Synthesis of Novel Indolo-Spirocyclic Compounds

Mardia T. El-Sayed,[a,b]* Kazem Mahmoud,[a] Andreas Hilgeroth,[a] and Issa M. I. Fakhr[b]

[a]Martin Luther University, Institute of Pharmacy, Research Group of Drug Development and Analysis, Wolfgang-Langenbeck-Straße 4, 06120 Halle (Saale), Germany
[b]Applied Organic Chemistry Department, National Research Centre, Cairo, Egypt
*E-mail: mardia_elsayed2009@yahoo.com

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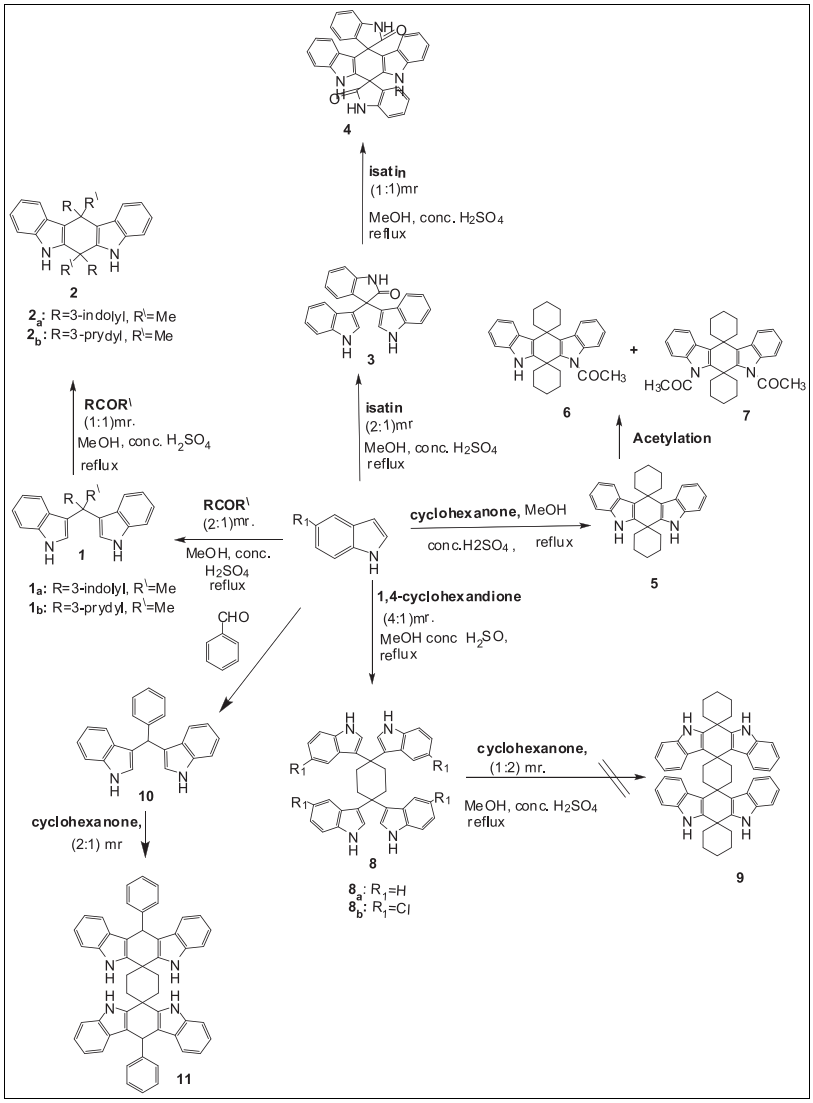


In the present work, we succeeded to synthesize the novel indolo-spirocyclic compounds (4–7 and 11) via electrophilic condensation reactions of indoles with carbonyl compounds including different types of ketones, for example, heteroacetyl ketones (3-acetylindole and 3-acetylpyridine), cyclohexanone, isatin, cyclohexane-1,4-dione, whereas an attempt to prepare the spirocyclic 9 failed. This new idea will open a high prospective for continuous investigations related to the synthesis of novel indolo-spirocyclic compounds.

INTRODUCTION

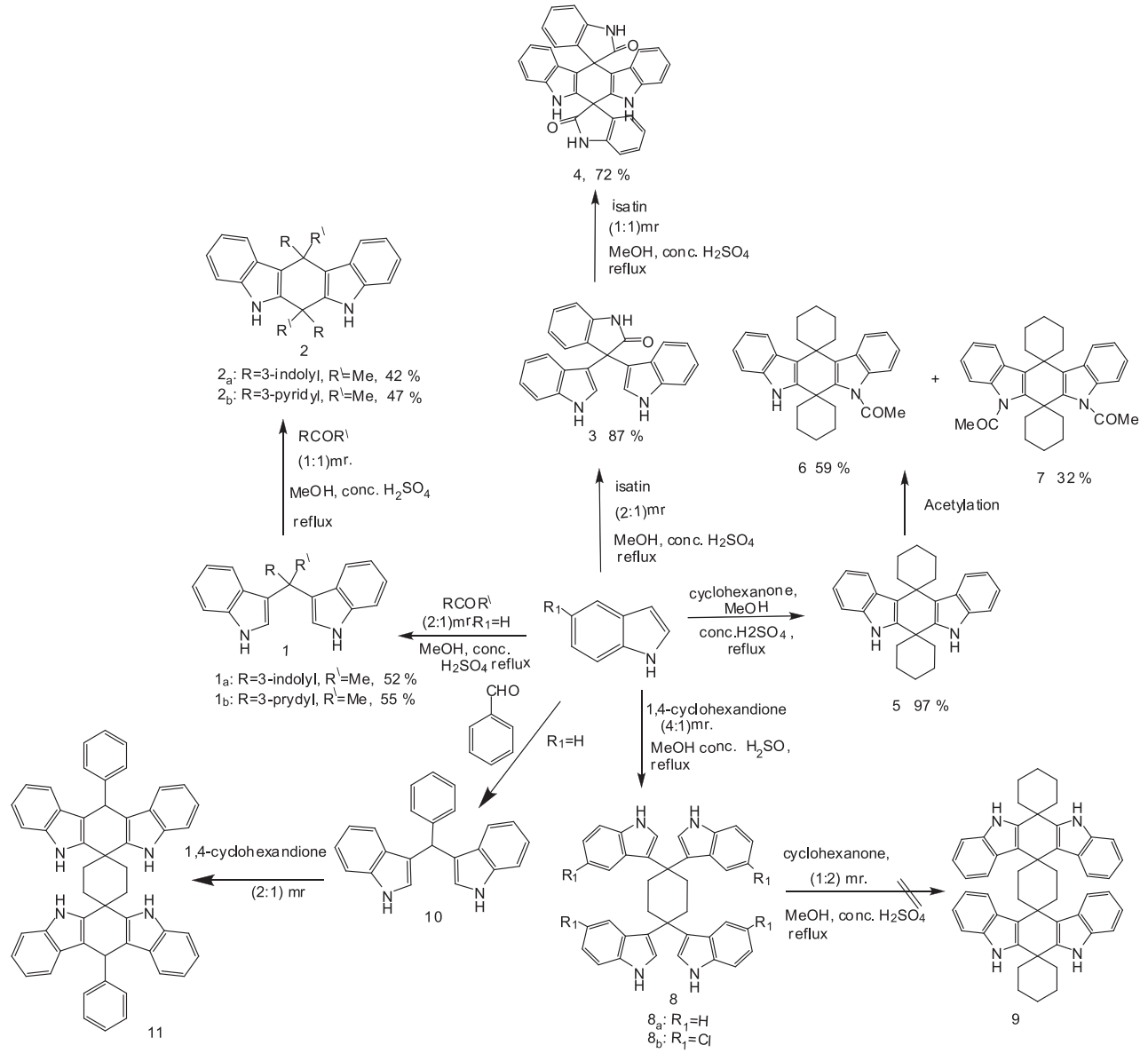
Spirocyclic compounds are essentially important because of their unique structure characteristics and diverse biological activities [1–9]. The indolo-spirocyclic scaffold is frequently found as a core structure of a large family of bioactive natural products and series of compounds of pharmaceutical significance, for instance, alstonisine and spirotyprostatine [7]. In addition, several spirocyclic

compounds have been used for the synthesis of new ligands and catalysts, such as spinol [10]. Indolo-carbazoles and indolo-spirocyclic compounds have been reported as primary compounds for the synthesis of various drugs and possess important biological, pharmacological, and medicinal activities [11–13]. Indolo-carbazoles are associated with anticancer, antimicrobial, and antifungal activities. In most of these cases, the biological activity is correlated with indolo-carbazoles that contain one heteroatom. The biological activity depends on the interaction ability with DNA [14,15]. Furthermore, most of the experimental studies have indicated that the size, shape, and planarity of this structure are very important criteria for such potential DNA interactions [16]. The electron-rich indole nucleus indicates an enhanced reactivity towards carbon electrophiles that generally results in the formation of a substitution at the 3-position of the indole ring [1–5]. The 3-position of the indole is the preferred site for the electrophilic substitution reactions. A 3-alkyl or 3-acyl indoles are important intermediates for the synthesis of a wide range of indole derivatives [17]. A direct method for the synthesis of 3-alkylated indoles involves the condensation with aliphatic or aromatic aldehydes. Normally, these reactions occur in the presence of several types of catalysts, for example, protic or Lewis acids. Protic acids are used to catalyze the reaction, for example, silica sulphuric acid [18], oxalic acid [19], zeolites HY [1,2] and ZnY [3], amberlyst [20,21], HBr [22,23], HCl [24,25], HCOOH [26,27], CH_3COOH [28–30], *p*-TsOH [31], $NaHSO_3$ [32], $KHSO_4$ [33], H_3PO_4-SiO_2 [13]. Lewis acids are lanthanide resins [34], zeolite (ZnY) [14], bentonic clay/infrared (IR) [35], montmorillonite clay K-10 [36,37], cerium ammonium nitrate [15], $ZrCl_4$ [16], $IndF_3$ [38], $Bi(OTf)_3$ [39], $TiCl_4$ [40], and $Al(OTf)_3$ [41]. As seen from the reported literature, numerous catalysts can efficiently promote the reaction of aldehydes or ketones and indoles affording 3-alkylated indole compounds in good to high yield in a reasonable time.

RESULTS AND DISCUSSION

The condensation of ketones was carried out in a molar ratio of (1:2), 1 mole of ketone with 2 moles of indole to afford the corresponding bisindolylmethanes (BIMs). These BIMs were isolated from the reaction mixture as in the case of compounds $1_{a,b}$ or directly used without an isolation from the reaction mixture to condense with another equivalent mole of ketones for the formation of tetrahydroindolo[2,3-*b*]carbazole ($2_{a,\ b}$). The main purpose of this work was an attempt to synthesize novel spirocyclic based on indole structures. The formation of BIMs derived from ketone follows the similar reaction mechanism of the formation of BIMs derived from aldehydes and their corresponding tetrahydroindolocarbazoles (Scheme 1). It has been reported that the short reaction time is important to promote the reaction in direction of forming our cis isomer. While the formation of the trans isomer of the tetrahydroindolo[3,2-*b*]carbazoles has also been confirmed by Rong Gu *et al*. [40] However, the reaction has been done under completely different reaction conditions of using indoles with aromatic aldehydes in a (1:1) molar ratio in the presence of 2 mol% of iodine as a catalyst in acetonitrile under refluxing for 14 h affording the 6,12 trans isomer of tetrahydroindolo[3,2-*b*]carbazole derivative. Our derivatives were synthesized by using indole (two equivalents) through condensation reaction with acetyl indole or acetyl pyridine (one equivalent) in methanolic solution containing drops of conc. H_2SO_4 under reflux [42]. The reaction afforded BIMs of type $1_{a,b}$ in yields of 52% and 55%, respectively. The formed moderate yield is because of the lower reactivity of ketones if compared with aldehydes. Thus, the reaction was accomplished under vigorous conditions and producing moderate yields. Under similar reaction conditions, we had the primary intention to use ketones as precursors for the preparation of the corresponding tetrahydroindolo[2,3-*b*]carbazoles of type $2_{a,b}$, (Scheme 1). BIMs $1_{a,b}$ were isolated from the reaction mixture and were used in a new reaction flask with an equivalent amount of the desired ketone in methanol sulphuric acid solution under reflux affording compounds $2_{a,b}$. Compounds $1_{a,b}$ and $2_{a,b}$ have been identified by means of their spectroscopic data. Isatin, as an example of a 1,2-diketone, was condensed with indole for the preparation of the indole trimer by following the similar reaction conditions. The use of methanol sulphuric acid solution with a molar ratio of two equivalents of indole and one equivalent of isatin under reflux for 2 h yielded the trisindole 3 in an 87% yield. This method is considered to be simple and efficient if compared with the reported chemical procedures for the preparation of 3 [43]. The spectral data of our synthesized trisindoline (3) were identical with those of the natural product isolated from the marine sponge *Hyrtios alum* [43]. The trisindoline (3) was used as a precursor for a condensation with an equimolar amount of isatin as a possible way for the synthesis of the expected novel spirocyclic structure 4. The structure of 4 was confirmed on the basis of its spectroscopic data, where the ^{1}H-NMR spectrum demonstrated the presence of four multiplet signals, each one for four aromatic protons, and two broad signals, each one for two NH protons. Cyclohexanone was condensed with indole using different types of catalysts as well as aldehyde. Using the method of MeOH/conc. H_2SO_4 in the reaction of indole with cyclohexanone in a molar ratio of 2:1, the known (3,3′-(cyclohexane-1,1-diyl)bis(1-*H*-indole)) was isolated. It was detected by thin-layer chromatography (TLC) and ESIMS (electrospray ionization mass spectroscopy)of the reaction mixture and not isolated from the reaction mixture but directly used into the second condensation step with the second mole of cyclohexanone under the same conditions of MeOH/conc. H_2SO_4

Scheme 1. Condensation reactions of indole or bisindolylmethanes with different types of ketones.



leading to our second novel spirocyclic structure 5 in a 97% yield. Compound 5 was determined to be the 2,8,2′,8′-bis (cyclohexane-1,1-diyl)-1,2,3,8-tetrahydroindolo- [2,3-*b*]carbazole (5) (Scheme 1). The spirocyclic structure 5 exhibited an EI-MS with m/z 395 [M^+], and its ^{1}H-NMR spectra showed five multiplet signals for the 20 aliphatic protons (10 CH_2) of the cyclohexyl groups and one singlet signal at 10.66 ppm for two NH indole protons. The ^{13}C-NMR (*Apt*) spectra of compound 5 showed the presence of five carbon signals for the five CH_2 groups and one signal for the spirocyclic atom. Eight signals were observed for the aromatic indole carbons. Based on these data, it was suggested that compound 5 possesses an asymmetrical structure. In order to verify the structure of compound 5, it was acetylated using acetic anhydride in the presence of 4-(dimethylamino)pyridine (DMAP) as a catalyst. The reaction afforded two products; one was determined as monoacetylated product (6) in a 59% yield and was confirmed by its ESIMS, ^{1}H-NMR, ^{13}C-NMR, and IR spectra. These data showed the presence of the carbonyl group in the ^{13}C-NMR spectrum at $\delta = 169.66$ ppm and a carbon signal at $\delta = 14.54$ ppm for the methyl group. The IR spectrum of compound 6 exhibited a strong peak at 1670 cm^{-1} for the C=O group.

The ^{1}H-NMR indicated the disappearance of one NH indole proton and the presence of singlet signal at $\delta = 2.69$ ppm integrated for three protons for the acetyl methyl group. ESIMS showed the molecular weight of compound 5 plus only one acetyl group. The second reaction product had a lower R_f value and was identified based on its

spectroscopic data as the diacetylated product (7) in a lower yield of 32% than that of the monoacetylated product 6. Thus, the acetylation reaction takes place stepwise, and the formation of the diacetylated products needs some more time.

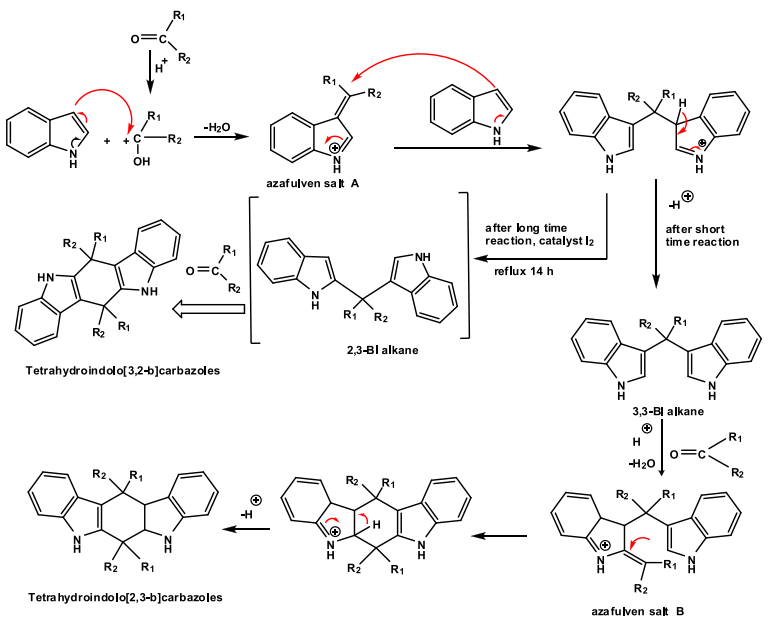
The electrophilic substitution reactions of indoles with cyclohexan-1,4-dione has been reported in the literature as a possible way for the synthesis of the extended supramolecular compounds 8a,b named as 1,1,4,4-tetrakis(1H-indol-3-yl)cyclohexane (8a). The reaction takes place in the presence of catalyst such as iodine and N-bromosuccinimide (NBS) [40] affording the tetra-substituted product in good yield. In the course of this study, cyclohexan-1,4-dione was condensed with indole in MeOH/conc. H2SO4 solution in a molar ratio of 1:4 yielding compounds 8a,b in 82% and 87% yield, respectively, after refluxing for 2 h (Scheme 1). The spectroscopic data of compound 8a were identical to the data of the reported tetra-substituted indole product [35,36]. The other novel derivative 8b using 5-chloroindole was synthesized and elucidated in the same manner. An attempt to prepare the spirocyclic compound 9 under similar reaction conditions failed.

The extended spirocyclic structure (11) was synthesized in better yield of 52%, by the way of MeOH and conc. H2SO4 using BIM (10) [1,3,36] (2 mole equivalents) and 1,4-cyclohexanedione (1 mole equivalent). The reaction solution turned from pink to dark violet by leaving it stirring for 1 h under reflux. The product was detected, purified, and confirmed by means of ESIMS (m/z):719.29 [M+-H] and EI-MS (m/z):720 [M+]. Its 1H-NMR spectrum showed a single signal at $\delta = 5.91$ ppm value for two protons (2 CH) and two triplet signals every one for four protons for two CH2 at $\delta = 2.03$ and 2.27 ppm. The four NH indole protons appeared at 9.94 ppm as a broad signal. The structure was confirmed additionally by its APT 13C-NMR spectrum that showed the presence of only 26 carbon signals as two signals for two CH2 carbons, 11 signals for quaternary carbons, 1 carbon signal for one CH aliphatic carbon, and 13 carbon signals for 13 CH aromatic carbons. These data proved that the novel spirocyclic compound 11 owns a symmetrical structure.

PROPOSED REACTION MECHANISM

The mechanism of the reaction follows the same previous mechanism of condensation reactions of indoles with aldehydes. In our reaction, using BIMs and ketones in methanolic sulphuric acid solution under refluxing for 1 h (short time reaction) afforded the cis-isomer and tetrahydroindolo[2,3-b]carbazoles (2a,b) in good yields which were given without isolation of the other trans isomeric tetrahydroindolo[3,2-b]carbazoles. Scheme 2 showed the mechanism for the formation of our [2,3-b]carbazoles (cis form) and the other [3,2-b]carbazoles (trans form). It has been reported that the short reaction time is important to promote the reaction in the direction of forming our cis-isomer (2a,b). While, the trans form was formed under long time reaction in the presence of iodine as a catalyst. This behavior is due to that the iodine catalyzes the transformation or the isomerization of 3,3/-BIMs into 2,3-BIMs under a long time reaction conditions in acetonitrile as solvent (the Plancher rearrangement). Then, the 2,3-BIMs can undergo an electrophilic attack at a carbonyl group of the second molecule of aldehyde leading to the formation of tetrahydroindolo[3,2-b]carbazoles. The reaction of indoles with aromatic ketones or aldehydes using iodine as a catalyst is a selective reaction for the

Scheme 2. Reaction mechanism. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]



preparation of tetrahydroindolo[3,2-b]carbazoles, and none of the other isomer tetrahydroindolo[2,3-b]carbazoles was observed in the reaction mixture [40–42]. Whereas, the application of the reaction with a short reaction time is selective for the formation of the cis form. Our novel spirocyclic compounds have been formed under a short reaction time conditions as in the reported formation of the tetrahydroindolo[2,3-b]carbazoles. The acetylation reaction of compound 5 was formed in the presence of 4-(Dimethylamino)pyridine (DMAP) as catalyst. The reaction tends to the final products that are either mono or di, acetic acid, and regenerated 4-DMAP [44].

CONCLUSION

The novel indolo-spirocyclic compounds 4–7 and 11 have been successfully synthesized via condensation reaction of indole or bisindolylmethanes with ketones in the presence of strong acid (conc. H_2SO_4) as catalyst under short time reflux. The successful synthesis of this important class of organic heterocyclic compounds will open a new prospective for continuous investigation of novel indolo-spirocyclic compounds.

EXPERIMENTAL SECTION

The melting points were measured on a Boetius-Mikroheiztisch from the company VEB weighing Rapido Radebeul/VEB NAGEMA (Dresden, Germany) measured and are uncorrected. The TLC for the analyses were performed with aluminum foil fluorescent indicator from Merck KGaA (silica gel 60 F254, layer thickness 0.2 mm; Darmsdadt, Germany). R_f -values (run level relative to the solvent front) were given on the next sections. The separations were carried out on column chromatography at atmospheric pressure on silica gel 60 (grain size from 0.063 to 0.200 mm) from Merck KGaA. The NMR spectra were recorded on a Gemini 2000 (400/100 MHz; CA, USA). The ATR spectra were recorded on a Fourier transform infrared spectrometer IFS 28 from Bruker Corp. (MA, USA). The ESI mass spectra were recorded on a Finnigan LCQ Classic (MA, USA). The EI mass spectra were recorded on an Intel 402.

Procedure for Preparation of Compound $1_{a,b}$. A 1 mmol (0.159 g) of acetylindole or 1 mmol (0.121 g) of acetylpyridine and 2 mmol (0.234 g) of indole were added to a flask that contained 50 mL MeOH under heating until it completely dissolved. The reaction mixture was stirred under heating until the reaction solution became clear. Then, a few drops of conc. H_2SO_4 were added. The reaction solution became pink. The color turned to dark red by leaving it to stir under reflux for 1 h. Upon the reaction completion as monitored by TLC (5% MeOH/CH_2Cl_2), the reaction was worked up by adding 50 mL water and neutralized by NH_4OH. The water phase was extracted with 100 mL ethyl acetate,for two times washed with 200 mL water and 200 mL brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The crude reaction mixture was purified via column chromatography.

3,3′,3″-(Ethane-1,1,1-Triyl)Tris(1*H*-Indole) (1_a). $C_{26}H_{21}N_3$, 375.47 g/mol, light brown powder mp: 110–115°C, ESIMS: (m/z) = 376.14 [M^++H], 374 [M^+-H], IR. (ATR, cm^{-1}) = 2923 (CH_3), 3403 (NH), ^{1}H-NMR: (400 MHz, acetone-d_6) δ (ppm): 2.44 (s, 3H, Me), 6.76 (t, 3H, J = 7.5 Hz), 6.92 (d, 3H, J = 2 Hz), 6.97 (t, 3H, J = 7.6 Hz), 7.34 (d, 2H, J = 8.1 Hz), 7.38 (d, 4H, J = 8.1 Hz), 9.89 (s, 3H, 3NH), ^{13}C-NMR: (100 MHz, acetone-d_6) δ (ppm): 8.60 (Me), 39.86 (CMe), 111.87, 111.92, 118.50, 121.21, 122.28, 123.75, 123.91, 124.12, 124.16, 127.45, 127.48, 138.15, 138.31, EA: calcd. C, 83.17; H, 5.64; N, 11.19. Found: C, 83.18, H, 5.68; N, 11.22, R_f. 0.7 (CH_2Cl_2). yield: (391 mg), 52%.

3,3′-(Pyridin-3-yl)Ethane-1,1-Diyl)bis(1*H*-Indole (1_b). $C_{23}H_{19}N_3$, 337.42 g/mol, light yellow crystals, mp. 180–182°C, ESIMS: (m/z) = 338.17 [M^++H], EI-MS (m/z): 337 [M^+] 45%, 322 [M^+-Me] 100%, 259 [M^+-pyridyl] 15%, 220 [M^+-indolyl] 99%, 205 [M^+-Me-indolyl] 55%, 117 [indolyl] 98%, 90 [Ph.CH] 90%, IR. (ATR, cm^{-1}): 2920 (CH_3), 3411 (NH), ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 2.33 (s, 3H, Me), 6.81 (t, 2H, J = 7.6Hz), 6.86 (d, 2H, J = 7.3 Hz), 7.01–7.07 (m, 4H), 7.39 (d, 2H, J = 8.1 Hz), 7.95 (dd, 1H, J = 7.6, 8.1 Hz), 8.46 (d, 1H, J = 8.3 Hz), 8.65 (s, 1H), 8.77 (d, 1H, J = 7.4 Hz), 11.13 (d, 2H, 2NH), ^{13}C-NMR: (100 MHz, DMSO-d_6) δ (ppm) = 28.27 (Me), 42.19 (C-Me), 111.88, 118.47, 119.98, 120.13, 120.89, 124.02, 125.15, 126.40, 137.09, 139.58, 140.19, 144.54, 147.79, EA: calcd. C, 81.87; H, 5.68; N, 12.45. Found: C, 81.89, H, 5.75; N, 12.48, R_f. 0.48 (7% MeOH/CH_2Cl_2), yield: (371 mg), 55%.

Procedure for the Preparation of Compounds $2_{a,b}$. Compound 1_a 1 mmol (0.375 g) or 1 mmol (0.337 g) of compound 1_b and 1 mmol (0.159 g) of acetylindole or 1 mmol (0.121 g) of acetylpyridine, respectively, were added to a flask containing 50 mL MeOH under heating until it completely dissolved. When the reaction solution became clear, a few drops of conc. H_2SO_4 were added. The reaction solution became pink; then, the color turned to dark red by leaving it stirring under reflux for 1 h. Upon the reaction completion, as monitored by TLC (7.5% MeOH/CH_2Cl_2), the reaction was worked up by adding 50 mL of water and neutralized by NH_4OH; the water phase was extracted with 100 mL ethyl acetate, for two times washed with 200 mL water and 200 mL brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The crude reaction mixture was purified via column chromatography on silica gel eluted with (7.5% MeOH/CH_2Cl_2) affording compounds 2_a and 2_b, respectively.

2,8-Di(1*H*-Indol-3-yl)-2,8-Dimethyl-1,2,3,8-Tetrahydroindolo [2,3-*b*]Carbazole (2_a). $C_{36}H_{28}N_4$, 516.63 g/mol, violet

powder, mp. 190–193°C, ESIMS: (m/z) = 517.45 [M^++H], EI-MS: (m/z) = 516 [M^+] 25%, 501 [M^+-Me] 100%, 117 [indolyl] 30%, IR. (ATR, cm^{-1}): 2851, 2923 (CH_3), 3255 (NH), ^{1}H-NMR: (400 MHz, acetone-d_6) δ (ppm): 2.31 (s, 3H, Me), 3.29 (s, 3H, Me), 6.99 (t, 2H, J = 7.4 Hz), 7.11 (t, 1H, J = 7.4 Hz), 7.26 (t, 1H, J = 7.5 Hz), 7.34 (d, 3H, J = 7.8 Hz), 7.39 (t, 1H, J = 7.8 Hz), 7.44 (d, 1H, J = 8.4 Hz), 7.64 (d, 1H, J = 8 Hz), 7.69 (d, 1H, J = 8.4 Hz), 7.79–7.84 (m, 3H), 8.19 (d, 1H, J = 8 Hz), 8.29 (s, 1H), 8.35 (s, 1H), 8.40 (s, 1H), 11.88 (s, 2H, 2NH), 12.72 (s, 2H, 2NH), ^{13}C-NMR: (400 MHz, acetone-d_6) δ (ppm): 26.05 (Me), 26.39 (Me), 48.75 (C-Me), 53.27 (C-Me), 113.46, 114.12, 119.36, 120.92, 121.38, 121.62, 122.79, 123.71, 123.79, 123.98, 125.06, 125.37, 126.87, 134.37, 139.17, 141.72, R_f -value: 0.15 (10% MeOH/CH_2Cl_2), Yield: (434 mg), 42%.

2,8-Dimethyl-2,8-di(Pyridin-3-yl)-1,2,3,8-Tetrahydroindolo [2,3-*b*]Carbazole(2_b). $C_{30}H_{24}N_4$, 440.54 g/mol, dark yellow powder, mp. 155–160°C, ESIMS (m/z): 442.18 [M^++H], 440.28 [M^+-H]. ^{1}H-NMR: (400 MHz, acetone-d_6) δ (ppm): 1.43 (s, 3H, Me), 1.85 (s, 3H, Me), 6.74 (s, 1H), 6.80 (t, 1H, J = 7.8 Hz), 6.99–7.05 (m, 2H), 7.09–7.17 (m, 2H), 7.28–7.33 (m, 2H), 7.40 (t, 2H, J = 9 Hz), 7.73 (dd, 1H, J = 1.6, 7.4 Hz), 7.78 (dd, 1H, J = 1.6, 7.4 Hz), 8.31 (dd, 1H, J = 1.53, 7.73 Hz), 8.43 (dd, 1H, J = 1.53, 7.73 Hz), 8.67 (t, 2H, J = 7.8 Hz), 10.12 (s, 1H, 1NH), 10.48 (s, 1H, 1NH) , ^{13}C-NMR: (100 MHz, acetone-d_6) δ (ppm): 18.99 (Me), 28.16 (C), 112.37, 113.19, 119.31, 119.54, 120.25, 120.69, 121.62, 121.85, 122.12, 123.56, 123.61, 123.71, 124.32, 124.43, 126.41, 134.28, 135.54, 138.33, 142.68, 143.18, 145.81, 147.11, 147.61, 148.15, 148.91, 149.89, EA: calcd. C, 81.79, H, 5.49, N, 12.72. Found: C, 81.78, H, 5.52; N, 12.59, R_f. 0.7 (10% MeOH/CH_2Cl_2), Yield: (414 mg), 47%.

Preparation of 3,3-Di(3-Indolyl)-2-Indoline (3). A 1 mmol (0.147 g) of isatin and 2 mmol (0.234 g) of indole were added to a flask which contained 50 mL of MeOH under stirring and heating until it completely dissolved. When the reaction solution became clear, a few drops of conc. H_2SO_4 were added. The reaction solution became pink; the color was turned to dark red by leaving it to about 2 h under stirring and reflux. Upon the reaction completion, as monitored by TLC (5% MeOH/CH_2Cl_2), the reaction was worked up by adding 50 mL of water, neutralized by NH_4OH, extracted with 100 mL ethyl acetate, for two times washed with 200 mL water and 200 mL brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The crude reaction mixture was purified via column chromatography on silica gel eluted with (5% MeOH/CH_2Cl_2) to afford compound 3, $C_{24}H_{17}N_3O$, 363.41 g/mol, light pink powder, mp. 290–293°C, ESIMS: (m/z): 363.20 [M^+], 362.28 [M^+-H]. IR.(ATR,cm^{-1}): 1687 (C = O), 3439 (NH), ^{1}H-NMR: (400 MHz, $CDCl_3$) δ (ppm): 6.69 (d, 2H, J = 1.9 Hz), 6.78–6.82 (m, 2H), 6.97–7.05 (m(t,d), 4H, J = 7, 7.4 Hz), 7.13–7.23 (m, 6H), 7.94 (s, br., 2H, 2NH), 8.45 (s, br., 1H, 1NH), ^{13}C-NMR: (100 MHz, $CDCl_3$) δ (ppm): 53.25, 110.02, 111.36, 114.87, 119.41, 119.66, 120.00, 121.19, 121.61, 121.67, 122.61, 124.05, 125.51, 125.44, 125.82, 126.01, 126.39, 127.96, 134.52, 136.02, 136.92, 139.94, 141.00, 180.03 (C = O), EA: calcd. C, 79.32; H, 4.72; N, 11.56. Found: C, 79.40, H, 4.75; N, 11.61, R_f: 0.43 (7% MeOH/CH_2Cl_2), Yield: (316 mg), 87%.

Preparation of 2,8,2′,8′-Bis(1*H*-Indolonyl)-1,2,3,8-Tetrahydroindolo[2,3-*b*]Carbazole (4). A 1 mmol (0.147 g) of isatin and 1 mmol (0.363 g) of compound 3 were added to the flask that contained 50 mL of MeOH under stirring and heating until it completely dissolved. Upon the reaction solution became clear, a few drops of conc. H_2SO_4 were added dropwisely. The reaction solution became pink and the color turned to dark red by leaving it stirring under reflux for about 1 h. Upon the reaction completion, as monitored by TLC (5% MeOH/CH_2Cl_2), the reaction was worked up by adding 50 mL of water, neutralized by NH_4OH, extracted with 100 mL ethyl acetate, for two times washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The crude reaction mixture was purified via column chromatography on silica gel eluted with (7% MeOH/CH_2Cl_2) to afford compound 4, $C_{32}H_{20}N_4O_2$, 492.53 g/mol, light green powder, mp. > 350°C, ESIMS: (m/z) 493.16 [M^++H], IR-Spectrum: (ATR, cm^{-1}): 1699 (C = O), 3273–3450 (br., NH), ^{1}H-NMR: (400 MHz, DMSO-d_6) δ (ppm): 6.80–6.90 (m, 4H), 6.92–7.01 (m, 4H), 7.12–7.24 (m, 4H), 7.26–7.42 (m, 4H), 10.66 (s, br., 2H, 2NH), 10.93 (s, br., 2H, 2NH), EA: calcd. C, 78.03; H, 4.09; N, 11.38. Found: C, 78.00, H, 4.06; N, 11.39, R_f . 0.28 (7% MeOH/CH_2Cl_2), yield: (355 mg), 72%.

Preparation of 2,8,2′,8′-Bis(Cyclohexyl)-1,2,3,8-Tetrahydroindolo[2,3-*b*]Carbazole (5). A 2.5 Mmol (0.25 g) of cyclohexanone and 2 mmol (0.234 g) of indole were added to a flask that contained 50 mL MeOH under stirring and heating until it completely dissolved. When the reaction solution became clear, a few drops of conc. H_2SO_4 were added. The reaction solution became pink; then the color turned to dark red by leaving it to stir under reflux for about 1 h. Upon the reaction completion, as monitored by TLC (100% CH_2Cl_2), the reaction was worked up by adding 50 mL of water. The reaction mixture was neutralized with NH_4OH, extracted with 100 mL ethyl acetate, for two times washed with 200 mL water and 200 mL brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The crude reaction mixture was purified via column chromatography on silica gel eluted with (100% CH_2Cl_2) to afford compound 6, $C_{28}H_{30}N_2$, 394.55 g/mol, light yellow crystals, mp. 90–92°C, EI-MS (m/z): 395

[M^+] 20%, 394 [M^+-H] 65%, 393 [M^+-2H] 40%, 314 [M^+-cyclohexanone-2H] 100%, 285 [314-2CH_2] 20%, 271 [314-3CH_2] 99%, 257 [314-4CH_2] 65%, 245 [indolyl.CH.indolyl] 20%, 130 [indolyl.CH] 98%, 117 [indolyl] 95%, 90 [PhCH] 97%, IR: (ATR, cm^{-1}): 2925 (CH_2), 3404 (NH), ^{1}H-NMR: (400 MHz, DMSO-d_6) δ (ppm): 1.48–1.49 (m, 4H), 1.50–1.60 (m, 4H), 1.70–1.74 (m, 4H), 2.19–2.29 (m(tt), 4H, J = 6.64, 6.5 Hz), 2.39–2.46 (m, 4H), 6.65 (t, 2H, J = 7.6 Hz), 6.85 (t, 2H, J = 7.5 Hz), 7.22 (d, 1H, J = 8 Hz), 7.26 (d, 1H, J = 7.5 Hz), 7.32 (d, 2H, J = 7.9 Hz), 10.66 (s, br., 2H, 2NH), ^{13}C-NMR: (100 MHz, DMSO-d_6) δ (ppm): 22.55 (CH_2), 26.30 (CH_2), 26.35 (CH_2), 36.63 (CH_2), 38.87 (CH_2), 40.13 (C), 111.21, 117.35, 120.01, 120.49, 121.94, 122.03, 125.85, 136.90, EA: calcd. C, 85.24; H, 7.66; N, 7.10. Found: C, 85.18, H, 7.69, N, 7.15, R_f 0.75 (100% CH_2Cl_2), Yield: (383 mg), 97%.

General Procedure for Acetylation Reaction (Compounds 6 and 7). Compound 5 (1 mmol, 0.395 g) was added to a flask containing 5 mL CH_2Cl_2, 0.1 mmol of 4-(dimethylamino) pyridine (DMAP), 1.2 mmol of triethylamine, and 2.2 mmol of acetic anhydride. The reaction mixture was left for stirring at room temperature for several days. The products formation was detected by TLC (100% CH_2Cl_2). After several days, the reaction was worked up, and the solution was neutralized with NH_4OH solution, extracted with CH_2Cl_2, washed with 200 mL water and 200 mL brine, and dried over anhydrous sodium sulphate. The product was purified by using 100% CH_2Cl_2 to collect the monoacetylated spirocyclic product 7 first and then the diacetylated spirocyclic product 7.

2,8,2′,8′-Bis(Cyclohexyl)-1-Acetylindolyl-1,2,3,8-Tetrahydroindolo[2,3-*b*]Carbazole (6). $C_{30}H_{32}N_2O$, 436.59 g/mol, white powder, mp. 290–293°C, ESIMS: (m/z) = 435.34 [M^+-H], IR. (ATR, cm^{-1}): 1677 (C = O), 2949 (CH_2), 3287 (NH), ^{1}H-NMR: (400 MHz, DMSO-d_6) δ (ppm): 1.52–1.59 (m, 4H, 2CH_2), 1.67–1.73 (m, 6H, 3CH_2), 2.07 (d, 4H, J = 7.9 Hz, 2 CH_2), 2.69 (s, 3H, COMe), 6.94–6.96 (m, 4H), 7.15–7.21 (m, 2H), 7.69 (t, 1H, J = 10 Hz), 8.33 (d, 1H, J = 9.95 Hz), 10.66 (s, 1H, 1NH), ^{13}C-NMR: (100 MHz, DMSO-d_6) δ (ppm): 14.54 (Me), 23.23 (CH_2), 23.33 (CH_2), 23.89 (CH_2), 24.47 (CH_2), 24.82 (CH_2), 25.71 (CH_2), 31.13 (CH_2), 35.48 (CH_2), 43.39 (CH_2), 48.82, 55.35, 112.47, 116.45, 118.98, 119.84, 120.63, 120.72, 122.29, 123.37, 124.64, 124.69, 124.91, 126.00, 129.68, 136.21, 140.83, 149.74, 169.66 (C = O), EA: calcd. C, 82.53; H, 7.39; N, 6.42. Found: C, 82.56, H, 7.42; N, 6.50, R_f 0.66 (100% CH_2Cl_2), Yield: (258 mg), 59%.

2,8,2′,8′-Bis(Cyclohexyl)-bis(1-Acetylindolyl)-1,2,3,8-Tetrahydroindolo[2,3-*b*]Carbazole (7). $C_{32}H_{34}N_2O_2$, 478.62 g/mol, white powder, mp. >350°C, ESIMS: (m/z) = 477.52 [M^+-H], IR. (ATR, cm^{-1}) = 1680 (C = O), 2949 (CH_2), ^{1}H-NMR: (400 MHz, acetone-d_6) δ (ppm): 1.41–1.43 (m,4H, 2CH_2), 1.46–1.59 (m,4 H, 2CH_2), 1.90–1.92 (m, 4H, 2CH_2), 2.14 (d, 4H, J = 7.8 Hz), 2.42 (t, 4H, CH_2, J = 7.9 Hz), 2.63 (s, 6H, 2COMe), 6.79–6.83 (m, 2H), 6.99 (t, 2H, J = 7 Hz), 7.42 (d, 2H, J = 7.8 Hz), 7.84 (s, 1H), 8.24 (d, 1H, J = 8.3 Hz), ^{13}C-NMR: (100 MHz, acetone-d_6) δ (ppm): 19.67 (Me), 22.51 (CH_2), 23.37 (Me), 26.44 (CH_2), 26.64 (CH_2), 28.49 (CH_2), 28.65 (CH_2), 28.79 (CH_2), 29.11 (CH_2), 29.20 (CH_2), 29.27 (CH_2), 29.42 (CH_2), 35.99, 38.89, 100.81, 116.14, 121.09, 122.55, 123.63, 124.12, 127.21, 129.39, 136.59, 162.02 (C = O), 168.90 (C = O), R_f : 0.58 (CH_2Cl_2), Yield: (153 mg), 32 %.

Procedure for the Preparation of Compound ($8_{a,b}$). A 1 mmol (0.112 g) of cyclohexane-1,4-dione and 4 mmol (0.468 g) of indole or 4 mmol (0.606 g) of 5-chloroindole were added to a flask without solvent, and 22 mmol (0.39 g) of N-bromosuccinimide was slowly added to the mixture and the reaction mixture was left for stirring at room temperature overnight. Upon the reaction completion, as monitored by TLC (100% CH_2Cl_2), the reaction was worked up by adding 50 mL of water, the solution was extracted with 100 mL ethyl acetate for two times, washed with 200 mL water and 200 mL brine, dried over Na_2SO_4 anhydrous, filtered, and concentrated in vacuum. The crude reaction mixture was purified via column chromatography on silica gel eluted with (100% CH_2Cl_2) to afford compound $9_{a,b}$, respectively.

1,1,4,4-Tetrakis(1*H*-Indol-3-yl)Cyclohexane (8_a). $C_{38}H_{32}N_4$, 544.69 g/mol, light green crystals mp. 122–125°C, ESIMS: (m/z) = 543.19 [M^+-H], EI-MS: (m/z) = 544 [M^+] 50%, 427 [M^+-indolyl] 58%, 399 [M^+-indolyl-2CH_2] 100%, 310 [M^+-2indolyl] 25%, 258 [indolyl.C.CH_2.indolyl] 55%, 117 [indolyl] 60%, 90 [Ph.CH] 30%, IR-Spectrum: (ATR,cm^{-1}) = 2923 (CH_2), 3399 (NH), ^{1}H-NMR: (400 MHz, $CDCl_3$) δ (ppm): 2.06 (s, 4H), 2.09–2.14 (m, 2H), 2.18–2.22 (m, 8H), 2.27–2.31 (m, 4H), 2.49–2.62 (m, 2H), 2.65–2.69 (m, 2H), 2.72–2.76 (m, 2H), 6.49 (d, H, J = 8 Hz), 6.60 (d, H, J = 7.5 Hz), 6.84 (t, H, J = 7.6 Hz), 6.98 (t, H, J = 7.2 Hz), 7.05–7.07 (m, H), 7.09–7.21 (m, H), 7.26 (t, H, J = 6.9 Hz), 7.30 (t, H, J = 7.6 Hz), 7.45 (d, H, J = 7.9 Hz), 7.51 (d, H, J = 8.23 Hz), 7.62 (d, H, J = 7.9 Hz), 7.71 (d, H, J = 7.6 Hz), 7.77 (s, H), 7.92 (s, H), 8.23 (s, 2H, 2NH), 8.46 (s, 2H, 2NH), ^{13}C-NMR: (100 MHz, $CDCl_3$) δ (ppm): 33.61 (CH_2), 33.92 (CH_2), 37.05 (CH_2), 38.09 (CH_2), 51.85 (C), 60.40 (C), 110.78, 111.20, 111.39, 111.73, 115.48, 117.98, 118.13, 119.42, 119.59, 119.66, 119.73, 119.98, 120.28, 120.38, 120.81, 120.93, 121.02, 121.28, 121.38, 121.99, 122.33, 124.28, 125.99, 127.78, 128.65, 134.62, 135.66, 136.02, 136.94, 136.99, 137.08, 137.18, 141.35, 143.62, R_f 0.66 (CH_2Cl_2), Yield: (447 mg), 82%.

1,1,4,4-Tetrakis(5-Chloro-1*H*-Indol-3-yl)Cyclohexane (8_b). $C_{38}H_{28}Cl_4N_4$, 682.47 g/mol, white powder mp. 320–323°C, ESIMS: (m/z) = 681.11 [M^+-H], IR: (ATR, cm^{-1}) = 1194 (CCl), 2993 (CH_2), 3373 (NH), ^{1}H-NMR:

(400 MHz, DMSO-d_6) δ (ppm): 2.48–2.53 (m, 8H, 4CH_2), 6.89 (dd, 4H, J = 1.9, 8.6 Hz), 7.22 (d, 4H, J = 7.9 Hz), 7.28 (d, 4H, J = 8.6 Hz), 7.37–7.49 (m, 4H), 10.98 (s, 4H, 4NH), ^{13}C-NMR: (100 MHz, DMSO-d_6) δ (ppm): 28.39 (CH_2), 30.54 (CH_2), 47.62 (C), 48.57 (C), 99.88, 112.92, 119.37, 120.20, 122.15, 126.71, 135.49, 147.08, EA: calcd. C, 66.88; H, 4.14; N, 8.21. Found: C, 66.79, H, 4.20, Cl, 20.82, N, 8.25, R_f: 0.72 (CH_2Cl_2), Yield: (594 mg), 87%.

Procedure of the Preparation of the Spirocyclic Structure (11). In a round bottom flask containing 50 mL of MeOH 2 mmol (0.65 g) of diindolylmethane, derivative 10 was added under stirring until it completely dissolved. Cyclohexane-1,4-dione (1 mmol, 0.112 g) was added to the reaction mixture. When the reaction solution became clear, few drops of conc. H_2SO_4 were added slowly. The reaction solution became pink, and the color turned to dark violet by leaving it stirring under reflux for 1 h. Upon the reaction completion as monitored by TLC (100% CH_2Cl_2), the reaction was worked up by adding 50 mL of water, neutralized by NH_4OH, extracted with 200 mL ethyl acetate, for two times washed with 200 mL water and 200 mL brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The crude reaction mixture was purified via column chromatography on silica gel eluted with (30% EtAc/hexane) to afford compound 11 in a moderate yield 52% as light pink powder, mp 149–152°C, $C_{52}H_{40}N_4$, 720.90 g/mol, ESIMS 719.29[M^+-H], EI-MS: 720 [M^+] 32%, 322 [3,3'-(phenylmethylene)bis (1H-indole)] 100%, 245 [indolyl.CH.indolyl] 75%, 117 [indolyl] 75%, 90 [Ph.CH] 31%, IR(ATR,cm^{-1}): 3409 (NH), ^{1}H-NMR(400 MHz,acetone-d_6): δ (ppm): 2.03 (t, 4H, 2CH_2, J = 7Hz), 2.27(t, 4H, 2CH_2, J = 11.4Hz), 5.91(s, 2H, 2CH), 6.79(s, 2H), 6.88(t, 2H, J = 7.5Hz), 7.04(t, 4H, J = 7.6Hz), 7.11-7.20(m, 4H), 7.25(t, 4H, J = 7.5Hz), 7.35(dd, 4H, J = 7.9, 15.8Hz), 7.38(d, 4H, J = 8Hz), 7.47(t, 2H, J = 8.8Hz), 9.94(s, br., 2H, 2NH), ^{13}C-NMR(100 MHz, acetone-d_6)δ(ppm): 26.69(CH_2), 26.96(CH_2), 29.66(CH), 29.69(C), 110.22, 111.73, 117.21, 118.48, 120.39, 122.24, 123.27, 125.58, 125.65, 126.72, 127.82, 128.22, 128.50, 128.82, 128.84, 129.46, 130.09, 130.86, 130.89, 134.11, 137.03, 140.96, R_f 0.97 (CH_2Cl_2).

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