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Aminocarbonylation

Acylative Coupling of Amine and Indole Using Chloroform as a Carbonyl Group

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Abstract: Chloroform-mediated acylative coupling of amines with indoles has been developed. When indoles and amines in chloroform were treated with dimethylzinc in the presence of air, the three-component aminocarbonylation reaction proceeded via in-situ generation of phosgene from chloroform and O_2 to provide indole-3-carboxamides in a single operation. Application to the synthesis of biologically active compounds and intramolecular acylation are also described.

Introduction

Indole-3-carboxamides are widely found in natural products such as scholarisine N,[1] leptoclinidamine C[2] and kingamide A[3] (Figure 1). The structure also is found in pharmaceutically relevant small molecules. For example, RO5028442 displays potent and selective brain-penetrant hV1a antagonist activity.[4] Therefore, much effort has focused on the synthesis of indole-3-carboxamide.

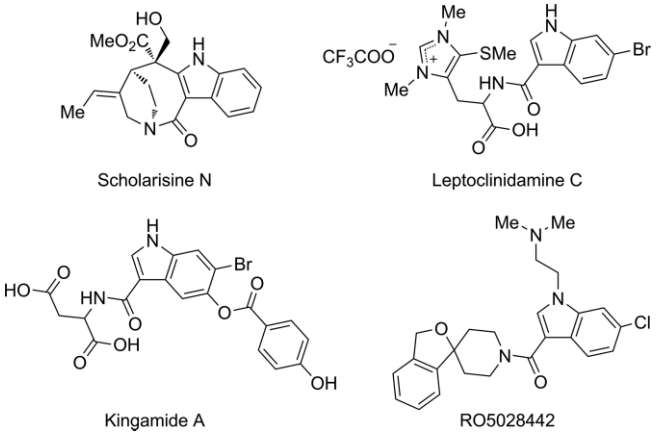
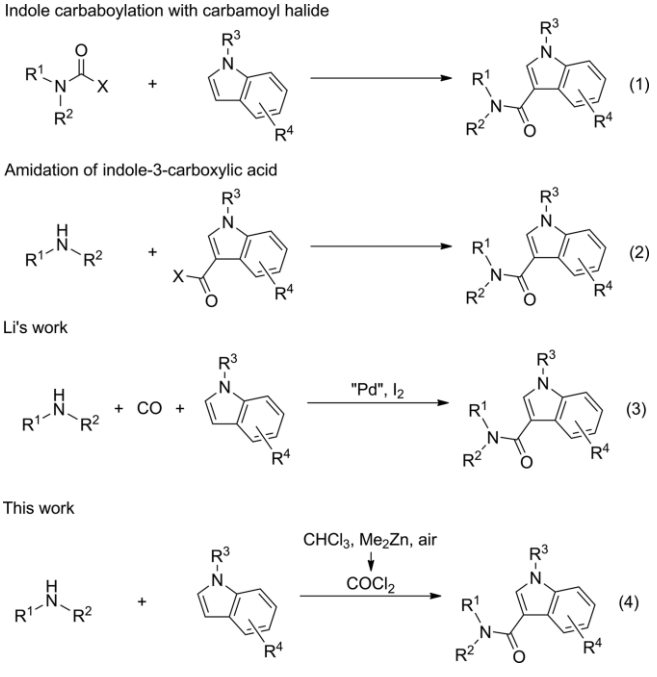


Figure 1. Natural compounds and biologically active indole-3-carboxamides.

Traditional nucleophilic acyl substitution reactions are a well-known synthetic strategy for these compounds, though these methods need a pre-installed carbonyl moiety in the amine or indole skeleton [Scheme 1, Equation (1) and Equation (2)].[5] Aminocarbonylation of indole with carbon monoxide and amines via the generation of the 3-iodoindole intermediate in the presence of a palladium catalyst and iodine have also been reported [Equation (3)].[6]



Scheme 1. Strategy for the synthesis of indole-3-carboxamides.

We propose using phosgene to achieve direct carbamoylation of indole with amines without pre-functionalization.[7] Phosgene is a versatile reagent for the synthesis of some important classes of organic compounds, including acyl chloride, isocyanate, ureas, carbonates, acid anhydrides, and heterocycles through chlorination, acylation, and dehydration reactions.[8] However, phosgene is difficult to handle and is a highly toxic gas. Therefore, less harmful phosgene equivalents such as diphosgene and triphosgene were developed; however, these

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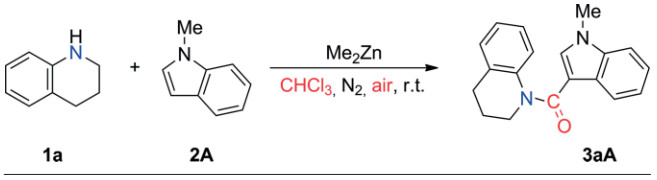
species were less reactive than phosgene.[9] Alternatively, in-situ generation of phosgene[8a,8b] provides a safer method, because highly reactive phosgene is consumed immediately by nucleophiles, ensuring low stationary concentrations.[10,11] We recently reported a novel method for in-situ generation of phosgene from chloroform in the presence of dimethylzinc and O_2, and its application to the chlorolactamization of homoallylic amines.[12] As part of our program studying the utility of chloroform as a C1 unit,[12,13] we report a direct three-component coupling of amine, indole, and phosgene generated in situ from chloroform via Friedel–Crafts-type carbamoylation [Equation (4)].

Results and Discussion

We initially executed a screening experiment to determine the optimal conditions for acylative coupling of tetrahydroquinoline with 1-methylindole (Table 1). A chloroform solution of tetrahydroquinoline **1a** and indole **2A** (1 equiv. each) was treated with dimethylzinc (8 equiv.) in the presence of air.[12] The desired indole-3-carboxamide **3aA** was formed, albeit in low yield. Nucleophilic attack of indole was considered rather ineffective because the formation of complex side products, including urea derivatives of **1a** and *N*-acetyltetrahydroquinoline formed by nucleophilic acyl substitution of carbamoyl chloride **B** with **1a** or dimethylzinc, was observed. To improve the yield of **3aA**, the amount of nucleophile **2A** was increased and reaction time was extended (entries 2–5). As expected, an excellent yield of **3aA** was obtained when the reaction was carried out with 4 equiv. of **2A** for 48 h (entry 5).[14] Decreasing the amount of dimethylzinc from 8 to 6 equiv. led to a lower yield of the desired product (entry 6).

Table 1. Optimization of the reaction conditions.[a]

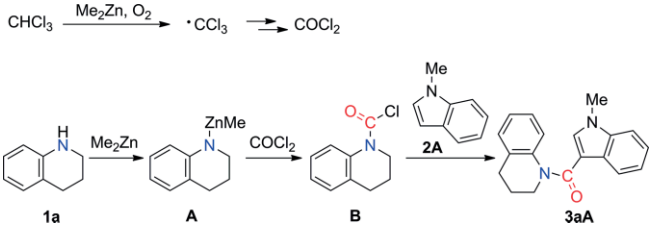


1a **2A** **3aA**

Entry	**1a** [equiv.]	**2A** [equiv.]	Me_2Zn [equiv.]	Time [h]	Yield [%][b]
1	1	1	8	24	18
2	1	2	8	24	20
3	1	2	8	48	56
4	1	3	8	48	67
5	1	4	8	48	93
6	1	4	6	48	76

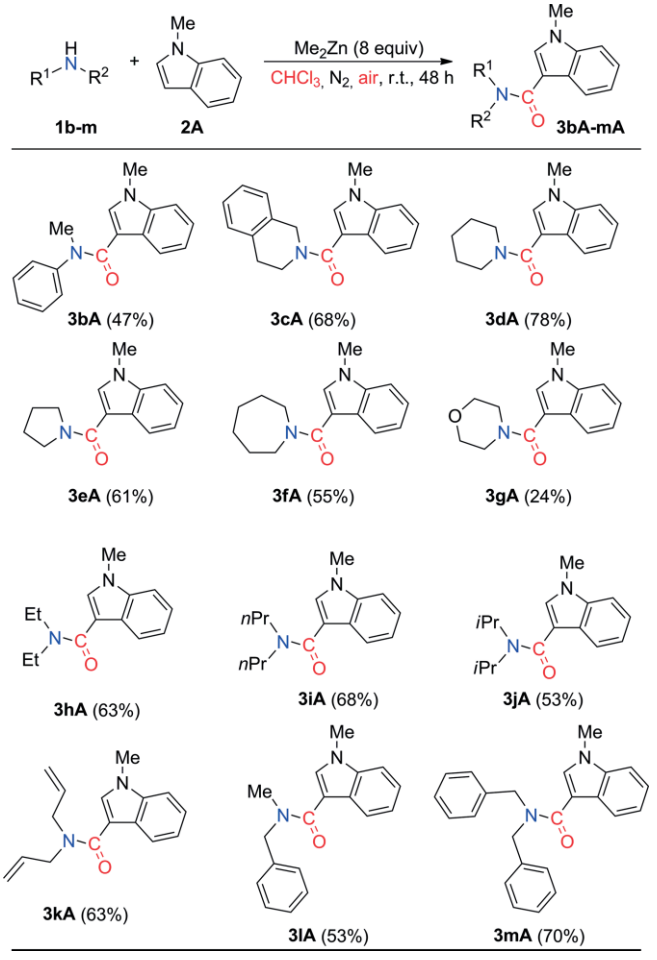
[a] Reactions were performed with 0.3 mmol of **1a** at a 0.1 M concentration. [b] Isolated yield.

The possible reaction mechanism for this acylative coupling is outlined in Scheme 2. Dimethylzinc and O_2 initiated radical decomposition of chloroform to form phosgene via the trichloromethyl radical.[13] Phosgene is consumed immediately for the acylation of zinc amide **A**, which leads to the formation of the carbamoyl chloride **B**. Subsequent Friedel–Crafts-type aminocarbonylation of indole **2A** with carbamoyl chloride **B** provides carboxamide **3aA**.



Scheme 2. Proposed reaction mechanism for acylative coupling.

With the optimized condition (Table 1, entry 5) in hand, various amines were surveyed (Scheme 3). *N*-Methylaniline, an acyclic aromatic amine, gave the desired amide **3bA**. Aliphatic amines were then examined. Cyclic amines such as tetrahydroisoquinoline and piperidine gave corresponding amides **3cA** and **3dA** in good yields. Several aliphatic cyclic amines of different ring sizes also gave carbamoylated products **3eA** and **3fA**. A lower yield was obtained with morpholine, probably due to the instability of morpholine in the presence of radicals.[15]

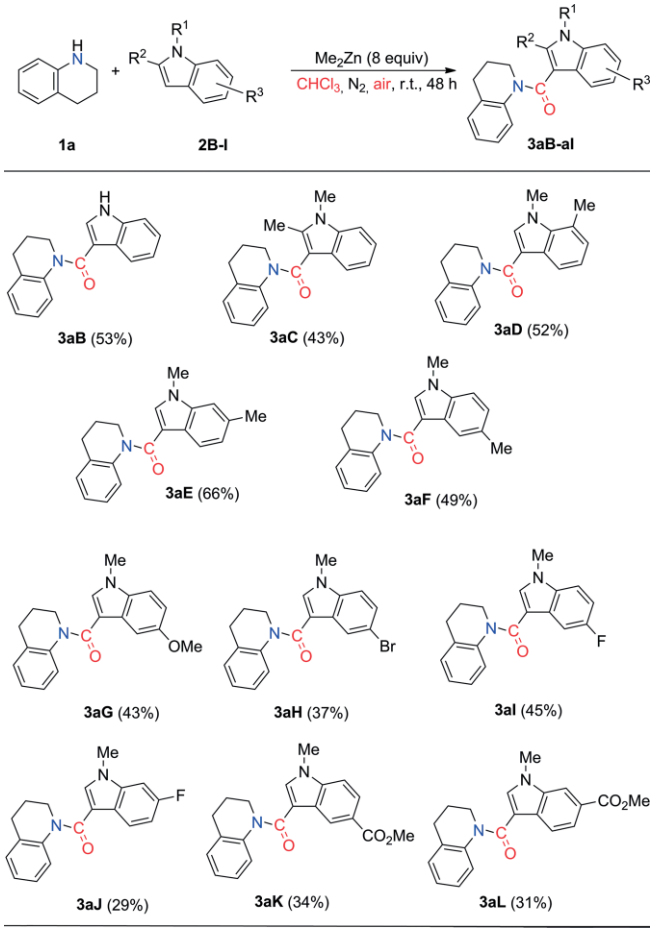


Scheme 3. Reaction of various amines with Me_2Zn and $CHCl_3$. Conditions: **1b**–**m** (0.3 mmol), **2A** (1.2 mmol), Me_2Zn (2.4 mmol), $CHCl_3$ (3.0 mL). Yields of isolated products are given in parentheses.

Furthermore, aliphatic acyclic amines were examined. The reaction with primary amines did not give the desired product due to the predominant formation of urea derivatives. Simple dialkylamines such as diethylamine, di-*n*-propylamine, and di-

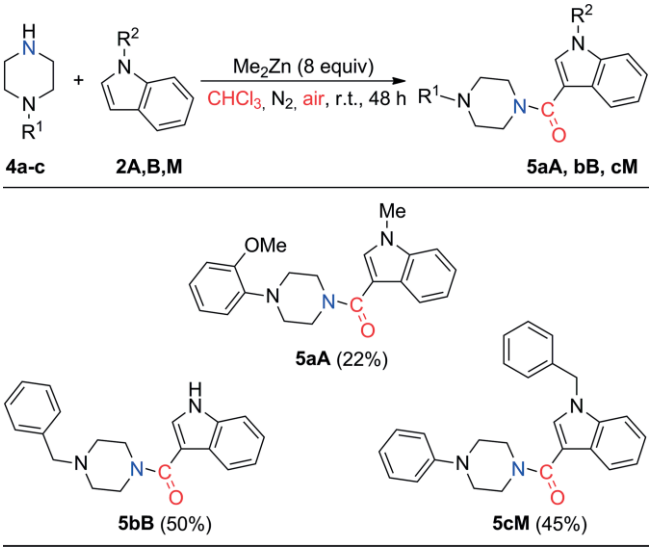
isopropylamine were tolerated and converted into the corresponding indole-3-carboxamides **3hA**–**3jA**, along with minor amount of urea derivatives. Notably, the allylic moiety of diallylamine did not impede the reaction and **3kA** formed in 63 % yield. In the case of *N*-benzylamines, it is noteworthy that the formation of indolinone derivatives by intramolecular Friedel–Crafts-type aminocarbonylation was not observed.[8c] Thus, the desired intermolecular acylative coupling products **3lA** and **3 mA** were formed selectively.

Several indole derivatives were next tested under optimized reaction conditions (Scheme 4). Indole (**2B**) reacted selectively at the indole 3-position to give the corresponding 3-aminocarbonylated product **3aB**, in which acylation of the indole nitrogen atom did not occur. The methyl group at the indole 2-position did not prevent the reaction and the desired amide **3aC** was obtained in 43 % yield. In addition, substituents such as methyl, methoxy, halogen, ester group were investigated. The methyl group on the benzene ring was tolerated, giving the desired indole-3-carboxamides in moderate yields (**3aD**–**3aF**). However, the methoxy, halogen, and ester substituted substrate resulted in diminished yields (**3aG**–**3aL**).



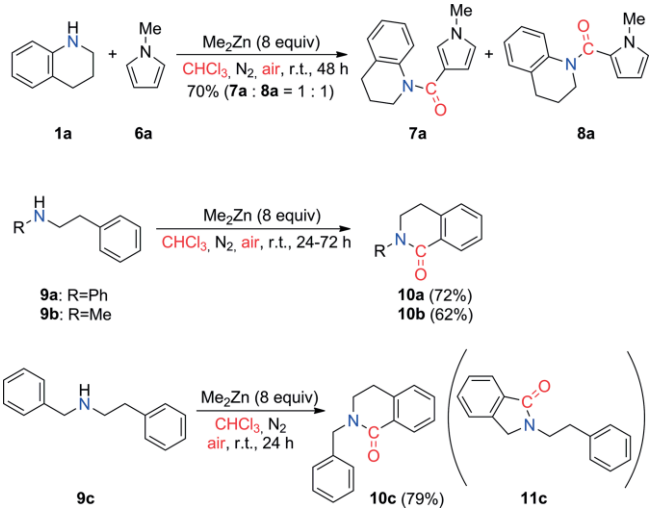
Scheme 4. Reaction of various indole derivatives with Me_2Zn and $CHCl_3$. Conditions: **1a** (0.3 mmol), **2B**–**L**(1.2 mmol), Me_2Zn (2.4 mmol), $CHCl_3$ (3.0 mL). Yields of isolated products are given in parentheses.

To determine the applicability of this aminocarbonylation reaction, we next examined the reaction of indole with piperazine to synthesize biologically active indole alkaloids with properties such as cytotoxicity against the A375 human melanoma cell line (**5aA**),[16] inhibitor of p38α MAP kinase (**5bB**),[17] and dopamine D_4 receptor agonist (**5cM**)[18] (Scheme 5). Reaction of the corresponding piperazines and indoles under optimized conditions gave the desired biologically active compounds **5aA**, **5bB** and **5cM** in just one step.



Scheme 5. Reaction of piperazine derivatives for the preparation of biologically active compounds. Conditions for **5aA** and **5bB**: piperazines **4a**–**b** (0.3 mmol), indoles **2A**–**B** (1.2 mmol), Me_2Zn (2.4 mmol), $CHCl_3$ (3.0 mL). Conditions for **5cM**: piperazine **4c** (0.15 mmol), indole **2M** (0.6 mmol), Me_2Zn (1.2 mmol), $CHCl_3$ (1.5 mL). Yields of isolated products are given in parentheses.

The scope of the three-component coupling reaction was expanded to the synthesis of pyrrolecarboxyamides, which are found in many biologically active compounds, such as atorvastatin[19] (Scheme 6). The three-component coupling reaction of *N*-methylpyrrole (**6a**) with tetrahydroquinoline **1a** in chloroform proceeded efficiently to give a 1:1 mixture of pyrrole-3-



Scheme 6. Intermolecular reaction with pyrroles and intramolecular reaction of phenylethylamines.

carboxyamide **7a** and pyrrole-2-carboxyamide **8a** in good yields. Finally, the possibility of an intramolecular acylative coupling was investigated for the construction of dihydroisoquinolinone, which is an important core structure, especially in alkaloids.[20] When *N*-phenyl- or *N*-methyl-phenylethylaniline **9a** and **9b** was treated with Me_2Zn in chloroform, the expected acylative cyclization provided dihydroisoquinolinones **10a** and **10b** in good yields. It is noted that the reaction of *N*-benzylphenylamine (**9c**) gave dihydroisoquinolinone **10c** as a sole product despite the possibility of forming indolinone **11c**.

Conclusions

We have developed a novel Friedel–Crafts-type aminocarbonylation reaction using chloroform as a phosgene precursor. The three-component coupling of amine, indole, and phosgene generated in situ from chloroform provided biologically important indolecarboxamides, while an intramolecular version of this reaction produced dihydroisoquinolinone. Efforts to further clarify the reaction mechanism, determine the scope of the proposed methodology, and demonstrate the synthetic utility of the products are currently underway in our laboratory.

Experimental Section

General Information: Melting points (uncorrected) were determined on BÜCHI M-565 or Yanaco NP-S3. IR spectra were obtained on a Parkin Elmer SpectrumOne A spectrometer. NMR spectra were recorded at 300 MHz/75 MHz (^{1}H NMR/^{13}C NMR), 500 MHz/125 MHz (^{1}H NMR/^{13}C NMR) or 600 MHz/150 MHz (^{1}H NMR/^{13}C NMR) using Varian Gemini-300 (300 MHz), Varian MERCURY plus 300 (300 MHz), Varian NMR system AS 500 (500 MHz), or Bruker Avance III HD (600 MHz) spectrometers. Chemical shifts (δ) are reported in ppm with solvent resonance or tetramethylsilane as the internal standard. High-resolution mass spectra were obtained by ESI method on a Thermo Fisher Scientific Exactive. Flash column chromatography was performed using E. Merck Kieselgel 60 (230–240 mesh). Medium-pressure column chromatography was performed using Lobar größe B (E. Merck 310–25, Lichroprep Si60). Preparative TLC separation was carried out on precoated silica gel plates (E. Merck $60F_{254}$). $CHCl_3$ (stabilized by amylene for HPLC, Cat. No. 07278–1B) and Me_2Zn (1.0 M *n*-hexane solution, Cat. No. 11384–25) were purchased from Kanto Chemical Co., Inc. Unless otherwise stated, all the reagents and solvents were used as received from the manufacturer. Starting materials **2D**,[21a] **2E**,[21b] **2F**,[21c,21d] **2G**,[21e,21f] **2H**,[21c,21d] **2I**,[21a] **2J**,[21g] **2K**,[21h] **2L**,[21b] **2M**,[21i] **4b**,[22a] **9a**[23a] and **9b**[23b] were prepared according to the literature procedures. The physical and spectroscopic data of **2D**,[21a] **2E**,[21b] **2F**,[21j] **2G**,[21j] **2H**,[21d] **2I**,[21a] **2J**,[21g] **2K**,[21k] **2L**,[21b] **2M**,[21d] **4b**,[22b] **9a**[23c,23d] and **9b**[23b] were consistent with those reported in the literature.

General Procedure for Friedel–Crafts-Type Carbamoylation: [Table 1 **entry 5**, Scheme 3 **and** Scheme 4]. **1a**–**m** (0.3 mmol) and **2A**–**F** (1.2 mmol) were dissolved in $CHCl_3$ (3.0 mL) under air atmosphere. Me_2Zn (1.0 M in hexane, 2.4 mL, 2.4 mmol) was added to the mixture under nitrogen atmosphere at room temperature. After being stirred at the same temperature for 48 h, the reaction mixture was diluted with sat. NH_4Cl and extracted with $CHCl_3$. The organic phase was dried with $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by preparative TLC (hexane/AcOEt = 2:1) afforded **3aA**–**mA**, **3aB**–**aI** in the yields shown in Table 1 entry 5, Scheme 3 and Scheme 4, respectively.

[3′,4′-Dihydro-1′(2′*H*)-quinolinyl](1-methyl-1*H*-indol-3-yl)methanone (3aA): Colorless crystals; 80.8 mg, 93 %; M.p.: 153–154 °C (hexane/$CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3009, 2948, 1615, 1602, 1579, 1531 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.62 (d, J = 8.0 Hz, 1 H), 7.30–7.04 (m, 6 H), 6.98 (t, J = 7.0 Hz, 1 H), 6.86 (t, J = 7.0 Hz, 1 H), 3.97 (t, J = 6.5 Hz, 2 H), 3.72 (s, 3 H), 2.87 (t, J = 6.5 Hz, 2 H), 2.05 (quint, J = 6.5 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.2, 140.0, 136.4, 133.2, 131.3, 128.2, 126.5, 125.6, 124.9, 124.0, 122.2, 121.3, 121.0, 110.9, 109.3, 44.6, 33.2, 27.1, 24.4 ppm. HRMS (ESI) *m/z*: calcd. for $C_{19}H_{19}N_2O$ [M + H]$^+$ 291.1492, found 291.1483.

***N*,1-Dimethyl-*N*-phenyl-1*H*-indole-3-carboxamide (3bA):**[24] Colorless crystals; 37.5 mg, 47 %; M.p.: 131–136 °C (hexane/$CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3690, 1613, 1594, 1529 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.30–8.24 (m, 1 H), 7.39–7.16 (m, 8 H), 6.12 (s, 1 H), 3.52 (s, 3 H), 3.49 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.9, 145.7, 136.0, 132.7, 129.4, 128.1, 127.7, 127.0, 122.43, 122.40, 121.2, 109.4, 109.0, 38.2, 33.0 ppm. HRMS (ESI) *m/z*: calcd. for $C_{17}H_{17}N_2O$ [M + H]$^+$ 265.1335, found 265.1332.

[3′,4′-Dihydro-2′(1′*H*)-isoquinolinyl](1-methyl-1*H*-indol-3-yl)-methanone (3cA): A colorless oil; 58.9 mg, 68 %. IR (neat): $\tilde{\nu}$ = 3000, 2931, 1611, 1533 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.58 (d, J = 8.0 Hz, 1 H), 7.26 (s, 1 H), 7.22–6.96 (m, 6 H), 6.91 (m, 1 H), 4.73 (s, 2 H), 3.78 (t, J = 5.5 Hz, 2 H), 3.66 (s, 3 H), 2.82 (t, J = 5.5 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.6, 136.4, 134.5, 133.5, 131.0, 128.6, 126.4, 126.23, 126.16, 122.3, 120.75, 120.73, 110.6, 109.6, 109.3, 47.5, 43.2, 33.1, 29.3 ppm. HRMS (ESI) *m/z*: calcd. for $C_{19}H_{19}N_2O$ [M + H]$^+$ 291.1492, found 291.1488.

(1-Methyl-1*H*-indol-3-yl)(piperidin-1′-yl)methanone (3dA):[25] A yellow solid; 56.7 mg, 78 %; M.p.: 99–101 °C (hexane/$CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3000, 2940, 1600, 1538 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.67 (d, J = 7.5 Hz, 1 H), 7.34 (s, 1 H), 7.32–7.12 (m, 3 H), 3.75 (s, 3 H), 3.66–3.60 (m, 4 H), 1.73–1.54 (m, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.1, 136.1, 130.8, 126.0, 122.0, 120.4 (2 C), 110.8, 109.4, 46.1 (br), 32.9, 26.3, 24.7 ppm. HRMS (ESI) *m/z*: calcd. for $C_{15}H_{19}N_2O$ [M + H]$^+$ 243.1492, found 243.1488.

(1-Methyl-1*H*-indol-3-yl)(pyrrolidin-1′-yl)methanone (3eA):[25] A white solid; 41.7 mg, 61 %; M.p.: 105–108 °C (hexane/$CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3694, 2991, 1598, 1536 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.13 (d, J = 7.5 Hz, 1 H), 7.32 (s, 1 H), 7.30–7.16 (m, 3 H), 3.75 (s, 3 H), 3.65 (m, 4 H), 1.92 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.1, 136.2, 130.4, 127.3, 122.3, 122.0, 120.7, 111.1, 109.1, 47.5 (br), 33.1, 25.5 (br) ppm. HRMS (ESI) *m/z*: calcd. for $C_{14}H_{17}N_2O$ [M + H]$^+$ 229.1335, found 229.1332.

(Azepan-1′-yl)(1-methyl-1*H*-indol-3-yl)methanone (3fA):[25] A white solid; 42.0 mg, 55 %; M.p.: 113–114 °C (hexane/$CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 2935, 1600, 1538 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.79 (d, J = 8.0 Hz, 1 H), 7.32–7.13 (m, 4 H), 3.77 (s, 3 H), 3.68 (t, J = 6.0 Hz, 4 H), 1.76 (m, 4 H), 1.60 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.0, 136.3, 129.5, 126.7, 122.2, 121.1, 120.4, 112.2, 109.3, 48.1 (br), 33.0, 28.7 (br), 27.5 (br) ppm. HRMS (ESI) *m/z*: calcd. for $C_{16}H_{21}N_2O$ [M + H]$^+$ 257.1648, found 257.1664.

(1-Methyl-1*H*-indol-3-yl)-4-morpholinylmethanone (3gA):[26] A colorless oil; 17.3 mg, 24 %. IR (neat): $\tilde{\nu}$ = 3478, 2966, 2914, 2853, 1611, 1536 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.70–7.65 (m, 1 H), 7.44 (s, 1 H), 7.35 (dd, J = 8.5, 0.5 Hz, 1 H), 7.32–7.19 (m, 2 H), 3.82 (s, 3 H), 3.74 (s, 8 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.6, 136.4, 131.6, 125.8, 122.4, 120.9, 120.4, 110.1, 109.7, 67.1, 45.8, 33.1 ppm. HRMS (ESI) *m/z*: calcd. for $C_{14}H_{17}N_2O_2$ [M + H]$^+$ 245.1285, found 245.1283.

***N*,*N*-Diethyl-1-methyl-1*H*-indole-3-carboxamide (3hA):**[27] A colorless oil; 43.3 mg, 63 %. IR (neat): $\tilde{\nu}$ = 2970, 2935, 1721, 1609, 1536 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.76 (dd, *J* = 8.0, 1.0 Hz, 1 H), 7.34–7.15 (m, 4 H), 3.80 (s, 3 H), 3.57 (q, *J* = 7.0 Hz, 4 H), 1.22 (t, *J* = 7.0 Hz, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.7, 136.3, 129.3, 126.6, 122.3, 120.8, 120.5, 111.1, 109.4, 41.2 (br), 33.0, 13.8 ppm. HRMS (ESI) *m*/*z*: calcd. for $C_{14}H_{19}N_2O$ $[M + H]^+$ 231.1492, found 231.1489.

1-Methyl-*N*,*N*-dipropyl-1*H*-indole-3-carboxamide (3iA): A colorless oil; 52.4 mg, 68 %. IR (neat): $\tilde{\nu}$ = 2961, 2931, 2875, 1611, 1536 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 8.0 Hz, 1 H), 7.33–7.14 (m, 4 H), 3.76 (s, 3 H), 3.48 (t, *J* = 7.5 Hz, 4 H), 1.72–1.55 (m, 4 H), 0.88 (br. t, *J* = 7.0 Hz, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.2, 136.2, 129.6, 126.4, 122.1, 120.6, 120.4, 111.2, 109.4, 48.2 (br), 32.9, 21.3, 11.1 ppm. HRMS (ESI) *m*/*z*: calcd. for $C_{16}H_{23}N_2O$ $[M + H]^+$ 259.1805, found 259.1803.

1-Methyl-*N*,*N*-bis(1′-methylethyl)-1*H*-indole-3-carboxamide (3jA): Colorless crystals; 40.9 mg, 53 %; M.p.: 162–165 °C (hexane/$CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3694, 1604, 1538 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.72 (d, *J* = 7.5 Hz, 1 H), 7.29–7.18 (m, 2 H), 7.16–7.10 (m, 2 H), 3.95 (m, 2 H), 3.74 (s, 3 H), 1.38 (d, *J* = 6.5 Hz, 12 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.3, 136.2, 127.8, 126.7, 122.1, 120.4, 120.1, 113.0, 109.2, 48.1, 32.9, 21.3 ppm. HRMS (ESI) *m*/*z*: calcd. for $C_{16}H_{23}N_2O$ $[M + H]^+$ 259.1805, found 259.1802.

1-Methyl-*N*,*N*-di-(2′-propen-1′-yl)-1*H*-indole-3-carboxamide (3kA): A colorless oil; 47.9 mg, 63 %. IR (neat): $\tilde{\nu}$ = 2918, 1615, 1531 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.93 (dt, *J* = 8.0, 1.0 Hz, 1 H), 7.37 (s, 1 H), 7.35–7.18 (m, 3 H), 5.96–5.82 (m, 2 H), 5.27 (s, 2 H), 5.22 (dd, *J* = 6.5, 1.5 Hz, 2 H), 4.15 (d, *J* = 5.5 Hz, 4 H), 3.79 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.0, 136.4, 133.7, 129.6, 127.1, 122.4, 121.2, 120.8, 117.0, 109.8, 109.3, 49.1 (br), 33.1 ppm. HRMS (ESI) *m*/*z*: calcd. for $C_{16}H_{19}N_2O$ $[M + H]^+$ 255.1492, found 255.1490.

***N*,1-Dimethyl-*N*-(phenylmethyl)-1*H*-indole-3-carboxamide (3lA):**[26] A colorless oil; 44.3 mg, 53 %. IR (neat): $\tilde{\nu}$ = 2914, 1611, 1533 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.85 (dd, *J* = 7.0, 1.0 Hz, 1 H), 7.38–7.15 (m, 9 H), 4.78 (s, 2 H), 3.72 (s, 3 H), 3.05 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.4, 137.5, 136.4, 130.4, 128.5, 127.3, 127.2, 126.9, 122.3, 121.1, 120.8, 110.2, 109.4, 53.1 (br), 35.3, 33.0 ppm. HRMS (ESI) *m*/*z*: calcd. for $C_{18}H_{19}N_2O$ $[M + H]^+$ 279.1492, found 279.1487.

1-Methyl-*N*,*N*-bis(phenylmethyl)-1*H*-indole-3-carboxamide (3mA): A colorless foam; 74.5 mg, 70 %. IR (neat): $\tilde{\nu}$ = 3026, 2914, 1710, 1615, 1531 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.96–7.92 (m, 1 H), 7.39–7.18 (m, 14 H), 4.72 (s, 4 H), 3.70 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.6, 137.3, 136.5, 129.9, 128.6, 127.5, 127.2, 127.1, 122.5, 121.1, 120.9, 109.8, 109.4, 49.6 (br), 33.1 ppm. HRMS (ESI) *m*/*z*: calcd. for $C_{24}H_{23}N_2O$ $[M + H]^+$ 355.1805, found 335.1802.

[3′,4′-Dihydro-1′(2′*H*)-quinolinyl](1*H*-indol-3-yl)methanone (3aB): A white powder; 43.6 mg, 53 %; M.p.: 187–192 °C (hexane/$CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3690, 3026, 1600 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 9.23 (br. s, 1 H), 7.61 (d, *J* = 8.0 Hz, 1 H), 7.26–7.01 (m, 6 H), 6.95 (td, *J* = 7.5, 1.5 Hz, 1 H), 6.84 (td, *J* = 7.5, 1.5 Hz, 1 H), 3.95 (t, *J* = 6.5 Hz, 2 H), 2.84 (t, *J* = 6.5 Hz, 2 H), 2.02 (quint, *J* = 6.5 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.2, 139.7, 135.7, 131.5, 129.4, 128.4, 125.7, 125.6, 125.0, 124.3, 122.5, 121.1, 120.7, 111.6, 44.8, 26.9, 24.3 ppm. HRMS (ESI) *m*/*z*: calcd. for $C_{18}H_{17}N_2O$ $[M + H]^+$ 277.1335, found 277.1332.

[3′,4′-Dihydro-1′(2′*H*)-quinolinyl](1,2-dimethyl-1*H*-indol-3-yl)-methanone (3aC): Yellowish crystals; 39.4 mg, 43 %; M.p.: 172–175 °C (hexane/$CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3694, 2996, 2931, 2250, 1600, 1538 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.45 (d, *J* = 8.0 Hz, 1 H), 7.23 (d, *J* = 6.5 Hz, 1 H), 7.18–6.98 (m, 4 H), 6.91 (td, *J* = 7.0, 1.0 Hz, 1 H), 6.86–6.79 (m, 1 H), 4.08–3.96 (m, 1 H), 3.90–3.75 (m, 1 H), 3.63 (s, 3 H), 2.91–2.82 (m, 2 H), 2.32 (s, 3 H), 2.02 (quint, *J* = 6.5 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.4, 139.6, 139.5, 136.3, 130.4, 128.3, 125.9, 125.6, 123.8, 123.6, 121.3, 120.5, 119.7, 109.2, 108.8, 45.1, 29.6, 27.3, 24.3, 11.4 ppm. HRMS (ESI) *m*/*z*: calcd. for $C_{20}H_{21}N_2O$ $[M + H]^+$ 305.1648, found 305.1642.

[3′,4′-Dihydro-1′(2′*H*)-quinolinyl](1,7-dimethyl-1*H*-indol-3-yl)-methanone (3aD): Colorless crystals; 47.5 mg, 52 %; M.p.: 190–191 °C (hexane/AcOEt). IR ($CHCl_3$): $\tilde{\nu}$ = 3007, 1618, 1578, 1492 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.51 (dd, *J* = 7.5, 1.0 Hz, 1 H), 7.14 (br. d, *J* = 7.2 Hz, 1 H), 7.06 (dd, *J* = 7.0, 1.5 Hz, 1 H), 6.98–6.84 (m, 5 H), 3.95 (s, 3 H), 3.94 (t, *J* = 6.5 Hz, 2 H), 2.85 (t, *J* = 6.5 Hz, 2 H), 2.72 (s, 3 H), 2.02 (quint, *J* = 6.5 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.1, 139.9, 135.1, 134.4, 131.1, 128.2, 127.5, 125.5, 124.9, 124.8, 123.8, 121.1, 119.3, 110.5, 44.7, 37.4, 27.2, 24.5, 19.8 ppm. HRMS (ESI) *m*/*z*: calcd. for $C_{20}H_{21}N_2O$ $[M + H]^+$ 305.1648, found 305.1649.

[3′,4′-Dihydro-1′(2′*H*)-quinolinyl](1,6-dimethyl-1*H*-indol-3-yl)-methanone (3aE): Colorless crystals; 60.3 mg, 66 %; M.p.: 187–188 °C (hexane/AcOEt). IR ($CHCl_3$): $\tilde{\nu}$ = 3007, 1617, 1602, 1543, 1492 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.45 (d, *J* = 8.0 Hz, 1 H), 7.14 (d, *J* = 7.0 Hz, 1 H), 7.09–7.04 (m, 1 H), 7.07 (s, 1 H), 7.05 (s, 1 H), 6.95 (td, *J* = 7.0, 1.0 Hz, 1 H), 6.91 (d, *J* = 8.0, 1.0 Hz, 1 H), 3.95 (t, *J* = 6.5 Hz, 2 H), 3.67 (s, 3 H), 2.85 (t, *J* = 6.5 Hz, 2 H), 2.45 (s, 3 H), 2.03 (quint, *J* = 6.5 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.5, 140.1, 136.8, 133.0, 132.1, 131.3, 128.3, 125.7, 124.9, 124.2, 124.0, 122.8, 120.9, 110.7, 109.4, 44.5, 33.0, 27.0, 24.3, 21.7 ppm. HRMS (ESI) *m*/*z*: calcd. for $C_{20}H_{21}N_2O$ $[M + H]^+$ 305.1648, found 305.1647.

[3′,4′-Dihydro-1′(2′*H*)-quinolinyl](1,5-dimethyl-1*H*-indol-3-yl)-methanone (3aF): A colorless oil; 44.4 mg, 49 %. IR (neat): $\tilde{\nu}$ = 2944, 1624, 1579, 1529 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.48 (d, *J* = 0.5 Hz, 1 H), 7.19–6.94 (m, 6 H), 6.87 (td, *J* = 7.5, 1.0 Hz, 1 H), 3.96 (t, *J* = 6.5 Hz, 2 H), 3.66 (s, 3 H), 2.86 (t, *J* = 6.5 Hz, 2 H), 2.37 (s, 3 H), 2.03 (quint, *J* = 6.5 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.4, 140.1, 134.9, 133.1, 131.4, 130.4, 128.1, 126.9, 125.5, 125.0, 123.9, 123.8, 121.1, 110.2, 109.0, 44.6, 33.1, 27.1, 24.5, 21.5 ppm. HRMS (ESI) *m*/*z*: calcd. for $C_{20}H_{21}N_2O$ $[M + H]^+$ 305.1648, found 305.1645.

[3′,4′-Dihydro-1′(2′*H*)-quinolinyl](5-methoxy-1-methyl-1*H*-indol-3-yl)methanone (3aG): Colorless crystals; 41.4 mg, 43 %; M.p.: 128–130 °C (hexane/$CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 1622, 1604, 1576, 1529 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.20–7.04 (m, 5 H), 6.98 (td, *J* = 7.5, 1.5 Hz, 1 H), 6.88 (dd, *J* = 7.5, 1.5 Hz, 1 H), 6.84 (dd, *J* = 9.0, 3.5 Hz, 1 H), 3.98 (t, *J* = 6.5 Hz, 2 H), 3.73 (s, 3 H), 3.68 (s, 3 H), 2.86 (t, *J* = 6.5 Hz, 2 H), 2.06 (quint, *J* = 6.5 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.3, 155.1, 140.2, 133.5, 131.6, 131.5, 128.1, 127.1, 125.7, 124.9, 124.0, 113.1, 110.3, 110.1, 102.6, 55.6, 44.4, 33.3, 27.2, 24.5 ppm. HRMS (ESI) *m*/*z*: calcd. for $C_{20}H_{21}N_2O_2$ $[M + H]^+$ 321.1598, found 321.1592.

[3′,4′-Dihydro-1′(2′*H*)-quinolinyl](5-bromo-1-methyl-1*H*-indol-3-yl)methanone (3aH): A colorless oil; 40.7 mg, 37 %. IR (neat): $\tilde{\nu}$ = 2944, 1622, 1579, 1527 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.74 (d, *J* = 2.0 Hz, 1 H), 7.28–6.95 (m, 6 H), 6.88–6.82 (m, 1 H), 3.94 (t, *J* = 6.5 Hz, 2 H), 3.66 (s, 3 H), 2.85 (t, *J* = 6.5 Hz, 2 H), 2.04 (quint, *J* = 6.5 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.5, 139.8, 135.1, 133.9, 131.8, 128.3, 128.1, 125.6, 125.2, 124.8, 124.4, 124.0,

114.7, 110.8, 110.5, 44.4, 33.3, 27.1, 24.4 ppm. HRMS (ESI) *m/z*: calcd. for $C_{19}H_{18}N_2O^{79}Br$ $[M + H]^+$ 369.0597, found 369.0597.

[3′,4′-Dihydro-1′(2′*H*)-quinolinyl](5-fluoro-1-methyl-1*H*-indol-3-yl)methanone (3aI): A colorless oil; 41.7 mg, 45 %. IR (neat): $\tilde{\nu}$ = 3009, 1624, 1578, 1485 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.23 (dd, *J* = 10.0, 2.5 Hz, 1 H), 7.19–7.14 (m, 2 H), 7.11 (s, 1 H), 7.02–6.90 (m, 3 H), 6.85 (td, *J* = 8.0, 1.0 Hz, 1 H), 3.95 (t, *J* = 6.5 Hz, 2 H), 3.70 (s, 3 H), 2.86 (t, *J* = 6.5 Hz, 2 H), 2.05 (quint, *J* = 6.5 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.0, 159.7, 157.8, 140.0, 134.7, 133.1, 131.8, 128.4, 127.3, 127.2, 125.8, 124.9, 124.4, 110.9, 110.7, 110.2, 110.1, 106.7, 106.5, 44.4, 33.4, 27.1, 24.4 ppm. HRMS (ESI) *m/z*: calcd. for $C_{19}H_{18}N_2OF$ $[M + H]^+$ 309.1398, found 309.1396.

[3′,4′-Dihydro-1′(2′*H*)-quinolinyl](6-fluoro-1-methyl-1*H*-indol-3-yl)methanone (3aJ): A colorless oil; 26.6 mg, 29 %. IR (neat): $\tilde{\nu}$ = 2918, 1621, 1531, 1490 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.51 (dd, *J* = 9.0, 5.5 Hz, 1 H), 7.18 (d, *J* = 7.0 Hz, 1 H), 7.09 (s, 1 H), 7.03–6.96 (m, 2 H), 6.97–6.92 (m, 1 H), 6.89–6.82 (m, 2 H), 3.96 (t, *J* = 6.5 Hz, 2 H), 3.67 (s, 3 H), 2.86 (t, *J* = 6.5 Hz, 2 H), 2.05 (quint, *J* = 6.5 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.0, 161.5, 158.3, 139.9, 136.6, 136.5, 133.6, 131.7, 128.3, 125.7, 124.9, 124.3, 122.9, 122.4, 122.3, 111.1, 110.0, 109.6, 96.1, 95.7, 44.4, 33.3, 27.1, 24.4 ppm. HRMS (ESI) *m/z*: calcd. for $C_{19}H_{18}N_2OF$ $[M + H]^+$ 309.1398, found 309.1399.

Methyl 1-Methyl-3-(1,2,3,4-tetrahydroquinoline-1-carbonyl)-1*H*-indole-5-carboxylate (3aK): A colorless oil; 35.2 mg, 34 %. IR (neat): $\tilde{\nu}$ = 2948, 1712, 1617 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.30 (br. s, 1 H), 7.91 (dd, *J* = 8.5, 1.5 Hz, 1 H), 7.28 (br. d, *J* = 8.5 Hz, 1 H), 7.22 (s, 1 H), 7.21–7.18 (br. d, *J* = 7.5 Hz, 1 H), 7.03–6.95 (m, 2 H), 6.89–6.82 (m, 1 H), 3.98 (t, *J* = 6.5 Hz, 2 H), 3.89 (s, 3 H), 3.75 (s, 3 H), 2.90 (t, *J* = 6.5 Hz, 2 H), 2.07 (quint, *J* = 6.5 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.4, 165.3, 139.5, 138.6, 134.2, 132.0, 128.1, 125.6, 125.5, 124.7, 124.4, 123.9, 123.5, 122.9, 112.3, 109.1, 51.9, 44.6, 33.5, 27.1, 24.5 ppm. HRMS (ESI) *m/z*: calcd. for $C_{21}H_{21}O_3N_2$ $[M + H]^+$ 349.1547, found 349.1548.

Methyl 1-Methyl-3-(1,2,3,4-tetrahydroquinoline-1-carbonyl)-1*H*-indole-6-carboxylate (3aL): A colorless oil; 32.5 mg, 31 %. IR (neat): $\tilde{\nu}$ = 2948, 1714, 1619 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.03 (br. s, 1 H), 7.75 (dd, *J* = 8.5, 1.5 Hz, 1 H), 7.55 (d, *J* = 8.5 Hz, 1 H), 7.28 (d, *J* = 5.0 Hz, 1 H), 7.18 (br. d, *J* = 7.5 Hz, 1 H), 7.01–6.96 (m, 2 H), 6.87–6.81 (m, 1 H), 3.97 (t, *J* = 6.5 Hz, 2 H), 3.92 (s, 3 H), 3.78 (s, 3 H), 2.87 (t, *J* = 6.5 Hz, 2 H), 2.07 (quint, *J* = 6.5 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.4, 165.4, 139.5, 135.9, 135.7, 131.6, 129.7, 128.1, 125.6, 124.6, 124.2, 123.8, 121.8, 120.7, 111.8, 111.2, 52.1, 44.4, 33.5, 27.2, 24.5 ppm. HRMS (ESI) *m/z*: calcd. for $C_{21}H_{21}O_3N_2$ $[M + H]^+$ 349.1547, found 349.1549.

[4′-(2′-Methoxyphenyl)-piperazin-1′-yl](1-methyl-1*H*-indol-3-yl)-methanone (5aA):[16] Compound **4a** (57.7 mg, 0.3 mmol) and **2A** (157.4 mg, 1.2 mmol) were dissolved in $CHCl_3$ (3.0 mL) under air atmosphere. Me_2Zn (1.0 M in hexane, 2.4 mL, 2.4 mmol) was added to the mixture under a nitrogen atmosphere at room temperature. After being stirred at the same temperature for 72 h, the reaction mixture was diluted with sat. NH_4Cl and extracted with $CHCl_3$. The organic phase was dried with $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by preparative TLC (hexane/AcOEt = 1:1) afforded **5aA** (23.0 mg, 22 %) as colorless crystals; M.p.: 90–92 °C (hexane/$CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3690, 3000, 2940, 2819, 1602, 1536 cm^{-1}. ^1H NMR (500 MHz, CD_3OD): δ = 7.71 (dt, *J* = 7.5, 1.0 Hz, 1 H), 7.60 (s, 1 H), 7.44 (dt, *J* = 8.5, 1.0 Hz, 1 H), 7.26 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1 H), 7.19 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1 H), 7.01 (ddd, *J* = 8.0, 7.0, 2.0 Hz, 1 H), 6.95 (td, *J* = 8.0, 1.5 Hz, 2 H), 6.89 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1 H), 3.90 (t, *J* = 5.0 Hz, 4 H), 3.85 (s, 6 H), 3.05 (t, *J* = 5.0 Hz, 4 H) ppm. ^{13}C NMR (125 MHz, CD_3OD): δ = 168.8, 154.0, 142.1, 138.2, 133.1, 127.7, 124.9, 123.6, 122.2, 122.0, 121.3, 119.8, 112.9, 111.09, 111.05, 56.0, 52.4, 46.6 (br), 33.3 ppm. HRMS (ESI) *m/z*: calcd. for $C_{21}H_{24}N_3O_2$ $[M + H]^+$ 350.1863, found 350.1857.

(1*H*-Indol-3-yl)[4′-(phenylmethyl)piperazin-1′-yl]methanone (5bB):[17] Compound **4b** (52.8 mg, 0.3 mmol) and **2B** (140.6 mg, 1.2 mmol) were dissolved in $CHCl_3$ (3.0 mL) under air atmosphere. Me_2Zn (1.0 M in hexane, 0.6 mL, 0.6 mmol) was added 4 times at 2 h intervals to the mixture under a nitrogen atmosphere at room temperature. After being stirred at the same temperature for 48 h, the reaction mixture was diluted with sat. NH_4Cl and extracted with $CHCl_3$. The organic phase was dried with $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by preparative TLC (hexane/AcOEt = 1:1) afforded **5bB** (47.5 mg, 50 %) as colorless crystals; M.p.: 184–187 °C (hexane/$CHCl_3$). IR ([D$_6$]DMSO): $\tilde{\nu}$ = 3694, 3470, 3004, 2815, 1604, 1540 cm^{-1}. ^1H NMR (500 MHz, [D$_6$]DMSO): δ = 11.56 (br. s, 1 H), 7.67–7.64 (m, 2 H), 7.42 (dt, *J* = 8.0, 1.0 Hz, 1 H), 7.33–7.30 (m, 4 H), 7.28–7.22 (m, 1 H), 7.13 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1 H), 7.08 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1 H), 3.61 (br. t, *J* = 4.0 Hz, 4 H), 3.51 (s, 2 H), 2.41 (br. t, *J* = 4.0 Hz, 4 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 165.4, 137.8, 135.6, 128.9, 128.2, 127.9, 127.0, 125.9, 121.8, 120.09, 120.07, 111.9, 109.7, 61.9, 52.8, 44.4 (br) ppm. HRMS (ESI) *m/z*: calcd. for $C_{20}H_{22}N_3O$ $[M + H]^+$ 320.1757, found 320.1750.

[1-(Phenylmethyl)-1*H*-indol-3-yl](4′-phenylpiperazin-1′-yl)methanone (5cM):[18] Compound **4c** (24.3 mg, 0.15 mmol) and **2 M** (124.4 mg, 0.6 mmol) were dissolved in $CHCl_3$ (1.5 mL) under air atmosphere. Me_2Zn (1.0 M in hexane, 1.2 mL, 1.2 mmol) was added to the mixture under a nitrogen atmosphere at room temperature. After being stirred at the same temperature for 72 h, the reaction mixture was diluted with sat. NH_4Cl and extracted with $CHCl_3$. The organic phase was dried with $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by preparative TLC (hexane/AcOEt = 1:1) afforded **5cM** (26.9 mg, 45 %) as colorless crystals; M.p.: 135–138 °C (hexane/$CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3621, 3017, 2974, 1611, 1598, 1538 cm^{-1}. ^1H NMR (500 MHz, [D$_6$]DMSO): δ = 7.97 (s, 1 H), 7.73 (d, *J* = 7.5 Hz, 1 H), 7.50 (d, *J* = 8.0 Hz, 1 H), 7.34–7.29 (m, 2 H), 7.28–7.20 (m, 5 H), 7.18–7.10 (m, 2 H), 6.97 (d, *J* = 8.0 Hz, 2 H), 6.80 (t, *J* = 7.0 Hz, 1 H), 5.47 (s, 2 H), 3.78 (t, *J* = 5.0 Hz, 4 H), 3.20 (t, *J* = 5.0 Hz, 4 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 165.1, 150.9, 137.5, 135.5, 131.5, 129.0, 128.6, 127.5, 127.2, 126.6, 122.1, 120.6, 120.5, 119.2, 115.8, 110.8, 109.2, 49.3, 48.7, 48.2, 46.2, 44.5 (br) ppm. HRMS (ESI) *m/z*: calcd. for $C_{26}H_{26}N_3O$ $[M + H]^+$ 396.2070, found 396.2066.

Procedure for Friedel–Crafts-Type Carbamoylation of Pyrroles: [Scheme 6]. **1a** (40.0 mg, 0.3 mmol) and **6a** (1.2 mmol) were dissolved in $CHCl_3$ (3.0 mL) under air atmosphere. Me_2Zn (1.0 M in hexane, 2.4 mL, 2.4 mmol) was added to the mixture under a nitrogen atmosphere at room temperature. After being stirred at the same temperature for 48 h, the reaction mixture was diluted with sat. NH_4Cl and extracted with $CHCl_3$. The organic phase was dried with $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by preparative TLC (hexane/AcOEt = 1:1) afforded **7a** and **8a**.

[3′,4′-Dihydro-1′(2′*H*)-quinolinyl](1-methyl-1*H*-pyrrol-3-yl)methanone (7a): Colorless crystals; 24.4 mg, 34 %; M.p.: 93–96 °C (hexane/$CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3690, 1602 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.14–7.04 (m, 2 H), 7.04–6.92 (m, 2 H), 6.87 (s, 1 H), 6.34 (t, *J* = 2.0 Hz, 1 H), 5.86 (t, *J* = 2.0 Hz, 1 H), 3.88 (t, *J* = 6.5 Hz, 2 H), 3.56 (s, 3 H), 2.76 (t, *J* = 6.5 Hz, 2 H), 1.99 (quint, *J* = 6.5 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.0, 140.1, 131.9, 127.9, 126.3, 125.6, 125.3, 124.1, 121.2, 119.5, 110.3, 44.1, 36.3, 26.9, 24.4 ppm.

HRMS (ESI) *m/z*: calcd. for $C_{15}H_{17}N_2O$ $[M + H]^+$ 241.1335, found 241.1333.

[3′,4′-Dihydro-1′(2′*H*)-quinolinyl](1-methyl-1*H*-pyrrol-2-yl)methanone (8a): Colorless crystals; 26.2 mg, 36 %; M.p.: 108–111 °C (hexane/$CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3690, 3017, 1602 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.16–7.10 (m, 1 H), 7.04–6.94 (m, 3 H), 6.50 (t, *J* = 2.0 Hz, 1 H), 6.03 (dd, *J* = 4.0, 1.5 Hz, 1 H), 5.94 (dd, *J* = 4.0, 2.5 Hz, 1 H), 3.92 (t, *J* = 6.5 Hz, 2 H), 3.80 (s, 3 H), 2.81 (t, *J* = 6.5 Hz, 2 H), 2.01 (quint, *J* = 6.5 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.2, 139.8, 130.9, 128.7, 128.3, 126.5, 126.3, 126.2, 125.5, 124.7, 124.2, 122.7, 121.0, 115.2, 107.1, 45.8, 44.8, 35.9, 27.0, 26.9, 24.3, 23.5 ppm. HRMS (ESI) *m/z*: calcd. for $C_{15}H_{17}N_2O$ $[M + H]^+$ 241.1335, found 241.1333. ^{13}C NMR signals were observed as a mixture of rotamers.

2-Phenyl-3,4-dihydroisoquinolin-1(2*H*)-one (10a):[28] Compound **9a** (59.2 mg, 0.3 mmol) was dissolved in $CHCl_3$ (30.0 mL) under air atmosphere. Me_2Zn (1.0 M in hexane, 2.4 mL, 2.4 mmol) was added to the solution of **9a** in $CHCl_3$ under a nitrogen atmosphere at room temperature. After being stirred at the same temperature for 24 h, the reaction mixture was diluted with sat. NH_4Cl and extracted with $CHCl_3$. The organic phase was dried with $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by preparative TLC (hexane/AcOEt = 5:1) afforded **10a** (47.9 mg, 72 %) as a white solid; M.p.: 99–102 °C (hexane/$CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3009, 1652, 1495 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.15 (d, *J* = 7.5 Hz, 1 H), 7.48–7.32 (m, 6 H), 7.28–7.16 (m, 2 H), 3.95 (t, *J* = 6.5 Hz, 2 H), 3.10 (t, *J* = 6.5 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.0, 143.0, 138.2, 131.9, 130.0, 128.7, 128.5, 127.0, 126.8, 126.1, 125.2, 49.2, 28.4 ppm. HRMS (ESI) *m/z*: Calcd for $C_{15}H_{14}NO$ $[M + H]^+$ 224.1070, found 224.1069.

2-Methyl-3,4-dihydroisoquinolin-1(2*H*)-one (10b):[29] Compound **9b** (40.6 mg, 0.3 mmol) was dissolved in $CHCl_3$ (30.0 mL) under air atmosphere. Me_2Zn (1.0 M in hexane, 2.4 mL, 2.4 mmol) was added to the solution of **9b** in $CHCl_3$ under a nitrogen atmosphere at room temperature. After being stirred at the same temperature for 24 h, the reaction mixture was diluted with sat. NH_4Cl and extracted with $CHCl_3$. The organic phase was dried with $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by preparative TLC (hexane/AcOEt = 5:1) afforded **10b** (29.8 mg, 62 %) as a colorless oil. IR (neat): $\tilde{\nu}$ = 3491, 2944, 2858, 1645, 1604, 1576 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.08 (ddd, *J* = 7.5, 1.0, 0.5 Hz, 1 H), 7.40 (td, *J* = 7.0, 1.5 Hz, 1 H), 7.36–7.28 (m, 1 H), 7.17 (dt, *J* = 7.5, 0.5 Hz, 1 H), 3.56 (t, *J* = 6.5 Hz, 2 H), 3.15 (s, 3 H), 3.00 (t, *J* = 6.5 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.7, 137.8, 131.4, 129.2, 127.9, 126.9, 126.8, 48.0, 35.1, 27.7 ppm. HRMS (ESI) *m/z*: Calcd for $C_{10}H_{12}NO$ $[M + H]^+$ 162.0913, found 162.0912.

2-Phenylmethyl-3,4-dihydroisoquinolin-1(2*H*)-one (10c):[30] Compound **9c** (31.7 mg, 0.15 mmol) was dissolved in $CHCl_3$ (15.0 mL) under air atmosphere. Me_2Zn (1.0 M in hexane, 1.2 mL, 1.2 mmol) was added to the solution of **9c** in $CHCl_3$ under a nitrogen atmosphere at room temperature. After being stirred at the same temperature for 24 h, the reaction mixture was diluted with sat. NH_4Cl and extracted with $CHCl_3$. The organic phase was dried with $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by preparative TLC (hexane/AcOEt = 5:1) afforded **10c** (28.1 mg, 79 %) as a colorless oil. IR (neat): $\tilde{\nu}$ = 3026, 2901, 1650, 1602 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.15 (dd, *J* = 7.5, 1.5 Hz, 1 H), 7.45–7.24 (m, 7 H), 7.16 (br. d, 1 H), 4.80 (s, 2 H), 3.49 (t, *J* = 6.5 Hz, 2 H), 2.93 (t, *J* = 6.5 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.4, 137.9, 137.3, 131.6, 129.3, 128.5, 128.4, 127.9, 127.3, 126.9, 126.8, 50.5, 45.5, 28.2 ppm. HRMS (ESI) *m/z*: Calcd for $C_{16}H_{16}NO$ $[M + H]^+$ 238.1227, found 238.1224.

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Keywords: Acylation · Nitrogen heterocycles · Radical reactions · Indole · Chloroform

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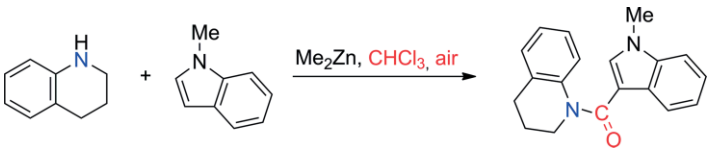

Chloroform-mediated acylative coupling of amines and indoles has been developed. Indoles and amines in chloroform were treated with dimethylzinc in the presence of air, resulting in a three-component acylative coupling reaction in which in-situ generation of phosgene produces indole-3-carboxamides.

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