Sequential Sonogashira and Suzuki Cross-Coupling Reactions in the Indole and Indazole Series

Bernhard Witulski,*[a] Javier Ramon Azcon, Carole Alayrac,[a] Anca Arnautu,[b] Valérie Collot,[b] Sylvain Rault*[b]

[a] Westfälische Wilhelms-Universität Münster, Organische Chemie Institut, Corrensstr. 40, 48143 Münster, Germany
Fax +49(251)8336501; E-mail: witulski@uni-muenster.de

[b] CERMN, UFR des Sciences Pharmaceutiques, 5 rue Vaubénard, 14032 Caen cedex, France

Received 5 August 2004; revised 24 November 2004

Abstract: 3-Iodoindoles, 5-bromo-3-iodoindoles and 5-bromo-3-iodoindazoles have been studied with respect to their reactivity and selectivity in palladium catalyzed Sonogashira and Suzuki cross-coupling reactions. As a result, sequential Sonogashira–Sonogashira, Sonogashira–Suzuki, and Suzuki–Sonogashira reactions with 5-bromo-3-iodoindoles or indazoles were used to obtain a large range of new functionalized indoles and indazoles, which are potential 5-HT receptor ligands.

Key words: palladium, catalysis, alkynes, indoles, indazoles

The neurotransmitter serotonin (5-hydroxytryptamine) mediates a wide range of physiological functions by interacting with multiple receptors.[1,2] In the past eighteen years, seven distinct families (5-HT_1–5-HT_7), compromising a total of at least fourteen structurally and pharmacologically distinct mammalian 5-HT receptor subtypes have been identified. The function of many 5-HT receptors can be unequivocally associated with specific physiological responses, ranging from modulation of neuronal activities, transmitter releases, to behavioral changes. In contrast to 5-HT_1–5-HT_4 receptors, the 5-HT_5–5-HT_7 receptors have been less intensively studied and much less is known about them. The function of the 5-HT_5 receptors remains unidentified and no selective agent of 5-HT_5 receptors has been developed yet.[3] Interestingly, most recently disclosed agents which act on 5-HT_6 receptors are sulfonamides or derivatives of tryptamines bearing a *N*-arylsulfonyl moiety.[4] The design of selective ligands for the 5-HT_5–5-HT_7 receptors shall offer much promise for future drug development.

As part of our ongoing program on the synthesis of functionalized indoles[5] and carbazoles[6] via transition metal catalyzed reactions we became interested in the development of a strategy for the synthesis of alkynyl and/or aryl analogues of serotonin based on palladium catalyzed cross-coupling reactions.[7] Sonogashira[8] as well as Suzuki[9] reactions with 3,5-bis-halogenated indoles or their 2-azabioisosteres, indazoles, and various alkynyl- or arylamines should lead to the preparation of conjugated serotonin derivatives where inherent functional groups are elongated through a rigid spacer (Figure 1). Furthermore, the introduction of such spacer groups, like alkynyl or aryl moieties, should have the following consequences: (i) distinct spacing of significant functional groups, such as the amino function and the indole nitrogen atom, (ii) changing their pK_a values, and (iii) implementing conformational restrictions within the molecule. Finally, such modifications shall influence affinity, selectivity and agonist versus antagonist character of these potential 5-HT receptor ligands.

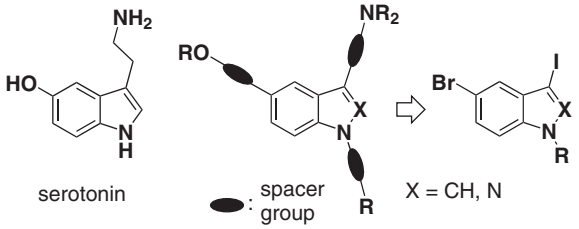


Figure 1

Starting from 3,5-bis-halogenated indoles or indazoles as molecular scaffolds, their potential for combinatorial modifications via sequential palladium-catalyzed cross-coupling reactions was investigated.[10] Palladium catalyzed cross-coupling reactions tend to be more facile with aryl iodines than with aryl bromides and for aryl chlorides specific ligands are required.[11] Commonly used procedures for cross-coupling reactions with aryl iodines employ room temperature, whereas elevated reaction temperatures are necessary for aryl bromides. We therefore anticipated, that 3-iodo-5-bromo indoles or indazoles are suitable building blocks for the purpose of sequential modifications of indoles or indazoles in the 3- and 5-position, because palladium catalyzed cross-couplings should first proceed at the position where the iodine atom is located.

Preliminary studies by us have already disclosed that 3-aryl- as well as 3-alkynyl-indazoles are readily accessible from 3-iodoindazoles by either a Suzuki or Sonogashira cross-coupling reaction.[12,13] Moreover, 3-iodoindoles have been used in Heck and Stille reactions,[14,15] in palladium catalyzed cyanations,[16] and a few examples of Sonogashira couplings with 1-methylsulfonyl-3-iodoindole and simple terminal alkynes have been reported.[17]

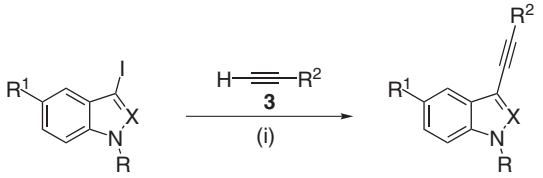
In order to test the feasibility of the Sonogashira reaction in sequential palladium catalyzed reactions in the indole and indazole series and with the attempt to synthesize a

SYNTHESIS 2005, No. 5, pp 0771–0780
Advanced online publication: 14.02.2005
DOI: 10.1055/s-2005-861825; Art ID: T09204SS

variety of 3-alkynyl indoles structurally related to serotonin, cross-couplings with the 3-iodoindoles **1a–h** and a series of alkynylamines and amides were performed (Scheme 1 and Table 1).

Table 1 Synthesis of the Indoles **4a–m** and the Indazoles **5a**,**b** Starting from 3-Iodoindoles **1a–h** and 1-Boc-5-bromo-3-indazole **2**

Entry	1/2	R	R^1	R^2	Product 4/5	Yield (%)
1	**1a**	Boc	H	CH_2NMe_2	**4a**	69
2	**1a**	Boc	H	CH_2NHTs	**4b**	81
3	**1b**	Ts	H	CH_2NHTs	**4c**	84
4	**1c**	Boc	OMe	CH_2NMe_2	**4d**	97
5	**1c**	Boc	OMe		**4e**	93
6	**1d**	SO_2Ph	OMe	CH_2NMe_2	**4f**	94
7	**1d**	SO_2Ph	OMe	CH_2NHTs	**4g**	96
8	**1d**	SO_2Ph	OMe	CH_2OH	**4h**	91
9	**1e**	Ts	OMe	Ph	**4i**	76
10	**1f**	Boc	Br	CH_2NHTs	**4j**	91
11	**1g**	SO_2Ph	Br	CH_2NMe_2	**4k**	88
12	**1h**	Ts	Br	CH_2NHTs	**4l**	90
13	**1h**	Ts	Br	CH_2OH	**4m**	79
14	**2**	Boc	Br	CH_2NHTs	**5a**	91
15	**2**	Boc	Br	CH_2NMe_2	**5b**	98



1a–h: X = CH
2: X = N

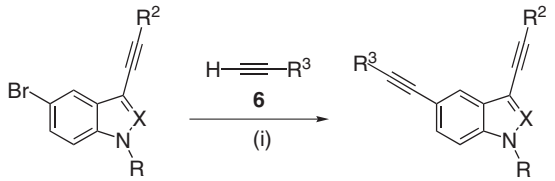
4a–m: X = CH
5a–b: X = N

Scheme 1 *Reagents and conditions*: (i) **3** (1.2 equiv), $PdCl_2(PPh_3)_2$ (5 mol%), CuI (10 mol%), Et_3N–DMF (2:1), 20 °C, 12 h, for details see Table 1.

The 3-iodoindoles **1** were obtained from the corresponding indoles by direct iodination followed by N-protection of the indole nitrogen as described by us earlier.[18] Palladium-promoted cross-coupling reactions of 3-iodo-indoles **1a–h** or the indazole **2** with a set of terminal alkynes **3** proceeded under very mild conditions. The reaction could be carried out already at room temperature in the presence of 5 mol% $PdCl_2(PPh_3)_2$ and 10 mol% CuI as catalysts. The new 3-alkynyl indoles **4a–m**, as well as the 3-alkynyl indazoles **5a** and **5b** were obtained in good to excellent yields after isolation and purification by column chromatography on silica gel or on aluminium oxide (Table 1). However, in all cases the protection of the nitrogen atom at the N-1 position was necessary in order to avoid any coupling at this position. While the Boc group in the indazole series[13] proved to be much more suitable than the tosyl group, which was partially cleaved under these reaction conditions, the choice of the protecting group (Boc, tosyl or phenylsulfonyl group) did not play any significant role in the indole series. Moreover, electron-deficient alkynylamides, such as the 1-propioloylpyrrolidine,[19] proved to be efficient cross-coupling partners here (Table 1, entry 5). Electron-deficient alkynes are known to be poor substrates in Sonogashira reactions.[20,21] However, a few examples of efficient couplings with electron-deficient propiolic amides have been described by us and others recently.[13,22]

The nature of the substituent R^1 on the benzene moiety of either the indole or indazole showed no relevant influence on the course of the coupling reaction. Importantly, substrates bearing an iodine atom at the 3-position and a bromine atom at the 5-position were exclusively functionalized at position 3 when the reactions were carried out at room temperature. In these cases no double ethynylated product was observed (Table 1, entries 10–15). The selectivity thus achieved was crucial for allowing further sequential modifications via additional palladium catalyzed cross-coupling reactions at the remaining 5-position.

Consequently, Sonogashira–Sonogashira sequential cross-couplings in both the indole and the indazole series were examined next (Scheme 2 and Table 2). Aryl bromides are known to be less reactive than the parent iodides in palladium catalyzed cross-coupling reactions. Indeed, the conversion of 5-bromoindoles **4** and 5-bromoindazoles **5** into their bis-alkynylated derivatives **7** and **8** did not proceed at room temperature[23] but required heating at 70 °C. In these cases an additional amount of 10 mol% PPh_3 was necessary in order to stabilize the active catalyst and to keep the overall efficiency of the catalysis.



4j–l: X = CH
5a–b: X = N

7a–d: X = CH
8a–d: X = N

Scheme 2 *Reagents and conditions*: (i) **6** (2–3 equiv), $PdCl_2(PPh_3)_2$ (10 mol%), CuI (20 mol%), PPh_3 (10 mol%), Et_3N–DMF (2:1), 70 °C, 48 h for X = CH, 24 h for X = N; for details see Table 2.

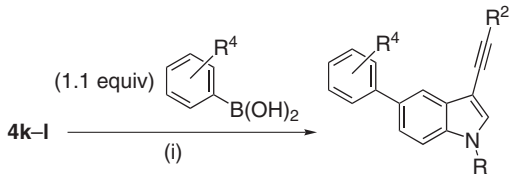
Still, the coupling reactions proved to be relatively slow (up to 3 d) and therefore a higher catalyst loading [10 mol% $PdCl_2(PPh_3)_2$, 20 mol% CuI] and 2–3 equivalents of monoalkynes **6** were used. Under these modified conditions, the coupling reactions advanced in one day (indazole) or two days (indole) to give the indoles **7** and the

Table 2 Sonogashira Cross-Coupling Reactions of 3-Alkynyl-5-bromo-indoles **4j–l** and Indazoles **5a** and **5b**

Entry	4/5	R	R^2	R^3	Products 7/8	Yield (%)
1	**4j**	Boc	CH_2NHTs	CH_2NHTs	**7a**	55
2	**4k**	SO_2Ph	CH_2NMe_2	CH_2NHTs	**7b**	83
3	**4k**	SO_2Ph	CH_2NMe_2	CH_2OH	**7c**	74
4	**4l**	Ts	CH_2NHTs	CH_2NMe_2	**7d**	77
5	**5a**	Boc	CH_2NHTs	CH_2NMe_2	**8a**	54
6	**5b**	Boc	CH_2NMe_2	CH_2NHTs	**8b**	76
7	**5b**	Boc	CH_2NMe_2	CH_2OH	**8c**	80
8	**5b**	Boc	CH_2NMe_2	Ph	**8d**	78

indazoles **8** in up to 83% yield (Table 2). *N*-Boc substrates bearing a tosylamide group on the alkynyl moiety were transformed in lower yields (Table 2, entries 1 and 5) probably because of their lower thermal stability.

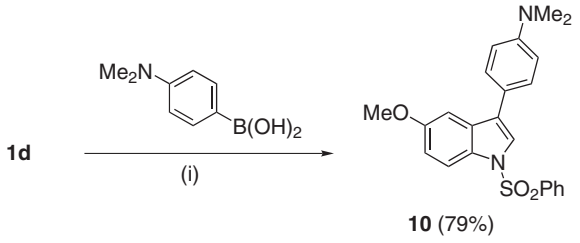
Next our efforts focused on the synthesis of the 3-alkynyl-5-aryl substitution pattern via sequential Sonogashira–Suzuki cross-couplings. For this purpose the 3-alkynyl-5-bromoindoles **4k–l** were subjected to Suzuki cross-coupling reactions with 3- or 4-methoxybenzeneboronic acids leading to the new substituted indoles **9a–c** in good to excellent yields (Scheme 3).



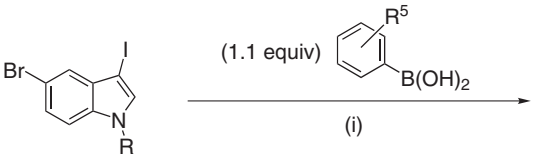
9a: R = SO_2Ph, R^2 = CH_2NMe_2, R^4 = 4-OMe
9b: R = SO_2Ph, R^2 = CH_2NMe_2, R^4 = 3-OMe
9c: R = Ts, R^2 = CH_2NHTs, R^4 = 3-OMe

Scheme 3 *Reagents and conditions:* (i) $Pd(PPh_3)_4$ (2 mol%), Na_2CO_3 (1.5.equiv), DME–H_2O (2:1), 80 °C, 1–6 h, **9a** (89%), **9b** (98%), **9c** (75%).

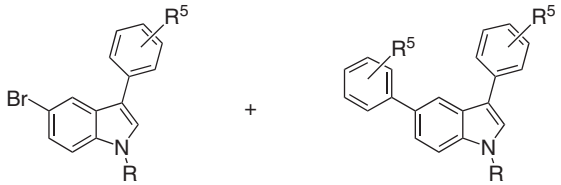
The choice of base proved to be crucial here. Indeed, while a significant amount of cleavage of the sulfonyl group occurred with $Ba(OH)_2$, a clean reaction was obtained with Na_2CO_3. Under optimized reaction conditions, i.e. 1.1 equivalents of areneboronic acids, 2 mol% of $Pd(PPh_3)_4$, 1.5 equivalents of base, and a solvent mixture of DME and water (2:1), a full conversion was achieved after 1–6 hours at 80 °C. This protocol was also applied to the cross-coupling reaction of 5-methoxy-3-iodoindole **1d** with 4-dimethylaminobenzeneboronic acid and afforded the corresponding 5-methoxy-3-aryl indole **10** in 79% yield (Scheme 4).



10 (79%)



1g: R = SO_2Ph
1h: R = Ts



11a: R = SO_2Ph, R^5 = 4-NMe_2 (93%)
11b: R = Ts, R^5 = 3-OMe (94%)

12a: R = SO_2Ph, R^5 = 4-NMe_2 (<3%)
12b: R = Ts, R^5 = 3-OMe (<3%)

Scheme 4 *Reagents and conditions*: (i) $Pd(PPh_3)_4$ (2 mol%), Na_2CO_3 (1.5 equiv), DME–H_2O (2:1), 70–80 °C, 12–24 h.

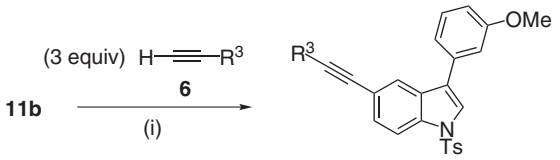
We then attempted the opposite substitution pattern, i.e. the synthesis of 5-alkynyl-3-aryl indoles, by means of sequential Suzuki–Sonogashira cross-coupling reactions starting from the same 3-iodo-5-bromoindoles **1g–h**.

The Suzuki reaction between 5-bromo-3-iodoindole **1h** (R = Ts) and 3-methoxybenzeneboronic acid under the previously described conditions was low-yielding and less selective (53% mono-coupling and 4% bis-coupling products) than the above investigated Sonogashira coupling. However, by performing the reaction at 70 °C instead of 80 °C a significant improvement concerning reactivity and selectivity was observed. Under these conditions the indole **11b** was obtained in 94% yield (Scheme 4).

This cross-coupling reaction was also attempted at 60 °C but was too slow at this temperature to go to completion in a reasonable time scale. Under optimized conditions, the Suzuki reaction of 5-bromo-3-iodoindole **1g** (R = SO_2Ph) with 4-dimethylaminobenzeneboronic acid yielded the 5-bromoindole **11a** in 93% yield after 24 hours of heating. Thus compared to the Sonogashira reaction, the Suzuki cross-coupling reactions seem to be less selective in the 5-bromo-3-iodoindole series since some bis-coupling product **12** (3%) was also isolated. However, this

minor side product could be easily separated from indole **11** by simple column chromatography.

Having the 5-bromoindole **11b** in hand, the complementary substitution pattern to indole **9b** via sequential Suzuki–Sonogashira reactions was facile. The coupling reaction of the 5-bromoindole **11b** with the terminal alkynes **6** at an elevated temperature of 70 °C and in the presence of 10 mol% $PdCl_2(PPh_3)_2$ and 20 mol% CuI resulted in the indoles **13a**,**b** in high yields (Scheme 5).



13a: $R^3 = CH_2NMe_2$ (78%)
13b: R^3 = Ph (85%)

Scheme 5 *Reagents and conditions*: [$PdCl_2(PPh_3)_2$] (10 mol%), CuI (20 mol%), PPh_3 (10 mol%), Et_3N–DMF (2:1), 70 °C, 48 h.

In conclusion, with the aim of developing a flexible strategy for the design of a new indole and indazole library closely related to the structural motif of serotonin, we have studied the reactivity and the selectivity of 3-iodo- as well as 5-bromo-3-iodo-indoles and indazoles in palladium catalyzed cross-coupling reactions. Sonogashira reactions proceeded smoothly affording a large range of new alkynylated indoles or indazoles. Furthermore, sequential Sonogashira–Sonogashira, Sonogashira–Suzuki, as well as Suzuki–Sonogashira couplings were possible starting from 5-bromo-3-iodo-indoles and indazoles by using the remaining bromine group as a synthetic handle. Preliminary results of binding properties of these new (aza) analogues of serotonin towards the 5-HT_4 to 5-HT_7 receptors are promising in view of the result of compound **4c** (IC50 ca 1 μM versus 5-HT_5 receptor). Additional experiments are on the way.

All reagents used were analytical grades and all solvents were purified by standard methods and distilled prior to use. All reactions were run under Ar using vacuum lines in Schlenk tubes in oven-dried glassware. Reaction mixtures were stirred magnetically and were monitored by TLC using Polygram Sil G/UV254 silica plates from Macherey–Nagel & Co. (Düren, Germany). Flash column chromatography (FCC) was performed with Merck silica gel 60 (40–60 μm). Microanalysis was performed using a Perkin-Elmer Elementaranalyzer EA 240 and a Perkin-Elmer Elementaranalyzer 2400 CHN. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AC200 and Bruker AMX400 spectrometers using TMS (δ = 0.00 ppm for ^{1}H) and $CDCl_3$ (δ = 77.0 ppm, ^{13}C) as internal standards. ^{13}C NMR assignments were made on the basis of DEPT experiments. Mass spectra were obtained on a Finnigan MAT 90 spectrometer (EI, 70 eV) and on a Quattro-LCZ from Waters-Micromass (ESI). IR spectra were recorded as solids in KBr pellets or as film on NaCl plates on a Perkin-Elmer FT-IR spectrometer. Melting points were recorded on a Büchi apparatus, and are uncorrected. Compounds **1a**–**h**[18] and **2**[12] were prepared according to the literature.

3-Alkynyl-Indoles 4a–m and Indazoles 5a,b; General Procedure

In a Schlenk tube with screw cap were introduced under Ar indole **1a**–**h** or indazole **2** (1.0 mmol), alkyne **3** (1.2 mmol, 1.2 equiv), $PdCl_2(PPh_3)_2$ (35 mg, 5 mol%), CuI (19 mg, 10 mol%), then anhyd Et_3N (10 mL) and anhyd DMF (5 mL). The reaction mixture was stirred at r.t. for 12 h and then poured into water and extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were washed with brine (2 × 15 mL), dried over $MgSO_4$, filtered through celite and evaporated to dryness. The residue was purified by flash chromatography (petroleum ether–Et_2O or petroleum ether–EtOAc) on silica gel (**4b–c**, **4e**, **4h–j**, **4l,m** and **5a**) or alumina (**4a**, **4d**, **4k**, **4f,g** and **5b**).

3-[3-(Dimethylamino)-prop-1-ynyl]-indole-1-carboxylic Acid *tert*-Butyl Ester (4a)

Yield: 69%; white crystals; mp 68–69 °C ($CHCl_3$–pentane).

IR (KBr): 2977, 2944, 2779, 1730, 1612, 1455, 1371, 1276, 1232, 1154, 1098, 1031, 762 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.67 (s, 9 H), 2.41 (s, 6 H), 3.56 (s, 2 H), 7.27–7.37 (m, 2 H), 7.68–7.66 (m, 1 H), 7.74 (s, 1 H), 8.13 (d, *J* = 8.1 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.1 (q), 44.2 (q), 48.8 (t), 76.9 (s), 84.1 (s), 87.8 (s), 103.3 (s), 115.2 (d), 120.0 (d), 123.1 (d), 125.0 (d), 128.6 (d), 130.7 (s), 134.6 (s), 149.1 (s).

MS (EI, 70 eV): *m*/*z* (%) = 298 (51) [M$^+$], 242 (74), 197 (100), 154 (85), 82 (9).

HRMS (ESI): *m*/*z* [MH$^+$] calcd for $C_{18}H_{23}N_2O_2$: 299.1754; found: 299.1752.

3-[3-(Toluene-4-sulfonylamino)-prop-1-ynyl]-indole-1-carboxylic Acid *tert*-Butyl Ester (4b)

Yield: 81%; yellow crystals; mp 119–120 °C ($CHCl_3$–pentane).

IR (KBr): 3266, 3056, 2979, 2245, 1715, 1600, 1454, 1421, 1383, 1343, 1284, 1235, 1164, 1102, 1062, 892, 811, 766, 736, 670, 585, 550 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.66 (s, 9 H), 2.29 (s, 3 H), 4.15 (d, *J* = 6.0 Hz, 2 H), 4.84 (t, *J* = 6.0 Hz, 1 H), 7.22–7.26 (m, 3 H), 7.31–7.37 (m, 2 H), 7.53 (s, 1 H), 7.83 (d, *J* = 8.2 Hz, 2 H), 8.08 (d, *J* = 8.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.3 (q), 28.0 (q), 33.9 (t), 76.9 (s), 84.5 (s), 86.6 (s), 102.2 (s), 115.2 (d), 119.8 (d), 123.0 (d), 125.1 (d), 127.4 (d), 129.2 (s), 129.6 (d), 130.0 (d), 134.4 (s), 136.9 (s), 143.8 (s), 149.0 (s).

MS (EI, 70 eV): *m*/*z* (%) = 423 (10) [M$^+$], 367 (28), 323 (27), 258 (32), 245 (18), 231 (18), 185 (41), 168 (100), 155 (34), 143 (66), 115 (31), 91 (70), 84 (47).

Anal. Calcd for $C_{23}H_{24}N_2O_4S$ (423.60): C, 65.16; H, 5.67; N, 6.61. Found: C, 64.84; H, 5.68; N, 6.52.

4-Methyl-*N*-{3-[1-(toluene-4-sulfonyl)-1*H*-indol-3-yl]-prop-2-ynyl}-benzenesulfonamide (4c)

Yield: 84%; white crystals; mp 165–166 °C ($CHCl_3$–pentane).

IR (KBr): 3268, 1597, 1447, 1381, 1325, 1281, 1233, 1187, 1173, 1159, 1127, 1104, 1089, 993, 817, 746, 664, 568 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.20 (s, 3 H), 2.33 (s, 3 H), 4.12 (d, *J* = 6.1 Hz, 2 H), 4.97 (t, *J* = 6.1 Hz, 1 H), 7.18–7.24 (m, 4 H), 7.30–7.34 (m, 3 H), 7.47 (s, 1 H), 7.73 (d, *J* = 8.5 Hz, 2 H), 7.80 (d, *J* = 8.3 Hz, 2 H), 7.90–7.93 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2 (q), 21.5 (q), 33.8 (t), 76.0 (s), 87.5 (s), 104.0 (s), 113.4 (d), 120.4 (d), 123.6 (d), 125.4 (d),

126.8 (d), 127.4 (d), 129.2 (s), 129.6 (d), 130.0 (d), 130.3 (d), 133.9 (s), 134.7 (s), 136.8 (s), 143.8 (s), 145.4 (s).

MS (EI, 70 eV): *m*/*z* (%) = 477 (5) [M$^+$], 423 (8), 367 (24), 323 (27), 258 (36), 231 (18), 168 (100), 141 (57), 91 (86).

Anal. Calcd for $C_{25}H_{22}N_2O_4S_2$ (477.6): C, 62.81; H, 4.61; N, 5.86. Found: C, 62.45; H, 4.57; N, 5.78.

3-(3-Dimethylamino-prop-1-ynyl)-5-methoxy-indole-1-carboxylic Acid *tert*-Butyl Ester (4d)
Yield: 97%; yellow crystals; mp 69–70 °C ($CHCl_3$–pentane).

IR (KBr): 2937, 2781, 1728, 1615, 1479, 1451, 1378, 1330, 1289, 1245, 1156, 1090, 1036, 1017, 853, 807, 764 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.65 (s, 9 H), 2.40 (s, 6 H), 3.55 (s, 2 H), 3.87 (s, 3 H), 6.95 (dd, *J* = 9.0, 2.6 Hz, 1 H), 7.10 (d, *J* = 2.6 Hz, 1 H), 7.70 (s, 1 H), 7.99 (d, *J* = 9.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.1 (q), 44.2 (q), 48.8 (t), 55.7 (q), 76.9 (s), 84.0 (s), 87.9 (s), 102.3 (d), 103.1 (s), 114.0 (d), 116.0 (d), 129.2 (d), 131.5 (s), 149.0 (s), 156.3 (s).

MS (EI, 70 eV): *m*/*z* (%) = 328 (63) [M$^+$], 272 (74), 227 (100), 213 (52), 184 (96), 113 (7).

Anal. Calcd for $C_{19}H_{24}N_2O_3$ (327.7): C, 69.58; H, 7.32; N, 8.54. Found: C, 69.43; H, 7.40; N, 8.47.

3-(2-Pyrrolidinocarboxy-prop-1-ynyl)-5-methoxy-indole-1-carboxylic Acid *tert*-Butyl Ester (4e)
Yield: 93%; white crystals; mp 166–167 °C (petroleum ether–Et_2O).

IR (KBr): 2975, 2932, 2875, 1750, 1628, 1482, 1450, 1394, 1332, 1249, 1155, 1091, 1035, 1020, 853, 798, 762 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.66 (s, 9 H), 1.96–2.04 (m, 4 H), 3.56 (t, *J* = 6.3 Hz, 2 H), 3.80 (t, *J* = 6.4 Hz, 2 H), 3.88 (s, 3 H), 6.98 (dd, *J* = 9.0, 2.3 Hz, 1 H), 7.11 (d, *J* = 2.3 Hz, 1 H), 7.89 (s, 1 H), 8.02 (d, *J* = 8.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.9, 25.6, 28.3, 45.6, 48.4, 55.9, 82.1, 84.9, 86.8, 100.8, 102.6, 114.7, 116.4, 129.4, 131.1, 132.2, 153.1, 156.8.

MS (EI, 70 eV): *m*/*z* (%) = 368 (42) [M$^+$], 312 (100), 268 (70), 239 (30), 198 (55), 170 (14).

Anal. Calcd for $C_{21}H_{24}N_2O_4$ (368.44): C, 68.46; H, 6.57; N, 7.90. Found: C, 68.29; H, 6.68; N, 7.81.

[3-(1-Benzenesulfonyl-5-methoxy-1*H*-indol-3-yl)-prop-2-ynyl]-dimethyl-amine (4f)
Yield: 94%; pale yellow crystals; mp 84–85 °C ($CHCl_3$–pentane).

IR (KBr): 3198, 3187, 2768, 1610, 1482, 1445, 1378, 1294, 1248, 1215, 1176, 1128, 1085, 1032, 994, 856, 818, 726, 685, 612, 582 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.32 (s, 6 H), 3.47 (s, 2 H), 3.76 (s, 3 H), 6.89 (dd, *J* = 2.6, 9.0 Hz, 1 H), 6.97 (d, *J* = 2.1 Hz, 1 H), 7.31–7.51 (m, 3 H), 7.60 (s, 1 H), 7.77–7.81 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 44.7 (q), 49.2 (t), 56.1 (q), 76.5 (s), 89.5 (s), 103.0 (d), 105.8 (s), 114.9 (d), 115.2 (d), 127.2 (d), 129.3 (s), 129.77 (d), 129.79 (d), 132.5 (s), 134.4 (d), 138.3 (s), 157.3 (s).

MS (EI, 70 eV): *m*/*z* (%) = 368 (53) [M$^+$], 324 (37), 227 (100), 212 (34), 183 (93), 168 (25), 146 (15), 78 (13).

Anal. Calcd for $C_{20}H_{20}N_2O_3S$ (368.45): C, 65.19; H, 5.47; N, 7.60. Found: C, 65.10; H, 5.51; N, 7.59.

***N*-[3-(1-Benzenesulfonyl-5-methoxy-1*H*-indol-3-yl)-prop-2-ynyl]-4-methyl-benzenesulfonamide (4g)**
Yield: 96%; yellow crystals; mp 153 °C ($CHCl_3$–pentane).

IR (KBr): 3251, 1612, 1475, 1445, 1377, 1327, 1291, 1249, 1215, 1163, 1124, 1094, 1029, 988, 942, 846, 816, 723, 684, 601 cm^{-1}.

^{1}H NMR (200 MHz; $CDCl_3$): δ = 2.27 (s, 3 H), 3.85 (s, 3 H), 4.15 (d, *J* = 6.0 Hz, 2 H), 4.92 (t, *J* = 6.0 Hz, 1 H), 6.84 (d, *J* = 2.4 Hz, 1 H), 6.98 (dd, *J* = 2.2, 9.1 Hz, 1 H), 7.24 (d, *J* = 8.5 Hz, 2 H), 7.43–7.64 (m, 4 H), 7.82–7.90 (m, 5 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.7 (q), 34.4 (t), 56.2 (q), 76.5 (s), 88.2 (s), 102.9 (d), 104.7 (s), 114.9 (d), 115.4 (d), 127.2 (d), 127.9 (d), 129.0 (s), 129.8 (d), 130.1 (d), 130.2 (d), 131.9 (s), 134.6 (d), 137.2 (s), 138.2 (s), 144.4 (s), 157.3 (s).

MS (EI, 70 eV): *m*/*z* (%) = 494 (56) [M$^+$], 429 (7), 401 (7), 338 (38), 311 (21), 289 (33), 260 (31), 214 (30), 197 (51), 183 (33), 170 (89), 155 (54), 91 (100), 78 (31).

Anal. Calcd for $C_{25}H_{22}N_2O_5S_2$ (494.58): C, 60.71; H, 4.48; N, 5.66. Found: C, 60.48; H, 4.48; N, 5.66.

3-(1-Benzenesulfonyl-5-methoxy-1*H*-indol-3-yl)-prop-2-yn-1-ol (4h)
Yield: 91%; yellow crystals; mp 179–180 °C ($CHCl_3$–pentane).

IR (KBr): 3565, 3117, 1610, 1482, 1447, 1364, 1313, 1290, 1251, 1212, 1175, 1147, 1127, 1097, 1025, 991, 970, 841, 812, 759, 725, 690, 610, 582 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.80 (br s, 1 H), 3.84 (s, 3 H), 4.56 (s, 2 H), 6.96 (dd, *J* = 9.0, 2.6 Hz, 1 H), 7.02 (d, *J* = 2.4 Hz, 1 H), 7.42–7.45 (m, 2 H), 7.54 (tt, *J* = 7.5, 1.2 Hz, 1 H), 7.69 (s, 1 H) 7.84–7.87 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 51.8 (t), 55.7 (q), 76.9 (s), 91.7 (s), 102.3 (d), 104.7 (s), 114.5 (d), 115.1 (d), 126.8 (d), 128.8 (s), 129.4 (d), 129.9 (d), 131.7 (s), 134.1 (d), 137.8 (s), 157.0 (s).

MS (EI, 70 eV): *m*/*z* (%) = 341 (100) [M$^+$], 200 (57), 185 (51), 170 (54), 157 (60), 134 (15), 78 (25).

Anal. Calcd for $C_{18}H_{15}NO_4S$ (341.38): C, 63.32; H, 4.42; N, 4.10. Found: C, 63.22; H, 4.55; N, 4.13.

5-Methoxy-3-phenylethynyl-1-(toluene-4-sulfonyl)-1*H*-indole (4i)
Yield: 76%; brown crystals; mp 127–128 °C ($CHCl_3$–pentane).

IR (KBr): 3124, 1611, 1476, 1445, 1371, 1301, 1214, 1164, 1118, 1093, 1028, 976, 892, 818, 758, 679, 589 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.29 (s, 3 H), 3,80 (s, 3 H), 6,92 (dd, *J* = 9.0, 2.4 Hz, 1 H), 7.05 (d, *J* = 2.4 Hz, 1 H), 7.18 (d, *J* = 8.6 Hz, 2 H), 7.30–7.32 (m, 3 H), 7.49–7.52 (m, 2 H), 7.70–7.72 (m, 3 H), 7.82 (d, *J* = 9.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5 (q), 55.7 (q), 80.4 (s), 93.6 (s), 102.6 (d), 105.2 (s), 114.6 (d), 114.8 (d), 123.0 (s), 126.8 (d), 128.38 (s), 128.40 (d), 128.9 (d), 129.4 (d), 129.9 (d), 131.5 (d) 131.8 (s), 134.9 (s), 145.2 (s), 156.9 (s).

MS (EI, 70 eV): *m*/*z* (%) = 401 (57) [M$^+$], 246 (100), 231 (25), 203 (18), 176 (9), 82 (11).

Anal. Calcd for $C_{24}H_{19}NO_3S$ (401.48): C, 71.74; H, 4.76; N, 3.48. Found: C, 71.41; H, 4.74; N, 3.43.

5-Bromo-3-[3-(toluene-4-sulfonylamino)-prop-1-ynyl]-indole-1-carboxylic Acid *tert*-Butyl Ester (4j)
Yield: 91%; pale yellow crystals; mp 147–148 °C ($CHCl_3$–pentane).

IR (KBr): 3280, 2970, 1721, 1600, 1453, 1426, 1383, 1343, 1285, 1270, 1228, 1165, 1116, 1094, 1055, 892, 862, 814, 798, 670 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.66 (s, 9 H), 2.25 (s, 3 H), 4.15 (d, *J* = 6.0 Hz, 2 H), 4.89 (t, *J* = 6.0 Hz, 1 H), 7.25–7.27 (m, 2 H), 7.40–7.44 (m, 2 H), 7.52 (s, 1 H), 7.82 (d, *J* = 8.5 Hz, 2 H), 7.95 (d, *J* = 8.7 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.3 (q), 28.1 (q), 33.9 (t), 76.0 (s), 85.0 (s), 87.2 (s), 101.6 (s), 116.62 (s), 116.64 (d), 122.6 (d), 127.4 (d), 128.1 (d), 129.7 (d), 130.1 (d), 131.7 (s), 133.1 (s), 136.8 (s), 143.8 (s), 148.5 (s).

MS (EI, 70 eV): *m*/*z* (%) = 404, 402 [M^+ – Boc] (7), 249 (8), 248 (20), 247 (10), 246 (20), 184 (9), 171 (87), 155 (89), 107 (32), 91 (100).

Anal. Calcd for $C_{23}H_{23}BrN_2O_4S$ (503.41): C, 54.87; H, 4.61; N, 5.56. Found: C, 55.08; H, 4.69; N, 5.45.

[3-(1-Benzenesulfonyl-5-bromo-1*H*-indol-3-yl)-prop-2-ynyl]-dimethyl-amine (4k)

Yield: 88%; yellow crystals; mp 125 °C ($CHCl_3$–pentane).

IR (KBr): 3132, 2936, 2800, 1445, 1372, 1291, 1258, 1189, 1148, 1108, 986, 873, 838, 799, 753 721, 686, 626, 599, 575, 556 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.38 (s, 6 H), 3.52 (s, 2 H), 7.43–7.49 (m, 3 H), 7.57 (t, *J* = 7.6 Hz, 1 H), 7.69 (s, 1 H), 7.75 (d, *J* = 1.9 Hz, 1 H), 7.84–7.88 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 44.3 (q), 48.7 (t), 75.2 (s), 89.6 (s), 104.7 (s), 115.0 (d), 117.5 (s), 123.3 (d), 126.8 (d), 128.4 (d), 129.5 (d), 129.6 (d), 132.6 (s), 132.9 (s), 134.3 (d), 137.6 (s).

MS (EI, 70 eV): *m*/*z* (%) = 419 (5), 418 (20) [M^+], 417 (15), 416 (19) [M^+], 374 (17), 372 (17), 337 (12), 335 (12), 277 (92), 275 (90), 234 (16), 232 (15),196 (83), 141 (58), 83 (100).

Anal. Calcd for $C_{19}H_{17}BrN_2O_2S$ (417.32): C, 54.68; H, 4.10; N, 6.71. Found: C, 54.41; H, 4.11; N, 6.59.

***N*-{3[5-Bromo-1-(toluene-4-sulfonyl)-1*H*-indol-3-yl]-prop-2-ynyl}-4-methyl-benzenesulfonamide (4l)**

Yield: 90%; white crystals; mp 183–184 °C ($CHCl_3$–pentane).

IR (KBr): 3261, 1596, 1440, 1372, 1328, 1288, 1258, 1225, 1190, 1158, 1106, 986, 916, 870, 808, 752, 668, 580, 537 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.19 (s, 3 H), 2.35 (s, 3 H), 4.12 (d, *J* = 6.0 Hz, 2 H), 4.68 (t, *J* = 6.0 Hz, 1 H), 7.20–7.25 (m, 4 H), 7.39–7.42 (m, 2 H), 7.47 (s, 1 H), 7.71 (d, *J* = 8.3 Hz, 2 H), 7.77–7.80 (m, 3 H).

^{13}C NMR (100 MHz, DMSO): δ = 21.0 (q), 21.5 (q), 33.2 (t), 74.3 (s), 90.6 (s), 103.7 (d), 115.8 (d), 117.2 (s), 123.0 (d), 127.4 (d), 128.9 (d), 129.7 (d), 130.8 (d), 130.9 (s), 132.2 (s), 133.8 (s), 138.3 (s), 143.1 (s), 146.7 (s).

MS (EI, 70 eV): *m*/*z* (%) = 557, 555 (3) [M^+], 402 (7), 400 (7), 220 (5), 218 (5), 171 (30), 155 (82), 139 (18), 107 (13), 91 (100).

Anal. Calcd for $C_{25}H_{21}BrN_2O_4S_2$ (557.48): C, 53.86; H, 3.79; N, 5.02. Found: C, 53.60; H, 3.62; N, 4.98.

3-[5-Bromo-1-(toluene-4-sulfonyl)-1*H*-indol-3-yl]-prop-2-yn-1-ol (4m)

Yield: 79%; white crystals; mp 129–130 °C ($CHCl_3$–pentane).

IR (KBr): 3363, 3137, 2231, 1597, 1574, 1494, 1447, 1378, 1335, 1301, 1263, 1231, 1189, 1172, 1152, 1112, 1090, 1034, 983, 802, 869, 751, 670, 585, 569, 539 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.90 (s, 1 H), 2.34 (s, 3 H), 4.54 (s, 2 H), 7.21–7.24 (m, 2 H), 7.43 (dd, *J* = 8.9, 1.4 Hz, 1 H), 7.70–7.44 (m, 4 H), 7.82 (d, *J* = 8.7 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6 (q), 51.6 (t), 76.1 (s), 92.0 (s), 103.9 (s), 115.0 (d), 117.5 (s), 123.2 (d), 126.9 (d), 128.4 (d), 130.1 (d), 130.2 (d), 132.3 (s), 132.8 (s), 134.5 (s), 145.7 (s).

MS (EI, 70 eV): *m*/*z* (%) = 404 (48) [M^+], 402 (47) [M^+], 249 (7), 247 (7), 232 (15), 230 (15), 169 (44), 155 (61), 91 (100), 84 (41).

Anal. Calcd for $C_{18}H_{14}BrNO_3S$ (403.90): C, 53.48; H, 3.47; N, 3.47. Found: C, 53.32; H, 3.37; N, 3.46.

5-Bromo-3-[3-(toluene-4-sulfonylamino)-prop-1-ynyl]-indazole-1-carboxylic Acid *tert*-Butyl Ester (5a)

Yield: 91%; white crystals; mp 151–152 °C ($CHCl_3$–pentane).

IR (KBr): 3279, 2986, 1741, 1596, 1494, 1386, 1326, 1158, 810 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.60 (s, 9 H), 2.14 (s, 3 H), 4.13 (d, *J* = 6.0 Hz, 2 H), 4.86 (t, *J* = 6.0 Hz, 1 H), 7.17 (s, 1 H), 7.19 (s, 1 H), 7.47–7.48 (m, 1 H), 7.54 (dd, *J* = 8.8, 1.8 Hz, 1 H), 7.75 (dt, *J* = 8.4 Hz, *J* = 1.8 Hz, 2 H), 7.95 (d, *J* = 8.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.3 (q), 28.0 (q), 33.6 (t), 74.6 (s), 86.0 (s), 90.2 (s), 116.1 (d), 117.4 (s), 122.9 (d), 127.4 (d), 127.8 (s), 129.7 (d), 132.4 (d), 132.6 (s), 136.6 (s), 138.4 (s), 143.9 (s), 148.2 (s).

MS (EI, 70 eV): *m*/*z* (%) = 405, 403 (11) [M^+ – Boc], 404 (4), 250 (92), 249 (43), 248 (100), 247 (35), 223 (9), 222 (28), 221 (10), 220 (26), 199 (5), 155 (33), 139 (28), 91 (90).

Anal. Calcd for $C_{22}H_{22}BrN_3O_4S$ (504.40): C, 52.39; H, 4.40; N, 8.33. Found: C, 52.32; H, 4.38; N, 8.35.

5-Bromo-3-(3-dimethylamino-prop-1-ynyl)-indazole-1-carboxylic Acid *tert*-Butyl Ester (5b)

Yield: 98%; yellow solid; mp 66–68 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.64 (s, 9 H), 2.37 (s, 6 H), 3.56 (s, 2 H), 7.55 (dd, *J* = 8.9, 1.8 Hz, 1 H), 7.84 (dd, *J* = 7.9, 0.7 Hz, 1 H), 7.99 (dd, *J* = 9.0, 0.7 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 28.1 (q), 44.2 (q), 48.5 (t), 75.4 (s), 85.8 (s), 91.7 (s), 116.2 (d), 117.4 (s), 123.2 (d), 128.4 (s), 132.4 (d), 133.7 (s), 138.6 (s), 148.4 (s).

MS (EI, 70 eV): *m*/*z* (%) = 379, 377 (0.6) [M^+], 364 (0.6), 362 (0.6), 336 (12), 334 (13), 278 (30), 262 (5), 235 (13), 168 (3), 126 (9), 57 (100).

HRMS (ESI): *m*/*z* [MH^+] calcd for $C_{17}H_{21}BrN_3O_2$: 378.0812; found: 378.0825.

3,5-Bis-Alkynyl-Indoles 7a–d and Indazoles 8a–d; General Procedure

In a Schlenk tube with screw cap were introduced under Ar indole **4i–k** or indazole **5a**,**b** (0.5 mmol), alkyne **6** (1–1.5 mmol, 2–3 equiv), $PdCl_2(PPh_3)_2$ (35 mg, 10 mol%), CuI (19 mg, 20 mol%), PPh_3 (13 mg, 10 mol%), then anhyd Et_3N (6 mL) and anhyd DMF (3 mL). Then the reaction mixture was stirred at 70 °C. The reaction was monitored by TLC. After 24 h (indazole series) or 48 h (indole series) of heating, the reaction mixture was poured into water and extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine (2 × 10 mL), dried over $MgSO_4$, filtered through celite and evaporated to dryness. The residue was purified by flash chromatography (alumina, petroleum ether–Et_2O or petroleum ether–EtOAc) with the exception of **7a** (silica gel, petroleum ether–Et_2O, 1:1).

3,5-Bis-[3-(Toluene-4-sulfonylamino)-prop-1-ynyl]-indole-1-carboxylic Acid *tert*-Butyl Ester (7a)

Yield: 55%; white solid; mp 138–140 °C.

IR (KBr): 3358, 3283, 2981, 2234, 1737, 1597, 1438, 1371, 1156, 812 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.66 (s, 9 H), 2.25 (s, 3 H), 2.33 (s, 3 H), 4.09 (d, *J* = 5.9 Hz, 2 H), 4.13 (d, *J* = 5.9 Hz, 2 H), 4.96 (t, *J* = 6.0 Hz, 1 H), 5.01 (t, *J* = 6.0 Hz, 1 H), 7.09 (dd, *J* = 8.7, 1.6 Hz,

1 H), 7.22–7.31 (m, 5 H), 7.53 (s, 1 H), 7.81–7.84 (m, 4 H), 7.96 (d, *J* = 8.5 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5 (q), 21.6 (q), 28.2 (q), 34.0 (t), 34.1 (t), 76.4 (s), 77.4 (s) 82.7 (s), 85.1 (s), 87.3 (s), 102.3 (s), 115.2 (d), 117.0 (s), 123.7 (d), 126.0 (d), 127.6 (d), 127.62 (d), 128.6 (d), 129.8 (d), 129.9 (d), 130.06 (d), 130.1 (s), 136.9 (s), 137.0 (s), 139.3 (s), 143.7 (s), 143.9(s), 144.0 (s), 148.7 (s).

MS (EI, 70 eV): *m*/*z* (%) = 262 (14), 183 (14), 171 (9), 155 (10), 107 (10), 91 (27), 56 (100).

HRMS (ESI): *m*/*z* [MNa^+] calcd for $C_{33}H_{33}N_3O_6S_2Na$: 654.1703; found: 654.1654.

_N_-{3-[1-Benzenesulfonyl-3-(3-dimethylamino-prop-1-ynyl)-1*H*-indol-5-yl]-prop-2-ynyl}-4-methyl-benzenesulfonamide (7b)

Yield: 83%; white crystals; mp 147–148 °C ($CHCl_3$–pentane).

IR (KBr): 3010, 1462, 1362, 1327, 1158, 1128, 1095, 988, 809, 752, 584 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.26 (s, 3 H), 2.39 (s, 6 H), 3.53 (s, 2 H), 4.06 (s, 2 H), 5.04 (s, 1 H), 7.10 (dd, *J* = 8.7, 1.6 Hz, 1 H), 7.23 (d, *J* = 7.9 Hz, 2 H), 7.43–7.48 (m, 3 H), 7.56–7.59 (m, 1 H), 7.70 (s, 1 H), 7.80 (d, *J* = 8.4 Hz, 2 H), 7.83–7.88 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4 (q), 33.8 (t), 44.3 (q), 48.7 (t), 75.4 (s), 83.0 (s), 84.5 (s), 89.6 (s), 105.1 (s), 113.4 (d), 117.7 (s), 124.0 (d), 126.9 (d), 127.4 (d), 128.8 (d), 129.50 (d), 129.53 (d), 129.7 (d), 130.8 (s), 133.6 (s), 134.3 (d), 136.9 (s), 137.7 (s), 143.7 (s).

MS (EI, 70 eV): *m*/*z* (%) = 545 (0.9) [M^+], 400 (1), 279 (41), 228 (21), 215 (27), 167 (59), 149 (100), 113 (14), 112 (9), 83 (6), 57 (17).

Anal. Calcd for $C_{29}H_{27}N_3O_4S_2$ (545.67): C, 63.23; H, 4.99; N, 7.70. Found: C, 63.25; H, 5.12; N, 7.47.

3-[1-Benzenesulfonyl-3-(3-dimethylamino-prop-1-ynyl)-1*H*-indol-5-yl]-prop-2-yn-1-ol (7c)

Yield: 74%; yellow crystals; mp 142–143 °C ($CHCl_3$–pentane).

IR (film): 3340, 3133, 2933, 2856, 1468, 1377, 1294, 1175, 1139, 1099, 1033, 801, 721, 685, 603 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.30 (s, 6 H), 3.45 (s, 2 H), 4.39 (s, 2 H), 7.29–7.37 (m, 4 H), 7.45 (m, 1 H), 7.61–7.63 (m, 2 H), 7.77–7.82 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 44.1 (q), 48.5 (t), 51.1 (t), 75.7 (s), 84.6 (s), 87.9 (s), 89.1 (s), 105.1 (s), 113.5 (d), 118.5 (s), 123.9 (d), 126.8 (d), 128.4 (d), 128.6 (d), 128.9 (d), 129.4 (d), 129.5 (s), 130.9 (s), 132.0 (d), 132.1 (s), 133.6 (s), 134.3 (d), 137.6 (s).

MS (EI, 70 eV): *m*/*z* (%) = 392 (3) [M^+], 362 (13), 318 (4), 277 (13), 251 (17), 221 (43), 208 (4), 178 (14), 128 (13), 77 (51), 57 (100), 32 (81).

Anal. Calcd for $C_{22}H_{20}N_2O_3S$ (392.45): C, 67.33; H, 5.14; N, 7.14. Found: C, 67.37; H, 5.15; N, 7.12.

_N_-{3-[5-(3-Dimethylamino-prop-1-ynyl)-1-(toluene-4-sulfonyl)-1*H*-indol-3-yl]-prop-2-ynyl}-4-methyl-benzenesulfonamide (7d)

Yield: 77%; white crystals; mp 162–163 °C ($CHCl_3$–pentane).

IR (KBr): 3059, 2946, 2861, 1596, 1462, 1376, 1332, 1295, 1176, 1158, 1131, 1097, 1065, 1019, 996, 913, 798, 763, 675, 582 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.14 (s, 3 H), 2.32 (s, 3 H), 2.37 (s, 6 H), 3.48 (s, 2 H), 4.10 (s, 2 H), 7.16 (d, *J* = 8.0 Hz, 2 H), 7.22 (d, *J* = 8.1 Hz, 2 H), 7.37–7.46 (m, 4 H), 7.72 (d, *J* = 8.5 Hz, 2 H), 7.80 (d, *J* = 8.3 Hz, 2 H), 7.84 (d, *J* = 8.7 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.3 (q), 21.7 (q), 33.8 (t), 44.3 (q), 48.6 (t), 75.1 (s), 84.5 (s), 85.1 (s), 88.9 (s), 104.3 (s), 113.6 (d), 118.8 (s), 124.0 (d), 127.0 (d), 127.5 (d), 128.7 (d), 129.6 (d), 130.2 (d), 130.5 (s), 132.1 (d), 133.4 (s), 134.6 (s), 137.6 (s), 143.5 (s) 145.8 (s).

MS (EI, 70 eV): *m*/*z* (%) = 559 (5) [M^+], 477 (11), 404 (15), 333 (5), 322 (24), 295 (5), 221 (10), 205 (13), 178 (18), 139 (14), 126 (12), 91 (100), 80 (33).

HRMS (ESI): *m*/*z* [MH^+] calcd for $C_{30}H_{30}N_3O_4S_2$: 560.1672; found: 560.1662.

5-(3-Dimethylamino-prop-1-ynyl)-3-[3-(toluene-4-sulfonylamino)-prop-1-ynyl]-indazole-1-carboxylic Acid *tert*-Butyl Ester (8a)

Yield: 54%; pale yellow solid; mp 138–139 °C (CH_3Cl_3–pentane).

IR (KBr): 3453, 2954, 2829, 1737, 1598, 1498, 1461, 1383, 1328, 1256, 1162, 1096, 1067, 754 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.70 (s, 9 H), 2.20 (s, 3 H), 2.45 (s, 6 H), 3.56 (s, 2 H), 4.19 (s, 2 H), 5.25 (s, 1 H), 7.23 (d, *J* = 8.2 Hz, 2 H), 7.54 (s, 1 H), 7.57 (dd, *J* = 8.7, 1.6 Hz, 1 H), 7.82 (d, *J* = 8.2 Hz, 2 H), 8.06 (d, *J* = 9.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.3 (q), 28.1 (q), 33.7 (t), 44.3 (q), 48.5 (t), 74.9 (s), 84.67 (s), 84.74 (s), 85.9 (s), 90.2 (s), 114.7 (d), 119.1 (s), 123.8 (d), 126.3 (s), 127.4 (d), 129.8 (d), 132.8 (d), 133.4 (s), 136.7 (s), 138.9 (s), 143.9 (s), 148.3 (s).

MS (EI, 70 eV): *m*/*z* (%) = 280 (5), 250 (3), 249 (2), 206 (2), 192 (1), 171 (49), 139 (2), 107 (24), 91 (100).

HRMS (ESI): *m*/*z* [MH^+] calcd for $C_{27}H_{31}N_4O_4S$: 507.2061; found: 507.2075.

3-(3-Dimethylamino-prop-1-ynyl)-5-[3-(toluene-4-sulfonylamino)-prop-1-ynyl]-indazole-1-carboxylic Acid *tert*-Butyl Ester (8b)

Yield: 76%; beige solid; mp 120–121 °C (CH_3Cl_3–pentane).

IR (KBr): 3271, 2926, 2858, 1740, 1599, 1498, 1463, 1384, 1343, 1278, 1257, 1159, 1093, 813 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.71 (s, 9 H), 2.33 (s, 3 H), 2.43 (s, 6 H), 3.63 (s, 2 H), 4.09 (s, 2 H), 5.36 (s, 1 H), 7.24–7.28 (m, 3 H), 7.61 (s, 1 H), 7.83 (d, *J* = 8.3 Hz, 2 H), 8.03 (d, *J* = 8.7 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4 (q), 28.0 (q), 33.7 (t), 44.2 (q), 48.5 (t), 75.5 (s), 83.6 (s), 83.9 (s), 85.8 (s), 91.8 (s), 114.6 (d), 118.1 (s), 124.0 (d), 126.7 (s), 127.4 (d), 129.6 (d), 132.4 (d), 134.4 (s), 136.9 (s), 139.1 (s), 143.6 (s), 148.4 (s).

MS (EI, 70 eV): *m*/*z* (%) = 462 (7), 405 (5), 363 (3), 277 (10), 206 (6), 171 (52), 107 (21), 91 (100).

HRMS (ESI): *m*/*z* [MH^+] calcd for $C_{27}H_{31}N_4O_4S$: 507.2061; found: 507.2094.

3-(3-Dimethylamino-prop-1-ynyl)-5-(3-hydroxy-prop-1-ynyl)-indazole-1-carboxylic Acid *tert*-Butyl Ester (8c)

Yield: 80%; beige solid; mp 115–116 °C (CH_3Cl_3–pentane).

IR (KBr): 3094, 2984, 2826, 2229, 1923, 1732, 1614, 1497, 1461, 1386, 1347, 1256, 1159, 1095, 830 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.64 (s, 9 H), 2.36 (s, 6 H + OH), 3.56 (s, 2 H), 4.44 (s, 2 H), 7.48 (d, *J* = 8.7 Hz, 1 H), 7.76 (s, 1 H), 8.01 (d, *J* = 8.7 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.0 (q), 44.0 (q), 48.4 (t), 51.3 (t), 75.6 (s), 84.5 (s), 87.9 (s), 89.5 (s), 91.5 (s), 114.8 (d), 118.7 (s), 124.0 (d), 126.8 (s), 132.6 (d), 134.4 (s), 139.1 (s), 148.4 (s).

MS (EI, 70 eV): *m*/*z* (%) = 353 (2) [M^+], 338 (2), 310 (52), 254 (80), 252 (61), 210 (51), 192 (6), 152 (9), 127 (3), 82 (7), 57 (100).

HRMS (ESI): *m/z* [MH$^+$] calcd for $C_{20}H_{24}N_3O_3$: 354.1812; found: 354.1819.

3-(3-Dimethylamino-prop-1-ynyl)-5-phenylethynyl-indazole-1-carboxylic Acid *tert*-Butyl Ester (8d)
Yield: 78%; pale yellow crystals; mp 117–118 °C ($CHCl_3$–pentane).

IR (KBr): 3432, 2935, 2825, 2781, 1728, 1595, 1501, 1387, 1243, 1154, 1079, 1041, 882, 753 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.64 (s, 9 H), 2.35 (s, 6 H), 3.55 (s, 2 H), 7.26–7.28 (m, 3 H), 7.46–7.49 (m, 2 H), 7.60 (dd, *J* = 8.8, 2.0 Hz, 1 H), 7.87 (s, 1 H), 8.06 (d, *J* = 8.7 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.0 (q), 44.2 (q), 48.5 (t), 75.5 (s), 85.6 (s), 88.7 (s), 89.5 (s), 91.8 (s), 114.8 (d), 119.2 (s), 122.9 (s), 123.8 (d), 126.9 (s), 128.32 (d), 128.37 (d), 131.5 (d), 132.6 (d), 134.6 (s), 139.0 (s), 148.5 (s).

MS (EI, 70 eV): *m/z* (%) = 399 (1) [M$^+$], 356 (13), 298 (79), 284 (12), 268 (38), 256 (100), 226 (28), 149 (19), 127 (15), 82 (7).

Anal. Calcd for $C_{25}H_{25}N_3O_2$ (399.49): C, 75.16; H, 6.31; N, 10.51. Found: C, 75.11; H, 6.31; N, 10.12.

3-Alkynyl-5-aryl Indoles 9a–c and 3-Aryl Indoles 10 and 11a,b; General Procedure
In a Schlenk tube with screw cap were introduced under Ar indole **4j**,**k** or **1d** or **1g**,**h** (0.3 mmol), 3-methoxy- or 4-methoxy- or 4-dimethylamino-boronic acid (1.1 equiv), and [Pd(PPh$_3$)$_4$] (7 mg, 2 mol%), then DME (4 mL) was added followed by the addition of Na_2CO_3 (48 mg, 1.5 equiv) in H_2O (2 mL). The reaction mixture was vigorously stirred and heated at 80 °C or 70 °C. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was diluted with CH_2Cl_2 (10 mL) and the organic layer was washed with brine (2 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to dryness under reduced pressure. The residue was purified by flash chromatography on alumina (**9a,b**) or silica gel (**9c**, **10** and **11a,b**).

{3-[1-Benzenesulfonyl-5-(4-methoxy-phenyl)-1*H*-indol-3-yl]-prop-2-ynyl}-dimethylamine (9a)
Yield: 89%; white crystals; mp 130–131 °C ($CHCl_3$–pentane).

IR (film): 2938, 2777, 1732, 1608, 1519, 1463, 1372, 1248, 1173, 1038, 993, 814, 752, 722, 685 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.39 (s, 6 H), 3.54 (s, 2 H), 3.85 (s, 3 H), 6.97–6.99 (m, 2 H), 7.44–7.48 (m, 2 H), 7.51–7.56 (m, 4 H), 7.72 (s, 1 H), 7.75 (d, *J* = 1.2 Hz, 1 H), 7.90–7.93 (m, 2 H), 8.00 (d, *J* = 8.7 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 44.3 (q), 48.8 (t), 55.4 (q), 76.0 (s), 89.2 (s), 105.6 (s), 113.7 (d), 114.3 (d), 118.4 (d), 124.8 (d), 126.9 (d), 128.4 (d), 129.2 (d), 129.4 (d), 131.5 (s), 133.2 (s), 133.5 (s), 134.1 (d), 137.1 (s), 137.9 (s), 159.2 (s).

MS (EI, 70 eV): *m/z* (%) = 444 (32) [M$^+$], 400 (10), 303 (100), 288 (9), 260 (27), 259 (50), 222 (23), 216 (18), 207 (4), 149 (2), 83 (3), 69 (6), 57 (15), 32 (26).

Anal. Calcd for $C_{26}H_{24}N_2O_3S$ (444.55): C, 70.25; H, 5.44; N, 6.30. Found: C, 70.25; H, 5.44; N, 6.28.

{3-[1-Benzenesulfonyl-5-(3-methoxy-phenyl)-1*H*-indol-3-yl]-prop-2-ynyl}-dimethylamine (9b)
Yield: 98%; yellow oil.

IR (film): 2936, 2777, 1728, 1599, 1463, 1090, 1032, 995, 758, 685, 603 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.39 (s, 6 H), 3.54 (s, 2 H), 3.86 (s, 3 H), 6.88–6.91 (m, 1 H), 7.13 (m, 1 H), 7.17–7.20 (m, 1 H), 7.34–7.38 (m, 1 H), 7.45–7.49 (m, 2 H), 7.57–7.59 (m, 2 H), 7.74 (s, 1 H), 7.80 (m, 1 H), 7.91–7.93 (m, 2 H), 8.02 (d, *J* = 8.6 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 44.2 (q), 48.7 (t), 55.3 (q), 76.0 (s), 89.1 (s), 105.6 (s), 112.5 (d), 113.2 (d), 113.7 (d), 118.9 (d), 119.9 (d), 125.1 (d), 126.9 (d), 129.4 (d), 129.5 (d), 129.8 (d), 131.4 (s), 133.6 (s), 134.1 (d), 137.2 (s), 137.9 (s), 142.5 (s), 159.9 (s).

MS (EI, 70 eV): *m/z* (%) = 444 (0.2) [M$^+$], 390 (0.2), 338 (0.2), 303 (0.9), 279 (18), 223 (0.3), 214 (23), 183 (10), 167 (38), 149 (100), 113 (11), 83 (8), 71 (19), 57 (30), 43 (51).

HRMS (ESI): *m/z* [MH$^+$] calcd for $C_{26}H_{25}N_2O_3S$: 445.1580; found: 445.1605.

***N*-{3-[5-(3-Methoxy-phenyl)-1-(toluene-4-sulfonyl)-1*H*-indol-3-yl]-prop-2-ynyl}-4-methyl-benzenesulfonamide (9c)**
Yield: 75%; white solid; mp 103–105 °C ($CHCl_3$–pentane).

IR (film): 3285, 2919, 1728, 1598, 1463, 1376, 1161, 1091, 812, 757, 667, 583 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.10 (s, 3 H), 2.34 (s, 3 H), 3.86 (s, 3 H), 4.14 (d, *J* = 6.1 Hz, 2 H), 4.96 (t, *J* = 6.1 Hz, 1 H), 6.90 (dd, *J* = 8.1, 2.6 Hz, 1 H), 7.10–7.17 (m, 4 H), 7.24 (d, *J* = 8.5 Hz, 2 H), 7.36 (t, *J* = 7.8 Hz, 1 H), 7.49–7.51 (m, 2 H), 7.55 (dd, *J* = 8.6, 1.8 Hz, 1 H), 7.77 (t, *J* = 8.5 Hz, 4 H), 7.95 (d, *J* = 8.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.1 (q), 21.5 (q), 33.9 (t), 55.3 (q), 75.9 (s), 87.8 (s), 104.3 (s), 112.4 (d), 113.3 (d), 113.7 (d), 118.7 (d), 119.8 (d), 125.0 (d), 126.9 (d), 127.3 (d), 129.5 (s), 129.6 (d), 129.7 (d), 129.8 (d), 130.0 (d), 130.8 (s), 133.4 (s), 136.8 (s), 137.1 (s), 142.2 (s), 143.8 (s), 145.5 (s), 159.9 (s).

MS (EI, 70 eV): *m/z* (%) = 584 (0.9) [M$^+$], 429 (0.2), 336 (0.5), 300 (0.2), 246 (1), 203 (0.6), 155 (2), 149 (5), 117 (2), 91 (11), 61 (12), 43 (100).

Anal. Calcd for $C_{32}H_{28}N_2O_5S_2$ (584.71): C, 65.73; H, 4.83; N, 4.79. Found: C, 65.49; H, 4.92; N, 4.82.

[4-(1-Benzenesulfonyl-5-methoxy-1*H*-indol-3-yl)-phenyl]-dimethylamine (10)
Yield: 79%; white crystals; mp 126–127 °C ($CHCl_3$–pentane).

IR (film): 2935, 2897, 1615, 1516, 1448, 1367, 1132, 1034, 851, 724, 686, 605 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.95 (s, 6 H), 3.77 (s, 3 H), 6.79 (d, *J* = 8.8 Hz, 2 H), 6.95 (dd, *J* = 9.0, 2.5 Hz, 1 H), 7.19 (d, *J* = 2.5 Hz, 1 H), 7.33–7.45 (m, 5 H), 7.55 (s, 1 H), 7.85 (d, *J* = 7.3 Hz, 2 H), 7.95 (d, *J* = 9.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 40.5 (q), 55.7 (q), 103.3 (d), 112.8 (d), 113.7 (d), 114.8 (d), 120.8 (s), 122.6 (d), 124.7 (s), 126.7 (d), 128.6 (d), 129.2 (d), 130.4 (s), 131.0 (s), 133.7 (d), 138.2 (s), 150.1 (s), 156.8 (s).

MS (EI, 70 eV): *m/z* (%) = 406 (10) [M$^+$], 265 (100), 250 (14), 222 (30), 178 (5).

Anal. Calcd for $C_{23}H_{22}N_2O_3S$ (406.50): C, 67.96; H, 5.46; N, 6.89. Found: C, 67.97; H, 5.48; N, 6.89.

[4-(1-Benzenesulfonyl-5-bromo-1*H*-indol-3-yl)-phenyl]-dimethylamine (11a)
Yield: 93%; yellow crystals; mp 130–131 °C ($CHCl_3$–pentane).

IR (film): 2890, 2800, 1615, 1515, 1441, 1176, 1142, 1113, 1090, 787, 734, 685, 600 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.99 (s, 6 H), 6.80 (d, *J* = 8.8 Hz, 2 H), 7.41–7.44 (m, 5 H), 7.50–7.54 (m, 1 H), 7.58 (s, 1 H), 7.86–7.88 (m, 3 H), 7.92 (d, *J* = 8.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 40.5 (q), 112.8 (d), 115.3 (d), 117.2 (s), 119.9 (s), 122.7 (d), 123.5 (d), 124.0 (s), 126.8 (d), 127.6

(d), 128.6 (d), 129.4 (d), 131.7 (s), 134.0 (d), 134.3 (s), 138.0 (s), 150.3 (s).

MS (EI, 70 eV): *m*/*z* (%) = 456, 454 (15) [M+], 315 (100), 313 (94), 299 (10), 297 (6), 234 (9), 197 (19), 190 (17), 110 (15), 77 (22), 43 (92).

Anal. Calcd for $C_{22}H_{19}BrN_2O_2S$ (455.37): C, 58.03; H, 4.21; N, 6.15. Found: C, 57.98; H, 4.20; N, 6.15.

5-Bromo-3-(3-methoxy-phenyl)-1-(toluene-4-sulfonyl)-1*H*-indole (11b)

Yield: 94%; yellow oil.

IR (film): 2934, 2963, 1732, 1596, 1439, 1372, 1248, 1175, 1023, 739, 697, 657, 584, 537 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.34 (s, 3 H), 3.86 (s, 3 H), 6.92 (dd, *J* = 8.3, 2.4 Hz, 1 H), 7.07 (s, 1 H), 7.12 (d, *J* = 7.5 Hz, 1 H), 7.23 (d, *J* = 8.3 Hz, 2 H), 7.38 (t, *J* = 7.5 Hz, 1 H), 7.44 (dd, *J* = 8.8, 1.6 Hz, 1 H), 7.68 (s, 1 H), 7.77 (d, *J* = 8.3 Hz, 2 H), 7.88 (s, 1 H), 7.92 (d, *J* = 8.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6 (q), 55.3 (q), 113.1(d), 113.6 (d), 115.2 (d), 117.2 (s), 120.2 (d), 123.19 (d), 123.25 (s), 124.1 (d), 126.8 (d), 127.8 (d), 130.0 (d), 130.1 (d), 131.0 (s), 133.6 (s), 134.1 (s), 134,9 (s), 145.3 (s), 160.0 (s).

MS (EI, 70 eV): *m*/*z* (%) = 457 (35) [M+], 455 (38) [M+], 377 (39), 302 (61), 300 (63), 257 (3), 222 (100), 178 (21), 151 (22), 91 (43).

3,5-bis-(4-Dimethylamino-phenyl)-1-benzenesulfonyl-1*H*-indole (12a)

Yield: 3%; oil.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.99 (s, 6 H), 3.02 (s, 6 H), 6.79–6.84 (m, 4 H), 7.42–7.56 (m, 8 H), 7.59 (s, 1 H), 7.90–7.95 (m, 3 H), 8.06 (d, *J* = 8.7 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 40.5 (q), 40.6 (q), 112.77 (d), 112.81 (d), 113.9 (d), 118.1 (d), 120.9 (s), 122.0 (d), 123.8 (d), 124.8 (s), 126.8 (d), 128.0 (d), 128.7 (d), 129.2 (d), 129.5 (s), 130.4 (s), 133.7 (d), 134.3 (s), 137.2 (s), 138.3 (s), 149.8 (s), 150.1 (s).

3,5-bis-(3-Methoxy-phenyl)-1-(toluene-4-sulfonyl)-1*H*-indole (12b)

Yield: 4% (when the Suzuki reaction was performed at 80 °C); pale yellow crystals; mp 164–166 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.36 (s, 3 H), 3.86 (s, 3 H), 3.87 (s, 3 H), 6.89 (dd, *J* = 8.2, 2.6 Hz, 1 H), 6.93 (dd, *J* = 8.2, 2.6 Hz, 1 H), 7.10–7.24 (m, 6 H), 7.33–7.41 (m, 2 H), 7.58 (dd, *J* = 8.7, 1.8 Hz, 1 H), 7.72 (s, 1 H), 7.84 (d, *J* = 8.4 Hz, 2 H), 7.94 (d, *J* = 1.8 Hz, 1 H), 8.10 (d, *J* = 8.5 Hz, 1 H).

5-Alkynyl-3-aryl Indoles (13a,b); General Procedure

In a Schlenk tube with screw cap were introduced under Ar indole **11b** (0.2 mmol), alkyne **6** (0.6 mmol, 3 equiv), $PdCl_2(PPh_3)_2$ (14 mg, 10 mol%), CuI (8 mg, 20 mol%), PPh_3 (5 mg, 10 mol%), then anhyd Et_3N (4 mL) and anhyd DMF (2 mL). Then the reaction mixture was stirred at 70 °C for 48 h. The reaction mixture was poured into water and extracted with CH_2Cl_2 (2 × 8 mL). The combined organic layers were washed with brine (2 × 8 mL), dried over $MgSO_4$, filtered through celite and evaporated to dryness. The residue was purified by flash chromatography (petroleum ether–EtOAc) on alumina (**13a**) or silica gel (**13b**).

{3-[3-(3-Methoxy-phenyl)-1-(toluene-4-sulfonyl)-1*H*-indol-5-yl]-prop-2-ynyl}-dimethylamine (13a)

Yield: 78%; yellow oil.

IR (film): 2939, 1732, 1596, 1557, 1455, 1373, 1267, 1173, 1137, 1024, 812, 667, 590, 538 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.30 (s, 3 H), 2.35 (s, 6 H), 3.44 (s, 2 H), 3.85 (s, 3 H), 6.91 (dd, *J* = 8.2, 2.5 Hz, 1 H), 7.08–7.45 (m, 6 H), 7.70 (s, 1 H), 7.78 (d, *J* = 8.4 Hz, 2 H), 7.87 (s, 1 H), 7.98 (d, *J* = 8.4 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.5 (q), 44.3 (q), 48.6 (t), 55.3 (q), 84.0 (s), 85.1 (s), 112.9 (d), 113.6 (d), 113.7 (d), 118.5 (s), 120.3 (d), 123.6 (s), 123.7 (d), 123.9 (d), 126.8 (d), 128.4 (d), 129.2 (s), 129.9 (d) (2 peaks), 133.8 (s), 134.7 (s), 134.9 (s), 145.2 (s), 159.9 (s).

MS (EI, 70 eV): *m*/*z* (%) = 458 (22) [M+], 414 (9), 303 (43), 260 (40), 216 (9), 190 (3), 149 (5), 124 (13), 91 (28), 32 (100).

HRMS: *m*/*z* [M+] calcd for $C_{27}H_{26}N_2O_3S$: 458.1664; found: 458.1651.

3-(3-Methoxy-phenyl)-5-phenylethynyl-1-(toluene-4-sulfonyl)-1*H*-indole (13b)

Yield: 85%; yellow crystals; mp 139–140 °C ($CHCl_3$–pentane).

IR (film): 2931, 1732, 1595, 1493, 1456, 1373, 1299, 1275, 1248, 1189, 1146, 1128, 1090, 1023, 969, 891, 812, 755, 738, 672, 589 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.29 (s, 3 H), 3.83 (s, 3 H), 6.95 (dd, *J* = 8.3, 2.5 Hz, 1 H), 7.17–7.24 (m, 3 H), 7.33–7.42 (m, 5 H), 7.54–7.60 (m, 3 H), 7.77 (s, 1 H), 7.84 (d, *J* = 8.4 Hz, 2 H), 8.01 (d, *J* = 0.8 Hz, 1 H), 8.07 (d, *J* = 8.3 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.5 (q), 55.3 (q), 88.8 (s), 89.6 (s), 113.0 (d), 113.7 (d), 113.9 (d), 118.7 (s), 120.4 (d), 123.2 (s), 123.7 (s), 123.89 (d), 123.94 (d), 126.8 (d), 128.2 (d), 128.3 (d), 128.4 (d), 129.3 (s), 130.01 (d), 130.02 (d), 131.5 (d), 133.9 (s), 134.9 (s), 135.0 (s), 145.3 (s), 160.0 (s).

MS (EI, 70 eV): *m*/*z* (%) = 477 (54) [M+], 323 (77), 322 (100), 292 (3), 277 (7), 252 (13), 139 (9), 91 (24).

HRMS (ESI): *m*/*z* [MNa^+] calcd for $C_{30}H_{23}NNaO_3S$: 500.1291; found: 500.1300.

Acknowledgment

Financial support from the Fonds der Chemischen Industrie is gratefully acknowledged.

References

(1) (a) Hoyer, D.; Hannon, J. P.; Martin, G. R. *Pharmacol. Biochem. Behav.* **2002**, *71*, 533. (b) Barnes, N. M.; Sharp, T. *Neuropharmacology* **1999**, *38*, 1083.

(2) von Bohlen und Halbach, O.; Dermietzel, R. *Neurotransmitters and Neuromodulators*; Wiley-VCH: Weinheim, **2002**, 107–115.

(3) For a recent review about 5-HT_5, 5-HT_6 and 5-HT_7 receptors, see: Glennon, R. A. *J. Med. Chem.* **2003**, *46*, 2795.

(4) (a) Tsai, Y.; Dukat, M.; Slassi, A.; MacLean, N.; Demchyshyn, L.; Savage, J. E.; Roth, B. L.; Hufesein, S.; Lee, M.; Glennon, R. A. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2295. (b) Glennon, R. A.; Lee, M.; Rangisetty, J. B.; Dukat, M.; Roth, B. L.; Savage, J. E.; McBride, A.; Rauser, L.; Hufeisen, S.; Lee, D. K. H. *J. Med. Chem.* **2000**, *43*, 1011. (c) Bromidge, S. M.; Brown, A. M.; Clark, S. E.; Dodgson, K.; Gager, T.; Grassam, H. L.; Jeffrey, P. M.; Joiner, G. F.; King, F. D.; Middlemiss, D. N.; Moss, S. F.; Newman, H.; Riley, G.; Routledge, C.; Wyman, P. *J. Med. Chem.* **1999**, *42*, 202. (d) Sleight, A. J.; Boess, F. G.; Bös, M.; Levet-Trafit, B.; Riemer, C.; Bourson, A. *Br. J. Pharmacol.* **1998**, *124*, 556.

(5) (a) Witulski, B.; Alayrac, C.; Tevzadze-Saeftel, L. *Angew. Chem. Int. Ed.* **2003**, *42*, 4257; *Angew. Chem.* **2003**, *115*, 4392. (b) Witulski, B.; Stengel, T. *Angew. Chem. Int. Ed.* **1998**, *37*, 489; *Angew. Chem.* **1998**, *110*, 495.
(6) Witulski, B.; Alayrac, C. *Angew. Chem. Int. Ed.* **2002**, *41*, 3281; *Angew. Chem.* **2002**, *114*, 3415.
(7) (a) Li, J. J.; Gribble, G. W. *Palladium in Heterocyclic Chemistry, Tetrahedron Organic Chemistry Series*, Vol. 20; Pergamon: Oxford, **2000**. (b) *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F.; Stang, P. J., Eds.; Wiley-VCH: Weinheim, **1998**. (c) Brandsma, L.; Vasilevsky, S. F.; Verkruijsse, H. D. *Application of Transition Metal Catalysts in Organic Synthesis*; Springer: Berlin, **1998**.
(8) (a) Sonogashira, K. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F.; Stang, P. J., Eds.; Wiley-VCH: Weinheim, **1998**, 203–229. (b) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467. (c) Sonogashira, K. In *Comprehensive Organic Syntheses*, Vol. 3; Trost, B.; Fleming, I., Eds.; Pergamon Press: New York, **1991**, 521–549.
(9) (a) Suzuki, A. In *Modern Arene Chemistry*; Astruc, D., Ed.; Wiley-VCH: Weinheim, **2002**, 53–106. (b) Watanabe, T.; Miyaura, N.; Suzuki, A. *Synlett* **1992**, 207. (c) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
(10) (a) For sequential Stille and Heck cross-coupling reactions towards 3,4-diallyl indoles, see: Brown, M. A.; Kerr, M. A. *Tetrahedron Lett.* **2001**, *42*, 983. (b) For combined N- and C-arylations with boronic acids in the indazole series, see: Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron Lett.* **2000**, *41*, 9053. (c) For the synthesis of 3,5-diaryl indoles via tandem Pd-promoted cross coupling reactions, see: Yang, Y.; Martin, A. R. *Synth. Commun.* **1992**, *22*, 1757. (d) For sequential multi Pd-catalyzed cross-coupling reactions in benzofuran series, see: Bach, T.; Bartels, M. *Synlett* **2001**, 1284. (e) Bach, T.; Bartels, M. *Synthesis* **2003**, 925.
(11) For Suzuki and Sonogashira reactions with aryl chlorides, see: (a) Herrmann, W. A. *Angew. Chem. Int. Ed.* **2002**, *41*, 1290; *Angew. Chem.* **2002**, *114*, 1342. (b) Littke, A. F.; Fu, G. C. *Angew. Chem. Int. Ed.* **2002**, *41*, 4176; *Angew. Chem.* **2002**, *114*, 4350. (c) Köllhofer, A.; Pullmann, T.; Plenio, H. *Angew. Chem. Int. Ed.* **2003**, *42*, 1056; *Angew. Chem.* **2003**, *115*, 1086. (d) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2004**, *43*, 1871; *Angew. Chem.* **2004**, *116*, 1907. (e) G elman, D.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2003**, *43*, 5993; *Angew. Chem.* **2003**, *115*, 6175.
(12) (a) Arnautu, A.; Collot, V.; Calvo Ros, J.; Alayrac, C.; Wituski, B.; Rault, S. *Tetrahedron Lett.* **2002**, *43*, 2695. (b) Collot, V.; Dallemagne, P.; Bovy, P. R.; Rault, S. *Tetrahedron* **1999**, *55*, 6917.
(13) For other recent work on the functionalisation of indazoles in position 3, see: (a) Yang, Y.; Knochel, P. *Synlett* **2004**, 2303. (b) Hari, Y.; Shoji, Y.; Aoyama, T. *Synthesis* **2004**, 1183. (c) Gordon, D. W. *Synlett* **1998**, 1065. (d) Welch, W. M.; Hanau, C. E.; Whalen, W. M. *Synthesis* **1992**, 937.
(14) (a) Harrington, P. J.; Hegedus, L. S.; McDaniel, K. F. *J. Am. Chem. Soc.* **1987**, *109*, 4335. (b) Hegedus, L. S.; Sestrick, M. R.; Michaelson, E. T.; Harrington, P. J. *J. Org. Chem.* **1989**, *54*, 4141. (c) Merlic, C. A.; Semmelhack, M. F. *J. Organomet. Chem.* **1990**, *391*, C23. (d) Bando, T.; Shishido, K. *Heterocycles* **1997**, *46*, 111.
(15) For the synthesis of 3-alkynyl indoles by palladium catalysed Stille reactions, see: (a) Sakamoto, T.; Yasuhara, A.; Kondo, Y.; Yamanaka, H. *Synlett* **1992**, 502. (b) Kanekiyo, N.; Kuwada, T.; Choshi, T.; Nobuhiro, J.; Hibino, S. *J. Org. Chem.* **2001**, *66*, 8793.
(16) (a) Sakamoto, T.; Ohsawa, K. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2323. (b) Jiang, B.; Kan, Y.; Zhang, A. *Tetrahedron* **2001**, *57*, 1581.
(17) Sakamoto, T.; Nagano, T.; Kondo, Y.; Yamanaka, H. *Chem. Pharm. Bull.* **1988**, *36*, 2248.
(18) Witulski, B.; Buschmann, N.; Bergsträßer, U. *Tetrahedron* **2000**, *56*, 8473.
(19) Papanastassiou, Z. B.; Bruni, R. J.; White, E. *J. Med. Chem.* **1967**, *10*, 701.
(20) (a) Yoneda, N.; Matsuoka, S.; Miyaura, N.; Fukuhara, T.; Suzuki, A. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2124. (b) Sakamoto, T.; Shiga, F.; Yasuhara, A.; Uchiyama, D.; Kondo, Y.; Yamanaka, H. *Synthesis* **1992**, 746. (c) Kundu, N. G.; Dasgupta, S. K. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2657.
(21) For examples of Sonogashira couplings between electron deficient alkynes and diaryliodonium salts, see: Radhakrishnan, U.; Stang, P. J. *Org. Lett.* **2001**, *3*, 859.
(22) Lynne, A. H.; Koenig, T. M.; Ginah, F. O.; Copp, J. D.; Mitchell, D. *J. Org. Chem.* **1998**, *63*, 5050.
(23) (a) Sonogashira reactions of aryl bromides at r.t. using $Pd(PhCN)_2Cl_2/P(t\text{-}Bu)_3$ as catalyst have been reported, see: Hundertmark, T.; Littke, A. F.; Buchwald, S. L.; Fu, G. C. *Org. Lett.* **2000**, *2*, 1729. (b) In our hands, application of this protocol to our substrates has not been satisfactory so far.