creased serum and hepatic cholesterol concentrations in the cholesterol-fed rat. Subsequent papers will describe the structure–activity studies that led to the selection of 1, the pharmacokinetic investigation used to characterize the absorption and metabolism of the compound, and the hypocholesterolemic activity of 1 in other species. Compound 1 is about to enter clinical trials as a hypolipidemic/antiatherosclerotic agent.

Registry No. 1, 96224-26-9; 2, 96224-27-0; 3, 96224-28-1; 4, 96224-29-2; *t*-$BuCH_2Ph$, 1007-26-7; $Me(CH_2)_6NH_2$, 111-68-2; 2,4-$F_2C_6H_3NCO$, 59025-55-7; oxalyl chloride, 79-37-8; acyl-CoA:cholesterol *O*-acyltransferase, 9027-63-8; cholesterol, 57-88-5.

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9-(2-Fluorobenzyl)-6-(methylamino)-9*H*-purine Hydrochloride. Synthesis and Anticonvulsant Activity

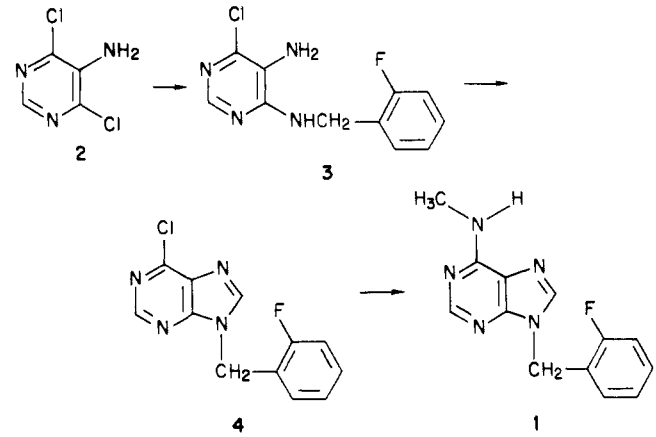
Sir:

Despite the availability and optimal use of several antiepileptic drugs, many patients with epilepsy do not experience satisfactory seizure control with them, or they do so at the expense of significant side effects.[1] Phenytoin, first marketed in 1938, is still the drug of choice for the treatment of many epileptic seizures despite its side effects and other disadvantages.[2] New antiepileptic drugs with fewer side effects and lower toxicity are needed.

As part of a program for new antiepileptic drugs with improved properties, a number of compounds were tested for anticonvulsant activity in several animal models.[3,4] From this program emerged 9-(2-fluorobenzyl)-6-(methylamino)-9*H*-purine (BW A78U (1)), a novel, orally active anticonvulsant with potent activity against maximal electroshock-induced seizures (MES) in animal models that predict antiepileptic activity in man.

Chemistry. BW A78U (1) was prepared from 5-amino-4,6-dichloropyrimidine (**2**) by modification of a general literature method[5,6] for the unambiguous synthesis of 9-substituted purines. Amination of **2** (Scheme I) with 2-fluorobenzylamine in refluxing 1-butanol gave diaminopyrimidine **3** in 82% yield, mp 220–223 °C. Condensation of **3** with ethanesulfonic acid and triethyl orthoformate[7,8] gave chloropurine **4** in 95% yield, mp 97–99 °C. Reaction of **4** with 40% aqueous methylamine in ethanol at ambient temperature gave 1 in high yield, mp

Scheme I



151–153 °C. Compound 1 was converted to the water-soluble hydrochloride salt in ethanol with concentrated hydrochloric acid in 90% yield, mp 255–259 °C (eff.).

Pharmacology. BW A78U had potent anticonvulsant activity in animal models that are predictive for antiepileptic activity in man. The compound protected Sprague–Dawley male rats against maximal electroshock-induced seizures (MES) with an oral ED_{50} of 2.5 ± 0.4 mg/kg under conditions where phenytoin had an ED_{50} of 20 ± 3 mg/kg (Table I). When administered by the ip and iv routes, BW A78U was active with ED_{50} values of 1.7 ± 0.4 and 0.2 ± 0.06 mg/kg, respectively. The duration of BW A78U's anticonvulsant activity in the MES test by the oral route was greater than 5 h at a submaximal dose of 5 mg/kg, which was 2–3 h shorter than that of phenytoin at 25 mg/kg. The compound also blocked 3-mercaptopropionic acid induced seizures with an ip ED_{50} of 16 ± 2 mg/kg under conditions where phenytoin had an ED_{50} of 21 ± 2 mg/kg ip. As with phenytoin, BW A78U did not protect rats against metrazol-, strychnine-, or picrotoxin-induced seizures at doses as high as 25 mg/kg ip or 50 mg/kg po.

BW A78U was also active in protecting CD1 Charles River male mice against MES with an oral ED_{50} of 14 ± 2 mg/kg. This level of activity was comparable to that of phenytoin, which had an ED_{50} of 22 ± 3 mg/kg. When administered ip and iv, BW A78U was active, with ED_{50} values of 5 ± 1 and 4 ± 0.2 mg/kg, respectively. Neither BW A78U nor phenytoin protected mice against metrazol-induced or low-frequency minimal electroshock-induced convulsions at an ip dose of 50 mg/kg. However, BW A78U blocked audiogenic seizures in mice with an ip ED_{50} of 3.7 ± 0.3 mg/kg under conditions where phenytoin had an ED_{50} of 6.4 ± 0.8 mg/kg.

BW A78U did not induce tolerance in mice under conditions where phenytoin was ineffective against MES. When phenytoin was administered to mice at a dose (10 mg/kg ip) that protected 84% of the animals through day 3, only 33% of the animals were protected by day 9 and none by day 13. In contrast, BW A78U protected 66–100% of the mice at 15 mg/kg ip throughout the 13-day period. Thus, in contrast with phenytoin, significant tolerance to BW A78U did not develop upon repeated administration.

BW A78U had minimal toxicity in acute tests in rats and mice. In rats the oral LD_{50} was >1000 mg/kg with the first visible sign of ataxia at 500 mg/kg. In mice the oral LD_{50} was >500 mg/kg with the first visible sign of ataxia at 250 mg/kg. The acute toxicity data and the anticonvulsant ED_{50} values were determined by the method of Miller and Tainter.[9]

BW A78U is a potent, orally active anticonvulsant with an activity profile in the rodent that suggests it may be

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Table I. Anticonvulsant Activity of BW A78U[a]

compound	MES in rats: ED_{50}, mg/kg			MES in mice: ED_{50}, mg/kg		
	po	ip	iv	po	ip	iv
BW A78U (1)[b]	2.5 ± 0.4	1.7 ± 0.4	0.2 ± 0.06	14 ± 2	5 ± 1	4 ± 0.2
phenytoin	20 ± 3	10 ± 2	4 ± 0.6	22 ± 3	9 ± 2	1.8 ± 0.4

[a] The compounds were tested for their ability to protect animals 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. For each ED_{50} value the number of animals was greater than 18. [b] Tested as the hydrochloride salt.

useful in the treatment of seizure disorders for which phenytoin is presently indicated. It is more potent than phenytoin, has appreciable water solubility and does not induce tolerance upon repeated administration. Amongst commonly used anticonvulsants, BW A78U has a unique structure that provides a novel lead for the development of agents that may be useful in the treatment of seizure disorders.

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Registry No. 1, 101155-02-6; 1·HCl, 101190-60-7; 2, 5413-85-4; 3, 101155-07-1; 4, 101155-08-2; 2-fluorobenzylamine, 89-99-6; triethyl orthoformate, 122-51-0.

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Articles

Novel 1,3-Bis(aryloxy)propanes as Leukotriene D_4 Antagonists[1]

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The synthesis and structure–activity relationships of a number of 1,3-bis(aryloxy)propanes, which are in vivo antagonists of LTD_4 in the guinea pig, are described. One of these compounds, 4 (Wy-44,329), was not only approximately equipotent with the standard 1 (FPL 55712) in the LTC_4 (ID_{50} = 0.17 and 0.23 mg/kg iv, respectively) and LTD_4 (ID_{50} = 0.11 and 0.15 mg/kg iv, respectively) challenge models but also possessed greater potency in the ovalbumin challenge model (ID_{50} = 0.47 mg/kg and 4.1 mg/kg iv, respectively) and a longer duration of action. This compound was a competitive LTD_4 antagonist on guinea pig ileum (pA_2 = 9.4) and possessed mediator release (rat PCA, ID_{50} = 0.26 mg/kg iv) and 5-lipoxygenase (IC_{50} = 32 μM vs. 5-HETE) inhibitory activities.

The identification of SRS-A as a mixture of LTC_4, LTD_4, and LTE_4 and the mounting evidence that these substances are mediators in human allergic asthma has stimulated considerable interest in the development of both inhibitors of the synthesis of leukotrienes and antagonists acting at leukotriene receptors.[2] The development of the prototype drug in this latter category 1 (FPL-55712) has been hampered by both its short biological half-life and its lack of oral activity.[3,4] Numerous chemical efforts to improve upon 1 have met with mixed results.[5]

We have previously reported on the orally active mediator release inhibitors **2** (Wy-16,922) and **3** (Wy-41,195), the latter of which is undergoing clinical trials.[6,7] The stereoelectronic similarity of the chromonecarboxylate portion of 1 to these compounds prompted us to synthesize hybrid structures **4–12** with the goal of obtaining a compound that was not only a mediator release inhibitor but also a leukotriene antagonist.[8] In this paper, we describe

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