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Multicomponent Cascade Reactions: A Novel and Expedient Approach to Functionalized Indoles by an Unprecedented Nucleophilic Addition-Heterocyclization-Oxidative Alkoxycarbonylation Sequence

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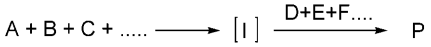
Abstract: A novel multicomponent cascade process is reported, based on the sequential combination between an initial nucleophilic attack step to an imine moiety and a palladium-catalyzed oxidative heterocyclization-alkoxycarbonylation process. By this new process, five simple molecules [2-alkynylaniline imines, alcohol (ROH), carbon monoxide (CO), alcohol (ROH), and oxygen (O_2)] are sequentially activated, selectively leading to high value-added functionalized indole derivatives in a single operation.

Keywords: carbonylation; cascade reactions; cyclization; indoles; palladium

Introduction

Cascade reactions have recently acquired an increasing importance in synthesis, owing to the possibility to obtain the target molecule through the concatenation of different steps, occurring *in situ* in ordered sequence.[1] Of particular interest are multicomponent cascade reactions, in which the final product is obtained by the sequential assembly of several simple building blocks. This approach, in fact, permits one to construct multifunctionalized, high value-added compounds in a single operation through the concatenation of several steps, each one employing readily available starting materials, as shown in Scheme 1 in the case of 2 steps.

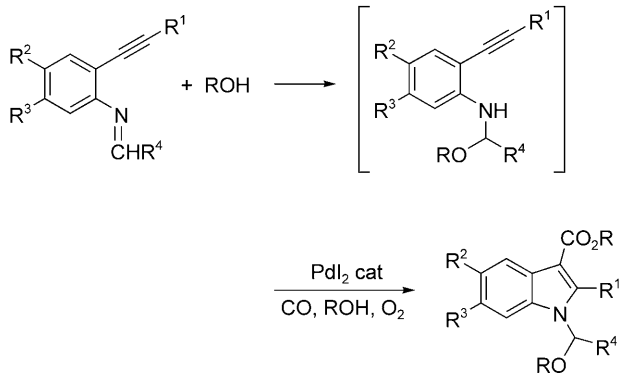


Scheme 1. A schematic representation of a 2-step multicomponent cascade reaction. A, B,…F are the reactants; I is the intermediate product ensuing from the first step; P is the final product.

In this work, we report a novel multicomponent cascade process, which allows a convenient direct synthesis of functionalized indoles through an unprecedented sequence of steps, involving ROH addition to the imino group of 2-alkynylaniline imines to give [(alkoxymethyl)(2-alkynylaryl)]amines as intermediates, followed by the PdI_2-catalyzed reaction of the latter with CO, ROH, and O_2 to give the final products [1-(alkoxyarylmethyl)indole-3-carboxylic esters, Scheme 2]. Thus, five simple molecules (2-alkynylaniline imines, ROH, CO, ROH, and O_2) are sequentially activated in a 2-step cascade process, selectively leading to highly substituted, functionalized indole derivatives in a single operation.

Results and Discussion

We began our investigations with benzylidene-(2-phenylethynyl)phenylamine **3aa** ($R^1=R^4=$Ph, $R^2=R^3=$H), obtained from the reaction between 2-(phenylethynyl)aniline **1a** with benzaldehyde **2a** in the presence of molecular sieves 4 Å. Owing to the sensitivity of the imino group to hydrolysis, **3aa** was used the

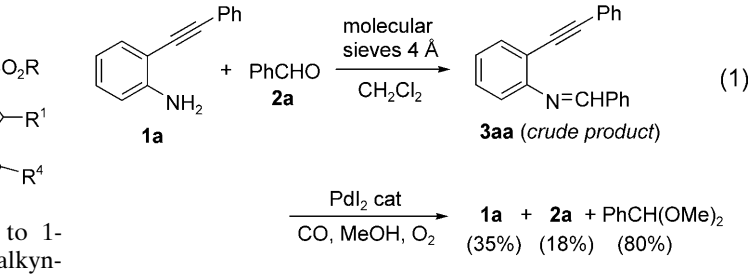


Scheme 2. Multicomponent cascade reaction leading to 1-(alkoxyarylmethyl)indole-3-carboxylic esters from 2-alkynylaniline imines through the intermediate formation of [(alkoxymethyl)(2-alkynylaryl)]amines.

crude material without further purification, which also simplified the synthetic procedure (see the Experimental Section for details). Thus, crude **3aa** was initially allowed to react in MeOH (R = Me) at 80 °C and under 20 atm of a 4:1 mixture of CO-air[2] for 15 h, in the presence of catalytic amounts of PdI_2 (2 mol%) in conjunction with KI (20 mol%).[3] Under these conditions, however, the substrate underwent hydrolysis, and was converted into a mixture of **1a**, **2a**, and benzaldehyde dimethyl acetal, together with unidentified heavy products [Eq. (1) and Table 1, entry 1].

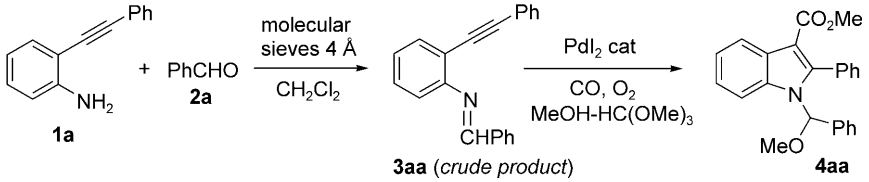
In order to hinder this substrate hydrolysis, we then carried out the reaction in the presence of a dehydrating agent, such as trimethyl orthoformate. To our delight, working under conditions similar to those given above, but in a 1:1 mixture MeOH-$HC(OMe)_3$ as the solvent, the reaction course changed completely, with formation of methyl 1-(methoxyphenylmethyl)-2-phenylindole-3-carboxylate **4aa** in 51% HPLC yield (46% isolated) based on starting **1a** (Table 1, entry 2). Formation of **4aa** corresponded to a novel multicomponent cascade process, involving MeOH addition to the imino group of **3aa** followed by PdI_2-catalyzed oxidative *5-endo-dig* cyclization-alkoxycarbonylation (Scheme 3).[4]

Having assessed the possibility to realize a direct synthesis of indole-3-carboxylic ester derivative **4aa**



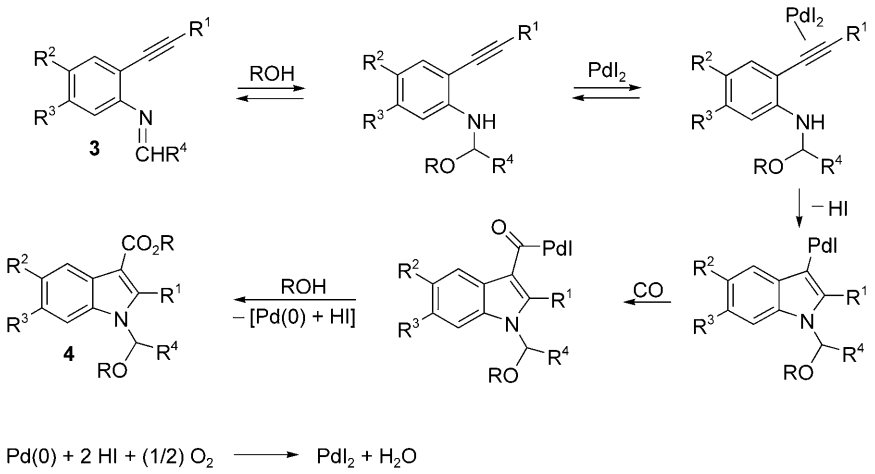
(1)

Table 1. Reactions of benzylidene-(2-phenylethynyl)phenylamine **3aa** with CO, MeOH, and O_2 under different conditions.[a]



Entry	KI:PdI_2 molar ratio	Solvent	T [°C]	Substrate concentration[b]	t [h]	Yield [%][c] of **4aa**
1[d]	10	MeOH	80	0.10	15	–
2	10	$HC(OMe)_3$-MeOH, 1:1 v/v	80	0.10	15	51 (46)
3	10	$MeC(OMe)_3$-MeOH, 1:1 v/v	80	0.10	15	35
4	10	$HC(OMe)_3$-MeOH, 1:1 v/v	100	0.10	4	45
5	5	$HC(OMe)_3$-MeOH, 1:1 v/v	80	0.10	15	47
6	50	$HC(OMe)_3$-MeOH, 1:1 v/v	80	0.10	15	51
7	10	$HC(OMe)_3$-MeOH, 2:1 v/v	80	0.10	15	55
8	10	$HC(OMe)_3$-MeOH, 3:1 v/v	80	0.10	15	58
9	10	$HC(OMe)_3$-MeOH, 4:1 v/v	80	0.10	15	45
10[e]	10	$HC(OMe)_3$-MeOH, 1:1 v/v	80	0.10	15	61
11	10	$HC(OMe)_3$-MeOH, 1:1 v/v	80	0.05	15	60

[a] Unless otherwise noted, all reactions were carried out using 2 mol% of PdI_2 under 20 atm (at 25 °C) of a 4:1 mixture of CO-air. Conversion of **3aa** was practically quantitative in all cases (by HPLC).
[b] Mmol of starting **1a** per mL of solvent.
[c] HPLC yield (isolated yield) based on starting **1a**.[d]
[d] The reaction led to the formation of **1a** (35%), **2a** (18%) and benzaldehyde dimethyl acetal (80%), together with unidentified heavy products (chromatographically immobile materials).
[e] The reaction was carried out under 40 atm (at 25 °C) of a 4:1 mixture of CO-air.



Scheme 3. Proposed reaction mechanism for the formation of 1-(alkoxyarylmethyl)indole-3-carboxylic esters **4** from 2-alkynylaniline imines **3**.

from 2-(phenylethynyl)aniline **3aa** through a multicomponent cascade process, we then screened the reaction conditions in order to improve the yield and the selectivity toward the desired product, taking the reaction of Table 1, entry 2, as the model reaction. The use of $MeC(OMe)_3$ in place of $HC(OMe)_3$ led to a significantly lower yield of **4aa** (35%, entry 3). A lower selectivity toward **4aa** was also obtained when working at 100 °C rather than 80 °C (entry 4) or using a lower KI:PdI_2 molar ratio (5 rather than 10, entry 5), while with a large excess of KI the results were practically unchanged with respect to those obtained with a KI:PdI_2 molar ratio of 10 (entry 6). On the other hand, a higher yield of **4aa** was obtained when the reaction was carried out in 2:1 or 3:1 $HC(OMe)_3$-MeOH mixtures (entries 7 and 8, respectively), although the use of a 4:1 $HC(OMe)_3$-MeOH mixture was detrimental (entry 9). A higher yield of **4aa** was obtained by working under a total pressure of 40 atm rather than 20 atm (entry 10) or with a lower substrate concentration (0.05 rather than 0.1 mmol per mL of solvent, entry 11).

On the basis of these results, the next experiments were carried out under the following optimized conditions: 2 mol% of PdI_2, KI:PdI_2 molar ratio = 10, T = 80 °C, solvent: 3:1 $HC(OMe)_3$-MeOH, substrate concentration = 0.05 mmol of substrate per mL of solvent, total pressure = 40 atm (4:1 CO-air). Under these conditions, the product **4aa** was obtained in 65% HPLC yield based on starting **1a** (60% isolated, Table 2, entry 1). The reaction was then generalized to other variously substituted 2-alkynylaniline imines **3**, obtained from different aryl aldehydes, and bearing alkyl or aryl groups on the triple bond and electron-withdrawing as well as π-donating groups on the aromatic ring. The results, shown in Table 2, confirm that the process is quite general, the corresponding indole-3-carboxylic ester derivatives being selectively formed in 52–73% isolated yields (based on starting 2-alkynylaniline **1**) with 2–5 mol% of catalyst.

Conclusions

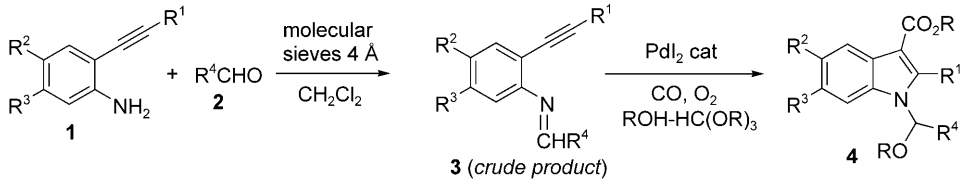
In conclusion, we have disclosed an unprecedented multicomponent cascade reaction, consisting of ROH addition of the imino group of 2-alkynylaniline imines **3** (obtained as crude products from the condensation between alkynylanilines **1** and benzaldehydes **2**) followed by PdI_2-catalyzed oxidative 5-*endo-dig* cyclization–alkoxycarbonylation. The possibility to assembly multifunctional indole derivatives, such as 1-(alkoxyarylmethyl)indole-3-carboxylic esters **4**, starting from simple and readily available molecules (2-alkynylanilines, benzaldehydes, CO, ROH, and O_2) is remarkable,[5–7] also in view of the importance of the indole heterocyclic core in general,[8] and of the indole-3-carboxylic ester motif in particular.[9,10]

Experimental Section

General Remarks

Solvents and chemicals were reagent grade and were used without further purification. Substrates were prepared and characterized as described in the Supporting Information. All reactions were analyzed by TLC on silica gel 60 F_{254}, HPLC or GLC. HPLC experiments were performed using a Shimadzu LC-20AB HPLC system with a Shimadzu SPD20A detector and with a C-18 reverse phase silica column (Supelco Discovery 4.6×150 mm, 5 μm). The wavelength for UV detection was set at 254 nm and the dwell time in the gamma detector was 1 s in a 10 μL loop. The elution conditions were as follows: solvent A = H_2O (1%

Table 2. Synthesis of 1-(alkoxyarylmethyl)indole-3-carboxylic esters **4** from 2-alkynylaniline imines **3** by the multicomponent cascade reaction.[a]



Entry	PdI_2 [mol%]	**1**	R^1	R^2	R^3	**2**	R^4	**4**	R	Yield [%][b] of **4**
1	2	**1a**	Ph	H	H	**2a**	Ph	**4aa**	Me	60
2	2	**1b**	*p*-Br-C_6H_4	H	H	**2a**	Ph	**4ba**	Me	51
3	5	**1b**	*p*-Br-C_6H_4	H	H	**2a**	Ph	**4ba**	Me	60
4	2	**1c**	*p*-Me-C_6H_4	H	H	**2a**	Ph	**4ca**	Me	60
5	2	**1d**	3-thienyl	H	H	**2a**	Ph	**4da**	Me	45
6	5	**1d**	3-thienyl	H	H	**2a**	Ph	**4da**	Me	58
7	2	**1e**	Bu	H	H	**2a**	Ph	**4ea**	Me	46
8	5	**1e**	Bu	H	H	**2a**	Ph	**4ea**	Me	55
9	5	**1e**	Bu	H	H	**2a**	Ph	**4ea′**	Et	52
10	2	**1f**	Ph	Cl	H	**2a**	Ph	**4fa**	Me	70
11	2	**1f**	Ph	Cl	H	**2a**	Ph	**4fa′**	Et	50
12	5	**1f**	Ph	Cl	H	**2a**	Ph	**4fa′**	Et	68
13	2	**1g**	Bu	Ph	H	**2a**	Ph	**4ga**	Me	62
14	2	**1h**	Bu	Me	H	**2a**	Ph	**4ha**	Me	52
15	2	**1i**	Ph	H	Me	**2a**	Ph	**4ia**	Me	56
16	5	**1i**	Ph	H	Me	**2a**	Ph	**4ia**	Me	73
17	2	**1j**	Ph	H	CF_3	**2a**	Ph	**4ja**	Me	40
18	5	**1j**	Ph	H	CF_3	**2a**	Ph	**4ja**	Me	55
19	2	**1a**	Ph	H	H	**2b**	*p*-Me-C_6H_4	**4ab**	Me	49
20	5	**1a**	Ph	H	H	**2b**	*p*-Me-C_6H_4	**4ab**	Me	60
21	2	**1a**	Ph	H	H	**2c**	*p*-Br-C_6H_4	**4ac**	Me	62

[a] Unless otherwise noted, all reactions were carried out at 80 °C in a 3:1 (v/v) mixture of $HC(OR)_3$-ROH as the solvent (0.05 mmol of starting **1** per mL of solvent), under 40 atm (at 25 °C) of a 4:1 mixture of CO-air for 15 h. Conversion of **3** was practically quantitative in all cases (by HPLC).

[b] Isolated yield based on starting **1**.

AcOH), solvent B = CH_3CN; 0–5 min 25% B; 5–35 min 25% B to 88% B; 35–37 min 88% B; 37–38 min 88% B to 25% B; 38–43 min 25% B. The flow rate was maintained at 1 mL min^{-1}. The GLC analyses was performed using a capillary column with polymethylsilicone +5% phenylsilicone as the stationary phase (HP-5). Column chromatography was performed on silica gel 60 (70–230 mesh). Evaporation refers to the removal of solvent under reduced pressure.

Melting points are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded at 25 °C on a Bruker DPX Avance 300 Spectrometer in $CDCl_3$ solutions at 300 MHz and 75 MHz, respectively, with Me_4Si as internal standard. ^{19}F NMR spectra were recorded at 25 °C on a Bruker DPX Avance 500 Spectrometer in $CDCl_3$ solutions at 471 MHz with CF_2Br_2 as internal standard. Chemical shifts (δ) and coupling constants (*J*) are given in ppm and in Hz, respectively. IR spectra were taken with a JASCO FT-IR 4200 spectrometer. Mass spectra were obtained using a Shimadzu QP-2010 GC-MS apparatus at 70 eV ionization voltage. Microanalyses were carried out with a Carlo Erba Elemental Analyzed Mod. 1106.

General Procedure for the Catalytic Synthesis of 1-(Alkoxyarylmethyl)indole-3-carboxylic Esters 4

1st Step: preparation of crude 2-alkynylaniline imines 3: A mixture of aldehyde **2** (10 mmol) (benzaldehyde **2a**: 1.06 g; 4-methylbenzaldehyde **2b**: 1.20 g; 4-bromobenzaldehyde **2c**: 1.85 g), 2-alkynylaniline **1** (6.67 mmol) [2-phenylethynylaniline **1a**: 1.289 g; 2-(4-bromophenylethynyl)aniline **1b**: 1.815 g; 2-*p*-tolylethynylaniline **1c**: 1.382 g; 2-thiophen-3-ylethynylaniline **1d**: 1.329 g; 2-hex-1-ynylaniline **1e**: 1.156 g; 4-chloro-2-phenylethynylaniline **1f**: 1.519 g; 2-hex-1-ynyl-4-phenylaniline **1g**: 1.663 g; 2-hex-1-ynyl-4-methylaniline **1h**: 1.250 g; 5-methyl-2-phenylethynylaniline **1i**: 1.382 g; 2-phenylethynyl-5-trifluoromethylaniline **1j**: 1.743 g] and molecular sieves 4 Å (2 g) in anhydrous CH_2Cl_2 (3 mL), was stirred at room temperature for 16 h (**1a–1i**) or at 40 °C for 24 h (**1j**). The mixture was filtered on celite and the solvent was removed under vacuum. The crude imine thus obtained was diluted with $HC(OR)_3$ (R = Me or Et, 25 mL) and the solution used as such for the next step.

2nd Step: catalytic oxidative carbonylation procedure leading to 1-(alkoxyarylmethyl)indole-3-carboxylic esters 4: A 250-mL stainless steel autoclave was charged in the presence of air with PdI_2 (7.3 mg, 2.03×10^{-2} mmol, or 18.2 mg, 5.05×10^{-2} mmol, see Table 2), KI (33.5 mg, 0.20 mmol, or 84.0 mg, 0.51 mmol, see Table 2), 11.3 mL of $HC(OR)_3$ (R = Me or Et), anhydrous ROH (R = Me or Et, 5.1 mL), and 3.8 mL of the solution of the crude imine in $HC(OR)_3$ (R = Me or Et), prepared as described above (formally deriving from 1.01 mmol of starting **1**). The autoclave was sealed and, while the mixture was stirred, the autoclave was pressurized with CO (32 atm) and air (up to 40 atm). After being stirred at 80 °C for 15 h, the autoclave was cooled, degassed and opened. The solvent was evaporated, and the products were purified by column chromatography on silica gel using 95:5 hexane-AcOEt (for **4aa**, **4ba**, **4ea**, **4fa**, **4ga**, **4ja**, **4ab**, and **4ac**), 98:2 hexane-AcOEt (for **4ca**, **4ha**, and **4ia**), 9:1 hexane-AcOEt (for **4da** and **4fa′**), or 99:1 hexane-AcOEt (for **4ea′**).

1-(Methoxyphenylmethyl)-2-phenylindole-3-carboxylic acid methyl ester (4aa): Yield: 225.3 mg (60% based on starting **1a**; Table 2, entry 1); yellow solid; mp 110–115 °C. IR (KBr): ν = 1712 (s), 1546 (w), 1485 (w), 1454 (m), 1401 (m), 1335 (w), 1256 (m), 1190 (w), 1147 (s), 1085 (s), 1073 (m), 707 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.25–8.21 (m, 1H, H-4), 7.57–7.36 (m, 5H, aromatic), 7.34–7.19 (m, 7H, aromatic), 7.11–7.04 (m, 1H, aromatic), 6.18 (s, 1H, C*H*OMe), 3.78 (s, 3H, CO_2Me), 3.25 (s, 3H, $CHOCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.5, 147.4, 138.0, 134.2, 131.4, 129.3, 128.5, 128.4, 128.3, 127.2, 125.9, 123.0, 122.5, 121.8, 114.1, 106.3, 87.2, 56.0, 50.9; GC-MS: *m/z* = 371 (M^+, 8), 235 (3), 190 (5), 179 (3), 122 (8), 121 (100), 105 (4), 91 (12), 77 (17); anal. calcd. for $C_{24}H_{21}NO_3$ (371.43): C 77.61, H 5.70, N 3.77; found: C 77.73; H, 5.68, N 3.76.

2-(4-Bromophenyl)-1-(methoxyphenylmethyl)indole-3-carboxylic acid methyl ester (4ba): Yield: 273.0 mg (60% based on starting **1b**; Table 2, entry 3); colorless solid; mp 158–159 °C. IR (KBr): ν = 1697 (s), 1486 (w), 1438 (w), 1389 (m), 1343 (m), 1194 (m), 1161 (m), 1083 (s), 1009 (w), 764 (m), 700 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.25–8.20 (m, 1H, H-4), 7.68–7.52 (m, 2H, aromatic), 7.36–7.16 (m, 9H, aromatic), 7.14–7.05 (m, 1H, aromatic), 6.16 (s, 1H, C*H*OMe), 3.80 (s, 3H, CO_2Me), 3.25 (s, 3H, $CHOCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.4, 145.8, 137.9, 134.6, 131.6, 130.4, 128.6, 127.2, 125.9, 123.8, 123.3, 122.6, 121.9, 114.1, 106.8, 87.5, 56.1, 50.9; GC-MS: *m/z* = 451 [$(M+2)^+$, 3], 449 (M^+, 2), 249 (3), 190 (5), 178 (2), 122 (9), 121 (100), 105 (5), 91 (13), 78 (3), 77 (19); anal. calcd. for $C_{24}H_{20}BrNO_3$ (450.32): C 64.01, H 4.48, Br, 17.74, N 3.11; found: C 64.15; H, 4.49, Br, 17.81, N 3.10.

1-(Methoxyphenylmethyl)-2-*p*-tolylindole-3-carboxylic acid methyl ester (4ca): Yield: 233.9 mg (60% based on starting **1c**; Table 2, entry 4); colorless solid; mp 127–129 °C. IR (KBr): ν = 1688 (s), 1547 (w), 1496 (m), 1386 (m), 1332 (m), 1251 (m), 1189 (m), 1164 (m), 1119 (s), 1074 (m), 989 (m), 756 (m), 730 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.23–8.19 (m, 1H, H-4), 7.34–7.19 (m, 11H, aromatic), 7.10–7.03 (m, 1H, aromatic), 6.20 (s, 1H, C*H*OMe), 3.80 (s, 3H, CO_2Me), 3.24 (s, 3H, $CHOCH_3$), 2.42 (s, 3H, Me); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.6, 147.8, 139.2, 138.0, 134.2, 129.1, 128.5, 128.4, 128.2, 127.2, 125.9, 122.9, 122.4, 121.7, 114.1, 106.1, 87.1, 55.9, 50.9, 21.5; GC-MS: *m/z* = 385 (M^+, 10), 249 (5), 204 (4), 193 (3), 122 (8), 121 (100), 105 (4), 91 (14), 77 (20); anal. calcd. for $C_{25}H_{23}NO_3$ (385.46): C 77.90, H 6.01, N 3.63; found: C 77.80; H, 6.03, N 3.62.

1-(Methoxyphenylmethyl)-2-thiophen-3-ylindole-3-carboxylic acid methyl ester (4da): Yield: 220.7 mg (58% based on starting **1d**; Table 2, entry 6); colorless solid; mp 179–180 °C. IR (KBr): ν = 1693 (s), 1575 (w), 1495 (m), 1444 (m), 1407 (m), 1335 (m), 1298 (w), 1239 (m), 1184 (m), 1151(m), 1088 (m), 957 (m), 789 (m), 755 (m), 730 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.24–8.19 (m, 1H, H-4), 7.46–7.42 (m, 2H, aromatic), 7.34–7.18 (m, 8H, aromatic), 7.11–7.04 (m, 1H, aromatic), 6.28 (s, 1H, C*H*OMe), 3.91 (s, 3H, CO_2Me), 3.28 (s, 3H, $CHOCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.5, 142.1, 138.0, 134.4, 130.8, 129.3, 128.5, 128.4, 127.2, 126.7, 125.8 (2 C), 123.0, 122.4, 121.7, 113.9, 106.8, 87.3, 55.9, 51.0; GC-MS: *m/z* = 377 (M^+, 10), 185 (3), 122 (9), 121 (100), 105 (5), 91 (12), 77 (17); anal. calcd. for $C_{22}H_{19}NO_3S$ (377.46): C 70.00, H 5.07, N 3.71, S 8.50; found: C 70.92; H, 5.06, N 3.72, S 8.46.

2-Butyl-1-(methoxyphenylmethyl)indole-3-carboxylic acid methyl ester (4ea): Yield: 195.0 mg (55% based on starting **1e**; Table 2, entry 8); yellow solid; mp 93–96 °C. IR (KBr): ν = 1695 (s), 1528 (w), 1461 (m), 1437 (m), 1408 (m), 1335 (m), 1226 (m), 1136 (w), 1114 (m), 1023 (w), 781 (w), 758 (m), 732 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.15 (d, br, *J* = 8.1 Hz, 1H, H-4), 7.33–7.15 (m, 7H, aromatic), 7.09–7.01 (m, 1H, aromatic), 6.59 (s, 1H, C*H*OMe), 3.95 (s, 3H, CO_2Me), 3.43–3.30 (m, 1H, C*H*$HCH_2CH_2CH_3$), 3.38 (s, 3H, $CHOCH_3$), 3.21–3.08 (m, 1H, CH*H*$CH_2CH_2CH_3$), 1.68–1.35 (m, 4H, $CH_2CH_2CH_2CH_3$), 0.90 (t, *J* = 7.3 Hz, 3H, $CH_2CH_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.3, 150.2, 138.0, 135.1, 128.55, 128.51, 127.1, 125.8, 122.3, 122.0, 121.5, 112.7, 105.0, 86.4, 56.2, 50.8, 31.8, 25.7, 22.9, 13.7; GC-MS: *m/z* = 351 (M^+, 12), 156 (5), 129 (4), 122 (13), 121 (100), 105 (5), 91 (17), 77 (19); anal. calcd. for $C_{22}H_{25}NO_3$ (351.44): C 75.19, H 7.17, N 3.99; found: C 75.22; H, 7.16, N 3.99.

2-Butyl-1-(ethoxyphenylmethyl) indole-3-carboxylic acid ethyl ester (4ea′): Yield: 198.8 mg (52% based on starting **1e**; Table 2, entry 9); yellow oil. IR (film): ν = 2958 (m), 2871 (m), 1695 (s), 1536 (m), 1459 (m), 1414 (m), 1379 (m), 1337 (m), 1287 (m), 1259 (m), 1219 (m), 1157 (m), 1109 (m), 1034 (m), 790 (m), 732 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.19–8.14 (m, 1H, H-4), 7.34–7.16 (m, 7H, aromatic), 7.09–7.02 (m, 1H, aromatic), 6.69 (s, 1H, C*H*OEt), 4.42 (q, *J* = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 3.70–3.57 (m, 1H, $CHOCHHCH_3$), 3.52–3.40 (m, 1H, $CHOCHHCH_3$), 3.40–3.27 (m, 1H, C*H*$HCH_2CH_2CH_3$), 3.19–3.07 (m, 1H, CH*H*$CH_2CH_2CH_3$), 1.67–1.34 (m, 4H, $CH_2CH_2CH_2CH_3$), 1.47 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.26 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 0.88 (t, *J* = 7.1 Hz, 3H, $CH_2CH_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.8, 149.8, 138.6, 135.5, 128.54, 128.46, 127.4, 126.0, 122.3, 121.9, 121.6, 112.6, 106.1, 85.1, 64.4, 59.5, 31.9, 25.9, 23.0, 14.8, 14.7, 13.7; GC-MS: *m/z* = 379 (M^+, 5), 334 (1), 217 (1), 174 (3), 156 (2), 136 (9), 135 (88), 108 (8), 107 (100), 91 (8), 79 (86), 77 (24); anal. calcd. for $C_{24}H_{29}NO_3$ (379.49): C 75.96, H 7.70, N 3.69; found: C 75.90; H, 7.70, N 3.70.

5-Chloro-1-(methoxyphenylmethyl)-2-phenylindole-3-carboxylic acid methyl ester (4fa): Yield: 286.0 mg (70% based on starting **1f**; Table 2, entry 10); yellow solid; mp 171–173 °C. IR (KBr): ν = 1708 (s), 1543 (w), 1455 (m), 1374 (m), 1340 (w), 1254 (m), 1189 (w), 1153 (m), 1133 (m), 1075 (m),

1028 (w), 971 (w), 873 (m), 807 (m), 715 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.21$ (d, $J = 2.0$ Hz, 1H, H-4), 7.56–7.43 (m, 4H, aromatic), 7.37–7.28 (m, 4H, aromatic), 7.26–7.18 (m, 2H, aromatic), 7.14 (distorted d, $J = 8.9$ Hz, 1H, H-7), 7.03 (distorted dd, $J = 8.9$, 2.0 Hz, 1H, H-6) 6.15 (s, 1H, C*H*OMe), 3.79 (s, 3H, CO_2Me), 3.25 (s, 3H, $CHOCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 165.0$, 148.4, 137.7, 132.6, 131.5, 130.9, 129.7, 129.5, 128.64, 128.60, 128.5, 128.4, 125.8, 123.5, 121.4, 115.1, 106.0, 87.4, 56.0, 51.0; GC-MS: $m/z = 407$ [$(M+2)^+$, 2], 405 (M^+, 4), 284 (1), 269 (4), 213 (2), 190 (5), 163 (2), 122 (9), 121 (100), 105 (4), 91 (13), 77 (19); anal. calcd. for $C_{24}H_{20}ClNO_3$ (405.87): C 71.02, H 4.97, N 3.45; found: C 71.10; H, 4.96, N 3.46.

5-Chloro-1-(ethoxyphenylmethyl)-2-phenylindole-3-carboxylic acid ethyl ester (4fa′): Yield: 298.5 mg (68% based on starting **1f**; Table 2, entry 12); yellow solid; mp 159–161 °C. IR (KBr): $\nu = 2978$ (m), 1689 (s), 1539 (w), 1450 (m), 1408 (m), 1342 (m), 1315 (m), 1238 (w), 1173 (s), 1080 (s), 1030 (m), 887 (m), 786 (m), 713 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.23$ (distorted d, $J = 2.0$ Hz, 1H, H-4), 7.53–7.35 (m, 5H, aromatic), 7.34–7.27 (m, 3H, aromatic), 7.26–7.19 (m, 3H, aromatic), 7.20 (distorted d, $J = 8.9$ Hz, 1H, H-7), 7.03 (distorted dd, $J = 8.9$, 2.0 Hz, 1H, H-6), 6.24 (s, 1H, C*H*OEt), 4.28–4.16 (m, 2H, $CHOCH_2CH_3$), 3.40 (q, $J = 6.9$, 2H, $CO_2CH_2CH_3$), 1.18 (t, $J = 7.3$ Hz, 3H, $CHOCH_2CH_3$), 1.14 (t, $J = 6.9$ Hz, 3H, $CO_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 164.6$, 147.9, 137.9, 132.7, 131.1, 130.5 (br), 129.5 (br), 129.4, 128.55, 128.48, 128.33, 128.28, 125.9, 123.3, 121.3, 115.17, 106.0, 85.7, 63.9, 59.7, 14.7, 14.1; GC-MS: $m/z = 433$ (M^+, 5), 270 (3), 253 (3), 207 (3), 199 (5), 190 (9), 136 (10), 135 (100), 107 (50), 79 (53), 77 (18); anal. calcd. for $C_{26}H_{24}ClNO_3$ (433.93): C 71.97, H 5.57, N 3.23; found: C 71.90; H, 5.58, N 3.22.

2-Butyl-1-(methoxyphenylmethyl)-5-phenylindole-3-carboxylic acid methyl ester (4ga): Yield: 267.3 mg (62% based on starting **1g**; Table 2, entry 13); colorless solid; mp 48–49 °C. IR (KBr): $\nu = 2954$ (m), 1697 (s), 1601 (w), 1536 (m), 1468 (m), 1409 (w), 1265 (m), 1151 (w), 1117 (m), 764 (m), 698 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.38$–8.36 (m, 1H, H-4), 7.67–7.60 (m, 2H, aromatic), 7.45–7.37 (m, 2H, aromatic), 7.34–7.28 (m, 6H, aromatic), 7.25–7.20 (m, 2H, aromatic), 6.60 (s, 1H, C*H*OMe), 3.97 (s, 3H, CO_2Me), 3.45–3.31 (m, 1H, $CHHCH_2CH_2CH_3$), 3.41 (s, 3H, $CHOCH_3$), 3.23–3.10 (m, 1H, $CHHCH_2CH_2CH_3$), 1.72–1.36 (m, 4H, $CH_2CH_2CH_2CH_3$), 0.91 (t, $J = 7.3$ Hz, $CH_2CH_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 166.2$, 150.7, 142.3, 137.9, 135.5, 134.5, 128.7, 128.6, 127.6, 127.5, 126.5, 125.8, 122.1, 120.0, 112.8, 105.3, 86.5, 56.2, 50.9, 31.8, 25.8, 22.9, 13.7; GC-MS: $m/z = 427$ (M^+, 10), 396 (1), 264 (2), 232 (3), 204 (3), 122 (8), 121 (100), 91 (11), 77 (13); anal. calcd. for $C_{28}H_{29}NO_3$ (427.53): C 78.66, H 6.84, N 3.28; found: C 78.46; H, 6.86, N 3.28.

2-Butyl-1-(methoxyphenylmethyl)-5-methylindole-3-carboxylic acid methyl ester (4ha): Yield: 191.4 mg (52% based on starting **1h**; Table 2, entry 14); yellow oil. IR (film): $\nu = 2860$ (m), 2828 (w), 1697 (s), 1620 (w), 1538 (m), 1074 (m), 1031 (w), 987 (m), 945 (w), 881 (m), 788 (m), 761 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.96$–7.93 (m, 1H, H-4), 7.32–7.26 (m, 3H, aromatic), 7.23–7.16 (m, 2H, aromatic), 7.13 (d, br, $J = 8.1$ Hz, 1H, H-7), 6.87 (distorted dd, $J = 8.1$, 2.0 Hz, 1H, H-6), 6.55 (s, 1H, C*H*OMe), 3.95 (s, 3H, CO_2Me), 3.43–3.28 (m, 1H, $CHHCH_2CH_2CH_3$), 3.37 (s, 3H, $CHOCH_3$), 3.19–3.06 (m, 1H, $CHHCH_2CH_2CH_3$), 2.43 (s, br, 3H, CH_3 at C-5), 1.69–1.33 (m, 4H, $CH_2CH_2CH_2CH_3$), 0.89 (t, $J = 7.3$ Hz, $CH_2CH_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 166.3$, 150.1, 138.1, 133.4, 131.4, 129.0, 128.5, 127.4, 125.8, 123.8, 121.3, 112.3, 104.6, 86.4, 56.1, 50.7, 31.8, 25.7, 22.9, 21.5, 13.7; GC-MS: $m/z = 365$ (M^+, 9), 170 (2), 142 (2), 122 (9), 121 (100), 105 (3), 91 (11), 77 (13); anal. calcd. for $C_{23}H_{27}NO_3$ (365.47): C 75.59, H 7.45, N 3.83; found: C 75.46; H, 7.44, N 3.84.

1-(Methoxyphenylmethyl)-6-methyl-2-phenylindole-3-carboxylic acid methyl ester (4ia): Yield: 282.5 mg (73% based on starting **1i**; Table 2, entry 16); yellow solid; mp 149–150 °C. IR (KBr): $\nu = 2949$ (m), 1701 (s), 1604 (w), 1545 (m), 1483 (m), 1398 (m), 1337 (m), 1257 (m), 1231 (m), 1146 (m), 1082 (m), 1027 (w), 817 (m), 759 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.10$ (d, br, $J = 8.1$ Hz, 1H, H-4), 7.55–7.37 (m, 5H, aromatic), 7.34–7.20 (m, 5H, aromatic), 7.08 (dd, $J = 8.1$, 1.1 Hz, 1H, H-5), 7.04–7.01 (m, 1H, H-7), 6.15 (s, 1H, C*H*OMe), 3.76 (s, 3H, CO_2Me), 3.25 (s, 3H, $CHOCH_3$), 2.30 (s, 3H, Me at C-6); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 165.6$, 146.9, 138.0, 134.7, 132.8, 131.5, 130.3 (br), 129.1, 128.5, 128.4, 128.3, 125.9, 125.1, 124.3, 121.4, 113.9, 106.2, 87.2, 56.0, 50.8, 21.8; GC-MS: $m/z = 385$ (M^+, 17), 354 (1), 294 (1), 264 (1), 249 (2), 232 (1), 204 (1), 193 (2), 178 (1), 122 (10), 121 (100), 105 (4), 91 (10), 77 (17); anal. calcd. for $C_{25}H_{23}NO_3$ (385.46): C 77.90, H 6.01, N 3.63; found: C 77.98; H, 6.03, N 3.62.

1-(Methoxyphenylmethyl)-2-phenyl-6-trifluoromethylindole-3-carboxylic acid methyl ester (4ja): Yield: 244.6 mg (55% based on starting **1j**; Table 2, entry 18); colorless solid; mp 163–166 °C. IR (KBr): $\nu = 1714$ (s), 1548 (w), 1482 (w), 1449 (m), 1384 (m), 1320 (m), 1272 (w), 1234 (w), 1150 (m), 1094 (m), 1075 (m), 878 (w), 848 (w), 823 (m), 756 (m), 731 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.33$ (d, br, $J = 8.6$ Hz, 1H, H-4), 7.59–7.38 (m, 7H, aromatic), 7.35–7.27 (m, 3H, aromatic), 7.26–7.18 (m, 2H, aromatic), 6.20 (s, 1H, C*H*OMe), 3.92 (s, 3H, CO_2Me), 3.29 (s, 3H, $CHOCH_3$), 2.30 (s, 3H, Me); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 165.0$, 149.4, 137.3, 133.3, 130.7, 130.4 (br), 129.6, 129.5 (br), 128.8, 128.7, 128.5, 125.69, 125.65 (q, $J = 271.7$ Hz), 125.04 (q, $J = 32.1$ Hz), 122.3, 119.1 (q, $J = 3.6$ Hz), 111.5 (q, $J = 4.5$ Hz), 106.5, 87.6, 56.2, 51.1; ^{19}F NMR (471 MHz, $CDCl_3$): $\delta = -61.0$ (s, 3F, CF_3); GC-MS: $m/z = 439$ (M^+, 4), 303 (3), 190 (2), 122 (9), 121 (100), 105 (3), 91 (10), 77 (17); anal. calcd. for $C_{25}H_{20}F_3NO_3$ (439.43): C 68.33, H 4.59, N 3.19; found: C 68.38; H, 4.60, N 3.18.

1-(Methoxy-*p*-tolylmethyl)-2-phenylindole-3-carboxylic acid methyl ester (4ab): Yield: 233.0 mg (60% based on starting **1a**; Table 2, entry 20); yellow solid; mp 141–143 °C. IR (KBr): $\nu = 1688$ (s), 1603 (w), 1537 (m), 1480 (m), 1444 (s), 1387 (m), 1314 (w), 1250 (m), 1203 (m), 1181 (s), 1078 (m), 819 (m), 708 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.27$–8.21 (m, 1H, H-4), 7.57–7.34 (m, 5H, aromatic), 7.29–7.19 (m, 2H, aromatic), 7.16–7.03 (m, 5H, aromatic), 6.15 (s, 1H, C*H*OMe), 3.77 (s, 3H, CO_2Me), 3.22 (s, 3H, $CHOCH_3$), 2.30 (s, 3H, $CH_3C_6H_4$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 165.6$, 147.4, 138.2, 135.0, 134.2, 131.44, 131.39, 130.3, 129.2, 128.3, 127.2, 125.8, 122.9, 122.4, 121.7, 114.2, 106.1, 87.3, 55.9, 50.9, 21.1; GC-MS: $m/z = 385$ (M^+, 6), 250 (2), 235 (5), 190 (5), 179 (4), 136 (10), 135 (100), 119 (8), 105 (5), 91 (21), 77 (2); anal. calcd. for $C_{25}H_{23}NO_3$ (385.46): C 77.90, H 6.01, N 3.63; found: C 77.98; H, 6.00, N 3.62.

1-[(4-Bromophenyl)methoxymethyl]-2-phenylindole-3-carboxylic acid methyl ester (4ac): Yield: 281.1 mg (62% based on starting **1a**; Table 2, entry 21); yellow solid; mp 173–176 °C. IR (KBr): $\nu = 1706$ (s), 1537 (w), 1482 (m), 1453 (m), 1384 (s), 1342 (w), 1257 (m), 1197 (w), 1145 (m), 1105 (w), 1078 (w), 1011 (m), 838 (m), 757 (m), 728 (m), 795 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.25$–8.21 (m, 1H, H-4), 7.56–7.32 (m, 7H, aromatic), 7.31–7.23 (m, 1H, aromatic), 7.22–7.16 (m, 1H, aromatic), 7.15–7.06 (m, 3H, aromatic), 6.10 (s, 1H, C*H*OMe), 3.78 (s, 3H, CO_2Me), 3.24 (s, 3H, $CHOCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 165.4$, 147.2, 137.1, 134.1, 131.7, 131.2, 129.3, 128.4, 127.7, 127.3, 123.2, 122.6, 121.9, 113.9, 106.6, 86.7, 56.0, 50.9; GC-MS: $m/z = 451$ [$(M+2)^+$, 10], 449 (M^+, 10), 250 (5), 235 (10), 201 (96), 199 (100), 190 (12), 179 (9), 165 (5), 120 (9), 92 (23), 91 (22), 77 (8); anal. calcd. for $C_{24}H_{20}BrNO_3$ (450.32): C 64.01, Br, 17.74, H 4.48, N 3.11; found: C 64.07; Br, 17.85, H, 4.49, N 3.10.

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