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Synthesis of *N*-Alkyl Substituted Benzimidazoquinazolinones

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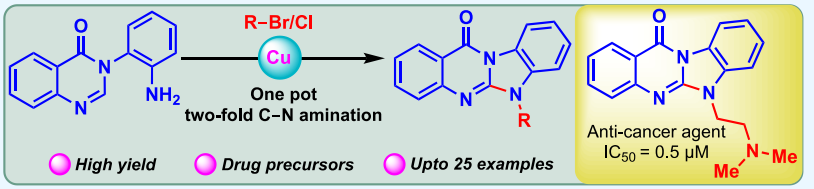

ABSTRACT: Aromatic *N*-heterocycles, especially benzimidazoquinazolinones featuring alkyl chains, hold significant pharmaceutical relevance. Here, we introduce a streamlined one-pot, 2-fold Cu-catalyzed C−N bond formation protocol for the efficient synthesis of diverse *N*-alkyl benzimidazoquinazolinone derivatives. This method showcases a broad substrate scope, leveraging readily accessible alkyl halides and delivers the desired cyclized products in excellent yields. Additionally, the methodology enabled the synthesis of an antitumor agent with satisfactory yield, highlighting its utility in medicinal chemistry endeavors.

INTRODUCTION

N-heterocycles are attractive scaffolds in the field of medicinal chemistry, and their building blocks are used in various biologically active compounds, natural products, advanced materials, and drug precursors.[1−4] In particular, fused *N*-heterocycles display a wide range of vital medicinal properties, such as in anticancer, antiviral, antibacterial, anti-inflammatory, anticonvulsant, and immunosuppresors.[5−12]

Among these, *N*-alkyl substituted benzimidazoquinazolinones are of great interest owing to their importance as alkaloid, antitumor activity and show significant therapeutic activities (Figure 1).[13−18] Therefore, the synthesis and derivatization of *N*-alkyl benzimidazoquinazolinones have been of great research interest. Studies of their functionalization are particularly valuable. Regioselective introduction of an alkyl or an aryl group into benzimidazoquinazolinones is of great interest as it can significantly diversify the structures and biological activity of the resulting products.[14−19] Alternatively, C−N bond formation via C−H functionalization has received significant importance over classical cross-coupling reactions.[20−22] Despite the efficiency of the Cu-catalyzed C−N bond formation protocol for synthesizing *N*-alkyl benzimidazoquinazolinones, it is important to note that the presence of free amine groups in the molecule can potentially poison the metal catalyst by forming stable complexes. This can adversely affect the catalytic activity, especially for further functionalization reactions.[21−24] Therefore, protecting the free amine group can increase the catalytic activity in the reaction. Such methods for one-pot *N*-alkylation as well as cyclization are limited and scarce in the literature. Recently, the scientific community reported the C−N bond formation to generate nitrogen-fused heterocycles.[25−34]

The synthesis of benzimidazoquinazolinones has been documented in several reports. In 2009, Molina and co-workers reported the synthesis of benzimidazoquinazolinones using an aza-Wittig reaction.[29a] Wang and co-workers

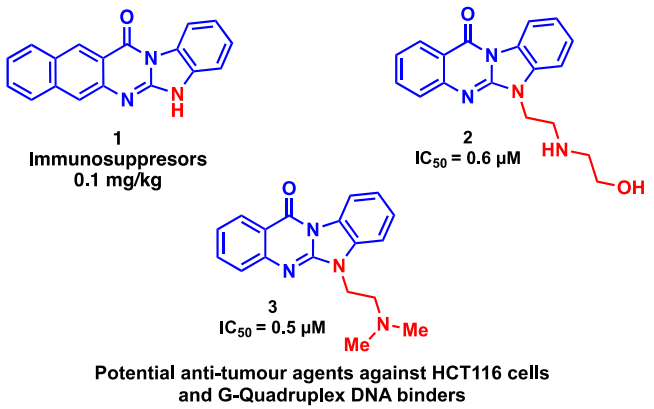

Figure 1. Representative biologically active *N*-heterocycles.

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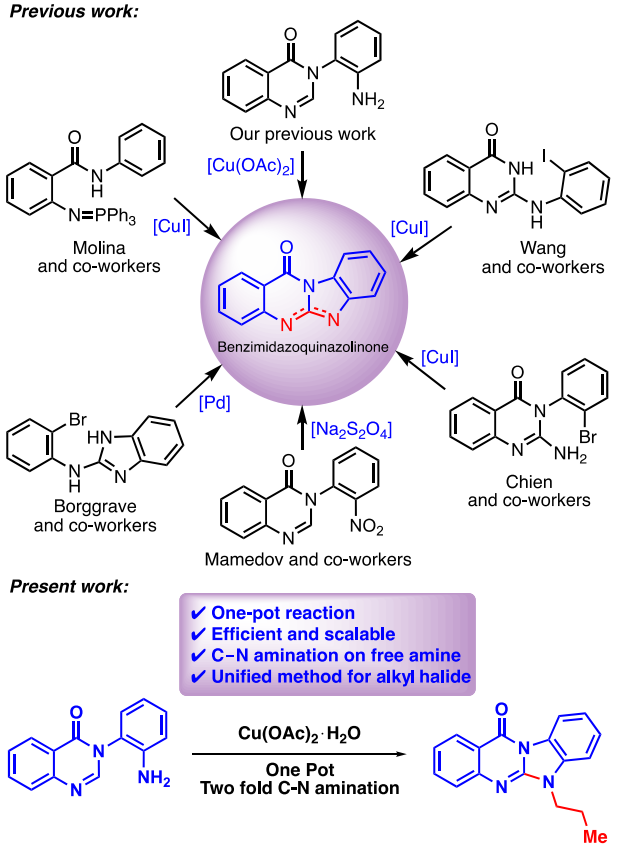
demonstrated C−N bond formation on benzimidazoquinazolinones using CuI as a catalyst, a strategy similar to that employed by Chien and co-workers.[30,31] Mamedov and co-workers described a method involving the reduction of the nitro group using $Na_2S_2O_4$ and Zn in AcOH.[32a,b] Recently, Borggrave reported the synthesis of benzimidazoquinazolinones[33] using a Pd catalyst with ex situ generation of CO (Scheme 1). To the best of our knowledge, there are few

Scheme 1. Strategies Toward Benzimidazoquinazolinones



reports on the alkylation of benzimidazoquinazolinone's imidazole nitrogen.[29a,b] These compounds exhibit high biological activities.[13−17] Our group has been contributing to copper-catalyzed amination reactions for over a decade.[23−28]

We have developed a robust copper-catalyzed one-pot C−N amination protocol for the efficient synthesis of *N*-aryl substituted benzimidazoquinazolinones.[34] Initially, our approach involved a Cu-catalyzed, 2-fold C−N bond formation protocol to couple 3-(2-aminophenyl)quinazolin-4(3H)-one with various aryl halides, yielding the desired products with significant success (Scheme 1). Building on this foundation, we now present an advanced one-pot, 2-fold C−N bond amination method specifically tailored for the synthesis of a series of biologically active *N*-alkyl benzimidazoquinazolinones (Scheme 1).

RESULTS AND DISCUSSION

In the initial phase of our study, we commenced our investigation using 3-(2-aminophenyl)quinazolin-4(3*H*)-one (**4**) and 1-bromopropane (**5a**) as our model substrates. Our first attempts involved reacting **4** with **5a** in the presence of CuI (20 mol %), KI (1.0 equiv), 1,10-phenanthroline (30 mol %), and K_3PO_4 in DMF at 120 °C for 24 h, which yielded **6a** in a modest 37% yield (Table 1, entry 1). Subsequently, employing CuCl as the catalyst led to a decrease in the yield of **6a** to 30% (Table 1, Entry 2). Upon testing various Cu(II) catalysts such as $CuBr_2$ and CuO, we observed a slight improvement in yields up to 55%. However, $Cu(OAc)_2{\cdot}H_2O$ emerged as the optimal catalyst, affording the desired product in an 88% yield (Table 1, entry 4). Further increasing the catalyst loading did not confer any advantages. We explored alternative nitrogen-containing ligands including 2,2′-bipyridine, pyridone, and pyridine due to their chelation properties. While 2,2′-bipyridine yielded the product in 46% yield, pyridine and pyridones only provided trace amounts of the product. Interestingly, phosphorus-based ligands such as PPh_3 and XantPhos completely inhibited the reaction (Supporting Information, S3).

In our investigation, we examined a variety of solvents, encompassing both polar and nonpolar such as dimethyl sulfoxide (DMSO), toluene, 1,4-dioxane, *N*,*N*-dimethylformamide (DMF), and acetonitrile (MeCN). Through this exploration, DMF emerged as the optimal solvent choice, providing the best yields for the desired products (Supporting Information, S5). Furthermore, we screened various inorganic and organic bases, but no significant improvements in yield were observed (Supporting Information, S6). Notably, in the presence of triethylamine, the reaction was completely suppressed. Employing three equivalents of K_3PO_4 was found to be suitable for this protocol (Supporting Information, S7). Omitting KI from the reaction mixture did not affect the product yield, suggesting its insignificant role in the reaction mechanism (Table 1, entry 15). We explored variations in reaction temperature but did not achieve better results than our optimal conditions. The conditions outlined in entry 15, Table 1, provided the highest yield of **6a**; thus, we established them as optimal and proceeded to investigate the substrate scope of this protocol (Scheme 2).

Expanding our scope, we successfully synthesized various cyclized *N*-alkyl benzimidazoquinazolinones (**6a**−**6c**) with good to excellent yields by reacting 3-(2-aminophenyl)-quinazolin-4(3*H*)-one (**4**) with aliphatic bromides of varying chain lengths (Scheme 2). Different chain-elongated and substituted allyl bromides yielded the desired products (**6d**−**6i**) in excellent yields. Furthermore, both electron-donating and electron-withdrawing group substituted benzyl bromides provided the desired products (**6j**−**6t**) in moderate to good yields. Remarkably, electron-donating groups yielded better results than electron-withdrawing substrates. The reaction with benzyl chloride and *p*-methoxybenzyl chloride yielded (**6o**) in 66% and (**6r**) in 68%, respectively. These results suggest that alkyl chlorides afford lower yields compared to those of their bromide counterparts. Encouragingly, our protocol was applicable to secondary alkyl bromides such as isopropyl bromide, for which we successfully obtained the crystal structure of **6u** (Scheme 2). Unfortunately, our attempts to use coupling partners such as epichlorohydrin, cyanomethyl bromide, and propargyl bromide were unsuccessful. We suspect that the nitrile group of cyanomethyl bromide acts as a catalytic poison. Additionally, we observed that at 120 °C, DMF's high reactivity can lead to its reaction with epichlorohydrin, involving epoxide ring opening and S_N2 displacement of the chloride, potentially facilitated by copper as a Lewis acid. The reaction is also amenable to gram-scale

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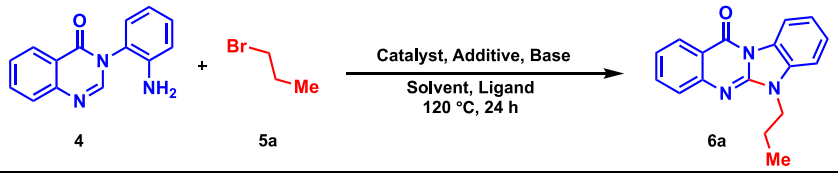
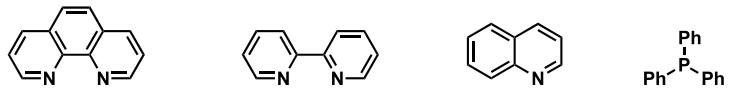
Table 1. Summary of Optimization of Reaction Conditions[a]



4 5a 6a

Entry	Catalyst	Ligand	Additive	Base	Solvent	Yield (%)
1	CuI	1,10-Phenanthroline	KI	K_3PO_4	DMF	37
2	CuCl	1,10-Phenanthroline	KI	K_3PO_4	DMF	30
3	$CuBr_2$	1,10-Phenanthroline	KI	K_3PO_4	DMF	55
4	$Cu(OAc)_2·H_2O$	1,10-Phenanthroline	KI	K_3PO_4	DMF	88
5	$Cu(OAc)_2·H_2O$	Quinoline	KI	K_3PO_4	DMF	23
6	$Cu(OAc)_2·H_2O$	2,2'-Bipyridine	KI	K_3PO_4	DMF	46
7	$Cu(OAc)_2·H_2O$	PPh_3	KI	K_3PO_4	DMF	Trace
8	$Cu(OAc)_2·H_2O$	1,10-Phenanthroline	KI	K_3PO_4	1,4-Dioxane	40
9	$Cu(OAc)_2·H_2O$	1,10-Phenanthroline	KI	K_3PO_4	CH_3CN	Trace
10	$Cu(OAc)_2·H_2O$	1,10-Phenanthroline	KI	Cs_2CO_3	DMF	52
11	$Cu(OAc)_2·H_2O$	1,10-Phenanthroline	KI	K_2CO_3	DMF	55
12	$Cu(OAc)_2·H_2O$	1,10-Phenanthroline	KI	Et_3N	DMF	NR
13	$Cu(OAc)_2·H_2O$	1,10-Phenanthroline	KI	NaOMe	DMF	Trace
14	$Cu(OAc)_2·H_2O$	1,10-Phenanthroline	KI	NaO^{t}Bu	DMF	81
15	**$Cu(OAc)_2·H_2O$**	1,10-Phenanthroline	**-**	**K_3PO_4**	**DMF**	**88**

Ligands:



1,10-Phenanthroline 2,2'-Bipyridine Quinoline PPh_3

[a]Reaction conditions: **4** (1.0 equiv), **5a** (2.0 equiv), catalyst (20 mol %), base (3.0 equiv), ligand (30 mol %), solvent (2.0 mL), 24 h.

synthesis, as demonstrated by a 73% yield when scaled up to a one-gram reaction.

We observed varying results when we substituted the amine moiety and performed the reaction under the same conditions. The reaction with 3-(2-aminophenyl)-6-methylquinazolin-4(3H)-one yielded the desired product in 76% yield. However, the reaction with 3-(2-aminophenyl)-6-methoxyquinazolin-4(3H)-one resulted in the formation of two nonseparable regioisomers. (Scheme 3).[28]

The synthetic utility of the developed methodology was further demonstrated through the late-stage diversification of **6d** for the synthesis of antitumor agent **3**.[16] Dihydroxylation of **6d** was performed with osmium tetraoxide to produce 1,2-diol **9**. This was treated by sodium metaperiodate to yield the corresponding aldehyde; without purification, this aldehyde was subjected to reductive amination to yield antitumor agent **3** (Scheme 4).

To gain more insights into the reaction mechanism, several control experiments were conducted. When the reaction was conducted in the presence of TEMPO, it proceeded well, indicating that it did not follow a radical mechanism. However, when the reaction was performed under an oxygen atmosphere, product formation was completely inhibited.

This suggests that the Cu^I catalyst generated in situ under the reaction conditions might be completely reoxidized to Cu^{II} by oxygen,[35a] and the unavailability of the active Cu^I catalyst led to the isolation of unchanged starting material. This highlights the importance of the Cu^I species, which is required for the polarization of 1-bromopropane. In further support of a mechanism involving Cu^I, when this reaction was carried out in the presence of CuI as a catalyst, 37% of the desired product was isolated (Table 1, entry 1). Moreover, it is well-established that Cu^{II} can be reduced to Cu^I by the mild reducing action of DMF.[35] These observations lead to the conclusion that Cu^{II} is the active species involved in the C−N amination reaction; also, this active species could be generated in situ by the oxidation of Cu^I with small quantities of dissolved oxygen present in the solvent system.

Based on the above investigations, a plausible mechanism for the synthesis of *N*-alkyl using $Cu(OAc)_2·H_2O$ is outlined here (Scheme 5). According to the literature precedent, the reductive generation of the active catalyst phen-Cu^I **A** was

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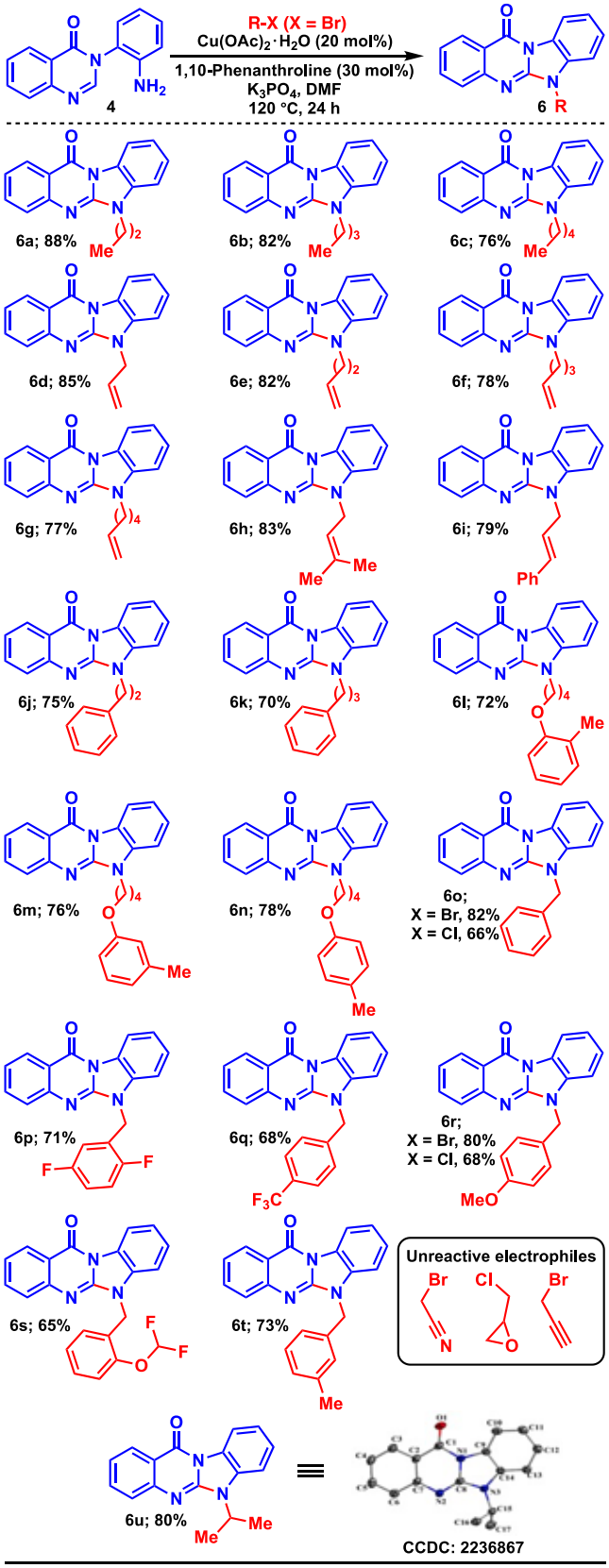
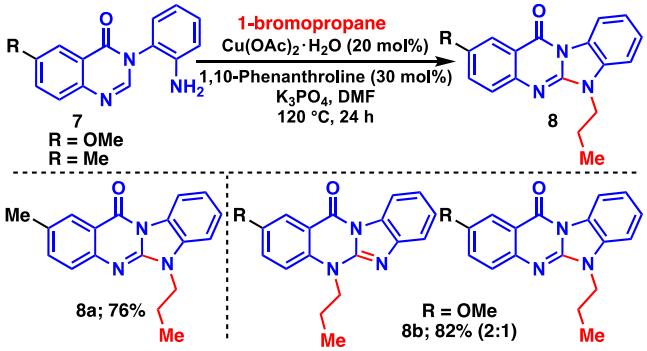
ACS Omega 2024, 9, 33805−33814

Scheme 2. Scope of *N*-Alkyl Benzimidazoquinazolinones[a]

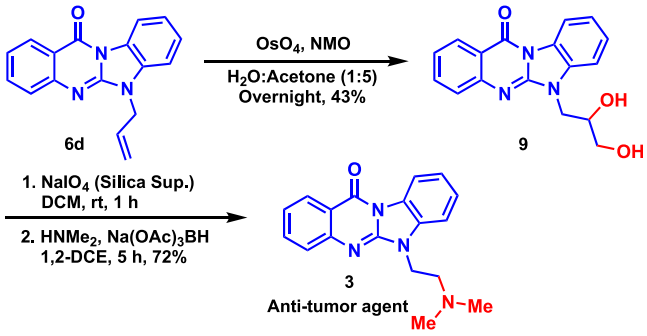


[a]Reaction conditions: **4** (1.0 equiv), **5** (2.0 equiv), $Cu(OAc)_2{\cdot}H_2O$ (20 mol %), 1,10-phenanthroline (30 mol %), K_3PO_4 (3.0 equiv), DMF (2.0 mL), 120 °C, 24 h.

Scheme 3. Substrate Scope with Amine Variation



Scheme 4. Synthesis of Antitumor Agent



achieved from $Cu(OAc)_2{\cdot}H_2O$ by the mild reducing action of DMF.[35] Then, phen-Cu^I A undergoes oxidative addition[36] of 1-bromopropane to yield the Cu^{III} species **B**. Subsequently, reductive C−N coupling takes place to give Cu^I species **D**. This Cu^I species is oxidized in situ to provide Cu^{III} intermediate **E**,[37] which, in turn, undergoes acetate-ligand-assisted, concerted C−N amination to afford **F**. Finally, reductive elimination gives product **6a** and regenerates the intermediate **A** for the sequent catalytic cycle.

CONCLUSIONS

In summary, we have developed a synthetic route for producing *N*-alkyl substituted benzimidazoquinazolinone derivatives using a Cu(II) catalyst with various alkyl and substituted alkyl halides. This protocol demonstrates tolerance toward different aliphatic halides, including those with terminal and internal olefin moieties. Additionally, substituted benzyl bromides with both electron-donating and -withdrawing groups are compatible with our method. We achieved a late-stage modification of our product, leading to the successful synthesis of an antitumor agent: 6-(2-(dimethylamino)ethyl)-benzo[4,5]imidazo[2,1-*b*]quinazolin-12(6H)-one **3**.

EXPERIMENTAL SECTION

General Information. Unless otherwise mentioned, all chemicals were obtained from commercial suppliers and used without further purification. Column chromatography purifications were performed using 100−200 mesh silica gel with freshly distilled solvents. Commercial grade solvents and reagents were used without further purification. Experiments involving moisture and/or air sensitive components were performed in oven-dried glassware under a positive pressure of nitrogen by using freshly distilled solvents. Analytical thin-layer chromatography (TLC) was performed using a Merck 60 F254

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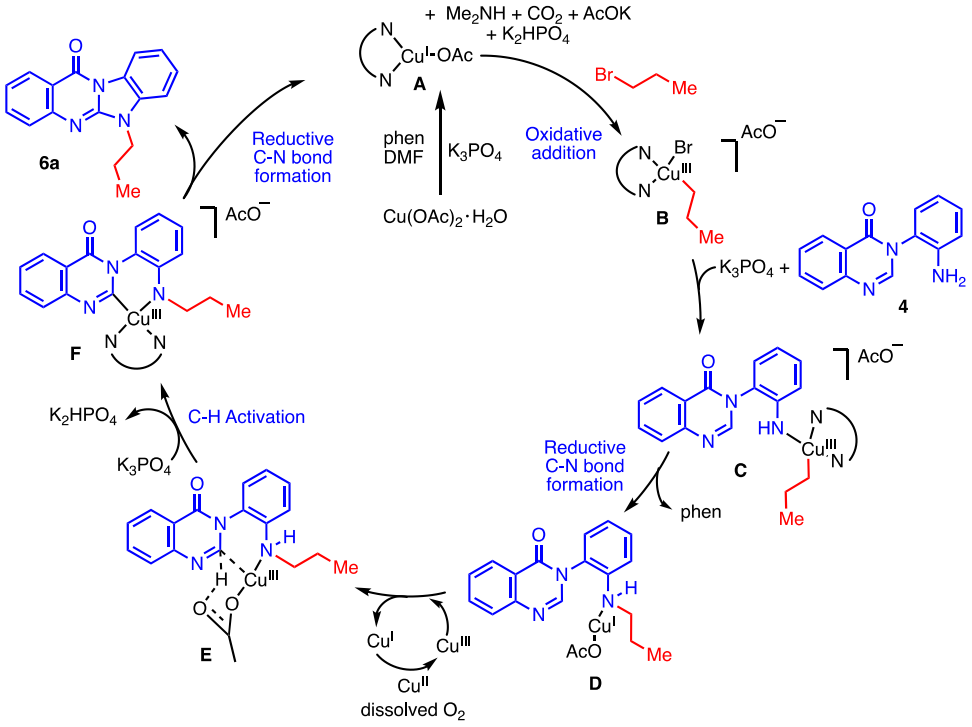
Scheme 5. Plausible Reaction Mechanism



precoated silica gel plate (0.2 mm thickness). Subsequent to elution, plates were visualized using UV radiation (254 nm). Further visualization was possible by staining with a basic solution of potassium permanganate or an acidic solution of ceric ammonium phosphomolybdate. For some compounds, column chromatography was performed using neutral alumina. Columns were typically packed as slurry and equilibrated with the appropriate solvent system prior to use. Melting points were uncorrected and were recorded on a Buchi B-545 melting point apparatus. IR spectra were recorded with a JASCO V-570 instrument. High-resolution mass spectral analysis (HRMS) was performed on a Bruker maXis impact 282001.00081 ESI-QTOF instrument. ^{1}H NMR and ^{13}C NMR experiments were performed with a Bruker AVANCE III HD 400 and 500 MHz NMR spectrometer. Chemical shifts for 1H NMR spectra are reported as δ in units of parts per million (ppm) downfield from tetramethylsilane (δ = 0.0) and relative to the residual solvent signals ($CDCl_3$, δ = 7.26 (s). Chemical shifts of proton decoupled ^{13}C NMR spectra are reported as δ in units of parts per million (ppm) relative to the solvent signal ($CDCl_3$, δ = 77.2, multiplicities have been represented as s (singlet); d (doublet); t (triplet); q (quartet); quint (quintet); hept (heptet); dd (doublets of doublet); dt (doublets of triplet), or m (multiplets). The number of protons (n) for a given resonance was indicated by nH. Coupling constants are reported as J values in Hz.

Synthesis of *N*-Alkyl Substituted Benzimidazoquinazolinones (General Procedure 1-GP1). To an oven-dried screw cap reaction tube charged with a magnetic stir-bar, $Cu(OAc)_2{\cdot}H_2O$ (0.2 equiv) and K_3PO_4 (3.0 equiv) were added to a mixture of 3-(2-aminophenyl)quinazolin-4(3*H*)-one **4** (1.0 equiv) and phenanthroline (0.3 equiv) in dry DMF under N_2 atmosphere. The reaction was stirred at room temperature for 15 min, and then aliphatic bromide (2 equiv) was added under N_2 atmosphere. Then, the reaction mixture was closed with a screw cap and degassed by a N_2 stream for 2 min. The reaction tube was kept in an oil bath and stirred at 120 °C for 24 h. The reaction mixture was brought to room temperature, filtered through a pad of Celite, and further washed with EtOAc. The combined filtrates were concentrated. The crude product was purified by column chromatography to give compound **6**.

6-Propylbenzo[4,5]imidazo[2,1-*b*]quinazolin-12(6*H*)-one (6a). Following **GP1**, a reaction was carried out between 3-(2-aminophenyl)quinazolin-4(3*H*)-one **4** (100 mg, 0.42 mmol, 1.0 equiv) and 1-bromopropane (102 mg, 0.84 mmol, 2.0 equiv). Product **6a** (103 mg, 88%) was obtained as a white solid. Mp: 206−207 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 (d, J = 8.0 Hz, 1H), 8.39 (d, J = 8.0 Hz, 1H), 7.71 (t, J = 7.6 Hz, 1H), 7.64 (d, J = 7.8 Hz, 1H), 7.43 (t, J = 7.8 Hz, 1H), 7.34−7.25 (m, 3H), 4.24 (t, J = 7.3 Hz, 2H), 1.98−1.92 (m, 2H), 1.05 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.1, 149.3, 146.4, 134.3, 131.9, 126.9, 125.9, 125.8, 2.6, 122.8, 121.9, 116.7, 116.3, 108.1, 77.4, 77.1, 76.7, 43.7, 21.4, 11.4; FT-IR (KBr, cm^{-1}): 3566, 3042, 2937, 2353, 1682, 1624, 1602, 1466, 1195, 747, 718; m/z: calc. for $C_{17}H_{16}N_3O$ $[M + H]^+$ is 278.1288, found 278.1287.

6-Butylbenzo[4,5]imidazo[2,1-*b*]quinazolin-12(6*H*)-one (6b). Following **GP1**, a reaction was carried out between 3-(2-aminophenyl)quinazolin-4(3*H*)-one **4** (100 mg, 0.42 mmol, 1.0 equiv) and 1-bromobutane (116 mg, 0.84 mmol, 2.0 equiv). Product **6b** (101 mg, 82%) was obtained as a white solid. Mp: 202−203 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 (d, J = 8.0 Hz, 1H), 8.40 (d, J = 8.0 Hz, 1H), 7.71 (t, 7.22 Hz, 1H), 7.65 (d, J = 8.2 Hz, 1H), 7.44 (t, J = 7.8 Hz, 1H), 7.33−7.26 (m, 3H), 4.28 (t, J = 7.4 Hz, 2H), 1.93−1.86 (m, 2H), 1.51−1.42 (m, 2H), 1.00 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.1, 149.2, 146.2, 134.3, 131.8, 126.9, 125.9, 125.8, 125.6, 122.8, 121.9, 116.7, 116.3, 108.1, 77.7, 77.0, 76.7, 41.9, 30.1, 20.1, 13.8; FT-IR (KBr, cm^{-1}): 3491, 2934, 1683, 1625, 1602, 1465, 746; m/z: calc. for $C_{18}H_{18}ON_3$ $[M + H]^+$ 292.1444, found 292.1444.

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6-Pentylbenzo[4,5]imidazo[2,1-*b*]quinazolin-12(6*H*)-one (6c). Following **GP1**, a reaction was carried out between 3-(2-aminophenyl)quinazolin-4(3*H*)-one **4** (100 mg, 0.42 mmol, 1.0 equiv) and 1-bromopentane (127 mg, 0.84 mmol, 2.0 equiv). Product **6c** (99 mg, 76%) was obtained as a white solid. Mp: 198−199 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 (d, J = 7.7 Hz, 1H), 8.41 (d, J = 7.7 Hz, 1H), 7.72 (t, J = 7.1 Hz, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.43 (t, J = 7.4 Hz, 1H), 7.34−7.26 (m, 3H), 4.27 (t, J = 7.0 Hz, 2H), 1.97−1.92 (m, 2H), 1.45−1.41 (m, 4H), 0.93 (t, J = 6.7 Hz 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.1, 149.4, 146.8, 134.3, 131.8, 126.9, 125.9, 125.8, 125.7, 122.7, 121.9, 116.7, 116.3, 108.1, 77.3, 77.1, 76.8, 42.1, 28.9, 27.7, 22.4, 13.9; FT-IR (KBr, cm^{-1}): 3844, 3734, 3616, 3498, 2934, 1679, 1620, 1605, 1467, 1239, 1191, 858, 747; m/z: calc. for $C_{19}H_{20}N_3O$ $[M + H]^+$ is 306.1601 found 306.1600.

6-Allylbenzo[4,5]imidazo[2,1-*b*]quinazolin-12(6*H*)-one (6d). Following **GP1**, a reaction was carried out between 3-(2-aminophenyl)quinazolin-4(3*H*)-one **4** (100 mg, 0.42 mmol, 1.0 equiv) and 3-bromoprop-1-ene (102 mg, 0.84 mmol, 2.0 equiv). Product **6d** (99 mg, 85% yield) was obtained as a white solid. Mp: 203−205 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.66 (d, J = 7.5 Hz, 1H), 8.42 (d, J = 7.5 Hz, 1H), 7.73 (d, J = 6.9 Hz, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.43 (d, J = 7.3 Hz, 1H), 7.35 (d, J = 6.6 Hz, 2H), 7.28 (d, J = 7.8 Hz, 1H), 6.11−5.99 (m, 1H), 5.33−5.29 (m, 2H), 4.95 (d, J = 5.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.0, 149.2, 146.3, 134.4, 131.6, 130.9, 126.9, 125.9, 125.9, 125.7, 122.9, 122.2, 118.4, 116.8, 116.3, 108.7, 77.4, 77.0, 76.7, 44.3; FT-IR (KBr, cm^{-1}): 3061, 2938, 1684, 1618, 1601, 1471, 1408, 1339, 1188, 922, 1151, 756; m/z: calc. for $C_{17}H_{13}ON_3Na$ $[M + Na]^+$ is 298.0951 found 298.0951.

6-(But-3-en-1-yl)benzo[4,5]imidazo[2,1-*b*]quinazolin-12(6*H*)-one (6e). Following **GP1**, a reaction was carried out between 3-(2-aminophenyl)quinazolin-4(3*H*)-one **4** (100 mg, 0.42 mmol, 1.0 equiv) and bromobut-1-ene (114 mg, 0.84 mmol, 2.0 equiv). Product **6e** (101 mg, 82%) was obtained as a white solid. Mp: 215−216 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, J = 7.9 Hz, 1H), 8.39 (dd, J = 7.9, 1.3 Hz, 1H), 7.73−7.71 (m, 1H), 7.64 (d, J = 8.2 Hz, 1H), 7.45−3.41 (m, 1H), 7.34−7.30 (m, 2H), 7.27 (s, 1H), 5.93−5.83 (m, 1H), 5.13−5.03 (m, 2H), 4.33 (t, J = 7.4, 2H), 2.68 (q, J = 7.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 149.3, 146.3, 134.3, 134, 131.7, 127.1, 126.9, 125.9, 125.8, 125.7, 122.8, 121.9, 117.9, 116.8, 116.4, 116.3, 108.1, 77.4, 77, 76.7, 41.5, 32.2; FT-IR (KBr, cm^{-1}): 3823, 3591, 3425, 3057, 2930, 2342, 1732, 1679, 1654, 1625, 1604, 1557, 1466, 1407, 1372, 1346, 1246, 1189, 1064, 996, 915.0; m/z: calc. for $C_{19}H_{18}ON_3$ $[M + H]^+$ is 290.1288 found 290.1285.

6-(Pent-4-en-1-yl)benzo[4,5]imidazo[2,1*b*]-quinazolin-12(6*H*)-one (6f). Following **GP1**, a reaction was carried out between 3-(2-aminophenyl)quinazolin-4(3*H*)-one **4** (100 mg, 0.42 mmol, 1.0 equiv) and 5-bromopent-1-ene (125 mg, 0.84 mmol, 2.0 equiv). Product **6f** (100 mg, 78%) was obtained as a white solid. Mp: 190−191 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, J = 7.9 Hz, 1H), 8.37 (dd, J = 8.0, 1.2 Hz, 1H), 7.73−7.69 (m, 1H), 7.61 (d, J = 7.9 Hz, 1H), 7.41 (t, J = 7.8 Hz, 1H), 7.34−7.25 (m, 3H), 5.91−5.81 (m, 1H), 5.11−5.02 (m, 2H), 4.26 (t, J = 7.3 Hz, 2H), 2.19 (dd, J = 14.1, 7.0 Hz, 2H), 2.07−1.99 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 149.3, 146.4, 137.1, 134.3, 131.8, 127.1, 127, 126.9, 125.9, 125.8, 125.7, 122.8, 121.9, 116.7, 116.4, 116.3, 115.8, 108, 77.3, 77, 76.7, 41.5, 30.8, 26.8; FT-IR (KBr, cm^{-1}): 3965, 3737, 3564, 3061, 2925, 1678, 1618, 1602, 1466, 1411, 1241, 1183, 1159, 1071; m/z: calc. for $C_{19}H_{18}ON_3$ $[M + H]^+$ is 304.1444 and found 304.1443.

6-(Hex-5-en-1-yl)benzo[4,5]imidazo[2,1-*b*]-quinazolin-12(6*H*)-one (6g). Following **GP1**, a reaction was carried out between 3-(2-aminophenyl)quinazolin-4(3*H*)-one **4** (100 mg, 0.42 mmol, 1.0 equiv) and 6-bromohex-1-ene (137 mg, 0.84 mmol, 2.0 equiv). Product **6g** (103 mg, 77%) was obtained as a white solid. Mp: 154−155 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, J = 8.0 Hz, 1H), 8.39 (d, J = 8.0 Hz, 1H), 7.71 (t, J = 7.6 Hz, 1H), 7.63 (d, J = 8.2 Hz, 1H), 7.42 (t, J = 7.7 Hz, 1H), 7.37−7.23 (m, 3H), 5.83−5.73 (m, 1H), 5.04−4.94 (m, 2H), 4.27 (t, J = 7.3 Hz, 2H), 2.15 (q, J = 7.1 Hz, 2H), 1.96−1.88 (m, 2H), 1.57−1.50 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 149.4, 146.4, 138.1, 134.3, 131.8, 127.1, 126.9, 126.9, 125.9, 125.8, 125.7, 122.8, 121.91, 116.7, 116.4, 116.3, 115.1, 108, 77.4, 77.1, 76.7, 41.9, 33.3, 27.4, 26.1; FT-IR (KBr, cm^{-1}): 3777, 3560, 3436, 2914, 1676, 1618, 1601, 1465, 1184, 914; m/z: calc. for $C_{20}H_{20}ON_3$ $[M + H]^+$ is 318.1601 found 318.160.

6-(3-Methylbut-2-en-1-yl)benzo[4,5]imidazo[2,1 *b*]-quinazolin-12(6*H*)-one (6h). Following **GP1**, a reaction was carried out between 3-(2-aminophenyl)quinazolin-4(3*H*)-one **4** (100 mg, 0.42 mmol, 1.0 equiv) and 1-bromo-3-methylbut-2-ene (126 mg, 0.84 mmol, 2.0 equiv). Product **6h** (106 mg, 83%) was obtained as a white solid. Mp: 203−204 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 (d, J = 7.9 Hz, 1H), 8.40 (dd, J = 8.0, 1.2 Hz, 1H), 7.74−7.70 (m, 1H), 7.65 (d, J = 7.8 Hz, 1H), 7.45−7.41 (m, 1H), 7.34−7.29 (m, 2H), 7.24 (d, J = 8.0 Hz, 1H), 5.38−5.35 (m, 1H), 4.91 (d, J = 6.8 Hz, 2H), 1.96 (s, 3H), 1.76 (d, J = 0.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.1, 149.3, 146.2, 137.7, 134.3, 131.6, 126.9, 125.9, 125.6, 122.7, 121.9, 117.8, 116.7, 116.2, 108.4, 77.4, 77.1, 76.7, 40.1, 25.7, 18.3; FT-IR (KBr, cm^{-1}): 2911, 1688, 1603, 1624, 1466, 1180, 764; m/z: calc. for $C_{19}H_{18}ON_3$ $[M + H]^+$ is 304.1444 found 304.1445.

6-Cinnamylbenzo[4,5]imidazo[2,1-*b*]quinazolin-12(6*H*)-one (6i). Following **GP1**, a reaction was carried out between 3-(2-aminophenyl)quinazolin-4(3*H*)-one **4** (100 mg, 0.42 mmol, 1.0 equiv) and cinnamyl bromide (166 mg, 0.84 mmol, 2.0 equiv). Product **6i** (117 mg, 79%) was obtained as a white solid. Mp: 215−216 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.68 (d, J = 8.1 Hz, 1H), 8.44 (d, J = 7.9 Hz, 1H), 7.76 (t, J = 7.4 Hz, 1H), 7.69 (d, J = 8.2 Hz, 1H), 7.47−7.41 (m, 1H), 7.41−7.31 (m, 7H), 7.30−7.22 (m, 2H), 6.73 (d, J = 15.9 Hz, 1H), 6.40 (dt, J = 15.9, 5.9 Hz, 1H), 5.11 (d, J = 5.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.1, 149.2, 146.3, 135.9, 134.4, 133.7, 131.6, 128.6, 128.1, 127.1, 126.6, 126.1, 125.9, 125.7, 123.1, 122.3, 122.2, 116.9, 116.3, 108.7, 77.4, 77.1, 76.7, 44.1; FT-IR (KBr, cm^{-1}): 3047, 2945, 1686, 1622, 1600, 1469, 1180, 910, 968, 739; m/z: calc. for $C_{23}H_{18}ON_3$ $[M + H]^+$ is 352.1444 found 352.1442.

6-Phenethylbenzo[4,5]imidazo[2,1-*b*]quinazolin-12(6*H*)-one (6j). Following **GP1**, a reaction was carried out between 3-(2-aminophenyl)quinazolin-4(3*H*)-one **4** (100 mg, 0.42 mmol, 1.0 equiv) and (2-bromoethyl)benzene (156 mg, 0.84 mmol, 2.0 equiv). Product **6j** (107 mg, 75%) was obtained as a white solid. Mp: 118−119 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.61 (d, J = 7.7 Hz, 1H), 8.40 (d, J = 7.8 Hz, 1H), 7.72 (t, J = 7.4 Hz, 1H), 7.67 (d, J = 7.9 Hz, 1H), 7.74−7.66 (m, 2H), 7.24 (d, J = 14.5 Hz, 6H), 7.05 (d, J = 7.6 Hz, 1H), 4.48 (t, J = 7.1 Hz, 2H), 3.20 (t, J = 7.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.1, 149.3, 146.3, 137.9, 134.4,

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131.6, 128.9, 128.7, 126.9, 126.9, 125.9, 125.7, 122.9, 121.9, 116.8, 116.3, 107.9, 77.4, 77.1, 76.7, 43.7, 34.2; FT-IR (KBr, cm^{-1}): 3843, 3051, 2933, 1682, 1619, 1602, 1463, 1408, 1173, 874, 741; *m/z*: calc. for $C_{22}H_{18}N_3O$ $[M + H]^+$ is 340.1444 found 340.1441.

6-(3-Phenylpropyl)benzo[4,5]imidazo[2,1 *b*]-quinazolin-12(6*H*)-one (6k). Following **GP1**, a reaction was carried out between 3-(2-aminophenyl)quinazolin-4(3*H*)-one **4** (100 mg, 0.42 mmol, 1.0 equiv) and (3-bromopropyl)-benzene (168 mg, 0.84 mmol, 2.0 equiv). Product **6k** (101 mg, 70%) was obtained as a white solid. Mp: 155−156 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.65 (d, J = 7.9 Hz, 1H), 8.43 (d, J = 8.0 Hz, 1H), 7.76 (t, J = 7.0 Hz, 1H), 7.68 (d, J = 8.2 Hz, 1H), 7.44 (t, J = 7.7 Hz, 1H), 7.40−7.33 (m, 2H), 7.28 (t, J = 7.3 Hz, 3H), 7.20 (dd, J = 17.7, 6.9 Hz, 4H), 4.34 (t, J = 7.2 Hz, 2H), 2.82 (t, J = 7.5 Hz, 2H), 2.35−2.27 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.1, 149.3, 146.4, 140.6, 134.4, 131.7, 128.4, 128.3, 127, 126.2, 125.9, 125.9, 125.8, 122.9, 122, 116.8, 116.7, 108.1, 77.4, 77.1, 76.7, 41.6, 32.9, 29.1; FT-IR (KBr, cm^{-1}): 3838, 3043, 2926, 1686, 1624, 1603, 1468, 1239, 1171, 748; *m/z*: calc. for $C_{23}H_{19}ON_3Na$ $[M + Na]^+$ is 376.1420, found 376.1420.

6-(4-(o-Tolyloxy)butyl)benzo[4,5]imidazo[2,1 b]-quinazolin-12(6*H*)-one (6l). Following **GP1**, a reaction was carried out between 3-(2-aminophenyl)quinazolin-4(3*H*)-one **4** (100 mg, 0.42 mmol, 1.0 equiv) and 1-(4-bromobutoxy)-2-methylbenzene (335 mg, 0.84 mmol, 2.0 equiv). Product **6l** (121 mg, 72%) was obtained as a white solid. Mp: 159−161 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.67 (d, J = 7.9 Hz, 1H), 8.41 (dd, J = 8.0, 1.4 Hz, 1H), 7.74−7.70 (m, 1H), 7.64−7.62 (m, 1H), 7.46−7.42 (m, 1H), 7.35−7.27 (m, 3H), 7.13−7.10 (m, 2H), 6.85 (td, J = 7.4, 0.8 Hz, 1H), 6.79 (d, J = 8.3 Hz, 1H), 4.39 (t, J = 7.1 Hz, 2H), 4.06 (t, J = 6.0 Hz, 2H), 2.19 (s, 3H), 2.18−2.13 (m, 1H), 1.98−1.91 (m, 2H), 1.71 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.1, 156.9, 149.3, 146.5, 134.3, 131.7, 130.7, 126.9, 126.8, 126.1, 125.9, 125.7, 122.9, 122.1, 120.4, 116.8, 116.4, 110.9, 108.1, 77.4, 77.1, 76.7, 66.9, 41.7, 26.6, 24.8, 16.3; FT-IR (KBr, cm^{-1}): 3885, 3571, 2926, 1685, 1625, 1604, 1468, 1244, 745; *m/z*: calc. for $C_{25}H_{24}N_3O_2$ $[M + H]^+$ is 398.1863 found 398.1864.

6-(4-(m-Tolyloxy)butyl)benzo[4,5]imidazo[2,1 b]-quinazolin-12(6*H*)-one (6m). Following **GP1**, a reaction was carried out between 3-(2-aminophenyl)quinazolin-4(3*H*)-one **4** (100 mg, 0.42 mmol, 1.0 equiv) and 1-(4-bromobutoxy)-3-methylbenzene (335 mg, 0.84 mmol, 2.0 equiv). Product **6m** (128 mg, 76%) was obtained as a white solid. Mp: 98−99 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.65 (d, J = 7.9 Hz, 1H), 8.40 (dd, J = 8.0, 1.3 Hz, 1H), 7.74−7.70 (m, 1H), 7.64 (d, J = 8.2 Hz, 1H), 7.44−7.42 (m, 1H), 7.34−7.26 (m, 3H), 7.14 (t, J = 7.7 Hz, 1H), 6.80−6.72 (m, 1H), 6.68 (d, J = 8.8 Hz, 2H), 4.43−4.33 (m, 2H), 4.04 (t, J = 6.1 Hz, 2H), 2.29 (d, J = 11.3 Hz, 3H), 2.19−2.09 (m, 2H), 1.96−9.91 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 158.8, 149.3, 146.4, 139.5, 134.4, 131.7, 129.2, 126.9, 126.1, 125.9, 125.7, 122.7, 122.1, 121.6, 116.8, 116.4, 115.4, 111.3, 108.1, 77.4, 77.1, 76.7, 66.9, 41.7, 26.5, 24.8, 21.5; FT-IR (KBr, cm^{-1}): 3482, 2931, 1684, 1625, 1603, 1467, 1263, 1056, 765; *m/z*: calc. for $C_{25}H_{23}N_3O_2$ $[M + H]^+$ is 398.1863 found 398.1865.

6-(4-(p-Tolyloxy)butyl)benzo[4,5]imidazo[2,1 b]-quinazolin-12(6*H*)-one (6n). Following **GP1**, a reaction was carried out between 3-(2-aminophenyl)quinazolin-4(3*H*)-one **4** (100 mg, 0.42 mmol, 1.0 equiv) and 1-(4-bromobutoxy)-4-methylbenzene (335 mg, 0.84 mmol, 2.0 equiv). Product **6n** (131 mg, 78%) was obtained as a white solid. Mp: 134−135 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, J = 7.9 Hz, 1H), 8.41 (d, J = 8.0 Hz, 1H), 7.72 (t, J = 7.6 Hz, 1H), 7.64 (d, J = 8.2 Hz, 1H), 7.44 (t, J = 7.6 Hz, 1H), 7.38−7.27 (m, 3H), 7.05 (d, J = 8.3 Hz, 2H), 6.77 (d, J = 8.4 Hz, 2H), 4.37 (t, J = 7.2 Hz, 2H), 4.02 (t, J = 6.0 Hz, 2H), 2.28 (s, 3H), 2.19−2.09 (m, 2H), 1.97−1.86 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 156.7, 149.3, 146.5, 134.3, 131.7, 130.1, 129.9, 126.9, 126.1, 125.9, 125.7, 122.9, 122.1, 116.7, 116.4, 114.4, 108.1, 77.4, 77.1, 76.7, 67.2, 41.7, 26.5, 24.8, 20.5; FT-IR (KBr, cm^{-1}): 3711, 2938, 1685, 1625, 1604, 1509, 1468, 1405, 1244, 1180, 1038, 914, 765; *m/z*: calc. for $C_{25}H_{23}N_3O_2$ $[M + H]^+$ is 398.1863 found 398.1863.

6-Benzylbenzo[4,5]imidazo[2,1-*b*]quinazolin-12(6*H*)-one (6o). Following **GP1**, a reaction was carried out between 3-(2-aminophenyl)quinazolin-4(3*H*)-one **4** (100 mg, 0.42 mmol, 1.0 equiv) and benzyl bromide (335 mg, 0.84 mmol, 2.0 equiv). Product **6o** (112 mg, 82%) was obtained as a white solid. Mp: 218−220 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 (d, J = 7.8 Hz, 1H), 8.42 (d, J = 8.0 Hz, 1H), 7.74 (t, J = Hz, 1H), 7.67 (d, J = 8.2 Hz, 1H), 7.42−7.36 (m, 4H), 7.37−7.32 (m, 4H), 7.31−7.27 (m, 3H), 7.16 (d, J = 7.8 Hz, 1H), 5.49 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.2, 149.4, 147.0, 135.5, 134.5, 131.7, 129.1, 128.2, 127.7, 127.2, 126.2, 125.9, 123.2, 122.4, 117.1, 116.5, 108.9, 77.5, 77.1, 76.8, 45.8; FT-IR (KBr, cm^{-1}): 2923, 1682, 1624, 1603, 1556, 1467, 1406, 1181, 749 *m/z*: calc. for $C_{21}H_{15}N_3O$ $[M + H]^+$ is 326.1298 found 326.1288.

6-(2,5-Difluorobenzyl)benzo[4,5]imidazo[2,1 *b*]-quinazolin-12(6*H*)-one (6p). Following **GP1**, a reaction was carried out between 3-(2-aminophenyl)quinazolin-4(3*H*)-one **4** (100 mg, 0.42 mmol, 1.0 equiv) and 2-(bromomethyl)-1,4-difluorobenzene (335 mg, 0.84 mmol, 2.0 equiv). Product **6p** (108 mg, 71%) was obtained as a white solid. Mp: 201−203 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.63 (d, J = 7.3 Hz, 1H), 8.41 (d, J = 7.4 Hz, 1H), 7.70 (dd, J = 25.8, 7.2 Hz, 2H), 7.43−7.30 (m, 3H), 7.25 (d, J = 7.3 Hz, 1H), 7.11 (d, J = 18.3 Hz, 2H), 6.96 (s, 1H), 5.50 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.0, 149.0, 146.5, 146.3, 134.4, 133.1, 127, 126.2, 125.8, 123.2, 122.5, 116.6, 116.3, 108.3, 38.7; ^{19}F NMR (376 MHz, $CDCl_3$): −117.4, −123.5; FT-IR (KBr, cm^{-1}): 3432, 2917, 1695, 1384, 1208, 1018, 824, 745, 709; *m/z*: calc. for $C_{21}H_{13}F_2N_3O$ $[M + H]^+$ is 362.1104 found 362.1099.

6-(4(Trifluoromethyl)benzyl)benzo[4,5]imidazo[2,1-*b*]quinazolin-12(6H)-one (6q). Following **GP1**, a reaction was carried out between 3-(2-aminophenyl)quinazolin-4(3*H*)-one **4** (100 mg, 0.42 mmol, 1.0 equiv) and 1-(bromomethyl)-4-(trifluoromethyl)benzene (201 mg, 0.84 mmol, 2.0 equiv). Product **6q** (113 mg, 68%) was obtained as a white solid. Mp: 234−235 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.66 (d, J = 7.9 Hz, 1H), 8.43 (d, J = 7.9 Hz, 1H), 7.75 (t, J = 7.0 Hz, 1H), 7.67 (d, J = 8.2 Hz, 1H), 7.45 (d, J = 8.5 Hz, 2H), 7.37.7.31 (m, 3H), 7.17 (t, J = 8.2 Hz, 3H), 5.49 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.0, 149.1, 146.6, 134.5, 134.1, 131.3, 129.1, 127.1, 126.1, 126.0, 125.8, 123.2, 122.5, 121.4, 117.0, 116.5, 108.4, 44.9; ^{19}F NMR (470 MHz, $CDCl_3$): −57.9; FT-IR (KBr, cm^{-1}): 3433, 2922, 1626, 1408, 1274, 1039; *m/z*: calc. for $C_{20}H_{20}ON_3$ $[M + H]^+$ is 394.1089 found 394.1086.

6-(3-Methoxybenzyl)benzo[4,5]imidazo[2,1 *b*]-quinazolin-12(6*H*)-one (6r). Following **GP1**, a reaction was carried out between 3-(2-aminophenyl)quinazolin-4(3*H*)-one **4** (100 mg, 0.42 mmol, 1.0 equiv) and 1-(chloromethyl)-

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4-methoxybenzene (169 mg, 0.84 mmol, 2.0 equiv). Product **6r** (118 mg, 80%) was obtained as a white solid. Mp: 210−211 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.66 (d, J = 7.8 Hz, 1H), 8.45 (d, J = 8.0 Hz, 1H), 7.80−7.75 (m, 1H), 7.73 (d, J = 8.1 Hz, 1H), 7.38 (t, J = 7.8 Hz, 4H), 7.32 (t, J = 7.7 Hz, 1H), 7.22 (d, J = 7.8 Hz, 1H), 6.88 (d, J = 8.1 Hz, 2H), 5.47 (s, 2H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.4, 146.7, 134.4, 131.5, 129.1, 127.8, 127.0, 126.0, 125.7, 123.0, 122.2, 116.8, 116.3, 114.3, 108.8, 77.3, 77.0, 76.8, 55.3, 45.2; FT-IR (KBr, cm^{-1}): 3840, 3444, 3220, 2911, 1678, 1606, 1466, 1244, 1176, 1039, 756; m/z: calc. for $C_{22}H_{18}O_2N_3$ $[M + H]^+$ is 356.1394, found 356.1393.

6-(2(Difluoromethoxy)benzyl)benzo[4,5]imidazo[2,1-*b*]quinazolin-12(6*H*)-one (6s). Following **GP1**, a reaction was carried out between 3-(2-aminophenyl)quinazolin-4(3*H*)-one **4** (100 mg, 0.42 mmol, 1.0 equiv) and 1-(bromomethyl)-2-(difluoromethoxy)benzene (199 mg, 0.84 mmol, 2.0 equiv). Product **6s** (107 mg, 65% yield) was obtained as a white solid. Mp: 220−221 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.7 (d, J = 7.8 Hz, 1H), 8.4 (dd, J = 8.0, 1.2 Hz, 1H), 7.77−7.72 (m, 1H), 7.7 (d, J = 8.1 Hz, 1H), 7.34−7.31 (m, 5H), 7.20 (dd, J = 12.9, 8.0 Hz, 2H), 7.11 (t, J = 7.5 Hz, 1H), 6.70 (t, J = 73.5 Hz, 1H), 5.58 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.0, 148.9, 146.7, 134.5, 131.5, 129.5, 129.3, 127.1, 126.9, 126.2, 125.9, 125.7, 123.6, 122.4, 118.9, 116.9, 116.3, 116.1, 114.0, 108.7, 77.3, 77.0, 76.8, 40.2; ^{19}F NMR (470 MHz, $CDCl_3$): −80.4, −80.6; FT-IR (KBr, cm^{-1}): 2342, 1679, 1620, 1601, 1468, 1132, 751, 1034, 123; m/z calc. for $C_{22}H_{16}F_2N_3O_2$ $[M + H]^+$ is 392.1205 found 392.1209.

6-(3-Methylbenzyl)benzo[4,5]imidazo[2,1 *b*]-quinazolin-12(6*H*)-one (6t). Following **GP1**, a reaction was carried out between 3-(2-aminophenyl)quinazolin-4(3*H*)-one **4** (100 mg, 0.42 mmol, 1.0 equiv) and 1-(bromomethyl)-3-methylbenzene (156 mg, 0.84 mmol, 2.0 equiv). Product **6t** (104 mg, 73%) was obtained as a white solid. Mp: 220−221 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.65 (d, J = 7.8 Hz, 1H), 8.43 (d, J = 7.9 Hz, 1H), 7.75 (t, J = 7.4 Hz, 1H), 7.69 (d, J = 8.1 Hz, 1H), 7.41−7.28 (m, 3H), 7.24−7.13 (m, 4H), 7.10 (d, J = 6.7 Hz, 1H), 5.47 (s, 2H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.1, 149.2, 146.7, 138.7, 135.2, 134.4, 131.6, 128.9, 128.8, 128.1, 127.0, 126.1, 126.0, 125.8, 124.6, 123.0, 122.2, 116.9, 116.3, 108.8, 77.4, 77.0, 76.7, 45.6, 21.4; FT-IR (KBr, cm^{-1}): 3586, 2941, 1686, 1623, 1603, 1466, 1403, 1344, 1181, 748; m/z: calc. for $C_{18}H_{18}ON_3$ $[M + H]^+$ is 340.1444, and found is 340.1444.

6-Isopropylbenzo[4,5]imidazo[2,1-*b*]quinazolin-12(6*H*)-one (6u). Following **GP1**, a reaction was carried out between 3-(2-aminophenyl)quinazolin-4(3*H*)-one **4** (100 mg, 0.42 mmol, 1.0 equiv) and 2-bromopropane (103 mg, 0.84 mmol, 2.0 equiv). Product **6u** (93 mg, 80%) was obtained as a white solid. Mp: 189−191 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.71 (d, J = 7.9 Hz, 1H), 8.40 (d, J = 7.9 Hz, 1H), 7.72 (t, J = 7.4 Hz, 1H), 7.64 (d, J = 8.2 Hz, 1H), 7.48−7.39 (m, 2H), 7.33 (d, J = 7.0 Hz, 2H), 5.33 (, 1H), 1.72 (s, 3H), 1.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.2, 149.7, 146.1, 134.3, 130.5, 126.9, 126.2, 125.7, 125.6, 122.7, 121.6, 116.5, 109.7, 77.3, 77.0, 76.7, 46.8, 20.1; FT-IR (KBr, cm^{-1}): 3487, 2978, 2343, 1683, 1598, 1557, 1463, 1395, 1132, 909, 748; m/z: calc. for $C_{17}H_{16}N_3O$ $[M + H]^+$ is 278.1288 found 278.1288; recrystallization solvent: dichloromethane.

2-Methyl-6-propylbenzo[4,5]imidazo[2,1-*b*]-quinazolin-12(6*H*)-one (8a). Following **GP1**, a reaction was carried out between 3-(2-aminophenyl)-6-methylquinazolin-4(3*H*)-one **7a** (100 mg, 0.42 mmol, 1.0 equiv) and 1-bromopropane **5a** (103 mg, 0.84 mmol, 2.0 equiv). Product **8a** (88 mg, 76%) was obtained as a white solid. Mp: 201−203 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, J = 7.8 Hz, 1H), 8.19 (s, 1H), 7.55 (s, 2H), 7.43 (d, J = 7.3 Hz, 1H), 7.34−7.24 (m, 2H), 4.26−4.21 (m, 2H), 2.49 (s, 3H), 1.96 (dd, J = 14.8, 7.4 Hz, 2H), 1.05 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.1, 147.4, 146.2, 136.0, 132.6, 132.0, 126.2, 125.9, 125.5, 121.8, 116.5, 116.4, 108.1, 77.5, 77.5, 76.8, 43.7, 21.4, 21.2, 11.5; FT-IR (KBr, cm^{-1}): 2960, 1683, 1615, 1605, 1490, 1190, 1136, 744; m/z: calc. for $C_{18}H_{18}ON_3$ $[M + H]^+$ is 292.1244, found 292.1483.

2-Methoxy-6-propylbenzo[4,5]imidazo[2,1-*b*]-quinazolin-12(6*H*)-one (8b). Following **GP1**, a reaction was carried out between 3-(2-aminophenyl)-6-methoxyquinazolin-4(3*H*)-one **7b** (100 mg, 0.37 mmol, 1.0 equiv) and 1-bromopropane **5a** (1 mg, 0.84 mmol, 2.0 equiv). Product **8a** (88 mg, 76%) was obtained as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 3.0 Hz, 1H), 7.60 (d, J = 9.0 Hz, 1H), 7.54 (d, J = 3.1 Hz, 1H), 7.43 (dd, J = 7.8, 1.0 Hz, 1H), 7.36 (dd, J = 9.0, 3.0 Hz, 1H), 7.34−7.27 (m, 1H), 7.11 (dd, J = 9.2, 3.1 Hz, 1H), 4.28 (t, J = 6.7 Hz, 2H), 4.25−4.19 (m, 1H), 3.93 (s, 2H), 3.82 (s, 3H), 1.95 (dd, J = 14.8, 7.4 Hz, 1H), 1.81 (dd, J = 14.2, 6.9 Hz, 2H), 1.04 (td, J = 7.4, 2.2 Hz, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9, 159.3, 155.7, 155.0, 144.2, 134.2, 132.2, 127.3, 126.1, 125.8, 125.3, 122.8, 121.8, 120.4, 116.8, 116.5, 115.3, 108.1, 106.0, 67.3, 55.9, 55.8, 43.8, 29.8, 22.1, 21.8, 11.6, 10.6; FT-IR (KBr, cm^{-1}): 3890, 3617, 2951, 1678, 1616, 1488, 1403, 1228, 1038, 825; m/z: calc. for $C_{18}H_{18}N_3O_2$ $[M + H]^+$ is 308.1394, found 308.1393. (Mixture of two nonseparable regioisomers)

Synthesis of 6-(2,3-Dihydroxypropyl)benzo[4,5]-imidazo[2,1-*b*]quinazolin-12(6*H*)-one (9). To a solution of compound **6d** (172 mg, 0.59 mmol) in H_2O:acetone (1:5, 6 mL) was added NMO (200 mg, 1.48 mmol), followed by the addition of OsO_4 (2 M solution in ^{t}BuOH, 0.12 mL, 0.06 mmol) at room temperature. The resulting mixture was stirred overnight before it was quenched with aq. $NaHSO_3$ (3 M,10 mL). The mixture was stirred for 30 min before it was diluted with brine and extracted with ethyl acetate (4 × 20 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude reaction mixture was purified by silica gel column chromatography using ethyl acetate/hexanes (4:1) to give 6-(2,3-dihydroxypropyl)benzo-[4,5]imidazo[2,1-*b*]quinazolin-12(6*H*)-one (**9**) as a white solid (84 mg, 43%). Mp: 136−140 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.63 (d, J = 8.0 Hz, 1H), 8.38 (d, J = 8.0 Hz, 1H), 7.89 (s, 1H), 7.79 (t, J = 7.4 Hz, 1H), 7.52 (s, 2H), 7.43 (t, J = 7.3 Hz, 2H), 4.75−4.51 (m, 2H), 4.27−4.17 (m, 1H), 3.73 (d, J = 4.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO): δ 159.6, 149.3, 147.1, 134.9, 133.0, 126.9, 126.4, 125.8, 125.6, 123.1, 122.1, 116.5, 115.4, 110.5, 69.5, 63.9, 45.9; FT-IR (KBr, cm^{-1}): 3420, 2918, 1839, 1600, 1468, 1361, 765, 751; m/z: calc. for $C_{17}H_{15}N_3O_3$ $[M + H]^+$ is 310.1186 found 310.1182.

6-(2-(Dimethylamino)ethyl)benzo[4,5]imidazo[2,1-*b*]-quinazolin-12(6*H*)-one (3). To a solution of **7** (78 mg, 0.252 mmol) in CH_2Cl_2 (10 mL) was added silica supported $NaIO_4$ (66 mg, 0.50 mmol). The slurry was stirred for 1 h and filtered, and the filtrate was evaporated under reduced pressure. The crude aldehyde was dissolved in 1,2-dichloroethane and treated with dimethyl amine (0.56 mmol, 1.12 mL, 2 M in THF) and $Na(OAc)_3BH$ (243 mg, 1.15 mmol). The resulting mixture was stirred at room temperature for 2 h and quenched with an

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aqueous saturated solution of $NaHCO_3$ (10 mL). After extraction with dichloromethane, the combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude reaction mixture was purified by flash column chromatography on silica gel to give desired product **3** as a white solid (56 mg, 72%). Mp: 162−164 °C; ^{1}H NMR (400 MHz, DMSO): δ 8.47 (d, J = 8.0 Hz, 1H), 8.23 (dt, J = 10.0, 5.0 Hz, 1H), 7.83−7.73 (m, 1H), 7.61 (dd, J = 11.6, 8.3 Hz, 2H), 7.55−7.48 (m, 1H), 7.39−7.31 (m, 2H), 4.37 (t, J = 6.4 Hz, 2H), 2.73 (t, J = 6.4 Hz, 2H), 2.22 (s, 6H); ^{13}C NMR (100 MHz, DMSO): 159.6, 149.4, 146.7, 134.9, 132.2, 126.9, 126.6, 126.0, 125.6, 123.1, 122.2, 116.5, 115.6, 109.9, 56.7, 45.8. (One carbon merging with DMSO-d_6 solvent at 40.28 confirmed by DEPT); FT-IR (KBr, cm^{-1}): 2918, 2854, 2355, 2332, 1620, 1605, 1407, 1046, 1022, 822, 766, 748; m/z: calc. for $C_{18}H_{19}N_4O$ $[M + H]^+$ is 307.1553 found 307.1554.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its online Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.4c03327.

Detailed experimental procedures, characterization data, NMR spectra, and X-ray crystal data of synthesized compounds (PDF)

Accession Codes

CCDC 2236867 contain 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/ structures or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 44 1223 336033.

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Notes

The authors declare no competing financial interest.

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