Novel Non-Nucleoside Inhibitors of Human Immunodeficiency Virus Type 1 Reverse Transcriptase. 6. 2-Indol-3-yl- and 2-Azaindol-3-yl-dipyridodiazepinones[1]

Terence A. Kelly,* Daniel W. McNeil, Janice M. Rose, Eva David,† Cheng-Kon Shih, and Peter M. Grob

Research and Development Center, Boehringer Ingelheim Pharmaceuticals Inc., 900 Ridgebury Road, P.O. Box 368, Ridgefield, Connecticut 06877

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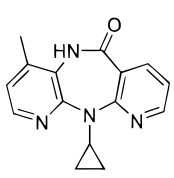
Modification of the non-nucleoside inhibitor of HIV-1 reverse transcriptase nevirapine (Viramune) by incorporation of a 2-indolyl substituent confers activity against several mutant forms of the enzyme.

Introduction

Nevirapine[2] (Viramune, **1**) represents the first member of the non-nucleoside class of inhibitors of reverse transcriptase (RT) to receive approval for the treatment of human immunodeficiency virus (HIV) infections. This drug binds to an allosteric region on the protein and induces conformational changes that halt the polymerase activity of the enzyme.[3] In clinical settings, mutations to wild-type RT have been observed that are resistant to nevirapine and thus require that this class of inhibitor be used in combination with other drugs.[4] Recently, Proudfoot *et al.* reported that incorporation of aryl substituents at the 2-position of the dipyridodiazepinone ring system to generate structures such as **2** can confer activity against mutant forms of the enzyme including the clinically important Y181C.[5] The current work expands on this theme by exploring the effect of changing the 2-pyrrolyl substituent to larger, indole-based rings on the molecules' potency against an expanded panel of RT mutants.



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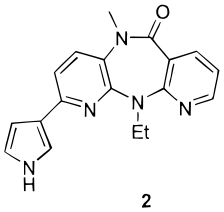

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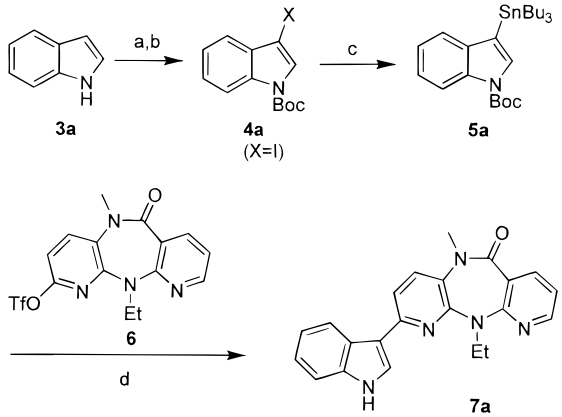
Chemistry

A general synthesis of the 2-indol-3-yl derivatives is outlined in Scheme 1 for the synthesis of the unsubstituted compound **7a**. Halogenation of indole (**3a**) with ICl in pyridine[6] produced 3-iodoindole, which was immediately converted to its *N*-Boc derivative (**4a**) by treatment with Boc_2O in the presence of DMAP. (For compounds **3d**,[7] **3e**,[7] and **3f**,[7] we proceeded via the previously reported bromination[8] rather than iodination procedure to generate the known 3-bromo derivatives.) Lithium−halogen exchange on derivative **4a** induced by the reaction with *n*-BuLi in the presence of TMEDA at −78 °C generated an anion which was trapped with Bu_3SnCl to give **5a**. The organostannane was then coupled to the triflate **6**[5] in the presence of $Pd(Ph_3P)_2Cl_2$ and LiCl in DMF at 110 °C.[9] This generated product **7a** in 64% isolated yield. All of the other 2-indol-3-yl compounds were produced in a similar manner, but it should be noted that the isolated yields of the cross-coupling reactions of the azaindol-3-yl derivatives (**7d**−**g**) were very low (5−15%) due largely to difficulties in purification.

Scheme 1. Representative Synthesis of 2-Indolyl Derivatives



[a] Reagents: (i) ICl, pyridine, 0 °C (generates 3-iodo compound) *or* Br_2, CCl_4, *i*-$PrNEt_2$, 0 °C (generates 3-bromo compound); (ii) Boc_2O, DMAP, dioxane; (iii) (a) *n*-BuLi, TMEDA, THF, −78 °C, (b) $SnBu_3Cl$; (iv) $PdCl_2(PPh_3)_2$, LiCl, DMF, 110 °C.

Results and Discussion

Compounds were first screened against purified wild-type HIV-1-RT as well as the Y181C mutant and the Y188L mutant. IC_{50}'s were calculated on compounds that showed the potential for generating complete dose−response curves (*i.e.* compounds with approximately 50% inhibition at a concentration of 1 μM). The results of testing are shown in Table 1. The details of the enzyme assays which measure the incorporation of [^{3}H]-dGTP into a poly(rC):oligo(dG) template have been published previously.[2b] When a compound showed an IC_{50} of less then 1 μM against all three enzymes, it was then screened against a panel of four other mutants of HIV-1-RT derived from clinical isolates. These tests were performed with partially purified cell lysates. The secondary evaluation was assessed against the following mutants: K103N, V106A, G190A, and P236L.[10] These results are shown in Table 2.

Initial screening of the unsubstituted 2-indol-3-yl derivative **7a** demonstrated that the region of the RT enzymes that binds the 2-aryl substituents is large enough to tolerate the increase in size observed in going

† Deceased August 19, 1995.

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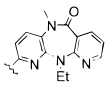
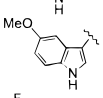
Table 1. Activity of 2-Indol-3-yldipyridodiazepinones (**7**) vs WT and Mutant HIV-1 RT[a]



CMPD	2-Position	Wild Type % inh @ 1μM	Wild Type IC_{50} (nM)	Y181C % inh @ 1μM	Y181C IC_{50} (nM)	Y188L % inh @ 1μM	Y188L IC_{50} (nM)
2		95	33	91	50	78	100
7a		96	28	93	28	72	90
7b		61	200	45	230	58	730
7c		63	706	59	555	17	nd
7d		21	nd	18	nd	37	nd
7e		87	130	66	222	3	nd
7f		94	44	81	98	64	384
7g		76	210	70	200	39	1300

[a] nd = not determined.

Table 2. Secondary Evaluation of 2-Indol-3-yldipyridodiazepinones

compd	IC_{50} (nM) K103N	V106A	G190A	P236L
2	50	1000	320	130
7a	97	49	12	79
7b	935	3090	600	404
7f	32	228	19	<1

from a pyrrole to an indole moiety (**2** vs **7a**, Table 1). The IC_{50}'s of **7a** were 28, 28, and 90 nM against WT, Y181C, and Y188L, respectively, vs 33, 50, and 100 nM for compound **2** against the same series. More significantly, as compared to compound **2**, compound **7a** exhibits dramatically improved potency against two of the four secondary mutant enzymes (V106A (49 vs 1000 nM) and G190A (12 vs 320 nM)) while still retaining activity against the K103N and P236L mutants (Table 2).

These results encouraged us to explore this region more thoroughly. The first two compounds, **7b** and **7c**, which were made from commercially available indoles, contained the 5-methoxy- and 5-fluoroindolyl substituent. These derivatives both lost considerable potency against the wild-type enzyme when compared with the unsubstituted compound **7a** (200 and 706 nM vs 28 nM, respectively). Lower potency was also observed when gauged against the two primary mutant enzymes. For compound **7b**, results shown in Table 2 demonstrate that this trend continued across all of the tested mutants.

At this point in the project we observed that the indole-based compounds were increasingly less soluble than the pyrrole presumably due to an increase in lipophilicity. Consequently, we explored the azaindole series **7d**−**g** to see if it was possible to retain the potency of compound **7a** while possibly alleviating some of the solubility concerns.

Proceeding sequentially around the ring, the 4-azaindol-3-yl compound (**7d**) had only weak activity in the primary screening assays. The next compound, the 5-azaindol-3-yl derivative (**7e**), had good potency against both the WT and Y181C enzymes but showed only 3% inhibition of Y188L at the 1 μM screening concentration. The 6-azaindol-3-yl compound (**7f**) regained activity against all three of the primary mutants but was 4-fold less potent than the starting indol-3-yl compound (**7a**) against the Y188L mutant. However, against some of the secondary panel, this derivative (**7f**) was exceptionally potent, in particular against both the K103N (32 nM) and P236L (1 nM) mutants. The 7-azaindol-3-yl compound **7g** had good activity against both the WT and Y181C enzymes, but its potency vs the Y188L mutant was over a log weaker than the potency of **7a**. We are currently exploring QSAR studies to explain the observed differences in the profile of these compounds.

It should be noted that these compounds are not being pursued due to unacceptable levels of cytotoxicity in the MTT cellular assay (for example, compound **7f** was toxic to half of the cells at concentrations below 25 μM). The source of this unwanted activity has not been pinpointed, but it unfortunately precludes the evaluation of these compounds in cell-passaging experiments which would allow for the selection of resistant mutants. Regardless, the results from this series demonstrates the possibility of producing nevirapine derivatives with broad spectrum activity against a variety of HIV reverse transcriptase enzymes. The hypothesis that such activity can lead to more effective antivirals *in vitro* is supported by previous work.[5,11]

Conclusions

It has been proposed that the administration of compounds that have complimentary activity against various forms of RT could be clinically useful in the treatment of this viral infection. Clearly a simpler approach would be to develop reagents that have broad spectrum activity against the same targets. The series of compounds presented in this work demonstrates the possibility of producing derivatives of nevirapine that have activity against several clinically relevant forms of HIV-1 reverse transcriptase.

Experimental Section

General Experimental. For general experimental details, see ref 2b. For details on the construction of mutant HIV-1 RT clones and the expression of the enzymes, see ref 10 and references therein. Starting materials **3a**, **3b**, **3c**, and **3g** are commercially available (Aldrich). Starting materials **3d**, **3e**, and **3f** were prepared[7] and brominated[8] in accord with previously reported literature procedures.

Reverse Transcriptase Assay. Composition of stock and reaction mixture:

stock reagent	2.4× mix concn	final assay concn
1 M Tris pH 7.8	120 mM	50 mM
1 M dithiothrietol	9.6 mM	4 mM
1 M NaCl	144 mM	60 mM
1 M $MgCl_2$	4.8 mM	2.0 mM
[poly $r(C)_{500}$/oligo $d(G)_{10}$] (27:1)	11.6 μg/mL	4.8 μg/mL
[^{3}H]dGTP (93 μM, 10.7 Ci/mmol)	1.1 μM	0.45 μM
Chaps		0.02%
RT enzyme		0.63 nM
test compound		10 μg/mL

This enzyme assay has been adapted to a 96-well microtiter plate system and has been previously described.[12] Tris buffer (50 mM, pH 7.8), vehicle (solvent diluted to match the compound dilution), or compounds in vehicle are dispensed into 96-well microtiter plates (10 μL/well; 3 wells/compound). The HIV-1 RT enzyme is thawed, diluted in 50 mM Tris, pH 7.8, containing 0.05% Chaps to give 1.5 nM enzyme, and 25 μL are dispensed per well. Ten microliters of 0.5 M EDTA are added to the first three wells of the microtiter plate. EDTA chelates the Mg^{2+} present and prevents reverse transcription. This group serves as background polymerization which is subtracted from all other groups. Twenty-five microliters of the 2.4× reaction mixture are added to all wells, and the assay is allowed to incubate at room temperature for 30 min. The assay is terminated by precipitating the DNA in each well with 60 μL of sodium pyrophosphate (2% w/v) in 10% trichloracetic acid (TCA, 10% w/v). The microtiter plate is incubated for 15 min at 4 °C, and the precipitate is harvested onto no. 30 glass fiber paper (Schleicher & Schuell) using a Tomtech 96-well harvester. The filters are then dried, placed into plastic bags with Betaplate scintillation cocktail (Pharmacia/LKB), and counted in the Betaplate counter (Pharmacia/LKB).

MTT Assay. The MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay is based on cleavage of tetrazolium bromide by metabolically active cells, resulting in a highly quantitative blue color. This assay has been previously described[13a] but has been optimized for the purposes of the testing reported herein.

The C8166-45 cell line,[13b] a fusion of umbilical blood lymphocytes and T-cells from leukemia−lymphoma patients grown in RPMI 1640 supplemented with 10% fetal bovine serum, is used as the target cell line in the assay. Cells (100 μL) are plated in microtest plate wells at a concentration of 10^5 cells/mL in the presence of varying concentrations of inhibitor in 50 μL of RPMI 1640. The cells are incubated at 37 °C in a humidified CO_2 incubator. Five days later, 20 μL of MTT (5 mg/mL in RPMI 1640, warmed, 0.2 μm filtered, and stored at 4 °C) is added to each well. After 4 h additional incubation at 37 °C, 60 μL of 0.01 N HCl in 10% Triton X-100 is added to each well and thoroughly mixed to aid the solubilization of the crystals. A bunsen burner is briefly run across the top of the plate to disrupt bubbles, and the plate is read at 600 nm after 10 min. The average blank reading is subtracted from all wells, and inhibition is calculated.

General Procedure for the Synthesis of Compounds 4. A. 3-Iodo Derivatives. The indole compound **3** (10 mmol) was dissolved in 10 mL of pyridine and cooled in an ice bath. A solution of ICl (1 M in CH_2Cl_2; 11 mmol) was added over 5 min. After 15 min the cooling bath was removed, and after another 30 min the solution was diluted with 100 mL of EtOAc. The organic solution was washed sequentially with 1 N HCl and 1 N NaOH, dried over $MgSO_4$, and concentrated to give a residue which was immediately protected as its Boc derivative.

B. 3-Bromo Derivatives. The indole compound **3** (2.29 mmol) was dissolved in 5 mL of $CHCl_3$ and cooled in an ice bath. Bromine (4.85 mmol) was dissolved in 5 mL of CCl_4 and added dropwise to the reaction mixture until no compound **3** was observed by TLC. The mixture was diluted with 20 mL of CH_2Cl_2 and extracted into 2 N HCl. The HCl extracts were neutralized with concentrated NaOH, and the resulting precipitate was collected, dried, and protected immediately as its Boc derivative.

Boc Protection of 3-Haloindoles (4). The 3-haloindole compounds from above were dissolved in dioxane (50 mL) and treated with Boc_2O (1.1 equiv) and DMAP (0.1 equiv). After the mixture was stirred at room temperature overnight, excess Boc_2O was destroyed by the addition of 1 mL of *N*,*N*-dimethylethylenediamine. The solution was then washed with 0.1 N HCl and saturated NaCl, dried over $MgSO_4$, and concentrated. Flash chromatography (5% EtOAc:hexanes) over silica gel produced the desired products.

1-(*tert*-Butyloxycarbonyl)-3-iodoindole (4a). Two-step yield from indole (**3a**): 92%; ^{1}H NMR ($CDCl_3$) δ 1.69 (s, 9 H), 7.2−7.41 (m, 3 H), 7.72 (s, 1 H), 8.15 (d, J = 5 Hz, 1 H).

1-(*tert*-Butyloxycarbonyl)-3-iodo-5-methoxyindole (4b). Two-step yield from 5-methoxyindole (**3b**): 70%; ^{1}H NMR ($CDCl_3$) δ 1.63 (s, 9 H), 3.89 (s, 3 H), 6.83 (d, J = 1 Hz, 1 H), 7.00 (dd, J = 5, 1 Hz, 1 H), 7.69 (s, 1 H), 8.01 (d, J = 5 Hz, 1 H); MS (CI) m/z 374 (MH^+, 65), 318 (100).

1-(*tert*-Butyloxycarbonyl)-5-fluoro-3-iodoindole (4c). Two-step yield from 5-fluoroindole (**3c**): 97%; ^{1}H NMR ($CDCl_3$) δ 1.66 (s, 9 H), 6.99−7.10 (m, 2 H), 7.72 (s, 1 H), 8.08 (m, 1 H).

4-Aza-3-bromo-1-(*tert*-butyloxycarbonyl)indole (4d). Yield from 4-aza-3-bromoindole: 76%; ^{1}H NMR ($CDCl_3$) δ 1.67 (s, 9 H), 7.28 (dd, J = 8, 5 Hz, 1 H), 7.89 (s, 1 H), 8.33 (d, J = 8 Hz, 1 H), 8.59 (d, J = 5 Hz, 1 H).

5-Aza-3-bromo-1-(*tert*-butyloxycarbonyl)indole (4e). Yield from 5-aza-3-bromoindole: 42%; ^{1}H NMR ($CDCl_3$) δ 1.67 (s, 9 H), 7.64 (s, 1 H), 7.97 (d, J = 6 Hz, 1 H), 8.53 (d, J = 6 Hz, 1 H), 8.83 (s, 1 H).

6-Aza-3-bromo-1-(*tert*-butyloxycarbonyl)indole (4f). Yield from 6-aza-3-bromoindole: 42%; ^{1}H NMR ($CDCl_3$) δ 1.69 (s, 9 H), 7.45 (d, J = 5 Hz, 1 H), 7.99 (s, 1 H), 8.53 (bs, 1 H), 9.45 (bs, 1 H).

7-Aza-1-(*tert*-butyloxycarbonyl)-3-iodoindole (4g). Two-step yield from 7-azaindole (**3g**): 64%; ^{1}H NMR ($CDCl_3$) δ 1.70 (s, 9 H), 7.28 (dd, J = 8, 5 Hz, 1 H), 7.72 (dd, J = 8, 1 Hz, 1 H), 7.80 (s, 1 H), 8.49 (dd, J = 5, 1 Hz, 1 H).

General Procedure for the Synthesis of Compounds 5. Compounds of structure **4** (1.47 mmol) were dissolved in 40 mL of THF and cooled to −78 °C under an inert atmosphere. A solution of *n*-BuLi (2.5 M; 1.50 mmol) was introduced over a period of time such that the reaction temperature did not rise more than 5 °C. After addition was complete, the mixture was stirred for 15 min and then treated with Bu_3SnCl (1.66 mmol). The bath was then removed, and the solution was allowed to warm to room temperature over 2 h. The mixture was diluted with 150 mL of hexane and washed with H_2O and a saturated NaCl solution. The organics were dried over $MgSO_4$ and concentrated. In general the stannanes were difficult to purify and could be used without further purification. In cases where they were purified, chromatography over neutral alumina (Fischer A950-500 deactivated with 5% H_2O) using 5% EtOAc in hexanes as the eluant usually sufficed. When noted, it was necessary to purify the compounds over a C_{18} column.

1-(*tert*-Butyloxycarbonyl)-3-(tri-*n*-butylstannyl)indole (5a): yield 14%; ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 7 Hz, 9 H), 1.11 (m, 6 H), 1.35 (m, 6 H), 1.60 (m, 6 H), 1.81 (s, 9 H), 7.18−7.40 (m, 2 H), 7.45−7.55 (m, 2 H), 8.10 (d, J = 5 Hz, 1 H).

1-(*tert*-Butyloxycarbonyl)-5-methoxy-3-(tri-*n*-butylstannyl)indole (5b): crude material; ^{1}H NMR ($CDCl_3$) δ 0.95 (m, 9 H), 1.15 (m, 6 H), 1.45−1.90 (m, 21 H), 3.92 (s, 3 H), 6.80−7.05 (m, 2 H), 7.50−7.65 (m, 1 H), 8.00 (m, 1 H).

1-(*tert*-Butyloxycarbonyl)-5-fluoro-3-(tri-*n*-butylstannyl)indole (5c): purified over C_{18}; yield 56%; ^{1}H NMR ($CDCl_3$) δ 0.89 (t, J = 7 Hz, 9 H), 1.16 (m, 6 H), 1.34 (m, 6 H), 1.68 (m, 6 H), 1.70 (s, 9 H), 7.02 (dt, J = 7, 1 Hz, 1 H), 7.12 (dt, J = 7, 1 Hz, 1 H), 7.50 (s, 1 H), 8.05 (m, 1 H).

4-Aza-1-(*tert*-butyloxycarbonyl)-3-(tri-*n*-butylstannyl)-indole (5d): yield 18% (approximately 50% pure); ^{1}H NMR (major component, $CDCl_3$) δ 0.88 (m, 9 H), 1.1−1.8 (m, 27 H), 7.09 (m, 1 H), 7.70 (bs, 1 H), 8.20 (broad d, 1 H), 8.45 (m, 1 H).

5-Aza-1-(*tert*-butyloxycarbonyl)-3-(tri-*n*-butylstannyl)-indole (5e): yield 14%; ^{1}H NMR ($CDCl_3$) δ 0.89 (t, J = 7 Hz, 9 H), 1.21 (m, 6 H), 1.25−1.70 (m, 12 H), 1.74 (s, 9 H), 7.47 (m 1 H), 7.95 (broad d, 1 H), 8.44 (d, J = 6 Hz, 1 H), 8.80 (s, 1 H).

6-Aza-1-(*tert*-butyloxycarbonyl)-3-(tri-*n*-butylstannyl)-indole (5f): yield 20%; ^{1}H NMR ($CDCl_3$) δ 0.91 (t, J = 7 Hz, 9 H), 1.15−1.70 (m, 18 H), 1.78 (s, 9 H), 7.40 (d, J = 6 Hz, 1 H), 7.61 (m, 1 H), 8.38 (d, J = 6 Hz, 1 H), 9.35 (s, 1 H).

7-Aza-1-(*tert*-butyloxycarbonyl)-3-(tri-*n*-butylstannyl)-indole (5g): yield 19%; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 7 Hz, 9 H), 1.20 (m, 6 H), 1.20−1.65 (m, 12 H), 1.68 (s, 9 H), 7.12 (dd, J = 8, 5 Hz, 1 H), 7.51, (s, 1 H), 7.75 (dd, J = 8, 1 Hz, 1 H), 8.51 (dd, J = 5, 1 Hz, 1 H).

General Procedure for the Synthesis of Compounds 7. Organostannane **5** (0.438 mmol) was added to a DMF (2.5 mL) solution containing compound **6** (0.266 mmol), $Pd(Cl)_2$-$(Ph_3P)_2$ (0.02 mmol), and LiCl (1.49 mmol) under an argon atmosphere. The mixture was then heated at 110 °C overnight. Upon cooling, the solution was partitioned between EtOAc and H_2O. After the EtOAc layer was dried ($MgSO_4$)

and concentrated, the residue was chromatographed (1:1 EtOAc:hexanes) to yield the desired product. This material was recrystallized from CH_3CN.

5,11-Dihydro-11-ethyl-2-indol-3-yl-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (7a): yield 64%; mp 241−241.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.31 (t, J = 6 Hz, 3 H), 3.52 (s, 3 H), 4.39 (q, J = 6 Hz, 2 H), 7.00 (dd, J = 8, 5 Hz, 1 H), 7.21 (m, 2 H), 7.42 (m, 1 H), 7.51 (m, 2 H), 7.79 (d, J = 1 Hz, 1 H), 8.17 (dd, J = 8, 2 Hz, 1 H), 8.49 (m, 3 H); MS (CI) m/z 370 (MH^+). Anal. Calcd for $C_{22}H_{19}N_5O$: C, H, N.

5,11-Dihydro-11-ethyl-2-(5-methoxyindol-3-yl)-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (7b): yield 27%; mp 234.5−235.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.31 (t, J = 6 Hz, 3 H), 3.51 (s, 3 H), 3.99 (s, 3 H), 4.42 (q, J = 6 Hz, 2 H), 6.93 (dd, J = 8, 1 Hz, 1 H), 6.99 (dd, J = 8, 5 Hz, 1 H), 7.21 (d, J = 8 Hz, 1 H), 7.42 (m, 2 H), 7.68 (d, J = 1 Hz, 1 H), 7.96 (AB q, 2 H), 8.29 (broad s, 1 H), 8.38 (dd, J = 8, 2 Hz, 1 H); MS (CI) m/z 400 (MH^+). Anal. Calcd for $C_{23}H_{21}N_5O_2$: H, N; C: calcd 69.16, found 68.72.

5,11-Dihydro-11-ethyl-2-(5-fluoroindol-3-yl)-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (7c): yield 57%; mp 234−235 °C; ^{1}H NMR ($CDCl_3$) δ 1.35 (t, J = 6 Hz, 3 H), 3.55 (s, 3 H), 4.38 (q, J = 6 Hz, 2 H), 6.99 (m, 2 H), 7.21 (dd, J = 8, 5 Hz, 1 H), 7.45 (AB q, 2 H), 7.77 (d, J = 1 Hz, 1 H), 8.10 (m, 2 H), 8.40 (m, 2 H); MS (CI) m/z 388 (MH^+). Anal. Calcd for $C_{22}H_{18}FN_5O$: C, H, N.

2-(4-Azaindol-3-yl)-5,11-dihydro-11-ethyl-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (7d): yield 5%; mp >140 °C dec; ^{1}H NMR ($CDCl_3$) δ 1.35 (t, J = 6 Hz, 3 H), 3.58 (s, 3 H), 4.35 (q, J = 6 Hz, 2 H), 7.05 (dd, J = 8, 5 Hz, 1 H), 7.2−7.4 (m, 2 H), 7.59 (AB q, 2 H), 7.82 (d, J = 8 Hz, 1 H), 8.12 (dd, J = 8, 2 Hz, 1 H), 8.47 (m, 2 H), 9.45 (broad s, 1 H); MS (CI) m/z 371 (MH^+); HRMS calcd for $C_{21}H_{19}N_6O$ 371.162 034, found 371.162 51.

2-(5-Azaindol-3-yl)-5,11-dihydro-11-ethyl-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (7e): yield 11%; mp 274−276 °C; ^{1}H NMR ($CDCl_3$) δ 1.35 (t, J = 6 Hz, 3 H), 3.55 (s, 3 H), 4.38 (q, J = 6 Hz, 2 H), 7.02 (dd, J = 8, 5 Hz, 1 H), 7.30 (m, 1 H), 7.34 (d, J = 8 Hz, 1 H), 7.50 (AB q, 2 H), 7.78 (s, 1 H), 8.12 (dd, J = 8, 2 Hz, 1 H), 8.43 (m, 2 H), 9.80 (broad s, 1 H); MS (CI) m/z 371 (MH^+); HRMS calcd for $C_{21}H_{19}N_6O$ 371.162 034, found 371.161 76.

2-(6-Azaindol-3-yl)-5,11-dihydro-11-ethyl-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (7f): yield 14%; mp 251−252 °C; ^{1}H NMR ($CDCl_3$) δ 1.34 (t, J = 6 Hz, 3 H), 3.58 (s, 3 H), 4.35 (q, J = 6 Hz, 2 H), 7.04 (dd, J = 8, 5 Hz, 1 H), 7.45 (AB q, 2 H), 7.95 (s, 1 H), 8.12 (dd, J = 8, 2 Hz, 1 H), 8.30−8. 45 (m, 4 H), 8.85 (broad s, 1 H); MS (CI) m/z 371 (MH^+) Anal. Calcd for $C_{21}H_{18}N_6O\cdot 0.25H_2O$: C, H, N.

2-(7-Azaindol-3-yl)-5,11-dihydro-11-ethyl-5-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one (7g): yield 7%; mp 246−247 °C; ^{1}H NMR ($CDCl_3$) δ 1.35 (t, J = 6 Hz, 3 H), 3.55 (s, 3 H), 4.36 (q, J = 6 Hz, 2 H), 7.04 (dd, J = 8, 5 Hz, 1 H), 7.26 (m, 1 H), 7.49 (AB q, 2 H), 7.86 (d, J = 2 Hz, 1 H), 8.13 (dd, J = 8, 2 Hz, 1 H), 8.40 (m, 2 H), 8.81 (d, J = 8 Hz, 1 H), 9.42 (broad s, 1 H); MS (CI) m/z 371 (MH^+); HRMS calcd for $C_{21}H_{19}N_6O$ 371.162 034, found 371.163 44.

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Supporting Information Available: ^{1}H-NMR spectra of **7d**, **7e**, and **7g** (3 pages). Ordering information is given on any current masthead page.

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(1) For previous paper in this series, see: Kelly, T. A.; Proudfoot, J. R.; McNeil, D. W.; Patel, U. R.; David, E.; Hargrave, K. D.; Grob, P. M.; Cardozo, M.; Agarwal, A.; Adams, J. Novel Non-Nucleoside Inhibitors of Human Immunodeficiency Virus Type 1 Reverse Transcriptase. 5. Structure-Activity Relationships of 4-Substituted and 2,4-Disubstituted Analogs of Nevirapine. *J. Med. Chem.* **1995**, *38*, 4839−47.

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