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ARTICLE

A Microwave-Assisted Multicomponent Synthesis of Substituted 3,4-Dihydroquinazolinones

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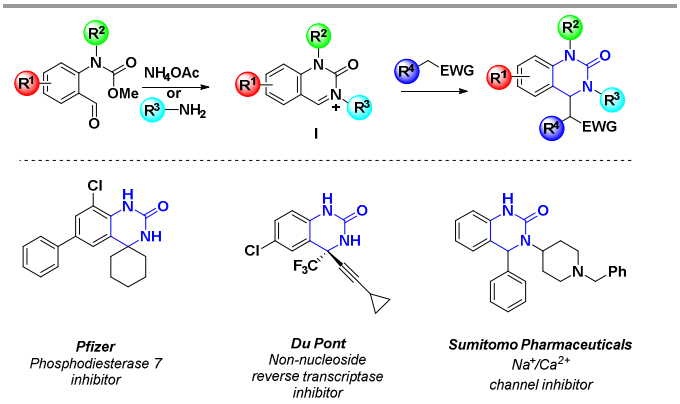
A microwave-assisted, multicomponent protocol for the synthesis of substituted 3,4-dihydroquinazolinones via a novel cascade imine/cyclization/*aza*-Henry reaction sequence is reported. Starting from o-carbamoyl aldehydes, a series of structurally diverse 3,4-dihydroquinazolinones was synthesized via a cyclicminium ion intermediate in moderate to excellent yields. Notably, the reaction is fast, flexible, simple to perform and tolerates a variety of functional groups.

Introduction

The 3,4-dihydroquinazolinone scaffold is present in a wide range of biologically active molecules utilized in the treatment of convulsive disorders,[1] infectious diseases,[2] autoimmune diseases,[3] cardiovascular conditions[4] and inflammatory diseases[5] (see Scheme 1). Given their biological relevance, significant effort has been directed towards the synthesis of 3,4-dihydroquinazolinones. The most commonly employed methods include a cyclization/reduction sequence starting from 2-trichloroacetamidobenzophenones,[4a,6] the ring closure of 2-acyl or 2-cyanocarbamates,[7] reaction of *o*-acyl or *o*-amino anilines with a suitable carbonyl compound,[1,4b,8] or by using Grignard reagents to effect a cyclization of 2-carboxamidobenzonitriles.[9] More recently, Glorius and co-workers reported a Rh-catalyzed synthetic route using *N*-methoxy, *N*'- arylureas,[10] and Sotelo and co-workers disclosed the synthesis of a quinazoline using a Vilsmeier–Haack-based carboannulation strategy.[11] Despite these advances, the currently available procedures[12] still suffer from a number of drawbacks, including multistep reaction sequences, lack of flexibility, the use of moisture-sensitive organometallic reagents and costly transition metal catalysts. Consequently, the development of new, flexible, expedient and metal-free protocols for the preparation of this valuable heterocycle is of significant importance.



Scheme 1. Elaboration of cyclic iminium ion I via aza-Henry/ Mannich reactions leading to the dihydroquinazolinone scaffold with 5 points of diversity. Also displayed are three representative 3,4-dihydroquinazolinones

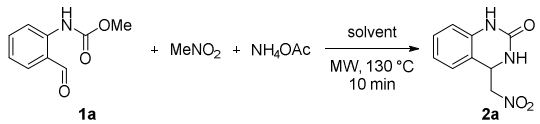
As part of our continued interest in the efficient synthesis of *N*-heterocycles,[13] we decided to explore a multi-component[14] synthesis of 3,4-dihydroquinazolinones (Scheme 1). It was envisioned that treatment of an *o*-formyl carbamate with a primary amine would lead to the formation of a cyclic iminium ion intermediate *via* an imine formation/cyclization sequence.[7a] Iminium ion **I** would then be poised to undergo subsequent *aza*-Henry[15] or Mannich[16] reactions with an appropriate carbon nucleophile, generating the target structures. Although the *aza*-Henry reaction between amines, aldehydes and nitroalkanes has been extensively studied, to the best of our knowledge, this is the first example of the use of an *o*-formyl carbamate as the

carbonyl component. Such an approach would allow unprecedented access to diversely substituted 3,4-dihydroquinazolinones in a rapid, convergent and efficient fashion generating only methanol and water as byproducts. Herein, we report a simple and efficient, one-pot, three-component procedure for the microwave-assisted synthesis of 3,4-dihydroquinazolinones using readily available starting materials.

Results and Discussion

As a starting point for our investigation, we chose to examine the reaction between methylcarbamate **1a**, nitromethane and NH_4OAc. Carbamate **1a** and NH_4OAc were chosen to minimize any potentially unfavorable steric effects and nitromethane due to its known propensity to participate in *aza*-Henry reactions. Gratifyingly, microwave irradation of **1a** with an excess of nitromethane and NH_4OAc in MeOH for 10 minutes at 130 °C gave dihydroquinazolinone **2a** in 71% isolated yield (Table 1). Next, we examined the effect of different solvents on the reaction outcome. Polar solvents proved to be the most productive and AcOH delivered **2a** in 81% yield and was identified as the solvent of choice (entry **4**). Reduction to 2 equivalents of nitromethane furnished **2a** in a slightly reduced yield of 71% yield but simplified purification considerably (entry **5**). Increasing the reaction scale to 3 mmol and heating for 20 min gave **2a** in 88% yield (Scheme 2). Notably, full conversion of **1a** to the cyclized product was not achieved with conventional heating, even after prolonged reaction time (Scheme 2).

Table 1 - Investigation of reaction conditions for the cyclization of 1a using $MeNO_2$ and NH_4OAc[a]

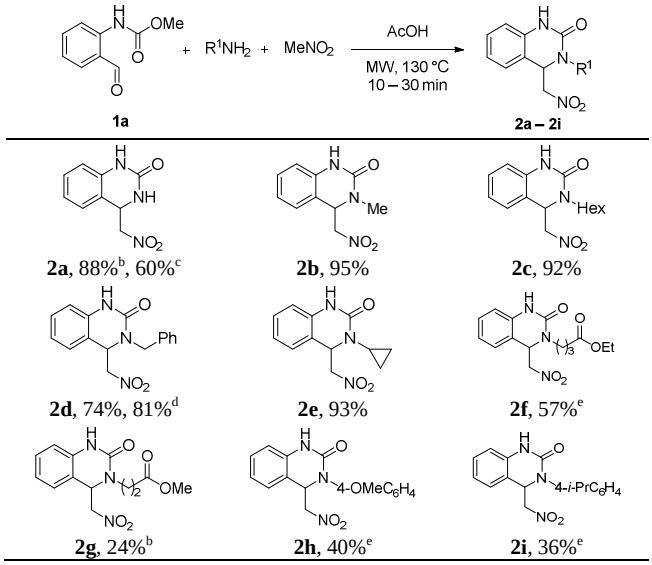


entry	solvent	yield(%)
1	methanol	71
2	2-propanol	45
3	ethanol	79
4	acetic acid	81
5	acetic acid	71[b]
6	DMF	58
7	water	48
8	ethyl acetate	36
9	DME	24
10	THF	-[c]

[a]Isolated yields. Typical procedure: Compound **1a** (0.2 mmol), NH_4OAc (0.4 mmol), $MeNO_2$ (2 mmol) and glacial acetic acid (1.0 mL), heated by MW for 10 min at 130 °C in a sealed vessel. [b]2 equiv nitromethane. [c]No product isolated

With these conditions in hand, we then sought to explore the scope and limitations of our methodology by exploring various amine nucleophiles. As seen in Scheme 2, the reaction performed well with a range of primary amines, with methylamine and hexylamine giving isolated yields over 90% (entries **2b** and **2c**). Benzylamine was found to be a productive substrate (**2d**) and the presence of an alpha substituent was well tolerated, with cyclopropylamine returning an excellent 93% yield of **2e**. The introduction of an electron-withrawing ester substituent proved to be detrimental to the reaction, presumably due to the lower nucleophilicity of these substrates (**2f** and **2g**). Similarly, the use of substituted anilines afforded moderate yields of the *N*3-aryl substituted quinazolinone products **2h** and **2i**.

Scheme 2 - Effect of variation of amine nucleophiles[a]

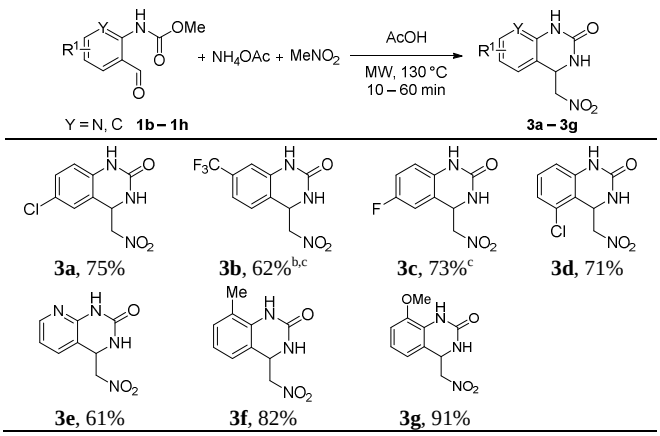


[a]Isolated yields. [b]Heated for 20 min. [c]Conventional heating for 2 h. [d]One-pot, two step procedure. [e]Heated for 30 min

We then proceeded to investigate the effect of different aryl substituents on the *o*-formyl carbamate component (Scheme 3). Electron-withdrawing substituents gave good, albeit slightly lowered yields (**3a-3e**), most probably due to their tendency to reduce the rate of amine-induced cyclization (see below for a mechanistic discussion). In the case of **3b**, prolonged heating and addition of 6 equiv. of nitromethane was required for full consumption of the starting material. Notably, the pyridine aldehyde **1f** was transformed into **3e** in 61% yield. Conversely, substrates containing electron-donating susbtituents performed well, affording very good to excellent yields of the desired products **3f** and **3g**.

The compatibility of the protocol with different carbon nucleophiles was then examined (Scheme 4). The reaction performed well with a range of substituted nitroalkanes, affording moderate to good yields of the target products **4a–4d**. In general, the isolated yield was found to decrease as a factor of increasing steric bulk at the alpha carbon and unsymmetrically substituted nitroalkanes gave mixtures of diastereomers in **4a** and **4b**. Next, we examined the effect of using different carbon nucleophiles. Initial test reactions with diethyl malonate showed extensive formation of a styrene derivative via a competing Knoevenagel condensation with **1a**.

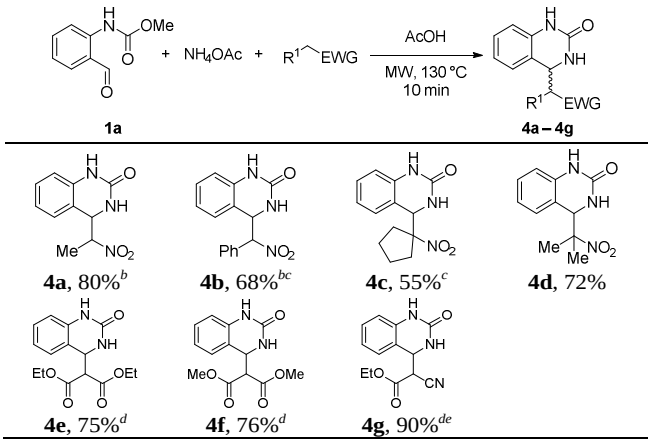
Scheme 3. - Aryl substrate scope[a]



[a]Isolated yields. [b]60 min of heating. [c]4 equiv $MeNO_2$.

Further attempts to transform this intermediate into the desired product, through extended heating and the addition of excess ammonium acetate, were unsuccessful. In order to overcome this, a one-pot, two-step protocol was developed whereby aldehyde **1a** and NH_4OAc were first heated at 130 °C for 10 minutes to afford the putative cyclic imine intermediate **I** (monitored by ESI-MS). Diethyl malonate was then added and the mixture heated for an additional 10 minutes at 130 °C. Gratifyingly, this modified protocol resulted in full conversion of the starting material and **4e** was isolated in 75% yield. Dimethyl malonate and ethyl cyanoacetate were also successfully introduced into the quinazolinone products **4f** and **4g**, with **4g** being isolated as a diastereomeric mixture in an excellent yield of 90%.

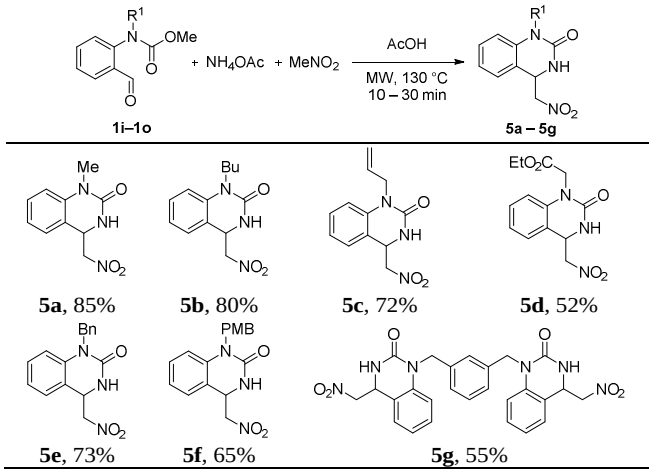
Scheme 4. Effect of variation of carbon nucleophile[a]



[a] Isolated yields. [b]Mixture of diastereomers. [c]Heated for 20 min. [d]One-pot, two-step procedure. [e]4 equiv ethyl cyanoacetate.

Next, we investigated the effect of substitution in the *N*-1 position of the o-formyl carbamate component (Scheme 5). Carbamates bearing alkyl and allyl substituents in the *N*-1 position (**5a**–**5c**) were cyclized in good to very good yields. *N*-1 benzyl and *para*-methoxybenzyl substrates (**5e** and **5f**) returned comparable results to the parent o-formyl carbamate, indicating a tolerance for steric hindrance at *N*-1. The introduction of an ethyl ester led to a reduction in the isolated yield (**5d**), due to competing intramolecular cyclization of the starting carbamate **1l**. Finally, the *bis*-quinazolinone **5g** was prepared from the corresponding benzyl-linked bis o-formyl carbamate **1o** in 53% yield.

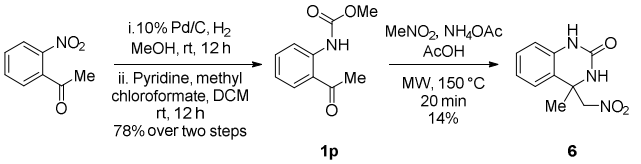
Scheme 5. Substrate scope of *N*-1 substituted *o*-formyl carbamates



Isolated yields.

To futher investigate the scope and limitations, our protocol was applied to the cyclization of an *o*-keto carbamate[17] (Scheme 6, **1p**). When the reaction was performed using our optimized conditions, only traces of the desired product **6** were observed by LC/MS analysis. Increasing the reaction temperature to 150 °C and reaction time to 20 min led to noticeable conversion and compound **6** could be isolated in 14% yield. Unfortunately, further increasing the reaction temperature or time did not lead to any improvements in the isolated yield. Despite the low yield of **6**, the formation of a quaternary carbon center using this methodology is noteworthy

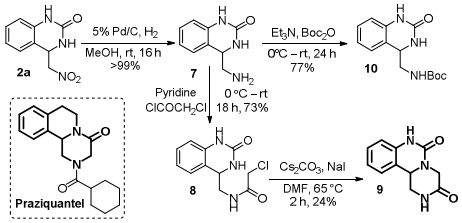
Scheme 6. Synthesis of 4-methyl 3,4-dihydroquinazolinone **6**



Finally, to demonstrate the utility of our protocol towards the synthesis of aminomethyl dihydroquinazolinone derivatives, compound **2a** was reduced to the corresponding amine **7** in quantitative yield, thus unmasking an excellent handle for further functionalization or the preparation of biologically relevant compound libraries. To demonstrate this, **7** was acylated using chloroacetyl chloride to provide **8** in 73% yield.

Subsequent base mediated cyclization afforded **9**, which contains a previously unreported fused piperazinonequinazolinone skeleton that is structurally related to the antihelminthic drug praziquantel. Finally, the *N*-Boc protected amine **10** could be prepared from compound **2a** in 76% yield.

Scheme 7 - Synthetic utility of compound **2a**



Based on the results above we believe that the reaction proceeds by the pathway presented in Figure 1. The reaction begins with formation of imine **b** from the amine nucleophile and *o*-formyl carbamate **a**. Intramolecular attack of the imine nitrogen on the carbonyl carbon of the pendant carbamate, followed by the loss of methanol generates the cyclic iminium ion **c**. Finally, attack on the electrophilic carbon in **c** by an enol nucleophile generates the final product **d** and the structure of **4e** was confirmed by X-ray crystallographic analysis[18] (see Figure 2). However, an alternative pathway could be proposed whereby imine **b** is attacked by an enol nucleophile, generating the acyclic *aza*-Henry intermediate **f**. This may then undergo cyclization *via* attack on the carbonyl, providing final product **d**. However, despite careful monitoring (ESI-MS), **f** could not be detected under the acidic reaction conditions even at reduced temperatures. Similarly, formation of nitrostyrene **e** and its amine adduct **f** was not observed, suggesting that that the reaction proceeds *via* the cyclic aldimine **c** (detected by ESI-MS). Attempts to independently synthesize[19] nitrostyrene **e** and amine adduct **f**, which could then be cyclized under acidic reaction conditions, were unsuccessful, resulting almost exclusively in the formation of iminium ion **c**. Futhermore, **2d** was also synthesized via a two-step protocol where **1a** and benzylamine were first heated in acetic acid to give a single intermediate with an *m*/*z* consistent with the formation of the corresponding cyclic iminium ion. This was further supported by NMR analysis that showed the absence of the characteristic OMe signal at 3.80 ppm and the appearance of a signal from the imine proton at 5.26 ppm (see Electronic Supplementary Information). Subsequent addition of $MeNO_2$ and heating gave **2d** in 81% isolated yield. Taken together, these data provide support for the facile formation of an electrophilic imine/iminium ion intermediate, which is highly favored under our acidic reaction conditions.

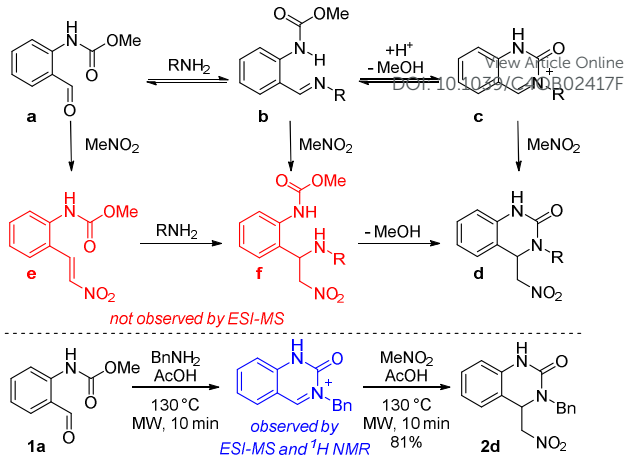


Figure 1. Proposed reaction pathway and two-step formation of **2d**.

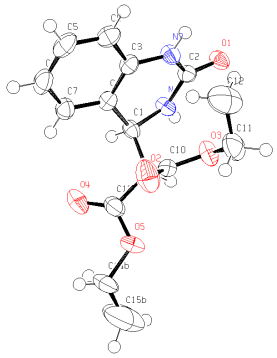


Figure 2. ORTEP representation of **4e**

Conclusions

In summary, a novel and expedient one-pot multicomponent protocol for the synthesis of substituted 3,4-dihydroquinazolinones from *o*-formyl methylcarbamates utilizing a variety of activated carbon and primary amine nucleophiles is reported. Notably, the reaction allows for the introduction of five points of diversity in a single operation, facilitating the preparation of various 3,4-dihydroquinazolinones in a highly flexible and controlled manner. Yields range from moderate to excellent, and in general, slightly lower yields were obtained using electron-poor or sterically hindered substrates or nucleophiles. This methodology has been utilized to prepare 31 novel compounds bearing different aryl, nitrogen and α-carbon substituents. Furthermore, the reaction was exemplified by transforming **2a** into a number of useful derivatives, including the hitherto unknown fused piperazinonequinazolinone **9**. We have demonstrated, for the first time, that the amine induced cyclization of *o*-formyl methylcarbamates is a facile process and provides a novel synthetic platform for the preparation of 3,4-dihydroquinazolinones. Work is currently underway in our laboratory to further expand the scope of this process and to develop an asymmetric version of this synthetic protocol.

Experimental

General Methods

Analytical thin-layer chromatography was performed on silica gel 60 F-254 plates and visualized by UV light or ninhydrin stain. Flash column chromatography was performed using silica gel (60, particle size 40-63 nm). ^{1}H NMR spectra were recorded at 400 MHz and ^{13}C NMR spectra at 100 MHz. The chemical shifts for ^{1}H NMR and ^{13}C NMR were referenced to TMS via residual solvent signals (^{1}H, $CDCl_3$ at 7.26 ppm; ^{13}C, $CDCl_3$ at 77.36 ppm; ^{1}H, DMSO-d_6 at 2.45 ppm; ^{13}C, DMSO-d_6 at 39.43 ppm, ^{1}H, CD_3OD at 3.31 ppm; ^{13}C, CD_3OD at 49.0 ppm). Microwave reactions were performed in an Initiator single mode reactor producing controlled irradiation at 2450 MHz and the temperature was monitored using the built in online IR sensor. LC/MS was performed on an instrument equipped with a CP-Sil 8 CB capillary column (50 x 3.0 mm, particle size 2.6 µm, pore size 100 Å) operating at an ionization potential of 70 eV using a CH_3CN/H_2O gradient (0.05% HCOOH). Accurate mass values were determined on a mass spectrometer equipped with an electrospray or electron impact ion source and 7-T hybrid ion trap (LTQ) or TOF detector, respectively. All reactions were performed in sealed Pyrex microwave-transparent process vials designed for 0.5–2 mL reaction volumes. Reagents were purchased at the highest commercial quality and were used without further purification. Solvents used for extraction and silica gel chromatography (EtOAc, hexanes, *n*-pentane and dichloromethane) were used without purification or removal of water.

General procedure for preparation of carbamates 1c–1h, exemplified by methyl (4-fluoro-2-formylphenyl)carbamate (1d). Starting from the known or commercially available amino alcohol, carbamates **1b**–**1g** were prepared in two steps following the procedure outlined below.

Moc protection. To a stirred solution of (2-amino-5-fluorophenyl)methanol[20] (0.75 g, 5.32 mmol) and pyridine (557 µL, 6.92 mmol) in dichloromethane (20 mL) at 0 °C was slowly added methyl chloroformate (453 µL, 5.86 mmol). After 5 min of stirring, the reaction was brought to room temperature and stirred for 16 h. The reaction was quenched by the addition of 0.1 M HCl and extracted twice with DCM (30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Silica gel chromatography (1:2 EtOAc/hexanes) provided the desired compound as a white solid (0.91 g, 86%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (s, 3H), 4.62 (d, *J* = 5.7 Hz, 2H), 6.90 (dd, *J* = 8.6, 3.0 Hz, 1H), 6.95 – 7.02 (m, 1H), 7.67 (s, 1H), 7.76 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.8, 63.9, 115.7 (d, $^2J_{CF}$ = 22.0 Hz), 115.8 (d, $^2J_{CF}$ = 22.9 Hz), 123.6, 133.6, 155.2, 159.2 (d, $^1J_{CF}$ = 243.5 Hz).

Oxidation of alcohol. To a stirred solution of methyl (2-(hydroxymethyl)-4-methylphenyl)carbamate (0.80 g, 4.02 mmol) in DCM (20 mL) was added MnO_2 (3.49 g, 40.2 mmol). After 16 h, the reaction mixture was passed through a short silica gel column to provide the title compound as a white solid (0.62 g, 78%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 (s, 3H), 7.21 (dd, *J* = 8.5, 3.5 Hz, 1H), 7.25 (dd, *J* = 7.8, 3.1 Hz, 2H), 8.36 (dd, *J* = 9.1, 4.6 Hz, 1H), 9.76 (s, 1H), 10.33 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.6, 120.3 (d, $^3J_{CF}$ = 6.8 Hz), 120.8 (d, $^2J_{CF}$ = 22.4 Hz), 121.9 (d, $^3J_{CF}$ = 5.5 Hz), 123.1 (d, $^2J_{CF}$ = 22.2 Hz), 137.4 (d, $^4J_{CF}$ = 2.7 Hz), 154.0, 157.2 (d, $^1J_{CF}$ = 243.7 Hz). 193.9. MS (ESI) calc´d for $C_9H_9FNO_3^+$ [M + H$^+$] *m/z* 198.0561, found *m/z* 198.0557.

General procedure for preparation of compounds 2a–2i, 3a–3g, 4a–4d, 5a–5g and 6, exemplified by 4-(nitromethyl)-3,4-dihydroquinazolin-2(1*H*)-one (2a). A Pyrex process vial (0.5–2 mL) was charged with **1a** (89.6 mg, 0.50 mmol), AcOH (1 mL), NH_4OAc (77.0 mg, 1.00 mmol) and $MeNO_2$ (55.2 µL, 1.00 mmol). The resulting solution was heated by microwave irradiation at 130 °C for 10 min, and then concentrated *in vacuo*. The residue was purified by silica gel chromatography (50–100% EtOAc in *n*-pentane) to provide the title compound as a white solid (74 mg, 71%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.63 – 4.65 (m, 2H), 5.04 – 5.08 (m, 1H), 6.82 (d, *J* = 7.2 Hz, 1H), 6.89 (dt, *J* = 9.4 and 1.2 Hz, 1H), 7.17 – 7.20 (m, 2H), 7.29 (s, 1H), 9.28 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 51.9, 80.4, 114.0, 116.3, 121.1, 126.3, 128.8, 137.7, 152.7. MS (ESI) calc'd. for $C_9H_{10}N_3O_3^+$ [M + H$^+$] *m/z* 208.0722, found *m/z* 208.0724.

General procedure for preparation of compounds 4e–4g and 2d, exemplified by diethyl 2-(2-oxo-1,2,3,4-tetrahydroquinazolin-4-yl)malonate (4e). A 0.5-2 mL process vial equipped with a stirring bar was charged with compound **1a** (90 mg, 0.5 mmol), NH_4OAc (77 mg, 1 mmol) and acetic acid (1.0 mL). The vessel was sealed under air and exposed to microwave heating for 10 min at 130 °C. Diethyl malonate (305 µL, 2 mmol) was added and the mixture was once again subjected to microwave heating for 10 min at 130 °C. The resulting mixture was cooled to room temperature and concentrated under reduced pressure. The residue was thereafter purified by flash column chromatography on silica gel (gradient from 20–100% EtOAc in pentane) to provide the title compound as yellow crystals, mp 117–122 °C (96 mg, 75%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.06 (dt, *J* = 16.8, 7.1 Hz, 6H), 3.65 (d, *J* = 6.4 Hz, 1H), 3.82 – 4.12 (m, 4H), 5.00 (dd, *J* = 6.4, 3.7 Hz, 1H), 6.66 – 6.88 (m, 3H), 6.98 – 7.31 (m, 2H), 9.24 (d, *J* = 2.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.7, 52.8, 58.6, 61.2, 61.3, 113.9, 118.0, 121.0, 126.3, 128.5, 137.9, 153.3, 166.4, 166.6. MS (ESI) calcd. for $C_{15}H_{19}N_2O_5^+$ [M + H$^+$] *m/z* 307.1288, found *m/z* 307.1293.

Preparation of methyl (2-formylphenyl)carbamate (1a). Prepared according to the literature procedure.[21] Spectral data were in agreement with reported values.

Preparation of methyl (4-chloro-2-formylphenyl)carbamate) (1b). Following a modified version of the literature procedure,[21] the title compound was obtained after silica gel chromatography (15% EtOAc in petroleum ether) as a pink solid, used in the next step without further purification (3.65 g, 98%). MS (ESI) $C_8H_9ClNO_2^+$ [M + H$^+$] *m/z* 185.89. To a stirred solution of the above solid (1.86 g, 10.0 mmol) in anhydrous THF (20 mL) under N_2 atmosphere at

-78 °C was added *sec*-BuLi (18 mL, 1.4M in cyclohexane). After 4h at -20 °C, DMF (1.20 mL, 15.6 mmol) was added and the reaction mixture stirred for 60 min, before being partitioned between H_2O and EtOAc (50 mL of each). The aqueous layer was extracted with EtOAc (50 mL) and the combined organics were concentrated *in vacuo*, dried over $MgSO_4$ and purified by silica gel chromatography (20% EtOAc in petroleum ether) to provide the title compound as a yellow solid (0.92 g, 43%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76 (s, 3H), 7.78 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.98 (d, *J* = 2.5 Hz, 1H), 8.14 (d, *J* = 9.0 Hz, 1H), 9.97 (s, 1H), 10.40 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 52.9, 121.4, 124.5, 127.0, 133.7, 135.5, 139.4, 154.1, 194.5. MS (EI) calc´d for $C_9H_8ClNO_3^+$ [M^+] *m/z* 213.0193, found *m/z* 213.0188.

Preparation of methyl (3-formylpyridin-2-yl)carbamate (1f). Following a modified version of the literature procedure,[22] the title compound was obtained a yellow solid (0.15 g, 25%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.83 (s, 3H), 7.16 (dd, *J* = 7.6, 4.9 Hz, 1H), 8.01 (dd, *J* = 7.6, 2.0 Hz, 1H), 8.66 (dd, *J* = 4.9, 2.0 Hz, 1H), 9.92 (s, 1H), 10.36 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.7, 116.7, 118.0, 143.8, 152.0, 154.4, 193.0. MS (ESI) calc'd. for $C_8H_9N_2O_3^+$ [M + H^+] *m/z* 181.0622, found *m/z* 181.0613.

General procedure for preparation of carbamates 1i–1o, exemplified by methyl (2-formylphenyl)(4-methoxybenzyl)carbamate (1n). To a stirred solution of **1a** (100 mg, 0.55 mmol) in 5 mL anhydrous MeCN was added 4-methoxybenzyl chloride (131 mg, 0.84 mmol) and anhydrous K_2CO_3 (154 mg, 1.11 mmol). After 20 h of heating at reflux under N_2 atmosphere, the reaction mixture was taken up in H_2O and extracted with EtOAc. Concentration and purification by silica gel chromatography (15% EtOAc in *n*-pentane) provided the title compound as a colourless oil (91 mg, 55%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.52 – 3.70 (m, 3H), 3.76 (s, 3H), 4.65 – 5.10 (m, 2H), 6.59 – 6.90 (m, 2H), 7.05 – 7.09 (m, 2H), 7.09 – 7.18 (m, 1H), 7.42 (dt, *J* = 7.6, 0.9 Hz, 1H), 7.52 – 7.71 (m, 1H), 7.84 (dd, *J* = 7.8, 1.7 Hz, 1H), 9.71 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.3, 54.5, 55.2, 113.9, 127.9, 128.4, 128.9, 129.0, 130.3, 132.9, 134.8, 143.3, 156.1, 159.3, 189.6. MS (ESI) calc'd. for $C_{17}H_{17}NO_4Na^+$ [M + Na^+] *m/z* 322.1055, found *m/z* 322.1071.

Preparation of methyl (2-acetylphenyl)carbamate (1p). A solution of o-nitroacetophenone (0.5 g, 3.03 mmol) and 10% Pd/C (50 mg) in MeOH (10 ml) was hydrogenated at atm. pressure for 12 h. After consumption of starting material (as confirmed by TLC, 10% EtOAc in hexanes, ninhydrin stain), the reaction mixture was filtered through a pad of Celite, washed with methanol and concentrated under reduced pressure to afford a yellow oil (0.41 g). The crude compound was used for next step without any further purification. MS (ESI) for $C_8H_{11}NO^+$ [M + H^+] *m/z* 136.08.

To a stirred solution of the above oil (0.41 g, 3.02 mmol) and pyridine (0.36 g, 4.54 mmol) in DCM (8 mL) at ambient temperature was added methyl chloroformate (0.37 g, 3.93 mmol). After 5 h of stirring, 0.1 M HCl (10 mL) was added and the resulting aqueous layer extracted with DCM (2 x 30 mL). The combined organics were washed with sat. $NaHCO_3$ (50 mL) and H_2O (50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel chromatography (10% EtOAc in hexanes) to yield the title compound as a white solid (0.46 g, 79%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.64 (s, 3H), 3.77 (s, 3H), 6.89 – 7.17 (m, 1H), 7.53 (t, *J* = 7.7 Hz, 1H), 7.86 (d, *J* = 7.3 Hz, 1H), 8.46 (d, *J* = 8.5 Hz, 1H), 11.19 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.0, 52.7, 119.6, 121.8, 121.9, 132.1, 135.5, 141.8, 154.8, 202.7. MS (ESI) calc'd. for $C_{10}H_{12}NO_3^+$ [M + H^+] *m/z* 194.0817, found *m/z* 194.0824.

Methyl (2-formyl-5-(trifluoromethyl)phenyl)carbamate (1c). Following the general procedure starting from (2-amino-4-(trifluoromethyl)phenyl)methanol,[23] the title compound was obtained as a white solid (0.65 g, 65%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84 (s, 3H), 7.31 – 7.57 (m, 1H), 7.61 – 8.04 (m, 1H), 8.80 (s, 1H), 9.99 (s, 1H), 10.64 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.7, 115.6 (q, $^3J_{CF}$ = 4.1 Hz), 118.3 (q, $^3J_{CF}$ = 4.0 Hz), 122.8 (q, $^4J_{CF}$ = 1.4 Hz), 122.9 (q, $^1J_{CF}$ = 236.7 Hz) 136.2 (s), 136.8 (d, $^2J_{CF}$ = 32.6 Hz), 141.5, 153.9, 194.4. MS (ESI) calc´d for $C_{10}H_8F_3NO_3^+$ [M^+] *m/z* 247.0456, found *m/z* 247.0452.

Methyl (3-chloro-2-formylphenyl)carbamate (1e). Following the general procedure starting from (2-amino-6-chlorophenyl)methanol, the title compound was obtained as a white solid (79 mg, 14%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 3H), 7.10 (d, *J* = 7.9 Hz, 1H), 7.48 (t, *J* = 8.3 Hz, 1H), 8.42 (d, *J* = 8.7 Hz, 1H), 10.56 (s, 1H), 11.09 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 49.5, 117.5, 124.9, 136.8, 139.6, 143.4, 154.7, 159.2, 192.9. MS (EI) calc´d for $C_9H_8ClNO_3^+$ [M^+] *m/z* 213.0186, found *m/z* 213.0193.

Methyl (2-formyl-6-methylphenyl)carbamate (1g). Following the general procedure starting from (2-amino-3-methylphenyl)methanol,[24] the title compound was obtained as a white solid (80 mg, 22%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.01 (s, 3H), 3.46 (s, 3H), 6.92 – 7.03 (m, 1H), 7.17 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.24 – 7.31 (m, 1H), 8.05 (br s, 1H), 9.68 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.9, 53.2, 125.9, 132.0, 135.4, 137.4, 137.6, 137.7, 155.1, 193.7. MS (ESI) calc'd. for $C_{10}H_{12}NO_3^+$ [M + H^+] *m/z* 194.0817, found *m/z* 194.0821.

Methyl (2-formyl-6-methoxyphenyl)carbamate (1h). Following the general procedure starting from (2-amino-3-methoxyphenyl)methanol,[23] the title compound was obtained as a white solid (0.27 g, 57%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 3H), 3.89 (s, 3H), 7.07 – 7.19 (m, 2H), 7.21 – 7.31 (m, 1H), 7.46 (dd, *J* = 7.8, 1.3 Hz, 1H); 10.03 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.1, 56.1, 115.6, 120.9, 125.9, 128.2, 130.0, 152.0, 155.8, 189.9. MS (ESI) calc'd. for $C_{10}H_{12}NO_4^+$ [M + H^+] *m/z* 210.0771, found *m/z* 210.0766.

Methyl (2-formylphenyl)(methyl)carbamate (1i) Following the general procedure but with 10 equiv. alkyl halide, the title compound was obtained as a white solid (91 mg, 85 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.33 (s, 3H), 3.53 – 3.69 (m, 3H), 7.27 (d, *J* = 7.8 Hz, 1H), 7.43 (d, *J* = 1.6 Hz, 1H), 7.58 – 7.65 (m, 1H), 7.90 (ddd, *J* = 7.8, 1.6, 0.5 Hz, 1H), 10.08 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.6, 53.2, 127.7, 129.5, 132.2,

133.5, 134.9, 144.9, 156.1, 189.6. MS (ESI) calc'd. for $C_{10}H_{12}NO_3^+$ [M + H$^+$] *m/z* 194.0817, found *m/z* 194.0820.

Methyl butyl(2-formylphenyl)carbamate (1j). Following the general procedure, the title compound was obtained as a white solid (70 mg, 53%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, *J* = 7.3 Hz, 3H), 1.25 (s, 2H), 1.47 – 1.65 (m, 2H), 3.52 – 3.66 (m, 3H), 3.66 – 3.74 (m, 2H), 7.35 – 7.06 (m, 1H), 7.44 (tt, J = 7.5, 0.9 Hz, 1H), 7.63 (ddd, J = 8.0, 7.4, 1.7 Hz, 1H), 7.93 (ddd, J = 7.7, 1.7, 0.5 Hz, 1H), 10.10 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 20.0, 29.7, 51.2, 53.1, 127.7, 128.6, 132.8, 134.8, 189.8. MS (ESI) calc'd. for $C_{13}H_{18}NO_3^+$ [M + H+] m/z 236.1287, found m/z 236.1279.

Methyl allyl(2-formylphenyl)carbamate (1k). Following the general procedure, the title compound was obtained as a white solid (48 mg, 78%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.63 (s, 3H), 4.12 – 4.45 (m, 2H), 5.07 – 5.25 (m, 2H), 5.90 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 1H), 7.22 – 7.28 (m, 1H), 7.44 (t, *J* = 7.6 Hz, 1H), 7.62 (ddd, *J* = 7.9, 7.5, 1.7 Hz, 1H), 7.90 (dd, *J* = 7.7, 1.7 Hz, 1H), 10.07 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.3, 54.0, 119.1, 127.9, 128.7, 129.5, 132.5, 132.7, 134.8, 143.5, 155.8, 189.9. MS (ESI) calcd. for $C_{12}H_{14}NO_3^+$ [M + H$^+$] *m/z* 220.0974, found *m/z* 220.0972.

Ethyl N-(2-formylphenyl)-N-(methoxycarbonyl)glycinate (1l). Following the general procedure but with 4 h of heating*, the title compound was obtained as a white solid (40 mg, 27%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, *J* = 6.9 Hz, 3H), 3.67 (s, 3H), 4.21 (q, *J* = 7.0 Hz, 2H), 4.27 – 4.45 (m, 2H), 7.41 – 7.53 (m, 1H), 7.63 (td, *J* = 7.7, 1.7 Hz, 1H), 7.92 (dd, *J* = 7.8, 1.7 Hz, 1H), 10.27 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1. 52.4, 53.6, 61.5, 128.1, 128.2, 129.4, 132.5, 134.8, 143.3, 155.9, 169.1, 190.2. MS (ESI) calc'd. for $C_{13}H_{16}NO_5^+$ [M + H$^+$] *m/z* 266.1028, found *m/z* 266.1029.

Methyl benzyl(2-formylphenyl)carbamate (1m). Following the general procedure, the title compound was obtained as a white solid (147 mg, 98%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.63 (s, 3H), 4.65 – 5.01 (m, 2H), 7.09 – 7.15 (m, 1H), 7.15 – 7.20 (m, 2H), 7.21 – 7.28 (m, 3H), 7.37 – 7.44 (m, 1H), 7.56 (dtd, *J* = 7.3, 7.5, 1.7 Hz, 1H), 7.84 (dd, *J* = 7.7, 1.7 Hz, 1H), 9.73 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.4, 55.1, 127.9, 128.0, 128.6, 128.8, 129.2, 132.8, 134.8, 136.4, 143.2, 156.1, 189.5. MS (ESI) calc'd. for $C_{16}H_{16}NO_3^+$ [M + H$^+$] *m/z* 270.1130, found *m/z* 270.1132.

Methyl(2-formylphenyl)(2(((methoxycarbonyl)(phenyl)amino)methyl) benzyl)carbamate (1o). Following the general procedure, the title compound was obtained as a white solid (92 mg, 71%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.63 (s, 6H), 4.30 – 4.98 (m, 4H), 7.01 – 7.16 (m, 6H), 7.39 (tt, *J* = 7.6, 0.9 Hz, 2H), 7.46 – 7.63 (m, 2H), 7.78 (dd, *J* = 7.7, 1.8 Hz, 2H), 9.60 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 51.4, 53.8, 128.5, 128.8, 129.3, 130.0, 130.3, 131.0, 133.2, 135.2, 142.9, 156.3, 189.5. MS (ESI) calc'd. for $C_{26}H_{25}N_2O_6^+$ [M + H$^+$] *m/z* 461.1713, found *m/z* 461.1712.

* Dialkylation was observed

Preparation of 2a by conventional heating. A 2–5 mL Pyrex process vial equipped with a magnetic stirring bar was charged with **1a** (45.1 mg, 0.25 mmol), NH_4OAc (45 mg, 0.59 mmol) and AcOH (1 mL). The vial was sealed and the reaction mixture brought to 130 °C on a heating plate. After 2 h, the vial was cooled to ambient temperature and purified following the general procedure.

3-Methyl-4-(nitromethyl)-3,4-dihydroquinazolin-2(1*H*)-one (2b). Following the general procedure, the title compound was obtained as a white solid (105 mg, 95%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.00 (s, 3H), 4.86 (t, *J* = 5.3 Hz, 1H), 5.25 (t, *J* = 5.3 Hz, 1H), 6.85 (d, *J* = 8.0 Hz, 1H), 6.95 (t, *J* = 7.5 Hz, 1H), 7.19 (d, *J* = 7.6 Hz, 1H), 7.23 (td, *J* = 7.6, 1.6 Hz, 1H), 9.44 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 33.3, 59.2, 77.7, 114.1, 117.2, 121.7, 126.5, 129.4, 138.0, 153.2. MS (ESI) calc'd. for $C_{10}H_{12}N_3O_3^+$ [M + H$^+$] *m/z* 222.0879, found *m/z* 222.0881.

3-Hexyl-4-(nitromethyl)-3,4-dihydroquinazolin-2(1*H*)-one (2c). Following the general procedure (0.3 mmol scale), the title compound was obtained as a white solid (78 mg, 92%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.51 – 0.93 (m, 3H), 1.01 – 1.25 (m, 6H), 1.29 – 1.57 (m, 2H), 2.90 (ddd, *J* = 13.9, 8.5, 5.5 Hz, 1H), 3.76 (ddd, *J* = 13.7, 8.7, 6.6 Hz, 1H), 4.70 (dd, *J* = 5.5, 1.8 Hz, 2H), 5.15 (t, *J* = 5.5 Hz, 1H), 6.78 (dd, *J* = 8.0, 1.1 Hz, 1H), 6.86 (td, *J* = 7.5, 1.1 Hz, 1H), 7.11 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.15 (td, *J* = 7.7, 1.5 Hz, 1H), 9.33 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) 14.8, 22.9, 26.7, 28.3, 31.8, 45.6, 57.5, 78.6, 114.6, 118.2, 122.2, 126.9, 129.9, 138.6, 153.6. MS (ESI) calcd. for $C_{17}H_{25}N_4O_3^+$ [M + H$^+$ + MeCN] *m/z* 333.1940, found *m/z* 333.1937.

3-Benzyl-4-(nitromethyl)-3,4-dihydroquinazolin-2(1*H*)-one (2d). Following the general procedure, the title compound was obtained as a white solid (110 mg, 74%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.24 (d, *J* = 15.7 Hz, 1H), 4.69 – 4.94 (m, 2H), 5.06 (t, *J* = 5.2 Hz, 1H), 5.18 (d, *J* = 15.7 Hz, 1H), 6.78 – 6.93 (m, 2H), 7.10 (d, *J* = 7.5 Hz, 1H), 7.20 (t, *J* = 7.6 Hz, 1H), 7.24 – 7.29 (m, 3H), 7.29 – 7.37 (m, *J* = 8.0 Hz, 2H), 9.43 – 9.70 (m, 1H); ^{13}C NMR
(100 MHz, DMSO-d_6) δ 48.1, 57.1, 78.3, 117.8, 122.3, 126.9, 128.2, 128.3, 129.5, 130.0, 138.4, 138.5, 153.7. MS (ESI) calc'd. for $C_{16}H_{16}N_3O_3^+$ [M + H$^+$] *m/z* 298.1192, found *m/z* 298.1202.

Preparation of 2d using one-pot, two-step protocol. Following the general procedure, the title compound was obtained as a white solid (54 mg, 81%).

3-Cyclopropyl-4-(nitromethyl)-3,4-dihydroquinazolin-2(1*H*)-one (2e). Following the general procedure, the title compound was obtained as a white solid (115 mg, 93%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.54 (dd, *J* = 8.3, 4.4 Hz, 1H), 0.66 (d, *J* = 8.2 Hz, 2H), 0.90 (td, *J* = 7.4, 6.6, 2.6 Hz, 1H), 2.62 (td, *J* = 5.5, 2.6 Hz, 1H), 4.83 (dd, *J* = 5.3, 2.2 Hz, 2H), 5.16 (t, *J* = 5.4 Hz, 1H), 6.71 – 6.86 (m, 1H), 6.90 (t, *J* = 7.5 Hz, 1H), 7.18 (t, *J* = 7.2 Hz, 2H), 9.49 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 5.7, 11.0, 28.1, 58.2, 78.1, 114.1, 117.9, 121.6, 126.6, 129.4, 137.5, 153.9. MS (ESI) calc'd. for $C_{12}H_{14}N_3O_3^+$ [M + H$^+$] *m/z* 248.1035, found *m/z* 248.1038.

Ethyl 4-(4-(nitromethyl)-2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)butanoate (2f). Following the general procedure (0.3 mmol scale) but with 30 min of heating and 1.3 equiv. amine, the title compound was obtained as a white solid (51 mg, 57%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (t, *J* = 7.1 Hz, 3H), 1.85 – 2.07 (m, 2H), 2.32 (t, *J* = 7.2 Hz, 2H), 3.04 (ddd, *J* = 13.9, 7.7, 6.1 Hz, 1H), 3.93 – 4.18 (m, 3H), 4.38 – 4.65 (m, 2H), 5.18 (t, *J* = 6.7 Hz, 1H), 6.89 (dd, *J* = 8.0, 1.1 Hz, 1H), 6.99 (td, *J* = 7.8, 1.1 Hz, 1H), 7.08 (ddd, *J* = 7.8, 1.5, 0.6 Hz, 1H), 7.27 (ddd, *J* = 8.0, 7.4, 1.5 Hz, 1H), 8.97 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 23.6, 29.7, 31.2, 45.7, 57.8, 60.5, 114.6, 117.1, 122.7, 125.7, 129.8, 136.8, 154.5, 172.9. MS (ESI) calc'd. for $C_{15}H_{20}N_3O_5^+$ [M + H$^+$] *m/z* 322.1403, found *m/z* 322.1404.

Methyl 4-(4-(nitromethyl)-2-oxo-1,4-dihydroquinazolin-3(2*H*)-yl)propanoate (2g). Following the general procedure (0.45 mmol scale) but with 30 min of heating and 1.8 equiv. amine, the title compound was obtained as a white solid (32 mg, 24 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.62 (dt, *J* = 17.0, 5.1 Hz, 1H), 2.80 (ddd, *J* = 17.0, 8.9, 5.8 Hz, 1H), 3.39 (ddd, *J* = 14.2, 8.9, 5.3 Hz, 1H), 3.61 (s, 3H), 4.14 (dt, *J* = 14.1, 5.4 Hz, 1H), 4.46 (dd, *J* = 11.9, 6.6 Hz, 1H), 4.62 (dd, *J* = 11.9, 6.6 Hz, 1H), 5.41 (t, *J* = 6.6 Hz, 1H), 6.83 – 6.90 (m, 1H), 6.99 (td, *J* = 7.6, 1.1 Hz, 1H), 7.10 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.22 – 7.30 (m, 1H), 8.85 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.5, 43.3, 51.8, 59.2, 77.4, 114.6, 117.3, 122.8, 125.7, 129.8, 136.6, 154.3, 172.3. MS (ESI) calc'd. for $C_{13}H_{16}N_3O_5^+$ [M + H$^+$] *m/z* 294.1090, found *m/z* 294.1095.

3-(4-Methoxyphenyl)-4-(nitromethyl)-3,4-dihydroquinazolin-2(1*H*)-one (2h). Following the general procedure (0.2 mmol scale) but with 30 min of heating, the title compound was obtained as a white solid (28mg, 40%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82 (s, 3H), 4.57 (dd, *J* = 11.9, 7.3 Hz, 1H), 4.68 (dd, *J* = 11.9, 5.3 Hz, 1H), 5.44 (dd, *J* = 7.3, 5.3 Hz, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 6.95 (d, *J* = 8.7 Hz, 2H), 7.00 (t, *J* = 7.6 Hz, 1H), 7.10 (d, *J* = 7.5 Hz, 1H), 7.23 – 7.27 (m, 1H), 7.30 (d, *J* = 8.7 Hz, 2H), 8.25 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.7, 61.5, 76.9, 114.9, 115.0, 117.1, 122.9, 126.0, 129.1, 130.1, 132.8, 136.9, 153.3, 159.0. MS (ESI) calc'd. for $C_{16}H_{16}N_3O_4^+$ [M + H$^+$] *m/z* 314.1141, found *m/z* 314.1139.

3-(4-*iso*-propylphenyl)-4-(nitromethyl)-3,4-dihydroquinazolin-2(1*H*)-one (2i). Following the general procedure but with 30 min of heating, the title compound was obtained as a white solid (26 mg, 36%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (dd, *J* = 6.9, 0.6 Hz, 6H), 2.79 – 3.10 (m, 1H), 4.61 (dd, *J* = 11.9, 7.8 Hz, 1H), 4.70 (dd, *J* = 11.9, 5.1 Hz, 1H), 6.83 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.02 (td, *J* = 7.5, 1.1 Hz, 1H), 7.08 – 7.14 (m, 1H), 7.25 – 7.30 (m, 2H), 7.32 (s, 4H), 8.32 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.9, 33.8, 47.0, 61.0, 76.6, 114.7, 117.1, 122.8, 125.9, 127.3, 127.7, 130.0, 136.6, 137.5, 148.5. MS (ESI) calc'd. for $C_{18}H_{20}N_3O_3^+$ [M + H$^+$] *m/z* 326.1505, found *m/z* 326.1510.

6-Chloro-4-(nitromethyl)-3,4-dihydroquinazolin-2(1*H*)-one (3a). Following the general procedure (0.2 mmol scale), the title compound was obtained as a yellow solid (35 mg, 75%); ^{1}H NMR (400 MHz, DMSO-*d6*) δ 4.71 4.73 (m, 2H), 5.10 – 5.13 (m, 1H), 6.83 (d, *J* = 8.8 Hz, 1H), 7.26 (dd, *J* = 8.8 and 2.0 Hz, 1H), 7.35 – 7.37 (m, 2H), 9.40 (s, 1H); ^{13}C NMR (100 MHz, DMSO-*d6*) δ 51.4, 80.2, 115.6, 118.3, 126.2, 128.7, 136.8, 152.4. MS (ESI) calc'd. for $C_9H_8ClN_3O_3^+$ [M + H$^+$] *m/z* 242.0332, found *m/z* 242.0335.

4-(Nitromethyl)-6-(trifluoromethyl)-3,4-dihydroquinazolin-2(1*H*)-one (3b). Following the general procedure (0.3 mmol scale) but with 30 min of heating and 4 equiv. $MeNO_2$, the title compound was obtained as a white solid (40 mg, 62%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.70 (ddd, *J* = 17.2, 12.7, 5.5 Hz, 2H), 5.12 – 5.20 (m, 1H), 7.06 (s, 1H), 7.20 (d, *J* = 8.1 Hz, 1H), 7.40 (s, 1H), 7.43 (dd, *J* = 6.8, 3.1 Hz, 1H), 9.51 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 51.6, 80.2, 110.3 (q, $^3J_{CF}$ = 4.4 Hz), 117.7 (q, $^3J_{CF}$ = 4.3 Hz), 124.2 (q, $^1J_{CF}$ = 272.0 Hz), 129.3 (d, $^2J_{CF}$ = 31.5 Hz), 138.8,152.3. MS (ESI) calc'd. for $C_{10}H_9F_3N_3O_3^+$ [M + H$^+$] *m/z* 276.0596, found *m/z* 276.0604.

6-Fluoro-4-(nitromethyl)-3,4-dihydroquinazolin-2(1*H*)-one (3c). Following the general procedure (0.5 mmol scale) but with 4 equiv. of $MeNO_2$, the title compound was obtained as a white solid (91 mg, 73 %); ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.28 – 4.83 (m, 2H), 5.09 (dd, *J* = 9.3, 5.2 Hz, 1H), 6.81 (dd, *J* = 8.8, 4.8 Hz, 1H), 7.04 (td, *J* = 8.9, 3.4 Hz, 1H), 7.16 (dd, *J* = 9.3, 3.4 Hz, 1H), 7.33 (br s, 1H), 9.34 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 52.2, 80.6, 113.5 (d, $^2J_{CF}$ = 22.9 Hz), 115.7 (d, $^3J_{CF}$ = 8.2 Hz), 116.1 (d, $^2J_{CF}$ = 22.9 Hz), 118.3 (d, $^3J_{CF}$ = 7.9 Hz), 134.9 (d, $^4J_{CF}$ = 2.3 Hz), 153.1, 157.2 (d, $^1J_{CF}$ = 236.7 Hz). MS (ESI) calc'd. for $C_9H_9FN_3O_3^+$ [M + H$^+$] *m/z* 226.0628, found *m/z* 226.0631.

5-Chloro-4-(nitromethyl)-3,4-dihydroquinazolin-2(1*H*)-one (3d). Following the general procedure (0.4 mmol scale), the title compound was obtained as a white solid (64 mg, 71%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.48 – 4.79 (m, 2H), 5.18 (dt, *J* = 6.8, 4.3 Hz, 1H), 6.85 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.05 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.26 (d, *J* = 8.0 Hz, 1H), 7.70 (d, *J* = 4.0, 1.2 Hz, 1H), 9.69 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 51.0, 79.2, 113.8, 114.6, 122.5, 131.1, 140.6, 153.1. MS (ESI) calc'd. for $C_9H_9ClN_3O_3^+$ [M + H$^+$] *m/z* 242.0327, found *m/z* 242.0325.

4-(Nitromethyl)-3,4-dihydropyrido[2,3-d]pyrimidin-2(1*H*)-one (3e). Following the general procedure (0.1 mmol scale), the title compound was obtained as a yellow solid (11 mg, 61%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.69 – 4.80 (m, 2H), 5.13 – 5.17 (m, 1H), 6.94 – 6.97 (m, 1H), 7.43 (s, 1H), 7.66 (dd, *J* = 7.2,1.6 Hz, 1H), 8.14 (dd, *J* = 5.2, 1.6 Hz, 1H), 9.75 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 50.7, 80.2, 111.8, 117.3, 134.9, 148.0, 150.3, 152.8. MS (ESI) calc'd. for $C_8H_9N_3O_4^+$ [M + H$^+$] *m/z* 209.0675, found *m/z* 209.0668.

8-Methyl-4-(nitromethyl)-3,4-dihydroquinazolin-2(1*H*)-one (3f). Following the general procedure (0.4 mmol scale), the title compound was obtained as a white solid (74 mg, 82%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.19 (s, 3H), 4.65 (d, *J* = 5.9 Hz, 2H), 5.03 – 5.09 (m, 1H), 6.83 (t, *J* = 7.6 Hz, 1H), 7.01 – 7.09 (m, 2H), 7.35 – 7.41 (m, 1H), 8.60 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 17.1, 52.0, 80.5, 116.7, 121.2, 122.4, 124.1, 130.3, 135.8, 153.1. MS (ESI) calc'd. for $C_{10}H_{12}N_3O_3^+$ [M + H$^+$] *m/z* 222.0879, found *m/z* 222.0873.

8-Methoxy-4-(nitromethyl)-3,4-dihydroquinazolin-2(1*H*)-one (3g). Following the general procedure, the title compound was obtained as a white solid (53 mg, 91%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.79 (s, 3H), 4.66 – 4.68 (m, 2H), 5.07 – 5.10 (m, 1H), 6.80 – 6.82 (m, 1H), 6.90 – 6.91 (m, 2H), 7.35 (s, 1H), 8.18 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 51.9, 55.6, 80.2, 110.6, 116.9, 117.9, 121.5, 126.6, 145.1, 152.3. MS (ESI) calc'd. for $C_{10}H_{11}N_3O_4^+$ [M + H$^+$] *m/z* 238.0828, found *m/z* 238.0835.

4-(1-Nitroethyl)-3,4-dihydroquinazolin-2(1*H*)-one (4a). Following the general procedure, the title compound was obtained as a white solid (90 mg, 80% as a 0.7:1 mixture of diastereomers); ^{1}H NMR (400 MHz, DMSO-d_6, major isomer) δ 1.33 (d, *J* = 9.8 Hz, 3H), 4.69 – 4.81 (m, 1H), 4.96 – 5.03 (m, 1H), 6.83 (dd, *J* = 8.0, 2.9 Hz, 1H), 6.90 (t, *J* = 7.4 Hz, 1H), 7.12 (dd, *J* = 14.6, 7.5 Hz, 1H), 7.20 (t, *J* = 7.7 Hz, 1H), 7.31 – 7.37 (m, 1H), 9.31 (s, 1H), ,; ^{13}C NMR (100 MHz, DMSO-d_6) δ 12.4, 56.5, 87.4, 114.1, 116.3, 121.3, 126.7, 129.0, 138.0, 153.3. MS (ESI) calc'd. for $C_{10}H_{12}N_3O_3^+$ [M + H$^+$] *m/z* 222.0879, found *m/z* 222.0876.

4-(Nitro(phenyl)methyl)-3,4-dihydroquinazolin-2(*1H*)-one (4b). Following the general procedure (0.3 mmol scale) but with 20 min of heating, the title compound was obtained as a white solid (54 mg, 68% as a 1:1 mixture of diastereomers); ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.34 (dd, *J* = 9.5, 4.4 Hz, 1H), 5.46 (dd, *J* = 6.7, 4.0 Hz, 1H), 5.68 (d, *J* = 9.5 Hz, 1H), 6.38 (dd, *J* = 7.8, 1.5 Hz, 1H), 6.53 (td, *J* = 7.5, 1.2 Hz, 1H), 6.70 – 6.75 (m, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 6.89 (td, *J* = 7.5, 1.2 Hz, 1H), 7.06 (td, *J* = 7.7, 1.5 Hz, 1H), 7.11 – 7.20 (m, 3H), 7.27 – 7.44 (m, 11H), 7.65 (s, 1H), 9.09 (s, 1H), 9.38 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 55.8, 56.4, 93.6, 94.1, 127.0, 127.7, 127.7, 128.9, 129.0, 129.2, 129.3, 129.4, 129.6, 130.1, 130.5, 131.2, 131.7, 138.5, 138.8, 153.5, 153.9. MS (ESI) calc'd. for $C_{15}H_{14}N_3O_3^+$ [M + H$^+$] *m/z* 284.1035, found *m/z* 284.1037.

4-(1-Nitrocyclopentyl)-3,4-dihydroquinazolin-2(1*H*)-one (4c). Following the general procedure (0.3 mmol scale), the title compound was obtained as a white solid (40 mg, 55%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.41 – 1.52 (m, 2H), 1.52 – 1.63 (m, 2H), 1.85 – 1.95 (m, 1H), 2.09 – 2.20 (m, 1H), 2.21 – 2.30 (m, 1H), 2.30 – 2.39 (m, 1H), 4.94 (d, *J* = 4.1 Hz, 1H), 6.80 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.86 (td, *J* = 7.5, 1.2 Hz, 1H), 6.96 – 7.01 (m, 1H), 7.13 – 7.21 (m, 1H), 7.13 – 7.21 (m, 1H), 7.58 (dd, *J* = 4.0, 2.1 Hz, 1H), 9.20 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 23.9, 24.1, 32.8, 34.2, 59.6, 105.9, 115.0, 117.0, 121.9, 128.0, 129.9, 139.4, 154.3. MS (ESI) calc'd. for $C_{13}H_{16}N_3O_3^+$[M + H$^+$] *m/z* 262.1192, found *m/z* 262.1193.

4-(2-Nitropropan-2-yl)-3,4-dihydroquinazolin-2(1*H*)-one (4d). Following the general procedure (0.2 mmol scale), the title compound was obtained as a white solid (38 mg, 72%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.42 (s, 3H), 1.52 (s, 3H), 4.88 (d, *J* = 4.4 Hz, 1H), 6.79 – 6.97 (m, 2H), 6.97 – 7.07 (m, 1H), 7.26 (td, *J* = 7.6, 1.5 Hz, 1H), 7.52 – 7.76 (m, 1H), 9.34 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.9, 22.4, 61.1, 94.1, 115.0, 121.9, 128.4, 130.1, 139.6, 154.5. MS (ESI) calc'd. for $C_{11}H_{14}N_3O_3^+$ [M + H$^+$] *m/z* 236.1035, found *m/z* 236.1031.

Dimethyl 2-(2-oxo-1,2,3,4-tetrahydroquinazolin-4-yl)malonate (4f). Following the general procedure, the title compound was obtained as a yellow solid (104 mg, 76%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.55 (s, 3H), 3.62 (s, 3H), 3.72 (d, *J* = 6.6 Hz, 1H), 5.02 (dd, *J* = 6.6, 3.6 Hz, 1H), 6.81 (d, *J* = 7.6 Hz, 1H), 6.85 (d, *J* = 6.4 Hz, 1H), 6.98 (s, 1H), 7.09 (d, *J* = 7.5 Hz, 1H), 7.16 (t, *J* = 7.6 Hz, 1H), 9.27 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 52.4, 52.5, 52.9, 58.3, 114.0, 117.9, 121.0, 126.2, 128.6, 137.9, 153.4, 166.8, 166.9. MS (ESI) calc'd. for $C_{13}H_{15}N_2O_5^+$ [M + H$^+$] *m/z* 279.0981, found *m/z* 279.0984.

Ethyl 2-cyano-2-(2-oxo-1,2,3,4-tetrahydroquinazolin-4-yl)acetate (4g). Following the general procedure (0.3 mmol scale), the title compound was obtained as a yellow oil (81 mg, 90% as a 0.8:1 mixture of diastereomers); ^{1}H NMR (400 MHz, DMSO-d_6, major isomer) δ 1.16 – 1.28 (m, 3H), 4.13 – 4.17 (m, 2H), 4.43 (d, *J* = 3.3 Hz, 1H), 5.13 (t, *J* = 3.3 Hz, 1H), 6.78 (ddd, *J* = 9.3, 8.1, 1.1 Hz, 1H), 6.84 – 6.88 (m, 1H), 6.89 – 6.95 (m, 1H), 7.10 – 7.21 (m, 1H), 7.38 (dd, *J* = 3.5, 2.0 Hz, 1H), 9.30 9.22 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.1, 48.3, 54.5, 63.0, 114.6, 116.0, 116.4, 121.7, 127.0, 129.5, 138.3, 152.9, 164.5. MS (ESI) calc'd. for $C_{13}H_{14}N_3O_3^+$ [M + H$^+$] *m/z* 260.1035, found *m/z* 260.1038.

1-Methyl-4-(nitromethyl)-3,4-dihydroquinazolin-2(1*H*)-one (5a). Following the general procedure (0.2 mmol scale), the title compound was obtained as a white solid (46 mg, 85%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.33 (s, 3H), 4.42 (dd, *J* = 13.4, 4.1 Hz, 1H), 4.62 (dd, *J* = 13.4, 9.3 Hz, 1H), 5.21 (dt, *J* = 9.3, 3.7 Hz, 1H), 6.27 – 6.47 (m, 1H), 6.96 (dd, *J* = 8.4, 1.1 Hz, 1H), 7.06 (td, *J* = 7.4, 1.1 Hz, 1H), 7.10 – 7.15 (m, 1H), 7.36 (ddd, *J* = 8.4, 7.4, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.8, 51.9, 79.7, 113.9, 117.9, 122.9, 126.4, 130.0, 139.2, 154.0. MS (ESI) calc'd. for $C_{10}H_{12}N_3O_3^+$ [M + H$^+$] *m/z* 222.0879, found *m/z* 222.0870.

1-Butyl-4-(nitromethyl)-3,4-dihydroquinazolin-2(1*H*)-one (5b). Following the general procedure (0.2 mmol scale), the title compound was obtained as a white solid (36 mg, 80%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (t, *J* = 7.3 Hz, 3H), 1.37 – 1.50 (m, 2H), 1.55 – 1.80 (m, 2H), 3.61 – 4.07 (m, 2H), 4.43 (ddd, *J* = 13.5, 4.0, 0.6 Hz, 1H), 5.20 (dd, *J* = 9.1, 4.0 Hz, 1H), 6.13 (s, 1H), 6.93 – 6.99 (m, 1H), 7.01 – 7.07 (m, 1H), 7.12 (ddd, *J* = 7.1, 1.6, 0.9 Hz, 1H), 7.39 – 7.31 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 20.1, 29.1, 42.1, 51.7, 79.7, 114.1, 117.7, 122.6, 126.6, 129.8, 137.8, 153.4. MS (ESI) calc'd. for $C_{13}H_{18}N_3O_3^+$ [M + H$^+$] *m/z* 264.1348, found *m/z* 264.1343.

1-Allyl-4-(nitromethyl)-3,4-dihydroquinazolin-2(1*H*)-one (5c). Following the general procedure (0.2 mmol scale), the title compound was obtained as a white solid (25 mg, 72%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.34 – 4.50 (m, 2H), 4.58 – 4.74 (m, 2H), 5.12 – 5.29 (m, 3H), 5.90 (ddt, *J* = 17.3, 10.5, 4.8 Hz, 1H), 6.95 (d, *J* = 8.4 Hz, 1H), 6.35 (s, 1H), 7.04 (td, *J* = 7.5, 1.0 Hz, 1H), 7.12 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.31 (td, *J* = 8.1, 7.3, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 45.3, 52.2, 80.0, 115.1, 117.1, 118.0, 123.1, 126.7, 130.0, 132.8, 138.4, 153.8. MS (ESI) calc'd. for $C_{13}H_{18}N_3O_3^+$ [M + H$^+$] *m/z* 248.1035, found *m/z* 248.1040.

Ethyl 2-(4-(nitromethyl)-2-oxo-3,4-dihydroquinazolin-1(2*H*)-yl)acetate (5d). Following the general procedure (0.1 mmol scale), the title compound was obtained as a white solid (20 mg, 52%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, *J* = 7.1 Hz, 3H), 4.22 (q, *J* = 7.1 Hz, 2H), 4.46 (dd, *J* = 13.8, 4.0 Hz, 1H), 4.60 (d, *J* = 17.9 Hz, 1H), 4.71 – 4.80 (m, 2H), 5.20 (dt, *J* = 9.4, 3.7 Hz, 1H), 6.09 (d, *J* = 3.4 Hz, 1H), 6.75 – 6.81 (m, 1H), 7.08 (td, *J* = 7.5, 1.0 Hz, 1H), 7.15 (ddt, *J* = 7.6, 1.7, 0.5 Hz, 1H), 7.32 (ddd, *J* = 8.3, 7.4, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 44.1, 52.0, 62.0, 79.5, 113.9, 118.5, 123.6, 126.9, 130.2, 138.2, 153.8, 169.1,. MS (ESI) calc'd. for $C_{13}H_{16}N_3O_5^+$ [M + H^+] *m/z* 294.1090, found *m/z* 294.1089.

1-Benzyl-4-(nitromethyl)-3,4-dihydroquinazolin-2(1*H*)-one (5e). Following the general procedure (0.2 mmol scale), the title compound was obtained as a white solid (40 mg, 73%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.47 (dd, *J* = 13.5, 3.9 Hz, 1H), 4.65 (dd, *J* = 13.5, 9.2 Hz, 1H), 5.04 (d, *J* = 16.6 Hz, 1H), 5.20 – 5.33 (m, 2H), 6.40 (s, 1H), 6.83 (dd, *J* = 8.3, 1.0 Hz, 1H), 7.01 (td, *J* = 7.5, 1.0 Hz, 1H), 7.11 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.19 (ddd, *J* = 8.3, 7.4, 1.6 Hz, 1H), 7.22 – 7.28 (m, 2H), 7.28 – 7.36 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.4, 46.9, 52.5, 80.6, 115.6, 118.3, 123.5, 127.0, 127.0, 127.9, 129.5, 120.4, 137.5, 138.7, 154.5. MS (ESI) calc'd. for $C_{16}H_{16}N_3O_3^+$ [M + H^+] *m/z* 298.1192, found *m/z* 298.1186.

1-(4-Methoxybenzyl)-4-(nitromethyl)-3,4-dihydroquinazolin-2(1*H*)-one (5f). Following the general procedure (0.1 mmol scale), the title compound was obtained as a white solid (26 mg, 65%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (s, 3H), 4.46 (dd, *J* = 13.7, 3.8 Hz, 1H), 4.62 (dd, *J* = 13.7, 9.3 Hz, 1H), 5.00 (d, *J* = 16.3 Hz, 1H), 5.17 (d, *J* = 16.3 Hz, 1H), 5.21 – 5.29 (m, 1H),), 6.16 (s, 1H), 6.82 – 6.93 (m, 3H), 7.01 (td, *J* = 7.5, 1.0 Hz, 1H), 7.11 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.16 – 7.24 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 45.7, 51.9, 55.3, 79.9, 114.3, 115.1, 117.6, 122.8, 126.3, 127.7, 128.8, 129.8, 138.0, 153.7, 158.8. MS (ESI) calc'd. for $C_{16}H_{16}N_3O_3^+$ [M + H^+] *m/z* 328.1297, found *m/z* 328.1300.

***meso*-1,1'-(1,3-Phenylenebis(methylene))bis(4-(nitromethyl)-3,4-dihydroquinazolin-2(1*H*)-one) (5g)**. Following the general procedure (0.1 mmol scale), the title compound was obtained as a white solid (20 mg, 55%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.75 – 4.89 (m, 4H), 5.07 – 5.16 (m, 3H), 5.17 – 5.28 (m, 3H), 6.71 – 6.77 (m, 2H), 6.94 – 7.04 (m, 2H), 7.04 – 7.11 (m, 2H), 7.15 – 7.25 (m, 2H), 7.27 – 7.37 (m, 2H), 7.85 7.73 (m, 2H); ^{13}C NMR (100 MHz, DMSO-*d6*) δ 51.8, 81.1, 114.7, 119.0, 122.4, 125.6, 126.9, 127.3, 129.5, 134.5, 138.6, 153.3, 176.6. MS (ESI) calc'd. for $C_{26}H_{25}N_6O_6^+$ [M + H^+] *m/z* 517.1836, found *m/z* 517.1832.

4-Methyl-4-(nitromethyl)-3,4-dihydroquinazolin-2(1H)-one (6). Following the general procedure but on a 0.25 mmol scale and with heating at 150 °C, the title compound was obtained as a white solid (8 mg, 14%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.56 (s, 3H), 4.58 (d, *J* = 11.6 Hz, 1H), 4.83 (d, *J* = 11.6 Hz, 1H), 6.75 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.89 (td, *J* = 7.6, 1.3 Hz, 1H), 7.14 (ddd, *J* = 8.1, 7.3, 1.4 Hz, 1H), 7.19 – 7.23 (m, 1H), 7.31 (dd, *J* = 7.8, 1.4 Hz, 1H), 9.24 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 28.3, 58.0, 85.1, 114.9, 121.6, 122.1, 126.1, 129.7, 137.9, 152.9. MS (ESI) calc´d for $C_{10}H_{12}N_3O_3^+$ [M + H^+] *m/z* 222.0879, found *m/z* 222.0880.

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Synthetic utility of compound 2a.

4-(Aminomethyl)-3,4-dihydroquinazolin-2(1H)-one (7). Compound **2a** (180 mg, 0.87 mmol) in methanol (40 mL) was hydrogenated in the presence of Pd/C (5% on charcoal, 40 mg) for 16 h. Upon full consumption of starting material (as confirmed by TLC, 100% EtOAc, ninhydrin stain), the reaction mixture was filtered through a pad of celite and concentrated *in vacuo* to afford a white solid (153 mg, 99%). The residue was used in the next step without further purification; ^{1}H NMR (400 MHz, CD_3OD) δ 2.70 – 2.97 (m, 2H), 4.42 (t, *J* = 5.6 Hz, 1H), 6.81 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.10 – 7.14 (m, 1H), 7.17 (td, *J* = 7.7, 1.4 Hz, 1H), 7.87 (s, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 49.6, 57.5, 115.4, 120.6, 123.4, 127.3, 129.5, 138.2, 156.9. MS (ESI) calc'd for $C_9H_{12}N_3O^+$ [M + H^+] *m/z* 178.0980, found *m/z* 179.0978.

2-chloro-N-((2-oxo-1,2,3,4-tetrahydroquinazolin-4-yl)methyl)acetamide (8). To a stirred solution of **7** (50.0 mg, 0.28 mmol) in anhydrous dichloromethane (6 mL) at 0 °C was added pyridine (67.0 mg, 0.85 mmol). After 10 min of stirring, chloroacetyl chloride (41.0 mg, 0.37 mmol) was added and the reaction mixture slowly brought to ambient temperature during a period of 30 min. The reaction mixture was stirred for 18 h at ambient temperature, and upon full consumption of starting material (as confirmed by TLC, 8% MeOH in DCM), the volatiles were removed *in vacuo*. The residue was purified by silica gel chromatography to afford 2-chloro-*N*-((2-oxo-1,2,3,4-tetrahydroquinazolin-4-yl)methyl)acetamide as a white solid (52 mg, 73%); ^{1}H NMR (400 MHz, CD_3OD) δ 3.30 – 3.64 (m, 2H), 4.04 (s, 2H), 4.61 (dd, *J* = 7.0, 5.1 Hz, 1H), 6.82 (dd, *J* = 8.0, 1.1 Hz, 1H), 6.97 (td, *J* = 7.5, 1.2 Hz, 1H), 7.13 – 7.16 (m, 1H), 7.19 (td, *J* = 7.7, 1.5 Hz, 1H), 8.33 (d, *J* = 7.4 Hz, 1H) , 7.16 – 7.13 (m, 1H),3.64 3.30 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 41.7, 45.9, 52.9, 113.9, 118.9, 121.9, 126.1, 128.3, 136.7, 155.4, 168.3. MS (ESI) $C_{11}H_{13}ClN_3O_2^+$ [M + H^+] *m/z* 254.0696, found *m/z* 254.0689.

1,2,7,11b-tetrahydro-6*H*-pyrazino[1,2-c]quinazoline-3,6(4*H*)-dione (9). A stirred solution of **8** (25.0 mg, 0.10 mmol), NaI (16.3 mg, 0.11 mmol) and Cs_2CO_3 (96.3, 0.30 mmol) in anhydrous DMF (2 mL) was heated at 65 °C for 2 h. After evaporation of the volatiles, the residue was purified by silica gel chromatography to provide the title compound as a white solid (5 mg, 24%); ^{1}H NMR (400 MHz, CD_3OD) δ 3.36 – 3.46 (m, 1H), 3. 47 – 3.54 (m, 1H), 3.75 (dd, *J* = 18.2, 0.8 Hz, 1H), 4.83 (d, *J* = 18.2 Hz, 1H), 5.01 (dd, *J* = 10.9, 4.0 Hz, 1H), 6.79 – 6.83 (m, 1H), 6.96 – 7.01 (m, 1H), 7.16 – 7.23 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 45.4, 46.7, 53.7, 113.9, 122.1, 125.7, 128.9, 135.8, 147.1, 168.4. MS (ESI) calc'd for $C_{13}H_{15}N_4O_2^+$ [M + MeCN + H^+] *m/z* 259.1195, found *m/z* 259.1200.

Tert-butyl ((2-oxo-1,2,3,4-tetrahydroquinazolin-4-yl)methyl)carbamate (10). To a stirred solution of **7** (30.0 mg, 0.17 mmol) in anhydrous dichloromethane (6 mL) at 0 °C was

added Et_3N (17.0 mg, 0.17 mmol) and the resulting mixture stirred for 5 min. Boc-anhydride (37.0 mg, 0.17 mmol) was then added and the reaction mixture was stirred at ambient temperature for 24 h. Upon full consumption of starting material (as confirmed by TLC, 6% MeOH in DCM), the volatiles were removed *in vacuo* and the residue purified by silica gel chromatography, providing the title compound as a white solid (36 mg, 77%); ^{1}H NMR (400 MHz, CD_3OD) δ 1.35 (s, 9H), 3.13 – 3.17 (m, 2H), 4.37 – 4.55 (m, 1H), 6.70 – 6.86 (m, 1H), 6.86 – 6.98 (m, 1H), 7.00 – 7.25 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 28.5, 46.7, 54.9, 80.1, 115.1, 120.3, 123.0, 127.4, 129.3, 137.9, 156.6. MS (ESI) calc'd for $C_{14}H_{20}N_3O_3^+$ [M + H$^+$] *m/z* 278.1505, found *m/z* 278.1506.

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Author Statement

The authors declare no competing financial interest.

Notes and references

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18. CCDC **1026056** contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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