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PAPER

Investigation of the one-pot synthesis of quinolin-2-(1*H*)-ones and the discovery of a variation of the three-component Ugi reaction†

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Rapid access to the quinolin-2-(1*H*)-one scaffold is afforded by a sequential 4 component Ugi–Knoevenagel condensation of an aminophenylketone, an aromatic aldehyde possessing electron donating moieties, cyanoacetic acid and an aliphatic isocyanide, in moderate to good yields (49–71%). Interestingly, when the reaction is performed using aromatic aldehydes bearing electron withdrawing moieties or isocyanides containing aromatic or ester units, a mixture of a quinolin-2-(1*H*)-one and an α-amino amide (Ugi three-component adduct) is afforded in varying ratios. Further when the reaction is performed utilizing a combination of an isocyanide-containing aromatic or carbonyl unit, and an aldehyde possessing an electron withdrawing functionality, the Ugi three-component adduct is exclusively afforded. In our hands this new variation of the Ugi 3CR proved to be efficient and robust affording analogues in good yields (51–70%).

Introduction

The success of a medicinal chemistry program is inexorably linked to developing and utilizing synthetically accessible scaffolds that are amenable to diverse functional group alterations. To this end we place synthetic elegance over complexity focusing on high yielding and multi-component chemistry to drive diversity-oriented synthesis.[1] This ethos has afforded our team a suite of biologically active scaffolds including the *dynoles* (**1**),[2] Bis-Ts (**2**),[3,4] and iminodyns (**3**),[5] which are potent dynamin GTPase inhibitors, and the isoindole-3-carboxamide (**4**) scaffold which has displayed promising cytotoxicity activity against a panel of human cancer cell lines (Fig. 1).[6,7]

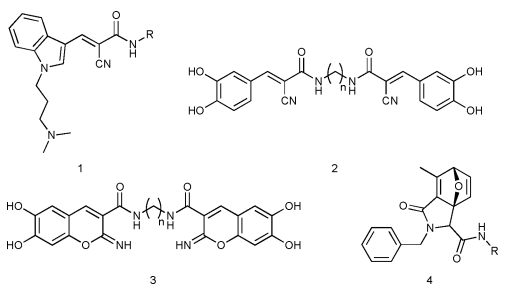

Fig. 1 Generic structures of the dynole (**1**), Bis-T (**2**), iminodyn (**3**), and isoindole-3-carboxamide (**4**) scaffolds.

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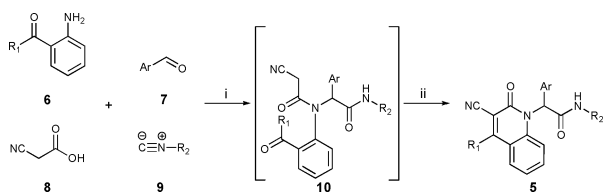
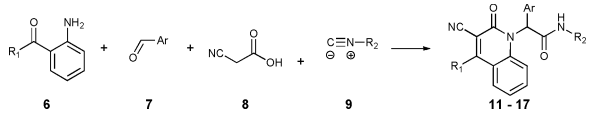
The pivotal reaction affording the *dynoles* (**1**), Bis-T's (**2**), and iminodyns (**3**) is the Knoevenagel condensation which in our hands (and those of others) has continually proven to be a high yielding and extremely robust reaction.[2–21] Similarly the Ugi 4-component reaction (Ugi 4CR), utilized to access the isoindole-3-carboxamide scaffold (**4**),[6,7,22–27] has proven a high yielding reaction tolerating a diverse range of functional groups. Consequently in our efforts to unearth additional series' of biologically active scaffolds our attention was drawn to a series of quinolin-2-(1*H*)-ones (**5**).[28] Entry to the quinolin-2-(1*H*)-ones scaffold could be afforded *via* a one-pot sequential Ugi 4CR followed by spontaneous intramolecular Knoevenagel cyclisation. The reaction entails treating an aminophenyl ketone (**6**) with an aromatic aldehyde (**7**), followed by addition of cyanoacetic acid (**8**), and an isocyanide (**9**) to form the corresponding Ugi product (**10**) which undergoes spontaneous intramolecular Knoevenagel condensation between the cyanoacetic acid moiety and the carbonyl derived from the aminophenyl ketone (Scheme 1).



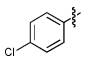
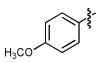
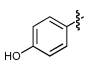
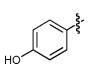
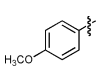
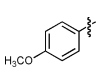
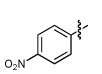
Scheme 1 Reagents and conditions: (i) MeOH, rt; (ii) spontaneous.

Following the reported synthetic route we examined a number of aromatic aldehydes, two aminophenylketones (2-aminobenzophenone and 1-(2-aminophenyl)ethanone), and a number of aliphatic isocyanides. Typically these reactions proceeded

Table 1 Isolated yields of quinolin-2-(1*H*)-ones (**11–17**) arising from the 4-component Ugi-Knoevenagel reaction



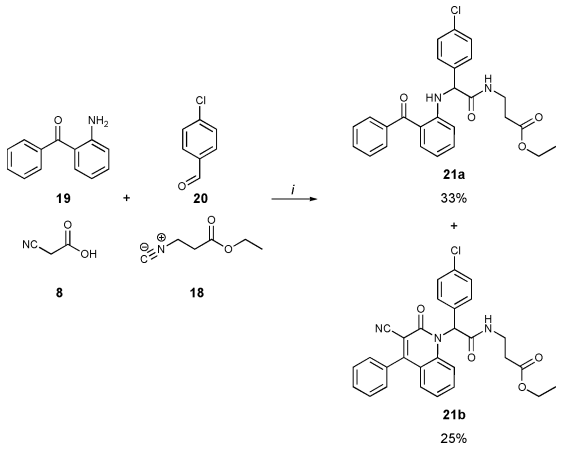
6 7 8 9 11 - 17

Entry (compound)	R_1	Ar	R_2	Yield (%)
1 (**11**)				56
2 (**12**)				68
3 (**13**)				71
4 (**14**)				66
5 (**15**)				49
6 (**16**)				68
7 (**17**)				49

smoothly in moderate to good isolated yields (49–71%, Table 1).[19]

The Ugi–Knoevenagel reaction tolerates a range of differing aldehydes, with electron donating aldehydes affording higher isolated yields (Table 1, entries 2–4 and 6). Electron withdrawing aldehydes (Table 1, entries 1 and 7) appear to provide lower yields of the Ugi–Knoevenagel product. We also investigated the synthesis of **13** in CH_2Cl_2 and THF, and in both instances noted a significant reduction in product yield isolating 52% and 43%, respectively. This suggests, that of the solvent systems examined, CH_3OH is the favoured system for this transformation. Of the Table 1 entries, entry 5 is the sole example utilizing a functionalised isocyanide, and it too affords a low yield of the Ugi–Knoevenagel product, even in the presence of 4-methoxybenzaldehyde, which afforded a good yield with simple isocyanides (Table 1, entries 2 and 6). As such we thought that the increased functionality afforded by the ester moiety might be responsible for the reduced yield observed. Accordingly we examined this reaction with the related ethyl isocyanopropionate (**18**) (Scheme 2).

In this instance we observed two distinct products by TLC. Subsequent isolation *via* silica gel flash chromatography and characterization revealed that the higher R_f compound was an α-amino amide, **21a**, an Ugi three-component (Ugi 3CR) adduct, whereas the lower R_f compound was the anticipated Ugi–Knoevenagel adduct, **21b** in a 58% combined yield. The isolation of an Ugi 3CR product as the major component of this reaction mixture was unexpected, and as far as we are aware, not known for systems such as these. This observation warranted further examination. An additional series of reactions investigating a number of aliphatic, a hindered aromatic, and two ester containing isocyanides (Table 2) was thus conducted.



19 + 20 → 21a 33% + 21b 25%; 8 18

Scheme 2 Reagents and conditions; (i) MeOH, rt, 24 h.

As with our initial investigations, moderate to good (combined) yields (58–74%) were observed (Table 2), but now we note the presence of both the Ugi 4CR and Ugi 3CR products. Entries 1–5 (Table 2) indicate the presence of Ugi 4CR and Ugi 3CR in varying ratios, with the Ugi 4CR product being the major product isolated in entries 2–4, and the Ugi 3CR in entries 1 and 5. Interestingly with entries 6 and 7, the Ugi 3CR product is the sole reaction product. Thus a trend was emerging, with reactions utilizing aldehydes bearing electron donating moieties favouring the formation of the Ugi 4CR, whilst utilization of electron withdrawing aldehydes favoured the Ugi 3CR outcome. However the reaction drivers are more complex with the isocyanide moiety also important in governing the reaction outcome with the introduction of an ester moiety (Table 2 entry 3) resulting in a change in product distribution from 1 : 2.7 (Ugi 3CR : Ugi 4CR; Table 2 entry 2) to 1 : 1.1 (Ugi 3CR : Ugi 4CR; Table 2 entry 3). The ester isocyanide reaction also affords a higher (combined) yield at 72% *versus* 49%. The best yield obtained in this series is 74% (Table 2, entry 7), and this reaction utilized the sterically bulky 2,6-dimethylphenyl isocyanide, suggesting that an isocyanide bearing a bulky aromatic and ester moiety may favour the Ugi 3CR product over the Ugi 4CR product.

To further evaluate the influence of the isocyanide moiety we examined an additional series of reactions utilising the bulky aromatic isocyanides 2,6-dimethylphenyl isocyanide and 2-isocyanonaphthalene (Table 3).

In all instances, the reactions utilizing either 2,6-dimethylphenyl isocyanide or 2-isocyanonaphthalene afforded only the Ugi 3CR products in moderate to good yields (Table 3, 51–70%). Also of note here is that the presence of electron donating aldehydes (Table 3, entries 2 and 5) and electron withdrawing aromatic aldehydes (Table 3, entries 1, 3 and 4) do not effect the Ugi 3CR outcome. This suggests that the nature of the isocyanide is of far greater importance in governing the reaction outcome. The reaction proceeded well with both 2-aminobenzophenone and 1-(2-aminophenyl)ethanone, also affording the Ugi 3CR outcome.

The Ugi 3CR reaction has been reported on a handful of occasions,[26–30] but until now has required the addition of $B(OMe)_3$[29] or catalytic quantities of exotic organic acids such as phenylphosphonic and phenylphosphinic acid.[26–30] However, this variant of the reaction was conducted in the absence of an added catalyst. Given the different reaction outcomes *via* the

Table 2 Isolated yields of α-amino amides (**21a–25a**, **26** and **27**) and quinolin-2-(1*H*)-ones (**21b–25b**) arising from the attempted Ugi–Knoevenagel condensation reaction

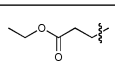
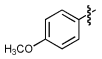
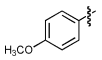
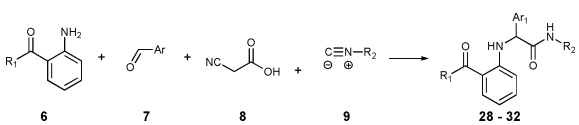
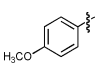
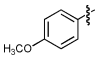
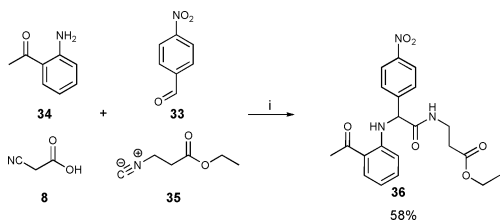
Entry (compound)	R_1	Ar	R_2	Yield% (a)	Yield% (b)	a : b
1 (**21a** and **21b**)				33	25	1.3 : 1
2 (**22a** and **22b**)				16	43	1 : 2.7
3 (**23a** and **23b**)				35	37	1 : 1.1
4 (**24a** and **24b**)				31	38	1 : 1.2
5 (**25a** and **25b**)				42	26	1.1 : 1
6 (**26**)				58	0	—
7 (**27**)				74	0	—

Table 3 Isolated yields of α-amino amides (**28–32**) arising from the Ugi 3CR using bulky aromatic isocyanides



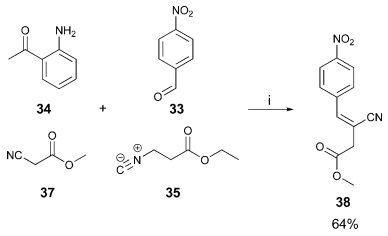
Entry (compound)	R_1	Ar	R_2	Yield% (a)
1 (**28**)				54
2 (**29**)				69
3 (**30**)				51
4 (**31**)				51
5 (**32**)				70

Ugi 3CR and Ugi 4CR, it is logical that the cyanoacetic acid had two distinct roles in this series of Ugi 3/4CRs. Accordingly a series of reactions were conducted in a bid to elucidate the role of cyanoacetic acid in this new variation of the Ugi 3CR. Initially we conducted a point of reference reaction whereby a methanolic solution of 4-nitrobenzaldehyde (**33**) was treated with 1-(2-aminophenyl)ethanone (**34**), ethyl isocyanopropionate (**35**) and a stoichiometric amount of cyanoacetic acid (**8**), which afforded the Ugi 3CR adduct **36** (Scheme 3) in a 58% yield. The reaction was subsequently attempted with a catalytic amount, and in the absence of cyanoacetic acid, respectively, and in both cases only starting materials were returned, clearly demonstrating that cyanoacetic acid plays a crucial role and is required in stoichiometric quantities for the Ugi 3CR.



Scheme 3 Reagents and conditions; (i) MeOH, 24 h, rt.

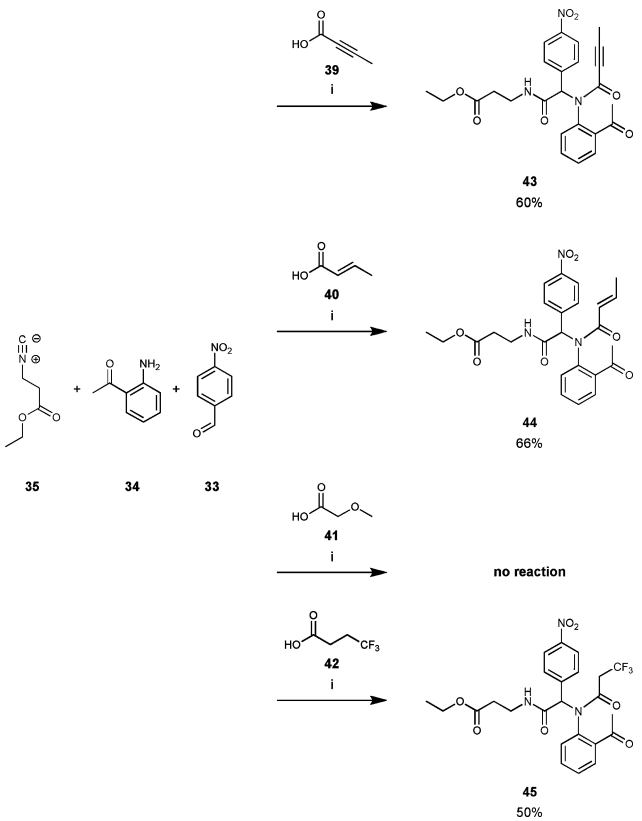
It was postulated that the 'malonic-like' methylene carbon of cyanoacetic acid may be influencing the reaction, possibly acting *via* a similar mechanism to that proposed for phenyl phosphinic acid.[15] To investigate this inference the reaction was repeated replacing cyanoacetic acid with methyl cyanoacetate (**37**) and, as outlined in Scheme 4, this reaction exclusively afforded the Knoevenagel adduct **38**. Thus it was apparent that the 'malonic-like' methylene carbon of the cyanoacetic acid was unlikely to



Scheme 4 Reagents and conditions; (i) MeOH, 24 h, rt.

be influencing the reaction, rather the carboxylic acid proton is pivotal to this variant of the Ugi 3CR.

However, as yet it was not clear if a simple carboxylic acid, rather than cyanoacetic acid, would also facilitate access to the Ugi 3CR. Accordingly, four additional reactions were performed using 2-butynoic acid (**39**), 2-butenoic acid (**40**), 2-methoxyacetic acid (**41**) and 3,3,3-trifluoropropionic acid (**42**) (Scheme 5). In these reactions no product was isolated with 2-methyoxyacetic acid, and only the Ugi 4CR adducts were observed in 60% (**43**), 66% (**44**) and 50% (**45**) yields, respectively, thus emphasizing the importance of cyanoacetic acid to this Ugi 3CR.



Scheme 5 Reagents and conditions; (i) MeOH, 24 h, rt.

Mechanistically both the Ugi 3CR and 4CR are believed to proceed *via* a nitrilium ion intermediate (**46**) which results from the addition of the isocyanide to an *in situ* generated iminium ion (**47**).[18,31–33] To afford the Ugi 4CR product it is proposed the carboxylate ion adds to the nitrilium ion *via* nucleophilic addition whereas during the Ugi 3CR it is proposed that water, generated during the initial imine formation, acts as the internal nucleophile (Fig. 2).[28]

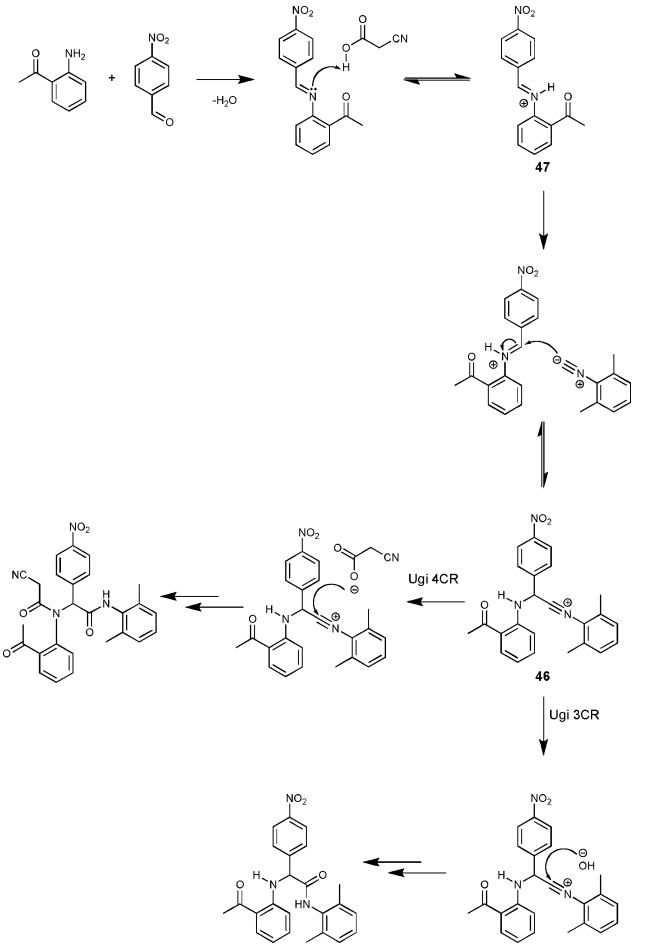


Fig. 2 Partial proposed mechanism for the Ugi 4CR and 3CR reactions.

We believed that this new variation of the Ugi 3CR was controlled by two factors, firstly the reduced nucleophilicity of cyanoacetic acid resulting from the electron withdrawing effect of the nitrile moiety, and secondly the stability of the nitrilium ion. Thus it was anticipated that as the stability of the nitrilium ion increased the ability of the cyanoacetic acid anion, a poor nucleophile, to react with the nitrilium intermediate would be reduced. This would allow water to act as the internal nucleophile and favour the formation of the Ugi 3CR over the Ugi 4CR.

In summary, we have unearthed a new variation of the Ugi 3CR. Evidence indicates that the reaction is promoted by the reduced nucleophilicity of the cyanoacetic acid anion. In our hands this new variation of the Ugi 3CR proved to be efficient and robust affording analogues in good yields with little to no purification required. Further studies in our laboratory are underway to investigate a range of electron deficient carboxylic acids and will be reported in due course.

Experimental section

All reagents were purchased from Sigma-Aldrich, Matrix Scientific or Lancaster Synthesis and were used without purification. With the exception of THF (anhydrous > 99%) obtained from Sigma–Aldrich, all solvents were re-distilled from glass prior to use.

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance™ AMX 300 MHz spectrometer at 300.1315 and 75.4762 MHz,

respectively. Chemical shifts (δ) are reported in parts per million (ppm) measured relative to the internal standards, and coupling constants (J) are expressed in Hertz (Hz). Mass spectra were recorded on a Shimadzu LCMS 2010 EV using a mobile phase of 1 : 1 acetonitrile–H_2O with 0.1% formic acid.

Melting points were recorded on a Stuart Scientific melting point apparatus (UK) and are uncorrected. Thin layer chromatography (TLC) was performed on Merck silica gel 60 F_{254} pre-coated aluminium plates with a thickness of 0.2 mm. Column chromatography was performed under 'flash' conditions on Merck silica gel 60 (230–400 mesh) or using the Biotage SP4 flash purification system with a 100 g pre-packed snap column.

General procedure

2-(4-Chlorophenyl)-2-(3-cyano-2-oxo-4-phenylquinolin-1(2*H*)-yl)-*N*-((trimethylsilyl)methyl)acetamide (11). A solution of MeOH (5.0 mL), 2-aminobenzophenone (0.60 g, 3.00 mmol) and 4-chlorobenzaldehye (0.42 g, 3.00 mmol) was stirred at room temperature for 0.5 h. To the stirred solution was added cyanoacetic acid (0.25 g, 3.00 mmol) followed by the addition of (trimethylsilyl)methyl isocyanide (0.42 mL, 3.00 mmol). The reaction mixture was stirred at room temperature for 24 h and the resulting precipitate was collected, washed with diethyl ether, and dried to afford **11** (0.84 g, 56%) as a yellow solid (mp 168–170 °C). IR (KBr) 3435 (NH), 3057 (CH), 2951, 2856 (CH), 2229 (CN), 1654 (CO), 1604 (CC), 1552 (NH), 858 (SiC), 758 (CH), 700 (CCl) cm^{-1}. ^1H NMR (300 MHz) ($CDCl_3$) δ 7.74–7.62 (4 H, m), 7.62–7.55 (3 H, m), 7.54–7.47 (2 H, m), 7.41 (4 H, s), 7.28–7.20 (1 H, m), 7.02 (1 H, bs), 6.25 (1 H, bs), 2.84 (2 H, AB q, J = 23.4, 5.8 Hz), 0.03 (9 H, s); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 169.3, 163.3, 162.2, 142.4, 136.8, 136.2, 136.0, 134.9, 132.9, 132.5, 131.9, 131.7, 131.6, 131.6, 131.4, 126.3, 122.9, 120.5, 117.3, 108.8, 62.9, 33.1, 0.01; MS (ESI^-) m/z 498 (M–1, 100%); HRMS (ESI^-) for $C_{28}H_{25}ClN_3O_2Si$, calculated 498.1483, found 498.1483.

2-(3-Cyano-2-oxo-4-phenylquinolin-1(2*H*)-yl)-2-(4-methoxyphenyl)-*N*-(pentan-2-yl)acetamide (12). Synthesized utilizing the general procedure described above, from 2-aminobenzophenone (0.52 g, 2.70 mmol), 4-methoxybenzaldehyde (0.32 mL, 2.70 mmol), cyanoacetic acid (0.23 g, 2.70 mmol) and 2-pentylisocyanide (0.32 mL, 2.70 mmol) in MeOH (5.0 mL) to afford **12** (0.88 g, 68%) as a yellow solid (158–159 °C). IR (KBr) 3336 (NH), 3058 (CH), 2953, 2929, 2870 (CH), 2837 (CH), 2228 (CN), 1652 (CO), 1604 (CC), 1512 (NH), 1249 (CO), 757 (CH) cm^{-1}. ^1H NMR (300 MHz) (Acetone-d_6) δ 7.68–7.61 (3 H, m), 7.60–7.49 (3 H, m), 7.46 (1 H, dd, J = 8.2, 0.6 Hz), 7.47–7.39 (2 H, m), 7.37–7.31 (1 H, m), 7.26–7.18 (1 H, m), 7.12–7.07 (1 H, m), 7.01 (1 H, bs), 7.05–6.98 (1 H, m), 6.94–6.88 (2 H, m), 4.12–3.93 (1 H, m), 3.77 (3 H, s), 3.35 (3H, s), 1.60–1.25 (3 H, m), 1.06, 0.89 (1 H, d, J = 6.6 Hz, dr 1 : 3), 0.95–0.84 (2 H, m), 0.74, 0.66 (3 H, t, J = 7.3 Hz, dr 3 : 1); ^{13}C NMR (75 MHz) (Acetone-d_6) δ 165.9, 165.8, 159.4, 158.8, 158.6, 139.7, 133.7, 132.4, 129.4, 129.3, 129.2, 128.8, 128.6, 128.3, 128.3, 128.2, 128.1, 125.9, 125.8, 122.6, 119.6, 117.5, 117.4, 114.3, 113.3, 59.6, 59.5, 54.2, 52.3, 44.9, 44.8, 37.8, 37.5, 26.5, 26.1, 19.7, 19.4, 18.7, 18.2, 12.8, 12.7, 9.6, 9.1; MS (ESI^+) m/z 480 (M+1, 100%); HRMS (ESI^+) for $C_{30}H_{30}N_3O_3$, calculated 480.2209 found 480.2207.

2-(3-Cyano-2-oxo-4-phenylquinolin-1(2*H*)-yl)-2-(4-hydroxyphenyl)-*N*-(pentan-2-yl)acetamide (13)

Synthesized utilizing the general procedure described above, from 2-aminobenzophenone (0.52 g, 2.63 mmol), 4-hydroxybenzaldehyde (0.32 g, 2.63 mmol), cyanoacetic acid (0.23 g, 2.63 mmol) and 2-pentylisocyanide (0.32 mL, 2.63 mmol) in MeOH (5.0 mL) to afford **13** (0.87 g, 71%) as a yellow solid (mp 203–205 °C). IR (KBr) 3407 (NH), 3245 (OH), 3057 (CH), 2961, 2930, 2871 (CH), 2231 (CN), 1665, 1650 (CO), 1605 (CC), 1517 (NH), 757 (CH) cm^{-1}. ^1H NMR (300 MHz) (DMSO-d_6) δ 9.53 (1 H, bs), 7.82 (1 H, d, J = 6.7 Hz), 7.75–7.40 (6 H, m), 7.28–7.13 (3 H, m), 6.99 (1 H, bs), 6.97 (1 H, d, J = 7.3 Hz), 6.74 (2 H, d, J = 8.3 Hz), 3.87, 3.63 (1 H, m, d.r. 3 : 1), 1.60–1.13 (4 H, m), 1.09, 0.89 (3 H, d, J = 6.5 Hz, d.r. 1 : 3), 0.69, 0.57 (3 H, t, J = 7.2 Hz, d.r. 3 : 1); ^{13}C NMR (75 MHz) (DMSO-d_6) δ 166.6, 166.1, 159.5, 159.4, 158.8, 156.7, 139.8, 133.6, 132.7, 129.9, 129.4, 129.3, 128.8, 128.6, 124.8, 124.6, 123.0, 119.5, 118.1, 115.4, 115.0, 105.8, 59.4, 52.3, 44.8, 44.6, 37.8, 37.5, 30.6, 26.7, 26.2, 20.6, 20.2, 19.0, 18.4, 13.7, 13.6, 10.6, 9.9; MS (ESI^-) m/z 464 (M–1, 50%); HRMS (ESI^-) for $C_{29}H_{26}N_3O_3$, calculated 464.2052 found 464.2052.

2-(3-Cyano-4-methyl-2-oxoquinolin-1(2*H*)-yl)-2-(4-hydroxyphenyl)-*N*-(pentan-2-yl)acetamide (14). Synthesized utilizing the general procedure described above, from 1-(2-aminophenyl)ethanone (0.59 g, 4.30 mmol), 4-hydroxybenzaldehyde (0.53 g, 4.30 mmol), cyanoacetic acid (0.37 g, 4.30 mmol) and 2-pentylisocyanide (0.52 mL, 4.30 mmol) in MeOH (5.0 mL) to afford **14** (1.14 g, 66%) as a white solid (mp 198–199 °C). IR (KBr) 3367 (NH), 3232 (OH), 3057 (CH), 2962, 2931, 2872 (CH), 2230 (CN), 1664, 1640 (CO), 1611 (CC), 1512 (NH), 753 (CH) cm^{-1}. ^1H NMR (300 MHz) (DMSO-d_6) δ 9.43 (1 H, s), 7.95 (1 H, d, J = 8.1 Hz), 7.74 (1 H, d, J = 8.1 Hz), 7.57–7.47 (1 H, m), 7.44–7.33 (1 H, m), 7.29 (1 H, t, J = 7.6 Hz), 7.07 (2 H, dd, J = 8.5, 2.1 Hz), 6.94–6.86 (1 H, m), 6.69 (2 H, d, J = 8.5 Hz), 3.92–3.75, 3.68–3.52 (1 H, m, d.r. 3 : 1), 2.77 (3 H, s), 1.50–1.12 (4 H, m), 1.08–1.02, 0.91–0.80 (3 H, m, d.r. 1 : 3), 0.67, 0.51 (3 H, t, J = 7.3 Hz, d.r. 3 : 1); ^{13}C NMR (75 MHz) (DMSO-d_6) δ 166.7, 166.1, 158.7, 157.7, 157.7, 156.6, 139.0, 132.6, 129.3, 129.2, 127.0, 124.8, 124.8, 124.7, 122.9, 119.6, 117.9, 115.6, 114.9, 105.8, 59.0, 58.8, 52.2, 44.7, 44.5, 37.8, 37.5, 30.6, 26.7, 26.2, 20.5, 20.2, 19.0, 18.3, 18.3, 13.7, 13.6, 10.6, 10.0; MS (ESI^-) m/z 402 (M–1, 60%); HRMS (ESI^-) for $C_{24}H_{24}N_3O_3$, calculated 402.1896 found 402.1895.

Methyl 2-(2-(3-cyano-4-methyl-2-oxoquinolin-1(2*H*)-yl)-2-(4-methoxyphenyl)acetamido)acetate (15). Synthesized utilizing the general procedure described above, from 1-(2-aminophenyl)ethanone (0.80 mL, 6.54 mmol), 4-methoxybenzaldehyde (0.89 g, 6.54 mmol), cyanoacetic acid (0.56 g, 6.54 mmol) and methylisocyanoacetate (0.80 mL, 6.54 mmol) in MeOH (5.0 mL) to afford **15** (1.34 g, 49%) as a light brown solid (mp 245–246 °C). IR (KBr) 3367 (NH), 2985, 2951 (CH), 2844 (CH), 2228 (CN), 1742 (COO), 1675, 1656 (CO), 1609 (CC), 1512 (NH), 1246 (CO), 754 (CH) cm^{-1}. ^1H NMR (300 MHz) (DMSO-d_6) δ 8.49 (1 H, t, J = 5.0 Hz), 7.96 (1 H, d, J = 8.1 Hz), 7.55 (1 H, t, J = 7.6), 7.45–7.26 (4 H, m), 7.10 (1 H, bs), 6.88 (2 H, d, J = 8.7 Hz), 3.92–3.76 (2 H, m), 3.70 (3 H, s), 3.61 (3 H, s), 2.77 (3 H, s); ^{13}C NMR (75 MHz) (DMSO-d_6) δ 169.9, 167.5, 158.7, 158.6, 158.0, 138.7, 132.8, 129.5, 128.0, 127.2, 126.0, 123.0, 119.7, 117.8, 115.5, 113.9, 113.7, 105.6, 58.3, 55.0, 51.6, 41.1, 18.3; MS (ESI^-)

m/z 418 (M–1, 100%); HRMS (ESI$^-$) for $C_{23}H_{20}N_3O_5$, calculated 418.1481 found 418.1481.

2-(3-Cyano-4-methyl-2-oxoquinolin-1(2*H*)-yl)-2-(4-methoxyphenyl)-*N*-(2,4,4-trimethylpentan-2-yl)acetamide (16). Synthesized utilizing the general procedure described above, from 1-(2-aminophenyl)ethanone (0.52 g, 3.80 mmol), 4-methoxybenzaldehyde (0.50 mL, 3.80 mmol), cyanoacetic acid (0.33 g, 3.80 mmol) and 1,1,3,3-tetramethylbutylisocyanide (0.70 mL, 3.80 mmol) in MeOH (5.0 mL) to afford **16** (1.18 g, 68%) as a white solid (mp 187–188 °C). IR (KBr) 3430 (NH), 2953, 2909 (CH), 2839 (CH), 2227 (CN), 1684, 1659 (CO), 1607 (CC), 1514 (NH), 1246 (CO), 755 (CH) cm^{-1}. ^{1}H NMR (300 MHz) (DMSO-d_6) δ 7.94 (1 H, d, J = 8.0 Hz), 7.57–7.40 (2 H, m), 7.35 (1 H, bs), 7.32–7.24 (1 H, m), 7.18 (2 H, d, J = 8.4 Hz), 6.94–6.84 (3 H, m), 3.70 (3 H, s), 2.76 (3 H, s), 1.73–1.54 (2 H, m), 1.29 (6 H, d, J = 11.0 Hz), 0.85 (9 H, s); ^{13}C NMR (75 MHz) (DMSO-d_6) δ 165.7, 158.6, 158.4, 157.7, 139.1, 132.4, 129.0, 126.9, 122.8, 119.5, 118.1, 115.5, 113.7, 105.6, 60.0, 55.0, 54.7, 50.9, 31.1, 30.9, 28.5, 28.4, 18.2; MS (ESI$^-$) *m/z* 458 (M–1, 100%); HRMS (ESI$^-$) for $C_{28}H_{32}N_3O_3$, calculated 458.2522 found 458.2522.

2-(3-Cyano-4-methyl-2-oxoquinolin-1(2*H*)-yl)-2-(4-nitrophenyl)-*N*-(2,4,4-trimethylpentan-2-yl)acetamide (17). Synthesized utilizing the general procedure described above, from 1,1-(2-aminophenyl)ethanone (0.60 g, 4.40 mmol), 4-nitrobenzaldehyde (0.67 g, 4.40 mmol), cyanoacetic acid (0.38 g, 4.40 mmol) and 1,1,3,3-tetramethylbutylisocyanide (0.80 mL, 4.40 mmol) in MeOH (5.0 mL) to afford **17** (1.02 g, 49%) as a yellow solid (mp 167–168 °C). IR (KBr) 3325 (NH), 3058 (CH), 2957, 2946 (CH), 2225 (CN), 1681, 1633 (CO), 1608 (CC), 1558 (NO_2), 1514 (NH), 1346 (NO_2), 756 (CH) cm^{-1}. ^{1}H NMR (300 MHz) (DMSO-d_6) δ 8.16 (2 H, d, J = 8.7 Hz), 8.00 (1 H, dd, J = 8.0, 1.6 Hz), 7.65 (1 H, s), 7.54 (1 H, t, J = 7.4, 7.4 Hz), 7.45 (2 H, d, J = 8.7 Hz), 7.33 (1 H, t, J = 7.6 Hz), 7.27 (1 H, d, J = 8.6 Hz), 6.95 (1 H, s), 2.79 (3 H, s), 1.71 (1 H, d, J = 14.6 Hz), 1.52 (1 H, d, J = 14.6 Hz), 1.24 (6 H, d, J = 4.2 Hz), 0.82 (9 H, s); ^{13}C NMR (75 MHz) (DMSO-d_6) δ 164.6, 158.6, 158.1, 152.7, 146.6, 142.5, 138.8, 132.9, 131.6, 130.5, 129.2, 127.3, 124.1, 124.0, 123.2, 123.1, 119.7, 117.4, 115.4, 105.8, 59.9, 55.0, 50.7, 31.1, 30.7, 28.7, 28.0, 18.3; MS (ESI$^-$) *m/z* 473 (M–1, 100%); HRMS (ESI$^-$) for $C_{27}H_{29}N_4O_4$, calculated 473.2267 found 473.2267.

Ethyl-3-(2-(2-benzoylphenylamino)-2-(4-chlorophenyl)acetamido)propanoate (21a) and ethyl-3-(2-(4-chlorophenyl)-2-(3-cyano-2-oxo-4-phenylquinolin-1(2*H*)-yl)acetamido)propanoate (21b). Synthesized utilizing the general procedure described above, from 2-aminobenzophenone (0.60 g, 3.00 mmol), 4-chlorobenzaldehyde (0.42 g, 3.00 mmol), cyanoacetic acid (0.25 g, 3.00 mmol) and ethyl isocyanopropionate (0.4 mL, 3.00 mmol) in MeOH (5.0 mL). The crude reaction mixture was subjected to flash silica gel column chromatography (4 : 1 hexanes–EtOAc) to afford **21a** (0.46 g, 33%) as a yellow oil. IR (film) 3331 (NH), 3077 (CH), 2978 (CH), 2225 (CN), 1732 (COO), 1660, 1624 (CO), 1563, 1511 (NH), 1254 (CO), 753 (CH), 701 (CCl) cm^{-1}. ^{1}H NMR (300 MHz) ($CDCl_3$) δ 9.14 (1 H, d, J = 4.1 Hz), 7.62 (2 H, d, J = 8.0 Hz), 7.53–7.36 (6 H, m), 7.34–7.26 (4 H, m), 6.59 (2 H, d, J = 8.5 Hz), 4.94 (1 H, d, J = 4.1 Hz), 3.94 (2 H, q, J = 6.6 Hz), 3.49–3.42 (2 H, m), 2.42 (2 H, t, J = 5.9 Hz), 1.12 (3 H, t, J = 6.9 Hz); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 199.0, 171.4, 170.0, 148.9, 139.2, 136.0, 134.8, 134.4, 133.7, 130.8, 128.7, 127.9, 127.6, 118.3, 115.4, 111.9, 61.6, 60.1, 34.6, 33.1, 28.7, 13.5; MS (ESI$^+$) *m/z* 465 (M+1, 100%); HRMS (ESI$^+$) for $C_{26}H_{25}ClN_2O_4$, calculated 464.1503 found 464.1504.

Further elution (4 : 1 hexanes–EtOAc) afforded **21b** (0.38 g, 25%) as a yellow oil. IR (film) 3346 (NH), 3058 (CH), 2980, 2937 (CH), 2230 (CN), 1730 (COO), 1657 (CO), 1605 (CC), 1554 (NH), 1254 (CO), 760 (CH), 703 (CCl) cm^{-1}. ^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.54–7.44 (3 H, m), 7.43–7.27 (7 H, m), 7.21 (1 H, s), 7.12–6.96 (2 H, m), 6.85 (1 H, bs), 4.01–3.86 (2 H, m), 3.48–3.34 (2 H, m), 2.47–2.32 (2 H, m), 1.09 (1 H, t, J = 7.1 Hz); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 171.3, 166.5, 160.0, 158.8, 139.2, 133.7, 133.1, 132.8, 131.4, 129.7, 129.4, 129.1, 128.4, 128.1, 123.1, 119.6, 116.5, 114.2, 105.6, 60.0, 59.9, 35.1, 32.9, 30.3, 28.7, 13.5; MS (ESI$^-$) *m/z* 512 (M–1, 100%); HRMS (ESI$^-$) for $C_{29}H_{24}ClN_3O_4$, calculated 513.1455 found 513.1455.

2-(2-Benzoylphenylamino)-*N*-cyclohexyl-2-(4-methoxyphenyl)-acetamide (22a) and 2-(3-cyano-2-oxo-4-phenylquinolin-1(2*H*)-yl)-*N*-cyclohexyl-2-(4-methoxyphenyl)acetamide (22b). Synthesized utilizing the general procedure, described above, from 2-aminobenzophenone (0.02 g, 1.00 mmol), 4-methoxybenzaldehyde (0.12 mL, 1.00 mmol), cyanoacetic acid (0.09 g, 1.00 mmol) and cyclohexylisocyanide (0.12 mL, 1.00 mmol) in MeOH (5.0 mL). The crude material was subjected to flash silica gel column chromatography (4 : 1 hexanes–EtOAc) to afford **22a** (0.07 g, 16%) as a yellow oil. IR (film) 3305 (NH), 3070 (CH), 2929, 2857 (CH), 1650 (CO), 1507 (NH), 1250 (CO), 749 (CH) cm^{-1}. ^{1}H NMR (300 MHz) ($CDCl_3$) δ 9.14 (1 H, d, J = 4.1 Hz), 7.62 (2 H, d, J = 8.0 Hz), 7.44 (3 H, m), 7.33 (1 H, t, J = 5.2 Hz), 7.29 (2 H, d, J = 7.4 Hz), 6.64 (1 H, d, J = 7.6 Hz), 6.59 (2 H, d, J = 8.5 Hz), 4.94 (1 H, d, J = 4.1 Hz), 3.86 (1H, m), 3.83 (3H, s), 2.02–1.80 (5H, m), 1.68 (2H, m), 1.50–1.27 (4H, m), 1.11 (2H, m); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 199.0, 169.6, 159.1, 149.4, 139.3, 134.7, 134.5, 130.8, 129.5, 128.7, 128.4, 127.8, 132.6, 118.2, 115.5, 114.0, 113.6, 112.4, 62.56, 54.75, 47.6, 32.3, 24.2, 24.1; MS (ESI$^+$) *m/z* 443 (M+1, 100%); HRMS (ESI$^+$) for $C_{28}H_{30}N_2O_3$, calculated 442.2256 found 442.2256.

Further elution (4 : 1 hexanes–EtOAc) afforded **22b** (0.21 g, 43%) as a yellow crystalline solid (mp 174–175 °C). IR (KBr) 3341 (NH), 3058 (CH), 2929, 2852 (CH), 2228 (CN), 1654 (CO), 1605 (CC), 1512 (NH), 1250 (CO), 757 (CH) cm^{-1}. ^{1}H NMR (300 MHz) ($CDCl_3$) δ 7.60–7.52 (3 H, m), 7.52–7.50 (2 H, m), 7.50–7.40 (2 H, m), 7.40–7.33 (3 H, m), 7.18–7.06 (1 H, m), 6.89 (2 H, d, J = 8.6 Hz), 6.64 (1H, bs), 5.97 (1 H, d, J = 4.1 Hz), 3.78 (3H, s), 2.07–1.91 (1H, m), 1.83–1.52 (5H, m), 1.37–1.25 (2H, m), 1.19–1.00 (3H, m); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 166.6, 160.4, 159.8, 159.6, 140.5, 133.7, 133.5, 130.3, 129.9, 129.8, 129.1, 128.9, 125.9, 123.4, 120.3, 117.2, 114.9, 114.7, 114.1, 106.7, 62.0, 55.5, 53.9, 49.0, 32.8, 32.8, 31.9, 29.4, 25.6, 24.9; MS (ESI$^-$) *m/z* 490 (M–1, 100%); HRMS (ESI$^-$) for $C_{31}H_{28}N_3O_3$, calculated 490.2209 found 490.2209.

Methyl-2-(2-(2-benzoylphenylamino)-2-(4-methoxyphenyl)acetamido)acetate (23a) and methyl-2-(2-(3-cyano-2-oxo-4-phenylquinolin-1(2*H*)-yl)-2-(4-methoxyphenyl)acetamido)acetate (23b). Synthesized utilizing the general procedure, described above, from 2-aminobenzophenone (0.20 g, 1.00 mmol), 4-methoxybenzaldehyde (0.12 mL, 1.00 mmol), cyanoacetic acid (0.09 g, 1.00 mmol) and methylisocyanoacetate (0.10 mL, 1.00 mmol) in MeOH (5.0 mL). The crude reaction material

was subjected to flash silica gel column chromatography (1 : 1 hexanes–EtOAc) to afford **23a** (0.17 g, 35%) as a yellow oil. IR (film) 3311 (NH), 3064 (CH), 2952, 2837 (CH), 1753 (COO), 1664, 1623 (CO), 1510 (NH), 1252 (CO), 1178 (CO), 753 (CH) cm^{-1}. ^1H NMR (300 MHz) (Acetone-d_6) δ 7.64–7.42 (8 H, m), 7.38–7.30 (1 H, m), 6.93 (2 H, d, J = 8.8 Hz), 6.76 (1 H, d, J = 8.6 Hz), 6.64–6.56 (1 H, m), 5.27 (1 H, s), 4.02 (1 H, dd, J = 17.5, 1.0 Hz), 3.90 (1 H, dd, J = 17.6, 1.0 Hz), 3.77 (3 H, s), 3.62 (3 H, s); ^{13}C NMR (75 MHz) (Acetone-d_6) δ 199.4, 171.8, 170.7, 160.5, 150.4, 141.2, 135.7, 135.5, 131.9, 131.7, 129.9, 129.5, 129.0, 119.1, 115.7, 115.0, 113.8, 61.3, 55.6, 52.2, 41.6; MS (ESI$^+$) m/z 433 (M+1, 100%); HRMS (ESI$^+$) for $C_{25}H_{25}N_2O_5$, calculated 433.1685 found 433.1687.

Further elution (1 : 1 hexanes–EtOAc) afforded **23b** (0.18 g, 37%) as a yellow oil. IR (film) 3406 (NH), 2969, 2834 (CH), 2229 (CN), 1750 (COO), 1686 (CO), 1653 (CO), 1606 (CC), 1514 (NH), 1251, 1181 (CO), 758 (CH) cm^{-1}. ^1H NMR (300 MHz) (Acetone-d_6) δ 7.70–7.60 (5 H, m), 7.60–7.47 (5 H, m), 7.34 (1 H, dd, J = 8.1, 1.2 Hz), 7.28–7.20 (1 H, m), 7.19 (1 H, bs), 6.92 (2 H, d, J = 8.8 Hz), 4.05–3.98 (2 H, m), 3.78 (3 H, s), 3.66 (3 H, s); ^{13}C NMR (75 MHz) (Acetone-d_6) δ 170.8, 168.6, 168.5, 161.0, 160.5, 160.1, 141.1, 135.2, 134.0, 131.0, 130.9, 130.3, 129.8, 129.7, 129.7, 127.0, 124.1, 121.1, 118.9, 115.7, 114.9, 60.6, 55.6, 52.3, 42.0; MS (ESI$^-$) m/z 480 (M−1, 100%); HRMS (ESI$^-$) for $C_{28}H_{22}N_3O_5$, calculated 480.1638 found 480.1636.

2-(2-Benzoylphenylamino)-2-(1-methyl-1*H*-indol-3-yl)-*N*-(pentan-2-yl)acetamide (24a) and 2-(3-cyano-2-oxo-4-phenylquinolin-1(2*H*)-yl)-2-(1-methyl-1*H*-indol-3-yl)-*N*-(pentan-2-yl)acetamide (24b). Synthesized utilizing the general procedure described above, from 2-aminobenzophenone (0.52 g, 2.66 mmol), 1-methyl-1*H*-indole-3-carbaldehyde (0.42 g, 2.66 mmol), cyanoacetic acid (0.23 g, 2.66 mmol) and 2-pentylisocyanide (0.32 mL, 2.66 mmol) in MeOH (5.0 mL). The crude material was subjected to silica gel column chromatography (1 : 1 hexanes–EtOAc) to afford **24a** (0.37 g, 31%) as a yellow solid (mp 197–199 °C). IR (KBr) 3263 (NH), 3078 (CH), 2956, 2928 (CH), 1648, 1621 (CO), 1555 (NH), 1251, 1181 (CO), 750, 739 (CH) cm^{-1}. ^1H NMR (300 MHz) (DMSO-d_6) δ 9.24 (1 H, d, J = 5.2 Hz), 8.14–7.96 (1 H, m), 7.88–7.73 (1 H, m), 7.62–7.44 (6 H, m), 7.42–7.29 (4 H, m), 7.14 (1H, t, J = 7.4 Hz), 7.05–6.95 (1 H, m), 6.90–6.79 (1 H, m), 6.53 (1 H, t, J = 7.4 Hz), 5.57–5.35 (1 H, m), 3.35 (3 H, s), 1.33–1.17 (2 H, m), 1.06, 0.89 (3 H, d, J = 6.6 Hz, dr 3 : 1), 0.87–0.76 (2 H, m), 0.64, 0.50 (3 H, t, J = 7.3 Hz, dr 3 : 1); ^{13}C NMR (75 MHz) (DMSO-d_6) δ 198.0, 169.4, 149.7, 149.6, 139.9, 136.7, 134.7, 131.1, 130.9, 128.5, 128.1, 125.7, 121.3, 119.4, 118.8, 117.2, 114.1, 112.3, 111.4, 109.7, 53.6, 44.2, 44.2, 38.1, 37.9, 32.3, 26.7, 20.6, 20.5, 18.8, 18.4, 13.7, 13.5, 10.4, 10.0; MS (ESI$^+$) m/z 454 (M+1, 100%); HRMS (ESI$^+$) for $C_{29}H_{32}N_3O_2$, calculated 454.2416 found 454.2416.

Further elution (1 : 1 hexanes–EtOAc) afforded **24b** (0.38 g, 28%) as a yellow solid (mp 218–220 °C). IR (KBr) 3327 (NH), 3056 (CH), 2961, 2929 (CH), 2227 (CN), 1659 (CO), 1594 (CC), 1519 (NH), 763, 754, 741 (CH) cm^{-1}. ^1H NMR (300 MHz) (DMSO-d_6) δ 7.67–7.61 (3 H, m), 7.60–7.50 (3 H, m), 7.49–7.39 (2 H, m), 7.38–7.31 (1 H, m), 7.26–7.18 (1 H, m), 7.13–7.07 (1 H, m), 7.06–6.98 (1 H, m), 6.94–6.88 (2 H, m), 4.12–3.93 (1 H, m), 3.77 (3 H, s), 1.52–1.34 (2 H, m), 1.19–1.08 (3 H, m), 0.95–0.84 (2 H, m), 0.74, 0.66 (3 H, t, J = 7.3 Hz, dr 3 : 1); ^{13}C NMR (75 MHz) (DMSO-d_6) δ 160.2, 158.5, 158.4, 139.8, 133.7, 130.1, 129.8, 129.2, 128.7, 128.5, 127.9, 122.9, 117.8, 116.1, 115.3, 106.0, 53.6, 32.3, 20.6, 20.5, 18.8, 18.4, 13.7, 13.5, 10.4, 10.0; MS (ESI$^-$) m/z 501 (M-1, 100%); HRMS (ESI$^+$) for $C_{32}H_{29}N_4O_2$, calculated 502.2369 found 502.2369.

2-(2-Acetylphenylamino)-2-(4-nitrophenyl)-*N*-(pentan-2-yl)acetamide (25a) and 2-(3-cyano-4-methyl-2-oxoquinolin-1(2*H*)-yl)-2-(4-nitrophenyl)-*N*-(pentan-2-yl)acetamide (25b). Synthesized utilizing the general procedure described above, from 1-(2-aminophenyl)ethanone (0.57 g, 4.19 mmol), 4-nitrobenzaldehyde (0.63 g, 4.19 mmol), cyanoacetic acid (0.35 g, 4.19 mmol) and 2-pentylisocyanide (0.50 g, 4.19 mmol) in MeOH (5.0 mL). The crude reaction material was subjected to flash silica gel column chromatography (4 : 1 hexanes–EtOAc) to afford **25a** (0.68 g, 42%) as a yellow solid (mp 237–239 °C). IR (KBr) 3268 (NH), 3075 (CH), 2964, 2933 (CH), 1649, 1642 (CO), 1560 (NO_2), 1519, 1511 (NH), 1346 (NO_2), 748 (CH). ^1H NMR (300 MHz) (DMSO-d_6) δ 9.86–9.71 (1 H, m), 8.34–8.26 (1 H, m), 8.21 (2 H, d, J = 8.9 Hz), 7.85 (1 H, dd, J = 8.0, 1.2 Hz), 7.80–7.68 (2 H, m), 7.26 (1 H, t, J = 7.2 Hz), 6.60 (1 H, t, J = 7.5 Hz), 6.38 (1 H, dd, J = 8.2, 5.6 Hz), 5.43–5.31 (1 H, m), 3.78–3.63, 3.54–3.43 (1 H, m, d.r. 3 : 1), 2.56 (3 H, s), 1.32–1.18 (2 H, m), 1.06, 0.89 (3 H, d, J = 6.6 Hz, d.r. 1 : 3), 0.86–0.77 (2 H, m), 0.64, 0.50 (3 H, t, J = 7.3 Hz) ^{13}C NMR (75 MHz) (DMSO-d_6) δ 200.6, 168.2, 167.6, 167.6, 147.7, 147.2, 147.0, 134.8, 133.1, 127.7, 123.7, 123.7, 118.1, 115.1, 112.1, 59.0, 58.9, 51.8, 44.5, 44.3, 37.9, 30.6, 28.0, 26.8, 26.7, 20.6, 20.2, 18.7, 18.4, 13.7, 13.4, 10.3, 9.8; MS (ESI$^+$) m/z 384 (M+1, 100%); HRMS (ESI$^+$) for $C_{21}H_{26}N_3O_4$, calculated 384.1845 found 384.1844.

Further elution (1 : 1 hexanes–EtOAc) afforded **25b** (0.47 g, 26%) as a cream solid (mp 248–249 °C). IR (KBr) 3323 (NH), 3078 (CH), 2963, 2930 (CH), 2227 (CN), 1687, 1632 (CO), 1608 (CC), 1558 (NO_2), 1518 (NH), 1346 (NO_2), 756 (CH) cm^{-1}. ^1H NMR (300 MHz) (DMSO-d_6) δ 8.14 (2 H, d, J = 8.9 Hz), 8.04 (1 H, dd, J = 8.4, 0.9 Hz), 8.00–7.83 (1 H, m), 7.64–7.55 (3 H, m), 7.36 (1 H, t, J = 7.6 Hz), 7.29–7.18 (1 H, m), 7.07 (1 H, bs), 3.93–3.73, 3.40–3.29 (1 H, m, d.r. 3 : 1), 2.82 (3 H, s), 1.51–1.08 (4 H, m), 1.04, 0.86 (3 H, d, J = 7.1 Hz, d.r. 1 : 3), 0.61, 0.39 (3 H, t, J = 7.3, 7.3 Hz, d.r. 3 : 1); ^{13}C NMR (75 MHz) (DMSO-d_6) δ 165.0, 158.6, 158.0, 158.0, 146.6, 142.0, 141.9, 138.8, 133.2, 129.6, 127.5, 123.3, 122.8, 119.9, 116.7, 116.6, 115.4, 106.1, 58.8, 44.9, 44.7, 37.8, 37.2, 30.5, 26.7, 25.9, 20.5, 20.0, 19.0, 18.3, 18.1, 13.7, 13.5, 10.6, 9.7; MS (ESI$^-$) m/z 431 (M−1, 100%); HRMS (ESI$^-$) for $C_{24}H_{23}N_4O_4$, calculated 431.1798 found 431.1798.

Methyl-2-(2-(2-acetylphenylamino)-2-(4-chlorophenyl)acetamido)acetate (26). Synthesized utilizing the general procedure described above, from 1-(2-aminophenyl)ethanone (0.80 mL, 6.54 mmol), 4-chlorobenzaldehyde (0.92 g, 6.54 mmol), cyanoacetic acid (0.56 g, 6.54 mmol) and methylisocyanoacetate (0.80 mL, 6.54 mmol) in MeOH (5.0 mL) to afford **26** (1.43 g, 58%) as a pale yellow solid (mp 239–240 °C). IR (KBr) 3358 (NH), 3078 (CH), 2954, 2939 (CH), 1746 (COC), 1643 (CO), 1563, 1511 (NH), 1232 (COC), 754 (CH) cm^{-1}. ^1H NMR (300 MHz) (DMSO-d_6) δ 9.65 (1 H, d, J = 6.7 Hz), 8.81 (1 H, t, J = 5.8 Hz), 7.84 (1 H, dd, J = 8.0, 1.1 Hz), 7.49 (2 H, d, J = 8.5 Hz), 7.41 (2 H, d, J = 8.5 Hz), 7.29 (1 H, t, J = 7.7 Hz), 6.66 (1 H, t, J = 7.5 Hz), 6.48 (1 H, d, J = 8.4 Hz), 5.31 (1 H, d, J = 6.7 Hz), 3.98–3.79 (2 H, m), 3.58 (3 H, s), 2.55 (3 H, s); ^{13}C NMR (75 MHz) (DMSO-d_6) δ 200.6, 170.0, 169.8, 147.9, 137.7, 134.8, 132.9, 132.4, 128.6, 128.5, 118.0, 115.0, 112.2,

58.5, 51.7, 40.6, 28.0; MS (ESI$^+$) m/z 375 (M+1, 100%); HRMS (ESI$^+$) for $C_{19}H_{20}ClN_2O_4$, calculated 375.1033 found 375.1033.

2-(2-Benzoylphenylamino)-2-(4-chlorophenyl)-*N*-(2,6-dimethylphenyl)acetamide (27). Synthesized utilizing the general procedure described above, from 2-aminobenzophenone (0.60 g, 3.00 mmol) 4-chlorobenzaldehyde (0.42 g, 3.00 mmol), cyanoacetic acid (0.25 g, 3.00 mmol) and 2,6-dimethylphenylisocyanide (0.40 g, 3.00 mmol) in MeOH (5.0 mL) to afford **27** (1.04 g, 74%) as a yellow solid (mp 168–170 °C). IR (KBr) 3446, 3244 (NH), 3061 (CH), 1655, 1625 (CO), 1565, 1515 (NH), 748 (CH), 699(CCl); ^{1}H NMR (300 MHz) (DMSO-d_6) δ 9.82 (1 H, s), 9.44 (1 H, d, J = 6.5 Hz), 7.70 (2 H, d, J = 8.3 Hz), 7.62–7.46 (7 H, m), 7.44–7.32 (2 H, m), 7.11–6.94 (3 H, m), 6.69 (1 H, d, J = 8.4 Hz), 6.60 (1 H, t, J = 7.5 Hz), 5.55 (1 H, d, J = 6.5 Hz), 1.91 (6 H, bs); ^{13}C NMR (75 MHz) (DMSO-d_6) δ 198.2, 167.9, 148.6, 139.6, 138.0, 135.1, 134.8, 134.7, 134.0, 132.6, 131.1, 128.7 (3C), 128.2, 127.7, 126.7, 117.8, 114.9, 112.6, 59.1, 17.6; MS (ESI$^+$) m/z 469 (M+1, 100%); HRMS (ESI$^+$) for $C_{29}H_{26}ClN_2O_2$, calculated 469.1605 found 469.1605.

2-(2-Benzoylphenylamino)-*N*-(2,6-dimethylphenyl)-2-(4-nitrophenyl)acetamide (28). Synthesized utilizing the general procedure described above, from 2-aminobenzophenone (0.60 g, 3.00 mmol), 4-nitrobenzaldehyde (0.45 g, 3.00 mmol), cyanoacetic acid (0.25 g, 3.00 mmol) and 2,6-dimethylphenylisocyanide (0.40 g, 3.00 mmol) in MeOH (5.0 mL) to afford **28** (0.78 g, 54%) as a yellow solid (mp 226–228 °C). IR (KBr) 3447, 3234 (NH), 3059 (CH), 2923, 2853 (CH), 1653, 1624 (CO), 1568 (NH), 1510, 1345 (NO_2), 750 (CH) cm^{-1}. ^{1}H NMR (300 MHz) (DMSO-d_6) δ 9.97 (1 H, s), 9.55 (1 H, d, J = 6.5 Hz), 8.32 (2 H, d, J = 8.5 Hz), 7.96 (2 H, d, J = 8.5 Hz), 7.68–7.48 (5 H, m), 7.46–7.33 (2 H, m), 7.09–6.95 (3 H, m), 6.72–6.57 (2 H, m), 5.74 (1 H, d, J = 6.5 Hz), 1.90 (6 H, bs); ^{13}C NMR (75 MHz) (DMSO-d_6) δ 198.1, 167.2, 148.4, 147.3, 146.8, 139.6, 135.2, 135.1, 134.9, 133.9, 131.3, 128.8, 128.3 (2C), 127.9, 126.9, 124.0, 118.0, 115.3, 112.7, 59.3, 17.7; MS (ESI$^+$) m/z 480 (M+1, 100%); HRMS (ESI$^+$) for $C_{29}H_{26}N_3O_4$, calculated 480.1845 found 480.1845.

2-(2-Acetylphenylamino)-*N*-(2,6-dimethylphenyl)-2-(4-methoxyphenyl)acetamide (29). Synthesized utilizing the general procedure described above, from 1-(2-aminophenyl)ethanone (0.60 g, 4.40 mmol), 4-methoxybenzaldehyde (0.60 g, 4.40 mmol), cyanoacetic acid (0.38 g, 4.40 mmol) and 2,6-dimethylphenylisocyanide (0.60 g, 4.40 mmol) in MeOH (5.0 mL) to afford **29** (1.14 g, 69%) as a pale yellow solid (mp 184–185 °C). IR (KBr) 3446, 3212 (NH), 3030 (CH), 2961, 2931 (CH), 1645 (CO), 1564, 1508 (NH), 1244 (CO), 762 (CH) cm^{-1}. ^{1}H NMR (300 MHz) (DMSO-d_6) δ 9.79–9.54 (2 H, m), 7.85 (1 H, d, J = 8.1 Hz), 7.51 (2 H, d, J = 8.3 Hz), 7.33 (1 H, t, J = 7.7 Hz), 7.10–6.83 (5 H, m), 6.71–6.49 (2 H, m), 5.35 (1 H, d, J = 3.6 Hz), 3.73 (3 H, s), 2.55 (3 H, s), 1.90 (6 H, bs); ^{13}C NMR (75 MHz) (DMSO-d_6) δ 200.5, 168.7, 158.9, 148.2, 135.1, 134.7, 134.2, 133.1, 133.0, 130.8, 128.0, 127.6, 126.5, 118.0, 114.9, 114.7, 113.9, 112.4, 59.1, 55.0, 28.0, 17.6; MS (ESI$^+$) m/z 403 (M+1, 100%); HRMS (ESI$^+$) for $C_{25}H_{27}N_2O_3$, calculated 403.1943 found 403.1944.

2-(2-Acetylphenylamino)-*N*-(2,6-dimethylphenyl)-2-(4-nitrophenyl)acetamide (30). Synthesized utilizing the general procedure described above, from 1-(2-aminophenyl)ethanone (0.58 g, 4.30 mmol), 4-nitrobenzaldehyde (0.65 g, 4.30 mmol), cyanoacetic acid (0.36 g, 4.30 mmol) and 2,6-dimethylphenylisocyanide (0.56 g, 4.30 mmol) in MeOH (5.0 mL) to afford **30** (0.88 g, 51%) as a pale yellow solid (mp 184–185 °C). IR (KBr) 3446, 3217 (NH), 3027 (CH), 2924, 2859 (CH), 1645 (CO), 1562 (NH), 1520, 1348 (NO_2), 763 (CH) cm^{-1}. ^{1}H NMR (300 MHz) (DMSO-d_6) δ 10.00′9.82 (2 H, m), 8.29 (2 H, d, J = 8.7 Hz), 7.98–7.82 (3 H, m), 7.32 (1 H, t, J = 7.7 Hz), 7.10–6.95 (3 H, m), 6.65 (1 H, t, J = 7.4 Hz), 6.55 (1 H, d, J = 8.4 Hz), 5.67 (1 H, d, J = 6.6 Hz), 2.58 (3 H, s), 1.90 (6 H, bs); ^{13}C NMR (75 MHz) (DMSO-d_6) δ 200.8, 167.1, 147.7, 147.2, 146.8, 135.0, 134.9, 133.8, 133.1, 128.1, 127.7, 126.8, 123.8, 118.3, 115.3, 112.3, 59.2, 28.0, 17.6; MS (ESI$^+$) m/z 418 (M+1, 100%); HRMS (ESI$^+$) for $C_{24}H_{24}N_3O_4$, calculated 418.1689 found 418.1691.

2-(2-Acetylphenylamino)-*N*-(naphthalen-2-yl)-2-(4-nitrophenyl)acetamide (31). Synthesized utilizing the general procedure described above, from 1-(2-aminophenyl)ethanone (0.17 g, 1.40 mmol), 4-nitrobenzaldehyde (0.21 g, 1.40 mmol), cyanoacetic acid (0.12 g, 1.40 mmol) and 2-isocyanonaphthalene (0.22 g, 1.40 mmol) in MeOH (5.0 mL) to afford **31** (0.35 g, 57%) as a light brown solid (mp 242–244 °C). IR (KBr) 3447, 3259 (NH), 3074 (CH), 1665, 1641 (CO), 1561 (NH), 1519, 1346 (NO_2), 751 (CH) cm^{-1}. ^{1}H NMR (300 MHz) (DMSO-d_6) δ 10.80 (1 H, s), 9.96 (1 H, d, J = 6.8 Hz), 8.29–8.21 (3 H, m), 7.92–7.84 (4 H, m), 7.82 (2 H, d, J = 8.2 Hz), 7.58 (1 H, dd, J = 8.8, 1.3 Hz), 7.50–7.28 (3 H, m), 6.66 (1 H, t, J = 7.5 Hz), 6.52 (1 H, d, J = 8.5 Hz), 5.67 (1 H, d, J = 6.8 Hz), 2.59 (3 H, s); ^{13}C NMR (75 MHz) (DMSO-d_6) δ 200.9, 167.5, 147.6, 147.2, 146.2, 135.6, 135.0, 133.1, 130.0, 128.5, 128.0 (2C), 127.4, 127.3, 126.5, 124.9, 124.0, 119.7, 118.3, 115.9, 115.4, 112.1, 59.6, 28.0; MS (ESI$^+$) m/z 440 (M+1, 100%); HRMS (ESI$^+$) for $C_{26}H_{22}N_3O_4$, calculated 440.1532 found, 440.1532.

2-(2-Acetylphenylamino)-2-(4-methoxyphenyl)-*N*-(naphthalen-2-yl)acetamide (32). Synthesized utilizing the general procedure described above, from 1-(2-aminophenyl)ethanone (0.17 mL, 1.38 mmol), 4-methoxybenzaldehyde (0.17 mL, 1.38 mmol), cyanoacetic acid (0.11 g, 1.38 mmol) and 2-isocyanonaphthalene (0.21 g, 1.38 mmol) in MeOH (5.0 mL) to afford **32** (0.41 g, 70%) as a light brown solid (mp 184–185 °C). IR (KBr) 3452, 3264 (NH), 2998, 2958 (CH), 1655, 1643 (CO), 1558, 1509 (NH), 1244 (CO) cm^{-1}. ^{1}H NMR (300 MHz) (DMSO-d_6) δ 10.57 (1 H, s), 9.80 (1 H, d, J = 6.7 Hz), 8.27 (1 H, s), 7.93–7.75 (5 H, m), 7.59 (1 H, dd, J = 8.8, 1.8 Hz), 7.52 (2 H, d, J = 8.6 Hz), 7.49–7.27 (4 H, m), 6.94 (2 H, d, J = 8.7 Hz), 6.63 (1 H, d, J = 7.7 Hz), 6.58 (1 H, d, J = 8.0 Hz), 5.40 (1 H, d, J = 6.7 Hz), 3.70 (3H, s), 2.58 (3 H, s); ^{13}C NMR (75 MHz) (DMSO-d_6) δ 200.6, 169.1, 158.9, 148.2, 136.0, 134.8, 133.2, 133.0, 130.3, 129.8, 128.4, 127.9, 127.3, 127.2, 126.4, 124.7, 119.8, 118.0, 115.6, 114.8, 114.1, 112.1, 59.4, 55.0, 28.0; MS (ESI$^+$) m/z 425 (M+1, 100%); HRMS (ESI$^+$) for $C_{27}H_{25}N_2O_3$, calculated 425.1787, found 425.1787.

Ethyl-3-(2-(2-acetylphenylamino)-2-(4-nitrophenyl)acetamido)-propanoate (36). Synthesized utilizing the general procedure described above, from 1-(2-aminophenyl)ethanone (0.35 mL, 2.80 mmol), 4-nitrobenzaldehyde (0.42 g, 2.80 mmol), cyanoacetic acid (0.24 g, 2.80 mmol) and ethyl isocyanopropionate (0.36 mL, 2.80 mmol) in MeOH (5.0 mL) to afford **36** (0.67 g, 58%) as a pale yellow solid (mp 262–263 °C). IR (KBr) 3452, 3250 (NH), 1724 (COO), 1644 (CO), 1561 (NH), 1520, 1349 (NO_2), 1240 (CO) cm^{-1}. ^{1}H NMR (300 MHz) (DMSO-d_6) δ 9.77 (1 H, d, J = 6.3 Hz), 8.62

(1 H, s), 8.18 (2 H, d, J = 7.9 Hz), 7.83 (1 H, d, J = 7.9 Hz), 7.71 (2 H, d, J = 7.9 Hz), 7.24 (1 H, t, J = 7.5, 7.5 Hz), 6.59 (1 H, t, J = 7.3, 7.3 Hz), 6.39 (1 H, d, J = 8.3 Hz), 5.37 (1 H, d, J = 6.3 Hz), 3.94 (2 H, q, J = 6.7 Hz), 3.37–3.24 (2 H, m), 2.55 (3 H, s), 2.40 (2 H, t, J = 5.8 Hz), 1.06 (3 H, t, J = 6.9 Hz); ^{13}C NMR (75 MHz) (DMSO-d_6) δ 200.7, 170.9, 168.6, 147.6, 147.0, 146.7, 134.8, 133.0, 127.8, 123.6, 118.1, 115.1, 112.1, 59.8, 58.8, 34.9, 33.2, 27.9, 13.7; MS (ESI$^+$) m/z 414 (M+1, 100%); HRMS (ESI$^+$) for $C_{21}H_{24}N_3O_6$, calculated 414.1587 found, 414.1585.

(*Z*)-Ethyl-3-cyano-4-(4-nitrophenyl)but-3-enoate (38). Synthesized utilizing the general procedure described above, from 1-(2-aminophenyl)ethanone (0.33 mL, 2.77 mmol), 4-nitrobenzaldehyde (0.42 g, 2.77 mmol), 2-ethylcyanoacetate (0.24 mL, 2.77 mmol) and ethyl isocyanopropionate (0.35 mL, 2.77 mmol) in MeOH (5.0 mL) to afford **38** (0.41 g, 64%) as a pale yellow solid (mp 262–263 °C). IR (KBr) 3444 (OH), 3119 (CH), 2225 (CN), 1718 (CO), 1612 (CC), 1529, 1346 (NO_2), 1228 (CO) cm^{-1}. ^{1}H NMR (300 MHz) (DMSO-d_6) δ 8.49 (1 H, s), 8.35 (2 H, d, J = 8.7 Hz), 8.19 (2 H, d, J = 8.7 Hz), 3.87 (2 H, s); ^{13}C NMR (75 MHz) (DMSO-d_6) δ 161.5, 152.5, 149.1, 137.0, 131.5, 124.0, 114.7, 106.2, 53.5; MS (ESI$^+$) m/z 233 (M+1, 100%); HRMS (ESI$^+$) for $C_{11}H_9N_2O_4$, calculated 233.0484 found, 233.0484.

Ethyl-3-(2-(*N*-(2-acetylphenyl)but-2-ynamido)-2-(4-nitrophenyl)acetamido)propanoate (41). Synthesized utilizing the general procedure described above, from 1-(2-aminophenyl)ethanone (0.43 g, 3.20 mmol), 4-nitrobenzaldehyde (0.49 g, 3.20 mmol), 2-butynoic acid (0.27 g, 3.20 mmol) and ethyl isocyanopropionate (0.41 mL, 3.20 mmol) in MeOH (5.0 mL). The crude reaction material was subjected to flash silica gel chromatography (1 : 1 hexanes–EtOAc) to afford **41** (0.91 g, 60%) as a yellow oil. IR (KBr) 3399 (NH), 3114 (CH), 2982 (CH), 2231 (CC), 1725, 1673, 1644 (CO), 1516, 1363 (NO_2), 1190 (CO), 761 (CH) cm^{-1}. ^{1}H NMR (300 MHz) (Acetone-d_6) δ 8.28 (2 H, d, J = 8.8 Hz), 8.24 (2 H, d, J = 8.8 Hz), 7.95 (2 H, d, J = 8.8 Hz), 7.84 (1 H, dd, J = 7.9, 1.0 Hz), 7.76 (1 H, t, J = 5.8, 5.8 Hz), 7.72–7.62 (3 H, m), 7.49 (2 H, d, J = 8.8 Hz), 7.34 (1 H, dt, J = 7.6, 1.1 Hz), 6.09 (1 H, s), 6.01 (1 H, s), 4.23–3.79 (4 H, m), 3.64–3.46 (4 H, m), 2.68–2.46 (4 H, m), 2.39 (3 H, s), 2.02 (1 H, s), 1.65 (1 H, s), 1.23–1.08 (4 H, m), 0.88 (6 H, m); ^{13}C NMR (75 MHz) (Acetone-d_6) δ 197.9, 170.7, 170.6, 170.3, 170.1, 168.3, 167.3, 167.3, 154.3, 153.9, 153.1, 147.3, 147.1, 146.9, 142.7, 142.6, 140.7, 136.7, 136.3, 132.6, 131.6, 129.9, 129.7, 129.1, 128.1, 123.2, 122.9, 122.5, 121.9, 89.8, 89.4, 88.7, 73.8, 72.5, 72.3, 64.0, 63.8, 60.2, 59.5, 59.5, 59.4, 59.3, 42.9, 39.8, 34.9, 33.8, 33.0, 31.6, 31.2, 29.0, 28.2, 27.7, 21.9, 13.1, 13.0; MS (ESI$^+$) m/z 480 (M+1, 100%); HRMS (ESI$^+$) for $C_{25}H_{26}N_3O_7$, calculated 480.1693 found, 480.1693.

Ethyl-3-(2-(*N*-(2-acetylphenyl)but-2-enamido)-2-(4-nitrophenyl)acetamido)propanoate (42). Synthesized utilizing the general procedure described above, from 1-(2-aminophenyl)ethanone (0.43 g, 3.20 mmol), 4-nitrobenzaldehyde (0.49 g, 3.20 mmol), 2-butenoic acid (0.27 g, 3.20 mmol) and ethyl isocyanopropionate (0.41 mL, 3.20 mmol) in MeOH (5.0 mL). The crude reaction material was subjected to flash silica gel chromatography (1 : 1 hexanes–EtOAc) to afford **42** (1.01 g, 66%) as a yellow oil. IR (KBr) 3257 (NH), 3088 (CH), 2959 (CH), 2231 (CC), 1736, 1725, 1663 (CO), 1517, 1345 (NO_2), 1251, 1179 (CO), 969 (CC), 738 (CH). ^{1}H NMR (300 MHz) (Acetone-d_6) δ 8.28–8.11 (2 H, m), 7.92–7.85 (1 H, m), 7.51–7.46 (1 H, m), 7.45–7.29 (2 H, m), 7.24–7.14 (2 H, m), 7.02–6.90 (1 H, m), 6.87–6.75 (1 H, m), 5.59 (1 H, s), 4.01 (2 H, q, J = 7.1 Hz), 3.61–3.32 (2 H, m), 2.54–2.40 (2 H, m), 2.25–2.12 (3 H, m), 2.14 (3 H, s), 1.14 (3 H, t, J = 7.1 Hz); ^{13}C NMR (75 MHz) (Acetone-d_6) δ 197.9, 170.7, 170.6, 168.9, 168.8, 166.1, 165.9, 164.9, 146.9, 143.8, 143.6, 141.4, 140.9, 140.5, 136.9, 136.6, 132.9, 131.9, 131.6, 130.2, 129.7, 129.3, 128.0, 122.8, 122.8, 122.3, 121.9, 63.9, 59.4, 59.3, 41.3, 34.8, 34.7, 33.1, 31.2, 28.9, 28.7, 27.8, 21.9, 16.8, 16.5, 13.0, 13.0; MS (ESI$^+$) m/z 482 (M+1, 100%); HRMS (ESI$^+$) for $C_{25}H_{28}N_3O_7$, calculated 482.1849 found, 482.1851.

Ethyl-3-(2-(*N*-(2-benzoylphenyl)-3,3,3-trifluoropropanamido)-2-(4-nitrophenyl)acetamido)propanoate (43). Synthesized utilizing the general procedure described above, from 1-(2-aminophenyl)ethanone (0.40 mL, 3.20 mmol), 4-nitrobenzaldehyde (0.49 g, 3.20 mmol), 3,3,3-trifluoropropanoic acid (0.30 mL, 3.20 mmol) and ethyl isocyanopropionate (0.41 mL, 3.20 mmol) in MeOH (5.0 mL) to afford **43** (0.841 g, 50%) as a yellow solid (mp 152–154 °C). ^{1}H NMR (300 MHz) (DMSO-d_6) δ 7.95 (2 H, d, J = 8.8 Hz), 7.88 (1 H, d, J = 7.8), 7.62 (1 H, ddd, J = 7.7, 7.7, 1.7 Hz), 7.52 (1 H, ddd, J = 7.8, 7.8, 1.6 Hz), 7.49 (1 H, d, J = 8.9 Hz), 7.48–7.40 (1 H, m), 7.31–7.25 (2 H, m), 6.05 (1 H, s), 4.20–4.02 (2 H, m), 3.67–3.42 (2 H, m), 2.61–2.50 (3H, m), 2.12 (3H, s) 1.21 (3 H, t, J = 7.1); ^{13}C NMR (75 MHz) (DMSO-d_6) δ 199.0, 170.9, 168.7, 163.5, 146.9, 140.8, 135.8, 135.5, 133.4, 133.0, 131.7, 130.4, 129.3, 123.2, 122.7, 62.5, 59.8, 34.9, 33.3, 28.8, 13.8; MS (ESI$^+$) m/z 524.

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Notes and references

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