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Synthesis of new 3-(substituted-phenyl)-*N*-(2-hydroxy-2-(substituted-phenyl)ethyl)-*N*-methylthiophene-2-sulfonamide derivatives as antiproliferative agents

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N-N-Dimethylethylenediamine
2-(Methylamino)-1-phenylethanol

ABSTRACT

In the present work, we report the synthesis of a series of 3-(substituted phenyl)-*N*-(2-hydroxy-2-(substituted-phenyl)ethyl)-*N*-methylthiophene-2-sulfonamide derivatives through Suzuki and Buchwald reaction. We have optimized methodology for targets from milligram to multi-gram scale. The newly synthesized compounds were characterized by ^{1}H NMR, ^{19}F NMR, ^{13}C NMR, LC-MS techniques and purity was further checked by HPLC. The compounds were evaluated for their *in-vitro* antiproliferative activity against MCF-7, HeLa, A-549 and Du-145 cancer cell lines by CCK-8 assay. The preliminary bioassay suggests that most of the compounds show antiproliferation with different degrees and 5-fluorouracil was used as positive control. Among these compounds 2d, 2g, 2i, 4e, 4h and 4k are most active compared to the standard. All the synthesized compounds show IC_{50} values from 1.82-9.52 μM in different cell lines. Amongst these, compounds 2d, 2g, 2i, 4e, 4h and 4k were most potent, with IC_{50} values ranging from 1.82-4.28 μM in different cell lines.

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1. Introduction

Thiophene is a class of heterocyclic compounds, showing varying activity in medicinal and pharmaceutical fields. Various derivatives of thiophene are used as biologically active compounds for a variety of diseases [1,2]. They act as organic light-emitting diodes, organic field-effect transistors and also used in organic solar cells [3]. The linkage of thiophene is an important component in drug discovery. Substituted thiophene shows good anticancer [4] and antiproliferative activity [5]. Thiophene coupled with thiazole act as adenosine receptor antagonists [6]. Thiophene coupled with imidazole act as anti-mycobacterial agents [7]. Thiophene-2-carboxylic acid shows good agonist activity against the GPR35 [8]. The substituted thiophene acts as redoxactive inhibitors of keratinocyte hyperproliferation [9]. Thiophene act as anti-microbial [10] and anticancer agent [11-13]. Thiophene coupled with different heterocycles are reported different activeties like potential inducer of apoptosis [14], inhibitors of JAK-2 as potential treatments for myeloproliferative neoplasms [15], MMP-12 inhibitors [16], antitubercular agents [17], S6K inhibitors [18], MEK inhibitors [19] as well as antimitotic agents [20]. The carbon-nitrogen and carbon-carbon bonds aree formed by Buchwald and Suzuki coupling reactions [21,22], which is used for the different couplings in present manuscript. Our research group previously reported synthesis, characterization, biological evaluation for derivatives of thiazole, piperidone, amides and sulfonamides [23-27]. In continuation of our research, we have synthesized new derivatives containing amide, sulfonamide along with thiophene in one frame work. The synthetic methods adopted for the preparation of the 3-(substituted-phenyl)-*N*-(2-hydroxy-2-(substituted phenyl)ethyl)-*N*-methylthiophene-2-sulfonamide compounds (**2a-i** and **4a-o**) are depicted in Scheme 1 and 2 presented below. We herein report the synthesis of new substituted thiophene-sulfonamide coupled derivatives (Scheme 1) having C-N, C-O (Scheme 2) and C-C bond. Total 24 derivatives were synthesized with the aim of investigating their antiproliferative activity. The synthetic methods adopted for the preparation of the title compounds (**2a-i** and **4a-o**) are presented below.

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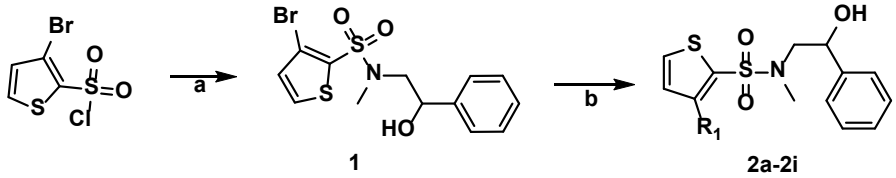

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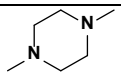
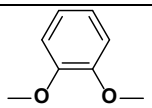
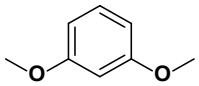
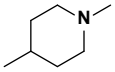
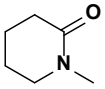
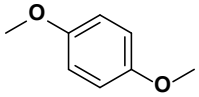
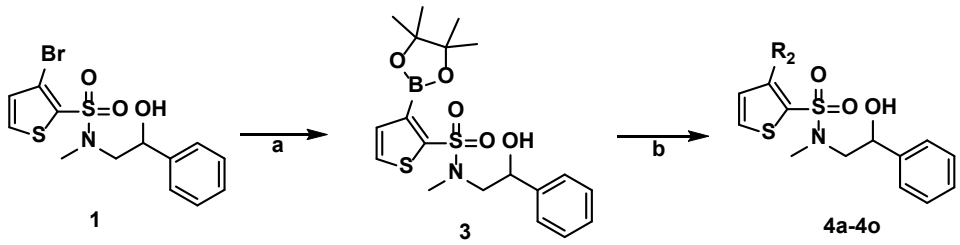
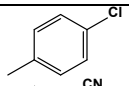
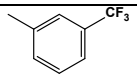
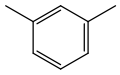
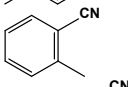
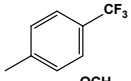
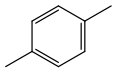
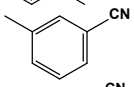
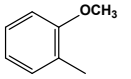
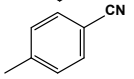
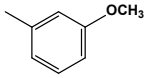
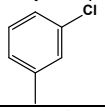
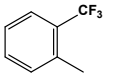
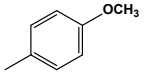
2a		2d		2g	
2b		2e		2h	
2c		2f		3i	

Reagent and conditions: (**a**) DMF, potassium carbonate, 2-(methylamino)-1-phenylethanol, tetra-*n*-butyl ammonium iodide 130 °C for 2 h. (**b**) DMF, amines, copper acetate, potassium phosphate, *N*,*N*-dimethylethylenediamine 110 °C for 12 h.

Scheme 1



Compound	R1	Compound	R1	Compound	R1
4a		4f		4k	
4b		4g		4l	
4c		4h		4m	
4d		4i		4n	
4e		4j		4o	

Reagent and conditions: (**a**) dioxane, water, 4,4,4',4',5,5,5',5'-octamethyl-2,2'-*bis*-(1,3,2-dioxaborolane), potassium acetate, [1,1′-*bis*(diphenylphosphino) ferrocene]dichloropalladium(II), 110 °C for 6 h. (**b**) dioxane, aromatic bromides, palladium acetate, potassium phosphate, 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl 110 °C for 12 h.

Scheme 2

We have tried to develop simplified reaction conditions for all the steps by avoiding costly reagents, tedious purifications and longer reaction times.

2. Experimental

2.1. Instrumentation and materials

All chemicals, unless otherwise specified, were purchased from commercial sources and they were used without further purification. The major chemicals were purchased from Sigma Aldrich and Avra labs. The development of reactions was monitored by thin layer chromatography (TLC) analysis on Merck pre-coated silica gel 60 F_{254} aluminum sheets, visualized by UV light. IR spectra were recorded on a FT-IR (Bruker). Melting points were recorded on SRS Optimelt, melting point apparatus and are uncorrected. The ^{1}H NMR spectra were recorded on a 400 MHz Varian NMR spectrometer. The ^{13}C were recorded on a 100 MHz Varian NMR spectrometer. The chemical shifts are reported as NMR spectra δ_{ppm} units. The following abbreviations are used; singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m) and broad (br). Mass spectra were taken with Micromass-QUATTRO-II of WATER mass spectrometer.

2.2. Synthesis

2.2.1. Synthesis of compound 1

To a stirred solution of 3-bromothiophene-2-sulfonyl chloride (2.61 g, 1 mmol) in DMF (10 mL) was added potassium carbonate (2.07 g, 15 mmol), 2-(methylamino)-1-phenylethanol (1.66 g, 11 mmol) and tetra-*n*-butyl ammonium iodide (0.026 g, 1 mmol). The reaction mixture was heated to 130 °C for 2 h and the progress of reaction was monitored by TLC. Cold water (50 mL) was added and stirred the reaction mass for 1 h. The solid precipitates out, filter it and wash it with excess of water and dry it properly to obtain compound **1**.

3-Bromo-N-(2-hydroxy-2-phenylethyl)-N-methylthiophene-2-sulfonamide (**1**): Color: White. Yield: 3.4 g, 90%. M.p.: 115-116 °C. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.76 (t, 3H, N-CH_3), 3.13-3.09 (m, 2H, CH_3-N-CH_2), 4.81-4.71 (m, 1H, OH-CH), 5.65 (d, *J* = 4.4 Hz, 1H, OH), 7.30-7.22 (m, 1H, Ar-H), 7.34 (m, 4H, Ar-H), 7.39 (d, *J* = 5.2 Hz, 1H, Ar-H), 7.49 (d, *J* = 5.2 Hz, 1H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 139.35, 131.12, 129.96, 128.75, 128.26, 127.31, 126.44, 126.33, 121.40, 70.66, 57.35, 36.34. LC-MS (*m/z*): 376 (M+H). HPLC [t_R(min) (content)]: 6.50 (95.4%).

2.2.2. General procedure for synthesis of compounds 2a-i

To a stirred solution of compound **1** (1 mmol) in DMF were added substituted amines (2 mmol), copper acetate (0.2 mmol), potassium phosphate (3 mmol) and *N,N*-dimethyl ethylenediamine (0.1 mmol). Degas reaction mixture using argon and heat reaction mixture to 110 °C for 12 h. Progress of reaction was monitored by TLC. Pour the reaction mixture on chilled water and stir it for 10 min. The mixture was extracted with 2 × 10 mL of ethyl acetate. Collected organic layer was washed with 10 mL of water and 10 mL of brine. The organic layer was dried over anhydrous sodium sulfate, evaporated under reduced pressure to obtain gummy material. Purification done by silica gel (100-200 mesh) column chromatography by using 40-80 % ethyl acetate-hexane to obtain the compounds **2a**-**i**.

N-(2-Hydroxy-2-phenylethyl)-N-methyl-3-(piperidin-1-yl) thiophene-2-sulfonamide (**2a**): Color: White. Yield: 0.348 g, 91%. M.p.: 111-113 °C. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.86-1.79 (q, *J* = 9.8, 4.8 Hz, 2H, CH_2-CH_2), 1.98-1.90 (q, *J* = 12.4, 4.2 Hz, 2H, N-CH_2-CH_2), 2.68-2.41 (q, *J* = 12.2, 4.2 Hz, 4H, N-CH_2-CH_2), 2.74 (s, 3H, N-CH_3), 3.16-3.02 (m, 2H, CH_3-N-CH_2), 3.82-3.80 (q, 2H, N-CH_2), 4.72-4.60 (m, 1H, OH-CH), 5.61 (d, *J* = 6.2 Hz, 1H, OH), 6.81 (d, *J* = 6.8 Hz, 1H, Ar-H), 7.42-7.16 (m, 5H, Ar-H), 7.47-7.42 (d, 1H, *J* = 7.2 Hz, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 140.35, 131.32, 129.76, 128.95, 128.46, 127.33, 126.40, 126.35, 121.40, 70.66, 57.35, 48.12, 36.34, 28.12, 28.11, 25.46. LC-MS (*m/z*): 381 (M+H). Anal. calcd. for $C_{18}H_{24}N_2O_3S_2$: C, 56.82; H, 6.36; N, 7.36. Found: C, 57.21; H, 6.76; N, 7.76%. HPLC [t_R(min) (content)]: 6.51 (96.4%).

N-(2-Hydroxy-2-phenylethyl)-N-methyl-3-(pyrrolidin-1-yl) thiophene-2-sulfonamide (**2b**): Color: White. Yield: 88%. M.p.: 106-108 °C. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.22-2.08 (q, *J* = 13.2, 4.8 Hz, 2H, CH_2-CH_2), 2.60-2.50 (q, *J* = 12.2, 4.4 Hz, 2H, CH_2-CH_2), 2.78 (s, 3H, N-CH_3), 3.26-3.02 (m, 4H, CH_3-N-CH_2, N-CH_2), 3.82-3.80 (q, *J* = 12.2, 4.6 Hz, 2H, N-CH_2), 4.78-4.68 (m, 1H, OH-CH), 5.60 (d, *J* = 6.2 Hz, 1H, OH), 6.71 (d, *J* = 7.2 Hz, 1H, Ar-H), 7.38-7.22 (m, 5H, Ar-H), 7.48-7.40 (d, *J* = 7.6 Hz, 1H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 140.25, 131.42, 120.76, 128.85, 128.66, 127.73, 126.42, 126.36, 121.40, 70.66, 57.35, 48.12, 45.32, 36.34, 28.12. LC-MS (*m/z*): 367 (M+H). Anal. calcd. for $C_{17}H_{22}N_2O_3S_2$: C, 55.71; H, 6.05; N, 7.64. Found: C, 55.31; H, 5.65; N, 7.26%. HPLC [t_R(min) (content)]: 6.80 (99.24%).

N-(2-Hydroxy-2-phenylethyl)-N-methyl-3-(4-methylpiperidin-1-yl)thiophene-2-sulfonamide (**2c**): Color: Yellow. Yield: 83%. M.p.: 86-87 °C. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.42-1.36 (m, 4H, CH-CH_2), 1.76 (d, *J* = 6.8 Hz, 3H, CH-CH_3), 1.96 (q, *J* = 4.4 Hz, 1H, CH_3-CH), 2.76 (t, 3H, N-CH_3), 3.13-3.09 (m, 2H, CH_3-N-CH_2), 3.82-3.80 (q, *J* = 11.2, 3.8 Hz, 4H, N-CH_2), 4.81-4.71 (m, 1H, OH-CH), 5.65 (d, *J* = 5.4 Hz, 1H, OH), 7.30-7.22 (m, 1H, Ar-H), 7.34 (m, 4H, Ar-H), 7.39 (d, *J* = 5 Hz, 1H, Ar-H), 7.49 (d, *J* = 5 Hz, 1H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 139.45,131.22, 129.76, 128.45, 128.36, 127.51, 126.44, 126.39, 121.41, 70.66, 57.35, 46.35, 36.34, 36.33, 20.23. LC-MS (*m/z*): 395 (M+H). Anal. calcd. for $C_{19}H_{26}N_2O_3S_2$: C, 57.84; H, 6.64; N, 7.10. Found: C, 58.24; H, 7.04; N, 7.50%. HPLC [t_R(min) (content)]: 6.81 (99.14%).

N-(2-Hydroxy-2-phenylethyl)-N-methyl-3-(4-methylpiperazin-1-yl)thiophene-2-sulfonamide (**2d**): Color: White. Yield: 83%. M.p.: 116-117 °C. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.22 (s, 3H, N-CH_3), 2.42 (s, 4H, N-CH_2-CH_2), 2.76 (t, *J* = 7.6 Hz, 3H, N-CH_3), 3.13-3.09 (m, 6H, CH_3-N-CH_2, N-CH_2-CH_2), 4.81-4.71 (m, 1H, OH-CH), 5.65 (d, *J* = 5.4 Hz, 1H, OH), 7.30-7.22 (m, 1H, Ar-H), 7.34 (m, 4H, Ar-H), 7.39 (d, *J* = 5 Hz, 1H, Ar-H), 7.49 (d, *J* = 5 Hz, 1H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 139.65, 132.12, 129.96, 129.75, 128.36, 127.31, 126.54, 126.43, 121.60, 70.60, 57.35, 56.11, 46.36, 40.88, 36.30. LC-MS (*m/z*): 396 (M+H). Anal. calcd. for $C_{18}H_{25}N_3O_3S_2$: C, 54.66; H, 6.37; N, 10.62. Found: C, 54.26; H, 5.97; N, 10.22%. HPLC [t_R(min) (content)]: 6.82 (99.22%).

N-(2-Hydroxy-2-phenylethyl)-N-methyl-3-(2-oxopyrrolidin-1-yl)thiophene-2-sulfonamide (**2e**): Color: White. Yield: 87%. M.p.: 96-98 °C. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.22-2.08 (q, *J* = 13.2, 3.6 Hz, 2H, CH_2-CH_2), 2.61-2.51 (q, *J* = 11.2, 3.8 Hz, 2H, N-CH_2), 2.74 (s, 3H, N-CH_3), 3.16-3.02 (m, 2H, CH_3-N-CH_2), 3.82-3.80 (q, *J* = 9.8, 3.4 Hz, 2H, N-CO-CH_2), 4.78-4.70 (m, 1H, OH-CH), 5.61 (d, *J* = 6.4 Hz, 1H, OH), 6.71 (d, *J* = 6.8 Hz, 1H, Ar-H), 7.41-7.22 (m, 5H, Ar-H), 7.49-7.42 (d, *J* = 7.8 Hz, 1H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 176.12, 139.35, 131.12, 129.96, 128.75, 128.26, 127.31, 126.44, 126.33, 121.40, 70.66, 57.35, 36.40.32, 35.12, 34.22, 20.88. LC-MS (*m/z*): 381 (M+H). Anal. calcd. for $C_{17}H_{20}N_2O_4S_2$: C, 53.67; H, 5.30; N, 7.36. Found: C, 54.06; H, 5.70; N, 7.76%. HPLC [t_R(min) (content)]: 6.15 (99.7%).

N-(2-Hydroxy-2-phenylethyl)-N-methyl-3-(2-oxopiperidin-1-yl)thiophene-2-sulfonamide (**2f**): Color: White. Yield: 84%. M.p.: 104-105 °C. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.86-1.79 (q, *J* = 13.6, 3.6 Hz, 2H, CH_2-CH_2), 1.98-1.90 (q, *J* = 12.4, 4.4 Hz, 2H, CO-CH_2-CH_2), 2.61-2.51 (q, *J* = 12.2, 4.6 Hz, 2H, N-CH_2), 2.74 (s, 3H, N-CH_3), 3.16-3.02 (m, 2H, CH_3-N-CH_2), 3.82-3.80 (q, *J*= 10.2, 3.6 Hz, 2H, N-CO-CH_2), 4.72-4.60 (m, 1H, OH-CH), 5.61 (d, *J* = 6 Hz, 1H, OH), 6.81 (d, *J* = 7.2 Hz, 1H, Ar-H), 7.40-7.18 (m, 5H, Ar-H), 7.47-7.42 (d, *J* = 7.2 Hz, 1H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 175.62, 139.45, 132.12, 129.76, 128.45, 128.26, 127.81, 126.64, 126.53, 121.63, 70.56, 57.45, 38.64, 36.34, 35.12, 26.46, 26.41. LC-MS (*m/z*): 395 (M+H). Anal. calcd. for $C_{18}H_{22}N_2O_4S_2$: C, 54.80; H, 5.62; N, 7.10. Found: C, 54.4; H, 5.22; N, 6.10%. HPLC [t_R(min) (content)]: 6.41 (95.4%).

N-(2-Hydroxy-2-phenylethyl)-3-(2-methoxyphenoxy)-N-methylthiophene-2-sulfonamide (**2g**): Color: White. Yield: 78%. M.p.: 116-118 °C. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.70 (s, 3H, N-CH_3), 3.09-3.02 (m, 2H, CH_3-N-CH_2), 3.77 (s, 3H, Ar-OCH_3), 4.73-4.71 (m, 1H, OH-CH), 6.53 (d, *J* = 5 Hz, 1H, OH), 7.0 (t, *J* = 7.8 Hz, 1H, Ar-H), 7.23 (m, 2H, Ar-H), 7.33-7.26 (m, 7H, Ar-H), 7.36 (d, *J* = 7.4 Hz, 1H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 151.32, 147.31, 139.45, 131.22, 129.76, 128.75, 128.56, 127.41, 126.64, 126.53, 122.21, 122.11, 121.40, 70.56, 57.35, 55.46, 36.34. LC-MS (*m/z*): 420 (M+H). Anal. calcd. for $C_{20}H_{21}NO_5S_2$: C, 57.26; H, 5.05; N, 3.34. Found: C, 57.38; H, 4.98; N, 3.33%. HPLC [t_R(min) (content)]: 8.42 (99.66%).

N-(2-Hydroxy-2-phenylethyl)-3-(3-methoxyphenoxy)-N-methylthiophene-2-sulfonamide (**2h**): Color: White. Yield: 74%. M.p.: 136-138 °C. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.73 (s, 3H, N-CH_3), 3.14-3.04 (m, 2H, CH_3-N-CH_2), 3.75 (s, 3H, Ar-OCH_3), 4.76-4.71 (m, 1H, OH-CH), 5.59 (d, *J* = 5.2 Hz, 1H, OH), 6.72 (d, *J* = 5 Hz, 1H, Ar-H), 6.86-6.78 (m, 3H, Ar-H), 7.28-7.24 (m, 1H, Ar-H), 7.35-7.32 (m, 5H, Ar-H), 7.42 (d, *J* = 5 Hz, 1H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 162.12, 158.6, 139.35, 131.12, 129.96, 130.46, 128.75, 128.66, 127.31, 126.44, 126.33, 121.60, 108.68, 106.46, 105.20, 70.69, 57.35, 56.31, 36.42. LC-MS (*m/z*): 420 (M+H). Anal. calcd. for $C_{20}H_{21}NO_5S_2$: C, 57.26; H, 5.05; N, 3.34. Found: C, 57.36; H, 5.07; N, 3.32%. HPLC [t_R(min) (content)]: 7.67 (99.78%).

N-(2-Hydroxy-2-phenylethyl)-3-(4-methoxyphenoxy)-N-methylthiophene-2-sulfonamide (**2i**): Color: White. Yield: 82%. M.p.: 126-127 °C. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.66 (s, 3H, N-CH_3), 3.12-3.02 (m, 2H, CH_3-N-CH_2), 3.76 (s, 3H, Ar-OCH_3), 4.68-4.62 (m, 1H, OH-CH), 5.58 (d, *J* = 5 Hz, 1H, OH), 6.76 (d, *J* = 5.5 Hz, 1H, Ar-H), 7.01 (d, *J* = 5 Hz, 2H, Ar-H), 7.24-7.19 (m, 6H, Ar-H), 7.35 (d, *J* = 6 Hz, 1H, Ar-H), 7.41-7.39 (d, *J* = 5 Hz, 1H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 155.8, 150.7, 139.45, 131.12, 129.76, 128.65, 128.26, 127.51, 126.44, 126.33, 121.60, 115.61, 115.42, 70.66, 57.35, 56.63, 36.38. LC-MS (*m/z*): 420 (M+H). Anal. calcd. for $C_{20}H_{21}NO_5S_2$: C, 57.26; H, 5.05; N, 3.34. Found: C, 57.28; H, 5.01; N, 3.36%. HPLC [t_R(min) (content)]: 8.38 (99.72%).

2.2.3. Synthesis of compound 3

To a stirred solution of compound **1** (3.76 g, 10 mmol) in dioxane (5 mL) water (1 mL) was added 4,4,4',4',5,5,5',5'-octamethyl-2,2'-*bis*-(1,3,2-dioxaborolane) (5.08 g, 20 mmol), potassium acetate (2.94 g, 30 mmol) and [1,1′-*bis*(diphenylphosphino)ferrocene]dichloro palladium(II) (1.63 g, 0.2 mmol). Degas reaction mixture using argon and heat reaction mixture to 110 °C for 6 h. Progress of reaction was monitored by TLC. Cooled reaction mixture to room temperature, filtered it through a pad of celite and filtrate evaporated under reduced pressure. Extracted it with ethyl acetate (2 × 10 mL), separated, washed with water (10 mL) and brine (10 mL). Organic layer was dried over anhydrous sodium sulfate evaporated under reduced pressure to obtain gummy material. Purification done by silica gel (100-200 mesh) column chromatography by using 40-80 % ethyl acetate-hexane to obtain compound **3**.

N-(2-Hydroxy-2-phenylethyl)-N-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-sulfonamide (**3**): Color: White. Yield: 3.80 g, 90%. M.p.: 95-96 °C. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 0.4 (s, 12H, B-C(CH_3)$_4$), 2.78 (t, *J* = 7.6 Hz, 3H, N-CH_3), 3.13-3.06 (m, 2H, CH_3-N-CH_2), 4.81-4.71 (m, 1H, OH-CH), 5.61 (d, *J* = 5 Hz, 1H, OH), 7.30-7.20 (m, 1H, Ar-H), 7.34 (m, 4H, Ar-H), 7.36 (d, *J* = 5 Hz, 1H, Ar-H), 7.48 (d, *J* = 5 Hz, 1H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 139.35, 131.12, 129.96, 128.75, 128.26, 127.31, 126.44, 126.33, 121.40, 83.55, 70.66, 57.35, 36.34, 22.26. LC-MS (*m/z*): 424 (M+H). HPLC [t_R(min) (content)]: 6.50 (95.40%).

2.2.4. General procedure for synthesis of compounds 4a-o

To a stirred solution of compound **3** (1 mmol) in dioxane was added aromatic bromides (2 mmol), palladium acetate (0.2 mmol), potassium phosphate (3 mmol) and 2-dicyclohexyl phosphino-2',6'-dimethoxybiphenyl (0.1 mmol). Degas reaction mixture using argon and heat reaction mixture to 110 °C for 12 h. Progress of reaction was monitored by TLC. Cooled reaction mixture to room temperature, filtered it through a pad of celite and filtrate evaporated under reduced pressure. Extracted it with ethyl acetate (2 × 10 mL). Collected organic layer was washed with 10 mL of water and 10 mL of brine. Organic layer was dried over anhydrous sodium sulfate evaporated under reduced pressure to obtain gummy material. Purification done by silica gel (100-200 mesh) column chromatography by using 30-80 % ethyl acetate-hexane to obtain the compound **4a**-**4o**.

N-(2-Hydroxy-2-phenylethyl)-N-methyl-3-(o-tolyl)thiophene-2-sulfonamide (**4a**): Color: White. Yield: 0.036 g, 90%. M.p.: 126-127 °C. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.39 (s, 3H, Ar-CH_3), 2.79 (s, 3H, N-CH_3), 3.15 (m, 2H, CH_3-N-CH_2), 4.79-4.77 (m, 1H, OH-CH), 5.64 (d, *J* = 4.4 Hz, 1H, OH), 7.31-7.26 (m, 4H, Ar-H), 7.35-7.32 (m, 5H, Ar-H), 7.44 (d, *J* = 3.2 Hz, 1H, Ar-H), 7.64 (d, *J* = 4 Hz, 1H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 140.43, 138.64, 136.33,133.45, 131.14, 128.95, 128.18, 127.35, 127.34, 126.24, 126.23, 125.59, 125.54, 124.68, 124.32, 124.22, 71.58, 57.38, 36.35, 24.45. LC-MS (*m/z*): 410 (M+Na). Anal. calcd. for $C_{20}H_{21}NO_3S_2$: C, 61.99; H, 5.46; N, 3.61. Found: C, 61.59; H, 5.06; N, 3.21%. HPLC [t_R(min) (content)]: 8.13 (97.3%).

N-(2-Hydroxy-2-phenylethyl)-N-methyl-3-(m-tolyl)thiophene-2-sulfonamide (**4b**): Color: White. Yield: 87%. M.p.: 148-149 °C. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.33 (s, 3H, Ar-CH_3), 2.78 (s, 3H, N-CH_3), 3.11 (m, 2H, CH_3-N-CH_2), 4.83-4.75 (m, 1H, OH-CH), 5.62 (d, *J* = 4.4 Hz, 1H, OH), 7.22 (d, *J* = 8 Hz, 1H, Ar-H), 7.29-7.25 (m, 1H, Ar-H), 7.35-7.32 (m, 4H, Ar-H), 7.55-7.51 (m, 3H, Ar-H), 7.62-7.58 (m, 2H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 140.59, 138.74, 136.39, 133.25, 131.14, 128.85, 128.14, 127.35, 127.34, 126.14, 126.13, 125.5, 125.44, 124.68, 124.32, 124.22, 71.48, 57.42, 36.37, 24.53. LC-MS (*m/z*): 370 (M-H_2O). Anal. calcd. for $C_{20}H_{21}NO_3S_2$: C, 61.99; H, 5.46; N, 3.61. Found: C, 62.39; H, 5.86; N, 4.01%. HPLC [t_R(min) (content)]: 8.21 (99.3%).

N-(2-Hydroxy-2-phenylethyl)-N-methyl-3-(p-tolyl)thiophene-2-sulfonamide (**4c**): Color: White. Yield: 93%. M.p.: 129-130 °C. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.39 (s, 3H, Ar-CH_3), 2.83 (s, 3H, N-CH_3), 3.17 (m, 2H, CH_3-N-CH_2), 4.83-4.79 (m, 1H, OH-CH), 5.62 (d, *J* = 4.4 Hz, 1H, OH), 7.27-7.25 (m, 3H, Ar-H), 7.35-7.34 (m, 4H, Ar-H), 7.56 (d, *J* = 4 Hz, 1H, Ar-H), 7.63-7.60 (m, 3H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 140.41, 138.34, 136.19, 133.15, 131.14, 128.85, 128.44, 127.35, 127.24, 126.14, 126.13, 125.5, 125.64, 124.68, 124.22, 124.21, 71.38, 57.41, 36.37, 24.52. LC-MS (*m/z*): 370 (M-H_2O). Anal. calcd. for $C_{20}H_{21}NO_3S_2$: C, 61.99; H, 5.46; N, 3.61. Found: C, 61.59; H, 5.06; N, 3.21%. HPLC [t_R(min) (content)]: 8.16 (98.9%).

3-(2-Chlorophenyl)-N-(2-hydroxy-2-phenylethyl)-N-methylthiophene-2-sulfonamide (**4d**): Color: White. Yield: 86%. M.p.: 134-135 °C. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.80 (s, 3H, N-CH_3), 3.19-3.11 (m, 2H, CH_3-N-CH_2), 4.79-4.76 (m, 1H, OH-CH), 5.64 (d, *J* = 4.4 Hz, 1H, OH), 7.28-7.25 (m, 1H, Ar-H), 7.35-7.32 (m, 4H, Ar-H), 7.48-7.44 (m, 2H, Ar-H), 7.55 (d, *J* = 4 Hz, 1H, Ar-H), 7.64-7.62 (m, 1H, Ar-H), 7.73 (d, *J* = 4 Hz, 1H, Ar-H), 7.74-7.71 (m, 1H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 147.63, 142.87, 136.39, 134.22, 134.16, 133.25, 131.14, 128.75, 128.14, 127.45, 127.34, 126.44, 126.43, 125.53, 125.44, 124.78, 71.58, 57.42, 36.36. LC-MS (*m/z*): 408 (M+H). Anal. calcd. for $C_{19}H_{18}ClNO_3S_2$: C, 55.94; H, 4.45; N, 3.43. Found: C, 56.34; H, 4.85; N, 3.83%.HPLC [t_R(min) (content)]: 8.06 (97.09%).

3-(3-Chlorophenyl)-N-(2-hydroxy-2-phenylethyl)-N-methylthiophene-2-sulfonamide (**4e**): Color: White. Yield: 91%. M.p.: 155-156 °C. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.80 (s, 3H, N-CH_3), 3.16-3.13 (m, 2H, CH_3-N-CH_2), 4.78-4.77 (m, 1H, OH-CH), 5.61 (d, *J* = 4.4 Hz, 1H, OH), 7.28-7.27 (m, 1H, Ar-H), 7.35-7.32 (m, 4H, Ar-H), 7.48-7.46 (m, 2H, Ar-H), 7.73-7.64 (m, 3H, Ar-H), 7.85 (s, 1H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 147.59, 142.94, 136.39, 134.10, 134.06, 133.25, 131.14, 128.85, 128.14, 127.35, 127.34, 126.14, 126.13, 125.5, 125.44, 124.68, 71.48, 57.42, 36.37. LC-MS (*m/z*): 408 (M+H). Anal. calcd. for $C_{19}H_{18}ClNO_3S_2$: C, 55.94; H, 4.45; N, 3.43. Found: C, 56.34; H, 4.85; N, 3.83%. HPLC [t_R(min) (content)]: 8.07 (97.8%).

3-(4-Chlorophenyl)-N-(2-hydroxy-2-phenylethyl)-N-methylthiophene-2-sulfonamide (**4f**): Color: White. Yield: 85%. M.p.: 150-151 °C. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.79 (s, 3H, N-CH_3), 3.15-3.12 (m, 2H, CH_3-N-CH_2), 4.78-4.75 (m, 1H, OH-CH), 5.63 (d, *J* = 4.4 Hz, 1H, OH), 7.28-7.26 (m, 1H, Ar-H), 7.35-7.34 (m, 4H, Ar-H), 7.51 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.66-7.63 (q, *J* = 8.4 & 4 Hz, 2H, Ar-H), 7.77 (d, *J* = 8.8 Hz, 2H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 147.57, 142.84, 136.42, 134.13, 134.16, 133.25, 131.14, 128.75, 128.14, 127.35, 127.34, 126.24, 126.23, 125.5, 125.44, 124.78, 71.49, 57.39, 36.35. LC-MS (*m/z*): 430 (M+Na). Anal. calcd. for $C_{19}H_{18}ClNO_3S_2$: C, 55.94; H, 4.45; N, 3.43. Found: C, 55.54; H, 4.05; N, 3.03%. HPLC [t_R(min) (content)]: 8.25 (99.08%).

3-(2-Cyanophenyl)-N-(2-hydroxy-2-phenylethyl)-N-methylthiophene-2-sulfonamide (**4g**): Color: White. Yield: 84%. M.p.: 114-115 °C. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.77 (s, 3H, N-CH_3), 3.14-3.10 (m, 2H, CH_3-N-CH_2), 4.78-4.77 (m, 1H, OH-CH), 5.64 (d, *J* = 4.4 Hz, 1H, OH), 7.32-7.30 (m, 1H, Ar-H), 7.35-7.35 (m, 4H, Ar-H), 7.49-7.42 (m, 3H, Ar-H), 7.56 (m, 1H, Ar-H), 7.61 (d, *J* = 7.6 Hz, 1H, Ar-H), 7.90 (s, 1H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 170.51, 147.71, 142.96, 137.42, 136.44, 132.28, 129.86, 129.46, 129.19, 128.81, 128.15, 128.14, 127.65, 127.35, 126.96, 126.63, 126.61, 71.52, 57.41, 36.42. LC-MS (*m/z*): 399 (M+H). Anal. calcd. for $C_{20}H_{18}N_2O_3S_2$: C, 60.28; H, 4.55; N, 7.03. Found: C, 60.68; H, 4.95; N, 7.83%. HPLC [t_R(min) (content)]: 6.07 (99.5%).

3-(3-Cyanophenyl)-N-(2-hydroxy-2-phenylethyl)-N-methylthiophene-2-sulfonamide (**4h**): Color: White. Yield: 89%. M.p.: 110-111 °C. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.80 (s, 3H, N-CH_3), 3.19-3.11 (m, 2H, CH_3-N-CH_2), 4.80-4.76 (m, 1H, OH-CH), 5.64 (d, *J* = 4.4 Hz, 1H, OH), 7.32-7.24 (m, 1H, Ar-H), 7.37-7.34 (m, 4H, Ar-H), 7.68-7.63 (m, 2H, Ar-H), 7.95(d, *J* = 4.4 Hz, 1H, Ar-H), 7.86 (d, *J* = 7.6 Hz, 1H, Ar-H), 8.05-8.04 (m, 1H, Ar-H), 8.32 (s, 1H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 170.47, 147.68, 142.2, 137.41, 136.47, 132.68, 129.96, 129.56, 129.49, 128.81, 128.15, 128.14, 127.65, 127.55, 126.96, 126.63, 126.61, 71.6, 57.38, 36.35. LC-MS (*m/z*): 421 (M+Na). Anal. calcd. for $C_{20}H_{18}N_2O_3S_2$: C, 60.28; H, 4.55; N, 7.03. Found: C, 60.68; H, 4.95; N, 7.83%. HPLC [t_R(min) (content)]: 8.96 (95.01%).

3-(4-Cyanophenyl)-N-(2-hydroxy-2-phenylethyl)-N-methylthiophene-2-sulfonamide (**4i**): Color: White. Yield: 85%. M.p.: 144-145 °C. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.80 (s, 3H, N-CH_3), 3.16-3.11 (m, 2H, CH_3-N-CH_2), 4.80-4.75 (m, 1H, OH-CH), 5.64 (d, *J* = 4.4 Hz, 1H, OH), 7.28-7.26 (m, 1H, Ar-H), 7.35-7.32 (m, 4H, Ar-H), 7.69 (d, *J* = 4 Hz, 1H, Ar-H), 7.83 (d, *J* = 8 Hz, 1H, Ar-H), 7.97-7.90 (m, 4H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 170.4, 147.81, 142.66, 137.62, 136.64, 132.28, 129.96, 129.46, 129.29, 128.81, 128.15, 128.14, 127.75, 127.45, 126.96, 126.73, 126.71, 71.38, 57.38, 36.41. LC-MS (*m/z*): 421 (M+Na). Anal. calcd. for $C_{20}H_{18}N_2O_3S_2$: C, 60.28; H, 4.55; N, 7.03. Found: C, 59.88; H, 4.55; N, 7.43%. HPLC [t_R(min) (content)]: 5.83 (98.76%).

N-(2-Hydroxy-2-phenylethyl)-N-methyl-3-(2(trifluoromethyl)phenyl) thiophene-2-sulfonamide (**4j**):Color: White. Yield: 82%. M.p.: 127-128 °C. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.79 (s, 3H, N-CH_3), 3.18-3.10 (m, 2H, CH_3-N-CH_2), 4.80-4.76 (m, 1H, OH-CH), 5.64 (d, *J* = 4.4 Hz, 1H, OH), 7.32-7.24 (m, 2H, Ar-H), 7.45-7.34 (m, 4H, Ar-H), 7.65-7.64 (m, 2H, Ar-H), 7.79-7.69 (m, 2H, Ar-H), 7.90 (d, *J* = 8 Hz, 1H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 147.53, 142.74, 136.73, 133.28, 133.13, 130.39, 130.33, 129.06, 128.23, 127.33, 126.14, 126.13, 125.73, 125.49, 125.19, 122.58, 122.34, 122.32, 71.47, 57.40, 36.34. LC-MS (*m/z*): 424 (M-H_2O). Anal. calcd. for $C_{20}H_{18}F_3NO_3S_2$: C, 54.41; H, 4.11; N, 3.17. Found: C, 54.81; H, 4.51; N, 3.57%. HPLC [t_R(min) (content)]: 5.921 (98.58%).

N-(2-Hydroxy-2-phenylethyl)-N-methyl-3-(3-(trifluoromethyl)phenyl) thiophene-2-sulfonamide (**4k**): Color: White. Yield: 89%. M.p.: 124-125 °C. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.80 (s, 3H, N-CH_3), 3.20-3.12 (m, 2H, CH_3-N-CH_2), 4.79 (m, 1H, OH-CH), 5.62 (d, *J* = 4.4 Hz, 1H, OH), 7.28-7.25 (m, 1H, Ar-H), 7.35-7.32 (m, 4H, Ar-H), 7.71-7.67 (m, 2H, Ar-H), 7.77-7.75 (d, 1H, Ar-H), 7.81 (d, *J* = 4 Hz, 1H, Ar-H), 8.04 (s, 1H, Ar-H), 8.07 (s, 1H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 147.43, 142.94, 136.76, 133.28, 133.13, 130.49, 130.3, 129.99, 128.13, 127.33, 126.14, 126.13, 125.83, 125.49, 125.19, 122.48, 122.36, 122.32, 71.49, 57.39, 36.35. LC-MS (*m/z*): 441 (M+H). Anal. calcd. for $C_{20}H_{18}F_3NO_3S_2$: C, 54.41; H, 4.11; N, 3.17. Found: C, 54.81; H, 4.51; N, 3.57%. HPLC [t_R(min) (content)]: 7.77 (98.76%).

N-(2-Hydroxy-2-phenylethyl)-N-methyl-3-(4-(trifluoromethyl)phenyl) thiophene-2-sulfonamide (**4l**): Color: White. Yield: 81%. M.p.: 120-121 °C. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.81 (s, 3H, N-CH_3), 3.19-3.17 (m, 2H, CH_3-N-CH_2), 4.80-4.76 (m, 1H, OH-CH), 5.63 (d, *J* = 4.4 Hz, 1H, OH), 7.29-7.27 (m, 1H, Ar-H), 7.35-7.32 (m, 4H, Ar-H), 7.69 (d, *J* = 4.4 Hz, 1H, Ar-H), 7.79-7.69 (m, 3H, Ar-H), 7.96 (d, *J* = 8, 1.4 Hz, 2H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 147.36, 142.94, 137.16, 135.9, 133.33, 133.32, 129.14, 128.82, 128.15, 128.14, 127.36, 127.35, 126.69, 126.65, 126.17, 126.14, 71.46, 57.41, 36.35. LC-MS (*m/z*): 441 (M+H). Anal. calcd. for $C_{20}H_{18}F_3NO_3S_2$: C, 54.41; H, 4.11; N, 3.17. Found: C, 54.01; H, 3.71; N, 2.77%. HPLC [t_R(min) (content)]: 4.21 (99.77%).

N-(2-Hydroxy-2-phenylethyl)-3-(2-methoxyphenyl)-N-methylthiophene-2-sulfonamide (**4m**): Color: White. Yield: 84%. M.p.: 132-133 °C. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.81 (s, 3H, N-CH_3), 3.16-3.06 (m, 2H, CH_3-N-CH_2), 3.95 (s, 3H, Ar-OCH_3), 4.79-4.74 (m, 1H, OH-CH), 5.61 (d, *J* = 4.4 Hz, 1H, OH), 7.06 (t, *J* = 7.2 Hz, 1H, Ar-H), 7.26 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.30-7.21 (m, 1H, Ar-H), 7.41-7.34 (m, 5H, Ar-H), 7.59 (d, *J* = 4.4 Hz, 1H, Ar-H), 7.65 (d, *J* = 4.4 Hz, 1H, Ar-H), 7.88 (d, *J* = 8, 1.4 Hz, 1H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 160.51, 142.96, 137.42, 136.44, 132.28, 129.86, 129.46, 129.19, 128.81, 128.15, 128.14, 127.65, 127.35, 126.96, 126.63, 126.61, 71.5, 57.4, 55.49, 36.42. LC-MS (*m/z*): 404 (M+H). Anal. calcd. for $C_{20}H_{21}NO_4S_2$: C, 59.53; H, 5.25; N, 3.47. Found: C, 59.93; H, 5.65; N, 3.87%. HPLC [t_R(min) (content)]: 8.14 (99.00%).

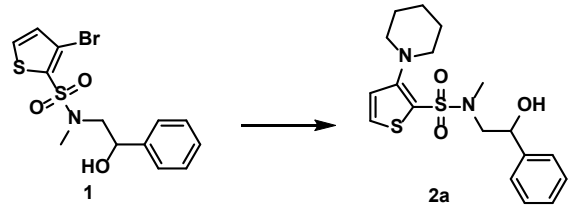
N-(2-Hydroxy-2-phenylethyl)-3-(3-methoxyphenyl)-N-methylthiophene-2-sulfonamide (**4n**): Color: White. Yield: 81%. M.p.: 138-139 °C. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.79 (s, 3H, N-CH_3), 3.24-3.14 (m, 2H, CH_3-N-CH_2), 3.81 (s, 3H, Ar-OCH_3), 4.83-4.75 (m, 1H, OH-CH), 5.62 (d, *J* = 4.4 Hz, 1H, OH), 6.99-6.97 (dd, *J* = 8, 2 Hz, 1H, Ar-H), 7.32-7.26 (m, 4H, Ar-H), 7.38-7.34 (m, 4H, Ar-H), 7.65-7.58 (q, *J* = 9.6, 4 Hz, 2H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 160.41, 142.86, 137.22, 136.24, 132.28, 129.66, 129.26, 129.19, 128.61, 128.15, 128.14, 127.45, 127.35, 126.86, 126.63, 126.61, 71.51, 57.34, 55.33, 36.35. LC-MS (*m/z*): 426 (M+Na). Anal. calcd. for $C_{20}H_{21}NO_4S_2$: C, 59.53; H, 5.25; N, 3.47. Found: C, 59.93; H, 5.65; N, 3.87%. HPLC [t_R(min) (content)]: 8.65 (97.0%).

N-(2-Hydroxy-2-phenylethyl)-3-(4-methoxyphenyl)-N-methylthiophene-2-sulfonamide (**4o**): Color: White. Yield: 87%. M.p.: 152-153 °C. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.78 (s, 3H, N-CH_3), 3.17-3.11 (m, 2H, CH_3-N-CH_2), 3.79 (s, 3H, Ar-OCH_3), 4.79-4.75 (m, 1H, OH-CH), 5.61 (d, *J* = 4.4 Hz, 1H, OH), 7.01 (d, *J* = 8.8, 4.4 Hz, 2H, Ar-H), 7.28-7.26 (m, 1H, Ar-H), 7.35-7.32 (m, 4H, Ar-H), 7.49 (d, *J* = 4, 2.1 Hz, 1H, Ar-H), 7.58 (d, *J* = 4, 2.1 Hz, 1H, Ar-H), 7.67 (d, *J* = 8.8, 3.4 Hz, 2H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 160.41, 142.66, 137.12, 136.44, 132.38, 129.26, 129.16, 129.12, 128.81, 128.35, 128.24, 127.65, 127.35, 126.86, 126.63, 126.62, 71.49, 57.39, 55.38, 36.38. LC-MS (*m/z*): 386 (M-H_2O). Anal. calcd. for $C_{20}H_{21}NO_4S_2$: C, 59.53; H, 5.25; N, 3.47. Found: C, 59.13; H, 4.85; N, 3.07%. HPLC [t_R(min) (content)]: 6.74 (96.0 %).

2.3. Antiproliferative activity

The synthesized compounds were evaluated for their *in vitro* antiproliferative activity against human lung cancer cell

Table 1. Screening of catalyst and ligand for compound **2a**.



Entry	Catalyst	Ligand [a]	Base	Solvent	Temperature (°C)	Yield (%) [b]
1	$Cu(OAc)_2$	-	KO_tBu	Toluene	110	-
2	$Cu(OAc)_2$	-	K_3PO_4	Toluene	110	-
3	$Cu(OAc)_2$	-	K_2CO_3	DMF	150	15
4	$Cu(OAc)_2$	-	Na_2CO_3	Toluene	110	-
5	$Cu(OAc)_2$	-	Pyridine	DMF	140	25
6	$Cu(OAc)_2$	-	TEA	DMF	140	-
7	$Cu(OAc)_2$	1	K_3PO_4	DMF	110	90
8	$Cu(OAc)_2$	1	KOtBu	Toluene	110	45
9	$Cu(OAc)_2$	1	Pyridine	DMF	140	30
10	$Cu(OAc)_2$	2	K_3PO_4	Toluene	110	15
11	$Cu(OAc)_2$	2	KO_tBu	Toluene	110	25
12	$Cu(OAc)_2$	2	Pyridine	DMF	140	-
13	$Cu(NO_3)_2$	-	TMEDA	MeOH	80	20
14	$Cu(OAc)_2$	3	K_3PO_4	Toluene	110	10
15	$Cu(OAc)_2$	4	K_3PO_4	DMF	140	-
16	$Pd(OAc)_2$	5	Na_tBu	Toluene	110	30
17	$Pd(OAc)_2$	4	Na_tBu	Toluene	110	20
18	$Cu(OAc)_2$	-	K_3PO_4	DMF	110	20
19	$Cu(OAc)_2$	2	K_3PO_4	DMF	110	25
20	$Cu(OAc)_2$	3	K_3PO_4	DMF	110	28
21	$Cu(OAc)_2$	5	K_3PO_4	DMF	110	20

[a] Ligands 1: *N*-methylethylenediamine; 2: Cu(1)-thiophene-2-carboxylate; 3: (2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl); 4: 4,5-*Bis*(diphenyl phosphino)-9,9-dimethylxanthene; 5: 2,2-*Bis*(diphenylphosphino)-1,1-binaphthyl; 6: (2-Biphenyl)di-*tert*-butylphosphine); 7: 1,1-*Bis*(diphenylphosphino) ferrocene).

[b] Isolated yield, compound **1** (1 equiv.), piperdine (2 equiv.), time: 12 h.

Table 2. Screening of solvents for synthesis of compound **2a**.

Sr. No.	Solvent	Yield (%) [a]
1	Dioxane	70
2	DMF	90
3	IPA	50
4	NMP	45
5	ACN	60
6	Toluene	50

[a] Isolated yield, compound **1** (1 equiv.), piperdine (2 equiv.), $Cu(OAc)_2$, K_3PO_4, Ligand 1: *N*-methylethylenediamine, time: 12 h.

line (A549), cervical (HeLa) cancer cell line, breast cancer cell line (MCF-7) and prostate cell line (Du-145) using 5-fluorouracil as a reference drug. The anticancer activity test is performed according to the procedure developed by the National Cancer Institute (NCI, USA) in the 'In vitro Anticancer Drug Discovery Screen' that uses the protein-binding dye sulforhodamine B (SRB) to assess cell growth [28,29]. Briefly, cells are grown in 96-well plates in suspension and then were exposed for 48 hours to four serial concentrations of 1×10^{-7}, 1×10^{-6}, 1×10^{-5}, 1×10^{-4} and 1×10^{-3} Molar (M) of each compound. Following this, cells were fixed and stained with protein binding SRB stain. Excess stain is washed and bound stain was solubilized, and the absorbance was measured at 492 nm in a plate reader. Concentration of the compounds that inhibited 50% of the net cell growth, growth inhibition of 50% (GI50), was calculated from the dose response curve obtained for each test compound and cell line. GI50 values were presented in micro molar (μM) concentration. 5-Flourouracil (5-Fu) was used as positive control for the comparison of cytotoxicity of synthesized compounds. Assays were performed in triplicate on three independent experiments and their mean values are taken as a final reading. All experiments were performed in duplicate and repeated three times.

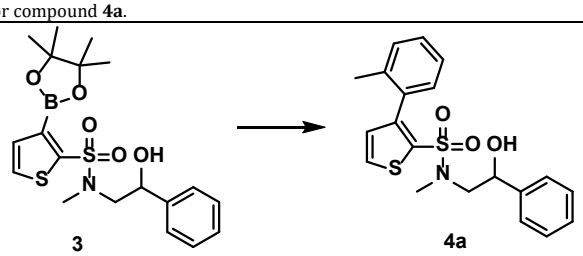
3. Results and discussion

We have screened catalysts, ligands, bases, solvents and time for Buchwald and Suzuki coupling reaction conditions (Table 1-5) to obtain better yield, good purity, shorter reaction time and mainly reproducibility of the yields. Synthesized derivatives **2a-i** and **4a-o** are shown in Scheme 1 and 2.

These derivatives were synthesized from commercially available 3-bromothiophene-2-sulfonyl chloride as shown in Scheme 1 and 2 as per the given procedure.

We have optimized the reaction conditions by varying different catalysts, ligands, bases, solvents, temperature and calculated the reaction time and its effect on yield. From (Table 1, Entries 1-12 and 18-21) it is clear that using copper(II) acetate as catalyst and without ligand in a number of bases and solvents does give the product. In entries 3 and 5, there is 15 and 25% product formation observed. The obtained yield was very low. Nevertheless, all of these yields were generally low from 10 to 45% in entries 8 to 21 before further optimizations in entries. But from Table 1 (Entry 7) changing the ligand to *N*-methylethylenediamine (NMM), base to Tripotassium phosphate in DMF as a solvent at 110°C gave completion of the reaction in 12 h and the highest yield of 90%. We have carried out the same reaction condition by changing the ligands in entries 18-21, in all these 4 reactions, the yield is in the range of 20-28% by changing the different ligands there is no remarkable increase in the yields. Mixed results are obtained in all the optimizations, *N*-methyl-ethylenediamine is the ligand for intrest when we used KOtBu, pyridine as bases and toluene and DMF as solvents the yields are 45 and 30%, respectively.

Table 3. Screening of catalyst and ligand for compound **4a**.



Entry	Catalyst	Ligand [a]	Yield (%) [b]
1	$Pd_2(dba)_3$	4	-
2	$Pd_2(dba)_3$	3	20
3	$Pd_2(dba)_3$	6	22
4	$Pd(PPh_3)_4$	4	-
5	$Pd(PPh_3)_4$	3	-
6	$Pd(PPh_3)_2Cl_2$	4	10
7	$Pd(PPh_3)_2Cl_2$	3	30
8	$Pd(PPh_3)_2Cl_2$	6	40
9	$Pd(PPh_3)_2CHCl_2$	4	25
10	$Pd(PPh_3)_2CHCl_2$	3	30
11	$Pd(OAc)_2$	4	45
12	$Pd(OAc)_2$	3	65
13	$Pd(OAc)_2$	6	35
14	$PdCl_2(CH_3CN)_2$	6	-
15	$NiCl_2$	3	-
16	$NiCl_2$(DPPF)	3	15
17	$Ni(OAc)_2$	3	-
18	Na_2PdCl_4	7	-

[a] Ligands, 3: (2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl); 4: 4,5-*Bis*(diphenylphosphino)-9,9-dimethylxanthene; 6: (2-Biphenyl)di-*tert*-butyl phosphine); 7: 1,1-*Bis*(diphenylphosphino)ferrocene).
[b] Isolated yield, compound **3** (1 equiv.) and 1-bromo-2-methylbenzene (2 equiv.), K_3PO_4, toluene, time 12 h, temperature 110 °C.

Table 4. Screening of solvents for synthesis of compound **4a**.

Sr. No.	Solvent	Time	Yield (%) [a]
1	Toluene	12	65
2	Dioxane	12	90
3	IPA	12	50
4	NMP	12	45
5	ACN	12	60
6	Toluene	12	50

[a] Isolated yield, compound **3** (1 equiv.), 1-bromo-2-methylbenzene (2 equiv.), K_3PO_4, Pd(OAc), time 12 h, temperature 110 °C.

Table 5. Screening of base for synthesis of compound **4a**.

Sr.No.	Base	Yield (%) [a]
1	K_3PO_4	90
2	KOtBu	60
3	K_2CO_3	50
4	NatBu	35
5	Cs_2CO_3	30

[a] Isolated yield, compound 3 (1 equiv.), 1-bromo-2-methylbenzene (2 equiv.), Pd(OAc), dioxane, time 12 h, temperature 110 °C.

With other ligands 2, 3, 4 and 5 the reactions fail to give good yields for Buchwald reaction, only ligand *N*-methyl-ethylenediamine gives better results due to its association with compound 1 and amine. This reaction conditions were the best hence, we decided to further carry out optimizations of solvent to get higher yield and less reaction time. We have screened a series of 6 solvents for the synthesis of compound **2a** in Table 2 and among those solvents DMF after 12 h of heating gave a yield of 90% (Table 2, Entry 2). Hence, DMF was chosen as the solvent for further synthesis of compounds **2b**-**i**. We have optimized conditions for C-C and C-O bond formation and given condition, works well for C-C bond formations **2a**-**f** with yields in the range of 80-90%. For compounds **2g**, **2h** and **2i,** the yield is in the range of 70 to 80%.

We have optimized the reaction conditions for Suzuki coupling the results of screenings are tabulated in Table 3. We kept base, solvent and reaction temperature constant, i.e. K_3PO_4, toluene and 110 °C, respectively, by varying the catalyst and ligand. In Table 3, we have screened the catalyst and ligand by keeping remaining parameters consgtant and we obtained one set of catalyst and ligand. In Table 4, we have varied the solvents by keeping the parameters of Table 3 constant. In Table 5, we varied the bases by keeping the parameters of Tables 3 and 4 constant.

From Table 3, it is clear that using 4,5-*bis*(diphenylphosphino)-9,9-dimethylxanthene (X-Phos), 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (S-Phos) and 2-biphenyl)di-*tert*-butylphosphine (John Phos) as ligands and catalysts $Pd_2(dba)_3$ [*Tris*(dibenzylideneacetone) dipalladium (0)], $Pd(PPh_3)_4$ [*tetrakis*(triphenylphosphine) palladium(0)] and $Pd(PPh_3)_2Cl_2$ [*bis*(triphenylphosphine) palladium(II) dichloride] (Entries 1, 2, 3, 4, and 5) does not affect the yield significantly. The obtained yields were very low. Nevertheless, all of these yields were generally low before further optimizations. After changing the catalyst to $Pd(OAc)_2$, the yield was found to increase at 45% (Table 3, Entry 11). Using the same catalyst by changing ligand to S-Phos, the yield obtained was the highest of 65% (Table 3, Entry 12). Hence, these reaction conditions were chosen for further reactions. The results of screening for solvents and bases are tabulated in Tables 4 and 5, respectively, for Scheme 2. In Table 4, we have screened the solvents for increasing the yield of compound **4a**.

Table 6. *In vitro* antiproliferative activity screening of the synthesized compounds against four cell lines. Data are expressed as IC_{50} µM±SD (n = 3) [a].

Compounds	A-549 [b]	HeLa [c]	MCF-7 [d]	Du-145 [e]
2a	2.72±0.11	3.87±0.08	4.12±0.06	3.86±0.22
2b	3.81±0.11	4.32±0.04	5.32±0.06	3.73±0.12
2c	4.81±0.11	6.32±0.04	4.32±0.06	3.73±0.12
2d	2.82±0.11	1.99±0.22	3.36±0.12	2.82±0.11
2e	3.86±0.08	4.38±0.06	3.63±0.12	6.52±0.22
2f	5.72±0.11	6.87±0.08	4.12±0.06	8.86±0.22
2g	1.82±0.11	1.99±0.22	2.36±0.12	2.52±0.11
2h	8.48±0.14	9.12±0.08	7.82±0.08	9.12±0.06
2i	1.82±0.11	1.99±0.22	2.66±0.12	2.52±0.11
4a	4.13±0.12	5.16±0.08	6.12±0.12	4.52±0.11
4b	5.06±0.12	3.12±0.08	2.52±0.16	5.12±0.08
4c	2.52±0.11	6.52±0.11	3.48±0.08	4.08±0.11
4d	4.48±0.08	4.98±0.11	5.17±0.22	6.18±0.18
4e	2.73±0.08	2.12±0.12	3.12±0.08	3.12±0.04
4f	4.15±0.18	5.12±0.08	7.17±0.08	8.15±0.06
4g	4.11±0.08	6.52±0.08	2.98±0.06	7.76±0.12
4h	2.82±0.12	3.15±0.18	3.98±0.08	4.12±0.08
4i	8.12±0.08	2.48±0.08	4.82±0.11	4.52±0.06
4j	3.02±0.11	4.12±0.08	3.12±0.08	5.32±0.11
4k	2.82±0.12	3.16±0.21	4.28±0.06	2.82±0.18
4l	3.42±0.16	3.98±0.11	4.12±0.18	4.52±0.08
4m	3.81±0.13	4.92±0.08	5.32±0.22	2.82±0.12
4n	1.98±0.12	2.83±0.16	3.12±0.06	2.86±0.16
4o	3.42±0.16	3.98±0.11	4.12±0.18	4.52±0.08
5-Fluorouracil	1.71±0.11	1.82±0.13	1.91±0.08	1.82±0.08

[a] IC_{50}: The concentration required to inhibit 50% of cell population.
[b] A-549: Human lung cancer cell line.
[c] HeLa: Human cervical cancer cell line (ATCC No. CCL-2).
[d] MCF-7: Human breast cancer cell line.
[e] DU-145: Human prostate cancer cell line.

From Table 4, a number of solvents were screened, though toluene had good to moderate yield of 65% (Entry 1) but the 90% yield was obtained in dioxane (Entry 2). Hence, dioxane was chosen as the solvent for further synthesis. In Table 5, we have screened the required bases for the synthesis of compound **4a**. From Table 5, a number of bases were screened but the highest yield of 90% was obtained in K_3PO_4 (Entry 1). Hence, K_3PO_4 was chosen as the base for further synthesis. From all the screenings for the synthesis of final analogues of compounds **2a**-**i** and **4a**-**o** we have an optimized condition for Buchwald and Suzuki coupling reactions. We have synthesized the bispinacol ester of compound **1** and which is further used for synthesis of C-C bond analogues by avoiding costly boronic acids instead of using different aromatic bromides. We finaly used $Pd(OAc)_2$ as catalyst, S-Phos as ligand, dioxane as solvent and K_3PO_4 as base to get 90% of compound **4a**. For remaining compounds **4b** to **o** we got yields in the range of 75 to 95% for all the derivatives. We have coupled the electron donating and electron withdrawing substituents. The comppunds with electron donating nature gives better yields than electron withdrawing confirmed from isolated yields of all the compounds.

The synthesized compounds were evaluated for their *in vitro* anticancer activity against human lung cancer cell line (A549), cervical (HeLa) cancer cell line, breast cancer cell line (MCF-7) and prostate cell line (DU-145) using 5-fluorouracil as reference drug. 5-Flourouracil used as standard for many sulfonamide and amide linkage of compounds so it is used as a reference for the sulfonamide amide coupled compounds in this work. The cytotoxic studies are performed to test their general cytotoxicity, if any due to their nonspecific binding to the basic cell macromolecules like protein, carbohydrate, plasma membrane etc., and also to test their biocompatibility to eukaryotic cells. The response parameter calculated was the IC_{50} value, which corresponds to the concentration required for 50% inhibition of cell viability. The results are presented in Table 6, where all compounds exhibit moderate to good activity compared to 5-fluorouracil as positive control. In the case of the human lung cancer cell line (A549) compounds **2g** and **2i** from Scheme 1 and **4c** and **4n** from Scheme 2 were most potent, with IC_{50} values of 1.82, 1.82, 2.52 and 1.98 µMi respectively. The compounds **2a**, **2i**, **4e**, **4h** and **4k** were also potent with IC_{50} values ranging from 2.72 to 2.82 for most of the compounds. The compound **2a** is having piperidone substitution which showed highter activity than the remaining nitrogen analogs. The compound 4-methyl piperzine showed promising activity, electron donating methyl group on nitrogen increased the activity as we have seen in the case of compound **2g** and **2i** where *ortho*-methoxy and *para*-methoxy groups on benzene ring showed promising activity compared to meta methoxy group on benzene. In latter case for compounds **4e**, **4h** and **4k** having meta chloro, cyano and triflouromethyl groups showed promising activity than the remaining *ortho* and *para* analogs, which was interesting. On the HeLa cell line the compounds **2d**, **2g**, **2i** and **4e** with IC_{50} = 1.99, 1.99, 1.99 and 2.12 µM, respectively, were most active. Interestingly, compound **2d** was having 4-methylpiperazine substitution along with compounds **2g** and **2i** both having *ortho*- and *para*-methoxy substitutions were most active. Compounds **4i**, **4b**, **4h**, **4k** and **4n** were also active, all were having IC_{50} values in the range of 2.48-3.16 µM. Interestingly, all were having electron donating group at *meta* positions compared to other analogs which were less active. In case of the MCF-7 breast cancer cell line compounds **2g**, **2i**, **4b** and **4g** were most active with IC_{50} = 2.36, 2.36, 2.52 and 2.98 µM, respectively. The compounds having *ortho* and *para* methoxy ring showed good activity compared to *meta* substituted electron donating group. The compounds **2d**, **2c**, **2e**, **4c**, **4h**, **4j** and **4n** were active compounds with IC_{50} values ranging from 3.12-4.12 µM. Same results were obtained for the Du-145 prostate cancer cell lines where the most potent candidates were compounds **2g**, **2i** and **4k** (IC_{50} = 2.52 µM and 2.82 µM). It was observed that compound **2g** was highly potent in almost all four cell lines. Generally, the lung (A549) and cervical (HeLa) cancer cell lines were most sensitive to the synthesized compounds. With regard to broad spectrum antiproliferative activity, close examination of the data presented in Table 6, reveals that compounds **2d**, **2g**, **2i**, **4e**, **4h** and **4k** were most active, showing the effectiveness toward the four cell lines when compared with the standard. From the cell line data the results can be drawn like compounds having electron donating group at *ortho* and *para* position of aromatic ring are most

active on all four cell lines **2g** and **2i** and that of electron withdrowing groups are less active on all cell lines except compound **2d** which is having *N*-methyl piperazine group in C-N bond coupled compounds. The C-C bond coupled compounds the electron donating groups like methyl and methoxy are moderate to less active and that of electron withdrawing compounds with *meta* directing groups are very activie compared to *ortho* and *para* directing substituents and with standard as seen in compounds **4e**, **4h** and **4k**. In conclusion, the bonding on thiophene plase a important role in cell line activity, further studies on most active compounds are in progress.

4. Conclusion

In conclusion, by using our newly developed methodology, a series of 3-(substituted phenyl)-*N*-(2-hydroxy-2-(substituted phenyl)ethyl -*N*-methylthiophene-2-sulfonamide derivatives were synthesized and evaluated. We have developed easy and relatively effortless method for the synthesis of thiophene-sulfonamide derivatives having C-C, C-O and C-N bond by simple reaction steps. No any pre-purification is needed and all the compounds synthesized are obtained in good yields. The advantages of this method are mild reaction conditions, shorter reaction time and potential anticancer activity. The compounds **2d**, **2g**, **2i**, **4e**, **4h** and **4k** show potent antiproliferative activity in the four cell lines tested.

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Disclosure statement

Conflict of interests: The authors declare that they have no conflict of interest.
Author contributions: All authors contributed equally to this work.
Ethical approval: All ethical guidelines have been adhered.
Sample availability: Samples of the compounds are available from the author.

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