to allow color development. Diethyl N-(p-aminobenzyl)-L-glutamate (3) gave an intense purple color under these conditions and was used as the positive control, whereas with methotrexate and diethyl N-(p-nitrobenzyl)-L-glutamate (4) the solution remained practically colorless. With aminopterin a faint purple color was observed, which probably represented contamination by a trace of N-(p-aminobenzoyl)-L-glutamic acid. Compounds 1, 9, and 10 all gave only a faint violet tinge intermediate between methotrexate and aminopterin and were thus judged to lack a diazotizable amino group.

Biological Testing. Cytotoxicity assays in 48-h cultures were performed as previously described.[8] Dihydrofolate reductase inhibition was determined spectrophotometrically at 340 nm against *Lactobacillus casei* enzyme (New England Enzyme Center, Boston, MA) and by competitive [^{3}H]methotrexate binding against partially purified L1210 leukemic cell enzyme as reported earlier.[7,8] In vivo antitumor tests were conducted according to NCI protocols.[23]

Acknowledgment. This work was supported in part by Grants CA25394 and CA19589 from the National Cancer Institute, National Institutes of Health, DHHS. The authors acknowledge the technical assistance of Linda Anderson and Carol Ginty in carrying out in vivo antitumor assays and in vitro enzyme inhibition experiments. Cell culture data were kindly provided by Dr. Michael Wick.

(23) Geran, R. I.; Greenberg, N. H.; Macdonald, M. M.; Schumacher, A. M.; Abbott, B. J. *Cancer Chemother. Rep., Part 3* **1972**, *3*(3), 1.

2-Amino-6-chloro-4-(*N*-methylpiperazino)pyrimidines, Inhibitors of Spiroperidol Binding

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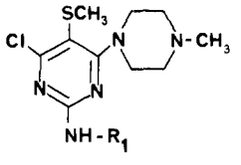
A series of 30 6-chloro-2,4-diaminopyrimidines was synthesized and tested in vitro as inhibitors of [^{3}H]spiroperidol binding. The affinity for the dopamine receptor was shown to be related to the 6-chloro-4-(*N*-methylpiperazine)pyrimidine structure bearing a NH_2 or NHR_1 group as a substituent in position 2, provided that R_1 was not an α branched alkyl group. The nature of the substituent in position 5 is also of importance for the affinity; 2-(benzylamino)-6-chloro-4-(*N*-methylpiperazino)-5-(methylthio)pyrimidine (**22**) is the most active member of the series. Molecular structures of three compounds were analyzed by X-ray diffraction and PCILO computation.

A prior communication[1] described the synthesis and the pharmacological activities of a number of 5-(methylthio)-4-piperazinopyrimidines. Two of them, mezilamine (1) and UK-177 (**22**), were shown to be dopamine (DA)

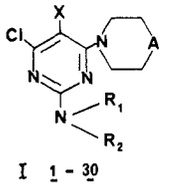


1, $R_1 = CH_3$, mezilamine

22, $R_1 = CH_2-C_6H_5$, UK-177

antagonists and potential antipsychotic drugs.[2-4] Although these compounds fall into the Janssen definition,[5] they do not seem to be related to any well-established class of neuroleptics.

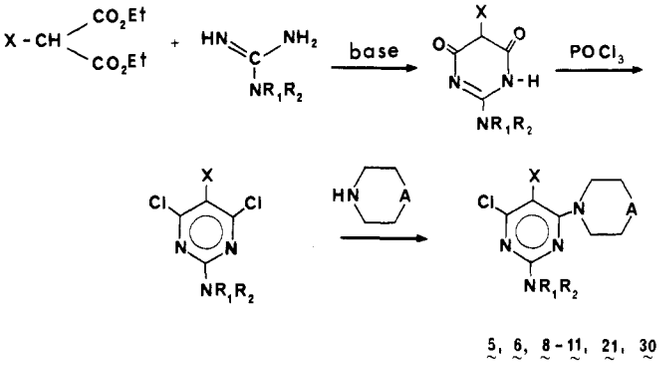
The atypical structure of 4-piperazinopyrimidines prompted us to synthesize a series of mezilamine analogues (I). In the present report we describe the synthesis of



I **1**–**30**

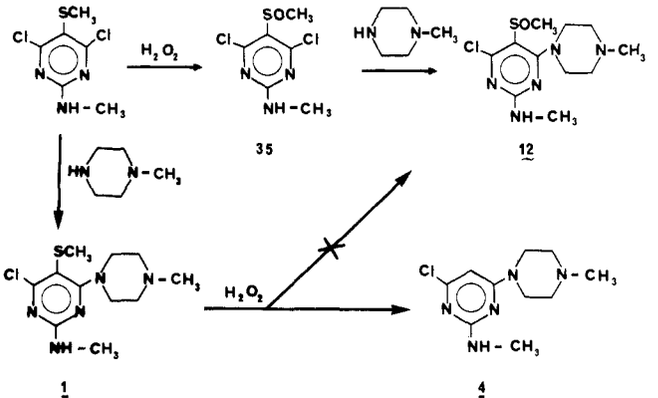
these derivatives (listed in Table I) and their effects on the binding of [^{3}H]spiroperidol. The molecular structures of two active compounds (1 and **22**) and of one inactive

Scheme I



5, **6**, **8**–**11**, **21**, **30**

Scheme II



1 **4**

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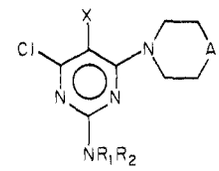
Table I. Physical and Biological Data of 2-Amino-6-chloropyrimidine Derivatives

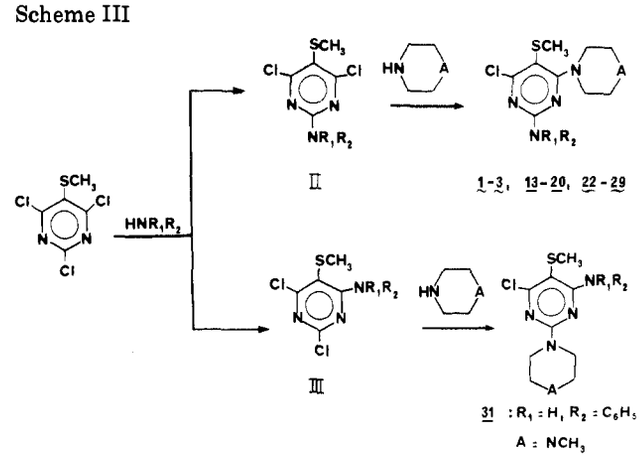


compd	X	R_1	R_2	A	formula	mp, °C	crystn solvent	inhibn of [^{3}H]-spiro-peridol binding: K_i, nM	95% CL
1	SCH_3	CH_3	H	NCH_3	$C_{11}H_{18}ClN_5S\cdot HCl$	>260	EtOH	40	22-65
2	SCH_3	CH_3	H	O	$C_{10}H_{15}ClN_4OS$	139	EtOH-H_2O (2:1)	20 000	12 500-49 000
3	SCH_3	CH_3	H	CH_2	$C_{11}H_{17}ClN_4S$	124	EtOH-H_2O (1:1)	40 000	19 300-62 600
4	H	CH_3	H	NCH_3	$C_{10}H_{16}ClN_5$	118	cyclohexane	1 600	882-2 300
5	CH_3	CH_3	H	NCH_3	$C_{11}H_{18}ClN_5\cdot 2HCl$	>260	MeOH	480	233-640
6	C_2H_5	CH_3	H	NCH_3	$C_{12}H_{20}ClN_5\cdot 2HCl$	>260	MeOH	640	449-950
7	Br	CH_3	H	NCH_3	$C_{10}H_{15}BrClN_5$	158	AcOEt	72	49-102
8	Cl	CH_3	H	NCH_3	$C_{10}H_{15}Cl_2N_5$	149	AcOEt	140	80-218
9	OCH_3	CH_3	H	NCH_3	$C_{11}H_{18}ClN_5O\cdot HCl$	>260		3 000	1 455-4 322
10	OC_2H_5	CH_3	H	NCH_3	$C_{12}H_{20}ClN_5O$	154	EtOH	800	412-1 256
11	SC_2H_5	CH_3	H	NCH_3	$C_{12}H_{20}ClN_5S$	124	MeOH-H_2O (2:1)	20	9-32
12	$SOCH_3$	CH_3	H	NCH_3	$C_{11}H_{18}ClN_5OS$	223	EtOH	22 000	11 900-51 500
13	SCH_3	CH_3	CH_3	NCH_3	$C_{12}H_{20}ClN_5S\cdot HCl$	163	EtOH	1 000	491-1 413
14	SCH_3	H	H	NCH_3	$C_{10}H_{16}ClN_5S\cdot HCl$	>260	EtOH	120	58-210
15	SCH_3	C_2H_5	H	NCH_3	$C_{12}H_{20}ClN_5S\cdot HCl$	232	EtOH	34	16-52
16	SCH_3	n-C_3H_7	H	NCH_3	$C_{13}H_{22}ClN_5S\cdot HCl$	120	EtOH	100	48-149
17	SCH_3	i-C_3H_7	H	NCH_3	$C_{13}H_{22}ClN_5S$	145	EtOH	8 000	3 495-11 435
18	SCH_3	n-C_4H_9	H	NCH_3	$C_{14}H_{24}ClN_5S$	87	EtOH	32	14-50
19	SCH_3	t-C_4H_9	H	NCH_3	$C_{14}H_{24}ClN_5S$	157	EtOH	40 000	19 800-64 500
20	SCH_3	n-C_6H_{13}	H	NCH_3	$C_{16}H_{22}ClN_5S$	67	EtOH	140	77-223
21	SCH_3	C_6H_5	H	NCH_3	$C_{16}H_{20}ClN_5S\cdot HCl$	246	H_2O	52	24-74
22	SCH_3	$CH_2C_6H_5$	H	NCH_3	$C_{17}H_{22}ClN_5S$	123	EtOH	5	2-7
23	SCH_3	$CH_2CH_2C_6H_5$	H	NCH_3	$C_{18}H_{24}ClN_5S\cdot HCl$	228	EtOH	16	7-23
24	SCH_3	CH_2(4-F-C_6H_4)	H	NCH_3	$C_{17}H_{21}ClFN_5S$	143	EtOH	23	10-36
25	SCH_3	CH_2(4-OCH_3-C_6H_4)	H	NCH_3	$C_{18}H_{24}ClN_5OS$	112	EtOH	16	8-27
26	SCH_3	CH_2(2-Cl-C_6H_4)	H	NCH_3	$C_{17}H_{21}Cl_2N_5S$	120	EtOH	117	55-174
27	SCH_3	CH_2(4-t-Bu-C_6H_4)	H	NCH_3	$C_{21}H_{30}ClN_5S$	110	EtOH	385	201-548
28	SCH_3	CH_2(4-Cl-C_6H_4)	H	NCH_3	$C_{17}H_{21}Cl_2N_5S$	124	EtOH	18	7-30
29	SCH_3	CH_2(2-OCH_3-C_6H_4)	H	NCH_3	$C_{18}H_{24}ClN_5OS$	124	EtOH	185	91-282
30	OCH_3	$CH_2C_6H_5$	H	NCH_3	$C_{17}H_{22}ClN_5O\cdot HCl$	232	H_2O	44	21-68
haloperidol								2	0.5-4
chlorpromazine								14	7-25
clozapine								320	170-581
sulpiride								1 600	883-2 252

compound (**17**) were analyzed by X-ray diffraction and PCILO computation. Requirements for DA receptor affinity are discussed.

Chemistry. Scheme I shows the classical synthetic route[6] used for the preparation of **5**, **6**, **8–11**, **21**, and **30**, starting from substituted diethyl malonates and the appropriate guanidine derivatives. In our experimental conditions, condensation of diethyl bromomalonate with methylguanidine did not yield the required 5-bromo-4,6-dihydroxy-2-(methylamino)pyrimidine. Therefore, **7** was prepared by aqueous bromine treatment of the methylthio analogue **1**, as previously described.[7]

Scheme III



Sulfoxide **12** was obtained as shown in Scheme II. Treatment of **1** in acetic acid by hydrogen peroxide did not give **12** but the demethylthio compound **4**.[8] To obtain **12**, the methylthio group had to be oxidized before intro-

(1) Mattioda, G.; Obellianne, P.; Gauthier, H.; Loiseau, G.; Millischer, R.; Donadieu, A. M.; Mestre, M. *J. Med. Chem.* **1975**, *18*, 553.
(2) Uzan, A.; Le Fur, G.; Mitrani, N.; Kabouche, M.; Donadieu, A. M. *Life Sci.* **1978**, *23*, 261.
(3) Le Fur, G.; Mizoule, J.; Rataud, J.; Uzan, A. *Eur. J. Pharmacol.* **1979**, *58*, 359.
(4) Le Fur, G.; Guilloux, F.; Uzan, A. *Biochem. Pharmacol.* **1980**, *29*, 267.
(5) Janssen, P. A. J. "Structure–Activity Relationships"; Pergamon Press: New York, 1973; Vol. I, Chapter 2.
(6) Brown, D. J. "The Pyrimidines"; Interscience: New York, 1962; Supplement I, 1970.
(7) Mattioda, G.; Rocquet, F. French Patent 2 311 776, 1978.
(8) Barieux, J. J.; Mattioda, G.; Rocquet, F., unpublished results.

Table II. Final Positions ($\times 10^4$) with Estimated Standard Deviations in Parentheses, Derived from the Block-Diagonal Least-Squares Refinement for 1

atoms	x	y	z	atoms	x	y	z
C(1)	−4016 (2)	1329 (2)	−3041 (1)	N(10)	1188 (2)	3799 (2)	−2013 (1)
N(2)	−5394 (2)	1932 (2)	−3817 (1)	C(11)	1147 (3)	2323 (2)	−1673 (2)
C(3)	−7048 (2)	1165 (2)	−4313 (1)	C(12)	−499 (2)	1332 (2)	−2531 (2)
N(4)	−7435 (2)	−242 (2)	−4164 (1)	S(13)	−2852 (1)	−787 (1)	−1481 (0)
C(5)	−6074 (2)	−770 (2)	−3356 (2)	C(14)	−2739 (4)	889 (3)	−260 (2)
C(6)	−4336 (2)	−64 (2)	−2693 (2)	Cl(15)	−6609 (1)	−2561 (1)	−3133 (1)
N(7)	−2338 (2)	2170 (2)	−2549 (1)	N(16)	−8457 (2)	1828 (2)	−5055 (1)
C(8)	−2305 (3)	3684 (2)	−2856 (2)	C(17)	−8232 (3)	3357 (3)	−5249 (2)
C(9)	−609 (3)	4628 (2)	−1988 (2)	C(18)	2839 (3)	4710 (3)	−1236 (2)

ducing the piperazinic substituent.

Most of the methylthio derivatives (**1–3**, **13–20**, and **22–29**) were prepared from 5-(methylthio)-2,4,6-trichloropyrimidine,[1] according to Scheme III. Condensation of primary or secondary amines (R_1R_2NH) with 5-(methylthio)-2,4,6-trichloropyrimidines yielded a mixture of isomers II and III bearing the amino substituent in position 2 or 4, respectively. The assigned structures for II and III were based upon ^{13}C NMR data as previously published, [C(4) and C(6) being equivalent for II and nonequivalent for III].[1] In most cases, one or several crystallizations of the mixture yielded the required isomer II, the condensation of which with piperidine, morpholine, or *N*-methylpiperazine gave I. However, with $R_1R_2NH = C_6H_5NH_2$, recrystallization of the crude product gave III, the condensation of which with *N*-methylpiperazine yielded **31**. Therefore, the required isomer **21** was obtained from diethyl methylthiomalonate and phenylguanidine according to the method shown in Scheme I. This nonambiguous synthesis of **21** led us to rectify the structure previously assigned to the compound obtained by Mattioda et al.[1] starting from 5-(methylthio)-2,4,6-trichloropyrimidine and aniline. Actually, the compound numbered **7** in their paper is 6-chloro-2-(*N*-methylpiperazino)-5-(methylthio)-4-(phenylamino)pyrimidine (**31**).

Spiroperidol Receptor Binding Study. Compounds **1–30** were evaluated in vitro in a DA receptor binding assay for their ability to displace [^3H]spiroperidol, as described under Experimental Section. The results are shown in Table I.

Starting from mezilamine (**1**), replacement of *N*-methylpiperazine by morpholine (**2**) or piperidine (**3**) gave inactive compounds. Replacement of the methylamino group by the dimethylamino group resulted in a substantial decrease in affinity. Therefore, the affinity for the DA receptor was considered to be related to the 6-chloro-4-(*N*-methylpiperazino)pyrimidine structure bearing a primary or a secondary amino group as a substituent in position 2.

Replacement of the methylthio group of mezilamine by different X substituents (**4–12**) led to a series with activity varying over a very large range: SC_2H_5 (K_i = 20 nM) > SCH_3 > Br > Cl > CH_3 > C_2H_5 > OC_2H_5 > H > OCH_3 ≫ $SOCH_3$ (K_i = 22 000 nM).

Replacement of the methylamino group of **1** by NH_2 or NHR_1 (**14–21**) did not substantially affect the activity, provided that R_1 was not an α branched alkyl group. Branched R_1 alkyl groups, such as *i*-C_3H_7 (**17**) or *t*-C_4H_9 (**19**), led to a dramatic decrease of affinity. The phenyl derivative (**21**) is approximately as active as **1**, but replacement of the methylamino group of **1** by benzylamino (**22**) or phenethylamino (**23**) induced an important increase of affinity. Likewise, in the methoxy series, replacement of the methylamino group by the benzylamino group strongly increased the affinity, **30** being 60 times better than **9**. Attempts to optimize the binding affinity of **22** by introducing substituents in the phenyl ring (**25–29**) did not give any significant improvement.

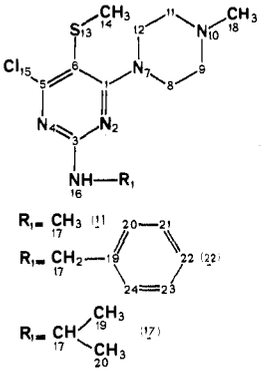


Figure 1. Numbering of atoms.

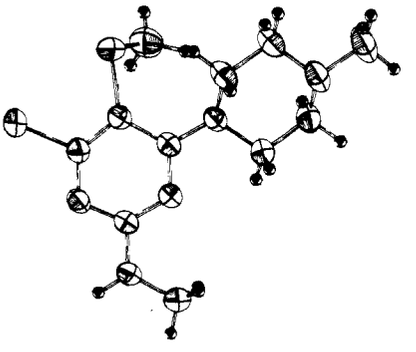


Figure 2. ORTEP drawing of **1**.

The nature of the NHR_1 group seems to be the most critical factor for the potency of binding affinity, at least for the 5-methylthio derivatives. An important parameter may be the steric hindrance in the vicinity of the nitrogen atom rather than the volume occupied by the R_1 group. This hypothesis could account for the low affinity of isopropyl and *tert*-butyl derivatives **17** and **19**. A preliminary quantitative study of **1**, **17**, and **22** using the SURVOL program[24] showed the nitrogen accessibility surface is minimal with **17**.

Furthermore, the high degree of affinity shown by **22** and **23** suggests that the phenyl ring of the benzyl or phenethyl group is a possible additional binding site for these molecules.

Conformational Analysis of 1, 17, and 22. X-ray Crystallography. The solid-state conformations of the three molecules were solved by single-crystal X-ray analysis. In discussing the conformations, we shall make use of our standardized crystallographic numbering of atoms (Figure 1). ORTEP[9] drawings of the molecules showing the non-hydrogen atoms with ellipsoids of thermal

(9) Johnson, C. K. "ORTEP", Oak Ridge National Laboratory: Oak Ridge, TN, 1965, Report ORNL-3794.

Table III. Final Positions ($\times 10^4$) with Estimated Standard Deviations in Parentheses, Derived from Block-Diagonal Least-Squares Refinement for 17

atoms	x	y	z	atoms	x	y	z
C(1)	−1022 (2)	−3455 (2)	−5642 (2)	C(11)	397 (2)	−1454 (3)	−7109 (3)
N(2)	−1044 (1)	−3208 (2)	−4412 (2)	C(12)	65 (2)	−2771 (3)	−7380 (3)
C(3)	−1905 (2)	−3217 (2)	−3830 (2)	S(13)	−1855 (1)	−4300 (1)	−7909 (1)
N(4)	−2752 (1)	−3437 (2)	−4406 (2)	C(14)	−2167 (3)	−5919 (3)	−7742 (4)
C(5)	−2690 (2)	−3704 (2)	−5602 (3)	Cl(15)	−3793 (0)	−4027 (1)	−6327 (1)
C(6)	−1860 (2)	−3774 (2)	−6330 (2)	N(16)	−1936 (2)	−2942 (2)	−2593 (2)
N(7)	−121 (1)	−3446 (2)	−6191 (2)	C(17)	−1085 (2)	−2699 (3)	−1829 (3)
C(8)	705 (2)	−3386 (3)	−5346 (3)	C(18)	1538 (2)	−149 (3)	−6031 (4)
C(9)	1013 (2)	−2062 (3)	−5077 (3)	C(19)	−589 (3)	−3882 (4)	−1404 (4)
N(10)	1222 (1)	−1430 (2)	−6271 (2)	C(20)	−1368 (2)	−1897 (3)	−696 (3)

Table IV. Final Positions ($\times 10^4$) with Estimated Standard Deviations in Parentheses, Derived from the Block-Diagonal Least-Squares Refinement for 22

atoms	x	y	z	atoms	x	y	z
C(1)	3924 (3)	205 (6)	4121 (1)	S(13)	1238 (1)	1168 (2)	4332 (0)
N(2)	4967 (3)	387 (5)	4224 (1)	C(14)	1114 (4)	3643 (8)	3982 (1)
C(3)	4973 (3)	2124 (6)	4511 (1)	Cl(15)	1671 (1)	5451 (2)	4917 (0)
N(4)	4003 (2)	3804 (5)	4710 (1)	N(16)	6041 (3)	2317 (6)	4610 (1)
C(5)	2956 (3)	3457 (6)	4627 (1)	C(17)	7056 (3)	444 (7)	4462 (1)
C(6)	2790 (3)	1705 (6)	4340 (1)	C(18)	6861 (5)	−731 (10)	2469 (1)
N(7)	4003 (3)	−1569 (5)	3812 (1)	C(19)	8033 (3)	628 (6)	3970 (1)
C(8)	5155 (4)	−3201 (7)	3647 (1)	C(20)	8048 (4)	2512 (8)	3686 (1)
C(9)	6260 (4)	−2186 (8)	3232 (1)	C(21)	8965 (4)	2521 (10)	3235 (2)
N(10)	5807 (3)	−1744 (6)	2868 (1)	C(22)	9871 (5)	652 (11)	3070 (2)
C(11)	4676 (4)	−129 (8)	3028 (1)	C(23)	9858 (5)	−1204 (10)	3357 (2)
C(12)	3561 (4)	−1146 (8)	3445 (1)	C(24)	8949 (4)	−1216 (8)	3804 (2)

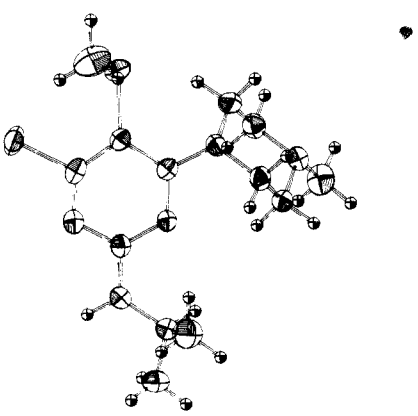


Figure 3. ORTEP drawing of **17**.

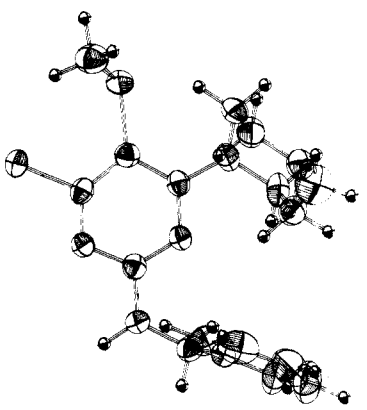


Figure 4. ORTEP drawing of **22**.

vibration are depicted in Figures 2–4. The final coordinates for non-hydrogen atoms with their standard deviations are listed in Tables II–IV. Sufficient torsion angles for the construction of accurate molecular models are given in Table V. In all three molecules, the piperazine ring is in a chair conformation with an almost exact mirror plane passing through N(7) and N(10). However, in **17** and **22**, the pyrimidine ring is in an axial orientation relative to the piperazine ring, and the lone pairs on N(7) and N(10) are cis to one another. In **1**, the pyrimidine ring is equatorally oriented relative to the piperazine ring, and the lone pairs on N(7) and N(10) are orthogonal to one another. The dihedral angle between the plane of the pyrimidine and the basic plane of the piperazine (defined as the obtuse angle subtended by the plane normals) is 149° in **1**, 97° in **22**, and 100° in **17**. With N(10) being protonated in the salt forms, its distances from the plane of the pyrimidine and from π (center of the pyrimidine ring) have been calculated: 0.652 (2) and 5.59 (1) Å in **1**, 2.244 (3) and 5.05 (1) Å in **22**, 2.040 (2) and 5.01 (1) Å in **17**. The position of the pyrimidine ring with respect to that of the piperazine ring is defined by a torsion angle ϑ = 6-1-7-8 which is −171° in **1**, −173° in **22**, and −166° in **17**. The position of the

Table V. Sufficient Torsion Angles to Describe the Molecular Conformations

	torsion angle, deg		
	1	22	17
6-1-7-8	−171	−173	−166
4-5-6-13	170	170	173
5-6-13-14	−120	80	−67
4-3-16-17	178	172	179
3-16-17-19		80	−80
3-16-17-20			155
16-17-19-20		5	
1-7-8-9	164	−90	−90
12-7-8-9	−56	57	55
7-8-9-10	58	−57	−57
8-9-10-11	−60	57	57
9-10-11-12	60	−57	−57
10-11-12-7	−58	58	55
11-12-7-8	56	−56	−53
8-9-10-18	177	179	−179

S-CH_3 group is characterized by the two torsion angles 4-5-6-13 and 5-6-13-14, which are 170 and −120° in **1**, 170 and 80° in **22**, and 173 and −67° in **17**. Finally, the position of the R_1 group is defined by a torsion angle ψ = 4-3-16-17,

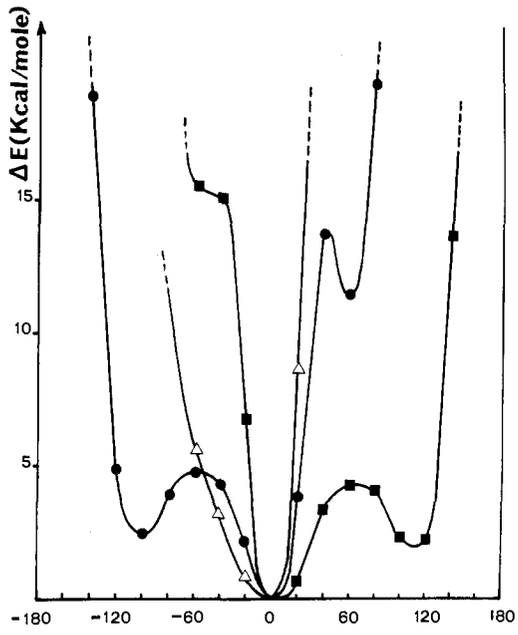


Figure 5. Potential energy curves: (△) 1, (●) 17, (■) 22.

which is 178° in 1, 172° in **22**, and 179° in **17**.

PCILO Calculations. The PCILO method, being successfully used in the prediction of the conformation of a wide variety of biomolecules,[10] is particularly well suited for our series. The calculations were carried out with 20° increments for the rotation around the bond connecting the piperazine and the pyrimidine ring systems. The potential energy curves for the three molecules are depicted in Figure 5. It is clear that the energetically favored conformation for each molecule virtually coincides with the experimental conformation ($\Delta\vartheta = 0$). In **22**, a secondary minimum about 2.0 kcal/mol above the absolute is found at 110° removed from the absolute minimum; i.e., $\vartheta = -63°$. In **17**, a secondary minimum about 2.5 kcal/mol above the absolute is found at 100° removed from the absolute minimum; i.e., $\vartheta = -66°$. [The secondary minimum in **22** and **17** corresponds to the conformation in which the alternate piperazine ring bond N(7)–C(12) is antiperiplanar to the C(1)–C(6) bond.] This result indicates that in both molecules there are two possible conformations, the first one with $\vartheta \simeq 180°$ and the second one with $\vartheta \simeq -60°$. In contrast, 1 exists under a single conformation corresponding to a value of ϑ close to 180°. This is due to the large steric hindrance between the methyl group substituting S(13) and the piperazine ring (Figure 2). Bear in mind that the torsion angle 5-6-13-14 is −120° in 1 instead of 80 and −67° in **22** and **17**, respectively. In fact, since the C(14)-methyl position would vary in conformation as the piperazine ring is rotated around the C(1)–N(7) bond, in solution 1 would also exist under the conformation corresponding to $\vartheta \simeq -60°$.

Comparison with Clozapine. Among known neuroleptics only clozapine,[11] a semirigid neuroleptic drug, seems to exhibit some structural similarities with 4-piperazinopyrimidines (Figure 6). In order to find a common figure, it seems worthwhile to compare the distances d_1 [N-(10)–middle of C(5)–C(6)], d_2 [N(2)–N(10)], and d_3 [distance of N(10) from the plane of the pyrimidine ring (plane I)] with the corresponding distances for clozapine, as shown in Figure 6. The results are listed in Table VI.

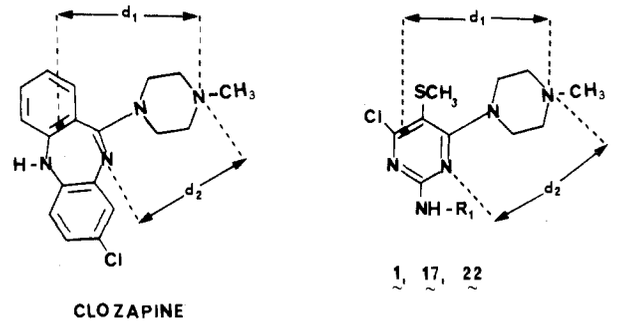


Figure 6. Comparison between clozapine and 4-piperazinopyrimidines.

Table VI. Conformational Parameters

drugs	conformation	d_1,[c] Å	d_2,[c] Å	d_3, Å, N(10)/plane I[d]
clozapine	I[a]	5.64	4.97	0.48
	II[b]	5.65	4.93	0.48
1		5.83	4.89	0.66
17	I[a]	5.50	4.20	2.04
	II[b]	5.57	4.04	1.58
22	I[a]	5.43	4.24	2.24
	II[b]	5.55	4.04	1.67

[a] Favored conformation found by X-ray analysis and by quantum mechanical study (clozapine[12]). [b] Less preferred conformation found by quantum mechanical study. [c] See Figure 6. [d] Plane I is the plane of the pyrimidine ring in our molecules and the plane defined by the corresponding atoms of C(1), N(2), C(6), and N(7) in clozapine.

Because the pyrimidine is equatorial to the piperazine in 1 (just as the tricyclic group is in clozapine), a good agreement is found between 1 and clozapine in d_1, d_2, and d_3 values. As the pyrimidine is axially oriented relative to the piperazine in **17** and **22**, only the d_1 values tally with that found in 1 and clozapine. From these results, it seems that the equatorial or axial orientation of the pyrimidine substituents on the piperazine could be relevant to activity. The similarity between 1 and clozapine suggests that the equatorial orientation corresponds to the active conformation. However, it does not explain the activity of **22** and the lack of activity of **17**, this difference in activity being merely due to be the steric requirements of the receptor near the nitrogen atom of the NHR_1 group.

Experimental Section

Chemistry. Melting points were determined on a Kofler hot stage. NMR spectra were recorded on a Varian T-60 or JEOL-90 spectrometer; 70–230 mesh silica gel was used for column chromatography. The purity of compounds was checked by TLC analysis on silica gel GF plates, and components were visualized by UV fluorescence properties. All compounds exhibited proper spectral characteristics and were homogeneous by TLC analysis. Microanalysis results on new compounds are within ±0.4% of the theoretical values unless otherwise indicated.

The previously known pyrimidines 1,[1] **7**,[7] **14–20**, and **22**[13] were synthesized by literature procedures; melting points and crystallization solvents are reported in Table I.

6-Chloro-2-(methylamino)-5-(methylthio)-4-morpholinopyrimidine (2). 4,6-Dichloro-2-(methylamino)-5-(methylthio)-

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(13) Obellianne, P.; Carbonnel, P.; Loiseau, G.; Millischer, R. French Patent 2 173 746, 1975. Loiseau, G.; Mattioda, G.; Millischer, R.; Obellianne, P. French Patent 2 257 294, 1977. Loiseau, G.; Mattioda, G.; Millischer, R.; Obellianne, P. French Patent 2 281 117, 1978.

pyrimidine[14] (11.2 g, 0.05 mol), morpholine (13.05 g, 0.15 mol), and toluene (250 mL) were refluxed for 1 h. After the solution was cooled and evaporated to dryness, the residue was purified by chromatography on silica gel (700 g), eluting with toluene–MeOH (9:1). Crystallization from EtOH–H_2O (2:1) gave **2** (8.7 g, 63%), mp 139 °C. Anal. ($C_{10}H_{15}N_4ClOS$) C, H, N.

6-Chloro-2-(methylamino)-5-(methylthio)-4-piperidinopyrimidine (3). This compound was prepared as above: from 4,6-dichloro-2-(methylamino)-5-(methylthio)pyrimidine (11.2 g, 0.05 mol) and piperidine (12.8 g, 0.15 mol) **3** was obtained in 42% yield (5.8 g), mp 124 °C. Anal. ($C_{11}H_{17}N_4ClS$) C, H, N.

6-Chloro-2-(methylamino)-4-(*N*-methylpiperazino)pyrimidine (4). H_2O_2 (44.7 mL), 30% was added to a cooled solution (13 °C) of **1** (43.8 g, 0.15 mol) in AcOH (300 mL). The mixture was stirred for 2 h without cooling (the reaction temperature rose to 80 °C); after cooling (cold water bath), the mixture was stirred overnight, then poured into ice–water, made alkaline with 10 N NaOH (750 mL), and extracted with Et_2O (3 × 700 mL). The organic phase was washed with H_2O (2 × 700 mL) and evaporated in vacuo. Cyclohexane (160 mL) was added to the residue, and the mixture was heated to reflux; an insoluble oil was discarded, and the hot solution was filtered. After standing at room temperature, **4** was collected (15.4 g, 32%), mp 118 °C. Anal. ($C_{10}H_{16}N_5Cl$) C, H, N.

6-Chloro-5-methyl-2-(methylamino)-4-(*N*-methylpiperazino)pyrimidine Dihydrochloride (5). Methylguanidine hydrochloride (27.5 g, 0.25 mol) and diethyl methylmalonate (43.5 g, 0.25 mol) were added to a solution of EtONa in EtOH obtained by dissolving Na (11.5 g, 0.5 mol) in EtOH (600 mL). The mixture was refluxed for 5 h, cooled, and poured into H_2O (1 L). AcOH (100 mL) was added, and the resultant precipitate was filtered off and dried [crude 4,6-dihydroxy-5-methyl-2-(methylamino)-pyrimidine as white crystals, 25 g]. This compound was turned into its dichloro derivative by heating with $POCl_3$ (100 mL) for 3 h at reflux. After cooling, the mixture was poured into 310 mL of NH_4OH (*d* 0.90) containing 750 g of ice and extracted with $CHCl_3$ (2 × 250 mL). The organic layer was washed with H_2O and evaporated to dryness to give 4,6-dichloro-5-methyl-2-(methylamino)pyrimidine (**32**; 12.3 g, 25%). After crystallization from cyclohexane, an analytical sample melted at 185 °C. Anal. ($C_6H_7N_3Cl_2$) C, H, N, Cl.

Compound **32** (11.5 g, 0.06 mol), *N*-methylpiperazine (12 g, 0.12 mol), K_2CO_3 (4.2 g) in H_2O (7.5 mL) and methyl ethyl ketone (MEK; 200 mL) were refluxed for 8 h. After cooling to room temperature, the mixture was filtered and evaporated in vacuo; the residue was chromatographed on silica gel (800 g), eluting with toluene–diethylamine (9:1). It was converted to the dihydrochloride, and recrystallization from MeOH gave **5** (8.4 g, 44%), mp >260 °C. Anal. ($C_{11}H_{18}N_5Cl{\cdot}2HCl$) C, H, N, Cl.

6-Chloro-5-ethyl-2-(methylamino)-4-(*N*-methylpiperazino)pyrimidine Dihydrochloride (6). The method described for **5** was followed, using methylguanidine hydrochloride (22 g, 0.2 mol) and diethyl ethylmalonate (39.6 g, 0.2 mol); 11 g of **6** was obtained (overall yield 16%), mp >260 °C. Anal. ($C_{12}H_{20}N_5Cl{\cdot}2HCl$) C, H, N.

5,6-Dichloro-2-(methylamino)-4-(*N*-methylpiperazino)-pyrimidine Hydrochloride (8). The method described for **5** was followed; **8** was obtained as ocher crystals, mp 149 °C. Anal. ($C_{10}H_{15}N_5Cl_2$) C, H, N.

6-Chloro-5-methoxy-2-(methylamino)-4-(*N*-methylpiperazino)pyrimidine Hydrochloride (9). Methylguanidine hydrochloride (6.6 g, 0.06 mol), MeONa (5.4 g, 0.1 mol), and MeOH (50 mL) were heated to reflux, and diethyl methoxymalonate[15] (9.5 g, 0.05 mol) was added dropwise. The mixture was refluxed for 5 h, then poured into 200 mL of ice–water, acidified with AcOH (10 mL), and evaporated to dryness in vacuo. MeOH (10 mL) was added to the residue, and the mixture was stirred for 10 min. When acetone (100 mL) was added a precipitate formed, which was collected and dried under pressure at 50 °C. Chlorination was made by slowly heating the solution with $POCl_3$ (50 mL) up to reflux; the dark solution obtained was then poured into 0.5 L of ice–water and extracted with CH_2Cl_2 (3 × 100 mL); the organic layer was washed with H_2O (2 × 100 mL), dried with Na_2SO_4, and evaporated in vacuo. The residue was purified by chromatography on silica gel, eluting with toluene–AcOEt (8:2), to give 4,6-dichloro-5-methoxy-2-(methylamino)pyrimidine (**33**; 0.75 g, 7%), mp 159 °C. Anal. ($C_6H_7N_3Cl_2O$) C, H, N, Cl.

Heating **33** with *N*-methylpiperazine in MEK under reflux for 2 h afforded **9** as an insoluble material, which was filtered off (0.55 g, 49%), mp >260 °C. Anal. ($C_{11}H_{18}N_5ClO{\cdot}HCl$) C, H, N.

6-Chloro-5-ethoxy-2-(methylamino)-4-(*N*-methylpiperazino)pyrimidine (10). This compound was prepared according to the method described for **5**: a white crystalline material was obtained, mp 152 °C. Anal. ($C_{12}H_{20}N_5ClO$) C, H, N.

6-Chloro-5-(ethylthio)-2-(methylamino)-4-(*N*-methylpiperazino)pyrimidine (11). According to the method described for **5**, starting from methylguanidine hydrochloride (49.5 g, 0.45 mol) and diethyl ethylthiomalonate[16] (99 g, 0.45 mol) **11** was obtained (6 g, 5%), mp 124 °C. Anal. ($C_{12}H_{20}N_5ClS$) C, H, N, Cl, S.

6-Chloro-2-(methylamino)-4-(*N*-methylpiperazino)-5-(methylsulfinyl)pyrimidine (12). 4,6-Dichloro-2-(methylamino)-5-(methylthio)pyrimidine[14] (48 g, 0.25 mol), AcOH (900 mL), and a 30% solution of H_2O_2 (27 g, 0.24 mol) were stirred at room temperature for 100 h. The mixture was poured into H_2O (1 L) and ice (1 kg) and neutralized with 10 N NaOH. The resultant precipitate was filtered and crystallized from EtOH to give 4,6-dichloro-2-(methylamino)-5-(methylsulfinyl)pyrimidine (**34**; 42 g, 81%), mp 187 °C. Anal. ($C_6H_7N_3Cl_2OS$) C, H, N, S.

To a suspension of **34** (36 g, 0.15 mol) in EtOH (750 mL) was added dropwise a solution of *N*-methylpiperazine (18 g, 0.18 mol) in EtOH (75 mL) below 20 °C for 0.5 h; the mixture was stirred at room temperature for 24 h. The solid material was filtered and then crystallized from EtOH to give **12** (28 g, 61%), mp 223 °C. Anal. ($C_{11}H_{18}N_5ClOS$) C, H, N, Cl, S.

6-Chloro-2-(dimethylamino)-4-(*N*-methylpiperazino)-5-(methylthio)pyrimidine Hydrochloride (13). 4,6-Dichloro-2-(dimethylamino)-5-(methylthio)pyrimidine[17] (30 g, 0.126 mol), *N*-methylpiperazine (12.6 g, 0.126 mol), triethylamine (15 g, 0.148 mol), and benzene (250 mL) were refluxed for 3 h. After cooling, the mixture was filtered and evaporated in vacuo; the residue was extracted with Et_2O, and the etheral layer was washed with H_2O and concentrated. The hydrochloride was prepared, and two crystallizations from MeOH gave **13** (21 g, 49%), mp 163 °C. Anal. ($C_{12}H_{20}N_5ClS{\cdot}HCl$) C, H, N.

2-Anilino-6-chloro-4-(*N*-methylpiperazino)-5-(methylthio)pyrimidine Hydrochloride (21). This compound was prepared according to the procedure described for **5**, starting from diethyl methylthiomalonate[16] (59.2 g, 0.29 mol) and phenylguanidine carbonate[18] (57.2 g, 0.29 mol). Crude dihydroxypyrimidine derivative was obtained, the chlorination of which afforded the crude dichloro derivative. Chromatography on silica gel, eluting with $CHCl_3$–MeOH (95:5), yielded the pure 2-anilino-4,6-dichloro-5-(methylthio)pyrimidine (**35**; 23.6 g, 28%): mp 119 °C; ^{13}C NMR δ 166.8 (C_4, C_6), 157.1 (C_2), 118.0 (C_5). Anal. ($C_{11}H_9N_3Cl_2S$) C, H, N, Cl. Condensation of **35** with *N*-methylpiperazine gave **21**, base. An analytical sample, crystallized from aqueous EtOH, melted at 86 °C. It was converted to the hydrochloride, and crystallization from H_2O gave **21** (20.6 g, 71%), mp 246 °C. Anal. ($C_{16}H_{20}N_5ClS{\cdot}HCl$) H, N, C: calcd, 49.74; found, 48.80.

6-Chloro-4-(*N*-methylpiperazino)-5-(methylthio)-2-(phenethylamino)pyrimidine Hydrochloride (23). To a cooled (10 °C) solution of 5-(methylthio)-2,4,6-trichloropyrimidine (92 g, 0.4 mol) in MEK (900 mL) was added over 1 h phenethylamine (52 mL, 0.4 mol) and then K_2CO_3 (28 g, 0.2 mol) in H_2O (50 mL) over 0.5 h. The mixture was stirred at room temperature for 24 h, filtered, and evaporated in vacuo. The residue was heated with EtOH (150 mL) and filtered. The filtrate was cooled to 5 °C, and after crystallization, 4-(phenethylamino)-2,6-dichloro-5-(meth-

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ylthio)pyrimidine (**37**) was collected (39 g, 31%): mp 121 °C; ^{13}C NMR δ 167.09 (C_2), 159.92 (C_4, C_6), 115.11 (C_5). Anal. ($C_{13}H_{13}N_3Cl_2S$) C, H, N, Cl. Condensation of **37** with *N*-methylpiperazine, by the procedure described for **5**, afforded **23**, base, mp 130 °C. The hydrochloride was prepared, and two recrystallizations from EtOH gave **23** (52%), mp 228 °C. Anal. ($C_{18}H_{24}N_5ClS\cdot HCl$) C, H, N.

2-[(Substituted-benzyl)amino]-6-chloro-4-(*N*-methylpiperazino)-5-(methylthio)pyrimidines (24–29). The method described for **23** was followed, starting from substituted benzylamine instead of phenethylamine. The following compounds were obtained: **24**, 10% overall yield, mp 143 °C. Anal. ($C_{17}H_{21}N_5ClFS$) C, H, N. **25**, 16%, mp 112 °C. Anal. ($C_{18}H_{24}N_5OS$) C, H, N. **26**, 18%, mp 120 °C. Anal. ($C_{17}H_{21}N_5Cl_2S$) C, H, N. **27**, 10%, mp 170 °C. Anal. ($C_{21}H_{30}N_5ClS$) C, H, N. **28**, 14%, mp 124 °C. Anal. ($C_{17}H_{21}N_5Cl_2S$) C, H, N. **29**, 15%, mp 124 °C. Anal. ($C_{18}H_{24}N_5ClOS$) C, H, N.

2-(Benzylamino)-6-chloro-4-(*N*-methylpiperazino)-5-methoxypyrimidine Hydrochloride (30). According to the method described for **5**, starting from diethyl methoxymalonate[15] (32.3 g, 0.17 mol) and benzylguanidine sulfate (33.6 g, 0.17 mol) was obtained **30** (21.5 g, 33%), mp 232 °C. Anal. ($C_{17}H_{22}N_5ClO\cdot HCl$) C, H, N, Cl.

4-Anilino-6-chloro-2-(*N*-methylpiperazino)-5-(methylthio)pyrimidine Hydrochloride (31). 5-(Methylthio)-2,4,6-trichloropyrimidine[19] (115 g, 0.5 mol), aniline (47 g, 0.5 mol), K_2CO_3 (35 g, 0.25 mol) in H_2O (60 mL), and MEK (600 mL) were stirred for 24 h at room temperature.

Water (100 mL) was added, and the mixture was concentrated under reduced pressure: the resulting precipitate was collected, washed with MEK (2 × 50 mL), and dried in vacuo to give 4-anilino-2,6-dichloro-5-(methylthio)pyrimidine (**36**; 91.7 g, 64%): mp 131 °C; ^{13}C NMR δ 164.4 (C_6), 162.0 (C_2), 159.2 (C_4). Anal. ($C_{11}C_9N_3Cl_2S$) C, H, N, Cl. Condensation of **36** with *N*-methylpiperazine by the procedure described for **5** afforded **31**, base. An analytical sample crystallized from EtOH, mp 116 °C. It was converted to the hydrochloride, and crystallization from H_2O gave **31** (33.8 g, 58%), mp 263 °C. Anal. ($C_{16}H_{20}N_5ClS\cdot HCl$) C, H, N, Cl; H: calcd, 5.44; found, 5.89.

X-ray Crystallography. Suitable crystals for X-ray analysis of all three compounds were obtained by slow evaporation of ethanol solutions.

1: $C_{11}H_{18}ClSN_5$, M = 287.82, triclinic, space group $P\bar{1}$, a = 7.256 (1), b = 8.809 (1), c = 11.900 (1) Å, α = 103.40 (1), β = 106.16 (1), γ = 86.00 (1)°, V = 710.7 (2) Å^3, Z = 2, D_c = 1.345 g·cm^{-3}.

17: $C_{13}H_{22}ClSN_5$, M = 315.87, monoclinic, space group $P2_1/n$, a = 13.987 (2), b = 10.810 (2), c = 10.563 (1) Å, β = 90.23 (1)°, V = 1596.9 (2) Å^3, Z = 4, D_c = 1.313 g·cm^{-3}.

22: $C_{17}H_{22}ClSN_5$, M = 363.9, monoclinic, space group $P2_1/c$, a = 11.137 (1), b = 5.496 (1), c = 32.225 (6) Å, β = 65.85 (1)°, V = 1799.8 (3) Å^3, Z = 4, D_c = 1.344 g·cm^{-3}.

Crystals of dimensions ca. 0.55 × 0.17 × 0.12 mm (**1**), 0.60 × 0.06 × 0.04 (**22**), and 0.25 × 0.25 × 0.08 mm (**17**) were selected from the recrystallized material, and preliminary unit-cell dimensions and space groups were determined from Weissenberg photographs. Three-dimensionsl intensity data were collected on a fully automated Enraf-Nonius CAD-4 diffractometer by use of graphite-monochromatized Cu $K\alpha$ radiation (λ = 1.54178 Å). All available symmetry-independent reflections out to θ = 78° (**1** and **17**) and θ = 60° (**22**) were measured. For the three compounds, 3008, 2733, and 3531 measurements yielded, respectively, 2559, 1710, and 2649 significant [$I \geq 2\sigma(I)$] diffraction maxima. Data were corrected for Lorentz and polarization effects and placed on an absolute scale by means of Wilson plots: B = 3.42, 3.59, and 3.30 Å^2.

All three structures were solved by direct methods.[20] In each case, all non-hydrogen atoms of the molecule could be located in the first E map. All structures were refined by block-diagonal least squares, initially with isotropic and then with anisotropic thermal parameters. Hydrogen atoms were introduced in calculated positions or positions derived from difference Fourier synthesis and then refined with isotropic thermal parameters together with the other atoms. The final R factors were 0.041 (**1**), 0.036 (**22**), and 0.051 (**17**). Final positions of the non-hydrogen atoms and standard deviations estimated from block-diagonal refinement are presented in Tables II–IV. Anisotropic parameters of non-hydrogen atoms, positions of hydrogen atoms, and interatomic distances and angles are available as supplementary material (see paragraph at the end of paper).

PCILO Calculations. The PCILO method[21] (the designation stands for perturbative configuration interaction using localized orbitals) was developed some 10 years ago;[22] the study consists in the construction of potential energy curves by varying the torsion angle τ with 20° increments. Bear in mind that the torsion angle τ of the bonded atoms 6-1-7-8 is the angle between the planes 6-1-7 and 1-7-8. Viewed from the direction of 6, τ is positive for clockwise and negative for anticlockwise rotations. The geometrical input data (bond lengths and angles) were provided by the crystallographic study.

Biological Methods. The [^{3}H]spiroperidol binding (26.4 Ci/mmol, New England Nuclear Corp.) was performed in rat striatal membranes according to the method of Briley and Langer.[23] Incubation time was 15 min at 37 °C. [^{3}H]Spiroperidol concentration was 0.3 nM, and 5 μM haloperidol was used for nonspecific binding. IC_{50} values were determined by log probit analysis (four to six concentrations, in triplicate, of drugs were used). K_i values were calculated from the equation: $K_i = IC_{50}/1 + S/K_D$.

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Supplementary Material Available: Full X-ray crystallographic data for compounds **1**, **17**, and **22** (9 pages). Ordering information is given on any current masthead page.

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