Design and Synthesis of [(2,3-Dichlorophenyl)piperazin-1-yl]alkylfluorenylcarboxamides as Novel Ligands Selective for the Dopamine D_3 Receptor Subtype

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The dopamine D_3 receptor subtype has been recently targeted as a potential neurochemical modulator of the behavioral actions of psychomotor stimulants, such as cocaine. However, definitive behavioral investigations have been hampered by the lack of highly selective D_3 agonists and antagonists. In an attempt to design a novel class of D_3 ligands with which to study this receptor system, a series of chemically divergent compounds that possessed various structural features that exist within several classes of reputed D_3 agents was screened and compared to the recently reported NGB 2904 (**58b**). On the basis of these results, a novel series of compounds was designed that included functional moieties that were required for high-affinity and selective binding to D_3 receptors. All the compounds in this series included an aryl-substituted piperazine ring, a varying alkyl chain linker (C3−C5), and a terminal aryl amide. The compounds were synthesized and evaluated in vitro for binding in CHO cells transfected with human D_2, D_3, or D_4 receptor cDNAs. D_3 binding affinities ranged from K_i = 1.4 to 1460 nM. The most potent analogue in this series, **51**, demonstrated a D_3/D_2 selectivity of 64 and a D_3/D_4 selectivity of 1300. Structure−activity relationships for this class of ligands at D_3 receptors will provide new leads toward the development of highly selective and potent molecular probes that will prove useful in the elucidation of the role D_3 receptors play in the psychomotor stimulant and reinforcing properties of cocaine.

Dopamine has been implicated as the primary neurotransmitter associated with the psychomotor stimulant and reinforcing effects of cocaine.[1,2] These findings have resulted in intensive efforts to characterize and elucidate the roles of the various dopamine receptor subtypes in the pharmacology and reinforcing effects of this drug of abuse.[3] A decade ago, the dopamine D_3 receptor subtype was identified and data from this report supported a potential role in the pharmacological effects of psychostimulant drugs.[4,5] Subsequently, the brain distribution of D_3 receptors was described as residing in the mesolimbic region.[6,7] Adaptive increases in D_3 receptors were also reported to be present in human cocaine fatalities,[8,9] lending further validity to developing D_3-selective agents to further study the role of this receptor subtype in cocaine's actions.

An early report on the purported D_3-selective agonist 7-OH DPAT [7-hydroxy-2-(di-*n*-propylamino)tetralin] suggested that D_3 receptors played a modulatory role in the self-administration of cocaine.[10] The results of this study showed that 7-OH DPAT decreased cocaine self-administration in doses that were not reinforcing, in and of themselves. More recently, Sokoloff and colleagues reported on a highly selective D_3 partial agonist, BP 897 (1-(4-(2-naphthoylamino)butyl)-4-(2-methoxyphenyl)-1A-piperazine), suggesting that this compound could attenuate cocaine-seeking behavior.[11] In addition, BP 897 was found to attenuate the discriminative stimulus effects of both cocaine and D-amphetamine, in mice, and was not self-administered in monkeys.[12] These reports supported further development of D_3 (partial) agonists as cocaine abuse medications. Recently, the dopamine D_3 receptor antagonist nafadotride has been described as inhibiting locomotor sensitization to amphetamine, perhaps suggesting another relationship between D_3 receptors and psychostimulant drugs.[13] In fact, in vitro functional assays to assess efficacy at D_3 receptors have provided conflicting results, and a recent report characterizing BP 897 as a D_3 antagonist suggests that its potential as a cocaine treatment maybe attributed to its antagonist actions.[14]

Despite the early encouraging results with 7-OH DPAT and BP 897, presently, the in vivo function of the D_3 receptor and its role in cocaine's actions remains debatable. Several reports describing 7-OH DPAT and other purported D_3 agonists that suggest the lack of D_3-receptor selectivity of these agents may confound the interpretation of results that previously implicated a role of D_3 in the interactions of these drugs with cocaine.[15−19] In addition, studies in D_3 knockout mice showed that D_3-selective agonists, such as PD 128907 [S(+)-(4a*R*,10b*R*)-3,4,4a,10b-tetrahydro-4-propyl-2*H*,5*H*-[1]benzopyrano[4,3-*b*]-1,4-oxazin-9-ol], manifested no differences in behavior, as compared to wild-type mice,

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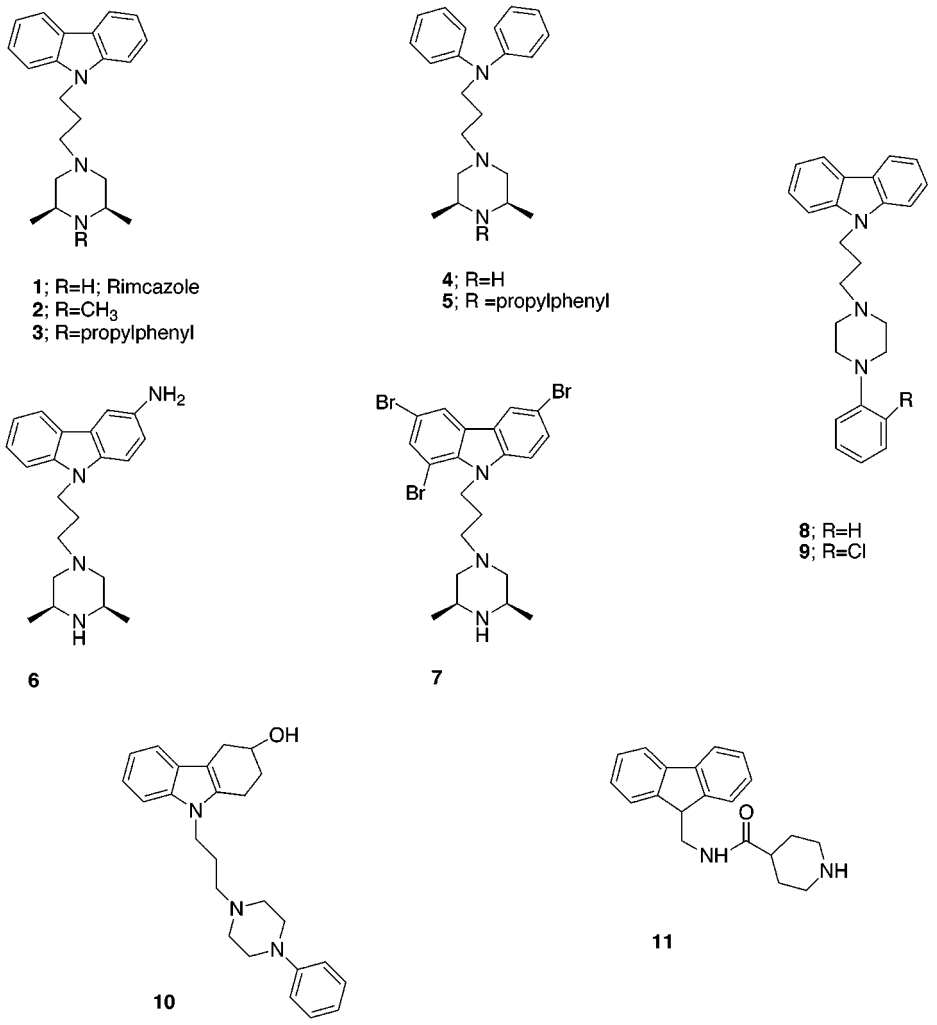
Chart 1. Ligands Screened for D_3 Receptor Binding



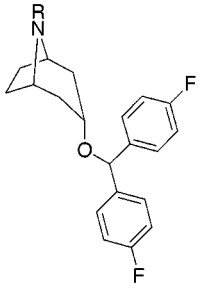
further lending skepticism toward assignment of the in vivo function of these receptors.[20,21] Thus, the development of more selective and useful molecular tools to definitively separate D_3 actions from those mediated by D_2 receptors is required. Furthermore, the ability to assess efficacy that is relevant to the D_3-mediated behavior of these agents will provide another challenge for investigators.

In an effort to design and synthesize improved ligands, as tools with which to study the role of D_3 receptors in the pharmacology of cocaine, we first gleaned structural requirements for high-affinity binding at D_3 from the literature. We noted that the prototypic D_3 agonist 7-OH-DPAT was reported to bind with high affinity at σ receptors.[17] As we have synthesized numerous σ ligands,[22−24] several of these compounds were selected for evaluation. In addition, other compounds previously synthesized in our laboratory had shown activity at D_3 receptors when screened for multiple receptor binding (Novascreen, Hanover, MD). We chose a total of 25 candidates that possessed structural features that might be important for D_3 binding and screened these agents for displacement of [^{3}H]YM 09151-2 binding from cloned human D_2, D_3, and D_4 receptors stably transfected into CHO cells. The structures of these compounds are displayed in Charts 1 and 2, and the results of this screening may be seen in Table 1. Although none of this initial group of compounds demonstrated selectivity for D_3 receptors, over D_2 and D_4, several compounds showed moderate to high affinity (K_i < 100 nM) for D_3 receptors. At this time, a report appeared that described two highly selective D_3 antagonists, NGB 2849 (**58a**) and NGB 2904 (**58b**).[25] A comparison of these two compounds with the structures of the compounds that were screened led to the design of the compounds shown in Chart 3. These compounds were synthesized and evaluated for binding at D_2, D_3, and D_4 receptors.

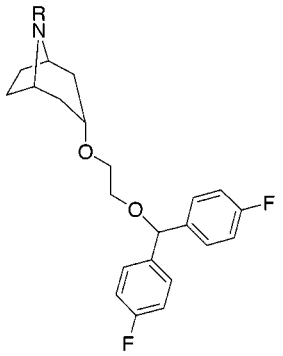
Chemistry

The syntheses of 13 novel ligands are depicted in Schemes 1−7. In Scheme 1, the synthesis of the synthons in which the 1-phenylpiperazine was either unsubstituted (**30a**) or substituted with the 2,3-dichloro substituent pattern (**30b**) and the chain length between the piperazine ring and the terminal amine was three carbons began with the protection of 3-bromopropylamine (**26**) with benzylchloroformate to give the carbobenzoxy-protected intermediate **27** in quantitative yield. Alkylation with 1-phenylpiperazine (**28a**) or 1-(2,3-dichloro)phenylpiperazine (**28b**) gave **29a** or **29b**, respectively in 69% yield. Deprotection with iodotrimethylsilane gave products **30a**,**b** as oils. In Scheme 2, the synthesis of the synthon **33**, wherein the alkyl chain

Chart 2. Ligands Screened for D_3 Receptor Binding



12; R=phenyl-n-butyl
13; R=methyl-1-naphthyl
14; R=methyl-2-indole
15; R=3',4'-dichlorobenzyl
16; R=2-ethyl-(bis-4'-fluorophenyl)methoxy
17; R=benzyl
18; R=CH_3
19; R=allyl



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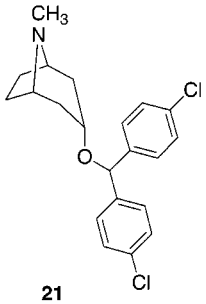

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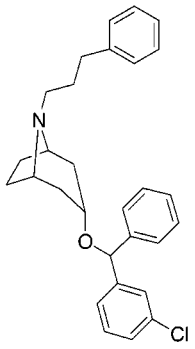

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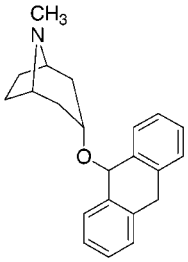

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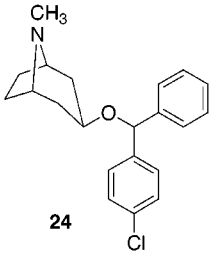

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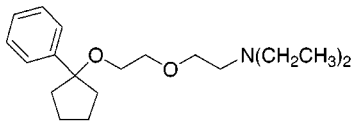

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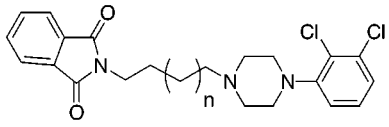
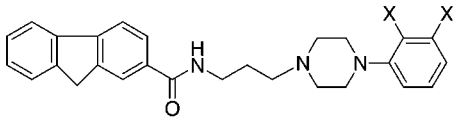
between the piperazine and the terminal amine was increased to four carbons, began with the phthalimido-protected 1-bromobutylamine (**31**) that was reacted with **28b** to give the protected intermediate **32** in 63% yield. Deprotection with hydrazine gave **33** as an oil. In Scheme 3, the synthon **38**, wherein the linking chain was five carbons, began with treatment of the 5-bromopentyl acetate (**34**) with phthalimide to give **35** in 90% yield. Reduction of the ester followed by conversion to the alkylating agent **36** and treatment with **28b** gave the phthalimido-protected **37**. Deprotection with hydrazine afforded **38** as an oil. In Scheme 4, Compounds **40a**,**b**, in which the phenylpiperazine was linked to the 1-position of the fluorenyl-ring system with a 3-carbon linked amide chain, were prepared by converting 1-fluorenylcarboxylic acid (**39**) to its acid chloride in refluxing thionyl chloride and reacting it with the synthons **30a** or **30b**, under Schotten−Baumann conditions, to give **40a** or **40b**. In Scheme 5, amido linkage to the 2-position of the fluorenyl ring system was achieved by starting with Jones oxidation of the 2-fluorenecarboxaldehyde (**41**) to the carboxylic acid **42** and amide coupling via the acid chloride, as described for compounds **40a**,**b**, to give **43a**,**b**, in excellent overall yield. In Scheme 6, the amide linkage was directed at the 9-position of the fluorenyl ring system and reaction of the acid chloride of **44** with synthons **30a**, **30b**, or **33** gave the products **45**, **46**, or **47**, respectively. In Scheme 7, the 9-fluorenone-4-carbonyl chloride (**48**) was reacted with the synthons **30a**, **30b**, **33**, or **38** to give **49**, **50**, **51**, or **52**, respectively. All final products were purified by flash column chromatography and crystallized as their HCl salts.

Although compounds **10** and **11** were part of the initial screening group, their synthesis has not previously been reported. Hence in Scheme 8, the alcohol **53** was treated with 2-(3-bromopropoxy)tetrahydropyran followed by deprotection in aqueous acetic acid/THF to give intermediate **54**. Conversion of the resulting alcohol to the alkylbromide with triphenylphosphine and carbon tetrabromide was followed by alkylation with **28a** to give product **10**, in good overall yield. In Scheme 9, 9-fluorenone (**55**) was converted to the nitrile **56** using tosylmethyl isocyanide (TosMIC). Reduction to the amine **57** with BH_3-DMS was followed by reaction with

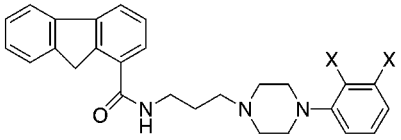
Chart 3. Novel D_3 Ligands



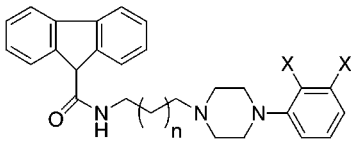
32; n=1
37; n=2



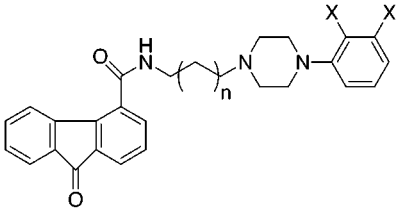
43a; X=H
43b; X=Cl



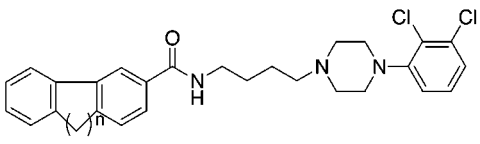
40a; X=H
40b; X=Cl



45; n=1, X=H
46; n=1, X=Cl
47; n=2, X=Cl



49; n=1, X=H
50; n=1, X=Cl
51; n=2, X=Cl
52; n=3, X=Cl



58a, NGB 2849, n=0
58b, NGB 2904, n=1

Table 1. Radiolabeled Binding Assay Screen for D_2, D_3, and D_4 Receptors

	K_i (nM)[a]				
compd	D_3	D_2	D_4	D_2/D_3	D_4/D_3
1	>8000	NT[b]	NT		
2	>8000	NT	NT		
3	>4000	NT	NT		
4	>8000	NT	NT		
5	>5000	NT	NT		
6	>8000	NT	NT		
7	>8000	NT	NT		
8	2420 ± 310	NT	NT		
9	>4000	NT	NT		
10	4010 ± 640	180 ± 46	>4000	0.05	
11	>8000	NT	NT		
12	13.8 ± 1.1	81.3 ± 13	68.1 ± 4.4	6	5
13	112 ± 28	379 ± 27	120 ± 7.3	3	1
14	53.2 ± 4.9	218 ± 19	172 ± 18	4	3
15	277 ± 34	625 ± 49	349 ± 29	2	1
16	214 ± 14	927 ± 110	868 ± 54	4	4
17	63.3 ± 5.0	132 ± 11	640 ± 21	2	10
18	145 ± 11	NT	NT		
19	130 ± 21	NT	NT		
20	2520 ± 410	1120 ± 95	>4000	0.4	
21	220 ± 21	NT	NT		
22	72.7 ± 8.7	59.0 ± 4.3	222 ± 9.1	1	3
23	193 ± 33	672 ± 44	541 ± 25	4	3
24	5380 ± 93	1740 ± 140	1000 ± 110	0.3	
25	6100 ± 750	NT	NT		

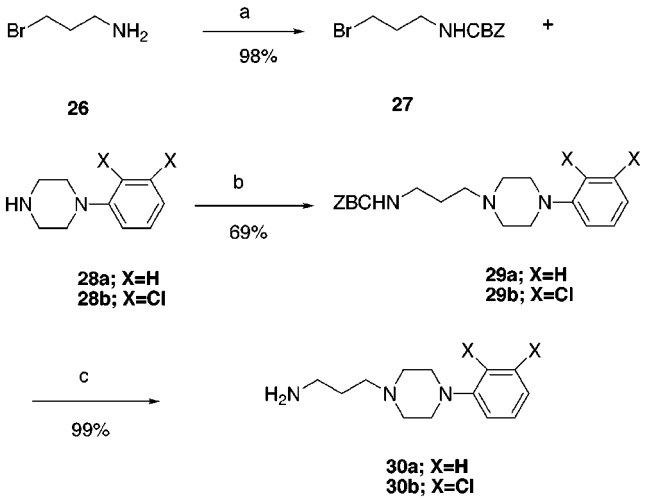
[a] Each K_i value represents data from two or three independent experiments, each performed in duplicate. [b] Not tested.

the carbobenzoxy-protected isonipecotic acid and deprotection, using iodotrimethylsilane, to give product **11**.

Structure−Activity Relationships

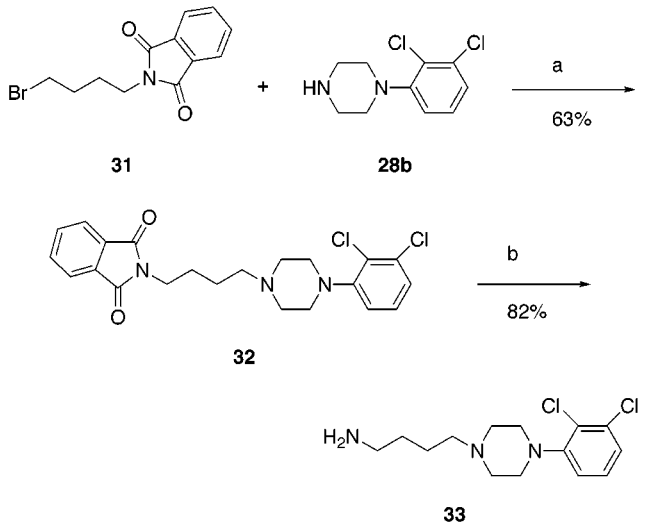
The initial group of compounds chosen for screening at D_2, D_3, and D_4 receptors comprised of the compounds depicted in Charts 1 and 2. The compounds in Chart 1 are related to rimcazole (**1**), a compound that has historically been characterized as an atypical antipsychotic, due to its low affinity for dopamine D_2 receptors and its moderate affinity for σ receptors.[26,27] The analogues **2**−**11** had previously been prepared as mixed dopamine uptake inhibitor/σ ligands and possessed a tricyclic ring system linked via an alkyl chain to a piperazine or piperidine ring, structural features that have been reported for D_3 selective ligands.[28−32] The 3α-(diphenylmethoxy)tropane (benztropine) analogues **12**−**24** were prepared as dopamine uptake inhibitors.[33−37] However, some of these analogues bind with high affinity to σ receptors (unpublished data), and as stated above, many D_3 agonists have high affinity for σ receptors as well. Furthermore, the tropane ring can be considered a structurally rigid piperidine and the diphenyl ether provided a multiaryl ring system that might bind similarly to the aryl ring systems reported for other D_3 ligands. Compound **25** was selected as it binds with high affinity to σ receptors[22] and in a NOVAscreen evaluation was found to have an IC_{50} value of $<10\ \mu$M at D_3 receptors. The binding data for D_2, D_3, and D_4 can be seen, for this group of compounds, in Table 1. None of this group of compounds exhibited selective binding for D_3 receptors. However, several benztropine analogues (**12**, **13**, **14**, **17**, and **22**) exhibited high to moderate binding affinities for D_3 ($K_i = 14-112$ nM). As the rimcazole analogues were essentially inactive at D_3, it was clear that those D_3 structural components were not adequate or in an appropriate relationship to one another to afford high-affinity binding at D_3.

Scheme 1[a]



[a] Reagents: (a) benzylchloroformate; (b) K_2CO_3, DMF, 80 °C; (c) TMSiI, MeCN.

Scheme 2[a]



[a] Reagents: (a) K_2CO_3, DMF, 80 °C; (b) NH_2NH_2, EtOH, reflux.

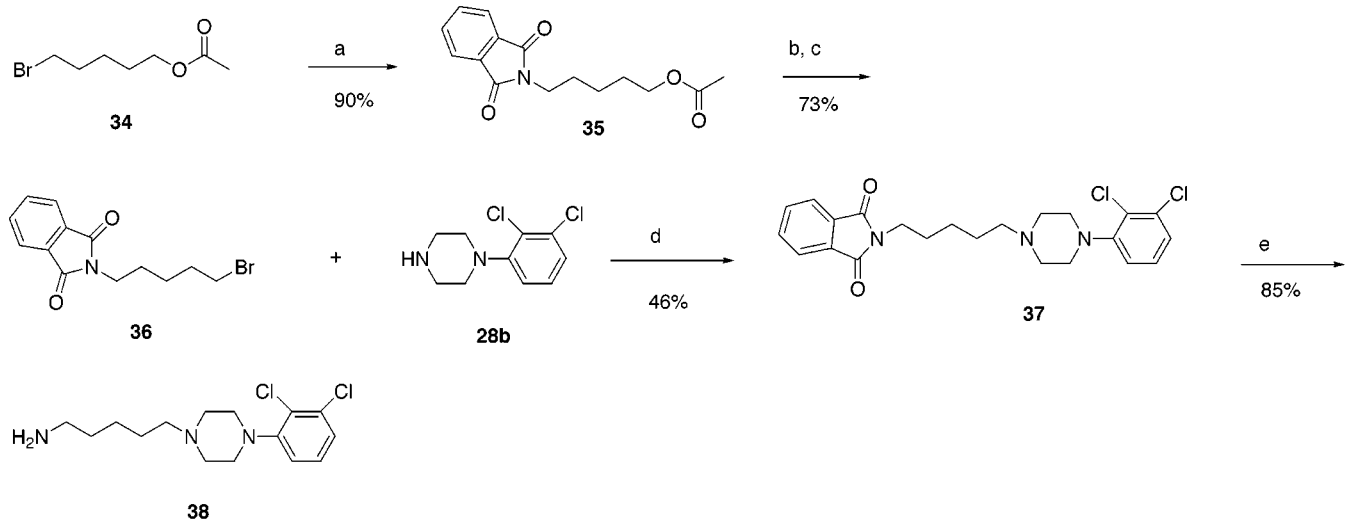
Table 2. Radiolabeled Binding Assay Results for Novel Ligands at D_2, D_3, and D_4 Receptors

	K_i (nM)[a]				
compd	D_3	D_2	D_4	D_2/D_3	D_4/D_3
32	4.1 ± 1.0	120 ± 18	368 ± 15	30	92
37	7.8 ± 2.1	11 ± 1.1	105 ± 9	1.4	13
40a	430 ± 16	473 ± 31	791 ± 67	1	2
40b	170 ± 14	1680 ± 230	326 ± 31	10	2
43a	1460 ± 110	825 ± 38	679 ± 11	0.6	0.5
43b	110 ± 8.7	2570 ± 240	350 ± 39	24	3
45	340 ± 21	606 ± 5.2	2170 ± 220	2	6
46	24 ± 7.4	414 ± 29	1140 ± 34	17	47
47	19 ± 3.0	10 ± 1.0	391 ± 12	0.5	21
49	430 ± 51	777 ± 39	1380 ± 100	2	3
50	36 ± 2.1	512 ± 20	3990 ± 13	14	11
51	1.4± 0.6	89 ± 4	1850 ± 106	64	1319
52	28 ± 3.0	5.0 ± 1.1	530 ± 31	0.2	19
58a[b]	0.9 ± 0.3	262 ± 21	>5000	290	>5000
58b[b]	1.4 ±0.6	217 ± 12	>5000	155	>3500

[a] Each K_i value represents data from two or three independent experiments, each performed in duplicate. [b] Data from ref 25.

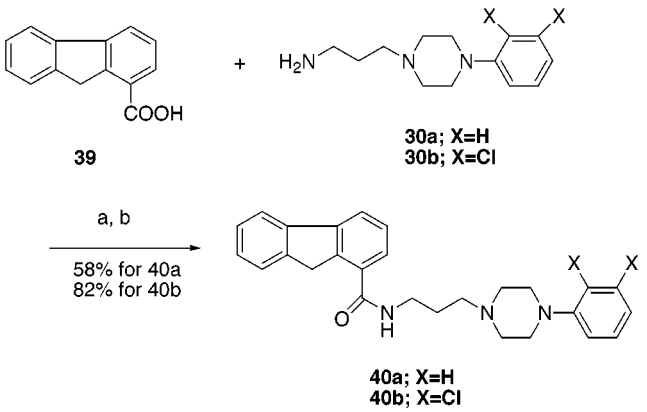
When compounds **58a** and **58b** (NGB 2849 and NGB 2904, respectively) were reported to have exceptional binding affinity and selectivity for D_3 receptors,[25] a series of compounds (Chart 3) were designed to further determine optimal structure−activity relationships at D_3 receptors. On the basis of the structures of these compounds and the structure−activity relationships deduced from our screen, the fluorenyl ring was selected as an optimal structural feature; however, its position with regard to the rest of the molecule had not been explored. Hence, the amide linkage was placed at the 1-, 2-, 4-, or 9-position. Although the alkyl linker between the amido-fluorene and the terminal piperazine in the Neurogen compounds was four carbons in length, it had not been determined whether that was optimal, and hence, both the 3- and 5-carbon chains were explored. Finally, comparisons between the 2,3-dichloro-substituted phenylpiperazine versus the unsubstituted analogues were also investigated. The results of binding experiments on these 13 novel analogues were compared to those of **58a** and **58b** and can be seen in Table 2. The most potent analogue in this series was compound **51**, which was equipotent to **58a** and **58b** at D_3 receptors

Scheme 3[a]



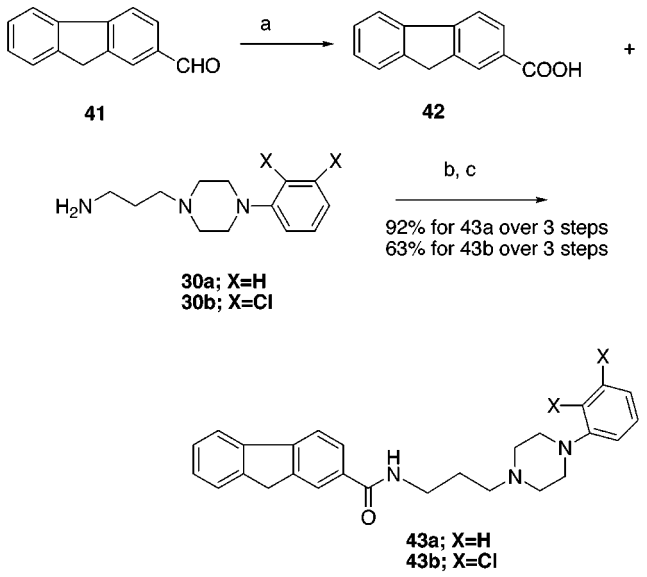
[a] Reagents: (a) potassium phthalimide, DMF, rt; (b) K_2CO_3, MeOH; (c) PPh_3, CBr_4, MeCN; (d) K_2CO_3, DMF, 80 °C; (e) NH_2NH_2, EtOH, reflux.

Scheme 4[a]



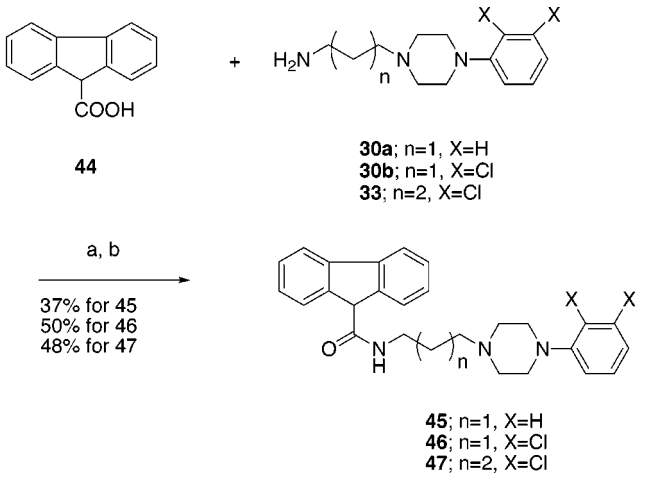
[a] (a) $SOCl_2$; (b) $CHCl_3$, aq $NaHCO_3$.

Scheme 5[a]



[a] Reagents: (a) Jones oxidation; (b) $SOCl_2$; (c) $CHCl_3$, aq $NaHCO_3$.

Scheme 6[a]

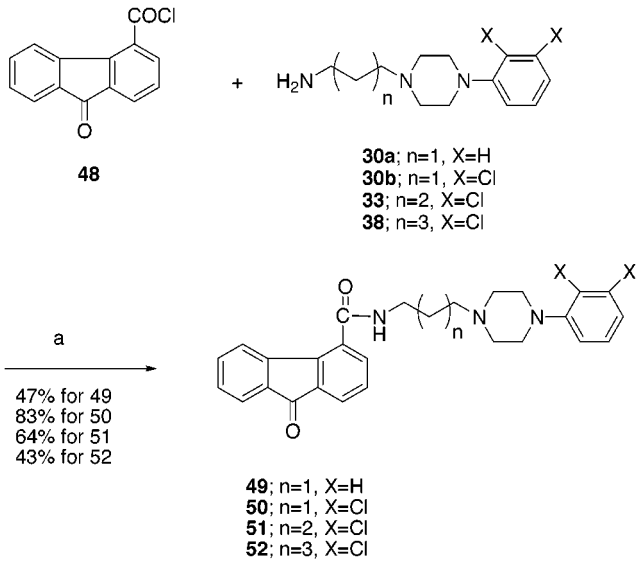


[a] Reagents: (a) $SOCl_2$; (c) $CHCl_3$, aq $NaHCO_3$.

but approximately 2-fold more potent at D_2, rendering it less D_3-selective than these compounds.

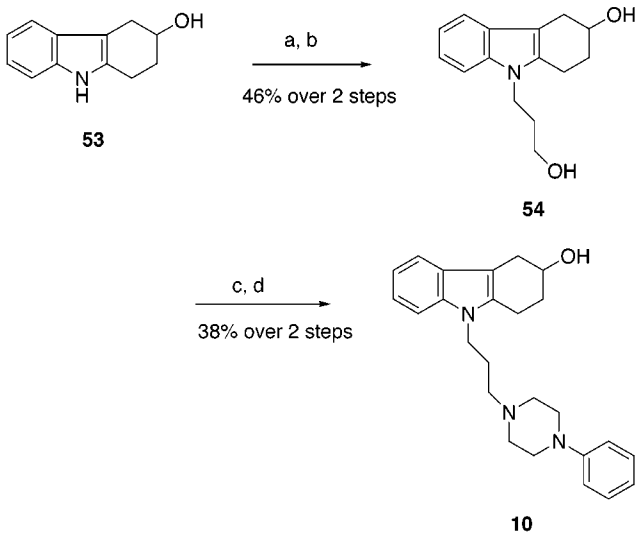
Structure−activity relationships demonstrated that the 2,3-dichloro-substituted phenylpiperazine was required for high-affinity binding at D_3, wherein every compound with this substituent was more potent than its unsubstituted homologue (for example **45** vs **46**). The optimum alkyl chain length between the amido-aryl function and the phenylpiperazine was four carbons. Although the 5-carbon linked **37** and **52** exhibited reasonably high affinity for D_3 receptors, D_2 affinity was also very high. In fact, compound **52** was actually ~5-fold D_2-selective. The 3-carbon chained analogues resulted in less potent binding at D_3, which was supported by the data in Table 1, with the rimcazole analogues, wherein the carbazole ring system was linked to the piperazine ring with a 3-carbon chain. The position of the amide-linkage on the fluorenyl ring appears to be optimal at either the 3- or 4-positions, as seen with **58b** and **51**, respectively. The 9-position ketone analogue of **58b** demonstrated reduced affinity for D_3 (unpublished data), suggesting that reduction of this functional group on compound **51** may further enhance binding affinity

Scheme 7[a]



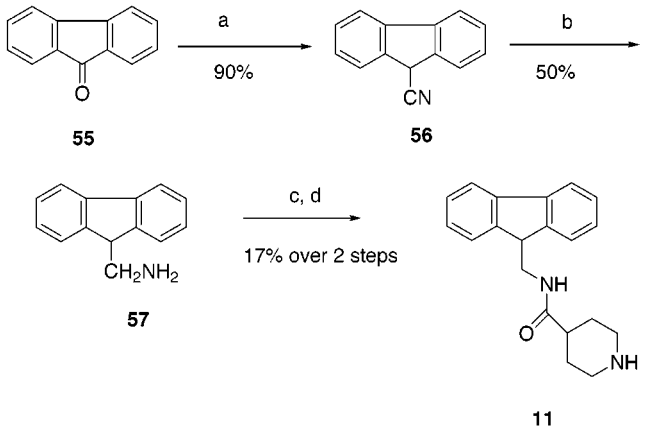
[a] Reagents: (a) $CHCl_3$, aq $NaHCO_3$.

Scheme 8[a]



[a] Reagents: (a) NaH, DMF, 2-(3-bromopropoxy)tetrahydropyran, 70 °C; (b) $HOAc/H_2O/THF$, 50 °C; (c) PPh_3, CBr_4; (d) **28a**, K_2CO_3, toluene, 80 °C.

Scheme 9[a]



[a] Reagents: (a) TosMIC, ^{t}BuOK, −70 °C; (b) BH_3-DMS, THF, 50 °C; (c) CBZ-isonipecotic acid, DCC, HOBt; (d) TMSiI.

and selectivity for D_3. Compounds **37**, **47**, and **52** demonstrated the highest affinities for D_2, in this series. None of the compounds displayed appreciable affinity for D_4.

Summary

A series of novel dopamine D_3 receptor ligands were designed, synthesized, and evaluated for D_2, D_3, and D_4 receptor binding in stably transfected CHO cells. Structural features for optimal D_3 binding were identified, and the most potent and selective compound, **51**, has been chosen for further in vitro and in vivo evaluation. Compounds **51** and **58b** have been resynthesized on a multigram scale and are currently being evaluated in models of psychostimulant abuse, both alone and in combination with cocaine and methamphetamine. We anticipate that these studies will shed light on the role that D_3 receptors play in the psychomotor stimulant and subjective effects of cocaine and methamphetamine. Furthermore, although these analogues are presumed to be antagonists, based on the in vitro profile of compound **58b**, their pharmacological efficacy in vivo will need to be further investigated to validate in vitro models, as well as to determine whether a D_3 agonist, partial agonist, or antagonist should be targeted for the potential development of medications for cocaine abuse.

The high lipophilicity of both **58b** and **51** may prove to be problematic pharmacokinetically and for in vivo localization at D_3 receptors. This problem has been suggested to contribute to the failure of [^{11}C]BP 897 as a PET ligand.[38] Thus, now that structure−activity relationships for this class of D_3 receptors have been established, future investigation toward developing ligands that retain high affinity for D_3 receptors, but are less lipophilic, will be warranted.

Finally, in addition to the therapeutic target of cocaine addiction, D_3 receptor ligands have received attention for their potential as antipsychotic and antiparkinsonian drugs.[39] Numerous reports have appeared in the past year describing highly selective and potent D_3 antagonists toward these therapeutic targets.[40−44] Although the clinical efficacy of these agents has yet to be substantiated, highly selective and potent tools with which to further investigate dopamine D_3 receptors remains an important research goal.

Experimental Section

Chemistry. All melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. The ^{1}H NMR spectra were recorded on a Bruker (Billerica, Mass) AC-300 instrument. Samples were dissolved in an appropriate deuterated solvent ($CDCl_3$). Proton chemical shifts are reported as parts per million (δ) relative to tetramethylsilane (Me_4Si; 0.00 ppm), which was used as an internal standard. Chemical shifts for ^{13}C NMR spectra are reported as δ relative to deuterated chloroform ($CDCl_3$, 77.0 ppm). Infrared spectra were recorded on a Perkin-Elmer 1600 Series FTIR. Microanalyses were performed by Atlantic Microlab, Inc. (Norcross, GA) and agree within ±0.4% of calculated values. TLC solvent used was $CHCl_3$/MeOH/NH_4OH (CMA) unless otherwise indicated. All chemicals and reagents were purchased from Aldrich Chemical Co. or Lancaster Synthesis, Inc., unless otherwise indicated, and used without further purification.

General Procedures. Method A: Nitrogen Alkylation. The free base form of phenylpiperazine (**28a**) or (2,3-dichlorophenyl)piperazine (**28b**), the alkyl bromide (1.1 equiv), and K_2CO_3 (2 equiv) were heated to 80 °C in DMF (3 mL/mmol of phenylpiperazine) for 5 h, under an atmosphere of argon. The mixture was cooled to room temperature and H_2O was added. The organics were extracted with ethyl acetate (3×). The combined ethyl acetate extracts were back-washed with H_2O (2×) and brine (1×). The organic extract was dried ($MgSO_4$) and filtered and solvent evaporated in vacuo to give the product as a clear oil.

Method B: Acid Chloride Formation. A solution of fluorenyl acid in thionyl chloride (1 mL/mmol of acid) was stirred at reflux for 3 h. Excess thionyl chloride was removed by distillation followed by addition and distillation of dry toluene (3 × 2 mL) to give the acid chloride product as an oil, which was used in the amidation reaction, without further purification.

Method C: Amidation Procedure. The fluorenyl acid chloride was dissolved in amylene-stabilized $CHCl_3$ (1 mL/mmol of acid chloride) and added dropwise to a two-phase reaction mixture of the amine (1 equiv free base), H_2O (5 mL/mmol of amine), $CHCl_3$ (10 mL/mmol of amine), and $NaHCO_3$ (6 equiv) at pH 8−9, at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 1 h. The $CHCl_3$ layer was removed and the aqueous portion was washed with $CHCl_3$ (2×). The combined organic portions were washed with H_2O (1×), dried ($MgSO_4$), and filtered, and the solvent was removed in vacuo to give the product as an oil.

(3-Bromopropyl)carbamic Acid Benzyl Ester (27). Benzylchloroformate (17.13 mL, 120 mmol) was added to a stirred mixture of 3-bromopropylamine hydrobromide (13.14 g, 60 mmol) in $CHCl_3$ (200 mL) and 3 N NaOH (200 mL) at 0 °C. The two-phase reaction mixture was allowed to stir at room temperature overnight. The $CHCl_3$ layer was separated and washed with H_2O (2 × 75 mL) and brine, dried ($MgSO_4$), and filtered, and the solvent was removed in vacuo to give the product as a colorless liquid. Column chromatography (20% ethyl acetate/hexane, R_f 0.3) gave 16.12 g (98%) of the product as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.01−2.10 (m, 2H), 3.33 (q, J = 6.4 Hz, 2H), 3.42 (t, J = 6.5 Hz, 2H), 5.10 (s, 2H), 7.35 (s, 5H); IR (NaCl plate, neat) 697, 1134, 1260, 1538, 1694, 2946, 3332 cm^{-1}.

1-(2,3-Dichlorophenyl)piperazine (28b). Under an atmosphere of argon, P_2O_5 (11.36 g, 80 mmol) and triethylamine hydrochloride (11.04 g, 80 mmol) were combined. The mixture was heated to a melt (220 °C) and stirred mechanically with an overhead stirrer. To this mixture were added 2,3-dichloroaniline (3.24 g, 20 mmol) and diethanolamine (2.31 g, 22 mmol). The mixture was stirred under argon for 4 h and then allowed to cool to ∼150 °C. The reaction was quenched by careful addition of boiling H_2O (300 mL). The tarry reaction mixture was allowed to cool and was then extracted with ethyl acetate (2 × 100 mL). The aqueous mixture was cooled in an ice bath and the pH was adjusted to 10−11 by addition of 50% aqueous NaOH. The aqueous phase was extracted with ethyl

acetate (3 × 75 mL). The combined ethyl acetate extracts were washed with H_2O (1 × 100 mL) and brine (1 × 100 mL), dried ($MgSO_4$), and filtered, and the solvent was removed in vacuo to give the product as a brown oil. The HCl salt was formed and recrystallized from 2-PrOH/hexane to give 1.68 g (31%) of product: mp 239−242 °C; lit. mp (Chess Fine Organics, Mannheim, Germany) 240−244 °C; ^{1}H NMR δ 2.99−3.06 (m, 8H), 6.93−6.97 (m, 1H), 7.11−7.16 (m, 2H); ^{13}C NMR δ 46.1, 52.7, 118.6, 124.5, 127.4, 127.6, 134.0, 151.7; IR (KBr pellet) 791, 952, 1041, 1144, 1253, 1440, 1579, 2471, 2771 cm^{-1}.

[3-(4-Phenylpiperazin-1-yl)carbamic Acid Benzyl Ester (29a). Using general procedure A with **28a** and **27** gave the product **29a** as an oil. The HCl salt was formed and recrystallized from 2-PrOH/hexane to give 8.10 g (69%) of pure product: ^{1}H NMR δ 1.65−1.75 (m, 2H), 2.49 (t, J = 6.5 Hz, 2H), 2.59 (t, J = 4.7 Hz, 4H), 3.18 (t, J = 5.1 Hz, 4H), 3.30 (q, J = 6.0 Hz, 2H), 5.09 (s, 2H), 5.87 (bs, 1H), 6.84−6.93 (m, 3H), 7.24−7.35 (m,7H); IR (KBr pellet) 694, 757, 1236, 1499, 1599, 1718, 2819, 2945, 3335 cm^{-1}.

{3-[4-(2,3-Dichlorophenyl)piperazin-1-yl)]propyl}carbamic Acid Benzyl Ester (29b). Using general procedure A with 1-(2,3-dichlorophenyl)piperazine (**28b**) gave the product **29b** as an oil. Column chromatography (100% ethyl acetate, R_f 0.4) gave 2.31 g (68%) of the pure product as a colorless oil.

3-(4-Phenylpiperazin-1-yl)propylamine (30a). Compound **29a** (5.80 g, 16.4 mmol) was converted to its free base form by extraction with $CHCl_3$ (3 × 50 mL) from 20% aqueous NH_4OH (60 mL), drying, and evaporating in vacuo to an oil. Iodotrimethylsilane (8.39 mL, 58.9 mmol) was added to a solution of **29a** in acetonitrile (60 mL). The reaction mixture was stirred for 15 min at room temperature and then quenched with MeOH (20 mL) and stirred for an additional 10 min. Volatiles were removed in vacuo, and the residue was dissolved in 3 N HCl (60 mL) and extracted with ether (3 × 50 mL). The aqueous portion was neutralized to pH 9−10 with aqueous NH_4OH. Extraction with $CHCl_3$ (3 × 50 mL) and drying ($MgSO_4$) followed by evaporation yielded the product as a clear viscous oil that was used in the next reaction without further purification.

3-[4-(2,3-Dichlorophenyl)piperazin-1-yl]propylamine (30b). Iodotrimethylsilane (2.78 mL, 19.4 mmol) was added to a solution of **29b** (2.31 g, 5.4 mmol) in acetonitrile (40 mL). The reaction mixture was stirred for 15 min at room temperature, quenched with MeOH (10 mL), and stirred for an additional 10 min. Volatiles were removed in vacuo; the residue was dissolved in 3 N HCl (40 mL) and extracted with ether (3 × 50 mL). The aqueous portion was neutralized to pH 9−10 with aqueous NH_4OH. Extraction with $CHCl_3$ (3 × 50 mL) and drying ($MgSO_4$) followed by evaporation yielded the product as a clear viscous oil that was used in the next reaction without further purification.

2-{4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butyl}isoindoline-1,3-dione (32). Using general procedure A with amine **28b** and commercially available 2-(4-bromobutyl)isoindoline-1,3-dione (**31**) gave the product as an oil. Column chromatography (95% CMA, R_f 0.6) followed by treatment with HCl-saturated MeOH and crystallization from 2-PrOH gave 1.48 g (63%) of **32** as the HCl salt: mp >250 °C dec; ^{1}H NMR δ 1.52−1.62 (m, 2H), 1.69−1.76 (m, 2H), 2.44 (t, J = 7.4 Hz, 2H), 2.61 (bs, 4H), 3.04 (bs, 4H), 3.72 (t, J = 6.9 Hz, 2H), 6.92−6.95(m, 1H), 7.09−7.15 (m, 2H), 7.68−7.73(m, 2H), 7.80−7.85 (m, 2H); ^{13}C NMR δ 24.2, 26.6, 37.8, 51.3, 53.3, 57.9, 118.6, 123.2, 124.5, 127.4, 132.1, 133.9, 134.0, 151.3, 168.4. Anal. ($C_{22}H_{23}Cl_2N_3O_2$·HCl·0.25H_2O) C, H, N.

4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butylamine (33). Anhydrous hydrazine (0.14 mL, 4.4 mmol) was added to a solution of **32** (1.0 g, 2.1 mmol) in EtOH (20 mL). The mixture was heated to reflux for 2 h and then allowed to cool to room temperature. The volatiles were removed in vacuo, and the solid residue was dissolved in 40% KOH (w/v, 50 mL). The product was extracted with ether (4 × 50 mL) and dried ($MgSO_4$). Evaporation of the solvent gave 0.52 g (82%) of **33** as an oil that was used in the next reaction without further purification.

5-(1,3-Dioxoisoindolin-2-ly)pentyl Acetate (35). Potassium phthalimide (4.08 g, 22 mmol) was added to a solution of 5-bromopentyl acetate (**34**, 3.33 mL, 20 mmol) in DMF (50 mL). The mixture was stirred at room temperature for 16 h and poured into ice water (300 mL), and the product **35** was isolated by filtration and recrystallized from 2-PrOH to give 4.94 g (90%) of **35**: mp 39−41 °C; ^{1}H δ 1.35−1.46 (m, 2H), 1.62−1.76 (m, 4H), 2.02 (s, 3H), 3.69 (t, J = 7.1 Hz, 2H), 4.04 (t, J = 6.6 Hz, 2H), 7.69−7.73 (m, 2H), 7.81−7.85 (m, 2H).

2-(5-Bromopentyl)isoindoline-1,3-dione (36). To a solution of **35** (1.1 g, 4 mmol) in MeOH (50 mL) was added K_2CO_3 (50 mg, catalytic). The mixture was stirred at room temperature overnight. Evaporation of the volatiles gave an oil that was dissolved in ether (50 mL), washed with H_2O (2 × 50 mL), dried ($MgSO_4$), and evaporated to give the crude intermediate as a viscous clear oil. Triphenylphosphine (1.15 g, 4.4 mmol) and CBr_4 (1.46 g, 4.4 mmol) were added to a solution of the crude oil in acetonitrile (30 mL). The mixture was stirred for 16 h at room temperature. Evaporation of the volatiles gave a thick oil that was stirred in ether (50 mL). Filtration of the triphenylphosphine oxide and evaporation of the ether filtrate gave the product as an oil. Column chromatography (50% ethyl acetate/hexane, R_f 0.8) gave 0.86 g (73% over two steps) of the product as a clear oil: ^{1}H NMR δ 1.45−1.55 (m, 2H), 1.67−1.77 (m, 2H), 1.87−2.05 (m, 2H), 3.40 (t, J = 6.7 Hz, 2H), 3.70 (t, J = 7.3 Hz, 2H), 7.70−7.75 (m, 2H), 7.82−7.86 m, 2H); IR (NaCl, neat) 717, 1031, 1395, 1708, 1770, 2938 cm^{-1}.

2-{5-[4-(2,3-Dichlorophenyl)piperazin-1-yl]pentyl}isoindoline-1,3-dione (37). Using general procedure A with amine **28b** and bromide **36** yielded the product **37** as an oil. Column chromatography (95% CMA, R_f 0.6) followed by treatment with HCl-saturated MeOH and crystallization from 2-PrOH gave 0.55 g (46%) of **37** as the HCl salt: mp 238−240 °C; ^{1}H NMR δ 1.33−1.43 (m, 2H), 1.53−1.63 (m, 2H), 1.67−1.77 (m, 2H), 2.40 (t, J = 7.4 Hz, 2H), 2.62 (bs, 4H), 3.05 (bs, 4H), 3.70 (t, J = 7.2 Hz, 2H), 6.93−6.96(m, 1H), 7.10−7.15 (m, 2H), 7.70−7.73(m, 2H), 7.83−7.86 (m, 2H). Anal. ($C_{23}H_{25}Cl_2N_3O_2$·HCl) C, H, N.

5-[4-(2,3-Dichlorophenyl)piperazin-1-yl]pentylamine (38). Anhydrous hydrazine (0.07 mL, 2.1 mmol) was added to a solution of **37** (480 mg, 1.0 mmol) in EtOH (20 mL). The reaction mixture was stirred at reflux for 2 h and then allowed to cool to room temperature. The volatiles were removed in vacuo, and the solid residue was dissolved in 40% KOH (50 mL, w/v). The product was extracted with ether (4 × 50 mL) and dried ($MgSO_4$). Evaporation of the solvent gave 0.27 g (85%) of **38** as an oil that was used in the next reaction without further purification.

Fluorenyl-*N*-[3-(4-phenylpiperazin-1-yl)propyl]carboxamide (40a). Using general procedure B with 1-fluorenecarboxylic acid (**39**) gave the corresponding acid chloride, which was converted to the desired product (oil) using general procedure C with amine **30a**. Column chromatography (95% CMA, R_f 0.3) followed by treatment with HCl-saturated MeOH and crystallization from MeOH gave 3.10 g (58%) of the **40a** as the HCl salt: mp 283−285 °C; ^{1}H NMR δ 1.84−1.88 (m, 2H), 2.61−2.68 (m, 6H), 3.12−3.15 (m, 4H), 3.62 (t, J = 5.7 Hz, 2H), 4.26 (s, 2H), 4.75 (bs, 1H), 6.85−6.90 (m, 3H), 7.24−7.40 (m, 5H), 7.54 (dd, J = 6.7, 18.3 Hz, 2H), 7.80 (dd, J = 7.5, 17.4 Hz, 2H); ^{13}C NMR δ 24.7, 37.7, 40.2, 49.3, 53.4, 58.1, 116.2, 119.9, 120.0, 122.2, 124.5, 125.0, 126.6, 126.9, 127.3, 129.1, 131.8, 140.5, 143.1, 143.2, 143.9, 151.1, 168.0; IR (KBr pellet) 690, 743, 1277, 1489, 1529, 1659, 23.97, 2379, 3385 cm^{-1}. Anal. ($C_{27}H_{29}N_3O$·HCl·0.5H_2O) C, H, N.

***N*-{3-[4-(2,3-Dichlorophenyl)piperazin-1-yl]propyl}fluorenylcarboxamide (40b).** Using general procedure B with 1-fluorenecarboxylic acid (**39**) gave the corresponding acid chloride, which was converted to the desired product **40b** as an oil using general procedure C with amine **30b**. Column chromatography (95% CMA, R_f 0.4) followed by treatment with HCl-saturated MeOH and crystallization from MeOH gave 2.12 g (82%) of **40b** as the HCl salt: mp 242−244 °C; ^{1}H NMR δ 1.83−1.89 (m, 2H), 2.64−2.68 (m, 6H), 2.94 (bs, 4H), 3.63 (t, J = 6.1 Hz, 2H), 4.27 (s, 2H), 6.72 (dd, J = 1.5, 7.5 Hz, 1H),

7.08−7.17 (m, 2H), 7.31−7.41 (m, 3H), 7.57 (t, J = 8.0 Hz, 2H), 7.79 (d, J = 6.9 Hz, 1H), 7.87 (d, J = 7.5 Hz, 1H); ^{13}C NMR δ 24.6, 29.7, 37.7, 40.3, 51.2, 53.4, 58.1, 118.5, 119.9, 122.1, 124.7, 124.8, 125.0, 126.7, 126.9, 127.3, 127.4, 132.2, 134.0, 140.5, 142.9, 143.2, 143.8, 151.0, 168.0; IR (KBr pellet) 751, 780, 957, 1277, 1455, 1522, 1579, 1636, 2598, 2929, 3384 cm^{-1}. Anal. ($C_{27}H_{27}Cl_2N_3O$·HCl) C, H, N.

Fluoren-2-yl-*N*-[3-(4-phenylpiperazin-1-yl)propyl]carboxamide (43a). Jones reagent was added dropwise to a solution of 2-fluorenecarboxaldehyde (**41**, 1.0 g, 5 mmol) in acetone (10 mL) until a persistent orange color was observed. After 10 min, the reaction was quenched by dropwise addition of 2-PrOH. The reaction mixture was diluted with ether (50 mL), followed by H_2O (10 mL), to dissolve the inorganic residue. Following removal of the ethereal phase, the aqueous phase was re-extracted with ether (50 mL). The combined ether extracts were washed with H_2O (1 × 50 mL) and brine (1 × 50 mL) and dried ($MgSO_4$). The solvent was removed in vacuo to give compound **42** as an oil, which crystallized on standing. Using general procedure B with **42** gave the corresponding acid chloride, which was converted to the desired product (**43a**) that was isolated as an oil using general procedure C with amine **30a**. Column chromatography (95% CMA, R_f 0.3) followed by treatment with HCl-saturated MeOH and crystallization from MeOH gave 1.98 g (92% over three steps) of **42** as the HCl salt: mp 257−259 °C; ^{1}H NMR δ 1.84−1.87 (m, 2H), 2.64−2.70 (m, 6H), 3.23 (t, J = 4.8 Hz, 4H), 3.61−3.66 (m, 2H), 3.73 (s, 2H), 6.87−6.91 (m, 3H), 7.22−7.40 (m, 4H), 7.45 (d, J = 7.2 Hz, 1H), 7.75 (t, J = 8.0 Hz, 2H), 7.86 (d, J = 8.0 Hz, 1H), 7.99 (s, 1H), 8.35 (bs, 1H); ^{13}C NMR δ 24.4, 36.7, 40.8, 49.3, 53.4, 58.5, 116.1, 119.7, 120.1, 120.5, 123.6, 125.1, 126.0, 126.9, 127.5, 129.1, 132.9, 140.6, 143.2, 144.0, 144.7, 151.2, 167.5; IR (KBr pellet) 693, 752, 1314, 1454, 1532, 1634, 2581, 2924, 3256 cm^{-1}. Anal. ($C_{27}H_{29}N_3O$·HCl) C, H, N.

***N*-{3-[4-(2,3-Dichlorophenyl)piperazin-1-yl]propyl}-fluoren-2-ylcarboxamide (43b).** Using general procedure B with 2-fluorenecarboxylic acid (**42**) gave the corresponding acid chloride that was converted to the desired product **43b** as an oil, using general procedure C with amine **30b**. Column chromatography (95% CMA, R_f 0.4) followed by treatment with HCl saturated MeOH and crystallization from 2-PrOH gave 1.63 g (63% over three steps) of **43b** as the HCl salt: mp 233−235 °C; ^{1}H NMR δ 1.80−1.88 (m, 2H), 2.65−2.69 (m, 6H), 3.01 (s, 4H), 3.61−3.66 (m, 2H), 3.87 (s, 2H), 6.73 (d, J = 8.0 Hz, 1H), 6.94 (t, J = 8.0 Hz, 1H), 7.13 (dd, J = 1.2, 8.1 Hz, 1H), 7.32−7.43 (m, 2H), 7.52 (d, J = 7.2 Hz, 1H), 7.77−7.87 (m, 3H), 8.01(s, 1H), 8.35 (s, 1H); ^{13}C NMR δ 24.5, 36.9, 40.7, 51.2, 53.4, 58.3, 118.3, 119.6, 120.4, 123.8, 124.8, 125.2, 126.1, 127.0, 127.3, 127.5, 127.6, 133.4, 134.1, 140.7, 143.2, 143.9, 144.6, 150.9, 167.7. Anal. ($C_{27}H_{27}Cl_2N_3O$·HCl) C, H, N.

Fluoren-9-yl-*N*-[3-(4-phenylpiperazin-1yl)propyl]carboxamide (45). Using general procedure B with 9-fluorenecarboxylic acid (**44**) gave the corresponding acid chloride, which was converted to the desired product (oil) using general procedure C with amine **30a**. Column chromatography (95% CMA, R_f 0.3) followed by treatment with HCl-saturated MeOH and crystallization from acetone/hexane gave 1.52 g (37%) of **45** as the HCl salt: mp 226−228 °C; ^{1}H NMR δ 1.52−1.62 (m, 2H), 2.26 (t, J = 6.5 Hz, 2H), 2.34 (bs, 4H), 2.83 (bs, 4H), 3.29 (q, J = 5.6 Hz, 2H), 4.79 (s, 1H), 6.21 (bs, 1H), 6.84−6.90 (m, 3H), 7.26−7.39 (m, 7H), 7.64−7.69 (m, 3H); ^{13}C NMR δ 25.1, 39.1, 48.4, 53.1, 56.3, 56.9, 115.8, 119.5, 120.3, 126.2, 127.7, 128.3, 129.0, 141.3, 141.7, 141.8, 151.1, 170.7; IR (KBr pellet) 690, 740, 1239, 1446, 1627, 2382, 2819, 2944 cm^{-1}. Anal. ($C_{27}H_{29}N_3O$·HCl) C, H, N.

***N*-{3-[4-(2,3-Dichlorophenyl)piperazin-1-yl]propyl}-fluoren-9-ylcarboxamide (46)** Using general procedure B with 9-fluorenecarboxylic acid (**44**) gave the corresponding acid chloride, which was converted to the desired product (oil) using general procedure C with amine **30b**. Column chromatography (95% CMA, R_f 0.4) followed by treatment with HCl-saturated MeOH and crystallization from 2-PrOH gave 0.77 g (50%) of **46** as the HCl salt: mp 214−216 °C; ^{1}H NMR δ 1.51−1.59 (m, 2H), 2.26 (t, J = 6.5 Hz, 2H), 2.35 (bs, 4H), 2.72 (bs, 4H), 3.28 (q, J = 5.9 Hz, 2H), 4.81 (s, 1H), 6.07 (bs, 1H), 6.87−6.90 (m, 1H), 7.15−7.18 (m, 2H), 7.33−7.44 (m, 4H), 7.68−7.75 (m, 4H); ^{13}C NMR δ 25.3, 38.9, 50.1, 53.2, 56.3, 56.6, 118.6, 120.2, 124.5, 125.3, 127.3, 127.4, 127.7, 128.3, 134.0, 141.4, 141.8, 151.1, 170.7. Anal. ($C_{27}H_{27}Cl_2N_3O$·HCl·0.25H_2O) C, H, N.

***N*-{4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butyl}fluoren-9-ylcarboxamide (47).** Using general procedure B with 9-fluorenecarboxylic acid (**44**) gave the corresponding acid chloride, which was converted to the desired product as an oil, using general procedure C with amine **33**. Column chromatography (95% CMA, R_f 0.5) followed by treatment with HCl-saturated MeOH and crystallization from 2-PrOH gave 0.25 g (48%) of **47** as the HCl salt: mp 210−212 °C; ^{1}H NMR δ 1.34−1.38 (m, 4H), 2.29 (t, J = 6.8 Hz, 2H), 2.49 (bs, 4H), 2.98 (bs, 4H), 3.16 (q, J = 6.3 Hz, 2H), 4.80 (s, 1H), 5.33 (bs, 1H), 6.90−6.93 (m, 1H), 7.10−7.16 (m, 2H), 7.35 (dt, J = 1.3, 7.2 Hz, 2H), 7.44 (t, 2H), 7.69 (d, J = 7.7 Hz, 2H), 7.78 (d, J = 7.3 Hz, 2H); ^{13}C NMR δ 23.7, 27.3, 39.2, 39.4, 51.2, 53.1, 56.2, 57.9, 118.6, 120.3, 124.5, 125.3, 127.4, 127.5, 127.7, 128.3, 134.0, 141.3, 141.4, 141.6, 151.2, 170.6. Anal. ($C_{28}H_{29}Cl_2N_3O$·HCl·0.5H_2O) C, H, N.

(9-Oxofluoren-4-yl)-*N*-[3-(4-phenylpiperazin-1-yl)propyl]carboxamide (49). Using general procedure C with 9-fluorenone-4-carbonyl chloride (**48**) and amine **30a** gave product **49** as an oil. Column chromatography (95% CMA, R_f 0.3) followed by treatment with HCl-saturated MeOH and crystallization from 2-PrOH gave 0.87 g (47%) of **49** as the HCl salt: mp 213-215 °C; ^{1}H NMR δ 1.80−1.88 (m, 2H), 2.52−2.60 (m, 6H), 2.91 (t, J = 4.7 Hz, 4H), 3.62 (q, J = 5.7 Hz 2H), 6.76 (d, J = 8.1 Hz, 2H), 6.85 (t, J = 7.3 Hz, 1H), 7.15−7.31 (m, 4H), 7.43−7.47 (m, 2H), 7.57 (d, J = 7.3 Hz, 1H), 7.63 (d, J = 7.2 Hz, 1H), 7.80 (d, J = 7.7 Hz, 1H), 8.22 (bs, 1H); ^{13}C δ 24.5, 40.4, 49.1, 53.1, 57.6, 116.1, 120.0, 124.0, 124.1, 125.2, 128.8, 129.0, 129.4, 132.4, 132.9, 134.1, 134.8, 134.9, 140.9, 143.0, 150.9, 168.0, 192.8; IR (KBr pellet) 733, 1239, 1445, 1593, 1601, 1637, 1717, 2822, 2940, 3281 cm^{-1}. Anal. ($C_{27}H_{27}N_3O_2$·HCl·0.75H_2O) C, H, N.

***N*-{3-[4-(2,3-Dichlorophenyl)piperazin-1-yl]propyl}(9-oxofluoren-4-yl)carboxamide (50).** Using general procedure C with 9-fluorenone-4-carbonyl chloride (**48**) and amine **30b** gave product **50** as an oil. Column chromatography (95% CMA, R_f 0.3) followed by treatment with HCl-saturated MeOH and crystallization from MeOH gave 2.29 g (83%) of **50** as the HCl salt: mp 275−278 °C; ^{1}H NMR δ 1.84−1.88 (m, 2H), 2.57−2.70 (m, 10H), 3.68 (t, J = 5.9 Hz, 2H), 6.59 (d, J = 7.4 Hz, 1H), 7.09−7.17 (m, 2H), 7.27−7.35 (m, 2H), 7.47−7.56 (m, 2H), 7.68−7.72 (m, 2H), 7.85 (d, J = 7.6 Hz, 1H); ^{13}C NMR δ 24.1, 40.8, 51.1, 53.1, 57.9, 118.3, 124.1, 124.4, 124.9, 125.3, 127.5, 129.0, 129.6, 132.7 133.2, 134.0, 134.9, 135.0, 140.9, 143.2, 150.7, 167.9, 192.9; IR (KBr pellet) 737, 954, 1256, 1444, 1535, 1664, 1711, 2414, 2839, 2955, 3348 cm^{-1}. Anal. ($C_{27}H_{25}Cl_2N_3O_2$·HCl·0.75H_2O) C, H, N.

***N*-{4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butyl}(9-oxofluoren-4-yl)carboxamide (51).** Using general procedure C with 9-fluorenone-4-carbonyl chloride (**48**) and amine **33** gave carboxamide **51** as an oil. Column chromatography (95% CMA, R_f 0.4) followed by treatment with HCl-saturated MeOH and crystallization from 2-PrOH gave 0.35 g (64%) of **51** as the HCl salt: mp 185−187 °C; ^{1}H NMR δ 1.69−1.80 (m, 4H), 2.43 (t, J = 6.5 Hz, 2H), 2.51 (bs, 4H), 2.71 (bs, 4H), 3.56 (q, J = 5.6 Hz, 2H), 6.57−6.61 (m, 1H), 7.05−7.16 (m, 2H), 7.25−7.33 (m, 2H), 7.47 (t, J = 7.7 Hz, 2H), 7.65 (d, J = 7.4 Hz, 2H), 7.75 (d, J = 7.6 Hz, 1H), 8.08 (bs, 1H); ^{13}C NMR δ 24.6, 27.5, 39.8, 50.8, 53.1, 57.8, 118.3, 123.7, 124.3, 124.7, 125.2, 127.4, 129.0, 129.5, 132.7, 133.0, 133.9, 134.1, 134.8, 135.1, 140.9, 143.0, 150.7, 168.2, 192.9. Anal. ($C_{28}H_{27}Cl_2N_3O_2$·HCl·0.75H_2O) C, H, N.

***N*-{5-[4-(2,3-Dichlorophenyl)piperazin-1-yl]pentyl}(9-oxofluoren-4-yl)carboxamide (52).** Using general procedure C with 9-fluorenone-4-carbonyl chloride (**48**) and amine **38** gave carboxamide **52** as an oil. Column chromatography (95% CMA, R_f 0.4) followed by treatment with HCl-saturated MeOH and crystallization from 2-PrOH gave 0.23 g (43%) of **52** as the HCl salt: mp 244−246 °C; ^{1}H NMR δ 1.40−1.67 (m, 6H),

2.32−2.39 (m, 2H), 2.56 (bs, 4H), 2.97 (bs, 4H), 3.42−3.48 (m, 2H), 6.85−6.88 (m, 1H), 7.04−7.08 (m, 2H), 7.22−7.27 (m, 2H), 7.38−7.45 (m, 2H), 7.61 (t, J = 7.7 Hz, 2H), 7.73 (d, J = 7.8 Hz, 1H); ^{13}C NMR δ 24.7, 26.3, 29.1, 39.7, 51.1, 53.1, 58.2, 118.4, 123.9, 124.0, 124.4, 125.0, 127.3, 128.7, 129.3, 132.3, 133.0, 133.8, 133.9, 134.9, 143.0, 151.1, 168.2, 192.9. Anal. ($C_{29}H_{29}Cl_2N_3O_2$·HCl·0.25H_2O) C, H, N.

9-(3-Hydroxypropyl)-2,3,4,9-tetrahydro-1*H*-carbazol-3-ol (54). The alcohol (**53**, 1.48 g, 7.9 mmol), 2-(3-bromopropoxy)-tetrahydropyran (1.8 g, 8.1 mmol), and NaH (210 mg, 114 mmol) in DMF (30 mL) were stirred at 70 °C overnight. The reaction was cooled to room temperature, H_2O was added (40 mL), and the organics were extracted into ether/EtOAc (1:1, 3 × 50 mL) before drying (Na_2SO_4) and evaporation to a gum. The crude product was deprotected without further purification. To deprotect, the gum was taken up into AcOH/THF/H_2O (4:2:1, 60 mL) and warmed to 50 °C for 5 h. The mixture was diluted with H_2O (50 mL) and the organics extracted with EtOAc (3 × 50 mL). After drying (Na_2SO_4) and evaporation, the orange oil was purified by column chromatography (95% CMA) to yield 0.89 g (46% over 2 steps) of **54**: ^{1}H NMR δ 1.98 (2h, quin, J = 6 Hz), 2.00−2.12 (2H, m), 2.70−2.98 (3H, m), 3.11 (1H, m), 3.60 (2H, t, J = 6 Hz), 4.17 (2H, t, J = 7 Hz), 4.27 (1H, m), 7.07 (1H, dd, J = 7.1 Hz), 7.15 (1H, dd, J = 8.1 Hz), 7.32 (1H, d, J = 8.1 Hz), 7.46 (1H, d, J = 7.1 Hz); ^{13}C NMR δ 19.48, 30.58, 30.98, 32.74, 39.47, 59.68, 67.54, 106.14, 108.92, 117.77, 118.88, 120.92, 127.23, 134.05; EIMS 245 m/z (M^+, 70), 227 m/z ($M^+ - H_2O$, 10).

9-[3-(4-Phenylpiperazin-1-yl)propyl]-2,3,4,9-tetrahydro-1*H*-carbazol-3-ol (10). To compound **54** (0.66 g, 2.7 mmol) and PPh_3 (1.17 g, 4.5 mmol) in CH_3CN (9 mL) was added CBr_4 (1.49 g:4.5 mmol), and the mixture was stirred for 2 h. Ether (20 mL) and 10% NaOH (10 mL) were added, and the organic layer was collected, washed with H_2O (20 mL) and brine (20 mL), dried over Na_2SO_4, and evaporated to yield an oily solid. This was taken up into the minimal volume of ether and left to stand until the Ph_3P═O had precipitated out. The remainder was purified by column chromatography (hexane/EtOAc, 1:1) to give 400 mg (48%) of the intermediate bromide as a white foam (R_f 0.6, hexane/EtOAc, 1:1); ^{1}H NMR δ 2.05 (2H, m), 2.25 (2H, quin, J = 6.3 Hz), 2.65−2.95 (3H, m), 3.08 (1H, m), 3.32 (2H, t, J = 6.3 Hz), 4.15 (2H, t, J = 6.8 Hz), 4.23 (1H, m), 7.07 (1H, dd, J = 7.4 Hz), 7.15 (1H, dd, J = 8.0 Hz), 7.30 (1H, d, J = 8.0 Hz), 7.43 (1H, d, J = 7.4 Hz); ^{13}C NMR δ 19.63, 30.39, 30.52, 30.91, 33.02, 41.03, 67.49, 106.57, 108.83, 117.83, 119.06, 121.06, 127.27, 133.85, 136.65; EIMS 307 m/z, 309 m/z (M^+, 70%). The intermediate bromide (400 mg, 1.3 mmol), phenylpiperazine (0.21 mL, 1.4 mmol), and K_2CO_3 (0.58 g:4.2 mmol) were stirred in toluene (14 mL) at 80 °C for 24 h. H_2O (10 mL) and EtOAc (10 mL) were added and the organics collected, dried (Na_2SO_4), and evaporated. The crude material was purified by column chromatography (EtOAc) to yield 400 mg (79%) of product **10** (R_f 0.1, EtOAc): ^{1}H NMR δ 1.95 (4H, m), 2.47 (3H, t, J = 6.8 Hz), 2.57 (4H, t, J = 4.9 Hz), 2.65 (3H, m), 3.10 (1H, m), 3.23 (4H, t, J = 4.9 Hz), 4.10 (2H, t, J = 7.1 Hz), 4.25 (1H, m), 6.90 (3H, m), 7.06 (1H, dd, J = 7.4 Hz), 7.14 (1H, dd, J = 8.1 Hz), 7.25 (3H, m), 7.45 (1H, d, J = 7.4 Hz); ^{13}C NMR δ 19.61, 27.10, 30.58, 31.07, 40.62, 48.96, 53.04, 55.00, 67.44, 106.25, 109.01, 116.05, 117.71, 118.80, 119.83, 120.79, 127.17, 129.11, 133.98, 136.73, 151.12; CIMS 390 m/z ($M^+ + 1$, 100). Anal. ($C_{27}H_{29}N_3O$·HCl) C, H, N.

9*H*-Fluorene-9-carbonitrile (56). 9-Fluorenone (**55**, 3.55 g,19.7 mmol) was dissolved in CH_2Cl_2 (dry, 20 mL) and tosylmethyl isocyanide (Tos-MIC, 4.68 g, 24 mmol) was added. The solution was cooled to −70 °C and EtOH (1.1 mL) was added, followed by ^{t}BuOK (3.37 g, 27.6 mmol). The solution was allowed to warm to 10 °C over 3.5 h and then stirred at room temperature for 1.5 h. The solution was then diluted with $CHCl_3$ (300 mL) and acidified with 0.1 N HCl (300 mL). The organic layer was collected and the aqueous layer washed with $CHCl_3$ (2 × 100 mL). The combined organic layers were dried (Na_2SO_4) and evaporated to give a yellow gum. Column chromatography (R_f 0.85, 10% EtOAc/hexane) yielded 3.39 g (90%) of product as a white solid: ^{1}H NMR δ 4.92 (1H, s, CHCN), 7.3−7.5 (4H, m, Ph), 7.70−7.85 (4H, m, Ph); EIMS 191 m/z (M^+).

9*H*-Fluoren-9-ylmethanamine (57). The nitrile **56** (1.40 g, 7.32 mmol) was dissolved in THF (8.5 mL) and warmed to 50 °C before adding BH_3-DMS (0.95 mL, 8.8 mmol). The reaction was stirred at this temperature for 20 min before being allowed to cool to room temperature and acidifying carefully with 6 N HCl (5 mL). The mixture was stirred for 5 min and then basified with 15% NaOH to pH 10. The organics were extracted into EtOAc (2 × 15 mL), dried (Na_2SO_4), and evaporated to yield a red oil. The crude product was purified by column chromatography to give 0.71 g (50%) of pure amine (R_f 0.55, 90% CMA): IR ($CHCl_3$) 3377 (NH) cm^{-1}; ^{1}H NMR δ 1.09 (2H, s, NH_2), 3.33 (2H, d, CH_2), 4.03 (1H, t, CH), 7.38 (4H, m, Ph), 7.48 (2H, d, Ph), 7.75 (2H, d, Ph); EIMS 195 m/z (M^+), 178 ($M^+ - NH_3$).

Piperidine-1-carboxylic Acid (Carbazol-9-yl-methyl)-amide (11). The carbobenzoxy-protected isonipecotic acid (1.14 g, 4.3 mmol), DCC (623 mg, 3.02 mmol), and HOBt hydrate (926 mg, 6.85 mmol) were dissolved in DMF (70 mL, dry) with triethylamine (1.1 mL, 7.89 mmol). The amine **57** (0.77 g, 3.9 mmol) was added after 5 min and stirring continued for 2 days. After this time, ether (100 mL) and H_2O (150 mL) were added. The organics were collected, dried, and evaporated to give an off-white solid. Column chromatography (95% CMA) yielded 525 mg (30%) of the protected amide as a white solid: IR ($CHCl_3$) 3278 (NH), 1694 (CO of CBz), 1642 (CO of amide) cm^{-1}; ^{1}H NMR δ 1.91 (2H, m), 2.69 (2H, m), 3.92 (3H, m), 5.08 (2H, s). Deprotection with iodotrimethylsilane in acetonitrile, as described above, gave a white gummy solid (58%) that was purified by formation and recrystallization of the fumarate salt in MeOH/2-PrOH: mp 199−200 °C; ^{1}H NMR δ 1.94 (1H, tt, J = 11.5, 3.8 Hz, CHCO), 2.44 (2H, dt, J = 11.2, 2.8 Hz, 2 × CH of piperidine), 2.96 (2H, dt, J = 12.3, 3.0 Hz, 2 × CH of piperazine), 3.92 (2H, d, J = 5.0 Hz, CH_2NH), 4.19 (1H, t, J = 4.9 Hz, CH), 7.36 (4H, m, aryl-Hs), 7.56 (2H, d, J = 7.5 Hz, aryl-Hs), 7.76 (2H, d, J = 7.4 Hz, aryl-Hs); ^{13}C NMR δ 29.34, 40.87, 43.44, 45.57, 47.19, 119.83, 124.48, 127.12, 127.59, 141.35, 144.16, 175.03; IR ($CHCl_3$) 3300 (NH), 1661(CO) cm^{-1}. Anal. ($C_{20}H_{22}N_{2O}$·0.5$C_4H_4O_4$·H_2O) C, H, N.

Pharmacology. CHO Primate D_2 Membrane Preparation Protocol. For the cloned dopamine receptor assays, pellets containing cloned membranes were thawed on ice and resuspended in ice-cold 50 mM TRIS buffer (pH 7.6 at 25 °C) containing 2.5 mM EDTA, 200 mM PMSF, 0.5 μg/mL leupeptin, 2 μg/mL aprotinin. All subsequent work was performed on ice. The membranes were homogenized using a Brinkman Polytron (10 s, setting 5). The homogenate was centrifuged at 48000g and 4 °C for 10 min. The pellet was resuspended in fresh buffer and the centrifugation was repeated. The pellet was again resuspended in fresh buffer, aliquots for protein determination were taken, and the remainder was centrifuged a final time at 48000g and 4 °C for 10 min. The pellet was resuspended to the appropriate final protein concentration with 50 mM Tris buffer (pH 7.4 at 25 °C) containing 120 mM NaCl, 1 mM bacitracin, and 100 kIU/mL aprotinin. The protein content was determined using the Bio-Rad assay (Hercules. CA), with bovine plasma γ-globulin as the standard.

D_2 Binding Protocol. For D_2 binding, each compound, ranging in concentration from 0.1 nM to 10 μM, was tested in duplicate in a final volume of 0.25 mL in polypropylene microtube strips. As described previosuly,[45] reactions were initiated by the addition of 0.1 nM [^{3}H]YM-09151-2 (85.5 Ci/mmol; NEN DuPont) and CHO cell homogenate (40 μg of protein) in 50 mM Tris buffer (pH 7.4 at 25 °C) containing 120 mM NaCl, 1 mM bacitracin, and 100 mL of aprotinin. After a 2 h room temperature incubation, the samples were rapidly filtered through 1% PEI-treated GF/C filters using a Tomtec harvester 96. The filters were rinsed twice with ice cold 50 mM Tris buffer (pH 7.4 at 25 °C) containing 120 mM NaCl. After air-drying, bound radioactivity was quantitated via the BetaPlate scintillation counter at an efficiency of 65%. Nonspecific binding was defined with 10 μM Spiperone.

CHO Primate D_3 Membrane Preparation Protocol. For the cloned dopamine receptor assays, pellets containing cloned membranes were thawed on ice and resuspended in ice-cold 50 mM TRIS buffer (pH 14 at 25 °C) containing 1 mM EDTA, 5 mM $MgCl_2$, and 120 mM NaCl. All subsequent work was performed on ice. The membranes were homogenized using a Brinkman Polytron (10 s, setting 5). The homogenate was centrifuged at 48000*g* and 4 °C for 10 min. The pellet was resuspended in fresh buffer and the centrifugation was repeated. The pellet was again resuspended in fresh buffer, aliquots for protein determination were taken, and the remainder was centrifuged a final time at 48000*g* and 4 °C for 10 min. The pellet was resuspended to the appropriate final protein concentration with 50 mM Tris buffer (pH 7.4 at 25 °C) containing 120 mM NaCl. The protein content was determined using the Bio-Rad assay (Hercules, CA), with bovine plasma γ-globulin as the standard.

D_3 Binding Protocol. For D_3 binding, each compound, ranging in concentration from 0.1 nM to 10 μM, was tested in duplicate in a final volume of 0.25 mL in polypropylene microtube strips. As described previosuly,[45] reactions were initiated by the addition of 0.1 nM [^{3}H]YM-09151-2 (85.5 Ci/mmol NEN DuPont) and CHO cell homogenate (40 μg of protein in 50 mM Tris buffer, pH 7.4 at 25 °C) containing 120 mM NaCl. After a 2 h room temperature incubation, the samples were rapidly filtered through 1% PEI-treated GF/C filter using a Tomtec harvester 96. The filters were rinsed twice with ice-cold 50 mM Tris buffer (pH 7.4 at 25 °C) containing 120 mM NaCl. After air-drying, bound radioactivity was quantitated via the BetaPlate scintillation counter at an efficiency of 65%. Nonspecific binding was defined with 1 μM haloperidol.

CHO Human D_4 Membrane Preparation Protocol. For the cloned dopamine receptor assays, pellets containing cloned membranes were thawed on ice and resuspended in ice-cold 10 mM HEPES buffer (pH 7.6 at 25 °C) containing 2.5 mM EDTA, 200 mM PMSF, 0.5 μg/mL leupeptin, and 2 μg/mL aprotinin. All subsequent work was performed on ice. The membranes were homogenized using a Brinkman Polytron (10 s, setting 5). The homogenate was centrifuged at 48000*g* and 4 °C for 10 min. The pellet was resuspended in fresh buffer and the centrifugation was repeated. The pellet was again resuspended in fresh buffer, aliquots for protein determination were taken, and the remainder was centrifuged a final time at 48000*g* and 4 °C for 10 min. The pellet was resuspended to the appropriate final protein concentration with 50 mM Tris buffer (pH 7.4 at 25 °C) containing 120 mM NaCl, 1 mM bacitracin, and 100 kIU/mL aprotinin. The protein content was determined using the Bio-Rad assay (Hercules, CA) with bovine plasma γ-globulin as the standard.

D_4 Binding Protocol. For D_4 binding, each compound, ranging in concentration from 0.1 nM to 10 μM, was tested in duplicate in a final volume of 0.25 mL in polypropylene microtube strips. As described previosuly,[45] reactions were initiated by the addition of 0.1 nM [^{3}H]YM-09151-2 (85.5 Ci/mmol; NEN DuPont) and CHO cell homogenate (40 μg protein) in 50 mM Tris buffer (pH 7.4 at 25 °C) containing 120 mM NaCl. After a 2 h room temperature incubation, the samples were rapidly filtered through 1% PEI-treated GF/C filters using a Tomtec harvester 96. The filters were rinsed twice with ice-cold 50 mM Tris buffer (pH 7.4 at 25 °C) containing 120 mM NaCl. After air-drying, bound radioactivity was quantitated via the BetaPlate scintillation counter at an efficiency of 65%. Nonspecific binding was defined with 10 μM spiperone

Data Analysis. Binding data were analyzed by the nonlinear curve-fitting program SigmaPlot (Jandel). Kinetic data was converted to a K_d value using the following equation: $K_d = k - 1/k + 1$, such that $k + 1 = (k_{obs} - k - 1)/[L]$, where [L] is the radioligand concentration. Calculated IC_{50} values were converted to K_i values using the Cheng−Prusoff correction[46] with the following equation: $K_i = IC_{50}/(1 + [L]/K_d)$, where [L] is the radioligand concentration and K_d is the dissociation constant for the radioligand, as determined by saturation analysis.

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References

(1) Kuhar, M. J.; Ritz, M. C.; Boja J. W. The dopamine hypothesis of the reinforcing properties of cocaine. *Trends Neurosci.* **1991**, *14*, 299−301.
(2) Wise, R. A. Addictive drugs and brain stimulation reward. *Annu. Rev. Neurosci.* **1996**, *19*, 319−340.
(3) Le Foll, B.; Schwartz, J. C.; Sokoloff, P. Dopamine D_3 receptor agents as potential new medications for drug addiction. *Eur. J. Psychiatry* **2000**, *15*, 140−146.
(4) Sokoloff, P.; Giros, B.; Martres, M. P.; Bouthenet, M. L.; Schwartz, J. C.; Molecular cloning and characterization of a novel dopamine receptor (D_3) as a target for neuroleptics. *Nature* **1990**, *347*, 146−151.
(5) Schwartz, J. C.; Levesque, D.; Martres, M. P.; Sokoloff, P. Dopamine D_3 receptor: Basic and clinical aspects. *Clin. Neuropharmacol.* **1993**, *16*, 295−314.
(6) Levant, B. The D_3 dopamine receptor: Neurobiology and potential clinical relevance. *Pharm. Rev.* **1997**, *49*, 231−252.
(7) Shafer, R. A.; Levant, B. The D_3 dopamine receptors in cellular and organismal function. *Psychopharmocology* **1998**, *135*, 1−16.
(8) Staley, J. K.; Mash, D. C. Adaptive increases in D_3 dopamine receptors in the brain reward circuits of human cocaine fatalities. *J. Neurosci.* **1996**, *16*, 6100−6106.
(9) Segal, D. M.; Moraes, C. T.; Mash, D. C. Up-regulation of D_3 dopamine receptor mRNA in the nucleus accumbens of human cocaine fatalities. *Mol. Brain. Res.* **1997**, *45*, 335−339.
(10) Caine, S. B.; Koob, G. F. Modulation of cocaine self-administration in the rat through D-3 dopamine receptors. *Science* **1993**, *260*, 1814−1816.
(11) Pilla, M.; Perachon, S.; Sautel, F.; Garrido, F.; Mann, A.; Wermuth, C. G.; Schwartz, J. C.; Everitt, B. J.; Sokoloff, P. Selectivie inhibition of cocaine-seeking behavior by a partial dopamine D_3 receptor agonist. *Nature* **1999**, *400*, 371−375.
(12) Beardsley, P. M.; Sokoloff, P.; Balster, R. L.; Schwartz, J.-C. The D_3R partial agonist, BP 897, attenuates the discriminative stimulus effects of cocaine and D-amphetamine and is not self-administered. *Behav. Pharmacol.* **2001**, *12*, 1−11.
(13) Richtand, N. M.; Logue, A. D.; Welge, J. A.; Perdiue, J.; Tubb, L. J.; Spitzer, R. H.; Sethuraman, G.; Geracioti, T. D. The dopamine D_3 receptor antagonist nafadotride inhibits the development of locomotor sensitization to amphetamine. *Brain Res.* **2000**, *867*, 239−242.
(14) Wood, M. D.; Boyfield, I.; Nash, D. J.; Jewitt, F. R.; Avenell, K. Y.; Riley, G. J. Evidence for antagonist activity of the dopamine D_3 receptor partial agonist BP 897, at human dopamine D_3 receptor. *Eur. J. Pharmacol.* **2000**, *407*, 47−51.
(15) Millan, M. J.; Girardon, S.; Monneyron, S.; Dekeyne, A. Discriminative stimulus properties of the dopamine D_3 receptor agonists PD 128,907 and 7-OH-DPAT: a comparative characterization with novel ligands at D_3 versus D_2 receptors. *Neuropharmacology* **2000**, *39*, 586−598.
(16) Liu, J.-C.; Cox, R. F.; Greif, G. J.; Freedman, J. E.; Waszcak, B. L. The putative dopamine D_3 receptor agonist 7-OH DPAT: lack of mesolimbic selectivity. *Eur. J. Pharmacol.* **1994**, *264*, 269−278.
(17) Schoemaker, H. [^{3}H]7-OH-DPAT labels both dopamine D_3 receptors and σ sites in the bovine caudate nucleus. *Eur. J. Pharmacol.* **1993**, *242*, R1−R2.
(18) Baker, L. E.; Svensson, K. A.; Garner, K. J.; Goodwin, A. K. The dopamine D_3 receptor antagonist PNU-99194A fails to block (+)-7-OH-DPAT substitution for D-amphetamine or cocaine. *Eur. J. Pharmacol.* **1998**, *358*, 101−109.
(19) Cussac, D.; Newman-Tancredi, A.; Audinot, V.; Nicolas, J.-P.; Boutin, J.; Gobert, A.; Millan, M. J. The novel dopamine D_3 receptor partial agonist, BP 897, is a potent ligand at diverse adrenergic and serotonergic receptors. *Abstracts. Soc. Neurosci.* **2000**, abstr # 809.8, p 2154.
(20) Xu, M.; Koeltzow, T. E.; Cooper, D. C.; Tonegawa, S.; White, F. J. Dopamine D_3 receptor mutant and wild-type mice exhibit identical responses to putative D_3 receptor selective agonists and antagonists. *Synapse* **1999**, *31*, 210−215.
(21) Boulay, D.; Depoortere R.; Rostene, W.; Perrault, G.; Sanger, D. J. Dopamine D_3 receptor agonists produce similar decreases in body temperature and locomotor activity in D_3 knock-out and wild-type mice. *Neuropharmacology* **1999**, *38*, 555−565.
(22) Calderon, S. N.; Izenwasser, S.; Heller, B.; Gutkind, J. S.; Mattson, M.; Su, T.-P.; Newman, A. H. Novel 1-Phenylcycloalkanecarboxylic Acid Derivatives are Potent and Selective $Sigma_1$ Ligands. *J. Med. Chem.* **1994**, *37*, 2258−2261.

(23) Newman, A. H.; Shah, J. H.; Izenwasser, S.; Heller, B.; Mattson, M.; Tortella, F. C. Highly Selective σ_1 Ligands Based on Dextromethorphan. *Med. Chem. Res.* **1996**, *6*, 102−117.
(24) Husbands, S. H.; Kopajtic, T.; Izenwasser, S.; Bowen, W. D.; Vilner, B. J.; Katz, J. L. Newman, A. H. Structure−Activity Relationships at the Monoamine Transporters and σ Receptors for a Novel Series of 9-[3-*cis*-3,5-Dimethyl-1-piperazinyl)propyl] carbazole (Rimcazole) Analogs. *J. Med. Chem.* **1999**, *42*, 4446−4455.
(25) Yuan, J.; Chen, X.; Brodbeck, R.; Primus, R.; Braun, J.; Wasley, J. W. F.; Thurkauf, A. NGB 2904 and NGB 2849: Two highly selective dopamine D_3 receptor antagonists. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2715−2718.
(26) Ferris, R. M.; Harfenist, N.; McKenzie, G, M.; Cooper, B.; Soroko, F. E.; Maxwell, R. A. BW 234U (*cis*-9-[3-(3,5-dimethyl-1-piperazinyl)propyl]carbazole dihydrochloride): a novel antipsychotic agent. *J. Pharm. Pharmacol.* **1982**, *34*, 388−390.
(27) Ferris, R. M.; Tang, F. L. M.; Chang, K. J.; Russell, A. Evidence that the potential antipsychotic agent rimcazole (BW 234U) is a specific, competitive antagonist of sigma sites in brain. *Life Sci.* **1986**, *38*, 2329−2337.
(28) Murray, P. J.; Harrison, L. A.; Johnson, M. R.; Robertson, G. M.; Scopes, D. I. C.; Bull, D. R.; Graham, E. A.; Hayes, A. G.; Kilpatrick, G. J.; Daas, I. D.; Large, C.; Sheehan, M. J.; Stubbs, C. M.; Turpin, M. P. A novel series of arylpiperazines with high affinity and selectivity for dopamine D_3 receptor. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 219−222.
(29) Wright, J.; Heffner, T.; Pugsley, T.; MacKenzie R.; Wise, L. Discovery of selective dopamine D_3 ligands: II. 2-[4-[3-(4-aryl-1-piperazinyl)propoxy]phenyl benzamidazole partial agonists. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2547−2550.
(30) Belliotti, T. R.; Kesten S. R.; Rubin, J. R.; Wustrow, D. J.; Georgic, L. M.; Zoski, K. T.; Akunne, H. C.; Wise, L. D. Novel cyclohexyl amides as potent and selective D_3 dopamine receptor ligands. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2403−2408.
(31) Avenill, K. Y.; Boyfield, I.; Coldwell, M. C.; Hadley, M. S.; Healy, M. A. M.; Jeffrey, P. M.; Johnson, C. N.; Nash, D. J.; Riley, G. J.; Scott, E. E.; Smith, S. A.; Stacey, R.; Stemp, G.; Thewlis, K. M. Fused aminotetralins: novel antagonists with high selectivity for the dopamine D_3 receptor. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2859−2864.
(32) Austin, N. E.; Avenill, K. Y.; Boyfield, I.; Branch, C. L.; Coldwell, M. C.; Hadley, M. S.; Jeffrey, P.; Johns, A.; Johnson, C. N.; Nash, D. J.; Riley, G. J.; Smith, S. A.; Stacey, R. C.; Stemp, G.; Thewlis, K. M.; Vong, A. K. K. Novel 1,2,3,4-tetrahydroisoquinolines with high affinity and selectivity for the dopamine D_3 receptor. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 179−184.
(33) Newman, A. H.; Kline, R. H.; Allen, A. C.; Izenwasser, S.; George, C.; Katz, J. L. Novel 4′- and 4′,4″-Substituted-3α-(Diphenylmethoxy)tropane Analogues are Potent and Selective Dopamine Uptake Inhibitors. *J. Med. Chem.* **1995**, *38*, 3933−3940.
(34) Agoston, G. E.; Wu, J. H.; Izenwasser, S.; George, C.; Katz, J.; Kline, R. H.; Newman, A. H. Novel N-Substituted 4′,4″-difluoro-3α-(diphenylmethoxy)tropane Analogs: Selective Ligands for the Dopamine Transporter. *J. Med. Chem.* **1997**, *40*, 4329−4339.
(35) Newman, A. H.; Agoston, G. E. Novel Benztropine [3α-(Diphenylmethoxy) tropane] Analogs as Probes for the Dopamine Transporter. *Current Med. Chem.* **1998**, *5*, 301−315.
(36) Robarge, M. J.; Agoston, G. E.; Izenwasser, S.; Kopajtic, T.; George, C.; Katz, J. L.; Newman, A. H. Highly Selective Chiral N-Substituted 3α-[bis(4α-fluorophenyl)methoxy]tropane Analogues for the Dopamine Transporter: Synthesis and Comparative Molecular Field Analysis. *J. Med. Chem.* **2000**, *43*, 1085−1093.
(37) Newman, A. H.; Robarge, M. J.; Howard, I. M.; Wittkopp, S. L.; Kopajtic, T.; Izenwasser, S.; Katz, J. L. Structure−Activity Relationships at the Monoamine Transporters and Muscarinic Receptors for N-substituted-3α-[3′-Cl-,4′-Cl-,4′,4″-diCl-substituted)diphenyl]methoxytropanes. *J. Med. Chem.* **2001**, *44*, 633−640.
(38) Huang, Y.; Martinez, D.; Simpson, N.; Guo, N.; Montoya, J.; Laruelle, M. Synthesis and evaluation of [^{11}C]BP 897 as a potential PET radioligand for DA D_3 receptors. *Abstracts. Soc. Neurosci.* **2000**, abstr # 809.9, p 2154.
(39) Levant, B.; Ling, Z. D.; Carvey, P. M. Dopamine D_3 receptors. *CNS Drugs* **1999**, *12*, 391−402.
(40) Audinot, V.; Newman-Tancredi, A.; Goberti, A.; Rivet, J. M.; Brocco, M.; LeJeune, F.; Gluck, L.; Desposte, I.; Bervoets, k.; Dekeyne, A.; Millan, M. A comparative in vitro and in vivo pharmacological characterization of the novel dopamine D_3 receptor antagonists (+)-S 14297, nafadotride, GR 103, 691 and U 992194, *J. Pharmacol. Exp. Ther.* **1998**, *287*, 187−197.
(41) Stemp, G.; Ashmeade, T.; Branch, C. L.; Hadley, M. S.; Hunter, A. J.; Johnson, C. N.; Nash, D. J.; Thewlis, K. M.; Vong, A. K. K.; Austin, N. E.; Jeffrey, P.; Avenill, K. Y.; Boyfield, I.; Hagan, J. J.; Middlemiss, D. N.; Reavill, C.; Riley, G. J.; Routledge, C.; Wood, M. Design and synthesis of trans-N-[4-[2-(6-cyano-1,2,3,4-tetrahydroisoquinolin-2-yl)ethyl]cyclohexyl]-4-quinolinecarboxamide (SB-277011): A potent and selective dopamine D_3 receptor antagonist with high oral bioavailability and CNS penetration. *J. Med. Chem.* **2000**, *43*, 1878−1885.
(42) Reavill, C.; Taylor, S. G.; Wood, M. D.; Ashmeade, T.; Austin, N. E.; Avenill, K. Y.; Boyfield, I.; Branch, L.; Cilia, J.; Coldwell, M. C.; Hadley, M. S.; Hunter, A. J.; Jeffrey, P.; Jewitt, F.; Johnon, C. N.; Jones, D. N. C.; Medhurst, A. D.; Middlemiss, D. N.; Nash, D. J.; Riley, G. J.; Routledge, C.; Stemp, G.; Thewlis, K. M.; Trail, B.; Vong, A. K. K.; Hagan, J. J. Pharmacological actions of a novel, high affinity, and selective human dopamine D_3 receptor antagonist, SB-277011-A. *J. Pharmacol. Exp., Ther.* **2000**, *294*, 1154−1165.
(43) Millan, M. J.; Gobert, A.; Newman-Tancredi, A.; LeJeune, F.; Cussac, D.; Rivet, J. M.; Audinot, V.; Dubuffet, T.; Lavielle, G. S33084, A novel, potent, selective, and competitive antagonist at dopamine D_3-receptors: I. Receptorial, electrophysiological and neurochemical profile compared with GR218, 231 and L741, 626. *J. Pharmacol. Exp. Ther.* **2000**, *293*, 1048−1062.
(44) Millan, M. J.; Dekeyne, A.; Rivet, J. M.; DuBuffet, T.; LaVeille, G.; Brocco, M. S33084, A novel, potent, selective, and competitive antagonist at dopamine D_3-receptors: II. Functional and behavioral profile compared with GR218, 231 and L741, 626. *J. Pharmacol. Exp. Ther.* **2000**, *293*, 1063−103.
(45) Thurkauf, A.; Yuan, J.; Chen, X.; Wasley, J. W. F.; Meade, R.; Woodruff, K. H.; Huston, K.; Ross, P. C. 1-Phenyl-3-(aminomethyl)pyrroles as Potential Antipsychotic Agents. Synthesis and Dopamine Receptor Binding. *J. Med. Chem.* **1995**, *38*, 4950−4952.
(46) Cheng, V.; Prusoff, W. H. Relationship Between the Inhibition Constant (K_i) and the Concentration which Causes 50 Percent Inhibition (IC_{50}) of an Enzymatic Reaction. *Biochem. Pharmacol.* **1973**, *22*, 3099−3108.

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