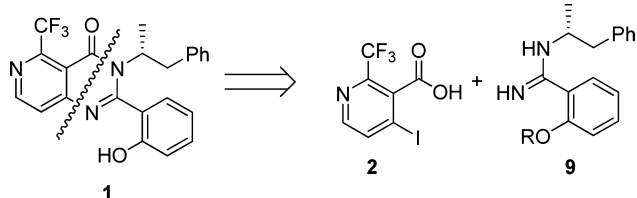


Scheme 2. Retrosynthesis of **1** via Amidine *N*-Arylation

Thus, amidine **9a** was prepared by following the Garigipati reaction.¹¹ Our first attempt using CuI mediated conditions gave the desired product **11**; however, the reaction proceeds to 50% conversion at best, despite all optimization efforts with or without ligands used in the reaction. We quickly switched over to Pd-catalyzed methods and found the Pd₂(dba)₃/Xantphos system gave complete conversion and afforded a clean reaction profile by HPLC analysis. Furthermore, it was noted the reaction was regiospecific at the unsubstituted nitrogen, probably attributed to the lower steric hindrance. Encouraged with these results, we investigated the possibility of directly employing the phenolic amidine in the reaction and went forward with the preparation of **9b**. Unfortunately a significant amount of *O*-arylation was observed under the same reaction conditions. It was also perceived that the methyl ester of **2** could be a better starting material to further shorten the synthesis. Unfortunately we found that the preparation of the methyl ester only worked well when diazomethane was used.

The coupled product **11** is zwitterionic, therefore cumbersome for its isolation. The synthesis was streamlined by directly carrying the reaction mixture to the cyclization by employing HBTU as the amide coupling reagent (Scheme 3). This afforded the penultimate intermediate **8** in 70% yield overall in two steps. The synthesis of **1** was completed with the deprotection of the methyl ether. Use of BCl₃ was complicated with the formation of several impurities, which affected the product quality and isolated yield.¹² Other commonly used demethylation conditions (BBR₃; HBr/NaI; L-methionine/methanesulfonic acid; TMSI; H₂SO₄; LiI) were also unsatisfactory.¹³ We reasoned that PhBCl₂, a widely used Lewis acid for aldol reaction, might be effective to achieve the deprotection and mild enough to give a clean cleavage.¹⁴ Indeed, the reaction employing PhBCl₂ (1 equiv) in toluene at 70 °C (88 h) gave a clean transformation. The reaction could be accelerated at higher temperature (110 °C, 14 h) without compromising the yield or quality.¹⁵ With the amidine arylation route fully

enabled, a multihundred gram synthesis of **1** was carried out successfully under GMP control.

The improved route was short and convergent in synthesis and offered much higher throughput. Furthermore, it provided the advantage of having the key intermediate **9a** that was not considered a “controlled substance”.¹⁶ The “non-controlled” status of the amidine **9a** offered an opportunity for outsourcing to a commercial supplier of L-amphetamine who is licensed to handle the material,¹⁷ which relieved the burden of maintaining a regulatory license for the handling of “controlled substances” in an internal scale-up facility.

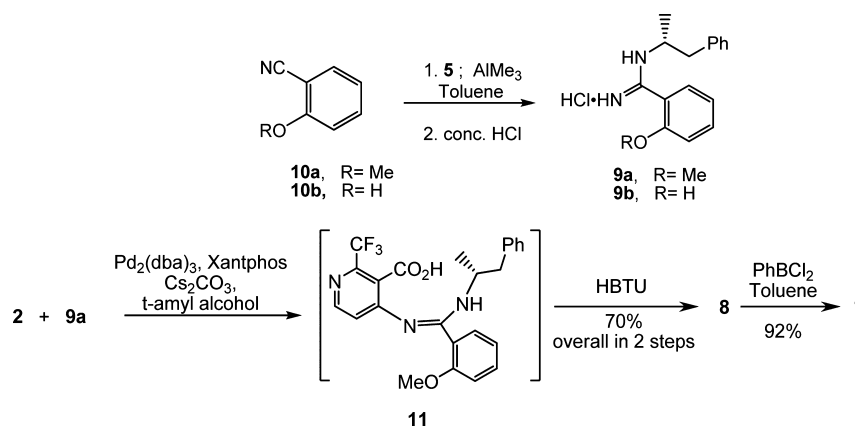
Because **2** is a rather electron-deficient system, it was unclear to us whether the reaction would work similarly for other aromatic substrates. We proceeded to explore the scope of the reaction using commercially available starting materials. 2-Bromo or iodo benzoate methyl esters were chosen, as we anticipated amidine arylated intermediates would cyclize directly to give quinazolin-4(3*H*)-ones under thermal conditions. The results are summarized in Table 1. Using the same

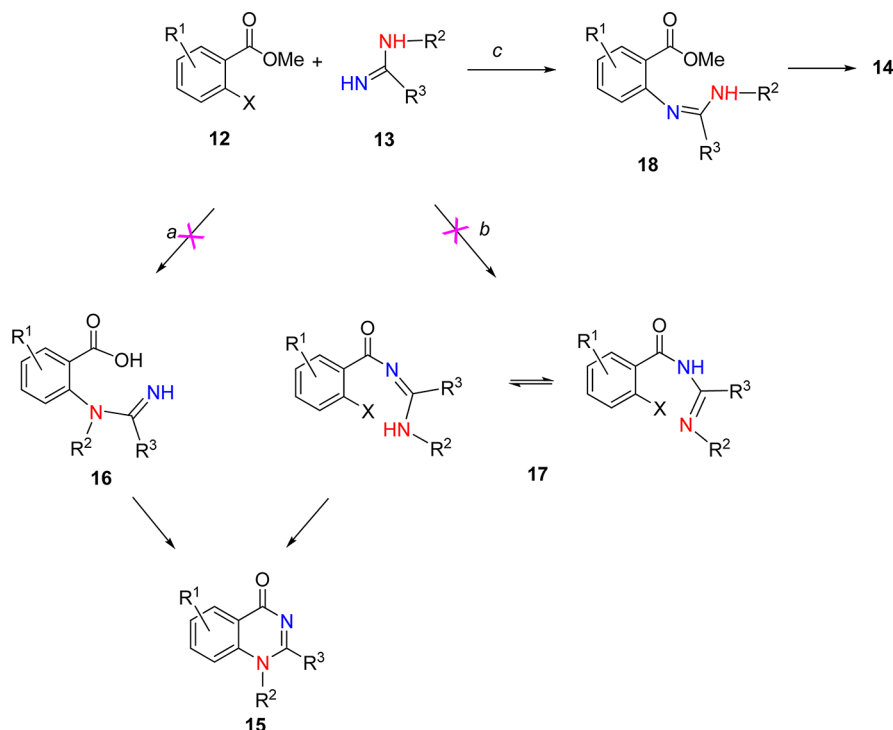
Table 1. One-Pot Synthesis of Quinazolin-4(3*H*)-ones

entry	12		13		14	product
	X	R ¹	R ²	R ³		
1	Br	H	Bn	Ph	83	14a
2	Br	5-NO ₂	Bn	Ph	44	14b
3	I	5-NO ₂	Bn	Ph	59	14b
4	Br	5-MeO	Ph	Ph	63	14c
5	Br	H	Ph	Ph	89	14d
6	Br	5-F	Ph	Ph	72	14e
7	Br	5-NO ₂	Ph	Ph	46	14f
8	Br	5-F	4-Cl-Ph	4-Cl-Ph	65	14g
9	Br	5-NO ₂	H	Ph	55	14h

reaction protocol, quinazolin-4(3*H*)-ones were isolated in 44–89% yields. Lower yields were observed when **12** is substituted with a nitro group at C-5 despite its electron-withdrawing effect.¹⁸

Again, we only observed quinazolin-4(3*H*)-one (**14**) obtained from *N*-arylation at the unsubstituted nitrogen.

Scheme 3. Final Synthesis of **1**

Scheme 4. Possible Pathways of Amidine *N*-Arylation of 2-Halo Benzoate Ester

Close examination of the reaction mixture did not reveal the presence of the other possible regioisomer (15) or its precursors (16 and 17, Scheme 4). In view of a report^{10c} suggesting that transamidation occurred initially under copper-catalyzed conditions, we carried out comparison reactions (using substrates from entries 2 and 5, Table 1) without the catalyst and ligand and did not observe the presence of the amide intermediate (17). This confirmed that the amidine *N*-arylation took place first followed by intramolecular transamidation to form the quinazolin-4(3H)-one. NMR HMBC studies of 14a and 14b provided further evidence of the structural confirmation.¹⁹

We have described a concise synthesis of pyrido[4,3-*d*]pyrimidin-4(3H)-one (1) via amidine *N*-arylation. The improved synthesis offered much higher throughput than the original route. Furthermore, it provided an outsourcing opportunity to avoid the handling of L-amphetamine, a controlled substance, in an internal manufacturing facility. An alternative demethylation method using dichlorophenylborane was discovered, which allowed the isolation of high quality 1 as the final API. The amidine *N*-arylation worked well with 2-bromo or iodo benzoate methyl esters to give quinazolin-4(3H)-ones in a one-pot synthesis.

EXPERIMENTAL SECTION

(*R*)-2-Methoxy-*N'*-(1-phenylpropan-2-yl)benzimidamide hydrochloride salt (9a). 2-Methoxybenzonitrile (11.8 g, 88.8 mmol) was charged to a 500 mL three-neck flask under nitrogen, equipped with a reflux condenser and a thermocouple. To the reaction was added L-amphetamine (10.0 g, 74.0 mmol, 1.0 equiv) and toluene (100 mL). A 2.0 M solution of AlMe₃ in toluene (55.5 mL, 111.0 mmol) was added via a drop funnel while keeping the reaction in an ice bath (Note: Highly exothermic addition! The exotherm is dose-controlled however). The ice bath was removed after the addition was complete. The mixture was heated at reflux (115 °C) for 14 h and then cooled to rt. The reaction was quenched by slowly pouring the mixture into a beaker containing 2 N NaOH (80 mL) stirring at 0 °C in an ice bath

(Note: Methane off gas! Exothermic. The off gas and exotherm were controllable by the feed rate of the quench). The mixture was then transferred to a separatory funnel. The aqueous layer was separated and extracted with toluene (60 mL). The combined toluene phase was treated with a conc. HCl solution (12.1 mL, 148 mmol). The mixture was then concentrated by rotovap (60 °C, 150 mmHg) to azeotropically remove water. After water was completely removed (confirmed by KF test at 0.1% water), acetone (120 mL) was added, which caused the precipitation of the product. After 2 h of stirring, the slurry was filtered and rinsed with acetone (2 × 10 mL). The filter cake was dried under nitrogen to give 9a (16.9 g, 55.5 mmol, 75%) as a white solid. Mp: 162–164 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.61 (d, *J* = 8.78 Hz, 1 H), 9.29 (br. s., 1 H), 9.21 (s, 1 H), 7.56–7.62 (m, 1 H), 7.32–7.36 (m, 4 H), 7.25–7.29 (m, 1 H), 7.20–7.24 (m, 2 H), 7.08 (t, *J* = 7.53 Hz, 1 H), 4.29–4.54 (m, 1 H), 3.80 (s, 3 H), 2.90 (dd, *J* = 6.90, 3.14 Hz, 2 H), 1.23 (d, *J* = 6.27 Hz, 3 H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 160.2, 156.4, 137.7, 133.3, 129.3, 128.2, 126.5, 120.2, 119.3, 112.2, 55.9, 49.9, 40.7, 19.4. Anal. calcd for C₁₇H₂₀N₂O•HCl: C, 66.98; H, 6.94; N, 9.19. Found: C, 66.83; H, 6.74; N, 9.09.

(*R*)-2-(2-Methoxyphenyl)-3-(1-phenylpropan-2-yl)-5-(trifluoromethyl)pyrido[4,3-*d*]pyrimidin-4(3H)-one (8). To a three-neck flask, equipped with a nitrogen inlet, vacuum inlet, and reflux condenser, was charged *tert*-amyl alcohol (100 mL). The solvent was sparged with dry nitrogen for 2 h. Amidine hydrochloride 9a (10.0 g, 32.8 mmol) was added, followed by cesium carbonate (36.6 g, 112 mmol), XANTPHOS (0.57 g, 0.984 mmol, 0.03 equiv), and Pd₂(dba)₃ (0.601 g, 0.656 mmol, 0.02 equiv). 2 (10.4 g, 32.8 mmol) was added last, and the resulting mixture was heated to reflux (104 °C, internal temp) under N₂ and monitored by HPLC. After 10 h of heating, *tert*-amyl alcohol was removed under vacuum and solvent exchanged with toluene. The mixture was kept at the lowest stirrable volume. Acetonitrile (150 mL) was added followed by the addition of HBTU (14.9 g, 39.4 mmol, 1.2 equiv), and the resulting mixture was stirred for 2 h. The reaction mixture was filtered, and the filter cake was rinsed with EtOAc (2 × 50 mL). The filtrate and rinses were combined and reduced to a minimum volume, EtOAc (80 mL) was added, and the resulting solution was washed with water (80 mL), a 1 N HCl solution (50 mL), a 10% sodium bicarbonate solution (50 mL), and a brine solution (50 mL) successively and then concentrated (50 °C, 150

mmHg) to a low stirrable volume (~20 mL EtOAc remained). The resulting mixture was stirred at RT overnight to give a thick slurry. The product was collected by filtration, and the filter was rinsed with cold EtOAc (10 mL). This gave the coupled product **8** (15.1 g, 23.0 mmol, 70%) as a white solid after drying under nitrogen. Mp: 145–147 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.87–8.80 (m, 1 H), 7.81–7.64 (m, 1 H), 7.61–7.43 (m, 1 H), 7.36–7.31 (m, 1 H), 7.27–7.09 (m, 4 H), 7.03–6.91 (m, 2 H), 6.83–6.77 (m, 2 H), 6.38 (dd, *J* = 1.5, 7.5 Hz, 1 H), 4.23 (ddd, *J* = 5.5, 6.7, 9.7 Hz, 1 H), 3.86–3.81 (m, 4 H), 3.65 (dd, *J* = 9.8, 13.6 Hz, 1 H), 3.37–3.28 (m, 1 H), 2.92 (dd, *J* = 5.5, 13.6 Hz, 1 H), 1.77 (d, *J* = 6.8 Hz, 3 H), 1.42 (d, *J* = 6.8 Hz, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ 160.7, 158.7, 154.8, 150.2, 138.1, 131.7, 129.6, 129.1, 129.0, 128.6, 128.6, 128.3, 126.7, 126.5, 124.5, 123.9, 121.4, 121.0, 116.3, 111.2, 110.4, 77.4, 77.0, 76.7, 61.3, 55.3, 38.6, 18.2, 16.2. Anal. calcd for C₂₄H₂₀F₃N₃O₂•0.3C₄H₈O₂: C, 64.97; H, 4.85; N, 9.02. Found: C, 64.80; H, 4.85; N, 9.04.

(R)-2-(2-Hydroxyphenyl)-3-(1-phenylpropan-2-yl)-5-(trifluoromethyl)pyrido[4,3-d]pyrimidin-4(3H)-one (1). Method A. The coupled product **8** (15.1g, 23.0 mmol) was combined with toluene (30 mL). The resulting solution was concentrated and then cooled. Dichloromethane (290 mL) was added, and the resulting solution was cooled to 0 °C. A boron trichloride solution in dichloromethane (5.4 g, 45 mmol) was added to the reaction mixture while keeping the reaction cold. The resulting mixture was stirred until the reaction was deemed complete by HPLC and inversely quenched into a stirred mixture of diethanolamine (15.7g, 149.5 mmol) and water (350 mL). The layers were separated, and the aqueous layer was extracted with dichloromethane. The combined dichloromethane phase was washed with aqueous hydrochloric acid and a brine solution successively. The organic phase is stirred with silica gel supported thiol (Ultra pure Silicycle Thiol) and anhydrous magnesium sulfate. The mixture was stirred and filtered. The filtrate was concentrated. The resulting crude product was chromatographed on silica gel eluting with a mixture of ethyl acetate and heptanes. The product-rich fractions were combined and filtered to render the solution free of particulates. The filtrate was then concentrated and cooled to induce crystallization. The resulting slurry was stirred at room temperature overnight. The solids were collected by filtration, washed with heptanes, and dried to provide **1** (5.64 g, 38.9%) as a white solid: Mp 198 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.76 (d, *J* = 5.52 Hz, 1 H), 8.32 (br. s., 1 H), 7.50 (d, *J* = 5.27 Hz, 1 H), 7.40 (t, *J* = 7.91 Hz, 1 H), 7.01–7.12 (m, 4 H), 6.95–7.01 (m, 2 H), 6.79 (d, *J* = 7.03 Hz, 2 H), 4.68 (dt, *J* = 9.60, 6.62 Hz, 1 H), 3.55 (dd, *J* = 13.80, 9.79 Hz, 1 H), 3.04 (dd, *J* = 13.80, 6.02 Hz, 1 H), 1.90 (d, *J* = 6.78 Hz, 3 H), 1.70 (br. s., 1 H); ¹³C NMR (100 MHz, CDCl₃) δ 181.6, 161.5, 159.1, 156.1, 155.7, 153.3, 150.5, 137.5, 132.9, 128.6, 128.6, 126.8, 123.4, 122.5, 120.1, 119.2, 118.1, 115.7, 62.4, 38.9, 19.0 ppm. HRMS (ESI, ion trap) *m/z* calcd for C₂₃H₁₉F₃N₃O₂ 426.14239, found 426.14228.

Method B. The coupled product **8** (4.98 g, 11.33 mmol) was combined in toluene (100 mL). The flask was purged with nitrogen. Dichlorophenylborane (3 mL, 22.89 mmol) was then added, and the resulting reaction was heated at 70 °C under nitrogen for 88 h. Upon completion, the reaction was reversely quenched into a stirred mixture of diethanolamine (10 mL, 103.86 mmol) and water (125 mL) at room temperature. The layers were separated, and the aqueous layer was extracted with toluene (40 mL). The combined organic layers were washed with saturated sodium bicarbonate (150 mL). The organic layer was washed with 1 N HCl (150 mL) and then dried over magnesium sulfate, filtered, and concentrated to dryness. The residue was dissolved in isopropyl alcohol and recrystallized with water. The mixture was stirred for 1 h, filtered, and dried overnight in a vacuum oven to give **1** (4.48 g, 92.9%) as an off-white solid. Spectroscopic data were identical to those of the product obtained from the BCl₃ method.

General Procedure for Synthesis of Quinazolin-4(3H)-ones.

Prior to use, nitrogen was bubbled through the *tert*-amyl alcohol at room temperature for 1 h. To a 20 dram vial were added amidine (1–2 mmol), cesium carbonate (2 equiv), Pd₂(dba)₃ (0.02 equiv), Xantphos (0.03 equiv), and *tert*-amyl alcohol (10 mL/g). The mixture was then flushed with nitrogen. The substituted 2-halo benzoate (1 equiv) was added, and the resulting mixture was heated to 100 °C for

4–14 h depending on the substrate. Upon completion, the reaction mixture was passed through a 2" pad of silica gel with 10–100% ethyl acetate/heptanes. The purest fractions were combined, concentrated, and then recrystallized with dichloromethane/heptanes. Melting points, characterization data, and elemental analyses were obtained on the isolated compounds.

3-Benzyl-2-phenylquinazolin-4(3H)-one (14a). 125 mg, 83%; mp 140–142 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.41 (d, *J* = 7.78 Hz, 1 H), 7.76–7.86 (m, 2 H), 7.53–7.59 (m, 1 H), 7.47–7.52 (m, 1 H), 7.43 (t, *J* = 7.53 Hz, 2 H), 7.34–7.39 (m, 2 H), 7.20–7.25 (m, 3 H), 6.92–6.99 (m, 2 H), 5.30 (s, 2 H); ¹³C NMR (100 MHz, CDCl₃) δ 162.5, 156.4, 147.3, 136.6, 135.3, 134.6, 129.9, 128.6, 128.5, 128.0, 127.6, 127.5, 127.2, 127.1, 127.0, 120.9, 48.8. Anal. calcd for C₂₁H₁₆N₂O•0.56 CH₂Cl₂: C, 71.95; H, 4.79; N, 7.78. Found: C, 72.17; H, 4.47; N, 8.03.

3-Benzyl-6-nitro-2-phenylquinazolin-4(3H)-one (14b). 87 mg, 59%; mp 177–179 °C; ¹H NMR (400 MHz, CDCl₃) δ 9.26 (d, *J* = 2.51 Hz, 1 H), 8.59 (dd, *J* = 2.64, 8.91 Hz, 1 H), 7.89 (d, *J* = 9.03 Hz, 1 H), 7.53–7.59 (m, 1 H), 7.48 (t, *J* = 7.65 Hz, 2 H), 7.38–7.43 (m, 2 H), 7.23–7.28 (m, 3 H), 6.92–6.98 (m, 2 H), 5.34 (s, 2 H); ¹³C NMR (100 MHz, CDCl₃) δ 161.5, 159.7, 151.2, 145.9, 135.8, 134.6, 130.6, 129.2, 128.8, 128.7, 128.6, 127.9, 127.9, 127.1, 123.9, 121.0, 49.3. Anal. calcd for C₂₁H₁₅N₃O₃•0.19 CH₂Cl₂: C, 68.14; H, 4.15; N, 11.25. Found: C, 67.96; H, 4.04; N, 11.32.

6-Methoxy-2,3-diphenylquinazolin-4(3H)-one (14c). 104 mg, 63%; mp 202–204 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.79 (d, *J* = 8.8 Hz, 1 H), 7.75 (d, *J* = 3.0 Hz, 1 H), 7.44 (dd, *J* = 8.9, 2.9 Hz, 1 H), 7.34 (q, *J* = 6.6 Hz, 5 H), 7.27–7.30 (m, 1 H), 7.21–7.27 (m, 3 H), 7.18 (d, *J* = 7.5 Hz, 2 H), 3.97 ppm (s, 3 H); ¹³C NMR (101 MHz, CDCl₃) δ 162.2, 158.8, 153.0, 142.2, 137.9, 135.5, 129.4, 129.1, 129.1, 129.0, 129.0, 128.4, 128.0, 124.9, 121.8, 106.6, 55.9. Anal. calcd for C₂₁H₁₆N₂O₂•0.05 CH₂Cl₂: C, 76.01; H, 4.88; N, 8.42. Found: C, 76.35; H, 4.44; N, 8.51.

2,3-Diphenylquinazolin-4(3H)-one (14d). 134 mg, 89%; mp 157–159 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.39 (d, *J* = 8.0 Hz, 1 H), 7.88–7.81 (m, 2 H), 7.60–7.52 (m, 1 H), 7.39–7.34 (m, 3 H), 7.34–7.31 (m, 1 H), 7.31–7.27 (m, 1 H), 7.27–7.25 (m, 1 H), 7.25–7.20 (m, 1 H), 7.18 (d, *J* = 7.8 Hz, 2 H); ¹³C NMR (100 MHz, CDCl₃) δ 162.3, 155.2, 147.5, 137.7, 135.5, 134.8, 129.3, 129.1, 129.0(2C), 128.4, 128.0, 127.8, 127.3, 127.2, 121.0. Anal. calcd for C₂₀H₁₄N₂O•0.03 CH₂Cl₂: C, 79.96; H, 4.71; N, 9.31. Found: C, 79.97; H, 4.57; N, 9.24.

6-Fluoro-2,3-diphenylquinazolin-4(3H)-one (14e). 115 mg, 72%; mp 153–155 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.01 (dd, *J* = 2.6, 8.4 Hz, 1 H), 7.86 (dd, *J* = 4.9, 8.9 Hz, 1 H), 7.56 (dt, *J* = 2.5, 8.4 Hz, 1 H), 7.39–7.21 (m, 9 H), 7.17 (d, *J* = 7.3 Hz, 2 H); ¹³C NMR (100 MHz, CDCl₃) δ 162.5, 161.6 (d, *J* = 3.7 Hz), 160.0, 154.6 (d, *J* = 2.2 Hz), 144.2 (d, *J* = 2.2 Hz), 137.5, 135.2, 130.2 (d, *J* = 8.8 Hz), 129.4, 129.1 (*J* = 2.2 Hz), 129.0, 128.6, 128.0, 123.3 (d, *J* = 24.2 Hz), 122.3 (d, *J* = 8.8 Hz), 112.1 (d, *J* = 23.5 Hz). Anal. calcd for C₂₀H₁₃FN₂O•0.04 CH₂Cl₂: C, 75.28; H, 4.12; N, 8.76. Found: C, 74.94; H, 3.99; N, 8.60.

6-Nitro-2,3-diphenylquinazolin-4(3H)-one (14f). 78 mg, 46%; mp 218–220 °C; ¹H NMR (400 MHz, CDCl₃) δ 9.22 (d, *J* = 2.5 Hz, 1 H), 8.62 (dd, *J* = 8.8, 2.5 Hz, 1 H), 7.96 (d, *J* = 9.0 Hz, 1 H), 7.36–7.42 (m, 5 H), 7.30–7.36 (m, 2 H), 7.24–7.30 (m, 3 H), 7.19 ppm (d, *J* = 6.8 Hz, 2 H); ¹³C NMR (100 MHz, CDCl₃) δ 161.2, 158.4, 151.5, 146.0, 137.0, 134.7, 130.1, 129.4, 129.3, 129.0, 129.0, 128.9, 128.2, 123.9, 121.2. Anal. calcd for C₂₀H₁₃N₃O₃•0.05 CH₂Cl₂: C, 69.28; H, 3.80; N, 12.09. Found: C, 69.22; H, 3.44; N, 11.97.

2,3-Bis(4-chlorophenyl)-6-fluoroquinazolin-4(3H)-one (14g). 98 mg, 65%; mp 238–240 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.04–7.11 (m, 2 H), 7.20–7.29 (m, 5 H), 7.30–7.37 (m, 2 H), 7.53 (td, *J* = 8.49, 2.93 Hz, 1 H), 7.80 (dd, *J* = 8.98, 4.68 Hz, 1 H), 7.95 (dd, *J* = 8.20, 3.12 Hz, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ 172.2, 162.6, 161.4, 161.3, 160.1, 153.0, 153.0, 144.0, 143.9, 136.0, 135.8, 134.9, 133.4, 130.4, 130.4, 130.3, 130.3, 129.6, 128.6, 123.7, 123.5, 122.1, 122.1, 112.3, 112.1. Anal. calcd for C₂₀H₁₁Cl₂FN₂O•0.1 CH₂Cl₂: C, 61.32; H, 2.87; N, 7.12. Found: C, 61.02; H, 2.49; N, 6.88.

6-Nitro-2-phenylquinazolin-4(3H)-one (14h). 373 mg, 55% mp 316–318 °C; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 13.01 (br. s., 1 H), 8.85 (d, J = 2.51 Hz, 1 H), 8.57 (dd, J = 9.16, 2.64 Hz, 1 H), 8.24 (d, J = 7.78 Hz, 2 H), 7.93 (d, J = 9.03 Hz, 1 H), 7.66 (d, J = 6.78 Hz, 1 H), 7.56–7.63 (m, 2 H); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 155.7, 144.7, 132.3, 132.0, 128.7, 128.5, 128.2, 122.0, 121.0. Anal. calcd for $\text{C}_{14}\text{H}_9\text{N}_3\text{O}_3 \cdot 0.05 \text{CH}_2\text{Cl}_2$: C, 62.16; H, 3.38; N, 15.48. Found: C, 62.11; H, 3.38; N, 15.50.

■ ASSOCIATED CONTENT

■ Supporting Information

Full compound characterization data as well as copies of ^1H and ^{13}C NMR spectra are given. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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