ChemPubSoc Europe

DOI: 10.1002/ejoc.201800660

EurJOC European Journal of Organic Chemistry

Full Paper

Ullman Reactions

Copper-Catalyzed Self-Condensation of Benzamide: Domino Reactions towards Quinazolinones

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Abstract: We herein report a simple and highly efficient microwave-assisted, copper-catalyzed and ligand-free synthetic method for 2-substituted 4(3*H*)-quinazolinones as domino reaction. This reaction proceeds via self-condensation of substrate (2-bromo/iodo benzamide) in the presence of a strong base and copper catalyst. The substituted quinazolinones were obtained in one-pot reaction by intramolecular cyclization (condensation) via Ullmann–type intermediate. Both the intermediates and quinazolinones were obtained in good yield and can be further used as building blocks for developing the potential novel drug-like compounds.

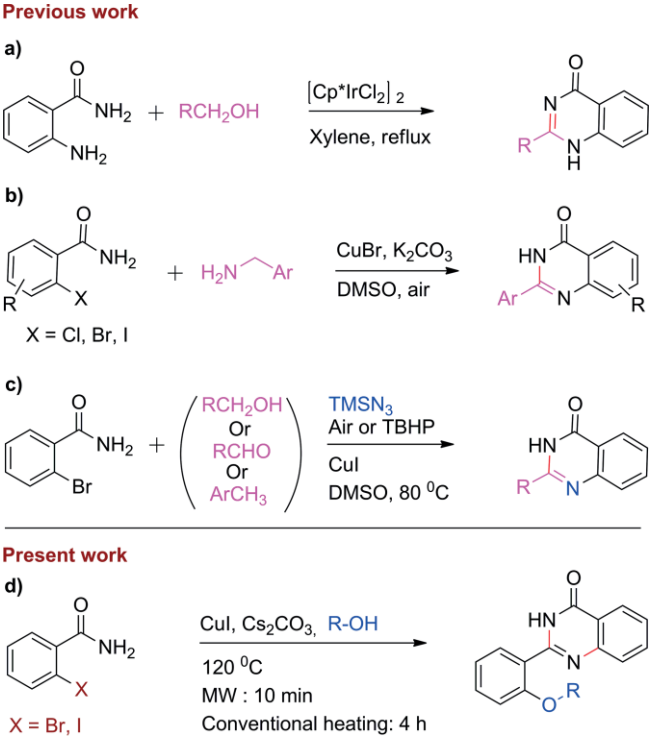
Introduction

Quinazolinones are valuable heterocyclic scaffolds that form the backbone of many biologically active molecules and are widespread in both natural products and pharmaceuticals.[1] They have been assigned as privileged structures in drug development.[2] The quinazolinone derivatives exhibit a wide range of pharmacological activities such as anticancer, anti-microbial, anti-inflammatory, antitubercular, antiviral,[1,3–7] and are core structures in several marketed drugs such as Methaqualone, Etaqualone, Afloqualone, Chloroqualone, Quinethazone, Fluproquazone, Tiacrilast, Raltitrexed etc.[5,6] Additionally, quinazolinones have been used as ligands in the central nervous system (CNS) as a CNS stimulant, analgesic, tranquilizer, and antianxietic etc.[8,9]

The stability of the quinazolinone nucleus towards the oxidation, reduction and hydrolysis reactions has motivated researchers to introduce many bioactive moieties to this nucleus and create new potential medicinal agents. Due to its broad synthetic and medicinal applications of these molecules, there has been much effort directed towards their synthesis.[10]

Over the years several new methodologies have been reported for the synthesis of quinazolinone by using different synthetic approach. However, the catalytic approach offers numerous synthetic benefits over classical approach[11] which includes; shorter reaction times, extended scope and reduced reaction temperatures.[10,12,13] Despite these advances, it has been a challenge to synthesize highly functionalized quinazolinones from easily accessible starting materials and by employing green chemistry techniques.

In 2011, Zhou et al.[14] for the first time demonstrated one-pot base-free domino reaction between primary alcohols and *o*-aminobenzamides via Iridium (Ir) catalyzed dehydrogenation, affording quinazolinones in good yields (Scheme 1a). Similarly,



Scheme 1. Metal catalyzed approach leading to quinazolinone.

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Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under https://doi.org/10.1002/ejoc.201800660.

Xu et al.[15] reported copper-catalyzed domino synthesis of quinazolinone via Ullmann-type coupling by aerobic oxidative C–H amidation (Scheme 1b). In 2016, Upadhyaya et al.[12] reported a one-pot synthesis of 2-substituted quinazolinones by employing ligand and base-free multi-pathway domino strategy with copper(I) iodide (CuI) as catalyst. This methodology provides a novel synthetic approach, utilizing inexpensive and readily available multiform substrates. Further, this one-pot reaction proceeds via multi-pathway coupled self-sequenced domino reaction involving oxidative addition, reductive amination, an intermolecular oxidative nitrogenation of benzylic C(sp^3)–H bond, intramolecular cyclization and oxidative dehydrogenation (Scheme 1c). However, this methodology utilizes *tert*-butyl hydroperoxide (TBHP) as an oxidant and trimethylsilyl azide ($TMSN_3$) as a nitrogen source, which are crucial for the reaction, making this methodology expensive and non-eco-friendly as well as inconvenient.

In recent years, Microwave assisted organic synthesis (MAOS) is preferred over conventional methods and has emerged as a new "lead" with wide applications in chemical synthesis. In comparison to conventional synthetic methods MAOS are simple, clean, fast, efficient, and economic mainly due to its highly accelerated rate of reaction leading to reduction in reaction time with increased yield and purity.[15] Similarly, MAOS technique offers an environmental friendly approach with the wide applications in the field of green chemistry. Further, this technique found to be compatible with almost all kinds of reactions such as heterocyclic synthesis,[16,17] organometallic cross-coupling reactions,[18–22] rearrangement,[23–26] cycloaddition[27,28] etc.

In our current approach, we present a straightforward, mild, economic and environmental friendly microwave assisted copper-catalyzed strategy for the synthesis of 2-substituted 4(3*H*)-quinazolinone derivatives. This reaction proceeds via self-condensation of 2-bromo/iodo benzamides (Scheme 1d). Thus the proposed methodology is very attractive in comparison with the earlier reported methods due to: a) absence of ligand and oxidant, b) use of common substrate (2-bromobenzamide) and c) alcohols acts as solvent as well as the substrate.

Results and Discussion

In the present work, we report a simple and efficient microwave assisted copper-catalyzed novel methodology to synthesize quinazolinone derivatives from 2-bromo/iodo benzamide. This reaction was performed in the presence of a base and different alcohols acting as both solvent and substrate. The preliminary reactions were performed with 0.25 equiv. $Cu(OAc)_2$ and 1.25 equiv. Cs_2CO_3 by varying reaction time and temperature. All the reactions were monitored by TLC. The best results were obtained at 120 °C in 10 min. By maintaining the optimized conditions (time: 10 min and temperature: 120 °C), the optimal stoichiometric ratio of base and catalyst loading with respect to substrate **A** (2-bromobenzamide) was determined. It was observed that the base (Cs_2CO_3) and catalyst [$Cu(OAc)_2$] played a crucial role (entry 16 and 23), and best yields were obtained at 1.25 equiv. of base and 0.1–0.25 equiv. of the copper catalyst (entry 19, 24). Further, the effect of dilution was investigated (Table S5), and it revealed that with the decrease in dilution drastically improved the yield of the desired product **B** (entry 28–32).

By taking the above preliminary optimization results in to an account, we have reported standard preliminary reaction conditions "**a**" (Table S2) and performed further screening of base (Table S6), catalyst (Table S7), solvent (Table S8) and leaving group (Table S9). Screening of eight different bases revealed that organic (entry 38–39) and weak inorganic bases (entry 36–37) resulted in no product, while the product formation was only observed with strong inorganic bases such as NaOH, KOH, and Cs_2CO_3 (entry 33–35). The optimal base performance was observed with Cs_2CO_3 (entry 35). In addition, screening of the catalyst indicated that both Copper **I** and **II** are equally the best catalysts for this transformation (entry 41–46), with $Cu^{I}I$ giving slightly better yields.

Our initial investigation showed that solvent played a crucial role and it also acted as a substrate. Performing the reaction in aprotic non-polar solvents (entry 61–68) resulted in no product formation while the desired product in good yield was obtained in polar solvents like alcohols (entry 53–58). Further, combination of the non-polar aprotic solvent such as 1,2-dichloroethane (DCE) and ethanol decreased the rate of product formation (entry 69–70). In addition, replacement of copper catalysts (entry 48–52) with other oxidants resulted in no product formation. This confirmed that the reaction proceeds via Ullmann-type. Study of different leaving groups (halogens) on substrate **A** (entry 71–76) revealed that iodine gave the best results, followed by bromine, while no product was obtained with chlorine as a substituent. Similarly, the reactions with fluoro and nitro derivatives of substrate **A** resulted in intermediate **C** only (entry 72, 74, 75), with incomplete consumption of the starting material **A**.

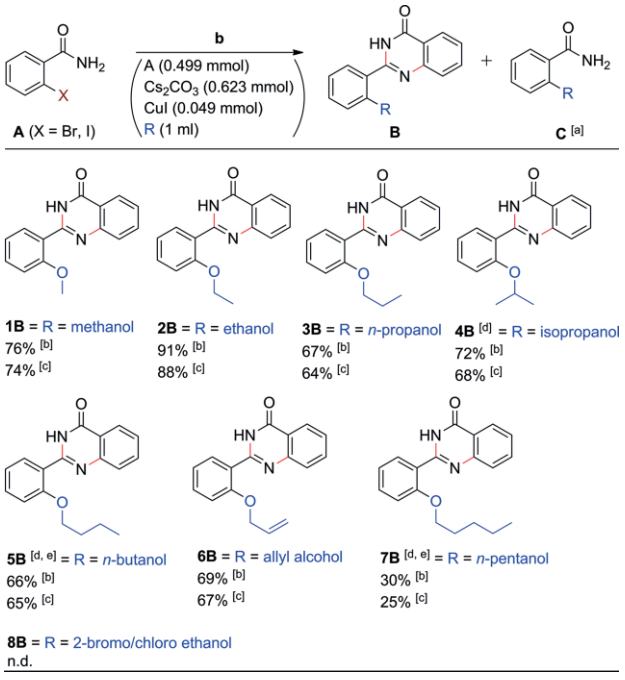
After optimizing the reaction condition "**b**" (Table S2), we also explored the scope of the reaction by using different alcohols as substrates, summarized in Table 1. Furthermore, the reactivity of different substituted 2-bromobenzamide (Substrate **A**) were investigated, revealing that the neutral groups, such as methyl substituents on the *ortho* and *para* positions gave high product yield 92 and 87 % respectively (entry 9 and 10) as presented in Table 2. It is notable that the substrates with electron withdrawing groups (bromo and chloro) afforded good yield (entry 11–13), while moderate yields were presented for substrates with electron donating substituents (entry 14–15).

The structure of the desired compound **6B** (CCDC 1834560) was confirmed by X-ray single crystal diffraction analysis (Figure 1).

Slightly, better yields were obtained when reactions were performed by conventional method (seal tube) as compared to the microwave synthesis (entry 77–83). However, the duration of the reaction time was quite long (4 h) at 120–150 °C (Table S10).

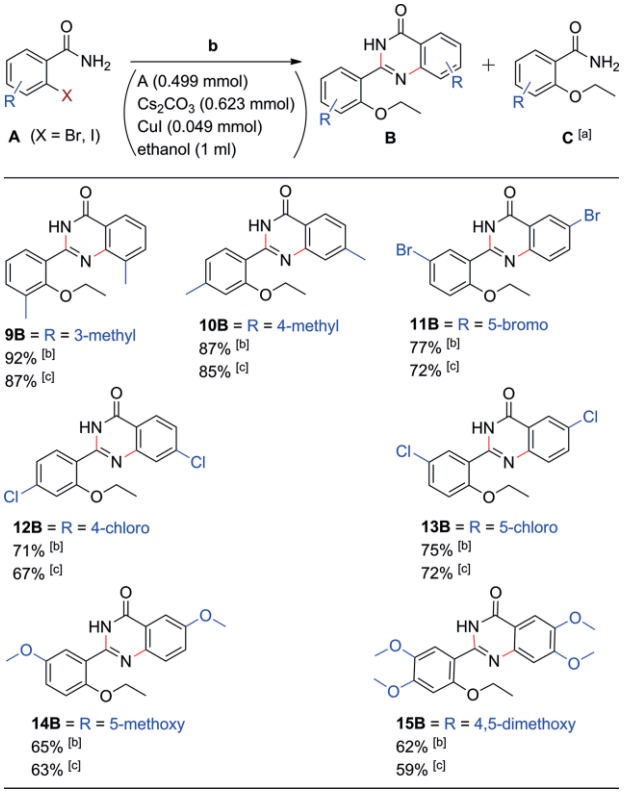
Unlike the conventional heating, the microwave synthesis was rapid (10 min), safer and with minimal solvent requirement.

Table 1. Derivatization using different solvents with optimized reaction condition (**b**).



[a] Detection (by ^{1}H NMR) of **C** (10–20 %) in each reaction. [b] Determined by ^{1}H NMR of crude reaction mixture. [c] Isolated yield. [d] Reaction time 20 min (10 + 10). [e] Water work up, extracted with Dichloromethane. n.d. Not Detected.

Table 2. Derivatization using different substituted 2-bromobenzamides (**A**) with optimized reaction condition (**b**).



[a] Detection (by ^{1}H NMR) of **C** (10–20 %) in each reaction. [b] Determined by ^{1}H NMR of crude reaction mixture. [c] Isolated yield.

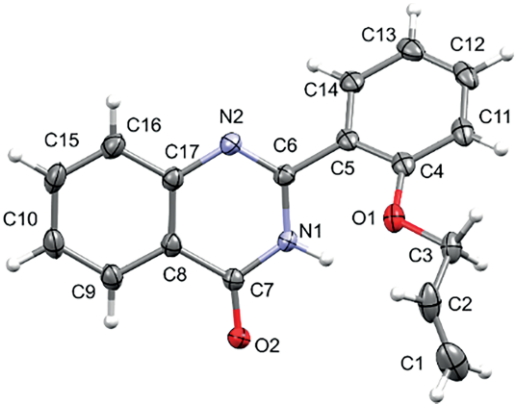
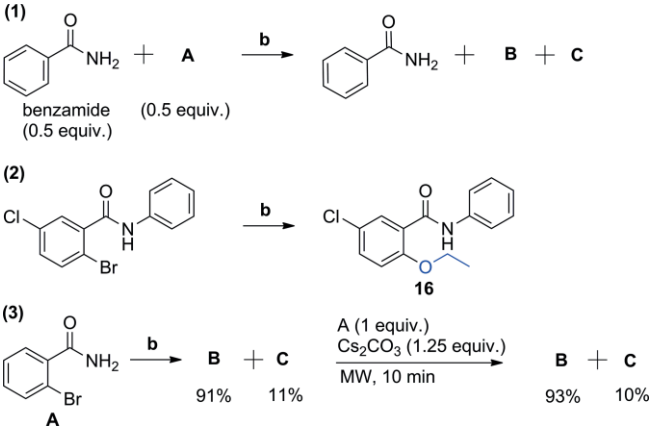


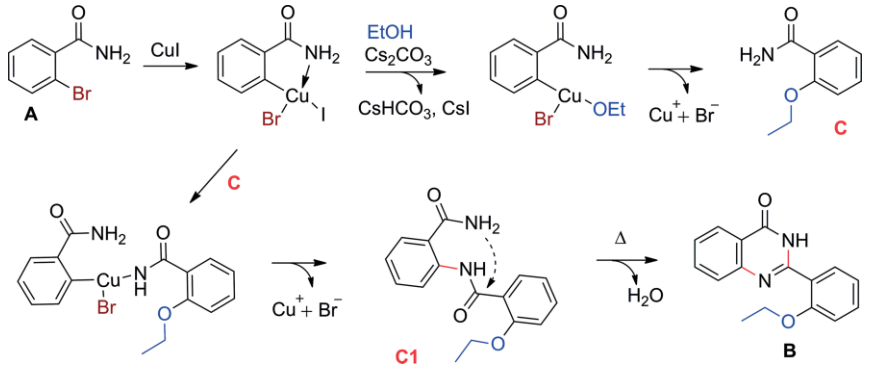
Figure 1. X-ray structure of compound **6B**.

Mechanistic Study/Controlled Reactions

To investigate the plausible reaction mechanism, controlled experiments were carried out with optimized reaction condition "**b**", as shown in Scheme 2. From the reaction of 2-bromobenzamide (substrate **A**) with benzamide resulted in complete consumption of substrate **A**, while the benzamide remained unreacted as shown in reaction Scheme 2-(1). This finding is in support of our assumption i.e. the reaction occurs by self-condensation of 2-bromobenzamide only. In addition, reaction with *N*-phenyl benzamide [Scheme 2-(2)] resulted in intermediate formation only. This further confirms our proposed reaction mechanism is Ullmann-type, where the intermediate **C** acts as a nucleophile resulting in the formation of intermediate **C1**. In addition, the relative rates of formation of intermediates **C** and **C1** were investigated. The reaction with substrate **A** [Scheme 2-(3)] was done under reaction condition "**b**", followed by stepwise excess addition of **A** at regular intervals for the consumption of the intermediate **C**. However, there was no significant increase in the yield ratio of **B** and **C**. Similarly, as mentioned earlier that decreasing the dilution increases the formation of product **B** (Table S5). From these investigations, it is confirmed that the rate of formation of intermediate **C** was faster than **C1**.



Scheme 2. Controlled reactions using optimized reaction condition (**b**) [A (0.499 mmol), Cs_2CO_3 (0.623 mmol), CuI (0.049 mmol), Ethanol (1 mL)]: **1)** 2-bromobenzamide and benzamide as starting material. **2)** 5-chloro, 2-bromo, *N*-phenyl benzamide. **3)** Stepwise addition of 2-bromobenzamide.



Scheme 3. Proposed reaction mechanism.

Proposed Reaction Mechanism

Based on our observations and results obtained, we propose a possible reaction mechanism for the quinazolinone synthesis (Scheme 3). This is a copper-catalyzed self-condensation of 2-bromo/iodo benzamide via Ullmann-type domino reaction. The reaction proceeds by formation of two intermediates C and C1. In case of C, solvent acts as a nucleophile while in case of C1 the intermediate C acts as a nucleophile. The intermediate **C1** further undergoes intramolecular cyclization (condensation) to yield the desired product **B**.

Conclusions

In summary, we have developed a novel synthetic methodology for the synthesis of substituted quinazolinones from cheap and commonly available reagents. To the best of our knowledge, our research group is the first to report one-pot Ullmann-type synthesis of pharmacologically important quinazolinone scaffold from a single substrate (2-bromobenzamide). The scope of this new methodology was further explored to obtain derivatives of quinazolinone by using different solvents. Both the scaffolds quinazolinone (**B**) and intermediate **C** can be used as a building block in developing pharmaceutically important bioactive molecules.[29,30,5] The most attractive feature of this methodology is that it is one-pot synthesis using inexpensive catalysts and single substrate. It is a simple and quick reaction with wide scope for derivatization employing green chemistry methods. This work will certainly attract the attention of researchers as well as industries.

Experimental Section

General Synthetic Procedure: By microwave: All the reagents and solvent were added in microwave reaction tube as per reaction condition "**a**" or "**b**" (Table S2), then reaction was continued in microwave reactor as per set parameters as shown in Table S3. Reaction progress was monitored with TLC in 50 % Ethyl acetate/Hexane or in DCM. **By conventional method:** All the reagents were added in reaction tube (seal tube), resulting reaction mixture heated to 120 °C for 4 h. Reaction progress was monitored with TLC in 50 % Ethyl acetate/hexane or in DCM. Column Purification: Solvent evaporated from reaction mixture on rotary evaporator, residue purified by column chromatography on neutral alumina (pH = 7), in dichloromethane as mobile phase.

2-(2-Methoxyphenyl)quinazolin-4(3*H*)-one (1B):[31,32] White solid, ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 10.94 (br. s, 1 H), 8.57 (dd, *J* = 8.0, 1.5 Hz, 1 H), 8.30 (dd, *J* = 8.0, 1.3 Hz, 1 H), 7.86 (d, *J* = 8.0 Hz, 1 H), 7.77 (t, *J* = 7.6 Hz, 1 H), 7.53 (t, *J* = 8.0 Hz, 1 H), 7.47 (t, *J* = 7.6 Hz, 1 H), 7.18 (t, *J* = 7.6 Hz, 1 H), 7.08 (d, *J* = 8.3 Hz, 1 H), 4.06 (s, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C): δ = 161.4, 158.0, 151.4, 148.0, 134.9, 134.1, 132.3, 127.3, 127.0, 126.8, 122.3, 118.9, 112.1, 56.5 ppm. Mass: HRMS (ESI$^+$) *m/z* for $C_{15}H_{12}N_2O_2$ + Na^+: calcd, 275.0796; found 275.0795.

2-(2-Ethoxyphenyl)quinazolin-4(3*H*)-one (2B):[32] White solid, ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 11.09 (br. s, 1 H), 8.54 (dd, *J* = 8.0, 1.7 Hz, 1 H), 8.30 (dd, *J* = 8.0, 1.1 Hz, 1 H), 7.79 (m, 1 H), 7.76 (m, 1 H), 7.49 (m, 1 H), 7.46 (m, 1 H), 7.16 (t, *J* = 7.7 Hz, 1 H), 7.05 (d, *J* = 8.2 Hz, 1 H), 4.30 (q, *J* = 7.0 Hz, 2 H), 1.60 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C): δ = 161.6, 157.1, 151.0, 149.3, 134.4, 133.2, 131.5, 127.9, 126.5, 126.4, 121.9, 121.4, 112.9, 65.4, 14.6 ppm. Mass: HRMS (ESI$^+$) *m/z* for $C_{16}H_{14}N_2O_2$ + Na^+: calcd, 289.0953; found 289.0962.

2-(2-Propoxyphenyl)quinazolin-4(3*H*)-one (3B): Pale yellow solid, ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 11.06 (br. s, 1 H), 8.48 (dd, *J* = 8.0, 1.7 Hz, 1 H), 8.22 (dd, *J* = 8.0, 1.4 Hz, 1 H), 7.74 (d, *J* = 8.0 Hz, 1 H), 7.69 (dt, *J* = 7.6, 1.5 Hz, 1 H), 7.42 (dt, *J* = 8.0, 1.7 Hz, 1 H), 7.39 (dt, *J* = 7.5, 1.4 Hz, 1 H), 7.08 (t, *J* = 7.7 Hz, 1 H), 6.98 (d, *J* = 8.4 Hz, 1 H), 4.11 (t, *J* = 6.5 Hz, 2 H), 1.93 (q, *J* = 7.0 Hz, 2 H), 1.09 (t, *J* = 7.4 Hz, 3 H), ppm. ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C): δ = 161.8, 157.5, 151.1, 149.3, 134.5, 133.3, 131.5, 127.8, 126.5, 126.5, 121.8, 121.2, 119.8, 112.9, 71.2, 22.5, 10.7 ppm. Mass: HRMS (ESI$^+$) *m/z* for $C_{17}H_{16}N_2O_2$ + H^+: calcd, 281.1290; found 281.1288.

2-(2-Isopropoxyphenyl)quinazolin-4(3*H*)-one (4B): Pale yellow solid, ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 11.23 (br. s, 1 H), 8.61 (d, *J* = 7.5 Hz, 1 H), 8.30 (d, *J* = 7.8 Hz, 1 H), 7.92 (d, *J* = 7.6 Hz, 1 H), 7.77 (t, *J* = 7.4 Hz, 1 H), 7.50 (t, *J* = 7.8 Hz, 1 H), 7.47 (t, *J* = 7.5 Hz, 1 H), 7.17 (t, *J* = 7.4 Hz, 1 H), 7.07 (d, *J* = 8.2 Hz, 1 H), 4.81 (m, 1 H), 1.51 (d, *J* = 6.0 Hz, 6 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C): δ = 161.3, 156.5, 151.4, 148.4, 134.8, 133.6, 131.9, 127.5, 126.8, 126.6, 122.1, 121.1, 119.8, 114.9, 73.3, 22.4 ppm. Mass: HRMS (ESI$^+$) *m/z* for $C_{17}H_{16}N_2O_2$ + Na^+: calcd, 303.1109; found 303.1113.

2-(2-Butoxyphenyl)quinazolin-4(3*H*)-one (5B): Yellow solid, ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 11.23 (br. s, 1 H), 8.76 (d, *J* = 8.0 Hz, 1 H), 8.30 (d, *J* = 8.0 Hz, 1 H), 8.24 (d, *J* = 6.0 Hz, 1 H), 7.83 (t, *J* = 7.5 Hz, 1 H), 7.57 (t, *J* = 8.0 Hz, 1 H), 7.53 (m, 1 H), 7.24 (t, *J* = 7.6 Hz, 1 H), 7.09 (d, *J* = 8.4 Hz, 1 H), 4.25 (t, *J* = 6.5 Hz, 2 H), 1.97 (m, 2 H), 1.59 (m, 2 H), 1.04 (t, *J* = 7.4 Hz, 3 H) ppm. ^{13}C NMR

(400 MHz, $CDCl_3$, 25 °C): δ = 160.5, 157.8, 146.0, 135.2, 134.8, 132.3, 127.3, 126.5, 126.0, 122.2, 120.4, 116.8, 113.0, 69.8, 31.0, 19.2, 14.0 ppm. Mass: HRMS (ESI^+) *m/z* for $C_{18}H_{18}N_2O_2$ + H^+: calcd, 295.1447; found 295.1445.

2-[2-(Allyloxy)phenyl]quinazolin-4(3*H*)-one (6B): White solid (crystal), ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 11.04 (br. s, 1 H), 8.43 (dd, *J* = 8.0, 1.6 Hz, 1 H), 8.25 (d, *J* = 8.0 Hz, 1 H), 7.73 (m, 2 H), 7.41 (m, 2 H), 7.09 (t, *J* = 7.6 Hz, 1 H), 6.98 (d, *J* = 8.3 Hz, 1 H), 6.08 (m, 1 H), 5.45 (d, *J* = 17.2 Hz, 1 H), 5.36 (d, *J* = 10.5 Hz, 1 H), 4.71 (d, *J* = 5.2 Hz, 2 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C): δ = 161.7, 156.7, 150.8, 149.3, 134.4, 133.0, 131.6, 131.5, 127.7, 126.4, 126.3, 121.9, 121.1, 120.2, 119.2, 113.2, 70.0 ppm. Mass: HRMS (ESI^+) *m/z* for $C_{17}H_{14}N_2O_2$ + Na^+: calcd, 301.0953; found 301.0959.

2-[2-(Pentyloxy)phenyl]quinazolin-4(3*H*)-one (7B): Semisolid, ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 11.03 (br. s, 1 H), 8.49 (dd, *J* = 8.0, 1.9 Hz, 1 H), 8.23 (d, *J* = 8.0 Hz, 1 H), 7.71 (m, 1 H), 7.69 (m, 1 H), 7.42 (m, 1 H), 7.38 (m, 1 H), 7.09 (t, *J* = 7.6 Hz, 1 H), 6.99 (d, *J* = 8.4 Hz, 1 H), 4.16 (t, *J* = 6.7 Hz, 2 H), 1.92 (m, 2 H), 1.48 (m, 2 H), 1.38 (m, 2 H), 0.98 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C): δ = 161.5, 157.4, 151.3, 149.0, 134.2, 132.9, 131.5, 127.8, 126.4, 126.2, 121.6, 121.4, 120.2, 112.7, 69.6, 28.6, 22.2, 22.3, 13.8 ppm. Mass: HRMS (ESI^+) *m/z* for $C_{17}H_{14}N_2O_2$ + H^+: calcd, 309.1603; found 309.1605.

2-(2-Ethoxy-3-methylphenyl)-8-methylquinazolin-4(3*H*)-one (9B): White solid, ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 10.88 (br. s, 1 H), 8.19 (dd, *J* = 7.0, 1.6 Hz, 1 H), 8.09 (dd, *J* = 8.0, 1.3 Hz, 1 H), 7.54 (d, *J* = 7.4 Hz, 1 H), 7.28 (t, *J* = 7.6 Hz, 1 H), 7.28 (d, *J* = 7.5 Hz, 1 H), 7.13 (t, *J* = 7.7 Hz, 1 H), 3.85 (q, *J* = 7.1 Hz, 2 H), 2.63 (s, 3 H), 2.29 (s, 3 H), 1.40 (t, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C): δ = 162.2, 155.9, 149.6, 147.8, 136.4, 135.1, 134.8, 132.4, 129.1, 126.2, 125.2, 125.0, 124.1, 121.4, 70.8, 17.7, 16.1, 15.5 ppm. Mass: HRMS (ESI^+) *m/z* for $C_{18}H_{18}N_2O_2$ + Na^+: calcd, 317.1266; found 317.1265.

2-(2-Ethoxy-4-methylphenyl)-7-methylquinazolin-4(3*H*)-one (10B): Pale yellow solid, ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 11.01 (br. s, 1 H), 8.34 (d, *J* = 8.0 Hz, 1 H), 8.09 (d, *J* = 8.0 Hz, 1 H), 7.52 (s, 1 H), 7.18 (d, *J* = 8.0 Hz, 1 H), 6.87 (d, *J* = 8.0 Hz, 1 H), 6.75 (s, 1 H), 4.19 (q, *J* = 7.0 Hz, 2 H), 2.43 (s, 3 H), 2.33 (s, 3 H), 1.52 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C): δ = 161.8, 157.2, 151.2, 149.4, 145.4, 144.2, 131.3, 127.9, 127.3, 126.2, 122.7, 118.7, 117.1, 113.6, 65.2, 22.0, 21.9, 14.8 ppm. Mass: HRMS (ESI^+) *m/z* for $C_{18}H_{18}N_2O_2$ + Na^+: calcd, 317.1266; found 317.1271.

6-Bromo-2-(5-bromo-2-ethoxyphenyl)quinazolin-4(3*H*)-one (11B): White solid, ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 11.04 (br. s, 1 H), 8.60 (d, *J* = 2.5 Hz, 1 H), 8.34 (d, *J* = 2.3 Hz, 1 H), 7.78 (dd, *J* = 8.6, 1.3 Hz, 1 H), 7.60 (d, *J* = 8.6 Hz, 1 H), 7.52 (dd, *J* = 9.0, 2.5 Hz, 1 H), 6.87 (d, *J* = 9.0 Hz, 1 H), 4.23 (q, *J* = 7.0 Hz, 2 H), 1.55 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C): δ = 160.5, 156.4, 149.9, 148.0, 137.9, 136.0, 134.0, 129.8, 129.1, 122.7, 121.3, 120.5, 114.9, 114.5, 65.9, 14.7 ppm. Mass: HRMS (ESI^+) *m/z* for $C_{16}H_{12}N_2O_2$ + Na^+: calcd, 444.9163; found 444.9169.

7-Chloro-2-(4-chloro-2-ethoxyphenyl)quinazolin-4(3*H*)-one (12B): White solid, ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 10.96 (br. s, 1 H), 8.42 (d, *J* = 8.0 Hz, 1 H), 8.13 (d, *J* = 8.6 Hz, 1 H), 7.72 (s, 1 H), 7.34 (d, *J* = 8.4 Hz, 1 H), 7.07 (d, *J* = 8.0 Hz, 1 H), 6.98 (s, 1 H), 4.2 (q, *J* = 6.6 Hz, 2 H), 1.56 (t, *J* = 6.6 Hz, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C): δ = 161.0, 157.7, 151.3, 149.9, 140.9, 139.5, 132.8, 128.0, 127.3, 127.2, 122.3, 119.7, 117.9, 113.6, 66.0, 14.7 ppm. Mass: HRMS (ESI^+) *m/z* for $C_{16}H_{12}N_2O_2Cl_2$ + Na^+: calcd, 357.0174; found 357.0179.

6-Chloro-2-(5-chloro-2-ethoxyphenyl)quinazolin-4(3*H*)-one (13B): White Solid, ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 11.09 (br. s, 1 H), 8.43 (d, *J* = 2.4 Hz, 1 H), 8.16 (s, 1 H), 7.65 (d, *J* = 8.7 Hz, 1 H), 7.62 (dd, *J* = 8.8, 2.5 Hz, 1 H), 7.36 (dd, *J* = 8.8, 2.5 Hz, 1 H), 6.92 (d, *J* = 8.9 Hz, 1 H), 4.22 (q, *J* = 7.0 Hz, 2 H), 1.53 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C): δ = 160.7, 155.9, 149.9, 147.7, 135.1, 133.0, 132.6, 131.0, 129.6, 127.3, 125.9, 122.4, 121.0, 114.5, 65.9, 14.7 ppm. Mass: HRMS (ESI^+) *m/z* for $C_{16}H_{12}N_2O_2Cl_2$ + Na^+: calcd, 357.0174; found 357.0178.

2-(2-Ethoxy-5-methoxyphenyl)-6-methoxyquinazolin-4(3*H*)-one (14B): Yellow solid, ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 11.18 (br. s, 1 H), 8.00 (d, *J* = 2.5 Hz, 1 H), 7.96 (dd, *J* = 9.0, 2.7 Hz, 1 H), 7.71 (d, *J* = 8.5 Hz, 1 H), 7.59 (d, *J* = 2.7 Hz, 1 H), 7.30 (dd, *J* = 8.8, 2.9 Hz, 1 H), 6.91 (d, *J* = 9.0 Hz, 1 H), 4.16 (q, *J* = 6.9 Hz, 2 H), 3.86 (s, 3 H), 3.82 (s, 3 H), 1.50 (t, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C): δ = 161.5, 158.4, 154.3, 151.4, 148.8, 143.7, 129.3, 124.9, 120.6, 119.6, 115.0, 114.5, 105.9, 66.1, 56.0, 55.9, 14.9 ppm. Mass: HRMS (ESI^+) *m/z* for $C_{18}H_{18}N_2O_4$ + Na^+: calcd, 349.1164; found 349.1167.

2-(2-Ethoxy-4,5-dimethoxyphenyl)-6,7-dimethoxyquinazolin-4(3*H*)-one (15B): Yellow solid, ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 11.01 (br. s, 1 H), 7.95 (s, 1 H), 7.51 (s, 1 H), 7.15 (s, 1 H), 6.48 (s, 1 H), 4.18 (q, *J* = 7.0 Hz, 2 H), 3.95 (s, 3 H), 3.92 (s, 3 H), 3.91 (s, 3 H), 3.87 (s, 3 H), 1.51 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C): δ = 161.1, 155.1, 152.8, 152.4, 149.7, 148.7, 145.5, 144.0, 114.2, 112.4, 111.4, 107.9, 105.4, 98.3, 66.5, 56.5, 56.3, 56.3, 56.2, 14.9 ppm. Mass: HRMS (ESI^+) *m/z* for $C_{20}H_{22}N_2O_6$ + Na^+: calcd, 409.1376; found 409.1378.

2-Methoxybenzamide (1C):[34,35] White solid, ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.12 (dd, *J* = 8.0, 1.5 Hz, 1 H), 7.66 (br. s, 1 H), 7.39 (t, *J* = 8.0 Hz, 1 H), 6.99 (t, *J* = 7.6 Hz, 1 H), 6.90 (d, *J* = 8.2 Hz, 1 H), 6.43 (br. s, 1 H), 3.87 (s, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C): δ = 167.3, 157.9, 133.4, 132.5, 121.2, 111.4, 77.4, 77.1, 76.8, 55.9 ppm. Mass: HRMS (ESI^+) *m/z* for $C_8H_9NO_2$ + Na^+: calcd, 174.0531; found 174.0532.

2-Ethoxybenzamide (2C):[36] White solid, ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.15 (dd, *J* = 8.0, 1.9 Hz, 1 H), 7.80 (br. s, 1 H), 7.38 (dt, *J* = 8.0, 1.9 Hz, 1 H), 6.99 (t, *J* = 7.6 Hz, 1 H), 6.89 (d, *J* = 8.5 Hz, 1 H), 6.08 (br. s, 1 H), 4.13 (q, *J* = 7.0 Hz, 2 H), 1.44 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C): δ = 167.3, 157.4, 133.4, 132.6, 121.2, 112.4, 77.3, 64.8, 14.9 ppm. Mass: HRMS (ESI^+) *m/z* for $C_9H_{11}NO_2$ + Na^+: calcd, 188.0687; found 188.0688.

2-Propoxybenzamide (3C):[33] Pale yellow solid, ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.13 (dd, *J* = 8.0, 2.0 Hz, 1 H), 7.78 (br. s, 1 H), 7.37 (dt, *J* = 7.8, 1.9 Hz, 1 H), 6.98 (dt, *J* = 7.6, 1.0 Hz, 1 H), 6.89 (d, *J* = 8.2 Hz, 1 H), 6.35 (br. s, 1 H), 4.01 (t, *J* = 6.5 Hz, 2 H), 1.82 (m, 2 H), 1.00 (t, *J* = 7.5 Hz, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C): δ = 167.4, 157.5, 133.4, 132.6, 121.1, 120.9, 112.4, 70.7, 22.6, 10.7 ppm. Mass: HRMS (ESI^+) *m/z* for $C_{10}H_{13}NO_2$ + Na^+: calcd, 202.0844; found 202.0839.

2-Isopropoxybenzamide (4C):[36] White solid, ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.13 (dd, *J* = 7.5, 2.0 Hz, 1 H), 7.86 (br. s, 1 H), 7.35 (dt, *J* = 7.9, 1.9 Hz, 1 H), 6.96 (t, *J* = 7.6 Hz, 1 H), 6.89 (d, *J* = 8.4 Hz, 1 H), 6.35 (br. s, 1 H), 4.67 (m, 1 H), 1.34 (d, *J* = 6.0 Hz, 6 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C): δ = 167.6, 156.3, 133.3, 132.7, 121.2, 113.8, 71.9, 22.2 ppm. Mass: HRMS (ESI^+) *m/z* for $C_{10}H_{13}NO_2$ + Na^+: calcd, 202.0844; found 202.0840 $[M + Na]^+$. ***Note:*** *reaction was incomplete.*

2-Butoxybenzamide (5C):[33] Pale yellow solid, ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.13 (dd, *J* = 8.0, 2.0 Hz, 1 H), 7.77 (br. s, 1 H), 7.36 (dt, *J* = 8.0, 2.0 Hz, 1 H), 6.97 (t, *J* = 7.5 Hz, 1 H), 6.89 (d, *J* =

8.2 Hz, 1 H), 6.47 (br. s, 1 H), 4.04 (t, *J* = 6.6 Hz, 2 H), 1.77 (m, 2 H), 1.43 (m, 2 H), 0.92 (t, *J* = 7.4 Hz, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C): δ = 167.6, 157.5, 133.3, 132.5, 121.0, 120.9, 112.3, 68.8, 31.2, 19.4, 13.8 ppm. Mass: HRMS (ESI$^+$) *m/z* for $C_{11}H_{15}NO_2$ + Na^+: calcd, 216.1000; found 216.0997.

2-(Allyloxy)benzamide (6C): Yellow solid, ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.13 (d, *J* = 7.5 Hz, 1 H), 7.72 (br. s, 1 H), 7.36 (t, *J* = 8.0 Hz, 1 H), 6.99 (t, *J* = 7.5 Hz, 1 H), 6.89 (d, *J* = 8.4 Hz, 1 H), 6.38 (br. s, 1 H), 6.01 (m, 1 H), 5.32 (m, 2 H), 4.60 (d, *J* = 5.5 Hz, 2 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C): δ = 167.4, 157.0, 133.3, 132.5, 132.1, 121.4, 119.3, 112.7, 77.4, 77.1, 76.8, 69.9 ppm. Mass: HRMS (ESI$^+$) *m/z* for $C_{10}H_{11}NO_2$ + Na^+: calcd, 200.0687; found 200.0683.

2-(Pentyloxy)benzamide (7C): White solid, ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.14 (dd, *J* = 8.0, 2.0 Hz, 1 H), 7.77 (br. s, 1 H), 7.37 (dt, *J* = 8.0, 2.0 Hz, 1 H), 6.99 (t, *J* = 7.6 Hz, 1 H), 6.89 (d, *J* = 8.2 Hz, 1 H), 6.10 (br. s, 1 H), 4.05 (t, *J* = 6.6 Hz, 2 H), 1.80 (m, 2 H), 1.37 (m, 4 H), 0.87 (t, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C): δ = 167.3, 157.5, 133.3, 132.6, 121.1, 120.9, 112.4, 69.2, 28.9, 28.3, 22.4, 14.0 ppm. Mass: HRMS (ESI$^+$) *m/z* for $C_{12}H_{17}NO_2$ + Na^+: calcd, 230.1157; found 230.1158.

2-Ethoxy-3-methylbenzamide (9C):[37] ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.82 (d, *J* = 8.0 Hz, 1 H), 7.66 (br. s, 1 H), 7.25 (d, *J* = 7.3 Hz, 1 H), 7.04 (t, *J* = 7.6 Hz, 1 H), 5.97 (br. s, 1 H), 3.86 (q, *J* = 7.0 Hz, 2 H), 2.24 (s, 3 H), 1.35 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C): δ = 168.1, 155.8, 134.8, 132.0, 129.4, 126.1, 124.3, 70.3, 16.0, 15.6 ppm.

2-Ethoxy-4-methylbenzamide (10C): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.02 (d, *J* = 8.0 Hz, 1 H), 7.77 (br. s, 1 H), 6.81 (d, *J* = 8.0 Hz, 1 H), 6.69 (s, 1 H), 5.95 (br. s, 1 H), 4.11 (q, *J* = 7.0 Hz, 2 H), 2.31 (s, 3 H), 1.43 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C): δ = 167.4, 157.3, 144.2, 132.6, 122.2, 118.1, 113.3, 64.6, 22.0, 15.1 ppm.

5-Bromo-2-ethoxybenzamide (11C):[38] ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.23 (d, *J* = 2.0 Hz, 1 H), 7.71 (br. s, 1 H), 7.45 (dd, *J* = 8.6, 2.5 Hz, 1 H), 6.77 (d, *J* = 8.8 Hz, 1 H), 6.16 (br. s, 1 H), 4.11 (q, *J* = 7.0 Hz, 2 H), 1.44 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C): δ = 165.8, 156.2, 135.8, 135.1, 122.5, 114.2, 113.4, 65.2, 14.8 ppm.

4-Chloro-2-ethoxybenzamide (12C): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.06 (d, *J* = 7.0 Hz, 1 H), 7.64 (br. s, 1 H), 6.96 (s, 1 H), 6.89 (s, 1 H), 6.08 (br. s, 1 H), 4.12 (q, *J* = 7.0 Hz, 2 H), 1.45 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C): δ = 166.2, 157.7, 139.2, 133.7, 121.4, 119.1, 112.9, 65.4, 14.6 ppm.

5-Chloro-2-ethoxybenzamide (13C): White Solid, ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.10 (d, *J* = 2.4 Hz, 1 H), 7.73 (br. s, 1 H), 7.31 (dd, *J* = 8.8, 2.5 Hz, 1 H), 6.83 (d, *J* = 8.9 Hz, 1 H), 6.00 (br. s, 1 H), 4.11 (q, *J* = 7.0 Hz, 2 H), 1.44 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C): δ = 165.8, 155.8, 133.0, 132.3, 126.6, 122.4, 114.5, 65.4, 14.8 ppm.

2-Ethoxy-5-methoxybenzamide (14C): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.93 (br. s, 1 H), 7.84 (d, *J* = 9.0 Hz, 1 H), 7.68 (d, *J* = 3.2 Hz, 1 H), 7.66 (d, *J* = 8.9 Hz, 1 H), 6.10 (br. s, 1 H), 4.08 (q, *J* = 7.0 Hz, 2 H), 3.75 (s, 3 H), 1.41 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C): δ = 167.0, 153.7, 151.4, 129.4, 121.2, 115.4, 114.0, 65.4, 55.9, 15.0 ppm.

2-Ethoxy-4,5-dimethoxybenzamide (15C): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.79 (br. s, 1 H), 7.64 (s, 1 H), 6.44 (s, 1 H), 6.16 (br. s, 1 H), 4.10 (q, *J* = 7.0 Hz, 2 H), 3.84 (s, 3 H), 3.82 (s, 3 H), 1.42 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C): δ = 167.1, 152.7, 143.2, 113.8, 112.5, 97.6, 65.7, 56.0, 15.0 ppm.

5-Chloro-2-ethoxy-*N*-phenylbenzamide (16): White solid, ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 9.95 (s, 1 H), 8.19 (d, *J* = 2.9 Hz, 1 H), 7.58 (d, *J* = 8.1 Hz, 2 H), 7.33–7.27 (m, 3 H), 7.06 (t, *J* = 7.5 Hz, 1 H), 6.86 (d, *J* = 8.7 Hz, 1 H), 4.18 (q, *J* = 7.0 Hz, 2 H), 1.56 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C): δ = 161.8, 155.1, 138.2, 132.7, 132.1, 129.1, 126.9, 124.3, 123.0, 120.0, 113.9, 65.5, 14.8, ppm. Mass: HRMS (ESI$^+$) *m/z* for $C_{15}H_{14}NO_2Cl$ + Na^+: calcd, 298.0611; found 298.0612.

CCDC 1834560 (for **6B**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

Acknowledgments

The authors wish to thank College of Health Science (CHS), UKZN (Westville campus) and National Research Foundation (NRF), South Africa (Grant No. 99546, 103728 and 112079) for financial support. Authors would like to acknowledge Mr Sizwe Zamisa for X-RAY crystal structure analysis and Ms Caryl K. A. Janse van Rensburg and Mr Craig Grimmer from School of Chemistry, University of KwaZulu-Natal (PMB campus), Pietermaritzburg, South Africa for HRMS and NMR analysis.

Keywords: Nitrogen heterocycles · Domino reactions · Synthetic methods · Homogeneous catalysis · Copper

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Received: April 28, 2018

Ullman Reactions

New synthetic method is developed to prepare 2-substituted 4(3*H*)-Quinazolinone using green chemistry technique. It is oxidant and ligand-free, copper-catalysed self-condensation of 2-halobenzamide.

DOI: 10.1002/ejoc.201800660