51; H, 7.90; N, 4.78; found: C, 65.15; H, 7.91; N, 4.61.

(*RS*)-[2-(tert-Butyl-dimethyl-silanyloxymethyl)-8-methyl-chroman-7-yl]-carbamic acid tert-butyl ester (18). A mixture of **17** (7.2 g, 24.5 mmol), t-butyldimethylsilyl chloride (4.1, 27.0 mmol), and imidazole (5.1 g, 73.6 mmol) in anhydrous DMF (50 mL) was stirrred for 15 h then poured into water (200 mL) and extracted with ether (2 x 150 mL). The organic layers were combined and washed again with water (80 mL), brine (80 mL), dried over anhydrous $MgSO_4$, filtered, and the solvent evaporated. Purification by flash chromatography (10% EtOAc-hexanes) afforded 9.7 g (96.8 %) of a clear oil which solidifies upon standing overnight: mp 61.5-62 °C; MS (EI) *m/e* 407 (M^+); ^1H NMR ($CDCl_3$) δ 0.09 (3H, s), 0.10 (3H, s), 0.92 (9H, s), 1.51 (9H, s), 1.66-1.76 (1H, m), 2.00-2.07 (1H, m), 2.08 (3H, s), 2.68-2.85 (2H, m), 3.74 (1H, dd, J=10.4, 5.7 Hz), 3.87 (1H, dd, J=10.4, 5.2 Hz), 4.01-4.05 (1H, m), 6.18 (1H, bs), 6.86 (1H, d, J=8.35 Hz), 7.21 (1H, d, J=8.35 Hz). Anal. calcd. for $C_{22}H_{37}NO_4Si$: C, 64.83; H, 9.15; N, 3.44; found: C, 64.78; H, 9.20; N, 3.32.

(*S*)-[2-(tert-Butyl-dimethyl-silanyloxymethyl)-8-methyl-chroman-7-yl]-carbamic acid tert-butyl ester [(*S*)-18]. Following the same procedure described above using (*S*)-**17** afforded (*S*)-**18** in 99 % yield: mp 63-64 °C; $[\alpha]^{25}_D$ +45.2° (c=1.0, $CHCl_3$). Anal. calcd. for $C_{22}H_{37}NO_4Si$: C, 64.83; H, 9.15; N, 3.44; found: C, 64.52; H, 9.05; N, 3.26.

(*R*)-[2-(tert-Butyl-dimethyl-silanyloxymethyl)-8-methyl-chroman-7-yl]-carbamic acid tert-butyl ester [(*R*)-18]. Following the same procedure described above using (*R*)-**17** afforded (*R*)-**18** in 97 % yield: mp 63-64 °C; $[\alpha]^{25}_D$ -42.2° (c=1.0, $CHCl_3$). Anal. calcd. for $C_{22}H_{37}NO_4Si$: C, 64.83; H, 9.15; N, 3.44; found: C, 64.79; H, 9.26; N, 3.40.

(*RS*)-7-(tert-Butoxycarbonyl-2,3,4,7-tetrahydro-pyrano[2,3-e]indol-2-yl)-methanol (19). To a solution of **18** (8.2 g, 20.1 mmol) in anhydrous THF (50 mL) containing 10 mg of 1,10-phenanthroline at -40 °C was slowly added 2.4 eq of 1.3 M s-butyl lithium (after 1 eq. of s-butyl lithium was added the deep red color of the indicator became apparent). The reaction was allowed to stand for 1.5 h after which anhydrous DMF (2 eq.) was added and the reaction was quenched with water (2 mL) after 15 min. The reaction mixture was diluted with ether (250 mL) and washed with saturated sodium bicarbonate (100 mL). The organic layer was separated and the solvent removed under vacuum. The reaction mixture was dissolved in 100 mL of THF containing 3 mL of concentrated hydrochloric acid. The solution was allowed to stir for 5 hr then poured into ether (250 mL) and washed with saturated aqueous sodium bicarbonate, dried over anhydrous $MgSO_4$, filtered, and the solvent evaporated. Chromatography (30 % EtOAc-hexanes) afforded 5.5 g (90 %) of desired product as a white solid: mp 102-104 °C: ^1H NMR ($CDCl_3$) δ 1.66 (9H, s), 1.88-2.03 (2H, m), 2.19 (1H, bs), 2.80-

3.00 (2H, m), 3.82-3.96 (2H, m), 4.29-4.26 (1H, m), 6.62 (1H, dd, J=3.5, 0.5 Hz), 6.98 (1H, d, J= 8.4 Hz), 7.46 (1H, d, J=3.5 Hz), 7.63 (1H, d, J=8.4 Hz); IR (film) 1735 cm^{-1}; MS EI *m/e* 303 (M^+); HRMS 303.14759 calcd for $C_{17}H_{21}NO_4$ found 303.1424259.

(*S*)-7-(tert-Butoxycarbonyl-2,3,4,7-tetrahydro-pyrano[2,3-e]indol-2-yl)-methanol [(*S*)-**19**]. Following the same procedure described above using (*S*)-**18** afforded (*S*)-**19** in 92 % yield: MS *m/e* 303 (M^+); $[\alpha]^{25}_D$ +83.5 ° (c=1.03, $CHCl_3$); HRMS 303.14759 calcd for $C_{17}H_{21}NO_4$ found 303.1424173.

(*R*)-7-(tert-Butoxycarbonyl-2,3,4,7-tetrahydro-pyrano[2,3-e]indol-2-yl)-methanol [(*R*)-**19**]. Following the same procedure described above using (*R*)-**18** afforded (*R*)-**19** in 90 % yield: MS *m/e* 303 (M^+); $[\alpha]^{25}_D$ -78.7 ° (c=1.1, $CHCl_3$); HRMS 303.14759 calcd for $C_{17}H_{21}NO_4$ found 303.1441.

(*RS*)-7-(tert-Butoxycarbonyl-2,3,4,7-tetrahydro-pyrano[2,3-e]indol-2-yl)-methylbromide (**20**). To a solution of **19** (4.93 g, 16.2 mmol) and CBr_4 (7.0 g, 21.1 mmol) in anhydrous CH_2Cl_2 (50 mL) at ambient temperature was slowly added a solution of triphenylphosphine in CH_2Cl_2 (30 mL). The reaction was stirred for 4 h then the solvent was removed and the crude product purified by flash chromatography (5 % EtOAc-hexanes) to afford 5.0 g (84 %) of desired product as a tannish oil: ^1H NMR (DMSO-d_6) δ 1.66 (9H, s,), 1.92-2.10 (1H, m), 2.10-2.29 (1H, m), 2.82-2.98 (2H, m), 3.58 (1H, dd, J=10.4, 6.4 Hz), 3.66 (1H, dd, J=10.4, 5.5 Hz), 4.32-4.38 (1H, m), 6.64 (1H, d, J=3.7 Hz), 6.98 (1H, d, J=8.3 Hz), 7.46 (1H, d, J=3.7 Hz), 7.63 (1H, d, J=8.3 Hz); IR (KBr) 1735 cm^{-1}; MS EI *m/e*: 365, 367 *m/e* (M^+).

(*S*)-7-(tert-Butoxycarbonyl-2,3,4,7-tetrahydro-pyrano[2,3-e]indol-2-yl)-methylbromide [(*S*)-**20**]. Following the same procedure described above using (*S*)-**19** afforded (*S*)-**20** in 80 % yield: mp 63-64 °C; MS FAB *m/e* 365/367 (M^+); $[\alpha]^{25}_D$ +57.1 (c=1.0, $CHCl_3$).

(*R*)-7-(tert-Butoxycarbonyl-2,3,4,7-tetrahydro-pyrano[2,3-e]indol-2-yl)-methylbromide [(*R*)-**20**]. Following the same procedure described above using (*R*)-**19** afforded (*R*)-**20** in 99 % yield: mp 100-103 °C; MS EI *m/e* 365/367 (M^+); $[\alpha]^{25}_D$ -68.1 (c=1.0, $CHCl_3$). Compounds *(S)*-**20** and(*R*)-**20** appear to be slightly unstable which accounts for the differences in melting points and optical rotations.

(*RS*)-Benzyl-(2,3,4,7-tetrahydro-pyrano[2,3-e]indol-2-ylmethyl)-amine (**7a**). A solution of **20** (1.0 g, 2.73 mmol), benzylamine (1.46 g, 13.6 mmol) in anhydrous DMSO (10 mL) was heated at 110 °C for

24 h. The reaction mixture was poured into 0.1 N NaOH (100 mL) and extracted with EtOAc (2 x 100 mL), dried over anhydrous $MgSO_4$, filtered, and the solvent evaporated. Purification by chromatography (3% MeOH-CH_2Cl_2) afforded 330 mg (41 %) of desired product as a tan oil: ^1H NMR ($CDCl_3$) δ 1.85-1.96 (1H, m), 2.06 (2H, m), 2.78-2.84 (1H, m), 2.91-3.07 (3H, m), 3.94 (2H, s), 4.32-4.38 (1H, m), 6.58 (1H, m), 6.88 (1H, d, J= 8.3 Hz), 6.91 (1H, d, J= 8.3 Hz), 7.07 (1H, dd, J=2.8, 2.4 Hz), 7.27-7.41 (5H, m), 8.02 (1H, bs); MS EI *m/e* 292 (M^+). The oxalate salt was prepared in isopropanol, mp 222-223 °C. Anal. calcd. for $C_{19}H_{20}N_2O \cdot C_2H_2O_4$: C, 65.96; H, 5.80; N, 7.33; found: C, 65.84; H, 5.74; N, 7.12.

(*RS*)-Propyl-(2,3,4,7-tetrahydro-pyrano[2,3-e]indol-2-ylmethyl)-amine (7c). Following the same procedure described above using propylamine afforded **7c** in 47 % yield. The oxalate salt was prepared in isopropanol: mp 193-195 °C; ^1H NMR (DMSO-d_6) δ 0.93 (3H, t, J=7.5), 1.66-1.78 (1H, m), 2.04-2.09 (2H, m), 2.71-2.77 (1H, m), 2.83-2.93 (1H, m), 2.96-3.08 (3H, m), 3.22-3.35 (2H, m), 4.36-4.41 (1H, m), 6.48 (1H, bs), 6.75 (1H, d, J= 8.2 Hz), 6.90 (1H, d, J= 8.2 Hz), 7.17 (1H, appt, J=2.8 Hz), 10.99 (1H, bs); MS EI *m/e* 244 (M^+). Anal. calcd. for $C_{15}H_{20}N_2O \cdot C_2H_2O_4 \cdot 0.5H_2O$: C, 59.46; H, 6.75; N, 8.16; found: C, 59.47; H, 6.50; N, 8.06.

(*RS*)-3-[(2,3,4,7-Tetrahydro-pyrano[2,3-e]indol-2-ylmethyl)-amino]-propan-1-ol (7d). Following the same procedure described above using 3-hydroxypropylamine afforded **7d** in 62 % yield. The oxalate salt was prepared in THF: mp 165-166 °C; ^1H NMR (DMSO-d_6) δ 1.66-1.88 (3H, m), 2.04-2.09 (1H, m), 2.70-2.75 (1H, m), 2.82-2.91 (1H, m), 3.01-3.05 (4H, m), 3.53 (2H, t, J=5.93 Hz), 4.39 (1H, m), 6.49 (1H, bs), 6.75 (1H, d, J= 8.4 Hz), 6.90 (1H, d, J= 8.2 Hz), 7.16 (1H, appt, J=2.4 Hz), 8.16 (3H, bs), 11.02 (1H, bs); MS EI *m/e* 260 (M^+). Anal. calcd. for $C_{15}H_{20}N_2O_2 \cdot C_2H_2O_4$: C, 58.27; H, 6.33; N, 7.99; found: C, 58.25; H, 6.54; N, 7.72.

(*RS*)-Furan-2-ylmethyll-(2,3,4,7-tetrahydro-pyrano[2,3-e]indol-2-ylmethyl)-amine (7e). Following the same procedure described above using 2-furanylmethylamine afforded **7e**: (38 % yield); ^1H NMR ($CDCl_3$) δ 1.86-1.96 (1H, m), 2.04 (2H, m), 2.76-2.82 (1H, m), 2.88-3.05 (3H, m), 3.91 (2H, s), 4.27-4.36 (1H, m), 6.23 (1H, dd, J=3.2, 0.8 Hz), 6.32 (1H, dd, J=3.2, 2.0 Hz), 6.57 (1H, m), 6.85 (1H, d, J=8.1 Hz), 6.90 (1 H, d, J=8.1 Hz), 7.07 (1H, dd, J=2.9, 3.1 Hz), 7.37 (1H, dd, 1.9, 0.77 Hz), 8.15 (1H, bs). The oxalate salt was prepared in THF: mp 187-188 °C. Anal. calcd. for $C_{17}H_{18}N_2O_2 \cdot C_2H_2O_4$: C, 61.28; H, 5.41; N, 7.52; found: C, 61.42; H, 5.46; N, 7.57.

(*RS*)-(2,3,4,7-Tetrahydro-pyrano[2,3-e]indol-2-ylmethyl)-(thiophen-2-ylmethyl)-amine (7f). Following the same procedure described above using 2-furanylmethylamine afforded **7e** (54 % yield): ^{1}H NMR ($CDCl_3$) δ 1.89-1.94 (1H, m), 2.02 (2H, m), 2.76-2.83 (1H, m), 2.89-3.06 (3H, m), 4.12 (2H, s), 4.28-4.34 (1H, m), 6.57 (1H, m), 6.84-6.98 (4H, m), 7.07 (1H, appt, J=3.0 Hz), 7.22 (1H, dd, J=4.72, 1.65 Hz), 8.15 (1H, bs). The oxalate salt was prepared in isopropanol: mp 223-224 °C. Anal. calcd. for $C_{17}H_{18}NOS•C_2H_2O_4$: C, 58.75; H, 5.19; N, 7.21; found: C, 58.63; H, 5.14; N, 7.06.

(*S*)-Benzyl-(2,3,4,7-tetrahydro-pyrano[2,3-e]indol-2-ylmethyl)-amine [(*S*-)-**7a**]. The title compound was prepared as described above by reacting (*S*)-**20** (850 mg, 2.3 mmol) with benzylamine to afford 375 mg (56 %) of product: MS EI *m/e* 292 (M^+); $[\alpha]^{25}_D$ +71.9 ° (c=1.0, $CHCl_3$). The oxalate salt was prepared from ethanol: mp 229-230 °C; $[\alpha]^{25}_D$ +88.7 °(c=1.0, DMSO). Anal. calcd. for $C_{19}H_{20}N_2O•C_2H_2O_4$: C, 65.96; H, 5.80; N, 7.33; found: C, 65.77; H, 5.79; N, 7.27.

(*R*)-Benzyl-(2,3,4,7-Tetrahydro-pyrano[2,3-e]indol-2-ylmethyl)-amine [(*R*)-**7a**]. The title compound was prepared as described above by reacting (*R*)-**20** (1.58 g, 4.20 mmol) with benzylamine to afford 680 mg (55 %) of product: MS EI *m/e* 292 (M^+); $[\alpha]^{25}_D$ -65.7 ° (c=1.0, $CHCl_3$). The oxalate salt was prepared from ethanol: mp 232-233 °C; $[\alpha]^{25}_D$ -93.6 ° (c=1.0, DMSO). Anal. calcd. for $C_{19}H_{20}N_2O•C_2H_2O_4$: C, 65.96; H, 5.80; N, 7.33; found: C, 65.86; H, 5.68; N, 7.17.

(*RS*)-2-(3,4,7,9-Tetrahydro-2H-pyrano[2,3-e]indol-8-one)-methanol (21). To a solution of **18** (10.0 g, 24.6 mmol) in anhydrous THF (120 mL) containing 10 mg of 1,10-phenanthroline at -40 °C was slowly added 49.3 mL of 1.3 M s-butyl lithium (after 24 mL of s-butyl lithium was added the deep red color of the indicator became apparent). The reaction was allowed to stand for 1.5 h after which carbon dioxide was bubbled into the solution for 30 min. The reaction was quenched with 1 N HCl (4 mL) and the solvent was removed. The dark oil was dissolved in MeOH (80 mL) containing water (8 mL), followed by the addition of 1 mL of concentrated hydrochloric acid. The reaction mixture was heated to reflux for 24 h whereupon the MeOH was evaporated and the reaction mixture was diluted with water (80 mL). The mixture was extracted with CH_2Cl_2 (3 x 200 mL) and the combined organic layers were dried over anhydrous $MgSO_4$, filtered, and the solvent removed under vacuum to afford an orange-tan solid. Trituration with ether afforded 2.13 g (40 %) of product: mp 214-215 °C; ^{1}H NMR (DMSO-d_6) δ 1.60-1.72 (1H, m), 1.93-1.99 (1H, m), 2.62-2.71 (2H, m), 3.24 (3H, s), 3.49-3.62 (2H, m), 3.96- 4.02 (1H, m), 4.83 (1H, t, J= 5.7 Hz, O**H**), 6.31 (1H, d, J=7.9 Hz),

6.85 (1H, d, J=7.9 Hz), 10.19 (1H, s, NH); MS EI *m/e* 219 (M^+); IR (KBr) 3500, 3190, 1695 cm^{-1}; HRMS 219.089544 calcd. for $C_{12}H_{13}NO_3$ found 219.088483.

(*S*)-2-(3,4,7,9-Tetrahydro-2H-pyrano[2,3-e]indol-8-one)-methanol [(*S*)-**21**]. Following the same procedure described above using (*S*)-**20** afforded (*S*)-**21** in 44 % yield: mp 203.5-204.5 °C; $[\alpha]^{25}_D$ + 88.5° (c=1.0, DMSO). Anal. calcd. for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.17; found: C, 65.44; H, 5.94; N, 6.17.

(*R*)-2-(3,4,7,9-Tetrahydro-2H-pyrano[2,3-e]indol-8-one)-methanol [(*R*)-**21**]. Following the same procedure described above using (*R*)-**20** afforded (*R*)-**21** in 56 % yield: mp 203-204 °C ; $[\alpha]^{25}_D$ -88.1° (c=1.0, DMSO). Anal. calcd. for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.17; found: C, 65.43; H, 5.93; N, 6.32.

(*RS*)-2-(p-Tolylsulfonylmethyl)-3,4,7,9-tetrahydro-2H-pyrano[2,3-e]indol-8-one (22b). To a solution of **21** (1.97 g, 9.0 mmol) in anhydrous pyridine (20 mL) was added p-tolylsulfonyl chloride (3.43 g, 18.0 mmol). The reaction was allowed to stir for 2 h at room temperature then quenched with water (10 mL). After stirring for 30 min the reaction was diluted with CH_2Cl_2 (300 mL) and washed with 1 N hydrochloric acid (2 x 150 mL). The organic layer was washed with water (80 mL) followed by saturated aqueous sodium bicarbonate (50 mL). The organic layer dried over anhydrous $MgSO_4$, filtered, and the solvent evaporated to afford a tan solid. Trituration with CH_2Cl_2-ether (1:1, 50 mL) afforded the desired product as a light tan solid (1.84 g). Concentration of the mother liquor and trituration afforded another crop of product (490 mg). The mother liquor was again concentrated, followed by column chromatography (3 % MeOH-CH_2Cl_2) to afford another 331 mg of product as an orange solid: (87 % yield); mp 209.5-210.5 °C; ^1H NMR (DMSO-d_6) δ 1.62-1.68 (1H, m), 1.87-1.93 (1H, m), 2.41 (3H, s), 2.61-2.69 (2H, m), 3.00 (1H, d J=22 Hz), 3.23 (1H, d, J=22 Hz), 4.14-4.19 (1H, m), 4.24-4.28 (2H, m), 6.32 (1H, d, J=7.9 Hz), 6.34 (1H, d, J=7.9 Hz), 7.46 (2H, d, J=8.6 Hz), 7.80 (2H, d, J=8.4 Hz), 10.23 (1H, s, NH); IR (KBr) 1695 cm^{-1}; MS EI *m/e* 373 (M^+).

(*S*)-2-(p-Tolylsulfonylmethyl)-3,4,7,9-tetrahydro-2H-pyrano[2,3-e]indol-8-one [(*S*)-**22b**]. Following the same procedure described above using (*S*)-**21** afforded (*S*)-**22** in 90 % yield: mp 187-188 °C; $[\alpha]^{25}_D$ + 12.3 ° (c=1.1, THF);); MS EI *m/e* 373 (M^+); HRMS 373.098397 calcd. for $C_{19}H_{119}NO_4S$ found 373.0925015.

(*R*)-2-(p-Tolylsulfonylmethyl)-3,4,7,9-tetrahydro-2H-pyrano[2,3-e]indol-8-one [(*R*)-**22b**]. Following the same procedure described above using (*R*)-**21** afforded (*R*)-**22** in 84 % yield: mp 193-194 °C;

$[\alpha]^{25}D$ -14.2 ° (c=1.0, THF); MS EI *m/e* 373 (M^+); HRMS 373.098397 calcd. for $C_{19}H_{119}NO_4S$ found 373.092844.

(*RS*)-2-(Benzylamino-methyl)-3,4,7,9-tetrahydro-2H-pyrano[2,3-e]indol-8-one [(*RS*)-**8a**]. A mixture of **22b** (1.1 g, 2.95 mmol) and benzylamine (631 mg, 5.89 mmol) in anhydrous DMSO (15 mL) containing triethylamine (2.95 mmol) was heated at 78 °C for 12 hr. The reaction mixture was then poured into CH_2Cl_2 (150 mL) and extracted with water (2 x 80 mL). The aqueous layer was basified with 50 % aqueous potassium carbonate and the aqueous layer washed with CH_2Cl_2 (100 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and the solvent was concentrated. Purification by chromatography (5 % MeOH- CH_2Cl_2) afforded 567 mg of a red-orange oil which solidifies upon standing: (62 % yield); mp 128-129°C; MS EI *m/e* 308 (M^+). The oxalate salt was prepared in THF: mp 254-255°C; ^1H NMR (DMSO-d_6) δ 1.66-1.71 (1H, m), 2.01 (2H, m), 2.64-2.73 (2H, m), 3.10-3.21 (2H, m), 3.33 (2H, s), 4.20 (1H, d, J=13.2 Hz), 4.26 (1H, d, J=13.2 Hz), 4.39 (1H, m), 6.37 (1H, d, J=7.9 Hz), 6.89 (1H, d, J=7.7 Hz), 7.38-7.45 (3H, m), 7.51-7.54 (2H, m), 10.27 (1H, s). Anal. calcd. for $C_{19}H_{20}N_2O_2 \cdot C_2H_2O_4 \cdot 0.5\ H_2O$: C, 61.28; H, 5.69; N, 6.88; found: C, 62.14; H, 5.49; N, 6.75.

(*RS*)-2-(4-Methoxy-benzylamino-methyl)-3,4,7,9-tetrahydro-2H-pyrano[2,3-e]indol-8-one (8b). Following the same procedure described above using 4-methoxybenzylamine afforded **8b** in 50 % yield. The oxalate salt was prepared in THF: mp 247-248 °C; ^1H NMR (DMSO-d_6) δ 1.65-1.70 (1H, m), 2.02 (2H, m), 2.66-2.73 (2H, m), 3.10-3.19 (2H, m), 3.33 (2H, d, J=2.0 Hz), 3.76 (3H, s), 4.14 (1H, d, J=13.2 Hz), 4.21 (1H, d, J=13.2 Hz), 4.40 (1H, m), 6.37 (1H, d, J=7.9 Hz), 6.88 (1H, d, J=7.7 Hz), 6.98 (1H, d, J=9.0 Hz), 7.45 (1H, d, J=8.8 Hz), 10.28 (1H, s); MS EI *m/e* 338 (M^+). Anal. calcd. for $C_{20}H_{22}N_2O_3 \cdot C_2H_2O_4 \cdot 0.5\ H_2O$: C, 60.41; H, 5.76; N, 6.40; found: C, 60.57; H, 5.66; N, 6.21.

(*RS*)-2-(4-Methyl-benzylamino-methyl)-3,4,7,9-tetrahydro-2H-pyrano[2,3-e]indol-8-one (8c). Following the same procedure described above using 4-methylbenzylamine afforded **8c** in 72 % yield: The oxalate salt was prepared in THF: mp 249-250 °C; ^1H NMR (DMSO-d_6) δ 1.64-1.70 (1H, m), 2.02 (1H, m), 2.31 (3H, s), 2.62-2.75 (2H, m), 3.06-3.17 (2H, m), 3.32 (2H, s), 4.13 (1H, d, J=13.2 Hz), 4.19 (1H, d, J=13.4 Hz, 4.39 (1H, m), 6.37 (1H, d, J=7.9 Hz), 6.88 (1H, d, J=7.9 Hz), 7.22 (1H, d, J=8.1 Hz), 7.40 (1H, d, J=7.9 Hz), 10.28 (1H, s); MS EI *m/e* 322 (M^+).. Anal. calcd. for $C_{20}H_{22}N_2O_2 \cdot C_2H_2O_4$; C, 64.07; H, 5.87; N, 6.79; found: 64.22; H, 5.98; N, 6.84.

(*RS*)-2-(4-Fluoro-benzylamino-methyl)-3,4,7,9-tetrahydro-2H-pyrano[2,3-e]indol-8-one (8d). Following the same procedure described above using 4-fluorobenzylamine afforded **8d** in 58 % yield. The oxalate salt was prepared in THF: mp 256-259 °C; ^{1}H NMR (DMSO-d$_6$) δ 1.66-1.72 (1H, m), 2.02 (2H, m), 2.64-2.73 (2H, m), 3.08-3.18 (2H, m), 3.33 (2H, s), 4.17 (1H, d, J=13.4 Hz), 4.23 (1H, d, J=13.4 Hz), 4.36-4.40 (1H, m), 6.37 (1H, d, J=7.7 Hz), 6.89 (1H, d, J=7.7 Hz), 7.27 (2H, appt, J=8.8 Hz), 7.55-7.59 (2H, m), 10.27 (1H, s). Anal. calcd. for $C_{20}H_{22}N_2O_2 \cdot C_2H_2O_4$; C, 60.57; H, 5.08; N, 6.73; found: C, 60.18; H, 4.97; N, 6.55.

(*RS*)-2-(4-Chloro-benzylamino-methyl)-3,4,7,9-tetrahydro-2H-pyrano[2,3-e]indol-8-one (8e). Following the same procedure described above using 4-chlorobenzylamine afforded **8e** in 62 % yield. The oxalate salt was prepared in THF: mp 250-251.5 °C; ^{1}H NMR (DMSO-d$_6$) δ 1.66-1.70 (1H, m), 2.02 (1H, m), 2.31 (3H, s), 2.63-2.73 (2H, m), 3.07-3.17 (2H, m), 3.33 (2H, d, J=1.54 Hz), 4.18 (1H, d, J=13.4 Hz), 4.22 (1H, d, J=13.4 Hz), 4.39 (1H, m), 6.37 (1H, d, J=7.7 Hz), 6.89 (1H, d, J=7.9 Hz), 7.48-7.55 (1H, d, J=8.1 Hz), 10.26 (1H, s); MS EI *m/e* 342/344 (M^+). Anal. calcd. for $C_{19}H_{19}N_2O_2Cl \cdot C_2H_2O_4$; C, 58.27; H, 4.89; N, 6.47; found: C, 58.66; H, 5.06; N, 6.15.

(*RS*)-2-(2,4-Dimethyl-benzylamino-methyl)-3,4,7,9-tetrahydo-2H-pyrano[2,3-e]indol-8-one (8f). Following the same procedure described above using 2,4-dimethylbenzylamine afforded **8f** in 46 % yield. The oxalate salt was prepared in isopropanol: mp 244-245 °C; ^{1}H NMR (DMSO-d$_6$) δ 1.63-1.68 (1H, m), 2.00 (1H, m), 2.22 (3H, s), 2.25 (3H, s), 2.61-2.81 (4H, m), 3.25 (2H, s), 3.69 (2H, s), 4.12 (1H, m), 6.31 (1H, d, J=7.7 Hz), 6.84-6.96 (3H, m), 7.17 (1H, d, J=7.7 Hz), 10.20 (1H, s); MS EI *m/e* 336 (M^+). Anal. calcd. for $C_{21}H_{24}N_2O_2 \cdot C_2H_2O_4$; C, 64.78; H, 6.15; N, 6.57; found: C, 64.53; H, 6.12; N, 6.59.

(*S*-)-2-(Benzylamino-methyl)-3,4,7,9-tetrahydro-2H-pyrano[2,3-e]indol-8-one [(*S*)-8a]. Following the same procedure described above using (*S*)-**22b** afforded (*S*)-**8a** in 56 % yield: mp 131-133 °C (free base); $[\alpha]^{25}_D$ +65.3 ° (c=1.01, $CHCl_3$, free base). Optical purity of free base determined to be 99.7 %. The fumarate salt was prepared in isopropanol: mp 203-204 °C; $[\alpha]^{25}_D$ +57.7 ° (c=1.0, DMSO). The optical purity of the fumarate was determined to be 100 %. Anal. calcd. for $C_{19}H_{20}N_2O_2 \cdot C_2H_2O_4$: C, 68.83; H, 6.05; N, 7.64; found: C, 69.19; H, 6.18; N, 7.55.

***(R)*-2-(Benzylamino-methyl)-3,4,7,9-tetrahydro-2H-pyrano[2,3-e]indol-8-one [(*R*)-8a].** Following the same procedure described above using (*R*)-**22b** afforded (*R*)-**8a** in 53 % yield: mp 133-134.5 °C (free base);

$[\alpha]^{25}_D$ -64.4 ° (c=1.04, $CHCl_3$, free base). The optical purity of the free base was determined to be 99.3 %. The fumarate salt was prepared in isopropanol: mp 203-204 °C ; $[\alpha]^{25}_D$ -53.9 (c=1.0, DMSO). The optical purity of the fumarate salt was observed to be 99.5 %. Anal. calcd. for $C_{19}H_{20}N_2O_2 \cdot C_2H_2O_4$: C, 68.83; H, 6.05; N, 7.64; found: C, 68.46; H, 6.08; N, 7.48.

Resolution of (*RS*)-2-(Benzylamino-methyl)-3,4,7,9-tetrahydro-2H-pyrano[2,3-e]indol-8-one [(*RS*)-**8a**]. (*RS*)-**8a** (440 mg) was submitted to semipreparative HPLC containing a Chiralcel AS column by using eighteen injections over a two day period and eluting (0.5 mL/min, pressure 50 bar, detection at 280 nm) with ethanol. The first peak at 17.4 min was collected to afford (+)-**8a** (188 mg) as a orange solid: (99.7 % optical purity): $[\alpha]^{25}$ +66.2 ° (c=1.0, $CHCl_3$); mp 135-136 °C. The (+)-free base (165 mg) was treated with fumaric acid in isopropanol to afford 176 mg of the hemifumarate salt: mp 203-204 °C; $[\alpha]^{25}$ +54.3 ° (c=1.0, DMSO). Anal. calcd. for $C_{19}H_{20}N_2O_2 \cdot 0.5C_4H_4O_4 \cdot 0.25H_2O$: C, 68.00; H, 6.11; N, 7.55; found: C, 68.25; H, 5.98; N, 7.51.

The second peak isolated with a retention time of 27.3 min was collected to afford the (-)-**8a** (198 mg) as an orange solid: (99.8 % optical purity): $[\alpha]^{25}$ -69.2 ° (c=1.0, $CHCl_3$); mp 136.5-137.5 °C. The (-)-free base (153 mg) was treated with fumaric acid in isopropanol to afford 165 mg of hemifumarate: mp 201-202 °C; $[\alpha]^{25}$ -57.6° (c=1.0, DMSO). Anal. calcd. for $C_{19}H_{20}N_2O_2 \cdot 0.5C_4H_4O_4 \cdot 0.25H_2O$: C, 68.00; H, 6.11; N, 7.55; found: C, 68.08; H, 5.94; N, 7.51.

Molecular Modeling

Computations were performed using Sybyl software package version 6.3 (Tripos Associates, St. Louis, Mo, USA) on a Silicon Graphic workstation. For Maximin calculations (Tripos force field), the Powell method was chosen (default values).

Biological Assays

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 prepared as previously described [13].

Receptor Binding Assays: hD_{2S}, hD_3, and $hD_{4.4}$ dopamine Receptors. See previously described methods [13].

Receptor Binding Assays: Dopamine D_2 High and Low affinity states: See previously described methods [13].

Receptor Binding Assays: 5-HT$_{1A}$ and α_1 Receptors: See previously described methods [13]

Mouse Hypolocomotion. See previously described methods [13].

Circling Methods. Rotational Behavior in 6-OHDA Lesioned Rats. Sprague-Dawley rats (Charles River) were prepared with unilateral 6-OHDA lesions of the nigrostriatal pathway according to previously described methods [26-29] and were evaluated for sensitivity to indirect and direct dopamine agonists. On the day of testing, animals (N = 8/dose group) were administered s.c. saline and allowed one hour acclimation to the test chambers (Med Associates Inc., St. Albans, VT). Immediately following acclimation, test compounds were administered s.c. and contralateral and ipsilateral rotations were recorded for one hour. Direct dopamine agoniststs induce contralateral rotations.

X-Ray Crystallographic Analysis

The absolute configuration of (*S*)-(-)-**15** was established by an X-ray analysis of its free base. A colorless prism cut to 0.32 x 0.32 x 0.50 mm in size was mounted on a glass fiber with epoxy cement and then transferred to a Siemens P4 diffractometer equipped with graphite-monchromated Mo Ka radiation (l = 0.71073 Å). The structure was solved in the orthorhombic space group $P2_12_12_1$ by direct methods (SHELXTL-PLUS, Release 4.21. Siemens Analytical X-ray Instruments, Inc., Madison, Wisconsin, USA.), and refined by full-matrix least-squares on F^2 using SHELXL-93 [30]. A total of 2566 reflections were measuresd, 2192 were unique (R_{int} = 1.63 %) and 1930 had I > 2s(I). Corrections were made for Lorentz and polarization effects but not for absorption. The non-hydrogen atoms were refined with anisotropic displacement coefficients, H atom positions were refined with isotropic displacement coefficients U(H) = 1.2U(C), an extinction parameter was included, and the weighting scheme employed was w = $1/[s^2(F_o^2) + (0.0582P)^2]$ where P =($F_o^2 + 2F_c^2$)/3. The amino H atoms were taken from a difference-Fourier map and included in the refinements with U(H) = 1.5U(N) and with their positional parameters free to vary.

Crystal data and structure refinement data for (*S*)-(-)-**15** ($C_{13}H_{17}FNO_3$): Orthorhombic, $P2_12_12_1$, a = 8.5195 (3)Å (a = 90 °), b = 11.1444 (5)Å (b = 90 °), c = 13.0325 (9)Å (g = 90 °); Radiation, Mo Ka (l = 0.71073 Å); J range for data collection 2.4 to 24.99°; Z value 4; D_{calc} 1.263 mg/m^3; Absorption coefficient, 0.090 mm^{-1}; F000, 504; J range for data collection, 2.4 to 24.99°; Index ranges, $0 \le h \le 10$, $0 \le k \le 13$, $0 \le l \le 15$ plus Friedel reflections; Reflections collected, 2566 Independent reflections, 2192 (R_{int} = 0.0163); Refinement method; Full-matrix least-squares on F^2; Data / Restraints / Paramters, 2192 / 0 / 193; Goodness-of-fit on F^2, 1.023; Final R indices [I>2s(I)] R1 = 0.0321, wR2 = 0.0860; R indices (all data) R1 = 0.0370, wR2 = 0.0884; Extinction coefficient, 0.031 (4); Largest diff. peak and hole, 0.156 and -0.105 eÅ^{-3}.

Supplementary X-ray analysis data have been deposited at the Cambridge Crystallographic data Centre and are available on request.

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