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Light induced cyclization of tryptamine-naphthoquinone hybrids

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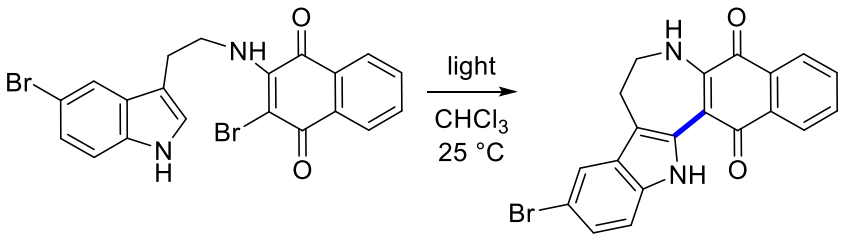
Abstract

Blue-LED light or direct sunlight induces cyclization in tryptamine-quinone hybrid compounds. Formation of a C-C bond between the C-2 atom of the indole and the bromo-naphthoquinone takes place in chloroform solution in air without the need for a photocatalyst. The reaction allows the presence of a bromine atom on the indole ring which can be used for subsequent cross coupling reactions. On the other hand, the bromine atom on the naphthoquinone is strictly necessary for the cyclization to occur. The cyclic products of these reactions are blue pigments with broad absorption in the visible region.



Keywords: Photocyclization, 2-indolylquinone, radical reaction, blue pigment

Introduction

Asterriquinones are 3-indolyl-quinone fungal metabolites that show anticancer,[1] anti-diabetic[2,3] and antiviral activity.[4] Their synthesis has been mainly based on the nucleophilic character of indole towards electrophiles to produce the characteristic indole(C-3)-quinone bond. In these methods Lewis acids[5,6] transition metal catalysis,[7] C-H activation,[8] activation "on water",[9] microwave irradiation[10] photo-induced addition to enones,[11] mechanochemical,[12] and oxidizing conditions have been employed.[13-15] In contrast, the formation of the isomeric C-2 Indole quinone compounds has been less studied.[16-19] In this regard, we considered that indole could selectively react at C-2 with quinone radicals generated by visible light irradiation using a tethered structure containing both indole and quinone fragments. Herein, we report our studies to form this bond in a model tryptamine-naphthoquinone hybrid using blue LED light at 460 nm, or sunlight. (Figure 1).

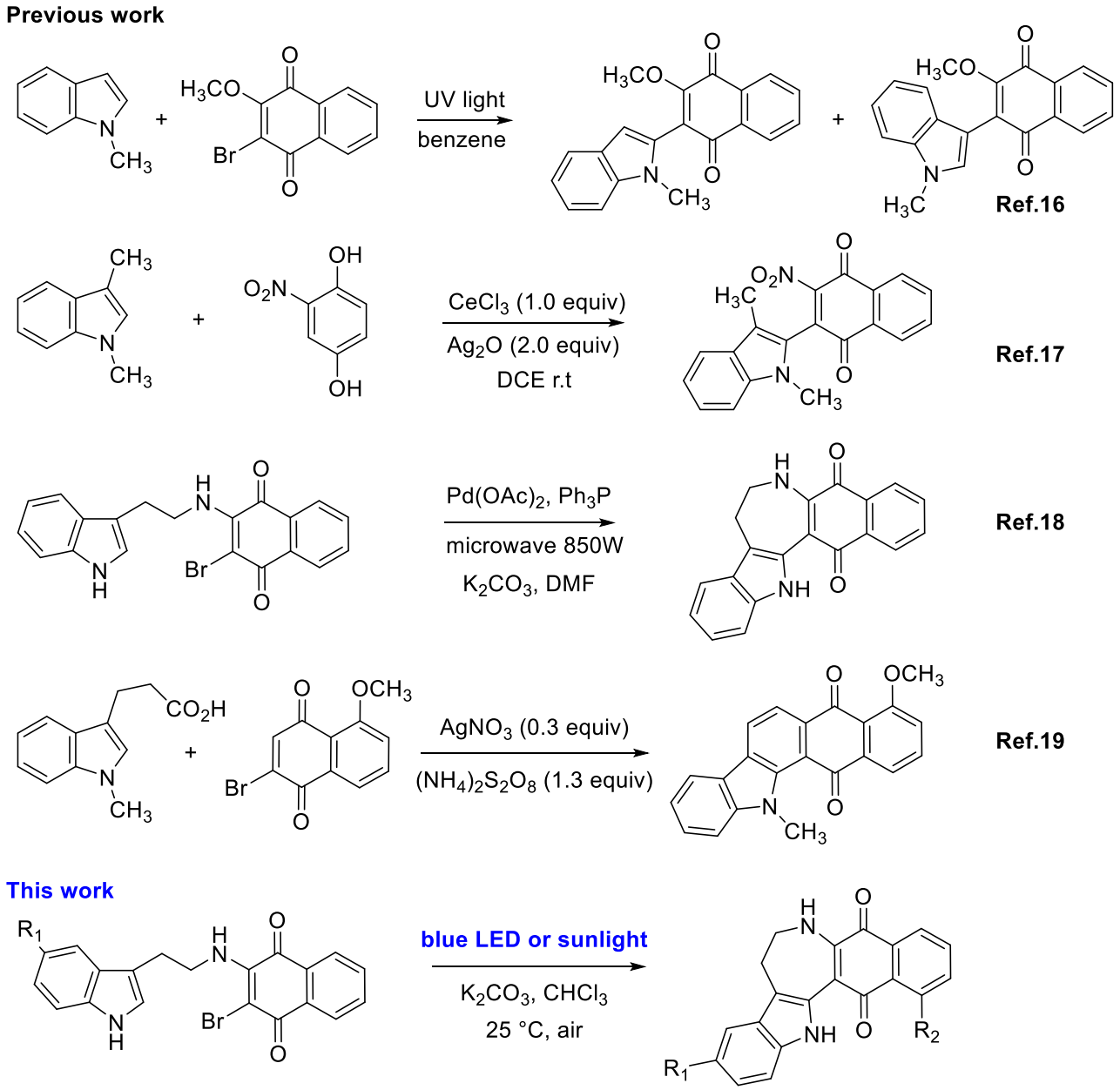
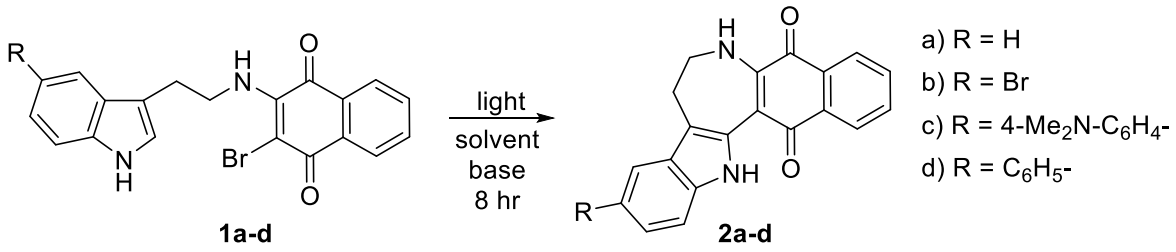


Figure 1. Methods for the synthesis of 2-indolylquinones

Results and Discussion

Quinones are redox active species capable to react with indole under electrochemical conditions.[20] In organic solvents quinones are considered to undergo two consecutive one-electron reductions, forming intermediate quinone radicals.[21] Given the rich chemistry of radical additions to indole driven by light[22] we considered that these quinone radicals could be generated by visible light-induced electron transfer and then react with indole, which shows selectivity to react at the C-2 position with electron deficient radicals.[23] Thus, we set to explore the feasibility of this approach using as a model compound the tryptamine-naphthoquinone hybrids **1a-d** which were prepared following reported protocols.[18,24,25] Initial exploration of the light-induced cyclization of **1a** to **2a** was carried out in several solvents under different colors of LED irradiation and the use of potassium carbonate as base, see Table 1. Under white LED irradiation only those reactions carried out in halogenated solvents (chloroform, entry 4) and methanol-CH_2Cl_2 (for solubility, entry 5) gave the desired product. At this point, we set to explore in more detail which color component of the white LED light was more active in the formation of the cyclic product **2a**. Consequently, the reaction of **1a** was carried out in blue (460 nm), green (532 nm), and red color (635 nm) of LED irradiation. It was observed that blue LED irradiation (entry 6) produced the desired compound **2a**. The corresponding experiment using green LED light (entry 7) gave traces of the desired compound. The change of solvent (entry 8) or use of Eosyn Y as photocatalyst[26] (entry 9) did not show any improvement. At this point, it was not surprising then that red LED irradiation of **1a** did not promote the formation of compound **2a** either (entry 10). After reaction conditions were set, the cyclization of compounds **1b-d** (entries 11-13) was conducted under blue OLED irradiation obtaining modest yields of the corresponding compounds **2b-d**.

Table 1. Exploration of the light induced formation of the 2-indolylnaphthoquinone 2.



Entry	LED color (wavelength, nm)	Compound (0.1 mmol)	Solvent (10 ml)	Base/additive (0.1 mmol)	Product (yield %)
1	white (460-635)	**1a**	Ethanol	K_2CO_3	**2a** (5)
2	white (460-635)	**1a**	Acetone	K_2CO_3	**2a** (0)
3	white (460-635)	**1a**	CH_3CN	K_2CO_3	**2a** (0)
4	white (460-635)	**1a**	$CHCl_3$	K_2CO_3	**2a** (79)
5	white (460-635)	**1a**	MeOH-CH_2Cl_2 3:1	Et_3N	**2a** (80)
6	**blue** (460)	**1a**	**$CHCl_3$**	**K_2CO_3**	**2a (90)**
7	green (532)	**1a**	$CHCl_3$	K_2CO_3	**2a** (3)
8	green (532)	**1a**	MeOH-CH_2Cl_2 3:1	Et_3N	**2a** (0)
9	green (532)	**1a**	MeOH-CH_2Cl_2 3:1	Et_3N, Eosyn Y	**2a** (0)
10	red (635)	**1a**	$CHCl_3$	K_2CO_3	**2a** (0)

11	blue (460)	**1b**	$CHCl_3$	K_2CO_3	**2b** (50)
12	blue (460)	**1c**	$CHCl_3$	K_2CO_3	**2c** (40)
13	blue (460)	**1d**	$CHCl_3$	K_2CO_3	**2d** (48)

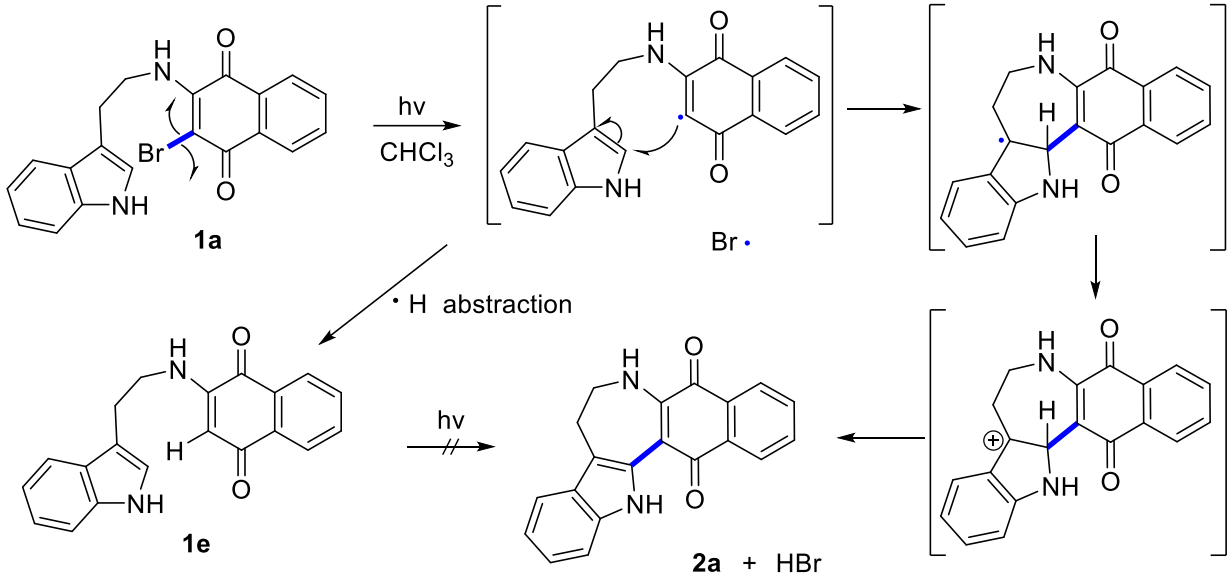
Once it was clear that white or blue-LED light drove the cyclization reaction of **1a**, it was obvious to us to observe the effect of direct sunlight irradiation on compounds **1a-d**. (Table 2). In all cases, formation of the corresponding products **2a-d** was observed without significant difference in chemical yields to the reactions using blue LEDS. However, the reaction of the dibromo compound **1b** (entry 2) was slow and needed 3 rounds of solar irradiation (8 h each for 3 days) to consume the starting material and produce **2b**. Besides the desired cyclization products **2a-2d**, in each reaction a complex mixture of other inseparable products was produced, which accounts for the modest yields obtained. From the reaction mixture of the reaction of **1a** to produce **2a** we could observe by TLC match with an authentic sample the debromination product **1e** shown in Scheme 1.

Table 2. Sunlight induced cyclization of **1a-d** to **2a-d**.

1a-d $\xrightarrow[CHCl_3,\ K_2CO_3]{\text{sunlight}}$ **2a-d**

Entry	compound	R	time (h)	yield %
1	**1a**	H	8	92
2	**1b**	Br	24	40
3	**1c**	$Me_2NC_6H_4$-	8	50
4	**1d**	C_6H_5-	8	45

The palladium catalyzed transformation of **1a** to **2a** under microwave irradiation has been reported,[18] without microwave irradiation this reaction is sluggish as we have observed in control experiments. On the other hand, both blue-LED and sunlight irradiation represent milder conditions for this transformation and gave satisfactory results without the need for a transition metal or photo catalyst. The light driven reaction can be explained by formation of a radical on the C-Br bond on the quinone system that reacts intramolecularly with the indole nucleus. (Scheme 1) It must be mentioned that the control experiment with compound **1e** which lacks the bromine atom on the naphthoquinone did not afford the cyclization product. In fact, the quenching of the quinone radical may account for the modest yields of the reactions of **1b-d**.



Scheme 1. Possible mechanism of the photocyclization of **1a** to **2a**.

The successful obtention of compound **2b** with a bromine atom on the indole ring allowed us to illustrate its synthetic value for further functionalization. Thus, Sonogashira coupling of **2b** with aryl acetylenes afforded products **3a-b** (Figure 2). The X-ray crystal structure of **2b** (Figure 3) unambiguously shows the selectivity of formation of the 2-indolyl-quinone bond and a nearly planar structure that allows electronic conjugation between the donor indole and the acceptor quinone unit. This structural feature helps to explain that these polycyclic (**2a-d** and **3a-b**) compounds are blue pigments. Absorption studies show that these compounds display two bands of absorption, an intense one around 350 nm in the UV region and another, very broad, less intense, in the visible region with a peak around 620 nm. (Figure 4)

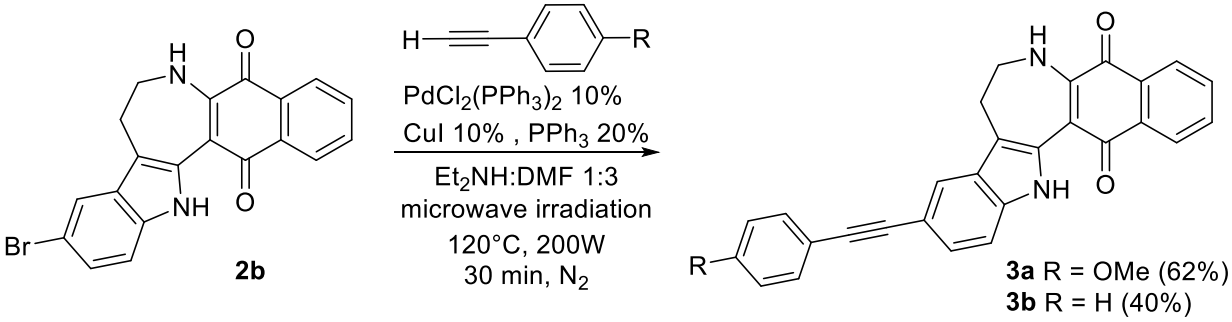


Figure 2. Sonogashira cross couplings of **2b**.

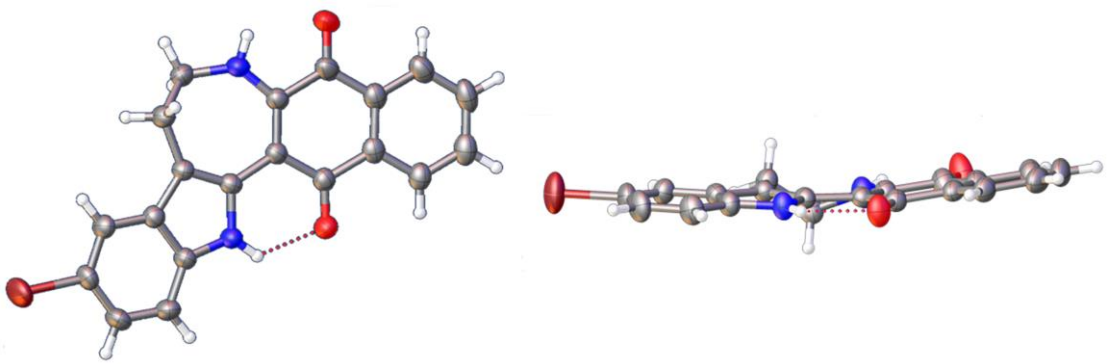


Figure 3. Front (left) and side (right) view of the X-ray crystal structure of compound **2b**

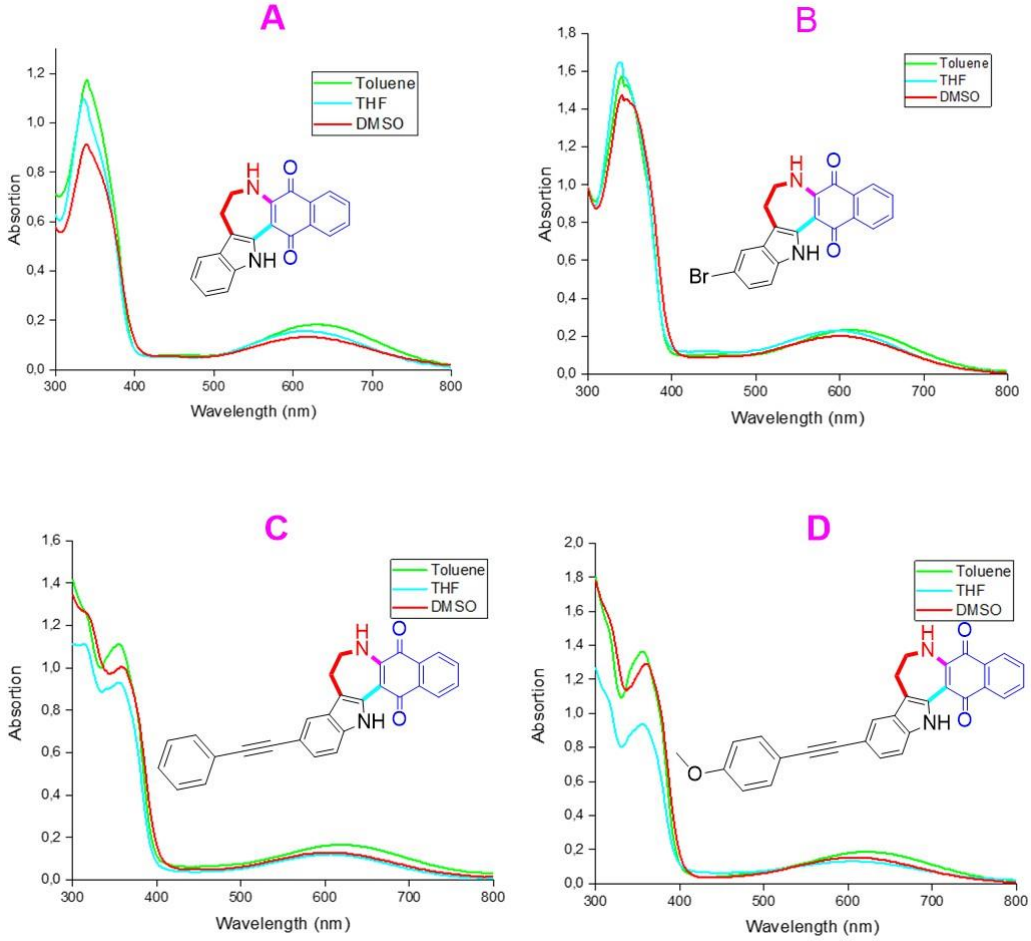


Figure 4. Absorption spectra of compounds **2a**, **2b**, **3a** and **3b** in toluene, THF and DMSO.

Conclusions

Selective formation of the 2-indolyl quinone bond through a reaction between indole and a quinone radical was realized under mild conditions using the tethered tryptamine-quinone hybrid compounds **1a-d**. Formation of the cyclic compounds **2a-d** occurred under LED (white or blue) or sunlight irradiation of their corresponding chloroform solutions at ambient temperature without the need for a photocatalyst, a transition metal or an oxidizing agent. The reaction requires a bromine atom in the naphthoquinone unit to proceed and allows the presence of a bromine atom on the indole which can serve for further functionalization.

Experimental Section

General. Chemical reagents and solvents were obtained from Aldrich and used as purchased. Melting points were determined on a Büchi Melting Point B-540 and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer FT-IR Spectrum GX spectrophotometer. NMR spectra were obtained on a Bruker Ascend 400 MHz (^{1}H) and 100 MHz (^{13}C); chemical shifts are indicated in ppm using residual $CHCl_3$ and TMS as reference. Flash chromatography was performed on Whatman 60 (230-400 mesh) silica gel.

Synthesis.

General procedure for synthesis compounds 2 a-d.

Method (a) With LED blue light. In a 50 ml flask, equipped with a magnetic stirrer, compounds **2** were added at room temperature were added compounds **2 a-d** (0.096 mmol, 1 eq.), potassium carbonate (13 mg, 0.096 mmol, 1.1 eq.) and chloroform (10 ml). It was placed into a dark chamber and allowed to react under blue LED light irradiation for 8 hours at room temperature, then concentrated and purified by flash chromatography using hexane/acetone 9:1 to obtain the desired compounds.

Method (b) With sunlight. In a 25 ml vial, provided with a magnetic stirrer, compounds **2 a-d** (0.096 mmol, 1 eq.), potassium carbonate (14 mg, 0.1056 mmol, 1.1 eq.) and chloroform (7 ml) were added at room temperature. It was allowed to react without stirring under sunlight irradiation for 8 hours at room temperature, then concentrated and purified by flash chromatography using hexane/acetone 9:1 to obtain the desired compounds.

2a. Dark blue solid, yield: 90%, 27 mg (method a), 92%, 28 mg (method b); mp 222-224 °C; UV-VIS (THF) 335, 616 nm; IR (KBr, ν, cm^{-1}) : 3435 (s, NH_2), 1560 (vs, C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ : 11.57 (s, 1H), 8.16 (dd, *J* 7.6, 1.3 Hz, 1H), 8.03 (dd, *J* 7.6, 1.3 Hz, 1H), 7.73 (td, *J* 7.6, 1.3 Hz, 1H), 7.61 (td, *J* 7.5, 1.2 Hz, 1H), 7.50 (d, *J* 7.9 Hz, 1H), 7.40 (d, *J* 8.1 Hz, 1H), 3.77 (dd, *J* 9.2, 5.1 Hz, 2H), 3.28 (t, *J* 5.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ : 184.62, 181.11, 144.64, 135.51, 134.90, 134.11, 132.45, 129.79, 129.73, 127.20, 126.70, 126.07, 122.52, 119.2, 117.62, 115.48, 111.13, 106.02, 45.10, 27.42.; HRMS (IE^+) *m/z* calcd. for $C_{20}H_{14}N_2O_2$: 314.1055, found: 314.1060.

2b. Dark blue solid, yield: 50%, 19 mg (method a), 40%, 15 mg (method b); mp 265-267 °C; UV-VIS (THF) 338, 595 nm; IR (KBr, ν, cm^{-1}) : 3420 (s, N-H), 1620(vs, C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ : 11.70 (s, 1H), 8.20 (d, *J* 7.8 Hz, 1H), 8.07 (d, *J* 7.6 Hz, 1H), 7.78 (t, *J* 7.5 Hz, 1H), 7.69 – 7.63 (m, 2H), 7.27 (m, 2H), 3.79 (d, *J* 4.9 Hz, 1H), 3.25 (d, *J* 4.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ : 184.53, 181.00, 144.99, 135.08, 134.05, 133.98, 132.58, 131.11, 129.67, 128.92, 126.76, 126.17, 125.11, 120.16, 114.50, 112.53, 112.46, 105.37, 45.07, 27.25.; HRMS (IE^+) *m/z* calcd. for $C_{20}H_{13}BrN_2O_2$: 392.016, found: 392.017.

2c. Blue solid, yield : 40% 17 mg (method a), 50% 21 mg (method b); (0.014 g); mp 260.262 ºC; IR (KBr, ν, cm^{-1}) : 3435 (s, NH_2), 1560 (vs, C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ : 11.60 (s, 1H), 8.22 (dd, *J* = 7.7, 0.9 Hz, 1H), 8.08 (dd, *J* 7.6, 0.9 Hz, 1H), 7.77 (td, *J* 7.6, 1.4 Hz, 1H), 7.68 – 7.63 (m, 2H), 7.61 – 7.57 (m, 2H), 7.48 – 7.43 (m, 2H), 7.25 (s, 1H), 6.90 – 6.85 (m, 2H), 3.83 (d, *J* 3.9 Hz, 2H), 3.36 (d, *J* 3.9 Hz, 2H), 3.02 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ : 184.71, 181.15, 149.46, 144.62, 134.92, 134.62, 134.18, 133.01, 132.48, 131.21, 130.18, 129.85, 127.88 (2 C), 127.74, 126.73, 126.05, 122.28, 115.71, 115.07, 113.06 (2 C), 111.23, 106.03 45.14, 40.80 (2 C), 29.71.; HRMS (IE^+) *m/z* calcd. for $C_{28}H_{23}N_3O_2$: 433.1790, found: 433.1800.

2d. Blue solid, yield : 48% 18 mg (method a), 45% 16.6 mg (method b); mp 248-250 ºC; IR (KBr, ν, cm^{-1}) : 3435 (s, NH_2), 1560 (vs, C=O), 1075 (w, C=C-N); ^{1}H NMR (400 MHz, $CDCl_3$) δ : 11.64 (s, 1H), 8.19 (d, *J* 7.7 Hz, 1H), 8.05 (d, *J* 7.6 Hz, 1H), 7.78 – 7.73 (m, 1H), 7.71 – 7.61 (m, 4H), 7.46 (d, *J* 1.7 Hz, 2H), 7.43 (dd, *J* 5.8, 4.3 Hz, 2H), 7.31 (t, *J* 7.4 Hz, 1H), 7.24 (s, 1H) 3.81 (q, *J* 4.6 Hz, 2H), 3.34 (t, *J* 4.6 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ : 184.67, 181.12, 144.74, 142.72, 135.07, 134.98, 134.13, 132.84, 132.52, 130.50, 129.80, 128.63 (2 C), 127.70, 127.33 (2 C), 126.75, 126.26, 126.09, 122.49, 116.11, 115.72, 111.35, 105.96, 45.13, 27.45.; HRMS (IE^+) *m/z* calcd. for $C_{26}H_{18}N_2O_2$: 390.1368, found: 390.1380.

General procedure for the Sonogashira coupling of compound 2b with arylacetylenes. Compound **2b** (20 mg, 0.05 mmol,1 eq.), arylalkyne (0.06 mmol, 1.2 eq.), dichloro palladium bis(triphenylphosphine) (3 mg, 0.005 mmol, 0.05 eq.), cuprous iodide (1 mg, 0.005 mmol, 0.05 eq.), triphenylphosphine (2 mg, 0.01 mmol, 0.2 eq), and purged with vacuum/nitrogen three times. Anhydrous diethylamine (1.5 ml) and anhydrous dimethylformamide (0.5 ml) were then added and allowed to react at 200 W, at a temperature of 120 °C for 30 minutes. Once the reaction was finished, it was extracted with ethyl acetate, the organic phase was washed with brine and dried over anhydrous sodium sulfate, the rest of the solvent was removed under reduced pressure. The residue was purified by chromatography using hexane/AcOEt 8:2 to obtain the desired product **3a** and **3b**.

3a. Dark blue solid, yield 62% (13 mg); mp 231-232 °C; UV-VIS (THF): 355, 609 nm; IR (KBr, ν, cm^{-1}) : 3425 (s, N-H), 2270 (m, C_{sp}-C_{sp}), 1640 (vs, C=O), 1350 (w, C-O-CH_3), 1060 (w, C=C-N); ^{1}H NMR (400 MHz, $CDCl_3$) δ : 11.70 (s, 1H), 8.21 (d, *J* 7.7 Hz, 1H), 8.07 (d, *J* 7.6 Hz, 1H), 7.78 (t, *J* 7.6 Hz, 1H), 7.73 (s, 1H), 7.66 (t, *J* 7.5 Hz, 1H), 7.51 (d, *J* 8.5 Hz, 2H), 7.38 (m, 2H), 7.24 (s, 1H), 6.91 (d, *J* 8.5 Hz, 2H), 3.86 (s, 3H), 3.81 (q, *J* 5.0 Hz, 2H), 3.30 (t, *J* 4.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ :184.58, 181.04, 159.22, 144.88, 135.03, 134.08, 134.08, 132.86, 132.56,132.19, 130.71, 129.75,128.45, 127.18, 126.77, 126.14, 126.07, 121.33, 116.21,115.29, 114.00, 113.95, 111.16, 105.66, 89.82, 86.90, 55.30, 45.07, 29.70.; HRMS (IE^+) *m/z* calcd. for $C_{29}H_{20}N_2O_3$: 444.1474, found: 444.1486.

3b. Dark blue solid, yield 40% (9 mg); mp 229-231 °C; UV-VIS (THF): 356, 606 nm; IR (KBr, ν, cm^{-1}) : 3430 (s, N-H), 2250 (m, C_{sp}-C_{sp}), 1630 (vs, C=O), 1080 (w, C=C-N); ^{1}H NMR (400 MHz, $CDCl_3$) δ : 11.72 (s, 1H), 8.21 (d, *J* 7.1 Hz, 1H), 8.07 (d, *J* 7.6 Hz, 1H), 7.80-7.75 (m, 2H), 7.65 (td, *J* 7.5, 1.0 Hz, 1H), 7.58 (dd, *J* 8.0, 1.4 Hz, 2H), 7.41-7.31 (m, 6H), 3.83 (q, *J* 5.1 Hz, 2H), 3.31 (t, *J* 4.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ : 184.53, 180.98, 144.86, 135.11, 135.01, 134.02, 132.54, 131.41, 130.76, 128.53, 129.68, 128.25, 127.62, 127.12, 126.73, 126.11, 126.07, 124.00, 121.53, 115.24, 113.60, 111.15, 109.99, 105.54, 91.28, 87.03, 45.03, 29.34.; HRMS (IE^+) *m/z* calcd. for $C_{28}H_{18}N_2O_2$: 414.1368, found: 414.1380

Supplementary Material

^{1}H and ^{13}C NMR spectra of the compounds. Experimental procedures for the synthesis of tryptamines and tryptamine-quinones are available.

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