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PII: S0040-4020(16)30461-6

DOI: 10.1016/j.tet.2016.05.054

Reference: TET 27781

To appear in: *Tetrahedron*

Received Date: 25 March 2016

Revised Date: 16 May 2016

Accepted Date: 20 May 2016

Please cite this article as: Yamashita M, Nishizono Y, Himekawa S, Iida A, One-pot synthesis of polyhydropyrido[1,2-*a*]indoles and tetracyclic quinazolinones from 2-arylindoles using copper-mediated oxidative tandem reactions, *Tetrahedron* (2016), doi: 10.1016/j.tet.2016.05.054.

Graphical Abstract

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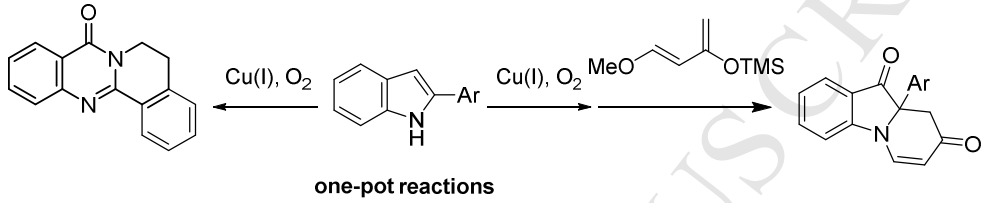


One-pot synthesis of Polyhydropyrido[1,2-*a*]indoles and Tetracyclic Quinazolinones from 2-Arylindoles Using Copper-mediated Oxidative Tandem Reactions

Mitsuaki Yamashita[a,*], Yukari Nishizono[a], Seiya Himekawa[a] and Akira Iida[a]

[a]School of Agriculture, Kindai University, Nakamachi, Nara 631-8505, Japan

Abstract

We developed facile one-pot methods for the transformation of 2-arylindoles to polyhydropyrido[1,2-*a*]indoles and tetracyclic quinazolinones. The copper-catalyzed oxidation of 2-arylindoles to *C*-acylimines followed by aza-Diels-Alder reactions or oxidative ring-expansion reactions afforded significant polycyclic heterocycles.

Keywords: Copper; Oxidation; aza-Diels-Alder; Rearrangement; Indoles

* Corresponding author. Tel./fax: +81-742-43-1770; e-mail: yamash@nara.kindai.ac.jp (M.Y.).

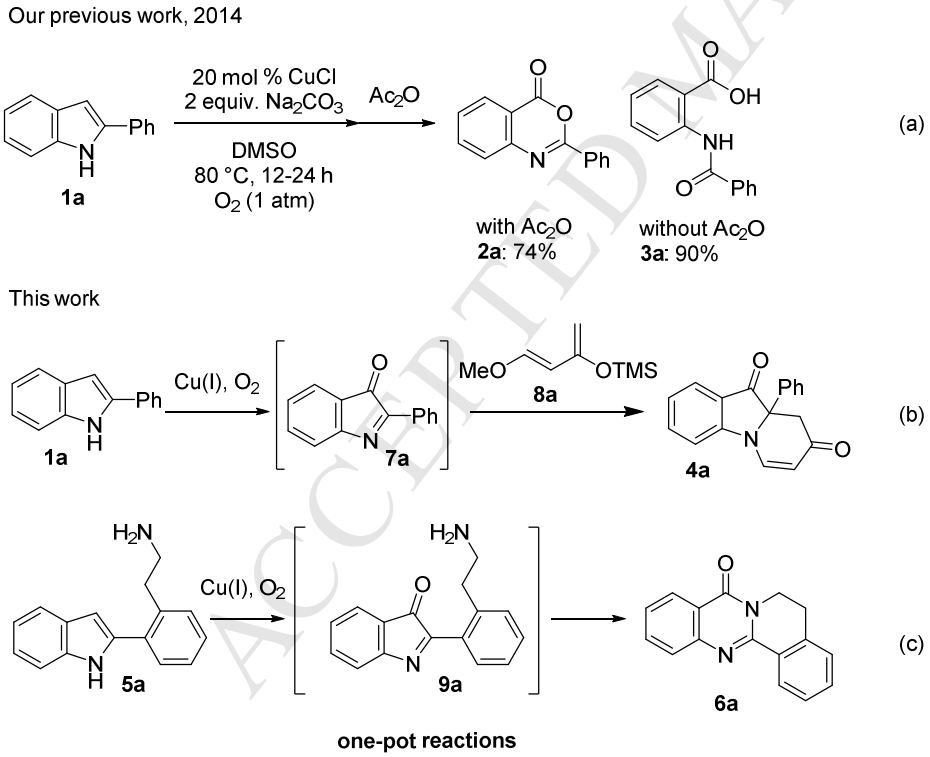
1. Introduction

Copper-catalyzed reactions are one of the most important and attractive strategies in organic synthesis due to their efficiency, good functional group tolerance, and economy.[1] As part of our work on one-pot catalysis,[2] we recently reported the synthesis of 2-arylbenzoxazinones and *N*-benzoyl anthranilic acids *via* copper-catalyzed tandem oxidative reactions of 2-arylindoles (Scheme 1a).[3] In this paper, plausible intermediate **7a** was proposed (Scheme 2a). To the best of our knowledge, synthesis methods for the *C*-acylimine species involved drawbacks such as a complex multistep procedure for the preparation of substrates, low reaction selectivity or yield, and the use of an expensive palladium catalyst.[4] Based on these reports and motivated by the interesting reactivities of *C*-acylimine species,[5] we decided to explore efficient methods to construct polycyclic heterocycles *via* the acylimino species. Herein, we report the synthesis of polyhydropyrido[1,2-*a*]indoles and tetracyclic quinazolinones from 2-arylindoles using a combination of copper-mediated oxidative tandem reactions and aza-Diels-Alder reactions or oxidative ring expansion reactions (Schemes 1b and 1c).

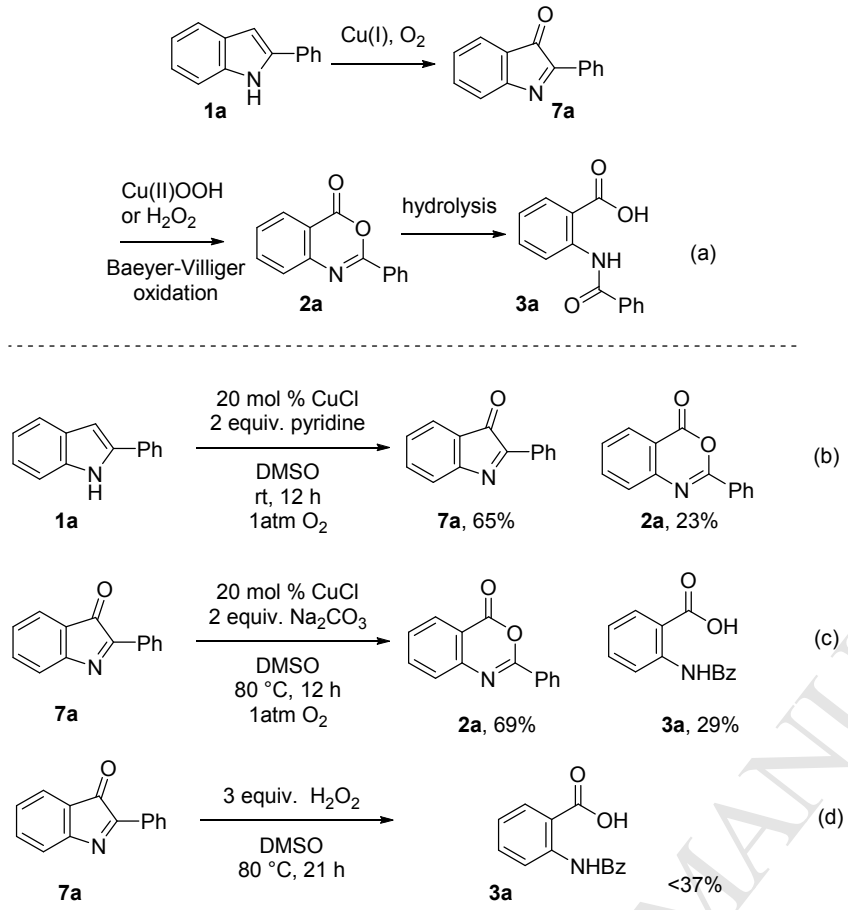
Preliminarily, we tested three reactions because we were unable to obtain **7a** in previous work, probably due to the fast conversion of **7a** to **2a** at high temperatures: (i) The reaction of 2-phenylindole **1a** with pyridine (2.0 equivalents) instead of Na_2CO_3 proceeded even at room temperature, giving 2-phenylbenzoxazinone **2a** and *N*-benzoyl anthranilic acid **3a** in 65% and 23%

yields, respectively (Scheme 2b); (ii) the reaction of 2-phenylindolone **7a** in the presence of CuCl (0.2 equivalents) and Na_2CO_3 (2.0 equivalents) in DMSO at 80 °C for 12 h under an O_2 atmosphere resulted in 2-phenylbenzoxazinone **2a** and *N*-benzoyl anthranilic acid **3a** in 69% and 29% yields, respectively (Scheme 2c); (iii) the reaction of 2-phenylindolone **7a** in the presence of H_2O_2 (3.0 equivalents) in DMSO at 80 °C for 21 h under O_2 atmosphere resulted in *N*-benzoyl anthranilic acid **3a** in <37% yield (Scheme 2d). These results indicate that **7a** is an intermediate of the transformation of 2-phenyl indole **1a** to 2-phenylbenzoxazinone **2a**.

Scheme 1. Copper-catalyzed oxidative reactions of 2-arylindoles



Scheme 2. Proposed mechanisms for the transformation of **1a** to **3a**

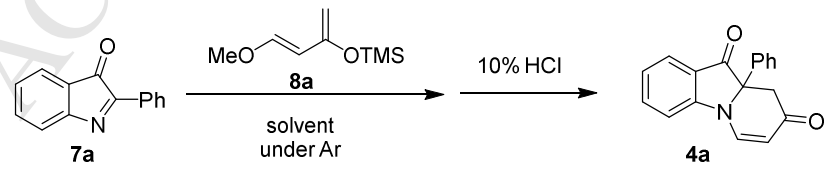


2. Results and Discussion

First, the results of our initial attempts to optimize the reaction conditions for the synthesis of a unique type of tricyclic scaffold, polyhydropyrido[1,2-a]indoles **4**, by an aza-Diels-Alder reaction are shown in Table 1. Polyhydropyrido[1,2-a]indoles exist widely as key structures in several biologically active materials such as cladoniamides,[6] canthine-6-ones,[7] and goniomitine.[8] The reaction of **1a** in DMSO, which is a suitable solvent for the previously reported copper-catalyzed oxidative reactions,[3] at rt for 24 h with Danishefsky's diene **8a** resulted in a moderate conversion to hydropyrido[1,2-a]indolone **4a** in 59% yield (Table 1, entry 1). The use of other solvents (i.e., acetonitrile, dichloromethane, and acetone) for this reaction did not improve results compared to

those obtained with DMSO (Table 1, entries 2–4). However, the yield of **4a** was substantially increased when the reaction was performed in benzene and toluene, demonstrating that toluene is the best solvent for this aza-Diels-Alder reaction (Table 1, entries 5 and 6). We also examined the other reaction conditions (e.g., temperature and number of equivalents of diene); however, there were no further improvements in chemical yields (Table 1, entries 7 and 8). A combination of the copper-catalyzed oxidative reactions and the aza-Diels-Alder reaction was then tested. Fortunately, the reaction of 2-phenylindole **1a** with CuCl (0.2 equivalents) and pyridine (2.0 equivalents) in toluene gave hydropyrido[1,2-a]indolone **4a** in moderate yield, while little improvement in the yield of **4a** was observed when the reaction was performed at 50 °C (Table 2, entries 1 and 2). Unfortunately, neither 1.0 nor 4.0 equivalents of pyridine resulted in a higher yield (Table 2, entry 3). No further improvement was obtained when 0.5 equivalents of CuCl was used (Table 2, entry 4). These results suggest that the optimum number of equivalents of pyridine and CuCl are 2.0 and 0.2, respectively.

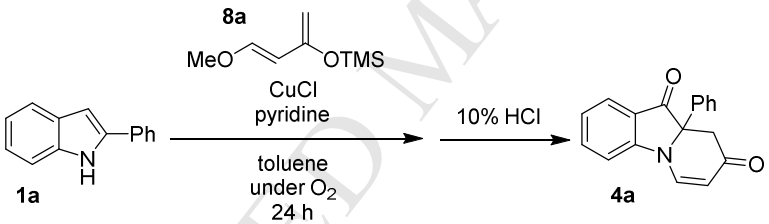
Table 1. Optimization of reaction conditions for the aza-Diels-Alder reaction[a]



Entry	Time (h)	Solvent	Diene **8a**, equiv.	Yield (%)[b]
				4a
1	24	DMSO	1.5	59
2	24	acetonitrile	1.5	57
3	24	DCM	1.5	36
4	24	acetone	1.5	66
5	24	benzene	1.5	76
6	24	toluene	1.5	82
7	16	toluene	3.0	54
8[c]	20	toluene	1.5	77

[a] Substrate **7a** (0.2 mmol) and diene **8a** were stirred in solvent (1.0 mL) at rt under Ar. After the reaction was completed, 10% HCl (1.0 mL) was added. [b] Isolated yield. [c] Reaction at 50 °C.

Table 2. Optimization of reaction conditions for the synthesis of hydropyrido[1,2-*a*]indolone **4a** from 2-arylindole **1a**[a]



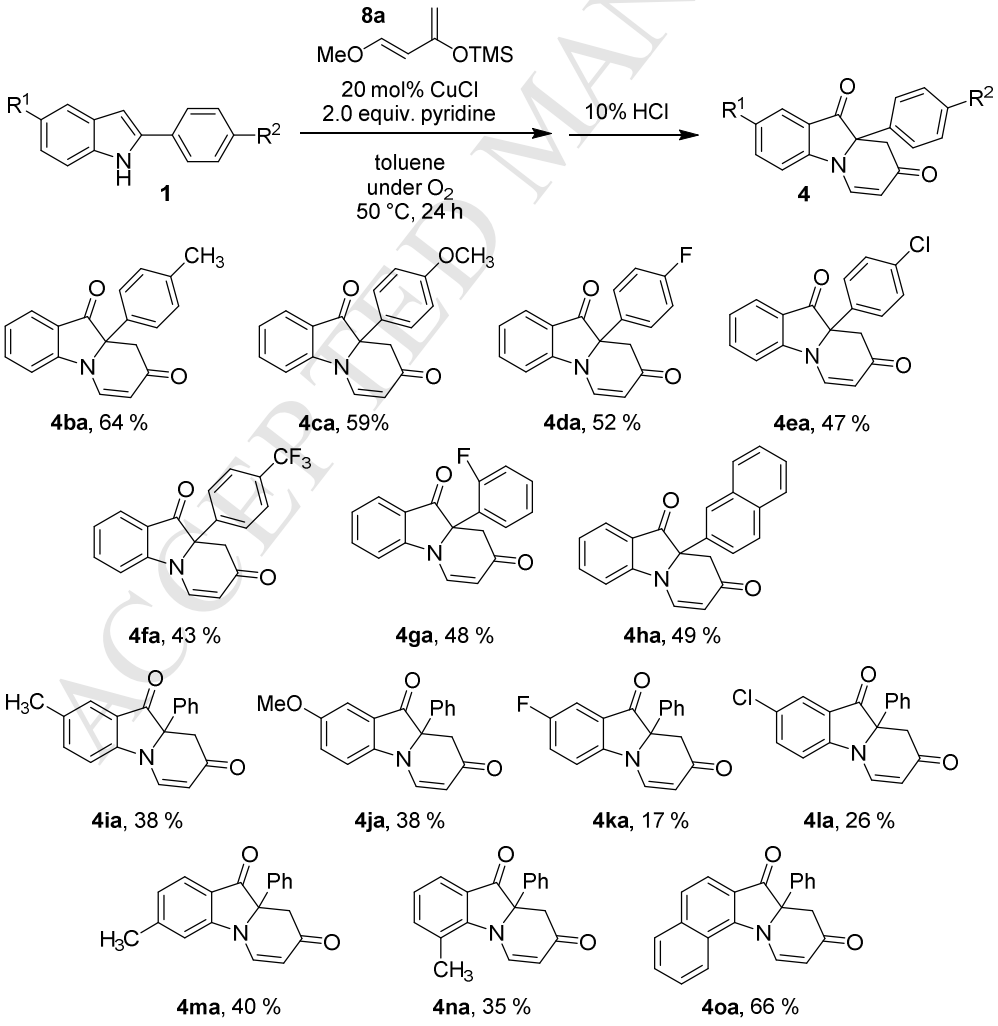
Entry	CuCl, equiv.	Temp., degree	Pyridine, equiv.	Yield (%)[b]
				4a
1	0.2	rt	2.0	55
2	0.2	50	2.0	58
3	0.2	50	1.0	37
4	0.2	50	4.0	53
5	0.5	50	2.0	47

[a] Substrate **1a** (0.2 mmol), CuCl, diene (0.3 mmol), and pyridine were stirred in toluene (1.0 mL) under O_2 (1 atm). After 24 h, 10% HCl (1.0 mL) was added. [b]Isolated yield.

Using the optimized conditions, we investigated other substrates to evaluate the developed methods, and the results are shown in Figure 1. Our reaction proved to be a general methodology for the

preparation of polyhydropyrido[1,2-*a*]indoles, and tolerated various functional groups. Notably, both electron-donating and electron-withdrawing functional groups on the 2-aryl ring were tolerated under the developed reaction conditions. The 2-arylindoles **1b**–**1h** reacted smoothly to give the corresponding polyhydropyrido[1,2-*a*]indoles **4ba**–**4ha** in modest yields. On the other hand, the reactions of 5-methyl-, methoxy-, fluoro-, chloro-, 6-methyl-, and 7-methyl- substituted indoles **1i**–**1n** gave the corresponding products **4ia**–**4na** in slightly lower yields compared to those of **4ba**–**4ha**. The reactions of benz[*g*]indole **1o** gave **4oa** in good yield.

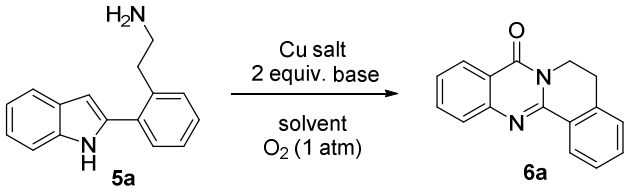
Figure 1. Reaction of various 2-arylindoles **1** under the optimized reaction conditions[a,b]



[a] Substrate **1** (0.2 mmol), CuCl (0.04 mmol), diene **8a** (0.3 mmol), and pyridine (0.4 mmol) were stirred in toluene (1.0 mL) at 50 °C under O_2 (1 atm). After 24 h, 10% HCl (1.0 mL) was added. [b] Isolated yields.

Quinazolinone derivatives are versatile building blocks in organic synthesis and medicinal chemistry.[9] In addition, they are widely found in various biological compounds and pharmaceutical drugs,[10] such as rutaecarpine[11] and luotonin A.[12] Therefore, the development of efficient methods to synthesize these compounds continues to be an active research area.[13] The results of our initial attempts to optimize the reaction conditions are shown in Table 3. The reaction of **5a** in NMP at 80 °C for 24 h with 10 mol% of CuBr under O_2 resulted in a low conversion to tetracyclic quinazolinone **6a** in 10% yield (Table 3, entry 1). Alternatively, the addition of 2 equivalents of Na_2CO_3 to the reaction mixture and an increase in the amount of CuBr improved the yield of **6a** (Table 3, entries 2 and 3). Meanwhile, the chemical yield was further improved when the reaction was performed at 60 °C in DMSO instead of NMP (Table 3, entries 4 and 5). Unfortunately, reaction at 40 °C did not result in a high yield, which suggests that the optimum reaction temperature is 60 °C (Table 3, entry 6). Other copper catalysts, such as CuCl, were also tested, but produced similar results to those with CuBr (Table 3, entry 7). The reaction with other bases (i.e., $NaHCO_3$ and Et_3N) produced results similar to those obtained with Na_2CO_3 (Table 3, entries 8 and 9). The addition of pyridine instead of Na_2CO_3 provided the best result (Table 3, entry 10).

Table 3. Optimization of reaction conditions for the synthesis of tetracyclic quinazolinone **6a** from indole **5a**[a]

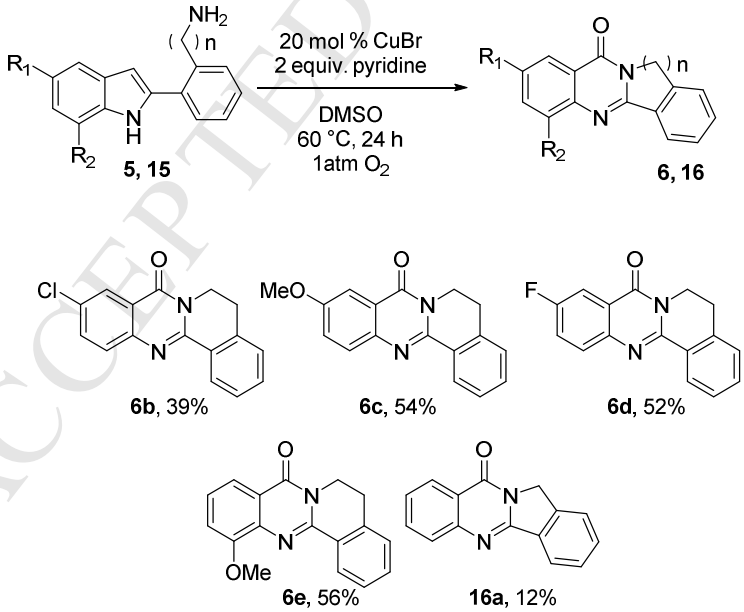


Entry	Time (h)	Cu salt, equiv.	base	Solvent	temp. (°C)	Yield (%)[b]
						6a
1	24	CuBr (0.1)	none	NMP	80	10
2	3.0	CuBr (0.1)	Na_2CO_3	NMP	80	45
3	3.0	CuBr (0.2)	Na_2CO_3	NMP	80	54
4	24	CuBr (0.2)	Na_2CO_3	NMP	60	59
5	24	CuBr (0.2)	Na_2CO_3	DMSO	60	65
6	24	CuCl (0.2)	Na_2CO_3	DMSO	60	66
7	24	CuBr (0.2)	Na_2CO_3	DMSO	40	51
8	24	CuBr (0.2)	$NaHCO_3$	DMSO	60	61
9	24	CuBr (0.2)	Et_3N	DMSO	60	62
10	24	CuBr (0.2)	pyridine	DMSO	60	71

[a] Substrate **5a** (0.2 mmol), Cu salt, and base (0.4 mmol) were stirred in solvent (1.0 mL) under O_2 (1 atm). [b] Isolated yield.

We then investigated other substrates to evaluate the developed methods; the results are shown in Figure 2. The 5-chloro-, methoxy-, fluoro-, and 7-methoxy-substituted indoles **5b**–**5e** reacted smoothly to give the corresponding tetracyclic quinazolinones **6b**–**6e** in 39%–56% yields, demonstrating that our reaction tolerated some functional groups. Meanwhile, the reaction of 2-[2-(aminomethyl)phenyl]indole **15a** gave a lower yield of tetracyclic quinazolinone **16a**, because of the formation of unknown byproducts. These results indicate that the length of the aminoalkyl chain on the 2-aryl group is crucial in the developed reactions.

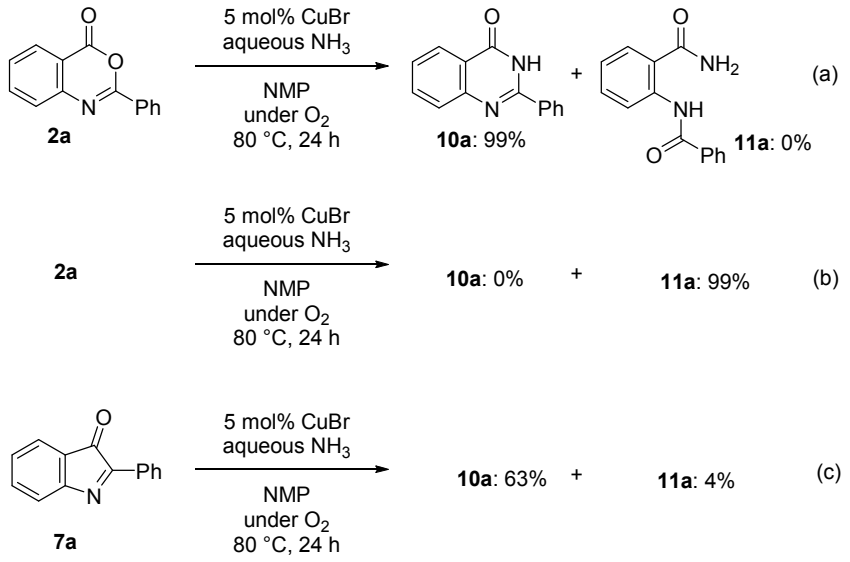
Figure 2. Oxidation of 2-arylindoles **1** in the presence of CuBr for the synthesis of tetracyclic quinazolinones from indoles[a,b]



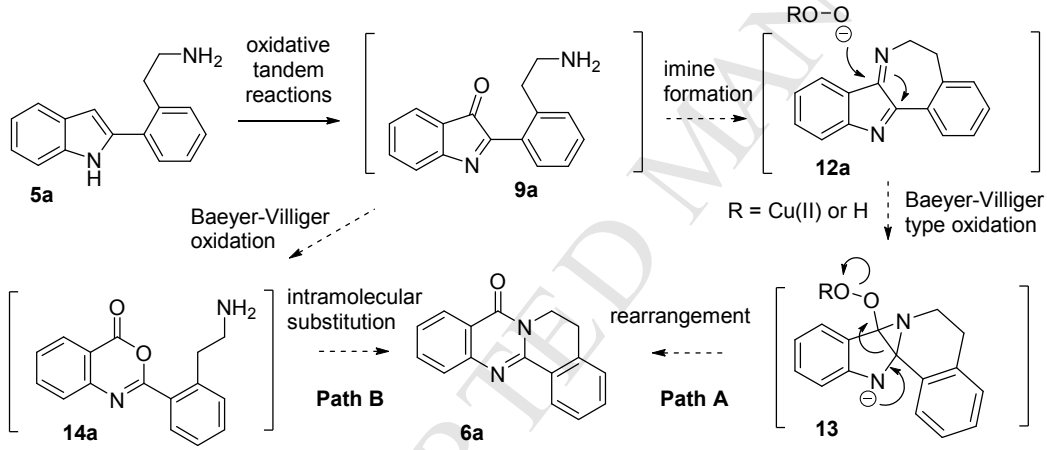
[a] Substrate **1** (0.2 mmol), CuBr (0.04 mmol), and Na_2CO_3 (0.4 mmol) were stirred in DMSO (1.0 mL) at 80 °C under O_2 (1 atm). [b] Isolated yields.

During our investigations, similar copper-catalyzed reactions of substituted 2-arylindoles to form 2-arylquinazolinones with amines or ammoniums were reported.[14] In this paper, Cui's group reported that the reaction of **2a** with excess aqueous NH_3 afforded only quinazolinone **10a** (Scheme 3a). Contrary to their report, we observed that the reaction of **2a** under the same reaction conditions as Cui's group gave only ring-opened amide **11a** (Scheme 3b).[15] Moreover, the reaction of **7a** under the same reaction conditions afforded **10a** and **11a** in 63% and 4% yields, respectively. Thus, a proposed mechanism on the basis of previous reports and our findings for the reaction is shown in Scheme 4. Initially, the copper-catalyzed aerobic oxidation of **5a** to **9a** proceeded. The following imine formation and Baeyer–Villiger-type oxidative reaction[16] of **12a**, possibly mediated by a Cu(II) hydroperoxo species or by a peroxide such as H_2O_2, gave **6a** (Path A).[17] Usually, harsh reaction conditions such as high temperature[18] or microwave irradiation[19] are needed to construct quinazolinone motifs *via* benzoxazinone intermediates, while our reaction proceeded even at 40 °C (Table 3, entry 7) and formation of ring-opened amide was not observed. Thus, we suppose that the formation of benzoxazinone **14a** and the subsequent intramolecular substitution reaction (Path B) is unlikely in the developed reactions; however, the exact intermediates responsible for the transformation of **9a** to **6a** remain unknown at this stage since intermediates **9a** and **12a** were not isolated. Further studies are necessary to elucidate the detailed mechanism.

Scheme 3. Test reactions of **2a** and **7a** under the copper-catalyzed oxidative reaction conditions



Scheme 4. Proposed mechanisms for the transformation of **5a** to **6a**



3. Conclusion

In conclusion, we demonstrated a facile access to polyhydropyrido[1,2-*a*]indoles and tetracyclic quinazolinones from 2‑arylindoles *via C*-acylimine intermediates, generated *in situ* by using copper-catalyzed oxidative reactions. Notably, the developed methods proceed under simple and mild reaction conditions and tolerate some functional groups. Future applications of this strategy for

the synthesis of biologically active compounds are still under investigation and will be reported in due course.

4. Experimental

4.1. General Information: All melting points were taken on a Yanagimoto micromelting point apparatus and were uncorrected. ^{1}H-NMR spectra (400 MHz) were obtained in $CDC1_3$, unless otherwise noted. The chemical shift values are expressed in ppm relative to internal tetramethylsilane. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad. Purification was performed using silica gel column chromatography. All reagents including **1a** and **8a** were purchased from chemical companies and used as received. Starting materials **1b**–**1o**[3] and **7a**[16] were prepared according to a known literature procedure.

4.2. General Procedure for the Synthesis of polyhydropyrido[1,2-*a*]indoles 4:
A mixture of compound **1** (0.20 mmol), CuCl (4.0 mg, 0.04 mmol) and pyridine (32 µg, 0.40 mmol) in toluene (1.0 mL) was stirred at 50 °C under an oxygen atmosphere (1 atm). After 24 h, 10% HCl (1.0 ml) was added, and the mixture was stirred for an additional 0.5 h. Then, the mixture was extracted with EtOAc. The organic extracts were washed with H_2O and brine, dried over Na_2SO_4, and then concentrated. The crude product was chromatographed on silica gel.

4.2.1. 9a-phenyl-9,9a-dihydropyrido[1,2-*a*]indole-8,10-dione (4aa): yield 58% (30 mg). white solid. mp >216 °C dec. rf (hexane/EtOAc = 2/1) = 0.10. ^{1}H-NMR: δ 2.89 (d, 1H, *J* = 16 Hz), 3.42 (dd, 1H, *J* = 1.1, 16 Hz), 5.36 (dd, 1H, *J* = 1.1, 7.5 Hz), 7.14 (ddd, 1H, *J* = 0.3, 7.6, 7.6 Hz), 7.29–7.39 (m, 6H), 7.70–7.74 (m, 2H), 7.83 (d, 1H, *J* = 7.5 Hz). ^{13}C-NMR: δ 42.4, 71.2, 105.9, 110.0, 122.9, 123.2, 125.6, 126.4, 128.9, 129.2, 133.6, 137.7, 138.0, 152.2, 191.1, 197.0. IR (KBr): 1719, 1654, 1598, 1575, 1475, 1334, 1282, 1228, 756. HRMS (ESI) *m*/*z*: $[M+Na]^+$ calcd for $[C_{18}H_{13}NO_2Na]^+$, 298.0844; Found, 298.0844.

4.2.2. 9a-(4-methylphenyl)-9,9a-dihydropyrido[1,2-*a*]indole-8,10-dione (4ba): yield 64% (37 mg). white solid. mp 168–169 °C. rf (hexane/EtOAc = 2/1) = 0.15. ^{1}H-NMR: δ 2.28 (s, 3H), 2.86 (d, 1H, *J* = 16 Hz), 3.39 (dd, 1H, *J* = 1.2, 16 Hz), 5.36 (dd, 1H, *J* = 1.2, 7.7 Hz), 7.11–7.16 (m, 3H), 7.24–7.26 (m, 2H), 7.36 (d, 1H, *J* = 8.6 Hz), 7.70–7.74 (m, 2H), 7.81 (d, 1H, *J* = 7.7 Hz). ^{13}C-NMR: δ 21.0, 42.2, 71.1, 105.8, 110.0, 122.9, 123.2, 125.5, 126.4, 129.9, 130.5, 137.7, 138.0, 138.9, 152.1, 191.3, 197.1. IR (KBr): 1714, 1651, 1598, 1573, 1508, 1475, 1419, 1334, 1282, 1228, 1197, 752. HRMS (ESI) *m*/*z*: $[M+Na]^+$ calcd for $[C_{19}H_{15}NO_2Na]^+$, 312.1000; Found, 312.1001.

4.2.3. 9a-(4-methoxyphenyl)-9,9a-dihydropyrido[1,2-a]indole-8,10-dione (4ca): yield 59% (36 mg). white solid. mp 134–135 °C. rf (hexane/EtOAc = 2/1) = 0.2. ^{1}H-NMR: δ 2.85 (d, 1H, *J* = 16 Hz), 3.36 (dd, 1H, *J* = 1.1, 16 Hz), 3.75 (s, 3H), 5.37 (dd, 1H, *J* = 1.1, 7.6 Hz), 6.83 (m, 2H), 7.14 (dd, 1H, *J* = 7.5, 7.5 Hz) 7.26–7.30 (m, 2H,), 7.36 (d, 1H, *J* = 7.9 Hz), 7.70–7.74 (m, 2H), 7.80 (d, 1H, *J* = 7.6 Hz). ^{13}C-NMR: δ: 42.2, 55.3, 70.8, 105.8, 110.0, 114.6, 122.9, 123.2, 125.4, 126.4, 126.9, 137.7, 137.9, 152.1, 160.0, 191.3, 197.2. IR (KBr): 1716, 1653, 1598, 1573, 1508, 1475, 1334, 1255, 1230, 752. HRMS (ESI) *m*/*z*: $[M+Na]^+$ calcd for $[C_{19}H_{15}NO_3Na]^+$, 328.0950; Found, 328.0958.

4.2.4. 9a-(4-fluorophenyl)-9,9a-dihydropyrido[1,2-*a*]indole-8,10-dione (4da): yield 52% (30 mg). white solid. mp 149–151 °C. rf (hexane/EtOAc = 2/1) = 0.20. ^{1}H-NMR: δ 2.88 (d, 1H, *J* = 16 Hz), 3.34 (dd, 1H, *J* = 1.2, 16 Hz), 5.39 (dd, 1H, *J* = 1.2, 7.6 Hz), 6.99–7.04 (m, 2H), 7.14–7.18 (m, 1H), 7.34–7.39 (m, 3H) 7.71–7.76 (m, 2H), 7.82 (d, 1H, *J* = 7.6 Hz). ^{13}C-NMR: δ 42.4, 70.6, 106.0, 110.1, 116.3 (d, *J* = 21.9 Hz), 122.7, 123.4, 126.5, 127.6 (d, *J* = 8.1 Hz), 129.4 (d, *J* = 2.9 Hz), 137.9, 138.1, 152.1, 163.1 (d, *J* = 148.9 Hz), 191.0, 196.8. IR (KBr): 1719, 1654, 1598, 1575, 1475, 1334, 1282, 1228, 756. HRMS (ESI) *m*/*z*: $[M+Na]^+$ calcd for $[C_{18}H_{12}FNO_2Na]^+$, 316.0750; Found, 316.0731.

4.2.5. 9a-(4-chlorophenyl)-9,9a-dihydropyrido[1,2-a]indole-8,10-dione (4ea): yield 47% (29 mg). white solid. mp 129–130 °C. rf (hexane/EtOAc = 2/1) = 0.05. ^{1}H-NMR: δ 2.88 (d, 1H, *J* = 16 Hz), 3.34 (dd, 1H, *J* = 1.1, 16 Hz), 5.39 (dd, 1H, *J* = 1.1, 7.5 Hz), 7.14–7.18 (m, 1H), 7.28–7.38 (m, 5H), 7.72–7.76 (m, 2H), 7.82 (d, 1H, *J* = 7.5 Hz). ^{13}C-NMR: δ 42.4, 70.7, 106.1, 110.1, 122.7, 123.5, 126.5, 127.1, 129.4, 132.3, 135.1, 138.0, 138.0, 152.1, 190.8, 196.6. IR (KBr): 1718, 1654, 1647, 1598, 1575, 1475, 1327, 1128, 1070, 754. HRMS (ESI) *m*/*z*: $[M+Na]^+$ calcd for $[C_{18}H_{12}ClNO_2Na]^+$, 332.0454; Found, 332.0461.

4.2.6. 9a-(4-(trifluoromethyl)phenyl)-9,9a-dihydropyrido[1,2-a]indole-8,10-dione (4fa): yield 43% (29 mg). white solid. mp 137–138 °C. rf (hexane/EtOAc = 1/1) = 0.13. ^{1}H-NMR: δ 2.93 (d, 1H, *J* = 16 Hz), 3.38 (dd, 1H, J= 1.1, 16 Hz), 5.40 (dd, 1H, *J* = 1.1, 7.6 Hz), 7.16–7.19 (m, 1H), 7.40 (d, 1H, *J* = 8.3 Hz), 7.54 (d, 2H, *J* = 8.4 Hz), 7.59 (d, 2H, *J* = 8.4 Hz), 7.73–7.78 (m, 2H), 7.86 (d, 1H, *J* = 7.6 Hz). ^{13}C-NMR: δ 42.6, 70.9, 106.2, 110.2, 122.6, 123.6, 123.7 (q, *J* = 272.4 Hz), 126.1 (q, *J* = 4.3 Hz), 126.2, 126.5, 131.1 (d, *J* = 34.2 Hz), 137.9, 138.1, 138.1, 152.2, 190.5, 196.2. IR (KBr): 1716, 1563, 1598, 1575, 1485, 1327, 1282, 1228, 1168, 1126, 1070, 754. HRMS (ESI) *m*/*z*: $[M+Na]^+$ calcd for $[C_{19}H_{12}F_3NO_2Na]^+$, 366.0718; Found, 366.0712.

4.2.7. 9a-(2-fluorophenyl)-9,9a-dihydropyrido[1,2-*a*]indole-8,10-dione (4ga): yield 48% (28 mg). white solid. mp 182–183 °C. rf (hexane/EtOAc = 2/1) = 0.2. ^{1}H-NMR: δ 2.83 (d, 1H, *J* = 16.4 Hz), 3.54 (dd, 1H, *J* = 1.1, 16.4 Hz), 5.39 (dd, 1H, *J* = 0.6, 7.5 Hz), 7.0 (ddd, 1H, *J* = 1.3, 8.2, 12.3 Hz) 7.09–7.19 (m, 2H), 7.29–7.37 (m, 3H), 7.71–7.75 (m, 2H), 7.78 (d, 1H, *J* = 7.5 Hz). ^{13}C-NMR: δ

40.8 (d, *J* = 3.3 Hz), 69.7 (d, *J* = 3.0 Hz), 106.1, 110.2, 117.2 (d, *J* = 22.9 Hz), 121.5 (d, *J* = 12.0 Hz), 123.2 (d, *J* = 2.9 Hz), 123.3, 124.5 (d, *J* = 3.7 Hz), 126.0, 129.0 (d, *J* = 3.7 Hz), 131.1 (d, *J* = 8.9 Hz), 137.7, 138.7, 152.4, 161.1 (d, *J* = 251.4 Hz), 191.6, 196.6. IR (KBr): 1718, 1653, 1600, 1575, 1475, 1456, 1334, 1303, 1287, 1272, 1230, 753. HRMS (ESI) *m*/*z*: $[M+H]^+$ calcd for $[C_{18}H_{13}FNO_2]^+$, 294.0930; Found, 294.0936.

4.2.8. 9a-(2-naphthalenyl)-9,9a-dihydropyrido[1,2-*a*]indole-8,10-dione (4ha): yield 49% (32 mg). white solid. mp 239–240 °C. rf (hexane/EtOAc = 2/1) = 0.15. ^{1}H-NMR: δ 2.96 (d, 1H, *J* = 16.2 Hz), 3.55 (d, 1H, *J* = 16.2 Hz), 5.38 (d, 1H, *J* = 7.4 Hz), 7.15 (dd, 1H, *J* = 7.4, 7.4 Hz), 7.42–7.48 (m, 4H), 7.73–7.81 (m, 6H), 7.89 (d, 1H, *J* = 7.4 Hz). ^{13}C-NMR: δ 42.3, 71.3, 106.0, 110.1, 122.7, 122.9, 123.3, 125.4, 126.5. 126.6, 126.8, 127.6, 128.2, 129.3, 130.9, 133.1, 133.2, 137.8, 138.1. IR (KBr): 1718, 1653, 1600, 1575, 1475, 1334, 754. HRMS (ESI) *m*/*z*: $[M+H]^+$ calcd for $[C_{22}H_{16}NO_2]^+$, 326.1181; Found, 326.1190.

4.2.9. 2-methyl-9a-phenyl-9,9a-dihydropyrido[1,2-a]indole-8,10-dione (4ia): yield 38% (22 mg). white solid. mp 205–206 °C. rf (hexane/EtOAc = 2/1) = 0.05. ^{1}H-NMR: δ 2.37 (s, 3H), 2.87 (d, 1H, *J* = 16 Hz), 3.39 (dd, 1H, *J* = 1.0, 16 Hz), 5.34 (d, 1H, *J* = 1.0, 7.4 Hz), 7.26–7.38 (m, 6H), 7.28–7.55 (m, 2H), 7.81 (d, 1H, *J* = 7.4 Hz). ^{13}C-NMR: δ 20.8, 42.3, 71.3, 105.2, 109.8, 123.1, 125.6, 125.9, 128.8, 129.1, 133.4, 133.7, 138.2, 138.9, 150.4, 191.1, 197.0. IR (KBr): 1718, 1653, 1618, 1595, 1575, 1494, 1332, 1282, 734. HRMS (ESI) *m*/*z*: $[M+Na]^+$ calcd for $[C_{19}H_{15}NO_2Na]^+$, 312.1000; Found, 312.0994.

4.2.10. 2-methoxy-9a-phenyl-9,9a-dihydropyrido[1,2-a]indole-8,10-dione (4ja): yield 38% (23 mg). white solid. mp 212–213 °C. rf (hexane/EtOAc = 2/1) = 0.05. ^{1}H-NMR: δ 2.88 (d, 1H, *J* = 16 Hz), 3.39 (d, 1H, *J* = 16 Hz), 5.32 (d, 1H, *J* = 7.4 Hz), 7.13 (d, 1H, *J* = 2.3 Hz), 7.28–7.39 (m, 7H), 7.77 (d, 1H, *J* = 7.4 Hz) ^{13}C-NMR: δ 42.3, 56.0, 71.6, 104.7, 106.6, 111.3, 123.7, 125.6, 127.5, 128.9, 129.2, 133.7, 138.3, 147.0, 156.2, 190.9, 197.1. IR (KBr): 1716, 1653, 1647, 1597, 1575, 1492, 1327, 1278. HRMS (ESI) *m*/*z*: $[M+Na]^+$ calcd for $[C_{19}H_{15}NO_3Na]^+$, 328.0950; Found, 328.0943.

4.2.11. 2-fluoro-9a-phenyl-9,9a-dihydropyrido[1,2-a]indole-8,10-dione (4ka): yield 17% (10 mg). white solid. mp 150–151 °C. rf (hexane/EtOAc = 2/1) = 0.15. ^{1}H-NMR: δ 2.90 (d, 1H, *J* = 16 Hz), 3.40 (dd, 1H, *J* = 1.0, 16 Hz), 5.37 (d, 1H, *J* = 1.0, 7.5 Hz), 7.31–7.44 (m, 7H), 7.45 (ddd, 1H, *J* = 2.7, 8.8. 8.8 Hz), 7.78 (d, 1H, *J* = 7.5 Hz). ^{13}C-NMR: δ 42.4, 71.9, 105.9, 111.2 (d, *J* = 7.8 Hz), 111.8 (d, *J* = 23.3 Hz), 124.0 (d, *J* = 7.8 Hz), 125.5 (d, *J* = 25.6 Hz), 125.5, 129.0, 129.2, 133.2, 137.9, 148.6, 158.6 (d, *J* = 247 Hz), 190.6, 196.3 (d, *J* = 3.0 Hz). IR (KBr): 1718, 1654, 1647, 1577, 1489, 1336, 1263. HRMS (ESI) *m*/*z*: $[M+Na]^+$ calcd for $[C_{18}H_{12}FNO_2Na]^+$, 316.0750; Found, 316.0756.

4.2.12. 2-chloro-9a-phenyl-9,9a-dihydropyrido[1,2-a]indole-8,10-dione (4la): yield 26% (16 mg). white solid. mp >220 °C dec. rf (hexane/EtOAc = 2/1) = 0.15. ^{1}H-NMR: δ 2.89 (d, 1H, *J* =16 Hz), 3.41 (d, 1H, *J* = 1.0, 16 Hz), 5.39 (d, 1H, *J* =7.5 Hz), 7.30–7.36 (m, 6H), 7.65–7.68 (m, 2H), 7.78 (d, 1H, *J* = 7.5 Hz). ^{13}C-NMR: δ 42.4, 71.8, 106.5, 111.2, 124.1, 125.5, 125.9, 128.8, 129.1, 129.3, 133.1, 137.6, 137.6, 150.5, 190.7, 195.8. IR (KBr): 1724, 1670, 1653, 1647, 1593, 1571, 1477, 1336, 1282, 1228. HRMS (ESI) *m*/*z*: $[M+Na]^+$ calcd for $[C_{18}H_{12}ClNO_2Na]^+$, 332.0454; Found, 332.0454.

4.2.13. 3-methyl-9a-phenyl-9,9a-dihydropyrido[1,2-a]indole-8,10-dione (4ma): yield 40% (23 mg). white solid. mp 242–243 °C. rf (hexane/EtOAc = 2/1) = 0.05. ^{1}H-NMR: δ 2.52 (s, 3H), 2.87 (d, 1H, *J* = 15.9 Hz), 3.40 (dd, 1H, *J* = 0.8, 15.9 Hz), 5.35 (d, 1H, *J* = 7.5 Hz), 7.00 (d, 1H, *J* = 8.0 Hz), 7.17 (s,1H), 7.28–7.38 (m, 5H), 7.60 (d, 1H, *J* = 8.0 Hz), 7.80 (d, 1H, *J* = 7.5 Hz). ^{13}C-NMR: δ 22.8, 42.4, 71.4, 105.7, 110.2, 120.6, 124.8, 125.6, 126.1, 128.8, 129.1, 133.9, 138.0, 149.8, 152.6, 191.2, 196.4. IR (KBr): 1707, 1651, 1612, 1597, 1570, 1465, 1340, 1325. HRMS (ESI) *m*/*z*: $[M+H]^+$ calcd for $[C_{19}H_{16}NO_2]^+$, 290.1181; Found, 290.1178.

4.2.14. 3-methyl-9a-phenyl-9,9a-dihydropyrido[1,2-a]indole-8,10-dione (4na): yield 35% (20 mg). white solid. mp 197–198 °C. rf (hexane/EtOAc = 2/1) = 0.10. ^{1}H-NMR: δ 2.73 (s, 3H), 2.91 (d, 1H, *J* = 16.3 Hz), 3.41 (d, 1H, *J* = 16.3 Hz), 5.35 (d, 1H, *J* = 7.6 Hz), 7.07 (d, 1H, *J* = 7.7 Hz), 7.29–7.34 (m, 3H), 7.38–7.41 (m, 2H), 7.48 (d, 1H, *J* = 7.3 Hz), 7.61 (d, 1H, *J* = 7.7 Hz), 8.16 (d, 1H, *J* = 7.6 Hz). ^{13}C-NMR: δ 20.8, 42.3, 71.8, 105.7, 122.7, 123.6, 124.0, 124.1, 125.5, 128.8, 129.1, 133.7, 140.7, 140.9, 150.7, 190.7, 197.5. IR (KBr): 1718, 1650, 1593, 1492, 1470, 1446, 1437, 1413, 1329, 1281, 1247, 1226, 954, 786, 756, 705. HRMS (ESI) *m*/*z*: $[M+H]^+$ calcd for $[C_{19}H_{16}NO_2]^+$, 290.1181; Found, 290.1182.

4.2.15. 7a-phenyl-7a,8-dihydrobenzo[*g*]pyrido[1,2-a]indole-7,9-dione (4oa): yield 66% (43 mg). white solid. mp 243–244 °C. rf (hexane/EtOAc = 2/1) = 0.15. ^{1}H-NMR: δ 3.00 (d, 1H, *J* = 16.3 Hz), 3.49 (d, 1H, *J* = 16.3 Hz), 5.45 (d, 1H, *J* = 7.7 Hz), 7.29–7.33 (m, 3H), 7.48–7.50 (m, 2H), 7.58 (d, 1H, *J* = 8.4 Hz), 7.67 (d, 1H, *J* = 8.4 Hz), 7.73–7.77 (m, 2H), 8.01 (dd, 1H, *J* = 1.8, 8.2 Hz), 8.44 (d, 1H, *J* = 7.9 Hz), 8.58 (d, 1H, *J* = 7.7 Hz). ^{13}C-NMR: δ 43.0, 72.6, 106.6, 120.2, 120.7, 121.4, 123.7, 125.3, 125.4, 127.8, 128.9, 129.2, 130.2, 130.4, 139.5, 140.9, 152.0, 190.9, 197.3. IR (KBr): 1706, 1684, 1654, 1623, 1590, 1564, 1526, 1459, 1442, 1381, 1330, 1292, 1265, 1241, 1107, 798, 756, 694. HRMS (ESI) *m*/*z*: $[M+H]^+$ calcd for $[C_{19}H_{16}NO_2]^+$, 290.1181; Found, 290.1182.

4.3. Procedure for the Synthesis of Substrate amine 5 and 15:

4.3.1. *tert*-butyl (2-(1H-indol-2-yl)phenethyl)carbamate: To a solution of *tert*-butyl (2-bromophenethyl)carbamate[20] (2.1 g, 7.0 mmol) in DMF (10.0 mL) were added $CsCO_3$ (9.3 g, 28 mmol), $PdCl_2(dppf)\cdot CH_2Cl_2$ (343 mg, 0.42 mmol) and 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-

yl)-1*H*-Indole (2.6 g, 10.7 mmol). The reaction mixture was heated to 50 °C for 3 h under Ar. The reaction was cooled down, EtOAc and a saturated aqueous solution of NH_4Cl were added and the mixture was stirred for 30 min. After extracting with EtOAc, the organic extracts were washed with H_2O and brine, dried over Na_2SO_4, and then concentrated. The crude product was chromatographed on silica gel. yield 88% (2.1 g). pale yellow oil. rf (hexane/EtOAc = 15/1) = 0.20. ^{1}H-NMR: δ 1.43 (s, 9H), 2.93 (t, 2H, *J* = 7.9 Hz), 3.30 (dt, 2H, *J* = 7.9, 6.7 Hz), 4.80 (s, 1H), 6.61 (s, 1H), 7.12 (ddd, 1H, *J* = 7.5, 7.5, 1.1 Hz), 7.20 (ddd, 1H, *J* = 7.6, 7.6, 1.2Hz), 7.26–7.32 (m, 3H), 7.51–7.62 (m, 2H), 7.64 (d, 1H, *J* = 7.8 Hz), 9.66 (s, 1H). ^{13}C-NMR δ 28.6, 34.3, 42.4, 79.8, 102.6, 111.6, 119.9, 120.4, 121.9, 126.8, 128.2, 128.7, 130.5, 130.7, 133.2, 136.5, 137.1, 137.8, 156.8. IR (KBr): 3404, 3319, 2978, 1689, 1508, 1365, 1296, 1273, 1251, 1168, 750. HRMS (ESI) *m*/*z*: $[M+Na]^+$ calcd for $[C_{21}H_{24}N_2O_2Na]^+$, 359.1735; Found, 359.1717.

2-(2-(1*H*-indol-2-yl)phenyl)ethanamine (5a): To a solution of *tert*-butyl (2-(1*H*-indol-2-yl)phenethyl)carbamate (1.42 g, 4.23 mmol) in CH_2Cl_2 (30 mL) was added trifluoroacetic acid (0.40 mL, 5.00 mmol) at 0 °C, and then, the mixture was stirred at rt for 4 h. After the solvent was evaporated, the residue was dissolved in EtOAc, washed with saturated $NaHCO_3$, H_2O and brine, dried over Na_2SO_4, and then concentrated. Recrystallization from EtOH afforded the titled compound. yield 54% (537 mg). colorless plates. mp 138–139 °C. ^{1}H-NMR: δ 1.76 (brs, 2H), 3.20 (t, 2H, J = 6.4 Hz), 2.95 (t, 1H, *J* = 6.4 Hz), 6.57 (s, 1H), 7.08 (ddd, 1H J= 7.5, 7.5, 1.0 Hz), 7.16 (ddd, 1H, *J* = 7.5, 7.5, 1.2Hz), 7.26–7.38 (m, 3H), 7.42 (dd, 1H, *J* = 8.1, 0.9 Hz), 7.57 (dd, 1H, *J* = 7.6, 1.3 Hz), 7.65 (d, 1H, *J* = 7.8 Hz), 12.2 (s, 1H). ^{13}C-NMR: δ 34.3, 42.3, 101.3, 111.2, 119.3, 120.3, 121.3, 126.6, 128.2, 128.8, 130.1, 130.7, 134.6, 136.5, 137.0, 138.8. IR (KBr): 3057, 2862, 1560, 1541, 1477, 1448, 1298, 750. HRMS (ESI) *m*/*z*: $[M+H]^+$ calcd for $[C_{16}H_{17}N_2]^+$, 237.1392; Found, 237.1402.

4.3.2. 2-(2-(5-chloro-1*H*-indol-2-yl)phenyl)ethan-1-amine (5b): Starting from *tert*-butyl (2-bromobenzyl)carbamate and 5-chloro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole, this compound was prepared according to the procedure for the synthesis of **5a**. white solid. mp 58–59 °C. ^{1}H-NMR: δ 2.89 (t, 2H, *J* = 5.8 Hz), 3.19 (m, 2H), 6.49 (s, 1H), 7.08 (dd, 1H, *J* = 2.0, 8.9 Hz), 7.19–7.40 (m, 4H), 7.55 (d, 1H, *J* = 7.5 Hz), 7.59 (d, 1H, *J* = 1.7 Hz), 12.7 (s, 1H). ^{13}C-NMR: δ 34.7, 42.4, 100.8, 112.4, 119.5, 121.4, 124.8, 126.7, 128.4, 129.9, 130.2, 130.7, 134.2, 134.9, 137.1, 140.5. IR (KBr): 3115, 3010, 2927, 1577, 1473, 1444, 1317, 1215, 1058, 916, 867, 796, 759. HRMS (ESI) *m*/*z*: $[M+H]^+$ calcd for $[C_{16}H_{15}ClN_2]^+$, 271.1002; Found, 271.1001.

***tert*-butyl (2-(5-chloro-1*H*-indol-2-yl)phenethyl)carbamate:** white solid. mp 117–118 °C. rf (hexane/acetone = 4/1) = 0.30. ^{1}H-NMR: δ 1.44 (s, 9H), 2.91 (t, 2H, *J* = 8.1 Hz), 3.28 (td, 2H, *J* = 8.1, 7.2 Hz), 4.90 (brs, 1H), 6.52 (s, 1H), 7.13 (dd, 1H, *J* = 8.5, 1.9 Hz), 7.14–7.22 (m, 1H), 7.22–7.30 (m, 2H), 7.45 (d, 1H, *J* = 8.5 Hz), 7.50–7.61 (m, 2H), 10.1 (brs, 1H). ^{13}C-NMR: δ 28.5, 34.5, 42.6, 80.1, 102.1, 112.6, 119.5, 122.0, 125.3, 126.9, 128.3, 129.5, 130.6, 130.7, 132.5, 135.5, 135.9, 139.2, 157.0. IR (KBr): 3421, 3302, 2978, 2933, 1685, 1508, 1490, 1465, 1458, 1446, 1365,

1313, 1274, 1251, 1166, 759. HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $[C_{21}H_{23}ClN_2O_2Na]^+$, 393.1346; Found, 393.1335.

4.3.2. 2-(2-(5-methoxy-1*H*-indol-2-yl)phenyl)ethan-1-amine (5b): Starting from *tert*-butyl (2-bromobenzyl)carbamate and 5-methoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole, this compound was prepared according to the procedure for the synthesis of **5a**. pale yellow oil. ^{1}H-NMR: δ 1.73 (s, 1H), 2.90 (t, 2H, *J* = 6.0 Hz), 3.14 (t, 2H, *J* = 6.0 Hz), 3.85 (s, 3H), 6.49 (s, 1H), 6.82 (dd, 1H, *J* = 2.4, 8.7 Hz), 7.10 (d, 1H, *J* = 2.4 Hz), 7.26–7.31 (m, 4H), 7.54 (m, 1H), 12.0 (s, 1H). ^{13}C-NMR: δ 34.7, 42.4, 100.8, 112.4, 119.5, 121.4, 124.8, 126.7, 128.4, 129.9, 130.2, 130.7, 134.2, 134.9, 137.1, 140.5. IR (KBr): 3378, 2938, 1623, 1588, 1492, 1480, 1450, 1215, 1146, 1115, 1031, 797, 759. HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $[C_{17}H_{19}N_2O]^+$, 267.1497; Found, 267.1493.

***tert*-butyl (2-(5-methoxy -1*H*-indol-2-yl)phenethyl)carbamate:** white solid. mp 128–129 °C. rf (hexane/acetone = 10/1) = 0.35. ^{1}H-NMR: δ 1.45 (s, 9H), 2.94 (t, 2H, *J* = 8.3 Hz), 3.28–3.33 (m, 2H), 3.85 (s, 3H), 4.84 (s, 1H), 6.52 (s, 1H), 6.86 (dd, 1H, *J* = 2.4, 8.8 Hz), 7.09 (d, 1H, *J* = 2.4 Hz), 7.19–7.28 (m, 3H), 7.42 (d, 1H, *J* = 8.2 Hz), 7.54 (s, 1H), 9.63 (s, 1H). ^{13}C-NMR: δ 28.5, 34.4, 42.5, 55.9, 79.9, 101.9, 102.4, 112.2, 112.2, 126.8, 128.0, 128.8, 130.4, 130.6, 132.3, 133.1, 136.1, 138.4, 154.2, 156.7. IR (KBr): 3415, 3322, 2977, 1690, 1509, 1452, 1215, 1166, 759. HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $[C_{22}H_{27}N_2O_3]^+$, 367.2022; Found, 367.2032.

4.3.3. 2-(2-(5-fluoro-1*H*-indol-2-yl)phenyl)ethan-1-amine (5c): Starting from *tert*-butyl (2-bromobenzyl)carbamate and 5-fluoro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole, this compound was prepared according to the procedure for the synthesis of **5a**. pale yellow oil. ^{1}H-NMR: δ 1.73 (s, 1H), 2.90 (t, 2H, *J* = 6.0 Hz), 3.14 (t, 2H, *J* = 6.0 Hz), 3.85 (s, 3H), 6.49 (s, 1H), 6.82 (dd, 1H, *J* = 2.4, 8.7 Hz), 7.10 (d, 1H, *J* = 2.4 Hz), 7.26–7.31 (m, 4H), 7.54 (m, 1H), 12.0 (s, 1H). ^{13}C-NMR: δ 34.7, 42.4, 100.8, 112.4, 119.5, 121.4, 124.8, 126.7, 128.4, 129.9, 130.2, 130.7, 134.2, 134.9, 137.1, 140.5. IR (KBr): 3380, 2946, 2867, 1587, 1327, 1202, 1130, 1108, 953, 854, 792, 759. HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $[C_{16}H_{16}FN_2]^+$, 255.1298; Found, 255.1286.

***tert*-butyl (2-(5-fluoro-1*H*-indol-2-yl)phenethyl)carbamate:** white solid. mp 130–131 °C. rf (hexane/acetone = 10/1) = 0.40. ^{1}H-NMR: δ 1.45 (s, 9H), 2.92 (t, 2H, *J* = 7.6 Hz), 3.26–3.30 (m, 2H), 4.87 (s, 1H), 6.55 (s, 1H), 6.90–6.95 (m, 1H), 7.18–7.29 (m, 4H), 7.45–7.55 (m, 2H), 9.96 (s, 1H). ^{13}C-NMR: δ 28.5, 34.4, 42.6, 80.1, 102.6 (d, *J* = 4.5 Hz), 104.8 (d, *J* = 23.3 Hz), 110.1 (d, *J* = 26.3 Hz), 112.2 (d, *J* = 8.6 Hz), 126.9, 128.3, 128.7 (d, *J* = 10.1 Hz), 130.5, 130.7, 132.7, 133.7, 136.0, 139.5, 156.9, 158.1 (d, *J* = 230 Hz). IR (KBr): 3421, 3302, 2978, 2933, 1685, 1508, 1490, 1465, 1458, 1446, 1365, 1313, 1274, 1251, 1166, 759. HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $[C_{21}H_{24}FN_2O_2]^+$, 355.1822; Found, 355.1830.

4.3.4. 2-(2-(7-methoxy-1*H*-indol-2-yl)phenyl)ethan-1-amine (5e): Starting from *tert*-butyl (2-bromobenzyl)carbamate and 7-methoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole, this compound was prepared according to the procedure for the synthesis of **5a**. white solid.

mp 141–142 °C. ^{1}H-NMR: δ 2.85–3.35 (m, 4H), 3.95 (s, 3H), 6.54 (s, 1H), 6.61 (d, 1H, *J* = 7.8 Hz), 7.00 (dd, 1H, *J* = 7.9, 7.9 Hz), 7.19–7.36 (m, 4H), 7.55 (d, 1H, *J* = 7.6 Hz), 12.33 (s, 1H). ^{13}C-NMR: δ 35.4, 42.6, 55.5, 101.4, 101.6, 113.2, 119.6, 126.5, 127.2, 128.1, 130.2, 130.2, 130.7, 134.6, 137.6, 138.5, 146.4. IR (KBr): 3016, 1251, 1215, 1097, 754. HRMS (ESI) *m*/*z*: $[M+H]^+$ calcd for $[C_{17}H_{19}N_2O]^+$, 267.1497; Found, 267.1500.

***tert*-butyl (2-(7-methoxy-1*H*-indol-2-yl)phenethyl)carbamate:** pale yellow oil. rf (hexane/acetone = 4/1) = 0.30. ^{1}H-NMR: δ 1.36 (s, 9H), 2.92 (t, 2H, *J* = 7.3 Hz), 3.17–3.31 (m, 2H), 3.90 (s, 3H), 4.52 (s, 1H), 6.50 (s, 1H), 6.63 (d, 1H, *J* = 7.7 Hz), 7.03 (dd, 1H, *J* = 7.7, 7.7 Hz), 7.19–7.32 (m, 4H), 7.39 (d, 1H, *J* = 7.2 Hz), 8.77(s, 1H). ^{13}C-NMR: δ 28.4, 33.7, 41.5, 55.3, 79.2, 101.9, 103.0, 113.2, 120.4, 126.6, 126.8, 128.4, 130.3, 130.2, 130.4, 133.3, 136.9, 137.6, 146.0, 155.9. IR (KBr): 3408, 3348, 2976, 2933, 1693, 1627, 1583, 1504, 1483, 1446, 1394, 1365, 1328, 1311, 1257, 1168, 1097, 1056, 758. HRMS (ESI) *m*/*z*: $[M+H]^+$ calcd for $[C_{22}H_{27}N_2O_3]^+$, 367.2022; Found, 367.2021.

4.3.5. (2-(1*H*-indol-2-yl)phenyl)methanamine (15a): Starting from *tert*-butyl (2-bromobenzyl)carbamate [21] and 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole, this compound was prepared according to the procedure for the synthesis of **5a**. white solid. mp 91–92 °C. ^{1}H-NMR: δ 1.78 (brs, 2H), 3.88 (s, 2H), 6.70 (s, 1H), 7.05–7.13 (m, 1H), 7.13–7.32 (m, 1H), 7.23–7.28 (m, 2H), 7.31–7.38 (m, 1H), 7.41 (d, 1H, *J* = 8.1 Hz), 7.66 (d, 1H, *J* = 7.6 Hz), 7.74 (d, 1H, *J* = 7.7 Hz), 12.67 (s, 1H). ^{13}C-NMR: δ 46.2, 100.6, 111.4, 119.4, 120.4, 121.5, 127.6, 128.4, 128.7, 130.2, 131.2, 134.4, 136.7, 136.8, 139.2. IR (KBr): 3057, 1450. 1300, 750. HRMS (ESI) *m*/*z*: $[M+Na]^+$ calcd for $[C_{15}H_{14}N_2Na]^+$, 245.1055; Found, 245.1055.

***tert*-butyl (2-(1*H*-indol-2-yl)benzyl)carbamate:** white solid. mp 106–108 °C. rf (hexane/acetone = 2/1) = 0.50. ^{1}H-NMR δ 1.44 (s, 9H), 4.35 (d, 2H, *J* = 6.3 Hz), 5.14 (s, 1H), 6.56 (s, 1H), 7.11 (ddd, 1H, *J* = 1.0, 7.5, 7.5 Hz), 7.18 (ddd, 1H, *J* = 1.0, 7.6, 7.6 Hz), 7.27–7.38 (m, 3H), 7.40 (d, 1H, *J* = 7.9 Hz), 7.45–7.52 (m, 1H), 7.62 (d, 1H, *J* = 7.8 Hz), 10.0 (s, 1H). ^{13}C-NMR: δ 28.4, 42.6, 80.2, 102.4, 111.3, 119.8, 120.4, 121.9, 127.6, 128.3, 128.7, 129.3, 130.4, 132.6, 136.5, 136.7, 137.2, 156.5. IR (KBr): 3406, 2978, 1685, 1654, 1508, 1490, 1456, 1365, 1296, 1247, 1166, 750. HRMS (ESI) *m*/*z*: $[M+Na]^+$ calcd for $[C_{20}H_{22}N_2O_2Na]^+$, 345.1579; Found, 345.1551.

4.4. General Procedure for the Synthesis of Tetracyclic Quinazolinones 6 and 16:

A mixture of compound **1** (0.20 mmol), CuBr (6.3 mg, 0.04 mmol) and pyridine (32 μL, 0.40 mmol) in DMSO (1.0 mL) was stirred at 60 °C under an oxygen atmosphere (1 atm). After 24 h, the mixture was quenched with H_2O and extracted with EtOAc. The organic extracts were washed with H_2O and brine, dried over Na_2SO_4, and then concentrated. The crude product was chromatographed on silica gel.

4.4.1. 5*H*-isoquinolino[1,2-*b*]quinazolin-8(6*H*)-one (6a):[22] yield 71% (35 mg). white solid. rf (hexane/EtOAc = 5/1) = 0.20. ^{1}H-NMR δ 8.48 (d, 1H, *J* = 7.9 Hz), 8.31 (d, 1H, *J* = 7.9 Hz), 7.72–7.77 (m, 2H), 7.40–7.48 (3H, m), 7.27 (d, 1H, *J* = 7.4 Hz), 4.41 (t, 2H, *J* = 6.4 Hz), 3.09 (t, 2H, *J* = 6.4 Hz). ^{13}C-NMR: δ 27.4, 39.5, 120.7, 126.46, 126.8, 127.4, 127.5, 127.9, 129.5, 131.6, 134.1, 136.9, 147.7, 149.3, 161.6.

4.4.2. 10-chloro-5,6-dihydro-8*H*-isoquinolino[1,2-*b*]quinazolin-8-one (6b):[22] yield 39% (22 mg). white solid. rf (hexane/EtOAc = 4/1) = 0.35. ^{1}H-NMR: δ 8.45 (d, 1H, *J* = 7.8 Hz), 8.26 (d, 1H, *J* = 2.3 Hz), 7.63–7.73 (m, 2H), 7.49 (dd, 1H, *J* = 7.3, 1.5 Hz), 7.43 (dd, 1H, *J* = 1.5, 7.6 Hz), 7.28 (dd, 1H, J = 7.3, 0.5 Hz), 4.28 (t, 2H, *J* = 6.5 Hz), 3.11 (t, 2H, *J* = 6.4 Hz,). ^{13}C-NMR: δ 26.2, 39.4, 121.5, 125.2, 127.2, 127.4, 127.8, 128.8, 129.5, 130.6, 131.9, 134.5, 137.8, 146.0, 149.8, 159.7.

4.4.3. 10-methoxy-5,6-dihydro-8*H*-isoquinolino[1,2-*b*]quinazolin-8-one (6c): yield 54% (28 mg). white solid. mp 172–173 °C. rf (hexane/EtOAc = 2/1) = 0.40. ^{1}H-NMR: δ 3.10 (t, 2H, *J* = 6.4 Hz), 3.93 (s, 3H), 4.42 (t, 2H, *J* = 6.4 Hz), 7.28 (d, 2H, *J* = 7.7 Hz), 7.35 (dd, 1H, J = 2.8, 8.8 Hz), 7.40–7.47 (m, 2H), 7.67 (d, 1H, *J* = 2.9 Hz), 7.70 (d, 1H, *J* = 8.8 Hz), 8.44 (d, 1H, *J* = 7.7 Hz). ^{13}C-NMR: δ 27.5, 39.8, 55.9, 106.2, 121.5, 124.7, 127.5, 127.6, 127.7, 129.3, 129.7, 131.3, 136.7, 142.5, 147.4, 158.3, 161.5. IR (KBr): 1662, 1616, 1558, 1490, 1472, 1442, 1419, 1386, 1362, 1324, 1264, 1220, 1144, 1108, 1092, 1031, 867, 832, 779, 739, 706. HRMS (ESI) *m*/*z*: $[M+H]^+$ calcd for $[C_{17}H_{15}N_2O_2]^+$, 279.1134; Found, 279.1125.

4.4.4. 10-fluoro-5,6-dihydro-8*H*-isoquinolino[1,2-*b*]quinazolin-8-one (6d): yield 52% (27 mg). white solid. mp 211–212 °C. rf (hexane/EtOAc = 2/1) = 0.40. ^{1}H-NMR: δ 3.10 (t, 2H, *J* = 6.4 Hz), 4.41 (t, 2H, *J* = 6.4 Hz), 7.28 (d, 2H, *J* = 7.4 Hz), 7.41–7.50 (m, 3H), 7.77 (dd, 1H, *J* = 4.9, 8.9 Hz), 7.93 (dd, 1H, *J* = 2.9, 8.5 Hz), 8.45 (d, 1H, *J* = 7.6 Hz). ^{13}C-NMR: δ 27.4, 39.8, 111.7 (d, *J* = 23.4 Hz), 121.9 (d, *J* = 8.5 Hz), 123.0 (d, *J* = 24.1 Hz), 127.6, 127.7, 127.9, 129.4, 123.0 (d, *J* = 8.0 Hz), 131.8, 136.9, 144.5, 148.8 (d, *J* = 2.1 Hz), 160.8 (d, *J* = 248 Hz), 161.1 (d, *J* = 3.4 Hz). IR (KBr): 1669, 1654, 1592, 1565, 1491, 1484, 1471, 1394, 1347, 1329, 1253, 1137, 895, 849, 784, 771, 736, 706, 685. HRMS (ESI) *m*/*z*: $[M+H]^+$ calcd for $[C_{16}H_{12}FN_2O]^+$, 267.0934; Found, 267.0934.

4.4.5. 12-methoxy-5,6-dihydro-8*H*-isoquinolino[1,2-*b*]quinazolin-8-one (6e):[22] yield 56% (31 mg). white solid. rf (hexane/EtOAc = 2/1) = 0.35. ^{1}H-NMR: δ: 8.55 (dd, 1H, *J* = 1.7, 7.5 Hz), 7.91 (dd, 1H, *J* = 1.3, 8.0 Hz), 7.49–7.40 (m, 3H), 7.29–7.26 (m, 1H), 7.20 (dd, 1H, *J* = 1.2, 8.0 Hz), 4.42 (t, 2H, *J* = 6.9 Hz), 4.05 (s, 3H), 3.10 (t, 2H, *J* = 6.9 Hz,). ^{13}C-NMR: δ 27.6, 39.9, 56.6, 114.3, 118.5, 122.1, 126.9, 127.5, 127.8, 128.5, 129.8, 131.8, 136.9, 138.7, 148.9, 154.9, 161.7.

4.4.6. isoindolo[1,2-*b*]quinazolin-10(12*H*)-one (16a):[23] yield 12% (5.6 mg). white solid. rf (hexane/EtOAc = 1/1) = 0.30. ^{1}H-NMR: δ 8.36 (dd, 1H, *J* = 8.0, 1.0 Hz), 8.16 (d, 1H, *J* = 7.6 Hz),

7.80 (m, 2H), 7.63 (m, 2H), 7.58 (m, 1H), 7.49 (m, 1H), 5.16 (s, 2H). ^{13}C-NMR: δ 49.9, 120.7, 123.5, 123.6, 126.5, 126.6, 127.5, 129.0, 132.4, 132.8, 134.4, 139.7, 149.6, 155.0, 160.8.

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