Pyridazines 92 [1]. Synthesis of Dialkyldipyridazinodiazepinones as Potential HIV-1 Reverse Transcriptase Inhibitors

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Two methods for the preparation of dialkylsubstituted dipyridazino[4,3-*b*:3',4'-*e*][1,4]diazepinones and dipyridazino[3,4-*b*:3',4'-*e*][1,4]diazepinones are reported. The new compounds were evaluated for their inhibitory effects against the replication of human immunodeficiency virus [HIV-1(III_B) and HIV-2(ROD)] in MT-4 cells.

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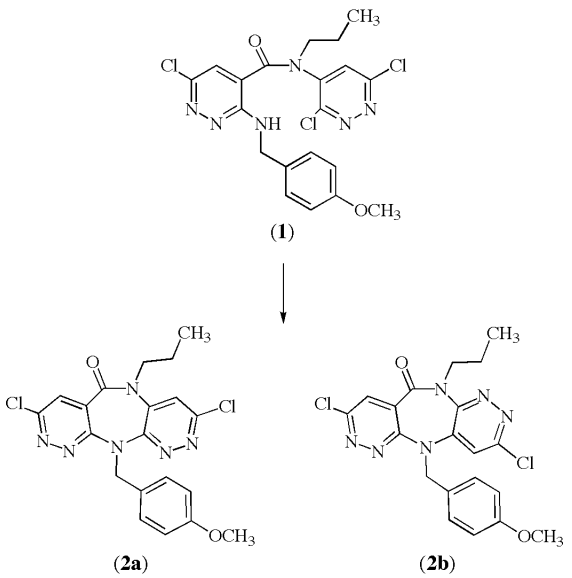
Recently we reported that two novel tricycles *i.e.* dipyridazino[4,3-*b*:3',4'-*e*][1,4]diazepinones and dipyridazino[3,4-*b*:3',4'-*e*][1,4]diazepinones can be prepared by treatment of 6-chloro-*N*-(3,6-dichloropyridazin-4-yl)-3-(4-methoxybenzylamino)-*N*-propylpyridazine-4-carboxamide (**1**) with base. [2] Whereas the 3,8-dichloro-5,11-dihydro-11-(4-methoxybenzyl)-5-propyldipyridazino[4,3-*b*:3',4'-*e*][1,4]diazepinone (**2a**) represents the expected reaction product, formation of isomer **2b** can be explained *via* Smiles rearrangement. We found that the reaction conditions (*i.e.* solvent and base) influence the formation of isomers [2,3].

Since derivatives of diannelated 1,4-diazepinones represent essential subunits of a wide variety of bioactive compounds, [4a-l] especially non-nucleoside HIV reverse transcriptase inhibitors (NNRTIs), [5a/b] appropriately substituted dipyridazinodiazepinones became an object of our interest as potential bioisosters of the *nevirapine* type.

Scheme 1



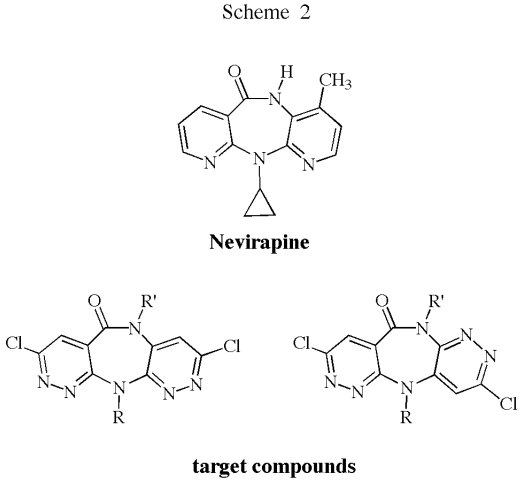
For the synthesis of the target compounds we envisaged two different procedures. First, starting from the recently prepared tricycles **2a** and **2b** [2] *via* the *N*(5) or *N*(11) unsubstituted congeners and subsequent alkylation.

The second way involves the reaction of 3,6-dichloro-*N*-(3,6-dichloropyridazin-4-yl)-*N*-propylpyridazine-4-carboxamide (**5**) [2] with the appropriate primary amine, followed by cyclisation.

Here we want to report the preparation of such dialkyldipyridazinodiazepinones and the results of antiviral evaluation against human immunodeficiency virus (HIV).

Starting from the methoxybenzyl substituted tricycles of type **2**, splitting off of the 4-methoxybenzyl protecting group was achieved by treatment of **2a** and **2b** with an excess of trifluoroacetic acid at room temperature (**2b**) or at 80 °C (**2a**), respectively. Thus, the 11- and 5-unsubstituted derivatives **3a**/**b** became accessible in satisfactory yields. These tricycles were then *N*-alkylated using methyl iodide and potassium hydroxide in a dimethyl sulfoxide solution to yield the target compounds **4a/b**, but only in moderate yields (30 or 37%).

Scheme 2



Scheme 3

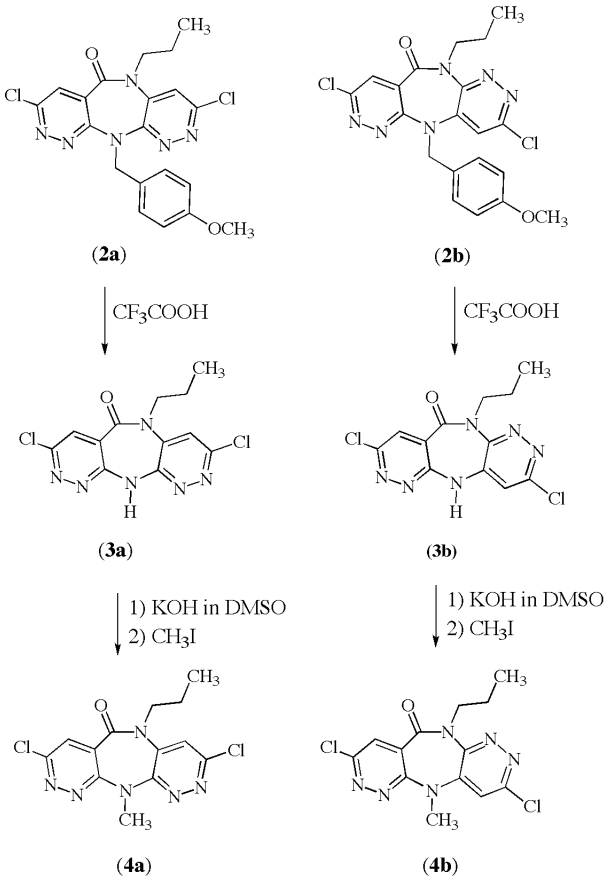
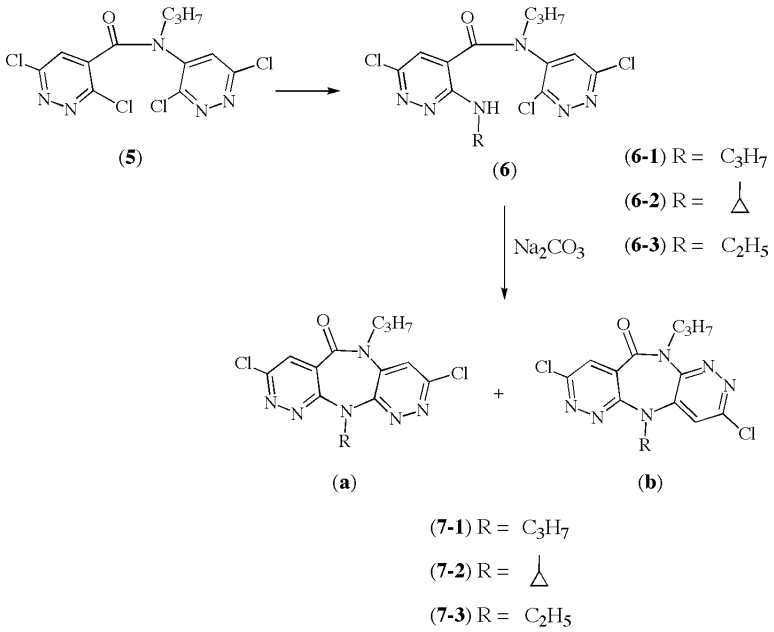


Table 1

No	R	Yield Isomer **a**	Yield Isomer **b**	Ratio of the Isomers a:b
7-1	C_3H_7	30 %	64 %	1:2.1
7-2	c-C_3H_5	44 %	53 %	1:1.2
7-3	C_2H_5	24 %	66 %	1:2.8

Using the alternative pathway, 3,6-dichloro-*N*-(3,6-dichloropyridazin-4-yl)-*N*-propylpyridazine-4-carboxamide (**5**) was reacted with propyl- or cyclopropylamine in anhydrous dichloromethane at 40 °C or with ethylamine hydrochloride and base (sodium hydride) in anhydrous 1,4-dioxane solution at 40 °C, respectively. Cyclisation was performed by treatment of compounds of type **6** with anhydrous sodium carbonate in anhydrous dimethyl sulfoxide at 50 °C. These conditions were chosen since in the case of the 4-methoxybenzylamino derivatives a 1:1 mixture of both isomers (**2a/b**) was obtained. [2] Since we are interested in both isomers, this procedure was chosen for the preparation of the target compounds of type **7**. The products were obtained in very good yields (90-97%) and the isomers could be easily separated by column chromatography (diisopropyl ether/tetrahydrofuran, 5:1). It can be noted that there is an effect of the alkyl substituent on the isomeric mixtures obtained (see Table 1). Whereas in the case of the ethyl and propyl compounds the isomers of type **b** predominates, the cyclopropyl derivative **6-2** affords an almost 1:1 mixture of the two isomers (**7-2a/b**). The isomeric structures could be differentiated by NOE difference experiments.

Scheme 4



All new dialkylated tricycles were evaluated for their inhibitory effect against the cytopathicity of HIV-1(III_B) and HIV-2(ROD). All compounds tested were inactive against the replication of HIV-1(III_B) and HIV-2(ROD) at subtoxic concentrations in MT-4 cells (data not shown).

EXPERIMENTAL

Melting points were determined with a Kofler hot-stage microscope (Reichert) and are uncorrected. IR spectra were recorded on a Mattson Galaxy Series FTIR 3000 spectrophotometer from KBr pellets. MS were obtained on a Finnigan MAT SSQ 7000. ^{1}H and ^{13}C nmr spectra were recorded on a Varian Gemini 200 spectrometer (^{1}H: 199.98 MHz, ^{13}C: 50.29 MHz). The centre of the solvent multiplet (dimethyl-d_6 sulfoxide or deuteriochloroform) was used as internal standard (chemical shifts in δ ppm), which was related to TMS with δ 2.49 ppm for ^{1}H and δ 39.5 ppm for ^{13}C (dimethyl-d_6 sulfoxide) or with δ 7.26 ppm for ^{1}H and δ 77.0 ppm for ^{13}C (deuteriochloroform). The standard Varian programme NOEDIF was used to generate NOE. Reactions were monitored by tlc using Polygram® SIL G/UV_{254} (Macherey-Nagel) plastic-backed plates (0.25 mm layer thickness). Column chromatography was performed using Kieselgel 60 (40-63 µm, Merck). Elemental analyses were performed at the Institute of Physical Chemistry (Mag. J. Theiner), University of Vienna. The yields are not optimized.

3,8-Dichloro-5,11-dihydro-5-propyldipyridazino[4,3-*b*:3',4-*e*]-[1,4]diazepin-6-one (**3a**) and 3,8-Dichloro-5,11-dihydro-11-propyldipyridazino[3,4-*b*:3',4'-*e*][1,4]diazepin-10-one (**3b**).

A solution of 3,8-dichloro-5,11-dihydro-5-(4-methoxybenzyl)-11-propyldipyridazino[3,4-*b*:3',4'-*e*][1,4]diazepin-10-one (**2a**) (0.50-1.00 g, 1.12-2.24 mmol) or 3,8-dichloro-5,11-dihydro-11-(4-methoxybenzyl)-5-propyldipyridazino[4,3-*b*:3',4'-*e*][1,4]diazepin-6-one (**2b**) (0.29-0.50 g, 0.65-1.12 mmol) in trifluoroacetic acid (5-10 mL) was stirred at 80 °C for 4 hours (**2a**) or at room temperature for 30 minutes (**2b**), respectively. Trifluoro acetic acid was evaporated *in vacuo*, then the residue was taken up in dichloromethane, the solution was washed with saturated sodium hydrogencarbonate solution three times, then washed with water and brine, dried over anhydrous sodium sulfate and evaporated. The product was purified by column chromatography (dichloromethane/ethyl acetate, 9:1), followed by recrystallization.

3,8-Dichloro-5,11-dihydro-5-propyldipyridazino[4,3-*b*:3',4'-*e*]-[1,4]diazepin-6-one (**3a**).

Compound **3a** was obtained in 65% of yellow crystals, recrystallized from diisopropyl ether/ethyl acetate, mp 252-258 °C; ir (potassium bromide): ν 1663 (CO) cm^{-1}; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 10.72 (s, 1H, NH), 8.02 (s, 1H), 7.92 (s, 1H) (H-4, H-7), 4.07-4.00 (m, 2H, C*H*$_2$CH$_2$CH$_3$), 1.64-1.46 (m, 2H, CH$_2$C*H*$_2$CH$_3$), 0.80 (t, J = 7.4 Hz, 3H, CH$_2$CH$_2$C*H*$_3$); ^{1}H nmr (deuteriochloroform): δ 8.37 (s, 1H, NH), 7.93 (s, 1H), 7.27 (s, 1H) (H-4, H-7), 4.04-3.97 (m, 2H, C*H*$_2$CH$_2$CH$_3$), 1.86-1.67 (m, 2H, CH$_2$C*H*$_2$CH$_3$), 0.99 (t, J = 7.4 Hz, 3H, CH$_2$CH$_2$C*H*$_3$); ^{13}C nmr (deuteriochloroform): δ 162.3, 156.1, 153.2, 153.1, 152.4 (C-3, C-6, C-8, C-10a, C-11a), 133.7, 123.2 (C-4a, C-6a), 131.8 (C-4), 120.4 (C-7), 52.1 (*C*H$_2$CH$_2$CH$_3$), 20.8 (CH$_2$*C*H$_2$CH$_3$), 11.0 (CH$_2$CH$_2$*C*H$_3$); ei ms (70 eV): m/z = 324 [M$^+$].

Anal. Calcd. for $C_{12}H_{10}Cl_2N_6O$: C, 44.33; H, 3.10; N, 25.85. Found: C, 44.54; H, 3.01; N, 25.73.

3,8-Dichloro-5,11-dihydro-11-propyldipyridazino[3,4-*b*:3',4'-*e*]-[1,4]diazepin-10-one (**3b**).

Compound **3b** was obtained in 70% of yellow crystals, recrystallized from diisopropyl ether/ethyl acetate/dichloromethane, mp 210-215 °C. ir (potassium bromide): ν 1661, 1655 (CO) cm^{-1}; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 10.61 (s, 1H, NH), 8.05 (s, 1H), 7.51 (s, 1H) (H-4, H-9), 4.13-4.05 (m, 2H, C*H*$_2$CH$_2$CH$_3$), 1.75-1.64 (m, 2H, CH$_2$C*H*$_2$CH$_3$), 0.85 (t, J = 7.5 Hz, 3H, CH$_2$CH$_2$C*H*$_3$); ^{1}H nmr (deuteriochloroform): δ 9.50 (s, 1H, NH), 8.13 (s, 1H), 7.72 (s, 1H) (H-4, H-9), 4.35-4.28 (m, 2H, C*H*$_2$CH$_2$CH$_3$), 1.86-1.75 (m, 2H, CH$_2$C*H*$_2$CH$_3$), 0.95 (t, J = 7.5 Hz, 3H, CH$_2$CH$_2$C*H*$_3$); ^{13}C nmr (deuteriochloroform): δ 161.6, 157.2, 153.8, 153.1, 148.6 (C-3, C-8, C-10, C-4a, C-5a), 133.6 (C-4), 139.1, 124.7 (C-9a, C-11a), 118.2 (C-9), 51.5 (*C*H$_2$CH$_2$CH$_3$), 21.2 (CH$_2$*C*H$_2$CH$_3$), 11.2 (CH$_2$CH$_2$*C*H$_3$); ei ms (70 eV): m/z = 324 [M$^+$].

Anal. Calcd. for $C_{12}H_{10}Cl_2N_6O$: C, 44.33; H, 3.10; N, 25.85. Found: C, 44.55; H, 3.07; N, 25.64.

Methylation of 3,8-Dichloro-5,11-dihydro-5-propyldipyridazino[4,3-*b*:3',4'-*e*][1,4]diazepin-6-one (**3a**) and 3,8-Dichloro-5,11-dihydro-11-propyldipyridazino[3,4-*b*:3',4'-*e*][1,4]-diazepin-10-one (**3b**).

To a solution of **3a**/**3b** (0.488 g, 1.5 mmol) in anhydrous dimethyl sulfoxide (50 mL) was added powdered potassium hydroxide (2 equivalents, 0.168 g, 3.0 mmol) under a nitrogen atmosphere. After stirring at room temperature for one hour, methyl iodide (2.5 equivalents, 0.546 g, 3.75 mmol) was added. Stirring was continued until the starting material was completely consumed (30 minutes to 4.5 hours; tlc monitoring, dichloromethane/ethyl acetate, 9:1), then the reaction mixture was poured into cold 0.5 *N* HCl (100 mL). The mixture was extracted with dichloromethane, the organic phase was washed with water and brine, dried over anhydrous sodium sulfate and evaporated. The products were purified by column chromatography (dichloromethane/ethyl acetate, 9:1) and recrystallization.

3,8-Dichloro-5,11-dihydro-11-methyl-5-propyldipyridazino-[4,3-*b*:3',4'-*e*][1,4] diazepin-6-one (**4a**).

Compound **4a** was obtained in 30% yield as yellow crystals, recrystallized from diisopropyl ether, mp 248-252 °C. ir (potassium bromide): ν 1664 (CO) cm^{-1}; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 8.04 (s, 1H, H-7), 8.02 (s, 1H, H-4), 4.06 (t, J = 7.3 Hz, 2H, C*H*$_2$CH$_2$CH$_3$), 3.61 (s, 3H, CH$_3$), 1.65-1.47 (m, 2H, CH$_2$C*H*$_2$CH$_3$), 0.80 (t, J = 7.4 Hz, 3H, CH$_2$CH$_2$C*H*$_3$); ^{1}H nmr (deuteriochloroform): δ 7.82 (s, 1H), 7.28 (s, 1H) (H-4, H-7), 4.04-3.97 (m, 2H, C*H*$_2$CH$_2$CH$_3$), 3.80 (s, 3H, CH$_3$), 1.84-1.65 (m, 2H, CH$_2$C*H*$_2$CH$_3$), 0.96 (t, J = 7.3 Hz, 3H, CH$_2$CH$_2$C*H*$_3$); ^{13}C nmr (deuteriochloroform): δ 163.0, 157.9, 155.8 (C-5, C-10a, C-11a), 153.2, 153.2 (C-3, C-8), 135.4, 125.5 (C-4a, C-6a), 130.7 (C-4), 120.3 (C-7), 51.8 (*C*H$_2$CH$_2$CH$_3$), 36.8 (CH$_3$), 20.8 (CH$_2$*C*H$_2$CH$_3$), 11.0 (CH$_2$CH$_2$*C*H$_3$); ei ms (70 eV): m/z = 338 [M$^+$].

Anal. Calcd. for $C_{13}H_{12}Cl_2N_6O$: C, 46.04; H, 3.57; N, 24.78. Found: C, 45.79; H, 3.47; N, 24.52.

3,8-Dichloro-5,11-dihydro-5-methyl-11-propyldipyridazino-[3,4-*b*:3',4'-*e*] [1,4]diazepin-10-one (**4b**).

Compound **4b** was obtained in 37% yield as yellow crystals, recrystallized from diisopropyl ether/tetrahydrofuran, mp 151-155 °C. ir (potassium bromide): ν 1658 (CO) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 8.06 (s, 1H, H-9), 7.86 (s, 1H, H-4), 4.17-4.10 (m, 2H, CH_2CH$_2$CH$_3$), 3.52 (s, 3H, CH$_3$), 1.79-1.61 (m, 2H, CH$_2$CH_2CH$_3$), 0.84 (t, J = 7.5 Hz, 3H, CH$_2$CH$_2$CH_3); ^1H nmr (deuteriochloroform): δ 7.91 (s, 1H), 7.25 (s, 1H) (H-4, H-9), 4.33-4.26 (m, 2H, CH_2CH$_2$CH$_3$), 3.60 (s, 3H, CH$_3$), 1.90-1.71 (m, 2H, CH$_2$CH_2CH$_3$), 0.93 (t, J = 7.3 Hz, 3H, CH$_2$CH$_2$CH_3); ^{13}C nmr (deuteriochloroform): δ 162.5, 157.4, 154.1, 153.9, 150.9, 144.6 (C-3, C-8, C-10, C-4a, C-5a, C-11a), 131.4 (C-9), 126.2 (C-9a), 117.6 (C-4), 51.3 (*C*H$_2$CH$_2$CH$_3$), 36.6 (CH$_3$), 21.2 (CH$_2$*C*H$_2$CH$_3$), 11.2 (CH$_2$CH$_2$*C*H$_3$); ei ms (70 eV): m/z = 338 [M^+].

Anal. Calcd for $C_{13}H_{12}Cl_2N_6O$: C, 46.06; H, 3.57; N, 24.78. Found: C, 46.06; H, 3.71; N, 24.69.

Reaction of **5** with Propylamine and Cyclopropylamine, Respectively.

3-Alkylamino-6-chloro-*N*-(3,6-dichloropyridazine-4-yl)-*N*-propylpyridazin-4-carboxamides (**6-1**, **6-2**).

A solution of **5** (1.0 g, 2.6 mmol) and 5 equivalents (13.0 mmol) of the appropriate alkylamine (0.776 g propylamine or 0.749 g cyclopropylamine) in anhydrous dichloromethane (50 mL) was stirred at 40 °C for 7 days under a nitrogen atmosphere. Then the reaction mixture was diluted with dichloromethane and washed twice with water and brine, dried over anhydrous sodium sulfate and evaporated. The products were purified by column chromatography (dichloromethane/ethyl acetate, 9:1). The oily products were crystallized from diisopropyl ether.

6-Chloro-*N*-(3,6-dichloropyridazine-4-yl)-*N*-propyl-3-propylaminopyridazin-4-carboxamide (**6-1**).

Compound **6-1** was obtained in 78% as colorless crystals, mp 116-119 °C. ir (potassium bromide): ν 3220 (NH), 1660 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.66 (s, 1H) 7.25 (s, 1H) (pyridazine-H-5, -H-5'), 6.58 ("t", 1H, NH), 3.95-3.87 (m, 2H, CH_2CH$_2$CH$_3$), 3.20-3.10 (m, 2H, CH_2CH$_2$CH$_3$), 1.83-1.64 (m, 2H, CH$_2$CH_2CH$_3$), 1.57-1.38 (m, 2H, CH$_2$CH_2CH$_3$), 0.97 (t, J = 7.3 Hz, 3H, CH$_2$CH$_2$CH_3), 0.90 (t, J = 7.3 Hz, 3H, CH$_2$CH$_2$CH_3); ei ms (70 eV): m/z = 402 [M^+].

Anal. Calcd. for $C_{15}H_{17}Cl_3N_6O$: C, 44.63; H, 4.24; N, 20.82. Found: C, 44.42; H, 4.00; N, 20.55.

6-Chloro-*N*-(3,6-dichloropyridazine-4-yl)-3-cyclopropyl-*N*-propylaminopyridazin-4-carboxamide (**6-2**).

Compound **6-2** was obtained in 28% as colorless crystals, mp 155-160 °C. ir (potassium bromide): ν 3230 (NH), 1670 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.90 (s, 1H) 7.73 (s, 1H) (pyridazine-H-5, -H-5'), 6.76 ("t", 1H, NH), 3.36-3.26 (m, 2H, CH_2CH$_2$CH$_3$), 3.03-2.92 (m, 1H, CH), 1.58-1.43 (m, 2H, CH$_2$CH_2CH$_3$), 1.05-1.02 (m, 2H), 0.98-0.87 (m, 5H) (CH$_2$, CH$_2$, CH$_2$CH$_2$CH_3); ei ms (70 eV): m/z = 401 [M^+].

Anal. Calcd. for $C_{15}H_{15}Cl_3N_6O{\cdot}0.2H_2O{\cdot}0.1$ethyl acetate: C, 44.67; H, 3.94; N, 20.29. Found: C, 44.65; H, 3.95; N, 20.12.

Reaction of **5** with Ethylamine.

6-Chloro-*N*-(3,6-dichloropyridazine-4-yl)-3-ethylamino-*N*-propylpyridazine-4-carboxamide (**6-3**).

To a solution of **5** (1.0 g, 2.6 mmol) in anhydrous 1,4-dioxane (50 mL) were added 10 equivalents (2.1 g, 26.0 mmol) of ethylamine hydrochloride and 10 equivalents (1.0 g, 26 mmol) of sodium hydride (60% dispersion in oil). The reaction mixture was stirred under a nitrogen atmosphere at 40 °C until the starting material was completely consumed (tlc monitoring, dichloromethane/ethyl acetate, 9:1, *ca*. 7 days). Then the reaction mixture was poured under a nitrogen atmosphere into 100 mL of cold 0.5 *N* HCl and the mixture was extracted with dichloromethane. The organic phase was washed with water and brine, dried over anhydrous sodium sulfate and evaporated. The product was purified by column chromatography (dichloromethane/ethyl acetate, 9:1) and crystallised from diisopropyl ether; 41% of colorless crystals, mp 144-150 °C. ir (potassium bromide): ν 3218 (NH), 1662 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.73 (s, 1H) 7.26 (s, 1H) (pyridazine-H-5, -H-5'), 6.60 ("t", 1H, NH), 4.06-3.95 (m, 2H, CH_2CH$_2$CH$_3$), 3.26-3.15 (m, 2H, CH_2CH$_3$), 1.60-1.42 (m, 2H, CH$_2$CH_2CH$_3$), 1.32 (t, J = 7.1 Hz, 3H, CH$_2$CH_3), 0.92 (t, J = 7.4 Hz, 3H, CH$_2$CH$_2$CH_3); ei ms (70 eV): m/z = 390 [M^+].

Anal. Calcd for $C_{14}H_{15}Cl_3N_6O$: C, 43.15; H, 3.88; N, 21.57. Found: C, 43.04; H, 3.81; N, 21.27.

General Procedure for the Cyclisation.

To a solution of the appropriate 3-alkylamino-6-chloro-*N*-(3,6-dichloropyridazine-4-yl)-*N*-propylpyridazine-4-carboxamide (**6-1, 6-2, 6-3**) (0.25-0.35 g, 0.6-0.9 mmol) in anhydrous dimethyl sulfoxide (30 mL) 5 equivalents of anhydrous sodium carbonate (0.32-0.48 g, 3.0-4.5 mmol) was added and the mixture stirred at 50 °C until the starting material was completely consumed (tlc, dichloromethane/ethyl acetate, 9:1; 45 minutes to 5 hours). The reaction mixture was poured into cold 0.5 *N* HCl (100 mL) and was then extracted with dichloromethane. The organic phase was washed with water and brine, dried over anhydrous sodium sulfate and evaporated. Separation of the two isomeric products was achieved by column chromatography (diisopropyl ether/tetrahydrofuran, 5:1), following by crystallization from diisopropyl ether.

3,8-Dichloro-5,11-dihydro-5,11-dipropyldipyridazino-[4,3-*b*:3',4'-*e*][1,4]diazepin-6-one (**7-1a**). Compound **7-1a** was obtained in 30% yield as yellow crystals, mp 110-115 °C. ir (potassium bromide): ν 1664 (CO) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 8.10 (s, 1H, H-4), 8.03 (s, 1H, H-7), 4.27 (t, J = 6.9 Hz, 2H, CH_2CH$_2$CH$_3$), 4.15-4.08 (m, 2H, CH_2CH$_2$CH$_3$), 1.69-1.46 (m, 4H, 2 × CH$_2$CH_2CH$_3$), 0.88 (t, J = 7.5 Hz, 3H, CH$_2$CH$_2$CH_3), 0.79 (t, J = 7.3 Hz, 3H, CH$_2$CH$_2$CH_3); ^1H nmr (deuteriochloroform): δ 7.78 (s, 1H), 7.29 (s, 1H) (H-4, H-7), 4.51-4.44 (m, 2H, CH_2CH$_2$CH$_3$), 4.04 (t, J = 7.2 Hz, 2H, CH_2CH$_2$CH$_3$), 1.80-1.68 (m, 4H, 2 × CH$_2$CH_2CH$_3$), 1.00-0.91 (m, 6H, 2 × CH$_2$CH$_2$CH_3); ^{13}C nmr (deuteriochloroform): δ 163.2, 158.3, 156.2 (C-5, C-10a, C-11a), 153.2, 153.2 (C-3, C-8), 136.1, 126.5 (C-4a, C-6a), 130.7 (C-4), 120.8 (C-7), 51.2, 49.7 (2 × *C*H$_2$CH$_2$CH$_3$), 20.8, 20.6 (2 × CH$_2$*C*H$_2$CH$_3$), 11.4, 11.0 (2 × CH$_2$CH$_2$*C*H$_3$); ei ms (70 eV): m/z = 366 [M^+].

Anal. Calcd. for $C_{15}H_{16}Cl_2N_6O$: C, 48.35; H, 4.49; N, 22.25. Found: C, 48.31; H, 4.23; N, 22.37.

3,8-Dichloro-5,11-dihydro-5,11-dipropyldipyridazino-[3,4-*b*:3',4'-*e*][1,4]diazepin-10-one (**7-1b**).

Compound **7-1b** was obtained in 64% yield as colorless crystals, mp 124-127 °C. ir (potassium bromide): ν 1662 (CO) cm^{-1}. ^1H nmr (dimethyl-d_6 sulfoxide): δ 8.06 (s, 1H, H-9), 8.01 (s, 1H, H-4), 4.24 (t, J = 7.2 Hz, 2H, CH_2CH$_2$CH$_3$), 4.08 (t, J = 7.0 Hz, 2H, CH$_2$CH$_2$CH$_3$), 1.66-1.54 (m, 4H, 2 × CH$_2$CH$_2$CH$_3$), 0.90-0.78 (m, 6H, 2 × CH$_2$CH$_2$CH_3); ^1H nmr (deuteriochloroform): δ 7.87 (s, 1H), 7.27 (s, 1H) (H-4, H-9), 4.41-4.34 (m, 2H, CH_2CH$_2$CH$_3$), 4.08 (t, J = 6.8 Hz, 2H, CH_2CH$_2$CH$_3$), 1.80-1.69 (m, 4H, 2 × CH$_2$CH$_2$CH$_3$), 1.01-0.88 (m, 6H, 2 × CH$_2$CH$_2$CH_3); ^{13}C nmr (deuteriochloroform): δ 162.8, 157.7, 154.1, 153.9, 152.0, 144.6 (C-3, C-8, C-10, C-4a, C-5a, C-11a), 131.3 (C-9), 127.4 (C-9a), 119.2 (C-4), 50.6, 49.9 (2 × CH$_2$CH$_2$CH$_3$), 21.2, 20.1 (2 × CH$_2$CH$_2$CH$_3$), 11.2, 11.1 (2 × CH$_2$CH$_2$CH$_3$); ei ms (70 eV): m/z = 366 [M^+].

Anal. Calcd. for $C_{15}H_{16}Cl_2N_6O$: C, 49.06; H, 4.36; N, 22.88. Found: C, 48.81; H, 4.25; N, 22.65.

3,8-Dichloro-11-cyclopropyl-5,11-dihydro-5-propyl-dipyridazino[4,3-*b*:3',4'-*e*][1,4]diazepin-6-one (**7-2a**).

Compound **7-2a** was obtained in 44% yield as colorless crystals, mp 238-240 °C. ir (potassium bromide): ν 1666 (CO) cm^{-1}. ^1H nmr (dimethyl-d_6 sulfoxide): δ 8.07 (s, 1H), 8.03 (s, 1H) (H-4, H-7), 4.40-4.25 (m, 1H, CH), 3.89-3.76 (m, 2H, CH_2CH$_2$CH$_3$), 1.59-1.34 (m, 2H, CH$_2$CH_2CH$_3$), 1.03-1.00 (m, 2H, CH$_2$), 0.76 (t, J = 7.1 Hz, 3H, CH$_2$CH$_2$CH_3), 0.65-0.58 (m, 1H), 0.42-0.34 (m, 1H) (CH$_2$); ^1H nmr (deuteriochloroform): δ 7.79 (s, 1H), 7.27 (s, 1H) (H-4, H-7), 4.42-4.26 (m, 1H), 3.82-3.60 (m, 1H) (CH_2CH$_2$CH$_3$), 4.13-4.02 (m, 1H, CH), 1.86-1.62 (m, 2H, CH$_2$CH_2CH$_3$), 1.26-1.10 (m, 2H), 0.58-0.48 (m, 2H) (CH$_2$, CH$_2$), 0.89 (t, J = 7.3 Hz, 3H, CH$_2$CH$_2$CH_3); ei ms (70 eV): m/z = 364 [M^+].

Anal. Calcd for $C_{15}H_{14}Cl_2N_6O$: C, 49.33; H, 3.86; N, 23.01. Found: C, 49.24; H, 4.00; N, 22.74.

3,8-Dichloro-5-cyclopropyl-5,11-dihydro-11-propyl-dipyridazino[3,4-*b*:3',4'-*e*][1,4]diazepin-10-one (**7-2b**).

Compound **7-2b** was obtained in 53% yield as colorless crystals, mp 138-142 °C. ir (potassium bromide): ν 1656 (CO) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 8.11 (s, 1H, H-4), 8.06 (s, 1H, H-9), 4.15 (t, J = 7.1 Hz, 2H, CH_2CH$_2$CH$_3$), 3.78-3.68 (m, 1H, CH), 1.72-1.52 (m, 2H, CH$_2$CH_2CH$_3$), 1.12-1.00 (m, 2H), 0.74-0.36 (m, 2H) (CH$_2$, CH$_2$), 0.77 (t, J = 7.4 Hz, CH$_2$CH$_2$CH_3); ^1H nmr (deuteriochloroform): δ 7.89 (s, 1H), 7.55 (s, 1H) (H-4, H-9), 4.32-4.30 (m, 2H, CH_2CH$_2$CH$_3$), 3.70-3.64 (m, 1H, CH), 1.77-1.66 (m, 2H, CH$_2$CH_2CH$_3$), 1.30-1.10 (m, 2H), 0.80-0.46 (m, 2H) (CH$_2$, CH$_2$), 0.86 (t, J = 7.3 Hz, 3H, CH$_2$CH$_2$CH_3); ei ms (70 eV): m/z = 364 [M^+].

Anal. Calcd. for $C_{15}H_{14}Cl_2N_6O$: C, 49.33; H, 3.86; N, 23.01. Found: C, 49.10; H, 3.66; N, 22.82.

3,8-Dichloro-11-ethyl-5,11-dihydro-5-propyldipyridazino-[4,3-*b*:3',4'-*e*][1,4]diazepin-6-one (**7-3a**).

Compound **7-3a** was obtained in 24% yield as yellow crystals, mp 110-115 °C. ir (potassium bromide): ν 1660 (CO) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 8.09 (s, 1H, H-4), 8.03 (s, 1H, H-7), 4.32 (q, J = 7.0 Hz, 2H, CH_2CH$_2$CH$_3$), 4.14-4.08 (m, 2H, CH_2CH$_3$), 1.56-1.47 (m, 2H, CH$_2$CH_2CH$_3$), 1.22 (t, J = 7.0 Hz, 3H, CH$_2$CH_3), 0.78 (t, J = 7.4 Hz, 3H, CH$_2$CH$_2$CH_3); ^1H nmr (deuteriochloroform): δ 7.79 (s, 1H), 7.29 (s, 1H) (H-4, H-7), 4.53 (q, J = 7.0 Hz, 2H, CH_2CH$_3$), 4.08-4.01 (m, 2H, CH_2CH$_2$CH$_3$), 1.76-1.64 (m, 2H, CH$_2$CH_2CH$_3$), 1.34 (t, J = 7.0 Hz, 3H, CH$_2$CH_3), 0.94 (t, J = 7.3 Hz, 3H, CH$_2$CH$_2$CH_3); ^{13}C nmr (deuteriochloroform): δ 163.2, 158.2, 155.9 (C-5, C-10a, C-11a), 153.2, 153.2 (C-3, C-8), 136.2, 126.4 (C-4a, C-6a), 130.6 (C-4), 120.8 (C-7), 51.2 (*C*H$_2$CH$_2$CH$_3$), 43.0 (*C*H$_2$CH$_3$), 20.7 (CH$_2$*C*H$_2$CH$_3$), 13.1 (CH$_2$*C*H$_3$), 10.8 (CH$_2$CH$_2$*C*H$_3$); ei ms (70 eV): m/z = 352 [M^+].

Anal. Calcd. for $C_{14}H_{14}Cl_2N_6O \cdot 0.3\ H_2O \cdot 0.1$tetrahydrofuran: C, 47.28; H, 4.24; N, 22.97. Found: C, 47.21; H, 4.02; N, 22.77.

3,8-Dichloro-5-ethyl-5,11-dihydro-11-propyldipyridazino-[3,4-*b*:3',4'-*e*][1,4]diazepin-10-one (**7-3b**).

Compound **7-3b** was obtained in 66% yield as colorless crystals, mp 152-155 °C. ir (potassium bromide): ν 1668 (CO) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 8.06 (s, 1H, H-9), 7.98 (s, 1H, H-4), 4.25-4.09 (m, 4H, CH_2CH$_2$CH$_3$, CH_2CH$_3$), 1.72-1.54 (m, 2H, CH$_2$CH_2CH$_3$), 1.18 (t, J = 6.9 Hz, 3H, CH$_2$CH_3), 0.82 (t, J = 7.5 Hz, 3H, CH$_2$CH$_2$CH_3); ^1H nmr (deuteriochloroform): δ 7.87 (s, 1H), 7.27 (s, 1H) (H-4, H-9), 4.35 (t, J = 7.3 Hz, 2H, CH_2CH$_2$CH$_3$), 4.16 (q, J = 7.0 Hz, 2H, CH_2CH$_3$), 1.80-1.69 (m, 2H, CH$_2$CH_2CH$_3$), 1.34 (t, J = 7.0 Hz, 3H, CH$_2$CH_3), 0.92 (t, J = 7.5 Hz, 3H, CH$_2$CH$_2$CH_3); ^{13}C nmr (deuteriochloroform): δ 162.8, 157.6, 154.2, 153.9, 152.1, 144.4 (C-3, C-8, C-10, C-4a, C-5a, C-11a), 131.3 (C-9), 127.4 (C-9a), 119.0 (C-4), 50.7, 43.0 (*C*H$_2$CH$_2$CH$_3$, *C*H$_2$CH$_3$), 21.1 (CH$_2$*C*H$_2$CH$_3$), 12.6 (CH$_2$*C*H$_3$), 11.0 (CH$_2$CH$_2$*C*H$_3$); ei ms (70 eV): m/z = 353 [M^+].

Anal. Calcd. for $C_{14}H_{14}Cl_2N_6O \cdot 0.2H_2O$: C, 47.13; H, 4.07; N, 23.55. Found: C, 47.10; H, 3.82; N, 23.33.

In vitro Anti-HIV Assay.

The antiviral experiments using MT-4 cell cultures and HIV-1(III_B) and HIV-2(ROD) were performed following procedures that have been previously described. [6, 7]

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