Studies on pyrimidine-annelated heterocycles: synthesis of novel pyrazolo[3′,4′:4,5]pyrido[2,3-*d*]pyrimidines by intramolecular 1,3-dipolar cycloadditions

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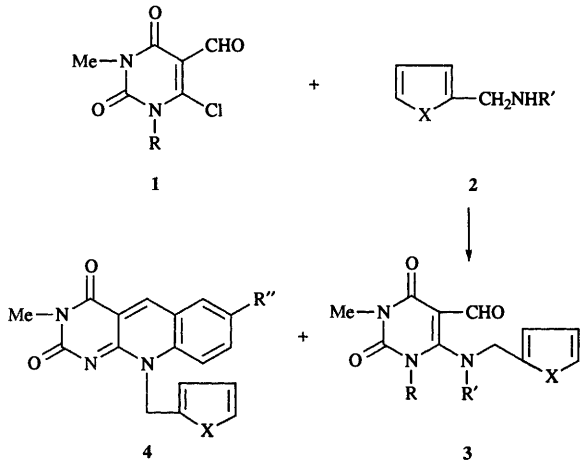
Suitably functionalised 1,3-substituted 6-chloro-1,2,3,4-tetrahydro-2,4-dioxopyrimidine-5-carbaldehydes 3a–l cyclise intramolecularly to yield novel furo- and thieno-[2″,3″:4′,5′]pyrazolo[3′,4′:4,5]pyrido-[2,3-*d*]pyrimidines 8a–l in fair to good yields together with the pyrazolopyrimidines 7 as side products. Remarkably, this synthesis not only left the pyrimidine nucleus unaffected but also gave no dimer formation.

The importance of pyrimidine and its annelated substrates is well recognised,[1,2] numerous uracil/pyrimidine based molecules[3] active against cancer and viruses[4] having been synthesized; several of these are in clinical use (*e.g.* AZT, DDC, BVDU). Intramolecular cycloaddition provides a powerful synthetic tool for a variety of heterocycles[5] and natural products,[6] although only rarely have heterocyclic dipoles or dipolarophiles been used.[7,8] Thus, there appears to be one earlier report to intramolecular 1,3-dipolar cycloaddition of azides under thermolytic conditions.[9] In this, the pyrimidine ring was ruptured and the parent molecule underwent rearrangement. In continuation of our studies[10] on fused pyrimidine derivatives here we report a synthesis of novel furo- and thieno-[2″,3″:4′,5′]pyrazolo[3′,4′:4,5]pyrido[2,3-*d*]pyrimidines **8a–l** using intramolecular 1,3-dipolar cycloaddition strategy, where the pyrimidine ring remains intact.

Results and discussion

6-Chloro-5-formyl-3-methylbarbituric acid **1** (R = H), readily accessible from the corresponding 3-methylbarbituric acid *via* a Vilsmeier reaction, was treated with various substituted furfuryl-[11] or thienylmethyl-amines **2**. The desired 6-(*N*-furfuryl-*N*-*p*-ethoxyphenylamino)-5-formyl-3-methyl-1,2,3,4-tetrahydropyrimidine **3a** was isolated in 30% yields together with 5-deazaflavine **4a**. The structure of the latter was assigned by comparison of its elemental analysis and spectral data with those of related compounds.[12,13] The ^{1}H NMR spectra showed a characteristic lowfield H-5 singlet at (δ 9.86–9.97), suggesting that the 5-position, being the most electron deficient, is very reactive to nucleophiles. Similarly, the deazaflavines **4b** and **4f** were obtained (50–55% yields) along with the uracil **3**, when the uracil **1** reacted with the corresponding secondary amines **2**. The formation of the uracil **3** was thought to proceed by addition followed by elimination rather than by direct displacement of the halogen from C-6 of **1**, the formyl group activating the double bond for the addition. This postulate was supported by an improved yield of **3** when triethylamine was used to capture the eliminated hydrogen chloride in this reaction. The uracil **3** was then converted into its hydrazone **5** by treatment with phenylhydrazine hydrochloride and sodium acetate.

The nitrile imine intermediate **6**, generated[14] *in situ* by heating the hydrazone **5a** in refluxing dioxane for 20 h, underwent subsequent intramolecular cyclisation to give the cycloadduct pyrazolopyridopyrimidine **8a** (35%) together with 5-methyl-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione **7a** (50%), as a major product (Scheme 2). The structure of **8a** was established on the basis of its spectral data

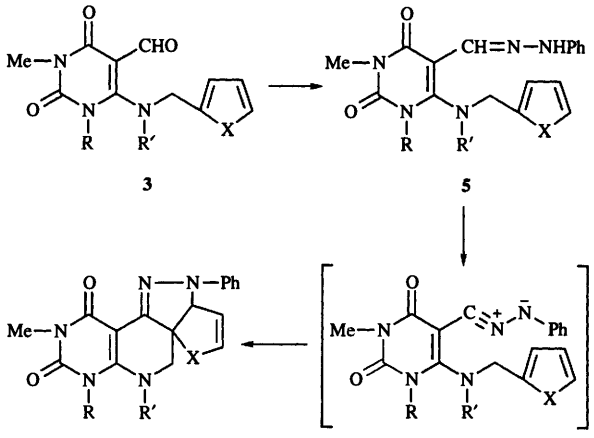


Deazaflavin is formed, when
R = H, R′ = C_6H_4OEt-*p*, X = O
R = H, X = O, R′ = Ph
R′ = H, X = S, R′ = C_6H_4OMe-*p*

Scheme 1

and elemental analysis. The ^{1}H NMR 300 MHz spectrum showed signals at δ 1.30–1.50 (t, 3 H, OCH_2CH_3), 3.40 (s, 3 H, NCH_3), 4.02 (q, 2 H, OCH_2CH_3), 4.15, 4.32 (each d, 2 H, d, 1 H, 4-H), 5.30 (d, 1 H, H), 5.00 (q, 1 H, H_2), 6.15 (d, 1 H, H_3) and 6.90–7.30 (m, 9 H, ArH). Since the NMR spectra of this cycloadduct showed no proton signal typical of a furan ring, it is clear that one of the furan double bonds had taken part in the cycloaddition. In this intramolecular capture of nitrile imines there was no evidence of any dimer formation. Similarly, uracil derivatives **3b–f** provided the corresponding pyrazolopyrido-pyrimidines **8b–f** (25–30%) and pyrazolopyrimidines **7** (50–55%).[15]

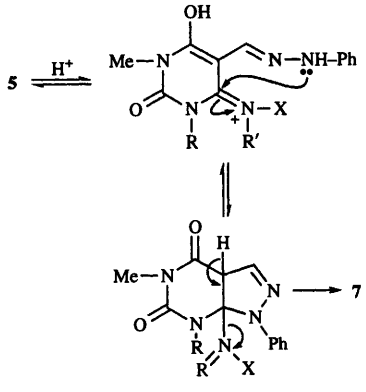
To further investigate the synthetic scope of this intramolecular cycloaddition for pyrimidine derivatives, we decided to expand our work to include compounds of the relatively inert[16] thiophene ring which has only a small degree of π-character.[16] Although bimolecular cycloadditions involving furan and thiophenes are known[17] little has been reported about their intramolecular counterpart.[18] Interestingly, the 1,2,3,4-tetrahydropyrimidine **3f**, as its hydrazone **5f** undergoes intramolecular, 1,3-dipolar (nitrile imine) cycloaddition under thermolytic conditions with the thiophene double bond to give the expected pyrazolopyridopyrimidine **8f** (25%). The pyrazolopyrimidine **7** was also isolated in this reaction (*ca.* 55%) as a side product. The structure of **8f** was confirmed on the basis of microanalytical



8	R	X	R′
a	H	O	C_6H_4OEt-*p*
b	H	O	Ph
c	H	O	cyclohexyl
d	H	O	Me
e	H	S	Et
f	H	S	C_6H_4Me-*p*
g	Me	O	C_6H_4OEt-*p*
h	Me	O	CH_2Ph
i	Me	O	cyclohexyl
j	Me	O	Me
k	Me	S	C_6H_4Me-*p*

Scheme 2

and spectral data (see Experimental section). We then allowed the corresponding dimethyluracil derivatives **1** (R = Me) to undergo intramolecular cyclisation in a similar fashion to give the cycloadducts **8g–l** (40%) together with 1,5-electrocyclisation product **7** (50%). Formation of the pyrazolopyrimidine **7** can be explained as follows: in competition with the 1,2-hydrogen shift, the nitrogen atom in the hydrazone **5** undergoes nucleophilic attack at the 6-position to give the pyrazolopyrimidinedione **9**, which subsequently loses the amine function to give **7** (Scheme 3).



Scheme 3

The formation in low yield of the pyrazolopyridopyrimidines **8a–l** prompted us to investigate further the final step in order to enhance the yield by optimising the reaction conditions. The hydrazone **5a**, when heated for additional 20 h, provided no characterisable products, decomposition having occurred. Acid catalysts[19] also failed to improve the product yields. Finally, we attempted to oxidise the hydrazone **5** with lead tetraacetate[20] in dry acetonitrile at 0 to −15 °C, to give first the nitrile imine intermediates **6** and thence the intramolecular cyclised products. Unsatisfactory results, with only minor improvements of yield (*ca.* 10%) over the above-mentioned thermal process were obtained.

In conclusion, we have demonstrated that a 1,3-dipole (nitrile imine) generated from the corresponding hydrazone either thermolytically or oxidatively undergoes intramolecular 1,3-dipolar cycloaddition across the hetero aromatic π-bonds to provide novel tricyclic nucleobases in fair to good yields and in a stereocontrolled fashion. We selected methylbarbituric acid for synthetic manipulation since with this the N-1 position (NH) allows attachment of side chains of clinically employed antiviral agents or glycosidation or phosphorylation to give a host of potential anticancer and antiviral compounds.[21]

Experimental

Mps were determined by using a Buchi melting point apparatus and are uncorrected. IR spectra were obtained by using Perkin-Elmer 237 and 5808 infrared spectrometers in KBr disks. The 270 and 300 MHz NMR spectra were recorded with tetramethylsilane as internal standard (by RSIC, Shillong). Mass spectra were recorded on an AEIMS-30 spectrometer. Elemental analyses were performed on a Hitachi 026 CHN analyser. All solvents were dried by standard methods before use. The progress of most reactions was monitored by TLC. Chromatographic purification was performed with silica gel 60 (120 mesh, Merck). The methyl- and dimethyl-barbituric acids were prepared according to a literature procedure.[22] Chloroformylation was achieved with dimethylformamide and phosphorus oxychloride.

General procedure for the synthesis of 5-formyl-6-(*N*-furfuryl-*N*-arylamino)-3-methyluracils

6-Chloro-5-formyl-3-methyluracil **1a** (R = H) (1.88 g, 10 mmol) was dissolved in dry dichloromethane (50 ml) and *N*-(2-furfuryl)-*p*-ethoxyaniline **2a** (2.17 g, 10 mmol) was added slowly to the solution with stirring, followed by anhydrous triethylamine (1.01 g, 10 mmol). Stirring was continued for 8–12 h after which the solvent was removed under reduced pressure to give an oily material. This was purified by column chromatography on silica gel using chloroform–ethyl acetate (4:1) as eluent to give 5-formyl-6-(*N*-furfuryl-*N*-*p*-ethoxyphenylamino)-3-methyluracil **3a** (30%) together with 5-deazaflavin **4a** (50%). Other 5-formyl-6-(*N*-furfuryl-*N*-arylamino)-3-methyluracils **3b–f**, 5-formyl-6-(*N*-furfuryl-*N*-arylamino)-1,3-dimethyluracils **3g–l** and 5-deazaflavins **4a,b,f** were obtained similarly and their characteristics are recorded below.

3a (R = H, X = O, R′ = C_6H_4OEt-*p*): (30%), mp 157–158 °C; ν_{max}(KBr)/cm^{-1} 3020 (NH), 1710 and 1645 (C=O); δ_H(300 MHz, $CDCl_3$) 1.44 (t, 3 H, OCH_2CH_3), 3.22 (s, 3 H, NCH_3), 4.00 (q, 2 H, OCH_2CH_3), 5.03 (s, 2 H, CH_2), 6.11 (d, 1 H), 6.28 (q, 1 H), 6.91–7.13 (m, 4 H), 7.37 (d, 1 H), 7.73 (br, 1 H) and 9.02 (s, 1 H, CHO); *m/z* 369 (M^+) (Found: C, 61.85; H, 5.23; N, 11.29. $C_{19}H_{19}N_3O_5$ requires C, 61.79; H, 5.15; N, 11.38%).

3b (R = H, X = O, R′ = Ph): (35%), mp 144–145 °C; ν_{max}(KBr)/cm^{-1} 3100 (NH), 1650 and 1700 (C=O); δ_H(300 MHz, $CDCl_3$) 3.20 (s, 3 H, NCH_3), 4.92 (s, 2 H, CH_2), 6.02 (d, 1 H, furan), 6.22 (dd, 1 H, furan), 6.85–7.15 (m, 5 H) and 9.76 (s, 1 H, CHO); *m/z* 339 (M^+) (Found: C, 62.60; H, 4.75; N, 13.07. $C_{17}H_{15}N_3O_4$ requires C, 62.77; H, 4.62; N, 12.92%).

3c (R = H, X = O, R′ = c-C_6H_{11}): (40%), mp 142–143 °C; ν_{max}(KBr)/cm^{-1} 3120 (NH), 1650 and 1710 (C=O); δ_H(300 MHz, $CDCl_3$) 0.92–2.16 (m, 11 H, cyclohexyl), 3.24 (s, 3 H, NCH_3), 4.80 (s, 2 H, CH_2), 6.08 (d, 1 H, furan), 6.24 (dd, 1 H, furan, 7.23 (d, 1 H, furan), 7.63 (br, 1 H) and 9.76 (s, 1 H, CHO); *m/z* 331 (M^+) (Found: C, 61.52; H, 6.28; N, 12.74. $C_{17}H_{21}N_3O_4$ requires C, 61.63; H, 6.34; N, 12.69%).

3d (R = H, X = O, R′ = Me): (50%), mp 127–129 °C; ν_{max}(KBr)/cm^{-1} 3100 (NH), 1660 and 1710 (C=O); δ_H(300 MHz,

$CDCl_3$) 2.82 (s, 3 H, NCH_3), 3.12 (s, 3 H, NCH_3), 4.56 (s, 2 H, CH_2), 6.16 (d, 1 H, furan), 6.32 (dd, 1 H, furan), 7.34 (d, 1 H, furan), 7.72 (br, 1 H) and 9.65 (s, 1 H, CHO); *m/z* 263 (M^+) (Found: C, 54.86; H, 5.08; N, 15.82. $C_{12}H_{13}N_3O_4$ requires C, 54.75; H, 4.97; N, 15.96%).

3e (R = H, X = O, R′ = Et): (50%), mp 131–132 °C; ν_{max}(KBr)/cm^{-1} 3100 (NH), 1650 and 1710 (C=O); δ_H(300 MHz, $CDCl_3$) 1.32 (t, 3 H, CH_2CH_3), 2.96 (s, 3 H, NCH_3), 4.06 (q, 2 H, CH_2CH_3), 5.04 (s, 2 H, CH_2), 6.12 (d, 1 H, furan), 6.34 (dd, 1 H, furan), 7.26 (d, 1 H, furan), 7.66 (br, 1 H) and 9.74 (s, 1 H, CHO); *m/z* 277 (M^+) (Found: C, 56.40; H, 5.30; N, 15.30. $C_{13}H_{15}N_3O_4$ requires C, 56.32; H, 5.42; N, 15.16%).

3f (R = H, X = S, R′ = C_6H_4Me-*p*): (35%), mp 123–124 °C; ν_{max}(KBr)/cm^{-1} 3120 (NH), 1660 and 1700 (C=O); δ_H(300 MHz, $CDCl_3$) 1.36 (s, 3 H, CH_3), 3.02 (s, 3 H, NCH_3), 4.82 (s, 2 H, CH_2), 5.96 (d, 1 H, thiophene), 6.14 (dd, 1 H, thiophene), 6.96–7.24 (m, 5 H, ArH and 1 H-thiophene), 7.36 (br, 1 H) and 9.14 (s, 1 H, CHO); *m/z* 355 (M^+) (Found: C, 60.94; H, 5.29; N, 11.21. $C_{18}H_{17}N_3O_3S$ requires C, 60.82; H, 4.82; N, 11.82%).

4a (R″ = OEt, X = O): (50%), mp 163–164 °C; δ_H(270 MHz, $CDCl_3$) 1.32 (t, 3 H, OCH_2CH_3), 3.12 (s, 3 H, NCH_3), 4.16 (q, 2 H, OCH_2CH_3), 4.96 (s, 2 H, CH_2), 6.12 (d, 1 H), 6.24 (dd, 1 H), 6.92–7.20 (m, 4 H, ArH), 7.34 (d, 1 H) and 9.90 (s, 1 H); *m/z* 351 (M^+) (Found: C, 64.89; H, 4.77; N, 11.86. $C_{19}H_{17}N_3O_4$ requires C, 64.96; H, 4.84; N, 11.97%).

4b (R″ = H, X = O): (55%), mp 156–157 °C; δ_H(270 MHz, $CDCl_3$) 3.21 (s, 3 H, NCH_3), 4.34 (s, 2 H, CH_2), 6.12 (d, 1 H, furan), 6.31 (dd, 1 H, furan), 6.92–7.21 (m, 5 H, ArH), 7.28 (d, 1 H, furan) and 9.82 (s, 1 H, H-5); *m/z* 307 (M^+) (Found: C, 66.53; H, 4.16; N, 13.59. $C_{17}H_{13}N_3O_3$ requires C, 66.45; H, 4.23; N, 13.68%).

4f (R″ = Me, X = S): (50%), mp 167–168 °C; δ_H(270 MHz, $CDCl_3$) 1.32 (s, 3 H, CH_3), 3.12 (s, 3 H, NCH_3), 4.72 (s, 2 H, CH_2), 5.82 (d, 1 H, thiophene), 6.16 (dd, 1 H, thiophene), 6.85–7.16 (m, 5 H, ArH and 1 H thiophene), 9.82 (s, 1 H, H-5); *m/z* 337 (M^+) (Found: C, 64.21; H, 4.61; N, 12.34. $C_{18}H_{15}N_3O_2S$ requires C, 64.07; H, 4.48; N, 12.45%).

General procedure for the synthesis of the phenylhydrazones of compounds 3

The uracil **3a** (370 mg, 10 mmol) in ethanol (10 ml) was added dropwise to a well stirred solution of phenylhydrazine hydrochloride (1.44 g, 10 mmol) and sodium acetate (2.05 g, 25 mmol) in water (5 ml). Stirring was continued for 10–15 min after which the reaction mixture was warmed on a water-bath for 15 min. The precipitated hydrazone was filtered off, washed with water, dried and recrystallised from ethanol. Concentration of the mother liquor gave additional (10%) hydrazone **5a**; mp 172–173 °C; total yield 80%. Similarly other hydrazones **5b–l** were prepared.

5a (R = H, X = O, R′ = C_6H_4OEt-*p*): (80%), mp 172–173 °C; ν_{max}(KBr)/cm^{-1} 3120 (NH), 1700 and 1610 (C=O, C=N); δ_H(300 MHz, $CDCl_3$) 1.62 (t, 3 H, OCH_2CH_3), 1.88 (br, 1 H, NH), 3.50 (s, 3 H, NCH_3), 4.02 (q, 2 H, OCH_2CH_3), 4.92 (s, 2 H, CH_2), 6.12 (d, 1 H), 6.26 (dd, 1 H), 6.75–7.36 (m, 11 H), 7.60 (d, 1 H) and 8.28 (s, 1 H, CH=N); *m/z* 459 (M^+) (Found: C, 65.42; H, 5.38; N, 15.31. $C_{25}H_{25}N_5O_4$ requires C, 65.36; H, 5.45; N, 15.25%).

5b (R = H, X = O, R′ = Ph): (75%), mp 162–163 °C; ν_{max}(KBr)/cm^{-1} 3130 (NH), 1710 and 1600 (C=O, C=N); δ_H(300 MHz, $CDCl_3$) 1.84 (br, 1 H, NH), 3.42 (s, 3 H, NCH_3), 4.80 (s, 2 H, CH_2), 6.02 (d, 1 H), 6.28 (dd, 1 H), 6.86–7.42 (m, 11 H), 7.44 (d, 1 H) and 8.22 (s, 1 H); *m/z* 415 (M^+) (Found: C, 66.58; H, 5.13; N, 16.92. $C_{23}H_{21}N_5O_3$ requires C, 66.51; H, 5.06; N, 16.92%).

5c (R = H, X = O, R′ = c-C_6H_{11}): (70%), mp 164–65 °C; ν_{max}(KBr)/cm^{-1} 3120 (NH), 1690 and 1600 (C=O, C=N); δ_H(300 MHz, $CDCl_3$) 1.08–2.18 (m, 11 H, c-C_6H_{11}), 1.92 (br, 1 H, NH), 3.32 (s, 3 H, NCH_3), 4.88 (s, 2 H, CH_2), 5.92 (d, 1 H), 6.30 (dd, 1 H), 6.88–7.36 (m, 6 H), 7.48 (d, 1 H) and 8.28 (s, 1 H); *m/z* 421 (M^+) (Found: C, 65.62; H, 6.49; N, 16.58. $C_{23}H_{27}N_5O_3$ requires C, 65.56; H, 6.41; N, 16.63%).

5d (R = H, X = O, R′ = Me): (75%), mp 156–157 °C; ν_{max}(KBr)/cm^{-1} 3140 (NH), 1690 and 1610 (C=O, C=N); δ_H(300 MHz, $CDCl_3$) 1.88 (br, 1 H, NH), 3.18 (s, 3 H, NCH_3), 3.32 (s, 3 H, NCH_3), 4.85 (s, 2 H, CH_2), 6.10 (d, 1 H), 6.40 (dd, 1 H), 6.92–7.48 (m, 6 H), 7.62 (d, 1 H) and 8.16 (s, 1 H, CH=NH); *m/z* 353 (M^+) (Found: C, 61.25; H, 5.43; N, 19.90. $C_{18}H_{19}N_5O_3$ requires C, 61.19; H, 5.38; N, 19.83%).

5e (R = H, X = O, R′ = Et): (75%), mp 159–160 °C; ν_{max}(KBr)/cm^{-1} 3100 (NH), 1680 and 1620 (C=O, C=N); δ_H(300 MHz, $CDCl_3$) 1.32 (t, 3 H, CH_2CH_3), 1.86 (br, 1 H, NH), 3.18 (s, 3 H, NCH_3), 4.12 (q, 2 H, CH_2CH_3), 4.22 (s, 2 H, CH_2), 6.02 (d, 1 H), 6.32 (dd, 1 H), 6.78–7.32 (m, 6 H), 7.52 (d, 1 H) and 8.22 (s, 1 H, CH=N); *m/z* 367 (M^+) (Found: C, 62.20; H, 5.76; N, 19.13. $C_{19}H_{21}N_5O_3$ requires C, 62.13; H, 5.72; N, 19.07%).

5f (R = H, X = S, R′ = C_6H_4Me-4): (80%), mp 178–179 °C; ν_{max}(KBr)/cm^{-1} 3020 (NH), 1710 and 1620 (C=O, C=N); δ_H(300 MHz, $CDCl_3$) 1.42 (s, 3 H, CH_3), 1.90 (br, 11 H, NH), 3.16 (s, 3 H, NCH_3), 4.66 (s, 2 H, CH_2), 6.04 (d, 1 H), 6.36 (dd, 1 H), 6.72–7.28 (m, 10 H), 7.48 (d, 1 H) and 8.20 (s, 1 H); *m/z* 445 (M^+) (Found: C, 64.58; H, 5.27; N, 15.84. $C_{24}H_{23}N_5O_2S$ requires C, 64.69; H, 5.20; N, 15.71%).

5g (R = Me, X = O, R′ = C_6H_4OEt-*p*): (70%), mp 186–187 °C; ν_{max}(KBr)/cm^{-1} 3120 (NH), 1690 and 1600 (C=O, C=N); δ_H(300 MHz, $CDCl_3$) 1.32 (t, 3 H, CH_2CH_3), 1.86 (br, 1 H, NH), 3.18 (s, 3 H, NCH_3), 3.36 (s, 3 H, NCH_3), 4.02 (q, 2 H, OCH_2CH_3), 4.88 (s, 2 H, CH_2), 5.96 (d, 1 H), 6.32 (dd, 1 H), 6.86–7.34 (m, 9 H), 7.48 (d, 1 H) and 8.22 (s, 1 H); *m/z* 473 (M^+) (Found: C, 65.88; H, 5.66; N, 14.92. $C_{26}H_{27}N_5O_4$ requires C, 65.96; H, 5.71; N, 14.80%).

5h (R = Me, X = O, R′ = $PhCH_2$): (70%), mp 166–168 °C; ν_{max}(KBr)/cm^{-1} 3140 (NH), 1680 and 1620 (C=O, C=N); δ_H(300 MHz, $CDCl_3$) 1.90 (br, 1 H, NH), 2.98 (s, 3 H, NCH_3), 3.46 (s, 3 H, NCH_3), 4.10 (s, 2 H, CH_2), 4.76 (s, 2 H, CH_2), 6.02 (d, 1 H), 6.26 (dd, 1 H), 6.74–7.32 (m, 10 H), 7.48 (d, 1 H) and 8.18 (s, 1 H); *m/z* 443 (M^+) (Found: C, 67.82; H, 5.75; N, 15.68. $C_{25}H_{25}N_5O_3$ requires C, 67.72; H, 5.64; N, 15.80%).

5i (R = Me, X = O, R′ = c-C_6H_{11}): (75%), mp 156–157 °C; ν_{max}(KBr)/cm^{-1} 3120 (NH), 1700 and 1610 (C=O, C=N); δ_H(300 MHz, $CDCl_3$) 0.96–2.18 (m, 11 H, c-C_6H_{11}), 1.88 (br, 1 H, NH), 3.12 (s, 3 H, NCH_3), 3.54 (s, 3 H, NCH_3), 4.62 (s, 2 H, CH_2), 6.02 (d, 1 H), 6.36 (dd, 1 H), 6.84–7.26 (m, 5 H), 7.42 (d, 1 H) and 8.24 (s, 1 H); *m/z* 435 (M^+) (Found: C, 66.13; H, 6.78; N, 16.16. $C_{24}H_{29}N_5O_3$ requires C, 66.21; H, 6.66; N, 16.09%).

5j (R = Me, X = O, R′ = Me): (80%), mp 140–141 °C; ν_{max}(KBr)/cm^{-1} 3100 (NH), 1680 and 1620 (C=O, C=N); δ_H(300 MHz, $CDCl_3$) 2.85 (s, 3 H, NCH_3), 3.32 (s, 3 H, NCH_3), 3.66 (s, 3 H, NCH_3), 4.52 (s, 2 H, CH_2), 6.12 (d, 1 H), 6.36 (dd, 1 H), 6.94–7.36 (m, 5 H), 7.52 (d, 1 H) and 8.28 (s, 1 H); *m/z* 367 (M^+) (Found: C, 62.22; H, 5.61; N, 19.12. $C_{19}H_{21}N_5O_3$ requires C, 62.13; H, 5.72; N, 19.07%).

5k (R = Me, X = O, R′ = Et): (85%), mp 147–149 °C; ν_{max}(KBr)/cm^{-1} 3120 (NH), 1690 and 1610 (C=O, C=N); δ_H(300 MHz, $CDCl_3$) 1.34 (t, 3 H, CH_2CH_3), 1.88 (br, 1 H, NH), 3.28 (s, 3 H, NCH_3), 3.70 (s, 3 H, NCH_3), 4.12 (q, 2 H, CH_2), 4.58 (s, 2 H, CH_2), 6.12 (d, 1 H), 6.42 (dd, 1 H), 6.86–7.38 (m, 5 H), 7.50 (d, 1 H) and 8.22 (s, 1 H); *m/z* 381 (M^+) (Found: C, 62.88; H, 6.16; N, 18.42. $C_{20}H_{23}N_5O_3$ requires C, 62.99; H, 6.04; N, 18.37%).

5l (R = Me, X = O, R′ = C_6H_4Me-*p*): (80%), mp 196–198 °C; ν_{max}(KBr)/cm^{-1} 3120 (NH), 1700 and 1620 (C=O, C=N); δ_H(300 MHz, $CDCl_3$) 1.90 (br, 1 H, NH), 2.52 (s, 3 H, CH_3), 3.30 (s, 3 H, NCH_3), 3.65 (s, 3 H, NCH_3), 4.02 (s, 2 H, CH), 5.98 (d, 1 H), 6.26 (dd, 1 H), 6.90–7.42 (m, 9 H), 7.58 (d, 1

H) and 8.20 (s, 1 H); *m/z* 459 (M^+) (Found: C, 65.38; H, 5.56; N, 15.40. $C_{25}H_{25}N_5O_2S$ requires C, 65.33; H, 5.48; N, 15.23%).

7-(4-Ethoxyphenyl)-8-methyl-9,11-dioxo-6,7,8,9,10,11-hexahydro-2a*H*-furo[2″,3″:4′,5′]pyrazolo[4′,3′:3,4]pyrido[2,3-d]pyrimidine: general procedure

Method A: thermolytic. A solution of the uracil hydrazone **5a** (0.460 g, 10 mmol) in dry benzene (15 ml) was heated under reflux under a nitrogen atmosphere for 40 h after which the solvent was evaporated to dryness. The residue was subjected to column chromatography on silica gel using $CHCl_3$–MeOH (8:1) as eluent to afford **8a** (0.16 g, 35%) and **7** (0.23 g, 50%). Similarly, the pyrazolopyridopyrimidines **8b–l** were prepared.

Method B: oxidation with LTA. A solution of lead tetraacetate (2.3 g, 5.2 mmol) in dry acetonitrile (30 ml) was added dropwise to a stirred and cooled solution of uracil hydrazone **5a** (0.16 g, 3.48 mmol) in dry acetonitrile (100 ml) at −16 °C during 1 h after which the reaction mixture was set aside at the same temperature. The resultant precipitate was filtered off and filtrate was evaporated to dryness. The residue was poured into water and extracted with dichloromethane (50 ml × 4). The extract was washed with water several times, dried and evaporated to afford a residue, crystallisation of which from ethanol gave **8a** (50%). The ethanol filtrate was evaporated to dryness and the residue was subjected to column chromatography to give **7** (30%). To prepare the pyrazolopyridopyrimidines **8b–l**, the oxidation of **5b–l** with LTA was carried out in dry acetonitrile at −15 °C. The result of these reactions together with the physical properties and the spectral data for compounds **8** and **7** are given below.

7a (R = H): (50%), mp 240 °C; ν_{max}(KBr)/cm^{-1} 1690 and 1650 (CO); δ_H(270 MHz, $CDCl_3$) 3.24 (s, 3 H, NCH_3), 6.85–7.46 (m, 5 H, ArH) and 7.96 (s, 1 H, 3-H); *m/z* 242 (M^+) (Found: C, 59.65; H, 4.26; N, 23.01. $C_{12}H_{10}N_4O_2$ requires C, 59.60; H, 4.13; N, 23.14%).

7g (R = Me): (55%), mp 238 °C; ν_{max}(KBr)/cm^{-1} 1700 and 1660 (CO); δ_H(270 MHz, $CDCl_3$) 3.22 (s, 3 H, NCH_3), 3.48 (s, 3 H, NCH_3), 6.88–7.34 (m, 5 H, ArH) and 8.02 (s, 1 H, 3-H); *m/z* 256 (M^+) (Found: C, 60.83; H, 4.78; N, 21.96. $C_{13}H_{12}N_4O_2$ requires C, 60.94; H, 4.67; N, 21.88%).

8a (R = H, X = O, R′ = C_6H_4OEt-*p*): (25%, 35% LTA), mp 224–225 °C; ν_{max}(KBr)/cm^{-1} 3120 (NH), 1700 and 1650 (C=O); δ_H(300 MHz, $CDCl_3$) 1.30–1.50 (t, 3 H, OCH_2CH_3), 3.40 (s, 3 H, *N*-CH_3), 4.02 (q, 2 H, OCH_2CH_3), 4.15, 4.32 (each d, 2 H, d, 1 H, 4-H), 5.30 (d, 1 H, H), 5.00 (q, 1 H, 2-H), 6.15 (d, 1 H, 3-H) and 6.90–7.30 (m, 9 H, ArH); *m/z* 457 (M^+) (Found: C, 65.72; H, 5.11; N, 15.28. $C_{25}H_{23}N_5O_4$ requires C, 65.65; H, 5.03; N, 15.32%).

8b (R = H, X = O, R′ = Ph): (30%, 42% LTA), mp 210–211 °C; ν_{max}(KBr)/cm^{-1} 3120 (NH), 1710 and 1650 (C=O); δ_H(270 MHz, TFA) 3.15 (s, 3 H, NCH_3), 4.05, 4.22 (each 1 H, d, 2 H, 4-H), 5.50 (d, 1 H, 3-H), 5.00 (q, 1 H, 2-H), 6.30 (d, 1 H, 1-H) and 6.90–7.35 (m, 10 H, ArH); *m/z* 413 (M^+) (Found: C, 66.90; H, 4.48; N, 17.06. $C_{23}H_{19}N_5O_3$ requires C, 66.83; H, 4.60; N, 16.95%).

8c (R = H, X = O, R′ = c-C_6H_{11}): (26%, 35% LTA), mp 206–207 °C; ν_{max}(KBr)/cm^{-1} 3120 (NH), 1700 and 1655 (C=O); δ_H(270 MHz, TFA) 0.90–2.20 (m, 11 H, c-C_6H_{11}), 3.30 (s, 3 H, NCH_3), 4.10, 4.25 (each 1 H, d, 2 H, 4-H), 5.48 (d, 1 H, 3-H), 5.04 (q, 1 H, 2-H), 6.40 (d, 1 H, 1-H) and 6.80–7.30 (m, 5 H, ArH); *m/z* 419 (M^+) (Found: C, 65.79; H, 5.89; N, 16.68. $C_{23}H_{25}N_5O_3$ requires C, 65.87; H, 5.97; N, 16.71%).

8d (R = H, X = O, R′ = Me): (30%, 40% LTA), mp 178–179 °C; ν_{max}(KBr)/cm^{-1} 3120 (NH), 1710 and 1650 (C=O); δ_H(270 MHz, $CDCl_3$) 2.65 (s, 3 H, NCH_3), 3.20 (s, 3 H, NCH_3), 4.20, 4.35 (each 1 H, d, 2 H, 4-H), 5.10 (q, 1 H, 2-H), 5.80 (d, 1 H, 3-H), 6.25 (d, 1 H, 1-H) and 6.90–7.30 (m, 5 H, ArH); *m/z* 351 (M^+) (Found: C, 61.43; H, 4.76; N, 19.86. $C_{18}H_{17}N_5O_3$ requires C, 61.54; H, 4.84; N, 19.94%).

8e (R = H, X = O, R′ = Et): (28%, 40% LTA); mp 197–198 °C; ν_{max}(KBr)/cm^{-1} 3110 (NH), 1700 and 1650 (C=O); δ_H(270 MHz, $CDCl_3$) 1.20 (t, 3 H, CH_2CH_3), 3.15 (s, 3 H, NCH_3), 4.20 (m, 4 H, CH_2 and CH_2CH_3), 5.60 (d, 1 H, 3-H), 5.04 (q, 1 H, 2-H), 5.60 (d, 1 H, 3-H), 6.30 (d, 1 H, 1-H) and 6.80–7.35 (m, 5 H, ArH); *m/z* 365 (M^+) (Found: C, 62.56; H, 5.29; N, 16.88. $C_{19}H_{19}N_5O_3$ requires C, 62.47; H, 5.21; N, 19.18%).

8f (R = H, X = S, R′ = C_6H_4Me-*p*): (26%, 35% LTA); mp 192–193 °C; ν_{max}(KBr)/cm^{-1} 3120 (NH), 1700 and 1650 (C=O); δ_H(270 MHz, $CDCl_3$) 1.40 (s, 3 H, CH_3), 2.95 (s, 3 H, NCH_3), 4.30, 4.45 (each 1 H, d, 2 H, 4-H), 5.00 (q, 1 H, 2-H), 5.50 (d, 1 H, 3-H), 6.30 (d, 1 H, 1-H), 6.90–7.35 (m, 9 H, ArH); *m/z* 443 (M^+) (Found: C, 64.87; H, 4.84; N, 15.92. $C_{24}H_{21}N_5O_2S$ requires C, 64.99; H, 4.77; N, 15.79%).

8g (R = Me, X = O, R′ = C_6H_4OEt-*p*): (28%, 40% LTA); mp 201–202 °C; δ_H(270 MHz, $CDCl_3$) 1.20 (t, 3 H, CH_2CH_3), 2.90 (s, 3 H, NCH_3), 3.30 (s, 3 H, NCH_3), 4.05–4.35 (m, 4 H, CH_2CH_3 and CH_2), 5.04 (q, 1 H, 2-H), 5.40 (d, 1 H, 3-H), 6.20 (d, 1 H, 1-H) and 6.75–7.30 (m, 9 H, ArH); *m/z* 471 (M^+) (Found: C, 66.33; H, 5.24; N, 14.95. $C_{26}H_{25}N_5O_4$ requires C, 66.24; H, 5.31; N, 14.86%).

8h (R = Me, X = O, R′ = $PhCH_2$): (27%, 40% LTA); mp 190–192 °C; δ_H(270 MHz, $CDCl_3$) 3.00 (s, 3 H, NCH_3), 3.30 (s, 3 H, NCH_3), 4.04–4.40 (m, 4 H, $C_6H_5CH_2$ and CH_2), 5.10 (q, 1 H, 2-H), 5.60 (d, 1 H, 3-H), 6.40 (d, 1 H, 1-H) and 6.80–7.35 (m, 10 H, ArH); *m/z* 441 (M^+) (Found: C, 68.12; H, 5.10; N, 15.73. $C_{25}H_{23}N_5O_3$ requires C, 68.03; H, 5.22; N, 15.87%).

8i (R = Me, X = O, R′ = c-C_6H_{11}): (28%, 36% LTA); mp 189–190 °C; δ_H(270 MHz, $CDCl_3$), 1.00–2.25 (m, 1 H, C_6H_{11}), 2.95 (s, 3 H, NCH_3), 3.30 (s, 3 H, NCH_3), 4.10–4.25 (each 1 H, d, 2 H, 4-H), 5.04 (q, 1 H, 2-H), 5.50 (d, 1 H, 3-H), 6.30 (d, 1 H, 1-H) and 6.80–7.35 (m, 5 H, ArH); *m/z* 433 (M^+) (Found: C, 66.45; H, 6.16; N, 16.10. $C_{24}H_{27}N_5O_3$ requires C, 66.51; H, 6.24; N, 16.17%).

8j (R = Me, X = O, R′ = Me): (40%); mp 188–189 °C; δ_H(270 MHz, $CDCl_3$) 2.55 (s, 3 H, NCH_3), 3.00 (s, 3 H, NCH_3), 3.40 (s, 3 H, NCH_3), 4.05, 4.20 (each 1 H, d, 2 H, 4-H), 5.00 (q, 1 H, 2-H), 5.50 (d, 1 H, 3-H), 6.20 (d, 1 H, 1-H) and 6.70–7.30 (m, 5 H, ArH); *m/z* 365 (M^+) (Found: C, 62.35; H, 5.30; N, 19.26. $C_{19}H_{19}N_5O_3$ requires C, 62.47; H, 5.21; N, 19.18%).

8k (R = Me, X = O, R′ = Et): (40%); mp 190–192 °C; δ_H(270 MHz, $CDCl_3$) 1.25 (t, 3 H, CH_2CH_3), 2.95 (s, 3 H, NCH_3), 3.35 (s, 3 H, NCH_3), 4.30 (m, 4 H, CH_2CH_3 and CH_2), 5.04 (q, 1 H, CH_2), 5.40 (d, 1 H, 3-H), 6.20 (d, 1 H, 1-H) and 6.40–7.20 (m, 5 H, ArH); *m/z* 379 (M^+) (Found: C, 63.41; H, 5.66; N, 18.32. $C_{20}H_{21}N_5O_3$ requires C, 63.32; H, 5.54; N, 18.47%).

8l (R = Me, X = S, R′ = C_6H_4Me-*p*): (33%); mp 219–220 °C; δ_H(270 MHz, $CDCl_3$) 1.35 (s, 3 H, CH_3), 2.95 (s, 3 H, NCH_3), 3.40 (s, 3 H, NCH_3), 4.10, 4.25 (each 1 H, d, 2 H, 4-H), 5.04 (q, 1 H, 2-H), 5.50 (d, 1 H, 3-H), 6.25 (d, 1 H, 1-H) and 6.85–7.30 (m, 9 H, ArH); *m/z* 457 (M^+) (Found: C, 65.70; H, 5.12; N, 15.27. $C_{25}H_{23}N_5O_2S$ requires C, 65.52; H, 5.06; N, 15.31%).

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