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Furan ring opening–indole ring closure: $SnCl_2$-induced reductive transformation of difuryl(2-nitroaryl)methanes into 2-(2-acylvinyl)indoles

Maxim G. Uchuskin[a], Natalia V. Molodtsova[a], Vladimir T. Abaev[b], Igor V. Trushkov[c,d], Alexander V. Butin[a,e,*]

[a] Research Institute of Heterocyclic Compounds Chemistry, Kuban State Technological University, Moskovskaya 2, Krasnodar 350072, Russian Federation
[b] North-Ossetian State University, Vatutina 46, Vladikavkaz 362025, Russian Federation
[c] M.V. Lomonosov Moscow State University, Department of Chemistry, Leninskie Gory 1/3, Moscow 119991, Russian Federation
[d] Federal Research Center of Pediatric Hematology, Oncology and Immunology, Laboratory of Chemical Synthesis, Leninskii av. 117/2, Moscow 117997, Russian Federation
[e] Perm State University, Bukireva 15, Perm 614990, Russian Federation

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ABSTRACT

A simple and efficient method for the synthesis of 2-(2-acylvinyl)-3-(5-alkyl-2-furyl)indoles by reductive recyclization of bis(5-alkyl-2-furyl)(2-nitroaryl)methanes is reported. This transformation was carried out by heating the substrates with $SnCl_2 \cdot 2H_2O$ in ethanol. The intermediate nitrosoarene moiety interacted with the furan ring via electrophilic nitrogen attack onto the C(2) position of the furan ring. It was shown that the related bis(5-alkyl-2-thienyl)(2-nitroaryl)methanes under the same reaction conditions failed to undergo the analogous recyclization and were transformed into bis(5-alkyl-2-thienyl)(2-aminoaryl)methanes.

1. Introduction

For many years indoles have attracted the attention of organic chemists due to their significant role in biology and medicine.[1] Among the multiple approaches for the construction of indole ring systems, an overwhelming majority of methods are based on nitroarene transformations. Having an important practical advantage, namely, ready availability of the starting compounds these methods require a subsequent reduction step for incorporation of the nitro-group nitrogen into the indole ring. The Leimgruber–Batcho, Reissert, Makosza, and some other nitroarene-into-indole transformations are based on the obvious reduction of nitrobenzenes into anilines followed by spontaneous *in situ* cyclization of the formed amino group onto an electrophilic carbon atom.[1,2] However, depending on the conditions, the quite common reaction course consists of the interception of the products of incomplete reduction of the nitro-group with appropriate internal functional groups. Thus the intermediate hydroxylamine[3] or nitrosoarene[4,5] can participate in the indole formation. Another example is the Cadogan indole synthesis and related processes consisting of thermal deoxygenation of nitroarenes with various P(III) compounds[6] in which the corresponding nitrenes have been postulated as intermediates.

In 1979 deoxygenation of (2-nitrophenyl)bis(2-furyl)methanes **1** with triethyl phosphite affording furo[3,2-*c*]carbazoles **2** was reported (Scheme 1).[7] The reaction was postulated to proceed through the nitrene attack onto the furan ring followed by rearrangement of the adduct to give a 2-(2-acylvinyl)-3-furylindole, an Arbuzov-like reaction with one more triethyl phosphite molecule and a secondary cyclization generated furocarbazole **2**. Under the same conditions, (2-nitrophenyl)bis(pyrrol-2-yl)methane (**3**, R=Me) yielded pyrrolo[3,2-*b*]quinoline **4**. (2-Nitrophenyl)bis(thienyl)methanes reacted similarly to **3** furnishing the corresponding thienoquinolines.[7,8]

On the other hand, it was recently shown that **3** (R=H) and its derivatives are transformed into **4** on heating with $SnCl_2 \cdot 2H_2O$ in methanol.[9] Evidently, a nitrene cannot be involved in this process. The authors rationalized the results by electrophilic attack of a nitrosoarene or hydroxylamine intermediate onto the electron-rich heteroaromatic substituent. Similarly, some years ago we reported one example of the recyclization of **1a** (R=Me) into 2-(2-acylvinyl)-3-furylindole **5a** by treatment with $SnCl_2 \cdot 2H_2O$

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* Corresponding author. Fax: +7 342 237 1480; e-mail addresses: alexander_butin@mail.ru, av_butin@yahoo.com (A.V. Butin).

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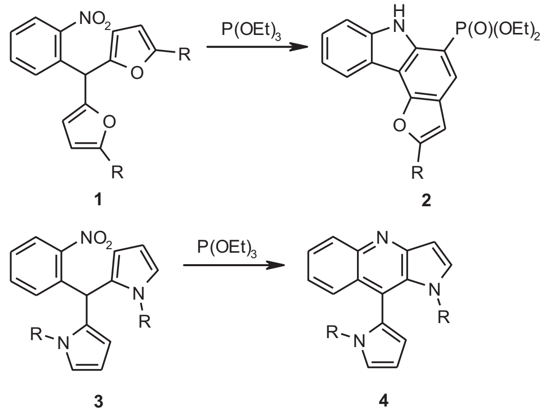
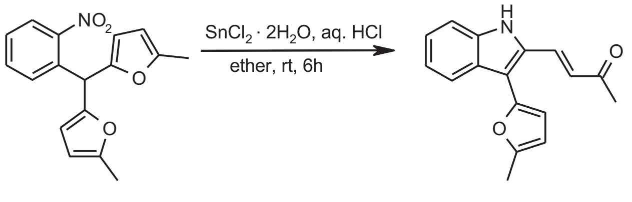


Scheme 1. Reductions of bis(hetaryl)(2-nitrophenyl)methanes with triethyl phosphite.

(Scheme 2) and proved that this reaction proceeded through formation of a nitrosoarene.[10] It is necessary to point out that compounds of type **5** were proposed as intermediates in the formation of **2** from **1** and triethyl phosphite.



1a **5a**

Scheme 2. Reduction of bis(2-furyl)(2-nitrophenyl)methane **1a** with $SnCl_2 \cdot 2H_2O$.

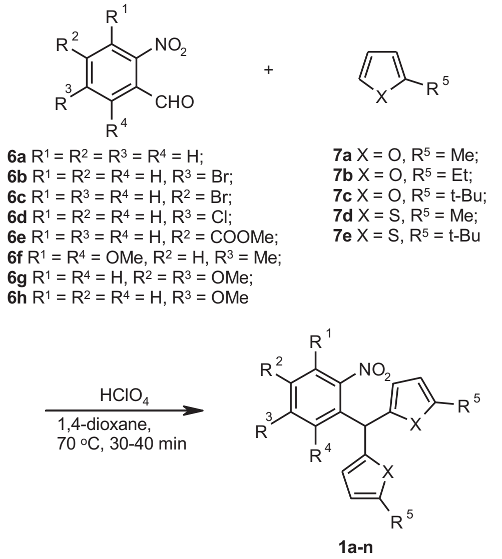
We supposed that **5a** was formed through the intramolecular Diels–Alder reaction between the nitroso moiety and furan ring followed by rearrangement of the cycloadduct. The similar process cannot be realized for thienyl and pyrrolyl analogues due to the much lower ability of these five-membered rings to react as dienes in [4+2]-cycloaddition reactions.

The different reactivity of furans and other (het)arenes was also found in many intramolecular electrophilic reactions.[11] Namely, electrophiles usually attack at the *ipso*-position of 2,5-disubstituted furans but at the unsubstituted *ortho*-atom in other (het)arenes. Thus, 2-(acylamino)diphenylmethanes underwent cyclization to give dibenzazepines via Bischler–Napieralski-like reactions.[12] A similar process was reported for 2-[2-(aminocarbamoyl)benzyl] thiophenes.[13] However, 2-[2-(acylamino)benzyl]furans were transformed under these conditions into quinoline derivatives rather than into furo[3,2-*c*][1]benzazepines.[14] Another example is an interaction of 2-(het)arylanilines with aldehydes under Pictet–Spengler conditions, which usually yield quinolines annulated to an *ortho*-hetaryl group.[15] Conversely, under the same conditions 2-(2-furyl)anilines undergo furan ring opening furnishing 3-(2-acylvinyl)-2-(het)arylindoles.[16] The report about the electrophilic mechanism of cyclization in reaction of **3** with $SnCl_2$ stimulated us to study the corresponding reaction of **1** in more detail as a development of our investigations of furan-into-indole recyclizations.[16,17] Herein, we report the results of this study.

2. Results and discussion

The parent difuryl(2-nitroaryl)methanes **1a**–**l** were synthesized by $HClO_4$-catalyzed condensation of 2-nitrobenzaldehydes **6** with 2-alkylfurans **7a**–**c** (Table 1). The analogous condensation of aldehydes **6a** with 2-alkylthiophenes **7d**,**e** provided (2-nitrophenyl) bis(thienyl)methanes **1m**,**n**.

Table 1
Synthesis of nitroarenes **1**



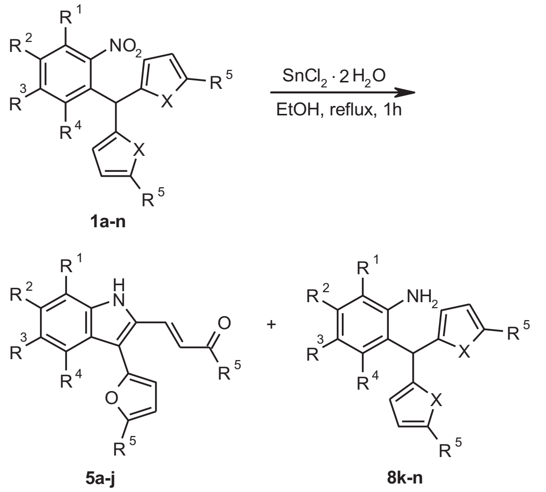
Entry	X	R^1	R^2	R^3	R^4	R^5	Yield, %
a	O	H	H	H	H	Me	74
b	O	H	H	H	H	Et	72
c	O	H	H	H	H	*t*-Bu	92
d	O	H	H	Br	H	*t*-Bu	73
e	O	H	Br	H	H	*t*-Bu	71
f	O	H	H	Cl	H	*t*-Bu	76
g	O	H	CO_2Me	H	H	*t*-Bu	72
h	O	OMe	H	Me	OMe	Me	70
i	O	OMe	H	Me	OMe	Et	76
j	O	OMe	H	Me	OMe	*t*-Bu	87
k	O	H	OMe	OMe	H	*t*-Bu	94
l	O	H	H	OMe	H	*t*-Bu	81
m	S	H	H	H	H	*t*-Bu	88
n	S	H	H	H	H	Me	78

The prepared difuryl(2-nitroaryl)methanes **1a**–**l** were treated with $SnCl_2 \cdot 2H_2O$ under the reaction conditions applied earlier for the transformation of **3** into **4**.[15] We found that the substrates **1a**–**j** afforded 2-(2-acylvinyl)-3-furylindoles **5a**–**j** in moderate to good yields (Table 2). Substitution of ethanol for methyl alcohol has no effect on both the direction of reaction and yields of products. Similarly to the pyrrolo[3,2-*b*]quinoline **4** formation, this transformation is a fast process; full conversion of **1** was achieved after heating the reaction mixture at reflux for 40–60 min.

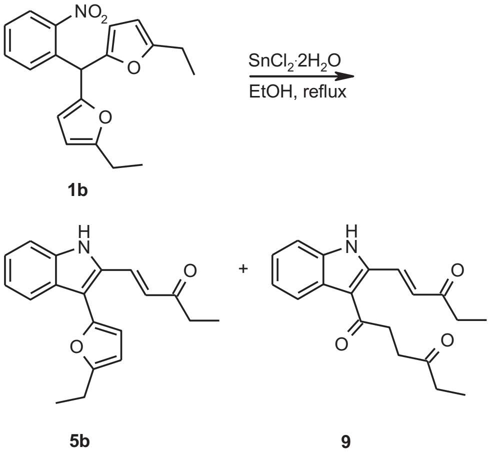
On the contrary, (2-nitrophenyl)bis(thienyl)methanes **1m**,**n** were reduced by $SnCl_2$ to the corresponding anilines **8**. Similarly, anilines were obtained in reaction of difuryl(2-nitrophenyl)methanes **1k**,**l** containing a strongly electron-donating methoxy substituent *para* to the nitro-group. It is interesting that an *ortho*-methoxy group does not interfere the formation of indoles **5**.

Comparison of the results obtained for various 2-alkylfurans, demonstrates clearly that the better yields were obtained in reactions of **1c**–**h** having 5-*tert*-butyl-substituted furyl groups. It can be explained by the formation of side-products when the furan ring contains methyl or ethyl group at the C(5) position. Presumably, it is related to the possibility of deprotonation of the 5-alkyl group in these cases. For substances **1a**,**i**,**j** we did not identify by-products. Careful separation of the reaction mixture obtained by reduction of **1b** allowed us to isolate in minor quantities triketoindole **9** along with 3-furylindole **5b** (Scheme 3). The analogous furan ring opening of 3-(5-alkyl-2-furyl)indoles was found earlier in other acid-catalyzed recyclizations of aryldifurylmethanes.[17e,f]

Table 2
Preparation of indoles **5** by reductive cyclization of nitroarenes **1** with $SnCl_2 \cdot 2H_2O$



Entry	X	R^1	R^2	R^3	R^4	R^5	Yield, %	
							5	**8**
a	O	H	H	H	H	Me	37	—
b	O	H	H	H	H	Et	40	—
c	O	H	H	H	H	*t*-Bu	60	—
d	O	H	H	Br	H	*t*-Bu	65	—
e	O	H	Br	H	H	*t*-Bu	61	—
f	O	H	H	Cl	H	*t*-Bu	73	—
g	O	H	CO_2Me	H	H	*t*-Bu	62	—
h	O	OMe	H	Me	OMe	*t*-Bu	67	—
i	O	OMe	H	Me	OMe	Me	30	—
j	O	OMe	H	Me	OMe	Et	44	—
k	O	H	OMe	OMe	H	*t*-Bu	—	51
l	O	H	H	OMe	H	*t*-Bu	—	55
m	S	H	H	H	H	*t*-Bu	—	54
n	S	H	H	H	H	Me	—	63



Scheme 3. Preparation of 3-furylindole **5b** and triketoindole **9**.

The obtained results and previous data[9,10] are consistent with the mechanism demonstrated in Scheme 4. Reduction of nitroarene **1** leads to the formation of nitrosoarene **10**, which attacks the electron-enriched heteroaromatic ring. The electrophilic nature of the nitrogen atom in nitrosoarenes is well-known; it was exploited in the syntheses of both indoles[18] and other heterocycles.[19] In the discussed reaction the nitrogen electrophilicity is possibly increased by tin chloride or proton coordination to the nitroso group oxygen. The electrophilic nitrogen attacks the *ortho*-position of the pyrrole ring in **3** leading to compounds **4** but the *ipso*-position in the case of furans **1**. The formed σ-complex **11** rearranges into 2-(2-acylvinyl)indole **5**. It can also loose a proton from the alkyl group at the C(5) atom of the furan ring if this is a methyl or ethyl group. It explains the formation of various by-products and tar in reactions of **1a**,**b**,**i**,**j**. Thiophenes are much less nucleophilic than furans or pyrroles. As a result, the intermediate nitroso group fails to attack the thiophene ring in **10m**,**n** and these compounds undergo smooth reduction to anilines **8**. The formation of 2-[bis(furyl)methyl]anilines **8k**,**l** is also consistent with this mechanism. In this case the *para*-methoxy group strongly decreases the electrophilicity of the nitrosoarene nitrogen. So, the reduction of **10k**,**l** proceeds much faster than cyclization, and only anilines were isolated.

The alternative mechanism including Diels–Alder reaction[10] between the furyl and nitroso moieties in **10** seems to be less probable as it is inconsistent with better yields in reactions of **1c**–**h** having bulky *tert*-butyl group in comparison with **1a**,**b**,**i**,**j**.

3. Conclusion

In summary, we have demonstrated that the reduction of bis(2-furyl)(2-nitrophenyl)methanes with $SnCl_2 \cdot 2H_2O$ at reflux in ethanol afforded 2-(2-acylvinyl)indoles as a result of the electrophilic attack of the intermediate nitrosoarene onto the *ipso*-position of the furan ring. We believe that the described procedure would be useful for organic chemists as a simple route to these highly functionalized indoles. Reduction of (2-nitrophenyl)bis(2-thienyl)methanes under the above conditions leads to the formation of anilines.

These results and earlier reported transformation of (2-nitrophenyl)bis(2-pyrrolyl)methane into pyrrolo[3,2-*b*]quinoline under the same treatment can be explained by interception of the intermediate electrophilic nitrosoarenes by the highly nucleophilic furan and pyrrole rings. On the contrary, the less nucleophilic thiophenes failed to react under these conditions resulting in further reduction of the nitrosoarene intermediate to give the corresponding anilines.

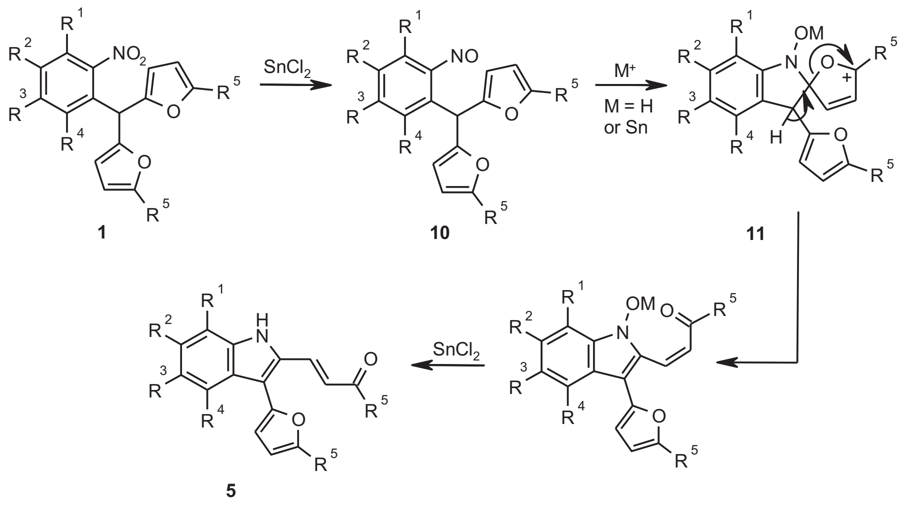
4. Experimental section

4.1. General

Melting points are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded on Bruker DPX 300 and JEOL Delta ECA 400 spectrometers at room temperature; the chemical shifts δ were measured in parts per million with respect to the solvent ($CDCl_3$, ^1H: δ=7.26 ppm, ^{13}C: δ=77.0 ppm; DMSO-d_6, ^1H: δ=2.50 ppm, ^{13}C: δ=39.5 ppm). Coupling constants (*J*) are given in hertz. Splitting patterns of an apparent multiplet associated with an averaged coupling constants were designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublets) and br (broadened). IR spectra were measured as KBr plates on Prestige-21 FT-IR and Bruker Alpha FT-IR spectrophotometers. Mass spectra were recorded on a Kratos MS-30 instrument with 70 eV electron impact ionization at 200 °C. Column chromatography was performed on silica gel KSK (50–160 μm, LTD Sorbpolymer). The starting 2-nitrobenzaldehydes **6a**–**d** were commercial reagents. Other aldehydes were synthesized according to published procedures.[20–22] 2-*tert*-Butylfuran **7c** was obtained by described procedure.[23] 2-*tert*-Butylthiophene was synthesized similarly starting from 5-*tert*-butylthiophene-2-carboxylic acid.[24] All the reactions were carried out using freshly distilled and dry solvents from solvent stills.

4.2. General procedure for synthesis of nitroarenes 1a–n

Aq. $HClO_4$ (70%, 0.3 mL) was added to solution of 2-nitrobenzaldehyde **6** (5 mmol) and compound **7** (12.5 mmol) in



Scheme 4. Proposed mechanism of 2-(2-acylvinyl)indoles **5** formation.

1,4-dioxane (15 mL). The reaction mixture was stirred at 70 °C for 40–60 min (TLC control), then poured into cold water (200 mL). The product was extracted with ethyl acetate (3×50 mL). The combined organic fractions were dried with Na_2SO_4 and evaporated to dryness under reduced pressure. The product was purified by flash chromatography using CH_2Cl_2/petroleum ether (1:9) mixture as an eluent. Compounds **1b**–**g**,**j**,**k**,**m**,**n** were obtained as light-yellow oils and used without additional purification.

*4.2.1. Bis(5-methyl-2-furyl)(2-nitrophenyl)methane (**1a**).*[11a] Pale-brown solid; yield 74% (1.10 g); mp 82–83 °C; δ_H (300 MHz, $CDCl_3$) 7.93–7.97 (1H, m, H_{Ar}), 7.61–7.69 (1H, m, H_{Ar}), 7.49–7.57 (1H, m, H_{Ar}), 7.28–7.32 (1H, m, H_{Ar}), 6.16 (1H, s, CH), 5.96 (2H, d, *J* 3.2 Hz, H_{Fur}), 5.88 (2H, d, *J* 3.2 Hz, H_{Fur}), 2.23 (6H, s, CH_3).

*4.2.2. (2,5-Dimethoxy-3-methyl-6-nitrophenyl)bis(5-methyl-2-furyl)methane (**1h**).* Pale-green solid; yield 70% (1.30 g); mp 131–132 °C. Found: C, 64.45; H, 5.69; N, 3.73. $C_{20}H_{21}NO_6$ requires C, 64.68; H, 5.70; N, 3.77%. R_f=0.53 (acetone/CH_2Cl_2/petroleum ether=1:1:3); ν_{max} (KBr) 1605, 1566, 1535, 1479, 1468, 1402, 1369, 1325, 1242, 1215, 1140, 1096, 1036, 961, 810, 785 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.78 (1H, s, H_{Ar}), 5.98 (2H, d, *J* 3.2 Hz, H_{Fur}), 5.88 (2H, d, *J* 3.2 Hz, H_{Fur}), 5.82 (1H, s, CH), 3.80 (3H, s, OCH_3), 3.47 (3H, s, OCH_3), 2.33 (3H, s, CH_3), 2.23 (6H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 151.5 (2C), 150.2, 149.8 (2C), 147.0, 140.2, 134.3, 126.0, 114.0, 109.7 (2C), 106.6 (2C), 61.1, 56.7, 37.3, 17.1, 13.7 (2C); *m*/*z* (EI, 70 eV) 371 (M$^+$, 38), 354 (100), 309 (50), 274 (45), 214 (20), 162 (20), 110 (25), 58 (18), 44 (63).

*4.2.3. Bis(5-ethyl-2-furyl)(2,5-dimethoxy-3-methyl-6-nitrophenyl)methane (**1i**).* Pale-brown solid; yield 76% (1.52 g); mp 105–106 °C. Found: C, 66.39; H, 6.30; N, 3.53. $C_{22}H_{25}NO_6$ requires C, 66.15; H, 6.31; N, 3.51%. R_f=0.59 (acetone/CH_2Cl_2/petroleum ether=1:1:3); ν_{max} (KBr) 1604, 1562, 1537, 1476, 1404, 1371, 1329, 1254, 1233, 1182, 1103, 1051, 1018, 1007, 966, 814, 787, 766 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.78 (1H, s, H_{Ar}), 5.98 (2H, d, *J* 3.2 Hz, H_{Fur}), 5.89 (2H, d, *J* 3.2 Hz, H_{Fur}), 5.84 (1H, s, CH), 3.80 (3H, s, OCH_3), 3.46 (3H, s, OCH_3), 2.58 (4H, q, *J* 7.6 Hz, CH_2), 2.33 (3H, s, CH_3), 1.18 (6H, t, *J* 7.6 Hz, CH_3); δ_C (100 MHz, $CDCl_3$) 157.2 (2C), 150.2, 149.7 (2C), 147.0, 140.2, 134.3, 126.1, 114.0, 109.5 (2C), 105.0 (2C), 61.1, 56.7, 37.4, 21.5 (2C), 17.1, 12.4 (2C); *m*/*z* (EI, 70 eV) 399 (M$^+$, 20), 382 (100), 323 (35), 288 (34), 258 (15), 228 (14), 123 (72), 101 (20), 59 (34), 43 (48).

*4.2.4. Bis(5-tert-butyl-2-furyl)(5-methoxy-2-nitrophenyl)methane (**1l**).* Dark-yellow solid; yield 81% (1.66 g); mp 69–70 °C. Found: C, 70.23; H, 7.14; N, 3.38. $C_{24}H_{29}NO_5$ requires C, 70.05; H, 7.10; N, 3.40%. R_f=0.61 (acetone/CH_2Cl_2/petroleum ether=1:1:3); ν_{max} (KBr) 2969, 1602, 1589, 1555, 1513, 1491, 1480, 1461, 1336, 1265, 1231, 1195, 1125, 1067, 1034, 1018, 838, 800, 790, 750 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.04 (1H, d, *J* 9.0 Hz, H_{Ar}), 6.83 (1H, dd, *J* 9.0, 2.7 Hz, H_{Ar}), 6.77 (1H, d, *J* 2.7 Hz, H_{Ar}), 6.40 (1H, s, CH) 5.90 (2H, d, *J* 3.0 Hz, H_{Fur}), 5.85 (2H, d, *J* 3.0 Hz, H_{Fur}), 3.77 (3H, s, OCH_3), 1.22 (18H, s, $C(CH_3)_3$); δ_C (75 MHz, $CDCl_3$) 164.1 (2C), 163.2, 150.7 (2C), 141.8, 138.5, 127.8, 115.6, 113.2, 108.6 (2C), 102.5 (2C), 55.8, 40.5, 32.8 (2C), 29.2 (6C); *m*/*z* (EI, 70 eV) 411 (M$^+$, 23), 394 (100), 272 (18), 216 (12), 57 (58), 43 (32).

4.3. General procedure for synthesis of indoles 5a–j

A mixture of **1** (2 mmol), $SnCl_2\cdot 2H_2O$ (2.26 g; 10 mmol) and ethanol (20 mL) was heated at reflux for 40–60 min (TLC control). Then the reaction mixture was poured into cold water (250 mL) and aq $NaHCO_3$ was added to be the neutral reaction. The precipitate was filtered off. The aqueous layer was extracted with ethyl acetate (3×30 mL). The precipitate was extracted with 1,4-dioxane (4×50 mL). The combined organic fractions were dried with Na_2SO_4 and evaporated to dryness under reduced pressure. Products were purified by column chromatography on silica gel using CH_2Cl_2/petroleum ether (1:5) mixture as an eluent and recrystallized from CH_2Cl_2/petroleum ether.

*4.3.1. (3E)-4-[3-(5-Methyl-2-furyl)-1H-indol-2-yl]but-3-en-2-one (**5a**).* Pale-brown solid; yield 37% (0.20 g); mp 215–216 °C. Found: C, 77.07; H, 5.84; N, 5.27. $C_{17}H_{15}NO_2$ requires C, 76.96; H, 5.70; N, 5.28%. R_f=0.32 (acetone/CH_2Cl_2/petroleum ether=1:1:3); ν_{max} (KBr) 3296, 1640, 1602, 1326, 1269, 1234, 1032, 969, 743 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 11.74 (1H, s, NH), 7.99 (1H, d, *J* 16.2 Hz, =CH), 7.88–7.85 (1H, m, H_{Ar}), 7.42–7.40 (1H, m, H_{Ar}), 7.31–7.26 (1H, m, H_{Ar}), 7.15–7.09 (1H, m, H_{Ar}), 6.83 (1H, d, *J* 16.2 Hz, =CH), 6.71 (1H, d, *J* 3.3 Hz, H_{Fur}), 6.29 (1H, d, *J* 3.3 Hz, H_{Fur}), 2.41 (3H, s, CH_3), 2.36 (3H, s, CH_3); δ_C (75 MHz, DMSO-d_6) 197.4, 151.3, 147.3, 137.8, 131.8, 129.5, 125.7, 125.0, 124.8, 120.8, 120.4, 112.0, 111.7, 108.8, 107.9, 27.2, 13.4; *m*/*z* (EI, 70 eV) 265 (M$^+$, 100), 248 (25), 222 (78), 194 (95), 180 (38), 167 (16), 125 (11), 43 (27).

*4.3.2. (1E)-1-[3-(5-Ethyl-2-furyl)-1H-indol-2-yl]pent-1-en-3-one (**5b**).* Dark-yellow solid; yield 40% (0.23 g); mp 196–197 °C. Found: C, 77.92; H, 6.78; N, 4.77. $C_{19}H_{19}NO_2$ requires C, 77.79; H, 6.53; N, 4.77%. R_f=0.43 (acetone/CH_2Cl_2/petroleum ether=1:1:3); ν_{max} (KBr) 3293, 2964, 1649, 1609, 1331, 1261, 1201, 1190, 1031, 959, 738 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 11.74 (1H, s, NH), 8.05 (1H, d, *J*

16.0 Hz, =CH), 7.86–7.84 (1H, m, H_{Ar}), 7.42–7.40 (1H, m, H_{Ar}), 7.31–7.26 (1H, m, H_{Ar}), 7.14–7.10 (1H, m, H_{Ar}), 6.90 (1H, d, *J* 16.0 Hz, =CH), 6.70 (1H, d, *J* 3.2 Hz, H_{Fur}), 6.28 (1H, d, *J* 3.2 Hz, H_{Fur}), 2.76 (2H, q, *J* 7.6 Hz, CH_2), 2.73 (2H, q, *J* 7.2 Hz, CH_2), 1.29 (3H, t, *J* 7.6 Hz, CH_3), 1.07 (3H, t, *J* 7.2 Hz, CH_3); δ_C (100 MHz, DMSO-d_6) 199.7, 156.5, 147.3, 137.7, 130.5, 129.7, 124.9, 124.8, 124.6, 120.7, 120.4, 111.9, 111.6, 108.4, 106.5, 33.2, 20.9, 12.1, 8.3; *m*/*z* (EI, 70 eV) 293 (M^+, 100), 264 (48), 236 (32), 222 (14), 208 (16), 57 (54), 44 (28).

*4.3.3. (1E)-1-[3-(5-tert-Butyl-2-furyl)-1H-indol-2-yl]-4,4-dimethylpent-1-en-3-one (**5c**).* Orange solid; yield 60% (0.42 g); mp 188–189 °C. Found: C, 79.03; H, 7.62; N, 4.18. $C_{23}H_{27}NO_2$ requires C, 79.05; H, 7.79; N, 4.01%. R_f=0.61 (acetone/CH_2Cl_2/petroleum ether=1:1:3); ν_{max} (KBr) 3316, 2966, 1659, 1573, 1475, 1327, 1283, 1231, 1088, 1006, 737 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 11.75 (1H, s, NH), 8.20 (1H, d, *J* 15.6 Hz, =CH), 7.85–7.83 (1H, m, H_{Ar}), 7.45 (1H, d, *J* 15.6 Hz, =CH), 7.45–7.42 (1H, m, H_{Ar}), 7.33–7.27 (1H, m, H_{Ar}), 7.16–7.10 (1H, m, H_{Ar}), 6.67 (1H, d, *J* 3.3 Hz, H_{Fur}), 6.25 (1H, d, *J* 3.3 Hz, H_{Fur}), 1.36 (9H, s, $C(CH_3)_3$), 1.20 (9H, s, $C(CH_3)_3$); δ_C (75 MHz, DMSO-d_6) 202.7, 162.8, 147.2, 137.6, 130.8, 130.2, 125.0, 124.7, 120.5, 120.4, 119.8, 111.9, 111.5, 108.0, 104.3, 42.7, 32.3, 28.9 (3C), 26.0 (3C); *m*/*z* (EI, 70 eV) 349 (M^+, 96), 334 (77), 292 (100), 277 (45), 248 (22), 236 (35), 209 (35), 180 (40), 85 (18), 69 (40), 57 (34), 42 (47).

*4.3.4. (1E)-1-[5-Bromo-3-(5-tert-butyl-2-furyl)-1H-indol-2-yl]-4,4-dimethylpent-1-en-3-one (**5d**).* Orange solid; yield 65% (0.56 g); mp 212–213 °C. Found: C, 64.38; H, 6.24; N, 3.16. $C_{23}H_{26}BrNO_2$ requires C, 64.49; H, 6.12; N, 3.27%. R_f=0.53 (acetone/CH_2Cl_2/petroleum ether=1:1:3); ν_{max} (KBr) 3283, 2968, 1659, 1566, 1477, 1365, 1273, 1092, 967, 780 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.63 (1H, s, NH), 8.29 (1H, d, *J* 15.6 Hz, H_{Ar}), 8.04 (1H, d, *J* 1.8 Hz, H_{Ar}), 7.36 (1H, dd, *J* 8.7, 1.8 Hz, H_{Ar}), 7.20 (1H, d, *J* 8.7 Hz, H_{Ar}), 6.94 (1H, d, *J* 15.6 Hz, =CH), 6.51 (1H, d, *J* 3.3 Hz, H_{Fur}), 6.10 (1H, d, *J* 3.3 Hz, H_{Fur}), 1.38 (9H, s, $C(CH_3)_3$), 1.24 (9H, s, $C(CH_3)_3$); δ_C (75 MHz, $CDCl_3$) 203.7, 164.8, 146.6, 136.1, 131.9, 130.9, 128.4, 127.8, 124.4, 118.9, 114.3, 114.0, 112.6, 109.4, 104.2, 43.4, 33.0, 29.4 (3C), 26.7 (3C); *m*/*z* (EI, 70 eV) 429/427 (M^+, 48/48), 414/412 (15/14), 373/371 (62/60), 355 (15), 316 (12), 279 (20), 207 (24), 178 (12), 101 (24), 83 (16), 69 (30), 57 (100), 43 (72).

*4.3.5. (1E)-1-[6-Bromo-3-(5-tert-butyl-2-furyl)-1H-indol-2-yl]-4,4-dimethylpent-1-en-3-one (**5e**).* Orange solid; yield 61% (0.52 g); mp 211–212 °C. Found: C, 64.33; H, 6.14; N, 3.01. $C_{23}H_{26}BrNO_2$ requires C, 64.49; H, 6.12; N, 3.27%. R_f=0.63 (acetone/CH_2Cl_2/petroleum ether=1:1:3); ν_{max} (KBr) 3302, 2965, 1658, 1558, 1278, 1224, 1193, 1091, 1037, 1010, 800 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.40 (1H, s, NH), 8.27 (1H, d, *J* 15.6 Hz, H_{Ar}), 7.77 (1H, d, *J* 8.4 Hz, H_{Ar}), 7.49 (1H, d, *J* 1.8 Hz, H_{Ar}), 7.27 (1H, dd, *J* 8.4, 1.8 Hz, H_{Ar}), 6.90 (1H, d, *J* 15.6 Hz, =CH), 6.51 (1H, d, *J* 3.3 Hz, H_{Fur}), 6.11 (1H, d, *J* 3.3 Hz, H_{Fur}), 1.39 (9H, s, $C(CH_3)_3$), 1.25 (9H, s, $C(CH_3)_3$); δ_C (75 MHz, $CDCl_3$) 203.5, 164.8, 146.7, 138.2, 131.7, 130.4, 125.2, 124.6, 123.0, 119.3, 118.6, 114.7, 114.1, 109.5, 104.2, 43.4, 33.0, 29.4 (3C), 26.7 (3C); *m*/*z* (EI, 70 eV) 429/427 (M^+, 38/38), 414/412 (24/25), 373/371 (59/59), 355 (29), 313 (29), 291 (15), 276 (17), 233 (15), 207 (22), 178 (22), 101 (28), 83 (19), 69 (32), 57 (100), 42 (98).

*4.3.6. (1E)-1-[5-Chloro-3-(5-tert-butyl-2-furyl)-1H-indol-2-yl]-4,4-dimethylpent-1-en-3-one (**5f**).* Pale-orange solid; yield 73% (0.56 g); mp 209–210 °C; Found: C, 72.08; H, 6.82; N, 3.67. $C_{23}H_{26}ClNO_2$ requires C, 71.96; H, 6.83; N, 3.65%; R_f=0.58 (acetone/CH_2Cl_2/petroleum ether=1:1:3); ν_{max} (KBr) 3294, 2967, 1661, 1567, 1476, 1273, 1092, 1008, 968, 778 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.90 (1H, s, NH), 8.33 (1H, d, *J* 15.9 Hz, =CH), 7.87 (1H, s, H_{Ar}), 7.23 (2H, s, H_{Ar}), 6.99 (1H, d, *J* 15.9 Hz, =CH), 6.49 (1H, d, *J* 3.3 Hz, H_{Fur}), 6.08 (1H, d, *J* 3.3 Hz, H_{Fur}), 1.36 (9H, s, $C(CH_3)_3$), 1.24 (9H, s, $C(CH_3)_3$); δ_C (75 MHz, $CDCl_3$) 203.9, 164.5, 146.4, 135.7, 131.9, 130.8, 126.9, 126.5, 125.7, 120.9, 118.5, 113.9, 112.0, 109.0, 104.0, 43.2, 32.8, 29.1 (3C), 26.5 (3C); *m*/*z* (EI, 70 eV) 385/383 (M^+, 30/90), 370/368 (25/72), 326 (54), 312 (44), 271 (25), 242 (22), 207 (21), 57 (100), 43 (54).

*4.3.7. Methyl 2-[(1E)-4,4-dimethyl-3-oxopent-1-enyl]-3-(5-tert-butyl-2-furyl)-1H-indole-6-carboxylate (**5g**).* Yellow solid; yield 62% (0.50 g); mp 218–219 °C. Found: C, 73.61; H, 7.10; N, 3.31. $C_{25}H_{29}NO_4$ requires C, 73.69; H, 7.17; N, 3.44%. R_f=0.55 (acetone/CH_2Cl_2/petroleum ether=1:1:3); ν_{max} (KBr) 2964, 1706, 1673, 1596, 1508, 1436, 1365, 1309, 1292, 1272, 1214, 1081, 1007, 974, 776, 742 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 9.45 (1H, s, NH), 8.32 (1H, d, *J* 15.9 Hz, =CH), 8.07 (1H, d, *J*=1.5 Hz, H_{Ar}), 7.91 (1H, d, *J* 8.7 Hz, H_{Ar}), 7.81 (1H, dd, *J* 8.7, 1.5 Hz, H_{Ar}), 7.15 (1H, d, *J* 15.9 Hz, =CH), 6.52 (1H, d, *J* 3.3 Hz, H_{Fur}), 6.09 (1H, d, *J* 3.3 Hz, H_{Fur}), 3.91 (3H, s, OCH_3), 1.37 (9H, s, $C(CH_3)_3$), 1.22 (9H, s, $C(CH_3)_3$); δ_C (75 MHz, $CDCl_3$) 204.1, 168.0, 164.4, 146.5, 136.7, 132.6, 131.7, 129.2, 126.2, 121.5, 121.1, 119.9, 114.0, 113.4, 109.0, 104.0, 52.3, 43.3, 33.0, 29.1 (3C), 26.4 (3C); *m*/*z* (EI, 70 eV) 407 (M^+, 100), 392 (25), 350 (95), 334 (44), 294 (38), 266 (33), 234 (25), 69 (25), 57 (69), 42 (75).

*4.3.8. 1-[3-(5-tert-Butyl-2-furyl)-4,7-dimethoxy-5-methyl-1H-indol-2-yl]-4,4-dimethylpent-1-en-3-one (**5h**).* Dark-orange solid; yield 67% (0.57 g); mp 225–226 °C. Found: C, 73.61; H, 7.84; N, 3.19. $C_{26}H_{33}NO_4$ requires C, 73.73; H, 7.85; N, 3.31%. R_f=0.57 (acetone/CH_2Cl_2/petroleum ether=1:1:3); ν_{max} (KBr) 3268, 2964, 1664, 1576, 1318, 1270, 1223, 1195, 1095, 1042, 1006, 925, 805 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 11.79 (1H, s, NH), 7.76 (1H, d, *J* 16.0 Hz, =CH), 7.63 (1H, d, *J* 16.0 Hz, =CH), 6.66 (1H, s, H_{Ar}), 6.46 (1H, d, *J* 3.2 Hz, H_{Fur}), 6.16 (1H, d, *J* 3.2 Hz, H_{Fur}), 3.94 (3H, s, OCH_3), 3.30 (3H, s, OCH_3), 2.27 (3H, s, CH_3), 1.33 (9H, s, $C(CH_3)_3$), 1.17 (9H, s, $C(CH_3)_3$); δ_C (100 MHz, DMSO-d_6) 203.1, 163.2, 146.0, 144.7, 141.9, 131.8, 130.5, 127.9, 120.5, 120.4, 120.1, 111.2, 110.6, 107.5, 103.7, 60.3, 55.5, 42.8, 32.3, 28.9 (3C), 25.9 (3C), 15.4; *m*/*z* (EI, 70 eV) 423 (M^+, 100), 408 (28), 366 (83), 293 (58), 282 (25), 265 (20), 236 (33), 222 (13), 208 (14), 194 (13), 180 (20), 167 (13), 57 (87), 44 (32).

*4.3.9. 4-[4,7-Dimethoxy-5-methyl-3-(5-methyl-2-furyl)-1H-indol-2-yl]but-3-en-2-one (**5i**).* Yellow solid; yield 30% (0.20 g); mp 234–235 °C. Found: C, 70.90; H, 6.21; N, 4.08. $C_{20}H_{21}NO_4$ requires C, 70.78; H, 6.24; N, 4.13%. R_f=0.34 (acetone/CH_2Cl_2/petroleum ether=1:1:3); ν_{max} (KBr) 3215, 1638, 1609, 1512, 1319, 1265, 1227, 1196, 1045 cm^{-1}; δ_H (400 MHz, DMSO) 11.78 (1H, s, NH), 7.62 (1H, d, *J* 16.4 Hz, =CH), 7.11 (1H, d, *J* 16.4 Hz, =CH), 6.65 (1H, s, H_{Ar}), 6.46 (1H, d, *J* 3.2 Hz, H_{Fur}), 6.20 (1H, d, *J*=3.2 Hz, H_{Fur}), 3.92 (3H, s, OCH_3), 3.36 (3H, s, OCH_3), 2.36 (3H, s, CH_3), 2.27 (6H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 197.4, 151.4, 146.0, 144.6, 142.0, 131.2 (2C), 128.1, 125.9, 120.6, 120.3, 111.3, 111.2, 107.7, 107.4, 60.3, 55.5, 27.6, 15.4, 13.4; *m*/*z* (EI, 70 eV) 339 (M^+, 100), 324 (66), 282 (15), 266 (15), 127 (10), 101 (14), 57 (14), 42 (27).

*4.3.10. 1-[3-(5-Ethyl-2-furyl)-4,7-dimethoxy-5-methyl-1H-indol-2-yl]pent-1-en-3-one (**5j**).* Yellow solid; yield 44% (0.32 g); mp 211–212 °C. Found: C, 71.88; H, 6.85; N, 3.88. $C_{22}H_{25}NO_4$ requires C, 71.91; H, 6.86; N, 3.81%. R_f=0.42 (acetone/CH_2Cl_2/petroleum ether=1:1:3); ν_{max} (KBr) 3229, 1654, 1616, 1510, 1348, 1331, 1302, 1267, 1227, 1186, 1148, 1036, 797 cm^{-1}; δ_H (400 MHz, DMSO) 11.77 (1H, s, NH), 7.67 (1H, d, *J* 16.4 Hz, =CH), 7.20 (1H, d, *J* 16.4 Hz, =CH), 6.65 (1H, s, H_{Ar}), 6.50 (1H, d, *J* 3.2 Hz, H_{Fur}), 6.24 (1H, d, *J* 3.2 Hz, H_{Fur}), 3.92 (3H, s, OCH_3), 3.34 (3H, s, OCH_3), 2.67 (2H, q, *J* 7.6 Hz, CH_2), 2.58 (2H, q, *J* 7.2 Hz, CH_2), 2.26 (3H, s, CH_3), 1.23 (3H, t, *J* 7.6 Hz, CH_3), 1.00 (3H, t, *J* 7.2 Hz, CH_3); δ_C (100 MHz, $CDCl_3$) 200.3, 157.4, 146.6, 145.2, 142.6, 131.9, 130.6, 128.6, 125.3, 121.1, 120.8, 111.8, 111.5, 108.2, 106.5, 60.9, 56.1, 34.4, 21.5, 16.0, 12.8, 8.8; *m*/*z* (EI, 70 eV) 367 (M^+, 100), 352 (73), 338 (40), 310 (20), 252 (12), 183 (10), 101 (10), 83 (10), 59 (14), 43 (32%).

*4.3.11. 2-[Bis(5-tert-butyl-2-furyl)methyl]-4,5-dimethoxyaniline (**8k**).*[17f] Pale-yellow solid; yield 51% (0.42 g); mp 118–119 °C; δ_H

(300 MHz, $CDCl_3$) 6.44 (1H, s, H_{Ar}), 6.32 (1H, s, H_{Ar}), 5.89 (4H, s, H_{Fur}), 5.36 (1H, s, CH), 3.83 (3H, s, OCH_3), 3.68 (3H, s, OCH_3), 3.16 (2H, br s, NH_2), 1.16 (18H, s, $C(CH_3)_3$).

*4.3.12. 2-[Bis(5-tert-butyl-2-furyl)methyl]-4-methoxyaniline (**8l**).* Dark-yellow solid; yield 55% (0.42 g); mp 76–77 °C. Found: C, 75.46; H, 8.19; N, 3.52. $C_{24}H_{31}NO_3$ requires C, 75.56; H, 8.19; N, 3.67%. R_f=0.69 (acetone/CH_2Cl_2/petroleum ether=1:1:3); ν_{max} (KBr) 3430, 3358, 2971, 1504, 1433, 1286, 1271, 1217, 1194, 1134, 1102, 809, 796, 782, 730 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.72 (1H, d, *J* 8.4 Hz, H_{Ar}), 6.67 (1H, dd, *J*=8.4, 2.7 Hz, H_{Ar}), 6.47 (1H, d, *J* 2.7 Hz, H_{Ar}), 5.87 (2H, d, *J* 3.3 Hz, H_{Fur}), 5.86 (2H, d, *J* 3.3 Hz, H_{Fur}), 5.45 (1H, s, CH), 3.95 (2H, br s, NH_2), 3.65 (3H, s, OCH_3), 1.24 (18H, s, $C(CH_3)_3$); δ_C (75 MHz, $CDCl_3$) 163.9 (2C), 153.7, 151.3 (2C), 136.7, 128.2, 118.4, 114.5, 113.8, 108.2 (2C), 102.5 (2C), 55.7, 40.9, 32.7 (2C), 29.2 (6C); *m*/*z* (EI, 70 eV) 381 (M^+, 100), 324 (10), 282 (14), 200 (25), 57 (32), 43 (20).

*4.3.13. 2-[Bis(5-tert-butyl-2-thiophenyl)methyl]aniline (**8m**).* Pale-yellow solid; yield 54% (0.41 g); mp 93–94 °C. Found: C, 71.98; H, 7.65; N, 3.58; S, 16.93. $C_{23}H_{29}NS_2$ requires C, 72.01; H, 7.62; N, 3.65; S, 16.72%. R_f=0.63 (acetone/CH_2Cl_2/petroleum ether=1:1:3); ν_{max} (KBr) 3434, 3357, 2964, 1625, 1487, 1456, 1364, 1256, 813, 794, 753 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.14–7.09 (1H, m, H_{Ar}), 7.04–7.01 (1H, m, H_{Ar}), 6.83–6.77 (1H, m, H_{Ar}), 6.76–6.74 (1H, m, H_{Ar}), 6.64 (2H, d, *J* 3.6 Hz, H_{Th}), 6.62 (2H, d, *J* 3.6 Hz, H_{Th}), 5.78 (1H, s, CH), 4.09 (2H, br s, NH_2), 1.35 (18H, s, $C(CH_3)_3$); δ_C (75 MHz, $CDCl_3$) 157.1 (2C), 142.8 (2C), 130.1, 129.0, 128.1, 125.7 (2C), 121.7, 120.7 (2C), 119.6, 117.1, 43.0, 34.7 (2C), 32.6 (6C); *m*/*z* (EI, 70 eV) 383 (M^+, 100), 368 (15), 326 (64), 242 (31), 186 (36), 97 (10), 57 (42), 43 (43).

*4.3.14. 2-[Bis(5-methyl-2-thiophenyl)methyl]aniline (**8n**).* Pale-green solid; yield 63% (0.38 g); mp 91–92 °C. Found: C, 68.06; H, 5.73; N, 4.52; S, 21.63. $C_{17}H_{17}NS_2$ requires C, 68.19; H, 5.72; N, 4.68; S, 21.41%. R_f=0.58 (acetone/CH_2Cl_2/petroleum ether=1:1:3); ν_{max} (KBr) 3447, 3364, 1620, 1580, 1490, 1455, 1291, 1225, 1030, 813, 795, 770, 749 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.13–7.07 (1H, m, H_{Ar}), 7.02–6.99 (1H, m, H_{Ar}), 6.78–6.73 (1H, m, H_{Ar}), 6.70–6.67 (1H, m, H_{Ar}), 6.63 (2H, d, *J* 3.6 Hz, H_{Th}), 6.60 (2H, d, *J* 3.6 Hz, H_{Th}), 5.71 (1H, s, CH), 3.61 (2H, s, NH_2), 2.44 (6H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 143.9, 143.7 (2C), 139.3 (2C), 129.2, 128.5, 127.9, 126.0 (2C), 124.7 (2C), 118.8, 116.4, 42.7, 15.4 (2C); *m*/*z* (EI, 70 eV) 299 (M^+, 100), 284 (25), 266 (15), 207 (15), 200 (80), 101 (20), 76 (20), 59 (58), 43 (58).

*4.3.15. 1-[2-(3-Oxopent-1-enyl)-1H-indol-3-yl]hexane-1,4-dione (**9**).* Yellow solid; yield 12% (0.08 g); mp 200–201 °C. Found: C, 73.13; H, 6.79; N, 4.64. $C_{19}H_{21}NO_3$ requires C, 73.29; H, 6.80; N, 4.50%. R_f=0.42 (acetone/CH_2Cl_2/petroleum ether=1:1:3); ν_{max} (KBr) 3280, 1709, 1660, 1441, 1409, 1363, 1201, 1161, 979, 749 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 10.31 (1H, s, NH), 8.06 (1H, d, *J* 16.8 Hz, =CH), 7.87–7.85 (1H, m, H_{Ar}), 7.44–7.41 (1H, m, H_{Ar}), 7.31–7.26 (1H, m, H_{Ar}), 7.22–7.17 (1H, m, H_{Ar}), 6.64 (1H, d, *J* 16.8 Hz, =CH), 3.36–3.32 (2H, m, CH_2), 2.99–2.95 (2H, m, CH_2), 2.67 (2H, q, *J* 7.5 Hz, CH_2), 2.59 (2H, q, *J* 7.5 Hz, CH_2), 1.18 (3H, t, *J* 7.5 Hz, CH_3), 1.12 (3H, t, *J* 7.5 Hz, CH_3); δ_C (75 MHz, $CDCl_3$) 211.8, 202.3, 195.9, 137.8, 137.0, 132.5, 129.2, 126.5, 125.0, 122.7, 121.8, 117.6, 112.4, 37.5, 36.3, 36.0, 31.6, 8.2, 8.1; *m*/*z* (EI, 70 eV) 311 (M^+, 8), 272 (12), 254 (100), 198 (18), 170 (18), 59 (12), 43 (20).

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Supplementary data

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