Synthesis of Imidazo[1,2-*b*]pyridazines: Fenbendazole, Oxifenbendazole Analogs and Related Derivatives

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Dedicated to the Memory of Roland K. Robins

A series of imidazo[1,2-*b*]pyridazines has been prepared and evaluated for macrofilaricidal activity against *Brugia pahangi* or *Acanthocheilonema viteae* infections in jirds. The imidazo[1,2-*b*]pyridazine analogs of fenbendazole and oxifenbendazole are reported. In addition, several 6-aminoimidazo[1,2-*b*]pyridazine derivatives have been prepared. None of these compounds possessed significant activity against human cytomegalovirus (HCMV) or filarial infections.

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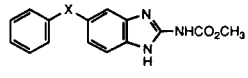
Introduction.

We have previously reported modifications of a variety of heterocyclic systems to develop an orally active macrofilaricidal agent [1-3]. In the preceding paper [4] we described the synthesis of imidazo[1,2-*b*]pyridazines which are similar to the anthelmintic methyl benzimidazole carbamates, mebendazole and flubendazole. Another class of methyl benzimidazole carbamates which has shown good anthelmintic activity is fenbendazole (**1a**) and oxifenbendazole (**1b**) which possess a 5-thiophenyl and 5-phenylsulfoxide moiety, respectively. In this paper we report a series of imidazo[1,2-*b*]pyridazine analogs of fenbendazole and oxifenbendazole.



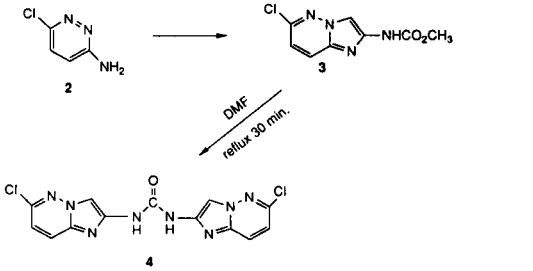
1a X = S
1b X = SO

We envisioned, a priori, that methyl 6-chloroimidazo-[1,2-*b*]pyridazine-2-carbamate (**3**) would be a key intermediate capable of further modification for the preparation of a wide range of compounds. To prepare compound **3**, we applied a methodology which has been previously reported for the synthesis of other imidazo[1,2-*b*]pyridazines [5]. Initially we sought to prepare 2-amino-6-chloroimidazo-[1,2-*b*]pyridazine *via* the condensation of 3-amino-6-chloropyridazine (**2**) with chloroacetamide. However, under a number of conditions no condensation reaction occurred and the starting material was recovered unchanged. At elevated temperatures an intractable reaction mixture was obtained. To circumvent this problem, 3-amino-6-chloropyridazine (**2**) was treated with an equimolar amount of methyl (chloroacetyl)carbamate, prepared according to a known procedure [6]. Condensing **2** with methyl (chloroacetyl)carbamate smoothly afforded the desired bicyclic product, methyl 6-chloroimidazo[1,2-*b*]pyridazine-2-carbamate (**3**) in 50% yield. Compound **3** showed a remarkable lack of solubility in a variety of solvents, which prompted us to attempt its crystallization from boiling dimethylformamide. However, heating compound **3** in dimethylformamide afforded a compound with a different melting point, thin-layer chromatograph motility and ^{1}H-nmr spectrum. The ^{1}H-nmr spectrum of the new product showed an absence of the methyl signal at δ 3.71 and the presence of two exchangeable protons at δ 9.71 ppm. Also apparent in this spectrum was a peak pattern associated with 2,6-disubstituted imidazo[1,2-*b*]pyridazines [7-9]. The ir spectrum of the new compound showed the absence of an OH stretching vibration at 3600 cm^{-1} and the presence of a NH stretching vibration at 3339 and 3170 cm^{-1}, and a carbonyl stretching at 1714 cm^{-1}. These data suggest that the product was *N,N'*-bis-(6-chloroimidazo[1,2-*b*]pyridazin-2-yl)urea (**4**). Presumably, compound **4** was formed through the hydrolysis of the methyl ester followed by decarboxylation and formation of the nucleophilic species 2-amino-6-chloroimidazo[1,2-*b*]pyridazine which in turn reacted with the remaining **3**. The dimeric structure of **4** was confirmed by electron impact mass spectrometry, which showed a molecular ion (M^+) of 363 which compares favorably with the calculated molecular weight of **4** (363.16 g/m). Reaction of **3** with sodium phenylthiolate afforded an intractable mixture rather than the desired methyl 6-(phenylthio)-imidazo[1,2-*b*]pyridazine-2-carbamate (**8**), the direct analog of fenbendazole (**1a**). However, **8** was prepared in 56% yield by the treatment of 3-amino-6-(phenylthio)pyridazine (**5**) [10] with methyl (chloroacetyl)carbamate in dimethylformamide.

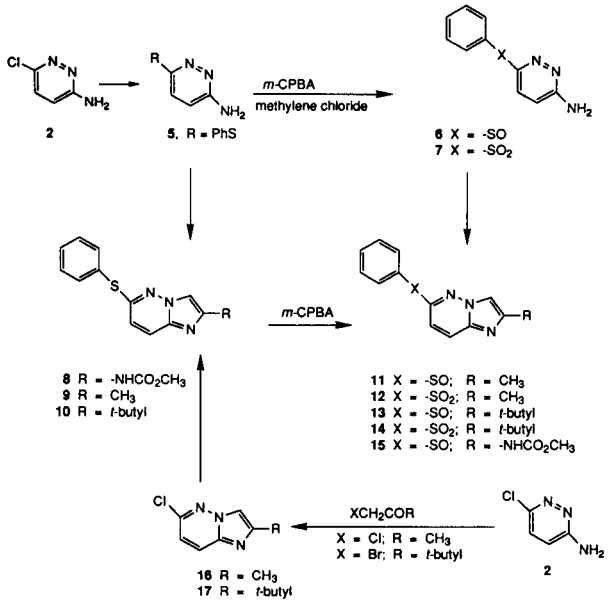
We also sought to introduce a *t*-butyl group or a methyl group at the 2-position of the imidazo[1,2-*b*]pyridazine. The synthesis of these derivatives was approached by a variety of methods. 3-Amino-6-phenylsulfinylpyridazine (**6**) and 3-amino-6-phenylsulfonylpyridazine (**7**) were prepared by the treatment of 3-amino-6-phenylthiopyridazine (**5**) with *m*-chloroperoxybenzoic acid (*m*-CPBA) in dichloromethane. The extent of the oxidation could be controlled by varying the amount of the oxidant. Thus, reacting **5**

with a molar equivalent of *m*-CPBA afforded compound **6** in 82% yield. By using two molar equivalents of *m*-CPBA compound **7** was isolated in 44% yield (Scheme II). The structure of both compounds was established by ^{1}H-nmr spectroscopy and supported by ir spectra and elemental analysis. It is worth mentioning that the introduction of the second oxygen atom was more difficult than the introduction of the initial oxygen atom to form the sulfinyl derivative **6**. A mixture of compounds **6** and **7** was always produced in the oxidation reaction, even when forcing conditions were employed, and, compound **7** was always formed as the minor component in each reaction.

Scheme I



Scheme II



Having compounds **6** and **7** in hand, the preparation of 2-methyl-6-(phenylsulfinyl)imidazo[1,2-*b*]pyridazine (**11**), 2-methyl-6-(phenylsulfonyl)imidazo[1,2-*b*]pyridazine (**12**), 2-*t*-butyl-6-(phenylsulfinyl)imidazo[1,2-*b*]pyridazine (**13**), 2-*t*-butyl-6-(phenylsulfonyl)imidazo[1,2-*b*]pyridazine (**14**), and methyl 6-(phenylsulfinyl)imidazo[1,2-*b*]-pyridazine-2-carbamate (**15**), was achieved by condensation of **6** and **7** with the requisite 1-halocarbonyl reagent. Alternatively, compounds **11-15** could also be prepared *via* the oxidation of the phenylthio derivatives **8, 9** and **10**. The compounds 2-methyl-6-(phenylthio)imidazo[1,2-*b*]pyridazine (**9**) and 2-*t*-butyl-6-(phenylthio)imidazo[1,2-*b*]pyridazine (**10**) were prepared by either condensing **5** with 1-chloroacetone or 1-bromopinacolone which afforded **9** and **10** in 66 and 71% yields, respectively, or by using a two step procedure. The second procedure involved treatment of 3-amino-6-chloropyridazine (**2**) with one equivalent of 1-chloroacetone or 1-bromopinacolone to afford the intermediates 6-chloro-2-methylimidazo[1,2-*b*]pyridazine (**16**) and 2-*t*-butyl-6-chloroimidazo[1,2-*b*]pyridazine (**17**) in 52 and 76% yields, respectively. Subsequent nucleophilic substitution of the 6-chloro group in **16** with phenylthiolate proceeded smoothly to produce **9** in 81% yield. The oxidation of **8, 9** and **10** was found to be a superior approach to the target compounds **11-15** in terms of the yields obtained.

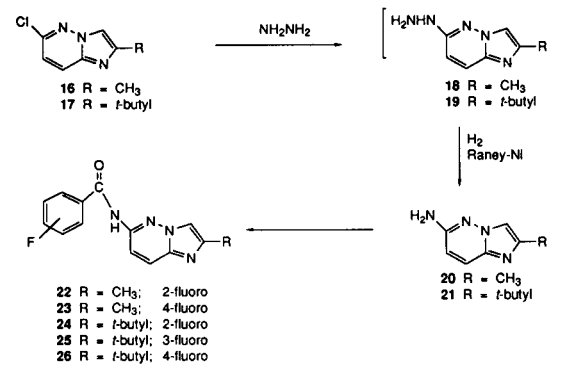
To prepare the target compounds **22-26** with a -NH bridge at the 6-position it was necessary to first prepare the intermediate 2-substituted-6-aminoimidazo[1,2-*b*]pyridazines. To prepare these compounds, we chose a direct nucleophilic substitution with ammonia of the chloro atom at the 6-position of the imidazo[1,2-*b*]pyridazine ring system. Several attempts were conducted under a variety of conditions including liquid ammonia at 100° in the presence of powdered copper as a catalyst but in each case the starting material was recovered unchanged. However, heating 6-chloro-2-methylimidazo[1,2-*b*]pyridazine (**16**) or 2-*t*-butyl-6-chloroimidazo[1,2-*b*]pyridazine (**17**) in anhydrous hydrazine at reflux for 2 hours afforded the unstable 6-hydrazino compounds **18** and **19**, respectively. Subsequent reduction of **18** and **19** using Raney nickel catalytic hydrogenation at atmospheric pressure produced 6-amino-2-methylimidazo[1,2-*b*]pyridazine (**20**) and 6-amino-2-*t*-butylimidazo[1,2-*b*]pyridazine (**21**), respectively, in near quantitative yields. The structure of **20** and **21** was substantiated from their ^{1}H-nmr data which showed a signal at δ 6.16 (singlet, 2H, deuterium oxide exchangeable) in both compounds which was assigned to the NH_2 and the signals corresponding to the 2-methyl (δ 2.25, 3H, singlet) in **20** and the 2-*t*-butyl groups (δ 1.26, 9H, singlet) in **21**. The signals of the ring protons for both **20** and **21** were consistent with the desired substitution pattern. The ir spectrum of **20**, showed the NH stretching vibration of an amino group at 3496 and 3378 cm^{-1}, the aromatic CH stretching at 3162 cm^{-1} and the aliphatic CH stretching at 2985 cm^{-1}.

With these intermediates in hand, we initiated the synthesis of the benzamides **22-26**, designed as flubendazole congeners with a NH spacer between the heterocyclic ring system and the fluoro substituted benzoyl group. The position of the fluorine atom was varied about the phenyl ring to determine if the position of the fluoro group might have an effect on the biological activity. Thus, treatment of the 6-amino-2-substituted imidazo[1,2-*b*]pyridazines **20** and **21**

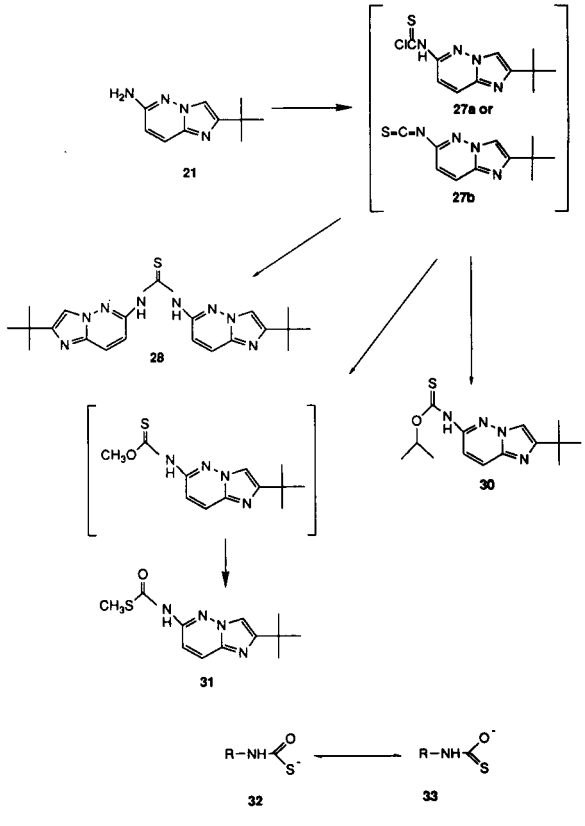
with a molar equivalent of *o*-, *m*-, or *p*-fluorobenzoyl chloride at room temperature produced the corresponding 2-substituted 6-(fluorobenzamido)imidazo[1,2-*b*]pyridazines **22-26** in good yields. The structure of compounds **22-26** was established by ^{1}H-nmr spectroscopy and confirmed by their analytical data and ir spectrum.

Recently, a series of benzothiazoles which possess a *t*-butyl group at C-2 and an isothiocyanate group at the C-6 position were reported to possess both micro- and macrofilarial activity [11]. In an attempt to prepare 2-*t*-butyl-6-isothiocyanatoimidazo[1,2-*b*]pyridazine and 6-thiocarbamate derivatives, 2-*t*-butyl-6-chloroimidazo[1,2-*b*]pyridazine (**17**) was treated with potassium thiocyanate under a variety of conditions [12-15] including high temperature in a pressure reaction vessel. However, each reaction failed to afford the isothiocyanate derivative **27b**. We then focused our efforts on converting 6-amino-2-*t*-butylimidazo[1,2-*b*]pyridazine (**21**) to the desired isothiocyanates. The reaction of **21** with carbon disulfide and sodium hydroxide followed by decomposition of the intermediate dithiocarbamic acid salt by using ethyl chloroformate [16,17] was unsuccessful. However, treatment of compound **21** with one equivalent of thiophosgene at room temperature, while carefully monitoring the reaction mixture on tlc, resulted in the formation of a complex reaction mixture from which one major component was isolated and characterized as *N,N'*-bis-(2-*t*-butylimidazo[1,2-*b*]pyridazin-6-yl)thiourea (**28**). The structure of this compound was established by its ^{1}H-nmr spectrum and confirmed by its analytical data and ir spectrum. The fact that **28** was formed in the reaction was not unexpected, since aromatic amines with electron withdrawing substituents have been shown to produce *N,N'*-bis-substituted thioureas as by products together with the desired isothiocyanate [18-21]. Attempts to decrease the formation of the side product by the addition of a small excess of thiophosgene were unsuccessful and the thiourea derivative **28** was isolated as the major product. In fact, **28** was the only product in a reaction in which thiophosgene was added in portions to a solution of **21** in acetone. These results suggest that an intermediate thiocarbamoyl chloride, **27a**, or 2-*t*-butyl-6-isothiocyanatoimidazo[1,2-*b*]pyridazine (**27b**) reacted with another molecule of **21** to form **28**. If the reaction was quenched by the addition of 2-propanol or methanol, the *O*-isopropyl 2-*t*-butylimidazo[1,2-*b*]pyridazine-6-thiocarbamate (**30**) or *S*-methyl 2-*t*-butylimidazo[1,2-*b*]pyridazine-6-thiocarbamates (**31**) were isolated in practically quantitative yields, respectively. The isolation of **31** from the reaction was unexpected since thiocarbamates, exhibit a state of equilibrium between the two forms (**32** and **33**) [12b] which is shifted in most cases almost exclusively to structure **32**. The shift in equilibrium has been attributed to the fact that sulfur forms weak double bonds due to poor orbital overlap. In the case of compound **31** we found that the methyl group

Scheme III



Scheme IV



resided on the sulfur with no trace of it being on the oxygen atom. This was established on the basis of an ^{1}H-nmr spectrum which showed the methyl signal at δ 2.50 (s). If the methyl group was located on the oxygen atom, one would expect a chemical shift of approximately 3.7 ppm for this methyl group. In addition, the ir spectrum of compound **31** showed an NH stretching vibration at 3129 cm^{-1} and a carbonyl stretching vibration at 1624 cm^{-1}. The absence in the ir spectra of SH or OH stretching vibration excludes the possibility of the methyl group residing on the exocyclic nitrogen [22,23]. This isomerization was not observed for compound **30**. This rearrangement is under further investigation.

None of the target compounds demonstrated any significant activity against *B. pahangi* or *A. viteae* filarial infections in jirds, or against human cytomegalovirus (HCMV) infections.

EXPERIMENTAL

Melting points are uncorrected. Rotary evaporation was conducted at less than 50°, using a water aspirator (15 mm Hg) or a vacuum pump (1 mm Hg). Low-pressure chromatography was performed using a Michel-Miller column (4 cm x 30 ml) which was packed with normal phase silica (EM Reagent Kieselgel 60 (230-400) mesh ASTM). Centrifugal chromatography was performed using a model 7924T Chromatotron. Flash and open-bed chromatography was performed using normal phase silica, EM Reagent Kieselgel 60 (70-230 mesh ASTM). All eluent systems are stated as volume to volume ratios. Thin layer chromatography (tlc) was accomplished using Analtech, SilicAR (250 micrometer layer) on prescored glass plates (2.5 cm x 8 cm). Proton nuclear magnetic resonance (^{1}H-nmr) spectra were obtained using a Bruker WM 360 or IBM WP 270 SY spectrometer. The nmr spectra were recorded using either deuteriochloroform as a solvent and tetramethylsilane as an internal standard of dimethyl sulfoxide-d_6 as a solvent. The following abbreviations were used to designate the multiplicity of the individual signals: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = double doublet, bs = broad singlet. The ir spectra were recorded using a Perkin-Elmer 281 spectrometer or a Nicolet DX system FT-ir. Mass spectral data were obtained on a Finnigan Model 4023 GC/MS using electron ionization or chemical ionization. Elemental analyses were obtained from M-H-W Laboratories, Phoenix, AZ.

Methyl 6-Chloroimidazo[1,2-*b*]pyridazine-2-carbamate (**3**).

Methyl (chloroacetyl)carbamate [6] (3.62 g, 24 mmoles) and 3-amino-6-chloropyridazine (**2**) [24] (3.12 g, 24 mmoles) were dissolved in 30 ml of hexamethylphosphoramide and the solution was heated at 100° for 5 hours with continuous stirring. At the end of this period the reaction mixture was cooled to room temperature and water (150 ml) was added to furnish a light pink precipitate. This precipitate was collected by filtration, washed with water (100 ml), methanol (100 ml), and methylene chloride (100 ml) then dried at room temperature to give compound **3** (2.72 g, 50%). An analytical sample was prepared by recrystallization from methanol; R_f: 0.71 (chloroform/methanol, 9/1), mp 259-260°; ir (potassium bromide): 3184, 3093, 3008, 2948, 1728, 1605, 1581, 1518 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 3.70 (s, 3H, CH_3), 7.31 (d, 1H, H_8), 8.03 (d, 1H, H_7), 8.12 (s, 1H, H_3), 10.62 (s, 1H, NH, deuterium oxide exchangeable).

Anal. Calcd. for $C_8H_7ClN_4O_2$ (226.619): C, 42.40; H, 3.11; N, 24.72. Found: C, 42.52; H, 3.25; N, 24.53.

N,N'-Bis-(6-chloroimidazo[1,2-*b*]pyridazin-2-yl)urea (**4**).

Methyl 6-chloroimidazo[1,2-*b*]pyridazine-2-carbamate (**3**) (2 g, 8.8 mmoles) was heated at reflux in dimethylformamide (30 ml) for 30 minutes and then the mixture was cooled to room temperature. A white precipitate formed which was collected by filtration and washed with methanol (100 ml) to furnish 1.55 g (48% yield) of **4**. An analytical sample of compound **4** was prepared by recrystallization from methanol; R_f: 0.42 (chloroform/methanol, 9/1), mp 308-309° dec; ir (potassium bromide): 3339, 3219, 3170, 3043, 1714, 1546, 1510 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 7.33 (d, 2H, H_8, $H_{8'}$), 8.05 (d, 2H, H_7, $H_{7'}$), 8.16 (s, 2H, H_3, $H_{3'}$), 9.71 (s, 2H, NH, deuterium oxide exchangeable); ms: electron impact (EI) mass spectrum, m/z 363 (M^+).

Anal. Calcd. for $C_{13}H_8Cl_2N_8O$ (363.16): C, 42.99; H, 2.22; N, 30.86. Found: C, 43.27; H, 2.41; N, 30.63.

3-Amino-6-(phenylsulfinyl)pyridazine (**6**).

3-Amino-6-(phenylthio)pyridazine (**5**) [25] (4.06 g, 20 mmoles) was dissolved in methylene chloride (100 ml) and to this solution was added *m*-chloroperoxybenzoic acid (4.06 g, 20 mmoles in methylene chloride, 100 ml) with continuous stirring at room temperature. The reaction was monitored by tlc and terminated after 24 hours when no further progress was detected. The reaction mixture was extracted with sodium bicarbonate (500 ml, saturated aqueous solution), then water (3 x 100 ml), dried over anhydrous magnesium sulfate, filtered, and the solvent was evaporated under reduced pressure. The residue was then applied to the top of a normal phase silica column (4.5 cm x 20 cm) and eluted using ethyl acetate/hexanes, (3/1). The fractions containing the product (R_f: 0.16, ethyl acetate/hexanes, 3/1) were combined, evaporated to dryness under reduced pressure, and weighed (3.6 g, 82%). An analytical sample was recrystallized from methanol, mp 213°; ir (potassium bromide): 3371, 3306, 3182, 3025, 1638, 1579, 1454 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 6.89 (d, 1H, pyridazine H_4), 6.98 (s, 2H, NH_2, deuterium oxide exchangeable), 7.55 (m, 4H, phenyl-H), 7.68 (m, 2H, phenyl-H and pyridazine H_5).

Anal. Calcd. for $C_{10}H_9N_3OS$ (219.256): C, 54.78; H, 4.14; N, 19.16. Found: C, 54.71; H, 4.15; N, 19.24.

3-Amino-6-(phenylsulfonyl)pyridazine (**7**).

To a stirred solution of compound **5** (4.06 g, 20 mmoles) dissolved in methylene chloride (100 ml) was added a solution of *m*-chloroperbenzoic acid (8.59 g, 49 mmoles) dissolved in methylene chloride (100 ml). The reaction was stirred at room temperature for 24 hours. The reaction mixture then was extracted with aqueous saturated sodium bicarbonate (5 x 50 ml) and water (3 x 100 ml), dried over anhydrous magnesium sulfate, filtered and the solvent evaporated under reduced pressure. The resulting residue which was a mixture of **6** and **7**, was purified by low pressure chromatography using normal phase silica and ethyl acetate/hexanes (3/1), as eluent. Isolated from the appropriate fractions were **6** (0.9 g) and **7** (2.1 g, 44%). An analytical sample of **7** was recrystallized from ethanol; R_f: 0.32 (ethyl acetate/hexanes, 3/1), mp 243°; ir (potassium bromide): 3437, 3326, 3227, 3188, 3044, 1624, 1572 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 6.87 (d, 1H, pyridazine H_4), 7.35 (s, 2H, NH_2, deuterium oxide exchangeable), 7.65 (m, 3H, phenyl-H), 7.87 (d, 1H, pyridazine H_5), 7.94 (m, 2H, phenyl-H).

Anal. Calcd. for $C_{10}H_9N_3O_2S$ (235.256): C, 51.05; H, 3.86; N, 17.86. Found: C, 50.92; H, 3.77; N, 17.97.

Methyl 6-(Phenylthio)imidazo[1,2-*b*]pyridazine-2-carbamate (**8**).

Compound **8** was prepared in 4.5 g (60% yield) from 3-amino-6-phenylthiopyridazine (**5**) and methyl (chloroacetyl)carbamate using the same procedure which afforded compound **3**. An analytical sample was recrystallized from dimethylformamide/methanol (1/2), mp 221-222°; ir (potassium bromide): 3177, 3078, 2952, 1728 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 3.69 (s, 3H, CH_3), 6.88 (d, 1H, H_8), 7.4-7.7 (m, 5H, aromatic), 7.84 (d, 1H, H_7), 7.94 (s, 1H, H_3), 10.51 (s, 1H, NH, deuterium oxide exchangeable).

Anal. Calcd. for $C_{14}H_{12}N_4O_2S$ (300.334): C, 55.98; H, 4.03; N, 18.66. Found: C, 55.98; H, 4.06; N, 18.46.

2-Methyl-6-(phenylthio)imidazo[1,2-*b*]pyridazine (**9**).

Method 1.

Compound **9** was prepared in 3.2 g (66% yield) from 3-amino-6-(phenylthio)pyridazine (**5**) and chloroacetone using a procedure similar to that used to prepare compound **10**. An analytical sample was prepared by flash chromatography using normal phase silica and chloroform as an eluent. The pure product was a purple viscous liquid, bp >90° at 1 mm Hg; R_f: 0.72 (chloroform/methanol, 96/4); ir (neat, sodium chloride plates): 3186, 3057, 2926, 1605, 1579, 1520, 1474, 1441 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 2.33 (s, 3H, CH_3), 6.84 (d, 1H, H_8), 7.47 (m, 3H, phenyl-H), 7.58 (m, 2H, phenyl-H), 7.86 (d, 1H, H_7), 7.94 (s, 1H, H_3).

Anal. Calcd. for $C_{13}H_{11}N_3S$ (241.304): C, 64.70; H, 4.60; N, 17.41. Found: C, 64.90; H, 4.59; N, 17.61.

Method 2.

Sodium (0.345 g, 15 mmoles) was dissolved in 30 ml of absolute ethanol under an atmosphere of nitrogen and to this solution was added thiophenol (1.65 g, 15 mmoles) and the mixture was stirred for 30 minutes at room temperature. 6-Chloro-2-methylimidazo-[1,2-*b*]pyridazine (**16**) (2.34 g, 14 mmoles) was then added and the solution was sealed in a steel reaction vessel and heated to 100° for 2 hours. At the end of this period, the vessel was allowed to cool to room temperature, opened and the solvent was removed *in vacuo* and the residue was purified by flash chromatography as before (method 1) to yield 2.72 g (81%) of pure **9** which was identical in all respects to the product obtained by method 1.

2-*t*-Butyl-6-(phenylthio)imidazo[1,2-*b*]pyridazine (**10**).

3-Amino-6-(phenylthio)pyridazine (**5**) (7.11 g, 35 mmoles) and 1-bromopinacolone (6.27 g, 35 mmoles) was heated at 100° for 5 hours in dimethylformamide (30 ml). At the end of this period, water (150 ml) was added to the reaction mixture and the whole solution was repeatedly extracted with ethyl ether (10 x 50 ml). The ether extracts were then combined, washed with water (100 ml), dried over anhydrous magnesium sulfate, filtered, and evaporated to afford crystalline **10** (9 g, 71%). An analytically pure sample was obtained by recrystallization from ether; mp 199°; R_f: 0.22 (chloroform): ir (potassium bromide): 3064, 2966, 2717, 2652, 1631, 1579, 1474 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 1.35 (s, 9H, *t*-Bu), 7.45 (d, 1H, H_8), 7.60 (m, 5H, phenyl), 8.15 (d, 1H, H_7), 8.35 (s, 1H, H_3).

Anal. Calcd. for $C_{16}H_{17}N_3S \cdot 0.75HBr \cdot H_2O$ (362.21): C, 53.05; H, 5.28; N, 11.65. Found: C, 53.36; H, 5.03; N, 11.68.

2-Methyl-6-(phenylsulfinyl)imidazo[1,2-*b*]pyridazine (**11**).

Compound **11** was prepared by two methods:

Method 1.

Using a procedure similar to that used for the preparation of compound **6**, 2-methyl-6-(phenylthio)imidazo[1,2-*b*]pyridazine (**9**) and *m*-chloroperoxybenzoic acid were reacted to give **11** in 0.22 g (86% yield). An analytical sample was recrystallized from methanol; R_f: 0.15 (ethyl acetate/hexanes, 3/1), 0.55 (chloroform/methanol, 96/4), mp 125-126°; ir (potassium bromide): 3129, 3077, 2925, 1536, 1513, 1441, 1350, 1340, 1055 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 2.39 (s, 3H, CH_3), 7.45 (d, 1H, H_8), 7.57 (m, 3H, phenyl-H), 7.74 (m, 2H, phenyl-H), 8.17 (d, 1H, H_7), 8.20 (s, 1H, H_3).

Anal. Calcd. for $C_{13}H_{11}N_3OS$ (257.304): C, 60.68; H, 4.31; N, 16.33. Found: C, 60.75; H, 4.37; N, 16.36.

Method 2.

3-Amino-6-(phenylsulfinyl)pyridazine (**6**) and 1-chloroacetone were condensed using a procedure similar to that used for the preparation of compound **3**. The yield of **11** was 0.22 g (47%). The material was identical in all respects with **11** obtained in method 1.

2-Methyl-6-(phenylsulfonyl)imidazo[1,2-*b*]pyridazine (**12**).

Compound **12** was prepared by two methods:

Method 1.

2-Methyl-6-(phenylthio)imidazo[1,2-*b*]pyridazine (**9**) (0.54 g, 2 mmoles) was dissolved in dichloromethane (25 ml). To this solution was added *m*-chloroperoxybenzoic acid (0.96 g, 4 mmoles) and the mixture was stirred for 48 hours. At the end of this period, the reaction mixture was washed with saturated sodium bicarbonate (3 x 50 ml) with water (2 x 50 ml), dried over anhydrous magnesium sulfate, filtered, and the solvent was removed *in vacuo* to yield an oil. This oil was applied to the top of a normal phase silica column (2.5 cm x 15 cm) and the column was eluted with chloroform. The fractions containing the product (R_f: 0.66, chloroform/methanol, 96/4) were combined and evaporated to dryness to give 0.17 g (31%) of **12**. Also isolated was 0.18 g (34%) of compound **11**. An analytical sample of compound **12** was recrystallized from ethyl acetate/hexanes, (1/1); mp 143°; ir (potassium bromide): 3129, 3103, 3070, 2926, 1533, 1507, 1448, 1330, 1166 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 2.41 (s, 3H, CH_3), 7.65 (d, 1H, H_8), 7.75 (m, 3H, phenyl-H), 8.02 (t, 2H, phenyl-H), 8.28 (d, 1H, H_7), 8.29 (s, 1H, H_3).

Anal. Calcd. for $C_{13}H_{11}N_3O_2S$ (273.304): C, 57.13; H, 4.06; N, 15.37. Found: C, 57.28; H, 4.15; N, 15.14.

Method 2.

Compound **12** was prepared from 3-amino-6-(phenylsulfonyl)-pyridazine (**7**) and 1-chloroacetone in 0.31 g (57% yield) using a procedure similar to that used for the preparation of compound **3**. Compound **12** was purified by column chromatography using normal phase silica and chloroform as the eluent. All properties of this material were identical with **12** prepared by method 1.

2-*t*-Butyl-6-(phenylsulfinyl)imidazo[1,2-*b*]pyridazine (**13**).

Compound **13** was prepared by two methods:

Method 1.

Using a procedure similar to that used to prepare **6**, compound **13** was obtained in 0.93 g (90% yield) from the reaction of 2-*t*-butyl-6-(phenylthio)imidazo[1,2-*b*]pyridazine (**10**) and *m*-chloroperoxybenzoic acid. The product was purified by flash chromatography. An analytical sample was recrystallized from an ethyl acetate/hexanes mixture (1/2); R_f: 0.77 (chloroform/methanol, 9/1), mp 136-139°; ir (potassium bromide): 3156, 3110, 3064, 2966, 1513, 1448, 1291, 1049 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 1.31 (s, 9H, *t*-Bu), 7.48 (d, 1H, H_8), 7.57-7.77 (m, 5H, phenyl-H), 8.23 (d, 1H, H_7), 7.25 (s, 1H, H_3).

Anal. Calcd. for $C_{16}H_{17}N_3OS$ (299.384): C, 64.18; H, 5.72; N, 14.03. Found: C, 63.89; H, 5.97; N, 13.86.

Method 2.

Compound **13** was prepared in 0.167 g (28% yield) from the condensation of 3-amino-6-(phenylsulfinyl)pyridazine (**6**) and 1-

bromopinacolone following the same procedure used to prepare compound **3**. The material obtained was identical with **13** prepared in method 1.

2-*t*-Butyl-6-(phenylsulfonyl)imidazo[1,2-*b*]pyridazine (**14**).

Method 1.

Using a procedure similar to that used to obtain **12**, compound **14** was prepared from the reaction of 2-*t*-butyl-6-(phenylthio)-imidazo[1,2-*b*]pyridazine (**10**) and *m*-chloroperoxybenzoic acid. The reaction mixture was purified by open-bed silica chromatography (2.5 cm x 25 cm), using chloroform as the eluent. 2-*t*-Butyl-6-(phenylsulfinyl)imidazo[1,2-*b*]pyridazine (**13**) R_f = 0.77 (chloroform/methanol, 9/1) was also isolated in 0.5 g (36% yield). Fractions containing compound **14** were pooled and evaporated to furnish a solid which was triturated with hexanes and collected by filtration (37% yield). An analytical sample was prepared by recrystallization from ethyl acetate/hexanes, (1/1); R_f: 0.73 (chloroform/methanol, 96/4), mp 161-162°; ir (potassium bromide): 3110, 3070, 2966, 1513, 1441, 1330, 1166, 721 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 1.31 (s, 9H, *t*-Bu), 7.68 (d, 1H, H_8), 7.78 (m, 3H, phenyl-H), 8.03 (m, 2H, phenyl-H), 8.33 (d, 1H, H_7), 8.35 (s, 1H, H_3).

Anal. Calcd. for $C_{16}H_{17}N_3O_2S \cdot 0.75H_2O$ (328.896): C, 58.43; H, 5.67; N, 12.78. Found: C, 58.68; H, 5.26; N, 12.66.

Method 2.

Compound **14** was prepared from 3-amino-6-(phenylsulfonyl)-pyridazine (**7**) and 1-bromopinacolone in 0.26 g (16% yield) using a procedure similar to that used for the preparation of compound **3**. Compound **14** was purified by column chromatography using normal phase silica and chloroform as the eluent. All properties of this material were identical with **14** prepared by method 1.

Methyl 6-(Phenylsulfinyl)imidazo[1,2-*b*]pyridazine-2-carbamate (**15**).

Compound **15** was prepared by two methods:

Method 1.

From methyl 6-(phenylthio)imidazo[1,2-*b*]pyridazine-2-carbamate (**8**) and *m*-chloroperoxybenzoic acid in 64% yield using a procedure similar to that used to prepare compound **11**. The product in this procedure was purified by flash chromatography using normal phase silica and chloroform as an eluent. An analytical sample was recrystallized from methanol; R_f: 0.39 (ethyl acetate/hexanes, 3/1), mp 232-233°; ir (potassium bromide): 3214, 3142, 3005, 2953, 1736, 1618, 1605, 1291, 748 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 3.07 (s, 3H, CH_3), 7.48 (d, 1H, H_8), 7.56-7.77 (m, 5H, phenyl-H), 8.12 (d, 1H, H_7), 8.15 (s, 1H, H_3), 10.67 (s, 1H, NH, deuterium oxide exchangeable).

Anal. Calcd. for $C_{14}H_{12}N_4O_3S$ (316.334): C, 53.15; H, 3.82; N, 17.71. Found: C, 52.91; H, 3.88; N, 17.57.

Method 2.

Using a procedure similar to that used to prepare **3**, compound **15** was prepared from the condensation of 3-amino-6-(phenylsulfinyl)pyridazine (**6**) and methyl (chloroacetyl)carbamate to yield 91 mg (29% yield) of **15**.

6-Chloro-2-methylimidazo[1,2-*b*]pyridazine (**16**).

Compound **16** was isolated in 4.35 g (52% yield) from the condensation of 3-amino-6-chloropyridazine (**2**) and chloroacetone using the same procedure which produced compound **3**. An analytical sample was recrystallized from hexanes, mp 134°; ir (potassium bromide): 3177, 3072, 2952 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 2.38 (s, 3H, CH_3), 7.27 (d, 1H, H_8), 8.07 (d, 1H, H_7), 8.12 (s, 1H, H_3).

Anal. Calcd. for $C_7H_6ClN_3$ (167.591): C, 50.16; H, 3.61; N, 25.07. Found: C, 50.02; H, 3.56; N, 25.03.

2-*t*-Butyl-6-chloroimidazo[1,2-*b*]pyridazine (**17**).

Compound **17** was prepared by a condensation of 1-bromopinacolone and 3-amino-6-chloropyridazine (**2**) in 6.5 g (76% yield) using the same procedure which produced compound **3**. An analytical sample was recrystallized from hexanes, mp 129-130°; ir (potassium bromide): 3121, 3071, 2959, 1595, 1518, 1454 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 1.33 (s, 9H, *t*-Bu), 7.28 (d, 1H, H_8), 8.12 (d, 1H, H_7), 8.13 (s, 1H, H_3).

Anal. Calcd. for $C_{10}H_{12}ClN_3$ (209.673): C, 57.28; H, 5.77; N, 20.04. Found: C, 57.11; H, 5.60; N, 19.97.

6-Amino-2-methylimidazo[1,2-*b*]pyridazine (**20**).

Compound **20** was prepared in 2.4 g (61% yield) using 6-chloro-2-methylimidazo[1,2-*b*]pyridazine (**16**) as the starting material and the same procedure which produced compound **21** (*vida infra*). An analytical sample was recrystallized from methanol, mp 170°; R_f: 0.51 (chloroform/methanol, 9/1); ir (potassium bromide): 3496, 3378, 3162, 2985, 1651, 1618, 1559, 1494 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 2.25 (s, 3H, CH_3), 6.16 (s, 2H, NH_2, deuterium oxide exchangeable), 6.53 (d, 1H, H_8), 7.48 (s, 1H, H_3), 7.56 (d, 1H, H_7).

Anal. Calcd. for $C_7H_8N_4$ (148.164): C, 56.74; H, 5.44; N, 37.82. Found: C, 56.59; H, 5.63; N, 37.66.

6-Amino-2-*t*-butylimidazo[1,2-*b*]pyridazine (**21**).

2-*t*-Butyl-6-chloroimidazo[1,2-*b*]pyridazine (**17**) (2.09 g, 10 mmoles) was heated at reflux for 2 hours in anhydrous hydrazine (30 ml) under an atmosphere of nitrogen. At the end of this period, water (100 ml) was added and the mixture was extracted with ether (5 x 100 ml). The ether extracts were then dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness. The resulting oily residue was further dried under high vacuum while keeping the temperature below 40° and then was dissolved in ethanol (100 ml). Raney nickel (0.5 g) was added to the solution and the mixture was submitted to hydrogenation at 15 psi for 4 hours. At the end of this period, the catalyst was removed by filtration through a Celite pad, and the filtrate was concentrated to 20 ml. Ethyl acetate/hexanes (1/1) (100 ml) was added to this solution, which resulted in the precipitation of **21**. The product was collected by filtration (1.80 g, 92% crude yield). An analytical sample was recrystallized from ethyl acetate/hexanes (1/1); R_f: 0.5 (chloroform/methanol, 9/1), mp 154-155°; ir (potassium bromide): 3411, 3306, 3162, 2966, 1631, 1552, 1480 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 1.26 (s, 9H, *t*-Bu), 6.16 (s, 2H, NH_2, deuterium oxide exchangeable), 6.54 (d, 1H, H_8), 7.46 (s, 1H, H_3), 7.61 (d, 1H, H_7).

Anal. Calcd. for $C_{10}H_{14}N_4 \cdot 0.25H_2O$ (194.744): C, 61.67; H, 7.50; N, 28.77. Found: C, 61.80; H, 7.52; N, 28.69.

6-(2-Fluorobenzamido)-2-methylimidazo[1,2-*b*]pyridazine (**22**).

To a solution of 6-amino-2-methylimidazo[1,2-*b*]pyridazine (**20**) (0.45 g, 3 mmoles) dissolved in anhydrous pyridine (10 ml) was added an equimolar amount of 2-fluoro-

benzoyl chloride (0.47 g, 3 mmoles) with continuous stirring under an atmosphere of nitrogen. The reaction was stirred for 1 hour at room temperature and then the solvent was removed *in vacuo*. The resulting residue was subjected to flash chromatography (column size: 1 cm x 8 cm) using normal phase silica and chloroform as the eluent to yield 0.71 g (95%) of pure product. An analytical sample was recrystallized from methanol; R_f: 0.68 (chloroform/methanol, 9/1), mp 256° dec; ir (potassium bromide): 3417, 3077, 2966, 2927, 1683 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 2.39 (s, 3H, CH_3), 7.34 (m, 2H, benzamido H_3 and H_4), 7.62 (m, 1H, benzamido H_5), 7.73 (m, 1H, benzamido H_6), 7.85 (d, 1H, H_8), 7.95 (s, 1H, H_3), 8.05 (d, 1H, H_7), 11.19 (s, 1H, NH, deuterium oxide exchangeable).

Anal. Calcd. for $C_{14}H_{11}FN_4O$ (270.26): C, 62.21; H, 4.10; N, 20.73. Found: C, 62.26; H, 4.28; N, 20.78.

6-(4-Fluorobenzamido)-2-methylimidazo[1,2-*b*]pyridazine (**23**).

To a solution of 6-amino-2-methylimidazo[1,2-*b*]pyridazine (**20**) (0.45 g, 3 mmoles) dissolved in anhydrous pyridine (10 ml), was added 4-fluorobenzoyl chloride (0.47 g, 0.003 moles) with continuous stirring under an atmosphere of nitrogen. After 1 hour at room temperature, a mixture of ethyl acetate/hexanes (1/1) (30 ml) was added to the solution and the product which precipitated was collected by filtration (0.79 g, 91% crude yield). An analytical sample was recrystallized from ethyl acetate/hexanes, (1/3); R_f: 0.56 (chloroform/methanol, 9/1), mp 227-228°; ir (potassium bromide): 3310, 3060, 2966, 2930, 1680 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 2.37 (s, 3H, CH_3), 7.96 (t, 2H, benzamido H_3 and H_5), 7.76 (d, 1H, H_8), 7.93 (s, 1H, H_3), 8.00 (d, 1H, H_7), 8.10 (q, 2H, benzamido H_2 and H_6), 11.14 (s, 1H, NH, deuterium oxide exchangeable).

Anal. Calcd. for $C_{14}H_{11}FN_4O$ (270.26): C, 62.21; H, 4.10; N, 20.73. Found: C, 62.30; H, 4.17; N, 20.81.

2-*t*-Butyl-6-(2-fluorobenzamido)imidazo[1,2-*b*]pyridazine (**24**).

Compound **24** was prepared in 0.78 g (83% yield) from 6-amino-2-*t*-butylimidazo[1,2-*b*]pyridazine (**21**) and 2-fluorobenzoyl chloride using the same procedure which afforded compound **25**. An analytical sample was prepared by flash chromatography using normal phase silica and chloroform as an eluent; R_f: 0.30 (chloroform), mp 170°; ir (potassium bromide): 3254, 3208, 3149, 3077, 2966, 1677, 1278 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 1.35 (s, 9H, *t*-Bu), 7.35 (m, 2H, benzamido H_3 and H_4), 7.60 (m, 1H, benzamido H_5), 7.72 (m, 1H, benzamido H_6), 7.83 (d, 1H, H_8), 7.94 (s, 1H, H_3), 8.07 (d, 1H, H_7), 11.20 (s, 1H, NH, exchangeable with deuterium oxide).

Anal. Calcd. for $C_{17}H_{17}FN_4O$ (312.34): C, 65.37; H, 5.49; N, 17.94. Found: C, 65.17; H, 5.52; N, 18.14.

2-*t*-Butyl-6-(3-fluorobenzamido)imidazo[1,2-*b*]pyridazine (**25**).

To a solution of 6-amino-2-*t*-butylimidazo[1,2-*b*]pyridazine (**21**) (0.28 g, 1.5 mmoles) dissolved in anhydrous pyridine (10 ml) was added 3-fluorobenzoyl chloride (0.23 g, 0.18 ml, 1.5 mmoles) with continuous stirring under a nitrogen atmosphere. After 1 hour at room temperature, the solvent was removed *in vacuo*. The resulting residue was subjected to flash chromatography (column size: 1 cm x 8 cm) using normal phase silica and chloroform as an eluent to yield 0.41 g (88%) of pure product. An analytical sample was prepared by centrifugal chromatography on a 2 mm plate and using chloroform/methanol, (95/5) as the eluent, mp 80° dec; R_f: 0.31 (chloroform); ir (potassium bromide): 3241, 3051, 2966, 1664, 1592, 1552, 1533, 1467 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 1.34 (s, 9H, *t*-Bu), 7.47-8.08 (m, 7H, aromatic), 11.23 (s, 1H, NH, deuterium oxide exchangeable).

Anal. Calcd. for $C_{17}H_{17}FN_4O$ (312.34): C, 65.37; H, 5.49; N, 17.94. Found: C, 65.49; H, 5.36; N, 17.91.

2-*t*-Butyl-6-(4-fluorobenzamido)imidazo[1,2-*b*]pyridazine (**26**).

Compound **26** was prepared in 0.91 g (97% yield) from 6-amino-2-*t*-butylimidazo[1,2-*b*]pyridazine (**21**) and 4-fluorobenzoyl chloride. An analytical sample was prepared by flash chromatography using normal phase silica and chloroform as an eluent; R_f: 0.36 (chloroform), mp 115-116°; ir (potassium bromide): 3280, 3156, 3084, 2966, 1677 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 1.35 (s, 9H, *t*-Bu), 7.35 (m, 2H, benzamido (H_3 and H_5)), 7.77 (d, 1H, H_8), 7.92 (s, 1H, H_3), 8.05 (m, 3H, H_7 and benzamido (H_2 and H_6)), 11.18 (s, 1H, NH, deuterium oxide exchangeable).

Anal. Calcd. for $C_{17}H_{17}FN_4O$ (312.34): C, 65.37; H, 5.49; N, 17.94. Found: C, 65.23; H, 5.54; N, 17.80.

N,N-Bis-(2-*t*-butylimidazo[1,2-*b*]pyridazin-6-yl)thiourea (**28**).

To a stirred solution of 6-amino-2-*t*-butylimidazo[1,2-*b*]pyridazine (**21**) (0.19 g, 1 mmole) in acetone (20 ml) was added thiophosgene (0.115 g, 1 mmole) in three portions. After 1 hour the precipitate which formed during the course of the reaction was collected by filtration. The solid was dissolved in methanol (10 ml), adsorbed on normal phase silica (0.5 g), applied to the top of a normal phase silica column (1 cm x 7 cm) and purified by flash chromatography using chloroform as the eluent to give 0.35 g (83%) of analytically pure product; R_f: 0.73 (chloroform/methanol, 9/1), mp 220-222°; ir (potassium bromide): 3210, 3050, 2962, 1638, 1482, 1345, 1315, 1225, 1195 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 1.35 (s, 18H, 2 x *t*-Bu), 7.36 (d, 2H, H_8 and $H_{8'}$), 8.02 (s, 2H, H_3 and $H_{3'}$), 8.04 (d, 2H, H_7 and $H_{7'}$), 11.74 (s, 2H, NH, deuterium oxide exchangeable).

Anal. Calcd. for $C_{21}H_{26}N_8S$ (422.54): C, 59.69; H, 6.20; N, 26.52; S, 7.59. Found: C, 59.79; H, 6.49; N, 26.34; S, 7.31.

O-(isopropyl) 2-*t*-Butylimidazo[1,2-*b*]pyridazine-6-thiocarbamate (**30**).

To a vigorously stirred solution of thiophosgene (0.115 g, 1 mmole) in dry acetone (20 ml) at room temperature was added portionwise 6-amino-2-*t*-butylimidazo[1,2-*b*]pyridazine (**21**) (0.19 g, 1 mmole). After 3 hours the precipitate which formed during the reaction was collected by filtration, washed with acetone (10 ml), and immediately dissolved in dry 2-propanol (30 ml). This mixture was heated at reflux for 1 hour, filtered and cooled to room temperature during which time a precipitate formed. The precipitate was collected by filtration to give 0.28 g (96%) of pure product. An analytical sample was obtained by flash chromatography (1 cm x 6 cm) using normal phase silica and ethyl acetate as the eluent; R_f: 0.58 (ethyl acetate/hexanes, 3/1), mp 181°; ir (potassium bromide): 3136, 3057, 2959, 1611, 1546, 1454, 1304, 1212, 1094, 996, 754 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 1.31 (s, 9H, *t*-Bu), 1.32 (d, 6H, 2 x CH_3), 5.50 (m, 1H, CH), 7.35 (d, 1H, H_8), 7.93 (s, 1H, H_3), 8.00 (d, 1H, H_7), 11.55 (s, 1H, NH, deuterium oxide exchangeable).

Anal. Calcd. for $C_{14}H_{20}N_4OS$ (292.394): C, 57.50; H, 6.89; N, 19.16. Found: C, 57.48; H, 7.00; N, 19.15.

S-Methyl 2-*t*-Butylimidazo[1,2-*b*]pyridazine-6-thiocarbamate (**31**).

To a vigorously stirred solution of thiophosgene (0.23 g, 2 mmoles) dissolved in dry acetone (40 ml) was added portionwise at room temperature 6-amino-2-*t*-butylimidazo[1,2-*b*]pyridazine (**21**) (0.38 g, 2 mmoles). At the end of 3 hours the precipitate which formed during the reaction was collected by filtration, washed with acetone (10 ml), and dissolved in dry methanol (60 ml). This mixture was heated at reflux for 1 hour, treated with charcoal, filtered and cooled to room temperature. A mixture of ethyl acetate/hexanes (1/1) (30 ml) was added to the filtrate at room temperature and the precipitate which formed was collected by filtration to afford 0.52 g (quantitative). An analytical sample was recrystallized from methanol; R_f: 0.41 (ethyl acetate/hexanes, 75/25), mp 149° dec; ir (potassium bromide): 3129, 3064, 2959, 1624, 1546, 1520, 1448, 1304, 1193, 1147, 1134, 1029 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 1.35 (s, 9H, *t*-Bu), 2.50 (s, 3H, CH_3), 6.98 (s, 1H, NH, deuterium oxide exchangeable), 7.05 (d, 1H, H_8), 7.90 (d, 1H, H_7), 7.94 (s, 1H, H_3).

Anal. Calcd. for $C_{12}H_{16}N_4OS$ (264.344): C, 54.52; H, 6.10; N, 21.20. Found: C, 54.58; H, 6.18; N, 21.04.

Antifilarial and Antiviral Studies.

All compounds were evaluated for antifilarial activity against the adult worms of *B. pahangi* and *A. viteae* in jirds (*Meriones unguiculatus*, males), usually using dual infections of *B. pahangi* and *A. viteae*. The jirds were given 10 (5 male and 5 female) adult *A. viteae* by surgical implantation in subcutaneous tissue 21-28 days prior to treatment and either 50 infective larvae of *B. pahangi* by intraperitoneal inoculation 60-100 days prior to drug treatment or 20 (10 male and 10 female) adult *B. pahangi* surgically implanted into the peritoneal cavity 4-60 days pretreatment [26]. The drugs were administered as solutions of suspension in aqueous 1% (hydroxyethyl)cellulose and 0.1% Tween 80 (HEC Tween 80) once daily for 5 days to three to five implanted jirds. Fifty-five to 70 days after the first drug dose, surviving animals were sacrificed and examined for adult worms by searching the pleural and peritoneal cavities. The number of surviving worms at necropsy was scored as a percentage relative to controls. Compounds were considered to be active when the number of adult worms was less than 60% of the controls.

Human cytomegalovirus (HCMV) plaque reduction experiments were performed using monolayer cultures of HFF cells by a literature procedure [27].

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