Studies in Potential Filaricides. 18. Synthesis of 2,2'-Disubstituted 5,5'-Dibenzimidazolyl Ketones and Related Compounds as Potential Anthelmintics[1]

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A series of 2,2'-disubstituted 5,5'-dibenzimidazolyl ketones (**5–8**) and related compounds (**10–13**) have been synthesized of which 2,2'-bis(carbomethoxyamino)-5,5'-dibenzimidazolyl ketone (**5**) exhibited a broad spectrum of anthelmintic activity in experimental animals. At doses of 10–50 mg/kg given intraperitoneally, **5** killed 100% of the adult worms of *Litomosoides carinii*, *Dipetalonema viteae*, and *Brugia malayi*. By the oral route the macrofilaricidal efficacy of **5** was 97–100% at 100–200 mg/kg × 5 days. The treated animals showed gradual disappearance of microfilariae and before autopsy they became amicrofilariaemic. Some of the compounds (**5**, **10**, **11**) also showed 100% efficacy against the human hookworms and tapeworm, *Ancylostoma ceylanicum* in hamsters, and *Hymenolepis nana* in rats at a single oral dose of 50–250 mg/kg. Compound **5** was also effective against *Syphacia obvelata* in mice at a single oral dose of 100 mg/kg and was found to be well tolerated by mice up to an oral dose of 2500 mg/kg.

Despite remarkable advances made in the chemotherapy of parasitic diseases, the successful treatment and eventual eradication of filariasis even today remains as one of the major public health problems of the tropics. This can be ascribed to the lack of a suitable drug capable of eliminating both microfilariae and the adult worms with least toxicity to the host. Attempts to innovate new "structural leads" in the chemotherapy of helminthiasis have led to the discovery of a series of benzimidazole anthelmintics possessing potent activity against different helminth parasites of man and domestic animals.[2,3] Consequently, potent anthelmintics like mebendazole, flubendazole, ciclobendazole, fenbendazole, and albendazole (PhCO, 4-FC_6H_4CO, cyclopropylcarbonyl, PhS, and PrS linked to methyl benzimidazole-2-carbamate residue) were discovered.[2,3] For example, mebendazole shows marked activity against intestinal and tissue dwelling helminths in man and animals.[2] However, this drug too suffers from several shortcomings,[4,5] and therefore, search for better benzimidazole anthelmintics still continues.

During our efforts to develop better anthelmintics, we have already reported the synthesis and anthelmintic activity of a series of bisbenzimidazoles[6-9] where the two benzimidazole nuclei have been linked through sulfide, sulfone, dithio, sulfonoethyl, oxide, 1-carbonylpiperazine, and 1,4-dicarbonylpiperazine bridges at the 5(6)-position. Some of them have been found to possess potent activity against nematodes and cestodes in experimental animals.

In continuation of our endeavor to develop ideal filaricides,[10] it was considered rational to undertake the synthesis of 2,2'-disubstituted 5,5'-dibenzimidazolyl ketones (**5–8**)[11] and the corresponding methanes (**10–13**) where the phenyl group of mebendazole has been substituted by the potentially more active benzimidazole residue. The compounds were tested for their anthelmintic activity against *Ltiomosoides carinii*, *Dipetalonema viteae*, *Brugia malayi*, *Ancylostoma ceylanicum*, *Syphacia obvelata*, and *Hymenolepis nana* in rodents when 2,2'-bis(carbomethoxyamino)-5,5'-dibenzimidazolyl ketone (**5**) emerged as a potent anthelmintic. The present paper describes the synthesis and anthelmintic activity of compounds **5–13**.

Chemistry

Nitration of 4,4'-dichlorobenzophenone (**1**) yielded 4,4'-dichloro-3,3'-dinitrobenzophenone (**2**).[12] Condensation of **2** with ammonia in Me_2SO at 140 °C afforded 4,4'-diamino-3,3'-dinitrobenzophenone (**3**),[13] which was hydrogenated in the presence of Raney nickel catalyst to yield 3,3',4,4'-tetraaminobenzophenone (**4**).[14] Cyclization of **4** with 1,3-dicarbalkoxy-*S*-methylisothioureas in refluxing ethanol gave 2,2'-bis(carbalkoxyamino)-5,5'-dibenzimidazolyl ketones (**5**, **6**) while 5,5'-dibenzimidazolyl ketone (**7**) and 2,2'-dimethyl-5,5'-dibenzimidazolyl ketone (**8**) were obtained by treating **4** with formic and acetic acids, respectively.

Wolff–Kishner reduction of **3** with hydrazine hydrate and KOH in a steel bomb at 170 °C directly yielded 3,3',4,4'-tetraaminodiphenylmethane (**9**),[14] which was cyclized with 1,3-dicarbalkoxy-*S*-methylisothioureas to give 2,2'-bis(carbalkoxyamino)-5,5'-dibenzimidazolylmethanes (**10**, **11**). Reaction of **9** with formic acid and acetic acid afforded 5,5'-dibenzimidazolylmethane (**12**) and 2,2'-dimethyl-5,5'-dibenzimidazolylmethane (**13**), respectively (Scheme I).

Results and Discussion

All the benzimidazoles prepared were tested for their antihookworm activity against *A. ceylanicum* in hamsters, antioxyurid activity against *S. obvelata* in mice, and antitapeworm activity against *H. nana* in rats by using standard methods.[15-17] Thus, compounds **5–8** and **10–13**

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Scheme I

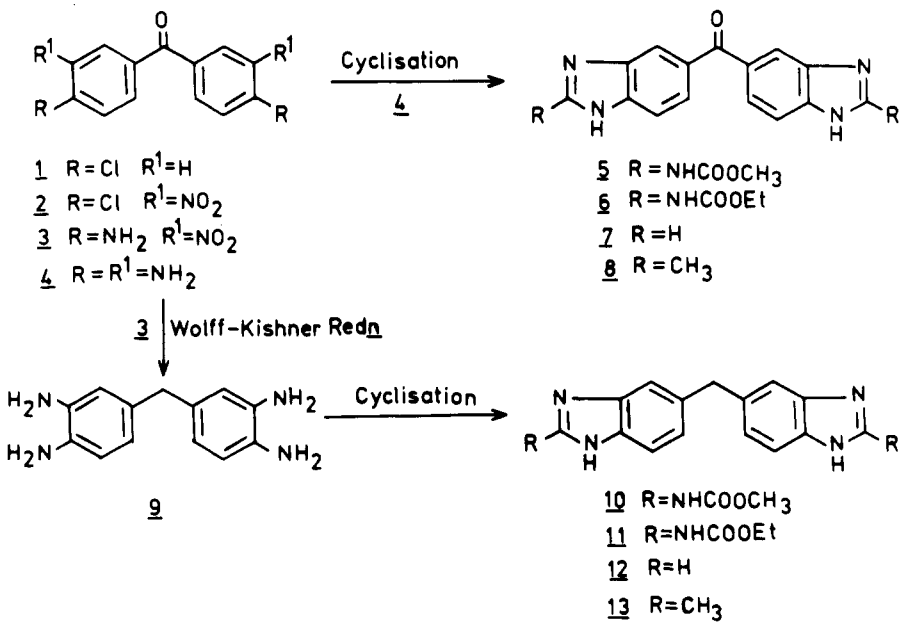

Table I. Comparative Anthelmintic Activity of 5 and Mebendazole

parasite	compound	dose, mg/kg, po	% animal cured	% worm reduction compared to control
A. ceylanicum (hookworm)	5	50 × 1	100	100
		25 × 1	50	60
		12.5 × 1	0	40.4
		6.25 × 1	0	0
	mebendazole	1 × 1	100	100
		0.5 × 1	37.5	72
	control		0	a[a]
S. obvelata (oxyurid)	5	100 × 1	100	
		50 × 1	66.6	
		25 × 1	0	
	mebendazole	100 × 1	66.6	
		50 × 1	0	
	control		0	b[a]
H. nana (cestode)	5	250 × 1	100	
		100 × 1	50	
		50 × 1	16.6	
	mebendazole	400 × 3	0	
	control		0	c[a]

[a] Worm recovery from control (mean with range) a = 40 (36–43), b = 30 (16–75), c = 20 (8–95).

were given to hamsters infected with *A. ceylanicum* at a dose of 250 mg/kg, po, for 1 day. Compounds **5**, **10**, and **11** removed all the hookworms while other compounds were inactive. At a lower dose of 50 mg/kg × 1 only **5** was 100% effective while **10** eliminated 93.5% of the worms and **11** was inactive. For assessment of cestodicidal activity, the compounds **5–8** and **10–13** were administered orally to rats experimentally infected with *H. nana* using a dose of 250 mg/kg. In this test, compounds **5**, **10**, and **11** removed 100% of the tapeworms along with their scolices, whereas at single oral dose of 50 mg/kg they failed to exert any noteworthy cestodicidal efficacy. In a comparative study, mebendazole was used as the standard drug, which eliminated all *A. ceylanicum* in hamsters at a single oral dose of 1 mg/kg while it was totally ineffective against *H. nana* in rats even at a dose of 400 mg/kg × 3 (Table I).

Compound **5** also exhibited 100% antioxyurid activity against *S. obvelata* in mice at a single oral dose of 100 mg/kg. At the lower dose of 50 kg/kg × 1, it was only 66.6% effective. Mebendazole, used as the standard drug in these tests, was also 66.6% effective at a dose of 100 mg/kg and it had no effect on these worms at a single oral dose of 50 mg/kg (Table I).

All the benzimidazoles (**5–8**, **10–13**) were tested initially against *L. carinii* in cotton rats with a dose of 50 mg/kg, ip, × 5 days. In this test all the compounds were found to be inactive except **5**, which exhibited marked filaricidal activity. Thus, the antifilarial activity of compound **5** was evaluated in detail against *L. carinii* in cotton rats and against *D. viteae* and *B. malayi* in *M. natalensis*.[18,19]

Almost identical filaricidal activity (100% macrofilaricidal) of compound **5** and mebendazole was observed against *L. carinii* at a dose of 10 mg/kg, ip, × 5 days (Table II). However, by the oral route mebendazole demonstrated poor macrofilaricidal action even at 300 mg/kg (33.8% activity). Compound **5**, on the other hand, was very effective by the oral route, killing 100% of the adult *L. carinii* worms at 100 mg/kg × 5 days. Diethylcarbamazine (DEC) removed 97% of the microfilariae of

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Table II. Comparative Filaricidal Efficacy of 5 and Mebendazole

parasite	compound	dose, mg/kg × 5	route of administration	% removal of microfilariae on day 8	21	42	63	91	% death of adult worms on autopsy
L. carinii in cotton rats	**5**	10	ip	65.6	100	100			100
	mebendazole	10	ip	58.6	96.3	100			100
	DEC	6	ip	97.1	60.9	0			0
	5	100	oral	72	80.9	100			100
	mebendazole	300	oral	48.8	57.7	74.3			33.8
	control			0	0	0			a[a]
D. viteae in *Mastomys*	**5**	25	sc	0	58.8	100			100
	mebendazole	6.25	sc	53.1	100	100			100
	DEC	175	sc	99.6	94.1	51.6			0
	5	150	oral	0	0	100			100
	mebendazole	300	oral	0	85.5	100			85.4
	control			0	0	0			b[a]
B. malayi in *Mastomys*	**5**	50	ip	0	60.1	89	89.4	93	99
	mebendazole	50	ip	0	65.3	100	100	100	100
	DEC	50	ip	95.9	88.6	90.7	71.6	91.6	57.8
	5	200	oral	0	0	30	63.9	94	97
	mebendazole	200	oral	0	0	0	0	0	0
	control			0	0	0	0	0	c[a]

[a] Worm recovery from control (mean with range): a = 14.5 (13–16), b = 11.4 (5–17), c = 14.7 (11–21).

L. carinii at a dose of 6 mg/kg, ip, × 5 days but was totally ineffective against adult worms.

By the subcutaneous route, mebendazole was found more active against *D. viteae* than the compound **5**. However, by the oral route compound **5** had superiority over mebendazole. Thus, to bring out 100% macrofilaricidal action, the dose requirements for mebendazole and **5** were 300 and 150 mg/kg, po, respectively, given for 5 days. DEC had no effect on the adult worms of *D. viteae* up to a dose of 175 mg (base)/kg, sc, × 5 days, which happens to be the drug's MTD in *Mastomys*.

Compound **5** and mebendazole showed similar nature of filaricidal action against *B. malayi* in *Mastomys* at a dose of 50 mg/kg, ip, × 5 days. By the oral route, mebendazole was totally inactive at 200 mg/kg × 5 days whereas compound **5**, at the same dose level, was almost 100% effective against the macrofilariae. DEC was also found to be less effective against *B. malayi* when compared with compound **5** (Table II).

Compound **5** was also found to be well tolerated by mice up to an oral dose of 2500 mg/kg.

Conclusion

Since the demonstration of broad-spectrum anthelmintic activity associated with alkyl 5(6)-substituted benzimidazole-2-carbamates, a large number of 2,5-disubstituted benzimidazoles were synthesized both to pursue the development of better benzimidazole anthelmintics and to delineate definite structure–activity relationships in this class of compounds.[2,3] All these studies point out that a methyl benzimidazole-2-carbamate (MBC) is undoubtedly a pharmacophore of choice in parasite chemotherapy and that the activity can be enhanced by introducing a proper substituent at the 5(6)-position, for example through a CO, S, SO, or O bridge.

The present study indicates that, in the case of 2,2′-disubstituted 5,5′-dibenzimidazolyls bridged by sulfide, sulfoxide, sulfone, dithio, and sulfonoethyl, oxide, methane, ketone, and 1-carbonyl- or 1,4-dicarbonylpiperazine units prepared in this laboratory,[6–9,11] the presence of a ketone at the 5(6)-position of the MBC provides an optimal electronic and geometrical state to the molecule for maximal activity. This observation is complementary to earlier findings in the alkyl 5(6)-substituted benzimidazole-2-carbamate series where mebendazole, flubendazole, and ciclobendazole with RCO groups (R = Ph, 4-FC_6H_4, and cyclopropyl, respectively) at the 5(6)-position of MBC provide potent anthelmintic activity.

This study also suggests that **5** may be taken as a template molecule for the synthesis of various bis-MBC's, which may be expected to yield compounds with better activity against different helminths. However, it seems that **5** exhibits the optimal structural requirements for high and broad-spectrum anthelmintic action and deserves a clinical evaluation, which is currently underway in this laboratory.

Table III. Physical Data of Compounds

no.	R	mol formula[a]	mp, °C	yield, %
5	$NHCOOCH_3$	$C_{19}H_{16}N_6O_5$	>280	65
6	$NHCOOC_2H_5$	$C_{21}H_{20}N_6O_5$	>280	64
7	H	$C_{15}H_{10}N_4O$	>280	74
8	CH_3	$C_{17}H_{14}N_4O$	108–110	52
10	$NHCOOCH_3$	$C_{19}H_{18}N_6O_4$	>300	63
11	$NHCOOC_2H_5$	$C_{21}H_{22}N_6O_4$	>280	60
12	H	$C_{15}H_{12}N_4$	120–122	70
13	CH_3	$C_{17}H_{16}N_4$	165–166	56

[a] The compounds gave satisfactory C, H, N analysis.

Experimental Section

The structure of all compounds was checked by IR spectra recorded on Perkin-Elmer 157 and 177 Infracord spectrophotometers, and NMR spectra were taken on Varian 360L (60 MHz) and Perkin-Elmer R-32 (90 MHz) spectrometers with Me_4Si as internal reference. Mass spectra were taken on a JEOL JMS D300 instrument. The purity of compounds was checked on silica gel G plates, and the spots were located by iodine vapors or by $KMnO_4$ spray. Melting points were taken in a sulfuric acid bath and are uncorrected. The physical data of the compounds are recorded in Table III.

2,2′-Bis(carbomethoxyamino)-5,5′-dibenzimidazolyl Ketone (5). A solution of **4** (5.0 g, 20 mmol) and 1,3-dicarbomethoxy-*S*-methylisothiourea (8.6 g, 41 mmol) in 20 mL of ethanol was refluxed on a water bath for 12 h. The separated solid was filtered after cooling of the reaction mixture, dried, and recrystallized from acetic acid–water. NMR (TFA): δ 3.62 (s, 6, 2 OCH_3), 7.40–7.85 (m, 6, Ar H). IR (KBr): 3300 (NH), 1705, 1630 (CO) cm^{-1}. Anal. ($C_{19}H_{16}N_6O_5$) C, H, N.

Similarly, compounds **6**, **10**, and **11** were prepared by treating **4** and **9** with the corresponding 1,3-dicarbalkoxy-*S*-methylisothioureas (Table III).

2,2′-Dimethyl-5,5′-dibenzimidazolyl Ketone (8). A solution of **4** (1.0 g, 4.1 mmol) in 20 mL of glacial acetic acid was refluxed for 3 h. The reaction mixture was cooled and neutralized with 30% aqueous ammonia solution. The solid that separated was filtered, washed with water, dried, and recrystallized from ethanol. NMR (TFA): δ 2.62 (s, 6, 2 CH_3), 7.56–8.0 (m, 6, Ar H). IR (KBr):

3100–3200 (NH), 1640 (CO) cm^{-1}. EI MS: m/e 290 (M^+). Anal. ($C_{17}H_{14}N_4O$) C, H, N.

Similarly, compounds **7**, **12**, and **13** were synthesized by reacting **4** and **9** with formic and glacial acetic acids, respectively (Table III).

Anthelmintic Test Methods. Antihookworm Screening. Hamsters of either sex (40–60 g) were infected orally with 60 (third stage) larvae of *A. ceylanicum*. After 17–20 days of inoculation, the animals were checked for infection by ovoscopic examination, and those found positive for infection were used for screening the test compounds with standard drugs as control. In each experiment, three to six animals were used per dose schedule and three were kept as controls in this screening and also in antioxyurid and antitapeworm screenings. The animals were starved overnight prior to administration of the compounds. The compounds, insoluble in water, were given orally as a suspension in Tween 80 at an initial dose of 250 mg/kg × 3 days. All the treated and control animals were starved overnight again and then sacrificed on day 3 posttreatment. The total number of worms present in the intestine of hamsters was counted on autopsy and the percent deparasitization was calculated by the formula $[(N - n)/N]$ 100, where N and n are the number of worms in control and treated animals, respectively.

Antioxyurid Screening. Swiss male albino mice (20–25 g) naturally infected with *Syphacia obvelata* were used for antioxyurid drug testing. Food was withheld for 5–6 h before the animals were fed with the test compounds. On the third day of drug treatment, animals were again starved for 5–6 h and then sacrificed to ascertain the number of worms in the caecum. Total clearance of the worms was the criterion of efficacy.

Antitapeworm Screening. Newly weaned University of Freiburg strain of male albino rats (25–30 g) or Swiss male mice (18–20 g) were infected by feeding orally 200 mature viable ova of *H. nana*. On the 17th day of infection, feces of all the animals were examined, and those showing *H. nana* eggs were used. Starved animals were treated with the compounds at an initial dose of 250 mg/kg. Treated animals were sacrificed in the same way as mentioned in the antioxyurid screening technique. The intestine of each animal was individually examined for the worms and scolices under a dissecting microscope. Because of the large variation in the number of adult worms recovered by feeding 200 viable eggs, total clearance of worms along with their scolices was taken as the criterion for denoting antitapeworm activity at a particular dose in each animal.

Antifilarial Screening. The micro- and macrofilaricidal activities of compounds were evaluated against *L. carinii* infection in cotton rats (*Sigmodon hispidus*) and *D. viteae* and *B. malayi* infections in *Mastomys natalensis*. *L. carinii* was transmitted to cotton rats through the vector *Liponyssus bacoti* by the method of Hawking and Sewell.[18] The *D. viteae* and *B. malayi* infections were transmitted to *Mastomys* through their respective vectors *Ornithodoros mobata* and *Aedes aegypti* by the methods of Worms et al.[19] and Murthy et al.,[20] respectively. At the end of prepatent period, animals showing 250 or more microfilariae per 5 μL of blood were chosen for screening. Five animals formed an experimental group. Blood samples of experimental and control animals were examined before starting the treatment. The compounds were suspended in water in the presence of Tween 80 and administered intraperitoneally, subcutaneously, or orally for 5 consecutive days. Blood smears of animals infected with *L. carinii* or *D. viteae* were examined for microfilariae at weekly intervals up to 6 weeks from the start of the treatment. On day 42, all the treated and control animals were sacrificed and the condition of adult male and female worms observed. The micro- and macrofilaricidal action of the compounds were assessed as described by Laemmler et al.[21]

For monitoring of the microfilaricidal activity, blood samples of the rodents infected with *L. carinii* or *D. viteae* were examined at weekly intervals up to day 91. In the case of *B. malayi* infection, blood was examined at fortnightly intervals up to day 91. To demonstrate the correct trend in the course of microfilariaemia in the treated animals, the microfilarial counts on days 8, 21, 42, 63, and 91 are incorporated in Table II.

Data on control animals, which were generally vehicle treated, are also given in Table II. The general dose schedule for both mebendazole and compound **5** were 200, 100, 50, 25, 12.5, 6.25, and 3.12 mg/kg of body weight. Only those doses of **5** and mebendazole showing maximum efficacy are included in Table II.

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Synthesis and Evaluation of 2-Substituted 1-Methyl-1-(4-tolylsulfonyl)hydrazines as Antineoplastic Agents

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Several N-2 substituted 1-methyl-1-(4-tolylsulfonyl)hydrazines were synthesized and evaluated for antineoplastic activity against the L1210 leukemia and the B16 melanoma. The most active compound to emerge from this study, 2-(methylsulfonyl)-1-methyl-1-(4-tolylsulfonyl)hydrazine, produced maximum percent T/C values with L1210 leukemia and B16 melanoma tumor bearing mice of 207 and 209, respectively. While the attachment of an aryl-, aralkyl-, or alkylsulfonyl moiety to N-2 resulted in retention of activity against both tumor systems, the corresponding benzoyl, 4-nitrobenzoyl, and (2-nitrophenyl)sulfenyl analogues only displayed activity against the L1210 leukemia.

A recent report from our laboratory has described the effectiveness of several 1,2-bis(arylsulfonyl)-1-methylhydrazines (**1**) against the L1210 leukemia in mice.[1] Base-catalyzed elimination in vivo to generate the putative alkylating species **2** was postulated to account for the observed biological activity of agents of this class. Since the acidity of the proton β to the leaving group would be expected to influence the rate of breakdown of these compounds to the active species **2**, we have synthesized a series of N-2 substituted 1-methyl-1-(4-tolylsulfonyl)hydrazines and have evaluated them for antitumor activity against both the L1210 leukemia and the B16 melanoma.

$ArSO_2N(CH_3)NHSO_2Ar$ (**1**) $\quad ArSO_2N{=}{=}NCH_3$ (**2**)

Chemistry. Compounds **4**–**12** (Table I) were prepared by reacting the appropriate acid chloride with 1-methyl-

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