of 50% aqueous HBF_4 at 70 °C and added to an ice-cold solution of 4.16 g of $NaNO_2$ (60.3 mmol) in 40 mL of H_2O at a rate such that the internal temperature did not rise above 25 °C. This solution was stirred in the cold for 0.5 h, and then the yellow diazonium tetrafluoroborate was filtered off and kept wet. It was added portionwise to a well-stirred solution of 200 g of $Na_2S_2O_4$ in 800 mL of H_2O. After the solution was stirred for 10 min, the product was extracted into Et_2O. Evaporation of the Et_2O phase gave 11.8 g (71%) of **16**, which had mp 170 °C dec after recrystallization from Et_2O–hexane. Anal. ($C_{13}H_8ClFN_2O_2$) C, H, N.

7-Chloro-3-(2-fluorophenyl)-6-hydroxy-1*H*-indazole (11a). Compound **16** (10.80 g, 39 mmol) was dissolved in 200 mL of MeOH containing 5 mL of concentrated hydrochloric acid and treated with 12 g of $SnCl_2 \cdot 2H_2O$. After 0.5 h, the reaction mixture was poured into H_2O, and the precipitated **11a** was filtered off and dried to give 8.40 g (82%), mp 212–214 °C. An analytical sample was recrystallized from Et_2O–hexane and had mp 214–215 °C. Anal. ($C_{13}H_8ClFN_2O$) H, N; C: calcd, 59.44; found, 58.86.

Ethyl [[7-chloro-3-(2-fluorophenyl)-1*H*-indazol-6-yl]oxy]acetate (12a) and the corresponding acid **2a** were synthesized by standard conditions, reported above. Their physical properties are reported in Tables I and II.

7-Chloro-3-(2-fluorophenyl)-6-methoxy-1,2-benzisothiazole (17a) and 3-(2,3-Dichloro-4-methoxyphenyl)-1,2-benzisothiazole (18). Benzophenone **1a** (16.8 g, 56 mmol) was heated in a sealed reaction vessel with 85 mL of ethylene glycol methyl ether containing 8.5 g of NH_3 and 1.9 g of sulfur. It was heated for 13 h at 130 °C and then allowed to cool to room temperature. A quantity of 4-chloro-3-methoxy-9*H*-thioxanthen-9-one (**19**) separated at this time, which was filtered off and recrystallized from toluene to give 5.2 g (34%), mp 225 °C. Anal. ($C_{14}H_9ClO_2S$) C, H. The filtrate, containing both **17a** and **18**, was evaporated, and the mixture was separated by preparative HPLC (40% CH_2Cl_2–hexane, 250 mL/min). Combination of the appropriate fractions gave 2.96 g (18%) of **17a** after recrystallization from hexane, mp 127–128 °C. Anal. ($C_{14}H_9ClFNOS$) C, H, N. In like manner, 2.61 g (15%) of **18** was obtained after recrystallization from CH_3CN, mp 176–177 °C. Anal. ($C_{14}H_9Cl_2NOS$) C, H, N.

7-Chloro-6-methoxy-3-phenylbenzisothiazole (17b). 2,3-Dichloro-4-methoxybenzophenone (**5c**; 18.0 g, 64 mmol) was treated with NH_3 and sulfur as for **5a** above. Evaporation of the reaction mixture and two recrystallizations from ethyl acetate gave 5.9 g (34%) of **17b**, mp 174–175 °C. Anal. ($C_{14}H_{10}ClNOS$) C, H, N.

7-Chloro-3-(2-fluorophenyl)-6-hydroxy-1,2-benzisothiazole (20) and 3-(2,3-dichloro-4-hydroxyphenyl)-1,2-benzisothiazole (21) were obtained from **17a** and **18**, respectively, by treatment with BBr_3 in refluxing 1,2-dichloroethane, a method previously reported.[1] Their properties are reported in Table II. The hydroxy compound derived in like manner from **17b** was taken on to the corresponding oxyacetic acid (**3b**) without purification. The other acids in the benzisothiazole series (**3a** and **22**) were likewise obtained from **20** and **21**, respectively, without isolation of the intermediate esters. The properties of **3a,b** and **22** are given in Table I.

[[7-Chloro-3-(2-fluorophenyl)-1,2-benzisothiazol-6-yl]oxy]acetic Acid 1,1-Dioxide (4). Acid **3a** (4.60 g, 13.6 mmol) was warmed for 1 h at 90 °C in 300 mL of glacial HOAc containing 75 mL of 30% H_2O_2. At the end of this time the reaction mixture was poured into ice–H_2O, and the product was filtered off. The physical properties of **4** are reported in Table I.

4-(1,2-Benzisothiazol-3-yl)-2,3-dichlorophenoxyacetic acid 1′,1′-dioxide (23) was synthesized in like manner. Its physical properties are reported in Table I.

Acute Diuretic Evaluation in Sodium-Loaded Mice. The acute sodium-loaded mouse experiments were performed with groups of male CD-1 mice weighing 18–24 g. Drugs were prepared in 1% saline and orally administered in a dosage volume of 10 mL/kg. The animals were housed in metabolic cages, each treatment group consisting of 10 animals, 5 per cage. Tests consisted of a vehicle control and potential diuretic agent given at 64 mg/kg. The pooled urine samples were analyzed for sodium by a flame photometer (IL Model 343). Sodium values were expressed as the mean milliequivalents (mequiv) per kilogram per 5 h.

Acknowledgment. The authors express their appreciation to Marc Agnew and Anastasia Rizwaniuk for spectral data and to Susan C. Nicolacopulos, Suzanne Raite, and Karen Zalenski for performing pharmacological assays. We also gratefully acknowledge Grace M. Naumovitz for assistance in preparation of this manuscript.

Registry No. **1a**, 72482-82-7; **1b**, 72498-57-8; **2a**, 85893-69-2; **2b**, 85893-70-5; **3a**, 85893-71-6; **3b**, 85893-72-7; **4**, 85893-73-8; **5a**, 72498-53-4; **5c**, 85893-74-9; **6a**, 85893-75-0; **6b**, 85893-76-1; **7a**, 85893-77-2; **7b**, 85893-78-3; **8a**, 85893-79-4; **8b**, 85893-80-7; **9a**, 85893-81-8; **9b**, 85893-82-9; **10**, 85893-83-0; **11a**, 85893-84-1; **12a**, 85893-85-2; **12b**, 85893-86-3; **13**, 56619-93-3; **14**·HCl, 85893-87-4; **15**, 85893-88-5; **16**, 85893-89-6; **17a**, 85893-98-9; **17b**, 85893-91-0; **18**, 85893-92-1; **19**, 85893-93-2; **20**, 85908-79-8; **21**, 85893-94-3; **22**, 85893-95-4; **23**, 85893-96-5; 2-chloro-3-methoxy-*N*-pivaloylaniline, 85893-97-6; methylhydrazine, 60-34-4; hydrazine, 302-01-2; ethyl bromoacetate, 105-36-2; 2-fluorobenzonitrile, 394-47-8.

N^2-1*H*-Benzimidazol-2-yl-N^4-phenyl-2,4-pyrimidinediamines and N^2-1*H*-Benzimidazol-2-yl-5,6,7,8-tetrahydro-N^4-phenyl-2,4-quinazolinediamines as Potential Antifilarial Agents[1,2]

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A series of N^2-1*H*-benzimidazol-2-yl-N^4-phenyl-2,4-pyrimidinediamines and N^2-1*H*-benzimidazol-2-yl-5,6,7,8-tetrahydro-N^4-phenyl-2,4-quinazolinediamines (XI) was synthesized for antifilarial evaluation. Condensation of the requisite β-keto ester (VI) with *N*-cyanoguanidine afforded 2-pyrimidinylcyanamides (VIIa,b) and (5,6,7,8-tetrahydro-4-hydroxy-2-quinazolinyl)cyanamide (VIIc). Reaction of VII with a substituted *o*-phenylenediamine gave 2-(1*H*-benzimidazol-2-ylamino)-4-pyrimidinols and 2-[(5,6-dichloro-1*H*-benzimidazol-2-yl)amino]-5,6,7,8-tetrahydro-4-quinazolinol (IX). Chlorination with phosphoryl chloride, followed by condensation with the appropriate substituted benzenamine, gave the desired N^2-1*H*-benzimidazol-2-yl-N^4-phenyl-2,4-pyrimidinediamines and N^2-1*H*-benzimidazol-2-yl-5,6,7,8-tetrahydro-N^4-phenyl-2,4-quinazolinediamines (XI). None of these compounds possessed antifilarial activity against *Litomosoides carinii* or *Brugia pahangi* infections in jirds.

Filariasis is a nematode infection that invades the lymphatic system or connective tissue and affects millions worldwide. Its main human forms results from the parasites *Wuchereria bancrofti*, *Brugia malayi*, and *Oncho-*

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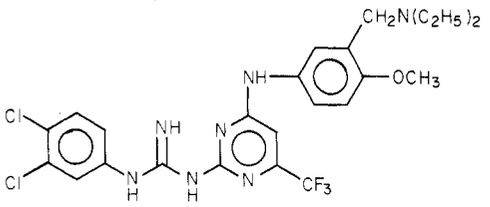
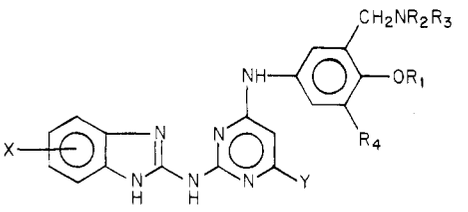
cerca volvulus. As we indicated in the preceding paper,[3] adequate drug therapy for this disease problem is not available.

The activity found for the guanidinopyrimidines (I)



I



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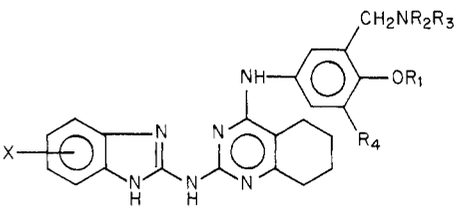

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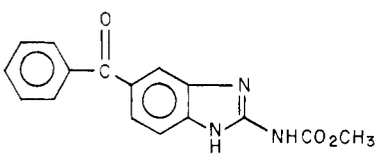
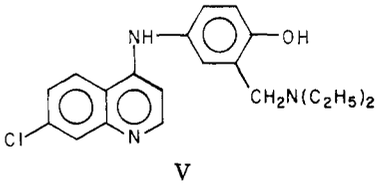


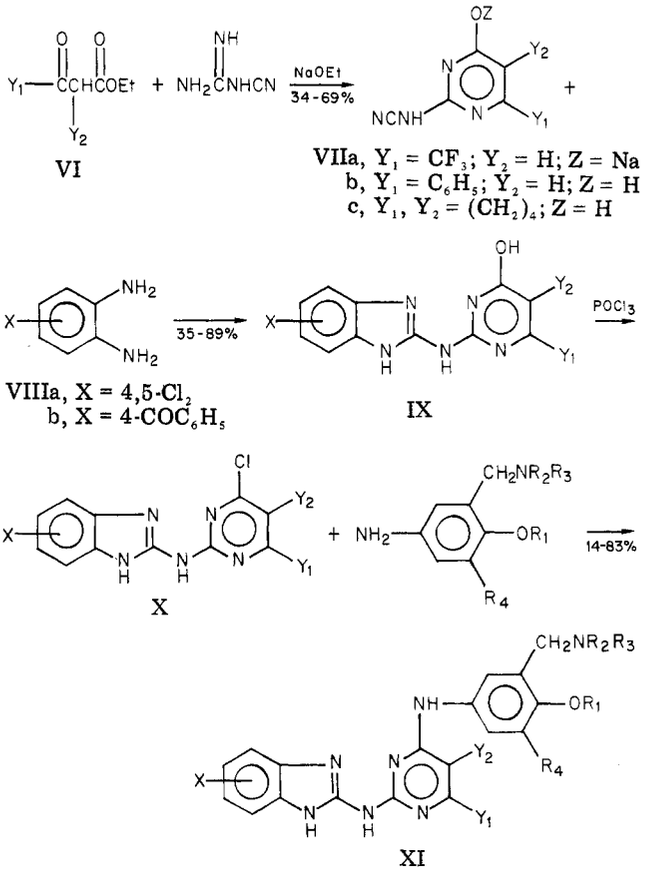
IV



V

against experimental filarial models,[3-5] the pursuit of which we have described in the preceding paper,[3] also spurred the investigation of N^2-1*H*-benzimidazol-2-yl-N^4-phenyl-2,4-pyrimidinediamines (II) and the related N^2-1*H*-benzimidazol-2-yl-5,6,7,8-tetrahydro-N^4-phenyl-2,4-quinazolinediamines (III). Compounds II and III could conceivably be formed by a dehydrogenation in vivo of I, resulting in ring closure of the unsubstituted nitrogen of the guanidine moiety on to the ortho position of the phenyl ring. In addition, the antifilarial activity of the benzimidazole anthelmintic mebendazole[6-9] (IV) also encouraged investigation of these structures. As noted previously[3] amodiaquine (V) itself possesses antifilarial activity, and it was of interest to incorporate specifically the amodiaquine side chain in our current studies.

Scheme I



A number of N^2-1*H*-benzimidazol-2-yl-N^4-[(dialkylamino)alkyl]-2,4-pyrimidinediamines and a few N^2-1*H*-benzimidazol-2-yl-N^4-phenyl-2,4-pyrimidinediamines with amodiaquine-type side chains had been synthesized previously as potential antimalarial agents[10] but were not tested against filariasis. In these studies, primarily aliphatic side chains were used, because introduction of the amodiaquine side chain resulted in a drastic loss of antimalarial potency.[10] In contrast, the tests against *L. carinii* in the guanidinopyrimidine series indicated that the derivatives with amodiaquine-type side chains were the superior filaricides.[4] Consequently, it was decided to synthesize compounds II and III specifically with amodiaquine-type side chains. A number of compounds were synthesized with Y in II as the trifluoromethyl group because of the superior activity of trifluoromethyl in the corresponding guanidinopyrimidine series.[3] Also, a few compounds with X in II as the 5-benzoyl group were prepared to mimic the structure of mebendazole (IV).

Chemistry. The synthesis of N^2-1*H*-benzimidazol-2-yl-N^4-phenyl-2,4-pyrimidinediamines and N^2-1*H*-benzimidazol-2-yl-5,6,7,8-tetrahydro-N^4-phenyl-2,4-

(1) This is paper 4 of a series on antifilarial drugs. For paper 3 see ref 3.

(2) This investigation received financial support from the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases.

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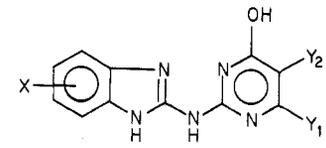
Table I. 2-(1*H*-Benzimidazol-2-ylamino)-4-pyrimidinols and 2-[(5,6-Dichloro-1*H*-benzimidazol-2-yl)amino]-5,6,7,8-tetrahydro-4-quinazolinols



no.	X	Y_1, Y_2[a]	mp, °C	yield purified, %	purifcn solvent	procedure	formula[b]
1	5,6-Cl_2	CH_3	>300	67	EtOH	*c*	$C_{12}H_9Cl_2N_5O$
2	5,6-Cl_2	CF_3	>300	79	EtOH	A	$C_{12}H_6Cl_2F_3N_5O$
3	5,6-Cl_2	C_6H_5	>300	35	DMF	A	$C_{17}H_{11}Cl_2N_5O$
4	5-COC_6H_5	CF_3	>300	89	EtOH	A	$C_{19}H_{12}F_3N_5O_2$
5	5,6-Cl_2	Y_1, Y_2 = $(CH_2)_4$	>300	50	EtOH	A	$C_{15}H_{13}Cl_2N_5O$

[a] Y_2 is H unless otherwise indicated. [b] These compounds were spectrally characterized and used in the next step without microanalysis. [c] Literature procedure; see ref 9.

quinazolinediamines (XI) (compounds **6–25**, Table II) involved modifications of previous procedures[10–13] and is depicted in Scheme I. The requisite β-keto ester (VI) was condensed with *N*-cyanoguanidine in ethanol in the presence of sodium ethoxide to provide substituted 2-pyrimidinylcyanamides (VIIa,b) in 34–69% yield. The preparation of (5,6,7,8-tetrahydro-4-hydroxy-2-quinazolinyl)cyanamide (VIIc) is described in the literature.[13] When VII was allowed to react with a substituted 1,2-benzenediamine (VIII) in aqueous 2-ethoxyethanol (generally in the presence of concentrated hydrochloric acid), the corresponding 2-(1*H*-benzimidazol-2-ylamino)-4-pyrimidinols (IX) (compounds **1–4**, Table I) were obtained in 35–89% yield (procedure A), and 2-[(5,6-dichloro-1*H*-benzimidazol-2-yl)amino]-5,6,7,8-tetrahydro-4-quinazolinol (compound **5**, Table I) was obtained in 50% yield. Chlorination with phosphoryl chloride (procedure B), followed by condensation of the *N*-(4-chloro-2-pyrimidinyl)-1*H*-benzimidazol-2-amines and 4-chloro-*N*-(5,6-dichloro-1*H*-benzimidazol-2-yl)-5,6,7,8-tetrahydro-2-quinazolinamine (X) with the appropriate substituted benzenamine in DMF or phenol, afforded the corresponding N^2-1*H*-benzimidazol-2-yl-N^4-phenyl-2,4-pyrimidinediamines and N^2-1*H*-benzimidazol-2-yl-5,6,7,8-tetrahydro-N^4-phenyl-2,4-quinazolinediamines (XI) in 14–83% yield (procedures C–E).

Antifilarial Screening in Jirds. Compounds **6–25** were evaluated in jirds (meriones unguiculatus, males) with dual infections of *Litomosoides carinii* and *Brugia pahangi* by the oral and/or the parenteral route generally at 100 mg/kg.[14,15] Groups of three to five jirds per dose were inoculated intraperitoneally with 24–25 *L. carinii* larvae[16] 76–133 days prior to drug treatment. Subsequently, a *B. pahangi* infection was introduced by inoculation of the animals with 49–50 immature larvae 60–100 days prior to drug treatment or by implanting surgically 15 or 20 adult worms into the peritoneal cavity[17] 4–60 days pretreatment. The drugs were administered once daily for 5 days as solutions or suspensions in aqueous 1% (hydroxyethyl) cellulose and 0.1% Tween 80 (HEC Tween 80). 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 55–70 days after the first drug dose, by searching the pleural and peritoneal cavities. The number of live worms at autopsy was scored as a percentage relative to sham-dosed controls. Compounds are considered to be active when the reduction of adult worms exceeds 60% or when the reduction of circulating *L. carinii* microfilaria exceeds 90%.

Compounds **6–25** were also evaluated by the parenteral route in jirds containing a single infection of *B. pahangi*.[19,20] All compounds were administered subcutaneously at 100 mg/(kg day) for 5 days, 3–4 days after the adult worms had been implanted surgically into the peritoneal cavity. The jirds were sacrificed and autopsied 2 to 4 weeks after treatment.

Results and Conclusion

Compounds **6–25** were inactive against *L. carinii* adults and microfilaria and also were inactive against *B. pahangi* in both test systems. Activity against *B. pahangi* infections is viewed as particularly desirable, since it is considered currently to be the more relevant model for human filarial disease. Thus, these compounds, despite their relationship to several known active types, are not useful as filaricides.

Experimental Section

Melting points (uncorrected) were taken on a Thomas-Hoover capillary melting point apparatus. The following intermediates were prepared according to the cited literature references: 4-amino-2-[(diethylamino)methyl]phenol dihydrochloride, 5-amino-*N*,*N*-diethyl-2-methoxybenzenemethanamine dihydrochloride, and 5-amino-*N*,*N*-diethyl-2-ethoxybenzenemethanamine dihydrochloride, ref 21; 5-amino-*N*-ethyl-2-methoxybenzenemethanamine dihydrochloride, ref 5; 5-amino-3-[(diethylamino)methyl][1,1′-biphenyl]-2-ol dihydrochloride, ref 3; 4-amino-2-(1-pyrrolidinylmethyl)phenol dihydrochloride and 4-amino-2-[(4-methyl-1-piperazinyl)methyl]phenol trihydrochloride, ref 22; ethyl 4-[(5-amino-2-hydroxyphenyl)methyl]-1-

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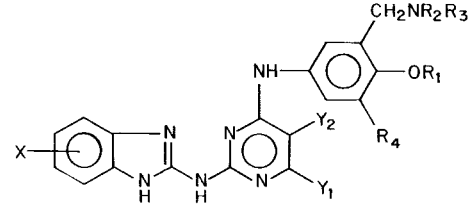
Table II. N^2-1*H*-Benzimidazol-2-yl-N^4-phenyl-2,4-pyrimidinediamines and N^2-1*H*-Benzimidazol-2-yl-N^4-phenyl-5,6,7,8-tetrahydro-2,4-quinazolinediamines



no.	X	Y_1, Y_2[a]	R_1	NR_2R_3, R_4[b]	mp, °C	yield purified, %	purifcn solvent	procedure	formula	anal.
6	5,6-Cl_2	CH_3	H	$N(C_2H_5)_2$	318–325	35	MeOH-Et_2O	C	$C_{23}H_{25}Cl_2N_7O\cdot 2HCl\cdot H_2O$	C, H, N, Cl, H_2O[c]
7	5,6-Cl_2	CH_3	H	$N(CH_2)_4$	315 dec	54	MeOH	C	$C_{23}H_{23}Cl_2N_7O\cdot 2.2HCl\cdot H_2O$	C, H, N, Cl, H_2O
8	5,6-Cl_2	CH_3	CH_3	$N(C_2H_5)_2$	240 dec	68	MeOH-Et_2O	C[d]	$C_{24}H_{27}Cl_2N_7O\cdot 2HCl\cdot 0.7H_2O$	C, H, N, Cl, H_2O
9	5,6-Cl_2	CH_3	C_2H_5	$N(C_2H_5)_2$	235 dec	79	EtOH	C[d]	$C_{25}H_{29}Cl_2N_7O\cdot 2HCl\cdot 0.3H_2O$	C, H, N, H_2O; Cl[e]
10	5,6-Cl_2	CH_3	H	$N[(CH_2)_2]_2NCH_3$	275 dec	18	DMF-MeOH	C	$C_{24}H_{26}Cl_2N_8O\cdot 0.2H_2O$	C, H, N, Cl, H_2O
11	5,6-Cl_2	CH_3	CH_3	NHC_2H_5	252 dec	81	H_2O-EtOH-Et_2O	C	$C_{22}H_{23}Cl_2N_7O\cdot 2HCl\cdot H_2O$	C, H, N, H_2O; Cl[f]
12	5,6-Cl_2	CH_3	H	NH CH_3	>260	70	MeOH	C	$C_{20}H_{19}Cl_2N_7O\cdot 2HCl\cdot 1.5H_2O$	C, H, N; H_2O[g]
13	5,6-Cl_2	CF_3	CH_3	$N(C_2H_5)_2$	235 dec	41	MeOH	C	$C_{24}H_{24}Cl_2F_3N_7O\cdot 2HCl\cdot 1.8H_2O$	C, H, N, H_2O
14	5,6-Cl_2	CF_3	H	$N(C_2H_5)_2$	217 dec	59	MeOH	C	$C_{23}H_{22}Cl_2F_3N_7O\cdot 2C_2HF_3O_2\cdot H_2O$	C, H, N, H_2O
15	5,6-Cl_2	Y_1, Y_2 = $(CH_2)_4$	H	$N(C_2H_5)_2$	>260	70	MeOH-Et_2O	C	$C_{26}H_{29}Cl_2N_7O\cdot 2HCl\cdot H_2O$	C, H, N, H_2O
16	5,6-Cl_2	Y_1, Y_2 = $(CH_2)_4$	CH_3	NH[C_2H_5]	>270	83	MeOH-Et_2O	C	$C_{25}H_{27}Cl_2N_7O\cdot 2HCl\cdot 0.3H_2O$	C, H, N, H_2O
17	5,6-Cl_2	Y_1, Y_2 = $(CH_2)_4$	C_2H_5	$N(C_2H_5)_2$	273 dec	81	MeOH-Et_2O	C	$C_{28}H_{33}Cl_2N_7O\cdot 2HCl\cdot 1.5H_2O$	C, H, N, H_2O
18	5,6-Cl_2	Y_1, Y_2 = $(CH_2)_4$	H	$N[(CH_2)_2]_2NCH_3$	>280	14	MeOH	C	$C_{27}H_{30}Cl_2N_8O\cdot 3HCl\cdot 2.5H_2O$	C, H, N, Cl, H_2O
19	5,6-Cl_2	CF_3	H	$N(C_2H_5)_2$, C_6H_5	295–300	32	MeOH-DMF	D	$C_{29}H_{36}Cl_2F_3N_7O\cdot 0.7C_3H_7NO$	C, H, N
20	5,6-Cl_2	CF_3	H	$N[(CH_2)_2]_2NCO_2C_2H_5$, C_6H_5	267–271	73	EtOH	D	$C_{26}H_{25}Cl_2F_3N_8O_3$	C, H, N
21	5,6-Cl_2	C_6H_5	H	$N(C_2H_5)_2$	>270	65	DMF-H_2O	E	$C_{28}H_{27}Cl_2N_7O$	C, H, N
22	5-COC_6H_5	CF_3	H	$N(C_2H_5)_2$	149 dec	21	$CHCl_3$-hexane	D	$C_{30}H_{28}F_3N_7O_2\cdot 0.3H_2O$	C, H, N; H_2O[h]
23	5-COC_6H_5	CF_3	CH_3	$N(C_2H_5)_2$	163–168	37	Me_2SO	D	$C_{31}H_{30}F_3N_7O_2\cdot C_2H_6SO$	C, H, N
24	5-COC_6H_5	CF_3	CH_3	NHC_2H_5	263 dec	26	95% EtOH	C	$C_{29}H_{26}F_3N_7O_2\cdot 2HCl\cdot 1.5H_2O$	C, H, N, H_2O[i]
25	5-COC_6H_5	CF_3	H	$N[(CH_2)_2]_2NCH_3$	159 dec	23	$CHCl_3$-PE[j]	C	$C_{31}H_{29}F_3N_8O_2\cdot 0.3H_2O$	C, H, N, H_2O

[a] Y_2 is H unless otherwise indicated. [b] R_4 is H unless otherwise indicated. [c] H_2O: calcd, 3.12; found, 2.61. [d] Prepared previously in the literature; see ref 9. [e] Cl: calcd, 23.93; found, 23.46. [f] Cl: calcd, 25.18; found, 24.76. [g] H_2O: calcd, 4.97; found, 3.93. [h] H_2O: calcd, 0.94; found, 0.43. [i] H_2O: calcd, 4.09; found, 5.83. [j] PE = petroleum ether.

piperazinecarboxylate dihydrochloride, ref 3; and (5,6,7,8-tetrahydro-4-hydroxy-2-quinazolinyl)cyanamide (VIIc), ref 13.

Preparation of [4-Hydroxy-6-(trifluoromethyl)-2-pyrimidinyl]cyanamide Sodium Salt (VIIa). To a solution of sodium ethoxide in EtOH prepared from sodium (37.9 g, 1.65 mol) and anhydrous EtOH (980 mL) was added *N*-cyanoguanidine (6.31 g, 0.75 mol), followed by ethyl 4,4,4-trifluoro-3-oxobutanoate[23] (207.1 g, 1.13 mol). The stirred mixture was heated under reflux for 60 h. The reaction mixture was then concentrated to ca. 350 mL in vacuo. Ethyl ether (2 L) was added, and the resulting precipitate was collected and washed with ethyl ether. The crude product (182 g) was dissolved in H_2O (1.8 L) and passed over a column of Amberlite IRC-50 resin (700 mL, 2.45 equiv), which proved to be insufficient to convert the sodium salt to the hydroxy compound. The eluate was concentrated in vacuo, and the resulting solids were dried in vacuo at 70 °C to give a light tan solid (144.5 g) in three crops. Two crops (63.5 g) were slurried with hot EtOAc, and the resulting solid was dried at 100 °C in vacuo to give an off-white solid, "A" (71.7 g), which contained 0.8 mol of EtOAc per mole of product by NMR. The remaining crop (81.0 g) was recrystallized from anhydrous EtOH (2.5L) to give a white solid, "B" (55.9 g), which was collected, triturated with ether, and dried in vacuo at 100 °C. The yield of A and B was 69%. The product was spectrally characterized and used in the next step without microanalysis.

Preparation of (4-Hydroxy-6-phenyl-2-pyrimidinyl)-cyanamide (VIIb). To a solution of sodium ethoxide in EtOH prepared from sodium (50.6 g, 2.20 mol) and anhydrous EtOH (1.5 L) was added *N*-cyanoguanidine (84.1 g, 1.00 mol), followed by ethyl β-oxobenzenepropanoate (211.4 g, 1.10 mol). The stirred mixture was heated under reflux for 6 days. The reaction mixture was cooled in an ice bath to give a white solid (181.6 g). The filtrate was concentrated in vacuo to 300 mL, and Et_2O (1.2 L) was added to give a second crop (50.6 g). The first crop was dissolved in H_2O (1 L), the solution was filtered, and the filtrate was acidified with concentrated HCl (128 mL) to give a solid (90.9 g). The second crop was treated similarly to give additional crude product (15.5 g). The first crop was dissolved in DMF (500 mL) at 100 °C, the solution was filtered, and H_2O (425 mL) was added. The mixture was cooled, and the solid was collected and triturated with H_2O. Drying in vacuo at 80 °C afforded the title compound (62.7 g), mp 250 °C dec. The second crop from above was treated similarly to give additional product (8.7 g). The combined yield was 34%.

Preparation of 2-(1*H*-Benzimidazol-2-ylamino)-4-pyrimidinols (IX) (Compounds 1–4, Table I) and 2-[(5,6-Dichloro-1*H*-benzimidazol-2-yl)amino]-5,6,7,8-tetrahydro-4-quinazolinol (IX) (Compound 5, Table I). Procedure A. A stirred mixture of 4,5-dichloro-1,2-benzenediamine (VIIIa; 26.6 g, 0.015 mol) and (5,6,7,8-tetrahydro-4-hydroxy-2-quinazolinyl)-cyanamide (VIIc; 28.5 g, 0.015 mol) in 2-ethoxyethanol (170 mL), H_2O (40 mL), and concentrated HCl (12.9 mL) was heated under reflux for 24 h. The mixture was allowed to cool to room temperature, and the solid was collected. The solid was then slurried with hot anhydrous EtOH (400 mL) twice and dried in vacuo at 80 °C to give 2-[(5,6-dichloro-1*H*-benzimidazol-2-yl)amino]-5,6,7,8-tetrahydro-4-quinazolinol (**5**; 26.5 g, 50%), mp >300 °C.

Compound **2** was similarly prepared from the sodium salt VIIa, and the reaction mixture was heated under reflux for 40 h. In the preparation of compound **4**, HCl was omitted, since the hydrochloride of (3,4-diaminophenyl)phenylmethanone VIIIb was used. After the crude compound **3** was slurried with hot EtOH, it was further slurried with DMF at 100 °C and finally triturated with H_2O to give pure **3**.

Preparation of *N*-(4-Chloro-2-pyrimidinyl)-1*H*-benzimidazol-2-amines and 4-Chloro-*N*-(5,6-dichloro-1*H*-benzimidazol-2-yl)-5,6,7,8-tetrahydro-2-quinazolinamine (X). Procedure B. A suspension of 2-[(5,6-dichloro-1*H*-benzimidazol-2-yl)amino]-5,6,7,8-tetrahydro-4-quinazolinol (**5**; 26.3 g, 0.075 mol) in $POCl_3$ (180 mL) was heated on the steam bath for 1.5 h. The mixture was then cooled in an ice bath and added cautiously to vigorously stirred water (1.3 L) cooled in an ice bath, maintaining the temperature below 30 °C. The solid was collected, washed with cold H_2O, and then slurried twice with hot MeOH (350 mL). Drying in vacuo over P_2O_5 gave 4-chloro-*N*-(5,6-dichloro-1*H*-benzimidazol-2-yl)-5,6,7,8-tetrahydro-2-quinazolinamine as a mixture of salts (27.2 g), mp >300 °C. The product was characterized spectrally and used directly in the next step. [[2-[[4-Chloro-6-(trifluoromethyl)-2-pyrimidinyl]amino]-1*H*-benzimidazol-5-yl]phenyl]methanone was slurried with MeCN at room temperature instead of hot MeOH to give the product as a mixture of salts, mp >300 °C. 5,6-Dichloro-*N*-[4-chloro-6-(trifluoromethyl)-2-pyrimidinyl]-1*H*-benzimidazol-2-amine (91%), mp >300 °C, was isolated as the free base. 5,6-Dichloro-*N*-(4-chloro-6-phenyl-2-pyrimidinyl)-1*H*-benzimidazol-2-amine was obtained as a mixture of salts, mp >300 °C. 5,6-Dichloro-*N*-(4-chloro-6-methyl-2-pyrimidinyl)-1*H*-benzimidazol-2-amine was prepared according to the literature procedure[10] and was isolated as the free base.

Preparation of N^2-1*H*-Benzimidazol-2-yl-N^4-phenyl-2,4-pyrimidinediamines and N^2-1*H*-Benzimidazol-2-yl-5,6,7,8-tetrahydro-N^4-phenyl-2,4-quinazolinediamines (Compounds 6–25, Table II). Procedure C. A stirred mixture of crude 4-chloro-*N*-(5,6-dichloro-1*H*-benzimidazol-2-yl)-5,6,7,8-tetrahydro-2-quinazolinamine (4.8 g, 0.012 mol assuming 90% free base) and 5-amino-*N*-ethyl-2-methoxybenzenemethanamine dihydrochloride (3.3 g, 0.013 mol) in DMF (110 mL) was heated at 110 °C for 3 h. The mixture was cooled, and the solid was collected, washed with cold DMF, and then ether. The crude product (6.6 g) was dissolved in hot MeOH (250 mL), treated with Darco, and filtered, and the resulting solution was concentrated in vacuo until crystallization began (ca. 60 mL). Ethyl ether (150 mL) was added, and the resulting solid was collected and washed with ether to give N^2-(5,6-dichloro-1*H*-benzimidazol-2-yl)-N^4-[3-[(ethylamino)methyl]-4-methoxyphenyl]-5,6,7,8-tetrahydro-2,4-quinazolinediamine dihydrochloride (**16**; 5.9 g, 83%), mp >270 °C.

Crude compound **7** was obtained by concentrating the reaction mixture in vacuo, and crude compound **9** was obtained by adding Et_2O to the reaction mixture to give a gum, which solidified. Purification then proceeded as above.

For compound **24**, a small amount of insoluble material was removed from the reaction mixture by filtration, and the filtrate was added to EtOAc. The crude product was recrystallized first from MeOH/Et_2O and then from 95% EtOH to give pure **24**.

Crude compound **11** was dissolved in hot H_2O/EtOH (1:4), and then addition of Et_2O provided pure material.

The MeOH solution of crude compound **18** was concentrated to one-fifth of its original volume, and the mixture was cooled to remove unreacted tetrahydrochloroquinazoline. The filtrate was then further concentrated to afford pure **18**.

Crude compound **14** was dissolved in CF_3CO_2H, and H_2O was added to give a precipitate, which was recrystallized from MeOH.

Crude compound **10** from MeOH/Et_2O was dissolved in hot anhydrous EtOH, and a dark brown solid was removed by filtration after cooling to room temperature. Addition of Et_2O to the filtrate gave an off-white solid, which was converted to the free base by dissolving in MeOH and adding to dilute aqueous NH_4OH. The resulting solid was dissolved in DMF, and the product was obtained by the addition of MeOH.

For compound **25**, the reaction mixture was filtered and poured into acetone to give a solid, which was purified initially from MeOH/Et_2O and then converted to the free base by dissolving in MeOH and adding to dilute aqueous NH_4OH. The resulting solid was dissolved in $CHCl_3$ (12 mL/g), and a sixfold volume of petroleum ether was added to give a brown solid, which was discarded. Further dilution with petroleum ether gave the product.

Procedure D. A mixture of 5,6-dichloro-*N*-[4-chloro-6-(trifluoromethyl)-2-pyrimidinyl]-1*H*-benzimidazol-2-amine (5.0 g, 0.013 mol) and crude 5-amino-3-[(diethylamino)methyl][1,1'-biphenyl]-2-ol dihydrochloride (6.7 g, assume 0.020 mol) in DMF (100 mL) was stirred and heated at 100 °C for 2.5 h, allowed to cool to room temperature, and poured into a solution of 2 N NH_4OH (25 mL) in H_2O (1.8 L). The resulting precipitate was collected and triturated successively with boiling EtOH and boiling $CHCl_3$. The insoluble solid remaining was recrystallized from boiling MeOH/DMF (1:4) to give, after drying in vacuo at 110 °C for 4 days, 5-[[2-[(5,6-dichloro-1*H*-benzimidazol-2-yl)-

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amino]-6-(trifluoromethyl)-4-pyrimidinyl]amino]-3-[(diethylamino)methyl][1,1'-biphenyl]-2-ol (**19**; 2.6 g, 32%), mp 295–300 °C.

The free base of compound **20** was recrystallized from DMF to remove unreacted 5,6-dichloro-*N*-[4-chloro-6-(trifluoromethyl)-2-pyrimidinyl]-1*H*-benzimidazol-2-amine as the insoluble solid. The filtrate was poured into H_2O, and the precipitate was triturated with boiling EtOH to give a first crop of product as an insoluble solid. A second crop was obtained by chilling the filtrate.

The free base of **22** was stirred with hot MeCN (35 mL/g), and some insoluble material was removed by filtration. The filtrate was concentrated to one-half its volume and poured into H_2O. The resulting solid was recrystallized from anhydrous EtOH to give a brown solid in two crops. The combined solids were heated with $CHCl_3$ (3 mL/g), the insolubles were removed, and hexane was added to the filtrate to give **22**.

The free base of **23** was extracted with boiling $CHCl_3$ (17 mL/g), and the extract was discarded. The insoluble solid was extracted again with boiling $CHCl_3$ (100 mL/g). The extract was treated with Darco and concentrated in vacuo to one-tenth its volume. Addition of petroleum ether gave a white solid, which was recrystallized from boiling Me_2SO, collected, and washed with H_2O to give **23**.

Procedure E. A stirred mixture of crude 5,6-dichloro-*N*-(4-chloro-6-phenyl-2-pyrimidinyl)-1*H*-benzimidazol-2-amine (5.8 g, 0.011 mol), assuming 74% free base) and phenol (5 g) was heated to 100 °C, and powdered potassium iodide (25 mg) was added. The mixture was stirred at 100 °C for 5 min, and then 4-amino-2-[(diethylamino)methyl]phenol dihydrochloride (3.2 g, 0.012 mol) was added. The reaction mixture was stirred at 100 °C for 4.5 h and then allowed to cool to room temperature. Ethyl ether (300 mL) was added to the reaction mixture to give a solid, which was collected and washed with ether. The crude product (9.1 g) was recrystallized from MeOH (Darco) to give a yellow solid (4.8 g) in two crops. The solids were combined, pulverized, and dissolved in DMF (70 mL). The solution was immediately added to a solution of 2 N NH_4OH (25 mL) in H_2O (500 mL), and the resulting solid was collected. Drying in vacuo at 65 °C gave 4-[[2-[(5,6-dichloro-1*H*-benzimidazol-2-yl)amino]-6-phenyl-4-pyrimidinyl]amino]-2-[(diethylamino)methyl]phenol (**21**; 3.9 g, 65%), mp >270 °C.

Preparation of 2-[(Methylamino)methyl]-4-nitrophenol (26). To a stirred mixture of 40% aqueous methylamine (198 g, 2.7 mol) in THF (500 mL) was added a solution of 2-(chloromethyl)-4-nitrophenol (50.0 g, 0.27 mol) in THF (500 mL) dropwise over 45 min. The reaction mixture was stirred at room temperature for 0.75 h and then concentrated in vacuo to ca. 150 mL. The resulting yellow solid was collected, and the filtrate was concentrated to ca. 100 mL to give a second crop. The two crops were combined and triturated with boiling EtOH to give a yellow solid. The filtrate was cooled to give a second crop. The two crops were combined and triturated with hot DMF to give an insoluble solid. The EtOH filtrate from above was concentrated to dryness in vacuo, and the residue was triturated with hot DMF to give an insoluble solid. The DMF filtrates were combined and cooled to give additional solid. The three crops of solid from DMF were combined and dried in vacuo at 100 °C to give the title compound (28.5 g, 49%), mp 224–226 °C. Anal. ($C_8H_{10}N_2O_3$) C, H, N.

Preparation of 4-Amino-2-[(methylamino)methyl]phenol (27). 2-[(Methylamino)methyl]-4-nitrophenol (28.3 g, 0.16 mol) was dissolved in MeOH (100 mL) and 2-propanol (100 mL) and reduced with H_2/Ra Ni (3 g). The reaction mixture was filtered into 2-propanol saturated with HCl (0.4 mol). The resulting mixture was concentrated in vacuo to a small volume, and 2-propanol (400 mL) plus 2-propanol saturated with HCl (0.2 mol) was added. The mixture was stirred for 1 h, and the solid was collected (27.6 g, 78%), mp 260–262 °C. Anal. ($C_8H_{12}N_2O$·2HCl·0.2$(CH_3)_2CHOH$) C, H, N.

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Registry No. 1, 42388-61-4; **2**, 86260-49-3; **3**, 86260-50-6; **4**, 86260-51-7; **5**, 86260-52-8; **6**·2HCl, 86260-53-9; **7**·HCl, 86260-54-0; **8**·2HCl, 86260-55-1; **9**·2HCl, 86260-56-2; **10**, 86260-57-3; **11**·2HCl, 86260-58-4; **12**·2HCl, 86260-59-5; **13**·2HCl, 86260-60-8; **14**·$2F_3CCO_2H$, 86260-62-0; **15**·2HCl, 86260-63-1; **16**·2HCl, 86260-64-2; **17**·2HCl, 86260-65-3; **18**·3HCl, 86260-66-4; **19**, 86272-00-6; **20**, 86272-01-7; **21**, 86260-67-5; **22**, 86260-68-6; **23**, 86260-69-7; **24**·2HCl, 86260-70-0; **25**, 86260-71-1; **26**, 35039-53-3; **27**, 86260-72-2; VIIa, 86177-60-8; VIIb, 6112-68-1; VIIc, 86260-73-3; VIIIa, 5348-42-5; X [X = 5,6-Cl_2; $Y_1 = Y_2 = (CH_2)_4$], 86260-74-4; X (X = 5-COC_6H_5; $Y_1 = CF_3$; Y_2 = H), 86272-02-8; X (X = 5,6-Cl_2; $Y_1 = CF_3$; Y_2 = H), 86260-75-5; X (X = 5,6-Cl_2; $Y_1 = C_6H_5$; Y_2 = H), 86260-76-6; X (X = 5,6-Cl_2; $Y_1 = CH_3$; Y_2 = H), 42388-69-2; 5-amino-*N*-ethyl-2-methoxybenzenemethanamine dihydrochloride, 51388-03-5; 5-amino-3-[(diethylamino)methyl][1,1'-biphenyl]-2-ol dihydrochloride, 86260-77-7; 4-amino-2-[(diethylamino)methyl]-phenol dihydrochloride, 6297-14-9; 5-amino-*N*,*N*-diethyl-2-methoxybenzenemethanamine dihydrochloride, 86260-78-8; 4-amino-2-(1-pyrrolidinylmethyl)phenol dihydrochloride, 86260-79-9; 4-amino-2-[(4-methyl-1-piperazinyl)methyl]phenol trihydrochloride, 86260-80-2; ethyl 4-[(5-amino-2-hydroxyphenyl)-methyl]-1-piperazinecarboxylate dihydrochloride, 86177-10-8; 5-amino-*N*,*N*-diethyl-2-ethoxybenzenemethanamine dihydrochloride, 42389-43-5; *N*-cyanoguanidine, 461-58-5; ethyl 4,4,4-trifluoro-3-oxobutanoate, 372-31-6; ethyl β-oxobenzenepropanoate, 94-02-0; 2-(chloromethyl)-4-nitrophenol, 2973-19-5.