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One-Pot Synthesis of 2-Arylquinazolines and Tetracyclic Isoindolo[1,2-*a*]quinazolines *via* Cyanation Followed by Rearrangement of *ortho*-Substituted 2-Halo-*N*-arylbenzamides

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Abstract: The one-pot synthesis of substituted 2-arylquinazoline derivatives and tetracylic isoindolo[1,2-*a*]quinazoline *via* cyanation followed by rearrangement of *ortho*-substituted 2-halo-*N*-arylbenzamides is described. Using dimethyl sulfoxide (DMSO) as the solvent, the cleavage of the tetracyclic isoindole fused quinazoline leads to the formation of 2-arylquinazoline derivatives. When 1,4-dioxane is used as the solvent, tetracyclic isoindole fused quinazolines are produced in good yield. A wide range of products, including 2-phenylquinazolin-4-amine, 4-methyl-2-phenylquinazoline and long-chain 2-phenyl-4-styrylquinazoline derivatives were produced in moderate to good yields using DMSO as the solvent. However, various tetracyclic isoindole fused quinazoline derivatives were obtained in good yields when 1,4-dioxane was used as the solvent.

Keywords: 2-arylquinazolines; C–C bond formation; copper catalysts; isoindolo[1,2-*a*]quinazolines; rearrangement

Introduction

The synthesis of nitrogen heterocycles *via* transition metal-mediated cross-coupling reactions has become an area of interest. This may be due to the fact that traditional synthetic methods are often laborious and the desired products are produced in relatively lower yields. Syntheses of these nitrogen heterocycles *via* copper-catalyzed and copper-mediated C–C and C–N bond coupling reactions are very popular. Copper catalysts are inexpensive, less toxic and the use of air-sensitive and expensive ligands that are used with palladium and other metal complex-based methodologies can be avoided. Furthermore, applications of such copper-mediated handy protocols on 2-haloarylbenzamide derivatives with structural changes at the amidic position leads to the formation of multicyclic fused rings *via* multibond formation. Structural motifs such as dibenzoxazepinones, indoloquinolines and tetracyclic fused N-heterocyclic compounds can be easily synthesized using these methodologies, compared to traditional multistep synthesis.[1]

2-Arylquinazolines are an important class of structural motifs that possess remarkable pharmacological properties such as anticonvulsant, antibacterial, antiviral, antitubercular, antiplasmodial, anticancer and topoisomerase I inhibitory activities.[2] In addition to 2-arylquinazolines, tetracyclic isoindolo[1,2-*a*]quinazoline derivatives are ubiquitous structural motifs and possess excellent biological activities. A structural analogue such as batracylin has potent activity against colon carcinomas, cisplatin- and doxorubicin-resistant tumors. A luotonin derivative was also reported to be effective against leukemia cells. Recent reports indicate that tryptanthrin can be used effectively as a chemotherapeutic agent in the treatment of sleeping disorders.[3] During our literature review we found very few reports on the synthesis of isoindolo[1,2-*a*]quinazoline derivatives.[4] Numerous approaches are available for the synthesis of 2-arylquinazoline derivatives.[5] However, the synthesis of 2-arylquinazoline derivatives is a cumbersome task, since it involves either the use of starting materials such as 2-(aminomethyl)aniline, benzimidamide, which are not readily available, or the use of dangerous peroxides or hazardous reagents.[6] We wish to report herein on the solvent-dependent one-pot synthesis of multi-substituted 2-arylquinazoline and tetracyclic isoindolo[1,2-

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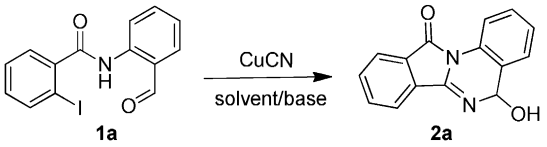
a]quinazoline derivatives *via* cyanation followed by rearrangement of the resulting *ortho*-substituted 2-halo-*N*-arylbenzamide.

Results and Discussion

Our group previously reported on numerous protocols for the synthesis of medicinally active N-heterocycles.[7] In a continuation of this interest, we noted the recently published articles on copper-catalyzed reactions of ethyl cyanoacetate and ethyl 2-(2-bromobenzamido)benzoate for the synthesis of isoquinolino[2,3-*a*]quinazolinones by Fu and co-workers[8a] and Pal and co-workers.[8b] Based on these reports, we hypothesized that the reaction of **1a** with CuCN would first undergo cyanation followed by cyclization in the presence of an amidic N–H, which would lead to the formation of the tetracyclic compound **2a** (Scheme 1). Furthermore, the hydroxy group can be easily functionalized using various protocols. To investigate this hypothesis, we treated **1a** in the presence of CuCN in DMSO and K_2CO_3 as a base at 100 °C. The reaction resulted in multiple spots on TLC after 2 h, however, when the reaction was continued for a period of up to 16 h, a new compound was observed with a higher R_f than the starting material (Table 1, entry 1). The compound was isolated and purified by column chromatography. Further characterization by ^{1}H NMR, ^{13}C NMR, LR-MS, HR-MS, single crystal X-ray diffraction revealed that the compound was 2-phenylquinazoline (**3a**, Figure 1) and not compound **2a** (Scheme 1).

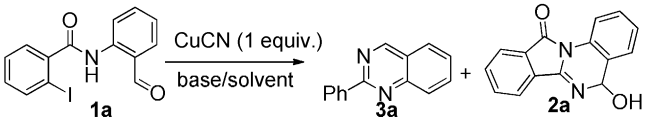


Scheme 1. Synthesis of tetracyclic compound **2a** from **1a**.

Interestingly, the combination of such a strained five-membered ring and a strong base leads to base-catalyzed cleavage of the C–N bond in compound **2a**. Moreover, further decarboxylation resulted in the formation of compound **3a** (Scheme 1). To our knowledge, such types of cleavages have not been reported in the literature. This motivated us to study this reaction further.

To optimize the reaction conditions, we increased the reaction temperature from 100 °C to 120 °C and then to 135 °C. An elevation in the temperature resulted in an increase in yield to 24% and 74%, respectively (Table 1, entries 2 and 3). However, a further increase in temperature failed to result in any improvement in yield (entry 4). Next, various inorganic bases such as Na_2CO_3, $NaHCO_3$, K_3PO_4, Cs_2CO_3 we examined for the reaction (entries 5–8) but these re-

Table 1. Optimization of reaction conditions.



Entry	Solvent	Base	Temp. [°C]	Time [h]	Yield [%][a,b]	
					3a	2a
1	DMSO	K_2CO_3	100	16	10	-
2	DMSO	K_2CO_3	120	24	23	-
3	**DMSO**	**K_2CO_3**	**135**	**9**	**74**	-
4	DMSO	K_2CO_3	140	14	58	-
5	DMSO	Na_2CO_3	135	11	65	-
6	DMSO	$NaHCO_3$	135	13	39	-
7	DMSO	K_3PO_4	135	24	-	-
8	DMSO	Cs_2CO_3	135	4	-	-
9	DMSO	DABCO	135	13	51	-
10	DMSO	DBU	135	11	28	-
11	DMSO	DIPEA	135	12	62	-
12	DMF	K_2CO_3	135	24	45	-
13	DMA	K_2CO_3	135	16	55	-
14	**1,4 dioxane**	**K_2CO_3**	**101**	**8**	-	**79**
15	ACN	K_2CO_3	81	24	-	31
16	EtOH	K_2CO_3	78	24	-	28
17	1,4 dioxane	K_3PO_4	101	15	-	53
18	1,4 dioxane	Cs_2CO_3	101	13	-	57
19	1,4 dioxane	Na_2CO_3	101	19	-	40
20	1,4 dioxane	DABCO	101	16	-	43
21	1,4 dioxane	DBU	101	18	-	39
22	1,4 dioxane	DIPEA	101	36	-	21

[a] Reactions were performed on 0.5 mmol of **1a**, CuCN (1 equiv.) and base (2.5 equiv,).
[b] Yields refer to isolated and purified compounds.

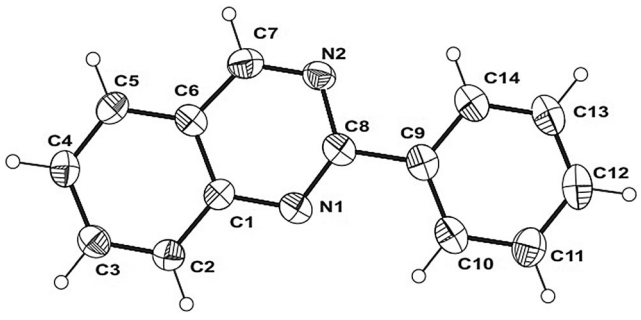


Figure 1. X-ray crystal structure of **3a** (ORTEP diagram).[9]

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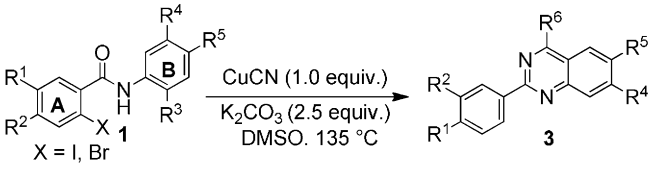
sulted in either a lower yield of the desired product or no product being formed. Furthermore, the use of organic bases also resulted in lower yields of compound **3a** (entries 9–11). Based on this information, it was concluded that K_2CO_3 was the preferred base for use in this transformation. Different solvents were then examined. However, we found that the product was formed in DMF and DMA but afforded a lower yield of **3a** (entries 12 and 13).

We next examined the use of refluxing 1,4-dioxane as the solvent for 12 h. Interestingly, a highly polar compound was produced, as evidenced by its TLC properties. The compound was isolated and purified. ^{1}H NMR, ^{13}C NMR, LR-MS, HR-MS data revealed that the compound formed was a tetracyclic isoindole fused quinazoline (**2a**) and was produced in 79% yield (entry 14). Further screening of the reaction using other solvents such as acetonitrile and ethanol failed to improve product yield (entries 15 and 16). Fine tuning of organic and inorganic bases also failed to improve reaction yield (entries 17–22). Finally, based on the optimization study, the reaction of **1a** with 1 equivalent of CuCN using K_2CO_3 as a base in 1,4-dioxane at 101 °C were the optimal conditions for the preparation of tetracyclic isoindole fused quinazoline (**2a**) and the reaction with K_2CO_3 as a base and DMSO as a solvent at 135 °C were the optimized conditions for the preparation of 2-phenylquinazoline (**3a**).

After optimizing the reaction conditions, the scope of the reaction was studied, first with unsubstituted ring **A** and ring **B** substituted compounds with aldehyde, ketone and cyanide groups at the *ortho* position. The reaction of CuCN with a model substrate **1a** containing an aldehyde at the *ortho* position afforded the 2-phenylquinazoline derivative (**3a**) in 74% yield (entry 1, Table 2). However, the reaction of CuCN with **1b** and **1c** bearing ketone and cyanide groups at the *ortho* position yielded 4-methyl-2-phenylquinazoline **3b** and 2-phenylquinazolin-4-amine **3c** in 77% and 57% yields, respectively, with longer reaction times. The longer reaction time for compounds **3b** and **3c** may be due to the less electrophilic nature of the ketone and the nitrile functional groups. Next, electron-donating amides were examined. The reaction afforded the corresponding quinazoline derivatives in moderate to good yields but a longer reaction time was needed in most cases (entries 4 to 9). Surprisingly, the reaction with *N*-(2-cyanophenyl)-2-iodo-4,5-dimethoxybenzamide (**1h**) reached completion within 9 h, producing a product yield of 74% (entry 8). Furthermore, a similar trend was observed, when electron-withdrawing amide-containing substrates were used in the reaction. Nitro-substituted amides formed the corresponding 2-arylquinazoline derivatives in good yields, but a longer reaction time was needed (entries 10–12).

Table 2. Synthesis of 2-arylquinazolines from various 2-halobenzamides.



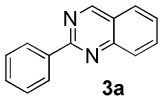
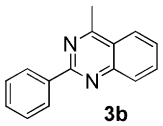
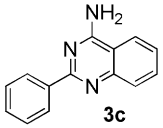
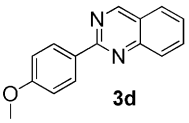
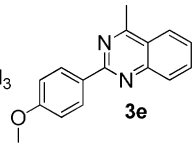
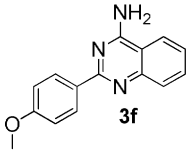
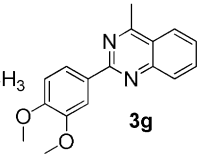
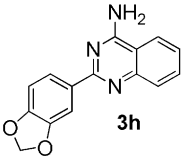
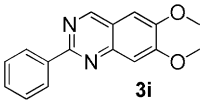
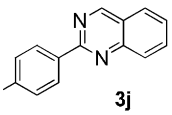
Entry	1				Product	Time [h]	Yield [%][a,b]
	A		B				
1	R^1 = H R^2 = H X = I	**1a**	R^3 = CHO R^4 = H R^5 = H		**3a**	9	74
2	R^1 = H R^2 = H X = I	**1b**	R^3 = $COCH_3$ R^4 = H R^5 = H		**3b**	11	77
3	R^1 = H R^2 = H X = I	**1c**	R^3 = CN R^4 = H R^5 = H		**3c**	15	57
4	R^1 = OMe R^2 = H X = I	**1d**	R^3 = CHO R^4 = H R^5 = H		**3d**	9	70
5	R^1 = OMe R^2 = H X = I	**1e**	R^3 = $COCH_3$ R^4 = H R^5 = H		**3e**	11	75
6	R^1 = OMe R^2 = H X = I	**1f**	R^3 = CN R^4 = H R^5 = H		**3f**	14	54
7	R^1 = OMe R^2 = OMe X = I	**1g**	R^3 = $COCH_3$ R^4 = H R^5 = H		**3g**	16	57
8	R^1+ R^2 = -OCH_2- X = I	**1h**	R^3 = CN R^4 = H R^5 = H		**3h**	9	74
9	R^1 = H R^2 = H X = I	**1i**	R^3 = CHO R^4 = OMe R^5 = OMe		**3i**	14	67
10	R^1 = NO_2 R^2 = H X = I	**1j**	R^3 = CHO R^4 = H R^5 = H		**3j**	11	73

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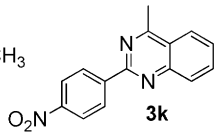
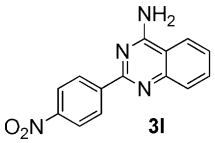
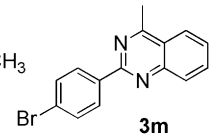
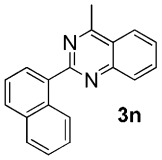
Table 2. (Continued)

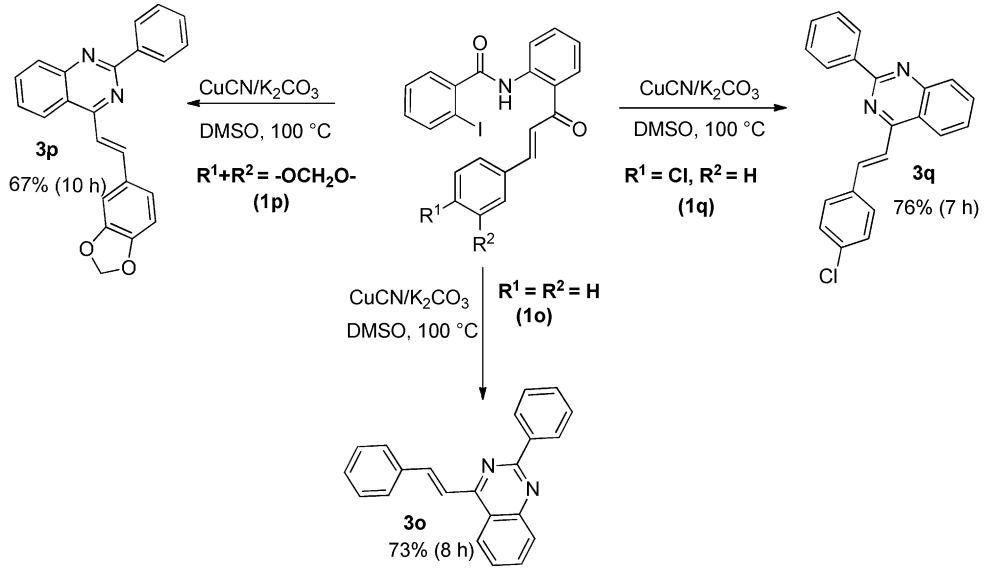
Entry	1 A		1 B	Product	Time [h]	Yield [%][a,b]
11	$R^1 = NO_2$, $R^2 = H$, X = Br	**1k**	$R^3 = COCH_3$, $R^4 = H$, $R^5 = H$	 **3k**	14	79
12	$R^1 = NO_2$, $R^2 = H$, X = I	**1l**	$R^3 = CN$, $R^4 = H$, $R^5 = H$	 **3l**	16	73
13	$R^1 = Br$, $R^3 = H$, X = I	**1m**	$R^3 = COCH_3$, $R^4 = H$, $R^5 = H$	 **3m**	9	76
14	naphthyl, X = Br	**1n**	$R^3 = COCH_3$, $R^4 = H$, $R^5 = H$	 **3n**	9	77

[a] Reactions were performed on 0.5 mmol of **1**, CuCN (1 equiv.) and K_2CO_3 (2.5 equiv.) at 135 °C.
[b] Yields refer to isolated and purified compounds.

However, the use of electron-withdrawing amides afforded better product yields than electron-donating amides. The reaction also proceeded when amides bearing bromo and bulkier naphthyl groups were used, resulting in the formation of the corresponding products **3m** and **3n** in good yield.

As an expansion of this study, we further explored the scope of the protocol with amidic linkages using chalcone derivatives as depicted in Scheme 2. The reaction of CuCN with the unsubstituted chalcone amide (**1o**) resulted in the formation of the corresponding 2-aryl-4-styrylquinazoline (**3o**) in 73% yield. In the case of an electron-donating substituent on the chalcone, the yield of the respective compound **3p** was reduced to 67% and a longer reaction time was needed. However, an electron-withdrawing substituent on the chalcone (**1q**) resulted in a slightly increased product yield and a reduced reaction time for the synthesis of 4-(4-chlorostyryl)-2-phenylquinazoline (**3q**).

Furthermore, we used the optimum reaction conditions to check the scope of the tetracyclic isoindole fused quinazoline, as depicted in Table 3. First, the reaction was screened when the ring **B** contained aldehyde, ketone and cyanide groups at the *ortho* position. The reaction of *N*-(2-formylphenyl)-2-iodobenzamide (**1a**) with CuCN in 1,4-dioxane afforded the hydroxy-substituted tetracyclic isoindole fused quinazoline derivative in 79% (entry 1). Whereas, when a ketone group was located at the *ortho* position, the corresponding tetracyclic derivative (**2b**) was obtained in good yield. The lower yield of compound **2c** was observed, when the reaction was carried out with the *ortho*-cyano-substituted *N*-(2-phenyl)-2-iodobenzamide as a substrate (entry 3). Further, when ring **A** contained an electron-donating dioxymethylene group, the reaction produced a moderate yield of the desired product (**2r**) and a slightly longer reaction time was needed (entry 4). However, electron-withdrawing bromo substituents on ring **A** and ring **B** afforded moderate yields of compounds **2m** and **2s**. Fur-



Scheme 2. Synthesis of 2-aryl-4-styrylquinazoline derivatives from 2-halo-*N*-arylbenzamide.

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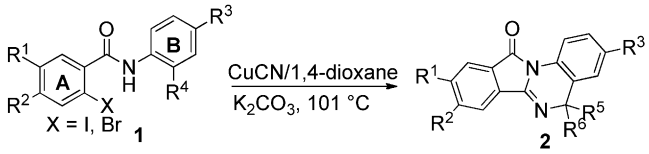
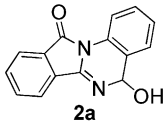
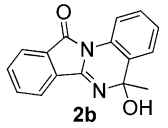
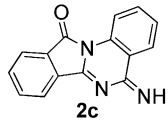
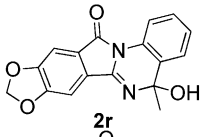
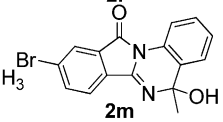
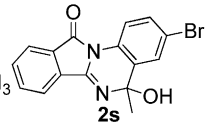
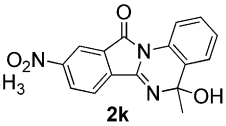
Table 3. Synthesis of isoindole fused quinazolines from various 2-halobenzamides.



Entry	1 A		1 B	Product	Time [h]	Yield [%][a,b]
1	R^1 = H, R^2 = H, X = I	**1a**	R^3 = H, R^4 = CHO	 **2a**	9	79
2	R^1 = H, R^2 = H, X= I	**1b**	R^3= H, R^4 = $COCH_3$	 **2b**	16	72
3	R^1 = H, R^2 = H, X = I	**1c**	R^3 = H R^4 = CN	 **2c**	14	63
4	R+R^2 = -OCH_2O-, X = I	**1r**	R^3 = H, R^4 = $COCH_3$	 **2r**	19	54
5	R^1 = Br, R^2 = H, X = I	**1m**	R^3 = H, R^4 = $COCH_3$	 **2m**	11	66
6	R^1 = H, R^2 = H, X = I	**1s**	R^3 = Br, R^4 = $COCH_3$	 **2s**	15	60
7	R^1 = NO_2, R^2 = H, X = Br	**1k**	R^3 = H, R^4 = $COCH_3$	 **2k**	28	–[c]

[a] Reactions were performed on 0.5 mmol of **1**, CuCN (1 equiv.) and K_2CO_3 (2.0 equiv.) at 101 °C.
[b] Yields refer to isolated and purified compounds.
[c] Inseparable mixture

thermore, the protocol failed to form compound **2k**, when the strong electron-withdrawing nitro-substituted **1k** was used as a substrate.

A plausible mechanism for the formation both **2** and **3** is depicted in Scheme 3. The reaction is initiated by the formation of intermediate **I** through cyanation in the presence a base and CuCN, which may undergo intramolecular cyclization *via* the nucleophilic addition of the amidic nitrogen to the cyanide functionality to generate the imine intermediate **II**. This intermediate further undergoes an intramolecular cyclization *via* the nucleophilic addition of the imine nitrogen to the aldehyde functionality to produce the tetracyclic compound **2**. The tetracyclic compound **2** then undergoes decarboxylation in the presence of the base to form compound **3**.

To support our proposed mechanism, we carried out, two control experiments. In the first experiment, we carried out the reaction of **1b** with CuCN and potassium carbonate in 1,4-dioxane as the solvent to obtain **2b**. After the complete conversion of **1b** to the tetracyclic compound **2b**, which was confirmed by TLC, DMSO was then added and the reaction mixture heated at 110 °C. The reaction produced **3b** in 51% yield after 16 h of reaction (Scheme 4).

In the second control experiment, we treated the tetracyclic compound **2a** with potassium carbonate in the absence copper in DMSO as the solvent at 135 °C. Under these conditions, we observed the conversion of **2a** into the corresponding 2-phenylquinazoline derivative in 50% yield (Scheme 5).

The findings from the control experiments indicate that the formation of 2-phenylquinazoline derivative from the thermal decomposition of tetracyclic compound is facilitated by the base.

Conclusions

In conclusion, we report on the synthesis of a series of substituted 2-arylquinozaline derivatives and tetracyclic isoindolo[1,2-*a*]quinazoline derivatives in moderate to good yield in a one-pot process simply by changing solvent and temperature. A novel base-catalyzed cleavage of tetracyclic isoindolo[1,2-*a*]quinazolines was observed during the synthesis of the 2-arylquinazolines. Furthermore, the syntheses of 2-arylquinazolin-4-amine and 2-phenyl-4-styrylquinazoline were achieved very efficiently compared to currently used methods. Good yields of the tetracyclic isoindolo[1,2-*a*]quinazoline derivatives were achieved by using 1,4-dioxane as the solvent.

Experimental Section

General Procedure for the Synthesis of Substituted 2-Halo-*N*-arylbenzamides (1a–s)

In a stir-bar-equipped flame-dried 50-mL round-bottom flask containing 2-halobenzoic acid (**A**) (4 mmol), $SOCl_2$ (2 mL) was carefully added, dropwise, followed by adding one drop of DMF. The reaction mixture was then stirred at 80 °C for 3 h. The reaction mixture was then evaporated under reduced pressure at 40–45 °C to remove excess $SOCl_2$. The resulting acid chloride was diluted in DCM (15 mL) and then added dropwise to an ice-cold solution of substituted aniline (**B**) (6 mmol) and pyridine (3 mL) in DCM (10 mL). The reaction mixture was then allowed to warm to

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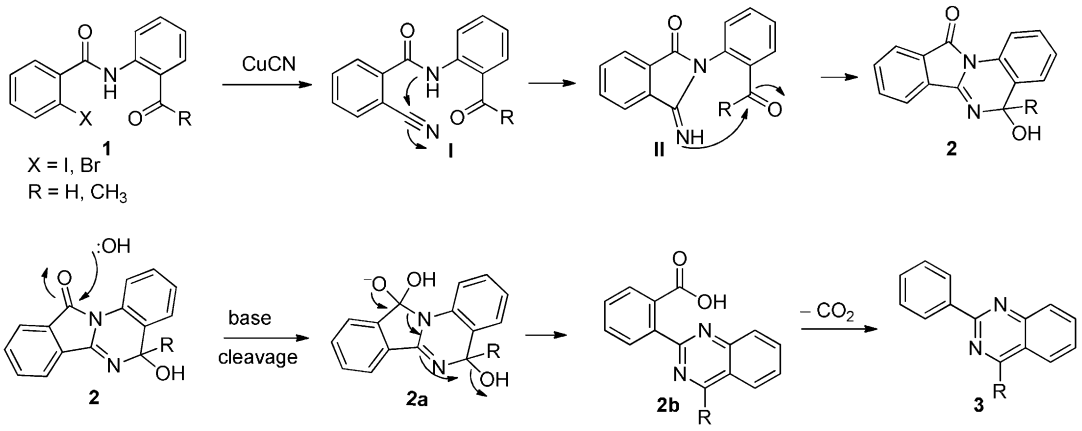
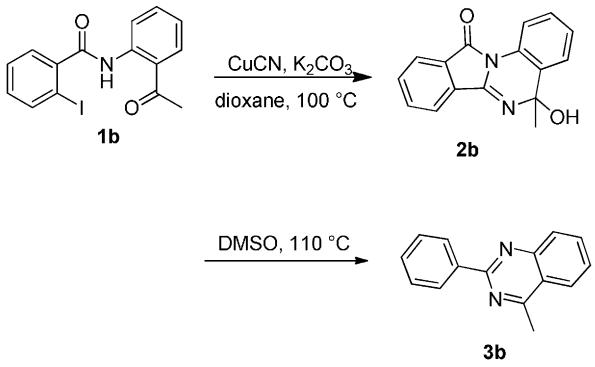
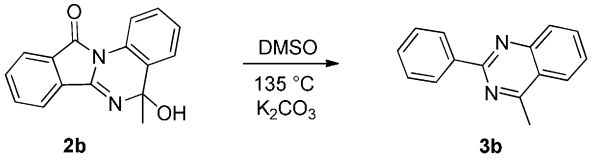


Scheme 3. Plausible mechanism for the synthesis of compound **2** and **3**.



Scheme 4. Control experiment 1.



Scheme 5. Control experiment 2.

room temperature with stirring overnight. After completion of the reaction as determined by TLC analysis, the reaction mixture was evaporated under reduced pressure and the residue poured on crushed ice (50 g). The resulting solid was washed with excess of ice-cold water to afford the pure compound **1a–s**.

Typical Procedure for the Synthesis of 2-Arylquinazolines (3a–q)

In an oven-dried, 10-mL round-bottom flask equipped with a magnetic stirrer, **1a** (0.5 mmol), CuCN (1.0 equiv.), K_2CO_3 (2.5 equiv.) in DMSO (2 mL) were added. The reaction mixture was then stirred at 135 °C under a nitrogen atmosphere. After completion of the reaction, as determined by TLC, the reaction mixture was allowed to cool to room temperature. The crude reaction mixture was then purified by column chromatography without work-up using hexane-ethyl acetate as the eluent to yield compound **3a**.

Typical Procedure for the Synthesis of Isoindole Fused Quinazoline Derivatives (2a–c, 2m, 2r and 2s)

In an oven-dried, 10-mL round-bottom flask equipped with magnetic stirrer was added **1a** (0.5 mmol), CuCN (1.0 equiv.), K_2CO_3 (2.5 equiv.) in 1.4-dioxane (2 mL). The reaction mixture was then stirred at 101 °C under a nitrogen atmosphere. After completion of the reaction, as determined by TLC, the reaction mixture was allowed to cool to room temperature. The crude reaction mixture was then purified by column chromatography without workup using dichloromethane-methanol as the eluent to yield compound **2a**.

Spectral Data for Compounds

2-Phenylquinazoline (3a): Yield: 74%; white solid; mp 100–101 °C; FT-IR (KBr): $\nu = 1641\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 9.09$ (brs, 1H), 8.62–8.64 (m, 2H), 8.11 (d, $J = 8.4$ Hz, 1H), 7.90–7.95 (m, 2H), 7.63 (t, $J = 7.5$ Hz, 1H), 7.52–7.58 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 161.3$, 160.7, 151.0, 138.3, 134.3, 130.8, 128.9, 128.83, 128.80, 127.5, 127.3, 123.8; LR-MS (EI): *m/z* (relative intensity) = 207 (100) $[M+H]^+$, 314 (100); HR-MS (MALDI): *m/z* = 207.0924, calcd. for $C_{14}H_{11}N_2$ $[M+H]^+$: 207.0922.

4-Methyl-2-phenylquinazoline (3b): Yield: 77%; yellow solid; mp 88–90 °C; FT-IR (KBr): $\nu = 1635\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.62$–8.64 (m, 2H), 8.08–8.11 (m, 2H), 7.85–7.89 (m, 1H), 7.56–7.61 (m, 2H), 7.51–7.54 (m, 2H), 3.03 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta =$ 168.4, 160.3, 150.6, 138.5, 133.6, 130.5, 129.4, 128.73, 128.71, 127.0, 125.1, 123.2, 22.2; LR-MS (ESI): *m/z* (relative intensity) = 220 (100) $[M]^+$, 204 (40); HR-MS: *m/z* = 220.1003, calcd. for $C_{15}H_{12}N_2$ $[M]^+$: 220.1000.

2-Phenylquinazolin-4-amine (3c): Yield: 57%; yellow solid; mp 144–145 °C; FT-IR (KBr): $\nu = 3470$, 3350, 1644, 1250 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.51$ (d, $J =$ 6.7 Hz, 2H), 7.97 (d, $J = 8.3$ Hz, 1H), 7.73–7.80 (m, 2H), 7.44–7.51 (m, 4H), 5.72 (bs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 162.1$, 159.7, 150.4, 138.6, 132.9, 129.9, 128.2, 127.8, 127.7, 125.2, 123.6, 113.3; LR-MS (ESI): *m/z* (relative intensity = 222 (100) $[M+H]^+$, 189 (20); HR-MS: *m/z* = 222.1023, calcd. for $C_{14}H_{12}N_3$ $[M+H]^+$: 222.1031.

2-(4-Methoxyphenyl)quinazoline (3d): Yield: 70%; white solid; mp 92–94 °C; FT-IR (KBr): $\nu = 1650$, 1240, 1125 cm^{-1};

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^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.42 (bs, 1H), 8.59 (d, J = 8.6 Hz, 2H), 8.05 (d, J = 8.4 Hz, 1H), 7.86–7.90 (m, 1H), 7.57 (t, J = 7.4 Hz, 1H), 7.06 (d, J = 8.7 Hz, 2H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.1, 161.1, 160.6, 151.1, 134.2, 131.0, 130.4, 128.7, 127.3, 126.9, 123.6, 114.2, 55.6; LR-MS (ESI): *m/z* (relative intensity) = 237 (100) $[M+H]^+$, 179 (20); HR-MS: *m/z* = 237.1022, calcd. for $C_{15}H_{13}N_2O$ $[M+H]^+$: 237.1028.

2-(4-Methoxyphenyl)-4-methylquinazoline (3e): Yield: 75%; yellow solid; mp 68–70 °C; FT-IR (KBr): ν = 1648, 1220, 1130 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.60 (d, J = 8.6 Hz, 2H), 8.04 (t, J = 7.2 Hz, 2H), 7.83 (t, J = 7.6 Hz, 1H), 7.53 (t, J = 7.5 Hz, 1H), 7.04 (d, J = 8.6 Hz, 2H), 3.89 (s, 3H), 2.99 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 168.2, 161.9, 160.2, 150.6, 133.6, 131.2, 130.4, 129.6, 125.2, 122.9, 114.1, 55.6, 22.2; LR-MS (MALDI): *m/z* (relative intensity) = 251 (100) $[M]^+$, 221 (65); HR-MS: *m/z* = 251.1191, calcd. for $C_{16}H_{15}N_2O$ $[M+H]^+$: 251.1184.

2-(4-Methoxyphenyl)quinazolin-4-amine (3f): Yield: 54%; yellow solid; mp 179–181 °C; FT-IR (KBr): ν = 3470, 3350, 1641, 1250, 1220, 1130 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.41 (d, J = 8.6 Hz, 2H), 8.22 (d, J = 8.1 Hz, 1H), 7.70–7.77 (m, 4H), 7.42 (t, J = 6.9 Hz, 1H), 7.04 (d, J = 8.6 Hz, 2H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 161.9, 160.9, 159.5, 150.3, 132.9, 130.9, 129.4, 127.3, 124.7, 123.6, 113.5, 113.0, 55.2; LR-MS (MALDI): *m/z* (relative intensity) = 251 (100) $[M+H]^+$; HR-MS: *m/z* = 252.1142, calcd. for $C_{15}H_{14}N_3O$ $[M+H]^+$:252.1137.

2-(3,4-Dimethoxyphenyl)-4-methylquinazoline (3g): Yield: 57%; yellow solid; mp 179–181 °C; FT-IR (KBr): ν = 1650, 1156, 1239 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.27 (dd, J = 8.44, 1.76 Hz, 1H), 8.22 (d, J = 1.52 Hz, 1H), 8.05 (t, J = 6.9 Hz, 2H), 7.84 (t, J = 7.96 Hz, 1H), 7.54 (t, J = 7.6 Hz, 1H), 7.01 (d, J = 8.4 Hz, 1H), 4.07 (s, 3H), 3.98 (s, 3H), 2.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.2, 160.0, 151.5, 150.7, 149.3, 133.6, 131.4, 129.2, 126.6, 125.2, 122.9, 122.2, 111.5, 111.1, 56.2, 56.2, 22.2; LR-MS (ESI): *m/z* (relative intensity) = 281 (100) $[M+H]^+$, 220 (40); HR-MS: *m/z* = 281.1284, calcd. for $C_{17}H_{17}N_2O_2$ $[M+H]^+$: 281.1290.

2-(Benzo[*d*][1,3]dioxol-5-yl)quinazolin-4-amine (3h): Yield: 74%; white solid; mp 193–195 °C; FT-IR (KBr): ν = 3470, 3350, 1641, 1250, 1150 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.21 (d, J = 8.0 Hz, 1H), 8.07 (d, J = 8.0 Hz, 1H), 7.93 (s, 1H), 7.70–7.76 (m, 4H), 7.43 (t, J = 7.1 Hz, 1H), 7.01 (d, J = 8.2 Hz, 1H), 6.10 (bs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.9, 159.6, 150.4, 148.9, 147.4, 132.9, 132.8, 127.5, 124.8, 123.5, 122.4, 113.1, 107.9, 107.6,101.3; LR-MS (MALDI): *m/z* (relative intensity) = 266 (100) $[M+H]^+$, 243 (30); HR-MS: *m/z* = 266.0935, calcd. for $C_{15}H_{11}N_3O_2$ $[M+H]^+$: 266.0930.

6,7-Dimethoxy-2-phenylquinazoline (3i): Yield: 67%; white solid; mp 176–178 °C; FT-IR (KBr): ν = 1635, 1230, 1140 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.23 (bs, 1H), 8.55 (d, J = 8.3 Hz, 2H), 7.48–7.55 (m, 3H), 7.38 (m, 1H) 7.11 (s, 1H), 4.09 (s, 3H), 4.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.2, 157.3, 156.5, 150.6, 148.8, 138.6, 130.3, 128.8, 128.3, 119.6, 107.1, 104.2, 56.7, 56.4; LR-MS (EI): *m/z* (relative intensity) = 266 (100) $[M]^+$, 265 (80); HR-MS: *m/z* = 266.1049, calcd. for $C_{16}H_{14}N_2O_2$ $[M]^+$: 266.1055.

2-(4-Nitrophenyl)quinazoline (3j): Yield: 73%; dark yellow solid; mp 218–220 °C; FT-IR (KBr): ν = 3439, 3400, 1520, 1350 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.52 (s, 1H), 8.82 (d, J = 8.8 Hz, 2H), 8.37 (d, J = 8.8 Hz, 2H), 8.14 (d, J = 8.4 Hz, 1H), 7.96–8.00 (m, 2H), 7.71(t, J = 7.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.9, 159.0, 150.8, 149.4, 144.0, 134.8, 129.6, 129.1, 128.5, 127.4, 124.1, 124.0; LR-MS (EI): *m/z* (relative intensity) = 251 (100) $[M]^+$, 205 (40); HR-MS: *m/z* = 251.0690, calcd. for $C_{14}H_9N_3O_2$ $[M]^+$: 251.0695.

4-Methyl-2-(4-nitrophenyl)quinazoline (3k): Yield: 79%; red solid; mp 174–176 °C; FT-IR (KBr): ν = 3468, 1636, 1520, 1350 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.81 (d, J = 8.9 Hz, 2H), 8.35 (d, J = 8.9 Hz, 2H), 8.10–8.15 (m, 2H), 7.93 (t, J = 7.6 Hz, 1H), 7.67 (t, J = 7.6 Hz, 1H), 3.05 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 168.9, 158.0, 150.3, 149.2, 144.3, 134.2, 129.6, 129.5, 128.1, 125.2, 123.8, 123.4, 22.2; LR-MS (MALDI): *m/z* (relative intensity) = 265 (100) $[M+H]^+$, 220 (28); HR-MS: *m/z* = 265.0846, calcd. for $C_{15}H_{11}N_3O_2$ $[M]^+$: 265.0851.

2-(4-Nitrophenyl)quinazolin-4-amine (3l): Yield: 73%); dark yellow solid; mp 220–222 °C; FT-IR (KBr): ν = 3470, 3350, 1641, 1520, 1350 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.66 (d, J = 8.6 Hz, 2H), 8.35 (d, J = 8.6 Hz, 2H), 8.28 (d, J = 8.2 Hz, 1H), 8.00 (bs, 2H), 7.81 (bs, 2H), 7.53 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.3, 157.8, 150.1, 148.3, 144.6, 133.3, 128.8, 127.9, 126.0, 123.6, 123.5, 113.4; LR-MS (MALDI): *m/z* (relative intensity) = 267 (100) $[M]^+$, 221 (45); HR-MS: *m/z* = 267.0893, calcd. for $C_{14}H_{10}N_4O_2$ $[M+H]^+$: 267.0882.

2-(4-Bromophenyl)-4-methylquinazoline (3m): Yield: 76%; yellow solid; mp 105–107 °C; FT-IR (KBr): ν = 1636, 585 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.52 (d, J = 8.4 Hz, 2H), 8.05–8.10 (m, 2H), 7.82 (t, J = 7.6 Hz, 1H), 7.65 (d, J = 8.4 Hz, 2H), 7.60 (t, J = 7.5 Hz, 1H), 3.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.6, 159.5, 150.6, 137.5, 133.9, 131.9, 130.4, 129.5, 127.3, 125.4, 125.2, 123.3, 22.2; LR-MS (ESI): *m/z* (relative intensity) = 298 (98) $[M]^+$, 300(100); HR-MS (ESI): *m/z* = 298.0111, calcd. for $C_{15}H_{11}BrN_2$ $[M]^+$: 298.0106.

4-Methyl-2-(naphthalen-1-yl)quinazoline (3n): Yield: 77%; white solid; mp 119–121 °C; FT-IR (KBr): ν = 1645, 1537, 1357 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.66 (d, J = 8.4 Hz, 1H), 8.15–8.20 (m, 3H), 7.99 (d, J = 8.2 Hz, 1H), 7.92–7.96 (m, 2H), 7.68 (t, J = 7.7 Hz, 1H), 7.63 (t, J = 7.7 Hz, 1H), 7.53–7.56 (m, 2H), 3.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.6, 162.9, 150.3, 136.8, 134.4, 134.0, 131.5, 130.3, 129.5, 129.4, 128.6, 127.6, 126.9, 126.2, 126.0, 125.5, 125.2, 122.8, 22.2; LR-MS (MALDI): *m/z* (relative intensity) = 271 (100) $[M+H]^+$; HR-MS: *m/z* = 271.1241, calcd. for $C_{19}H_{14}N_2$ $[M+H]^+$: 271.1235.

(*E*)-2-Phenyl-4-styrylquinazoline (3o): Yield: 73%; yellow solid; mp 138–140 °C; FT-IR (KBr): ν = 3480, 1545, 1378, 719 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.76 (d, J = 7.3 Hz, 2H), 8.46 (d, J = 15.4 Hz, 1H), 8.27 (d, J = 8.3 Hz, 1H), 8.10 (d, J = 8.4 Hz, 1H), 7.96 (d, J = 15.4 Hz, 1H), 7.87 (t, J = 7.7 Hz, 1H), 7.77 (d, J = 7.4 Hz, 2H), 7.53–7.61 (m, 4H), 7.42–7.50 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.1, 160.3, 152.2, 139.6, 138.7, 136.3, 133.6, 130.6, 129.8, 129.5, 129.1, 128.8, 128.7, 128.2, 127.0, 124.0, 121.8, 121.1; LR-MS (ESI): *m/z* (relative intensity) = 308 (100) $[M]^+$, 307 (80); HR-MS: *m/z* = 308.1317, calcd. for $C_{22}H_{16}N_2$ $[M]^+$: 308.1313.

(*E*)-4-[2-(Benzo[*d*][1,3]dioxol-5-yl)vinyl]-2-phenylquinazoline (3p): Yield: 67%; yellow solid; mp:169–171 °C; FT-IR

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(KBr): ν = 1643, 1230, 1150, 1140 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.71 (d, J = 6.8 Hz, 2H), 8.37 (d, J = 15.3 Hz, 1H), 8.26 (d, J = 8.3 Hz, 1H), 8.08 (d, J = 8.4 Hz, 1H), 7.86 (t, J = 7.5 Hz, 1H), 7.78 (d, J = 15.4 Hz, 1H), 7.52–7.61 (m, 4H), 7.29 (s, 1H), 7.23 (d, J = 8.0 Hz, 1H), 6.88 (d, J = 8.0 Hz, 1H), 6.02 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.2, 160.3, 152.2, 149.3, 148.6, 139.4, 138.8, 133.6, 130.9, 130.5, 129.5, 128.8, 128.7, 126.9, 124.2, 124.0, 121.8, 119.2, 108.9, 106.8, 101.7; LR-MS (EI): *m/z* (relative intensity) = 352 (100) [M^+], 351 (60); HR-MS: *m/z* = 352.1209, calcd. for $C_{23}H_{16}N_2O_2$ [M^+]: 352.1212.

(*E*)-4-(4-Chlorostyryl)-2-phenylquinazoline (3q): Yield: 76%; yellow solid; mp 150–152 °C; FT-IR (KBr): ν = 1635, 715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.71 (d, J = 8.2 Hz, 2H), 8.37 (d, J = 15.4 Hz, 1H), 8.24 (d, J = 8.3 Hz, 1H), 8.09 (d, J = 8.4 Hz, 1H), 7.85–7.92 (m, 2H), 7.68 (d, J = 8.4 Hz, 2H), 7.53–7.61 (m, 4H), 7.43 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.7, 160.3, 152.3, 138.7, 138.1, 135.6, 134.8, 133.7, 130.7, 129.6, 129.4, 129.3, 128.8, 128.7, 127.1, 123.9, 121.8, 121.6; LR-MS (EI): *m/z* (relative intensity) = 342 (100) [M^+], 341 (75); HR-MS: *m/z* = 342.0922, calcd. for $C_{22}H_{15}ClN_2$ (M^+): 342.0924.

5-Hydroxyisoindolo[2,1-*a*]quinazolin-11(5*H*)-one (2a): Yield: 79%; white solid; mp 151–152 °C; FT-IR (KBr): ν = 3379 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 8.48 (d, J = 8.2 Hz, 1H), 7.97 (d, J = 7.3 Hz, 1H), 7.93 (d, J = 7.2 Hz, 1H), 7.78–7.88 (m, 2H), 7.53 (d, J = 7.4 Hz, 1H), 7.40 (d, J = 7.7 Hz, 1H), 7.31 (t, J = 7.4 Hz, 1H), 6.72 (d, J = 7.3 Hz, 1H), 6.17 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$); δ = 165.1, 146.4, 134.2, 133.3, 132.8, 131.4, 131.1, 128.7, 127.9, 125.4, 123.5, 123.4, 121.8, 114.7, 76.9; LR-MS (ESI): *m/z* (relative intensity) = 251 (100) [M + H^+]; HR-MS (ESI): *m/z* = 249.0665, calcd. for $C_{15}H_9N_2O_2$ (M − H^-): 249.0664.

5-Hydroxy-5-methylisoindolo[2,1-*a*]quinazolin-11(5*H*)-one (2b): Yield: 72%; white solid; mp 180–182 °C; FT-IR (KBr): ν = 3467 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 8.50 (d, J = 8.1 Hz, 1H), 7.98 (d, J = 7.3 Hz, 1H), 7.93 (d, J = 7.2 Hz, 1H), 7.78–7.87 (m, 2H), 7.65 (d, J = 7.4 Hz, 1H), 7.42 (t, J = 7.4 Hz, 1H), 7.30 (t, J = 7.4 Hz, 1H), 6.48 (s, 1H), 1.59 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.1, 144.4, 134.2, 133.3, 132.7, 131.1, 130.5, 128.2, 128.0, 127.1, 125.4, 123.4, 121.8, 114.5, 81.3, 33.2; LR-MS (ESI): *m/z* (relative intensity) = 251 (100) [M + H^+], 247 (39); HR-MS (ESI): *m/z* = 265.0977, calcd. for $C_{16}H_{13}N_2O_2$ (M + H^+): 265.0977.

5-Iminoisoindolo[2,1-*a*]quinazolin-11(5*H*)-one (2c): Yield: 63%; white solid; mp 178–180 °C; FT-IR (KBr): ν = 3489 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 10.76 (bs, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.88 (d, J = 7.6 Hz, 1H), 7.77 (t, J = 7.5 Hz, 1H), 7.64–7.66 (m, 1H), 7.51–7.57 (m, 2H), 7.44 (t, J = 7.5 Hz, 1H), 7.25–7.29 (m, 1H), 6.72 (d, J = 7.3 Hz, 1H), 6.17 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.8, 141.8, 139.6, 139.2, 133.8, 133.3, 131.4, 128.2, 128.1, 126.4, 126.1, 116.7, 108.3, 93.4; LR-MS (ESI): *m/z* (relative intensity) = 248 (50) [M + H^+], 231(75); HR-MS: *m/z* = 248.0830, calcd. for $C_{15}H_9N_2O$ (M + H^+): 248.0824.

5-Hydroxy-5-methyl[1,3]dioxolo[4′,5′:5,6] isoindolo[2,1-*a*]quinazolin-12(5*H*)-one (2r): Yield: 54%; grey solid; mp 187–189 °C; FT-IR (KBr): ν = 3334, 3459 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 8.41 (d, J = 8.2 Hz, 1H), 7.62 (d, J = 7.6 Hz, 1H), 7.36–7.40 (m, 3H), 7.26 (t, J = 7.4 Hz, 1H), 6.41 (s, 1H), 6.27 (s, 2H), 1.57 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.6, 152.7, 151.5, 144.1, 130.6, 129.1, 128.2, 127.8, 127.0, 126.0, 125.0, 114.1, 103.1, 101.7, 81.3, 33.2; LR-MS (ESI): *m/z* (relative intensity) = 309 (100) [M + H^+], 291 (82); HR-MS: *m/z* = 309.0871, calcd. for $C_{17}H_{13}N_2O_4$ (M + H^+): 309.0875.

9-Bromo-5-hydroxy-5-methylisoindolo[2,1-*a*]quinazolin-11(5*H*)-one (2m): Yield: 66%; white solid; mp 166–168 °C; FT-IR (KBr): ν = 3379, 717 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 8.46 (d, J = 8.2 Hz, 1H), 7.10 (s, 1H), 8.01–8.03 (m, 1H), 7.90 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 7.4 Hz, 1H), 7.42 (t, J = 7.5 Hz, 1H), 7.31 (t, J = 7.5 Hz, 1H), 6.51 (bs, 1H), 1.59 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 163.7, 143.8, 136.9, 133.2, 132.3, 130.3, 128.3, 127.9, 127.2, 126.1, 125.9, 125.7, 123.7, 114.6, 81.5, 33.2; LR-MS (ESI): *m/z* (relative intensity) = 343 (100) [M + H^+], 345 (95); HR-MS: *m/z* = 343.0078, calcd. for $C_{16}H_{12}N_2O_2$ (M + H^+): 343.0082.

3-Bromo-5-hydroxy-5-methylisoindolo[2,1-*a*]quinazolin-11(5*H*)-one (2s): Yield: 60%; white solid; mp 174–176 °C; FT-IR (KBr): ν = 3570, 3348 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 8.42 (d, J = 8.8 Hz, 1H), 7.97 (d, J = 7.4 Hz, 1H), 7.91 (d, J = 7.3 Hz, 1H), 7.84 (t, J = 7.4 Hz, 1H), 7.75–7.80 (m, 2H), 7.60 (dd, J = 8.8 Hz, 1.8 Hz, 1H), 1.60 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 165.0, 144.2, 134.4, 133.2, 132.9, 131.1, 131.0, 130.4, 129.8, 129.6, 123.5, 121.9, 117.3, 116.8, 81.2, 33.1; LR-MS (ESI): *m/z* (relative intensity) = 342 (100) [M^+], 344 (95); HR-MS: *m/z* = 342.0006, calcd. for $C_{16}H_{11}N_2O_2$ (M^+): 342.0004.

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[9] CCDC 993227 (**3a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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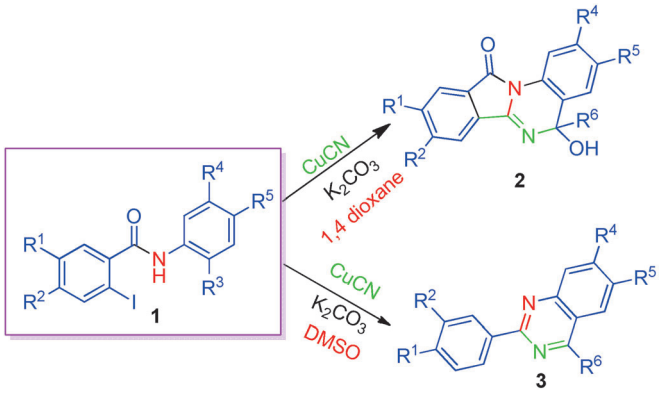

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