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Synthesis of Halogenated 1*H*-Cyclohepta[2,1-*b*:3,4-*b'*]diindoles and Their Nucleophilic Aromatic Substitution Reactions

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Abstract Halogenated 1*H*-cyclohepta[2,1-*b*:3,4-*b'*]diindoles **5**–**8** were synthesized and their nucleophilic aromatic substitution reactions with amines and alcohols were studied. Compounds **5**–**7** were obtained by condensation of 2,2'-diindole (**9**) with 3-(dimethylamino)-2-haloacroleins in the presence of trifluoromethanesulfonic anhydride as a dehydrating reagent. On the other hand, 6,8-dichloro-1*H*-cyclohepta[2,1-*b*:3,4-*b'*]diindole (**8**) was synthesized in two steps from **9** via enolketone **13**. It was found that **8** underwent substitution reactions with amines and alcohols to afford the 6,8-substituted products in moderate to good yields, while compounds **5**–**7** showed reluctance to undergo substitution reactions. The phenomenon is rationalized by relative stability of the possible reaction intermediates based on DFT calculations.

Keywords Biindole, Nucleophilic aromatic substitution, X-ray crystallographic analysis, Amine, DFT calculations

1. Introduction

In 1999 Higa *et al*. reported isolation of a marine natural product, iheyamine A (**1**), from a colonial ascidian, *Polycitorella sp*. [1] The structure of **1** consists of two indole units around a unsaturated nitrogen-containing seven-membered ring in the middle of the molecule, having an aromatic 1,4-diazaazulene skeleton as a partial structure. In addition to its unique structural feature, **1** exhibits cytotoxic activity against tumor cells. [1]

In respect to its prospective biological activity as an anti-cancer drug, various compounds (**2**–**4**) structurally related to **1** have been synthesized. (Figure 1) [2-4] We recently reported synthesis of non-substituted compound **4** and its spectroscopic properties. [4] In order to provide novel drug candidates having the structure of **4**, we have continued our research on development of a divergent method for synthesizing its derivatives. Herein we describe the synthesis of halogen-substituted derivatives **5**–**8** and their nucleophilic aromatic substitution (S_NAr) reactions. [5-6]

2. Results and Discussion

2.1. Synthesis of halogenated 1*H*-cyclohepta[2,1-*b*:3,4-*b'*] diindoles (5–8)

Synthetic routes forming the central seven-membered ring to 7-halo- and 6,8-dichloro-1*H*-cyclohepta [2,1-*b*:3,4-*b'*] diindoles **5**–**8** from 2,2'-biindole (**9**) [7] are depicted in Schemes 1 and 2, respectively.

Halogenated compounds, **5**–**7**, were synthesized from **9** in a similar way of previously reported syntheses of **3** and **4**. [4] Reactions of **9** with 3-(dimethylamino)-2-haloacroleins (**10**–**12**) in the presence of trifluoromethanesulfonic anhydride (Tf_2O) in refluxing 1,2-dichloroethane (DCE) provided **5**–**7** in good yields. Also oxalyl chloride and phosphorus oxybromide could be used as a dehydrating reagent for syntheses of **5** and **6**, respectively. However, when oxalyl chloride was used as a dehydrating reagent in the reaction of **9** and **11**, a mixture of **5** and **6** formed probably by a halogen-exchanging reaction. Although Tf_2O can be used in all annulation reactions, other dehydrating reagents should be selected for an appropriate substrate of 3-(dimethylamino)-2-haloacroleins. On the other hand, 6,8-dichloro compound **8** was synthesized in two steps from **9**. Reaction of **9** with malonyl chloride in dichloromethane (DCM) produced **13** in 76% yield. The ^{1}H-NMR spectrum of **13** indicates that **13** exists not as a diketone form but as a form of the keto-enol in solution, as depicted in Scheme 2. Subsequent reaction of **13** with phosphorus oxychloride in the presence of ethyldiisopropylamine provided **8** in 58% yield. Unfortunately, similar reaction of **13** with phosphorus

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oxybromide instead of phosphorus oxychloride did not give any clear product. Structures of all new halogenated compounds **5**–**8** were confirmed by spectroscopic analyses.

2.2. Nucleophilic Aromatic Substitution Reactions (S_NAr) of 5–8

Like halopyridines, halogenated 1-azaazulenes and 2,3-benzo-1-azaazulenes are known to behave as good acceptors against nucleophiles in their substitution reactions. [8-11] Therefore, we expected that the halogenated compounds **5**–**8** could also undergo S_NAr reactions. Indeed, dichloride **8** reacts secondary amines to give diamino derivatives **14**–**18** in good to high yields (Scheme 3).

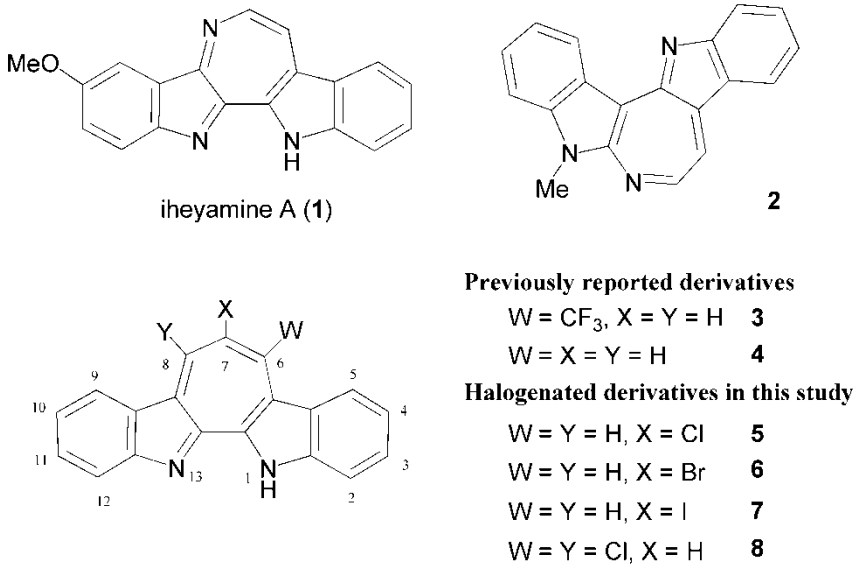
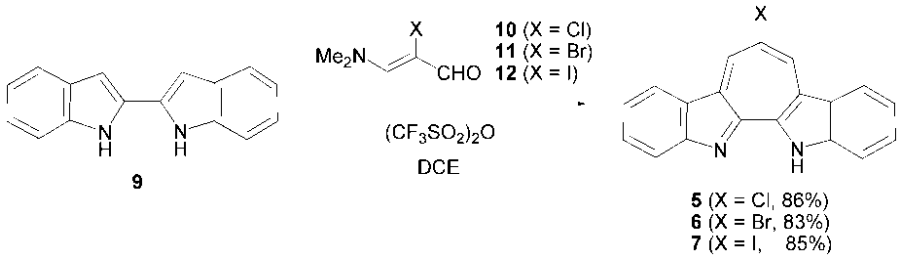
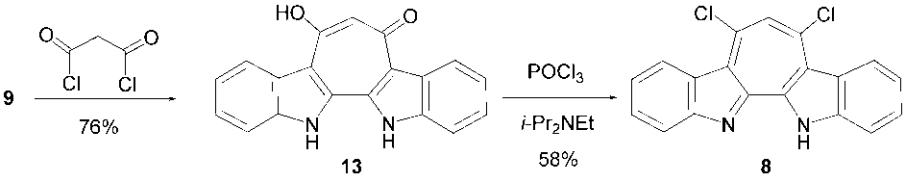


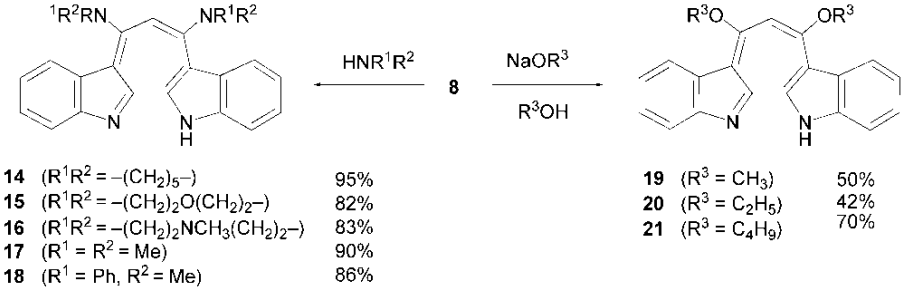
Figure 1. Iheyamine A (**1**) and structurally related synthetic compounds (**2**–**8**)



Scheme 1. Synthesis of **5**–**7**



Scheme 2. Synthesis of **8**

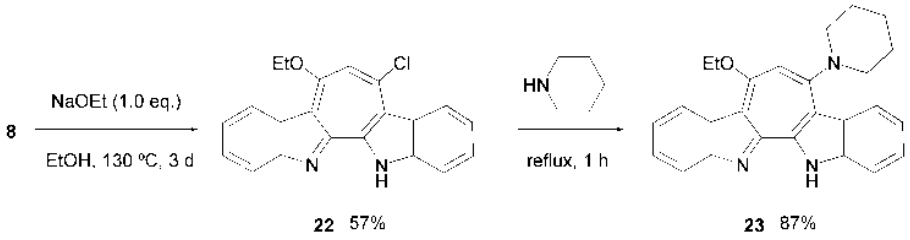


Scheme 3. The nucleophilic substitution reactions of **8**

Under the conditions with piperidine, morpholine and *N*-methylpiperazine as a solvent at 100–120 ℃ in a sealed tube, diamino compounds **14**–**16** were obtained in 82–95% yields. The bis(dimethylamino) compound **17** was obtained in 90% yield under the conditions with 2.2 equiv. of dimethylamine hydrochloride and 4.0 equiv. of triethylamine in dimethylformaide (DMF) at 100 ℃ and the reaction of **8** with an excess of *N*-methylaniline produced **18** in 86% yield. Also, **8** reacts with two equivalent of alkoxides to give dialkoxy derivatives **19**–**21** in moderate yields. Although the reactions of **8** with amines completed in a short reaction time, the reactions of **8** with alkoxides proceeded slower even at 130 ℃ and required a longer time to complete. The result led us to synthesize unsymmetrically substituted derivatives, as follows. The reaction of **8** with an equivalent of sodium ethoxide in ethanol provided the chloro-ethoxy derivative **22**, which underwent the substitution reaction with piperidine to lead to the product **23** (Scheme 4). It is worthy to note that these findings make possible to synthesize a wide variety of the derivatives having either symmetrical or unsymmetrical substituents at the 6 and 8 positions from **8**.

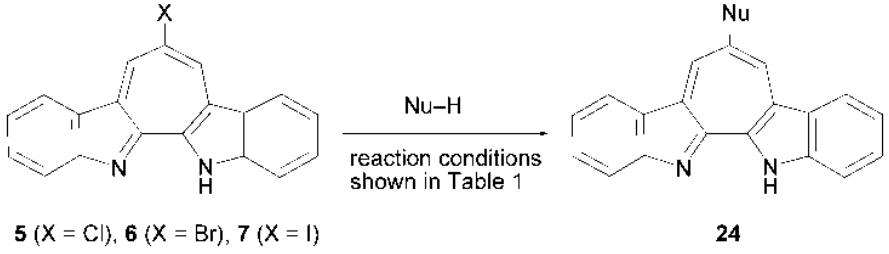
On the other hand, reactivity of **5**–**7** against nucleophiles was found quite poor compared with that of **8**. Results of the nucleophilic substitution reactions are shown in Table 1. So far alkoxylation of **5**–**7** has not been observed despite various attempts (entry 1, 2, 4, and 6). The amino-substituted product **24** (Nu = piperidino) was obtained only from **5** in 16% yield, not from either **6** or **7**. These results clearly indicate a difference in the reactivity at the 6(or 8)- and 7-positions in their substitution reactions. Since S_NAr reactions are widely accepted to proceed through the addition-elimination mechanism, [12-14] the anionic intermediates **25** and **26** are expected to form in the reactions of **5**–**7** and **8**, respectively. While aromatic stabilization of the five-membered rings of the indole units in **26** is retained, that in **25** is destructed by the exo-dimethylene structure (Scheme 5).

We assume that this instability of **25** may account for the poor reactivity of **5**–**7**. Indeed, the relative stability of **26** over **25** is supported by DFT calculations [15] at B3LYP/6–31+G(d) level of theory for simplified molecules (Y = W = X = Nu = H). [16]



Scheme 4. Synthesis of unsymmetrical derivatives

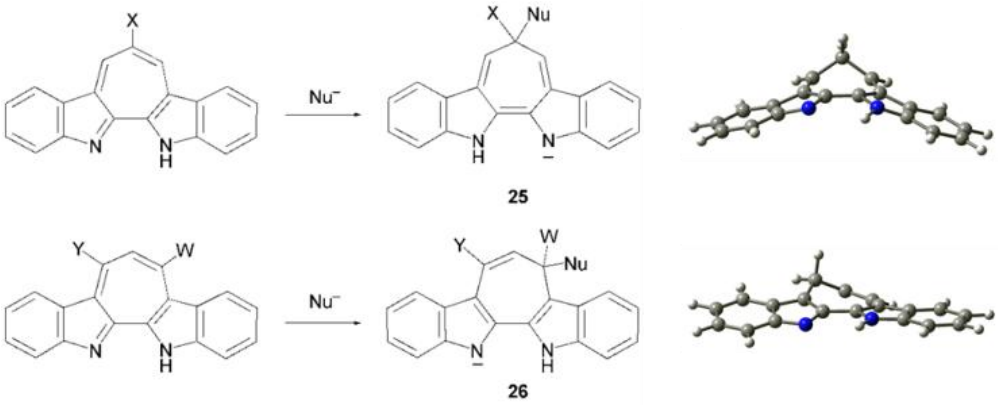
Table 1. Results of nucleophilic aromatic substitution reactions of **5**–**7**



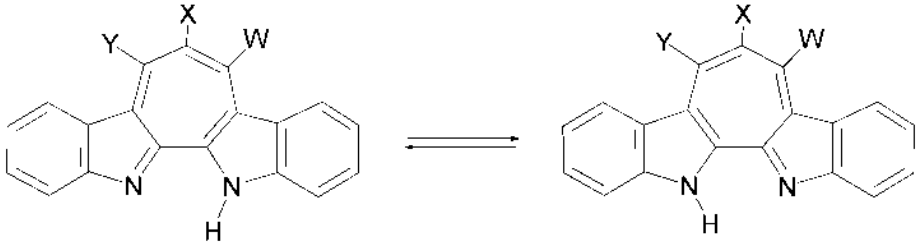
5 (X = Cl), **6** (X = Br), **7** (X = I) **24**

entry	X	Nucleophile/reaction condition	result
1	Cl	MeONa/MeOH/150 ℃/52 h	NR[a]
2	Cl	EtONa/EtOH/160 ℃/74 h	NR[a]
3	Cl	Piperidine/130 ℃/62 h	24 (Nu = piperidino, 16%)
4	Br	MeONa/MeOH/150 ℃/52 h	NR[a]
5	Br	Piperidine/130 ℃/66 h	NR[a]
6	I	MeONa/MeOH/150 ℃/52 h	NR[a]
7	I	Piperidine/130 ℃/62 h	Recovery of 7 (25%)[b]

[a] No reaction was observed under the conditions.
[b] No desired product **24** was obtained but a trace amount of the reduced product **4**.



Scheme 5. Expected anionic intermediates in the substitution reactions and the calculated structures of their simplified molecules (right)



Scheme 6. Tautomerism of 1*H*-cyclohepta[2,1-*b*:3,4-*b'*]diindoles

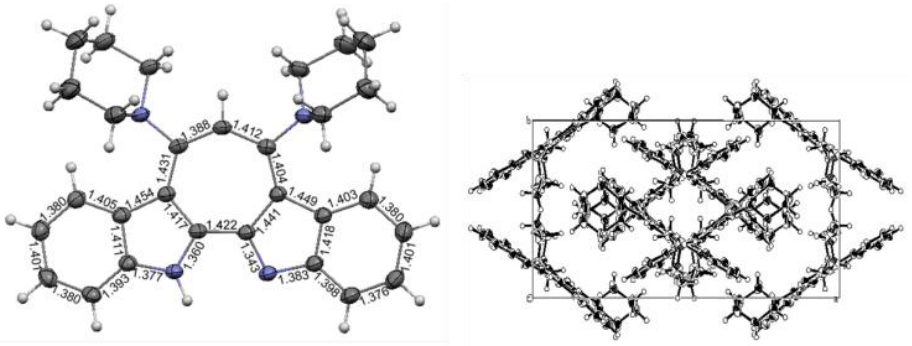


Figure 2. ORTEP drawing of **14** with bond lengths (left) and its packing diagram viewed along *c* axis (right)

Some structural features of the substitution products **14**–**21** should be commented. The ^{1}H-NMR spectra of **14**–**16** at room temperature show very broad signals for the methylene protons in their saturated heterocycles probably because of their restricted rotation around the C–N single bonds. Those signals appear sharpened at elevated temperatures. Their shift values shown in experiments were obtained by the measurements at the elevated temperatures. Besides, the ^{1}H- and ^{13}C-NMR spectra of **14**–**21** indicate that these compounds in solution undergo quick tautomerization between the two tautomers, as seen in **4** (Scheme 6). On the other hand, the solid-state structure of **14**, determined by X-ray crystallographic analysis at –100 ℃, appears not as an averaged structure but as one form of the tautomers with alternating bond-lengths around its seven- and five-membered rings. An ORTEP drawing, packing in a crystal cell, and bond lengths are shown in Figure 2.

3. Experiments

3.1. General

Melting points were measured on a Yanaco MP-3 and are uncorrected. IR spectra were recorded on JEOL Diamond-20 and JASCO FT/IR-4100 spectrometers. UV-vis spectra were measured on a Shimadzu UV-2550 spectrometer. ^{1}H- and ^{13}C-NMR spectra were recorded on JEOL λ400 and ECA500 spectrometers. Chemical shift values of tetramethylsilane (δ = 0 ppm) for ^{1}H-NMR spectra and $CDCl_3$ (δ = 77.0 ppm) for ^{13}C-NMR spectra were used as internal standard. Mass spectra were measured on a JMS-700 mass spectrometer. Column chromatography was performed with Silica gel 60N from Kanto Chem. DCM, DCE and DMF were purchased from Kanto Chem. and was distilled over CaH_2. Dimethylaminoacrolein and oxalyl chloride were purchased from Wako Chemical Co. and were used without purification. Tf_2O and *N*-halosuccinimides were purchased from Tokyo

Chemical Industry, Inc. 2,2'-Biindole was prepared in two steps from 2-methylaniline according to a procedure reported by Bergman *et al.* [5]

3.2. 3-(Dimethylamino)-2-haloacroleins 10–12

3-(Dimethylamino)-2-haloacroleins **10**–**12** were prepared from 3-(dimethylamino)acrolein by halogenation with *N*-halosuccinimides.[17–19] Following are selected spectral data of **10**–**12**.

2-Chloro-3-(dimethylamino)acrolein **10**: Colorless solids, mp = 45–48 ℃ [lit. 40–43 ℃] [17]; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 3.36 (br, 6H), 6.89 (s, 1H), 8.69 (s, 1H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ = 39.3, 47.2, 104.2, 154.0, 183.0 ppm; MS (70 eV) *m/z* (%) = 135 (M^+, 33), 133 (M^+, 100), 118 (45), 98 (21), 89 (17), 55 (14). HRMS Calcd for $C_5H_8{}^{35}ClNO$ 133.0294; found 133.0292.

2-Bromo-3-(dimethylamino)acrolein **11**: Colorless needless, mp = 65–68 ℃ [lit. 54.5–56 ℃] [18]; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 3.31 (br, 6H), 7.12 (s, 1H), 8.79 (s, 1H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ = 40.0, 47.4, 92.9, 155.9, 183.4 ppm; MS (70 eV) *m/z* (%) = 179 (M^+, 51), 177 (M^+, 53), 162 (36), 160 (35), 98 (100), 55 (38). HRMS Calcd for $C_5H_8{}^{79}BrNO$ 176.9789; found 176.9787.

3-(Dimethylamino)-2-iodoacrolein **12**: Colorless needless, mp = 74–76 ℃ [19-20]; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 3.34 (br, 6H), 7.34 (s, 1H), 8.29 (s, 1H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ = 42.4, 46.7, 66.8, 159.4, 185.6 ppm; MS (70 eV) *m/z* (%) = 225 (M^+, 49), 127 (7), 118 (45), 98 (100), 68 (8), 55 (22). HRMS Calcd for C_5H_8INO 224.9651; found 224.9649.

3.3. 7-Halo-1*H*-cyclohepta[2,1-*b*;1,2-*b'*]diindoles (5–7)

A solution of 3-(dimethylamino)-2-haloacrolein (2.00 mmol) in 4 ml of DCE was added dropwise to a solution of Tf_2O (336 μL, 2.00 mmol) in 3 ml of DCE at 0 ℃. After being stirred at room temperature for 15 min, a suspension of **9** (697 mg, 3.00 mmol) in 20 ml of DCE was added to the reaction solution. Then, the reaction mixture was heated to 100°C for 1 h under nitrogen atmosphere. After being cooled to room temperature, the reaction mixture was poured into a saturated sodium bicarbonate solution (30 ml) and extracted with chloroform (100 ml x 3). The combined organic layer was washed with brine and dried over Na_2SO_4. Then, the solvent was removed under reduced pressure and the residue was crystallized from chloroform to give the product as dark red microcrystals. The filtrate was purified by silica gel column chromatography. Elution with ethanol/chloroform (7/93) provided the product further.

5: Dark red microcrystals, mp = 279–283 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.43–7.53 (m, 6H), 8.32 (d, *J* = 7.8 Hz, 2H), 8.97 (s, 2H) ppm [21]; ^{13}C NMR (126 MHz, $CDCl_3$) δ = 116.2, 120.3, 122.1, 126.9, 127.0, 129.0, 129.6, 130.8, 144.2, 146.9 ppm; IR (KBr) ν_{max} = 1397vs, 1362vs, 1234s, 1194s, 741vs cm^{-1}; UV-vis (CH_3CN) λ_{max} = 227 (logε = 4.51), 321 (4.72), 335 (4.69), 366 (4.23), 408 (3.58), 433 (3.52), 517 (3.67) nm; MS (70 eV) *m/z* (%) = 304 (M^+, 34), 302 (M^+, 100), 266 (16), 151 (10). HRMS Calcd for $C_{19}H_{11}{}^{35}ClN_2$ 302.0611; found 302.0609.

6: Dark red plates, mp = 284–288 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.75 (br, 1H), 7.48 (t, *J* = 7.8 Hz, 2H), 7.59 (t, *J* = 7.8 Hz, 2H), 7.64 (d, *J* = 7.8 Hz, 2H), 7.31 (d, *J* = 7.8 Hz, 2H), 9.11 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 115.6, 115.9, 120.4, 122.3, 126.6, 129.2, 130.0, 133.7, 144.4, 149.0 ppm; IR (KBr) ν_{max} = 1398vs, 1363vs, 1192s, 745vs cm^{-1}; UV-vis (MeCN) λ_{max} = 284sh (logε = 4.22), 298sh (4.40), 322 (4.72), 337 (4.70), 366 (4.24), 408 (3.58), 434 (3.52), 518 (3.69) nm; MS (70 eV) *m/z* (%) = 348 (M^+, 98), 346 (M^+, 100), 266 (31), 240 (18), 173 (11), 133 (12). HRMS Calcd for $C_{19}H_{11}{}^{79}BrN_2$ 346.0106; found 346.0107.

7: Dark red microcrystals, mp = 284–287°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.45–7.47 (m, 2H), 7.53-7.57 (m, 4H), 8.29 (d, *J* = 7.8 Hz, 2H), 9.27 (s, 2H) ppm [21]; ^{13}C NMR (500 MHz, $CDCl_3$) δ = 87.0, 116.1, 120.3, 122.2, 126.5, 128.9, 130.8, 139.8, 144.5, 146.7 ppm; IR (KBr) ν_{max} = 1474s, 1403s, 1363s, 1241s, 1193s, 1107s, 755s, 745vs, cm^{-1}; UV-vis (CH_3CN) λ_{max}= 223 (logε = 4.41), 251sh (4.07), 323 (4.66), 338 (4.62), 367 (4.18), 408sh (3.51), 435 (3.42), 519 (3.58) nm; MS (70 eV) *m/z* (%) = 394 (M^+, 100), 267 (33), 260 (22), 240 (16). HRMS Calcd for $C_{11}H_{19}IN_2$ 393.9967; found 393.9967.

3.4. 1,6,13-Trihydro-8-hydroxycyclohepta[2,1-*b*;3,4-*b'*]-diindol-6-one (13)

To a solution of malonyl chloride (617 mg, 4.40 mmol) in 20 ml of DCE was added a suspension of **9** (929 mg, 4.00 mmol, 1 eq.) in 15 ml of DCE with cooling on an ice bath. After refluxing of the reaction mixture under nitrogen atmosphere for 3.5 h, the solvent was removed under reduced pressure. The residue was homogenously suspended in 30 ml of a saturated sodium bicarbonate solution and solids were collected by filtration. The solid obtained was washed with water (20 ml), acetone (20 ml) and ethanol (20 ml), and dried under vacuum to give 907 mg (76%) of **13** as brown solids. Mp > 300 ℃ (decomp.). ^{1}H NMR (500 MHz, DMSO-d_6, 60 ℃) δ = 3.75 (brs, 2H, N-H & O-H), 7.47 (t, *J* = 7.8 Hz, 2H), 7.51 (s, 1H), 7.65 (t, *J* = 7.8 Hz, 2H), 7.82 (d, *J* = 7.8 Hz, 2H), 8.66 (d, *J* = 7.8 Hz, 2H) ppm; ^{13}C NMR (126 MHz, DMSO-d_6, 60 ℃) δ = 105.4, 111.8, 114.9, 122.5, 124.40, 124.43, 127.3, 133.6, 137.3, 168.3 ppm; IR (KBr) ν_{max} = 3158s, 3097s, 3076s, 3030s, 2983s, 1495s, 1455s, 1426s, 1389vs, 1359s, 1324s, 1248s, 1223s, 748s cm^{-1}; UV-vis (EtOH) λ_{max} = 213 (logε = 4.42), 230sh (4.27), 300 (4.76), 324sh (4.19), 339sh (4.05), 349sh (4.02), 367 (4.10), 385 (4.18) nm; MS (FAB) *m/z* (%) = 301 (MH^+, 32), 153 (81), 136 (100), 107 (37), 73 (87), 51 (23). HRMS Calcd for $C_{19}H_{13}N_2O_2{}^+$ 301.0972; found 301.0977.

3.5. 6,8-Dichloro-1*H*-cyclohepta[2,1-*b*;3,4-*b*']diindole (8)

Phosphorus oxychloride (1.44 ml, 15.4 mmol) was carefully added to a mixture of *i*-Pr_2EtN (0.54 ml, 3.1 mmol) and **13** (463 mg, 1.54 mmol) with cooling on an ice bath. The reaction mixture was heated at 100 ℃ for 2 h under argon

atmosphere. After being cooled to room temperature, the reaction mixture was poured into a 30 ml of saturated sodium carbonate aqueous solution and extracted with chloroform (40 ml x 3). The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography. Elution with ethanol/chloroform (5:95) gave 301 mg (58%) of **8** as red prisms. Mp = 279–282 ℃. ^{1}H NMR (500 MHz, $CDCl_3$, 40 ℃) δ = 7.55 (ddm, J = 8.4, 7.2 Hz, 2H), 7.74 (ddm, J = 8.1, 7.2 Hz, 2H), 7.96 (dm, J = 8.1 Hz, 2H), 8.14 (s, 1H), 8.94 (dm, J = 8.4 Hz, 2H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ = 114.8, 124.42, 124.46, 125.6, 126.7, 130.1, 131.3, 137.6, 142.1, 143.4 ppm; IR (KBr) ν_{max} = 1559s, 1396vs, 1373vs, 1111s, 740vs cm^{-1}; UV-vis (CH_3CN) λ_{max} = 225 (logε = 4.41), 261 (4.05), 322 (4.66), 342 (4.60), 370sh (4.15), 408 (3.65), 435 (3.60), 508 (3.64) nm; MS (70 eV) *m/z* (%) = 340 (M^+, 12), 338 (M^+, 65), 336 (M^+, 100), 266 (26), 265 (12). HRMS Calcd for $C_{19}H_{10}{}^{35}Cl_2N_2$ 336.0221; found 336.0226.

3.6. 6,8-Dipiperidino- 6,8-dimoripholino-, and 6,8-bis(*N*-methylpiperzino)-1*H*-cyclohepta[2,1-*b*;3,4-*b*']-diindoles (14–16)

A mixture of **8** (30 mg, 0.089 mmol) and piperidine (1.0 ml) was heated at 120 ℃ for 1 h in a sealed tube purged by argon. After being cooled to room temperature, the reaction mixture was poured into 40 ml of 0.2 M hydrochloric acid. The resulted mixture was extracted with chloroform (20 ml x 3), and the combined organic layer was washed with a saturated sodium bicarbonate solution (20 ml x 2) and was dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by silica gel chromatography. Elution with ethanol/chloroform (5/95) gave 37 mg (95%) of **14** as orange prisms. Mp = 271–272 ℃ (decomp.). ^{1}H NMR (500 MHz, DMSO-d_6, 100 ℃) δ = 1.72 (quin, J = 5.5 Hz, 4H), 1.87 (quin, J = 5.5 Hz, 8H), 3.38 (t, J = 5.5 Hz, 8H), 7.13 (s, 1H), 7.29 (t, J = 7.8 Hz, 2H), 7.43 (t, J = 7.8 Hz, 2H), 7.79 (d, J = 7.8 Hz, 2H), 8.47 (d, J = 7.8 Hz, 2H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ = 24.5, 26.3, 54.4, 107.4, 115.3, 119.3, 120.7, 123.2, 125.8, 126.6, 144.7, 144.9, 159.3 ppm; IR (KBr) ν_{max} = 1556s, 1532s, 1449s, 1409s, 1362s, 1341s, 1240s, 1225s, 1199s, 1122s, 1102s, 749s cm^{-1}; UV-vis (CH_3CN) λ_{max} = 224 (logε = 4,49), 237sh (4.35), 333 (4.86), 357sh (4.48), 417 (4.04), 471sh (3.78) nm; MS (70 eV) *m/z* (%) = 434 (M^+, 100), 433 (11), 365 (12), 351 (16), 294 (10), 281 (12),. 281 (12), 268 (17), 217 (9). HRMS Calcd for $C_{29}H_{30}N_4$ 434.2471, found 434.2476.

Compounds **15–16** were synthesized similarly from **8** with morpholine and *N*-methylpiperzine in 82 and 90% yields, respectively.

15: Orange prisms, mp = 271–272 ℃ (decomp.). ^{1}H NMR (500 MHz, DMSO-d_6, 100 ℃) δ = 3.39 (t, J = 4.4 Hz, 8H), 3.99 (t, J = 4.4 Hz, 8H), 7.08 (s, 1H), 7.34 (t, J = 7.6 Hz, 2H), 7.46 (t, J = 7.6 Hz, 2H), 7.81 (d, J = 7.6 Hz, 2H), 8.54 (d, J = 7.6 Hz, 2H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$, 50 ℃) δ = 53.12, 67.0, 106.2, 115.6, 119.7, 121.3, 123.3, 126.2, 126.6, 145.0, 145.3, 158.1 ppm; IR (KBr) ν_{max} = 1534s, 1445s, 1374s, 1345s, 1332s, 1220s, 1208s, 1029s, 887s, 770s, 746s cm^{-1}; UV-vis (CH_3CN) λ_{max} = 225 (logε = 4.45), 331 (4.82), 357sh (4.45), 378sh (4.08), 395 (3.97), 418 (3.95), 474sh (3.72) nm; MS (70 eV) *m/z* (%) = 438 (M^+, 100), 295 (10), 294 (11), 281 (10). HRMS Calcd for $C_{27}H_{26}N_4O_2$ 438.2056, found 438.2052.

16: Orange solids, mp = 245 ℃ (decomp.). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 2.47 (s, 6H), 2.77 (br, 4H), 2.86 (br, 4H), 3.30 (br, 4H), 3.64 (br, 4H), 7.17 (s, 1H), 7.35 (t, J = 7.5 Hz, 2H), 7.40 (t, J = 7.5 Hz, 2H) 7.57 (d, J = 7.5 Hz, 2H), 8.61 (d, J = 7.5 Hz, 2H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 46.2, 52.7, 55.2, 106.5, 115.5, 119.3, 120.9, 123.2, 126.1, 144.8, 145.0, 158.3 ppm. IR (KBr) ν_{max} = 1449s, 1357s, 1201s, 1008s, 751s cm^{-1}. UV-vis (CH_3CN) λ_{max} = 224 (logε = 4.47), 332 (4.83), 356sh (4.47), 417 (3.97), 464 (3.75) nm. MS (70 eV) *m/z* (%) = 464 (94, M^+), 394 (100). HRMS Calcd for $C_{29}H_{32}N_6$ 464.2689; found 464.2691.

3.7. 6,8-Bis(dimethylamino)-1*H*-cyclohepta[2,1-*b*;3,4-*b*']-diindole (17)

A mixture of **8** (20 mg, 0,059 mmol), dimethylamine hydrochloride (11 mg, 0.12 mmol) and triethylamine (24 mg, 0.24 mmol) in 2 ml of dry DMF was heated to 100 ℃ for 2 h under nitrogen atmosphere. After being cooled to room temperature, the reaction mixture was poured into water (5 ml) and the precipitate formed was filtered off. The solid was purified by alumina column chromatography. Elution with methanol/dichloromethane (4/96) gave 19 mg (90%) of **17** as orange solids. Mp = 245–250 ℃. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 3.18 (s, 6H), 6.80 (s, 1H), 7.31 (t, J = 7.7 Hz, 2H), 7.36 (t, J = 7.7 Hz, 2H), 7.60 (d, J = 7.7 Hz, 2H), 8.19 (d, J = 7.7 Hz, 2H) ppm [21]; ^{13}C NMR (126 MHz, $CDCl_3$) δ = 44.6, 104.5, 115.3, 116.7, 120.5, 122.8, 125.0, 126.1, 144.2, 144.5, 158.4 ppm; IR (KBr) ν_{max} = 1556s, 1402s, 1354vs, 1120s, 750s cm^{-1}; UV-vis (CH_3CN) λ_{max} = 226 (logε = 4.42), 236sh (4.35), 332 (4.82), 414 (3.96), 466 (3.71) nm; MS (70 eV) *m/z* (%) = 354 (M^+, 100), 353 (13), 339 (19), 310 (9), 296 (16), 268 (11). HRMS Calcd for $C_{23}H_{22}N_4$ 354.1845; found 354.1841.

3.8. 6,8-Bis(*N*-methylanilino)-1*H*-cyclohepta-[2,1-*b*;3,4-*b*']diindole (18)

A mixture of **8** (10 mg, 0,029 mmol) and *N*-methyaniline (1 mL) was heated to 120 ℃ for 4 h under argon atmosphere. After being cooled to room temperature, the reaction mixture was poured into 1N HCl (5 ml) and was extracted with chloroform (20 mL x 3). The combined organic layer was washed with a saturated sodium bicarbonate solution (20 ml x 2) and was dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by alumina chromatography. Elution with chloroform/hexane (5/1) gave 12 mg (86%) of **18** as red solids. Mp = 245 ℃ (decomp.). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 3.44 (s, 6H), 4.95 (br, 1H), 6.83 (t, J = 7.7 Hz, 2H), 6.86 (d, J = 7.7 Hz, 4H), 7.17 (t, J = 7.7 Hz, 4H), 7.20 (s, 1H), 7.29 (t, J = 7.8 Hz, 2H), 7.51 (t, J = 7.8 Hz, 2H), 7.70 (d, J = 7.8 Hz, 2H), 8.18 (d,

J = 7.8 Hz, 2H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 40.2, 115.6, 115.8, 119.8, 122.1, 123.9, 125.6, 127.8, 129.1, 145.0, 146.0, 148.1, 153.6 ppm. IR (KBr) ν_{max} = 1495s, 1390s, 1108s, 750s cm^{-1}. UV-vis (CH_3CN) λ_{max} = 226 (logε = 4.53), 235sh (4.50), 341 (4.59), 455 (4.03), 518sh (3.81) nm. MS (70 eV) *m/z* (%) = 479 (M^++1, 37), 478 (100, M^+), 372 (12), 371 (19), 357 (19), 356 (15). HRMS Calcd for $C_{33}H_{26}N_4$ 478.2158; found 478.2158.

3.9. 6,8-Dimethoxy-, 6,8-diethoxy-, and 6,8-di-*n*-butoxy-1*H*-cyclohepta[2,1-*b*;3,4-*b*']diindoles (19–21)

A mixture of **8** (27 mg, 0.080 mmol) and sodium methoxide (8.8 mg, 0.16 mmol) in 2 ml of methanol was heated at 130 ℃ for 51 h in a sealed tube purged with argon. After being cooled to room temperature, the reaction mixture was poured into water (5 ml). Precipitates formed were filtered and washed with water (5 ml) and ethanol (3 ml). The solid obtained was purified by alumina column chromatography (eluted with 2/98 methanol/DCM), followed by silica gel column chromatography (eluted with 1/9 methanol/DCM), to give 13 mg (50%) of **19** as yellow powder. Mp = 280–281 ℃ (decomp.). ^{1}H NMR (500 MHz, DMSO-d_6, 80 ℃) δ = 4.41 (s, 6H), 6.96 (s, 1H), 7.32 (t, J = 7.8 Hz, 2H), 7.49 (t, J = 7.8 Hz, 2H), 7.84 (d, J = 7.8 Hz, 2H), 8.50 (d, J = 7.8 Hz, 2H) ppm; ^{13}C NMR (126 MHz, DMSO-d_6, 80 ℃) δ = 56.2, 91.6, 113.8, 114.9, 120.6, 123.7, 125.3, 125.8, 142.6, 144.6, 164.3 ppm; IR (KBr) ν_{max} = 1362s, 1298s cm^{-1}; UV-vis (CH_3CN) λ_{max} = 223 (log ε = 4.48), 234sh (4.34), 272 (4.16), 307 (4.80), 321 (4.70), 333 (4.75), 373 (4.13), 429 (3.57) nm. MS (70 eV) *m/z* (%) = 328 (M^+, 100), 281 (12),. 285 (14), 270 (10), 242 (15). HRMS Calcd for $C_{21}H_{16}N_2O_2$ 328.1212; found 328.1207.

Compounds **20–21** were synthesized similarly from **8** with sodium alkoxide in alcohol.

20: Orange prisms, mp = 277–278^{o}C (decomp). ^{1}H NMR (500 MHz, DMSO-d_6, 90 ℃) δ = 1.70 (t, J = 6.9 Hz, 6H), 4.68 (q, J = 6.9 Hz, 4H), 6.96 (s, 1H), 7.33 (t, J = 7.6 Hz, 2H), 7.50 (t, J = 7.6 Hz, 2H), 7.85 (d, J = 7.6 Hz, 2H), 8.52 (d, J = 7.6 Hz, 2H) ppm [21]; ^{13}C NMR (126 MHz, DMSO-d_6, 90 ℃) δ = 14.2, 65.3, 93.3, 114.2, 114.9, 121.1, 123.9, 125.7, 125.9, 142.1, 144.2, 164.2 ppm; IR (KBr) ν_{max} = 1583s, 1548s, 1413s, 1365vs, 1296s, 1243s, 1226s, 1209s, 1126s, 793s, 743s cm^{-1}; UV-vis (CH_3CN) λ_{max} = 222 (logε = 4.34), 232sh (4.23), 272 (4.62), 307 (4.67), 320sh (4.56), 333 (4.61), 371 (4.00), 430 (3.41) nm; MS (70 eV) *m/z* (%) = 356 (M^+, 100), 357 (26), 242 (15), 243 (11), 271 (21). HRMS Calcd for $C_{23}H_{20}N_2O_2$ 356.1525; found. 356.1529.

21: Orange microcrystals, mp = 245 ℃ (decomp.). ^{1}H NMR (500 MHz, DMSO-d_6, 80 ℃) δ = 1.08 (t, J = 7.5 Hz, 6H), 1.69 (sextet, J = 7.8 Hz, 4H), 2.11 (quintet, J = 6.3 Hz, 4H), 4.65 (t, J = 6.3 Hz, 4H), 6.98 (s, 1H), 7.34 (t, J = 7.8 Hz, 2H), 7.50 (t, J = 7.8 Hz, 2H), 7.86 (d, J = 7.8 Hz, 2H), 8.53 (d, J = 7.8 Hz, 2H) ppm. ^{13}C NMR (126 MHz, DMSO-d_6, 120 ℃) δ = 13.0, 18.4, 30.3, 68.8, 92.8, 113.9, 114.9, 120.4, 123.4, 125.1, 125.8, 142.6, 144.5, 163.7 ppm. IR (KBr) ν_{max} = 1365s, 1302s, 746s cm^{-1}. UV-vis (DMSO) λ_{max} = 311 (logε = 4.72), 337 (4.67), 373 (4.10), 438 (3.55) nm. MS (70 eV) *m/z* (%) = 412 (100, M^+), 300 (26), 271 (16), 243 (11). HRMS Calcd for $C_{27}H_{28}N_2O_2$ 412.2151; found 412.2156.

3.10. 6-Chloror-8-ethoxy-1*H*-cyclohepta[2,1-*b*;3,4-*b*'] -diindole (22)

A mixture of **8** (34 mg, 0.10 mmol) and sodium ethoxide (6.8 mg, 0.10 mmol) in 1 ml of ethanol was heated at 130 ℃ for 39 h in a sealed tube purged by argon. After being cooled to room temperature, the reaction mixture poured into water (5 ml) and the precipitate formed was filtered off. The solid obtained was purified by alumina column chromatography. Elution with methanol/dichloromethane (10/90) gave 24 mg (69%) of **22** as orange solids. Mp = 292– 294 ℃. ^{1}H NMR (500 MHz, DMSO-d_6, 100 ℃) δ = 1.68 (t, J = 6.9 Hz, 3H), 4.64 (q, J = 6.9 Hz, 2H), 7.31 (s, 1H), 7.40 (t, J = 7.8 Hz, 1H), 7.43 (t, J = 7.8 Hz, 1H), 7.58 (t, J = 7.8 Hz, 1H), 7.64 (t, J = 7.8 Hz, 1H), 7.88 (d, J = 7.8 Hz, 1H), 7.96 (d, J = 7.8 Hz, 1H), 8.56 (d, J = 7.8 Hz, 1H), 8.82 (d, J = 7.8 Hz, 1H) ppm [21]; ^{13}C NMR (126 MHz, DMSO-d_6, 100 ℃) δ = 14.4, 65.9, 107.8, 113.7, 115.0, 118.0, 121.6, 121.9, 122.4, 124.3, 124.6, 124.9, 126.9, 127.4, 127.7, 128.6, 140.7, 141.1, 142.1, 145.7, 161.4 ppm; IR (KBr) ν_{max} = 1574s, 1557s, 1531s, 1411s, 1395vs, 1372vs, 1270vs, 1262vs, 1234s, 1213s, 1196vs, 1114s, 863s, 806s, 754vs, 743vs cm^{-1}; UV-vis (CH_3CN) λ_{max} = 221 (logε = 4.41), 232sh (4.26), 263sh (3.94), 316 (4.65), 335 (4.64), 354sh (4.23), 372sh (3.91), 389 (3.75), 413 (3.51), 470 (3.66) nm; MS (70 eV) *m/z* (%) = 348 (M^+, 35), 346 (M^+, 100), 318 (28), 291 (10), 289 (28), 283 (11), 255 (21), 254 (11), 253 (15). HRMS Calcd for $C_{21}H_{15}{}^{35}ClN_2O$; 346.0873; found 346.0868.

3.11. 6-Ethoxy-8-piperidino-1*H*-cyclohepta[2,1-*b*;3,4-*b*'] -diindole (23)

A mixture of **22** (24 mg, 0.069 mmol), piperidine (7 μl, 6 mg, 0.07 mmol) and triethylamine (10 μl, 7 mg, 0.07 mmol) in 1.5 ml of dry DMF was heated at 110 ℃ for 1 h under argon atmosphere. After being cooled to room temperature, the reaction mixture was poured into water (5 ml) and precipitates formed were filtered off. The solid obtained was purified by alumina column chromatography. Elution with methanol/dichloromethane (3/97) gave 25 mg (93%) of **23** as yellow solids. Mp = 260–263 ℃. ^{1}H NMR (500 MHz, $CDCl_3$, 50 ℃) δ = 1.74 (t, J = 6.9 Hz, 3H), 1.86–1.99 (m, 4H), 3.04 (br, 2H), 3.67 (br, 2H), 4.45 (q, J = 6.9 Hz, 2H), 6.95 (s, 1H), 7.30 (t, J = 7.7 Hz, 1H), 7.32 (t, J = 7.7 Hz, 1H), 7.37 (t, J = 7.7 Hz, 1H), 7.38 (t, J = 7.7 Hz, 1H), 7.53 (d, J = 7.7 Hz, 1H), 7.57 (d, J = 7.7 Hz, 1H), 8.54 (d, J = 7.7 Hz, 1H), 8.61 (d, J = 7.7 Hz, 1H) ppm [21]; ^{1}H NMR (500 MHz, DMSO-d_6, 100 ℃) δ = 1.68 (t, J = 6.8 Hz, 3H), 1.73 (br, 2H), 1.89 (br, 4H), 3.42 (br, 4H), 4.63 (q, J = 6.8 Hz, 2H), 7.05 (s, 1H), 7.30 (t, J = 7.7 Hz, 1H), 7.33 (t, J = 7.7 Hz, 1H), 7.46 (t, J = 7.7 Hz, 2H), 7.82 (d, J = 7.7 Hz, 2H), 8.49 (d, J = 7.7 Hz, 1H), 8.52 (d, J = 7.7 Hz, 1H) ppm [21]; ^{13}C NMR (126 MHz, $CDCl_3$, 50 ℃) δ = 14.9, 24.4, 26.1, 54.4, 65.0, 100.2, 115.3, 115.4, 116.5, 118.4, 120.8, 121.3, 123.1, 124.4, 125.9, 126.1, 126.5,

126.6, 143.9, 144.1, 144.2, 145.3, 160.3, 163.7 ppm; IR (KBr) ν_{max} = 1559s, 1540s, 1410s, 1361s, 1226s, 1203s, 749s, cm^{-1}; UV-vis (CH_3CN) λ_{max} = 217 (logε = 4.80), 234sh (4.66), 319sh (4.72), 335 (4.89), 392 (4.16), 418 (4.11), 462sh (3.49) nm; MS (70 eV) *m/z* (%) = 395 (M^+, 100), 366 (15), 284 (12), 283 (11), 255 (17). HRMS Calcd for $C_{26}H_{25}N_3O$ 395.1998; found 395.1991.

3.12. 7-Piperidino-1*H*-cyclohepta[2,1-*b*;3,4-*b*']diindole (24, Nu = piperidino)

A mixture of **5** (50 mg, 0.17 mmol) and piperidine (1.0 ml) was heated at 130 ℃ for 62 h in a sealed tube purged by nitrogen. After being cooled to room temperature, the reaction mixture was poured into a saturated sodium bicarbonate solution (20 ml) and was extracted with DCM (30 x 3 ml). The combined organic layer was washed with brine (25 ml) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (eluted with ethanol/chloroform, 7/93), followed by alumina column chromatography (eluted with ethyl acetate/chloroform, 50/50) to give 9 mg (16%) of **24** as dark purple solids. Mp > 200 ℃ (decomp.). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.73 (quin, *J* = 5.3 Hz, 2H), 1.95 (quin, *J* = 5.3 Hz, 4H), 3.41 (t, *J* = 5.3 Hz, 4H), 7.39 (t, *J* = 7.7 Hz, 2H), 7.51 (t, *J* = 7.7 Hz, 2H), 7.56 (d, *J* = 7.7 Hz, 2H), 8.31 (d, *J* = 7.7 Hz, 2H), 8.64 (s, 2H) ppm [21]; ^{13}C NMR (126 MHz, $CDCl_3$) δ = 24.1, 26.7, 54.5, 115.6, 120.0, 121.0, 124.7, 127.2, 128.4, 130.2, 142.4, 146.6, 148.0 ppm; IR (KBr) ν_{max} =1496s, 1410s, 1366s, 1196s, 1110s, 744s cm^{-1}; UV-vis (CH_3CN) λ_{max} = 225 (logε = 4.30), 234sh (4.28), 278 (4.17), 318 (4.57), 331 (4.52), 347 (4.15), 362sh (4.05), 381sh (4.02), 535 (3.61) nm; MS (70 eV) m/z (rel int.) = 351 (M^+, 100), 352 (27), 266 (12), 267 (10), 268 (22), 295 (10), 349 (12), 350 (19). HRMS Calcd for $C_{24}H_{21}N_3$, 351.1735; found 351.1738.

3.13. X-ray Crystallographic Analysis of 14

Diffraction measurements were conducted using a Rigaku R-AXIS RAPID diffractometer at –100 ℃. Crystal data for **14** are as follows; monoclinic, space group; C2/c (# 15), *a*; 25.1397(5) Å, *b*; 10.4773(2) Å, *c*; 21.4999(4) Å, β; 123.6023(7) °, *V*; 4716.7(2) $Å^3$, *Z*; 8, *R*; 0.0454, *wR2*; 0.1054, *R1*; 0.0418 (*I*>2.00σ(*I*)), and *S*; 1.081. Tables of fractional atomic coordinates, thermal parameters, bond lengths, and angles have been deposited at the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, United Kingdom (CCDC 1427913) [Direct line: +44 1223 762910, Fax: +44 (0) 1233 336033, e-mail: deposit@ccdc.cam.ac.uk].

4. Conclusions

We have demonstrated that the halogenated compounds **5–8** could be synthesized from 2,2'-biindole (**9**) and studied on their nucleophilic substitution reactions. While **8** undergoes the substitution reaction with amine and alcohol to afford the various 6,8-substituted products, compounds **5–7** showed rather reluctance to undergo substitution reactions. Again, it should be addressed that many kinds of the 6,8-disubstituted derivatives can be synthesized from **8** by the method developed in this study. The difference in the reactivity between **5–7** and **8** was rationalized by the relative stability of the expected anionic intermediates based on the results of DFT calculations. Further derivatization at the halogenated positions of **5–8** by metal-catalyzed couplings with boronic acids, organozincates and stannanes is now in progress.

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Supplementary Material

Output files for computations reported in this work are available upon request from the corresponding author.

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