a large number of binding modes of the large substituents is possible, depending on the conformation of the substituents relative to the site points used to bind them, very few common site points are found to be capable of explaining the data set. In order to explain the low binding energy of the pyrimidines, it is necessary to assume a steric surface that will exclude some of the binding modes, since the substituted benzyl ring may otherwise occupy some common space occupied by the phenyl ring of the triazines. The model fails to predict the biological data of nonaminoquinazolines, thereby indicating the possibility of an alternate binding mode in which the 6-substituents cannot reach the necessary site points of the present model. The various interesting predictions regarding the molecular modifications to be made to get potent dihydrofolate reductase inhibitors merit actual synthesis and biological evaluation.

A three-dimensional structure directed QSAR is necessary for many reasons. Even when the X-ray crystallographic structure of an inhibitor-bound receptor is known, information that is seldom available, we are not sure about the quantitative energetics of the interaction of the ligand with the receptor site. Our calculations may be done not only when the crystallographic information is not available, but also to determine the interaction energies for a binding site of known structure. Crystallographic receptor structures at high resolution are, of course, the most desirable data on the drug-design problem. However, such studies suffer from the difficulty of crystallizing the binary or ternary complexes. Even a single complex takes considerable time and effort, so studies on several inhibitors or enzymes are unlikely in the near future. On the other hand, 3-D QSAR, as we have been developing, is much easier. Although the 2-D QSAR is even faster than the 3-D QSAR, it is limited to a single class of compounds and even may often lead to wrong conclusions for flexible molecules. 2-D QSAR may be recommended only as the first step of a 3-D QSAR. A 3-D QSAR, in theory, may suggest a new lead. However, extensive collaborative work between the experimental and theoretical medicinal chemistry groups is necessary in order to explore the possibilities completely.

Acknowledgment. This work was supported by grants from the National Institutes of Health (1-R10-AM28140-03 and 5-R01-GM30561-02) and the Robert A. Welch Foundation. Acknowledgment is also made to the Donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

Notes

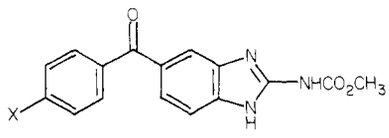
Synthesis of Potential Antifilarial Agents. 1. 1-(5-Benzoylbenzimidazol-2-yl)-3-alkyl- and -arylureas

Siya Ram,[†] Mike Skinner,[†] Doug Kalvin,[†] Dean S. Wise,[†] Leroy B. Townsend,*[,†] John W. McCall,[‡] Don Worth,[§] Don Ortwine,[§] and Leslie M. Werbel[§]

Department of Medicinal Chemistry, College of Pharmacy, and Department of Chemistry, University of Michigan, Ann Arbor, Michigan 48109, Department of Parasitology, College of Veterinary Medicine, The University of Georgia, Athens, Georgia 30602, and Chemistry Department, Warner-Lambert/Parke-Davis Pharmaceutical Research Division, Warner-Lambert Co., Ann Arbor, Michigan 48106. *Received June 9, 1983*

A series of 1-(5-benzoylbenzimidazol-2-yl)-3-substituted ureas have been synthesized by reacting an appropriate isocyanate with 2-amino-5-benzoylbenzimidazole or by reacting methyl (5-benzoylbenzimidazol-2-yl)carbamate with various amines. Several of the compounds have demonstrated antifilarial activity against *Brugia pahangi* and *Litomosoides carinii*.

Benzimidazole derivatives have exhibited a broad range of pharmacological actions, including anticonvulsant,[1-4] analgesic,[5] tranquilizing,[6] and paralyzing activities,[7] immunosuppression, and viral inhibition.[8] Recently, methyl (5-benzoylbenzimidazol-2-yl)carbamate (1, mebendazole)



1, X = H (mebendazole)
2, X = F (flubendazole)

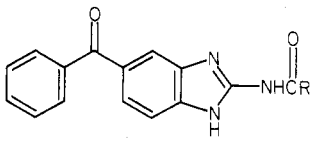
and methyl [5-(*p*-fluorobenzoyl)benzimidazol-2-yl]carbamate (2, flubendazole) have demonstrated significant antifilarial activity[9] in addition to a broad spectrum of anthelmintic activity.[10,11] However, poor water solubility and

[†] University of Michigan.
[‡] The University of Georgia.
[§] Warner-Lambert Co.

(1) E. E. Domino, R. J. Peterson, and K. R. Unna, *J. Pharmacol. Exp. Ther.*, 342 (1951).
(2) J. M. Singh, *J. Med. Chem.*, 12, 962 (1969).
(3) S. S. Parmar, A. K. Gupta, H. H. Singh, and T. K. Gupta, *J. Med. Chem.*, *15*, 999 (1972).
(4) S. S. Parmar, R. S. Misra, A. Chandhari, and T. K. Gupta, *J. Pharm. Sci.*, *61*, 1322 (1972).
(5) F. Gross and H. Turrian, *Experientia*, 13, 400 (1975).
(6) N. P. Buu-Hoi, P. Jacquignon, and J. P. Hoeffinger, *Arzneim.-Forsch.*, 856 (1963).
(7) E. E. Domino, K. R. Unna, and J. Kerwin, *J. Pharmacol Exp. Ther.*, *105*, 486 (1952).
(8) C. J. Paget, K. Kisner, R. L. Stone, and D. C. Delong, *J. Med. Chem.*, *12*, 1010 (1969).
(9) WHO Scientific Working Group on Filariasis Report No. TDR/Filsing (3) 79.3 (1979).
(10) J. S. Keystone and J. K. Murdoch, *Ann. Intern. Med.*, 91, 582 (1979).

0022-2623/84/1827-0914$01.50/0

Table I. Physical Constants of 1-(5-Benzoylbenzimidazol-2-yl-3-substituted-ureas

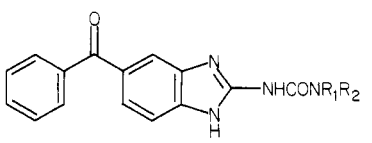


compd	R	mp, °C	yield, %	mol formula	anal.
5	$N[(CH_2)_2]_2NCH_3$	193	46	$C_{20}H_{21}N_5O_2$	C, H, N
7	$NH(CH_2)_2OH$	226–231	24	$C_{17}H_{16}N_4O_3$	C, H, N
8	$NH(CH_2)_2NH(CH_2)_2OH$	183–185	39	$C_{19}H_{21}N_5O_3 \cdot 0.2H_2O$	C, H, N
9	$N(CH_3)_2$	195–200	26	$C_{17}H_{16}N_4O_2$	C, H, N
10	$NHCH_3$	>300	67	$C_{16}H_{14}N_4O_2$	C, H, N
11	$NHCH_2CH_2CH_3$	>300	66	$C_{18}H_{18}N_4O_2$	C, H, N
12	C_6H_5NH	>300	66	$C_{21}H_{16}N_4O_2$	C, H, N
13	p-$CH_3C_6H_4NH$	>300	83	$C_{22}H_{18}N_4O_2$	C, H, N
14	m-$CH_3C_6H_4NH$	>300	83	$C_{22}H_{18}N_4O_2$	C, H, N
15	p-FC_6H_4NH	>300	87	$C_{21}H_{15}FN_4O_2$	C, H, N
16	o-FC_6H_4NH	>300	81	$C_{21}H_{15}FN_4O_2$	C, H, N
17	m,p-$Cl_2C_6H_3NH$	>300	69	$C_{21}H_{14}Cl_2N_4O_2$	C, H, N
18	o-$NO_2C_6H_4NH$	>300	86	$C_{21}H_{15}N_5O_4$	C, H, N
19	m-$NO_2C_6H_4NH$	>300	50	$C_{21}H_{15}N_5O_4$	C, H, N
20	p-$NO_2C_6H_4NH$	>300	55	$C_{21}H_{15}N_5O_4$	C, H, N

Table II. ^1H NMR Spectral Data of 1-(5-Benzoylbenzimidazol-2-yl)-3-alkyl- and -arylureas in Me_2SO-d_6

compd	chem shift, δ
10	2.8 (s, 3 H, NCH_3), 7.10 [br s, 1 H, NH (exchangeable with D_2O)], 7.42 (m, 8 H, Ar H), 11.03 [br s, 1 H, NH (exchangeable with D_2O)]
12	7.0–7.09 (m, 13 H, Ar H), 9.5 [s, 1 H, NH (exchangeable with D_2O)], 11.35 [m, 2 H, NH (exchangeable with D_2O)]
13	2.30 (s, 3 H, CH_3), 7.1–8.0 (m, 12 H, Ar H) 9.5 [s, 1 H, NH (exchangeable with D_2O)], 11.30 [br s, 2 H, 2 NH, (exchangeable with D_2O)]
14	2.10 (s, 3 H, CH_3), 6.70–7.80 (m, 12 H, Ar H), 9.40 [t, 1 H, NH (exchangeable with D_2O)], 11.30 [br s, 2 H, NH (exchangeable with D_2O)]
15	7.00–8.00 (m, 12 H, Ar H), 9.7 [s, 1 H, NH (exchangeable with D_2O)], 11.40 [br s, 2 H, NH (exchangeable with D_2O)]
16	7.0–8.0 (m, 12 H, Ar H), 9.80 [s, 1 H, NH (exchangeable with D_2O)], 10.40 [br s, 2 H, 2 NH (exchangeable with D_2O)]
17	7.40–8.10 (m, 11 H, Ar H), 9.8 [s, 1 H, NH (exchangeable with D_2O)], 11.60 (br s, 2 H, 2 NH (exchangeable with D_2O)]
18	7.1–8.5 (m, 12 H, Ar H), 10.3 [s, 1 H, NH (exchangeable with D_2O)], 11.90 [br s, 2 H, 2 NH (exchangeable with D_2O)]
19	7.30–8.0 (m, 11 H, Ar H), 8.9 (s, 1 H, Ar H), 9.9 [s, 1 H, NH (exchangeable with D_2O)], 11.70 [br s, 2 H, 2 NH (exchangeable with D_2O)]
20	7.5–8.5 (m, 12 H, Ar H), 9.7 [s, 1 H, NH (exchangeable with D_2O)], 10.2 [s, 1 H, NH (exchangeable with D_2O)], 11.80 [br s, 1 H, NH (exchangeable with D_2O)]

poor plasma and tissue absorption have limited the oral use of these agents in the treatment of filarial infections. We have recently initiated a program to develop more efficacious antifilarial agents, and during the course of this study we prepared 1-(5-benzoylbenzimidazol-2-yl)-3,3-dimethylurea (**9**) as a congener of **1**. In preliminary screening, **9** demonstrated some antifilarial activity. In order to establish a possible structure–activity relationship, several new 1-(5-benzoylbenzimidazol-2-yl)-3-alkyl- and -arylureas of general structures **4** and **5** were synthesized



4, R_1 = alkyl, aryl, H; R_2 = alkyl, aryl
5, R_1R_2 = c-$N(CH_2CH_2)_2N$-CH_3

and evaluated for antifilarial activity. Two approaches toward the synthesis of these ureas were investigated in an effort to provide the desired products, and these methods are outlined in Scheme I.

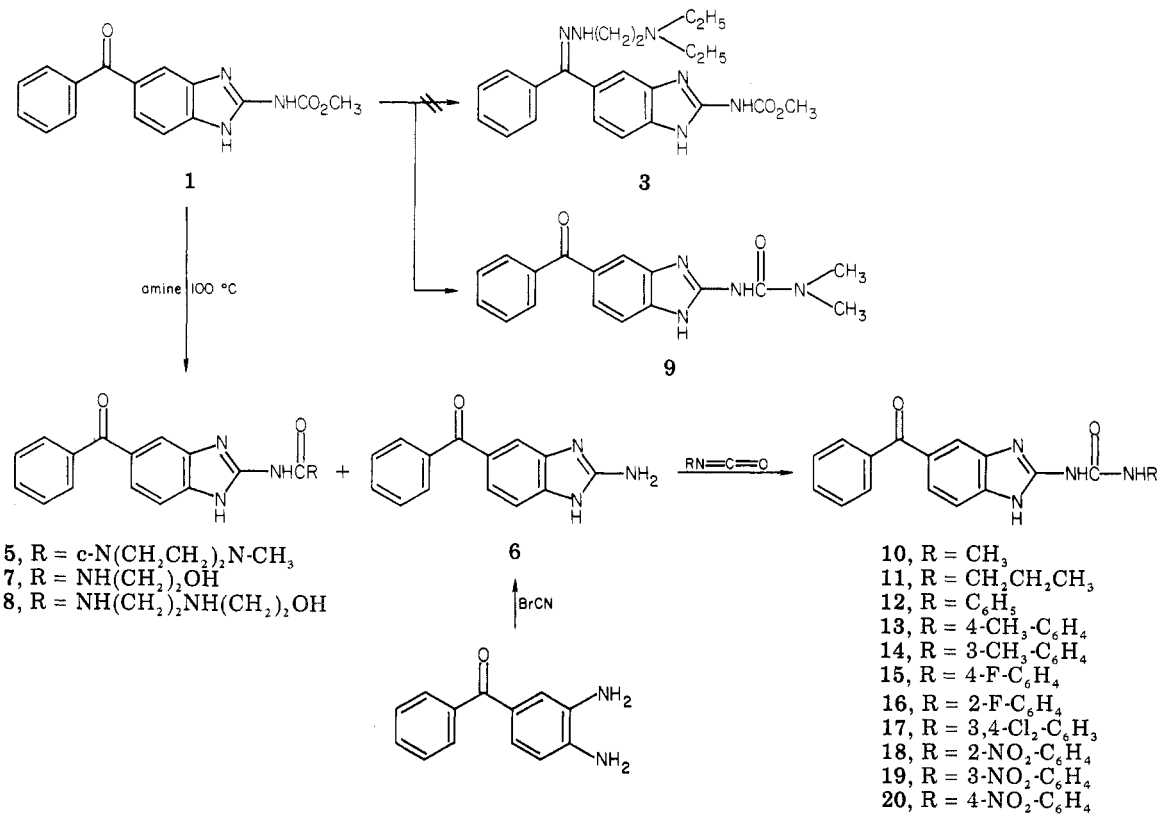
In the first approach, the target ureas (**5**, **7**, and **8**) were synthesized by a direct condensation of the carbamate **1** with the amines *N*-methylpiperazine, $H_2N(CH_2)_2OH$, and $H_2N(CH_2)_2NH(CH_2)_2OH$, respectively. As a general procedure, this method proved to be unsatisfactory, since in each case, mixtures of the urea and 2-amino-5-benzoylbenzimidazole (**6**) were obtained and were difficult to separate. In order to circumvent this problem, a second approach was investigated starting with 2-amino-5-benzoylbenzimidazole (**6**), which was prepared by either alkaline hydrolysis of mebendazole (**1**) or by treatment of 3,4-diaminobenzophenone hydrochloride with cyanogen bromide.[12] The resulting 2-amino-5-benzoylbenzimidazole (**6**) was subsequently reacted with various substituted alkyl or aryl isocyanates in an aprotic solvent (THF) to provide the desired benzimidazolyl ureas (**10–20**) in good yield (Scheme I). Interestingly, when **1** was heated with [(diethylamino)ethyl]hydrazine in dimethylformamide at 100 °C, the urea **9**, rather than the desired product **3**, was obtained in 26% yield. The formation of **9** must result from a decomposition of DMF in the presence of the [(diethylamino)ethyl]hydrazine to afford dimethylamine, which then reacts with **1**. The structure of all compounds were confirmed by IR, ^1H NMR, and mass spectroscopic data. The physicochemical data for the target ureas are listed in Tables I and II.

Biological Activity. All of the 1-(5-benzoylbenzimidazol-2-yl)-3-substituted-ureas were evaluated for antifilarial activity against both the microfilaria and adults

(11) J. P. Nozais, *Med. Afr. Noire*, *25*, 473 (1978).

(12) N. J. Leonard, D. Curtin and K. M. Beck, *J. Am. Chem. Soc.*, **69**, 2459 (1947).

Scheme I



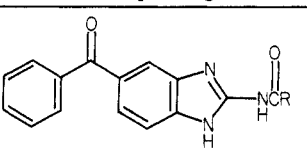
of *Brugia pahangi* and *Litomosoides carinii* in jirds.[13,14] Compound **9** demonstrated the most potent antifilarial activity in the series and was 100% macrofilaricidal against both *B. pahangi* and *L. carinii* at 100 mg/kg when administered subcutaneously and was 87% microfilaricidal at 25 mg/kg against *L. carinii* at the time of necropsy. 1-(5-Benzoylbenzimidazol-2-yl)-3-phenylurea (**12**), injected subcutaneously, exhibited marginal macrofilaricidal activity at 100 mg/kg against *L. carinii*. 1-(5-Benzoylbenzimidazol-2-yl)-3-(*p*-fluorophenyl)urea (**16**) exhibited marginal macrofilaricidal activity at 100 mg/kg against *B. pahangi* when injected subcutaneously and 100% microfilaricidal activity against the microfilaria of *L. carinii* at the time of necropsy. All additional compounds prepared in this study demonstrated little or no antifilarial activity at this dosage.

It may be concluded from this study that substitution of the methylcarbamoyl moiety of **1** by various ureas results in a substantial loss in antifilarial activity when compared to the antifilarial activity of **1**, which demonstrates 100% reduction of adult worms of both *B. pahangi* and *L. carinii* at 6.25 mg/kg on a 5-day schedule and a 97% reduction of *L. carinii* at 1.56 mg/kg. This may be due in part to the marked decrease in solubility, which was observed for the target ureas.

Experimental Section

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer Model 281 spectrophotometer and values are expressed in reciprocal centimeters. ^{1}H NMR spectra were obtained on a Varian EM-360, 60-MHz spectrometer, and chemical shift values (δ) are reported in parts per million downfield from the internal standard Me_4Si (s = singlet; d = doublet; t = triplet; m = multiplet; br = broad). Column chromatography was carried out on silica gel (60–200 mesh) and

Table III. Antifilarial Activity of Certain Benzimidazole Ureas against Infections of *B. pahangi* and *L. carinii* in Jirds



compd	dose[a]	route[b]	antifilarial act.: % reduction[c] of live worms: *B. pahangi*	*L. carinii*
5	100	sc	0	0
7	100	sc	15	20
9	100[d]	sc	100	100
	25	sc	0	87
	6.25	sc	0	61
11	100	sc	0	0
12[e]	100	sc	0	66
13	100	sc	0	27
14	100	sc	0	0
15	100	sc	6	66
16	100	sc	0	0
17	100	sc	0	9
18	100	sc	6	0
19	100	sc	0	32
20	100	sc	9	0
mebendazole	25	sc	100	100
	6.25	sc	100	100
	1.56	sc	12.5	97
suramin	25	po		71

[a] milligrams per kilogram per day for 5 days. [b] sc = subcutaneous; po = oral. [c] Percent reduction of live adult worms at necropsy relative to controls. Unless otherwise noted, results are averages for three animals. [d] Five animals were used. [e] Microfilaremia count was 0 at time of necropsy for this compound.

(13) J. W. McCall and H. H. Crouthamel, *J. Parasitol.*, **62**, 844 (1976).
(14) D. A. Denham, E. Brandt, and D. A. Liron, *J. Parasitol.*, **67**, 123 (1981).

Kieselgel $60F_{254}$ (70–230 mesh). Thin-layer chromatography (TLC) was performed on Analtech silica gel GF plates, and spots were visualized either by UV light or iodine. Microanalyses were performed by the M-H-W Laboratories, Phoenix, AZ, and are within ±0.4% of the required values.

2-Amino-5-benzoylbenzimidazole (6). A solution containing potassium hydroxide (29.0 g, 0.517 mol) in water (500 mL) was added to a stirred suspension of mebendazole[15] (**1**; 70.0 g, 0.24 mol) in methanol (2 L). The resulting solution was stirred and heated at reflux for 3–4 days under a nitrogen atmosphere. The reaction mixture was cooled to room temperature and poured into 5 L of water. The mixture was allowed to stand for 18 h, and the resulting solid was collected by filtration and air-dried. An additional amount of product was obtained by adjusting the pH of the filtrate to 8.0 and allowing the solution to stand at 5 °C for 18 h. The total yield of **6** was 55.6 g (98%): mp 193 °C; IR (KBr) ν_{max} 3448, 3180–3120, 1680, 1160–1155, 760, 718, 692 cm^{-1}; ^1H NMR ($CDCl_3$ + Me_2SO-d_6) δ 5.0–7.0 [br m, 2 H, NH_2, (exchangeable with D_2O)], 7.10–7.90 (m, 8 H, Ar H), 8.20 [br s, 1 H, NH (exchangeable with D_2O)].

1-(5-Benzoylbenzimidazol-2-yl)-3-(4-methylpiperazino)urea (5). A mixture of **1** (2.0 g, 0.006 mol) and *N*-methylpiperazine (15.0 mL) was heated at reflux for 5–6 h while stirring under a nitrogen atmosphere. The reaction mixture was cooled to room temperature and poured into hexane (300 mL), at which time a yellow solid separated. The solid was collected by filtration and air-dried. The crude compound was purified by chromatography on silica gel 60 F_{254} (50 g) (column size 50 × 2.5 cm), eluting with an ethyl acetate/methanol (95:5, v:v) mixture to afford 0.60 g (37%) of 2-amino-5-benzoylbenzimidazole (**6**). After the polarity of the elution solvent was increased to ethyl acetate/methanol (90:10, v:v), the desired product **5** was eluted (1.12 g, 46%). An analytical sample was obtained by recrystallization from an ethyl acetate/hexane mixture: mp 193 °C; IR (KBr) ν_{max} 3340, 2940, 2860, 2810, 1655–1620, 778, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.13–2.84 [m, 7 H, $H_3CN(CH_2)_2$], 3.80 [t, 4 H, $(CH_2)_2NC$], 6.83–8.17 (m, 8 H, Ar H), 9.73–12.07 [br m, 2 H, NH, (exchangeable with D_2O)].

1-(5-Benzoylbenzimidazol-2-yl)-3-(2-hydroxyethyl)urea (7). A mixture of compound **1** (5.0 g, 0.017 mol) and 2-aminoethanol (40 mL) was stirred at 100 °C for 72 h and poured into 700 mL of water. The pH of the solution was adjusted to 1 with 2 N HCl, and the mixture was extracted with ethyl acetate until no product was detectable (TLC) in the aqueous phase. The ethyl acetate extracts were combined, dried over $MgSO_4$, and filtered, and the filtrate was evaporated to dryness in vacuo. The residue was chromatographed over silica gel 60 F_{254} (460 g, column size 5 × 40 cm), eluting with $CHCl_3$/MeOH (4:1, v:v) (25-mL fractions, flow rate of 1.5 mL/min) to furnish 2.1 g (52%) of 2-amino-5-benzoylbenzimidazole and 1.5 g of **7** as an oil. Trituration of the oil with methanol, followed by recrystallization from acetonitrile, provided 1.3 g (24%) of **7**: mp 226–231 °C; pK_a (67% DMF) = 10.6; IR (KBr) ν_{max} 3350, 1695, 1630 (shoulder at 1640), 1555, 1300, 1285, 710 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.10–3.40 (m, 2 H, CH_2), 3.40–3.70 (m, 2 H, CH_2), 4.75 [t, 1 H, OH (exchangeable with D_2O)], 7.15 [t, 1 H, NH (exchangeable with D_2O)], 7.30–7.80 (m, 8 H, Ar H), 10.0 [br s, 1 H, NH (exchangeable with D_2O)], 11.60 [br s, 1 H, NH (exchangeable with D_2O)].

1-(5-Benzoylbenzimidazol-2-yl)-3-[2-[(2-hydroxyethyl)amino]ethyl]urea (8). This compound was prepared in a manner similar to the preparation of **7**, except that the reaction heating time was 2 h and the product was recrystallized from methanol: yield 39%; mp 183–185 °C; IR (KBr) ν_{max} 3350, 2950, 1690, 1635, 1560, 1290, 715 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.65 (q, 4 H, CH_2), 3.25 (q, 2 H, CH_2), 3.45 (t, 2 H, CH_2), 5.50–7.0 [br m, 4 H, NH and OH (exchangeable with D_2O)], 7.2 [t, 1 H, NH (exchangeable with D_2O)], 7.3–7.80 (m, 8 H, Ar H).

1-(5-Benzoylbenzimidazol-2-yl)-3,3-dimethylurea (9). A mixture of **1** (4.0 g, 0.014 mol) and [2-(diethylamino)ethyl]-hydrazine (5.3 g, 0.041 mol) in dry dimethylformamide (100 mL) was stirred at 100 °C for 72 h. The mixture was poured into 1.6 L of water, and the product was extracted from the solution with CH_2Cl_2 (50 mL × 3). The combined extracts were dried over $MgSO_4$ and evaporated to dryness in vacuo. The residue was chromatographed over silica gel 60 F_{254} (700 g, column size 5 × 60 cm) and eluted with a chloroform/methanol (9:1, v:v) mixture. The appropriate fractions were combined, and concentrated under reduced pressure, and the resulting residue was crystallized from acetonitrile: yield 1.1 g (26%); mp 195–200 °C; pK_a (67% DMF) = 11.6; IR (KBr) ν_{max} 3320, 1630 (shoulder at 1650 and 1670), 1560, 1320, 1300, 1280, 715 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.0 [s, 6 H, $N(CH_3)_2$], 7.30–7.80 (m, 8 H, Ar H), 11.40 (br s, 2 H, NH); MS, *m/e* 309, 308, 264, 263, 187, 186, 158, 105, 92, 91.

1-(5-Benzoylbenzimidazol-2-yl)-3-*n*-propylurea (11). *n*-Propyl isocyanate (0.790 g, 0.0113 mol) dissolved in dry THF (15 mL) was added to a stirred suspension of 2-amino-5-benzoylbenzimidazole (**6**; 1.47 g, 0.0062 mol) in dry THF (20 mL). The reaction mixture was heated at reflux under an atmosphere of N_2 with stirring for 24 h. The solid that separated during the course of the reaction was collected by filtration and washed with ethyl acetate (100 mL) and then ligroin (75 mL). The solid was dried under vacuum to furnish 1.33 g of **11**: yield 67%; mp 300 °C; ^1H NMR (Me_2SO-d_6) δ 0.9 (t, 3 H, CH_3), 1.6 (sextet, 2 H, CH_2), 3.40 (t, 2 H, $CNCH_2$), 7.60–8.20 (m, 8 H, Ar H), 8.40 [br s, 1 H (exchangeable with D_2O)], 10–11 [br s, 2 H, NH, (exchangeable with D_2O)]. Compound **10** was prepared in a manner similar to the preparation of **11**.

General Procedure for 1-(5-Benzoylbenzimidazol-2-yl)-3-arylureas (12–20). A solution of the appropriate isocyanate (0.0114 mol) in dry THF (15 mL) was added slowly over 30 min to a cold stirred suspension of 2-amino-5-benzoylbenzimidazole (**6**, 0.0057 mol) in dry THF (30 mL). The resulting reaction mixture was then stirred at reflux under an N_2 atmosphere for 5–36 h. During the course of the reaction a solid separated from the reaction mixture. At the end of the reaction period the solid was collected by filtration, washed with ethyl acetate and ligroin, and then dried under vacuum to furnish the desired target compounds.

Antifilarial Studies. All of the 1-(5-benzoylbenzimidazol-2-yl)-3-substituted-ureas were evaluated for antifilarial activity against the adult worms of *Brugia pahangi* and *Litomosoides carinii* in jirds (*Meriones unguiculatus*, males). The jirds were either inoculated intraperitoneally with 24–25 *L. carinii* larvae[16] 76–133 days prior to drug treatment and, subsequently, with an inoculation of 49–50 immature *B. pahangi* larvae 60–100 days prior to drug treatment or 15 to 20 adult *B. pahangi* worms were surgically implanted into the peritoneal cavity[17] 4–60 days pretreatment. The drugs were administered as solutions or suspensions in aqueous 1% (hydroxyethyl)cellulose and 0.1% Tween 80 (HEC Tween 80) once daily for 5 days to three to five implanted jirds. Microfilaria counts were made from blood drawn from the retro-ocular sinus[18] on the 1st day of dosing (day 0), day 4, 5, or 6, and at necropsy. Surviving animals were sacrificed and examined for adult worms 55 to 70 days after the first drug dose, by searching the pleural and peritoneal cavities. The number of surviving worms at autopsy was scored as a percentage relative to controls. Compounds were considered to be active when the reduction of adult worms exceeded 60% or when the reduction of circulating *L. carinii* microfilaria exceeded 90%.

Acknowledgment. This investigation was supported by the Filariasis Component of the World Bank/UNDP/WHO Special Program for Research and Training in Tropical Diseases (I.D. 800134).

Registry No. **1**, 31431-39-7; **5**, 89597-79-5; **6**, 52329-60-9; **7**, 89597-80-8; **8**, 89597-81-9; **9**, 89597-82-0; **10**, 89597-83-1; **11**, 89597-84-2; **12**, 89597-85-3; **13**, 89597-86-4; **14**, 89597-87-5; **15**, 89597-88-6; **16**, 89597-89-7; **17**, 89597-90-0; **18**, 89597-91-1; **19**, 89597-92-2; **20**, 89597-93-3; *N*-methylpiperazine, 109-01-3; 2-aminoethanol, 141-43-5; *n*-propyl isocyanate, 110-78-1.

(15) A. H. M. Raeymaekers, J. L. H. Van Gelder, L. F. C. Roevens, and P. A. J. Janssen, *Arzneim.-Forsch.*, **28**, 586 (1978).
(16) J. W. McCall, *J. Parasitol.* **62**, 585 (1976).
(17) R. R. Susivillo and D. A. Denham, *J. Parasitol.*, **63**, 591 (1977).
(18) P. E. Thompson, L. Boche, and L. S. Blair, *J. Parasitol.* **54**, 834 (1968).