# Synthesis and Anti-HIV-1 Activity of a Series of Imidazo[1,5-*b*]pyridazines

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A series of substituted imidazo[1,5-*b*]pyridazines have been prepared and tested for inhibitory activity against the reverse transcriptase of HIV-1 (RT) and their ability to inhibit the growth of infected MT-4 cells. Crystal data are reported on two compounds, **15c** and **33**. From the structure–activity relationships developed within this and other series, it is proposed that key features of the interaction with RT include hydrogen-bond acceptor and aromatic $\pi$-orbital bonding with the imidazopyridazine nucleus and a benzoyl function separated from the heterocycle by a suitable spacer group. Exceptional activity against the reverse transcriptase of HIV-1 ($IC_{50}$ = 0.65 nM) was obtained with a 2-imidazolyl-substituted derivative, 7-[2-(1*H*-imidazol-1-yl)-5-methylimidazo-[1,5-*b*]pyridazin-7-yl]-1-phenyl-1-heptanone (**33**) which is attributed to additional binding of the imidazole $sp^2$ nitrogen atom. A number of the compounds in this series also inhibit the replication of HIV-1 *in vitro* in MT-4 and C8166 cells at levels observed with the nucleoside AZT.

## Introduction

The isolation of the human immunodeficiency virus (HIV),[1,2] which is now recognized as the causative agent of AIDS, preluded a vast world-wide research effort aimed at understanding and controlling this virus, and many review articles on the molecular biology and biochemistry of HIV have been published.[3] A particularly attractive target for inhibition is the virally-encoded enzyme reverse transcriptase (RT), which acts at the beginning of the viral replication cycle after an HIV particle has bound to the outside of a host cell (a human T4 lymphocyte) and fusion of the viral and host cell membranes has occurred. The reverse transcriptase comprises polymerase and ribonuclease components which together are responsible for the transcription of viral RNA into double-stranded DNA prior to integration into the host cell genome.[3] As reverse transcription occurs within the cytoplasm of the infected cell, an inhibitor must penetrate T4 lymphocytes if it is to be therapeutically effective.

The only approved drugs for HIV therapy (zidovudine,[4] didanosine,[5] and zalcitabine[6]) are all nucleosides which rely on cellular kinases to convert them into their triphosphates, which are not only competitive inhibitors of the natural substrate for RT but also when incorporated into nascent DNA then act as chain terminators of DNA synthesis. An attractive alternative strategy which has been the subject of recent interest is the design of a suitable non-nucleoside inhibitor and a number of promising compounds with diverse chemical structure have been reported (Chart I); examples include nevirapine (**1**),[7] R82913 (**2**),[8] L-697,661 (**3**),[9] ateverdine (**4**),[10] and E-BPU (**5**).[11]

Our own random screening program identified the imidazo[1,5-*b*]pyridazine **6** as an inhibitor of HIV-1 RT (RT1) with a 50% inhibitory concentration ($IC_{50}$) of 1.34 $\mu$M. We now report some of the structure–activity relationships in this series and our efforts to optimize the biological activity of the initial lead.

## Synthetic Chemistry

Imidazo[1,5-*b*]pyridazines were prepared from the amine hydrochloride intermediates (**13a–d**) (Table I). The key synthetic step in the preparation of these amine hydrochlorides is the condensation of an appropriate benzoyl amino acid (**7a–d**) with ethyl succinoyl chloride (Scheme I). This reaction, which was first reported by Dakin and West,[12] proceeds *via* aza lactone (**8a–d**) and $\beta$-keto acid (**9a–d**) intermediates[13,14] and is catalyzed by 4-(dimethylamino)pyridine.[15] The product $\gamma$-keto esters **10a–d** were cyclized with hydrazine to yield dihydropyridazinones **11a–d** which were further elaborated to the amine hydrochlorides **13a–d**.[16,17] Acylation of these salts and cyclization with phosphoryl chloride yielded a range of 2-chloroimidazo[1,5-*b*]pyridazines (**15a–g**, **17a,c,d**) (Scheme II). The requisite acid chlorides were prepared by standard methods from carboxylic acids which were either commercially available or were prepared according to published procedures. The esters **15i** and **15j** were obtained from the benzoate **15a** by hydrolysis to the alcohol **15h** and subsequent reacylation (Scheme III).

The 2-chloroimidazopyridazine **15c** was chosen for further synthetic modification. Thus, catalytic hydrogenolysis furnished the 2-unsubstituted derivative **18** (Scheme IV), while nucleophilic reaction with sodium methoxide and sodium thiomethoxide enabled ether **19** and thioether **20** derivatives to be prepared. 2-Amino derivatives were prepared by reaction with aliphatic and alicyclic amines (Scheme V). The primary amine **24** could not be obtained by direct reaction of **15c** with ammonia but was synthesized *via* the *p*-methoxybenzylamine **23**. Treatment of **15c** with the anions of 1*H*-azoles yielded a series of imidazo[1,5-*b*]pyridazines substituted at the 2-position with a nitrogen-containing heterocycle (Schemes VI and VII). Mixtures of isomers **29** + **30** and **31** + **32**

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**Chart I**

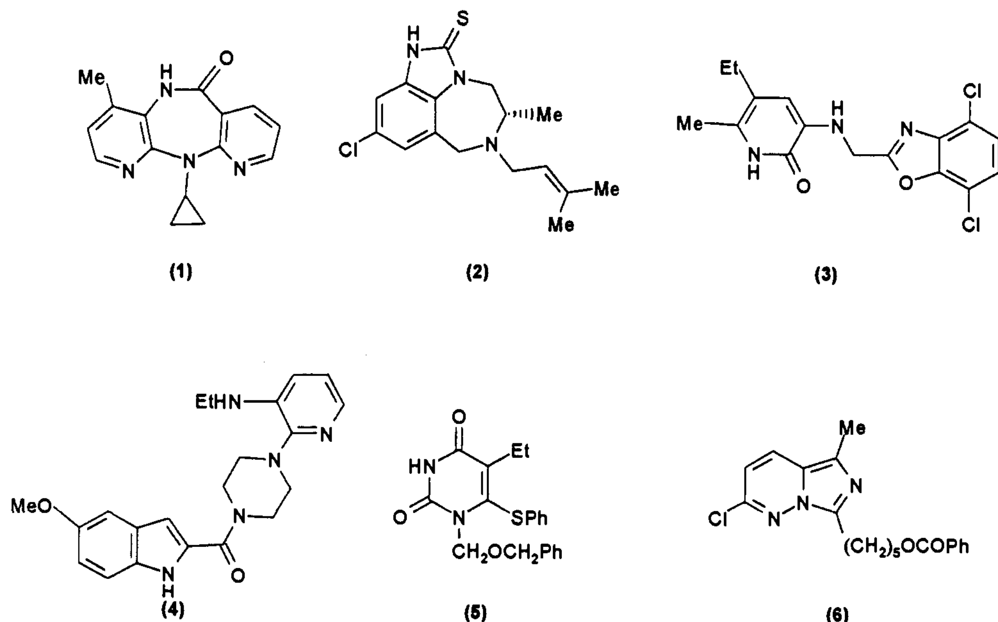


**Table I.** 1-(1,6-Dihydro-6-oxo-3-pyridazinyl)alkanamines

| no. | R′ | mp, °C | formula | method[a] |
|---|---|---|---|---|
| 13a[b] | H | 265–272[c] | $C_5H_8ClN_3O$[d] | A |
| 13b[b] | Me | 233–237[c] | $C_6H_{10}ClN_3O$[d] | A |
| 13c[b] | Et | 270–276[c] | $C_7H_{12}ClN_3O$ | A |
| 13d[b] | ${}^iPr$ | 254–256[c] | $C_8H_{14}ClN_3O$ | A |

[a] For methods, see the Experimental Section. [b] Isolated as hydrochloride salt. [c] Salts were crystallized from ethyl acetate–ethanol mixtures. [d] See ref 17.

were obtained from the reactions with 1*H*-1,2,4- and -1,2,3-triazoles and were readily separated by flash column chromatography. A small amount of the 5-substituted compound **36** was isolated from the reaction of **15c** with 1*H*-4-methylimidazole after preparative high-pressure liquid chromatography.

Reduction of the carbonyl group in **15c** and **33** proceeded uneventfully with sodium borohydride in ethanol to yield the corresponding alcohols (Scheme VIII). The imidazole derivative **38** was also obtained from **37** by nucleophilic displacement of the chlorine atom.

## Biological Methods

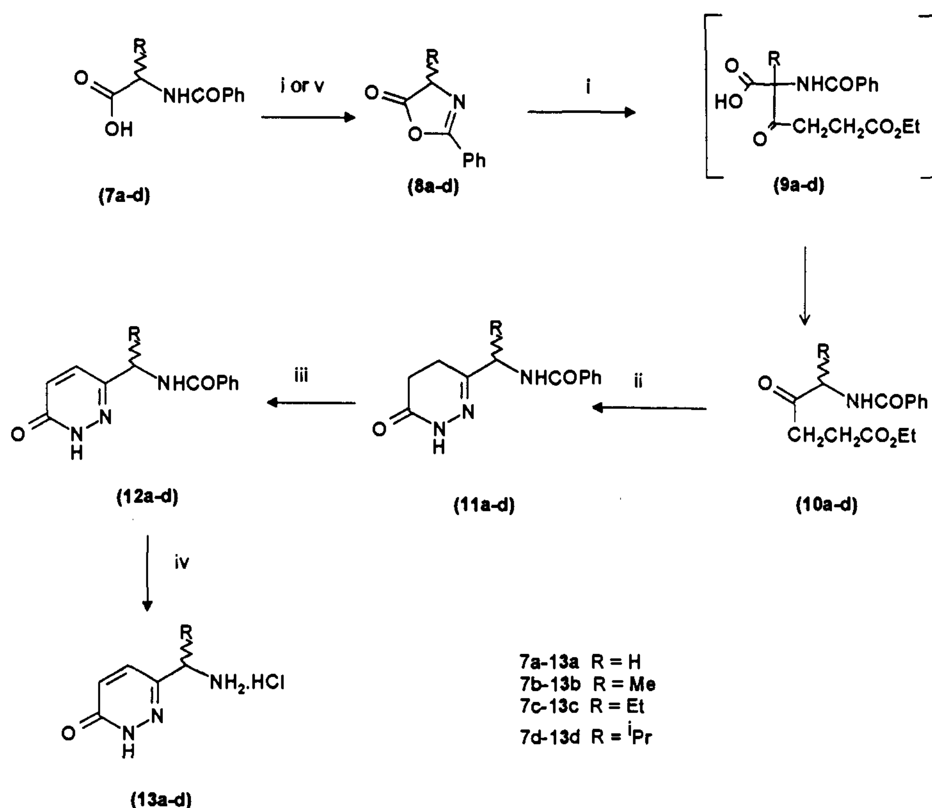
The imidazo[1,5-*b*]pyridazines described above were initially tested for their ability to inhibit poly(rA)·oligo(dT)$_{12-18}$-directed RT activity of HIV-1 in the presence of [$\alpha$-$^{35}$S]TTP as cosubstrate. In this assay, AZT triphosphate was employed as a positive control, and found to have an $IC_{50}$ of 20 nM ± 5 nM. Nevirapine (1) and benzoxazole **3** were also tested in this screen and found to have $IC_{50}$s of 280 and 850 nM, respectively. Compounds showing significant activity in this assay (RT1, $IC_{50}$ of a mean of two determinations generally <15 $\mu$M) were progressed to a primary *in vitro* screen. In this assay, compounds were tested against a suspension of MT-4 cells ($10^6$/mL) in RPMI 1640 growth medium infected with HIV-(strain RF) at a moi of $2 \times 10^{-3}$ units/cell ($EC_{50}$ of positive control AZT generally *ca.* 0.002–0.02 $\mu$M).[18]

Compounds which inhibited the cytopathic effect of HIV-1 infection on these cells (MTM, $EC_{50}$ of a mean of duplicate assays generally <10 $\mu$M) and which were acceptably nontoxic to uninfected MT-4 cells were progressed to further screens[18] designed to measure the inhibition of the formation of syncytia (SYN) in C8166 cells infected with HIV-1 (strain RF) at a moi of $1 \times 10^{-3}$ (determined as the mean of duplicate assays) ($EC_{50}$ of positive control AZT = 0.002–0.02 $\mu$M) and p24 antigen (p24) (mean of duplicate assays) ($EC_{50}$ of positive control AZT = 0.001–0.01 $\mu$M).

## Discussion

**7-Substituents.** Although the initial lead compound (**15a**) showed significant activity against RT (RT1, $IC_{50}$ = 1.3 $\mu$M), the benzoate ester group was found to be susceptible to metabolic hydrolysis to the inactive alcohol **15h**. A stable alternative 7-substituent was therefore required as an early priority for the project. The importance of the phenyl group for enzyme activity was established with the preparation of the inactive aliphatic esters **15i,j** (Table II). However, replacement of the ester carbonyl group in **15a** with a methylene group was more rewarding, and **15b** retained both enzyme and *in vitro* activity. Of major significance was the observation that replacement of the alkoxy oxygen atom of **15a** by methylene gave the ketone **15c** which displayed comparable enzyme activity to **15a** ($IC_{50}$ = 0.84 $\mu$M) and also had excellent activity comparable with that of AZT in cellular assays. However, the unsubstituted phenylheptyl derivative **15d** was much less active. Activity, particularly in the *in vitro* MTM assay, was also reduced when the carbonyl group was moved along the carbon chain (**15e**) or when the carbon chain was shortened (**15f**) or lengthened (**15g**). Reduction of the ketone group to yield the alcohol **37** was well tolerated, however, We speculate that activity *versus* the enzyme requires a lipophilic interaction of the phenyl group and a hydrogen-bonding interaction of a neighboring oxygen atom at the binding site on RT. The six-carbon chain presumably adopts a conformation in which these key groups are held at an optimum position relative to the heterocycle, in comparison with the somewhat less active five- and seven-carbon chains.

**Scheme I**[a]




[a] Reagents: (i) $EtO_2CCH_2CH_2COCl$, $Et_3N$, DMAP, THF; (ii) $N_2H_4{\cdot}H_2O$, EtOH, reflux; (iii) $Br_2$, HOAc, 40 °C; (iv) 6 M HCl, reflux; (v) $Ac_2O$, reflux.

**5-Substituents.** At the 5-position of the imidazopyridazine ring system, a clear correlation between enzyme activity and steric bulk was observed (Table III). The unsubstituted compound **17a** was the most potent inhibitor, but a methyl substituent led to greater antiviral activity *in vitro*.

**2-Substituents.** The 2-position of the heterocycle proved tolerant of a wide range of ether, thioether, and amine substituents, all of which retained good enzyme activity (Table IV). The pyrrolidine **26** was very active in the RT assay but unfortunately was cytotoxic, and its antiviral effect could not be determined. In an attempt to overcome the toxicity of this compound we prepared some heteroaromatic five-membered ring analogues. In the event, the pyrrole **28** retained the potent enzyme activity of the pyrrolidine **26** and was as active as AZT in all the cellular assays. Among compounds containing two nitrogen atoms, the pyrazole **27** was only moderately active in the enzyme assay, but the imidazole **33** proved to be a remarkably potent inhibitor of the RT of HIV-1 in our assay ($IC_{50}$ = 0.65 nM) and retained excellent *in vitro* activity. Of the four isomeric triazoles, only the 1,2,4- and 1,2,3-isomers retained submicromolar $IC_{50}$ values, and none was particularly active in the MTM assay.

The discovery of the first subnanomolar inhibitor of RT (**33**) prompted further work around this new lead. Methyl substitution at the 2′-, 4′-, and 5′-positions of the imidazole ring led to compounds with much reduced enzyme activity compared with the unsubstituted derivative (**33**), though the 5′-methyl derivative is still moderately potent ($IC_{50}$ = 100 nM). Reduction of the carbonyl group in the 7-side chain of the imidazole **33** led to a compound **38** which retained the excellent cellular activity of **33**.

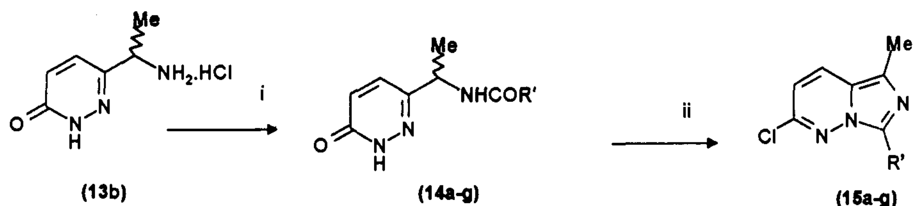
The selectivity of imidazo[1,5-*b*]pyridazines such as **33** for the reverse transcriptase of HIV-1 was confirmed by its lack of activity against a range of other enzymes including HIV protease and HSV-1 DNA polymerase.

In Table V we compare imidazole **33** with benzoxazole **3** and AZT in a range of cellular assays and include *in vitro* data for a modified MTM test (A17) using MT-4 cells infected with HIV-1 strain A17 (supplied by Merck Sharp & Dohme Research Laboratories, West Point, PA),[19] which includes a mutation of the tyrosine-181 residue to cysteine, and has become associated with the onset of resistance to non-nucleoside RT inhibitors (see below).

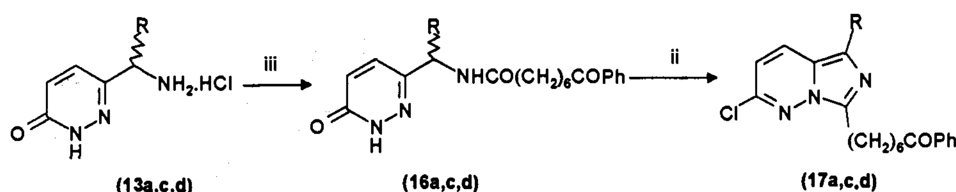
## X-ray Crystallography and Discussion of Binding Region

Crystals of the chloro-substituted imidazopyridazine **15c** (GR122989) were obtained from cyclohexane. The asymmetric unit contains two crystallographically independent molecules with very different conformations of the ($-CH_2-)_6$ chain (orthogonal view in Figure 1). One of these conformations is represented in Figure 2. The imidazole **33** (GR142086) crystallized from toluene in three practically identical conformations (Figures 3 and 4). The full crystal coordinate data for **15c** and **33** are available as supplementary material. Our compounds **15c**, **33** share with the disclosed non-nucleoside inhibitors (**1**–**5**) selectivity for the RT of HIV-1. Nevirapine (**1**)[20] and benzoxazole (**3**)[21] have independently been shown to bind to a region of the enzyme containing tyrosine residues at positions 181 and 188, and strains of HIV-1 which lack one or both of these residues are resistant to these agents.[19,22,23] Further evidence of the binding site of nevirapine follows from the reported crystal structure of reverse transcriptase with bound nevirapine,[24] which shows

**Scheme II**[a]



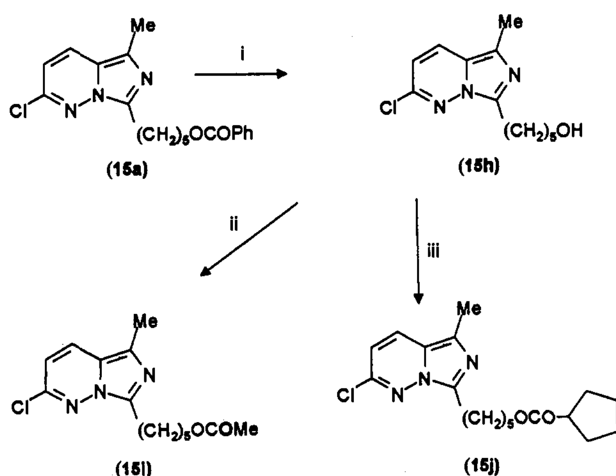

14a,15a R' = $(CH_2)_5OCOPh$
14b,15b R' = $(CH_2)_5OCH_2Ph$
14c,15c R' = $(CH_2)_6COPh$
14d,15d R' = $(CH_2)_7Ph$
14e,15e R' = $(CH_2)_5COCH_2Ph$
14f,15f R' = $(CH_2)_5COPh$
14g,15g R' = $(CH_2)_7COPh$




13a,16a,17a R = H
13c,16c,17c R = Et
13d,16d,17d R = $^{i}$Pr

[a] Reagents: (i) R'COCl, $Et_3N$, DMF; (ii) $POCl_3$, DCE, reflux; (iii) $PhCO(CH_2)_6COCl$, $Et_3N$, DMF.

**Scheme III**[a]




[a] Reagents: (i) $NH_3$, MeOH; (ii) $Ac_2O$, py, DMAP, DCM; (iii) cyclopentanecarboxyl chloride, py, DMAP, DCM.

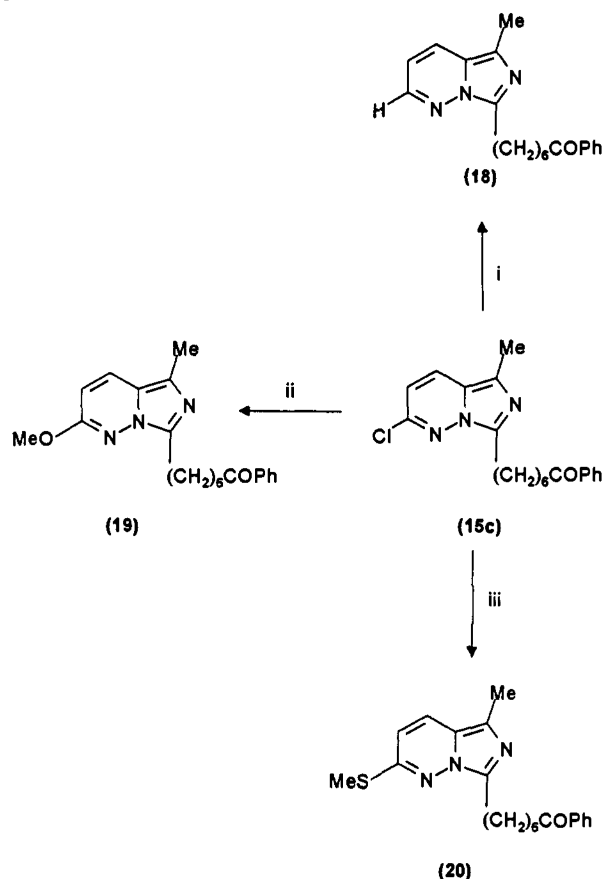
the proximity of one of its pyridyl rings to the tyrosine-181 residue.[25] The specificity for HIV-1, in-house enzyme kinetic experiments which demonstrated that 2 and 15c are mutually exclusive inhibitors of HIV-1,[26] and the observed reduction in *in vitro* activity against the A17 strain led us to believe that these structurally diverse compounds may act on similar regions of the enzyme. Published comparisons[27,28] based on the crystal structures of nevirapine (1) and benzodiazepinone 2 have highlighted some common structural features between these diverse series of non-nucleoside reverse transcriptase inhibitors. In comparison with these compounds, our imidazopyridazines have certain differences, notably the requirement for a benzoyl or benzyloxy function in a region remote from the heterocyclic ring. The exceptional activity of the imidazole **33** suggests an additional binding contribution from the imidazole $sp^2$ nitrogen atom. Semiempirical quantum mechanics calculations were performed using the AM1 Hamiltonian in MOPAC,[29] and the results were analyzed with SYBYL.[30] The calculations predict that the imidazole and pyridazine rings prefer to be coplanar, either in the *cis* or *trans* conformations, with insufficient conjugation across the rings to prevent rotational isomerism. The *cis* isomer of **33** is calculated to be more favored than the *trans* isomer by 0.17 kcal/mol, in agreement with the crystal structure. We presume that the weaker enzyme activity of the triazoles **29**, **30**, and **31** and the substituted imidazoles **34**, **35**, and **36** is associated with a relative destabilization of this planar *cisoid* arrangement compared with *trans* or non-planar orientations.

On the basis of the above structure–activity analysis, a schematic representation of what appear to be the key interactions of the potent inhibitor **33** with reverse transcriptase is shown in Figure 5. Consideration of these features, in comparison with other non-nucleoside RT inhibitors, may lead to the rational design of compounds with improved activity against resistant strains of HIV-1.

## Conclusions

Inhibition of the RT of HIV-1 has been identified in a novel series of imidazo[1,5-*b*]pyridazines, and the influence of substitution at the 2-, 5-, and 7-positions on biological activity has been investigated. One compound, the

Scheme IV[a]




[a] Reagents: (i) $H_2$, 10% Pd–C, MeOH, NaOAc; (ii) MeONa, MeOH, reflux; (iii) MeSH, NaH, THF, reflux.

imidazole derivative **33**, has been discovered to be an exceptionally potent inhibitor ($IC_{50}$ 0.65 nM). In comparison with other reported non-nucleoside inhibitors, this compound appears to have the capability to achieve additional enzyme-inhibitor interactions through an imidazole nitrogen atom and the side-chain benzoyl group. These substituents have a critical bearing on the observed enzyme activity in this series. Rapid onset of resistance to non-nucleoside RT inhibitors such as **1** and **3** has been demonstrated *in vitro*[19,22] and is associated with a tyrosine-181 to cysteine mutation. The clinical use of these agents has also been accompanied by the rapid emergence of strains of HIV-1 which are much less sensitive to members of this pharmacological class.[23,31] A derivative of ateverdine **4**, U-90152S, has recently been reported to induce a different mutation (proline-236 to leucine) with increased sensitivity to nevirapine **1** and L-697,661 **3**.[32] The significance of this result for the imidazopyridazine series of inhibitors is at present unknown.

## Experimental Section

Except where otherwise stated, the following procedures were adopted: $^1$H NMR spectra were recorded on a Bruker AM250 instrument, and $^1$H chemical shifts are expressed in ppm downfield from tetramethylsilane or sodium 3-(trimethylsilyl)-propionate. Organic solvents were purchased from Aldrich Chemical Co. (Sureseal). During workup, organic solutions were dried over anhydrous magnesium sulfate and evaporated on a Buchi rotary evaporator with a water bath temperature of 40 °C or below. Thin-layer chromatography was performed on silica plates (Merck Art. No. 5719), and flash column chromatography was carried out on silica (Merck Art. No. 9385). Melting points are uncorrected. Carboxylic acids were purchased from Lancaster Synthesis apart from 6-(benzyloxy)hexanoic acid, 6-benzoylhexanoic acid, and 8-phenyl-6-oxaoctanoic acid which were prepared by published procedures. Acid chlorides were generated from carboxylic acids with oxalyl chloride (1.1 equiv) and triethylamine (1.1 equiv) in dichloromethane solution and were used without purification. AZT triphosphate[33] and L-697,611[9] were prepared by published procedures. Nevirapine was supplied by Boehringer-Ingelheim Pharmaceuticals, Ridgefield, CT.

**7-(2-Chloro-5-methylimidazo[1,5-*b*]pyridazin-7-yl)-1-phenyl-1-heptanone (15c).** This procedure illustrates the general method of preparation of compounds **15a–g** and **17a,c,d**.

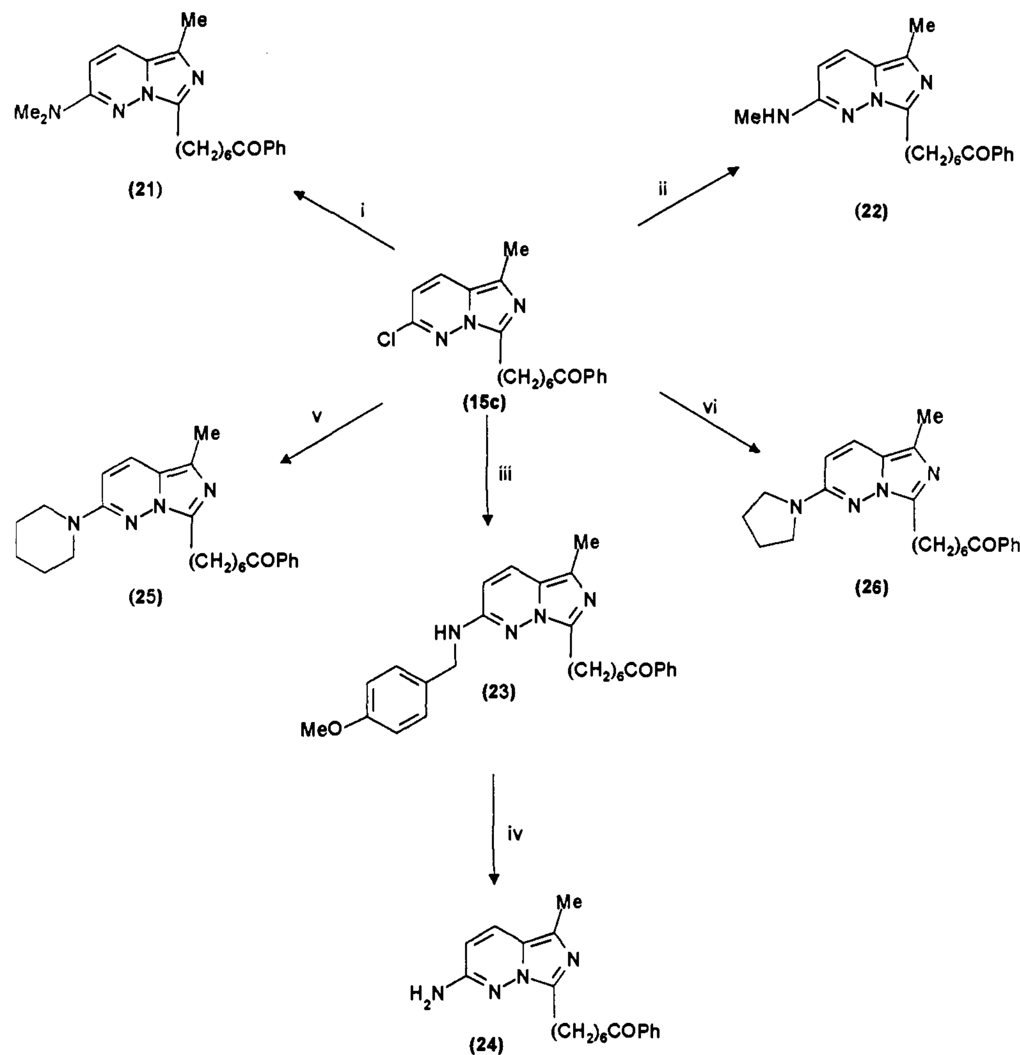
**Method A (See Table I). (a) 1-(1,6-Dihydro-6-oxo-3-pyridazinyl)ethanamine Hydrochloride (13b).** A mixture of the amide **11b**[16] (43.3 g, 178 mmol) and 6 M hydrochloric acid (1.3 L) was stirred under reflux for 18 h and then cooled to 20 °C. The mixture was filtered, and the filtrate was evaporated to dryness. The residue was stirred overnight with diethyl ether (1 L) and filtered. The solid was recrystallized from a mixture of ethanol (1.25 L) and ethyl acetate (1.25 L) and dried *in vacuo* to give the amine hydrochloride **13b** (25.67 g, 82%): mp 235–238 °C; $^1$H NMR ($d_6$-DMSO) $\delta$ 13.25 (1H, s, CONH*N*), 8.58 (3H, s, $NH_3^+$), 7.62 (1H, d, $J$ = 9 Hz, imidazopyridazine 4-H), 6.99 (1H, d, $J$ = 9 Hz, imidazopyridazine 3-H), 4.38 (1H, t, $J$ = 7 Hz, C*H*(Me)), 1.47 (3H, d, $J$ = 7 Hz, $CH_3$CH). Anal. $C_6H_9N_3O{\cdot}HCl$ (C, H, N).

**(b) (1'*RS*)-*N*-[1-(1,6-Dihydro-6-oxo-3-pyridazinyl)ethyl]-8-oxo-8-phenyloctanamide (14c).** A suspension of **13b** (6.59 g, 37.5 mmol) in *N,N*-dimethylformamide (55 mL) containing triethylamine (10.83 mL, 78 mmol) was stirred at 20 °C under nitrogen for 10 min, and a solution of 7-benzoylheptanoyl chloride (9.9 g, 39.25 mmol) in *N,N*-dimethylformamide (30 mL) was added, dropwise, over 10 min, causing an increase in temperature to *ca.* 40 °C. The resulting suspension was stirred at 20 °C for 24 h and then added, with stirring, to water (500 mL). The precipitate was filtered off, washed with water (2 × 75 mL), and air-dried for 30 min. The solid was slurried with ethyl acetate (200 mL), filtered, washed with ethyl acetate, and dried *in vacuo* at 50 °C over phosphorus pentoxide to give the amide **14c** (8.1 g, 61%) as an off-white solid: mp 160–162 °C; $^1$H NMR ($d_6$-DMSO) $\delta$ 12.85 (1H, s, CONH*N*), 8.22 (1H, d, CON*H*CH(Me)), 7.45–7.98 (5H, m, phenyl), 7.36 (1H, d, $J$ = 9 Hz, imidazopyridazine 4-H), 6.87 (1H, d, $J$ = 9 Hz, imidazopyridazine 3-H), 4.80 (1H, pn, $J$ = 7 Hz, C*H*(Me)NH), 3.00 (2H, t, $J$ = 7 Hz, $CH_2$CONH), 2.1 (2H, t, $J$ = 7 Hz, PhCO$CH_2$), 1.25 (3H, d, $J$ = 7 Hz, $CH_3$CH). Anal. $C_{19}H_{25}N_3O_3$ (C, H, N).

**(c) 7-(2-Chloro-5-methylimidazo[1,5-*b*]pyridazin-7-yl)-1-phenyl-1-heptanone (15c). Method B (See Tables II and III).** A suspension of **14c** (7.99 g, 22.5 mmol) in 1,2-dichloroethane (150 mL) and phosphoryl chloride (17 mL, 180 mmol) was heated to reflux with stirring for 3 h and then left at 20 °C for 18 h. The resulting solution was evaporated, and the residual oil was suspended in ethyl acetate (400 mL). This suspension was cooled to 0 °C and stirred, and sodium bicarbonate (350 mL) was added. The aqueous phase was separated and extracted with ethyl acetate (2 × 250 mL). The organic solutions were combined, washed with water (2 × 250 mL) and brine (250 mL), dried, and evaporated. The residual oil was purified by column chromatography using ethyl acetate–petroleum ether (40–60 °C) (1:1) as eluant giving the imidazopyridazine **15c** (5.1 g, 64%) as a yellow solid: mp 72–73 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.47–7.96 (3H, m, phenyl), 7.62 (1H, d, $J$ = 8 Hz, imidazopyridazine 4-H), 6.36 (1H, d, $J$ = 8 Hz, imidazopyridazine 3-H), 3.07 (2H, t, $J$ = 7 Hz, Het-$CH_2$), 2.97 (2H, t, $J$ = 7 Hz, PhCO$CH_2$), 2.48 (3H, s, Het-$CH_3$), 1.40–1.90 (8H, m, $(CH_2)_4$). Anal. $C_{20}H_{22}ClN_3O{\cdot}HCl{\cdot}0.25H_2O$ (C, H, N).

**5-(2-Chloro-5-methylimidazo[1,5-*b*]pyridazin-7-yl)pentan-1-ol (15h). Method C (See Table II).** A solution of the ester **15a** in a saturated solution of ammonia in methanol (50 mL) was stirred at 20 °C for 10 days. The reaction mixture was concentrated to give a yellow oil (0.47 g) which was purified by column chromatography to give a yellow solid (305 mg, 87%). A portion of this solid (52 mg) was dissolved in diethyl ether (5 mL) and treated with ethereal hydrogen chloride (0.5 mL). The resulting white precipitate was triturated with diethyl ether and recrystallized from diethyl ether–2-propanol (1:1) (2 mL). The product was collected by filtration, washed with diethyl ether,

Scheme V[a]




[a] Reagents: (i) $Me_2NH$, EtOH, reflux; (ii) $MeNH_2$, EtOH, reflux; (iii) $p$-MeO·$C_6H_4$·$CH_2NH_2$, reflux; (iv) TFA; (v) piperidine, reflux; (vi) pyrrolidine, reflux.

and dried *in vacuo* to give the hydrochloride salt of the alcohol **15h** (45 mg): mp 176–178 °C; $^1$H NMR ($D_2O$) $\delta$ 8.13 (1H, d, $J$ = 8 Hz, imidazopyridazine 4-H), 6.97 (1H, d, $J$ = 8 Hz, imidazopyridazine 3-H), 3.59 (2H, t, $CH_2OH$), 3.24 (2H, t, Het-$CH_2$), 2.58 (3H, s, Het-$CH_3$), 1.40–1.87 (6H, m, $(CH_2)_3$). Anal. $C_{12}H_{16}ClN_3O$·HCl·0.2$H_2O$ (C, H, N).

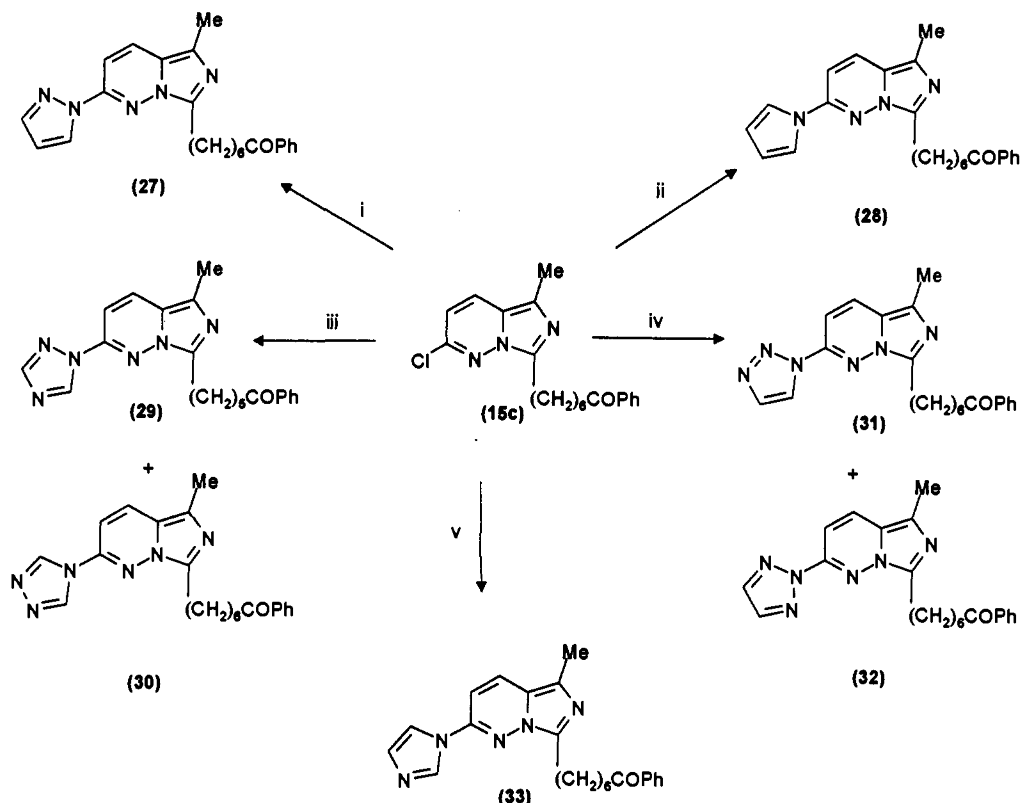
**5-(2-Chloro-5-methylimidazo[1,5-*b*]pyridazin-7-yl)-1-acetoxypentane (15i).** This procedure illustrates the general method of preparation of compounds **15i,j**.

**Method D (See Table II).** A solution of the alcohol **15h** (100 mg, 0.39 mmol) in dichloromethane (5 mL) was treated with acetic anhydride (44 $\mu$L, 0.47 mmol), pyridine (38 $\mu$L, 0.47 mmol), and 4-(dimethylamino)pyridine (2 mg). The solution was stirred at 20 °C for 2 h and then evaporated to give a yellow oil. This oil was dissolved in ethyl acetate (50 mL) and washed with water and brine. The organic solution was dried over magnesium sulfate and evaporated to give a yellow oil (130 mg). This oil was dissolved in diethyl ether (5 mL) and treated with ethereal hydrogen chloride (0.5 mL). The resulting white precipitate was triturated with diethyl ether and recrystallized from diethyl ether–2-propanol (3:1) (4 mL). The product was filtered off, washed with diethyl ether, and dried *in vacuo* to give the hydrochloride salt of the ester **15i** (95 mg, 73%): mp 149–151 °C; $^1$H NMR ($D_2O$) $\delta$ 8.15 (1H, d, $J$ = 8 Hz, imidazopyridazine 4-H), 6.98 (1H, d, $J$ = 8 Hz, imidazopyridazine 3-H), 4.09 (2H, t, $CH_2OAc$), 3.27 (2H, t, Het-$CH_2$), 2.58 (3H, s, Het-$CH_3$), 2.06 (3H, s, $OCOCH_3$), 1.42–1.88 (6H, m, $(CH_2)_3$). Anal. $C_{14}H_{18}ClN_3O_2$·HCl (C, H, N).

**7-(5-Methylimidazo[1,5-*b*]pyridazin-7-yl)-1-phenyl-1-heptanone Hydrochloride (18). Method E (See Table IV).** A slurry of 10% palladium-on-carbon (15 mg) in methanol (1 mL) was added to a solution of **15c** (100 mg, 0.28 mmol) and sodium acetate (38.2 mg, 0.28 mmol) in methanol (4 mL). The mixture was hydrogenated at atmospheric pressure for 7 h and then filtered through kieselguhr, washing through with ethyl acetate (30 mL). The filtrate was concentrated to give a yellow oil which was purified by column chromatography using ethyl acetate–petroleum ether (40–60 °C) (1:2, then 1:1) as eluant to give a yellow oil (65 mg). This oil was dissolved in diethyl ether (5 mL) and filtered. The filtrate was treated with excess ethereal hydrogen chloride. The resulting oil was triturated with diethyl ether to give a solid which was recrystallized from diethyl ether–2-propanol (3:1) (4 mL). The solid was filtered, washed with diethyl ether, and dried to give the imidazopyridazine **18** (51 mg, 51%): mp 136–138 °C; $^1$H NMR ($d_6$-DMSO) $\delta$ 8.60 (1H, dd, $J$ = 1.5, 4 Hz, imidazopyridazine 2-H), 8.38 (1H, dd, $J$ = 1.5, 8 Hz, imidazopyridazine 4-H), 7.47–8.00 (5H, m, phenyl), 6.97 (1H, dd, $J$ = 4, 8 Hz, imidazopyridazine 3-H), 3.20 (2H, t, $J$ = 7 Hz, Het-$CH_2$), 3.02 (2H, t, $J$ = 7 Hz, $PhCOCH_2$), 2.50 (3H, s, Het-$CH_3$), 1.30–1.90 (8H, m, $(CH_2)_4$). Anal. $C_{20}H_{23}N_3O$·HCl·0.75$H_2O$ (C, H, N).

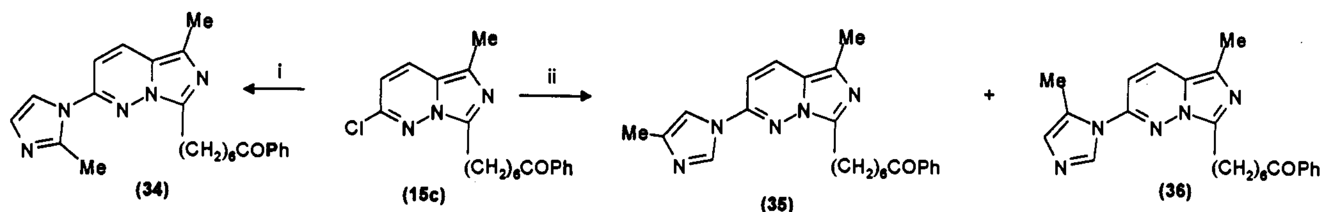
**7-(2-Methoxy-5-methylimidazo[1,5-*b*]pyridazin-7-yl)-1-phenyl-1-heptanone Hydrochloride (19). Method F (See Table IV).** Sodium (263 mg, 11.4 mmol) was reacted with methanol (20 mL) and the resulting solution was treated with the hydrochloride salt of **15c** (100 mg, 0.255 mmol). The solution was refluxed for 16 h and then partitioned between ethyl acetate (100 mL) and aqueous sodium bicarbonate (50 mL). The organic phase was washed with brine (50 mL), dried, and evaporated to give the free base of the methyl ether **19** as a yellow oil (85 mg). This oil was treated with ethereal hydrogen chloride, and the solid was filtered off, washed with diethyl ether, and dried *in*

**Scheme VI**[a]



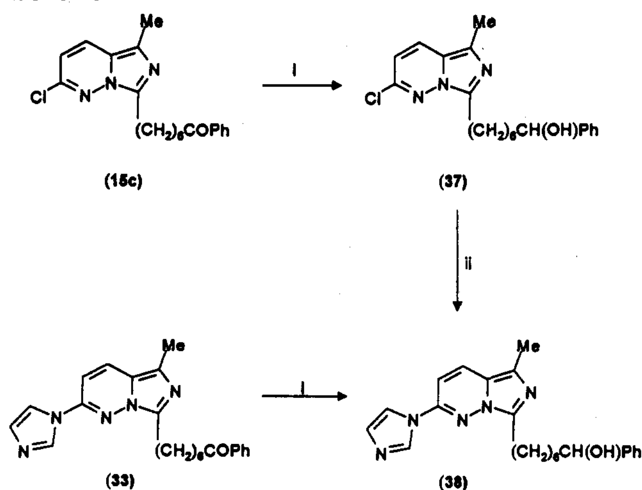

[a] Reagents: NaH, DMF, 60 °C + (i) pyrazole; (ii) pyrrole; (iii) 1,2,4-triazole; (iv) 1,2,3-triazole; (v) imidazole.

**Scheme VII**[a]




[a] Reagents: NaH, DMF, 60 °C + (i) 2-methylimidazole; (ii) 4-methylimidazole.

**Scheme VIII**[a]




[a] Reagents: (i) $NaBH_4$, EtOH; (ii) imidazole, NaH, DMF, 60 °C.

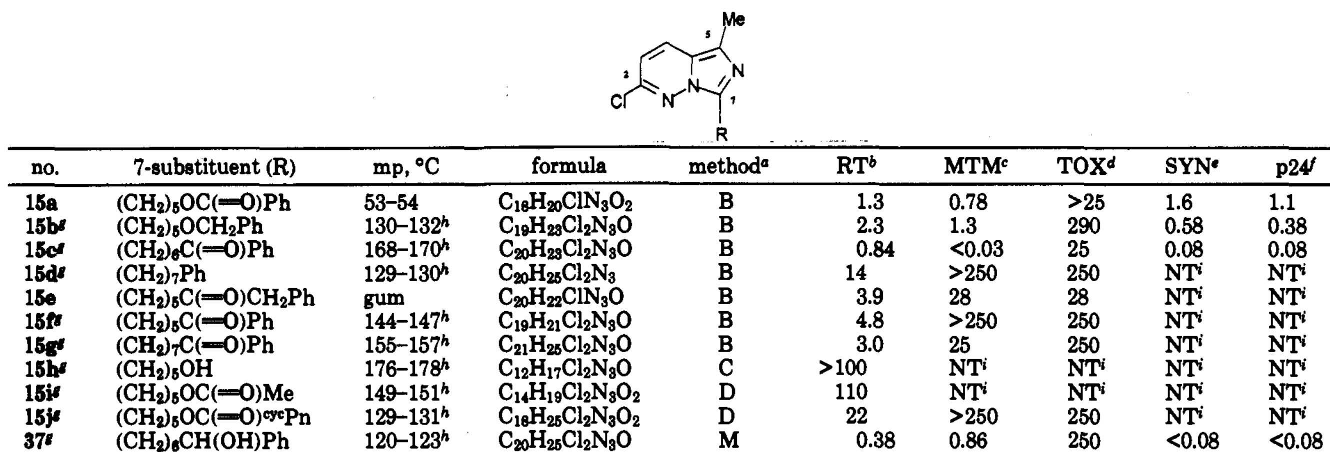
*vacuo* to give the hydrochloride salt (58 mg, 59%): mp 104–105 °C; $^1H$ NMR ($CDCl_3$) $\delta$ 7.47–7.96 (5H, m, phenyl), 7.70 (1H, d, $J$ = 10 Hz, imidazopyridazine 4-H), 6.52 (1H, d, $J$ = 10 Hz, imidazopyridazine 3-H), 4.04 (3H, s, $CH_3O$), 3.32 (2H, t, $J$ = 7.5 Hz, Het-$CH_2$), 2.98 (2H, t, $J$ = 7.5 Hz, $PhCOCH_2$), 2.68 (3H, s, Het-$CH_3$), 1.40–2.08 (8H, m, $(CH_2)_4$). Anal. $C_{21}H_{25}N_3O_2{\cdot}HCl{\cdot}0.4H_2O$ (C, H, N).

**7-[5-Methyl-2-(methylthio)imidazo[1,5-*b*]pyridazin-7-yl]-1-phenyl-1-heptanone (20). Method G (See Table IV).** A solution of compound **15c** (534 mg, 1.5 mmol) in tetrahydrofuran (40 mL) was stirred at 20 °C, and sodium hydride (54 mg, 2.25 mmol) was added. Methanethiol was passed for *ca.* 10 min, and the resulting suspension was heated to reflux for 16 h under nitrogen. The mixture was partitioned between ethyl acetate (200 mL) and water (50 mL). The organic phase was washed with water (50 mL) and brine (50 mL), dried, and evaporated. The residue was purified by chromatography using ethyl acetate–petroleum ether (60–80 °C) (1:1) to give the thioether **20** as a yellow solid (476 mg, 86%): mp 46–47 °C; $^1H$ NMR ($CDCl_3$) $\delta$ 7.40–7.90 (5H, m, phenyl and imidazopyridazine 4-H), 6.19 (1H, d, $J$ = 10 Hz, imidazopyridazine 3-H), 3.05 (2H, t, $J$ = 7.5 Hz, Het-$CH_2$), 2.95 (2H, t, $J$ = 7.5 Hz, $PhCOCH_2$), 2.55 (3H, s, Het-$CH_3$), 2.42 (3H, s, $CH_3S$), 1.37–1.90 (8H, m, $(CH_2)_4$). Anal. $C_{21}H_{25}N_3OS$ (C, H, N).

**7-[2-(Dimethylamino)-5-methylimidazo[1,5-*b*]pyridazin-7-yl]-1-phenyl-1-heptanone (21).** This procedure illustrates the general method of preparation of compounds **21** and **22**.

**Method H (See Table IV).** A solution of the hydrochloride salt of compound **15c** (300 mg, 0.765 mmol) in 33% w/w dimethylamine in ethanol (20 mL) was heated to reflux for 18 h. The solution was diluted with ethyl acetate (100 mL), washed with water (2 × 50 mL) and brine (50 mL), dried, and evaporated.

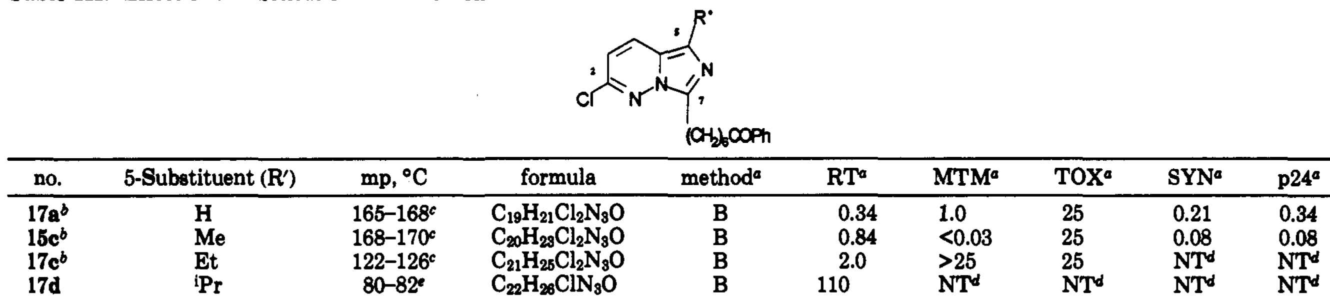
**Table II.** Effect of 7-Substitution on Inhibition of HIV-1 in a Series of Imidazopyridazines



| no. | 7-substituent (R) | mp, °C | formula | method[a] | RT[b] | MTM[c] | TOX[d] | SYN[e] | p24[f] |
|---|---|---|---|---|---|---|---|---|---|
| 15a | $(CH_2)_5OC(=O)Ph$ | 53–54 | $C_{18}H_{20}ClN_3O_2$ | B | 1.3 | 0.78 | >25 | 1.6 | 1.1 |
| 15b[g] | $(CH_2)_5OCH_2Ph$ | 130–132[h] | $C_{19}H_{23}Cl_2N_3O$ | B | 2.3 | 1.3 | 290 | 0.58 | 0.38 |
| 15c[g] | $(CH_2)_6C(=O)Ph$ | 168–170[h] | $C_{20}H_{23}Cl_2N_3O$ | B | 0.84 | <0.03 | 25 | 0.08 | 0.08 |
| 15d[g] | $(CH_2)_7Ph$ | 129–130[h] | $C_{20}H_{25}Cl_2N_3$ | B | 14 | >250 | 250 | NT[i] | NT[i] |
| 15e | $(CH_2)_5C(=O)CH_2Ph$ | gum | $C_{20}H_{22}ClN_3O$ | B | 3.9 | 28 | 28 | NT[i] | NT[i] |
| 15f[g] | $(CH_2)_5C(=O)Ph$ | 144–147[h] | $C_{19}H_{21}Cl_2N_3O$ | B | 4.8 | >250 | 250 | NT[i] | NT[i] |
| 15g[g] | $(CH_2)_7C(=O)Ph$ | 155–157[h] | $C_{21}H_{25}Cl_2N_3O$ | B | 3.0 | 25 | 250 | NT[i] | NT[i] |
| 15h[g] | $(CH_2)_5OH$ | 176–178[h] | $C_{12}H_{17}Cl_2N_3O$ | C | >100 | NT[i] | NT[i] | NT[i] | NT[i] |
| 15i[g] | $(CH_2)_5OC(=O)Me$ | 149–151[h] | $C_{14}H_{19}Cl_2N_3O_2$ | D | 110 | NT[i] | NT[i] | NT[i] | NT[i] |
| 15j[g] | $(CH_2)_5OC(=O)^{cyc}Pn$ | 129–131[h] | $C_{18}H_{25}Cl_2N_3O_2$ | D | 22 | >250 | 250 | NT[i] | NT[i] |
| 37[g] | $(CH_2)_6CH(OH)Ph$ | 120–123[h] | $C_{20}H_{25}Cl_2N_3O$ | M | 0.38 | 0.86 | 250 | <0.08 | <0.08 |

[a] For methods, see the Experimental Section. [b] $IC_{50}$ *versus* reverse transcriptase of HIV-1 (μM), AZT triphosphate control = 0.02 ± 0.005 μM. [c] $EC_{50}$ *versus* HIV-1 (strain RF)-infected MT-4 cells (μM), AZT triphosphate = 0.002–0.02 μM. [d] $IC_{50}$ *versus* uninfected MT-4 cells (μM). [e] $EC_{50}$ *versus* syncytia formation in infected C8166-cells (μM), AZT triphosphate = 0.02–0.2 μM. [f] $EC_{50}$ *versus* p24 antigen formation in infected C8166-cells (μM), AZT triphosphate = 0.02–0.2 μM. [g] Isolated as hydrochloride salt. [h] Salts were crystallized from 2-propanol–diethyl ether mixtures. [i] NT signifies not tested.

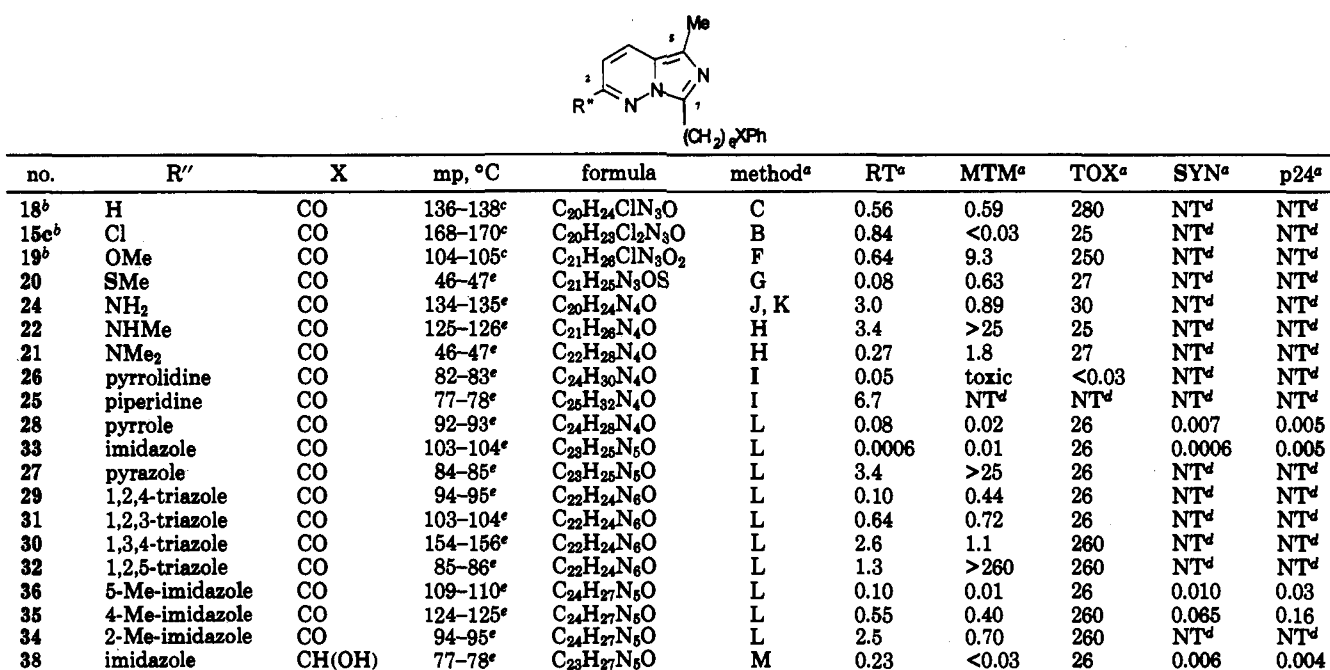
**Table III.** Effect of 5-Substitution on Inhibition of HIV-1



| no. | 5-Substituent (R′) | mp, °C | formula | method[a] | RT[a] | MTM[a] | TOX[a] | SYN[a] | p24[a] |
|---|---|---|---|---|---|---|---|---|---|
| 17a[b] | H | 165–168[c] | $C_{19}H_{21}Cl_2N_3O$ | B | 0.34 | 1.0 | 25 | 0.21 | 0.34 |
| 15c[b] | Me | 168–170[c] | $C_{20}H_{23}Cl_2N_3O$ | B | 0.84 | <0.03 | 25 | 0.08 | 0.08 |
| 17c[b] | Et | 122–126[c] | $C_{21}H_{25}Cl_2N_3O$ | B | 2.0 | >25 | 25 | NT[d] | NT[d] |
| 17d | $^iPr$ | 80–82[e] | $C_{22}H_{26}ClN_3O$ | B | 110 | NT[d] | NT[d] | NT[d] | NT[d] |

[a] For definitions, see Table II. [b] Isolated as hydrochloride salt. [c] Salts were crystallized from 2-propanol–diethyl ether mixtures. [d] NT signifies not tested. [e] Crystallized from ethyl acetate–cyclohexane mixtures.

**Table IV.** Effect of 2-Substitution on Inhibition of HIV-1



| no. | R″ | X | mp, °C | formula | method[a] | RT[a] | MTM[a] | TOX[a] | SYN[a] | p24[a] |
|---|---|---|---|---|---|---|---|---|---|---|
| 18[b] | H | CO | 136–138[c] | $C_{20}H_{24}ClN_3O$ | C | 0.56 | 0.59 | 280 | NT[d] | NT[d] |
| 15c[b] | Cl | CO | 168–170[c] | $C_{20}H_{23}Cl_2N_3O$ | B | 0.84 | <0.03 | 25 | NT[d] | NT[d] |
| 19[b] | OMe | CO | 104–105[c] | $C_{21}H_{26}ClN_3O_2$ | F | 0.64 | 9.3 | 250 | NT[d] | NT[d] |
| 20 | SMe | CO | 46–47[e] | $C_{21}H_{25}N_3OS$ | G | 0.08 | 0.63 | 27 | NT[d] | NT[d] |
| 24 | $NH_2$ | CO | 134–135[e] | $C_{20}H_{24}N_4O$ | J, K | 3.0 | 0.89 | 30 | NT[d] | NT[d] |
| 22 | NHMe | CO | 125–126[e] | $C_{21}H_{26}N_4O$ | H | 3.4 | >25 | 25 | NT[d] | NT[d] |
| 21 | $NMe_2$ | CO | 46–47[e] | $C_{22}H_{28}N_4O$ | H | 0.27 | 1.8 | 27 | NT[d] | NT[d] |
| 26 | pyrrolidine | CO | 82–83[e] | $C_{24}H_{30}N_4O$ | I | 0.05 | toxic | <0.03 | NT[d] | NT[d] |
| 25 | piperidine | CO | 77–78[e] | $C_{25}H_{32}N_4O$ | I | 6.7 | NT[d] | NT[d] | NT[d] | NT[d] |
| 28 | pyrrole | CO | 92–93[e] | $C_{24}H_{28}N_4O$ | L | 0.08 | 0.02 | 26 | 0.007 | 0.005 |
| 33 | imidazole | CO | 103–104[e] | $C_{23}H_{25}N_5O$ | L | 0.0006 | 0.01 | 26 | 0.0006 | 0.005 |
| 27 | pyrazole | CO | 84–85[e] | $C_{23}H_{25}N_5O$ | L | 3.4 | >25 | 26 | NT[d] | NT[d] |
| 29 | 1,2,4-triazole | CO | 94–95[e] | $C_{22}H_{24}N_6O$ | L | 0.10 | 0.44 | 26 | NT[d] | NT[d] |
| 31 | 1,2,3-triazole | CO | 103–104[e] | $C_{22}H_{24}N_6O$ | L | 0.64 | 0.72 | 26 | NT[d] | NT[d] |
| 30 | 1,3,4-triazole | CO | 154–156[e] | $C_{22}H_{24}N_6O$ | L | 2.6 | 1.1 | 260 | NT[d] | NT[d] |
| 32 | 1,2,5-triazole | CO | 85–86[e] | $C_{22}H_{24}N_6O$ | L | 1.3 | >260 | 260 | NT[d] | NT[d] |
| 36 | 5-Me-imidazole | CO | 109–110[e] | $C_{24}H_{27}N_5O$ | L | 0.10 | 0.01 | 26 | 0.010 | 0.03 |
| 35 | 4-Me-imidazole | CO | 124–125[e] | $C_{24}H_{27}N_5O$ | L | 0.55 | 0.40 | 260 | 0.065 | 0.16 |
| 34 | 2-Me-imidazole | CO | 94–95[e] | $C_{24}H_{27}N_5O$ | L | 2.5 | 0.70 | 260 | NT[d] | NT[d] |
| 38 | imidazole | CH(OH) | 77–78[e] | $C_{23}H_{27}N_5O$ | M | 0.23 | <0.03 | 26 | 0.006 | 0.004 |

[a] For definitions, see Table II. [b] Isolated as hydrochloride salt. [c] Salts were crystallized from 2-propanol–diethyl ether mixtures. [d] NT signifies not tested. [e] Crystallized from diethyl ether–petroleum ether mixtures.

The residue was purified by chromatography using ethyl acetate–petroleum ether (60–80 °C) (1:1) to give the amine **21** as a yellow solid (90 mg, 32%): mp 109–110 °C; $^1H$ NMR ($CDCl_3$) δ 7.39–7.94 (5H, m, phenyl and imidazopyridazine 4-H), 6.22 (1H, d, $J$ = 10 Hz, imidazopyridazine 3-H), 3.06 (6H, s, $(CH_3)_2N$–), 2.99 (2H, t, $J$ = 7.5 Hz, Het-$CH_2$), 2.94 (2H, t, $J$ = 7.5 Hz, $PhCOCH_2$), 2.40 (3H, s, Het-$CH_3$), 1.37–1.91 (8H, m, $(CH_2)_4$). Anal. $C_{22}H_{28}N_4O$ (C, H, N).

**Table V.** Comparison of **3**, **33**, and AZT

| no. | MTM[a] | SYN[a] | p24[a] | A17[b] |
|---|---|---|---|---|
| **3** | 0.007 | 0.007 | 0.007 | >10 |
| **33** | 0.008 | 0.0006 | 0.005 | 1.9 |
| AZT | 0.003 | 0.03 | 0.02 | 0.01 |

[a] For definitions, see Table II. [b] $EC_{50}$ *versus* HIV-1 (strain A17)-infected MT-4 cells (μM).

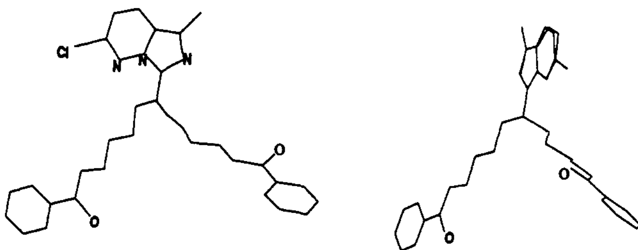



**Figure 1.** Crystal structure of **15c**.

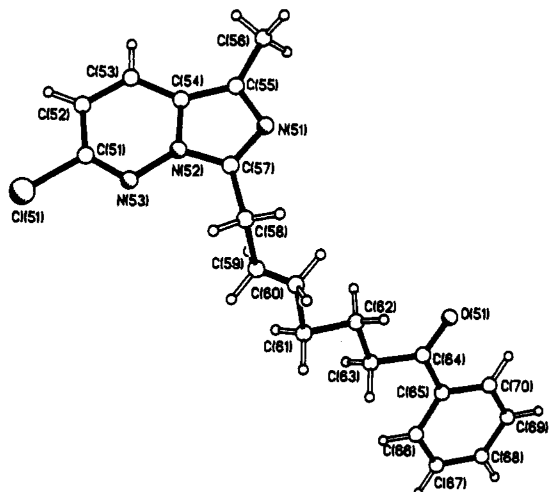



**Figure 2.** Representation of one conformer of crystal structure of **15c**.

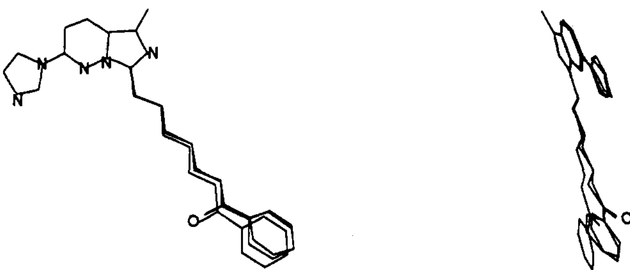



**Figure 3.** Crystal structure of **33**.

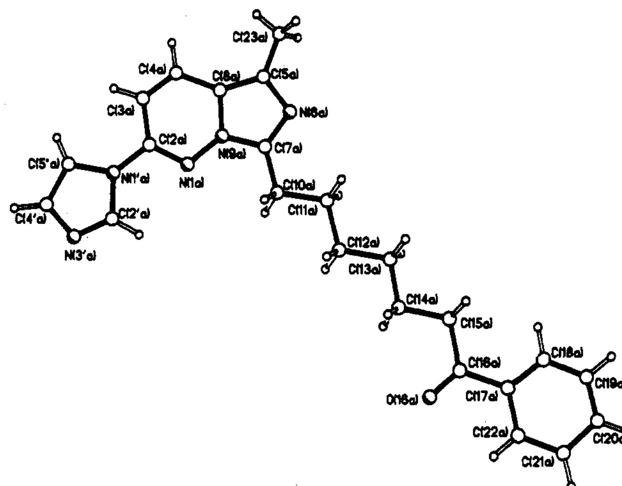


**Figure 4.** Representation of one conformer of crystal structure of **33**.

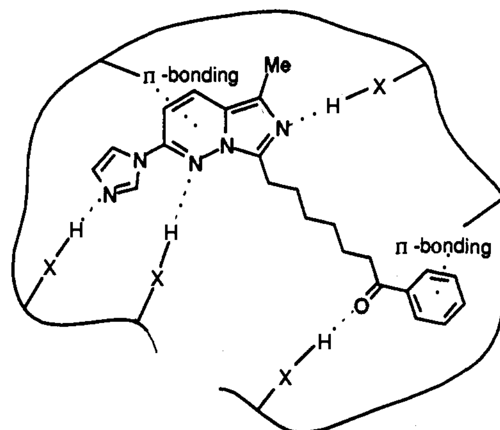



**Figure 5.** Possible interaction of **33** with RT.

**7-[5-Methyl-2-(1-pyrrolidinyl)imidazo[1,5-*b*]pyridazin-7-yl]-1-phenyl-1-heptanone (26).** This procedure illustrates the general method of preparation of compounds **25** and **26**.

**Method I (See Table IV).** A solution of compound **15c** (150 mg, 0.382 mmol) in pyrrolidine (15 mL) was heated at reflux for 18 h and then evaporated to dryness. The residue was partitioned between ethyl acetate (50 mL) and water (25 mL). The organic phase was washed with brine (25 mL), dried, and evaporated. The residue was purified by chromatography to give a yellow solid of the amine **26** (73 mg, 49%): mp 82–83 °C; $^1$H NMR ($CDCl_3$) δ 7.41–7.94 (5H, m, phenyl), 7.41 (1H, d, *J* = 10 Hz, imidazopyridazine 4-H), 6.08 (1H, d, *J* = 10 Hz, imidazopyridazine 3-H), 3.42–3.52 (4H, m, $(CH_2)_2N$), 2.98 (2H, t, *J* = 7.5 Hz, Het-$CH_2$), 2.94 (2H, t, *J* = 7.5 Hz, $PhCOCH_2$), 2.40 (3H, s, Het-$CH_3$), 1.95–2.04 (4H, m, $(CH_2CH_2)_2N$), 1.36–1.92 (8H, m, $(CH_2)_4$). Anal. $C_{24}H_{30}N_4O$ (C, H, N).

**7-[2-[[(4-Methoxyphenyl)methyl]amino]-5-methylimidazo[1,5-*b*]pyridazin-7-yl]-1-phenyl-1-heptanone (23). Method J (See Table IV).** A solution of the compound **15c** (178 mg, 0.5 mmol) in (4-methoxyphenyl)methylamine (5 mL) was heated to 100–120 °C under nitrogen for 16 h and then partitioned between ethyl acetate (100 mL) and water (50 mL). The organic phase was washed with water (25 mL) and brine (25 mL), dried, and evaporated. The residue was purified by chromatography using ethyl acetate–petroleum ether (60–80 °C) (1:1, 2:1) to give a yellow solid of the amine **23** (80 mg, 35%): mp 112–113 °C; $^1$H NMR ($CDCl_3$) δ 7.40–7.93 (5H, m, phenyl), 7.37 (1H, d, *J* = 10 Hz, imidazopyridazine 4-H), 7.32 (2H, d, *J* = 8 Hz) and 6.87 (2H, d, *J* = 8 Hz) ($MeOC_6H_4$), 5.82 (1H, d, *J* = 10 Hz, imidazopyridazine 3-H), 4.40–4.48 (3H, m, $CH_2NH$), 3.79 (3H, s, $OCH_3$), 2.97 (2H, t, *J* = 7.5 Hz, Het-$CH_2$), 2.93 (2H, t, *J* = 7.5 Hz, $PhCOCH_2$), 2.39 (3H, s, Het-$CH_3$), 1.38–1.90 (8H, m, $(CH_2)_4$). Anal. $C_{28}H_{32}N_4O \cdot 0.5H_2O$ (C, H, N).

**7-(2-Amino-5-methylimidazo[1,5-*b*]pyridazin-7-yl)-1-phenyl-1-heptanone (24). Method K (See Table IV).** A solution of compound **23** (3.3 g, 7.23 mmol) in a mixture of trifluoroacetic acid (20 mL) and anisole (4 mL) was stirred at 20 °C for 3 h. The solvent was evaporated, and residual trifluoroacetic acid was removed by addition and evaporation of ethanol (3 × 25 mL). The residue was partitioned between ethyl acetate (250 mL) and saturated sodium bicarbonate (100 mL). The organic phase was washed with water (100 mL) and brine (100 mL), dried, and evaporated. The residue was suspended in ethyl acetate (10 mL) and ether (40 mL), stirred, and filtered. The solid was dried *in vacuo* to give the amine **24** as a yellow solid (1.98 g, 81%): mp 134–135 °C; $^1$H NMR ($CDCl_3$) δ 7.40–7.96 (5H, m, phenyl), 7.96 (1H, d, *J* = 10 Hz, imidazopyridazine 4-H), 5.92 (1H, d, *J* = 10 Hz, imidazopyridazine 3-H), 4.33 (2H, br s, $NH_2$), 2.97 (2H, t, *J* = 7.5 Hz, Het-$CH_2$), 2.93 (2H, t, *J* = 7.5 Hz, $PhCOCH_2$), 2.40 (3H, s, Het-$CH_3$), 1.38–1.90 (8H, m, $(CH_2)_4$). Anal. $C_{20}H_{24}N_4O$ (C, H, N).

**7-[2-(1*H*-Imidazol-1-yl)-5-methylimidazo[1,5-*b*]pyridazin-7-yl]-1-phenyl-1-heptanone (33).** This procedure illustrates the general method of preparation of compounds **27–36**.

**Method L (See Table IV).** Imidazole (408 mg, 6 mmol) was added to a stirred suspension of sodium hydride (144 mg, 6 mmol) in *N,N*-dimethylformamide (25 mL) under an atmosphere of nitrogen, and the mixture was stirred at 20 °C for 30 min. The chloro compound **15c** (1.07 g, 3 mmol) was added, and the mixture was stirred at 60 °C for 18 h. The cooled solution was diluted with ethyl acetate (500 mL) and the organic solution washed with water (10 × 100 mL) and brine (100 mL). The solution was dried and evaporated to give an oil which solidified on standing. This was purified by column chromatography using ethyl acetate–ethanol (20:1) as eluant to give a yellow solid, which was washed with petroleum ether (40–60 °C) to give the imidazole **33** (1.01 g, 87%): mp 103–104 °C; $^1$H NMR ($CDCl_3$) $\delta$ 8.24 (1H, s, imidazole 2'-H), 7.84 (1H, d, $J$ = 8 Hz, imidazopyridazine 4-H), 7.45–7.95 (5H, m, phenyl), 7.65 (1H, s), + 7.24 (1H, s,) (imidazole 4'-H, 5'-H), 6.59 (1H, d, $J$ = 8 Hz, imidazopyridazine 3-H), 3.10 (2H, t, $J$ = 7 Hz, Het-$CH_2$), 2.97 (2H, t, $J$ = 7 Hz, $PhCOCH_2$), 2.52 (3H, s, Het-$CH_3$), 1.40–1.95 (8H, m, $(CH_2)_4$). Anal. $C_{23}H_{25}N_5O$ (C, H, N).

**(1'*RS*)-2-Chloro-5-methyl-α-phenyl-7-imidazo[1,5-*b*]pyridazineheptanol Hydrochloride (37).** This procedure illustrates the general method of preparation of compounds **37** and **38**.

**Method M (See Table IV).** A solution of **15c** (71 mg, 0.2 mmol) in ethanol (1 mL) was treated with sodium borohydride (15 mg, 0.4 mmol). The mixture was stirred at 20 °C under nitrogen for 16 h. More sodium borohydride (7.5 mg, 0.2 mmol) was then added, and the mixture was stirred for a further 3 days. The solvent was evaporated, and the residue was taken up in ethyl acetate (20 mL). The organic solution was washed with water (2 × 10 mL) and brine (10 mL), dried, and evaporated. The residue was purified by column chromatography using cyclohexane–ethyl acetate (1:1) as eluant to give a yellow gum (68 mg). This gum was dissolved in diethyl ether (2 mL), and an excess of ethereal hydrogen chloride was added dropwise. The mixture was stirred at 20 °C for 5 min, filtered, and washed with diethyl ether. The white solid was dried *in vacuo* at 20 °C to give the alcohol **37** (55 mg, 70%): mp 120–123 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.90 (1H, d, $J$ = 9 Hz, imidazopyridazine 4-H), 7.25–7.45 (5H, m, phenyl), 6.84 (1H, d, $J$ = 8 Hz, imidazopyridazine 3-H), 4.74 (1H, q, $CH(OH)$), 3.40 (2H, t, $J$ = 7 Hz, Het-$CH_2$), 2.80 (3H, s, Het-$CH_3$), 1.30–2.10 (11H, m, $(CH_2)_5$ and $OH$). Anal. $C_{20}H_{24}ClN_3O{\cdot}HCl$ (C, H, N).

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**Supplementary Material Available:** Atomic coordinates, bond lengths, bond angles, anisotropic displacement coefficients, and hydrogen coordinates for compounds **15c** and **33** (14 pages); structure factor listings for compounds **15c** and **33** (50 pages). Ordering information is given on any current masthead page.

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