5-[(1*H*-indol-2-ylcarbonyl)amino]-1*H*-indole-2-carboxylic acid, 101134-91-2; benzofuran-2-carboxylic acid, 496-41-3; ethyl 5-[(1*H*-benzofuran-2-ylcarbonyl)amino]-1*H*-indole-2-carboxylate, 112089-69-7; 5-[(1-*H*-benzofuran-2-ylcarbonyl)amino]-1*H*-indole-2-carboxylic acid, 110314-42-6; ethyl 5-[[(5-ureido-1*H*-indol-2-yl)carbonyl]amino]-1*H*-indole-2-carboxylate, 112112-49-9; 5-[[(5-ureido-1*H*-indol-2-yl)carbonyl]amino]-1*H*-indole-2-carboxylic acid, 101134-95-6; 5-[[[5-(benzoylamino)-1*H*-indol-2-yl]carbonyl]amino]-1*H*-indole-2-carboxylic acid, 101134-93-4; benzothiophene-2-carboxylic acid, 6314-28-9; 6-hydroxy-7-methoxy-2-indolecarboxylic acid, 112089-70-0; quinaldic acid, 93-10-7; 5-methoxy-2-indolecarboxylic acid, 4382-54-1.

Synthesis of Arginine-vasopressins, Modified in Positions 1 and 2, as Antagonists of the Vasopressor Response to the Parent Hormone

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In an attempt to determine some of the structural features in position 1 that account for antivasopressor activity, eight new 1-(β,β-dialkyl-substituted) analogues of 1-(3-mercaptopropanoic acid)-8-arginine-vasopressin and 1-(3-mercaptopropanoic acid)-2-*O*-methyltyrosine-8-arginine-vasopressin have been designed and synthesized. The protected precursors required for these peptides were obtained by a combination of solid-phase and solutions methods. Some of the reported analogues, namely 1-(1-mercapto-4-methylcyclohexaneacetic acid)-8-arginine-vasopressin, 1-(1-mercapto-4-methylcyclohexaneacetic acid)-2-*O*-methyltyrosine-8-arginine-vasopressin, 1-(4-*tert*-butyl-1-mercaptocyclohexaneacetic acid)-8-arginine-vasopressin, 1-(4-*tert*-butyl-1-mercaptocyclohexaneacetic acid)-2-*O*-methyltyrosine-8-arginine-vasopressin, 1-(1-mercapto-4-phenylcyclohexaneacetic acid)-8-arginine-vasopressin and 1-(1-mercapto-4-phenylcyclohexaneacetic acid)-2-*O*-methyltyrosine-8-arginine-vasopressin, are among the most potent and selective antagonists of the vasopressor response to arginine-vasopressin reported to date.

Vasopressin (AVP) interacts primarily with two distinct receptor types in the periphery designated as V_1 and V_2 and is believed to react also with receptors, so far largely uncharacterized, in the central nervous system.[1,2] V_1 receptors have been characterized in vascular smooth muscle and in liver cells. V_2 receptors are located in the renal tubule. The stimulation of V_1 vascular smooth muscle receptors leads to vasoconstriction and an increase in blood pressure. The stimulation of V_2 receptors in the kidney results in reabsorption of free water in the renal tubule (antidiuretic effect).

Attempts to develop clinically useful synthetic antagonists of the vasopressor response to arginine-vasopressin have led to the synthesis and pharmacological evaluation of hundreds of analogues of this hormone, which with different efficacy bind to and stimulate either the V_1 or both the V_1 and the V_2 type receptor. Some interesting results were obtained with modifications of positions 1 and 2 of the molecule, which are proposed to be key positions of antagonists of AVP.[3] This was recently discussed in more detail by Manning and Sawyer.[4]

It was shown that the incorporation in a cyclic structure of the β-carbon in position 1 in 1-(3-mercaptopropanoic acid)-8-arginine-vasopressin (dAVP) converted this highly active antidiuretic and vasopressor agonist into a very potent vasopressor antagonist 1-(1-mercaptocyclohexaneacetic acid)-8-arginine-vasopressin [d$(CH_2)_5$AVP].[3] The introduction of *O*-methyltyrosine in d$(CH_2)_5$AVP to give d$(CH_2)_5$Tyr(Me)AVP brought about almost a twofold enhancement in vasopressor antagonistic potency[3] which coupled with low antidiuretic activity endows this analogue with a high degree of specificity for V_1 receptors.[3] More recently a larger series of related compounds, also including analogues with additional substitutions in positions 4, 8 and both 4 and 8, were synthesized and examined, several of which turned out to be very efficient pressor antagonists.[5] With this in mind we decided to synthesize analogues of arginine-vasopressin which have larger and more lipophilic substituents on the β-carbon in position 1 of 1-(3-mercaptopropanoic acid)-8-arginine-vasopressin (dAVP) and 1-(3-mercaptopropanoic acid)-2-*O*-methyltyrosine-8-arginine-vasopressin [dTyr(Me)AVP]. Thus we synthesized these analogues in an attempt to obtain antagonists of the vasopressor response to arginine-vasopressin with increased potency and selectivity. Accordingly six peptides were designed: 1-(1-mercapto-4-methylcyclohexaneacetic acid)-8-arginine-vasopressin (MeCAAVP) (I), 1-(1-mercapto-4-methylcyclohexaneacetic acid)-2-*O*-methyltyrosine-8-arginine-vasopressin [MeCATyr(Me)AVP] (II), 1-(4-*tert*-butyl-1-mercaptocyclohexaneacetic acid)-8-arginine-vasopressin (BCAAVP) (III), 1-(4-*tert*-butyl-1-mercaptocyclohexaneacetic acid)-2-*O*-methyltyrosine-8-arginine-vasopressin [BCATyr(Me)AVP] (IV), 1-(1-mercapto-4-phenylcyclohexaneacetic acid)-8-arginine-vasopressin (PhCAAVP) (V), and 1-(1-mercapto-4-phenylcyclohexaneacetic acid)-2-*O*-methyltyrosine-8-arginine-vasopressin [PhCATyr(Me)AVP] (VI). It is known that the presence of a less hydrophobic group in position 1 of AVP should result in an analogue with reduced antagonistic potency.[4,5] Despite this, we made further two analogues, 1-(4-mercapto-1-methyl-4-piperidineacetic acid)-8-arginine-vasopressin (MePAAVP) (VII) and 1-(4-mercapto-1-methyl-4-piperidineacetic acid)-2-*O*-methyltyrosine-8-arginine-vasopressin [MePATyr(Me)AVP] (VIII), which were structurally very similar to MeCAAVP (I) and MeCATyr(Me)AVP (II), but con-

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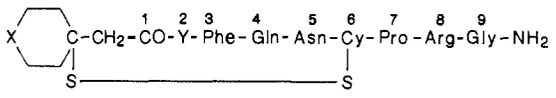
Table I. Pharmacological Data of New Vasopressin Analogues

peptide	antidiuresis		vasopressor		
	agonism (IU/mg)	antagonism	agonism (IU/mg)	antagonism (ED)[a]	recovery of AVP effect: time, min
MeCAAVP (I)	0.14 ± 0.02 (6)	weak, inconsistent	0	1.04 ± 0.09 (5)	214
MeCATyr(Me)AVP (II)	0.7 ± 0.1 (4)	0	0	1.5 ± 0.3 (4)	>140
BCAAVP (III)	0.13 ± 0.03 (7)	0	0.04	2.0 ± 0.4 (6)	125
BCATyr(Me)AVP (IV)	0.095 ± 0.006 (8)	0	0	1.0 ± 0.4 (3)	>115
PhCAAVP (V)	0.44 ± 0.04 (10)	weak, inconsistent	0	2.0 ± 0.8 (4)	>180
PhCATyr(Me)AVP (VI)	1.6 ± 0.1 (5)	–	0	2.0 ± 0.4 (4)	>180
MePAAVP (VII)	0.87 ± 0.09 (3)	0	0.4	0	
MePATyr(Me)AVP (VIII)	0.23 ± 0.09 (6)	weak, inconsistent	0	3.6 ± 0.7 (4)	110
d$(CH_2)_5$Tyr(Me)AVP[b]	–	–	0	1.3 ± 0.2 (6)	126

[a] The effective dose (ED) is defined as the dose in nanomoles/kilogram that reduces the response to $2x$ units to equal response to $1x$ units of agonist. [b] This compound was previously synthesized by Kruszynski et al.[3] They reported ED = 0.16 nmol/kg.[5]

taining a hydrophilic group in the residue of position 1. All synthesized analogues have the following general structure:



X = $CHCH_3$(I,II), $CHC(CH_3)_3$ (III,IV), CHC_6H_5 (V,VI), NCH_3 (VII, VIII)
Y = Tyr (I,III,V,VII), Tyr(Me) (II,IV,VI,VIII)

Results and Discussion

The eight peptides in Table I were synthesized by the combination of solid-phase and solutions methods. First, protected octapeptides were synthesized by stepwise coupling of Boc-amino acids to the growing peptide chain on a Merrifield resin. The protected peptides were cleaved from the resin by ammonolysis,[6] deblocked with trifluoroacetic acid, and coupled with protected mercapto acids by the DCC–HOBt preactivation method[7] to give the protected nonapeptide precursors. Each precursor was deblocked with sodium in liquid ammonia[8] and the resulting sulfhydryl compounds were subjected to oxidative cyclization with $K_3Fe(CN)_6$.[9] The crude peptides were desalted and then purified by gel filtration on a Sephadex G-15 column. The purity of analogues was checked on HPLC. The data from amino acid analysis of all analogues revealed the expected ratios of the amino acids.

The antivasopressor and antidiuretic potencies of the eight new analogues, together with the antivasopressor activity of 1-(1-mercaptocyclohexaneacetic acid)-2-*O*-methyltyrosine-8-arginine-vasopressin [d$(CH_2)_5$Tyr(Me)-AVP][3] are presented in Table I. None of the analogues exhibit any measurable pressor agonistic activity. Analogues I–VI are all potent antagonists of the vasopressor response to AVP. However, no clearly consistent pattern of increased antipressor potency with varied size of the cyclic substituent emerged. When the properties of MeCAAVP (I), BCAAVP (III), and PhCAAVP (V) are compared, the order of antagonistic potency is I > III ~ V, while in the Tyr(Me) series IV > VI with the activity of II overlapping IV and VI. All analogues have low antidiuretic agonistic activity ranging from 0.095 IU/mg to 1.6 IU/mg, which gives them high antivasopressor/antidiuretic selectivity. Moreover, they were pure vasopressor antagonists since they did not show any vasopressor agonism (with the exception of III and VII). The time for complete recovery of the AVP effect was also noted. Very potent in this respect were analogues PhCAAVP, PhCATyr-(Me)AVP, and MeCAAVP, which completely blocked the AVP effect for more then 3 h. In no cases was it possible to measure any antidiuretic antagonism though analogues MeCAAVP, PhCAAVP, and MePATyr(Me)AVP exhibited some week, inconsistent antagonism.

With respect to the properties of MePAAVP, the presence of a more hydrophilic group in position 1 resulted, as was expected, in the lack of antagonistic potency. However, when this substance was methylated at the tyrosin in position 2, it become a moderately potent pressor antagonist.

Conclusion

Six of the new analogues reported here, namely, MeCAAVP, MeCATyr(Me)AVP, BCAAVP, BCATyr(Me)-AVP, PhCAAVP, PhCATyr(Me)AVP, are among the most potent antagonists of the vasopressor response to AVP known to date. Furthermore, with the exception of III and VII, they lack partial agonism, and as they do not exhibit measurable antidiuretic agonism or antagonism, they are also highly selective. We observed an antagonistic potency with 1-mercapto-4-methylcyclohexaneacetic acid at least as high as with 1-mercaptocyclohexaneacetic acid in position 1. On further increasing the size of the 4-substituent in the cyclohexane ring up to phenyl, antagonistic potency was essentially retained but not improved. Much higher antivasopressor potencies of AVP analogues substituted in positions 1 and 2 have been presented earlier.[5] However, when one of the most potent of these analogues, d-$(CH_2)_5$Tyr(Me)AVP, was tested in our system, it gave an ED value of 1.3 nmol/kg compared to 0.16 nmol/kg by Manning et al.[5] Obviously any comparison must be done with caution with regard to activity figures obtained in different laboratories.

Experimental Section

The procedure of solid-phase synthesis used followed that previously published.[6,10] Chloromethylated resin (Bio-Rad, Bio-beads S×1) was esterified with Boc-Gly according to Gisin[11] to a load of 0.62 mmol/g. Boc–Tyr(Bzl)-Phe-Gln-Asn-Cys-(Bzl)-Pro-Arg(Tos)-Gly-NH_2 and Boc-Tyr(Me)-Phe-Gln-Asn-Cys(Bzl)-Pro-Arg(Tos)-Gly-NH_2 were synthesized as previously described.[12] The protected octapeptides gave satisfactory elemental and amino acid analyses. 4-Methyl-1-[(phenylmethyl)-thio]cyclohexaneacetic acid, 4-*tert*-butyl-1-[(phenylmethyl)-thio]cyclohexaneacetic acid, 4-phenyl-1-[(phenylmethyl)thio]-cyclohexaneacetic acid, and 1-methyl-4-[(phenylmethyl)thio]-4-

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Table II. Physicochemical Data for Protected Nonapeptide Intermediates[a]

substance	R_f in system A	B	C	D	$[\alpha]^{20}_D$, deg (*c* 1, DMF)	mp, °C
MeCA(Bzl)-Tyr(Bzl)-Phe-Gln-Asn-Cys(Bzl)-Pro-Arg(Tos)-Gly-NH_2 (1)		0.78	0.43	0.6	−44.4	180–183
MeCA(Bzl)-Tyr(Me)-Phe-Gln-Asn-Cys(Bzl)-Pro-Arg(Tos)-Gly-NH_2 (2)		0.79	0.5	0.59	−46.0	182–185
BCA(Bzl)-Tyr(Bzl)-Phe-Gln-Asn-Cys(Bzl)-Pro-Arg(Tos)-Gly-NH_2 (3)		0.78	0.46	0.74	−59.2	200–205
BCA(Bzl)-Tyr(Me)-Phe-Gln-Asn-Cys(Bzl)-Pro-Arg(Tos)-Gly-NH_2 (4)		0.89	0.48	0.66	−43.6	201–204
PhCA(Bzl)-Tyr(Bzl)-Phe-Gln-Asn-Cys(Bzl)-Pro-Arg(Tos)-Gly-NH_2 (5)	0.26	0.78		0.55	−45.0	198–200
PhCA(Bzl)-Tyr(Me)-Phe-Gln-Asn-Cys(Bzl)-Pro-Arg(Tos)-Gly-NH_2 (6)		0.78	0.34	0.55	−45.5	195–197
MePA(Bzl)-Tyr(Bzl)-Phe-Gln-Asn-Cys(Bzl)-Pro-Arg(Tos)-Gly-NH_2 (7)	0.30	0.46	0.30		−40.8	125–130
MePA(Bzl)-Tyr(Me)-Phe-Gln-Asn-Cys(Bzl)-Pro-Arg(Tos)-Gly-NH_2 (8)		0.33	0.32		−49.5	140–145

[a] All protected peptides gave correct C, H, and N elemental analyses. The symbols MeCA, BCA, PhCA, and MePA are used to indicate the 1-mercapto-4-methylcyclohexaneacetic acid, 4-*tert*-butyl-1-mercaptocyclohexaneacetic acid, 1-mercapto-4-phenylcyclohexaneacetic acid, and 4-mercapto-1-methyl-4-piperidineacetic acid.

Table III. Physicochemical Characteristics of AVP Analogues[a]

analogue	R_f in system B	C	E	$[\alpha]^{20}_D$, deg	amino acid analyses
MeCAAVP (I)	0.40	0.26	0.76	−69.0 (*c* 0.5, 1 M AcOH)	Tyr 1.01, Phe 1.03, Glu 1.00, Asp 0.99, $^1/_2$-Cys 0.94, Pro 0.99, Arg 1.04, Gly 1.02, NH_3 3.03
MeCATyr(Me)AVP (II)	0.32	0.30	0.78	−62.8 (*c* 0.4, 1 M AcOH)	Tyr 1.03, Phe 1.01, Glu 1.00, Asp 0.98, $^1/_2$-Cys 0.95, Pro 1.01, Arg 1.05, Gly 1.00, NH_3 2.97
BCAAVP (III)	0.41	0.16	0.86	−68.0 (*c* 0.5, 1 M AcOH)	Tyr 1.02, Phe 1.01, Glu 1.00, Asp 1.00, $^1/_2$-Cys 0.93, Pro 1.01, Arg 1.03, Gly 1.00, NH_3 3.03
BCATyr(Me)AVP (IV)	0.44	0.28	0.80	−60.5 (*c* 0.4, 1 M AcOH)	Tyr 1.01, Phe 0.99, Glu 1.02, Asp 0.99, $^1/_2$-Cys 0.95, Pro 0.98, Arg 1.03, Gly 1.00, NH_3 3.02
PhCAAVP (V)	0.40	0.26	0.85	−52.1 (*c* 0.5, 1 M AcOH)	Tyr 1.01, Phe 1.00, Glu 0.99, Asp 0.99, $^1/_2$-Cys 0.94, Pro 1.04, Arg 1.05, Gly 1.01, NH_3 3.04
PhCATyr(Me)AVP (VI)	0.39	0.27	0.86	−48.0 (*c* 0.4, 1 M AcOH)	Tyr 1.01, Phe 1.00, Glu 1.03, Asp 1.00, $^1/_2$-Cys 0.96, Pro 0.97, Arg 1.04, Gly 1.00, NH_3 3.01
MePAAVP (VII)	0.09	0.05	0.17	−41.9 (*c* 0.5, 1 M AcOH)	Tyr 1.01, Phe 1.02, Glu 1.00, Asp 0.99, $^1/_2$-Cys 0.97, Pro 0.99, Arg 1.04, Gly 1.02, NH_3 3.09
MePATyr(Me)AVP (VIII)	0.08	0.10	0.16	−46.6 (*c* 0.5, 1 M AcOH)	Tyr 1.02, Phe, 1.03, Glu 1.02, Asp 1.03, $^1/_2$-Cys 0.95, Pro 0.98, Arg 1.03, Gly 1.01, NH_3 2.94

[a] The symbols MeCA, BCA, PhCA, and MePA are used to indicate the 1-mercapto-4-methylcyclohexaneacetic acid, 4-*tert*-butyl-1-mercaptocyclohexaneacetic acid, 1-mercapto-4-phenylcyclohexaneacetic acid, and 4-mercapto-1-methyl-4-piperidineacetic acid.

piperidineacetic acid were obtained as previously described.[13] It was determined by ^1H NMR that all the three thiocyclohexaneacetic acid derivatives used in the syntheses were pure (4-*tert*-butyl) or essentially pure (≥95%, 4-methyl and 4-phenyl) isomers. On the basis of its ^{13}C NMR shift, the 4-methyl group was assigned an equatorial orientation.[13] *N,N*-Dimethylformamide (DMF) was distilled under reduced pressure; triethylamine (NEt_3) was distilled from ninhydrin. Other solvents and reagents were of analytical grade. Thin-layer chromatography (TLC) was carried out on silica plates (Merck), and the spots were visualized by ninhydrin or iodine. The following TLC systems were used: A, benzene–methanol–acetic acid (2:15:1, v/v/v); B, 1-butanol–acetic acid–water–pyridine (15:3:3:10, v/v/v/v); C, 1-butanol–acetic acid–water (4:1:5, v/v/v, upper phase); D, chloroform–methanol (7:3, v/v); E, ethanol–0.1 M aqueous pyridine–0.1 M aqueous acetic acid (4:1:1, v/v/v). The melting points are uncorrected. For amino acid analyses the peptides (0.5 mg) were hydrolyzed with constant-boiling hydrochloric acid (400 μL), containing phenol (20 μL), in evacuated, sealed ampules for 18 h at 110 °C. The analyses were performed with a one-column system (Durrum). The elemental analyses determined on a Carlo-Erba Model 1106 analyzer and indicated by the elemental symbols were within 0.4% of the theoretical values. The optical rotations were measured with a Hilger-Watts polarimeter with an accuracy of 0.01°. All AVP analogues were characterized by HPLC (Varian 5500). A reverse-phase column (μ-Bondapak C-18, 3.9 × 250 mm, Waters Associates) was used. The mobile phases for isocratic elution were 25%, 30%, and 39% acetonitrile in 0.1% TFA. All analogues gave a single peak. The purity of all analogues was between 98% and 99% as determined from the integrated areas recorded at 223 nm.

Synthesis of the Peptides. The protected acyloctapeptides were synthesized by acylation in a solution of octapeptides, obtained by the solid-phase method. First Boc-Tyr(Bzl)-Phe-Gln-Asn-Cys(Bzl)-Pro-Arg(Tos)-Gly-NH_2 and Boc-Tyr(Me)-Phe-Gln-Asn-Cys(Bzl)-Pro-Arg(Tos)-Gly-NH_2 were synthesized by the solid-phase procedure. These materials were dissolved in TFA and stirred at room temperature for 40 min. Cold diethyl ether was added, and the precipitated materials were filtered and washed several times with diethyl ether. The products were dried in vacuo over sodium hydroxide pellets. Both products were divided into four portions and dissolved in DMF, and a minute excess of *N*-methylmorpholine was added to give pH 7–8 to moist pH paper. The octapeptides were than coupled with 4-methyl-1-[(phenylmethyl)thio]cyclohexaneacetic acid, 4-*tert*-butyl-1-[(phenylmethyl)thio]cyclohexaneacetic acid, 4-phenyl-1-[(phenylmethyl)thio]cyclohexaneacetic acid, and 1-methyl-4-[(phenylmethyl)thio]-4-piperidineacetic acid hydrochloride by the DCC–HOBt preactivation method, to obtain the eight protected AVP analogues 1–8 (Table II). The protected peptides were treated with sodium in liquid ammonia[8] and the resulting dithiol compounds were subjected to oxidative cyclization with $K_3Fe(CN)_6$.[9] After lyophilization, the resulting materials were desalted and purified as previously described.[14] The data in Table III summarize the properties of the resulting eight AVP analogues.

Bioassay Methods. Antidiuretic assays were performed in anesthesized Sprague–Dawley female rats by intravenous injections.[15] The change of conductivity of secreted urine was taken as the effect parameter in agonistic and antagonistic experiments.

Vasopressor assays were done in anesthesized rats treated with dibenamine as described by Dekanski.[16] Agonistic activities were determined according to a four-point dosage schedule.[17] The antagonistic potency was expressed as effective dose (ED), defined as the dose in nanomoles/kilogram body weight of the antagonist,

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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.

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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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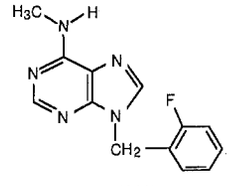
Several 9-alkyl-6-substituted-purines were synthesized and tested for anticonvulsant activity against maximal electroshock-induced seizures (MES) in rats. Most compounds were prepared in three steps from 5-amino-4,6-dichloropyrimidine or in two steps via alkylation of 6-chloropurine. Potent anticonvulsant 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-

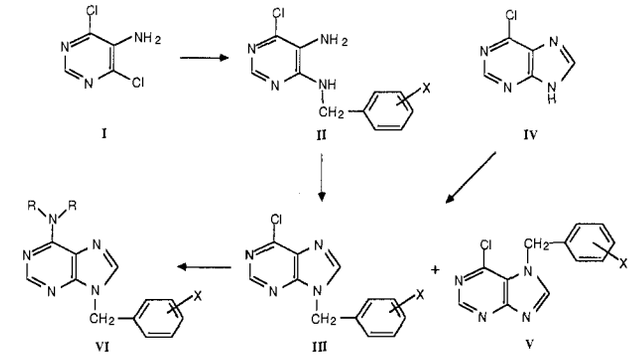


BW A78U (1)

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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