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Potential transition state phosphoramidate inhibitors of β-tubulin as antifilarial agents

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Abstract

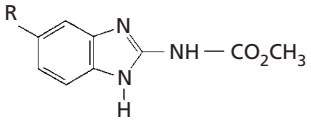
Transition state phosphoramidate inhibitors of β-tubulin were designed as potential antifilarial agents.

The reaction of 2-aminobenzimidazole with diisopropyl phosphite and carbon tetrachloride at a low temperature gave the unexpected 1-diisopropoxyphosphoryl-2-aminobenzimidazole, which on heating gave the novel benzimidazole derivative, 2-(diisopropoxyphosphoryl)-aminobenzimidazole. Both products were fully characterized and the synthetic procedure to both compounds was optimized. The procedure was used to prepare the related 5-benzoyl-2-(diisopropoxyphosphoryl)aminobenzimidazole and 5-benzoyl-2-(diethoxyphosphoryl)amino-benzimidazole (**1d**). In a preliminary trial against *Brugia pahangi* compound **1d** was found to have no antifilarial activity. This lack of activity may be attributed to its extreme insolubility and thus low bioavailability. The synthesis of analogous, more soluble, phosphorothioate-substituted benzimidazoles using the same methods may yield compounds with greater antifilarial activity.

Introduction

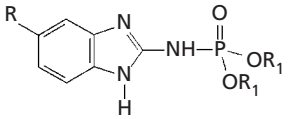
The antifilarial activity of the benzimidazoles, such as mebendazole and albendazole (Figure 1), is thought to be due to the formation of a covalent transition state complex between the benzimidazole and the β-tubulin of the filarial worms, formed by attack of the thiol group of the amino acid cysteine in the colchicine binding site of β-tubulin upon the carbamate moiety of these benzimidazoles (Lacey 1988). Formation of the complex can be considered as irreversible because the benzimidazole dissociates only extremely slowly from the transition state complex. Transition state analogues mimic the transition state geometry of the carbamate–tubulin complex and may therefore be expected to bind more strongly to β-tubulin, conferring inhibitory activity on such compounds.

As part of our antifilarial programme, the phosphoroamidate transition state analogue (**1a**) of the benzimidazole–tubulin complex was designed and this was expected to be readily obtainable from 2-aminobenzimidazole. The reactions of 2-aminobenzimidazole (**2**) have been extensively reviewed (Rastogi & Sharma 1983), including the synthesis of phosphoramidates analogous to the target compound. In particular, the method of Ji et al (1988) was used to prepare phosphoramidates from amino acids.



Albendazole: R = $S(CH_2)_2CH_3$

Mebendazole: R = COPh



1a: R = H, $R_1 = CH_3$
1b: R = H, $R_1 = CH(CH_3)_2$
1c: R = COPh, $R_1 = CH(CH_3)_2$
1d: R = COPh, $R_1 = CH_2CH_3$

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Figure 1 Structure of antifilarial benzimidazoles albendazole and mebendazole and synthetic analogues.

Materials and Methods

2-Aminobenzimidazole was supplied by Avocado Chemicals Ltd. Proton NMR spectra were obtained using a Jeol GSX NMR spectrometer at 270 MHz for proton and 67.8 MHz for carbon, or using a Bruker Avance 300 NMR spectrometer at 300 MHz for proton and 75.5 MHz for carbon. Phosphorus spectra were recorded on the Jeol GSX at 109.25 MHz, or on the Bruker Avance 300 at 121.5 MHz. Tetramethylsilane was used as internal standard for ^1H and ^{13}C spectra, and phosphoric acid was used as the internal standard for ^{31}P spectra. Coupling constants are reported in Hz. Mass (electron ionization) spectra were determined using either a Kratos MS80 or a Bruker Apex II FTMS for accurate mass determinations, or a VG Trio 2000 for fragmentation patterns.

1-Diisopropoxyphosphoryl-2-amino-benzimidazole (3b)

A solution of 2-aminobenzimidazole (1.33 g, 10 mmol) in triethylamine (5 mL), water (3 mL) and ethanol (2 mL) was cooled to 0°C and a mixture of diisopropyl phosphite (1.7 mL, 10 mmol) and carbon tetrachloride (3 mL) was added dropwise with stirring. After the addition was complete (approx. 30 min) the reaction became too viscous to stir and was extracted with dichloromethane (2 × 30 mL). The extracts were washed with water, adjusted to pH 7.0 with ammonia (2 × 20 mL), dried over magnesium sulfate and the solvent removed to give a white solid. The product was dissolved in dichloromethane (5 mL) and filtered through a short column of neutral alumina using dichloromethane–methanol (98:2) as eluent, yielding **3b**: 2.85 g (96%), mp 162–163 °C; TLC: alumina plates (carbon tetrachloride–methanol, 95:5) R_f 0.51, (ethyl acetate–methanol, 95:5) R_f 0.63, (toluene–*n*-butanol, 96:4) R_f 0.34, (dichloromethane–methanol, 95:5) R_f 0.89. Found: C, 52.67; H 6.75; N, 14.08. $C_{13}H_{20}N_3O_3P$ requires C, 52.5; H, 6.8; N, 14.1%. λ_{max} (ϵ_{max}) (CH_3OH, freshly prepared) 208 (66,900), 247 (20,600), 281 (8,300) nm; ν_{max} (KBr) 3378 (NH), 1660 (C=N) cm^{-1}; δ_H ($CDCl_3$) 1.2 (d, 6H, 2 × diastereotopic CH_3, J 6.3), 1.4 (d, 6H, 2 × diastereotopic CH_3, J 6.3), 4.7 (doublet of septets, 2H, 2 × OCH, J_{CCH} 6.3, $^3J_{POCH}$ 7.3), 6.6 (br s, 2H, exchangeable, NH_2), 7.0 (dd, 1H, H6, J 8.0 and 1.3), 7.1 (dd, 1H, H5, J 8.0 and 1.3), 7.3 (br d, 1H, H7, J 8.0), 7.35 (br d, 1H, H4, J 8.0); δ_C 23.6 (d, 2 × diastereotopic CH_3, $^3J_{POCC}$ 4.4), 24.1 (d, 2 × diastereotopic CH_3, $^3J_{POCC}$ 4.4), 74.5 (d, 2 × OCH, J_{POC} 5.5), 112.2 (s, C6), 116.3 (s, C5), 120.5 (s, C7), 123.8 (s, C4), 132.8 (d, C3a, $^3J_{PNCC}$ 4.3), 144.0 (d, C7a, J_{PNC} 13.3), 155.8 (d, C2, J_{PNC} 6.6); δ_P -6.5; m/z EIMS (%), M^+ 297.1253. $C_{13}H_{20}N_3O_3P$ requires 297.1266; M^+ (18), 213 (100), 195 (10), 133 (30), 132 (12), 105 (8).

2-(Diisopropoxyphosphoryl)amino-benzimidazole (1b)

Dry 1-diisopropoxyphosphoryl-2-aminobenzimidazole (**3b**) (1.0 g, 3.37 mmol) was heated at 175°C for 15–20 min. The white solid became light brown and sticky. On cooling to room temperature, it was crystallized from methanol to give fine white crystals, 600 mg (60%), mp 257–259°C; TLC: (chloroform–ethyl acetate–methanol, 5:2:1) R_f 0.76, (chloroform–methanol, 94:6) R_f 0.74. Found: C, 52.75; H, 6.75; N, 14.09. $C_{13}H_{20}N_3O_3P$ requires C, 52.5; H, 6.8; N, 14.1%. λ_{max} (ϵ_{max}) (CH_3OH) 208 (55,300), 285 (20,100) nm; ν_{max} (KBr) 3170 (NH), 1656 (C=N) cm^{-1}; δ_H (d_6-DMSO) 1.21 (d, 6H, 2 × diastereotopic CH_3, J 6.3), 1.22 (d, 6H, 2 × diastereotopic CH_3, J 6.3), 4.4 (doublet of septets, 2H, 2 × OCH, J_{CCH} 6.3, $^3J_{POCH}$ 7.3), 7.0 (dd, 2H, H5/6, J 5.8 and 3.1), 7.2 (dd, 2H, H4/7, J 5.8 and 3.1),11.1 (br s, 2H, exchangeable, NH_2); δ_C 23.5 (d, 2 × diastereotopic CH_3, $^3J_{POCC}$ 4.4), 25.6 (d, 2 × diastereotopic CH_3, $^3J_{POCC}$ 4.4), 68.8 (d, 2 × OCH, J_{POC} 5.5), 109.8 (s, C4/7), 121.1 (s, C5/6), 130.1 (d, C3a/7a), 151.5 (d, C2, J_{PNC} 7.70); δ_P 7.3; m/z EIMS (%), M^+ 297.1253. $C_{13}H_{20}N_3O_3P$ requires 297.126l; M^+ (20), 213 (80), 196 (18), 133 (100), 132 (20), 105 (18).

2-Amino-5-benzoyl-1-diisopropoxyphosphorylbenzimidazole (3c)

To a solution of 2-amino-5-benzoylbenzimidazole (2.37 g, 0.01 mol) in ethanol (2 mL), triethylamine (3 mL) and water (3 mL) at room temperature, a mixture of diisopropyl phosphite (1.49 mL, 0.01 mol) and car-

bon tetrachloride (4 mL) was added dropwise. The mixture was stirred for 18 h. The mixture was adjusted to pH 2 with dilute HCl and extracted with dichloromethane. The solution was dried ($MgSO_4$) and the solvent removed in-vacuo to give the crude product, which was subjected to column chromatography on neutral alumina (ethyl acetate–methanol, 95:5). Pale yellow crystals of **3c** were recovered: mp 112–113°C; TLC: alumina (ethyl acetate–methanol, 95:5) R_f 0.75. ν_{max} (KBr) 3395 (NH), 1641 (C=N), 1729 (C=O) cm^{-1}; δ_H ($CDCl_3$) 1.2 (d, 6H, 2 × diastereotopic CH_3, J 5.9), 1.4 (d, 6H, 2 × diastereotopic CH_3, J 5.9), 4.8 (m, 2H, 2 × OCH), 6.41 (br s, 2H, exchangeable, NH_2), 7.4 (1H, m, H6), 7.5 (2H, m, H3′/5′), 7.6 (1H, d, H4, J 2.2), 7.7 (1H, d, H7, J 8.0), 7.8 (3H, m, H2′/4′/6′); δ_C 23.3 (d, 2 × diastereotopic CH_3, $^3J_{POCC}$ 5.5), 23.7 (d, 2 × diastereotopic CH_3, $^3J_{POCC}$ 5.5), 74.8 (d, 2 × OCH, J_{POC} 5.5),114.0, 115.1, 127.6, 128.1, 128.1, 129.8, 131.7, 132.0 (C1′), 138.2 (C3a), 138.7 (C5), 148.2 (d, C7a, J_{PNC} 13.2), 157.7 (d, C2, J_{PNC} 5.6), 196.0 (s, C=O); δ_P −7.0; m/z EIMS (%) 401 (M^+, 20), 237 (85), 160 (100), 132 (18), 105 (27), 77 (14).

5-Benzoyl-2-(diisopropoxyphosphoryl)amino-benzimidazole (1c)

Dry 2-amino-5-benzoyl-1-diisopropoxyphosphorylbenzimidazole (**3c**) (1.0 g, 2.49 mmol) was heated at 165°C for 15 min. The solid turned to yellow and became sticky. After cooling to room temperature, the residue was recrystallized (methanol) to give (**1c**) as yellow needles: 700 mg (70%), mp 229–230°C; TLC: (chloroform–ethyl acetate–methanol, 5:2:1) R_f 0.84; ν_{max} (KBr) 3150 (NH), 1690 (C=N), 1620 (C=O) cm^{-1}; δ_H (d_6-DMSO) 1.2 (d, 6H, 2 × diastereotopic CH_3, J 4.0), 1.3 (d, 6H, 2 × diastereotopic CH_3, J 4.0), 4.5 (m, 2H, 2 × OCH), 7.3 (d, 1H, H7, J 7.9), 7.5 (dd, 1H, H6, J 7.9 and 1.3), 7.6 (d, 2H, H3′/H5′, J 7.9), 7.6 (d, 1H, H4, J 1.3), 7.7 (3H, m, H2′/H4′/H6′, J 7.9); δ_C 22.5 (CH_3), 69.7 (CH_2), 109.5 (C7), 111.5 (C4), 123.0 (C6), 127.5 (C3′/5′), 128.5 (C2′/6′), 130.0 (C5), 130.5 (C3a), 132.0 (C4′), 134.0 (C7a), 138.0 (C1′), 153.5 (C2), 194.5 (C=O); m/z EIMS (%) 402 (MH^+, 100), 360 (10), 280 (28), 238 (7), 105 (5).

5-Benzoyl-2-(diethoxyphosphoryl)amino-benzimidazole (1d)

The title compound was synthesized in the same manner as **1b** and **1c**, and recrystallized (ethanol) to give pale yellow needles: 176 mg (64%), mp 239°C; δ_H (d_6-DMSO) 1.2 (t, 3H, CH_3, J 7.1), 1.25 (t, 3H, CH_3, J 7.1), 4.0 (q, 2H, CH_2, J 7.1), 3.9 (q, 2H, CH_2, J 7.1), 3.3 (d, 1H, H7, J 8.3), 7.5 (dd, 1H, H6, J 8.3 and 1.6), 7.6 (dd, 2H, H3′/5′, J 6.8 and 7.6), 7.6 (d, 1H, H4, J 1.6), 7.6 (dd, 1H, H4′, J 7.4 and 2.2), 7.7 (dd, 2H, J 8.4 and 2.1), 11.4 (br s, 2H, 2 × NH); δ_C 17.0 (d, 2 × diastereotopic CH_3, J_{POCC} 6.8), 62.1 (d, 2 × CH_2, J_{POC} 5.6), 110.5 (C7), 112.7 (C4), 125.5 (C6), 129.2 (C3′/5′), 130.1 (C2′/6′), 131.2 (C5), 131.3 br (C3a), 132.7 (C4′), 135.3 br (C7a), 139.0 (C1′), 153.600 (d, C2, J_{PNC} 6.5),195.8 (C=O); δ_P 7.8; m/z (FTMS) M^+ 374.127. $C_{18}H_{20}N_3O_4P$ requires 374.127; M^+ (Na salt) 396.108. $C_{18}H_{20}N_3O_4PNa$ requires 396.108.

Antifilarial assay

The preliminary evaluation of compound **1d** was conducted using the jird–*Brugia pahangi* model using techniques similar to those described by Denham (1979). Five male and five female worms were transplanted into the peritoneal cavity of 8–10-week-old jirds. The drug was formulated in distilled water containing 0.5% hydroxycellulose and 0.1% Tween 80 (Sigma, UK), and was ball-milled for 4 h at 23°C before use. Remaining doses of the drug were stored at 5°C. One jird was treated with five daily doses of compound **1d** at 100 mg kg^{-1} on Days 3–7 after infection. Five control jirds received five daily doses of drug-free diluent, and two jirds received five daily doses of flubendazole (Janssen, Belgium) at 12.5 mg kg^{-1} as a positive control. All jirds were killed on Day 50 after infection.

Results and Discussion

Although our target compound was the dimethylphosphoramidate (to correspond to the dimethylcarbamate moiety of mebendazole and albendazole), it has been reported that the synthesis of the dimethylphosphoramidate is not easily achieved (Ji et al 1988), presumably due to hydrolysis of dimethylphosphite, or the intermediate dimethoxyphosphoryl chloride, or the final product. However, diisopropylphosphite gave good yields of the expected compounds, which were stable under the reaction conditions.

As expected, the reaction of 2-aminobenzimidazole with dimethyl phosphite did not give any phosphoramidate products and 2-aminobenzimidazole was recovered unchanged from these reactions. However, reaction of 2-aminobenzimidazole with diisopropyl phosphite in aqueous ethanol, carbon tetrachloride and triethylamine gave an unstable compound **3b** that did not correspond to the expected 2-aminophosphorami-

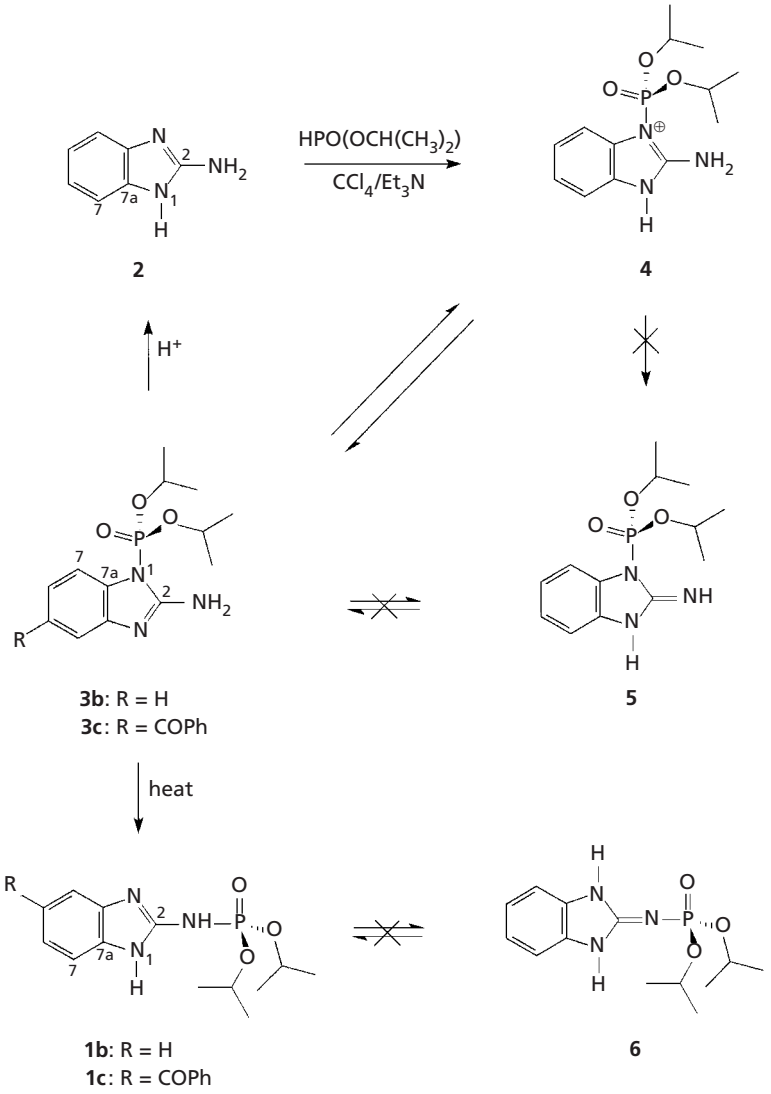

Figure 2 Synthesis of compounds **1b**–**c**.

date benzimidazole product (**1b**). Upon melting, this white solid product underwent a dramatic transformation of the microcrystalline material at approximately 160°C, without melting, into large needle-like crystals which eventually melted at 230°C. Variation of the reaction conditions to reduce contact of the unstable product (**3b**) with acid resulted in a synthetic procedure which gave high yields of pure **3b** which was stable to column chromatography and TLC on neutral alumina plates but not on silica. The thermal transformation was optimized to direct heating at 175°C in an oil bath for 15–20 min. After cooling to ambient temperature, the light brown residue was recrystallized to give white needle-like crystals that were stable to silica.

The IR and UV spectra of these compounds were clearly different but both compounds gave the same elemental analysis and showed the same EI mass spectrum, which corresponded to the desired diisopropylphosphoramidate (**1b**). Extensive high resolution studies were carried out on both compounds. It can be reasoned that the first step in the phosphorylation would involve the kinetically-controlled nucleophilic attack of the more basic ring nitrogen atom on phosphorus. On heating, rearrangement to the thermodynamically preferred exocyclic phosphoramidate would give the desired product **1b** (Figure 2). The initial product of phosphorylation (**4**) would readily lose a proton under the reaction conditions to give **3b** or **5**. Despite the

assignment of the 2-imino structure (**5**) to a number of different acylated compounds derived from 2-aminobenzimidazole (Rastogi & Sharma 1983), we have assigned the fully aromatic structure **3b** to the initial, low-melting solid; all the evidence available to date clearly supports the 2-amino tautomer as being overwhelmingly preferred in this class of compounds (North & Day 1969; Grimmett 1984a). By the same reasoning, structure **1b**, not **6**, can be assigned to the product of the thermal rearrangement, which is the target compound.

The NMR spectrum of the initial product **3b** showed two doublets corresponding to the diastereotopic methyl signals of the prochiral isopropyl groups with the methine proton of the isopropyl groups appearing as a doublet of septets, which showed a similar vicinal proton coupling to the methyl groups together with some further, larger splitting arising from the $^{3}J_{POCH}$ coupling. There was no evidence of any ^{4}J coupling of phosphorus with the protons of the methyl group. The aromatic protons all had different chemical shifts with H4 and H7 appearing as broad doublets, whereas the H5 and H6 signals were double doublets showing different *ortho* coupling (J = 7.4 and 8.0 Hz), with smaller *meta* coupling, to produce the observed splitting pattern. NOE difference spectra, obtained after irradiation of each of the methyl doublets, showed an enhancement of the signal associated with the H7 doublet indicating that both the isopropyl methyl groups are close to the H7 proton. The two amino protons appeared as a broad singlet which readily underwent exchange with deuterium oxide. The ^{13}C spectrum also showed different signals for the diastereotopic methyl carbon atoms which appeared as doublets (J = 4.4 Hz) due to $^{3}J_{POCC}$ coupling, whereas the methine carbon atom doublet showed larger $^{2}J_{POC}$ coupling (J = 5.5 Hz). The quaternary carbon atoms, C2 and C7a were strongly coupled to phosphorus ($^{2}J_{PNC}$ = 13.2 Hz), but as expected, the coupling to C3a was lesser ($^{3}J_{PNCC}$ = 4.3 Hz). The different chemical shifts for the protons and carbon atoms in this compound are consistent with structure **3b**, which has the phosphoryl substituent at position 1 of the benzimidazole ring.

The NMR spectrum of the high-melting compound **1b**, in d_6-DMSO, also showed signals for the diastereotopic methyl groups but with much smaller chemical shift differences, and the methine proton also appeared as a doublet of septets with coupling from the phosphorus atom. An NOE difference spectrum showed that irradiation of the methyl signals caused no changes in the aromatic proton intensity. The two NH protons gave a single broad peak at 11.09 ppm, which exchanged readily with deuterium oxide; the coincidence of NH signals derived from readily exchangeable protons is well known. The equivalence of the H4/7, H5/6, C3a/7a, C4/7 and C5/6 atoms very strongly supports the 2-substituted benzimidazole structure (**1b**) (Preston 1981; Pouchert 1983). The marked difference in the ^{31}P chemical shifts is consistent with the different environments of this atom in structures **3b** and **1b**.

Throughout these studies, compound **3b** was much less stable to acid, heat and electron ionization than the target phosphoramidate **1b**. This is consistent with the well known and facile transfer of acylating groups from imidazole-type nitrogen atoms (Grimmett 1984b). This simple stepwise phosphorylation reaction does not appear to have been previously noted. Rather, the reactions of 2-aminobenzimidazole with various organic acylating or sulfonating reagents results in either endocyclic or, more commonly, exocyclic products being formed independently of each another and, where migrations of the acylating group (from the endo to the exo position) occur, such reactions are usually base-catalysed. (Rastogi & Sharma 1983).

The 5-benzoyl group of mebendazole is thought to enhance binding of this benzimidazole by occupying more of the colchicine binding site (Lacey 1988). Analogous to this structure, and to improve the binding of our phosphoramidate benzimidazoles, 1-diisopropylphosphoryl-2-amino-5-benzoylbenzimidazole (**3c**) and 2-(diisopropylphosphoryl)amino-5-benzoylbenzimidazole (**1c**) were synthesized using the same procedure. Similar to the results reported above, the reaction yielded the less stable **3c** first, which was rearranged to the desired **1c** at 165°C. The spectra were essentially identical to those described for **1b** and **3b**, except for those signals relating to the benzoyl group, as expected. One further phosphoramidate benzimidazole derivative was synthesized, as the benzimidazoles mebendazole and albendazole have the sterically small methylcarbamate group on the 2-amino moiety. To ensure that the potential activity of these compounds was not being restricted by the sterically larger isopropyl group of compounds **1c** and **3c**, the corresponding diethyl analogue, 5-benzoyl-2-(diethoxyphosphoryl)aminobenzimidazole (**1d**), was synthesized by the same procedure.

Compound **1d** was evaluated for antifilarial activity in a preliminary screening using the jird–*Brugia pahangi* model and was found to be inactive, whereas the positive control drug, flubendazole, produced a 100 % reduction in parasite recovery. The disappointing lack of activity of compound **1d** was attributed to its extreme insolubility leading to low bioavailability. However, the synthesis of analogous, more soluble, phosphorothioate-

substituted benzimidazoles was achieved using the methods reported here and yielded compounds which may be useful as potential antifilarial agents.

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