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Synthesis and Biological Evaluation of 7-Arylindoline-1-Benzenesulfonamides as a Novel Class of Potent Anticancer Agents

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Contents:

General. (A) **Chemistry.** Nuclear magnetic resonance (^{1}H NMR) spectra were obtained with Bruker DRX-500 spectrometer (operating at 500 MHz), with chemical shift in parts per million (ppm, δ) downfield from TMS as an internal standard. High-resolution mass spectra (HRMS) were measured with a JEOL (JMS-700) electron impact (EI) mass spectrometer. Purity of the final compounds were determined using an Agilent 1100 series HPLC system using C-18 column (Agilent ZORBAX Eclipse XDB-C18 5 μm. 4.6 mm × 150 mm) and were found to be ≥ 95%. Flash column chromatography was done using silica gel (Merck Kieselgel 60, No. 9385, 230-400 mesh ASTM). All reactions were carried out under an atmosphere of dry nitrogen.

(B) **Biology. (a) Materials.** Regents for cell culture were obtained from Gibco-BRL Life Technologies (Gaitherburg, MD). Microtubule-associated protein (MAP)-rich tubulin was purchased from Cytoskeleton, Inc. (Denver, CO). [^{3}H]Colchicine (specific activity, 60-87 Ci/mmol) was purchased from PerkinElmer Life Sciences (Boston, MA).

(b) Cell Growth Inhibitory Assay. Human oral epidermoid carcinoma KB cells, non small cell lung carcinoma H460 cells, colorectal carcinoma HT29 cells, and stomach carcinoma MKN45 cells were maintained in RPMI-1640 medium supplied with 5% fetal bovine serum. KB-VIN10 cells were maintained in growth medium supplemented with 10 nM vincristine, generated from vincristine-driven selection, and displayed overexpression of P-gp170/MDR. Cell in logarithmic phase were cultured at a density of 5000 cells/mL/well in a 24-well plate. KB-VIN10 cells were cultured in drug-free medium for 3 days prior to use. The cells were exposed to various concentrations of the test drugs for 72 h. The methylene blue dye assay was used to evaluate the effect of the test compounds on cell growth as described previously.[1] The IC_{50} value resulting from 50% inhibition of cell growth was calculated graphically as a comparison with the control. Compounds were examined in at least three independent experiments, and the values shown for these compounds are the mean and standard deviation of these data.

(c) Tubulin Polymerization in Vitro Assay.[2,3] Turbidimetric assays of microtubules were performed as described by Bollag et al.[4] In brief, microtubule-associated protein (MAP)-rich tubulin (from bovine brain, Cytoskeleton, Denver, C.O.) had been dissolved in reaction buffer (100 mM PIPES (pH 6.9), 2 mM $MgCl_2$, 1 mM GTP) in preparing of 4 mg/mL tubulin solution. Tubulin solution (240 μg MAP-rich tubulin per well) was placed in 96-well microtiter plate in the presence of test compounds or 2% (v/v) DMSO as vehicle control. The increase in absorbance was measured at 350 nm in a PowerWave X Microplate Reader (BIO-TEK Instruments, Winooski, VT) at 37 °C and recorded every 30 s for 30 min. The area under the curve (AUC) used to determine the concentration that inhibited tubulin polymerization to 50% (IC_{50}). The AUC of the untreated control and 10μM of colchicine was set to 100% and 0% polymerization, respectively, and the IC_{50} was calculated by nonlinear regression in at least three experiments.

(d) Tubulin Competition-Binding Scintillation Proximity Assay.[5-7] This assay was performed in

a 96-well plate. In brief, 0.08 (micro)M of [^{3}H]colchicine was mixed with the test compound and 0.5 (micro)g special long-chain biotin-labeled tubulin (0.5 µg) and then incubated in 100 µl of reaction buffer (80 mM PIPES, pH 6.8, 1 mM EGTA, 10% glycerol, 1 mM $MgCl_2$, and 1 mM GTP) for 2h at 37°C. Then eighty (micro) g of Streptavidin-labeled SPA beads were added to each reaction mixture. Then the radioactive counts were directly measured by a scintillation counter.

HPLC purity determination:

The percentage purity of compounds were determined by an Agilent 1100 series HPLC system using C18 column.

Elution conditions: Mobile phase A-Acetonitrile; Mobile phase B-Water containing 0.1% formic acid + 10 mmol NH_4OAc. The flow-rate was 0.2 ml/min and the injection volume was 5 µl. The system operated at 25 °C. Peaks were detected at 210 nm.

Table 1. Elution condition

Time (min)	Mobile Phase A (ratio)	Mobile Phase B (ratio)
0	10	90
45	90	10
50	10	90
60	10	90

Table 2. Purity of compounds **7**-**25**

C18 column: Agilent ZORBAX Eclipse XDB-C18 5µm. 4.6 mm × 150 mm column

Compounds	Retention time (min)	% Purity
7	40.09	95.24
8	39.89	98.23
9	32.09	99.71
10	41.57	97.24
11	36.47	99.98
12	32.89	99.93
13	40.55	99.22
14	39.69	98.21
15	37.93	99.87
16	40.54	98.11
17	41.29	98.19

18	34.77	99.97
19	23.11	99.92
20	27.13	99.94
21	35.02	99.81
22	35.57	96.54
23	37.10	96.82
24	40.36	96.46
25	43.11	95.31

Spectral Data and Procedure of compounds 7-25.

General Procedure for the preparation of 7-arylindoline-1-benzenesulfonamides (7-23).

4-[1-(4-Methoxy-benzenesulfonyl)-2,3-dihydro-1*H*-indol-7-yl]-benzonitrile (**15**)

A solution of 7-bromoindole (**26**) (0.30 g, 1.53 mmol) in glacial acetic acid (1.5 mL) was treated with sodium cyanoborohydride (0.14 g, 2.29 mmol) under N_2 at 0°C. After aqueous sodium hydroxide solution was added to quench excess acid, the resulting mixture was then extracted with CH_2Cl_2 (20 mL × 3). The combined organic layers were dried over $MgSO_4$, the dried solution was filtered, and the filtrate was concentrated. The residue was dissolved in pyridine (1mL) and 4-methoxyphenylsulfonyl chloride (0.47 g, 2.29 mmol) was added. The reaction mixture was refluxed for 15h. The solvent was removed and the residue was purified by silica gel flash column chromatography (EtOAc: *n*-hexane = 1 : 2) to afford compound **28**, yield 87%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.40 (t, *J* = 7.22 Hz, 2H), 3.85 (s, 3H), 3.97 (t, *J* = 7.25 Hz, 2H), 6.88 (d, *J* = 8.9 Hz, 2H), 6.99 (t, *J* = 7.59 Hz, 1H), 7.04 (d, *J* = 7.02 Hz, 1H), 7.46 (d, *J* = 7.72 Hz, 1H), 7.60 (d, *J* = 8.89 Hz, 2H). A solution of **28** (0.15 g, 0.40 mmol) in toluene (10 mL) was treated with tetrakis(triphenylphosphine) palladium (0.02g, 0.02 mmol) under N_2. An aqueous solution of K_2CO_3 (2 M, 1.4 mL) was then added, followed by a solution of 4-cyanophenylboronic acid (0.24 g, 1.63 mmol) in EtOH (8 mL). The resulting mixture was refluxed for 24 h. The solvent was removed and the residue was purified by silica gel flash column chromatography (EtOAc : *n*-hexane = 1 : 3) to afford the desired compound **15** as white solid, yield 31%; mp: 157.2-158.9 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.34 (t, *J* = 7.4 Hz, 2H), 3.83 (s, 3H), 4.03 (t, *J* = 7.3 Hz, 2H), 6.79 (d, *J* = 8.8 Hz, 2H), 7.11 (d, *J* = 6.9 Hz, 1H), 7.24-7.31 (m, 4H), 7.70 (d, *J* = 8.3 Hz, 2H), 7.78 (d, *J* = 8.3 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.7, 51.8, 55.4, 110.1, 113.8, 119.1, 124.7, 127.4, 128.4, 128.8, 129.1, 129.3, 131.9, 133.4, 138.5, 140.0, 145.2, 163.2. MS (EI) *m/z*: 390 (M^+, 100%). HRMS (EI) calcd for $C_{22}H_{18}O_3N_2S_1$ (M^+): 390.1038; found 390.1040.

1-(4-Methoxy-benzenesulfonyl)-7-phenyl-2,3-dihydro-1H-indole (**7**)

The title compound as white solid was obtained in 52% overall yield from 7-bromoindole (**26**) and phenylboronic acid in a similar manner as described for the preparation of **15**; mp 165.9-167.8°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.00 (t, *J* = 7.32 Hz, 2H), 3.52 (s, 3H), 3.68 (t, *J* = 7.42 Hz, 2H), 6.50 (d, *J* = 8.83 Hz, 2H), 6.73 (d, *J* = 7.06 Hz, 1H), 6.88-6.96 (m, 4H), 7.30 (d, *J* =7.55 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.0, 51.9, 55.5, 114.0, 115.9, 123.5, 127.1, 127.9, 128.1, 129.2, 129.5, 129.8, 135.6, 138.2, 140.0, 142.0, 163.1. MS (EI) *m/z*: 365 (M^+, 20.0%), 194 (100.0%). HRMS (EI) for $C_{21}H_{19}NO_3S$ (M^+): calcd, 365.1086 ; found, 365.1081

1-(4-Methoxy-benzenesulfonyl)-7-(4-methoxy-phenyl)-2,3-dihydro-1H-indole (**8**)

The title compound as white solid was obtained in 44% overall yield from 7-bromoindole (**26**) and 4-methoxyphenylboronic acid in a similar manner as described for the preparation of **15**; mp 176.3-177.4°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.32 (t, *J* = 7.31 Hz, 2H), 3.81 (s, 3H), 3.84 (s, 3H), 4.02 (t, *J* = 7.34 Hz, 2H), 6.77 (d, *J* = 8.92 Hz, 2H), 6.95 (d, *J* = 8.72 Hz, 2H), 6.99 (d, *J* = 7.50 Hz, 1H), 7.18 (t, *J* = 7.52 Hz, 1H), 7.27 (d, *J* = 7.59 Hz, 1H), 7.32 (d, *J* = 8.9 Hz, 2H), 7.61 (d, *J* = 8.69 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.1, 51.0, 55.1, 55.5, 113.6, 123.0, 127.1, 129.2, 129.3, 129.5, 132.9, 135.4, 138.2, 139.9, 158.5, 163.1. MS (EI) *m/z*: 395 (M^+, 15.0%), 224 (100.0%). HRMS (EI) for $C_{22}H_{21}NO_4S$ (M^+): calcd, 395.1191 ; found, 395.1185

4-[1-(4-Methoxy-benzenesulfonyl)-2,3-dihydro-1H-indol-7-yl]-phenylamine (9)

A mixture of **14** (0.38 g, 0.93 mmol), iron (0.16 g, 2.77 mmol), and ammonium chloride (0.10 g, 1.85 mmol) in isopropanol (19 ml)-water (4 ml) was stirred at 100°C for 4h. After cooling, the reaction mixture was filtrated and extracted with CH_2Cl_2. The combined organic layer was dried by $MgSO_4$ and evaporated to give a residue that purified by silica gel flash column chromatography (EtOAc : *n*-hexane = 1 : 1) to afford compound **9** as pale brown solid, yield 82%; mp: 183.9-185.6°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.30 (t, *J* = 7.3 Hz, 2H), 3.81 (s, 3H), 4.01 (t, *J* = 7.4 Hz, 2H), 6.73-6.78 (m, 4H), 6.96 (d, *J* = 6.9 Hz, 1H), 7.17 (t, *J* = 7.5 Hz, 1H), 7.26-7.28 (m, 1H), 7.34-7.35 (m, 2H), 7.50-7.51 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.1, 51.9, 55.5, 113.7, 115.1, 122.6, 127.0, 129.1, 129.2, 129.3, 129.6, 130.8, 135.8, 138.2, 139.8, 145.4, 163.0. MS (EI) *m/z*: 380 (M^+, 15.4%), 249 (92.0%), 209 (100.0%), 193 (69.8%). HRMS (EI) for $C_{21}H_{20}N_2O_3S$ (M^+): calcd, 380.1195 ; found, 380.1198.

{4-[1-(4-Methoxy-benzenesulfonyl)-2,3-dihydro-1H-indol-7-yl]-phenyl}-dimethyl-amine (**10**)

The title compound as white solid was obtained in 33% overall yield from 7-bromoindole (**26**) and N,N-dimethylphenylboronic acid in a similar manner as described for the preparation of **15**; mp 178.4-179.7°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.30 (t, *J* =7.30 Hz, 2H), 2.99 (s, 6H), 3.81 (s, 3H),

4.02 (t, *J* = 7.34 Hz, 2H), 6.75-6.78 (m, 4H), 6.94 (d, *J* = 7.18 Hz, 1H), 7.16 (t, *J* = 7.53 Hz, 1H), 7.29 (d, *J* = 7.71 Hz, 1H), 7.34 (d, *J* = 8.77 Hz, 2H), 7.59 (d, *J* =8.74 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.0, 40.3, 51.8, 55.4, 112.0, 113.6, 122.2, 127.0, 128.4, 128.7, 128.9, 129.2, 129.5, 135.9, 138.1, 139.7, 149.3, 162.9. MS (EI) *m/z*: 408 (M^+, 20.6%), 237 (100.0%). HRMS (EI) for $C_{23}H_{24}N_2O_3S$ (M^+): calcd, 408.1507 ; found, 408.1511

1-(4-Methoxy-benzenesulfonyl)-7-(3,4,5-trimethoxy-phenyl)-2,3-dihydro-1*H*-indole (**11**)

The title compound as white solid was prepared in 53% overall yield in a manner similar to that described in **15**; mp: 202.5-204.8°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.21 (t, *J* = 7.28 Hz, 2H), 3.65 (s, 3H), 3.68 (s, 3H), 3.70 (s, 6H,), 3.85 (t, *J* = 7.33 Hz, 2H), 6.64 (d, *J* = 8.85 Hz, 2H), 6.71 (s, 2H), 6.89 (d, *J* = 7.22 Hz, 1H), 7.04 (t, *J* = 7.49 Hz, 1H), 7.12-7.14 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.3, 51.9, 55.4, 55.9, 60.8, 105.4, 113.7, 123.4, 126.9, 129.2, 129.4, 129.5, 135.2, 135.9, 137.0, 138.2, 139.9, 152.8, 163.0. MS (EI) *m/z*: 455 (M^+, 36.3%), 253 (100.0%). HRMS (EI) for $C_{24}H_{25}NO_6S$ (M^+): calcd, 455.1402 ; found, 455.1410.

4-[1-(4-Methoxy-benzenesulfonyl)-2,3-dihydro-1*H*-indol-7-yl]-phenol (**12**)

The title compound as white solid was prepared in 33% overall yield in a manner similar to that described in **15**; mp: 179.4-180.5°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.29 (t, *J* = 7.27 Hz, 2H), 3.80 (s, 3H), 4.02 (t, *J* =7.31 Hz, 2H), 6.79 (d, *J* = 8.83 Hz, 2H), 6.82 (d, *J* = 8.53 Hz, 2H), 6.98 (d, *J* =7.44 Hz, 1H), 7.18 (t, *J* =7.54 Hz, 1H), 7.28 (d, *J* = 7.61 Hz, 1H), 7.34 (d, *J* = 8.82 Hz, 2H), 7.55 (d, *J* =8.59 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 51.9, 55.5, 77.2, 113.8, 115.3, 123.0, 127.2, 129.0, 129.4, 129.6, 135.5, 138.2, 139.8, 154.8, 163.1; MS (EI) *m/z*: 381 (M^+, 7.0%), 210 (100.0%); HRMS (EI) for $C_{21}H_{19}NO_4S$ (M^+): calcd, 381.1034; found, 381.1033.

7-(4-Fluoro-phenyl)-1-(4-methoxy-benzenesulfonyl)-2,3-dihydro-1*H*-indole (**13**)

The title compound as white solid was obtained in 29% overall yield from 7-bromoindole (**26**) and 4-difluorophenylboronic acid in a similar manner as described for the preparation of **15**; mp: 178.1-179.4°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.33 (t, *J* = 7.33 Hz, 2H), 3.82 (s, 3H), 4.02 (t, *J* =7.38 Hz, 2H), 6.78 (d, *J* =8.77 Hz, 2H), 7.04 (d, *J* =7.30 Hz, 1H), 7.10 (t, *J* =8.66 Hz, 2H), 7.21 (t, *J* =7.50 Hz, 1H), 7.27 (d, *J* =7.89 Hz, 1H), 7.32 (d, *J* =8.77 Hz, 2H), 7.63 (d, *J* =7.95 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.0, 52.0, 55.5, 113.8, 115.2, 123.6, 127.2, 129.0, 129.4, 129.5, 129.7, 129.8, 136.4, 138.3, 140.0, 160.7, 163.1. MS (EI) *m/z*: 383 (M^+, 16.6%), 212 (100.0%). HRMS (EI) for $C_{21}H_{18}FNO_3S$ (M^+): calcd, 383.0991 ; found, 383.0992.

1-(4-Methoxy-benzenesulfonyl)-7-(4-nitro-phenyl)-2,3-dihydro-1*H*-indole (14)

The title compound as yellow solid was obtained in 75% overall yield from 7-bromoindole (**26**) and 4-nitrophenylboronic acid in a similar manner as described for the preparation of **15**; mp: 177.1-178.4°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.34 (t, *J* =7.40 Hz, 2H), 3.82 (s, 3H), 4.05 (t, *J* =7.47 Hz, 2H), 6.80 (d, *J* = 8.98 Hz, 2H), 7.14 (d, *J* = 7.07 Hz, 1H), 7.27-7.33 (m, 4H), 7.82-7.84 (m, 2H), 8.27-8.29 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.8, 51.9, 55.5, 113.9, 123.6, 125.0, 127.4, 128.4, 128.9, 129.2, 129.4, 133.1, 138.6, 140.1, 146.4, 147.4, 163.3. MS (EI) *m/z*: 410 (M^+, 5.2%), 237 (100.0%). HRMS (EI) for $C_{21}H_{18}N_2O_5S$ (M^+): calcd, 410.0936; found, 410.0940.

7-(3-Fluoro-phenyl)-1-(4-methoxy-benzenesulfonyl)-2,3-dihydro-1*H*-indole (**16**)

The title compound as white solid was prepared in 20% overall yield in a manner similar to that described in **15**; mp: 180.0-181.3°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.35 (t, *J* = 7.36 Hz, 2H), 3.82 (s, 3H), 4.02 (t, *J* =7.36 Hz, 2H), 6.79 (d, *J* = 8.82 Hz, 2H), 6.06-6.07 (m, 2H), 7.22 (d, *J* =7.50 Hz, 1H), 7.28-7.39 (m, 5H), 7.46 (d, *J* = 7.69 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.1, 52.0, 55.5, 113.8, 113.9, 115.0, 115.3, 123.9, 124.0, 127.2, 129.1, 129.4, 129.6, 129.7, 134.5, 138.4, 140.1, 142.5, 163.2. MS (EI) *m/z*: 383 (M^+, 20.6%), 212 (100.0%). HRMS (EI) for $C_{21}H_{18}FNO_3S$ (M^+): calcd, 383.0991; found, 399.0703.

7-(3,4-Difluoro-phenyl)-1-(4-methoxy-benzenesulfonyl)-2,3-dihydro-1*H*-indole (**17**)

The title compound as white solid was obtained in 43% overall yield from 7-bromoindole (**26**) and 3,4-difluorophenylboronic acid in a similar manner as described for the preparation of **15**; mp: 180.2-181.4°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.33 (t, *J* = 7.37 Hz, 2H), 3.82 (s, 3H), 4.02 (t, *J* = 7.38 Hz, 2H), 6.79 (d, *J* = 8.85 Hz, 2H), 7.06 (d, *J* = 7.03 Hz, 1H), 7.15-7.24 (m, 3H), 7.32 (d, *J* =8.81 Hz, 2H), 7.37-7.40 (m, 1H), 7.44-7.48 (m, 1H);^{13}C NMR (125 MHz, $CDCl_3$) δ 28.9, 52.0, 55.5, 113.8, 116.9, 117.1, 117.3, 124.1, 124.2, 124.3, 127.3, 128.9, 129.2, 129.5, 133.6, 137.4, 138.5, 140.0, 148.2, 148.3, 148.8, 149.0, 150.6, 150.8, 151.3, 151.4, 163.2; MS (EI) *m/z*: 400 (M^+-1, 2.0%), 230.2 (100%); HRMS (EI) for $C_{21}H_{17}F_2NO_3S$ (M^+): calcd, 401.0897; found, 401.0905.

1-(4-Methoxy-benzenesulfonyl)-7-pentafluorophenyl-2,3-dihydro-1*H*-indole (**18**)

The title compound as white solid was prepared in 32% overall yield in a manner similar to that described in **15**; mp: 108.1-109.2°C. ^{1}HNMR (500 MHz, $CDCl_3$) δ 2.87 (t, *J* = 8.4 Hz, 2H), 3.80 (s, 3H), 3.89 (t, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 6.96 (t, *J* = 7.4 Hz, 1H), 7.06 (d, *J* = 7.3 Hz, 1H), 7.18 (t, *J* = 7.7 Hz, 1H), 7.63 (d, *J* = 8.1 Hz, 1H), 7.71 (d, *J* = 8.9 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.8, 49.8, 55.5, 114.1, 115.0, 123.6, 125.0, 127.6, 128.5, 129.4, 131.7, 142.0, 163.2. MS (EI) *m/z*: 289 (66.7%), 118 (100.0%). HRMS (EI) for $C_{21}H_{14}NO_3F_5S$ (M^+): calcd, 455.0615; found, 455.0612.

1-(4-Methoxy-benzenesulfonyl)-7-pyridin-4-yl-2,3-dihydro-1*H*-indole (19)

The title compound as white solid was obtained in 47% overall yield from 7-bromoindole (**26**) and 4-pyridineboronic acid in a similar manner as described for the preparation of **15**; mp: 195.9-196.8°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.19 (t, *J* = 7.39 Hz, 2H), 3.80 (s, 3H), 3.92(t, *J* = 7.45 Hz, 2H), 6.70(d, *J* = 8.91 Hz, 2H), 7.03 (d, *J* =7.06 Hz, 1H), 7.15-7.22 (m, 4H), 7.55 (m, 2H), 8.44 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.8, 51.8, 55.5, 113.8, 122.8, 124.9, 127.3, 128.5, 129.0, 129.4, 132.7, 138.6, 140.1, 148.1, 149.7, 163.2. MS (EI) *m/z*: 366 (M^+, 34.1%), 195 (100.0%). HRMS (EI) for $C_{20}H_{18}N_2O_3S$ (M^+): calcd, 366.1038; found, 366.1041.

1-(4-Methoxy-benzenesulfonyl)-7-pyridin-3-yl-2,3-dihydro-1H-indole (20)

The title compound as white solid was prepared in 34% overall yield in a manner similar to that described in **15**; mp 179.8-181.0°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.22 (t, *J* =7.37 Hz, 2H), 3.76 (s, 3H), 3.92 (t, *J* = 7.44 Hz, 2H), 6.71 (d, *J* = 8.83 Hz, 2H), 7.01 (d, *J* = 6.69 Hz, 1H), 7.15-7.20 (m, 4H), 7.30 (q, *J* = 6.33 Hz, 1H), 7.93-7.96 (m, 1H), 8.36 (q, *J* = 4.78 Hz, 1H), 8.70 (d, *J* =1.83 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.0, 52.0, 55.5, 113.8, 123.1, 124.4, 127.3, 128.8, 129.3, 129.5, 132.1, 135.5, 136.2, 138.6, 140.3, 147.9, 148.9, 163.2 MS (EI) *m/z*: 366 (M^+, 40.7%), 195 (100.0%). HRMS (EI) for $C_{20}H_{18}N_2O_3S$ (M^+): calcd, 366.1038; found, 366.1036.

7-(6-Fluoro-pyridin-3-yl)-1-(4-methoxy-benzenesulfonyl)-2,3-dihydro-1H-indole (21)

The title compound as white solid was prepared in 42% overall yield in a manner similar to that described in **15**; mp 139.8-141.7°C, ^{1}NMR (500 MHz, $CDCl_3$) δ 2.36 (t, *J* = 7.3 Hz, 2H), 3.82 (s, 3H), 4.03 (t, *J* = 7.4 Hz, 2H), 6.80 (d, *J* = 8.7 HZ, 2H), 6.97 (dd, *J* = 8.4, 2.7 Hz, 1H), 7.11 (d, *J* = 6.7 Hz, 1H), 7.23-7.28 (m, 3H), 7.32 (d, *J* = 8.8 Hz, 2H), 8.08-8.12 (m, 1H), 8.45 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.0, 52.0, 55.5, 108.7, 113.9, 124.5, 127.4, 128.7, 129.1, 131.0, 134.1, 138.7, 140.3, 140.9, 146.3, 160.9, 163.3, 164.0. MS (EI) *m/z*: 384 (M^+, 13.5%), 213 (100.0%). HRMS (EI) for $C_{20}H_{17}N_2O_3FS$ (M^+): calcd, 384.0944; found, 384.0942.

1-(4-Methoxy-benzenesulfonyl)-7-thiophen-2-yl-2,3-dihydro-1H-indole (22)

The title compound as pale yellow solid was prepared in 65% overall yield in a manner similar to that described in **15**; mp 127.7-129.1°C . ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.40 (t, *J* = 7.23 Hz, 2H), 3.85 (s, 3H), 3.98 (t, *J* = 7.21 Hz, 2H), 6.80 (d, *J* = 8.85 Hz, 1H), 6.87 (d, *J* = 8.85 Hz, 2H), 6.89-7.05 (m, 3H), 7.46-7.60 (m, 2H),7.60 (d, *J* =8.85 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.9, 52.0, 55.5, 113.8, 115.9, 123.6, 125.7, 127.2, 127.9, 128.7, 129.3, 129.8, 132.6, 138.6, 140.0, 142.0, 163.2. MS (EI) *m/z*: 371 (M^+, 15.7%), 200 (100.0%). HRMS (EI) for $C_{19}H_{17}NO_3S_2$ (M^+): calcd, 371.0649 ; found, 371.0657.

7-Furan-2-yl-1-(4-methoxy-benzenesulfonyl)-2,3-dihydro-1H-indole (**23**)

The title compound as pale white soild was prepared in 45% overall yield in a manner similar to that described in **15**; mp 176.7-177.7°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.16 (t, *J* = 7.33 Hz, 2H), 3.83 (s, 3H), 4.00 (t, *J* = 7.40 Hz, 2H), 6.51 (q, *J* =1.71 Hz, 1H), 6.81 (d, *J* = 8.86 Hz, 2H), 6.95 (d, *J* = 7.57 Hz, 1H), 6.98 (d, *J* = 3.28 Hz, 1H), 7.19 (t, *J* = 7.61 Hz, 1H), 7.39 (d, *J* = 8.90 Hz, 2H), 7.51 (d, *J* = 1.12 Hz, 1H), 7.60 (d, *J* = 8.12 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.5, 52.1, 55.5, 108.9, 111.4, 113.8, 114.0, 123.3, 125.6, 125.9, 127.1, 128.7, 129.8, 138.4, 141.5, 151.8, 163.3. MS (EI) *m/z*: 355 (M^+, 15.7%), 184 (100.0%). HRMS (EI) for $C_{19}H_{17}NO_4S$ (M^+): calcd, 355.0878; found, 355.0881.

General Procedure for the preparation of 7-arylindole-1-benzenesulfonamides (24-25).

4-[1-(4-Methoxy-benzenesulfonyl)-1H-indol-7-yl]-benzonitrile (**24**)

Potassium hydroxide (0.25 g, 4.59 mmol) and tetra-*n*-butylammonium hydrogen sulfate (0.05 g, 0.15 mmol) were added to a solution of **26** (0.3 g, 1.53 mmol) in dichloromethane (15 mL) under N_2, and the reaction was stirred for 30 min. 4-Methoxysulfonyl chloride (0.63 g, 3.06 mmol) was added slowly to the reaction mixture. After 1 h, the reaction mixture was quenched with water and extracted with CH_2Cl_2 (10 ml × 3). The combined organic layer was dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography (EtOAc : *n*-hexane = 1 : 10) to afford compound **29**, yield 61%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.83 (s, 3H), 6.69 (d, *J* = 3.7 Hz, 1H), 6.90-6.93 (m, 2H), 7.03-7.06 (m, 1H), 7.44 (d, *J* = 7.5 Hz, 1H), 7.50 (d, *J* = 7.5 Hz, 1H), 7.72-7.75 (m, 2H), 7.89 (d, *J* = 8.3 Hz, 1H).

A solution of **29** (0.15 g, 0.40 mmol) in toluene (10 mL) was treated with tetrakis(triphenylphosphine) palladium (0.02g, 0.02 mmol) under N_2. An aqueous solution of K_2CO_3 (2 M, 1.4 mL) was added to the reaction mixture, followed by 4-cyanophenylboronic acid (0.24 g, 1.63 mmol) in EtOH (8 mL). The resulting mixture was heated under reflux for 24 h. The solvent was removed with a rotary evaporator and the reaction mixture was purified by flash chromatography (EtOAc : *n*-hexane = 1 : 3) to afford the desired compound **24** as white solid, yield 31%; mp: 163.5-164.6°C.^{1}H NMR (500 MHz, $CDCl_3$) δ 3.79 (s, 3H), 6.74-6.76 (m, 3H), 7.03 (d, *J* = 7.45 Hz, 1H), 7.19 (d, *J* = 8.86 Hz, 2H), 7.28 (d, *J* = 7.59 Hz, 1H), 7.40 (d, *J* = 8.07 Hz, 2H), 7.53 (d, *J* =7.87 Hz, 1H), 7.58 (d, *J* = 8.16 Hz, 2H), 7.65 (d, *J* = 3.73 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.6, 110.7, 110.8, 113.8, 119.0, 121.5, 124.0, 128.0, 128.5, 129.1, 129.2, 129.9, 131.0, 131.3, 133.2, 133.7, 145.7, 163.4. MS (EI) *m/z*: 388 (M^+, 43.3%), 216 (25.8%), 171 (100.0%). HRMS (EI) for $C_{22}H_{16}N_2O_3S$ (M^+): calcd, 388.0882; found, 388.0884.

7-(4-Fluoro-phenyl)-1-(4-methoxy-benzenesulfonyl)-1H-indole (**25**)

The title compound as pale pink soild was prepared in 25% overall yield in a manner similar to that

described in **24**; mp 181.2-182.4°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.79 (s, 3H), 6.73-6.74 (m, 3H), 6.95 (t, *J* = 8.63 Hz, 2H), 7.01 (d, *J* = 7.32 Hz, 1H), 7.18-7.24 (m, 5H), 7.49 (d, *J* =7.72 Hz, 1H), 7.70 (d, *J* = 3.63 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.6, 110.0, 113.8, 114.1, 120.6, 123.7, 128.6, 129.7, 129.8, 130.8, 131.0, 133.4, 133.5, 136.6, 136.7, 160.8, 163.2, 163.3. MS (EI) *m/z*: 381 (M^+, 57.7%), 210 (90.3%), 171 (100.0%). HRMS (EI) for $C_{21}H_{16}NO_3FS$ (M^+): calcd, 388.0835; found, 381.0835.

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