Design and Synthesis of Novel Inhibitors of HIV-1 Reverse Transcriptase

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A variety of N1-substituted pyrimido[5,4-*f*]benzo[1,4]thiazepines, **5**, designed as conformationally constrained analogs of 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine HEPT (**1**), were synthesized and evaluated for their inhibition of human immunodeficiency virus type 1 (HIV-1) reverse transcriptase (RT). The preparation of these compounds was carried out based on a Mannich-type cyclization of 6-[(2-aminophenyl)thio]uracils followed by alkylation at N1 by a one-pot Vorbruggen reaction. The pyrimidobenzothiazepines were developed to give molecules with IC_{50} values in the micromolar range, as exemplified by [[(2-ethoxyethyl)oxy]methyl]-pyrimido[5,4-*f*]benzo[1,4]thiazepine, **25**, (IC_{50} = 0.64 μM), the most active compound of this series. The structural and electronic features of this novel class of HIV-1 RT inhibitors are presented and compared with those of HEPT (**1**), TIBO (**2**), and nevirapine (**3**).

Introduction

Human immunodeficiency virus 1 (HIV-1) the causative agent of the acquired immune deficiency syndrome (AIDS)[1-3] utilizes a reverse transcriptase (RT) that plays a central role in the replicative life cycle of the virus. This enzyme to date has been one of the main chemotherapeutic targets in efforts to control infections. A large number of molecules have been designed and synthesized to target various active sites on this enzyme. Among these are the chain terminators, the nucleoside analogs, 3′-azidothymidine (AZT),[4] 2′,3′-dideoxycytidine (DDC),[5] 2′,3′-dideoxyinosine (DDI),[6] and more recently 2′,3′-didehydro-3′-deoxythymidine (d4T).[7] Although already approved for clinical use for patients with AIDS, the toxicity associated with these drugs together with the emergence of resistant strains of the virus have raised the need for molecules with a different mode of action. This, in part, has been achieved with the so called "non-nucleoside" inhibitors such as 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine (HEPT),[8] **1**; tetrahydroimidazo[4,5,1-*jk*]benzodiazepine-2(1*H*)-thione (TIBO),[9] **2**; the dipyridodiazepine, nevirapine (BI-RG-587,[10] **3**; and the 2-pyridinone derivatives, e.g., L 697,661,[11] **4** (Figure 1). Furthermore, mutational and kinetic studies have provided evidence that argues for a common site of action for HEPT, TIBO, and nevirapine.[12] This has been identified as the modulatory site, RT_1MS, and when occupied by any of these molecules the polymerase activity of RT is inhibited.[13,14]

Extensive structure–activity studies have been conducted on all of these compounds. However, no investigations seemed to have been made to develop cyclic variants in the HEPT series. The elaboration of such compounds seemed to be an attractive objective because information might be obtained concerning which of the conformational forms of this molecule is associated with its biological activity. This in turn would aid in the development of a specific subset of analogs of this class.

Our first goal, and the subject of this report, was the development of a series of compounds in which the rotation and positioning of the phenyl ring with respect to the pyrimidine ring is restricted. This objective had its origins in the observation that increasingly larger alkyl substituents at the 5-position of the HEPT molecule seemed to confer correspondingly greater biological activity. Thus, both the ethyl and propyl derivatives are considerably more potent than the 5-methyl homologue.[15] We concluded that the net effect of increasing bulk at the 5-position is to restrict the rotation of the phenyl group around both the Θ and Ψ bonds as shown in Figure 2 and thus to produce larger concentrations of the rotamer associated with biological activity.

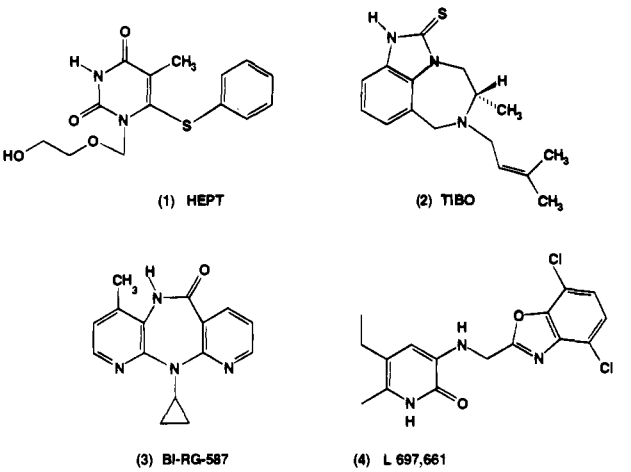

Figure 1. Non-nucleoside RT inhibitors: 1-[(2-hydroxyethoxy)-methyl]-6-(phenylthio)thymine (HEPT, 1); tetrahydroimidazo-[4,5,1-*jk*]benzodiazepine-2(1*H*)-thione (TIBO, **2**); nevirapine (BI-RG-587, **3**); and 2-pyridinone (L 697,661, **4**).

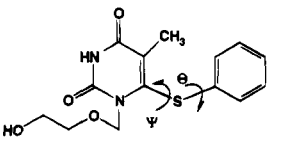

Figure 2. Rotors Θ and Ψ in HEPT.

The constraint used in this work is an aminomethyl bridge between the C5 of the pyrimidine and C2 of the thiophenyl group, thus generating compounds represented by **5** (Figure 3). This was chosen not only because it would constrain the rotations mentioned above but also because the resulting 6,7,6, tricyclic framework would likely be accommodated by the enzyme as judged from the activity of nevirapine (**3**). In

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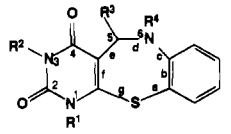
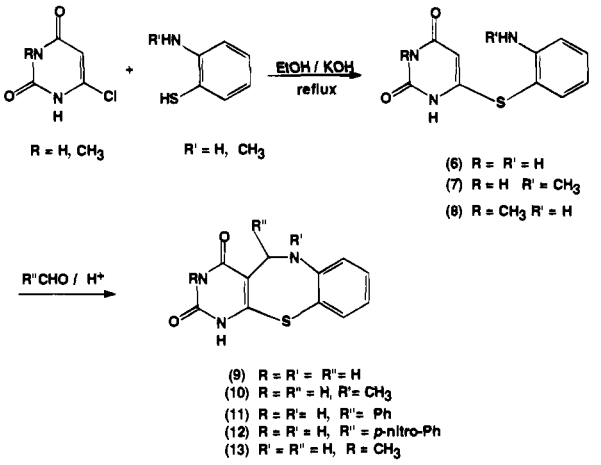


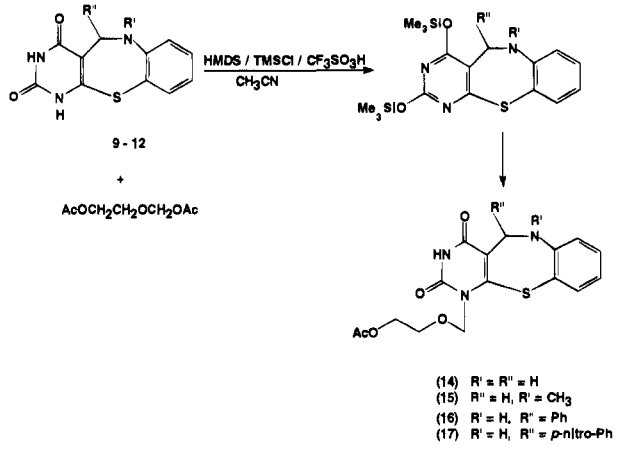
5

Figure 3. General structure of pyrimido[5,4-*f*]benzo[1,4]-thiazepine.

Scheme 1



Scheme 2



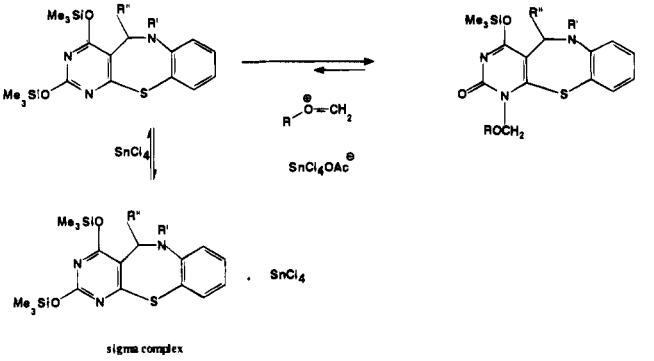
addition there was good literature precedent for the synthesis of such tricyclic molecules.[16] One of the early representatives of the new series showed a dose-dependent inhibition of HIV-1 RT,[17] and we now present the synthetic and biological results of our investigations on this novel class of inhibitors of HIV-1 RT.

Chemistry

The general approach utilized in the synthesis of the desired tricyclic compounds **5** is outlined in Schemes 1 and 2. The starting materials, 6-(arylthio)uracils **6**–**8** were synthesized by heating 6-chlorouracils with 2-aminothiophenols under reflux in ethanol in the presence of potassium hydroxide. The products were then treated with the appropriate aldehydes under acidic conditions, to yield the desired thiazepines **9**–**13** through an intramolecular Mannich-type cyclization.[16]

Thereafter, the trimethylsilyl derivatives of **9**–**12** were condensed with 2-acetoxyethyl acetoxymethyl ether in a one-pot Vorbruggen reaction[18] to yield **14**–**17** in moderate to good yields 50–71% (Scheme 2). This reaction was initially attempted employing stannic

Scheme 3



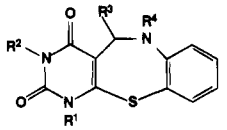
chloride[19] as the Lewis acid catalyst in methylene chloride, but the yields were low (10–20%). Previous work by Vorbruggen suggested the use of TMS-triflate as the Lewis acid catalyst and acetonitrile as the solvent medium. They identified that the formation of a σ complex between the silylated base and the catalyst was taking place and that this seemed to interfere with the progress of the reaction, increasing the reaction time and decreasing the yield. The stability of this complex would relate directly to the basicity of the heterocycle and inversely to both the strength of the Lewis acid catalyst and the polarity of the solvent.[20,21] Analogously, the highly basic nature of our benzothiazepine ring and our initial negative results indicated the formation of a remarkably stable σ-complex between these species (Scheme 3) with almost no reaction taking place. Hence, upon replacing $SnCl_4$ by the weaker Friedel–Crafts catalyst TMS-triflate and methylene chloride by acetonitrile, the yields were substantially improved.

It is noteworthy that upon applying Vorbruggen's exact conditions to **13**, alkylation at N1 did not take place. The silylation of these tricycles proceeded as expected (followed by ^1H NMR), and hence we suspect, based on molecular models (Hyperchem), that the N3-methyl reorientates the methyl groups of the silyl function of this compound toward N1. This conformational preference is consistent with the ideas of $A^{(1,3)}$ allylic strain.[22] The nitrogen then becomes embedded between these methyl groups and the sulfur atom and probably is no longer accessible to the acyl cation. In a simple alternate approach, compound **18** (Table 1) was synthesized by heating **14** with MeI (1.0 equiv) in the presence of K_2CO_3 with DMSO as solvent to give **18** in 70% yield.

Treatment of the acetate esters **14**, **16**, and **17** with ammonia then gave rise to the target molecules **19**–**21** (Table 1) in 50–60% yields. These proved to be highly insoluble materials, and it was possible to recrystallize only **20**. The X-ray analysis of this derivative however furnished proof of structure of these compounds as N1-alkylated pyrimido[5,4-*f*]benzo[1,4]thiazepines (Figure 4) and furthermore helped to validate the data obtained by molecular modeling calculations associated with our SAR studies.

The more constrained thiazepine **22** was obtained by boiling **6** triphosgene in acetonitrile for 48 h. The side chain at position 1 was introduced by the one-pot Vorbruggen method outlined above to afford **23** in 12% yield (Scheme 4). That selective alkylation had occurred at N1 was confirmed by the observation of an NOE of

Table 1. Structure and Antiviral Activity of Novel Pyrimidobenzothiazepines in the RT Assay[a]



compd no.	R^1	R^2	R^3	R^4	IC_{50}[b] (μM)
19	$HO(CH_2)_2OCH_2$	H	H	H	>100
9	H	H	H	H	>100
15	$AcO(CH_2)_2OCH_2$	H	H	Me	14.7
18	$AcO(CH_2)_2OCH_2$	Me	H	H	>100
16	$AcO(CH_2)_2OCH_2$	H	Ph	H	>100
20	$HO(CH_2)_2OCH_2$	H	Ph	H	>100
21	$HO(CH_2)_2OCH_2$	H	*p*-NO_2Ph	H	>100
23	$AcO(CH_2)_2OCH_2$	H	=O	H	>100
14	$AcO(CH_2)_2OCH_2$	H	H	H	11.5
24	$CH_3CH_2OCH_2$	H	H	H	50.20
25	$EtO(CH_2)_2OCH_2$	H	H	H	0.64

[a] The HIV-1 reverse transcriptase enzyme assay was performed in Boehringer Mannheim GmbH and the procedure is described elsewhere.[26] These compounds were rated against TIBO (IC_{50} = 0.16 μM) and BI-RG-587 (IC_{50} = 0.43 μM). [b] Concentration of inhibitor that produced 50% inhibition (mean values from at least two independent assays).

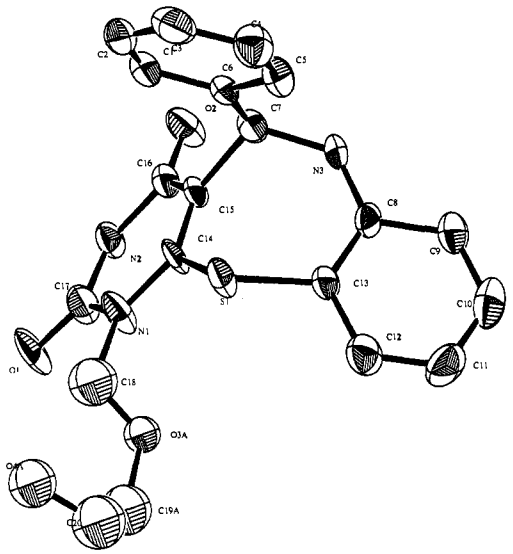
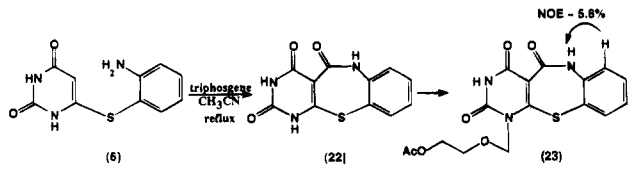


Figure 4. X-ray structure of **20**.

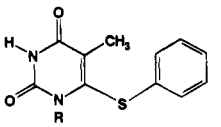
Scheme 4



5.82% between the azepine amino hydrogen and the aromatic hydrogen of the benzene ring (see arrows in Scheme 4).

Our initial biological results suggested the need to incorporate both the ethoxymethyl and [(2-ethoxyethyl)-oxy]methyl side chains onto the parent tricyclic intermediate **9**. This was accomplished by the condensation of **9** (as its trimethylsilyl derivative) with chloromethyl ethyl ether which afforded the target compound **24** (Table 1) in 33% yield. The synthesis of the other derivative, [[(2-ethoxyethyl)oxy]methyl]pyrimido[5,4-*f*]-benzo[1,4]thiazepine **25** (Table 1) was accomplished in 39% yield by allowing **19** to react with ethyl bromide in the presence of 2 equiv of sodium hydride in DMSO.

Table 2. Dependence of EC_{50}[a] in the Substituent at 1-Position of the Pyrimidine Moiety of HEPT[23]



compd	R	EC_{50} (μM)
HEPT	$HO(CH_2)_2OCH_2$	6.5 ± 1
	H	>250
BPT	$PhCH_2OCH_2$	0.088 ± 0.012
EPT	$CH_3CH_2OCH_2$	0.33 ± 0.3
O-methylated	$CH_3OCH_2CH_2OCH_2$	8.7 ± 0.1

[a] Effective concentration of compound required to achieve 50% protection of MT-4 cells against cytopathic effect of HIV-1.

Results and Discussion

The lead molecule [(2-hydroxyethoxy)methyl]pyrimidobenzothiazepine (**19**) was shown to exhibit dose-dependent inhibition of reverse transcriptase, although the IC_{50} proved to be disappointingly high. Structure–activity investigations performed on HEPT have revealed that the inhibitory profile shows a marked dependence on the nature of the side chain at the 1-position[23] (Table 2). In view of this, a series of analogous modifications were made to compound **19** and are exemplified with derivatives **9**, **14**, **24**, and **25**. The biological activities of these compounds are shown in Table 1.

Both the inactivity of compound **9**, which demonstrated the essential requirement for the side chain functionality, and the improved activity of the acetylated derivative **14**, relative to **19**, showed a behavior exactly paralleled in related HEPT analogs.[23] We therefore chose to synthesize compound **24**, which contained an ethoxymethyl side chain, the N1-substituent present in the most potent HEPT analog, namely EPT, shown in Table 2. Contrary to what was expected, the IC_{50} value of **24** was lower than that of **14**, demonstrating that although there is obviously a relationship among these thiazepine derivatives and the HEPT series, significant differences do exist.

In light of this result it was considered important to go back to the acetate derivative **14** to study this group in more detail. The nature of the interaction of this part of the molecule with the enzyme is not clear. However, it seemed likely that the methyl group of the acetyl function may be binding to a hydrophobic pocket in the active site of the enzyme. To optimize this interaction, it was decided to reduce the polarity of the side chain in **14** and prepare the [(ethoxyethyl)oxy]methyl ether derivative **25** in which the carbonyl group of the acetyl function has been replaced by a methylene group. Surprisingly, this modification generated the most active compound presented in this work, which showed a 20-fold increase in activity relative to compound **14**. This result would seem to support the above hypothesis.

In an attempt to improve the activity of these compounds further, our studies next focused on positions on the tricyclic framework amenable to modifications, such as N3, C5, and N6.

It has been shown that alkyl substitution at N3 in the HEPT series results in loss of inhibitory activity.[24]

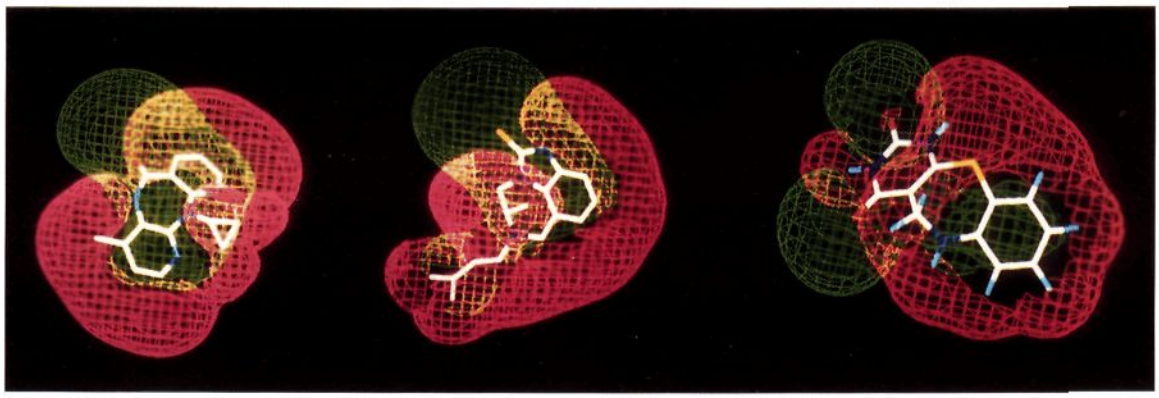


Figure 5. Electrostatic isopotential maps derived from a point charge model using MNDO charges:[25] (**3**) left, (**2**) middle, and (**14**) right.

Consistent with this result, compound **18** was found to be inactive, confirming that the imidic hydrogen of **14** is essential for activity.

The introduction of substituents at C5, as exemplified by compounds **16**, **20**, and **21**, also resulted in complete loss of activity. Furthermore, substitution at N6 was found to reduce activity, as exemplified by the comparison of the IC_{50} values of compounds **15** and **14**. These results can be interpreted in a number of ways; however, simple molecular mechanics studies suggested that a consequence of substitution at C5 is a reorientation of the benzene ring with respect to the pyrimidine moiety. Substitution at N6 results in a similar but smaller reorientation. The importance of the placement of these two aromatic moieties with respect to each other is emphasized in recent studies, in which the relative orientation of these two groups was shown to be a principal determinant of activity.[25,26] To validate the comparison between the molecules presented in Table 1 and those discussed by Schaeffer et al.,[25] we compared the electrostatic–isopotential surface of **14** with their compounds. It can be appreciated from the results shown in Figure 5 that compound **14** possesses a very similar electrostatic profile to those of the non–nucleoside inhibitors TIBO (**2**) and nevirapine (**3**), suggesting that these compounds act in a comparable manner.

The other aspect addressed in attempts to optimize the lead compound **19** was the introduction of further conformational constraint. This was explored with molecule **23** by including a carbonyl group in the thiazepine ring. The rigidity associated with the resultant lactam function significantly limits the number of conformations accessible to this molecule. Unfortunately, **23** proved inactive in our biological assay, suggesting that the polarity introduced by the carbonyl group disrupts the binding interaction with the enzyme. Other sp^2 nonpolar hybridized centers will be introduced at this site to test this hypothesis, and this will be the subject of a future publication.

Conclusion

This paper presents preliminary studies in the development of a novel series of non-nucleoside HIV-1 RT inhibitors. By applying standard medicinal chemistry techniques a structurally novel compound **25** with activity (0.64 μM) similar to that of other compounds currently undergoing clinical evaluation, namely BI-RG-587 (0.43 μM)[25] and TIBO (0.16 μM),[25] was developed. However, it is likely that the pharmacophoric pattern of the molecule is still not optimal. The constrained analog **19** (with IC_{50} > 100 μM) might have been expected to show enhanced activity compared with HEPT (IC_{50} = 66 μM)[27] because of the elimination of unfavorable entropic factors associated with the binding of the ligand to the enzyme. A different-sized tricyclic system or a different linker between the aromatic systems might possibly lead to further optimization of the desired biological activity of the heterocycle. Work along these lines is currently being conducted in our laboratories.

Experimental Section

Melting points were determined with a Thomas-Hoover capillary apparatus and are uncorrected. Infrared spectra were recorded with a Perkin-Elmer 1600 Series FT-IR spectrometer calibrated against a polystyrene standard. The ^{1}H-NMR spectra were recorded with a General Electric QE 300 MHz instrument, and the ^{13}C-NMR spectra were recorded with a Bruker 250 MHz instrument, in DMSO-d_6, except where otherwise indicated. Chemical shifts are given in δ (ppm). The assignments of all exchangeable protons were confirmed by addition of D_2O. Low-resolution mass spectra were obtained on a HP 5980A spectrometer by using electron impact ionization at 70 eV. High-resolution mass spectra were determined with a Kratos MS-890 instrument. Elemental analysis was performed by Galbraith Laboratories, Inc. The X-ray data was collected on an Enraf Nonius CAD4 diffractometer using Cu Kα radiation. Purity of each compound was checked by TLC on aluminum-backed silica gel 60 F_{254} plates, and the spots were examined by UV light. Developing solvents were (A) EtOAc–$CHCl_3$–AcOH (6:3:1); (B) $CHCl_3$–MeOH–AcOH (32:1:1); (C) $CHCl_3$–MeOH–AcOH (17:2:1); (D) CH_2Cl_2–EtOAc (1:1); (E) CH_2Cl_2–MeOH–AcOH (64:1:2); (F) CH_2Cl_2–MeOH–AcOH (18:1:1), and (G) EtOAc–CH_2Cl_2–AcOH (6:12:2). TLC plates (silica gel GF 200 μm; Analtech reagent) were utilized for preparative TLC and silica gel 60, particle size 0.063–0.2 (70–230 mesh ASTM; EM reagent), was used for flash chromatography Dimethyl sulfoxide and acetonitrile were distilled from calcium hydride and stored under a nitrogen atmosphere prior to use. All other solvents were of reagent quality and used without further purification. 6-Chlorouracil[28] and 2-(*N*-methylamino)thiophenol[29] were synthesized following available procedures. All other reagents were commercially available.

Some of the compounds presented here could only be obtained by precipitation as intractable amorphous solids which resisted attempts to remove residual solvents by common drying techniques. This was apparent from their NMR spectra and the microanalytical data which were consistent with one another in showing the presence of fractional amounts of solvents per mole.

6-[(2-Aminophenyl)thio]uracil (6). 2-Aminothiophenol (2.94 mL, 0.028 mol) was added to a mixture of 6-chlorouracil (3.68 g, 0.025 mol) and KOH (1.54 g, 0.028 mol) in 140 mL of

EtOH (200 proof). The suspension was refluxed for 4 h under a nitrogen atmosphere, and the solvent was then removed under reduced pressure. The solid residue was suspended in water and the residual KOH neutralized with HCl (2 N). The suspended solid was filtered and then washed with ether to remove traces of 2-aminothiophenol. A faint yellow precipitate was recovered in 83% yield: mp 207 °C; R_f 0.56 (C, sample dissolved in CF_3CO_2H); ^{1}H NMR δ 4.46 (s, 1, C=CH), 5.65 (s, 2, NH_2), 6.59 (t, 1, ArH), 6.81 (d, 1, ArH), 7.25 (m, 2, ArH), 10.87 (s, 1, NH), 11.48 (s, 1, NH); MS *m/e* (relative intensity) 235 (M^+, 79.76), 237 ($M^+ + 2$, 9.64). Anal. ($C_{10}H_9N_3O_2S$) requires C, 51.05; H, 3.86; N, 17.86; Found: C, 50.73; H, 3.82; N, 17.65.

6-[[2-(*N*-methylamino)phenyl]thio]uracil (7). Using the procedure for **6**, compound **7** was obtained from 2-(*N*-methylamino)thiophenol (3.03 g, 0.022 mol) and 6-chlorouracil (2.88 g, 0.020 mol). The product was recrystallized from EtOH (90%) in 36% yield: mp 208 °C dec; R_f 0.68 (G); ^{1}H NMR δ 2.73 (s, 3H, CH_3), 4.40 (s, 1H, C=CH), 5.80 (br, 1H, N*H*CH_3), 6.69 (m, 2H, ArH), 7.41 (m, 2H, ArH), 10.80 (s, 1H, NH), 11.50 (s, 1H, NH); MS *m/e* (relative intensity) 249 (M^+, 100), 251 ($M^+ + 2$, 6). Anal. ($C_{11}H_{11}N_3O_2S$) Calcd: C, 52.99; H, 4.45; N, 16.86. Found: C, 52.72; H, 4.43; N, 16.69.

Preparation of Pyrimido[5,4-*f*]benzo[1,4]thiazepines Derivatives 9–12. General Procedure. The aldehyde (1.1 equiv) was added to a solution of **6** or **7** in CF_3CO_2H (5 mL/mmol), and the mixture was stirred at room temperature (3 h). The solvent was then removed under reduced pressure and the remaining oil treated with ice-cold water to form a yellow suspension. The residual acid was neutralized by the addition of solid $NaHCO_3$, and the product was recovered by filtration as an amorphous solid.

Pyrimido[5,4-*f*]benzo[1,4]thiazepine (9). The reaction of **6** (5 g, 0.0216 mol) and paraformaldehyde (0.66 g, 0.022 mol) gave **9** in 89% yield: mp 192–193 °C; R_f 0.33; ^{1}H NMR δ 4.26 (d, 2, CH_2, J = 4.5 Hz), 6.34 (t, NH, J = 4.5 Hz), 6.56 (m, 2, ArH), 6.99 (t, 2, ArH), 11.21 (s, 1, NH), 11.43 (s, 1, NH); MS *m/e* (relative intensity) 247 (M^+, 100). Anal. ($C_{11}H_9N_3O_2S$) Calcd: C, 53.43; H, 3.66; N, 16.99; S, 12.97. Found: C, 53.20; H, 3.60; N, 16.86; S, 13.09.

6-*N*-Methylpyrimido[5,4-*f*]benzo[1,4]thiazepine (10). The reaction of **7** (1.0 g, 4.0 mmol) and paraformaldehyde (0.13 g, 4.2 mmol) gave **10** in 94% yield: ^{1}H NMR δ 2.90 (s, 3, CH_3), 3.90 (s, 2, CH_2), 6.95 (t, 1, ArH), 7.10 (d, 1, ArH), 7.32 (m, 2, ArH), 11.17 (s, 1, NH), 11.35 (s, 1H, NH). The product was recovered slightly impure and was used as such for the next step.

5-Phenylpyrimido[5,4-*f*]benzo[1,4]thiazepine (11). The reaction of **6** (2.0 g, 9.0 mmol) and benzaldehyde (1.5 mL, 14 mmol) gave **11**. Trifluoroacetic acid was replaced with DMSO (10 mL), containing a catalytic amount of *p*-toluenesulfonic acid, and the mixture was stirred at 50 °C (12 h). The product was recrystallized from acetone–water in 75% yield: mp 202 °C; R_f 0.15 (E), 0.55 (A); ^{1}H NMR δ 5.68 (d, 1, C*H*NH, J = 7.2 Hz), 6.63 (m, 2, ArH), 6.71 (d, 1, N*H*CH, J = 7.2 Hz), 7.12 (m, 7, ArH), 11.26 (s, 1, NH), 11.41 (s, 1, NH); HRMS calcd for $C_{17}H_{13}N_3O_2S$ 323.0729, found 323.0729.

5-(*p*-Nitrophenyl)pyrimido[5,4-*f*]benzo[1,4]thiazepine (12). Using the modified procedure for 11, compound **12** was synthesized from **6** (2.0 g, 8.6 mmol) and *p*-nitrobenzaldehyde (1.4 g, 9.46 mmol). The product was recrystallized from acetone–EtOAc in 72% yield: ^{1}H NMR δ 5.78 (d, 1, C*H*NH, J = 7.2 Hz), 6.67 (m, 2, ArH), 6.88 (d, 1, N*H*CH, J = 7.2 Hz), 7.07 (m, 2, ArH), 7.40 (d, J = 8.7 Hz, 2, ArH), 8.06 (d, J = 84 Hz, 2, ArH), 11.36 (s, 1, NH), 11.52 (s, 1, NH). The product was used as such for the next step.

Preparation of 1-[(2-Acetoxyethoxy)methyl]pyrimido-[5,4-*f*]benzo[1,4]thiazepines 14–17. General Procedure. To a mixture of **9**, **10**, 11, or **12** and [(2-acetoxyethyl)acetoxy]-methyl ester (1.1 equiv) in anhydrous CH_3CN (10 mL/mmol) under nitrogen atmosphere was added dropwise HMDS (1.75 equiv) followed by TMSCl (1.75 equiv) and trifluoromethanesulfonic acid (1.2 equiv). This reaction mixture was stirred at room temperature overnight, and the resulting slurry was poured over saturated $NaHCO_3$. The mixture was extracted with CH_2Cl_2 and then the organic extract was washed with brine and dried over Na_2SO_4. After filtration and concentration the resulting residue was purified by short-path column chromatography.

1-[(2-Acetoxyethoxy)methyl]pyrimido[5,4-*f*]benzo[1,4]-thiazepine (14). Compound **9** (300 mg, 1.2 mmol) gave **14** in 54% yield. The product was recovered as a fine yellow powder on trituration with ether after purification by short-path column chromatography with CH_2Cl_2–MeOH–AcOH (64:1:2) as the eluent: mp 126–128 °C; R_f 0.52 (D); ^{1}H NMR δ 2.00 (s, 3, CH_3CO), 3.65 (q, 2, CH_2), 3.99 (q, 2, CH_2), 4.59 (d, 2, CH_2-NH), 5.59 (s, 2, OCH_2N), 6.45 (m, 3, ArH and NHCH_2), 7.10 (t, 1, ArH), 7.20 (d, 1, ArH), 11.75 (s, 1, NH); ^{13}C NMR δ 20.90, 39.86, 63.09, 67.03, 74.30, 108.94, 116.57, 118.06, 118.18, 130.40, 133.77, 146,93, 151.02, 153.69, 161.42, 170.95; IR (KBr) 3399, 3024, 1750, 1725, 1640 cm^{-1}. Anal. ($C_{16}H_{17}N_3O_5S$) Calcd: C, 52.88; H, 4.72; N, 11.56. Found: C, 52.71; H, 4.72; N, 11.26.

1-[(2-Acetoxyethoxy)methyl]-6-*N*-methylpyrimido[5,4-*f*]benzo[1,4]thiazepine (15). Compound **10** (0.78 g, 3 mmol) gave **15** in 71% yield. The product was recovered as a fine yellow powder on trituration with ether after purification by short-path column chromatography with $CHCl_3$–MeOH–AcOH (48;1:2) as the eluent: mp 108–110 °C; R_f 0.41 (E); ^{1}H NMR δ 1.98 (s, 3, CH_3CO), 2.94 (s, 3, CH_3), 3.68 (q, 2, CH_2), 4.08 (q, 2, CH_2), 5.47 (s, 2, OCH_2N), 6.69 (t, 1, ArH), 6.83 (d, 1, ArH), 7.23 (m, 2, ArH), 11.64 (s, 1, NH); ^{13}C NMR δ 20.67, 42.72, 50.92, 63.03, 67.02, 74.15, 114.91, 115.45, 117.51, 119.44, 130.56, 132.89, 150,53, 150.75, 153.24, 160.87, 170.89; IR (KBr) 3174, 1725, 1594, 1588 cm^{-1}. Anal. ($C_{17}H_{19}N_3O_5S$) Calcd: C, 54.10; H, 5.08; N, 11.13. Found: C, 54.07; H, 5.18; N, 10.92.

1-[(2-Acetoxyethoxy)methyl]-5-phenylpyrimido[5,4-f]-benzo[1,4]thiazepine (16). Compound **11** (1.6 g, 4.8 mmol) gave **16** in 74% yield. The product was recovered as a fine white powder on trituration with ether after purification by short-path column chromatography with CH_2Cl_2–MeOH–CH_3CO_2H (64:1:2) as the eluent: mp 172–173 °C; R_f 0.4 (E); ^{1}H NMR δ 1.89 (s, 3, CH_3CO), 3.65 (q, 2, CH_2), 4.01 (m, 2, CH_2), 5.36 (d, 1, J = 10.5 Hz, OCH_aH_bN), 5.50 (d, 1, J = 10.8 Hz, OCH_aH_bN), 5.87 (d, 1, C*H*NH, J = 7.8 Hz), 6.54 (t, 1, ArH), 6.72 (d, 1, J = 8.1 Hz, N*H*CH), 7.03 (d, J = 7.5 Hz, 2, ArH), 7.17 (m, 6, ArH), 11.99 (s, 1, NH); ^{13}C NMR δ 20.56, 40.18, 50.15, 62.68, 66.27, 109.00, 118.00, 125.54 (2 C), 126.09, 127.94 (2 C), 130.09, 133.21, 145.00, 147.50, 149.90, 150.03, 162.00, 171.19; IR (KBr) 3378, 3190, 1725, 1653, 1548 cm^{-1}. Anal. ($C_{22}H_{21}N_3O_5S$) Calcd: C, 60.12; H, 4.82; N, 9.56. Found: C, 59.99; H, 5.01; N, 9.37.

1-[(2-Acetoxy-ethoxy)methyl]-5-(*p*-nitrophenyl)pyrimido[5,4-*f*]benzo[1,4]thiazepine (17). Compound **12** (1.68 g, 4.6 mmol) gave **17** in 55% yield. A fine yellow powder was recovered on trituration with ether after being purified by short-path column chromatography with CH_2Cl_2–MeOH–AcOH (64:1:2) as the eluent. This material, which exhibited satisfactory ^{1}H and ^{13}C NMR spectra, was hydrolized to **21** without further characterization: ^{1}H NMR ($CDCl_3$) δ 2.09 (s, 3, CH_3CO), 3.74 (q, 2, CH_2), 4.13 (m, 2, CH_2), 5.51 (d, 1, J = 10.5 Hz, OCH_aH_bN), 5.68 (d, 1H, J = 10.5 Hz, OCH_aH_bN), 6.15 (s, 1, C*H*NH), 6.69 (m, 2, ArH), 7.15 (t, 2, ArH), 7.51 (d, J = 8.4 Hz, 2, ArH), 8.12 (d, J = 8.7 Hz, 2, ArH), 10.11 (s, 1, NH).

1-[(2-Hydroxyethoxy)methyl]pyrimido[5,4-*f*]benzo[1,4]-thiazepine (19). Compound **14** (0.820 g, 2.3 mmol) was suspended in concentrated NH_4OH (20 mL/mmol) and stirred at 50 °C (48 h). This mixture was then neutralized with cold concentrated HCl, the solvent removed under reduced pressure, and the residue resuspended in water. Filtration gave **19** in 67% yield: mp 201–203 °C; ^{1}H NMR δ 3.95 (A_2B_2, 4, OCH_2CH_2O), 4.26 (s, 2, CH_2), 5.33 (t, 1, OH), 5.37 (s, 2, OCH_2N), 6.43 (t, 1, ArH), 6.77 (d, 1, ArH), 6.99 (d, 1, ArH), 7.14 (t, 1, ArH), 11.38 (br, 1, NH); ^{13}C NMR δ 35.78, 69.55, 74.69, 76.99, 97.64, 110.81, 116.09, 117.84, 131.63, 136.00, 148.43, 149.41, 160.33, 163.86; IR (KBr) 3420, 3194, 1719, 1677 cm^{-1}. Anal. ($C_{14}H_{15}N_3O_4S$) Calcd: C, 52.33; H, 4.70; N, 13.08. Found: C, 52.15; H, 4.60; N, 13.05.

1-[(2-Hydroxyethoxy)methyl]-5-phenylpyrimido[5,4-*f*]-benzo[1,4]thiazepine (20). Using the procedure for **19**, compound **16** (0.93 g, 2.1 mmol) gave **20** in 82% yield.

(Recrystallization from MeOH gave rodlike cylindrical crystals suitable for X-ray analysis): mp 185–187 °C; R_f 0.23 (E), 0.78 (A); ^{1}H NMR δ 3.46 (A_2B_2, 4, OCH_2CH_2O), 4.70 (t, 1, OH), 5.37 (d, 1, J = 9.9 Hz, OCH_aH_bN), 5.50 (d, 1, J = 10.5 Hz, OCH_aH_bN), 5.89 (d, 1, $CHNH$, J = 6.0 Hz), 6.53 (t, 1, ArH), 6.74 (d, 1, ArH), 7.2 (m, 8, ArH and NHCH), 11.89 (s, 1, NH); ^{13}C NMR δ 50.94, 60.46, 70.55, 75.00, 110.00, 118.29, 118.63, 118.80, 126.15 (2 C), 126.91, 128.65 (2 C), 130.82, 133.72, 144.73, 147.88, 150.90, 151.00, 162.19; HRMS calcd for $C_{20}H_{19}N_3O_4S$ 397.1096, found 397.1106.

1-[(2-Hydroxyethoxy)methyl]-5-(*p*-nitrophenyl)pyrimido[5,4-*f*]benzo[1,4]thiazepine (21). Using the procedure for **19**, compound **17** (0.72 g, 1.5 mmol) gave **21** in 47% yield after purification by short-path column chromatography with $CHCl_3$–EtOAc–AcOH (9:9:2) as eluant: mp 173 °C; R_f 0.15 (E); ^{1}H NMR δ 3.46 (A_2B_2, 4, OCH_2CH_2O), 4.62 (t, 1, OH), 5.34 (d, J = 10.5 Hz, 1, OCH_aH_bN), 5.47 (d, 1, J = 10.5 Hz, OCH_aH_bN), 5.92 (d, 1, $CHNH$, J = 7.8 Hz), 6.57 (t, 1, J = 7.2 Hz, ArH.), 6.75 (d, 1, J = 8.1 Hz), 7.09 (m, 2, ArH and NH), 7.30 (d, 1, J = 7.8 Hz), 7.54 (d, J = 8.4 Hz, 2, ArH), 8.16 (d, J = 8.7 Hz, 2, ArH), 11.86 (s, 1, NH); ^{13}C NMR δ 50.24, 60.01, 70.26, 73.20, 109.0, 117.56, 117.84, 117.94, 123.29 (2 C), 126.92 (2 C), 130.39, 133.26, 146.04, 146.86, 150.00, 150.30, 152.00, 161.48; IR (KBr) 3354, 3184, 1707, 1627 cm^{-1}; HRMS calcd for $C_{20}H_{18}N_4O_6S$ 442.0947, found 442.0969. Anal. ($C_{20}H_{18}N_4O_6S$. 0.5 H_2O) Calcd: C, 53.21; H, 4.24; N, 12.41. Found: C, 52.94; H, 4.20; N, 12.18.

1-[(2-Acetoxyethoxy)methyl]-3-*N*-methylpyrimido[5,4-*f*]benzo[1,4]thiazepine (18). Methyl iodide (0.051 mL, 0.825 mmol) was added to a mixture of **14** (300 mg, 0.825 mmol) and K_2CO_3 (114 mg, 0.825 mmol) in DMSO (3 mL), and the mixture was stirred at room temperature for 45 min. The solvent was removed under reduced pressure and the resulting oil treated with ice-cold HCl (1 N) and neutralized with solid $NaHCO_3$. The white precipitate formed was filtered and recrystallized from EtOAc/hexane to render **18** a white fine needles in 77% yield: mp 109 °C; R_f 0.41 (D); ^{1}H NMR ($CDCl_3$) δ 2.06 (t, 3, CH_3CO), 3.34 (s, 3, CH_3), 3.78 (m, 2, CH_2), 4.16 (m, 2, CH_2), 4.28 (br, 1, NH), 4.73 (d, 2, CH_2NH, J = 4.7 Hz, coalesced into a singlet with deuterium), 5.68 (s, 2, OCH_2N), 6.38 (d, 1, ArH), 6.56 (t, 1, ArH), 7.00 (t, Ar, 1H), 7.08 (d, 1, ArH); ^{13}C NMR ($CDCl_3$) δ 20.87, 28.54, 40.64, 63.08, 66.99, 76.09, 109.27, 115.73, 117.97, 118.21, 130.37, 133.77, 146.90, 151.17, 151.72, 161.33, 171.17; IR (KBr) 3350, 3091, 1736, 1694, 1635 cm^{-1}; HRMS calcd for $C_{17}H_{19}N_3O_5S$ 377. 1045, found 377.1045. Anal. ($C_{17}H_{19}N_3O_5S$ 0.1 H_2O) Calcd: C, 53.78; H, 5.11; N, 11.07. Found: C, 53.80; H, 5.17; N, 11.01.

5-Oxopyrimido[5,4-*f*]benzo[1,4]thiazepine (22). 6-[(2-Aminophenyl)thio]uracil (**6**) (1.0 g, 4.3 mmol) and triphosgene (0.428g, 1.42 mmol) were suspended in anhydrous acetonitrile (20 mL) under a nitrogen atmosphere and allowed to reflux for 48 h. The solvent was then removed under reduced pressure, and the resulting yellow precipitate was washed with heptane to remove any traces of triphosgene. This material proved to be highly insoluble and difficult to purify. It exhibited satisfactory ^{1}H and ^{13}C NMR spectra and was converted to **23** without further characterization: ^{1}H NMR δ 7.21 (m, 2, ArH), 7.46 (m, 2, ArH), 10.50 (s, 1, NH), 11.10 (s, 1, NH), 12.00 (s, 1, NH); ^{13}C NMR δ 108.71, 123.24, 125.30, 125.48, 130.73, 132.99, 139.88, 150.28, 155.53, 160.59, 163.28.

1-[(2-Acetoxyethoxy)methyl]-5-oxopyrimido[5,4-*f*]benzo[1,4]thiazepine (23). Using the general procedure for **14**–**17**, compound **22** (0.48 g, 1.84 mmol) gave **23** in 12% yield. The residue was purified by short-path column chromatography with EtOAc–AcOH (32:1) as the eluant and was recrystallized from MeOH: mp 152–154 °C; ^{1}H NMR δ 1.98 (s, 3, CH_3CO), 3.78 (q, 2, CH_2), 4.15 (m, 2, CH_2), 5.50 (d, 1, J = 10.0 Hz, OCH_aH_bN), 5.64 (d, 1, J = 10.8 Hz, OCH_aH_bN), 7.22 (m, 2, ArH), 7.42 (t, 1, ArH), 7.6 (d, 1, ArH), 10.8 (s, 1, NH), 11.79 (s, 1, NH); ^{13}C NMR δ 20.59, 62.96, 66.53, 73.89, 113.00, 123.03, 125.23, 126.00, 131.23, 133.89, 140.22, 148.87, 155.50, 158.77, 162.59, 171.00. Anal. ($C_{16}H_{15}N_3O_6S$ 0.5 MeOH) Calcd: C, 50.38; H, 4.36; N, 10.68. Found: C, 50.47; H, 4.29; N, 10.76.

1-(Ethoxymethyl)pyrimido[5,4-*f*]benzo[1,4]thiazepine (24). To a suspension of **9** (600 mg, 2.4 mmol), in anhydrous CH_3CN (24 mL) under a nitrogen atmosphere, was added dropwise HMDS (0.9 mL, 4.8 mmol) followed by TMSCl (0.55 mL, 4.08 mmol) and CF_3SO_3H (0.28 mL, 2.88 mmol). The mixture was stirred for 1 h at room temperature, chloromethyl ethyl ether (0.25 mL, 2.64) was added dropwise, and the reaction mixture was stirred for 8 h at room temperature. The resulting suspension was poured over aqueous $NaHCO_3$, stirred for 30 min, and extracted with CH_2Cl_2. The organic extract was washed with brine, dried over Na_2SO_4, filtered, and concentrated under vacuum to provide 320 mg of crude product. Preparative TLC EtOAc–$CHCl_3$ (1:1) furnished 250 mg (33%) of **24**: mp 159–160 °C; R_f 0.65 (D); ^{1}H NMR ($CDCl_3$) δ 1.20 (6, 3, CH_3), 3.60 (q, 2, CH_2), 4.49 (br, 1, $NHCH_2$), 4.69 (s, 2, CH_2NH), 5.29 (s, 2, OCH_2N), 6.38 (d, 1, ArH), 6.54 (t, 1, ArH), 6.98 (t, 1, ArH), 7.07 (d, 1, ArH), 10.01 (s, 1, NH); ^{13}C NMR ($CDCl_3$) δ 15.04, 39.90, 64.72, 74.04, 109.21, 116.39, 118.03, 118.11, 130.32, 133.83, 146.96, 150.94, 153.91, 161.46; IR (KBr) 3392, 2979, 1715, 1594 cm^{-1}. Anal. ($C_{14}H_{15}N_3O_3S$·0.1H_2O) Calcd: C, 55.05; H, 5.10; N, 13.26. Found: C, 54.76; H, 5.03; N, 13.51.

1-[(2-Ethoxyethoxy)methyl]pyrimido[5,4-*f*]benzo[1,4]thiazepine (25). Compound **19** (250 mg, 0.78 mmol) was added to a suspension of NaH (60% in oil, 65 mg, 1.638 mmol) in DMSO (2 mL) under a nitrogen atmosphere. The mixture was stirred at room temperature for 45 min, bromoethane (0.06 mL, 0.78 mmol) was then added dropwise, and the contents were stirred for 20 h. The DMSO was removed under reduced pressure, and the resulting oil was treated with ice-cold HCl (1 N). The white precipitate that formed was extracted with EtOAc, and the organic extract was washed with $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and then concentrated under vaccum. The residue was purified by preparative TLC (hexane–CH_2Cl_2–AcOH, 9:10:1) to give **25** in 39% yield: mp 132–133 °C; R_f 0.53 (D); ^{1}H NMR ($CDCl_3$) δ 1.20 (t, 3, CH_3), 2.71 (q, 2, CH_2), 3.99 (t, 2, CH_2), 4.21 (s, 2, CH_2NH), 4.29 (br, 2H, CH_2), 5.45 (br, 3H, $NHCH_2$, OCH_2N), 6.65 (t, 1, ArH), 6.77 (d, 1, ArH), 7.20 (t, 1, ArH), 7.38 (d, 1, ArH), 8.14 (s, 1, NH); ^{13}C NMR ($CDCl_3$) δ 14.84, 29.03, 36.27, 70.17, 75.36, 77.06, 100.00, 110.75, 117.12, 118.00, 129.83, 136.23, 148.42, 149.45, 160.52, 163.94; IR (KBr) 3350, 3041, 1713, 1667, 1158 cm^{-1}. Anal. ($C_{16}H_{19}N_3O_4S$·0.5H_2O) Calcd: C, 53.67; H, 5.62; N, 11.74. Found: C, 53.55; H, 5.48; N, 11.62.

Single-Crystal X-ray Analysis of 20. Crystal data: $C_{20}H_{19}N_3O_4S$ (397.45); triclinic space group $\bar{P}1$ (No. 2); a = 5.918(5) Å, b = 9.537(6) Å, c = 16.15(1) Å, α = 95.27(5)°, β = 93.77(5)°, γ = 93.77(5)°, γ = 93.77(5)°; V = 903.(1) Å^3, and Z = 2. A crystal was sealed in epoxy and mounted on the tip of a glass fiber. The unit cell was determined, and data were collected at ambient temperature with an Enraf-Nonius diffractometer using Cu Kα radiation. A total of 1387 unique reflections (with $I > 3\sigma I$) were collected using ω scans with $0 < 2\theta < 120$. The structure was solved with Direct Methods Program ORIENT, with isotropic refinement of the non-hydrogen atoms to give a final R (R_w) value of 0.097 (0.113) for a total of 240 variables. The side chain of N1 showed considerable disorder. An adequate model was fitted with a 2-fold disorder of this side chain. The structure diagrams show only one of the side chains.

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Supplementary Material Available: HIV-1 RT screening assays of compounds presented in this paper and tables with the final positional parameters, intramolecular and intermolecular distances, intramolecular bond angles, torsion angles

and U values in the crystal structure of compound **20** (16 pages). Ordering information is given on any current masthead page.

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