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A rapid synthesis of 2-alkynylindoles and 2-alkynylbenzofurans

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ABSTRACT

An expeditious synthesis of 2-alkynylindoles and 2-alkynylbenzofuran derivatives has been devised starting from easily available *ortho*-substituted aryl diynes.

1. Introduction

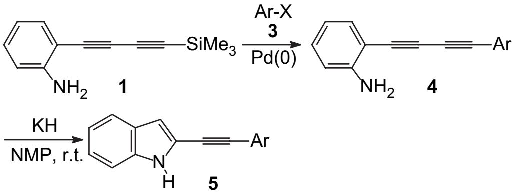
The indole nucleus is a prominent structural unit frequently found in numerous natural products and pharmaceutically active compounds.[1] Various 2-substituted indoles exhibit interesting pharmacological properties[2] such as antithrombotic,[2a] anticancer[2b] and histamine H_3 receptor antagonist.[2c] Consequently, the development of efficient methodologies for the synthesis of these compounds continues to be an active area of research.[3,4] Among the various synthetic strategies, one of the modern approaches for forming indoles is based upon the Pd-catalyzed ring closure of functionalised 2-alkynylaniline derivatives.[3b,c] Moreover, many kind of reagents have been reported for indole synthesis, such as the rhodium-catalyzed cycloisomerization of 2-alkynylanilines,[4b] the indole ring synthesis from 2-ethynylaniline derivatives catalyzed by Cu(II) salts[4m] and the synthesis of polyfunctional indoles mediated by caesium and potassium bases.[4p]

The benzofuran ring can be found as a key structural unit in many natural products and biologically active compounds,[5] and therefore a growing interest has been devoted towards the synthesis of benzofuran derivatives, because of their activities as antitumour agents,[6] as ligands of the adenosine A1 receptors,[7] and as inhibitors of 5-lipoxygenase.[8] A number of efficient and selective methods have been developed for their synthesis,[9] but generally benzofurans are prepared by either palladium-catalyzed one-pot annulations of *ortho*-hydroxy aryl halides with alkynes[3c,9a,c,g,10] or the metal-[4b,11] or base-mediated cyclization of *ortho*-alkynyl phenols.[4p,12]

We have recently reported successfully the applications of our methodology,[13] which led to the synthesis of a variety of unsymmetrically substituted conjugated diynes, to the preparation of a series of natural diacetylenic compounds,[14–16] and of naturally occurring polyacetylenes.[17] Moreover, more recently,[18] a further and successful application of our methodology led to a straightforward synthesis of a variety of bis-indolyl and bis-benzofuran derivatives. We now report a simple method to prepare both indole and benzofuran scaffolds bearing an alkyne at the 2-position and show the possibility of an expeditious synthesis of various functionalized 2-alkynylindoles and 2-alkynylbenzofurans starting from easily available *ortho*-substituted aryl diynes.[18]

2. Results and discussion

Relatively to the synthesis of 2-alkynylindole derivatives, as depicted in Scheme 1, our approach was based upon coupling reactions between the 2-(4-trimethylsilyl-1,3-butadiyn-1-yl)aniline **1**[18] and various aryl halides and subsequent annulation of the resulting products with bases. Then, we subjected the monosilylated compound **1** to a direct cross-coupling reaction with different aryl iodides **3**, according to our previously reported procedure,[13] in the presence of catalytic amounts of $Pd(PPh_3)_4$ and AgCl. Various aryl iodides **3** were used, bicyclic α-iodonaphtalene (entry 3), *ortho*-substituted (entry 5) and *para*-substituted (entries 2, 4 and 6) aryl iodides, and all the functionalized 1,3-butadiynes **4** were obtained in high yields (73–82%) (Table 1). Then, in order to demonstrate the versatility of compounds **4** as useful precursors of functionalized indole systems, we started to investigate the cyclization reaction conditions. We found that the substituted butadiynylaniline derivatives **4** were efficiently converted into



Scheme 1. Conversion of compound **1** into 2-alkynylindole derivatives **5**.

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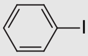
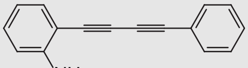
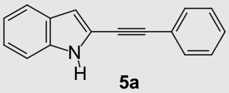
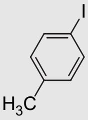
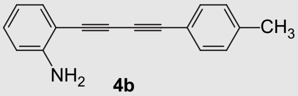
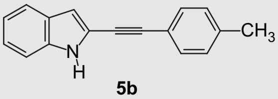
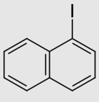
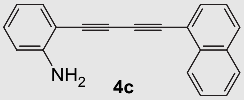
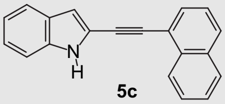
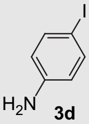
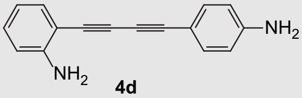
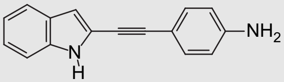
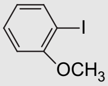
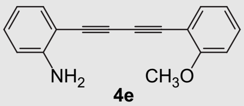
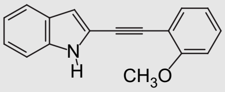
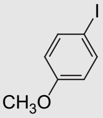
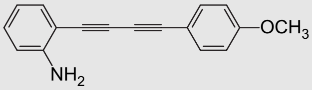
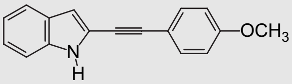
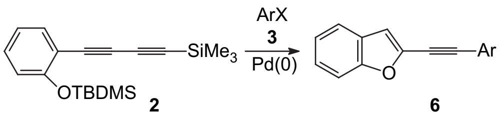
Table 1
Synthesis of 2-alkynylindoles **5** via Scheme 1

Entry	Ar–X **3**	Coupling products **4**[a]	Yields[b] (%)	2-Alkynylindoles **5**[c]	Yields[b] (%)
1	 **3a**	 **4a**	80	 **5a**	64
2	 **3b**	 **4b**	79	 **5b**	50
3	 **3c**	 **4c**	81	 **5c**	50
4	 **3d**	 **4d**	73	 **5d**	68[d]
5	 **3e**	 **4e**	76	 **5e**	64
6	 **3f**	 **4f**	82	 **5f**	63

[a] All reactions were carried out in DMF at 40 °C for 12 h, according to a general procedure.
[b] Yields of purified isolated products.
[c] Unless otherwise indicated, all reactions were carried out in NMP at room temperature for 1 h, according to a general procedure.
[d] Reaction performed at 55 °C for 20 h.

2-alkynylindole derivatives (50–68% yields) by means of KH in *N*-methylpyrrolidinone (NMP).[4p] It is noteworthy that the results have not been optimized (e.g., type of base for the cyclization) since we intended only to demonstrate the validity of our approach.

With regards to the synthesis of 2-alkynylbenzofuran derivatives we found that, by employing the same approach, (Scheme 2), based upon coupling and cyclization reactions, these compounds were obtained easily in one step by a tandem coupling/cyclization reaction. Indeed, starting from **2**,[18] 2-(4-trimethylsilyl-1,3-butadiyn-1-yl)-*tert*-butyldimethylsilylphenol, when we subjected this compound to the coupling reaction with various aryl halides, the heterocyclic 2-alkynylbenzofuran derivatives **6** were directly obtained in fair to good yields (40–85%). The overall results are reported in Table 2. Various *para*-substituted (entries 2, 4, 5 and 6) aryl halides were used and also heterocyclic halides (entries 7 and 8) and a vinyl bromide (entry 9) were used.



2 **6**

Scheme 2. Conversion of compound **2** into 2-alkynylbenzofuran derivatives **6**.

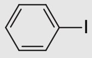
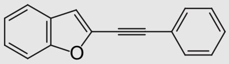
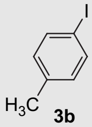
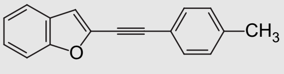
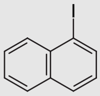
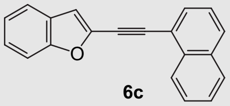
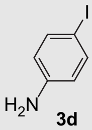
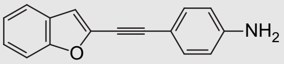
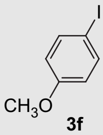
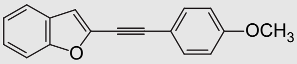
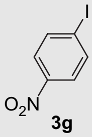
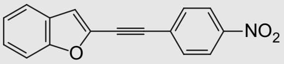
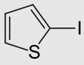
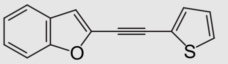
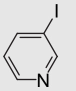
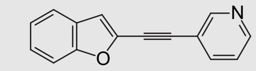
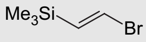
In summary, we have developed a convenient and rapid synthesis of 2-alkynylindoles and 2-alkynylbenzofurans employing readily accessible starting materials. A special advantage of our strategy is represented by the possibility of preparing different heterocyclic systems starting from the same compound and following the same reaction sequence. Moreover, in principle, we wish to underline that with this procedure it is sufficient to choose different aryl halides to perform with success, and in two or one step, the synthesis of various substituted 2-alkynylindoles and 2-alkynylbenzofurans, without the necessity of the preparation of different and not always available terminal alkynes, according to the general procedure reported in the literature. Therefore, we believe that this method represents one of the shortest and efficient routes for the access to this important class of compounds that compares favourably also with an alternative recent methodology.[19] Further investigations towards the synthesis of more complex and elaborate molecules, having the indole and the benzofuran skeleton as a core framework, are currently in progress.

3. Experimental

3.1. General

Macherey–Nagel silica gel (60, particle size 0.040–0.063 mm) for column chromatography and Macherey–Nagel aluminium sheets with silica gel 60 F_{254} for TLC were used. GC analysis was performed on a Varian 3900 gas chromatograph equipped with a Supelco capillary column (SLB™-5ms, 30 m×0.25 mm id). GC/mass-spectrometric analysis was performed on a Shimadzu

Table 2
Synthesis of 2-alkynylbenzofurans **6** via Scheme 2

Entry	Halides **3**	2-Alkynylbenzofurans **6**[a]	Yields[b] (%)
1	 **3a**	 **6a**	65
2	 **3b**	 **6b**	52
3	 **3c**	 **6c**	53
4	 **3d**	 **6d**	40
5	 **3f**	 **6f**	55
6	 **3g**	 **6g**	70
7	 **3h**	 **6h**	73
8	 **3i**	 **6i**	85
9	 **3j**	 **6j**	78

[a] All reactions were carried out in DMF at 40 °C for 1–5 h, according to a general procedure.
[b] Yields of purified isolated products.

GC–MS-QP5000 gas chromatograph–mass spectrometer equipped with a Supelco capillary column (SLB™-5ms, 30 m×0.25 mm id). ^{1}H NMR spectra were recorded in deuterochloroform or acetone-d_6 on a Bruker AM 500 spectrometer at 500 MHz or on a Varian Inova at 400 MHz. ^{13}C NMR spectra were recorded in deuterochloroform or acetone-d_6 on a Bruker AM 500 spectrometer at 125.7 MHz or on a Varian Inova at 100.6 MHz. IR spectra were recorded on a Perkin–Elmer FT-IR Spectrum Bx spectrometer. Melting points (uncorrected) were determined on a Reichert Microscope. Elemental analyses were recorded on a Carlo Erba EA 1108 elemental analyzer. *N*,*N*-Dimethylformamide was distilled over molecular sieves and commercial NMP was used as-supplied.

3.2. General procedure for the synthesis of compounds 4

To a solution (0.4 N) of aryl iodide **3** (1.0 equiv) in anhydrous DMF, at room temperature under nitrogen, were successively added Pd(PPh$_3$)$_4$ (0.05 equiv), AgCl (0.2 equiv) and K$_2$CO$_3$ (8.0 equiv). The resulting mixture was stirred for 5 min, then MeOH (8.0 equiv) was added followed by a solution (0.4 N) of 2-(4-trimethylsilyl-1,3-butadiyn-1-yl)aniline **1** (1.0 equiv) in anhydrous DMF. The reaction mixture was warmed to 40 °C and stirred at the same temperature for 12 h, then quenched with aqueous NH$_4$Cl and extracted with ethyl acetate. The organic extracts were washed with water, dried over anhydrous Na$_2$SO$_4$ and concentrated under vacuum. The residue was purified by column chromatography on silica gel.

3.2.1. *2-(4-Phenylbuta-1,3-diyn-1-yl)aniline (**4a**)*

Product **4a** was prepared from **1** (0.200 g, 0.94 mmol) and iodobenzene **3a** (0.192 g, 0.94 mmol) in accordance with general procedure. Purification by column chromatography (silica gel, 20% ethyl acetate/petroleum ether) afforded 0.163 g of product **4a** (80% yield) as a yellow-brown solid (mp=73–75 °C). [Found: C, 88.52; H, 5.15; N, 6.50. C$_{16}$H$_{11}$N requires C, 88.45; H, 5.10; N, 6.45%.] ν_{max} (KBr) 3466, 3376, 2205, 2137, 1607, 1450, 1307, 1254, 1157, 1069, 1022, 913, 750, 688; δ_H (500 MHz, CDCl$_3$) 7.55–7.50 (m, 2H), 7.38–7.30 (m, 4H), 7.15 (ddd, *J*=8.4, 7.4, 1.5 Hz, 1H), 6.71–6.65 (m, 2H), 4.31 (br s, 2H); δ_C (125.7 MHz, CDCl$_3$) 149.5, 133.0, 132.3, 130.6, 129.1, 128.4, 121.8, 117.9, 114.3, 106.0, 82.7, 79.0, 78.6, 73.9; MS *m*/*z* 217 (M$^+$, 100), 216 (44), 190 (10), 189 (25), 163 (5), 150 (3), 139 (3), 115 (3), 114 (4), 113 (4), 109 (25), 96 (10), 94 (26), 89 (10), 83 (8), 81 (10), 63 (7), 51 (7%).

3.2.2. *2-[4-(4-Methylphenyl)buta-1,3-diyn-1-yl]aniline (**4b**)*

Product **4b** was prepared from **1** (0.300 g, 1.41 mmol) and 4-iodotoluene **3b** (0.307 g, 1.41 mmol) in accordance with general procedure. The residue was purified by column chromatography (silica gel, 20% ethyl acetate/petroleum ether) leading to 0.257 g (79% yield) of compound **4b** as an orange solid (mp=107–109 °C). [Found: C, 88.32; H, 5.63; N, 6.00. C$_{17}$H$_{13}$N requires C, 88.28; H, 5.67; N, 6.06%.] ν_{max} (KBr) 3461, 3370, 2205, 2132, 1609, 1457, 1312, 1253, 1156, 1028, 810, 748, 522; δ_H (500 MHz, CDCl$_3$) 7.42 (d, *J*=8.1 Hz, 2H), 7.34 (dd, *J*=8.0, 1.4 Hz, 1H), 7.19–7.10 (m, 3H), 6.73–6.62 (m, 2H), 4.30 (br s, 2H), 2.36 (s, 3H); δ_C (125.7 MHz, CDCl$_3$) 149.5, 139.5, 133.0, 132.3, 130.5, 129.2, 118.7, 117.9, 114.3, 106.2, 83.0, 79.1, 78.2, 73.3, 21.6; MS *m*/*z* 231 (M$^+$, 100), 230 (38), 229 (10), 228 (16), 216 (14), 202 (20), 189 (7), 176 (4), 163 (4), 151 (4), 139 (4), 115 (62), 114 (39), 102 (28), 101 (38), 100 (13), 89 (20), 88 (24), 76 (11), 75 (11), 63 (15), 51 (12%).

3.2.3. *2-(4-Naphthalen-1-ylbuta-1,3-diyn-1-yl)aniline (**4c**)*

Compound **4c** was prepared from **1** (0.200 g, 0.94 mmol) and 1-iodonaphthalene **3c** (0.239 g, 0.94 mmol) in accordance with general procedure. Purification by column chromatography (silica gel, 20% ethyl acetate/petroleum ether) afforded compound **4c** (0.251 g, 81% yield) as a yellow-brown solid (mp=107–109 °C). [Found: C, 89.75; H, 4.85; N, 5.30. C$_{20}$H$_{13}$N requires C, 89.86; H, 4.90; N, 5.24%.] ν_{max} (KBr) 3447, 3360, 2201, 2132, 1610, 1488, 1450, 1311, 1252, 1157, 797, 769, 746; δ_H (500 MHz, CDCl$_3$) 8.37 (d, *J*=8.4 Hz, 1H), 7.86 (d, *J*=8.4 Hz, 2H), 7.78 (dd, *J*=7.1, 0.7 Hz, 1H), 7.63–7.57 (m, 1H), 7.56–7.51 (m, 1H), 7.43 (dd, *J*=8.2, 7.2 Hz, 1H), 7.40 (dd, *J*=7.9, 1.5 Hz, 1H), 7.20–7.14 (m, 1H), 6.74–6.67 (m, 2H), 4.37 (br s, 2H); δ_C (125.7 MHz, CDCl$_3$) 149.6, 133.8, 133.1, 133.0, 131.9, 130.7, 129.7, 128.4, 127.2, 126.7, 126.0, 125.2, 119.5, 118.0, 114.4, 106.1, 81.0, 79.7, 79.2, 78.5; MS *m*/*z* 267 (M$^+$, 100), 266 (49), 265 (15), 264 (16), 239 (18), 237 (9), 213 (3), 211 (2), 187 (3), 176 (2), 163 (4), 150 (3), 134 (43), 133 (26), 121 (11), 109 (71), 106 (29), 94 (10), 89 (20), 63 (7), 51 (5%).

3.2.4. 2-[4-(4-Aminophenyl)buta-1,3-diyn-1-yl]aniline (**4d**)

Compound **4d** was prepared from **1** (0.200 g, 0.94 mmol) and 4-iodoaniline **3d** (0.206 g, 0.94 mmol) in accordance with general procedure. Purification by column chromatography (silica gel, 50% ethyl acetate/petroleum ether) gave **4d** (0.159 g, 73% yield) as a yellow-brown solid (mp=140–143 °C). [Found: C, 82.75; H, 5.29; N, 12.00. $C_{16}H_{12}N_2$ requires C, 82.73; H, 5.21; N, 12.06%.] ν_{max} (KBr) 3432, 3325, 3204, 2199, 2131, 1594, 1481, 1449, 1301, 1260, 1173, 1155, 1093, 1023, 828, 741, 526; δ_H (500 MHz, acetone-d_6) 7.30–7.22 (m, 3H), 7.12–7.09 (m, 1H), 6.79 (d, *J*=8.4 Hz, 1H), 6.68 (d, *J*=8.7 Hz, 2H), 6.59 (t, *J*=7.5 Hz, 1H), 5.20 (br s, 2H), 5.18 (br s, 2H); δ_C (125.7 MHz, acetone-d_6) 151.7, 150.8, 134.5, 133.4, 131.1, 117.4, 115.0, 114.8, 108.9, 106.1, 84.9, 79.9, 78.7, 72.3; MS *m*/*z* 232 (M^+, 100), 231 (41), 214 (7), 204 (23), 203 (10), 176 (9), 151 (6), 117 (12), 116 (72), 115 (9), 102 (85), 90 (10), 89 (42), 88 (39), 77 (17), 76 (22), 75 (16), 63 (14), 62 (12), 52 (11), 51 (11), 41 (8%).

3.2.5. 2-[4-(2-Methoxyphenyl)buta-1,3-diyn-1-yl]aniline (**4e**)

Compound **4e** was prepared from **1** (0.200 g, 0.94 mmol) and 2-iodoanisole **3e** (0.220 g, 0.94 mmol) in accordance with general procedure. The residue was purified by column chromatography (silica gel, 20% ethyl acetate/petroleum ether) leading to product **4e** (0.177 g, 76% yield) as a yellow-brown solid (mp=46–48 °C). [Found: C, 82.65; H, 5.29; N, 5.69. $C_{17}H_{13}NO$ requires C, 82.57; H, 5.30; N, 5.66%.] ν_{max} (CCl_4) 3489, 3393, 2958, 2930, 2210, 2137, 1614, 1594, 1488, 1458, 1276, 1252, 1159, 1117, 1048, 1027; δ_H (500 MHz, $CDCl_3$) 7.47 (dd, *J*=7.6, 1.5 Hz, 1H), 7.35–7.29 (m, 2H), 7.13 (ddd, *J*=8.1, 7.4, 1.5 Hz, 1H), 6.91 (td, *J*=7.6, 0.9 Hz, 1H), 6.88 (d, *J*=8.4 Hz, 1H), 6.69–6.63 (m, 2H), 4.33 (br s, 2H), 3.90 (s, 3H); δ_C (125.7 MHz, $CDCl_3$) 161.3, 149.5, 134.4, 133.1, 130.7, 130.5, 120.6, 117.9, 114.3, 111.1, 110.7, 106.3, 79.3, 79.2, 79.1, 77.6, 55.8; MS *m*/*z* 247 (M^+, 100), 246 (69), 230 (8), 218 (25), 217 (36), 204 (34), 203 (20), 202 (12), 189 (9), 176 (21), 151 (11), 150 (8), 124 (14), 123 (34), 109 (20), 102 (22), 101 (11), 96 (12), 94 (24), 89 (28), 88 (26), 81 (11), 77 (11), 76 (15), 75 (22), 63 (13), 62 (11), 51 (14%).

3.2.6. 2-[4-(4-Methoxyphenyl)buta-1,3-diyn-1-yl]aniline (**4f**)

Compound **4f** was prepared from **1** (0.200 g, 0.94 mmol) and 4-iodoanisole **3f** (0.220 g, 0.94 mmol) in accordance with general procedure. Purification by column chromatography (silica gel, 30% ethyl ether/petroleum ether) gave 0.190 g (82% yield) of compound **4f** as a yellow-brown solid (mp=105–107 °C). [Found: C, 82.60; H, 5.29; N, 5.61. $C_{17}H_{13}NO$ requires C, 82.57; H, 5.30; N, 5.66%.] ν_{max} (KBr) 3454, 3364, 2922, 2208, 2132, 1616, 1596, 1507, 1485, 1458, 1450, 1288, 1244, 1171, 1023, 833, 757, 535; δ_H (500 MHz, $CDCl_3$) 7.46 (d, *J*=8.9 Hz, 2H), 7.33 (dd, *J*=8.2, 1.7 Hz, 1H), 7.16–7.10 (m, 1H), 6.85 (d, *J*=8.9 Hz, 2H), 6.70–6.65 (m, 2H), 4.30 (br s, 2H), 3.80 (s, 3H); δ_C (125.7 MHz, $CDCl_3$) 160.3, 149.5, 134.0, 133.0, 130.5, 117.9, 114.3, 114.1, 113.7, 106.3, 82.9, 79.2, 78.0, 72.7, 55.3; MS *m*/*z* 247 (M^+, 100), 233 (19), 232 (99), 204 (43), 203 (22), 176 (20), 151 (11), 150 (8), 124 (31), 108 (13), 102 (26), 95 (13), 89 (23), 88 (23), 75 (17), 63 (9), 62 (8), 51 (9%).

3.3. General procedure for the synthesis of compounds 5

KH (2.4 equiv) was dissolved in NMP (0.5 N) under nitrogen at room temperature, then a solution (0.2 N) of 2-(4-aryl-1,3-butadiyn-1-yl)aniline **4** (1.0 equiv) in NMP was added dropwise and the mixture was stirred for 1 h at room temperature. The reaction was quenched with water, extracted with ethyl acetate, dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by column chromatography on silica gel.

3.3.1. 2-(Phenylethynyl)-1H-indole (**5a**)[18–20]

Product **5a** was prepared from **4a** (0.046 g, 0.21 mmol) in accordance with general procedure. The residue was purified by column chromatography on silica gel (10% ethyl acetate/petroleum ether) leading to 0.029 g (64% yield) of compound **5a** as a pale orange solid (mp=168–170 °C, lit.[19] mp=161–162 °C). ν_{max} (KBr) 3374, 1592, 1530, 1480, 1440, 1394, 1347, 1303, 1104, 1024, 794, 747, 687, 653, 507; δ_H (500 MHz, $CDCl_3$) 8.21 (br s, 1H), 7.60 (dd, *J*=8.0, 0.8 Hz, 1H), 7.55–7.51 (m, 2H), 7.38–7.30 (m, 4H), 7.23 (ddd, *J*=8.0, 7.1, 1.0 Hz, 1H), 7.12 (ddd, *J*=8.0, 7.1, 1.0 Hz, 1H), 6.84–6.81 (m, 1H); δ_C (125.7 MHz, $CDCl_3$) 136.2, 131.5, 128.6, 128.5, 127.8, 123.5, 122.6, 120.9, 120.5, 118.8, 110.7, 108.8, 92.5, 81.8; MS *m*/*z* 217 (M^+, 100), 216 (33), 189 (14), 109 (26), 94 (18), 83 (6), 81 (7), 63 (7), 51 (6%).

3.3.2. 2-[(4-Methylphenyl)ethynyl]-1H-indole (**5b**)[20]

Compound **5b** was prepared from **4b** (0.150 g, 0.65 mmol) in accordance with general procedure. Purification by column chromatography (silica gel, 10% ethyl acetate/petroleum ether) afforded 0.075 g (50% yield) of product **5b** as a light brown solid (mp=186–188 °C, lit.[20] mp=178–182 °C). ν_{max} (KBr) 3397, 2961, 2923, 2852, 1260, 1099, 1018, 816, 793, 749, 735; δ_H (500 MHz, acetone-d_6) 10.67 (br s, 1H), 7.57 (d, *J*=8.1 Hz, 1H), 7.46–7.38 (m, 3H), 7.26–7.15 (m, 3H), 7.06 (t, *J*=7.5 Hz, 1H), 6.79 (br s, 1H), 2.34 (s, 3H); δ_C (125.7 MHz, acetone-d_6) 139.2, 137.2, 131.5, 129.7, 128.3, 123.4, 120.8, 120.3, 120.1, 119.3, 111.4, 108.1, 92.2, 81.9, 20.9; MS *m*/*z* 231 (M^+, 100), 230 (27), 228 (10), 216 (9), 202 (11), 189 (4), 115 (54), 114 (29), 102 (21), 101 (20), 89 (14), 88 (14), 76 (6), 75 (6), 63 (9), 51 (6%).

3.3.3. 2-(Naphthalen-1-ylethynyl)-1H-indole (**5c**)

Compound **5c** was prepared from **4c** (0.150 g, 0.56 mmol) in accordance with general procedure. Purification by column chromatography (silica gel, 10% ethyl acetate/petroleum ether) led to compound **5c** (0.075 g, 50% yield) as a light brown solid (mp=112–114 °C). [Found: C, 89.90; H, 4.93; N, 5.20. $C_{20}H_{13}N$ requires C, 89.86; H, 4.90; N, 5.24%.] ν_{max} (KBr) 3407, 2197, 1349, 1307, 796, 768, 750, 651, 486; δ_H (500 MHz, $CDCl_3$) 8.40 (d, *J*=8.4 Hz, 1H), 8.33 (br s, 1H), 7.86 (t, *J*=8.0 Hz, 2H), 7.76 (dd, *J*=7.2, 1.0 Hz, 1H), 7.65–7.58 (m, 2H), 7.56–7.52 (m, 1H), 7.46 (dd, *J*=8.1, 7.1 Hz, 1H), 7.36 (br d, *J*=8.1 Hz, 1H), 7.25 (ddd, *J*=8.1, 7.1, 1.0 Hz, 1H), 7.15 (ddd, *J*=7.9, 7.1, 0.8 Hz, 1H), 6.95–6.92 (m, 1H); δ_C (125.7 MHz, $CDCl_3$) 136.3, 133.2, 133.1, 130.4, 129.1, 128.4, 127.9, 126.9, 126.6, 126.1, 125.3, 123.6, 120.9, 120.6, 120.2, 118.9, 110.8, 109.1, 90.8, 86.5; MS *m*/*z* 267 (M^+, 100), 266 (34), 265 (10), 264 (13), 239 (13), 163 (3), 150 (3), 134 (41), 133 (18), 119 (40), 106 (18), 89 (11), 63 (6), 51 (4%).

3.3.4. 4-(1H-Indol-2-ylethynyl)aniline (**5d**)

KH (0.070 g, 1.72 mmol) was dissolved in NMP (2.1 mL) under nitrogen at room temperature, then a solution of **4d** (0.100 g, 0.43 mmol) in NMP (2.2 mL) was added dropwise and the mixture was warmed to 55 °C and stirred for 20 h. The reaction was quenched with water (20 mL), extracted with ethyl acetate (3×20 mL), dried over Na_2SO_4 and concentrated under vacuum. Purification by column chromatography (silica gel, 50% ethyl acetate/petroleum ether) led to compound **5d** (0.068 g, 68% yield) as a yellow solid (mp=205–208 °C). [Found: C, 82.80; H, 5.23; N, 12.00. $C_{16}H_{12}N_2$ requires C, 82.73; H, 5.21; N, 12.06%.] ν_{max} (KBr) 3447, 3386, 3359, 3314, 2201, 1603, 1500, 1296, 1263, 1173, 831, 801, 795, 740, 526; δ_H (400 MHz, acetone-d_6) 10.57 (br s, 1H), 7.53 (d, *J*=7.9 Hz, 1H), 7.38 (d, *J*=8.2 Hz, 1H), 7.25 (d, *J*=8.4 Hz, 2H), 7.15 (t, *J*=7.6 Hz, 1H), 7.03 (t, *J*=7.5 Hz, 1H), 6.73–6.63 (m, 3H), 5.11 (br s, 2H); δ_C (100.6 MHz, acetone-d_6) 149.6, 136.9, 132.8, 128.3, 122.7, 120.4, 120.1, 120.0, 114.2, 111.1, 109.8, 106.9, 93.3, 79.5; MS *m*/*z* 232 (M^+, 100), 231 (27), 214 (4), 204 (13), 177 (4), 176 (6), 151 (4), 117 (11), 116 (57), 102 (43), 89 (19), 88 (18), 77 (9), 76 (9), 63 (7), 51 (5), 44 (5%).

3.3.5. 2-[(2-Methoxyphenyl)ethynyl]-1H-indole (**5e**)

Compound **5e** was prepared from **4e** (0.101 g, 0.41 mmol) in accordance with general procedure. The residue was purified by column chromatography (silica gel, 10% ethyl acetate/petroleum ether) leading to 0.065 g (64% yield) of compound **5e** as a light brown solid (mp=105–107 °C). [Found: C, 82.65; H, 5.27; N, 5.61. $C_{17}H_{13}NO$ requires C, 82.57; H, 5.30; N, 5.66%.] ν_{max} (KBr) 3385, 2925, 2207, 1482, 1458, 1353, 1255, 1234, 1159, 1101, 1019, 797, 756, 750, 736, 651, 504. δ_H (400 MHz, $CDCl_3$) 8.33 (br s, 1H), 7.58 (d, *J*=7.9 Hz, 1H), 7.50 (d, *J*=7.4 Hz, 1H), 7.35–7.27 (m, 2H), 7.21 (t, *J*=7.6 Hz, 1H), 7.10 (t, *J*=7.4 Hz, 1H), 6.95 (t, *J*=7.6 Hz, 1H), 6.90 (d, *J*=8.4 Hz, 1H), 6.84 (br s, 1H), 3.91 (s, 3H); δ_C (100.6 MHz, $CDCl_3$) 160.1, 136.4, 133.6, 130.3, 128.1, 123.6, 121.0, 120.8, 120.6, 119.3, 112.0, 111.0, 110.9, 108.9, 89.2, 86.0, 56.0; MS *m/z* 247 (M^+, 100), 246 (80), 230 (8), 218 (18), 217 (17), 204 (30), 203 (14), 176 (13), 151 (8), 123 (56), 109 (21), 102 (39), 96 (20), 94 (23), 89 (33), 88 (26), 83 (16), 76 (11), 75 (18), 63 (11), 57 (17), 55 (13), 51 (10), 43 (17), 41 (11%).

*3.3.6. 2-[(4-Methoxyphenyl)ethynyl]-1H-indole (**5f**)*[20]

Compound **5f** was prepared from **4f** (0.101 g, 0.41 mmol) in accordance with general procedure. Purification by column chromatography (silica gel, 10% ethyl acetate/petroleum ether) afforded 0.064 g of compound **5f** (63% yield) as a light brown solid (mp=170–172 °C, lit.[20] mp=163–165 °C). ν_{max} (KBr) 3416, 2925, 1601, 1499, 1302, 1288, 1246, 1027, 836, 823, 798, 750, 739, 650, 535, 482; δ_H (500 MHz, $CDCl_3$) 8.2 (br s, 1H), 7.59 (d, *J*=7.9 Hz, 1H), 7.48 (d, *J*=8.9 Hz, 2H), 7.31 (d, *J*=8.4 Hz, 1H), 7.22 (t, *J*=8.1 Hz, 1H), 7.12 (t, *J*=8.1 Hz, 1H), 6.89 (d, *J*=8.9 Hz, 2H), 6.81–6.78 (m, 1H), 3.82 (s, 3H); δ_C (125.7 MHz, $CDCl_3$) 159.9, 136.1, 133.0, 127.9, 123.3, 120.7, 120.4, 119.2, 114.6, 114.1, 110.6, 108.3, 92.5, 80.4, 55.3; MS *m/z* 247 (M^+, 100), 233 (13), 232 (60), 204 (21), 203 (13), 176 (10), 151 (6), 124 (40), 108 (12), 102 (13), 95 (11), 89 (15), 88 (14), 75 (11), 63 (6), 51 (6%).

3.4. General procedure for the synthesis of compounds 6

To a solution (0.4 N) of halides **3** (1.0 equiv) in anhydrous DMF, at room temperature under nitrogen, were successively added $Pd(PPh_3)_4$ (0.05 equiv), AgCl (0.2 equiv) and K_2CO_3 (8.0 equiv). The resulting mixture was stirred for 5 min, then MeOH (8.0 equiv) was added followed by a solution (0.4 N) of 2-(4-trimethylsilyl-1,3-butadiyn-1-yl)-*tert*-butyldimethylsilylphenol **2**[18] (1.0 equiv) in anhydrous DMF. The reaction mixture was warmed to 40 °C and stirred at the same temperature for 1–5 h then quenched with aqueous NH_4Cl and extracted with ethyl acetate. The organic extracts were washed with water, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography on silica gel.

*3.4.1. 2-(Phenylethynyl)-1-benzofuran (**6a**)*[19]

Compound **6a** was prepared from **2** (0.200 g, 0.61 mmol) and iodobenzene **3a** (0.124 g, 0.61 mmol) in accordance with general procedure. Purification by column chromatography (silica gel, petroleum ether) afforded 0.086 g of compound **6a** (65% yield) as a pale yellow solid (mp=74–75 °C, lit.[19] mp=71–72 °C). ν_{max} (KBr) 2211, 1595, 1563, 1440, 1304, 1256, 1165, 944, 816, 746, 687; δ_H (400 MHz, $CDCl_3$) 7.70–7.56 (m, 3H), 7.49 (br d, *J*=8.2 Hz, 1H), 7.42–7.36 (m, 3H), 7.34 (dd, *J*=8.2, 1.0 Hz, 1H), 7.30–7.22 (m, 1H), 7.02 (br s, 1H); δ_C (100.6 MHz, $CDCl_3$) 154.8, 138.7, 131.6, 129.1, 128.4, 127.7, 125.5, 123.2, 121.8, 121.1, 111.6, 111.2, 95.0, 79.6; MS *m/z* 218 (M^+, 100), 189 (44), 163 (8), 109 (22), 94 (44), 81 (11), 63 (8), 51 (5%).

*3.4.2. 2-[(4-Methylphenyl)ethynyl]-1-benzofuran (**6b**)*

Compound **6b** was prepared from **2** (0.302 g, 0.92 mmol) and 4-iodotoluene **3b** (0.201 g, 0.92 mmol) in accordance with general procedure. The residue was purified by column chromatography on silica gel (10% ethyl acetate/petroleum ether) affording product **6b** (0.111 g, 52% yield) as a pale yellow solid (mp=106–108 °C after crystallization with hexane). [Found: C, 87.95; H, 5.15. $C_{17}H_{12}O$ requires C, 87.90; H, 5.21%.] ν_{max} (KBr) 2206, 1562, 1447, 1256, 1164, 1145, 1098, 945, 816, 806, 748, 740, 524; δ_H (400 MHz, $CDCl_3$) 7.48 (br d, *J*=7.7 Hz, 1H), 7.39 (d, *J*=8.0 Hz, 3H), 7.26–7.17 (m, 1H), 7.16–7.13 (m, 1H), 7.09 (d, *J*=8.0 Hz, 2H), 6.90 (br s, 1H), 2.29 (s, 3H); δ_C (100.6 MHz, $CDCl_3$) 155.1, 139.7, 139.2, 131.8, 129.5, 128.0, 125.7, 123.5, 121.3, 118.9, 111.5, 111.4, 95.5, 79.3, 21.9; MS *m/z* 232 (M^+, 100), 231 (26), 202 (22), 189 (7), 176 (3), 163 (3), 139 (3), 116 (24), 101 (29), 89 (7), 88 (12), 76 (7), 63 (7), 51 (4%).

*3.4.3. 2-(Naphthalen-1-ylethynyl)-1-benzofuran (**6c**)*

Compound **6c** was prepared from **2** (0.302 g, 0.92 mmol) and 1-iodonaphtalene **3c** (0.234 g, 0.92 mmol) in accordance with general procedure. Purification by column chromatography (silica gel, 5% ethyl acetate/petroleum ether) afforded compound **6c** (0.131 g, 53% yield) as a pale yellow solid (mp=108–110 °C after crystallization with hexane). [Found: C, 89.50; H, 4.58. $C_{20}H_{12}O$ requires C, 89.53; H, 4.51%.] ν_{max} (KBr) 2207, 1588, 1447, 1299, 1253, 1181, 1162, 1147, 1139, 1010, 941, 799, 773, 750, 453. δ_H (400 MHz, $CDCl_3$) 8.46 (d, *J*=8.3 Hz, 1H), 7.88 (d, *J*=8.1 Hz, 2H), 7.83 (d, *J*=6.5 Hz, 1H), 7.70–7.53 (m, 4H), 7.48 (t, *J*=8.0 Hz, 1H), 7.43–7.33 (m, 1H), 7.29 (t, *J*=7.2 Hz, 1H), 7.12 (br s, 1H); δ_C (100.6 MHz, $CDCl_3$) 155.0, 138.8, 133.1, 133.0, 130.8, 129.6, 128.4, 127.8, 127.1, 126.6, 126.0, 125.6, 125.2, 123.3, 121.2, 119.4, 111.7, 111.2, 93.4, 84.4; MS *m/z* 268 (M^+, 100), 239 (40), 237 (17), 134 (34), 119 (64), 106 (24), 94 (10), 80 (4), 63 (4), 51 (3%).

*3.4.4. 4-(1-Benzofuran-2-ylethynyl)aniline (**6d**)*

Compound **6d** was prepared from **2** (0.302 g, 0.92 mmol) and 4-iodoaniline **3d** (0.202 g, 0.92 mmol) in accordance with general procedure. Column chromatography (silica gel, 50% ethyl acetate/petroleum ether) followed by extraction with boiling hexane afforded product **6d** (0.086 g, 40% yield) as an orange solid (mp=125–128 °C). [Found: C, 82.31; H, 4.80; N, 6.05. $C_{16}H_{11}NO$ requires C, 82.38; H, 4.75%; N, 6.00%.] ν_{max} (KBr) 3473, 3381, 2197, 1617, 1601, 1569, 1506, 1471, 1447, 1284, 1257, 1095, 1018, 939, 805, 747, 526; δ_H (400 MHz, $CDCl_3$) 7.54 (d, *J*=7.1 Hz, 1H), 7.45 (d, *J*=8.2 Hz, 1H), 7.37 (d, *J*=8.5 Hz, 2H), 7.34–7.26 (m, 1H), 7.25–7.19 (m, 1H), 6.92 (br s, 1H), 6.62 (d, *J*=8.5 Hz, 2H); δ_C (100.6 MHz, $CDCl_3$) 154.7, 147.4, 139.4, 133.2, 127.9, 125.1, 123.1, 120.9, 114.6, 111.1, 110.8, 110.4, 96.0, 77.7; MS *m/z* 233 (M^+, 100), 204 (14), 117 (26), 102 (22), 89 (10), 88 (12), 77 (6), 76 (8), 75 (7), 63 (7), 51 (6%).

*3.4.5. 2-[(4-Methoxyphenyl)ethynyl]-1-benzofuran (**6f**)*

Compound **6f** was prepared from **2** (0.200 g, 0.61 mmol) and 4-iodoanisole **3f** (0.143 g, 0.61 mmol) in accordance with general procedure. Purification by column chromatography (silica gel, 10% ethyl acetate/petroleum ether) afforded 0.083 g of compound **6f** (55% yield) as a yellow solid (mp=101–102 °C after crystallization with hexane). [Found: C, 82.30; H, 4.93. $C_{17}H_{12}O_2$ requires C, 82.24; H, 4.87%.] ν_{max} (KBr) 2923, 2850, 2207, 1566, 1498, 1471, 1447, 1281, 1243, 1163, 1143, 1097, 1019, 945, 930, 837, 809, 750, 742, 722, 539; δ_H (400 MHz, $CDCl_3$) 7.58–7.49 (m, 3H), 7.46 (dd, *J*=8.3, 0.8 Hz, 1H), 7.32 (ddd, *J*=8.3, 7.3, 1.3 Hz, 1H), 7.28–7.20 (m, 1H), 6.95 (d, *J*=0.9 Hz, 1H), 6.88 (d, *J*=8.9 Hz, 2H), 3.82 (s, 3H); δ_C (100.6 MHz, $CDCl_3$) 160.3, 154.8, 139.1, 133.2, 127.8, 125.3, 123.2, 121.0, 114.1, 113.8, 111.1, 110.9, 95.2, 78.4, 55.3; MS *m/z* 248 (M^+, 100), 233 (56), 205 (25), 176 (23), 151 (14), 124 (38), 109 (4), 102 (4), 94 (13), 88 (20), 75 (13), 63 (8), 62 (7), 51 (7%).

*3.4.6. 2-[(4-Nitrophenyl)ethynyl]-1-benzofuran (**6g**)*

Compound **6g** was prepared from **2** (0.302 g, 0.92 mmol) and 4-nitroiodobenzene 3**g** (0.229 g, 0.92 mmol) in accordance with general procedure. Column chromatography (silica gel, 40% ethyl acetate/petroleum ether) followed by extraction with boiling hexane led to compound **6g** (0.169 g, 70% yield) as an orange solid (mp=229–231 °C). [Found: C, 73.05; H, 3.47; N, 5.30. $C_{16}H_9NO_3$

requires C, 73.00; H, 3.45; N, 5.32%.] ν_{max} (KBr) 2202, 1595, 1516, 1338, 1306, 1166, 1107, 945, 849, 831, 814, 757, 745; δ_H (400 MHz, $CDCl_3$) 8.23 (d, J=8.8 Hz, 2H), 7.70 (d, J=8.8 Hz, 2H), 7.59 (d, J=7.8 Hz, 1H), 7.48 (d, J=8.4 Hz, 1H), 7.39–7.33 (m, 1H), 7.30–7.23 (m, 1H), 7.10 (br s, 1H); δ_C (100.6 MHz, $CDCl_3$) 155.2, 147.4, 137.6, 132.2, 128.6, 127.4, 126.3, 123.8, 123.6, 121.5, 113.4, 111.4, 93.1, 84.6; MS m/z 263 (M^+, 100), 233 (19), 217 (18), 190 (10), 189 (49), 188 (17), 187 (24), 163 (10), 150 (6), 139 (5), 109 (5), 98 (5), 94 (24), 81 (19), 63 (10), 51 (9%).

*3.4.7. 2-(Thiophen-2-ylethynyl)-1-benzofuran (**6h**)*

Compound **6h** was prepared from **2** (0.200 g, 0.61 mmol) and 2-iodothiophene **3h** (0.128 g, 0.61 mmol) in accordance with general procedure. Purification by column chromatography (silica gel, petroleum ether) afforded compound **6h** (0.100 g, 73% yield) as a white solid (mp=69–70 °C after crystallization with hexane). [Found: C, 75.02; H, 3.58; S, 14.25. $C_{14}H_8OS$ requires C, 74.97; H, 3.60; S, 14.30%.] ν_{max} (KBr) 2196, 1445, 1413, 1342, 1270, 1254, 1199, 1161, 1142, 1107, 1090, 1037, 1003, 935, 883, 850, 833, 813, 749, 702; δ_H (400 MHz, $CDCl_3$) 7.60–7.50 (m, 1H), 7.48 (dd, J=8.3, 0.8 Hz, 1H), 7.38 (dd, J=3.7, 1.1 Hz, 1H), 7.37–7.31 (m, 2H), 7.28–7.23 (m, 1H), 7.03 (dd, J=5.1, 3.7 Hz, 1H), 7.01 (d, J=0.9 Hz, 1H); δ_C (100.6 MHz, $CDCl_3$) 154.9, 138.4, 133.2, 128.6, 127.6, 127.3, 125.7, 123.3, 121.6, 121.2, 111.8, 111.2, 88.4, 83.2; MS m/z 224 (M^+, 100), 195 (24), 169 (4), 152 (16), 151 (9), 126 (4), 112 (21), 97 (16), 76 (11), 63 (10), 51 (4), 45 (9%).

*3.4.8. 3-(1-Benzofuran-2-ylethynyl)pyridine (**6i**)*[19]

Compound **6i** was prepared from **2** (0.302 g, 0.92 mmol) and 3-iodopyridine **3i** (0.189 g, 0.92 mmol) in accordance with general procedure. Purification by column chromatography (silica gel, 30% ethyl acetate/petroleum ether) afforded 0.171 g (85% yield) of compound **6i** as a yellow solid (mp=77–78 °C after crystallization with hexane, lit.[19] mp=75–76 °C). ν_{max} (KBr) 2213, 1585, 1560, 1469, 1445, 1405, 1349, 1304, 1256, 1167, 1111, 1021, 1008, 945, 885, 813, 798, 747, 735, 696, 497, 444; δ_H (400 MHz, $CDCl_3$) 8.74 (br s, 1H), 8.52–8.47 (m, 1H), 7.73 (dt, J=7.9, 1.9 Hz, 1H), 7.50 (dd, J=7.8, 0.6 Hz, 1H), 7.40 (dd, J=8.3, 0.8 Hz, 1H), 7.31–7.24 (m, 1H), 7.22–7.14 (m, 2H), 6.98 (d, J=0.9 Hz, 1H); δ_C (100.6 MHz, $CDCl_3$) 154.8, 151.9, 149.1, 138.2, 137.8, 127.3, 125.8, 123.3, 122.9, 121.2, 118.9, 112.3, 111.1, 91.5, 82.7; MS m/z 219 (M^+, 100), 190 (19), 164 (10), 163 (23), 138 (5), 137 (4), 110 (11), 96 (10), 83 (10), 81 (16), 69 (9), 63 (8), 55 (5), 51 (5%).

*3.4.9. 2-[(3E)-4-Trimethylsilylbut-3-en-1-yn-1-yl]-1-benzofuran (**6j**)*

Compound **6j** (0.155 g, 70% yield, yellow oil) was obtained from **2** (0.302 g, 0.92 mmol) and (E)-1-bromo2-trimethylsilylethene **3j** (0.165 g, 0.92 mmol) after purification by column chromatography (silica gel, petroleum ether). [Found: C, 75.00; H, 6.78. $C_{15}H_{16}OSi$ requires C, 74.95; H, 6.71%.] ν_{max} (neat) 2955, 2191, 1581, 1448, 1249, 1199, 1009, 972, 862, 840, 806, 749, 739; δ_H (400 MHz, $CDCl_3$) 7.56–7.52 (m, 1H), 7.45 (dd, J=8.3, 0.8 Hz, 1H), 7.32 (ddd, J=8.4, 7.2, 1.3 Hz, 1H), 7.23 (ddd, J=8.3, 7.2, 1.0 Hz, 1H), 6.93 (d, J=0.9 Hz, 1H), 6.68 (d, J=19.3 Hz, 1H), 6.20 (d, J=19.3 Hz, 1H), 0.14 (s, 9H); δ_C (100.6 MHz, $CDCl_3$) 154.9, 148.1, 138.7, 127.7, 125.5, 123.2, 121.9, 121.1, 111.6, 111.2, 95.3, 79.8, −1.8; MS m/z 240 (M^+, 42), 226 (13), 225 (64), 200 (18), 199 (100), 165 (13), 147 (12), 135 (5), 115 (5), 105 (12), 100 (25), 85 (10), 73 (12), 63 (7), 59 (20), 53 (8), 45 (34), 43 (26%).

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