SYNTHESIS OF PYRAZINO[1,2-a:4,5-a']DI[1,8]NAPHTHYRIDINE AND PYRAZINO[1,2-a][1,8]NAPHTHYRIDINES

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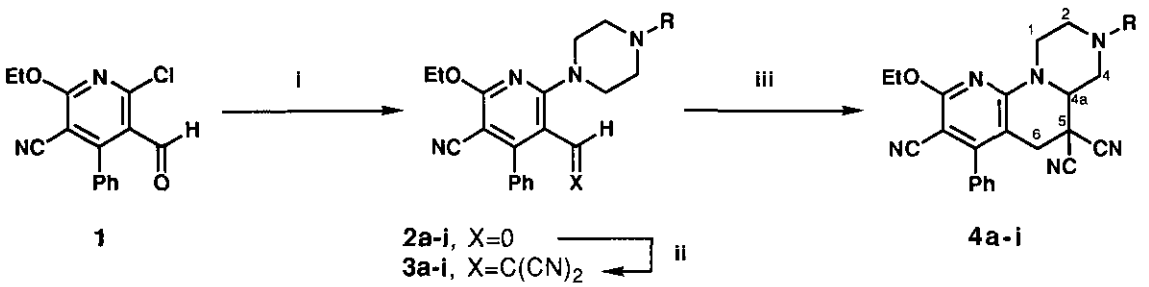
Abstract - A series of 3-alkyl-, 3-aryl- and 3-hetarylhexahydro-1H-pyrazino[1,2-a][1,8]naphthyridines (**4**) were prepared from 2-(4-substituted 1-piperazinyl)-3-formylpyridines (**2**) by condensation with malononitrile and subsequent thermal cyclization. Octahydro[1,2-a:4,5-a']di[1,8]naphthyridine (**7**) was also obtained.

We recently reported the synthesis of tri- and tetracyclic compounds containing the [1,8]naphthyridine ring by extending application of the "tert-amino effect"[1] to 2-amino-3-vinylpyridines.[2,3] The significant biological activity exhibited by pirazino[1,2-a]quinolines[4,5] or pirido[1,2-a][1,8]naphthyridines[6-8] prompted to us to apply this reaction principle to 2-(4-substituted 1-piperazinyl)-3-vinylpyridines (**3**) and prepare various pyrazino[1,2-a][1,8]naphthyridines in order to investigate their potential biological activity. In this work we developed a straightforward two-steps synthesis of 3-alkyl-, 3-aryl- and 3-hetaryl substituted hexahydropyrazino[1,2-a][1,8]naphthyridines (**4**) and octahydropyrazino[1,2-a:4,5-a']di[1,8]-naphthyridine (**7**).

The starting compounds for the thermal cyclization were prepared from the 2-chloro-3-formylpyridine derivative (**1**).[2] Reaction of compound (**1**) and a suitable N-monosubstituted piperazine gave the corresponding 2-piperazinyl-3-formylpyridine derivatives (**2a-i**) with excellent yields by refluxing for 10 min in tetrahydrofuran containing triethylamine. Formation of the desired aldehydes was confirmed by ^{1}H nmr [δ = 9.20-9.28 (s, CHO)] and decoupled ^{13}C nmr spectra [δ = 185.7-185.9 (CO)]. A Knoevenagel condensation of the carbonyl compounds **(2a-i)** with malononitrile (butylamine and ammonium acetate as catalyst)[9] in toluene under reflux for 20 min gave rise to the 2-piperazinyl-3-(2,2-dicyanovinyl)pyridine derivatives (**3a-i**). The signals of Py<u>H</u>CC(CN)$_2$ in the ^{1}H nmr spectra between δ = 7.42-7.56 as singlets and those of Py<u>H</u><u>C</u>C(CN)$_2$ in the decoupled ^{13}C nmr spectra between δ = 155.5-156.3 are typical of compounds (**3a-i**).

Scheme 1



Reagents:

i: N-monosubstituted piperazine, Et_3N,THF, reflux, 10 min. **ii**: 2 malononitrile, n-$BuNH_2$, NH_4OAc, toluene, reflux, 20 min. **iii**: DMSO, 140 °C, 7-70 h.

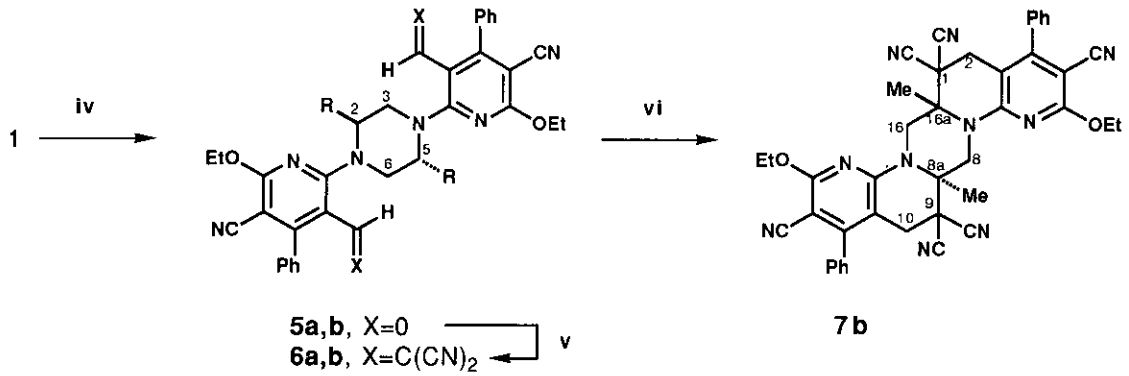
2-4, 8	R	2-4, 8	R	2-4, 8	R
a	Me	**d**	4-MeC_6H_4	**g**	4-NO_2Ph
b	CH_2Ph	**e**	4-FC_6H_4	**h**	2-pyrido
c	$CH_2CH_2(4\text{-}CF_3)C_6H_4$	**f**	4-ClC_6H_4	**i**	2-[1,3]pyrazino

Heating **3a-i** in dimethyl sulfoxide at 140 °C for 7-70 h resulted in the corresponding pyrazino[1,2-a][1,8]naphthyridines (**4a-i**) as colorless solids with moderate to good yields. The ^1H Nmr spectra of compounds (**4a-i**) include characteristic signals of bridgehead hydrogen atoms (H-4a) as double doublets between δ = 3.77-4.02.

Likewise, reaction of compound (**1**) with piperazine or 2,5-dimethylpiperazine (mixture of cis and trans) gave the corresponding bis(2-pyridyl)piperazines (**5a,b**) with good yields. In the case of the 2,5-dimethylpiperazine, we could only isolate the trans derivative (**5b**) with a 71 % yield, as confirmed by the ^1H and ^{13}C nmr spectra (only one doublet at δ = 1.36 for the two methyl groups). Knoevenagel condensations with malononitrile in methylene chloride yielded the vinyl derivatives (**6a,b**), which were subjected to thermal cyclization reaction Heating of **6a** in dimethyl sulfoxide until all the starting material had disapeared (5 d at 140 °C) gave decomposition products, whereas heating the trans-2,5-dimethyl derivative (**6b**) in dimethyl sulfoxide (50 h at 140 °C) resulted in only one cyclized product (**7b**) with an excellent yield (Scheme **2**), through reaction at the substituted carbons adjacent to the nitrogen atom. The structure of **7b** was concluded from the ^1H nmr spectrum of the reaction product, which included a characteristic singlet at δ = 1.57 that integrated for six protons and can only be assigned to $CC\underline{H}_3$ groups in an pyrazino[1,2-a:4,5-

a']di[1,8]naphthyridine structure. The ^{1}H and ^{13}C nmr spectra of compound (**7b**) also reveal that the trans geometry was selectively formed, because only methyl groups at 2,5-positions of the piperazine moiety in an equivalent arrangement (hence in the opposite side of the molecule) can give rise to the same absorption signal.

Scheme 2

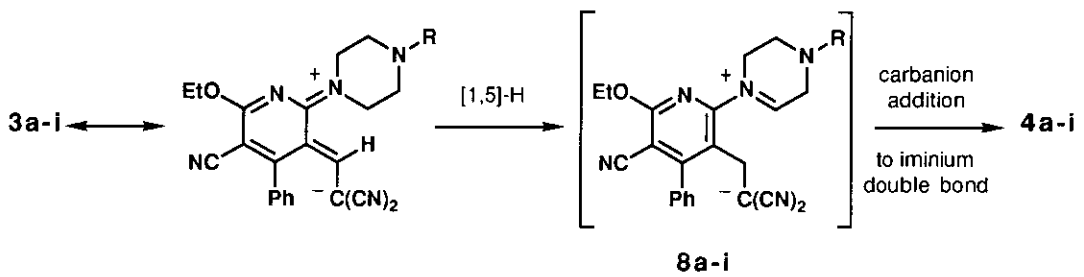


5,6 **a**, R = H
b, R = Me

Reagents:
iv: piperazine, Et_3N,THF, reflux, 30 min. **v**: 4 malononitrile, 2 n-$BuNH_2$, 2 NH_4OAc, CH_2Cl_2, reflux, 40 min. **vi**: DMSO, 140 °C, 2 h.

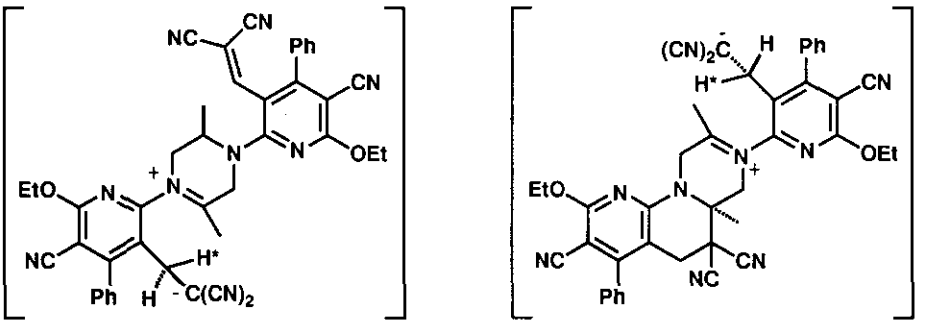
The thermal cyclization of **3a-i** proceeds in two consecutive reactions (Scheme 3).[10] The first step involves a thermal suprafacial [1,5]-hydrogen shift of one methylene proton adjacent to the nitrogen of the amino group in (**3a-i**) to yield the 1,5-dipolar intermediate (**8a-i**) (with its negative end stabilized by two electron-withdrawing groups). Subsequently, intramolecular addition of the carbanion to the iminium double bond gives rise to cyclized products (**4a-i**).

Scheme 3



The regiospecificity of the cyclization of **6** is consistent with the proposed mechanism. **6** has two types of hydrogen atoms liable to undergo sigmatropic rearrangement (H-2,5 and H-3,6); however, the fastest [1,5]-hydrogen shifts take place over the carbon atoms bearing the methyl groups (involving H* in scheme 4) because they lead to the more stable dipolar intermediates (**9**) and (**10**), with a tetrasubstituted iminium double bond in the "positive end". Diasteroselectivity arises from the reaction involving retention of configuration at the chiral centers, through of addition of the carbanions to the iminium double bonds exclusively from the side where migrating hydrogen atoms are transferred. This is the result of a partial rotation of the vinyl moiety in the [1,5]-hydrogen transfer process, which, without equilibration of the helicar dipolar intermediates (**9**) and (**10**), can proceed in the same way, thus enabling the selective carbanion additions.[11]

Scheme 4



9 **10**

EXPERIMENTAL SECTION

All reagents used were commercial grade chemicals from freshly opened containers. The amines were purchased from Aldrich Chemical Co. Silica gel 60 $HF_{254+366}$ for thin layer chromatography and silica gel 60 (230-400 mesh) for medium-pressure chromatography were purchased from Merck. Melting points were measured by using a Büchi 510 apparatus and are uncorrected. Ir spectra were recorded on a Perkin-Elmer 383 Ir spectrophotometer, ^1H and ^{13}C nmr spectra were acquired on a Bruker WM 250 spectrometer and ms were obtained on a Kratos MS-50 spectrometer.

2-(N-4-Substituted piperazinyl)-3-formylpyridine Derivatives (2a-i); General Procedure:

A solution of 2-chloro-5-cyano-6-ethoxy-3-formyl-4-phenylpyridine (**1**, 0.5 g, 1.75 mmol), a suitable N-monosubstituted piperazine (1.75 mmol) and Et_3N (0.27 ml, 1.95 mmol) in THF (10 ml) is refluxed for 10 min. Upon cooling, precipitated Et_3NHCl is filtered off, washed with THF (2 ml), and discarded. The solvent is removed under reduced pressure and the residue is purified by medium-pressure chromatography on a silica gel column (22 x 1.5 cm) to obtain (**2a-i**) as colorless solids.

All compounds (**2a-i**) exhibit typical absorption signals for the pyridine nucleus and its subtituents in the ^1H and ^{13}C Nmr: ^1H Nmr ($CDCl_3$, 250 MHz): 1.43-1.49 (3H,t, , J = ~7.1 Hz, OCH_2CH_3); 4.45-4.50 (2H,q, J = ~7.1 Hz, OCH_2); 7.42-7.60 (m, $5H_{arom}$). ^{13}C Nmr

($CDCl_3$, 62.8 MHz): 14.1-14.3($OCH_2\underline{C}H_3$); 63.7-63.9 (OCH_2); 86.1-87.0 (CN); 109.3-109.5, 115.0-115.4, 159.0-159.2, 164.2-164.3, 165.4-165.7 ($C_{pyridyl}$); 128.3-128.7, 129.6-129.8, 130.3-130.4, 133.8-134.2 (C_{phenyl}).

3-Cyano-2-ethoxy-5-formyl-6-(N-4-methylpiperazinyl)-4-phenylpyridine (**2a**): General procedure was followed; medium-pressure chromatography was performed by using CH_2Cl_2:EtOH 50:1 as eluent; yield: 0.59 g (97%); mp 155-157 °C (EtOH:hexane 4:1). ^{1}H Nmr ($CDCl_3$, 250 MHz): 2.38 (3H, s, NCH_3); 2.59-2.63 (4H, m, $MeNCH_2$); 3.73-3.75 (4H, m, $PyNCH_2$); 9.20 (1H, s, CHO). ^{13}C Nmr ($CDCl_3$, 62.8 MHz): 45.7 (NCH_3); 49.4, 54.9 (NCH_2); 185.7 (CHO). Ms (DEI, 70 eV): 350 (M^+, 9); 294 (23); 280 (6); 264 (5); 262 (4); 252 (17); 250 (4); 140 (4); 70 (100). Ms-high resolution: $C_{20}H_{22}N_4O_2$, calcd: 350.17436, found: 350.1729. Ir (KBr): 3040, 2980, 2940, 2900, 2880, 2800 (CH); 2220 (CN); 1670 (CO); 1580, 1560, 1520, 1510 (CC_{arom}) cm^{-1}.

2-(N-4-Benzylpiperazinyl)-5-cyano-6-ethoxy-3-formyl-4-phenylpyridine (**2b**): General procedure was followed; medium-pressure chromatography was performed by using CH_2Cl_2:EtOH 100:1 as eluent; yield: 0.61g (95%); mp 185-187 °C (EtOH:acetone 3:2). ^{1}H Nmr ($CDCl_3$, 250 MHz): 2.59-2.63 (4H, m, $BnNCH_2$); 3.59 (2H, s, NCH_2Ph); 3.71-3.75 (4H, m, $PyNCH_2$); 7.26-7.36 (m, $5H_{arom}$); 9.20 (1H, s, CHO). ^{13}C Nmr ($CDCl_3$, 62.8 MHz): 49.6 (NCH_2Ph); 53.1, 62.8 (NCH_2); 127.4, 128.4, 129.2, 137.6 (C_{arom}); 185.9 (CHO). Ms (DEI, 70 eV): 427 (M^++1, 11); 426 (M^+, 38); 375 (9); 373 (9); 297 (6); 255 (19); 212 (6); 146 (12); 91 (100). Ms-high resolution: $C_{26}H_{26}N_4O_2$, calcd: 426.20560, found: 426.2059. Ir (KBr): 3040, 2980, 2940, 2880, 2820, 2760 (CH); 2220 (CN); 1665 (CO); 1580, 1560, 1520 (CC_{arom}) cm^{-1}.

3-Cyano-2-ethoxy-5-formyl-4-phenyl-6-{N-4-[2-trifluoromethylphenethyl]piperazinyl}pyridine (**2c**): General procedure was followed; medium-pressure chromatography was performed by using CH_2Cl_2:EtOH 100:1 as eluent; yield: 0.75 g (98%); mp 140-142 °C (EtOH:hexane 1:10). ^{1}H Nmr ($CDCl_3$, 250 MHz): 2.64-2.74 (6H, m, $C\underline{H}_2NCH_2C\underline{H}_2Ph$); 2.99-3.05 (2H, m, $NC\underline{H}_2CH_2Ph$); 3.75-3.80 (4H, m, $PyNCH_2$); 7.28-7.38 (m, $3H_{arom}$); 7.61-7.65 (m,$1H_{arom}$); 9.21 (1H, s, CHO). ^{13}C Nmr ($CDCl_3$, 62.8 MHz): 30.0 ($NCH_2\underline{C}H_2Ph$); 49.6, 53.0, 69.8 (NCH_2); 125.9, 126.0, 126.1, 126.2, 126.3, 128.5, 128.9, 131.7, 131.8, 138.6 (C_{arom}); 185.8 (CHO). Ms (DEI, 70 eV): 509 (M^++1, 0.4); 508 (M^+, 2.4); 349 (23); 348 (100); 293 (20); 227 (36). Ms-high resolution: $C_{28}H_{27}F_3N_4O_2$, calcd: 508.20871, found: 508.2081. Ir (KBr): 3040, 2985, 2940, 2920, 2890, 2800, 2760 (CH); 2220 (CN); 1660 (CO); 1580, 1560, 1540, 1520 (CC_{arom}) cm^{-1}.

3-Cyano-2-ethoxy-5-formyl-4-phenyl-6-[N-4-(o-tolyl)piperazinyl]pyridine (**2d**): General procedure was followed; medium-pressure chromatography was performed by using CH_2Cl_2:hexane 3:1 as eluent; yield: 0.59 g (93%); mp 180-183 °C (EtOH). ^{1}H Nmr ($CDCl_3$, 250 MHz): 2.39 (3H, s, $PhCH_3$); 3.07-3.12 (4H, m, $PhNCH_2$); 3.88-3.92 (4H, m, $PyNCH_2$); 7.01-7.07 (m, $2H_{arom}$); 7.18-7.27 (m, $2H_{arom}$); 9.26 (1H, s, CHO). ^{13}C Nmr ($CDCl_3$, 62.8 MHz): 17.7 ($PhCH_3$); 50.1, 51.9 (NCH_2); 119.3, 123.8, 126.7, 131.2, 132.7, 150.7 (C_{arom}); 185.6 (CHO). Ms (DEI, 70 eV): 427 (M^++1, 4); 426 (M^+, 15); 293 (5); 280 (7); 278 (4); 262 (4); 252 (13); 250 (3); 159 (15); 147 (12); 146 (100); 143 (5); 132 (17); 118 (28). Ms-high resolution: $C_{28}H_{26}N_4O_2$, calcd: 426.20568, found: 426.2055. Ir (KBr): 3050, 3010, 2980, 2940, 2920, 2800, 2740 (CH); 2220 (CN); 1660 (CO); 1570, 1520 (CC_{arom}) cm^{-1}.

3-Cyano-2-ethoxy-6-[N-4-(4-fluorophenyl)piperazinyl]-5-formyl-4-phenylpyridine (**2e**): General procedure was followed; medium-pressure chromatography was performed by using CH_2Cl_2 as eluent; yield: 0.61 g (94%); mp 165-168 °C (EtOH). ^{1}H Nmr ($CDCl_3$, 250 MHz): 3.26-3.31 (4H, m, $PhNCH_2$); 3.85-3.89 (4H, m, $PyNCH_2$); 6.89-7.03 (m, $4H_{arom}$); 9.26 (1H, s, CHO). ^{13}C Nmr ($CDCl_3$, 62.8 MHz): 49.5, 50.4 (NCH_2); 115.7 (d, J = 22.1 Hz, C*orto*F), 118.3 (d, J = 7.1 Hz, C*meta*F), 147.5 (C*para*F), 157.5 (d, J = 239.2 Hz, C*ipso*F); 186.0 (CHO). Ms (DEI, 70 eV): 431 (M^++1, 12); 430 (M^+, 42); 429 (M^+-1, 6); 294 (7); 293 (33); 280 (19); 278 (8); 264 (8); 262 (7); 254 (6); 252 (34); 163 (33); 151 (13); 150 (100). Ms-high resolution: $C_{25}H_{23}FN_4O_2$, calcd: 430.18049, found: 430.1800. Ir (KBr): 3040, 2980, 2960, 2900, 2860, 2840, 2820, 2740 (CH); 2220 (CN); 1665 (CO); 1580, 1560, 1510 (CC_{arom}) cm^{-1}.

2-[N-4-(4-Chlorophenyl)piperazinyl]-5-cyano-6-ethoxy-3-formyl-4-phenylpyridine (**2f**): General procedure was followed; medium-pressure chromatography was performed by using CH_2Cl_2:hexane 3:1 as eluent; yield: 0.61 g (91%); mp 180-182 °C (EtOH:acetone 3:1). ^{1}H Nmr ($CDCl_3$, 250 MHz): 3.33-3.37 (4H, m, $PhNCH_2$); 3.84-3.88 (4H, m, $PyNCH_2$); 7.22, 7.25 (4H, AB system, J = 8.8 Hz, H_{arom}); 9.25 (1H, s, CHO). ^{13}C Nmr ($CDCl_3$, 62.8 MHz): 49.1, 49.3 (NCH_2); 117.4, 125.1, 129.1, 149.4, 165.6 (C_{arom}); 185.9 (CHO). Ms (DEI, 70 eV): 448 (M^++2, 6); 447 (M^++1, 6); 446 (M^+, 17); 294 (6); 293 (24); 280 (21); 278 (8); 264 (7); 252 (34); 181 (13); 179 (37); 166 (100); 140 (23). Ms-high resolution: $C_{25}H_{23}ClN_4O_2$, calcd: 446.1509, found: 446.1495. Ir (KBr): 3040, 2980, 2910, 2870, 2840, 2820 (CH); 2220 (CN); 1665 (CO); 1580, 1560, 1510, 1490 (CC_{arom}) cm^{-1}.

3-Cyano-2-ethoxy-5-formyl-6-[N-4-(4-nitrophenyl)piperazinyl]-4-phenylpyridine (**2g**): General procedure was followed; medium-pressure chromatography was performed by using CH_2Cl_2 as eluent; yield: 0.68 g (99%); mp 218-220 °C (EtOH:acetone 1:2). ^{1}H Nmr ($CDCl_3$, 250 MHz): 3.67-3.71 (4H, m, $PhNCH_2$); 3.86-3.90 (4H, m, $PyNCH_2$); 6.82, 8.15 (4H, AB system, J = 9.3 Hz, H_{arom}); 9.28 (1H, s, CHO). ^{13}C Nmr ($CDCl_3$, 62.8 MHz): 46.3, 48.5 (NCH_2); 112.3, 126.0, 138.8, 154.1 (C_{arom}); 185.2 (CHO). Ms (DEI, 70 eV): 459 (M^++2, 1); 458 (M^++1, 6); 457 (M^+, 20); 440 (10); 306 (16); 293 (78); 280 (89); 264 (20); 252 (81); 227 (13); 190 (51); 177 (100); 161 (33). Ms-high resolution: $C_{25}H_{23}N_5O_4$, calcd: 457.1750, found: 457.1755. Ir (KBr): 3080, 3050, 2980, 2930, 2880, 2860 (CH); 2220 (CN); 1670 (CO); 1600, 1580, 1560, 1515, 1500, 1485 (CC_{arom}) cm^{-1}.

3-Cyano-2-ethoxy-5-formyl-4-phenyl-6-[N-4-(2-pyridyl)piperazinyl]pyridine (**2h**): General procedure was followed; medium-pressure chromatography was performed by using CH_2Cl_2:EtOH 100:1 as eluent; yield: 0.55 g (92%); mp 150-155 °C (EtOH:hexane 1:3). ^{1}H Nmr ($CDCl_3$, 250 MHz): 3.76-3.78 (4H, m, $PhNCH_2$); 3.82-3.84 (4H, m, $PyNCH_2$); 6.64-6.69 (m, $3H_{pyridyl}$), 8.19-8.22 (m, $1H_{pyridyl}$); 9.25 (1H, s, CHO). ^{13}C Nmr ($CDCl_3$, 62.8 MHz): 44.8, 49.1 (NCH_2); 106.9, 113.7, 137.7, 148.0, 158.9 ($C_{pyridyl}$); 185.9 (CHO). Ms (DEI, 70 eV): 415 (M^++1, 7); 414 (M^+, 26); 396 (33); 384 (28); 367 (7); 319 (10); 306 (14); 293 (44); 278 (23); 264 (17); 252 (17); 195 (8); 147 (26); 134 (100); 122 (93). Ms-high resolution: $C_{24}H_{23}N_5O_2$, calcd: 397.1904, found: 397.1905. Ir (KBr): 3030, 3000, 2980, 2930, 2910, 2870, 2830, 2770 (CH); 2220 (CN); 1665 (CO); 1590, 1580, 1560, 1510 (CC_{arom}) cm^{-1}.

3-Cyano-2-ethoxy-5-formyl-4-phenyl-6-{N-4-[2-(1,3)pyrazinyl]piperazinyl}pyridine (**2i**): General procedure was followed; medium-pressure chromatography was performed by using CH_2Cl_2:EtOH 100:1 as eluent; yield: 0.61 g (98%); mp 204-207 °C (EtOH). ^{1}H Nmr ($CDCl_3$, 250 MHz): 3.76-3.80 (4H, m, $PhNCH_2$); 4.00-4.05 (4H, m, $PyNCH_2$); 6.55 (1H, t, J = 4.7 Hz, $H_{pirazinyl}$-5), 8.34 (2H, d, J = 4.7 Hz, $H_{pirazinyl}$-4,6); 9.25 (1H, s, CHO). ^{13}C Nmr ($CDCl_3$, 62.8 MHz): 43.3, 49.2 (NCH_2); 110.3, 157.7, 161,5 ($C_{pirazinyl}$); 186.0 (CHO). Ms (DEI, 70 eV): 397 (M^+, 23); 396 (M^+-1, 17); 395 (M^+-2, 60); 384 (5); 319 (4); 307 (8); 289 (8); 264 (6); 252 (8); 236 (4); 221 (3); 195 (5); 107 (100). Ms-high resolution: $C_{23}H_{22}N_6O_2$, calcd: 414.1805, found: 414.1809. Ir (KBr): 3040, 3010, 2870, 2770 (CH); 2220 (CN); 1660 (CO); 1580, 1560, 1520 (CC_{arom}) cm^{-1}.

2-(N-4-Substituted piperazinyl)-3-(2,2,-dicyanovinyl)pyridine Derivatives (3a-i); General Procedure:

A solution of 2-(N-substituted piperazinyl)-5-cyano-6-ethoxy-3-formyl-4-phenylpyridine (**2a-i**, 1.4 mmol), malononitrile (0.185 g, 2.8 mmol), n-butylamine (0.14 ml, 1.4 mmol) and NH_4OAc (0.11 g, 1.4 mmol) in toluene (15 ml) is refluxed for 20 min. Upon cooling, the solvent is removed under reduced pressure and the resulting solid is purified by medium-pressure chromatography on a silica gel column (15 x 1.5 cm) to obtain (**3a-i**) as dark yellow solids.

All compounds (**3a-i**) exhibit typical absorption signals for the pyridine nucleus and its subtituents in the ^{1}H and ^{13}C Nmr: ^{1}H Nmr ($CDCl_3$, 250 MHz): 1.44-1.49 (3H, t, J = ~7.1 Hz, $OCH_2\underline{CH_3}$); 4.48-4.55 (2H, q, J = ~7.1 Hz, OCH_2); 7.20-7.32 (m, $2H_{arom}$); 7.47-7.60 (m, $3H_{arom}$). ^{13}C Nmr ($CDCl_3$, 62.8 MHz): 14.1-14.2 ($OCH_2\underline{C}H_3$); 64.1-64.2 (OCH_2); 88.3-89.3 (CN); 103.2-103.6, 111.9-112.2, 159.1-159.8, 161.3-161.5, 163.7-164.0 ($C_{pyridyl}$); 128.4-128.5, 129.2-129.3, 130.3-130.5, 133.3-133.6 (C_{phenyl}).

3-Cyano-5-(2,2-dicyanovinyl)-2-ethoxy-6-(N-4-methylpiperazinidyl)-4-phenylpyridine (**3a**): General procedure was followed; medium-pressure chromatography was performed by using CH_2Cl_2:EtOH 50:1 as eluent; yield: 0.50 g (90%); mp 198-200 °C (EtOH/hexane). ^{1}H Nmr ($CDCl_3$, 250 MHz): 2.32 (3H, s, NCH_3); 2.46-2.50 (4H, m, CH_3NCH_2); 3.66-3.70 (4H, m, $PyNCH_2$); 7.42 (1H, s, =CH). ^{13}C Nmr ($CDCl_3$, 62.8 MHz): 45.8, 48.1 (NCH_2); 54.5 (NCH_3); 79.0 [$\underline{C}(CN)_2$]; 114.2, 114.4 (CN); 156.8 (=CH). Ms (DEI, 70 eV): 399 (M^++1, 7); 398 (M^+, 24); 383 (5); 326 (10); 300 (11); 277 (6); 262 (6); 248 (7); 70 (100). Ms-high resolution: $C_{23}H_{22}N_6O$, calcd: 398.1855, found: 398.1858. Ir (KBr): 3050, 2980, 2940, 2810, 2740 (CH); 2220 (CN); 1565, 1500, 1485 (CC_{arom}) cm^{-1}.

2-(N-4-Benzylpiperazinidyl)-5-cyano-3-(2,2-dicyanovinyl)-6-ethoxy-4-phenylpyridine (**3b**): General procedure was followed; medium-pressure chromatography was performed by using CH_2Cl_2:EtOH 100:1 as eluent; yield: 0.59 g (89%); mp 202-204 °C (EtOH). ^{1}H Nmr ($CDCl_3$, 250 MHz): 2.54-2.57 (4H, m, $BnNCH_2$); 3.57 (2H, s, CH_2Ph); 3.70-3.74 (4H, m, $PyNCH_2$); 7.25-7.35 (m, $5H_{arom}$); 7.43 (1H s,=CH). ^{13}C Nmr ($CDCl_3$, 62.8 MHz): 48.1, 52.5 (NCH_2); 62.2 (NCH_2Ph); 78.7 [$\underline{C}(CN)_2$]; 114.2, 114.4 (CN); 127.5, 129.0, 137.2 (C_{arom}); 156.8 (=CH). Ms (DEI, 70 eV): 476 (M^++2, 0.5); 475 (M^++1, 12); 474 (M^+, 36); 459 (3); 383 (4); 356 (2); 341 (2); 362 (4); 300 (2); 255 (3); 248 (2); 146 (41); 91 (100). Ms-high resolution: $C_{29}H_{26}N_6O$, calcd: 474.2168, found: 474.2161. Ir (KBr): 3050, 3020, 2960, 2900, 2800, 2760 (CH); 2220 (CN); 1580, 1560, 1510, 1485 (CC_{arom}) cm^{-1}.

3-Cyano-5-(2,2-dicyanovinyl)-2-ethoxy-4-phenyl-6-[N-4-[2-trifluoromethylphenethyl]piperazinyl]pyridine (**3c**): General procedure was followed; medium-pressure chromatography was performed by using CH_2Cl_2:EtOH 100:1 as eluent; yield: 0.72 g (93%); mp 183-185 °C (EtOH). ^{1}H Nmr ($CDCl_3$, 250 MHz): 2.60-2.70 (6H, m, $\underline{CH_2}NCH_2\underline{CH_2}Ph$); 2.97-3.03 (2H, m,$N\underline{CH_2}CH_2Ph$); 3.72-3.76 (4H, m, $PyNCH_2$); 7.28-7.40 (m, $3H_{arom}$); 7.45 (1H, s, =CH); 7.60-7.65 (m, $1H_{arom}$). ^{13}C Nmr ($CDCl_3$, 62.8 MHz): 29.9 ($NCH_2\underline{C}H_2Ph$); 48.1, 52.6 (NCH_2); 59.6 ($N\underline{C}H_2CH_2Ph$); 78.8 [$\underline{C}(CN)_2$]; 114.2, 114.4 (CN); 126.0, 126.1, 126.4, 128.7, 131.5, 131.8, 138.3 (C_{arom}); 156.8 (=CH). Ms (DEI, 70 eV): 556 (M^+, 15); 399 (11); 398 (64); 397 (100); 369 (4); 228 (17); 133 (8). Ms-high resolution: $C_{31}H_{27}F_3N_6O$, calcd: 556.2198, found: 556.2179. Ir (KBr): 3050, 3020, 2980, 2930, 2820, 2740 (CH); 2220 (CN); 1580, 1560, 1520, 1500 (CC_{arom}) cm^{-1}.

3-Cyano-5-(2,2-dicyanovinyl)-2-ethoxy-4-phenyl-6-[N-4-(o-tolyl)piperazinyl]pyridine (**3d**): General procedure was followed; medium-pressure chromatography was performed by using CH_2Cl_2:hexane 3:2 as eluent; yield: 0.63 g (95%); mp 186-187 °C (EtOH/acetone 2:1). ^{1}H Nmr ($CDCl_3$, 250 MHz): 2.38 (3H, s, $PhCH_3$); 3.00-3.04 (4H, m, $PhNCH_2$); 3.80-3.87 (4H, m, $PyNCH_2$); 6.99-7.08 (m, $2H_{arom}$); 7.22-7.31 (m, $2H_{arom}$); 7.49 (1H, s, =CH). ^{13}C Nmr ($CDCl_3$, 62.8 MHz): 17.8 ($PhCH_3$); 48.8, 51.7 (NCH_2); 79.1 [$\underline{C}(CN)_2$]; 114.3, 114.4 (CN); 119.2, 124.2, 126.8, 131.4, 132.9, 150.3 (C_{arom}); 156.8 (=CH). Ms (DEI, 70 eV): 475 (M^++1, 6); 474 (M^+, 19); 326 (9); 300 (5); 262 (6); 248 (6); 159 (7); 147 (12); 146 (100); 134 (9); 133 (5); 132 (8). Ms-high resolution: $C_{29}H_{26}N_6O$, calcd: 474.2168, found: 474.2170. Ir (KBr): 3050, 3020, 2980, 2900, 2820, 2740 (CH); 2220 (CN); 1580, 1560, 1520, 1510 (CC_{arom}) cm^{-1}.

3-Cyano-5-(2,2-dicyanovinyl)-2-ethoxy-6-[N-4-(4-fluorophenyl)piperazinyl]-4-phenylpyridine (**3e**): General procedure was followed; medium-pressure chromatography was performed by using CH_2Cl_2/hexane 3:1 as eluent; yield: 0.53 g (80%); mp 206-210 °C (EtOH). ^{1}H Nmr ($CDCl_3$, 250 MHz): 3.24-3.28 (4H, m, $PhNCH_2$); 3.80-3.84 (4H, m, $PyNCH_2$); 6.84-6.90 (m, $2H_{arom}$); 6.97-7.04 (m, $2H_{arom}$); 7.49 (1H, s, =CH). ^{13}C Nmr ($CDCl_3$, 62.8 MHz): 48.2, 49.7 (NCH_2); 79.5 [$\underline{C}(CN)_2$]; 114.1, 114.3 (CN); 115.7 (d, J = 22.6 Hz, C*orto*F),

118.0 (d, J = 7.6 Hz, C*meta*F), 147.0 (C*para*F), 157.6 (d, J = 241.9 Hz, C*ipso*F); 157.8 (=CH). Ms (DEI, 70 eV): 479 (M^++1, 12); 478 (M^+, 36); 449 (5); 326 (7); 300 (13); 262 (5); 163 (15); 150 (100); 138 (11); 122 (30). Ms-high resolution: $C_{28}H_{23}FN_6O$, calcd: 478.1917, found: 478.1923. Ir (KBr): 3060, 2980, 2900, 2840, 2820 (CH); 2220 (CN); 1580, 1565, 1510 (CC_{arom}) cm^{-1}.

2-[N-4-(4-Chlorophenyl)piperazinyl]-5-cyano-3-(2,2-dicyanovinyl)-6-ethoxy-4-phenylpyridine (**3f**): General procedure was followed; medium-pressure chromatography was performed by using CH_2Cl_2/hexane 2:1 as eluent; yield: 0.62 g (90%); mp 212-214 °C (EtOH). ^1H Nmr ($CDCl_3$, 250 MHz): 3.33-3.37 (4H, m, $PhNCH_2$); 3.78-3.82 (4H, m, $PyNCH_2$); 6.82, 7.25 (4H, AB system, J = 8.8 Hz, H_{arom}); 7.51 (1H, s, =CH). ^{13}C Nmr ($CDCl_3$, 62.8 MHz): 48.1, 48.3 (NCH_2); 79.5 [C(CN)$_2$]; 114.1, 114.3 (CN); 117.0, 125.3, 129.3, 148.8 (C_{arom}); 156.7 (=CH). Ms (DEI, 70 eV): 496 (M^++2, 9); 495 (M^++1, 8); 494 (M^+, 24); 341 (6); 293 (5); 328 (12); 300 (22); 262 (8); 248 (7); 181 (6); 179 (18); 168 (33); 166 (100); 138 (22). Ms-high resolution: $C_{28}H_{23}ClN_6O$, calcd: 494.1622, found: 494.1623. Ir (KBr): 3060, 2970, 2930, 2900, 2840 (CH); 2220 (CN); 1600, 1580, 1560, 1515, 1500 (CC_{arom}) cm^{-1}.

3-Cyano-5-(2,2-dicyanovinyl)-2-ethoxy-6-[N-4-(4-nitrophenyl)piperazinyl]-4-phenylpyridine (**3g**): General procedure was followed; medium-pressure chromatography was performed by using CH_2Cl_2/hexane 4:1 as eluent; yield: 0.62 g (88%); mp 246-249 °C (EtOH:acetone 2:1). ^1H Nmr ($CDCl_3$, 250 MHz): 3.75 (8H, br s, NCH_2); 6.72, 8.12 (4H, AB system, J = 9.3 Hz, H_{arom}); 7.56 (1H, s, =CH). ^{13}C Nmr ($CDCl_3$, 62.8 MHz): 44.5, 47.6 (NCH_2); 79.3 [C(CN)$_2$]; 113.9, 114.2 (CN); 111.5, 126.0, 138.6, 153.5 (C_{arom}); 156.4 (=CH). Ms (DEI, 70 eV): 506 (M^++1, 11); 505 (M^+, 33); 475 (24); 341 (14); 328 (35); 315 (8); 300 (47); 273 (7); 262 (16); 248 (9); 178 (100); 161 (39). Ms-high resolution: $C_{28}H_{23}N_7O_3$, calcd: 505.1863, found: 505.1870. Ir (KBr): 3020, 2970, 2930, 2860 (CH); 2220 (CN); 1600, 1580, 1560, 1520 (CC_{arom}) cm^{-1}.

3-Cyano-5-(2,2-diyanovinyl)-2-ethoxy-4-phenyl-6-[N-4-(2-pyridyl)piperazinyl]pyridine (**3h**): General procedure was followed; medium-pressure chromatography was performed by using CH_2Cl_2/EtOH 100:1 as eluent; yield: 0.56 g (87%); mp 202-204 °C (EtOH:acetone 5:1). ^1H Nmr ($CDCl_3$, 250 MHz): 3.71-3.80 (8H, m, NCH_2); 6.61 (1H, d, J = 8.5 Hz, $H_{pyridyl}$), 6.68 (1H, dd, J = 4.9, 7.1 Hz, $H_{pyridyl}$); 7.51 (1H, s, =CH); 8.20 (1H, dd, J = 4.9, 1.9 Hz, $H_{pyridyl}$). ^{13}C Nmr ($CDCl_3$, 62.8 MHz): 44.0, 44.8 (NCH_2); 79.0 [C(CN)$_2$]; 106.9, 113.7, 137.7, 148.0, 158.9 ($C_{pyridyl}$); 114.1, 114.3 (CN); 156.5 (=CH). Ms (DEI, 70 eV): 462 (M^++1, 1); 461 (M^+, 4); 434 (5); 396 (59); 145 (20); 133 (39); 121 (35); 107 (100). Ms-high resolution: $C_{27}H_{23}N_7O$, calcd: 461.1964, found: 461.1988. Ir (KBr): 3040, 2975, 2890, 2850 (CH); 2220 (CN); 1580, 1570, 1515, 1485 (CC_{arom}) cm^{-1}.

3-Cyano-5-(2,2-dicyanovinyl)-2-ethoxy-4-phenyl-6-[N-4-[2-(1,3)pyrazinyl]piperazinyl]pyridine (**3i**): General procedure was followed; medium-pressure chromatography was performed by using CH_2Cl_2/EtOH 100:1 as eluent; yield: 0.63 g (98%); mp 270 °C (decomp.) (EtOH/acetone 4:1). ^1H Nmr ($CDCl_3$, 250 MHz): 3.70-3.75 (4H, m, $PhNCH_2$); 4.00-4.04 (4H, m, $PyNCH_2$); 6.59 (1H, t, J = 4.7 Hz, $H_{pirazinyl}$-5); 7.52 (1H, s, =CH); 8.34 (2H, d, J = 4.7 Hz, $H_{pirazinyl}$-4,6). ^{13}C Nmr ($CDCl_3$, 62.8 MHz): 42.9, 48.1 (NCH_2); 79.1 [C(CN)$_2$]; 110.7, 156.6, 161.2 ($C_{pirazinyl}$); 114.1, 114.4 (CN); 157.9 (=CH). Ms (DEI, 70 eV): 463 (M^++1, 12); 462 (M^+, 37); 435 (18); 397 (100); 367 (9); 343 (13); 326 (10); 312 (8); 300 (18); 146 (56); 134 (86); 121 (66). Ms-high resolution: $C_{26}H_{22}N_8O$, calcd: 462.1917, found: 462.1915. Ir (KBr): 3060, 3020, 2990, 2940, 2920, 2860 (CH); 2220 (CN); 1585, 1560, 1545, 1510 (CC_{arom}) cm^{-1}.

Hexahydro-1H-pyrazino[1,2-a][1,8]naphthyridine Derivatives (4a-i); General Procedure:

A solution of 2-(N-4-substituted piperazinyl)-5-cyano-3-(2,2,-dicyanovinyl)-6-ethoxy-4-phenylpyridines (**3a-i**, 0.12 mmol) in DMSO (5 ml) is heated at 140 °C for until all starting material had disappeared as checked by tlc. Upon cooling, reaction crude is poured into water (50 ml) and extracted with ethyl acetate (2 x 10 ml). The combined organic layers are dried over Na_2SO_4 and the solvent is

removed under reduced pressure. The resulting solid is purified by medium-pressure chromatography on a silica gel column (12 x 1 cm) to obtain (**4a-i**) as colorless solids.

All compounds (**4a-i**) exhibit typical absorption signals for the pyridine nucleus and its subtituents in the ^{1}H and ^{13}C Nmr: ^{1}H Nmr ($CDCl_3$, 250 MHz): 1.42-1.47 (3H, t, J = ~7.1 Hz, OCH_2CH_3); 4.43-4.49 (2H, q, J = ~7.1 Hz, OCH_2); 7.15-7.24 (m, $1H_{arom}$), 7.27-7.40 (m, $1H_{arom}$); 7.40-7.60 (m, $3H_{arom}$). ^{13}C Nmr ($CDCl_3$, 62.8 MHz): 14.3-14.4 (OCH_2CH_3); 63.2-63.3 (OCH_2); 86.7-89.8 (CN); 99.9-100.2, 112.0-112.4, 154.2-154.5, 156.4-156.7, 163.7-163.8 ($C_{pyridyl}$); [127.7-127.8, 128.0-128.1, 129.0-129.8 (2 or 3 absorptions), 133.3-133.6 (C_{phenyl})].

9-Ethoxy-N-3-methyl-7-phenyl-2,3,4,4a,5,6-hexahydro-1H-pyrazino[1,2-a][1,8]naphthyridino-5,5,8-tricarbonitrile (**4a**): General procedure was followed, heating the reaction solution for 7 h; medium-pressure chromatography was performed by using CH_2Cl_2/EtOH 100:1 as eluent; yield: 0.050 g (50%); mp 202-204 °C (EtOH). ^{1}H Nmr ($CDCl_3$, 250 MHz): 2.25 (1H, m ~ td, J = ~11.0, ~3.0 Hz, H_{ax}-2); 2.30 (1H, t, J = 10.9 Hz, H_{ax}-4); 2.44 (3H, s, NCH_3); 2.94-3.00 (1H, m, H_{eq}-2); 3.08 (1H, td, J = ~11.0, ~3.4 Hz, H_{ax}-1); 3.10, 3.20 (2H, AB system, J = 16.0 Hz, H-6); 3.35 (1H, ddd, J = 11.0, 3.4, 1.8 Hz, H_{eq}-4); 3.77 (1H, dd, J = 10.8, 3.4 Hz, H-4a); 4.82 (1H, m ~ ddd, H_{eq}-1). ^{13}C Nmr ($CDCl_3$, 62.8 MHz): 33.8 (C-6); 34.1 (C-5); 43.9 (C-2); 45.8 (NCH_3); 53.7 (C-4); 56.9 (C-4a); 57.0 (C-1); 113.4, 115.3 (CN). Ms (DEI, 70 eV): 399 (M^++1, 6); 398 (M^+, 23); 370 (3); 342 (5); 341 (13); 328 (6); 326 (5); 313 (4); 301 (5); 300 (8); 273 (4); 262 (5); 248 (4); 262 (5); 248 (4); 70 (100). Ms-high resolution: $C_{23}H_{22}N_6O$, calcd: 398.1855, found: 398.1850. Ir (KBr): 3050, 2980, 2940, 2850, 2810 (CH); 2220 (CN); 1590, 1570, 1555, 1500 (CC_{arom}) cm^{-1}.

N-3-Benzyl-9-ethoxy-7-phenyl-2,3,4,4a,5,6-hexahydro-1H-pyrazino[1,2-a][1,8]naphthyridino-5,5,8-tricarbonitrile (**4b**): General procedure was followed, heating the reaction solution for 13 h; medium-pressure chromatography was performed by using CH_2Cl_2/hexane 3:1 as eluent; yield: 0.045 g (45%); mp 176-178 °C (EtOH). ^{1}H Nmr ($CDCl_3$, 250 MHz): 2.23 (1H, td, J = ~12.5, ~3.3 Hz, H_{ax}-2); 2.41 (1H, t, J = 10.9 Hz, H_{ax}-4); 2.97-3.08 (1H, m, H_{ax}-1 and H_{eq}-2); 3.08, 3.21 (2H, AB system, J = 16.0 Hz, H-6); 3.43 (1H, ddd, J = 10.9, 3.4, 1.9 Hz, H_{eq}-4); 3.56, 3.75 (2H, AB system, J = 12.9 Hz, NCH_2Ph); 3.80 (1H, dd, J = 10.9, 3.4 Hz, H-4a); 4.75-4.83 (1H, m ~ ddd, H_{eq}-1); 7.26-7.36 (m, $5H_{arom}$). ^{13}C Nmr ($CDCl_3$, 62.8 MHz): 34.0 (C-6); 34.2 (C-5); 44.1 (C-2); 51.2 (C-4); 55.5 (C-1); 57.3 (C-4a); 62.5 (CH_2Ph); 113.4, 115.4 (CN); 127.7, 128.6, 136.7 (C_{arom}). Ms (DEI, 70 eV): 475 (M^++1, 4); 474 (M^+, 13); 397 (3); 383 (5); 356 (3); 340 (28); 328 (5); 244 (10); 243 (61); 201 (18); 146 (100); 91 (83). Ms-high resolution: $C_{29}H_{26}N_6O$, calcd: 474.2168, found: 474.2085. Ir (KBr) : 3060, 3000, 2980, 2940, 2820, 2780 (CH); 2220 (CN); 1590, 1570, 1555, 1495(CC_{arom}) cm^{-1}.

9-Ethoxy-7-phenyl-N-3-(2-trifluoromethylphenethyl)-2,3,4,4a,5,6-hexahydro-1H-pyrazino[1,2-a][1,8]naphthyridino-5,5,8-tricarbonitrile (**4c**): General procedure was followed, heating the reaction solution for 6 h; medium-pressure chromatography was performed by using CH_2Cl_2/hexane 4:1 as eluent; yield: 0.040 g (40%); mp 218-220 °C (EtOH). ^{1}H Nmr ($CDCl_3$, 250 MHz): 2.36 (1H, td, J = 11.5, 2.9 Hz, H_{ax}-2); 2.46 (1H, t, J = 10.9 Hz, H_{ax}-4); 2.73-2.82 (2H, m, CH_2Ph); 3.00-3.20 (4H, m, H_{ax}-1, H_{eq}-2 and NCH_2); 3.07, 3.23 (2H, AB system, J = 16.0 Hz, H-6); 3.42-3.47 (1H, m ~ ddd, H_{eq}-4); 3.79 (1H, dd, J = 10.9, 2.9 Hz, H-4a); 4.82-4.88 (1H, m ~ ddd, H_{eq}-1); 7.30-7.40 (m, $2H_{arom}$); 7.50-7.60 (m, $1H_{arom}$); 7.65 ($1H_{arom}$, d, J= 7.8 Hz). ^{13}C Nmr ($CDCl_3$, 62.8 MHz): 29.9 (CH_2Ph); 34.0 (C-6); 34.1 (C-5); 44.0 (C-2); 51.4 (C-4); 55.4 (C-1); 57.2 (C-4a); 59.3 (NCH_2); 113.4, 115.3 (CN); 122.4, 126.2, 126.3, 126.6, 126.8, 128.5, 131.5, 131.9, 138.0 (C_{arom}). Ms (DEI, 70 eV): 556 (M^+, 0.3); 398 (28); 397 (100); 369 (5); 344 (7); 299 (1). Ms-high resolution: $C_{31}H_{27}F_3N_6O$, calcd: 556.2198, found: 556.2194. Ir (KBr): 3050, 2990, 2950 (CH); 2220 (CN); 1590, 1570, 1500 (CC_{arom}) cm^{-1}.

9-Ethoxy-7-phenyl-N-3-(o-tolyl)-2,3,4,4a,5,6-hexahydro-1H-pyrazino[1,2-a][1,8]naphthyridino-5,5,8-tricarbonitrile (**4d**): General procedure was followed, heating the reaction solution for 30 h; medium-pressure chromatography was performed by using CH_2Cl_2/hexane 2:1 as eluent; yield: 0.080 g (80%); mp 179-182 °C (EtOH). ^{1}H Nmr ($CDCl_3$, 250 MHz): 2.37 (3H, s, $PhCH_3$); 2.97 (1H, td, J = ~10.5, 3.0 Hz, H_{ax}-2); 3.05 (1H, t, J = 10.7 Hz, H_{ax}-4); 3.19, 3.25 (2H, AB system, J = 16.1 Hz, H-6); 3.18-3.30 (2H, m, H_{ax}-1 and H_{eq}-2); 3.64-3.70 (1H, m, H_{eq}-4); 3.93 (1H, dd, J = 10.6, 3.4 Hz, H-4a); 4.90-4.98 (1H, m, H_{eq}-1); 7.08-7.18 (m, $2H_{arom}$); 7.23-7.30 (m, $2H_{arom}$). ^{13}C Nmr ($CDCl_3$, 62.8 MHz): 17.7 ($PhCH_3$); 33.9 (C-5, C-6); 44.7 (C-2); 51.1 (C-4); 54.4 (C-1); 57.9 (C-4a); 113.4, 115.3 (CN); 119.3, 124.7, 127.0, 131.4, 132.7, 149.7 (C_{arom}). Ms (DEI, 70 eV): 475 (M^++1, 7); 474 (M^+, 20); 340 (4); 326 (4); 300 (5); 261 (6); 158 (3); 147 (23); 146 (100); 134 (14); 118 (36). Ms-high resolution: $C_{29}H_{26}N_6O$, calcd: 474.2168, found: 474.2153. Ir (KBr): 3050, 2970, 2950, 2900, 2850 (CH); 2220 (CN); 1585, 1570, 1560, 1490(CC_{arom}) cm^{-1}.

9-Ethoxy-N-3-(4-fluorophenyl)-7-phenyl-2,3,4,4a,5,6-hexahydro-1H-pyrazino[1,2-a][1,8]naphthyridino-5,5,8-tricarbonitrile (**4e**): General procedure was followed, heating the reaction solution for 22 h; medium-pressure chromatography was performed by using CH_2Cl_2/hexane 4:1 as eluent; yield: 0.070 g (70%); mp 214-216 °C (EtOH). ^{1}H Nmr ($CDCl_3$, 250 MHz): 2.99 (1H, td, J = 11.9, 3.3 Hz, H_{ax}-2); 3.05 (1H, t, J = 9.7 Hz, H_{ax}-4); 3.14, 3.25 (2H, AB system, J = 16.0 Hz, H-6); 3.19-3.30 (1H, td, J = ~12.9, 3.4 Hz, H_{ax}-1); 3.57-3.63 (1H, m ~ ddd, H_{eq}-2); 3.90-3.96 (1H, dd, J = ~9.7, 3.5 Hz, H-4a); 3.94-4.01 (1H, m ~ ddd, H_{eq}-4); 4.90-4.98 (1H, m ~ ddd, H_{eq}-1); 6.95-7.08 (m, $4H_{arom}$). ^{13}C Nmr ($CDCl_3$, 62.8 MHz): 33.9 (C-5, C-6); 43.9 (C-2); 50.2 (C-4); 53.3 (C-1); 57.4 (C-4a); 113.4, 115.2 (CN); 116.1 (d, J = 21.9 Hz, C*orto*-F), 119.5 (d, J = 7.9 Hz, C*meta*-F), 146.5 (C*para*-F), 158 (d, J = 241 Hz, C*ipso*-F). Ms (DEI, 70 eV): 479 (M^++1, 9); 478 (M^+, 29); 449 (5); 441 (4); 328 (7); 300 (8); 262 (6); 150 (100); 122 (22). Ms-high resolution: $C_{28}H_{23}FN_6O$, calcd: 478.1917, found: 478.1910. Ir (KBr): 2980, 2920, 2850 (CH); 2220 (CN); 1580, 1570, 1560, 1510 (CC_{arom}) cm^{-1}.

N-3-(4-Chlorophenyl)-9-ethoxy-7-phenyl-2,3,4,4a,5,6-hexahydro-1H-pyrazino[1,2-a][1,8]naphthyridino-5,5,8-tricarbonitrile (**4f**): General procedure was followed, heating the reaction solution for 14 h; medium-pressure chromatography was performed by using CH_2Cl_2/hexane 5:4 as eluent; yield: 0.070 g (70%); mp 208-210 °C (EtOH). ^{1}H Nmr ($CDCl_3$, 250 MHz): 3.05 (1H, td, J = 11.9, 3.3 Hz, H_{ax}-2); 3.13 (1H, m ~ dd, H_{ax}-4); 3.16, 3.28 (2H, AB system, J = 16.0 Hz, H-6); 3.24-3.35 (1H, m ~ td, H_{ax}-1); 3.92 (1H, dd, J = 10.5, 3.4 Hz, H-4a); 3.55-3.63 (1H, m ~ dq, H_{eq}-2); 4.06 (1H, ddd, J = 11.7, 3.4, 2.0 Hz, H_{eq}-4); 4.88-4.93 (1H, m ~ dt, H_{eq}-1); 6.94, 7.21 (4H, AB system, J = 8.9 Hz, H_{arom}). ^{13}C Nmr ($CDCl_3$, 62.8 MHz): 33.9 (C-5, C-6); 43.6 (C-2); 49.2 (C-4); 52.0 (C-1); 57.2 (C-4a); 113.3, 115.2 (CN); 118.5, 126.8, 129.1, 148.4 (C_{arom}). Ms (DEI, 70 eV): 496 (M^++2, 15); 495 (M^++1, 14); 494 (M^+, 37); 431 (4); 341 (14); 300 (22); 262 (12); 160 (100); 138 (29). Ms-high resolution: $C_{28}H_{23}N_6OCl$, calcd: 494.1623, found: 494.1630. Ir (KBr): 3060, 2990, 2920, 2860, 2740 (CH); 2220 (CN); 1580, 1570, 1555, 1500 (CC_{arom}) cm^{-1}.

9-Ethoxy-N-3-(4-nitrophenyl)-7-phenyl-2,3,4,4a,5,6-hexahydro-1H-pyrazino[1,2-a][1,8]naphthyridino-5,5,8-tricarbonitrile (**4g**): General procedure was followed, heating the reaction solution for 36 h; medium-pressure chromatography was performed by using EtOAc/hexane 1:3 as eluent; yield: 0.850 g (85%); mp 238-240 °C (EtOH/acetone). ^{1}H Nmr ($CDCl_3$, 250 MHz): 3.17, 3.27 (2H, AB system, J = 16.0 Hz, H-6); 3.43 (1H, td, J = 12.7, 3.3 Hz, H_{ax}-2); 3.53-3.69 (2H, m, H_{ax}-1,4); 3.94-4.02 (1H, m, H_{eq}-4); 4.04 (1H, dd, J = 10.2, 3.3 Hz, H-4a); 4.33 (1H, dd, J = 12.7, 2.6 Hz, H_{eq}-2); 4.70-4.78 (1H, m ~ dt, H_{eq}-1); 6.90, 8.17 (4H, AB system, J = 9.3 Hz, H_{arom}). ^{13}C Nmr ($CDCl_3$, 62.8 MHz): 33.6 (C-6); 34.1 (C-5); 42.2 (C-2); 46.9 (C-4); 48.4 (C-1); 57.4 (C-4a); 113.2, 115.4 (CN); 113.3, 126.1, 139.9, 153.2 (C_{arom}). Ms (DEI, 70 eV): 506 (M^++1, 16); 505 (M^+, 48); 490 (4); 476 (5); 475 (7); 385 (4); 341 (13); 328 (33); 300 (42); 273 (7); 262 (16); 178 (100); 177 (56); 161 (46). Ms-high resolution: $C_{28}H_{23}N_7O_3$, calcd: 505.1863, found: 505.1859. Ir (KBr): 3080, 2980, 2860 (CH); 2220 (CN); 1600, 1580, 1570, 1520, 1500 (CC_{arom}) cm^{-1}.

9-Ethoxy-7-phenyl-N-3-(pyridin-2-yl)-2,3,4,4a,5,6-hexahydro-1H-pyrazino[1,2-a][1,8]naphthyridino-5,5,8-tricarbonitrile (**4h**): General procedure was followed, heating the reaction solution for 60 h; medium-pressure chromatography was performed by using CH_2Cl_2 as eluent; yield: 0.050 g (50%); mp 259-260 °C (EtOH/acetone). ^{1}H Nmr ($CDCl_3$, 250 MHz): 3.13, 3.24 (2H, AB system, J = 16.0 Hz, H-6); 3.23-3.44 (3H, m, H_{ax}-1,2,3); 3.92 (1H, dd, J = 10.3, 3.5 Hz, H-4a); 4.18-4.23 (1H, m, H_{eq}-2); 4.77-4.83 (1H, m, H_{eq}-4); 4.93 (1H, ddd, J = 12.9, 3.4, 1.4 Hz, H_{eq}-1); 6.72-6.77 (2H, m, $H_{piyridyl}$-2,4); 7.50-7.60 (1H, m, $H_{pyridyl}$-3); 8.23-8.26 (1H, m, $H_{pyridyl}$-5). ^{13}C Nmr ($CDCl_3$, 62.8 MHz): 33.8 (C-5); 34.2 (C-6); 42.7 (C-2); 45.2 (C-4); 46.5 (C-1); 57.1 (C-4a); 113.3, 115.3 (CN); 107.5, 114.8, 138.1, 148.2, 157.9 ($C_{pyridyl}$). Ms (DEI, 70 eV): 462 (M^++1, 8); 461 (M^+, 20); 435 (22); 434 (50); 405 (5); 397 (9); 396 (26); 367 (18); 107 (100). Ms-high resolution: $C_{27}H_{23}N_7O$, calcd: 461.1964, found: 461.1969. Ir (KBr): 3050, 3000; 2980, 2930, 2900, 2850 (CH); 2220 (CN); 1590, 1580, 1570, 1550 (CC_{arom}) cm^{-1}.

9-Ethoxy-7-phenyl-N-3-[1,3]pyrazino-2,3,4,4a,5,6-hexahydro-1H-pyrazino[1,2-a][1,8]naphthyridino-5,5,8-tricarbonitrile (**4i**): General procedure was followed, heating the reaction solution for 70 h; medium-pressure chromatography was performed by using CH_2Cl_2 as eluent; yield: 0.050 g (50%); mp >270 °C(decomp.)(EtOH/acetone 1:1). ^{1}H Nmr ($CDCl_3$, 250 MHz): 3.12, 3.24 (2H, AB system, J = 16.0 Hz, H-6); 3.22-3.40 (2H, m, H_{ax}-1,2); 3.41 (1H, dd, J = 13.2, 10.5 Hz, H_{ax}-4); 3.85 (1H, dd, J = 10.5, 3.6 Hz, H-4a); 4.69-4.89 (2H, m, H_{eq}-2,4); 5.31 (1H, ddd, J = 13.2, 3.6, 1.5 Hz, H_{eq}-1); 6.64 (1H, t, J =4.7 Hz, $H_{pirazinyl}$-5); 8.39 (2H, d, J = 4.7 Hz, $H_{pyrazinyl}$-4,6). ^{13}C Nmr ($CDCl_3$, 62.8 MHz): 33.8 (C-5); 34.1 (C-6); 43.2 (C-2,4); 45.1 (C-1); 57.1 (C-4a); 113.2, 115.3 (CN); 111.5, 158.0, 161.1 ($C_{pyrazinyl}$). Ms (DEI, 70 eV): 463 (M^++1, 4); 462 (M^+, 16); 461 (M^+-1, 13); 460 (M^+-2, 40); 436 (10); 435 (33); 434 (14); 397 (27); 367 (8); 353 (55); 108 (100). Ms-high resolution: $C_{26}H_{22}N_8O$, calcd: 462.1917, found: 462.1902. Ir (KBr): 3050, 2980, 2900, 2860 (CH); 2220 (CN); 1580, 1550 (CC_{arom}) cm^{-1}.

N,N-1,4-Bis(5-formyl-pyridin-6-yl)piperazine Derivatives (5a,b):

A solution of 2-chloro-5-cyano-6-ethoxy-3-formyl-4-phenylpyridine (**1**, 0.5 g, 1.75 mmol), piperazine or 2,5-dimethylpiperazine (0.875 mmol) and Et_3N (0.27 ml, 1.95 mmol) in THF (50 ml) is refluxed for 30 min. Upon cooling, precipitated Et_3NHCl is filtered, washed with THF (2 ml), and discarded. The solvent is removed under reduced pressure and the residue is purified by medium-pressure chromatography on a silica gel column (22 x 1.5 cm)

N,N-1,4-Bis(3-cyano-2-ethoxy-5-formyl-4-phenylpyridin-6-yl)piperazine (**5a**): General procedure was followed; medium-pressure chromatography was performed by using CH_2Cl_2 as eluent; yield: 0.41 g (80%); mp >270 °C (CH_2Cl_2). ^{1}H Nmr ($CDCl_3$, 250 MHz): 1.47 (6H, t, J = 7.1 Hz, OCH_2CH_3); 3.90 (8H, s, NCH_2); 4.53 (4H, q, J = 0 Hz, OCH_2); 7.44-7.54 (m, 10H_{arom}); 9.28 (2H, s, CHO). ^{13}C Nmr ($CDCl_3$, 62.8 MHz):14 2(OCH_2CH_3);48.9 (NCH_2);63.9(OCH_2); 87.0(CN);109.5;115.0, 159.1, 164.3, 165.5 ($C_{pyridyl}$); 128.8, 129.7, 130.4, 133.9 (C_{arom}); 186.2 (CHO). Ms (DEI, 70 eV): 597 (M^++1, 1); 596 (M^+, 5); 568 (3); 364 (11); 336 (21); 316 (29); 306 (24); 294 (36); 287 (24); 278 (26); 264 (26); 252 (30); 236 (27); 140 (24). Ms-high resolution: $C_{34}H_{30}N_6O_4$, calcd: 586.2329, found: 586.2316. Ir (KBr): 3060, 3010, 2980, 2930, 2870 (CH); 2220 (CN); 1665 (CO); 1585, 1565, 1515, 1490 (CC_{arom}) cm^{-1}.

N,N-1,4-Bis(3-cyano-2-ethoxy-5-formyl-4-phenylpyridin-6-yl)-trans-2,5-dimethylpiperazine (**5b**): General procedure was followed; medium-pressure chromatography was performed by using CH_2Cl_2 as eluent; yield: 0.38 g (71%); mp >270 °C (CH_2Cl_2). ^{1}H Nmr ($CDCl_3$, 250 MHz): 1.30 (6H, d, J = 6.6 Hz, $NCHCH_3$); 1.47 (6H, t, J = 7.1 Hz, OCH_2CH_3); 3.71-3.78 (2H, m, NCH_{ax}); 4.10 (2H, dd, J = 14.0, 3.5 Hz, NCH_{eq}); 4.45-4.59 (4H, m, OCH_2); 4.60-4.75 (2H, m, $NCHCH_3$); 7.30-7.40 (m, 2H_{arom}); 7.50-7.60 (m, 8H_{arom}); 9.23 (2H, s, CHO). Ms (DEI, 70 eV): 614 (M^+, 6); 335 (24); 334 (100); 320 (20); 308 (70); 306 (50); 294 (58); 278 (66); 195 (36); 140 (55). Ms-

high resolution: $C_{36}H_{34}N_6O_4$, calcd: 614.2643, found: 614.2653. Ir (KBr): 3050, 3000, 2970, 2940, 2880 (CH); 2220 (CN); 1665 (CO); 1580, 1560, 1510 (CC_{arom}) cm^{-1}.

N,N-1,4-Bis(5-(2,2-dicyanovinyl)pyridin-6-yl)piperazine Derivatives (6a,b):

A solution of N,N-1,4-bis(5-formyl-pyridin-6-yl)piperazine derivative (**5a** or **5b**, 0.42 mmol), malononitrile (0.11 g, 0.42 mmol), *n-butylamine (0.04 ml, 0.42 mmol) and* NH_4OAc *(0.03 g, 0.42 mmol)* in CH_2Cl_2 (50 ml) is refluxed for 1 h. Upon cooling, the solvent is removed under reduced pressure and the resulting solid is purified by medium-pressure chromatography on a silica gel column (15 x 1.5 cm) using CH_2Cl_2 as eluent.

N,N-1,4-Bis(3-cyano-5-(2,2-dicyanovinyl)-2-ethoxy-4-phenylpyridin-6-yl)piperazine (**6a**): General procedure was followed; yield: 0.26g (91%); mp >270 °C (CH_2Cl_2). ^1H Nmr ($CDCl_3$, 250 MHz): 1.45 (6H, t, J = 7.1 Hz, OCH_2CH_3); 3.78 (8H, s, NCH_2); 4.58 (4H, q, OCH_2); 7.27-7.35 (m, $4H_{arom}$); 7.55-7.60 (8H, m, H_{arom} and =CH). ^{13}C Nmr ($CDCl_3$, 62.8 MHz): 14 0 (OCH_2CH_3); 47.0 (NCH_2); 63.8 (OCH_2); 78.8 [$C(CN)_2$]; 86.6 (PyCN); 103.4, 112.1, 158.2, 160.5, 162.7 ($C_{pyridyl}$); 128.8, 129.9, 133.6 (C_{arom}); 157.9 (=CH). Ms (DEI, *70 eV): 682 (M^+, 32); 655 (5); 617 (100);* 589 (12); 564 (12); 551 (15); 523 (7); 493 (4); 367 (14); 341 (17); 326 (13); 312 (17); 300 (36); 262 (16); 248 (22). Ms-high resolution: $C_{42}H_{34}N_{10}O_2$, calcd: 682.2553, found: 682.2581. Ir (KBr): 3060, 3020, 2990, 2920, 2860 (CH); 2220 (CN); 1570, 1510, 1490 (CC_{arom}) cm^{-1}.

N,N-1,4-Bis(3-cyano-5-(2,2-dicyanovinyl)-2-ethoxy-4-phenylpyridin-6-yl)-trans-2,5-dimethylpiperazine (**6b**): General procedure was followed; yield: 0.22g (75%); mp >270 °C (CH_2Cl_2). ^1H Nmr ($CDCl_3$, 250 MHz): 1.42 (6H, d, J = 6.1 Hz, $NCHCH_3$); 1.46 (6H, t, J = 7.1 Hz, OCH_2CH_3); 3.18 (2H, dd, J = 13.5, 6.3 Hz, NCH_{ax}); 3.53 (2H, br d, J = 13.5 Hz, NCH_{eq}); 4.44-4.60 (4H, m, OCH_2); 4.65-4.71 (2H, m, $NCHCH_3$); 7.25-7.33 (m, $2H_{arom}$); 7.52-7.67 (8H, m, $6H_{arom}$ and 2 =CH). ^{13}C Nmr ($CDCl_3$, 62.8 MHz): 14.2 (OCH_2CH_3); 18.1 ($NCHCH_3$); 51.7 (NCH_2); 54.2 ($NCHCH_3$); 64.2 (OCH_2); 80.9 [$C(CN)_2$]; 89.3 (PyCN); 103.9, 111.9, 159.4, 161.4, 103.6 ($C_{pyridyl}$); 113.6, 114.1 [$C(CN)_2$]; 128.4, 129.3, 130.5, 133.3 (C_{phenyl}). Ms (DEI, 70 eV): 711 (M^++ 1, 14), 710 (M^+, 30); 382 (46); 356 (50); 329 (100); 300 (46); 262 (59). Ms-high resolution: $C_{42}H_{34}N_{10}O_2$, calcd: 710.2867, found: 710.2872. Ir (KBr): 3050, 2975, 2930, 2860 (CH); 2220 (CN); 1580, 1560, 1520, 1490 (CC_{arom}) cm^{-1}.

5,13-Diethoxy-trans-8a,16a-dimethyl-3,11-diphenyl-1,2,8,8a,10,16,16a-octahydropyrazino[1,2-a:4,5-a']bis[1,8]naphthyridin-1,1,4,9,9,12-hexacarbonitrile (**7**): A solution of N,N-1,4-bis(3-cyano-5-(2,2-dicyanovinyl)-2-ethoxy-4-phenylpyridin-6-yl)-trans-2,5-dimethylpiperazine (**6**, 0.1 g) in DMSO (5 ml) is heated at 140 °C for until all starting material had disappeared as checked by tlc. Upon cooling, reaction crude is poured into water (50 ml) and extracted with ethyl acetate (2 x 10 ml). The combined organic layers are dried over Na_2SO_4 and the solvent is removed under reduced pressure. The resulting solid is purified by medium-pressure chromatography on a silica gel column (12 x 1 cm) to obtain 0.08 g (80%) of **7** as colorless solids. mp >270 °C (decomp) (CH_2Cl_2). ^1H Nmr ($CDCl_3$, 250 MHz): 1.47 (3H, t, J = 7.1 Hz, OCH_2CH_3); 1.57 (6H, s, $NCCH_3$); 3.22 (4H, s, H-2,10); 4.07, 5.00 (2H, AB system, J = 14.2 Hz, H-8,16); 4.50 (2H, q, J = 7.1 Hz, OCH_2); 7.21-7.24 (m, $2H_{pyridyl}$), 7.36-7.40 (m, $2H_{pyridyl}$); 7.53-7.64 (m, $6H_{pyridyl}$). ^{13}C Nmr ($CDCl_3$, 62.8 MHz): 14.3 (OCH_2CH_3); 17.8 [$C(CH_3)$]; 31.4 (C-2,10); 37.9 (C-1,9); 47.2 C-8,16); 59.3 (C-8a,16a); 63.8 (OCH_2); 89.2 (CN); 100.3, 113.1, 152.6, 159.3, 163.8 ($C_{pyridyl}$); 113.2, 114.6 [$C(CN)_2$]; 127.6, 128.1, 129.3, 129.7, 130.0, 134.1 (C_{phenyl})]. *Ms (DEI, 70 eV): 710 (M^+, 21);* 340 (13); 329 (100); 326 (25); 301 (30); 262 (42); 236 (24); 180 (35); 152 (36). Ms-high resolution: $C_{42}H_{34}N_{10}O_2$, calcd: 710.2867, found: 710.2880. Ir (KBr): 3050, 3000, 2980, 2930, 2870 (CH); 2220 (CN); 1580, 1565 (CC_{arom}) cm^{-1}.

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