6-(Alkylamino)-9-alkylpurines. A New Class of Potential Antipsychotic Agents

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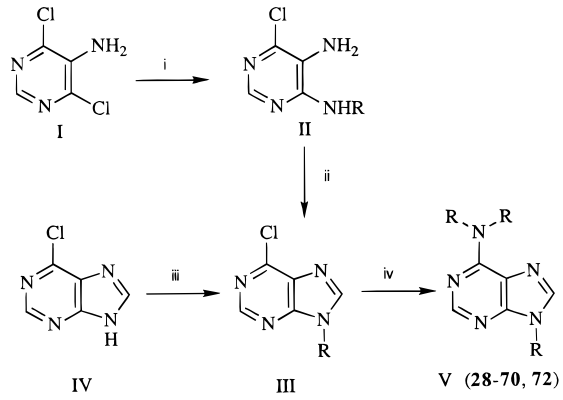
A series of 6-(alkylamino)-9-alkylpurines was synthesized and evaluated for the property of antagonizing the behavioral effects in animals of the dopamine agonist apomorphine. This model for identifying potential antipsychotic agents is based on the hypothesis that agents that antagonize apomorphine-induced aggressive behavior in rats and apomorphine-induced climbing in mice, but that do not block stereotyped behavior, could have an antipsychotic effect in humans without producing extrapyramidal side effects. The antiaggressive-behavior activity of lead compound **1** (6-(dimethylamino)-9-(3-phenylalaninamidobenzyl)-9*H*-purine) was improved 48-fold with 6-(cyclopropylamino)-9-(cyclopropylmethyl)-2-(trifluoromethyl)-9*H*-purine (**80**) (po ED_{50} of 2 mg/kg), which was obtained through an iterative sequence of structure−activity relationship studies that encompassed evaluation of the effects of structure variations at the purine 9-, 6-, and 2-positions. Potency was enhanced with a 9-cyclopropyl group, the duration of action was improved with the 6-(cyclopropylamino) substituent, potency was further enhanced with an *N*-formyl prodrug, and an agent with reduced cardiovascular effect emerged with the 2-trifluoromethyl purine **80**. This potential antipsychotic agent was not developed further due to undesirable effects on the stomach.

The introduction of chlorpromazine in the 1950s for the treatment of schizophrenia initiated a therapeutic revolution in the treatment of psychotic disorders.[1] Although chlorpromazine and other conventional antipsychotic agents are effective in alleviating the positive symptoms of many psychoses, they produce a high incidence of extrapyramidal side effects and tardive dyskinesias in patients.[2,3] The dopamine hypothesis of manic psychosis and schizophrenia proposes that these disorders arise from hyperactivity of dopaminergic neurotransmission; antipsychotic agents exert their effect through blockade of dopamine receptors.[4,5] The ability of compounds to antagonize the behavioral effects in animals of apomorphine, a dopamine agonist, has been used as a model for identifying potential antipsychotic agents.[6] However, agents that antagonize apomorphine-induced stereotyped behavior produce a high incidence of extrapyramidal side effects and tardive dyskinesias in humans.[7,8] Apomorphine also causes aggressive behavior in paired rats[9] and elicits climbing behavior in mice,[10] both of which are antagonized by neuroleptic agents. Apomorphine-induced climbing and aggressive behavior are probably a reflection of the stimulation of dopamine receptors in the limbic system, while stereotyped behavior is associated with dopamine receptor stimulation in the striatum.[6,10] Since the limbic system has been implicated in the etiology of psychotic behavior,[11] investigators proposed that an agent that antagonized apomorphine-induced aggression in rats and apomorphine-induced climbing in mice, but that did not block stereotyped behavior in either species, could have an antipsychotic effect in humans without producing extrapyramidal side effects.[12] Rimcazole (BW 234U, *cis*-9-[3-(3,5-dimethyl-1-piperazinyl)-propyl]carbazole dihydrochloride), a novel agent with antipsychotic potential, emerged from a research program based on this hypothesis.[13] During the screening of new compounds for central nervous system (CNS) activity, the ability of **1** (Table 3) to block apomorphine-induced aggressive behavior in rats was discovered. Owing to the novelty of this structural lead, a synthesis program was initiated to explore structure−activity relationships with the objective of increasing potency and specificity of action.

Scheme 1[a]



[a] Reagents: (i) BuOH, Et_3N, RNH_2; (ii) $HC(OEt)_3$, $EtSO_3H$; (iii) DMSO, K_2CO_3, RCl; (iv) EtOH, R_2NH.

Chemistry. Compounds **28**−**70** and **72** (Table 2) were prepared from 5-amino-4,6-dichloropyrimidine (**I**) or 6-chloropurine (**IV**) as outlined in Scheme 1. Amination of **I** with the appropriate amine by modification of a general literature method[14−16] gave the 4-substituted pyrimidines **II** in 59 to 95% yields (Table 1).

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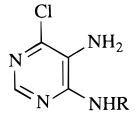
Table 1. Physical Properties of 4-Chloro-5,6-diaminopyrimidines



no.	R	method	yield, %	mp, °C	formula[a]
89	$CH_2CH_2CH_3$	A	95	113−114[b]	$C_7H_{11}ClN_4$
90	$(CH_2)_3CH_3$	A	71	80−81[c]	$C_8H_{13}ClN_4$
91	$(CH_3)_4CH_3$	A	91	84−85[c]	$C_9H_{15}ClN_4$
92	$CH(CH_3)CH_2CH_3$	A	77	130−132[d]	$C_8H_{13}ClN_4$
93	$CH_2CH(CH_3)_2$	A	59	120−121[e]	$C_8H_{13}ClN_4$
94	$CH_2C_3H_5$	A	88	152−153[f]	$C_8H_{11}ClN_4$
95	$CH_2C_4H_7$	A	75[f]	155−156	$C_9H_{13}ClN_4$
96	C_3H_5	B	94	156−158[f]	$C_7H_9ClN_4$
97	C_4H_7	A	93	139−140[f]	$C_8H_{11}ClN_4$
98	C_5H_9	A	77	138−140[e]	$C_9H_{13}ClN_4$
99	C_6H_{11}	A	82	137−138[c]	$C_{10}H_{15}ClN_4$
100	C_7H_{13}	A	77	138−140[c]	$C_{11}H_{17}ClN_4$
101	$CH(CH_3)C_3H_5$	A	61[e]	125−126	$C_9H_{13}ClN_4$

[a] All compounds were analyzed for C, H, N. [b] Recrystallized from heptane. [c] Recrystallized from cyclohexane [d] Recrystallized from dichloromethane. [e] Recrystallized from ethyl acetate:cyclohexane. [f] Recrystallized from toluene.

Condensation of **II** with triethyl orthoformate[17] and ethanesulfonic acid[18] provided the 6-chloropurines **III**. For preparation of 9-methylthiomethyl purine **67**, 6-chloropurine (**IV**) was alkylated with chloromethyl methyl sulfide to give intermediate chloropurine **105**.[19] The 6-chloro-9-substituted purines **III** were reacted with the appropriate amines to give **V** (**28**−**70** and **72**) in 6 to 86% yields (Table 2).

Several 6-cyclopropyl amino purines **VI** (Scheme 2) were converted to the N-formamido derivatives **73**−**76** and **78** (Table 2). Initial efforts to synthesize **VI** met with difficulties; however, use of 4-(dimethylamino)-pyridine and acetic formic anhydride[20] in hot dichloromethane gave the desired products in good yield. Acetylation of **62** with acetic anhydride provided acetamide **77** in 72% yield. The *N*-ethyl analogue **71** was prepared from **54** with sodium hydride and ethyl iodide (Table 2).

The 2-substituted purines **79**−**88** (Table 2) were prepared from 2,6-dichloropurine **109** or 6-chloro-2-trifluoromethylpurine **110**.[21] Alkylation of **109** (Scheme 3) with chloromethylcyclopropane did not give the desired product, due to facile hydrolysis of the 6-chloro substituent. Therefore, **109** was aminated with cyclopropylamine to give **111**, which reacted smoothly with chloromethylcyclopropane to give **79** in high yield. The 2-(trifluoromethyl)purine **80** was prepared from **110** in a similar manner via **112**. The structures of **79** and **80** as 9-substituted purines were based on earlier work showing that 6-(dimethylamino)-2-(trifluoromethyl)-9*H*-purine alkylates cleanly to give only 9-substituted purine.[21]

Compounds **82**−**88** were prepared from the common intermediate 2-chloropurine **79**. Amination of **79** with the appropriate amine in ethanol at 80 °C provided **82**−**84** in good yields. When **79** was heated at reflux in a basic solution of the appropriate alcohol, compounds **85**−**87** were obtained in good yields. If the time of reflux for preparation of **87** was extended to several days, substantial *N*-6 dealkylation occurred. Reaction of **79** with methyl mercaptan in ethanol containing sodium ethanolate gave **88**.

The 2-aminopurine **81** was prepared in two steps from 2-amino-6-chloro-9*H*-purine (**113**). Alkylation of **113** with chloromethylcyclopropane gave **114** in 45% yield. Amination of **114** with cyclopropylamine at 75 °C gave **81** in 64% yield. The structure of intermediate **114** was substantiated by conversion to the 6-(dimethylamino) analogue **115** with dimethylamine. The latter compound had an UV spectrum very similar to that of the 9-benzyl analogue.[22]

Biological Results and Discussion

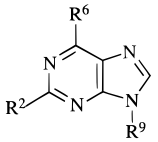
The compounds in Tables 3−7 were tested, by the oral and ip routes, for activity against apomorphine-induced aggression (fighting behavior as defined by McKenzie[9]) in rats.[9,12] The paired animals were observed for the presence or absence of stereotyped behavior during the fighting observation period. Five pairs of animals were used for each dose; approximate ED_{50} values were estimated from experiments at two or three doses that bracketed the ED_{50}. Most of the compounds were tested initially at 25 or 50 mg/kg ip; if activity was high, an ED_{50} was determined. Oral ED_{50}s were determined for the most active compounds.

9-(Benzyl)purines. Compound **1**, which has weak antirhinovirus activity,[23] was found to block apomorphine-induced aggressive behavior in rats with an ip ED_{50} of 27 mg/kg and an oral ED_{50} of 96 mg/kg (Table 3). The behavioral profile (blocked apomorphine-induced aggression but not stereotyped behavior) of **1** was similar to that of rimcazole,[12] which suggested that if **1** had antipsychotic activity in humans, it would not cause extrapyramidal side effects. Consequently, we initiated a synthesis program to explore structure−activity relationships with the objective of increasing potency and specificity of action.

Removal of the phenylalanine moiety of **1** gave the amine **2**, which was significantly more potent by the oral route with an ED_{50} of 58 mg/kg. The unsubstituted parent 9-benzylpurine **3** was about twice as potent as **1** after ip and po administration. Several para-substituted analogues were evaluated by the ip route of administration. Only the small fluoro (**4**) and hydrophilic amino (**11**) substituents gave compounds with activity comparable to **2** and **3** (Table 3). Among several meta-substituted analogues, only the (3-cyanobenzyl)purine **17** was as potent as the unsubstituted parent **3** with an ip ED_{50} of 13 mg/kg. Of several ortho-substituted derivatives only the (2-fluorobenzyl)purine **19** was active, although the ip ED_{50} was only 37 mg/kg. Thus, the phenylalaninamide moiety of lead compound **1** was not necessary for activity. The unsubstituted parent 9-benzylpurine **3** was most potent, with an oral ED_{50} of 52 mg/kg. Substitution on **3** with a variety of substituents did not improve potency.

9-Alkyl-6-(dimethylamino)purines. Since the antiaggression activity of **3** was not significantly improved by introduction of aryl substituents, the effects of other lipophilic purine 9-substituents were examined (Table 4). Reduction of the phenyl moiety gave (cyclohexylmethyl)purine **25**, which was not active at 50 mg/kg. However, the 9-methylpurine **26** reduced aggressive behavior by 30% at 25 mg/kg. The 9-ethyl (**27**), 9-(1-propyl) (**28**), and 9-(1-butyl) (**29**) analogues were as potent as **3** by the ip route, but the 9-(1-pentyl) (**30**) analogue lacked activity at 25 mg/kg.

Table 2. Physical Properties of Substituted Purines

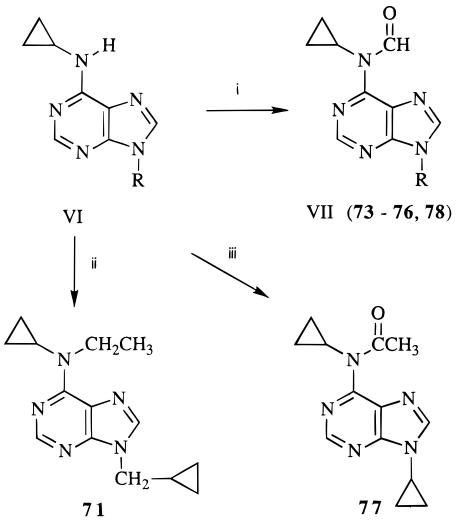


no.	R^2	R^6	R^9	method	yield, %	mp, °C	formula[a]
28	H	$N(CH_3)_2$	$CH_2CH_2CH_3$	C,D	64	53−56[b]	$C_{10}H_{15}N_5$
29	H	$N(CH_3)_2$	$(CH_2)_3CH_3$	C,D	59[c]	36−38	$C_{11}H_{17}N_5$
30	H	$N(CH_3)_2$	$(CH_2)_4CH_3$	C,D	62[b]	44−46	$C_{12}H_{19}N_5$
31	H	$N(CH_3)_2$	$CH(CH_3)_2$	A,C,D	28	66−67[b,d]	$C_{10}H_{15}N_5$
32	H	$N(CH_3)_2$	$C(CH_3)_3$	A,D,E	34	103−105[e]	$C_{11}H_{17}N_5$
33	H	$N(CH_3)_2$	$CH(CH_3)CH_2CH_3$	C,D	21	68−71[b]	$C_{11}H_{17}N_5$
34	H	$N(CH_3)_2$	$CH_2CH(CH_3)_2$	C, D	53	79−80[c]	$C_{11}H_{17}N_5$
35	H	$N(CH_3)_2$	$CH_2C_3H_5$	C,D	73[f]	68−70	$C_{11}H_{15}N_5$
36	H	$N(CH_3)_2$	$CH_2C_4H_7$	D,F	20[g]	185−189	$C_{12}H_{17}N_5$·HCl
37	H	$N(CH_3)_2$	C_3H_5	D,G	60[h]	120−121	$C_{10}H_{13}N_5$
38	H	$N(CH_3)_2$	C_4H_7	C,D	75[b]	91−92	$C_{11}H_{15}N_5$
39	H	$N(CH_3)_2$	C_5H_9	C,F	33[g]	182−188	$C_{12}H_{17}N_5$·HCl·$^1/_2H_2O$
40	H	$N(CH_3)_2$	C_6H_{11}	C,D	67[i]	87−88	$C_{13}H_{19}N_5$
41	H	$N(CH_3)_2$	C_7H_{13}	C,D	67[b]	60−62	$C_{14}H_{21}N_5$
42	H	$NHCH_3$	$CH_2C_3H_5$	C,D	**57**[j]	112−114	$C_{10}H_{13}N_5$
43	H	NH_2	$CH_2C_3H_5$	C,H	67[k]	190−193	$C_9H_{11}N_5$
44	H	$N(CH_3)CH_2CH_3$	$CH_2C_3H_5$	C,F	55[l]	157−159[t]	$C_{12}H_{17}N_5$·HCl
45	H	$N(CH_3)CH(CH_3)_2$	$CH_2C_3H_5$	C,F	66[l]	173−176	$C_{13}H_{19}N_5$·HCl
46	H	$N(CH_2CH_3)_2$	$CH_2C_3H_5$	C,D	56[g]	161−164	$C_{13}H_{19}N_5$·HCl
47	H	$N(CH_2)_3$	$CH_2C_3H_5$	C,D	40[b]	81−83	$C_{12}H_{15}N_5$
48	H	$N(CH_2)_5$	$CH_2C_3H_5$	C,F	15[g]	195−198	$C_{14}H_{19}N_5$·HCl
49	H	$NHCH_2CH_3$	$CH_2C_3H_5$	C,D	35[m]	71−73	$C_{11}H_{15}N_5$
50	H	$NHCH_2CH_2CH_3$	$CH_2C_3H_5$	C,D	66[m]	85−86	$C_{12}H_{17}N_5$
51	H	$NHC(CH_3)_3$	$CH_2C_3H_5$	C,F	50	200−204	$C_{13}H_{19}N_5$·HCl
52	H	$NHCH_2C_3H_5$	$CH_2C_3H_5$	C,F	12[g]	199−201	$C_{13}H_{17}N_5$·HCl
53	H	NHC_6H_5	$CH_2C_3H_5$	C,D[n]	81[j]	144−146	$C_{15}H_{15}N_5$
54	H	NHC_3H_5	$CH_2C_3H_5$	C,I	68[m]	112−113	$C_{12}H_{15}N_5$
55	H	$N(CH_3)C_3H_5$	$CH_2C_3H_5$	C,J	51[g]	168−171	$C_{13}H_{17}N_5$·HCl
56	H	NHC_4H_7	$CH_2C_3H_5$	C,F	50[g]	208−210	$C_{13}H_{17}N_5$·HCl
57	H	NHC_3H_5	$CH_2C_4H_7$	G,K	36[j]	98−100	$C_{13}H_{17}N_5$
58	H	NHC_3H_5	$CH_2C_5H_9$	A,G,K	46[j]	109−110	$C_{14}H_{19}N_5$
59	H	NHC_3H_5	$CH(CH_3)C_3H_5$	G,K	49[m]	110−112	$C_{13}H_{17}N_5$
60	H	NHC_3H_5	$CH(CH_3)C_3H_5(-)$[o]	A[p],G,K	48[m]	110−112	$C_{13}H_{17}N_5$
61	H	NHC_3H_5	$CH(CH_3)C_3H_5(+)$[q]	A[r]G,K	51[m]	111−112	$C_{13}H_{17}N_5$
62	H	NHC_3H_5	C_3H_5	G,B	85[j]	157−159	$C_{11}H_{11}N_5$
63	H	NHC_3H_5	C_4H_7	G,K	26[j]	132−134	$C_{12}H_{15}N_5$
64	H	NHC_3H_5	C_5H_9	G,K	51[j]	124−125	$C_{13}H_{17}N_5$
65	H	NHC_3H_5	$CH_2CH_2CH_3$	G,I	30[j]	98−100	$C_{11}H_{15}N_5$
66	H	NHC_3H_5	$CH(CH_3)_2$	G,K	42[j]	114−116	$C_{11}H_{15}N_5$
67	H	NHC_3H_5	CH_2SCH_3	I,L	6[j]	124−126	$C_{10}H_{13}N_5S$
68	H	NHC_3H_5	$(CH_2)_3CH_3$	G,J	32[g]	166−168	$C_{12}H_{17}N_5$·HCl
69	H	NHC_3H_5	$CH(CH_3)CH_2CH_3$	G,K	42[j]	100−103	$C_{12}H_{17}N_5$
70	H	NHC_3H_5	$CH_2CH(CH_3)_2$	G,K	61[j]	156−160	$C_{12}H_{17}N_5$
71	H	$N(CH_2CH_3)C_3H_5$	$CH_2C_3H_5$	M	97	oil	$C_{14}H_{19}N_5$·0.5H_2O
72	H	$N(CH_3)C_3H_5$	C_3H_5	G,K	27[m]	74−76	$C_{12}H_{15}N_5$
73	H	$N(C_3H_5)CHO$	$CH_2C_3H_5$	N	50[l]	156−158	$C_{13}H_{15}N_5O$
74	H	$N(C_3H_5)CHO$	$CH(CH_3)C_3H_5(-)$[s]	N	71[m]	101−102	$C_{14}H_{17}N_5O$
75	H	$N(C_3H_5)CHO$	$CH_2C_4H_7$	N	57[m]	74−77	$C_{14}H_{17}N_5O$
76	H	$N(C_3H_5)CHO$	C_3H_5	N	66[j]	125−126	$C_{12}H_{13}N_5O$
77	H	$N(C_3H_5)COCH_3$	C_3H_5	expl	72[l]	146−147	$C_{13}H_{15}N_5O$
78	H	$N(C_3H_5)CHO$	C_4H_7	N	65[j]	119−121	$C_{13}H_{15}N_5O$
79	Cl	NHC_3H_5	$CH_2C_3H_5$	expl	67	144−146[j]	$C_{12}H_{14}ClN_5$
80	CF_3	NHC_3H_5	$CH_2C_3H_5$	expl	66	101−103[m]	$C_{13}H_{14}F_3N_5$
81	NH_2	NHC_3H_5	$CH_2C_3H_5$	expl	64[l]	160−162	$C_{12}H_{16}N_6$
82	$NHCH_3$	NHC_3H_5	$CH_2C_3H_5$	O	62[l]	147−149	$C_{13}H_{18}N_6$
83	$NHCH_2CH_3$	NHC_3H_5	$CH_2C_3H_5$	O	82	150−152[l]	$C_{14}H_{20}N_6$
84	$N(CH_3)_2$	NHC_3H_5	$CH_2C_3H_5$	O	76[l]	133−135	$C_{14}H_{20}N_6$
85	OCH_3	NHC_3H_5	$CH_2C_3H_5$	P	72[j]	122−124	$C_{13}H_{17}N_5O$
86	OCH_2CH_3	NHC_3H_5	$CH_2C_3H_5$	P	48[m]	97−99	$C_{14}H_{19}N_5O$
87	$O(CH_2)_2CH_3$	NHC_3H_5	$CH_2C_3H_5$	P[t]	42[m]	87−89	$C_{15}H_{21}N_5O$
88	SCH_3	NHC_3H_5	$CH_2C_3H_5$	P[u]		120−122	$C_{13}H_{17}N_5S$

[a] All compounds were analyzed for C, H, N. [b] Recrystallized from pentane. [c] Recrystallized from petroleum ether (35−60 °C). [d] Dimorphic form isolated from a separate reaction with mp 50−52 °C. [e] Recrystallized from methanol:water. [f] Recrystallized from pentane:cyclohexane. [g] Recrystallized from ethyl acetate:ethanol. [h] Recrystallized from pentane:ethanol. [j] Recrystallized from petroleum ether (35−60 °C): ethanol. [j] Recrystallized from cyclohexane:ethyl acetate. [k] Recrystallized from ethanol. [l] Recrystallized from ethyl acetate. [m] Recrystallized from cyclohexane. [n] Reaction was heated to reflux for 6 h. [o] $[\alpha]^{20}_D$ − 39.5° (*c* 1.0, EtOH) [p] Prepared from **109**. [q] $[\alpha]^{20}_D$ +36.8° (*c* 1.0, EtOH) [r] Prepared from **108**. [s] $[\alpha]^{20}_D$ −36.0° (*c* 1.0, EtOH) [t] Crude product was purified by column chromatography as in method D. [u] Methyl mercaptan was added to the sodium ethanolate solution before addition of **79**.

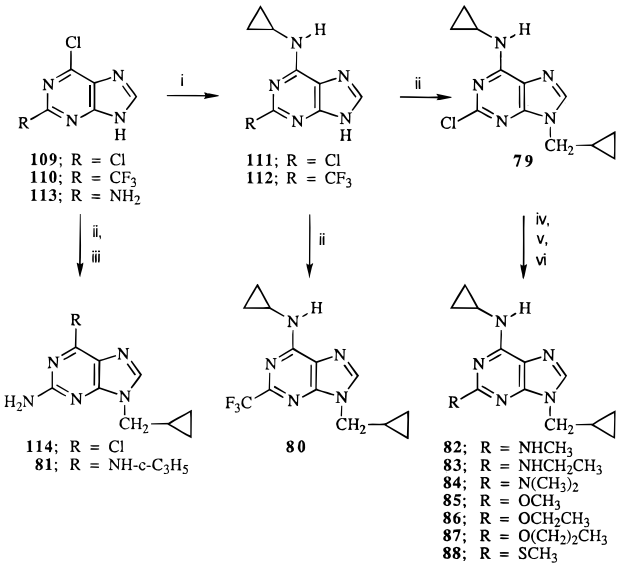
Several branched 9-alkyl substituents were examined. The 9-(2-propyl) analogue **31** had a low ip ED_{50} of 11 mg/kg, and its oral potency was excellent, with an ED_{50} of 15 mg/kg. This level of activity represented a 6-fold

Scheme 2[a]



[a] Reagents: (i) CH_2Cl_2, DMAP, AcOCHO; (ii) DMSO, NaH, EtI; (iii) Ac_2O.

Scheme 3[a]

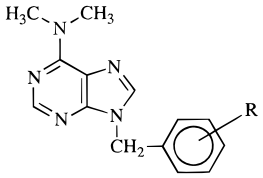


[a] Reagents: (i) EtOH, c-$C_3H_5NH_2$; (ii) DMSO, K_2CO_3, c-$C_3H_5CH_2Cl$; (iii) EtOH, H_2O, c-$C_3H_5NH_2$; (iv) EtOH, RRNH; (v) ROH, NaH; (vi) EtOH, NaH, CH_3SH.

improvement over the lead compound **1** and more than a 3-fold improvement over 9-benzylpurine **3**. Several 9-cycloalkyl-substituted purines (**35**−**41**) were evaluated. The cyclopropylmethyl (**35**), cyclopropyl (**37**), and cyclobutyl (**38**) analogues had good ip and oral antiaggression activity. However, **35** emerged as the most attractive 6-(dimethylamino)purine with an oral ED_{50} of 17 mg/kg and an oral LD_{50} of 570 mg/kg, for a safety ratio of 30. In addition to showing potent antagonism of apomorphine-induced aggression, **35** did not affect the performance of chewing and licking, or other components of stereotyped behavior.

Metabolism studies with **35** showed that its half-life was less than 10 min in mice after iv dosing.[24] The 6-methylamino (**42**) and 6-amino (**43**) derivatives (Table 5) were the main metabolites present in mouse serum with half-lives of 0.5 and 1 h, respectively. Since the antiaggression test was not initiated until 1 h after dosing, the concentration of **35** in the circulation was very low. Both **42** and **43** were much weaker antiaggression agents when tested individually (Table 5). These data suggested that an analogue of **35** that could not be readily dealkylated might be a more potent antagonist of apomorphine-induced aggression.

Table 3. Antagonism of Apomorphine-Induced Aggression by 9-Benzylpurines



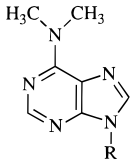
		ED_{50}, mg/kg[a]	
no.	R	ip	po
1[b]	3-NHCOCH(NH_2)$CH_2C_6H_5$	27	96
2[b]	3-NH_2	23	58
3[c]	H	15	52
4[c]	4−F	21	
5[c]	4-Cl	(0)[d]	
6[c]	4-CH_3	(0)[d]	
7[c]	4-OCH_3	58	
8[c]	4-NO_2	(0)[d]	
9[c]	4-CN	(0)[d]	
10[c]	4-OH	(0)[e]	
11[c]	4-NH_2	17	
12[f]	4-$NHCOCH_3$	(0)[d]	
13[c]	3-F	(6)[e]	
14[c]	3-Cl	50	
15[c]	3-CH_3	(12)[d]	
16[c]	3-OCH_3	(48)[d]	
17[c]	3-CN	13	
18[c]	3-OH	(33)[e]	
19[c]	2−F	37	
20[c]	2-Cl	(0)[e]	
21[c]	2-CH_3	(0)[e]	
22[c]	2-OMe	(0)[e]	
23[c]	2-NO_2	(0)[d]	
24[c]	2-NH_2	(0)[d]	

[a] The compounds were tested for their ability to antagonize apomorphine-induced aggression in male rats as described in refs 9 and 12. The ED_{50} was the dose needed to decrease the fighting time by 50%. The compounds were administered as solutions or fine dispersions in water or 0.5% methylcellulose. Values in parentheses are percent inhibition at the footnoted dose. The ED_{50} values are screening numbers that do not have a standard error. Five pairs of animals were used for each dose; approximate ED_{50} values were estimated from experiments at two or three doses that bracketed the ED_{50}. The ED_{50}s for BW 234U were 12.5 ± 3.2 mg/kg ip and 48 ± 6.9 mg/kg po.[12] [b] For synthesis, see ref 23. [c] For synthesis, see ref 16. [d] Percent inhibition at 50 mg/kg. [e] Percent inhibition at 25 mg/kg.

9-(Cyclopropylmethyl)purines. Fifteen 6-substituted analogues of **35** were synthesized and tested for antiaggression activity (see **42**-**56**, Table 5). All were less potent, except for the 6-cyclopropylamino purine **54**, which had ip and oral ED_{50}s of 4 and 12 mg/kg, respectively. In addition to excellent oral activity, **54** exhibited a long duration of action. When **54** was tested at 2 times its ED_{50}, fighting was blocked by 100% at 6 h. This marked improvement in the duration of action compared with **35** is apparently derived from the greater stability of the 6-(cyclopropylamino) substituent toward metabolic dealkylation. However, **54** was substantially more toxic than **35**. It had an oral LD_{50} = 160 mg/kg for an acute safety ratio of only 13.

6-(Cyclopropylamino)purines. Although **54** demonstrated good oral activity in antagonizing apomorphine-induced aggression in rats with a long duration of action, the compound was too toxic for further development. In an effort to identify a compound with

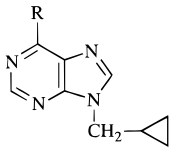
Table 4. Antagonism of Apomorphine-Induced Aggression by 9-alkyl-6-dimethylamino-9*H*-purines



		ED$_{50}$, mg/kg[a]	
no.	R	ip	po
3[b]	$CH_2C_6H_5$	15	52
25[b]	$CH_2C_6H_{11}$	(0)[c]	
26[b]	CH_3	(30)[d]	
27	CH_2CH_3	15	
28	$CH_2CH_2CH_3$	14	(15)[d]
29	$(CH_2)_3CH_3$	10	(0)[d]
30	$(CH_2)_4CH_3$	(0)[d]	
31	$CH(CH_3)_2$	11	15
32	$C(CH_3)_3$		(0)[d]
33	$CH(CH_3)CH_2CH_3$	14	
34	$CH_2CH(CH_3)_2$	5	22
35	$CH_2C_3H_5$	4.5	17
36	$CH_2C_4H_7$	8	(0)[d]
37	C_3H_5	9	25
38	C_4H_7	11	26
39	C_5H_9	(27)[d]	
40	C_6H_{11}	(70)[d]	
41	C_7H_{13}	(0)[d]	

[a] See footnote *a* in Table 3. [b] For synthesis see ref 16. [c] Percent inhibition at 50 mg/kg. [d] Percent inhibition at 25 mg/kg.

Table 5. Antagonism of Apomorphine−Induced Aggression by 6−Substituted 9−Cyclopropylmethylpurines

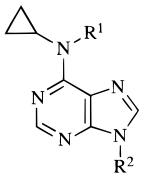


		ED$_{50}$, mg/kg[a]	
no.	R	ip	po
35	$N(CH_3)_2$	4.5	17
42	$NHCH_3$	12	(38)[b]
43	NH_2	20	
44	$N(CH_3)CH_2CH_3$	12.5	(0)[b]
45	$N(CH_3)CH(CH_3)_2$	(32)[b]	
46	$N(CH_2CH_3)_2$	(0)[b]	
47	$N(CH_2)_3$	(30)[b]	
48	$N(CH_2)_5$	(28)[b]	
49	$NHCH_2CH_3$	22	
50	$NHCH_2CH_2CH_3$	(0)[b]	
51	$NHC(CH_3)_3$	(0)[b]	
52	$NHCH_2C_3H_5$	(28)[b]	
53	NHC_6H_5	(0)[b]	
54	NHC_3H_5	4	12[c]
55	$N(CH_3)C_3H_5$	7.5	35
56	NHC_4H_9	(0)[b]	

[a] See footnote *a* in Table 3. [b] Percent inhibition at 25 mg/kg. [c] At twice the oral ED$_{50}$ fighting was inhibited by 100% at 6 h.

an improved overall profile, the 9-(cyclopropylmethyl) substituent of **54** was systematically varied (Table 6). The 9-(cyclobutylmethyl) (**57**) and 9-(cyclopentylmethyl) (**58**) analogues were less potent than **54**, but substitution of a methyl on the methylene of **54** gave racemic **59**, which was equipotent to **54** by the ip route. The individual enantiomers **60** and **61** were tested; the levorotatory isomer **60** was 6-fold more potent than the dextrorotatory isomer **61** with an ip ED$_{50}$ = 2 mg/kg and an oral ED$_{50}$ = 9 mg/kg. Three compounds with cyclic side chains had highly divergent activities: the

Table 6. Antagonism of Apomorphine−Induced Aggression by 6−(Cyclopropylamino)−9−substituted Purines



			ED$_{50}$, mg/kg[a]	
no.	R^1	R^2	ip	po
54	H	$CH_2C_3H_5$	4	12
57	H	$CH_2C_4H_7$	10	44
58	H	$CH_2C_5H_9$	15	
59	H	$CH(CH_3)C_3H_5$	4.5	25
60	H	$CH(CH_3)C_3H_5$ (−)	2	9
61	H	$CH(CH_3)C_3H_5$ (+)	12.5	>25
62	H	C_3H_5	4.5	20
63	H	C_4H_7	19	
64	H	C_5H_9	*d*	
65	H	$CH_2CH_2CH_3$	6	(0)[b]
66	H	$CH(CH_3)_2$	4	30
67	H	CH_2SCH_3	23	
68	H	$(CH_2)_3CH_3$	18	
69	H	$CH(CH_3)CH_2CH_3$	13.5	
70	H	$CH_2CH(CH_3)_2$	10	(0)[b]
55	CH_3	$CH_2C_3H_5$	7.5	35
71	CH_2CH_3	$CH_2C_3H_5$	20	
72	CH_3	C_3H_5	4.5	12.5
73	CHO	$CH_2C_3H_5$	8	30
74	CHO	$CH(CH_3)C_3H_5$ (−)	2.5	7.5
75	CHO	$CH_2C_4H_7$	7	
76	CHO	C_3H_5	2.4	7.4 ± 0.9[c]
77	$COCH_3$	C_3H_5	(22)[b]	
78	CHO	C_4H_7	20	(0)[b]

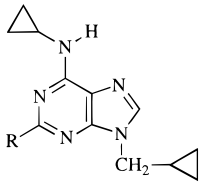
[a] See footnote *a* in Table 3. [b] Percent inhibition at 25 mg/kg. [c] At twice the ED$_{50}$, the duration of action was 14 h. [d] Toxic at 25 mg/kg.

9-cyclopentyl **64** was toxic at 25 mg/kg, cyclobutyl **63** had fair activity, and cyclopropyl **62** was equipotent to **54** by the ip route of administration. However, the oral ED$_{50}$ of **62** was 20 mg/kg, and it was relatively toxic with an LD$_{50}$ of 130 mg/kg. Noncyclic aliphatic 9-substituents gave analogues with ip ED$_{50}$s ranging from 4 mg/kg for 2-propyl **66** to 23 mg/kg for methylthiomethyl **67**, but the oral potency of **66** was much less than that of **54**.

Substitution on the 6-amino group of **54** with methyl (**55**) (Table 5) or ethyl (**71**) led to less active agents. However, N(6)-methylation of **62** gave **72**, which was equipotent with **54**, but the LD$_{50}$ was not improved. With the intention of decreasing toxicity, the *N*-formyl derivative of **54** (**73**) was evaluated. Indeed, the LD$_{50}$ for **73**, was much higher at 500 mg/kg, but the oral ED$_{50}$ was also higher, giving a safety ratio of 16. The formyl derivatives of **57**, **60**, **62**, and **63** were also evaluated (see **74**−**76**, **78**). Both **74** and **76** demonstrated excellent activity with ip and oral ED$_{50}$s of about 2.5 and 7.5 mg/kg, respectively. The oral LD$_{50}$ of **76** was 175 mg/kg, for a safety ratio of 23.

Metabolism studies revealed that **76** is rapidly converted to **62** *in vitro*.[24] When **76** was administered to mice po the plasma levels of **62** accounted for most of the compound within 5 min and levels were sustained over several hours. Although **76** is stable as a solid, in water (pH 7) it is 25% deformylated to **62** in 24 h. Thus, exposure to plasma considerably accelerates deformylation to generate **62**. Administration of **62** as the prodrug **76** results in increased plasma levels of **62** and

Table 7. Antagonism of Apomorphine−Induced Aggression by 2−Substituted−6−(cyclopropylamino)−9−cyclopropylmethylpurines



		ED_{50}, mg/kg[a]	
no.	R	ip	po
54	H	4	12
79	Cl	2.5	4
80	CF_3	0.9	2.0
81	NH_2	9	(26)[b]
82	$NHCH_3$	3	12.5
83	$NHCH_2CH_3$	9	11
84	$N(CH_3)_2$		
85	OCH_3		3.7
86	OCH_2CH_3	0.8	4
87	$O(CH_2)_2CH_3$	2.5	2.5
88	SCH_3	5	

[a] See footnote *a* in Table 3. [b] Percent inhibition at 25 mg/kg.

in an apparent improved pharmacological profile. However, secondary pharmacological studies revealed that **76** had a pronounced effect on the cardiovascular system. In unconscious dogs, iv administration of **76** resulted in tachycardia.[25]

2-Substituted-6-(cyclopropylamino)purines. To find an analogue free of cardiovascular effects, we examined a series of 2-substituted analogues of **54** (Table 7). The 2-chloro analogue **79** had improved potency, and the 2-(trifluoromethyl) analogue **80** was even more active with an ip ED_{50} of 0.9 mg/kg and an oral ED_{50} of 2 mg/kg, some 6-fold more potent than parent **54**. Its oral LD_{50} was greater than 100 mg/kg, for a safety ratio greater than 50, and the propensity to cause tachycardia was substantially less than that of **76**. Other 2-substituents such as amino (**81**) and alkylamino (**81**−**84**) gave analogues that were less active. The alkoxy analogues (**85**−**87**) had excellent oral activity, but they were too toxic to warrant further study.

The compounds in Tables 3−7 were tested for their ability to inhibit binding to dopamine D_1 and D_2 receptors. None of the compounds tested inhibited the binding of [^{3}H]SCH23390 to rat striatal dopamine D_1 receptors or the binding of [^{3}H]raclopride to rat striatal dopamine D_2 receptors by greater than 50% at a concentration of 10^{-5} M.

(Trifluoromethyl)purine **80** appeared to be an excellent candidate for development as an antipsychotic agent. However, in acute oral toxicity studies in fasted rats, the gross pathological findings revealed varying degrees of damage of stomach mucosa.[26] These findings prompted further study of the effect of **80** and several other analogues on stomach emptying. Compounds **35**, **60**, **76**, and **80** were studied in rats in a semiquantitative test for blockade of stomach emptying based on the elimination of phenol red dye.[27] Compounds were tested at the oral ED_{50} dose for blockage of apomorphine-induced aggression, and the degree of retardation of stomach emptying during a 1-h period was determined. Stomach emptying was retarded by 25−100% for **35** (100%), **60** (25%), **76** (100%), and **80** (45%) at oral doses relevant to the potential antipsychotic activity. This property was considered to be incompatible with further development of **80** as a candidate antipsychotic agent.

Conclusion

The synthesis and pharmacological evaluation of a series of 6-(alkylamino)-9-substituted purines has led to agents with potent activity in the apomorphine-induced aggressive behavior test. The activity of compound **1** was improved 48-fold with 2-(trifluoromethyl)-purine **80** (oral ED_{50} = 2 mg/kg) through an iterative series of structure-activity relationship studies that encompassed evaluation of the effect of structure variations at the purine 9-, 6-, and 2-positions. Potency was enhanced with the 9-(cyclopropylmethyl) group of **35**, the duration of action was improved with the 6-(cyclopropylamino) substituent of **54**, activity was further enhanced with the *N*-formyl prodrug **76**, and an agent with less cardiovascular effects emerged with 2-(trifluoromethyl)purine **80**. The lack of any inhibition of binding to either dopamine D_1 and D_2 receptors would indicate that the behavioral effects in these compounds are not caused by direct interaction with dopamine D_1 or D_2 receptors. Although the overall profile of **80** is incompatible with clinical development, the 6-(alkylamino)-9-alkylpurines represent a new class of candidate antipsychotic agents. These compounds may serve as useful leads for further research.

Experimental Section

5-Amino-4,6-dichloropyrimidine was purchased from Pacific Chemical Laboratories, and 100% formic acid was obtained from Fluka. Melting points were taken in capillary tubes on a Mel-Temp block or a Thomas-Hoover Unimelt and were uncorrected. UV spectra were measured on a Unicam SP 800 or a Cary 118 UV−vis spectrophotometer. NMR data were recorded on a Varian XL-100-15-FT, a Varian FT-80A, a Varian T-60, or an Hitachi Perkin-Elmer R-24 spectrometer with Me_4Si as an internal standard. Each analytical sample produced spectral data compatible with its assigned structure and moved as a single spot on TLC. TLCs were developed on Whatman 200 μm MK6F plates of silica gel with fluorescent indicator. Preparative flash chromatography[28] was performed on silica gel 60 (40−63 μM, E. Merck, no. 9385). In Tables 1−6 cycloalkanes are designated as follows: C_3H_5 for cyclopropyl, C_4H_7 for cyclobutyl, C_5H_9 for cyclopentyl, C_6H_{11} for cyclohexyl, and C_7H_{13} for cycloheptyl. All compounds were analyzed for C, H, N and gave values within 0.4% of the theoretical values. Elemental analyses were performed by Atlantic Microlab, Inc.

Method A. 5-Amino-4-chloro-6-(propylamino)pyrimidine (89). A mixture of 5-amino-4,6-dichloropyrimidine (10.0 g, 61.0 mmol), 1-propylamine (4.50 g, 76.2 mmol), 1-butanol (120 mL), and triethylamine (7.1 g, 76.2 mmol) was refluxed with stirring for 16 h. The resultant solution was spin evaporated *in vacuo*. The residual oil was dissolved in dichloromethane (125 mL) and washed with water (3 × 10 mL). The combined extracts were spin evaporated *in vacuo*, redissolved in dichloromethane, and added to silica gel 60. This mixture was spin evaporated, and the residual solids were introduced on a column of silica gel 60 wetted with ethyl acetate:cyclohexane 1:2. The column was eluted with the same solvent using the flash chromatography technique. The fractions were combined and spin evaporated to give 10.86 g (95%) of **89**, mp 113−114 °C, which was single spot on TLC (ethyl acetate-cyclohexane 1:2). Recrystallization of 1.00 g of **89** from cyclohexane gave 0.79 g of analytically pure material of unchanged melting point: ^{1}H NMR (DMSO-d_6) 7.72 (s, 1H, CH), 6.77 (br m, 1H, NH), 4.98 (br s, 2H, NH_2), 3.35 (q, 2H, NCH_2), 1.57 (m, 2H, CH_2CH_3), 0.92 (t, 3H, CH_3).

Method B. 5-Amino-4-chloro-6-(cyclopropylamino)-pyrimidine (96). A mixture of 5-amino-4,6-dichloropyrimidine (40.0 g, 244 mmol), 1-propanol (400 mL), and cyclopropyl amine (69.0 g, 1.208 mol) was refluxed with stirring for 3 h and then stirred at ambient temperature for 3 days. The resultant solution was spin evaporated. The residual oil was dissolved in dichloromethane (600 mL) and washed with water (3 × 50 mL). The combined aqueous extracts were back-washed with dichloromethane (4 × 50 mL). The combined dichloromethane solutions were filtered through glass wool and spin evaporated *in vacuo*. The yellow solid was stirred and heated with cyclohexane (300 mL), cooled, collected, and dried at 100 °C to give 42.40 g (94%) of **96**, mp 153−156 °C. Recrystallization of a sample from toluene gave the analytical sample: mp 156−158 °C; ^{1}H NMR (DMSO-d_6) δ 7.78 (s, 1H, NCHN), 6.92 (br s, 1H, NH), 4.95 (br s, 2H, NH_2), 2.87 (m, 1H, NCHC), 0.85−0.40 (m, 4H, CH_2CH_2).

Method C. 6-Chloro-9-(cyclopropylmethyl)-9*H*-purine (102). A mixture of dry **94** (11.86 g, 59.7 mmol), triethyl orthoformate (75 mL), and ethanesulfonic acid (0.125 mL) was stirred at ambient temperature for 68 h. The reaction was spin evaporated *in vacuo*. The brown residue was dissolved in dichloromethane (125 mL) and washed with 5% aqueous sodium bicarbonate (15 mL) and water (15 mL). The solution was filtered through glass wool and spin evaporated *in vacuo* to give a quantitative yield of **102**, which was essentially a single spot on TLC. This material was used without further purification in the next reaction: UV (0.1 N HCl plus 20% EtOH): λ_{max} 265 nm; UV (0.1 N NaOH plus 20% EtOH); λ_{max} 266 nm; ^{1}H NMR (DMSO-d_6) δ 8.70 (s, 2H, purine Hs), 4.10 (d, 2H, J = 6 Hz, NCH_2), 1.35 (m, 1H, CH), 0.45 (m, 4H, CH_2-CH_2).

Method D. 9-(Cyclopropylmethyl)-6-(dimethylamino)-9*H*-purine (35). A solution of **102** (10.2 g, 49.0 mmol), ethanol (50 mL), and 40% aqueous dimethylamine (25 mL) was stirred at ambient temperature for 18 h. The reaction was spin evaporated to remove the volatiles. The residue was dissolved in dichloromethane (200 mL) and washed with water (2 × 50 mL). The combined extracts were spin evaporated *in vacuo*, redissolved in dichloromethane, and added to silica gel 60. This mixture was spin evaporated, and the residual solids were introduced on a 5-cm-diameter column of silica gel 60 wetted with ethyl acetate. The column was eluted with ethyl acetate using the flash chromatography technique. The appropriate fractions were combined and spin evaporated to give a homogeneous residue, which was recrystallized from pentane: cyclohexane to give 7.86 g (73%) of **35**: mp 68−70°; ^{1}H NMR (DMSO-d_6) δ 8.23 (s, 1H, purine H), 8.20 (s, 1H, purine H), 4.03 (d, 2H, J = 7 Hz, NCH_2), 3.47 (s, 6H, $N(CH_3)_2$), 1.30 (m, 1H, CH), 0.50 (m, 4H, CH_2CH_2).

Method E. 9-*tert*-Butyl-6-chloro-9*H*-purine (103). A solution of 5-amino-4-(*tert*-butylamino)-6-chloropyrimidine (4.53 g, 22.6 mmol), triethyl orthoformate (50 mL), and ethanesulfonic acid (0.1 mL) was refluxed with stirring for 5 days. The reaction was spin evaporated *in vacuo*. The residue was dissolved in ethyl acetate (100 mL) and washed with 5% aqueous sodium bicarbonate (2 × 25 mL) and water (25 mL). The volatiles were removed by spin evaporation to give an oil that was crystallized from methanol to give 2.93 g of **103**, mp 144−146 °C. The mother liquors were processed to give an additional 0.52 g of crystals, mp 140−143.5 °C. A second recrystallization of the combined crops from heptane gave 3.06 g (64%) of **103**: mp 144−146 °C; ^{1}H NMR (DMSO-d_6) δ 8.75 (s, 1H, purine H), 8.67 (s, 1H, purine H), 1.78 (s, 9H, $(CH_3)_3$). Anal. ($C_9H_{11}ClN_4$) C, H, N.

Method F. 9-(Cyclopropylmethyl)-(*N*-methylethylamino)-9*H*-purine Hydrochloride (44). A solution of **102** (3.0 g, 14.4 mmol), ethanol (30 mL), ethylmethylamine hydrochloride (4.11 g, 42.9 mmol), triethylamine (5 mL), and water (15 mL) was stirred at ambient temperature for 66 h. The reaction was spin evaporated *in vacuo* to remove the volatiles. The residue was dissolved in dichloromethane (100 mL) and washed with water (2 × 25 mL). The combined extracts were spin evaporated *in vacuo*, dissolved in ether, and diluted with hydrogen chloride saturated ether. The solids were collected and recrystallized from ethyl acetate to give 2.15 g (55%) of **44**, mp 157−159 °C (with softening and resolidification at ∼134 °C); ^{1}H NMR (DMSO-d_6) δ 11.26 (br s, 1H, HCl), 8.57 (s, 1H, purine H), 8.43 (s, 1H, purine H), 4.2 (br m, 2H, NCH_2CH_3), 4.17 (d, 2H, J = 8 Hz, NCH_2CH), 3.37 (s, 3H, NCH_3), 1.27 (t, 3H, J = 7, CCH_3), 1.2 (br m, 1H, CH), 0.53 (m, 4H, CH_2CH_2).

Method G. 6-Chloro-9-cyclopropyl-9*H*-purine (104). A mixture of dry **96** (21.70 g, 117.5 mmol), triethyl orthoformate (300 mL), and ethanesulfonic acid (0.25 mL) was stirred at ambient temperature for 46 h. The reaction was spin evaporated *in vacuo*. The brown residue was dissolved in dichloromethane and added to silica gel 60. This mixture was spin evaporated *in vacuo* and the residual solids were introduced on a column of silica gel 60 wetted with ethyl acetate: cyclohexane 2:1. The column was eluted with ethyl acetate: cyclohexane 2:1 using the flash chromatography technique. The appropriate fractions were pooled and spin evaporated to give 18.40 g (80%) of **104**, mp 114−117 °C. Recrystallization of a sample from cyclohexane:ethyl acetate gave the analytical sample: mp 118−119 °C; ^{1}H NMR ($CDCl_3$) δ 8.77 (s, 1H, purine H), 8.13 (s, 1H, purine H), 3.53 (m, 1H, NCH), 1.2 (m, 4H, CH_2CH_2). Anal. ($C_8H_7ClN_4$) C, H, N.

Method H. 6-Amino-9-(cyclopropylmethyl)-9*H*-purine (43). A solution of **102** (5.00 g, 24.0 mmol) and methanol saturated with ammonia (75 mL) was heated at 90 °C in a stainless steel reaction vessel for 18 h. The vessel was cooled, and the solids were collected to give 3.11 g (68%) of **43**, mp 192−195 °C. The filtrates were evaporated, the residue was dispersed in water, and the solids were collected to give 0.60 g of a second crop. The combined solids were recrystallized from ethanol to give 3.06 g (67%) of 43: mp 190−193 °C; ^{1}H NMR (DMSO-d_6) δ 8.20 (s, 2H, purine Hs), 7.22 (br s, 2H, NH_2), 4.02 (d, 2H, J = 7 Hz, NCH_2), 1.27 (m, 1H, CH), 0.50 (m, 4H, CH_2CH_2).

Method I. 9-Cyclopropyl-6-(cyclopropylamino)-9*H*-purine (62). A solution of **104** (27.20 g, 140.0 mmol), cyclopropylamine (30 mL), triethylamine (40 mL), and ethanol (200 mL) was stirred at ambient temperature for 15 h. The reaction was spin evaporated to remove the volatiles. The residue was dissolved in dichloromethane (500 mL) and washed with water (2 × 50 mL). The solution was filtered through glass wool and spin evaporated *in vacuo*. The yellow residue was digested with hot cyclohexane (200 mL), cooled, collected, and dried at 80 °C to give 25.77 g (85%) of **62**, mp 156−158 °C, which was a single spot on TLC (ethyl acetate: ethanol 10:1). Recrystallization of 4.00 g of **62** from cyclohexane:ethyl acetate (charcoal) gave 2.80 g of analytically pure 62: mp 157−159 °C; ^{1}H NMR (DMSO-d_6) δ 8.30 (s, 1H, purine H), 8.13 (s, 1H, purine H), 7.82 (br d, 1H, NH), 3.50 (m, 1H, NCH), 3.13 (m, 1H, HNC*H*), 1.10 (m, 4H, CH_2CH_2), 0.73 (m, 4H, $HNCH(CH_2)_2$).

Method J. 9-Butyl-6-(cyclopropylamino)-9*H*-purine Hydrochloride (68). A solution of 9-butyl-6-chloro-9*H*-purine (9.50 g, 45.1 mmol), cyclopropylamine (15 mL), triethylamine (10 mL), and ethanol (100 mL) was stirred at ambient temperature for 72 h. The reaction was spin evaporated to remove the volatiles. The residue was dissolved in dichloromethane (200 mL) and washed with water (2 × 50 mL). The combined extracts were spin evaporated *in vacuo*, redissolved in dichloromethane, and added to silica gel 60. This mixture was spin evaporated, and the residual solids were introduced on a 5-cm-diameter column of silica gel 60 wetted with ethyl acetate. The column was eluted with 2% ethanol in ethyl acetate using the flash chromatography technique. The appropriate fractions were combined and spin evaporated to give 9.00 g (86%) of **68** as a homogeneous oil. The oil was dissolved in ethanol (100 mL), diluted with 12 N hydrochloric acid (5 mL), and spin evaporated *in vacuo* to remove the volatiles. The residue was recrystallized from ethyl acetate:ethanol to give 1.49 g (12%) of **68**·HCl, mp 166−168 °C. The volume of the mother liquors was condensed to give an additional 2.42 g (32% total) of **68**·HCl: mp 167−170 °C; ^{1}H NMR (DMSO-d_6) δ 12.2 (br, 1H, HCl), 10.07 (br, 1H, NH), 8.67 (s, 1H, purine H), 8.53 (s, 1H, purine H), 4.33 (t, 2H, J = 7 Hz, NCH_2), 3.13 (br, 1H, NCH), 1.88 (m, 2H, NCH_2CH_2), 1.5−0.67 (m, 9H, CH_2-CH_3, $NCH(CH_2)_2$).

Method K. 9-(1-(2-Methyl)propyl)-6-(cyclopropylamino)-9*H*-purine (70). A solution of 6-chloro-9-(1-(2-methyl)-propyl)-9*H*-purine (9.50 g, 45.1 mmol), cyclopropylamine (14 mL), triethylamine (10 mL), and ethanol (100 mL0 was stirred at ambient temperature for 72 h. The reaction was spin evaporated to remove the volatiles. The residue was dissolved in dichloromethane (200 mL) and washed with water (2 × 50 mL). The combined extracts were spin evaporated *in vacuo*, redissolved in dichloromethane, and added to silica gel 60. This mixture was spin evaporated, and the residual solids were introduced on a 5-cm-diameter column of silica gel 60 wetted with ethyl acetate. The column was eluted with 2% ethanol in ethyl acetate using the flash chromatography technique. The appropriate fractions were combined and spin evaporated to give a solid that was recrystallized from cyclohexane: ethyl acetate to give 6.39 g (61%) of 70: mp 156−160 °C; ^{1}H NMR (DMSO-d_6) δ 8.28 (s, 1H, purine H), 8.15 (s, 1H, purine H), 7.81 (br d, 2H, NH), 4.00 (d, 1H, I = 7 Hz, NCH_2), 3.13 (m, 1H, HNC*H*), 2.27 (m, 1H, C*H*$(CH_3)_2$) 0.83 (d, 6H, J = 6 Hz, $(CH_3)_2$), 0.67 (m, 4H, CH_2CH_2).

Method L. 6-Chloro-9-[(methylthio)methyl]-9*H*-purine (105). A mixture of 6-chloropurine (7.00 g, 45.3 mmol), dimethyl sulfoxide (100 mL), anhydrous potassium carbonate (8.00 g, 58.0 mmol), and chloromethyl methyl sulfide (3.90 g, 40.4 mmol) was stirred at ambient temperature for 6 days. The reaction was poured into ice water (400 mL) and extracted with dichloromethane (4 × 100 mL). The combined extracts were washed with water (6 × 50 mL), filtered through glass wool, and spin evaporated *in vacuo*. The residue was dissolved in dichloromethane and added to silica gel 60. This mixture was spin evaporated *in vacuo*, and the residual solids were introduced on a 4-cm-diameter column of silica gel 60 wetted with ethyl acetate:cyclohexane 1:1. The column was eluted with the same solvent using the flash chromatography technique. The fractions containing the higher R_f (major spot) were combined and spin evaporated to give 1.20 g (10%) of **105**, which was a single spot on TLC (ethyl acetate:cyclohexane 1:1): UV (0.1 *N* HCl) λ_{max} 265.5 nm; UV (0.1 *N* NaOH) λ_{max} 265.5 nm.

Method M. 9-(Cyclopropylmethyl)-6-(ethylcyclopropylamino)-9*H*-purine (71). To a magnetically stirred dispersion of cyclohexane-washed sodium hydride (60.2% in mineral oil) (2.60 g, 65.2 mmol) in dimethyl sulfoxide (75 mL) was added **54** (8.00 g, 34.8 mmol) in portions. After 1 h, when dissolution was complete, ethyl iodide (8 mL) was added, and the reaction was stirred for 2 h. The reaction was diluted with ethanol (10 mL) and then poured over ice water (300 mL). The mixture was acidified to pH 5−6 with acetic acid (5 mL) and extracted with dichloromethane (4 × 75 mL). The combined extracts were back-washed with water (5 × 50 mL) to remove residual dimethyl sulfoxide, filtered through glass wool, and spin evaporated *in vacuo*. The residual oil was dissolved in dichloromethane and applied to a 4-cm-diameter column of silica gel 60. The column was eluted with ethyl acetate: cyclohexane 1:1 using the flash chromatography technique. The appropriate fractions were pooled and spin evaporated to give 8.72 g (97%) of **71** as an oil, which was a single spot on TLC (ethyl acetate:cyclohexane 1:1): ^{1}H NMR (DMSO-d_6) δ 8.28 (s, 1H, purine H), 8.20 (s, 1H, purine H), 4.07 (q, 2H, C*H*$_2$-CH_3), 4.02 (d, 2H, C*H*$_2$CH), 3.17 (m, 1H, NCH), 1.17 (t, 3H, CH_3), 1.5−0.33 (m, 9H, $CH(CH_2)_2$, CH_2CH_2).

Method N. 6-(*N*-Cyclopropylformamido)-9-cyclopropyl-9*H*-purine (76). To a stirred, ice-bath-cooled solution of **62** (18.82 g, 87.5 mmol), 4-dimethyl-aminopyridine (11.00 g, 90.0 mmol), and dry dichloromethane (200 mL) was added the acetic formic anhydride prepared from acetic anhydride (100 mL) and 100% formic acid (50 mL).[20] The solution was refluxed with stirring for 1.5 h, cooled on ice, and recharged with the acetic formic anhydride prepared from acetic anhydride (50 mL) and 100% formic acid (25 mL). The solution was refluxed with stirring for 1.5 h and then stirred at ambient temperature for 15 h. The reaction was spin evaporated to remove the volatiles. The residue was dissolved in ethyl acetate (200 mL), cooled, and spin evaporated. The residual solid was dissolved in dichloromethane (400 mL), washed with water (3 × 25 mL), with 5% aqueous sodium bicarbonate (3 × 25 mL), with water (25 mL), and then filtered through glass wool. The solution was spin evaporated *in vacuo*. The residue was dissolved in dichloromethane and added to silica gel 60 wetted with ethyl acetate:cyclohexane 2:1. The column was eluted with ethyl acetate:cyclohexane 2:1 using the flash chromatography technique. The fractions containing the highest R_f (major spot) were combined and spin evaporated *in vacuo* to give 14.20 g (66%) of **76**, mp 122−124 °C, which was a single spot on TLC (ethyl acetate). Recrystallization from cyclohexane:ethyl acetate gave the analytical sample: mp 125−126 °C; ^{1}H NMR (DMSO-d_6) δ 9.75 (s, 1H, HCO), 8.77 (s, 1H, purine H), 8.53 (s, 1H, purine H), 3.60 (m, 1H, NCH), 3.00 (m, 1H, OCNCH), 1.33−0.43 (m, 8H, 2 CH_2CH_2).

Method O. 6-(Cyclopropylamino)-9-(cyclopropylmethyl)-2-(methylamino)-9*H*-purine (82). A mixture of **79** (5.25 g, 19.90 mmol), ethanol (50 mL), and 40% aqueous methylamine (20 mL) was heated at 80 °C in a stainless steel reaction vessel for 60 h. The vessel was cooled, and the contents were spin evaporated *in vacuo*. The residue was purified by the flash chromatography technique as described in method D to give 5.00 g (97%) of **82**, which was a single spot on TLC (ethyl acetate). Recrystallization from ethyl acetate gave 3.20 g (62%) of **82**: mp 147−149 °C; NMR (DMSO-d_6) δ 7.72 (s, 1H, H-8), 7.21 (d, 1H, J = 4.8 Hz, N*H*CH), 6.20 (q, 1H, J = 4.8, N*H*CH_3), 3.82 (d, 2H, J = 7.0 Hz, NCH_2), 3.0 (m, 1H, NCH), 2.79 (d, 2H, J = 4.8, CH_3), 1.2 (m, 1H, NCH_2CH), 0.70−0.39 (m, 8H, 2 CH_2CH_2).

Method P. 6-(Cyclopropylamino)-9-(cyclopropylmethyl)-2-ethoxy-9*H*-purine (86). Ethanol (100 mL) was added dropwise to sodium hydride (60.2% in mineral oil) (2.00 g, 50.0 mmol) under a nitrogen atmosphere with ice-bath cooling. Compound **79** (3.56 g, 13.5 mmol) was added to the solution of sodium ethoxide, and the reaction was refluxed with stirring for 20 h. The cooled solution was spin evaporated to dryness, and the residue was dissolved in dichloromethane (350 mL). The solution was washed with water (200 mL), filtered through glass wool, and spin evaporated *in vacuo*. The solid was recrystallized from cyclohexane to give 1.79 g (48%) of **86**: mp 97−99 °C; NMR (DMSO-d_6) δ 7.96 (s, 1H, 8-H), 7.85 (d, 1H, J = 7.0 Hz, NH), 4.30 (q, 2H, J = 7.0, OCH_2), 3.90 (d, 2H, J = 7.1, NCH_2), 3.0 (m, 1H, NCH), 1.31 (t, 3H, J = 7.0, CH_3), 1.2 (m, 1H, NCH_2CH), 0.73−0.38 (m, 8H, 2 CH_2CH_2).

9-Cyclopropyl-6-(*N*-cyclopropylacetamido)-9*H*-purine (77). A solution of **62** (2.00 g, 9.29 mmol) and acetic anhydride (10 mL) was refluxed with stirring for 15 min. The solution was spin evaporated *in vacuo*, diluted with ethyl acetate, and re-evaporated to remove the volatiles. The residue was recrystallized from ethyl acetate to give 1.74 g (72%) of **77**: mp 146−147 °C; ^{1}H NMR (DMSO-d_6) δ 8.83 (s, 1H, purine H), 8.54 (s, 1H, purine H), 3.6 (m, 1H, NCH), 3.2 (m, 1H, OCNCH), 2.11 (s, 3H, CH_3), 1.2−0.3 (m, 8H, 2 CH_2-CH_2).

2-Chloro-6-(cyclopropylamino)-9-(cyclopropylmethyl)-9*H*-purine (79). This compound was prepared from **111** (22.5 g, 107.4 mmol) and chloromethylcyclopropane (17.0 g, 188.0 mmol) by method L, except that the reaction was heated at 60 °C for 8 h and stirred at ambient temperature for 2 days. The chromatography solution was spin evaporated *in vacuo* to give 19.0 g (67%) of **79**, mp 139−142 °C. The analytical sample was recrystallized from cyclohexane:ethyl acetate: mp 144−146 °C; UV (0.1 N HCl) λ_{max} 281 nm; UV (0.1 N NaOH) λ_{max} 274 nm; ^{1}H NMR (DMSO-d_6) δ 8.36 (d, 1H, NH), 8.20 (s, 1H, H-8), 3.96 (d, 2H, J = 7.1 Hz, NCH_2), 3.0 (br, 1H, NCH), 1.3 (m, 1H, NCH_2CH), 0.7−0.4 (m, 8H, 2 CH_2CH_2); ^{13}CNMR (DMSO-d_6) δ 156.17 (C-6), 152.93 (C-2), 140.87 (C-8), 118.04 (C-5).

6-Cyclopropylamino)-9-(cyclopropylmethyl)-2-(trifluoromethyl)-9*H*-purine (80). This compound was prepared from **112** (1.61 g, 6.63 mmol) and chloromethylcyclopropane (1.10 g, 12.1 mmol) by method L, except that the reaction was heated at 60 °C for 5 h and stirred at ambient temperature for 2 days. The chromatography solution was spin evaporated *in vacuo* to give 1.30 g (66%) of **80**, which was one spot on TLC. The analytical sample was recrystallized from cyclohexane: mp 101−103 °C; UV (0.1 N HCl) λ_{max} 281 nm; UV (0.1 N NaOH) λ_{max} 271 nm; NMR (DMSO-d_6) δ 8.42 (d, 1H,

NH), 8.39 (s, 1H H-8), 4.06 (d, 2H, $J = 7.2$ Hz, NCH_2), 3.2 (br, 1H, NCH), 1.3 (m, 1H, NCH_2CH), 0.8−0.4 (m, 8H, 2 CH_2CH_2).

2-Amino-6-(cyclopropylamino)-9-(cyclopropylmethyl)-9*H*-purine (81). A solution of **114** (2.50 g, 11.18 mmol), ethanol (50 mL), cyclopropylamine (10 mL), and water (5 mL) was heated at 75 °C in a stainless steel reaction vessel for 48 h. The vessel was cooled, and the contents were spin evaporated *in vacuo*. The residue was dispersed in water (50 mL), and the solid was collected and washed with water. Recrystallization from ethyl acetate gave 1.75 g (64%) of **81**: mp 160−162 °C; UV (0.1 N HCl) λ_{max} 297, 257 nm; UV (0.1 N NaOH) λ_{max} 284, 262 (sh) nm; NMR (DMSO-d_6) δ 7.74 (s, 1H, H-8) 7.24 (d, 1H, $J = 4.5$ Hz, NH), 5.81 (s, 2H, NH_2), 3.80 (d, 2H, $J = 7.0$ Hz, NCH_2), 3.05 (m, 1H, NCH_2CH), 1.25 (m, 1H, NCH), 0.69−0.34 (m, 8H, 2 CH_2CH_2).

(Cyclopentylmethyl)amine Hydrochloride (106). A solution of 1 M borane in tetrahydrofuran (527 mL, 527 mmol) was added dropwise over 2 h to a stirred solution of cyclopentanecarbonitrile (45.6 g, 479 mmol) in dry tetrahydrofuran (50 mL). The resultant solution was refluxed with stirring for 18 h. The reaction was cooled to ambient temperature and cautiously diluted in small portions with methanol (670 mL). The solution was cooled on an ice bath, and hydrogen chloride gas was bubbled through the solution for 0.5 h. The reaction was refluxed for 1.5 h, and the volatiles were removed by spin evaporation *in vacuo*. Methanol (500 mL) was added to the residue, and the mixture was spin evaporated *in vacuo*. This methanol addition procedure was repeated twice to give a white solid, which was recrystallized from ethanol:ethyl acetate to give 36.2 g (56%) of (cyclopentylmethyl)amine hydrochloride, mp 226−230 °C (dec). Recrystallization from ethanol:*tert*-butyl methyl ether gave the analytical sample, mp 227.5−230 °C (dec) (lit.[29]). Anal. ($C_6H_{13}N$·HCl) C, H, N.

(rac)-1-Cyclopropylethylamine Hydrochloride (107). To ammonium acetate (230 g, 2.98 mol), which had been repeatedly diluted with 2-propanol and spin evaporated until a dry granular solid was obtained, were added dry methanol (500 mL), cyclopropyl methyl ketone (25.0 g, 282 mmol), and sodium cyanoborohydride (20.0 g, 318 mmol). The reaction was stirred under a calcium chloride tube at ambient temperature for 120 h. The reaction solution was cooled on an ice bath and cautiously acidified in an efficient hood to pH 1 with 12 M hydrochloric acid (225 mL). The resultant mixture was spin evaporated *in vacuo*, and the white residue was dissolved in water (800 mL). The solution was washed with three portions of diethyl ether (3 × 500 mL). The aqueous solution was cooled on an ice bath and basified to pH 11 with solid potassium hydroxide (120 g). This solution was extracted with diethyl ether (5 × 600 mL), and the combined extracts were dried with magnesium sulfate. The mixture was filtered, and the ether was removed by fractional distillation through a 30-cm Vigreux column on a hot-water bath at 50−60 °C. The residual amine was distilled through a 10-cm Vigreux column to give 32.3 g of crude 1-cyclopropylethylamine, bp 82−91 °C (lit.[30] bp 91−94 °C (740 mm)). This material was dissolved in ethanol (250 mL), diluted with 12 M hydrochloric acid (30 mL), and spin evaporated *in vacuo*. The residue was recrystallized from ethanol to give 10.16 g (29%) of **107** hydrochloride, mp 180−181 °C. The mother liquors were condensed to give an additional 6.57 g (48%) of product: mp 180−182 °C; ^{1}H NMR (DMSO-d_6) δ 8.75 (br s, 3H, NH_3Cl), 3.00 (m, 1H, NCH), 1.74 (d, 3H, $J = 6$ Hz, CH_3), 1.50 (m, 1H, $CH(CH_2)_2$), 1.00 (m, 4H, CH_2CH_2). Anal. ($C_5H_{11}N$·HCl) C, H, N.

(+)-1-Cyclopropylethylamine (108a). This compound was prepared by the method of Vogel and Roberts.[30] For characterization, a 5-g sample of liquid **108a** was dissolved in 100 mL of ethanol, diluted with 5 mL of concentrated hydrochloric acid, and spin evaporated *in vacuo*. The residue was covered with ethanol and re-evaporated. The residue was covered with diethyl ether, which induced crystallization, and the solids were collected and dried to give 2.55 g of the hydrochloride: mp 197−198 °C; $[\alpha]_D^{20}$ −3.6° (c 1.0, H_2O).

(−)-1-(Cyclopropyl)ethylamine (108b). To an ice-bath-cooled solution of L-tartaric acid (42.30 g, 281.8 mmol) in water (31 mL) was added a cold solution of racemic 1-cyclopropylethylamine (**107**) (23.93 g, 281.2 mmol) in water (25 mL). The resultant crystals were collected, washed with cold water (25 mL), and dried. The crude product was recrystallized eight times from ethanol:water to a constant melting point to give 15.08 g (45%) of the L-tartaric acid salt of **108b**: mp 163−164.5 °C. An additional recrystallization of a portion gave the analytical sample of unchanged melting point. Anal. ($C_9H_{17}NO_6$) C, H, N. Fourteen grams of the tartrate was cautiously added to a cold, saturated solution of potassium carbonate (100 g) in water (200 mL). The resultant mixture was extracted with diethyl ether (6 × 100 mL), and the combined extracts were dried over anhydrous potassium carbonate. The mixture was filtered, and the ether was removed by fractional distillation through a 30-cm Vigreux column on a hot-water bath at 50−60 °C. The residual amine (6.41 g), which contained some diethyl ether, was used without further purification in the next step. From a separate preparation, 8.70 g of **108b** was converted to the hydrochloride as described for **108a** to give 4.82 g of the hydrochloride of **108b**: mp 195−196.5 °C; $[\alpha]^{20}_D$ +3.3° (*c* 1.0, H_2O).

2-Chloro-6-(cyclopropylamino)-9*H*-purine (111). A mixture of 2,6-dichloropurine (**109**) (5.00 g, 26.5 mmol), ethanol (25 mL), and cyclopropylamine (5 mL) was stirred at ambient temperature for 24 h. The solid was collected by suction filtration and then dispersed in water (25 mL) with manual stirring. The white solid was collected and dried to give 4.52 g (81%) of **111**, mp 260−264 °C, which was one spot on TLC (silica gel, EtOH:EtOAc 1:10). Recrystallization of a portion from ethanol:water gave the analytical sample: mp 249−251 °C; NMR (DMSO-d_6) δ 8.23 (d, 1H, HNC_3H_5), 8.12 (s, 1H, H-8), 3.1 (br m, 1H, HNC*H*), 0.70 (m, 4H, CH_2CH_2). Anal. ($C_8H_8ClN_5$) C, H, N.

6-(Cyclopropylamino)-2-(trifluoromethyl)-9*H*-purine (112). This compound was prepared from **110**[21] (2.00 g, 8.98 mmol) as described for **111** to give 1.16 g (53%) of **112**, mp 270−274 °C, which was one spot on TLC (silica gel, EtOH:EtOAC 1:10). Recrystallization of a portion from ethyl acetate gave the analytical sample: mp 276−278 °C; NMR (DMSO-d_6) δ 8.32 (br s, 2H, H-8 and HNC_3H_5), 3.2 (br m, 1H, HNC*H*), 0.70 (m, 4H, CH_2CH_2). Anal. ($C_9H_8F_3N_5$) C, H, N.

2-Amino-6-chloro-9-(cyclopropylmethyl)-9*H*-purine (114). This compound was prepared from **113** (10.00 g, 58.97 mmol) and chloromethylcyclopropane (7.00 g, 77.31 mmol) by method L, except that the reaction was heated at 50 °C for 5 h and stirred at ambient temperature for 24 h. The chromatography solution was spin evaporated *in vacuo* to give 6.00 g (45%) of **114** mp 143−145 °C. The analytical sample was recrystallized from cyclohexane:ethyl acetate: mp 143−145 °C; NMR (DMSO-d_6) δ 8.18 (s, 1H, H-8), 6.89 (s, 2H, NH_2), 4.00 (d, 2H, $J = 7.1$ Hz, NCH_2), 1.3 (m, 1H, CH) 0.56−0.37 (m, 4H, CH_2CH_2). Anal. ($C_9H_{10}N_5Cl$) C, H, N.

2-Amino-9-(cyclopropylmethyl)-6-(dimethylamino)-9*H*-purine (115). This compound was prepared from **114** (3.00 g, 13.41 mmol) and 40% aqueous dimethylamine (25 mL) as for the preparation of **81**. Recrystallization from ethyl acetate gave 2.15 g (69%) of **115**: mp 175−178 °C; UV (0.1 N HCl) λ_{max} 292, 257 nm; UV (0.1 N NaOH) λ_{max} 285, sh 265 nm; NMR (DMSO-d_6) δ 7.76 (s, 1H, H-8), 5.78 (s, 2H, NH_2), 3.82 (d, 2H, $J = 7.0$ Hz, NCH_2), 3.36 (s, 6H, $N(CH_3)_2$), 1.2 (m, 1H, CH), 0.53−0.33 (m, 4H, CH_2CH_2). Anal. ($C_{11}H_{16}N_6$) C, H, N.

Dopamine Receptor Assays. Inhibition of binding to the dopamine D_1 receptor was assessed using a method adapted from Porceddu et al.[31] The test compounds were incubated at 10^{-5} M, with 0.2 nM [^{3}H]-SCH23390 and rat striatal membranes (10−15 μg protein per tube) for 15 min at 37 °C in a total volume of 0.5 mL. Nonspecific binding was determined using 0.1 μM SCH23390. Inhibition of binding to the dopamine D_2 receptor was assessed using a method adapted from Dewar, et al.[32] The test compounds were incubated at 10^{-5} M with 1.0 nM [^{3}H]-raclopride and rat striatal membrane preparation (60−65 μg protein per tube) for 30 min at room temperature in a total volume of 0.5 mL. Nonspecific binding was determined using 1 μM halperidol. Bound and free radioligand were separated by rapid filtration through Whatman GF/B filters using a Brandel M-24 cell harvester. Filters were washed once with 3 mL of ice-cold assay buffer, placed

in vials containing 10 mL scintillation fluid, and the radioactivity was measured using a liquid scintillation counter.

Retardation of Stomach Emptying. Stomach emptying was determined using a phenol red method.[27] Each rat was fasted overnight and treated by the oral route with the test compound or saline. One control group remained untreated. Fifteen minutes after the drug or saline administration, each animal received a 2 mL oral gavage of 0.05% phenol red in 1.5% carboxycellulose. The total stomach contents of phenol red were determined 5 min after gavage for the untreated control group and compared to values determined 1 h after gavage to calculate the extent of stomach emptying induced by the drug or saline treatments.

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