93781-99-8; **2j**, 81572-18-1; **2k**, 93782-00-4; **2l**, 81572-19-2; **2o**, 93782-01-5; **3a**, 39799-77-4; **3b**, 93782-02-6; **3c**, 93782-03-7; **3d**, 67909-04-0; **3e**, 33542-53-9; **3f**, 93782-04-8; **3g**, 53995-06-5; **3h**, 24631-04-7; **3i**, 2032-07-7; **3o**, 24138-94-1; **4a**, 93782-05-9; **4b**, 81572-20-5; **4c**, 81583-49-5; **4d**, 81572-22-7; **5a**, 93860-69-6; **5b**, 93782-06-0; **6a**, 93782-08-2; **6b**, 93782-08-2; **6c**, 93860-70-9; **6d**, 93782-09-3; D,L-phenylglycine methyl ester hydrochloride, 15028-40-7; D,L-alanine methyl ester hydrochloride, 13515-97-4.

1-[3-(Diarylamino)propyl]piperidines and Related Compounds, Potential Antipsychotic Agents with Low Cataleptogenic Profiles

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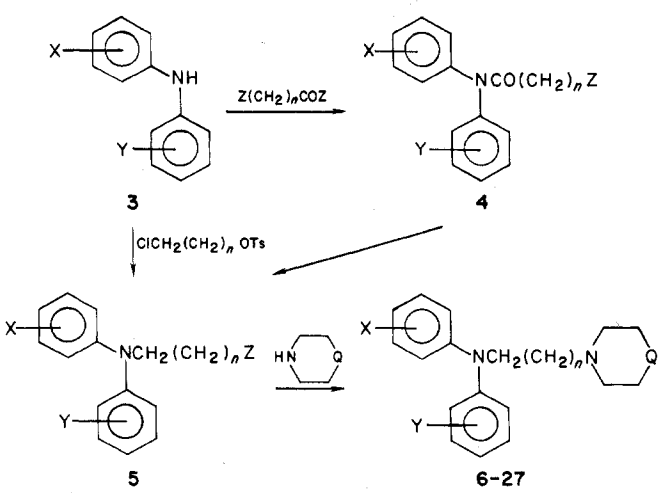
On the basis of a structural model of the postsynaptic dopaminergic antagonist pharmacophore, a series of 1-[3-(diarylamino)propyl]piperidines and related compounds was synthesized and evaluated for potential antipsychotic activity. For a rapid measure of activity, the target compounds were initially screened in vitro for inhibition of [^{3}H]haloperidol binding and in vivo in a test of locomotor activity. Behavioral efficacy of compounds identified from the initial screens was more accurately measured in rats by using a suppression of high base-line medial forebrain bundle self-stimulation test model. The propensity of these compounds for causing extrapyramidal side effects was evaluated by using a rat catalepsy method. On the basis of these test models, we have shown that the methine carbon of the 1-(4,4-diarylbutyl)piperidines can be advantageously replaced with a nitrogen atom. The 1-[3-(diarylamino)propyl]piperidines were less cataleptic than the corresponding 1-(4,4-diarylbutyl)piperidines. The compounds with the widest separation between efficacious dose and cataleptic dose are 8-[3-[bis(4-fluorophenyl)amino]propyl]-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one (**6**), 1-[1-[3-[bis(4-fluorophenyl)amino]propyl]-4-piperidinyl]-1,3-dihydro-2*H*-benzimidazol-2-one (**11**), 1-[1-[3-[bis(4-fluorophenyl)amino]propyl]-1,2,3,6-tetrahydro-4-pyridinyl]-1,3-dihydro-2*H*-benzimidazol-2-one (**22**), and 1-[3-[bis(4-fluorophenyl)amino]propyl]-4-(2-methoxyphenyl)piperazine (**26**).

In the past 25 years, the advent of antipsychotic drugs has resulted in a virtual revolution in the treatment of schizophrenia.[1] Although these agents have proven beneficial, their therapeutic effects are accompanied by distinct disadvantages including extrapyramidal side effects (EPS) and tardive dyskinesia (TD).[2] At one time, in fact, EPS was actually considered by many investigators as evidence of therapeutic efficacy. With the discovery of newer agents, sometimes described as atypical antipsychotic drugs, it has been suggested that the side effects (EPS and TD) could be separated from the therapeutic effects.[3] For example, the atypical antipsychotic agent, clozapine has been reported to be both effective and free of EPS in clinical studies although other problems have kept it from the market place.[4]

Therefore, the development of a compound for the treatment of schizophrenia with minimal EPS would represent a significant therapeutic improvement over existing drugs. This report summarizes some of the efforts from our laboratories directed toward this goal.

Studies of the structural features of the various classes of postsynaptic dopamine receptor antagonists used as antipsychotic agents have led investigators to identify a common pharmacophore responsible for their activities.[5] Two series of compounds incorporating this pharmacophore are the 1-[4,4-bis(4-fluorophenyl)butyl]piperidines and the phenothiazines typified by pimozide (**1**) and chlorpromazine (**2**), respectively. On the basis of the structural features of these two series of compounds, we became interested in the structure–activity relationships (SAR) of the [(diarylamino)alkyl]piperidines and -piperazines **6–27**, which may be thought of as arising through either replacement of the methine carbon atom of the 1-(4,4-diarylbutyl)piperidine structure with a tertiary nitrogen atom or elimination of the bridged sulfur atom from the phenothiazine moiety. The goal was to identify com-

Scheme I



† Department of Chemistry.
‡ Department of Pharmacology.

(1) Davis, J.; Janicak, P.; Linden, R.; Moloney, J.; Pavkovic, I. "Neutroleptics: Neurochemical, Behavioral, and Clinical Perspectives"; Coyle, J. T., Enna, S. J., Eds.; Raven Press: New York, 1983; p 15.
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(4) Tamminga, C. "Neuroleptics: Neurochemical, Behavioral, and Clinical Perspectives"; Coyle, J. T., Enna, S. J., Eds.; Raven Press: New York, 1983; p 281.

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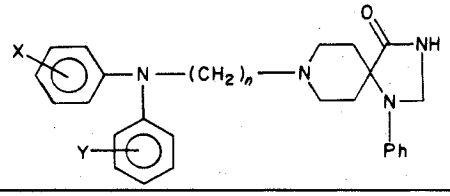
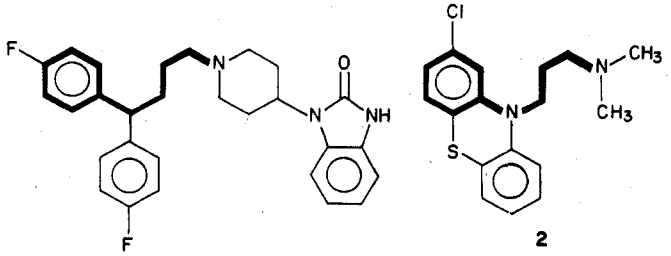
Table I. 8-[(Diarylamino)alkyl]-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-ones



no.	X	Y	n	method[a]	recrystn solvent	yield,[b] %	mp, °C	formula[c]	anal.[d]	inhib [^{3}H]-haloperidol binding,[e] %, 10^{-8} M	LAD,[f] mg/kg, ip	ED_{50}, mg/kg, po A[g]	ED_{50}, mg/kg, po B[h]
6	4-F	4-F	3	A	EtOAc	79	155–156	$C_{28}H_{30}F_2N_4O$	C, H, N	96[i]	5	1.65 (0.9)	81.2
7	4-F	4-F	2		EtOAc	7	154–156	$C_{27}H_{28}F_2N_4O$	C, H, N	33	100		
8	4-F	4-F	4		toluene–pet. ether	51	159.5–160.5	$C_{29}H_{32}F_2N_4O$	C, H, N	59	>100		
9	4-F	H	3	A	EtOAc	21	173–177	$C_{28}H_{31}FN_4O$	C,[j] H, N	72	30	11.7	156
10	4-F	3-Cl	3	B	EtOAc	78	163–165	$C_{28}H_{30}ClFN_4O$	C, H, N	86	30	12.7	289

[a] See Experimental Section for general preparative procedures. [b] No attempts were made to maximize yields. [c] Compounds were characterized as free bases except where salt is noted below. [d] Except where noted, values obtained agreed with calculated values within ±0.4%. [e] [^{3}H]Haloperidol binding to rat striatal membranes using 0.6 nM ligand was performed by the method of Burt et al.[7] Entries are one experiment done in triplicate. [f] Inhibition of locomotion–screen falloff test. With the exception of **6**, all compounds were evaluated at 10, 30, and 100 mg/kg. Each dose was replicated three times. The lowest active dose (LAD) was defined as being the lowest dose showing greater than 60% inhibition of locomotor activity and less than 60% screen falloff. [g] A = suppression of self-stimulation. ED_{50}'s were obtained by linear regression from one dose higher and one lower than the ED_{50} value. Correlation coefficients in parentheses are shown for compounds that were tested at more than two doses. [h] B = rat catalepsy. At least three doses of compounds were administered and eight animals were used at each dose. ED_{50}'s were obtained by a nonlinear regression analysis. [i] IC_{50} = 0.61 nM. [j] C: calcd, 73.33; found, 72.71.

pounds with a behavioral pharmacological profile similar to thioridazine or clozapine. Such compounds could have a lower propensity for side effects. We therefore synthesized and evaluated a select series of [(diarylamino)-alkyl]piperidines and -piperazines and explored their SAR.



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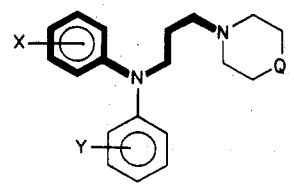

6,9-27

Chemistry. The general routes used for the synthesis of target compounds **6–27** are outlined in Scheme I. The sources for the various diarylamines, piperidines, and piperazines are listed in the Experimental Section. The 4-fluoro-*N*-(4-fluorophenyl)benzenamine (**3**, X = Y = 4-F) was prepared by a modification of the method of Leonard and Sutton[6] in which a mixture of 4-fluoroaniline, 1-bromo-4-fluorobenzene, acetic anhydride, potassium carbonate, and cuprous iodide was heated under nitrogen at 255–260 °C. By this process three steps, acylation, arylation, and hydrolysis, were carried out in a single pot to give the diarylamine directly. The target [(diarylamino)alkyl]piperidines and -piperazines **6–27** could be obtained in two steps by alkylation of the lithium salt of the diarylamine **3** with chloroalkyl tosylate to give the (diarylamino)alkyl halide **5**, which in turn was reacted with the piperidine or piperazine moiety (method A). Alternatively, acylation of **3** with either a chloroalkanoyl chloride or bromoalkanoyl bromide gave amide **4**. Reduction of **4** with either diborane or aluminum hydride afforded the (diarylamino)alkyl halide **5**, which in turn was used to alkylate the requisite amine to produce the target [(diarylamino)alkyl]piperidine or -piperazine **6–27** (method B).

Pharmacological Results and Discussion

As a simple, rapid measure of potential antipsychotic activity, the target compounds were screened for their ability to inhibit [^{3}H]haloperidol binding to dopaminergic receptors in homogenates of rat striatum.[7] The percent inhibitions of specific binding at 10^{-8} M concentration are listed in Tables I–III. The concentration required to inhibit 50% of the specific binding (IC_{50}) is also given for selected compounds.

Simultaneously, the target compounds were tested in our initial behavioral test in mice by intraperitoneal administration (IP) by using a two-part test designed to measure inhibition of spontaneous locomotor activity (LMA) and impairment of motor function (falling off an inverted screen).[8] This test is based on the observation that antipsychotic agents produce inhibition of spontaneous locomotion in mice at doses that do not produce severe depression, impaired motor function, or CNS toxicity. The compounds were rated according to their overall profile in this test, and the lowest active dose for each compound is shown in Tables I–III.

Compounds that were active in these two high-volume predictors of potential antipsychotic activity (i.e., >60% inhibition in binding at 10^{-8} M and a lowest active dose (LAD) ≤ 30 mg/kg in the inhibition of locomotor–screen test) were tested orally (PO) in more detail with use of

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(6) Leonard, N. J.; Sutton, L. E. *J. Am. Chem. Soc.* **1948**, *70*, 1564.
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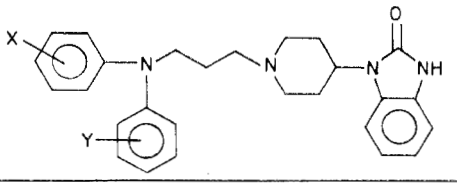
Table II. 1-[1-[3-(Diarylamino)propyl]-4-piperidinyl]-1,3-dihydro-2*H*-benzimidazol-2-ones



no.	X	Y	method[a]	recrystn solvent	yield,[b] %	mp, °C	formula[c]	anal.[d]	inhib [^{3}H]-haloperidol binding,[e] %, 10^{-8} M	LAD,[f] mg/kg, ip	ED_{50}, mg/kg, po A[g]	ED_{50}, mg/kg, po B[h]
11	4-F	4-F	B	EtOAc	74	183–184	$C_{27}H_{28}F_2N_4O$	C, H, N	94[i]	≤10	0.87 (0.9)	32.9
12	4-F	H	B	CH_3CN–EtOH	37	171–172.5	$C_{27}H_{29}FN_4O$	C, H, N[h]	84	30	8.37	76
13	4-F	2-F	B	EtOAc–*i*-PrOH	46	168–169	$C_{27}H_{28}F_2N_4O$	C, H, N	92	30	11.3	156
14	H	H	B	MeOH	48	289–291	$C_{27}H_{30}N_4O$·HCl	C, H, N	68	30	13.2	
15	3-Cl	H	B	MeOH	26	177–178.5	$C_{27}H_{29}ClN_4O$	C, H, N	36	>100		
16	3-CH_3	H	B	MeOH	22	232–234	$C_{28}H_{32}N_4O$·HCl	C, H, N	61			
17	4-NO_2	H	B	MeOH	33	275–276	$C_{27}H_{29}N_5O_3$·HCl	C, H, N[j]	17	100		

[a–h] See footnotes *a–h* respectively in Table I. [i] IC_{50} = 0.40 nM. [j] N: calcd, 12.60; found, 13.05.

suppression of high base-line self-stimulation with electrodes placed in the medial forebrain bundle of the posterior hypothalamus of male hooded rats.[9] This test system is based on the theory that psychotic agitation represents a condition in which there is pathological hyperactivity of the catecholamine reward system of the brain and that treatments that alleviate psychoses do so because they suppress this brain system by direct or indirect means. ED_{50} values were calculated for the active compounds and are also listed in Tables I–III.

Catelepsy is considered to be an indicator of a compound's propensity to produce undesirable extrapyramidal side effects.[10] Thus compounds that were highly active in the suppression of self-stimulation test were evaluated for their catalepsy potential in rats (PO). Potential atypical antipsychotic agents would be expected to show a large separation between their behaviorally effective doses and the doses that would cause catalepsy (e.g., clozapine vs. pimozide or fluspirilene, Table III).

The initial target selected for evaluation was compound **6**, when the 3-[bis(4-fluorophenyl)amino]propyl side chain replaced the corresponding 4,4-bis(4-fluorophenyl)butyl moiety of fluspirilene. As shown in Table I, compound **6** exhibited greater than nanomolar affinity in the in vitro [^{3}H]haloperidol binding assay and also was highly active in the initial in vivo locomotor activity–screen test. Compound **6** was also quite active in the suppression of self-stimulation test (ED_{50} = 1.65 mg/kg) and showed catalepsy only at very high doses (ED_{50} = 81.7 mg/kg). The (diarylamino)ethyl and (diarylamino)butyl analogues **7** and **8**, respectively, were examined to determine the chain length for best activity. Neither showed good activity in the initial screens, demonstrating that a three-carbon separation between nitrogen atoms was optimal. The 1-[3-[bis(4-fluorophenyl)amino]propyl]piperidine **11**, containing the piperidine moiety of pimozide, was also found to be active in the test predictive of efficacy and again showed a large separation between its ability to suppress self-stimulation and to cause catalepsy (ED_{50} of 0.87 mg/kg vs. 32.9 mg/kg) (Table II).

Subsequently, we elected to investigate the effects of altering the substitution pattern of the diarylamino moieties of these compounds. Removal of one of the fluorine atoms from either **6** or **11**, compounds **9** and **12**, respectively, resulted in definite decreases in potency. Both, however, continued to show an interesting separation between behavioral efficacy and catalepsy. The 3-chloro-4′-fluoro and analogue of **6** and the 2,4′-difluoro analogue of **11**, **10** and **13**, respectively, had similar profiles. The desfluoro compound **14** was only weakly active in the test models. Compounds with other substituents on the phenyl ring, e.g., 3-Cl and 4-NO_3, **15** and **17**, respectively, were inactive in both the in vitro and in vivo tests.

Because of the profiles of **6** and **11**, we became interested in expanding this series to include compounds incorporating other selected piperidine and piperazine moieties (Table III). Initially, three analogue of **11** in which the benzimidazole portion of the compound contained various substituents, **18–20**, and the benzimidazolethione **21** were examined. While they were active in the binding assay, none showed significant in vivo behavioral activity. Compound **22**, the tetrahydropyridine analogue of **11**, was quite active in the tests of efficacy and again showed catalepsy only at very high doses. Interestingly, while **23**, which incorporates the piperidino moiety of haloperidol, was active, the 4-(4-chlorobenzoyl)piperidinyl analogue **24** was devoid of in vivo and in vitro activity. Finally, of three piperazine analogues examined, only 1-(2-methoxyphenyl)piperazine **26** showed good activity in all three tests of antipsychotic efficacy and again caused catalepsy only at very high doses.

Like the 1-(4,4-diarylbutyl)piperidines, the 1-[3-(diarylamino)propyl]piperidines and related compounds are quite active in general tests predictive of antipsychotic efficacy. Within the bounds of the SAR developed in this paper, structural features similar to those of the 1-(4,4-diarylbutyl)piperidine series appear to be important in defining the activity of the [(diarylamino)alkyl]piperidines. For example, in each case, 4-fluoro substitution of the phenyl rings and a four-atom separation between the phenyl rings and the piperidine nitrogen atom maximize activity. However, unlike the 1-(4,4-diarylbutyl)piperidine class of antipsychotic agents, e.g., fluspirilene and pimozide in Table III, these compounds appear to have a greater separation between doses predictive of therapeutic efficacy as measured by the suppression of self-stimulation ED_{50} and doses that cause catalepsy. If, indeed, cataleptic activity is associated with a high incidence of EPS, com-

(9) Olds, J.; Miller, P. J. *Comp. Physiol. Psychol.* **1954**, *47*, 419.
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pounds of the (diarylamino)propyl type should have a lower propensity for causing EPS than do the (diarylbutyl)piperidines.

Experimental Section

Melting points were determined in a Thomas-Hoover melting point apparatus in open capillary tubes and are uncorrected. The structures of the compounds were confirmed by elemental analysis, infrared spectrometry, and NMR spectrometry. Infrared spectra were recorded on a Digilab FTP-14 infrared spectrometer, and NMR spectra were obtained on a Varian EM 390 90 MHz or Brucker WH 90 spectrometer and were consistent with the proposed structures. Where analyses are indicated by the symbols of the elements, the results are within 0.4% of the theoretical values. TLC was carried out with 0.25-mm silica gel 60 F254 (E. Merck) glass plates. GLC was carried out with a Shimadzu GC Mini 2 or a Perkin-Elmer Model 910 gas chromatograph equipped with FID.

***N*-Phenylbenzenamines 3.** The 4-fluoro-*N*-phenylbenzenamine was synthesized by the method of Lichtenberger and Thermet.[11] The 2-fluoro-*N*-(4-fluorophenyl)benzenamine and 3-chloro-*N*-(4-fluorophenyl)benzenamine were prepared according to the procedure outlined by Benington et al.[12] All other diphenylamines were obtained commercially from Aldrich Chemical Co.

4-Substituted Piperidines and Piperazines. (4-Chlorophenyl)-4-piperidinylmethanone,[13] 5-chloro-1,3-dihydro-1-(4-piperidinyl)-2*H*-benzimidazol-2-one,[14] 5,6-dichloro-1,3-dihydro-1-(4-piperidinyl)-2*H*-benzimidazol-2-one,[14] 1,3-dihydro-5,6-dimethyl-1-(4-piperidinyl)-2*H*-benzimidazol-2-one,[15] and 1,3-dihydro-1-(1,2,3,6-tetrahydro-4-pyridinyl)-2*H*-benzimidazol-2-one[15] were synthesized as described in the references cited. All other substituted piperidines and piperazines were obtained from Aldrich Chemical Co.

Improved Synthesis of 4-Fluoro-*N*-(4-fluorophenyl)-benzenamine. Under a nitrogen atmosphere, 11.1 g (0.10 mol) of 4-fluorobenzenamine was treated with a slow, steady stream of 11 g (0.11 mol) of acetic anhydride. An exothermic reaction ensued; the reaction temperature rose to 92 °C. The mixture was stirred for 1 min after which 19.0 g (0.108 mol) of 1-bromo-4-fluorobenzene, 19.0 g (0.138 mol) of K_2CO_3 and 2 g of CuI were added. The reaction mixture was heated to 260 °C for 3 h. The mixture was cooled, diluted with xylene, and filtered. The filtrate was concentrated in vacuo to afford 18.0 g of oil. The oil was chromatographed on a silica gel column (elution with toluene). There was obtained 12.0 g (59%) of oil, with subsequently solidified, mp 38–39 °C (lit.[6,11] mp 39–40 °C).

Method A. 8-[3-[(4-Fluorophenyl)phenylamino]-propyl]-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one (9). A solution of 37.4 g (0.2 mol) of 4-fluoro-*N*-phenylbenzenamine in 500 mL of anhydrous Et_2O under N_2 was treated with 130 mL of 1.70 M *n*-BuLi in hexane at room temperature. The reaction mixture was allowed to warm to 38 °C during the addition. After the reaction had stirred for 10 min, a solution of 50 g (0.2 mol) of 3-chloropropyl tosylate in 200 mL of anhydrous Et_2O was added. The reaction mixture was refluxed for 1 h. TLC (cyclohexane) indicated the presence of starting amine. An additional 13 mL of 1.7 M of *n*-BuLi in hexane and 5 g (0.02 mol) of 3-chloropropyl tosylate were added, and the reaction was refluxed for an additional 1 h. The mixture was cooled to room temperature and water was added. The layers were separated and the organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated. The 60 g of residue was chromatographed on a silica gel column (elution with cyclohexane). There was obtained 18.9 g of colorless oil. The oil was distilled to afford 15.0 g (28.4%) of *N*-(3-chloropropyl)-4-fluoro-*N*-phenylbenzenamine, bp 125–127 °C (1.0 mm). Anal. ($C_{15}H_{15}ClFN$) C, H, N.

A mixture of 25 g (0.1 mol) of 1-phenyl-1,3,8-triazaspiro-[4.5]decan-4-one, 27.3 g (0.10 mol) of *N*-(3-chloropropyl)-4-fluoro-*N*-phenylbenzamine, and 12 g (0.14 mol) of Na_2CO_3 in 400 mL of DMF was stirred at 80 °C for 16 h. The DMF was removed in vacuo and the residue was partitioned between EtOAc and water. The organic extracts were dried over $MgSO_4$, filtered, and evaporated. The partially crystalline residue was stirred with MeOH and was filtered to yield 16.0 g of **9**, mp 173–177 °C. Recrystallization from EtOAc–$CHCl_3$ afforded 9.8 g (21%) of analytical material, mp 173–177 °C. Anal. ($C_{28}H_{31}FN_4O$) H, N; C: calcd, 73.33; found 72.71.

Method B. 1-[1-[3-[Bis(4-fluorophenyl)amino]propyl]-4-piperidinyl]-1,3-dihydro-2*H*-benzimidazol-2-one (11). To a solution of 30.0 g (0.146 mol) of 4-fluoro-*N*-(4-fluorophenyl)-benzenamine in 150 mL of benzene was added 19.6 g (0.154 mol), of 3-chloropropanoyl chloride. The resulting solution was refluxed for 5 h with evolution of HCl gas. The solvent was removed in vacuo, and the residue was recrystallized from *i*-PrOH–Et_2O to yield 38.1 g (88%) of 3-chloro-*N*,*N*-bis(4-fluorophenyl)propanamide, mp 84–86 °C.

In several cases 3-bromopropanoyl bromide was used in place of 3-chloropropanoyl chloride to yield 3-bromo-*N*,*N*-bis(4-fluorophenyl)propanamide, mp 95.5–97.5 °C.

To a solution of 50.0 g (0.169 mol) of 3-chloro-*N*,*N*-bis(4-fluorophenyl)propanamide in 150 mL of THF at 5–10 °C was added 250 mL of 1 M BH_3 in THF (0.25 mol) over a 10 min period. After stirring at 5 °C for 1 h, the reaction mixture was allowed to warm to room temperature and stirred for an additional 2 h. With caution 100 mL of MeOH was added dropwise. The solvent was evaporated. The residue was chromatographed through a silica gel column (elution with CCl_4). The desired fractions yielded 35.9 g (75%) of *N*-(3-chloropropyl)-4-fluoro-*N*-(4-fluorophenyl)benzenamine as a colorless oil which was used without further purification.

Aluminum hydride was also used successfully as the reducing agent in the above reaction. *N*-(3-Bromopropyl)-4-fluoro-*N*-(4-fluorophenyl)benzenamine was prepared in a similar manner from the requisite bromo amide and used interchangeably in the alkylation reaction.

A mixture of 19.5 g (96 mmol) of *N*-(3-chloropropyl)-4-fluoro-*N*-(4-fluorophenyl)benzenamine, 15.0 g (96 mmol) of 1,3-dihydro-1-(4-piperidinyl)-2*H*-benzimidazol-2-one, 11.5 g (84 mmol) of K_2CO_3, and 2.0 g of NaI in 150 mL of 4-methyl-2-pentanone was stirred and refluxed for 110 h. The mixture was filtered. The solvent was removed in vacuo and the residue was partitioned between $CHCl_3$ and water. The organic extracts were dried over anhydrous $MgSO_4$, filtered, and evaporated. The product was recrystallized from EtOAc containing a small amount of MeOH to afford 23.6 g (74%) of **11** as white crystals, mp 183–184 °C.

In addition to the conditions described above, similar yields were obtained with Na_2CO_3, $NaHCO_3$, or an extra equivalent of the amine as the proton acceptor and DMF or 2-butanone as solvent.

1-[1-[3-[Bis(4-fluorophenyl)amino]propyl]-4-piperidinyl]-1,3-dihydro-2*H*-benzimidazole-2-thione (21). A mixture of 6.0 g (12.9 mmol) of **11** and 14.4 g (65 mmol) of phosphorus pentasulfide in 60 mL of pyridine was refluxed for about 20 h. The reaction mixture was cooled. Ice and 10% aqueous NaOH were added. The product was extracted into $CHCl_3$; the extracts were washed with water and passed through a silica gel column (elution with $CHCl_3$). The eluate was evaporated, and the residue was crystallized from acetone to yield 2.0 g (32%) of **21**, mp 191–192 °C. Anal. ($C_{27}H_{28}F_2N_4S$) C, H, N.

8-[2-[Bis(4-fluorophenyl)amino]ethyl]-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one (7). To 38.2 g (0.20 mol) of 4-fluoro-*N*-(4-fluorophenyl)benzenamine in 500 mL of anhydrous Et_2O was added 150 mL of 1.7 M *n*-BuLi in hexane dropwise over 5 min. The solution was allowed to warm to reflux temperature. After the solution had stirred for 10 min, a solution of 49.5 g (0.21 mol) of 2-chloroethyl tosylate in 125 mL of Et_2O was added over 5 min. The resulting mixture was stirred at room temperature for 18 h, washed with water, and dried over $MgSO_4$. The dried solution was filtered, and the solvent was removed in vacuo. The

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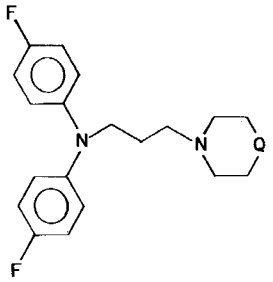
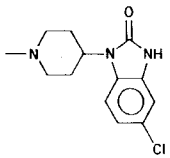
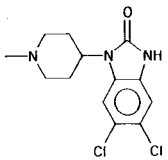
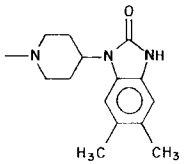
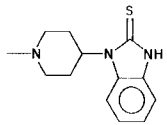
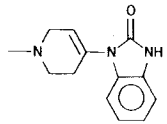
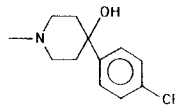
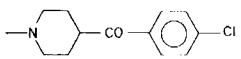
Table III. 1-[3-[Bis(4-fluorophenyl)amino]propyl]piperidines and -piperazines



compd	—N⟨Q⟩	method[a]	recrystn solvent	yield,[b] %	mp, °C	formula[c]	anal.[d]	inhib [^{3}H]-haloperidol binding,[e] %, 10^{-8} M	LAD,[f] mg/kg, ip	ED_{50}, mg/kg, po A[g]	ED_{50}, mg/kg, po B[h]
18		B	$CHCl_3$	75	201.5–203	$C_{27}H_{27}ClF_2N_4O$	C, H, N	95	>100		
19		B	EtOAc	36	212–213	$C_{27}H_{26}Cl_2F_2N_4O$	C, H, N	89	>100		
20		B	CH_3CN–$CHCl_3$	14	219–220.5	$C_{29}H_{32}F_2N_4O$	C, H, N	80	30	>16	
21			acetone	32	191–192	$C_{27}H_{28}F_2N_4S$	C, H, N	89	>100		
22		B	EtOH–H_2O	22	257–260	$C_{27}H_{28}F_2N_4O$·HCl	C, H, N	81[i]	30	5.55	105
23		B	*i*-PrOH	35	124–125	$C_{26}H_{27}ClF_2N_4O$·$C_2H_2O_4$	C,[j] H, N	74	30	4.42	
24		B	MeOH	50	201.5–203	$C_{27}H_{27}ClF_2N_2O$·$C_2H_2O_4$	C, H, N	8	>100		

25		B	*i*-PrOH	26	205–210	$C_{25}H_{27}F_2N_3$·2HCl	C, H, N	37	100				
26		B	dil HCl	41	224–226	$C_{26}H_{29}F_2N_3O$·2HCl	C, H, N	42[k]	30		5.50	160	
27		B	EtOH	54	231–232	$C_{21}H_{27}F_2N_3O$·2HCl	C, H, N	21	>100				
fluspirilene								96	≤10		1.28	10.8	
pimozide								>90[l]	30		0.20	3.06	
clozapine								25[m]	10		14.3	133	

[a-h] See footnotes a–h respectively in Table I. [i] ED_{50} = 0.32 nM. [j] C: calcd, 68.33; found, 67.92. [k] IC_{50} = 13 nM. [l] IC_{50} = 0.48 nM. [m] IC_{50} = 60.6 nM.

residual oil was chromatographed on a silical gel column (elution with cyclohexane). There was isolated 22.5 g of *N*-(2-chloroethyl)-4-fluoro-*N*-(4-fluorophenyl)benzenamine, which was used without further purification.

A mixture of 22.0 g (82.0 mmol) of the crude benzenamine, 19.0 g (82.0 mmol) of 1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one, 14.0 g (170 mmol) of $NaHCO_3$, and 10 g (67.0 mmol) of NaI in 100 mL of DMF was stirred for 40 h at 80–95 °C. The mixture was filtered, and the solvent was removed in vacuo. The oil was taken up in EtOAc and washed with water. The organic extracts were dried over anhydrous $MgSO_4$, filtered, and evaporated. TLC (EtOAc) indicated a mixture of starting materials and product. The residue was chromatographed through a silica gel column. The product was obtained by elution with toluene–methylene chloride (1:1). There was isolated 7.11 g of oil, which partially crystallized upon standing. The product was recrystallized twice from EtOAc to afford 2.97 g (7%) of 7, mp 154–156 °C. Anal. ($C_{27}H_{28}F_2N_4O$) C, H, N.

8-[4-[Bis(4-fluorophenyl)amino]butyl]-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one (8). To solution of 30.8 g (0.15 mol) of 4-fluoro-*N*-(4-fluorophenyl)benzenamine in 100 mL of toluene was added 21.1 g (0.15 mol) of 4-chlorobutanoyl chloride in one portion. The resulting solution was refluxed for 3 h after which the solvent was removed in vacuo. The residue was recrystallized from *i*-PrOH to afford 50.6 g of crude 4-chloro-*N*,*N*-bis(4-fluorophenyl)butanamide, which was used without further purification.

A solution of 8.0 g (0.06 mol) of anhydrous $AlCl_3$ in 150 mL of Et_2O was added to a suspension of 6.83 g (0.18 mol) of $LiAlH_4$ in 400 mL of THF and 175 mL of Et_2O at 10 °C. After addition was completed, the mixture was stirred for 10 min and cooled to 5 °C. To this suspension was added a solution of 50.6 g (0.16 mol) of the crude butanamide in 150 mL of Et_2O. The mixture was stirred at 5 °C for 30 min, after which the excess reducing agent was decomposed by careful addition of 9.0 mL of H_2O, 11 mL of 20% aqueous NaOH, and 4.5 mL of H_2O. The mixture was stirred overnight and filtered through Celite. The filtrate was dried over $MgSO_4$, filtered, and evaporated. The residue was chromatographed on a silica gel column (elution with toluene). There was obtained 32.8 g of crude *N*-(4-chlorobutyl)-4-fluoro-*N*-(4-fluorophenyl)benzenamine.

A mixture of 29.6 g (0.10 mol) of the butanamine, 30.2 g (0.12 mol) of 1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one, 13.4 g (0.16 mol) of $NaHCO_3$, and 6.10 g (0.04 mol) of NaI in 490 mL of DMF was heated at 80–90 °C for 22 h. The mixture was filtered and concentrated in vacuo and the residue was partitioned between EtOAc and water. The organic extracts were dried over $MgSO_4$, filtered, concentrated to ca. 150 mL, and cooled to 0 °C. There was deposited 27.7 g of crude 8, mp 158–161 °C. Recrystallization from toluene–petroleum ether afforded 25.1 g (51%) of 8, mp 159.5–160.5 °C. Anal. ($C_{29}H_{32}F_2N_4O$) C, H, N.

Pharmacological Methods. [^{3}H]Haloperidol Binding Assay.[7] The relative affinities of compounds for dopmaine receptors were evaluated on the basis of their ability to displace [^{3}H]haloperidol from striatal membranes prepared from Long–Evans hooded rats. Rats were decapitated; the brains were removed, and the corpus striata were dissected. The corpous striata were homogenized in 40 volumes of 50 mM tris buffer (pH 7.6) and centrifuged. Pellets were rehomogenized in 50 volumes of the same buffer and used for the binding assay. Incubations were carried out in 10 mL of 50 nM Tris-HCl buffer (pH 7.6) containing 2 mg/mL of original wet tissue weight of homogenate, 100 μL of test agent or solvent, and 0.6 nM of [^{3}H]haloperidol. Nonspecific binding was determined in the presence of 0.1 μM (+)-butaclamol. Samples were incubated in a reciprocating water bath at 25 °C for 40 min. Incubation was terminated by rapid filtration under reduced pressure through glass fiber filters (Whatman GF/B). The filters were rinsed three times with 10 mL of Tris-HCl buffer. The filters were placed in 10 mL of scintillation cocktail (Beckman Ready-Solv HP) and shaken for 1 h. Radioactivity retained on the filter was determined by liquid scintillation spectrophotometry. Compounds were initially evaluated at 10 nM. IC_{50}'s when determined were calculated from a nonlinear computer curve fit of the data from four or more concentrations, each done in triplicate.

Inhibition of Locomotion–Screen Falloff Test.[8] Nine unfasted Swiss–Webster male mice (Buckberg Laboratories) weighing

20–30 g were equally divided into three groups for each drug dose to be tested; that is, data for each dose level was generated by three separate groups of three mice each. Treatments were administered intraperitoneally 1 h prior to testing. All dosages were calculated as parent compound and were given in volumes of 10 mL/kg. Compounds were dissolved or suspended in 0.2% methocel. Control animals were injected with methocel. A two-part testing procedure was started 1 h postinjection. First the screen test was performed. The test consisted of placing mice on individual wire screens, which were rotated 180 ° at the start of a 60-s observation period. The number of mice falling off the inverted screen was recorded. Immediately following the screen test, the animals were tested for inhibition of locomotion. Each group of mice was placed in an actophotometer. The actophotometer consisted of a cylinderical chamber whose center containing the illumination of six photocells located on the perimeter of the chamber. Six light beam interruptions equaled one count. Locomotor activity was recorded by computer at 10-min intervals for 60 min. Data obtained from the screen test was expressed as percent of mice falling off the screen. Data derived from the locomotor activity of drug-treated mice were compared to the activity of vehicle-treated animals and were expressed as percent inhibition of spontaneous locomotion. All percentages for inhibition of locomotion were based upon data accumulated for 1 h. Both phases of testing were graded: A = 60–100%; C = 31–59%; N = 0–30%. An overall rating of A resulted from a A rating in inhibition of locomotion and either a C or N rating in screen falloff. A C rating resulted from an A rating in both of a C rating in locomotion and a C or N rating in the screen portion. All other combinations resulted in a N rating.

Suppression of High Base-Line Self-Stimulation.[9] Adult male hooded (Long–Evans) rats were implanted with permanent electrodes in the medial forebrain bundle of the posterior hypothalamus. After the animals recovered from surgery, they were trained in a Skinner box to press a lever to stimulate their own brains electrically (40 A, 0.4 s). The animals soon became expert at self-stimulation. The rapid response rates generated by these conditions served as behavioral base lines. Compounds were administered orally. During all tests the self-stimulation behavior of the animals was continuously recorded graphically on cumulative recorders. A compound was considered active if the base-line rates of self-stimulation were reduced by at least 50% for 1.5 h or more by the agent. Four rats were run for each dose level; ED_{50} dose levels were calculated by linear regression analysis.

Catalepsy Test.[10] Male Long–Evans hooded rats (180–200 g) were used one time for each compound tested. Drugs were given by oral intubation, and if insoluble, the compounds were suspended with 0.2% methylcellulose. A group of 24 animals was fasted overnight, and after dosing, two animals were placed in each rat cage. Tails were marked to identify the individual rat. At least three doses of the agent were administered to the rats and eight animals were used for each dose level. The rats were checked every 30 min for the first hour and then hourly for 6 h. If necessary, a 24-h reading was made. The animals were tested for catalepsy by placing their forepaws on a horizontal metal rod 11.5 cm above the table top and their hindpaws on the table top. An animal was considered fully cataleptic (scored as 1.0) if it maintained this abnormal position on the bar for 30 s. Partial catalepsy (scored 0.5) resulted when a rat remained on the rod from 20 to 29 s. A minimum of three attempts was made to obtain catalepsy. The maximum number of rats considered cataleptic at any one time for each dose was used to determine the ED_{50}. Partial catalepsy scores were summed and rounded off to the highest whole number. The ED_{50}'s were obtained by a nonlinear regression analysis.

Acknowledgment. We thank Dr. F. A. MacKellar and his associates for the microanalyses and spectral data and also Dr. F. M. Hershenson for his support and timely suggestions.

Registry No. **6**, 80120-14-5; **7**, 95017-48-4; **8**, 95017-49-5; **9**, 95017-50-8; **10**, 95017-51-9; **11**, 80119-34-2; **12**, 80119-49-9; **13**, 95017-52-0; **14**, 95017-53-1; **14**·HCl, 80119-37-5; **15**, 95017-54-2; **16**, 95017-55-3; **16**·HCl, 80119-41-1; **17**, 95017-56-4; **17**·HCl, 80119-39-7; **18**, 95017-57-5; **19**, 95017-58-6; **20**, 80119-53-5; **21**, 80119-36-4; **22**, 95044-84-1; **22**·HCl, 80119-35-3; **23**, 80119-59-1; **24**, 80120-09-8; **25**, 95017-59-7; **25**·2HCl, 80119-96-6; **26**, 95017-60-0; **26**·2HCl, 80119-95-5; **27**, 95017-61-1; **27**·2HCl, 80129-17-5; (4-chlorophenyl)(4-piperidinyl)methanone, 53220-41-0; 5-chloro-1,3-dihydro-1-(4-piperidinyl)-2*H*-benzimidazol-2-one, 53786-28-0; 5,6-dichloro-1,3-dihydro-1-(4-piperidinyl)-2*H*-benzimidazol-2-one, 58859-51-1; 1,3-dihydro-5,6-dimethyl-1-(4-piperidinyl)-2*H*-benzimidazol-2-one, 80119-44-4; 1,3-dihydro-1-(1,2,3,6-tetrahydro-4-pyridinyl)-2*H*-benzimidazol-2-one, 2147-83-3; 4-fluoro-*N*-phenylbenzenamine, 330-83-6; 4-fluorobenzenamine, 371-40-4; 1-bromo-4-fluorobenzene, 460-00-4; 3-chloropropyl tosylate, 632-02-0; *N*-(3-chloropropyl)-4-fluoro-*N*-phenylbenzenamine, 80119-48-8; 1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one, 1021-25-6; 3-chloropropanoyl chloride, 625-36-5; 3-chloro-*N*,*N*-bis(4-fluorophenyl)propanamide, 95017-62-2; 3-bromopropanoyl bromide, 7623-16-7; 3-bromo-*N*,*N*-bis(4-fluorophenyl)propanamide, 95017-63-3; *N*-(3-chloropropyl)-4-fluoro-*N*-(4-fluorophenyl)-benzenamine, 80119-31-9; 2-chloroethyl tosylate, 80-41-1; *N*-(2-chloroethyl)-4-fluoro-*N*-(4-fluorophenyl)benzenamine, 95017-64-4; 4-chlorobutanoyl chloride, 4635-59-0; 4-chloro-*N*,*N*-bis(4-fluorophenyl)butanamide, 95017-65-5; *N*-(4-chlorobutyl)-4-fluoro-*N*-(4-fluorophenyl)benzenamine, 95017-66-6.