which reduces the effect of dose $2x$ of the agonist to that of a dose x.

In the antagonistic experiments we used subthreshold doses for those analogues exhibiting agonism. Regarding analogues lacking agonism, maximal doses of 100 nmol/kg were tested. Arginine-vasopressin (408 IU/mg) was used as the standard when agonism was estimated as well as the agonist in the antagonistic experiments.

Acknowledgment. This work was supported by the Polish Academy of Sciences (CPBP 06.03.4.1) and the Swedish Natural Science Research Council.

Registry No. 1, 112195-99-0; 2, 112196-00-6; 3, 112196-01-7; 4, 112196-02-8; 5, 112196-03-9; 6, 112196-04-0; 7, 112196-05-1; 8, 112196-06-2; I, 112196-07-3; II, 112196-08-4; III, 112196-09-5; IV, 112196-10-8; V, 112196-11-9; VI, 112196-12-0; VII, 112196-13-1; VIII, 112196-14-2; AVP, 113-79-1; BOC-Tyr(Bzl)-Phe-Gln-Asn-Cys(Bzl)-Pro-Arg(Tos)-Gly-NH_2, 63491-78-1; BOC-Tyr(Me)-Phe-Gln-Asn-Cys(Bzl)-Pro-Arg(Tos)-Gly-NH_2, 67230-57-3; 4-methyl-1-[(phenylmethyl)thio]cyclohexaneacetic acid, 112196-15-3; 4-*tert*-butyl-1-[(phenylmethyl)thio]cyclohexaneacetic acid, 112196-16-4; 4-phenyl-1-[(phenylmethyl)thio]cyclohexaneacetic acid, 112196-17-5; 1-methyl-4-[(phenylmethyl)thio]-4-piperidineacetic acid hydrochloride, 112219-50-8.

6-(Alkylamino)-9-benzyl-9*H*-purines. A New Class of Anticonvulsant Agents

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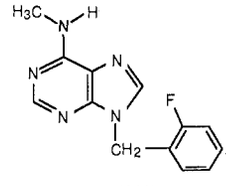
Several 9-alkyl-6-substituted-purines were synthesized and tested for anticonvulsant activity against maximal electroshock-induced seizures (MES) in rats. Most compounds were prepared in three steps from 5-amino-4,6-dichloropyrimidine or in two steps via alkylation of 6-chloropurine. Potent anticonvulsant activity against MES resided in compounds that contain a benzyl substituent at the 9-position of 6-(methylamino)- or 6-(dimethylamino)purine. Among commonly used agents for control of seizures, this type of structure represents a new class of potent anticonvulsant agents.

Several drugs are available for treatment of epilepsy, but many patients fail to experience satisfactory seizure control with them, or they do so at the expense of significant side effects.[1] Despite the many side effects associated with phenytoin, it is still the drug of choice for the treatment of many epileptic seizures.[2] Due to the need for new, improved antiepileptic drugs, a program was initiated to discover and develop candidate antiepileptic agents with improved properties.[3,4] From this program emerged 9-(2-fluorobenzyl)-6-(methylamino)-9*H*-purine [BW A78U (1)], a novel, orally active anticonvulsant with potent ac-

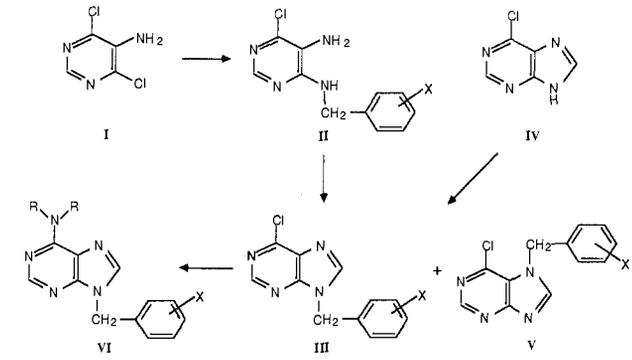


BW A78U (1)

tivity against maximal electroshock-induced seizures (MES) in rats and mice.[5,6] Compound 1 has activity against MES in the rat with an oral ED_{50} = 2.5 mg/kg. The oral LD_{50} is greater than 1000 mg/kg. Compound 1 did not produce tolerance to its anticonvulsant effect in mice under conditions where phenytoin was ineffective against MES. Compared to commonly used anticonvulsants, the structure of 1 is unique.[7]

A variety of biological activities have been reported for 9-benzylpurines. Certain derivatives have antianginal,[8] bronchodilating,[8] or antiinflammatory[9] activity, and 9-(2-chloro-6-fluorobenzyl)adenine is a potent anticoccidial agent.[10] Other 9-benzylpurines have activity as inhibitors of purine nucleoside phosphorylases[11,12] or adenosine deaminase.[13-16] Some of the earliest research on 9-benzylpurines was targeted to anticancer activity.[17]

Scheme I



We recently reported the weak antiviral activity of some 9-[(aminoacylamido)benzyl]purines.[18] This class of com-

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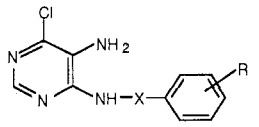
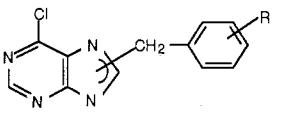
Table I. Physical Properties of 4-Chloro-5,6-diaminopyrimidines



no.	X	R	method	yield, %	mp, °C	formula[a]
2	CH(CH$_3$)-*R*	H	A[b]	85	168–171[c]	$C_{12}H_{13}ClN_4$
3	CH(CH$_3$)-*S*	H	A[d]	65	170–172[e]	$C_{12}H_{13}ClN_4$
4	CH_2	4-F	A	84	240–242[f]	$C_{11}H_{10}ClFN_4$
5	CH_2	3-Cl	A[b]	85	197–200[g]	$C_{11}H_{10}Cl_2N_4$
6	CH_2	3,4-Cl_2	A[b]	23[g]	195–197[h]	$C_{11}H_9Cl_3N_4$
7	CH_2	3-CH_3	A[b]	83	184–186[i]	$C_{12}H_{13}ClN_4$
8	CH_2	3-F	A	75	197–200[e]	$C_{11}H_{10}ClFN_4$
9	CH_2	3-OCH_3	A[b]	84	131–133[i]	$C_{12}H_{13}ClN_4O$
10	CH_2	2-Cl	A	79	197.5–199[e]	$C_{11}H_{10}Cl_2N_4$
11	CH_2	2-CH_3	A	72	199–200.5[e]	$C_{12}H_{13}ClN_4$
12	CH_2	2-F	A	82	220–223[f]	$C_{11}H_{10}ClFN_4$
13	CH_2	2-OCH_3	A	87	147–148[e]	$C_{12}H_{13}ClN_4O$

[a] All compounds were analyzed for C, H, N. [b] The cooled reaction solution was spin evaporated in vacuo to give the crude product. [c] Recrystallized from EtOAc. [d] The cooled reaction solution was spin evaporated in vacuo. The residual solid was dissolved in CH_2Cl_2, washed with H_2O, and evaporated to give the crude product. [e] Recrystallized from EtOAc–cyclohexane. [f] Recrystallized from EtOH. [g] Recrystallized from MeOH. [h] Mp 198–200 °C reported for this compound in ref 22. [i] Recrystallized from MeOH–H_2O.

Table II. Physical Properties of 6-Chloropurines



no.	R	isomer	method	yield, %	mp, °C	formula[a]
14	H	9	B	54	84–86[b,c]	$C_{12}H_9ClN_4$
15	4-Cl	9	B	59	133–135[b]	$C_{12}H_8Cl_2N_4$
16	4-Cl	7	C	19	168–170[b]	$C_{12}H_8Cl_2N_4$
17	4-CH_3	9	B	45	132–134[d]	$C_{13}H_{11}ClN_4$
18	4-CH_3	7	C	25	148–149[e]	$C_{13}H_{11}ClN_4$
19	4-F	9	D	92	118–120[f]	$C_{12}H_8ClFN_4$
20	4-OCH_3	9	B[g]	28	122–124[b]	$C_{13}H_{11}ClN_4O$
21	4-OCH_3	7	C[g]	9	134–136[h]	$C_{13}H_{11}ClN_4O$
22	3-CF_3	9	B	48[f]	116–117	$C_{13}H_8ClF_3N_4$
23	3-CF_3	7	C	13[i]	185–186	$C_{13}H_8ClF_3N_4$
24	3-I	9	B	26	156–156.5[i]	$C_{12}H_8ClIN_4$
25	3-I	7	C	10	170.5–171[i]	$C_{12}H_8ClIN_4$
26	3-Br	9	B	49	109–110[i]	$C_{12}H_8BrClN_4$
27	3-Br	7	C	19	151.5–153[i]	$C_{12}H_8BrClN_4$
28	3-Cl	9	D	70[j]	90–92	$C_{12}H_8Cl_2N_4$
29	3,5-Cl_2	9	B	27	164–165[i]	$C_{12}H_7Cl_3N_4$
30	3,5-Cl_2	7	C	4	168–170[i]	$C_{12}H_7Cl_3N_4$
31	3,4-Cl_2	9	D	57	151–153[d,k]	$C_{12}H_7Cl_3N_4$
32	3-CH_3	9	D	81	90–91[l]	$C_{13}H_{11}ClN_4$
33	3-F	9	D	93	103–105[i]	$C_{12}H_8ClFN_4$
34	3-OCH_3	9	D	92	103–104[l]	$C_{13}H_{11}ClN_4O$
35	3-$OCH_2C_6H_5$	9	exp	41	79–83[m]	$C_{19}H_{15}ClN_4O$
36	2-F	9	D	95	97–99[f]	$C_{12}H_8ClFN_4$

[a] All compounds were analyzed for C, H, N. [b] Recrystallized from C_6H_6–petroleum ether (30–60 °C). [c] Mp 86–87 °C reported for this compound in ref 17. [d] Recrystallized from MeOH. [e] Recrystallized from 2-PrOH. [f] Recrystallized from cyclohexane. [g] For the starting 4-methoxybenzyl bromide, see: Woodward, R. B. *J. Am. Chem. Soc.* **1940**, *62*, 1478. [h] Recrystallized from EtOAc. [i] Recrystallized from EtOAc–cyclohexane. [j] Recrystallized from toluene–petroleum ether (30–60 °C). [k] Mp 149–151 °C reported for this compound in ref 22. [l] Recrystallized from heptane. [m] Recrystallized from pentane.

pound also binds to the benzodiazepine receptor.[19] Because some agents that bind to this receptor are used in the treatment of epilepsy,[7,20] we tested a variety of purines for anticonvulsant activity. The chemistry and structure–activity relationships associated with the development of 9-benzylpurines with anticonvulsant activity are reported.

Chemistry. Most of the 9-substituted purines were prepared by one of two methods (Scheme I). Amination of 5-amino-4,6-dichloropyrimidine (I) with the appropriate amine by modification of a general literature method[21,22] gave the 4-substituted pyrimidines II (Table I). Condensation of II with triethyl orthoformate[23] and ethane-

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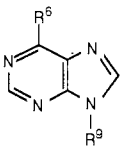
Table III. Physical Properties of 6,9-Disubstituted Purines



no.	R^6	R^9	method	yield, %	mp, °C	formula[a]
37	$N(CH_3)_2$	$CH_2C_6H_5$	E	87[b]	126–128[c]	$C_{14}H_{15}N_5$
38	$N(CH_3)_2$	CH_3	exp	26[d]	113–114[e]	$C_8H_{11}N_5$
39	$N(CH_3)_2$	C_6H_5	E[f]	89	161–163[g,h]	$C_{13}H_{13}N_5$
40	$N(CH_3)_2$	$CH_2CH_2C_6H_5$	E[i]	82[b]	70–72	$C_{15}H_{17}N_5$
41	$N(CH_3)_2$	$CH(CH_3)C_6H_5$-R^j	E	48[k]	104–105	$C_{15}H_{17}N_5$
42	$N(CH_3)_2$	$CH(CH_3)C_6H_5$-S^l	E	59[k]	104–105.5	$C_{15}H_{17}N_5$
43	$N(CH_3)_2$	$CH_2C_6H_{11}$[m]	F, exp	81[n]	78–80	$C_{14}H_{21}N_5$
44	$N(CH_3)_2$	$CH_2C_4H_3O$[o]	D, E,[p] exp	57[k]	118–119	$C_{12}H_{13}N_5O$
45	$N(CH_3)_2$	$CH_2C_4H_3S$[q]	B, E	80[k]	128–129	$C_{12}H_{13}N_5S$
46	$NHCH_3$	$CH_2C_6H_5$	E[r]	81[b]	130–132[s]	$C_{13}H_{13}N_5$
47	NH_2	$CH_2C_6H_5$	*t*	34[g]	231–234	$C_{12}H_{11}N_5$
48	H	$CH_2C_6H_5$	*u*	69[v]	96–98	$C_{12}H_{10}N_4$
49	$N(CH_3)CH_2CH_3$	$CH_2C_6H_5$	E[r]	62[w]	55.5–57	$C_{15}H_{17}N_5$
50	$N(CH_3)CH(CH_3)_2$	$CH_2C_6H_5$	E[x]	43[w]	52–55.5	$C_{16}H_{19}N_5$
51	$N(CH_3)C_5H_9$[y]	$CH_2C_6H_5$	E[x]	29[w]	58–60	$C_{18}H_{21}N_5$
52	$N(CH_2)_3$	$CH_2C_6H_5$	E[z]	37[aa]	168–170	$C_{15}H_{15}N_5$
53	NHC_3H_5[bb]	$CH_2C_6H_5$	E[x]	61[cc]	158–159	$C_{15}H_{15}N_5$
54	NHC_6H_5	$CH_2C_6H_5$	F	77[g]	187–189	$C_{18}H_{15}N_5$
55	$NHCH_2CH_2OH$	$CH_2C_6H_5$	F[dd]	89[ee]	118–120	$C_{14}H_{15}N_5O$
56	$N(CH_3)CHO$	$CH_2C_6H_5$	exp	58[ff]	162–164	$C_{14}H_{13}N_5O$
57	OH[gg]	$CH_2C_6H_5$	*hh*	54	295–298[g]	$C_{12}H_{10}N_4O$
58	OCH_3	$CH_2C_6H_5$	*ii*	71[d]	114–116	$C_{13}H_{12}N_4O$
59	SCH_3	$CH_2C_6H_5$	exp[jj]	64[ff]	115–116[kk]	$C_{13}H_{12}N_4S$

[a] All compounds were analyzed for C, H, N. [b] Recrystallized from toluene–petroleum ether (30–60 °C). [c] Mp 131–132 °C reported for this compound in ref 17. [d] Recrystallized from heptane. [e] Mp 114–115 °C reported for this compound in ref 28 by a different method. [f] For the starting purine see ref 22. [g] Recrystallized from EtOH. [h] Mp 168–169 °C reported for this compound in ref 22. [i] For the starting purine, see: Schaeffer, H. J.; Johnson, R. N. *J. Med. Chem.* **1968**, *11*, 21. [j] $[\alpha]^{20}_D$ −9.2° (*c* 1.0, MeOH). [k] Recrystallized from cyclohexane. [l] $[\alpha]^{20}_D$ +8.6° (*c* 1.0, MeOH). [m] Cyclohexylmethyl substituent. [n] Recrystallized from pentane. [o] Furfuryl substituent. [p] The crude product was purified by flash chromatography as in method B. [q] 2-Thienyl substituent. [r] The aqueous alkylamine was formed by dissolving a 3-fold excess of alkylamine hydrochloride in 2 molar equiv of 1 N NaOH. [s] Mp 133–134 °C reported for this compound by Fuji, T.; Saito, T. *Chem. Pharm. Bull.* **1985**, *33*, 3635. [t] Prepared by the method of Carraway, K. L.; Huang, P. C.; Scott, T. G. In *Synthetic Procedures in Nucleic Acid Chemistry*; Zorbach, W. W., Tipson, R. S., Eds.; Interscience: New York, 1968; Vol. 1, p 3; mp 233.5–235.5 °C. [u] Prepared by the method of ref 17, mp 100–101 °C. [v] Recrystallized from CCl_4–pentane. [w] Recrystallized from petroleum ether (30–60 °C). [x] A 3-fold excess of the amine was used in the reaction. [y] Cyclopentyl substituent. [z] An equimolar amount of triethylamine and trimethyleneimine was used, and the product was purified by flash chromatography. [aa] Recrystallized from cyclohexane–toluene. [bb] Cyclopropyl substituent. [cc] Recrystallized from EtOAc. [dd] A 2-fold excess of triethylamine was used in the reaction. [ee] Recrystallized from toluene. [ff] Recrystallized from cyclohexane–EtOAc. [gg] Present as the oxo tautomer. [hh] Prepared by the method of ref 17, mp >260 °C. [ii] Prepared by the method of ref 17, mp 128 °C. [jj] For the starting 6-thionopurine see ref 29. [kk] Mp 117–118 °C reported for this compound in ref 30 by a different method.

sulfonic acid[24] afforded the intermediate 6-chloro-9-substituted-purines III. Alternatively, 6-chloropurine (IV) was alkylated with the appropriate benzyl halide to give a mixture of the 7-benzyl-6-chloropurines (V) and 9-benzyl-6-chloropurines (III).[17] Isomers were easily separated by flash chromatography[25] to give the 9-isomers III in 26–59% yields (Table II). The 6-chloro-9-substituted-purines III were reacted with the appropriate amine to give most of the 6-(alkylamino)-9-benzylpurines (VI) in Tables III and IV. The UV spectra of the 6-(dimethylamino)purines were compatible with 9-substitution.[26]

The 6-(*N*-methylformamido)purine **56** (Table III) was prepared from **46** and acetic–formic anhydride.[27] The 9-(aminobenzyl)purines **68** and **87** (Table IV) were prepared from **64** and **86**, respectively, by catalytic hydrogenation. The 4-hydroxy compound **66** was prepared from **67** by catalytic hydrogenolysis of the *O*-benzyl moiety. Compound **67** was prepared from 4-(benzyloxy)benzaldehyde as described in the Experimental Section. The 3-benzyloxy compound **81**, available in four steps from 3-hydroxybenzyl alcohol, was cleaved with HBr in AcOH to give **80**.

Biological Results and Discussion

Compounds in Tables V–VII were evaluated for anticonvulsant activity in the maximal electroshock-induced seizure (MES) screen in Sprague–Dawley male rats.[4] The compounds were tested initially at 25 mg/kg ip, and if activity was high, an ED_{50} was determined. The most active compounds were also tested orally.

The parent 9-benzylpurine **37** (Table V) protected rats against MES with an oral ED_{50} = 12 mg/kg and an ip ED_{50} = 6 mg/kg. Variation of the purine 9-substituent had a substantial effect on anticonvulsant activity. The 9-methyl substituent (see **38**) gave a compound with about one-fifth the activity of **37**. The 9-phenyl compound **39** was not active as it gave no protection at 12.5 mg/kg. Substitution of the one-carbon bridge with a two-carbon bridge between the phenyl and purine rings (see **40**) resulted in about a 5-fold loss in activity. Substitution of a methyl group on the methylene bridge (see **41** and **42**) gave compounds that were less active than **37**. The 9-cyclohexylmethyl compound **43** was completely inactive at 25 mg/kg ip. However, the furfuryl and thenyl analogues **44** and **45** showed one-third and about one-half the activity, respectively, of

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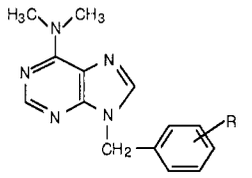
Table IV. Physical Properties of 9-Benzyl-6-(dimethylamino)purines



no.	R	methods	yield, %	mp, °C	formula[a]
60	4-Cl	E[b]	48[c]	134–136	$C_{14}H_{14}ClN_5$
61	4-CH_3	E[b]	61[d]	116–118	$C_{15}H_{17}N_5$
62	4-F	E	78[e]	131–133	$C_{14}H_{14}FN_5$
63	4-OCH_3	E[b]	77[d]	123–124	$C_{15}H_{17}N_5O$
64	4-NO_2	E[b,f]	93	211–213[c,g]	$C_{14}H_{14}N_6O_2$
65	4-CN	E[b,h]	79[i]	188–190	$C_{15}H_{14}N_6$
66	4-OH	exp	61[j]	214–217	$C_{14}H_{15}N_5O$
67	4-$OCH_2C_6H_5$	exp	63[k]	87–89[l]	$C_{21}H_{21}N_5O$
68	4-NH_2	G	61[c]	193–196	$C_{14}H_{16}N_6$
69	3-CF_3	E	73[e]	111–112	$C_{15}H_{14}F_3N_5$
70	3-I	E	72[k]	143–144	$C_{14}H_{14}IN_5$
71	3-Br	E	77[e]	108–109	$C_{14}H_{14}BrN_5$
72	3-Cl	E	77[m]	109–111	$C_{14}H_{14}ClN_5$
73	3,5-Cl_2	E	87[e]	124–126	$C_{14}H_{13}Cl_2N_5$
74	3,4-Cl_2	E[b]	68[n]	153–155	$C_{14}H_{13}Cl_2N_5$
75	3-CH_3	E[b]	67[m]	126–129	$C_{15}H_{17}N_5$
76	3-F	E	70[e]	90–92	$C_{14}H_{14}FN_5$
77	3-OCH_3	E[b]	59[d]	107–109	$C_{15}H_{17}N_5O$
78	3-NO_2	E[o]	72[c]	166–167[p]	$C_{14}H_{14}N_6O_2$
79	3-CN	E[h]	85	134–134.5[q]	$C_{15}H_{14}N_6$
80	3-OH	exp	79[c]	260–262	$C_{14}H_{15}N_5O$·HBr
81	3-$OCH_2C_6H_5$	E	68[d]	97–98	$C_{21}H_{21}N_5O$
82	2-Cl	E	77[k]	134.5–135	$C_{14}H_{14}ClN_5$
83	2-CH_3	E	80[e]	111–111.5	$C_{15}H_{17}N_5$
84	2-F	E	84[e]	137–139	$C_{14}H_{14}FN_5$
85	2-OCH_3	E	68[k]	157.5–158	$C_{15}H_{17}N_5O$
86	2-NO_2	E[b]	66[c]	164–167[r]	$C_{14}H_{14}N_6O_2$
87	2-NH_2	G	84[c]	196–198	$C_{14}H_{16}N_6$

[a] All compounds were analyzed for C, H, N. [b] A solution of 2.2 M dimethylamine and ethanol was used instead of 40% aqueous dimethylamine. [c] Recrystallized from EtOH. [d] Recrystallized from toluene–petroleum ether (30–60 °C). [e] Recrystallized from cyclohexane. [f] For the starting purine see ref 13. [g] Mp 211 °C reported for this compound in ref 13. [h] For the starting purine see ref 16. [i] Recrystallized from $CHCl_3$–EtOH. [j] Recrystallized from EtOAc. [k] Recrystallized from cyclohexane–EtOAc. [l] Melts with resolidification and remelts 93–95 °C. [m] Recrystallized from heptane. [n] Recrystallized from MeOH. [o] For the starting purine see ref 14. [p] Mp 156–157 °C reported for this compound in ref 14. [q] Recrystallized from toluene. [r] Mp 169–171 °C reported in ref 15.

the parent 9-benzylpurine **37**. Compounds that contain a flat, aromatic ring bonded to the 9-substituted purine by a methylene group possessed good anticonvulsant activity.

Variation of the 6-substituent of **37** had a substantial effect on the relative potency of 9-benzylpurines in protecting rats against MES (Table VI). Removal of a single methyl group (see **46**) had no effect on activity; however, the 6-aminopurine **47** and 6-hydrogen purine **48** were about 5-fold less active. Of eight other 6-substituted aminopurines, only **49** ($N(CH_3)CH_2CH_3$), **53** (NHC_3H_5), and **55** ($NHCH_2CH_2OH$) retained significant anticonvulsant activity. Although the hypoxanthine derivative **57** was essentially inactive, the 6-methoxypurine **58** had activity comparable to that of phenytoin.

Analogues of **37** that contain substitutions in the phenyl moiety are listed in Table VII. Analogues that contain a substituent in the para position were almost uniformly inactive at 25 mg/kg ip. Only the small fluoro (**62**) and hydrophilic amino (**68**) substituents gave compounds with detectable anticonvulsant activity at 25 mg/kg. Thus, with the exception of the amino and fluoro, substituents in the para position of **37** did not impart anticonvulsant activity to the compounds.

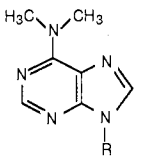
Several meta-substituted analogues of **37** had good anticonvulsant activity. The 3-chloro analogue **72** was slightly more active than **37** when administered ip. Addition of a second chlorine in the para position (see **74**) resulted in complete loss of activity. This result further substantiated the lack of tolerance for substituents in the para position. Substitution of trifluoromethyl (**69**), iodo (**70**), bromo (**71**), fluoro (**76**), or methoxy (**77**) for the chloro in **72** resulted in only a 2- to 3-fold loss in anticonvulsant activity. The less lipophilic nitro (**78**), cyano (**79**), and hydroxy (**80**) meta-substituted analogues of **37** had little or no anticonvulsant activity at 25 mg/kg. In general, meta-substituted analogues of **37** retained good anticonvulsant activity when the substituent was electron withdrawing and lipophilic.

Introduction of a second meta chloro group gave **73**, which had good anticonvulsant activity with an ip ED_{50} = 7 mg/kg. However, **73** was extremely toxic to mice. Its ip LD_{50} was less than 0.5 mg/kg. The monochloro analogue **72** was 100-fold less toxic with an ip LD_{50} = 54 mg/kg, whereas the parent 9-benzylpurine **37** was relatively innocuous with an ip LD_{50} > 500 mg/kg.

Several ortho-substituted analogues of **37** retained good anticonvulsant activity. There was no apparent correlation of activity with electronic, lipophilic, or size parameters of the ortho substituents. The fluoro- and methyl-substituted analogues (**84** and **83**, respectively) were only about 50% less active than the parent **37**.

Potent anticonvulsant activity resided in compounds that contained a benzyl group at the 9-position of 6-(methylamino)- or 6-(dimethylamino)purine. There was little or no tolerance for para substitution, whereas analogues with electron-withdrawing, lipophilic, meta substituents retained substantial anticonvulsant activity.

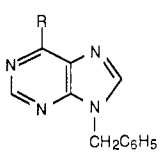
Table V. Anticonvulsant Activity of 9-Substituted 6-(Dimethylamino)purines[a]



no.	R	MES ED_{50}, mg/kg[b-d] ip	po
37	$CH_2C_6H_5$	6 ± 1	12 ± 3
38	CH_3	(33)	
39	C_6H_5	(0[e])	
40	$CH_2CH_2C_6H_5$	(33)	
41	$CH(CH_3)C_6H_5$-*R*	(33)	
42	$CH(CH_3)C_6H_5$-*S*	(33)	
43	$CH_2C_6H_{11}$[f]	(0)	
44	$CH_2C_4H_3O$[g]	18	
45	$CH_2C_4H_3S$[h]	10 ± 2.5	
phenytoin		9.6 ± 2.0	20 ± 3

[a] The compounds were tested for their ability to protect Sprague–Dawley male rats against maximal electroshock-induced seizures (MES) as described in ref 4. The ED_{50} was the dose needed to protect 50% of the animals against the hind-limb extensor component and were calculated by the method of Miller, L. C.; Tainter, M. L. *Proc. Soc. Exp. Biol. Med.* 1944, *57*, 261. [b] The compounds were administered as solutions or fine dispersions in water or 5% methylcellulose. [c] Values in parentheses are percent inhibition at 25 mg/kg. [d] Where ED_{50} values are presented with a standard error a minimum of 12 animals were used per dose level with four doses per compound. ED_{50} values without standard error were determined by using three doses of compound with six animals per point. [e] Inhibition at 12.5 mg/kg. [f] Cyclohexyl substituent. [g] Furfuryl substituent. [h] 2-Thenyl substituent.

Table VI. Anticonvulsant Activity of 6-Substituted 9-Benzylpurines[a]



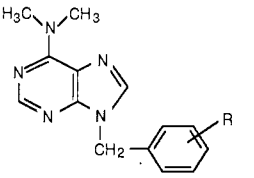
no.	R	MES ED_{50}, mg/kg[b-d] ip	po
37	$N(CH_3)_2$	6 ± 1	12 ± 3
46	$NHCH_3$	5 ± 1	12 ± 2
47	NH_2	(33)	
48	H	(33)	
49	$N(CH_3)CH_2CH_3$	8	30
50	$N(CH_3)CH(CH_3)_2$	(17)	
51	$N(CH_3)C_5H_9$[e]	(17)	
52	$N(CH_2)_3$	(17)	
53	NHC_3H_5[f]	8.6 ± 0.7	
54	NHC_6H_5	(0)	
55	$NHCH_2CH_2OH$	(84)	(17)
56	$N(CH_3)CHO$	(0)	
57	OH (oxo)	(17)	
58	OCH_3	10 ± 1.6	21 ± 3.6
59	SCH_3	(30)	

[a-d] See footnotes *a–d* in Table V. [e] Cyclopentyl substituent. [f] Cyclopropyl substituent.

Experimental Section

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 a Hitachi Perkin-Elmer R-24 spectrometer with Me_4Si as an internal standard. Each analytical sample had spectral data compatible with its assigned structure and moved as a single spot on TLC. TLC's

Table VII. Anticonvulsant Activity of 9-Benzyl-6-(dimethylamino)purines[a]



no.	R	MES ED_{50}, mg/kg[b-d] ip	po
37	H	6 ± 1	12 ± 3
60	4-Cl	(0)	
61	4-CH_3	(0)	
62	4-F	(33)	
63	4-OCH_3	(0)	
64	4-NO_2	(0)	
65	4-CN	(0)	
66	4-OH	(0)	
68	4-NH_2	25	
69	3-CF_3	12	
70	3-I	11	
71	3-Br	13	
72	3-Cl	4.5 ± 0.6	18 ± 2
73	3,5-Cl_2	7	
74	3,4-Cl_2	(0)	
75	3-CH_3	25	
76	3-F	8.4	
77	3-OCH_3	12.5	
78	3-NO_2	(17)	
79	3-CN	(17)	
80	3-OH	(0)	
81	3-$OCH_2C_6H_5$	(33)	
82	2-Cl	(84)	
83	2-CH_3	9	
84	2-F	8.8 ± 1.7	
85	2-OCH_3	(0)	
86	2-NO_2	25	
87	2-NH_2	20 ± 2	
phenytoin		9.6 ± 2.0	20 ± 3

[a-d] See footnotes *a–d* in Table V.

were developed on Whatman 200 μ MK6F plates of silica gel with fluorescent indicator. Preparative flash chromatography[25] was performed on silica gel 60 (40–63 μM, E.Merck, no. 9385). All compounds were analyzed for C, H, and N and gave values within 0.4% of theoretical values. Elemental analyses were performed by Atlantic Microlab, Inc.

Method A. 5-Amino-4-chloro-6-[(3-fluorobenzyl)amino]-pyrimidine (8). A mixture of 5-amino-4,6-dichloropyrimidine (10.0 g, 61.0 mmol), (3-fluorobenzyl)amine (97%) (7.9 g, 61.2 mmol), 1-BuOH (150 mL), and Et_3N (6.5 g, 64.2 mmol) was refluxed with stirring for 21 h. The dark solution was cooled to give a solid that was collected on a Büchner funnel and washed with cyclohexane. The white solid was dispersed in H_2O (100 mL), collected, and dried to give 11.5 g (75%) of 8, mp 196–200 °C. Recrystallization of a portion from EtOAc–cyclohexane gave the analytical sample: mp 197–200 °C; UV (0.1 N HCl + 10% EtOH) λ_{max} 304 nm (ϵ 12 500); UV (0.1 N NaOH + 10% EtOH) λ_{max} 263 nm (ϵ 9200), 269 (8900), 291 (8900); NMR (Me_2SO-d_6) δ 7.73 (s, 1 H, pyrimidine H), 7.5–7.0 (complex m, 5 H, aromatic H + NH), 5.05 (br s, 2 H, NH_2), 4.65 (d, collapsed to s with D_2O, 2 H, CH_2).

Method B. 9-(3-Bromobenzyl)-6-chloro-9*H*-purine (26). A mixture of 6-chloropurine (3.09 g, 20 mmol), DMSO (50 mL), anhydrous K_2CO_3 (3.45 g, 25 mmol), and 3-bromobenzyl bromide (5.0 g, 20 mmol) was stirred at ambient temperature for 39 h. The reaction solution was decanted from the solids, poured into ice water, and acidified to pH 5 with HOAc (0.5 mL). The mixture was extracted with EtOAc (4 × 200 mL). The combined extracts were washed with an equal volume of H_2O, dried ($MgSO_4$), and spin evaporated in vacuo. The residue was dissolved in CH_2Cl_2 (50 mL) and added to silica gel 60 (5 g). This mixture was spin evaporated in vacuo, and the residual solid was introduced on a column of silica gel 60 wetted with EtOAc–cyclohexane, 1:2. The column was eluted with EtOAc–cyclohexane, 1:2, by using the flash chromatography technique. The fractions containing the

higher R_f, major component were combined and spin evaporated in vacuo to give 3.20 g (49%) of **26**, which was a single spot on TLC. Recrystallization from EtOAc–cyclohexane gave the analytical sample: mp 109–110 °C; UV (pH 7 + 10% EtOH) λ_{max} 265.5 nm (ϵ 10 200); NMR (Me_2SO-d_6) δ 8.86 (s, 1 H, purine H), 8.80 (s, 1 H, purine H), 7.7–7.2 (m, 4 H, Ar H), 5.55 (s, 2 H, CH_2).

Method C. 7-(3-Bromobenzyl)-6-chloro-7*H*-purine (27). After elution of the 9-isomer **26**, the 7-isomer was isolated by changing the elution solvent to EtOAc–cyclohexane, 1:1. Fractions containing the lower R_f, 7-isomer were collected, combined, and spin evaporated in vacuo to give 1.24 g (19%) of **27**. Recrystallization from EtOAc–cyclohexane gave the analytical sample: mp 151.5–153 °C; UV (pH 7 + 10% EtOH) λ_{max} 268.5 nm (ϵ 8500); NMR (Me_2SO-d_6) δ 9.02 (s, 1 H, purine H), 8.84 (s, 1 H, purine H), 7.7–7.0 (m, 4 H, Ar H), 5.79 (s, 2 H, CH_2).

Method D. 6-Chloro-9-(3-fluorobenzyl)-9*H*-purine (33). A mixture of 8 (10.0 g, 39.6 mmol), $HC(OEt)_3$ (100 mL), and $EtSO_3H$ (100 mg) was stirred at ambient temperature for 41 h. The solution was spin evaporated in vacuo. The residual solid was dissolved in EtOAc (200 mL), washed with 5% aqueous $NaHCO_3$ (50 mL), H_2O (3 × 50 mL), and brine (50 mL), and then dried ($MgSO_4$). The solution was spin evaporated in vacuo to a residue that was collected and washed with cyclohexane to give 9.77 g (94%) of **33**, mp 100–103 °C. Recrystallization from cyclohexane–ethyl acetate gave the analytical sample: mp 103–105 °C; UV (pH 7 + 10% EtOH) λ_{max} 265 nm (ϵ 11 500), 269 (sh) (11 300); NMR (Me_2SO-d_6) δ 8.87 (s, 1 H, purine H), 8.82 (s, 1 H, purine H), 7.6–7.0 (complex m, 4 H, Ar), 5.59 (s, 2 H, CH_2).

Method E. 9-(4-Fluorobenzyl)-6-(dimethylamino)-9*H*-purine (62). A solution of **19** (4.01 g, 15.2 mmol), EtOH (20 mL), and 40% aqueous Me_2NH (10 mL) was stirred at ambient temperature for 15 h. The reaction mixture was spin evaporated in vacuo to remove the volatiles. The residue was dispersed in H_2O (50 mL) and stirred for several minutes. The solids were collected, washed with H_2O, and sucked dry to give 3.90 g (94%) of **62**, mp 130–132 °C. Recrystallization from cyclohexane gave 3.25 g (78%) of **62**: mp 131–133 °C; UV (0.1 N HCl + 10% EtOH) λ_{max} 270 nm (ϵ 19 200); UV (0.1 N NaOH + 10% EtOH) λ_{max} 277 nm (ϵ 19 100); NMR (Me_2SO-d_6) δ 8.28 (s, 2 H, purine Hs), 7.55–7.0 (m, 4 H, Ar), 5.40 (s, 2 H, CH_2), 3.47 (s, 6 H, $N(CH_3)_2$).

Method F. 9-(Cyclohexylmethyl)-6-(dimethylamino)-9*H*-purine (43). A mixture of **89** (4.96 g, 19.8 mmol) and 125 mL of a solution of Me_2NH in EtOH (100 g/L) was heated on a steam bath to effect dissolution. The reaction was left at ambient temperature for 17 h and spin evaporated in vacuo to remove the volatiles. The residue was dissolved in EtOAc and filtered to remove the insolubles. The EtOAc was evaporated to an oil that was dissolved in petroleum ether (30–60 °C), filtered through Celite (Preiser Scientific, Inc.) and spin evaporated in vacuo. The residual solid was recrystallized from pentane to give 4.19 g (81%) of **43**: mp 78–80 °C; UV (0.1 N HCl + 10% EtOH) λ_{max} 270 nm (ϵ 17 900); UV (0.1 N NaOH + 10% EtOH) λ_{max} 278 nm (ϵ 18 500).

Method G. 9-(4-Aminobenzyl)-6-(dimethylamino)-9*H*-purine (68). A mixture of **64** (5.00 g, 16.7 mmol), HOAc (200 mL), and 10% Pd/C (0.20 g) was shaken in the presence of hydrogen at 2–3 atm for 1 h. The reaction mixture was filtered through Celite and concentrated under reduced pressure. The residue was dispersed in a minimum of EtOH and collected to give 4.14 g (92%) of **68**, mp 190–192 °C. Recrystallization of a portion from EtOH gave the analytical sample: mp 193–196 °C; UV (0.1 N HCl + 10% EtOH) λ_{max} 268 nm (ϵ 19 300); UV (0.1 N NaOH + 10% EtOH) λ_{max} 277 nm (ϵ 21 000); NMR (Me_2SO-d_6) δ 8.25 (s, 1 H, purine H), 8.15 (s, 1 H, purine H), 7.07 (d, 2 H, J = 8 Hz, Ar), 6.52 (d, 2 H, J = 8 Hz, Ar), 5.18 (s, 2 H, CH_2), 5.07 (br s, 2 H, NH_2), 3.45 (s, 6 H, $N(CH_3)_2$).

9-[3-(Benzyloxy)benzyl]-6-chloro-9*H*-purine (35). A mixture of 3-hydroxybenzyl alcohol (9.30 g, 75 mmol), powdered anhydrous K_2CO_3 (10.5 g, 76 mmol), benzyltrimethylammonium hydroxide (1.5 mL, 40% solution in MeOH), and DMF (90 mL) was stirred under nitrogen at ambient temperature. After 30 min, benzyl chloride (97%) (8.3 mL, 70 mmol) was added, and the reaction was heated to 70 °C for 18 h. The volatiles were removed by spin evaporation in vacuo, and the residual oil was dissolved in Et_2O and washed with H_2O, 1 N NaOH, and again with H_2O. The solution was dried ($MgSO_4$) and spin evaporated in vacuo to give 13.7 g (85%) of 3-(benzyloxy)benzyl alcohol as an oil, which was used without further purification. The benzyl alcohol (combined product from two reactions) was converted to the benzyl chloride and reacted with 6-chloropurine as described for the para isomer **67** to give 14.5 g (30%) of **35**, mp 70–80 °C. Recrystallization of a portion from petroleum ether (60–68 °C)–ethyl acetate gave the analytical sample: mp 79–83 °C; UV (pH 7 + 10% EtOH) λ_{max} 268 nm (ϵ 9800); NMR (Me_2SO-d_6) δ 8.77 (s, 1 H, purine H), 8.74 (s, 1 H, purine H), 7.34 (s, 5 H, Ar), 7.02 (br m, 4 H, Ar), 5.48 (s, 2 H, CH_2), 5.05 (s, 2 H, CH_2).

6-(Dimethylamino)-9-methyl-9*H*-purine (38). A solution of 6-(dimethylamino)purine (6.00 g, 36.8 mmol), NaOMe (2.08 g, 38.5 mmol), and DMSO (13 mL) was stirred at ambient temperature under a blanket of nitrogen for 1 h. Methyl iodide (2.30 mL, 3.0 mmol) was added, and the resultant mixture was stirred for 1 h. The reaction was diluted with H_2O (50 mL) and extracted with CH_2Cl_2 (2 × 700 mL). The combined extracts were dried ($CaCl_2$) and spin evaporated in vacuo to give 5.06 g (78%) of crude **38**. This material was introduced on a column of silica gel (55 g, 70–325 mesh) and eluted with CH_2Cl_2–MeOH, 1:1. The appropriate fractions were combined and spin evaporated in vacuo to give 2.40 g (36%) of **38**, which was a single spot on TLC. Recrystallization from heptane gave 1.75 g (26%) of analytically pure material: mp 113–114 °C (lit.[28] mp 114–115 °C); UV (0.1 N HCl + 10% EtOH) λ_{max} 269.5 nm (ϵ 17 600); UV (0.1 N NaOH + 10% EtOH) λ_{max} 276 nm (ϵ 18 500).

9-Benzyl-6-(*N*-methylformamido)-9*H*-purine (56). To a stirred, ice-bath cooled solution of **46** (3.50 g, 14.6 mmol), 4-(dimethylamino)pyridine (1.80 g, 14.7 mmol), and CH_2Cl_2 (50 mL) was added the acetic–formic anhydride[27] prepared from 10 mL of Ac_2O and 5 mL of 100% HCO_2H. The reaction was stirred at ambient temperature for 16 h and then spin evaporated in vacuo. The residue was dissolved in CH_2Cl_2 (200 mL), washed with water (3 × 50 mL), and filtered through glass wool. The solution was spin evaporated in vacuo, and the residue was recrystallized from cyclohexane–EtOAc to give 2.30 g (58%) of **56**: mp 162–164 °C; NMR (Me_2SO-d_6) δ 10.32 (s, 1 H, CHO), 8.72 (s, 1 H, purine H), 8.70 (s, 1 H, purine H), 7.34 (s, 5 H, Ar), 5.53 (s, 2H, CH_2), 3.44 (s, 3 H, CH_3).

9-Benzyl-6-(methylthio)-9*H*-purine (59). To a vigorously stirred solution of 9-benzyl-6-mercaptopurine[29] (9.70 g, 40.0 mmol) in 1 N sodium hydroxide (42 mL) was added methyl iodide (10 mL) dropwise. A thick precipitate formed, and H_2O (40 mL) and EtOH (20 mL) were added to facilitate stirring. After 1 h, the solids were collected, washed with H_2O, and recrystallized from cyclohexane–EtOAc to give 6.58 g (64%) of **59**: mp 115–116 °C (lit.[30] mp 117–118 °C); UV (0.1 N HCl + 10% EtOH) λ_{max} 294.5 nm (ϵ 18 800), 286 (sh) (16 200), 305 (sh) (11 000); UV (pH 7 + 10% EtOH) λ_{max} 287 nm (ϵ 20 300), 293 (20 200); NMR (Me_2SO-d_6) δ 8.68 (s, 1 H, purine H), 8.55 (s, 1 H, purine H), 7.32 (s, 5 H, Ar), 5.48 (s, 2 H, CH_2), 2.68 (s, 3 H, CH_3).

6-(Dimethylamino)-9-(4-hydroxybenzyl)-9*H*-purine (66). A mixture of **67** (3.15 g, 8.77 mmol), HOAc (200 mL), and 5% Pd/C (0.6 g) was shaken in the presence of hydrogen at 2–3 atm for 20 h. An additional 200 mg of catalyst was added, and the reaction was shaken for an additional 60 h. The reaction mixture was filtered through Celite, and the filtrate was spin evaporated in vacuo. The residue was slurried with EtOH and reevaporated. The crystalline solid was collected and washed with EtOH to give 1.83 g (77%) of **66**, mp 215–218 °C. Recrystallization from EtOAc gave 1.44 g (61%) of analytically pure **66**: mp 214–217 °C; NMR (Me_2SO-d_6) δ 9.38 (br s, 1 H, OH), 8.22 (s, 1 H, purine H), 8.17 (s, 1 H, purine H), 7.17 (d, 2 H, J = 8 Hz, Ar), 6.70 (d, 2 H, J = 8 Hz, Ar), 5.23 (s, 2 H, CH_2), 3.43 (s, 6 H, $N(CH_3)_2$).

9-[4-(Benzyloxy)benzyl]-6-(dimethylamino)-9*H*-purine (67). A solution of 4-(benzyloxy)benzaldehyde (10.61 g, 50.0 mmol), EtOH (100 mL), and $NaBH_4$ (1.00 g) was stirred at ambient temperature for 16 h. The dark solution was spin evaporated in vacuo to give a solid residue that was dissolved in CH_2Cl_2 (50 mL) and spin evaporated to dryness. This procedure was repeated

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twice to give crude 4-(benzyloxy)benzyl alcohol. To an ice-bath-cooled solution of this benzyl alcohol in CH_2CL_2 (200 mL) was added $SOCl_2$ (5 mL) dropwise. After 0.5 h, the reaction solution was spin evaporated in vacuo. The residue was covered twice with CH_2Cl_2 and evaporated to give crude 4-(benzyloxy)-benzyl chloride. A mixture of this benzyl chloride, 6-chloropurine (7.72 g, 50.0 mmol), anhydrous K_2CO_3 (8.20 g, 59.3 mmol), and DMF (50 mL) was stirred at ambient temperature for 16 h. The reaction mixture was poured over 200 g of crushed ice and extracted twice with dichloromethane (200, 100 mL). The combined extracts were washed with H_2O, filtered through glass wool, and spin evaporated in vacuo. Ethanol was added to the residue, and the mixture was spin evaporated at 90 °C. This procedure was repeated several times to remove residual DMF. The mixture was purified by the flash chromatography technique as described in method B to give 4.00 g (22%) of 9-[4-(benzyloxy)benzyl]-6-chloro-9*H*-purine, mp 121–125 °C, which was a single spot on TLC. This 6-chloropurine was reacted with 40% aqueous Me_2NH as in method E to give 3.70 g (99%) of **67**, mp 87–89 °C. Recrystallization of a sample from cyclohexane–EtOAc gave analytically pure material in 63% yield and an unchanged melting point: UV (0.1 N HCl + 10% EtOH) λ_{max} 270 nm (ϵ 21 000); UV (pH 7 + 10% EtOH) λ_{max} 277 nm (ϵ 21 000); NMR (Me_2SO-d_6) δ 8.18 (s, 2 H, purine H's), 7.33 (s, 5 H, C_6H_5), 7.27 (d, 2 H, J = 8.5 Hz, Ar), 6.92 (d, 2 H, J = 8.5 Hz, Ar), 5.28 (s, 2 H, CH_2N), 5.03 (s, 2 H, CH_2O), 3.40 (s, 6 H, $N(CH_3)_2$).

6-(Dimethylamino)-9-(3-hydroxybenzyl)-9*H*-purine Hydrobromide (80). A solution of 81 (5.50 g, 15.3 mmol) in 30% HBr in HOAc (50 mL) was stirred at ambient temperature for 30 min. The volatiles were removed by spin evaporation in vacuo. The residue was recrystallized from EtOH to give 4.23 g (79%) of **80**, mp 260–262 °C. This impure solid was dissolved in 1 N NaOH and extracted with CH_2Cl_2. The aqueous layer was adjusted to pH 7 with HOAc, and the white precipitate was collected. Recrystallization from a dilute solution of 30% HBr in HOAc–EtOH gave 2.75 g (51%) of analytically pure **80**: mp 260–262 °C; UV (pH 7 + 10% MeOH) λ_{max} 276.5 nm (ϵ 21 900); NMR (Me_2SO-d_6) δ 10.45 (br s, 2 H, ArOH + HBr), 8.64 (s, 1 H, purine H), 8.45 (s, 1 H, purine H), 7.2–6.6 (br m, 4 H, Ar), 5.42 (s, 2 H, CH_2), 3.58 (s, 6 H, $N(CH_3)_2$).

5-Amino-4-chloro-6-[(cyclohexylmethyl)amino]pyrimidine (88). A mixture of 5-amino-4,6-dichloropyrimidine (7.00 g, 42.7 mmol), Et_3N (4.34 g, 42.9 mmol), (cyclohexylmethyl)amine (4.84 g, 42.8 mmol), and 1-BuOH (70 mL) was heated at reflux with stirring for 18 h. The cooled reaction was spin evaporated in vacuo to a dark residue. The residue was dissolved in EtOAc and filtered to remove the insoluble hydrochloride. The filtrate was evaporated to give a solid that was dispersed in CCl_4 and collected. The filtrate was diluted with hexane to give a second crop of crystals for a total yield of 9.0 g (88%) of **88**, mp 136–142 °C. Recrystallization from MeOH–H_2O gave the analytical sample: mp 143–145 °C; UV (0.1 N HCl + 10% EtOH) λ_{max} 306 nm (ϵ 12 000); UV (0.1 N NaOH + 10% EtOH) λ_{max} 266 nm (ϵ 9300), 292 (9100); NMR (Me_2SO-d_6) δ 7.70 (s, 1 H, pyrimidine H), 6.70 (br t, 1 H, NH), 4.99 (br s, 2 H, NH_2), 3.25 (t, 2 H, NCH_2), 1.9–0.9 (br, 11 H, C_6H_{11}). Anal. ($C_{11}H_{17}ClN_4$) C, H, N.

6-Chloro-9-(cyclohexylmethyl)-9*H*-purine (89). This compound was prepared from **88** and $HC(OEt)_3$ by method D to give 5.09 g (77%) of **89**: mp 75–76 °C; UV (pH 7 + 10% EtOH) λ_{max} 266.5 nm (ϵ 8600); NMR (Me_2SO-d_6) δ 8.75 (s, 1 H, purine H), 8.68 (s, 1 H, purine H), 4.18 (d, 2 H, NCH_2), 1.9–0.9 (br, 11 H, C_6H_{11}). Anal. ($C_{12}H_{15}ClN_4$) C, H, N.

5-Amino-4-chloro-6-(furfurylamino)pyrimidine (90). A mixture of 5-amino-4,6-dichloropyrimidine (10.0 g, 61.0 mmol), furfurylamine (8.00 g, 82.4 mmol), 1-BuOH (100 mL), and Et_3N (10 mL, 71.4 mmol) was refluxed with stirring for 21 h. The dark solution was cooled and spin evaporated in vacuo. The residue was dissolved in CH_2Cl_2 (250 mL) and washed with water (3 × 50 mL). The solution was filtered through glass wool and spin evaporated to dryness. The dark residue was recrystallized from cyclohexane-EtOAc to give 7.50 g (54%) of crude **90**, mp 116–121 °C. The analytical sample was prepared by purification of 1.88 g of crude **90** by flash chromatography as described in method B. Evaporation of the appropriate fractions and recrystallization from EtOH–cyclohexane gave 1.48 g (78%) of **90**: mp 136–138 °C; NMR (Me_2SO-d_6) δ 7.78 (s, 1 H, pyrimidine H), 7.57 (d, 1 H, J = 2 Hz, OCH), 7.23 (t, 1 H, NH), 6.35 (m, 2 H, furan Hs), 5.07 (br s, 2 H, NH_2), 4.63 (d, 2 H, CH_2). Anal. ($C_9H_9ClN_4O$) C, H, N.

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