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Synthesis of Benzopyridoindolone Derivatives via a One-Pot Copper Catalyzed Tandem Reaction of 2-Iodobenzamide Derivatives and 2-Iodobenzylcyanides

Veerababurao Kavala,[†] Zonghan Yang,[†] Ashok Konala, Chia-Yu Huang, Chun-Wei Kuo, and Ching-Fa Yao*

Department of Chemistry, National Taiwan Normal University, 88, Sec. 4, Ting-Chow Road, Taipei 116, Taiwan, R.O.C.

Supporting Information

ABSTRACT: An efficient approach for the synthesis of benzo-fused pyridoindolone derivatives via a one-pot copper catalyzed tandem reaction of 2-iodobenzamides with 2-iodobenzylcyanides has been developed. Using this protocol, benzo-fused pyridoindolone derivatives are obtained in high yields in a relatively short period of time under mild reaction conditions. To the best of our knowledge, this is the first approach where one can synthesize free indole N−H benzo-fused pyridoindolones. Also, both indole and pyridone cores are constructed during the course of the reaction. The methodology shows good functional group tolerance and allows synthesis of thiophene-fused pyridoindolones and fused indolobenzonaphthyridone derivatives.

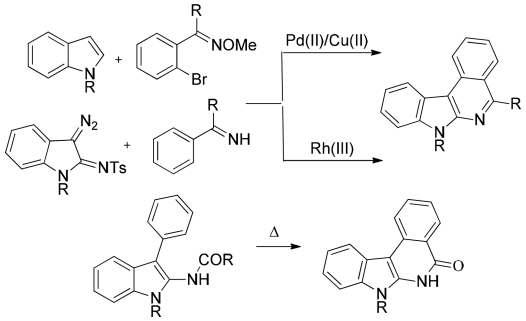
INTRODUCTION

Pyridoindolones and benzo-fused derivatives derived from them are known to have an antitumor activity.[1] Benzopyridoindolones, important precursors of indoloisoquinolines, exhibit a wide variety of biological activities that include antioxidant, antibacterial, antifungal, antihistaminic, and analgesic activities.[2] Despite the immense importance of benzopyridoindolone derivatives, very few synthetic methods are available for their preparation. Further, the reported procedures for the synthesis of benzopyridoindolones involve the use of functionalized starting materials, such as β-phenyl-α-substituted amino indole derivatives[3] and β-phenyl-α-isocyanatoindole derivatives.[4]

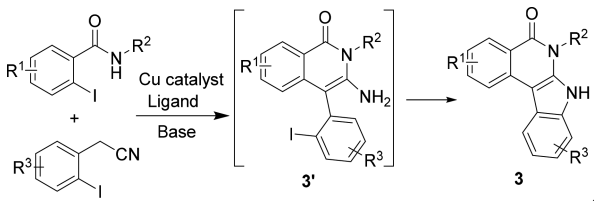
Roy and co-workers reported on the synthesis of benzopyridoindole from 2-(1-substituted-1*H*-indol-3-yl)benzaldehyde-*O*-methyl oxime derivatives.[5] Very recently, Wang et al. also reported on the synthesis of benzopyridoindole derivatives from the Rh(III) catalyzed C−C/C−N coupling of imidates and α-diazo imidamide (Scheme 1).[6] However, some of these reported procedures permit benzopyridoindole derivatives to be readily accessed. Drawbacks associated with the reported procedures involve the use of either indole functionalized starting materials or expensive metal catalysts. In addition, all reported approaches result in the formation of N-substituted pyridoindolone derivatives, as shown in Scheme 1.

Copper catalyzed tandem cyclization reactions of 2-iodobenzamide derivatives have gained considerable attention due to their use in the synthesis of various bioactive heterocycles compounds.[7] For the past few years, we have been interested in the synthesis of various fused heterocycle derivatives from 2-iodobenzamide derivatives through copper catalyzed tandem cyclization reactions.[8] In a continuation of this interest, we attempted to synthesize indoloisoquinolinone derivatives from the reaction of 2-iodobenzamide derivatives and substituted 2-iodobenzylcyanides via copper catalyzed tandem cyclization reactions, as shown in Scheme 2. The proposed strategy involved copper catalyzed coupling followed by an intramolecular attack by the amide nitrogen on the CN

Scheme 1. Previous Approaches



Scheme 2. Synthetic Strategy



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moiety[9] and the intramolecular coupling of the in situ regenerated amine moiety with the proximate halide.[10] We anticipated that both indole and pyridone cores could be constructed during the course of the reaction itself, which would allow us to synthesize a diverse array of indoloisoquinolinone derivatives.

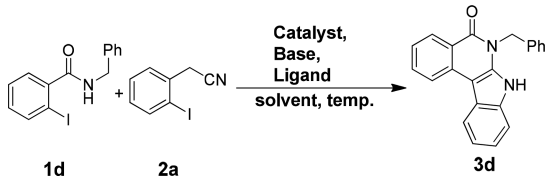
RESULTS AND DISCUSSION

At the outset, we used *N*-benzyl-2-iodobenzamide (**1a**) and 2-iodobenzylcyanide (**2a**) as substrates to optimize the reaction conditions. We initiated the reaction of **1d** and **2a** in the presence of cuprous chloride and potassium carbonate in DMSO as the solvent at room temperature under a nitrogen atmosphere. Unfortunately, two products corresponding to the intermediate (**3′**) (54%) and the desired benzopyridoindolone derivative (**3d**) (30%) were isolated (Table 1, entry 1). However, the reaction afforded the indoloisoquinolinone derivative (**3d**) in 65% yield when 30 mol % of proline was used as a ligand at 80 °C (Table 1, entry 2). With this initial success, we then screened various bases including cesium carbonate (Cs_2CO_3), potassium tertiary butoxide (*t*-BuOK), sodium hydroxide (NaOH), and organic bases including TEA and DBU in order to increase the yield of the product (Table 1, entries 3−7). In the presence of a strong base such as NaOH and *t*-BuOK, moderate yields of the desired product were obtained (Table 1, entries 3 and 4).

However, when a weak organic base such as TEA was used, the reaction failed to afford the desired product (Table 1, entry 5), and in the presence of a strong organic base such as DBU, the desired product was produced in 73% in 10 min (Table 1, entry 6). To our delight, the desired product **3d** was obtained in 89% yield when cesium carbonate was used as the base (Table 1, entry 7). We next screened the quantities of the reactants such as the catalyst, ligand, and base required for this reaction (Table 1, entries 8−13). Further, when the reaction was conducted under an atmosphere of air, the product was produced in only moderate yield (Table 1, entry 14). We next investigated the progress of the reaction in the presence of other ligands such as 1,10-phenanthroline and 8-hydroxyquinoline. In both cases (Table 1, entries 15 and 16), good product yields were obtained. However, a better yield was obtained when proline was used as a ligand. To test the effect of temperature on this reaction, we examined the reaction at 100 and 60 °C. The yields of the desired product were decreased slightly in both cases (Table 1, entries 17 and 18). A survey of various solvents such as DMSO, DMF, EtOH, CH_3CN, and 1,4-dioxane (Table 1, entries 19−22) suggested that better yields were obtained when DMSO was used as the solvent. We then screened copper catalysts such as cuprous chloride, cuprous bromide, cuprous iodide, cupric chloride, cupric sulfate, cupric oxide, and cupric acetate (Table 1, entries 23−28). Among these catalysts, cuprous chloride was found to be the most efficient catalyst for this reaction. Finally, optimization studies suggested that CuCl/L-proline as the catalyst and Cs_2CO_3 as the base in DMSO as the solvent at 80 °C were the optimum conditions for this reaction. Using these optimized reaction conditions, we explored the scope and limitations of this method. In this regard, we first explored the reactions of various N-substituted 2-iodobenzamide derivatives and 2-iodobenzylcyanide under the optimized reaction conditions (Table 2).

The reaction of 2-iodobenzamide and 2-iodobenzylcyanide furnished the corresponding benzopyridoindolone derivative

Table 1. Optimization Studies



entry	base[a]	solvent	catalyst (15% mol)	*T* (°C)	time	yield (%)[b]
1[c]	K_2CO_3	DMSO	CuCl	25	8 h	30
2	K_2CO_3	DMSO	CuCl	80	2 h	65
3	*t*-BuOK	DMSO	CuCl	80	20 min	62
4	NaOH	DMSO	CuCl	80	25 min	72
5	TEA	DMSO	CuCl	80	2 h	
6	DBU	DMSO	CuCl	80	10 min	73
7	Cs_2CO_3	DMSO	CuCl	80	20 min	89
8[d]	Cs_2CO_3	DMSO	CuCl	80	6 h	72
9[e]	Cs_2CO_3	DMSO	CuCl	80	24 h	62
10[f]	Cs_2CO_3	DMSO	CuCl	80	5 h	79
11[g]	Cs_2CO_3	DMSO	CuCl	80	12 h	72
12[h]	Cs_2CO_3	DMSO	CuCl	80	10 h	63
13[i]	Cs_2CO_3	DMSO	CuCl	80	24 h	46
14[j]	Cs_2CO_3	DMSO	CuCl	80	40 min	40
15[k]	Cs_2CO_3	DMSO	CuCl	80	30 min	79
16[l]	Cs_2CO_3	DMSO	CuCl	80	30 min	72
17	Cs_2CO_3	DMSO	CuCl	100	20 min	68
18	Cs_2CO_3	DMSO	CuCl	60	80 min	77
19	Cs_2CO_3	DMF	CuCl	80	60 min	73
20	Cs_2CO_3	CH_3CN	CuCl	80	25 min	63
21	Cs_2CO_3	dioxane	CuCl	80	12 h	
22	Cs_2CO_3	EtOH	CuCl	80	60 min	43
23	Cs_2CO_3	DMSO	CuBr	80	60 min	74
24	Cs_2CO_3	DMSO	CuI	80	90 min	34
25	Cs_2CO_3	DMSO	$CuCl_2$	80	20 min	51
26	Cs_2CO_3	DMSO	CuO	80	90 min	NR[m]
27	Cs_2CO_3	DMSO	$CuSO_4$	80	30 min	69
28	Cs_2CO_3	DMSO	$Cu(OAc)_2$	80	30 min	74

[a]All reactions were conducted under the same reaction conditions, unless otherwise noted: **1** (0.5 mmol), **2** (0.6 mmol), base (1.5 mmol), solvent (2.0 mL), catalyst (15 mol %), and proline (30 mol %), under N_2. [b]^{1}H NMR yields. [c]Reaction conducted at room temperature. [d]Catalyst used 10 mol % + 30 mol % proline. [e]Catalyst used 5 mol % + 30 mol % proline. [f]Catalyst used 15 mol % + 20 mol % proline. [g]Catalyst used 15 mol % + 10 mol % proline. [h]2 equiv of base used. [i]1.5 equiv of base used. [j]Under air. [k]1,10-Phenanthroline was used as the ligand. [l]8-Hydroxyquinoline was used as the ligand. [m]NR = no reaction.

(**3a**) in moderate yield in a short reaction time. Further, substrates having various N-substituents, including methyl, phenyl, benzyl, 2-phenylethyl, allyl, and 2-methoxyethyl groups, reacted with equal ease with 2-iodobenzylcyanide to provide the corresponding benzopyridoindolone derivatives (**3b−3g**) in good to excellent yields. We next investigated various substituted 2-iodobezamide derivatives and 2-iodobenzylcyanide under optimal reaction conditions (Table 2). 2-Iodobenzamide substrates equipped with an electron-donating group (OMe) or electron-withdrawing groups (F, Cl, and Br), regardless of their positions, participated well in the reaction to deliver the corresponding benzopyridoindolone derivatives (**3h−3n**) in good to excellent yields. Moreover, a substrate containing an electron-donating group required a slightly longer time to reach completion, compared to the reaction time of substrates

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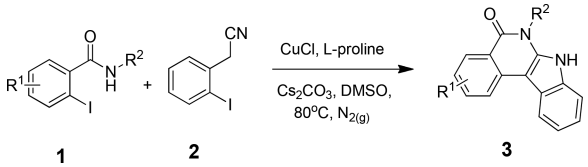
Table 2. Scope of the Reaction with Respect to 2-Iodobenzamide Derivatives



1 2 3

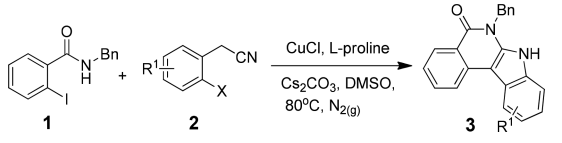
Entry[a]	Starting material	Product	Time (min)	Yield(%)[b]
1	1a	3a	5	74
2	1b	3b	15	86
3	1c	3c	20	91
4	1d	3d	20	85
5	1e	3e	20	81
6	1f	3f	20	90
7	1g	3g	20	83
8	1h	3h	15	91
9	1i	3i	20	88
10	1j	3j	20	89
11	1k	3k	70	94
12	1l	3l	25	87
13	1m	3m	30	90

[a]Reaction conditions: **1** (1 mmol), **2** (1.2 mmol), Cs_2CO_3 (3 mmol), DMSO (2.0 mL), CuCl (15 mol %), and proline (30 mol %) at 80 °C, under N_2. [b]Isolated yields.

containing an electron-withdrawing group. Furthermore, under the present reaction conditions, the halogen groups such as fluoro, chloro, and bromo groups were well tolerated.

In subsequent studies, we investigated the scope of the substituted 2-iodo/bromobenzylcyanides for the reaction. The results are shown in Table 3. As depicted in Table 3,

Table 3. Scope of the Reaction with Respect to 2-Iodo/Bromobenzylcyanide Derivatives



1 2 3

Entry[a]	Starting material	Product	Time (min)	Yield(%)[b]
1	2b	3n	10	76
2	2c	3o	25	81
3	2d	3p	90	78
4	2e	3q	4h	86
6	2g	3r	6h	84

[a]Reaction conditions: **1** (1 mmol), **2** (1.2 mmol), Cs_2CO_3 (3 mmol), DMSO (2.0 mL), CuCl (15 mol %), and proline (30 mol %) at 80 °C, under N_2. [b]Isolated yields.

the reaction of 2-iodo-*N*-benzylbenzamide and the bromo-substituted 2-iodobenzylcyanide proceeded smoothly to generate the corresponding benzopyridoindolone derivative (**3n**) in good yield. Further, the reaction of 2-iodobenzylcyanide equipped with an electron-donating group (OMe) and 2-iodo-*N*-benzylbenzamide furnished the corresponding benzopyridoindolone derivative (**3o**) in good yield. Moreover, the 2-iodobenzylcyanide derivative containing dimethoxy or methyleneoxy groups also reacted to furnish the desired benzopyridoindolone derivatives, **3p** and **3q**, in good yields. Furthermore, 2-(1-bromonaphthalen-2-yl)acetonitrile also reacted smoothly with 2-iodo-*N*-benzylbenzamide to give the corresponding fused polyheterocycle (**3r**) in good yield. However, these reactions required a longer time to reach completion.

To extend the scope of the reaction, we next examined the reaction of 2-iodothienyl-*N*-benzylcarboxamide with various substituted 2-iodobenzylcyanide derivatives. Interestingly, these reactions produced the corresponding thienopyridoindolone derivatives (**3s**–**3u**) in good yields (Table 4). The structure of

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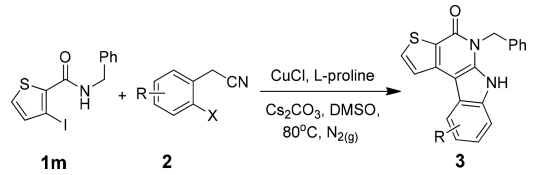
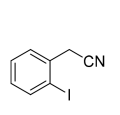
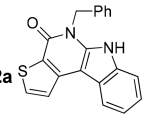
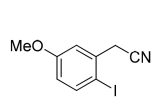
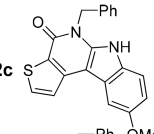
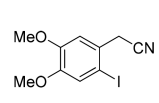
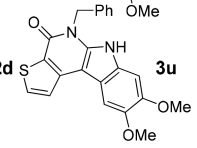
Table 4. Scope of the Reaction with Respect to 2-Iodothienylcarboxamide Derivatives



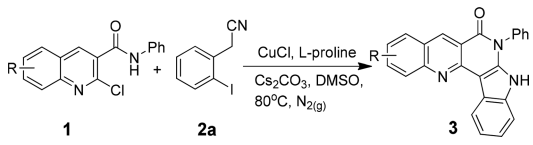
Entry[a]	Starting material	Product	Time (h)	Yield(%)[b]
1		 2a 3s	1.5	81
2		 2c 3t	3	85
3		 2d 3u	4	80

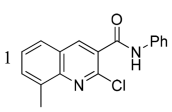
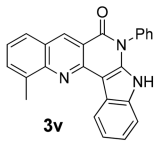
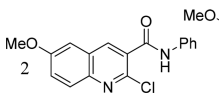
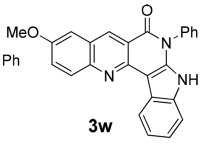
[a]Reaction conditions: **1** (1 mmol), **2** (1.2 mmol), Cs_2CO_3 (3 mmol), DMSO (2.0 mL), CuCl (15 mol %), and proline (30 mol %) at 80 °C, under N_2. [b]Isolated yields.

the tetracyclic compound (**3s**) was verified by a single crystal X-ray analysis of its structure (Supporting Information).[12]

We next investigated the scope of the reaction for substituted 2-chloro-*N*-phenylquinoline-3-carboxamide derivatives and 2-iodobenzylcyanide under the present reaction conditions. As shown in Table 4, the reaction of 8-methyl-2-chloro-*N*-phenylquinoline-3-carboxamide and 2-iodobenzylcyanide furnished the corresponding indole-fused naphthyridine derivative (**3v**) in moderate yield. However, 2-chloro-6-methoxy-*N*-phenylquinoline-3-carboxamide gave the desired product (**3w**) in good yield (Table 5). It is noteworthy that such

Table 5. Scope of the Reaction with Respect to 2-Chloro-*N*-phenylquinoline-3-carboxamide Derivatives



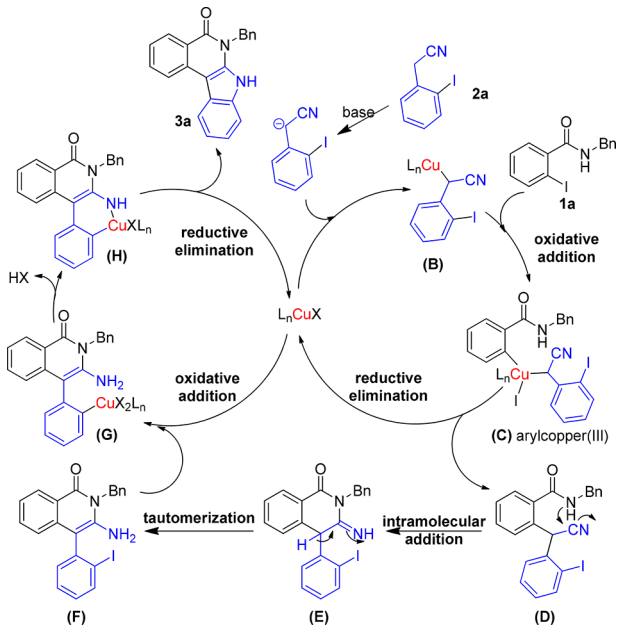
Entry[a]	Starting material	Product	Time (h)	Yield(%)[b]
1		 3v	4	63
2		 3w	1	81

[a]Reaction conditions: **1** (1 mmol), **2** (1.2 mmol), Cs_2CO_3 (3 mmol), DMSO (2.0 mL), CuCl (15 mol %), and proline (30 mol %) at 80 °C, under N_2. [b]Isolated yields.

benzonaphthyridine derivatives possess important biological activities.[11] We also investigated the reaction of 2-iodo-*N*-methyl-1*H*-indole-3-carboxamide and 2-iodobenzylcyanide under the present reaction conditions. Unfortunately, the reaction produced a complex mixture of products.

A plausible mechanism for the formation of benzopyridoindolone (**3a**) from a 2-iodobenzamide derivative (**1a**) and 2-iodobenzylcyanide (**2a**) in the presence of a copper catalyst is depicted in Scheme 3. As shown, the reaction is initiated

Scheme 3. Plausible Mechanism



by the formation of intermediate **B** via the reaction of the copper complex and benzylcyanide in the presence of cesium carbonate. The oxidative addition of complex **B** to the 2-iodobenzamide derivative produces intermediate **C**. The copper catalyst is then reductively eliminated from intermediate **C** with the generation of intermediate **D**. The intramolecular addition of the amide nitrogen to the cyano group in intermediate **D** gives intermediate **E**, which is then converted to intermediate **F** by tautomerization. Intermediate **F** then participates in a second copper catalytic cycle to produce **3a** via intermediates **G** and **H** (Scheme 3).

CONCLUSIONS

In conclusion, we report on the development of an efficient copper catalyzed one-pot tandem protocol for the synthesis of benzopyridoindolone derivatives. To the best of our knowledge, this is the first strategy for preparing free indole N−H benzopyridoindolones. Interestingly, both indole and pyridone cores are constructed during the course of the reaction itself in an unconventional approach. The broad substrate scope and good to excellent product yields suggest that this methodology will be synthetically useful. Further, the methodology was used to prepare biologically active fused thienopyridoindol-4-one and indolobenzonaphthyridine derivatives.

EXPERIMENTAL SECTION

General Information. Reagents and solvents were purchased from various commercial sources and were used directly without any further purification, unless otherwise stated. Column chromatography was

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performed using 63−200 mesh silica gel. ^{1}H and ^{13}C NMR spectra were recorded at 400/500/600 and 100/125/150 MHz, respectively. Chemical shifts were reported in parts per million (δ) using TMS and chloroform as internal standards, and coupling constants were expressed in Hertz. Melting points were recorded using an electrothermal capillary melting point apparatus and were uncorrected. HRMS spectra were recorded using the ESI-TOF or EI$^+$ mode. The starting 2-iodobenzamide derivatives **1** and 2-iodobenzylcyanide derivatives **2** were all synthesized following previously reported methods.

General Procedure for Preparing Substituted Indolyltetrahydroquinoline Derivatives. A 25 mL round-bottom flask was charged with 2 mL of DMSO, followed by the 2-iodobenzamide derivative (1 mmol), copper(I) chloride (0.15 mmol), proline (0.3 mmol), 2-iodobenzylcyanide (1.2 mmol) derivative, and cesium carbonate (3 mmol). The reaction mixture was stirred at 80 °C until the reaction reached completion as evidenced by TLC. After the completion of the reaction, ice/water was added to the reaction mixture. The solid was filtered off and dissolved in EtOAc. The filtrate (water phase) was extracted with EtOAc (2 × 10 mL). The organic layer was separated, dried over anhydrous $MgSO_4$, and filtered. The dried organic layer was then concentrated to give the crude product. The resulting residue was further purified by flash column chromatography using 1:5 (ethyl acetate/hexane) on silica gel.

Spectral Data of Compounds. *6,7-Dihydro-5H-indolo[2,3-c]isoquinolin-5-one (**3a**):*[4a] yellow solid; mp 353 °C (decompose); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.46 (s, 1H), 11.39 (s, 1H), 8.26 (d, J = 8.20 Hz, 2H), 8.09 (d, J = 6.9 Hz, 1H), 7.79−7.75 (m, 1H), 7.50 (dd, J = 7.0, 1.6 Hz, 1H), 7.34 (t, J = 7.50 Hz, 1H), 7.21−7.14 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.5, 138.3, 135.7, 135.1, 133.8, 128.8, 123.6, 123.2, 122.4, 121.9, 121.6, 121.2, 119.1, 112.2, 94.4; HRMS (ESI) m/z calcd for $C_{15}H_{10}N_2O$ (M + H)$^+$ 235.0866, found 235.0872.

*6-Methyl-6,7-dihydro-5H-indolo[2,3-c]isoquinolin-5-one (**3b**):* yellow solid; mp 379−381 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.99 (s, 1H), 8.32−8.26 (m, 2H), 8.15−8.13 (m, 1H), 7.77 (t, J = 7.60 Hz, 1H), 7.53−7.51 (m, 1H), 7.35 (t, J = 7.54 Hz, 1H), 7.25−7.21 (m, 2H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.8, 139.5, 134.6, 134.1, 132.8, 128.7, 123.2, 122.9, 121.7, 121.2, 120.8, 120.6, 118.9, 111.5, 93.8, 29.8; HRMS (EI) m/z calcd for $C_{16}H_{12}N_2O$ (M$^+$) 248.0944, found 248.0943.

*6-Phenyl-6,7-dihydro-5H-indolo[2,3-c]isoquinolin-5-one (**3c**):* yellow solid; mp 237−239 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, J = 8.04 Hz, 1H), 8.30 (d, J = 8.04 Hz, 1H), 8.16 (d, J = 7.96 Hz, 1H), 7.99 (s, 1H), 7.82 (t, J = 7.58 Hz, 1H), 7.58 (t, J = 7.60 Hz, 2H), 7.48 (m, 3H), 7.41 (t, J = 7.58 Hz, 1H), 7.33 (t, J = 7.52 Hz, 1H), 7.29 (d, J = 7.80 Hz, 1H), 7.22 (t, J = 7.54 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 138.4, 135.7, 135.2, 134.0, 133.5, 130.6, 130.0, 129.8, 128.5, 124.1, 124.0, 122.3, 122.2, 122.1, 121.8, 119.6, 111.5, 95.7; HRMS (EI) m/z calcd for $C_{21}H_{14}N_2O$ (M + H)$^+$ 311.1179, found 311.1165.

*6-Benzyl-6,7-dihydro-5H-indolo[2,3-c]isoquinolin-5-one (**3d**):* yellow crystal; mp 269−271 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.05 (s, 1H), 8.33 (d, J = 8.28 Hz, 2H), 8.19−8.17 (m, 1 H), 7.84−7.79 (m, 1H), 7.50 (dd, J = 6.74, 1.70 Hz, 1H), 7.40−7.37 (m, 1H), 7.32−7.26 (m, 4H), 7.25−7.19 (m, 3H), 5.56 (s, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.9, 138.9, 136.4, 134.7, 134.4, 133.2, 128.9, 128.5, 127.2, 126.8, 123.3, 123.2, 121.8, 121.4, 120.9, 120.7, 119.0, 111.7, 94.2, 45.8; HRMS (EI) m/z calcd for $C_{22}H_{16}N_2O$ (M$^+$) 324.1263, found 324.1269.

*6-Phenethyl-6,7-dihydro-5H-indolo[2,3-c]isoquinolin-5-one (**3e**):* yellow solid, mp 222−224 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, J = 8.04 Hz, 1H), 8.26 (d, J = 7.96 Hz, 2H), 8.10 (d, J = 7.88 Hz, 1H), 7.79 (d, J = 7.56 Hz, 1H), 7.40 (t, J = 7.58 Hz, 1H), 7.31−7.27 (m, 1H), 7.24−7.13 (m, 7H), 4.53 (t, J = 7.04 Hz, 2H), 3.17 (t, J = 7.02 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 139.1, 138.6, 134.9, 134.8, 133.2, 129.5, 129.2, 128.9, 127.3, 124.1, 123.9, 122.2, 122.1, 121.7, 119.6, 111.4, 96.3, 46.3, 34.8; HRMS (EI) m/z calcd for $C_{23}H_{18}N_2O$ (M + H)$^+$ 339.1492, found 339.1488.

*6-(3-Methoxypropyl)-6,7-dihydro-5H-indolo[2,3-c]isoquinolin-5-one (**3f**):* yellowish oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.93 (s, 1H), 8.51 (dd, J = 7.96, 0.88 Hz, 1H), 8.24 (d, J = 8.00 Hz, 1H), 8.13 (d, J = 7.80 Hz, 1H), 7.75 (td, J = 11.13, 1.32 Hz, 1H), 7.44 (d, J = 7.56 Hz, 1H), 7.40−7.36 (m, 1H), 7.35−7.31 (m, 1H), 7.29−7.25 (m, 1H), 4.43 (t, J = 6.08 Hz, 2H), 3.50 (s, 3H), 3.43 (t, J = 5.56 Hz, 2H), 2.21 (quint, J = 5.82 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 139.8, 135.0, 134.9, 133.0, 129.5, 124.5, 123.7, 122.0, 121.9, 121.8, 121.6, 119.6, 114.5, 95.8, 68.9, 58.7, 40.1, 28.2; HRMS (ESI) m/z calcd for $C_{19}H_{18}N_2O_2$ (M$^+$) 306.1363, found 306.1350.

*6-Allyl-6,7-dihydro-5H-indolo[2,3-c]isoquinolin-5-one (**3g**):* yellow solid, mp 243−245 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (s, 1H), 8.54 (d, J = 8.0 Hz, 1H), 8.26 (d, J = 8.0 Hz, 1H), 8.14 (d, J = 7.6 Hz, 1H), 7.80−7.78 (m, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.40 (d, J = 7.5 Hz, 1H), 7.34 (d, J = 7.4 Hz, 1H), 7.29−7.25 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8, 138.5, 134.9, 134.6, 133.3, 132.2, 129.9, 124.2, 124.1, 122.2, 122.0, 121.8, 119.8, 118.2, 111.6, 96.3, 45.3; HRMS (ESI) m/z calcd for $C_{18}H_{14}N_2O$ (M$^+$) 274.1106, found 274.1114.

*6-Benzyl-3-fluoro-6,7-dihydro-5H-indolo[2,3-c]isoquinolin-5-one (**3h**):* yellow crystal, mp 272−274 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.07 (s, 1H), 8.38 (q, J = 4.7 Hz, 1H), 8.16 (q, J = 3.0 Hz, 1H), 7.97 (dd, J = 7.8, 2.9 Hz, 1H), 7.67 (td, J = 13.0, 2.9 Hz, 1H), 7.51−7.48 (m, 1H), 7.33−7.20 (m, 7H), 5.54 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160 (d, J_{C-F} = 3.5 Hz), 158.4 (d, J_{C-F} = 240.9 Hz), 138.3, 135.4 (d, J_{C-F} = 156.8 Hz), 131.2 (d, J_{C-F} = 1.3 Hz), 128.5, 127.3, 126.8, 124.4 (d, J_{C-F} = 7.5 Hz), 122.8, 121.9 (d, J_{C-F} = 7.2 Hz), 121.7, 121.6, 121.5, 120.9, 118.8, 113.5 (d, J_{C-F} = 22.6 Hz), 111.7, 93.9, 46.0; HRMS (ESI) m/z calcd for $C_{22}H_{15}FN_2O$ (M + H)$^+$ 343.1241, found 343.1247.

*6-Benzyl-3-chloro-6,7-dihydro-5H-indolo[2,3-c]isoquinolin-5-one (**3i**):* yellow crystal, mp 289−291 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.13 (s, 1H), 8.32 (d, J = 8.7 Hz, 1H), 8.22 (d, J = 2.3 Hz, 1H), 8.14−8.11 (m, 1H), 7.78 (dd, J = 8.6, 2.3 Hz, 1H), 7.50−7.48 (m, 1H), 7.32−7.21 (m, 7H), 5.52 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.8, 139.0, 136.1, 134.7, 133.0, 132.9, 128.5, 127.7, 127.4, 127.3, 126.7, 124.0, 122.8, 121.9, 121.7, 121.0, 118.9, 111.7, 93.9, 46.0; HRMS (ESI) m/z calcd for $C_{22}H_{15}ClN_2O$ (M + H)$^+$ 359.0946, found 359.0952.

*6-Benzyl-3-bromo-6,7-dihydro-5H-indolo[2,3-c]isoquinolin-5-one (**3j**):* yellow solid, mp 287 °C (decompose); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.12 (s, 1H), 8.36 (s, 1H), 8.23 (d, J = 8.60 Hz, 1H), 8.11−8.09 (m, 1H), 7.87 (d, J = 8.48 Hz, 1H), 7.49−7.47 (m, 1H), 7.31−7.23 (m, 7H), 5.50 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.7, 139.1, 136.1, 135.6, 134.7, 133.1, 130.8, 128.6, 127.3, 126.7, 124.2, 122.8, 122.2, 121.8, 121.1, 119.0, 115.3, 111.8, 93.9, 46.0; HRMS (EI) m/z calcd for $C_{22}H_{15}BrN_2O$ (M$^+$) 402.0368, found 402.0380.

*6-Benzyl-3-methoxy-6,7-dihydro-5H-indolo[2,3-c]isoquinolin-5-one (**3k**):* yellow solid, mp 148−250 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.21 (d, J = 8.80 Hz, 1H), 8.10 (d, J = 7.72 Hz, 1H), 7.95 (d, J = 2.76 Hz, 1H), 7.43 (dd, J = 8.78, 2.70 Hz, 1H), 7.35 (d, J = 8.00 Hz, 1H), 7.30 (t, J = 7.50 Hz, 1H), 7.22−7.18 (m, 6H), 5.53 (s, 2H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 156.7, 137.1, 135.5, 134.5, 129.4, 129.2, 128.2, 126.8, 124.0, 123.8, 122.7, 122.1, 121.7, 119.5, 111.6, 110.0, 96.6, 55.7, 53.6, 46.6; HRMS (EI) m/z calcd for $C_{23}H_{18}N_2O_2$ (M$^+$) 354.1363, found 354.1369.

*2-Fluoro-6-phenyl-6,7-dihydro-5H-indolo[2,3-c]isoquinolin-5-one (**3l**):* pale yellow solid, mp 265−267 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (dd, J = 6.08, 8.92 Hz, 1H), 8.11 (d, J = 7.92 Hz, 1H), 7.90 (dd, J = 2.34, 10.06 Hz, 1H), 7.80 (s, 1H), 7.69 (t, J = 7.48 Hz, 2H), 7.61 (t, J = 7.40 Hz, 1H), 7.52 (d, J = 7.36 Hz, 2H), 7.40−7.33 (m, 2H), 7.29 (t, J = 3.68 Hz, 1H), 7.12 (td, J = 12.90, 2.35 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5 (d, J_{C-F} = 252.7 Hz), 161.4, 139.3, 137.3 (d, J_{C-F} = 11.2 Hz), 135.6, 133.9, 133.2 (d, J_{C-F} = 10.6 Hz), 130.9, 130.1, 128.6, 124.0, 122.6, 122.2, 119.4, 119.0, 112.5 (d, J_{C-F} = 23.3 Hz), 111.5, 107.7 (d, J_{C-F} = 23.1 Hz), 95.5; HRMS (ESI) m/z calcd for $C_{21}H_{13}FN_2O$ (M + H)$^+$ 329.1085, found 329.1086.

*2-Chloro-6-phenyl-6,7-dihydro-5H-indolo[2,3-c]isoquinolin-5-one (**3m**):* yellow crystal, mp 272.5−273.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, J = 8.64 Hz, 1H), 8.22 (d, J = 1.60 Hz, 1H), 8.11 (d, J = 8.00 Hz, 1H), 7.82 (s, 1H), 7.64 (t, J = 7.48 Hz, 2H),

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7.56 (t, J = 7.36 Hz, 1H), 7.48 (d, J = 7.28 Hz, 2H), 7.37−7.29 (m, 3H), 7.25−7.23 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 140.2, 139.2, 136.3, 135.5, 134.0, 131.7, 130.8, 130.1, 128.5, 124.5, 123.9, 122.6, 122.2, 121.8, 120.7, 119.6, 111.5, 95.0; HRMS (ESI) m/z calcd for $C_{21}H_{13}ClN_2O$ $(M + H)^+$ 345.0789, found 345.0779.

*6-Benzyl-10-bromo-6,7-dihydro-5H-indolo[2,3-c]isoquinolin-5-one (**3n**):* yellow solid, mp 288−290 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.18 (s, 1H), 8.31−8.24 (m, 3H), 7.76 (td, J = 11.09, 1.25 Hz, 1H), 7.42 (d, J = 8.52 Hz, 1H), 7.37 (t, J = 7.54 Hz, 1H), 7.32−7.26 (m, 5H), 7.24−7.20 (m, 1H), 5.50 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.8, 139.6, 136.2, 133.8, 133.4, 133.3, 128.8, 128.6, 127.3, 126.7, 124.9, 123.8, 123.6, 122.0, 121.0, 120.8, 113.4, 93.8, 45.9; HRMS (ESI) m/z calcd for $C_{22}H_{15}BrN_2O$ (M^+) 402.0368, found 402.0375.

*6-Benzyl-10-methoxy-6,7-dihydro-5H-indolo[2,3-c]isoquinolin-5-one (**3o**):* yellow solid, mp 275−276 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.86 (s, 1H), 8.32 (t, J = 7.54 Hz, 2H), 7.84−7.80 (m, 1H), 7.64 (d, J = 2.16 Hz, 1H), 7.39−7.36 (m, 2H), 7.32−7.23 (m, 5H), 6.84 (dd, J = 8.70, 2.26 Hz, 1H), 5.53 (s, 2H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.2, 155.0, 139.5, 136.5, 134.6, 133.6, 129.7, 129.2, 128.9, 127.6, 127.0, 123.9, 123.5, 122.1, 120.7, 112.6, 110.5, 102.7, 94.7, 56.0, 46.0; HRMS (ESI) m/z calcd for $C_{23}H_{18}N_2O_2$ $(M + H)^+$ 355.1441, found 355.1444.

*6-Benzyl-9,10-dimethoxy-6,7-dihydro-5H-indolo[2,3-c]-isoquinolin-5-one (**3p**):* yellow solid, mp 246−248 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.75 (s, 1H), 8.32 (dd, J = 7.96, 3.28 Hz, 2H), 7.80 (t, J = 7.50 Hz, 1H), 7.65 (s, 1H), 7.36 (t, J = 7.58 Hz, 1H), 7.32−7.22 (m, 5H), 7.03 (s, 1H), 5.52 (s, 2H), 3.91 (s, 3H), 3.81 (s, 3H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 160.5, 146.0, 145.3, 137.6, 136.5, 134.2, 133.0, 128.9, 128.8, 128.5, 127.2, 126.8, 123.0, 121.8, 120.5, 115.7, 103.0, 96.3, 94.5, 56.5, 55.8 45.7; HRMS (EI) m/z calcd for $C_{24}H_{20}N_2O_3$ (M^+) 384.1468, found 384.1456.

*6-Benzyl-6,7-dihydro-5H-[1,3]dioxolo[4′,5′:5,6]indolo[2,3-c]-isoquinolin-5-one (**3q**):* yellow solid, mp 291−293 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.85 (s, 1H), 8.29 (t, J = 7.50 Hz, 2H), 7.79−7.75 (m, 2H), 7.36 (t, J = 7.64 Hz, 1H), 7.32−7.22 (m, 5H), 7.03 (s, 1H), 6.01 (s, 2H), 5.51 (s, 2H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 160.4, 143.4, 143.1, 137.7, 136.4, 134.0, 129.2, 128.8, 128.5, 127.2, 126.7, 123.1, 121.7, 120.6, 116.5, 100.5, 98.9, 94.8, 93.3, 45.6; HRMS (ESI) m/z calcd for $C_{23}H_{16}N_2O_3$ $(M + H)^+$ 369.1234, found 369.1235.

*6-Benzyl-6,7-dihydro-5H-benzo[6,7]indolo[2,3-c]isoquinolin-5-one (**3r**):* yellow solid, mp 308−310 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.31 (s, 1H), 8.57 (d, J = 8.0 Hz, 1H), 8.49 (d, J = 7.7 Hz, 1H), 8.38 (dd, J = 19.9, 8.1 Hz, 2H), 8.00 (d, J = 7.8 Hz, 1H), 7.87−7.74 (m, 2H), 7.60 (t, J = 7.2 Hz, 1H), 7.45−7.43 (m, 2H), 7.31−7.23 (m, 5H), 5.74 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.6, 137.6, 136.9, 134.1, 133.1, 129.4, 128.9, 128.7, 128.5, 127.1, 126.8, 125.6, 123.8, 123.7, 122.0, 121.6, 121.5, 121.3, 119.2, 119.1, 96.1, 45.9; HRMS (ESI) m/z calcd for $C_{26}H_{18}N_2O$ $(M + H)^+$ 375.1492, found 375.1492.

*5-Benzyl-5,6-dihydro-4H-thieno[3′,2′:4,5]pyrido[2,3-b]indol-4-one (**3s**):* yellow solid, mp 268−270 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.04 (s, 1H), 8.22 (d, J = 5.20 Hz, 1H), 8.09 (dd, J = 5.88, 3.08 Hz, 1H), 8.01 (d, J = 5.24 Hz, 1H), 7.48 (dd, J = 5.92, 3.12 Hz, 1H), 7.32−7.21 (m, 7H), 5.57 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.9, 140.9, 140.3, 136.5, 136.1, 134.8, 128.8, 127.6, 127.0, 122.8, 122.3, 122.2, 121.4, 121.0, 118.9, 111.8, 96.0, 45.7; HRMS (ESI) m/z calcd for $C_{20}H_{14}N_2OS$ $(M + H)^+$ 331.0900, found 331.0906.

*5-Benzyl-9-methoxy-5,6-dihydro-4H-thieno[3′,2′:4,5]pyrido[2,3-b]indol-4-one (**3t**):* yellow solid, mp 295 °C (decompose); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.84 (s, 1H), 8.21 (d, J = 5.2 Hz, 1H), 8.08 (d, J = 5.2 Hz, 1H), 7.57 (d, J = 5.2 Hz, 1H), 7.37 (d, J = 8.7 Hz, 1H), 7.32−7.22 (m, 5H), 6.84 (dd, J = 8.7, 2.3 Hz, 1H), 5.53 (s, 2H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.6, 154.7, 140.7, 140.6, 136.4, 135.6 129.3, 128.5, 127.3, 126.8, 122.8, 122.6, 120.9, 112.2, 110.7, 101.9, 95.9, 55.7, 45.4; HRMS (ESI) m/z calcd for $C_{21}H_{16}N_2O_2S$ $(M + H)^+$ 361.1005, found 361.1012.

*5-Benzyl-8,9-dimethoxy-5,6-dihydro-4H-thieno[3′,2′:4,5]pyrido-[2,3-b]indol-4-one (**3u**):* yellow solid, mp 228−230 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.73 (s, 1H), 8.19 (d, J = 5.20 Hz, 1H), 8.08 (d, J = 5.16 Hz, 1H), 7.58 (s, 1H), 7.31−7.24 (m, 5H), 7.02 (s, 1H), 5.53 (s, 2H), 3.88 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.2, 146.4, 145.3, 140.4, 139.0, 136.4, 135.3, 128.9, 128.5, 127.3, 126.9, 122.8, 120.7, 114.6, 102.4, 96.1, 56.5, 55.8, 45.4; HRMS (ESI) m/z calcd for $C_{22}H_{18}N_2O_3S$ $(M + H)^+$ 391.1111, found 391.1118.

*12-Methyl-6-phenyl-5H-benzo[b]indolo[2,3-h][1,6]naphthyridin-7(6H)-one (**3v**):* orange solid, mp 264−266 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.22 (s, 1H), 8.79 (d, J = 7.88 Hz, 1H), 7.83 (t, J = 7.40 Hz, 2H), 7.73−7.66 (m, 3H), 7.62−7.55 (m, 3H), 7.42 (t, J = 7.60 Hz, 2H), 7.32 (d, J = 7.60 Hz, 1H), 7.29−7.25 (m, 1H), 3.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8, 150.6, 149.1, 140.8, 140.2, 136.8, 135.4, 133.8, 132.3, 130.9, 130.2, 128.6, 127.7, 125.3, 125.1, 124.6, 122.7, 122.6, 121.8, 117.9, 111.0, 98.1, 18.6; HRMS (ESI) m/z calcd for $C_{25}H_{17}N_3O$ $(M + H)^+$ 376.1444, found 376.1450.

*10-Methoxy-6-phenyl-5H-benzo[b]indolo[2,3-h][1,6]-naphthyridin-7(6H)-one (**3w**):* red solid, mp 269 °C (decompose); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1H), 8.52 (d, J = 9.2 Hz, 1H), 8.41 (d, J = 7.4 Hz, 1H), 8.18 (s, 1H), 7.65−7.55 (m, 5H), 7.43 (dd, J = 9.2, 2.9 Hz, 1H), 7.38−7.36 (m, 2H), 7.34 (d, J = 2.9 Hz, 1H), 7.26 (s, 1H), 3.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8, 156.2, 135.9, 135.3, 134.6, 131.9, 130.9, 130.5, 130.2, 130.1, 129.6, 128.7, 127.0, 125.6, 124.7, 124.0, 122.4, 121.8, 121.0, 119.2, 117.1, 114.5, 113.8, 98.6, 56.0; HRMS (ESI) m/z calcd for $C_{25}H_{17}N_3O_2$ $(M + H)^+$ 392.1394, found 392.1399.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00862.

X-ray crystallographic structures and data and ^{1}H and ^{13}C NMR spectra for all products (PDF)
X-ray crystallography data for **3d** (CIF)
X-ray crystallography data for **3s** (CIF)
X-ray crystallography data for **3v** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: cheyaocf@ntnu.edu.tw.

ORCID

Ching-Fa Yao: 0000-0002-8692-5156

Author Contributions

†These authors contributed equally.

Notes

The authors declare no competing financial interest.

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