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I-MCR-Ullmann cascade toward furo[2,3-*b*]indole scaffold

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ABSTRACT

An efficient method for the construction of furo[2,3-*b*]indole derivatives **5** via an isocyanide-based multicomponent reaction (I-MCR) and a copper-catalyzed intramolecular Ullmann reaction sequence was described. This two-step sequence can be performed in a one-pot manner to produce the desired product **5** in moderate to good yield (up to 90%).

1. Introduction

In recent decades, the searching for more efficient processes, which allow for the rapid generation of molecular complexity and diversity from simple and readily accessible starting materials have attracted much attention of organic chemists.[1] Among them, the strategical use of multicomponent reactions[2] (MCRs, especially isocyanide-based multicomponent reactions of I-MCRs[3]) followed by a metal-catalyzed intramolecular cyclization[4] has constituted an efficient method for the construction of complex molecules, such as indole and furan scaffolds. For an instance, Zhu and co-workers reported an elegant two-step sequence involving an Ugi four-component reaction (Ugi-4CR) and a palladium-catalyzed intramolecular amidation to construct functionalized oxindoles.[5] However, as stated in their work, cheap copper catalysts (CuI and $CuCl_2$) failed to effectively catalyze the formation of oxindole (~42% yield). More recently, Kaim and co-workers also described a novel access to indole scaffold via a modified Ugi–Smiles reaction in conjunction with a subsequent palladium-mediated Heck-isomerization.[6]

Indole and furan moieties are widely featured in a broad range of pharmacologically and biologically active compounds.[7] The synthesis and functionalization of indole and furan have been the focuses of research for a long time.[8] In this regard, the isocyanide-based multicomponent reaction (I-MCR) has emerged as an efficient method for the synthesis of a wide variety of fused furans.[9,10] For an example, a three-component condensation involving isocyanides, aldehydes, and 1,3-dicarbonyl compounds was developed for the synthesis of 2-aminofurans in the last decade.[9] It was found that the replacement of 1,3-dicarbonyl compounds by 4-hydroxycoumarin,[10a] 2-hydroxy-1,4-naphthoquinone,[10b] and 3-hydroxy-1*H*-phenalene-1-one[10c] could also lead to various furan derivatives. Thus, we envisaged that if the above I-MCRs was carried out using an *ortho*-halobenzaldehyde as a substrate, the product can be further manipulated via a metal-catalyzed intramolecular Ullmann reaction to generate interesting and highly fused furo[2,3-*b*]indole derivatives (**5**). In continuation of our interest in the application of MCRs[11] (especially I-MCRs[12]) in the synthesis of indole and furan skeletons, herein, we report an efficient method for the construction of furo[2,3-*b*]indole derivatives via an I-MCR and a copper-catalyzed intramolecular Ullmann reaction sequence. This two-step sequence can be performed in an one-pot manner to produce the desired products **5** in good yields (up to 90%).

2. Results and discussions

Initially, we studied the synthesis of precursor **4** for Ullmann coupling by using different substrates (Fig. 1). As shown in Table 1, the isocyanide-based multicomponent reactions (I-MCRs) involving substrate **1** (including 4-hydroxycoumarin **1a**, 4-hydroxy-1-methylquinolinone **1b**, and 2-hydroxy-1,4-naphthoquinone **1c**),

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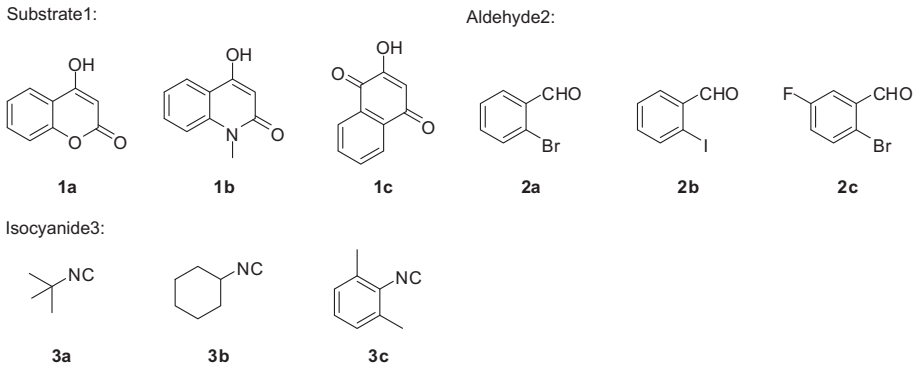
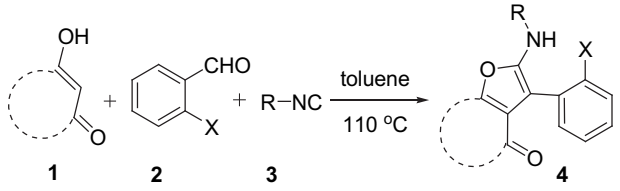


Fig. 1. Diversity of reagents used in the synthesis of furo[2,3-*b*]indole derivatives.

Table 1
Isocyanide-based multicomponent reaction for the synthesis of precursor **4**[a]



Entry	Substrate	Time (h)	Product	Yield (%)[b]
1	**1a**/**2a**/**3a**	24	**4a**	73
2	**1a**/**2a**/**3b**	24	**4b**	77
3	**1a**/**2a**/**3c**	24	**4c**	92
4	**1b**/**2a**/**3a**	20	**4d**	81
5	**1b**/**2a**/**3b**	22	**4e**	85
6	**1b**/**2a**/**3c**	24	**4f**	90
7	**1c**/**2a**/**3a**	6	**4g**	50
8	**1c**/**2a**/**3b**	4	**4h**	60
9	**1a**/**2c**/**3a**	18	**4i**	77
10	**1b**/**2c**/**3a**	18	**4j**	84
11	**1a**/**2b**/**3a**	48	**4k**	75[c]
12	**1b**/**2b**/**3c**	48	**4l**	77[c]

[a] Reaction condition: **1** (1 mmol), **2** (1 mmol), **3** (1.2 mmol) were stirred at 110 °C in toluene for a specific time (monitored by TLC) under nitrogen atmosphere.
[b] Isolated yield.
[c] Temperature: 80 °C.

2-halobenzaldehyde **2**, and isocyanide **3** proceeded efficiently in refluxing toluene for a specific time, leading to the desired product of **4** in moderate to good yields. Both alkyl and aryl isocyanides were good candidates for the reaction. In addition, the fluorine-containing benzaldehyde **2c** also reacted well to generate the desired product **4** in good yields (Table 1, entries 9 and 10).

With the precursor **4** (Fig. 2) in hand, we focused on the feasibility of the following metal-catalyzed intramolecular Ullmann cyclization reaction. Although successful examples on the palladium-catalyzed intramolecular cyclizations have been reported in isocyanide-based multicomponent reactions,[5,6] such reactions promoted by inexpensive metal catalysts (such as copper species) are still highly desirable. In recent decades, coupling reactions mediated by copper catalysts, as economic and powerful strategies for the construction of C–O and C–N bonds, have been well established.[13] For instance, more recently, Buchwald and Bolm disclosed that C–N bond formation could be effectively catalyzed by ppm-level copper contaminant.[14] This information encouraged us to perform the intramolecular Ullmann cyclization with the use of copper species.

The cyclization of **4a** was initially investigated in the presence of the commonly used CuI catalyst.[15] As shown in Table 2, the coupling reaction was surveyed by varying the solvents (entries 1–4), the bases (entries 4–7), and the ligands (entries 7–11). Among the various solvents and bases screened, the optimal result was obtained when toluene was used as solvent and potassium carbonate was employed as a base (entry 4). In addition, various ligands including L-proline (L1), DABCO (L2), DBU (L3), *N*,*N*-dimethylethane-1,2-diamine (L4), 1,10-phenanthroline (L5) were also screened and it was observed that L-proline was superior to other ligands in promoting the reaction. Besides, it is worthwhile to note that the reaction cannot take place in the absence of a ligand (Table 2, entry 12). Moreover, the influence of reaction time and the catalyst loading on the reaction were also investigated (Table 2, entries 13 and 14). It was found that performing the reaction in toluene for 24 h using 10 mol % CuI sufficed to promote this reaction. Under the optimized reaction conditions (10 mol % CuI, 10 mol % L-proline, K_2CO_3, toluene, 110 °C), the intramolecular Ullmann reaction proceeded efficiently to produce the desired product of **5a** in 97% yield (Table 2, entry 4). And its structure was further unambiguously confirmed by single-crystal X-ray analysis (Fig. 3).

With the success of above reactions, we continued to apply the optimized conditions to the synthesis of a wide variety of furo[2,3-*b*]indole derivatives **5** by using various substrates **4a**–**l**. The results are summarized in Table 3. As depicted in Table 3, in all cases, the intramolecular Ullmann coupling reaction occurred efficiently in the presence of CuI and L-proline. The desired products of furo[2,3-*b*]indole derivatives **5** were obtained in good to excellent yields (up to 99%). Unfortunately, the compounds **4i** and **4j** failed to undergo the coupling reaction under the present conditions, which might be due to the electronic effect of fluorine atom attached to the benzene ring. Previously, Ma and co-workers[15c] proposed the mechanism of Ulmann reaction (amino acids were used as the ligands) in detail, which involving chelation of the amino acid to the copper species, π-complexation of copper to the aryl ring, and an intramolecular nucleophilic substitution step. Because of the high electronic affinity of the fluorine atom, electronic density of the benzene ring was remarkably reduced. Consequently, it was difficult for the formation of the π-complex, which is an important intermediate of this Ullmann coupling reaction.[13a,h] We think the results obtained in our cases were consistent with the known process.

Finally, we envisioned that if the two-step sequence can be carried out in a one-pot manner without the isolation of the product **4**, the reaction efficiency would be greatly improved. Thus we continued our task by exploring the extension of this strategy to a more efficient one-pot procedure. After the three-component I-MCR reaction was stirred in refluxing toluene for an appropriate time (monitored by TLC), 0.2 equiv of trifluoroacetic acid[6] was added to the reaction mixture to destroy the remaining isocyanide. Then CuI, L-proline, and K_2CO_3 were added to the reaction mixture to initiate the following intramolecular Ullmann reaction in refluxing toluene. As expected, the two-step sequence also proceeded efficiently in a one-pot manner to afford the desired products of furo[2,3-*b*]indoles **5** in moderate to good yields (Table 4). The one-pot protocol provides great efficiency in the facile construction of furo[2,3-*b*]indoles **5** (Table 4).

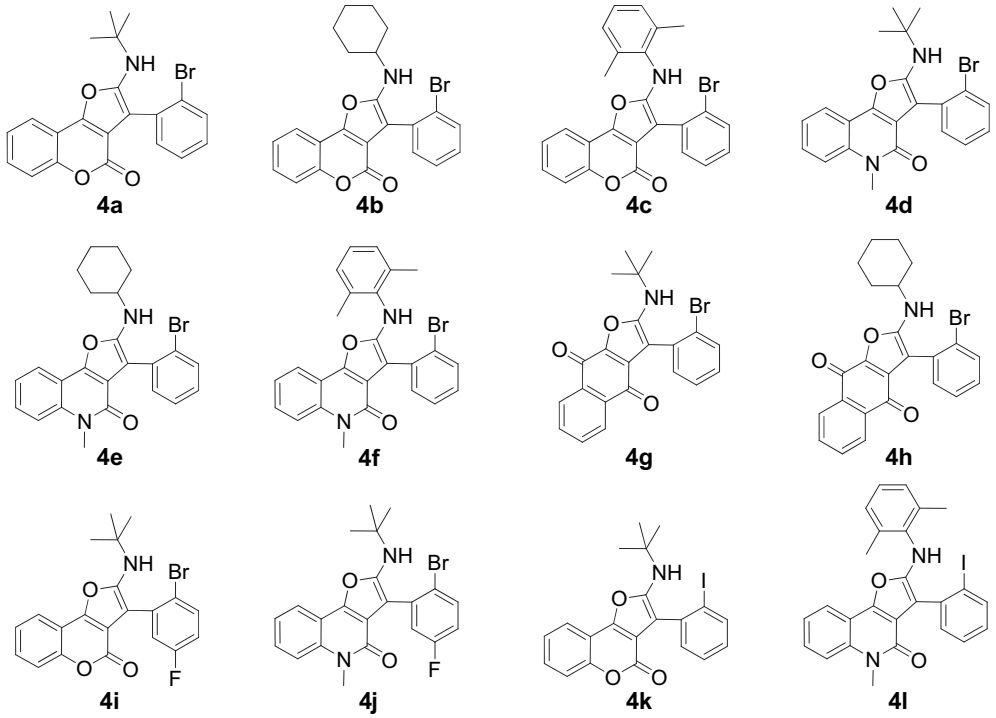
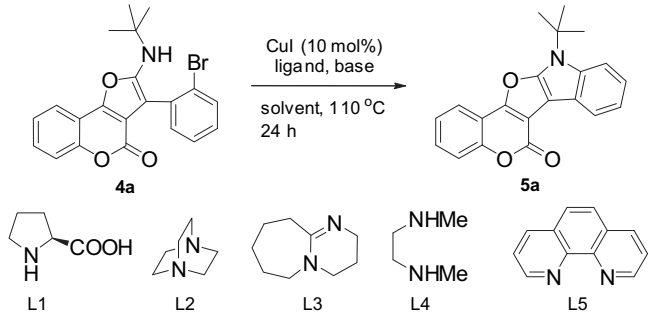


Fig. 2. The structure of products **4a**–**l**.

Table 2
Optimization of the intramolecular Ullmann reaction conditions[a]



Entry	Solvent	Base	Ligand	Yield (%)[b]
1	DMF	K_2CO_3	L1	80
2	DMSO	K_2CO_3	L1	64
3	Dioxane	K_2CO_3	L1	82[c]
4	Toluene	K_2CO_3	L1	97
5	Toluene	Cs_2CO_3	L1	50
6	Toluene	NaOH	L1	Trace
7	Toluene	Et_3N	L1	36
8	Toluene	K_2CO_3	L2	96
9	Toluene	K_2CO_3	L3	79
10	Toluene	K_2CO_3	L4	44
11	Toluene	K_2CO_3	L5	84
12	Toluene	K_2CO_3	–	0
13	Toluene	K_2CO_3	L1	78[d]
14	Toluene	K_2CO_3	L1	80[e]

[a] Unless otherwise noted, the reactions were carried out at 110 °C for 24 h using **4a** (0.25 mmol, 1 equiv), CuI (0.025 mmol, 10 mol %), L-proline (0.025 mmol, 10 mol %), and K_2CO_3 (0.5 mmol, 2 equiv) under argon atmosphere.
[b] Isolated yield.
[c] Under refluxing conditions.
[d] Reaction time: 12 h.
[e] CuI (5 mol %) was used.

3. Conclusions

In summary, we have developed an efficient strategy to construct the highly functionalized furo[2,3-*b*]indole scaffolds from readily accessible starting materials. The isocyanide-based multicomponent reaction and the subsequent copper-catalyzed intramolecular Ullmann reaction can be combined into a one-pot manner, by destroying the residual isocyanide before performing the ensuing copper-mediated intramolecular Ullmann coupling.

4. Experimental section

4.1. General procedure for the synthesis of compound 4

To a mixture of the substrate **1** (1 mmol) and 2-halobenzaldehyde **2** (1 mmol) in anhydrous toluene (3 mL) under nitrogen atmosphere was added isocyanide **3** (1.2 mmol). The reaction mixture was slowly heated to 110 °C and then refluxed for a specific time (monitored by TLC). After reaction, the organic solvent was removed under vacuo and the residue obtained was purified by silica gel column chromatography to afford the product **4**.

*4.1.1. 3-(2-Bromophenyl)-2-(tert-butylamino)-4H-furo[3,2-c]chromen-4-one (**4a**).* Yellow solid; mp: 155–157 °C. IR (KBr) ν 3397, 2975, 1738, 1615, 1530 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 1.25 (s, 9H, $3CH_3$), 5.33 (s, 1H, NH), 7.28–7.32 (m, 1H, ArH), 7.40–7.53(m, 5H, ArH), 7.67–7.70 (d, J=7.8 Hz, 1H, ArH), 7.82–7.84 (d, J=6.6 Hz, 1H, ArH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.8, 160.6, 156.3, 154.8, 138.5, 138.4, 137.7, 137.0, 134.8, 132.7, 130.8, 130.2, 125.1, 122.1, 117.6, 116.4, 107.3, 58.6, 35.5. HRMS (m/z) calcd for $C_{21}H_{18}BrNO_3$ (M^+) 411.0470, found 411.0468.

*4.1.2. 3-(2-Bromophenyl)-2-(cyclohexylamino)-4H-furo[3,2-c]chromen-4-one (**4b**).* Yellow oil. IR (KBr) ν 3299, 2930, 1689, 1604, 1521,

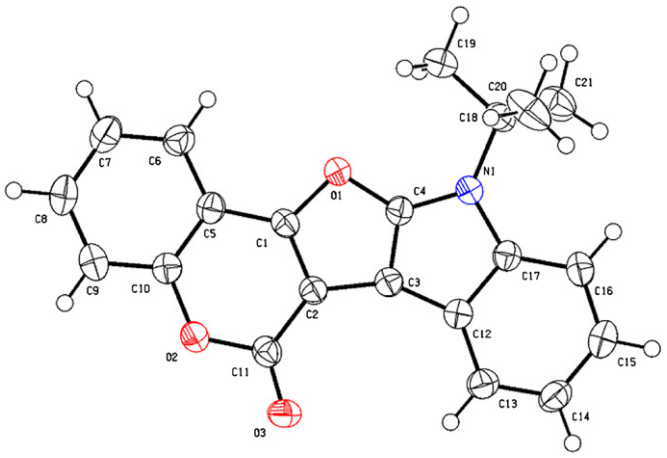
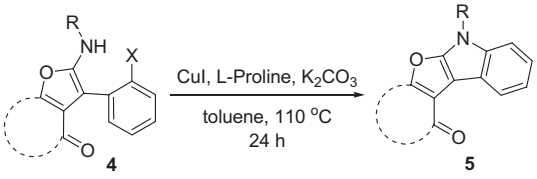
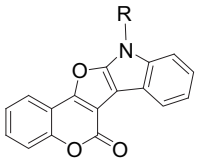
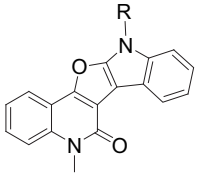
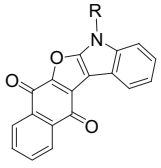


Fig. 3. The X-ray crystal structure of compound **5a**.

1469 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.17–1.34 (m, 6H, CH_2), 1.71–1.74 (m, 2H, CH_2), 2.00–2.07 (m, 2H, CH_2), 3.50 (s, 1H, CH), 3.96 (s, 1H, NH), 7.19–7.24 (m, 1H, ArH), 7.27–7.3 1(m, 1H, ArH), 7.35–7.41 (m, 4H, ArH), 7.67 (d, J=8.0 Hz, 1H, ArH), 7.77 (d, J=7.6 Hz, 1H, ArH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 157.1, 155.8, 151.1, 148.0, 134.1, 132.7, 132.6, 130.0, 129.2, 127.8, 126.8, 125.3, 119.7, 117.2, 112.9, 93.4, 79.9, 53.1, 33.9, 27.0, 25.5. HRMS (m/z) calcd for $C_{23}H_{20}BrNO_3$ (M^+) 437.0627, found 437.0624.

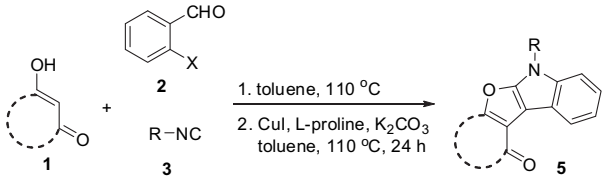
Table 3
Construction of furo[2,3-*b*]indole scaffolds **5** via a copper-catalyzed intramolecular Ullmann cyclization[a]



Entry	Substrate **4**	Product **5**		Yield (%)[b]
1	**4a** R=*t*-Bu	**5a**		97
2	**4b** R=Cy	**5b**		99
3	**4c** R=2,6-$Me_2C_6H_3$	**5c**		86
4	**4d** R=*t*-Bu	**5d**		96
5	**4e** R=Cy	**5e**		82
6	**4f** R=2,6-$Me_2C_6H_3$	**5f**		99
7	**4g** R=*t*-Bu	**5g**		89
8	**4h** R=Cy	**5h**		94
9	**4i**	**5i**	—	0
10	**4j**	**5j**	—	0
11	**4k**	**5a**		92
12	**4l**	**5f**		89

[a] Reaction condition: **4** (0.25 mmol), CuI (0.025 mmol), L-proline (0.025 mmol), and K_2CO_3 (0.5 mmol) were stirred at 110 °C in toluene for 24 h under nitrogen atmosphere.
[b] Isolated yield.

Table 4
One-pot strategy toward the synthesis of compound **5**[a]



Entry	Substrate	Product	Yield (%)[b]
1	**1a/2a/3a**	**5a**	79
2	**1a/2b/3a**	**5a**	75
3	**1a/2a/3b**	**5b**	80
4	**1a/2a/3c**	**5c**	82
5	**1b/2a/3a**	**5d**	78
6	**1b/2a/3b**	**5e**	71
7	**1b/2a/3c**	**5f**	90
8	**1b/2b/3c**	**5f**	85
9	**1c/2a/3a**	**5g**	49
10	**1c/2a/3b**	**5h**	61

[a] See the Supplementary data for detailed reaction conditions.
[b] Isolated yield based on 2-halobenzaldehyde (**2a**,**b**) as limiting reagent.

*4.1.3. 3-(2-Bromophenyl)-2-(2,6-dimethylphenylamino)-4H-furo[3,2-c]chromen-4-one (**4c**).* White solid; mp: 220–222 °C. IR (KBr) ν 3301, 2959, 1720, 1612, 1585, 1557, 1491 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.25 (s, 6H, CH_3), 5.77 (s, 1H, NH), 7.03–7.07 (m, 3H, ArH), 7.21–7.26 (m, 1H, ArH), 7.33–7.40 (m, 5H, ArH), 7.64–7.68 (m, 2H, ArH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 157.1, 153.8, 151.4, 148.7, 136.6, 135.2, 133.4, 133.3, 132.5, 131.5, 129.8, 128.7, 127.4, 126.3, 126.2, 125.5, 119.9, 117.4, 112.8, 112.7, 96.0, 19.0. HRMS (m/z) calcd for $C_{25}H_{18}BrNO_3$ (M^+) 459.0470, found 459.0471.

*4.1.4. 3-(2-Bromophenyl)-2-(tert-butylamino)-5-methylfuro[3,2-c]quinolin-4(5H)-one (**4d**).* Yellow solid; mp: 155–157 °C. IR (KBr) ν 3409, 2968, 1708, 1682, 1602, 1522 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 1.27 (s, 9H, CH_3), 3.61 (s, 3H, NCH_3), 5.10 (s, 1H, NH), 7.26–7.30 (m, 1H, ArH), 7.33–7.42 (m, 3H, ArH), 7.52–7.59 (m, 2H, ArH), 7.67 (d, J=8.0 Hz, 1H, ArH), 7.87 (d, J=7.6 Hz, 1H, ArH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 158.2, 155.1, 148.0, 143.3, 137.2, 133.8, 133.5, 132.7, 129.7, 128.9, 127.7, 126.3, 122.9, 120.1, 116.1, 112.7, 103.7, 53.8, 30.8, 29.5. HRMS (m/z) calcd for $C_{22}H_{21}BrN_2O_2$ (M^+) 424.0786, found 424.0791.

*4.1.5. 3-(2-Bromophenyl)-2-(cyclohexylamino)-5-methylfuro[3,2-c]quinolin-4(5H)-one (**4e**).* Yellow oil. IR (KBr) ν 3378, 2954, 1729, 1602, 1537, 1495 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.20–1.35 (m, 6H, CH_2), 1.72–1.76 (m, 2H, CH_2), 2.02–2.10 (m, 2H, CH_2), 3.52–3.54 (m, 1H, CH), 3.72 (s, 3H, NCH_3), 3.86 (s, 1H, NH), 7.22–7.29 (m, 1H, ArH), 7.38–7.41 (m, 1H, ArH), 7.43–7.45 (m, 4H, ArH), 7.68 (d, J=8.0 Hz, 1H, ArH), 7.92 (d, J=8.0 Hz, 1H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.7, 159.1, 154.3, 147.6, 136.7, 133.6, 132.9, 129.2, 127.7, 127.3, 125.7, 122.3, 119.9, 115.0, 113.2, 97.3, 53.9, 49.0, 34.4, 29.4, 25.8, 25.2. HRMS (m/z) calcd for $C_{24}H_{23}BrN_2O_2$ (M^+) 450.0943, found 450.0943.

*4.1.6. 3-(2-Bromophenyl)-2-(2,6-dimethylphenylamino)-5-methylfuro[3,2-c]quinolin-4(5H)-one (**4f**).* White solid; mp: 230–232 °C. IR (KBr) ν 3251, 2916, 1650, 1584, 1561, 1513 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.25 (s, 6H, CH_3), 3.74 (s, 3H, NCH_3), 5.73 (s, 1H, NH), 7.00–7.05 (m, 3H, ArH), 7.21–7.26 (m, 2H, ArH), 7.33–7.37 (m, 1H, ArH), 7.40–7.46

(m, 3H, ArH), 7.67 (d, J=8.0 Hz, 1H, ArH), 7.80 (d, J=8.0 Hz, 1H, ArH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 158.1, 153.2, 146.5, 137.4, 136.9, 134.9, 133.4, 132.8, 132.3, 129.3, 128.7, 128.6, 127.2, 126.6, 125.9, 122.9, 119.6, 117.1, 116.1, 112.5, 97.4, 29.5, 19.0. HRMS (m/z) calcd for $C_{26}H_{21}BrN_2O_2$ (M^+) 472.0786, found 472.0784.

*4.1.7. 3-(2-Bromophenyl)-2-(tert-butylamino)naphtho[2,3-b]furan-4,9-dione (**4g**).* Red solid; mp: 170–173 °C. IR (KBr) ν 3265, 2973, 1673, 1642, 1597, 1545 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.42 (s, 9H, CH_3), 7.13 (s, 1H, NH), 7.32–7.35 (m, 1H, ArH), 7.41–7.42 (m, 2H, ArH), 7.69–7.71 (m, 2H, ArH), 7.78–7.82 (m, 1H, ArH), 7.86 (d, J=6.4 Hz, 1H, ArH), 8.02 (d, J=6.4 Hz, 1H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.8, 169.6, 159.2, 143.9, 134.3, 134.0, 133.6, 133.5, 133.2, 132.5, 131.6, 131.1, 130.2, 127.9, 126.5, 126.4, 125.1, 99.2, 54.4, 30.2. HRMS (m/z) calcd for $C_{22}H_{18}BrNO_3$ (M^+) 423.0470, found 423.0473.

*4.1.8. 3-(2-Bromophenyl)-2-(cyclohexylamino)naphtho[2,3-b]furan-4,9-dione (**4h**).* Red solid; mp: 127–129 °C. IR (KBr) ν 3179, 2932, 1676, 1647, 1596, 1546 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20–1.35 (m, 6H, CH_2), 1.72–1.75 (m, 2H, CH_2), 2.02–2.09 (m, 2H, CH_2), 3.74–3.81 (m, 1H, CH), 4.56 (d, J=8.8 Hz, 1H, NH), 7.28–7.30 (m, 1H, ArH), 7.39–7.40 (m, 2H, ArH), 7.57–7.60 (m, 1H, ArH), 7.66–7.71 (m, 2H, ArH), 7.97 (d, J=7.6 Hz, 1H, ArH), 8.16 (d, J=7.6 Hz, 1H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.9, 169.6, 158.9, 143.1, 134.0, 133.6, 133.5, 133.4, 133.1, 132.4, 131.1, 130.1, 127.8, 126.6, 126.4, 125.3, 97.6, 52.7, 34.3, 34.1, 25.5, 25.0. HRMS (m/z) calcd for $C_{24}H_{20}BrNO_3$ (M^+) 449.0627, found 449.0629.

*4.1.9. 3-(2-Bromo-5-fluorophenyl)-2-(tert-butylamino)-4H-furo[3,2-c]chromen-4-one (**4i**).* Yellow solid; mp: 197–199 °C. IR (KBr) ν 3368, 2959, 1754, 1601, 1534, 1478 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.41 (s, 9H, CH_3), 3.86 (s, 1H, NH), 7.01–7.06 (m, 1H, ArH), 7.14–7.17 (m, 1H, ArH), 7.36–7.40 (m, 1H, ArH), 7.45–7.52 (m, 2H, ArH), 7.66–7.70 (m, 1H, ArH), 7.85 (d, J=7.6 Hz, 1H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.5, 160.2, 157.6, 155.0, 151.9, 151.0, 134.5, 134.4, 133.6, 133.5, 129.5, 124.6, 120.1, 119.8, 119.4, 117.3, 117.0, 113.0, 111.2, 101.1, 54.5, 30.6. HRMS (m/z) calcd for $C_{21}H_{17}BrFNO_3$ (M^+) 429.0376, found 429.0373.

*4.1.10. 3-(2-Bromo-5-fluorophenyl)-2-(tert-butylamino)-5-methylfuro[3,2-c]quinolin-4(5H)-one (**4j**).* Yellow solid; mp: 163–165 °C. IR (KBr) ν 3382, 2943, 1727, 1620, 1544, 1480 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (s, 9H, CH_3), 3.73 (s, 4H, NH and NCH_3), 6.95–7.00 (m, 1H, ArH), 7.13–7.16 (m, 1H, ArH), 7.29–7.32 (m, 1H, ArH), 7.41–7.51 (m, 2H, ArH), 7.61–7.65 (m, 1H, ArH), 7.94 (d, J=8.0 Hz, 1H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.4, 160.1, 158.9, 154.4, 148.9, 137.2, 134.9, 134.7, 134.1, 134.0, 128.4, 122.4, 120.4, 120.0, 116.9, 116.6, 115.5, 115.1, 113.1, 102.2, 102.2, 54.3, 30.7, 29.4. HRMS (m/z) calcd for $C_{22}H_{20}BrFN_2O_2$ (M^+) 442.0692, found 442.0689.

*4.1.11. 2-(tert-Butylamino)-3-(2-iodophenyl)-4H-furo[3,2-c]chromen-4-one (**4k**).* Yellow solid; mp: 157–159 °C. IR (KBr) ν 3390, 2973, 1738, 1612, 1558, 1485 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.39 (s, 9H, CH_3), 3.77 (s, 1H, NH), 7.11–7.14 (m, 1H, ArH), 7.35–7.38 (m, 2H, ArH), 7.46–7.50 (m, 3H, ArH), 7.85 (d, J=7.2 Hz, 1H, ArH), 8.01 (d, J=8.0 Hz, 1H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.9, 150.0, 147.2, 146.0, 134.9, 131.1, 127.3, 125.2, 124.6, 123.8, 119.8, 115.3, 112.5, 108.4, 106.6, 101.1, 97.1, 49.7, 26.0. HRMS (m/z) calcd for $C_{21}H_{18}INO_3$ (M^+) 459.0331, found 459.0327.

*4.1.12. 2-(2,6-Dimethylphenylamino)-3-(2-iodophenyl)-5-methylfuro[3,2-c]quinolin-4(5H)-one (**4l**).* White solid, mp: 185–187 °C. IR (KBr) ν 3248, 2920, 1678, 1566, 1559, 1519 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.26 (s, 6H, $2CH_3$), 3.74 (s, 3H, NCH_3), 5.61 (s, 1H, NH), 7.02–7.05 (m, 4H, ArH), 7.21–7.26 (m, 1H, ArH), 7.38–7.48 (m, 4H, ArH), 7.78 (d, J=8.0 Hz, 1H, ArH), 7.94 (d, J=8.0 Hz, 1H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.0, 151.2, 148.1, 139.0, 137.2, 136.7, 133.2, 132.1, 129.5, 128.9, 128.5, 128.2, 128.2, 125.3, 122.3, 120.5, 116.2, 115.0, 113.1, 104.4, 102.2, 29.4, 19.0. HRMS (m/z) calcd for $C_{26}H_{21}IN_2O_2$ (M^+) 520.0648, found 520.0644.

4.2. General procedure for the synthesis of compound 5

The compound **4** (0.25 mmol) was added to a pre-dried round-bottomed flask, then CuI (0.025 mmol), L-proline (0.025 mmol), and K_2CO_3 (0.5 mmol) was sequentially added to the flask under nitrogen atmosphere. The mixture was refluxed in anhydrous toluene for 24 h. After reaction, the organic solvent was removed under vacuo and the residue obtained was purified by recrystallization from acetone or by silica gel column chromatography to afford the product **5**.

*4.2.1. 11-(tert-Butyl)chromeno[3′,4′:4,5]furo[2,3-b]indol-6(11H)-one (**5a**).* Purified by recrystallization in acetone. Yellow solid; mp: 264–267 °C. IR (KBr) ν 2977, 1728, 1621, 1535, 1487 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.98 (s, 9H, CH_3), 7.26–7.29 (m, 2H, ArH), 7.31–7.35 (m, 1H, ArH), 7.43–7.47 (m, 2H, ArH), 7.70–7.72 (m, 1H, ArH), 7.84 (d, J=7.6 Hz, 1H, ArH), 8.14 (d, J=5.2 Hz, 1H, ArH). Due to the low solubility of **5a** in all commercially available deuterium solvents, the ^{13}C NMR spectra of the compound **5a** was not obtained, but the authenticity of **5a** can be unambiguously confirmed by single-crystal X-ray analysis. HRMS (m/z) calcd for $C_{21}H_{17}NO_3$ (M^+) 331.1208, found 331.1208.

*4.2.2. 11-Cyclohexylchromeno[3′,4′:4,5]furo[2,3-b]indol-6(11H)-one (**5b**).* Purified by recrystallization in acetone. Yellow solid; mp: 223–225 °C. IR (KBr) ν 2960, 1720, 1618, 1542, 1473 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.42–1.55 (m, 3H, CH_2), 1.86–1.90 (m, 1H, CH_2), 2.03–2.06 (m, 2H, CH_2), 2.14–2.22 (m, 4H, CH_2), 4.38–4.44 (m, 1H, CH), 7.28–7.3 9(m, 3H, ArH), 7.44–7.48 (m, 3H, ArH), 7.94 (d, J=7.6 Hz, 1H, ArH), 8.12 (d, J=8.0 Hz, 1H, ArH). Due to the low solubility of **5b** in all commercially available deuterium solvents, the ^{13}C NMR spectra of the compound **5b** was not obtained. HRMS (m/z) calcd for $C_{23}H_{19}NO_3$ (M^+) 357.1365, found 357.1359.

*4.2.3. 11-(2,6-Dimethylphenyl)chromeno[3′,4′:4,5]furo[2,3-b]indol-6(11H)-one (**5c**).* Yellow solid; mp: 235–237 °C. IR (KBr) ν 2920, 1746, 1621, 1544, 1462 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.06 (s, 6H, CH_3), 7.01 (d, J=8.0 Hz, 1H, ArH), 7.32–7.41 (m, 5H, ArH), 7.44–7.55 (m, 3H, ArH), 7.86 (d, J=8.0 Hz, 1H, ArH), 8.24 (d, J=7.6 Hz, 1H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.6, 156.0, 154.9, 151.9, 138.4, 137.8, 132.5, 129.9, 129.5, 129.1, 124.7, 123.3, 122.0, 121.5, 120.3, 119.2, 117.5, 113.9, 111.3, 108.8, 100.0, 18.0. HRMS (m/z) calcd for $C_{25}H_{17}NO_3$ (M^+) 379.1208, found 379.1208.

*4.2.4. 11-(tert-Butyl)-5-methyl-5H-indolo[3′,2′:4,5]furo[3,2-c]quinolin-6(11H)-one (**5d**).* Yellow solid; mp: 251–252 °C. IR (KBr) ν 2977, 1651, 1618, 1580, 1532 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.94 (s, 9H, CH_3), 3.80 (s, 3H, NCH_3), 7.24–7.26 (m, 2H, ArH), 7.39–7.43 (m, 1H, ArH), 7.58–7.62 (m, 1H, ArH), 7.69–7.71 (m, 1H, ArH), 7.87–7.89 (m, 1H, ArH), 7.80–8.03 (m, 2H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.0, 155.4, 153.4, 137.4, 137.2, 128.1, 122.4, 121.9, 121.6, 120.6, 120.6, 120.2, 115.2, 114.2, 114.1, 112.7, 101.0, 58.6, 30.2, 29.7. HRMS (m/z) calcd for $C_{22}H_{20}N_2O_2$ (M^+) 344.1525, found 344.1522.

*4.2.5. 11-Cyclohexyl-5-methyl-5H-indolo[3′,2′:4,5]furo[3,2-c]quinolin-6(11H)-one (**5e**).* Yellow solid; mp: 214–216 °C. IR (KBr) ν 2934, 1656, 1625, 1584, 1542 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.65–1.70 (m, 2H, CH_2), 1.93–1.97 (m, 1H, CH_2), 2.01–2.13 (m, 2H, CH_2), 2.22–2.30 (m, 5H, CH_2), 3.97 (s, 3H, NCH_3), 4.44–4.52 (m, 1H, CH), 7.36–7.44 (m, 3H, ArH), 7.51–7.53 (m, 1H, ArH), 7.56–7.61 (m, 2H,

ArH), 8.15 (d, J=7.6 Hz, 1H, ArH), 8.29 (d, J=8.8 Hz, 1H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.5, 155.1, 153.9, 137.4, 137.1, 128.1, 122.4, 121.8, 121.6, 120.7, 120.3, 119.6, 115.2, 114.2, 113.2, 110.4, 100.8, 55.6, 32.4, 29.7, 26.2, 25.7. HRMS (m/z) calcd for $C_{24}H_{22}N_2O_2$ (M^+) 370.1681, found 370.1682.

*4.2.6. 11-(2,6-Dimethylphenyl)-5-methyl-5H-indolo[3′,2′:4,5]furo [3,2-c]quinolin-6(11H)-one (**5f**).* Yellow solid; mp: 152–155 °C. IR (KBr) ν 2921, 1651, 1582, 1549, 1495 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.93 (s, 6H, CH_3), 3.80 (s, 3H, NCH_3), 6.93 (d, J=8.4 Hz, 1H, ArH), 7.24–7.34 (m, 3H, ArH), 7.37–7.40 (m, 2H, ArH), 7.45–7.48 (m, 1H, ArH), 7.54–7.58 (m, 1H, ArH), 7.68 (d, J=8.4 Hz, 1H, ArH), 7.88 (d, J=7.6 Hz, 1H, ArH), 8.05 (d, J=7.6 Hz, 1H, ArH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 158.8, 154.8, 154.2, 138.1, 137.5, 132.5, 130.4, 129.7, 129.4, 129.4, 123.4, 123.2, 122.1, 121.2, 120.5, 119.4, 116.4, 113.4, 113.2, 111.6, 100.2, 30.0, 17.8. HRMS (m/z) calcd for $C_{26}H_{20}N_2O_2$ (M^+) 392.1525, found 392.1528.

*4.2.7. 5-(tert-Butyl)-5H-naphtho[2′,3′:4,5]furo[2,3-b]indole-7,12-dione (**5g**).* Red solid; mp: 190–193 °C. IR (KBr) ν 2932, 1675, 1649, 1576, 1523 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.75 (s, 9H, CH_3), 7.13–7.23 (m, 2H, ArH), 7.63–7.71 (m, 2H, ArH), 7.76 (d, J=8.4 Hz, 1H, ArH), 7.85 (d, J=7.2 Hz, 1H, ArH), 7.89–7.93 (m, 2H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.9, 171.7, 158.8, 149.7, 140.1, 134.1, 133.6, 133.0, 132.7, 130.2, 127.0, 126.8, 124.1, 122.8, 121.7, 120.0, 114.8, 103.1, 59.5, 30.0. HRMS (m/z) calcd for $C_{22}H_{17}NO_3$ (M^+) 343.1208, found 343.1203.

*4.2.8. 5-Cyclohexyl-5H-naphtho[2′,3′:4,5]furo[2,3-b]indole-7,12-dione (**5h**).* Red solid; mp: 245–248 °C. IR (KBr) ν 2918, 1670, 1634, 1587, 1530 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.42–1.54 (m, 3H, CH_2), 1.81–1.84 (m, 1H, ArH), 2.01–2.04 (m, 2H, CH_2), 2.17–2.22 (m, 4H, CH_2), 4.33–4.40 (m, 1H, CH), 7.31–7.46 (m, 3H, ArH), 7.67–7.77 (m, 2H, ArH), 8.18–8.25 (m, 3H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.8, 171.8, 158.5, 150.1, 140.1, 134.1, 133.5, 133.0, 132.7, 127.6, 126.8, 126.8, 124.4, 122.6, 121.9, 119.0, 111.1, 102.8, 56.0, 31.9, 26.1, 25.3. HRMS (m/z) calcd for $C_{24}H_{19}NO_3$ (M^+) 369.1365, found 369.1367.

4.3. General procedure for the one-pot synthesis of 5

The mixture of substrate **1** (0.5 mmol), aldehyde **2** (0.5 mmol), and isocyanide **3** (0.6 mmol) was stirred at 110 °C in anhydrous toluene. Upon completion of the reaction as monitored by TLC, CF_3COOH (8 μL, 0.2 equiv) was added to the reaction mixture at room temperature. After that, CuI (0.05 mmol), L-proline (0.05 mmol), and K_2CO_3 (1 mmol) was added sequentially under nitrogen atmosphere and the mixture was refluxed for 24 h. After reaction, the organic solvent was removed under vacuo and the residue obtained was purified by recrystallization from acetone or by silica gel column chromatography to afford the pure products **5**. The compound **4** (0.25 mmol) was added to a pre-dried round-bottomed flask, then CuI (0.025 mmol), L-proline (0.025 mmol), and K_2CO_3 (0.5 mmol) was sequentially added to the flask under nitrogen atmosphere. The mixture was refluxed in anhydrous toluene for 24 h. After reaction, the organic solvent was removed under vacuo and the residue obtained was purified by recrystallization from acetone or by silica gel column chromatography to afford the product **5**.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.05.101.

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