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Synthesis of 1*H*-indol-2-yl-(4-aryl)-quinolin-2(1*H*)-ones via Pd-catalyzed regioselective cross-coupling reaction and cyclization

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Abstract

An efficient and novel route for the synthesis of 1*H*-indol-2-yl-(4-aryl)-quinolin-2(1*H*)-one **1** via palladium-catalyzed site-selective cross-coupling reaction and cyclization process was described. Reaction of 3-bromo-4-trifloxy-quinolin-2(1*H*)-one **3** with arylboronic acid catalyzed by $PdCl_2(PPh_3)_2$ afforded 3-bromo-4-aryl-quinolin-2(1*H*)-one **4**, which then reacted with 2-ethynylaniline **5** via Pd-catalyzed Sonogashira coupling and CuI-mediated cyclization leading to the desired 1*H*-indol-2-yl-(4-aryl)-quinolin-2(1*H*)-one **1** in good yields.
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Keywords: 1*H*-Indole-2-yl-(4-aryl)-quinolin-2(1*H*)-one; Palladium; Regioselective cross-coupling; Cyclization

1. Introduction

For chemistry to have its maximal effect on biology, efficient methods for discovering natural product-like compounds are in great demand in the field of chemical genetics.[1] Since KDR (kinase insert domain-containing receptor) is one of the human tyrosine kinases that has a high affinity for vascular endothelial growth factor (VEGF) and is believed to be a primary mediator of tumor-induced angiogenesis,[2] compounds, which inhibit or regulate the KDR kinase have attracted much attention and are of great interest as potential therapeutic agents. Recently, Merck reported a class of potent KDR kinase inhibitors containing the 1*H*-indol-2-yl-quinolin-2(1*H*)-one core structure, such as compound **A**, which has been utilized for clinical development for cancer therapy (Fig. 1). Therefore, synthesis of analogues with 1*H*-indol-2-yl-quinolin-2(1*H*)-one core has received considerable attention in the last 5 years.[3] Meanwhile, in recent years, an increasing interest in the synthesis of functionalized 4-aryl-quinolin-2(1*H*)-ones with promising biological properties has been observed.[4] A number of analogues of this class of heterocyclic structure have been reported as lead compounds or are currently undergoing clinical trials. In connection with a chemical genetic approach of analyzing biological systems by using interfacing libraries of natural product-like molecules with biological assays,[1] we became interested in developing new approaches for the synthesis of 1*H*-indol-2-yl-(4-aryl)-quinolin-2(1*H*)-one **1**.

Several different strategies have been utilized for the construction of 1*H*-indol-2-yl-quinolin-2(1*H*)-one scaffold **1**, which include Fisher indole reaction, reductive cyclization, as well as palladium-catalyzed Suzuki-coupling and amination reactions.[3] For example, most recently, Lautens et al.[3a] utilized the Pd-catalyzed tandem C–N and C–C coupling reactions using *gem*-dibromovinylaniline substrates with boronic acid for the synthesis of four potent KDR kinase inhibitors

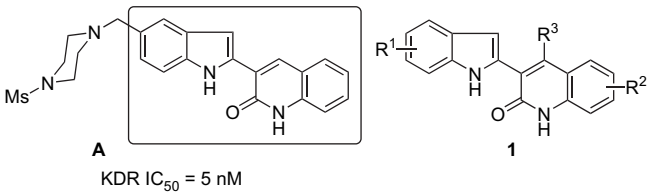

Figure 1.

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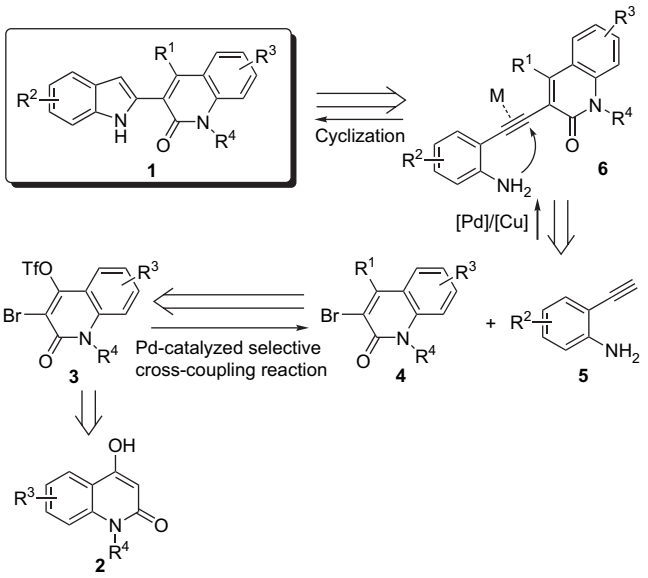


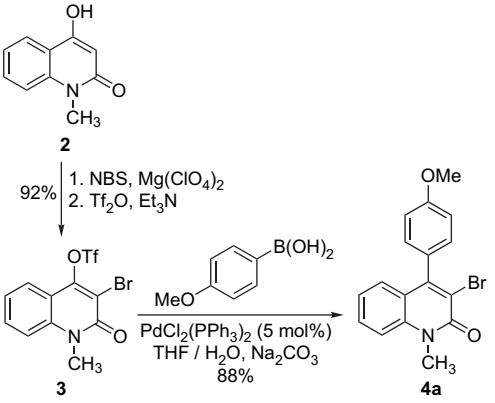
Scheme 1.

containing an 1*H*-indol-2-yl-quinolin-2(1*H*)-one structure. Payack et al.[3d] reported the synthesis of 3-[5-[[4-(methylsulfonyl)-1-piperazinyl]methyl]-1*H*-indol-2-yl]quinolin-2(1*H*)-one via a noncryogenic indole boronation and a dicyclohexylamine-mediated Suzuki coupling. Kuethe et al.[3c] demonstrated the reductive cyclization approach to be an efficient and high-yielding method for the construction of the target substrate **A** via six steps. All these procedures, however, were not easy to introduce diversity in the overall synthetic scheme and suffered from multisteps in each case. Especially, the preparation of analogues, e.g., varying the aryl group at C4 of quinolin-2(1*H*)-one, is a cumbersome and lengthy process. In this paper, we describe a novel and flexible synthetic protocol for the synthesis of 1*H*-indol-2-yl-(4-aryl)-quinolin-2(1*H*)-ones utilizing palladium-catalyzed site-selective cross-coupling reactions and cyclization process (Scheme 1).

The key compound in our overall synthetic route was identified as 3-bromo-4-trifloxy-quinolin-2(1*H*)-one **3**. Prompted by the recent advances of halogenation of 1,3-dicarbonyl compounds,[5] we envisioned that this compound could be generated by treatment of 4-hydroxyquinolin-2(1*H*)-one **2** with NBS/$Mg(ClO_4)_2$ and trifluoromethanesulfonic anhydride, subsequently. It is well known that 4-hydroxyquinolin-2(1*H*)-ones **2** are useful intermediates for many industrial products and several methods for their preparation have been reported.[6] To verify the practicability of the projected route as shown in Scheme 1, an initial model study was performed using the commercially available 4-hydroxyquinolin-2(1*H*)-one **2** as the starting material (Scheme 2).

2. Results and discussion

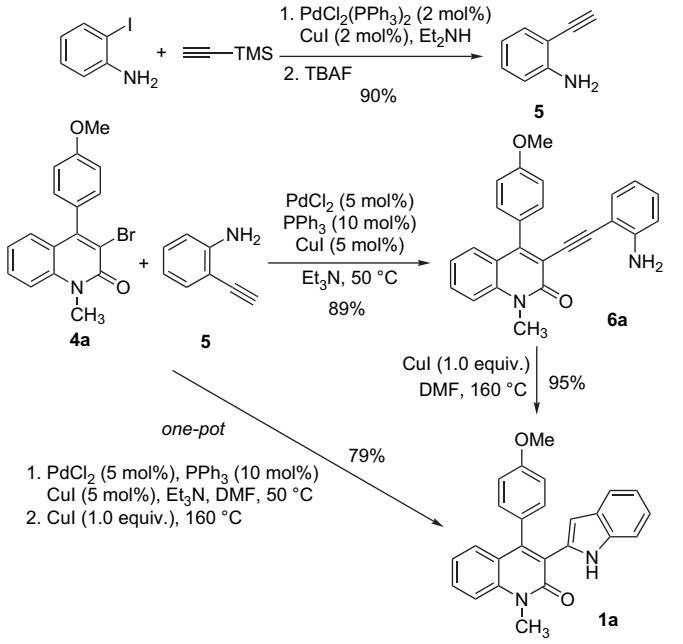
As described above, 3-bromo-4-trifloxy-quinolin-2(1*H*)-one **3** was easily synthesized in high yield (92%) in two steps from 4-hydroxy-quinolin-2(1*H*)-one **2**. We conceived that the



Scheme 2.

4-trifloxy group attached to the electron-withdrawing α,β-unsaturated double bond in compound **3** may increase its capability to oxidative addition to the transition metals. Therefore, the regioselective cross-couplings of **3** catalyzed by transition metal are possible. Due to their easy handling and long shelf life, arylboronic acid derivatives would be the starting materials of choice. Therefore, we started to explore the possibility of using **3** as an electrophile for the Suzuki–Miyaura reaction.[7] To our delight, we found that the corresponding product **4a** could be afforded in 88% yield under standard conditions [$PdCl_2(PPh_3)_2$, THF/H_2O, Na_2CO_3] for the reaction of 3-bromo-4-trifloxy-quinolin-2(1*H*)-one **3** with 4-methoxyphenylboronic acid (Scheme 2). With this compound in hand, we started to investigate further the indole formation at 3-position via transition metal catalyzed cyclization reaction. It is well-known that the transition metal catalyzed cyclization of alkynes possessing a nucleophile in proximity to the triple bond is an important process in organic synthesis, which can construct various heterocycles in an efficient and atom-economic way.[8–13] Over the past few years, the intramolecular annulations of amines,[8] amides,[9] imines,[10] carboxylic acids,[11] alcohols,[12] and phosphonic acid derivatives[13] to a triple bond have been extensively investigated using transition-metal reagents as effective catalysts. Compound **5**, prepared via Sonogashira coupling from the reaction of 2-iodoaniline with trimethylsilylacetylene, was employed in the reaction of compound **4a** in the presence of $PdCl_2(PPh_3)_2$ (10 mol %), CuI (10 mol %), and DIPEA in CH_3CN at 50 °C. However, no product was detected under this condition. Further screening revealed that the reaction proceeded smoothly in the presence of $PdCl_2$ (5 mol %), CuI (5 mol %), and PPh_3 (10 mol %) in Et_3N at 50 °C to afford the desired product **6a** in 89% yield. Subsequently, mediated by CuI in DMF, the final cyclization was performed to generate the corresponding 1*H*-indol-2-yl-(4-aryl)-quinolin-2(1*H*)-one **1a** in 95% yield (Scheme 3).

We also tested the one-pot reaction of 3-bromo-4-(4-methoxyphenyl)-quinolin-2(1*H*)-one **4a** with acetylene **5**. The operation is simple: after completion of the reaction of 3-bromo-4-(4-methoxyphenyl)-quinolin-2(1*H*)-one **4a** with acetylene **5** as indicated by TLC, CuI (1.0 equiv) was added directly in the reaction mixture and the mixture was stirred



Scheme 3.

at 160 °C for another 1 h. Gratifyingly, the reaction also proceeded well to generate the product **1a** in 79% yield. With this promising result in hand, to demonstrate the generality of this method, we next investigated the scope of this one-pot reaction under the conditions shown in Scheme 3 and the results are summarized in Table 1.

This condition was proved to be useful for one-pot synthesis of 1*H*-indol-2-yl-(4-aryl)-quinolin-2(1*H*)-one **1** (Table 1). Starting from 3-bromo-4-triflate-quinolin-2(1*H*)-one **3**, various aryl groups could be easily introduced at the 4-position of quinolin-2(1*H*)-one scaffold in good to excellent yields via Suzuki–Miyaura coupling reaction. The subsequent one-pot cyclization by Sonogashira coupling of vinyl bromide **4** and CuI-mediated reaction also proceeded well to generate the desired 1*H*-indol-2-yl-(4-aryl)-quinolin-2(1*H*)-one **1** in good yields. The reaction was found to be tolerable to a range of different aryl groups at 4-position with different electronic demands on aromatic rings involving electron-donating and electron-withdrawing groups. For instance, 3-bromo-4-(2-methoxyphenyl)-quinolin-2(1*H*)-one **4b** and acetylene **5** reacted under the conditions leading to the corresponding 1*H*-indol-2-yl-(4-(2-methoxyphenyl))-quinolin-2(1*H*)-one **1b** in 65% yield (entry 2) while the reaction of 3-bromo-4-(4-cyanophenyl)-quinolin-2(1*H*)-one **4f** and acetylene **5** afforded product **1f** in 80% yield (entry 6).

3. Conclusions

In summary, we have described an efficient and novel route for the synthesis of 1*H*-indol-2-yl-(4-aryl)-quinolin-2(1*H*)-one **1** via palladium catalyzed regioselective cross-coupling reaction and cyclization process, starting from 4-hydroxyquinolin-2(1*H*)-one. Introducing more diversity in the scaffold and screening for biological activity of these small molecules are under investigation in our laboratory.

4. Experimental section

4.1. General

All the reactions were performed in test tubes under air atmosphere at room temperature. Flash column chromatography was performed as described by Still et al. using silica gel (60-Å pore size, 32–63 μm, standard grade). Analytical thin-layer chromatography was performed using glass plates pre-coated with 0.25 mm 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Thin layer chromatographic plates were visualized by exposure to ultraviolet light. Organic solutions were concentrated on Büchi R-200 rotary evaporators at ~20 Torr (house vacuum) at 25–35 °C. Commercial reagents and solvents were used as-received. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded in parts per million from internal tetramethylsilane on the δ scale and are referenced from the residual protium in the NMR solvent ($CHCl_3$: δ 7.27).

4.2. General procedure for the preparation of compounds *4* through cross-coupling reaction between 3-bromo-4-trifloxy-quinolin-2(1H)-one and arylboronic acids

Potassium carbonate (2.0 M in water, 0.75 mL) was added to a solution of 3-bromo-4-trifloxy-quinolin-2(1*H*)-one **3** (192.5 mg, 0.50 mmol), $PdCl_2(PPh_3)_2$ (17.5 mg, 0.025 mmol), and boronic acid (1.1 equiv) in THF (4 mL) under nitrogen atmosphere. The reaction mixture was stirred overnight at room temperature. After completion of the reaction as monitored by TLC, the reaction mixture was diluted with ethyl acetate (20 mL) and separated. The solution was dried and filtered, and the filtrate was concentrated to a residue that was purified by flash chromatography (silica gel, 2/1 (v/v) petroleum ether/ethyl acetate) to give the corresponding product **4**.

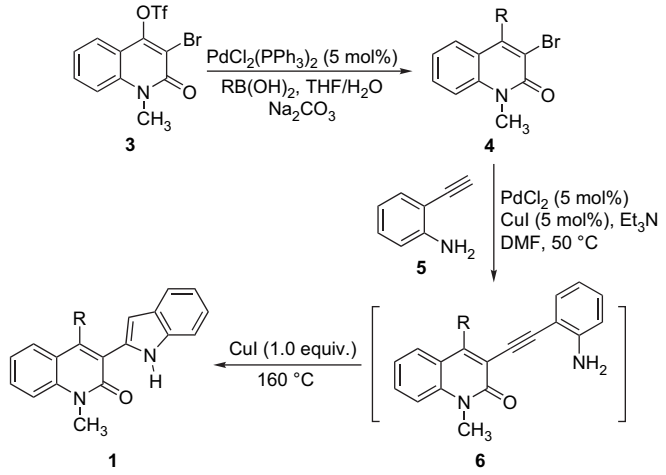
4.2.1. 3-Bromo-4-(4-methoxyphenyl)-1-methylquinolin-2(1H)-one (*4a*)[14]

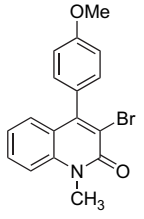
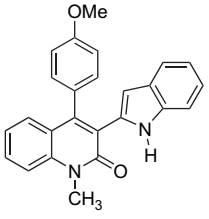
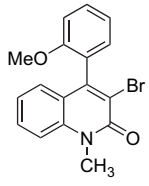
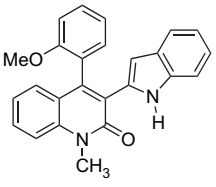
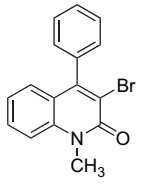
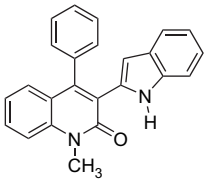
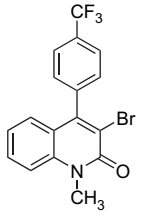
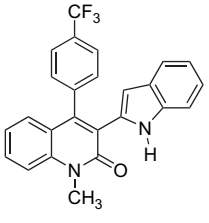
Yield 88%. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.60 (t, J=7.5 Hz, 1H), 7.43 (d, J=8.5 Hz, 1H), 7.20–7.28 (m, 3H), 7.14 (t, J=7.5 Hz, 1H), 7.07 (d, J=8.0 Hz, 2H), 3.91 (s, 3H), 3.89 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 159.9, 158.7, 150.6, 139.1, 131.0, 130.2, 129.8, 128.8, 122.7, 121.9, 119.8, 114.5, 114.3, 55.6, 31.5. MS (ESI): *m/z* 344.0 (M^++1).

4.2.2. 3-Bromo-4-(2-methoxyphenyl)-1-methylquinolin-2(1H)-one (*4b*)[14]

Yield 85%. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.56–7.61 (m, 1H), 7.48–7.52 (m, 1H), 7.43 (d, J=8.0 Hz, 1H), 7.07–7.17 (m, 5H), 3.89 (s, 3H), 3.74 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 159.6, 156.4, 148.4, 139.1, 131.1, 130.8, 130.6, 130.1, 128.2, 126.5, 122.7, 121.1, 120.2, 114.5, 111.7, 56.0, 31.4. MS (ESI): *m/z* 344.0 (M^++1).

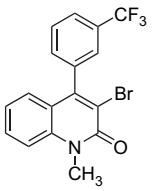
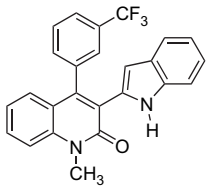
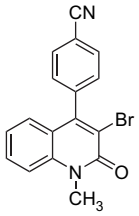
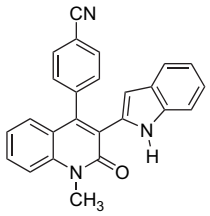
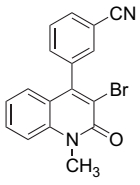
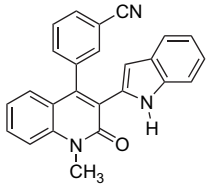
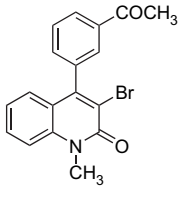
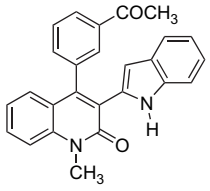
Table 1
Synthesis of 1*H*-indol-2-yl-quinolin-2(1*H*)-one **1** via Pd-catalyzed selective cross-coupling reaction and CuI-mediated cyclization



Entry	Product **4**	Yield[a] (%)	Product **1**	Yield[b] (%)
1	 **4a**	88	 **1a**	79
2	 **4b**	85	 **1b**	65
3	 **4c**	87	 **1c**	77
4	 **4d**	90	 **1d**	75

(*continued*)

Table 1 (*continued*)

Entry	Product **4**	Yield[a] (%)	Product **1**	Yield[b] (%)
5	 **4e**	85	 **1e**	68
6	 **4f**	70	 **1f**	80
7	 **4g**	73	 **1g**	78
8	 **4h**	75	 **1h**	74

[a] Isolated yield based on compound **3**.
[b] Isolated yield based on compound **4**.

*4.2.3. 3-Bromo-1-methyl-4-phenylquinolin-2(1H)-one (**4c**)*[14]

Yield 87%. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.58–7.63 (m, 1H), 7.49–7.58 (m, 3H), 7.44 (d, J=8.5 Hz, 1H), 7.26–7.30 (m, 2H), 7.10–7.20 (m, 2H), 3.90 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 158.6, 150.8, 139.1, 137.6, 131.0, 130.1, 128.8, 128.2, 127.7, 122.7, 121.6, 119.4, 114.5, 31.5. MS (ESI): *m/z* 314.0 (M^++1).

*4.2.4. 3-Bromo-1-methyl-4-(4-trifluoromethyl)-phenyl)quinolin-2(1H)-one (**4d**)*

Yield 90%. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.81 (d, J=8.0 Hz, 2H), 7.62 (t, J=7.3 Hz, 1H), 7.46–7.41 (m, 3H), 7.15 (t, J=7.3 Hz, 1H), 7.06 (d, J=7.8 Hz, 1H), 3.90 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 158.0, 149.0, 140.8, 138.8, 131.1, 129.1, 127.8, 125.8, 125.7, 122.7, 120.7, 119.1, 114.4, 31.2. MS (ESI): *m/z* 404.0 (M^++Na). Anal. Calcd for $C_{17}H_{11}BrF_3NO$: C, 53.43; H, 2.90; N, 3.67. Found: C, 53.34; H, 2.95; N, 3.62.

*4.2.5. 3-Bromo-1-methyl-4-(3-(trifluoromethyl)phenyl)-quinolin-2(1H)-one (**4e**)*[14]

Yield 85%. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.78 (d, J=8.0 Hz, 1H), 7.69 (t, J=7.5 Hz, 1H), 7.60–7.63 (m, 1H), 7.56 (s, 1H), 7.45–7.50 (m, 2H), 7.16 (t, J=7.5 Hz, 1H), 7.07 (d, J=8.5 Hz, 1H), 3.90 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 158.4, 149.1, 139.2, 138.3, 132.4, 131.7, 131.4, 129.6, 128.1, 125.8, 125.7, 125.1, 123.0, 121.1, 119.7, 114.8, 31.6. MS (ESI): *m/z* 382.0 (M^++1).

*4.2.6. 4-(3-Bromo-1-methyl-2-oxo-1,2-dihydroquinolin-4-yl)-benzonitrile (**4f**)*

Yield 70%. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.86 (d, J=7.8 Hz, 2H), 7.64 (t, J=7.8 Hz, 1H), 7.46 (d, J=8.3 Hz, 1H), 7.42 (d, J=8.2 Hz, 2H), 7.16 (t, J=8.2 Hz, 1H), 7.02 (d, J=8.2 Hz, 1H), 3.89 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 157.9, 148.4, 141.8, 138.9, 132.6, 131.2, 129.6, 127.6, 122.8, 120.4, 119.0, 118.3, 114.6, 112.7, 31.3. MS (ESI): *m/z* 361.0 (M^++Na). Anal. Calcd for $C_{17}H_{11}BrN_2O$: C, 60.20; H, 3.27; N, 8.26. Found: C, 60.04; H, 3.45; N, 8.01.

*4.2.7. 3-(3-Bromo-1-methyl-2-oxo-1,2-dihydroquinolin-4-yl)-benzonitrile (**4g**)*[14]

Yield 73%. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.82 (d, J=7.5 Hz, 1H), 7.59–7.71 (m, 3H), 7.53 (d, J=7.5 Hz, 1H), 7.47 (d, J=8.5 Hz, 1H), 7.16 (t, J=7.5 Hz, 1H), 7.03 (d, J=8.0 Hz, 1H), 3.90 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 158.2, 148.2, 139.2, 138.8, 133.5, 132.6, 132.5, 131.5, 130.1, 127.9, 123.1, 120.9, 119.9, 118.4, 114.9, 113.5, 31.6. MS (ESI): *m/z* 339.0 (M^++1).

*4.2.8. 4-(3-Acetylphenyl)-3-bromo-1-methylquinolin-2(1H)-one (**4h**)*

Yield 75%. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.11–8.09 (m, 1H), 7.89–7.88 (m, 1H), 7.69–7.51 (m, 2H), 7.50–7.45 (m, 2H), 7.14–7.10 (m, 2H), 3.89 (s, 3H), 2.65 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 197.2, 157.9, 149.2, 138.7, 137.6, 137.3, 133.1, 130.9, 129.0, 128.3, 127.8, 123.1, 120.7, 119.1, 114.3, 31.1, 26.6. MS (ESI): *m/z* 375.0 (M^++Na). Anal. Calcd for $C_{18}H_{14}BrNO_2$: C, 60.69; H, 3.96; N, 3.93. Found: C, 60.92; H, 3.99; N, 3.72.

*4.3. General procedure for the synthesis of 1H-indol-2-yl-(4-aryl)-quinolin-2(1H)-one **1** via Pd-catalyzed Sonogashira coupling and CuI-mediated cyclization*

2-Ethynylaniline (35.1 mg, 0.3 mmol) was added to a mixture of **4** (0.2 mmol), $PdCl_2(PPh_3)_2$ (7 mg, 0.01 mmol), CuI (1.9 mg, 0.01 mmol), and triethylamine (60.6 mg, 0.6 mmol) in DMF (2 mL) under nitrogen atmosphere. The reaction mixture was stirred at 50 °C overnight. After completion of the reaction as indicated by TLC, CuI (38.2 mg, 0.2 mmol) was added to the reaction mixture. After stirring at 160 °C for additional 1 h, the mixture was poured into water (5 mL) and extracted with ethyl acetate (3×5 mL). The organic layer was washed with water (2×10 mL) and brine (2×10 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification by flash column chromatography (silica gel, 2/1 (v/v) petroleum ether/ethyl acetate) gave the desired product **1**.

*4.3.1. 3-(1H-Indol-2-yl)-4-(4-methoxyphenyl)-1-methylquinolin-2(1H)-one (**1a**)*

Yield 79%. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 11.49 (s, 1H), 7.54 (t, J=8.3 Hz, 1H), 7.43 (d, J=8.3 Hz, 1H), 7.35 (t, J=7.8 Hz, 2H), 7.27–7.24 (m, 1H), 7.19–7.076 (m, 6H), 6.97 (t, J=7.8 Hz, 1H), 5.51 (s, 1H), 3.92 (s, 3H), 3.89 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 162.3, 159.7, 146.5, 138.2, 135.0, 133.3, 130.3, 130.1, 129.9, 128.6, 127.4, 122.5, 122.3, 122.2, 120.7, 120.5, 119.3, 114.9, 113.9, 111.2, 106.4, 55.3, 30.3. MS (ESI): *m/z* 403.2 (M^++Na). Anal. Calcd for $C_{25}H_{20}N_2O_2$: C, 78.93; H, 5.30; N, 7.36. Found: C, 78.91; H, 5.40; N, 7.15.

*4.3.2. 3-(1H-Indol-2-yl)-4-(2-methoxyphenyl)-1-methylquinolin-2(1H)-one (**1b**)*

Yield 65%. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 11.53 (s, 1H), 7.56–7.51 (m, 2H), 7.44–7.31 (m, 2H), 7.19–6.93 (m, 8H), 7.04–6.96 (m, 2H), 5.55 (s, 1H), 3.89 (s, 3H), 3.60 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 162.3, 156.7, 143.9, 138.1, 135.0, 133.4, 130.3, 130.2, 130.0, 128.0, 127.5, 126.5, 122.4, 122.1, 121.9, 121.8, 120.9, 120.4, 119.2, 113.9, 111.8, 111.2, 105.1, 55.8, 30.3. MS (ESI): *m/z* 403.2 (M^++Na). Anal. Calcd for $C_{25}H_{20}N_2O_2$: C, 78.93; H, 5.30; N, 7.36. Found: C, 78.56; H, 5.32; N, 7.04.

*4.3.3. 3-(1H-Indol-2-yl)-1-methyl-4-phenylquinolin-2(1H)-one (**1c**)*

Yield 77%. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 11.50 (s, 1H), 7.86–7.83 (m, 1H), 7.55–7.51 (m, 4H), 7.45–7.19 (m, 6H), 7.14–7.08 (m, 2H), 6.95 (t, J=7.3 Hz, 1H), 5.41 (s, 1H), 3.89 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 162.1, 146.5, 138.1, 137.7, 134.9, 133.0, 130.2, 129.4, 129.0, 128.5, 128.4, 127.3, 122.4, 122.3, 122.1, 120.4, 120.3, 119.3, 113.9, 111.2, 106.4, 30.3. MS (ESI): *m/z* 373.2 (M^++Na). Anal. Calcd for $C_{24}H_{18}N_2O$: C, 82.26; H, 5.18; N, 7.99. Found: C, 82.66; H, 4.94; N, 7.80.

*4.3.4. 3-(1H-Indol-2-yl)-1-methyl-4-(4-(trifluoromethyl)-phenyl)quinolin-2(1H)-one (**1d**)*

Yield 75%. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 11.40 (s, 1H), 7.82 (d, J=8.2 Hz, 2H), 7.57–7.55 (m, 1H), 7.46–7.28 (m, 5H), 7.17–6.95 (m, 4H), 5.35 (s, 1H), 3.89 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 161.9, 144.7, 141.6, 138.2, 135.1, 132.5, 130.8, 130.5, 129.8, 127.9, 127.2, 126.5, 126.4, 122.7, 122.6, 121.5, 120.6, 120.5, 119.5, 114.1, 111.2, 106.6, 30.4. MS (ESI): *m/z* 441.1 (M^++Na). Anal. Calcd for $C_{25}H_{17}F_3N_2O$: C, 71.76; H, 4.10; N, 6.70. Found: C, 71.30; H, 4.17; N, 6.46.

*4.3.5. 3-(1H-Indol-2-yl)-1-methyl-4-(3-(trifluoromethyl)-phenyl)-quinolin-2(1H)-one (**1e**)*

Yield 68%. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 11.45 (s, 1H), 7.61–7.56 (m, 2H), 7.48–7.11 (m, 9H), 6.97 (t, J=

8.0 Hz, 1H), 5.40 (s, 1H), 3.91 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 161.9, 150.0, 144.4, 139.7, 138.2, 135.1, 132.5, 131.1, 130.0, 128.0, 127.7, 127.3, 122.7, 122.6, 122.1, 121.6, 120.9, 120.5, 119.5, 114.1, 111.2, 106.6, 30.4. MS (ESI): *m/z* 457.1 (M^++K). Anal. Calcd for $C_{25}H_{17}F_3N_2O$: C, 71.76; H, 4.10; N, 6.70. Found: C, 71.81; H, 4.28; N, 6.40.

*4.3.6. 4-(3-(1H-Indol-2-yl)-1-methyl-2-oxo-1,2-dihydroquinolin-4-yl)benzonitrile (**1f**)*

Yield 80%. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 11.35 (s, 1H), 7.83 (d, *J*=7.8 Hz, 2H), 7.58 (t, *J*=7.7 Hz, 1H), 7.47–7.6.96 (m, 9H), 5.35 (s, 1H), 3.88 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 161.7, 144.1, 142.8, 138.2, 135.1, 133.1, 132.2, 130.6, 130.4, 127.6, 127.1, 122.8, 122.7, 121.0, 120.6, 120.5, 119.7, 118.4, 114.2, 112.4, 111.3, 106.7, 30.4. MS (ESI): *m/z* 398.2 (M^++Na). Anal. Calcd for $C_{25}H_{17}N_3O$: C, 79.88; H, 4.56; N, 11.19. Found: C, 79.47; H, 4.59; N, 10.95.

*4.3.7. 3-(3-(1H-Indol-2-yl)-1-methyl-2-oxo-1,2-dihydroquinolin-4-yl)benzonitrile (**1g**)*

Yield 78%. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 11.40 (s, 1H), 7.86–7.83 (m, 1H), 7.67–7.45 (m, 5H), 7.37 (d, *J*=8.2 Hz, 1H), 7.30 (d, *J*=8.2 Hz, 1H), 7.16–7.11 (m, 2H), 7.04–6.96 (m, 2H), 5.30 (s, 1H), 3.89 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 161.7, 143.5, 139.2, 138.2, 135.1, 134.0, 132.9, 132.3, 132.2, 130.6, 130.4, 127.6, 127.2, 122.8, 122.7, 121.3, 120.9, 120.5, 119.7, 118.2, 114.3, 113.7, 111.3, 106.7, 30.4. MS (ESI): *m/z* 398.2 (M^++Na). Anal. Calcd for $C_{25}H_{17}N_3O$: C, 79.88; H, 4.56; N, 11.19. Found: C, 79.51; H, 4.24; N, 10.73.

*4.3.8. 4-(3-Acetylphenyl)-3-(1H-indol-2-yl)-1-methylquinolin-2(1H)-one (**1h**)*

Yield 74%. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 11.50 (s, 1H), 8.15 (d, *J*=8.0 Hz, 1H), 7.91 (s, 1H), 7.68–7.24 (m, 6H), 7.14–7.09 (m, 3H), 6.95 (t, *J*=8.0 Hz, 1H), 5.34 (s, 1H), 3.91 (s, 3H), 2.60 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 197.5, 162.0, 145.2, 138.3, 138.2, 138.1, 135.1, 134.0, 132.8, 130.4, 129.9, 129.2, 128.3, 128.1, 127.2, 122.6, 122.5, 121.8, 120.6, 120.4, 119.5, 114.1, 111.2, 106.6, 30.4, 26.7. MS (ESI): *m/z* 415.2 (M^++Na). Anal. Calcd for $C_{26}H_{20}N_2O_2$: C, 79.57; H, 5.14; N, 7.14. Found: C, 79.61; H, 4.87; N, 6.85.

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