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Synthesis of Quinazolin-4-ones by Copper-Catalyzed Isocyanide Insertion

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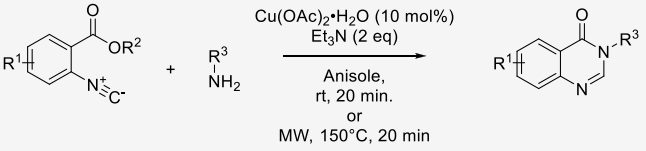
ABSTRACT: Herein, we report a novel copper-catalyzed imidoylative cross-coupling/cyclocondensation reaction between 2-isocyanobenzoates and amines efficiently producing quinazolin-4-ones. The reaction utilizes Cu(II) acetate as an environmentally benign catalyst in combination with a mild base and proceeds well in anisole, a recommended, sustainable solvent. Additionally, the reaction does not require dry conditions or inert atmospheres for optimal performance. The scope of this isocyanide insertion reaction is rather broad, tolerating various functionalized isocyanobenzoates and a range of substituted amines, although the use of aromatic amines as nucleophiles requires microwave heating.



INTRODUCTION

There are significant economic and sustainability incentives to replace the current transition-metal catalysts in isocyanide insertion processes with cheaper and more abundant base metals (e.g., iron, nickel, and copper).[1] Although the reactivity of isocyanides in copper catalysis has long been known,[2] isocyanide insertions using base metals are still underrepresented in the literature.[1] The copper-catalyzed reactions involving isocyanides toward N-containing heterocycles reported to date proceed under strong alkaline conditions[3] or involve otherwise rather harsh conditions under an inert atmosphere (Scheme 1),[3b,4a,b] though a notable exception was reported by us for isothiourea synthesis.[4c] Thus, there is a clear need for an efficient synthetic methodology that involves base metals such as copper-catalyzed isocyanide insertion processes to produce high-value products in a sustainable fashion.

Quinazolin-4-ones **3** can be considered a privileged structure, prevalent in natural compounds.[5] The quinazolin-4-one core can also be found in pharmaceuticals demonstrating hypnotic,[6] antifungal,[7] anticonvulsant,[8] kinase inhibitory,[9] or antimalarial[10] activity (Figure 1). Synthetic approaches, including methodology involving Pd-catalyzed isocyanide insertion, to access these high-valued heterocycles receive quite some attention.[11] We envisioned a robust transformation that takes advantage of economically more viable copper(II)-based catalytic systems combining isocyanobenzoates **1** and amines to access 3-substituted quinazolin-4-ones **3** (Scheme 1b).

RESULTS AND DISCUSSION

We started our studies by employing the conditions developed by Hong et al.,[3b,c] who utilized CuI under strongly basic conditions in a related reaction of aryl isocyanides to prepare the corresponding formimidates. However, under these conditions, the benchmark reaction of isocyanobenzoate **1a** and aniline **2a** gave only moderate formation of the product **3a** in various solvents (Table 1, entries 1−3). We quickly found that this transformation is more successful using Cu(II) acetate as the catalyst and the milder Et_3N as the base (entries 4−5). Other bases did not lead to a higher yield of the target quinazolinone **3a** regardless of their pK_a (entries 6−14). When we switched to the use of the recommended solvent anisole as an alternative to dimethylformamide (DMF), the isolated yield of **3a** improved a bit further (entry 17). Satisfyingly, use of Cu(II) acetate hydrate as a catalyst under an air atmosphere leads to only trace amounts of *N*-formyl anthranilate and ethyl anthranilate at elevated temperatures. In short, the reaction was optimized to afford the quinazolin-4-one **3a** using a benign catalyst and short reaction times under an air atmosphere in a green, recommended solvent.[12]

Next, we set out to investigate the scope of this reaction toward 3-arylated 4-quinazolinones **3** (Scheme 2).

The efficacy of utilizing anilines as coupling partners in this transformation correlates directly with their respective electron density. While the use of aniline and toluidines as well as 4-halogenated anilines led to formation of quinazolines **3a−d,g** in moderate to good yields, the application of m- or p-halogenated anilines afforded quinazolinones **3e** and **3h** in significantly lower yields. 2,6-Dichloroaniline did not afford

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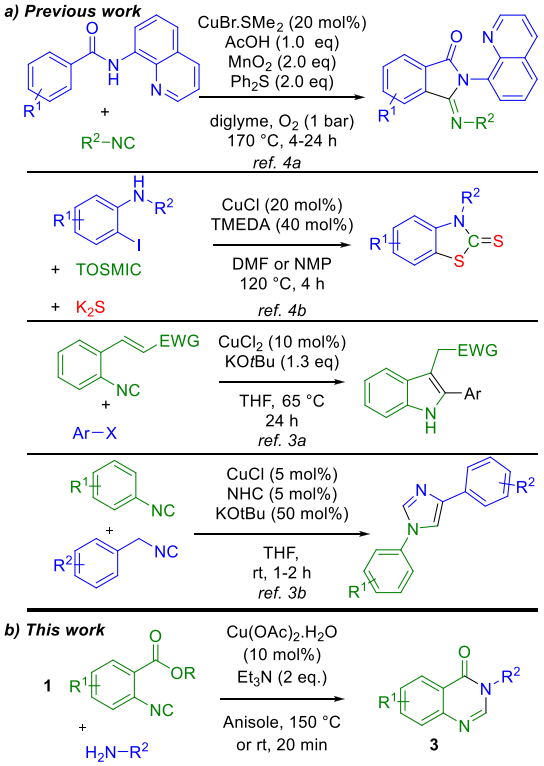
Scheme 1. Copper-Catalyzed Reactions with Isocyanides toward N-Containing Heterocycles



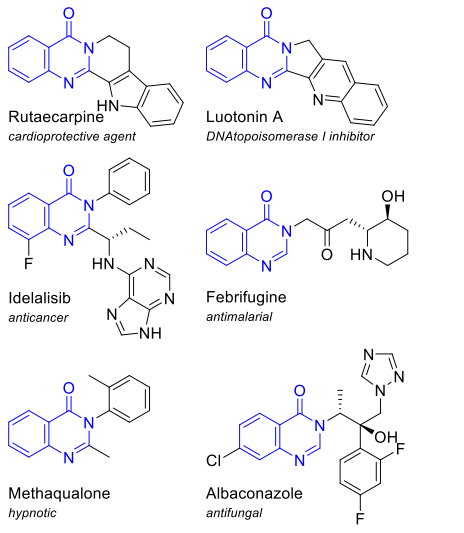
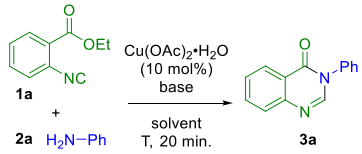


Figure 1. Selected natural products and pharmaceuticals bearing a quinazolin-4-one core.

any of the corresponding quinazolinone **3f**. The isolation of **3i** from anthranilic isocyanide and mesityl amine in a moderate yield indicated that the reaction can still proceed when sterically cumbersome anilines are employed. Curiously, use of the heteroaromatic 2-aminopyridine increased the yield to 71% (**3j**). Most likely, the additional coordination site provided by the more electron-deficient pyridine functionality is responsible for the observed higher reactivity. This is supported by the formation of quinazolinone **3k** in 90% yield when using 2-aminopyrazine. The use of 4-aminopyridine as a nucleophile did not furnish the corresponding quinazolinone **3m**, further corroborating this hypothesis. Finally, we were pleased to

Table 1. Optimization of the Reaction between Ethyl 2-Isocyanobenzoate and Aniline[a]



Entry	Solvent	T (°C)	Base (eq.)	**3a** (%)[b]
1[c]	THF	100	KO*t*Bu (1.0)	14
2[c]	DMC	100	KO*t*Bu (1.0)	15
3[c]	DMF	100	KO*t*Bu (1.0)	47
4	Dioxane	100	Et_3N (10)	76
5	DMF	150	Et_3N (10)	85
6	DMF	150	DMAP (10)	39
7	DMF	150	DBU (10)	29
8	DMF	150	DIPEA (10)	67
9	DMF	150	Pyridine (10)	59
10	DMF	150	K_3PO_4 (10)	35
11	DMF	150	K_2CO_3 (10)	16
12	DMF	150	Cs_2CO_3 (10)	Trace
13	DMF	150	NaOH (10)	Trace[d]
14	DMF	150	Et_3N (2)	76
15	Dioxane	150	Et_3N (2)	68
16	DCE	150	Et_3N (2)	0
17	**MeOPh**	**150**	**Et_3N (2)**	**79**
18	DMSO	150	Et_3N (2)	46

[a]Reaction conditions: **1a** (0.5 mmol, 1 equiv), aniline **2a** (1.0 mmol, 2 equiv), $Cu(OAc)_2 \cdot H_2O$ (0.05 mmol), and the base in the solvent (2 mL). [b]Yields were determined by ^1H NMR analysis by using 1,3,5-trimethoxybenzene as the internal standard. [c]CuI (0.05 mmol) was used as a catalyst. [d]Formyl anthranilate and ethyl anthranilate were observed as the main products. Solvent color according to the CHEM21 solvent selection guide:[12] red = (highly) hazardous, yellow = problematic, green = recommended.

discover that our methodology is also compatible with the use of arylhydrazines as nucleophiles, affording the corresponding 3-(arylamino)quinazolinones **3n,p** in moderate but still reasonable yields.

Formation of 3-alkyl-4-quinazolinones (**4**) by using the more nucleophilic aliphatic amines as coupling partners follows a similar trend in the optimization of reaction conditions as observed for the anilines. After a short optimization (see the Supporting Information), we were pleasantly surprised to find that the reaction between **1a** and aliphatic amines runs to completion in 20 min at ambient temperature. These optimized reaction conditions tolerate the use of primary amines, affording **4a−c** in good yields and clean conversion (Scheme 3). Benzylic amines also proved highly compatible with the devised methodology, as evidenced by the formation of **4d−h**. The electronic nature of the benzylic moiety did not influence the yield of the corresponding quinazolinone. More sterically encumbered secondary amines were also smoothly coupled with ethyl 2-isocyanobenzoate **1a**, affording quinazolinones **4i−k**. Unfortunately, the use of *tert*-butylamine did not afford quinazolinone **4l** in sufficient quantities for isolation and

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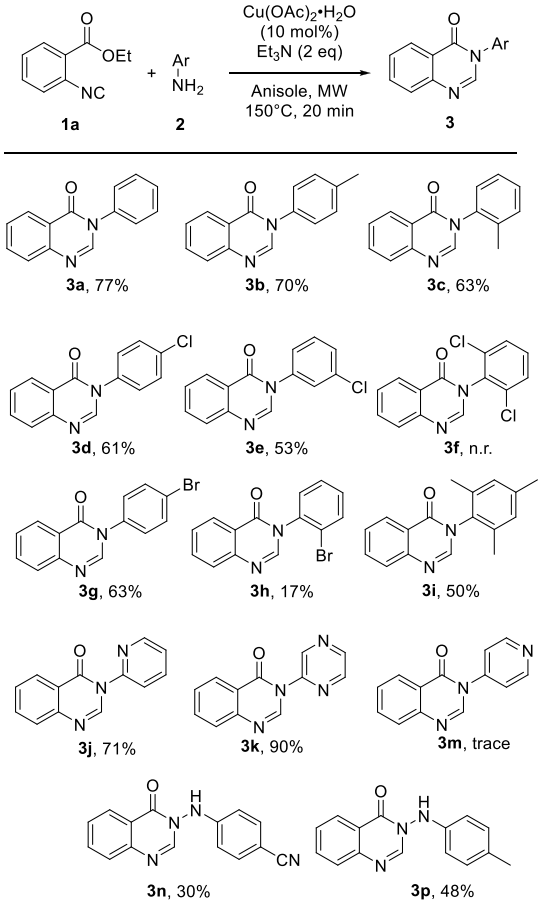
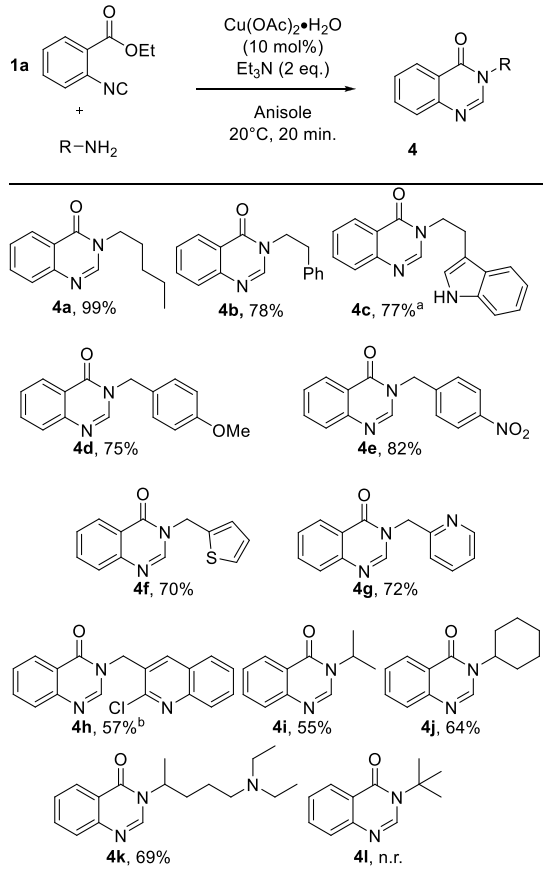
Scheme 2. Reaction Scope Using Aromatic Amines[a]



[a]Yields refer to isolated yields. Conditions: isocyanobenzoate **1a** (0.05 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.05 mmol), amine (1.0 mmol), and Et_3N (1.0 mmol) in anisole (2.0 mL).

Scheme 3. Reaction Scope Using Aliphatic Amines[a]



[a]Yields refer to isolated yields. Conditions: isocyanobenzoate **1a** (0.05 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.05 mmol), amine (1.0 mmol), and Et_3N (0.140 mL, 1.0 mmol) in anisole (2.0 mL). [b]Performed on a 5.0 mmol scale. [c]Performed on a 1.2 mmol scale.

purification. Functionalized anthranilic isocyanides afforded substituted quinazolinone products **5a−e**. The coupling of methyl 2-isocyano-3-methylbenzoate **1b** afforded 8-methylated quinazolinone **5a** in a good yield regardless of the temperature at which the reaction was performed (Scheme 4). However, when the electron-rich methyl 2-isocyano-4,5-dimethoxybenzoate (**1c**) was employed, a significantly lower yield of **5b** was observed. When the reaction was performed at an elevated temperature (150 °C, condition **B**), 6,7-dimethoxyquinazolinone **5b** was obtained in a good yield. This is most likely because the higher electron density at the isocyano moiety leads to less electrophilic character and thus a lower reactivity.

Additionally, the increased electron density also decreases the electrophilicity of the benzoate ester, impeding lactamization. Similarly, the introduction of a weakly electron-withdrawing group on *o*-isocyanobenzoate appears to activate the isocyanide toward amination. While the reaction of 5-bromo-2-isocyanobenzoate (**1d**) with aliphatic amines affords quinazolin-4-ones **5c−d** in yields comparable to those of unsubstituted isocyanobenzoates **1a** (Scheme 3), we were happily surprised to find that the 3-arylated product **5e** is isolated in good yields from both the reactions performed at 150 °C and at ambient temperature.

From the results described above, we propose the mechanism shown in Scheme 5. The electron-deficient isocyanobenzoate **1** coordinates to the Cu(II) center, forming intermediate **II**. This copper complex is either directly attacked by an ambient nucleophile to afford the carbamimidoyl copper intermediate **IV**[13] or, alternatively, undergoes base-mediated complexation with the amine **2** to furnish copper species **III**. This complex can also afford the same intermediate **IV** through 1,1-migratory insertion.[4b,14] The difference between Lewis acid catalysis (route **A**) and a 1,1-migratory insertion pathway (route **B**) is hard to distinguish. However, the notably increased difficulty in the synthesis of electron-rich **5b** and the relatively facile synthesis of **5e** imply that the reactivity is inversely correlated to the electron density around the isocyanide carbon. Therefore, it is likely the copper catalyst acts more as a Lewis acid, which is in line with recent results reported by us,[4c] Zhu,[15] and Ji.[16]

The synthetic utility of this methodology is underlined by the syntheses of several natural products in a single postinsertion/cyclocondensation reaction. First, we utilized our methodology to couple isocyanobenzoate **1a** with ethanolamine (**6**) to afford the plant alkaloid echinozolinone[17] (**7**) in 90% yield (Scheme 6a). Second, the tryptamine-derived quinazolinone **4c** was converted to the medicinally valuable[18] natural alkaloid rutaecarpine (**8**) in a one-pot, two-step oxidative annulation[15] in 56% over two steps (Scheme 6b). Additionally, palladium-catalyzed Heck-type cyclization[19] of quinazolinone **4h** afforded the pentacycle luotonin A (**9**), a

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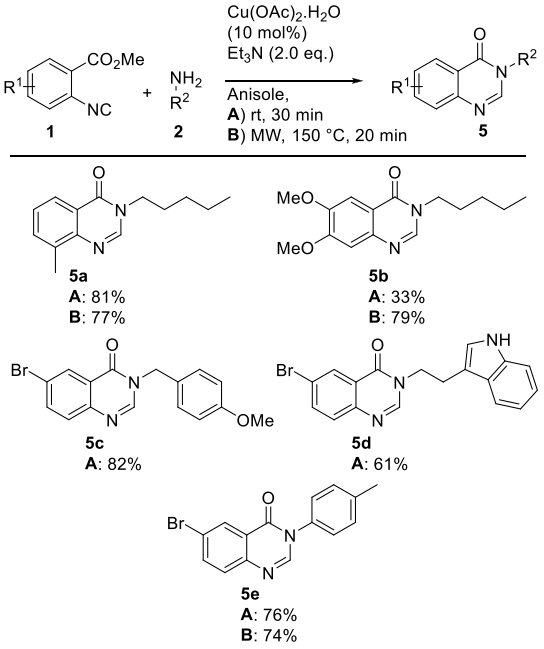
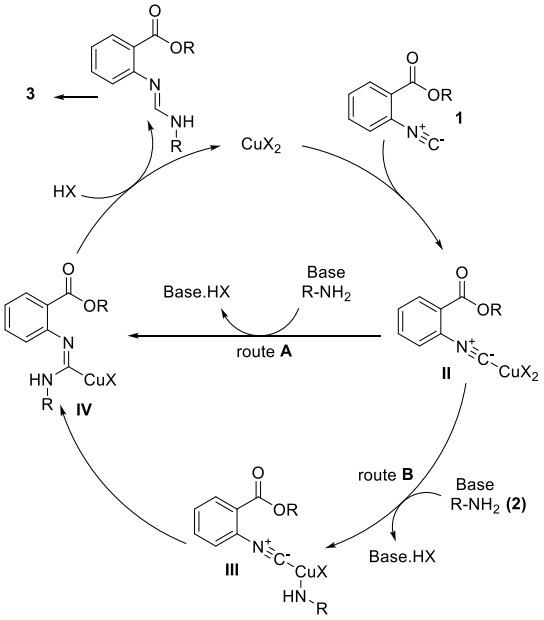
Scheme 4. Variation of Isocyanide[a]



[a]Yields refer to isolated yields. Conditions: isocyanobenzoate **1** (0.05 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.05 mmol), amine (1.0 mmol), and Et_3N (1.0 mmol) in anisole (2.0 mL).

Scheme 5. Proposed Mechanistic Pathways

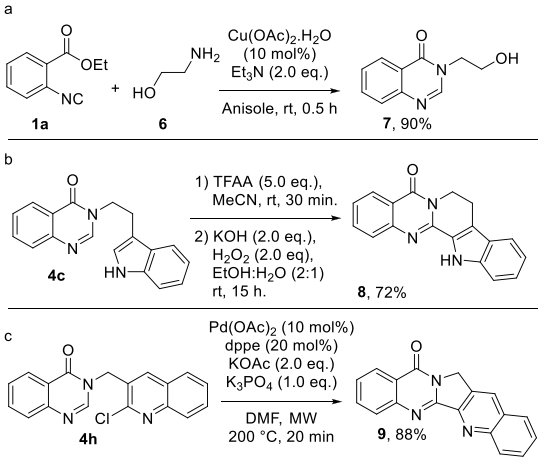


known DNA topoisomerase I inhibitor,[5b,19,20] in 88% yield in a single post-imidoylative transformation (Scheme 6c).

CONCLUSIONS

We have developed a one-pot cascade reaction to substituted quinazolin-4(3*H*)-ones via copper-catalyzed isocyanide insertion and subsequent cyclocondensation. The coupling is performed in the recommended solvent anisole under an air atmosphere and at ambient temperature. Coupling the anthranilic isocyanides with anilines requires microwave irradiation, which negates the necessity for longer reaction times. Generally, quinazolin-4(3*H*)-ones are isolated in good yields, although the yield is considerably lower when electron-deficient anilines are employed. Curiously, we observed a significant increase in the yields of quinazolinones when 2-aminopyridines or 2-aminopyrazines are used, presumably through additional coordinating effects. The synthetic utility of this catalytic transformation was highlighted by the total synthesis of several natural products by a single postcoupling reaction.

Scheme 6. Natural Compound Syntheses via Cu-Catalyzed Isocyanide Insertion



EXPERIMENTAL SECTION

General Information. Chemicals were purchased from Sigma-Aldrich or Fluorochem and were used without purification. Solvents were purchased from VWR Chemicals (CH_2Cl_2) or Sigma-Aldrich [toluene, dioxane, and dimethyl sulfoxide (DMSO)] and used without purification unless stated otherwise. Dry solvents were dried over an inert PS-MD-5 solvent purification system, equipped with an activated alumina/copper wire column. Microwave reactions were performed in a closed vessel in a Biotage Initiator, measuring temperature by IR. ^{1}H NMR measurements were acquired on a Bruker AVANCE 300 (300.13 MHz) or Bruker AVANCE 500 (500.23 MHz) spectrometer. ^{13}C NMR measurements were acquired on a Bruker AVANCE 500 (125.78 MHz) spectrometer. Chemical shifts are reported in parts per million downfield of tetramethylsilane and are corrected according to the solvent. Mass analysis was performed using a Bruker MicrOTOF-Q instrument on a positive ion polarity mode for ESI (electrospray ionization). Capillary charge: 4000 V. Melting points were measured using a Büchi M-565 melting point apparatus. SiO_2 column chromatography was performed using Merck silica gel C60 (particle size 40−60 μm). Thin-layer chromatography (TLC) was performed on Merck silica gel C60 F254 plates (silica coat on the aluminum support). All isolated yields are corrected for impurities (if present).

General Procedure 1 for the Synthesis of Alkyl 2-Isocyanobenzoates. A solution of acetic anhydride (47 mL, 500 mmol) and formic acid (57 mL, 1500 mmol) was stirred for 90 min at room temperature. Then, the mixture was cooled to 0 °C, and alkyl anthranilate (50 mmol) was added to the solution and stirred for another 2 h. CH_2Cl_2 (100 mL) was added to this mixture. The mixture was then separated, and the organic layer was washed with 2 M NaOH (100 mL) before being dried over Na_2SO_4, after which the solvent was removed in vacuo. Crude formyl anthranilate was dissolved in dry CH_2Cl_2 (200 mL). Et_3N (84 mL, 0.6 mol) was added, and the mixture was cooled to 0 °C. Then, $POCl_3$ (9.35 mL, 100 mmol) was added slowly, and the resulting mixture was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was quenched with 100 mL of 2 M NaOH and washed twice with water. The organic fraction was dried over Na_2SO_4, concentrated

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in vacuo, and purified by column chromatography (cHex/EtOAc = 9:1 to 4:1) to afford the pure 2-isocyanobenzoates **1**.

General Procedure 2 for the Synthesis of 3-Alkylated Quinazolinones 4. To a solution of ethyl 2-isocyanobenzoate (0.088 g, 0.5 mmol) in anisole (2.0 mL) was added Et_3N (0.140 mL, 1.0 mmol) and $Cu(OAc)_2{\cdot}H_2O$ (0.010 g, 0.05 mmol) was added aliphatic amine (1.0 mmol). The resulting mixture was stirred at room temperature for 20 min, after which CH_2Cl_2 and $NaHCO_3$ (saturated) were added. The aqueous layer was washed twice with CH_2Cl_2, and the combined organic fractions were dried over Na_2SO_4, concentrated in vacuo, and purified by column chromatography to afford 3-alkyl quinazolin-4(3*H*)-ones.

General Procedure 3 for the Synthesis of 3-Arylated Quinazolinones 3. To a solution of ethyl 2-isocyanobenzoate (0.088 g, 0.5 mmol) in anisole (2.0 mL) was added Et_3N (0.140 mL, 1.0 mmol) and $Cu(OAc)_2{\cdot}H_2O$ (0.010 g, 0.05 mmol) was added the aromatic amine (1.0 mmol). The resulting mixture was stirred under microwave irradiation for 20 min at 150 °C, after which CH_2Cl_2 and $NaHCO_3$ (saturated) were added. The aqueous layer was washed twice with CH_2Cl_2, and the combined organic fractions were dried over Na_2SO_4, concentrated in vacuo, and purified by column chromatography to afford 3-alkyl quinazolin-4(3*H*)-ones.

*Ethyl 2-Isocyanobenzoate (**1a**).* Compound **1a** was synthesized according to general procedure 1 and isolated as a pale yellow solid that rapidly reddens (7.07 g, 81%); R_f = 0.66 (cHex/EtOAc = 2:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93 (dd, J = 7.8, 2.1 Hz, 1H), 7.51 (tt, J = 7.6, 1.5 Hz, 1H), 7.42 (ddt, J = 8.0, 6.8, 1.7 Hz, 2H), 4.37 (qt, J = 7.2, 1.8 Hz, 2H), 1.37 (tt, J = 7.2, 1.8 Hz, 3H); ^{13}C NMR{^{1}H} (126 MHz, $CDCl_3$): δ 169.4, 163.9, 132.9, 131.2, 129.1, 128.7, 127.1 (t, J = 1.4 Hz), 125.3, 61.8, 14.0. HRMS (ESI) m/z: calcd for $C_{10}H_9O_2NNa$ $[M + Na]^+$, 198.0525; found, 198.0518. mp 31−34 °C.

*Methyl 2-Isocyano-3-methylbenzoate (**1b**).* Compound **1b** was synthesized on a 1.9 mmol scale according to general procedure 1 and isolated as a white solid (0.242 g, 73%). R_f = 0.71 (cHex/EtOAc = 2:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81 (dd, J = 7.8, 1.5 Hz, 1H), 7.49−7.46 (m, 1H), 7.36 (t, J = 7.7 Hz, 1H), 3.97 (s, 3H), 2.49 (s, 3H). ^{13}C NMR {^{1}H} (126 MHz, $CDCl_3$): δ 171.5, 165.1, 137.1, 134.3, 128.8, 128.7, 127.5, 52.8, 19.5. HRMS (ESI) m/z: calcd for $C_{10}H_{10}O_2N$ $[M + H]^+$, 176.0706; found, 176.0715. mp 39−40 °C.

*Methyl 2-Isocyano-4,5-dimethoxybenzoate (**1c**).* Compound **1c** was synthesized on a 2.0 mmol scale according to general procedure 1 and isolated as a white solid (0.212 g, 49%). R_f = 0.39 (cHex/EtOAc = 2:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43 (s, 1H), 6.89 (s, 1H), 3.94 (s, 3H), 3.92 (s, 6H). ^{13}C NMR{^{1}H} (126 MHz, $CDCl_3$): δ 168.1, 164.4, 152.3, 149.1, 119.6, 119.4, 112.6, 111.3, 56.6, 56.4, 52.6. HRMS (ESI) m/z: calcd for $C_{11}H_{12}O_4N$ $[M + H]^+$, 222.0761; found, 22.0768. mp 161−162 °C.

*Ethyl 5-Bromo-2-isocyanobenzoate (**1d**).* Compound **1d** was synthesized on a 20 mmol scale according to general procedure 1 and isolated as a dark-green solid (3.80 g, 75%). R_f = 0.55 (cHex/EtOAc = 4:1). ^{1}H NMR (500.23 MHz, $CDCl_3$): δ 8.13 (d, J = 2.3 Hz, 1H), 7.68 (dd, J = 2.3, 8.5 Hz, 1H), 7.35 (d, J = 8.5 Hz, 1H), 4.44 (q, J = 7.1 Hz, 2H), 1.44 (t, J = 7.1 Hz, 3H). ^{13}C NMR {^{1}H} (126 MHz, $CDCl_3$): δ 171.1, 162.7, 135.9, 134.3, 130.1, 128.7, 124.3, 123.1, 62.4, 14.0. HRMS (ESI) m/z: calcd for $C_{10}H_9NO_2Br$ $[M + H]^+$, 253.9811; found, 253.9800. mp 89 °C.

*3-Phenylquinazolin-4(3H)-one (**3a**).* Compound **3a** was synthesized according to general procedure 2 and isolated as an off-white solid (0.087 g, 77%). R_f = 0.38 (cHex/EtOAc = 2:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.38 (dt, J = 7.9, 1.0 Hz, 1H), 8.14 (s, 1H), 7.82 (ddd, J = 8.4, 6.9, 1.5 Hz, 1H), 7.78 (dd, J = 8.2, 1.7 Hz, 1H), 7.56 (td, J = 7.1, 1.1 Hz, 3H), 7.53−7.48 (m, 1H), 7.47−7.40 (m, 2H). ^{13}C NMR {^{1}H} (126 MHz, $CDCl_3$): δ 160.9, 148.0, 146.2, 137.6, 134.8, 129.8, 129.3, 127.8, 127.8, 127.4, 127.1, 122.5. HRMS (ESI) m/z: calcd for $C_{14}H_{11}N_2O$ $[M + H]^+$, 223.0866; found, 223.0863. mp 136 °C.

*3-(p-Tolyl)quinazolin-4(3H)-one (**3b**).* Compound **3b** was synthesized according to general procedure 3 and isolated as a gray solid (0.083 g, 70%). R_f = 0.42 (cHex/EtOAc = 2:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.37 (dd, J = 8.0, 1.5 Hz, 1H), 8.12 (s, 1H), 7.80 (ddd, J = 8.4, 6.9, 1.5 Hz, 1H), 7.76 (dd, J = 8.3, 1.4 Hz, 1H), 7.55 (ddd, J = 8.1, 6.9, 1.4 Hz, 1H), 7.37−7.33 (m, 2H), 7.32−7.28 (m, 2H), 2.44 (s, 3H). ^{13}C NMR {^{1}H} (126 MHz, $CDCl_3$): δ 161.1, 148.0, 146.5, 139.4, 135.0, 134.7, 130.4, 127.7, 127.7, 127.3, 126.9, 122.5, 21.4. HRMS (ESI) m/z: calcd for $C_{15}H_{13}N_2O$ $[M + H]^+$, 237.1022; found, 237.1032. mp 143 °C.

*3-(o-Tolyl)quinazolin-4(3H)-one (**3c**).* Compound **3c** was synthesized according to general procedure 3 and isolated as a brown solid (0.078 g, 63%). R_f = 0.44 (cHex/EtOAc = 2:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.41−8.35 (m, 1H), 8.00 (s, 1H), 7.87−7.74 (m, 2H), 7.56 (ddd, J = 8.2, 6.8, 1.5 Hz, 1H), 7.46−7.32 (m, 3H), 7.27−7.24 (m, 1H), 2.21 (s, 3H). ^{13}C NMR {^{1}H} (126 MHz, $CDCl_3$): δ 160.6, 148.2, 146.5, 136.8, 136.0, 134.7, 131.5, 129.9, 128.0, 127.8, 127.5, 127.3, 122.6, 17.9. HRMS (ESI) m/z: calcd for $C_{15}H_{13}N_2O$ $[M + H]^+$, 237.1022; found, 237.1028. mp 97 °C.

*3-(4-Chlorophenyl)quinazolin-4(3H)-one (**3d**).* Compound **3d** was synthesized according to general procedure 3 and isolated as a light-brown solid (0.079 g, 61%). R_f = 0.46 (cHex/EtOAc = 2:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.35 (dd, J = 8.1, 1.5 Hz, 1H), 8.08 (s, 1H), 7.81 (ddd, J = 8.4, 7.0, 1.6 Hz, 1H), 7.76 (dd, J = 8.3, 1.3 Hz, 1H), 7.60−7.46 (m, 3H), 7.42−7.35 (m, 2H). ^{13}C NMR {^{1}H} (126 MHz, $CDCl_3$): δ 160.7, 147.9, 145.7, 136.0, 135.3, 134.9, 130.0, 128.5, 128.0, 127.8, 127.3, 122.3. HRMS (ESI) m/z: calcd for $C_{14}H_{10}N_2OCl$ $[M + H]^+$, 257.0467; found, 257.0468. mp 180 °C.

*3-(3-Chlorophenyl)quinazolin-4(3H)-one (**3e**).* Compound **3e** was synthesized according to general procedure 3 and isolated as a light-brown solid (0.070 g, 53%). R_f = 0.42 (cHex/EtOAc = 2:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.36 (dd, J = 7.9, 1.5 Hz, 1H), 8.09 (s, 1H), 7.82 (td, J = 7.6, 7.0, 1.5 Hz, 1H), 7.77 (dd, J = 8.2, 1.3 Hz, 1H), 7.61−7.54 (m, 1H), 7.52−7.41 (m, 3H), 7.37−7.30 (m, 1H). ^{13}C NMR {^{1}H} (126 MHz, $CDCl_3$): δ 160.7, 147.9, 145.6, 138.5, 135.4, 135.0, 130.8, 129.6, 128.0, 127.8, 127.6, 127.3, 125.4, 122.3. HRMS (ESI) m/z: calcd for $C_{14}H_{10}N_2OCl$ $[M + H]^+$, 257.0476; found, 257.0467. mp 166 °C.

*3-(4-Bromophenyl)quinazolin-4(3H)-one (**3g**).* Compound **3g** was synthesized according to general procedure 3 and isolated as a light-gray solid (0.097 g, 63%). R_f = 0.38 (cHex/EtOAc = 2:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.34 (dd, J = 7.9, 1.5 Hz, 1H), 8.08 (s, 1H), 7.80 (ddd, J = 8.4, 7.0, 1.5 Hz, 1H), 7.75 (dd, J = 8.2, 1.3 Hz, 1H), 7.70−7.61 (m, 2H), 7.55 (ddd, J = 8.1, 7.0, 1.3 Hz, 1H), 7.36−7.24 (m, 2H). ^{13}C NMR {^{1}H} (126 MHz, $CDCl_3$): δ 160.6, 147.8, 145.6, 136.5, 134.9, 133.0, 128.7, 128.0, 127.8, 127.3, 123.3, 122.3. HRMS (ESI) m/z: calcd for $C_{14}H_{10}N_2OBr$ $[M + H]^+$, 300.9971; found, 300.9955. mp 187−189 °C.

*3-(2-Bromophenyl)quinazolin-4(3H)-one (**3h**).* Compound **3h** was synthesized according to general procedure 3 and isolated as an off-white solid (0.029 g, 17%). R_f = 0.43 (cHex/EtOAc = 2:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.38 (dd, J = 7.8, 1.5 Hz, 1H), 7.95 (s, 1H), 7.83 (ddd, J = 8.4, 6.9, 1.5 Hz, 1H), 7.80 (dd, J = 8.0, 1.4 Hz, 2H), 7.57 (ddd, J = 8.2, 6.8, 1.5 Hz, 1H), 7.52 (td, J = 7.6, 1.4 Hz, 1H), 7.47−7.38 (m, 2H). ^{13}C NMR {^{1}H} (126 MHz, $CDCl_3$): δ 160.4, 148.1, 146.0, 136.8, 134.9, 134.1, 131.4, 130.1, 129.0, 127.9, 127.9, 127.4, 122.6, 122.6. HRMS (ESI) m/z: calcd for $C_{14}H_{10}N_2OBr$ $[M + H]^+$, 300.9971; found, 300.9956. mp 182 °C.

*3-Mesitylquinazolin-4(3H)-one (**3i**).* Compound **3i** was synthesized according to general procedure 3 and isolated as a light-brown solid (0.066 g, 50%). R_f = 0.60 (cHex/EtOAc = 2:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.41−8.38 (m, 1H), 7.89 (s, 1H), 7.85−7.74 (m, 2H), 7.63−7.50 (m, 1H), 7.05 (s, 2H), 2.36 (s, 3H), 2.11 (s, 6H). ^{13}C NMR {^{1}H} (126 MHz, $CDCl_3$): δ 160.4, 148.4, 146.9, 139.6, 135.4, 134.7, 133.3, 129.7, 127.7, 127.6, 127.4, 122.7, 21.2, 18.0. HRMS (ESI) m/z: calcd for $C_{17}H_{17}N_2O$ $[M + H]^+$, 265.1335; found, 265.1344. mp 150 °C.

*3-(Pyridin-2-yl)quinazolin-4(3H)-one (**3j**).* Compound **3j** was synthesized according to general procedure 3 and isolated as an off-white solid (0.085 g, 71%). R_f = 0.25 (cHex/EtOAc = 2:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.63 (d, J = 4.0 Hz, 2H), 8.39 (dd, J = 8.0, 1.4 Hz, 1H), 7.95−7.88 (m, 2H), 7.80 (ddd, J = 12.9, 8.4, 6.9 Hz, 2H), 7.59−7.51 (m, 1H), 7.42−7.32 (m, 1H). ^{13}C NMR {^{1}H} (126 MHz, $CDCl_3$): δ 160.6, 149.8, 149.4, 147.8, 145.0, 138.2, 135.0, 127.8,

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127.8, 127.4, 123.7, 122.3, 121.7. HRMS (ESI): m/z calcd for $C_{13}H_{10}N_3O$ $[M + H]^+$, 257.0476; found, 257.0470. mp 131−132 °C.

*3-(Pyrazin-2-yl)quinazolin-4(3H)-one (**3k**).* Compound **3k** was synthesized according to general procedure 3 and isolated as an off-white solid (0.103 g, 90%). R_f = 0.10 (cHex/EtOAc = 2:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.32 (d, J = 1.5 Hz, 1H), 8.67 (d, J = 2.5 Hz, 1H), 8.65−8.59 (m, 2H), 8.40 (dd, J = 8.0, 1.5 Hz, 1H), 7.84 (ddd, J = 8.4, 7.0, 1.5 Hz, 1H), 7.79 (dd, J = 8.1, 1.3 Hz, 1H), 7.58 (ddd, J = 8.2, 7.0, 1.3 Hz, 1H). ^{13}C NMR {^{1}H} (126 MHz, $CDCl_3$): δ 160.3, 147.6, 146.50, 143.9, 143.9, 143.3, 143.3, 135.4, 128.2, 128.0, 127.5, 121.9. HRMS (ESI) m/z: calcd for $C_{12}H_9N_4O$ $[M + H]^+$, 225.0771; found, 225.0782. mp 158 °C.

*4-((4-Oxoquinazolin-3(4H)-yl)amino)benzonitrile (**3n**).* Compound **3n** was synthesized according to general procedure 3 and isolated as an orange solid (0.041 g, 30%). R_f = 0.14 (cHex/EtOAc = 2:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.29 (ddd, J = 8.1, 1.5, 0.6 Hz, 1H), 8.24 (s, 1H), 7.91−7.79 (m, 2H), 7.65−7.48 (m, 3H), 7.32 (s, 1H), 6.84−6.79 (m, 2H). ^{13}C NMR {^{1}H} (126 MHz, $CDCl_3$): δ 160.3, 150.2, 147.8, 147.6, 135.4, 134.1, 128.3, 128.1, 127.2, 122.4, 118.9, 114.3, 106.1. HRMS (ESI) m/z: calcd for $C_{15}H_{11}N_4O$ $[M + H]^+$, 263.0927; found, 263.0918. mp 190−193 °C.

*3-(p-Tolylamino)quinazolin-4(3H)-one (**3p**).* Compound **3p** was synthesized according to general procedure 3 and isolated as a light-yellow solid (0.062 g, 48%). R_f = 0.38 (cHex/EtOAc = 2:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.31 (s, 1H), 8.30−8.26 (m, 1H), 7.85−7.75 (m, 2H), 7.53 (ddd, J = 8.2, 5.8, 2.5 Hz, 1H), 7.20 (s, 1H), 7.09−7.02 (m, 2H), 6.73 (d, J = 8.5 Hz, 2H), 2.26 (s, 3H). ^{13}C NMR {^{1}H} (126 MHz, $CDCl_3$): δ 160.7, 148.3, 148.0, 144.1, 134.8, 132.9, 130.1, 128.0, 127.6, 127.0, 122.6, 115.0, 20.8. HRMS (ESI) m/z: calcd for $C_{15}H_{14}N_3O$ $[M + H]^+$, 252.1131; found: 252.1134. mp 137 °C.

*3-Pentylquinazolin-4(3H)-one (**4a**).* Compound **4a** was synthesized according to general procedure 2 and isolated as a light yellow solid (0.107 g, 99%). R_f = 0.39 (cHex/EtOAc = 2:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.32 (dd, J = 7.9, 1.5 Hz, 1H), 8.03 (s, 1H), 7.76 (ddd, J = 8.4, 7.0, 1.5 Hz, 1H), 7.71 (dd, J = 8.1, 1.2 Hz, 1H), 7.51 (ddd, J = 8.2, 7.0, 1.3 Hz, 1H), 4.02−3.97 (m, 2H), 1.84−1.75 (m, 2H), 1.37 (tt, J = 7.2, 2.9 Hz, 4H), 0.99−0.82 (m, 3H). ^{13}C NMR {^{1}H} (126 MHz, $CDCl_3$): δ 161.2, 148.3, 146.8, 134.3, 127.6, 127.4, 126.8, 122.3, 47.2, 29.2, 28.9, 22.4, 14.1. HRMS (ESI) m/z: calcd for $C_{13}H_{17}N_2O$ $[M + H]^+$, 217.1335; found, 217.1337. mp 60 °C.

*3-Phenethylquinazolin-4(3H)-one (**4b**).* Compound **4b** was synthesized according to general procedure 2 and isolated as an off-white solid (0.099 g, 78%). R_f = 0.24 (cHex/EtOAc = 2:1). ^{1}H NMR (500 MHz, CD_3OD): δ 8.28 (dd, J = 8.0, 1.4 Hz, 1H), 7.90 (s, 1H), 7.83 (ddd, J = 8.6, 7.1, 1.5 Hz, 1H), 7.64 (dd, J = 8.2, 1.1 Hz, 1H), 7.58 (ddd, J = 8.2, 7.1, 1.2 Hz, 1H), 7.29−7.24 (m, 2H), 7.23−7.20 (m, 1H), 7.20−7.16 (m, 2H), 4.29 (t, J = 7.0 Hz, 2H), 3.10 (t, J = 7.0 Hz, 2H). ^{13}C NMR {^{1}H} (126 MHz, CD_3OD): δ 162.6, 149.1, 149.0, 139.0, 135.8, 130.1, 129.8, 128.6, 127.9, 127.8, 127.4, 122.9, 49.8, 35.6. HRMS (ESI) m/z: calcd for $C_{16}H_{15}N_2O$ $[M + H]^+$, 251.1179; found, 251.1174. mp 100 °C.

*3-(2-(1H-Indol-3-yl)ethyl)quinazolin-4(3H)-one (**4c**).* Compound **4c** was synthesized according to general procedure 2 on a 5 mmol scale. To a solution of isocyanobenzoate **1a** (0.876 g, 5.0 mmol), Et_3N (1.14 mL, 10 mmol), and tryptamine (1.60 g, 10 mmol) in a 50 mL round-bottom flask was added $Cu(OAc)_2{\cdot}H_2O$ (0.100 g, 0.5 mmol). The resulting solution was stirred for 25 min at room temperature under an air atmosphere. After TLC indicated full conversion, the resulting mixture was diluted with CH_2Cl_2 and washed twice with saturated aqueous $NaHCO_3$. The organic layer was dried over Na_2SO_4, concentrated in vacuo, and loaded onto SiO_2. Column chromatography was carried out on a SiO_2 column, with a cHex/EtOAc/Et_3N eluent (gradient: 4:1:0.01 to 2:1:0.01). The compound was isolated as an off-white solid (1.121 g, 77%). R_f = 0.16 (cHex/EtOAc = 2:1). ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.37 (dd, J = 8.0, 1.6 Hz, 1H), 8.08 (s, 1H), 7.74 (ddd, J = 8.4, 7.1, 1.6 Hz, 1H), 7.65 (dd, J = 13.1, 8.1, 1.1 Hz, 2H), 7.54−7.48 (m, 2H), 7.37 (d, J = 8.2 Hz, 1H), 7.22 (ddd, J = 8.1, 6.9, 1.2 Hz, 1H), 7.14 (td, J = 7.5, 7.0, 1.1 Hz, 1H), 6.88 (d, J = 2.4 Hz, 1H), 4.30 (t, J = 6.8 Hz, 2H), 3.27 (t, J = 6.8 Hz, 2H). ^{13}C NMR {^{1}H} (126 MHz, DMSO-d_6): δ 161.3, 148.3, 146.9, 136.6, 134.3, 127.5, 127.3, 126.9, 126.8, 122.9, 122.6, 122.3, 119.9, 118.5, 111.6, 111.5, 47.7, 25.1. HRMS (ESI): m/z calcd for $C_{18}H_{16}N_3O$ $[M + H]^+$, 290.1288; found, 290.1274. mp 164 °C.

*3-(4-Methoxybenzyl)quinazolin-4(3H)-one (**4d**).* Compound **4d** was synthesized according to general procedure 2 and isolated as a light-yellow solid (0.068 g, 75%). R_f = 0.15 (cHex/EtOAc = 2:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.33 (dd, J = 7.9, 1.5 Hz, 1H), 8.11 (s, 1H), 7.75 (ddd, J = 8.5, 7.0, 1.5 Hz, 1H), 7.70 (dd, J = 8.2, 1.3 Hz, 1H), 7.51 (ddd, J = 8.1, 7.0, 1.3 Hz, 1H), 7.32 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 5.14 (s, 2H), 3.79 (s, 3H). ^{13}C NMR {^{1}H} (126 MHz, $CDCl_3$): δ 161.2, 159.7, 148.2, 146.4, 134.4, 129.8, 127.9, 127.6, 127.5, 127.0, 122.4, 114.5, 55.5, 49.4. HRMS (ESI): m/z calcd for $C_{16}H_{15}N_2O_2$ $[M + H]^+$, 267.1128; found, 267.1117. mp 134 °C.

*3-(4-Nitrobenzyl)quinazolin-4(3H)-one (**4e**).* Compound **4e** was synthesized according to general procedure 2 and isolated as a light-yellow solid (0.125 g, 82%). R_f = 0.10 (cHex/EtOAc = 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.32 (d, J = 8.0 Hz, 1H), 8.23 (s, 1H), 8.20 (d, J = 4.8 Hz, 2H), 7.86−7.72 (m, 2H), 7.59−7.49 (m, 3H), 5.29 (s, 2H). ^{13}C NMR {^{1}H} (126 MHz, $CDCl_3$): δ 161.1, 148.88, 147.87, 146.3, 146.1, 142.8, 134.9, 128.81, 128.0, 127.8, 124.4, 122.1, 49.5. HRMS (ESI) m/z: calcd for $C_{15}H_{12}N_3O_3$ $[M + H]^+$, 282.0873, found, 282.0860. mp 159 °C.

*3-(Thiophen-2-ylmethyl)quinazolin-4(3H)-one (**4f**).* Compound **4f** was synthesized according to general procedure 2 and isolated as a light-yellow solid (0.085 g, 70%). R_f = 0.36 (cHex/EtOAc = 2:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.37 (dd, J = 7.9, 1.5 Hz, 1H), 8.18 (s, 1H), 7.79 (ddd, J = 8.5, 7.0, 1.6 Hz, 1H), 7.73 (dd, J = 8.2, 1.2 Hz, 1H), 7.57−7.53 (t, 1H), 7.31 (dd, J = 5.1, 1.2 Hz, 1H), 7.19 (d, J = 3.5 Hz, 1H), 7.01 (dd, J = 5.1, 3.5 Hz, 1H), 5.39 (s, 2H). ^{13}C NMR {^{1}H} (126 MHz, $CDCl_3$): δ 160.9, 148.1, 145.9, 137.6, 134.5, 128.0, 127.7, 127.6, 127.3, 127.0, 126.8, 122.2, 44.4. HRMS (ESI) m/z: calcd for $C_{13}H_{11}N_2OS$ $[M + H]^+$, 243.0587; found, 243.0578. mp 119 °C.

*3-(Pyridin-2-ylmethyl)quinazolin-4(3H)-one (**4g**).* Compound **4g** was synthesized according to general procedure 2 and isolated as a light-yellow solid (0.087 g, 72%). R_f = 0.05 (cHex/EtOAc = 2:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.55 (d, J = 4.6 Hz, 1H), 8.33 (s, 1H), 8.30 (dd, J = 8.0, 1.5 Hz, 1H), 7.76 (ddd, J = 8.2, 6.7, 1.5 Hz, 1H), 7.73 (dd, J = 8.2, 1.6 Hz, 1H), 7.68 (td, J = 7.7, 1.8 Hz, 1H), 7.50 (ddd, J = 8.2, 6.8, 1.6 Hz, 1H), 7.43 (d, J = 7.8 Hz, 1H), 7.22 (ddd, J = 7.6, 4.9, 1.1 Hz, 1H), 5.28 (s, 2H). ^{13}C NMR {^{1}H} (126 MHz, $CDCl_3$): δ 161.2, 155.0, 149.9, 148.40, 147.2, 137.2, 134.5, 129.9, 127.7, 127.4, 123.3, 123.1, 122.3, 51.3. HRMS (ESI) m/z: calcd for $C_{14}H_{12}N_3O$ $[M + H]^+$, 238.0975; found, 238.0986. mp 113 °C.

*3-((2-Chloroquinolin-3-yl)methyl)quinazolin-4(3H)-one (**4h**).* Compound **4h** was synthesized according to a modified general procedure 2 using ethyl 2-isocyanobenzoate **1a** (0.210 g, 1.2 mmol) and (2-chloroquinolin-3-yl)methanamine (0.347 g, 1.8 mmol) and isolated as a white solid (0.220 g, 57%). R_f = 0.59 (cHex/EtOAc = 1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.34 (s, 1H), 8.31 (dd, J = 8.0, 1.5 Hz, 1H), 8.21 (s, 1H), 8.01 (d, J = 8.4 Hz, 1H), 7.84−7.77 (m, 2H), 7.79−7.70 (m, 2H), 7.59−7.51 (m, 2H), 5.42 (s, 2H). ^{13}C NMR {^{1}H} (126 MHz, $CDCl_3$): δ 161.4, 149.4, 148.2, 147.4, 146.6, 139.5, 134.8, 131.2, 128.4, 127.92, 127.86, 127.8, 127.7, 127.1, 126.93, 126.91, 122.2, 48.1. HRMS (ESI) m/z: calcd for $C_{18}H_{13}N_3OCl$ $[M + H]^+$, 322.0742; found, 322.0726. mp 208−210 °C.

*3-Isopropylquinazolin-4(3H)-one (**4i**).* Compound **4i** was synthesized according to general procedure 2 and isolated as a light-yellow solid (0.052 g, 55%). R_f = 0.33 (cHex/EtOAc = 2:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.30 (dd, J = 8.0, 1.5 Hz, 1H), 8.11 (s, 1H), 7.73 (ddd, J = 8.4, 6.9, 1.5 Hz, 1H), 7.68 (dd, J = 8.2, 1.3 Hz, 1H), 7.48 (ddd, J = 8.1, 6.9, 1.3 Hz, 1H), 5.19 (hept, J = 6.9 Hz, 1H), 1.48 (d, J = 6.9 Hz, 6H). ^{13}C NMR {^{1}H} (126 MHz, $CDCl_3$): δ 160.8, 147.7, 143.7, 134.3, 127.4, 127.3, 127.0, 122.1, 46.1, 22.1. HRMS (ESI) m/z: calcd for $C_{11}H_{13}N_2O$ $[M + H]^+$, 189.1022; found, 189.1018. mp 89 °C.

*3-Cyclohexylquinazolin-4(3H)-one (**4j**).* Compound **4j** was synthesized according to general procedure 2 and isolated as a light-yellow solid (0.078 g, 64%). R_f = 0.54 (cHex/EtOAc = 2:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.30 (d, J = 8.0 Hz, 1H), 8.11 (s, 1H),

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7.73 (t, J = 7.7 Hz, 1H), 7.68 (d, J = 8.1 Hz, 1H), 7.48 (t, J = 7.5 Hz, 1H), 4.81 (tt, J = 12.4, 3.7 Hz, 1H), 2.05−1.97 (m, 2H), 1.93 (d, J = 13.1 Hz, 2H), 1.78 (d, J = 13.0 Hz, 1H), 1.63 (qd, J = 12.3, 3.3 Hz, 2H), 1.57−1.42 (m, 2H), 1.25 (qt, J = 13.1, 3.8 Hz, 1H). ^{13}C NMR {^{1}H} (126 MHz, $CDCl_3$): δ 160.8, 147.6, 144.0, 134.2, 127.4, 127.2, 127.1, 122.0, 53.4, 32.7, 26.0, 25.4. HRMS (ESI) m/z: calcd for $C_{14}H_{17}N_2O$ [M + H]$^+$, 229.1335; found, 229.1325. mp 114 °C.

*3-(5-(Diethylamino)pentan-2-yl)quinazolin-4(3H)-one (**4k**).* Compound **4k** was synthesized according to general procedure 2 and isolated as a brown-orange oil (0.099 g, 69%). R_f = 0.47 (EtOAc/Et_3N = 1:0.05). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.30 (dd, J = 8.0, 1.4 Hz, 1H), 8.06 (s, 1H), 7.75 (ddd, J = 8.4, 7.0, 1.5 Hz, 1H), 7.70 (dd, J = 8.2, 1.3 Hz, 1H), 7.50 (ddd, J = 8.1, 7.0, 1.3 Hz, 1H), 5.06 (h, J = 7.1 Hz, 1H), 2.57−2.43 (m, 6H), 1.84 (q, J = 7.7 Hz, 2H), 1.59−1.39 (m, 5H), 1.02 (t, J = 7.2 Hz, 6H). ^{13}C NMR {^{1}H} (126 MHz, $CDCl_3$): δ 161.1, 147.6, 143.9, 134.4, 127.5, 127.4, 127.1, 122.0, 52.2, 46.8, 34.1, 31.1, 23.7, 20.8, 11.3. HRMS (ESI) m/z: calcd for $C_{17}H_{26}N_3O$ [M + H]$^+$, 288.2070; found, 288.2084.

*8-Methyl-3-pentylquinazolin-4(3H)-one (**5a**).* Compound **5a** was synthesized according to general procedure 2 and isolated as a light-red solid (0.094 g, 81%). R_f = 0.58 (cHex/EtOAc = 2:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.16 (d, J = 8.1 Hz, 1H), 8.04 (d, J = 1.8 Hz, 1H), 7.59 (dt, J = 7.3, 1.3 Hz, 1H), 7.38 (td, J = 7.7, 2.6 Hz, 1H), 4.02−3.95 (m, 2H), 2.61 (s, 3H), 1.90−1.68 (m, 2H), 1.36 (qp, J = 5.9, 3.1 Hz, 4H), 1.03−0.74 (m, 3H). ^{13}C NMR {^{1}H} (126 MHz, $CDCl_3$): δ 161.5, 146.9, 145.6, 135.8, 134.9, 126.9, 124.5, 122.3, 47.1, 29.1, 28.9, 22.4, 17.6, 14.1. mp 67 °C.

*6,7-Dimethoxy-3-pentylquinazolin-4(3H)-one (**5b**).* Compound **5b** was synthesized according to general procedure 3 and isolated as an off-white solid (0.109 g, 79%). R_f = 0.10 (cHex/EtOAc = 2:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95 (s, 1H), 7.63 (s, 1H), 7.09 (s, 1H), 4.00 (s, 8H), 1.79 (p, J = 7.4 Hz, 2H), 1.39−1.30 (m, 4H), 0.97−0.85 (m, 3H). ^{13}C NMR {^{1}H} (126 MHz, $CDCl_3$): δ 160.6, 154.8, 149.4, 145.5, 144.5, 115.7, 107.9, 105.6, 56.5, 56.4, 47.2, 29.3, 28.9, 22.4, 14.1. mp 109−110 °C.

*6-Bromo-3-(4-methoxybenzyl)quinazolin-4(3H)-one (**5c**).* Compound **5c** was synthesized according to general procedure 2 and isolated as an off-white solid (0.142 g, 82%). R_f = 0.67 (cHex/EtOAc = 1:1). ^{1}H NMR (500.23 MHz, $CDCl_3$): δ 8.45 (d, J = 2.4 Hz, 1H), 8.10 (s, 1H), 7.81 (dd, J = 8.7, 2.4 Hz, 1H), 7.56 (d, J = 8.7 Hz, 1H), 7.30 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 5.12 (s, 2H), 3.78 (s, 3H). ^{13}C NMR {^{1}H} (126 MHz, $CDCl_3$): δ 159.9, 159.6, 146.8, 146.5, 137.4, 129.6, 129.4, 129.3, 127.4, 123.5, 120.9, 114.4, 55.3, 49.4. HRMS (ESI) m/z: calcd for $C_{16}H_{14}BrO_2N_2$ [M + H]$^+$, 345.0233; found, 345.0217. mp 136 °C.

*3-(2-(1H-Indol-3-yl)ethyl)-6-bromoquinazolin-4(3H)-one (**5d**).* Compound **5d** was synthesized according to general procedure 2 and isolated as an off-white solid (0.113 g, 61%). R_f = 0.48 (cHex/EtOAc = 1:1). ^{1}H NMR (500.23 MHz, $CDCl_3$): δ 8.49 (d, J = 2.4 Hz, 1H), 8.07 (s, 1H), 7.81 (dd, J = 8.7, 2.4 Hz, 1H), 7.63 (d, J = 7.8 Hz, 1H), 7.50 (d, J = 8.7 Hz, 1H), 7.47 (s, 1H), 7.37 (d, J = 8.1 Hz, 1H), 7.22 (t, J = 7.6 Hz, 1H), 7.13 (t, J = 7.5 Hz, 1H), 6.86 (d, J = 2.4 Hz, 1H), 4.29 (t, J = 6.7 Hz, 2H), 3.26 (t, J = 6.7 Hz, 2H). ^{13}C NMR {^{1}H} (126 MHz, $CDCl_3$): δ 159.9, 147.03, 147.02, 137.4, 136.4, 129.3, 126.8, 123.5, 122.8, 122.5, 120.7, 119.9, 118.3, 111.6, 111.2, 47.7, 24.9. HRMS (ESI) m/z: calcd for $C_{18}H_{15}N_3OBr$ [M + H]$^+$, 368.0393; found, 368.0376. mp 212 °C.

*6-Bromo-3-(p-tolyl)quinazolin-4(3H)-one (**5e**).* Compound **5e** was synthesized according to modified general procedure 2, stirred at room temperature for 1 h, and isolated as a tan solid (0.120 g, 76%). R_f = 0.19 (cHex/EtOAc = 4:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.49 (d, J = 2.3 Hz, 1H), 8.11 (s, 1H), 7.87 (dd, J = 8.7, 2.3 Hz, 1H), 7.64 (d, J = 8.7 Hz, 1H), 7.35 (d, J = 8.1 Hz, 2H), 7.29 (d, J = 8.2 Hz, 2H), 2.44 (s, 3H). ^{13}C NMR {^{1}H} (126 MHz, $CDCl_3$): δ 159.9, 146.9, 146.86, 139.7, 137.8, 134.7, 130.5, 129.8, 129.5, 126.8, 123.9, 121.4, 21.4. HRMS (ESI) m/z: calcd for $C_{15}H_{12}N_2OBr$ [M + H]$^+$, 315.0128; found, 315.0106. mp 190−191 °C.

*Echinozolinone (**7**).* Compound 7 was synthesized according to modified general procedure 2, stirred for 1 h, and isolated as an off-white solid (0.086 g, 90%). R_f = 0.15 (EtOAc/Et_3N = 1:0.01). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.15 (d, J = 8.0 Hz, 1H), 8.09 (s, 1H), 7.72 (t, J = 7.6 Hz, 1H), 7.60 (d, J = 8.1, 1H), 7.44 (t, J = 7.6 Hz, 1H), 4.17 (t, J = 4.7, 2H), 4.04 (t, J = 4.7 Hz, 2H), 3.51 (bs, 1H). ^{13}C NMR {^{1}H} (126 MHz, $CDCl_3$): δ 161.4, 147.6, 147.4, 134.3, 127.3, 127.0, 126.5, 121.6, 60.5, 49.7. HRMS (ESI) m/z: calcd for $C_{10}H_{11}N_2O_2$ [M + H]$^+$, 191.0815; found, 191.0805. mp 156 °C.

*Rutaecarpine (**8**).* A solution of **4c** (0.147 g, 0.5 mmol) in dry acetonitrile (5 mL) was cooled to 0 °C, after which trifluoroacetic anhydride (0.347 mL, 2.5 mmol) was added dropwise. The ice bath was removed, and the solution was stirred at room temperature for 30 min until TLC indicated complete consumption of **4c**. The resulting solid was filtered off, transferred to a 50 mL round-bottom flask, and resolvated in H_2O/EtOH (2:1, 7.5 mL). To this mixture were added KOH (0.056 g, 1.0 mmol) and H_2O_2 (30%, 1.13 mL, 3.0 mmol), and the resulting mixture was heated in a heating mantle to 60 °C for 4 h. The crude product was diluted with CH_2Cl_2 and quenched with $NaHCO_3$ (sat. aq.). The organic layer was dried over Na_2SO_4, concentrated in vacuo, and loaded onto silica. Purification was done by column chromatography (gradient EtOAc in cHex, 0−50%). The compound was isolated as a white solid (0.104 g, 72%). R_f = 0.57 (cHex/EtOAc = 2:1). ^{1}H NMR (500.23 MHz, DMSO-d_6): δ 11.89 (bs, 1H), 8.17 (dd, J = 1.6, 7.9 Hz, 1H), 7.82, (ddd, J = 1.6, 7.0, 8.3 Hz, 1H), 7.69 (d, J = 8.1 Hz, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.51−7.44 (m, 2H), 7.27 (ddd, J = 1.1, 6.9, 8.3 Hz, 1H), 7.09 (t, J = 7.5 Hz, 1H), 4.45 (t, J = 6.9 Hz, 2H), 3.18 (t, J = 6.9 Hz, 2H). ^{13}C NMR {^{1}H} (126 MHz, DMSO-d_6): δ 160.6, 147.4, 145.3, 138.7, 134.5, 127.1, 126.6, 126.5, 126.0, 124.9, 124.8, 120.7, 120.0, 119.8, 117.9, 112.6, 40.9, 19.0. HRMS (ESI) m/z: calcd for $C_{18}H_{14}N_3O$ [M + H]$^+$, 288.1131; found, 288.1120. mp 261 °C.

*Luotonin A (**9**).* To a solution of **4h** [3-((2-chloroquinolin-3-yl)methyl)quinazolin-4(3*H*)-one] (0.101 g, 0.3 mmol), K_3PO_4 (0.063 g, 0.3 mmol), and KOAc (0.060 g, 0.6 mmol) in dry DMF (3.0 mL) were added $Pd(OAc)_2$ (0.007 g, 0.03 mmol) and dppe (0.024 g, 0.06 mmol) in an oven-dried microwave vial. The vial was capped under N_2 and heated by microwave irradiation to 200 °C for 30 min. The crude product was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. The organic layer was dried over Na_2SO_4, concentrated in vacuo, and loaded onto SiO_2. The product was purified by column chromatography (gradient, 0−50% EtOAc in cHex). The title compound luotonin A was isolated as a white solid exhibiting blue fluorescence (0.075 g, 88%). The spectral data were in accordance with the reported literature.[19] ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.74 (s, 1H), 8.31−8.22 (m, 2H), 8.15 (d, J = 8.2 Hz, 1H), 7.96−7.86 (m, 3H), 7.75 (t, J = 7.5 Hz, 1H), 7.67−7.57 (m, 1H), 5.29 (s, 2H). ^{13}C NMR {^{1}H} (126 MHz, DMSO-d_6): δ 159.7, 153.1, 151.5, 149.0, 148.4, 134.5, 131.8, 131.0, 130.5, 129.7, 128.48, 128.46, 128.3, 128.1, 127.2, 125.9, 121.1, 47.6.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c00771.

Optimization experiments and NMR spectra of all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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