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# Synthesis 5-(substituted phenyl)-N-(2-hydroxy-2-phenylethyl)-N-methylthiophene-2-sulfonamide Derivatives

**Pawar CD[1*] and Shinde DB[2]**

[1]Department of Chemical Technology, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad, India

[2]Department of Chemistry, Shivaji University, Kolhapur, India

## Research Article

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***For Correspondence**

Chandrakant Pawar, Department of Chemical Technology, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad, Maharashtra, India.

Tel: +912402403308, Fax: +912402400413

**E-mail:** dbschandrakant15@rediffmail.com

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**ABSTRACT**

At present work, we synthesized substituted thiophene sulfonamides compounds having tert-nitrogen and free hydroxyl group along with CH2 group. We have optimized methodology for targets from milligram scale to multi gram scale. We have developed a series of 5-(substituted phenyl)-N-(2-hydroxy-2-phenylethyl)-N-methylthiophene-2-sulfonamide derivatives (6a-o).

## INTRODUCTION

Thiophene is a class of heterocyclic compounds showing diversifying activity in medicinal and pharmaceutical fields. Many derivatives of thiophene used as biological active compounds for variety of diseases [1,2]. They act as organic light-emitting diodes, organic field-effect transistors and in organic solar cells [3]. The linkage of thiophene is important component in drug discovery. The C-N and C-C substituted thiophene shows good biological activities like as anticancer agents [4], antiproliferative activity [5]. Thiophene coupled with thiazole acts as adenosine receptor antagonists [6]. Thiophene coupled with imidazole acts as antimycobacterial agents [7]. Thiophene-2-carboxylic acid shows good agonist activity against the GPR35 [8]. The substituted thiophene acts as redox-active inhibitors if keratinocyte hyperproliferation [9]. Thiophene acts as antimicrobial agents [10]. Thiophene acts as antimicrobial and anticancer agents [11-13].

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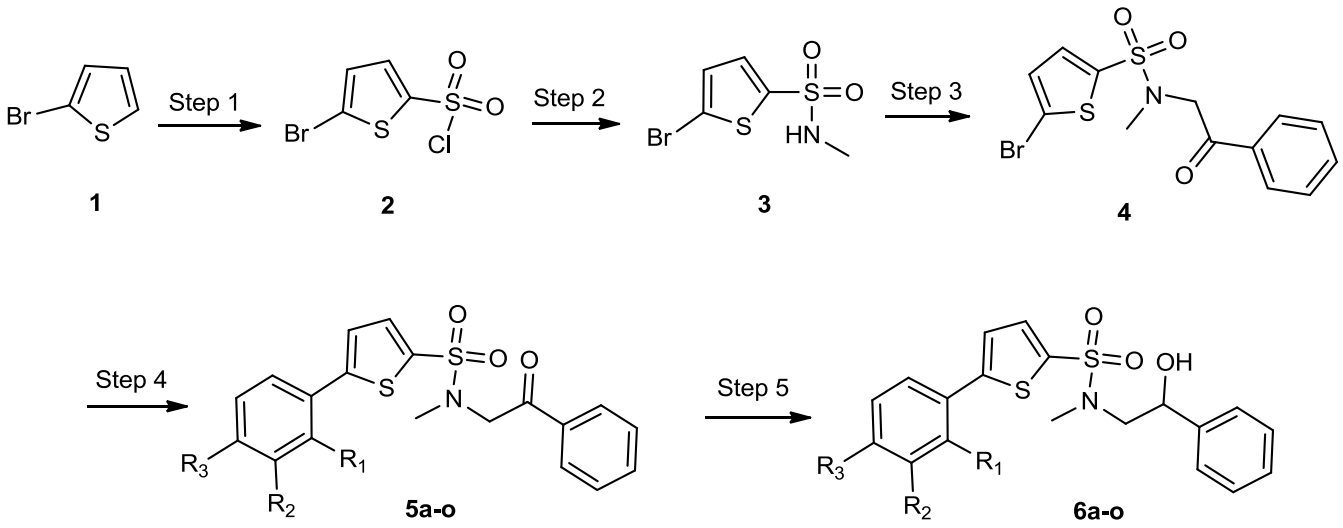


| | $R_1$ | $R_2$ | $R_3$ | | $R_1$ | $R_2$ | $R_3$ |
|---|---|---|---|---|---|---|---|
| 5a=6a | H | $-CH_3$ | H | 5i=6i | H | H | $-OCH_3$ |
| 5b=6b | $-CH_3$ | H | H | 5j=6j | $-CF_3$ | H | H |
| 5c=6c | H | H | $-CH_3$ | 5k=6k | H | $-CF_3$ | H |
| 5d=6d | H | -Cl | H | 5l=6l | H | H | $-CF_3$ |
| 5e=6e | H | H | -Cl | 5m=6m | -CN | H | H |
| 5f=6f | -Cl | H | H | 5n=6n | H | -CN | H |
| 5g=6g | $-OCH_3$ | H | H | 5o=6o | H | H | -CN |
| 5h=6h | H | $-OCH_3$ | H | | | | |

**Scheme 1.** Synthesis 5-(substituted phenyl)-N-(2-hydroxy-2-phenylethyl)-N-methylthiophene-2-sulfonamide derivatives (6a-o).

We have developed novel concept in the combination of thiophene sulfonamide having tertiary nitrogen atom, also it has active methylene $CH_2$ group **(Scheme 1)**. These types are highly insoluble compounds in water and required polar solvent to dissolve them, so we have inserted free hydroxyl group adjacent to active $CH_2$ group. Finally, those analogous were coupled with C-C bond formation using Suzuki-Miyaura reaction. Mostly these types of compounds show good biological activity in body mechanism because of presence of free hydroxyl group and active $CH_2$ group and two aromatic rings are present in all the analogous. In the present communication, we have synthesized targets which are novel, we have used series of reaction on 2-bromo thiophene to optimize sulfonation on thiophene at 5 position. We have developed simple and convenient method for chlorosulfonation, earlier reports are their but they have used harsh conditions and are low yielding [14]. In step 2 we have done sulfonamide coupling we have optimized it and later we have done series of reactions for C-C bond formation using Suzuki-Miyaura reactions and we have finalized catalyst, ligand, solvent, temperature and time that can give good yields for the series of compounds.

## EXPERIMENTAL

For step 3 we have treated compound 3 (1 eq.) with phenacyl bromide (1 eq.) by using inorganic base like potassium carbonate and cesium carbonate in acetone and tetra hydro furan respectively. The base used is 2 eq. in both the cases and reaction stirred for 2 h at room temperature. The first reaction with potassium carbonate (2 eq.) with phenacyl bromide (1 eq.) in acetone at room temperature gives 85% of product formation by LCMS and TLC so no need for further optimization and compound isolated by simple work up procedure evaporating acetone under reduced pressure and obtained gummy material added water to it and stirred reaction mass for 1 h. Solid precipitates out filter it and wash it with excess of water and dry it properly to obtain compound 4 as white solid which is used further for Suzuki reaction.

For step 4 we have screened different catalysts, ligands, base and solvents for doing all the step 4 derivatives for all the compound 5a-o, all results tabulated in **Table 1**.

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**Table 1.** Screening of sulfonyl chloride equivalent and solvent of compound (2).

| Entry | $ClSO_3H$ | Solvent | Time (h) | Yield[a] (%) |
|---|---|---|---|---|
| 1 | (3 eq) | Neat | 1 | 35 |
| 2 | (2 eq) | Neat | 1 | 40 |
| 3 | (3 eq) | DCM | 1 | 50 |
| 4 | (2 eq) | DCM | 1 | 60 |
| 5 | (1.1 eq) | DCM | 1 | 80 |
| 6 | (Excess) | DCM | 1 | 30 |
| 7 | (Excess) | Neat | 1 | 20 |
| [a]Isolated yield, sulfonyl chloride (2 eq) | | | | |

For the first 4 entries, we have used tetrakis as constant catalysts and we have varied different bases and ligands entry 1 and entry 4 giving 80% yields in dioxane: water and DMF: water. In entries 5 and 6 we have used palladium acetate along with X-phos as ligand with potassium phosphate as base in dimethyl formamide:water solvent is giving 70% yield that compared with entry 6 without ligand giving 50% yield. For entries 7 to 9 the reaction in entry 9 is giving 90% yield as compared it with entry 7 and 8 where we have not used any ligands the yield decreases. In entry 10 we have used nickel chloride/N-methyl piperazine combination in potassium phosphate base in DME gives 70% yield. In entry 11 and 12 also we got reasonable good yields. All tabulated in **Table 2**. The entry 9 reaction having dikis compound with x-phos as ligands in dioxane: water combination and sodium carbonate base gives yield in the range of 85-95% for all the examples. For work up of that reaction mass filtered through a pad of celite and obtain filtrate, which was evaporated under reduced pressure to obtain crude compound with reasonable purities more than 90% by HPLC for all the compounds 5a-o.

**Table 2.** Screening of catalyst, bases and solvent of compound (5a-o).

| Entry | Catalyst 10 mol% | Ligand 20 mol% | Base 2 eq | Solvent | Time (h) | Temp °C | Yield% |
|---|---|---|---|---|---|---|---|
| 1 | $Pd(PPh_3)_4$ | - | $Na_2CO_3$ | Dioxane:$H_2O$ | 6 | 100 | 75 |
| 2 | $Pd(PPh_3)_4$ | - | $CS_2CO_3$ | Dioxane:$H_2O$ | 6 | 100 | 65 |
| 3 | $Pd(PPh_3)_4$ | - | $K_3PO_4$ | Dioxane:$H_2O$ | 6 | 100 | 60 |
| 4 | $Pd(PPh_3)_4$ | X-PhOS | $K_3PO_4$ | DMF:$H_2O$ | 6 | 100 | 80 |
| 5 | $Pd(OAc)_2$ | X-PhOS | $K_3PO_4$ | DMF:$H_2O$ | 6 | 100 | 70 |
| 6 | $Pd(OAc)_2$ | - | $K_3PO_4$ | DMF:$H_2O$ | 6 | 100 | 50 |
| 7 | $Pd(dppf)Cl_2$ | - | $Na_2CO_3$ | Dioxane:$H_2O$ | 6 | 100 | 55 |
| 8 | $Pd(dppf)Cl_2$ | - | $CS_2CO_3$ | Dioxane:$H_2O$ | 6 | 100 | 60 |
| **9** | **$Pd(dppf)Cl_2$** | **X-PhOS** | **$Na_2CO_3$** | **Dioxane:$H_2O$** | **6** | **100** | **90** |
| 10 | $NiCl_2{\cdot}6H_2O$ | - | $K_3PO_4$ | DME | 6 | 100 | 70 |
| 11 | $PdCl_2/Ag_2O$ | X-PhOS | $K_3PO_4$ | DMA | 6 | 100 | 65 |
| 12 | $NiCl_2{\cdot}6H_2O$ | - | $K_3PO_4$ | IPA | 6 | 100 | 60 |

For step 5 we have done reduction by sing sodium borohydride (2 eq.) in methanol for 2 h at room temperature. The reaction was monitored by TLC and evaporated reaction mass under reduced pressure to obtained crude which is diluted with water and extracted with ethyl acetate. Washed organic layer with brine solution and evaporated it under reduced pressure to obtain desired compounds 6a-o **(Table 3)**, without further purifications. All the synthesized compounds (6a-6o) were screened for *in vitro* antimicrobial activity. The antibacterial activity was evaluated against two-gram positive bacteria *Staphylococcus aureus* (NCIM-2901), *Bacillus subtilus* (NCIM-2063), two gram negative bacteria, *Escherichia coli* (NCIM-2256), *Salmonella typhimurium* (NCIM-3471) and four fungal stains, *Candida albicans* (NCIM-3471), *Aspergillus flavus* (NCIM-539), *Aspergillus niger* (NCIM-1196) and *Cryptococcus neoformans* (NCIM-3378). For studying antimicrobial properties of compounds, Minimum Inhibitory Concentration (MIC, µg/mL), Minimum Bacterial Concentration (MBC) and Minimum Fungicidal Concentration (MFC) were studied by modified macrodilution technique. For bacterial strains MIC determination were done by a serial of microdilution technique using 96-well microtiter plate reader. Compounds (6a-60) are prepared in saline (0.8% NaCl) solution containing 5% Dimethyl sulfoxide (DMSO) for dissolution. All microbial strains were incubated with different concentration of each compound in 96-well microtiter plate for 20 h at 37 °C on Rotary shaker (160 rpm). After incubation, the lowest concentration value without growth were defined as MICs. For Fungal strains agar dilution technique, on Potato Dextrose Agar (PDA) Medium were used for MIC determination. The MBC and MFC of compounds were determined by serial sub cultivation after inoculated for 72 h with tested compounds dissolved in saline containing 5% DMSO. The lowest concentration with no visible growth was defined as MBC/MFC indicating 99.5% killing of the original inoculums. All the experiments performed in triplicates and mean reading is taken as final reading. 5% DMSO was used as a negative control along with Ciprofloxacin and Ampicillin as the standard antibacterial drugs and Fluconazole and Miconazole as the standard antifungal drugs **(Table 4)** [15,16].

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**Table 3.** Physical data of synthesized compounds (6a-o).

| Sr. No. | Compounds | Time | M.P. | Yield |
|---|---|---|---|---|
| 1 | 6a | 6 | 133 | 95 |
| 2 | 6b | 6 | 148 | 90 |
| 3 | 6c | 6 | 129 | 92 |
| 4 | 6d | 6 | 134 | 88 |
| 5 | 6e | 6 | 155 | 90 |
| 6 | 6f | 6 | 150 | 94 |
| 7 | 6g | 6 | 114 | 95 |
| 8 | 6h | 6 | 110 | 90 |
| 9 | 6i | 6 | 144 | **93** |
| 10 | 6j | 6 | 127 | 93 |
| 11 | 6k | 6 | 124 | 94 |
| 12 | 6l | 6 | 120 | 90 |
| 13 | 6m | 6 | 132 | 88 |
| 14 | 6n | 6 | 138 | 94 |
| 15 | 6o | 6 | 152 | 92 |

**Table 4** Antimicrobial activity of the synthesized compounds (6a-o).

| Compounds | MIC values[a] (µg/ml) | | | | | |
|---|---|---|---|---|---|---|
| | *B. subtilis* | *E. coli* | *S. aureus* | *C. albicans* | *A. flavus* | *A. niger* |
| 6a | 30 | 51 | 26 | 54 | 51 | 56 |
| 6b | 29 | 29 | 36 | 26 | 14.5 | 14.5 |
| 6c | 48 | 90 | 95 | 65 | 80 | 80 |
| 6d | 38 | 63 | 58 | 80 | 60 | 40 |
| 6e | 35 | 32 | 29 | 29 | 32 | 15.5 |
| 6f | 42 | 29 | 33 | 48 | 29 | 26 |
| 6g | 35 | 60 | 37 | 90 | 60 | 50 |
| 6h | 45 | 90 | 90 | 75 | 90 | 80 |
| 6i | 55 | 56 | 56 | 90 | 56 | 50 |
| 6j | 56 | 67 | 100 | 75 | 59 | 80 |
| 6k | 37 | 46 | 70 | 75 | 46 | 25 |
| 6l | 48 | 78 | 100 | 75 | 78 | 90 |
| 6m | 28 | 89 | 70 | 75 | 89 | 54 |
| 6n | 49 | 67 | 100 | 65 | 63 | 40 |
| 6o | 76 | 63 | 52 | 80 | 60 | 40 |
| Levofloxacin | 26 | 26 | 25 | - | - | - |
| Fluconazole | - | - | - | 36 | 23 | 23 |
| Miconazole | - | - | - | 13.5 | 13.5 | 13.5 |

[a]Values are the average of three readings.

From the antimicrobial data, it is observed that all the newly synthesized compounds show good to moderate level of antibacterial and antifungal activity **(Table 4)**. The antimicrobial activity data reveals that compounds (6b,6e,6f,6k and 6a) are found to be most active and potent as antimicrobial agents among the series. The antimicrobial activity data reveals that among the synthesized compounds 6b, 6e, and 6f compared with the standard. The compound 6m, 6n, 6o showed reduced antimicrobial activity. The compounds 6d, 6e,6f,6j,6k and 6l show intermediate antibacterial activity. The same compounds 6a, 6b, 6g and 6h showed higher antifungal activity when tested on the fungal strains. The structure-activity relationship of the series can be explained as follows. The compounds having methyl group at ortho position of aromatic shows promising antimicrobial activity among all the antimicrobial stains. The compounds having methoxy group on the ortho and para position of aromatic ring also shows promising antimicrobial activity. The reaming compounds having cyano group shows moderate antimicrobial activity. When ring is substituted with chloro and triflouromethyl there is less antimicrobial activity. In conclusion, the electron donating methyl and methoxy group on aromatic ring increases the antimicrobial activity.

From antimicrobial activity data confirms compounds 6a,6b,6e,6f and 6k are most active and remaining compounds are moderately active. Compounds having electron donating groups are most active compared to electron withdrawing groups.

**Procedure for Compound (6a-6o)- Synthesis of 5-Bromothiophene-2-Sulfonyl Chloride**

To a stirred solution of 2-bromothiophene (10 g, 61.3 mmol) in DCM (100 ml). Cooled reaction mass to 0°C, and then added chlorosulfonic acid (4.5 ml, 67.48 mmol) drop wise. Allowed reaction mass to come to room temperature and stirred for 1 h.

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Progress of reaction monitored by TLC. Evaporate reaction mixture under reduced pressure and obtained gummy material which is washed with cold hexane (100 ml) and it is crystalized from 10% ethyl acetate: hexane (50 ml) mixture to obtain 5-bromothiophene-2-sulfonyl chloride as white solid. Yield- 13 g (81.25%).

**Synthesis of 5-bromothiophene-2-sulfonyl Amide**

To a stirred solution of 5-bromothiophene-2-sulfonyl chloride (10 g, 38.3 mmol) in THF (100 ml). Cooled reaction mass to 0°C, and then added methyl amine (57 ml, 114 mmol). Allowed reaction mass to come to room temperature and stirred for 6 h. Progress of reaction monitored by TLC. Diluted reaction mass by water (100 ml) and extracted it twice with ethyl acetate (50 ml) to obtain white solid. Obtained solid compound washed with 20% Etoac:Hexane(50 ml), cold pentane (50 ml) and cold diethyl ether (50 ml) to obtained compound 5-bromothiophene-2-sulfonyl amide as white solid with purity more than 90%. Yield- 8 g (81.6%).

**Synthesis of 5-bromothiophene-2-sulfonyl Amide Coupled Compound**

To a stirred solution of 5-bromothiophene-2-sulfonyl amide (7.5 g, 29.2 mmol) in acetone (75 ml) and potassium carbonate (8.08 g, 58.59 mmol). Added Phenacyl bromide (5.83 g, 29.2 mmol). Stirred reaction mass at room temperature for 2 h. Progress of reaction monitored by TLC. Evaporated reaction mass under reduced pressure and obtained gummy material added cold water (100 ml) to it and stirred reaction mass for 1 h. Solid precipitates out filter it and wash it with excess of water and dry it properly to obtain compound 3 as white solid. Yield-9.5 g (86.7%).

**Synthesis of Compound (5a)**

To a stirred solution of compounds 4 (0.25 g, 0.66 mmol) in dioxane:water (5:1) added 3-methylphenyl boranic acid (0.134 g, 0.99 mmol) Added sodium carbonate (0.184 g, 1.33 mmol) again added dikis (25 mg) with x-phos (50 mg), degas reaction mass for 10 min. and heat reaction mixture to 100°C for 6 h. Progress of reaction was monitored by TLC. Filtered through a pad of celite and obtain filtrate which was evaporated under reduced pressure to obtain compound 5a with was 90% pure by HPLC. Yield 0.231 g (90%).

**The General Step for the Suzuki Reaction (5a-o)**

To a stirred solution of compounds 4 (1 eq.) in dioxane:water added substituted boranic acid (1.5 eq.) Added sodium carbonate (2 eq.) again added dikis (10 mol%) with x-phos (20 mol%), degas reaction mass for 10 min. and heat reaction mixture to 100°C for 6 h. Progress of reaction was monitored by TLC. Filtered through a pad of celite and obtain filtrate which was evaporated under reduced pressure to obtain crude compound with reasonably pure up to 90% by HPLC for all the compounds 5a-o.

**Synthesis of Compound (6a)**

To a stirred solution of compounds 5a (0.2 g, 0.52 mmol) in methanol (20 ml) Added sodium borohydride (0.04 g, 1.03 mmol) stirred reaction mixture at room temperature for 2 h. Reaction monitored by TLC. The evaporated reaction mass under reduced pressure to obtained crude which is diluted with water (20 ml) and extracted with ethyl acetate (20 ml). Washed organic layer with brine solution (10 ml) and evaporated it under reduced pressure to obtain desired compounds 6a without further purifications. Yield 0.19 g (95%).

**General Step for Reduction Reaction (6a-o)**

To a stirred solution of compounds 5a-o (1 eq.) in methanol (10 times of starting material) Added sodium borohydride (2 eq.) stirred reaction mixture at room temperature for 2 h. Reaction monitored by TLC. The evaporated reaction mass under reduced pressure to obtained crude which is diluted with water (10 times of reaction solvent) and extracted with ethyl acetate. Washed organic layer with brine solution and evaporated it under reduced pressure to obtain desired compounds 6a-o, without further purifications.

***N-(2-hydroxy-2-phenylethyl)-N-methyl-5-(m-tolyl)thiophene-2-sulfonamide (6a):*** White Solid, LC-MS m/z (%): 388 (M+H). 1H NMR (400 MHz, DMSO-d6)δ 7.622–7.589 (m, 2H), 7.555-7.518 (m, 3H), 7.358-7.322 (m, 4H), 7.290-7.254 (m, 1H), 7.222 (d, J=8 Hz, 1H), 5.622 (d, J=4.4 Hz, 1H, OH), 4.8-4.757 (m, 1H), 3.119 (m, 2H), 2.781 (s, 3H), 2.339 (s, 3H). HPLC 99.3%, RT 8. 21min. 13C NMR (CDCl3, 100MHZ): 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, 57.4, 36.37, 24.5.

***N-(2-hydroxy-2-phenylethyl)-N-methyl-5-(o-tolyl)thiophene-2-sulfonamide (6b):*** White Solid, LC-MS m/z (%): 388 (M+H). 1H NMR (400 MHz, DMSO-d6) δ 7.643 (d, J=4 Hz, 1H), 7.438 (d, J=7.2 Hz, 1H), 7.355-7.320 (m, 5H), 7.31-7.262 (m, 4H), 5.636 (d, J=4.4 Hz, 1H, OH), 4.791-4.773 (m, 1H), 3.151 (m, 2H), 2.796 (s, 3H), 2.392 (s, 3H). HPLC-97.3% RT 8.13 min. 13C NMR ($CDCl_3$,100 MHZ): 140.43, 138.64, 136.33,133.45, 131.14, 128.95, 128.18, 127.35, 127.34, 126.24, 126.23, 125.5, 125.54, 124.68, 124.32, 124.22, 71.58, 57.38, 36.35, 24.45.

***N-(2-hydroxy-2-phenylethyl)-N-methyl-5-(p-tolyl)thiophene-2-sulfonamide 6c):*** White Solid, LC-MS m/z (%): 388 (M+H). 1H NMR (400 MHz, DMSO-d6) δ 7.636-7.602 (m, 3H), 7.565 (d, J=4 Hz, 1H), 7.356-7.340 (m, 4H), 7.276-7.256 (m, 3H), 5.621 (d,

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J=4.4 Hz, 1H, OH), 4.8-4.791 (m, 1H), 3.17 (m, 2H), 2.8 (s, 3H), 2.39 (s, 3H). HPLC-98.9% RT 8.16 min. 13C NMR ($CDCl_3$, 100 MHZ): 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.

***5-(3-chlorophenyl)-N-(2-hydroxy-2-phenylethyl)-N-methylthiophene-2-sulfonamide (6d):*** White Solid, LC-MS m/z (%): 408 (M+H). 1H NMR (400 MHz, DMSO-d6) δ 7.851 (s, 1H), 7.731-7.642 (m, 3H), 7.483-7.468 (m, 2H), 7.358-7.325 (m, 4H), 7.282-7.27 (m, 1H), 5.618 (d, J=4.4 Hz, 1H, OH), 4.789-4.771 (m, 1H), 3.164-3.138 (m, 2H), 2.802 (s, 3H). HPLC-97.8% RT 8.07 min. 13C NMR ($CDCl_3$, 100 MHZ): 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, 57.4, 36.37.

***5-(4-chlorophenyl)-N-(2-hydroxy-2-phenylethyl)-N-methylthiophene-2-sulfonamide (6e):*** White Solid, LC-MS m/z (%):408 (M+H). 1H NMR (400 MHz, DMSO-d6) δ 7.773 (d, J=8.8 Hz, 2H), 7.665-7.634 (q, J=8.4 & 4 Hz, 2H), 7.517 (d, J=8.8 Hz, 2H), 7.356-7.342 (m, 4H), 7.288-7.26 (m, 1H), 5.633 (d, J=4.4 Hz, 1H, OH), 4.785-4.755 (m, 1H), 3.153-3.125 (m, 2H), 2.793 (s, 3H). HPLC-99.08% RT 8.25 min. 13C NMR (CDCl3, 100 MHZ): 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.

***5-(2-chlorophenyl)-N-(2-hydroxy-2-phenylethyl)-N-methylthiophene-2-sulfonamide (6f):*** White Solid, LC-MS m/z (%):408 (M+H). 1H NMR (400 MHz, DMSO-d6) δ 7.743-7.719 (m, 1H), 7.73 (d, J=4 Hz, 1H), 7.643-7.62 (m, 1H), 7.55 (d, J=4 Hz, 1H), 7.484-7.448 (m, 2H), 7.358-7.323 (m, 4H), 7.289-7.254 (m, 1H), 5.647 (d, J=4.4 Hz, 1H, OH), 4.792-4.763 (m, 1H), 3.192-3.118 (m, 2H), 2.801 (s, 3H). HPLC-97.09% RT 8.06 min. 13C NMR ($CDCl_3$, 100 MHZ): 147.6, 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, 57.4, 36.36.

***N-(2-hydroxy-2-phenylethyl)-5-(2-methoxyphenyl)-N-methylthiophene-2-sulfonamide (6g):*** White Solid, LC-MS m/z (%):404 (M+H). 1H NMR (400 MHz, DMSO-d6)δ 7.885 (d, J=8 Hz, 1H), 7.653 (d, J=4.4 Hz, 1H), 7.593 (d, J=4.4 Hz, 1H), 7.417-7.343 (m, 5H), 7.302-7.21 (m, 1H), 7.2 (d, J=8.4 Hz, 1H), 7.063 (t, J=8 Hz, 1H), 5.61 (d, J=4.4 Hz, 1H, OH), 4.791-4.749 (m, 1H), 3.951 (s, 3H), 3.169-3.066 (m, 2H), 2.815 (s, 3H). HPLC-% RT min. 13C NMR ($CDCl_3$, 100 MHZ): 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.

***N-(2-hydroxy-2-phenylethyl)-5-(3-methoxyphenyl)-N-methylthiophene-2-sulfonamide (6h):*** White Solid, LC-MS m/z (%):404 (M+H). 1H NMR (400 MHz, DMSO-d6) δ 7.655-7.581 (q, J=9.6 & 4 Hz, 2H), 7.389-7.343 (m, 4H), 7.324-7.26 (m, 4H), 6.995-6.97 (dd, J=8 Hz, 1H), 5.625 (d, J=4.4 Hz, 1H, OH), 4.8-4.757 (m, 1H), 3.817 (s, 3H), 3.24-3.14 (m, 2H), 2.79 (s, 3H). HPLC-% RT min. 13C NMR ($CDCl_3$,100MHZ): 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.

***N-(2-hydroxy-2-phenylethyl)-5-(4-methoxyphenyl)-N-methylthiophene-2-sulfonamide (6i):*** White Solid, LC-MS m/z (%):404 (M+H). 1H NMR (400 MHz, DMSO-d6)δ 7.67 (d, J=8.8 Hz, 2H), 7.583 (d, J=4 Hz, 1H), 7.49 (d, J=4 Hz, 1H), 7.357-7.323 (m, 4H), 7.282-7.268 (m, 1H), 7.01 (d, J=8.8 Hz, 2H), 5.616 (d, J=4.4 Hz, 1H, OH), 4.795-4.752 (m, 1H), 3.799 (s, 3H), 3.177-3.115 (m, 2H), 2.78 (s, 3H). HPLC-% RT min. 13C NMR ($CDCl_3$, 100 MHZ): 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.

***N-(2-hydroxy-2-phenylethyl)-N-methyl-5-(2-(trifluoromethyl)phenyl) thiophene- 2-sulfonamide (6j):*** White Solid, LC-MS m/z (%):442 (M+H). 1H NMR (400 MHz, DMSO-d6) δ 7.906 (d, J=8 Hz, 1H), 7.791-7.692 (m, 2H), 7.653-7.643 (m, 2H), 7.452-7.347 (m, 4H), 7.326-7.246 (m, 2H), 5.648 (d, J=4.4 Hz, 1H, OH), 4.809-4.767 (m, 1H), 3.180-3.108 (m, 2H), 2.792 (s, 3H). HPLC-% RT min. 13C NMR ($CDCl_3$, 100 MHZ): 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, 57.4, 36.34.

***N-(2-hydroxy-2-phenylethyl)-N-methyl-5-(3-(trifluoromethyl)phenyl)thiophene-2-sulfonamide (6k):*** White Solid, LC-MS m/z (%): 442 (M+H). 1H NMR (400 MHz, DMSO-d6) δ 8.075 (s, 1H), 8.043 (s, 1H), 7.819 (d, J=4 Hz, 1H), 7.777-7.758 (d, 1H), 7.714-7.67 (m, 2H), 7.359-7.325 (m, 4H), 7.283-7.253 (m, 1H), 5.628 (d, J=4.4 Hz, 1H, OH), 4.793 (m, 1H), 3.206-3.122 (m, 2H), 2.809 (s, 3H). HPLC-% RT min. 13C NMR ($CDCl_3$, 100 MHZ): 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.

***N-(2-hydroxy-2-phenylethyl)-N-methyl-5-(4-(trifluoromethyl)phenyl)thiophene-2-sulfonamide (6l):*** White Solid, LC-MS m/z (%): 442 (M+H). 1H NMR (400 MHz, DMSO-d6) δ 7.965 (d, J=8 Hz, 2H), 7.796-7.696 (m, 3H), 7.69 (d, J=4.4 Hz, 1H), 7.359-7.325 (m, 4H), 7.291-7.27 (m, 1H), 5.638 (d, J=4.4 Hz, 1H, OH), 4.806-4.763 (m, 1H), 3.190-3.178 (m, 2H), 2.813 (s, 3H). HPLC-% RT min. 13C NMR ($CDCl_3$,100 MHZ): 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.

***5-(2-cyanophenyl)-N-(2-hydroxy-2-phenylethyl)-N-methylthiophene-2-sulfonamide (6m):*** White Solid, LC-MS m/z (%):399 (M+H). 1H NMR (400 MHz, DMSO-d6) δ 7.906 (s, 1H), 7.6 (d, J=7.6 Hz, 1H), 7.567 (m, 1H), 7.492-7.427 (m, 3H), 7.359-7.352 (m, 4H), 7.326-7.305 (m, 1H), 5.644 (d, J=4.4 Hz, 1H, OH), 4.789-4.772 (m, 1H), 3.145-3.108 (m, 2H), 2.777 (s, 3H). HPLC-% RT min. 13C NMR (CDCl3, 100 MHZ): 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, 71.5, 57.4, 36.42.

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***5-(3-cyanophenyl)-N-(2-hydroxy-2-phenylethyl)-N-methylthiophene-2-sulfonamide (6n):*** White Solid, LC-MS m/z (%): 399 (M+H). 1H NMR (400 MHz, DMSO-d6) δ 8.3 (s, 1H), 8.059-8.05 (m, 1H), 7.860 (d, J=7.6 Hz, 1H), 7.950(d, J=4.4 Hz, 1H), 7.688-7.634 (m, 2H), 7.372-7.344 (m, 4H), 7.325-7.248 (m, 1H), 5.644 (d, J=4.4 Hz, 1H, OH), 4.805-4.762 (m, 1H), 3.196-3.114 (m, 2H), 2.807 (s, 3H). HPLC-% RT min. 13C NMR ($CDCl_3$, 100 MHZ): 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.

***5-(4-cyanophenyl)-N-(2-hydroxy-2-phenylethyl)-N-methylthiophene-2-sulfonamide (6o):*** White Solid, LC-MS m/z (%): 399 (M+H)1H NMR (400 MHz, DMSO-d6)δ 7.971-7.907 (m, 4H), 7.835 (d, J=8 Hz, 1H), 7.697 (d, J=4 Hz, 1H), 7.356-7.322 (m, 4H), 7.282-7.268 (m, 1H), 5.646 (d, J=4.4 Hz, 1H, OH), 4.801-4.759 (m, 1H), 3.166-3.116 (m, 2H), 2.808 (s, 3H). HPLC-% RT min. 13C NMR ($CDCl_3$, 100 MHZ): 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.

## RESULTS AND DISCUSSION

From the **Table 1** here we have optimized the condition for aromatic chlorosulfonation of 2-bromothiophene. The reactivity changes according to the equivalence of chlorosulfonic acid used. We have carried out 7 different combinations and optimized the reaction condition which reduced the efforts of tedious work up and purifications of intermediate for the first time for 2-bromothiophene.

For all the reactions, we have kept time constant. It is confirmed that when we use neat excess of chlorosulfonic acid without solvent there is 20% formation of required product, (entry 7) then we have used excess chlorosulfonic acid with dichloromethane (DCM) then yield was 30% (entry 6). From above these two conditions it is clear that we have to use chlorosulfonic acid in equivalents along with in neat and in DCM solvent conditions. The varied results are shown in **Table 1**. The entries (1, 2, 3 and 4) shows there is formation product along with side products, the yields are 35% to 60%. When we consider (entries 5) the yield is 80% when we used equivalent amount of chlorosulfonic acid (1.1 eq.) and DCM as solvent. Mainly there is formation of product and less side products in entries 3 and 4. But in entries 1 and 2 there is formation of multiple spots on TLC. The yields are isolated yields after series of reactions optimization and the condition of (entry 5) works well for 2-bromothiopene. By using this method, the work up is easy, we have to evaporate the reaction mixture under reduced pressure and obtained gummy material, which is washed with excess of n-hexane and it is recrystallized from 10% ethyl acetate: hexane mixture to obtain white solid which is used further for methylation reaction. In entries 1 to 4 the three is formation of polar junk material, which required purification by column chromatography so the yields are less, but in latter case purification not required pure compound obtained by washing with cold pentane and cold diethyl ether to obtain compound 2.

In step 2, we have done N-methylation by using 2 molar solution of methyl amine in THF. We have dome reaction using compound 2 and 3 eq. of methyl amine in acetonitrile from 0°C to room temperature for 4 h there is no any formation of desired product. Then we have used 3 eq. of methyl amine in DCM along with 3 eq. of triethyl amine as base there is formation of 35% of product after 4h after isolation by column chromatography. Then we have used 3 eq. of methyl amine in THF at 0°C to room temperature for 6 h there is 90% formation of compound 2. The reaction profile is very clean on TLC. We have modified the work up by not evaporating the reaction mixture we have diluted it to 10 times by water and extracted it twice with ethyl acetate to obtain the desired compound 3. The obtained solid compound washed with 10 ml of 20% Ethyl acetate: n-hexane and 10 ml of cold pentane and 10 ml cold diethyl ether to obtained compound 3 as white solid with purity more than 90%.

## CONCLUSIONS

In the present study, we have synthesized substituted thiophene sulfonamides compounds having tert-nitrogen and free hydroxyl group along with $CH_2$ group. We have optimized methodology for synthesis of these types of targets from milligram scale to multi gram scale. All functionality in one series of molecule; to develop new biological activities. Further work and biological activities are in progress.

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