# Synthesis of novel ethyl 1-aryl-3-methyl-8-oxo-1,8-dihydropyrano[2′,3′:4,5] pyrimido[6,1-*b*]quinazoline-2-carboxylate derivatives

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In this paper, a new series of ethyl 1-aryl-3-methyl-8-oxo-1,8-dihydropyrano[2′,3′:4,5]pyrimido[6,1-*b*]quinazoline-2-carboxylate derivatives was synthesised by the cyclisation of methyl anthranilate with ethyl 5-cyano-6-[(ethoxymethylene)amino]-2-methyl-4-aryl-4*H*-pyran-3-carboxylate derivatives, which were obtained from reaction of triethyl orthoformate with 6-amino-5-cyano-2-methyl-4-aryl-4*H*- pyran-3-carboxylate derivatives. The title compounds possessed good fluorescence properties. In addition, ethyl 5-cyano-6-[(ethoxymethylene) amino]-2-methyl-4-(*p*-tolyl)-4*H*-pyran-3-carboxylate and ethyl 3-methyl-8-oxo-1-(*p*-tolyl)-1,8-dihydropyrano[2′,3′:4,5]pyrimido[6,1-*b*] quinazoline-2-carboxylate were further determined by single crystal X-ray diffraction analysis.

**Keywords:** carboxylate, cyclisation, fluorescence, single crystal structure

Synthesis of privileged classes of heterocyclic molecules has become one of the prime research areas in the field of synthetic organic chemistry.[1,2] Quinazolines are also well-known as the 'privileged structures' for drug design,[3] which are defined as a class of molecules that are capable of binding to multiple receptors with high affinity. As an important class of nitrogen containing heterocycles, quinazolines and various derivatives are present in many synthetic and natural compounds.[4–8] Also, the quinazoline ring system is a prolific source of molecules possessing a wide spectrum of biological and pharmacological activities.[9–21] In addition, the quinazolinone compounds have a conjugate structure giving the compound strong fluorescence properties. At present, it has been reported that there are many ways to synthesise quinazolinone derivatives. In terms of synthetic raw materials, they are benzoic acid derivatives with *o*-$NH_2$ or other substituents[22–28] and isatin anhydride.[29–31] In general, the method of gaining quinazolinone derivatives from benzoic acid derivatives with *o*-$NH_2$ or other substituents is facile.

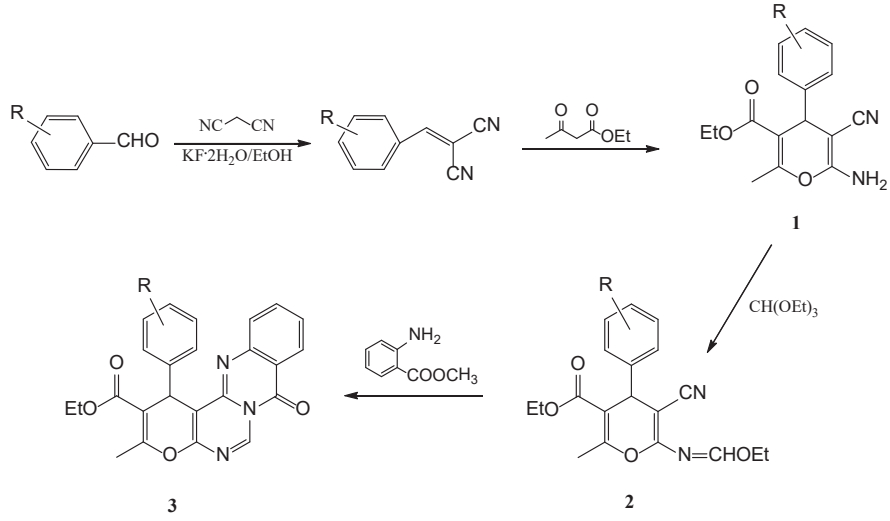
As a continuation of our synthesis of biological active heterocyclic systems, a new series of 1-aryl-3-methyl-8-oxo-1,8-dihydropyrano[2′,3′:4,5]pyrimido[6,1-*b*]quinazoline-2-carboxylate derivatives are reported in this paper.

## Results and discussion

6-Amino-5-cyano-2-methyl-4-aryl-4*H*-pyran-3-carboxylate derivatives **1** were prepared by the reaction of ethyl acetoacetate with 2-arylylidene malononitrile derivatives,[22] which were obtained according to reference[23] with appropriate modifications. Compounds **1** and excess triethyl orthoformate were heated under reflux in the presence of acetic anhydride to give 5-cyano-6-[(ethoxymethylene)amino]-2-methyl-4-aryl-4*H*-pyran-3-carboxylate derivatives **2**. Cyclisation of compounds **2** with methyl anthranilate afforded ethyl 1-aryl-3-methyl-8-oxo-1,8-dihydropyrano[2′,3′:4,5]pyrimido[6,1-*b*] quinazoline-2-carboxylate derivatives **3**. The melting points and yields of compounds **2** and **3** are shown in Tables 1 and 2, respectively.

The spectroscopic data (IR, $^1$H NMR and MS) are in accordance with the chemical structures of the target compounds.

In the $^1$H NMR spectrum of compound **2c**, a sharp single proton peak at δ 4.54 is observed for the 4-H proton. The structure of compound **2c** was further proved by IR through several characteristic absorption bands of 1711 cm$^{-1}$ (C=O); 2989 cm$^{-1}$ (–$CH_3$); 2924 cm$^{-1}$ (–$CH_2$–); 1616 cm$^{-1}$ (C=N) and 2212 cm$^{-1}$ for CN.




**Scheme 1** Synthetic route to title compounds **3**.

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**Table 1** Melting points and yield of compound **2a–h**[a]

| Entry | R | M.p. / °C | Yield[b] /% |
|---|---|---|---|
| **2a** | 4-$OCH_3$ | 153–155 | 75 |
| **2b** | 3,4-$(OCH_3)_2$ | 102–104 | 72 |
| **2c** | 4-$CH_3$ | 86–88 | 79 |
| **2d** | 2,4-$Cl_2$ | 98–100 | 69 |
| **2e** | 2-Cl | 116–118 | 64 |
| **2f** | 4-Cl | 96–98 | 67 |
| **2g** | H | 100–102 | 70 |
| **2h** | 3-$NO_2$ | 92–94 | 63 |

[a]Reaction conditions: 5 mmol compound **1**, 10 mL triethyl orthoformate, reflux.
[b]Isolated yields.

**Table 2** Melting points and yields of compound **3a–h**[a]

| Entry | R | M.p. / °C | Yield[b] /% |
|---|---|---|---|
| **3a** | 4-$OCH_3$ | 184–186 | 71 |
| **3b** | 3,4-$(OCH_3)_2$ | 206–208 | 68 |
| **3c** | 4-$CH_3$ | 186–188 | 70 |
| **3d** | 2,4-$Cl_2$ | 198–200 | 67 |
| **3e** | 2-Cl | 228–230 | 65 |
| **3f** | 4-Cl | 179–181 | 66 |
| **3g** | H | 226–228 | 70 |
| **3h** | 3-$NO_2$ | 208–210 | 65 |

[a]Reaction conditions: 5 mmol compound **2**, 5 mmol methyl anthranilate, 10 mL acetic acid, reflux.
[b]Isolated yields.

In the $^1$H NMR spectrum of compound **3c**, a sharp single proton peak at δ 5.66 observed for the 1-H proton. The structure of compound **3c** was further proved by IR through several characteristic absorption bands of 1663, 1716 cm$^{-1}$ (C=O); 2977 cm$^{-1}$ (–$CH_3$); 2920 cm$^{-1}$ (–$CH_2$–) and 1624 cm$^{-1}$ for C=N.

The fluorescence of ethyl 1-(2-chlorophenyl)-3-methyl-8-oxo-1,8-dihydropyrano[2′,3′:4,5]pyrimido[6,1-*b*]quinazoline-2-carboxylate **3e** in the solid state at room temperature was investigated. The longest wavelength of the excitation maximum of **3e** is located at *ca* 406 nm. Upon excitation, compound **3e** give a series of emission peaks at 471 nm, 505 nm and 546 nm.

## Conclusions

In summary, we have provided a method for the synthesis of a series of novel compounds 1-aryl-3-methyl-8-oxo-1,8-dihydropyrano[2′,3′:4,5]pyrimido[6,1-*b*]quinazoline-2-carboxylate derivatives **3** by Knoevenagel, Michael, cyclisation and condensation reactions in good yields. For synthesis of compounds **3**, we first prepared 5-cyano-6-[(ethoxymethylene) amino]-2-methyl-4-aryl-4*H*-pyran-3-carboxylate derivatives **2** by the reaction of triethyl orthoformate and 6-amino-5-cyano-2-methyl-4-aryl-4*H*-pyran-3-carboxylate derivatives under reflux. This methodology is of interest due to the use of triethyl orthoformate as reactant and solvent without the use of other organic solvents or toxic metal catalysts, thus minimising the cost, environmental pollution and operational hazards. Structures have been confirmed by spectroscopic methods and X-ray crystallography.

## Experimental

Melting points were obtained by an electrothermal apparatus and the temperatures were uncorrected. Microanalysis was performed by the PerkinElmer 2400 Microanalytical Service. IR spectra were determined on a PerkinElmer 1700 spectrophotometer. $^1$H NMR spectra were recorded on a Bruker ARX-400 instrument using $CDCl_3$ as solvent. The electrospray ionisation mass spectrometry (ESI-MS) were determined on an Aglient-6100 equipment. Fluorescence spectra were measured on a JASCO FP-6600 spectrofluorometer. The reactions were monitored by TLC, using 0.2 mm silica $GF_{254}$ (Merck) plates using UV light (254 and 365 nm) for detection.

*Synthesis of ethyl 5-cyano-6-[(ethoxymethylene)amino]-2-methyl-4-aryl-4H-pyran-3-carboxylate derivatives* (**2a–h**)*; general procedure*

The ethyl 6-amino-5-cyano-2-methyl-4-aryl-4*H*-pyran-3-carboxylate derivatives **1** (5 mmol) was added to triethyl orthoformate (10 mL). The mixture was heated to reflux for 3–4 h (monitored by TLC). The resulting dark brown solution was cooled to r.t. and evaporated under reduced pressure to give a brown residue. The crude product was filtered off and recrystallised from ethanol.

*Ethyl 5-cyano-6-[(ethoxymethylene)amino]-4-(4-methoxyphenyl)-2-methyl-4*H*-pyran-3-carboxylate* (**2a**): Yield 71%; m.p. 153–155 °C; IR ($\nu_{max}$, cm$^{-1}$) KBr: 2984, 2934, 2869, 2837, 2210, 1707, 1613; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H, -N=CHOEt), 7.20–7.14 (m, 2H, *o*-ArH), 6.88–6.83 (m, 2H, *m*-ArH), 4.53 (s, 1H, C4-H), 4.39 (qt, *J* = 7.2, 0.9 Hz, 2H, $CO_2CH_2CH_3$), 4.11–4.04 (m, 2H, $CHOCH_2CH_3$), 3.80 (s, 3H, $OCH_3$), 2.42 (d, *J* = 1.0 Hz, 3H, 2-$CH_3$), 1.37 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.15 (t, *J* = 7.1 Hz, 3H, $CHOCH_2CH_3$); Anal. calcd for $C_{20}H_{22}N_2O_5$: C, 64.85; H, 5.99; N, 7.56; found: C, 64.67; H, 6.18; N, 7.34%.

*Ethyl 5-cyano-4-(3,4-dimethoxyphenyl)-6-[(ethoxymethylene)amino]-2-methyl-4*H*-pyran-3-carboxylate* (**2b**): Yield 72%; m.p. 102–104 °C; IR ($\nu_{max}$, cm$^{-1}$) KBr: 2982, 2930, 2873, 2838, 2214, 1710, 1623; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H, -N=CHOEt), 6.85–6.75 (m, 3H, ArH), 4.53 (s, 1H, C4-H), 4.43–4.36 (m, 2H, $CO_2CH_2CH_3$), 4.11–4.05 (m, 2H, $CHOCH_2CH_3$), 3.90 (s, 3H, $OCH_3$), 3.87 (s, 3H, $OCH_3$), 2.43 (d, *J* = 1.0 Hz, 3H, 2-$CH_3$), 1.38 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.15 (t, *J* = 7.1 Hz, 3H, $CHOCH_2CH_3$); Anal. calcd for $C_{21}H_{24}N_2O_6$: C, 62.99; H, 6.04; N, 7.00; found: C, 63.21; H, 6.25; N, 6.74%.

*Ethyl 5-cyano-6-(ethoxymethyleneamino)-2-methyl-4-*p*-tolyl-4*H*-pyran-3-carboxylate* (**2c**): Yield 79%; m.p. 86–88 °C; IR ($\nu_{max}$, cm$^{-1}$) KBr: 2986, 2924, 2862, 2212, 1711, 1616; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, 1H, -N=CHOEt), 7.13 (d, *J* = 10.8 Hz, 4H, ArH), 4.54 (s, 1H, C4-H), 4.39 (q, *J* = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 4.07 (q, *J* = 7.3 Hz, 2H, $CHOCH_2CH_3$), 2.43 (s, 3H, 4′-$CH_3$), 2.33 (s, 3H, 2-$CH_3$), 1.37 (t, *J* = 7.3 Hz, 3H, $CO_2CH_2CH_3$), 1.14 (t, *J* = 7.1 Hz, 3H, $CHOCH_2CH_3$); Anal. calcd for $C_{20}H_{22}N_2O_4$: C, 67.78; H, 6.26; N, 7.90; found C, 67.63; H, 6.11; N, 7.83%.

*Ethyl 5-cyano-4-(2,4-dichlorophenyl)-6-[(ethoxymethylene)amino]-2-methyl-4*H*-pyran-3-carboxylate* (**2d**): Yield 69%; m.p. 98–100 °C; IR ($\nu_{max}$, cm$^{-1}$) KBr: 2983, 2933, 2870, 2211, 1717, 1617; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H, -N=CHOEt), 7.41 (d, *J* = 2.1 Hz, 1H, 3′-ArH), 7.26–7.16 (m, 2H, 5′-ArH, 6′-ArH), 5.17 (s, 1H, C4-H), 4.40 (q, *J* = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 4.05 (q, *J* = 7.1 Hz, 2H, $CHOCH_2CH_3$), 2.46 (s, 3H, 2-$CH_3$), 1.38 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.12 (t, *J* = 7.1 Hz, 3H, $CHOCH_2CH_3$); Anal. calcd for $C_{19}H_{18}Cl_2N_2O_4$: C, 55.76; H, 4.43; N, 6.84; found: C, 55.58; H, 4.59; N, 6.68%.

*Ethyl 4-(2-chlorophenyl)-5-cyano-6-[(ethoxymethylene)amino]-2-methyl-4*H*-pyran-3-carboxylate* (**2e**): Yield 64%; m.p. 116–118 °C; IR ($\nu_{max}$, cm$^{-1}$) KBr: 2986, 2936, 2868, 2210, 1719, 1619; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H, -N=CHOEt), 7.39–7.37 (m, 1H, 3′-ArH), 7.29–7.17 (m, 3H, ArH), 5.21 (s, 1H, C4-H), 4.42–4.36 (m, 2H, $CO_2CH_2CH_3$), 4.03 (qd, *J* = 7.1, 2.5 Hz, 2H, $CHOCH_2CH_3$), 2.46 (d, *J* = 1.1 Hz, 3H, 2-$CH_3$), 1.37 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.09 (t, *J* = 7.1 Hz, 3H, $CHOCH_2CH_3$); Anal. calcd for $C_{19}H_{19}ClN_2O_4$: C, 60.88; H, 5.11; N, 7.47; found: C, 61.05; H, 5.29; N, 7.20%.

*Ethyl 4-(4-chlorophenyl)-5-cyano-6-[(ethoxymethylene)amino]-2-methyl-4*H*-pyran-3-carboxylate* (**2f**): Yield 67%; m.p. 96–98 °C; IR ($\nu_{max}$, cm$^{-1}$) KBr: 2935, 2902, 2869, 2214, 1714, 1613; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.25 (s, 1H, -N=CHOEt), 7.33–7.30 (m, 2H, *m*-ArH), 7.22–7.19 (m, 2H, *o*-ArH), 4.57 (s, 1H, C4-H), 4.40 (qt, *J* = 7.1, 0.9 Hz, 2H, $CO_2CH_2CH_3$), 4.07 (qd, *J* = 7.1, 3.8 Hz, 2H, $CHOCH_2CH_3$), 2.44 (s, 3H, 2-$CH_3$), 1.38 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.14 (t, *J* = 7.1 Hz, 3H, $CHOCH_2CH_3$); Anal. calcd for $C_{19}H_{19}ClN_2O_4$: C, 60.88; H, 5.11; N, 7.47; found: C, 61.09; H, 5.27; N, 7.21%.

*Ethyl 5-cyano-6-[(ethoxymethylene)amino]-2-methyl-4-phenyl-4H-pyran-3-carboxylate* (**2g**): Yield 70%; m.p. 100–102 °C; IR ($\nu_{max}$, $cm^{-1}$) KBr: 2982, 2930, 2871, 2806, 2213, 1715, 1623; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.25 (s, 1H, -N=CHOEt), 7.36–7.23 (m, 5H, ArH), 4.58 (s, 1H, C4-H), 4.39 (qt, *J* = 7.1, 1.0 Hz, 2H, $CO_2CH_2CH_3$), 4.10-4.02 (m, 2H, $CHOCH_2CH_3$), 2.44 (d, *J* = 1.0 Hz, 3H, 2-$CH_3$), 1.37 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.12 (t, *J* = 7.1 Hz, 3H, $CHOCH_2CH_3$); Anal. calcd for $C_{19}H_{20}N_2O_4$: C, 67.05; H, 5.92; N, 8.23; found: C, 67.28; H, 6.10; N, 7.98%.

*Ethyl 5-cyano-6-[(ethoxymethylene)amino]-2-methyl-4-(3-nitrophenyl)-4H-pyran-3-carboxylate* (**2h**): Yield 63%; m.p. 92–94 °C; IR ($\nu_{max}$, $cm^{-1}$) KBr: 2993, 2942, 2906, 2871, 2212, 1719, 1617; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H, -N=CHOEt), 8.18–8.11 (m, 2H, 2′-ArH, 4′-ArH), 7.66 (dt, *J* = 7.8, 1.4 Hz, 1H, 6′-ArH), 7.54 (t, *J* = 7.9 Hz, 1H, 5′-ArH), 4.72 (s, 1H, C4-H), 4.45–4.39 (m, 2H, $CO_2CH_2CH_3$), 4.08 (qd, *J* = 7.1, 3.7 Hz, 2H, $CHOCH_2CH_3$), 2.49 (s, 3H, 2-$CH_3$), 1.39 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.15 (t, *J* = 7.1 Hz, 3H, $CHOCH_2CH_3$); Anal. calcd for $C_{19}H_{19}N_3O_6$: C, 59.22; H, 4.97; N, 10.90; found: C, 59.41; H, 4.76; N, 11.12%.

*Synthesis of 1-aryl-3-methyl-8-oxo-1,8-dihydropyrano[2′,3′:4,5]pyrimido[6,1-b]quinazoline-2-carboxylate derivatives* (**3a–h**)*; general procedure*

A mixture of ethyl 5-cyano-6-[(ethoxymethylene)amino]-2-methyl-4-aryl-4*H*-pyran -3-carboxylate **2** (5 mmol) and methyl anthranilate (5 mmol) was dissolved in acetic acid and heated to reflux for 6–8 h (monitored by TLC). The mixture was cooled to r.t., poured onto ice cold water, then neutralised with ammonia and stirred for another 30 min. The precipitate was filtered off, washed with water, dried, and further purified by column chromatography.

*Ethyl 3-methyl-8-oxo-1-(4-methoxyphenyl)-1,8-dihydropyrano-[2',3':4,5]pyrimido[6,1-*b*]quinazoline-2-carboxylate* (**3a**): Yield 71%; m.p. 184–186 °C; IR ($\nu_{max}$, $cm^{-1}$) KBr: 2986, 2914, 2841, 1708, 1662, 1617; $^1$H NMR (400 MHz, $CDCl_3$) δ 9.42 (s, 1H, NCHN), 8.36–8.34 (m, 1H, 9-ArH), 7.88–7.80 (m, 2H, 10-ArH, 12-ArH), 7.48–7.42 (m, 3H, 11-ArH, 2′-ArH, 6′-ArH), 6.81–6.78 (m, 2H, 3′-ArH, 5′-ArH), 5.54 (s, 1H, C1-H), 4.25–4.12 (m, 2H, $CO_2CH_2CH_3$), 3.74 (s, 3H, $OCH_3$), 2.61 (s, 3H, 3-$CH_3$), 1.28 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$); MS (ESI) *m/z*: 444.2 $[M + H]^+$; Anal. calcd for $C_{25}H_{21}N_3O_5$: C, 67.71; H, 4.77; N, 9.48; found: C, 67.84; H, 4.91; N, 9.25%.

*Ethyl 3-methyl-8-oxo-1-(3,4-dimethoxyphenyl)-1,8-dihydropyrano[2',3':4,5]pyrimido[6,1-*b*]quinazoline-2-carboxylate* (**3b**): Yield 68%; m.p. 206–208 °C; IR ($\nu_{max}$, $cm^{-1}$) KBr: 2986, 2937, 2838, 1715, 1670, 1626; $^1$H NMR (400 MHz, $CDCl_3$) δ 9.43 (dt, *J* = 3.5, 1.6 Hz, 1H, NCHN), 8.36 (d, *J* = 8.8 Hz, 1H, 9-ArH), 7.93–7.79 (m, 2H, 10-ArH, 12-ArH), 7.48 (tt, *J* = 6.7, 2.3 Hz, 1H, 11-ArH), 7.31 (d, *J* = 7.9 Hz, 1H, 2′-ArH), 6.94 (dt, *J* = 8.3, 1.5 Hz, 1H, 5′-ArH), 6.76 (d, *J* = 8.3 Hz, 1H, 6′-ArH), 5.54 (s, 1H, C1-H), 4.27–4.13 (m, 2H, $CO_2CH_2CH_3$), 3.92 (s, 3H, $OCH_3$), 3.80 (s, 3H, $OCH_3$), 2.63 (s, 3H, 3-$CH_3$), 1.28 (td, *J* = 7.2, 1.7 Hz, 3H, $CO_2CH_2CH_3$); MS (ESI) *m/z*: 474.2 $[M + H]^+$; Anal. calcd for $C_{26}H_{23}N_3O_6$: C, 65.95; H, 4.90; N, 8.87; found: C, 65.74; H, 5.12; N, 8.68%.

*Ethyl 3-methyl-8-oxo-1-(*p*-tolyl)-1,8-dihydropyrano[2',3':4,5]pyrimido[6,1-*b*]quinazoline-2-carboxylate* (**3c**): Yield 70%; m.p. 186–188 °C; IR ($\nu_{max}$, $cm^{-1}$) KBr: 2977, 2920, 2855, 1716, 1663, 1624; $^1$H NMR (400 MHz, $CDCl_3$) δ 9.44 (d, *J* = 2.3 Hz, 1H, NCHN), 8.37–8.32 (m, 1H, 9-ArH), 7.93–7.84 (m, 2H, 10-ArH, 12-ArH), 7.49–7.42 (m, 3H, 11-ArH, 2′-ArH, 6′-ArH), 7.07 (d, *J* = 7.9 Hz, 2H, 3′-ArH, 5′-ArH), 5.66 (s, 1H, C1-H), 4.18 (qd, *J* = 7.1, 3.1 Hz, 2H, $CO_2CH_2CH_3$), 2.62 (s, 3H, $C_6H_4CH_3$), 2.26 (s, 3H, 3-$CH_3$), 1.29 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$); MS (ESI) *m/z*: 428.2 $[M + H]^+$; Anal. calcd for $C_{25}H_{21}N_3O_4$: C, 70.25; H, 4.95; N, 9.83; found: C, 70.06; H, 5.13; N, 9.94%.

*Ethyl 3-methyl-8-oxo-1-(2,4-dichlorophenyl)-1,8-dihydropyrano[2',3':4,5]pyrimido[6,1-*b*]quinazoline-2-carboxylate* (**3d**): Yield 67%; m.p. 198–200 °C; IR ($\nu_{max}$, $cm^{-1}$) KBr: 2986, 2943, 1711, 1658, 1613; $^1$H NMR (400 MHz, $CDCl_3$) δ 9.44 (s, 1H, NCHN), 8.34 (dd, *J* = 8.1, 0.9 Hz, 1H, 9-ArH), 7.87–7.78 (m, 2H, 10-ArH, 12-ArH), 7.48–7.28 (m, 3H, 11-ArH, 3′-ArH, 5′-ArH), 7.16 (dd, *J* = 8.4, 2.2 Hz, 1H, 6′-ArH), 5.88 (s, 1H, C1-H), 4.26–4.13 (m, 2H, $CO_2CH_2CH_3$), 2.58 (d, *J* = 0.8 Hz, 3H, 3-$CH_3$), 1.28 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$); MS (ESI) *m/z*: 482.2 $[M + H]^+$; Anal. calcd for $C_{24}H_{17}Cl_2N_3O_4$: C, 59.77; H, 3.55; N, 8.71; found: C, 59.89; H, 3.41; N, 8.83%.

*Ethyl 3-methyl-8-oxo-1-(2-chlorophenyl)-1,8-dihydropyrano[2',3':4,5]pyrimido[6,1-b]quinazoline-2-carboxylate* (**3e**): Yield 65%; m.p. 228–230 °C; IR ($\nu_{max}$, $cm^{-1}$) KBr: 2985, 2929, 2898, 2857, 1718, 1659, 1619; $^1$H NMR (400 MHz, $CDCl_3$) δ 9.45 (s, 1H, NCHN), 8.33 (dt, *J* = 8.0, 1.1 Hz, 1H, 9-ArH), 7.89–7.80 (m, 2H, 10-ArH, 12-ArH), 7.56–7.42 (m, 2H, 11-ArH, 3′-ArH), 7.31 (dd, *J* = 7.9, 1.4 Hz, 1H, 4′-ArH), 7.20–7.08 (m, 2H, 5′-ArH, 6′-ArH), 5.98 (s, 1H, C1-H), 4.19 (qd, *J* = 7.2, 1.2 Hz, 2H, $CO_2CH_2CH_3$), 2.58 (d, *J* = 1.0 Hz, 3H, 3-$CH_3$), 1.27 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$); MS (ESI) *m/z*: 448.2 $[M + H]^+$; Anal. calcd for $C_{24}H_{18}ClN_3O_4$: C, 64.36; H, 4.05; N, 9.38; found: C, 64.54; H, 3.89; N, 9.49%.

*Ethyl 3-methyl-8-oxo-1-(4-chlorophenyl)-1,8-dihydropyrano[2',3':4,5]pyrimido[6,1-b]quinazoline-2-carboxylate* (**3f**): Yield 66%; m.p. 179–181 °C; IR ($\nu_{max}$, $cm^{-1}$) KBr: 2991, 2916, 2856,

**Table 3** Crystallographic data for compounds **2c** and **3c**

| Compound | **2c** | **3c** |
|---|---|---|
| CCDC No. | 1439542 | 1439543 |
| Empirical formula | $C_{20}H_{22}N_2O_4$ | $C_{25}H_{21}N_3O_4$ |
| Formula weight | 354.40 | 427.45 |
| Wavelength / nm | 0.71073 | 0.71073 |
| Crystal system | Triclinic | Monoclinic |
| Space group | *P-1* | $P2_1/c$ |
| *a* / Å | 10.005(5) | 10.450(3) |
| *b* / Å | 10.325(6) | 24.217(6) |
| *c* / Å | 10.450(6) | 8.757(2) |
| α/ ° | 85.352(5) | 90 |
| β/ ° | 62.751(4) | 104.130(2) |
| γ/ ° | 83.765(4) | 90 |
| Volume / $Å^3$ | 953.5(9) | 2149.1(9) |
| *Z* | 2 | 4 |
| Calculated density / g $cm^{-3}$ | 1.234 | 1.321 |
| Absorption coefficient / $mm^{-1}$ | 0.087 | 0.091 |
| *F*(000) | 376 | 896 |
| Final *R* indices [I > 2sigma(I)] | $R_1$ = 0.0421, $wR_2$ = 0.1106 | $R_1$ = 0.0485, $wR_2$ = 0.1446 |
| *R* indices (all data) | $R_1$ = 0.0664, $wR_2$ = 0.1295 | $R_1$ = 0.0951, $wR_2$ = 0.1819 |

1713, 1661, 1620; $^1$H NMR (400 MHz, $CDCl_3$) δ 9.44 (s, 1H, NCHN), 8.36 (dd, *J* = 8.1, 1.6 Hz, 1H, 9-ArH), 7.89–7.78 (m, 2H, 10-ArH, 12-ArH), 7.52–7.41 (m, 3H, 11-ArH, 3′-ArH, 5′-ArH), 7.27–7.19 (m, 2H, 2′-ArH, 6′-ArH), 5.56 (s, 1H, C1-H), 4.23–4.14 (m, 2H, $CO_2CH_2CH_3$), 2.62 (d, *J* = 0.9 Hz, 3H, 3-$CH_3$), 1.27 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$); MS (ESI) *m/z*: 448.2 $[M + H]^+$; Anal. calcd for $C_{24}H_{18}ClN_3O_4$: C, 64.36; H, 4.05; N, 9.38; found: C, 64.52; H, 3.87; N, 9.51%.

*Ethyl 3-methyl-8-oxo-1-phenyl-1,8-dihydropyrano[2',3':4,5]pyrimido[6,1-b]quinazoline-2-carboxylate* (**3g**): Yield 70%; m.p. 226–228 °C; IR ($\nu_{max}$, $cm^{-1}$) KBr: 2982, 2928, 2862, 1715, 1656, 1622; $^1$H NMR (400 MHz, $CDCl_3$) δ 9.47 (s, 1H, NCHN), 8.36 (dd, *J* = 8.1, 1.2 Hz, 1H, 9-ArH), 8.04 (d, *J* = 8.2 Hz, 1H, 10-ArH), 7.89 (s, 1H, 12-ArH), 7.59 (d, *J* = 7.6 Hz, 2H, 3′-ArH, 5′-ArH), 7.50 (t, *J* = 7.6 Hz, 1H, 11-ArH), 7.29–7.17 (m, 2H, 2′-ArH, 6′-ArH), 7.18 (d, *J* = 7.4 Hz, 1H, 4′-ArH), 5.86 (s, 1H, C1-H), 4.25–4.14 (m, 2H, $CO_2CH_2CH_3$), 2.63 (s, 3H, 3-$CH_3$), 1.29 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$); MS (ESI) *m/z*: 414.2 $[M + H]^+$; Anal. calcd for $C_{24}H_{19}N_3O_4$: C, 69.72; H, 4.63; N, 10.16; found: C, 69.55; H, 4.78; N, 10.34%.

*Ethyl 3-methyl-8-oxo-1-(3-nitrophenyl)-1,8-dihydropyrano[2',3':4,5]pyrimido[6,1-b]quinazoline-2-carboxylate* (**3h**): Yield 65%; m.p. 208–210 °C; IR ($\nu_{max}$, $cm^{-1}$) KBr: 2987, 2910, 2857, 1711, 1661, 1620; $^1$H NMR (400 MHz, $CDCl_3$) δ 9.44 (s, 1H, NCHN), 8.54 (t, *J* = 2.0 Hz, 1H, 2′-ArH), 8.35 (dd, *J* = 8.1, 1.5 Hz, 1H, 9-ArH), 8.03 (ddd, *J* = 8.2, 2.4, 1.1 Hz, 1H, 4′-ArH), 7.92–7.76 (m, 3H, 10-ArH, 12-ArH, 6′-ArH), 7.52–7.39 (m, 2H, 5′-ArH, 11-ArH), 5.66 (s, 1H, C1-H), 4.23–4.11 (m, 2H, $CO_2CH_2CH_3$), 2.66 (d, *J* = 0.9 Hz, 3H, 3-$CH_3$), 1.25 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$); MS (ESI) *m/z*: 459.3 $[M + H]^+$; Anal. calcd for $C_{24}H_{18}N_4O_6$: C, 62.88; H, 3.96; N, 12.22; found: C, 62.67; H, 3.83; N, 12.43%.

## Single crystal X-ray crystallography

Crystallographic data of **2c**, **3c** (Table 3) was obtained on Bruker SMART APEX-II CCD with Mo-Kα radiation (λ = 0.71073 Å) at 296(2) K. Absorption corrections were applied using SADABS. The structures were solved by direct methods with SHELXS-97 program and refinements on F2 were performed with SHELXL-97 program by full-matrix least-squares techniques.[33,34] Crystallographic data for the structures in this paper can be obtained free of charge from the Cambridge Crystallographic Data Centre. The single crystal structures of **2c** are shown in Fig. 1, the single crystal structures of **3c** are shown in Fig. 2.

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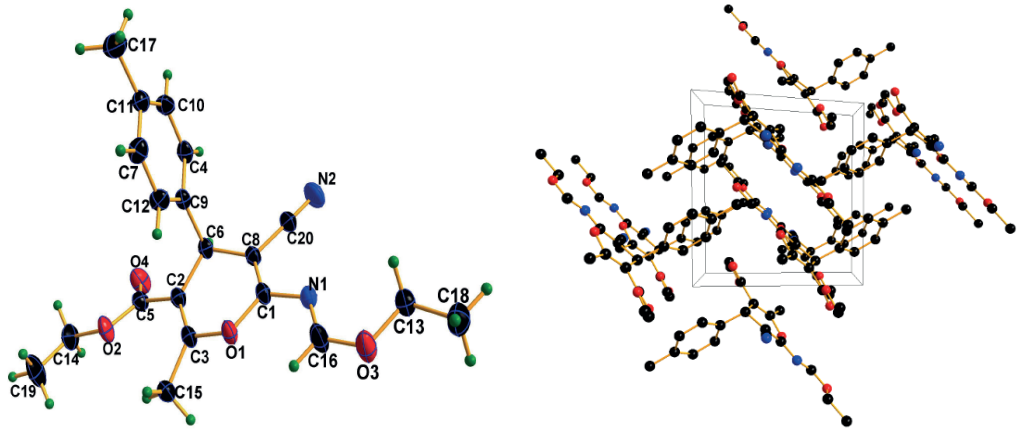


**Fig. 1** Molecular structure and packing diagram of compound **2c**. Displacement ellipsoids are drawn at the 30% probability level.

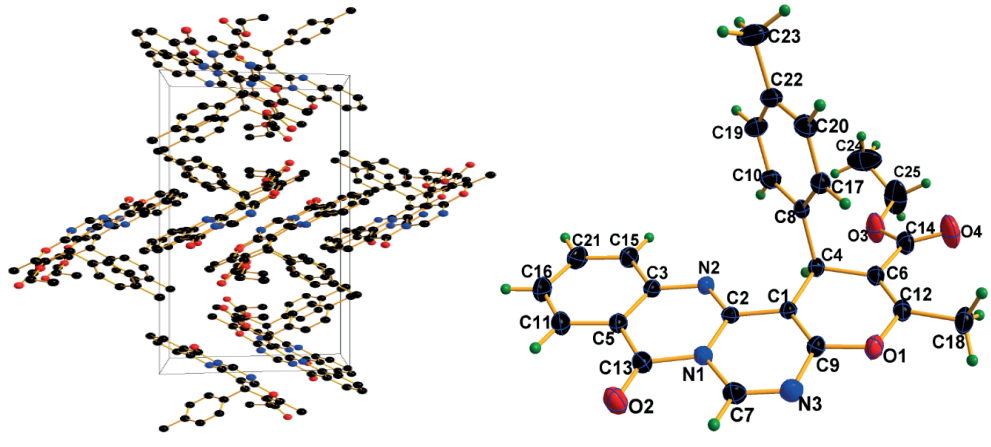


**Fig. 2** Molecular structure and packing diagram of compound **3c**. Displacement ellipsoids are drawn at the 30% probability level.

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