

# A facile synthesis and heteroannulation of pyrido[2,3-*d*]pyrimidine and related heterocyclic systems

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7-Amino-1,2,3,4-tetrahydro-4-oxo-2-thioxo-5-(3,4,5-trimethoxyphenyl)pyrido[2,3-*d*]pyrimidine (**1**) was prepared and reacted with methyl iodide and ethyl chloroacetate to give the *S*-alkylated products **2** and **3**, respectively. The reaction of **1** or **3** with hydrazine hydrate yielded the same 2-hydrazino derivative **4**. Treatment of **4** with 2,4-pentanedione, 2-acetylcyclohexanone and ethyl acetoacetate afforded the corresponding pyrazolylpyrido[2,3-*d*]pyrimidine derivatives (**5–7**), while phthalic anhydride gave the phthalazinyl compound **8**. Ethoxymethylenemalononitrile with the hydrazine **4** formed the fused 1,2,4-triazepine **9**, while triazolopyrido[2,3-*d*]pyrimidines were obtained from the reaction of **4** with benzylidene malononitrile or benzaldehyde (forming **10**), acetic acid/anhydride (giving **11**), and ethyl chloroformate (giving **12**).

**Keywords:** hydrazines, pyrazoles, fused pyridines, pyrimidines, 1,2,4-triazepines, 1,2,4-triazines

Pyrido[2,3-*d*]pyrimidines stand out for their antitumour,<sup>1</sup> anticonvulsive,<sup>2</sup> antiasthmatic, antiallergic<sup>3</sup> and antihypertensive<sup>4</sup> effects and are useful as diuretic compounds.<sup>5–7</sup> In earlier work, we have reported several new syntheses of fused heterocyclic compounds utilising laboratory available activated nitrile derivatives as starting materials.<sup>8–18</sup> We report here on the utility of the readily obtainable substituted  $\alpha$ -cyanocinnamonnitriles for the synthesis of several pyrido[2,3-*d*]pyrimidines in the search for new chemotherapeutic agents.

## Results and discussion

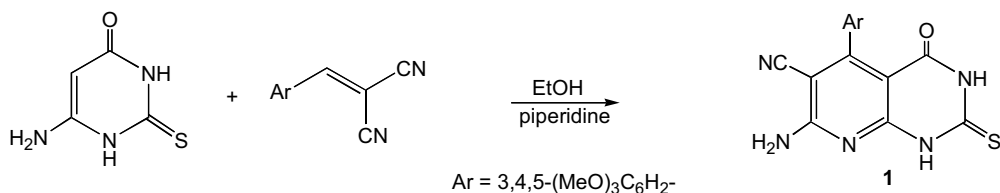
The reaction of  $\alpha$ -cyano-3,4,5-trimethoxycinnamonnitrile with 6-aminothiouracil in equimolar portions in ethanol in the presence of catalytic amount of piperidine to yield a 1:1 adduct which on aromatisation formed the pyrido[2,3-*d*]pyrimidine derivative **1**.

The structure of **1** was established as pyridopyrimidine on the basis of IR, MS, and <sup>1</sup>H and <sup>13</sup>C NMR spectra (see

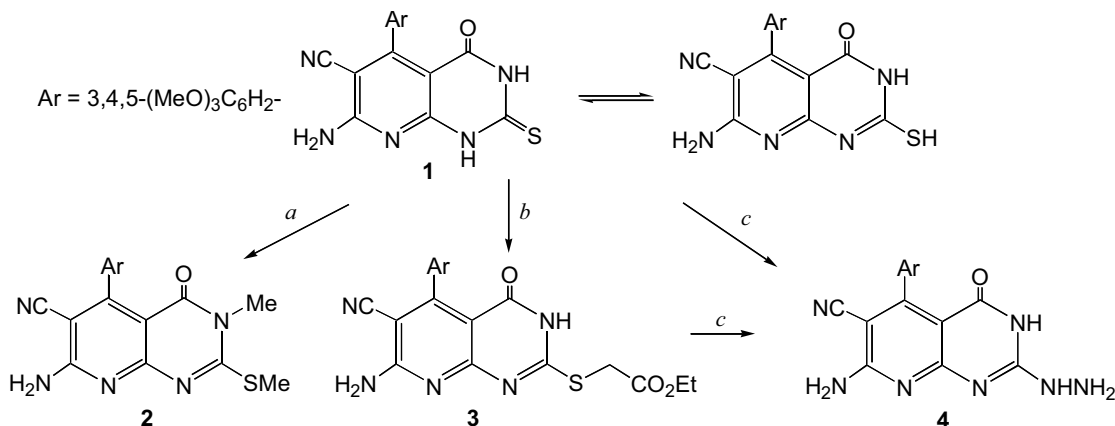
Experimental). The formation of **1** assumed to proceed *via* addition of thiouracil C-5 to the activated double bond in the cinnamonnitrile derivative followed by 1,6-*exo-dig* cyclisation of the Michael adduct, and aromatisation.

Methylation of **1** using methyl iodide in ethanolic sodium hydroxide resulted in the formation of a sole product of molecular formula C<sub>19</sub>H<sub>19</sub>N<sub>5</sub>O<sub>4</sub>S [*M* = 413 (100%)]. The microanalysis and mass spectrum indicates incorporation of two methyl groups in the reaction product. Several structures involve N- and S-alkylation could be suggested for this product. The IR spectrum of this product lacked the absorption band for  $\nu_{C=S}$  which suggest the S-methylation; furthermore, the lower value of  $\nu_{C=O}$  (1681 cm<sup>-1</sup>) than in the starting material (1687 cm<sup>-1</sup>) and the three bands for  $\nu_{NH_2}$  were in accordance with the proposed structure **2**. Structure **2** gets a further support from <sup>1</sup>H NMR spectrum (see Experimental).

Alkylation of **1** using ethyl chloroacetate in refluxing pyridine afforded the *S*-alkylated product ethyl [7-amino-



Scheme 1



Scheme 2 Reagents: a, MeI in MeOH/NaOH, Δ; b, ethyl chloroacetate in pyridine, Δ; c, hydrazine hydrate in ethanol, Δ

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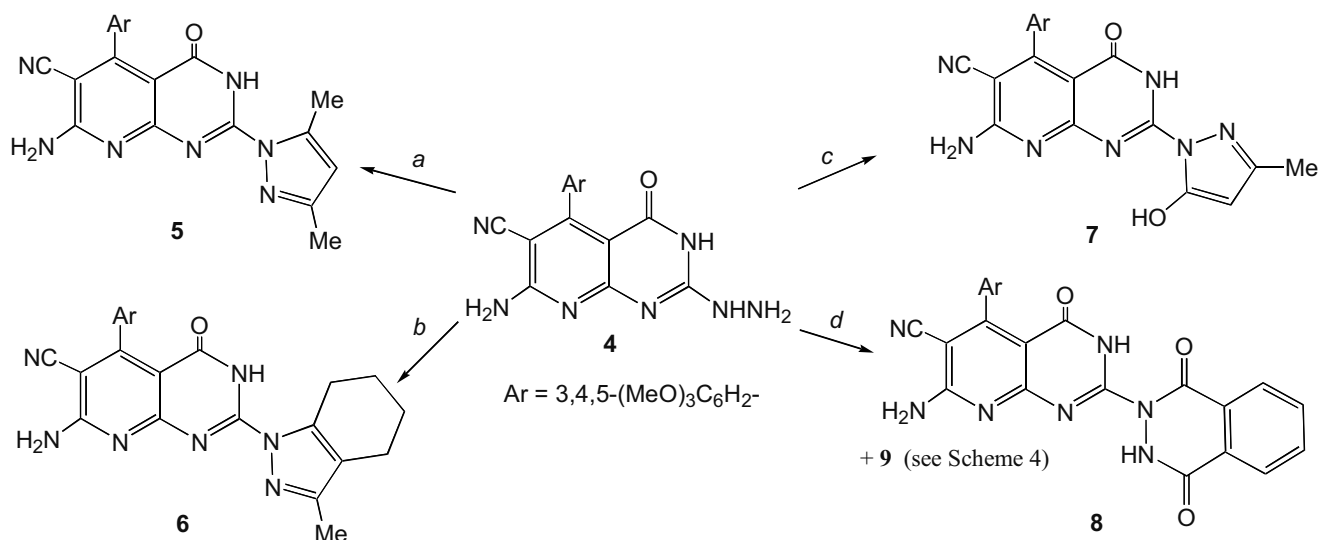
6-cyano-3,4-dihydro-4-oxo-5-(3,4,5-trimethoxyphenyl)-pyrido[2,3-*d*]pyrimidin-2-ylthio]acetate (**3**).

Treatment of pyridopyrimidine-2-thione **1** with hydrazine hydrate in boiling ethanol afforded a sulfur free compound which was identified as 7-amino-2-hydrazino-3,4-dihydro-4-oxo-5-(3,4,5-trimethoxyphenyl)pyrido[2,3-*d*]pyrimidine-6-carbonitrile (**4**). The same product was isolated in good yield on hydrazinolysis of compound **3** under the same conditions.

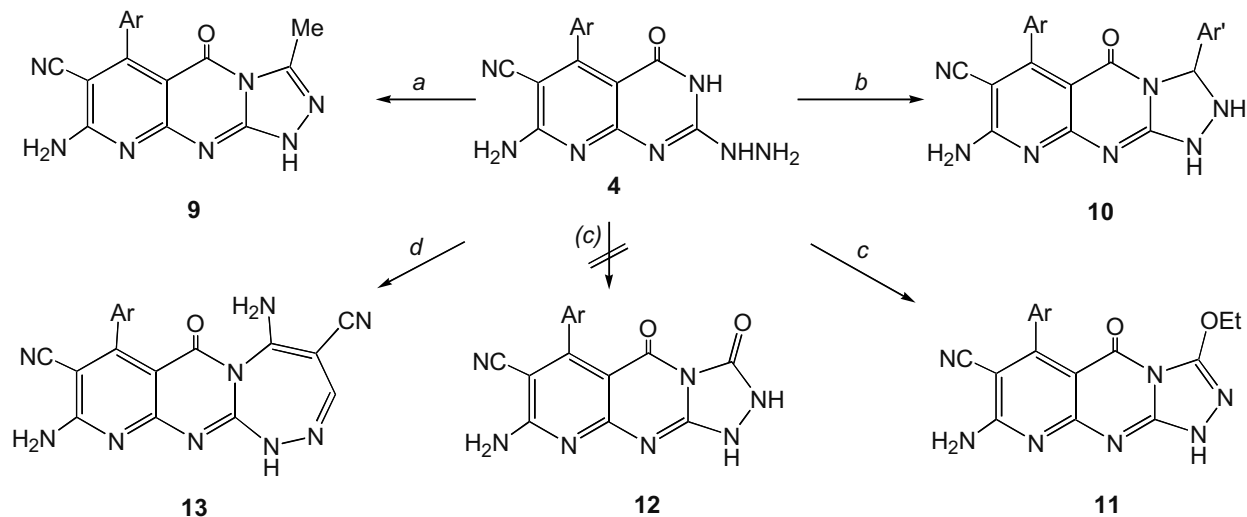
This hydrazine derivative **4** was used as the key intermediate in the synthesis of pyrazolyl- and triazolo-pyridopyrimidine triheterocycles.<sup>15</sup> The reactions provided both appended (Scheme 3) and fused ring products (Scheme 4). Thus, compound **4** when refluxed with 2,4-pentanedione, 2-acetylcyclohexanone or ethyl acetoacetate, it afforded the 7-amino-2-(3,5-dimethylpyrazol-1-yl)-4-oxo-5-(3,4,5-trimethoxyphenyl)-3,4-dihydropyrido[2,3-*d*]pyrimidine-6-carbonitrile (**5**), 7-amino-3,4-dihydro-2-(3-methyl-4,5,6,7-tetrahydroindazol-1-yl)-4-oxo-5-(3,4,5-trimethoxyphenyl)pyrido[2,3-*d*]pyrimidine-6-carbonitrile (**6**) and 7-amino-3,4-dihydro-2-(5-hydroxy-3-methyl-pyrazol-1-yl)-4-oxo-5-(3,4,5-trimethoxyphenyl)pyrido[2,3-*d*]pyrimidine-6-carbonitrile (**7**), respectively (Scheme 3).

When compound **4** was refluxed with phthalic anhydride in boiling acetic acid for 3 h the solid product obtained shows two spots by TLC, and it was possible to detect by GC-MS two different compounds. The major product proved to be the phthalazinedione derivative **8** (48%). The EI fragmentation pattern of the other product was completely in accordance with the fused triazole derivative **9** (32%). Formation of **9** can readily be explained by acetylation of the hydrazine by acetic phthalic anhydride formed in the reaction medium, followed by cyclisation with dehydration.

Compound **9**, 8-amino-1,5-dihydro-3-methyl-5-oxo-6-(3,4,5-trimethoxyphenyl)pyrido[2,3-*d*][1,2,4]triazolo[4,3-*a*]pyrimidine-7-carbonitrile, could also be prepared more conveniently by reflux of the hydrazine **4** in acetic acid and acetic anhydride (Scheme 4). After 3 h heating a yellow solid product with formula  $C_{19}H_{17}N_7O_4$  was obtained. The IR spectrum of this product displayed well defined absorption bands at 3373, 3340, and 3194  $\text{cm}^{-1}$  ( $\nu_{\text{NH}_2}$ ), 2219  $\text{cm}^{-1}$  ( $\nu_{\text{C}\equiv\text{N}}$ ), the  $\nu_{\text{C}=\text{O}}$  frequency at 1712  $\text{cm}^{-1}$  indicates that the carbonyl absorption band of pyrimidine is not enolisable which is in good accordance with structure **9**. The mass spectrum of **9** showed the expected molecular ion peak as the base peak at  $m/z$  407 (100%).



**Scheme 3** Reagents: *a*,  $(\text{MeCO})_2\text{CH}_2$ ; *b*, 2-acetylcyclohexanone; *c*,  $\text{MeCOCH}_2\text{CO}_2\text{Et}$ ; (*a-c*): all in pyridine,  $\Delta$ ; *d*, phthalic anhydride; in  $\text{AcOH}$ ,  $\Delta$



**Scheme 4** Reagents: *a*,  $\text{Ac}_2\text{O}$  in  $\text{AcOH}$ ,  $\Delta$ ; *b*,  $\text{Ar}'\text{CH}=\text{C}(\text{CN})_2$  or  $\text{Ar}'\text{CHO}$ ; *c*,  $\text{ClCO}_2\text{Et}$ ; *d*,  $\text{EtOCH}=\text{C}(\text{CN})_2$  (*b-d*): all in pyridine,  $\Delta$

When the hydrazino derivative **4** was subjected to react with 4-chloro- $\alpha$ -cyano-cinnamionitrile in refluxing pyridine for 6 h, 8-amino-3-(4-chlorophenyl)-1,2,3,5-tetrahydro-5-oxo-6-(3,4,5-trimethoxyphenyl)pyrido[2,3-*d*][1,2,4]triazolo[4,3-*a*]pyrimidine-8-carbonitrile **10** was obtained in good yield (87%). The mass spectrum of **10** shows the molecular ion peak at  $m/z$  505 (100%) as the base peak, and other peaks characteristic for ( $M + 1$ ) and ( $M + 2$ ) which indicated the presence of a chlorine atom. Confirmation of the structure of compound **10** was gained by the identity (m.p, mixed m.p, IR and TLC comparison) with an authentic sample formed by the reaction of **4** with *p*-chlorobenzaldehyde in refluxing pyridine.

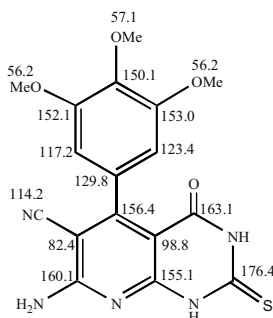
Another triazolopyridopyrimidine (**11**) was synthesised from the reaction of **4** with ethyl chloroformate in refluxing pyridine. Spectroscopic analysis confirmed the assignment of structure **11**. The  $^1\text{H}$  NMR spectrum of **11** (DMSO- $d_6$ ) displayed signals characteristic of an ethoxy group as a 3H triplet at  $\delta$  1.25 ppm and a 2H quartet at  $\delta$  4.02 ppm. This allows the expected triazolone structure **12** to be rejected as the reaction product. Furthermore, the mass spectrum of **11** shows the molecular ion peak at  $m/z$  437 (5.6%), which is in accord with structure **11** (Scheme 4).

The pyrido[2,3-*d*]pyrimidino[2,1-*c*][1,2,4]triazepine derivative **13** was obtained as the sole product (TLC) upon treatment of **4** with ethoxymethylene malononitrile in boiling pyridine.

## Experimental

The IR spectra are recorded on FTIR Mattson (infinity series) spectrometers from KBr discs. The  $^1\text{H}$  NMR spectra were measured on Varian Gemini 200 MHz instrument with chemical shifts ( $\delta$ ) expressed in ppm downfield from TMS.  $^{13}\text{C}$  NMR spectra were measured on a JEOL spectrometer at 75 MHz. EI-MS were measured on Shimadzu GC-MS QP 1000 EX instrument operating at 70 eV. Preparations were generally monitored by thin-layer chromatography using aluminium sheets coated with silica gel. Elemental analyses were carried out at the Microanalytical Unit, Faculty of Science, Ain Shams University with a Perkin-Elmer series 11 CHNS/O elemental analyser.

**7-Amino-1,2,3,4-tetrahydro-4-oxo-2-thioxo-5-(3,4,5-trimethoxyphenyl)pyrido[2,3-*d*]pyrimidine-6-carbonitrile (1):** 6-Aminothiouracil (1.43 g, 0.01 mol) and  $\alpha$ -cyano-3,4,5-trimethoxycinnamionitrile (2.44 g, 0.01 mol) were heated under reflux for 8 h in ethanol (50 mL) containing piperidine (0.5 mL). The solid which separated from the hot solution was filtered off, dried, and recrystallised from MeOH/DMF to give **1** as yellow crystals (1.54 g., 40%), m.p 330–332 °C. IR:  $\nu_{\text{max}}$  3439, 3338, 3233, 3180 ( $\text{NH}_2$ , 2NH), 2217 ( $\text{C}\equiv\text{N}$ ), 1687 ( $\text{C}=\text{O}$ ), 1645 ( $\text{C}=\text{N}$ ) and 1140  $\text{cm}^{-1}$  ( $\text{C}=\text{S}$ ).  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  12.3 (s, 2H, exchangeable with  $\text{D}_2\text{O}$ ), 6.9 (s, 2H<sub>arom.</sub>), 6.4 (s, 2H, exchangeable with  $\text{D}_2\text{O}$ ), 3.9, 3.8 (two s, 9H, 3  $\text{OCH}_3$ ). MS:  $m/z$  385 (100), 370 (37.3), 312 (12.6), 284 (15.3), 177 (18.2). Anal. Calcd for  $\text{C}_{17}\text{H}_{15}\text{N}_5\text{O}_4\text{S}$  (385.40): C, 52.98; H, 3.92; N, 18.17; S, 8.3. Found: C, 52.9; H, 4.2; N, 18.19; S, 8.7%.

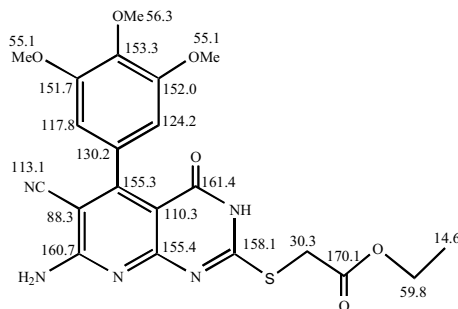


$^{13}\text{C}$  NMR for compound **1**

**Alkylation of 1 with methyl iodide:** 7-amino-3,4-dihydro-3-methyl-2-methylthio-4-oxo-5-(3,4,5-trimethoxyphenyl)pyrido[2,3-*d*]pyrimidine-6-carbonitrile (**2**): Compound **1** (3.85 g, 0.01 mol) and

methyl iodide (2.46 g, 0.02 mol) were dissolved in 10% ethanolic sodium hydroxide (30 mL) and stirred at room temperature for 1 h, then refluxed for another 1 hr. The solvent was evaporated *in vacuo*. The residue was acidified with cold dil. acetic acid and the precipitate was collected by filtration and recrystallised from methanol affording **2** as white crystals (3.51 g., 85%), m.p 315–317 °C. IR:  $\nu_{\text{max}}$  3480, 3325, 3269 ( $\text{NH}_2$ ), 2212 ( $\text{CN}$ ), 1681  $\text{cm}^{-1}$  ( $\text{CO}$ ).  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  7.52 (s, 2H, exchangeable with  $\text{D}_2\text{O}$ ), 6.59 (s, 2H<sub>arom.</sub>), 3.78 (s, 9H), 3.34 (s, 3H, *N*-Me), 2.65 (s, 3H, *S*-Me) MS:  $m/z$  413 (100), 366 (17.9), 246 (32.4), 167 (21.6), 77 (67.1). Anal. Calcd for  $\text{C}_{19}\text{H}_{19}\text{N}_5\text{O}_4\text{S}$  (413.45): C, 55.19; H, 4.63; N, 16.93; S, 7.75. Found: C, 55.16; H, 4.7; N, 17.06; S, 8.02%.

**Ethyl [7-amino-6-cyano-3,4-dihydro-4-oxo-5-(3,4,5-trimethoxyphenyl)pyrido[2,3-*d*]pyrimidin-2-ylthio]acetate (3):** Compound **1** (3.85 g, 0.01 mol) and ethyl chloroacetate (1.3 g, 0.01 mol) were heated under reflux for 4 h in methanol (50 mL) containing anhydrous sodium acetate (2.5 g, 0.03 mol). The solid product that separated from the hot mixture was filtered off, washed with hot water and then recrystallised from methanol to give **3** as colourless crystals (3.63 g., 77%), m.p. 261–263 °C. IR:  $\nu_{\text{max}}$  3441, 3345, 3142 ( $\text{NH}_2$ ), 2216 ( $\text{CN}$ ), 1713, 1686 ( $\text{CO}$ ), 1646  $\text{cm}^{-1}$  ( $\text{C}=\text{N}$ ).  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  10.51 (s, 1H,  $\text{NHCO}$ ), 7.6 (s, 2H,  $\text{NH}_2$ ), 6.5 (s, 2H<sub>arom.</sub>), 4.17 (m, 4H,  $\text{CH}_2\text{CH}_2\text{O}$ ,  $\text{S}-\text{CH}_2\text{CO}$ ), 3.75–3.74 (two s, 9H, 3  $\text{OCH}_3$ ), 1.26 (t, 3H,  $J = 6.9$  Hz,  $\text{CH}_3\text{CH}_2$ ). MS:  $m/z$  471 ( $\text{M}^+$ , 15), 425 ( $[\text{M}^+ - \text{EtOH}]$ , 100). Anal. Calcd for  $\text{C}_{21}\text{H}_{21}\text{N}_5\text{O}_6\text{S}$  (471.49): C, 53.49; H, 4.49; N, 14.85; S, 6.79. Found: C, 53.73; H, 4.83; N, 14.66; S, 6.6%.



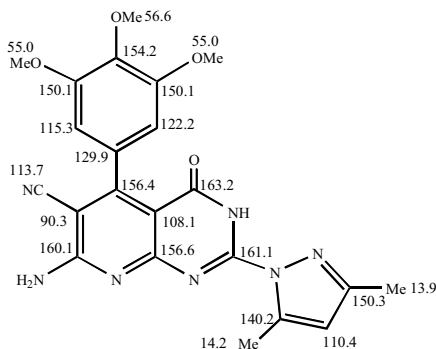
$^{13}\text{C}$  NMR for compound **3**

**7-Amino-2-hydrazino-3,4-dihydro-4-oxo-5-(3,4,5-trimethoxyphenyl)pyrido[2,3-*d*]pyrimidine-6-carbonitrile (4):** Method A: Either compound **1** or **3** (0.01 mol) was stirred for 1 h in ethanol (30 mL) at r.t. with hydrazine hydrate (1.6 g, 0.05 mol), and the solution was then heated under reflux for 2 h. The solid product that separated from the mixture after cooling was filtered off, dried and recrystallised from methanol to give **4** as pale green crystals (1.28 g, 33%), m.p 275–278 °C. IR:  $\nu_{\text{max}}$  3324, 3200, 3150 ( $\text{NH}_2$ ), 2210 ( $\text{C}\equiv\text{N}$ ), 1687  $\text{cm}^{-1}$  ( $\text{C}=\text{O}$ ). MS:  $m/z$  383 ( $\text{M}^+$ , 44), 353 ( $[\text{M} - \text{N}_2 - \text{H}_2]$ , 100). Anal. Calcd for  $\text{C}_{17}\text{H}_{17}\text{N}_7\text{O}_4$  (383.36): C, 53.26; H, 4.46; N, 25.57. Found: C, 53.17; H, 4.22; N, 25.59%. Method B: Compound **3** (1.3 g, 2.7 mmol) and hydrazine hydrate (80%) (1.3 g, 0.04 mol) in ethanol (20 mL) were stirred under reflux for 2 h until no more substrate remained. The solid that deposited after cooling was filtered off, dried and recrystallised from methanol to give **4** (0.64 g, 62%).

### Pyrazole and indazole derivatives **5**, **6**; general procedure

The hydrazine **4** (3.83 g, 0.01 mol) was stirred and heated under reflux in ethanol (50 mL) with the appropriate 1,3-diketone (pentane-2,4-dione, 2-acetylcyclohexanone) (0.01 mol) until no more substrate remained (4 h). The reaction mixture was concentrated and the solid deposited was filtered off, washed with ethanol, dried and recrystallised from methanol.

**7-Amino-2-(3,5-dimethylpyrazol-1-yl)-4-oxo-5-(3,4,5-trimethoxyphenyl)-3,4-dihydro-4-oxo-5-(3,4,5-trimethoxyphenyl)pyrido[2,3-*d*]pyrimidine-6-carbonitrile (5):** Yellow crystals (2.77 g, 62%), m.p. 320–322 °C. IR:  $\nu_{\text{max}}$  3483, 3345, 3287 ( $\text{NH}_2$ ), 3592 ( $\text{NH}$ , OH), 2210 ( $\text{CN}$ ), 1704 ( $\text{C}=\text{O}$ ), 1638  $\text{cm}^{-1}$  ( $\text{C}=\text{N}$ ).  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  11.06 (s, 1H,  $\text{NHCO}$ , exchangeable with  $\text{D}_2\text{O}$ ), 7.6 (s, 2H,  $\text{NH}_2$ , exchangeable with  $\text{D}_2\text{O}$ ), 6.68 (s, 2H<sub>arom.</sub>), 6.31 (s, 1H,  $\text{C}^4\text{-H}$ ), 3.85–3.8 (two s, 9H, 3  $\text{OCH}_3$ ), 2.62 (s, 3H, 3'- $\text{CH}_3$ ), 2.21 (s, 3H, 5'- $\text{CH}_3$ ). MS:  $m/z$  447 ( $\text{M}^+$ , 100), 353 (20), 280 (35), 167 (60), 77 (41). Anal. Calcd for  $\text{C}_{22}\text{H}_{21}\text{N}_7\text{O}_4$  (447.45): C, 59.05; H, 4.73; N, 21.91. Found: C, 58.73; H, 4.72; N, 21.51%.

<sup>13</sup>C NMR for compound 5

**7-Amino-3,4-dihydro-2-(3-methyl-4,5,6,7-tetrahydroindazol-1-yl)-4-oxo-5-(3,4,5-trimethoxyphenyl)pyrido[2,3-d]pyrimidine-6-carbonitrile (6):** Yellow crystals (3.28 g, 67%), m.p. 310–313 °C. IR:  $\nu_{\max}$  3480, 3344, 3210 (NH<sub>2</sub>), 2209 (CN), 1686 (C=O), 1636 cm<sup>-1</sup> (C=N). <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  10.2 (s, 1H, NHCO, exchangeable with D<sub>2</sub>O), 6.55 (m, 2H<sub>arom</sub>), 5.99 (br.s, 2H, NH<sub>2</sub>, exchangeable with D<sub>2</sub>O), 3.9–3.85 (two s, 9H, 3 OCH<sub>3</sub>), 2.75 (s, 3H, 3'-CH<sub>3</sub>), 2.7–1.3 (m, 8H, cyclohexyl protons). MS:  $m/z$  487 (M<sup>+</sup>, 100), 320 (12.7), 280 (31.4), 168 (44.1). Anal. Calcd for C<sub>25</sub>H<sub>25</sub>N<sub>7</sub>O<sub>4</sub> (487.52): C, 61.59; H, 5.16; N, 20.11. Found: C, 61.61; H, 4.87; N, 20.1%.

**7-Amino-3,4-dihydro-2-(5-hydroxy-3-methylpyrazol-1-yl)-4-oxo-5-(3,4,5-trimethoxyphenyl)pyrido[2,3-d]pyrimidine-6-carbonitrile (7):** The hydrazine **4** (3.83 g, 0.01 mol) was heated to reflux with ethyl acetoacetate (2.6 g, 0.02 mol) in pyridine (15 mL) for 6 h. On cooling, acidification with cold dilute acetic acid left a solid product which was collected by filtration, dried and recrystallised from ethanol to provide **7** (2.7 g, 60%), m.p. 210–212 °C. IR:  $\nu_{\max}$  3395, 3331, 3191 (NH<sub>2</sub>), 2218 (CN), 1703 (CO), 1648 cm<sup>-1</sup> (C=N). MS:  $m/z$  408 (16) [M<sup>+</sup> – HNCO], 369 (100) [M<sup>+</sup> – HNCO – MeCN]. Anal. Calcd for C<sub>21</sub>H<sub>19</sub>N<sub>7</sub>O<sub>5</sub> (449.42): C, 56.12; H, 4.26; N, 21.81. Found: C, 55.96; H, 4.0; N, 22.03%.

**Reaction of compound 4 with phthalic anhydride; formation of the phthalazinedione 8 and the pyrido-triazolo-pyrimidine 9:** The hydrazine **4** (0.77 g, 2 mmol) was refluxed with phthalic anhydride (0.30 g, 2 mmol) in boiling acetic acid (15 mL) for 3 h. The solid which was deposited after cooling was collected by filtration and showed two spots on TLC. Fractional crystallisation from methanol yielded the triazolo-fused product **9** (0.26 g, 32%, identical by m.p. and mixed m.p. with the product prepared as described below). Evaporation of the original mother liquor left a solid product which was recrystallised from dioxan to give **7-amino-3,4-dihydro-4-oxo-2-(1,2,3,4-tetrahydro-1,4-dioxophthalazin-2-yl)-5-(3,4,5-trimethoxyphenyl)pyrido[2,3-d]pyrimidine-6-carbonitrile (8)** (0.49 g, 48%), m.p. 282–285 °C. IR:  $\nu_{\max}$  3442, 3429 (br.) (NH<sub>2</sub>), 2217 (CN), 1736, 1702 (CO), 1650 cm<sup>-1</sup> (C=N). MS:  $m/z$  513 (M<sup>+</sup>, 43), 353 (19), 162 (100), 119 (30), 77 (66). Anal. Calcd for C<sub>25</sub>H<sub>19</sub>N<sub>7</sub>O<sub>6</sub> (513.47): C, 58.48; H, 3.72; N, 19.09. Found: C, 58.09; H, 4.0; N, 18.97%.

**8-Amino-1,5-dihydro-3-methyl-5-oxo-6-(3,4,5-trimethoxyphenyl)pyrido[2,3-d][1,2,4]triazolo[4,3-a]pyrimidine-7-carbonitrile (9):** The hydrazine **4** (3.83 g, 0.01 mol) was heated under reflux for 3 h in a mixture of glacial acetic acid (15 mL) and acetic anhydride (10 mL). The excess of solvent was removed *in vacuo*, and the semisolid residue was triturated with methanol. The remaining solid was filtered off, dried and recrystallised from methanol to give **9** as yellow crystals (2.44 g, 60%), m.p. 335–337 °C. IR:  $\nu_{\max}$  3373, 3340, 3194 (NH<sub>2</sub>, NH), 2219 (CN), 1712 (CO), 1637 cm<sup>-1</sup> (C=N). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$  7.2 (br.s, 2H, exchangeable with D<sub>2</sub>O), 6.9 (s, 2H<sub>arom</sub>), 6.7 (s, 1H, exchangeable with D<sub>2</sub>O), 3.9–3.8 (two s, 9H, 3OMe), 2.4 (s, 3H, Me). MS:  $m/z$  407 (M<sup>+</sup>, 100), 393 [20]. Anal. Calcd for C<sub>19</sub>H<sub>17</sub>N<sub>7</sub>O<sub>4</sub> (407.39): C, 56.02; H, 4.2; N, 24.06. Found: C, 55.83; H, 4.10; N, 23.97%.

**8-Amino-3-(4-chlorophenyl)-1,2,3,5-tetrahydro-5-oxo-6-(3,4,5-trimethoxyphenyl)pyrido[2,3-d][1,2,4]triazolo[4,3-a]pyrimidine-7-carbonitrile (10):** Method a: The hydrazine **4** (3.83 g, 0.01 mol) and 4-chloro- $\alpha$ -cyanocinnamionitrile (1.88 g, 0.01 mol) were heated under reflux for 3 h in pyridine (15 mL). The reaction mixture was acidified with cold dilute acetic acid and the solid obtained was filtered off,

dried and then recrystallised from methanol to give **10** as pale yellow crystals (4.15 g, 82%) m.p. >360 °C. IR:  $\nu_{\max}$  3433, 3355, 3112 (NH<sub>2</sub>), 2216 (CN), 1706 (CO), 1648 cm<sup>-1</sup> (C=N). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$  7.7 (br.s, 2H, exchangeable with D<sub>2</sub>O), 7.1–6.8 (m, 6H<sub>arom</sub>), 5.4 (d, 1H), 4.3 (br.s, 2H, exchangeable with D<sub>2</sub>O), 3.9–3.78 (two s, 9H). MS:  $m/z$  505/507 (M<sup>+</sup>, 100/32), 506 (43.3) (M + 1)<sup>+</sup>, 394 (84) [M<sup>+</sup> – C<sub>6</sub>H<sub>4</sub>Cl]. Anal. Calcd for C<sub>24</sub>H<sub>20</sub>ClN<sub>7</sub>O<sub>4</sub> (505.92): C, 56.97; H, 3.98; N, 19.37; Cl, 7.0. Found: C, 57.08; H, 4.23; N, 19.48; Cl, 7.05%. Method b: Compound **4** (0.38 g, 1 mmol) and *p*-chlorobenzaldehyde (0.14 g, 1 mmol) were heated under reflux in absolute ethanol (5 mL) for 6 h. The solid product was collected by filtration, dried and recrystallised from methanol to give **10** (identified by m.p., mixed m.p., TLC comparison).

**8-Amino-3-ethoxy-1,5-dihydro-5-oxo-6-(3,4,5-trimethoxyphenyl)pyrido[2,3-d][1,2,4]triazolo[4,3-a]pyrimidine-7-carbonitrile (11):** The hydrazine **4** (3.83 g, 0.01 mol) and ethyl chloroformate (5 mL) were refluxed in pyridine (20 mL) for 6 h. Acidification of the reaction mixture by cold dilute acetic acid deposited a semi solid product which was filtered off, dried and recrystallised from ethanol to give **11** as yellow crystals (2.27 g, 52%), m.p. 243–245 °C. IR:  $\nu_{\max}$  3427, 3368, 3220 (NH<sub>2</sub>), 2218 (CN), 1680 (CO), 1641 cm<sup>-1</sup> (C=N). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$  7.7–7.65 (2 s, 3H, NH<sub>2</sub>, NH), 6.64 (s, 2H<sub>arom</sub>), 4.02 (q, 2H, *J* = 7.1 Hz, CH<sub>2</sub>CH<sub>3</sub>), 3.8–3.75 (two s, 9H, 3OMe), 1.25 (t, 3H, *J* = 6.6 Hz, CH<sub>3</sub>–CH<sub>2</sub>). MS:  $m/z$  437 (M<sup>+</sup>, 5.6), 409 (100), 392 (13.4), 168 (17.7), 77 (55.1). Anal. Calcd for C<sub>20</sub>H<sub>19</sub>N<sub>7</sub>O<sub>5</sub> (437.41): C, 54.91; H, 4.37; N, 22.41. Found: C, 55.09; H, 4.56; N, 22.68%.

**5,10-Diamino-1,7-dihydro-7-oxo-8-(3,4,5-trimethoxyphenyl)pyrido[2',3':4,5]pyrimidino[2,1-c][1,2,4]triazepine-4,9-dicarbonitrile (13):** A mixture of compound **4** (3.83 g, 0.01 mol) and ethoxymethylenemalononitrile (1.22 g, 0.02 mol) in pyridine (15 mL) was heated under reflux for 4 h. Cold dilute acetic acid was added and the solid deposited was filtered off, dried and then recrystallised from methanol to give **13** as yellow crystals (1.97 g, 43%), m.p. 287–289 °C. IR:  $\nu_{\max}$  3336, 3208, 3115 (NH<sub>2</sub>), 2216 (CN), 1703 (CO), 1639 cm<sup>-1</sup> (C=N). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$  9.7 (s, 1H, exchangeable with D<sub>2</sub>O), 7.61–7.4 (br.s, 4H, exchangeable with D<sub>2</sub>O), 7.2–6.9 (m, 3H<sub>arom</sub> + C3'-H), 3.9 (s, 9H, 3 OCH<sub>3</sub>). MS:  $m/z$  459 (100). Anal. Calcd for C<sub>21</sub>H<sub>17</sub>N<sub>9</sub>O<sub>4</sub> (459.42): C, 54.09; H, 3.72; N, 27.43. Found: C, 54.37; H, 4.0; N, 27.29%.

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