Chromeno[3,4-*c*]pyridin-5-ones: Selective Human Dopamine D_4 Receptor Antagonists as Potential Antipsychotic Agents

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The discovery of a series of chromeno[3,4-*c*]pyridin-5-ones with selective affinity for the dopamine D_4 receptor is described. Target compounds were tested for binding to cloned human dopamine D_2, D_3, and D_4 receptor subtypes expressed in Chinese hamster ovary (CHO) K-1 cells. Several compounds demonstrated single digit nanomolar K_i values for binding to the D_4 receptor with several hundred-fold selectivities toward the D_2 and D_3 receptors. A limited SAR study of this series is discussed. In a mitogenesis assay measuring [^{3}H]thymidine uptake, the target compounds showed antagonist to weak partial agonist activity at the D_4 receptor, with intrinsic activities ranging from 0 to 35%. Compound **6**, 3-benzyl-8-methyl-1,2,3,4-tetrahydrochromeno[3,4-*c*]pyridin-5-one, increased DOPA (L-3,4-dihydroxyphenylalanine) synthesis 84% in the hippocampus and 10% in the striatum of rat brain when dosed orally at 10 mg/kg.

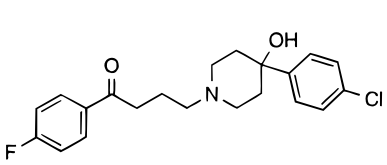
Introduction

Schizophrenia is a complex disorder affecting approximately 1% of the population.[1] The etiology of the disease is unknown, but classical antipsychotics such as haloperidol (**1**) are thought to act by blockade of dopamine D_2-like receptors in the brain.[2] Molecular biology techniques have now shown that these receptors are subdivided into D_2, D_3, and D_4 subtypes.[3] D_4 receptors are preferentially located in cortical and other areas of the brain believed to control emotional and cognitive functions.[4] Some studies[5,6] also suggest that the concentration of D_4 receptors in the brain is elevated in schizophrenia, although this assertion is controversial.[7]

Existing antipsychotic drugs, while generally effectively treating the positive symptoms of schizophrenia, can also induce the onset of Parkinson-like extrapyramidal side effects. The atypical antipsychotic clozapine (**2**) alleviates both positive and negative symptoms while inducing a very low incidence of undesirable motor side effects. Clozapine exhibits an approximately 10-fold selectivity for D_4 versus D_2 receptors, and this may be one possible mechanism contributing to the therapeutic value of the drug.[4,8] However, clozapine also has a high affinity for a variety of other brain receptors, which may explain in part its unique clinical profile.[9]

The recent cloning of the different dopamine (DA) receptor subtypes allows the identification of ligands selective for a single specific receptor subtype. Thus, there is a need for selective ligands to elucidate the pharmacological role of the D_4 receptor. A selective D_4 receptor antagonist may show antipsychotic activity devoid of undesirable side effects.

Selective D_4 receptor antagonists have recently been reported in several chemical series. These include the benzenesulfonamide U-101,387(**3**)[10] and the pyrrolo[2,3-*b*]pyridine L-745,870 (**4**),[11] as well as several others.[12−14] Screening of the Parke-Davis compound library identified a chromeno[3,4-*c*]pyridine **5** as a selective D_4 receptor antagonist. This chemical series is structurally quite different in comparison to the pyrrolo[2,3-*b*]-pyridines and other previously reported selective D_4 receptor antagonists. In this report we describe the synthesis and receptor binding activity of the chromeno-[3,4-*c*]pyridines.



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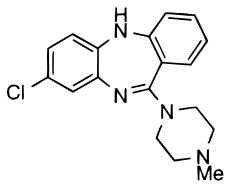

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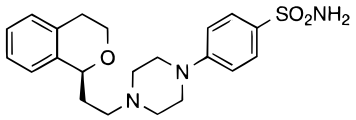

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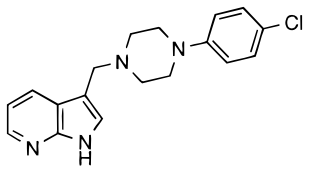

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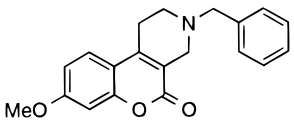

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Chemistry

Preparation of an initial group of chromeno[3,4-*c*]-pyridine target compounds is shown in Scheme 1. Condensation of an appropriate phenol with an *N*-benzylpiperidone ester under strongly acidic conditions (method A) gave the *N*-benzyl derivatives **5**−**8** (Table 1). Catalytic removal of the benzyl group of **5** and **6**

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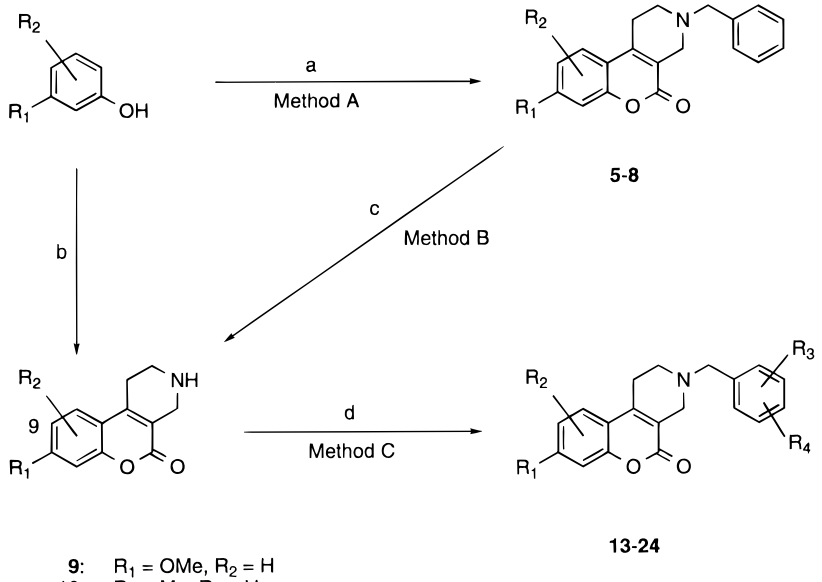
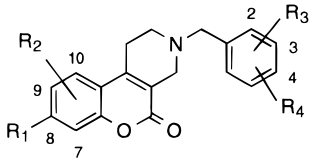
Scheme 1[a]



9: R_1 = OMe, R_2 = H
10: R_1 = Me, R_2 = H
11: R_1 = OMe, R_2 = 9-OMe
12: R_1 = OH, R_2 = H

[a] Reagents: (a) methyl 1-benzyl-4-oxo-3-piperidinecarboxylate hydrochloride, H_2SO_4; (b) methyl 4-oxo-3-piperidinecarboxylate hydrochloride, H_2SO_4; (c) 20% Pd/C, H_2, THF, MeOH; (d) R_3R_4PhCHO, $NaBH(OAc)_3$, THF, 1,3-dimethyl-2-imidazolidinone.

Table 1. Receptor Binding Data for *N*-Benzylchromeno[3,4-*c*]pyridines

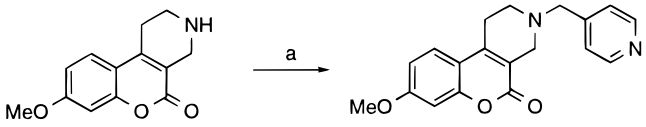


					K_i (nM)[a]			
compd	R_1	R_2	R_3	R_4	D_4	D_2	D_3	D_2/D_4
5	OMe	H	H	H	1.5	436	60	291
6	Me	H	H	H	3.6	774	338	216
7	OMe	7-OMe	H	H	16	659	1300	41
8	Me	10-OH	H	H	145			
13	OMe	H	4-Cl	H	8.7	>5800	2780	667
14	OMe	9-OMe	4-Cl	H	8.5	>5800	>3000	682
15	Me	H	4-Cl	H	11	1170		106
16	OH	H	4-Cl	H	2.4	2780	317	1160
17	OMe	H	4-F	H	4.3	>5800	548	1350
18	Me	H	4-F	H	7.5	>5800	2210	773
19	OMe	H	2-Cl	H	34	>5800	2620	171
20	OMe	H	3-Cl	H	17	5500	2630	324
21	OMe	H	3-Cl	4-Cl	61	>5800		95
22	OMe	H	4-Me	H	2.6	1170	491	450
23	OMe	H	4-OMe	H	84	>5800		69
24	OMe	H	4-CF_3	H	8.2	3700	966	451
31	OMe	H	4-NO_2	H	7.5	>5800	>3000	773

[a] Affinities for cloned human dopamine receptors; K_i values are means of one to four separate experiments obtained from six concentrations of each compound, run in triplicate. Variation between experiments was less than 15%.

(method B) yielded the intermediates **9** and **10**. Intermediates **9**−**12** were also accessible by condensation of phenols with an unsubstituted piperidone ester.[15] Reaction of **9**−**12** with substituted benzaldehydes in the presence of sodium triacetoxyborohydride[16] (method C) gave a series of substituted benzyl analogs **13**−**24**. A similar reaction with 4-pyridinecarboxaldehyde gave the pyridine derivative **25** (Scheme 2). Condensation of phenol **26** with the appropriate piperidone ester (Scheme 3) permitted preparation of an *N*-phenyl analog **27** and an isomeric pyridine ring derivative **28**. Acylation of **9**

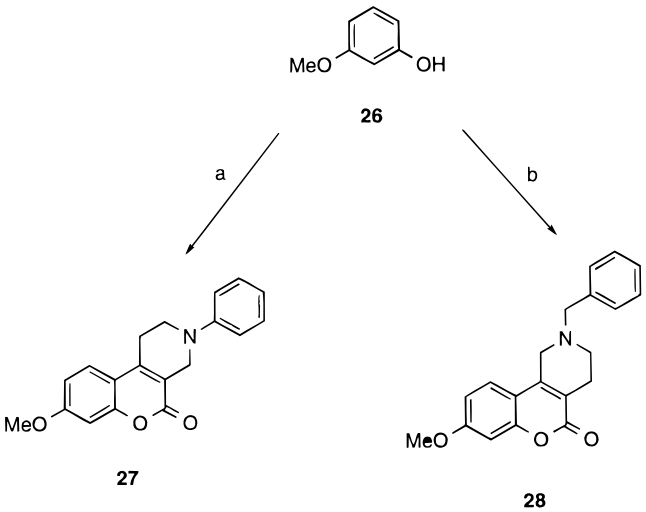
Scheme 2[a]



9 **25**

[a] Reagents: (a) 4-pyridinecarboxaldehyde, $NaBH(OAc)_3$, THF, 1,3-dimethyl-2-imidazolidinone.

Scheme 3[a]



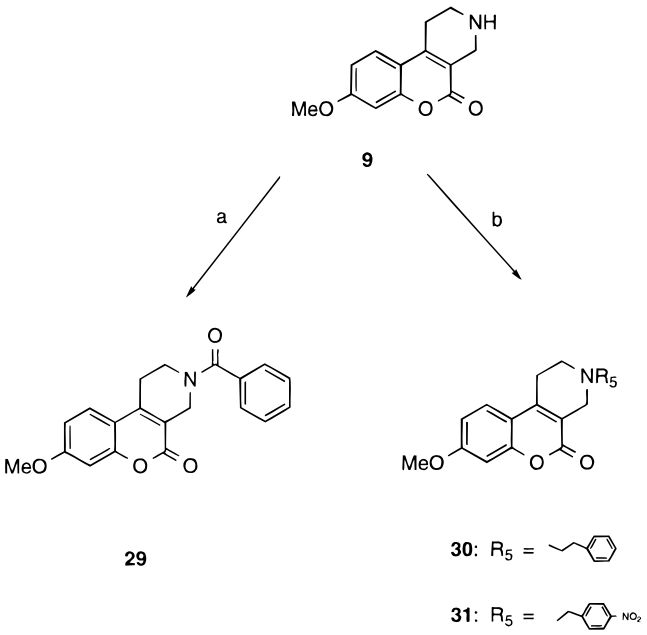
[a] Reagents: (a) ethyl 4-oxo-1-phenyl-3-piperidinecarboxylate hydrochloride, H_2SO_4; (b) ethyl 1-benzyl-3-oxo-4-piperidinecarboxylate hydrochloride, H_2SO_4.

with benzoyl chloride in pyridine gave the amide **29** (Scheme 4). Alkylation of **9** in DMF with alkyl bromides gave derivatives **30** and **31**. Physical data for the target compounds are shown in Table 3.

Results and Discussion

The affinities of the target compounds for the DA D_2, D_3, and D_4 receptors were determined *in vitro* by

Scheme 4[a]



[a] Reagents: (a) benzoyl chloride, pyridine; (b) R_5Br, K_2CO_3, DMF.

Table 2. Receptor Binding Data for Compounds **25** and **27**−**30** and Standards

	K_i (nM)[a]			
compd[b]	D_4	D_2	D_3	D_2/D_4
25	74	>5800		78
27	>3300			
28	>3300			
29	420			
30	7.9	>5800	591	734
1	2.2	1.6	2.2	0.73
2	16	91	222	5.7

[a] Affinities for cloned human dopamine receptors; K_i values are means of one to four separate experiments obtained from six concentrations of each compound, run in triplicate. Variation between experiments was less than 15%. [b] Compound structures are shown in Schemes 2−4.

measuring their ability to displace the DA ligand [^{3}H]-spiperone from cloned human DA receptor subtypes expressed in Chinese hamster ovary (CHO) K-1 cells.[17] Receptor affinities are presented as K_i values in Tables 1 and 2. Structure−activity relationships in the chromeno[3,4-*c*]pyridine system were explored with variation of the R_1 and R_2 phenyl substituents, the R_3 and R_4 benzyl side chain substituents, and the side chain itself.

The 8-methoxy compound (**5**) initially identified in the mass screening assay exhibited potent binding at the D_4 receptor as well as moderate selectivity. The cyclization reaction employed in the synthesis of the chromeno[3,4-*c*]pyridine ring system (method A of Scheme 1) requires an electron-donating function *meta* to the hydroxy group. On a practical basis, this requirement restricts SAR investigation of the fused aromatic ring substituents (especially R_1). Replacements of the R_1 methoxy group of **5** with methyl (**6**) resulted in a compound with slightly lower D_4 potency and less selectivity toward the D_2 receptor in comparison to **5**. A similar relationship between the 8-methoxy and 8-methyl derivatives was observed when the benzyl side chain contained a 4-chloro (**13** and **15**) or 4-fluoro (**17** and **18**) substituent. The 8-methoxy, 4-fluoro (**17**) and 8-hydroxy, 4-chloro (**16**) derivatives were the most selective compounds prepared. Substitution at the 7-position of the fused benzene ring (**7**) or at the 10-position (**8**) was detrimental, while substitution at the 9-position (**14**) was well tolerated.

In general, substitution at the benzyl 4-position (**13**, **17**, **22**, **24**, and **31**) improved selectivity of D_4 versus D_2 binding in comparison to **5**. The sole exception was the 4-methoxy derivative (**23**), which exhibited weak D_4 binding. Other benzyl aromatic ring substitution patterns (**19**, **21**) gave inferior compounds. Similarly, replacement of pyridine for benzene (**25**) or removal of the side chain methylene (**27**) decreased activity. Chain extension by one carbon (**30**) improved selectivity in comparison to **5**. The intermediates **9**−**12** (lacking a tertiary amine moiety) were without substantial activity, as were the amide **29** and isomeric piperidine derivative **28**.

The intrinsic activities of the more selective compounds were determined by measuring their ability to block stimulation of mitogenesis, specifically [^{3}H]thymidine uptake, caused by the full DA agonist quinpirole in CHO 10001 cells transfected with DA D_4 receptors.[17,18] The results are presented in Table 4 as percent intrinsic activity relative to the full agonist quinpirole. By definition, all compounds with 20% or less intrinsic activity in this model (**6**, **18**, **22**, and **24**) are antagonists, while those exhibiting >20% intrinsic activity (**5**, **13**, **14**, **16**, **17**, **20**, **30**, and **31**) are considered as partial agonists.

On the basis of its overall pharmacological profile, compound **6** was chosen for additional evaluation. In

Table 3. Physical Data for Chromeno[3,4-*c*]pyridin-5-ones

compd	% yield	mp (°C)	formula[a]
5	47	118−120	$C_{20}H_{19}NO_3$
6	60	109−111	$C_{20}H_{19}NO_2$
7	35	138−140	$C_{21}H_{21}NO_4$
8	5	225−228[b]	$C_{20}H_{19}NO_3$
13	70	140−142	$C_{20}H_{18}ClNO_3$
14	48	173−175	$C_{21}H_{20}ClNO_4$
15	65	147−149	$C_{20}H_{18}ClNO_2$
16	52[c]	>250	$C_{19}H_{16}ClNO_3$·HCl
17	36	110−112	$C_{20}H_{18}FNO_3$
18	57	130−131	$C_{20}H_{18}FNO_2$
19	65	137−139	$C_{20}H_{18}ClNO_3$
20	65	112−115	$C_{20}H_{18}ClNO_3$
21	65	144−146	$C_{20}H_{17}Cl_2NO_3$
22	72	147−149	$C_{21}H_{21}NO_3$
23	54	101−103	$C_{21}H_{21}NO_4$
24	70	203−206	$C_{21}H_{18}F_3NO_3$
25	53	119−122	$C_{19}H_{18}N_2O_3$
27	26	145−147	$C_{19}H_{17}NO_3$
28	5	120−122	$C_{20}H_{19}NO_3$
29	24	173−174	$C_{20}H_{17}NO_4$
30	27	135−136	$C_{21}H_{21}NO_3$
31	47	176−178	$C_{20}H_{18}N_2O_5$

[a] Compounds were analyzed for C, H, N. and are within ±0.4% of the theoretical values. [b] Literature mp 222−224 °C (ref 22). [c] Yield of the free base.

Table 4. Antagonism of Quinpirole-Induced Mitogenesis

compd	intrinsic activity[a]	compd	intrinsic activity[a]
5	23.2 ± 3.4	**18**	0
6	12.4 ± 2.0	**20**	30.7 ± 5.8
13	26.8 ± 7.4	**22**	10.0 ± 1.4
14	21.2 ± 7.8	**24**	0
16	23.2 ± 0.85	**30**	23.6 ± 8.9
17	35.2 ± 5.5	**31**	25.2 ± 5.2

[a] Percent stimulation of mitogenesis in transfected CHO 10001 cells in comparison to the full agonist quinpirole. Values are means of four experiments ± SEM.

agreement with its affinities for DA receptors, **6** inhibited the ability of the DA agonist quinpirole to stimulate [^{3}H]thymidine uptake in D_4 cells with an IC_{50} of 3.7 nM, but lacked significant activity in a similar DA D_2 assay. The functional role of brain D_4 receptors is still unclear. Thus, it is difficult to associate a given effect with a specific antagonism of D_4 receptors in the brain. *In vivo*, DA antagonists are known to increase the rate of brain DA synthesis in rodents. Pugsley et al.[19] recently reported that the Merck D_4 antagonist (**4**) increased catecholamine synthesis in striatal and hippocampal regions of rat brain in wildtype mice but not in D_4 knockout mice (that is, mice lacking functional D_4 receptors). These results suggested that D_4 receptors may play a role in modulating brain catecholamine synthesis in rodents. The effect of compound **6** on brain catecholamine synthesis in rats was evaluated by measuring the ability of **6** to increase the accumulation of the catecholamine precursor DOPA (L-3,4-dihydroxyphenylalanine) after inhibition of L-aromatic amino acid decarboxylase with NSD 1015.[17] When dosed orally at 10 mg/kg, **6** increased DOPA accumulation by 84% in the D_4-enriched hippocampus[20,21] (DOPA levels were 141 ± 13 ng/g for control versus 259 ± 4.4 ng/g for compound **6** treated animals). In contrast, DOPA levels in the predominantly D_2-expressing striatum were only increased by a nonsignificant 10% (control 1236 ± 60 ng/g versus 1358 ± 160 ng/g for **6**). In an additional study, compound **6** when dosed at 3−30 mg/kg ip also caused dose-dependent increases in hippocampal DOPA accumulation without increasing DOPA levels in the striatum. Thus, the large increase in catecholamine synthesis in the hippocampus compared to the lack of effect in the striatum may indicate a modulatory role for **6** mediated by interaction with D_4 receptors. Other possible mechanisms to explain the increase in catecholamine synthesis, such as antagonism of adrenergic or serotonergic receptors seem unlikely, as compound **6** had no appreciable affinity (K_i > 700 nm) for rat brain α_1, α_2, adrenergic, serotonin$_{1A}$, or serotonin$_{2A}$ receptors. Although not conclusive, since receptor occupancy has not been measured, these findings, together with previous data involving D_4 knockout mice, suggest the action of **6** in the hippocampus may be related to D_4 receptor antagonism. Thus, in both *in vitro* assays and *in vivo* in rats, compound **6** appears to have the profile of a selective DA D_4 antagonist.

We have described the synthesis and preliminary dopamine receptor binding SAR for a novel series of chromeno[3,4-*c*]pyridin-5-ones. These compounds will be useful tools in exploring the significance of the role of the D_4 receptor in schizophrenia.

Experimental Section

Melting points were determined on a Thomas-Hoover or Electrothermal capillary apparatus and are uncorrected. Elemental analyses were performed by the Analytical Chemistry staff at Parke-Davis (Ann Arbor, MI). The IR spectra were recorded as potassium bromide disks on a Mattson Cygnus 100 FTIR spectrometer. The ^{1}H NMR spectra were recorded on a Varian Unity 400 spectrometer with chemical shifts reported in ppm relative to internal tetramethylsilane. Mass spectra were recorded on a VG Masslab Trio-2A mass spectrometer. Reactions were usually run under a nitrogen atmosphere, and organic solutions were concentrated at aspirator pressure on a rotary evaporator. Flash chromatography was performed with E. Merck silica gel 60, 230−400 mesh ASTM.

Method A. 3-Benzyl-8-methoxy-1,2,3,4-tetrahydrochromeno[3,4-*c*]pyridin-5-one (5). A mixture of **26** (28.3 g, 227 mmol) and methyl 1-benzyl-4-oxo-3-piperidinecarboxylate hydrochloride (46.1 g, 162 mmol) was cooled in ice and treated dropwise with a solution of 38 mL of H_2O and 142 mL of concentrated H_2SO_4. The mixture was stirred at room temperature for 48 h and then added slowly to 500 g of ice and 100 mL of NH_4OH. Additional ice and NH_4OH were added until the pH of the resulting mixture was 10−11. Stirring was continued until the initial gummy precipitate became granular. The solid was filtered and washed with 3% aqueous NaOH solution, followed by 10% MeOH in H_2O. Recrystallization from 2-propanol gave 24.5 g (47%) of **5**: mp 118−120 °C; IR 1704, 1615, 1280, 1156 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.73 (t, J = 5.6 Hz, 2H, CH_2), 2.86 (m, 2H, CH_2), 3.25 (s, 2H, CH_2), 3.70 (s, 2H, CH_2Ph), 3.84 (s, 3H, OCH_3), 6.94−6.98 (m, 2H, 7,9-H), 7.26−7.36 (m, 5H, CH_2*Ph*), 7.60 (d, J = 8.7 Hz, 1H, 10-H); EIMS *m*/*z* 322 (MH^+). Anal. ($C_{20}H_{19}NO_3$) C,H,N.

Method B. 8-Methoxy-1,2,3,4-tetrahydrochromeno-[3,4-*c*]pyridin-5-one (9). A solution of **5** (8.2 g, 26 mmol) in 150 mL of MeOH and 100 mL of THF was hydrogenated at room temperature over a 20% palladium on carbon catalyst (0.85 g) for 18 h. The catalyst was filtered and the filtrate evaporated. Recrystallization of the residue from MeCN with a small amount of added H_2O gave 2.9 g (49%) of **9**: mp 179−181 °C (lit.[15] mp 179−183 °C); IR 3324, 1691, 1614, 1279 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.71 (m, 2H, CH_2), 2.97 (t, J = 5.7 Hz, 2H, CH_2), 3.53 (s, 2H, CH_2), 3.85 (s, 3H, OCH_3), 6.94−6.99 (m, 2H, 7,9-H), 7.61 (d, J = 8.6 Hz, 1H, 10-H); EIMS *m*/*z* 232 (MH^+). Anal. ($C_{13}H_{13}NO_3$) C, H, N.

Method C. 8-Methoxy-3-(4-methylbenzyl)-1,2,3,4-tetrahydrochromeno[3,4-*c*]pyridin-5-one (22). A solution of **9** (1.2 g, 5.2 mmol) and 4-methylbenzaldehyde (0.68 g, 5.7 mmol) in 20 mL of THF and 7 mL of 1,3-dimethyl-2-imidazolidinone was treated with acetic acid (0.29 mL, 5.2 mmol). The mixture was stirred for 10 min, and sodium triacetoxyborohydride (1.6 g, 7.5 mmol) was added over 30 min. The mixture was stirred for 18 h and added to 300 mL of ice and H_2O. The precipitated solid was filtered, washed with H_2O, and recrystallized from EtOAc to yield 1.2 g (70%) of **22**: mp 147−149 °C; IR 1706, 1611, 1237, 1085 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.30 (s, 3H, CH_3), 2.73 (t, J = 5.6 Hz, 2H, CH_2), 2.88 (m, 2H, CH_2), 3.23 (s, 2H, CH_2), 3.65 (s, 2H, *C*H_2Ph), 3.85 (s, 3H, OCH_3), 6.95−6.99 (m, 2H, 7,9-H), 7.15 (d, J = 7.7 Hz, CH_2*Ph*), 7.23 (d, J = 8.0 Hz, 2H, CH_2*Ph*), 7.62 (d, J = 8.7 Hz, 1H, 10-H); EIMS *m*/*z* 336 (MH^+). Anal. ($C_{21}H_{21}NO_3$) C, H, N.

3-(4-Chlorobenzyl)-8-hydroxy-1,2,3,4-tetrahydrochromeno[3,4-*c*]pyridin-5-one Hydrochloride (16). A solution of **12**[15] (1.1 g, 5.0 mmol) and 4-chlorobenzaldehyde (0.71 g, 5.1 mmol) was reacted with sodium triacetoxyborohydride (1.6 g, 7.5 mmol) as described in method C. The solid product was recrystallized from EtOH to give 0.89 g (52%) of the free base of **16**. A solution of this material (0.45 g, 1.3 mmol) in 100 mL of Et_2O was treated with HCl gas. The precipitated product was filtered and triturated in EtOH to yield 0.48 g (96%) of **16**: mp >250 °C; IR 2586, 1726, 1617, 1416 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.24 (m, 3H, CH_2), 3.70 (br s, 1H, CH_2), 3.95 (br s, 2H, CH_2), 4.51 (br s, 2H, CH_2), 6.79 (d, J = 2.2 Hz, 1H, 7-H), 6.88 (dd, J = 2.4, 8.7 Hz, 1H, 9-H), 7.57−7.72 (m, 5H, Ph), 10.75 (s, 1H, OH), 11.54 (br s, 1H, NH^+); EIMS *m*/*z* 342 (MH^+). Anal. ($C_{19}H_{16}ClNO_3$·HCl) C, H, N.

8-Methoxy-3-phenyl-1,2,3,4-tetrahydrochromeno[3,4-*c*]pyridin-5-one (27). Prepared from **26** (2.7 g, 22 mmol) as described in method A, except that the piperidone used was ethyl 4-oxo-1-phenyl-3-piperidinecarboxylate hydrochloride[23] (2.7 g, 9.7 mmol). Recrystallization of the product from EtOH gave 0.78 g (26%) of **27**: mp 145−147 °C; IR 1711, 1614, 1408, 1157 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.99 (m, 2H, CH_2), 3.58 (t, J = 5.7 Hz, 2H, CH_2), 3.86 (s, 3H, OCH_3), 4.04 (s, 2H, CH_2), 6.97−7.28 (m, 7H, Ph), 7.67 (d, J = 8.7 Hz, 1H, 10-H); EIMS *m*/*z* 308 (MH^+). Anal. ($C_{19}H_{17}NO_3$) C, H, N.

3-Benzyl-7-methoxy-1,2,3,4-tetrahydro-9-oxa-3-azaphenanthren-10-one (28). Prepared from **26** (12.0 g, 97 mmol) as described in method A, except that the piperidone used was ethyl 1-benzyl-3-oxo-4-piperidinecarboxylate hydro-

chloride (29.8 g, 100 mmol). The crude product after treatment with NH_4OH was extracted with EtOAc. The organic layer was washed with 2 N NaOH solution and brine, dried (Na_2SO_4), and evaporated. The residue was purified by chromatography (30% EtOAc in hexane elution) and recrystallized from EtOAc/hexane to yield 1.7 g (5%) of **28**: mp 120−122 °C; IR 1708, 1609, 1281, 1021 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.51 (m, 2H, CH_2), 2.66 (t, J = 5.7 Hz, 2H, CH_2), 3.71 (s, 2H, CH_2), 3.75 (s, 2H, CH_2), 3.84 (s, 3H, OCH_3), 6.91 (dd, J = 2.5, 8.8 Hz, 1H, 6-H), 6.97 (d, J = 2.7 Hz, 1H, 8-H), 7.26−7.41 (m, 5H, Ph), 7.44 (d, J = 8.7 Hz, 1H, 5-H); EIMS m/z 322 (MH^+). Anal. ($C_{20}H_{19}NO_3$) C, H, N.

3-Benzoyl-8-methoxy-1,2,3,4-tetrahydrochromeno[3,4-*c*]pyridin-5-one (29). A suspension of **9** (0.50 g, 2.2 mmol) in 5.0 mL of pyridine was cooled in a cold H_2O bath while benzoyl chloride (0.40 mL, 0.48 g, 3.4 mmol) was slowly added. The mixture was stirred at room temperature for 18 h and then added to 150 mL of ice cold 4 N HCl. The solid was filtered, stirred in 150 mL of 5% aqueous Na_2CO_3, and filtered again. Recrystallization from aqueous MeCN gave 0.17 g (24%) of **29**: mp 173−174 °C; IR 1708, 1613, 1278, 1156 cm^{-1}; ^1H NMR (DMSO-d_6), run at 95 °C, δ 2.94 (m, 2H, CH_2), 3.77 (m, 2H, CH_2), 3.86 (s, 3H, OCH_3), 4.39 (s, 2H, CH_2), 6.94−6.98 (m, 2H, 7,9-H), 7.44−7.49 (m, 5H, Ph), 7.62 (d, J = 8.4 Hz, 1H, 10-H); EIMS m/z 336 (MH^+). Anal. ($C_{20}H_{17}NO_4$) C, H, N.

8-Methoxy-3-phenethyl-1,2,3,4-tetrahydrochromeno-[3,4-*c*]pyridin-5-one (30). A mixture of **9** (1.5 g, 6.5 mmol), anhydrous K_2CO_3 (0.50 g, 4.7 mmol), and (2-bromoethyl)-benzene (1.0 mL, 1.4 g, 7.3 mmol) in 10 mL of DMF was heated at 90 °C for 18 h. The cooled reaction mixture was added to 300 mL of H_2O and 150 mL of Et_2O. The insoluble material was filtered and washed with fresh Et_2O. Recrystallization from aqueous 2-propanol gave 0.60 g (27%) of **30**: mp 135−136 °C; IR 1704, 1621, 1295, 1160 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.71 (m, 2H, CH_2), 2.97 (t, J = 5.7 Hz, 2H, CH_2), 3.53 (s, 2H, CH_2), 3.85 (s, 2H, OCH_3), 6.94−6.99 (m, 2H, 7,9-H), 7.61 (d, J = 8.6 Hz, 1H, 10-H); EIMS m/z 336 (MH^+). Anal. ($C_{21}H_{21}NO_3$) C, H, N.

8-Methoxy-3-(4-nitrobenzyl)-1,2,3,4-tetrahydrochromeno[3,4-*c*]pyridin-5-one (31). A mixture of **9** (1.2 g, 5.2 mmol), anhydrous K_2CO_3 (0.69 g, 5.0 mmol), and 4-nitrobenzyl bromide (1.1 g, 5.1 mmol) in 15 mL of DMF was heated at 90 °C for 4 h. The cooled reaction mixture was evaporated, and the residue was partitioned between EtOAc and brine. The organic layer was dried ($MgSO_4$) and evaporated. Recrystallization of the residue from EtOAc yielded 0.87 g (47%) of **31**: mp 176−178 °C; IR 1697, 1515, 1343, 1152 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.77 (t, J = 5.5 Hz, 2H, CH_2), 2.91 (m, 2H, CH_2), 3.30 (s, 2H, CH_2), 3.85 (s, 3H, OCH_3), 3.86 (s, 2H, CH_2Ph), 6.96−7.00 (m, 2H, 7,9-H), 7.62−7.67 (m, 3H, Ph), 8.22 (d, J = 8.7 Hz, 2H, Ph); EIMS m/z 367 (MH^+). Anal. ($C_{20}H_{18}N_2O_5$) C, H, N.

Pharmacology. Receptor Binding. The *in vitro* affinities of compounds for cloned human DA receptors versus [^3H]-spiperone in CHO K1 cells were determined as previously described.[17]

Mitogenesis Assay. The effects of test compounds on [^3H]-thymidine uptake were determined essentially as described by Chio.[18] In brief, CHO 10001 cells transfected with human D_4 receptors were plated on 96-well plates in a minimum essential medium (α MEM, Gibco) with 10% fetal calf serum containing penicillin (100 units/mL) and streptomycin (100 μg/mL). Forty-eight hours later, cells were washed with serum-free media and maintained thereafter in serum-free media. After 24 h, test compounds were added. Eighteen hours later, [^3H]thymidine (0.25 μCi/well) was added for 2 h, trypsin (100 μL of 0.25%) was added for 1 h, and the assay was terminated by filtration using a Brandel 96-well harvester. The filters were counted for radioactivity using the LKB β-plate counting system.

Effects on DA Synthesis.[17] Striatal and hippocampal DA synthesis were measured by HPLC with electrochemical detection in rats given drug (60 min) and the L-aromatic amino acid decarboxylase inhibitor NSD 1015 30 min prior to sacrifice by decapitation. Data are expressed as the percentage increase of DA synthesis (as indicated by DOPA levels) relative to control animals.

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Supporting Information Available: IR and ^1H NMR spectral data for compounds **6**−**8**, **13**−**15**, **17**−**21**, and **23**−**25** (3 pages). Ordering information is given on any current masthead page.

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