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DIVERGENT SYNTHESIS OF INDOLE-2-CARBOXYLIC ACID DERIVATIVES VIA LIGAND-FREE COPPER-CATALYZED ULLMANN COUPLING REACTION

Jiadi Zhou,[a] Yongjian Chen,[a] Junsong Huang,[a] and Jianjun Li[a,b]*

[a] Collaborative Innovation Center of Yangtze River Delta Region Green Pharmaceuticals, Zhejiang University of Technology, Hangzhou 310014, P. R. China

[b] National Engineering Research Center for Process Development of Active Pharmaceutical Ingredients, College of Pharmaceutical Sciences, Zhejiang University of Technology, Hangzhou 310014, P. R. China

*E-mail addresses: lijianjun@zjut.edu.cn

Abstract – This article describes a ligand-free copper-catalyzed Ullmann coupling reaction for the preparation of divergent indole-2-carboxylic acid derivatives including esters, amides and anhydrides. Various compounds **3**, which could be synthesized from aldehydes conveniently, were used as substrate to provide the corresponding indole-2-carboxylic acid derivatives in moderate to good yields.

INTRODUCTION

The indole scaffold represents one of the most significant heterocycles in biologically active and naturally occurring molecules.[1] Over a hundred years, much attention has been received for the synthesis of indoles and numerous synthesis routes have become available.[2] Transition-metal-catalyzed reactions are the most attractive methods for the facile construction of complicated heterocyclic molecules from readily accessible starting materials under mild conditions.[3] Mainly, the use of palladium- and copper-catalyzed aromatic carbon-nitrogen bond forming reactions by the cross-coupling of aryl halides or triflates with amines or amides have become increasingly useful synthetic tools.

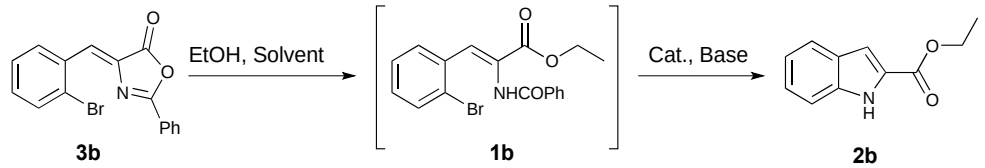
Copper catalysis has proven to be increasingly powerful in overcoming some of the hurdles encountered in the synthesis of indoles.[4] However, most of the methods could only acquire single type of products, and usually require ligands or the use of stoichiometric amounts of copper. In this paper, we developed the ligand-free copper-catalyzed one-pot intramolecular cyclization of compounds **3** leading to different

substituted indole-2-carboxylic acid derivatives including esters, amides and anhydrides. This work may provide an additional choice for the divergent synthesis of indole-2-carboxylates from cheap and easy to synthesized substrates.

RESULTS AND DISCUSSION

In our initial studies, compound **3b** was used as a model substrate to optimize the reaction conditions. In the first step, EtOH was used as the ring opening reagent at 70 °C for 1 h. In the second step, a series of reaction conditions were screened including solvents, copper catalysts, bases and temperature under air atmosphere (Table 1). Firstly, the aprotic solvents, such as dioxane, DMSO, toluene, DMF, DMA and DCE were tested in the presence of $Cu(OAc)_2$ (10 mol%) and Cs_2CO_3 (1 equiv.), DMF with stronger polarity proved to be the best solvent (Table 1, entries 1-6). Afterward, a range of copper salts, such as $Cu(OTf)_2$, CuO, CuCl, CuBr and CuI were tested, CuI proved to be the best catalyst (Table 1, entries 7-11). When CuI (5 mol%) or (15 mol%) was used, the yield of **2b** was obtained in 60% and 69%, respectively (Table 1, entries 12 and 13). Immediately after, screening the reaction temperature in the range of 60 to 130 °C, and the best yield of **2b** was obtained when the reaction was conducted at 110 °C (Table 1, entries 11, 14-17). Then several bases including Cs_2CO_3, Na_2CO_3, *t*-BuOK, K_2CO_3 were screened, and K_2CO_3 was found to be the most effective (Table 1, entries 11, 18-20). At last, conducting the reaction at nitrogen atmosphere, the yield has no improvement obviously (Table 1, entry 21). The optimized condition was that CuI (10 mol%) and K_2CO_3 (1 equiv.) in DMF under air atmosphere at 110 °C for 4 h, giving **2b** in 70% yield (Table 1, entry 20).

Table 1. Optimization of the reaction conditions for the synthesis of 1*H*-indole-2-carboxylic acid ethyl ester



3b **1b** **2b**

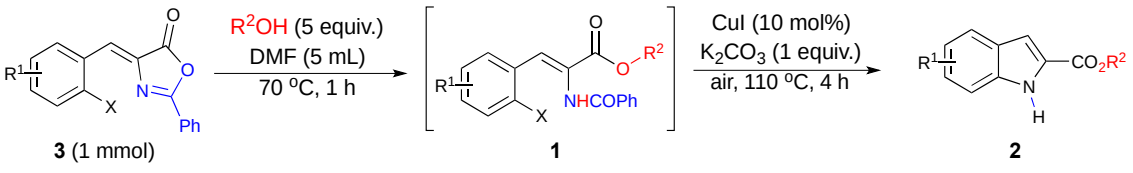
Entry[a]	Catalyst (mol%)	Base	Solvent	*T*[b] (°C)	Yield[c] (%)
1	$Cu(OAc)_2$ (10)	Cs_2CO_3	dioxane	reflux	40
2	$Cu(OAc)_2$ (10)	Cs_2CO_3	DMSO	110	48
3	$Cu(OAc)_2$ (10)	Cs_2CO_3	toluene	110	19
4	$Cu(OAc)_2$ (10)	Cs_2CO_3	DMF	110	58
5	$Cu(OAc)_2$ (10)	Cs_2CO_3	DMA	110	52
6	$Cu(OAc)_2$ (10)	Cs_2CO_3	DCE	reflux	trace
7	$Cu(OTf)_2$ (10)	Cs_2CO_3	DMF	110	60
8	CuO (10)	Cs_2CO_3	DMF	110	20
9	CuCl (10)	Cs_2CO_3	DMF	110	60
10	CuBr (10)	Cs_2CO_3	DMF	110	63

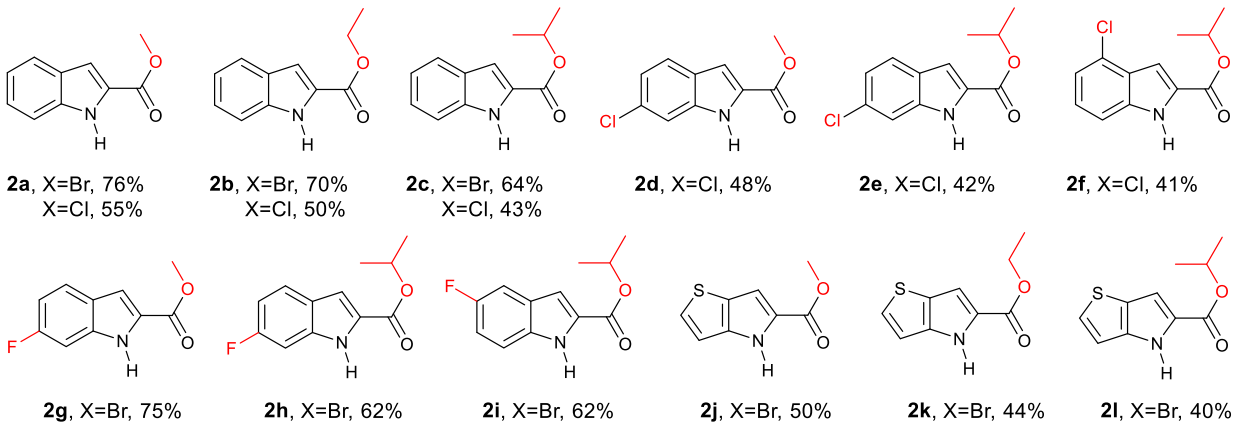
11	CuI (10)	Cs_2CO_3	DMF	110	68
12	CuI (5)	Cs_2CO_3	DMF	110	60
13	CuI (15)	Cs_2CO_3	DMF	110	69
14	CuI (10)	Cs_2CO_3	DMF	60	trace
15	CuI (10)	Cs_2CO_3	DMF	80	50
16	CuI (10)	Cs_2CO_3	DMF	100	66
17	CuI (10)	Cs_2CO_3	DMF	130	68
18	CuI (10)	Na_2CO_3	DMF	110	60
19	CuI (10)	*t*-BuOK	DMF	110	45
20	CuI (10)	K_2CO_3	DMF	110	70
21[d]	CuI (10)	K_2CO_3	DMF	110	70

[a] Reaction conditions: (1) compound **3b** (1 mmol), EtOH (5 equiv.), solvent (5 mL), 70 °C, 1 h; (2) catalyst, base (1 equiv.) under air atmosphere for 4 h. [b] Temperature of the second step. [c] Yield of isolated product based on **3b**. [d] Under a nitrogen atmosphere.

We next investigated the substrate scope of compounds **3** with diverse substituents. As shown in Table 2, a variety of 2-bromo or 2-chloro substituted compounds, bearing H, F, Cl at the different positions of the phenyl ring could react smoothly, and the expected products **2a** − **2i** were obtained in moderate to good yield. It was expected that 2-bromo substituted substrates gave higher yields than 2-chloro substituted substrates (**2a**, **2b** and **2c**). Notably, the introduction of Cl group at the *ortho* position or *para* position reduced the product yields (**2d**, **2e** and **2f**), and the introduction of F group at the *meta* position or *para* position did not affect the product yields evidently (**2g**, **2h** and **2i**). It is noteworthy that the benzene ring was replaced by the thiophene ring, the reaction could be carried out as well (**2j**, **2k** and **2l**).

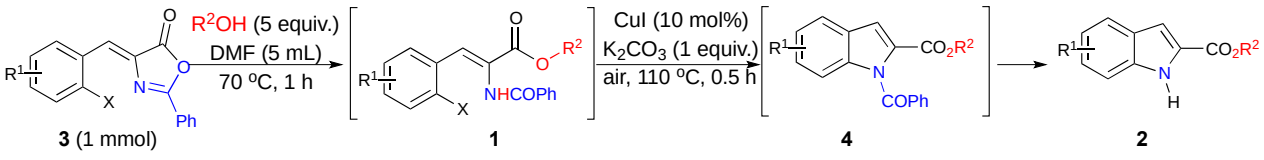
Table 2. The synthesis of the indole-2-carboxylates **2**[a]

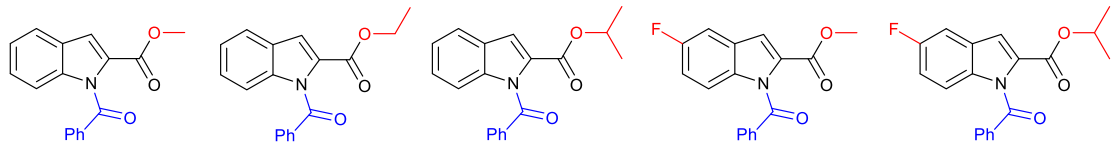




[a] Yield of isolated product based on **3**

Table 3. The separation of *N*-benzoyl-indole-2-carboxylates **4**[a]





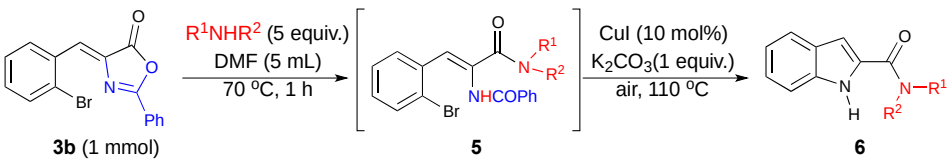
4a, X=Br, 70% X=Cl, 18% | **4b**, X=Br, 67% X=Cl, 12% | **4c**, X=Br, 58% X=Cl, 10% | **4d**, X=Br, 57% | **4e**, X=Br, 44%

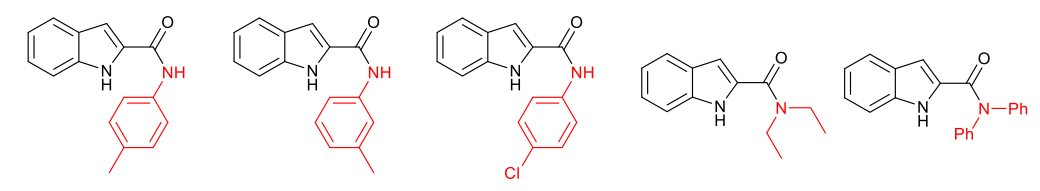
[a] Yield of isolated product based on **3**

Surprisingly, an intermediate was observed by TLC during the reaction process, which was isolated and identified to be ethyl 1-benzoyl-1*H*-indole-2-carboxylate **4** (Table 3). Using HPLC to monitor the conversion rate of each substance, the content of intermediate **4** first increased and then decreased gradually, and peaked at about 0.5 h. Separating the compounds **4** separately, we found that the yield of the product of 2-bromo substituted substrates was better than 2-chloro substituted substrates. The results indicated that 2-bromo substituted substrates were more active in this reaction to form intermediates **4**. Furthermore, the yield of **4** with different esters were measured, the methyl ester > ethyl ester > isopropyl ester.

Compounds **3b** also could react with amines to form the corresponding products **6** (Table 4). When ring opening of compound **3b** by corresponding amines, the indole-2-amides **6** could be obtained in the similar reaction condition (**6a**, **6b**, **6c** and **6d**). However, due to the influence of steric hindrance effect, only trace amount of **6e** was detected.

Table 4. The synthesis of indole-2-carboxylic acid amides **6**[a]



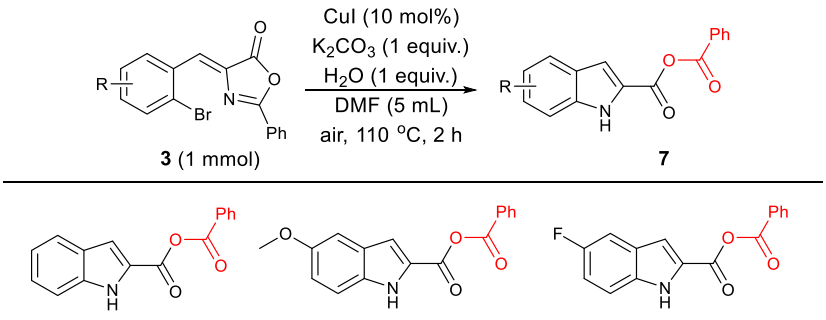


6a, 49% | **6b**, 50% | **6c**, 45% | **6d**, 69% | **6e**, trace

[a] Yield of isolated product based on **3b**

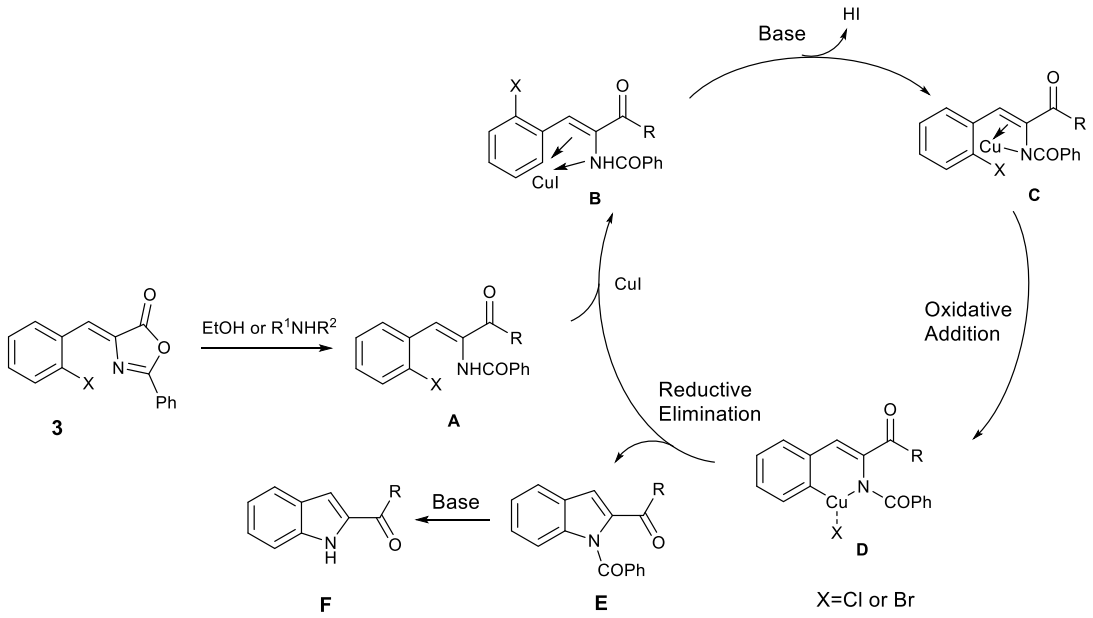
To further demonstrate the usefulness of this catalytic protocol, the application of this method in synthesis of indole-2-carboxylic acid anhydrides **7** was also investigated. When, H_2O (1 equiv.) was used as the ring opening reagent, **7** could be obtained in good to excellent yields under the similar conditions (Table 5).

Table 5. The synthesis of indole-2-carboxylic acid anhydrides **7**[a]



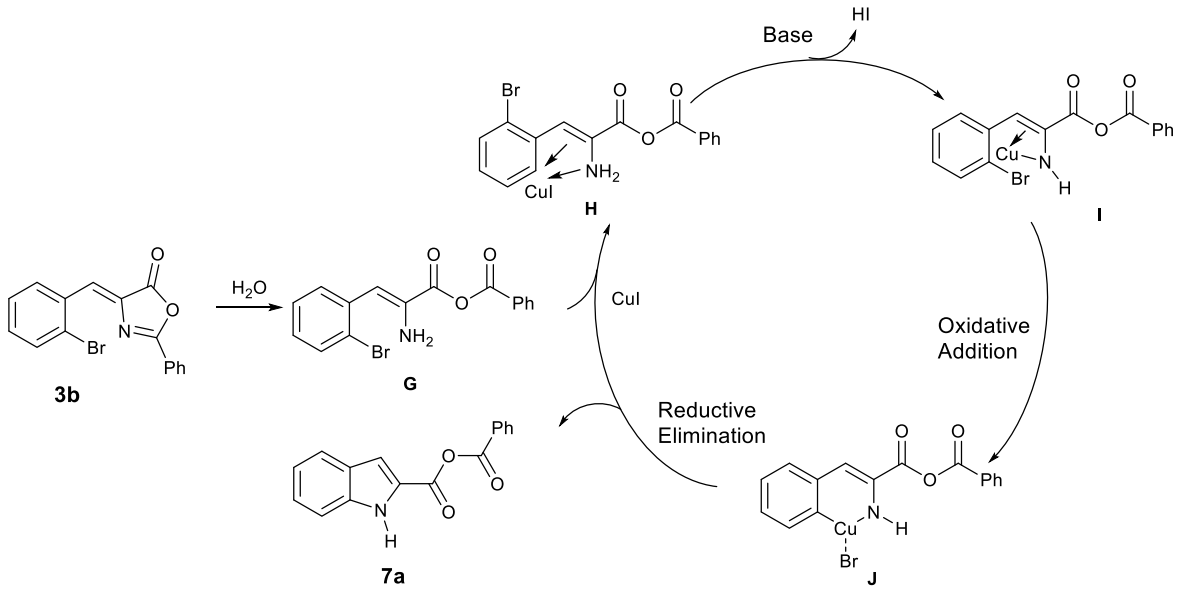
[a] Yield of isolated product based on **3**

Zeng[4e] and Fukuyama [5] have proposed the mechanism of copper-mediated intramolecular amination. A possible mechanism for the formation of indole-2-carboxylic acid esters and amides was proposed in Scheme 1. Intermediate **A** was obtained by ring opening of **3**. Then, coordination of **A** with CuI formed the intermediate **B**, which provided **C** in the presence of base (K_2CO_3). Next, the oxidative addition of **C** to form the transient Cu(III) species **D** which then reductively eliminates to give **E**, thereby freed the copper catalyst. Finally, **E** desorbed benzoyl to form **F** under the base condition.



Scheme 1. Reaction mechanism for preparing indole-2-carboxylates and indole-2-amides

On the other hand, a possible mechanism for the formation of indole-2-carboxylic acid anhydride was proposed in Scheme 2. Intermediate **G** was obtained by ring opening of **3b**. Then, coordination of **G** with CuI formed the intermediate **H**, which provided **I** in the presence of base (K_2CO_3). Next, the oxidative addition of **I** to form the transient Cu(III) species **J** which then reductively eliminates to give the product **7a**, thereby freed the copper catalyst.



Scheme 2. Reaction mechanism for preparing indole-2-carboxylic acid anhydride

CONCLUSIONS

In summary, we have developed a ligand-free copper-catalyzed one-pot intramolecular C-N coupling reaction with cheap substrates. The reaction provides an efficient approach for preparing various indole-2-carboxylic acid derivatives including esters, amides and anhydrides, which are important units in biologically active molecules.

EXPERIMENTAL

General information

Analytical grade solvents and commercially available reagents were used without further purification. Melting points were determined on a Büchi B-540 capillary melting point apparatus and uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz, 500 Hz or 600MHz spectrometer in $CDCl_3$ or DMSO-d_6 using TMS as an internal standard. Chemical shifts are reported in parts per million (δ), coupling constants (*J* values) are reported in Hertz (Hz) and spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), hept (heptet), m (multiplet), dd (double doublet), td (triple doublet). Precoated silica gel on glass plates were used for TLC analysis with a

mixture of petroleum ether (60 – 80 ºC) and EtOAc as eluent. Mass spectra were measured with Thermo Finnigan LCQ-Advantage. High resolution mass spectrometry (HRMS) was recorded with Bruker Compact.

Compounds **3** were prepared according to the known reference: *Synth. Commun*., 2012, **42**, 195.

The synthesis of compounds 2 and 6. A 25 mL round bottom flask was charged with **3** (1 mmol), R^1OH (5 equiv.) or R^2NHR^3 (5 equiv.), DMF (5 mL). The reaction was allowed to stir at 70 ºC for 1 h. Then, CuI (10 mol%), and K_2CO_3 (1 equiv.) were added and stirred at 110 ºC. After the completion of the reaction (as indicated by TLC), the reaction mixture was added EtOAc (10 mL) and washed with solution of NaCl (3 × 10 mL). The organic layers were dried with anhydrous Na_2SO_4 and concentrated in vacuo. The residue was then purified by column chromatography on silica gel (*n*-hexanes/EtOAc = 20:1) to indole-2-carboxylic ester **2** or indole-2-carboxylic amide **6**.

The synthesis of compounds 7. A 25 mL round bottom flask was charged with **3** (1 mmol), CuI (10 mol%), K_2CO_3 (1 equiv.) and DMF (5 mL). The reaction was allowed to stir at 110 ºC. After the completion of the reaction (as indicated by TLC), the reaction mixture was added EtOAc (10 mL) and washed with solution of NaCl (3 × 10 mL). The organic layers were dried with anhydrous Na_2SO_4 and concentrated in vacuo. The residue was then purified by column chromatography on silica gel (*n*-hexanes /EtOAc = 20:1) to benzoic 1*H*-indole-2-carboxylic anhydride **7**.

Methyl 1*H*-indole-2-carboxylate[6a] **(2a):** White solid; mp 151.6 – 152.9 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.01 (s, 1H), 7.67 (d, *J* = 8.2 Hz, 1H), 7.41 (dd, *J* = 8.3, 0.9 Hz, 1H), 7.31 (td, *J* = 7.6, 0.8 Hz, 1H), 7.21 (t, *J* = 1.0 Hz, 1H), 7.15 – 7.12 (m, 1H), 3.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 136.8, 127.4, 127.0, 125.3, 122.5, 120.7, 111.8, 108.8, 52.1; MS (ESI^+) *m/z* 176.2 $[M+H]^+$.

Ethyl 1*H*-indole-2-carboxylate[6b] **(2b):** White solid; mp 122.5 – 124.7 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.25 (s, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.42 (d, *J* = 8.5 Hz, 1H), 7.33 – 7.30 (m, 1H), 7.24 (s, 1H), 7.15 (t, *J* = 7.5 Hz, 1H), 4.43 (q, *J* = 7.0 Hz, 2H), 1.42 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 136.7, 128.8, 127.3, 125.1, 122.4, 120.6, 111.8, 108.5, 61.0, 14.5; MS (ESI^+) *m/z* 212.2 $[M+Na]^+$.

Isopropyl 1*H*-indole-2-carboxylate[6c] **(2c):** White solid; mp 124.3 – 124.7 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.36 (s, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.23 (t, *J* = 7.4 Hz, 1H), 7.16 (s, 1H), 7.07 (t, *J* = 7.4 Hz, 1H), 5.27 (hept, *J* = 6.1 Hz, 1H), 1.39 (d, *J* = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6, 136.8, 127.7, 127.3, 125.0, 122.4, 120.5, 111.8, 108.4, 68.7, 22.1; MS (ESI^+) *m/z* 204.0 $[M+H]^+$.

Methyl 6-chloro-1*H*-indole-2-carboxylate[6a] **(2d):** White solid; mp 172.8 – 173.5 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.15 (s, 1H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.40 (s, 1H), 7.17 (s, 1H), 7.10 (dd, *J* = 8.4, 1.6 Hz, 1H), 3.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 136.9, 131.2, 127.7, 125.9, 123.4, 121.8, 111.6, 108.7, 52.2; MS (ESI^-) *m/z* 208.3 $[M-H]^-$.

Isopropyl 6-chloro-1*H*-indole-2-carboxylate (2e): White solid; mp 182.8 – 183.8 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.11 (s, 1H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.40 (s, 1H), 7.16 (s, 1H), 7.09 (d, *J* = 8.4 Hz, 1H), 5.28 (hept, *J* = 6.1 Hz, 1H), 1.40 (d, *J* = 6.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 136.9, 131.0, 128.5, 125.9, 123.3, 121.7, 111.6, 108.4, 69.0, 22.1; HRMS (ESI^+): $C_{12}H_{12}ClNO_2Na$ $[M+Na]^+$; calculated: 260.0449, found: 260.0445.

Isopropyl 4-chloro-1*H*-indole-2-carboxylate (2f): White solid; mp 163.5 – 164.1 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.51 (s, 1H), 7.32 – 7.29 (m, 2H), 7.20 (t, *J* = 7.8 Hz, 1H), 7.12 (d, *J* = 7.2 Hz, 1H), 5.30 (hept, *J* = 6.3 Hz, 1H), 1.41 (d, *J* = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 136.9, 127.9, 127.4, 126.2, 125.2, 120.0, 110.3, 108.4, 69.2, 22.4; HRMS (ESI^+): $C_{12}H_{12}ClNO_2Na$ $[M+Na]^+$; calculated: 260.0449, found: 260.0449.

Methyl 6-fluoro-1*H*-indole-2-carboxylate[6a] (2g): White solid; mp 155.3 – 156.4 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.22 (s, 1H), 7.59 (dd, *J* = 8.6, 5.4 Hz, 1H), 7.18 (d, *J* = 1.2 Hz, 1H), 7.08 (dd, *J* = 9.2, 2.0 Hz, 1H), 6.91 (td, *J* = 9.2, 2.0 Hz, 1H), 3.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6, 161.1 (d, *J* = 239 Hz), 136.6 (d, *J* = 13 Hz), 128.6 (d, *J* = 16 Hz), 127.0 (d, *J* = 56 Hz), 123.7 – 123.7 (m), 110.2 (d, *J* = 25 Hz), 108.7 (d, *J* = 5 Hz), 97.6 (d, *J* = 26 Hz), 52.2 (d, *J* = 5 Hz); MS (ESI^-) *m/z* 192.2 $[M-H]^-$.

Isopropyl 6-fluoro-1*H*-indole-2-carboxylate (2h): White solid; mp 138.4 – 139.1 ºC. ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.33 (s, 1H), 7.60 (dd, *J* = 8.8, 5.4 Hz, 1H), 7.20 (dd, *J* = 2.1, 0.9 Hz, 1H), 7.09 (dd, *J* = 9.3, 2.1 Hz, 1H), 6.92 (td, *J* = 9.3, 2.4 Hz, 1H), 5.31 (hept, *J* = 6.3 Hz, 1H), 1.40 (d, *J* = 6.0 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.7 (d, *J* = 240 Hz), 161.6, 137.0 (d, *J* = 14 Hz), 128.5 (d, *J* = 3 Hz), 124.1, 123.7 (d, *J* = 10 Hz), 110.3 (d, *J* = 24 Hz), 108.6, 97.8 (d, *J* = 26 Hz), 68.8, 22.0; HRMS (ESI^+): $C_{12}H_{12}FNO_2Na$ $[M+Na]^+$; calculated: 244.0744, found: 244.0743.

Isopropyl 5-fluoro-1*H*-indole-2-carboxylate (2i): White solid; mp 129.5 – 129.9 ºC. ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.13 (s, 1H), 7.34 (dd, *J* = 8.9, 4.2 Hz, 1H), 7.29 (dd, *J* = 9.2, 2.3 Hz, 1H), 7.15 (d, *J* = 1.0 Hz, 1H), 7.06 (td, *J* = 9.1, 2.4 Hz, 1H), 5.31 – 5.25 (m, 1H), 1.40 (d, *J* = 6.2 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.4, 158.1 (d, *J* = 236 Hz), 133.4, 129.4, 127.6 (d, *J* = 9 Hz), 114.3 (d, *J* = 27 Hz), 112.8 (d, *J* = 10 Hz), 108.3 (d, *J* = 4 Hz), 106.7 (d, *J* = 22 Hz), 68.9, 22.0; HRMS (ESI^+): $C_{12}H_{12}FNO_2Na$ $[M+Na]^+$; calculated: 244.0744, found: 244.0738.

Methyl 4*H*-thieno[3,2-*b*]pyrrole-5-carboxylate[3c] (2j): White solid; mp 141.8 – 142.2 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.49 (s, 1H), 7.31 (d, *J* = 5.2 Hz, 1H), 7.13 (s, 1H), 6.94 (d, *J* = 5.2 Hz, 1H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 141.7, 129.6, 126.6, 124.8, 111.1, 107.8, 51.7; HRMS (ESI^+): $C_8H_7NO_2SNa$ $[M+Na]^+$; calculated: 204.0090, found: 204.0091.

Ethyl 4*H*-thieno[3,2-*b*]pyrrole-5-carboxylate[6d] (2k): White solid; mp 129.1 – 131.5 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.18 (s, 1H), 7.32 (d, *J* = 5.6 Hz, 1H), 7.14 (s, 1H), 6.95 (d, *J* = 5.2 Hz, 1H), 4.37 (q, *J* = 7.2 Hz, 2H), 1.39 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 141.5, 129.4, 127.0, 124.7,

111.1, 107.6, 60.7, 14.4; MS (ESI^+) *m/z* 195.04 $[M+H]^+$.

Isopropyl 4*H*-thieno[3,2-*b*]pyrrole-5-carboxylate (2l): White solid; mp 122.3 – 124.6 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 9.26 (s, 1H), 7.31 (d, *J* = 5.2 Hz, 1H), 7.13 (s, 1H), 6.95 (d, *J* = 5.2 Hz, 1H), 5.25 (hept, *J* = 6.3 Hz, 1H), 1.37 (d, *J* = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 141.4, 129.2, 127.5, 124.7, 111.1, 107.4, 68.3, 22.0; HRMS (ESI^+): $C_{10}H_{11}NO_2SNa$ $[M+Na]^+$; calculated: 232.0403, found: 232.0402.

Methyl 1-benzoyl-1*H*-indole-2-carboxylate (4a): White solid; mp 96.4 – 97.2 °C. ^1H NMR (600 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.4 Hz, 1H), 7.60 (d, *J* = 7.8 Hz, 3H), 7.48 (t, *J* = 7.5 Hz, 1H), 7.36 (t, *J* = 7.8 Hz, 2H), 7.31 – 7.28 (m, 2H), 7.20 (t, *J* = 7.8 Hz, 1H), 3.41 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.2, 161.4, 138.8, 135.6, 133.2, 130.7, 129.3, 128.8, 127.3, 127.2, 123.5, 122.6, 115.8, 114.1, 52.0; HRMS (ESI^+): $C_{17}H_{13}NO_3Na$ $[M+Na]^+$; calculated: 302.0788, found: 302.0780.

Ethyl 1-benzoyl-1*H*-indole-2-carboxylate (4b): White solid; mp 88.3 – 89.9 °C. ^1H NMR (600 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.4 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 3H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 2H), 7.42 – 7.38 (m, 2H), 7.30 (t, *J* = 7.5 Hz, 1H), 3.97 (q, *J* = 7.0 Hz, 2H), 1.09 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.1, 160.9, 138.8, 135.6, 133.1, 131.0, 129.4, 128.7, 127.2, 127.2, 123.4, 122.5, 115.6, 114.0, 61.3, 13.9; HRMS (ESI^+): $C_{18}H_{16}NO_3$ $[M+H]^+$; calculated: 294.1125, found: 294.1116.

Isopropyl 1-benzoyl-1*H*-indole-2-carboxylate (4c): White solid; mp 81.9 – 83.3 °C. ^1H NMR (600 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 8.4, 0.6 Hz, 1H), 7.72 – 7.69 (m, 3H), 7.58 – 7.56 (m, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 7.40 (m, 1H), 7.37 (d, *J* = 0.4 Hz, 1H), 7.30 – 7.28 (m, 1H), 4.86 (hept, *J* = 6.3 Hz, 1H), 1.05 (d, *J* = 6.0 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.2, 160.5, 138.9, 135.8, 133.2, 131.4, 129.5, 128.8, 127.2, 127.1, 123.4, 122.5, 115.4, 114.0, 69.3, 21.4; HRMS (ESI^+): $C_{19}H_{17}NO_3Na$ $[M+Na]^+$; calculated: 330.1101, found: 330.1091.

Methyl 1-benzoyl-5-fluoro-1*H*-indole-2-carboxylate (4d): White solid; mp 150.7 – 152.1 °C. ^1H NMR (600 MHz, $CDCl_3$) δ 7.77 (dd, *J* = 9.0, 4.2 Hz, 1H), 7.70 – 7.68 (m, 2H), 7.60 (t, *J* = 7.5 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 2H), 7.35 (dd, *J* = 8.7, 2.7 Hz, 1H), 7.32 (s, 1H), 7.15 (td, *J* = 9.0, 2.4 Hz, 1H), 3.50 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.9, 161.1, 159.40 (d, *J* = 240 Hz), 135.4, 135.2, 133.2, 132.0, 129.2, 128.8, 127.8 (d, *J* = 9 Hz), 115.6 (d, *J* = 26 Hz), 115.4 (d, *J* = 9 Hz), 115.0 (d, *J* = 4 Hz), 107.4 (d, *J* = 24 Hz), 52.1; HRMS (ESI^+): $C_{17}H_{12}FNO_3Na$ $[M+Na]^+$; calculated: 320.0693, found: 320.0695.

Isopropyl 1-benzoyl-5-fluoro-1*H*-indole-2-carboxylate (4e): White solid; mp 144.0 – 144.8 °C. ^1H NMR (600 MHz, $CDCl_3$) δ 7.81 – 7.78 (m, 1H), 7.69 (d, *J* = 7.8 Hz, 2H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 7.34 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.31 (s, 1H), 7.15 (td, *J* = 9.0, 2.4 Hz, 1H), 4.85 (hept, *J* = 6.0, 1H), 1.04 (d, *J* = 6.0 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.0, 160.2, 159.4 (d, *J* = 238 Hz), 135.4 (d, *J* = 44 Hz), 133.3, 132.7, 129.4, 128.8, 127.8 (d, *J* = 10 Hz), 115.6, 115.5, 115.2 (d, *J* = 9 Hz),

114.7 (d, J = 4 Hz), 107.3 (d, J = 24 Hz), 69.5, 21.3; HRMS (ESI$^+$): $C_{19}H_{16}FNO_3Na$ [M+Na]$^+$; calculated: 348.1006, found: 348.1008.

***N*-(*p*-Tolyl)-1*H*-indole-2-carboxamide[6e] (6a):** White solid; mp 160.2 – 163.7 ºC. ^{1}H NMR (600 MHz, DMSO) δ 11.71 (s, 1H), 10.12 (s, 1H), 7.68 (t, J = 9.3 Hz, 3H), 7.46 (d, J = 8.4 Hz, 1H), 7.40 (s, 1H), 7.22 (t, J = 7.5 Hz, 1H), 7.18 (d, J = 8.4 Hz, 2H), 7.07 (t, J = 7.5 Hz, 1H), 2.29 (s, 3H); ^{13}C NMR (150 MHz, DMSO) δ 160.0, 137.2, 136.9, 133.0, 132.1, 129.6, 127.5, 124.1, 122.2, 120.6, 120.3, 112.8, 104.1, 20.97; MS (ESI$^+$) *m/z* 251.07 [M+H]$^+$

***N*-(*m*-Tolyl)-1*H*-indole-2-carboxamide[6f] (6b):** White solid; mp 162.5 – 165.1 ºC. ^{1}H NMR (600 MHz, DMSO) δ 11.70 (s, 1H), 10.11 (s, 1H), 7.67 (d, J = 7.8 Hz, 1H), 7.62 (s, 2H), 7.47 (d, J = 8.4 Hz, 1H), 7.42 (s, 1H), 7.26 – 7.21 (t, 2H), 7.07 (t, J = 7.5 Hz, 1H), 6.93 (d, J = 7.8 Hz, 1H), 2.33 (s, 3H); ^{13}C NMR (150 MHz, DMSO) δ 160.1, 139.3, 138.3, 137.3, 132.0, 129.0, 127.5, 124.7, 124.2, 122.2, 121.1, 120.4, 117.8, 112.8, 104.3, 21.7; MS (ESI$^+$) *m/z* 251.07 [M+H]$^+$.

***N*-(4-Chlorophenyl)-1*H*-indole-2-carboxamide[6g] (6c):** White solid; mp > 250 ºC. ^{1}H NMR (400 MHz, DMSO) δ 11.75 (s, 1H), 10.32 (s, 1H), 7.87 (d, J = 8.8 Hz, 2H), 7.69 (d, J = 8.0 Hz, 1H), 7.49 (d, J = 8.4 Hz, 1H), 7.43 (m, 3H), 7.24 (t, J = 7.6 Hz, 1H), 7.08 (t, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO) δ 160.3, 138.4, 137.4, 131.7, 129.0, 127.6, 127.5, 124.3, 122.2, 122.1, 120.4, 112.9, 104.6; MS (ESI$^+$) *m/z* 271.06 [M+H]$^+$.

***N*, *N*-Diethyl-1*H*-indole-2-carboxamide[6h] (6d):** White solid; mp 155.1 – 157.0 ºC. ^{1}H NMR (400 MHz, DMSO) δ 11.54 (s, 1H), 7.65 (d, J = 7.6 Hz, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.20 (t, J = 7.4 Hz, 1H), 7.06 (t, J = 7.2 Hz, 1H), 6.80 (s, 1H), 3.60 (s, 4H), 1.25 (s, 6H); ^{13}C NMR (100 MHz, DMSO) δ 162.5, 136.2, 130.9, 127.6, 123.5, 121.8, 120.1, 112.4, 103.2, 41.8, 14.0; MS (ESI$^+$) *m/z* 217.05 [M+H]$^+$.

Benzoic 1*H*-indole-2-carboxylic anhydride (7a): White solid; mp 164.8 – 165.8 ºC. ^{1}H NMR (400 MHz, DMSO) δ 9.65 (s, 1H), 8.64 (s, 1H), 7.97 (d, J = 7.6 Hz, 2H), 7.79 (d, J = 7.6 Hz, 1H), 7.64 (t, J = 7.4 Hz, 1H), 7.56 (t, J = 7.4 Hz, 3H), 7.45 (d, J = 8.0 Hz, 1H), 7.39 (t, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 163.0, 155.4, 138.7, 137.5, 135.4, 133.9, 133.3, 132.8, 131.8, 130.2, 129.4, 124.6, 121.2; HRMS (ESI$^+$): $C_{16}H_{11}NO_3Na$ [M+Na]$^+$; calculated: 288.0631, found: 288.0639.

Benzoic 5-methoxy-1*H*-indole-2-carboxylic anhydride (7b): White solid; mp 160.0 – 161.1 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.58 (s, 1H), 8.62 (s, 1H), 7.97 (d, J = 7.6 Hz, 2H), 7.64 (t, J = 7.4 Hz, 1H), 7.56 (t, J = 7.4 Hz, 2H), 7.38 – 7.34 (m, 2H), 7.38 – 7.34 (m, 1H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ 166.3, 158.4, 156.6, 144.9, 134.0, 132.7, 129.1, 128.0, 126.6, 124.9, 120.4, 118.0, 117.4, 111.0, 56.2; HRMS (ESI$^+$): $C_{17}H_{13}NO_4Na$ [M+Na]$^+$; calculated: 318.0737, found: 318.0735.

Benzoic 5-fluoro-1*H*-indole-2-carboxylic anhydride (7c): White solid; mp 195.3 – 196.8 ºC. ^{1}H NMR (400 MHz, DMSO) δ 9.65 (s, 1H), 8.62 (s, 1H), 7.97 (d, J = 7.6 Hz, 2H), 7.86 (dd, J = 8.8, 6.8 Hz, 1H), 7.64 (t, J = 7.4 Hz, 1H), 7.56 (t, J = 7.4 Hz, 2H), 7.44 (dd, J = 9.6, 2.0 Hz, 1H), 7.28 (td, J = 8.8, 2.0 Hz,

1H); ^{13}C NMR (100 MHz, DMSO) δ 166.3, 163.1 (d, *J* = 247 Hz), 158.0, 151.6 (d, *J* = 13 Hz), 133.9, 132.7, 130.4 (d, *J* = 10 Hz), 129.1, 128.1, 127.3, 123.7 (d, *J* = 3 Hz), 116.7, 113.3 (d, *J* = 23 Hz), 104.2 (d, *J* = 26 Hz); HRMS (ESI$^+$): $C_{16}H_{10}FNO_3Na$ $[M+Na]^+$; calculated: 306.0537, found: 306.0543.

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