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Lewis Acid–Mediated Arylation of *N*-Protected Bromomethylindoles

Vasudevan Dhayalan, Neelamegam Ramesh, and Arasambattu K. Mohanakrishnan
Department of Organic Chemistry, University of Madras, Guindy Campus, Chennai, India

Abstract: Lewis acid–mediated arylation of *N*-protected 2/3-bromomethylindoles with different types of arenes is reported.

Keywords: Arene, arylation, bromomethylindole, Friedel–Crafts reaction

INTRODUCTION

Over the years, a plethora of substituted indole derivatives have been synthesized for their medicinal activity. During the past 20 years, a variety of indole derivatives have been explored as potential antitubulin agents.[1] In particular, 1-aroyl, 2-aroyl, and 3-aroylindoles have proved to be novel classes of potent tubulin-inhibitory, antimitotic agents.[2] Recently, 3-arylthioindole analogs also been explored as tubulin polymerase inhibitors.[3] Hence, syntheses of different types of substituted indole derivatives are necessitated to unravel their medicinal activity.

RESULTS AND DISCUSSION

In continuation of our work on studies related to the synthetic elaboration of bromomethylindoles,[4] we required different types of arylmethylindoles.

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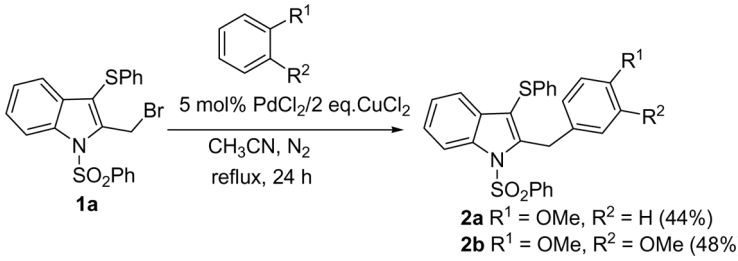
Address correspondence to Arasambattu K. Mohanakrishnan, Department of Organic Chemistry, University of Madras, Guindy Campus, Chennai 600 025, India. E-mail: mohan_67@hotmail.com



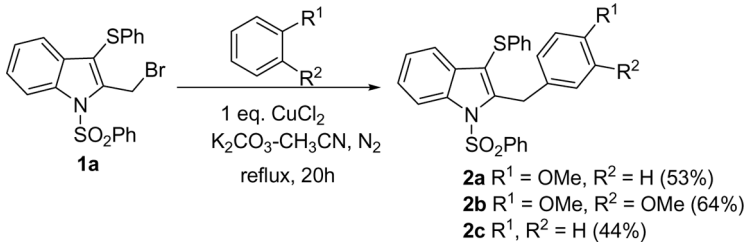
Scheme 1. $PdCl_2$–$CuCl_2$-catalyzed arylation of **1a.**

Over the years, a large number of arylation protocols have been developed for a benzylic system using different types of Pd catalyst.[5] Alternatively, Lewis acid-mediated arylation of benzylalcohol/benzylacetate to synthesize a variety of benzylic systems has also been explored.[6] Recently, Knochel and coworkers reported a copper-mediated arylation of a benzylic system using in situ generated organometallic reagents.[7] Nevertheless, these recent developments are yet to be adapted to the arylation of indolylmethylbromides. In particular, the promising antitubulin activity of various types of aroylindoles prompted us to develop a viable procedure for the synthesis of various types of 2/3-benzylindole analogs. It should be noted that once different types of benzylindoles are in hand, their transformation into the required aroylindoles can be achieved using a published procedure.[8]

Srinivasan and Rajeswaran reported[9] arylation of bromomethylindole **1a** with electron-rich arenes using $PdCl_2$ in acetonitrile at reflux in the presence of $CuCl_2$ to afford the arylated products **2a,b** in moderate yields (Scheme 1).

Because, Lewis acid–mediated arylation of benzyl alcohols is well established, we thought the arylation of bromo compound **1a** could be carried out in the absence of Pd catalyst. Accordingly, when bromo compound **1a** was refluxed with electron-rich arene, anisole, or veratrole in the presence of 1 eq. of anhydrous cupric chloride using K_2CO_3 as base in acetonitrile at reflux, products **2a** or **2b** formed in 53 and 64% yields, respectively. Using anhydrous $CuCl_2$, the arylation of bromomethylindoles **1a** could be carried out with unactivated arenes, namely benzene, to afford product **2c** in 44% yield (Scheme 2). It should be mentioned that the yield of the arylation products **2a,b** isolated using anhydrous $CuCl_2$ alone was found to better than with the expensive $PdCl_2$–$CuCl_2$ system.

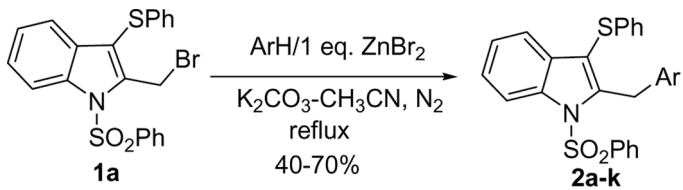
Instead of $CuCl_2$, anhydrous $ZnBr_2$ also effectively catalyzed a smooth arylation of bromo compound **1a** with different types of arenes as well as heteroarenes in acetonitrile at reflux to afford the products in **2a-k** in 40–70% yields (Scheme 3). The results are presented in Table 1.



Scheme 2. $CuCl_2$-catalyzed arylation of bromomethylindoles with arenas.

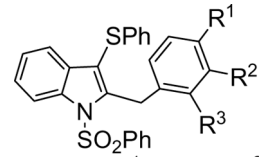
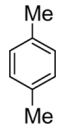
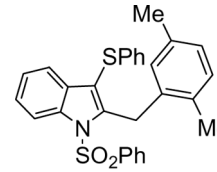
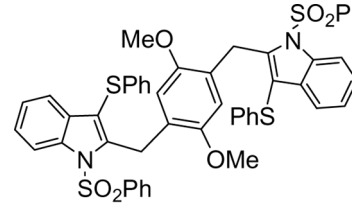
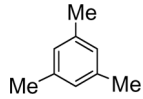
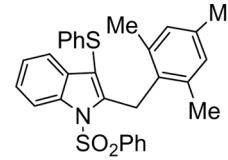
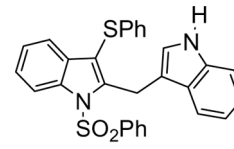
The results of various arylation products **2a-k** obtained using anhydrous $ZnBr_2$ are presented in Table 1. The $ZnBr_2$-mediated arylation of **1a** could be performed with mono-, di-, and trisubstituted arenes using K_2CO_3 as a base in dry acetonitrile at reflux. With the exception of 1,4-dimethoxybenzene (entry 3), in all other cases only the mono-arylation products were isolated. Hetero-arylation of **1a** was performed with indole or thiophene to afford the respective products **2j** or **2k** in low yields (entries 5, 6).

Next, the $ZnBr_2$-mediated veratrylation of different types of bromomethylindoles **3a–g** could be carried out using K_2CO_3 as base in 1,2-dimethoxyethane (DME) at reflux to afford the respective products **4a–g** in 52–73% yields. The type of bromo compounds employed and the resulting arylated products isolated along with their yields are presented in Table 2. The veratrylation could be smoothly performed with 2-bromomethyl **3a–d** as well as 3-bromomethyindoles **3f,g** in acceptable yields. The presence of an electron-withdrawing ester unit at the indole-3-position significantly reduced the yield of arylation product **4a** (entry 1). However, when the ester unit was connected through a vinyl spacer, the arylation yield was found to be the maximum (entry 2). The bis-veratrylation of 2,3-dibromethylindole **3e** could be achieved in 58% yield (entry 5). In comparison to the isomeric bromo compound **3a**, the veratrylation of 2-carbethoxy-3-bromomethylindole **3g** furnished the respective arylated product **4g** in relatively better yields (entry 7).



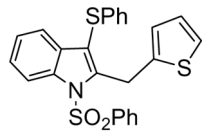
Scheme 3. $ZuBr_2$-catalyzed arylation of **1a** with arenas and heteroarenes.

Table 1. $ZnBr_2$-catalyzed arylation of **1a** with arenas and heteroarenes

Entry	ArH	Time	Arylated product	Yield (%)[a]
1		11 h 6 h 24 h 12 h 15 h 10 h	 **2a** R^1 = OMe, R^2, R^3 =H **2b** R^1, R^2 = OMe, R^3 = H **2c** R^1, R^2 , R^3 = H **2d** R^1, R^2 = Me, R^3 = H **2e** R^1, R^3 = Me, R^2 = H **2f** R^1, R^3 = OMe, R^2 = H	58 70 41 50 56 57
2		17 h	 **2g**	58
3		8 h	 **2h**	60
4		13 h	 **2i**	48
5		12 h	 **2j**	42

(*Continued*)

Table 1. Continued

Entry	ArH	Time	Arylated product	Yield (%)[a]
6		9 h	 **2k**	40

[a]Isolated yield after column chromatography.

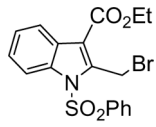
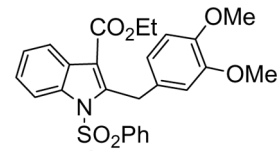
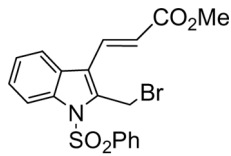
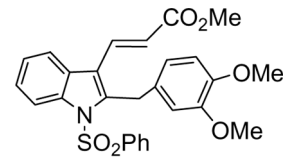
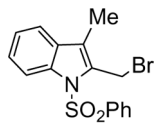
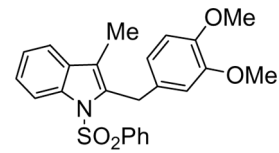
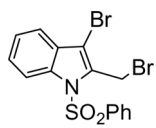
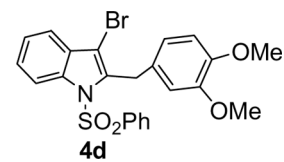
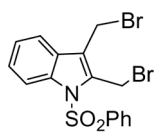
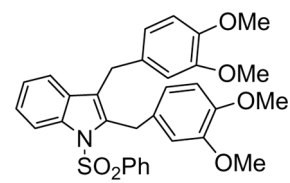
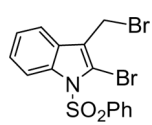
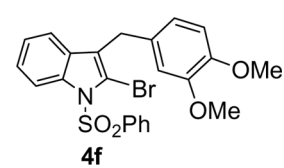
Finally, the $ZnBr_2$-mediated arylation of bromomethylindole **1a** with veratrole was carried out using six different types of Lewis acids (Scheme 4), and the results obtained are presented in Table 3. Among the various types of Lewis acids employed for veratrylation of **1a**, the maximum 76% yield of arylated product **2b** could be obtained using 20 mol% of $InBr_3$ in dry DME at reflux for 5 h. The yield of **2b** obtained was almost comparable with 1 eq. of $ZnBr_2$ as well as 20 mol% $InBr_3$. Even though the veratylation could be performed with other Lewis acids such as $CuCl_2$, $NiBr_2$, $FeCl_3$, and $Sc(OTf)_3$, the yield of the arylated product **2b** obtained was found to be somewhat less. Additionally, these Lewis acids also required longer reaction period (13–20 h) for completion of the veratrylation reaction (entries 3–6).

In conclusion, we have synthesized a wide variety of 2/3-benzylindole via $ZnBr_2$-mediated arylation of the respective indolylmethyl bromides. The arylation procedure developed herein is simple, clean, and economically viable for the synthesis of various types of arylmethylindoles. Further work on transformation of benzylindoles into the corresponding aroyl indoles and the exploration of their antitubulin activity is in progress.

EXPERIMENTAL

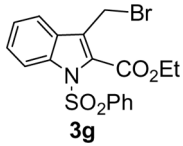
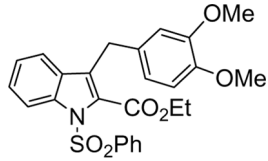
All melting points were uncorrected. Reagents were purchased from commercial sources and used as received without purification. Solvents were dried by standard procedures. Column chromatography was carried out on silica gel (grade 60, mesh size 230–400, Merck). IR spectra were recorded on a Shimadzu Fourier transform infrared (FT-IR) 8300 instrument. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ using tetramethylsilane (TMS) as an internal standard on a Jeol GSX 400 and Bruker-300 spectrometers. Chemical shift values were quoted in parts per million (ppm) and coupling constants were quoted in hertz (Hz).

Table 2. $ZnBr_2$-catalyzed arylation of bromomethylidnoles **3a–g** with veratrole

Entry	Bromomethylindoles	Time	Arylated product	Yield (%)[a]
1	 **3a**	20 h	 **4a**	52
2	 **3b**	10 h	 **4b**	73
3	 **3c**	7 h	 **4c**	67
4	 **3d**	15 h	 **4d**	70
5	 **3e**	8 h	 **4e**	58
6	 **3f**	12 h	 **4f**	73

(*Continued*)

Table 2. Continued

Entry	Bromomethylindoles	Time	Arylated product	Yield (%)[a]
7	 **3g**	6 h	 **4g**	68

[a]Isolated yield after column chromatography.

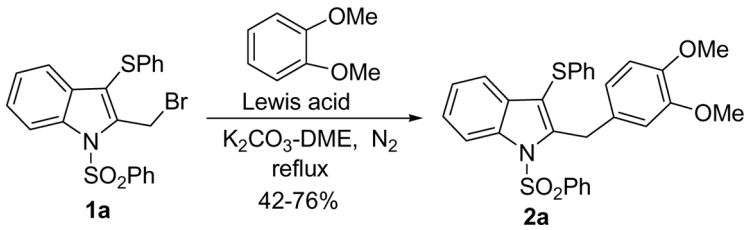
Chemical shift multiplicities were reported as s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. Mass spectra were recorded on a Jeol DX 303 HF spectrometer. Elemental analyses were carried out on Perkin-Elmer series II 2400 (IIT Madras) equipment.

General Procedure for Arylation of Bromomethylindole 1a Using $CuCl_2$

$CuCl_2$ (1.09 mmol), K_2CO_3 (2.18 mmol), and arene (2.18 mmol) were added to a solution of substrate **1a** (1.09 mmol) in dry acetonitrile (20 mL), The reaction mixture was then refluxed for 20 h under an N_2 atmosphere. It was then poured over ice water (30 mL) containing 1 mL of conc. HCl, extracted with $CHCl_3$ (3×10 mL), and dried (Na_2SO_4). Removal of solvent followed by column chromatographic purification (hexane–EA; 95:5) afforded the arylation product.

General Procedure for Arylation of Bromomethylindole 1a Using $ZnBr_2$

$ZnBr_2$ (1.09 mmol), K_2CO_3 (2.18 mmol), and arene (2.18 mmol) were added to a solution of substrate **1a** (1.09 mmol) in dry acetonitrile



Scheme 4. Lewis acid–catalyzed arylation of **1a** with veratrole.

Table 3. Lewis acid–catalyzed arylation of **1a** with veratrole

Entry	Lewisacid	Time	Yield of **2a** (%)[a]
1	20 mol% $InBr_3$	5 h	76
2	1eq. $ZnBr_2$	6 h	70
3	1eq. $CuCl_2$	20 h	64
4	1eq. $FeCl_3$	17 h	55
5	1eq. $NiBr_2$	24 h	42
6	1eq. $Sc(OTf)_3$	13 h	50

[a]Isolated yield after column chromatography.

(20 mL). The reaction mixture was then refluxed for specified time (refer to Table 1) under an N_2 atmosphere. It was then poured over ice water (30 mL) containing 1 mL of conc. HCl, extracted with $CHCl_3$ (3×10 mL), and dried (Na_2SO_4). Removal of solvent followed by column chromatographic purification (hexane–EA; 95:5) afforded the arylation product.

General Procedure for Arylation of Bromo Compounds 3a–g Using $ZnBr_2$

$ZnBr_2$ (1.09 mmol), K_2CO_3 (2.18 mmol), arene (2.18 mmol) were added to a solution of substrate **3a–g** (1.09 mmol) in dry DME (20 mL). The reaction mixture was then refluxed for specified time (refer to Table 2) under an N_2 atmosphere. It was then poured over ice water (30 mL) containing 1 mL of conc. HCl, extracted with $CHCl_3$ (3×10 mL), and dried (Na_2SO_4). Removal of solvent followed by column chromatographic purification (hexane–EA; 94:6) afforded the arylation product.

1-Phenylsulfonyl-2-(4-methoxybenzyl)-3-(phenylthio)-1*H*-indole (2a)

Yield: 0.30 g (58%). Mp: 114–115 °C (lit.[9] 117°C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.74 (s, 3H, $-OCH_3$), 4.65 (s, 2H, $-CH_2$), 6.69 (d, $J = 8.4$ Hz, 2H, Ar-H), 6.96 (d, $J = 8.0$ Hz, 2H, Ar-H), 7.05–7.12 (m, 5H, Ar-H), 7.20–7.24 (m, 3H, Ar-H), 7.33–7.47 (m, 5H, Ar-H), 8.19 (d, $J = 8.4$ Hz, 1H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 31.28, 55.26, 112.32, 113.76, 115.11, 120.03, 124.19, 125.27, 125.45, 126.48, 126.63, 128.79, 128.91, 129.75, 130.10, 130.50, 133.54, 136.21, 136.70, 138.43, 144.76, 158.22.

1-Phenylsulfonyl-2-(3, 4-dimethoxybenzyl)-3-(phenylthio)-1*H*-indole (2b)

Yield: 0.39 g (70%). Mp:171–172 °C (lit.[9] 173–174°C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.62 (s, 3H, $-OCH_3$), 3.85 (s, 3H, $-OCH_3$), 4.70 (s, 2H, $-CH_2$), 6.69 (d, $J = 8.1$ Hz, 2H, Ar-H), 6.77 (d, $J = 8.2$ Hz, 1H, Ar-H), 7.01 (d, $J = 6.9$ Hz, 2H, Ar-H), 7.09–7.18 (m, 3H, Ar-H), 7.22–7.28 (m, 3H, Ar-H), 7.35–7.51 (m, 5H, Ar-H), 8.25 (d, $J = 8.4$ Hz, 1H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 31.68, 55.67, 55.98, 111.21, 112.13, 112.35, 115.20, 120.13, 121.05, 124.25, 125.37, 125.51, 126.44, 128.88, 128.95, 130.49, 130.55, 133.59, 136.24, 136.78, 138.51, 144.57, 147.68, 148.84.

1-Phenylsulfonyl-2-benzyl-3-(phenylthio)-1*H*-indole (2c)

Yield: 0.20 g (41%). Mp: 120–122 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.78 (s, 2H, $-CH_2$), 7.02 (d, $J = 6.6$ Hz, 2H, Ar-H), 7.12–7.30 (m, 11H, Ar-H), 7.37–7.46 (m, 4H, Ar-H), 7.51 (t, $J = 7.8$ Hz, 1H, Ar-H), 8.25 (d, $J = 8.4$ Hz, Hz, 1H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 32.23, 112.76, 115.15, 120.11, 124.25, 125.35, 125.55, 126.38, 126.55, 126.61, 128.40, 128.77, 128.94, 128.99, 129.49, 130.54, 133.64, 136.18, 136.72, 138.09, 138.40, 144.25. Mass (m/z) %: 455 (M^+, 45%). Anal. calcd. for $C_{27}H_{21}NO_2S_2$: C, 71.18; H, 4.65; N, 3.07%. Found: C, 71.01; H, 4.89; N, 3.27%.

1-Phenylsulfonyl-2-(3,4-dimethylbenzyl)-3-(phenylthio)-1*H*-indole (2d)

Yield: 0.26 g (50%). Mp: 96–98 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.23 (s, 3H, $-CH_3$), 2.43 (s, 3H, $-CH_3$), 4.61 (s, 2H, $-CH_2$), 6.26 (d, $J = 7.8$ Hz, 1H, Ar-H), 6.52 (d, $J = 7.8$ Hz, 1H, Ar-H), 6.98–7.01 (m, 2H, Ar-H), 7.01–7.28 (m, 7H, Ar-H), 7.34–7.46 (m, 4H, Ar-H), 7.49 (d, $J = 7.2$ Hz, 1H, Ar-H), 8.27 (d, $J = 7.8$ Hz, 1H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.78, 20.86, 28.83, 114.97, 119.99, 124.09, 125.22, 125.46, 126.47, 126.58. 126.64, 127.19, 128.76, 128.86, 128.89, 130.37, 130.94, 133.32, 133.43, 135.53, 135.81, 136.29, 136.81, 138.55, 144.02. Mass (m/z) %: 483 (M^+, 52%). Anal. calcd. for $C_{29}H_{25}NO_2S_2$: C, 72.02; H, 5.21; N, 2.90%. Found: C, 72.22; H, 5.50; N, 2.65%.

1-Phenylsulfonyl-2-(2,4-dimethylbenzyl)-3-(phenylthio)-1*H*-indole (2e)

Yield: 0.29 g (56%). Mp: 102 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.14 (s, 3H, $-CH_3$), 2.34 (s, 3H, $-CH_3$), 4.53 (s, 2H, $-CH_2$), 6.17 (d, $J = 7.8$ Hz,

1H, Ar-H), 6.43 (d, $J = 7.8$ Hz, 1H, Ar-H), 6.90–7.11 (m, 8H, Ar-H), 7.17 (d, $J = 7.58$ Hz, 1H, Ar-H), 7.25–7.34 (m, 4H, Ar-H), 7.41 (d, $J = 7.5$ Hz, 1H, Ar-H), 8.19 (d, $J = 8.4$ Hz, 1H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.82, 20.89, 28.86, 112.87, 115.00, 120.03, 124.12, 125.26, 125.49, 126.51, 126.61, 126.66, 127.21, 128.89, 128.93, 130.39, 130.98, 133.36, 133.47, 135.56, 135.84, 136.31, 136.84, 138.56, 144.06. Mass (m/z) %: 483 (M^+, 65%). Anal. calcd. for $C_{29}H_{25}NO_2S_2$: C, 72.02; H, 5.21; N, 2.90%. Found: C, 72.27; H, 5.01; N, 2.63%.

1-Phenylsulfonyl-2-(2,4-dimethoxybenzyl)-3-(phenylthio)-1*H*-indole (2f)

Yield: 0.32 g (57%). Mp: 138–140 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.73 (s, 3H, $-OCH_3$), 3.83 (s, 3H, $-OCH_3$), 4.61 (s, 2H, $-CH_2$), 6.11 (d, $J = 4.8$ Hz, 1H, Ar-H), 6.44 (d, $J = 6.3$ Hz, 2H, Ar-H), 6.95 (d, $J = 5.4$ Hz, Hz, 2H, Ar-H), 7.04–7.09 (m, 3H, Ar-H), 7.24–7.29 (m, 3H, Ar-H), 7.36 (t, $J = 5.7$ Hz, 1H, Ar-H), 7.43–7.48 (m, 2H, Ar-H), 7.57 (d, $J = 5.7$ Hz, 2H, Ar-H), 8.28 (d, $J = 6.3$ Hz, 1H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.86, 55.24, 55.46, 98.38, 103.73, 113.00, 115.08, 119.22, 119.86, 124.05, 125.08, 125.30, 126.48, 126.57, 128.74, 128.99, 130.53, 133.54, 136.32, 136.88, 138.53, 144.06, 157.72, 159.31. Mass (m/z) %: 515 (M^+, 31%). Anal. calcd. for $C_{29}H_{25}NO_4S_2$: C, 67.55; H, 4.89; N, 2.72%. Found: C, 67.31; H, 4.59; N, 2.50%.

1-Phenylsulfonyl-2-(2,5-dimethylbenzyl)-3-(phenylthio)-1*H*-indole (2g)

Yield: 0.30 g (58%). Mp: 154–155 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.89 (s, 3H, $-CH_3$), 2.50 (s, 3H, $-CH_3$), 4.70 (s, 2H, $-CH_2$), 6.13 (s, 1H, Ar-H), 6.88 (d, $J = 7.5$ Hz, 1H, Ar-H), 7.00–7.23 (m, 8H, Ar-H), 7.32–7.46 (m, 5H, Ar-H), 7.60 (d, $J = 7.8$ Hz, 1H, Ar-H), 8.38 (d, $J = 8.4$ Hz, 1H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.02, 21.43, 29.59, 113.36, 115.54, 120.61, 124.65, 125.83, 126.09, 127.17, 127.29, 127.44, 128.55, 129.35, 129.48, 130.64, 130.94, 133.60, 134.11, 135.74, 136.63, 136.95, 137.33, 139.01, 144.44. Mass (m/z) %: 483 (M^+, 49%). Anal. calcd. for $C_{29}H_{25}NO_2S_2$: C, 72.02; H, 5.21; N, 2.90%. Found: C, 72.24; H, 5.40; N, 2.60%.

2,5-Bis[(1-phenylsulfonyl-3-phenylthioindol-2-yl)methyl]-1,4-dimethoxybenzene (2h)

Yield: 0.29 g (60%). Mp: 244–248 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.30 (s, 6H, $-OCH_3$), 4.62 (s, 4H, $-CH_2$), 5.97 (s, 2H, Ar-H), 7.00–7.11 (m,

10H, Ar-H), 7.22–7.25 (m, 6H, Ar-H), 7.38–7.46 (m, 10H, Ar-H), 8.31 (d, $J = 7.8$ Hz, 2H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.34, 55.90, 111.70, 113.16, 115.15, 120.00, 124.12, 125.04, 125.27, 125.48, 126.53, 126.57, 128.90, 130.41, 133.66, 136.30, 136.90, 138.32, 143.48, 150.71. Mass (m/z) %: 892 (M^+, 32%). Anal. calcd. for $C_{50}H_{40}N_2O_6S_4$: C, 67.24; H, 4.51; N, 3.14%. Found: C, 67.06; H, 4.74; N, 3.39%.

1-Phenylsulfonyl-2-(2,4,6-trimethylbenzyl)-3-(phenylthio)-1*H*-indole (2i)

Yield: 0.26 g (48%). Mp: 122 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.92 (s, 6H, $-CH_3$), 2.16 (s, 3H, $-CH_3$), 4.50 (s, 2H, $-CH_2$), 6.58 (s, 2H, Ar-H), 6.69–6.72 (m, 2H, Ar-H), 7.01 (d, $J = 4.5$ Hz, 3H, Ar-H), 7.21 (t, $J = 6.9$ Hz, 1H, Ar-H), 7.33–7.40 (m, 4H, Ar-H), 7.54 (t, $J = 6.6$ Hz, 1H, Ar-H), 7.65–7.68 (m, 2H, Ar-H), 8.34 (d, $J = 6.6$ Hz, 1H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.53, 20.80, 28.79, 111.72, 115.16, 119.84, 124.17, 124.90, 125.25, 126.08, 126.45, 128.46, 128.96, 129.23, 131.27, 131.35, 133.78, 135.79, 136.86, 136.98, 137.22, 139.03, 143.76. Mass (m/z) %: 497 (M^+, 38%). Anal. calcd. for $C_{30}H_{27}NO_2S_2$: C, 72.40; H, 5.47; N, 2.81%. Found: C, 72.24; H, 5.69; N, 2.99%.

1-Phenylsulfonyl-2-((1*H*-indol-3-yl)methyl)-3-(phenylthio)-1*H*-indole (2j)

Yield: 0.22 g (42%). Mp: 162–164 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.86 (s, 2H, $-CH_2$), 6.66 (s, 1H, Ar-H), 7.03–7.30 (m, 10H, Ar-H), 7.36–7.52 (m, 6H, Ar-H), 7.76 (d, $J = 7.8$ Hz, 2H, Ar-H), 8.29 (d, $J = 7.5$ Hz 1H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 110.94, 112.95, 115.32, 119.21, 119.56, 120.04, 122.05, 123.09, 124.24, 125.24, 125.48, 126.27, 126.63, 127.09, 128.71, 128.91, 129.14, 130.71, 133.42, 136.02, 136.42, 137.05, 138.44, 145.06. Mass (m/z) %: 494 (M^+, 42%). Anal. calcd. for $C_{29}H_{22}N_2O_2S_2$: C, 70.42; H, 4.48; N, 5.66%. Found: C, 70.65; H, 4.19; N, 5.50%.

1-Phenylsulfonyl-3-(phenylthio)-2-((thiophen-2-yl)methyl)-1*H*-indole (2k)

Yield: 0.20 g (40%). Mp: 128 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.89 (s, 2H, $-CH_2$), 6.82 (d, $J = 4.5$ Hz, 2H, Ar-H), 6.97 (d, $J = 6.9$ Hz, 2H, Ar-H), 7.07–7.13 (m, 4H, Ar-H), 7.15–7.36 (m, 4H, Ar-H), 7.41–7.49 (m, 4H, Ar-H), 8.17 (d, $J = 8.4$ Hz, 1H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.14, 112.34, 115.12, 120.24, 124.27, 125.48, 125.55, 126.09, 126.51, 126.61, 126.71, 128.92, 129.05, 130.35, 133.71, 135.91, 136.59, 138.40, 140.94, 143.76. Mass (m/z) %: 461 (M^+, 71%). Anal. calcd.

for $C_{25}H_{19}NO_2S_3$: C, 65.05; H, 4.15; N, 3.03%. Found: C, 65.25; H, 4.43; N, 3.27%.

Ethyl-1-phenylsulfonyl-2(3,4-dimethoxybenzyl)-1*H*-indole-3-carboxylate (4a)

Yield: 0.29 g (52%). Mp: 134–136 °C. IR (KBr): 1701 (CO_2Et), 1379 & 1189 (SO_2Ph) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.40 (t, $J = 7.2$ Hz, Hz, 3H, $-CH_3$), 3.75 (s, 3H, $-OCH_3$), 3.84 (s, 3H, $-OCH_3$), 4.41 (q, $J = 7.2$ Hz, 2H, $-OCH_2$), 5.00 (s, 2H, $-CH_2$), 6.70 (s, 2H, Ar-H), 6.77 (s, 1H, Ar-H), 7.26 (t, $J = 3.6$ Hz, 2H, Ar-H), 7.35–7.38 (m, 2H, Ar-H), 7.46–7.49 (m, 3H, Ar-H), 8.16–8.19 (m, 1H, Ar-H), 8.21–8.24 (m, 1H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.35, 31.20, 55.80, 55.95, 60.64, 111.18, 112.28, 113.21, 114.67, 120.70, 122.04, 124.45, 125.17 126.52, 127.27, 128.97, 130.32, 133.80, 136.05, 138.51, 146.58, 147.57, 148.78, 164.60. Mass (m/z) %: 479 (M^+, 39%). Anal. calcd. for $C_{26}H_{25}NO_6S$: C, 65.12; H, 5.25; N, 2.92%. Found: C, 65.35; H, 5.01; N, 2.68%.

(E)-Methyl-1-phenylsulfonyl-3-(2-(3,4-dimethoxybenzyl)-1*H*-indol-3-yl)acrylate (4b)

Yield: 0.41 g (73%). Mp: 138 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 3.71 (s, 3H, $-COOCH_3$), 3.78 (s, 3H, $-OCH_3$), 3.82 (s, 3H, $-OCH_3$), 4.60 (s, 2H, $-CH_2$), 6.56–6.68 (m, 4H, Ar-H), 7.20 (t, $J = 8.1$ Hz, 2H, Ar-H), 7.36–7.42 (m, 5H, Ar-H), 7.84 (d, $J = 6.9$ Hz, 1H, Ar-H), 7.91 (d, $J = 15.9$ Hz, Hz, 1H, vinylic-CH), 8.25 (d, $J = 8.1$ Hz, 1H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.82, 51.72, 55.79, 55.97, 111.34, 111.94, 115.15, 117.51, 119.15, 120.13, 120.52, 124.40, 125.27, 126.46, 127.26, 128.94, 130.06, 133.71, 135.67, 136.81, 138.47, 141.57, 147.81, 148.99, 167.53. Mass (m/z) %: 491 (M^+, 45%). Anal. calcd. for $C_{27}H_{25}NO_6S$: C, 65.97; H, 5.13; N, 2.85%. Found: C, 65.79; H, 5.39; N, 2.62%.

1-Phenylsulfonyl-2-(3,4-dimethoxybenzyl)-3-methyl-1*H*-indole (4c)

Yield: 0.38 g (67%). Mp: 108–110 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 2.23 (s, 3H, $-CH_3$), 3.72 (s, 3H, $-OCH_3$), 3.83 (s, 3H, $-OCH_3$), 4.39 (s, 2H, $-CH_2$), 6.65 (t, $J = 8.4$ Hz, 3H, Ar-H), 7.18 (t, $J = 7.8$ Hz, 2H, Ar-H), 7.25–7.32 (m, 3H, Ar-H), 7.37–7.47 (m, 3H, Ar-H), 8.20 (d, $J = 6.9$ Hz, 1H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 9.20, 30.83, 55.77, 55.97,

111.22, 111.83, 115.04, 118.15, 118.66, 120.34, 123.41, 124.51, 128.70, 131.04, 131.23, 133.12, 134.96, 136.56, 138.95, 147.52, 148.87. Mass (m/z) %: 421 (M^+, 66%). Anal. calcd. for $C_{24}H_{23}NO_4S$: C, 68.39; H, 5.50; N, 3.32%. Found: C, 68.55; H, 5.28; N, 3.50%.

1-Phenylsulfonyl-3-bromo-2-(3,4-dimethoxybenzyl)-1*H*-indole (4d)

Yield 0.39 g (70%). Mp: 102 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.73 (s, 3H, $-OCH_3$), 3.84 (s, 3H, $-OCH_3$), 4.51 (s, 2H, $-CH_2$), 6.68–6.76 (m, 3H, Ar-H), 7.19 (t, $J = 7.5$ Hz, 2H, Ar-H), 7.30–7.42 (m, 5H, Ar-H), 7.49–7.52 (m, 1H, Ar-H), 8.18 (d, $J = 7.2$ Hz, 1H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 31.92, 55.79, 55.98, 103.54, 111.26, 112.10, 115.04, 119.65, 120.81, 124.26, 125.69, 126.41, 128.87, 128.90, 129.94, 133.56, 135.91, 136.88, 138.37, 147.78, 148.91. Mass (m/z) %: 485 (M^+, 33%), 487 ($M^+ + 2$, 37%). Anal. calcd. for $C_{23}H_{20}BrNO_4S$: C, 56.80; H, 4.14; N, 2.88%. Found: C, 56.55; H, 4.38; N, 2.67%.

1-Phenylsulfonyl-2,3-bis(3,4-dimethoxybenzyl)-1*H*-indole (4e)

Yield 0.36 g (58%). Mp: 70–72 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.62 (s, 3H, $-OCH_3$), 3.63 (s, 3H, $-OCH_3$), 3.80 (s, 3H, $-OCH_3$), 3.81 (s, 3H, $-OCH_3$), 4.01 (s, 2H, $-CH_2$), 4.44 (s, 2H, $-CH_2$), 6.54–6.67 (m, 6H, Ar-H), 7.17–7.20 (m, 3H, Ar-H), 7.23–7.35 (m, 2H, Ar-H), 7.37–7.45 (m, 3H, Ar-H), 8.23 (d, $J = 8.4$ Hz, 1H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.73, 30.98, 55.69, 55.91, 111.17, 111.59, 111.83, 115.21, 119.41, 120.06, 120.51, 121.25, 123.60, 124.59, 126.26, 128.74, 130.53, 131.06, 131.66, 133.22, 136.02, 136.09, 138.88, 147.52, 148.55. Mass (m/z) %: 557 (M^+, 51%). Anal. calcd. for $C_{32}H_{31}NO_6S$: C, 68.92; H, 5.60; N, 2.51%. Found: C, 68.73; H, 5.32; N, 2.75%.

1-Phenylsulfonyl-2-bromo-3-(3,4-dimethoxybenzyl)-1*H*-indole (4f)

Yield: 0.41 g (73%). Mp: 105 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.71 (s, 3H, $-OCH_3$), 3.82 (s, 3H, $-OCH_3$), 3.96 (s, 2H, $-CH_2$), 6.57–6.71 (m, 3H, Ar-H), 7.19 (t, $J = 7.8$ Hz, 1H, Ar-H), 7.28–7.35 (m, 2H, Ar-H), 7.42 (t, $J = 7.8$ Hz, 2H, Ar-H), 7.56 (t, $J = 7.5$ Hz, 1H, Ar-H), 7.87 (d, $J = 7.8$ Hz, 2H, Ar-H), 8.31 (d, $J = 8.4$ Hz, 1H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.94, 55.77, 55.89, 109.98, 111.24, 111.54, 115.61, 119.09, 120.10, 124.07, 124.94, 125.17, 127.02, 129.08, 129.79, 130.73, 133.96, 137.78, 138.14, 147.64, 148.99. Mass (m/z) %: 485 (M^+, 45%),

487 ($M^+ + 2$, 48%). Anal. calcd. for $C_{23}H_{20}BrNO_4S$: C, 56.80; H, 4.14; N, 2.88%. Found: C, 56.98; H, 4.35; N, 2.64%.

Ethyl-1-phenylsulfonyl-3-(3,4-dimethoxybenzyl)-1*H*-indole-2-carboxylate (4g)

Yield: 0.38 g (68%). Mp: 114–116 °C. IR (KBr): 1716 (CO_2Et), 1372 & 1190 (SO_2Ph) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.40 (t, $J = 7.2$ Hz, 3H, $-CH_3$), 3.77 (s, 3H, $-OCH_3$), 3.81 (s, 3H, $-OCH_3$), 4.04 (s, 2H, $-CH_2$), 4.46 (q, $J = 7.2$ Hz, 2H, $-OCH_2$), 6.70 (s, 2H, Ar-H), 6.80 (s, 1H, Ar-H), 7.16 (t, $J = 7.8$ Hz, 1H, Ar-H), 7.33–7.39 (m, 4H, Ar-H), 7.48 (t, $J = 7.2$ Hz, 1H, Ar-H), 7.87 (d, $J = 7.8$ Hz, 2H, Ar-H), 8.01 (d, $J = 8.4$ Hz, 1H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.11, 30.12, 55.83, 55.88, 62.29, 111.17, 111.94, 115.54, 120.50, 121.07, 124.28, 126.83, 127.12, 127.85, 128.82, 128.95, 129.88, 131.08, 133.79, 137.13, 137.32, 147.66, 148.99, 162.57. Mass (m/z) %: 479 (M^+, 48%). Anal. calcd. for $C_{26}H_{25}NO_6S$: C, 65.12; H, 5.25; N, 2.92%. Found: C, 65.31; H, 5.48; N, 2.65%.

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