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Iodine Catalyzed Oxidative Synthesis of Quinazolin-4(3*H*)-ones and Pyrazolo[4,3-*d*]pyrimidin-7(6*H*)-ones via Amination of sp^3 C−H Bond

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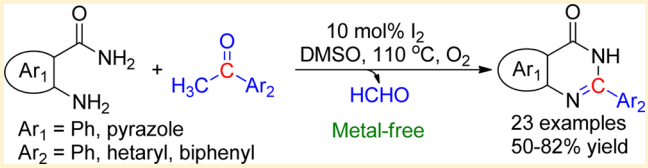
Supporting Information

ABSTRACT: Molecular iodine catalyzed oxidative coupling of 2-aminobenzamides with aryl methyl ketones produced 2-aryl quinazolin-4(3*H*)-ones. The reaction performed well in the absence of any metal or ligand. The quantity of iodine played a very crucial role in this transformation in order to selectively get 2-aryl quinazolin-4(3*H*)-ones. The utility of this protocol for synthesis of pyrazolo[4,3-*d*]pyrimidin-7(6*H*)-ones including a key intermediate involved in sildenafil synthesis has also been demonstrated.



Quinazolin-4(3*H*)-ones are an important class of fused heterocycles having wide occurrence among natural products[1−6] and bioactive compounds.[7,8] Especially, 2-substituted quinazolinones have been reported as potent kinase inhibitors (e.g., idelalisib).[9−11] Similarly, the pyrazolo[4,3-*d*]pyrimidin-7(6*H*)-one is another important class of fused heterocycles possessing promising biological activities.[12,13] The blockbuster drug sildenafil (Viagra)[13] which is used to treat erectile dysfunction contains a pyrazolo[4,3-*d*]pyrimidin-7(6*H*)-one pharmacophore. Because of their medicinal importance, synthetically, these scaffolds have been extensively explored.[14−16] Among various transformations reported for synthesis of quinazolinones, the condensation of 2-aminobenzamide with various simple aryl precursors using metal or metal-free conditions is one of the most elegant and widely studied approach. Various reports on this approach (summarized in Figure 1) includes: (a) the condensation of 2-aminobenzamide with aryl aldehyde,[15,17] aryl carboxylic acid,[18] aryl acid chloride;[19] (b) Pd,[20] Ir,[21] Zn,[22] or I_2/DMSO[23]-catalyzed benzylic C−H amidation with benzyl alcohols, or condensation with benzyl amine[24] or benzyl halides;[25] (c) $Pd(OAc)_2$/$BuPAd_2$/CO-catalyzed condensation with aryl bromides;[26] (d) $PdCl_2$/DPPP/$CaCl_2$-mediated condensation with aryl halides and via palladium-catalyzed isocyanide insertion;[27] (e) metal-free $(tBuO)_2$ (DTBP)/TsOH-mediated condensation with methylarenes or methylhetarenes;[28] (f) CuCl-catalyzed condensation with methylhetarenes;[29] and (g) TFA-catalyzed condensation with ketoalkynes.[30] Many of these protocols have certain disadvantages. The condensation with carbonyl compounds (aldehydes, acids, or acid chlorides) requires use of stoichiometric quantities of toxic oxidants (such as DDQ)[17] or coupling agents (such as EDCI)/ bases.[18] Furthermore, the condensation with benzyl alcohols[20−22] and aryl halides[26,27] requires metal catalysts. The present work describes the use of aryl methyl ketones as a coupling partner, which are cheap, commercially available, and relatively stable. Furthermore, the protocol is metal-free and requires catalytic amount of iodine and molecular oxygen as an oxidant.

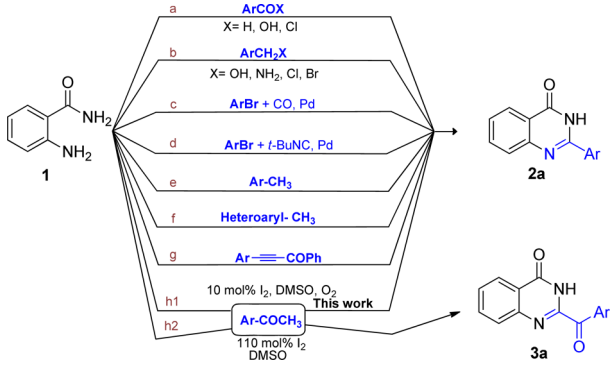


Figure 1. Literature reports (paths a−g and h2) and the present work (path h1) for synthesis of quinazolin-4(3*H*)-ones.

The use of molecular iodine as a catalyst is a promising strategy in organic synthesis which substitutes many transition metals. Especially, the amidation of C(sp^3)-H bonds using molecular iodine is very attractive, and it finds utility in synthesis of a wide range of *N*-heterocycles. Recently, Wu and co-workers[31] reported I_2/DMSO-catalyzed condensation of 2-aminobenzamide with acetophenone to produce 2-benzoyl-substituted quinazolinone **3a** (path h2 of Figure 1). Wu's protocol involved the use of stoichiometric quantity of molecular iodine (110 mol %), which led to the formation of 2-benzoyl-substituted quinazolinone **3a** via formation of glyoxal **7a** as a key intermediate (Figure 2). Interestingly, during our investigations, it was observed that on the use of catalytic amounts of iodine (10 mol %), the acetophenone **6a** forms

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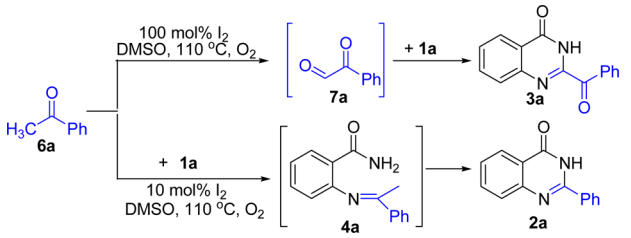


Figure 2. Catalyst loading as a key determinant factor for formation of **2a** versus **3a**.

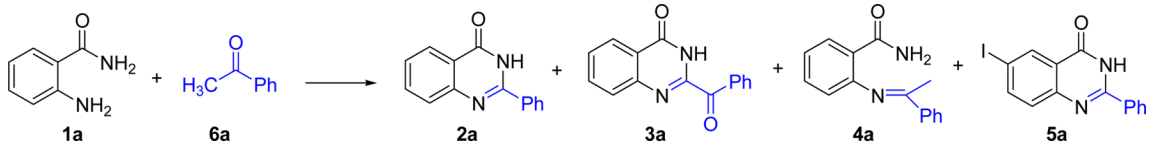
Schiff's base **4a** as a key intermediate, which then undergoes cyclization followed by formaldehyde loss to produce 2-aryl quinazolinone product **2a** (path h1 in Figure 1 and Figure 2) instead of 2-benzoyl quinazolinone **3a**. Thus, herein, we report an efficient metal-free approach for synthesis of 2-aryl quinazolin-4(3*H*)-ones **2** and pyrazolo[4,3-*d*]pyrimidin-7(6*H*)-ones **9** via condensation of 2-aminobenzamides **1** or 4-amino-1-methyl-3-propyl-1*H*-pyrazole-5-carboxamide **8** with aryl methyl ketones **6** using molecular iodine as a catalyst and molecular oxygen as an oxidant.

We began our efforts by examining the condensation reaction of 2-aminobenzamide (**1a**) with acetophenone (**6a**) under various conditions as shown in Table 1. On the basis of the recent report on the condensation of acetophenone with 2-aminobenzenethiol,[32] we investigated the reaction of **1a** with **6a** in DMSO and PhCl (1:1) as a solvent in an open air atmosphere (or molecular oxygen) at 140 °C; however, reaction does not proceed at all (entries 1−3), and even the Schiff's base **4a** was also not formed. Then, we used 10 mol % I_2 in DMSO at room temperature (entry 4) or under heating (entries 5−6) in air atmosphere (entries 4−6) or using molecular oxygen (entry 7), which led to formation of the desired product 2-aryl quinazolinone **2a** up to 30% yield along with Schiff's base **4a** (entries 4−7). This indicated that iodine acts as a Lewis acid to form Schiff's base **4a**. On the use of 100 and 150 mol % of I_2 in the presence of molecular oxygen, the benzoyl-substituted product **3a** was formed in 50% yield, whereas yield of **2a** remained 20% (entries 8−9). Further, when the mol % of I_2 was decreased from 100 to 50, the yield of **2a** was increased up to 35% (entry 10). Further decrease in the iodine quantity to 10 mol % resulted in further improvement in **2a** yield (entry 11). As seen in the entry 7, longer reaction time and 10 mol % I_2 produces only desired product **2a** along with Schiff's base **4a** without formation of undesired product **3a**; therefore, we further intended to use smaller equivalents of iodine and a longer reaction time. These efforts indicated that 10 mol % I_2 in DMSO in the presence of molecular oxygen for 16 h, results in formation of 73% of the desired 2-aryl quinazolinone **2a** (entry 12).

These results concluded that the catalyst loading played a crucial role in selective formation of 2-aryl **2a** versus 2-benzoyl product **3a**, as depicted in Figure 2. When iodine was used in stochiometric equivalent, acetophenone **6a** immediately gets converted to phenyl glyoxal **7a**, which further reacts with 2-aminobenzamide (**1a**) to produce **3a** as a major product. However, on the use of a catalytic amount of iodine (10 mol %), preferentially the Schiff's base **4a** gets formed which upon cyclization yields 2-aryl quinazolinone **2a** as a major product.

Under the optimized reaction conditions, the scope and generality of the oxidative condensation reaction was then explored (Scheme 1). The condensation with nonsubstituted acetophenone gave slightly lower yields in comparison to substituted acetophenones. The reactions with aryl methyl ketones bearing electron-donating groups on the aromatic ring proceeded smoothly to give the desired products in good yields (entries **2b**, **2c**, **2d**, and **2e**). Electron-withdrawing functional groups bearing aryl methyl ketones also gave good yields (entries **2f** and **2g**). These findings indicated that there is no effect of the type of substituents on the yield of the desired product. Mild EWGs such as fluoro, bromo were also well-tolerated under optimized reaction conditions (entries **2h−j**) while *ortho*-bromo substitution produced slightly lower yield (entry **2j**). Similarly, the 3-acetamido aryl methyl ketone yielded lesser yield (entry **2k**). It is noteworthy to mention that biphenyl (e.g., **2l**), heteroaryl (e.g., **2m−o**), and fused aryl (e.g., **2p**) ketones were also well-tolerated in this reaction, producing

Table 1. Optimization of the Reaction Conditions



						yield (%)[a]			
entry	iodine (mol %)	oxidant	solvent	temp (°C)	time (h)	**2a**	**3a**	**4a**	**5a**
1	0	air	DMSO + PhCl[b]	140	10	0	0	0	0
2	0	air	DMSO	140	10	0	0	0	0
3	0	O_2	DMSO	140	10	0	0	0	0
4	10	air	DMSO	rt	10	10	0	20	0
5	10	air	DMSO	110	10	30	0	20	0
6	10	air	DMSO	140	10	30	0	20	0
7	10	O_2	DMSO	rt	20	20	0	20	0
8	100	O_2	DMSO	110	4	20	50	0	traces
9	150	O_2	DMSO	110	4	20	50	0	10
10	50	O_2	DMSO	110	4	35	40	0	traces
11	10	O_2	DMSO	110	10	50	traces	traces	traces
12[c]	**10**	**O_2**	**DMSO**	**110**	**16**	**73**	**traces**	**traces**	**traces**

[a]Isolated yield. [b]DMSO: PhCl (1:1). [c]Optimized reaction condition.

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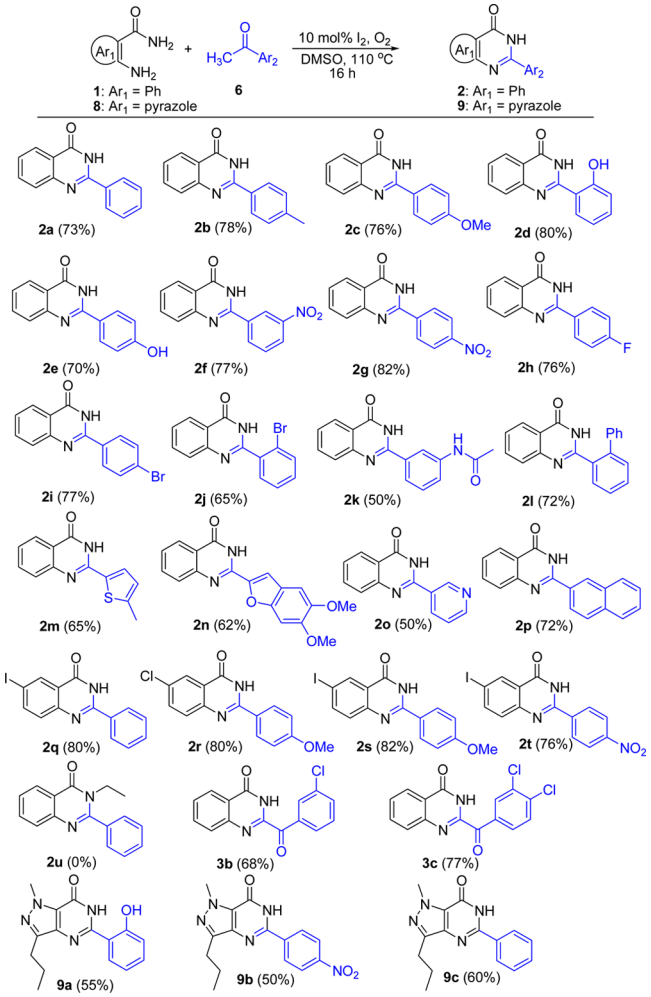
Scheme 1. Scope of the Reaction for Synthesis of Various Quinazolin-4(3*H*)-ones 2 and Pyrazolo[4,3-*d*]pyrimidin-7(6*H*)-ones 9[a]



[a]Reagents and conditions: 2-aminobenzamide (**1**, 1.0 equiv) or 4-amino-1-methyl-3-propyl-1H-pyrazole-5-carboxamide (**8**, 1.0 equiv), aryl methyl ketone (**6**, 1.0 equiv), 10 mol % I_2, DMSO, 110 °C, O_2 atmosphere, 16 h, 50−82%.

corresponding products in good yields. Like aryl methyl ketones, a series of halo-substituted 2-aminobenzamides such as chloro and iodo were also well-tolerated (**2q**−**t**) in this reaction. Further, in case of 2-amino-*N*-ethylbenzamide, reaction does not proceed (e.g., **2u**). For 3-chloro- and 3,4-dichloro-substituted aryl methyl ketones, the desired 2-aryl products were not obtained; instead benzoyl substituted products **3b** and **3c** were obtained. This could be due to the fact that the Schiff's base is not getting formed for these ketones under our optimized reaction conditions. Unfortunately, aliphatic ketones are also not suitable for this kind of transformation.

The pyrazolo[4,3-*d*]pyrimidin-7(6*H*)-ones are putative building blocks for synthesis of PDE5 inhibitors and kinase inhibitors. Therefore, we investigated the utility of this protocol for preparation of key building blocks for biologically important pyrazolo[4,3-*d*]pyrimidin-7(6*H*)-one class of compounds. Using this protocol, the pyrazolo-pyrimidinones **9a**−**9c** were prepared in 50−60% yield. In this case, comparatively lesser yields were obtained because the reaction did not go to completion under the optimized reaction condition. The pyrazolo[4,3-*d*]pyrimidin-7(6*H*)-one **9a** is a key intermediate in synthesis of a top-selling drug sildenafil, whereas **9b** could be utilized toward synthesis of potent mTOR inhibitors (Scheme 1). This approach for synthesis of **9a** allows further modifications (for further SAR studies) on the phenolic OH, whereas reported approaches of sildenafil synthesis has these limitations (which always involves alkylated phenolic OH right from the first step).[13,33]

To elucidate the reaction mechanism, we conducted a series of control experiments. Under the molecular oxygen, the reaction of α-iodo acetophenone **10** with 2-aminobenzamide **1a** produced product **3a** in good yield, both with I_2 (10 mol %) as well as without I_2 (Scheme S1a of the Supporting Information). The α-iodo acetophenone **10** gets immediately converted to phenyl glyoxal **7a** which then produces **3a**. Another experiment of phenyl glyoxal **7a** with 2-aminobenzamide **1a** proceeded smoothly to form **3a** as a major product (Scheme S1b of the Supporting Information). These two experiments indicated that the formation of our desired product **2a** does not involve α-iodo ketone **10** and glyoxal **7a** as intermediates. Once these intermediates (**10** and/or **7a**) get formed, preferentially **3a** gets formed with no opportunity to form **2a**. Next, in order to know the possible reaction intermediates, we performed MS analysis of the reaction mixtures at different time intervals. The MS spectrum after 1 h reaction time showed masses for Schiff's base **4a** or possibly its cyclized intermediate **I** (*m*/*z* 238) along with product **2a** (*m*/*z* 222), and *m*/*z* 364 (for iodinated intermediate **II**). Interestingly, after 4 h, we observed a mass *m*/*z* 146 for formaldehyde condensed byproduct quinazolin-4(3H)-one **11**. Additionally, we also observed the mass for iodinated byproduct **5a** (*m*/*z* 347). The MS analysis details are provided in Section S2 of Supporting Information. To prove the formation of formaldehyde adduct **11**, we conducted control reaction of 2-aminobenzamide **1a** with formaldehyde, wherein we observed formation of quinazolin-4(3H)-one **11** in 55% yield (Scheme S1c of Supporting Information). Thus, accordingly, we proposed a plausible reaction mechanism for formation of **2a** from **1a** and **6a** as depicted in Figure 3. In this reaction, iodine activates acetophenone **6a**, leading to the

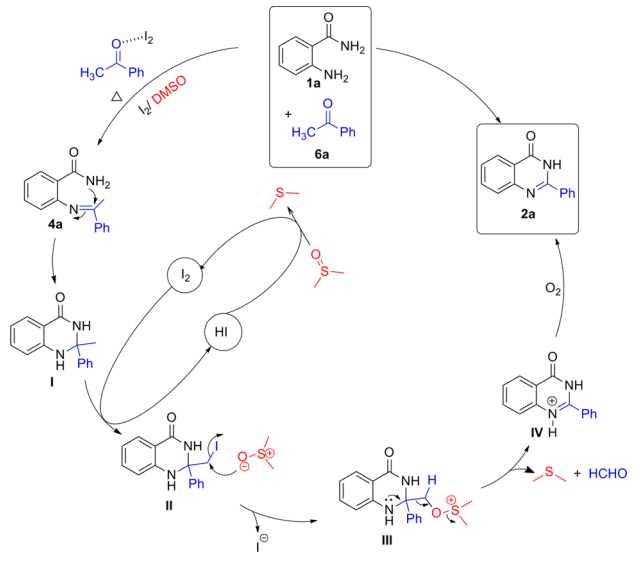


Figure 3. Proposed mechanism for synthesis of quinazolin-4(3*H*)-ones.

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formation of Schiff's base **4a**, which on cyclization produces intermediate **I**. Intermediate **I** undergoes iodination to produce **II**. The intermediate **II** on coupling with DMSO forms **III**. Elimination of dimethyl sulfide and formaldehyde from **III** leads to the formation of intermediate **IV**, which finally on oxidation by molecular oxygen produces product **2a**.

In conclusion, we have developed a new iodine-catalyzed synthesis of 2-aryl quinazolin-4(3*H*)-ones via condensation of 2-aminobenzamide with aryl methyl ketones using molecular oxygen as an oxidant. The utility of this protocol for preparation of pyrazolo[4,3-*d*]pyrimidin-7(6*H*)-ones has also been demonstrated.

EXPERIMENTAL SECTION

General Information. ^{1}H, ^{13}C, and DEPT NMR spectra were recorded on FT-NMR 500 and 400 MHz instruments. Chemical data for protons are reported in parts per million (ppm) downfield from tetramethylsilane and are referenced to the residual proton in the NMR solvent ($CDCl_3$: 7.26, CD_3OD: 3.28, and DMSO-d_6: 2.5 ppm). Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded at 125 or 100 MHz: chemical data for carbons are reported in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced to the carbon resonance of the solvent ($CDCl_3$: 77, CD_3OD: 49, and DMSO-d_6: 39.5 ppm). IR spectra were recorded on IR spectrophotometer. Melting points were recorded on digital melting point apparatus.

Optimized Procedure for Preparation of 2-aryl Quinazolin-4(3*H*)-ones (2) and Pyrazolo[4,3-*d*]-pyrimidin-7(6*H*)-ones (9). To the preheated mixture of 2-aminobenzamides **1** or 4-amino-1-methyl-3-propyl-1H-pyrazole-5-carboxamide **8** (100 mg, 1 equiv) and corresponding acetophenone **6** (1 equiv) in DMSO in a round-bottom flask in the presence of oxygen (supplied using oxygen balloon) was added iodine (10 mol %). Oxygen gas was continuously passed using an oxygen balloon, and reaction mixture was heated at 110 °C for 16 h. After completion of the reaction, water (20 mL) was added to the reaction mixture. A saturated $Na_2S_2O_3$ solution was then added until the brown color disappeared. Product was extracted with EtOAc (3 × 10 mL). The organic layer was collected, dried on anhydrous sodium sulfate, and the solvent was evaporated on a rotary evaporator to get the crude product. The crude product was purified by silica gel (no. 100–200) column chromatography using 2–20% EtOAc:*n*-hexane to get pure quinazolinone products. Most of the compounds were purified without column chromatography. MeOH was added to the crude product and the resulting suspension was filtered. Obtained residue was washed with MeOH 2–3 times and dried. To get good yield of the product, on addition of methanol, the product was allowed to settle down for 2–3 days, which resulted in formation of a crystalline pure product.

*2-Phenylquinazolin-4(3H)-one (**2a**, SS-730).*[28] White solid; yield: 73% (119 mg); mp 232–235 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.57 (s, 1H), 8.34 (d, J = 7.8 Hz, 1H), 8.26–8.24 (m, 2H), 7.86–7.80 (m, 2H), 7.60–7.50 (m, 3H), 7.52 (t, J = 7.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, ppm): δ 163.8, 151.9, 149.4, 134.9, 132.8, 131.6, 129.0, 127.9, 127.43, 126.8, 126.3, 120.8; IR ($CHCl_3$): ν_{max} 3436, 2926, 1666, 1481, 1297, 1144 cm^{-1}; ESI-MS: m/z 223.08 [M + H]$^+$; HR-ESIMS: m/z 223.0869 calcd for $C_{14}H_{10}N_2O$+H$^+$ (223.0871).

*2-(p-Tolyl)quinazolin-4(3H)-one (**2b**, SS-524).*[28] White solid; yield: 78% (135 mg); mp 239–242 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16–8.09 (m, 3H), 7.84 (t, J = 8.2 Hz, 1H), 7.74 (d, J = 7.8 Hz, 1H), 7.52 (t, J = 8.2 Hz, 1H), 7.37 (d, J = 8.0 Hz, 2H), 2.40 (s, 3H). IR ($CHCl_3$): ν_{max} 3436, 2918, 1667, 1600, 1486, 1241, 768 cm^{-1}; ESI-MS: m/z 237.10 [M + H]$^+$; HR-ESIMS: m/z 237.1029 calcd for $C_{15}H_{12}N_2O$+H$^+$ (237.1028).

*2-(4-Methoxyphenyl)quinazolin-4(3H)-one (**2c**, SS-743).*[28] White solid; yield: 76% (140 mg); mp 247–249 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (d, J = 7.8 Hz, 1H), 8.06 (d, J = 8.7 Hz, 2H), 7.79 (d, J = 4.0 Hz, 2H), 7.49 (dd, J = 3.9, 8.0 Hz, 1H), 7.06 (d, J = 8.6 Hz, 2H), 3.91 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6, ppm): δ 162.2, 161.8, 151.8, 148.8 134.5, 129.4, 127.2, 126.1, 125.8, 124.7, 120.6, 113.9, 55.4; IR ($CHCl_3$): ν_{max} 3436, 2920, 1678, 1600, 1484, 1031, 765 cm^{-1}; ESI-MS: m/z 253.09 [M + H]$^+$; HR-ESIMS: m/z 253.0967 calcd for $C_{15}H_{12}N_2O_2$+H$^+$ (253.0977).

*2-(2-Hydroxyphenyl)quinazolin-4(3H)-one (**2d**, SS-571).*[34] White solid; yield: 80% (140 mg); mp 252–255 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.24–8.16 (m, 2H), 7.87 (t, J = 8.2 Hz, 1H), 7.78 (d, J = 8.1 Hz, 1H), 7.59–7.54 (m, 1H), 7.49–7.44 (m, 1H), 7.03–6.95 (m, 2H); IR ($CHCl_3$): ν_{max} 3578, 3204, 2346, 1667, 1440, 1226 cm^{-1}; ESI-MS: m/z 239.07 [M + H] $^+$; HR-ESIMS: m/z 239.0811 calcd for $C_{14}H_{10}N_2O_2$+H$^+$ (239.0821).

*2-(4-Hydroxyphenyl)quinazolin-4(3H)-one (**2e**, SS-761).*[35] Yellow solid; yield: 70% (140 mg); mp >280 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.61 (s, 1H), 10.79 (s, 1H), 8.21 (d, J = 7.7 Hz, 1H), 8.09 (d, J = 8.7 Hz, 2H), 7.90 (t, J = 7.1 Hz, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.65 (t, J = 7.5 Hz, 1H), 6.93 (d, J = 8.7 Hz, 2H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 185.1, 163.5, 161.1, 149.8, 134.7, 133.7, 128.1, 125.9, 125.1, 122.5, 115.4; IR ($CHCl_3$): ν_{max} 3585, 3047, 2923, 1658, 1450, 1353, 1095, 640 cm^{-1}; ESI-MS: m/z 237.07 [M − H] $^-$.

*2-(3-Nitrophenyl)quinazolin-4(3H)-one (**2f**, SS-754).*[36] Yellow solid; yield: 77% (151 mg); mp 220–222 °C; ^{1}H NMR (400 MHz, CD_3OD): δ 8.43 (s, 1H), 8.08 (dd, J = 1.5, 8.1 Hz, 1H), 7.90 (d, J = 7.9 Hz, 1H), 7.65 (dd, J = 1.4, 7.7 Hz, 1H), 7.52 (t, J = 8.0 Hz, 1H), 7.29 (dd, J = 4.2, 11.2 Hz, 1H), 6.82 (d, J = 8.1 Hz, 1H), 6.71 (d, J = 7.8 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$ + CD_3OD): δ 167.1, 150.4, 149.6, 147.7, 135.8, 132.8, 130.8, 129.3, 124.0, 121.6, 120.0, 116.3; IR ($CHCl_3$): ν_{max} 3393, 2923, 1649, 1529, 1271, 1020 cm^{-1}; ESI-MS: m/z 266.0 [M − H]$^-$.

*2-(4-Nitrophenyl)quinazolin-4(3H)-one (**2g**, SS-769).*[34] Yellow solid; yield: 82% (160 mg); mp >300 °C; ^{1}H NMR (400 MHz, CD_3OD): δ 8.04 (d, J = 8.8 Hz, 2H), 7.62 (d, J = 8.8 Hz, 2H), 7.50 (dd, J = 1.3, 7.8 Hz, 1H), 7.18 (dd, J = 4.2 11.2, Hz, 1H), 6.70 (d, J = 8.1 Hz, 1H), 6.58 (t, J = 7.5 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 163.6, 155.3, 146.6, 133.5, 127.3, 126.5, 123.3, 117.3, 114.8, 114.3; IR ($CHCl_3$): ν_{max} 3410, 2921, 1681, 1517, 1470, 1351, 1020 cm^{-1}; ESI-MS: m/z 266.05 [M − H]$^-$; HR-ESIMS: m/z 266.0580 calcd for $C_{14}H_9N_3O_3$−H$^-$ (266.0571).

*2-(4-Fluorophenyl)quinazolin-4(3H)-one (**2h**, SS-744).*[28] White solid; yield: 76% (134 mg); mp 240–242 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.59 (s, 1H), 8.26 (dd, J = 5.5, 8.8 Hz, 2H), 8.16 (d, J = 7.2 Hz, 1H), 7.88–7.83 (m, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.53 (t, J = 7.4 Hz, 1H), 7.40 (t, J = 8.8 Hz, 2H); IR ($CHCl_3$): ν_{max} 3424, 2922, 2852, 2853, 1672, 1466, 1288, 1095 cm^{-1}; ESI-MS: m/z 241.07 [M + H]$^+$; HR-ESIMS: m/z 241.0782 calcd for $C_{14}H_9FN_2O$+H$^+$ (241.0777).

*2-(4-Bromophenyl)quinazolin-4(3H)-one (**2i**, SS-531).*[23] White solid; yield: 77% (169 mg); mp 292–295 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.66 (s, 1H), 8.19 (m, 3H),

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7.83 (m, 4H), 7.58 (t, J = 7.3 Hz, 1H); IR ($CHCl_3$): ν_{max} 3428, 2919, 1659, 1633, 1335, 1179, 768 cm^{-1}; ESI-MS: m/z 300.98 $[M + H]^+$; HR-ESIMS: m/z 302.9945 calcd for $C_{14}H_9{}^{81}BrN_2O$ $+H^+$ (302.9955).

*2-(2-Bromophenyl)quinazolin-4(3H)-one (**2j**, SS-802).*[37] White solid; yield: 65% (143 mg); mp 204−206 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 12.91 (s, 1H), 8.23 (m, 3H), 8.05 (dd, J = 2.3, 8.7 Hz, 1H), 7.75 (t, J = 3.7 Hz, 2H), 7.60 (d, J = 7.8 Hz, 2H); IR ($CHCl_3$): ν_{max} 3301, 2922, 1595, 1580, 1441, 1106, 1019 cm^{-1}; ESI-MS: m/z 300.99 $[M + H]^+$; HR-ESIMS: m/z 300.9962 calcd for $C_{14}H_9{}^{79}BrN_2O+H^+$ (300.9976).

*N-(3-(4-Oxo-3,4-dihydroquinazolin-2-yl)phenyl)acetamide (**2k**, SS-778).* White solid; yield: 50% (102 mg); mp >300 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 12.54 (s, 1H), 10.21 (s, 1H), 8.34 (s, 1H), 8.16 (d, J = 7.0 Hz, 1H), 7.85 (m, 2H), 7.76 (m, 2H), 7.54 (t, J = 7.2 Hz, 1H), 7.47 (t, J = 8.0 Hz, 1H), 2.09 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 168.6, 139.5, 134.6, 133.3, 128.9, 127.3, 126.6, 125.8, 122.1, 121.8, 120.9, 118.5, 23.9; IR ($CHCl_3$): ν_{max} 3585, 2923, 1658, 1405, 1255, 843 cm^{-1}; ESI-MS: m/z 280.10 $[M + H]^+$; HR-ESIMS: m/z 280.1076 calcd for $C_{16}H_{13}N_3O_2+H^+$ (280.1086).

*2-([1,1′-Biphenyl]-2-yl)quinazolin-4(3H)-one (**2l**, SS-777).* White solid; yield: 72% (157 mg); mp 226−228 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 12.58 (s, 1H), 8.20−8.17 (m, 4H), 7.90−7.71 (m, 3H), 7.66−7.49 (m, 6H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 171.2, 162.2, 152.2, 150.1, 148.7, 134.6, 132.6, 131.3, 128.5, 127.9, 127.8, 127.6, 126.5, 125.8, 120.9, 116.3, 114.3; IR ($CHCl_3$): ν_{max} 3195, 1667, 1558, 1452, 1296, 1144 cm^{-1}; ESI-MS: m/z 299.11 $[M + H]^+$; HR-ESIMS: m/z 299.1174 calcd for $C_{20}H_{14}N_2O+H^+$ (299.1184).

*2-(5-Methylthiophen-2-yl)quinazolin-4(3H)-one (**2m**, SS-755).*[38] White solid; yield: 65% (115 mg); mp 204−206 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 8.33−8.27 (m, 2H), 8.22 (d, J = 7.8 Hz, 1H), 7.94.7.90 (m, 2H), 7.72−7.66 (m, 1H), 7.09 (d, J = 3.8 Hz, 1H), 2.61 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 177.1, 161.4, 154.8, 148.3, 139.2, 136.1, 135.4, 129.4, 128.9, 128.2, 126.6, 123.5, 16.15; IR ($CHCl_3$): ν_{max} 3410, 2921, 1657, 1505, 1332, 1132, 1015 cm^{-1}; ESI-MS: m/z 243.05 $[M + H]^+$; HR-ESIMS: m/z 243.0597 calcd for $C_{13}H_{10}N_2OS+H^+$ (243.0592).

*2-(5,6-Dimethoxybenzofuran-2-yl)quinazolin-4(3H)-one (**2n**, SS-760).* Yellow solid; yield: 62% (146 mg); mp 231−233 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 10.29 (s, 1H), 8.33 (d, J = 7.9 Hz, 1H), 7.82−7.72 (m, 3H), 7.53−7.47 (m, 1H), 7.11 (d, J = 6.8 Hz, 2H), 3.99 (s, 3H), 3.97 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 161.5, 150.3, 150.1, 148.5, 147.1, 146.3, 144.2, 134.6, 127.3, 126.6, 125.9, 121.1, 119.1, 110.8, 102.9, 95.43, 55.9, 55.8; IR ($CHCl_3$): ν_{max} 3417, 2917, 1650, 1474, 1304, 1497, 1102, 1024 cm^{-1}; HR-ESIMS: m/z 322.0980 calcd for $C_{18}H_{14}N_2O_4{}^+$ (322.0954).

*2-(Pyridin-3-yl)quinazolin-4(3H)-one (**2o**, SS-758).*[39] White solid; yield: 50% (81 mg); mp 272−275 °C; ^1H NMR (400 MHz, CD_3OD): δ 9.26 (d, J = 1.9 Hz, 1H), 8.74 (d, J = 3.7 Hz, 1H), 8.51−8.47 (m, 1H), 8.30 (d, J = 8.1 Hz, 1H), 7.86−7.83 (m, 2H), 7.60−7.54 (m, 2H); IR ($CHCl_3$): ν_{max} 3585, 2921, 1673, 1467, 1169 cm^{-1}; ESI-MS: m/z 224.07 $[M + H]^+$; HR-ESIMS: m/z 224.0790 calcd for $C_{13}H_9N_3O+H^+$ (224.0824).

*2-(Naphthalen-2-yl)quinazolin-4(3H)-one (**2p**, SS-753).*[28] White solid; yield: 72% (144 mg); mp 247−249 °C; ^1H NMR (500 MHz, DMSO-d_6): δ 12.88 (s, 1H), 8.47 (d, J = 8.3 Hz, 1H), 8.29−8.24 (m, 2H), 8.16−8.11 (m, 2H), 7.91−7.81 (m, 1H), 7.69−7.65 (m, 5H); IR ($CHCl_3$): ν_{max} 3356, 2920, 1666, 1574, 1443, 1292, 1022, 773 cm^{-1}; ESI-MS: m/z 273.10 $[M + H]^+$; HR-ESIMS: m/z 273.1040 calcd for $C_{18}H_{12}N_2O+H^+$ (273.1028).

*6-Iodo-2-phenylquinazolin-4(3H)-one (**2q**, SS-795).* White solid; yield: 80% (106 mg); mp > 260 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 12.87 (s, 1H), 8.49−8.15 (m, 4H), 7.76 (t, J = 7.4 Hz, 1H), 7.62−7.53 (m, 3H); ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 187.0, 143.1, 142.9, 134.3, 134.1, 133.9, 131.6, 130.8, 128.6, 128.5, 127.8, 124.5; IR ($CHCl_3$): ν_{max} 3397, 2921, 1662, 1591, 1285, 1173, 843, 776 cm^{-1}; ESI-MS: m/z 348.98 $[M + H]^+$; HR-ESIMS: m/z 348.9822 calcd for $C_{14}H_9IN_2O$ $+H^+$ (348.9838).

*6-Chloro-2-(4-methoxyphenyl)quinazolin-4(3H)-one (**2r**, SS-748).*[39] White solid; yield: 80% (134 mg); mp 286−288 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 12.83 (s, 1H), 8.20−8.14 (m, 3H), 7.92 (dd, J = 2.2, 8.7 Hz, 1H), 7.81 (d, J = 8.7 Hz, 1H), 7.13 (d, J = 8.8 Hz, 2H), 3.90 (s, 3H); IR ($CHCl_3$): ν_{max} 3418, 2924, 1682, 1651, 1460, 1263, 1127 cm^{-1}; ESI-MS: m/z 287.05 $[M + H]^+$; HR-ESIMS: m/z 287.0583 calcd for $C_{15}H_{11}ClN_2O_2+H^+$ (287.0587).

*6-Iodo-2-(4-methoxyphenyl)quinazolin-4(3H)-one (**2s**, SS-796).* White solid; yield: 82% (118 mg); mp 220−222 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 12.81 (s, 1H), 8.52−8.13 (m, 4H), 7.56 (d, J = 8.5 Hz, 1H), 7.13 (d, J = 8.9 Hz, 2H), 3.89 (s, 3H); ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 185.6, 164.8, 160.4, 150.5, 146.9, 143.5, 134.8, 133.9, 126.9, 124.9, 114.5, 56.2; IR $CHCl_3$): ν_{max} 3418, 2920, 1658, 1457, 1313, 1167 cm^{-1}; ESI-MS: m/z 378.99 $[M + H]^+$; HR-ESIMS: m/z 378.9928 calcd for $C_{15}H_{11}IN_2O_2+H^+$ (378.9943).

*6-Iodo-2-(4-nitrophenyl)quinazolin-4(3H)-one (**2t**, SS-798).* White solid; yield: 76% (114 mg); mp >260 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 12.92 (s, 1H), 8.50 (s, 1H), 8.48−8.38 (m, 4H), 8.20 (dd, J = 1.9, 8.5 Hz, 1H), 7.57 (d, J = 8.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$ + DMSO-d_6): δ 185.8, 159.9, 150.0, 148.2, 146.1, 143.2, 139.2, 134.3, 132.2, 130.5, 124.5, 123.1; IR ($CHCl_3$): ν_{max} 3426, 2918, 1666, 1519, 1342, 1160, 1016 cm^{-1}; HR-ESIMS: m/z 391.9521 calcd for $C_{14}H_8N_3O_3I-H^-$ (391.9538).

*2-Benzoylquinazolin-4(3H)-one (**3a**, SS-789).*[31] White solid; yield: 50% (91 mg); mp 179−182 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 10.18 (s, 1H), 8.58−8.48 (m, 2H), 8.41 (dd, J = 1.0, 7.9 Hz, 1H), 7.98−7.84 (m, 2H), 7.72−7.64 (m, 2H), 7.56 (t, J = 7.8 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 185.6, 161.0, 147.9, 145.9, 134.9, 134.3, 134.0, 133.9, 131.8, 129.5, 129.4, 128.4, 126.9, 123.2; IR ($CHCl_3$): ν_{max} 3436, 2926, 1666, 1481, 1297, 1144 cm^{-1}; ESI-MS: m/z 251.08 $[M + H]^+$; HR-ESIMS: m/z 251.0812 calcd for $C_{15}H_{10}N_2O_2+H^+$ (251.0821).

*2-(3-Chlorobenzoyl)quinazolin-4(3H)-one (**3b**, SS-801).* White solid; yield: 68% (142 mg); mp 231−233 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 10.04 (s, 1H), 8.39 (d, J = 8.1 Hz, 1H), 7.82−7.78 (m, 2H), 7.71−7.63 (m, 2H), 7.58−7.50 (m, 2H), 7.44 (t, J = 8.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$+ CD_3OD): δ 188.8, 161.7, 147.4, 146.1, 134.9, 132.6, 130.8, 130.2, 129.5, 129.2, 126.6, 126.4, 123.0; IR ($CHCl_3$): ν_{max} 3439, 2923, 2853, 1456, 1430, 1238 cm^{-1}; ESI-MS: m/z 285.04 $[M + H]^+$; HR-ESIMS: m/z 285.0419 calcd for $C_{15}H_9ClN_2O_2+H^+$ (285.0431).

*2-(3,4-Dichlorobenzoyl)quinazolin-4(3H)-one (**3c**, SS-792).* White solid; yield: 77% (180 mg); mp 258−260 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 12.92 (s, 1H), 8.27−8.20 (m, 1H), 7.92−7.82 (m, 3H), 7.72−7.64 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$+CD_3OD): δ 185.1, 159.1, 144.8, 135.6, 132.3, 131.0,

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130.7, 129.2, 127.4, 126.9, 126.5, 124.2, 123.8; IR ($CHCl_3$): ν_{max} 3417, 2918, 1683, 1586, 1382, 1238, 1102 cm^{-1}; ESI-MS: m/z 319.00 $[M + H]^+$; HR-ESIMS: m/z 319.0039 calcd for $C_{15}H_8Cl_2N_2O_2+H^+$ (319.0041).

*5-(2-Hydroxyphenyl)-1-methyl-3-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (**9a**, SS-756).* White solid; yield: 55% (85 mg); mp 234−236 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 8.13 (dd, J = 1.3, 8.0 Hz, 1H), 7.44−7.37 (m, 1H), 7.03−6.91 (m, 2H), 4.16 (s, 3H), 2.80 (t, J = 7.4 Hz, 2H), 1.81−1.72 (m, 2H), 0.98−0.92 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.5, 153.9, 151.0, 143.7, 135.3, 132.7, 127.7, 124.3, 118.9, 117.5, 114.8, 27.1, 21.5, 13.7; IR ($CHCl_3$): ν_{max} 3418, 2960, 1687, 1500, 1433, 1237, 1097 cm^{-1}; ESI-MS: m/z 285.13 $[M + H]^+$; HR-ESIMS: m/z 285.1380 calcd for $C_{15}H_{16}N_4O_2+H^+$ (285.1352).

*1-Methyl-5-(4-nitrophenyl)-3-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (**9b**, SS-821).*[40] Yellow solid; yield: 50% (85 mg); mp 229−231 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 12.69 (s, 1H), 8.38−8.33 (m, 4H), 4.19 (s, 3H), 2.84−2.74 (m, 2H), 1.82−1.71 (m, 2H), 0.98−0.92 (m, 3H); IR ($CHCl_3$): ν_{max} 3410, 2920, 2837, 1681, 1517, 1351, 1110 cm^{-1}; ESI-MS: m/z 314.12 $[M + H]^+$; HR-ESIMS: m/z 314.1211 calcd for $C_{15}H_{15}N_5O_3+H^+$ (314.1253).

*1-Methyl-5-phenyl-3-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (**9c**, SS-808).*[26] White solid; yield: 60% (88 mg); mp 194−197 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 10.91 (s, 1H), 8.11 (dd, J = 3.1, 6.5 Hz, 2H), 7.54 (d, J = 2.0 Hz, 3H), 4.30 (s, 3H), 2.98−2.92 (m, 2H), 1.91−1.85 (m, 2H), 1.04 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.3, 149.0, 146.4, 138.8, 132.4, 130.5, 128.3, 126.6, 124.0, 37.6, 27.2, 21.8, 13.5; IR ($CHCl_3$): ν_{max} 3440, 2931, 1688, 1633, 1490, 1100 cm^{-1}; ESI-MS: m/z 269.14 $[M + H]^+$; HR-ESIMS: m/z 269.1389 calcd for $C_{15}H_{16}N_4O+H^+$ (269.1402).

*Quinazolin-4(3H)-one (**11**).*[41] Light pink solid; yield: 55% (59 mg); mp 218−220 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 12.25 (s, 1H), 8.17−8.07 (m, 2H), 7.82 (t, J = 7.2 Hz, 1H), 7.67 (d, J = 8.1 Hz, 1H), 7.53 (t, J = 7.4 Hz, 1H); IR ($CHCl_3$): ν_{max} 3417, 2921, 1675, 1517, 1453, 1110 cm^{-1}; ESI-MS: m/z 147.04 $[M + H]^+$; HR-ESIMS: m/z 147.0570 calcd for $C_8H_6N_2O+H^+$ (147.0558).

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, NMR spectra scans. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00989.

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Notes

The authors declare no competing financial interest.

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