SYNTHESIS AND ANTIMICROBIAL SCREENING OF 5-(SUBSTITUTED PHENYL)-N-(2-OXO-2-(SUBSTITUTED PHENYL)ETHYL)-N-METHYLFURAN-2-SULFONAMIDE DERIVATIVES

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We synthesized substituted furansulfonamide compounds and developed reaction conditions for a series of 5-(substituted phenyl)-N-(2-oxo-2-(substituted phenyl)ethyl)-N-methylfuran-2-sulfonamide derivatives (**4a**-**4m**). We have optimized methodology for targets from milligram scale to multi gram scale. The structure of synthesized compounds were elucidated and confirmed by 1H NMR, 13C NMR, LCMS and purity was checked by HPLC. All the synthesized final compounds (4a-4m) are screened for antimicrobial activity (minimum inhibitory concentration) against a series of strains of Bacillus subtillis, Staphylococcus aureus and Escherichia coli for antibacterial activity and against the strains of Candida albicans, Aspergillus flavus and Aspergillus niger for antifungal activity. The results of antimicrobial screening data revealed most of compounds (4a-4m) showed moderate to promising microbial inhibitions.

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INTRODUCTION

Medicinal chemistry deals with discovery, development and identification of mechanism of action of different compounds at molecular levels. Discovery for new antimicrobial drugs are still remains a challenge, because of development of resistance to old antimicrobial drugs.[1,2]

Furan-ring is a constituent of many natural products and furan derivatives are an important class of heterocycles have various types of biological activities. Furan-ring coupled with different groups showed varied biological activities such as antioxidant,[3] antimicrobial,[4] anti-inflammatory,[5] antitumor and antiviral.[6] Furan-amidine series acts as inhibitors of the enzyme quinone oxidoreductase-2,[7] some furonaphthoquinones shows anti-cancer activity,[8] cyclopenta[*b*]furans acts as inhibitors of CCR-2 as it is a G-protein coupled receptor of the chemokinine family[9] and some furan-2-carbohydrazides acts as glucagon receptor antagonists.[10] Some derivatives comprising thiophene and sulfur containing groups attatched with different groups showed as variety of biological activities.[11-13]

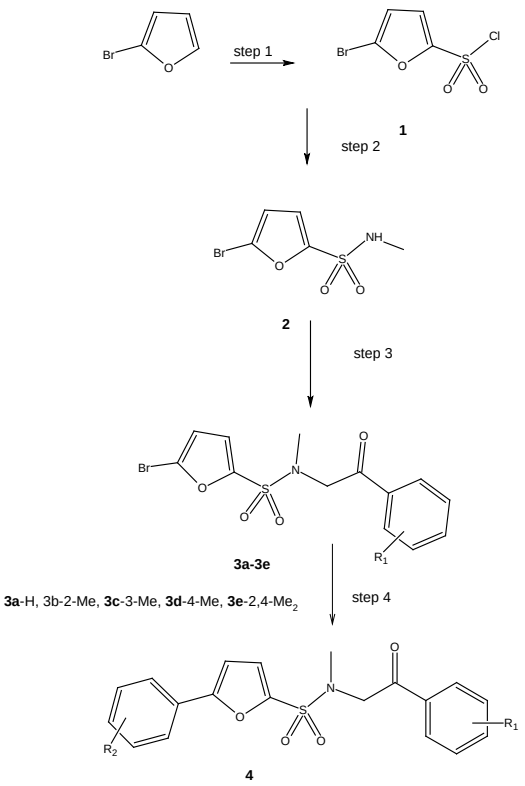
Some natural products with benzofuran scaffold display a variety of biological activities like anti-inflammatory, antibacterial, antitumor, antitubercular activities.[14-17] Some benzodifuran derivatives shows various biological activities like antimicrobial,[18] antifeedant[19] and anti-inflammatory.[20] Heterocyclic nuclei when coupled with different substituents in different reaction sequesces like Buchwald, Suzuki, peptide, oxidation or reduction reactions results novel heterocycles show variety of biological activities.[21-23] For example, benzodifuran scaffold can be easily utilized as dyes in solar cells,[24] building blocks for optoelectronic devices[25] and transistors.[26]

By considering the varied biological importance of furanes and sulfonamides and in continuation of research on heterocyclic compounds in our group for the development of antimicrobial and anticancer agent[27-29] we have synthesized a series of 5-(substituted phenyl)-N-(2-oxo-2-(substituted phenyl)ethyl)-N-methyl-furan-2-sulfonamide derivatives (**4a-4m**) depicted in Scheme 1 and tested their antimicrobial activity.

RESULT AND DISCUSSION

Synthesis of 5-(substituted phenyl)-N-(2-hydroxy-2-(phenyl)ethyl)-N-methylfuran-2-sulfonamide series starting from cheaply available 2-bromofuran through a series of reactions including aromatic sulfonation, sulfonamide formation, substitution and Suzuki reaction for the formation of C-C bond have been performed as depicted in Scheme 1. We have tried to optimize all the reaction steps for economy, safety, clean reaction conditions, yield, time and less harsh conditions.

In step 1 we have done aromatic chlorosulfonation by using chlorosulfonic acid. We have optimized the condition for aromatic chlorosulfonation of 2-bromofuran. The reactivity changes according to the equivalence of chlorosulfonic acid used.



R_1,R_2=H, 2-Me (**a**); H, 3-Me (**b**); H, 4-Me (**c**); H, H (**d**); 2-Me, H (**e**) , 3-Me, H (**f**); 4-Me, H (**g**); 2,4-Me_2, 2-Me (**h**); 2,4-Me_2, 3-Me (**i**); 2,4-Me_2, 4-Me (**j**); 2-Me, 2,4-Me_2 (**k**); 2-Me, 2,4-Me_2 (**l**); 2-Me, 2,4-Me_2 (**m**);

Scheme 1. Synthesis of 5-(substituted phenyl)-N-(2-oxo-2-substituted-phenylethyl)-N-methylfuran-2-sulfonamide derivatives **(4a-4m).** Reagents and conditions: Step 1- Chlorosulfonic acid, DCM, rt, 1 h; Step 2- $MeNH_2$, TEA, DCM, rt, 6 h; Step 3- substituted phencyl bromide, K_2CO_3, acetone, rt 2 h; Step 4- substituted boranic acid, $Pd(dppf)Cl_2$, Na_2CO_3, X-phos, Dioxane-H_2O.

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-bromofuran. For all the reactions we have kept the time to be 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 results are shown in Table 1.

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

Entry	$ClSO_3H$	Solvent	Yield[a] (%)
1	3 eq.	Neat	30
2	2 eq.	Neat	25
3	3 eq.	DCM	40
4	2 eq.	DCM	50
5	1.2 eq.	DCM	78
6	Excess	DCM	40
7	Excess	Neat	20

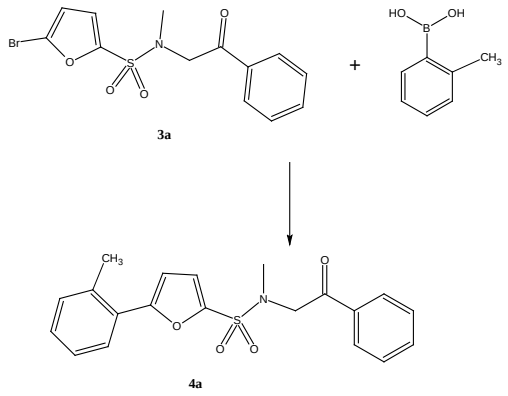
[a]Isolated yield, time 2 h

The entries (1, 2, 3 and 4) shows there is formation product along with side products, the yields are 25 % to 50 %. When we consider (entries 5) the yield is 78 % when we used equivalent amount of chlorosulfonic acid (1.1 eq.) and DCM as solvent. The yields are isolated yields after series of reactions optimization and the condition of (entry 5). 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 first three resulted in formation of polar junk material, which required purification by column chromatography, so the yields are less, but in the last case by washing with cold pentane and cold diethyl ether, pure compound 1 could be obtained.

In step 2 we have done sulfonamide preparation by using 2 molar solution of methyl amine in THF. We tried a reaction using compd. 1 and 3 eq. of methyl amine in acetonitrile from 0 °C to room temperature for 4 h but there was no formation of the desired product. Then we used 3 eq. of methyl amine in DCM along with 3 eq. of triethylamine as base when there was isolated 35 % of product with column chromatography after 4 h. Then we used 3 eq. of methyl amine in THF at 0 °C to room temperature for 6 h when there was 90 % formation of compound **2**. The reaction profile is very clean on TLC. We have modified the work up. Without evaporating the reaction mixture, that was diluted with 10 volumes of water and extracted twice with ethyl acetate to obtain the desired compound 2. The obtained solid compound washed with 10 ml of 20 % ethyl acetate : n-hexane, 10 ml of cold pentane and 10 ml cold diethyl ether to obtain compound **2**. Compound **2** is white solid with purity more than 90 %.

For step 3 we have treated compd. **2** (1 eq.) with substituted phenacyl bromide (1 eq.) by using inorganic base like K_2CO_3 (2 eq.) and Cs_2CO_3 (2 eq.) in acetone and THF, respectively, for 2 h at room temperature, to obtain 85 and 30 % isolated yields, respectively. The reaction with K_2CO_3 and acetone gave a simple work up procedure evaporating acetone under reduced pressure and adding water to the obtained gummy material with stirring the reaction mass for 1 h. A solid precipitates out was filtered off and washed with excess of water and dried properly to obtain compound **3a** as white solid which were used further for Suzuki-coupling reactions.

In step-4 we have done C-C bond formation by using Suzuki coupling reaction, we have done a series of optimization reactions to get better yield and less reaction time.



Scheme 2. Synthesis of compound **4a**.

Different catalysts, ligands, bases and solvents were screened. As model reaction we used the compound **3a** and 2-methylboronic acid. We used $Pd(PPh_3)_4$, $Pd(OAc)_2$, $Pd(dppf)Cl_2$ and $NiCl_2{\cdot}6H_2O$ as catalysts, X-phos, Xanthophos and BINAP as ligands. We used K_3PO_4, Na_2CO_3 and CS_2CO_3 as bases and dioxane-water, DMF-water and DME as solvents. For all the optimization reactions we used 2-methylboronic acid (1.5 eq.), catalyst (10 mol %), ligand (15 mol %) and base (2 eq.). All reactions were done at temperature 110 °C and for 6 h, the % yields are the isolated yields after purification, and the results of optimization reactions are tabulated in Table **2**.

Table 2. Screening of catalyst, bases and solvent for the synthesis of N-(2-oxo-2-(phenyl)ethyl)-N-methyl-5-(o-tolyl)-furan-2-sulfonamide 4a:

Catalyst	Ligand	Base	Solvent	Yield, %
$Pd(PPh_3)_4$	-	K_3PO_4	Dioxane:H_2O	40
$Pd(PPh_3)_4$	X-phos	K_3PO_4	DMF:H_2O	35
$Pd(OAc)_2$	X-phos	K_3PO_4	DMF:H_2O	50
$Pd(OAc)_2$	Xanth-ophos	K_3PO_4	DMF:H_2O	40
$Pd(dppf)Cl_2$	-	Na_2CO_3	Dioxane:H_2O	55
$Pd(dppf)Cl_2$	BINAP	Cs_2CO_3	Dioxane:H_2O	62
$Pd(dppf)Cl_2$	X-phos	Na_2CO_3	Dioxane:H_2O	85
$NiCl_2{\cdot}6H_2O$	BINAP	K_3PO_4	DME	40

In entries 1 and 2 we have used $Pd(PPh_3)_4$ as catalysts and K_3PO_4 as base we have used dioxane-water as solvent as no ligand we got 40 % yield of compound **4a**, in other case we used X-phos as ligand and DMF-H2O As solvent we for 35 % yield the yield is decreases. In entries 3 and 4 we have tried $Pd(OAc)_2$ as catalyst K_3PO_4 as base and DMF-H_2O as solvents we used X-phos and Xanthophos as ligands we got 50 % and 40 % yield, respectively. In entry 8 we have used $NiCl_2{\cdot}6H_2O$ as catalyst BINAP as ligand and K_3PO_4 as base and DME as solvent we got 40 % yield. In all these 5 optimization reactions we got yield in the range of 35 % to 50 %. In entry 5 we have used as $Pd(dppf)Cl_2$ catalyst and Na_2CO_3 as base, dioxane-H_2O as solvent we got 55 % yield which is higher than earlier 5 combinations. We have kept the same combination of catalyst solvents and varied the ligand and base in entries 6 and 7. In entry 6 we got 62 % yield and desired product and in entry 7 condition we got 85 % of desired product. The entry 7 reaction condition of $Pd(dppf)Cl_2$, X-phos, Na_2CO_3 dioxane-H_2O worked well in getting good yields. We have used the same set of condition for the synthesis of remaining derivatives **4b**-**4m**. The yields obtained are in the range of 75 to 85 %. The detailed experimental procedure and analytical data are given in experimental section.

Experimental procedure for synthesis of 5-(substituted phenyl)-N-(2-oxo-2-(substituted phenyl)ethyl)-N-methyl-furan-2-sulfonamides (**4a**-**4m**).

Step a: Synthesis of 5-bromofuran-2-sulfonyl chloride (1):

To a stirred solution of 2-bromofuran (10g, 68.03 mmol) in DCM (100 mL) chlorosulfonic acid (5.41 ml, 81.63 mmol) was added dropwise at 0 °C. Allowed the reaction mass to come to room temperature and stirred for 1 h. Progress of reaction and the consumption of starting material was monitored by TLC and LCMS, respectively. The reaction mixture was evaporated under reduced pressure to obtained a gummy material. The gummy material was washed with cold hexane (100 mL) and crystallized from EtOAc:hexane (10 %, 50 mL) mixture to obtain 5-bromofuran-2-sulfonyl chloride (1,14 g, 84 %) as an off-white solid.

Step b: Synthesis of 5- bromofuran-2-sulfonyl amide (2):

To a stirred solution of compound **1** (10 g, 40.73 mmol) methyl amine was added (61 mL, 122 mmol) in THF (100 mL) at 0 °C. The reaction mass was allowed to come to room temperature and stirred for 6 h. Progress of reaction and consumption of starting material were monitored by TLC and LCMS, respectively. After completion the reaction, the mixture was poured in H_2O (100 mL) and extracted with EtOAc (2 × 50 mL). The organic layer was collected, washed with brine (25 mL) and dried over anhydrous Na_2SO_4, and evaporated in vacuum. The obtained gummy material was washed with EtOAc:hexane (20 %, 50 mL), pentane (50 ml) and cold diethyl ether (50 ml) and dried it under vacuum to obtain compound **2** (8g, 82 %) as a white solid.

Step 3: General procedure for the synthesis of compounds 3a-3e:

To a stirred solution of compound 2 (1.0 mmol) in acetone (10 vol.) K_2CO_3 was added (2.0 mmol), the reaction mixture was stirred at room temperature for 30 min. Color change was observed from white to light pink. Substituted phenacyl bromide (a-H, b-2-Me, c-3-Me, d-4-Me, e-2,4-diMe) (1.0 mmol) was added and the mixture was stirred at room temperature for 2 h. Progress of reaction and the

consumption of starting material were monitored by TLC and LCMS, respectively. After completion the reaction, reaction mass was evaporated under reduced pressure to obtain a gummy material, which was poured into cold H_2O (10 vol.) and the mixture was stirred for 15 min. A solid was precipitated out from the reaction mass, that was filtered off and washed with H_2O, cold pentane and cold ether to obtain compounds **3a-3e** (60 to 87 %) as white solids.

Step 4: General procedure for the synthesis of compounds 4a-4m:

To a stirred solution of comp **3a-3e** (1.0 mmol) in dioxane:water was added substituted phenylboronic acid (**a**-2-Me, **b**-3-Me, **c**-4-Me, **d**-H, **e**-2,4diMe) (1.5 mmol). Na_2CO_3 (2.0 mmol), $Pd(dppf)Cl_2$ (10 mol %) and X-phos (15 mol%) were added, the reaction mass was inerzized with using argon for 10 min and the reaction mixture was heated until 100 °C for 6 h. Progress of reaction and consumption of starting material were monitored by TLC and LCMS. After completion the reaction, the reaction mixture was cooled to room temperature and filtered through a pad of celite to obtain a filtrate. The filtrate was evaporated under reduced pressure to obtain different crude compounds, **4a-4m**, these crude compounds were purified by flash column chromatography by using (silica gel 230-400 mesh; EtOAc:hexane 10-60:90-40) to obtain the desired compounds **4a-4m** (75% to 85%) as solids.

N-(2-Oxo-2-(phenyl)ethyl)-N-methyl-5-(o-tolyl)furan-2-sulfonamide (4a):

White solid; M.p. 163-164 °C; Yield: 78 %; IR (KBr) (ν_{max}, cm^{-1}): 1627 (C=O), 1580 and 1530 (Ar). Anal. calc. for $C_{20}H_{19}NO_4S$: C, 65.02; H, 5.18; N, 3.79; Found: C, 65.06; H, 5.11; N, 3.84. LC-MS m/z (%): 370 (M+H); HPLC-97.3 % RT 8.23 min; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.64 (d, *J* = 4.4 Hz, 1H, ArH), 7.43 (d, *J* = 7.2 Hz, 1H, ArH), 7.35-7.32 (m, 5H, ArH), 7.31-7.26 (m, 4H, ArH), 3.08 (s, 2H, CO-CH_2), 2.79 (s, 3H, N-CH_3), 2.39 (s, 3H, Ar-CH_3); ^{13}C NMR ($CDCl_3$,100 MHz): 169.6, 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, 57.38, 36.35, 24.45.

N-(2-Oxo-2-(phenyl)ethyl)-N-methyl-5-(m-tolyl)furan-2-sulfonamide (4b):

Off white solid; M.p. 169-170 °C; Yield: 77 %; IR (KBr) (ν_{max}, cm^{-1}): 1628 (C=O), 1584 and 1520 (Ar). Anal. calc. for $C_{20}H_{19}NO_4S$: C, 65.02; H, 5.18; N, 3.79; Found: C, 65.22; H, 5.22; N, 3.84. LC-MS m/z (%): 370 (M+H); HPLC 99.3 %, RT 8.13min; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.62–7.58 (m, 2H, ArH), 7.55-7.51 (m, 3H, ArH), 7.35-7.32 (m, 4H, ArH), 7.29-7.25 (m, 1H, ArH), 7.22 (d, *J* = 8.0 Hz, 1H, ArH), 3.11 (s, 2H, CO-CH_2), 2.78 (s, 3H, N-CH_3), 2.33 (s, 3H Ar-CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): 169.4, 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, 57.4, 36.37, 24.5.

N-(2-Oxo-2-(phenyl)ethyl)-N-methyl-5-(p-tolyl)furan-2-sulfonamide (4c):

Off white solid; M.p. 178-179 °C; Yield: 81 %; IR (KBr) (ν_{max}, cm^{-1}): 1628 (C=O), 1586 and 1524 (Ar). Anal. calc. for $C_{20}H_{19}NO_4S$: C, 65.02; H, 5.18; N, 3.79; Found: C, 64.97; H, 5.15; N, 3.75. LC-MS m/z (%): 370 (M+H); HPLC-98.9 %, RT 6.07 min; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.63-7.6 (m, 3H, ArH), 7.56 (d, *J* = 4.4 Hz, 1H, ArH), 7.35-7.34 (m, 4H, ArH), 7.27-7.25 (m, 3H, ArH), 3.17 (s, 2H, CO-CH_2), 2.8 (s, 3H, N-CH_3), 2.39 (s, 3H Ar-CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): 169.3, 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, 57.41, 36.37, 24.52.

N-(2-Oxo-2-(phenyl)ethyl)-N-methyl-5-(phenyl)furan-2-sulfonamide (4d):

White solid; M.p. 153-154 °C; Yield: 84 %; IR (KBr) (ν_{max}, cm^{-1}): 1628 (C=O), 1576 and 1516 (Ar). Anal. calc. for $C_{19}H_{17}NO_4S$: C, 64.21; H, 4.82; N, 3.94; Found: C, 64.17; H, 4.77; N, 3.91. LC-MS m/z (%): 356 (M+H); HPLC-97.3 %, RT 8.16 min; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.64 (d, *J* = 4.4 Hz, 1H, ArH), 7.43 (d, *J* = 7.2 Hz, 1H, ArH), 7.35-7.32 (m, 5H, ArH), 7.31-7.26 (m, 5H, ArH), 3.15 (s, 2H, CO-CH_2), 2.79 (s, 3H, N-CH_3). ^{13}C NMR ($CDCl_3$,100 MHz): 171.4, 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, 57.38, 36.35.

N-(2-Oxo-2-(o-tolyl)ethyl)-N-methyl-5-phenylfuran-2-sulfonamide (4e):

Off white solid; M.p. 162-163 °C; Yield: 76 %; IR (KBr) (ν_{max}, cm^{-1}): 1630 (C=O), 1586 and 1530 (Ar). Anal. calc. for $C_{20}H_{19}NO_4S$: C, 65.02; H, 5.18; N, 3.79; Found: C, 65.03; H, 5.19; N, 3.78. LC-MS m/z (%): 370 (M+H); HPLC-97.3 %, RT 8.14 min; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.64 (d, *J* = 4.4 Hz, 1H, ArH), 7.43 (d, *J* = 7.6 Hz, 1H, ArH), 7.35-7.32 (m, 5H, ArH), 7.31-7.26 (m, 4H, ArH), 3.15 (s, 2H, CO-CH_2), 2.79 (s, 3H, N-CH_3), 2.39 (s, 3H, Ar-CH_3); ^{13}C NMR ($CDCl_3$,100 MHz): 171.2, 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, 57.38, 36.35, 24.45.

N-(2-Oxo-2-(m-tolyl)ethyl)-N-methyl-5-phenylfuran-2-sulfonamide (4f):

Off white solid; m.p. 171-172 °C; Yield: 82 %; IR (KBr) (ν_{max}, cm^{-1}): 1620 (C=O), 1570 and 1528 (Ar). Anal. calc. for $C_{20}H_{19}NO_4S$: C, 65.02; H, 5.18; N, 3.79; Found: C, 65.03; H, 5.10; N, 3.85.LC-MS m/z (%): 370 (M+H); HPLC 99.3 %, RT 8.22 min; ^{1}H NMR (400 MHz, DMSO-d_6), δ 7.62–7.58 (m, 2H, ArH), 7.55-7.51 (m, 3H, ArH), 7.35-7.32 (m, 4H, ArH), 7.29-7.25 (m, 1H, ArH), 7.22 (d, *J* = 8.0 Hz, 1H, ArH), 3.11 (m, 2H, CO-CH_2), 2.78 (s, 3H, N-CH_3), 2.33 (s, 3H, Ar-CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): 170.2, 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, 57.4, 36.37, 24.5, 18.4.

N-(2-Oxo-2-(p-tolyl)ethyl)-N-methyl-5-phenylfuran-2-sulfonamide (4g):

Off white solid; M.p. 169-170 °C; Yield: 75 %; IR (KBr) (ν_{max}, cm^{-1}): 1628 (C=O), 1574 and 1526 (Ar). Anal. calc. for $C_{20}H_{19}NO_4S$: C, 65.02; H, 5.18; N, 3.79; Found: C, 65.04; H, 5.15; N, 3.81. LC-MS m/z (%): 370 (M+H); HPLC-98.9 %, RT 8.18 min; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.63-7.6 (m, 3H, Ar-H), 7.56 (d, *J* = 4.4 Hz, 1H, Ar-H), 7.35-7.34 (m, 4H, Ar-H), 7.27-7.25 (m, 3H, Ar-H), 3.17 (s, 2H, CO-CH_2), 2.8 (s, 3H, N-CH_3), 2.39 (s, 3H, Ar-CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): 168.9, 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, 57.41, 36.37, 24.52.

N-(2-(2,4-Dimethylphenyl)-2-oxoethyl)-N-methyl-5-(o-tolyl)furan-2-sulfonamide (4h):

White solid; M.p. 193-194 °C; Yield: 82 %; IR (KBr) (ν_{max}, cm^{-1}): 1634 (C=O), 1586 and 1528 (Ar). Anal. calc. for $C_{22}H_{23}NO_4S$: C, 66.48; H, 5.83; N, 3.51; Found: C, 66.52 H, 5.81; N, 3.54. LC-MS m/z (%): 398 (M+H); HPLC-97.3 %, RT 8.13 min; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.64 (d, *J* = 4.4 Hz, 1H, Ar-H), 7.43 (d, *J* = 7.2 Hz, 1H, Ar-H), 7.35-7.32 (m, 4H, Ar-H), 7.31-7.26 (m, 4H, Ar-H), 3.15 (s, 2H, CO-CH_2), 2.79 (s, 3H, N-CH_3), 2.39 (s, 3H, Ar-CH_3), 2.33 (s, 3H, Ar-CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): 169.8, 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, 57.38, 36.35, 24.45, 18.4.

N-(2-(2,4-Dimethylphenyl)-2-oxoethyl)-N-methyl-5-(m-tolyl)furan-2-sulfonamide (4i):

Off white solid; M.p. 201-202 °C; Yield: 79 %; IR (KBr) (ν_{max}, cm^{-1}): 1636 (C=O), 1576 and 1518 (Ar). Anal. calc. for $C_{22}H_{23}NO_4S$: C, 66.48; H, 5.83; N, 3.51; Found: C, 66.46 H, 5.85; N, 3.47. LC-MS m/z (%): 398 (M+H); HPLC 99.3 %, RT 8.20 min; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.62–7.58 (m, 2H, Ar-H), 7.55-7.51 (m, 3H, Ar-H), 7.35-7.32 (m, 3H, Ar-H), 7.29-7.25 (m, 1H, Ar-H), 7.22 (d, *J* = 8.4 Hz, 1H, Ar-H), 3.11 (s, 2H, CO-CH_2), 2.78 (s, 3H, N-CH_3), 2.33 (s, 3H, Ar-CH_3), 2.33 (s, 3H, Ar-CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): 170.2, 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, 57.4, 36.37, 24.5, 17.8.

N-(2-(2,4-Dimethylphenyl)-2-oxoethyl)-N-methyl-5-(p-tolyl)furan-2-sulfonamide (4j):

White solid; M.p. 198-199 °C; Yield: 84 %; IR (KBr) (ν_{max}, cm^{-1}): 1628 (C=O), 1586 and 1520 (Ar). Anal. calc. for $C_{22}H_{23}NO_4S$: C, 66.48; H, 5.83; N, 3.51; Found: C, 66.44 H, 5.79; N, 3.46. LC-MS m/z (%): 398 (M+H); HPLC-98.9 %, RT 8.18 min; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.63-7.6 (m, 3H, Ar-H), 7.56 (d, *J* = 4.4 Hz, 1H, Ar-CH_3), 7.35-7.34 (m, 3H, Ar-CH_3), 7.27-7.25 (m, 3H, Ar-CH_3), 3.17 (s, 2H, CO-CH_2), 2.8 (s, 3H, N-CH_3), 2.39 (s, 3H, Ar-CH_3), 2.33 (s, 3H, Ar-CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): 169.52, 140.41, 138.34, 136.19, 133.16, 131.14, 128.84, 128.44, 127.35, 127.24, 126.14, 126.13, 125.5, 125.64, 124.68, 124.23, 124.21, 57.41, 36.37, 24.51, 18.2.

5-(2,4-Dimethylphenyl)-N-methyl-N-(2-oxo-2-(o-tolyl)-ethyl)furan-2-sulfonamide (4k):

Off white solid; M.p. 193-194 °C; Yield: 76 %; IR (KBr) (ν_{max}, cm^{-1}): 1628 (C=O), 1580 and 1520 (Ar). Anal. calc. for $C_{22}H_{23}NO_4S$: C, 66.48; H, 5.83; N, 3.51; Found: C, 66.54 H, 5.87; N, 3.56. LC-MS m/z (%): 398 (M+H); HPLC-97.3 %, RT 8.13 min; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.64 (d, *J* = 4.6 Hz, 1H, Ar-H), 7.43 (d, *J* = 7.4 Hz, 1H, Ar-H), 7.35-7.32 (m, 4H, Ar-H), 7.31-7.26 (m, 4H, Ar-H), 3.15 (s, 2H, CO-CH_2), 2.79 (s, 3H, N-CH_3), 2.39 (s, 3H, Ar-CH_3), 2.33 (s, 3H, Ar-CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): 168.77, 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, 57.38, 36.35, 24.45, 18.6.

5-(2,4-Dimethylphenyl)-N-methyl-N-(2-oxo-2-(m-tolyl)-ethyl)furan-2-sulfonamide (4l):

Off white solid; M.p. 207-208 °C; Yield: 79 %; IR (KBr) (ν_{max}, cm^{-1}): 1624 (C=O), 1584 and 1528 (Ar). Anal. calc. for $C_{22}H_{23}NO_4S$: C, 66.48; H, 5.83; N, 3.51; Found: C, 66.50 H, 5.79; N, 3.45. LC-MS m/z (%): 398 (M+H); HPLC 99.3 %, RT 8.21min; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.62–7.58 (m, 2H, Ar-H), 7.55-7.51 (m, 3H, Ar-H), 7.35-7.32 (m, 3H, Ar-H), 7.29-7.25 (m, 1H, Ar-H), 7.22 (d, *J* = 8.8 Hz, 1H, Ar-H), 3.11 (s, 2H, CO-CH_2), 2.78 (s, 3H, N-CH_3), 2.33 (s, 3H, Ar-CH_3), 2.33 (s, 3H, Ar-CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): 169.4, 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, 57.4, 36.37, 24.5, 18.4.

5-(2,4-Dimethylphenyl)-N-methyl-N-(2-oxo-2-(p-tolyl)-ethyl)furan-2-sulfonamide (4m):

Off white solid; M.p. 195-196 °C; Yield: 76 %; IR (KBr) (ν_{max}, cm^{-1}): 1627 (C=O), 1582 and 1520 (Ar). Anal. calc. for $C_{22}H_{23}NO_4S$: C, 66.48; H, 5.83; N, 3.51; Found: C, 66.53 H, 5.86; N, 3.57. LC-MS m/z (%): 398 (M+H); HPLC-98.9 %, RT 8.16 min; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.63-7.6 (m, 3H, Ar-H), 7.58 (d, *J* = 4.6 Hz, 1H, Ar-H), 7.35-7.32 (m, 3H, Ar-H), 7.27-7.21 (m, 3H, Ar-H), 3.17 (s, 2H, CO-CH_3), 2.8 (s, 3H, N-CH_3), 2.39 (s, 3H, Ar-CH_3), 2.33 (s, 3H, Ar-CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): 169.4, 140.41, 138.33, 136.17, 133.15, 131.14, 128.85, 128.44, 127.35, 127.24, 126.14, 126.13, 125.75, 125.64, 124.68, 124.21, 124.21, 57.41, 36.37, 24.52, 18.6.

Table 3. Antimicrobial activity data for compounds **4a-4m**

Compounds	MIC values[a], μg mL^{-1}					
	B. subtilis	***E. coli***	***S. aureus***	***C. Albicans***	***A. Flavus***	***A. Niger***
4a	30	51	26	54	51	56
4b	29	29	36	26	14.5	14.5
4c	48	90	95	65	80	80
4d	38	63	58	80	60	40
4e	35	32	29	29	32	15.5
4f	42	29	33	48	29	26
4g	35	60	37	90	60	50
4h	45	90	90	75	90	80
4i	55	56	56	90	56	50
4j	56	67	100	75	59	80
4k	37	46	70	75	46	25
4l	48	78	100	75	78	90
4m	28	89	70	75	89	54
Ciprofloxacin	26	26	25	-	-	-
Fluconazole	-	-	-	36	23	23
Miconazole	-	-	-	13.5	13.5	13.5

[a]Values are the average of three readings.

Antimicrobial activity

All the synthesized compounds **(4a-4m)** 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), Gram negative bacteriaum, *Escherichia coli* (NCIM-2256), and four fungal strains *Candida albicans* (NCIM-3471), *Aspergillus flavus* (NCIM-539) and *Aspergillus niger* (NCIM-1196). For studying antimicrobial properties of compounds, Minimum Inhibitory Concentration (MIC, μg mL^{-1}), 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 **4a-4m** 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 as the standard antibacterial drugs and Fluconazole and Miconazole as the standard antifungal drugs.[30] The antimicrobial activity results were given in Table 3.

From the antimicrobial data, it is observed that all the newly synthesized compounds showed good to moderate level of antibacterial and antifungal activity. The antimicrobial activity data reveals that compounds **4a, 4b, 4e, 4f, 4k** and **4m** are found to be active and potent as antimicrobial agents among the series. The antimicrobial activity data reveals that among the synthesized compounds **4b, 4e** and **4f** are very active compared with the standard.

For antibacterial activity evaluated for Gram positive bacteria the compounds **4a, 4b, 4e, 4f** and **4m** are most active and that of compounds **4d, 4g** and **4k** are moderately active the remaining compounds are mostly inactive. For Gram negative bacteria the compounds **4b, 4e** and **4f** are most active and remaining compounds are moderately active or mostly inactive. For antifungal activity the compounds **4b, 4e** and **4f** are very active compared with standard the compound **4k** is moderately active the remaining compounds are moistly inactive. The furan sulfonamide compounds are active mostly on antifungal stains when compared with antibacterial stains.

The SAR can be drawn like that when aromatic ring was coupled with methyl group it shows good activity and among then the substitution on meta position is the favorable one compared with ortho and para substitution. When we increased this electron donating tendency then the activity decreases, due to steric hindrance and more crowing of groups. When unsubstituted compounds are there then the activity decreases also. The small electron donating group plays a key role in the antimicrobial activity in this series.

CONCLUSIONS

In the present paper we have synthesized 5-(substituted phenyl)-N-(2-oxo-2-(substituted phenyl)ethyl)-N-methylfuran-2-sulfonamides (**4a-4m**).

A total 13 derivatives were synthesized starting from 2-bromofuran, we have used substituted phenacyl bromides and substituted aromatic boronic acids, through series of coupling reactions. We have optimized the sulfonation reaction and Suzuki reaction for getting good yields and clean reaction profiles. The synthesized compounds were characterized by analytical data. All the synthesized derivatives further tested for antimicrobial activity. Most compounds showed moderate to good antimicrobial activity but the compounds having substitution on meta position of benzene ring increases the activity compared with other compounds, as the substitution increases there is decrease in the activity.

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