Tetrahedron 67 (2011) 5142–5149

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

A facile synthesis of indole–furan conjugates via integration of convergent and linear domino reactions

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ARTICLE INFO

Article history:
Received 24 March 2011
Received in revised form 6 May 2011
Accepted 13 May 2011
Available online 19 May 2011

Keywords:
Domino reaction
Friedel–Crafts alkylation
Paal–Knorr cyclization
Furan
Indole
Biheteroaryls

ABSTRACT

The convergent and linear domino reactions have been first integrated, for the first time, to provide an efficient synthesis of indole–furan conjugates from indoles, methyl ketones, and 1,3-dicarbonyl compounds.

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1. Introduction

In modern synthetic chemistry, a growing trend toward green and sustainable synthesis has been well illustrated by domino reactions,[1] which allow the direct synthesis of complex molecules in a highly efficient way. However, as many reactions are not compatable with each other in one domino process, a practical synthetic strategy usually has to consist of step-wise reactions. In this context, we envision that a series of coupled domino processes could be rationally designed for target molecules to minimize reaction steps and maximize synthetic efficiency.

Up to now, most domino reactions reported in the literature proceed along a linear route (Fig. 1a).[1] Because it would be more efficient if two or more parallel domino routes could coexist in one-pot and converge on the final product, we have developed a self-sorting domino reaction and a focusing domino reaction (Fig. 1b and c).[2] Considering the necessity of step-wise reactions for complex architectures, it would be particularly attractive if convergent and linear domino reactions could be efficiently integrated in two-step reactions to afford the desired products (Fig. 1d and e).

Because of the pharmacological importance of heterocycles, their efficient and elegant synthesis would be an ideal testing ground for demonstrating the power and potential of this strategy. The indole and furan skeletons are privileged scaffolds in medicinal chemistry, and they have been widely found in natural products and therapeutic agents.[3] As the combination of two or more different heterocyclic moieties in a single molecule would enhance biological activity significantly,[4] a series of promising biheteroaryls containing indole or furan skeletons have been prepared.[5] However, there are only few examples reported in the literature for the synthesis of 3-(furan-3-yl or 4-yl)indole derivatives,[6] partly due to the difficulty in obtaining the starting materials. Considering the potential biological activity of this class of biheterocyclic compounds, it is highly desirable to develop an efficient and practical method for their synthesis.

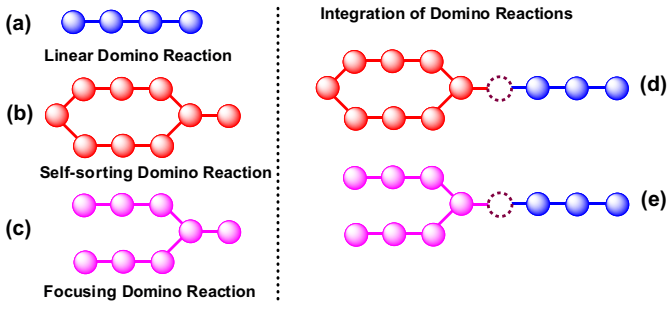

Fig. 1. Integration of convergent and linear domino reactions.

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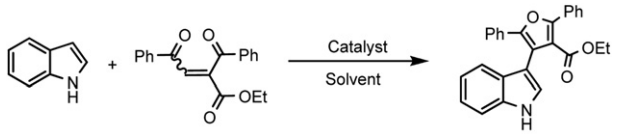
doi:10.1016/j.tet.2011.05.058

Recently, we have established two efficient convergent domino reactions for the preparation of various substituted 1,4-enediones: (a) homo-coupling of methyl ketones via self-sorting domino reaction; (b) hetero-coupling of 1,3-dicarbonyl compounds and methyl ketones or terminal aryl alkenes via focusing domino reaction (Scheme 1). Remarkably, both of them start from readily available, inexpensive substrates with good tolerance of various functional groups. Inspired by these discoveries, we envisaged that exposure of indoles to these 1,4-enedione electrophiles would undergo linear domino Friedel–Crafts alkylation/Paal–Knorr cyclization to afford the expected 3-(furan-3-yl or 4-yl)indole derivatives. In combination with the convergent domino synthesis of 1,4-enediones, this linear domino Friedel–Crafts alkylation/Paal–Knorr cyclization would enable a two-step synthesis of diverse 3-(furan-3-yl or 4-yl)indole derivatives.

2. Results and discussion

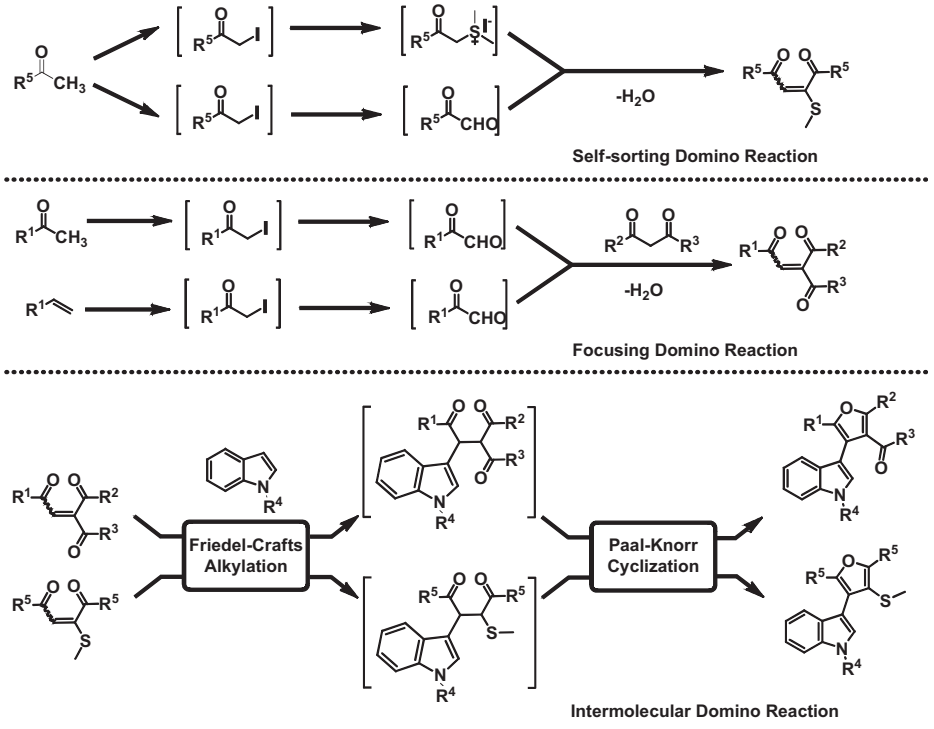
Our initial investigations were focused on the systematic evaluation of different catalysts for the desired domino Friedel–Crafts alkylation/Paal–Knorr cyclization of indole **1a** and 1,4-enedione **2a**[7] (Table 1). Different Lewis acids were first examined in this reaction, but the desired product **4a** was obtained in very low yields, such as $InCl_3$, $AlCl_3$, $ZnCl_2$, $CuCl_2$, $Cu(CF_3SO_3)_2$, and $FeCl_3$ (Table 1, entries 1–6). We reasoned that the poor catalytic activity of Lewis acids might be ascribed to their weak acidity and sensitivity of water. Accordingly, we began searching for the appropriate Brønsted acids that would readily catalyze the domino reaction. Gratifyingly, switching the catalyst to CH_3SO_3H (0.1 equiv) furnished the product **4a** in 74% yield after 12 h in MeCN at reflux (entry 7). Increasing the loading of catalyst to 0.5 equiv, the reaction could complete in less than 8 h with quantitative yield (entry 9). Other sulfonic acids tested could also promote this domino reaction, although lower yields were obtained (entries 10–12). When the reaction was carried out in the presence of other Brønsted acids, such as HCl, HOAc, and CF_3CO_2H, the yields decreased dramatically (entries 13–15). The reaction was also studied in other solvents, however, the yield of the desired product was decreased (entries 16–22). Thus, the use of CH_3SO_3H (0.5 equiv) in MeCN at reflux was found to be the most efficient conditions.

Table 1
Optimization of the reaction conditions[a]



Entry	Catalyst (equiv)	Solvent	Temp (°C)	Time (h)	Yield[b] (%)
1	$InCl_3$ (0.1)	CH_2Cl_2	40	12	27
2	$AlCl_3$ (0.1)	CH_2Cl_2	40	12	5
3	$ZnCl_2$ (0.1)	CH_2Cl_2	40	12	9
4	$CuCl_2$ (0.1)	CH_2Cl_2	40	12	0
5	$Cu(CF_3SO_3)_2$ (0.1)	CH_2Cl_2	40	12	20
6	$FeCl_3$ (0.1)	CH_2Cl_2	40	12	16
7	CH_3SO_3H (0.1)	CH_3CN	81	12	74
8	CH_3SO_3H (0.3)	CH_3CN	81	12	86
9	CH_3SO_3H (0.5)	CH_3CN	81	8	99
10	H_2SO_4 (0.5)	CH_3CN	81	8	90
11	CF_3SO_3H (0.5)	CH_3CN	81	8	82
12	PTSA (0.5)	CH_3CN	81	8	91
13	HCl (0.5)	CH_3CN	81	8	8
14	HOAc (0.5)	CH_3CN	81	8	0
15	CF_3COOH (0.5)	CH_3CN	81	8	15
16	CH_3SO_3H (0.5)	Toluene	110	8	49
17	CH_3SO_3H (0.5)	DCE	84	8	61
18	CH_3SO_3H (0.5)	CH_2Cl_2	40	8	90
19	CH_3SO_3H (0.5)	$CHCl_3$	62	8	59
20	CH_3SO_3H (0.5)	EtOAc	77	8	70
21	CH_3SO_3H (0.5)	DMSO	80	8	0
22	CH_3SO_3H (0.5)	EtOH	78	8	85

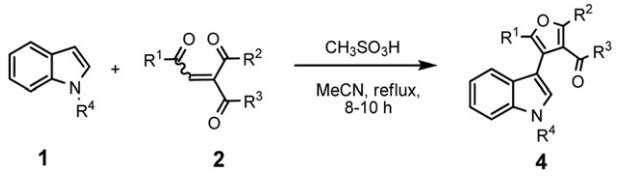
[a] Reaction conditions: **1a** (1.2 mmol) and **2a** (1.0 mmol) in 5 mL of solvent under an atmosphere of argon.
[b] Isolated yields. PTSA=*p*-toluenesulfonic acid; DCE=1,2-dichloroethane.



Scheme 1. Two-step synthesis of indole–furan conjugates.

Encouraged by the successful synthesis of 3-furyl-substituted indole **4a**, a series of unsymmetrical 1,4-enediones **2** were used to explore the scope of this synthetic strategy under optimal conditions. In general, this reaction showed broad tolerance for aromatic R^1 substituents (Table 2, entries 1–13). For example, substrates with electron-neutral (H, CH_3), electron-rich (OCH_3), electron-deficient (NO_2), and sterically hindered (1-naphthyl, 2-naphthyl) R^1 substituents all reacted efficiently to afford the desired products in excellent yields (Table 2, entries 1–6). Much to our satisfaction, high yields were also obtained with haolo-genated and hydroxylated substrates (Table 2, entries 7–11). The heteroaryl groups for R^1 were also investigated, such as 3-thienyl group, the corresponding product could be obtained in an excellent yield (Table 2, entry 12). However, only 26% yield was obtained with 2-benzofuryl group (Table 2, entry 13), while an intricate mixture of byproducts was formed with 2-furyl or 1-methyl-1*H*-pyrrol-3-yl group (Table 2, entries 14–15). We have also examined the effect on the yields by varying the electronic and steric nature of R^2, R^3, and R^4 substituents, while retaining R^1 as a phenyl group. As to the substituents R^2, various electron-donating, electron-withdrawing, and halogen groups on the aryl ring were compatible with the reaction conditions, and the corresponding products were obtained in high yields (Table 2, entries 16–20). Unfortunately, the yield was much lower with 2-furyl group for R^2 (Table 2, entry 21). To our delight, when R^2 and R^3 both were phenyl or methyl groups, the reaction proceeded cleanly to give the desired products (Table 2, entries 22–23). Furthermore, an excellent yield was observed when 1-methyl-1*H*-indole **1b** was used as a substrate (Table 2, entry 24).

Table 2
Reaction scope of indoles **1** and 1,4-enediones **2**[a]



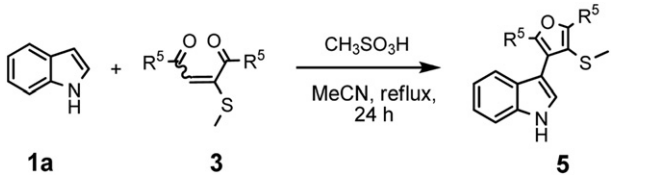
1 **2** **4**

Entry	R^1	R^2	R^3	R^4	**4**	Yield[b](%)
1	Ph	Ph	OEt	H	**4a**	99
2	4-MeC_6H_4	Ph	OEt	H	**4b**	94
3	4-MeOC_6H_4,	Ph	OEt	H	**4c**	96
4	4-$NO_2C_6H_4$	Ph	OEt	H	**4d**	92
5	1-Naphthyl	Ph	OEt	H	**4e**	85
6	2-Naphthyl	Ph	OEt	H	**4f**	95
7	4-ClC_6H_4	Ph	OEt	H	**4g**	84
8	3,4-$Cl_2C_6H_3$	Ph	OEt	H	**4h**	82
9	4-BrC_6H_4	Ph	OEt	H	**4i**	89
10	4-FC_6H_4	Ph	OEt	H	**4j**	90
11	4-OHC_6H_4	Ph	OEt	H	**4k**	83
12	3-Thienyl	Ph	OEt	H	**4l**	92
13	2-Benzofuryl	Ph	OEt	H	**4m**	26
14	2-Furyl	Ph	OEt	H	**4n**	—[c]
15	1-Methyl-1*H*-pyrrol-3-yl	Ph	OEt	H	**4o**	—[c]
16	Ph	3,4,5-$(MeO)_3$–C_6H_2	OEt	H	**4p**	85
17	Ph	4-$NO_2C_6H_4$	OEt	H	**4q**	97
18	Ph	3-$NO_2C_6H_4$	OEt	H	**4r**	95
19	Ph	4-ClC_6H_4	OMe	H	**4s**	92
20	Ph	4-FC_6H_4	OMe	H	**4t**	87
21	Ph	2-Furyl	OEt	H	**4u**	24
22	Ph	Ph	Ph	H	**4v**	94
23	Ph	Me	Me	H	**4w**	96
24	Ph	Ph	OEt	Me	**4x**	98

[a] Reaction conditions: **1** (1.2 mmol), **2** (1.0 mmol), and CH_3SO_3H (0.5 mmol) in MeCN (5 mL) at reflux for 8–10 h.
[b] Isolated yields.
[c] An intricate mixture of byproducts was formed.

Next, we extend this domino process to α-methylthio-substituted 1,4-enediones with the aim of introducing methylthio groups into the biheteroaryls. The methylthio-substituted heterocycles are particularly attractive since they are found as structural elements in many bioactive compounds as well as electronic, magnetic, and optical materials.[8] In addition, they are also versatile intermediates for further transformations, such as transition-metal-catalyzed cross-coupling reaction,[9] addition–elimination,[10] and electrophilic cyclization.[11] Therefore, the development of an efficient and convenient protocol for their synthesis remains an area of ongoing interest. Because of the electron-donating property of methylthio group compared to carbonyl group, the electrophilicity of α-methylthio-substituted 1,4-enediones was lower toward Friedel–Crafts alkylation and a prolonged reaction time was needed (Table 3, 24 h). In addition, the nature of substituents in the aromatic ring shows strong influence on the reaction efficiency. For example, substrates with electron-neutral (H–, Me–) and electron-withdrawing (NO_2–) groups gave higher yields (Table 3, entries 1–3) than electron-donating counterpart (MeO–) (Table 3, entry 4). Significantly, the steric (2-naphthyl) and halogen substituted (Cl–, Br–, F–) substrates could give their corresponding products in high yields (Table 3, entries 5–8). Furthermore, heterocyclic substrate for 3-thiophenyl group could also work well under this condition (Table 3, entry 9). Unfortunately, an intricate mixture of byproducts was formed with 2-furyl group (Table 3, entry 10).

Table 3
Reaction scope of α-methylthio-substituted 1,4-enediones **3a**[a]

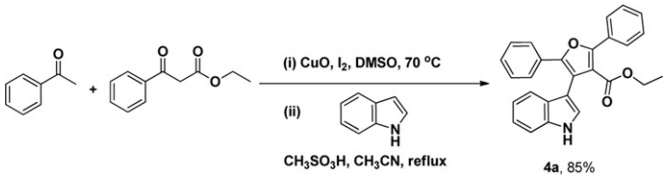


1a **3** **5**

Entry	**3**	R^5	**5**	Yield[b](%)
1	**3a**	Ph	**5a**	83
2	**3b**	4-MeC_6H_4	**5b**	86
3	**3c**	4-$NO_2C_6H_4$	**5c**	97
4	**3d**	4-MeOC_6H_4	**5d**	47
5	**3e**	2-Naphthyl	**5e**	91
6	**3f**	4-ClC_6H_4	**5f**	89
7	**3g**	4-BrC_6H_4	**5g**	87
8	**3h**	4-FC_6H_4	**5h**	92
9	**3i**	3-Thienyl	**5i**	82
10	**3j**	2-Furyl	**5j**	—[c]

[a] Reaction conditions: **1a** (1.2 mmol), **3** (1.0 mmol), and CH_3SO_3H (0.5 mmol) in MeCN (5 mL) at reflux for 24 h.
[b] Isolated yields.
[c] An intricate mixture of byproducts was formed.

Finally, we conducted the synthesis of **4a** as a direct two-step protocol without purification of the 1,4-enedione intermediates, the desired product was obtained in 85% overall yield on a 5 mmol scale (Scheme 2), which displayed the high efficiency of this synthetic strategy.



Scheme 2. A telescoped two-step synthesis of **4a**.

3. Conclusion

In summary, we have developed an efficient methodology for the synthesis of 3-(furan-3-yl or 4-yl)indole derivatives via the integration of convergent and linear domino reactions. It should be noted that this protocol has significant advantages over previous methods for the simple substrates and operational simplicity. Therefore, we believe that this protocol would be very useful in synthetic chemistry, as well as in medicinal chemistry.

4. Experimental section

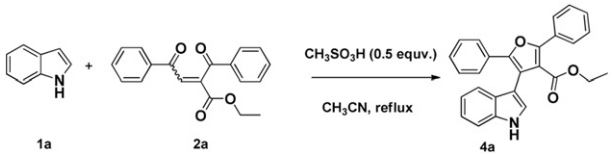
4.1. General methods

All reagents were purchased from commercial suppliers and used without further purification. Reactions were carried out under an argon atmosphere unless indicated otherwise. Solvents were dried according to published methods and distilled before use. IR spectra were recorded on an infrared spectrometer as KBr pellets with absorption in cm^{-1}. ^1H spectra were recorded in $CDCl_3$ on 400/600 MHz NMR spectrometers and resonances (δ) are given in parts per million relative to tetramethylsilane. Data are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, dd=doublet of doublets, m=multiplet), coupling constants (Hz), and integration. ^{13}C spectra were recorded in $CDCl_3$ on 100/150 MHz spectrometers and resonances (δ) are given in ppm relative to the center line of a triplet at 77.0 ppm of chloroform-*d*. HRMS were obtained on an FT-ICR MS equipped with an electrospray source. Column chromatography was performed on silica gel (200–300 mesh).

4.2. Synthesis of 1,4-enediones 2 and 3

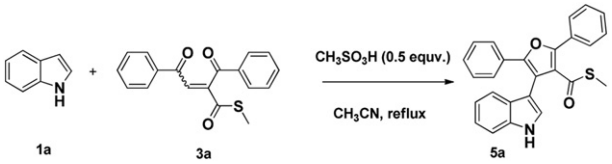
The preparation and characterization of the 1,4-enediones **2** and **3** have been previously reported.[2]

4.3. General procedure for the preparation of 4 (4a as an example)



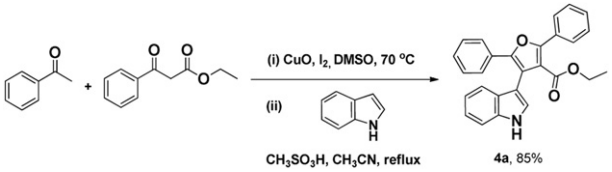
CH_3SO_3H (48.0 mg, 0.5 mmol) was added to a solution of 1*H*-indole **1a** (140 mg, 1.2 mmol) and ethyl 2-benzoyl-4-oxo-4-phenylbut-2-enoate **2a** (308 mg, 1.0 mmol) in CH_3CN (5 mL) under argon. The reaction mixture was stirred at reflux for 8 h and monitored to completion by TLC analysis. After cooling to room temperature, saturated aq $NaHCO_3$ (10 mL) was then added and the aqueous mixture was extracted with diethyl acetate (3×20 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: petroleum ether/EtOAc) to afford the desired product **4a** (403 mg, 99%) as a yellow solid. ^1H NMR ($CDCl_3$, 600 MHz): δ (ppm) 8.29 (br s, 1H), 7.93 (d, *J*=7.2 Hz, 2H), 7.54 (d, *J*=7.2 Hz, 2H), 7.47 (t, *J*=7.2 Hz, 2H), 7.42–7.39 (m, 3H), 7.26–7.17 (m, 5H), 7.06 (t, *J*=7.2 Hz, 1H), 3.99 (q, *J*=7.2 Hz, 2H), 0.78 (t, *J*=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 164.8, 153.8, 149.2, 136.0, 130.4, 129.9, 128.9, 128.3, 128.2, 127.5, 127.3, 125.5, 124.0, 122.0, 120.0, 119.7, 117.9, 115.9, 111.1, 107.4, 60.6, 13.2; IR (KBr): 3339, 1699, 1486, 1235, 1067, 767, 747, 691 cm^{-1}; HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{27}H_{22}NO_3$: 408.1594; found: 408.1599.

4.4. General procedure for the preparation of 5 (5a as an example)



CH_3SO_3H (48.0 mg, 0.5 mmol) was added to a solution of 1*H*-indole **1a** (140 mg, 1.2 mmol) and 2-(methylthio)-1,4-diphenylbut-2-ene-1,4-dione **3a** (282 mg, 1.0 mmol) in CH_3CN (5 mL) under argon. The reaction mixture was stirred at reflux for 24 h and monitored to completion by TLC analysis. After cooling to room temperature, saturated aq $NaHCO_3$ (10 mL) was then added and the aqueous mixture was extracted with diethyl acetate (3×20 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: petroleum ether/EtOAc) to afford the desired product **5a** (316 mg, 83%) as a white solid. ^1H NMR ($CDCl_3$, 600 MHz): δ (ppm) 8.33 (br s, 1H), 8.27 (d, *J*=7.2 Hz, 2H), 7.56 (d, *J*=7.2 Hz, 1H), 7.49–7.45 (m, 3H), 7.39 (s, 1H), 7.35 (t, *J*=7.2 Hz, 1H), 7.32 (d, *J*=7.8 Hz, 1H), 7.24–7.14 (m, 5H), 7.05 (t, *J*=7.2 Hz, 1H), 1.94 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 152.0, 148.6, 136.0, 130.8, 130.7, 128.4, 128.2, 127.8, 127.2, 126.8, 126.1, 125.2, 124.2, 122.2, 120.2, 119.9, 117.7, 111.2, 107.4, 18.8; IR (KBr): 3344, 1697, 1501, 1236, 841, 751, 695 cm^{-1}; HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{25}H_{20}NOS$: 382.1260; found: 382.1255.

4.5. A telescoped two-step synthesis of 4a (5 mmol scale)



A mixture of acetophenone (0.60 g, 5.0 mmol), ethyl benzoylacetate (0.99 g, 5.0 mmol), iodine (1.40 g, 5.5 mmol), and CuO (0.44 g, 5.5 mmol) in 20 mL of DMSO was stirred at 70 °C for 12 h. After the reaction completed (monitored by TLC), the reaction mixture was cooled to room temperature, then filtered through a layer of silica gel and eluted with EtOAc. The filtrate was diluted with water and the aqueous phase was extracted with additional EtOAc (3×50 mL), then the combined organic layers were washed with $Na_2S_2O_3$ (5% w/w, aq) and brine successively. After drying over Na_2SO_4 and evaporation, the crude product was dissolved in CH_3CN (20 mL) under argon, then 1*H*-indole **1a** (0.70 g, 6.0 mmol) and CH_3SO_3H (0.24 g, 2.5 mmol) were added. The reaction mixture was stirred at reflux for 8 h and monitored to completion by TLC analysis. After cooling to room temperature, saturated aq $NaHCO_3$ (40 mL) was added and the aqueous mixture was extracted with diethyl acetate (3×50 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: petroleum ether/EtOAc) to afford the desired product **4a** (1.73 g, 85%) as a yellow solid.

4.6. Spectroscopic data

*4.6.1. Ethyl 4-(1H-indol-3-yl)-2,5-diphenylfuran-3-carboxylate (**4a**).* Yield 99%; yellow solid; ^1H NMR ($CDCl_3$, 600 MHz): δ (ppm) 8.29 (br s, 1H), 7.93 (d, *J*=7.2 Hz, 2H), 7.54 (d, *J*=7.2 Hz, 2H), 7.47 (t,

J=7.2 Hz, 2H), 7.42–7.39 (m, 3H), 7.26–7.17 (m, 5H), 7.06 (t, J=7.2 Hz, 1H), 3.99 (q, J=7.2 Hz, 2H), 0.78 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 164.8, 153.8, 149.2, 136.0, 130.4, 129.9, 128.9, 128.3, 128.2, 127.5, 127.3, 125.5, 124.0, 122.0, 120.0, 119.7, 117.9, 115.9, 111.1, 107.4, 60.6, 13.2; IR (KBr): 3339, 1699, 1486, 1235, 1067, 767, 747, 691 cm^{-1}; HRMS (ESI): m/z [M+H]$^+$ calcd for $C_{27}H_{22}NO_3$: 408.1594; found: 408.1599.

*4.6.2. Ethyl 4-(1H-indol-3-yl)-2-phenyl-5-p-tolylfuran-3-carboxylate (**4b**).* Yield 94%; yellow solid; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 8.27 (br s, 1H), 7,93 (d, J=7.8 Hz, 2H), 7.47–7.39 (m, 7H), 7.21 (t, J=7.2 Hz, 2H), 7.06 (t, J=7.2 Hz, 1H), 7.00 (d, J=7.8 Hz, 2H), 3.98 (q, J=7.2 Hz, 2H), 2.27 (s, 3H), 0.78 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 164.8, 153.6, 149.6, 137.4, 136.0, 130.0, 129.0, 128.8, 128.3, 127.7, 127.6, 127.5, 125.5, 123.8, 122.1, 120.2, 119.9, 117.9, 115.1, 111.0, 108.0, 60.5, 21.2, 13.3; IR (KBr): 3380, 1702, 1488, 1231, 1135, 762 cm^{-1}; HRMS (ESI): m/z [M+H]$^+$ calcd for $C_{28}H_{24}NO_3$: 422.1751; found: 422.1745.

*4.6.3. Ethyl 4-(1H-indol-3-yl)-5-(4-methoxyphenyl)-2-phenylfuran-3-carboxylate (**4c**).* Yield 96%; yellow solid; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 8.40 (br s, 1H), 7.91 (d, J=7.8 Hz, 2H), 7.47–7.43 (m, 4H), 7.39–7.34 (m, 3H), 7.18–7.17 (m, 2H), 7.04 (t, J=7.2 Hz, 1H), 6.70 (d, J=8.4 Hz, 2H), 3.99 (q, J=7.2 Hz, 2H), 3.70 (s, 3H), 0.78 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 164.9, 158.9, 153.3, 149.4, 136.0, 130.0, 128.7, 128.2, 127.5, 127.4, 127.0, 124.0, 123.3, 122.0, 120.0, 119.8, 117.8, 114.3, 113.7, 111.1, 107.7, 60.6, 55.1, 13.3; IR (KBr): 3374, 1703, 1606, 1493, 1251, 833, 747, 689 cm^{-1}; HRMS (ESI): m/z [M+H]$^+$ calcd for $C_{28}H_{24}NO_4$: 438.1700; found: 438.1706.

*4.6.4. Ethyl 4-(1H-indol-3-yl)-5-(4-nitrophenyl)-2-phenylfuran-3-carboxylate (**4d**).* Yield 92%; yellow solid; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 8.41 (br s, 1H), 8.05 (d, J=9.0 Hz, 2H), 7.93 (d, J=7.8 Hz, 2H), 7.68 (d, J=7.2 Hz, 2H), 7.51–7.46 (m, 4H), 7.36 (s, 1H), 7.32 (d, J=7.8 Hz, 1H), 7.26–7.24 (m, 1H), 7.08 (t, J=7.2 Hz, 1H), 4.02 (q, J=7.2 Hz, 2H), 0.83 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 164.3, 155.4, 146.7, 146.0, 136.2, 136.0, 129.5, 129.3, 128.4, 127.6, 126.6, 125.4, 124.3, 123.7, 122.4, 120.2, 120.0, 119.7, 118.5, 111.4, 106.4, 60.9, 13.3; IR (KBr): 3363, 1694, 1595, 1511, 1338, 1237, 1110, 855, 747, 693 cm^{-1}; HRMS (ESI): m/z [M+H]$^+$ calcd for $C_{27}H_{21}N_2O_5$: 453.1445; found: 453.1450.

*4.6.5. Ethyl 4-(1H-indol-3-yl)-5-(naphthalen-1-yl)-2-phenylfuran-3-carboxylate (**4e**).* Yield 85%; brown oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.09 (d, J=8.4 Hz, 1H), 7.95–7.94 (m, 3H), 7.81 (d, J=8.4 Hz, 1H), 7.76 (d, J=8.4 Hz, 1H), 7.47–7.35 (m, 7H), 7.24–7.18 (m, 2H), 7.09 (t, J=7.2 Hz, 1H), 6.97 (t, J=7.2 Hz, 1H), 6.87 (s, 1H), 4.05 (q, J=7.2 Hz, 2H), 0.80 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 165.2, 154.8, 149.5, 135.7, 133.6, 131.7, 129.9, 129.1, 128.9, 128.8, 128.3, 128.2, 127.7, 127.4, 127.3, 126.4, 125.9, 125.0, 123.8, 121.7, 119.5, 118.5, 116.5, 111.0, 107.2, 60.9, 13.3; IR (KBr): 3413, 1708, 1233, 1110, 765, 743, 692 cm^{-1}; HRMS (ESI): m/z [M+H]$^+$ calcd for $C_{31}H_{24}NO_3$: 458.1751; found: 458.1759.

*4.6.6. Ethyl 4-(1H-indol-3-yl)-5-(naphthalen-2-yl)-2-phenylfuran-3-carboxylate (**4f**).* Yield 95%; yellow solid; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 8.30 (br s, 1H), 8.11 (s, 1H), 7.98 (d, J=7.2 Hz, 2H), 7.72–7.67 (m, 2H), 7.60–7.55 (m, 2H), 7.50 (t, J=7.2 Hz, 2H), 7.46–7.40 (m, 5H), 7.31 (d, J=1.8 Hz, 1H), 7.23 (t, J=7.2 Hz, 1H), 7.05 (t, J=7.2 Hz, 1H), 4.01 (q, J=7.2 Hz, 2H), 0.80 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 164.8, 154.1, 149.3, 136.0, 133.1, 132.5, 129.9, 129.0, 128.3, 128.2, 127.9, 127.7, 127.6, 127.5, 127.4, 126.2, 126.0, 124.5, 124.1, 123.5, 122.1, 120.1, 119.9, 118.0, 116.4, 111.1, 107.5, 60.7, 13.3; IR (KBr): 3472, 1727, 1197, 1117, 1063, 747 cm^{-1}; HRMS (ESI): m/z [M+H]$^+$ calcd for $C_{31}H_{24}NO_3$: 458.1751; found: 458.1757.

*4.6.7. Ethyl 5-(4-chlorophenyl)-4-(1H-indol-3-yl)-2-phenylfuran-3-carboxylate (**4g**).* Yield 84%; yellow solid; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 8.34 (br s, 1H), 7.91 (d, J=7.8 Hz, 2H), 7.47–7.46 (m, 4H), 7.42–7.40 (m, 2H), 7.36 (d, J=7.8 Hz, 1H), 7.25–7.21 (m, 2H), 7.16–7.15 (m, 2H), 7.07 (t, J=7.8 Hz, 1H), 4.00 (q, J=7.2 Hz, 2H), 0.80 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 164.5, 154.1, 148.2, 136.0, 133.2, 129.8, 129.1, 128.9, 128.5, 128.3, 127.5, 127.2, 126.7, 123.9, 122.3, 120.1, 118.0, 116.3, 111.2, 107.4, 60.6, 13.3; IR (KBr): 3360, 1698, 1483, 1241, 1091, 1069, 1012, 829, 745, 690 cm^{-1}; HRMS (ESI): m/z [M+H]$^+$ calcd for $C_{27}H_{21}ClNO_3$: 442.1204; found: 442.1213.

*4.6.8. Ethyl 5-(3,4-dichlorophenyl)-4-(1H-indol-3-yl)-2-phenylfuran-3-carboxylate (**4h**).* Yield 82%; yellow solid; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 8.48 (br s, 1H), 7.90 (d, J=7.8 Hz, 2H), 7.71 (d, J=1.8 Hz, 1H), 7.47 (t, J=7.8 Hz, 2H), 7.41 (t, J=7.8 Hz, 1H), 7.36–7.32 (m, 2H), 7.24–7.14 (m, 4H), 7.06 (t, J=7.8 Hz, 1H), 4.01 (q, J=7.2 Hz, 2H), 0.81 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 164.5, 154.5, 146.7, 136.0, 132.4, 131.1, 130.3, 130.2, 129.5, 129.3, 128.3, 127.6, 126.9, 124.5, 124.1, 122.3, 120.1, 119.8, 118.0, 117.5, 111.3, 106.7, 60.8, 13.3; IR (KBr): 3366, 1701, 1465, 1338, 1134, 1104, 766 cm^{-1}; HRMS (ESI): m/z [M+H]$^+$ calcd for $C_{27}H_{20}Cl_2NO_3$: 476.0815; found: 476.0814.

*4.6.9. Ethyl 5-(4-bromophenyl)-4-(1H-indol-3-yl)-2-phenylfuran-3-carboxylate (**4i**).* Yield 89%; yellow solid; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 8.43 (br s, 1H), 7.90 (d, J=7.8 Hz, 2H), 7.45 (t, J=7.2 Hz, 2H), 7.41–7.34 (m, 5H), 7.28 (t, J=9.0 Hz, 2H), 7.20–7.17 (m, 2H), 7.05 (t, J=7.2 Hz, 1H), 4.00 (q, J=7.2 Hz, 2H), 0.80 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 164.6, 154.1, 148.2, 137.3, 136.0, 131.4, 129.7, 129.3, 129.1, 128.3, 127.5, 127.1, 126.9, 124.0, 122.2, 121.4, 120.0, 117.9, 116.5, 111.2, 107.1, 60.7, 13.3; IR (KBr): 3387, 1715, 1589, 1246, 1068, 1009, 748 cm^{-1}; HRMS (ESI): m/z [M+H]$^+$ calcd for $C_{27}H_{21}BrNO_3$: 486.0699; found: 486.0706.

*4.6.10. Ethyl 5-(4-fluorophenyl)-4-(1H-indol-3-yl)-2-phenylfuran-3-carboxylate (**4j**).* Yield 90%; yellow solid; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 8.35 (br s, 1H), 7.92 (d, J=7.2 Hz, 2H), 7.52–7.39 (m, 6H), 7.36 (d, J=7.8 Hz, 1H), 7.25–7.20 (m, 2H), 7.06 (t, J=7.2 Hz, 1H), 6.88 (t, J=8.4 Hz, 2H), 4.00 (q, J=7.2 Hz, 2H), 0.80 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 164.6, 162.0 (d, J_{CF}=248.0 Hz), 153.9, 148.5, 136.0, 129.9, 129.0, 128.3, 127.51, 127.4 (d, J_{CF}=8.9 Hz), 127.30, 126.7, 123.9, 122.2, 120.05, 119.97, 117.9, 115.5, 115.3 (d, J_{CF}=20.9 Hz), 111.1, 107.5, 60.6, 13.3; IR (KBr): 3378, 1709, 1493, 1233, 1069, 836, 763 cm^{-1}; HRMS (ESI): m/z [M+H]$^+$ calcd for $C_{27}H_{21}FNO_3$: 426.1500; found: 426.1505.

*4.6.11. Ethyl 5-(4-hydroxyphenyl)-4-(1H-indol-3-yl)-2-phenylfuran-3-carboxylate (**4k**).* Yield 83%; yellow solid; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 8.22 (br s, 1H), 7.90 (d, J=7.8 Hz, 2H), 7.45 (t, J=7.8 Hz, 2H), 7.41–7.38 (m, 5H), 7.23 (d, J=1.8 Hz, 1H), 7.20 (t, J=7.8 Hz, 1H), 7.06 (t, J=7.8 Hz, 1H), 6.61 (d, J=8.4 Hz, 2H), 5.01 (br s, 1H), 3.99 (q, J=7.2 Hz, 2H), 0.79 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 165.1, 155.3, 153.5, 149.5, 136.0, 130.0, 128.8, 128.5, 128.2, 127.5, 127.3, 123.9, 123.3, 122.1, 120.1, 119.9, 117.6, 115.2, 114.1, 111.1, 107.8, 60.7, 13.3; IR (KBr): 3476, 3402, 1730, 1608, 1492, 1333, 1200, 1121, 1068, 835, 749, 690 cm^{-1}; HRMS (ESI): m/z [M+H]$^+$ calcd for $C_{27}H_{22}NO_4$: 424.1543; found: 424.1534.

*4.6.12. Ethyl 4-(1H-indol-3-yl)-2-phenyl-5-(thiophen-3-yl)furan-3-carboxylate (**4l**).* Yield 92%; brown solid; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 8.43 (br s, 1H), 7.92 (d, J=7.8 Hz, 2H), 7.46–7.36

(m, 4H), 7.32–7.30 (m, 2H), 7.18–7.16 (m, 2H), 7.10–7.04 (m, 3H), 4.00 (q, J=7.2 Hz, 2H), 0.79 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 164.7, 153.6, 147.1, 135.9, 131.3, 129.9, 128.9, 128.2, 127.5, 127.4, 125.3, 124.2, 122.0, 121.0, 119.9, 119.8, 117.4, 114.9, 111.1, 107.1, 60.6, 13.2; IR (KBr): 3340, 1690, 1487, 1242, 1118, 1070, 769, 743 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{25}H_{20}NO_3S$: 414.1158; found: 414.1148.

*4.6.13. Ethyl 5-(benzofuran-2-yl)-4-(1H-indol-3-yl)-2-phenylfuran-3-carboxylate (**4m**).* Yield 26%; yellow oil; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 8.22 (d, J=8.4 Hz, 1H), 8.15 (s, 1H), 8.13 (br s, 1H), 7.73 (d, J=7.8 Hz, 1H), 7.67 (d, J=7.8 Hz, 1H), 7.56 (t, J=7.2 Hz, 2H), 7.51–7.33 (m, 7H), 7.25–7.23 (m, 1H), 7.17 (t, J=7.2 Hz, 1H), 4.14 (q, J=7.2 Hz, 2H), 1.03 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 167.7, 155.5, 155.0, 140.9, 139.1, 137.2, 129.0, 128.8, 127.9, 127.3, 126.8, 126.7, 124.5, 124.3, 123.9, 123.1, 122.8, 122.7, 122.0, 121.1, 120.0, 111.4, 110.8, 105.3, 60.9, 13.7; IR (KBr): 3587, 3419, 3267, 1701, 1453, 1319, 1252, 1210, 1157, 751, 739 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{29}H_{22}NO_4$: 448.1543; found: 448.1551.

*4.6.14. Ethyl 4-(1H-indol-3-yl)-5-phenyl-2-(3,4,5-trimethoxyphenyl) furan-3-carboxylate (**4p**).* Yield 85%; yellow solid; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 8.44 (br s, 1H), 7.55–7.54 (m, 2H), 7.41 (d, J=7.8 Hz, 2H), 7.28 (s, 2H), 7.22–7.18 (m, 5H), 7.07 (t, J=7.2 Hz, 1H), 3.95–3.93 (m, 11H), 0.71 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 164.9, 153.6, 153.0, 148.9, 138.8, 136.0, 130.4, 128.3, 127.5, 125.6, 125.4, 123.7, 122.1, 120.0, 119.9, 117.8, 115.9, 111.1, 107.8, 105.0, 60.9, 60.6, 56.2, 13.3; IR (KBr): 3370, 1722, 1503, 1225, 1127, 1072, 762, 747, 689 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{30}H_{28}NO_6$: 498.1911; found: 498.1912.

*4.6.15. Ethyl 4-(1H-indol-3-yl)-2-(4-nitrophenyl)-5-phenylfuran-3-carboxylate (**4q**).* Yield 97%; orange solid; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 8.33–8.31 (m, 3H), 8.15 (d, J=8.4 Hz, 2H), 7.57–7.56 (m, 2H), 7.52 (d, J=8.4 Hz, 1H), 7.38 (d, J=7.8 Hz, 1H), 7.24–7.23 (m, 5H), 7.08 (t, J=7.2 Hz, 1H), 4.01 (q, J=7.2 Hz, 2H), 0.77 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 164.3, 151.0, 150.5, 147.2, 136.0, 135.7, 129.8, 128.4, 128.2, 127.6, 127.3, 125.8, 123.9, 123.8, 122.4, 121.0, 120.1, 120.0, 116.6, 111.2, 107.2, 61.1, 13.2; IR (KBr): 3455, 1720, 1596, 1517, 1341, 747, 693 cm^{-1}; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{27}H_{20}N_2NaO_5$: 475.1264; found: 475.1265.

*4.6.16. Ethyl 4-(1H-indol-3-yl)-2-(3-nitrophenyl)-5-phenylfuran-3-carboxylate (**4r**).* Yield 95%; yellow solid; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 8.86 (s, 1H), 8.33–8.31 (m, 2H), 8.25 (d, J=7.8 Hz, 1H), 7.65 (t, J=7.8 Hz, 1H), 7.57–7.56 (m, 2H), 7.45 (d, J=8.4 Hz, 1H), 7.38 (d, J=7.8 Hz, 1H), 7.28 (d, J=2.4 Hz, 1H), 7.25–7.22 (m, 4H), 7.08 (t, J=7.2 Hz, 1H), 4.02 (q, J=7.2 Hz, 2H), 0.79 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 164.2, 151.0, 150.5, 148.3, 136.1, 133.2, 131.5, 129.9, 129.4, 128.5, 128.1, 127.4, 125.8, 124.1, 123.3, 122.4, 122.3, 120.1, 119.9, 119.7, 116.4, 111.3, 107.1, 61.1, 13.3; IR (KBr): 3391, 1697, 1527, 1346, 1096, 763, 690 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{27}H_{21}N_2O_5$: 453.1445; found: 453.1451.

*4.6.17. Methyl 2-(4-chlorophenyl)-4-(1H-indol-3-yl)-5-phenylfuran-3-carboxylate (**4s**).* Yield 92%; yellow solid; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 8.30 (br s, 1H), 7.85 (d, J=8.4 Hz, 2H), 7.52–7.50 (m, 2H), 7.44 (d, J=8.4 Hz, 2H), 7.41 (d, J=7.8 Hz, 1H), 7.34 (d, J=7.8 Hz, 1H), 7.26–7.25 (m, 1H), 7.22–7.18 (m, 4H), 7.05 (t, J=7.8 Hz, 1H), 3.52 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 165.0, 152.8, 149.6, 136.0, 134.9, 130.2, 128.7, 128.6, 128.4, 128.3, 127.7, 127.1, 125.7, 124.0, 122.2, 120.0, 117.8, 115.9, 111.2, 107.3, 51.7; IR (KBr): 3342, 1702, 1485, 1237, 1092, 832, 746, 694 cm^{-1}; HRMS (ESI): m/z $[M-H]^-$ calcd for $C_{26}H_{17}ClNO_3$: 426.0902; found: 426.0897.

*4.6.18. Methyl 2-(4-fluorophenyl)-4-(1H-indol-3-yl)-5-phenylfuran-3-carboxylate (**4t**).* Yield 87%; yellow solid; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 8.31 (br s, 1H), 7.90 (dd, J_1=8.4 Hz, J_2=5.4 Hz, 2H), 7.51–7.50 (m, 2H), 7.40 (d, J=8.4 Hz, 1H), 7.35 (d, J=7.8 Hz, 1H), 7.24 (d, J=2.4 Hz, 1H), 7.21–7.14 (m, 6H), 7.05 (t, J=7.2 Hz, 1H), 3.51 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 165.0, 163.0 (d, J_{CF}=248.3 Hz), 153.3, 149.4, 136.0, 130.3, 129.6 (d, J_{CF}=9.2 Hz), 128.3, 127.6, 127.1, 126.3, 125.6, 124.0, 122.2, 119.99, 119.96 117.2, 115.8, 115.5 (d, J_{CF}=20.8 Hz), 111.2, 107.4, 51.6; IR (KBr): 3400, 1482, 1098, 925, 767, 748, 690 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{26}H_{19}FNO_3$: 412.1343; found: 412.1333.

*4.6.19. Ethyl 4-(1H-indol-3-yl)-5-phenyl-2,2′-bifuran-3-carboxylate (**4u**).* Yield 24%; brown oil; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 8.30 (br s, 1H), 7.59 (s, 1H), 7.55–7.54 (m, 2H), 7.42 (d, J=8.4 Hz, 1H), 7.37 (d, J=8.4 Hz, 1H), 7.33 (d, J=3.0 Hz, 1H), 7.22–7.18 (m, 5H), 7.06 (t, J=7.2 Hz, 1H), 6.57 (s, 1H), 3.99 (q, J=7.2 Hz, 2H), 0.74 (q, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 163.7, 149.2, 146.8, 144.7, 143.32, 143.26, 135.9, 130.2, 128.2, 127.7, 125.7, 123.7, 122.0, 120.1, 116.5, 115.4, 112.1, 111.9, 111.8, 111.1, 107.8, 60.4, 13.3; IR (KBr): 3403, 1707, 1614, 1458, 1239, 1076, 1017, 743, 693 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{25}H_{20}NO_4$: 398.1387; found: 398.1385.

*4.6.20. (4-(1H-Indol-3-yl)-2,5-diphenylfuran-3-yl)(phenyl)methanone (**4v**).* Yield 94%; brown solid; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 8.17 (br s, 1H), 7.79 (d, J=7.2 Hz, 2H), 7.68 (d, J=7.2 Hz, 2H), 7.61 (d, J=7.2 Hz, 2H), 7.31–7.29 (m, 3H), 7.26–7.19 (m, 6H), 7.15 (t, J=7.2 Hz, 2H), 7.11–7.09 (m, 2H), 6.94 (t, J=7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 194.0, 150.6, 148.8, 137.2, 135.8, 133.1, 130.5, 129.7, 129.6, 128.5, 128.3, 128.1, 127.5, 126.3, 126.2, 125.5, 124.7, 124.3, 122.1, 120.3, 119.8, 116.5, 111.0, 107.1; IR (KBr): 3359, 1661, 1598, 1485, 1447, 1346, 1235, 906, 765, 742, 690 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{31}H_{22}NO_2$: 440.1645; found: 440.1649.

*4.6.21. 1-(4-(1H-Indol-3-yl)-2-methyl-5-phenylfuran-3-yl)ethanone (**4w**).* Yield 96%; yellow solid; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 8.65 (br s, 1H), 7.42–7.39 (m, 4H), 7.23 (t, J=7.2 Hz, 1H), 7.12–7.08 (m, 5H), 2.69 (s, 3H), 1.85 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 196.9, 157.6, 148.5, 136.2, 130.4, 128.2, 127.7, 127.1, 125.3, 125.1, 123.7, 122.5, 120.3, 119.6, 113.2, 111.4, 108.3, 29.9, 14.7; IR (KBr): 3413, 1660, 1558, 1419, 1392, 1241, 770, 693 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{21}H_{18}NO_2$: 316.1332; found: 316.1329.

*4.6.22. Ethyl 4-(1-methyl-1H-indol-3-yl)-2,5-diphenylfuran-3-carboxylate (**4x**).* Yield 98%; white solid; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 7.91 (d, J=7.8 Hz, 2H), 7.56 (d, J=7.8 Hz, 2H), 7.47–7.45 (m, 2H), 7.41–7.35 (m, 3H), 7.25–7.16 (m, 5H), 7.04 (t, J=7.8 Hz, 1H), 4.01 (q, J=7.2 Hz, 2H), 3.85 (s, 3H), 0.82 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 164.7, 153.5, 149.0, 136.8, 130.5, 130.0, 128.8, 128.5, 128.24, 128.20, 127.8, 127.4, 125.5, 121.6, 120.3, 119.4, 118.0, 115.9, 109.1, 105.9, 60.5, 32.8, 13.3; IR (KBr): 1724, 1487, 1372, 1214, 1188, 1129, 1070, 913, 744, 689 cm^{-1}; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{28}H_{23}NNaO_3$: 444.1570; found: 444.1559.

*4.6.23. 3-(4-(Methylthio)-2,5-diphenylfuran-3-yl)-1H-indole (**5a**).* Yield 83%; white solid; ^{1}H NMR ($CDCl_3$, 600 MHz): δ (ppm) 8.33 (br s, 1H), 8.27 (d, J=7.2 Hz, 2H), 7.56 (d, J=7.2 Hz, 1H), 7.49–7.45 (m, 3H), 7.39 (s, 1H), 7.35 (t, J=7.2 Hz, 1H), 7.32 (d, J=7.8 Hz, 1H), 7.24–7.14 (m, 5H), 7.05 (t, J=7.2 Hz, 1H), 1.94 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 152.0, 148.6, 136.0, 130.8, 130.7, 128.4, 128.2, 127.8, 127.2, 126.8, 126.1, 125.2, 124.2, 122.2, 120.2, 119.9, 117.7, 111.2, 107.4, 18.8; IR (KBr): 3344, 1697, 1501, 1236, 841,

751, 695 cm^{-1}; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{25}H_{20}NO_5S$: 382.1260; found: 382.1255.

*4.6.24. 3-(4-(Methylthio)-2,5-di-p-tolylfuran-3-yl)-1H-indole (**5b**).* Yield 86%; yellow solid; ^1H NMR ($CDCl_3$, 600 MHz): δ (ppm) 8.25 (br s, 1H), 8.15 (d, *J*=7.8 Hz, 2H), 7.43 (d, *J*=7.8 Hz, 2H), 7.39 (d, *J*=8.4 Hz, 1H), 7.32–7.31 (m, 2H), 7.27 (d, *J*=7.8 Hz, 2H), 7.20 (t, *J*=7.8 Hz, 1H), 7.03 (t, *J*=7.8 Hz, 1H), 6.97 (d, *J*=7.8 Hz, 2H), 2.40 (s, 3H), 2.24 (s, 3H), 1.91 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 152.0, 148.6, 137.7, 136.9, 136.0, 129.1, 128.9, 128.14, 128.05, 126.9, 126.1, 125.1, 124.1, 122.1, 120.4, 119.8, 119.0, 116.8, 111.2, 107.8, 21.4, 21.2, 18.8; IR (KBr): 3417, 1499, 1454, 1419, 1093, 925, 821, 744 cm^{-1}; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{27}H_{24}NOS$: 410.1573; found: 410.1572.

*4.6.25. 3-(4-(Methylthio)-2,5-bis(4-nitrophenyl)furan-3-yl)-1H-indole (**5c**).* Yield 97%; orange solid; ^1H NMR ($CDCl_3$, 600 MHz): δ (ppm) 8.71 (br s, 1H), 8.49 (d, *J*=8.4 Hz, 2H), 8.34 (d, *J*=8.4 Hz, 2H), 8.05 (d, *J*=8.4 Hz, 2H), 7.69 (d, *J*=8.4 Hz, 2H), 7.54–7.52 (m, 2H), 7.28 (t, *J*=7.8 Hz, 1H), 7.21 (d, *J*=7.8 Hz, 1H), 7.07 (t, *J*=7.8 Hz, 1H), 1.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 151.0, 147.9, 146.7, 146.3, 136.1, 135.8, 126.5, 125.8, 125.6, 124.5, 124.0, 123.8, 122.8, 122.7, 120.5, 119.7, 111.7, 105.8, 18.5; IR (KBr): 3423, 1594, 1512, 1337, 1109, 855, 747, 697 cm^{-1}; HRMS (ESI): *m/z* $[M-H]^-$ calcd for $C_{25}H_{16}N_3O_5S$: 470.0816; found: 470.0814.

*4.6.26. 3-(2,5-Bis(4-methoxyphenyl)-4-(methylthio)furan-3-yl)-1H-indole (**5d**).* Yield 47%; brown solid; ^1H NMR ($CDCl_3$, 600 MHz): δ (ppm) 8.33 (br s, 1H), 8.19 (d, *J*=9.0 Hz, 2H), 7.46 (d, *J*=9.0 Hz, 2H), 7.43 (d, *J*=7.8 Hz, 1H), 7.36 (d, *J*=1.8 Hz, 1H), 7.31 (d, *J*=7.8 Hz, 1H), 7.21 (t, *J*=7.8 Hz, 1H), 7.04 (t, *J*=7.8 Hz, 1H), 7.01 (d, *J*=9.0 Hz, 2H), 6.71 (d, *J*=9.0 Hz, 2H), 3.87 (s, 3H), 3.72 (s, 3H), 1.92 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 159.1, 158.6, 151.7, 148.2, 136.0, 127.6, 126.9, 126.6, 124.1, 123.9, 123.8, 122.2, 120.4, 119.9, 118.0, 115.8, 113.8, 113.7, 111.2, 107.9, 55.3, 55.1, 18.9; IR (KBr): 3419, 1611, 1500, 1250, 1178, 1030, 834, 746 cm^{-1}; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{27}H_{24}NO_3S$: 442.1471; found: 442.1458.

*4.6.27. 3-(4-(Methylthio)-2,5-di(naphthalen-2-yl)furan-3-yl)-1H-indole (**5e**).* Yield 91%; brown solid; ^1H NMR ($CDCl_3$, 600 MHz): δ (ppm) 8.78 (s, 1H), 8.49 (d, *J*=8.4 Hz, 1H), 8.40 (br s, 1H), 8.16 (s, 1H), 7.99 (d, *J*=7.8 Hz, 1H), 7.96 (d, *J*=8.4 Hz, 1H), 7.88 (d, *J*=7.8 Hz, 1H), 7.72–7.68 (m, 2H), 7.63–7.59 (m, 2H), 7.54–7.47 (m, 4H), 7.41–7.36 (m, 3H), 7.25–7.23 (m, 1H), 7.03 (t, *J*=7.8 Hz, 1H), 2.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 152.3, 148.9, 136.1, 133.3, 133.2, 132.8, 132.4, 128.6, 128.3, 128.2, 128.1, 128.0, 127.8, 127.6, 126.9, 126.3, 126.1, 125.9, 125.4, 124.3, 124.1, 124.0, 123.5, 122.3, 120.6, 120.4, 120.1, 118.4, 111.2, 107.7, 18.9; IR (KBr): 3451, 1626, 1597, 1090, 859, 820, 747 cm^{-1}; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{33}H_{24}NOS$: 482.1573; found: 482.1574.

*4.6.28. 3-(2,5-Bis(4-chlorophenyl)-4-(methylthio)furan-3-yl)-1H-indole (**5f**).* Yield 89%; red solid; ^1H NMR ($CDCl_3$, 600 MHz): δ (ppm) 8.37 (br s, 1H), 8.20 (d, *J*=8.4 Hz, 2H), 7.47–7.40 (m, 6H), 7.27–7.23 (m, 2H), 7.15 (d, *J*=8.4 Hz, 2H), 7.06 (t, *J*=7.2 Hz, 1H), 1.92 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 151.2, 147.8, 136.0, 133.7, 133.0, 129.04, 128.96, 128.7, 128.5, 127.3, 126.4, 124.2, 122.4, 120.4, 120.2, 118.3, 111.3, 107.0, 18.6; IR (KBr): 3421, 1481, 1090, 1011, 831, 743, 497 cm^{-1}; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{25}H_{18}Cl_2NOS$: 450.0481; found: 450.0482.

*4.6.29. 3-(2,5-Bis(4-bromophenyl)-4-(methylthio)furan-3-yl)-1H-indole (**5g**).* Yield 87%; red solid; ^1H NMR ($CDCl_3$, 600 MHz): δ (ppm) 8.34 (br s, 1H), 8.13 (d, *J*=8.4 Hz, 2H), 7.58 (d, *J*=8.4 Hz, 2H), 7.43 (d, *J*=7.8 Hz, 1H), 7.38–7.36 (m, 3H), 7.28–7.22 (m, 4H), 7.05 (t, *J*=7.2 Hz, 1H), 1.89 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 151.2, 147.8, 136.0, 131.6, 131.4, 129.4, 129.3, 127.5, 126.7, 126.3, 124.2, 122.4, 121.9, 121.3, 120.6, 120.2, 120.1, 118.5, 111.3, 107.0, 18.7; IR (KBr): 3439, 1628, 1480, 826, 746, 490 cm^{-1}; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{25}H_{18}Br_2NOS$: 539.9460; found: 539.9458.

*4.6.30. 3-(2,5-Bis(4-fluorophenyl)-4-(methylthio)furan-3-yl)-1H-indole (**5h**).* Yield 92%; yellow solid; ^1H NMR ($CDCl_3$, 600 MHz): δ (ppm) 8.36 (br s, 1H), 8.24–8.22 (m, 2H), 7.51–7.48 (m, 2H), 7.45 (d, *J*=7.8 Hz, 1H), 7.39 (s, 1H), 7.27 (d, *J*=8.4 Hz, 1H), 7.24–7.22 (m, 1H), 7.16 (t, *J*=8.4 Hz, 2H), 7.05 (t, *J*=7.8 Hz, 1H), 6.87 (t, *J*=8.4 Hz, 2H), 1.91 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 162.3 (d, J_{CF}=246.2 Hz), 161.9 (d, J_{CF}=246.2 Hz), 151.3, 147.8, 136.1, 128.0 (d, J_{CF}=6.3 Hz), 127.0 (d, J_{CF}=12.6 Hz), 126.6, 124.2, 124.1, 122.4, 120.2, 120.1, 119.4, 117.2, 115.5 (d, J_{CF}=21.5 Hz), 115.2 (d, J_{CF}=13.2 Hz), 111.3, 107.3, 18.7; IR (KBr): 3409, 1669, 1599, 1498, 1233, 1157, 837, 744 cm^{-1}; HRMS (ESI): *m/z* $[M-H]^-$ calcd for $C_{25}H_{16}F_2NOS$: 416.0926; found: 416.0927.

*4.6.31. 3-(4-(Methylthio)-2,5-di(thiophen-3-yl)furan-3-yl)-1H-indole (**5i**).* Yield 82%; brown oil; ^1H NMR ($CDCl_3$, 600 MHz): δ (ppm) 8.33 (br s, 1H), 8.08 (d, *J*=2.4 Hz, 1H), 7.92 (d, *J*=4.8 Hz, 1H), 7.42 (d, *J*=8.4 Hz, 1H), 7.38 (dd, J_1=4.8 Hz, J_2=3.0 Hz, 1H), 7.34–7.33 (m, 2H), 7.25–7.22 (m, 2H), 7.09–7.06 (m, 3H), 1.93 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 149.3, 146.0, 136.0, 131.9, 131.7, 126.9, 125.8, 125.5, 125.33, 125.25, 124.2, 122.3, 121.7, 120.4, 120.3, 120.0, 118.3, 116.1, 111.3, 107.2, 18.7; IR (KBr): 3383, 1697, 1488, 1238, 1119, 745, 696 cm^{-1}; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{21}H_{16}NOS_3$: 394.0389; found: 394.0383.

Acknowledgements

We thank the National Natural Science Foundation of China (Grant 20872042 and 21032001) and the Doctor Independent Foundation of Central China Normal University (No. 2009007). We also thank Prof. Yuanjiang Pan and Dr. Cheng Guo, Zhejiang University, for analytical support.

Supplementary data

The general experimental methods and the characterizing data including ^1H NMR, ^{13}C NMR, IR, and HRMS for compounds **4** and **5** are available. Supplementary data associated with this article can be found in online version, at doi:10.1016/j.tet.2011.05.058

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