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One-Pot Synthesis of Quinazolinones via Iridium-Catalyzed Hydrogen Transfers

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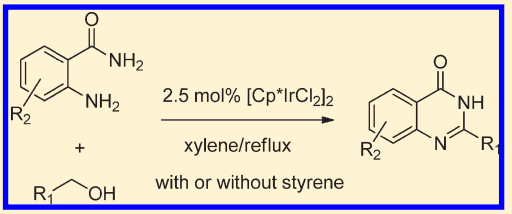
Supporting Information

ABSTRACT: A one-pot oxidative cyclization of primary alcohols with *o*-aminobenzamides to quinazolinones was successfully achieved using $[Cp^*IrCl_2]_2$ (Cp^* = pentamethylcyclopentadienyl) as a catalyst under hydrogen transfer conditions.



INTRODUCTION

Quinazolinones occur widely in natural products that exhibit a variety of important biological and pharmacological activities.[1] For example, luotonine A (Figure 1) was isolated from a Chinese plant named Luo-Tuo-Hao and showed cytotoxicity toward the murine leukemia P388 cell line (IC_{50} = 1.8 μg/mL),[2] and rutaecarpine (Figure 1) is the major alkaloid component of a Chinese herbal drug, Wu-Chu-Yu, used extensively as a remedy for headache, cholera, and dysentery.[3] The quinazolinones were assigned as privileged structures in drug discovery, and their syntheses have been widely explored.[1,4] As shown in Scheme 1, one of the synthetic methods to quinazolinones **3** utilized condensation between aldehydes **4** and *o*-aminobenzamides **2** followed by oxidation of the aminal intermediate **5**. Stoichiometric or large excess amounts of toxic oxidants were required for this oxidation; e.g., DDQ,[5] $CuCl_2$,[6] MnO_2,[7] and $KMnO_4$[8] were used. Another drawback of this method is that aldehydes **4** were chemically unstable and their syntheses from readily available alcohols were achieved through oxidation methods, e.g., DMP,[9] TPAP,[10] Swern oxidation,[11] and TEMPO[12] catalyzed oxidations with bleach. We were interested in exploring the possibility to combine the two oxidations from **1** to **4** and **5** to **3** in a one-pot reaction, thus avoiding the isolation of either aldehyde **4** or aminal intermediate **5**. The oxidations we want employ would preferentially utilize catalytic methods, thus adding atom economy[13] to this operationally convenient method. Oxidation of alcohol to aldehyde utilizing a hydrogen transfer process attracted our attention because only a catalytic metal complex (e.g, Ru and Ir) is needed, either without a hydrogen acceptor (with release of H_2) or with a nontoxic hydrogen acceptor (e.g., oxygen or acetone), and the byproducts would be environmentally benign water, H_2, or nontoxic organics (e.g., 2-propanol).[14] We imagined that, in a domino sequence as shown in Scheme 1, alcohol **1** was oxidized to aldehyde **4** via catalytic hydrogen transfer. Its condensation with *o*-aminobenzamide **2** after loss of water led to aminal intermediate **5**, which was oxidized further to quinazolinone **3** under the same hydrogen transfer catalysis.

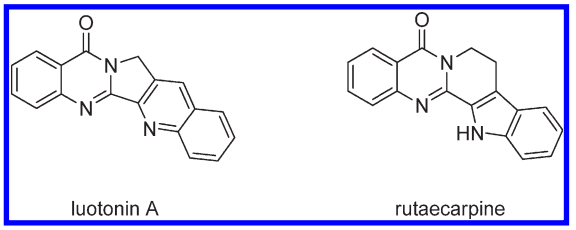
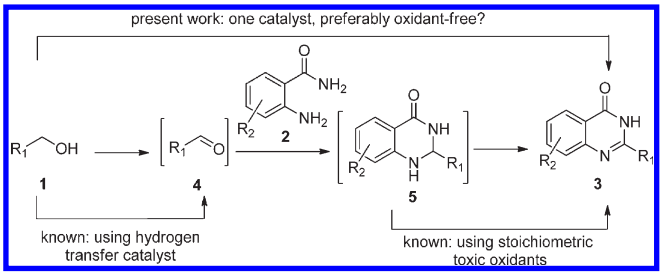


Figure 1. Examples of natural quinazolinones.

Scheme 1. Proposed One-Pot Synthesis of Quinazolinones Starting with Alcohols



Oxidant-free hydrogen transfer catalysis using Ir and Ru complexes has emerged as an atom-economical method for the transformation of alcohols to aldehydes.[15] Our proposed quinazolinone synthesis is thus very attractive and has the advantage that no stoichiometric oxidant would be added throughout, with generation of environmentally benign H_2 and water.

RESULTS AND DISCUSSION

Because there are no literature precedents for the oxidation of cyclic aminal **5** to quinazolinones via hydrogen transfer catalysis,

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Scheme 2. Ir-Catalyzed Dehydrogenations of Aminal 5a

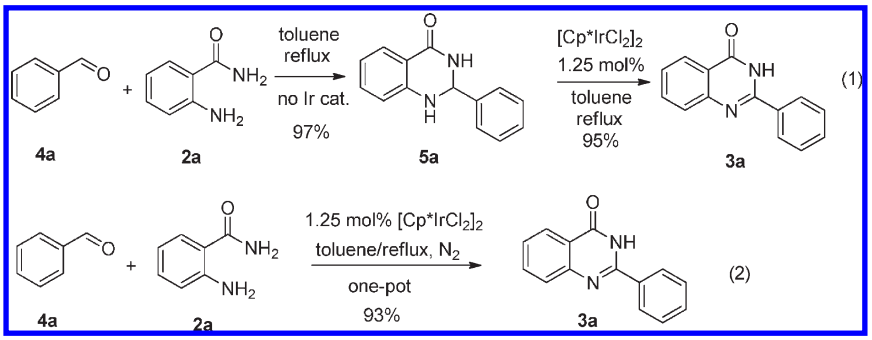
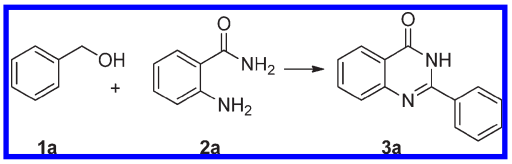


Table 1. Synthesis of Quinazolinone between 1a and 2a: Optimization of the Conditions[a]



	catalyst	additive	solvent	yield[b] (%)	conversion (%)	time (h)
1	$[Cp^*IrCl_2]_2$	AcOH[c]	toluene	54	100	88
2	$[Cp^*IrCl_2]_2$	NaOH	toluene	75	100	62
3	$[Cp^*IrCl_2]_2$	*t*-BuONa	toluene	85	100	62
4	$[Cp^*IrCl_2]_2$	Cs_2CO_3	toluene	66	80	84
5	$[Cp^*IrCl_2]_2$	K_2CO_3	toluene	82	100	90
6	$[Cp^*IrCl_2]_2$	no base	toluene	29	44	84
7	$[Cp^*IrCl_2]_2$	K_2CO_3	xylene	70	100	62
8	$[Cp^*IrCl_2]_2$	No Base	xylene	92[d]	100	48
9	$[Cp^*IrCl_2]_2$[e]	no base	xylene	93[d]	100	36
10	$[Cp^*IrCl_2]_2$	no base	DMF	63	100	70
11	$[Cp^*IrCl_2]_2$	no base	DMSO[f]	35	100	62
12	$[Cp^*IrCl_2]_2$	no base	1,4-dioxane	10	18	70
13	$[Ru(p\text{- cymene})Cl_2]_2$[g]	K_2CO_3	xylene	89	100	62
14	$[Ir(cod)Cl]_2$[h]	KOH	xylene	21	40	62
15	$[Cp^*IrI_2]_2$[e]	no base	xylene	55	68	62
16	$IrCl_3$[i]	no base	xylene	trace	trace	62
17	$RuCl_2(PPh_3)_3$[e]	KOH	xylene	13	20	62

[a] Conditions: **1a** (1 mmol), **2a** (1 mmol), catalyst (1.25 mol %), and base (20 mol %) in refluxing temperature of solvent under N_2. [b] ^1H NMR yield. [c] 5 mol % AcOH. [d] Isolated yield. [e] A 2.5 mol % amount of catalyst was used. [f] The reaction temperature was 140 °C. [g] A 2.5 mol % amount of dppf was added. [h] A 2.0 mol % amount of catalyst was used. [i] A 2.5 mol % amount of catalyst and 7.5 mol % PPh_3 were used.

we first carried out experimentations to test the possibility. Thus, aldehyde **4a** was first condensed with **2a** in refluxing toluene under N_2. Not surprisingly, without a metal catalyst, cyclic aminal **5a** was formed in 97% isolated yield with no **3a** detected. After addition of $[Cp^*IrCl_2]_2$ (1.25 mol %)[16] as a catalyst, aminal **5a** was transformed smoothly to **3a** in 95% isolated yield within 2 h (Scheme 2, eq 1). A one-pot reaction between **4a** and **2a** without isolation of **5a** under the same Ir catalysis in refluxing toluene under N_2 also afforded **3a** in 93% isolated yield within 3 h (Scheme 2, eq 2). These results prompted us to further explore whether one catalyst (e.g., $[Cp^*IrCl_2]_2$) can effect the proposed one-pot synthesis of quinazolinones starting with alcohols.

Initially, benzyl alcohol **1a** with 2-aminobenzamide (**2a**; 1:1 molar ratio) was selected as the model substrate to test the domino reaction. As shown in Table 1, additives were first added together with $[Cp^*IrCl_2]_2$ (1.25 mol %) in refluxing toluene under N_2 (entries 1−5). Base additives (*t*-BuONa in entry 3 and K_2CO_3 in entry 5) gave better yields (>82%) as compared with an acid additive (AcOH in entry 1), although all reactions required >62 h for full conversions. The reaction was sluggish when no additives were added, leading to lower conversion (44%) even after 84 h (entry 6). Thus, the reaction was carried out in refluxing xylene to increase the reaction rate (entries 7 and 8). Indeed the yield of **3a** increased to 92% with full conversion in a relatively shorter time of 48 h without additives (entry 8). Interestingly, the addition of K_2CO_3 gave a lower yield in refluxing xylene than in toluene (70% in entry 7 vs 82% in entry 5) due to significant byproduct formation. The reaction without additives was also tested in other solvents, e.g, DMF, DMSO, and

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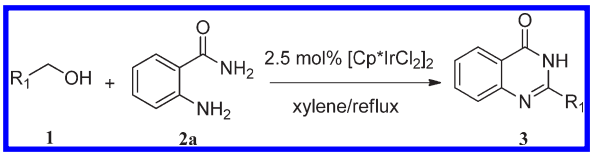
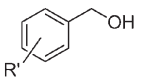
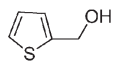
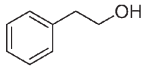
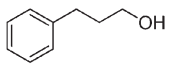
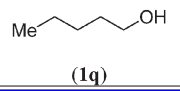
Table 2. Reactions of 2a with Various Primary Alcohols[a]



entry	primary alcohol **1**	Product **3** yield[b] (reaction time)
		
1	R' = 2-Cl (**1b**)	**3b** 85% (120 h)
2	R' = 3-Cl(**1c**)	**3c** 76% (72 h)
3	R' = 4-Cl (**1d**)	**3d** 75% (72 h)
4	R' = 2,4-diCl (**1e**)	**3e** 65% (120 h)
5	R' = 3-Br (**1f**)	**3f** 72% (72 h)
6	R' = 4-Br (**1g**)	**3g** 73% (48 h)
7	R' = 3-NO_2 (**1h**)	**3h** 75% (96 h)
8	R' = 4-NO_2 (**1i**)	**3i** 50% (120 h)
9	R' = 3-Me (**1j**)	**3j** 93% (36 h)
10	R' = 4-Me (**1k**)	**3k** 87% (36 h)
11	R' = 3-OMe (**1l**)	**3l** 94% (24 h)
12	R' = 4-OMe (**1m**)[c]	**3m** 93% (24 h)
13	 (**1n**)[c]	**3n** 74% (48 h)
14	 (**1o**)	**3o** 86% (72 h)
15	 (**1p**)	**3p** 91% (72 h)
16	 (**1q**)	**3q** 84% (72 h)

[a] Conditions: **1** (1 mmol), **2a** (1 mmol), and catalyst (2.5 mol %) in refluxing xylene under N_2. [b] Isolated yield. [c] A 2.0 equiv amount of styrene was used.

1,4-dioxane (entries 10−12), but all gave inferior results compared to those in xylene. When a catalyst loading of 2.5 mol % $[Cp^*IrCl_2]_2$ was used in refluxing xylene, the reaction time was further shortened to 36 h with a comparably excellent yield of 93% (entry 9 vs entry 8). Among other Ir and Ru catalysts screened (entries 13−17), $[Ru(p\text{-cymene})Cl_2]_2$[17] also gave a good yield (entry 13, 89%), but full conversion was achieved in a longer reaction time (62 h). After examining the reaction profiles, we decided to select the conditions of entry 9 (2.5 mol % $[Cp^*IrCl_2]_2$ in refluxing xylene without additives) as the optimal conditions for our next investigations of the substrate scope of this domino reaction.

Various primary alcohols (**1b**−**1q**) were further examined to react with *o*-aminobenzamide (**2a**), and the results are summarized in Table 2. For different substituted benzyl alcohols, reactions with electron-withdrawing groups (entries 1−8) required longer reaction times (>48 h) to reach full conversion than that of unsubstituted benzyl alcohol (**1a**), with isolated yields ranging from 50% (4-NO_2 substitution, entry 8) to 85% (2-Cl substitution, entry 1). This reflected the lower reactivity of benzyl alcohols with electron-withdrawing groups toward oxidation to aldehydes using the same catalyst.[16] Reactions with electron-donating groups on the benzene ring, however, performed very well. Methyl-substituted benzyl alcohols **1j** (entry 9) and **1k** (entry 10) gave 93% and 87% isolated yields of the corresponding quinazolinones **3j** and **3k**, respectively, with efficiency comparable to that of alcohol **1a** (36 h). Benzyl alcohol **1l** with 3-methoxy substitution (entry 11) showed higher reactivity, and the reaction was complete within 24 h to afford quinazolinone **3l** in 94% yield. When 4-methoxy analogue **1m** was employed under the same reaction conditions, *N*-alkylation product 2-((4-methoxybenzyl)amino)benzamide (**6**) was formed together with the desired product **3m** in an approximately 1:1 ratio and did not react further with more time. We reasoned that hydrogen transfer to the C═N bond of an imine intermediate, **7**, explained the formation of **6** (Scheme 3, eq 3),[18] which was in competition with the formation of cyclic aminal intermediate type **5** and the dehydrogenation thereafter. Thus, styrene was added as a sacrificial hydrogen acceptor[19] together with **1m** within the reaction mixture under otherwise the same conditions. Quinazolinone product **3m** was indeed the only product formed with 93% yield after 24 h without contamination of byproduct **6** (entry 12, Table 2). A separate reaction of **6** under Ir catalysis with styrene additive (Scheme 3, eq 4) gave no **3m** formation, which implied that hydrogen transfer to styrene happened before hydrogenation of the imine **7**. This phenomenon was also observed with electron-rich 2-thiophenemethanol

Scheme 3. Possible Pathway to 6 from Hydrogenation of Imine 7 (Eq 3) and Reaction of 6 in the Presence of Styrene (Eq 4)

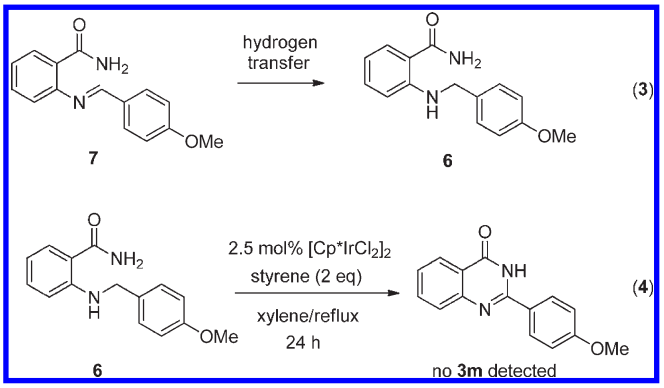


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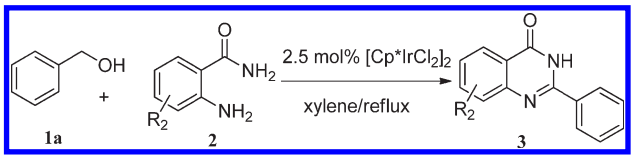
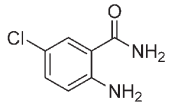
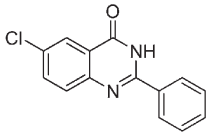
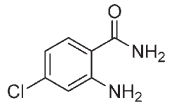
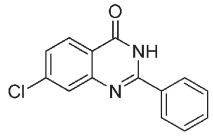
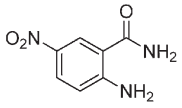
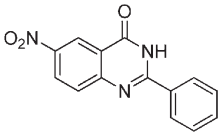
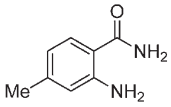
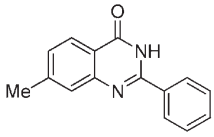
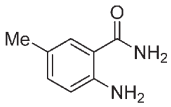
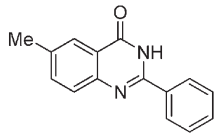
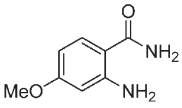
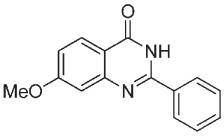
Table 3. Reactions of 1a with Various *o*-Aminobenzamides 2[a]



1a 2 3

entry	*o*-Aminobenzamide **2**	Product **3**: Yield[b](reaction time)
1	 **2b**	 **3bb** 84% (48 h)
2	 **2c**	 **3cc** 68% (62 h)
3	 **2d**	 **3dd** 61% (48 h)
4	 **2e**	 **3ee** 91% (24 h)
5	 **2f**	 **3ff** 91% (20 h)
6	 **2g**	 **3gg** 87% (48 h)

[a] Conditions: **1** (1 mmol), **2a** (1 mmol), and catalyst (2.5 mol %) in refluxing xylene under N_2. [b] Isolated yield.

(**1n**), in which styrene was also required to achieve full conversion to quinazolinone **3n** with 74% yield (entry 13). Primary alcohols with an extended carbon chain (entries 14−16) worked uneventfully under our acceptorless conditions to afford quinazolinones **3o** and **3p** in good yield (84−91%) although in a longer reaction time (72 h). As a natural product, glycosminine **3o** was previously synthesized from anthranilic acid in 40% overall yield.[20]

o-Aminobenzamides **2b**−**2g** were next investigated for reactions with benzyl alcohol **1a**. The results in Table 3 show an electronic effect of substitution on the benzene ring of *o*-aminobenzamides similar to that of substituted benzyl alcohols in Table 2. Reactions with electron-withdrawing groups (entries 1−3) required longer reaction times (48−62 h) than that with unsubstituted *o*-aminobenzamide (**2a**), with isolated yields ranging from 50% (5-NO_2 substitution, entry 3) to 84% (5-Cl substitution, entry 1). Substituted benzamides **2e**−**2g** with electron-donating groups gave good yields of quinazolinone products (91% for both **3ee** and **3ff**, 87% for **3gg**) within a 20−48 h time period.

A possible mechanism for the domino reaction to quinazolinones is suggested in Scheme 4. The first catalytic cycle of the reaction would involve the dehydrogenation of primary alcohol **1** to aldehyde **4** accompanied by β-H elimination to generate a hydridoiridium species, [Cp*Ir]−H, the oxidative addition of alcohol **1** to which would be followed by hydrogen release and generation of an iridium alkoxide.[21] The condensation between **2** and **4** would occur to give cyclic aminal **5**. The second catalytic cycle is dehydrogenation of **5**, in which the more basic nitrogen would probably bind to Ir as shown followed by β-H elimination to give the final quinazolinone product **3**.

CONCLUSION

We have demonstrated a one-pot synthesis of quinazolinones between primary alcohols **1** and *o*-aminobenzamides **2** via Ir-catalyzed dehydrogenations under base-free conditions. Except reactions with electron-rich alcohols **1m** and **1n**, which required hydrogen acceptor styrene to prevent *N*-alkylation byproduct formation, all other primary alcohols reacted without any hydrogen acceptors. This method utilized a catalytic amount of air- and water-stable Ir catalyst; the only byproducts are environmentally benign H_2 and water. To the best of our knowledge, this is the first example of syntheses of quinazolinones **3** via a domino reaction starting with primary alcohols **1** under Ir-catalyzed dehydrogenation conditions.

EXPERIMENTAL SECTION

General Methods for the Synthesis of Quinazolinones. *o*-Aminobenzamides **2** (1 mmol) and $[Cp^*IrCl_2]_2$ (0.025 mmol) were added to an oven-dried carousel tube, followed by benzyl alcohols **1** (1 mmol) in anhydrous xylene (2 mL). Then the system was degassed and filled with nitrogen. The reaction mixture was stirred and heated to reflux, and the progress of the reaction was monitored by HPLC. After completion of the reaction, the resulting solution was cooled to room temperature, and the solvent was removed with the aid of a rotary evaporator. The residue was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (3:1 to 1:1) as the eluent to provide the desired products **3**.

2-Phenylquinazolin-4(3*H*)-one (3a).[22] Eluent: petroleum ether/ethyl acetate (2:1). Yield: 206 mg (93%). White solid. Mp: 234−235 °C (lit.[22] 236−237 °C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 11.70 (s, br, 1H), 8.33 (d, J = 8.0 Hz, 1H), 8.26 (dd, J = 8.0, 4.0 Hz, 2H), 7.79−7.85 (m, 2H), 7.58−7.60 (m, 3H), 7.51 (t, J = 8.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.8, 151.7, 149.5, 134.8, 132.8, 131.6,

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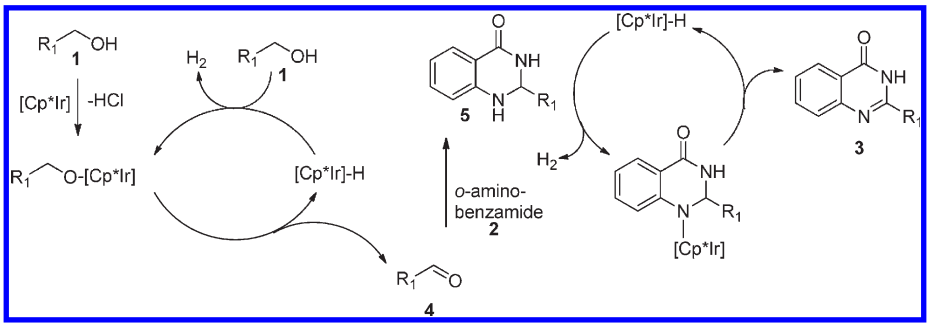
Scheme 4. Possible Mechanism for $[Cp^*IrCl_2]_2$-Catalyzed Quinazolinone Formation



129.0, 128.0, 127.4, 126.7, 126.3, 120.8. HRMS (ESI): m/z calcd for $C_{14}H_{11}N_2O$, 223.0871; found, 223.0854.

2-(2-Chlorophenyl)quinazolin-4(3*H*)-one (3b). Eluent: petroleum ether/ethyl acetate (2:1). Yield: 218 mg (85%). White solid. Mp: 196−197 °C (lit.[23] 195 °C). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.65 (s, br, 1H), 8.17 (d, J = 8.0 Hz, 2H), 7.83−7.87 (m, 1H), 7.66−7.71 (m, 2H), 7.47−7.63 (m, 4H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 161.4, 152.2, 148.4, 134.5, 133.7, 131.5, 131.4, 130.8, 129.5, 127.3, 127.1, 127.0, 125.8, 121.1. HRMS (ESI): m/z calcd for $C_{14}H_{10}ClN_2O$, 257.0482; found, 257.0475.

2-(3-Chlorophenyl)quinazolin-4(3*H*)-one (3c).[24] Eluent: petroleum ether/ethyl acetate (2:1). Yield: 195 mg (76%). White solid. Mp: 296−297 °C (lit.[24] 297−298 °C). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.63 (s, br, 1H), 8.23 (s, 1H), 8.14−8.16 (m, 2H), 7.85 (t, J = 8.0 Hz, 1 H), 7.76 (d, J = 8.0 Hz, 1 H), 7.66 (d, J = 8.0 Hz, 1 H), 7.52−7.60 (m, 2 H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 162.0, 153.4, 150.9, 148.4, 134.6, 133.4, 131.1, 130.4, 127.6, 127.5, 126.9, 126.4, 125.8, 121.0. HRMS (ESI): m/z calcd for $C_{14}H_{10}ClN_2O$, 257.0482; found, 257.0478.

2-(4-Chlorophenyl)quinazolin-4(3*H*)-one (3d).[22] Eluent: petroleum ether/ethyl acetate (3:1). Yield: 192 mg (75%). White solid. Mp: 299−300 °C (lit.[22] 298−300 °C). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.61 (s, br, 1H), 8.14−8.21 (m, 3H), 7.84 (t, J = 8.0 Hz, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.62 (d, J = 8.0 Hz, 2H), 7.53 (t, J = 8.0 Hz, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 162.1, 151.3, 148.5, 136.2, 134.6, 131.5, 129.5, 128.6, 127.4, 126.7, 125.8, 120.9. HRMS (ESI): m/z calcd for $C_{14}H_{10}ClN_2O$, 257.0482; found, 257.0470.

2-(2,4-Dichlorophenyl)quinazolin-4(3*H*)-one (3e).[25] Eluent: petroleum ether/ethyl acetate (2:1). Yield: 190 mg (65%). White solid. Mp: 224−225 °C (lit.[25] 225 °C). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.67 (s, br, 1H), 8.17 (d, J = 8.0 Hz, 1H), 7.86 (t, J = 8.0 Hz, 1H), 7.82 (s, 1H), 7.71 (d, J = 8.0 Hz, 2H), 7.56−7.60 (m, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 161.3, 151.8, 148.4, 135.4, 134.6, 132.7, 132.6, 132.2, 129.1, 127.4, 127.1, 125.8, 121.2. HRMS (ESI): m/z calcd for $C_{14}H_9Cl_2N_2O$, 291.0092; found, 291.0071.

2-(3-Bromophenyl)quinazolin-4(3*H*)-one (3f) Eluent: petroleum ether/ethyl acetate (2:1). Yield: 216 mg (72%). White solid. Mp: 295−296 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.63 (s, br, 1H), 8.37 (s, 1H), 8.18 (d, J = 8.0 Hz, 1H), 8.15 (d, J = 8.0 Hz, 1H), 7.75−7.87 (m, 3H), 7.49−7.56 (m, 2H). 13C NMR (DMSO-d_6, 100 MHz): δ 162.04, 150.8, 148.4, 134.8, 134.6, 134.0, 130.7, 130.3, 127.5, 126.9, 126.7, 125.8, 121.8, 121.0. HRMS (ESI): m/z calcd for $C_{14}H_{10}BrN_2O$, 300.9977; found, 300.9987.

2-(4-Bromophenyl)quinazolin-4(3*H*)-one (3g).[24] Eluent: petroleum ether/ethyl acetate (2:1). Yield: 219 mg (73%). White solid. Mp: 296−297 °C (lit.[24] 296−297 °C). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.61 (s, br, 1H), 8.11−8.15 (m, 3H), 7.84 (t, J = 8.0 Hz, 1H), 7.73−7.77 (m, 3H), 7.53 (t, J = 8.0 Hz, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 162.1, 151.4, 148.4, 134.6, 131.8, 131.6, 129.7, 127.4, 126.7, 125.8, 125.2, 120.9. HRMS (ESI): m/z calcd for $C_{14}H_{10}BrN_2O$, 300.9977; found, 300.9965.

2-(3-Nitrophenyl)quinazolin-4(3*H*)-one (3h).[24] The product was washed by petroleum ether/ethyl acetate (4:1). Yield: 200 mg (75%). Brown solid. Mp: >300 °C (lit.[24] >300 °C). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.87 (s, br, 1H), 9.02 (s, 1H), 8.61 (d, J = 8.0 Hz, 1H), 8.43 (d, J = 8.0 Hz, 1H), 8.18 (d, J = 8.0 Hz, 1H), 7.80−7.89 (m, 3H), 7.57 (t, J = 8.0 Hz, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 162.1, 150.4, 148.2, 147.9, 134.7, 134.2, 133.9, 130.2, 127.6, 127.1, 125.9, 125.8, 122.6, 121.2. HRMS (ESI): m/z calcd for $C_{14}H_{10}N_3O_3$, 268.0722; found, 268.0726.

2-(4-Nitrophenyl)quinazolin-4(3*H*)-one (3i).[24] The product was washed with petroleum ether/ethyl acetate (5:1). Yield: 134 mg (50%). Brown solid. Mp: >300 °C (lit.[24] >300 °C). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.83 (s, br, 1H), 8.37−8.43 (m, 4H), 8.18 (d, J = 8.0 Hz, 1H), 7.88 (t, J = 8.0 Hz, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.58 (t, J = 8.0 Hz, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 162.0, 150.7, 148.9, 148.3, 138.5, 134.7, 129.2, 127.7, 127.3, 125.8, 123.6, 121.1. HRMS (ESI): m/z calcd for $C_{14}H_{10}N_3O_3$, 268.0722; found, 268.0710

2-(*m*-Tolyl)quinazolin-4(3*H*)-one (3j).[26] Eluent: petroleum ether/ethyl acetate (2:1). Yield: 219 mg (93%). White solid. Mp: 210−211 °C (lit.[26] 210−212 °C). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.48 (s, br, 1H), 8.15 (d, J = 8.0 Hz, 1H), 8.02 (s, 1H), 7.81−7.85 (m, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.50−7.53 (m, 1H), 7.39−7.45 (m, 2H), 2.42 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 162.1, 152.3, 148.6, 137.8, 134.5, 132.5, 131.9, 128.4, 128.2, 127.4, 126.4, 125.8, 124.8, 120.9, 20.9. HRMS (ESI): m/z calcd for $C_{15}H_{13}N_2O$, 237.1028; found, 237.1017.

2-(*p*-Tolyl)quinazolin-4(3*H*)-one (3k).[22] Eluent: petroleum ether/ethyl acetate (2:1). Yield: 205 mg (87%). White solid. Mp: 259−260 °C (lit.[22] 261−263 °C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 11.83 (s, br, 1H), 8.33 (d, J = 8.0 Hz, 1H), 8.18 (d, J = 8.0 Hz, 2H), 7.77−7.84 (m, 2H), 7.49 (t, J = 8.0 Hz, 1H), 7.37 (d, J = 8.0 Hz, 2H), 2.52 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.9, 151.8, 149.5, 142.2, 134.8, 129.8, 129.7, 127.8, 127.4, 126.5, 126.3, 120.7, 21.5. HRMS (ESI): m/z calcd for $C_{15}H_{13}N_2O$, 237.1028; found, 237.1013.

2-(3-Methoxyphenyl)quinazolin-4(3*H*)-one (3l). Eluent: petroleum ether/ethyl acetate (2:1). Yield: 237 mg (94%). White solid. Mp: 209−210 °C (lit.[27] 209−211 °C). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.54 (s, br, 1H), 8.15 (d, J = 8.0 Hz, 1H), 7.73−7.86 (m, 4H), 7.43−7.54 (m, 2H), 7.15 (d, J = 8.0 Hz, 1H), 3.86 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.6, 160.1, 151.5, 149.4, 134.8, 134.1, 130.1, 128.0, 126.8, 126.3, 120.9, 119.5, 118.2, 112.1, 55.6. HRMS (ESI): m/z calcd for $C_{15}H_{13}N_2O_2$, 253.0977; found, 253.0955.

2-(4-Methoxyphenyl)quinazolin-4(3*H*)-one (3m).[22] Eluent: petroleum ether/ethyl acetate (2:1). Yield: 234 mg (93%). White solid. Mp: 247−248 °C (lit.[22] 247−248 °C). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.41 (s, br, 1H), 8.18 (d, J = 8.0 Hz, 2H), 8.12 (d, J = 8.0 Hz, 1H), 7.80 (t, J = 8.0 Hz, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.47 (t, J = 8.0 Hz, 1H), 7.07 (d, J = 8.0 Hz, 2H), 3.83 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 162.2, 161.8, 151.7, 148.8, 134.4, 129.4, 127.2, 126.0, 125.7, 124.7, 120.6, 113.9, 55.3. HRMS (ESI): m/z calcd for $C_{15}H_{13}N_2O_2$, 253.0977; found, 253.0972.

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2-(Thiophene-2-yl)quinazolin-4(3*H*)-one (3n).[22] Eluent: petroleum ether/ethyl acetate (2:1). Yield: 169 mg (74%). White solid. Mp: 275−276 °C (lit.[22] 275−276 °C). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.64 (s, br, 1H), 8.23 (d, J = 8.0 Hz, 1H), 8.12 (d, J = 8.0 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.79 (t, J = 8.0 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.48 (t, J = 8.0 Hz, 1H), 7.23 (t, J = 8.0 Hz, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 161.7, 148.5, 147.8, 137.3, 134.6, 132.1, 129.3, 128.4, 126.8, 126.2, 125.9, 120.8. HRMS (ESI): m/z calcd for $C_{12}H_9N_2OS$, 229.0436; found, 229.0411.

2-Benzylquinazolin-4(3*H*)-one (3o).[28] Eluent: petroleum ether/ethyl acetate (2:1). Yield: 203 mg (86%). White solid. Mp: 244−246 °C (lit.[28] 245−247 °C). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.42 (s, br, 1H), 8.07 (d, J = 8.0 Hz, 1H), 7.76 (t, J = 8.0 Hz, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.45 (t, J = 8.0 Hz, 1H), 7.38 (d, J = 8.0 Hz, 2H), 7.31 (t, J = 8.0 Hz, 2H), 7.23 (t, J = 8.0 Hz, 1H), 3.93 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 161.8, 155.9, 148.7, 136.5, 134.3, 128.8, 128.4, 126.8, 126.7, 126.1, 125.6, 120.6, 40.7. HRMS (ESI): m/z calcd for $C_{15}H_{13}N_2O$, 237.1028; found, 237.1015.

2-Phenethylquinazolin-4(3*H*)-one (3p).[29] Eluent: petroleum ether/ethyl acetate (2:1). Yield: 227 mg (91%). White solid. Mp: 207−208 °C (lit.[29] 208 °C). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.25 (s, br, 1H), 8.09 (d, J = 8.0 Hz, 1H), 7.78 (t, J = 8.0 Hz, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.47 (t, J = 8.0 Hz, 1H), 7.27−7.29 (m, 4H), 7.16−7.20 (m, 1H), 3.05 (t, J = 8.0 Hz, 2H), 2.89 (t, J = 8.0 Hz, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 161.6, 156.7, 148.4, 140.6, 134.3, 128.3, 128.3, 126.4, 126.0, 125.7, 120.7, 36.2, 32.4. HRMS (ESI): m/z calcd for $C_{16}H_{15}N_2O$, 251.1184; found, 251.1150.

2-Butylquinazolin-4(3*H*)-one (3q). Eluent: petroleum ether/ethyl acetate (2:1). Yield: 170 mg (84%). White solid. Mp: 108−109 °C (lit.[30] 109−110 °C). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.16 (s, br, 1H), 8.06 (d, J = 8.0 Hz, 1H), 7.75 (t, J = 8.0 Hz, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.44 (t, J = 8.0 Hz, 1H), 2.58 (t, J = 8.0 Hz, 2H), 1.65−1.73 (m, 2H), 1.29−1.38 (m, 2H), 0.89 (t, J = 8.0 Hz, 3H), ^{13}C NMR (DMSO-d_6, 100 MHz): δ 161.7, 157.4, 148.8, 134.2, 126.7, 125.8, 125.6, 120.7, 34.1, 28.8, 21.6, 13.6. HRMS (ESI): m/z calcd for $C_{12}H_{15}N_2O$, 203.1184; found, 203.1160.

6-Chloro-2-phenylquinazolin-4(3*H*)-one (3bb).[22] Eluent: petroleum ether/ethyl acetate (2:1). Yield: 215 mg (84%). White solid. Mp: 296−297 °C (lit.[22] 295−296 °C). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.70 (s, br, 1H), 8.17 (d, J = 8.0 Hz, 2H), 8.09 (s, 1H), 8.17 (dd, J = 8.0 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.53−7.62 (m, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 161.1, 152.8, 147.4, 134.6, 132.4, 131.5, 130.7, 129.7, 128.5, 127.8, 124.8, 122.2. HRMS (ESI): m/z calcd for $C_{14}H_{10}ClN_2O$, 257.0482; found, 257.0466.

7-Chloro-2-phenylquinazolin-4(3*H*)-one (3cc).[31] Eluent: petroleum ether/ethyl acetate (2:1). Yield: 174 mg (68%). White solid. Mp: 287−288 °C (lit.[31] 286−288 °C). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.66 (s, br, 1H), 8.13−8.18 (m, 3H), 7.79 (s, 1H), 7.53−7.61 (m, 4H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 161.6, 153.7, 149.8, 139.1, 132.3, 131.6, 128.6, 127.9, 127.8, 126.7, 126.5, 119.7. HRMS (ESI): m/z calcd for $C_{14}H_{10}ClN_2O$, 257.0482; found, 257.0451.

6-Nitro-2-phenylquinazolin-4(3*H*)-one (3dd).[32] The product was washed with petroleum ether/ethyl acetate (5:1). Yield: 163 mg (61%). Brown solid. Mp: 297−298 °C (lit.[32] 297−299 °C). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 13.01 (s, br, 1H), 8.81 (s, 1H), 8.53 (d, J = 8.0 Hz, 1H), 8.21 (d, J = 8.0 Hz, 2H), 7.89 (d, J = 8.0 Hz, 1H), 7.55−7.65 (m, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 161.8, 155.8, 152.9, 144.5, 132.1, 128.9, 128.6, 128.5, 128.3, 128.2, 127.0, 122.0, 120.9. HRMS (ESI): m/z calcd for $C_{14}H_{10}N_3O_3$, 268.0722; found, 268.0705.

7-Methyl-2-phenylquinazolin-4(3*H*)-one (3ee).[22] Eluent: petroleum ether/ethyl acetate (2:1). Yield: 215 mg (91%). Slight yellow soild. Mp: 240−241 °C (lit.[22] 240−241 °C). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.45 (s, br, 1H), 8.16 (d, J = 8.0 Hz, 2H), 8.03 (d, J = 8.0 Hz, 1H), 7.54−7.58 (m, 4H), 7.34 (d, J = 8.0 Hz, 1H), 2.47 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 162.0, 152.3, 148.7, 145.0, 132.7, 131.3, 128.5, 128.0, 127.6, 127.0, 125.6, 118.5, 21.3. HRMS (ESI): m/z calcd for $C_{15}H_{13}N_2O$, 237.1028; found, 237.1019.

6-Methyl-2-phenylquinazolin-4(3*H*)-one (3ff).[31] Eluent: petroleum ether/ethyl acetate (2:1). Yield: 215 mg (91%). White solid. Mp: 238−239 °C (lit.[31] 238−240 °C). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.46 (s, br, 1H), 7.95 (s, 1H), 7.63−7.67 (m, 2H), 7.51−7.59 (m, 3H), 2.45 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 162.1, 151.4, 146.6, 136.2, 135.8, 132.7, 131.1, 128.5, 127.5, 127.3, 125.0, 120.6, 20.8. HRMS (ESI): m/z calcd for $C_{15}H_{13}N_2O$, 237.1028; found, 237.1009.

7-Methoxy-2-phenylquinazolin-4(3*H*)-one (3gg).[33] Eluent: petroleum ether/ethyl acetate (2:1). Yield: 219 mg (87%). White solid. Mp: 235−236 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.41 (s, br, 1H), 8.17 (d, J = 8.0 Hz, 2H), 8.04 (d, J = 8.0 Hz, 1H), 7.52−7.59 (m, 3H), 7.18 (d, J = 8.0 Hz, 1H), 7.09 (dd, J = 8.0 Hz, 1H), 3.91 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 164.1, 161.7, 152.8, 150.9, 132.6, 131.3, 128.5, 127.6, 127.4, 116.1, 114.3, 108.4, 55.6. HRMS (ESI): m/z calcd for $C_{15}H_{13}N_2O_2$, 253.0977; found, 253.0975.

2-Phenyl-2,3-dihydroquinazolin-4(1*H*)-one (5a).[24] To *o*-aminobenzamide (**2a**; 1.36 g, 10 mmol) in toluene (20 mL) was added benzaldehyde (**4a**; 1.06 g, 10 mmol) under N_2 at room temperature. The reaction mixture was refluxed for 8 h. The solution was then cooled to room temperature, the solvent was removed, and the residue was purified by silica gel chromatography (EtOAc:*n*-heptane = 1:5). Yield: 2.08 g (97%). White solid. Mp: 218−219 °C (lit.[24] 218−219 °C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.95 (d, J = 8.0 Hz, 1H), 7.59−7.60 (m, 2H), 7.44−7.46 (m, 3H), 7.37 (t, J = 8.0 Hz, 1H), 6.91 (t, J = 8.0 Hz, 1H), 6.67 (d, J = 8.0 Hz, 1H), 5.91 (s, 1H), 5.76 (s, 1H), 4.39 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.6, 147.2, 138.5, 134.0, 130.1, 129.1, 128.7, 127.2, 119.7, 115.6, 114.5, 69.1. HRMS (ESI): m/z calcd for $C_{14}H_{13}N_2O$, 225.1028; found, 225.1029.

■ ASSOCIATED CONTENT

Supporting Information. Description of the general experimental procedures and NMR spectra of the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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