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Synthesis of arylpiperazine substituted bisindolylmethanes as possible pharmacologically active new compounds

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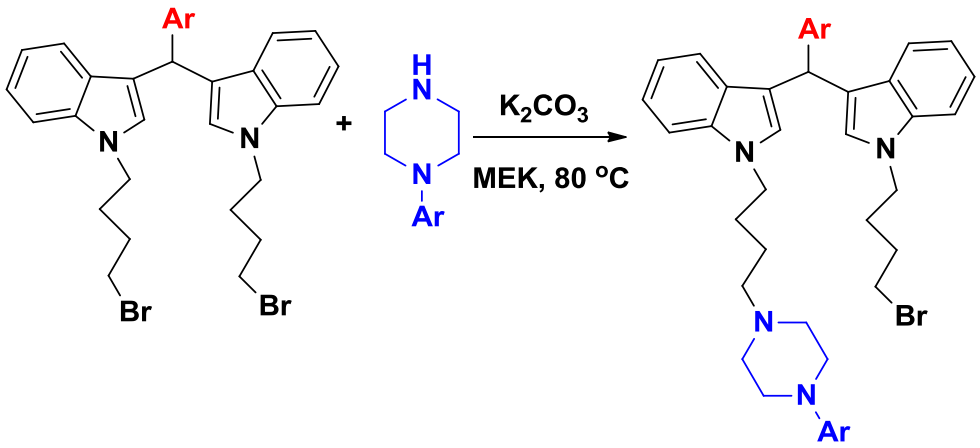
Abstract

Nitrogen containing heterocyclic rings with a piperazine group are valuable target compounds in medicinal chemistry due to their diversified biological activities. In recent years, many organocatalytic/metal free synthetic pathways towards bisindolylmethanes have been reported.[1-3] In the present work, we combined bisindolylmethanes with arylpiperazines using hydrophobic moiety (alkyl chain) to obtain heterocycles that can be evaluated in pharmacologically and may be more active than the already active bisindolylmethane alkaloids.



Keywords: Arylpiperazines, bisindoylmethanes, DBDMH, biologically active molecules

Introduction

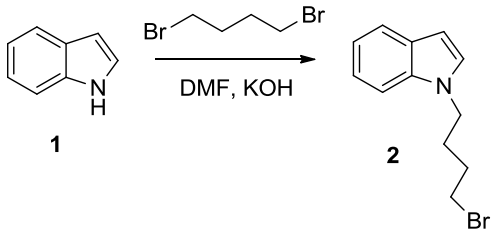
Bisindolylmethanes constitute an important class of heterocyclic compounds containing an indole ring and exhibiting a variety of pharmacological activities such as antifungal, antihyperglycemic, anti-inflammatory, antibacterial, anti-cancer, antimicrobial and anti-leishmanial activities, including enzyme inhibition activity.[4-7] Some of them are accountable for beneficial estrogen metabolism and induce apoptosis in cancer cells of human.[8] They also exhibit inhibitory activity against bladder cancer[9] and renal cell carcinoma growth[10] and inhibit lung[11] and colon cancers.[12] Some bisindolylmethanes showed carbonic anhydrase II inhibitor.[13] On the other hand, dietary nature indoles like 3,3'-diindolylmethane[14] that are generated from cruciferous vegetables can both stimulate apoptosis and confer protection against DNA damage in human colon cell lines.

The most common method for the synthesis of BIMs involves consecutive nucleophilic addition of two molecules of indole (nucleophile) to an aldehyde (electrophile) as a one-pot reaction in the presence of a number of catalysts like Brønsted, Lewis acids such as $LiClO_4$, $In(OTf)_3$, $Dy(OTf)_3$, $Sc(OTf)_3$, CAN, $ZrOCl_2$, $InCl_3$, heteropoly acids, ionic liquids, surfactants.[15-17]

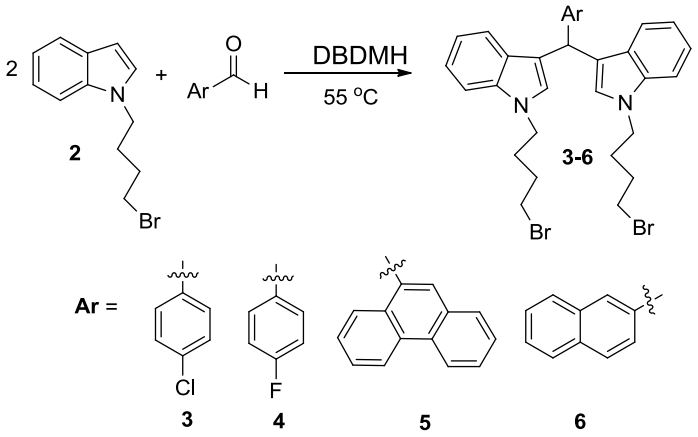
In our previous work, several UV-active bis(indolyl)methanes were prepared in the presence of 1,3-dibromo-5,5-dimethylhydantoin (DBDMH)[18] and the UV-absorbing activity were investigated both in solution and polymer substrate. This study focuses on design and discovery of new bisindolylmethanes including arylpiperazine group. We think that these compounds could show various biological activities and even be employed in vivo studies owing to the fact that they carry two biologically important structural units, namely, the bisindolylmethane and a 1-arylpiperazinyl unit.

Results and Discussion

1*H*-Indole (**1**) react with 1,4-dibromobutane react to afford 1-(4-bromobutyl)-1*H*-indole (**2**)[19] which under treatment with *p*-chlorobenzaldehyde, *p*-fluorobenzaldehyde, phenanthrene-9-carbaldehyde and 2-naphtaldehyde, respectively, in the presence of 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) leads to new compounds **3–6** in good yields (Schemes 1 and 2).

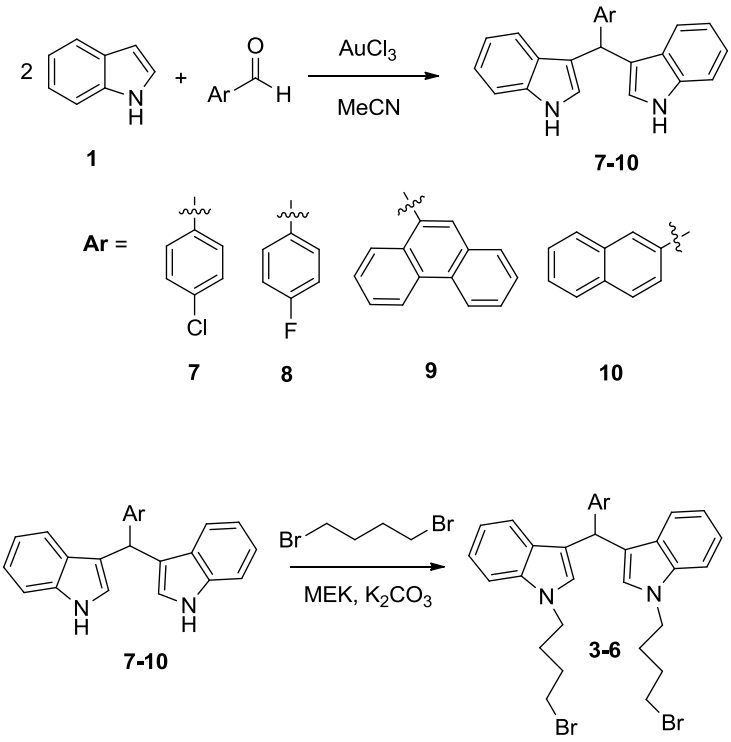


Scheme 1. Preparation of **2**.



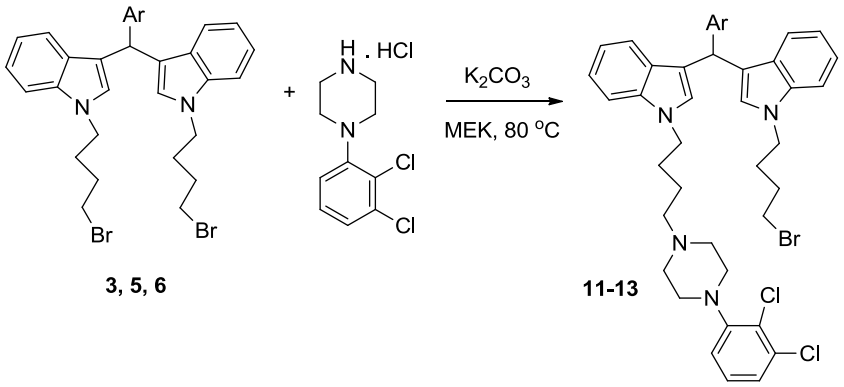
Scheme 2. Synthesis of **3-6**.

Alternatively, reaction of 1-*H*-indole and aldehydes in the presence of gold chloride III ($AuCl_3$) as catalyst, in acetonitrile under nitrogen atmosphere resulted to the formation of compounds **3-6** in higher yields (Scheme 3).



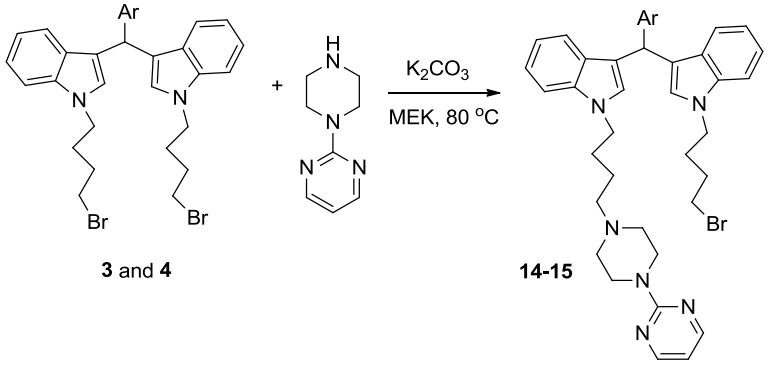
Scheme 3. Synthesis of **3-6**.

Compounds **3**, **5** and **6,** respectively reacted with 2 moles of 1-(2,3-dichlorophenyl)piperazine hydrochloride with K_2CO_3 in MEK to give new derivatives **11-13** (Scheme 4). Spectroscopic studies showed that one piperazine ring was present in the product, and the reactions were repeated a few times.



Scheme 4. Synthesis of **11-13**.

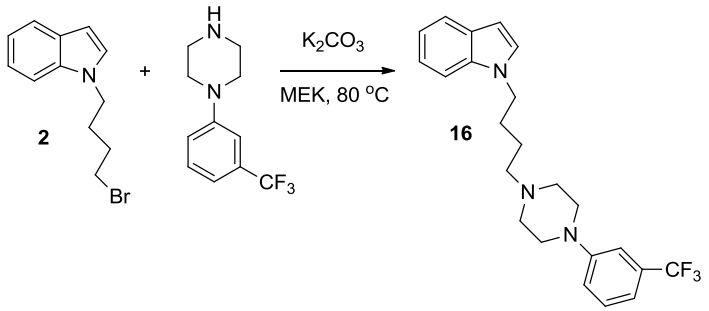
Furthermore, compounds **3** and **4** were reacted with 2 moles of 2-(piperazin-1-yl)pyrimidine under same conditions to give compounds **14** and **15** (Scheme 5).



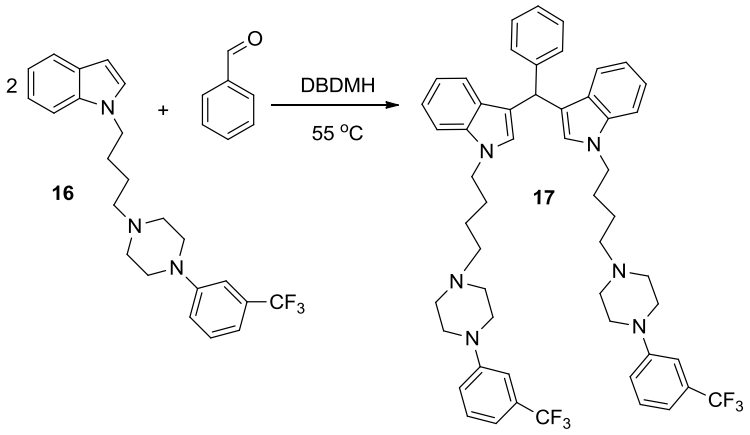
Scheme 5. Synthesis of **14-15**.

The mono piperazinyl substitution pattern in compounds **14** and **15** was confirmed primarily by ^{1}H NMR spectroscopy. Equivalent protons adjacent to the nitrogens in the piperazine ring showed a doublet for two protons at 8.30-8.32 ppm in the spectra. The structures were also supported by HRMS results.

Initially, we also tried to attach the piperazine ring to compound **2** and then to obtain new bisindolylmethanes. According to literature procedure[20] 1-(3-trifluoromethyl)piperazine has been used to obtain compound **16** (Scheme 6). Subsequently, reaction of two moles of compound **16** with benzaldehyde led to the formation of compound **17** in low yield (Scheme 7). All the new compounds were characterized with ^{1}H NMR, ^{13}C NMR, FTIR and LC-MSMS(Qtof) spectral data.



Scheme 6. Preparation of **16**.



Scheme 7. Synthesis of **17**.

Conclusions

It is well known that bisindoylmethane alkoloids have shown a wide spectrum of pharmacological activities that have been successfully screened for especially anti-cancer, antimicrobial, anti-inflammatory, antiviral and anti-leishmanial activities. On the other hand, aryl piperazines themselves are currently used as medicines and exhibit a wide range of activity in combination with various groups. Herein, we combined two important groups, bisindolylmethane and aryl piperazine with a hydrophobic chain for future activity studies. We anticipate significant biological activity from these substrates.

Experimental Section

General. All reagents were purchased from Aldrich or Merck and were used without further purification. The solvents were dried and distilled according to standard procedures. All melting points were determined on a Gallenkamp digital thermometer, are uncorrected. Reactions were monitored using TLC. Visualizations of the chromatograms were performed either with UV light or vanillin stain.

IR spectra were obtained with a Perkin Elmer Spectrum One FTIR Spectrometer and are reported in terms of the frequency of absorption (cm^{-1}). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance III-500 MHz NMR spectrometer relative to tetramethylsilane (δ = 0.00 ppm), with coupling constant (*J*) values in Hertz (Hz). Peak multiplicities are designated by the following abbreviations: s, singlet; d, doublet; dd, double doublet; t, triplet; pt, pentet; dt, double triplet; m, multiplet; br, broad. Mass spectra were measured on an Agilent 6890N/5973 GC/IMSD system or LCMS 6400 Series Triple Quadrupole B.08.02 (B8260.0). High-resolution mass spectra were acquired in the positive ion mode using an Agilent G6530B TOF/Qtof Mass spectrometer.

General procedure for synthesis of compounds (3 - 6). Compound **2** (2 mmol), aromatic aldehyde (1 mmol) (*p*-chlorobenzaldehyde, *p*-fluorobenzaldehyde, phenanthrene-9-carboxaldehyde or 2-naphthaldehyde, respectively) and 1,3-dibromo-5,5-dimethyl hydantoin (DBDMH) (0.005 mmol) were stirred at 55 °C for 16 hours without any solvent. After completion of the reaction with TLC control, crude products were purified by column chromatography.

3,3'-((4-Chlorophenyl)methylene)bis(1-(4-bromobutyl)-1*H*-indole) (3). Pink solid (438 mg, 70% isolated yield). mp 50 °C. R_f = 0.58 (1:5, ethyl acetate/*n*-hexane). FTIR (KBr, cm^{-1}): 3046, 2937, 2872, 1611 (C=C), 1547 (C=C), 1487, 1465, 1088, 798, 736, 702. ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H 1.74-1.80 (4H, m, CH_2), 1.89-1.95 (4H, m, CH_2), 3.31 (4H, t, *J* 6.62 Hz, CH_2), 4.05 (4H, dt, *J* 2.52 and *J* 6.62 Hz, CH_2), 5.83 (1H, s, C*H*), 6.51 (2H, s, =C*H*), 6.99 (2H, dt, *J* 0.94 and *J* 7.88 Hz, Ar*H*), 7.18 (2H, dt, *J* 0.94 and *J* 7.88 Hz, Ar*H*), 7.24-7.26 (4H, m, Ar*H*), 7.31 (4H, dd, *J* 8.19 and *J* 12.29 Hz, Ar*H*). ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C 28.7 (2x*C*H_2), 29.9 (2x*C*H_2), 32.9 (2x*C*H_2), 39.5 (*C*H), 45.3 (2x*C*H_2), 109.2 (2x*C*Ar), 117.9 (*C*Ar), 118.8 (*C*Ar), 120.0 (2x*C*Ar), 121.6 (*C*Ar), 127.0 (4x*C*), 127.4 (*C*Ar), 128.3 (2x *C*Ar), 130.0 (2x *C*Ar), 131.7 (2x*C*), 131.8 (*C*) 136.6 (2x*C*Ar), 142.7 (*C*). HRMS for $C_{31}H_{31}Br_2ClN_2$ calculated: 626.8522; Found 627.0408 $[M+H]^+$.

3,3'-((4-Fluorophenyl)methylene)bis(1-(4-bromobutyl)-1*H*-indole) (4). Dark pink solid (372 mg, 61% isolated yield). mp 53 °C. R_f = 0.56 (1:3, ethyl acetate/*n*-hexane). FTIR (KBr, cm^{-1}): 3046, 2922, 2851, 1601 (C=C), 1547 (C=C), 1504, 1479, 1465, 1092, 805, 783, 737. ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H 1.78 (4H, pt, *J* 6. 93 Hz, CH_2), 1.92 (4H, pt, *J* 6.93 Hz, CH_2), 3.31 (4H, t, *J* 6.62 Hz, CH_2), 4.04 (4H, dt, *J* 2.20 and *J* 6.62 Hz, CH_2), 5.84 (1H, s, C*H*), 6.51 (2H, s, =C*H*), 6.94-7.00 (4H, m, Ar*H*), 7.18 (2H, t, *J* 7.25 Hz, Ar*H*), 7.27 (2H, dt, *J* 2.20 and *J* 5.67 Hz, Ar*H*), 7.30 (2H, d, *J* 8.19 Hz, Ar*H*), 7.33 (2H, d, *J* 7.88 Hz, Ar*H*). ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C 28.7 (2x*C*H_2), 29.9 (2x*C*H_2), 32.9 (2x*C*H_2), 39.4 (*C*H), 45.3 (2x*C*H_2), 109.2 (2x*C*Ar), 114.8 (*C*Ar), 115.0 (*C*Ar), 118.3 (*C*), 118.8 (2x*C*Ar) 120.1 (2x*C*Ar), 121.6 (2x*C*Ar), 127.0 (2x*C*Ar), 127.4 (2x*C*), 129.9 (*C*Ar), 130.0 (*C*Ar), 136.6 (2x*C*), 139.8 (*C*), 160.4 (*C*), 162.3 (*C*). LCMS for $C_{31}H_{31}Br_2FN_2$ calculated: 608.0837; Found 609.1000 $[M+H]^+$.

3,3'-(Phenanthren-9-ylmethylene)bis(1-(4-bromobutyl)-1*H*-indole) (5). Pink solid (393 mg, 57% isolated yield). mp 89 °C. R_f = 0.45 (1:5, ethyl acetate/*n*-hexane). FTIR (KBr, cm^{-1}): 3015, 2961, 2921, 2851, 1654 (C=C), 1610 (C=C), 1545, 1465, 1446, 1081, 864, 796, 747, 728. ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H 1.69 (4H, pt, *J* 6.62 Hz, CH_2), 1.88 4H, (pt, *J* 6.62 Hz, CH_2), 3.25 (4H, t, *J* 6.62 Hz, CH_2), 4.02 (4H, t, *J* 6.62 Hz, CH_2), 6.49 (2H, s, =C*H*), 6.63 (1H, s, C*H*), 6.98 (2H, dt, *J* 0.94 and *J* 7.88 Hz, Ar*H*), 7.20 (2H, dt, *J* 0.94 and *J* 8.19 Hz, Ar*H*), 7.33 (2H, d, *J* 8.19 Hz, Ar*H*), 7.42 (2H, d, *J* 7.88 Hz, Ar*H*), 7.44-7.50 (3H, m, Ar*H*), 7.58-7.64 (3H, m, Ar*H*), 8.17 (1H, d, *J* 8.19 Hz, Ar*H*), 8.69 (1H, d, *J* 8.19 Hz, Ar*H*), 8.76 (1H, d, *J* 8.19 Hz, Ar*H*). ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C 28.7 (2x*C*H_2), 29.7 (*C*H_2), 29.9 (2x*C*H_2), 32.9 (2x*C*H_2), 38.9 (*C*H), 45.2 (*C*H_2), 109.2 (2x*C*Ar), 117.7 (2x*C*Ar), 118.8 (*C*Ar), 120.1 (*C*Ar), 121.5 (2x*C*Ar), 122.3 (*C*Ar), 122.9 (*C*Ar), 125.1 (*C*Ar), 125.9 (*C*Ar), 126.1 (*C*Ar), 126.3 (*C*Ar), 126.5 (*C*Ar), 126.7 (*C*Ar), 127.7 (2x*C*), 128.0 (2x*C*Ar), 128.7 (2x*C*Ar), 129.5 (*C*Ar), 129.8 (*C*), 130.8 (*C*), 131.3 (*C*), 131.7 (*C*), 136.7 (2x*C*), 137.8 (*C*). LCMS for $C_{39}H_{36}Br_2N_2$ calculated: 690.1245; Found 691.1000 $[M+H]^+$.

3,3'-(Naphthalen-2-ylmethylene)bis(1-(4-bromobutyl)-1*H*-indole) (6). Light pink solid (531 mg, 83% isolated yield). mp 142 °C. R_f = 0.45 (1:5, ethyl acetate/*n*-hexane). FTIR (KBr, cm^{-1}): 3126, 3048, 2940, 2877, 1610 (C=C), 1601 (C=C), 1549, 1478, 1466, 1444, 1434, 1096, 830, 804, 778, 766, 739. ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H 1.78 (4H, pt, *J* 6.62 Hz, CH_2), 1.92 (4H, pt, *J* 6.62 Hz, CH_2), 3.31 (4H, t, *J* 6.62 Hz, CH_2), 4.03-4.07 (4H, m, CH_2), 6.03 (1H, s, C*H*), 6.54 (2H, s, =C*H*), 6.97 (2H, dt, *J* 0.94 and *J* 7.88 Hz, Ar*H*), 7.18 (2H, dt, *J* 0.94 and *J* 8.19 Hz, Ar*H*), 7.31 (2H, d, *J* 8.19 Hz, Ar*H*), 7.39 (2H, d, *J* 7.88 Hz, Ar*H*), 7.42 (1H, dd, *J* 1.26 and *J* 3.15 Hz, Ar*H*), 7.43 (1H, d, *J* 9.45 Hz, Ar*H*), 7.50 (1H, dd, *J* 1.57 and *J* 8.19 Hz, Ar*H*), 7.72-7.74 (2H, m, Ar*H*), 7.77 (1H, d, *J* 8.51 Hz, Ar*H*), 7.80-7.82 (1H, m, Ar*H*). ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C 28.7 (2x*C*H_2), 30.0 (2x*C*H_2), 33.0 (2x*C*H_2), 40.2 (*C*H), 45.3 (2x*C*H_2), 109.1 (2x*C*Ar), 118.2 (2x*C*Ar), 118.8 (2x*C*Ar), 120.2 (2x*C*Ar), 121.5 (2x*C*Ar), 125.2 (*C*Ar), 125.6 (*C*Ar), 126.7 (*C*Ar), 127.3 (*C*Ar), 127.4 (*C*Ar), 127.5 (*C*Ar), 127.6 (2x*C*Ar), 127.7 (2x*C*Ar), 127.9 (*C*Ar), 132.3 (2x*C*), 133.5 (*C*), 136.6 (*C*), 141.7 (*C*). LCMS for $C_{35}H_{34}Br_2N_2$ calculated: 640.1088; Found 640.9000 $[M+H]^+$.

General procedure for synthesis of compounds (7 - 10). To a solution of the indole (3 mmol) and aryl aldehyde (1 mmol) in MeCN (2.5 mL) was added a solution of $AuCl_3$ (1 mol%) in MeCN (1 mL) under an atmosphere of nitrogen. After stirring the reaction mixture at r.t. for 12 h, it was filtered to remove insoluble

impurities. The residue was purified by silica gel column chromatography (100-200 mesh silica gel, hexane-EtOAc, 95:5) to afford the products.

General procedure for synthesis of compounds (11 - 13). A mixture of compound **3**, **5** or **6** (1 mmol), 1-(2,3-dichlorophenyl)piperazine hydrochloride (2 mmol), and anhydrous K_2CO_3 (2 mmol) in MEK (50 mL) was heated at 80 ^{o}C for 16 h. After completion of the reaction with TLC control, the solvent was evaporated and the residue was purified by column chromatography using ethyl acetate/*n*-hexane as the eluent to give pure products **11**, **12** or **13**.

1-(4-Bromobutyl)-3-((4-chlorophenyl)(1-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butyl)-1*H*-indol-3-yl)methyl)-1*H*-indole (11). Light pink solid (494 mg, 61% isolated yield). mp 57 °C. R_f = 0.22 (10:1, ethyl acetate/*n*-hexane). FTIR (KBr, cm^{-1}): 3045, 2927, 2852, 2810, 1610 (C=C), 1583 (C=C), 1545, 1487, 1466, 1445, 1087, 795, 737. ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H 1.49 (2H, pt, *J* 6.93 Hz, CH_2), 1.68-1.73 (1H, m, CH_2), 1.76-1.85 (3H, m, CH_2), 1.92 (2H, pt, *J* 6.93 Hz, CH_2), 2.38 (2H, t, *J* 7.56 Hz, CH_2), 2.55 (4H, brs, CH_2), 3.02 (4H, brs, CH_2), 3.31 (1H, t, *J* 6.62 Hz, CH_2), 4.05 (5H, t, *J* 6.93 Hz, CH_2), 5.84 (1H, s, C*H*), 6.53 (2H, s, =C*H*), 6.95 (1H, dd, *J* 2.52 and *J* 6.93 Hz, Ar*H*), 6.99 (2H, t, *J* 7.25 Hz, Ar*H*), 7.15 (2H, d, *J* 7.88 Hz, Ar*H*), 7.18 (2H, t, *J* 7.25 Hz, Ar*H*), 7.25 (4H, d, *J* 3.46 Hz, Ar*H*), 7.30 (1H, d, *J* 8.19 Hz, Ar*H*), 7.32-7.35 (3H, m, Ar*H*). ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C 24.1 (*C*H_2), 28.1 (*C*H_2), 28.7 (*C*H_2), 29.6 (*C*H_2), 29.9 (*C*H_2), 32.9 (*C*H_2), 39.6 (*C*H), 44.3 (*C*H_2), 45.3 (*C*H_2), 46.1 (*C*H_2), 51.2 (*C*H_2), 53.1 (*C*H_2), 57.8 (*C*H_2), 109.2 (*C*Ar), 109.4 (*C*Ar), 117.6 (*C*), 117.9 (*C*), 118.0 (*C*), 118.5 (*C*Ar), 118.7 (*C*Ar), 118.8 (*C*Ar), 120.0 (*C*Ar), 120.1 (*C*Ar), 121.4 (*C*Ar), 121.6 (*C*Ar), 124.5 (*C*Ar), 127.0 (*C*Ar), 127.2 (*C*Ar), 127.3 (*C*), 127.4 (*C*Ar), 127.5 (*C*), 128.3 (2x*C*Ar), 130.0 (2x*C*Ar), 131.7 (*C*), 134.0 (*C*), 136.6 (*C*), 136.7 (*C*), 142.8 (*C*), 151.2 (*C*). HRMS for $C_{41}H_{42}BrCl_3N_4$ calculated: 774.1658; found: 775.1992 $[M+H]^+$.

1-(4-Bromobutyl)-3-((1-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butyl)-1*H*-indol-3-yl)(phenanthren-9-yl)methyl)-1*H*-indole (12). Light pink solid (655 mg, 77.9% isolated yield). mp 76 °C. R_f = 0.63 (20:1, ethyl acetate/*n*-hexane). FTIR (KBr, cm^{-1}): 3052, 2922, 2850, 1611 (C=C), 1577 (C=C), 1465, 1448, 1421, 1043, 780, 740, 726, 713, 671. ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H 1.39 (2H, pt, *J* 7.56 Hz, CH_2), 1.47 (2H, pt, *J* 6.30 Hz, CH_2), 1.76-1.80 (6H, m, CH_2), 2.33 (2H, t, *J* 7.56 Hz, CH_2), 2.47-2.50 (2H, m, CH_2), 2.96-2.99 (2H, m, CH_2), 3.95 (2H, t, *J* 6.30 Hz, CH_2), 3.99-4.04 (6H, m, CH_2), 6.50 (1H, s, =C*H*), 6.52 (1H, s, =C*H*), 6.64 (1H, s, C*H*), 6.91 (1H, dd, *J* 2.20 and *J* 7.25 Hz, Ar*H*), 6.97 (2H, t, *J* 7.88 Hz, Ar*H*), 7.15 (2H, d, *J* 2.20 Hz, Ar*H*), 7.19 (2H, ddd, *J* 2.20 and *J* 4.49 and *J* 9.77 Hz, Ar*H*), 7.32 (1H, d, *J* 8.19 Hz, Ar*H*), 7.35 (1H, d, *J* 8.19 Hz, Ar*H*), 7.41 (2H, dd, *J* 3.78 and *J* 7.78 Hz, Ar*H*), 7.44-7.48 (3H, m, Ar*H*), 7.57-7.62 (3H, m, Ar*H*), 8.18 (1H, d, *J* 8.19 Hz, Ar*H*), 8.68 (1H, d, *J* 8.51 Hz, Ar*H*), 8.75 (1H, d, *J* 8.19 Hz, Ar*H*). ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C 25.8 (*C*H_2), 26.7 (2x*C*H_2), 28.0 (*C*H_2), 29.7 (2x*C*H_2), 36.0 (*C*H), 45.7 (*C*H_2), 46.0 (*C*H_2), 51.0 (*C*H_2), 53.0 (*C*H_2), 57.8 (*C*H_2), 63.8 (*C*H_2), 109.2 (*C*Ar), 109.3 (*C*Ar), 117.3 (*C*), 117.6 (*C*), 118.5 (*C*Ar), 118.6 (*C*Ar), 118.7 (*C*Ar), 120.0 (2x*C*Ar), 121.3 (*C*Ar), 121.4 (*C*Ar), 122.3 (*C*Ar), 122.9 (*C*Ar), 124.6 (*C*Ar), 125.2 (*C*Ar), 125.9 (*C*Ar), 126.1 (*C*Ar), 126.2 (*C*Ar), 126.5 (*C*Ar), 126.7 (*C*Ar), 127.4 (*C*Ar), 127.6 (2x*C*), 127.7 (*C*), 128.1 (2x*C*Ar), 128.7 (*C*Ar), 129.8 (2x*C*), 130.8 (*C*), 131.3 (*C*), 131.7 (*C*), 134.0 (*C*), 136.7 (2x*C*), 137.9 (*C*). HRMS for $C_{49}H_{47}BrCl_2N_4$ calculated: 842.7343; found: 843.2392 $[M+H]^+$.

1-(4-Bromobutyl)-3-((1-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butyl)-1*H*-indol-3-yl)(naphthalen-2-yl)methyl)-1*H*-indole (13). White solid (641.5 g, 81% isolated yield). mp 87 °C. R_f = 0.30 (8:1, ethanol/*n*-hexane) FTIR (KBr, cm^{-1}): 3001, 2926, 2850, 1572 (C=C), 1408, 1012, 738, 673, 646. ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H 1.47 (4H, pt, *J* 7.56 and *J* 14.81 Hz, CH_2), 1.81 (4H, pt, *J* 7.56 and *J* 14.81 Hz, CH_2), 2.36 (4H, t, *J* 7.56 Hz, CH_2), 2.52 (6H, brs, CH_2), 2.99 (6H, brs, CH_2), 6.03 (1H, s, C*H*), 6.57 (2H, s, =C*H*), 6.92 (1H, dd, *J* 2.20 and *J* 6.93 Hz, Ar*H*), 6.95 (2H, t, *J* 7.56 Hz, Ar*H*), 7.12-7.18 (6H, m, Ar*H*), 7.32 (2H, d, *J* 8.19 Hz, Ar*H*), 7.38-7.40 (3H, m, Ar*H*), 7.49-7.51 (1H, m, Ar*H*), 7.70-7.72 (1H, m, Ar*H*), 7.74-7.77 (1H, m, Ar*H*), 7.78-7.80 (1H, m, Ar*H*). ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C 24.1 (*C*H_2), 28.1 (2x*C*H_2), 29.6 (*C*H_2), 40.3 (*C*H), 46.1 (*C*H_2), 51.2 (4x*C*H_2), 53.1 (2x*C*H_2), 57.9 (*C*H_2), 109.2 (*C*Ar), 117.9 (2x*C*), 118.5 (2x*C*Ar), 118.6 (*C*Ar), 120.1 (2x*C*Ar), 121.3 (2x*C*Ar), 124.5 (*C*Ar), 125.2

(*C*Ar), 125.6 (*C*Ar), 126.6 (*C*Ar), 127.4 (2x*C*Ar), 127.5 (*C*Ar), 127.6 (2x*C*), 127.7 (*C*Ar), 127.8 (*C*Ar), 127.9 (*C*Ar), 128.2 (*C*Ar), 130.0 (*C*Ar), 132.2 (*C*), 133.5 (*C*), 133.9 (*C*), 136.6 (2x*C*), 141.9 (*C*), 151.2 (2x*C*). HRMS for $C_{45}H_{45}BrCl_2N_4$ calculated: 792.6756; found: 793.2226 $[M+H]^+$.

General procedure for synthesis of compounds (14 and 15). A mixture of compound **3** or **4** (1 mmol), 2-(piperazin-1-yl)pyrimidine (2 mmol), and anhydrous K_2CO_3 (2 mmol) in MEK (50 mL) was heated at 80 ^oC for 20 h. After completion of the reaction with TLC control, the solvent was evaporated and the residue was purified by column chromatography using ethyl acetate/*n*-hexane (30:1) as the eluent to give pure products **14** or **15**.

1-(4-Bromobutyl)-3-((4-chlorophenyl)(1-(4-(4-(pyrimidin-2-yl)piperazin-1-yl)butyl)-1*H*-indol-3-yl)methyl)-1*H*-indole (14). Red solid (372 mg, 52.6% isolated yield). mp 64 °C. R_f = 0.22 (10:1, ethyl acetate/*n*-hexane). FTIR (KBr, cm^{-1}): FTIR (KBr, cm^{-1}): 3045, 2927, 2852, 2810, 1610 (C=C), 1583 (C=C), 1545, 1487, 1466, 1445, 1087, 795, 737. ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H 1.49 (2H, pt, *J* 7.56 Hz, CH_2), 1.57 (2H, pt, *J* 7.56 Hz, CH_2), 1.81 (4H, pt, *J* 7.56 Hz, CH_2), 2.34 (2H, t, *J* 7.56 Hz, CH_2), 2.42 (4H, t, *J* 5.04 Hz, CH_2), 3.80 (4H, t, *J* 4.41 Hz, CH_2), 4.00-4.06 (6H, m, CH_2), 5.83 (1H, s, C*H*), 6.48 (1H, t, *J* 4.72 Hz, Ar*H*), 6.52 (2H, s, =C*H*), 6.90 (2H, dt, *J* 2.83 and *J* 7.56 Hz, Ar*H*), 7.11 (2H, dt, *J* 1.26 and *J* 8.51 Hz, Ar*H*), 7.17 (4H, brd, *J* 1.26 Hz, Ar*H*), 7.23-7.25 (4H, m, Ar*H*), 8.30 (2H, d, *J* 4.72 Hz, Ar*H*). ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C 23.9 (*C*H_2), 26.0 (2x*C*H_2), 26.8 (*C*H_2), 28.0 (*C*H_2), 29.6 (*C*H_2), 39.6 (*C*H), 43.4 (*C*H_2), 45.7 (*C*H_2), 46.0 (*C*H_2), 52.9 (*C*H_2), 57.9 (*C*H_2), 63.8 (*C*H_2), 109.2 (*C*Ar), 109.3 (*C*Ar), 109.8 (*C*Ar), 117.6 (*C*), 117.8 (*C*), 118.6 (*C*Ar), 118.7 (*C*Ar), 120.0 (2x *C*Ar), 121.4 (*C*Ar), 121.5 (*C*Ar), 127.1 (*C*Ar), 127.2 (*C*Ar), 127.3 (*C*), 127.4 (*C*), 128.3 (2x*C*Ar), 130.0 (2x*C*Ar), 131.6 (*C*), 136.6 (2x*C*), 142.8 (*C*), 157.7 (2x*C*Ar), 161.56 (*C*). HRMS for $C_{39}H_{42}BrClN_6$ calculated: 708.2369; found: 747.2048 $[M+K]^+$.

1-(4-Bromobutyl)-3-((4-fluorophenyl)(1-(4-(4-(pyrimidin-2-yl)piperazin-1-yl)butyl)-1*H*-indol-3-yl)methyl)-1*H*-indole (15). Yellow solid (323 mg, 46.6% isolated yield). mp 84 °C. R_f =0.25 (12:1, ethyl acetate/*n*-hexane) FTIR (KBr, cm^{-1}): 3045, 2932, 2853, 2810, 1583 (C=C), 1546 (C=C), 1504, 1480, 1466, 1445, 1043, 834, 795, 737. ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H 1.48 (2H, pt, *J* 7.33 Hz, CH_2), 1.56 (2H, pt, *J* 6.84 Hz, CH_2), 1.81 (4H, pt, *J* 6.84 Hz, CH_2), 2.33 (2H, t, *J* 7.33 Hz, N-CH_2), 2.40 (4H, t, *J* 5.38 Hz, N-CH_2), 3.78 (4H, t, *J* 5.38 Hz, N-CH_2), 4.01 (2H, t, *J* 6.84 Hz, N-CH_2), 4.04 (4H, t, *J* 6.84 Hz, N-CH_2), 5.84 (1H, s, C*H*), 6.47(1H, t, *J* 4.89 Hz, Ar*H*), 6.52 (2H, brd, *J* 1.95 Hz , =C*H*), 6.94-6.99 (4H, m, Ar*H*), 7.17 (2H, t, *J* 7.82 Hz, Ar*H*), 7.28 (2H, dd, *J* 2.93 and *J* 8.31 Hz, Ar*H*), 7.32-7.36 (4H, m, Ar*H*), 8.32 (2H, d, *J* 4.89 Hz, Ar*H*). ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C 24.0 (*C*H_2), 26.0 (*C*H_2), 26.8 (*C*H_2), 28.1 (*C*H_2), 39.5 (*C*H), 43.6 (2x *C*H_2), 45.7 (*C*H_2), 46.0 (*C*H_2), 53.0 (*C*H_2), 58.0 (*C*H_2), 63.8 (2x *C*H_2), 109.2 (*C*Ar), 109.3 (*C*Ar), 109.8 (*C*Ar), 114.8 (*C*Ar), 114.9 (*C*Ar), 118.0 (*C*), 118.2 (*C*), 118.6 (*C*Ar), 118.7 (*C*Ar), 120.1 (*C*Ar), 120.2 (*C*Ar), 121.4 (*C*Ar), 121.5 (*C*Ar), 127.1 (*C*Ar), 127.2 (*C*Ar), 127.4 (*C*), 127.5 (*C*), 129.9 (*C*Ar), 130.0 (*C*Ar), 136.6 (*C*), 139.9 (*C*), 157.6 (2x*C*Ar), 160.3 (*C*), 161.6 (*C*), 162.3 (*C*). HRMS for $C_{39}H_{42}BrFN_6$ calculated: 693.2675; found: 694.2655 $[M+H]^+$.

Synthesis of 1-(4-(4-(3-(Trifluoromethyl)phenyl)piperazin-1-yl)butyl)-1*H*-indole (16). A mixture of compound **2** (252.15 mg, 1 mmol), 1-(3-(trifluoromethyl)phenyl)piperazine (535.2 mg, 1 mmol), and anhydrous K_2CO_3 (276 mg, 2 mmol) in MEK (10 mL) was heated at 80 ^oC for 16 h. After completion of the reaction with TLC control, the solvent was evaporated and the residue was purified by column chromatography using ethyl acetate/*n*-hexane (1:1) as the eluent to give pure product **16** [15]. White solid (300 mg, 75% isolated yield). bp 523 °C. R_f =0.36 (1:1, ethyl acetate/*n*-hexane) FTIR (KBr, cm^{-1}): 3099, 3053, 2953, 2873, 1611, 1515, 1484, 1463, 1084 (C-N), 763, 738, 718. ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H 1.57 (2H, pt, *J* 7.25 Hz, CH_2), 1.90 (2H, pt, *J* 7.25 Hz, CH_2), 2.42 (2H, t, *J* 7.56 Hz, CH_2), 2.58 (4H, t, *J* 5.04 Hz, CH_2), 3.22 (4H, t, *J* 5.04 Hz, CH_2), 4.17 (2H, t, *J* 7.25 Hz, CH_2), 6.49 (1H, dd, *J* 0.94 and *J* 3.15 Hz, Ar*H*), 7.04 (1H, dd, *J* 2.52 and *J* 8.51 Hz, Ar*H*), 7.07-7.12 (4H, m, Ar*H*), 7.21 (1H, ddd, *J* 1.26 and *J* 8.19 and *J* 15.44 Hz, Ar*H*), 7.32-7.36 (2H, m, Ar*H*), 7.64 (1H, d, *J* 7.88 Hz, Ar*H*). GC-MS (EI, 70 eV) : $C_{23}H_{26}F_3N_3$ *m/z*= 401 $[M]^+$.

Synthesis of 3,3'-(Phenylmethylene)bis(1-(4-(4-(3-8trifluoromethyl)phenyl)piperazin-1-yl)butyl)-1*H*-indole (17). Compound **16** (2 mmol), benzaldehyde (1 mmol) and 1,3-dibromo-5,5-dimethyl hydantoin (DBDMH) (0.005 mmol) were stirred at 55 ^{o}C for 16 hours without any solvent. After completion of the reaction with TLC control, the solvent was evaporated and the residue was purified by column chromatography using ethyl acetate/*n*-hexane (1:1) as the eluent to give pure product **17**. Light pink solid (428 mg, 48% isolated yield). mp 73 °C. R_f = 0.18 (5:1, ethyl acetate/*n*-hexane). FTIR (KBr, cm^{-1}): 3015, 2966, 2923, 2882, 2853, 1609 (C=C), 1494, 1466, 1452, 1098, 782, 740, 695. ^{1}H NMR ($CDCl_3$, 500 MHz): δ_H 1.47 (4H, pt, *J* 7.56 Hz, CH_2), 1.81 (4H, pt, *J* 7.56 Hz, CH_2), 2.34 (4H, t, *J* 7.56 Hz, CH_2), 2.48 (8H, t, *J* 5.04 Hz, CH_2), 3.16 (8H, t, *J* 5.04 Hz, CH_2), 4.04 (4H, t, *J* 6.93 Hz, CH_2), 5.87 (1H, s, C*H*), 6.56 (2H, s, =C*H*), 6.96 (2H, dt, *J* 0.94 and *J* 7.88 Hz, Ar*H*), 7.02 (2H, dd, *J* 2.20 and *J* 8.51 Hz, Ar*H*), 7.06-7.08 (4H, m, Ar*H*), 7.15-7.21 (m3H,, Ar*H*), 7.25-7.28 (3H, m, Ar*H*), 7.30-7.37 (7H, m, Ar*H*). ^{13}C NMR ($CDCl_3$, 125 MHz): δ_C 24.0 (2xCH$_2$), 28.0 (2xCH$_2$), 40.2 (*C*H), 46.0 (2xCH$_2$), 48.5 (4xCH$_2$), 52.8 (4xCH$_2$), 57.8 (2xCH$_2$), 109.2 (2x*C*Ar), 112.0 (*C*Ar), 112.1 (*C*Ar), 115.7 (*C*Ar), 115.8 (*C*Ar), 118.2 (2x*C*), 118.6 (4x*C*Ar), 120.2 (2x*C*Ar), 121.3 (2x*C*Ar), 126.0 (*C*Ar), 127.2 (2x*C*Ar), 127.6 (2x*C*), 128.1 (2x*C*Ar), 128.7 (2x*C*Ar), 129.5 (4x*C*Ar), 131.2 (*C*), 131.5 (*C*), 132.5 (*C*), 136.6 (2x*C*), 144.3 (*C*), 151.3 (*C*). HRMS for $C_{53}H_{56}F_6N_6$ calculated: 891.4548; found: 892.4575 $[M+H]^+$.

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Supplementary Material

New bisindolylmethanes list and IR, ^{1}H-NMR, ^{13}C-NMR, Qtof or LCMS spectra of new compounds.

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