New Generation Dopaminergic Agents. 6. Structure−Activity Relationship Studies of a Series of 4-(Aminoethoxy)indole and 4-(Aminoethoxy)indolone Derivatives Based on the Newly Discovered 3-Hydroxyphenoxyethylamine D_2 Template

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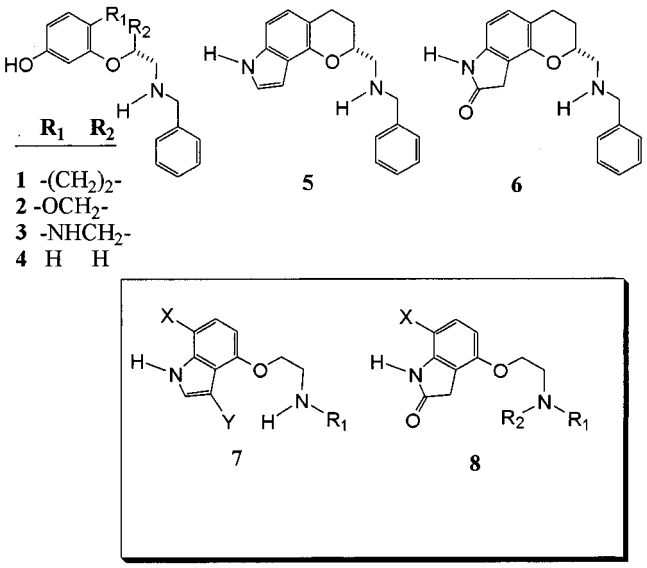
A series of 4-(aminoethoxy)indoles **7** and a related series of 4-(aminoethoxy)indolones **8** were synthesized and evaluated for their affinity for both the high- and low-affinity agonist states (D_2^{High} and D_2^{Low}, respectively) of the dopamine (DA) D_2 receptor. The 4-aminoethoxy derivatives (i.e., **7** and **8)** were designed as bioisosteric analogues based on the phenol prototype **4**. The indolones **8** were observed to have high affinity for the D_2^{High} receptor. Comparison of their previously reported chroman analogues with the more flexible 4-(aminoethoxy)indoles revealed the chroman analogues to be more potent, whereas little loss in D_2^{High} affinity was observed when comparing the 4-(aminoethoxy)indolones with their respective chroman analogues. Several regions of the phenoxyethylamine framework were modified and recognized as potential sites to modulate the level of intrinsic activity. A conformational analysis was performed and a putative bioactive conformation was proposed which fulfilled the D_2 agonist pharmacophore criteria based on the McDermed model. 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

Ever since the link between psychosis and dopamine was established over 40 years ago, researchers have focused on various approaches toward modulating dopaminergic activity via the dopamine (DA) D_2 receptors as a potential means of treating schizophrenia.[1] Unfortunately, current antipsychotics which rely on their ability to completely block the postsynaptic D_2 receptors are not efficacious in treating all schizophrenic patients and cause motor disorders such as extrapyramidal side effects (EPS). Another approach, whose therapeutic utility is currently being investigated, is based on identifying D_2 agonists which selectively activate the inhibitory D_2 autoreceptors while weakly antagonizing the postsynaptic D_2 receptors.[2] In a hypoactive dysfunctional state the D_2 receptor would be expected to be supersensitized and therefore be activated by an agonist of lower intrinsic activity. As such a D_2 partial agonist would theoretically be clinically effective in treating schizophrenic forms whose etiology is based on hyperactivity (positive symptoms) or hypoactivity (negative symptoms).

Recently work in our laboratories led to the discovery of several novel scaffolds which can be used to access the D_2 agonist pharmacophore.[3−5] Unlike traditionally designed D_2 agonists which exploit the phenethylamine scaffold,[6] phenols **1**−**4** (Chart 1) embrace a completely novel framework unexploited in the dopamine field. Soon after the discovery of the phenolic prototypes **1**−**4**, we reported that the angular indole **5** and indol-8-one **6** were potent D_2 partial agonists.[7] Previously we reported a conformational analysis which revealed that the roles of the chroman and benzodioxan rings were to allow the methylamino and hydrogen bond-donating groups ready access to the D_2 agonist pharmacophore.[3,8] Other ring systems such as the benzofuran, benzotet-

Chart 1



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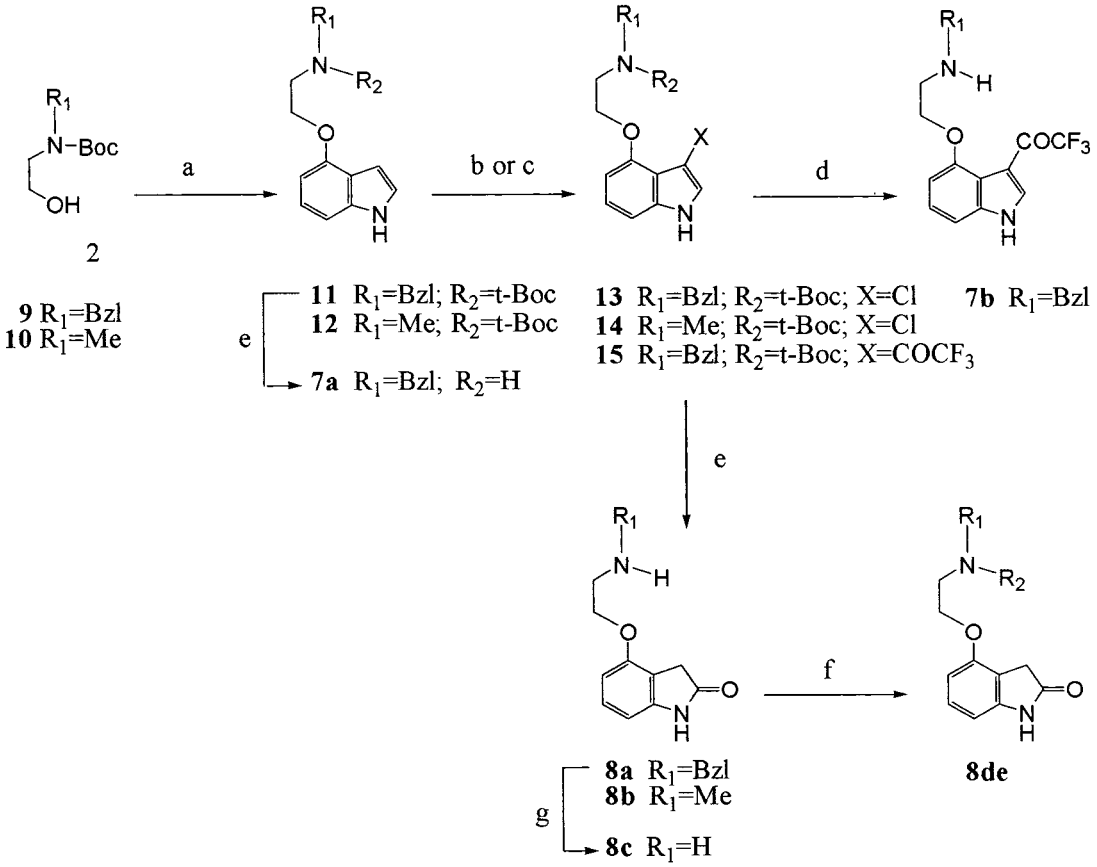
Scheme 1[a]



[a] Reagents: (a) DEAD, PPh_3, 4-hydroxyindole (method A); (b) NCS, THF (method B); (c) TFAA; (d) TFA; (e) H_3PO_4, $MeOCH_2CH_2OH$ (method C); (f) RCl, DMF (method E); (g) Pd/C, H_2 (method D).

rahydrofuran, and tetralin rings were ineffective scaffolds for the D_2 agonist pharmacophore and led to compounds of inferior D_2 affinity.[3,9] Though the phenolic derivatives **1**−**4**, indole **5**, and indolone **6** were structurally similar, quite different profiles in vitro and in vivo were observed. Comparison of the affinities for the agonist state (high-affinity state, D_2^{High}) of the D_2 receptor of **1** (K_i = 0.2 nM) and **2** (K_i = 0.4 nM) clearly revealed that beneficial conformational effects were imparted by the pyran and dioxan rings when compared to the more conformationally promiscuous aryloxyethylamine derivative **4**.[4] Even so, exploiting the simpler phenolic template **4** by preparing the indole and indolone analogues (i.e., **7a** and **8a**, respectively) appeared to be an appealing strategy toward the discovery of potentially interesting dopaminergic agents. Any conformational restrictions imparted by the proximal pyrrole and lactam ring systems onto the aminoethoxy side chain could potentially result in a beneficial effect on D_2^{High} affinity. From a synthetic point of view, the truncated analogues of indole **5** and indolone **6** should be more readily accessible and chemically versatile. We now report the syntheses and structure−activity relationships (SAR) of the two new classes of 4-(aminoethoxy)indole and 4-(aminoethoxy)indolone analogues (**7, 8**) based on the phenolic template **4**.

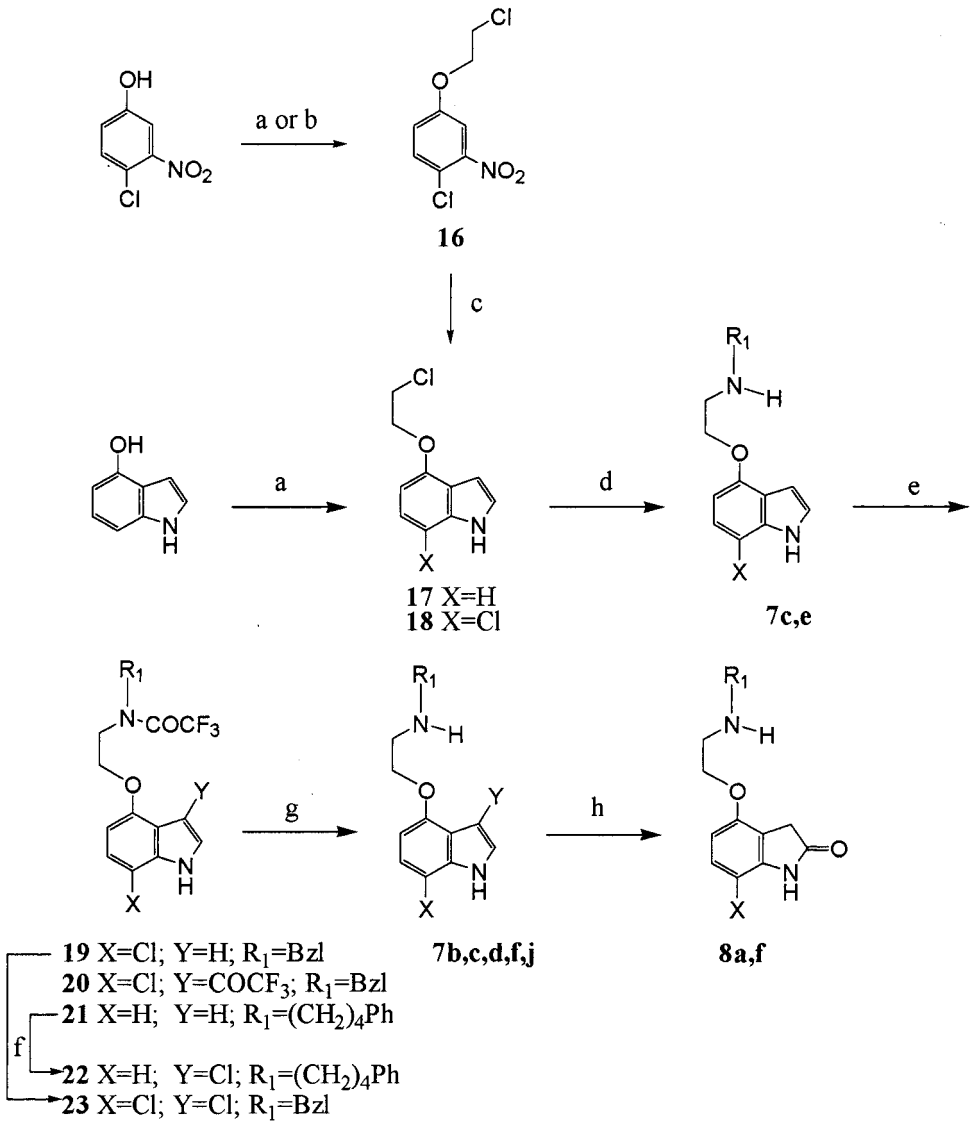
Chemistry

Shown in Scheme 1 is the general synthetic route used to prepare the indoles **7a,b** and indolones **8a**−**e**. 4-Hydroxyindole was coupled to alcohols **9** and **10** using Mitsunobu protocol[10] to afford the 4-(aminoethoxy)-indoles **11** and **12**. Removal of the Boc group was achieved with phosphoric acid to afford **7a**. Chlorination using NCS of indoles **11** and **12** led to the 3-chloroindoles **13** and **14**, which were hydrolyzed with phosphoric acid in 2-methoxyethanol to produce indolones **8a,b**. Hydrogenolysis of **8a** with 10% palladium on carbon afforded **8c**. Alkylation of **8b** provided indolones **8d,e**. Treatment of **11** with trifluoroacetic anhydride (TFAA) afforded **15** which upon exposure to TFA provided **7b**.

Commercially available 4-chloro-3-nitrophenol could be converted to the chloroethoxy derivative **16** either by coupling 2-chloroethanol using Mitsunobu conditions[10] or more preferably by reacting either 1,2-bromochloroethane or 1,2-dichloroethane (Scheme 2). Utilization of the Bartoli indole protocol[11] allowed for the conversion of **16** to the 7-chloroindole **18**. Treatment of **17** and **18** with the appropriate amines afforded indoles **7c,e**. Protection of **7c** using TFAA afforded amide **21**. Indole **7e** when reacted with an excess of trifluoroacetic anhydride produced **19**, as well as the diacylated product **20**. Chlorination of **19** and **21** led to the 3-chloroindoles (i.e., **23** and **22,** respectively). Deprotection of the trifluoroacetyl group produced indoles **7b,f,j**. Acid hydrolysis of the 3-chloroindoles **7b,f** gave the corresponding indolones **8a,f**.

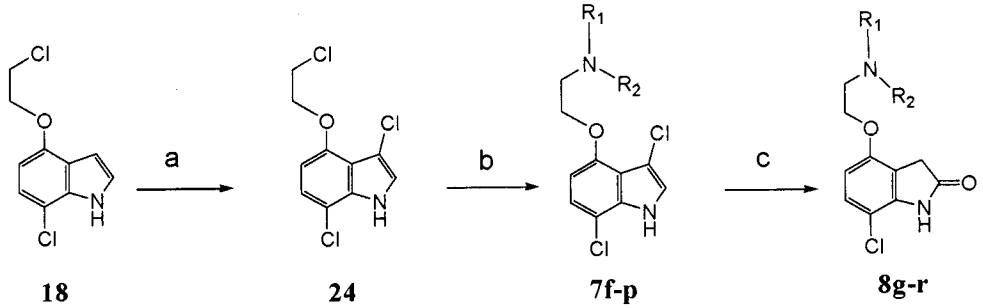
A more expedient route to the 7-chloroindoles and 7-chloroindolones is shown in Scheme 3. Key intermediate **18** was chlorinated using trichloroisocyanuric acid

Scheme 2[a]



[a] Reagents: (a) DEAD, chloroethanol, PPh_3 (method A); (b) $ClCH_2CH_2Cl$/or $BrCH_2CH_2Cl$, K_2CO_3, butanone (method G or H); (c) CH_2=$CHMgBr$; (d) RNH_2, DMSO (method I); (e) TFAA; (f) NCS (method B); (g) K_2CO_3, $MeOH/H_2O$; (h) H_3PO_4, methoxyethanol (method C).

Scheme 3[a]

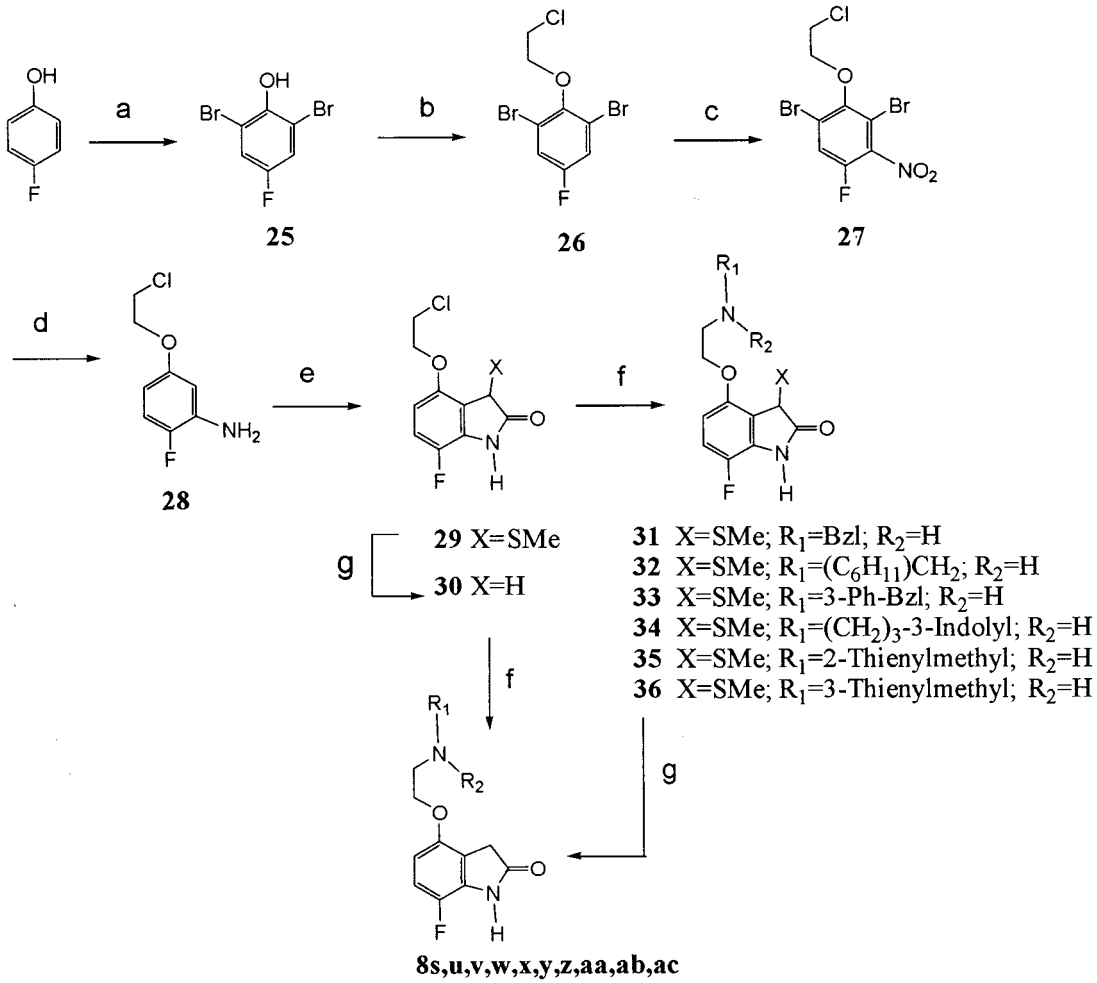


[a] Reagents: (a) NCS or TCICA (method J or K); (b) NR_1R_2, DMSO (method I); (c) H_3PO_4, methoxyethanol (method C).

or NCS to afford **24** which was subsequently converted to the corresponding 4-(aminoethoxy)indoles and 4-(aminoethoxy)indolones.

Shown in Scheme 4 is the general route used to prepare the 7-fluoroindolones. 4-Fluorophenol was brominated using 2 equiv of bromine to afford **25** in excellent yield. Attachment of the chloroethenyl side chain afforded **26** which was subsequently mononitrated. Exhaustive hydrogenation of **27** led to **28** which was converted to indolone **29** using the Gassman protocol.[12] Removal of the thiomethyl group of **29** using Raney nickel afforded **30**. Target indolones (**8s,u**−**z**,**aa**,**ab**,**ac**) were prepared by treatment of the appropriate amines with either **29** or **30**.

Scheme 4[a]



[a] Reagents: (a) Br_2; (b) $Cl(CH_2)_2Br$, K_2CO_3; (c) HNO_3/H_2SO_4; (d) H_2, Pd/C; (e) (i) $MeSCH_2CO_2Et$, SO_2Cl_2, (ii) NEt_3, (iii) AcOH; (f) R_1R_2NH; (g) Ra/Ni.

Pharmacology

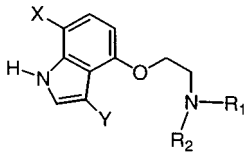
All compounds were evaluated for their affinity to rat striatal DA D_2 receptors using the agonist [^{3}H]quinpirole to label the high-affinity state (D_2^{High}) and the antagonist [^{3}H]spiperone plus GTP to label the low-affinity state (D_2^{Low}). Ketanserin (30 nM) was present in all assays with [^{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.[13,14] Additionally, the majority of quinpirole 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 are expressed as K_i values using the Cheng−Prussoff equation.[15]

The compound's intrinsic activity was predicted upon the preferential antagonism of agonist versus antagonist radioligand binding, based upon a similar method previously reported by Lahti[16] and Wasik.[17] 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 ($K_i^L = K_iD_2^{Low}$; $K_i^H = K_iD_2^{High}$). The ratio (i.e., K_i^L/K_i^H) was shown to be a reliable estimate of 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 that of talipexole[18] ($K_i^L/K_i^H = 466^3$) and SDZ-208-911[19] ($K_i^L/K_i^H = 1.1^3$) were subsequently evaluated in vivo by utilizing the well-established phenomenon of receptor-mediated feedback inhibition of the presynaptic neuron.[20] Effects in mouse exploratory locomotor activity (LMA) 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−Activity Relationships. Binding affinities for the D_2^{High}, D_2^{Low}, 5-HT_{1A}, and α_1 receptors for the 4-(aminoethoxy)indoles **7a**−**k** and 4-(aminoethoxy)-indolones **8a**−**z**,**aa**,**ab**,**ac** are reported in Tables 1 and

Table 1. 4-(Aminoethoxy)indole Derivatives **7**



					K_i (nM)[a,b]				
compd	X	Y	R_1	R_2	D_2^{High}	D_2^{Low}	5-HT_{1A}	α_1	ratio (D_2^{Low}/D_2^{High})
7a	H	H	Bzl	H	9.7 ± 1.7	39.3 ± 0.0	18	675	4
7b	H	$COCF_3$	Bzl	H	3.0 ± 0.2	16.6 ± 5.9	30	60	6
7c	H	H	$(CH_2)_4Ph$	H	5.3 ± 1.3	14.4 ± 0.0	0.4	11.5	3
7d	H	Cl	$(CH_2)_4Ph$	H	4.8 ± 1.1	15.7 ± 0.6	0.5	8.5	3
7e	Cl	H	Bzl	H	7.4 ± 1.6	14.4 ± 4.4	193	138.5	2
7f	Cl	Cl	Bzl	H	7.0 ± 0.2	19.9 ± 0.0	219	66	3
7g	Cl	Cl	Bzl	Me	*	*	*	*	
7h	Cl	Cl	4-Cl-Bzl	H	77.1 ± 5.8	29.8 ± 12.1	*	458	0.4
7i	Cl	Cl	4-F-Bzl	H	50.0 ± 2.4	59.5 ± 3.3	685	229	1
7j	Cl	$COCF_3$	Bzl	H	30.3 ± 2.9	32.9 ± 2.1	51	97.5	1
7k	Cl	Cl	2-thiophenemethyl	H	12.3 ± 1.0	38.4 ± 6.7	0% (0.1)	*	3
7l	Cl	Cl	3-thiophenemethyl	H	*	*	*	*	
7m	Cl	Cl	*n*-Bu	H	*	*	*	*	
7n	Cl	Cl	4-MeBzl	H	*	*	*	*	
7o	Cl	Cl	4-Ph-Bzl	H	*	*	*	*	
7p	Cl	Cl	$Ph(CH_2)_2$-	$-CH_2-$	*	*	*	*	
7q	Cl	Cl	$PhCH_2$-	$-CH_2-$	*	*	*	*	
7r	Cl	Cl	2-naphthylmethyl	H	*	*	*	*	
1[c]					0.2 ± 0.02	3.3 ± 0.8	22.5	212	16
2[c]					0.4 ± 0.2	5.7 ± 3.7	156	254	14
3[d]					6.7 ± 0.6	130 ± 0.0	*	*	19
4[e]					3.6 ± 0.1	115 ± 14	1782	5291	32
5[f]					1.9 ± 0.8	35.9 ± 4.7	0.4	24	18
6[f]					0.14 ± 0.01	5.9 ± 0.3	8.5 ± 4	165 ± 21	42

[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. Percentages represent inhibition of binding at the micromolar concentration shown in parentheses. [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] Reference 3. [d] Reference 5. [e] Reference 4. [f] Reference 7. * Not determined.

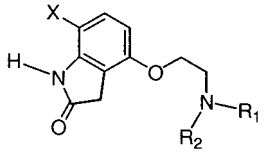
2, respectively. A direct comparison of the chroman **1** (K_i = 0.2 nM) and the corresponding phenoxyethylamine derivative **4** (K_i = 3.6 nM) revealed an 18-fold difference in affinity attributed to the conformational role of the chroman ring (Table 1). However, when the same comparison is made between chroman **5** (K_i = 1.9 nM) and **7a** (K_i = 9.7 nM), only a 5-fold difference in affinity was observed, suggesting that the pyrrole moiety may be having a beneficial conformational effect. Attachment of a chlorine atom at the 7 position of **7a** (i.e., **7e**) had little effect on D_2^{High} affinity; however, an 11-fold loss in 5-HT_{1A} affinity and a 4-fold increase in α_1 receptor affinity were observed. The benzyl group, identified in our earlier work[3] to be the side chain of choice to induce D_2^{High} selectivity, was again verified to impart selectivity when comparing **7a** to **7c**. Incorporation of substituents at the 3-position of the indole moiety had only a slight effect on D_2^{High} affinity (**7a** vs **7b**, **7c** vs **7d**). In general, no improvement of the profile of **7a** was observed from modifications of its core structure. Upon this observation, our investigation focused on establishing SAR on the corresponding 4-(aminoethoxy)indolones **8**.

Surprisingly, indolone **8a** revealed an even more striking similarity to its chroman analogue **6** than the above-mentioned indoles (i.e., **7a** vs **5**) in terms of D_2^{High} affinity. As shown in Table 2, virtually identical D_2^{High} affinities were observed between indolone **6** (K_i = 0.14 nM) and **8a** (K_i = 0.2 nM), suggesting no advantage in utilizing the chroman ring to constrain the pharmacophoric elements (i.e., basic amine and NH of indolone moiety). Since we had shown in our previous report that the 7-OH-(aminomethyl)chroman **1** and its indolone analogue **6** can mimic each other in terms of hydrogen-bonding capabilities with respect to the D_2^{High} receptor, a conformational effect appears to be the obvious explanation for the unexpected 17-fold increase in affinity when comparing the 3-(aminoethoxy)phenol **4** with its indolone counterpart (i.e., **8a**). Apparently the *N*-benzylaminoethoxy side chains of **7a** and **8a** become progressively more optimized conformationally toward accessing the D_2 agonist pharmacophore when replacing the phenol with the indole and indolone moieties. A more detailed analysis of the cause of this effect is discussed below in the molecular modeling studies.

A 3−4-fold loss in D_2^{High} affinity was observed when a halogen was placed in the 7-position of **8a** (i.e., **8h,s**); however, selectivity over 5-HT_{1A} receptors improved. Attaching substituents to the benzyl group of **8a** had deleterious effects on D_2^{High} affinity (**8h** vs **8j−m**, **8s** vs **8u**,**v**). A loss in D_2^{High} affinity was observed when comparing the secondary amines to their corresponding tertiary amines (**8a** vs **8d**, **8h** vs **8i**), a trend previously observed in the chroman series. However, excellent D_2^{High} affinity could be achieved by a tertiary amine when the benzyl group was embedded within a ring system (**8i** vs **8n,o**). Replacement of the benzyl group with other various side chains had little effect on D_2^{High} affinity (**8h** vs **8p−r**, **8s** vs **8w−ac**).

Intrinsic Activity and in Vivo Studies. An assessment of intrinsic activity was initially 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.

Table 2. 4-(Aminoethoxy)indolone Derivatives **8**



				K_i (nM)[a,b]				
compd	R_1	R_2	X	D_2^{High}	D_2^{Low}	5-HT_{1A}	α_1	ratio (D_2^{Low}/ D_2^{High})
8a	Bzl	H	H	0.21 ± 0.01	11.4 ± 1.2	306 ± 2	1448 ± 150	54
8b	Me	H	H	2.0 ± 0.2	147 ± 75	276	1057	74
8c	H	H	H	6.93 ± 0.02	268 ± 0.0	664	11081	39
8d	Bzl	Me	H	0.76 ± 0.01	49.6 ± 0.9	6262	4829	65
8e	$(CH_2)_3$CO-F-Ph	Me	H	3.1 ± 0.03	24.1 ± 3.0	253	9.5	8
8f	$(CH_2)_4$Ph	H	H	0.23 ± 0.04	2.06 ± 0.11	1.9	13.0	9
8g	*n*-Bu	H	7-Cl	0.84 ± 0.1	14.6 ± 3.3	0% (0.1)	11% (0.1)	17
8h	Bzl	H	7-Cl	0.41 ± 0.04	2.8 ± 0.04	2657 ± 52	350	7
8i	Bzl	Me	7-Cl	2.6 ± 0.7	23.4 ± 5.3	8% (1)	41% (1)	9
8j	4-F-Bzl	H	7-Cl	1.3 ± 0.7	13.8 ± 1.5	6564	431	11
8k	4-Cl-Bzl	H	7-Cl	1.4 ± 0.3	4.1 ± 1.2	1895	134	3
8l	4-Me-Bzl	H	7-Cl	0.64 ± 0.09	5.5 ± 1.0	1169	334	9
8m	4-Ph-Bzl	H	7-Cl	17.4 ± 3.9	46.7 ± 4.5	38% (1)	268	3
8n	$(CH_2)_2$Ph	$(CH_2)_2$	7-Cl	0.55 ± 0.11	4.27 ± 2.1	17% (1)	143	8
8o	CH_2Ph	CH_2	7-Cl	0.44 ± 0.17	2.85 ± 4.83	41% (1)	85	6
8p	2-naphthyl	H	7-Cl	6.34 ± 2.6	15.3 ± 0.1	41% (1)	292	2
8q	2-thiophenemethyl	H	7-Cl	0.60 ± 0.05	3.94 ± 1.32	59% (0.1)	5% (0.1)	7
8r	3-thiophenemethyl	H	7-Cl	0.24 ± 0.12	3.32 ± 1.23	83% (0.1)	14% (0.1)	14
8s	Bzl	H	7-F	0.63 ± 0.17	5.30 ± 1.63	535	52% (1)	8
8t	H	H	F	12.1 ± 1.5	916 ± 46	25% (1)	21% (1)	76
8u	4-Ph-Bzl	H	7-F	4.8 ± 0.7	27.4 ± 3.72	340	220	6
8v	3-Ph-Bzl	H	7-F	0.93 ± 0.35	3.92 ± 0.26	625	2899	4
8w	2-naphthyl	H	7-F	0.63 ± 0.10	9.0 ± 0.3	121	154	14
8x	2-thiophenemethyl	H	7-F	0.66 ± 0.02	21.8 ± 9.4	39% (1)	32% (1)	33
8y	3-thiophenemethyl	H	7-F	0.84 ± 0.43	17.8 ± 7.6	24% (1)	39% (1)	21
8z	$CH_2(C_6H_{11})$	H	7-F	0.65 ± 0.15	5.60 ± 2.2	17% (0.1)	380	9
8aa	$(CH_2)_2$Ph	CH_2	7-F	0.86 ± 0.06	5.02 ± 0.87	25% (1)	128	6
8ab	CH_2Ph	CH_2	7-F	2.08 ± 0.52	16.0 ± 4.2	13% (1)	268	7
8ac	$(CH_2)_3$-3-indolyl	H	7-F	0.15 ± 0.07	3.03 ± 0.36	12	26	20

[a,b] See footnotes of Table 1.

A comparison of the results obtained with the six standards using the current methodology agrees well with that reported by Lahti et al.[16] 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., $K_iD_2^{Low}/K_iD_2^{High} = K_i^L/K_i^H$).

As shown in Table 1 the 4-(aminoethoxy)indole derivatives **7a**−**k** were all predicted to have low intrinsic activity ($K_i^L/K_i^H \leq 6$). Indoles **7h,i**, having halogenated side chains, were predicted to have the lowest intrinsic activities ($K_i^L/K_i^H \leq 1$). Comparing the predicted intrinsic activity ratio of **7a** (K_i^L/K_i^H) = 4] to its chroman analogue **5** ($K_i^L/K_i^H = 18$) suggests the chroman ring may be playing a role toward increasing both affinity and intrinsic activity.

In contrast to the previous comparison between **5** and **7a**, removal of the pyran ring of chroman **6** (i.e., **8a**) resulted in a higher predicted intrinsic activity ratio. Halogenation of the 7-position of **8a** (i.e., **8h,s**) again led to lower intrinsic activity ratios, a trend observed with the 4-(aminoethoxy)indoles as well as noted in our previously reported 7-OH-(aminomethyl)chroman SAR study.[3] The introduction of large lipophilic side chains in place of the simple benzyl side chain also resulted in lowering the predicted intrinsic activity ratios (i.e., **8a** vs **8e,f**). In general, the predicted intrinsic activity ratios of the 4-(aminoethoxy)indolones **8a**−**z**,**aa**,**ab**,**ac** were observed to be much higher than their corresponding 4-(aminoethoxy)indole congeners **7a**−**k**. Further in vivo behavioral evaluations were performed on a selected group of 4-(aminoethoxy)indolones (i.e., **8a**,**d**,**h**,**j**−**l**,**r**,**s**,**aa**).

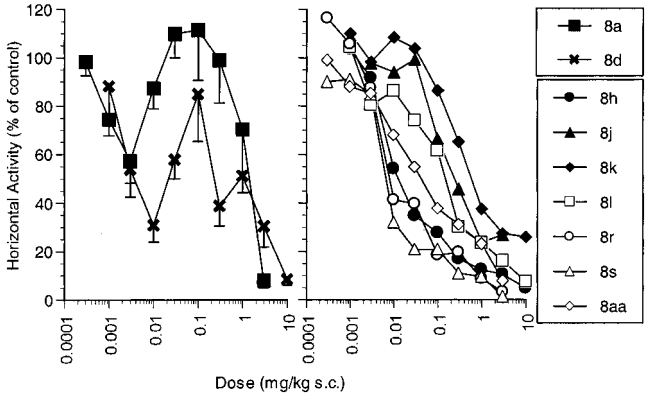


Figure 1. Dose−response curves for inhibition of spontaneous locomotor activity for **8a**,**d**,**h**,**j**,**k**,**l**,**r**,**s**,**aa**.

In vivo behavioral studies in mice revealed that all compounds reduced spontaneous locomotor activity (Figure 1). Our previous reports indicated a relationship between the estimated intrinsic activity and the shape of the locomotor activity dose−effect curve.[3] Compounds with high intrinsic activity estimates produce dose−effects curves with an initial phase of reduced activity

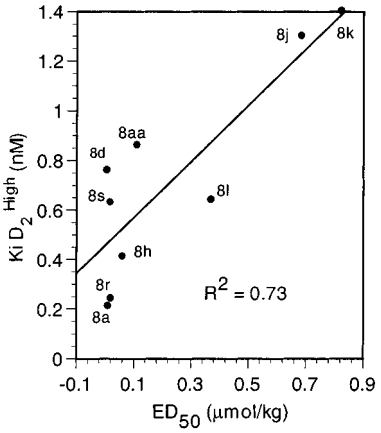


Figure 2. Correlation between D_2^{High} affinity and in vivo potency for compounds **8a**,**d**,**h**,**j**,**k**,**l**,**r**,**s**,**aa**.

followed by a second phase where motor activity is less reduced and returns toward baseline. The initial low-dose phase presumably is generated by stimulation of presynaptic dopamine autoreceptors regulating firing rates and neurotransmitter release from dopaminergic neurons. The second high-dose phase presumably results from stimulation of postsynaptic dopamine receptors. The difference in sensitivity to dopamine agonist effects has been proposed to be related to the high receptor reserve at presynaptic dopamine receptors with low receptor occupancy being required to produce maximal presynaptic responses to high intrinsic activity agonists.[21] Thus, low doses of an agonist preferentially stimulate presynaptic receptors. This type of dose-effect curve was observed when **8a**,**d** were tested, consistent with the high intrinsic activity ratios shown in Table 2. Several other analogues of **8a**, specifically **8h**−**l**,**r**,**s**,**aa**, all produced only a single-phase dose−effect curve (Figure 1). This result is consistent with the low intrinsic activity ratios observed for all of these analogues (Table 2). Although it cannot be concluded that these latter compounds fail to stimulate presynaptic receptors, on the basis of these results, they appear to have insufficient intrinsic activity to stimulate normosensitive postsynaptic receptors and, therefore, show a primarily antagonist-like profile. When the ED_{50} for hypolocomotor effects of each compound was compared with the K_i for the D_2^{High}, a statistically significant correlation between receptor affinity and in vivo potency was observed (Figure 2). The initial phase of hypolocomotion was used in the case of **8a**,**d** for the estimation of this ED_{50}. Although locomotor activity was reduced at even higher doses of **8a,d**, as was observed in the testing of previous compounds with high intrinsic activity,[3] the mechanism for this high dose effect would not correlate well with in vitro affinity for the D_2 receptor.

Compounds **8a**,**h** were taken into additional assays to address their in vivo agonist efficacy. In rats with unilateral lesions of the nigrostriatal dopamine pathway, direct dopamine agonists stimulate supersensitive postsynaptic striatal receptors to induce contralateral rotations. At doses of 0.03 and 0.3 mg/kg sc **8a** produced a mean (±SEM) of 502 (±136) and 363 (±82) contralateral rotations in 60 min compared to a mean of 4 (±4) contralateral rotations during a predrug control period of equal length. In contrast, **8h** was less effective producing mean (±SEM) contralateral rotations of 59 (±36), 151 (±66), and 153 (±63) at doses of 0.03, 0.3, and 3 mg/kg sc, respectively, compared to 1.3 (±1.3) contralateral rotations following vehicle treatment. In addition, **8a**,**h** were tested against apomorphine (1 mg/kg sc)-induced stereotypic sniffing and climbing behaviors in mice. **8h** blocked apomorphine-induced climbing and stereotypy with ED_{50} values of 0.24 and 0.3 mg/kg sc, respectively, whereas **8a** blocked apomorphine-induced climbing only with an ED_{50} of 0.13 mg/kg sc. Stereotypy was not significantly affected at doses of **8a** up to 3 mg/kg sc. However, **8a** (0.03−1 mg/kg sc) failed to induce apomorphine-like behaviors in mice pretreated with reserpine (5 mg/kg sc, 20 h) and only weakly induced stereotypy, but not climbing, in mice treated with the D_1 agonist SKF-38393 (10 mg/kg ip). These data are in contrast to the effects of the D_2 agonist quinpirole in these assays.[22] Together, these data suggest that both **8a**,**h** are partial agonists, capable of stimulating postsynaptic dopamine receptors under certain conditions, with **8h** having lower efficacy than **8a**.

Molecular Modeling Studies. The majority of traditional D_2 agonists have been based on the 3-OH-phenethylamine moiety whose pharmacophoric requirements are represented by the McDermed DA D_2 model.[23] Recently, our laboratories have discovered several entirely novel frameworks which can be used as scaffolds to access the D_2 agonist pharmacophore. The 7-OH-2-(aminomethyl)chroman (**1**) and 7-OH-2-(aminomethyl)-benzodioxan (**2**) were observed to have low-energy conformations which adhered to most of the criteria outlined by the McDermed D_2 model. A comparison of the D_2^{High} affinities of the aryloxyethylamine (**4**) versus its chroman (**1**) and benzodioxan (**2**) analogues clearly reveal that the pyran and dioxan rings are constraining the *N*-benzyl-2-aminomethyl group so that the D_2 agonist pharmacophore can be easily accessed from analogous low-energy state conformations.

A Monte Carlo conformational search was performed on **4** and **8a** using the MM3 force field as implemented in Macromodel 6.0 where all rotatable bonds, angles and torsions were allowed to move. Ring conformations were allowed to be flexible. Since the McDermed model outlines conformations which specifically examine the basic nitrogen and aryl centroid geometry, the benzyl substituents were not initially considered in these calculations. The basic nitrogen was protonated in all calculations, and a formal charge of 1 was used to adequately reflect the protonation state. An initial Monte Carlo calculation used 10 000 steps to generate conformations which were not necessarily fully minimized. A subsequent calculation to determine the local conformation for each originally generated structure ensured that all final conformations were fully minimized.

Though the global energy conformation for the desbenzyl analogue of **8a** (i.e., **8c**) did not meet the D_2 agonist pharmacophore criteria as described by the McDermed model, a conformation only 0.014 kcal/mol higher in energy closely abided the requirements of the D_2 agonist pharmacophore (Figure 3). In analogy to compound **8c**, the D_2 agonist conformation for the desbenzyl analogue of **4** (i.e., **4′**) was found to be 0.17 kcal/mol higher in energy that its global minimum. The energy difference of **4′** and **8c** between their respective global minimum conformations suggests that the in-

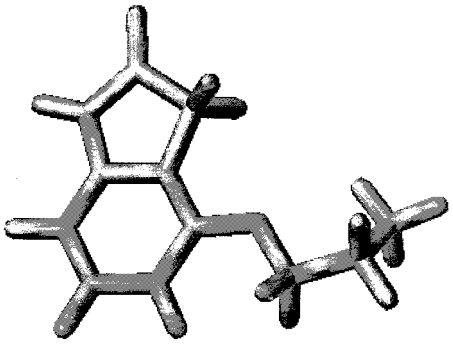


Figure 3. Putative D_2 agonist pharmacophoric conformation of **8c**.

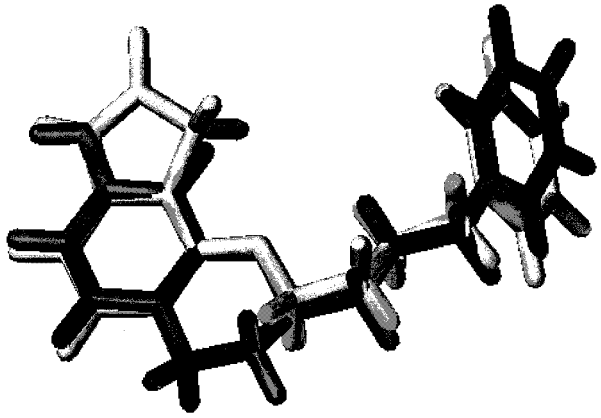


Figure 4. Superposition of **8a** and **1** in their putative D_2 agonist pharmacophoric conformations.

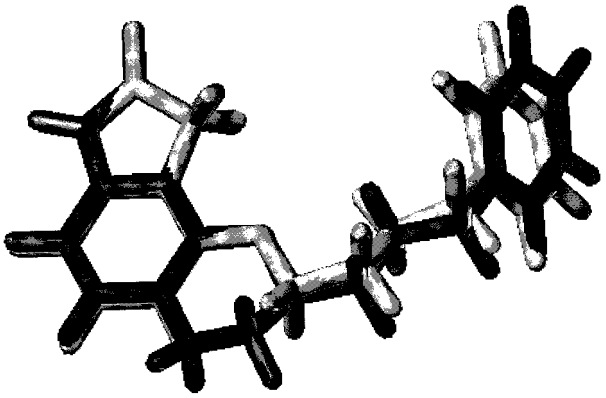


Figure 5. Superposition of **8a** and **6** in their putative D_2 agonist pharmacophoric conformations.

dolone ring of **8c** may be imparting a rigidifying effect allowing **8c** easier access than **4′** to the D_2 agonist pharmacophore (compare K_i values for **4** vs **8a**: **4**, K_i = 3.6 nM vs **8a**, K_i = 0.2 nM). Using the above-mentioned putative bioactive conformation of **8c** as a starting point, the benzyl side chain was attached (i.e., **8a**) and minimized to an analogous conformation previously identified for chroman **1** (Figure 4). Shown in Figure 5 is the superposition of **8a** and **6** in their putative D_2 agonist pharmacophoric conformations.

Conclusions

We have identified two novel classes of D_2 partial agonists (i.e., **7** and **8**) which are based on the 3-OH-phenoxyethylamine template **4**. The indolones **8** were observed to be more potent than their phenolic prototype **4**. Intrinsic activity could be modulated by attachment of a halogen at the 7-position of both the indoles **7** and the indolones **8** or by increasing lipophilicity to the side chain appendage. In vivo studies were observed to corroborate the predictive activity ratios of several members of the indolone derivatives. Molecular modeling reveals that the indolone ring of **8** was having a rigidifying effect which allowed easy access to the D_2 agonist pharmacophore conformation. Studies in our laboratories have been focused on expanding our knowledge of the D_2 agonist pharmacophore by the identification of novel ligands belonging to a new generation of dopaminergic agents.

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. 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.

Benzyl(2-hydroxyethyl)carbamic Acid *tert*-Butyl Ester (9). A solution of *N*-benzylaminoethanol (4.8 g, 31.9 mmol) and di-*tert*-butyl dicarbonate (7.5 g, 34.4 mmol) in anhydrous THF (30 mL) was stirred at ambient temperature for 18 h. The solvent was removed and the product purified by flash chromatography (EtOAc−hexane, 1:1) to afford 8.0 g (99%) of a thick oil: MS EI *m/e* 251 (M^+); IR (film) 1675, 1690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.47 (9H, s), 2.44 (bs, 1H, O**H**), 3.39 (2H, bs), 3.70 (2H, bs), 4.48 (2H, bs), 7.22−7.35 (5H, m). Anal. ($C_{14}H_{21}NO_3$) C, H, N.

Methyl(2-hydroxyethyl)carbamic Acid *tert*-Butyl Ester (10). Using the same general procedure as described above for **9** utilizing *N*-methylaminoethanol afforded **10** in 84% yield as a clear oil: MS *m/e* 175 (M^+); ^{1}H NMR ($CDCl_3$) δ 1.37 (9H, s), 2.49 (3H, bs), 3.18 (2H, appt, J = 6.04 Hz), 3.44 (2H, appq, J = 11.6, 5.7 Hz), 4.64 (1H, bs, O**H**). Anal. ($C_8H_{17}NO_3$) C, H, N.

Method A. Benzyl[2-(1*H*-indol-4-yloxy)ethyl]carbamic Acid *tert*-Butyl Ester (11). To a solution of **9** (12.68 g, 50.5 mmol), 4-hydroxyindole (4.48 g, 33.6 mmol), and triphenylphosphine (14.1 g, 53.8 mmol) in anhydrous THF (130 mL) was slowly added a solution of diethyl azidocarboxylate (9.38 g, 53.8 mmol) in THF (15 mL) at room temperature. The reaction was allowed to stir for 16 h, then the solvent removed, and the crude product dissolved in ether and diluted with hexanes. After standing for 30 min, the solid was filtered and the filtrate concentrated. The product was purified by flash chromatography to afford 8.6 g (70%) of a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.44 and 1.50 (2H, s, rotamers), 3.60 and 3.71 (2H, m, rotamers), 4.21 and 4.29 (2H, m, rotamers), 4.67 (2H, s), 6.47 (1H, appt, J = 8.3 Hz), 6.63 (1H, appt, J = 2.5 Hz), 7.00−7.11 (3H, m), 7.23−7.34 (5H, m), 8.27 (1H, bs); IR (film) 1680 cm^{-1}; MS EI *m/e* 366 (M^+). Anal. ($C_{22}H_{26}N_2O_3$) C, H, N.

Methyl[2-(1*H*-indol-4-yloxy)ethyl]carbamic Acid *tert*-Butyl Ester (12). Treatment of **10** according to method A above afforded **12** in 77% yield as a yellow oil: MS EI *m/e* 290 (M^+); HRMS calcd for $C_{16}H_{22}N_2O_3$ 290.1630, observed 290.1593.

Method B. Benzyl[2-(3-chloro-1*H*-indol-4-yloxy)ethyl]-carbamic Acid *tert*-Butyl Ester (13). To a solution of **11** (6.3 g, 17.2 mmol) in THF (100 mL) was added NCS (2.3 g, 17.2 mmol) in two portions over 1 h. The reaction was allowed to stir for 18 h and the solvent removed under vacuum. The mixture was dissolved in ether, and the insoluble solids were filtered. The solvent was again removed and the product purified by chromatography (30% EtOAc−hexanes) to afford 5.65 g (82%) of white solid: mp 114−116 °C; ^{1}H NMR ($CDCl_3$) δ 1.43 and 1.50 (2H, s, rotamers), 3.63 and 3.72 (2H, m, rotamers), 4.19 and 4.25 (2H, m, rotamers), 4.75 (2H, bs), 6.49 (1H, d, J = 7.5 Hz), 6.94 (1H, d, J = 8.1 Hz), 7.04−7.11 (2H, m), 7.23−7.34 (5H, m), 8.21 (1H, bs); IR (KBr) 1680 cm^{-1}; MS EI *m/e* 400/402 (M^+). Anal. ($C_{22}H_{25}ClN_2O_3$) C, H, N.

Methyl[2-(3-chloro-1*H*-indol-4-yloxy)ethyl]carbamic Acid *tert*-Butyl Ester (14). The title compound was prepared from **12** in 75% yield as a white solid according to method B: mp 153−154 °C; MS FAB *m/z* 325 ($M^+ + H^+$); HRMS FAB calcd for $C_{26}H_{26}N_2O_5$ 325.1370, observed 325.1375. Anal. ($C_{16}H_{21}ClN_2O_3$) C, H, N.

***N*-Benzyl-*N*-[2-(3-(2,2,2-trifluoroethanoyl)-1*H*-indol-4-yloxy)ethyl]carbamic Acid *tert*-Butyl Ester (15).** To a solution of **11** (1.85 g, 5.05 mmol) and triethylamine (0.8 mL, 0.6 g, 6 mmol) in anhydrous CH_2Cl_2 was added trifluoroacetic acid anhydride (1.1 mL, 1.6 g, 7.8 mmol) over 5 min at room temperature. The reaction mixture was stirred at room temperature overnight. The reaction was washed twice with water and then dried over anhydrous $MgSO_4$. Filtration and evaporation of solvent gave 3.38 g of residue. Purification by chromatography (20% EtOAc−hexanes) gave the title compound as an amorphous light yellow solid: 1.15 g (49%); MS EI *m/e* 462 (M^+); IR (KBr) 1719, 1744 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.33 and 1.38 (2s, 9H, rotamers), 3.50−3.63 (2m, 2H, rotamers), 4.15 (t, 2H, J = 5.5 Hz), 4.54 (s, 2H), 6.77 (d, 1H, J = 7.9 Hz), 7.15 (d, 1H, J = 8.1 Hz), 7.20−7.27 (m, 4H), 7.29−7.35 (m, 2H), 8.32 (s, 1H), 12.58 (s, 1H).

1-[4-(2-Benzylaminoethoxy)-1*H*-indol-3-yl]-2,2,2-trifluoroethanone (7b). To a solution of **15** (1.1 g, 2.4 mmol) in CH_2Cl_2 (60 mL) was added trifluoroacetic acid (TFA) (1.87 g, 16.3 mmol). The reaction mixture was allowed to stir overnight and poured into an aqueous solution of saturated $NaHCO_3$ (40 mL). The organic layer was dried over anhydrous $MgSO_4$ and filtered. Evaporation of the solvent followed by purification by chromatography (CH_2Cl_2−CH_3OH: 96/4) gave the 780 mg (90%) product as a light tan oil.

To a warm solution of fumaric acid (0.26 g, 2.2 mmol) in EtOH (15 mL) was added a warm solution of the above product as a free base in EtOH (15 mL). This mixture was allowed to stand at room temperature for 2 h and then filtered to give 0.54 g (54%) of the title compound as a white powder: mp >220 °C dec; MS EI *m/e* 362 (M^+); IR (KBr) 1660 cm^{-1}. Anal. ($C_{19}H_{17}F_3N_2O_2\cdot 0.5C_4H_4O_4$) C, H, N.

Method C. 4-(2-Benzylaminoethoxy)-1,3-dihydroindol-2-one (8a). A mixture of **13** (5.4 g, 13.5 mmol) in 2-methoxyethanol (25 mL) containing 85% phosphoric acid (10 mL) was heated at 100 °C for 1 h. The reaction was allowed to cool and then basified with 2 N sodium hydroxide and extracted with CH_2Cl_2 (2 × 150 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and chromatographed (5% MeOH−CH_2Cl_2) to afford 3.28 g (86%) of a grayish white solid: mp 145−146 °C; IR (KBr) 1690 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.03 (2H, t, J = 5.3 Hz), 3.44 (2H, s), 3.88 (2H, s), 4.14 (2H, t, J = 5.5 Hz), 6.50 (1H, d, J = 7.7 Hz), 6.56 (1H, d, J = 8.6 Hz), 7.15 (1H, appt, J = 8.6 Hz), 7.26−7.35 (5H, m), 7.82 (1H, bs); MS FAB *m/z* 383 ($M^+ + H^+$). The fumarate salt was prepared in 2-propanol: mp 220−221 °C. Anal. ($C_{17}H_{18}N_2O_2\cdot C_4H_4O_4$) C, H, N.

4-(2-Methylaminoethoxy)-1,3-dihydroindol-2-one (8b). The title compound was prepared from **14** according to method C in 66% yield as a grayish white solid: mp 153−156 °C; MS EI *m/e* 206 (M^+); HRMS EI calculated for $C_{11}H_{14}N_2O_2$ 206.1055, observed 206.1061. The fumarate salt was prepared in 2-propanol: mp 212−214 °C. Anal. ($C_{11}H_{14}N_2O_2\cdot C_4H_4O_4$) C, H, N.

***N*-Benzyl-2-(1*H*-indol-4-yloxy)ethylamine (7a).** The title compound was prepared from **11** in 26% yield according to method C. The fumarate salt was prepared in 2-propanol: mp 158−165 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.08 (2H, t, J = 5.6 Hz), 3.97 (2H, s), 4.21 (2H, t, J = 5.6 Hz), 6.45−6.48 (2H, m), 6.50 (2H, s), 6.93−7.15 (2H, m), 7.18−7.29 (1H, m), 7.25−7.31 (1H, m), 7.32−7.38 (2H, m), 7.40−7.45 (2H, m) 11.06 (1H, s). Anal. ($C_{17}H_{18}N_2O\cdot C_4H_4O_4$) C, H, N.

Method D. 4-Aminoethoxy-1,3-dihydroindol-2-one (8c). A mixture of **8a** (1.93 g, 6.84 mmol) in absolute EtOH (50 mL) containing 10% palladium on carbon (400 mg) was shaken in a Parr hydrogenator for 4 days at room temperature. The catalyst was filtered and washed with MeOH. The solvent was removed under vacuum to afford a light tan solid (1.15 g, 88%): mp 136−138 °C; MS EI *m/e* 192 (M^+). Anal. ($C_{10}H_{12}N_2O_2$) C, H, N.

Method E. 4-(2-Benzylmethylaminoethoxy)-1,3-dihydroindol-2-one (8d). A mixture of **8b** (480 mg, 2.33 mmol), benzyl chloride (324 mg, 25.6 mmol), and K_2CO_3 (676 mg, 48.9 mmol) in anhydrous DMF (10 mL) was heated to 85 °C for 2 h, then poured into water (100 mL), and extracted with EtOAc (2 × 150 mL). The organic layer was dried over anhydrous $MgSO_4$ and filtered and the solvent removed under vacuum. The product was chromatographed (5% MeOH−CH_2Cl_2) to afford a yellow oil (354 mg, 51%): MS EI *m/e* 296 (M^+). The fumarate salt was prepared in warm 2-propanol: mp 114−116 °C. Anal. ($C_{18}H_{20}N_2O_4\cdot 0.5C_4H_4O_4\cdot 0.75H_2O$) C, H, N.

4-[2-[[4-(4-Fluorophenyl)-4-oxobutyl]methylamino]-ethoxy]-1,3-dihydroindol-2-one (8e). A mixture of **8b** (600 mg, 2.91 mmol), 2-(3-chloropropyl)-2-(4-fluorophenyl)-1,3-dioxolane (1.16 g, 4.76 mmol), and K_2CO_3 (844 mg, 6.1 mmol) in anhydrous DMF (12 mL) containing KI (80 mg) was allowed to react according to method E. Purification by chromatography (5% MeOH−CH_2Cl_2) afforded 800 mg of a red oil: MS EI *m/e* 414 (M^+); HRMS EI calcd for $C_{23}H_{27}N_2O_4F$ 414.1955, observed 414.1911. This material was dissolved in MeOH (25 mL) containing 2 mL of concentrated HCl and allowed to stir at reflux temperature for 3 h. The reaction mixture was allowed to cool and the solid filtered to afford a light yellow solid which was washed with MeOH (5 mL) to afford 415 mg (55%) of product as the HCl salt: mp 246−248 °C. Anal. ($C_{21}H_{23}FN_2O_3\cdot HCl\cdot 0.5H_2O$) C, H, N.

1-(2-Chloroethoxy)-4-chloro-3-nitrobenzene (16). The title compound was prepared by reacting 4-chloro-3-nitrophenol with 2-chloroethanol according to method A to afford a white solid in 93% yield: mp 46−48 °C; MS EI *m/e* 235, 237, 239 (M^+); ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.95 (2H, t, J = 5.2 Hz), 4.36 (2H, t, J = 5.2 Hz), 7.32 (1H, dd, J = 3.2, J = 8.9 Hz), 7.66 (1H, d, J = 9 Hz), 7.69, (1H, d, J = 3.2 Hz). Anal. ($C_8H_7Cl_2NO_3$) C, H, N.

Method G. 1-(2-Chloroethoxy)-4-chloro-3-nitrobenzene (16). To a 2-L three-neck round-bottom flask were added 4-chloro-3-nitrophenol (50 g, 0.29 mol), K_2CO_3 (100 g, 0.72 mol), dichloroethane (315 g, 3.2 mol), KI (5 g), and 2-butanone (1 L). The mixture was mechanically stirred and heated to reflux for 44 h and then allowed to cool to room temperature, and the solids were filtered. The solvent was evaporated under vacuum and the oil dissolved in diethyl ether (300 mL) and washed with 10% sodium hydroxide. The organic layer was dried over anhydrous $MgSO_4$ and filtered and the solvent removed under vacuum. The product was dissolved in 1:1 CH_2Cl_2−hexanes and filtered through silica. Upon concentration 54.5 g (78%) of product was afforded as a white solid.

Method H. 1-(2-Chloroethoxy)-4-chloro-3-nitrobenzene (16). To a 500-mL three-neck round-bottom flask were added 4-chloro-3-nitrophenol (10 g, 0.058 mol), K_2CO_3 (20 g, 0.14 mol), 1-bromo-2-chloroethane (34.5 g, 0.24 mol), and 2-butanone (200 mL). The mixture was mechanically stirred and heated to reflux for 20 h under nitrogen and then allowed to cool to room temperature, and the solids were filtered. The solvent was evaporated under vacuum and the oil dissolved in diethyl ether (300 mL) and washed with 10% sodium hydroxide. The organic layer was dried over anhydrous $MgSO_4$ and filtered and the solvent removed under vacuum. The

product was dissolved in 1:1 CH_2Cl_2−hexanes and filtered through a short pad silica. Upon concentration and standing 12.9 g (95%) of light yellow crystalline solid was afforded.

2-(1*H*-Indol-4-yloxy)chloroethane (17). The title compound was prepared from 4-hydroxyindole and 2-chloroethanol in 57% yield according to method A to afford a white solid: mp 62−63 °C; ^{1}H NMR ($CDCl_3$) δ 3.88 (2H, t, J = 6.2 Hz), 4.38 (2H, t, J = 6.2 Hz), 6.52 (1H, d, J = 7.3 Hz), 6.68 (1H, app. t, J = 2.2 Hz), 7.02−7.12 (3H, m), 8.14 (1H, s).

7-Chloro-4-(2-chloroethoxy)-1*H*-indole (18). To a solution of **16** (10.0 g, 42.4 mol) in THF (230 mL) stirred in a cold bath at −50 to −40 °C was added a solution of vinylmagnesium bromide (132 mL, 1.0 M, 0.132 mol) in THF over 2 min. After stirring in the cold bath for 2.5 h, saturated aqueous NH_4Cl (150 mL) was added to the cold solution, and it was removed from the cold bath. A 1 M HCl solution was added to dissolve the precipitated solids, and the mixture was stirred for 0.5 h. The layers were separated, and the aqueous phase was extracted once with diethyl ether (80 mL). The organic layer was combined, dried over anhydrous $MgSO_4$, and filtered and the solvent evaporated to give 15.4 g of a dark oil. Purification by chromatography (hexanes− CH_2Cl_2, 2:1) afforded a solid which was triturated with hexane and filtered to afford 3.51 g (36%) of the product as a yellowish white solid: mp 73−75 °C; MS EI *m/e* 229/231/233 (M^+); ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.99 (t, 2H;, J = 5.1 Hz), 4.34 (t, 2H, J = 5.0 Hz), 6.51 (t, 1H, J = 2.7 Hz), 6.53 (d, 1H, J = 7.8 Hz), 7.04 (d, 1H, J = 8.0 Hz), 7.29 (t, 1H, J = 2.7 Hz), 11.43 (s, 1H). Anal. ($C_{10}H_9Cl_2NO$) C, H, N.

Method I. [2-(1*H*-Indol-4-yloxy)ethyl](4-phenylbutyl)amine (7c). A solution of the **17** (1.80 g, 9.20 mmol) and 4-phenyl-1-aminobutane (4.12 g, 27.6 mmol) in anhydrous DMSO (25 mL) was heated to 80 °C for 6 h. The reaction mixture was poured into water (150 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, and filtered and the solvent concentrated. Purification by flash chromatography (5−10% MeOH−CH_2Cl_2) afforded 1.89 g (66%) of a tan oil: MS *m/e* 308 (M^+). The oxalate salt was prepared in THF: mp 202−204 °C. Anal. ($C_{20}H_{24}N_2O\cdot C_2H_2O_4\cdot 0.5H_2O$) C, H, N.

Benzyl[2-(7-chloro-1*H*-indol-4-yloxy)ethyl]amine (7e). The title compound was prepared by reacting **17** with benzylamine according to method I in 86% yield. The fumarate salt was prepared in 2-propanol as colorless crystals: mp 167−168 °C; ^{1}H NMR (DMSO-d_6) δ 3.01 (2H, t, J = 5.6 Hz), 3.90 (2H, s), 4.18 (2H, t, J = 5.6 Hz), 6.49 (1H, d, J = 8.3 Hz), 6.53 (1H, s), 6.54−6.57 (1H, m), 7.03 (1H, d, J = 8.3 Hz), 7.22−7.29 (2H, m), 7.30−7.36 (2H, m), 7.37−7.39 (2H, m), 11.41 (1H, s); MS EI *m/e* 300, 302 (M^+). Anal. ($C_{17}H_{17}ClN_2O\cdot 0.5C_4H_4O_4\cdot 0.25C_3H_8O$) C, H, N.

***N*-Benzyl-*N*-[2-(7-chloro-1*H*-indol-4-yloxy)ethyl]-2,2,2-trifluoroacetamide (19) and *N*-Benzyl-*N*-[2-(7-chloro-3-trifluoroacetyl-1*H*-indol-4-yloxy)ethyl]-2,2,2-trifluoroacetamide (20).** To a solution of **7e** (4.55 g, 15.1 mmol) in CH_2Cl_2 (200 mL) at room temperature was added triethylamine (2.15 mL, 1.56 g, 15.4 mmol), followed by the addition of trifluoroacetic acid anhydride (4.5 mL, 6.7 g, 32 mmol) over 20 min. The solution was stirred at room temperature overnight and then washed twice with water and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave 7.33 g of residue which consisted primarily of the two products. Purification by chromatography on silica gel with a gradient of CH_2Cl_2/hexane/EtOAc (10/80/10, 4/82/14, 0/86/14, 0/80/20) first afforded **19** as light yellow crystals: 2.79 g (47%); mp 114−116 °C; MS EI *m/e* 396 (M^+); IR (KBr) 1682 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 and 3.86 (2t, 2H, J = 5.6 Hz, J = 5.0 Hz, rotamers), 4.28 and 4.31 (2t, 2H, J = 5.6 Hz, J = 5.0 Hz, rotamers), 4.89 and 4.93 (2s, 2H, rotamers), 6.38 and 6.40 (2d, 1H, J = 8.3 Hz, J = 8.5 Hz, rotamers), 6.64−6.68 (m, 1H), 7.05 and 7.08 (2d, 1H, J = 8.1 Hz, J = 8.3 Hz, rotamers); 7.19−7.44 (m, 6H), 8,42 (s, 1H). Anal. ($C_{19}H_{16}ClF_3N_2O_2$) C, H, N.

20 was then eluted off the column to afford 3.18 g (43%) of crystalline solid: mp 152−154 °C; MS FAB *m/e* 493 (MH^+); IR (KBr) 1685, 1699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84 and 4.01 (2t, 2H, J = 5.0 Hz, J = 5.3 Hz, rotamers), 4.26 and 4.31 (2t, 2H, J = 5.5 Hz, J = 5.0 Hz, rotamers), 4.92 and 5.00 (2s, 2H, rotamers), 6.63 and 6.66 (2d, 1H, J = 8.8 Hz, J = 8.8 Hz, rotamers), 7.27−7.42 (m, 6H), 8.04−8.08 (m, 1H), 9.13 (s, 1H). Anal. ($C_{21}H_{15}ClF_6N_2O_3$) C, H, N.

[2-(1*H*-Indol-4-yloxy)ethyl](4-phenylbutyl)trifluoroacetylamide (21). To a solution of **7c** (2.38 g, 7.72 mmol) and triethylamine (1.56 g, 15.4 mmol) in anhydrous CH_2Cl_2 (30 mL) at room temperature was slowly added trifluoroacetic anhydride (2.42 g, 11.6 mmol) over 10 min. The reaction was stirred for 1 h, then poured into a 1:1 solution of saturated Na_2CO_3−water (50 mL), and extracted with CH_2Cl_2 (2 × 100 mL). The organic layer dried over anhydrous $MgSO_4$ and filtered and the solvent evaporated. Purification by flash chromatography (20% EtOAc−hexanes) afforded 1.61 g (52%) of an off-white solid: mp 70−72 °C; MS *m/e* 404 (M^+); IR (KBr) 3360, 2950, 1725 cm^{-1}.

[2-(3-Chloro-1*H*-indol-4-yloxy)ethyl]-(4-phenylbutyl)-trifluoroacetylamide (22). To a solution of **21** (1.55 g, 3.83 mmol) in anhydrous THF (20 mL) at 5 °C was added NCS (512 mg, 3.83 mmol) in two portions over 30 min. After stirring for another 45 min the reaction was allowed to warm to room temperature and stirred for another 3 h. The reaction mixture was poured into EtOAc (150 mL) and washed with water (60 mL). The organic layer dried over anhydrous $MgSO_4$ and filtered and the solvent evaporated. Purification using flash chromatography (20% EtOAc−hexanes) afforded 1.2 g (71%) of a grayish white solid: mp 113−114 °C; MS *m/e* 438 (M^+). Anal. ($C_{22}H_{22}ClF_3N_2O_2$) C, H, N.

***N*-Benzyl-*N*-[2-(3,7-dichloro-1*H*-indol-4-yloxy)ethyl]-2,2,2-trifluoroacetamide (23).** The title compound was prepared from **19** in 82% yield according to method B to afford a white solid: mp 156−158 °C; MS EI *m/e* 430/432/434 (M^+); IR (KBr) 1680 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76 and 3.81 (2t, 2H, J = 1.3 Hz, J = 1.4 Hz, rotamers), 4.14 and 4.15 (2t, 2H, J = 1.5 Hz, J = 1.6 Hz, rotamers), 4.95 and 4.96 (2s, 2H, rotamers), 6.41 and 6.43 (2d, 1H, J = 8.4 Hz, J = 8.7 Hz, rotamers), 7.095 and 7.097 (2d, 1H, J = 8.2 Hz, J = 8.2 Hz, rotamers), 7.16 (d, 1H, J = 2.5 Hz), 7.22−7.41 (m, 5H), 8.27−8.35 (m, 1H). Anal. ($C_{19}H_{15}Cl_2F_3N_2O_2$) C, H, N.

Method J. 3,7-Dichloro-4-(2-chloroethoxy)-1*H*-indole (24). To a solution of **18** (4.61 g, 20.0 mmol) in acetonitrile (100 mL) was added NCS (2.94 g, 2.20 mmol) at room temperature. The reaction was allowed to stir for 1.5 h, then poured into water (100 mL), and extracted with CH_2Cl_2 (200 mL). The organic layer was dried over anhydrous $MgSO_4$ and filtered, and the solvent was removed under vacuum to afford a dark solid. Purification by chromatography (CH_2Cl_2−hexanes: 1:2) afforded 4.15 g (78%) as a white solid: mp 106−107.5 °C; IR (KBr) 3400 cm^{-1}; MS EI *m/e* 263/265/267/269 (M^+); ^{1}H NMR ($CDCl_3$) δ 3.91 (2H, t, J = 6.2 Hz), 4.33 (2H, t, J = 6.2 Hz), 6.47 (1H, d, J = 8.4 Hz), 7.08−7.13 (2H, m), 8.26 (1H, bs, NH). Anal. ($C_{10}H_8Cl_3NO$) C, H, N.

Method K. 3,7-Dichloro-4-(2-chloroethoxy)-1*H*-indole (24). To a solution of **17** (10.0 g, 37.8 mmol) in MeOH (200 mL) under nitrogen containing sodium acetate (6.0 g) and AcOH (1 mL) was added portionwise trichloroisocyanic acid (4.0 g, 17.2 mmol) at 2 °C. The reaction temperature was maintained below 8 °C and the mixture was allowed to stir for 4 h then diluted with ether (200 mL), and washed with 10% NaOH. The organic layer dried over anhydrous $MgSO_4$ and filtered, and the solvent removed under vacuum to afford an oil. This material was dissolved in CH_2Cl_2, filtered over a short pad of silica and concentrated to afford 10.0 g (87%) a yellowish white solid.

Benzyl[2-(3,7-dichloro-1*H*-indol-4-yloxy)ethyl]amine (7f). The title compound was prepared in 46% yield by reacting **24** with benzylamine according to the method I: mp 129−130 °C; ^{1}H NMR (DMSO-d_6) δ 2.98 (2H, t, J = 5.5 Hz), 3.85 (2H, s), 4.14 (2H, t, J = 5.5 Hz), 6.55 (1H, d, J = 8.3 Hz), 6.53 (1H, s), 6.57 (1H, s), 7.11 (1H, d, J = 8.3 Hz), 7.21−7.26 (1H, m), 7.28−7.37 (1H, m), 7.37−7.39 (2H, m), 7.40 (1H, m), 11.68 (1H, s); MS *m/e* 334/336/338 (M^+).

***N*-Methyl-*N*-benzyl[2-(3,7-dichloro-1*H*-indol-4-yloxy)-ethyl]amine (7g).** The title compound was prepared in 73% yield by reacting **24** with 4-methylbenzylamine according to method I: MS EI *m/e* 348/350/352 (M^+). Anal. ($C_{18}H_{18}Cl_2N_2O$) C, H, N.

4-Chlorobenzyl[2-(3,7-dichloro-1*H*-indol-4-yloxy)ethyl]amine (7h). The title compound was prepared by reacting **24** with 4-chlorobenzylamine in 60% yield according method I: mp 115−116 °C; MS EI *m/e* 368/370/372/374 (M^+); HRMS calcd for $C_{17}H_{15}N_2OCl_3$ 368.024997, observed 368.0215531. Anal. ($C_{17}H_{15}Cl_3N_2O\cdot0.25H_2O$) C, H, N.

4-Fluorobenzyl[2-(3,7-dichloro-1*H*-indol-4-yloxy)ethyl]amine (7i). The title compound was prepared by reacting **24** with 4-fluorobenzylamine in 64% yield according to method I: mp 102.5−103.5 °C; MS EI *m/e* 352 (M^+). Anal. ($C_{17}H_{15}Cl_2FN_2O$) C, H, N.

[2-(3,7-Dichloro-1*H*-indol-4-yloxy)ethyl]thiophene-2-ylmethylamine (7k). The title compound was prepared in 76% yield by reacting **24** with 2-thiophenemethylamine according to method I to afford an orange solid: mp 99−101 °C; MS EI *m/e* 340/342/344 (M^+). Anal. ($C_{15}H_{14}Cl_2N_2OS$) C, H, N.

[2-(3,7-Dichloro-1*H*-indol-4-yloxy)ethyl]thiophene-3-ylmethylamine (7l). The title compound was prepared in 70% yield by reacting **24** with 3-thiophenemethylamine according to method I to afford a yellow solid: mp 123−125 °C. Anal. ($C_{15}H_{14}Cl_2N_2OS$) C, H, N.

1-Butyl[2-(3,7-dichloro-1*H*-indol-4-yloxy)ethyl]amine (7m). The title compound was prepared in 69% yield by reacting **24** with *n*-butylamine according to method I to afford a tan solid: mp 109−111.5 °C. Anal. ($C_{14}H_{18}Cl_2N_2O$) C, H, N.

4-Methylbenzyl[2-(3,7-dichloro-1*H*-indol-4-yloxy)ethyl]amine (7n). The title compound was prepared by reacting **24** with 4-methylbenzylamine in 88% yield according to method I to afford a reddish brown solid: mp 116−118 °C; MS EI *m/e* (M^+).

4-Phenylbenzyl[2-(3,7-dichloro-1*H*-indol-4-yloxy)ethyl]amine (7o). The title compound was prepared by reacting **24** with 4-phenylbenzylamine in 36% yield according to method I to afford a tan oil: MS EI *m/e* 411/413/415 (M^+).

2-[2-(3,7-Dichloro-1*H*-indol-4-yloxy)ethyl]-1,2,3,4,4a,8a-hexahydroisoquinoline (7p). The title compound was prepared 59% yield by reacting **24** with dihydroisoquinoline to afford a brown solid: mp 179−180 °C; MS EI *m/e* 359/361/363 (M^+). Anal. ($C_{19}H_{18}Cl_2N_2O$) C, H, N.

3,7-Dichloro-4-[2-(1,3-dihydroisoindol-2-yl)ethoxy]-1*H*-indole (7q). The title compound was prepared by reacting **24** with isoindoline in 59% yield: MS EI *m/e* 345/347/349 (M^+).

2-Naphthyl[2-(3,7-dichloro-1*H*-indol-4-yloxy)ethyl]-amine (7r). The title compound was prepared by reacting **24** with 2-naphthylmethylamine in 49% yield: MS EI *m/e* 384/386/388 (M^+).

Method L. [2-(3-Chloro-1*H*-indol-4-yloxy)ethyl]-(4-phenylbutyl)amine (7d). A mixture of **22** (1.15 g, 2.62 mmol) and K_2CO_3 (2.53 g, mmol) in a solution of MeOH−water (50 mL:3 mL) was heated to reflux for 3 h. The solvent was removed under vacuum, and the crude product was dissolved in CH_2Cl_2 (150 mL) and washed with water (100 mL). The aqueous layer was extracted again with CH_2Cl_2 (100 mL), the combined organic layers were dried over anhydrous $MgSO_4$ and filtered, and the solvent was evaporated. The product was purified by flash chromatography (5% MeOH−CH_2Cl_2) to afford 847 mg (94%) of a tan oil: MS *m/e* 342/344 (M^+). The fumarate salt was prepared in 2-propanol: mp 195−196 °C. Anal. ($C_{20}H_{23}ClN_2O\cdot0.5C_4H_4O_4$) C, H, N.

Benzyl[2-(3,7-dichloro-1*H*-indol-4-yloxy)ethyl]amine (7f). The title compound could also be prepared from **23** in 92% yield according to method L. The fumarate salt was prepared as a white powder: mp 201−202 °C; MS EI *m/e* 334/336/338 (M^+). Anal. ($C_{17}H_{16}Cl_2N_2O\cdot0.5C_4H_4O_4$) C, H, N.

1-[4-(2-Benzylaminoethoxy)-7-chloro-1*H*-indol-3-yl]-2,2,2-trifluoroethanone (7j). The title compound was prepared from **20** in 78% yield according to method L. The fumarate salt was prepared in EtOH as a white powder: mp 215 °C dec; MS FAB *m/e* 397 (MH^+). Anal. ($C_{19}H_{16}ClF_3N_2O_2\cdot0.5C_4H_4O_4$) C, H, N.

4-[2-(4-Phenylbutylamino)ethoxy]-1,3-dihydroindol-2-one (8f). The title compound was prepared from **7d** in 91% yield according method C as a grayish solid: mp 81−83 °C. The fumarate salt was prepared from 2-propanol: mp 191−193 °C; MS *m/e* 324 (M^+). Anal. ($C_{20}H_{24}N_2O_2\cdot C_4H_4O_4\cdot0.1H_2O$) C, H, N.

4-(2-Butylaminoethoxy)-7-chloro-1,3-dihydroindol-2-one (8g). The title compound was prepared from **7m** in 35% yield according to method C. The fumarate salt was prepared in EtOH: mp 218−219 °C. Anal. ($C_{14}H_{19}ClN_2O_2\cdot0.5C_4H_4O_4$) C, H, N.

4-(2-Benzylaminoethoxy)-7-chloro-1,3-dihydroindol-2-one (8h). The title compound was prepared from **7f** in 71% yield according to method C as a grayish white solid: mp 161−163 °C. The hemifumarate salt was prepared in EtOH: mp 199−200 °C; MS EI *m/e* 316/318 (M^+). Anal. ($C_{17}H_{17}ClN_2O_2\cdot0.5C_4H_4O_4$) C, H, N.

4-[2-(*N*-Benzyl-*N*-methylamino)ethoxy]-7-chloro-1,3-dihydroindol-2-one (8i). The title compound was prepared from **7g** in 82% yield according to method C. The fumarate salt was prepared in EtOH: mp 153−173 °C. Anal. ($C_{18}H_{19}ClN_2O_2\cdot0.5C_4H_4O_4\cdot0.5H_2O$) C, H, N.

7-Chloro-4-[2-(4-fluorobenzylamino)]ethoxy]-1,3-dihydroindol-2-one (8j). The title compound was prepared from **7i** in 82% yield according to method C: mp 148−149.5 °C; MS EI *m/e* 334/336. The fumarate salt was prepared in 2-propanol: mp 225−226 °C; MS EI *m/e* 334 (M+). Anal. ($C_{17}H_{16}ClFN_2O_6\cdot0.5H_2O\cdot0.25C_3H_8O$) C, H, N.

7-Chloro-4-[2-(4-chlorobenzylamino)ethoxy]-1,3-dihydroindol-2-one (8k). The title compound was prepared from **7h** in 84% yield according to method C: mp 158−159.5 °C. The fumarate salt was prepared in EtOH: mp 217−218 °C; MS EI *m/e* 350 (M^+). Anal. ($C_{17}H_{16}Cl_2N_2O_2\cdot C_4H_4O_4$) C, H, N.

7-Chloro-4-[2-(4-methylbenzylamino)]ethoxy]-1,3-dihydroindol-2-one (8l). The title compound was prepared from **7n** in 76% yield according to method C. The fumarate salt was prepared in EtOH: mp 205−206 °C; MS EI *m/e* 330 (M+). Anal. ($C_{18}H_{19}ClN_2O_2\cdot C_4H_4O_4$) C, H, N.

4-{2-[(Biphenyl-4-ylmethyl)amino]ethoxy}-7-chloro-1,3-dihydroindol-2-one (8m). The title compound was prepared from **7o** in 52% yield according to method C. The fumarate salt was prepared in EtOH: mp 221−222 °C. Anal. ($C_{23}H_{21}ClN_2O_2\cdot0.5\ C_4H_4O_4$) C, H, N.

7-Chloro-4-[2-(3,4-dihydro-1*H*-isoquinolin-2-yl)ethoxy]-1,3-dihydroindol-2-one (8n). The title compound was prepared from **7p** in 38% yield according to method C. The fumarate salt was prepared in EtOH: mp 214−216.5 °C. Anal. ($C_{19}H_{19}ClN_2O_2\cdot0.5C_4H_4O_4$) C, H, N.

7-Chloro-4-[2-(1,3-dihydroisoindol-2-yl)ethoxy]-1,3-dihydroindol-2-one (8o). The title compound was prepared from **7q** in 84% yield according to method C. The fumarate salt was prepared in EtOH: mp 220−224 °C. Anal. ($C_{18}H_{17}ClN_2O_2\cdot C_4H_4O_4$) C, H, N.

7-Chloro-4-{2-[(naphthalen-2-ylmethyl)amino]ethoxy}-1,3-dihydroindol-2-one (8p). The title compound was prepared from **7r** in 22% yield according to method C. The fumarate salt was prepared in EtOH: mp 165−176 °C. Anal. ($C_{21}H_{19}ClN_2O_2\cdot0.7C_4H_4O_4$) C, H, N.

7-Chloro-4-{2-[(thiophene-2-ylmethyl)amino]ethoxy}-1,3-dihydroindol-2-one (8q). Treatment of **7k** according to method C afforded 1.15 g (86%) of the title compound: mp 154−155 °C. The fumarate salt was prepared in EtOH to give a slightly yellow white powder: mp 203−204 °C; MS EI *m/e* 323/324 (M^+). Anal. ($C_{15}H_{15}ClN_2O_2S\cdot0.5C_4H_4O_4$) C, H, N.

7-Chloro-4-{2-[(thiophene-3-ylmethyl)amino]ethoxy}-1,3-dihydroindol-2-one (8r). Treatment of **7l** according to method C afforded the title compound in 40% yield. The fumarate salt was prepared in EtOH as a light brown solid: mp 191.5−193 °C; MS EI *m/e* 323/324 (M^+). Anal. ($C_{15}H_{15}ClN_2O_2S\cdot0.5C_4H_4O_4$) C, H, N.

2,6-Dibromo-4-fluorophenol (25). To a solution of 4-fluorophenol (25 g, 0.22 mol) in AcOH (200 mL) at room temper-

ature was slowly added dropwise bromine (78 g, 0.49 mol) while being mechanically stirred. After 1 h the reaction mixture was poured into ice water (1.5 L) followed by 100 mL of saturated aqueous sodium bisulfite. The solid precipitate was filtered and dried to afford 51.8 g (86%) of a white solid: mp 54−55 °C; ^{1}H NMR ($CDCl_3$) δ 5.69 (1H, s, O**H**), 7.25 (2H, d, J = 7.5 Hz); MS EI *m/e* 268/270/272 (M^+). Anal. ($C_6H_3Br_2$-FO) C, H, N.

1-(2-Chloroethoxy)-2,6-dibromo-4-fluorobenzene (26). A mixture of **25** (55 g, 0.20 mol), K_2CO_3 (60 g, 0.43 mol), 1-bromo-2-chloroethane (32.5 g, 0.23 mol), and 2-butanone (500 mL) was heated to reflux for 2 h and allowed to cool to ambient temperature. The solids were filtered, and the solvent was removed under vacuum to afford an oil. The oil was dissolved in ether (300 mL), washed with water, dried over anhydrous $MgSO_4$, treated with decolorizing carbon, and filtered through Solka floc to afford 65.9 g (97%) of an oil: MS EI *m/e* 330/332/334/336 (M^+); ^{1}H NMR ($CDCl_3$) δ 3.89 (2H, t, J = 6.1 Hz), 4.23 (2H, t, J = 6.1 Hz), 7.28 (2H, d, J = 7.5 Hz).

1-(2-Chloroethoxy)-2,6-dibromo-4-fluoro-3-nitrobenzene (27). To a solution of **26** (65.8 g, 0.20 mol) in concentrated sulfuric acid (165 mL) maintained at room temperature using a water bath was slowly added a solution of HNO_3 in H_2SO_4 (10 mL of HNO_3 in 165 mL of H_2SO_4). The reaction was allowed to stir at room temperature for 1 h, then poured into ice (1.5 L), and extracted with CH_2Cl_2 (2 × 300 mL). The combined organic layers were washed with aqueous Na_2CO_3 (150 mL), dried over anhydrous $MgSO_4$, and filtered, and the solvent was removed under vacuum to afford 73.3 g (97%) of a white crystalline solid: mp 56−57 °C; MS EI *m/e* 375/377/379/381; ^{1}H NMR ($CDCl_3$) δ 3.91 (2H, t, J = 5.9 Hz), 4.29 (2H, d, J = 5.9 Hz), 7.54 (8.1 Hz). Anal. ($C_8H_5Br_2ClFNO_3$) C, H, N.

1-(2-Chloroethoxy)-4-fluoro-3-aminobenzene (28). A solution of **27** (73.2 g, 0.19 mol) in ethanol (1.1 L) containing 7.3 g of 10% palladium on carbon was hydrogenated at 40 psi for 2 days. The catalyst was filtered, and the solvent was removed. The residue was dissolved in ether (300 mL) and washed with saturated aqueous Na_2CO_3 (200 mL). The organic layer separated, washed with water, dried over anhydrous $MgSO_4$, and filtered, and the solvent removed to afford an oil which solidified to afford 32.5 g (90%) of a dark solid: mp 42−43 °C; MS EI *m/e* 189/191 (M^+); ^{1}H NMR ($CDCl_3$) δ 3.40−3.60 (2H, bs, NH_2), 3.77 (2H, d, J = 6 Hz), 4.14 (2H, d, J = 6 Hz), 6.19−6.23 (1 H, m), 6.36 (1H, dd, J = 7, 3 Hz), 6.88 (1H, dd, J = 11, 9 Hz). Anal. (C_8H_9ClFNO) C, H, N.

4-(2-Chloroethoxy)-7-fluoro-3-thiomethyl-1,3-dihydroindol-2-one (29). To a solution of ethyl(methylthio)acetate (7.2 g, 53.4 mmol) in anhydrous CH_2Cl_2 (200 mL) at −78 °C was added sulfuryl chloride (8.1 g, 59.7 mmol), and the mixture was stirred for 20 min. A solution of **29** (10.0 g, 52.8 mmol) and Proton Sponge (13.9 g) in CH_2Cl_2 (100 mL) was added dropwise and stirred for 2 h, followed by the addition of triethylamine (6.5 g, 64.5 mmol). The temperature was maintained at −78 °C, and the reaction mixture was allowed to stir for 1 h. After warming to room temperature, the mixture was poured into brine (200 mL), dried over anhydrous $MgSO_4$, and filtered, and the solvent was removed to afford an oil. AcOH (75 mL) was added to the oil and the mixture allowed to stand for 18 h; then the solvent was removed under vacuum. The residue was partitioned between ether (400 mL) and 2.5 N aqueous HCl (150 mL). The organic layer was separated, and dried over anhydrous $MgSO_4$, and filtered, and the solvent was removed to afford a solid. Trituration of the solid with a small amount of ether (30 mL) afforded 8.8 g (60%) of a yellow solid: mp 140−141 °C; MS EI *m/e* 275/277 (M^+); ^{1}NMR ($CDCl_3$) δ 2.14 (3H, s), 3.79−3.87 (2H, m), 4.25−4.33 (2H, m), 4.35 (1H, s), 6.51 (1H, dd, J = 9.1, 3.3 Hz), 6.99 (1H, app. t, J = 9.1 Hz), 8.09 (1H, s). Anal. ($C_{11}H_{11}ClFNO_2S$) C, H, N.

4-(2-Chloroethoxy)-7-fluoro-1,3-dihydroindol-2-one (30). To a solution of **29** (5.0 g, 18.1 mmol) in formic acid (75 mL) was added Raney nickel (10 g), and the mixture was stirred at room temperature for 6 h. The reaction mixture was diluted with ether (150 mL) and the catalyst filtered through Celite; and upon addition of water a precipitate formed. The solid was filtered and air-dried to afford 1.3 g of product. The ether layer dried over anhydrous $MgSO_4$ and filtered, and the solvent removed under vacuum to afford another 1.5 g of product: total yield 2.8 g (67%); mp 192−193 °C; MS EI *m/e* 229/231 (M^+); ^{1}H NMR ($CDCl_3$) δ 3.53 (2H, s), 3.80 (2H, t, J = 5.7 Hz), 4.25 (2H, J = 5.7 Hz), 6.46 (1H, dd, J = 3.3, 9.2 Hz), 6.93(1H, app t, J = 9.2 Hz), 7.70 (1H, bs).

4-(2-Benzylaminoethoxy)-7-fluoro-3-thiomethyl-1,3-dihydroindol-2-one (31). The title compound was prepared from **29** (1.5 g, 5.44 mmol) and benzylamine (2.33 g, 21.8 mmol) in DMSO (8 mL) according to method I to afford 1.14 g (61%) of a yellow oil: MS EI *m/e* 346 (M^+); ^{1}H NMR ($CDCl_3$) δ 1.96 (3H, s), 2.96−3.13 (2H, m), 3.89 (2H, AB, J = 13 Hz), 4.10−4.21 (2H, m), 4.28 (1H, s), 6.46 (1H, dd, J = 9, 3 Hz), 6.95 (1H, app t, J = 9 Hz), 7.21−7.40 (5H, m).

4-(2-Cyclohexylmethylaminoethoxy)-7-fluoro-3-thiomethyl-1,3-dihydroindol-2-one (32). The title compound was prepared from **29** in 48% yield according to method I: MS EI *m/e* 352 (M^+).

4-[2-(Biphenyl-3-ylmethylamino)ethoxy]-7-fluoro-3-thiomethyl-1,3-dihydroindol-2-one (33). The title compound was prepared from **29** in 61% yield according to method I: MS EI *m/e* 422 (M^+).

4-{2-[3-(1*H*-Indolyl)propylamino]ethoxy}-7-fluoro-3-thiomethyl-1,3-dihydroindol-2-one (34). The title compound was prepared from **29** in 64% yield according to method I.

4-[2-(2-Thienyl)aminoethoxy]-7-fluoro-3-thiomethyl-1,3-dihydroindol-2-one (35). The title compound was prepared from **29** in 77% yield according method I: MS EI *m/e* 352 (M^+).

4-[2-(3-Thienyl)aminoethoxy]-7-fluoro-3-thiomethyl-1,3-dihydroindol-2-one (36). The title compound was prepared from **29** according to method I and converted to its fumarate salt in EtOH to afford a white solid: mp 152.5−155 °C; MS EI *m/e* 352 (M^+). Anal. ($C_{16}H_{17}FN_2O_2S_2\cdot C_4H_4O_4$) C, H, N.

Method M. 4-(2-Benzylaminoethoxy)-7-fluoro-1,3-dihydroindol-2-one (8s). To a solution of **31** (1.05 g, 3.04 mmol) in EtOH (50 mL) was added 2 teaspoons of Raney nickel at room temperature. After 2 h the catalyst was filtered, the solvent removed, and the solid dissolved in a minimum amount of a solution of MeOH in CH_2Cl_2 and passed through a silica gel column (5% MeOH in CH_2Cl_2) to afford 590 mg (65%) of a pale yellow solid: mp 162−163 °C; MS EI *m/e* 300 (M^+); ^{1}H NMR (DMSO-d_6) δ 2.80 (2H, t, J = 6 Hz), 3.42 (2H, s), 3.74 (2H, s), 4.03 (2H, t, J = 6 Hz), 6.54 (1H, d, J = 9, 3 Hz), 7.01 (1H, app t, J = 9 Hz), 7.18−7.34 (5H, m), 10.81 (1H, d, J = 10 Hz). The fumarate salt was prepared in EtOH to afford a yellow solid: mp 202−203 °C. Anal. ($C_{17}H_{17}FN_2O_2\cdot 0.5C_4H_4O_4$) C, H, N.

4-(2-Benzylaminoethoxy)-7-fluoro-1,3-dihydroindol-2-one (8s). The title compound could also be prepared by treatment of **30** with benzylamine according to method I in 82% yield.

4-(2-Aminoethoxy)-7-fluoro-1,3-dihydroindol-2-one (8t). A mixture of **8s** (1.8 g, 6.0 mmol) and 10% palladium on carbon in EtOH (250 mL) at room temperature was hydrogenated at 54 psi for 11 h. The catalyst was filtered through Celite and the solvent evaporated to afford 1.21 g (96%) of a tan solid: mp 138−141 °C; MS *m/e* 210 (M^+). The fumarate salt was prepared in EtOH: mp 218−221 °C. Anal. ($C_{10}H_{11}FN_2O_2\cdot 0.5C_4H_4O_4\cdot 0.25H_2O$) C, H, N.

4-{2-[(Biphenyl-4-ylmethyl)amino]ethoxy}-7-fluoro-1,3-dihydroindol-2-one (8u). Treatment of **30** with biphenyl-2-ylmethylamine according to method I afforded the title compound in 42% yield. The fumarate salt was prepared in EtOH: mp 193−198 °C; MS EI *m/e* 376 (M^+). Anal. ($C_{23}H_{21}FN_2O_2\cdot C_4H_4O_4$) C, H, N.

4-{2-[(Biphenyl-3-ylmethyl)amino]ethoxy}-7-fluoro-1,3-dihydroindol-2-one (8v). The title compound was prepared from **33** in 29% yield according to method M; MS EI *m/e* 376 (M^+). The fumarate salt was prepared in EtOH: mp 200−201 °C. Anal. ($C_{23}H_{21}FN_2O_2\cdot C_4H_4O_4$) C, H, N.

7-Fluoro-4-{2-[(naphthalen-2-ylmethyl)amino]ethoxy}-1,3-dihydroindol-2-one (8w). Treatment of **30** with 2-naphthylmethylamine according to method I afforded the title compound in 82%yield: MS EI *m/e* 350 (M^+). The fumarate salt was prepared in EtOH: mp 189−193 °C. Anal. ($C_{21}H_{19}FN_2O_2 \cdot 0.5C_4H_4O_4$) C, H, N.

7-Fluoro-4-{2-[(thiophene-2-ylmethyl)amino]ethoxy}-1,3-dihydroindol-2-one (8x). Prepared from **35** according to method M in 30% yield. The fumarate salt was prepared from EtOH as yellow crystals: mp 184−185.5 °C; MS EI *m/e* 306 (M^+). Anal. ($C_{15}H_{15}FN_2O_2S \cdot 0.5\ C_4H_4O_4 \cdot 0.25H_2O$) C, H, N.

7-Fluoro-4-{2-[(thiophene-3-ylmethyl)amino]ethoxy}-1,3-dihydroindol-2-one (8y). The title compound was prepared from **36** according to method M in 21% yield to afford a light yellow solid: mp 154−157 °C; MS EI *m/e* 306 (M^+); ^{1}H NMR (DMSO-d_6) δ 2.80 (2H, t, J = 6 Hz), 3.42 (2H, s), 3.74 (2H, s), 4.03 (2H, t, J = 6 Hz), 6.54 (1H, d, J = 9, 3 Hz), 7.01 (1H, app t, J = 9 Hz), 7.18−7.34 (5H, m), 10.81 (1H, d, J = 10 Hz). The fumarate salt was prepared in EtOH to afford a yellow solid: mp 186.5−187 °C. Anal. ($C_{15}H_{15}FN_2O_2S \cdot 0.5\ C_2H_4O_4$) C, H, N.

4-[2-(Cyclohexylmethylamino)ethoxy]-7-fluoro-1,3-dihydroindol-2-one (8z). The title compound was prepared from **32** as a light brown crystal in 28% according to method M: mp 215−216 °C; MS EI *m/e* 306 (M^+). Anal. ($C_{17}H_{23}FN_2O_2 \cdot C_4H_4O_4$) C, H, N.

4-[2-(3,4-Dihydro-1*H*-isoquinolin-2-yl)ethoxy]-7-fluoro-1,3-dihydroindol-2-one (8aa). Treatment of **30** with dihydroisoquinoline according to method I afforded the title compound in 45% yield. The fumarate salt was made in EtOH: mp 230−235 °C. Anal. ($C_{19}H_{19}FN_2O_2 \cdot 0.5C_4H_4O_4 \cdot 0.25H_2O$).

4-[2-(1,3-Dihydroisoindol-2-yl)ethoxy]-7-fluoro-1,3-dihydroindol-2-one (8ab). Treatment of **30** with isoindoline according to method I afforded the title compound in 75% yield as a thick oil: MS EI *m/e* 312 (M^+). The fumarate salt was prepared in EtOH: mp 210−212 °C. Anal. ($C_{18}H_{17}FN_2O_2 \cdot 0.5C_4H_4O_4 \cdot 0.25C_4H_8O$) C, H, N.

4-{2-[3-(1*H*-Indolyl)propylamino]ethoxy}-7-fluoro-1,3-dihydroindol-2-one (8ac). The title compound was prepared from **34** in 19% yield according to method M: MS EI *m/e* 367 (M^+). The fumarate salt was prepared in EtOH: mp 189−190 °C. Anal. ($C_{21}H_{22}FN_3O_2 \cdot C_4H_4O_4$) C, H, N.

Molecular Modeling. All computations were performed using Macromodel 6.0 (Columbia University, Department of Chemistry, New York, NY 10027) and a Silicon Graphic workstation. All molecular mechanics calculations utilized MM3 as implemented in Macromodel 6.0.

Receptor Binding Assays. 1. 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 of 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 TomTec96 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,[15] using nine concentrations of the drug, in triplicate.

2. 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.,[24] and Morrow et al.,[25] 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.[15]

Mouse Hypolocomotion.[26] 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.[27,28] Induction of apomorphine-like stereotypy and climbing behaviors was 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 5 dose levels (6 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.

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