Novel Furanylarylene Arylsulfonylindolesulfonamides: Synthesis and Their Antibacterial Evaluation

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An array of furanylarylene arylsulfonylindolesulfonamides was synthesized through multi-step synthetic protocols involving bromination, stannylation, Stille cross coupling, reduction, arylsulfonylation, chlorosulfonylation, and condensation reactions. As a preliminary evaluation, these analogs were tested for antibacterial activity against a series of bacterial strains such as *Bacillus subtilis*, *Enterococcus faecalis*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, and *Klebsiella pneumoniae* using a two-fold serial dilution assay. Whereas analogs possessing unsubstitution, bromosubstitution, or methyl substitution on the benzene ring of benzenesulfonyl group were less active/inactive, the methoxy and chloro substituted counterparts were demonstrated to be comparatively more active. A few of them were found to exhibit better activity than the standard, streptomycin against selective organisms.

Key words diarylfuran; indole; chlorosulfonylation; Stille cross coupling; condensation; antibacterial activity

Considering the increased incidence of severe disseminated infections produced by bacteria in immunocompromised hosts, there is an emerging need for new antibacterial agents with potent activity. Consequently, the search for new antimicrobial agents always remains as an important and challenging task for medicinal chemists. The development of sulfonamides is a fascinating and informative area in medicinal chemistry, highlighting the role of skillful planning and serendipity in drug research. Sulfonamide derivatives are widely used in various conditions including gastrointestinal and urinary tract infections.[1,2] Many representatives of this class of compounds were reported to have antibacterial activity.[3—7] A few of them are human immunodeficiency virus (HIV) protease inhibitors,[8—11] carbonic anhydrase inhibitors,[12—17] antiepileptic agents,[18—20] and anticonvulsant agents.[21—24] However, the most common side effects of this class of drugs are diarrhea, anorexia, nausea, vomiting, and hypersensitivity reaction.[25]

Being a structural building block in many natural products and biopertinent chemical targets, the indole ring is one of the most commonly encountered heterocycles in medicinal chemistry.[26,27] A careful perusal of literature revealed that indole based chemical entities possess diverse biological activities including antibacterial and antifungal activities.[28—37] Particularly, indole carrying sulfonamide- or sulfone moieties at carbon-3 has attracted considerable interest. For instance, a few indole 3-sulfonamides have been investigated as inhibitors of HIV-1 reverse transcriptase,[38,39] while a series of closely related sulfones has been shown to possess activity against resistant HIV-1 mutants.[40] Recently, short peptide derivatives have been demonstrated to exhibit *in vitro* activity against HIV-1 wild type and mutants possessing non-nucleoside reverse transcriptase inhibitor resistance.[41] On the other hand, various target chemical entities with diarylfuran scaffold have been claimed to exhibit appreciable biological activity.[42,43] In this article, we present synthesis of a series of novel heterocyclic sulfonamides possessing indole and diarylfuran scaffolds together as antibacterial agents.

Results and Discussion

The synthetic pathway for the construction of target furanylarylene arylsulfonylindolesulfonamides is furnished in Chart 1. Diaminodiarylfurans (**5**) were synthesized from readily available furan (**1**) by adopting bromination followed by stannylation, Stille cross coupling, and reduction reactions. Initially, furan (**1**) was treated with bromine in *N*,*N*-dimethylformamide (DMF) to afford 2,5-dibromofuran (**2**). 2,5-Di(tributylstannyl)furan (**3**), resulting from 2,5-dibromofuran (**2**) by lithiation using *n*-butyllithium in ether followed by tributylstannylation, on treatment with 1-bromo-4-nitroarenes in the presence of catalytic amount of tetrakis-(triphenylphosphine)palladium and cesium fluoride in 1,4-dioxane, 2,5-bis(4-nitroaryl)furans (**4**) were obtained. The nitro groups of 2,5-bis(4-nitroaryl)furans (**4**) were reduced to amino groups to yield 2,5-bis(4-aminoaryl)furans (**5**) using stannous chloride in ethanol/dimethyl sulfoxide (DMSO). On the other hand, 1-arylsulfonylation of indole (**6**) with various arylsulfonyl chlorides was carried out under phase-transfer catalytic conditions to give their corresponding 1-arylsulfonyl-1*H*-indoles (**7**), which upon treatment with chlorosulfonic acid, the corresponding 3-chlorosulfonylated indole derivatives (**8**) were obtained. Eventually, condensation between the 2,5-bis(4-aminoaryl)furans (**5**) and the 3-chlorosulfonylated indole derivatives (**8**) in the presence of triethylamine in DMF afforded their corresponding target sulfonamides, *N*,*N*′-[4,4′-(furan-2,5-diyl)bis(4,1-arylene)]bis[1-(arylsulfonyl)-1*H*-indole-3-sulfonamides] (**9**) as pure solids after column chromatographic separation.

As a preliminary evaluation, target sulfonamides **9a**—**j** were assayed for their *in vitro* antibacterial activity against a panel of bacterial strains such as *Bacillus subtilis*, *Enterococcus faecalis*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, and *Klebsiella pneumoniae* using a two-fold serial dilution method. Standard antibiotic and solvent control used were streptomycin and *N*,*N*-dimethyl formamide (DMF), respectively and the media used were Nutrient broth (NB). Microdilution panels were prepared containing two-fold dilutions of the compounds and standard drug in DMF ranging from 100 to 12.5 $\mu g\,ml^{-1}$. The inhibition con-

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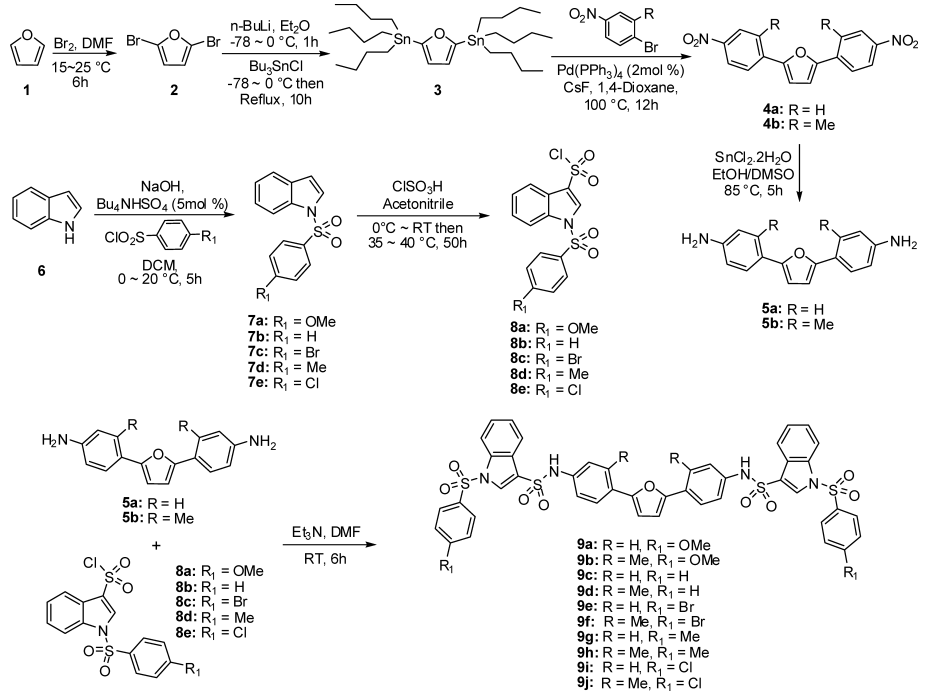

Chart 1. Synthesis of Target Heterocyclic Sulfonamides

Table 1. Minimum Inhibitory Concentration (MIC in μg/ml) of Target Sulfonamides **9a**—**j** and Standard against Bacterial Strains

Compound	*Bacillus subtilis*	*Enterococcus faecalis*	*Staphylococcus aureus*	*Pseudomonas aeruginosa*	*Escherichia coli*	*Klebsiella pneumoniae*
9a	25	25	50	12.5	12.5	25
9b	50	25	25	12.5	25	12.5
9c	—	—	100	100	100	100
9d	—	—	100	100	100	100
9e	100	100	100	—	—	—
9f	100	—	100	100	50	50
9g	—	—	—	100	100	100
9h	—	—	—	100	100	100
9i	25	25	50	50	25	50
9j	50	50	100	50	50	25
Streptomycin	12.5	25	50	25	12.5	25

centration of the commonly used antibiotic, streptomycin and the target sulfonamide analogs **9a**—**h** were compared. The results are summarized in Table 1.

Using this reliable assay, it was found that target sulfonamides bearing methoxy substituent on 4-position of the aryl group of 1-arylsulfonyl moiety (**9a**, **9b**) were the most active among the target sulfonamides against *P. aeruginosa*, *E. coli* and *K. pneumoniae* except **9b** against *E. coli* and notably, these compounds were markedly active than the standard antibiotic streptomycin against *P. aeruginosa* and *K. pneumoniae* except **9a** against *K. pneumoniae*, which showed similar activity as the standard. Against *E. coli*, **9a** exerted similar activity with that of the standard while **9b** showed less activity. Furthermore, the sulfonamide **9b** was more active than the standard against *S. aureus* while **9a** exhibited similar activity. Against *B. subtilis*, these **9a** and **9b** showed less activity compared to the standard while against *E. faecalis*, these targets showed similar activity.

Among the sulfonamides **9c**—**h**, the analogs without any substituent on 4- position of the aryl group of 1-arylsulfonyl moiety (**9c**, **9d**) and the analogs with methyl group on 4-position of the aryl group of 1-arylsulfonyl moiety (**9g**, **9h**) did not show any antibacterial activity against *B. subtilis*, *E. faecalis* and *S. aureus* except **9c** and **9d** against *S. aureus* which exhibited activity at the highest concentration. While the bromo analog **9f** was inactive only against *E. faecalis*, the bromo analog **9e** did not exhibit activity against *P. aeruginosa*, *E. coli* and *K. pneumoniae*. Of the sulfonamides possessing chloro groups **9i** and **9j**, the analog **9i** was less active compared to standard antibiotic against all the organisms except *E. faecalis* and *S. aureus* and, against these couple of organisms, it displayed similar activity with that of standard. Furthermore, the chloro analog **9j** exerted less activity compared to its chloro counterpart **9i** against all the organisms except *P. aeruginosa* and *K. pneumoniae*. Against the former, the minimum inhibitory concentration of **9j** was similar to that of **9i**, while against the latter, the minimum inhibitory concentration of **9j** was two-fold lower than that of **9i**.

Conclusion

A series of heterocyclic sulfonamides, *N*,*N*′-[4,4′-(furan-2,5-diyl)bis(4,1-arylene)]bis[1-(arylsulfonyl)-1*H*-indole-3-sulfonamides] was synthesized by adopting a multi-step synthetic strategy involving bromination, stannylation, Stille cross coupling, reduction, arylsulfonylation, chlorosulfonylation, and condensation reactions. As a preliminary evaluation of their antimicrobial activity, these analogs were tested against a series of bacterial strains such as *B. subtilis*, *E. faecalis*, *S. aureus*, *P. aeruginosa*, *E. coli*, and *K. pneumoniae* using a two-fold serial dilution technique. Among them, the more active compounds were identified as the sulfonamides with methoxy or chloro substituents on the benzene ring of benzenesulfonyl moiety and some of them were more active than the standard, streptomycin as well. The interesting antibacterial activity of these novel heterocyclic sulfonamides induced us for further investigation to establish their mode of action and will be carried out in due course. Besides, the information gained in this study would be useful in the design of structurally similar analogs with improved efficacy.

Experimental

All the solvents were distilled prior to use and all reagents were reagent grade and were used without further purification. Thin layer chromatography was performed on Silica gel 60 F plates eluting with the solvents indicated. Column chromatography was performed on Silica gel 230—400 mesh slurry packed in glass columns with the eluent system as indicated. All the reported melting points were measured in open capillaries and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were acquired at 400 MHz and 100 MHz, respectively (Bruker Avance) using either DMSO-d_6 or $CDCl_3$ as a solvent and tetramethylsilane (TMS) as an internal standard. Infrared spectra were measured on Mattson Galaxy 7020A (KBr pellet). Mass spectra were measured on Shimadzu QP5000. Elemental analyses were acquired on Fisone, EA 1106. The abbreviations br s, s, d, dd, dt, and m stand for the resonance multiplicities broad singlet, singlet, doublet, doublet of doublet, doublet of triplet, and multiplet, respectively.

Synthesis of 2,5-Dibromofuran (2) To a stirring solution of furan (7.3 ml, 100 mmol) in *N*,*N*-dimethylformamide (100 ml) at 15—20 °C, was added bromine (10.3 ml, 200 mmol) carefully in a dropwise fashion. After the addition was completed, the resulting dark solution was further stirred for over night while not allowing the temperature to rise above 25 °C. Then the mixture was poured into water (500 ml) and extracted with diethyl ether (50 ml×5). The combined ether layers were washed with saturated sodium bicarbonate (50 ml×2) followed by water (50 ml×2). After drying with magnesium sulfate, the solvent was evaporated and the concentrated mixture was subjected to vacuum distillation to afford 2,5-dibromofuran as a viscous liquid (yield 14 g, 62%) which was used directly for the next step.

Synthesis of 2,5-Bis(tributylstannyl)furan (3) To a stirring cooled (−78 °C) solution of 2,5-dibromofuran (7.9 g, 35.0 mmol) in diethyl ether (140 ml), was added *n*-BuLi (30.4 ml, 76 mmol). After the stirring was continued for 1 h. while attaining the reaction temperature ambient, the mixture was again cooled to −78 °C. After the dropwise addition of tributyltin chloride (21.5 ml, 76 mmol), the temperature of the reaction was allowed to reach ambient. Then the mixture was refluxed for 10 h, cooled and water (400 ml) was added. The organic layer was separated and the aqueous layer was extracted with diethyl ether (100 ml×2). After drying over magnesium sulfate, the combined organic layers were evaporated under reduced pressure. Vacuum distillation of the residue afforded 2,5-bis(tributylstannyl)furan as a viscous liquid. Yield 16.74 g, 74%. ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C) δ: 6.59 (2H, s), 1.61—1.50 (12H, m), 1.38—1.24 (12H, m), 1.10—0.98 (12H, m), 0.87 (18H, t, J=7.2 Hz).

Synthesis of 2,5-Bis(4-nitrophenyl)furan (4a)[44] In a two-neck round bottom flask equipped with reflux condenser under nitrogen atmosphere, was taken 1-bromo-4-nitrobenzene (1.6 g, 8.0 mmol), 2,5-bis(tributylstannyl)furan (2.6 g, 4 mmol), cesium fluoride (2.4 g, 16 mmol), tetrakis-(triphenylphosphine palladium (0.28 g, 0.24 mmol) and 1,4-dioxane (40 ml). Then the mixture was heated to 100 °C with periodical stirring and maintained for 12 h. After evaporating the solvent, dichloromethane (50 ml) was added. The obtained organic fraction after aqueous workup was passed through a short silica gel column. The solvent was removed and the product thus obtained was purified by column chromatography over silica gel using *n*-hexane/dichloromethane (1 : 1) as an eluent. Yield 1.13 g, 91%. mp 269—271 °C. ^{1}H-NMR (400 MHz, DMSO-d_6, 25 °C) δ: 8.30 (4H, d, J=8.4 Hz), 8.10 (4H, d, J=8.6 Hz), 7.51 (2H, s).

2,5-Bis(2-methyl-4-nitrophenyl)furan (4b)[45] This compound was synthesized from 2-bromo-5-nitrotoluene (1.73 g, 8.0 mmol) and 2,5-bis(tributylstannyl)furan (2.6 g, 4.0 mmol) by adopting the method akin to the synthesis of 2,5-bis(4-nitrophenyl)furan. Yield 1.24 g, 92%. mp 240—241 °C. ^{1}H-NMR (400 MHz, DMSO-d_6, 25 °C) δ: 8.26 (2H, d, J=1.5 Hz), 8.20—8.17 (2H, m), 8.14 (2H, d, J=8.6 Hz), 7.35 (2H, s) 2.70 (6H, s).

Synthesis of 2,5-Bis(4-aminophenyl)furan (5a)[44] Tin chloride ($SnCl_2\cdot 2H_2O$; 4.1 g, 18.0 mmol) was added to a suspension of 2,5-bis(4-nitrophenyl)furan (0.93 g, 3.0 mmol) in absolute ethanol/dimethyl sulfoxide (85 : 15) under nitrogen atmosphere and the mixture was heated to 85 °C for 5 h. After the completion of the reaction, it was cooled and the pH of the solution was raised between 7 and 8 by the addition of aqueous sodium hydroxide. The combined extracts after extraction with ethyl acetate (50 ml×5) were washed with water (50 ml×2) followed by brine (50 ml×2). Evaporation of the solvent after dried with sodium sulfate afforded a crude mass which was crystallized from benzene/hexane to give pure 2,5-bis(4-aminophenyl)furan as a brownish yellow solid. Yield 0.59 g, 78%. mp 217—219 °C. ^{1}H-NMR (400 MHz, DMSO-d_6, 25 °C) δ: 7.35 (4H, d, J=8.6 Hz), 6.54 (4H, d, J=8.0 Hz), 6.49 (2H, s), 5.19 (4H, br s). ^{13}C-NMR (100 MHz, DMSO-d_6, 25 °C) δ: 152.57, 148.41, 124.67, 119.18, 114.31, 104.15. GC/MS (m/z): 250 (M^+; $C_{16}H_{14}N_2O$).

2,5-Bis(4-amino-2-methylphenyl)furan (5b)[45] This compound was synthesized from its corresponding 2,5-bis(2-methyl-4-nitrophenyl)furan (1.0 g, 3 mmol) by using a method as described for the synthesis of 2,5-bis(4-aminophenyl)furan. Yield 0.63 g, 75%. mp 176—178 °C. ^{1}H-NMR (400 MHz, DMSO-d_6, 25 °C) δ: 7.39 (2H, d, J=8.0 Hz), 6.49 (4H, dd, J=10.6, 2.5 Hz), 6.44 (2H, s), 5.19 (4H, br s), 2.35 (6H, s). ^{13}C-NMR (100 MHz, DMSO-d_6, 25 °C) δ: 151.85, 148.11, 134.66, 127.59, 118.27, 116.26, 112.00, 107.56, 22.04. GC/MS (m/z): 278 (M^+; $C_{18}H_{18}N_2O$).

General Procedure for the Synthesis of 1-(Arylsulfonyl)-1*H*-indole (7a—e) In a two neck flask under nitrogen atmosphere, was added finely powdered sodium hydroxide (10 mmol), tetrabutylammonium hydrogensulfate (TBAHS) (0.1 mmol) and dichloromethane (15 ml). The mixture was stirred for 10 min while cooling in an ice bath (0—5 °C) and then indole (3.3 mmol) was added at the same temperature. After stirring for a couple of minutes, a solution of corresponding arylsulfonyl chlorides (3.3 mmol) in dichloromethane (10 ml) was added dropwise over a period of 15 min while not allowing the temperature to surpass ambient temperature. The stirring was continued further for 3 h and the mixture was filtered and concentrated after rinsing the solid with dichlormethane (10 ml). The obtained solid was subjected to column chromatographic separation over silica gel using *n*-hexane–ethyl acetate (100 : 15) as an eluent to afford their corresponding 1-(arylsulfonyl)-1*H*-indoles as pure solids.

1-(4-Methoxyphenylsulfonyl)-1*H*-indole (7a)[46] Yield 88%. mp 110—111 °C. ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C) δ: 7.98 (1H, d, J=8.4 Hz), 7.79—7.76 (3H, m), 7.54—7.52 (1H, m), 7.27—7.25 (1H, m), 7.14 (1H, t, J=2.4 Hz), 6.94—6.91 (1H, m), 6.86—6.84 (1H, m), 6.63 (1H, t, J=2.4 Hz), 3.74 (3H, s). ^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C) δ: 128.7, 128.3, 127.6, 126.4, 124.3, 123.9, 123.5, 121.5, 120.9, 120.1, 114.2, 109.1, 55.8.

1-(Phenylsulfonyl)-1*H*-indole (7b)[47] Yield 94%. mp 78—79 °C. ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C) δ: 7.99 (1H, dt, J=0.8, 8.0 Hz), 7.88—7.85 (2H, m), 7.58 (1H, d, J=3.59 Hz), 7.52—7.50 (2H, m), 7.42—7.40 (2H, m), 7.31—7.30 (1H, m), 7.22—7.19 (1H, m), 6.64 (1H, d, J=3.59 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C) δ: 138.4, 133.9, 130.9, 129.4, 126.9, 126.5, 124.8, 123.5, 121.6, 115.3, 113.7, 109.4.

1-(4-Bromophenylsulfonyl)-1*H*-indole (7c)[46] Yield 92%. mp 73—74 °C. ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C) δ: 8.08 (1H, dt, J=1.2, 8.0 Hz), 7.76 (1H, d, J=3.6 Hz), 7.66—7.63 (1H, m), 7.42—7.40 (3H, m), 7.24—7.21 (3H, m), 6.66 (1H, d, J=3.6 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C) δ: 136.2, 134.9, 131.5, 130.5, 128.3, 128.0, 124.5, 123.5, 121.9, 121.7, 113.2, 107.6.

1-(4-Methylphenylsulfonyl)-1*H*-indole (7d)[48] Yield 90%. mp 87—88 °C. ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C) δ: 7.98 (1H, d, J=8.4 Hz), 7.75—7.73 (2H, m), 7.56 (1H, d, J=3.6 Hz), 7.50 (1H, d, J=8.4 Hz), 7.24—7.20 (4H, m), 6.64 (1H, d, J=3.6 Hz), 2.30 (3H, s). ^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C) δ: 145.1, 130.1, 130.0, 127.0, 126.5, 124.7, 124.1, 123.4, 121.5, 120.9, 113.7, 109.2, 21.7.

1-(4-Chlorophenylsulfonyl)-1*H*-indole (7e)[46] Yield 91%. mp 78—79 °C. ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C) δ: 8.11 (1H, dd, J=1.8, 7.8 Hz),

7.79 (1H, d, J=3.6 Hz), 7.64—7.61 (2H, m), 7.40—7.37 (3H, m), 7.23—7.21 (2H, m), 6.68 (1H, d, J=3.6 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C) δ: 136.1, 134.4, 131.7, 130.3, 128.0, 127.9, 122.3, 121.9, 121.8, 121.6, 113.1, 107.5.

General Procedure for the Synthesis of 1-(Arylsulfonyl)-1*H*-indole-3-sulfonyl Chloride (8a—e) In a two-neck flask equipped with air condenser, was taken 1-(arylsulfonyl)-1*H*-indole (1.5 mmol) and acetonitrile (7 ml). After cooling (0—5 °C) in an ice bath, chlorosulfonic acid (6.0 mmol) was added carefully in a dropwise fashion and the dark brown solution was allowed to reach ambient temperature over a couple of hours, and was stirred for 48 h while maintaining the reaction temperature between 35—40 °C. Then the mixture was poured into crushed ice (200 g) and extracted with dichloromethane (20 ml×5). The combined organic layers were washed with saturated aqueous sodium hydrogencarbonate (25 ml×2) followed by brine (25 ml×2). Removal of the solvent under vacuum after drying over magnesium sulfate gave their corresponding 1-(arylsulfonyl)-1*H*-indole-3-sulfonyl chlorides as solids. An analytically pure sample was obtained after crystallization from acetonitrile.

1-(4-Methoxyphenylsulfonyl)-1*H*-indole-3-sulfonyl Chloride (8a) Yield 74%. mp 157—158 °C. ^{1}H-NMR (400 MHz, DMSO-d_6, 25 °C) δ: 7.97—7.91 (3H, m), 7.78 (1H, d, J=8.0 Hz), 7.62 (1H, s), 7.37 (1H, t, J=7.8 Hz), 7.28 (1H, t, J=7.5 Hz), 7.09 (2H, dd, J=9.0, 2.5 Hz), 3.78 (3H, s). ^{13}C-NMR (100 MHz, DMSO-d_6, 25 °C) δ: 164.3, 134.4, 130.5, 129.6, 128.6, 127.5, 125.2, 124.2, 123.6, 122.1, 115.5, 113.3, 56.2.

1-(Phenylsulfonyl)-1*H*-indole-3-sulfonyl Chloride (8b)[49] Yield 82%. mp 143—144 °C. ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C) δ: 8.40 (1H, s), 8.05—7.96 (4H, m), 7.70—7.65 (1H, m), 7.60—7.44 (4H, m). ^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C) δ: 136.9, 135.5, 134.5, 131.2, 130.2, 127.6, 127.3, 125.8, 125.2, 123.9, 120.6, 114.0.

1-(4-Bromophenylsulfonyl)-1*H*-indole-3-sulfonyl Chloride (8c) Yield 78%. mp 149—150 °C. ^{1}H-NMR (400 MHz, DMSO-d_6, 25 °C) δ: 7.99—7.93 (3H, m), 7.85—7.81 (3H, m), 7.71 (1H, s), 7.42—7.38 (1H, m), 7.35—7.32 (1H, m). ^{13}C-NMR (100 MHz, DMSO-d_6, 25 °C) δ: 136.4, 134.4, 133.4, 133.2, 130.9, 129.5, 129.0, 127.6, 125.5, 124.2, 124.0, 122.2, 113.3.

1-(4-Methylphenylsulfonyl)-1*H*-indole-3-sulfonyl Chloride (8d)[49] Yield 76%. mp 159—160 °C. ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C) δ: 8.38 (1H, s), 8.04—8.01 (1H, m), 7.98—7.95 (1H, m), 7.89 (2H, d, J=8.5 Hz), 7.54—7.43 (2H, m), 7.35 (2H, d, J=8.5 Hz), 2.40 (3H, s). ^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C) δ: 147.1, 134.5, 133.9, 131.2, 130.8, 127.7, 127.2, 125.7, 125.0, 123.9, 120.5, 114.0, 21.9.

1-(4-Chlorophenylsulfonyl)-1*H*-indole-3-sulfonyl Chloride (8e) Yield 79%. mp 168—169 °C. ^{1}H-NMR (400 MHz, DMSO-d_6, 25 °C) δ: 8.06 (2H, d, J=8.5 Hz), 7.93 (1H, d, J=8.6 Hz), 7.81 (1H, d, J=7.5 Hz), 7.70—7.66 (3H, m), 7.41—7.37 (1H, m), 7.34—7.30 (1H, m). ^{13}C-NMR (100 MHz, DMSO-d_6, 25 °C) δ: 140.3, 136.0, 134.4, 131.1, 130.5, 129.1, 127.6, 125.5, 124.1, 124.0, 122.2, 113.2.

General Procedure for the Synthesis of *N*,*N*′-[4,4′-(Furan-2,5-diyl)bis(4,1-arylene)]bis[1-(arylsulfonyl)-1*H*-indole-3-sulfonamides] (9a—j) To a solution of 2,5-bis(4-aminoaryl)furan (0.4 mmol) in *N*,*N*-dimethylformamide (8.0 ml) under nitrogen atmosphere, was added 1-(arylsulfonyl)-1*H*-indole-3-sulfonyl chloride (0.8 mmol). The mixture was stirred at ambient temperature for 6 h. after the addition of triethyl amine (0.86 mmol), and was extracted with ethyl acetate (10 ml×5) after adding water (50 ml). The combined organic fractions were washed with water (15 ml×2), dried over magnesium sulfate and evaporated under reduced pressure. Column chromatographic separation of the obtained crude solid over silica gel using *n*-hexane/ethyl acetate (40 : 60) as an eluent afforded their corresponding pure *N*,*N*′-[4,4′-(furan-2,5-diyl)bis(4,1-arylene)]bis[1-(arylsulfonyl)-1*H*-indole-3-sulfonamides] as solids.

***N*,*N*′-[4,4′-(Furan-2,5-diyl)bis(4,1-phenylene)]bis[1-(4-methoxyphenylsulfonyl)-1*H*-indole-3-sulfonamide] (9a)** Yield, 89%. mp 141—142 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 10.74 (2H, br s), 8.40 (2H, s), 7.94—7.88 (8H, m), 7.63 (4H, d, J=8.6 Hz), 7.46—7.37 (4H, m), 7.16 (4H, d, J=8.5 Hz), 6.95—6.93 (6H, m), 3.47 (6H, s). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 164.5, 152.3, 136.9, 134.1, 131.6, 130.1, 127.3, 126.6, 126.0, 125.0, 124.7, 124.6, 120.6, 119.9, 119.5, 115.4, 113.8, 107.9, 55.9. IR (KBr), cm^{-1}: 3446.3, 1594.3, 1498.4, 1445.3, 1381.2, 1267.1, 1190.9, 1168.3, 1150.8, 1110.7, 1092.5, 1021.9, 944.9, 833.6, 804.6, 756.1, 715.2, 671.7, 618.7, 566.6, 543.2. *Anal.* Calcd for $C_{46}H_{36}N_4O_{11}S_4$: C, 58.21; H, 3.82; N, 5.90; S, 13.51. Found: C, 58.25; H, 3.79; N, 5.94; S, 13.49.

***N*,*N*′-[4,4′-(Furan-2,5-diyl)bis(3-methyl-4,1-phenylene)]bis[1-(4-methoxyphenylsulfonyl)-1*H*-indole-3-sulfonamide] (9b)** Yield, 90%. mp 115—116 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 10.73 (2H, br s), 8.44 (2H, s), 7.96—7.89 (8H, m), 7.61 (2H, d, J=8.5 Hz), 7.46—7.38 (4H, m), 7.06 (2H, dd, J=8.5, 2.0 Hz), 7.01 (2H, d, J=2.0 Hz), 6.92 (4H, d, J=9.0 Hz), 6.75 (2H, s), 3.49 (6H, s), 2.37 (6H, s). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 164.5, 151.5, 136.9, 135.3, 134.1, 131.6, 130.1, 127.7, 127.4, 126.6, 125.1, 125.0, 124.7, 121.1, 120.6, 120.0, 116.5, 115.4, 113.8, 110.8, 55.9, 22.2. IR (KBr), cm^{-1}: 3446.1, 1594.3, 1496.9, 1445.1, 1381.5, 1267.2, 1168.6, 1151.0, 1110.7, 1092.6, 1020.9, 944.6, 832.9, 756.7, 715.8, 671.4, 621.7, 567.0, 544.3. *Anal.* Calcd for $C_{48}H_{40}N_4O_{11}S_4$: C, 59.00; H, 4.13; N, 5.73; S, 13.13. Found: C, 59.05; H, 4.15; N, 5.72; S, 13.16.

***N*,*N*′-[4,4′-(Furan-2,5-diyl)bis(4,1-phenylene)]bis[1-(phenylsulfonyl)-1*H*-indole-3-sulfonamide] (9c)** Yield, 88%. mp 163—164 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 10.71 (2H, br s), 8.41 (2H, s), 8.02—8.00 (4H, m), 7.94 (2H, d, J=8.0 Hz), 7.89 (2H, d, J=8.0 Hz), 7.61 (4H, d, J=8.0 Hz), 7.53—7.49 (6H, m), 7.45—7.38 (4H, m), 7.15 (4H, d, J=8.0 Hz), 6.93 (2H, s). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 152.3, 136.3, 134.2, 130.3, 127.5, 126.8, 125.2, 124.8, 124.6, 124.5, 120.7, 120.6, 119.9, 119.8, 113.8, 107.9. IR (KBr), cm^{-1}: 3446.4, 1612.4, 1587.8, 1528.3, 1502.8, 1449.1, 1391.9, 1272.0, 1190.4, 1153.9, 1135.5, 1111.3, 1086.1, 1072.1, 1005.7, 948.2, 825.4, 745.9, 703.9, 615.3, 562.1, 467.6. *Anal.* Calcd for $C_{44}H_{32}N_4O_9S_4$: C, 59.45; H, 3.63; N, 6.30; S, 14.43. Found: C, 59.42; H, 3.67; N, 6.32; S, 14.42.

***N*,*N*′-[4,4′-(Furan-2,5-diyl)bis(3-methyl-4,1-phenylene)]bis[1-(phenylsulfonyl)-1*H*-indole-3-sulfonamide] (9d)** Yield, 86%. mp 126—127 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 10.75 (2H, br s), 8.49 (2H, s), 8.05 (4H, d, J=7.5 Hz), 7.96 (2H, d, J=8.0 Hz), 7.91 (2H, d, J=7.6 Hz), 7.59 (2H, d, J=8.6 Hz), 7.54 (2H, d, J=7.5 Hz), 7.50—7.46 (6H, m), 7.42 (2H, d, J=7.5 Hz), 7.07—7.00 (4H, m), 6.76 (2H, s), 2.37 (6H, s). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 151.4, 136.3, 135.5, 135.3, 134.2, 131.5, 130.3, 127.7, 127.5, 126.8, 125.3, 125.2, 124.7, 121.4, 120.7, 116.8, 113.8, 110.9, 22.1. IR (KBr), cm^{-1}: 3446.0, 3322.9, 1611.3, 1528.6, 1496.5, 1447.1, 1375.0, 1326.3, 1269.4, 1187.9, 1151.6, 1112.0, 1090.7, 1052.0, 965.4, 947.0, 867.7, 796.4, 746.0, 730.8, 703.7, 684.3, 621.8, 566.2, 548.8. *Anal.* Calcd for $C_{46}H_{36}N_4O_9S_4$: C, 60.25; H, 3.96; N, 6.11; S, 13.99. Found: C, 60.29; H, 3.96; N, 6.14; S, 13.95.

***N*′,*N*′-[4,4′-(Furan-2,5-diyl)bis(4,1-phenylene)]bis[1-(4-bromophenylsulfonyl)-1*H*-indole-3-sulfonamide] (9e)** Yield, 79%. mp 152—153 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 10.76 (2H, br s), 8.48 (2H, s), 7.98—7.93 (8H, m), 7.69 (4H, d, J=8.5 Hz), 7.66 (4H, d, J=8.5 Hz), 7.49—7.42 (4H, m), 7.19 (4H, d, J=8.5 Hz), 6.96 (2H, s). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 152.3, 136.8, 135.4, 134.2, 133.4, 131.7, 130.0, 129.4, 126.9, 126.2, 125.3, 124.8, 124.7, 120.8, 119.6, 113.8, 108.0. IR (KBr), cm^{-1}: 3446.2, 1616.5, 1574.5, 1530.1, 1503.8, 1473.3, 1445,4, 1393.2, 1318.8, 1270.7, 1188.0, 1151.2, 1137.6, 1110.8, 1089.1, 1070.2, 1009.8, 945.9, 822.9, 745.9, 708.5, 618.4, 565.8, 425.2. *Anal.* Calcd for $C_{44}H_{30}Br_2N_4O_9S_4$: C, 50.48; H, 2.89; N, 5.35; S, 12.25. Found: C, 50.50; H, 2.91; N, 5.32; S, 12.28.

***N*,*N*′-[4,4′-(Furan-2,5-diyl)bis(3-methyl-4,1-phenylene)]bis[1-(4-bromophenylsulfonyl)-1*H*-indole-3-sulfonamide] (9f)** Yield, 75%. mp 140—141 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 10.76 (2H, br s), 8.50 (2H, s), 7.97 (4H, d, J=8.5 Hz), 7.94—7.91 (4H, m), 7.65 (4H, d, J=8.5 Hz), 7.61 (2H, d, J=8.6 Hz), 7.49—7.41 (4H, m), 7.07 (2H, dd, J=8.6, 2.0 Hz), 6.98 (2H, d, J=2.0 Hz), 6.76 (2H, s), 2.37 (6H, s). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 151.6, 136.7, 135.4, 135.3, 134.2, 133.4, 131.6, 130.0, 129.3, 127.7, 126.9, 125.3, 124.8, 121.3, 120.9, 120.8, 116.6, 113.8, 110.9, 22.2. IR (KBr), cm^{-1}: 3446.2, 1574.9, 1473.1, 1445.2, 1392.7, 1188.0, 1151.3, 1110.7, 1089.1, 1070.1, 1010.0, 945.5, 745.8, 708.2, 618.6, 565.9. *Anal.* Calcd for $C_{46}H_{34}Br_2N_4O_9S_4$: C, 51.40; H, 3.19; N, 5.21; S, 11.93. Found: C, 51.44; H, 3.18; N, 5.24; S, 11.91.

***N*,*N*′-[4,4′-(Furan-2,5-diyl)bis(4,1-phenylene)]bis[1-(4-methylphenyl)-1*H*-indole-3-sulfonamide] (9g)** Yield, 82%. mp 170—171 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 10.70 (2H, br s), 8.36 (2H, s), 7.90 (4H, dd, J=7.5, 1.5 Hz), 7.81 (4H, d, J=8.0 Hz), 7.63 (4H, d, J=9.0 Hz), 7.45—7.36 (4H, m), 7.20 (4H, d, J=8.0 Hz), 7.16 (4H, d, J=9.0 Hz), 6.95 (2H, s), 1.93 (6H, s). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 152.3, 146.5, 136.9, 134.1, 133.2, 131.8, 130.7, 127.5, 126.7, 126.0, 125.1, 124.7, 124.6, 120.6, 120.0, 119.5, 113.8, 107.9, 20.9. IR (KBr), cm^{-1}: 3446.1, 3301.0, 1596.1, 1504.0, 1473.6, 1445.5, 1379.4, 1338.3, 1190.7, 1176.4, 1150.8, 1109.2, 1089.4, 1052.7, 944.9, 904.5, 843.8, 812.6, 755.4, 711.9, 665.7, 617.5, 563.4, 533.9. *Anal.* Calcd for $C_{46}H_{36}N_4O_9S_4$: C, 60.25; H, 3.96; N, 6.11; S, 13.99. Found: C, 60.28; H, 3.97; N, 6.09; S, 14.05.

***N*,*N*′-[4,4′-(Furan-2,5-diyl)bis(3-methyl-4,1-phenylene)]bis[1-(4-methylphenyl)-1*H*-indole-3-sulfonamide] (9h)** Yield, 87%. mp 125—126 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 10.74 (2H, br s), 8.45 (2H, s), 7.93—7.90 (4H, m), 7.85 (4H, d, J=8.0 Hz), 7.62 (2H, d, J=8.6 Hz), 7.46—7.38 (4H, m), 7.17 (4H, d, J=8.5 Hz), 7.06 (2H, dd, J=8.3, 2.2 Hz), 7.01

(2H, d, J=2.0 Hz), 6.77 (2H, s), 2.37 (6H, s), 1.91 (6H, s). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 151.5, 146.5, 136.9, 135.2, 134.2, 133.3, 131.7, 130.6, 127.7, 127.4, 126.7, 125.2, 125.1, 124.8, 121.3, 120.7, 120.2, 116.6, 113.8, 110.9, 22.2, 20.9. IR (KBr), cm^{-1}: 3445.6, 3277.7, 1615.0, 1529.9, 1495.7, 1445.8, 1382.6, 1330.4, 1271.0, 1225.8, 1190.7, 1177.4, 1150.9, 1110.2, 1089.9, 1053.3, 1017.5, 969.3, 944.9, 812.3, 755.7, 711.3, 666.1, 621.8, 566.1, 535.0. *Anal.* Calcd for $C_{48}H_{40}N_4O_9S_4$: C, 61.00; H, 4.27; N, 5.93; S, 13.57. Found: C, 60.97; H, 4.27; N, 5.96; S, 13.53.

***N*,*N*′-[4,4′-(Furan-2,5-diyl)bis(4,1-phenylene)]bis[1-(4-chlorophenylsulfonyl)-1*H*-indole-3-sulfonamide] (9i)** Yield, 81%. mp 137—138 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 10.76 (2H, br s), 8.47 (2H, s), 8.05 (4H, d, J=8.6 Hz), 7.95—7.89 (4H, m), 7.62 (4H, d, J=8.5 Hz), 7.54 (4H, d, J=8.5 Hz), 7.48—7.40 (4H, m), 7.15 (4H, d, J=8.5 Hz), 6.94 (2H, s). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 152.2, 140.8, 136.8, 134.9, 134.2, 131.8, 130.5, 129.4, 126.9, 126.1, 125.3, 124.8, 124.6, 120.7, 120.6, 119.5, 113.8, 108.0. IR (KBr), cm^{-1}: 3446.5, 3296.0, 1584.5, 1530.4, 1503.8, 1476.5, 1445.7, 1388.4, 1337.4, 1270.5, 1220.4, 1186.4, 1151.3, 1137.8, 1110.9, 1086.5, 1053.3, 1013.3, 946.4, 911.5, 828.6, 757.4, 710.2, 630.0, 566.2, 480.5. *Anal.* Calcd for $C_{44}H_{30}Cl_2N_4O_9S_4$: C, 55.17; H, 3.16; N, 5.85; S, 13.39. Found: C, 55.19; H, 3.15; N, 5.88; S, 13.34.

***N*,*N*′-[4,4′-(Furan-2,5-diyl)bis(3-methyl-4,1-phenylene)]bis[1-(4-chlorophenylsulfonyl)-1*H*-indole-3-sulfonamide] (9j)** Yield, 83%. mp 135—137 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 10.76 (2H, br s), 8.50 (2H, s), 8.06 (4H, d, J=9.0 Hz), 7.96 (2H, d, J=8.0 Hz), 7.92 (2H, d, J=7.0 Hz), 7.60 (2H, d, J=8.5 Hz), 7.50 (4H, d, J=9.0 Hz), 7.47—7.40 (4H, m), 7.06 (2H, dd, J=8.5, 2.0 Hz), 6.99 (2H, d, J=2.0 Hz), 6.76 (2H, s), 2.37 (6H, s). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 149.8, 139.1, 134.9, 133.4, 133.1, 132.3, 129.7, 128.5, 127.5, 125.8, 125.0, 123.4, 122.9, 119.4, 119.0, 118.9, 114.8, 111.9, 109.0, 20.3. IR (KBr), cm^{-1}: 3446.1, 1576.6, 1530.1, 1495.6, 1476.6, 1445.5, 1387.2, 1332.0, 1271.0, 1186.9, 1151.8, 1110.7, 1086.5, 1053.1, 1013.2, 945.8, 827.2, 757.5, 709.9, 634.0, 566.3, 480.3. *Anal.* Calcd for $C_{46}H_{34}Cl_2N_4O_9S_4$: C, 56.04; H, 3.48; N, 5.68; S, 13.01. Found: C, 56.08; H, 3.51; N, 5.64; S, 13.05.

Antibacterial Evaluation The *in vitro* antibacterial activities were examined by the two-fold serial dilution technique. The medium used for the bacteria was Nutrient broth (NB). Microdilution panels were prepared containing two-fold dilutions of the compounds and standard drug in dimethyl formamide (DMF) ranging from 100 to 12.5 μg ml^{-1}. Seeded broth (broth containing microbial spores) was prepared in NB from 24 h old bacterial cultures on nutrient agar at 37±1 °C. The colony forming units (cfu) of the seeded broth were determined by plating method and adjusted in the range of 102—105 cfu ml^{-1}. Testing was performed at pH 7.4±0.2. A set of assay tubes containing only inoculated broth was kept as control and likewise solvent controls were also run simultaneously. The tubes were incubated in BOD incubators at *ca.* 37 °C. The minimum inhibitory concentrations (MICs) were recorded by visual observations after 24 h of incubation. For the standard, Streptomycin was used while DMF was used as a solvent control.

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