SYNTHESIS OF TETRACYCLIC ARYLPYRIDODIAZEPINES AS POTENTIAL ANTI HIV-1 AGENTS

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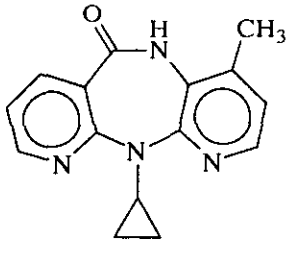
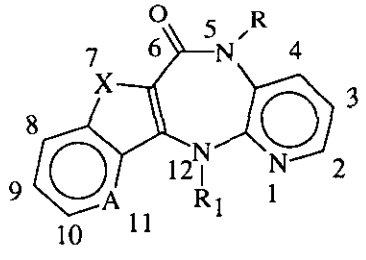
Abstract - Some tetracyclic compounds containing the pyridodiazepine system condensed with the pyridofuro, pyridothieno and indolo groups were synthesized. In the case of indole derivatives the outcome of the reaction is highly dependent by the nature of the substituents.

The viral reverse transcriptase (RT) is an important target for the development of potential drug for the treatment of AIDS. Nevirapine,[1] a derivative of dipyrido[3,2-b:2',3'-*e*][1,4]diazepin-6-one, is one of the most promising non nucleosidic inhibitor of HIV-1 RT especially when used in combination with zidovudine.[2]

Figure I



Nevirapine



A = N, CH X = O, S, NH

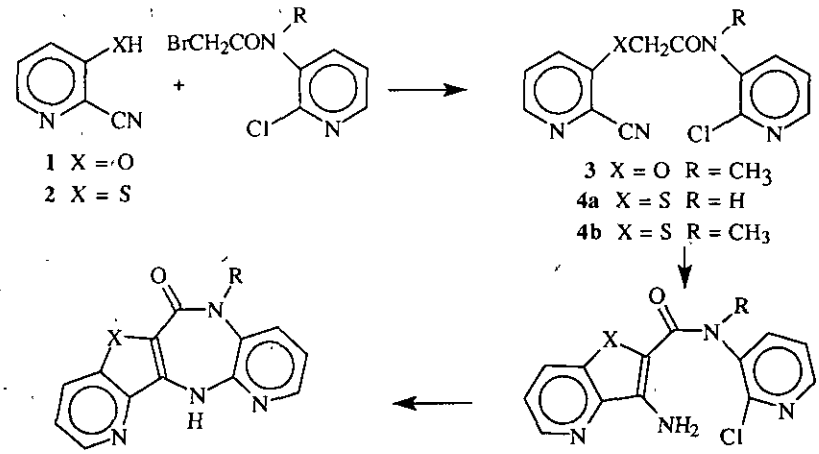
I

Our previous experiences on the synthesis of condensed policyclic molecules [3,4] prompted us to synthesize the new tetracyclic compounds of type **I** related to nevirapine with the formal substitution of a pyridine ring with a bicyclic system.

The compounds were synthesized according a modification of the previously described procedure [3] outlined in the Scheme I. Thus the sodium salt of 2-cyano-3-hydroxypyridine (**1**, X=O)[5] was condensed with 2-chloro-3-(*N*-bromoacetyl, *N*-methyl)aminopyridine (or alternatively with 2-chloro-3-bromoacetylaminopyridine followed by methylation on the CO-NH group) to obtain compound (**3**). Cyclization of **3** in DMF with sodium carbonate gave the final compound (**7**) *via* the non-isolated intermediate (**5**).[3] Seemingly the nucleophilic attack on the cyano group under basic condition by the deprotonated methylenic carbon atom of **3** leads to the formation of the furan moiety of **5** and subsequently to the final molecule (**7**). Since no cyclization occurred when the secondary amide (R = H) is present, methylation of the nitrogen atom in the amide moiety of **3** is necessary in order to overcome the formation of an anionic charge on the amide with the consequent reduction in the acidity of the neighbouring methylenic hydrogen.

When 2-cyano-3-mercaptopyridine (**2**, X = S) was used, the intermediate (**4**) could not be isolated and the reaction spontaneously proceeded directly to the compound (**6**) even at room temperature. The formation of the thieno ring was so favored that even the non-methylated compound (**6a**) could be synthesized in these conditions without the isolation of the intermediate (**4a**). Final cyclization to **8** was done in DMF with sodium carbonate under reflux as previously reported.[3,4]

Scheme I



1 X = O
2 X = S

3 X = O R = CH_3
4a X = S R = H
4b X = S R = CH_3

7 X = O R = CH_3
8a X = S R = H
8b X = S R = CH_3

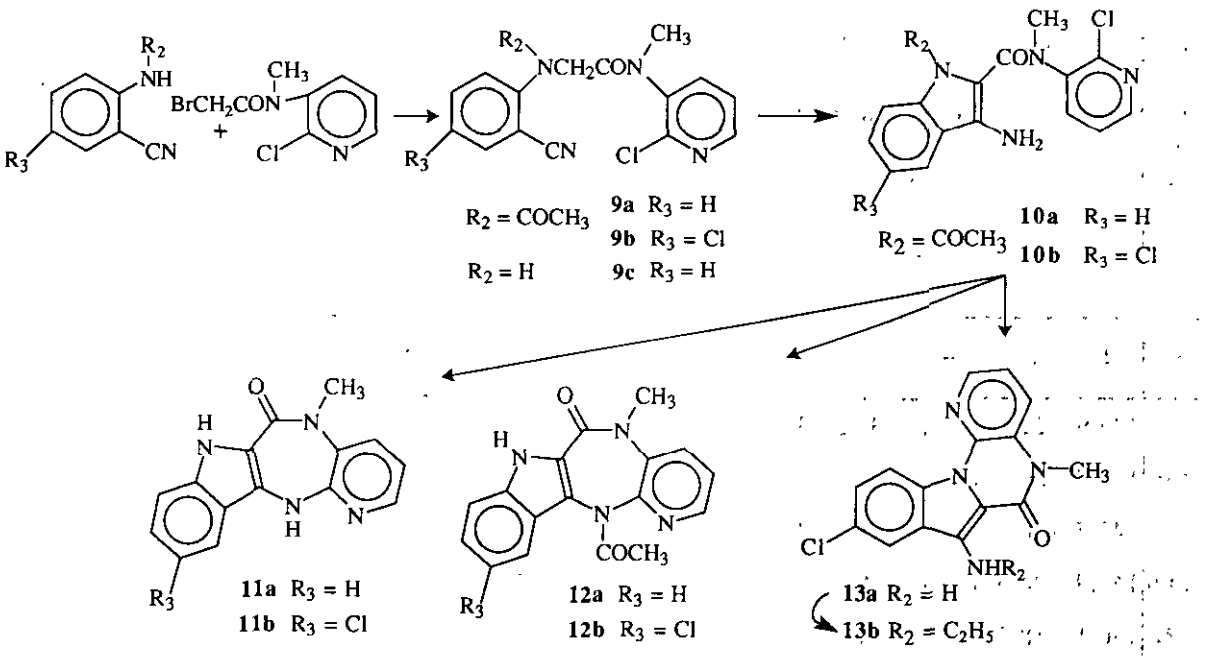
5 X = O R = CH_3
6a X = S R = H
6b X = S R = CH_3

Similar conditions were used to synthesize the indole derivative of type I (X = NR_2) according the Scheme II. When R_2 = H, the acidity of methylenic hydrogen in compound (**9c**) was highly reduced by the basicity of the NH group preventing the expected cyclization; therefore, in order to avoid this undesired effect, R_2 must be an

electron-withdrawing group. In previously reported similar cases[4] acyl groups like acetyl and 2-nitrobenzoyl were successfully used for this purpose. When R_2 = acetyl, the indol derivative (**10a**) was obtained in moderate yield at room temperature and, as in the case of compound (**6a**), isolation of the intermediate (**9a**) could not be achieved.

Final cyclization was reached by heating the reaction mixture to reflux temperature but the product (**11a**) of cyclization showed a complete deacetylation of the indolyl nitrogen, as indicated by the presence of two broad singlets at 9.31 ppm (assigned to NH in position 7) and at 7.16 (assigned to NH in position 12) in ^{1}H nmr spectrum and the absence of any signal due to the acetyl group. Also the acetylated compound (**12a**) (singlet at 2.15 ppm in ^{1}H and two peaks at 24.2 (CH_3) and 172.3 (CO) ppm in ^{13}C) was obtained in the reaction, but the presence of the broad singlet at 11.93 ppm, assigned to NH in position 7, indicated a migration of the acetyl group from nitrogen in position 7 to the more basic one in position 12.

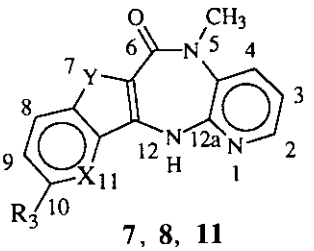
Scheme II



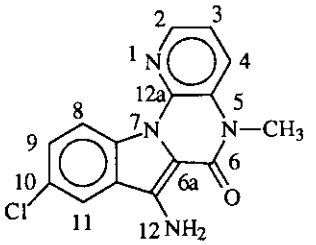
In case of the 10-Cl analogue, compound (**11b**) was isolated together with the acetyl derivative (**12b**) and a product (**13a**) with a broad singlet at 6.13 ppm assigned to a NH_2 group; the ensueing monoethylation gave a crystallizable compound (**13b**) whose structure could be determined by X-ray analysis (Figure II). The compounds (**11b**) and (**13a**) were quite stable in the reaction conditions indicating that they must be generated indipendently from the common indermediate (**10b**); probably deacetylation of the indolyl nitrogen of **10b** made

feasible the formation of the piperazine ring of **13a** in alternative to the diazepine of **11b** and **12b**. Also in the case of **11a** nmr spectra of the rough material indicated the probable presence, in traces, of a product of type **13**.

Table 1: ^{1}H and ^{13}C nmr chemical shifts and ^{1}H-^{1}H coupling constants



7, 8, 11



13a (a)

^{1}H	2	3	4	5 (CH_3)	7	8	9	10	11	12	J (Hz)
7 (b)	8.03	7.03	7.40	3.39	-	7.75	7.33	8.54	-	7.37	$J_{2,3}$ = 4.4; $J_{3,4}$ = 8.0; $J_{9,10}$ = 3.9; $J_{8,9}$ = 8.8
8b (b)	8.01	7.04	8.00	3.42	-	8.08	7.36	8.65	-	8.01	$J_{2,3}$ = 4.7; $J_{3,4}$ = 8.0; $J_{9,10}$ = 4.6; $J_{8,9}$ = 8.3; $J_{8,10}$ = 1.4
11a (b)	7.98	7.09	7.38	3.54	9.31	7.32	7.29	7.01	7.65	7.16	$J_{2,3}$ = 4.7; $J_{3,4}$ = 8.0; $J_{2,4}$ = 1.5; $J_{9,10}$ = 4.8; $J_{8,9}$ = 5.2; $J_{10,11}$ = 8.2
11a (c)	7.92	7.00	7.53	3.27	8.89	7.30	7.20	6.97	8.11	6.92	$J_{2,3}$ = 4.8; $J_{3,4}$ = 7.9
11b (c)	7.96	7.06	7.60	3.33	11.28	7.26	7.19	-	8.21	9.02	$J_{2,3}$ = 4.7; $J_{3,4}$ = 7.1; $J_{2,4}$ = 1.4; $J_{8,9}$ = 8.8; $J_{9,11}$ = 2.0
13a (c)	8.08	7.14	7.56	3.28	-	8.80	7.46	-	8.08	6.13 (2H)	$J_{2,3}$ = 4.9; $J_{3,4}$ = 8.1; $J_{2,4}$ = 1.3; $J_{8,9}$ = 9.0; $J_{9,11}$ = 2.2

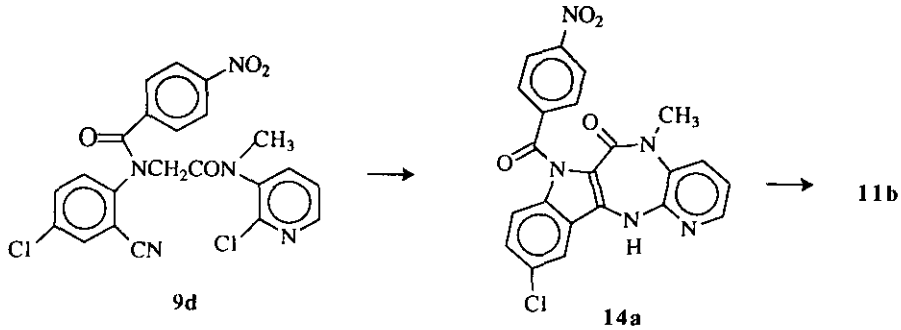
^{13}C	2	3	4	4a	5 (CH_3)	6	6a	7a	8	9	10	11	11a	11b	12a
7 (b)	145.9	121.7	134.1	130.2	38.7	164.6	137.0	150.3	121.8	124.6	148.3		141.0	137.0	155.8
8b (b)	144.7	120.4	132.1	117.7	38.1	166.4	129.5	146.9	131.8	122.9	147.9		143.0	135.6	153.8
11a (c)	142.7	118.3	131.4	118.1	36.1	164.1	128.5	136.2	111.9	125.2	118.2	120.1	130.2	115.7	155.6
11b (c)	144.9	120.5	133.7	119.1	38.2	165.8	130.3	136.4	115.6	127.2	124.9	121.3	131.4	120.8	157.4
13a (c)	140.1	118.2	121.6	(d)	26.9	157.2	(d)	(d)	117.5	126.3	(d)	119.5	(d)	(d)	(d)

(a) atoms of structure (**13a**) hold the same locants of the corresponding ones of the structures (**7,8,11**) resulting in an unusual numbering ; (b) in $CDCl_3$; (c) in DMSO-d_6; (d) resonances associated to quaternary carbons were not assigned; they were 106.5, 121.5, 125.2, 125.8,129.4, 133.0, 139.1

In order to overcome the undesidered migration of the protective group, other acyl groups were tested. As shown in Scheme III, when R_2 = 4-nitrobenzoyl, the intermediate (**9d**), which was obtained at room

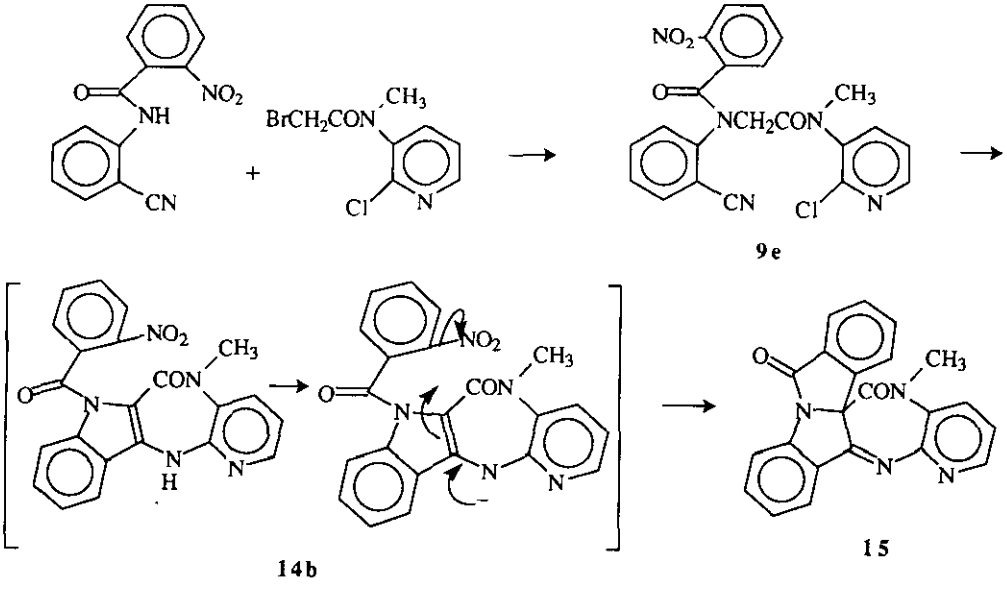
temperature, gave only compound (**14a**) (singlet at 9.92 ppm assigned to NH in position 12) and practically neither the compound with migration of the acyl moiety nor the rearranged one could be isolated. The protective 4-nitrobenzoyl group was easily removed by aminolysis[4] giving compound (**11b**) in high yield (Scheme III). 4-Nitrobenzoyl group was therefore a reliable protective group for the synthesis of derivatives of type **11**.

Scheme III



When R_2 = 2-nitrobenzoyl, compound (**9e**) reacted very slowly in refluxing DMF with sodium carbonate giving a complex mixture of unidentified products. With a stronger base like NaH the reaction proceeded smoothly to completion in few hours at 60°C, but instead of the expected derivative (**14b**), the compound (**15**), as clearly demonstrated by mass spectroscopy and X ray analysis (Figure II), was obtained .

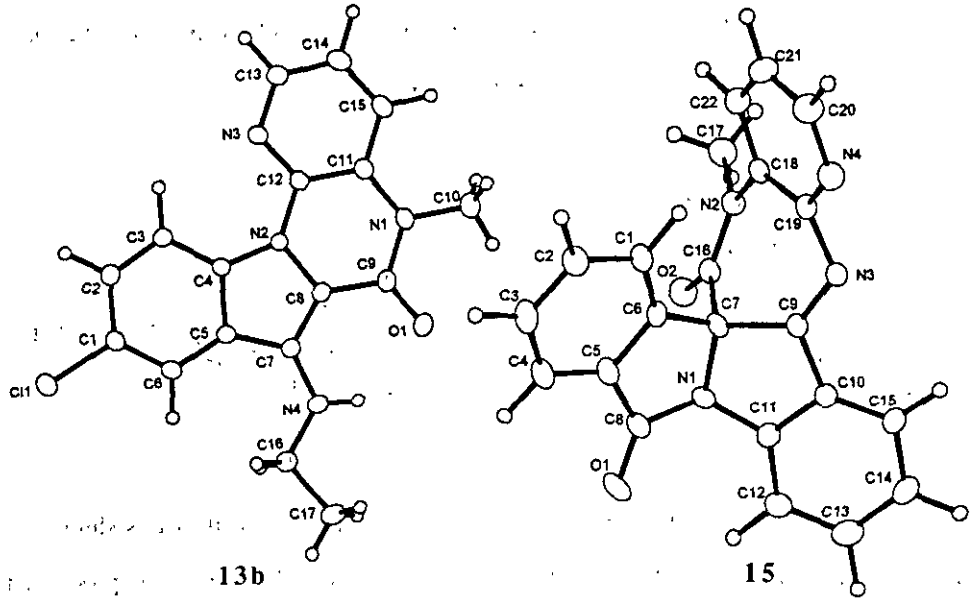
Scheme IV



As depicted in the Scheme IV, probably the use of a strong base such as NaH, which was necessary to force the desired cyclization, made the reaction medium basic enough to take out the hydrogen on the nitrogen in

position 12 of the newly formed compound (**14b**) inducing an aromatic nucleophilic substitution on the 2-nitrobenzoyl moiety which produced the unexpected hexacyclic molecule (**15**).

Figure II: ORTEP drawings of the structures (13b) and (15)



13b **15**

The new policyclic compounds and some of their alkylated derivatives were *in vitro* tested for anti HIV-1 activity in human CD4+ lymphoblastoid cell line and the most interesting compounds[6] (MEN 10880 and MEN 10979) were selected for a pharmacological deepening.

EXPERIMENTAL

Melting ponts were determined by a Mettler FP81 apparatus. Ir spectra were recorded on a Perkin Elmer FT/IR 1710 spectrophotometer. All the nmr spectra were measured on a Varian Gemini spectrometer operating at 200 MHz for proton and 50.3 MHz for carbon and were recorded in $CDCl_3$ unless otherwise stated. Data were transferred to a Macintosh computer and processed using the program SwaN-MR.[7] DQF-COSY and heteronuclear correlation spectra were recorded using the standard Varian software. Two different spectra with the latter sequence were recorded for each compound of Table 1; the two spectra were optimized, respectivelly, to reveal one-bond and long-range connectivities. Steady-state NOE spectra were acquired in the differential mode; typical targets for pre-irradiation were H12 and the methyl in position 5. Saturation of the latter assigned the H4 signal, while H12 was saturated to assign H11 in compound (**11a**). Mass spectra were taken with a Hewlett Packard 5988A spectrometer and the samples were introduced *via* a direct inlet probe.

***N*-(2-Chloropyridin-3-yl)-*N*-methyl-2-[(2-cyanopyridin-3-yl)oxy]acetamide (3).** 2-Bromoacetyl bromide (3 ml, 34.4 mmol) was slowly added to a solution of 2-chloro-3-methylaminopyridine

(3.1 g, 22 mmol) and triethylamine (5 ml, 36.1 mmol) in CH_2Cl_2 (50 ml) in an ice bath keeping the temperature below 30° C. When the addition was over, the reaction was left at room temperature under stirring for additional 2 h and poured into water (200ml). Extraction with CH_2Cl_2 (3x100 ml) followed by washing with water, 5% $NaHCO_3$ solution and brine, gave an yellow oil which was submitted to flash chromatography on silica gel with petroleum ether/EtOAc 3:1; 2-chloro-3-(*N*-methyl-2-bromoacetylamino)pyridine (3.7 g, 64%) was obtained as a solid. Nmr (δ in ppm) ^1H : 3.19 (s, 3H), 3.43 (d, 1H, CH_2, J=13.1), 3.62 (d, 1H, CH_2, J=13.1), 7.39 (1H), 7.81 (1H), 8.42 (1H); ^{13}C : 28.3 (CH_3) 38.6 (CH_2) 125.8, 140.7, 151.8, (Ar CH) 138.8, 152.0 (C^S Ar), 168.2 (CO).

2-Cyano-3-hydroxypyridine (1.44 g 12 mmol)[5] was dissolved in DMF (15 ml) and treated with NaH 80% (0.36 g, 12 mmol) at room temperature under stirring. 2-Chloro-3-(*N*-methyl-2-bromoacetylamido)pyridine (3.16 g, 12 mmol) was added 0.5 h later and the reaction was kept at room temperature under stirring for 4 h. The solution was poured into water and extracted with EtOAc. Removal of the organic solvent afforded an oil which was purified by flash chromatography on silica gel with EtOAc to obtain compound (**3**) (2.9 g, 83%); mp 183° C (decomp.) (ethanol). Ir (nujol): ν 2236 (CN), 1703 (CO) cm^{-1}. Nmr (δ in ppm) ^1H : 3.21 (s, 3H), 4.48 (d, 1H, CH_2, J=14.5), 4.59 (d, 1H, CH_2, J=14.5), 7.28 (1H), 7.42 (2H), 7.82 (1H), 8.23 (1H), 8.43 (1H); ^{13}C : 38.2 (CH_3), 70.0 (CH_2),122.6, 126.4, 129.8, 141.0, 145.5, 152.2 (Ar CH), 116.9 (CN), 137.5, 151.8, 159.2 (C^S Ar), 167.7 (CO); ms: m/z 288 (M^+). Anal. Calcd for $C_{14}H_{11}N_4O_2Cl$: C, 55.55; H, 3.66; N, 18.51. Found: C, 55.19; H, 3.99; N, 18.30.

With a similar procedure the following compounds were obtained as solid crude intermediates:

***N*-(2-Chloropyridin-3-yl)-*N*-methyl-2-[*N'*-(4-nitrobenzoyl)-*N'*-(2-cyano-4-chlorophenyl)-amino]acetamide (9d)** (from 1-(4-nitrobenzoyl)amino-2-cyano-4-chlorobenzene); yield 62%; nmr (DMSO-d_6, δ in ppm) ^1H : 3.08 + 3.19 (br s, 3H, CH_3), 4.12 (d, 1H, J=16.8), 4.63 (d, 1H, J=16.8), 7.51-8.56 (m, 11H Ar); ms: m/z 483 (M^+).

***N*-(2-Chloropyridin-3-yl)-*N*-methyl-2-[*N'*-(2-nitrobenzoyl)-*N'*-(2-cyanophenyl)amino] acetamide (9e)** (from 1-(2-nitrobenzoyl)amino-2-cyanobenzene); yield 74%; nmr (δ in ppm) ^1H :3.29 (s, 3H, CH_3), 3.78 + 4.85 (v br s, 2H, CH_2), 7.21-8.17 (m , 10H Ar), 8.50 (m, 1H Ar); ms: m/z 449 (M^+).

2-[*N*-Methyl-*N*-(2-chloropyridin-3-yl)carboxamide]-3-aminopyrido[3,2-*b*]thiophene (6b). 2-Cyano-3-mercaptopyridine[8] (0.5 g, 3.6 mmol) was added to a solution of sodium (85 mg, 3.6 mmol) dissolved in methanol (20 ml); after 15 min 2-chloro-3-(*N*-methyl-2-bromoacetylamino)pyridine (0.9 g, 3.6 mmol) was added and the solution was kept under stirring at room temperature. In a few minutes a solid began to precipitate and the reagents were almost completely consumed in 4 h (tlc with EtOAc/hexane 1:1). The precipitated solid was collected by filtration, washed with methanol and dried. Yield 0.93 g (81%); mp 202-203° C (ethanol). Ir (nujol): ν 3430, 3304 (NH_2), 1619 (CO) cm^{-1}. Nmr (δ in ppm) ^1H : 3.38 (s, 3H, CH_3), 6.73 (s, 2H, NH_2), 7.25 (dd, 1H, J=4.4, 8.0), 7.37 (dd, 1H, J=4.2, 7.2), 7.75 (dd, 1H, J=1.4, 7.2), 7.77 (dd, 1H, J=1.2, 8.0), 8.55 (dd, 1H, J=1.4, 4.2), 8.65 (dd, 1H, J=1.2, 4.4) ; ^{13}C : 38.7 (CH_3), 123.8, 125.1, 132.1, 141.8, 148.1, 151.2 (Ar CH), 121.9, 135.2, 139.3, 147.8, 150.9, 153.4 (C^S Ar), 167.7 (CO); ms: m/z 318 (M^+). Anal. Calcd for $C_{14}H_{11}N_4OClS$: C, 52.75; H, 3.48; N, 17.58. Found: C, 53.04; H, 3.63; N, 17.41.

Similarly **2-[*N*-(2-chloropyridin-3-yl)carboxamide]-3-aminopyrido[3,2-*b*]thiophene (6a)** was obtained. Yield 88%; mp 224-225° C (ethanol). Ir (nujol): ν 3444, 3397, 3314 (NH_2 + NH), 1651 (CO) cm^{-1}; nmr (DMSO-d_6, δ in ppm) ^1H : 6.95 (s, 2H, NH_2), 7.51 (dd, 1H, J=4.4, 8.0), 7.57 (dd, 1H, J=4.4, 8.2), 8.15 (dd, 1H, J=1.6, 8.2), 8.31 (m, 1H, J=4.4), 8.47 (d, 1H, J=8), 8.72 (d, 1H, J=4.4), 9.43 (br s, 1H, NH); ^{13}C : 124.6, 125.2, 133.7, 137.8, 147.9, 148.6 (Ar CH), 102.0, 133.9, 134.2, 147.7, 148.5, 149.2 (C^S Ar), 165.2 (CO); ms: m/z 304 (M^+). Anal. Calcd for $C_{13}H_9N_4OClS$: C, 51.24; H, 2.98; N, 18.38. Found: C, 50.85; H, 3.15; N, 18.76.

6,7-Dihydro-7-methylpyrido[2,3-*b*]pyrido[2',3'-4,5]furo[2,3-*f*][1,4]diazepin-6(12*H*)-one (7). Compound (**3**) (1.7 g, 5.9 mmol) was dissolved in DMF (50 ml), sodium carbonate (0.3 g, 2.8 mmol) was added and the mixture was heated at reflux for 8 h. The solvent was removed under reduced pressure and the solid residue was poured into water and filtered. Yield 1.39 g (89%). Recrystallization from ethanol gave a white solid; mp 183-5°C (decomp.). Ir (nujol): ν 3267 (NH), 1672 (CO) cm^{-1}; nmr in Table 1; ms: m/z 266 (M^+). Anal. Calcd for $C_{14}H_{10}N_4O_2$: C, 63.15; H, 3.79; N, 21.04. Found: C, 63.51; H, 4.02; N, 21.66.

With the same procedure the following compounds were obtained:

6,7-Dihydro-7-methylpyrido[2,3-*b*]pyrido[2',3'-4,5]thieno[2,3-*f*][1,4]diazepin-6(12*H*)-one (8b) (from **6b**) Yield 89%; mp 230-231°C (ethanol). Ir (nujol): ν 3343 (NH), 1640 (CO) cm^{-1}; nmr in Table 1; ms: m/z 282 (M^+). Anal. Calcd for $C_{14}H_{10}N_4OS$: C, 59.56; H, 3.57; N, 19.84. Found: C, 59.96; H, 3.52; N, 19.57.

6,7-Dihydropyrido[2,3-*b*]pyrido[2',3'-4,5]thieno[2,3-*f*][1,4]diazepin-6(12*H*)-one (8a) (from **6a**) Yield 64%; mp 247-249°C (decomp.) (ethanol). Ir (nujol): ν 3428, 3305 (NH), 1616 (CO) cm^{-1}; nmr (DMSO-d_6, δ in ppm) ^1H : 7.28 (s, 2H, 2NH), 7.48 (dd, 1H, J=5.1, 8.0), 7.58 (dd, 1H, J=4.2, 8.0), 8.17 (d, 1H, J=8.0), 8.29 (d, 1H, J=5.1), 8.51 (d, 1H, J=8), 8.75 (d, 1H, J=4.2); ^{13}C : 122.9, 124.1, 128.2, 133.4, 144.5, 148.6 (Ar CH), 123.9, 134.9, 135.0, 147.5, 147.6, 159.8 (C^S Ar), 162.1 (CO);ms: m/z 268 (M^+). Anal. Calcd for $C_{13}H_8N_4OS$: C, 58.20; H, 3.01; N, 20.88. Found: C, 58.53; H, 2.99; N, 20.43.

1-Acetyl-2-[*N*-methyl-*N*-(2-chloropyridin-3-yl)carboxamide]-3-aminoindole (10a). NaH 80% (60 mg, 2.1 mmol) was added to a solution of 2-acetylaminobenzonitrile (570 mg, 2 mmol) in DMF (15 ml) under stirring. 2-Chloro-3-(*N*-methyl-*N*-bromoacetyl)aminopyridine (530 mg, 2 mmol) was added 1 h later and the mixture was kept at room temperature for additional 4 h. The solvent was removed and the residue purified by column chromatography on silica gel with EtOAc/cyclohexane 1:1 obtaining 505 mg (74%) of a clear oil. Ir (neat): ν 3443, 3312 (NH), 1656, 1621 (CO) cm^{-1}; nmr (δ in ppm) ^1H : 2.45 (s, 3H, $COCH_3$), 3.31 (s, 3H, NCH_3), 4.72 (br s, 2H, NH_2), 7.08 (m, 2H), 7.24 (m, 2H), 7.41 (d, 1H, J=7.9), 7.53 (d, 1H, J=8.2), 8.12 (d, 1H, J=4.6); ^{13}C : 27.9, 33.3 (CH_3), 116.8, 121.2, 124.9, 125.0, 129.8, 139.8, 149.7 (Ar CH), 112.5, 125.6, 138.0, 139.2, 150.5, 154.5 (C^S Ar), 166.7, 170.4 (CO); ms: m/z 342 (M^+). Anal. Calcd for $C_{17}H_{15}N_4O_2Cl$: C, 59.57; H, 4.41; N, 16.34. Found: C, 59.53; H, 4.19; N, 16.73. From the reaction mixture a crude solid product was isolated in very low yield (less than 5%) which probably was **5,6-dihydro-5-methyl-7-acetylpyrido[3',2'-2,3][1,4]diazepino[5,6-*b*]indol-6(12*H*)-one**; nmr (DMSO-d_6, δ in ppm) ^1H : 2.43 (s, 3H, $COCH_3$), 3.30 (s, 3H, NCH_3), 7.23-7.36 (m,

2H), 7.52 (m, 1H), 7.85 (d, 1H, J=8.1), 8.13 (d, 1H, J=4.5), 8.17 (d, 1H, J=8.6), 8.27 (d, 1H, J=7.3), 9.89 (s, 1H, NH).

5,6-Dihydro-5-methylpyrido[3',2'-2,3][1,4]diazepino[5,6-*b*]indol-6(12*H*)-one (11a). Compound (**10a**) (1.45 g, 4.5 mmol) was dissolved in DMF (10 ml), potassium carbonate (0.32 g, 2.3 mmol) was added and the mixture was kept under reflux for 8 h. The mixture was then poured into water (200 ml) and the precipitate was collected by filtration. The solid was suspended in ethanol and the insoluble material removed. Evaporation of a solvent gave a solid: yield 0.38 g (32%), mp 208-210°C (EtOAc). Ir (KBr): ν 3287 (NH), 1619 (CO) cm^{-1}; nmr in Table 1; ms : m/z 264 (M^+). Anal. Calcd for $C_{15}H_{12}N_4O$: C, 68.17; H, 4.58; N, 21.20. Found: C, 68.52; H, 4.56; N, 21.47. The ethanol-insoluble material was: **5,6-dihydro-5-methyl-12-acetylpyrido[3',2'-2,3][1,4]diazepino[5,6-*b*]indol-6(12*H*)-one (12a).** Yield 0.26 g (19%); mp 304-306°C (decomp.) (DMF/ethanol 1:3); ir (nujol): ν 3209 (NH), 1662, 1641 (CO) cm^{-1}; nmr (DMSO-d_6, δ in ppm) ^1H : 2.15 (s, 3H, $COCH_3$), 3.52 (s, 3H, NCH_3), 7.11 (m, 1H), 7.29 (m, 1H), 7.40-7.58 (m, 3H), 8.08 (d, 1H, J=7.5), 8.36 (d, 1H, J=3.7); ms: m/z 306 (M^+). Anal. Calcd for $C_{17}H_{14}N_4O_2$: C, 66.66; H, 4.61; N, 18.29. Found: C, 66.83; H, 4.28; N, 18.67.

Compounds (**11a**) and (**12a**) were also directly obtained from 2-acetylaminobenzonitrile without isolation of the intermediate (**10a**) with comparable total yields.

Similarly, in a "one pot " synthesis from 2-acetylamino-5-chlorobenzonitrile (3 g, 15.4 mmol) a mixture of the following compounds (which were separeted by flash chromatography on silica gel with EtOAc) were obtained :

5,6-Dihydro-5-methyl-10-chloropyrido[3',2'-2,3][1,4]diazepino[5,6-*b*]indol-6(12*H*)-one (11b): yield 1.01g (22%); mp 164-165°C (EtOAc). Ir (KBr): ν 3295, 3159 (NH), 1636 (CO) cm^{-1}; nmr in Table 1; ms: m/z 298 (M^+). Anal. Calcd for $C_{15}H_{11}N_4OCl$: C, 60.31; H, 3.71; N, 18.75. Found: C, 59.97; H, 3.79; N, 18.67.

5,6-Dihydro-5-methyl-10-chloro-12-acetylpyrido[3',2'-2,3][1,4]diazepino[5,6-*b*]indol-6(12*H*)-one (12b): yield 1.05 g (20%); mp 270°C (decomp.) (DMF/ethanol 1:3). Ir (KBr): ν 3296 (NH), 1635 (CO) cm^{-1}; nmr (DMSO-d_6, δ in ppm) ^1H : 2.16 (s, 3H, $COCH_3$), 3.52 (s, 3H, NCH_3), 7.29 (d, 1H, J=8.9), 7.42-7.60 (m, 3H), 8.09 (d, 1H, J=8.0), 8.37 (d, 1H, J=4.1); ^{13}C : 24.1, 37.9 (CH_3), 116.3, 121.8 (v br), 125.9, 126.8, 135.1, 147.0 (Ar CH), 124.0, 124.9, 126.2, 136.1, 137.5, 150.8 (C^s Ar), 162.1, 170.5 (CO); ms: m/z 340 (M^+). Anal. Calcd for $C_{17}H_{13}N_4O_2Cl$: C, 59.92; H, 3.85; N, 16.44. Found: C, 60.21; H, 3.55; N, 16.21.

5,6-Dihydro-5-methyl-7-amino-9-chloropyrido[3',2'-2,3]piperazino[4,5-*b*]indol-6-one (13a): yield 1.15 g (25%); mp 164-165°C (decomp.) (EtOAc); ir (nujol): ν 3296, 3263 (NH_2), 1709 (CO) cm^{-1},(nmr in Table 1) ms: m/z 298 (M^+). Anal. Calcd for $C_{15}H_{11}N_4OCl$: C, 60.31; H, 3.71; N, 18.75. Found: C, 60.27; H, 3.35; N, 18.96.

5,6-Dihydro-5-methyl-7-ethylamino-9-chloropyrido[3',2'-2,3]piperazino[4,5-*b*]indol-6-one (13b). Compound (**13a**) (150 mg, 0.5 mmol) in DMF (10 ml) was treated with NaH 80% (18 mg, 0.6 mmol) and, after 1 h, with ethyl iodide (100 µl, 1.3 mmol). The solution was kept under stirring at room temperature for additional 1 h, was then poured into cold water and extracted with $CHCl_3$. Evaporation of the organic solvent gave a solid material which was chromatographed on silica gel with EtOAc/petroleum ether 1:1. Yield 75 mg (46%); mp 180-183°C (decomp.) (EtOAc); nmr (δ in ppm) ^1H : 1.35 (t, CH_3, J=7.2), 3.40 (s, 3H, CH_3), 3.63

(q, CH_2, J=7.2), 6.17 (v br s, 1H, NH) 6.96, (dd, 1H, J=5.0, 8.2), 7.19 (dd, 1H, J=1.2, 8.2), 7.32 (dd, 1H, J =1.8, 9.0), 7.82 (d, 1H, J=1.8), 8.03 (dd, 1H, J=1.2, 5), 8.89 (d, 1H, J = 9.0); ^{13}C 17.7, 28.8 (CH_3), 42.6 (CH_2), 119.5, 120.0, 122.1, 122.1, 128.4, 142.3 (Ar CH), 105.0, 123.4, 128.1, 132.7, 133.1, 137.4, 141.7 (C^S Ar), 160.1 (CO); ms: m/z 326 (M^+). Anal. Calcd for $C_{17}H_{15}N_4OCl$: C, 62.48; H, 4.63; N, 17.14. Found: C, 62.71; H, 4.44; N, 17.51.

5,6-Dihydro-5-methyl-7-(4-nitrobenzoyl)-10-chloropyrido[3',2'-2,3][1,4]diazepino[5,6-*b*]indol-6(12*H*)-one (14a). Compound (**9d**) (0.6 g, 1.2 mmol) was cyclized in refluxing DMF with sodium carbonate (0.13 g, 1.2 mmol) for 1 h. Yield 0.3 g (56%) (solid); nmr (DMSO-d_6, δ in ppm) ^1H : 2.95 (s, 3H, CH_3), 7.25 (dd, 1H, J=4.8, 8.0), 7.57 (dd, 1H, J=2.0, 8.9), 7.67 (d, 1H, J=8.0), 7.92 (d, 2H, J=8.8), 8.05 (d, 1H, J=8.9), 8.13 (d, 1H, J=4.8), 8.24 (d, 2H, J=8.8), 8.49 (d, 1H, J=2.0), 9.92 (s, 1H, NH); ^{13}C 37.7 (CH_3), 117.9, 122.1, 122.4, 125.0 (2C), 130.1, 131.4 (2C), 135.2, 145.6 (Ar CH), 118.3, 124.1, 129.8, 130.9, 137.9, 141.0, 143.2, 150.9, 156.7 (Ar C^S), 165.2, 167.8 (CO); ms: m/z 447 (M^+).

Compound (**14a**) was also directly obtained from 2-(4-nitrobenzoylamino)benzonitrile without the isolation of the intermediate (**9d**) with a comparable total yield.

Deprotection of compound (**14a**) . 3-Dimethylaminopropylamine (2 equivalents) was added to compound (**14a**) in ethyl alcohol and the solution was kept at room temperature for 0.5 h. The solution was poured into water and hydrochloric acid was added to pH 4. The insoluble yellow compound (**11b**) was collected by filtration and air dried; yield 76%.

5-Methyl-5,6-dihydropyrido[3',2'-2,3][1,4]diazepino[6,5-*b*]isoindolo[2,3-*a*]indole-6,11(11*H*)-dione (15). Compound (**9e**) (450 mg, 1 mmol) in DMF (10 ml) was treated with NaH 80% (45 mg, 1.5 mmol) and kept at 60°C for 2 h. The solution was poured into crushed ice and the insoluble material collected by filtration. Yield 238 mg (65%); mp 324°C (decomp.) (ethanol). Ir (nujol): ν 1772, 1687,1656 (CO, C=N) cm^{-1}; nmr (δ in ppm) ^1H : 3.47 (s, 3H, CH_3), 5.25 (d, 1H, J=8.1), 7.01, (t, 1H, J=7.9), 7.22-7.48 (m, 3H), 7.61 (t, 1H, J=7.9), 7.83 (m, 2H), 7.99 (t, 2H, J=9.3), 8.64 (d, 1H, J=4.4); ^{13}C 39.6 (CH_3), 118.6, 123.6, 125.8, 127.1, 127.3, 127.8, 131.9, 134.0, 135.3, 137.5, 148.5 (Ar CH), 83.4, 130.0, 131.6, 141.3, 149.3, 155.3, 164.5 (Ar C^S), 166.6, 168.9 (CO); ms: m/z 366 (M^+). Anal. Calcd for $C_{22}H_{14}N_4O_2$: C, 72.12; H, 3.85; N, 15.29. Found: C, 72.37; H, 3.99; N, 15.03.

Compound (**15**) could be directly obtained from 2-(2-nitrobenzoylamino)benzonitrile and 2-chloro-3-(*N*-methyl-*N*-bromoacetyl)aminopyridine by treatment with two equivalents of NaH without isolation of the intermediate (**9e**) with a comparable total yield.

X-ray Crystallographic Data

Compound (**13b**)[9] crystallizes in the monoclinic system, space group C2/c with a = 18.663(9), b = 16.455(7), c = 13.949(8) Å, β = 135.90(8)°; Z = 8; V = 298(3) $Å^3$; μ = 2.67 cm^{-1}; D_C = 1.46 g cm^{-3}; 2620 indipendent reflections were collected on an Enraf-Nonius CAD4 automatic diffractometer in the range $5 < 2\theta < 50°$, using Mo-Kα radiation (λ = 0.7107 Å), θ–2θ scan mode. An adsorption correction was applied using the DIFABS program.[10] The structure was solved by direct methods of SIR92[11] and refined by full-matrix least-squares SHELX93[12] to R = 0.057 for the 2132 reflections having $I > 2\sigma$ (I). All non-hydrogen atoms were refined

anisotropically, whereas for the hydrogen atoms, which were introduced in calculated positions, an overall isotropic factor U was refined to a value of 0.069(6)Å^2.

Compound (**15**)[9] crystallizes in the monoclinic system, space group $P2_1/n$ with a = 11.901(5), b = 11.507 (9), c = 13.035 (9) Å, β = 103.72 (5)°; Z = 4; V = 1734(2) Å^3; μ = 0.93 cm^{-1}; D_C = 1.40 g cm^{-3}; 2263 indipendent reflections were collected in the range $5 < 2\theta < 45°$, using the diffractometer, the radiation and the scan mode reported for previous compound. The adsorption correction, the structure solution and the refinement procedure were analogues as for compound (**13b**); the final R factor calculated with 1496 reflections having $I > 2\sigma$ (I) was R = 0.077, the overall isotropic temperature factor for the hydrogen atoms was 0.07(5)Å^2.

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