Gold-catalyzed intramolecular hydroamination of terminal alkynes in aqueous media: efficient and regioselective synthesis of indole-1-carboxamides†

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Using [Au(PPh_3)]Cl/Ag_2CO_3-catalyzed 5-*endo-dig* cyclization in water under microwave irradiation, we developed a fast and green route to prepare indole-1-carboxamides from *N*′-substituted *N*-(2-alkynylphenyl)ureas. The described method is tolerant to a variety of functional groups, including *N*′-aryl, alkyl, heterocyclic, various *N*-(substituted-2-ethynylphenyl) and *N*-(2-ethynylpyridin-3-yl)ureas and affords moderate to high yields of the desired products.

Introduction

Over recent years great efforts have been made in the field of green chemistry to adopt methods and processes that use less toxic chemicals, produce smaller amounts of by-products and use less energy.[1] As part of this green concept, water and microwave irradiation have become very popular and received substantial interest.[2] Water is environmentally benign, abundant and cheap solvent. In addition, it often exhibits unique reactivity and selectivity that cannot be attained in conventional organic solvents.[3] Microwave-assisted organic synthesis (MAOS) is time- and energy-saving, and compound libraries can be rapidly synthesized either in a parallel or sequential format. Meanwhile, it often facilitates the discovery of novel reaction pathways.[4]

Indole derivatives are found in many natural and synthetic products that exhibit a wide range of biological activities.[5] The development of efficient methods for their synthesis has continuously attracted the attentions of many chemists. Besides classical methods (*e.g.* Fischer, Reissert, Madelung, and Larock reactions),[5a,6] catalytic transformation by using transition-metal catalysts is one of the modern approaches for forming indoles.[7,8] In particular, intramolecular cyclizations of functionalized *o*-alkynylaniline derivatives are some of the most efficient approaches. Pd- or Cu-catalyzed cyclization of *o*-alkynylanilines in the presence of alkyl, vinyl, or aryl halides has been reported to give various 2-substituted and 2,3-disubstituted indoles.[9,10] Rh-catalyzed reactions of *o*-alkynylaniline to 2,3-unsubstituted indoles[11] and Pt-catalyzed intramolecular C–N bond addition of amides to alkynes to form polyfunctionlized indoles have been developed.[12] The synthesis of 2-substituted indoles through Cu- or Pd-catalyzed domino reactions of *N*-protected *o*-iodoaniline derivatives with 1-alkynes has been also reported.[13] Additionally, Yamamoto and co-workers reported tandem cyclization of 2-alkynylaniline in the presence of certain nucleophiles to give the nucleophile incorporated indoles.[14]

On the other hand, indole-1-carboxamide compounds have been used for the treatment of inflammatory diseases[15] and diabetes.[16] However, so far, only a few methods for the synthesis of indole-1-carboxamides have been described.[17] These procedures use anhydrous conditions, toxic organic solvents (*e.g.* ether[17a,b] or THF[17c]), and are limited in scope and selectivity. Recently, a $PdCl_2$-catalyzed cyclization of 2-alkynylbenzenamines with isocyanates to form 2-substituted indole-1-carboxamides was developed.[18] This reaction is performed in THF at 80 °C for 20 h, and is only limited to the internal alkynes and aryl isocyanates. Consequently, the development of faster and greener protocols to assemble indole-1-carboxamides, especially 2-unsubstituted indole-1-carboxamides, is still a synthetic challenge.

In recent times, gold-catalyzed intramolecular hydroaminations of alkynes for the preparation of various *N*-heterocycles, such as indoles,[19] pyrroles,[20] quinolines,[21] and isoquinolines,[22] have received much attention. Some Au-catalyzed procedures that performed in water or under neat conditions were also reported.[23] In addition, we have previously found that *N*′-substituted *N*-(2-halophenyl)ureas can be efficiently transformed to *N*-substituted 1,3-dihydrobenzimidazol-2-ones.[24] Prompted by these results, here we would like to describe a green protocol for the synthesis of indole-1-carboxamides mediated by Au-catalyzed intramolecular hydroamination of *N*-(2-ethynylphenyl)ureas in water under microwave irradiation.

Results and discussion

We initiated our studies by examining catalyst and reaction conditions using *N*′-benzyl-*N*-(2-ethynylphenyl)ureas (**1a**) as

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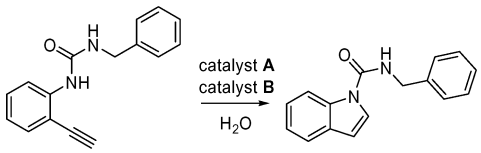
† Electronic supplementary information (ESI) available: Labeling studies experimental details, ^1H and ^{13}C NMR spectra. CCDC reference numbers 721328 for **2a**. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b904044g

Table 1 Optimization of the reaction conditions[a]

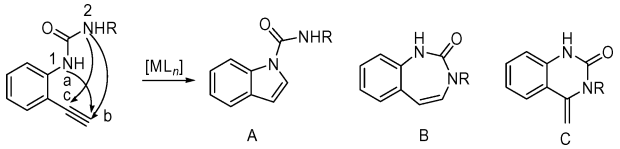


1a 2a

Entry	Catalyst **A** (mol%)	Catalyst **B** (mol%)	T/°C	t	Yield [%][b]
1	—	—	100	30 min	0
2	[Au(PPh$_3$)]Cl (10)	—	120	30 min	20
3	[Au(PPh$_3$)]Cl (10)	—	150	10 min	75
4	AuCl (10)	—	150	10 min	35
5	AuCl$_3$ (10)	—	150	10 min	74
6	—	AgOTf (10)	150	10 min	23
7	—	Ag_2CO_3 (10)	150	10 min	75
8	[Au(PPh$_3$)]Cl (10)	Ag_2CO_3 (10)	150	10 min	90
9	[Au(IPr)]Cl (10)[c]	Ag_2CO_3 (10)	150	10 min	83
10	Au catalyst **X** (10)[d]	Ag_2CO_3 (10)	150	10 min	85
11	[Au(PPh$_3$)]Cl (10)	AgOTf (10)	150	10 min	85
12	[Au(PPh$_3$)]Cl (10)	$AgSbF_6$ (10)	150	10 min	84
13	[Au(PPh$_3$)]Cl (10)	$AgBF_4$ (10)	150	10 min	80
14	[Au(PPh$_3$)]Cl (5)	Ag_2CO_3 (5)	150	10 min	82
15	[Au(PPh$_3$)]Cl (10)	Ag_2CO_3 (10)	100	4 h	89
16[e]	[Au(PPh$_3$)]Cl (10)	Ag_2CO_3 (10)	100	4 h	69
17[e]	[Au(PPh$_3$)]Cl (10)	Ag_2CO_3 (10)	90	16 h	89

[a] Reaction conditions: **1a** (0.2 mmol), catalyst **A** (0.02 mmol), catalyst **B** (0.02 mmol), H_2O (3 mL). [b] Yield of isolated products based on **1a**. [c] [Au(IPr)]Cl = 1,3-bis(2,6-diisopropylphenyl-imidazol-2-ylidene)gold(I) chloride. [d] Au catalyst **X** = [tris(2,4-di-*tert*-butylphenyl)phosphite]gold chloride. [e] The classical method using oil bath heating was adopted.

a model substrate. The results are shown in Table 1. Under catalyst-free conditions, no reaction took place and only the starting material **1a** was recovered (Table 1, entry 1). However, in the presence of [Au(PPh$_3$)]Cl (10 mol%) in water at 120 °C under microwave heating for 30 min, we observed the formation of a product in 20% yield (Table 1, entry 2). When the reaction temperature increased to 150 °C, the yield improved to 75% (Table 1, entry 3). In principle, there are three possible mechanisms for cyclization: 5-endo, leading to structure A, 7-endo, leading to sturcture B and 6-exo, leading to struture C (Scheme 1).[25] Structure elucidation by ^{1}H, ^{13}C NMR, mass spectroscopy, and X-ray crystallography proved that our product has the desired structure A and no other products were detected by TLC (Fig. 1).† Further screening of metal catalysts revealed that AuCl and AgOTf were less effective, while AuCl$_3$ and Ag_2CO_3 were as effective as [Au(PPh$_3$)]Cl (Table 1, entries 4–7). Surprisingly, the yield improved significantly in the presence of catalytic amounts of both [Au(PPh$_3$)]Cl and Ag_2CO_3 (90% yield Table 1, entry 8), in which the synergistic effect of the two metals makes the catalytic cycle operative. Subsequently switching



Scheme 1 5-*endo*, 7-*endo* and 6-*exo* hydroamination of terminal alkynes.

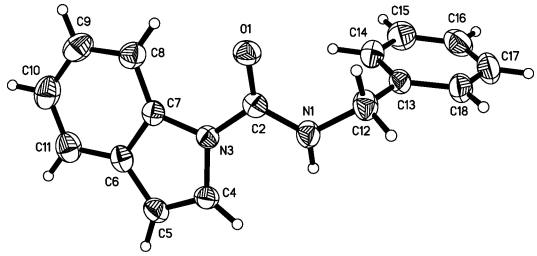


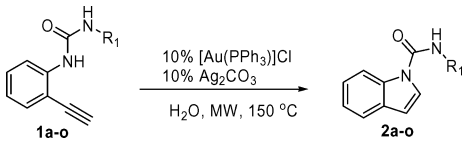
Fig. 1 X-Ray structure of compound **2a**.

Au(PPh$_3$)]Cl to other Au(I) catalysts, such as [Au(IPr)]Cl[26] or [tris(2,4-di-*tert*-butylphenyl)phosphite]gold chloride,[27] led to slightly decreased yields (Table 1, entries 9 and 10). In addition, several other Ag salts with low pK_a values, such as AgOTf, $AgSbF_6$ and $AgBF_4$, proved to be less effective synergists than Ag_2CO_3 (Table 1, entries 11–13). We also found that compound **2a** was obtained in a lower yield (82% yield Table 1, entry 14) when decreasing the [Au(PPh$_3$)]Cl/Ag_2CO_3 catalyst loading from 10 to 5 mol%. Finally, we performed the reactions at 100 °C for 4 h to compare the results using MAOS and the classical method, which gave 89% and 69% yields, respectively (Table 1, entries 15 and 16). An 89% yield was obtained when the reaction was carried out at 90 °C for 16 h using classical method (Table 1, entry 17). From the results, the MAOS method is more effective as it has a significant effect on the increase in the yield and the decrease in the reaction time. Therefore, we chose to employ MAOS method in the next investigation.

After determining the optimized conditions (10 mol% [Au(PPh$_3$)]Cl, 10 mol% Ag_2CO_3, H_2O, MW, 150 °C, 10 min), we examined the generality of the process. First, we demonstrated that a variety of *N*′-substituted-*N*-(2-ethynylphenyl)ureas, including *N*′-aliphatic, *N*′-aromatic, and *N*′-heterocyclic substituted ureas can provide the desired products **2a–o** in moderate to good yields (40–91%) (Table 2, entries 1–15). The electron-withdrawing substituents on the *N*′-R$_1$ group of **1** gave lower yields in the cases of *N*′-4-cyanophenyl and *N*′-naphthyl substituted ureas, presumably due to the significantly decreased nucleophilicity of the N atom of the substrates. We did observe the hydrolytic decomposition of the corresponding materials (Table 2, entries 7 and 13).[28] It is worth noting that the corresponding product yields increased greatly when the reactions were performed at 90 °C for 24 h using classical method (81% for **2g** and 76% for **2m**). The *ortho*-, *meta*-, and *para*-substituents had no significant steric effects (Table 2, entries 9–11). Nevertheless, the introduction of a bulky 2,6-diisopropylphenyl group to the *N*′-R$_1$ led to strongly decreased reactivity, with only a 40% yield of **2n** along with 51% recovered starting material. Carrying out the reaction at 90 °C with oil bath heating and prolonging the time to 48 h did not improve the yield (Table 2, entry 14). This contrasts with the substrates **1g** and **1m** bearing an electron-withdrawing substituent, as described above. Additionally, *N*′-heterocyclic groups such as pyridin-4-yl produced **2o** in good yield (Table 2, entry 15).

We next explored the substrate scope in variation of *N*′-benzyl-*N*-(substituted-2-ethynylphenyl)ureas (Table 2, entries 16–20). Our investigations revealed that the reaction was significantly affected by the electronic properties of R$_3$ substituents. *N*′-benzyl-*N*-(substituted-2-ethynylphenyl)ureas with substituents

Table 2 Synthesis of *N*-substituted indole-1-carboxamides in water[a]



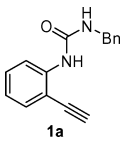
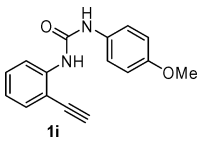
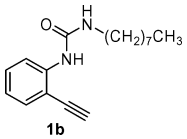
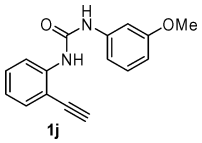
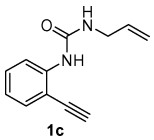
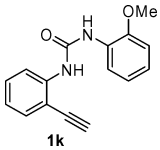
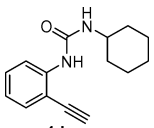
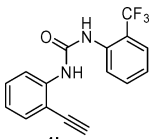
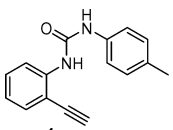
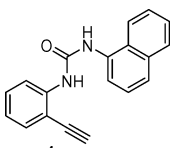
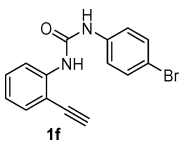
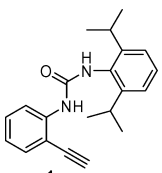
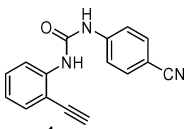
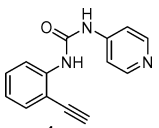
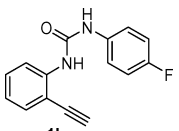
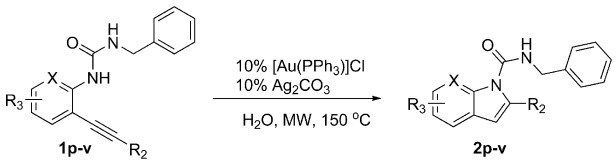
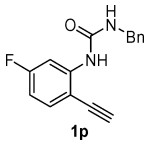
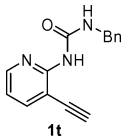
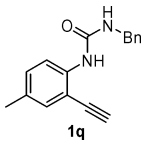
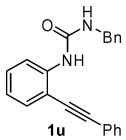
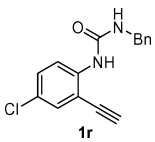
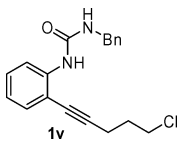
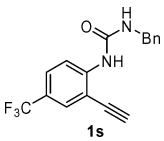
Entry	Substrate **1**	Product **2**: yield (%)[b]	Entry	Substrate **1**	Product **2**: yield (%)[b]
1	 **1a**	**2a**: 90	9	 **1i**	**2i**: 82
2	 **1b**	**2b**: 91	10	 **1j**	**2j**: 84
3	 **1c**	**2c**: 80	11	 **1k**	**2k**: 83
4	 **1d**	**2d**: 83	12	 **1l**	**2l**: 81
5	 **1e**	**2e**: 86	13	 **1m**	**2m**: 41[c] 76[d]
6	 **1f**	**2f**: 83	14	 **1n**	**2n**: 40[e] 48[f]
7	 **1g**	**2g**: 62[c] 81[d]	15	 **1o**	**2o**: 52[c] 75[d]
8	 **1h**	**2h**: 89			

Table 2 *(Contd.)*



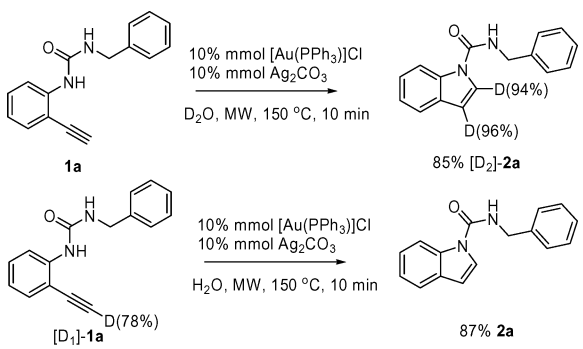
Entry	Substrate **1**	Product **2**: yield (%)[b]	Entry	Substrate **1**	Product **2**: yield (%)[b]
16	 **1p**	**2p**: 85	20	 **1t**	**2t**: 83
17	 **1q**	**2q**: 86	21	 **1u**	**2u**: 0 [h]
18	 **1r**	**2r**: 51	22	 **1v**	**2v**: 0 [h]
19	 **1s**	**2s**: 0[g]			

[a] Reaction conditions: **1** (0.2 mmol), [Au(PPh$_3$)]Cl (0.02 mmol), Ag_2CO_3 (0.02 mmol), H_2O (3 mL). [b] Yield of isolated products based on **1**. [c] Decomposition occurred. [d] The reactions were performed at 90 °C for 24 h using classical method. [e] 51% of starting material was recovered. [f] The reaction was carried out at 90 °C for 48 h using classical method. [g] No desired product **2s** but the 1,2-unsubstituted indole product was observed. [h] 100% of starting material was recovered.

R_3 bearing a fluorine *meta* or an electron-rich methyl *para* to the urea group are tolerant of the cyclization (Table 2, entries 16 and 17). However, relatively lower yields were obtained in the case of substrates with substituents R_3 bearing an electron-neutral Cl or an electron-deficient CF_3 *para* to the urea group (Table 2, entries 18 and 19).[29] Besides *N*′-benzyl-*N*-(substituted-2-ethynylphenyl)ureas **1p–s**, *N*′-benzyl-*N*-(2-ethynylpyridin-3-yl)urea **1t** was also a good substrate for this kind of transformation (83% yield, Table 2, entry 20). Lastly, we also realized the limitation of the reaction. We did not obtain any of the desired products **2u** or **2v** under the optimized conditions when the internal alkyne substrates **1u** and **1v**, respectively, were used and 100% of the starting materials were recovered (Table 2, entries 21 and 22).

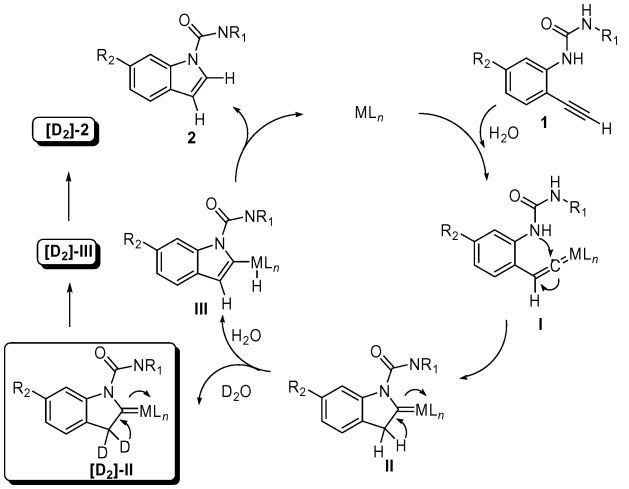
To gain insight into the mechanism of the reaction, we performed labeling studies with deuterated starting materials or solvents. The reaction of **1a** in D_2O under the standard conditions afforded the 2,3-bideuterated compound [D_2]-**2a**. Reaction of the deuterated alkyne [D_1]-**1a** in H_2O led to the formation of non-deuterated product **2a** (Scheme 2).

On the basis of these observations, we proposed a reaction mechanism (Scheme 3). Coordination of the alkyne substrate **1** with transition metal-catalyst, followed by rearrangement,



Scheme 2 Labeling studies with D_2O or deuterated starting material.

leads to a vinylidene intermediate **I**.[30] The key intermediate may undergo nucleophilic capture by the adjacent atom N1 to generate carbene complex **II**, which is followed by tautomerization and reductive elimination of the metal hydride complex to form the desired product **2** and regenerate the active catalyst. Labeling experiments discussed previously revealed that both the vinyl hydrogen atoms of [D_2]-**2a** and **2** came from the solvent. The formation of [D_2]-**2a** directly from D_2O is consistent with existing literature, in that hydrogen atoms in the position α to the



Scheme 3 Proposed mechanism.

carbene group can be exchanged with D_2O (Scheme 2).[23a,31] More support for this reaction mechanism proposal can be found in the comparison of terminal and internal alkyne substrates (Table 2). Since only terminal alkynes can yield such vinylidene intermediates, no reaction occurred for the internal alkyne substrates (Table 2, entries 21 and 22). An alternative mechanism involving the formation of π-complex *via* coordination of the catalyst to the alkyne to induce nucleophilic attack by the amino group in *endo* mode was proposed as well.[18,19a] However, this mechanism can not explain the lack of reactivity of internal alkynes and the formation of the 2,3-bideuterated compound.

Conclusion

In summary, we have developed an Au(I)-catalyzed regioselective cyclization reaction for the preparation of 2,3-unsubstituted indole-1-carboxamides under microwave irradiation in water. Substrates are readily available and functional-group tolerance is high for this atom-economical reaction. A mechanism involving a metal vinylidene intermediate was proposed based on the labeling studies which distinguishes this process from other gold-catalyzed cyclization methods. Collectively, the present method is a simple, fast, efficient and green route to assemble biologically interesting indoles.

Experimental

General experimental procedures

The reagents were purchased from commercial sources and used without further purification. Analytical thin layer chromatography (TLC) was HSGF 254 (0.15–0.2 mm thickness, Yantai Huiyou Company, China). All of the microwave-assisted reactions were performed in an InitiatorTM EXP microwave system (Biotage, Inc.) at the specified temperature using the standard mode of operation. Column chromatography was performed with Combi*Flash*® Companion system (Teledyne Isco, Inc.). All reactions were carried out under Ar atmosphere. Proton and carbon magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded using tetramethylsilane (TMS) in the solvent of $CDCl_3$ as the internal standard (^{1}H NMR: TMS at 0.00 ppm, $CHCl_3$ at 7.24 ppm ^{13}C NMR: $CDCl_3$ at 77.0 ppm) or were recorded using tetramethylsilane (TMS) in the solvent of DMSO-d_6 as the internal standard (^{1}H NMR: TMS at 0.00 ppm, DMSO at 2.50 ppm ^{13}C NMR: DMSO at 40.0 ppm). Low- and high-resolution mass spectra (LRMS and HRMS) were measured on Finnigan MAT 95 spectrometer. All melting points are uncorrected.

General experimental procedure for the synthesis of 2,3-unsubstituted indole-1-carboxamides in water

Microwave method. A mixture of *N*′-substituted *N*-(2-alkynylphenyl)ureas **1** (0.2 mmol), [Au(PPh$_3$)]Cl (0.02 mmol) and Ag_2CO_3 (0.02 mmol) was stirred in water (3–5 mL) under Ar atmosphere. The vial was sealed and the mixture was then irradiated for 10 min at 150 °C. After the reaction was cooled to ambient temperature, the crude reaction mixture was extracted three times with ethyl acetate (EA) (3 × 15 mL). The combined organic phase was washed with saturated $NaHCO_3$ solution, brine, dried with Na_2SO_4 and concentrated. The residue was purified by column chromatography on Combi*Flash*® to provide the desired product.

Classical method using a thermostatted oil bath. A mixture of *N*′-substituted *N*-(2-alkynylphenyl)ureas **1** (0.2 mmol), [Au(PPh$_3$)]Cl (0.02 mmol) and Ag_2CO_3 (0.02 mmol) was stirred in water (3–5 mL) under Ar atmosphere. The vial was sealed and the mixture was then stirred at 90 °C or 100 °C with oil heating for 3–48 h. After the reaction was cooled to ambient temperature, the crude reaction mixture was extracted three times with EA (3 × 15 mL). The combined organic phase was washed with saturated $NaHCO_3$ solution, brine, dried with Na_2SO_4 and concentrated. The residue was purified by column chromatography on combiflash to provide the desired product.

***N*-Benzyl-1*H*-indole-1-carboxamide 2a.** Compound **2a** was obtained as a white solid after purification by flash chromatography (SiO_2, 300–400 mesh EA:PE, 1:15 to 1:9) (yield, 90%), mp 85–86 °C. ^{1}H NMR δ (300 MHz, $CDCl_3$, ppm) 4.650 (d, J = 5.7 Hz, 2H, CH_2 of Bn), 5.921 (br, s, 1H, NH), 6.620 (d, J = 3.6 Hz, 1H, C5-H), 7.207–7.416 (m, 7H), 7.450 (d, J = 3.9 Hz, 1H, C4-H), 7.605 (d, J = 7.8 Hz, 1H, ArH), 8.105 (d, J = 8.1 Hz, 1H, ArH) ^{13}C NMR δ (75 MHz, $CDCl_3$, ppm): 44.9 (CH_2), 107.2 (C5), 114.1 (C_{Ar}), 121.2 (C_{Ar}), 122.3 (C_{Ar}), 123.9 (C_{Ar}), 124.2, 127.8, 128.9, 130.2 (C_{Ar}), 135.1 (C_{Ar}), 137.7 (C_{Ar}), 152.1 (C=O) ESI-MS m/z 251 [M + H]$^+$ 100% HRMS (ESI) calcd for $C_{16}H_{14}N_2ONa$ [M + Na]$^+$ 273.1004, found 273.1000.

***N*-Octyl-1*H*-indole-1-carboxamide 2b.** Compound **2b** was obtained as a white foam after purification by flash chromatography (SiO_2, 300–400 mesh EA:PE, 1:15 to 1:8) (yield, 91%) ^{1}H NMR δ (300 MHz, $CDCl_3$, ppm) 0.897 (t, J = 6.6 Hz, 1H, CH_3), 1.289–1.415 (br, m, 10H), 1.602–1.705 (m, 2H), 3.424–3.490 (m, NCH_2, 1H), 5.718 (br, s, 1H, NH), 6.610 (d, J = 3.9 Hz, 1H, C5-H), 7.199–7.349 (m, 2H, ArH), 7.480 (d, J = 3.6 Hz, 1H, C4-H), 7.600 (d, J = 7.8 Hz, 1H, ArH), 8.105 (d, J = 8.1 Hz, 1H, ArH) ^{13}C NMR δ (75 MHz, $CDCl_3$, ppm): 14.1 (CH_3), 22.6 (CH_2), 26.9 (CH_2), 29.1 (CH_2), 29.2 (CH_2), 29.7 (CH_2), 31.7 (CH_2), 40.9 (CH_2), 106.7, 113.9, 121.1, 122.1, 124.0, 124.1, 130.1, 135.0, 152.1 (C=O) ESI-MS m/z 273 [M + H]$^+$ 100% HRMS

(ESI) calcd for $C_{17}H_{24}N_2ONa$ [M + Na]$^+$ 295.1786, found 295.1806.

***N*-Allyl-1*H*-indole-1-carboxamide 2c.** Compound **2c** was obtained as yellow oil after purification by flash chromatography (SiO_2, 300–400 mesh EA:PE, 1:12 to 1:8) (yield, 80%) ^{1}H NMR δ (300 MHz, $CDCl_3$, ppm) 4.089–4.128 (m, 2H, N-CH_2), 5.219–5.350 (m, 2H, =CH_2), 5.713 (br, s, 1H, NH), 5.921–6.051 (m, 1H, =CH), 6.630 (d, J = 3.9 Hz, 1H, C5-H), 7.209–7.357 (m, 2H, ArH), 7.480 (d, J = 3.6 Hz, 1H, C4-H), 7.600 (d, J = 7.2 Hz, 1H, ArH), 8.100 (d, J = 7.5 Hz, 1H, ArH) ^{13}C NMR δ (75 MHz, $CDCl_3$, ppm): 43.3 (N–CH_2), 107.1, 114.0, 117.1 (=CH_2), 121.2, 122.3, 124.0, 124.2, 130.1, 133.7, 135.0, 151.9 (C=O) ESI-MS m/z 201 [M + H]$^+$ 100% HRMS (ESI) calcd for $C_{12}H_{12}N_2ONa$ [M + Na]$^+$ 223.0847, found 223.0847.

***N*-Cyclohexyl-1*H*-indole-1-carboxamide 2d.** Compound **2d** was obtained as a light yellow oil after purification by flash chromatography (SiO_2, 300–400 mesh EA:PE, 1:15 to 1:10) (yield, 83%) ^{1}H NMR δ (300 MHz, $CDCl_3$, ppm) 1.214–1.517 (m, 5H), 1.643–1.827 (m, 3H), 2.089–2.176 (br, m, 2H), 3.889–3.933 (m, 1H), 5.451 (br, 1H, NH), 6.610 (d, J = 3.9 Hz, 1H, C5-H), 7.198–7.350 (m, 2H, ArH), 7.482 (d, J = 3.6 Hz, 1H, C4-H), 7.600 (d, J = 8.1 Hz, 1H, ArH), 8.030 (d, J = 8.4 Hz, 1H, ArH) ^{13}C NMR δ (75 MHz, $CDCl_3$, ppm): 24.8 (CH_2), 25.4 (CH_2), 33.3 (CH_2), 49.9 (N–CH), 106.6, 113.7, 121.2, 122.1, 124.0, 124.3, 134.9, 151.2 (C=O) ESI-MS m/z 243 [M + H]$^+$ 100% HRMS (ESI) calcd for $C_{15}H_{18}N_2ONa$ [M + Na]$^+$ 265.1317, found 265.1331.

***N*-*p*-Tolyl-1*H*-indole-1-carboxamide 2e.** Compound **2e** was obtained as a white solid after purification by flash chromatography (SiO_2, 300–400 mesh EA:PE, 1:15 to 1:11) (yield, 86%), mp 119–120 °C. ^{1}H NMR δ (300 MHz, $CDCl_3$, ppm) 2.349 (s, 3H), 6.650 (d, J = 3.6 Hz, 1H, C5-H), 7.170 (d, J = 8.1 Hz, 2H, ArH), 7.240–7.412 (m, 5H), 7.545 (d, J = 3.6 Hz, 1H, C4-H), 7.630 (d, J = 6.6 Hz, 1H, ArH), 8.120 (d, J = 8.1 Hz, 1H, ArH) ^{13}C NMR δ (75 MHz, $CDCl_3$, ppm): 20.8 (CH_3), 107.5, 114.0, 120.7, 121.3, 122.5, 124.1, 124.3, 129.7, 130.3, 134.3, 134.6, 135.0, 149.7 (C=O) ESI-MS m/z 251 [M + H]$^+$ 100% HRMS (ESI) calcd for $C_{16}H_{14}N_2ONa$ [M + Na]$^+$ 273.1004, found 273.1005.

***N*-(4-Bromophenyl)-1*H*-indole-1-carboxamide 2f.** Compound **2f** was obtained as a white solid after purification by flash chromatography (SiO_2, 300–400 mesh EA:PE, 1:14 to 1:11) (yield, 83%), mp 124–126 °C. ^{1}H NMR δ (300 MHz, $CDCl_3$, ppm) 6.710 (d, J = 3.6 Hz, 1H, C5–H), 7.268–7.560 (m, 8H), 7.652 (d, J = 7.8 Hz, 1H, ArH), 8.110 (d, J = 8.4 Hz, 1H, ArH) ^{13}C NMR δ (75 MHz, $CDCl_3$, ppm): 108.1, 114.0, 117.5, 121.5, 121.9, 122.8, 124.0, 124.6, 130.4, 132.2, 135.1, 136.2, 149.7 (C=O) ESI-MS m/z 313 [M – H]$^-$ 100% HRMS (ESI) calcd for $C_{15}H_{11}N_2OBrNa$ [M + Na]$^+$ 336.9952, found 336.9959.

***N*-(4-Cyanophenyl)-1*H*-indole-1-carboxamide 2g.** Compound **2g** was obtained as a white solid after purification by flash chromatography (SiO_2, 300–400 mesh EA:PE, 1:8 to 1:5) (yield, 62% under microwave irradiation and 81% under oil heating for 24 h), mp 200–202 °C. ^{1}H NMR δ (300 MHz, d_6-DMSO, ppm) 6.801 (d, J = 3.6 Hz, 1H, C5–H), 7.225–7.358 (m, 2H), 7.650 (d, J = 7.5 Hz, 1H, ArH), 7.839–7.911 (m, 4H), 8.045 (d, J = 3.6 Hz, 1H, C4–H), 8.230 (d, J = 7.8 Hz, 1H, ArH), 10.461 (s, 1H, NH) ^{13}C NMR δ (75 MHz, d_6-DMSO, ppm): 105.4, 106.9, 115.1, 119.1, 120.3, 121.0, 122.6, 124.0, 125.7, 129.8, 133.2, 135.3, 143.1, 149.6 (C=O) ESI-MS m/z 260 [M – H]$^-$ 100% HRMS (ESI) calcd for $C_{16}H_{11}N_2ONa$ [M + Na]$^+$ 284.0800, found 284.0790.

***N*-(4-Fluorophenyl)-1*H*-indole-1-carboxamide 2h.** Compound **2h** was obtained as a white solid after purification by flash chromatography (SiO_2, 300–400 mesh EA:PE, 1:14 to 1:10) (yield, 89%), mp 170–172 °C. ^{1}H NMR δ (300 MHz, $CDCl_3$, ppm) 6.680 (dd, J = 0.9, 3.6 Hz, 1H, C5-H), 7.049–7.106 (m, 2H), 7.244–7.298 (m, 1H), 7.330–7.409 (m, 2H), 7.463–4.509 (m, 2H), 7.545 (d, J = 3.6 Hz, 1H, C4-H), 7.652 (dd, J = 0.9, 8.4 Hz, 1H, ArH), 8.110 (dd, J = 0.9, 8.1 Hz, 1H, ArH) ^{13}C NMR δ (75 MHz, $CDCl_3$, ppm): 107.9, 114.0, 115.8, 116.0, 121.4, 122.5, 122.6, 122.7, 123.9, 124.5, 130.3, 132.9, 135.1, 149.8 (C=O), 158.5(C–F), 160.9 (C–F) ESI-MS m/z 255 [M + H]$^+$ 100% HRMS (ESI) calcd for $C_{15}H_{11}N_2OFNa$ [M + Na]$^+$ 277.0753, found 277.0760.

***N*-(4-Methoxyphenyl)-1*H*-indole-1-carboxamide 2i.** Compound **2i** was obtained as a white solid after purification by flash chromatography (SiO_2, 300–400 mesh EA:PE, 1:14 to 1:9) (yield, 82%), mp 148–150 °C. ^{1}H NMR δ (300 MHz, $CDCl_3$, ppm) 3.807 (s, 3H, OMe), 6.650 (dd, J = 0.9, 3.6 Hz, 1H, C5–H), 6.890 (dd, J = 2.4, 6.6 Hz, 2H), 7.255–7.421 (m, 5H), 7.550 (d, J = 3.6 Hz, 1H, C4–H), 7.620 (d, J = 7.5 Hz, 1H, ArH), 8.116 (d, J = 7.2 Hz, 1H, ArH) ^{13}C NMR δ (75 MHz, $CDCl_3$, ppm): 55.4, 107.5, 114.1, 114.3, 121.3, 122.5, 122.8, 124.0, 124.3, 129.7, 130.2, 135.1, 150.1 (C=O), 156.9 ESI-MS m/z 267 [M + H]$^+$ 100% HRMS (ESI) calcd for $C_{16}H_{14}N_2O_2Na$ [M + Na]$^+$ 289.0953, found 289.0969.

***N*-(3-Methoxyphenyl)-1*H*-indole-1-carboxamide 2j.** Compound **2j** was obtained as a white solid after purification by flash chromatography (SiO_2, 300–400 mesh EA:PE, 1:14 to 1:9) (yield, 84%), mp 111–112 °C. ^{1}H NMR δ (300 MHz, $CDCl_3$, ppm) 3.823 (d, J = 1.2 Hz, 3H, OMe), 6.660 (dd, J = 0.9, 3.9 Hz, 1H, C5–H), 6.730 (dt, J = 1.2, 8.4 Hz, 1H), 7.045 (dt, J = 0.9, 8.1 Hz, 1H), 7.241–7.384 (m, 4H), 7.443 (br, s, 1H, NH), 7.550 (d, J = 3.6 Hz, 1H, C4-H), 7.630 (d, J = 7.2 Hz, 1H, ArH), 8.110 (d, J = 8.4 Hz, 1H, ArH) ^{13}C NMR δ (75 MHz, $CDCl_3$, ppm): 55.3, 106.1, 107.7, 110.5, 112.5, 114.0, 121.4, 122.6, 122.8, 124.0, 124.4, 129.9, 130.3, 135.0, 138.2, 149.5 (C=O), 160.3 ESI-MS m/z 267 [M + H]$^+$ 100% HRMS (ESI) calcd for $C_{16}H_{14}N_2O_2Na$ [M + Na]$^+$ 289.0953, found 289.0965.

***N*-(2-Methoxyphenyl)-1*H*-indole-1-carboxamide 2k.** Compound **2k** was obtained as a white solid after purification by flash chromatography (SiO_2, 300–400 mesh EA:PE, 1:14 to 1:9) (yield, 83%), mp 81–83 °C. ^{1}H NMR δ (300 MHz, $CDCl_3$, ppm) 3.958 (s, 3H, OMe), 6.710 (d, J = 3.3 Hz, 1H, C5–H), 6.970 (dd, J = 1.5, 7.5 Hz, 1H), 7.067–7.135 (m, 2H), 7.261–7.421 (m, 2H), 7.644–7.675 (m, 2H), 8.169 (br, s, 1H, NH), 8.190 (dd, J = 0.9, 8.4 Hz, 1H, ArH), 8.340 (dd, J = 1.8, 8.1 Hz, 1H, ArH) ^{13}C NMR δ (75 MHz, $CDCl_3$, ppm): 55.8, 107.4, 110.0, 113.7, 119.4, 121.2, 121.4, 122.5, 123.9, 124.3, 124.4, 126.9, 130.4, 134.8, 148.1, 149.0 (C=O) ESI-MS m/z 267 [M + H]$^+$ 100% HRMS (ESI) calcd for $C_{16}H_{14}N_2O_2NaF_3$ [M + Na]$^+$ 289.0953, found 289.0961.

***N*-(2-(Trifluoromethyl)phenyl)-1*H*-indole-1-carboxamide 2l.** Compound **2l** was obtained as a light yellow solid after purification by flash chromatography (SiO_2, 300–400 mesh EA:PE, 1:10 to 1:8) (yield, 81%), mp 125–127 °C. ^{1}H NMR δ (300 MHz, $CDCl_3$, ppm) 6.750 (d, J = 3.6 Hz, 1H, C5–H), 7.267–7.419 (m, 3H), 7.515 (d, J = 3.6 Hz, 1H, C4–H), 7.638–7.709 (m, 4H), 8.200 (d, J = 8.4 Hz, 1H, ArH), 8.270 (d, J = 8.7 Hz, 1H, ArH) ^{13}C NMR δ (75 MHz, $CDCl_3$, ppm): 108.7, 114.3, 121.4, 122.9, 123.4, 124.3, 124.8, 126.2, 126.3, 130.3, 133.1, 134.9, 135.3, 149.2 (C=O) ESI-MS m/z 305 $[M + H]^+$ 100% HRMS (ESI) calcd for $C_{16}H_{11}N_2OF_3Na$ $[M + Na]^+$ 327.0721, found 327.0728.

***N*-(Naphthalen-1-yl)-1*H*-indole-1-carboxamide 2m.** Compound **2m** was obtained as a white solid after purification by flash chromatography (SiO_2, 300–400 mesh EA:PE, 1:15 to 1:10) (yield, 41% under microwave irradiation and 76% under oil heating for 24 h), mp 204–205 °C. ^{1}H NMR δ (300 MHz, $CDCl_3$, ppm) 6.755 (d, J = 4.2 Hz, 1H, C5–H), 7.296–7.414 (m, 2H), 7.518–7.592 (m, 3H), 7.668 (br, s, 1H, NH), 7.690 (d, J = 3.6 Hz, 2H), 7.795–7.968 (m, 4H), 8.220 (d, J = 8.4 Hz, 1H, ArH) ^{13}C NMR δ (75 MHz, $CDCl_3$, ppm): 107.9, 114.2, 120.8, 121.4, 121.7, 122.7, 124.1, 124.6, 125.7, 126.3, 126.7, 126.8, 127.9, 128.9, 130.4, 131.7, 134.2, 135.2, 150.4 (C=O) ESI-MS m/z 287 $[M + H]^+$ 100% HRMS (ESI) calcd for $C_{19}H_{14}N_2ONa$ $[M + Na]^+$ 309.1004, found 309.0994.

***N*-(2,6-Diisopropylphenyl)-1*H*-indole-1-carboxamide 2n.** Compound **2n** was obtained as a white solid after purification by flash chromatography (SiO_2, 300–400 mesh EA:PE, 1:15 to 1:11) (yield, 40% under microwave irradiation and 48% under oil heating for 48 h), mp 204–205 °C. ^{1}H NMR δ (300 MHz, $CDCl_3$, ppm) 1.240 (d, J = 7.2 Hz, 12H), 3.212 (m, 2H), 6.715 (d, J = 3.3 Hz, 1H, C5-H), 6.863 (s, 1H, NH), 7.252–7.417 (m, 5H), 7.625 (d, J = 3.0 Hz, 1H, C4–H), 7.670 (d, J = 7.8 Hz, 1H), 8.150 (d, J = 8.4 Hz, 1H, ArH) ^{13}C NMR δ (75 MHz, $CDCl_3$, ppm): 32.7, 28.8, 107.4, 114.1, 121.3, 122.5, 123.8, 124.2, 124.6, 128.8, 130.1, 130.3, 135.2, 146.5, 151.1 (C=O) ESI-MS m/z 321 $[M + H]^+$ 100% HRMS (ESI) calcd for $C_{21}H_{24}N_2ONa$ $[M + Na]^+$ 343.1786, found 343.1769.

***N*-(Pyridin-4-yl)-1*H*-indole-1-carboxamide 2o.** Compound **2o** was obtained as a light yellow solid after purification by flash chromatography (SiO_2, 300–400 mesh CH_3OH:CH_2Cl_2, 1:30 to 1:15) (yield, 52% under microwave irradiation and 75% under oil heating for 24 h), mp 73–74 °C. ^{1}H NMR δ (300 MHz, $CDCl_3$, ppm) 6.645 (d, J = 3.6 Hz, 1H, C5-H), 7.245 (dt, J = 0.9, 7.5 Hz, 1H), 7.360 (dt, J = 0.9, 8.1 Hz, 1H), 7.452 (br, 1H, NH), 7.573–7.610 (m, 3H), 7.640 (d, J = 3.9 Hz, 1H, C4-H), 8.169 (d, J = 8.1 Hz, 1H), 8.460 (dd, J = 1.2, 4.8 Hz, 2H) ^{13}C NMR δ (75 MHz, $CDCl_3$, ppm): 108.4, 114.1, 114.6, 121.3, 123.0, 123.9, 124.7, 130.2, 135.3, 145.7, 149.3 (C=O), 150.2 ESI-MS m/z 238 $[M + H]^+$ 100% HRMS (ESI) calcd for $C_{14}H_{12}N_3O$ $[M + H]^+$ 230.3980, found 230.0989.

***N*-Benzyl-6-fluoro-1*H*-indole-1-carboxamide 2p.** Compound **2p** was obtained as a light yellow solid after the purification by flash chromatography (SiO_2, 300–400 mesh EA:PE, 1:11 to 1:6) (yield, 85%), mp 100–102 °C. ^{1}H NMR δ (300 MHz, $CDCl_3$, ppm): 4.630 (d, J = 5.4 Hz, 2H, CH_2), 5.859 (br, s, 1H, NH), 6.588 (d, J = 3.6 Hz, 1H, C5–H), 6.995 (dt, J = 2.4, 9.3 Hz, 1H), 7.324–7.393 (m, 6H), 7.500 (dd, J = 5.1, 8.1 Hz, 1H), 7.955 (dd, J = 2.1, 10.2 Hz, 1H) ^{13}C NMR δ (75 MHz, $CDCl_3$, ppm): 44.9, 101.7 (C-8), 102.0 (C-8), 107.3, 110.7, 111.1, 121.6, 121.7, 123.6, 126.1, 127.8, 127.9, 128.9, 135.6, 137.5, 151.8 (C=O), 159.7 (C-9), 162.1 (C-9) ESI-MS m/z 269 $[M + H]^+$ 100% HRMS (ESI) calcd for $C_{16}H_{13}N_2ONaF$ $[M + Na]^+$ 291.0910, found 291.0912.

3-Benzyl-5-methyl-1*H*-indole-1-carboxamide 2q. Compound **2q** was obtained as a white solid after purification by flash chromatography (SiO_2, 300–400 mesh EA:PE, 1:13 to 1:8) (yield, 86%), mp 100–101 °C. ^{1}H NMR δ (300 MHz, $CDCl_3$, ppm) 2.435 (s, 3H), 4.660 (d, J = 5.7 Hz, 2H, CH_2), 5.791 (br, s, 1H, NH), 6.640 (d, J = 3.0 Hz, 1H, C5-H), 7.120 (dd, J = 1.8, 8.4 Hz, 1H), 7.319–7.423 (m, 7H), 7.940 (d, J = 8.7 Hz, 1H) ^{13}C NMR δ (75 MHz, $CDCl_3$, ppm): 21.3, 44.9, 106.9, 113.6, 121.0, 124.0, 125.6, 127.9, 128.9, 130.5, 131.8, 133.3, 137.7, 152.0 (C=O) ESI-MS m/z 265 $[M + H]^+$ 100% HRMS (ESI) calcd for $C_{17}H_{16}N_2ONa$ $[M + Na]^+$ 287.1160, found 287.1151.

3-Benzyl-5-chloro-1*H*-indole-1-carboxamide 2r. Compound **2r** was obtained as a white solid after purification by flash chromatography (SiO_2, 300–400 mesh EA:PE, 1:13 to 1:9) (yield, 51%), mp 170–172 °C. ^{1}H NMR δ (300 MHz, $CDCl_3$, ppm): 4.640 (d, J = 6.3 Hz, 2H, CH_2), 5.841 (br, s, 1H, NH), 6.440 (d, J = 3.6 Hz, 1H, C5-H), 7.247–7.428 (m, 7H), 7.550 (d, J = 2.1 Hz, 1H), 8.100 (d, J = 9.0 Hz, 1H) ^{13}C NMR δ (75 MHz, $CDCl_3$, ppm): 44.9, 106.7, 115.6, 120.5, 124.5, 124.7, 127.9, 128.0, 128.9, 130.5, 131.1, 133.7, 137.5, 151.6 (C=O) ESI-MS m/z 285 $[M + H]^+$ 100% HRMS (ESI) calcd for $C_{16}H_{13}N_2ONaCl$ $[M + Na]^+$ 307.0614, found 307.0639.

***N*-benzyl-1*H*-pyrrolo[2,3-b]pyridine-1-carboxamide 2t.** Compound **2r** was obtained as a white solid after purification by flash chromatography (SiO_2, 300–400 mesh EA:PE, 1:8 to 1:5) (yield, 83%), mp 100–101 °C. ^{1}H NMR δ (300 MHz, $CDCl_3$, ppm): 4.750 (d, J = 6.0 Hz, 2H, CH_2), 6.550 (d, J = 4.2 Hz, 1H, C5-H), 7.180 (dd, J = 5.1, 8.4 Hz, 1H), 7.285–7.453 (m, 5H), 7.930 (dd, J = 1.2, 8.4 Hz, 1H), 8.030 (d, J = 3.9 Hz, 1H), 8.260 (dd, J = 1.5, 4.8 Hz, 1H), 10.177 (br, s, 1H, NH) ^{13}C NMR δ (75 MHz, $CDCl_3$, ppm): 44.1, 102.9, 117.9, 123.5, 126.3, 127.3, 127.5, 128.6, 129.9, 138.4, 142.4 146.6, 151.8 (C=O) ESI-MS m/z 262 $[M + H]^+$ 100% HRMS (ESI) calcd for $C_{15}H_{13}N_3ONa$ $[M + Na]^+$ 274.0956, found 274.0971.

Procedures for labeling studies see in ESI.

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