Synthesis of a novel series of pyrimido- and triazino[4,5-*b*] quinolines

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New tetrahydropyrimido[4,5-*b*]quinolines, hexahydropyrimido[4,5-*b*]quinolines, a thioxohexahydropyrimido[4,5-*b*] quinoline, an octahydropyrimido[4,5-*b*]quinoline and a tetrahydro[1,2,3]triazino[4,5-*b*]quinoline have been synthesised. A series of *S*-alkyltetrahydroprimido[4,5-*b*]quinolines was obtained by the reaction of the thioxohexahydropyrimido[4,5-*b*]quinoline with allyl bromide, propargyl bromide or with epichlorohydrin. All newly synthesised compounds were characterised by IR, ^{1}H, ^{13}C NMR and elemental analysis.

Keywords: pyrimido[4,5-*b*]quinolines, thioxopyrimido[4,5-*b*]quinoline, triazino[4,5-*b*] quinoline and *S*-alkylprimido[4,5-*b*] quinolines

Quinolines and symmetrical heterocycles bearing pyrimido or triazinoquinoline moieties have been found to possess a broad spectrum of pharmacological and medicinal[1,2] properties, including antimicrobial,[3–9] antihypertensive,[10] CNS depressant,[11] anti-HIV infective,[12] antimalarial,[13] antihistaminic,[14] antitumour[15] activities and more recently for the treatment of pain,[16] antithrombotic activity[17] and as new inhibitions of bacterial DNA gyrase B.[18] In addition, quinolines were reported to exert antifungal,[19] anticancer,[20] antiviral,[21] analgesic[22] and antiinflammatory activities.[23] Also, several reduced quinoline derivatives have shown significant anticancer activity.[24] Recently, several pyrimidine derivatives were reported to have antimicrobial,[25, 26] antiinflammatory[9] and antioxidant[22] activities. In the light of these facts, we now report the synthesis of series of reduced quinoline, pyrimidoquinoline, and triazinoqunoline derivatives.

Results and discussion

In this investigation, a series of new pyrimido[4,5-*b*]quinolines **2–9**, triazino[4,5-*b*]quinoline **10**, and *S*-alkylpyrimido[4,5-*b*] quinolines **11–13** were designed and synthesised. 2-Amino-7,7-dimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxamide **1** was prepared according to the literature procedure.[27–29] Reaction of the carboxamide **1** with formic acid, or triethyl orthoformate or formamide afforded the pyrimido[4,5-*b*]quinoline derivative **2** as shown in Scheme 1. The IR spectrum of compound **2** displayed adsorption bands at 3470 (NH) and at 1692 and 1672 cm^{-1} for two amide C=O groups. The ^{1}H NMR spectrum of **2** showed signals at δ 0.97, 1.04, 1.96, 2.29, and 4.82 ppm for two CH_3 groups, two CH_2 groups and the CH-Ph proton, in addition to signals at δ 9.28 and 10.1 ppm for two NH groups. The ^{13}C NMR spectrum showed signals at δ 26.9, 27.7 ($2 \times CH_3$), 32.7 $C(CH_3)_2$, 39.9 C-5 (CH-Ph), 40.1 (C-9) and 50.72 (C-7). Treatment of compound **1** with phenyl and methyl isothiocyanate in the presence of acetic acid led, remarkably, to the formation of the thioxo-2,3,7,8,9,10-hexahydropyrimido[4,5-*b*]quinoline-4,6(1*H*,5*H*)-diones **3a, b** (Scheme 1). Nucleophilic attack of the C-2 amino group of compound **1** on the isothiocyanate produces the corresponding thiourea derivative, which in turn cyclizes onto the amide group to give **3a, b**. A similar pathway resulting in the formation of fused pyrimidinediones has been noted previously.[30] The ^{1}H NMR spectrum of compound **3a** showed a signal at δ 4.82 ppm characteristic of the (H-5) CH-Ph proton. In the ^{13}C NMR spectrum, signals for the C=S and two C=O groups appeared at 162.2, 170.7 and 194.8 ppm, respectively. Whilst, the ^{1}H NMR spectrum for compound **3b** showed signals at δ 3.39 and 4.78 ppm for the NCH_3 and (H-5) CH-Ph protons respectively, in addition to multiplet aromatic signals at δ 7.12–7.33 ppm for the phenyl group.

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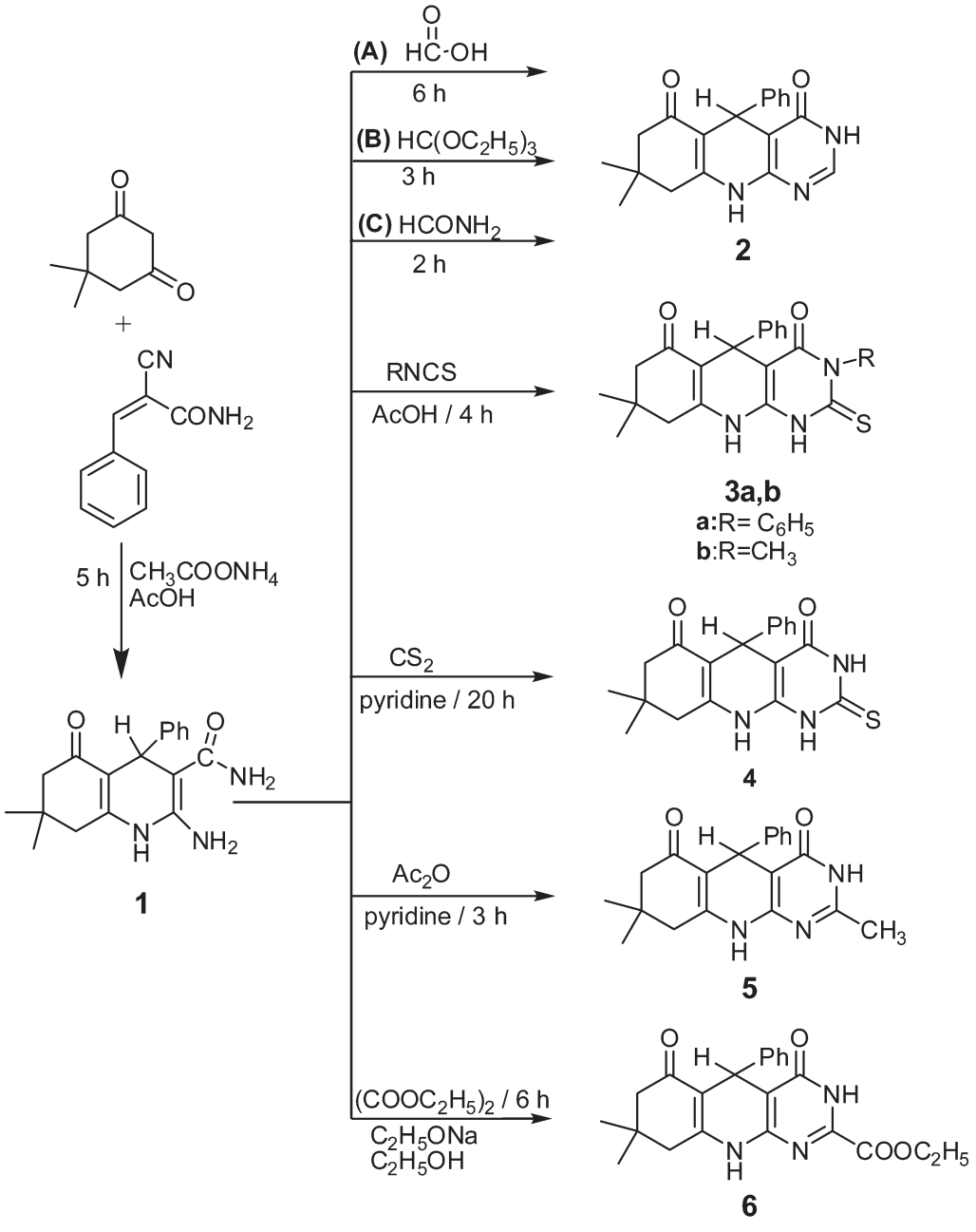
The reaction of compound **1** with carbon disulfide provided **4** whilst acylation with acetic anhydride in pyridine generated the pyrimido[4,5-*b*]quinolinedione **5** as shown in Scheme 1. The IR spectrum of compound **4** gave absorption bands at 3430 (NH) and at 1690 and 1666 cm^{-1} for two C=O groups. The ^{1}H and ^{13}C NMR spectra and elemental analysis of compound **4** are collated in the experimental section. Characteristic ^{1}H NMR signals for compound **5** appeared at δ 2.38 and 4.89 for the CH_3 group at C-2 and the H-5 proton respectively, the ^{13}C NMR spectrum was also fully consistent with the constitution of this compound. The pyrimidine ester **6** was obtained by condensation of **1** with diethyl oxalate in presence of sodium ethoxide in absolute ethanol (Scheme 1). The spectral data (IR, ^{1}H, ^{13}C NMR) and elemental analysis of **6** were in agreement with the assigned structure (see experimental section).

Cyclocondensation of **1** with carbonyl compounds gave the pyridopyrimidine derivatives **7–9**. Treatment of **1** with an equimolar amount of benzaldehyde provided **7** (60%) whilst condensation with cyclohexanone afforded the spirocycle **8** (70%). Acylation of **1** with, 4-nitrobenzoyl chloride in pyridine provided the pyrimidinedione **9** in 70% yield (Scheme 2). Structures of these compounds were fully supported by their spectral data *i.e* IR, ^{1}H, ^{13}C NMR as well as elemental analysis. Compound **7** was isolated by crystallisation as a single isomer, which was confirmed by the ^{1}H and ^{13}C NMR spectra. The ^{1}H NMR spectrum of **7** indicated the presence of signals at δ 4.88 and 5.98 which correlated to the CH-Ph (H-5) and the NCHPhN (H-2) protons respectively, whilst the ^{13}C NMR spectrum showed signals at δ 51.8 and 62.1 characteristic for C-7 and C-2 respectively. The IR spectrum of compound **8** exhibited bands for an NH, two amide C=O groups and an *α,β*-unsaturated ketone at 3408, 1695 and 1668 cm^{-1}, respectively. In the ^{1}H NMR spectrum of **8** multiplet signals in the range δ 1.43–1.53 correspond to three CH_2 units of the cyclohexane ring whilst a further two methylene groups resonated as a broad triplet centred at 1.73 ppm. The C-5 methine proton absorbed at 4.82 ppm in addition to an NH signal corresponding to three protons at δ 10.01. The ^{13}C NMR spectrum of **8** showed signals at 23.5, 25.8 and 35.9 ppm characteristic of five cyclohexane-ring carbons, in addition to a signal at 50.8 ppm for the quaternary C-2 carbon. The ^{1}H NMR spectrum of compound **9** revealed the presence of a signal at δ 4.89 ppm for the C-5 methine proton, in addition to signals characteristic of the *p*-nitrophenyl protons at δ 8.18 and 8.31 ppm (d, J = 8.80 Hz).

The ^{13}C NMR spectrum of **9** exhibited a signal at δ 39.9 ppm for C-5, in addition to 15 signals for the sp^2 and aromatic carbon atoms, C=N unit and two C=O groups.

Diazotisation of **1** by treatment with sodium nitrite in HCl–AcOH gave the triazino[4,6-*b*]quinolinedione **10** in 60% yield (Scheme 2). The ^{1}H NMR spectrum of the latter showed signals at δ 4.78 and 10.01 ppm for the C-5 and NH protons



Scheme 1

respectively, whilst the ^{13}C spectrum gave signals at δ 50.5, 170.7 and 194.9 ppm characteristic for C-5, and two C=O groups.

Alkylation of **3a** with allyl bromide, propargyl bromide or with epichlorohydrin in presence of potasium carbonate in dry acetone afforded the corresponding *S*-alkylated derivatives **11–13** (Scheme 3). The IR spectra of these compounds revealed the absence of bands at 1230 cm^{-1} characteristic for C=S groups, in addition to the presence of bands for the two C=O groups.

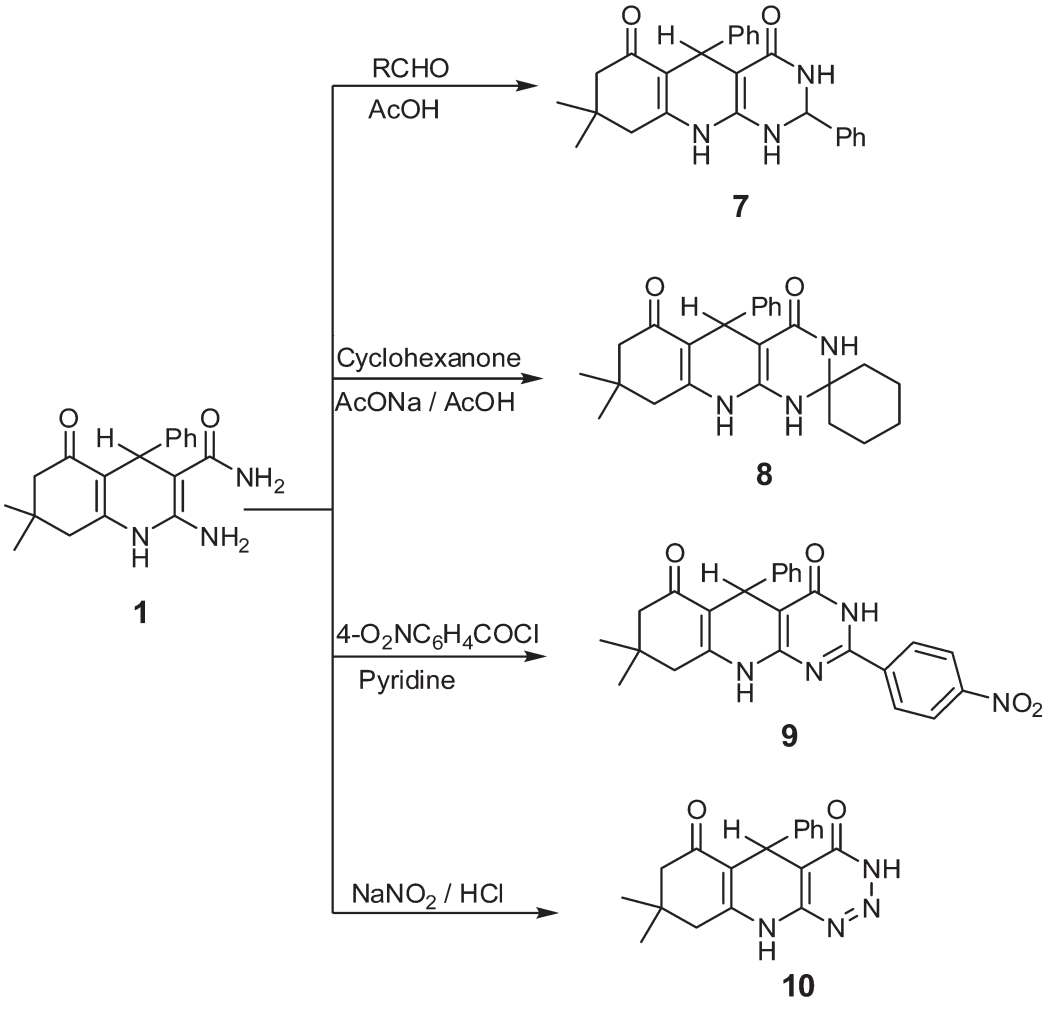
The ^1H NMR spectrum of compound **11** showed signals at δ 3.48 and 4.80 for CH_2S and H-5 protons respectively, in addition to signals at δ 5.08, 5.18 and 6.03 characteristic for the alkenic protons of the allyl group. Its ^{13}C NMR spectrum exhibited signals at δ 40.8 and 51.5 for CH_2S and C-5 carbons, in addition to the aromatics and other sp^2 signals (experimental section). The IR, ^1H, ^{13}C NMR and elemental analysis data of compound **12** were in agreement with the assigned structure.

The ^1H NMR spectrum of **13** indicated the presence of signals in the range δ 2.38–3.12 as multiplets for CH_2O, CHO and CH_2S units of the 2,3-epoxypropyl group, in addition to, signal at 4.78 ppm for H-5.

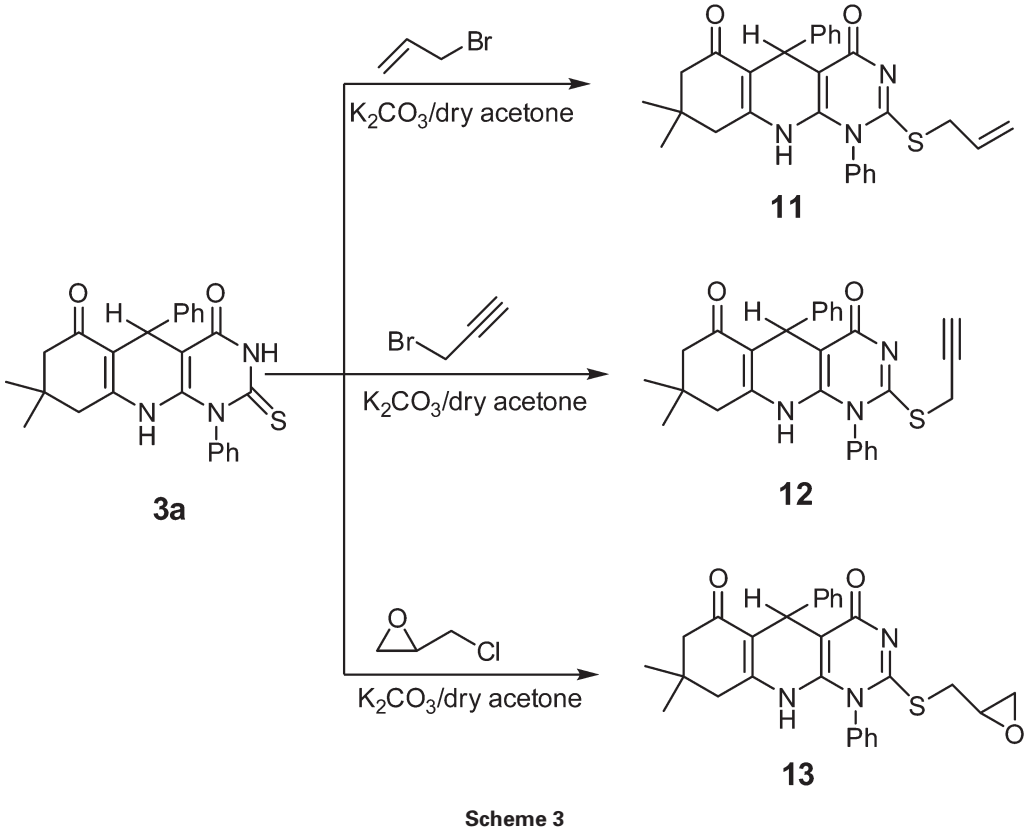
Experimental

All melting points were taken on an Electrothermal IA 9100 series digital melting point apparatus. The IR spectra (KBr) discs were recorded on a Perkin-Elmer 1650 spectrometer (USA). ^1H, ^{13}C NMR spectra were determined on Bruker AC-300 MHz instrument. Chemical shifts are expressed as δ (ppm) relative to TMS as internal standard and DMSO-d_6 as solvent. The elemental analysis was carried by the Micro-analytical Centre, Cairo University.

2-Amino-7,7-dimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxamide (**1**): A mixture of dimedone (5,5-dimethyl-1,3-cyclohexane dione) (1.40 g, 10 mmol), benzylidenecyanoacetamide[28,29] (1.70 g, 10 mmol) and ammonium acetate (1.15 g, 15 mmol) was heated under reflux for 5 h then poured into ice-water. The solid product was filtered off, dried and recrystallised from ethanol to give **1** as yellowish white solid. Yield 70%; m.p. 229–230 °C. IR (KBr): 3510–3420 (NH), 1665 (C=O, amide), 1698 cm^{-1} (C=O). ^1H NMR (DMSO-d_6): δ = 0.95 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 2.07 (s, 2H, CH_2), 2.34 (s, 2H, CH_2), 5.10 (s, 1H, CH-Ph), 7.06–7.35 (m, 5H,



Scheme 2



Scheme 3

ArH), 8.08 (br, 2H, NH_2), 8.51 (s, 2H, $CONH_2$). Anal. Calcd for $C_{18}H_{21}N_3O_2$ (311.38): C, 69.43; H, 6.80; N, 13.49. Found: C, 69.28; H, 6.82; N, 13.48%.

*8,8-Dimethyl-5-phenyl-7,8,9,10-tetrahydropyrimido[4,5-*b*]quinoline-4,6(3*H*,5*H*)-dione* (**2**)*: Method (A)*: A mixture of **1** (3.11 g, 10 mmol) and formic acid (20 mL) was refluxed for 6 h. After cooling, the solid product was filtered off, dried and recrystallised from methanol to give **2** as yellow solid. Yield 60%. m.p. 262–264 °C.

Method (B): A mixture of **1** (3.11 g, 10 mmol) and triethyl orthoformate (15 mL) was refluxed for 3 h. After cooling, the reaction mixture was poured into cold water the solid product was filtered off, washed with water, dried and recrystallised from methanol to give **2**. Yield 62%. m.p. 262–264 °C

Method (C): A mixture of **1** (3.11 g, 10 mmol) and formamide (20 mL) was boiled under reflux for 2 h. After cooling the reaction mixture was poured into cold water, the product was filtered off, washed with water, dried and recrystallised from methanol to give **2**. Yield 50%. m.p. 262– 264 °C. IR (KBr): 3470 (NH), 1692 and 1672 cm^{-1} for (2C=O). ^1H NMR (DMSO-d_6): δ = 0.97 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 1.96 (s, 2H, CH_2), 2.29 (s, 2H, CH_2), 4.82 (s, 1H, CH-Ph), 7.02–7.50 (m, 6H, ArH), 9.28 (s, 1H, NH), 10.1 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ = 26.9, 27.7 (2 × CH_3), 32.7 (C-8), 39.9 (C-5), 40.1 (C-9), 50.72 (C-7), 101.2, 111.9, 125.7, 126.9, 128.9, 143.4, 147.6, 149.7, 153.1, 170.7 and 194.8 (ArC, C=N and 2 × C=O). Anal. Calcd for $C_{19}H_{19}N_3O_2$ (321.37): C, 71.01; H, 5.96; N, 13.08. Found: C, 71.20; H, 5.98; N, 13.12%.

*8,8-Dimethyl-3,5-diphenyl-2-thioxo-2,3,7,8,9,10-hexahydropyrimido[4,5-*b*]quinoline-4,6(1*H*,5*H*)-dione* (**3a**): A mixture of **1** (3.11 g, 10 mmol) and phenyl isothiocynate (1.35 g, 10 mmol) in acetic acid (20 mL) was refluxed for 4 h. After cooling the solid product was filtered off, dried and recrystallised from ethanol to give **3a** as red crystals. Yield 75%. m.p. 214–215 °C. IR (KBr): 3480 (NH), 1698 (C=O), 1668 (C=O, amide), 1230 cm^{-1} (C=S). ^1H NMR (DMSO-d_6): δ = 0.98 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 1.89 (s, 2H, CH_2), 2.28 (s, 2H, CH_2), 4.82 (s, 1H, CH-Ph), 6.25–7.33 (m, 10H, ArH), 9.28 (s, 1H, NH), 10.2 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ = 26.9, 27.8 (2 × CH_3), 32.8 (C-8), 39.8 (C-5), 40.0 (C-9), 50.6 (C-7), 80.2 (C-4a), 111.9, 125.9, 126.9, 128.0, 128.3, 128.9, 143.4, 144.4, 147.6, 149.7, 153.1, 162.2, 170.7 and 194.8 (ArC, 2 C=O and C=S). Anal. Calcd for $C_{25}H_{23}N_3O_2S$ (429.53): C, 69.91; H, 5.40; N, 9.78. Found: C, 69.94; H, 5.41; N, 9.80%.

*3,8,8-Trimethyl-5-phenyl-2-thioxo-2,3,7,8,9,10-hexahydropyrimido[4,5-*b*]quinoline-4,6(1*H*,5*H*)-dione* (**3b**): A mixture of **1** (3.11 g, 10 mmol) and methyl isothiocyanate (0.73 g, 10 mmol) in acetic acid (20 mL) was refluxed for 4 h. After cooling the solid product was filtered off, dried and recrystallised from ethanol to give **3a**. Yield 72%. m.p. 208–210 °C.

^1H NMR (DMSO-d_6): δ = 0.97 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 1.88 (s, 2H, CH_2), 2.27 (s, 2H, CH_2), 3.39 (s, 3H, NCH_3), 4.78 (s, 1H, CH-Ph), 7.12–7.33 (m, 5H, ArH), 9.10 (s, 1H, NH), 10.01 (s, 1H, NH). Anal. Calcd for $C_{20}H_{21}N_3O_2S$ (367.46): C, 65.37; H, 5.76; N, 11.44. Found: C, 63.35; H, 5.81; N, 11.64%.

*8,8-Dimethyl-5-phenyl-2-thioxo-2,3,7,8,9,10-hexahydropyrimido[4,5-*b*]quinoline-4,6(1*H*,5*H*)-dione* **(4):** A mixture of **1** (3.11 g, 10 mmol) and carbon disulfide (1.56 g, 20 mmol) in dry pyridine (20 mL) was refluxed for 20 h (until the evolution of H_2S was complete). After cooling the reaction mixture was poured into cold dil. HCl, the solid product was filtered off, dried and recrystallised from methanol to give **4** as yellow crystals. Yield 60%. m.p. 226–227 °C. IR (KBr): 3430 (NH), 1690 (C=O), 1666 (C=O, amide) and 1235 cm^{-1} (C=S). ^1H NMR (DMSO-d_6): δ = 0.97 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 1.93 (s, 2H, CH_2), 2.33 (s, 2H, CH_2), 4.80 (s, 1H, CH-Ph), 7.02–7.25 (m, 5H, ArH), 8.29 (s, 1H, NH), 10.0 (s, 2H, 2NH). ^{13}C NMR (DMSO-d_6): δ = 27.0, 27.6 (2CH_3), 32.9 (C-8), 39.8 (C-5), 40.01 (C-9), 50.0 (C-7), 87.8 (C-4a), 111.9, 125.9, 126.9, 128.0, 128.9, 143.4, 149.7, 153.1, 170.7 and 194.8 (ArC, 2 × C=O and C=S). Anal. Calcd for $C_{19}H_{19}N_3O_2S$ (353.44): C, 64.57; H, 5.42; N, 11.89. Found: C, 64.70; H, 5.46; N, 11.92%.

*2,8,8-Trimethyl-5-phenyl-7,8,9,10-tetrahydropyrimido[4,5-*b*]quinoline-4,6(3*H*,5*H*)-dione* **(5):** Compound **1** (3.11 g, 10 mmol) was added to a mixture of acetic anhydride and pyridine (3:1, 20 mL), then refluxed for 3 h. After cooling, the reaction mixture was poured into cold dil. HCl, the product was filtered off, dried and recrystallised from dioxane to give **5**. Yield 75%. m.p. 242–244 °C**.** IR (KBr): 3402 (NH), 1695 (C=O), 1662 cm^{-1} (C=O, amide). ^1H NMR (DMSO-d_6): δ = 0.95 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 1.88 (s, 2H, CH_2), 2.34 (s, 2H, CH_2), 2.38 (s, 3H, CH_3), 4.89 (s, 1H, CH-Ph), 7.22–7.38 (m, 5H, ArH), 9.20 (s, 1H, NH), 10.20 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ = 25.9, 27.3, 27.8 (3 × CH_3), 32.8 (C-8), 39.8 (C-5), 40.21 (C-9), 51.2 (C-7), 101.1, 111.8, 125.6, 126.9, 128.4, 128.9, 143.4, 149.7, 153.2, 170.2 and 195.2 (ArC, C=N and 2 × C=O). Anal. Calcd for $C_{20}H_{21}N_3O_2$ (335.40): C, 71.62; H, 6.31; N, 12.53. Found: C, 71.70; H, 6.36; N, 12.52%.

*Ethyl 8,8-dimethyl-4,6-dioxo-5-phenyl-3,4,5,6,7,8,9,10-octahydropyrimido[4,5-*b*]quinoline-2-carboxylate* **(6):** A mixture of **1** (3.11 g, 10 mmol), diethyl oxalate (1.46 g, 10 mmol) and sodium ethoxide (15 mmol) in absolute ethanol (20 mL) was heated under reflux for 6 h. After cooling the reaction mixture was poured into ice-cold dil. HCl, the solid product was filtered off, dried and recrystallised from ethanol to give **6** as white crystals. Yield 65%. m.p. 218–219 °C. IR (KBr): 3438 (NH), 1725 (C=O, ester), 1695 (C=O) and 1670 cm^{-1} (C=O, amide). ^1H NMR (DMSO-d_6): δ = 0.85 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 1.29 (t, 3H, *J* = 7.0 Hz, CH_3CH_2), 1.88 (s, 2H, CH_2), 2.35 (s, 2H, CH_2), 4.13 (q, 2H, *J* = 7.0 Hz CH_2CH_3), 4.82 (s, 1H, CH-Ph), 7.02–7.29 (m, 5H, ArH), 9.28 (s, 1H, NH), 10.19 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ = 13.9, 27.1, 27.6 (3 × CH_3), 32.7 (C-8), 39.8 (C-5), 40.1 (C-9), 51.0 (C-7), 59.8 (OCH_2), 100.8, 112.8, 125.9, 126.9, 128.0, 128.9, 143.4, 147.6, 149.7, 153.1, 170.7 and 194.9 (ArC, C=N and 3 × C=O). Anal. Calcd for $C_{22}H_{23}N_3O_4$ (393.44): C, 67.16; H, 5.89; N, 10.68. Found: C, 66.98; H, 5.88; N, 10.69%.

*8,8-Dimethyl-2,5-diphenyl-2,3,7,8,9,10-hexahydropyrimido[4,5-*b*]quinoline-4,6(1*H*,5*H*)-dione* **(7):** To a solution of **1** (3.11 g, 10 mmol) in acetic acid (20 mL), benzaldehyde (1.06 g, 10 mmol) was added, then the reaction mixture was heated under reflux for 6 h. The solid product was filtered off, dried and recrystallised from chloroform to give **7** as yellow crystals. Yield 60%. m.p. 240–242 °C. ^1H NMR (DMSO- d_6): δ = 0.89 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), 1.88 (s, 2H, CH_2), 2.30 (s, 2H, CH_2), 4.88 (s, 1H, CH-Ph), 5.98 (s, 1H, NCHPhN), 7.10–7.51 (m, 10H, ArH), 8.94 (s, 1H, NH), 10.23 (s, 2H, 2NH). ^{13}C NMR (DMSO-d_6): δ = 27.2, 27.8 (2 × CH_3), 32.8 (C-8), 39.8 (C-5), 40.1 (C-9), 51.8 (C-7), 62.1 (C-2), 108.9, 112.8, 126.9, 127.2, 127.4, 128.9, 129.0, 129.6, 143.4, 143.8, 153.1, 168.9, 170.7 and 194.9 (ArC and 2 × C=O). Anal. Calcd for $C_{25}H_{25}N_3O_2$ (399.48): C, 75.16; H, 6.31; N, 10.52. Found: C, 75.28; H, 6.50; N, 10.53%.

*8′,8′-Dimethyl-5′-phenyl-7′,8′,9′,10′-tetrahydro-1′*H*-spiro[cyclohexane-1′,2′-pyrimido[4,5-*b*]quinoline]-4′,6′(3′*H*,5′*H*)-dione* **(8):** A mixture of **1** (3.11 g, 10 mmol), cyclohexanone (0.98 g, 10 mmol) and sodium acetate (2.00 g) in acetic acid (20 mL) was refluxed for 5 h. The product was filtered off, dried and recrystallised from methanol to give **8** as white crystals. Yield 70%. m.p. 223–224 °C. IR (KBr): 3408 (NH), 1695 (C=O), 1668 cm^{-1} (C=O, amide). ^1H NMR (DMSO-d_6): δ = 0.97 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 1.43 (m, 2H, CH_2, cyclohexane), 1.47 (m, 2H, CH_2, cyclohexane), 1.53 (m, 2H, CH_2 cyclohexane), 1.73 (br.t, 4H, 2 × CH_2, cyclohexane), 1.89 (s, 2H, CH_2), 2.31(s, 2H, CH_2), 4.82 (s, 1H, CH-Ph), 7.02–7.42 (m, 5H, ArH), 10.01 (s, 3H, 3NH). ^{13}C NMR (DMSO-d_6): δ = 23.5, 25.8, 35.9 (cyclohexane-CH_2), 27.2, 27.5 (2 × CH_3), 32.8 (C-8), 39.8 (C-5), 40.1 (C-9), 50.8 (C-2), 51.4 (C-7), 85.5 (C-4a), 112.8, 126.9, 127.2, 128.6, 128.9, 143.4, 153.1, 170.7, and 194.9 (ArC and 2 × C=O). Anal. Calcd for $C_{24}H_{29}N_3O_2$ (391.51): C, 73.63; H, 7.47; N, 10.73. Found: C, 73.65; H, 7.50; N, 10.82%.

*8,8-Dimethyl-2-(4-nitrophenyl)-5-phenyl-7,8,9,10-tetrahydropyrimido[4,5-*b*]quinoline-4,6(3*H*,5*H*)-dione* **(9):** A mixture of **1** (3.11 g, 10 mmol), and 4-nitrobenzoyl chloride (1.86 g, 10 mmol) in dry pyridine (20 mL) was refluxed for 5 h. After cooling the reaction mixture was poured into ice cold HCl, the product was filtered off, dried and recrystallised from ethanol to give **9** as yellow crystals. Yield 70%. m.p. 236–237 °C. ^1H NMR (DMSO-d_6): δ = 0.97 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 1.88 (s, 2H, CH_2), 2.33 (s, 2H, CH_2), 4.89 (s, 1H, CH-Ph), 7.01–7.33 (m, 5H, ArH), 8.18 (d, 2H, *J* = 8.8 Hz ArH), 8.31 (d, 2H, *J* = 8.8 Hz, ArH), 10.21 (s, 2H, 2 × NH). ^{13}C NMR (DMSO-d_6): δ = 27.2, 27.4 (2 × CH_3), 32.7 (C-8), 39.9 (C-5), 40.2 (C-9), 51.2 (C-7), 100.2, 111.9, 124.1, 126.9, 128.0, 128.2, 128.9, 131.1, 136.8, 149.7, 150.5, 153.1, 166.2, 170.7 and 194.9 (ArC, C=N and 2 C=O). Anal. Calcd for $C_{25}H_{22}N_4O_4$ (442.47): C, 67.86; H, 5.01; N, 12.66. Found: C, 67.85; H, 5.21; N, 12.76%.

*8,8-Dimethyl-5-phenyl-7,8,9,10-tetrahydro[1,2,3]triazino[4,5-*b*]quin-oline-4,6(3*H*,5*H*)-dione* **(10):** To a cold solution of **1** (3.11 g, 10 mmol), in a mixture of hydrochloric acid (15 mL) and acetic acid (15 mL), a solution of sodium nitrite (2.00 g)in water (15 mL) was added with stirring. After complete addition, the reaction mixture was stirred at room temperature for another 2 h. The solid product was

filtered off, dried and recrystallised from methanol to give **10** as white crystals. Yield 60%. m.p. 218–220 °C. ^{1}H NMR (DMSO-d_6): δ = 0.97 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 2.10 (s, 2H, CH_2), 2.41 (s, 2H, CH_2), 4.78 (s, 1H, CH-Ph), 7.10–7.27 (m, 5H, ArH), 10.01 (s, 2H, 2NH). ^{13}C NMR (DMSO-d_6): δ = 27.7, 27.9 (2 × CH_3), 32.7 (C-8), 39.9 (C-5), 40.8 (C-9), 51.5 (C-7), 111.9, 112.8, 126.9, 128.9, 132.0, 143.3, 149.5, 153.1, 170.7, and 194.9 (ArC and 2 C=O). Anal. Calcd for $C_{18}H_{18}N_4O_2$ (322.36): C, 67.07; H, 5.63; N, 17.38. Found: C, 67.17; H, 5.58; N, 17.29%.

S-*Alkyltetrahydropyrimido[4,5-*b*]quinoline-4,6(1*H,*5*H*)-diones* **(11–13):** *general procedure*: A mixture of **3a** (10 mmol), potassium carbonate (10 mmol) and the appropriate alkylating agent, *i.e.* allyl bromide, propargyl bromide or epichlorohydrin (10 mmol) in dry acetone (20 mL) was heated under reflux for 6 h. After cooling, the mixture was filtered off. The filterate was concentrated to afforded the products which were recrystallised from ethanol.

*2-(Allylthio)-8,8-dimethyl-1,5-diphenyl-7,8,9,10-tetrahydropyrimido [4,5-*b*]quinoline-4,6(1*H,*5*H*)-dione* **(11):** Brown crystals, Yield 75%. m.p.152–153 °C. IR (KBr): 3458 (NH), 1685(C=O), 1668 cm^{-1} (C=O, amide); ^{1}H NMR (DMSO-d_6): δ = 0.99 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 1.92 (s, 2H, CH_2), 2.30 (s, 2H, CH_2), 3.48 (d, 2H, *J* = 5.5 Hz, SCH_2), 4.80 (s, 1H, CH-Ph), 5.08 (d, *J* = 9.8 Hz, =CHH), 5.18 (d, 1H, *J* = 15.9 Hz, =CHH), 6.03 (m, 1H, CH=CH_2), 6.25–7.33 (m, 10H, ArH), 10.01 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ = 27.2, 27.8 (2 × CH_3), 32.8 (C-8), 34.2 (SCH_2), 39.9 (C-5), 40.8 (C-9), 51.3 (C-7), 95.2 (C-4a), 111.4, 118.3, 122.4, 122.8, 126.9, 128.0, 129.5, 131.5, 141.2, 143.8, 144.4, 149.7, 157.5, 163.2, 170.1 and 194.8 (ArC, C=C, C=N and 2 × C=O). Anal. Calcd for $C_{28}H_{27}N_3O_2S$ (469.60): C, 71.61; H, 5.80; N, 8.95. Found: C, 71.68; H, 5.88; N, 8.79%.

*8,8-Dimethyl-1,5-diphenyl-2-(prop-2-ynylthio)-7,8,9,10-tetrahydropyrimido[4,5-*b*]quinoline-4,6(1*H,*5*H*)-dione* **(12):** Pale brown crystals, Yield 77%. m.p. 149–150 °C. IR (KBr): 3458 (NH), 1692(C=O), 1665 cm^{-1} (C=O, amide). ^{1}H NMR (DMSO-d_6): δ = 0.98 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 1.88 (s, 2H, CH_2), 2.27 (s, 2H, CH_2), 2.39 (d, 1H, *J* = 2.3 Hz, C≡CH), 4.35 (app.d, 2H, *J* = ~2 Hz, SCH_2), 4.79 (s, 2H, CH-Ph), 6.25–7.33 (m, 10H, ArH), 10.01 (s, 1H, NH). Anal. Calcd for $C_{28}H_{25}N_3O_2S$ (467.58): C, 71.92; H, 5.39; N, 8.99. Found: C, 72.01; H, 5.38; N, 8.98%.

*8,8-Dimethyl-2-[(oxiran-2-ylmethyl)thio]-1,5-diphenyl-7,8,9,10-tetrahydropyrimido[4,5-*b*]quinoline-4,6(1*H,*5*H*)-dione* **(13):** Yellow crystals, Yield 65%. m.p. 170–172 °C. IR (KBr): 3450 (NH), 1695 (C=O), 1670 (C=O, amide), 1185 cm^{-1} (cyclic ether). ^{1}H NMR (DMSO-d_6): δ = 0.99 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 1.89 (s, 2H, CH_2), 2.28 (s, 2H, CH_2), 2.38 (m, 1H), 2.63 (m, 1H), 2.85(m, 1H), 2.89–3.12 (m, 2H, SCH_2), 4.78 (s, 1H, CH-Ph), 6.23–7.35 (m, 10H, ArH), 10.04 (s, 1H, NH). ^{13}C NMR (DMSO- d_6): δ = 27.2, 27.8 (2 × CH_3), 28.8 (SCH_2), 32.8 (C-8), 39.8 (C-5), 40.4 (C-9), 48.5 (CH_2O, oxirane), 51.1 (C-7), 51.9 (CHO, oxirane), 90.9 (C-4a), 119.1, 122.4, 122.8, 125.7, 127.7, 128.6, 129.5, 141.2, 144.5, 149.5, 157.8, 164.3, 170.1 and 194.8 (ArC, C=N and 2 × C=O). Anal. Calcd for $C_{28}H_{27}N_3O_3S$ (485.60): C, 69.25; H, 5.60; N, 8.65. Found: C, 69.38; H, 5.62; N, 8.67%.

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