Notes

Novel Non-nucleoside Inhibitors of HIV-1 Reverse Transcriptase. 3. Dipyrido[2,3-*b*:2′,3′-*e*]diazepinones

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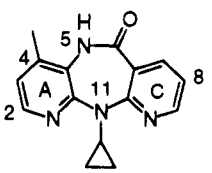
We have explored the potential of derivatives of the dipyrido[2,3-*b*:2′,3′-*e*][1,4]diazepinone ring system as inhibitors of HIV-1 reverse transcriptase (RT). These compounds are isomeric to the potent RT inhibitor nevirapine and are available via a novel Smiles rearrangement on intermediates used for the synthesis of nevirapine analogs. Derivatives of this isomeric series are weaker inhibitors of RT than corresponding nevirapine analogs, although with appropriate substitution of the A- and C-pyridine rings activity can be improved.

Introduction

Nevirapine (**1**)[1] is a potent non-nucleoside inhibitor of HIV-1 reverse transcriptase (RT) and is currently undergoing clinical evaluation as a therapeutic agent for the treatment of AIDS. In the course of the structure–activity relationship (SAR) studies which led to the discovery[2] of nevirapine, we found, as shown in Scheme 1, that the intermediate **4a** used for the synthesis of the dipyrido[3,2-*b*:2′,3′-*e*]diazepinone **6a** related to nevirapine also gives, via a novel Smiles rearrangement, the isomeric dipyrido[2,3-*b*:2′,3′-*e*]diazepinone **5a**.[3] The isomer **5a** is a weaker inhibitor of RT than the corresponding nevirapine analog **6a** (Table 1, entries 2 and 2a). However, lipophilic substitution on the A-ring and the amino substituent at position 8 on the C-ring of dipyrido[3,2-*b*:2′,3′-*e*]diazepinones[2,4] and other tricyclic RT inhibitors related to nevirapine[5,6] can enhance enzyme inhibition, and we hoped that similar substitution on **5a** would improve potency in this isomeric series.



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A methyl group on the dipyrido[3,2-*b*:2′,3′-*e*]diazepinone ring system at N(5) or C(4) is required for good inhibition of RT in analogs of **1**.[2] In the isomeric dipyrido[2,3-*b*:2′,3′-*e*]diazepinones, only the *N*-methyl amide analogs are accessible since a nitrogen atom occupies the position corresponding to C(4) in nevirapine (**1**) and **6a**. At the position corresponding to N(11) in nevirapine, we concentrated on the preferred *N*-ethyl and *N*-cyclopropyl substituents.[2]

Chemistry

We applied the Smiles rearrangement (Scheme 1) to the synthesis of several of the analogs characterized in Table 1. Amides **2a–i** are accessible by general methods previously described[2,3] and are readily transformed to the *N*-methyl amides **3a–i**. Reaction of these compounds with ethylamine or cyclopropylamine results in displacement of the chloro substituent activated by the adjacent carbonyl group to give the alkylamino derivatives **4a–i**. Deprotonation and cyclization gives a mixture of the dipyrido[2,3-*b*:2′,3′-*e*]diazepinones **5a–i** and the dipyrido[3,2-*b*:2′,3′-*e*]diazepinones **6a–i**. The ratio of isomers varies with the pyridine ring substituents. In some cases only a low yield of the rearranged tricyclic material **5** is obtained, even with conditions previously found to favor this product (LHMDS in THF at ambient temperature).[3] The Smiles intermediate in the conversion of **4a** to **5a** and **6a** has been characterized previously.[3] The corresponding intermediates in the reactions of **4b–i** were not characterized in these studies, although their presence was noted by TLC during the cyclization reactions of **4d,i**. The reactions conducted under conditions favoring the rearrangement (cyclizations of **4b–d,f,g,i**) were allowed to proceed to completion until only products **5** and **6** were visible by TLC. This typically involved extended reaction times compared to those previously reported,[3] especially for those compounds **4** bearing electron donating (R_1 = Me) substituents. The tricyclic isomers **4** and **5** were readily separated by chromatography, and the structure assignments were accomplished by NOE experiments.[3]

Some of the compounds described were obtained by further manipulation of dipyridodiazepinones above. We explored the electrophilic substitution of **5a** (Scheme 2) and found that nitration with nitronium tetrafluoroborate led to substitution at the 2-position of the more electron rich A-ring giving **5j**. Reaction with bromine in acetic acid did not give the analogous 2-bromo derivative, but instead bromination occurred at the 8-position of the C-ring giving **5i** which had already been

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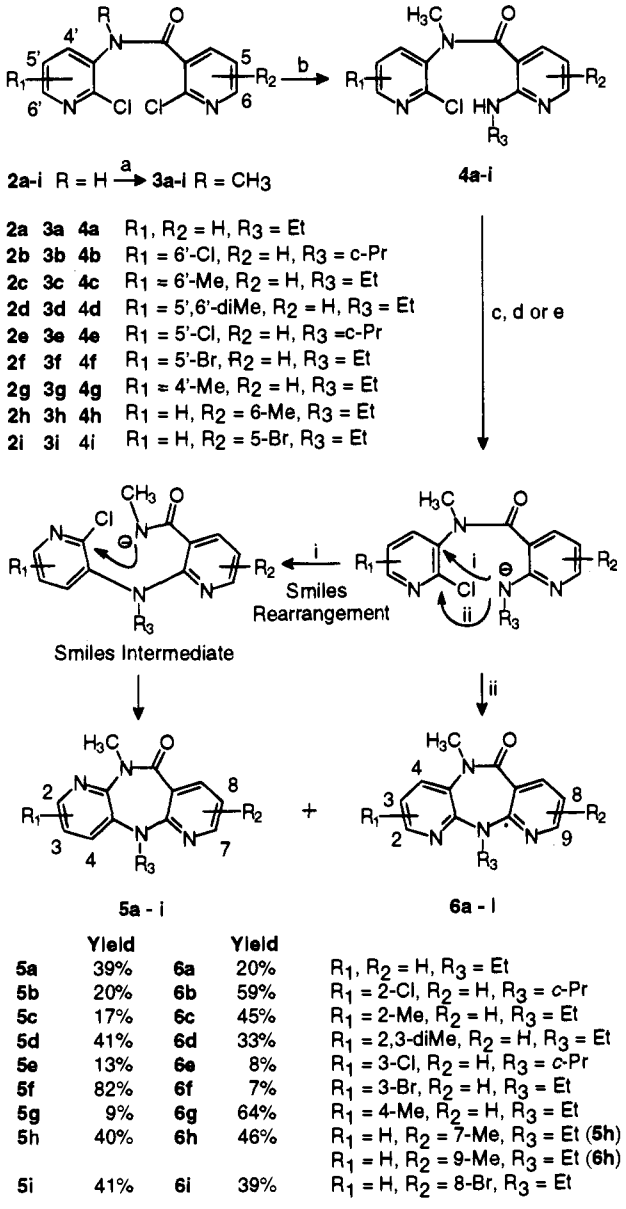
Scheme 1[a]



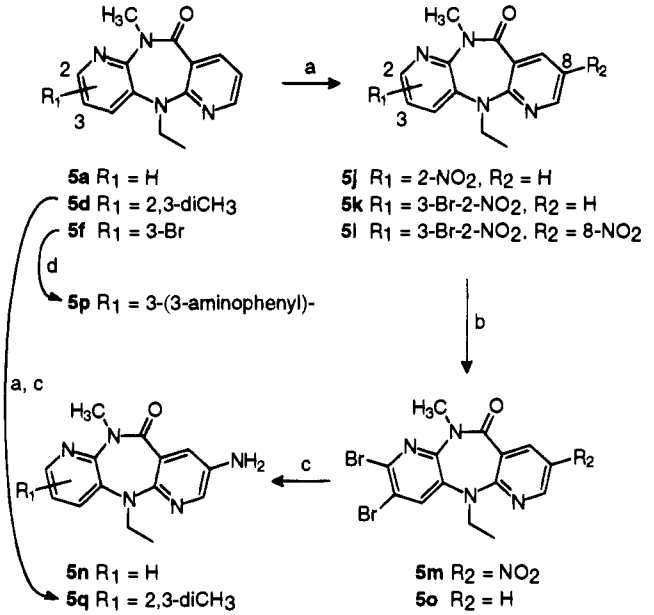
	Yield		Yield	
5a	39%	6a	20%	R_1, R_2 = H, R_3 = Et
5b	20%	6b	59%	R_1 = 2-Cl, R_2 = H, R_3 = *c*-Pr
5c	17%	6c	45%	R_1 = 2-Me, R_2 = H, R_3 = Et
5d	41%	6d	33%	R_1 = 2,3-diMe, R_2 = H, R_3 = Et
5e	13%	6e	8%	R_1 = 3-Cl, R_2 = H, R_3 = *c*-Pr
5f	82%	6f	7%	R_1 = 3-Br, R_2 = H, R_3 = Et
5g	9%	6g	64%	R_1 = 4-Me, R_2 = H, R_3 = Et
5h	40%	6h	46%	R_1 = H, R_2 = 7-Me, R_3 = Et (**5h**) R_1 = H, R_2 = 9-Me, R_3 = Et (**6h**)
5i	41%	6i	39%	R_1 = H, R_2 = 8-Br, R_3 = Et

[a] (a) NaH or NaHMDS or KO^{t}Bu, DMSO, rt, MeI; (b) $EtNH_2$ or c-$PrNH_2$, dioxane or xylene, sealed tube, heat; (c) LHMDS, THF, for **4a** (rt, 0.5 h), for **4b** (rt, 0.5 h), for **4c** (rt, 66 h), for **4d** (rt 24 h, reflux 1 h), for **4g** (rt, 48 h), for **4i** (rt, 18 h); (d) LHMDS, THF, −20 °C to rt (0.5 h) for **4f**; (e) NaH, xylene, reflux for **4e**,**h**.

prepared as in Scheme 1 above. Protonation of the A-ring pyridine nitrogen under the acidic reaction conditions may render this ring less reactive and favor bromination on the C-ring.

The 3-bromo compound **5f** was used for the synthesis of several derivatives (Scheme 2). Nitration gave a mixture of the mononitro derivative **5k** and the dinitro derivative **5l**, the ratio depending on the amount of nitronium tetrafluoroborate used. Compounds **5l** was transformed into the 8-amino derivative **5n** as follows. Heating in HBr/acetic acid resulted in replacement of the 2-nitro substituent on the A-ring with a bromo substituent[7] to give the 2,3-dibromo 8-nitro derivative **5m**. Catalytic transfer hydrogenation[8] then removed both halogens and reduced the nitro group to the amino substituent giving **5n**. The nitro group of **5k** could also be replaced giving the 2,3-dibromo derivative **5o**. The 3-aminophenyl derivative **5p** was also derived from **5f**

Scheme 2[a]



[a] (a) NO_2BF_4, CH_3CN, rt (**5j**, 57%; **5l**, 43%, **5k**, 29%); (b) HBr, AcOH, 120 °C (**5m**, 63%, or **5o**, 57%); (c) ammonium formate, 10% Pd/C, EtOH (**5n**, 86%; **5q**, 63%); (d) 3-(tributylstannyl)aniline, $Pd(Ph_3P)_2Cl_2$, NMP, 115 °C, 50%.

by palladium-catalyzed cross-coupling[9] with 3-(tributylstannyl)aniline.

The 2,3-dimethyl 8-amino derivative **5q** was obtained from the 2,3-dimethyldipyridodiazepinone **5d** (Scheme 2). We expected that nitration of **5d** would not occur on the A-ring since the only available position, the 4-position, is not readily subject to electrophilic substitution in pyridines. Nitration occurred exclusively on the C-ring giving the 2,3-dimethyl 8-nitro derivative which was reduced as above to the amine **5q**.

Biology

The in vitro RT inhibitory[10] activity of dipyrido[2,3-*b*]diazepinone **5a** and its derivatives is presented in Table 1. For comparison, data for corresponding derivatives of dipyrido[3,2-*b*]diazepinone **6a**[11] are included when available.

In almost every instance, the derivatives of **6a**, i.e., nevirapine analogs, are more potent inhibitors of RT. Since substitution at the 2-position of tricyclic **6a** leads to an enhancement of enzyme inhibition,[2,4] we expected that substitution at the corresponding 3-position of **5a** should have a similar effect. A modest 2-fold increase in potency over the unsubstituted parent **5a** (entry 2) is seen for the 3-chloro analog **5e** (Table 1, entry 9) which mirrors the effect of this substituent in the dipyrido[3,2-*b*]diazepinone series (compare entries 2a and 9a). In contrast, the 3-(3-aminophenyl) derivative **5p** (entry 10) is inactive even though the corresponding dipyrido[3,2-*b*]diazepinone analog **6p**[4,12] (entry 10a) is more potent than the parent **6a**. In compound **5g** (entry 11), a methyl group at the 4-position is found to extinguish inhibitory activity. The corresponding position is not available for substitution in derivatives of **6a**. Of the A-ring-substituted dipyrido[2,3-*b*]diazepinones synthesized, only the 2,3-dimethyl derivative **5d** approached the analogous nevirapine derivative **6d** in potency (entries 7 and 7a).

Table 1. Inhibition of HIV-1 RT by Dipyridodiazepinones

entry	compd	R_1, R_2	R_3	mp (°C)	recryst solvent	formula	Anal.	IC_{50} (μM)[a]
1	1							0.084[b]
2	**5a**	H	Et	159–161	hexane	$C_{14}H_{14}N_4O$	C, H, N	1.3
2a	**6a**	H	Et	130–132	EtOAc/hexane	$C_{14}H_{14}N_4O$	C, H, N	0.13[b]
3	**5b**	2-chloro	c-Pr	152–154	heptane	$C_{15}H_{13}ClN_4O$	C, H, N	1.0
3a	**6e**	3-chloro	c-Pr	143–144	hexane	$C_{15}H_{13}N_4OCl$	C, H, N	0.29
4	**5j**	2-nitro	Et	142–144	EtOAc/hexane	$C_{14}H_{13}N_5O_3$	C, H, N	≫1.0[c]
4a	**6j**	3-nitro	Et	154–156	EtOAc/hexane	$C_{14}H_{13}N_5O_3$	C, H, N	≫1.0[b,c]
5	**5c**	2-methyl	Et	109–110	hexane	$C_{15}H_{16}N_4O$	C, H, N	1.76
5a	**6k**	3-methyl	Et	94–96	hexane	$C_{15}H_{16}N_4O$	C, H, N	0.76[b]
6	**5o**	2,3-dibromo	Et	206–210	heptane	$C_{14}H_{12}Br_2N_4O$	C, H, N	≫1.0[c]
7	**5d**	2,3-dimethyl	Et	145–147	hexane	$C_{16}H_{18}N_4O{\cdot}0.25H_2O$	C, H, N	0.19
7a	**6d**	2,3-dimethyl	Et	143–145	hexane	$C_{16}H_{18}N_4O$	C, H, N	0.24[b]
8	**5f**	3-bromo	Et	134–136	EtOAc/^{i}Pr$_2$O	$C_{14}H_{13}BrN_4O$	C, H, N	0.55
9	**5e**	3-chloro	c-Pr	219–220	EtOAc/hexane	$C_{15}H_{13}ClN_4O$	C, H, N	0.76
9a	**6b**	2-chloro	c-Pr	220–221	EtOAc/hexane	$C_{15}H_{13}N_4OCl$	C, H, N	0.09
10	**5p**	3-(3-aminophenyl)	Et	206–208	EtOAc/hexane	$C_{20}H_{19}N_5O{\cdot}0.25EtOAc$	C, H, N	≫1.0[c]
10a	**6p**	2-(3-aminophenyl)	Et	155–157	EtOAc/^{i}Pr$_2$O	$C_{20}H_{19}N_5O$	C, H, N	0.07
11	**5g**	4-methyl	Et	110–112	hexane/$CHCl_3$	$C_{15}H_{16}N_4O$	C, H, N	≫1.0[c]
12	**5h**	7-methyl	Et	144–146	hexane	$C_{15}H_{16}N_4O$	C, H, N	≫1.0[c]
12a	**6h**	9-methyl	Et	79–93	hexane	$C_{15}H_{16}N_4O$	C, H, N	1.0[b]
13	**5i**	8-bromo	Et	162–164	*d*	$C_{14}H_{13}BrN_4O$	C, H, N	≫1.0[c]
13a	**6i**	8-bromo	Et	142–144	*d*	$C_{14}H_{13}BrN_4O$	C, H, N	1.3
14	**5n**	8-amino	Et	199–201	EtOAc/hexane	$C_{14}H_{15}N_5O$	C, H, N[e]	0.28
14a	**6n**	8-amino	Et	193–194	CH_2ClCH_2Cl/hexane	$C_{14}H_{15}N_5O{\cdot}0.5H_2O$	C, H, N[f]	0.13
15	**5q**	2,3-dimethyl 8-amino	Et	208–211	^{i}Pr$_2$O	$C_{16}H_{19}N_5O$	C, H, N	0.15

[a] For details, see ref 2. [b] Data for these compounds were originally reported in ref 2. [c] Inhibition <35% at 1 μM; IC_{50} was not determined. [d] Purified by chromatography; no recrystallization necessary. [e] N: calcd, 26.01; found, 25.53. [f] C: calcd, 60.42; found, 60.94.

On the C-ring, our focus was the 8-amino substitution which is tolerated in the dipyrido[3,2-*b*]diazepinones[2b] and other tricyclic RT inhibitors.[5] The 8-aminodipyrido-[2,3-*b*]diazepinone **5n** is about 2-fold less effective in inhibiting RT than the nevirapine analog **6n**[2b] (entries 14 and 14a) but is considerably more potent than the unsubstituted parent **5a**. This prompted the synthesis of the 2,3-dimethyl 8-amino derivative **5q** in which the best A-ring and C-ring substituents are combined. In this derivative (entry 15), there is a further increase in potency, and **5q** is the most potent RT inhibitor synthesized in this dipyrido[2,3-*b*]diazepinone series.

Conclusion

The dipyrido[2,3-*b*]diazepinones are generally weaker inhibitors of HIV-1 RT than the isomeric nevirapine analogs. Although inhibitory activity can be enhanced by the appropriate combination of A- and C-ring substituents, the inherent low potency of the series when compared to other non-nucleoside RT inhibitors makes it unattractive for further development.

Experimental Section

General experimental details are as described in refs 2 and 3. Representative reactions for the conversions of **4** to **5** and **6** are as follows (spectroscopic data for all final products are given below). All J values are reported in hertz (Hz).

Reaction of 4f To Give 5f and 6f. To a solution of **4f** (1.04 g, 2.83 mmol) in THF (20 mL) cooled to −20 °C under argon was added dropwise LHMDS (1 M in THF, 3.1 mL). The mixture was stirred coming to room temperature for 35 min. The reaction mixture was evaporated to dryness and fractionated directly by flash chromatography (EtOAc/hexane, 1/9). The major product **5f** eluted first (0.768 g, 82%). Further elution gave the minor product **6f** (0.062 g, 7%).

Reaction of 4g To Give 5g and 6g. To a solution of **4g** (1.726 g, 5.67 mmol) in THF (12 mL) cooled on ice under argon was added dropwise LHMDS (1 M in THF, 6.0 mL). The mixture was allowed to warm to room temperature and stirred for 48 h. The mixture was diluted with EtOAc, washed with water, dried, filtered, and evaporated. The residue was dissolved in ^{i}Pr$_2$O (20 mL), and the major product **6g** (0.997 g, 64%) was collected by filtration. Fractionation of the supernatant by preparative layer chromatography (EtOAc/hexane, 1/5) gave the minor product **5g** (0.131 g, 9%).

Reaction of 4h To Give 5h and 6h. To a solution of **4h** (2.90 g, 9.54 mmol) in xylene (15 mL) was added NaH (50% in oil, 0.49 g, 10.2 mmol). The mixture was heated at reflux for 45 min and cooled to room temperature and the reaction quenched with ethanol. The mixture was diluted with EtOAc, washed with water, dried, filtered, and evaporated. The residue was fractionated by chromatography over silica gel (EtOAc/hexane 15/85) to give **5h** (1.02 g, 40%) followed by **6h** (1.18 g, 46%).

Spectroscopic Data for Compounds 5b–i and 6b–i. **5b**: ^{1}H NMR ($CDCl_3$) δ 8.44 (1H, dd, J = 2, 5), 8.13 (1H, dd, J = 2, 8), 7.70 (1H, d, J = 8), 7.16 (1H, d, J = 8), 7.09 (1H, dd, J = 5, 8), 3.55 (3H, s), 3.49 (1H, m), 1.05 (1H, m), 0.91 (1H, m), 0.68 (1H, m), 0.44 (1H, m); MS (CI) 301 (MH^+). Anal. ($C_{15}H_{13}ClN_4O$) C, H, N.

6b: ^{1}H NMR ($CDCl_3$) δ 8.48 (1H, dd, J = 2, 5), 8.10 (1H, dd, J = 2, 8), 7.43 (1H, d, J = 8), 7.12 (1H, d, J = 8), 7.07 (1H, dd, J = 5, 8), 3.69 (1H, m), 3.45 (3H, s), 1.03–1.00 (2H, m), 0.54–0.46 (2H, m); MS (CI) 301 (MH^+). Anal. ($C_{15}H_{13}ClN_4O$) C, H, N.

5c: ^{1}H NMR ($CDCl_3$) δ 8.32 (1H, dd, J = 2, 5), 8.07 (1H, dd, J = 2, 8), 7.34 (1H, d, J = 8), 6.99 (1H, dd, J = 5, 8), 6.95 (1H, d, J = 8), 4.2 (1H, br), 3.62 (3H, s), 3.55 (1H, br), 2.47 (3H, s), 1.22 (3H, t, J = 7); MS (CI) 269 (MH^+). Anal. ($C_{15}H_{16}N_4O$) C, H, N.

6c: ^{1}H NMR ($CDCl_3$) δ 8.37 (1H, dd, J = 2, 5), 8.08 (1H, dd, J = 2, 8), 7.36 (1H, d, J = 8), 6.98 (1H, dd, J = 5, 8), 6.92 (1H, d, J = 8), 4.18 (2H, q, J = 7), 3.47 (3H, s), 2.45 (3H, s), 1.24 (3H, t, J = 7); MS (CI) 269 (MH^+). Anal. ($C_{15}H_{16}N_4O$) C, H, N.

5d: ^{1}H NMR ($CDCl_3$) δ 8.31 (1H, dd, J = 2, 5), 8.06 (1H, dd, J = 2, 8), 7.18 (1H, s), 6.97 (1H, dd, J = 5, 8), 4.2 (1H, br), 3.60 (3H, s), 3.55 (1H, br), 2.41 (3H, s), 2.23 (3H, s), 1.22 (3H, t, J = 7); MS (CI) 283 (MH^+). Anal. ($C_{16}H_{18}N_4O{\cdot}0.25H_2O$) C, H, N.

6d: ^{1}H NMR ($CDCl_3$) δ 8.35 (1H, dd, J = 2, 5), 8.06 (1H, dd, J = 2, 8), 7.18 (1H, s), 6.96 (1H, dd, J = 5, 8), 4.16 (2H, q, J = 7), 3.48 (3H, s), 2.39 (3H, s), 2.26 (3H, s), 1.23 (3H, t, J = 7); MS (CI) 283 (MH^+). Anal. ($C_{16}H_{18}N_4O$) C, H, N.

5e: ^{1}H NMR ($CDCl_3$) δ 8.43 (1H, dd, J = 2, 5), 8.17 (1H, d, J = 2), 8.12 (1H, dd, J = 2, 8), 7.70 (1H, d, J = 2), 7.08 (1H, dd, J = 5, 8), 3.54 (3H, s), 3.48 (1H, m), 1.08 (1H, m), 0.97

(1H, m), 0.68 (1H, m), 0.46 (1H, m); MS (CI) 301 (MH^+). Anal. ($C_{15}H_{13}ClN_4O$) C, H, N.

6e: ^1H NMR ($CDCl_3$) δ 8.48 (1H, dd, J = 2, 5), 8.21 (1H, d, J = 2), 8.09 (1H, dd, J = 2, 8), 7.45 (1H, d, J = 2), 7.07 (1H, dd, J = 5, 8), 3.67 (1H, m), 3.47 (3H, s), 0.99 (2H, m), 0.56 (1H, m), 0.45 (1H, m); MS (CI) 301 (MH^+). Anal. ($C_{15}H_{13}ClN_4O$) C, H, N.

5f: ^1H NMR ($CDCl_3$) δ 8.37 (1H, dd, J = 2, 5), 8.26 (1H, d, J = 2), 8.11 (1H, dd, J = 2, 8), 7.56 (1H, d, J = 2), 7.05 (1H, dd, J = 5, 8), 4.3–3.5 (2H, br), 3.59 (3H, s), 1.25 (3H, t, J = 7); MS (CI) 333 (MH^+). Anal. ($C_{14}H_{13}BrN_4O$) C, H, N.

6f: ^1H NMR ($CDCl_3$) δ 8.40 (1H, dd, J = 2, 5), 8.23 (1H, d, J = 2), 8.10 (1H, dd, J = 2, 8), 7.59 (1H, d, J = 2), 7.03 (1H, dd, J = 5, 8), 4.15 (2H, q, J = 7), 3.50 (3H, s), 1.24 (3H, t, J = 7); MS (CI) 333 (MH^+). Anal. ($C_{14}H_{13}BrN_4O$) C, H, N.

5g: ^1H NMR ($CDCl_3$) δ 8.36 (1H, dd, J = 2, 5), 8.14 (2H, m), 6.97 (2H, m), 4.66 (1H, m), 3.62 (3H, s), 3.40 (1H, m), 2.36 (3H, s), 1.30 (3H, t, J = 7); MS (CI) 269 (MH^+). Anal. ($C_{15}H_{16}N_4O$) C, H, N.

6g: ^1H NMR ($CDCl_3$) δ 8.36 (1H, dd, J = 2, 5), 8.09 (1H, d, J = 5), 8.05 (1H, dd, J = 2, 8), 7.01 (1H, dd, J = 5, 8), 6.92 (1H, d, J = 5), 4.17 (2H, m), 3.36 (3H, s), 2.35 (3H, s), 1.27 (3H, t, J = 7); MS (CI) 269 (MH^+). Anal. ($C_{15}H_{16}N_4O$) C, H, N.

5h: ^1H NMR ($CDCl_3$) δ 8.20 (1H, dd, J = 2, 5), 7.98 (1H, d, J = 8), 7.45 (1H, dd, J = 2, 8), 7.10 (1H, dd, J = 5, 8), 6.84 (1H, d, J = 8), 4.2 (1H, br), 3.60 (3H, s), 3.55 (1H, br), 2.46 (3H, s), 1.21 (3H, t, J = 7); MS (CI) 269 (MH^+). Anal. ($C_{15}H_{16}N_4O$) C, H, N.

6h: ^1H NMR ($CDCl_3$) δ 8.19 (1H, dd, J = 2, 5), 7.97 (1H, d, J = 8), 7.46 (1H, dd, J = 2, 8), 7.07 (1H, dd, J = 5, 8), 6.84 (1H, d, J = 8), 4.18 (2H, m), 3.49 (3H, s), 2.47 (3H, s), 1.24 (3H, t, J = 7); MS (CI) 269 (MH^+). Anal. ($C_{15}H_{16}N_4O$) C, H, N.

5i: ^1H NMR ($CDCl_3$) δ 8.36 (1H, d, J = 2), 8.24 (1H, dd, J = 2, 5), 8.19 (1H, d, J = 2), 7.45 (1H, dd, J = 2, 8), 7.14 (1H, dd, J = 5, 8), 4.2 (1H, br), 3.61 (3H, s), 3.5 (1H, br), 1.22 (3H, t, J = 7); MS (CI) 333 (MH^+). Anal. ($C_{14}H_{13}BrN_4O$) C, H, N.

6i: ^1H NMR ($CDCl_3$) δ 8.41 (1H, d, J = 3), 8.22 (1H, dd, J = 2, 5), 8.19 (1H, d, J = 3), 7.50 (1H, dd, J = 2, 8), 7.12 (1H, dd, J = 5, 8), 4.16 (2H, q, J = 7), 3.50 (3H, s), 1.25 (3H, t, J = 7); MS (CI) 333 (MH^+). Anal. ($C_{14}H_{13}BrN_4O$) C, H, N.

5-Ethyl-11-methyl-2-nitrodipyrido[2,3-*b*:2′,3′-*e*][1,4]diazepin-10-one (5j). To a solution of **5a** (0.089 g, 0.35 mmol) in acetonitrile (4 mL) was added nitronium tetrafluoroborate (85%, 0.061 g) as a solid. After 0.5 h the mixture was diluted with EtOAc, washed with water, dried, filtered, and evaporated. The residue was fractionated by preparative layer chromatography (CH_2Cl_2) to give **5j** (0.059 g, 0.20 mmol, 57%): mp 142–144 °C (EtOAc/hexane); ^1H NMR ($CDCl_3$) δ 8.41 (1H, dd, J = 2, 5), 8.14 (1H, dd, J = 2, 8), 8.08 (1H, d, J = 9), 7.66 (1H, d, J = 9), 7.11 (1H, dd, J = 5, 8), 4.01 (2H, br), 3.68 (3H, s), 1.28 (3H, t, J = 7); MS (CI) 300 (MH^+). Anal. ($C_{14}H_{13}N_5O_3$) C, H, N.

3-Bromo-5-ethyl-11-methyl-2-nitrodipyrido[2,3-*b*:2′,3′-*e*][1,4]diazepin-10-one (5k) and 3-Bromo-5-ethyl-11-methyl-2,8-dinitrodipyrido[2,3-*b*:2′,3′-*e*][1,4]diazepin-10-one (5l). To a solution of **5f** (0.150 g, 0.45 mmol) in acetonitrile (4 mL) stirred at room temperature was added nitronium tetrafluoroborate (85%, 0.164 g) portionwise as a solid over 1 h. The mixture was diluted with EtOAc, washed, dried, filtered, and evaporated. Fractionation of the residue over silica gel (CH_2Cl_2) gave (a) the dinitro derivative **5l** (0.081 g, 0.19 mmol, 43%): mp 224–227 °C (EtOAc/$^iPr_2O$); ^1H NMR ($CDCl_3$) δ 9.22 (1H, d, J = 3), 8.93 (1H, d, J = 3), 7.82 (1H, s), 4.09 (2H, q, J = 7), 3.61 (3H, s), 1.33 (3H, t, J = 7); MS (CI) 423 (MH^+). Anal. ($C_{14}H_{11}N_6O_5Br$) C, H, N. (b) the mononitro derivative **5k** (0.049 g, 0.13 mmol, 29%): mp 186–188 °C (EtOAc/hexane); ^1H NMR ($CDCl_3$) δ 8.42 (1H, dd, J = 2, 5), 8.14 (1H, dd, J = 2, 8), 7.75 (1H, s), 7.13 (1H, dd, J = 5, 8), 3.96 (2H, br), 3.60 (3H, s), 1.28 (3H, t, J = 7); MS (CI) 378 (MH^+). Anal. ($C_{14}H_{12}N_5O_3Br$) C, H, N.

8-Amino-5-ethyl-11-methyldipyrido[2,3-*b*:2′,3′-*e*][1,4]diazepin-10-one (5n). A solution of **5l** (0.044 g, 0.10 mmol) in 30% HBr/AcOH (0.4 mL) was heated in a sealed tube at 120 °C for 5 h. The mixture was cooled to room temperature, diluted with EtOAc/water, and washed with 10% aqueous NaOH. The organic phase was separated, dried, filtered, and evaporated to give 2,3-dibromo-5-ethyl-11-methyl-8-nitrodipyrido[2,3-*b*:2′,3′-*e*][1,4]diazepin-10-one (**5m**) (0.029 g, 0.063 mmol, 63%): mp 234–237 °C (EtOAc); ^1H NMR ($CDCl_3$) δ 9.17 (1H, d, J = 3), 8.89 (1H, d, J = 3), 7.63 (1H, s), 4.05 (2H, br), 3.58 (3H, s), 1.26 (3H, t, J = 7). Anal. ($C_{14}H_{11}N_5O_3Br_2$) C, H, N.

A mixture of **5m** (0.041 g, 0.09 mmol), ammonium formate (0.641 g), and 10% Pd/C (0.041 g) in EtOH (5 mL) was stirred at room temperature under N_2 for 3 days. The mixture was diluted with EtOAc, washed, dried, filtered, and evaporated to give the product **5n** (0.021 g, 0.078 mmol, 86%): mp 199–201 °C (EtOAc); ^1H NMR ($CDCl_3$) δ 8.19 (1H, dd, J = 2, 5), 7.85 (1H, d, J = 3), 7.44 (2H, m), 7.11 (1H, dd, J = 5, 8), 4.13 (1H, br), 3.62 (3H, s), 3.56 (3H, br, 2 × NH, N-*CH*CH_3), 1.21 (3H, t, J = 7); MS (CI) 270 (MH^+). Anal. ($C_{14}H_{15}N_5O$) H, N; C: calcd, 26.00; found, 25.53.

2,3-Dibromo-5-ethyl-11-methyldipyrido[2,3-*b*:2′,3′-*e*][1,4]diazepin-10-one (5o). A solution of **5k** (0.029 g, 0.077 mmol) in 30% HBr/AcOH (0.2 mL) was heated in a sealed tube at 120 °C for 1.5 h. The mixture was diluted with EtOAc, washed with aqueous K_2CO_3, dried, filtered, and evaporated. The residue was purified by preparative layer chromatography (EtOAc/hexane) to give **5o** which crystallized from heptane (0.018 g, 0.044 mmol, 57%): mp 206–210 °C (heptane); ^1H NMR ($CDCl_3$) δ 8.36 (1H, dd, J = 2, 5), 8.11 (1H, dd, J = 2, 7), 7.59 (1H, s), 7.06 (1H, dd, J = 5, 7), 3.95 (2H, br), 3.58 (3H, s), 1.24 (3H, t, J = 7); MS (CI) 411 (MH^+). Anal. ($C_{14}H_{12}N_4OBr_2$) C, H, N.

8-Amino-5-ethyl-2,3,11-trimethyldipyrido[2,3-*b*:2′,3′-*e*][1,4]diazepin-10-one (5q). To a solution of **5d** (0.082 g, 0.29 mmol) in acetonitrile (3 mL) stirred at room temperature was added nitronium tetrafluoroborate (85%, 0.33 g) as a solid in portions over 1 h. The mixture was stirred for an additional 0.5 h, the reaction quenched with aqueous K_2CO_3, and the mixture extracted with EtOAc. The organic phase was dried, filtered, and evaporated, and the residue was fractionated over silica gel (EtOAc/hexane) to give (a) 8-nitro-5-ethyl-2,3,11-trimethyldipyrido[2,3-*b*:2′,3′-*e*][1,4]diazepin-10-one (0.023 g, 0.070 mmol, 24%) and (b) recovered **5d** (0.017 g, 0.060 mmol, 21%). The nitro derivative (0.023 g, 0.070 mmol) was dissolved in ethanol (5 mL), and ammonium formate (0.325 g) and 10% Pd/C (0.032 g) were added. The mixture was stirred under argon for 2 h when TLC showed complete consumption of starting material. The reaction mixture was diluted with EtOAc and water, and the organic phase was separated, dried, filtered, and evaporated. Crystallization of the residue from $^iPr_2O$ gave **5q** (0.013 g, 0.044 mmol, 63%): mp 208–211 °C ($^iPr_2O$); ^1H NMR ($CDCl_3$) δ 7.81 (1H, d, J = 3), 7.40 (1H, d, J = 3), 7.15 (1H, s), 4.1 (1H, br), 3.59 (3H, s), 3.5 (3H, br, NH_2, N-*CH*CH_3), 2.39 (3H, s), 2.22 (3H, s), 1.18 (3H, t, J = 7). Anal. ($C_{16}H_{19}N_5O$) C, H, N.

3-(3-Aminophenyl)-5-ethyl-11-methyldipyrido[2,3-*b*:2′,3′-*e*][1,4]diazepin-10-one (5p). (a) 3-(Tributylstannyl)aniline. To a solution of 3-bromoaniline (0.537 g, 3.1 mmol) in THF (15 mL) cooled below −60 °C was added *tert*-butyllithium (1.7 M in pentane, 7.5 mL, 12.75 mmol) at such a rate that the internal temperature did not exceed −50 °C. The mixture was stirred at −50 °C for an additional 20 min, and tributyltin chloride (1.0 mL, 3.6 mmol) was added all at once. The mixture was stirred for 15 min, the reaction quenched with aqueous potassium fluoride,[13] and the mixture allowed to warm to room temperature. The mixture was diluted with EtOAc, washed, dried, filtered, and evaporated. Chromatography of the residue over silica gel (EtOAc/hexane) gave 3-(tributylstannyl)aniline as an oil (0.951 g, 2.4 mmol, 78%): ^1H NMR ($CDCl_3$) δ 7.13 (1H, m), 6.87 (1H, m), 6.80 (1H, m), 6.65 (1H, m), 3.60 (2H, br, NH), 1.51 (6H, m, 3 × CH_2), 1.34 (6H, m, 3 × CH_2), 1.06 (6H, m, 3 × CH_2), 0.89 (9H, t, J = 7, 3 × CH_3).

(**b**) A solution of **5f** (0.032 g, 0.10 mmol), 3-(tributylstannyl)aniline (0.102 g, 0.27 mmol), and $Pd(Ph_3P)_2Cl_2$ (0.005 g) in *N*-methylpyrrolidinone was heated at 115 °C in a sealed tube for 5.5 h. The mixture was cooled to room temperature, and tetrabutylammonium fluoride (1 M in THF, 1 mL) was added.

After 18 h the mixture was diluted with EtOAc, washed, dried, filtered, and evaporated. The residue was fractionated by preparative layer chromatography (EtOAc/hexane) to give **5p** (0.018 g, 0.05 mmol, 50%): mp 206–208 °C (EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ 8.41 (1H, d, J = 2), 8.37 (1H, dd, J = 2, 5), 8.13 (1H, dd, J = 2, 8), 7.59 (1H, d, J = 2), 7.25 (1H, m), 7.04 (1H, dd, J = 5, 8), 6.91 (1H, m), 6.83 (1H, m), 6.73 (1H, m), 4.20 (1H, br), 3.80 (2H, NH_2), 3.75 (1H, br), 3.66 (3H, s), 1.27 (3H, t, J = 7); MS (CI) 346 (MH^+). Anal. ($C_{20}H_{19}N_5O$·0.25EtOAc) C, H, N.

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Supplementary Material Available: Characterization (melting points, ^{1}H NMR and mass spectral data, and elemental analyses) of intermediates **2b–d,f,h,i**, **3b–d,g–i**, and **4c,d,f–i** (3 pages). Ordering information is given on any current masthead page.

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