Methyl Imidazo[1,2-*b*]pyridazine-2-carbamates and Related Compounds as Potential Antifilarial Agents

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A series of imidazo[1,2-*b*]pyridazines have been synthesized for antifilarial evaluation. The compounds prepared include methyl 6-benzoylimidazo[1,2-*b*]pyridazine-2-carbamate (**12**), 6-benzoyl-2-*t*-butylimidazo[1,2-*b*]pyridazine (**13**), methyl 6-(4-fluorobenzoyl)imidazo[1,2-*b*]pyridazine-2-carbamate (**14**), and methyl 6-(2-thienylcarbonyl)imidazo[1,2-*b*]pyridazine-2-carbamate (**15**) which are aza analogs of the anthelmintic agents mebendazole, flubendazole and nocadazole. In addition, the preparation of a series of 2-*t*-butylimidazo[1,2-*b*]-pyridazine-6-carboxylic acid derivatives is described. Electrophilic bromination and iodination substitutions of 2-*t*-butyl-6-methylimidazo[1,2-*b*]pyridazine afforded 3-halo derivatives. Methyl 6-(4-fluorobenzoyl)pyridazine-3-carbamate was also prepared for antifilarial evaluation. None of these compounds possessed significant antifilarial activity against *Brugia pahangi* or *Acanthocheilonema viteae* infections in jirds.

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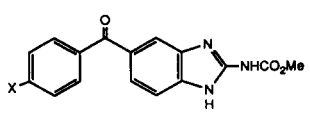
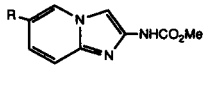
Introduction.

One of the medicinal needs in world health today is for a safe and reliable macrofilaricidal agent which would be effective in controlling the adult worm of the diseases caused by the filarial parasites *Onchocerca volvulus, Wuchereria bancrofti, Brugia malayi* and *Brugia timori.* These four parasites affect some 375 million people in the world causing disability, disfigurement, and blindness [1]. Although the macrocyclic lactone antibiotic, ivermectin, has recently been used to treat the early larval stages (microfilariae) of the disease caused by *O. volvulus* [2,3], no drug has been found to be effective for general use against the adult worm. These points have provided the impetus for these studies to develop an agent which would be effective against the adult worm. Several methyl benzimidazole-2-carbamates including mebendazole (**Ia**) and flubendazole (**Ib**) have demonstrated macrofilaricidal activity in animal studies when they were administered subcutaneously [4,5]. However, low bioavailability of these agents has limited the use of these drugs in the oral treatment of these extraintestinal infections.

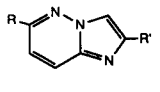
Related to the methyl benzimidazole-2-carbamates are the methyl imidazo[1,2-*a*]pyridine-2-carbamates **II**, which possess a structure-activity relationship similar to the methyl benzimidazole-2-carbamate anthelmintics [6-9]. Since several imidazo[1,2-*b*]pyridazines have demonstrated biological activity including inhibitors of the central nervous system [10], antipyritic and hypothermal activity [11], anticonvulsant activity, analgesic, and antispasmotic activity [12-14], we have prepared a series of methyl imidazo[1,2-*b*]pyridazine-2-carbamates and related derivatives of the general structure **III** for evaluation as anthelmintics.



Ia X = H
b X = F



II where, R = $C_6H_5S(O)$-, $C_6H_5C(O)$-, etc.

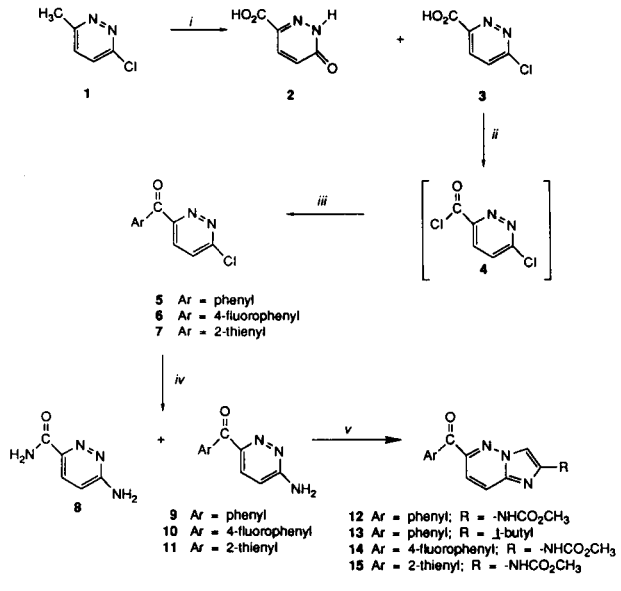


III where, R' = $NHCO_2Me$, Me
R = $C_6H_5C(O)$

To prepare the imidazo[1,2-*b*]pyridazine analogs of the methyl benzimidazole-2-carbamates mebendazole and flubendazole, it was first necessary to prepare the substituted ketone derivatives **5**, **6** and **7**. This was accomplished by Friedel-Craft's acylation of 3-chloropyridazine-6-carboxylic acid chloride (**4**) [15-18]. To prepare the carboxylic acid, **3**, a literature preparation was followed [17,18] which involved the oxidation of 3-chloro-6-methylpyridazine (**1**) with powdered potassium dichromate in concentrated sulfuric acid. From this reaction, **3** was obtained in a 35% yield (Scheme I) along with pyridazin-3-one-6-carboxylic acid monohydrate (**2**) in 31% yield. The formation of compound **2** in this reaction had not been previously observed [15,16]. It was found that compound **2** could be obtained exclusively if the oxidation process was not worked up immediately. We attribute the fact that **2** escaped detection in the initial report because of its high polarity and extreme solubility in the reaction mixture while at the same time this compound has very poor solubility in organic solvents. To prepare the required acid chloride, **3** was heated at reflux in thionyl chloride to produce 3-chloropyridazine-6-carboxylic acid chloride (**4**) in quantitative yield, as indicated by thin layer chromatography. This material was used directly in the subsequent reactions without purification. The Friedel-Craft's condensation of the unstable acid chloride **4** with benzene, fluorobenzene, and thiophene in

the presence of the Lewis acid, anhydrous aluminum chloride [5,6] produced the intermediates 3-benzoyl-6-chloropyridazine (**5**), 3-chloro-6-(4-fluorobenzoyl)pyridazine (**6**) and 3-chloro-6-(2-thienylcarbonyl)pyridazine (**7**) in 90, 88, and 50% yields, respectively. Amination of **5** or **6** using liquid ammonia in a high pressure reaction vessel, proceeded smoothly to yield 3-amino-6-benzoylpyridazine (**9**) and 3-amino-6-(4-fluorobenzoyl)pyridazine (**10**), in 92 and 86% yields, respectively. Amination of **7** under the same conditions produced not only the desired 3-amino-6-(2-thienylcarbonyl)pyridazine (**11**) but also 3-aminopyridazine-6-carboxamide (**8**) in a 2:1 ratio. The formation of **8** most likely occurs *via* a nucleophilic displacement of the thiophene ring. The structure of compounds **5-10** was established by their ^{1}H-nmr spectra and confirmed by elemental analysis and ir data. The ^{1}H-nmr spectrum of **9** showed in addition to a signal at δ 7.30 (s, exchangeable) for the primary amine hydrogens, two doublets centered at δ 6.88 and δ 7.88 which were assigned to the pyridazine H_4 and H_5 protons, respectively. The signals for the H_4, H_5, and H_3 protons of the thiophene ring in **11** appeared at δ 7.26, 8.05, and 8.27, respectively. The splitting pattern of the thiophene hydrogens supported the fact that the Friedel-Craft's acylation took place exclusively at the 2-position. The ir spectrum of **11** revealed a carbonyl at 1624 cm^{-1} and the symmetric and asymmetric stretching vibration of a NH_2 absorbtion at 3450 and 3286 cm^{-1}, respectively. The ir spectra of compounds **5-10** all showed similar patterns.

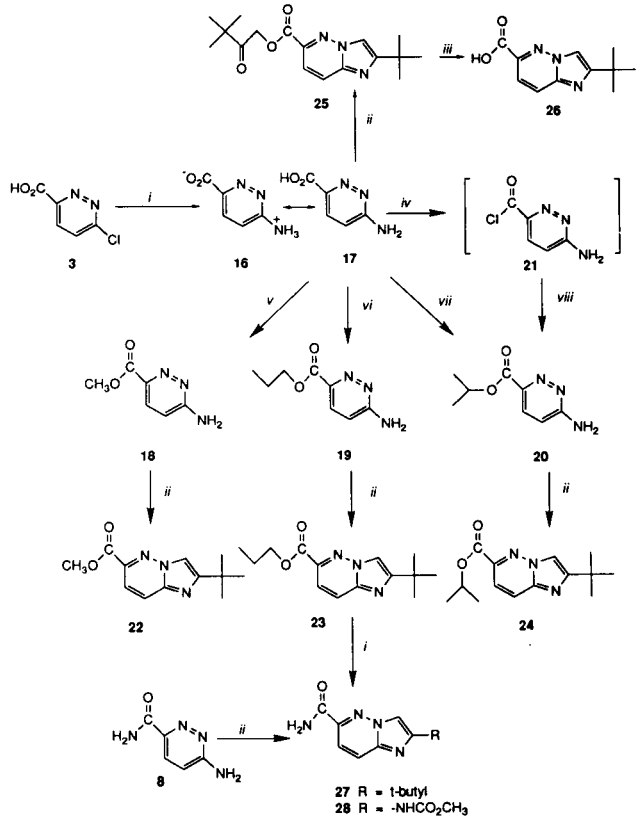
Scheme I



i. potassium dichromate, sulfuric acid; *ii*. thionyl chloride; *iii*. benzene, fluorobenzene or thiophene, aluminum chloride; *iv*. ammonia; *v*. methyl(chloroacetyl)carbamate of 1-bromopinacolone.

Reaction of the 3-amino-6-substituted pyridazines **9**, **10**, and **11** with methyl (chloroacetyl)carbamate afforded the target compounds methyl 6-benzoylimidazo[1,2-*b*]pyridazine-2-carbamate (**12**), methyl 6-(4-fluorobenzoyl)imidazo-[1,2-*b*]pyridazine-2-carbamate (**14**), and methyl 6-(2-thienylcarbonyl)imidazo[1,2-*b*]pyridazine-2-carbamate (**15**), respectively. Since in a previous study [19] it was found that moderate antifilarial activity is retained if the 2-methylcarbamoyl group in mebendazole is replaced by a 2-*t*-butyl group we initiated the synthesis of the 2-*t*-butyl and 2-methyl derivatives in the imidazo[1,2-*b*]pyridazine series. 6-Benzoyl-2-*t*-butylimidazo[1,2-*b*]pyridazine (**13**), was prepared by the reaction of **9** with a molar equivalent of 1-bromopinacolone. The introduction of a *t*-butyl group in **13** instead of the methyl carbamate group in **12** dramatically enhanced the solubility of these compounds in organic solvents. The structures of compounds **12-15** were determined from analysis of their ^{1}H-nmr spectra and further confirmed by the ir spectra and analytical data. The ^{1}H-nmr spectrum of **14** showed two signals at δ 3.75 (s, 3 hydrogens) and δ 10.75 (s, 1 hydrogen, deuterium oxide exchangeable) which were assigned to the methyl and NH groups respectively. The spectrum also showed two sets of doublets at δ 7.83 (1 hydrogen) and δ 8.09 (1 hydrogen) which corresponded to the H_8 and H_7 protons in the pyrid-

Scheme II



i. ammonia; *ii*. 1-bromopinacolone; *iii*. conc. hydrochloric acid, △; *iv*. thionyl chloride; *v*. methanol; *vi*. 1-propanol; *vii*. 2-propanol.

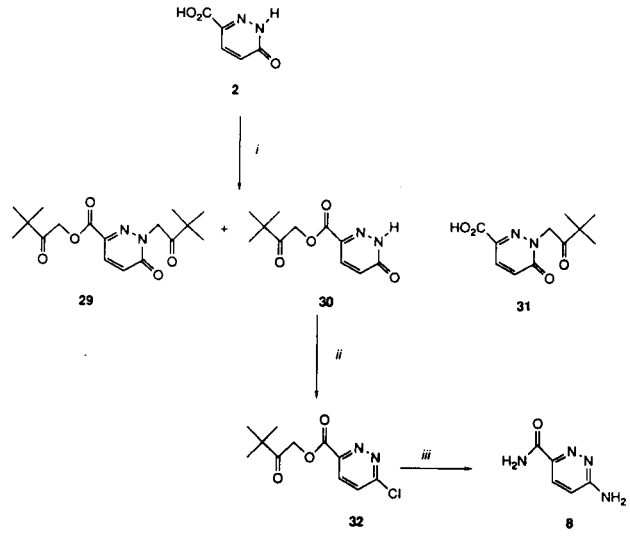
azine ring. In addition, two multiplets were observed at δ 7.91 (m, 3H, H_3 and phenyl H_3 and H_5) and δ 8.08 (m, 2H, phenyl H_2 and H_6). The ir spectrum of **14** supported the assigned structure by showing in addition to the absorbances at 3208, 3012 and 2971 cm^{-1}, assigned to NH and CH (aromatic and aliphatic) stretching vibrations; two absorbances observed at 1736 and 1664 cm^{-1}, which are characteristic of the ester and the ketone carbonyl moieties, respectively. The ir spectra of compounds **12** and **15** were similar to **14**.

To prepare the series of imidazo[1,2-*b*]pyridazine-6-carboxylic esters **22-24**, 3-aminopyridazine-6-carboxylic acid (**17**) [16-18] was initially esterfied and subsequently converted to the bicyclic system. Treatment of **17** with the appropriate alcohol furnished the intermediates methyl 3-aminopyridazine-6-carboxylate (**18**), *n*-propyl 3-aminopyridazine-6-carboxylate (**19**), and isopropyl 3-aminopyridazine-6-carboxylate (**20**), according to a literature procedure [18]. The reaction of **18, 19** and **20** with 1-bromopinacolone, produced the alkyl 2-*t*-butylimidazo[1,2-*b*]-pyridazine-6-carboxylates, methyl 2-*t*-butylimidazo[1,2-*b*]-pyridazine-6-carboxylate (**22**), *n*-propyl 2-*t*-butylimidazo-[1,2-*b*]pyridazine-6-carboxylate (**23**), and isopropyl 2-*t*-butylimidazo[1,2-*b*]pyridazine-6-carboxylate (**24**), in good yields (70-90%). The ^{1}H-nmr spectra of **22, 23** and **24** exhibited a pattern of signals characteristic of the 2,6-disubstituted imidazo[1,2-*b*]pyridazine ring system. The structure of these compounds was further supported by the analytical data and ir spectra. Treatment of **17** with 1-bromopinacolone, resulted in the formation of 1-pinacolyl 2-*t*-butylimidazo[1,2-*b*]pyridazine-6-carboxylate (**25**) in 50% yield. The lack of formation of 2-*t*-butylimidazo[1,2-*b*]-pyridazine-6-carboxylic acid (**26**), in this process suggests that the esterification of the carboxyl group most likely occurs prior to the nucleophilic attack of the pyridazine N-2 that is necessary for the formation of the imidazo[1,2-*b*]-pyridazine ring system. Compound **26** was obtained by the hydrochloric acid catalyzed hydrolysis of the ester **25**. The ir spectrum of **26** showed the distinct absorbances of the OH group at 3200 and 2500 cm^{-1}.

The condensation of 3-aminopyridazine-6-carboxamide (**8**) [18] with 1-bromopinacolone and methyl (chloroacetyl)-carbamate produced 2-*t*-butyl-6-carboxamidoimidazo[1,2-*b*]pyridazine (**27**) and methyl 6-carboxamidoimidazo[1,2-*b*]pyridazine-2-carbamate (**28**), respectively. Compound **27** was also obtained in quantitative yield by heating **23** in liquid ammonia in a high pressure reaction vessel.

Treatment of pyridazin-6-one-3-carboxylic acid (**2**) with excess 1-bromopinacolone afforded a mixture of 1-pinacolyl *N*1-[1-pinacolyl]pyridazin-6-one-3-carboxylate (**29**) along with 1-pinacolyl pyridazin-6-one-3-carboxylate (**30**) in 58 and 10% yields, respectively. None of the *N*-monosubstituted free carboxylic acid **31** was observed. Chlorination of **30** by heating at reflux in phosphorous oxychloride furnished 1-pinacolyl 3-chloropyridazine-6-carboxylate (**32**) in quantitative yield. Treatment of **32**, with liquid ammonia, resulted in the formation of 3-aminopyridazine-6-carboxamide (**8**) with no trace of 1-pinacolyl 3-aminopyridazine-6-carboxylate present as determined by thin layer chromatography.

Scheme III



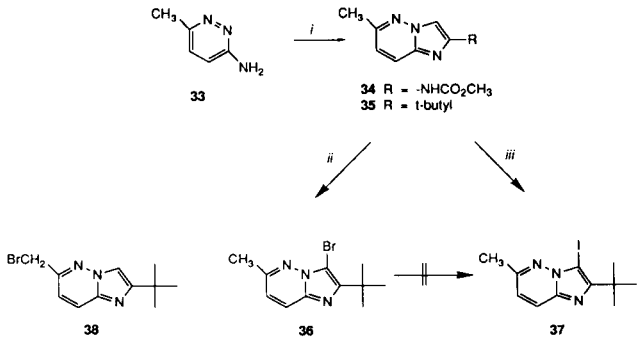
i. 1-bromopinacolone; thionyl chloride; *iii*. ammonia.

3-Amino-6-methylpyridazine (**33**) [18] was condensed with methyl (chloroacetyl)carbamate and 1-bromopinacolone to afford methyl 6-methylimidazo[1,2-*b*]pyridazine-2-carbamate (**34**) and 2-*t*-butyl-6-methylimidazo[1,2-*b*]pyridazine (**35**) in 68 and 57% yields, respectively. The structure of both compounds was established by the ^{1}H-nmr data, ir spectra and analytical data. The ir spectrum of **34** supported the structure by showing the stretching vibrations of the NH and the ester carbonyl at 3201 and 1723 cm^{-1}, respectively.

Since the C-3 position in **35** would be expected to be sterically hindered due to the bulky *t*-butyl group at position 2 an attempt was made to prepare the 6-bromomethyl derivative **38**. Compound **35** was reacted with *N*-bromosuccinimide under free radical conditions, in benzene in the presence of 2,2′-azobis(2-methylpropionitrile). However, this reaction resulted in the formation of 3-bromo-2-*t*-butyl-6-methylimidazo[1,2-*b*]pyridazine (**36**) in quantitative yield rather than of the desired 6-bromomethyl analog. The structure of compound **36** was established by ^{1}H-nmr and ir spectra. The ^{1}H-nmr spectrum showed, in addition to the signals at δ 1.44 (s, 9H) and δ 2.56 (s, 3H), assigned to the *t*-butyl and methyl groups, respectively; two sets of doublets at δ 7.18 and δ 7.98 which could be assigned to the protons H_8 and H_7, respectively. The spectrum was devoid of any absorbance that would correspond

to the H_3 proton. The synthesis of 2-*t*-butyl-3-iodo-6-methylimidazo[1,2-*b*]pyridazine (**37**) in 64% yield was accomplished by reaction of **35** with *N*-iodosuccinimide.

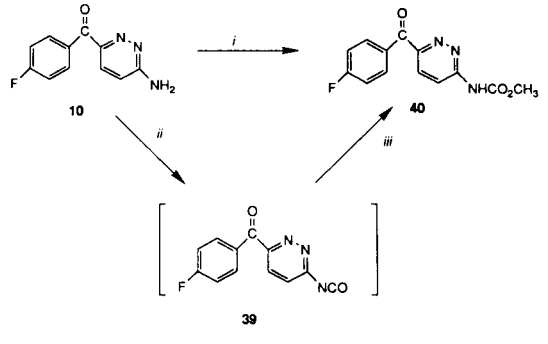
Scheme IV



i: methyl(chloroacetyl)carbamate or 1-bromopinacolone; *ii*: N-bromosuccinimide, 2,2'-azobis-(2-methylpropionitrile), benzene; *iii*: N-iodosuccinimide, 2,2'-azobis(2-methylpropionitrile).

Methyl 6-(4-fluorobenzoyl)pyridazine-3-carbamate (**40**), was prepared by two methods. Heating 3-amino-6-(4-fluorobenzoyl)pyridazine (**10**) with methyl chloroformate at reflux for 12 hours under a nitrogen atmosphere (Scheme V), produced the target compound **40** in 94% yield. Alternatively, compound **40** was also prepared by heating equimolar amounts of **10** and oxalyl chloride at reflux, with the exclusion of moisture for 2 hours. The resulting unstable isocyanate derivative **39** was treated with methanol to produce **40** in 42% yield. The ^{1}H-nmr spectrum showed the pattern for the aromatic moiety of the molecule as well as the signals corresponding to the -NH and methyl groups at δ 11.33 and δ 3.75, respectively. The ir spectrum supported the structure by showing the stretching vibrations at 1795 and 1736 cm^{-1} characteristic of the carbonyl and ester carbonyl, respectively. Also apparent in this spectrum was the absorbance corresponding to the CH stretching vibration at 2966 cm^{-1}. The absence of absorbance of a $-NH_2$ symmetric and asymmetric vibrations at 3489 and 3332 cm^{-1} is a further evidence for the formation of the target compound.

Scheme V



i: methyl chloroformate; *ii*: oxalyl chloride, 1,2-dichloroethane; *iii*: methanol.

The antifilarial testing results for the compounds prepared in this study are summarized in Table I. None of the target compounds demonstrated any significant activity. This is interesting in view of the significant antifilarial activity which is observed for mebendazole and flubendazole. Several of the intermediate 3-chloro-6-substituted pyridazines exhibited activity against *A. viteae* at the dosage tested. No activity against *B. pahangi* was observed for these compounds.

Table I

Antifilarial Effects of Some Imidazo[1,2-*b*]pyridazines and Related Compounds Against Transplanted Adult *B. pahangi* and *A. viteae* in Jirds (*Meriones unguiculatus*)

Compound	Macrofilariae at necropsy [a] % Reduction in Comparison to untreated controls	
	Bp [b]	Av [c]
5	0	60
6	0	69
7	54	7
8	0	19
9	0	7
10	14	87
11	42	64
12	0	0
13	0	0
14	0	0
15	0	0
22	0	38
23	0	0
25	0	37
26	0	64
27	9	---
28	26	---
29	0	---
30	12	0
32	21	---
35	0	81
36	0	42
40	0	---
Flubendazole [d]	100	100

[a] All compounds were administered subcutaneously at a dosage of 100 mg/kg for 5 days. A compound is considered active if the percent reduction of macrofilariae is greater than 65% compared to untreated controls. [b] *Brugia pahangi*. [c] *Acanthocheilonema viteae*. [d] Administered at a subcutaneous dosage of 1.56 mg/kg for 5 days.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. Rotary evaporations were 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 cm) which was packed with normal phase silica, (EM Reagent Kiesgel 60 (230-400) mesh ASTM). Flash and open-bed chromatography was preformed using normal phase silica, EM Reagent Kieselgel 60

(230-400 mesh ASTM). The ^{1}H-nmr spectra were obtained using IBM WM 360 or IBM WP 270 SY spectrometers. Nmr spectra were recorded using either deuteriochloroform as a solvent and tetramethylsilane as an internal standard or dimethyl sulfoxide-d_6 (DMSO-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. Analytical samples were dried *in vacuo* (vacuum pump) at 78° in the presence of phosphorus pentoxide for at least 12 hours unless otherwise specified. Elemental analyses were obtained from M-H-W Laboratories, Phoenix, AZ.

3-Benzoyl-6-chloropyridazine (**5**).

3-Chloropyridazine-6-carboxylic acid (**3**) [15,16] (1.58 g, 10 mmoles) was heated at reflux for 2 hours in thionyl chloride (75 ml) under an argon atmosphere. The excess thionyl chloride was removed under aspirator pressure and the resulting residue was co-evaporated with benzene (50 ml) under high vacuum. Benzene (75 ml) was added to the residue and the reaction flask was chilled to 0° in a sodium chloride/ice bath. Anhydrous aluminum chloride (3.3 g, 25 mmoles) was added portionwise to the stirred solution. After the addition was complete, the mixture was allowed to warm to room temperature and then was heated at reflux for 6 hours. The excess benzene was removed under aspirator pressure leaving a dark brown solid which was added portionwise to crushed ice (200 g). The mixture was allowed to warm to room temperature and then extracted with diethyl ether (5 x 100 ml). The organic extracts were combined, dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness. The residue was then applied to the top of a silica column (2.5 x 30 cm column) and eluted with chloroform/hexanes, (1/1). The fractions containing the product; R_f, 0.5 (chloroform) were combined and evaporated to dryness under aspirator pressure to yield 1.94 g of analytically pure product (89%), mp 82° dec; ir (potassium bromide): 3051, 1651, 1598, 1559, 1448, 1402, 1337, 1271, 1140, 695 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 7.58 (m, 2H, phenyl H_3 and H_5), 7.71 (m, 1H, phenyl H_4), 7.99 (d, 2H, pyridazine H_4 and H_5), 8.21 (m, 2H, phenyl H_2 and H_6).

Anal. Calcd. for $C_{11}H_7ClN_2O$: C, 60.42; H, 3.23; N, 12.82. Found: C, 60.66; H, 3.41; N, 12.62.

3-(4-Fluorobenzoyl)-6-chloropyridazine (**6**).

3-Chloropyridazine-6-carboxylic acid (**3**) (1.58 g, 10 mmoles) was heated at reflux for 2 hours in thionyl chloride (75 ml) under an atmosphere of argon. The excess thionyl chloride was removed under aspirator pressure followed by high vacuum while maintaining the temperature below 40°. Fluorobenzene (75 ml) was added to the residue and the flask was chilled to 0° in a sodium chloride/ice bath. Anhydrous aluminum chloride (3.3 g, 25 mmoles) was added to the stirred solution portionwise. After the addition was complete, the mixture was allowed to warm to room temperature and then was heated at reflux for 6 hours. The excess fluorobenzene was removed under aspirator pressure followed by high vacuum. The residue was added portionwise to crushed ice (200 g). The mixture was allowed to warm to room temperature and then extracted with chloroform (5 x 100 ml). The organic extracts were combined, washed with water (100 ml), dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness. The residue was then applied to the top of a silica column (2.5 x 30 cm) and eluted with chloroform. The fractions containing the product; R_f, 0.3 (chloroform) were combined and evaporated to dryness under aspirator pressure to yield 2.07 g (88%) of pure product. An analytical sample was prepared by flash chromatography on normal phase silica gel using chloroform as the eluent; R_f, 0.3 (chloroform), mp 107-108°; ir (potassium bromide): 3116, 3077, 3038, 1664, 1598, 1559, 1500 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 7.42 (m, 2H, phenyl H_3 and H_5), 8.13 (m, 2H, phenyl H_2 and H_4), 8.19 (d, 1H, pyridazine H_5), 8.25 (d, 1H, pyridazine H_4).

Anal. Calcd. for $C_{11}H_6ClFN_2O$: C, 55.83; H, 2.56; N, 11.84. Found: C, 55.63; H, 2.67; N, 11.80.

3-Chloro-6-(2-thienylcarbonyl)pyridazine (**7**).

3-Chloropyridazine-6-carboxylic acid (**3**) (3.17 g, 20 mmoles) was heated at reflux for 2 hours in thionyl chloride (100 ml) under an argon atmosphere. The excess thionyl chloride was removed under reduced pressure and methylene chloride (100 ml) was added to the residue and the solution was chilled to 0°. Anhydrous aluminum chloride (2.67 g, 20 mmoles) was added portionwise to the solution while the temperature was maintained at 0°. After complete addition, thiophene (1.68 g, 1.61 ml, 20 mmoles) was added with continuous stirring. The solution was maintained at 0° for an additional 2 hours and then allowed to warm to room temperature. Ice cold water (100 ml) was added to the mixture and the organic layer was decanted. The water layer was extracted with diethyl ether (4 x 100 ml). The ether extracts were combined with the methylene chloride, dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure. The residue was purified by column chromatography (2 x 30 cm) using normal phase silica gel and chloroform as the eluent. The fractions containing the product; R_f, 0.36 (chloroform) were combined and the solvent removed under reduced pressure to yield 2.29 g (51%) of analytically pure product, mp 139-140°; ir (potassium bromide): 3103, 1644, 1559, 1500, 1409, 1363, 1147 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 7.34 (q, 1H, thiophene H_4), 8.19 (d, 1H, pyridazine H_4), 8.22 (q, 1H, thiophene H_5), 8.30 (m, 2H, pyridazine H_5 and thiophene H_3).

Anal. Calcd. for $C_9H_5ClN_2OS$: C, 48.11; H, 2.24; N, 12.47. Found: C, 48.05; H, 2.32; N, 12.24.

3-Amino-6-benzoylpyridazine (**9**).

3-Benzoyl-6-chloropyridazine (**5**) (1.43 g, 6.5 mmoles) was heated to 100° with liquid ammonia (50 ml) in a sealed steel reaction vessel for 36 hours. At the end of this period, the reactor was cooled (−78°) in a dry ice/2-propanol bath, opened and the excess ammonia was allowed to evaporate. The remaining residue (1.26 g, 98% crude yield) was purified by flash chromatography (1 cm x 10 cm column) using normal phase silica gel and chloroform as the eluent to give 1.23 g (95%) of analytically pure product; R_f, 0.32 (chloroform), mp 122°; ir (potassium bromide): 3352, 3175, 3051, 1651, 1618, 1598, 1448, 1382, 1297, 702 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 6.89 (d, 1H, pyridazine H_4), 7.24 (2H, NH_2, deuterium oxide exchangeable), 7.51 (m, 2H, phenyl H_3 and H_5), 7.62 (m, 1H, phenyl H_4), 7.87 (d, 1H, pyridazine H_5), 7.96 (m, 2H, phenyl H_2 and H_6).

Anal. Calcd. for $C_{11}H_9N_3O$: C, 66.32; H, 4.55; N, 21.09. Found: C, 66.13; H, 4.68; N, 20.88.

3-Amino-6-(4-fluorobenzoyl)pyridazine (**10**).

3-(4-Fluorobenzoyl)-6-chloropyridazine (**7**) (2.36 g, 10 mmoles) was heated to 100° with liquid ammonia (50 ml) in a sealed steel reaction vessel for 36 hours. At the end of this period, the reactor was cooled (−78°) in a dry ice/2-propanol bath, opened and the excess ammonia was allowed to evaporate. The remaining residue (1.9 g, 90% crude yield) was purified by flash chromatography (1 x 10 cm column) using normal phase silica gel and chloroform as an eluent to afford 1.86 g (86%) of pure product. An analytical sample was prepared by flash chromatography using normal phase silica gel and chloroform/methanol (95/5) as an eluent; R_f, 0.34 (chloroform/methanol, 9/1), mp 153°; ir (potassium bromide): 3489, 3332, 3162, 3044, 1651, 1618, 1598, 1509, 1461 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 6.89 (d, 1H, pyridazine H_4), 7.26 (s, 2H, NH_2, deuterium oxide exchangeable), 7.33 (m, 2H, phenyl H_3 and H_5), 7.85 (d, 1H, pyridazine H_5), 8.10 (m, 2H, phenyl H_2 and H_6).

Anal. Calcd. for $C_{11}H_8FN_3O$: C, 60.83; H, 3.71; N, 19.35. Found: C, 60.75; H, 3.85; N, 19.27.

3-Amino-6-(2-thienylcarbonyl)pyridazine (**11**) and 3-Aminopyridazine-6-carboxamide (**8**).

A mixture of 3-chloro-6-(2-thienylcarbonyl)pyridazine (**7**) (1.12 g, 5 mmoles) with liquid ammonia (50 ml) was heated in a sealed reaction vessel at 100° for 36 hours. At the end of this period, the reactor was cooled to −78° in a dry ice/2-propanol bath, opened and the excess ammonia was allowed to evaporate. The crude reaction mixture was purified by absorbing it on a small quantity of silica gel (15 g) and applying it to the top of a column (1 x 20 cm) packed with normal phase silica gel and chloroform as an eluent. Two products were obtained. Eluting first from the column was the desired 3-amino-6-(2-thienylcarbonyl)pyridazine (**11**) (yield 65%); R_f, 0.36 (chloroform/methanol, 9/1), mp 172-173°; ir (potassium bromide): 3450, 3286, 3110, 3077, 1624, 1592, 1500, 1467, 1409 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 6.88 (d, 1H, pyridazine H_4), 7.26 (q, 1H, thiophene H_4), 7.86 (d, 1H, pyridazine H_5), 8.05 (q, 1H, thiophene H_5), 8.27 (q, 1H, thiophene H_3).

Anal. Calcd. for $C_9H_7N_3OS$: C, 52.67; H, 3.44; N, 20.47. Found: C, 52.69; H, 3.61; N, 20.41.

Continued elution with chloroform gave 3-aminopyridazine-6-carboxamide (**8**) (yield 30%); R_f, 0.15 (chloroform/methanol, 9/1), mp 264° (lit [18] 260-262°), ir (potassium bromide): 3463, 3378, 3313, 3254, 3123, 3038, 1683, 1579, 1474, 1415 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 6.81 (d, 1H, H_4), 6.89 (s, 2H, NH_2 (amine), deuterium oxide exchangeable), 7.39 (s, 1H, NH (amide), deuterium oxide exchangeable), 7.74 (d, 1H, H_5), 8.02 (s, 1H, NH (amide), deuterium oxide exchangeable).

Methyl 6-Benzoylimidazo[1,2-*b*]pyridazine-2-carbamate (**12**).

Methyl (chloroacetyl)carbamate [3] (0.25 g, 1.65 mmoles) and 3-amino-6-benzoylpyridazine (**9**) (0.3 g, 1.5 mmoles) were dissolved in 10 ml of dimethylformamide 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 150 ml of water 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 in the air to give compound **12** (0.28 g, 62%). An analytical sample was prepared by recrystallization from methanol; R_f, 0.61 (chloroform/methanol, 9/1), mp 255-256°; ir (potassium bromide): 3201, 3031, 2959, 1742, 1664, 1598, 1269, 1265 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 3.73 (s, 3H, CH_3), 7.56 (d, 1H, H_8), 7.67 (m, 2H, phenyl H_3 and H_5), 7.81 (m, 1H, phenyl H_4), 7.89 (d, 1H, H_7), 8.09 (m, 3H, H_3 and phenyl H_2 and H_6), 10.31 (s, 1H, NH, deuterium oxide exchangeable).

Anal. Calcd. for $C_{15}H_{12}N_4O_3$: C, 60.80; H, 4.08; N, 18.91. Found: C, 60.54; H, 4.27; N, 18.69.

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

3-Amino-6-benzoylpyridazine (**9**) (0.3 g, 1.5 mmoles) and 1-bromopinacolone (0.3 g, 1.7 mmoles) were heated at 100° for 5 hours in 10 ml of dimethylformamide. At the end of this period, water (150 ml) was added to the reaction mixture and the whole solution was repeatedly extracted with chloroform (10 x 50 ml). The organic extracts were then combined, washed with water (100 ml), dried over anhydrous magnesium sulfate, filtered, and evaporated to the product (0.27 g, 65%). An analytical sample was prepared by flash chromatography on normal phase silica gel using chloroform as the eluent; R_f, 0.5 (hexane/ethyl acetate, 3/1), 0.5 (chloroform/methanol, 96/4), mp 105-107°; ir (potassium bromide): 3149, 3070, 3044, 2972, 1657, 1598, 1520, 1448, 1278 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 1.34 (s, 9H, *t*-Bu), 7.56 (m, 2H, phenyl H_3 and H_5), 7.66 (d, 1H, H_8), 7.73 (m, 1H, phenyl H_4), 8.02 (m, 2H, phenyl H_2 and H_6), 8.22 (s, 1H, H_3), 8.23 (d, 1H, H_7).

Anal. Calcd. for $C_{17}H_{17}N_3O$: C, 73.09; H, 6.14; N, 15.04. Found: C, 72.97; H, 6.03; N, 14.98.

Methyl 6-(4-Fluorobenzoyl)imidazo[1,2-*b*]pyridazine-2-carbamate (**14**).

Methyl (chloroacetyl)carbamate [3] (0.24 g, 1.6 mmoles) and 3-amino-6-(4-fluorobenzoyl)pyridazine (**10**) (0.32 g, 1.47 mmoles) were dissolved in 10 ml of dimethylformamide 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 150 ml of water was added to furnish a precipitate. This precipitate was collected by filtration, washed with water (100 ml), methanol (100 ml), and methylene chloride (100 ml) then dried in the air to give compound **7** (0.2 g, 45%). An analytical was prepared by recrystallization from methanol. An analytical sample was prepared by open bed chromatography on normal phase silica gel and using chloroform as the eluent; R_f, 0.66 (chloroform/methanol, 9/1), mp 269-271°; ir (potassium bromide): 3208, 3182, 3012, 2971, 1736, 1664, 1598, 1507 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 3.75 (s, 3H, CH_3), 7.83 (d, 1H, H_8), 7.91 (m, 3H, H_3 and phenyl H_3 and H_5), 8.08 (m, 2H, phenyl H_2 and H_6), 8.09 (d, 1H, H_7), 10.75 (s, 1H, NH, deuterium oxide exchangeable).

Anal. Calcd. for $C_{15}H_{11}FN_4O_3$: C, 57.32; H, 3.53; N, 17.83. Found: C, 57.20; H, 3.65; N, 17.68.

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

Methyl (chloroacetyl)carbamate [3] (0.260 g, 1.7 mmoles) and 3-amino-6-(2-thienylcarbonyl)pyridazine (**11**) (0.31 g, 1.5 mmoles) were dissolved in 10 ml of dimethylformamide 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 150 ml of water was added to furnish a precipitate. This precipitate was collected by filtration, washed with water (100 ml), methanol (100 ml), and methylene chloride (100 ml) then dried in the air to give compound **15** (0.263 g, 58%). An analytical sample was prepared by recrystallization from methanol; R_f, 0.46 (chloroform/methanol, 96/4), mp 233-235°; ir (potassium bromide): 3188, 3116, 3084, 2953, 1736, 1710, 1631, 1579,

1409, 1369, 1271 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 3.73 (s, 3H, CH_3), 7.31 (q, 1H, thiophene H_4), 7.73 (d, 1H, H_8), 8.08 (s, 1H, H_3), 8.14 (q, 1H, thiophene H_5), 8.26 (m, 2H, H_7 and thiophene H_3), 10.73 (s, 1H, NH, deuterium oxide exchangeable).

Anal. Calcd. for $C_{13}H_{10}N_4O_3S$: C, 51.65; H, 3.33; N, 18.53. Found: C, 51.47; H, 3.46; N, 18.37.

3-Aminopyridazine-6-carboxamide (**8**).

1-Pinacolyl 3-chloropyridazine-6-carboxylate (**33**) (0.5 g, 2 mmoles) and 20 ml of liquid ammonia were heated to 100° for 22 hours in a sealed steel reaction vessel. At the end of this period, the vessel was cooled in a dry ice/2-propanol bath (−78°), opened, and allowed to warm up to room temperature and the excess ammonia to evaporate at a slow rate. The white residue that remained was crystallized from ethanol to give 0.24 g (90%) of product; R_f, 0.15 (chloroform/methanol, 9/1), mp 264° (lit [18] 260-262°). Physicochemical data compared identically with **8** prepared previously.

2-*t*-Butyl-6-carboxamidoimidazo[1,2-*b*]pyridazine (**27**).

Method A.

n-Propyl 2-*t*-butylimidazo[1,2-*b*]pyridazine-6-carboxylate (**23**) (0.27 g, 1 mmole) and 20 ml of liquid ammonia were heated at 100° for 22 hours in a sealed reaction vessel. The vessel was cooled in a dry ice/2-propanol bath (−78°), opened, and allowed to warm to room temperature and the excess ammonia to evaporate at a slow rate. The residue was crystallized from methanol to afford **27** in quantitative yield; R_f, 0.5 (chloroform/methanol, 9/1), mp 175-176°; ir (potassium bromide): 3404, 3299, 3182, 2959, 1670, 1605, 1520 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 1.35 (s, 9H, *t*-Bu), 7.63 (d, 1H, H_8), 7.81 (s, 1H, NH, deuterium oxide exchangeable), 8.04 (s, 1H, H_3), 8.13 (d, 1H, H_7), 8.30 (s, 1H, NH, deuterium oxide exchangeable).

Anal. Calcd. for $C_{11}H_{14}N_4O$: C, 60.53; H, 6.46; N, 25.67. Found: C, 60.76; H, 6.59; N, 25.48.

Method B.

3-Aminopyridazine-6-carboxamide (**8**) (0.138 g, 1 mmoles) and 1-bromopinacolone (0.3 g, 1.6 mmoles) were mixed and heated at 100° in dimethylformamide (10 ml) for 5 hours. The solvent was then removed under reduced pressure (aspirator followed by high vacuum) and the residue was extracted with hexanes (4 x 25 ml). The hexanes extracts were combined and evaporated to dryness to afford **27** (0.15 g, 70% crude yield). The compound was identical in all respects with the compound prepared according to Method A.

Methyl 6-Carboxamidoimidazo[1,2-*b*]pyridazine-2-carbamate Hydrate (**28**).

3-Aminopyridazine-6-carboxamide (**8**) (0.3 g, 2 mmoles) and methyl (chloroacetyl)carbamate (0.4 g, 2.6 mmoles) were heated with continuous stirring at 100° in dimethylformamide (10 ml) for 10 hours. The reaction mixture was cooled to room temperature and water (50 ml) was added to effect the formation of a precipitate which was collected by filtration, washed with water (10 ml), methanol (10 ml), then chloroform (10 ml) to give 0.43 g of product (85%). An analytical sample was prepared by recrystallization from methanol; R_f, 0.43 (chloroform/methanol, 9/1), mp 293°; ir (potassium bromide): 3476, 3286, 3175, 3005, 2959, 1729, 1700, 1611, 1592, 1461, 1435 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 3.71 (s, 3H, CH_3), 7.67 (d, 1H, H_8), 7.80 (s, 1H, NH amide, deuterium oxide exchangeable), 8.04 (d, 1H, H_7), 8.08 (s, 1H, H_3), 8.20 (s, 1H, NH amide, deuterium oxide exchangeable), 10.68 (s, 1H, NH (carbamate), deuterium oxide exchangeable).

Anal. Calcd. for $C_9H_9N_5O_3 \cdot \frac{1}{2}H_2O$: C, 44.26; H, 4.12; N, 28.68. Found: C, 44.26; H, 4.00; N, 28.62.

Isopropyl 3-aminopyridazine-6-carboxylate (**20**).

Method A.

3-Aminopyridazine-6-carboxylic acid (**17**) [8] (1.8 g, 13 mmoles) was heated at reflux in a mixture of 2-propanol/benzene (200 ml, 1/1) and concentrated hydrochloric acid (38%, 1 ml) for 24 hours under a Dean-Stark trap (20 ml capacity). At the end of this period, the solvent was removed under aspirator pressure and 200 ml of additional fresh solvent was added. The solution was heated at reflux for an additional 24 hours. At the end of this period, the reaction mixture was filtered hot. Normal phase silica gel (7 gm) was added to the filtrate and the solvent was removed under aspirator pressure followed by high vacuum. The residue was then applied to the top of a silica column (2.5 x 20 cm) and eluted with chloroform to give 1.49 g (63%) of pure product; R_f, 0.25 (chloroform/methanol, 9/1), mp 168-170°; ir (potassium bromide): 3391, 3326, 3195, 3070, 2979, 1723, 1644, 1598, 1474, 1356, 1284, 1160, 1108 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 1.3 (d, 6H, 2 x CH_3), 5.13 (m, 1H, CH-O), 6.77 (d, 1H, H_4), 7.12 (s, 1H, NH_2, deuterium oxide exchangeable), 7.73 (d, 1H, H_5).

Anal. Calcd. for $C_8H_{11}N_3O_2$: C, 53.03; H, 6.12; N, 23.19. Found: C, 52.89; H, 6.01; N, 23.12.

Method B.

3-Aminopyridazine-6-carboxylic acid (**17**) [4] (0.5 g, 3.6 mmoles) was heated at reflux for 3 hours in thionyl chloride (25 ml) under an atmosphere of argon. Excess thionyl chloride was removed under aspirator pressure and 2-propanol (50 ml) was added. The mixture was heated at reflux for 1 hour. The excess 2-propanol was removed under aspirator pressure and the residue was applied to the top of a silica column (normal phase, 2 cm x 10 cm) and eluted with chloroform to give 0.21 g of product (32%); R_f, 0.25 (chloroform/methanol, 9/1), mp 168-170°; ir (potassium bromide): 3391, 3326, 3195, 3070, 2979, 1723, 1644, 1598, 1474, 1356, 1284, 1160, 1108 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 1.3 (d, 6H, CH_3), 5.13 (m, 1H, CH), 6.77 (d, 1H, H_4), 7.12 (s, 1H, deuterium oxide exchangeable), 7.73 (d, 1H, H_5).

Methyl 2-*t*-Butylimidazo[1,2-*b*]pyridazine-6-carboxylate (**22**).

Methyl 3-aminopyridazine-6-carboxylate (**18**) [18] (0.153 g, 1 mmole) and 1-bromopinacolone (0.19 g, 1.1 mmoles) were heated at 100° for 5 hours in 10 ml of dimethylformamide. At the end of this period, water (50 ml) was added to the reaction mixture and the whole solution was repeatedly extracted with chloroform (10 x 50 ml). The chloroform extracts were then combined, washed with water (100 ml), dried over anhydrous magnesium sulfate, filtered, and evaporated to the product (0.21 g, 90%). An analytical sample was prepared by flash chromatography (1 x 7 cm column) on normal phase silica gel and using chloroform as an eluent; R_f, 0.71 (chloroform/methanol, 9/1), mp 104°; ir (potassium bromide): 3125, 2966, 1729, 1611, 1526, 1435, 1284 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 1.34 (s, 9H, *t*-Bu), 3.93 (s, 3H, CH_3), 7.66 (d, 1H, H_8), 8.17 (d, 1H, H_7), 8.28 (s, 1H, H_3).

Anal. Calcd. for $C_{12}H_{15}N_3O_2$: C, 61.78; H, 6.48; N, 18.01. Found: C, 61.47; H, 6.47; N, 17.89.

n-Propyl 2-*t*-Butylimidazo[1,2-*b*]pyridazine-6-carboxylate (**23**).

Compound **23** was prepared in 70% yield (crude) from *n*-propyl 3-aminopyridazine-6-carboxylate (**19**) [18] (0.36 g, 2 mmoles), and 1-bromopinacolone (0.5 g, excess) using the same procedure applied to afford compound **13**. An analytical sample was prepared by flash chromatography on normal phase silica gel using chloroform as an eluent; R_f, 0.77 (chloroform/methanol, 9/1), mp 98-100°; ir (potassium bromide): 3123, 3077, 2966, 1735, 1611, 1539, 1533, 1291 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 0.96 (t, 3H, CH_3), 1.35 (s, 9H, *t*-Bu), 1.73 (m, 2H, CH_2), 4.31 (t, 2H, CH_2-O), 7.66 (d, 1H, H_8), 8.16 (d, 1H, H_7), 8.30 (s, 1H, H_3).

Anal. Calcd. for $C_{14}H_{19}N_3O_2$: C, 64.34; H, 7.33; N, 16.08. Found: C, 64.52; H, 7.30; N, 15.93.

Isopropyl 2-*t*-Butylimidazo[1,2-*b*]pyridazine-6-carboxylate (**24**).

Compound **24** was prepared in 74% yield (crude) from isopropyl 3-aminopyridazine-6-carboxylate (**20**), and 1-bromopinacolone using the same procedure applied to prepare compound **22**. An analytical sample was prepared by flash chromatography using chloroform as the eluent; R_f, 0.76 (chloroform/methanol, 9/1), mp 116-117°; ir (potassium bromide): 3123, 3084, 2966, 1736, 1605, 1530, 1526, 1291 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 1.33 (s, 9H, *t*-Bu), 1.35 (d, 6H, 2 x CH_3), 5.21 (m, 1H, CH-O-CO), 7.64 (d, 1H, H_8), 8.15 (d, 1H, H_7), 8.30 (s, 1H, H_3).

Anal. Calcd. for $C_{14}H_{19}N_3O_2$: C, 64.34; H, 7.33; N, 16.08. Found: C, 64.57; H, 7.43; N, 16.19.

1-Pinacolyl 2-*t*-Butylimidazo[1,2-*b*]pyridazine-6-carboxylate (**25**).

3-Aminopyridazine-6-carboxylic acid (**17**) (1 g, 7 mmoles) and 1-bromopinacolone (2 g, 11 mmoles) were heated in dimethylformamide (25 ml) at 100° for 5 hours. Water (100 ml) was added to the mixture and the solution was extracted with chloroform (5 x 100 ml). The combined chloroform extracts were then washed with water (100 ml), dried over anhydrous magnesium sulfate, filtered, and reduced to dryness under aspirator pressure. The residue was then purified by flash chromatography using normal phase silica gel and chloroform as an eluent. The fractions containing the product; R_f, 0.56 (chloroform/methanol, 96/4), R_f, 0.75 (chloroform/methanol, 9/1) were combined and evaporated to dryness under aspirator pressure to give 1.19 g (52%) of analytically pure product, mp 163°; ir (potassium bromide): 3110, 3084, 2966, 1755, 1723, 1611, 1539, 1520, 1284, 1225, 1075 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 1.16 (2, 9H, *t*-Bu, keto ester), 1.35 (s, 9H, *t*-Bu of imidazo ring), 5.37 (s, 2H, CH_2), 7.67 (d, 1H, H_8), 8.20 (d, 1H, H_7), 8.30 (s, 1H, H_3).

Anal. Calcd. for $C_{17}H_{23}N_3O_3$: C, 64.33; H, 7.30; N, 13.24. Found: C, 64.13; H, 7.40; N, 13.07.

2-*t*-Butylimidazo[1,2-*b*]pyridazine-6-carboxylic Acid (**26**).

1-Pinacolyl 2-*t*-butylimidazo[1,2-*b*]pyridazine-6-carboxylate (**25**) (0.65 g, 2 mmoles) and water (50 ml) that contained concentrated hydrochloric acid (1 ml) was heated at reflux for 12 hours. At the end of this period thin layer chromatography showed the complete disappearance of the starting material and the formation of a much more polar compound that remained at the origin. At this point the mixture was filtered and evaporated to dryness under high vacuum (>50°). The white solid that remained was triturated with acetone then chloroform and finally air dried to give 0.41 g of pure product (80%), mp 230-231°; ir (potassium bromide): 3200-2500, 1755, 1651, 1552, 1467, 1389, 1369, 1193, 1147 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 1.38 (s, 9H, *t*-Bu), 3.90 (bs, 1H, OH), 7.89 (d, 1H, H_8), 8.30 (d, 1H, H_7), 8.45 (s, 1H, H_3).

Anal. Calcd. for $C_{11}H_{13}N_3O_2 \cdot \frac{1}{2}HCl \cdot \frac{3}{4}H_2O$: C, 52.64; H, 6.02; N, 16.74. Found: C, 52.49; H, 6.07; N, 16.28.

1-Pinacolyl *N*-[1-Pinacolyl]pyridazin-6-one-3-carboxylate (**29**) and 1-Pinacolyl Pyridazin-6-one-3-carboxylate (**30**).

Pyridazin-6-one-3-carboxylic acid (**2**) (1.39 g, 1 mmole) and 1-bromopinacolone (2 g, 1.1 mmoles) were dissolved in boiling dimethylformamide (25 ml) for 5 minutes and then stirred at 100° for 5 hours. The mixture was cooled to room temperature and water (100 ml) was added. The solution was extracted with methylene chloride (6 x 50 ml). The organic extracts were combined, washed with water (100 ml), dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness under reduced pressure (water aspirator followed by high vacuum). The residue was applied to the top of a silica column (2.5 x 15 cm) packed with normal phase silica gel and eluted with chloroform. Two compounds were separated by this technique.

Compound **29**.

The fractions which contained **29** [R_f, 0.53 (ethyl acetate/hexanes, 3/1), 0.9 (chloroform/methanol, 9/1)] were combined and evaporated to yield 0.37 g (10%) of **29**, mp 178°; ir (potassium bromide): 3090, 3057, 2972, 1755, 1723, 1677, 1592, 1297, 1180, 1140, 1068 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 1.16 (s, 9H, *t*-Bu of the keto-ester), 1.20 (s, 9H, *t*-Bu), 5.28 (s, 2H, CH_2), 5.29 (s, 2H, CH_2), 7.08 (d, 1H, H_4), 7.92 (d, 1H, H_5).

Anal. Calcd. for $C_{17}H_{24}N_2O_5$: C, 60.70; H, 7.19; N, 8.33. Found: C, 60.48; H, 7.40; N, 8.23.

Compound **30**.

The fractions which contained **30** [R_f, 0.25 (ethyl acetate/hexanes, 3/1), 0.57 (chloroform/methanol, 9/1)] were combined and evaporated to yield 1.39 g (58%) of **30**, mp 175°; ir (potassium bromide): 3207, 3149, 3052, 2968, 1744, 1724, 1673, 1589 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 1.15 (s, 9H, *t*-Bu) 5.27 (s, 2H, CH_2), 6.98 (d, 1H, H_4), 7.83 (d, 1H, H_5), 13.67 (s, 1H, NH, deuterium oxide exchangeable).

Anal. Calcd. for $C_{11}H_{14}N_2O_4$: C, 55.45; H, 5.92; N, 11.76. Found: C, 55.56; H, 6.11; N, 11.87.

1-Pinacolyl 3-Chloropyridazine-6-carboxylate (**32**).

1-Pinacolyl pyridazine-6-one-3-carboxylate (**30**) (0.85 g, 3.5 mmoles) was heated at reflux in phosphorus oxychloride (25 ml) for 45 minutes. The excess phosphorus oxychloride was removed under reduced pressure (aspirator followed by high vacuum) and the resulting beige residue was dissolved in water (25 ml, 0°). The water was extracted with chloroform (5 x 20 ml). The combined extracts were washed with brine (25 ml), dried over anhydrous magnesium sulfate, and evaporated to dryness under reduced pressure to yield 0.9 g (98%) of pure product. An analytical sample was prepared by recrystallization from ethyl acetate; R_f, 0.3 (chloroform), mp 195-196°; ir (potassium bromide): 3028, 2979, 1749, 1723, 1559, 1539, 1409, 1284 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.24 (s, 9H, *t*-Bu), 5.25 (s, 2H, CH_2), 7.66 (d, 1H, H_4), 8.15 (d, 1H, H_5).

Anal. Calcd. for $C_{11}H_{13}ClN_2O_3$: C, 51.47; H, 5.10; N, 10.92. Found: C, 51.70; H, 5.10; N, 10.75.

Methyl 6-Methylimidazo[1,2-*b*]pyridazine-2-carbamate (**34**).

3-Amino-6-methylpyridazine (**33**) [18] (2.2 g, 20 mmoles) was

stirred in dimethylformamide (35 ml) and to this solution was added methyl (chloroacetyl)carbamate (3.1 g, 20.4 mmoles). The mixture was heated in a boiling water bath for 5 hours. At the end of this period, 10 g of normal phase silica gel was added to the reaction mixture and the solvent was evaporated to dryness under reduced pressure (aspirator followed by high vacuum) and temperature below 50°. The residue was then applied to the top of a silica column (4 x 20 cm) packed with normal phase silica and eluted with chloroform/methanol, 95/5. The fractions containing the product; R_f, 0.7 (chloroform/methanol, 9/1) were combined and evaporated to dryness under reduced pressure to give 2.8 g (68%). An analytical sample was recrystallized from ethyl acetate, mp 250-251°; ir (potassium bromide): 3437, 3201, 3156, 3060, 2966, 1723, 1618, 1570, 1546 cm^{-1}; ^1H-nmr (DMSO-d_6): δ 2.45 (s, 3H, ring methyl), 3.63 (s, 3H, ester methyl), 7.04 (d, 1H, H_8), 7.79 (d, 1H, H_7), 7.90 (s, 1H, H_3), 10.37 (s, 1H, NH, deuterium oxide exchangeable).

Anal. Calcd. for $C_9H_{10}N_4O_2$: C, 52.42; H, 4.89; N, 27.17. Found: C, 52.44; H, 4.93; N, 27.11.

2-*t*-Butyl-6-methylimidazo[1,2-*b*]pyridazine (**35**).

3-Amino-6-methylpyridazine (**33**) (2.2 g, 20 mmoles) and 1-bromopinacolone (4.2 g, excess) were mixed in dimethylformamide (50 ml) and heated in a boiling water bath for 5 hours. At the end of this period the solvent was removed under reduced pressure (aspirator followed by high vacuum) while the temperature was kept below 60°. The residue after evaporation was extracted with hexanes (6 x 10 ml) and the extracts were combined and evaporated to dryness under aspirator pressure to afford 2.4 g (63% crude) of product. The product was purified by flash chromatography (1 x 15 cm column) using normal phase silica and chloroform as an eluent to give 2.2 g of pure product (57%). An analytical sample was recrystallized from hexanes, mp 135°; R_f, 0.78 (chloroform/methanol, 9/1), 0.43 (ethyl acetate/hexanes, 3/1), ir (potassium bromide): 3124, 3064, 2959, 1618, 1552, 1533 cm^{-1}; ^1H-nmr (DMSO-d_6): δ 1.32 (s, 9H, *t*-Bu), 2.48 (s, 3H, CH_3), 7.04 (d, 1H, H_8), 7.90 (d, 1H, H_7), 7.92 (s, 1H, H_3).

Anal. Calcd. for $C_{11}H_{15}N_3$: C, 69.81; H, 7.99; N, 22.20. Found: C, 69.65; H, 8.12; N, 22.03.

3-Bromo-2-*t*-butyl-6-methylimidazo[1,2-*b*]pyridazine (**36**).

2-*t*-Butyl-6-methylimidazo[1,2-*b*]pyridazine (**35**) (0.5 g, 2.6 mmoles) and 2,2'-azobis(2-methylpropionitrile) (AIBN) (0.002 g) were dissolved in benzene (25 ml). To this solution was added *N*-bromosuccinimide (NBS) (0.49 g, 2.8 mmoles) with continuous stirring. After 1 hour, petroleum ether (50 ml, boiling range 40-60°) was added and a precipitate formed which was filtered and discarded. The filtrate was evaporated to dryness under reduced pressure and the residue was recrystallized from hexanes to give 0.68 g (96%) of **37**. An analytical sample was obtained by flash chromatography (1 x 8 cm column) using chloroform as the eluent on normal phase silica; R_f, 0.32 (chloroform), 0.86 (chloroform/methanol, 9/1), 0.59 (ethyl acetate/hexane, 3/1), mp 108°; ir (potassium bromide): 3057, 2972, 1605, 1539, 1494 cm^{-1}; ^1H-nmr (DMSO-d_6): δ 1.44 (s, 9H, *t*-Bu), 2.56 (s, 3H, CH_3), 7.18 (d, 1H, H_8), 7.98 (d, 1H, H_7).

Anal. Calcd. for $C_{11}H_{14}N_3Br$: C, 49.27; H, 5.26; N, 15.67. Found: C, 49.48; H, 5.43; N, 15.46.

2-*t*-Butyl-3-iodo-6-methylimidazo[1,2-*b*]pyridazine (**37**).

Compound **37** was prepared in 64% yield from 2-*t*-butyl-6-methylimidazo[1,2-*b*]pyridazine (**35**), AIBN and *N*-iodosuccinimide (NIS) by applying the same procedure used for the preparation of compound **36**. The product was purified by using open-bed column chromatography with normal phase silica and chloroform as an eluent; R_f, 0.18 (chloroform), 0.82 (chloroform/methanol, 9/1), mp 153-155°; ir (potassium bromide): 3077, 2979, 1605, 1592, 1539, 1487, 1297, 1225, 1173, 1127, 1003 cm^{-1}; ^1H-nmr (DMSO-d_6): δ 1.47 (s, 9H, *t*-Bu), 2.55 (s, 3H, CH_3), 7.13 (d, 1H, H_8), 7.99 (d, 1H, H_7).

Anal. Calcd. for $C_{11}H_{14}IN_3$: C, 41.92; H, 4.48; N, 13.33. Found: C, 42.03; H, 4.56; N, 13.33.

Methyl 6-(4-Fluorobenzoyl)pyridazine-3-carbamate Hydrate (**40**).

Method A.

3-Amino-6-(4-fluorobenzoyl)pyridazine (**10**) (0.217 g, 1 mmole) was heated at reflux in methyl chloroformate (30 ml) under an argon atmosphere for 12 hours. The excess methyl chloroformate was evaporated under aspirator pressure followed by high vacuum. The residue was dissolved in ethyl acetate, filtered, and crystallized by addition of hexanes to yield 0.268 g of pure product (94%). An analytical sample was prepared by flash chromatography using normal phase silica and chloroform as the eluent; R_f, 0.77 (chloroform/methanol, 9/1), mp 178-180°; ir (potassium bromide): 3182, 3129, 3012, 2966, 1795, 1736, 1657, 1598, 1369 cm^{-1}; ^1H-nmr (DMSO-d_6): δ 3.75 (s, 3H, CH_3), 7.41 (m, 2H, phenyl H_3 and H_5), 8.20 (m, 3H, pyridazine H_4, H_5 and phenyl H_6), 8.35 (m, 1H, phenyl H_2), 11.33 (s, 1H, NH, deuterium oxide exchangeable).

Anal. Calcd. for $C_{13}H_{10}FN_3O_3 \cdot \frac{1}{2}H_2O$: C, 54.93; H, 3.90; N, 14.78. Found: C, 55.12; H, 3.88; N, 14.99.

Method B.

To 3-amino-6-(4-fluorobenzoyl)pyridazine (**10**) (0.162 g, 0.7 mmole) at 0° in 1,2-dichloroethane (10 ml) was added oxalyl chloride (0.09 g, 0.07 ml. 0.7 mmole) under an argon atmosphere. After 1 hour the reaction mixture was heated at reflux for 2 hours, cooled to 0°, and methanol (15 ml) was carefully added while maintaining stirring. The precipitate formed was collected by filtration and crystallized from methanol to give 0.04 g (42%) of pure product; mp 178-180° (mixed mp with **40** from method A showed no depression). This compound was identical in all aspects with the compound prepared in Method A.

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 [21]. The jirds were also given 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 [21]. The drugs were administered as solutions or suspensions in aqueous 1% (hydroxyethyl)cellulose and 0.1% Tween 80 (HEC Tween 80) once daily for 5 days to three to five implanted jirds. Fifty-five to seventy 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 if the percent reduction of adult worms was greater than 65% of the untreated controls.

These compounds were found to be essentially devoid of antiviral activity against HCMV in a plaque reduction assay [22].

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