Preparation of symmetrical C2-C2-linked bis- and tris-6-bromoindoles by Sonogashira couplings and 5-*endo-dig* cyclization induced by nBu_4NF

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Abstract

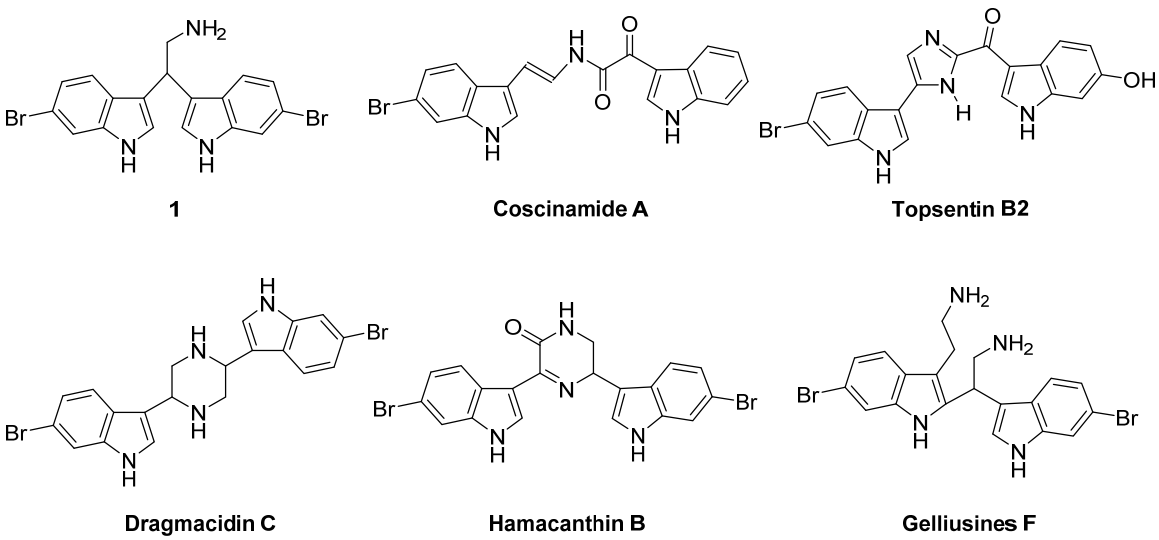
Preparation of symmetrical C2-C2 linked bis-6-bromoindoles and one tris-6-bromoindole containing ether spacers is described. Double regioselective Sonogashira coupling at the C-I bond of benzyl (5-bromo-2-iodophenyl)carbamate with dialkynes allowed preparation of the corresponding bis-benzyl(2-alkynyl-5-bromo)carbamates. Tetrabutylammonium fluoride (TBAF) promoted 5-*endo-dig* cyclization was successful with substrates derived from alkyldialkynes but failed with substrates derived from aryldialkynes as base catalysis was not sufficient to promote nucleophilic attack on these electron rich alkynes.

Keywords: Bis-indoles, tris-indoles, Sonogashira coupling, 5-*endo-dig* cyclization, TBAF

Introduction

The indole nucleus is a privileged structure present in a myriad of bioactive compounds many of which have been translated in pharmaceutical leads. In this regard, an increasingly number of brominated bis- and tris-indoles isolated from marine organisms that include, among others, the unnamed alkaloid **1** and coscinamides, topsentins, dragmacidins, hamacanthins and gelliusines have shown antiviral, antiproliferative and antitumoral activity.[1-3] Scheme 1. It is noteworthy that structural modifications of these natural products had led to synthetic analogs with DNA-quadruplex recognition,[4] antibacterial,[5,6] antilesihmanial,[7] antitumoral,[8-11] and angiogenesis inhibition[12] activity. Most of these compounds are linked through the indole C3 position, with only a few exceptions such as Gelliusines F which is a C2-C3 linked bis-indole. In view of the structural diversity of these compounds it is likely that the C2-C2 bis-indoles hold promise for

new discoveries. Here we would like to present our work aimed to prepare C2-C2 symmetrical bis-6-bromoindoles.

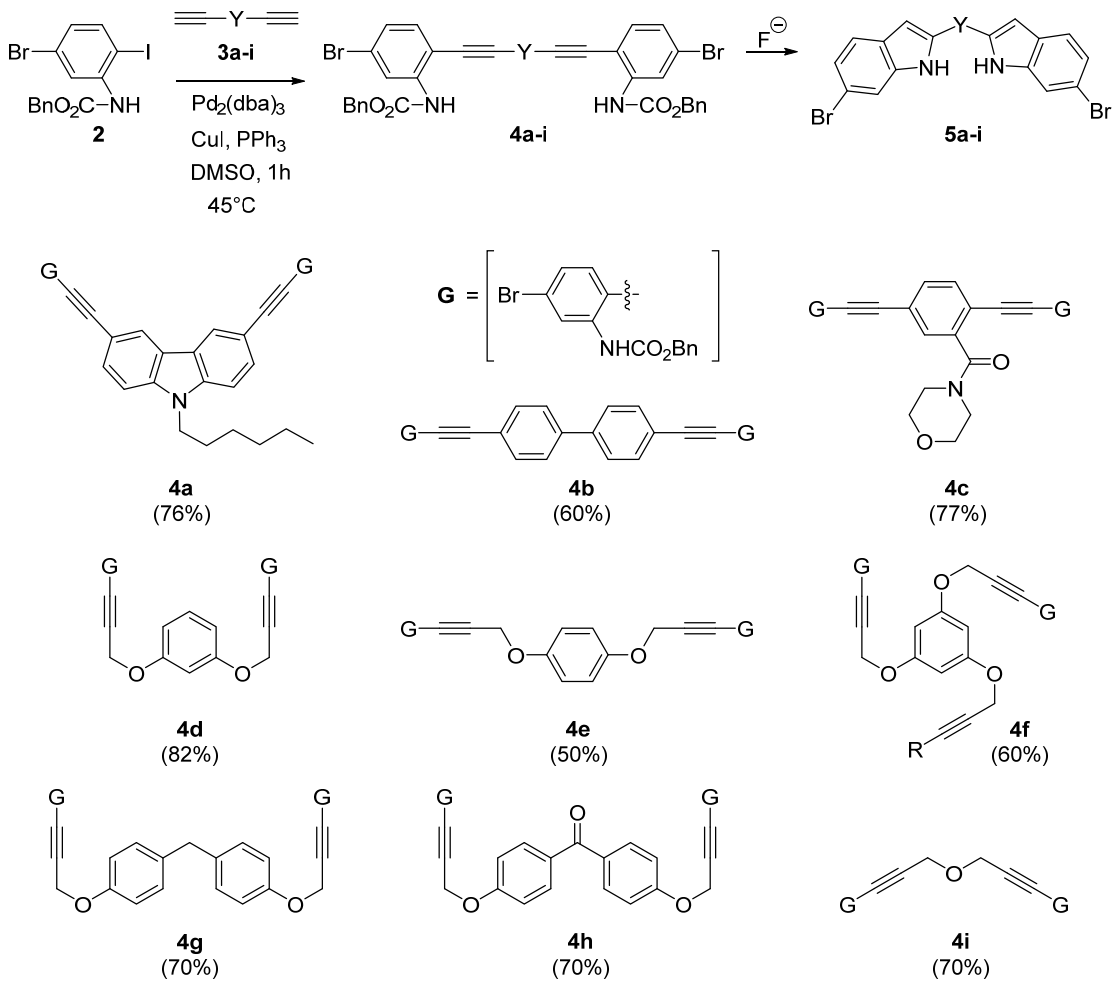


Scheme 1

Results and Discussion

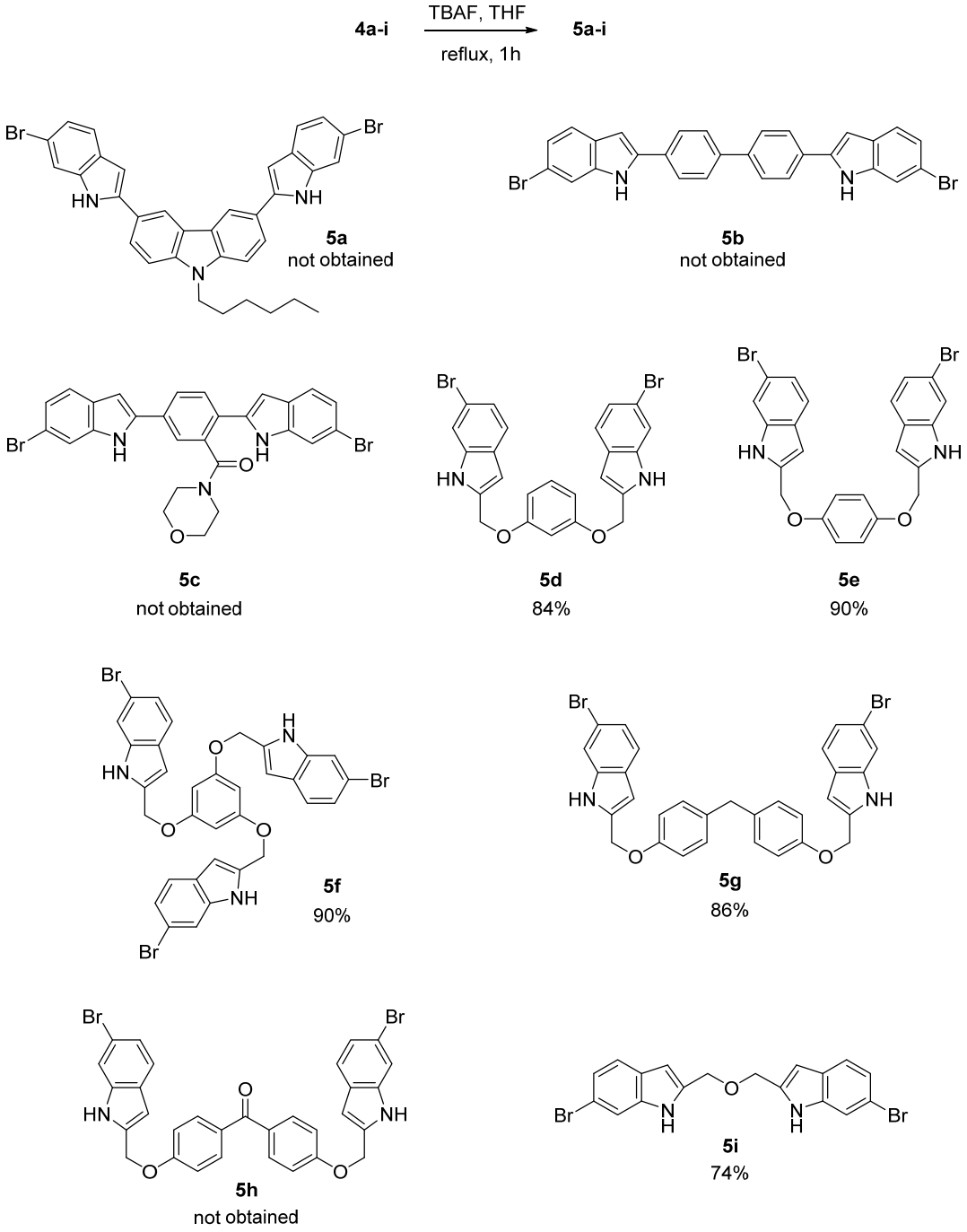
Among the methods to prepare indoles,[13,14] cyclization of ortho-alkynylaniline derivatives is a very robust method to prepare 2-substituted indoles. Thus the synthesis of the target C2-C2 bis-indoles of type **5** was designed in two steps: a regioselective double Sonogashira coupling of arene **2**[15] with dialkynes **3a-i** to afford the corresponding coupling products **4a-i** followed by 5-*endo-dig* cyclization promoted by fluoride. Scheme 2.

Initially it was necessary to find suitable conditions to effect the double Sonogashira coupling of the dihaloarene **2** with several dialkynes while maintaining the regioselective coupling at the C-I bond. From previous work in our laboratory, it was found that double Sonogashira coupling of related arenes with aryldialkynes worked well using $Pd_2(dba)_3$, CuI, PPh_3 in DMSO as solvent.[16] Thus, a model set of aryldialkynes **3a-c** and alkyldialkynes **3d-i** were prepared (See supporting information) and their regioselective Sonogashira coupling with **2** proceeded uneventfully to give the corresponding products **4a-i**.



Scheme 2

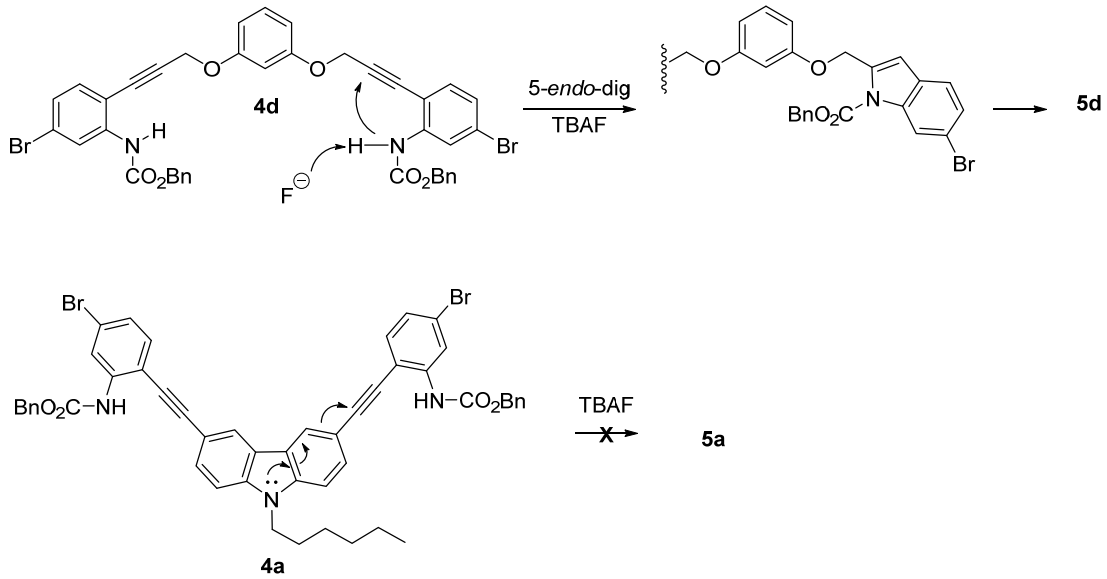
With these coupling products in hand, their cyclization to produce indoles was investigated. The 5-*endo*-*dig* cyclization of *ortho*-alkynylaniline derivatives can be conducted by bases,[16-22] metals[23-28] and in the presence of electrophiles that can add functional groups to the indole nucleus.[29-36] In order to keep the procedure simple, the protocol using tetrabutylammonium fluoride (TBAF)[17,18] was chosen. Thus alkynes **4a-i** were treated with TBAF (3 equiv for each carbamate group) in refluxing THF (Scheme 3). Reactions of aryldialkynes **4a-c** were sluggish, starting material decomposition was observed but no evidence of formation of the desired products could be found by ^{1}H NMR analysis of the reaction crude complex mixtures. On the other hand, the alkyldialkynes **4d-i** underwent smooth cyclization to afford the desired bis-indoles **5d,e,g,i** and the tris-indole **5f**, the exception being ketone **4h** which decomposed in the reaction conditions and did not give any of the expected indole **5h**. (Scheme 3)



Scheme 3

Failure of aryldialkynes **4a-c** to cyclize is likely due these to the presence of aryl rings with electron rich groups that make the alkyne group too electron-rich to undergo the base promoted cyclization. Compare for example the successful cyclization reaction of **4d** *vs.* the failed reaction of **4a**. Electron delocalization in **4a** from the carbazole unit towards the alkyne carbon which should undergo nucleophilic attack from the carbamate anion renders the alkyne unreactive; on the contrary, in **4d** no such electron delocalization is possible and the alkyne underwent

cyclization (Scheme 4). Recent literature reports describe similar diarylalkyne substrates which have required gold catalysts using microwave[4] or ultrasound[37] techniques or indium tribromide[27] to accomplish the 5-*endo*-dig cyclization.



Scheme 4

Conclusions

We have found an efficient protocol for the C-I regioselective consecutive Sonogashira coupling of benzyl (5-bromo-2-iodophenyl)carbamate **2** with aryldialkynes and alkyldialkynes to afford the corresponding bis-alkynes. The scope of the reaction indicates that only alkyldialkynes underwent TBAF induced 5-*endo-dig* cyclization to form bis-indoles while aryldialkynes failed to cyclize. Despite this limitation, the protocol shown here is simple, reaction conditions for both the Sonogashira coupling and cyclization are mild and the reaction sequence was efficient for the synthesis of symmetrical C2-C2 bis-6-bromoindoles and one tris-6-bromoindole. Such structures are building blocks for further development of new bioactive compounds.

Experimental Section

General. All commercial reagents, including $Pd_2(dba)_3{\cdot}CHCl_3$, CuI (99.999%), PPh_3 (Reagent Plus®, 99%) dry DMSO, *i*-Pr_2NH (99.5%) and TBAF 1M in THF were obtained from Aldrich and used as purchased. Column chromatography was performed using Whatman silica gel 60 (230-400 mesh) and thin layer chromatography (TLC) was done on Merck F254 plates.

Visualization of TLC plates was carried out with a UV lamp (254, 365 nm) and staining with cerium molybdate solution. IR spectra were obtained on a Perkin-Elmer FT-IR Spectrum GX spectrometer. High resolution mass spectra were obtained either on a JEOL GCmate spectrometer by electronic impact (IE+) at 70 eV or on a Maxis Impact ESI-QTOF MS, Bruker Daltonics with chemical ionization (CI). Melting points were determine on a Büchi® Melting Point B-540 apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained in $CDCl_3$ or DMSO-d6 solutions on a Varian VNM System 400 MHz spectrometer using TMS (δ= 0.0 ppm) $CDCl_3$ (δ = 77.16 ppm) and DMSO-*d6* (δ= 29.84 ppm) as internal references.

General procedure for Sonogashira cross coupling of benzyl (5-bromo-2-iodophenyl)carbamate 2 with dialkynes 3a-i for preparation of carbamates 4a-i.

In a dry, one neck, round bottom flask equipped with a stirring bar under N_2 atmosphere, was added 0.5 mmol of the dialkyne **3a-i** (1.0 equiv), followed by the carbamate **2** (1 mmol, 2 equiv for dialkynes **3a-e, 3g-i** and 1.5 mmol, and 3.0 equiv of **2** for coupling with trialkyne **3f**) and 13 mg of $Pd_2(dba)_3{\cdot}CHCl_3$ (0.05 equiv), 3 mg of CuI (0.03 equiv) and 8 mg of PPh_3 (0.06 equiv) in 5 mL of DMSO. The flask was purged by alternate vacuum and a current of N_2. Then 180 μL of *i*-Pr_2NH (2.50 equiv) was added and the solution was stirred under a N_2 atmosphere at 45°C for 1h. The reaction crude was diluted with 100 mL of ethyl acetate and washed with water (3X 60 mL) and brine (1x50 mL). The organic portion was dried with anh. Na_2SO_4, filtered and concentrated to approx. 40-50 mL and absorbed in silica gel then dried under vacuum. Unless otherwise indicated, column chromatography used elution with a gradient of hexanes-acetone, starting at 5% acetone and up to 30% acetone, followed by evaporation of the fractions to give the desired products **4a-i**.

Dibenzyl [[(9-hexyl-9*H*-carbazol-3,6-diyl)bis(ethyne-2,1-diyl)]bis(5-bromo-2,1-phenylene)]-dicarbamate (**4a**). Column chromatography used gradients of hexanes-CH_2Cl_2. The product was obtained in 76% yield as a viscous yellow oil that solidified upon standing; mp 181-182 ºC; R_f = 0.50 (30% acetone/hexanes); IR (KBr) ν 3395 m, 3036 m, 2926 m, 2856 w, 2202 w, 1740 s, 1569 m, 1216 s, 1041 s cm^{-1}; ^{1}H RMN (400 MHz, $CDCl_3$): δ 8.44 (s, 2H), 8.21 (d, J = 1.2 Hz, 2H), 7.62 (dd, J = 8.5 Hz, J = 1.6 Hz, 2H), 7.57 (br, 2H), 7.44-7.31 (m, 14H), 7.16 (dd, J = 8.5, J = 2 Hz, 2H), 5.23 (s, 4H), 4.27 (t, J = 7.2 Hz, 2H), 1.9 (quintet, J = 7.2 Hz, 2H), 1.37-1.24 (m, 6H), 0.87-0.84 (m, 3H); ^{13}C RMN (100 MHz, $CDCl_3$): δ 152.7, 140.8, 139.6, 135.8, 132.5, 129.8, 128.6, 128.5, 128.3, 125.8, 124.2, 123.3, 122.4, 120.7, 112.8, 110.8, 109.3, 98.5, 81.9, 67.3, 43.4, 31.5, 28.9, 26.9, 22.5, 14.0; HRMS (CI) *m/z* calc. for $C_{50}H_{42}Br_2N_3O_4$ ($M+H^+$): 908.1522, found: 908.1523.

Dibenzyl [[(1,1'-biphenyl)-4,4'-diylbis(ethyne-2,1-diyl)]bis(5-bromo-2,1-phenylene)] dicarbamate (**4b**)**.** Obtained in 60% yield as a white solid; mp 248-250 ºC; R_f = 0.73 (20% EtOAc/hexanes); IR (KBr) ν 3311 s, 3034 m, 2958 m, 2856 w, 2231 m, 1706 s, 1568 m cm^{-1}; ^{1}H RMN (400 MHz, $CDCl_3$): δ 8.46 (s, 2H), 7.61 (s, 8H), 7.41 (m, 14H), 7.18 (dd, J = 8.26 Hz, 1.9 Hz, 2H), 5.26 (s, 4H); ^{13}C RMN (100 MHz, $CDCl_3$): δ 152.7, 140.5, 139.7, 135.7, 132.7, 132.1,

128.7, 128.5, 128.4, 127.1, 125.9, 124.0, 121.5, 120.8, 110.2, 97.0, 84.4, 67.4, 40.8, 29.5; HRMS (CI) *m/z* calc. for $C_{44}H_{31}Br_2N_2O_4$ ($M+H^+$): 811.0630, found: 811.0630.

Dibenzyl [[2-(morpholine-4-carbonyl)-1,4-phenylene]bis(ethyne-2,1-diyl)]bis(5-bromo-2,1-phenylene)]dicarbamate (**4c**). Column chromatography used gradients of hexane: EtOAc (90:10, 80:20 and 70:30) to obtain this compound in 77% yield as a white solid, mp 156-157 ºC; R_f = 0.30 (20% EtOAc/hexanes); IR (KBr) ν 3331 m, 3037 m, 2922 m, 2852 w, 2218 m, 1735 s, 1624 m cm^{-1}; ^{1}H RMN (400 MHz, $CDCl_3$): δ 8.57 (d, J = 1.65 Hz, 1H), 8.46 (s,1H), 7.76 (s, 1H), 7.58-7.14 (m, 18H), 5.27 (s, 2H), 5.25 (s, 2H), 3.59-3.43 (6H), 3.34-3.23 (m, 2H); ^{13}C RMN (100 MHz, $CDCl_3$): δ 167.7, 153.2, 152.6, 140.9, 139.8, 138.2, 135.9, 135.6, 132.9, 132.9, 132.3, 132.2, 129.0, 128.7, 128.7, 128.6, 128.6, 128.5, 128.4, 126.0, 125.7, 124.8, 124.6, 122.6, 121.2, 121.0, 120.7, 109.5, 109.1, 95.7, 93.7, 90.1, 86.5, 67.5, 67.3, 66.9, 66.7, 47.7, 42.2; HRMS (CI) *m/z* calc. for $C_{43}H_{34}Br_2N_3O_6$ ($M+H^+$): 848.0794, found: 848.0785.

Dibenzyl [[[1,3-phenylenebis(oxy)]bis(prop-1-yne-3,1-diyl)]bis(5-bromo-2,1-phenylene)]-dicarbamate (4d). Obtained in 82% yield as a white solid; mp 133-135 ºC (dec.); R_f = 0.33 (20% EtOAc/Hexane); IR (KBr) ν 3328 m, 3064 m, 2928 m, 2225 w, 1715 s, 1522 m, 1243 s, 1047 s cm^{-1}; ^{1}H RMN (400 MHz, $CDCl_3$): δ 8.40 (s, 1H), 7.41-7.08 (m, 7H), 6.64-6.59 (m, 2H), 5.20 (s, 2H) 4.88 (s, 2H); ^{13}C RMN (100 MHz, $CDCl_3$): δ 158.7, 152.5, 140.1, 135.7, 133.0, 130.3, 128.7, 128.6, 128.5, 125.7, 124.4, 120.7, 109.0, 107.8, 102.4, 91.8, 81.7, 67.4, 56.4; HRMS (EI+) *m/z* calc. for $C_{40}H_{30}Br_2N_2O_6$: 793.05254, found: 793.0515.

Dibenzyl [[[1,4-phenylenebis(oxy)]bis(prop-1-yne-3,1-diyl)]bis(5-bromo-2,1-phenylene)]-dicarbamate (**4e**)**.** Obtained in 50% yield as a white solid; mp 161-163 ºC (dec.); R_f = 0.36 (20% EtOAc/Hexane); IR (KBr) ν 3338 m, 3074 m, 2923 m, 2221 m, 1704 s, 1528 m, 1236 s, 1029 m cm^{-1}; ^{1}H RMN (400MHz, $CDCl_3$): δ 8.40 (s, 2H), 7.32-7.34 (m, 10H), 7.26 (d, J = 3.8 Hz, 2H) 7.19 (d, J = 8.3 Hz, 2H), 7.10 (dd, J = 8.3 Hz, J = 1.9 Hz, 2H), 6.90 (s, 4H), 5.19 (s, 4H), 4.84 (s, 4H); ^{13}C RMN (100 MHz, $CDCl_3$): δ 152.6, 152.2, 140.2, 135.6, 133.0, 128.7, 128.6, 128.5, 125.7, 124.38, 120.8, 116.2, 109.1, 92.2, 81.6, 67.4, 57.1; HRMS (CI) *m/z* calc. for $C_{40}H_{31}Br_2N_2O_6$ ($M+H^+$): 795.0529, found: 795.0523.

Tribenzyl [[[1,3,5-phenylenetris(oxy)]tris(prop-1-yne-3,1-diyl))tris(5-bromo-2,1-phenyl-ene)]tricarbamate (**4f**). Obtained in 60% yield as a white solid; mp 160-162 ºC (dec.); R_f = 0.36 (20% EtOAc/Hexane); IR (KBr) ν 3301 m, 3068 m, 3061 m, 2930 m, 2232 m, 1709 s, 1525 m, 1237 m, 1065 m cm^{-1}; ^{1}H RMN (400 MHz, DMSO-*d6*): δ 9.07 (s, 3H), 7.95 (d, J = 1.7 Hz, 3H), 7.42-7.28 (m, 9H) 7.26 (d, J = 8.4 Hz, 3H), 7.21 (dd, J = 4.1 Hz, J = 2.0 Hz, 3H), 6.39 (s, 3H) 5.16 (s, 6H), 4.99 (s, 6H); ^{13}C RMN (100 MHz, DMSO-*d6*): δ 159.6, 153.9, 141.1, 136.6, 134.4, 128.8, 128.6, 127.0, 124.4, 122.9, 113.1, 95.6, 92.1, 82.0, 66.8, 57.0; HRMS (CI) *m/z* calc. for $C_{57}H_{43}Br_3N_3O_9$ ($M+H^+$): 1154.0509, found: 1154.0514.

Dibenzyl [[[methylenebis(4,1-phenylene)]bis(oxy)]bis(prop-1-yne-3,1-diyl)]bis(5-bromo-2,1-phenylene)]dicarbamate (4g). Obtained in 70% yield as a white solid; mp 165-167 ºC (dec.); R_f = 0.66 (30% EtOAc/Hexane); IR (KBr) ν 3320 s, 3030 m, 2931 m, 2860 w, 2223 m, 1706 s, 1525 m, 1273 s, 1055 s cm^{-1}; ^{1}H RMN (400 MHz, $CDCl_3$): δ 8.41 (s, 2H), 7.39-7.31 (m, 12H), 7.20 (d, J = 8.3 Hz, 2H) 7.15 (dd, J = 8.3 Hz, J = 1.9 Hz, 2H), 7.04 (d, J = 8.6 Hz, 4H), 6.90-6.88

(m, 4H), 5.17 (s, 4H), 4.91 (s, 4H), 3.8 (s, 2H); ^{13}C RMN (100 MHz, $CDCl_3$): δ 155.8, 152.6, 140.2, 135.6, 134.6, 133.0, 129.9, 128.7, 128.5, 128.5, 125.7, 124.3, 120.8, 114.9, 109.1, 92.2, 81.5, 67.4, 56.5, 40.1; HRMS (EI) *m/z* calc. for $C_{47}H_{37}Br_2N_2O_6$ ($M+H^+$): 885.0998, found: 885.0982.

Dibenzyl [[[[carbonylbis-(4,1-phenylene)]bis(oxy)]bis(prop-1-yne-3,1-diyl)]bis(5-bromo-2,1-phenylene)]dicarbamate (**4h**). Obtained in 70% yield as a white solid; mp 140-142 ºC (dec.); R_f = 0.46 (30% EtOAc /Hexane); IR (KBr) ν 3291 s, 3070 m, 3035 m, 2929 m, 2859 w, 2227 m, 1704 s, 1524 m, 1235 s, 1054 s, cm^{-1}; ^{1}H RMN (400 MHz, $CDCl_3$): δ 8.41 (s, 2H), 7.78 (d, J = 8.8 Hz, 4H) 7.38-7.26 (m, 12H), 7.22 (d, J = 8.3 Hz, 2H), 7.11 (dd, J = 8.8 Hz, J = 1.8 Hz, 2H) 7.04 (d, J = 8.8 Hz, 4H), 5.18 (s, 4H), 5.02 (s, 4H); ^{13}C RMN (100 MHz, $CDCl_3$): δ 194.1, 160.6, 152.6, 140.3, 135.6, 133.1, 132.3, 131.4, 128.7, 128.6, 128.5, 125.8, 124.6, 120.9, 114.3, 108.8, 91.2, 82.3, 67.5, 56.4; HRMS (CI) *m/z* calc. for $C_{47}H_{35}Br_2N_2O_7$ ($M+H^+$): 899.0791, found: 899.0780.

Dibenzyl [[oxybis(prop-1-yne-3,1-diyl)]bis-(5-bromo-2,1-phenylene)]dicarbamate (**4i**). Obtained in 70% yield as a white solid; mp120-122 ºC (dec.); R_f = 0.63 (20% EtOAc /Hexane); IR (KBr) ν 3326 s, 3069 m, 3036 m, 2928 m, 2346 m, 1706 s, 1527 m, 1247 s, 1064 s cm^{-1}; ^{1}H RMN (400 MHz, $CDCl_3$): δ 8.41 (s, 2H), 7.40-7.33 (m, 12H), 7.21 (d, J = 8.2 Hz, 2H), 7.11 (dd, J = 8.2, 1.7 Hz, 2H), 5.19 (s, 4H), 4.54 (s, 4H); ^{13}C RMN (100 MHz, $CDCl_3$): δ 152.7, 140.1, 135.5, 133.1, 128.7, 128.6, 128.5, 125.8, 124.4, 120.9, 109.2, 92.2, 81.5, 67.5, 57.5; HRMS (EI) *m/z* calc. for $C_{34}H_{26}N_2O_5Br_2$: 700.0209, found: 700.0218.

General procedure for cyclization of carbamates 4c-i with TBAF in THF for preparation of indoles 5d-g and 5i.

In a round-bottom flask, equipped with a condenser and a stirring bar, under a N_2 atmosphere was placed 0.3 mmol of the corresponding carbamate **4d-i** in 5 mL of dry THF and 1.8 mL of a solution of 1M de TBAF (1.8 mmol, 6.0 equiv) in THF for all bis-carbamates **4d,e**, **4g-i** and 2.7 mL of 1M TBAF (2.7 mmol, 9.0 equiv) for tris-carbamate **4f** (*i.e*. 3.0 equivalents of TBAF for each carbamate group that undergoes cyclization). The solution was heated to reflux for 1h under N_2 and then cooled to room temperature, diluted with 200 mL of ethyl acetate and washed with water (3x60 mL) and brine (1x50mL). The organic phase was dried with anh. Na_2SO_4, absorbed in sílica gel and dried under vacuum. Column chromatography using gradients of hexanes:THF (95:5, 90:10, 80:20) gave the indoles **5d-i**.

1,3-Bis-[(6-bromo-1*H*-indol-2-yl)methoxy]benzene (**5d**). Obtained in 84% yield as a white solid; mp 198-200 ºC (dec.); R_f = 0.33 (20% EtOAc/hexanes); IR (KBr) ν 3391 s, 3059 m, 2937 m, 1611 s cm^{-1}; ^{1}H RMN (400 MHz, DMSO-*d6*): δ 11.49 (s, 2H), 7.53 (s, 2H), 7.46 (d, J = 8.4 Hz, 2H), 7.21 (t, J = 8.2 Hz, 1H), 7.11 (dd, J = 8.4 Hz, J = 1.8 Hz, 2H), 6.74 (t, J = 2.2 Hz, 1H), 6.66 (dd, J = 8.2 Hz, J = 2.3 Hz, 2H), 6.53 (d, J = 1.2 Hz, 2H), 5.19 (s, 4H); ^{13}C RMN (100 MHz, DMSO-*d6*): δ 159.7, 137.9, 136.0, 130.5, 127.0, 122.4, 114.5, 114.3, 107.92, 102.3, 102.2, 63.4; HRMS (EI) *m/z* calc. for $C_{24}H_{18}N_2O_2Br_2$: 523.9735, found: 523.9749.

1,4-Bis-[(6-bromo-1*H*-indol-2-yl)methoxy]benzene (**5e**). Obtained in 90% yield as a white solid; mp 176-177 ºC (dec.); R_f = 0.26 (20% EtOAc/hexanes); IR (KBr) ν 3437 m, 3059 m, 2929 m, 1506 s cm^{-1}; ^{1}H RMN (400 MHz, DMSO-*d6*): δ 11.47 (s, 2H), 7.50 (d, J = 0.8 Hz, 2H), 7.45 (d, J = 8.4 Hz, 2H), 7.08 (dd, J = 8.4 Hz, J = 1.8 Hz, 2H), 6.97, (s, 4H), 6.49 (d, J = 1.1 Hz, 2H), 5.12, (s, 4H); ^{13}C RMN (100 MHz, DMSO-*d6*): δ 152.8, 137.7, 136.1, 127.0, 122.3 (overlap of two signals, see supporting material), 116.1, 114.4, 114.2, 102.0, 63.8; HRMS (EI) *m/z* calc. for $C_{24}H_{18}N_2O_2Br_2$: 523.9735, found: 523.9756.

1,3,5-Tris-[(6-bromo-1*H*-indol-2-yl)methoxy]benzene (**5f**). Obtained in 90% yield as a white solid; mp 165.5-167 ºC (dec.); R_f = 0.33 (30% EtOAc/hexanes); IR (KBr) ν 3394 m, 3056 m, 2937 m, 1594 s cm^{-1}; ^{1}H RMN (400 MHz, DMSO-*d6*): δ 11.5 (s, 3H), 7.54 (s, 3H), 7.46 (d, J = 8.4 Hz, 3H), 7.11 (dd, J = 8.4 Hz, J = 1.7 Hz, 3H), 6.52 (s, 3H), 6.38 (s, 3H), 5.18 (s, 6H); ^{13}C RMN (100 MHz, DMSO-*d6*): δ 160.3, 137.8, 135.7, 127.0, 122.3 (overlap of two signals, see supporting material), 114.5, 114.2, 102.2, 95.2, 63.5, 31.1; HRMS (EI) *m/z* calc. for $C_{33}H_{24}N_3O_3Br_3$: 746.9368, found: 746.9338.

Bis-[4-[(6-bromo-1*H*-indol-2-yl)methoxy]phenyl]methane (**5g**). Obtained in 86% yield as a white solid; mp 175-176 ºC (dec.); R_f = 0.26 (20% THF/hexanes); IR (KBr) ν 3403 m, 3052 m, 2928 m, 2858 m, 1611 s cm^{-1}; ^{1}H RMN (400 MHz, DMSO-*d6*): δ 11.45 (s, 2H), 7.51 (d, *J* = 0.89 Hz, 2H) 7.45 (d, J = 8.4 Hz, 2H), 7.09 (m, AA'BB', 4H), 7.09 (d, J = 8.4 Hz, 2H), 6.95-6.93 (m, AA'BB',4H), 6.5 (d, J = 1.24 Hz, 2H), 5.14 (s, 4H), 3.78 (s, 2H); ^{13}C RMN (100 MHz, DMSO-*d6*): δ 156.8, 137.7, 136.0, 134.5, 130.0, 127.0, 122.3, 115.1, 114.3, 114.2, 102.1, 63.3, one Csp^3 signal is overlapped with residual DMSO signals; HRMS (CI) *m/z* calc. for $C_{31}H_{24}Br_2N_2O_2$ ($M+H^+$): 617.02625, found: 617.0253.

2,2'-[Oxybis(methylene)]bis-(6-bromo-1*H*-indole) (**5i**). Obtained in 74% yield as a white solid; mp 195 ºC (dec.); R_f = 0.36 (30% EtOAc/hexanes); IR (KBr) ν 3403 m, 3120 m, 2946 m, 2863 m, 1548 s cm^{-1}; ^{1}H RMN (400 MHz, DMSO-*d6*): δ 11.35 (s, 2H), 7.5 (m, 2H), 7.44 (d, J = 8.4 Hz, 2H), 7.08 (dd, J = 8.4 Hz, J = 1.8 Hz, 2H), 6.42 (d, J = 1.3 Hz, 2H), 4.62 (s, 4H); ^{13}C RMN (100 MHz , DMSO-*d6*): δ 137.8, 137.1, 127.1, 122.2, 122.2, 114.2, 114.2, 101.6, 64.9; HRMS (EI) *m/z* calc. for $C_{24}H_{18}N_2O_2Br_2$: 431.9473, found: 431.9494.

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