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Synthesis of Fused Pyrido[2,3-*d*]pyrimidines by Thermal Isomerization of 4-Amino-5-vinylpyrimidines

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Abstract: 4-dialkylamino-5-(2,2-dicyanovinyl)pyrimidines **4a-c** react thermally in DMSO via [1,5] hydrogen transfer followed by carbon-carbon bond formation to yield fused pyrido[2,3-*d*]pyrimidines **6a-c**. 4-alkylarylamino-5-(2,2-dicyanovinyl)pyrimidines **5a-c** lend themselves more readily to thermal electrocyclic ring-closure followed by aromatization, to give tetracyclic fused pyrido[2,3-*d*]pyrimidines **7a-c.**

The term "*tert*-amino effect" was introduced by Meth-Cohn and Suschitzky to generalize cyclization reactions of *ortho*-substituted tertiary anilines with at least one heteroatom in the unsaturated *ortho*-substituent.[1] The first reaction of this type was reported by Pinnow.[2] The scope and limitations of the *tert*-amino effect for the synthesis of heterocyclic compounds has been published on the application of this principle, notably by Verboom and Reinhoudt's group.[3] They have discovered a variety of new reaction types of the t-amino effect and applied them to key target syntheses. Recently, Meth-Cohn collected the available material related to this topic and classifies the reactions into five types.[4]

In the course of our investigations of the t-amino effect in heterocyclic chemistry we have recently reported the formation of several heterotri- and heterotetracyclic compounds by extending application of the t-amino effect to 2-amino-3-vinylpyridines and introduced the electrocyclization of 3-aza-hexatriene systems in the t-amino chemistry as a convenient approach to several fused [1,8]naphthyridines.[5] These new heterotetracyclic compounds containing the [1,8]naphthyridine group were synthesized in two ways: by a t-amino effect similar to those reported by Reinhoudt *et al*, [6] or by an electrocyclization/aromatization sequence which involved an unprecedented reaction in the *tert*-amino effect chemistry [5e]. The significant biological activity exhibited by *N*-heterocyclic compounds containing the pyrimidine ring, particularly in cancer and virus research,[7] prompted us to apply the same methodology to 2-vinyl substituted 4-aminopyrimidines. This paper reports a convenient route to the synthesis of new tricyclic and tetracyclic 1,3,4-triazanaphthalene derivatives **6a-c** and **7a-c**. These *N*-heterocycles containing the pyrido[2,3-*d*]pyrimidine nucleus are expected to show interesting biological properties.

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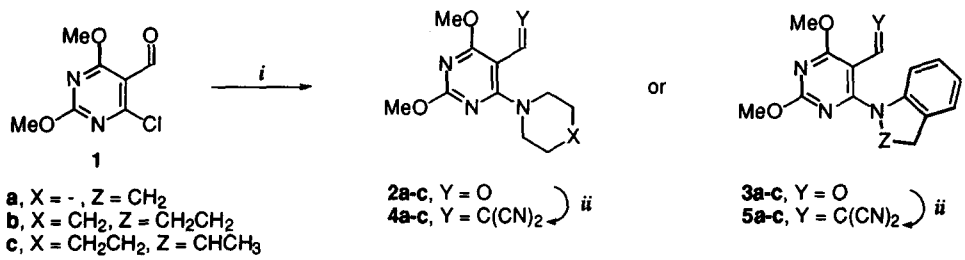
The starting compounds for the thermal isomerization were conveniently prepared from 4-chloro-5-formyl-2,6-dimethoxypyrimidine **1**, which was obtained as reported in the literature.[8] Nucleophilic substitution of the chlorine atom of 4-chloro-5-formyl derivative **1** by an appropriate secondary amine in tetrahydrofuran in the presence of triethylamine gave, in yields of more than 90% after flash chromatography, the corresponding 4-dialkylamino-5-formylpyrimidine derivatives **2a-c** or 4-alkylarylamino-5-formylpyrimidine **3a-c** (see scheme 1). The formation of the desired aldehydes **2** and **3** was concluded by ^{1}H NMR [δ = 9.86-10.16, (1H, s, CHO)] and decoupled ^{13}C NMR spectroscopy [δ = 184.0-184.9 (CO)]. Knoevenagel condensation of **2a-c** or **3a-c** with malononitrile in toluene at room temperature (piperidine as catalyst) afforded the corresponding 4-dialkylamino- **4a-c** or 4-alkylarylamino-5-(2,2-dicyanovinyl)pyrimidine derivatives **5a-c**. After purification by column chromatography, compounds **4** and **5** could be isolated as yellow-orange solids with high yields. The signals of R$\underline{H}$CC(CN)$_2$ in the ^{1}H NMR spectra between δ = 7.71 and 8.03 as singlets and the RH$\underline{C}$C(CN)$_2$ absorption in the decoupled ^{13}C NMR spectra between δ = 152.3 and 154.3 are typical of these dicyanoethylene derivatives.

Scheme 1



a, X = -, Z = CH_2
b, X = CH_2, Z = CH_2CH_2
c, X = CH_2CH_2, Z = $CHCH_3$

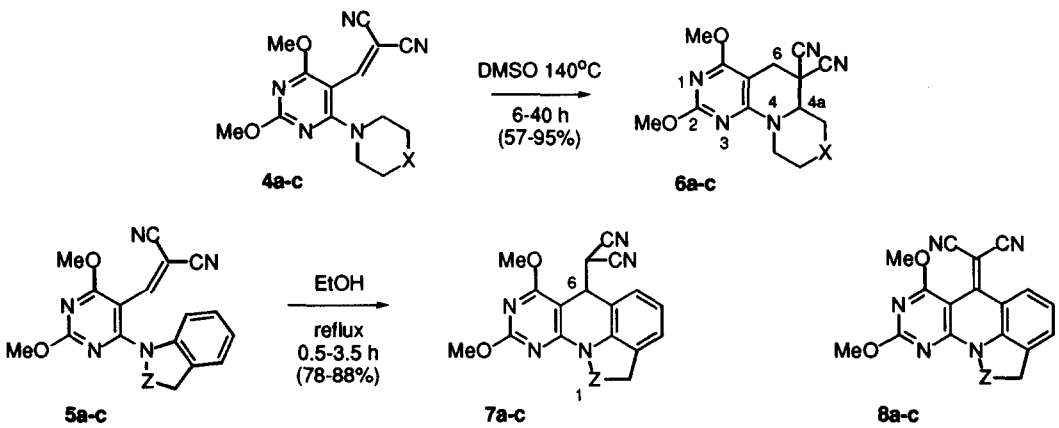
2a-c, Y = O
4a-c, Y = $C(CN)_2$

3a-c, Y = O
5a-c, Y = $C(CN)_2$

Reagents and conditions:
i. amine, Et_3N, THF, rt. or reflux, 5 min to 24 h (80-99%). *ii.* malononitrile, toluene, rt or reflux, 1 to 5 h (90-99%)

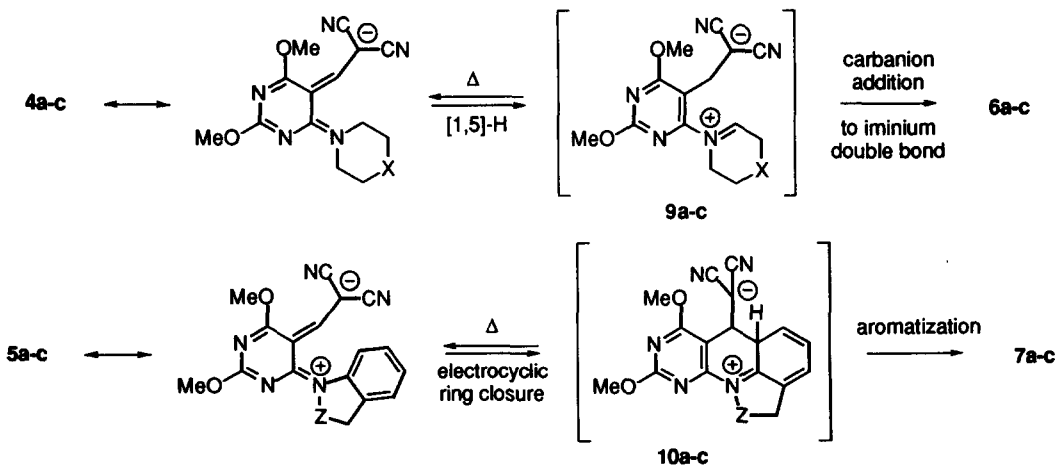
Heating **4a-c** in dimethyl sulfoxide (at 140 °C) resulted in the corresponding fused heterocyclic compounds **6a-c** as colorless solids with moderate to good yields (see scheme 2). All these compounds exhibited one characteristic signal in the ^{1}H NMR for the methylene protons at the position 6 as AB quartets with δ = 2.03-3.14 and 3.37-3.40 and a coupling constant of *ca* 16 Hz. Heating of a solution of β,β-dicyanoethylene derivatives **5a,b** in a polar solvent (DMSO, ethanol or methanol) converted them into the corresponding cyclized products **7a** and **7b** in 78 and 73 %, respectively. The ^{1}H NMR spectra of compounds **7a** and **7b** show characteristics signals at δ = 4.08 and 4.98 (AB system, J = 4.1 Hz) for **7a** and δ = 3.83 and 4.88 (AB system, J = 4.7 Hz) for **7b** for the R$_2\underline{H}$C$\underline{C}$H(CN)$_2$ absorptions. Correlation of these signals with the R$_2$H$\underline{C}\underline{C}(CN)_2$ absorptions (at δ = 30.0 and 38.1 for **7a** and δ = 30.2 and 37.9 for **7b**) in the ^{13}C NMR spectra was checked by ^{1}H-^{13}C CORR experiments. Similarly, heating **5c** gave rise to the cyclic compound **7c**, which was obtained as a mixture of two diastereoisomers in a 4:1 ratio, that was calculated by integration of analogous signals in the ^{1}H NMR spectra. Fused pyridopyrimidines **7a-c** were partially oxidized to derivatives **8a-c** when chromatographyed on silica gel. Thus, compounds **7a-c** were purified by crystallization.

Scheme 2



The thermal isomerization can be assumed to occur in two consecutive reactions (Scheme 3). The first step in the cyclization of **4a-c** involves a thermal suprafacial [1,5]-hydrogen shift of one of the α-methylene protons adjacent to the nitrogen of the amino group to yield the 1,5-dipolar intermediate **9**. The " negative end " of **9** is stabilised by the presence of two electron withdrawing groups. Subsequently, intramolecular addition of the carbanion to the iminium double bond affords the cyclized products **6a-c**. Cyclization of 4-alkylarylamino-5-vinylpyrimidines **5a-c** implicates the formation of a new carbon-carbon bond between the α-position of the vinyl group and a β-methine group to the nitrogen of the amino moiety, which must involve a 1,5-dipolar intermediate **10**, the result of the electrocyclization of the 3-aza-1,3,5-hexatriene system included in one resonance canonical form of **5**. Subsequently, loss of a proton by intermediate **10** in an aromatization process makes the cyclization irreversible. This electrocyclization process, which involves a 3-aza-1,3,5-hexatriene system, while scarcely mentioned in the literature has so far been used in the synthesis of pyridines,[9] quinolines,[10] acridines,[11] and phenanthiridines[12].

Scheme 3



EXPERIMENTAL PART

All reagents used were commercial grade chemicals from freshly opened containers. Melting points were determined on a Büchi 510 apparatus and are reported uncorrected. IR (υ, cm^{-1}) spectra were recorded as potassium bromide disks on a Perkin-Elmer 383 spectrophotometer. ^1H (δ, ppm) and ^{13}C NMR (δ, ppm) spectra were obtained on a Brucker AC 200F instrument at room temperature. Mass spectra (EI, m/z, %) were obtained at 70eV using a VG QUATTRO spectrometer. The Silica gel 60 $HF_{254+366}$ sheets used for analytical thin layer chromatography and the Silica gel 60 (230-400 mesh) employed for flash chromatography were purchased from Merck. Microanalyses for C, H, and N were performed by the Elemental Analyses General Service of the Universidade da Coruña.

4-Amino-5-formyl-2,6-dimethoxypyrimidines 2a-c, 3a-c. General Procedure

A solution of 4-chloro-5-formyl-2,6-dimethoxypyrimidine **1** (0.5 g, 2.47 mmol), a suitable secondary amine (2.72 mmol) and Et_3N (0.52 mL, 3.7 mmol) in THF (8 mL) was stirred at room temperature for 15 min (methylindoline for 24 h and 1,2,3,4-tetrahidroquinoline at reflux for 7 h). The Et_3NHCl precipitated is filtered off, washed with THF (10 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-c** and **3a-c** as colorless solids or oils.

5-formyl-2,6-dimethoxy-4-(*N*-pyrrolidinyl)pyrimidine **2a**: General procedure was followed; medium-pressure chromatography was performed by using CH_2Cl_2/AcOEt (97:3) as eluent to yield: 0.59 g (100%) of 2a as a pale yellow oil. ^1H-NMR: 1.90 (4H, m, $NCH_2C\underline{H}_2$); 3.49 (4H, m, NCH_2); 3.92 (3H, s, OCH_3); 3.98 (3H, s, OCH_3); 10.06 (1H, s, CHO). ^{13}C-NMR: 25.1 ($NCH_2\underline{C}H_2$); 50.6 (NCH_2); 54.2 (OCH_3); 54.5 (OCH_3); 96.2, 161.0, 164.2, 174.4 (Py); 184.9 (CHO). MS: 238 (M^++1, 8); 237 (M^+, 56); 222 (12); 220 (34); 209 (23); 208 (57); 181 (41); 180 (100); 168 (41); 149 (62). IR: 2950, 2870 (CH); 1660 (CO); 1580, 1520 (CC). Anal. Calcd. for $C_{11}H_{15}N_3O_3$: C, 55.69; H, 6.37; N, 17.71. Found: C, 55.60; H, 6.47; N, 17.90.

5-formyl-2,6-dimethoxy-4-(*N*-piperidinyl)pyrimidine **2b**: General procedure was followed; medium-pressure chromatography was performed by using AcOEt/hexane (1:3) as eluent; yield: 0.59 g (95%); mp 62-64 °C (EtOH). ^1H-NMR: 1.64 (6H, m, $NCH_2C\underline{H}_2C\underline{H}_2$); 3.55 (4H, m, NCH_2); 3.91 (3H, s, OCH_3); 3.98 (3H, s, OCH_3); 9.92 (1H, s, CHO). ^{13}C-NMR: 24.1 ($NCH_2CH_2\underline{C}H_2$); 26.0 ($NCH_2\underline{C}H_2$); 50.2 ($NCH_2$); 54.4 ($OCH_3$); 54.6 ($OCH_3$); 96.1, 163.4, 164.9, 175.4 (Py); 184.0 (CHO). MS: 252 (M^++1, 4); 251 (M^+, 31); 250 (M^+-1, 3); 234 (73); 168 (22); 86 (43); 84 (100). IR: 2930, 2860 (CH); 1670 (CO); 1580, 1530 (CC). Anal. Calcd. for $C_{12}H_{17}N_3O_3$: C, 57.36; H, 6.82; N, 16.72. Found: C, 57.20; H, 6.89; N, 16.80.

5-formyl-4-(*N*-hexamethyleneiminyl)-2,6-dimethoxypyrimidine **2c**: General procedure was followed; medium-pressure chromatography was performed by using AcOEt/hexano (1:3) as eluent to yield: 0.65 g (99%) of 2c as a pale yellow oil. ^1H-NMR: 1.53 (4H, m, $NCH_2CH_2C\underline{H}_2$); 1.90 (4H, m, $NCH_2C\underline{H}_2$); 3.58 (4H, br s, NCH_2); 3.95 (3H, s, OCH_3); 4.02 (3H, s, OCH_3); 10.03 (1H, s, CHO). ^{13}C-NMR: 27.5 ($NCH_2CH_2\underline{C}H_2$); 28.0 ($NCH_2\underline{C}H_2$); 51.2 ($NCH_2$); 54.4 ($OCH_3$); 54.6 ($OCH_3$); 96.1, 163.7, 164.0, 175.2 (Py); 184.8 (CHO). MS: 266 (M^++1, 6); 265 (M^+, 47); 264 (M^+-1, 15); 248 (100); 208 (19); 180 (16). IR: 2940, 2850 (CH); 1660 (CO); 1580, 1510 (CC). Anal. Calcd. for $C_{13}H_{19}N_3O_3$: C, 58.85; H, 7.22; N, 15.84. Found: C, 58.77; H, 7.29; N, 15.72.

5-formyl-4-(*N*-indolinyl)-2,6-dimethoxypyrimidine **3a**: General procedure was followed; medium-pressure chromatography was performed by using CH_2Cl_2/hexane (3:1) as eluent; yield: 0.70 g (100%); mp 154-156 °C (EtOH). ^1H-NMR: 3.13 (2H, t, J = 7.9 Hz, $NCH_2C\underline{H}_2$); 3.94-4.03 (5H, m, NCH_2, OCH_3); 4.07 (3H, s, OCH_3); 7.01-7.05 (1H, m, Ph); 7.17-7.26 (2H, m, Ph); 7.63-7.68 (1H, m, Ph); 10.16 (1H, s, CHO). ^{13}C-NMR: 28.9 ($NCH_2\underline{C}H_2$); 54.1 (NCH_2); 54.6 (OCH_3); 55.1 (OCH_3); 117.9, 123.7, 124.8, 126.3, 133.1, 143.0 (Ph); 97.5, 160.1, 164.9, 174.5 (Py); 184.7 (CHO). MS: 286 (M^++1, 16); 285 (M^+, 90); 284 (M^+-1, 15); 268 (26); 256 (52); 242 (22); 140 (23); 118 (100); 117 (43). IR: 3000, 2960, 2920, 2850 (CH); 1660 (CO); 1580, 1540, 1520 (CC). Anal. Calcd. for $C_{15}H_{15}N_3O_3$: C, 63.15; H, 5.30; N, 14 73. Found: C, 63.28; H, 5.35; N, 14.60.

5-formyl-2,6-dimethoxy-4-(*N*-1,2,3,4-tetrahydroquinolenyl)pyrimidine **3b**: General procedure was followed; medium-pressure chromatography was performed by using CH_2Cl_2/hexane (3:1) as eluent; yield: 0.59 g (80%); mp 152-154 °C (EtOH). ^{1}H-NMR: 2.02 (2H, tt., J = 6.7, 6.4 Hz, $NCH_2C\underline{H}_2$); 2.84 (2H, t, J = 6.7 Hz, CH_2Ph); 3.88 (2H, t, J = 6.4 Hz, NCH_2); 3.96 (3H, s, OCH_3); 4.06 (3H, s, OCH_3); 6.96-7.18 (4H, m, Ph); 9.86 (1H, s, CHO). ^{13}C-NMR: 23.8 ($NCH_2\underline{C}H_2$); 26.5 (CH_2Ph); 48.4 (NCH_2); 54.6 (OCH_3); 54.9 (OCH_3); 120.1, 123.9, 126.0, 129.0, 130.5, 141.6 (Ph); 98.7, 164.5, 165.4, 173.8 (Py); 184.3 (CHO). MS: 300 (M^++1, 15); 299 (M^+, 100); 298 (M^+-1, 21); 283 (15); 282 (96); 270 (23); 132 (75); 130 (48). IR: 2920, 2850 (CH); 1670 (CO); 1570, 1530 (CC). Anal. Calcd. for $C_{16}H_{17}N_3O_3$: C, 64.20; H, 5.72; N, 14.04. Found: C, 64.32; H, 5.84; N, 14.10.

5-formyl-2,6-dimethoxy-4-(*N*-2-methylindolinyl)pyrimidine **3c**: General procedure was followed; medium-pressure chromatography was performed by using CH_2Cl_2/hexane (3:1) as eluent to yield: 0.73 g (99%) of 3c as a pale yellow oil. ^{1}H-NMR: 1.40 (3H, d, J = 6.1 Hz, $NCHC\underline{H}_3$); 2.76 (1H, dd, J = 4.9, 15.4 Hz, $PhC\underline{H}_2$); 3.40 (1H, dd, J = 8.5, 15.4 Hz, $PhC\underline{H}_2$); 4.03 (3H, s, OCH_3); 4.10 (3H, s, OCH_3); 4.94-5.04 (1H, m, $NC\underline{H}CH_3$); 6.90-7.11 (3H, m, Ph); 7.19-7.27 (1H, m, Ph); 10.05 (1H, s, CHO). ^{13}C-NMR: 19.8 ($NCH\underline{C}H_3$); 36.5 ($PhCH_2$); 54.7 (OCH_3); 55.0 (OCH_3); 60.1 ($N\underline{C}HCH_3$); 113.9, 122.9, 125.1, 126.3, 131.6, 143.1 (Ph); 99.3, 160.1, 165.5, 173.9 (Py); 184.2 (CHO). MS: 300 (M^++1, 13); 299 (M^+, 83); 298 (M^+-1, 17); 284 (35); 281 (20); 266 (50); 256 (30); 209 (28); 132 (100); 130 (42); 117 (46). IR: 2940, 2920, 2850 (CH); 1680 (CO); 1570, 1530 (CC). Anal. Calcd. for $C_{16}H_{17}N_3O_3$: C, 64.20; H, 5.72; N, 14.04. Found: C, 64.29; H, 5.80; N, 13.97.

4-Amino-5-(2,2-dicyanovinyl)-2,6-dimethoxypyrimidines 4a-c, 5a-c. General Procedure

A solution of **2a-c** or **3a-c** (1.3 mmol), malononitrile (0.17 g, 2.6 mmol) and piperidine (2 drops) in toluene was stirred at room temperature for 1-5 h (TLC monitored). The solvent was removed under reduced pressure and the resulting solid was purified by MPLC on a silica gel column (15 x 1.5 cm) to obtain **4a-c** and **5a-c**.

5-(2,2-dicyanovinyl)-2,6-dimethoxy-4-(*N*-pirrolidinyl)pyrimidine **4a**: General procedure was followed; medium-pressure chromatography was performed by using CH_2Cl_2 as eluent; yield: 0.37 g (100%); mp 143-145 °C (EtOH). ^{1}H-NMR: 2.03 (4H, m, $NCH_2C\underline{H}_2$); 3.44 (4H, m, NCH_2); 3.97 (3H, s, OCH_3); 4.02 (3H, s, OCH_3); 8.03 (1H, s, CH=C). ^{13}C-NMR: 25.3 ($NCH_2\underline{C}H_2$); 50.6 (NCH_2); 54.4 (OCH_3); 54.9 (OCH_3); 76.7 ($\underline{C}(CN)_2$); 112.3 (CN); 115.2 (CN); 153.6 ($\underline{C}H$=C); 91.1, 161.4, 164.5, 170.4 (Py). MS: 286 (M^++1, 11); 285 (M^+, 74); 270 (63); 259 (25); 256 (43); 245 (43); 231 (42); 220 (47); 70 (100). IR: 2940, 2920, 2860 (CH); 2220 (CN); 1570, 1530 (CC). Anal. Calcd. for $C_{14}H_{15}N_5O_2$: C, 58.94; H, 5.30; N, 24.55. Found: C, 59.18; H, 5.38; N, 24.41.

5-(2,2-dicyanovinyl)-2,6-dimethoxy-4-(*N*-piperidinyl)pyrimidine **4b:** General procedure was followed; medium-pressure chromatography was performed by using CH_2Cl_2/MeOH (99:1) as eluent; yield: 0.38 g (99%); mp 106-108 °C (EtOH). ^{1}H-NMR: 1.62 (6H, m, $NCH_2C\underline{H}_2C\underline{H}_2$); 3.56 (4H, m, NCH_2); 3.94 (3H, s, OCH_3); 3.99 (3H, s, OCH_3); 7.71 (1H, s, CH=C). ^{13}C-NMR: 24.1 ($NCH_2CH_2\underline{C}H_2$); 26.1 ($NCH_2\underline{C}H_2$); 49.9 ($NCH_2$); 54.5 ($OCH_3$); 55.1 ($OCH_3$); 76.8 ($\underline{C}(CN)_2$); 113.1 (CN); 115.5 (CN); 153.4 ($\underline{C}H$=C); 91.3, 165.3, 165.7, 170.8 (Py). MS: 300 (M^++1, 9); 299 (M^+, 37); 259 (100); 234 (48); 232 (42); 218 (50); 217 (41); 192 (40); 149 (86). IR: 2960, 2940, 2850 (CH); 2220 (CN); 1560, 1520 (CC). Anal. Calcd. for $C_{15}H_{17}N_5O_2$: C, 60.19; H, 5.72; N, 23.40. Found: C, 60.05; H, 5.63; N, 23.52.

5-(2,2-dicyanovinyl)-4-(*N*-hexamethyleneiminyl)-2,6-dimethoxypyrimidine **4c:** General procedure was followed; medium-pressure chromatography was performed by using CH_2Cl_2 as eluent; yield: 0.38 g (94%); mp 89-91 °C (EtOH). ^{1}H-NMR: 1.57 (4H, m, $NCH_2CH_2C\underline{H}_2$); 1.96 (4H, m, $NCH_2C\underline{H}_2$); 3.48 (4H, m, NCH_2); 3.98 (3H, s, OCH_3); 4.02 (3H, s, OCH_3); 8.02 (1H, s, CH=C). ^{13}C-NMR: 27.4 ($NCH_2CH_2\underline{C}H_2$); 28.2 ($NCH_2\underline{C}H_2$); 51.1 ($NCH_2$); 54.6 ($OCH_3$); 54.8 ($OCH_3$); 75.8 ($\underline{C}(CN)_2$); 112.5 (CN); 115.2 (CN); 154.3 ($\underline{C}H$=C); 90.3, 164.1, 164.5, 170.9 (Py). MS: 314 (M^++1, 6); 313 (M^+, 32); 274 (14); 273 (100); 248 (44); 245 (30). IR: 2920, 2850 (CH); 2220 (CN); 1580, 1530 (CC). Anal. Calcd. for $C_{16}H_{19}N_5O_2$: C, 61.33; H, 6.11; N, 22.35. Found: C, 61.46; H, 6.03; N, 22.27.

5-(2,2-dicyanovinyl)-4-(*N*-indolinyl)-2,6-dimethoxypyrimidine **5a:** General procedure was followed; medium-pressure chromatography was performed by using CH_2Cl_2/hexane (3:1) as eluent; yield: 0.43 g (100%); mp 184-186 °C (EtOH). ^{1}H-NMR: 3.20 (2H, t, J = 7.8 Hz, $NCH_2C\underline{H}_2$); 4.01 (3H, s, OCH_3); 4.09

(3H, s, OCH_3); 4.18 (2H, t, J = 7.8 Hz, NCH_2); 6.77-6.80 (1H, m, Ph); 6.98-7.06 (1H, m, Ph); 7.10-7.18 (1H, m, Ph); 7.25-7.29 (1H, m, Ph); 7.93 (1H, s, CH=C). ^{13}C-NMR: 28.8 ($NCH_2\underline{C}H_2$); 53.6 (NCH_2); 54.8 (OCH_3); 55.3 (OCH_3); 79.8 ($\underline{C}(CN)_2$); 111.8 (CN); 114.6 (CN); 114.6, 123.9, 125.3, 126.1, 134.1, 140.9 (Ph); 152.5 ($\underline{C}H$=C); 92.7, 159.6, 165.5, 170.7 (Py). MS: 334 (M^++1, 21); 333 (M^+, 98); 318 (32); 293 (25); 292 (22); 268 (46); 252 (25); 195 (33); 118 (100); 117 (70). IR: 2960, 2920, 2850 (CH); 2220 (CN); 1570, 1530, 1500 (CC). Anal. Calcd. for $C_{18}H_{15}N_5O_2$: C, 64.86; H, 4.54; N, 21.01. Found: C, 64.95; H, 4.63; N, 20.90.

5-(2,2-dicyanovinyl)-2,6-dimethoxy-4-(*N*-1,2,3,4-tetrahydroquinolenyl) pyrimidine **5b**: General procedure was followed; medium-pressure chromatography was performed by using CH_2Cl_2 as eluent; yield: 0.41 g (90%); mp 157-159 °C (EtOH). ^{1}H-NMR: 2.05 (2H, q, J = 6.5 Hz, $NCH_2C\underline{H}_2$); 2.86 (2H, t, J = 6.5 Hz, CH_2Ph); 3.97 (2H, t, J = 6.5 Hz, NCH_2); 4.02 (3H, s, OCH_3); 4.05 (3H, s, OCH_3); 6.76-6.80 (1H, m, Ph); 7.00-7.23 (4H, m, CH=C, Ph). ^{13}C-NMR: 23.9 ($NCH_2\underline{C}H_2$); 26.6 (CH_2Ph); 47.2 (NCH_2); 54.4 (OCH_3); 55.1 (OCH_3); 82.8 ($\underline{C}(CN)_2$); 112.3 (CN); 113.7 (CN); 120.3, 124.5, 126.5, 129.6, 132.1, 139.9 (Ph); 154.1 ($\underline{C}H$=C); 92.4, 163.7, 165.8, 169.9 (Py). MS: 348 (M^++1, 10); 347 (M^+, 43); 307 (43); 282 (59); 132 (51); 130 (100); 117 (48); 115 (58); 103 (45). IR: 2960, 2920, 2850 (CH); 2220 (CN); 1570, 1540 (CC). Anal. Calcd. for $C_{19}H_{17}N_5O_2$: C, 65.70; H, 4.93; N, 20.16. Found: C, 65.59; H, 4.72; N, 20.30.

5-(2,2-dicyanovinyl)-2,6-dimethoxy-4-(*N*-2-methylindolinyl)pyrimidine **5c**: General procedure was followed; medium-pressure chromatography was performed by using CH_2Cl_2 as eluent; yield: 0.45 g (100%); mp 128-130 °C (EtOH). ^{1}H-NMR: 1.50 (3H, d, J = 6.2 Hz, $NCHC\underline{H}_3$); 2.74 (1H, dd, J = 3.4, 15.2 Hz, $PhC\underline{H}_2$); 3.50 (1H, dd, J = 8.1, 15.2 Hz, $PhC\underline{H}_2$); 4.04 (3H, s, OCH_3); 4.09 (3H, s, OCH_3); 4.91-4.99 (1H, m, $NC\underline{H}CH_3$); 6.43 (1H, m, Ph); 7.10 (2H, m, Ph); 7.25 (1H, m, Ph); 7.79 (1H, s, CH=C). ^{13}C-NMR: 19.7 ($NCH\underline{C}H_3$); 37.2 ($PhCH_2$); 54.7 (OCH_3); 55.2 (OCH_3); 62.0 ($N\underline{C}HCH_3$); 80.4 ($\underline{C}(CN)_2$); 111.9 (CN); 114.5 (CN); 113.8, 123.8, 125.8, 125.9, 133.6, 139.9 (Ph); 152.3 ($\underline{C}H$=C); 92.9, 159.0, 165.6, 170.8 (Py). MS: 348 (M^++1, 13); 347 (M^+, 69); 333 (12); 332 (70); 307 (28); 282 (28); 266 (29); 132(45); 130 (32); 117 (40); 84 (100). IR: 2930, 2860 (CH); 2220 (CN); 1570, 1530 (CC). Anal. Calcd. for $C_{19}H_{17}N_5O_2$: C, 65.70; H, 4.93; N, 20.16. Found: C, 65.63; H, 4.85; N, 20.27.

Pyrido[2,3-*d*]pyrimidine-Containing Heterotricyclic compounds 6a-c and 7a-c. General procedure

Method A: A solution of **4** (1 mmol) in DMSO (3 mL) was heated at 140 °C until all starting material has disappeared as checked by TLC (40 h for **4a**, 20 h for **4b**, and 6 h for **4c**). The solvent was removed under reduced pressure and the resulting solid was purified by MPLC on a silica gel (12 x1 cm) using AcOEt/hexane (1:4) as eluent to obtain **6a-c**. Method B: A solution of **5** (1 mmol) in EtOH (10 mL) was refluxed until all starting material has disappeared as checked by TLC (3.5 h for **7a**, 0.5 h for **7b**, and 2.0 h for **7c**). Upon cooling, the solvent was removed under reduced pressure and the resulting solid was recrystallized from EtOH to obtain **7a-c**.

6,8-dimethoxy-1,2,3,3a-tetrahydropyrrolo[1,2-*e*]pyrido[2,3-*d*]pyrimidin-4,4(5*H*)-dicarbonitrile **6a**: Method A was followed; medium-pressure chromatography was performed by using AcOEt/hexane (1:4) as eluent; yield: 0.17 g (57%); mp 116-118 °C (EtOH). ^{1}H-NMR: 1.99-2.29 (4H, m, H-2,3); 2.52-2.60 (1H, m, Hax-1); 2.96, 3.04, 3.59, 3.67 (2H, AB sist, J = 16.0 Hz, H-5); 3.56-3.66 (1H, m, H-3a); 3.69-3.93 (1H, m, Hec-1); 3.94 (3H, s, OCH_3); 3.96 (3H, s, OCH_3). ^{13}C-NMR: 22.7 (C-2); 30.1 (C-3); 31.4 (C-5); 33.4 (C-4); 46.9 (C-1); 53.9 (OCH_3); 54.4 (OCH_3); 62.1 (C-3a); 82.9 (C-5a); 112.5 (CN); 114.3 (CN); 158.7, 164.9 (C-6, 9a); 167.7 (C-8). MS: 286 (M^++1, 23); 285 (M^+, 100); 284 (M^+-1, 43); 270 (41); 259 (25); 257 (48); 256 (54); 245 (29); 231 (29); 220 (42); 217 (34); 192 (33); 180 (40); 162 (26); 149 (30). IR: 2960, 2880 (CH); 2230 (CN); 1600, 1570, 1520 (CC). Anal. Calcd. for $C_{14}H_{15}N_5O_2$: C, 58.94; H, 5.30; N, 24.55. Found: C, 59.09; H, 5.28; N, 24.43.

7,9-dimethoxy-2,3,4,4a,5,6-hexahydro-1*H*-pyrido[1,2-*e*]pyrido[2,3-*d*]pyrimidin-5,5-dicarbonitrile **6b**: Method A was followed; medium-pressure chromatography was performed by using AcOEt/hexane (1:4) as eluent; yield: 0.22 g (74%); mp 134-136 °C (EtOH). ^{1}H-NMR: 1.42-1.90 (4H, m, Hax-2,3,4; Hec-3 ó 4); 1.90-2.04 (1H, m, Hec-3 ó 4); 2.22-2.29 (1H, m, Hec-2); 2.64-2.78 (1H, m, Hax-1); 3.10, 3.18, 3.33, 3.41 (2H, AB sist, J = 16.1 Hz, H-6); 3.55 (1H, dd, J = 2.9, 11.1 Hz, H-4a); 3.90 (3H, s, OCH_3); 3.93 (3H, s, OCH_3); 4.86-4.95 (1H, m, Hec-1). ^{13}C-NMR: 23.1, 24.1 (C-2, C-3); 28.6 (C-4); 29.0 (C-6); 35.7 (C-5);

45.4 (C-1); 54.1 (OCH_3); 54.5 (OCH_3); 58.8 (C-4a); 84.2 (C-6a); 113.4 (CN); 114.4 (CN); 160.5, 163.9 (C-7, C-10a); 168.5 (C-9). MS: 300 (M^++1, 19); 299 (M^+, 98); 298 (M^+-1, 37); 284 (29); 259 (27); 245 (75); 231 (87); 219 (41); 217 (100); 180 (64). IR: 2950, 2880 (CH); 2230 (CN); 1600, 1560, 1520 (CC). Anal. Calcd. for $C_{15}H_{17}N_5O_2$: C, 60.19; H, 5.72; N, 23.40. Found: C, 60.15; H, 5.68; N, 23.42.

8,10-dimethoxy-1,2,3,4,5,5a-hexahydroazepino[1,2-*e*]pyrido[2,3-*d*]pyrimidin-6,6(7*H*)-dicarbonitrile **6c:** Method A was followed; medium-pressure chromatography was performed by using AcOEt/hexane (1:4) as eluent; yield: 0.30 g (95%); mp 114-116 °C (EtOH). ^{1}H-NMR: 1.19-2.23 (8H, m, H-2,3,4,5); 3.04-3.19 (1H, m, Hax-1); 2.99, 3.07, 3.36, 3.44 (2H, AB sist, J = 16.5 Hz, H-7); 3.91 (3H, s, OCH_3); 3.94 (3H, s, OCH_3); 3.91-4.01 (1H, m, H-5a); 4.57-4.70 (1H, m, Hec-1). ^{13}C-NMR: 25.3, 25.9 (C-3, C-4); 26.7 (C-2); 27.4 (C-5); 30.3 (C-7); 32.6 (C-6); 47.3 (C-1); 53.8 (OCH_3); 54.2 (OCH_3); 61.0 (C-4a); 84.2 (C-5a); 82.0 (C-7a); 114.1 (CN); 114.2 (CN); 158.2, 163.8 (C-8, C-11a); 168.0 (C-10). MS: 314 (M^++1, 9); 313 (M^+, 49); 312 (M^+-1, 12); 298 (18); 273 (29); 248 (44); 245 (52); 231 (38); 218 (30); 217 (46); 180 (100); 111 (63). IR: 2930, 2860 (CH); 2240 (CN); 1600, 1580 (CC). Anal. Calcd. for $C_{16}H_{19}N_5O_2$: C, 61.33; H, 6.11; N, 22.35. Found: C, 61.26; H, 6.14; N, 22.38.

6-(1,1-dicyanomethyl)-7,9-dimethoxy-2,6-dihydro-1*H*-indolo[1,8,7-*e,f*]pyrido[2,3-*d*]pyrimidine **7a:** Method B was followed; yield: 0.30 g (78%); mp 188-190 °C (EtOH). ^{1}H-NMR: 3.16-3.50 (2H, m, H-2); 3.92-4.56 (2H, m, H-1); 3.99 (3H, s, OCH_3); 4.04 (3H, s, OCH_3); 4.08 (1H, d, J = 4.1 Hz, $HC(CN)_2$); 4.98 (1H, d, J = 4.1 Hz, H-6); 7.01-7.09 (1H, m, Ph); 7.22-7.33 (1H, m, Ph); 7.38-7.46 (1H, m, Ph). ^{13}C-NMR: 28.2 (C-2); 30.0 ($\underline{C}H(CN)_2$); 38.1 (C-6); 46.6 (C-1); 54.3 (OCH_3); 54.7 (OCH_3); 86.4 (C-6a); 111.5 (CN); 112.3 (CN); 113.2 (C-5a); 123.8, 125.5, 126.2, 130.1, 142.2 (Ph); 158.6, 164.8 (C-7, C-10a); 167.8 (C-9). MS: 333 (M^+, 2); 332 (M^+-1, 3); 329 (13); 284 (30); 269 (20); 268 (M^+-CH(CN)$_2$, 100); 266 (13); 254 (27). IR: 2960, 2920, 2850 (CH); 2220 (CN); 1610, 1590, 1550, 1500 (CC). Anal. Calcd. for $C_{18}H_{15}N_5O_2$: C, 64.86; H, 4.54; N, 21.01. Found: C, 64.93; H, 4.60; N, 21.12.

7-(1,1-dicyanomethyl)-8,10-dimethoxy-1,2,3,7-tetrahydroquino[1,9,8-*e,f*]pyrido[2,3-*d*]pyrimidine **7b:** Method B was followed; yield: 0.25 g (73%); mp 204-206 °C (EtOH). ^{1}H-NMR: 2.00-2.16 (2H, m, H-3); 2.83-2.92 (2H, m, H-2); 3.83 (1H, d, J = 4.7 Hz, $HC(CN)_2$); 3.86-3.99 (1H, m, Hax-1); 4.00 (3H, s, OCH_3); 4.05 (3H, s, OCH_3); 4.13-4.19 (1H, m, Hec-1); 4.88 (1H, d, J = 4.7 Hz H-7); 7.00-7.08 (1H, m, Ph); 7.16-7.19 (1H, m, Ph); 7.30-7.34 (1H, m, Ph). ^{13}C-NMR: 20.8 (C-2); 27.7 (C-3); 30.3 ($\underline{C}H(CN)_2$); 38.0 (C-7); 43.5 (C-1); 54.3 (OCH_3); 54.7 (OCH_3); 86.0 (C-7a); 111.6 (CN); 112.0 (CN); 116.9 (C-6a); 122.4, 125.8, 127.5, 130.1, 136.2 (Ph); 158.5, 164.2 (C-8, C-11a); 168.1 (C-10). MS: 346 (M^+-1, 6); 345 (30); 283 (21); 282 (M^+-CH(CN)$_2$, 100); 254 (18). IR: 2960, 2930, 2850 (CH); 2220 (CN); 1580, 1550 (CC). Anal. Calcd. for $C_{19}H_{17}N_5O_2$: C, 65.70; H, 4.93; N, 20.16. Found: C, 65.69; H, 4.82; N, 20.14.

6-(1,1-dicyanomethyl)-1-methyl-7,9-dimethoxy-2,6-dihydro-1*H*-indolo[1,8,7-*e,f*]pyrido[2,3-*d*] pyrimidine **7c:** Method B was followed; yield: 0.31 g (88%). ^{1}H-NMR (minor isomer): 1.50 (3H, d, J = 6.3 Hz, CH_3); 2.77-2.84 (1H, m, Hax-2); 3.43-3.56 (1H, m, Hec-2); 3.92-4.08 (6H, m, OCH_3); 4.18 (1H, d, J = 3.4 Hz, $HC(CN)_2$); 4.69-4.89 (1H, m, H-1); 5.02 (1H, d, J = 3.4 Hz, H-6); 7.02-7.48 (3H, m, Ph). ^{13}C-NMR: 19.0 (C-1); 30.2 ($\underline{C}H(CN)_2$); 36.8 (C-2); 37.9 (C-6); 54.1 (OCH_3); 54.5 (OCH_3); 55.9 (CH_3); 86.8 (C-6a); 111.5 (CN); 112.5 (CN); 113.2 (C-5a); 123.5, 125.4, 125.8, 128.7, 140.5 (Ph); 157.4, 164.2 (C-7, C-10a); 167.8 (C-9). ^{1}H-NMR (major isomer): 1.60 (3H, d, J = 6.3 Hz, CH_3); 2.93 (1H, dd, J = 5.4, 16.6 Hz, Hax-2); 3.43-3.56 (1H, m, Hec-2); 3.99 (3H, s, OCH_3); 4.03 (3H, s, OCH_3); 3.92-4.08 (1H, m, $HC(CN)_2$); 4.69-4.89 (1H, m, H-1); 4.95 (1H, d, J = 3.9 Hz, H-6); 7.02-7.48 (3H, m, Ph). ^{13}C-NMR: 20.7 (C-1); 29.9 ($\underline{C}H(CN)_2$); 36.8 (C-2); 37.9 (C-6); 54.1 (OCH_3); 54.5 (OCH_3); 55.2 (CH_3); 86.2 (C-6a); 111.5 (CN); 112.2 (CN); 113.0 (C-5a); 123.6, 125.4, 126.0, 128.7, 141.5 (Ph); 157.9, 164.5 (C-7, C-10a); 167.7 (C-9). MS: 297 (2); 296 (6); 283 (20); 282 (M^+-CH(CN)$_2$, 100); 268 (5); 141 (9). IR: 2960, 2920, 2860 (CH); 2230; 2210 (CN); 1620, 1600, 1570 (CC). Anal. Calcd. for $C_{19}H_{17}N_5O_2$: C, 65.70; H, 4.93; N, 20.16. Found: C, 65.59; H, 4.97; N, 20.18.

6-(2,2-dicyanovinyl)-7,9-dimethoxy-1,2-dihydro-indolo[1,8,7-*e,f*]pyrido[2,3-*d*]pyrimidine **8a**: ^{1}H-NMR: 3.47-3.55 (2H, m, H-2); 4.10 (3H, s, OCH_3); 4.24 (3H, s, OCH_3); 4.48-4.57 (2H, m, H-1); 7.25-7.33 (1H, m, Ph); 7.46-7.50 (1H, m, Ph); 8.49-8.53 (1H, m, Ph). ^{13}C-NMR: 27.8 (C-2); 47.5 (C-1); 54.2 (OCH_3); 55.5 (OCH_3); 93.4 (C-6a); 116.5, 116.8, 117.3 (CN, C-5a); 123.3, 124.8, 128.1, 131.3, 140.4 (Ph); 151.5 (C-6); 154.8, 165.3 (C-7, C-10a); 169.1 (C-9). MS: 332 (M^++1, 22); 331 (M^+, 100); 303 (23); 291 (22); 261 (35); 204 (27). IR: 3020, 2960 (CH); 2220 (CN); 1640, 1590, 1550, 1520, 1480 (CC). Anal. Calcd. for $C_{18}H_{13}N_5O_2$: C, 65.25; H, 3.96; N, 21.14. Found: C, 65.23; H, 4.08; N, 21.12.

7-(2,2-dicyanovinyl)-8,10-dimethoxy-1,2-dihydro-1H-quino[1,8,7-*ef*]pyrido[2,3-*d*]pyrimidine **8b**: ^{1}H-NMR: 2.15-2.27 (2H, m, H-3); 3.02 (2H, t, J = 5.9 Hz, H-2); 4.10 (3H, s, OCH_3); 4.24 (3H, s, OCH_3); 4.35 (2H, t, J = 5.9 Hz, H-1); 7.24-7.31 (1H, m, Ph); 7.41-7.46 (1H, m, Ph); 8.29-8.34 (1H, m, Ph). ^{13}C-NMR: 20.8 (C-2); 27.7 (C-3); 45.2 (C-1); 54.2 (OCH_3); 55.4 (OCH_3); 92.4 (C-7a); 116.0, 116.8 (CN); 119.6 (C-6a); 122.9, 124.5, 126.1, 132.6, 134.5 (Ph); 153.2 (C-7); 155.5, 165.1 (C-8, C-11a); 168.7 (C-10). MS: 346 (M^++1, 18); 345 (M^+, 79); 275 (35); 218 (30); 217 (54); 164 (34); 72 (60); 70 (68). IR: 2950, 2880 (CH); 2230 (CN); 1600, 1570, 1530 (CC). Anal. Calcd. for $C_{19}H_{15}N_5O_2$: C, 66.08; H, 4.38; N, 20.28. Found: C, 66.15; H, 4.29; N, 20.33.

6-(2,2-dicyanovinyl)-1-methyl-7,9-dimethoxy-1,2-dihydro-indolo[1,8,7-*ef*]pyrido[2,3-*d*]pyrimidine **8c**: ^{1}H-NMR: 1.69 (3H, d, J = 6.4 Hz, CH_3); 3.05-3.16 (1H, dd, J = 4.1, 16.9 Hz, Hax-2); 3.66-3.79 (1H, dd, J = 9.4, 16.9 Hz, Hec-2); 4.10 (3H, s, OCH_3); 4.24 (3H, s, OCH_3); 5.09-5.21 (1H, m, H-1); 7.30-7.34 (1H, m, Ph); 7.45-7.49 (1H, m, Ph); 8.48-8.53 (1H, m, Ph). ^{13}C-NMR: 21.2 (C-1); 36.7 (C-2); 54.1 (OCH_3); 55.4 (OCH_3); 57.0 (CH_3); 93.0 (C-6a); 116.5, 116.6 (CN, C-5a); 123.3, 124.9, 128.1, 130.1, 140.0 (Ph); 151.5 (C-6); 153.0 (C-6); 155.0, 165.0 (C-7, C-10a); 169.0 (C-9). MS: 346 (M^++1, 4); 345 (M^+, 16); 217 (5); 204 (5); 111 (11); 97 (19); 85 (23); 72 (33); 57 (100). IR: 2960, 2880 (CH); 2220 (CN); 1610, 1550, 1520 (CC). Anal. Calcd. for $C_{19}H_{15}N_5O_2$: C, 66.08; H, 4.38; N, 20.28. Found: C, 66.23; H, 4.27; N, 20.12.

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