(Aryloxy)alkylamines as Selective Human Dopamine D_4 Receptor Antagonists: Potential Antipsychotic Agents

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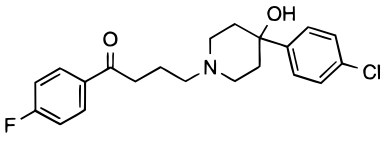
The discovery of a series of novel (aryloxy)alkylamines with selective affinity for the dopamine D_4 receptor is described. Target compounds were tested for binding to cloned human dopamine D_2, D_3, and D_4 receptor subtypes expressed in Chinese hamster ovary (CHO) K-1 cells. A number of compounds demonstrated subnanomolar K_i values for binding to the D_4 receptor, with several 100-fold selectivities toward the D_2 and D_3 receptors. Several compounds with combined D_3/D_4 receptor binding selectivity were also identified. A limited structure−activity relationship study of this chemical series is discussed. In a mitogenesis functional assay, the effect of the test compounds on cellular uptake of [^{3}H]thymidine in D_4-transfected CHO 10001 cells was measured and compared to the response of the full dopamine agonist quinpirole. The activity of the compounds varied from full antagonist to weak partial agonist activity (intrinsic activity of 0−19% in comparison to quinpirole).

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] Receptor cloning techniques have demonstrated that these receptors are subdivided into D_2, D_3, and D_4 subtypes.[3] Existing antipsychotic drugs, while generally useful in treating the positive symptoms of schizophrenia, can also induce the onset of Parkinson-like extrapyramidal side effects. This propensity is believed to be due to blockade of the D_2 receptor subtype, concentrated primarily in striatal areas of the brain. D_4 receptors are preferentially located in cortical and other areas of the brain believed to control emotional and cognitive functions.[4]



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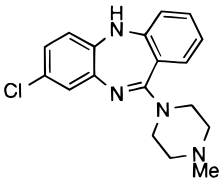

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Clozapine (**2**) is an atypical antipsychotic drug in that it alleviates both positive and negative symptoms of the disease while inducing a low incidence of undesirable motor side effects. The fact that clozapine exhibits an approximately 10-fold selectivity for D_4 versus D_2 receptors may contribute to the therapeutic value of the drug,[4,5] although clozapine also has a high affinity for a variety of other brain receptors.[6] The cloning of the different dopamine receptor subtypes has permitted the identification of ligands selective for a specific receptor subtype. Thus, there is a need for selective ligands to elucidate the specific pharmacological role of the D_4 receptor. A selective D_4 receptor antagonist may show antipsychotic activity with a lower propensity for undesirable side effects.[7]

Selective D_4 receptor antagonists, including the benzenesulfonamide U-101,387[8] and the pyrrolo[2,3-b]pyridine L-745,870,[9] have been reported in a variety of chemical series.[10−12] We recently described[13] the discovery of a series of chromeno[3,4-*c*]pyridines with selectivity for the human dopamine D_4 receptor. Continued screening of the Parke-Davis compound library has now identified a series of (aryloxy)alkylamines as selective D_4 receptor antagonists. The synthesis and receptor binding activity of this series are presented.

Chemistry

Preparation of the target compounds (Tables 1 and 2) is shown in Schemes 1 and 2. The primary synthetic method used was the reaction of (aryloxy)alkylamines or arylalkylamines with (aryloxy)alkyl bromides (Scheme 1). Similarly, compounds **25**−**28** were prepared from (aryloxy)alkylamines and (arylthio)alkyl bromides, prepared in turn from thiophenols. The amines used were commercially available or were prepared by standard methods, such as the Gabriel phthalimide synthesis or by reduction of nitriles. Most of the bromide starting materials were prepared by bromination of phenoxyethyl carbinols or from phenols by alkylation with 1,2-dibromoethane or 1,3-dibromopropane. Compound **9** was prepared from an (aryloxy)alkyl iodide, while **13** was obtained by saponification of the corresponding ethyl ester intermediate. Compound **31** was obtained by $LiAlH_4$ reduction of intermediate amide **30** (Scheme 2).

Results and Discussion

The affinities of the target compounds for the dopamine D_2, D_3, and D_4 receptors were determined in vitro by measuring their ability to displace the ligand [^{3}H]-spiperone from cloned human dopamine receptor subtypes expressed in Chinese hamster ovary (CHO) K-1 cells.[14] Receptor affinities are presented as K_i values

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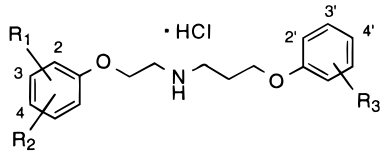
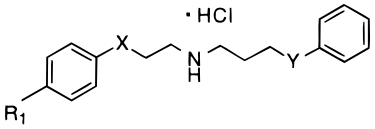
Table 1. Receptor Binding Data for (Aryloxy)alkylamines **3**−**24**



				K_i[a] (nM)			
compd	R_1	R_2	R_3	D_4	D_2	D_3	D_2/D_4
3	H	H	H	2.0	251	136	126
4	2-Cl	H	H	4.4	112	17	25
5	2-Me	H	H	74	20		0.27
6	3-Cl	H	H	0.31	22		71
7	3-Me	H	H	0.46	61		133
8	4-Me	H	H	0.52	268	169	515
9	4-OMe	H	H	5.4	1950	369	361
10[b]	4-OH	H	H	3.1	556	236	179
11	4-Cl	H	H	0.53	228	31	430
12	4-NO_2	H	H	4.4	1400	345	318
13	4-CO_2H	H	H	>1000			
14	4-Me	3-Cl	H	0.52	299	3.9	575
15	4-Me	3-Me	H	0.35	143	73	409
16	4-Cl	H	4′-Me	5.6	1320	177	236
17	4-Cl	H	4′-Br	38	>5880		155
18	4-Cl	H	4′-F	0.84	245	98	292
19	H	H	4′-Me	2.7	64	66	24
20	4-Me	H	2′-Me	1.1	296	381	269
21	4-Me	H	3′-Me	1.2	292	192	243
22	4-Me	H	4′-Me	11	277	235	25
23	4-Me	H	4′-Br	27	5730	1700	212
24	4-Me	H	4′-F	0.96	391	232	407

[a] Affinities for cloned human dopamine receptors with [^{3}H]spiperone as ligand; 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] Data for the hydrobromide salt.

Table 2. Receptor Binding Data for (Aryloxy)alkylamines **25**−**29**, **31**

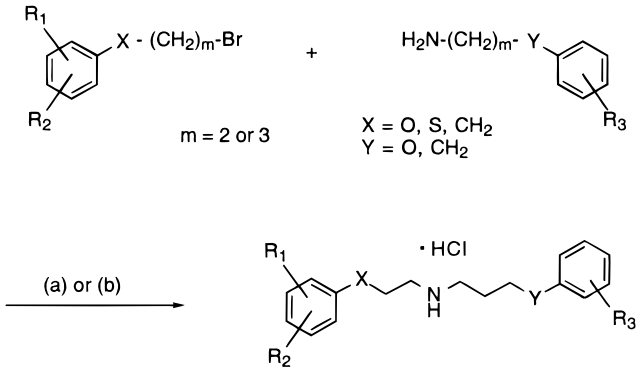


				K_i(nM)[a]			
compd	X	Y	R_1	D_4	D_2	D_3	D_2/D_4
25	O	S	Cl	1.4	227	95	162
26	O	S	Me	0.80	118	56	148
27[b]	S	O	Cl	33	352		11
28	S	O	Me	30	222		7.4
29	CH_2	O	H	3.3	519	17	157
31	CH_2	O	Me	4.7	364	347	77
1				2.2	1.6	2.2	0.73
2				16	91	222	5.7

[a] Affinities for cloned human dopamine receptors with [^{3}H]spiperone as ligand; 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] Data for the free base.

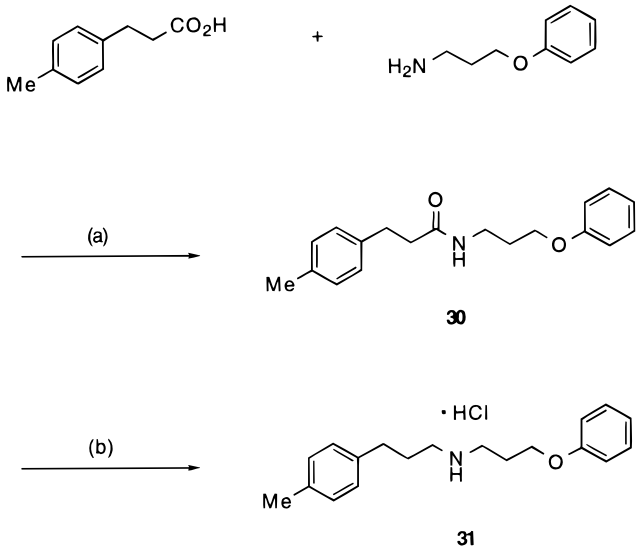
in Tables 1 and 2. Structure−activity relationships in the (aryloxy)alkylamine system were explored by variation of the substituent patterns on the two terminal aromatic rings, by replacement of the oxygen atoms of the center chain, and by modification of the amine nitrogen. Compound **3**, unsubstituted on both terminal phenyl rings, exhibited potent binding at the D_4 receptor as well as moderate selectivity toward binding at the D_2 and D_3 receptors. Variation of the R_1 and R_2 aromatic ring substituents of **3** gave compounds **4**−**15**.

Scheme 1.[a] General Preparative Methods



[a] Reagents: (a) 2 equiv of amine, benzene, toluene, or 2-propanol, 18−33 h reflux, HCl; (b) 1 equiv of amine, Na_2CO_3 or K_2CO_3, DMF, 90 °C, 18 h, HCl.

Scheme 2.[a] Preparation of Compound **31**



[a] Reagents: (a) isobutyl chloroformate, Et_3N, THF; (b) $LiAlH_4$, THF, HCl.

The 4-methyl (**8**) and 4-chloro (**11**) analogues exhibited especially potent binding at the D_4 receptor with selectivity in comparison to D_2 binding. A number of other 2- and 3-substituted derivatives were also prepared and found to be less selective than the analogous 4-substituted compounds. Two 3,4-substituted compounds (**14** and **15**) were also quite potent, with **14** showing significant binding at the D_3 receptor. Such compounds with combined D_3, D_4 selectivity are also of interest as potential antipsychotics.[15] Compounds **16**−**24** with an R_3 substituent varied in binding potency and selectivity. All were inferior to **8** and **11**, with the 4′-fluoro derivatives **18** and **24** being the most potent of the group. In compounds **25**−**31** one of the center chain oxygen atoms was replaced by sulfur or carbon. Once again, these derivatives were inferior to **8** and **11**. *N*-Methyl analogues of **8** and **11**, as well as the amide intermediate **30**, had greatly reduced binding activity (data not shown), demonstrating the necessity of the center chain secondary amine.

Agonist activation of dopamine receptors is known to stimulate mitogenesis in Chinese hamster ovary (CHO) cells.[14,16] This response can be quantitated for a test compound by measuring the cellular uptake of [^{3}H]-

Table 3. Antagonism of Quinpirole-Induced Mitogenesis

compd	D_4 IC_{50},[a] nM	intrinsic activity[b]
8	1.5 (0.76−2.4)	0
11	6.9 (0.99−48)	0
14	3.4 (0.89−12.9)	0
15	0.53 (0.074−3.9)	17 ± 7.3
24	1.3 (0.52−3.4)	19 ± 5.8

[a] Inhibition of [^{3}H]thymidine uptake in CHO 10001 cells transfected with D_4 receptors. IC_{50} values are derived from six to seven concentrations run in quadruplicate. 95% confidence limits are in parentheses. [b] Percent stimulation of mitogenesis ±S.E.M. in comparison to the full agonist quinpirole (100%).

thymidine and comparing the response to that of the full dopamine agonist quinpirole (defined as 100%). Several of the more selective target compounds were tested for their ability to block stimulation of mitogenesis in D_4-transfected CHO 10001 cells. The results are presented in Table 3 as IC_{50} values for inhibition of mitogenesis as well as intrinsic activity in comparison to quinpirole. Compounds **8**, **11**, and **14** were found to be potent antagonists at the D_4 receptor, while **15** and **24** showed partial agonist activity.

We have described the synthesis and dopamine receptor binding activity for a novel series of (aryloxy)-alkylamines. A number of compounds demonstrated subnanomolar K_i values for binding to the D_4 receptor, with several 100-fold selectivities toward the D_2 and D_3 receptors. A limited structure−activity relationship study for this chemical series indicated that compounds with 4-methyl or 4-chloro substituents exhibited optimum binding preference for the dopamine D_4 receptor. In a mitogenesis functional assay, the profile of the compounds varied from that of a full antagonist to a weak partial agonist. These compounds will be useful tools in exploring 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.

General Method A. (3-Phenoxypropyl)(3-phenylpropyl)amine Hydrochloride (29). A mixture of (3-bromopropoxy)benzene (1.6 mL, 2.2 g, 10 mmol) and benzenepropanamine (2.8 mL, 2.7 g, 20 mmol) in 20 mL of toluene was stirred at reflux for 18 h. The mixture was cooled, and the precipitated HBr salt of the amine was filtered and washed with toluene. The combined filtrates were washed with brine, dried (Na_2SO_4), and treated with HCl gas. The precipitated product was filtered and washed with Et_2O. Recrystallization from EtOH/*t*-BuOMe gave 0.90 g (30%) of **29**: mp 188−191 °C; IR 2784, 1598, 1498, 1243 cm^{-1}, ^{1}H NMR (DMSO-d_6) δ 1.94 (m, 2H, CCH_2), 2.09 (m, 2H, CCH_2), 2.66 (t, J = 7.8 Hz, 2H, PhCH_2), 2.91 (t, J = 7.8 Hz, 2H, NCH_2), 3.05 (t, J = 7.6 Hz, 2H, NCH_2), 4.05 (t, J = 6.2 Hz, 2H, OCH_2), 6.92−6.96 (m, 3H, Ph), 7.19−7.33 (m, 7H, Ph), 8.97 (br s, 2H, NH_2^+); EIMS *m*/*z* 270 (MH^+). Anal. ($C_{18}H_{23}NO$·HCl) C, H, N.

Similarly prepared by this method were compounds **3**, **4**, **6**, **7**, **14**, and **15**.

General Method B. (3-Phenoxypropyl)[2-(*p*-tolyloxy)-ethyl]amine Hydrochloride (8). A solution of 3-phenoxy-1-propanamine[17] (3.0 g, 20 mmol) in 10 mL of benzene was heated to reflux and treated over 15 min with a solution of 1-(2-bromoethoxy)-4-methylbenzene[18] (2.2 g, 10 mmol) in 10 mL of benzene. The mixture was heated at reflux for 18 h and cooled, and the precipitated HBr salt of the amine was filtered. A solution (3.0 mL) of 4.0 N HCl in dioxane was added to the filtrate. After being stirred for 15 min, the precipitated product was filtered and recrystallized from EtOH to yield 1.8 g (56%) of **8**: mp 210−215 °C; IR 2951, 1599, 1514, 1250 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.14 (m, 2H, CCH_2), 2.24 (s, 3H, CH_3), 3.16 (t, J = 7.6 Hz, 2H, NCH_2), (H_2O peak overlaps one NCH_2), 4.08 (t, J = 6.1 Hz, 2H, OCH_2), 4.24 (t, J = 5.1 Hz, 2H, OCH_2), 6.88−6.96 (m, 5H, Ph), 7.12 (d, J = 8.5 Hz, 2H, Ph), 7.28−7.32 (m, 2H, Ph), 9.17 (br s, 2H, NH_2^+); EIMS *m*/*z* 286 (MH^+). Anal. ($C_{18}H_{23}NO_2$·HCl) C, H, N.

Similarly prepared by this method were compounds **11**, **12**, **20**, and **21**.

General Method C. [2-(*p*-Tolyloxy)ethyl][3-(*p*-tolyloxy)propyl]amine Hydrochloride (22). A mixture of 2-(4-methylphenoxy)ethanamine[19] (1.5 g, 10 mmol), 1-(3-bromopropoxy)-4-methylbenzene[20] (2.3 g, 10 mmol), and anhydrous Na_2CO_3 (0.75 g, 7.1 mmol) in 15 mL of DMF was heated in an oil bath at 90 °C for 18 h. The cooled reaction mixture was added to 300 mL of H_2O and extracted with toluene. The combined organic layers were washed with brine, dried (Na_2SO_4), and evaporated. The residue was dissolved in 100 mL of Et_2O, and the solution was treated with HCl gas. The precipitated product was filtered, washed with Et_2O, and recrystallized from MeCN/MeOH to yield 1.1 g (33%) of **22**: mp 230−232 °C; IR 2462, 1514, 1243, 1054 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.11 (m, 2H, CCH_2), 2.23 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 3.15 (t, J = 7.6 Hz, 2H, NCH_2), (H_2O peak overlaps one NCH_2), 4.03 (t, J = 6.0 Hz, 2H, OCH_2), 4.22 (t, J = 5.1 Hz, 2H, OCH_2), 6.82−6.90 (m, 4H, Ph), 7.08−7.13 (m, 4H, Ph), 9.05 (br s, 2H, NH_2^+); EIMS *m*/*z* 300 (MH^+). Anal. ($C_{19}H_{25}NO_2$·HCl) C, H, N.

Similarly prepared by this method were compounds **16**−**19** and **23**−**28**.

***N*-(3-Phenoxypropyl)-3-(*p*-tolylpropyl)propionamide (30).** A solution of 3-*p*-tolylpropionic acid[21] (2.0 g, 12 mmol) and Et_3N (4.3 mL, 3.1 g, 31 mmol) in 80 mL of THF was cooled in ice and treated dropwise with isobutyl chloroformate (1.7 mL, 1.8 g, 13 mmol). The mixture was stirred for 1 h, and a solution of 3-phenoxy-1-propanamine (1.9 g, 13 mmol) in 10 mL of THF was added slowly. The mixture was stirred at room temperature for 18 h and then added to 400 mL of brine. The mixture was acidified with 4.0 N HCl and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4), and evaporated. Recrystallization of the residue from EtOAc/hexane gave 2.2 g (61%) of intermediate **30**: mp 101−102 °C; IR 3304, 1637, 1544, 1247 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.79 (m, 2H, CCH_2), 2.22 (s, 3H, CH_3), 2.33 (t, J = 7.8 Hz, 2H, CH_2CO), 2.75 (t, J = 7.7 Hz, 2H, PhCH_2), 3.17 (q, J = 5.8 Hz, 2H, NCH_2), 3.87 (t, J = 6.4 Hz, 2H, OCH_2), 6.88−6.94 (m, 3H, Ph), 7.03−7.08 (m, 4H, Ph), 7.26−7.30 (m, 2H, Ph), 7.89 (t, J = 5.4 Hz, 1H, NH); EIMS *m*/*z* 298 (MH^+). Anal. ($C_{19}H_{23}NO_2$) C, H, N.

(3-Phenoxypropyl)(3-*p*-tolylpropyl)amine Hydrochloride (31). A solution of intermediate amide **30** (1.0 g, 3.4 mmol) in 15 mL of THF was added dropwise to a solution of 1.0 M $LiAlH_4$ (8.0 mL, 8.0 mmol) in 15 mL of THF. The mixture was stirred at reflux for 3 h and then cooled in ice while 10 mL of H_2O was added dropwise. Toluene (30 mL) was added, and the inorganic solids were filtered and washed with H_2O and toluene. The organic layer was separated from the combined filtrates, and the aqueous layer was washed with fresh toluene. The combined organic layers were washed with brine, dried (Na_2SO_4), and evaporated. The residue was dissolved in 100 mL of Et_2O and recrystallized from MeCN to yield 0.60 g (55%) of **31**: mp 214−217 °C; IR 2947, 1598, 1498, 1243 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.91 (m, 2H, CCH_2), 2.09 (m, 2H, CCH_2), 2.27 (s, 3H, CH_3), 2.61 (t, J = 7.6 Hz, 2H, PhCH_2), 2.89 (t, J = 7.8 Hz, 2H, NCH_2), 3.04 (t, J = 7.6 Hz, 2H, NCH_2), 4.05 (t, J = 6.0 Hz, 2H, OCH_2), 6.92−6.96 (m, 3H,

Ph), 7.11 (s, 4H, Ph), 7.28−7.31 (m, 2H, Ph), 8.97 (br s, 2H, NH_2^+); EIMS *m/z* 284 (MH^+). Anal. ($C_{19}H_{25}NO$·HCl) C, H, N.

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Supporting Information Available: Full experimental details and spectral data for compounds **5**, **9**, **10**, and **13**. Physical data for compounds **3**−**29** and **31** (6 pages). Ordering information is given on any current masthead page.

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