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KO^{t}Bu promoted access to indolyl quinazolinones and intramolecular Mitsunobu annulation to rutaecarpine analogues

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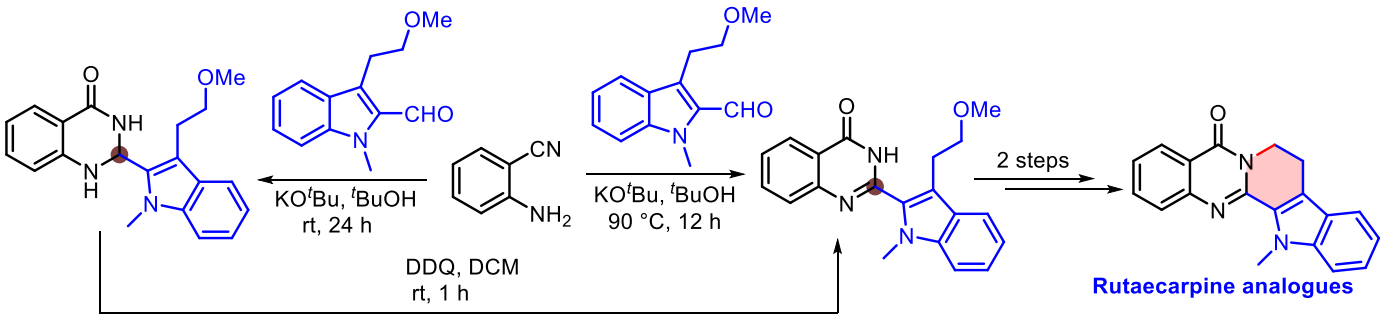
Abstract

We report a KO^{t}Bu promoted, temperature-divergent synthesis of indole-linked dihydroquinazolinones and quinazolinones from 2-aminobenzonitriles and indole-2-carbaldehydes in ^{t}BuOH. At room temperature, indolyl dihydroquinazolinones are selectively formed, whereas heating to 90 °C enables direct one-pot access to quinazolinones via cyclization followed by aerial oxidation. The dihydroquinazolinones can also be oxidized to quinazolinones using DDQ under mild conditions. Subsequent BBr_3-mediated demethylation and intramolecular Mitsunobu cyclization furnish rutaecarpine analogues in two steps. The method tolerates electron-donating and halogen substituents and is further applicable to the synthesis of natural product bouchardatine precursor and a carbazole-linked quinazolinone. This operationally simple strategy enables rapid access to diverse indoloquinazolinone frameworks relevant to natural product synthesis and medicinal chemistry.



Keywords: 2-aminobenzonitriles, indole-2-carbaldehydes, indolodihydroquinazolinones, indoloquinazolinones, Mitsunobu cyclization, rutaecarpine analogues

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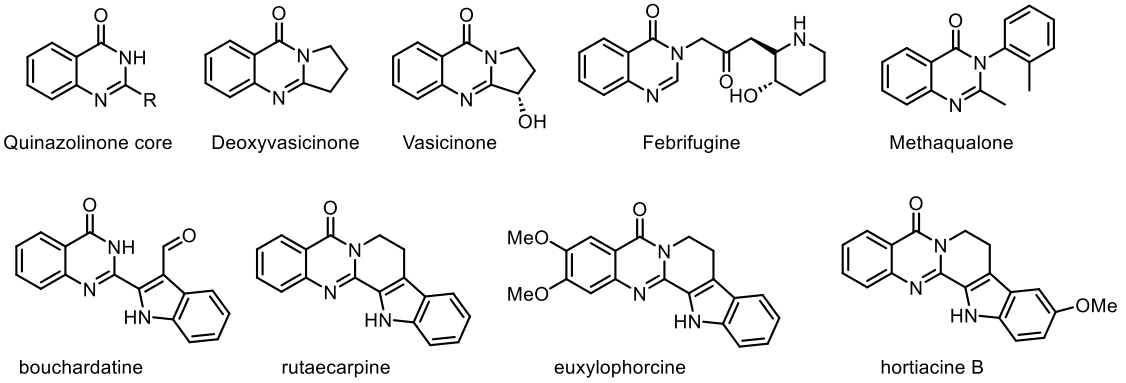
Introduction

Quinazolinone **A** is a key component of over 250 naturally occurring alkaloids found in various plant families, marine sources, and microorganisms. Some quinazolinone core containing natural products are listed in scheme 1, including deoxyvasicinone and vasicinone.[1] Subsequently, a wide range of quinazolinone containing natural products have been identified, isolated, characterized, and synthesized. The first synthetic quinazolinone compound, 2-cyanoquinazolinone, was synthesized in the late 1860s via the reaction between anthranilic acid and cyanogens.[2,3] The potential of quinazolinone derivatives in medicinal chemistry came to light in the 1950s, following the discovery of the quinazolinone alkaloid febrifugine, from the Asian plant *Dichroa febrifuga*,[4] a traditional Chinese herbal remedy effective against malaria. This discovery inspired the synthesis of new medicines, including methaqualone, a widely recognized synthetic quinazolinone drug known for its powerful sedative and hypnotic effects.[5] Quinazolinones and their derivatives exhibit a broad spectrum of biological activities, including hypnotic, sedative, pain-relieving, anti-seizure, cough-suppressing, antibacterial, anti-diabetic, anti-inflammatory, anti-tumour, and various other valuable properties.[6] For instance, the dried fruit of *Evodia rutaecarpa*, used in traditional Chinese medicine, is a rich source of quinazolinone alkaloids and has been historically employed to treat headaches, dysentery, cholera, parasitic infections, and postpartum complications.[7] Quinazolinone alkaloids, especially rutaecarpine and euxylophorcine,[8] which exhibit extensive pharmacological effects, including analgesic, anti-hypertensive, anti-emetic, uterotonic, and COX-2 inhibitory actions[9-14] that are pivotal in anti-inflammatory drug development. Further, studies on rutaecarpine have shown it can prevent platelet plug formation in mesenteric venules and increase intracellular Ca^{2+} levels in endothelial cells,[15-17] suggesting its potential in thrombosis prevention and vascular health improvement.



Scheme 1. Quinazolinone containing natural products.

Consequently, the synthesis of quinazolinone and related natural products has drawn a lot of interest for organic and medicinal chemists. Scheme 2 presents some key methodologies for synthesizing quinazolinone derivatives.[18-23] In 2011, Fu et al. reported a copper-catalyzed approach for synthesizing quinazolinone **3,** readily available starting materials 2-halobenzamide **1** and 2-arylmethanamine **2** (Scheme 2a).[18] In 2013, Chiba and colleagues developed an innovative oxygen-mediated method in DMSO at elevated temperature, enabling efficient formation of substituted quinazolinone **5** through an oxidative radical rearrangement of 5-aryl-4,5-dihydro-1,2,4-oxadiazoles **4** (Scheme 2b).[19] That same year, two new methodologies for quinazolinone synthesis were introduced. Deng developed a method for synthesizing 2,3-diarylquinazolinones using 1,1'-bis(diphenylphosphino)ferrocene as a catalyst. This process involves the reaction of 2-nitrobenzamides **6** with

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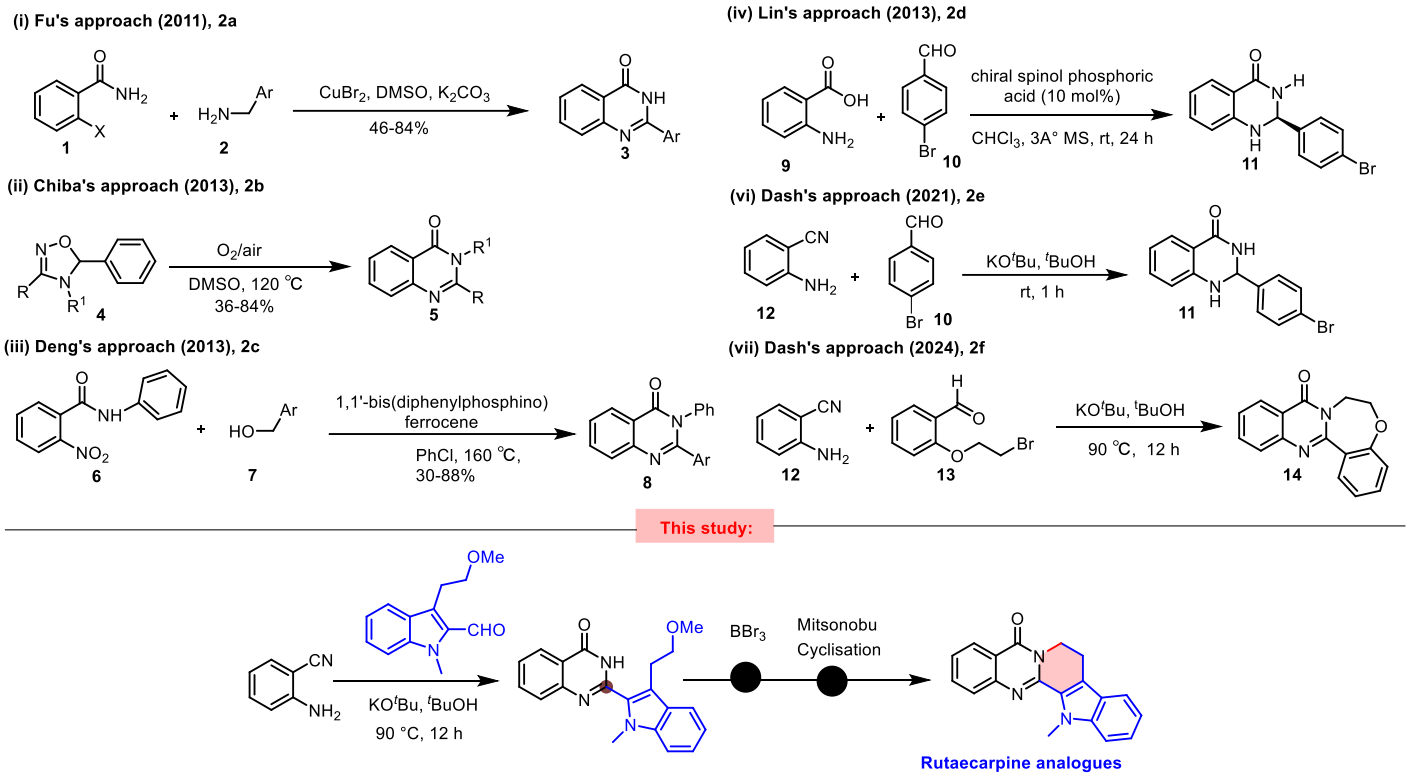
alcohols **7** in chlorobenzene solvent at high temperatures, where the nitro group is reduced to form the quinazolinone core (Scheme 2c).[20] Lin et al. reported an asymmetric synthesis of dihydroquinazolinone **11** using anthranilic acid **9**, 4-bromobenzaldehyde **10** and a chiral SPINOL catalyst (Scheme 2d).[21] In 2021, we achieved synthesis of dihydroquinazolinone **11** with excellent yields using KO^{t}Bu as a base from 2-aminobenzonitrile **16** and 4-bromobenzaldehyde **10** as starting materials (Scheme 2e).[22] Building on this methodology, we further synthesized quinazolinobenzoxazepine analogues **14** in one step with good yields (Scheme 2f).[23]



Scheme 2. Previously reported approaches to quinazolinone synthesis and current study.

In this work, we explore the synthesis of the indole ring-linked quinazolinone core (Scheme 2), a fundamental unit of bouchardatine and rutaecarpine, using readily available starting materials. Our approach employs KO^{t}Bu as a base to yield two distinct outcomes: at room temperature, it generates indole ring-linked dihydroquinazolinones **20** from the substituted indole-2-carbaldehyde **19** and 2-aminobenzonitrile **12**; while at 90 °C, the reaction produces indole ring-linked quinazolinones **21**. Moreover, we demonstrate the oxidation of dihydroquinazolinone analogues **20** to quinazolinones **21** using DDQ as the oxidant. This methodology further enabled the efficient construction of rutaecarpine analogues **23** from quinazolinones **21** in just two straightforward steps involving demethylation and intramolecular Mitsunobu cyclization.

Results and Discussion

First, aldehyde **19** was synthesized from indole-3-carbaldehyde **15** by a sequence of reactions. N-methylation of **15** using NaH/ MeI,[24] followed by Wittig olefination of the resulting compound **16** using methoxymethyl

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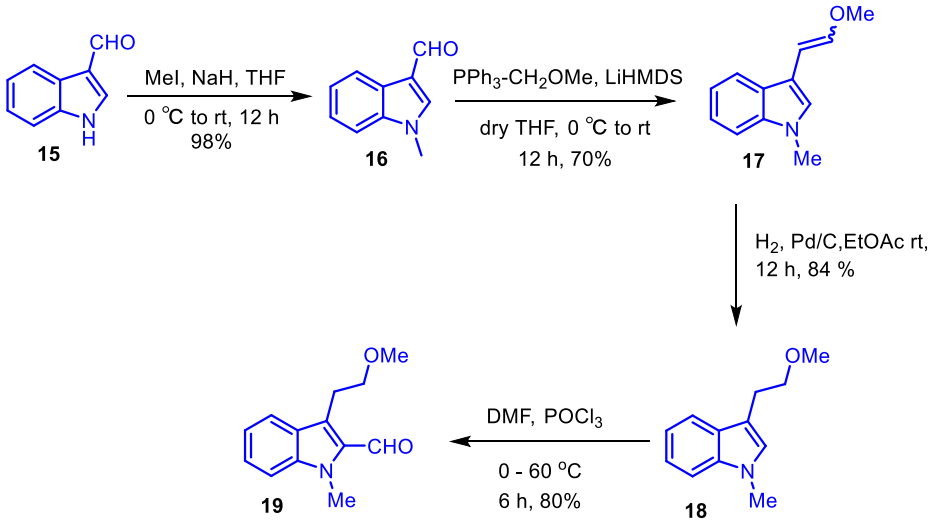
triphenylphosphine chloride in the presence of LiHMDS produced compound **17,** which was subsequently hydrogenated using Pd/C to give 3-(2-methoxyethyl)-1-methyl indole **18**. Compound **18** was then subjected to a Vilsmeier–Haack reaction using DMF/$POCl_3$ to afford the substituted indole-2-carbaldehyde **19** in an overall good yield of 46% over four steps (Scheme 3).



Scheme 3. Synthesis of substituted indole-2-carbaldehyde **19**.

Next, we planned to synthesize dihydroquinazolinones **20** from 2-aminobenzonitrile **12** and aldehyde **19**. Dihydroquinazolinone **20a** was successfully synthesized in 76% yield by the reaction of 2-aminobenzonitrile **12a** with substituted indole-2-carbaldehyde **19** in ^{t}BuOH at room temperature for 24 h (Scheme 4).

2-Aminobenzonitrile **12b** containing an electron donating group, provided the corresponding dihydroquinazolinone **20b** in an excellent yield of 79% (Scheme 3). Similarly, halogen-substituted 2-aminobenzonitriles **12c** and **12d** underwent the reaction smoothly to afford the corresponding dihydroquinazolinones **20c** and **20d** in 68% and 74%, respectively (Scheme 4). These results suggest that the electronic nature of substituents do not significantly impact on reactivity. Furthermore, oxidation of dihydroquinazolinones **20a–d** with DDQ in DCM efficiently furnished the corresponding quinazolinones **21a–d** in good yields (Scheme 4).

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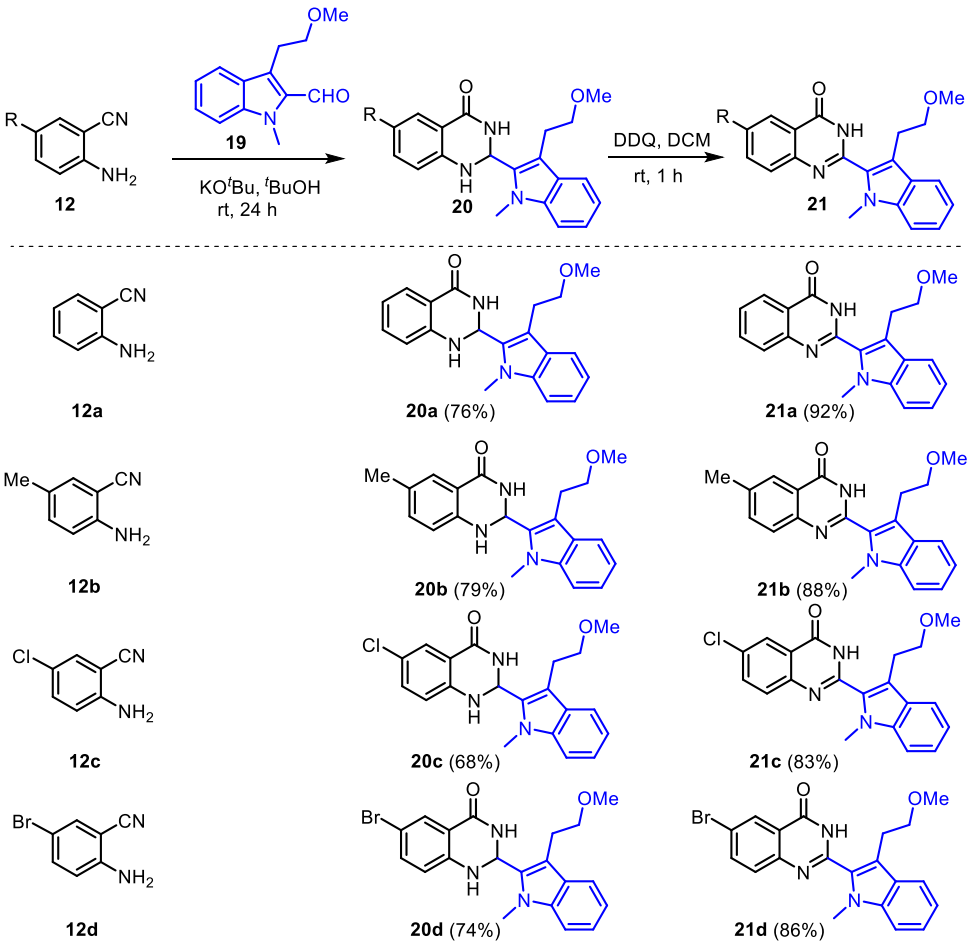

[a]Reaction conditions: 2-Aminobenzonitrile analogues **12** (1 equiv), methoxyethyl-substituted indole-2-carbaldehyde **19** (1.2 equiv) and KO^{t}Bu (2 equiv) were stirred in ^{t}BuOH solvent at room temperature for 24 h. [b]Dihydroquinazolinones **20** and DDQ (1.2 equiv) were stirred in CH_2Cl_2 (DCM) solvent at room temperature for 1 h. [c]Isolated yields.

Scheme 4. Synthesis of dihydroquinazolinones **20a-d**[a,c] and quinazolinones **21a-d**.[b,c]

Interestingly, a different outcome was observed when a mixture of 2-aminobenzonitrile **12a**, substituted indole-2-carbaldehyde **19**, and KO^{t}Bu was heated at 90 °C, leading to the formation of quinazolinone **21a**. At room temperature, stirring the reaction mixture for 1 h in the presence of KO^{t}Bu did not afford the desired product (Table 1, entry 1). Extending the reaction time to 12 h at room temperature resulted in only 20% yield of **21a** (Table 1, entry 2). Increasing the reaction temperature to 45 °C and 60 °C improved the yield of the desired quinazolinone **21a** to 42% and 56%, respectively (Table 1, entry 3 and 4). Further increasing the temperature to 90 °C furnished quinazolinone **21a** in 68% yield (Table 1, entry 6). In contrast, when the reaction was conducted under an argon atmosphere, the yield of **21a** decreased markedly to 32%, compared to 68% under open-air conditions (Table 2). These observations suggest that elevated temperature and open-air conditions facilitate the aerobic oxidation of the intermediate dihydroquinazolinone **20a**, leading to the formation of quinazolinone **21a**.[25]

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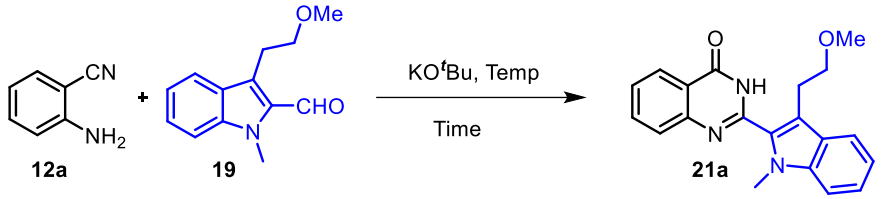
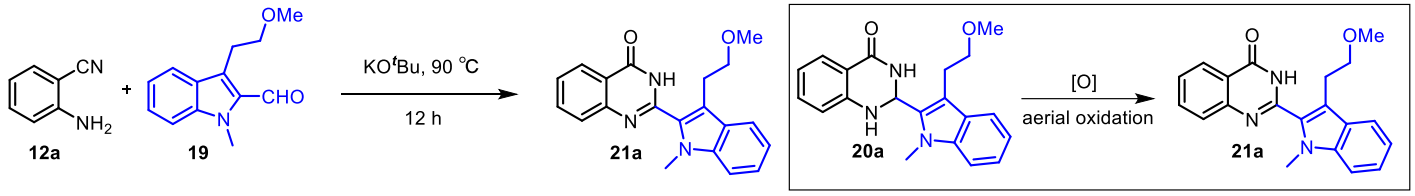
Table 1. Optimization of reaction conditions[a]



Entry	Temperature	Time (h)	Yield (%)[b,c]
1	rt	1	NR
2	rt	12	20
3	45 °C	12	42
4	60 °C	12	56
5	90 °C	12	68

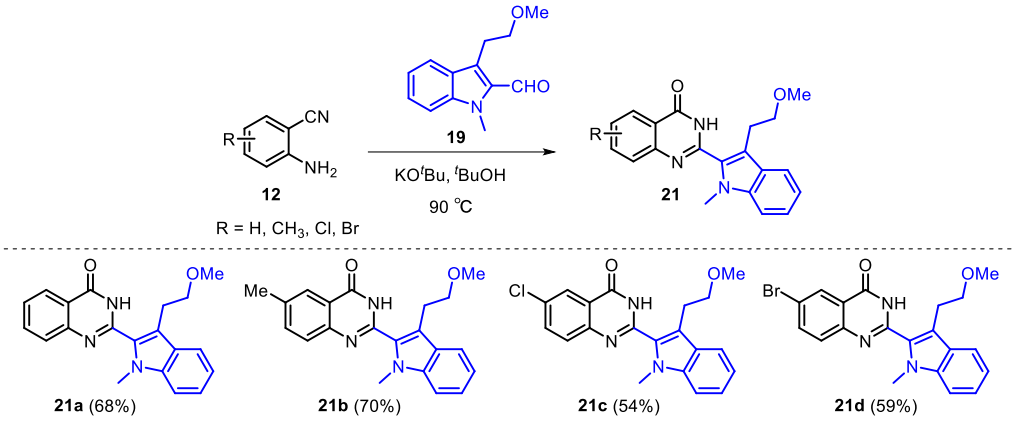
[a] Reaction conditions: compound **12a** (1 equiv), **19** (1.2 equiv), KO^{t}Bu (2 equiv), ^{t}BuOH (4 mL); [b] Isolated yields; [c] NR: No reaction

Table 2. Optimization of reaction conditions[a]



Entry	Reaction Conditions	Time (h)	Yield (%)[b,c]
1	under argon atmosphere	12	32
2	air	12	**68**

[a] Reaction conditions: compound **12a** (1 equiv), **19** (1.2 equiv), KO^{t}Bu (2 equiv), ^{t}BuOH (4 mL) stirred at 90 °C; [b] Isolated yields



[a] Reaction conditions: 2-Aminobenzonitriles **12** (1 equiv), methoxyethyl-substituted indole-2-carbaldehyde **19** (1.2 equiv), and KO^{t}Bu (2 equiv) were stirred in ^{t}BuOH solvent at 90 °C for 12 h. [b] Isolated yields.

Scheme 5. Synthesis of quinazolinones.[a,b]

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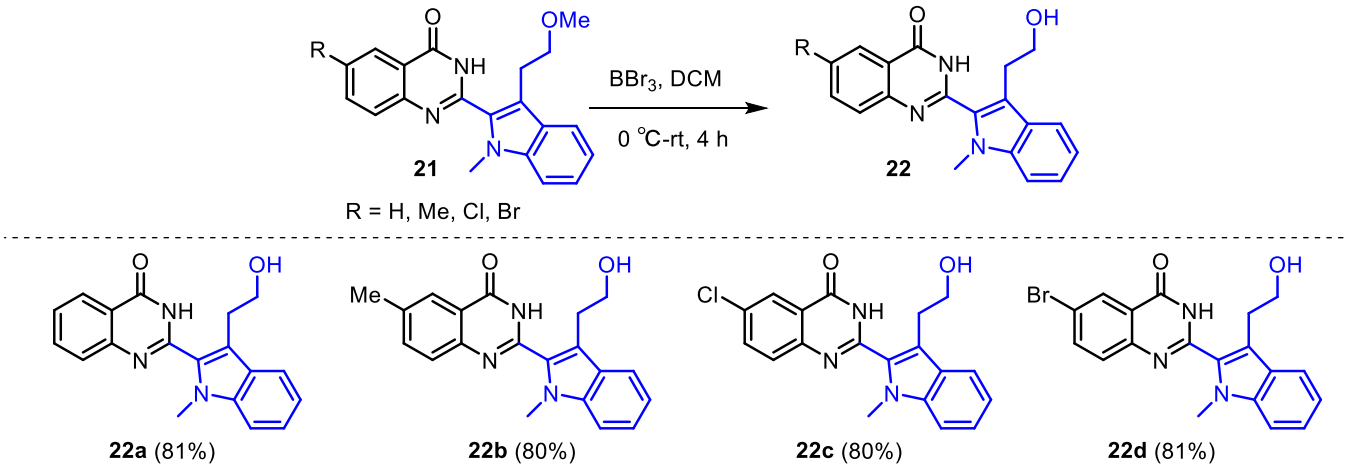
After establishing the optimized conditions, the substrate scope was expanded by incorporating 2-aminobenzonitrile analogues **12** and indole-2-carbaldehyde **19**. 2-Aminobenzonitrile **12b,** which contains an electron donating group, provided the corresponding quinazolinone **21b** in high yield (70%) (Scheme 5). While 2-aminobenzonitriles **12c-d,** bearing halogen substituents (Cl, Br) furnished the desired quinazolinone products **21c** and **21d** in moderate yields of 54% and 59% respectively (Scheme 5). This method enabled a two-step process in a single reaction vessel, where dihydroquinazolinone formation and subsequent aerial oxidation occurred sequentially.

We then proceeded to construct natural product rutaecarpine analogues **23** by further transforming indolyl quinazolinones **21** through a two-step process. The first step involved BBr_3-mediated demethylation of the OMe group (Scheme 6), followed by intramolecular Mitsunobu cyclization in the second step (Scheme 7). Quinazolinone analogues **21a-d** were transformed into the corresponding 2-hydroxyethyl derivatives **22a-d**, using BBr_3 (1M in DCM) at room temperature, as shown in scheme 6.



[a] Reaction conditions: Quinazolinone analogues **21a-d** (1 equiv) and BBr_3 (1.5 equiv, 1M in DCM) were stirred at room temperature in DCM solvent for 4 h.[b] Isolated yields.

Scheme 6. Demethylation of quinazolinones **21**.[a,b]

Next, natural product rutaecarpine analogues **23a-d** were constructed from compounds **22a-d** through an intramolecular Mitsonobu reaction using PPh_3/DIAD system.[26,27] The reaction conditions were optimized by varying temperature and reaction time (Table 3). 13-Methyl rutaecarpine **23a** was obtained in 80% yield at room temperature after 1 h (Table 3, entry 1). Under these conditions, 13-methyl rutaecarpines **23b-d** were also obtained in very high yields (Scheme 7). The halo substituents in rutaecarpines **23c** and **23d** offer versatile handle for further functionalization, such as cross-coupling reactions or other modifications to enhance the properties or bio-activity of the molecules.

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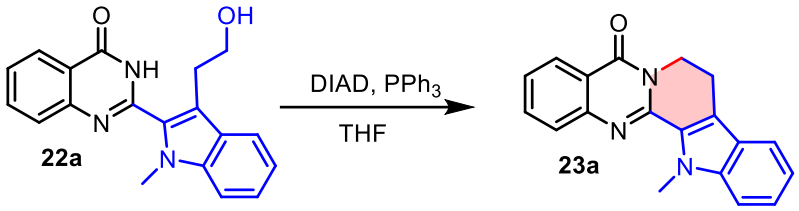
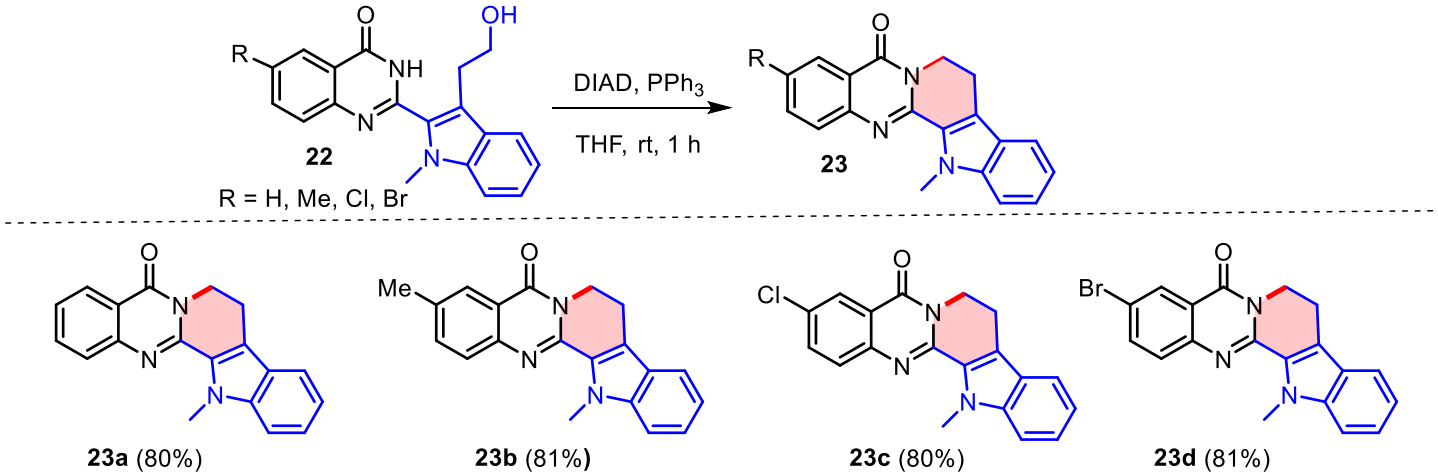
Table 3. Optimization of Mitsonobu cyclization of **22a** to **23a**



Entry	Temperature	Time	Yield (%) [a, b]
1	**rt**	**1 h**	**80**
2	rt	12 h	80
3	60 °C	1 h	34
4	60 °C	12 h	52

[a] Reaction conditions: compound **22a** (1 equiv), **PPh3** (2.3 equiv), **DIAD** (2.3 equiv) and THF solvent (10 mL).
[b]Isolated yields.



[a]Reaction conditions: Hydroxyethyl-substituted indolyl quinazolinone analogues **22a-d** (1 equiv), PPh_3 (2.3 equiv), DIAD (2.3 equiv), and THF (10 mL) were stirred at room temperature for 1 h.
[b] Isolated yields.

Scheme 7. Construction of rutaecarpine analogues.[a,b]

The reaction of indole-2-carbaldehyde **24** with 2-aminobenzonitrile **12a** in presence of KO^{t}Bu base at 90 °C resulted in the formation of quinazolinone **25** in 62% yield (Scheme 8). This quinazolinone **25** serves as a precursor to the natural product bouchardatine.[28] Given that carbazole derivatives are known to exhibit a broad spectrum of biological activities, including potent anticancer properties,[29,30] we explored the applicability of the protocol toward the synthesis of a carbazole-containing quinazolinone. Accordingly, reaction of 2-aminobenzonitrile **12a** with 9-methyl-9H-carbazole-3-carbaldehyde **26** in the presence of KO^{t}Bu at 90 °C for 12 h efficiently furnished the carbazole-linked quinazolinone **27** in 60% yield.

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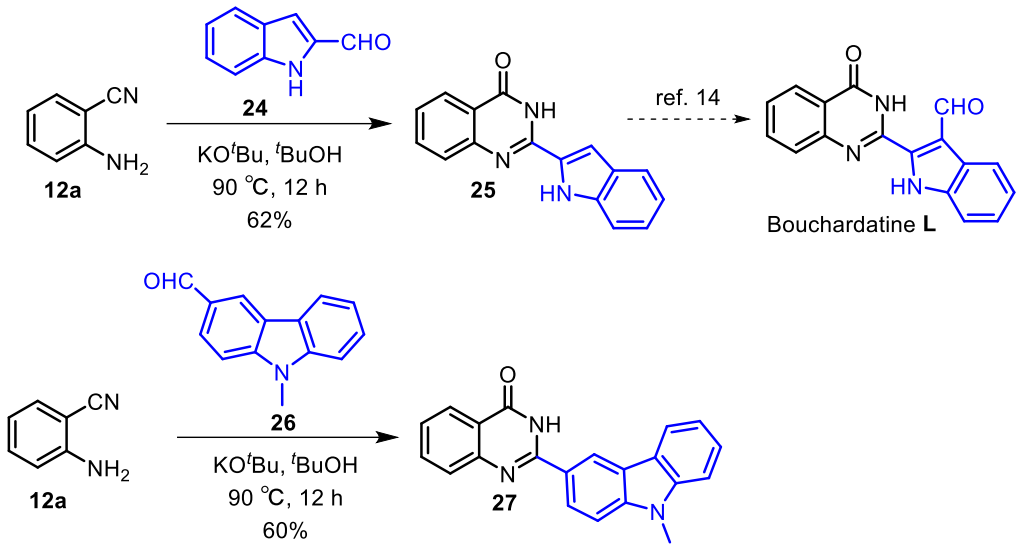

[a] Reaction conditions: 2-Aminobenzonitrile **12a** (1 equiv), indole-2-carbaldehyde **24** (1 equiv), KO^{t}Bu (2 equiv) and ^{t}BuOH (5 mL) were stirred at 90 °C for 12 h. [b] Reaction conditions: 2-Aminobenzonitrile **12a** (1 equiv), 9-methyl-9H-carbazole-3-carbaldehyde **26** (1 equiv), KO^{t}Bu (2 equiv) and ^{t}BuOH (5 mL) were stirred at 90 °C for 12 h.

Scheme 8. Synthesis of indoloquinazolinone.[a,b]

Conclusions

In conclusion, we have established efficient and complementary protocols for the synthesis of indole-linked quinazolinones frameworks through KO^{t}Bu-promoted reactions of 2-aminobenzonitriles with substituted indole-2-carbaldehydes. Product formation is controlled by reaction temperature; room temperature affords dihydroquinazolinones, while heating enables direct formation of quinazolinones through cyclization and aerial oxidation. The dihydroquinazolinones can also be smoothly oxidized to quinazolinones using DDQ, providing additional synthetic flexibility. The quinazolinone products were further elaborated into rutaecarpine analogues via sequential demethylation and intramolecular Mitsunobu cyclization. The method was successfully applied to the synthesis of a bouchardatine precursor and a carbazole-linked quinazolinone. The protocol exhibits broad functional group tolerance and affords the desired products in good yields under operationally simple conditions. Overall, this practical approach offers a reliable route to structurally diverse indoloquinazolinone frameworks of significance in natural product synthesis and medicinal chemistry.

Experimental Section

General. All solvents and reagents were purified by standard techniques or used as supplied from commercial sources. All reactions were generally carried out under inert/ open-air atmosphere unless otherwise noted. TLC was performed on Kieselgel 60 F254 plates, and spots were visualized under UV light. Products were purified by column chromatography on silica gel (100-200 mesh). ^{1}H and ^{13}C NMR spectra were recorded on 600 (600 MHz and 176 MHz), 500 (500 MHz and 126 MHz), 400 (400 MHz and 101 MHz), or 300 (300 MHz and

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76 MHz) instruments using deuterated solvents as detailed and at ambient probe temperature (300 K). Chemical shifts are reported in parts per million (ppm) relative to the residual solvent peak (Chloroform-*d*, 7.26 ppm for ^{1}H NMR and 77.2 ppm for ^{13}C{^{1}H} NMR; DMSO-d_6, 2.50 ppm for ^{1}H NMR, 39.6 ppm for ^{13}C{^{1}H} NMR). The following notations are used: singlet (s); doublet (d); triplet (t); quartet (q); multiplet (m); broad (br). Coupling constants are quoted in Hertz and are denoted as *J*. Mass spectra were recorded on a Micromass® Q-Tof (ESI) spectrometer.

1-Methyl-1*H*-indole-3carbaldehyde (16). To a solution of sodium hydride 60% in parafin oil (3 g, 75 mmol, 2.5 equiv) in dry THF at 0 ℃ under an argon atmosphere, indole-3-carbaldehyde **15** (5 g, 30 mmol, 1 equiv) was added pinch wise for 20 minutes. The solution was stirred for 30 minutes and then methyl iodide (2.4 mL, 39 mmol, 1.3 equiv) was added dropwise over 5 minutes. The mixture was stirred for 12 h at room temperature. The reaction mixture was quenched with cold water. THF was removed in vacuo and the resultant mixture was extracted with EtOAc (3 x 50 mL), washed with water, brine, dried (Na_2SO_4), filtered and concentrated in *vacuo*. The crude residue was then purified by column chromatography on silica gel with ethylacetate–hexane (20: 80) to obtain **16** (4.7 g, 98%) as a reddish oil.

(*E*), (*Z*)-3-(2-Methoxyvinyl)-1-methyl-1*H*-indole (17). To a suspension of methoxymethyl triphenylphosphine chloride (12.5 g, 47 mmol, 1.2 equiv) in dry THF at 0 ℃ under an argon atmosphere, 1.0 M solution of LiHMDS (38.6 mL, 51 mmol, 1.3 equiv) was added dropwise. The resulting dark red solution was stirred for 30 minutes at 0 ℃. A solution of compound **16** (4.7 g, 29.5 mmol, 1 equiv) in THF was then added dropwise to the mixture at 0 ℃ over 15 minutes. The mixture was stirred 16 h at room temperature. The reaction mixture was quenched with saturated solution of NH_4Cl and again stirred for 15 minutes. The aqueous phase was extracted with EtOAc (3 x 50 mL), washed with water, brine, dried Na_2SO_4, filtered and concentrated in *vacuo*. The crude residue was purified by column chromatography on silica gel with ethylacetate-hexane (4:96) to obtain **17** [3.9 g, 70%, E and Z inseparable mixture (1:1)] as a yellowish oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.87 – 7.80 (m, 2H), 7.69 – 7.65 (m, 1H), 7.39 (s, 4H), 7.29 (s, 2H), 7.22 – 7.16 (m, 1H), 7.01 (s, 1H), 6.26 (dd, *J* = 6.5, 1.9 Hz, 1H), 6.14 (dt, *J* = 12.3, 3.7 Hz, 1H), 5.75 (dd, *J* = 9.6, 4.8 Hz, 1H), 3.92 (d, *J* = 3.8 Hz, 3H), 3.84 (d, *J* = 6.5 Hz, 6H), 3.77 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 146.7, 144.6, 137.4, 136.3, 128.5, 127.2, 126.3, 125.3, 121.8, 121.6, 119.8, 119.2, 119.0, 118.8, 110.9, 109.9, 109.4, 109.1, 97.8, 97.1, 60.2, 56.5, 32.7, 32.5; HRMS (ESI) calcd for $C_{12}H_{14}NO$ [M + H^{+}] : 188.1075, found : 188.1073.

3-(2-Methoxyethyl)-1-methyl-1*H*-indole (18). To a solution of compound **17** (3.9 g, 20.8 mmol, 1 equiv) in ethyl acetate (15 mL), 10% Pd/C (390 mg, 1 equiv) was added. The solution was stirred for 12 h in the presence of hydrogen gas. The reaction mixture was then filtered over a pad of celite. The filtrate was concentrated and the residue was purified by column chromatography on silica gel with ethylacetate- hexane (8:92) to obtain **18** (3.3 g, 84%) as a yellowish oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.66 (d, *J* = 7.8 Hz, 1H), 7.33 (d, *J* = 8.4 Hz, 1H), 7.27 (t, *J* = 7.5 Hz, 1H), 7.18 – 7.14 (m, 1H), 6.95 (s, 1H), 3.77 (s, 3H), 3.73 (t, *J* = 7.1 Hz, 2H), 3.45 (s, 3H), 3.09 (t, *J* = 7.1 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 137.1, 128.1, 126.9, 121.6, 119.0, 118.8, 111.6, 109.3, 73.2, 58.7, 32.6, 25.7; HRMS (ESI) calcd for $C_{12}H_{16}NO$ [M + H^{+}] : 190.1266, found: 190.1264.

3-(2-Methoxyethyl)-1-methyl-1*H*-indole-2-carbaldehyde (19). In a 50 mL two neck round bottom flask, 5 mL dry DMF was added and cooled to 0 ℃ under an argon atmosphere. Next, 5 mL dry $POCl_3$ was added to the solution and the reaction mixture was stirred for 20 minutes until the solution became red colour. Subsequently, a solution of compound **18** (3.3 g, 17.4 mmol, 1 equiv) in dry DMF was added dropwise to this reaction mixture. The solution was stirred for 6 h at 60 ℃. After confirming the product formation by TLC, the reaction mixture was added to an ice-cold solution of $NaHCO_3$, and the solution was stirred for 1 h. The aqueous phase was extracted with ethyl acetate (3 x 50 mL), washed with water, brine, dried (Na_2SO_4) and

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concentrated in *vacuo*. The crude residue was purified by column chromatography on silica gel with ethylacetate- hexane (8:92) to obtain **19** (2.8 g, 80%) as a yellowish oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.14 (s, 1H), 7.73 (d, *J* = 8.1 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.35 (d, *J* = 8.5 Hz, 1H), 7.16 (t, *J* = 7.4 Hz, 1H), 4.06 (s, 3H), 3.64 (t, *J* = 6.9 Hz, 2H), 3.35 (t, *J* = 6 Hz, 2H), 3.34 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, Chloroform-*d*) δ 182.2, 139.9, 131.9, 127.3, 127.1, 126.4, 121.3, 120.4, 110.4, 73.2, 58.9, 31.7, 24.6; HRMS (ESI) calcd for $C_{13}H_{16}NO_2$ [M + Na$^+$]: 240.1000, found: 240.1000.

2-(3-(2-Methoxyethyl)-1-methyl-1*H*-indol-2-yl)-2,3-dihydroquinazolin-4(1*H*)-one (20a). To a mixture of 2-aminobenzonitrile **12a** (120 mg, 1 mmol, 1 equiv) and aldehyde **19** (261 mg, 1.2 mmol, 1.2 equiv) in ^{t}BuOH (4 mL), KO^{t}Bu (224 mg, 2 mmol, 2 equiv) was added. The mixture was stirred in a reaction tube for 24 h at room temperature and the progress of reaction was monitored by TLC. After completion of the reaction, the mixture was diluted by an aq. $KHSO_4$ solution and extracted with EtOAc (3 X 15 mL). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was then purified by column chromatography on silica gel with ethylacetate–hexane (40:60) to obtain **20a** (255 mg, 76%) as a yellow solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.97 (d, *J* = 7.6 Hz, 1H), 7.57 (d, *J* = 7.9 Hz, 1H), 7.37 – 7.29 (m, 3H), 7.15 (t, *J* = 7.4 Hz, 1H), 6.91 (t, *J* = 7.5 Hz, 1H), 6.68 (d, *J* = 8.0 Hz, 1H), 6.38 (s, 1H), 5.90 (s, 1H), 4.67 (s, 1H), 4.02 (s, 3H), 3.53 (ddd, *J* = 6.8, 5.6, 3.3 Hz, 2H), 3.30 (s, 3H), 3.06 (td, *J* = 6.8, 6.0, 3.8 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, Chloroform-*d*) δ 165.4, 148.0, 138.3, 134.2, 131.1, 129.0, 126.4, 123.4, 119.9, 119.7, 119.1, 115.8, 115.0, 113.8, 109.7, 72.7, 62.0, 58.9, 32.1, 24.8; HRMS (ESI) calcd for $C_{20}H_{21}N_3O_2$ [M + H$^+$] : 336.1707, found : 336.1713.

2-(3-(2-Methoxyethyl)-1-methyl-1*H*-indol-2-yl)-6-methyl-2,3-dihydroquinazolin-4(1*H*)-one (20b). To a mixture of 2-amino-5-methylbenzonitrile **12b** (134 mg, 1 mmol, 1 equiv) and aldehyde **19** (261 mg, 1.2 mmol, 1.2 equiv) in ^{t}BuOH (4 mL), KO^{t}Bu (224 mg, 2 mmol, 2 equiv) was added. The mixture was stirred in a reaction tube for 24 h at room temperature and the progress of reaction was monitored by TLC. After completion of the reaction, the mixture was diluted by an aq. $KHSO_4$ solution and extracted with EtOAc (3 X 15 mL). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was then purified by column chromatography on silica gel with ethylacetate–hexane (30:70) to obtain **20b** (276 mg, 79%) as a yellow solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.80 (s, 1H), 7.57 (d, *J* = 7.9 Hz, 1H), 7.36 (d, *J* = 8.3 Hz, 1H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.16 (q, *J* = 7.6, 7.0 Hz, 2H), 6.61 (d, *J* = 8.1 Hz, 1H), 6.34 (s, 1H), 5.87 (s, 1H), 4.52 (s, 1H), 4.03 (s, 3H), 3.55 – 3.50 (m, 2H), 3.30 (s, 3H), 3.06 (dd, *J* = 6.6, 4.4 Hz, 2H), 2.32 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, Chloroform-*d*) δ 165.6, 145.8, 138.3, 135.1, 131.2, 129.4, 128.9, 126.4, 123.3, 119.7, 119.1, 115.8, 115.1, 113.7, 109.7, 72.7, 62.2, 58.9, 32.1, 24.8, 20.6; HRMS (ESI) calcd for $C_{21}H_{23}N_3O_2$ [M + H$^+$] : 350.1869, found : 350.1875.

6-Chloro-2-(3-(2-methoxyethyl)-1-methyl-1*H*-indol-2-yl)-2,3-dihydroquinazolin-4(1*H*)-one (20c). To a mixture of 2-amino-5-chlorobenzonitrile **12c** (154 mg, 1 mmol, 1 equiv) and aldehyde **19** (260 mg, 1.2 mmol, 1.2 equiv) in ^{t}BuOH, KO^{t}Bu (224 mg, 2 mmol, 2 equiv) was added. The mixture was stirred in a reaction tube for 24 h at room temperature and the progress of reaction was monitored by TLC. After completion of the reaction, the mixture was diluted by an aq. $KHSO_4$ solution and extracted with EtOAc (3 X 15 mL). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was then purified by column chromatography on silica gel with ethylacetate–hexane (35:65) to obtain **20c** (252 mg, 68%) as a yellow solid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.92 (s, 1H), 7.55 (d, *J* = 7.9 Hz, 1H), 7.35 (d, *J* = 8.3 Hz, 1H), 7.32 – 7.26 (m, 2H), 7.14 (t, *J* = 7.4 Hz, 1H), 6.62 (d, *J* = 8.6 Hz, 1H), 6.33 (s, 1H), 6.07 (s, 1H), 4.81 (s, 1H), 3.97 (s, 3H), 3.52 (q, *J* = 5.4 Hz, 2H), 3.29 (s, 3H), 3.07 – 3.03 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, Chloroform-*d*) δ 164.2, 146.3, 138.2, 134.1, 130.7, 128.5, 126.3, 124.9, 123.4, 119.7, 119.1, 116.8, 116.4, 113.9, 109.6, 72.6, 61.9, 58.9, 32.0, 24.7; HRMS (ESI) calcd for $C_{20}H_{20}ClN_3O_2$ [M + H$^+$] : 370.1322, found : 370.1321.

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6-Bromo-2-(3-(2-methoxyethyl)-1-methyl-1*H*-indol-2-yl)-2,3-dihydroquinazolin-4(1*H*)-one (20d). To a mixture of 2-amino-5-bromobenzonitrile **12d** (104 mg, 0.52 mmol, 1 equiv) and aldehyde **19** (135.4 mg, 0.62 mmol, 1.2 equiv) in ^{t}BuOH, KO^{t}Bu (116 mg, 1.04 mmol, 2 equiv) was added. The mixture was stirred in a reaction tube for 24 h at room temperature and the progress of reaction was monitored by TLC. After completion of the reaction, the mixture was diluted by an aq. $KHSO_4$ solution and extracted with EtOAc (3 X 15 mL). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was then purified by column chromatography on silica gel with ethylacetate–hexane (32:68) to obtain **20d** (165 mg, 74%) as a yellow solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.96 (d, *J* = 7.7 Hz, 1H), 7.59 (d, *J* = 7.9 Hz, 2H), 7.39 (d, *J* = 8.3 Hz, 1H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.17 (t, *J* = 7.4 Hz, 1H), 6.80 (t, *J* = 7.8 Hz, 1H), 6.44 (s, 1H), 5.96 (s, 1H), 5.04 (s, 1H), 4.03 (s, 3H), 3.57 – 3.48 (m, 2H), 3.32 (s, 3H), 3.06 (t, *J* = 5.7 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, Chloroform-*d*) δ 164.3, 145.4, 138.4, 137.1, 130.6, 128.4, 126.3, 123.5, 120.1, 119.8, 119.2, 116.9, 114.3, 109.7, 109.0, 72.5, 61.7, 59.1, 32.1, 24.9; HRMS (ESI) calcd for $C_{20}H_{20}BrN_3O_2$ [M + H$^+$] : 414.0817, found : 414.0817.

2-(3-(2-Methoxyethyl)-1-methyl-1*H*-indol-2-yl)quinazolin-4(3*H*)-one (21a). Conditions A. To a mixture of 2-aminobenzonitrile **12a** (120 mg, 1 mmol, 1 equiv) and aldehyde **19** (261 mg, 1.2 mmol, 1.2 equiv) in ^{t}BuOH, KO^{t}Bu (224 mg, 2 mmol, 2 equiv) was added. The mixture was stirred in a flame dried reaction tube for 12 h at 90 °C under open air and the progress of reaction was monitored by TLC. After completion of the reaction, the mixture was diluted by an aq. $KHSO_4$ solution and extracted with EtOAc (3 X 15 mL). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was then purified by column chromatography on silica gel with ethylacetate–hexane (25:75) to obtain **21a** (227 mg, 68%) as a white solid.

Conditions B. Compound **20a** (240 mg, 0.72 mmol, 1 equiv) was dissolved in dry DCM (8 mL) followed by the addition of DDQ (195 mg, 0.86 mmol, 1.2 equiv). The reaction was stirred for 1 h under an argon atmosphere. The reaction was quenched with 2M NaOH solution and extracted with DCM (3 x 25 mL). The combined organic phase was washed with 2M NaOH solution again, brine, dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was then purified by column chromatography on silica gel with ethylacetate-hexane (25:75) to obtain **21a** (219.3 mg, 92%) as a white solid.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 12.24 (s, 1H), 8.35 (d, *J* = 7.8 Hz, 1H), 7.78 (d, *J* = 4.2 Hz, 2H), 7.60 (d, *J* = 8.3 Hz, 1H), 7.49 (ddd, *J* = 8.2, 5.0, 3.4 Hz, 1H), 7.43 (d, *J* = 8.3 Hz, 1H), 7.37 (t, *J* = 7.5 Hz, 1H), 7.19 (t, *J* = 7.4 Hz, 1H), 4.06 (s, 3H), 3.89 (t, *J* = 5.3 Hz, 2H), 3.52 (s, 3H), 3.23 (t, *J* = 5.1 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 162.6, 149.3, 146.6, 139.1, 134.5, 130.7, 127.8, 126.8, 126.7, 126.6, 124.5, 121.6, 120.2, 119.4, 115.5, 110.5, 72.9, 59.0, 32.0, 25.6; HRMS (ESI) calcd for $C_{20}H_{20}N_3O_2$ [M + H]$^+$: 334.1556, found : 334.1554.

2-(3-(2-Methoxyethyl)-1-methyl-1*H*-indol-2-yl)-6-methylquinazolin-4(3*H*)-one (21b).

Conditions A. To a mixture of 2-amino-5-methylbenzonitrile **12b** (132 mg, 1 mmol, 1 equiv) and aldehyde **19** (261 mg, 1.2 mmol, 1.2 equiv) in ^{t}BuOH, KO^{t}Bu (224 mg, 2 mmol, 2 equiv) was added. The mixture was stirred in a flame dried reaction tube for 12 h at 90 °C under open air and the progress of reaction was monitored by TLC. After completion of the reaction, the mixture was diluted by an aq. $KHSO_4$ solution and extracted with EtOAc (3 X 15 mL). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was then purified by column chromatography on silica gel with ethylacetate–hexane (22:78) to obtain **21b** (240 mg, 70%) as a yellow solid.

Conditions B. Compound **20b** (171 mg, 0.49 mmol, 1 equiv) was dissolved in dry DCM (8 mL) followed by the addition of DDQ (134 mg, 0.59 mmol, 1.2 equiv). The reaction was stirred for 1 h under an argon atmosphere. The reaction was quenched with 2M NaOH solution and extracted with DCM (3 x 25 mL). The combined

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organic phase was washed with 2M NaOH solution again, brine, dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was then purified by column chromatography on silica gel with ethylacetate-hexane (22:78) to obtain **21b** (150 mg, 88%) as a yellow solid.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 12.15 (s, 1H), 8.14 (s, 1H), 7.68 (d, *J* = 8.2 Hz, 1H), 7.59 (d, *J* = 7.7 Hz, 2H), 7.43 (d, *J* = 8.3 Hz, 1H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.18 (t, *J* = 7.4 Hz, 1H), 4.04 (s, 3H), 3.89 (t, *J* = 5.1 Hz, 2H), 3.51 (s, 3H), 3.22 (t, *J* = 5.1 Hz, 2H), 2.52 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 162.6, 147.3, 145.8, 139.0, 137.1, 136.0, 130.8, 127.6, 126.7, 126.1, 124.3, 121.4, 120.1, 119.3, 115.2, 110.5, 72.9, 59.0, 32.0, 25.6, 21.5; HRMS (ESI) calcd for $C_{21}H_{22}N_3O_2$ [M + H] $^+$: 348.1712, found: 348.1710.

6-Chloro-2-(3-(2-methoxyethyl)-1-methyl-1*H*-indol-2-yl)quinazolin-4(3*H*)-one (21c).

Conditions A. To a mixture of 2-amino-5-chlorobenzonitrile **12c** (154 mg, 1 mmol, 1 equiv) and aldehyde **19** (261 mg, 1.2 mmol, 1.2 equiv) in ^{t}BuOH, KO^{t}Bu (224 mg, 2 mmol, 2 equiv) was added. The mixture was stirred in a flame dried reaction tube for 12 h at 90 ℃ under open air and the progress of reaction was monitored by TLC. After completion of the reaction, the mixture was diluted by an aq. $KHSO_4$ solution and extracted with EtOAc (3 X 15 mL). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was then purified by column chromatography on silica gel with ethylacetate–hexane (30:70) to obtain **21c** (198 mg, 54%) as a white solid.

Conditions B. Compound **20c** (145 mg, 0.39 mmol, 1 equiv) was dissolved in dry DCM (8 mL) followed by the addition of DDQ (107 mg, 0.47 mmol, 1.2 equiv). The reaction was stirred for 1 h under an argon atmosphere. The reaction was quenched with 2M NaOH solution and extracted with DCM (3 x 25 mL). The combined organic phase was washed with 2M NaOH solution again, brine, dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was then purified by column chromatography on silica gel with ethylacetate-hexane (26:74) to obtain **21c** (120 mg, 83%) as a white solid.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 12.34 (s, 1H), 8.30 (s, 1H), 7.72 (d, *J* = 8.8 Hz, 2H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.43 (d, *J* = 8.3 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.20 (t, *J* = 7.4 Hz, 1H), 4.04 (s, 3H), 3.89 (t, *J* = 5.2 Hz, 2H), 3.51 (s, 3H), 3.23 (t, *J* = 5.3 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 161.5, 147.8, 146.8, 139.2, 134.9, 132.5, 130.3, 129.4, 126.6, 126.0, 124.7, 122.7, 120.3, 119.4, 115.8, 110.5, 72.9, 59.0, 32.1, 25.6; HRMS (ESI) calcd for $C_{20}H_{19}ClN_3O_2$ [M + H] $^+$: 368.1166, found : 368.1167.

6-Bromo-2-(3-(2-methoxyethyl)-1-methyl-1*H*-indol-2-yl)quinazolin-4(3*H*)-one (21d).

Conditions A. To a mixture of 2-amino-5-bromobenzonitrile **12d** (102 mg, 0.52 mmol, 1 equiv) and aldehyde **19** (135 mg, 0.6 mmol, 1.2 equiv) in ^{t}BuOH, KO^{t}Bu (116 mg, 1.04 mmol, 2 equiv) was added. The mixture was stirred in a flame dried reaction tube for 12 h at 90 ℃ under open air and the progress of reaction was monitored by TLC. After completion of the reaction, the mixture was diluted by an aq. $KHSO_4$ solution and extracted with EtOAc (3 X 15 mL). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was then purified by column chromatography on silica gel with ethylacetate–hexane (26:74) to obtain **21d** (84 mg, 59%) as a white solid.

Conditions B. Compound **20d** (181 mg, 0.44 mmol, 1 equiv) was dissolved in dry DCM (8 mL) followed by the addition of DDQ (119.9 mg, 0.53 mmol, 1.2 equiv). The reaction was stirred for 1 h under an argon atmosphere. The reaction was quenched with 2M NaOH solution and extracted with DCM (3 x 25 mL). The combined organic phase was washed with 2M NaOH solution again, brine, dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was then purified by column chromatography on silica gel with ethylacetate-hexane (26:74) to obtain **21d** (156 mg, 86%) as a white solid.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 12.44 (s, 1H), 8.30 (d, *J* = 7.9 Hz, 1H), 8.04 (d, *J* = 7.7 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 8.3 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.31 (t, *J* = 7.8 Hz, 1H), 7.19 (t, *J* = 7.4 Hz, 1H), 4.18 (s, 3H), 3.91 (t, *J* = 5.2 Hz, 2H), 3.52 (s, 3H), 3.25 (t, *J* = 5.4 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, Chloroform-*d*) δ 161.4,

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148.1, 147.0, 139.2, 137.7, 130.4, 129.5, 129.2, 126.6, 124.7, 123.0, 120.3, 120.2, 119.4, 115.9, 110.5, 72.9, 59.0, 32.1, 25.6; HRMS (ESI) calcd for $C_{20}H_{19}BrN_3O_2$ [M + H] $^+$: 412.0661, found : 412.0663.

2-(3-(2-Hydroxyethyl)-1-methyl-1*H*-indol-2-yl)quinazolin-4(3*H*)-one (22a). Compound **21a** (127 mg, 0.67 mmol, 1 equiv) was dissolved in dry DCM and stirred at 0 ℃ under an argon atmosphere. Then BBr_3 (1 mL, 1 mmol, 1.5 equiv, 1 M in DCM) was added dropwise and the reaction mixture was stirred for 4 h. The reaction was quenched with $NaHCO_3$ solution and extracted with DCM (3 x 25 mL). The organic phase was washed with water, brine, dried (Na_2SO_4), filtered and concentrated in vacuo. The crude residue was purified by column chromatography on silica gel with ethylacetae-hexane (30:70) to obtain **22a** (169 mg, 81%) as a yellow solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.28 (s, 1H), 8.34 (d, *J* = 8.1 Hz, 1H), 7.82 (dd, *J* = 3.6, 2.0 Hz, 2H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.54 (ddd, *J* = 8.2, 5.3, 3.1 Hz, 1H), 7.46 – 7.35 (m, 3H), 7.22 (t, *J* = 7.4 Hz, 1H), 3.94 (s, 3H), 3.82 (t, *J* = 6.9 Hz, 2H), 3.53 (t, *J* = 6.9 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 160.5, 146.8, 145.6, 140.6, 140.1, 134.3, 127.0, 126.6, 126.3, 125.1, 123.6, 123.4, 120.1, 119.2, 115.8, 110.6, 44.4, 32.2, 19.0; HRMS (ESI) calcd for $C_{19}H_{18}N_3O_2$ [M - H_2O + H]$^+$: 302.1293, found: 302.1266.

2-(3-(2-Hydroxyethyl)-1-methyl-1*H*-indol-2-yl)-6-methylquinazolin-4(3*H*)-one (22b). Compound **21b** (152 mg, 0.44 mmol, 1 equiv) was dissolved in dry DCM and stirred at 0 ℃ under an argon atmosphere. Then BBr_3 (0.5 mL, 0.52 mmol, 1.2 equiv, 1 M in DCM) was added dropwise and the reaction mixture was stirred for 4 h. The reaction was quenched with $NaHCO_3$ solution and extracted with DCM (3 x 25 mL). The combined organic phase was washed with water, brine, dried (Na_2SO_4), filtered and concentrated in vacuo. The crude residue was purified by column chromatography on silica gel with ethylacetae-hexane (28:72) to obtain **22b** (117 mg, 80%) as a yellow solid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 10.74 (s, 1H), 8.10 (s, 1H), 7.73 (d, *J* = 8.3 Hz, 1H), 7.67 – 7.63 (m, 2H), 7.43 – 7.37 (m, 2H), 7.22 (t, *J* = 7.4 Hz, 1H), 3.92 (s, 3H), 3.79 (t, *J* = 7.1 Hz, 2H), 3.52 (t, *J* = 7.1 Hz, 2H), 2.52 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 160.4, 150.1, 144.8, 144.7, 140.8, 140.0, 139.0, 135.9, 135.8, 135.6, 135.4, 126.9, 126.7, 126.6, 126.0, 125.8, 125.7, 124.8, 123.6, 123.3, 120.9, 120.6, 120.5, 120.0, 120.0, 118.8, 118.5, 116.1, 111.0, 110.6, 44.7, 32.2, 20.8, 19.0; HRMS (ESI) calcd $C_{20}H_{19}N_3O_2$ [M - H_2O + H] $^+$: 316.1450, found: 316.1430.

6-Chloro-2-(3-(2-hydroxyethyl)-1-methyl-1*H*-indol-2-yl)quinazolin-4(3*H*)-one (22c). Compound **21c** (110 mg, 0.3 mmol, 1 equiv) was dissolved in dry DCM and stirred at 0 ℃ under an argon atmosphere. Then BBr_3 (0.4 mL, 0.36 mmol, 1.2 equiv, 1 M in DCM) was added dropwise and the reaction mixture was stirred for 4 h. The reaction was quenched with $NaHCO_3$ solution and extracted with DCM (3 x 25 mL). The combined organic phase was washed with water, brine, dried (Na_2SO_4), filtered and concentrated in vacuo. The crude residue was purified by column chromatography on silica gel with ethylacetae-hexane (32:68) to obtain **22c** (84.9 mg, 80%) as a yellow liquid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.74 (s, 1H), 8.13 (d, *J* = 2.5 Hz, 1H), 7.91 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.76 (dd, *J* = 12.1, 8.3 Hz, 2H), 7.56 (d, *J* = 8.3 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.16 (t, *J* = 7.5 Hz, 1H), 3.82 (s, 3H), 3.73 (t, *J* = 7.4 Hz, 2H), 3.44 (t, *J* = 7.4 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 160.7, 147.2, 145.6, 140.2, 137.2, 129.7, 126.4, 126.1, 125.3, 124.9, 123.6, 122.5, 119.8, 119.6, 114.8, 110.4, 34.1, 32.2, 28.0; HRMS (ESI) calcd $C_{19}H_{16}ClN_3O_2$ [M - H_2O + H] $^+$: 336.0903, found: 336.0873

6-Bromo-2-(3-(2-hydroxyethyl)-1-methyl-1*H*-indol-2-yl)quinazolin-4(3*H*)-one (22d). Compound **21d** (56 mg, 0.14 mmol, 1 equiv) was dissolved in dry DCM and stirred at 0 ℃ under an argon atmosphere. Then BBr_3 (0.4 mL, 0.16 mmol, 1.2 equiv, 1 M in DCM) was added dropwise and the reaction mixture was stirred for 4 h. The reaction was quenched with $NaHCO_3$ solution and extracted with DCM (3 x 25 mL). The combined organic phase was washed with water, brine, dried (Na_2SO_4), filtered and concentrated in vacuo. The crude residue was purified by column chromatography on silica gel with ethylacetae-hexane (32:68) to obtain **22d** (45.2 mg, 81%) as a yellow solid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 10.39 (s, 1H), 8.28 (d, *J* = 8.0 Hz, 1H), 8.09 (d, *J* = 7.8 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 8.3 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.36 (t, *J* = 7.8 Hz, 1H), 7.23 (t, *J*

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= 7.5 Hz, 1H), 4.05 (s, 3H), 3.92 (t, *J* = 6.9 Hz, 2H), 3.59 (t, *J* = 6.9 Hz, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*) δ 161.7, 146.9, 146.1, 139.3, 138.7, 129.7, 127.8, 126.7, 126.3, 125.2, 123.3, 122.9, 120.8, 119.9, 116.6, 110.7, 34.2, 32.3, 28.8; HRMS (ESI) calcd $C_{19}H_{16}BrN_3O_2$ [M - H_2O + H]$^+$: 380.0398, found : 380.0370.

13-Methyl-7,8-dihydroindolo[2',3':3,4]pyrido[2,1-*b*]quinazolin-5(13*H*)-one (23a). To a stirred of solution compound **22a** (71 mg, 0.22 mmol, 1 equiv) in dry THF under an argon atmosphere, PPh_3 (134 mg, 0.51 mmol, 2.3 equiv) and DIAD (72 µL, 0.51 mmol, 2.3 equiv) were added successively. The solution was stirred for 1 h at room temperature. After confirming the product formation by TLC, THF was removed under vacuo. The crude residue was purified by column chromatography on silica gel with ethylacetate-hexane (10:90) to obtain **23a** (54.9 mg, 80%) as a white solid. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.32 (d, *J* = 8.0 Hz, 1H), 7.72 (d, *J* = 7.3 Hz, 2H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.45 – 7.37 (m, 3H), 7.19 (t, *J* = 7.5 Hz, 1H), 4.55 (t, *J* = 6.7 Hz, 2H), 4.35 (s, 3H), 3.19 (t, *J* = 6.7 Hz, 2H); $^{13}C\{^1H\}$ NMR (151 MHz, Chloroform-*d*) δ 161.9, 147.5, 145.7, 140.7, 134.3, 127.4, 127.3, 127.2, 126.4, 125.3, 124.2, 121.0, 120.4, 120.1, 119.2, 110.4, 41.1, 32.6, 20.0; HRMS (ESI) calcd for $C_{19}H_{16}N_3O$ [M + H] $^+$: 302.1293, found: 302.1294.

3,13-Dimethyl-7,8-dihydroindolo[2',3':3,4]pyrido[2,1-*b*]quinazolin-5(13H)-one (23b). To a stirred of solution compound **22b** (42 mg, 0.13 mmol, 1 equiv) in dry THF under an argon atmosphere, PPh_3 (53 mg, 0.202 mmol, 1.6 equiv) and DIAD (39.6 µL, 0.2 mmol, 1.6 equiv) were added successively. The solution was stirred for 1 h at room temperature. After confirming the product formation by TLC, THF was removed under vacuo. The crude residue was purified by column chromatography on silica gel with ethyl acetate-hexane (10:90) to obtain **23b** (32.2 mg, 81%) as a white solid. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.10 (s, 1H), 7.62 (t, *J* = 8.0 Hz, 2H), 7.54 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.43 – 7.36 (m, 2H), 7.18 (t, *J* = 7.5 Hz, 1H), 4.54 (t, *J* = 6.6 Hz, 2H), 4.33 (s, 3H), 3.17 (t, *J* = 6.7 Hz, 2H), 2.49 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*) δ 161.9, 145.5, 145.0, 140.7, 136.5, 135.7, 127.5, 127.2, 126.6, 125.2, 124.3, 120.7, 120.4, 120.0, 118.8, 110.4, 41.1, 32.6, 21.5, 20.0; HRMS (ESI) calcd for $C_{20}H_{18}N_3O$ [M + H] $^+$: 316.1450, found : 316.1452.

3-Chloro-13-methyl-7,8-dihydroindolo[2',3':3,4]pyrido[2,1-*b*]quinazolin-5(13*H*)-one (23c). To a stirred of solution compound **22c** (50 mg, 0.14 mmol, 1 equiv) in dry THF under an argon atmosphere, PPh_3 (59 mg, 0.22 mmol, 1.6 equiv) and DIAD (100 µL, 0.22 mmol, 1.6 equiv) were added successively. The solution was stirred for 1 h at room temperature. After confirming the product formation by TLC, THF was removed under vacuo. The crude residue was purified by column chromatography on silica gel with ethylacetate-hexane (12:88) to obtain **23c** (38 mg, 80%) as a white solid, mp 304-305 °C. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.27 (s, 1H), 7.63 (d, *J* = 8.0 Hz, 3H), 7.40 (q, *J* = 8.1 Hz, 2H), 7.19 (t, *J* = 7.2 Hz, 1H), 4.53 (t, *J* = 6.7 Hz, 2H), 4.31 (s, 3H), 3.18 (t, *J* = 6.7 Hz, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*) δ 160.9, 146.1, 146.0, 140.9, 134.7, 132.0, 129.0, 127.1, 126.6, 125.6, 124.2, 122.0, 120.6, 120.2, 119.6, 110.5, 41.3, 32.6, 20.0; HRMS (ESI) calcd for $C_{19}H_{15}ClN_3O$ [M + H] $^+$: 336.0904, found: 336.0905.

3-Bromo-13-methyl-7,8-dihydroindolo[2',3':3,4]pyrido[2,1-*b*]quinazolin-5(13*H*)-one (23d). To a stirred of solution compound **22d** (35 mg, 0.09 mmol, 1 equiv) in dry THF under an argon atmosphere, PPh_3 (47.2 mg, 0.18 mmol, 2 equiv) and DIAD (40 µL, 0.18 mmol, 2 equiv) were added successively. The solution was stirred for 1 h at room temperature. After confirming the product formation by TLC, THF was removed under vacuo. The crude residue was purified by column chromatography on silica gel with ethylacetate-hexane (10:90) to obtain **23d** (27 mg, 81%) as a white solid. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.26 (d, *J* = 7.9 Hz, 1H), 7.99 (d, *J* = 7.9 Hz, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.44 (d, *J* = 8.3 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 1H), 7.26 (t, *J* = 8 Hz, 1H), 7.19 (t, *J* = 7.4 Hz, 1H), 4.53 (t, *J* = 6.8 Hz, 2H), 4.43 (s, 3H), 3.20 (t, *J* = 6.8 Hz, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*) δ 161.3, 146.3, 145.5, 141.0, 137.8, 127.0, 126.7(2C), 125.7, 124.2, 122.6, 122.5, 120.6, 120.3, 119.7, 110.6, 41.2, 32.9, 20.0; HRMS (ESI) calcd for $C_{19}H_{15}BrN_3O$ [M + H] $^+$: 380.0398, found : 380.0398.

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2-(1*H*-Indol-2-yl)quinazolin-4(3*H*)-one (25). To a clean, oven-dried screw cap 20 mL reaction tube, 2-aminobenzonitrile **12a** (122 mg, 1 equiv, 1.02 mmol), indole-2-carbaldehyde **24** (150 mg, 1.2 equiv, 1.03 mmol) and KO^{t}Bu (231 mg, 2 equiv, 2.06 mmol) in ^{t}BuOH (5 mL) were added in an open-air environment. The solution was stirred at 90 °C in an oil bath for 12 h. Product formation was confirmed by conducting TLC analysis and solvent was removed under vacuum. The concentrated reaction mixture was diluted with aq. $KHSO_4$ solution and extracted with ethyl acetate (3 x 10 mL). The combined organic layer was washed with brine (1 x 10 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The resulting crude mixture was purified via column chromatography on silica gel, using an ethylacetate-hexane eluting system (60:40) to yield the corresponding 2-(1H-indol-2-yl)quinazolin-4(3H)-one **25** (167 mg, 62%) as yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.59 (s, 1H), 11.78 (s, 1H), 8.15 (d, *J* = 7.8 Hz, 1H), 7.84 (t, *J* = 7.6 Hz, 1H), 7.73 (d, *J* = 8.1 Hz, 1H), 7.64 (t, *J* = 7.5 Hz, 2H), 7.53 – 7.48 (m, 2H), 7.22 (t, *J* = 7.4 Hz, 1H), 7.06 (t, *J* = 7.4 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 162.3, 149.2, 147.0, 138.1, 135.2, 130.5, 127.9, 127.4, 126.7, 126.5, 124.5, 122.0, 121.6, 120.4, 112.9, 105.4; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{16}H_{12}N_3O$ 262.0980; Found 262.0981.

2-(9-Methyl-9*H*-carbazol-3-yl)quinazolin-4(3*H*)-one (27). To a clean, oven-dried screw cap 20 mL reaction tube, 2-aminobenzonitrile **12a** (100 mg, 1 equiv, 0.8 mmol), 9-methyl-9H-carbazole-3-carbaldehyde **26** (145 mg, 1 equiv, 0.8 mmol) and KO^{t}Bu (179 mg, 2 equiv, 1.6 mmol) in ^{t}BuOH (5 mL) were added in an open-air environment. The solution was stirred at 90 °C in an oil bath for 12 h. Product formation was confirmed by conducting TLC analysis and solvent was removed under vacuum. The concentrated reaction mixture was diluted with aq. $KHSO_4$ solution and extracted with ethyl acetate (3 x 10 mL). The combined organic layer was washed with brine (1 x 10 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The resulting crude mixture was purified via column chromatography on silica gel, using an ethylacetate-hexane eluting system (45:55) to yield the corresponding quinazolinone **27** (194 mg, 60%) as a brown solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.48 (s, 1H), 9.12 (d, *J* = 1.6 Hz, 1H), 8.40 (dd, *J* = 8.7, 1.8 Hz, 1H), 8.24 (d, *J* = 7.6 Hz, 1H), 8.17 (d, *J* = 7.9 Hz, 1H), 7.85 (t, *J* = 8.3 Hz, 1H), 7.77 (dd, *J* = 8.8, 4.3 Hz, 2H), 7.68 (d, *J* = 8.2 Hz, 1H), 7.57 – 7.47 (m, 2H), 7.32 (t, *J* = 7.4 Hz, 1H), 3.96 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 162.4, 152.9, 149.2, 142.3, 141.3, 134.6, 127.3, 126.4, 126.0, 125.9, 125.6, 123.0, 122.2, 121.9, 1207, 120.4, 120.2, 119.7, 109.7, 109.3, 29.3; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{21}H_{16}N_3O$ 326.1293; Found 326.1292.

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Supplementary Material

Copies of ^{1}H and ^{13}C NMR spectra of the products are available in the supplementary material file associated with this paper.

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