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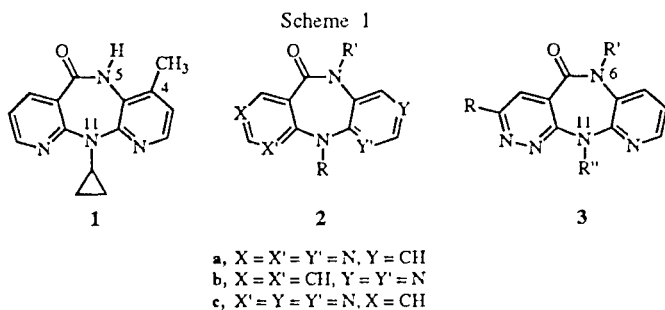
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Dedicated with best personal wishes to Professor Dr. W. Wiegrebe Regensburg on the occasion of his 65th anniversary

The preparation of pyridazino[3,4-*e*]pyrido[3,2-*b*][1,4]diazepin-5-ones **8** and **9** starting from appropriately substituted pyridazine-4-carboxamides is reported. The new compounds were tested for HIV-1 reverse transcriptase inhibitory activity.

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Derivatives of diannelated 1,4-diazepin(ones) are known to exhibit a wide variety of biological activities, e.g. antidepressive [2a,2b,3], psychotropic [2a,2b,4], antihistaminic [2a,2b,5], antimuscarinic [2a,2b,6], analgesic [2b], and antiviral [7,8] activity. Of particular interest is the dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one derivative nevirapine (**1**) which represents a potent non-nucleoside HIV reverse transcriptase inhibitor [7]. In order to alter the pharmacological and pharmacokinetic profile of this anti-AIDS agent, various structural modifications of the tricyclic system including replacement of one of the pyridine moieties by a pyrimidine system **2a,c**, have been carried out [8]. The corresponding pyridazino[3,4-*e*]pyrido[3,2-*b*][1,4]diazepin-5-one system, however, so far remained unexplored. In this publication we report the synthesis of selected derivatives of this novel ring system, compounds of type **3**, and on the evaluation of their activity against HIV-1 reverse transcriptase.



It is well documented in the literature that in the series of dipyriddiazepinones **2** (X = Y = CH, X' = Y' = N, and R' = H) maximum HIV-1 reverse transcriptase inhibition is exhibited by compounds bearing a methyl group at position 4. If position 4 is unsubstituted a methyl substituent at the lactam-nitrogen atom is required. Moreover, small aliphatic alkyl substituents such as ethyl or cyclopropyl at N-11 are known to be essential for optimum activity [7]; 11-cyclopropyl substituted derivatives exhibit greater bioavailability. Thus, derivatives of type **3** con-

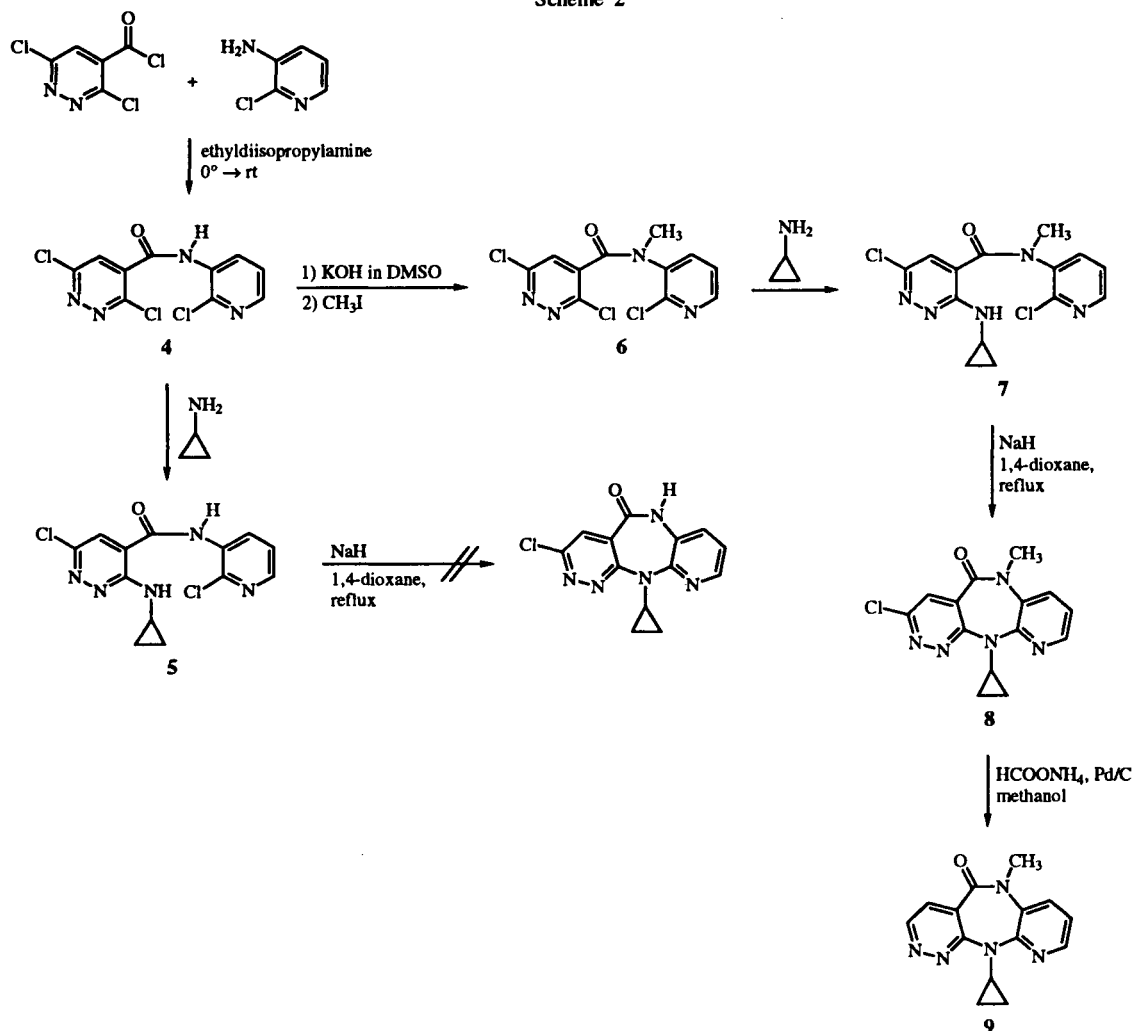
taining a cyclopropyl substituent at N-11 and a methyl group at position 6 became an object of our interest.

From previous investigations of reactions of 3,6-dichloropyridazine-4-carboxylic acid derivatives with various N-nucleophiles [9,10] it is known that with primary aliphatic amines selective substitution of the chloro function at position 3 takes place. Accordingly, the 6-chloro-3-cyclopropylaminopyridazine-4-carboxamide **5** could be smoothly prepared by stirring the 3,6-dichloropyridazine-4-carboxamide derivative **4** with an excess of 3-cyclopropylamine in dry dichloromethane. Whereas initial attempts to achieve cyclisation by refluxing compound **5** in dry 1,4-dioxane with 10 equivalents of sodium hydride had failed (after 7 days only unchanged starting material could be recovered), the corresponding N-methyl derivative **6**, prepared by N-alkylation of compound **4** and subsequent exchange of the 3-chloro function by a cyclopropylamino moiety, could be smoothly transformed into the novel 11-cyclopropyl-6-methyl substituted pyridazino[3,4-*e*]pyrido[3,2-*b*][1,4]diazepin-5-one **8**.

The finding that only in the N-methylated compound **7** the 2-chloro substituent is sufficiently reactive to serve as a leaving group is in accord with our observations previously made in the pyridazino[3,4-*b*][1,5]benzodiazepin-5-one series [10]. This can be explained by protection of the carboxamide substructure, thus avoiding the formation of a carboxamide anion under the reaction conditions required. The pyridazino[3,4-*e*]pyrido[3,2-*b*][1,4]diazepin-5-one **9** devoid of any substituent in the heteroaromatic rings finally became smoothly accessible by reductive dehalogenation using ammonium formate as the hydrogen source. All previously unreported compounds were fully characterised by elemental analysis, IR and NMR data.

The novel pyridazino[3,4-*e*]pyrido[3,2-*b*][1,4]diazepin-5-ones **8** and **9** were screened *in vitro* for HIV-1 reverse transcriptase inhibition. Concentrations of 330 μM and 33 μM were used. The results obtained (see Table 1) indicate the azanevirapine derivatives **8** and **9** to be less active than nevirapine (**1**) [7] which was used as the reference. Moreover, as

Scheme 2



shown by comparison with the recently prepared pyridazino[3,4-*b*][1,5]benzodiazepin-5-ones **10a/b** [10], introduction of a nitrogen atom into this pyridazine-containing tricyclic system does not increase the reverse transcriptase

inhibitory potency. It should be noted that, by contrast, Hargrave *et al.* had found that dipyridodiazepinones are more active than pyridobenzodiazepinones [7].

In conclusion, the previously unreported pyridazino[3,4-*e*]pyrido[3,2-*b*][1,4]diazepin-5-ones of type 3 can be prepared smoothly *via N*-substituted 3-amino-6-chloro-*N*-(2-chloro-3-pyridinyl)pyridazine-4-carboxamides, *e.g.* compound 7. This synthetic approach can be expected to permit variation of the substituent pattern in the pyridine ring as well as in positions 3, 6, and 11 within a wide range. Employment of this novel tricyclic system for the synthesis of further potential biologically active compounds is envisaged.

Table 1  
Inhibition of HIV-1 Reverse Transcriptase

No.	X	R	Inhibition at	
			330 $\mu\text{M}$	33 $\mu\text{M}$
<b>8</b>	N	Cl	64	20
<b>9</b>	N	H	69	37
<b>10a</b> [10]	CH	Cl	72	56
<b>10b</b> [10]	CH	H	72	26
nevirapine (1)			100	-99

## EXPERIMENTAL

Melting points were determined on a Kofler hot-stage microscope (Reichert) and are uncorrected. The ir spectra were

observed on a Mattson Galaxy Series FT-IR 3000 spectrophotometer (potassium bromide pellets). The  $^1\text{H}$  and  $^{13}\text{C}$  nmr spectra were recorded on a Varian Gemini 200 spectrometer ( $^1\text{H}$ : 199.98 MHz,  $^{13}\text{C}$ : 50.29 MHz). The center of the solvent multiplet (DMSO- $d_6$  or deuteriochloroform) was used as internal standard (chemical shifts in  $\delta$  ppm), which was related to tetramethylsilane with  $\delta$  2.49 ppm for  $^1\text{H}$  and  $\delta$  39.5 ppm for  $^{13}\text{C}$  (DMSO- $d_6$ ) or with  $\delta$  7.26 ppm for  $^1\text{H}$  and  $\delta$  77.0 ppm for  $^{13}\text{C}$  (deuteriochloroform). Reactions were monitored by tlc using Polygram<sup>®</sup> SIL G/UV<sub>254</sub> (Macherey-Nagel) plastic-backed plates (0.25 mm layer thickness). Column chromatography was performed using Kieselgel 60 (0.040-0.063 mm, Merck). Microanalyses were performed at the Institute of Physical Chemistry (Mag. J. Theiner), University of Vienna, Austria. Light petroleum refers to the fraction of bp 40-60°. The yields are not optimised.

#### Starting Materials.

3,6-Dichloropyridazine-4-carboxylic acid chloride was available from 3,6-dichloro-4-methylpyridazine [11] by oxidation with potassium dichromate in concentrated sulfuric acid [12] and subsequent treatment with thionyl chloride [9].

#### Procedures for the Acylation Reactions.

3,6-Dichloro-*N*-(2-chloro-3-pyridinyl)pyridazine-4-carboxamide (4).

To an ice-cooled solution of 3-amino-2-chloropyridine (0.643 g, 5.00 mmoles) and ethyldiisopropylamine (0.646 g, 5.00 mmoles) in dry dichloromethane (20 ml) was added dropwise a solution of 3,6-dichloropyridazine-4-carboxylic acid chloride (1.057 g, 5.00 mmoles) in dry dichloromethane (10 ml) under a nitrogen atmosphere. The mixture was stirred at room temperature for 4 hours, then the suspension was diluted with 30 ml of dichloromethane and washed with water (3x) and saturated sodium chloride solution. The organic phase was dried over anhydrous sodium sulphate and evaporated. The residue was recrystallized from tetrahydrofuran/diethyl ether to yield 1.265 g (83%) of colourless crystals, mp 191-194.5°; ir:  $\nu$  3233, 3019, 1694  $\text{cm}^{-1}$ ;  $^1\text{H}$ -nmr (DMSO- $d_6$ ):  $\delta$  10.76 (s, 1H, NH), 8.41-8.28 (m, 3H), 7.58-7.50 (m, 1H) (pyridine-H4, -H5, -H6, pyridazine-H5);  $^{13}\text{C}$ -nmr (DMSO- $d_6$ ):  $\delta$  161.2 (C=O), 156.3, 152.1 (pyridazine-C-3, C-6), 147.1 (pyridine-C-6), 143.9, 137.8 (pyridazine-C-4, pyridine-C-2), 131.0 (pyridine-C-3), 134.8, 129.5 (pyridazine-C-5, pyridine-C-4), 124.0 (pyridine-C-5).

*Anal.* Calcd. for  $\text{C}_{10}\text{H}_5\text{Cl}_3\text{N}_4\text{O}$ : C, 39.57; H, 1.66; N, 18.46. Found: C, 39.81; H, 1.42; N, 18.56.

#### Procedure for *N*-Alkylation.

3,6-Dichloro-*N*-(2-chloro-3-pyridinyl)-*N*-methylpyridazine-4-carboxamide (6).

A mixture of 4 (0.910 g, 3 mmoles) and 6 mmoles of powdered potassium hydroxide (0.337 g) in dry dimethyl sulfoxide (15 ml) was stirred for 1 hour under a nitrogen atmosphere. Methyl iodide (0.639 g, 4.5 mmoles) was added and stirring continued until the starting material was completely consumed (tlc monitoring, ether, ca. 30 minutes). The reaction mixture then was poured into water (100 ml), the solution was neutralised and the mixture was extracted exhaustively with diethyl ether. The organic phase was washed with water and saturated sodium chloride solution, dried over anhydrous sodium sulphate and evaporated. The product was purified by column chromatography (dichloromethane/ethyl acetate, 9:1) followed by

recrystallization from ethyl acetate/diethyl ether to yield 0.825 g (82%) of colourless crystals, mp 103-120°; ir:  $\nu$  1655  $\text{cm}^{-1}$ ;  $^1\text{H}$ -nmr (deuteriochloroform):  $\delta$  8.37 (dd,  $J = 4.7$  Hz,  $J = 1.8$  Hz, 1H, pyridine-H6), 7.82 (dd,  $J = 7.8$  Hz,  $J = 1.8$  Hz, 1H, pyridine-H4), 7.50 (s, 1H, pyridazine-H5), 7.28 (dd,  $J = 7.8$  Hz,  $J = 4.7$  Hz, 1H, pyridine-H5), 3.44 (s, 3H,  $\text{CH}_3$ ).

*Anal.* Calcd. for  $\text{C}_{11}\text{H}_7\text{Cl}_3\text{N}_4\text{O} \cdot 0.2\text{CH}_3\text{COOC}_2\text{H}_5$ : C, 42.28; H, 2.59; N, 16.72. Found: C, 42.17; H, 2.59; N, 16.69.

General Procedure for the Preparation of 6-Chloro-*N*-(2-chloro-3-pyridinyl)-3-cyclopropylaminopyridazine-4-carboxamides 5 and 7.

To a stirred solution or suspension of 2.0 mmoles of the appropriate 3,6-dichloro-*N*-(2-chloropyridyl)pyridazine-4-carboxamide 4 or 6, in dry dichloromethane (15 ml) was added cyclopropylamine (50 mmoles) at room temperature under a nitrogen atmosphere. The reaction mixture was stirred until tlc indicated no further conversion (reaction times varied between 2 and 4 days). Then the mixture was poured into water (ca. 150 ml) and the mixture was extracted with dichloromethane. The organic layer was washed with water and saturated sodium chloride solution, dried over sodium sulphate and evaporated. The residue thus obtained was purified by column chromatography (ethyl acetate), and then recrystallized from diisopropyl ether.

6-Chloro-*N*-(2-chloro-3-pyridinyl)-3-cyclopropylaminopyridazine-4-carboxamide (5).

The yield of 5 was 0.565 g (87%) as yellow crystals, mp 207-211°; ir:  $\nu$  3350, 1669  $\text{cm}^{-1}$ ;  $^1\text{H}$ -nmr (deuteriochloroform):  $\delta$  8.73 (s, 1H, NH), 8.57 (dd,  $J = 8.1$  Hz,  $J = 1.6$  Hz, 1H, pyridine-H4), 8.23 (dd,  $J = 4.7$  Hz,  $J = 1.6$  Hz, 1H, pyridine-H6), 7.47 (s, 1H, pyridazine-H5), 7.46 (s br, 1H, NH), 7.34 (dd,  $J = 8.1$  Hz,  $J = 4.7$  Hz, 1H, pyridine-H5), 3.03-2.90 (m, 1H, CH), 0.93-0.83 (m, 2H,  $\text{CH}_2$ ), 0.61-0.53 (m, 2H,  $\text{CH}_2$ );  $^{13}\text{C}$ -nmr (deuteriochloroform):  $\delta$  163.9, 156.4 (C=O, pyridazine-C-3), 145.7 (pyridazine-C-6), 145.6 (pyridine-C-6), 141.7, 130.8 (pyridine-C-3, pyridine-C-2), 130.6, 125.1, 123.3 (pyridazine-C-5, pyridine-C-4, pyridine-C-5), 116.9 (pyridazine-C-4), 24.4 (CH), 7.3 (2 x  $\text{CH}_2$ ).

*Anal.* Calcd. for  $\text{C}_{13}\text{H}_{11}\text{Cl}_2\text{N}_5\text{O}$ : C, 48.17; H, 3.42; N, 21.60. Found: C, 48.12; H, 3.82; N, 21.50.

6-Chloro-*N*-(2-chloro-3-pyridinyl)-3-cyclopropylamino-*N*-methylpyridazine-4-carboxamide (7).

The yield of 7 was 0.588 g (87%) as yellow crystals, mp 69-74°; ir:  $\nu$  3389, 1659  $\text{cm}^{-1}$ ;  $^1\text{H}$ -nmr (deuteriochloroform):  $\delta$  8.38 (dd,  $J = 4.7$  Hz,  $J = 1.7$  Hz, 1H, pyridine-H6), 7.59 (d,  $J = 6.5$  Hz, 1H, pyridine-H4), 7.33-7.29 (m, 1H, pyridine-H5), 6.70 (s br, 1H, pyridazine-H5), 6.09 (s br, 1H, deuterium oxide-exchangeable, NH), 3.37 (s, 3H,  $\text{CH}_3$ ), 2.98-2.86 (m, 1H, CH), 0.93-0.83 (m, 2H,  $\text{CH}_2$ ), 0.60-0.52 (m, 2H,  $\text{CH}_2$ );  $^{13}\text{C}$ -nmr (deuteriochloroform):  $\delta$  165.8, 155.6 (C=O, pyridazine-C-3), 149.6 (pyridine-C-6), 149.2, 145.8, (pyridazine-C-6, pyridine-C-2), 137.6, 125.6, 123.7 (pyridazine-C-5, pyridine-C-4, pyridine-C-5), 136.9 (pyridine-C-2), 120.3 (pyridazine-C-4), 24.5, 22.8 (CH,  $\text{CH}_3$ ), 7.4 (2 x  $\text{CH}_2$ ).

*Anal.* Calcd. for  $\text{C}_{14}\text{H}_{13}\text{Cl}_2\text{N}_5\text{O}$ : C, 49.72; H, 3.87; N, 20.71. Found: C, 49.67; H, 3.59; N, 20.69.

#### Procedure for the Cyclisation.

3-Chloro-11-cyclopropyl-6,11-dihydro-6-methyl-5*H*-pyridazino[3,4-*e*]pyrido[3,2-*b*][1,4]diazepin-5-one (8).

Sodium hydride (0.500 g of a 60% dispersion in oil, 12.5 mmoles) was added at room temperature to a suspension of **7** (0.500 g, 1.48 mmoles) in dry 1,4-dioxane (40 ml) under an atmosphere of nitrogen, and the mixture was refluxed for 30 minutes. After cooling to room temperature, the solution was poured under a nitrogen atmosphere into cold 0.5*N* hydrochloric acid (80 ml), the resulting crystals were collected, washed with water and subsequently with light petroleum, and dried *in vacuo*. The products were purified by recrystallization from ethanol to yield 0.379 g (84%) of yellow crystals, mp 226-232°; ir:  $\nu$  1659  $\text{cm}^{-1}$ ;  $^1\text{H-nmr}$  (deuteriochloroform):  $\delta$  8.34 (dd,  $J_{8/9} = 4.6$  Hz,  $J_{7/9} = 1.6$  Hz, 1H, H<sub>9</sub>), 7.80 (s, 1H, H<sub>4</sub>), 7.53 (dd,  $J_{7/8} = 8.0$  Hz,  $J_{7/9} = 1.6$  Hz, 1H, H<sub>7</sub>), 7.21 (dd,  $J_{7/8} = 8.0$  Hz,  $J_{8/9} = 4.6$  Hz, 1H, H<sub>8</sub>), 3.94-3.83 (m, 1H, CH), 3.50 (s, 3H, CH<sub>3</sub>), 1.20-1.10 (m, 2H, CH<sub>2</sub>), 0.64-0.46 (m, 2H, CH<sub>2</sub>);  $^{13}\text{C-nmr}$  (deuteriochloroform):  $\delta$  164.2, 160.7 (C-5, C-11a), 153.7, 152.8 (C-3, C-10a), 145.5 (C-9), 131.1, 130.1 (C-4, C-7), 130.2, 126.4 (C-4a, C-6a), 120.8 (C-8), 37.6, 29.5 (CH, CH<sub>3</sub>), 9.0 (2 x CH<sub>2</sub>).

*Anal.* Calcd. for C<sub>14</sub>H<sub>12</sub>ClN<sub>5</sub>O•0.1C<sub>2</sub>H<sub>5</sub>OH: C, 55.68; H, 4.15; N, 22.86. Found: C, 55.73; H, 4.12; N, 22.69.

Synthesis of 11-Cyclopropyl-6,11-dihydro-6-methyl-5*H*-pyridazino[3,4-*e*]pyrido[3,2-*b*][1,4]diazepin-5-one (**9**) by Reductive Dehalogenation.

A mixture of **8** (0.250 g, 0.83 mmole), ammonium formate (0.262 g, 4.15 mmoles) and 0.050 g of Pd/C (10%) in 15 ml of methanol was stirred under a nitrogen atmosphere at 48° for 30 minutes. The catalyst was filtered, the solvent was removed *in vacuo*, and the residue was taken up in dichloromethane. This solution was washed with water and saturated sodium chloride solution, dried over anhydrous sodium sulphate and evaporated. The product thus obtained was purified by column chromatography (ethyl acetate), followed by recrystallization (ethanol) to give 0.175 g (77%) of light yellow crystals, mp 220-224.5°; ir:  $\nu$  1647  $\text{cm}^{-1}$ ;  $^1\text{H-nmr}$  (deuteriochloroform):  $\delta$  9.06 (d,  $J_{3/4} = 4.9$  Hz, 1H, H<sub>3</sub>), 8.34 (dd,  $J_{8/9} = 4.6$  Hz,  $J_{7/9} = 1.5$  Hz, 1H, H<sub>9</sub>), 7.78 (d,  $J_{3/4} = 4.9$  Hz, 1H, H<sub>4</sub>), 7.53 (dd,  $J_{7/8} = 8.0$  Hz,  $J_{7/9} = 1.5$  Hz, 1H, H<sub>7</sub>), 7.19 (dd,  $J_{7/8} = 8.0$  Hz,  $J_{8/9} = 4.6$  Hz, 1H, H<sub>8</sub>), 4.01-3.90 (m, 1H, CH), 3.51 (s, 3H, CH<sub>3</sub>), 1.18-1.03 (m, 2H, CH<sub>2</sub>), 0.67-0.45 (m, 2H, CH<sub>2</sub>);  $^{13}\text{C-nmr}$  (deuteriochloroform):  $\delta$  165.5, 161.3 (C-5, C-11a), 154.4 (C-10a), 148.4, 145.3 (C-3, C-9), 130.4, 124.0 (C-4a, C-6a), 130.9, 128.6 (C-4, C-7), 120.5 (C-8), 37.5, 29.5 (CH, CH<sub>3</sub>), 9.0 (2 x CH<sub>2</sub>).

*Anal.* Calcd. for C<sub>14</sub>H<sub>13</sub>N<sub>5</sub>O•0.1C<sub>2</sub>H<sub>5</sub>OH•0.1H<sub>2</sub>O: C, 62.32; H, 5.08; N, 25.59. Found: C, 62.30; H, 4.80; N, 25.46.

#### HIV-1 Reverse Transcriptase Inhibition.

##### General.

The measurement of *in vitro* HIV-1 reverse transcriptase inhibition was performed with the nonradioactive RT-Kit from Boehringer Mannheim. For exact composition and concentration of the solutions and for precise working procedure see instructions of the assay (Catalog No. 1468 120)-ELISA-Reader: Digi scan reader (ASYS Hitech GmbH).

##### General Procedure.

The compounds were dissolved in dimethyl sulfoxide (20 mmoles l<sup>-1</sup>) and further diluted with lysis buffer (5  $\mu\text{l}$  of the dimethyl sulfoxide solution and 95  $\mu\text{l}$  of lysis buffer = solution 1; 10  $\mu\text{l}$  of solution 1 and 90  $\mu\text{l}$  of lysis buffer = solution 2) shortly before use.

#### Test Compounds.

Five  $\mu\text{l}$  of reverse transcriptase dilution (5 ng/well), 15  $\mu\text{l}$  of lysis buffer, 20  $\mu\text{l}$  of a solution of the compound (0.1 mmole l<sup>-1</sup> in dimethyl sulfoxide/lysis buffer), and 20  $\mu\text{l}$  of reaction mixture (template and nucleotides) were incubated for 1 hour at 37°.

#### Reverse Transcriptase Standards.

Five  $\mu\text{l}$  of reverse transcriptase dilution (1, 2 or 5 ng/well, respectively), 35  $\mu\text{l}$  of lysis buffer, and 20  $\mu\text{l}$  of reaction mixture (template and nucleotides) were incubated for 1 hour at 37°.

#### Blank Value.

Forty  $\mu\text{l}$  of lysis buffer and 20  $\mu\text{l}$  of reaction mixture (template and nucleotides) were incubated for 1 hour at 37°.

The reaction solutions were then transferred into streptavidin-coated microplate modules and incubated again for 1 hour at 37°. The samples were discarded and the plates were washed five times with washing buffer. After washing, 200  $\mu\text{l}$  of anti DIG-peroxidase conjugate (an antibody to digoxigenin that is conjugated to peroxidase) (200 mUml<sup>-1</sup>) was added to each well and the resulting mixtures were incubated for 1 hour at 37°. After additional washing (5 x), 200  $\mu\text{l}$  of POD substrate (the substrate for the enzyme peroxidase) (2,2'-azinobis-3-ethylbenzothiazoline-6-sulfonate) was added to each well and the mixtures were subsequently incubated at room temperature (10-20 minutes). The absorbance of the samples was measured at 405 nm with a reference wavelength at 490 nm using a microtiter plate (ELISA) reader.

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