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Copper-Catalyzed Cascade Amination Route to *N*-Aryl Benzimidazoquinazolinones

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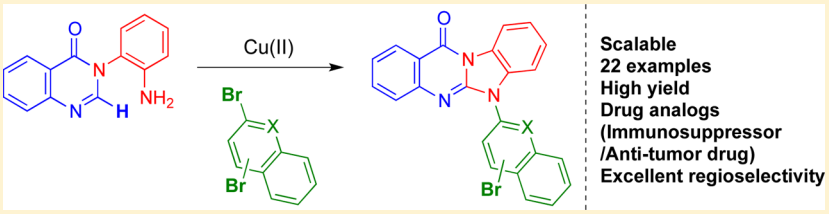
Supporting Information



ABSTRACT: An efficient one-pot Cu-catalyzed C−H functionalization/two-fold C−N bond formation protocol for the syntheses of *N*-aryl benzimidazoquinazolinones is being reported. This strategy involves a Cu-catalyzed C−N bond coupling reaction between *N*-anilinoquinazolinones and aryl/heteroaryl halides followed by acetate ligand-assisted intramolecular C−H amination.[1a] This reaction is high-yielding and straightforward for the synthesis of anti-cancer drug analogues of benzimidazoquinazolinones.

INTRODUCTION

Benzimidazole and quinazolinone are the privileged heterocycles[1b−h] present in many biologically active natural products (Figure 1).[2] Benzimidazoquinazolinones, another class of fused

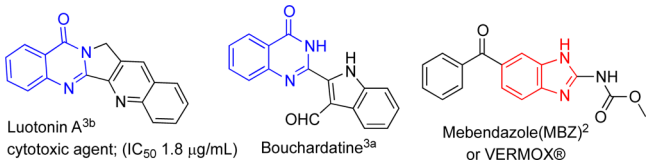


Figure 1. Natural and pharmaceutical importance of quinazolinone and benzimidazole.

heterocycles, are reported as promising anti-cancer drug analogues[3] and immunosuppressors, and they show anti-tumor activities by truncating the proliferation of human tumor cell lines (Figure 2).[4] In view of their broad spectrum of biological activities, several approaches have been developed to synthesize benzimidazoquinazolinone derivatives.[5] However, most of the existing methods suffer from conventional multi-step protocols, harsh reaction conditions, acid-mediated cyclative condensations, and low-atom-economic coupling sequences.

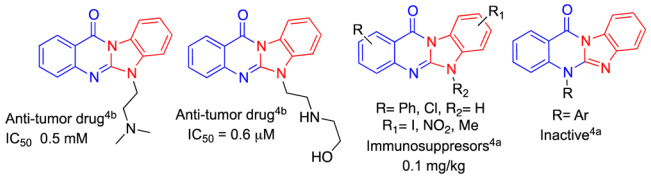


Figure 2. Biological importance of benzimidazoquinazolinones.

Over the decades, the transition-metal-catalyzed direct C−H functionalization has renewed the interest of synthetic chemists to develop environmentally benign methodologies for pharmacophores and biologically active molecules.[6,7] Amine substrates could poison catalytic activity of the metals by forming stable complexes,[8] which in turn makes C−N bond formation reactions most challenging. The greater difficulty lies in dealing with amino heterocycles due to the dominating effect of many heteroatoms. Hence, this necessitates the use of exceptional ligands and additives to enhance the catalytic action.[9]

One-pot/cascade reactions have been successfully employed to synthesize a variety of target molecules efficiently as they are not only attractive but also reduce the number of steps significantly. Although multi-fold bond formations using C−H functionalization are widely known with expensive metal catalysts,[10] use of inexpensive copper salts for such cascade reactions are not much explored.[11] Moreover, copper-catalyzed consecutive C−N bond formation strategy via Ullmann-type cross coupling[12a] followed by C−H aminations are uncommon,[12b] due to the requirement of variable active catalytic species, which are inevitable to carry out these cascade processes.

Recently, Qiao and co-workers[13] described an efficient copper-catalyzed intramolecular oxidative C−H amination to *N*-alkyl benzimidazoquinazolinones from (2-aminophenyl)(1*H*-

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Scheme 1. C−H Amination Routes to Benzimidazoquinazolinones

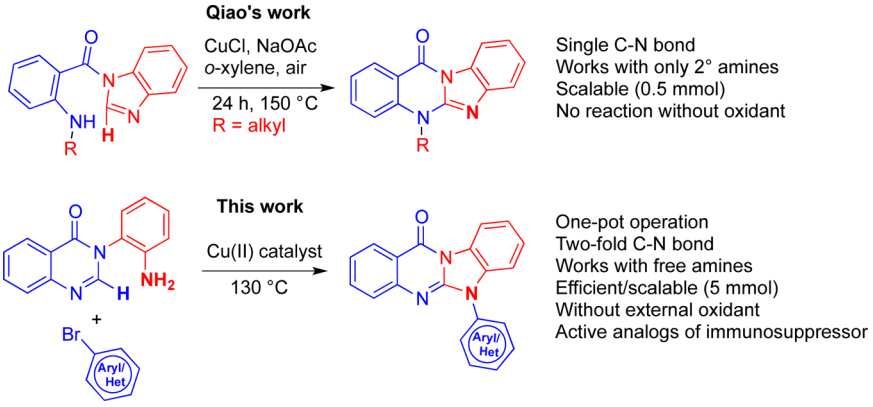
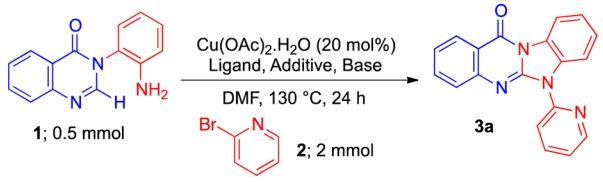


Table 1. Optimization of the Reaction Conditions



entry	ligand (30 mol%)	base (3.0 equiv)	oxidant (50 mmol%)	additive (1.0 equiv)	isolated yield (%)
[a]1	[c]bipy	K_3PO_4		KI	80
[a]2	[c]DMEDA	K_3PO_4		KI	61
[a]3	Xantphos	K_3PO_4		KI	51
[a]**4**	[c]**phen**	**K_3PO_4**		**KI**	**96**
[a]5	phen	K_3PO_4		[c]TBAI	59
[a]6	phen	K_3PO_4	$AgNO_3$		95
[a]7	phen	NaO^{t}Bu		KI	91
[a]8	phen	NaO^{t}Bu		TBAI	72
[a]9	phen	NaO^{t}Bu	$AgNO_3$		91
[b]10	phen	NaO^{t}Bu	$AgNO_3$		81
[b]11	phen	NaO^{t}Bu		TBAI	15
[b]12	phen	NaO^{t}Bu		NaI	39
[b]13	phen	K_3PO_4	$AgNO_3$		48
[b]14	phen	LiO^{t}Bu	$AgNO_3$		68
[b]15	phen	K_3PO_4		KI	53

[a]Under non-degassed condition. [b]Degassed condition. [c]phen =1,10-phenanthroline; TBAI = tetra-*n*-butylammonium iodide; bipy =2,2′-bipyridyl; DMEDA = *N*,*N*′-dimethylethylenediamine.

azol-1-yl)methanone (Scheme 1). Although this method provides the required product through a direct C−N bond formation, this fails to introduce the substituent on the benzimidazole nitrogen, which constitutes the core structure of many active drugs including the anti-tumor agents (Figure 2).

Further, aromatic heterocycles show promising DNA intercalator/anti-tumor activity;[14] however, the available methods have failed to exemplify an efficient protocol for the *N*-aryl benzimidazoquinazolinones. Hence, to advance the ability of DNA intercalator and other bio-activities, the scope of the *N*-aryl derivatives of benzimidazoquinazolinones needs to be explored. As a part of our ongoing studies in developing efficient/scalable protocols of copper-catalyzed C−H amination route to biologically relevant heterocycles syntheses,[15] we focused our investigation to the synthesis of benzimidazoquinazolinones. Herein, we report a one-pot copper-catalyzed two-fold C−N bond formation route to *N*-aryl benzimidazoquinazolinones via an Ullmann-type C−N coupling followed by C−H amination (Scheme 1).

RESULTS AND DISCUSSION

To investigate the proposed Cu-catalyzed two-fold C−N bond protocol, we selected 3-(2-aminophenyl)quinazolin-4(3*H*)-one (**1**) and 2-bromopyridine (**2**) as model substrates. We commenced the reaction optimization by screening various ligands with $Cu(OAc)_2{\cdot}H_2O$ as catalyst, KI[16] as additive, and K_3PO_4 as base in commercial-grade DMF (Table 1, entries 1−4). Subsequently, we found the formation of product **3a** in 96% yield (entry 4). When the additive was replaced with TBAI, the yield dropped significantly to 59% (entry 5). To improve the yield of the reaction further, we introduced $AgNO_3$[17] as a terminal oxidant, and we were happy to isolate the desired product **3a** in 95% yield (entry 6). We have screened various bases to examine the product formation. When NaO^{t}Bu was used as base, the product was obtained in 91% (entry 7). Although Ullmann reaction was proved to work under inert

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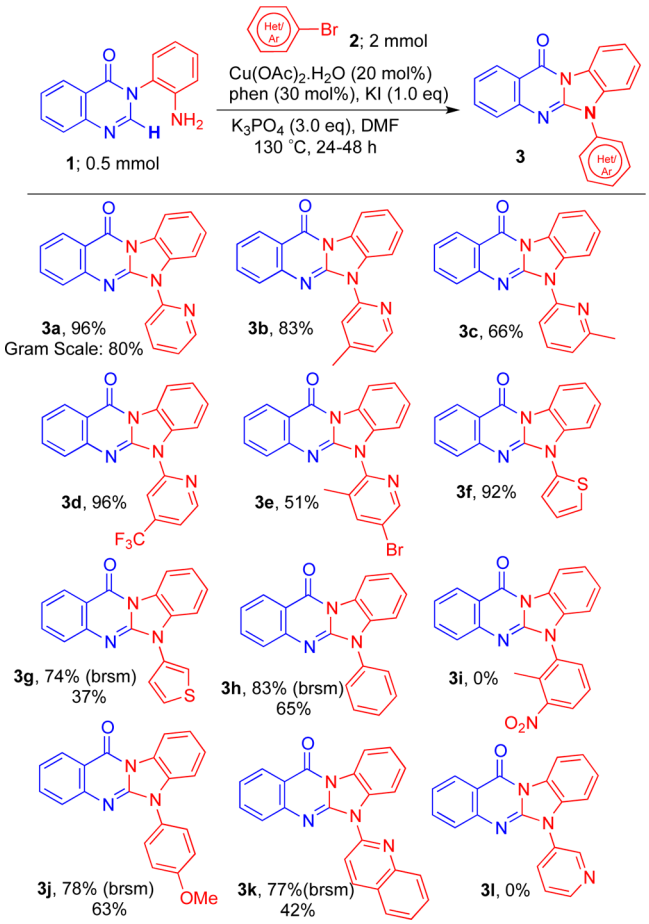
atmosphere and in degassed solvents,[12] our optimized conditions delivered products efficiently in non-degassed DMF. When the reaction was performed under nitrogen atmosphere, product **3a** was isolated in low yield (entries 10–15). Further, it is noteworthy that, in the absence of ligands, there was no formation of required product.

With the optimized conditions in hand, we investigated the scope of the reaction with a range of bromides including simple bromoarenes and bromoheteroarenes (Scheme 2), and in all

Scheme 2. Transformation of *N*-Anilinoquinazolinone and Bromoarenes[a]

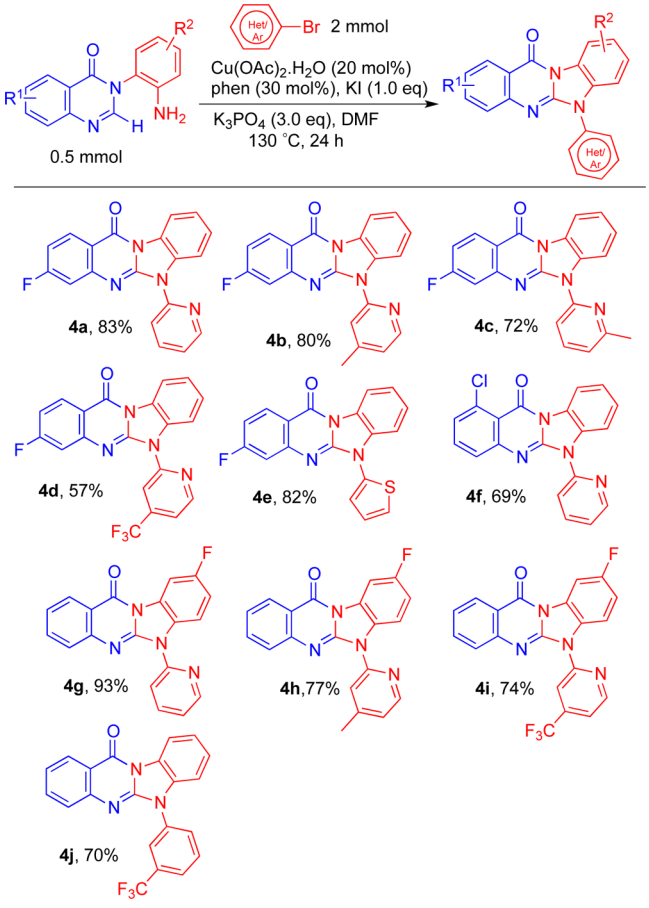


[a]"brsm" means yield based on recovered starting material.

the cases, desired products were obtained in good to excellent yields. The cascade reaction proceeded smoothly with various electron-withdrawing and electron-donating aryl bromides. The bromides on non-electrophilic carbons in dibromoheteroarenes remained inactive under the optimized condition. This provided an additional opportunity for further functional group manipulations of useful drug candidates. The optimized reaction provided the best yield of the products for electron-deficient heterocyclic bromides. However, a hindered aryl bromide like 1-bromo-2-methyl-3-nitrobenzene failed to produce the corresponding product **3i** under the optimized conditions. When 3-iodopyridine was used in an attempt to carry out the transformation under the optimized conditions, it failed to produce the desired product **3l** (Scheme 2). A possible reason could be depicted as, in 2-haloheteroarenes, the heteroatom is facilitating the initial halogen exchange with KI,[16] thereby promoting oxidative addition, but in 3- or 4-haloheteroarenes such activation is absent, which could explain the lower yield (**3g**) or failed attempts (**3l**) with some substrates.

Fluoro compounds[18] are biologically more active than their hydrogen analogues due to (i) their characteristic lipophilicity that potentially favors the membrane penetration and, therefore, increases the bioavailability and (ii) the fact that fluorine makes stronger bonds with carbon (up to 544 kJ/mol), which in turn increases the thermal and oxidative stability of the compound, making it then less sensitive to metabolic degradations. Hence, we further extended the scope of our methodology for the fluoro analogues of benzimidazoquinazolinones (Scheme 3). The reaction successfully provided the desired products in good yields with various amines.

Scheme 3. Fluoro Analogues of Benzimidazoquinazolinones



After examining various bromides including heteroaryl bromides and phenyl bromides, the scope of this two-fold cascade amination protocol was further extended using various haloazoles (**2a–e**, Figure 3) with 3-(2-aminophenyl)quinazolin-4(3*H*)-one (**1**). However, disappointingly, in all cases intractable complex mixtures were obtained.

CONCLUSIONS

In summary, we have developed a direct Cu-catalyzed C–H amination route for the syntheses of *N*-aryl benzimidazoquinazolinones. To the best of our knowledge, this is the first report on Cu-catalyzed C–H activation/two-fold C–N bond route for *N*-aryl benzimidazoquinazolinones. This protocol works

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Figure 3. Attempted substrate scope with azolyl halides.

efficiently with halogen-containing amine substrates without any side product formation. We have also examined the viability of this protocol with electron-rich and electron-poor substrates. We believe that this efficient strategy would be useful for the syntheses of biologically important *N*-aryl benzimidazoquinazolinone heterocycles in high yields.

EXPERIMENTAL SECTION

General Information. All starting materials and reagents were obtained from commercial suppliers and used after further purification as detailed below. All solvents for routine isolation of products and chromatography were reagent-grade and glass-distilled. Reaction flasks were dried in oven at 130 °C for 12 h. Air- and moisture-sensitive reactions were performed under an argon/UHP nitrogen atmosphere. Column chromatography was performed using silica gel (100−200 mesh size) with indicated solvents. Thin-layer chromatography (TLC) was conducted with silica gel 60 F_{254} precoated plates (0.25 mm) and visualized with UV, potassium permanganate, ceric ammonium molybdate, or iodine staining as appropriate. All ^{1}H NMR spectra were recorded on 400 and 500 MHz spectrometers and have been reported in ppm using solvents as internal standards ($CDCl_3$ at 7.26 ppm, DMSO-d_6 at 2.50 ppm). All proton-decoupled ^{13}C NMR spectra were recorded at 100 and 125 MHz and have been reported in ppm using solvents as internal standards ($CDCl_3$ at 77.2 ppm, DMSO-d_6 at 39.5 ppm). ^{19}F NMR spectra were recorded at 376 and 470 MHz operating frequencies. Compounds were analyzed for HRMS on an ESI-QTOF mass spectrometer using electrospray ionization in the positive ion mode. IR spectra were recorded with KBr on an FT-IR spectrometer and have been reported in wavenumber (cm^{-1}). All the compounds were solid, and melting points were measured on a micro-melting point apparatus. A few general procedures were followed during the course of reactions, and they are explained later.

General Procedure for C−H Functionalization Reactions. All the reactions were carried out with 0.5 mmol of starting material amines.

To a mixture of *N*-anilinoquinazolinones (0.5 mmol, 1.0 equiv), KI (0.5 mmol, 1.0 equiv), and 1,10-phenanthroline (0.15 mmol, 30 mol %) in dry DMF (3 mL) were added sequentially $Cu(OAc)_2{\cdot}H_2O$ (0.1 mmol, 20 mol%), K_3PO_4 (1.5 mmol, 3.0 equiv), and 2-bromopyridine (1.0 mmol, 2.0 equiv) at room temperature. The reaction mixture was stirred at 130 °C for 24−48 h and then quenched with H_2O after monitoring by TLC. The aqueous layer was extracted with ethyl acetate (4 × 50 mL). The combined organic layers were washed with water (4 × 50 mL), dried over anhydrous Na_2SO_4, and concentrated. The crude product was purified by silica gel column chromatography with a gradient of 2−5% ethyl acetate in petroleum ether to obtain the desired product.

*6-(Pyridin-2-yl)benzo[4,5]imidazo[2,1-b]quinazolin-12(6H)-one (**3a**).* Following the general procedure, the reaction between 3-(2-aminophenyl)quinazolin-4(3*H*)-one (**1**; 0.119 g, 0.5 mmol, 1.0 equiv) and 2-bromopyridine (95 μL, 1.0 mmol, 2.0 equiv) provided 0.150 g (96%) of the title compound **3a** as a white solid: mp = 244−246 °C; R_f = 0.88 (50% EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (dd, *J* = 7.7, 0.8 Hz, 1H), 8.68−8.66 (m, 1H), 8.47 (d, *J* = 8.3 Hz, 1H), 8.44 (dd, *J* = 8.0, 1.4 Hz, 1H), 8.18 (dd, *J* = 8.2, 0.8 Hz, 1H), 8.01 (ddd, *J* = 9.4, 7.5, 2.0 Hz, 1H), 7.74 (ddd, *J* = 8.4, 7.0, 1.6 Hz, 1H), 7.67 (d, *J* = 8.2 Hz, 1H), 7.47 (td, *J* = 7.6, 1.3 Hz, 1H), 7.43−7.35 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 149.4, 148.6, 148.6, 145.5, 138.6, 134.6, 130.6, 127.1, 126.4, 126.3, 124.1, 123.7, 122.4, 120.0, 117.8, 116.2, 113.1; HRMS (ESI-QTOF) calcd for $C_{19}H_{13}N_4O$ $(M+H)^+$ 313.1084, found 313.1089; IR (KBr, cm^{-1}) 3060, 2922, 2852, 1694, 1626, 1608, 1589, 1467, 1440, 1400, 1328, 1211, 1140, 1062.

Gram-Scale Reaction. To a mixture of 3-(2-aminophenyl)-quinazolin-4(3*H*)-one (**1**; 1.185 g, 5.0 mmol), KI (0.830 g, 5.0 mmol), and 1,10-phenanthroline (0.300 g, 1.5 mmol) in dry DMF (30 mL) at room temperature were added sequentially $Cu(OAc)_2{\cdot}H_2O$ (0.200 g, 1.0 mmol), K_3PO_4 (3.184 g, 15.0 mmol), and 2-bromopyridine (0.95 mL, 10.0 mmol). The reaction mixture was stirred at 130 °C for 24 h and then quenched with H_2O after monitoring by TLC. The aqueous layer was extracted with ethyl acetate (4 × 150 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under low pressure. The crude product was purified by silica gel column chromatography to obtain the desired product (1.25 g, 80% yield) as a fluffy white solid.

*6-(4-Methylpyridin-2-yl)benzo[4,5]imidazo[2,1-b]quinazolin-12(6H)-one (**3b**).* Following the general procedure, the reaction between 3-(2-aminophenyl)quinazolin-4(3*H*)-one (**1**; 0.119 g, 0.5 mmol, 1.0 equiv) and 2-bromo-4-methylpyridine (111 μL, 1.0 mmol, 2.0 equiv) provided 0.135 g (83%) of the title compound **3b** as a white solid: mp = 248−250 °C; R_f = 0.90 (50% EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (dd, *J* = 7.7, 1.9 Hz, 1H), 8.52 (d, *J* = 5.1 Hz, 1H), 8.44 (dd, *J* = 8.0, 1.4 Hz, 1H), 8.18 (s, 1H), 8.07 (dd, *J* = 8.1, 0.9 Hz, 1H), 7.74 (td, *J* = 6.8, 1.6 Hz, 1H), 7.68 (d, *J* = 7.7 Hz, 1H), 7.45 (td, *J* = 7.6, 1.3 Hz, 1H), 7.39 (td, *J* = 8.0, 1.3 Hz, 2H), 7.20 (d, *J* = 4.7 Hz, 1H), 2.55 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 150.3, 149.2, 148.6, 148.5, 145.6, 134.6, 130.8, 127.1, 126.5, 126.4, 126.3, 124.0, 123.8, 123.6, 120.8, 117.7, 116.3, 112.8, 21.7; HRMS (ESI-QTOF) calcd for $C_{20}H_{14}N_4NaO$ $(M+Na)^+$ 349.1060, found 349.1060; IR (KBr, cm^{-1}) 3016, 2924, 2862, 1695, 1631, 1611, 1596, 1556, 1492, 1472, 1463, 1427, 1374, 1330, 1273, 1231, 1187, 1154, 1065, 1019.

*6-(6-Methylpyridin-2-yl)benzo[4,5]imidazo[2,1-b]quinazolin-12(6H)-one (**3c**).* Following the general procedure, the reaction between 3-(2-aminophenyl)quinazolin-4(3*H*)-one (**1**; 0.119 g, 0.5 mmol, 1.0 equiv) and 2-bromo-6-methylpyridine (114 μL, 1.0 mmol, 2.0 equiv) provided 0.108 g (66%) of the title compound **3c** as a white solid: mp = 258−260 °C; R_f = 0.9 (50% EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (dd, *J* = 7.8, 0.7 Hz, 1H), 8.43 (dd, *J* = 8.1, 1.4 Hz, 1H), 8.22 (d, *J* = 8.1 Hz, 1H), 8.14 (dd, *J* = 7.8, 0.7 Hz, 1H), 7.88 (t, *J* = 7.8 Hz, 1H), 7.73 (td, *J* = 7.0, 1.6 Hz, 1H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.45 (td, *J* = 7.6, 1.2 Hz, 1H), 7.41−7.36 (m, 2H), 7.21 (d, *J* = 7.5 Hz, 1H), 2.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 158.1, 148.7, 148.6, 145.6, 138.9, 134.6, 130.7, 127.1, 126.5, 126.4, 126.3, 124.0, 123.6, 121.9, 117.7, 116.9, 116.2, 113.0, 24.4; HRMS (ESI-QTOF) calcd for $C_{20}H_{15}N_4O$ $(M+H)^+$ 327.1240, found 327.1240; IR (KBr, cm^{-1}) 3027, 2929, 2857, 1695, 1625, 1610, 1465, 1456, 1403, 1327, 1274, 1209, 1164, 1092, 1069, 1022.

*6-(4-(Trifluoromethyl)pyridin-2-yl)benzo[4,5]imidazo[2,1-b]-quinazolin-12(6H)-one (**3d**).* Following the general procedure, the reaction between 3-(2-aminophenyl)quinazolin-4(3*H*)-one (**1**; 0.119 g, 0.5 mmol, 1.0 equiv) and 2-bromo-4-(trifluoromethyl)pyridine (124 μL, 1.0 mmol, 2.0 equiv) provided 0.183 g (96%) of the title compound **3d** as a white solid: mp = 230−232 °C; R_f = 0.91 (50% EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.1 (s, 1H), 8.79 (d, *J* = 5.0 Hz, 1H), 8.71 (d, *J* = 7.9 Hz, 1H), 8.40 (d, *J* = 8.1 Hz, 1H), 8.38 (d, *J* = 8.2 Hz, 1H), 7.75 (t, *J* = 7.9 Hz, 1H), 7.66 (d, *J* = 8.1 Hz, 1H), 7.53 (d, *J* = 4.9 Hz, 1H), 7.45 (t, *J* = 8.3 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.7, 150.9, 149.2, 148.0, 145.2, 140.7 (q, $^2J_{C-F}$ = 33.7 Hz), 134.8, 129.9, 127.1, 126.6, 126.5, 126.5, 124.6, 124.3, 122.8 (q, $^1J_{C-F}$ = 272.5 Hz), 118.0, 117.2 (q, $^3J_{C-F}$ = 2.5 Hz), 116.2, 115.2 (q, $^3J_{C-F}$ = 3.7 Hz), 114.1; ^{19}F NMR (470 MHz, $CDCl_3$) δ −64.7 (s, 3F); HRMS (ESI-QTOF) calcd for $C_{20}H_{11}F_3N_4NaO$ $(M+Na)^+$ 403.0777, found 403.0779; IR (KBr, cm^{-1}) 2926, 2868, 1698, 1629, 1610, 1599, 1561, 1469, 1462, 1427, 1337, 1260, 1217, 1194, 1177, 1129, 1088, 1022.

*6-(5-Bromo-3-methylpyridin-2-yl)benzo[4,5]imidazo[2,1-b]-quinazolin-12(6H)-one (**3e**).* Following the general procedure, the reaction between 3-(2-aminophenyl)quinazolin-4(3*H*)-one (**1**; 0.119 g, 0.5 mmol, 1.0 equiv) and 2,5-dibromo-3-methylpyridine (0.251 g, 1.0 mmol, 2.0 equiv) provided 0.103 g (51%) of the title compound **3e**

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as a white solid: mp >275 °C; R_f = 0.87 (50% EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74−8.72 (m, 1H), 8.63 (dd, J = 2.6, 0.5 Hz, 1H), 8.43 (dd, J = 8.1, 1.2 Hz, 1H), 7.96 (dd, J = 2.6, 0.7 Hz, 1H), 7.74 (ddd, J = 8.4, 7.0, 1.5 Hz, 1H), 7.59 (dd, J = 8.3, 0.5 Hz, 1H), 7.46−7.38 (m, 3H), 7.29−7.27 (m, 1H), 2.56 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.0, 148.7, 146.0, 145.3, 144.1, 137.0, 136.9, 134.9, 131.4, 130.6, 127.2, 126.6, 126.5, 126.3, 124.1, 123.8, 117.7, 116.9, 108.8, 22.5; HRMS (ESI-QTOF) calcd for $C_{20}H_{14}BrN_4O$ $(M+H)^+$ 407.0327, found 407.0328; IR (KBr, cm^{-1}) 3054, 2926, 2856, 1731, 1689, 1602, 1417, 1332, 1297, 1265, 1237, 1183, 1165, 1151, 1136, 1102, 1053, 1023.

*6-(Thiophen-2-yl)benzo[4,5]imidazo[2,1-b]quinazolin-12(6H)-one (**3f**).* Following the general procedure, the reaction between 3-(2-aminophenyl)quinazolin-4(3*H*)-one (**1**; 0.119 g, 0.5 mmol, 1.0 equiv) and 2-bromothiophene (97 μL, 1.0 mmol, 2.0 equiv) provided 0.145 g (92%) of the title compound **3f** as a white solid: mp >275 °C; R_f = 0.85 (50% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.70 (td, J = 7.5, 1.2 Hz, 1H), 8.43 (ddd, J = 8.0, 1.5, 0.4 Hz, 1H), 7.72 (ddd, J = 8.4, 7.0, 1.6 Hz, 1H), 7.66 (dd, J = 7.8, 0.6 Hz, 1H), 7.46 (dd, J = 5.6, 1.4 Hz, 1H), 7.43 (dd, J = 7.9, 1.4 Hz, 1H), 7.40−7.37 (m, 4H), 7.21 (dd, J = 5.6, 3.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.0, 148.9, 146.5, 134.7, 134.1, 132.7, 127.1, 126.5, 126.5, 126.3, 126.2, 125.5, 125.3, 124.0, 123.5, 117.6, 116.5, 109.6; HRMS (ESI-QTOF) calcd for $C_{18}H_{12}N_3OS$ $(M+H)^+$ 318.0696, found 318.0701; IR (KBr, cm^{-1}) 3110, 2926, 2852, 1688, 1624, 1603, 1465, 1458, 1400, 1330, 1314, 1287, 1260, 1210, 1024.

*6-(Thiophen-3-yl)benzo[4,5]imidazo[2,1-b]quinazolin-12(6H)-one (**3g**).* Following the general procedure, the reaction between 3-(2-aminophenyl)quinazolin-4(3*H*)-one (**1**; 0.119 g, 0.5 mmol, 1.0 equiv) and 3-bromothiophene (94 μL, 1.0 mmol, 2.0 equiv) provided 0.078 g [37% (overall), 74% (brsm)] of the title compound **3g** as a white solid: mp = 268−270 °C; R_f = 0.89 (50% EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (d, J = 7.4 Hz, 1H), 8.43 (d, J = 8.0 Hz, 1H), 7.82−7.73 (m, 3H), 7.61 (s, 1H), 7.52−7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 149.2, 146.1, 134.6, 132.0, 131.6, 127.1, 126.5, 126.4, 126.4, 126.2, 124.9, 123.7, 123.2, 120.7, 117.4, 116.6, 109.5; HRMS (ESI-QTOF) calcd for $C_{18}H_{12}N_3OS$ $(M+H)^+$ 318.0696, found 318.0692; IR (KBr, cm^{-1}) 3112, 2924, 2852, 1687, 1624, 1603, 1465, 1444, 1399, 1327, 1314, 1282, 1259, 1213, 1180.

*6-Phenylbenzo[4,5]imidazo[2,1-b]quinazolin-12(6H)-one (**3h**).* Following the general procedure, the reaction between 3-(2-aminophenyl)quinazolin-4(3*H*)-one (**1**; 0.119 g, 0.5 mmol, 1.0 equiv) and iodobenzene (111 μL, 1.0 mmol, 2.0 equiv) provided 0.101 g [65% (overall), 83% (brsm)] of the title compound **3h** as a white solid: mp = 265 °C; R_f = 0.90 (50% EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75−8.73 (m, 1H), 8.43 (dd, J = 8.1, 1.2 Hz, 1H), 7.72−7.68 (m, 3H), 7.67−7.63 (m, 2H), 7.60 (dd, J = 8.3, 0.6 Hz, 1H), 7.54 (tt, J = 7.4, 1.3 Hz, 1H), 7.42−7.34 (m, 3H), 7.28 (dd, J = 7.9, 1.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.2, 149.0, 146.3, 134.6, 134.0, 132.4, 130.1, 129.0, 127.3, 127.1, 126.4, 126.3, 126.2, 123.6, 123.1, 117.4, 116.7, 109.3; HRMS (ESI-QTOF) calcd for $C_{20}H_{14}N_3O$ $(M+H)^+$ 312.1131, found 312.1130; IR (KBr, cm^{-1}) 2923, 2850, 1691, 1583, 1558, 1418, 1340, 1212, 1048, 1024.

*6-(4-Methoxyphenyl)benzo[4,5]imidazo[2,1-b]quinazolin-12(6H)-one (**3j**).* Following the general procedure, the reaction between 3-(2-aminophenyl)quinazolin-4(3*H*)-one (**1**; 0.119 g, 0.5 mmol, 1.0 equiv) and 4-bromoanisole (125 μL, 1.0 mmol, 2.0 equiv) provided 0.102 g [63% (overall), 78% (brsm)] of the title compound **3j** as a white solid: mp >275 °C; R_f = 0.87 (50% EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (dd, J = 7.3, 0.8 Hz, 1H), 8.43 (dd, J = 8.0, 1.3 Hz, 1H), 7.69 (ddd, J = 8.4, 7.0, 1.6 Hz, 1H), 7.61−7.56 (m, 3H), 7.42−7.33 (m, 3H), 7.21 (dd, J = 8.0, 1.5 Hz, 1H), 7.17−7.13 (m, 2H), 3.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 159.7, 149.2, 134.3, 132.7, 128.5, 126.9, 126.3, 126.1, 125.9, 123.2, 122.7, 117.1, 116.4, 115.2, 109.0, 55.7; HRMS (ESI-QTOF) calcd for $C_{21}H_{16}N_3O_2$ $(M+H)^+$ 342.1237, found 342.1238; IR (KBr, cm^{-1}) 2922, 2854, 1683, 1624, 1604, 1519, 1463, 1328, 1263, 1250, 1211, 1173, 1132, 1108, 1032, 1021.

*6-(Quinolin-2-yl)benzo[4,5]imidazo[2,1-b]quinazolin-12(6H)-one (**3k**).* Following the general procedure, the reaction between 3-(2-aminophenyl)quinazolin-4(3*H*)-one (**1**; 0.119 g, 0.5 mmol, 1.0 equiv) and 2-bromoquinoline (0.208 g, 1.0 mmol, 2.0 equiv) provided 0.067 g [42% (overall), 77% (brsm)] of the title compound **3k** as a white solid: mp = 272−274 °C; R_f = 0.92 (50% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.78 (dd, J = 7.9, 0.6 Hz, 1H), 8.68 (d, J = 8.8 Hz, 1H), 8.48−8.43 (m, 3H), 8.15 (d, J = 8.5 Hz, 1H), 7.94 (d, J = 7.8 Hz, 1H), 7.82−7.75 (m, 2H), 7.71 (d, J = 7.6 Hz, 1H), 7.65−7.61 (m, 1H), 7.52 (td, J = 7.7, 1.7 Hz, 1H), 7.46−7.41 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.0, 148.8, 148.6, 146.9, 145.7, 138.7, 134.7, 130.7, 130.5, 128.8, 127.8, 127.2, 127.2, 127.1, 126.7, 126.6, 126.4, 124.2, 124.0, 118.2, 117.9, 116.3, 113.7; HRMS (ESI-QTOF) calcd for $C_{23}H_{15}N_4O$ $(M+H)^+$ 363.1246, found 363.1245; IR (KBr, cm^{-1}) 2945, 2922, 2851, 1692, 1628, 1609, 1567, 1502, 1467, 1432, 1404, 1329, 1220, 1025.

*3-Fluoro-6-(pyridin-2-yl)benzo[4,5]imidazo[2,1-b]quinazolin-12(6H)-one (**4a**).* Following the general procedure, the reaction between 3-(2-aminophenyl)-7-fluoroquinazolin-4(3*H*)-one (**11**; 0.128 g, 0.5 mmol, 1.0 equiv) and 2-bromopyridine (95 μL, 1.0 mmol, 2.0 equiv) provided 0.137 g (83%) of the title compound **4a** as a white solid: mp = 264−266 °C; R_f = 0.90 (50% EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (dd, J = 7.6, 1.0 Hz, 1H), 8.68 (dd, J = 4.6, 1.1 Hz, 1H), 8.45−8.40 (m, 2H), 8.15 (d, J = 7.9 Hz, 1H), 8.01 (td, J = 8.1, 1.9 Hz, 1H), 7.47 (td, J = 7.7, 1.2 Hz, 1H), 7.43−7.37 (m, 2H), 7.29 (dd, J = 10.3, 2.4 Hz, 1H), 7.10 (td, J = 8.6, 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0 (d, $^1J_{C-F}$ = 252.0 Hz), 159.3, 151.0 (d, $^3J_{C-F}$ = 14.0 Hz), 149.2, 148.7, 146.3, 138.7, 130.5, 129.8 (d, $^3J_{C-F}$ = 12.0 Hz), 126.6, 126.3, 123.9, 122.6, 120.1, 116.2, 114.5, 113.2, 113.1 (d, $^2J_{C-F}$ = 24.0 Hz), 111.4 (d, $^2J_{C-F}$ = 23.0 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ −103.48 (dd, J = 9.4, 4.7 Hz, 1F); HRMS (ESI-QTOF) calcd for $C_{19}H_{12}FN_4O$ $(M+H)^+$ 331.0990, found 331.0987; IR (KBr, cm^{-1}) 3018, 2954, 2926, 2872, 2854, 1697, 1616, 1586, 1481, 1469, 1450, 1440, 1404, 1320, 1216, 1169, 1136, 1062.

*3-Fluoro-6-(4-methylpyridin-2-yl)benzo[4,5]imidazo[2,1-b]quinazolin-12(6H)-one (**4b**).* Following the general procedure, the reaction between 3-(2-aminophenyl)-7-fluoroquinazolin-4(3*H*)-one (**11**; 0.128 g, 0.5 mmol, 1.0 equiv) and 2-bromo-4-methylpyridine (111 μL, 1.0 mmol, 2.0 equiv) provided 0.138 g (80%) of the title compound **4b** as a white solid: mp = 275 °C; R_f = 0.92 (50% EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (dd, J = 7.8, 0.9 Hz, 1H), 8.53 (d, J = 5.0 Hz, 1H), 8.44 (dd, J = 8.9, 6.3 Hz, 1H), 8.11 (s, 1H), 8.04 (dd, J = 8.3, 0.7 Hz, 1H), 7.46 (td, J = 7.7, 1.3 Hz, 1H), 7.40 (td, J = 7.9, 1.3 Hz, 1H), 7.31 (dd, J = 10.3, 2.4 Hz, 1H), 7.22 (d, J = 4.9 Hz, 1H), 7.11 (td, J = 8.5, 2.4 Hz, 1H), 2.65 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0 (d, $^1J_{C-F}$ = 252.5 Hz), 159.3, 151.0 (d, $^3J_{C-F}$ = 17.5 Hz), 150.4, 149.0, 148.6, 148.5, 146.3, 130.7, 129.8 (d, $^3J_{C-F}$ = 11.2 Hz), 126.6, 126.3, 124.1, 123.8, 121.0, 116.3, 114.5, 113.0 (d, $^2J_{C-F}$ = 21.2 Hz), 111.5 (d, $^2J_{C-F}$ = 21.2 Hz), 21.7; ^{19}F NMR (470 MHz, $CDCl_3$) δ −103.58 (dd, J = 9.4, 4.7 Hz, 1F); HRMS (ESI-QTOF) calcd for $C_{20}H_{14}FN_4O$ $(M+H)^+$ 345.1146, found 345.1148; IR (KBr, cm^{-1}) 2945, 2917, 2840, 1706, 1618, 1596, 1558, 1478, 1467, 1450, 1426, 1382, 1275, 1160, 1133.

*3-Fluoro-6-(6-methylpyridin-2-yl)benzo[4,5]imidazo[2,1-b]quinazolin-12(6H)-one (**4c**).* Following the general procedure, the reaction between 3-(2-aminophenyl)-7-fluoroquinazolin-4(3*H*)-one (**11**; 0.128 g, 0.5 mmol, 1.0 equiv) and 2-bromo-6-methylpyridine (114 μL, 1.0 mmol, 2.0 equiv) provided 0.124 g (72%) of the title compound **4c** as a white solid: mp >275 °C; R_f = 0.91 (50% EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (d, J = 7.8 Hz, 1H), 8.43 (dd, J = 8.9, 6.4 Hz, 1H), 8.14 (d, J = 8.1 Hz, 1H), 8.11 (d, J = 8.1 Hz, 1H), 7.89 (t, J = 7.8 Hz, 1H), 7.47 (t, J = 7.6 Hz, 1H), 7.41 (t, J = 7.8 Hz, 1H), 7.29 (dd, J = 10.3, 2.3 Hz, 1H), 7.26−7.24 (m, 1H), 7.10 (td, J = 8.5, 2.3 Hz, 1H), 2.68 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0 (d, $^1J_{C-F}$ = 251.2 Hz), 159.3, 158.3, 151.1 (d, $^3J_{C-F}$ = 13.7 Hz), 148.4, 146.4, 138.9, 130.7, 129.8 (d, $^3J_{C-F}$ = 11.2 Hz), 126.5, 126.4, 123.8, 122.2, 117.1, 116.2, 114.5, 113.1, 112.9 (d, $^2J_{C-F}$ = 23.7 Hz), 111.4 (d, $^2J_{C-F}$ = 22.5 Hz), 24.4; HRMS (ESI-QTOF) calcd for $C_{20}H_{14}FN_4O$ $(M+H)^+$ 345.1146, found 345.1145; IR (KBr, cm^{-1})

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2953, 2922, 2852, 1636, 1459, 1406, 1376, 1310, 1251, 1216, 1180, 1049.

*3-Fluoro-6-(4-(trifluoromethyl)pyridin-2-yl)benzo[4,5]imidazo-[2,1-b]quinazolin-12(6H)-one (**4d**).* Following the general procedure, the reaction between 3-(2-aminophenyl)-7-fluoroquinazolin-4(3*H*)-one (**11**; 0.128 g, 0.5 mmol, 1.0 equiv) and 2-bromo-4-(trifluoromethyl)pyridine (124 μL, 1.0 mmol, 2.0 equiv) provided 0.113 g (57%) of the title compound **4d** as a white solid: mp = 202−204 °C; R_f = 0.88 (50% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.99 (s, 1H), 8.33 (d, *J* = 5.0 Hz, 1H), 8.73 (dd, *J* = 7.7, 0.8 Hz, 1H), 8.43 (dd, *J* = 8.9, 6.3 Hz, 1H), 8.36 (dd, *J* = 8.2, 0.8 Hz, 1H), 7.57 (dd, *J* = 5.1, 0.7 Hz, 1H), 7.49 (td, *J* = 7.7, 1.4 Hz, 1H), 7.44 (td, *J* = 7.9, 1.3 Hz, 1H), 7.32 (dd, *J* = 10.0, 2.5 Hz, 1H), 7.16−7.13 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.1 (d, $^1J_{C-F}$ = 253.7 Hz), 159.0, 150.6, 150.4 (d, $^3J_{C-F}$ = 13.7 Hz), 149.4, 146.0, 140.8 (q, $^2J_{C-F}$ = 33.7 Hz), 129.9, 129.8 (d, $^4J_{C-F}$ = 0.5 Hz), 126.6, 126.5, 124.5, 123.9, 122.8 (q, $^1J_{C-F}$ = 271.2 Hz), 117.6 (q, $^3J_{C-F}$ = 3.7 Hz), 116.2, 115.4 (q, $^3J_{C-F}$ = 3.7 Hz), 114.8 (d, $^3J_{C-F}$ = 2.2 Hz), 114.1, 113.6 (d, $^2J_{C-F}$ = 23.7 Hz), 111,7 (d, $^2J_{C-F}$ = 22.5 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ −64.70 (s, 3F), −102.92 (q, *J* = 9.4 Hz, 1F); HRMS (ESI-QTOF) calcd for $C_{20}H_{11}F_4N_4O$ $(M+H)^+$ 399.0864, found 399.0869; IR (KBr, cm^{-1}) 2953, 2922, 2852, 1693, 1615, 1599, 1482, 1466, 1450, 1428, 1348, 1333, 1318, 1280, 1261, 1216, 1176, 1162, 1134.

*3-Fluoro-6-(thiophen-2-yl)benzo[4,5]imidazo[2,1-b]quinazolin-12(6H)-one (**4e**).* Following the general procedure, the reaction between 3-(2-aminophenyl)-7-fluoroquinazolin-4(3*H*)-one (**11**; 0.128 g, 0.5 mmol, 1.0 equiv) and 2-bromothiophene (97 μL, 1.0 mmol, 2.0 equiv) provided 0.137 g (82%) of the title compound **4e** as a white solid: mp = 268−270 °C; R_f = 0.86 (50% EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (dd, *J* = 7.3, 1.2 Hz, 1H), 8.42 (dd, *J* = 8.8, 6.3 Hz, 1H), 7.48 (dd, *J* = 5.6, 1.3 Hz, 1H), 7.44 (dd, *J* = 7.5, 1.4 Hz, 1H), 7.41 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.38−7.36 (m, 2H), 7.29 (dd, *J* = 10.4, 2.4 Hz, 1H), 7.21 (dd, *J* = 5.5, 3.7 Hz, 1H), 7.12−7.07 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0 (d, $^1J_{C-F}$ = 253.7 Hz), 159.3, 151.2 (d, $^3J_{C-F}$ = 13.7 Hz), 147.2, 133.7, 132.6, 129.7 (d, $^3J_{C-F}$ = 11.2 Hz), 126.6, 126.4, 126.0, 125.8, 125.6, 123.8, 116.5, 114.4, 112.9 (d, $^2J_{C-F}$ = 23.7 Hz), 111.6 (d, $^2J_{C-F}$ = 22.5 Hz), 109.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ −103.30 (q, *J* = 9.4 Hz, 1F); HRMS (ESI-QTOF) calcd for $C_{18}H_{10}FN_3NaOS$ $(M+Na)^+$ 358.0421, found 358.0425; IR (KBr, cm^{-1}) 3019, 2954, 2921, 2851, 1697, 1614, 1604, 1567, 1508, 1477, 1467, 1399, 1377, 1303, 1216, 1161, 1126, 1049.

*5-Chloro-6-(pyridin-2-yl)benzo[4,5]imidazo[2,1-b]quinazolin-12(6H)-one (**4f**).* Following the general procedure, the reaction between 3-(2-aminophenyl)-5-chloroquinazolin-4(3*H*)-one (**9**; 0.136 g, 0.5 mmol, 1.0 equiv) and 2-bromopyridine (95 μL, 1.0 mmol, 2.0 equiv) provided 0.119 g (69%) of the title compound **4f** as a white solid: mp = 208−210 °C; R_f = 0.82 (50% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.78 (d, *J* = 7.7 Hz, 1H), 8.67 (dd, *J* = 4.7, 1.1 Hz, 1H), 8.42 (d, *J* = 8.2 Hz, 1H), 8.18 (d, *J* = 7.9 Hz, 1H), 8.00 (td, *J* = 7.7, 1.3 Hz, 1H), 7.56 (d, *J* = 4.5 Hz, 2H), 7.47 (td, *J* = 8.6, 1.0 Hz, 1H), 7.42−7.36 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 151.3, 149.1, 148.7, 148.7, 145.5, 138.7, 134.7, 133.8, 130.5, 126.9, 126.6, 126.5, 125.7, 124.0, 122.6, 120.0, 116.5, 113.1; HRMS (ESI-QTOF) calcd for $C_{19}H_{11}ClN_4NaO$ $(M+Na)^+$ 369.0514, found 369.0514; IR (KBr, cm^{-1}) 3019, 2954, 2919, 2870, 2850, 1697, 1632, 1607, 1585, 1557, 1464, 1439, 1396, 1378, 1215, 1171, 1048.

*9-Fluoro-6-(pyridin-2-yl)benzo[4,5]imidazo[2,1-b]quinazolin-12(6H)-one (**4g**).* Following the general procedure, the reaction between 3-(2-amino-5-fluorophenyl)quinazolin-4(3*H*)-one (**10**; 0.128 g, 0.5 mmol, 1.0 equiv) and 2-bromopyridine (95 μL, 1.0 mmol, 2.0 equiv) provided 0.153 g (93%) of the title compound **4g** as a white solid: mp = 264−266 °C; R_f = 0.86 (50% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (dd, *J* = 4.8, 1.1 Hz, 1H), 8.57 (d, *J* = 8.3 Hz, 1H), 8.51 (dd, *J* = 8.5, 2.6 Hz, 1H), 8.43 (dd, *J* = 8.0, 1.2 Hz, 1H), 8.26 (dd, *J* = 9.0, 4.7 Hz, 1H), 8.01 (ddd, *J* = 8.3, 7.6, 2.0 Hz, 1H), 7.76 (ddd, *J* = 8.4, 7.2, 1.5 Hz, 1H), 7.67 (d, *J* = 8.1 Hz, 1H), 7.43−7.39 (m, 1H), 7.36 (ddd, *J* = 7.3, 4.9, 7.3 Hz, 1H), 7.19 (td, *J* = 9.0, 2.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.8, 159.1 (d, $^1J_{C-F}$ = 240.0 Hz), 149.5, 148.5, 148.5, 145.7, 138.7, 134.9, 127.2, 126.8 (d, $^3J_{C-F}$ = 10.0 Hz), 126.4, 124.3, 122.3, 119.5, 117.5, 114.3, 114.2 (d, $^3J_{C-F}$ = 8.7 Hz), 113.3 (d, $^2J_{C-F}$ = 23.7 Hz), 104.3 (d, $^2J_{C-F}$ = 30.0 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ −116.96 (sex, *J* = 4.7 Hz, 1F); HRMS (ESI-QTOF) calcd for $C_{19}H_{11}FN_4NaO$ $(M+Na)^+$ 353.0809, found 353.0808; IR (KBr, cm^{-1}) 3031, 2920, 2849, 1703, 1632, 1601, 1598, 1489, 1469, 1422, 1333, 1260, 1240, 1218, 1099, 1050.

*9-Fluoro-6-(4-methylpyridin-2-yl)benzo[4,5]imidazo[2,1-b]-quinazolin-12(6H)-one (**4h**).* Following the general procedure, the reaction between 3-(2-amino-5-fluorophenyl)quinazolin-4(3*H*)-one (**10**; 0.128 g, 0.5 mmol, 1.0 equiv) and 2-bromo-4-methylpyridine (111 μL, 1.0 mmol, 2.0 equiv) provided 0.132 g (77%) of the title compound **4h** as a white solid: mp = 273−275 °C; R_f = 0.88 (50% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51−8.49 (m, 2H), 8.43 (dd, *J* = 7.3, 0.7 Hz, 1H), 8.28 (s, 1H), 8.15 (dd, *J* = 9.0, 4.6 Hz, 1H), 7.76 (t, *J* = 7.0 Hz, 1H), 7.68 (d, *J* = 8.2 Hz, 1H), 7.41 (t, *J* = 7.8 Hz, 1H), 7.20−7.16 (m, 2H), 2.56 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.9, 159.1 (d, $^1J_{C-F}$ = 240.0 Hz), 150.3, 149.4, 148.7, 148.3, 134.9, 127.2, 126.4, 124.2, 123.7, 120.2, 117.5, 114.0, 113.9, 113.3 (d, $^2J_{C-F}$ = 23.7 Hz), 104.3 (d, $^2J_{C-F}$ = 30.0 Hz), 21.7; ^{19}F NMR (470 MHz, $CDCl_3$) δ −117.16 (s, 1F); HRMS (ESI-QTOF) calcd for $C_{20}H_{14}FN_4O$ $(M+H)^+$ 345.1152, found 345.1150; IR (KBr, cm^{-1}) 3039, 2917, 2849, 1725, 1705, 1632, 1611, 1598, 1489, 1469, 1422, 1333, 1264, 1237, 1217, 1150, 1099, 1056.

*9-Fluoro-6-(4-(trifluoromethyl)pyridin-2-yl)benzo[4,5]imidazo-[2,1-b]quinazolin-12(6H)-one (**4i**).* Following the general procedure, the reaction between 3-(2-amino-5-fluorophenyl)quinazolin-4(3*H*)-one (**10**; 0.128 g, 0.5 mmol, 1.0 equiv) and 2-bromo-4-(trifluoromethyl)pyridine (124 μL, 1.0 mmol, 2.0 equiv) provided 0.147 g (74%) of the title compound **4i** as a white solid: mp = 210 °C; R_f = 0.87 (50% EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.17 (s, 1H), 8.76 (d, *J* = 5.1 Hz, 1H), 8.45−8.41 (m, 2H), 8.36 (d, *J* = 8.0 Hz, 1H), 7.78−7.73 (m, 1H), 7.64 (d, *J* = 8.2 Hz, 1H), 7.51 (d, *J* = 5.0 Hz, 1H), 7.40 (t, *J* = 7.9 Hz, 1H), 7.17 (td, *J* = 9.0, 2.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.5, 159.4 (d, $^1J_{C-F}$ = 241.3 Hz), 150.8, 149.0, 147.9, 145.3, 140.7 (q, $^2J_{C-F}$ = 33.7 Hz), 135.0, 127.1, 126.9 (d, $^3J_{C-F}$ = 13.7 Hz), 126.6, 126.0 (d, $^4J_{C-F}$ = 1.6 Hz), 124.8, 122.8 (q, $^1J_{C-F}$ = 271.2 Hz), 117.7, 117.1 (q, $^3J_{C-F}$ = 3.7 Hz), 115.5 (d, $^3J_{C-F}$ = 8.7 Hz), 114.6 (q, $^3J_{C-F}$ = 3.7 Hz), 113.3 (d, $^2J_{C-F}$ = 23.7 Hz), 104.2 (d, $^2J_{C-F}$ = 30.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −64.78 (s, 3F), −115.93 (sex, *J* = 4.0 Hz, 1F); HRMS (ESI-QTOF) calcd for $C_{20}H_{11}F_4N_4O$ $(M+H)^+$ 399.0864, found 399.0863; IR (KBr, cm^{-1}) 3120, 3091, 2924, 2854, 1703, 1637, 1602, 1563, 1489, 1469, 1422, 1337, 1329, 1258, 1240, 1218, 1177, 1168, 1124, 1091, 1056, 1020.

*6-(3-(Trifluoromethyl)phenyl)benzo[4,5]imidazo[2,1-b]-quinazolin-12(6H)-one (**4j**).* Following the general procedure, the reaction between 3-(2-aminophenyl)quinazolin-4(3*H*)-one (**1**; 0.119 g, 0.5 mmol, 1.0 equiv) and 1-iodo-3-(trifluoromethyl)benzene (144 μL, 1.0 mmol, 2.0 equiv) provided 0.133 g (70%) of the title compound **4j** as a white solid: mp = 266 °C; R_f = 0.85 (50% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.74 (dd, *J* = 7.4, 1.5 Hz, 1H), 8.43 (dd, *J* = 8.0, 1.2 Hz, 1H), 8.03 (s, 1H), 7.98−7.96 (m, 1H), 7.80 (d, *J* = 5.1 Hz, 2H), 7.74−7.71 (m, 1H), 7.60 (d, *J* = 8.2 Hz, 1H), 7.45−7.37 (m, 3H), 7.29 (dd, *J* = 6.6, 1.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.1, 148.9, 146.0, 134.7, 132.6 (q, $^2J_{C-F}$ = 33.7 Hz), 131.6, 130.7, 130.4, 127.1, 126.5, 126.4, 126.3, 125.5 (q, $^3J_{C-F}$ = 3.7 Hz), 124.0 (d, $^3J_{C-F}$ = 3.7 Hz), 123.9, 123.7 (q, $^1J_{C-F}$ = 272.5 Hz), 123.5, 117.6, 116.8, 109.0; ^{19}F NMR (470 MHz, $CDCl_3$) δ −62.66 (s, 3F); HRMS (ESI-QTOF) calcd for $C_{21}H_{13}F_3N_3O$ $(M+H)^+$ 380.1011, found 380.1014; IR (KBr, cm^{-1}) 2918, 2851, 1693, 1627, 1608, 1557, 1498, 1465, 1406, 1336, 1260, 1235, 1215, 1169, 1132, 1112, 1070, 1022.

General Procedure for Preparation of 3-(2-Nitrophenyl)-quinazolin-4(3*H*)-one Derivatives.[19] To a mixture of quinazolin-4(3*H*)-one[20] (6.9 mmol, 1.0 equiv) in 25 mL of *N*,*N*-dimethylformamide (DMF) were added K_2CO_3 (10.3 mmol, 1.5 equiv) and 1-fluoro-2-nitrobenzene (8.2 mmol, 1.2 equiv) sequentially. The mixture was refluxed at 80−90 °C for 6−8 h in a flask equipped with a guard tube. The reaction was quenched with H_2O after monitoring by TLC. The

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aqueous layer was extracted with ethyl acetate (4 × 75 mL), and the combined organic layers were washed several times with H_2O and finally with brine solution, dried over anhydrous Na_2SO_4, and concentrated under low pressure. Crude product was recrystallized from ethyl acetate to obtain the desired product as a yellow solid.

*3-(2-Nitrophenyl)quinazolin-4(3H)-one (**5**).*[21] Following the general procedure, the reaction between quinazolin-4(3*H*)-one[20] (1.0 g, 6.9 mmol, 1.0 equiv) and 1-fluoro-2-nitrobenzene (867 μL, 8.2 mmol, 1.2 equiv) provided 1.61 g (88%) of the title compound **5** as a yellow solid: mp = 184−186 °C; R_f = 0.40 (50% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (dd, *J* = 8.1, 1.1 Hz, 1H), 8.21 (dd, *J* = 8.2, 1.4 Hz, 1H), 8.12 (s, 1H), 7.85−7.78 (m, 3H), 7.70 (td, *J* = 8.2, 1.4 Hz, 1H), 7.55 (ddd, *J* = 8.1, 6.9, 1.5 Hz, 1H), 7.49 (dd, *J* = 7.8, 1.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.4, 147.8, 146.3, 144.9, 135.3, 134.9, 131.1, 130.8, 130.2, 128.2, 127.9, 127.4, 126.0, 121.9; HRMS (ESI-QTOF) calcd for $C_{14}H_9N_3NaO_3$ $(M+Na)^+$ 290.0536, found 290.0537; IR (KBr, cm^{-1}) 3060, 2956, 2920, 2851, 1669, 1600, 1523, 1468, 1404, 1345, 1298, 1250, 1187, 1145, 1114, 1019.

*5-Chloro-3-(2-nitrophenyl)quinazolin-4(3H)-one (**6**).* Following the general procedure, the reaction between 5-chloroquinazolin-4(3*H*)-one[22a] (1.28 g, 7.09 mmol, 1.0 equiv) and 1-fluoro-2-nitrobenzene (897 μL, 8.51 mmol, 1.2 equiv) provided 1.38 g (65%) of the title compound **6** as a yellow solid: mp >275 °C; R_f = 0.30 (50% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (dd, *J* = 8.2, 1.4 Hz, 1H), 8.05 (s, 1H), 7.82 (td, *J* = 7.7, 1.5 Hz, 1H), 7.72−7.64 (m, 3H), 7.52 (dd, *J* = 6.6, 2.4 Hz, 1H), 7.48 (dd, *J* = 7.8, 1.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.6, 150.4, 146.2, 145.5, 135.0, 135.0, 134.6, 131.0, 130.9, 130.5, 127.3, 126.1, 119.4; HRMS (ESI-QTOF) calcd for $C_{14}H_9ClN_3O_3$ $(M+H)^+$ 302.0327, found 302.0325; IR (KBr, cm^{-1}) 3073, 2923, 2876, 2853, 1698, 1623, 1593, 1540, 1488, 1457, 1413, 1358, 1299, 1288, 1269, 1229, 1193, 1103, 1035.

*7-Fluoro-3-(2-nitrophenyl)quinazolin-4(3H)-one (**7**).* Following the general procedure, the reaction between 7-fluoroquinazolin-4(3*H*)-one[22b,c] (1.0 g, 6.1 mmol, 1.0 equiv) and 1-fluoro-2-nitrobenzene (772 μL, 7.32 mmol, 1.2 equiv) provided 1.13 g (65%) of the title compound **7** as a yellow solid: mp = 214−216 °C; R_f = 0.40 (50% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (dd, *J* = 8.8, 6.0 Hz, 1H), 8.24 (dd, *J* = 8.2, 1.4 Hz, 1H), 8.11 (s, 1H), 7.85 (td, *J* = 7.7, 1.4 Hz, 1H), 7.73 (td, *J* = 8.1, 1.1 Hz, 1H), 7.49 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.45 (dd, *J* = 9.4, 2.5 Hz, 1H), 7.29−7.25 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0 (d, $^1J_{C-F}$ = 253.7 Hz), 159.8, 150.2 (d, $^3J_{C-F}$ = 12.5 Hz), 146.6, 146.3, 135.0, 131.0, 130.9, 130.4, 130.3 (d, $^3J_{C-F}$ = 10.0 Hz), 126.2, 118.7, 116.9 (d, $^2J_{C-F}$ = 23.7 Hz), 113.6 (d, $^2J_{C-F}$ = 22.5 Hz); HRMS (ESI-QTOF) calcd for $C_{14}H_9FN_3O_3$ $(M+H)^+$ 286.0622, found 286.0621; IR (KBr, cm^{-1}) 2957, 2924, 2853, 1672, 1614, 1600, 1525, 1508, 1473, 1384, 1344, 1327, 1290, 1267, 1198, 1126, 1110, 1057.

*3-(5-Fluoro-2-nitrophenyl)quinazolin-4(3H)-one (**8**).* Following the general procedure, the reaction between quinazolin-4(3*H*)-one[20] (1.33 g, 9.11 mmol, 1.0 equiv) and 2,4-difluoro-1-nitrobenzene (1.2 mL, 10.93 mmol, 1.2 equiv) provided 1.066 g (41%) of the title compound **8** as a yellow solid: mp = 216−218 °C; R_f = 0.40 (50% EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32−8.28 (m, 2H), 8.06 (s, 1H), 7.87−7.78 (m, 2H), 7.57 (ddd, *J* = 7.1, 7.0, 1.4 Hz, 1H), 7.40 (ddd, *J* = 9.4, 7.0, 2.6 Hz, 1H), 7.24 (dd, *J* = 7.8, 3.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1 (d, $^1J_{C-F}$ = 259.0 Hz), 160.3, 147.8, 144.1, 135.5, 133.4, 128.6, 128.5, 128.4, 128.1, 127.5, 121.9, 118.2, 118.1 (d, $^2J_{C-F}$ = 25.0 Hz), 117.7 (d, $^2J_{C-F}$ = 22.0 Hz); HRMS (ESI-QTOF) calcd for $C_{14}H_8FN_3NaO_3$ $(M+Na)^+$ 308.0442, found 308.0446; IR (KBr, cm^{-1}) 3065, 2912, 2906, 2846, 1685, 1600, 1561, 1529, 1489, 1470, 1426, 1351, 1316, 1297, 1273, 1245, 1187.

General Procedures for Preparation of 3-(2-aminophenyl)-quinazolin-4(3*H*)-one Derivatives.[23] *Procedure A.* To a methanolic solution (40 mL) of nitro compound (1.5 g, 5.62 mmol, 1.0 equiv) was added Pd−C (10% on carbon) (0.480 g) under N_2 atmosphere. The reaction mixture was flushed with H_2 and allowed to stir under H_2 at room temperature for 10−12 h. Completion of the reaction was monitored by TLC. The reaction mass was filtered through a Celite bed. Filtrate was collected and concentrated under reduced pressure. Crude product was purified by silica gel column chromatography using 25−30% ethyl acetate in petroleum ether.

*3-(2-Aminophenyl)quinazolin-4(3H)-one (**1**).* Following the general procedure A, the reduction of 3-(2-nitrophenyl)quinazolin-4(3*H*)-one (**5**; 1.5 g, 5.62 mmol, 1.0 equiv) using Pd−C (0.480 g) provided 1.3 g (98%) of the title compound **9** as a white solid: mp = 182−184 °C; R_f = 0.42 (50% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (d, *J* = 7.8 Hz, 1H), 8.07 (s, 1H), 7.83−7.77 (m, 2H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.29 (t, *J* = 7.5 Hz, 1H), 7.13 (d, *J* = 7.7 Hz, 1H), 6.91 (t, *J* = 8.2 Hz, 2H), 3.83 (bs, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.6, 148.1, 147.3, 143.3, 134.9, 130.7, 128.4, 127.9, 127.7, 127.3, 124.5, 122.3, 119.8, 118.0; HRMS (ESI-QTOF) calcd for $C_{14}H_{12}N_3O$ $(M+H)^+$ 238.0980, found 238.0970; IR (KBr, cm^{-1}) 3433, 3371, 3348, 3235, 3059, 3034, 2922, 2854, 2812, 1673, 1660, 1610, 1565, 1500, 1474, 1319, 1297, 1254, 1215, 1188, 1155, 1112, 1081, 1056, 1020.

*3-(2-Aminophenyl)-5-chloroquinazolin-4(3H)-one (**9**).* Following the general procedure A, the reduction of 5-chloro-3-(2-nitrophenyl)-quinazolin-4(3*H*)-one (**6**; 1.00 g, 3.31 mmol, 1.0 equiv) using Pd−C (0.300 g) provided 0.577 g (64%) of the title compound **10** as a white solid: mp = 198−200 °C; R_f = 0.35 (50% EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.68−7.63 (m, 2H), 7.53 (dd, *J* = 6.7, 2.3 Hz, 1H), 7.29 (td, *J* = 7.9, 1.2 Hz, 1H), 7.11 (dd, *J* = 8.1, 1.2 Hz, 1H), 6.92−6.89 (m, 2H), 3.54 (bs, 2H); ^{13}C NMR (125 MHz, DMSO-d_6, $CDCl_3$) δ 157.2, 134.8, 134.0, 133.3, 126.9, 126.1, 125.9, 124.9, 122.4, 121.5, 121.4, 115.3, 115.0; HRMS (ESI-QTOF) calcd for $C_{14}H_{11}ClN_3O$ $(M+H)^+$ 272.0585, found 272.0589; IR (KBr, cm^{-1}) 3359, 2922, 2852, 2820, 1685, 1636, 1616, 1597, 1550, 1501, 1456, 1399, 1302, 1291, 1219, 1193, 1049.

*3-(2-Amino-5-fluorophenyl)quinazolin-4(3H)-one (**10**).* Following the general procedure A, the reduction of 7-fluoro-3-(2-nitrophenyl)-quinazolin-4(3*H*)-one (**8**; 0.750 g, 2.63 mmol, 1.0 equiv) using Pd−C (0.250 g) provided 0.630 g (94%) of the title compound **11** as a white solid: mp = 189−192 °C; R_f = 0.42 (50% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (dd, *J* = 7.9, 0.9 Hz, 1H), 8.05 (s, 1H), 7.82 (td, *J* = 8.2, 1.3 Hz, 1H), 7.77 (d, *J* = 7.9 Hz, 1H), 7.55 (td, *J* = 8.0, 0.9 Hz, 1H), 7.06 (td, *J* = 8.7, 2.8 Hz, 1H), 6.95−6.90 (m, 2H), 3.46 (bs, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.4, 156.4 (d, $^1J_{C-F}$ = 238.7 Hz), 147.9, 146.6, 139.2, 135.1, 128.1, 127.9, 127.8, 127.4 (d, $^3J_{C-F}$ = 6.2 Hz), 122.2, 119.2 (d, $^3J_{C-F}$ = 8.7 Hz), 117.7 (d, $^2J_{C-F}$ = 22.5 Hz), 115.4 (d, $^2J_{C-F}$ = 25.0 Hz); HRMS (ESI-QTOF) calcd for $C_{14}H_{10}FN_3NaO$ $(M+Na)^+$ 278.0700, found 278.0703; IR (KBr, cm^{-1}) 33602, 3234, 2919, 2812, 2725, 1662, 1605, 1509, 1475, 1441, 1384, 1352, 1322, 1291, 1270, 1248, 1169, 1023.

Procedure B. To a suspension of 7-fluoro-3-(2-nitrophenyl)-quinazolin-4(3*H*)-one (**7**; 1.0 g, 3.51 mmol, 1.0 equiv) in a 2:2:1 mixture of AcOH, EtOH, and H_2O (50 mL) was added activated Fe powder (0.980 g, 17.55 mmol, 5.0 equiv). The reaction mass was allowed to stir for 3 h at room temperature. Completion of the reaction was monitored by TLC. The reaction mass was filtered through a Celite bed. Filtrate was collected, and EtOH was removed under reduced pressure. Remaining AcOH and H_2O were removed by making an azeotrope using toluene. Crude mass was purified by silica gel column chromatography using 25−30% ethyl acetate in petroleum ether as eluent.

*3-(2-Aminophenyl)-7-fluoroquinazolin-4(3H)-one (**11**).* Following the general procedure B, the reduction of 7-fluoro-3-(2-nitrophenyl)-quinazolin-4(3*H*)-one (**7**; 1.0 g, 3.51 mmol, 1.0 equiv) using Fe powder (0.980 g, 17.55 mmol, 5.0 equiv) provided 0.680 g (76%) of the title compound **12** as a white solid: mp = 192−194 °C; R_f = 0.42 (50% EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (dd, *J* = 8.8, 6.0 Hz, 1H), 8.05 (s, 1H), 7.41 (dd, *J* = 9.5, 2.5 Hz, 1H), 7.32−7.23 (m, 2H), 7.13−7.11 (m, 1H), 6.93−6.89 (m, 2H), 3.81 (bs, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8 (d, $^1J_{C-F}$ = 253.7 Hz), 159.9, 150.4 (d, $^3J_{C-F}$ = 13.7 Hz), 148.5, 143.3, 130.8, 130.1 (d, $^3J_{C-F}$ = 10.0 Hz), 128.4, 124.2, 119.8, 119.0, 118.0, 116.6 (d, $^2J_{C-F}$ = 23.7 Hz), 113.3 (d, $^2J_{C-F}$ = 22.5 Hz); HRMS (ESI-QTOF) calcd for $C_{14}H_{11}FN_3O$ $(M+H)^+$ 256.0881, found 256.0879; IR (KBr, cm^{-1})

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3350, 3233, 3035, 2928, 1678, 1607, 1501, 1478, 1391, 1314, 1288, 1235, 1198, 1157, 1127, 1105, 1053, 1029.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01287.

^{1}H, ^{13}C, and ^{19}F NMR spectra for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(16) (a) The role of an additive (TBAI) was well studied in our earlier report.[15b] Hence, it is expected that KI would also undergo an iodo-exchange reaction with 2-bromopyridine to afford the 2-iodopyridine. As iodo compounds react much faster in oxidative addition, this iodo exchange might be the reason for yield improvement. (b) A control experiment, using the optimized conditions but without adding KI, failed to provide the desired product.

(17) Besides working as a terminal oxidant, $AgNO_3$ is also a well-known halogen scavenger. It removes bromide impurities from the copper(III) catalytic species, which in turn would improve the yield of the reaction.

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