Tandem addition-cyclization reactions of 2-alkynylbenzenamines with isocyanates catalyzed by $PdCl_2$†‡

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Tandem addition-cyclization reactions of 2-alkynylbenzenamines with isocyanates catalyzed by palladium chloride are described. This reaction is performed in the presence of 10 mol% of palladium chloride in THF at 80 °C, which provides an efficient and practical route for the synthesis of 1,2-disubstituted indoles.

Introduction

The increasing significance of combinatorial chemistry in pharmaceutical and material sciences demands the development of new strategies to synthesize a collection of analogues of interesting compounds.[1] Since the indole skeleton is an important substructure in both natural products and therapeutic agents, as well as the wide application of indoles in pharmaceutical research,[2] the development of efficient methods for indole synthesis has continuously attracted the attentions of many chemists. Among the synthetic strategies developed, catalytic transformations utilizing transition-metal catalysts is one of the popular approaches for forming indoles.[3,4] In particular, using functionalized 2-alkynylbenzenamines as starting material is one of the most efficient ways.[5–8] For instance, palladium(II)-catalyzed intramolecular cyclization of 2-alkynylbenzenamines can produce 2-substituted indoles in high yield.[5d] Regioselective synthesis of 3-allylindoles *via* palladium-catalyzed cyclization of *o*-alkynyltrifluoroacetanilides with allyl esters was achieved by Cacchi and co-workers.[6a] Polyfunctionalized indoles were generated in the presence of large excess amount of cesium and potassium bases (such as CsO-*t*-Bu, KO-*t*-Bu, and KH) in *N*-methylpyrrolidinone.[6b] Hiroya and coworkers developed Cu(II)-catalyzed indole formation and applied this method in natural product syntheses.[6c,d] Arcadi and coworkers reported reactions of 2-alkynylbenzenamines to give rise to *C*-3-alkylindoles catalyzed by gold catalyst.[6e] Yamamoto and coworkers reported tandem cyclization of 2-alkynylbenzenamines in the presence of certain nucleophiles to give the nucleophile incorporated indoles.[7] Li described an efficient double-hydroamination reaction of 2-alkynylbenzenamines with terminal alkynes leading to *N*-alkenylindoles using gold(III) as a catalyst under neat conditions.[8]

As part of a continuing effort in our laboratory toward the development of new methods for the expeditious synthesis of biologically relevant heterocyclic compounds,[9] we became interested in the possibility of developing novel and efficient method to construct poly-substituted indoles, with a hope of finding more active hits or leads for our particular biological assays. Herein, we would like to disclose our recent efforts for the synthesis of 1,2-disubstituted indoles *via* $PdCl_2$-catalyzed tandem reaction of 2-alkynylbenzenamine with isocyanate.

Among the strategies used for the construction of small molecules, the design and synthesis of natural product-like compounds *via* tandem reactions have attracted much attention, and the development of tandem reactions has been a fertile area in organic synthesis.[10] In particular, the development of tandem reactions for the efficient construction of small molecules is an important goal in combinatorial chemistry from the viewpoints of operational simplicity and assembly efficiency. In our previous reports,[9a,b,e] we found that *o*-alkynylbenzaldehyde[11] was a versatile building block in tandem reactions for the construction of 1,2-dihydroisoquinoline skeleton. Prompted by these results, we envisioned that 2-alkynylbenzenamine could be also utilized as starting material due to the structural similarity for synthesis of *N*-heterocycles *via* tandem addition-cyclization reaction. The projected synthetic route is shown in Scheme 1. We conceived that in the presence of suitable catalyst, 2-alkynylbenzenamine would react with isocyanate leading to the intermediate **A**. Meanwhile, the formed metal-complex renders the carbon-carbon unsaturated bond moiety electrophilic, which triggers intramolecular attack of the nucleophile, giving rise to the final product **3** or **4**.

Results and discussion

To identify suitable conditions for the proposed metal-catalyzed tandem addition-cyclization process, reaction screening involving 2-alkynylbenzenamine **1a**, phenyl isocyanate **2a**, and a series of metal catalysts was carried out at room temperature. Results of this preliminary survey are shown in Table 1. In an initial experiment,

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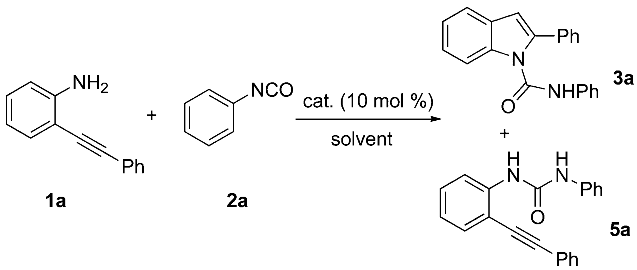
† Electronic supplementary information (ESI) available: General experimental information, characterization data, and copies of ^{1}H and ^{13}C NMR spectra of compound **3**. CCDC reference number 695031. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b812015c

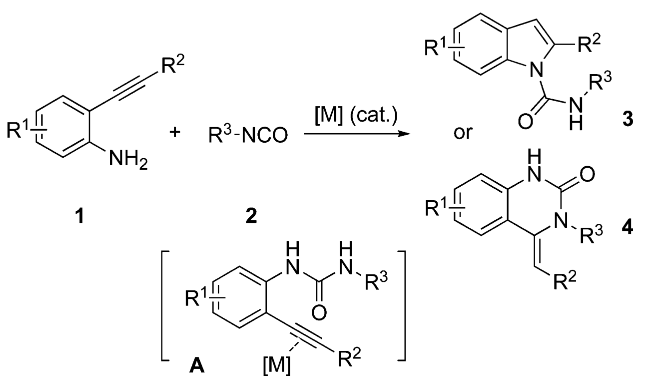
‡ Crystal data and structure refinement for compound **3a**. Empirical formula: $C_{21}H_{16}N_2O$ (Molecular weight: 312.36), Crystal system: Monoclinic, Unit cell dimensions: a = 10.974(5) A alpha = 90 deg., b = 14.927(6) A, beta = 95.267(6) deg., c = 9.978(4) A, gamma = 90 deg. Volume: 1627.6(12) A$\hat{3}$, refine_1s_shift/su_max 0.000 mean 0.000, Temperature: 293(2) K, space group: P2(1)/c, Z, Calculated density : 4, 1.275 Mg/m$\hat{3}$, Reflections collected/unique: 6575/2852 [R(int) = 0.0507], Final R indices [I>2sigma(I)]: R1 = 0.0505, wR2 = 0.1155, R indices (all data): R1 = 0.0830, wR2 = 0.1226

Table 1 Screening of Conditions for the Reaction of 2-Alkynylbenzenamine **1a** with Phenyl Isocyanate **2a**[a]



Entry	Lewis acid	Solvent	T (°C)	Time (h)	Yield (%)[b]
1	AgOTf (10 mol%)	THF	25	4.5	90 (**5a**)
2	CuI (10 mol%)	THF	25	24	95 (**5a**)
3	$FeCl_3$ (10 mol%)	THF	25	24	85 (**5a**)
4	$In(OTf)_3$ (10 mol%)	THF	25	40	85 (**5a**)
5	$Bi(OTf)_3$ (10 mol%)	THF	25	24	80 (**5a**)
6	$PdCl_2$ (10 mol%)	THF	25	24	15 (**3a**)/70 (**5a**)
7	$AgSbF_6$ (10 mol%)	EtOH	80	36	52 (**3a**)
8	$PdCl_2$ (10 mol%)	EtOH	80	7	58 (**3a**)
9	$PdCl_2$ (10 mol%)	MeCN	80	20	64 (**3a**)
10	$PdCl_2$ (10 mol%)	Toluene	80	24	trace
11	$PdCl_2$ (10 mol%)	THF	80	10	87 (**3a**)
12	$PdCl_2$ (10 mol%)	$(CH_2Cl)_2$	80	20	43 (**3a**)
13	$PdCl_2$ (10 mol%)	CH_3NO_2	80	20	35 (**3a**)
14	$PdCl_2$ (10 mol%)	1,4-dioxane	80	20	54 (**3a**)
15	$PdCl_2$ (5 mol%)	THF	80	20	20 (**3a**)

[a] Reaction conditions: 2-alkynylbenzenamine **1a** (0.50 mmol), phenyl isocyanate **2a** (0.75 mmol, 1.5 equiv), solvent (2.0 mL). [b] Isolated yield based on 2-alkynylbenzenamine **1a**.



Scheme 1 Proposed tandem reaction of 2-alkynylbenzenamine with isocyanate.

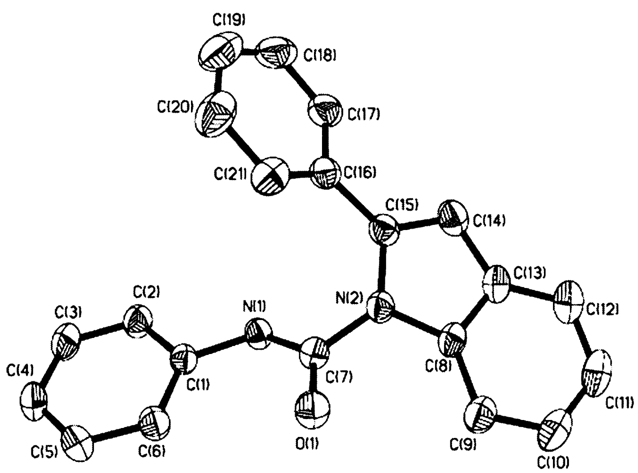
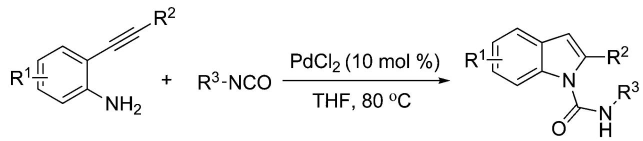


Fig. 1 ORTEP illustration of 1,2-disubstituted indole **3a** (30% probability ellipsoids).

only normal addition product **5a** (90% yield, Table 1, entry 1) was generated when AgOTf (10 mol%) was employed in the reaction at room temperature in THF. Similar results were observed when other metal catalysts such as CuI, $FeCl_3$, $In(OTf)_3$, and $Bi(OTf)_3$ were utilized (Table 1, entries 2–5). To our delight, we observed the formation of the desired product **3a** (15% yield) when the reaction was performed in THF catalyzed by $PdCl_2$ (10 mol%) (Table 1, entry 6) although 70% of compound **5a** was obtained meanwhile. The structure of **3a** was verified by ^1H and ^{13}C NMR, mass spectroscopy, as well as X-ray diffraction analysis (Fig. 1, also see Supporting Information). We also found that indole **3a** could be produced in the presence of $AgSbF_6$ as catalyst in EtOH at 80 °C (52% yield, Table 1, entry 7), while 58% yield of compound **3a** was generated when the reaction was catalyzed by $PdCl_2$ (Table 1, entry 8). Further screening of solvents revealed that the yield could be dramatically improved when THF was utilized in the reaction (87% yield, Table 1, entry 11). Inferior results were displayed when other solvents were used. When the catalytic amount of $PdCl_2$ was decreased to 5 mol%, the desired product was afforded in only 20% yield (Table 1, entry 15).

Subsequently, to investigate the scope of this reaction, various 2-alkynylbenzenamines **1** were treated with isocyanates **2** under the optimized conditions [$PdCl_2$ (10 mol%), THF, 80 °C] (Table 2). With respect to the aryl isocyanates, as expected both electron-rich and electron-poor aryl isocyanates are suitable partners in this process due to their high electrophilicity. The expected 1,2-disubstituted indoles resulting from reactions

Table 2 Tandem Reaction of 2-Alkynylbenzenamine **1** with Isocyanate **2** Catalyzed by Palladium Chloride



1 **2** **3**

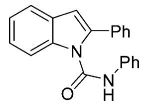
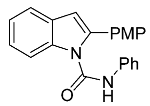
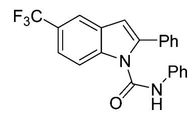
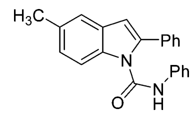
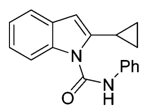
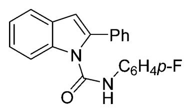
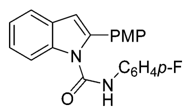
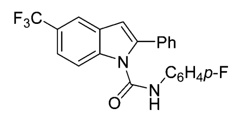
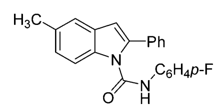
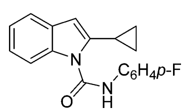
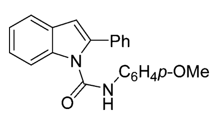
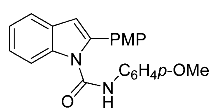
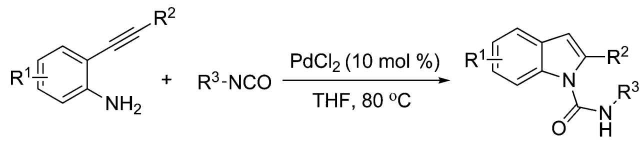
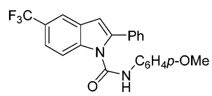
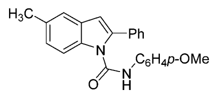
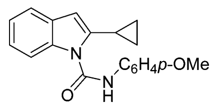
Entry	R^1/R^2	R^3	Indole **3**	Yield (%)[a]
1	H/C_6H_5 (**1a**)	C_6H_5 (**2a**)		87 (**3a**)
2	H/4-MeOC_6H_4 (**1b**)	C_6H_5 (**2a**)		53 (**3b**)
3	4-CF_3/C_6H_5 (**1c**)	C_6H_5 (**2a**)		46 (**3c**)
4	4-CH_3/C_6H_5 (**1d**)	C_6H_5 (**2a**)		74 (**3d**)
5	H/Cyclopropyl (**1e**)	C_6H_5 (**2a**)		90 (**3e**)
6	H/C_6H_5 (**1a**)	4-FC_6H_4 (**2b**)		75 (**3f**)
7	H/4-MeOC_6H_4 (**1b**)	4-FC_6H_4 (**2b**)		65 (**3g**)
8	4-CF_3/C_6H_5 (**1c**)	4-FC_6H_4 (**2b**)		60 (**3h**)
9	4-CH_3/C_6H_5 (**1d**)	4-FC_6H_4 (**2b**)		72 (**3i**)
10	H/Cyclopropyl (**1e**)	4-FC_6H_4 (**2b**)		72 (**3j**)
11	H/C_6H_5 (**1a**)	4-MeO C_6H_4 (**2c**)		86 (**3k**)
12	H/4-MeOC_6H_4 (**1b**)	4-MeO C_6H_4 (**2c**)		73 (**3l**)

Table 2 *(Contd.)*



1 2 3

Entry	R^1/R^2	R^3	Indole **3**	Yield (%)[a]
13	4-CF_3/C_6H_5 (**1c**)	4-MeO C_6H_4 (**2c**)		43 (**3m**)
14	4-CH_3/C_6H_5 (**1d**)	4-MeO C_6H_4 (**2c**)		83 (**3n**)
15	H/Cyclopropyl (**1e**)	4-MeO C_6H_4 (**2c**)		88 (**3o**)

[a] Isolated yield based on 2-alkynylbenzenamine **1**.

of 2-alkynylbenzenamine **1** could be obtained and isolated in moderate to good yields. Better results were obtained when 2-alkynylbenzenamine substituted with an electron-rich substituent on the aromatic ring was employed. For instance, trifluoromethyl-substituted 2-alkynylbenzenamine **1c** reacted with phenyl isocyanate **2a** led to the desired product **3c** in 46% yield (Table 2, entry 3), while 74% yield of indole **3d** was afforded when methyl-substituted 2-alkynylbenzenamine **1d** was utilized in the reaction (Table 2, entry 4). Similar results were observed when 4-fluorophenyl isocycanate **2b** and 4-methoxyphenyl isocycanate **2c** reacted with 2-alkynylbenzenamine **1c** or **1d** (Table 2, entries 8, 9, 13, 14). When R^2 was changed to cyclopropyl group, the reactions also occurred smoothly to generate the corresponding products **3** in good yields. For example, reaction of 2-alkynylbenzenamine **1e** with phenyl isocycanate **2a** gave rise to the indole **3e** in 90% yield (Table 2, entry 5). 88% yield of compound **3o** was generated when 4-methoxyphenyl isocycanate **2c** was used as a replacement (Table 2, entry 15), whereas product **3j** was afforded in 72% yield for the reaction of 4-fluorophenyl isocycanate **2b** (Table 2, entry 10). From the results shown in Table 2, the reactions showed very high regioselectivity. We reasoned that in the reaction process, it may presumably involve the formation of π-complex *via* coordination of the alkynyl moiety of **1** to Pd(II), thus activating the triple bond for regioselective nucleophilic attack by the amino group in *endo* mode. Although factors affecting the above regioselectivity are not yet very clear, generally in the presence of palladium, 5-*endo*-cyclization is favorable.[13]

Conclusions

In summary, we have described a novel and efficient method for the synthesis of 1,2-disubstituted indoles *via* $PdCl_2$-catalyzed tandem addition-cyclization reactions of 2-alkynylbenzenamines with isocyanates. The efficiency of this method combined with the operational simplicity of the present process makes it potential attractive for library construction. Construction of a small library and biological screening of these small molecules are under investigation in our laboratory, and the results will be reported in due course.

Experimental Section

All reactions were performed in test tubes under nitrogen atmosphere. Flash column chromatography was performed using silica gel (60-Å pore size, 32–63 µm, standard grade). Analytical thin–layer chromatography was performed using glass plates pre-coated with 0.25 mm 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Thin layer chromatography plates were visualized by exposure to ultraviolet light. Organic solutions were concentrated on rotary evaporators at ~20 Torr (house vacuum) at 25–35 °C. Commercial reagents and solvents were used as received.

General procedure for reaction of 2-alkynylbenzenamine 1 with isocyanate 2 catalyzed by palladium chloride

A solution of 2-alkynylbenzenamine **1**[12] (0.50 mmol) and isocyanate **2** (0.75 mmol, 1.5 equiv) in THF (2.0 mL) was stirred at 80 °C for 3 h. Then $PdCl_2$ (10 mol%) was added to the mixture. After completion of reaction as indicated by TLC, the solvent was evaporated and the residue was quenched with water (10 mL), extracted with EtOAc (2 × 10 mL), dried by anhydrate Na_2SO_4. Evaporation of the solvent followed by purification on silica gel provided the corresponding product **3**.

N,2-Diphenyl-1H-indole-1-carboxamide 3a

Colorless oil, yield: 87%; IR (KBr): ν_{max}/cm^{-1} 3298 (NH), 1670 (CO), 1598, 1532, 1440 (C=C); UV: λ_{max} = 204.0 nm, λ = 293.0 nm, λ = 253.0 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ6.69 (s, 1H), 6.72 (br, 1H), 7.04–7.08 (m, 3H), 7.20–7.27 (m, 3H), 7.33 (dt, *J* = 1.5, 7.82 Hz, 1H), 7.42–7.47 (m, 3H), 7.54–7.56 (m, 2H), 7.59 (d, J = 7.8 Hz, 1H), 8.20 (d, J = 8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.1, 114.3, 119.6, 120.6, 122.7,124.4, 124.6, 128.6, 128.8, 128.9, 129.1, 132.0, 136.7, 137.6, 137.9, 149.4; MS (ESI) m/z 313 (M^++H); HRMS calcd for $C_{21}H_{16}N_2O$ (M^++H): 313.1341; Found: 313.1370.

2-(4-Methoxyphenyl)-N-phenyl-1H-indole-1-carboxamide 3b

Colorless oil, yield: 53%; IR (KBr): ν_{max}/cm^{-1} 3257 (NH), 1680 (CO), 1593, 1542, 1491, 1445 (C=C); UV: λ_{max} = 202.0 nm, λ = 295.0 nm, λ = 242.0 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85 (s, 3H), 6.64 (s, 1H), 6.82 (br, 1H), 6.99 (d, J = 8.8 Hz, 2H), 7.06–7.13 (m, 3H), 7.23–7.27 (m, 3H), 7.33 (t, J = 7.3 Hz, 1H), 7.50 (d, J = 8.8 Hz, 2H), 7.58 (d, J = 7.8 Hz, 1H), 8.23 (d, J = 8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.4, 108.6, 114.5, 114.6, 119.7, 120.4, 122.7, 124.2, 124.3, 124.6, 128.7, 129.0, 130.3, 136.8, 137.4, 137.8, 149.5, 160.2; MS (ESI) m/z 343 (M^++H); HRMS calcd for $C_{22}H_{18}N_2O_2$ (M^++H): 343.1447; Found: 343.1470.

N,2-Diphenyl-5-(trifluoromethyl)-1H-indole-1-carboxamide 3c

Colorless oil, yield: 46%; IR (KBr): ν_{max}/cm^{-1} 3288 (NH), 1690 (CO), 810; UV: λ_{max} = 230.0 nm, λ = 292.0 nm, λ = 248.0 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75 (br, 1H), 6.77 (s, 1H), 7.04–7.12 (m, 3H), 7.23–7.27 (m, 2H), 7.49–7.51 (m, 3H), 7.56–7.59 (m, 3H), 7.89 (s, 1H), 8.30 (d, J = 8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 108.9, 114.9, 118.1 (q, $^3J_{CF}$ = 3.8 Hz), 119.7, 121.1 (q, $^3J_{CF}$ = 3.8 Hz), 124.8 (q, $^1J_{CF}$ = 270.8 Hz), 124.9, 125.0 (q, $^2J_{CF}$ = 31.5 Hz), 128.2, 129.0, 129.1, 129.3, 129.5, 131.3, 136.4, 139.3, 148.9; MS (ESI) m/z 381 (M^++H); HRMS calcd for $C_{22}H_{15}F_3N_2O$ (M^++H): 381.1215; Found: 381.1241.

5-Methyl-N,2-diphenyl-1H-indole-1-carboxamide 3d

Colorless oil, yield: 74%; IR (KBr): ν_{max}/cm^{-1} 3334 (NH), 1670 (CO), 1598, 1521, 1440 (C=C); UV: λ_{max} = 203.0 nm, λ = 296.0 nm, λ = 255.0 nm, λ = 230.0 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.45 (s, 3H), 6.62 (s, 1H), 6.70 (br, 1H), 7.04–7.06 (m, 3H), 7.15 (d, J = 8.3 Hz, 1H), 7.22 (t, J = 7.8 Hz, 2H), 7.37 (s, 1H), 7.42–7.48 (m, 3H), 7.54–7.56 (m, 2H), 8.10 (d, J = 8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 109.1, 114.2, 119.6, 120.4, 124.5, 126.0, 128.9, 129.0, 129.1, 132.1, 132.2, 136.2, 136.8, 137.6, 149.5; MS (ESI) m/z 327 (M^++H); HRMS calcd for $C_{22}H_{18}N_2O$ (M^++H): 327.1497; Found: 327.1527.

2-Cyclopropyl-N-phenyl-1H-indole-1-carboxamide 3e

Colorless oil, yield: 90%; IR (KBr): ν_{max}/cm^{-1} 3293 (NH), 1690 (CO), 1598, 1537, 1455 (C=C); UV: λ_{max} = 203.0 nm, λ = 261.0 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.71–1.75 (m, 2H), 1.87–1.91 (m, 2H), 2.90–3.00 (m, 1H), 7.03 (s, 1H), 7.89–7.93 (m, 2H), 7.96–8.00 (m, 1H), 8.13 (t, J = 8.3 Hz, 2H), 8.20 (d, J = 8.3 Hz, 1H), 8.32 (d, J = 8.3 Hz, 2H), 8.83 (d, J = 8.3 Hz, 1H), 9.05 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.2, 10.3, 105.4, 114.1, 119.6, 120.1, 122.3, 123.6, 124.5, 128.4, 129.2, 137.0, 137.3, 140.0, 149.8; MS (ESI) m/z 277 (M^++H); HRMS calcd for $C_{18}H_{16}N_2O$ (M^++H): 277.1341; Found: 277.1358.

N-(4-Fluorophenyl)-2-phenyl-1H-indole-1-carboxamide 3f

Colorless oil, yield: 75%; IR (KBr): ν_{max}/cm^{-1} 3288 (NH), 1675 (CO), 1547, 1506 (C=C), 846; UV: λ_{max} = 201.0 nm, λ = 292.0 nm, λ = 250.0 nm, λ = 230.0 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69 (br, 1H), 6.70 (s, 1H), 6.91 (t, J = 8.7 Hz, 2H), 6.98–7.02 (m, 2H), 7.24–7.28 (m, 1H), 7.34 (dt, J = 1.5, 8.3 Hz, 1H), 7.44–7.49 (m, 3H), 7.54–7.57 (m, 2H), 7.59 (d, J = 7.8 Hz, 1H), 8.19 (d, J = 8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.3, 114.4, 115.6 (d, $^2J_{CF}$ = 22.9 Hz), 120.6, 121.4 (d, $^3J_{CF}$ = 7.6 Hz), 122.8, 124.6, 128.6, 128.9, 129.0, 129.1, 132.0, 132.7 (d, $^4J_{CF}$ = 2.8 Hz), 137.5, 137.9, 149.5, 159.6 (d, $^1J_{CF}$ = 243.1 Hz); MS (ESI) m/z 331 (M^++H); HRMS calcd for $C_{21}H_{15}FN_2O$ (M^++H): 331.1247; Found: 331.1271.

N-(4-Fluorophenyl)-2-(4-methoxyphenyl)-1H-indole-1-carboxamide 3g

Colorless oil, yield: 65%; IR (KBr): ν_{max}/cm^{-1} 3283 (NH), 1665 (CO), 1609, 1552, 1496, 1450 (C=C), 840; UV: λ_{max} = 204.0 nm, λ = 294.0 nm, λ = 241.0 nm; ^{1}H NMR(400 MHz,$CDCl_3$) δ 3.86 (s, 3H), 6.64 (s, 1H), 6.81 (br, 1H), 6.94 (t, J = 8.3 Hz, 2H), 7.00 (d, J = 8.8 Hz, 2H), 7.05–7.09 (m, 2H), 7.25 (dt, J = 1.5, 8.3 Hz, 1H), 7.33 (dt, J = 1.5, 8.3 Hz, 1H), 7.49 (d, J = 8.8 Hz, 2H), 7.58 (d, J = 7.8 Hz, 1H), 8.21 (d, J = 8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.4, 108.7, 114.4, 114.6, 115.6 (d, $^2J_{CF}$ = 22.9 Hz), 120.4, 121.5 (d, $^3J_{CF}$ = 8.6 Hz), 122.7, 124.1, 124.3, 128.7, 130.3, 132.8, 137.3, 137.8, 149.7, 159.6 (d, $^1J_{CF}$ = 242.1 Hz), 160.2; MS (ESI) m/z 383 (M^++Na); HRMS calcd for $C_{22}H_{17}FN_2O_2$ (M^++Na): 383.1172; Found: 383.1200.

N-(4-Fluorophenyl)-2-phenyl-5-(trifluoromethyl)-1H-indole-1-carboxamide 3h

Colorless oil, yield: 60%; IR (KBr): ν_{max}/cm^{-1} 3421 (NH), 1711 (CO), 1537, 1511 (C=C); UV: λ_{max} = 200.0 nm, λ = 290.0 nm, λ = 247.0 nm, λ = 231.0 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.70 (br, 1H), 6.77 (s, 1H), 6.91–7.00 (m, 4H), 7.50–7.52 (m, 3H), 7.56–7.58 (m, 3H), 7.89 (s, 1H), 8.28 (d, J = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.0, 114.8, 115.8 (d, $^2J_{CF}$ = 22.9 Hz), 118.1 (q, $^3J_{CF}$ = 3.8 Hz), 121.1 (q, $^3J_{CF}$ = 3.1 Hz), 121.6 (d, $^3J_{CF}$ = 7.6 Hz), 124.7 (q, $^1J_{CF}$ = 270.2 Hz), 125.2 (q, $^2J_{CF}$ = 32.1 Hz), 128.1, 129.1, 129.4, 129.6, 131.3, 132.3, 139.1, 139.2, 149.0, 159.8 (d, $^1J_{CF}$ = 243.4 Hz); MS (ESI) m/z 399 (M^++H); HRMS calcd for $C_{22}H_{14}F_4N_2O$ (M^++H): 399.1121; Found: 399.1150.

N-(4-Fluorophenyl)-5-methyl-2-phenyl-1H-indole-1-carboxamide 3i

Colorless oil, yield: 72%; IR (KBr): ν_{max}/cm^{-1} 3304 (NH), 1690 (CO), 1511 (C=C); UV: λ_{max} = 206.0 nm, λ = 293.0 nm, λ = 254.0 nm, λ = 229.0 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.45 (s, 3H), 6.62 (s, 1H), 6.68 (br, 1H), 6.90 (t, J = 8.8 Hz, 2H), 6.98–7.01 (m, 2H), 7.15 (d, J = 8.3 Hz, 1H), 7.37 (s, 1H), 7.42–7.48 (m, 3H), 7.52–7.55 (m, 2H), 8.07 (d, J = 8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 109.3, 114.2, 115.7 (d, $^2J_{CF}$ = 21.9 Hz), 120.5, 121.6 (d, $^3J_{CF}$ = 7.6 Hz), 126.2, 129.0, 129.2, 132.3, 132.4, 132.9 (d, $^4J_{CF}$ = 2.8 Hz), 136.3, 137.6, 149.8, 159.7 (d, $^1J_{CF}$ = 243.1 Hz); MS (ESI) m/z 345 (M^++H); HRMS calcd for $C_{22}H_{17}FN_2O$ (M^++H): 345.1403; Found: 345.1432.

2-Cyclopropyl-N-(4-fluorophenyl)-1H-indole-1-carboxamide 3j

Colorless oil, yield: 72%; IR (KBr): ν_{max}/cm^{-1} 3293 (NH), 1680 (CO), 1608, 1542, 1506, 1445 (C=C); UV: λ_{max} = 204.0 nm, λ = 259.0 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97–1.01 (m, 2H), 1.12–1.17 (m, 2H), 2.15–2.24 (m, 1H), 6.30 (s, 1H), 7.08 (t, J = 7.3 Hz, 2H), 7.18 (dt, J = 1.3, 7.8 Hz, 1H), 7.25 (dt, J = 1.5, 8.6 Hz, 1H), 7.47 (d, J = 7.3 Hz, 1H), 7.52–7.55 (m, 2H), 8.08 (d, J = 8.3 Hz, 1H), 8.33 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.2, 10.4, 105.7, 114.4, 115.9 (d, $^2J_{CF}$ = 21.9 Hz), 120.1, 121.4 (d, $^3J_{CF}$ = 8.6 Hz), 122.4, 123.7, 128.4, 133.3 (d, $^4J_{CF}$ = 2.8 Hz), 137.0, 139.9, 150.0, 159.5 (d, $^1J_{CF}$ = 242.1 Hz); MS (ESI) m/z 317 (M^++Na); HRMS calcd for $C_{18}H_{15}FN_2O$ (M^++Na): 317.1066; Found: 317.1092.

N-(4-Methoxyphenyl)-2-phenyl-1H-indole-1-carboxamide 3k

Colorless oil, yield: 86%; IR (KBr): v_{max}/cm^{-1} 3304 (NH), 1696 (CO), 1603, 1516, 1450 (C=C); UV: λ_{max} = 203.0 nm, λ = 292.0 nm, λ = 255.0 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.73 (s, 1H), 6.61 (br, 1H), 6.69 (s, 1H), 6.75 (d, J = 8.8 Hz, 2H), 6.97 (d, J = 8.3 Hz, 2H), 7.24 (t, J = 7.3 Hz, 1H), 7.32 (dt, J = 1.5, 8.3 Hz, 1H), 7.42–7.47 (m, 3H), 7.54–7.60 (m, 3H), 8.18 (d, J = 8.3 Hz, 1H);^{13}C NMR (100 MHz, $CDCl_3$) δ 55.4, 108.8, 114.1, 114.2, 120.6, 121.7, 122.6, 124.4, 128.6, 128.8, 129.0, 129.7, 132.0, 137.6, 137.9, 149.6, 156.7; MS (ESI) m/z 343 (M^++H); HRMS calcd for $C_{22}H_{18}N_2O_2$ (M^++H): 343.1477; Found: 343.1487.

N,2-Bis(4-methoxyphenyl)-1H-indole-1-carboxamide 3l

Colorless oil, yield: 73%; IR (KBr): v_{max}/cm^{-1} 3283 (NH), 1665 (CO), 1593, 1542, 1506, 1445 (C=C); UV: λ_{max} = 204.0 nm, λ = 293.0 nm, λ = 256.0 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (s, 3H), 3.85 (s, 3H), 6.62 (s, 1H), 6.70 (br, 1H), 6.78 (d, J = 8.8 Hz, 2H), 6.99 (d, J = 8.8 Hz, 2H), 7.03 (d, J = 8.3 Hz, 2H), 7.24 (d, J = 7.3 Hz, 1H), 7.31 (dt, J = 1.0, 8.3 Hz, 1H), 7.49 (d, J = 8.3 Hz, 2H), 7.57 (d, J = 7.8 Hz, 1H), 8.20 (d, J = 8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.4, 108.3, 114.1, 114.4, 114.5, 120.3, 121.7, 122.6, 124.1, 124.2, 128.7, 129.8, 130.2, 137.5, 137.8, 149.8, 156.7, 160.1; MS (ESI) m/z 373 (M^++H); HRMS calcd for $C_{23}H_{20}N_2O_3$ (M^++H): 373.1552; Found: 373.1579.

N-(4-Methoxyphenyl)-2-phenyl-5-(trifluoromethyl)-1H-indole-1-carboxamide 3m

Colorless oil, yield: 43%; IR (KBr): v_{max}/cm^{-1} 3349 (NH), 1685 (CO), 1598, 1511 (C=C); UV: λ_{max} = 200.0 nm, λ = 291.0 nm, λ = 251.0 nm, λ = 231.0 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76 (s, 3H), 6.62 (br, 1H), 6.76–6.79 (m, 3H), 6.98 (d, J = 7.3 Hz, 2H), 7.49–7.51 (m, 3H), 7.55–7.58 (m, 3H), 7.89 (s, 1H), 7.28 (d, J = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.5, 108.8, 114.3, 114.8, 118.2 (q, $^3J_{CF}$ = 4.7 Hz), 121.1 (q, $^3J_{CF}$ = 2.9 Hz), 121.9, 124.9 (q, $^1J_{CF}$ = 269.8 Hz), 125.1 (q, $^2J_{CF}$ = 31.5 Hz), 128.2, 129.1, 129.5, 129.7, 131.5, 139.3, 139.4, 149.3, 157.1; MS (ESI) m/z 433 (M^++Na); HRMS calcd for $C_{23}H_{17}F_3N_2O_2$ (M^++Na): 433.1140; Found: 433.1163.

N-(4-Methoxyphenyl)-5-methyl-2-phenyl-1H-indole-1-carboxamide 3n

Colorless oil, yield: 83%; IR (KBr): v_{max}/cm^{-1} 3329 (NH), 1675 (CO), 1598, 1511, 1465 (C=C); UV: λ_{max} = 206.0 nm, λ = 293.0 nm, λ = 257.0 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3H), 3.73 (s, 3H), 6.60 (br, 1H), 6.61 (s, 1H), 6.75 (d, J = 8.8 Hz, 2H), 6.97 (d, J = 8.8 Hz, 2H), 7.14 (d, J = 8.1 Hz, 1H), 7.36 (s, 1H), 7.41–7.46 (m, 3H), 7.51–7.55 (m, 2H), 8.06 (d, J = 8.3 Hz, 1H);^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 55.4, 108.8, 114.0, 114.1, 120.3, 121.6, 125.9, 128.7, 128.8, 129.0, 129.8, 132.0, 132.2, 136.2, 137.6, 149.7, 156.6; MS (ESI) m/z 357 (M^++H); HRMS calcd for $C_{23}H_{20}N_2O_2$ (M^++H): 357.1603; Found: 357.1629.

2-Cyclopropyl-N-(4-methoxyphenyl)-1H-indole-1-carboxamide 3o

Colorless oil, yield: 88%; IR (KBr): v_{max}/cm^{-1} 3298 (NH), 1675 (CO), 1593, 1521, 1450 (C=C); UV: λ_{max} = 202.0 nm, λ = 265.0 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94–0.98 (m, 2H), 1.10–1.05 (m, 2H), 2.16–2.24 (m, 1H), 3.80 (s, 3H), 6.27 (s, 1H), 6.91 (d, J = 9.3 Hz, 2H), 7.16 (t, J = 7.3 Hz, 1H), 7.23 (t, J = 7.8 Hz, 1H), 7.46 (t, J = 8.8 Hz, 3H), 8.07 (d, J = 8.3, 1H), 8.17 (br, 1H);^{13}C NMR (100 MHz, $CDCl_3$) δ 8.2, 10.3, 55.5, 105.2, 114.0, 114.4, 120.0, 121.6, 122.2, 123.5, 128.4, 130.3, 137.0, 140.1, 150.1, 156.7; MS (ESI) m/z 307 (M^++H); HRMS calcd for $C_{19}H_{18}N_2O_2$ (M^++H): 307.1447; Found: 307.1473.

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