Efficient synthesis of arylaldehyde oxime ethers functionalised with 3,4-dihydropyrimidinones and 2,5-quinazolinediones via a one-pot two-step method

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New arylahdehyde oxime ethers functionalised with *N*3-3,4-dihydropyrimidinone and 2,5-quinazolinedione groups were synthesised in moderate to good yields by the reaction of the corresponding 3,4-dihydropyrimidinones and quinazolinediones with paraformaldehyde and arylaldehyde oximes via a one-pot two-step strategy in the presence of chlorotrimethylsilane. The advantages of this method are the simple procedure, the high regioselectivity of the products and the mild reaction conditions.

Keywords: arylaldehyde oximes, aldoxime ethers, 3,4-dihydropyrimidin-2-ones, 2,5-quinazolinedione derivatives, three-component reaction

In continuation of our previous studies,[1] the one-pot, two-step reaction of simple nucleophiles (alcohols, amines) with paraformaldehyde and 3,4-dihydropyrimidin-2-ones (DHPMs) in the presence of chlorotrimethylsilane to produce N3-substituted 3,4-dihydropyrimidin-2-ones, we report the use of the more complex aldoximes and ketoximes as the nucleophiles in the synthesis of some oxime ether derivatives of N3-methyl-3,4-dihydropyrimidin-2-ones and also of N3-methyl-2,5-quinazolinediones.

Oxime ethers are important sub-structures of biologically active compounds that are used extensively by the pharmaceutical and agrochemical industries.[2,3,4] Although some newer methods of synthesis of oxime ethers have been reported recently, the need for the development of a more general and efficient method providing highly functionalised oxime ethers remains.

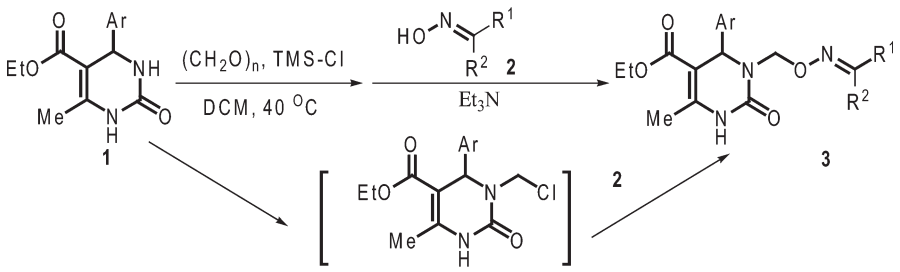
3,4-Dihydropyrimidin-2-ones (DHPMs) have attracted considerable interest due to their interesting pharmacological properties, such as calcium channel modulators, antihypertensives, α_{1a} adrenergic agonists, mitotic kinesin inhibitors, and hepatitis B virus replication suppressors.[5] Among DHPM derivatives, most of the pharmacologically attractive forms are /N3/-substituted analogues.[6] In the context of our interest in the synthesis of functionalised DHPM derivatives,[7] we here report the synthesis of 14 N3-methyl-DHPMs modified with oxime ethers by reaction of DHPMs with paraformaldehyde and arylaldehydes oximes in the presence of trimethylsilyl chloride (TMSCl). We have also accomplished the synthesis of six N3-methyl-substituted 2,5-quinazolinediones by a similar process starting from 2,5-quinazolinediones.

Results and discussion

The two-step synthesis of N3-methyl-substituted 4,5,6-trisubstituted 3,4-dihydropyrimidin-2-ones (DHPMs) **3** is summarised in Scheme 1, with the structure of the putative intermediate shown in square brackets. Firstly, DHPM **1** was treated with paraformaldehyde in the presence of TMSCl at 40 °C in dichloromethane (DCM) for 24 h. Then arylaldehyde oxime **2** and Et_3N were added to the mixture which was refluxed for 12 h to give the N3-substituted-DHPM product **3**. A variety of DHPMs and arylaldehyde oximes as substrates were examined and the corresponding oxime ethers were regioselectively obtained (Table 1). In general, the electronics of the 4-aryl substituents of the DHPMs did not appear to influence the process, as substrates substituted with methyl methoxy or chloro groups all gave the products in good yields (entries 2–6). Substitution on the phenyl ring of the oxime moiety is not limited to a chloro group, but those with *p*-nitro and *p*-methoxy groups were equally effective in giving the desired products in good yields (entries 8 and 9). Use of ketone oximes instead of aldehyde oximes also gave the corresponding oxime ethers **3j–n** in good yields (entries 10–14). ^{1}H NMR spectra of all products showed that the reaction occurred exclusively at the *N3* position of the DHPMs 1. The regioselectivity of the reaction is consistent with our previous results[1,7] and other results of alkylation reactions.[8]

To further explore the scope of the one-pot reaction, we then used 2,5-quinazolinedione derivatives **4a–e** as substrates to synthesise the oxime ethers functionalised with quinazolinone (Table 2). As expected, the desired products **5a–f** were obtained smoothly when using ketone oximes as well as aldehyde oximes, though this reaction had to be carried out in 1,4-dioxane at 100 °C.

In conclusion, a variety of oxime ethers functionalised DHPMs and 2,5-quinazolinediones with were regioselectively prepared through a one-pot two step reaction between DHPM and 2,5-quinazolinedione derivatives, paraformaldehyde, chlorotrimethylsilane, and various arylaldehyde oximes. The



Scheme 1 Synthesis of oxime ethers **3** from DHPMs **1**, $(CH_2O)_n$ and oximes **2**.

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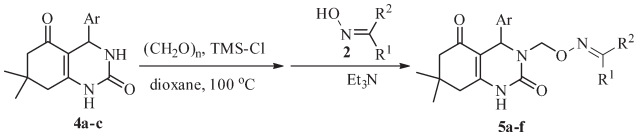
Table 1 Synthesis of oxime ethers **3** from 3,4-dihydropyrimidinones (DHPMs) **1** paraformaldehyde and aldehyde and ketone oximes **2**[a]

Entry	Ar	R^1	R^2	Product	Yield/%[b]
1	C_6H_5	*p*-Cl-C_6H_4	H	**3a**	71
2	*p*-MeC_6H_4	*p*-Cl-C_6H_4	H	**3b**	74
3	*p*-MeOC_6H_4	*p*-Cl-C_6H_4	H	**3c**	73
4	*p*-Cl-C_6H_4	*p*-Cl-C_6H_4	H	**3d**	76
5	*o*-MeOC_6H_4	*p*-Cl-C_6H_4	H	**3e**	72
6	*o*-Cl-C_6H_4	*p*-Cl-C_6H_4	H	**3f**	75
7	C_6H_5	C_6H_5	H	**3g**	73
8	C_6H_5	*p*-NO_2-C_6H_4	H	**3h**	75
9	C_6H_5	*p*-OCH_3-C_6H_4	H	**3i**	74
10	C_6H_5	C_6H_5	C_6H_5	**3j**	70
11	*p*-MeC_6H_4	C_6H_5	C_6H_5	**3k**	74
12	*p*-MeOC_6H_4	C_6H_5	C_6H_5	**3l**	72
13	*o*-Cl-C_6H_4	C_6H_5	C_6H_5	**3m**	75
14	*o*-MeOC_6H_4	C_6H_5	C_6H_5	**3n**	71

[a]Reaction procedure of DHPM (**1**, 1.0 mmol), $(CH_2O)_n$ (4.0 mmol), TMS-Cl (2.5 mmol), CH_2Cl_2 (5 mL), 40 °C, 24 h; then oxime (**2**, 1 mmol), Et_3N (2.5 mmol), 40 °C, 12 h.
[b]Isolated yield.

Table 2 Synthesis of ether oximes **5** from quinazolinones **4**, paraformaldehyde and aldehyde and ketone oximes **2**[a]



Entry	Ar	R^1	R^2	Product	Yield/%[b]
1	C_6H_5	C_6H_5	C_6H_5	**5a**	71
2	*p*-MeC_6H_4	C_6H_5	C_6H_5	**5b**	74
3	*p*-Cl-C_6H_4	C_6H_5	C_6H_5	**5c**	73
4	C_6H_5	H	*p*-Cl-C_6H_4	**5d**	76
5	*p*-Cl-C_6H_4	H	*p*-Cl-C_6H_4	**5e**	72
6	*p*-MeC_6H_4	H	*p*-Cl-C_6H_4	**5f**	75

[a]Reaction procedure: 2,5-quinazolinediones (**4**, 1.0 mmol), $(CH_2O)_n$ (4.0 mmol), TMSCl (2.5 mmol), 1,4-dioxane (5 mL), 100 °C, 24 h; then oxime (**2**, 1.0 mmol), Et_3N (2.5 mmol), 100 °C, 12 h.
[b]Isolated yield.

method provides a highly efficient and convenient synthesis oxime ethers. Synthesis and screening of compounds based on DHPM scaffolds may lead to the discovery of interesting biological activities.

Experimental

Melting points were determined on an XT-4 electrothermal micromelting point apparatus and are uncorrected. NMR spectra were recorded at 400 (^{1}H) and 100 (^{13}C) MHz, respectively, on a Varian Mercury plus-400 instrument using $CDCl_3$ as solvent and TMS as an internal standard. Elemental analyses were performed on a Carlo-Erba 1106 Elemental Analysis instrument. Mass spectra were obtained on a Bruker Daltonics APEXII 47e FT-ICR spectrometer. Column chromatography was performed on silica gel (300–400 mesh). Commercially available reagents were used without further purification. Solvents were purified prior to use according to the standard methods.

Synthesis of oxime ethers; general procedure

3,4-Dihydropyrimidinone (**1**, 1.0 mmol), paraformaldehyde (4.0 mmol), and trimethylsilyl chloride (TMSCl) (2.5 mmol) were refluxed in anhydrous CH_2Cl_2 (5 mL) for 24 h. To this mixture was added arylaldehyde oxime (**2**, 1.2 mmol) and Et_3N (2.5 mmol). The combined mixture was refluxed for 12 h. After completion of the reaction, which was monitored by thin layer chromatography (TLC), any solid particles were filtered off and the filtrate evaporated. The crude product was purified by column chromatography over silica gel with ethyl acetate and petroleum ether to afford the pure oxime ether **3** as the unique product (no/*cis*/isomer was obtained).

For the analogous reaction of the 2,5-quinazolinediones (**4**, 1.0 mmol), anhydrous CH_2Cl_2 (5 mL) was replaced by anhydrous 1,4-dioxane (5 mL) (reflux temperature 100°C).

Ethyl 3-[({[(E)-4-chlorobenzylidene]amino}oxy)methyl]-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3a**): White powder, m.p. 142–144 °C; ^{1}H NMR: δ = 7.96 (s, 1H, =CH), 7.82 (br s, 1H, NH), 7.50 (d, J = 8.0 Hz, 2H, ArH), 7.51–7.23 (m, 7H, ArH), 5.78 (d, J = 11.2 Hz, 1H, NCH_2), 5.75 (s, 1H, CH), 4.97 (d, J = 11.2 Hz, 1H, NCH_2), 4.13–4.05 (m, 2H, CH_2), 2.37 (s, 3H, CH_3), 1.21 (m, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR: δ = 169.2, 166.9, 165.7, 160.1, 139.7, 129.2, 128.0, 113.1, 60.7, 44.6, 25.8, 24.8, 23.2, 13.5; MS: *m/z* = 427 (M^+); Anal. Calcd for $C_{22}H_{22}ClN_3O_4$: C, 61.75; H, 5.18; N, 9.82. Found: C, 61.80; H, 5.23; N, 9.78%.

Ethyl 3-[({[(E)-4-chlorobenzylidene]amino}oxy)methyl]-6-methyl-2-oxo-4-(p-tolyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3b**): White powder, m.p. 124–126 °C; ^{1}H NMR: δ = 8.15 (s, 1H, =CH), 7.96 (br s, 1H, NH), 7.50 (d, J = 8.0 Hz, 2H, ArH), 7.35–7.26 (m, 4H, ArH), 7.09 (d, J = 8.0 Hz, 2H, ArH), 5.79 (d, J = 11.2 Hz, 1H, NCH_2), 5.70 (s, 1H, CH), 4.96 (d, J = 11.2 Hz, 1H, NCH_2), 4.12–4.06 (m, 2H, CH_2), 2.33 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 1.21 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR: δ = 165.4, 152.9, 148.9, 145.6, 137.0, 137.7, 136.0, 130.3, 129.2, 128.9, 128.4, 127.3, 102.7, 77.8, 60.0, 59.2, 21.1, 18.6, 14.2; MS: *m/z* = 441 (M^+); Anal. Calcd for $C_{23}H_{24}ClN_3O_4$: C, 62.51; H, 5.47; N, 9.51. Found: C, 62.46; H, 5.39; N, 9.39%.

Ethyl 3-[({[(E)-4-chlorobenzylidene]amino}oxy)methyl]-6-methyl-2-oxo-4-(4-methoxyphenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3c**): White powder, m.p. 112–114 °C; ^{1}H NMR: δ = 8.47 (br s, 1H, NH), 7.97 (s, 1H, =CH), 7.50 (d, J = 8.0 Hz, 2H, ArH), 7.35–7.27 (m, 4H, ArH), 6.81 (d, J = 8.0 Hz, 2H, ArH), 5.79 (d, J = 11.2 Hz, 1H, NCH_2), 5.69 (s, 1H, CH), 4.98 (d, J = 11.2 Hz, 1H, NCH_2), 4.08 (q, J = 7.2 Hz, 2H, CH_2), 3.76 (s, 3H, OCH_3), 2.34 (s, 3H, CH_3), 1.21 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR: δ = 165.5, 159.2, 153.1, 148.8, 145.6, 136.0, 134.3, 130.3, 128.9, 128.6, 128.3, 113.8, 102.6, 77.6, 60.0, 58.9, 55.2, 18.5, 14.2; MS: *m/z* = 457 (M^+); Anal. Calcd for $C_{23}H_{24}ClN_3O_5$: C, 60.33; H, 5.28; N, 9.18. Found: C, 60.40; H, 5.25; N, 9.29%.

Ethyl 3-[({[(E)-4-chlorobenzylidene]amino}oxy)methyl]-6-methyl-2-oxo-4-(4-chlorophenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3d**): White powder, m.p. 115–116 °C; ^{1}H NMR: δ = 7.90 (s, 1H, =CH), 7.48 (d, J = 8.0 Hz 2H, ArH), 7.36–7.23 (m, 6H, ArH), 7.14 (br s, 1H, NH), 5.72 (d, J = 11.2 Hz, 1H, NCH_2), 5.71 (s, 1H, CH), 5.03 (d, J = 11.2 Hz, 1H, NCH_2), 4.10 (q, J = 7.2 Hz, 2H, CH_2), 2.33 (s, 3H, CH_3), 1.22 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR: δ = 165.2, 152.9, 149.0, 146.0, 140.6, 136.1, 133.7, 130.1, 129.0, 128.7, 128.7, 128.3, 102.3, 78.0, 60.2, 59.0, 18.7, 14.2; MS: *m/z* = 461 (M^+); Anal. Calcd for $C_{22}H_{21}Cl_2N_3O_4$: C, 57.15; H, 4.58; N, 9.18. Found: C, 57.31; H, 5.65; N, 9.31%.

Ethyl 3-[({[(E)-4-chlorobenzylidene]amino}oxy)methyl]-6-methyl-2-oxo-4-(2-methoxyphenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3e**): White powder, m.p. 243–245 °C; ^{1}H NMR: δ = 8.15 (s, 1H, =CH), 8.13 (br s, 1H, NH), 7.38–7.32 (m, 4H, ArH), 7.25–7.23 (m, 2H, ArH), 6.95–6.84 (m, 2H, ArH), 6.11 (s, 1H, CH), 5.54 (d, J = 9.6 Hz, 1H, NCH_2), 4.89 (d, J = 9.6 Hz, 1H, NCH_2), 4.02–4.98 (m, 2H, CH_2), 4.03–3.97 (m, 2H, CH_2), 3.83 (s, 3H, OCH_3), 2.37 (s, 3H, CH_3), 1.10 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR: δ = 165.1, 157.1, 152.3, 145.4, 136.0, 132.1, 130.0, 129.9, 128.7, 128.4, 128.2, 120.9, 111.1, 101.2, 72.7, 60.0, 57.0, 55.6, 18.6, 14.0; MS: *m/z* = 457 (M^+); Anal. Calcd for $C_{23}H_{24}ClN_3O_5$: C, 60.33; H, 5.28; N, 9.18. Found: C, 60.45; H, 5.22; N, 9.10%.

Ethyl 3-[({[(E)-4-chlorobenzylidene]amino}oxy)methyl]-6-methyl-2-oxo-4-(2-chlorophenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3f**): White powder, m.p. 210–212 °C; ^{1}H NMR: δ = 7.90 (s, 1H, =CH), 7.51–7.46 (m, 3H, ArH), 7.38 (br s, 1H, NH), 7.35–7.32 (m, 3H, ArH), 6.95–6.84 (m, 2H, ArH), 6.11 (s, 1H, CH), 5.54 (d, J = 10.8 Hz, 1H, NCH_2), 4.89 (d, J = 10.8 Hz 1H, NCH_2), 4.04 (q, J = 7.2 Hz, 2H, CH_2), 2.39 (s, 3H, CH_3), 1.16 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR: δ = 165.1, 152.0, 148.9, 146.2, 140.0, 136.0, 133.0, 130.4, 130.0, 129.5, 129.3, 128.9, 128.4, 127.7, 101.8, 77.6, 60.1, 56.2, 18.5, 14.1; MS: *m/z* = 461 (M^+); Anal. Calcd for $C_{22}H_{21}Cl_2N_3O_4$: C, 57.15; H, 4.58; N, 9.09, Found: C, 57.30; H, 4.61; N, 9.25%.

Ethyl 3-[({(E)-benzylideneamino}oxy)methyl]-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3g**): White powder, m.p. 181–183 °C; ^{1}H NMR: δ = 8.76 (br s, 1H, NH), 8.04 (s, 1H, =CH), 7.50–7.22 (m, 10H, ArH), 5.84 (d, J = 11.2 Hz, 1H, NCH_2),

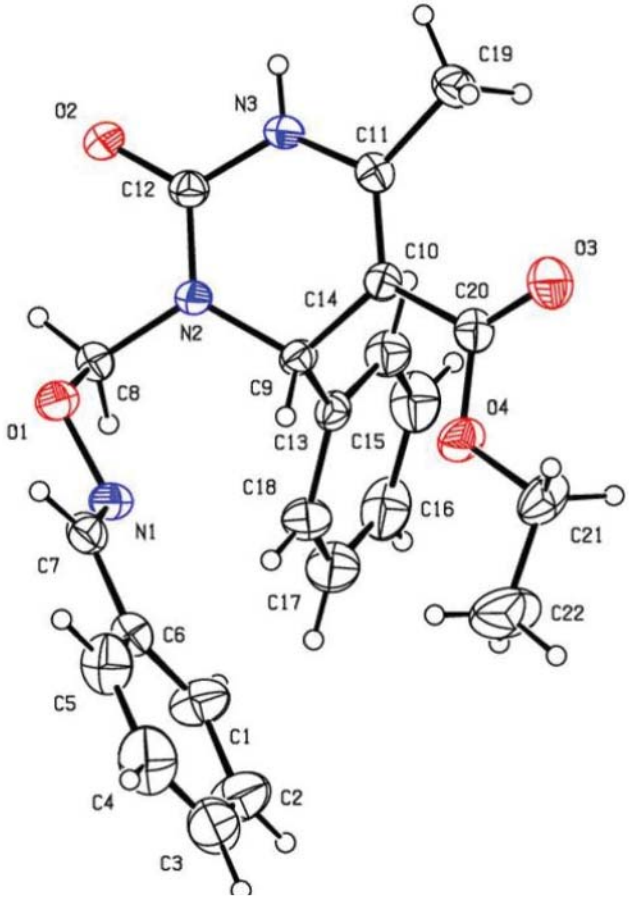


Fig. 1 The single crystal X-ray crystallography of product **3g**.

5.81 (s, 1H, CH), 4.95 (d, J = 11.2 Hz, 1H, NCH_2), 4.12–4.04 (m, 2H, CH_2), 2.36 (s, 3H, CH_3), 1.20 (m, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR: δ = 165.5, 153.3, 150.1, 146.2, 142.1, 131.8, 130.1, 128.6, 128.5, 127.9, 127.4, 127.2, 102.3, 77.5, 59.9, 59.4, 18.5, 14.1; MS: m/z = 393 (M^+); Anal. Calcd for $C_{22}H_{23}N_3O_4$: C, 67.16; H, 5.89; N, 10.68. Found: C, 67.21; H, 5.85; N, 10.65%.

Ethyl 3-[({[(E)-4-nitrobenzylidene]amino}oxy)methyl]-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3h**): White powder, m.p. 168–169 °C; ^{1}H NMR: δ = 8.70 (br s, 1H, NH), 8.23 (d, J = 8.0 Hz, 2H, ArH), 8.03 (s, 1H, =CH), 7.72 (d, J = 8.0 Hz, 2H, ArH), 7.41–7.22 (m, 5H, ArH), 5.82 (d, J = 12.4 Hz, 1H, NCH_2), 5.73 (s, 1H, CH), 5.10 (d, J = 11.6 Hz, 1H, NCH_2), 4.15–4.06 (m, 2H, CH_2), 2.36 (s, 3H, CH_3), 1.22 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR: δ = 165.4, 153.2, 153.1, 148.4, 147.9, 145.9, 145.8, 141.9, 137.8, 128.5, 128.0, 127.8, 127.3, 123.9, 102.5, 78.3, 60.1, 59.6, 18.5, 14.2; MS: m/z = 438 (M^+); Anal. Calcd for $C_{22}H_{22}N_4O_6$: C, 60.27; H, 5.06; N, 12.78. Found: C, 60.42; H, 5.11; N, 12.71%.

Ethyl 3-[({[(E)-2-methoxybenzylidene]amino}oxy)methyl]-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3i**): White powder, m.p. 153–155 °C; ^{1}H NMR: δ = 8.48 (s, 1H, =CH), 8.40 (br s, 1H, NH), 7.82 (dd, J = 1.6 Hz, 3.6 Hz, 1H, ArH), 7.43–7.24 (m, 6H, ArH), 6.97–6.89 (m, 2H, ArH), 5.85 (d, J = 11.2 Hz, 1H, NCH_2), 5.82 (s, 1H, CH), 4.88 (d, J = 11.2 Hz, 1H, NCH_2), 4.11–4.03 (m, 2H, CH_2), 3.84 (s, 3H, OCH_3), 2.35 (s, 3H, CH_3), 1.20 (m, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR: δ = 165.5, 157.7, 153.1, 146.2, 146.1, 142.1, 131.4, 128.5, 127.9, 127.5, 126.4, 120.7, 120.4, 111.1, 102.4, 77.3, 59.9, 59.2, 55.5, 18.5, 14.1; MS: m/z = 423 (M^+); Anal. Calcd for $C_{23}H_{25}N_3O_5$: C, 65.24; H, 5.95; N, 9.92. Found: C, 65.38; H, 6.01; N, 10.2%.

Ethyl 3-[({[diphenylmethylene]amino}oxy)methyl]-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3j**): White powder, m.p. 232–234 °C; ^{1}H NMR: δ = 8.60 (br s, 1H, NH), 7.51–7.22 (m, 14H, ArH), 5.89 (d, J = 10.4 Hz, 1H, NCH_2), 5.78 (s, 1H, CH), 4.89 (d, J = 10.4 Hz, 1H, NCH_2), 4.14–4.06 (m, 2H, CH_2), 2.32 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 1.20 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR: δ = 165.5, 158.4, 148.5, 146.0, 141.8, 136.0, 132.8, 129.6, 129.1, 128.9, 128.5, 128.2, 128.1, 128.0, 127.9, 127.4, 102.4, 77.4, 60.0, 58.7, 18.6, 14.2; MS: m/z = 469 (M^+); Anal. Calcd for $C_{28}H_{27}N_3O_4$: C, 71.62; H, 5.80; N, 8.95. Found: C, 71.50; H, 5.75; N, 8.88%.

Ethyl 3-[({[diphenylmethylene]amino}oxy)methyl]-6-methyl-2-oxo-4-(p-tolyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3k**): White powder, m.p. 200–202 °C; ^{1}H NMR: δ = 8.20 (br s, 1H, NH), 7.50–7.06 (m, 14H, ArH), 5.88 (d, J = 11.2 Hz, 1H, NCH_2), 5.74 (s, 1H, CH), 4.87 (d, J = 11.2 Hz, 1H, NCH_2), 4.12–4.07 (m, 2H, CH_2), 2.31 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 1.21 (t, J = 6.8 Hz, 3H, CH_3); ^{13}C NMR: δ = 165.5, 158.3, 152.9, 145.9, 138.9, 137.6, 136.1, 132.8, 129.5, 129.2, 129.1, 128.9, 128.2, 128.0, 127.9, 127.3, 102.6, 70.0, 59.9, 58.4, 21.1, 18.5, 14.2; MS: m/z = 483 (M^+); Anal. Calcd for $C_{29}H_{29}N_3O_4$: C, 72.03; H, 6.05; N, 8.69. Found: C, 72.15; H, 6.10; N, 8.79%.

Ethyl 3-[({[diphenylmethylene]amino}oxy)methyl]-6-methyl-2-oxo-4-(4-methoxyphenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3l**): White powder, m.p. 183–185 °C; ^{1}H NMR: δ = 8.32 (br s, 1H, NH), 7.5 (d, J = 8.0 Hz, 2H, ArH), 7.43–7.26 (m, 10H, ArH), 6.79 (d, J = 8.0 Hz, 2H, ArH), 6.09 (s, 1H, CH), 5.87 (d, J = 10.8 Hz, 1H, NCH_2), 5.71 (s, 1H, CH), 4.88 (d, J = 11.2 Hz, 1H, NCH_2), 4.14–4.08 (m, 2H, CH_2), 3.76 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 1.20 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR: δ = 165.5, 159.2, 158.3, 153.0, 145.9, 136.1, 134.1, 132.8, 129.5, 129.1, 128.9, 128.6, 128.2, 128.0 and 128.0, 113.8, 102.6, 77.2, 59.9, 58.1, 55.2, 18.5, 14.2; MS: m/z = 499 (M^+); Anal. Calcd for $C_{29}H_{29}N_3O_5$: C, 69.72; H, 5.85; N, 8.41. Found: C, 69.89; H, 5.79; N, 8.32%.

Ethyl 3-[({[diphenylmethylene]amino}oxy)methyl]-6-methyl-2-oxo-4-(2-chlorophenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3m**): White powder, m.p. 174–176 °C; ^{1}H NMR: δ = 8.14 (br s, 1H, NH), 7.47–7.20 (m, 14H, ArH), 5.82 (d, J = 11.2 Hz, 1H, NCH_2), 5.73 (s, 1H, CH), 4.95 (d, J = 11.2 Hz, 1H, NCH_2), 4.17–4.05 (m, 2H, CH_2), 2.32 (s, 3H, CH_3), 1.21 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR: δ = 165.3, 158.4, 152.9, 146.5, 140.4, 135.9, 133.6, 132.7, 129.6, 129.1, 128.9, 128.7, 128.6, 128.2, 128.0, 127.9, 102.1, 77.6, 77.2, 60.0, 58.2, 18.5, 14.2; MS: m/z = 503 (M^+); Anal. Calcd for $C_{28}H_{26}ClN_3O_4$: C, 66.73; H, 5.20; N, 8.34. Found: C, 66.59; H, 5.12; N, 8.41%.

(E)-ethyl 3-[({[diphenylmethylene]amino}oxy)methyl]-6-methyl-2-oxo-4-(2-methoxyphenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**3n**): White powder, m.p. 236–238 °C; ^{1}H NMR: δ = 7.73 (br s, 1H, NH), 7.53–7.20 (m, 12H, ArH), 6.88–6.81 (m, 2H, ArH), 6.09 (s, 1H, CH), 5.89 (d, J = 10.8 Hz, 1H, NCH_2), 4.89 (d, J = 10.8 Hz, 1H, NCH_2), 4.05 (q, J = 7.2 Hz, 2H, CH_2), 3.73 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 1.15 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR: δ = 165.7, 157.9, 157.3, 152.6, 146.1, 136.2, 132.9, 130.1, 129.4, 129.3, 129.2, 129.1, 128.8, 128.1, 128.0, 127.9, 120.4, 110.8, 100.6, 77.2, 59.7, 55.3, 54.4, 18.4, 14.1; MS: m/z = 499 (M^+); Anal. Calcd for $C_{29}H_{29}N_3O_5$: C, 69.72; H, 5.85; N, 8.41. Found: C, 69.79; H, 5.77; N, 8.50%.

3-({[(Diphenylmethylene)amino]oxy}methyl)-7,7-dimethyl-4-phenyl-3,4,7,8-tetrahydroquinazoline-2,5(1H,6H)-dione (**5a**): White powder; m.p. 199–201 °C. ^{1}H NMR: δ = 9.15 (br s, 1H, NH), 7.96 (s, 1H, NCH), 7.96–7.21 (m, 9H, ArH), 5.84 (d, J = 10.4 Hz, 1H, NCH_2), 5.80 (s, 1H, CH), 4.98 (d, J = 10.4 Hz, 1H, NCH_2), 2.44–2.12 (m, 4H, CH_2), 1.07 (s, 3H, CH_3), 0.93 (s, 3H, CH_3); ^{13}C NMR: δ = 193.6, 153.3, 149.5, 149.1, 141.4, 136.1, 130.1, 129.0, 128.6, 128.4, 127.9, 127.1, 110.2, 78.0, 57.3, 50.3, 39.9, 32.8, 29.3, 27.1. MS: m/z = 479 (M^+); Anal. Calcd for $C_{30}H_{29}N_3O_3$: C, 75.13; H, 6.10; N, 8.76. Found: C, 75.05; H, 6.19; N, 8.63%.

3-({[(Diphenylmethylene)amino]oxy}methyl)-7,7-dimethyl-4-(p-tolyl)-3,4,7,8-tetrahydroquinazoline-2,5(1H,6H)-dione (**5b**): White powder; m.p. 205–207°C. ^{1}H NMR: δ = 8.92 (br s, 1H, NH), 7.47–7.25 (m, 12H, ArH), 7.07 (d, J = 8.0 Hz, 2H, ArH), 5.92 (d, J = 10.8 Hz, 1H, NCH_2), 5.76 (s, 1H, CH), 4.88 (d, J = 10.8 Hz, 1H, NCH_2), 2.40–2.05 (m, 4H, CH_2), 1.05 (s, 3H, CH_3), 0.93 (s, 3H, CH_3); ^{13}C NMR: δ = 193.6, 158.4, 153.2, 149.5, 138.3, 137.5, 136.0, 132.8, 129.6, 129.2, 129.1, 128.9, 128.2, 128.1, 128.0, 127.1, 77.5, 56.2, 50.3, 39.8, 32.8, 29.3, 27.2, 21.1. MS: m/z = 493 (M^+); Anal. Calcd for $C_{31}H_{31}N_3O_3$: C, 75.43; H, 6.33; N, 8.51. Found: C, 75.32; H, 6.27; N, 8.64%.

3-({[(Diphenylmethylene)amino]oxy}methyl)-7,7-dimethyl-4-(4-chlorophenyl)-3,4,7,8-tetrahydroquinazoline-2,5(1H,6H)-dione (**5c**): White powder; m.p. 215–217 °C. ^{1}H NMR: δ = 8.60 (br s, 1H, NH), 7.45–7.19 (m, 14H, ArH), 5.83 (d, J = 11.2 Hz, 1H, NCH_2), 5.77 (s, 1H, CH), 4.98 (s, J = 11.2 Hz, 1H, NCH_2), 2.41–2.16 (m, 4H, CH_2), 1.06 (s, 3H, CH_3), 0.91 (s, 3H, CH_3); ^{13}C NMR: δ = 193.5, 158.5, 152.9, 149.6, 139.9, 135.9, 133.5, 132.7, 129.7, 129.1, 129.0, 128.7,

128.4, 128.3, 128.1, 128.0, 110.0, 77.9, 56.1, 50.3, 39.9, 32.8, 29.3, 27.1. MS: *m/z* = 513 (M^+); Anal. Calcd for $C_{30}H_{28}ClN_3O_3$: C, 70.10; H, 5.49; N, 8.17. Found: C, 70.21; H, 5.53; N, 8.08%.

4-Chlorobenzaldehyde-O-[((E)-7,7-dimethyl-2,5-dioxo-4-phenyl-1,2,5,6,7,8-hexahydroquinazolin-3(4H)-yl)methyl)oxime (**5d**): White powder; m.p. 199–201 °C. ^{1}H NMR: δ = 9.15 (br s, 1H, NH), 7.96 (s, 1H, =CH), 7.96–7.21 (m, 9H, ArH), 5.84 (d, *J* = 11.2 Hz, 1H, NCH_2), 5.80 (s, 1H, CH), 4.98 (d, *J* = 11.2 Hz, 1H, NCH_2), 2.44–2.12 (m, 4H, CH_2), 1.07 (s, 3H, CH_3), 0.93 (s, 3H, CH_3); ^{13}C NMR: δ = 193.6, 153.3, 149.5, 149.1, 141.4, 136.1, 130.1, 129.0, 128.6, 128.4, 127.9, 127.1, 110.2, 78.0, 57.3, 50.3, 39.9, 32.8, 29.3, 27.1. MS: *m/z* = 437 (M^+); Anal. Calcd for $C_{24}H_{24}ClN_3O_3$: C, 65.82; H, 5.52; N, 9.60. Found: C, 65.69; H, 5.46; N, 9.69%.

4-Chlorobenzaldehyde-O-{([(E)-4-(4-chlorophenyl)-7,7-dimethyl-2,5-dioxo-1,2,5,6,7,8-hexahydroquinazolin-3(4H)-yl]methyl}oxime (**5e**): White powder; m.p. 212–214 °C. ^{1}H NMR: δ = 8.69 (br s, 1H, NH), 7.91 (s, 1H, =CH), 7.46 (d, *J* = 4 Hz, 2H, ArH), 7.45–7.19 (m, 6H, ArH), 5.83 (d, *J* = 10.4 Hz, 1H, NCH_2), 5.77 (s, 1H, CH), 4.98 (d, *J* = 10.4 Hz, 1H, NCH_2), 2.41–2.16 (m, 4H, CH_2), 1.07 (s, 3H, CH_3), 0.91 (s, 3H, CH_3); ^{13}C NMR: δ = 193.5, 158.5, 152.9, 149.6, 139.9, 135.9, 133.5, 132.7, 129.7, 129.1, 129.0, 128.7, 128.4, 128.3, 128.1, 128.0, 110.0, 77.9, 56.1, 50.3, 39.9, 32.8, 29.3, 27.1. MS: *m/z* = 471 (M^+); Anal. Calcd for $C_{24}H_{23}Cl_2N_3O_3$: C, 61.02; H, 4.91; N, 8.90. Found: C, 60.91; H, 4.85; N, 8.83%.

4-Chlorobenzaldehyde-O-{[(E)-7,7-dimethyl-2,5-dioxo-4-(p-tolyl)-1,2,5,6,7,8-hexahydroquinazolin-3(4H)-yl]methyl}oxime (**5f**): White powder; m.p. 220–222 °C. ^{1}H NMR: δ = 8.65 (br s, 1H, NH), 7.97 (s, 1H, =CH), 7.49 (d, *J* = 12 Hz, 2H, ArH), 7.36–7.26 (m, 4H, ArH), 7.10 (d, *J* = 8 Hz, 2H, ArH), 5.83 (d, *J* = 11.2 Hz, 1H, NCH_2), 5.74 (s, 1H, CH), 4.95 (d, *J* = 11.2 Hz, 1H, NCH_2), 2.42–2.11 (m, 7H, CH_2 and CH_3), 1.07 (s, 3H, CH_3), 0.94 (s, 3H, CH_3); ^{13}C NMR: δ = 193.6, 152.2, 149.3, 149.1, 138.4, 137.6, 136.1, 130.2, 129.3, 129.0, 128.4, 127.1, 110.3, 77.86, 57.0, 50.3, 39.9, 32.8, 29.3, 27.2, 21.1. MS: *m/z* = 451 (M^+); Anal. Calcd for $C_{25}H_{26}ClN_3O_3$: C, 66.44; H, 5.80; N, 9.30. Found: C, 66.53; H, 5.86; N, 9.21%.

Crystallographic data for the structure analysis have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication, CCDC No. 822849 for **3g**. Copies of these information can be obtained, free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (44) 01223 336033 or E-mail: deposit@ccdc.cam.ac.uk).

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