A Convenient One-pot Synthesis of Pyrimido[4,5-*b*]quinolines as 5-Deaza Non-classical Antifolate Inhibitors†

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A convenient one-pot synthesis of pyrimido[4,5-*b*]quinolines as non-classical 5-deaza antifolate inhibitors by the reaction of 6-amino-4-oxo-2-thioxotetrahydropyrimidine **1** with aromatic aldehydes and dimedone is reported.

Analogues of folic acid, particularly inhibitors of dihydrofolate reductase (DHFR), constitute a class of cytotoxic drugs, the antifolates, which are important anticancer, antimalarial and antibacterial agents.[1–3] A disadvantage of classical folates is that they require a transport mechanism into the cell.[4] Thus cells which lack this trans-port mechanism are not susceptible to the action of classical antifolates. As part of our program directed towards the synthesis and biological evaluation of condensed azines[5–8] *via* simple-route and laboratory-available starting materials, we report here, a convenient, general and simple route for the synthesis of pyrimido[4,5-*b*]quinolines.

Refluxing a mixture of equimolecular amounts of 6-amino-4-oxo-2-thioxotetrahydropyrimidine **1**, benzaldehyde **2a** and dimedone **3** in absolute ethanol containing a catalytic amount of piperidine resulted in the formation of a compound of molecular formula $C_{19}H_{19}N_3O_2S$ [*m/z* 353(M$^+$)] in excellent yield (Scheme 1). This may be formulated as either pyrimido[4,5-*b*]isoquinoline **6a** or pyrimido[4,5-*b*]quinoline **8a**. The pyrimido[4,5-*b*]quinoline derivative **8a** was considered most likely based on analytical and spectral data. The ^{1}H NMR spectra showed a sharp singlet at δ 4.75 that integrated for one proton which was assigned to CH-5. It is difficult to rationalise this signal if the reaction product was **6a**, since it will appear at a higher field (C_a δ 3.7–4.0). 1,4-Dihydropyridines are known to exhibit such a proton signal at a lower field.[9,10] In addition the ^{1}H NMR spectrum of **8a** showed signals for ring NH, aromatic, two methylene and two methyl groups (see Experimental section). The ^{13}C NMR spectrum for the reaction product showed the pattern shown in Scheme 2. It is of note that this compound in its ^{13}C NMR spectra showed signals for C-9a and C-10a at high δ values (151.1, 152.3) while carbon atoms C-4a and C-5a appeared at unusually low δ values (95.9, 109.7). This finding can be rationalised for by the strong push–pull effect of the NH and CO substituents linked to the C4a–C10a and C5a–C9a double bonds. Similarly, compound **1** reacted with **2b–d** and dimedone **3** to afford **8b–d**. The structure assigned for the reaction products was established based on analytical and spectral data. In each case ^{1}H NMR spectroscopy showed a sharp singlet at δ 4.7–4.85 assigned to CH-5.

	Ar
2, 4, 8a	Ph
b	$C_6H_4OMe\text{-}p$
c	$C_6H_4Cl\text{-}p$
d	2-furyl
e	2-thienyl
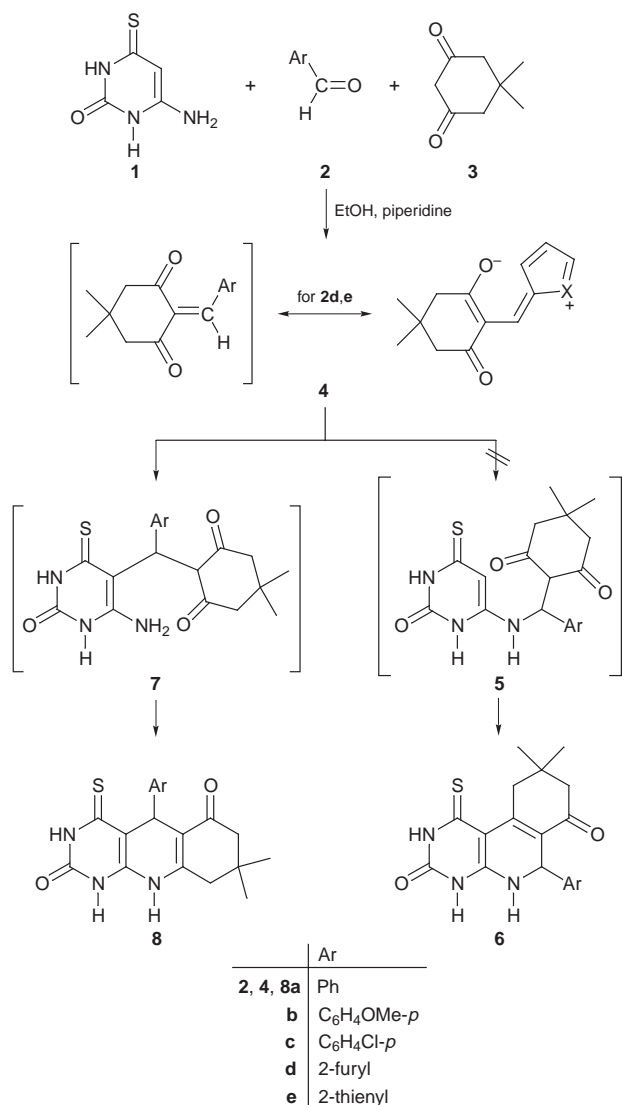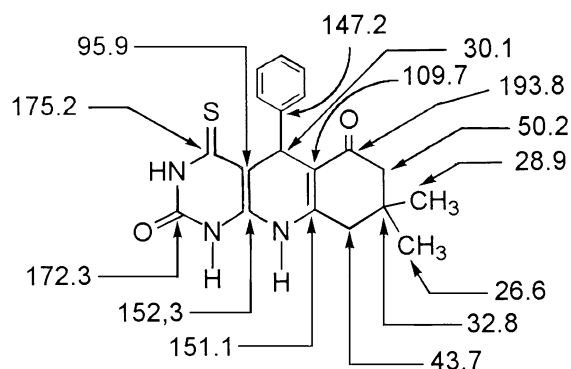
Scheme 1

127.59, 127.5, 125.49 (aromatic *o*-, *m*-, *p*-carbons)

Scheme 2 ^{13}C NMR pattern for **8a**

Compounds **8a–d** were assumed to be formed by initial condensation of the aromatic aldehyde and dimedone to form the ylidine derivative **4** since the methylene group flanked by the two carbonyl groups is highly reactive. This was followed by Michael addition of activated CH-5 of compound **1** to the activated double bond in **4** to form the acyclic adduct **7**. This was followed by 6-*exo-dig*. cyclization and oxidation under the applied reaction conditions.[11,12] Alternatively, addition of the exocyclic amino group of **1** to the activated double bond in **4** and cyclization will lead to the formation of the cyclized product **6**. In contrast to this behaviour, reaction of compound **1** with **2e** and **3** led to the formation of **4e**. The fact that reaction of **2e** has stopped only at ylidene formation can be readily understood in terms of the high contribution of charge separated resonance form. This is not so for other aldehydes as the sulfur can more readily accommodate the positive charge.

Experimental

Melting points are uncorrected. IR spectra were recorded (KBr) on a Shimadzu 470 spectrophotometer. ^{1}H and ^{13}C NMR spectra were measured in $(CD_3)_2SO$ on a JNM-LA 400 (400 MHz) spectrometer with Me_4Si as internal standard; chemical shifts are expressed in ppm. Mass spectra were determined on a JEOL JMS 600 spectrometer operating at 70 eV. Microanalyses were performed by the Microanalytical Data Unit at Cairo University.

General Procedure for the Synthesis of the Substituted Pyrimido[4,5-b]*quinolines* **7a–e** *and Ylidene Derivatives.*—To a solution of **1** (0.01 mol), **2** (0.01 mol) and **3** (0.01 mol) in absolute ethanol (30 ml), was added a catalytic amount of piperidine (1 ml). The reaction mixture was heated under reflux for 30 min. After cooling to room temperature, the solid product formed was collected by filtration, dried and recrystallized from ethanol.

Compound **8a**.—85% Yield, mp 296–298 °C; v_{max}/cm^{-1} 3100 (NH), 2950 (aliphatic CH) and 1640 (CO). δ_H 1.02 (s, 3H, CH$_3$), 1.63 (s, 3H, CH$_3$), 1.98 (d, 1H, CH-7a, $J = 16$ Hz), 2.01 (d, 1H, CH-7b, $J = 16$ Hz), 2.37 (d, 1H, CH-9a, $J = 17$ Hz), 2.44 (d, 1H, CH-9b, $J = 17$ Hz), 4.75 (s, 1H, H-5), 7.02 (t, 1 Ar-H, $J = 6.5$ Hz), 7.13–7.18 (m, 4 Ar-H), 11.10 (s, 1H, NH) (Found: C, 64.7; H, 5.5; N, 11.7; S, 8.9. C$_{19}$H$_{19}$N$_3$O$_2$S requires C, 64.57; H, 5.42; N, 11.89; S, 9.07%). m/z 353 (M$^+$, 58%).

Compound **8b**.—87% Yield, mp 316–318 °C; v_{max}/cm^{-1} 3300 (NH), 2950 (aliphatic CH) and 1640 (CO). δ_H 1.01 (s, 3H, CH$_3$), 1.2 (s, 3H, CH$_3$), 1.99 (d, 1H, CH-7a, $J = 16$ Hz), 2.17 (d, 1H, CH-7b, $J = 16$ Hz), 2.45 (d, 1H, CH-9a, $J = 14$ Hz), 2.48 (d, 1H, CH-9b, $J = 14$ Hz), 3.60 (s, 3H, CH$_3$), 4.60 (s, 1H, H-5), 6.72 (d, 2Ar-H,

$J = 8.5$ Hz), 7.08 (d, 2Ar-H, $J = 8.5$ Hz), 11.09 (s, 1H, NH) (Found: C, 62.5; H, 5.7; N, 10.8; S, 8.5. C$_{20}$H$_{21}$N$_3$O$_3$S requires C, 62.64; H, 5.52; N, 10.96; S, 8.36%).

Compound **8c**.—80% Yield, mp 308–310 °C; v_{max}/cm^{-1} 3200 (NH), 2950 (aliphatic CH) and 1640 (CO). δ_H 0.99 (s, 3H, CH$_3$), 1.5 (s, 3H, CH$_3$), 1.98 (d, 1H, CH-7a, $J = 16$ Hz), 2.16 (d, 1H, CH-7b, $J = 16$ Hz), 2.36 (d, 1H, CH-9a, $J = 17$ Hz), 2.43 (d, 1H, CH-9b, $J = 17$ Hz), 4.73 (s, 1H, H-5), 7.10–7.22 (m, Ar-H), 11.15 (s, 1H, NH) (Found: C, 58.7; H, 4.8; Cl, 8.9; N, 11.0; S, 8.4. C$_{19}$H$_{18}$ClN$_3$O$_2$S requires C, 58.83; H, 4.68; Cl, 9.15; N, 10.83; S, 8.26%).

Compound **8d**.—79% Yield, mp 245–246 °C; v_{max}/cm^{-1} 3200 (NH), 2950 (aliphatic CH) and 1640 (CO). δ_H not available (insoluble in common solvents) (Found: C, 59.7; H, 5.2; N, 9.5. C$_{17}$H$_{17}$N$_3$O$_3$S requires C, 59.46; H, 4.99; N, 12.24; S, 9.34%).

Compound **4e**.—90% Yield, mp 266–268 °C; v_{max}/cm^{-1} 2970 (aliphatic CH) and 1640 (CO). δ_H 0.94 (s, 3H, CH$_3$), 1.0 (s, 3H, CH$_3$), 2.06 (d, 2H, CH$_2$), 2.20 (d, 2H, CH$_2$), 5.08 (s, 1H, ylidene CH), 6.70–6.80 (m, 1H, thiophene H-4), 7.13 (d, 1H, thiophene H-5, $J = 1.2$ Hz); 7.14 (d, 1H, thiophene H-3, $J = 1.2$ Hz). m/z 231 (M$^+$, 13%) (Found: C, 66.5; H, 6.2; S, 13.9. C$_{13}$H$_{14}$O$_2$S requires C, 66.64; H, 6.02; S, 13.68%).

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