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Synthesis and antibacterial activity studies of 2,4-di substituted furan derivatives

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ABSTRACT

2,4 disubstitiuted furan derivatives (**8A–8M**) were prepared from furan-4-carboxylic acid ethyl ester (**1**). Antibacterial activity of new 2,4 di substituted furan derivatives was studied against Gram (+) and Gram (−) bacteria. **8F**, **8E**, **8D** and **8J** were found to be effective against Gram (−) bacteria whereas, **8A** and **8L** were effective against Gram (+) bacteria. Least MIC value was found as 100 μg/ml against *Escherichia coli* (for **8D** and **8F**), and *Proteus vulgaris* (for **8E** and **8F**). Antibacterial activity is correlated with different substituents. Products exhibited better antibacterial activities especially towards *Streptococcus pyogenes*, *Proteus vulgaris*, and *Escherichia coli*.

1. Introduction

1.1. Importance of furans

Heterocyclic compounds containing oxygen/nitrogen atoms have received significant attention in view of their spectrum of effective pharmacological activities (Ahmad et al., 2013). A significant and enduring area of research interest for chemists is synthesis of substituted furans as furan ring is an imperative structural unit in various biologically active and natural products (Joule and Mills, 2010; Sniady et al., 2008). Extensive gamut of insecticidal and phytocidal activities are exhibited by furan derivatives (Wakita et al., 2003; Shimokawatoko and Yamada, 2006). Their diverse array of encouraging pharmacological properties helps to use them antidepressant, antimicrobial and anti-inflammatory agents (Burch et al., 1980). Their lofty therapeutic properties of furan derivatives encourage synthesizing a number of chemotherapeutic agents as they operate on different receptors/targets (Banerjee et al., 2012).

1.2. Methodologies for synthesis of furans and need for new drugs

Furan is a versatile synthon (Wright, 2005) and Zheng et al. (2011) reported that furan ring has shown better antimicrobial activity compared to other substituents. Different synthetic routes were reported in literature for synthesis of molecules incorporated with furan moiety (Salem, 2016). Substituted furans are synthesised by two key approaches. In the first approach, furan ring is raised by an array of various strategies which include cycloisomerization (Pridmore et al., 2009), cyclization (Wang et al., 2010), intramolecular couplings and ring closing metathesis (Moran and Rodriguez, 2012). The second strategy involves functionalization of existing furan rings. In classical approaches furans are synthesised by cyclization suitable precursors in presence of strong mineral acids (Paal-Knorr reaction) (Li, 2014) or metal catalysts (Aponick et al., 2009; Gabriele et al., 2010). Substituted furan derivatives were synthesized with involvement of transition metal salts (Sumit et al., 2007), in the presence of a gold (I) catalyst by a Claisen-type rearrangement (Florin and Fabien, 2011), under continuous-flow conditions (York, 2011). New synthetic routes were established for the preparation of 2,4-disubstituted furans (Katritzky et al., 2004), 2,3-disubstituted furans by ortho lithiation (Tofi et al., 2005). Synthesis and biological activity studies of furan derivatives were reviewed by Logoglu et al. (2010) and Zheng et al. (2011).

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In the subtropical regions of the world, around 20,000 deaths per year were due to parasitic bacterial infections (Rani et al., 2015). In spite of availability of several antibiotics in the market, there is an ample requirement for novel anti-bacterial agents in view of rapid developing of antibiotic resistant bacteria (Shekhar, 2010).

1.3. Objectives of study

The present study is aimed at synthesis of 2,4-disubstituted furans having different substituents on aromatic ring in order to understand their antibacterial activities as they are widely distributed in nature (Cheng et al., 2010) and the existence of furan ring could significantly enhance the antibacterial activity (Jumina and Zulkarnain, 2002).

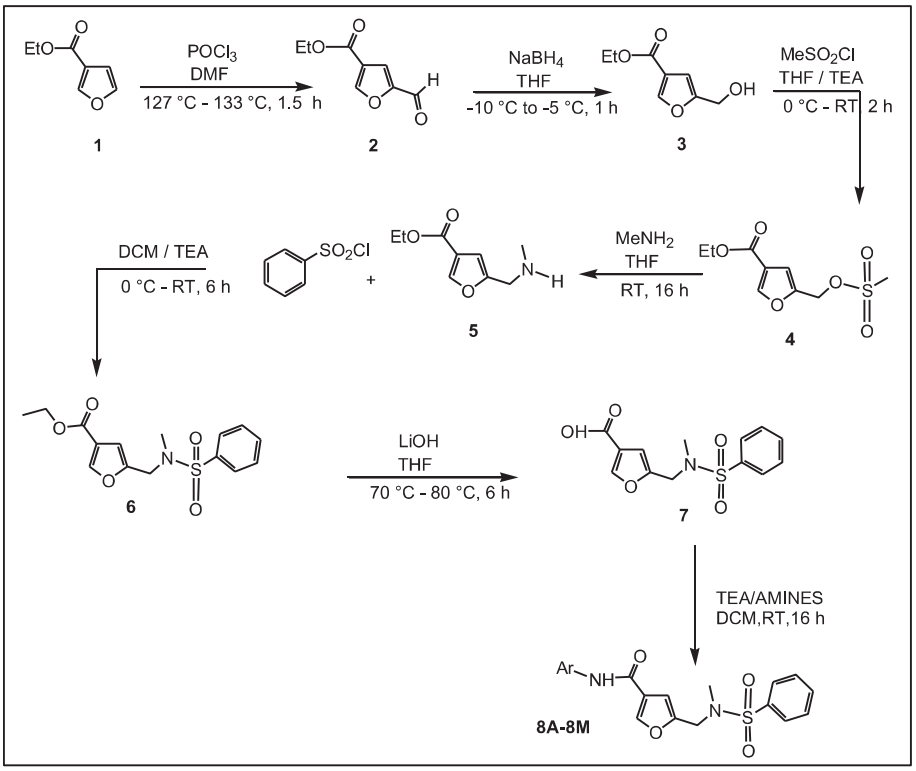
2. Materials and methods

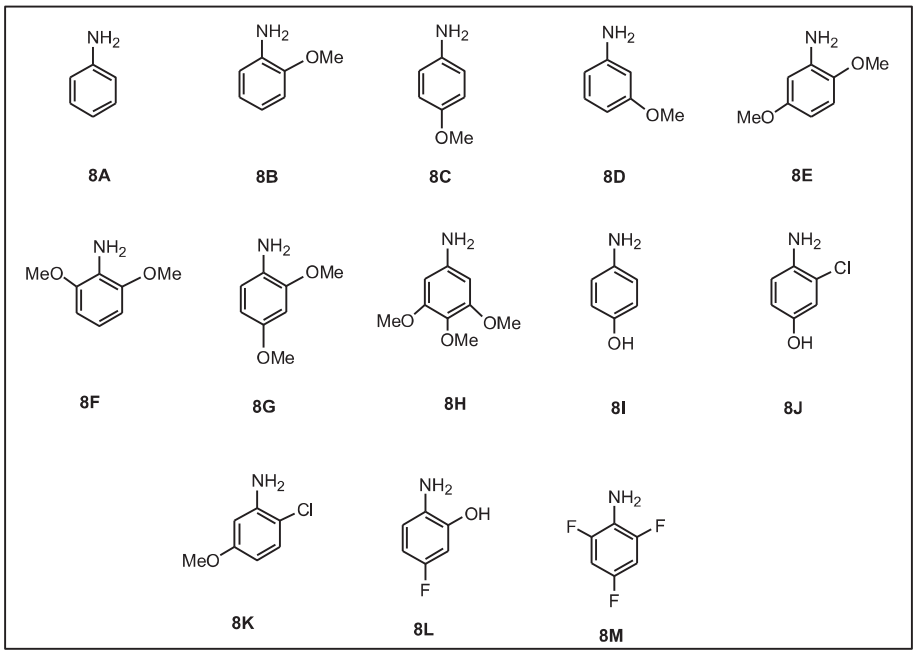
Melting points were determined using open glass capillaries on a Mel-temp apparatus and are uncorrected. Thin layer chromatography (TLC) was performed on E. Merk AL silica gel 60 F254 plates and visualized under UV light. The IR spectra were recorded on a Perkin Elmer FT-IR spectrometer. The ^{1}H NMR spectra were recorded on a Varian EM-360 spectrometer (400 MHz). All chemical shifts were reported in δ (ppm) using TMS as an internal standard. The mass spectra were recorded on Agilent ion trap MS. Analytical and Laboratory Reagent grade chemicals of Merck India Co. Ltd. were used in the present study. MIC (Minimum Inhibitory Concentration) values of tested compounds against bacterial strains were determined by broth microdilution method (CLSI, 2012).

3. Experimental part

3.1. Scheme and procedure for synthesis of 2,4 disubstituted furan derivatives

Synthetic route implied to prepare compounds (**8A–8M**) is outlined in the given below scheme.





3.2. Procedure for the synthesis of compounds **2** to **8**

Representative procedure for the intermediates and final products involved in the above given synthetic route is briefed below.

3.2.1. 5-Formayl-furan-3-carboxylic acid ethyl ester (**2**)

To the stirred mixture of $POCl_3$ (34 ml) and DMF (37 ml), compound **1** (40 g, 285 m mol) was added in three portions. Then the mixture was heated under reflux conditions for 1½ h. The contents were cooled by quenching with water and ethyl acetate was used to extract the product. Water and saturated NaCl were employed to wash the extracted organic layer. Then $MgSO_4$ crystals were added to dry the organic layer, filtered and evaporated in vacuum. A pale yellow liquid (compound-2, 26.4 g, 55%) was obtained by purifying the residue with flash column chromatography (silica gel, 3:1 hexane/ethyl acetate).

3.2.2. 5-Hydroxymethyl-furan-3-carboxylic acid ethyl ester (**3**)

To the stirred solution of compound **2** (8 g, 47 mmol) in THF (80 ml), sodium borohydride was added in two portions and mixture was stirred at −10 °C to −5 °C for 1 h. A pale yellow liquid (compound-3, 5.26 g, 65%) was obtained by repeating the above processes viz., quenching, extracting with ethyl acetate, washing, drying, evaporation and purification by flash column chromatography.

3.2.3. 4-(Ethoxy carbonyl)furan-2-yl)methyl methane sulfonate (**4**)

To the stirred solution of compound **3** (5 g) in THF (50 mL), TEA was added at 0 °C and then methane sulfonyl chloride was added slowly at same temperature. Stirring was continued for another 2 h at room temperature. For further step, the crude product was taken as such which was obtained by repeating the above processes (viz., quenching, extracting with ethyl acetate, washing, drying and evaporation) to the reaction mixture.

3.2.4. Ethyl 5-((methyl amino)methyl)furan-3-carboxylate (**5**)

Crude compound **4** (5.3 g) in THF (30 mL) was cooled to 0 °C and then 2.0 M $MeNH_2$ was slowly added with continuous stirring. The mixture was stirred in sealed tube for 16 h at room temperature. Then THF was distilled off completely and crude compound was taken into next step.

3.2.5. Ethyl 5-[(Benzene sulfonyl-methyl-amino)-methyl]-furan-3-carboxylate (**6**)

The mixture of compound **5** (5.8 g), and TEA (3.0 eq) was taken in DCM (60 mL). Then benzene sulfonyl chloride (4.45 g) was added drop wise to the mixture at 0 °C. The solution was stirred for 6 h at room temperature. Water was added and organic layer was extracted with ethyl acetate (3 × 10 mL) which was washed with water. The solid product was dried to afford compound **5** as a white solid (5.08 g).

3.2.6. 5-[(Benzene sulfonyl-methyl-amino)-methyl]-furan-3-carboxylic acid (**7**)

To a stirred solution of compound **6** (5 g) in THF, LiOH was added and then heated to 70–80 °C for 6 h. To the mixture, water was added and then pH was adjusted to 2.0 using hydrochloric acid. A white solid (2.08 g, Yield: 98%) was obtained by washing the collected precipitate with water followed by drying.

3.2.7. Synthesis of amides (**8A**–**8M**)

Amides were synthesized using activating reagent (EDC·HCl: *N*-(3-dimethylaminopropyl)-*N*′-ethyl carbodiimide hydrochloride), base (TEA: Triethyalamine), solvent (CH_2Cl_2: dichloromethane) and additive (HOBt: 1-hydroxybenzotriazole hydrate). To a solution of dichloromethane containing compound-**7** (500 mg) and amine (A–M), added EDC. HCl (1.5 eq) and HOBt (1.2 eq) at 0 °C. Finally TEA (2 eq) was added and stirred overnight at RT. After completion of the reaction, the reaction mixture was distilled and the obtained crude compound was dissolved in EtOAc, washed with water, brine solution, dried over Na_2SO_4, filtered and

evaporated under vacuum to obtain the crude amide derivatives which were purified by column chromatography.

3.3. Characterization of synthesized compounds

The synthesized compounds were characterized by melting point, spectral data of IR, ^{1}H NMR, ^{13}C NMR and MS. The data is given below.

3.3.1. 5-Formayl-furan-3-carboxylic acid ethyl ester (**2**)

A pale yellow liquid, b.p.269–270 °C. IR spectrum (KBr), ν, cm^{-1}: 3030 (Ar—C—H str), 2825 (C—H str), 2720 (aldehyde—C—H str), 1724 (ester—C=O str), 1692 (aldehyde—C=O str), 1521 (Ar—C=C str), 1400 (C—H bend), 1212 (Ar—C—O str), 1085 (ester—C—O), 846 (furan—C—H ben) cm^{-1}; ^{1}H NMR spectrum ($CDCl_3$, 300 MHz) δ, ppm (J, Hz): 9.7 (1H, s, —CHO), 8.2 (1H, s, Furan—H), 7.58 (1H, s, Furan—H), 4.4 (2H, q, J = 7.12 Hz, —CH_2), 1.4 (3H, t, J = 7.12 Hz, —CH_3); ^{13}C NMR ($CDCl_3$, 200 MHz) δ, ppm: 178.1 (—CHO), 159.4 (ester C=O), 154.3 (Furan—C), 148.8 (Furan—C), 120.8 (Furan—C), 116.5 (Furan—C), 60.9 (—CH_2—ester), 14.1 (—CH_3); Mass spectrum (EI, 70 eV): Found, m/z: 168.1 [M]$^+$. $C_8H_8O_4$. Calculated, m/z: 168.05.

3.3.2. 5-Hydroxymethyl-furan-3-carboxylic acid ethyl ester (**3**)

A pale yellow liquid, b.p. 310–314 °C. IR spectrum (KBr), ν, cm^{-1}: 3076 (Ar—C—H str), 2985, 2944 (C—H str), 1717, 1702 (C=O str), 1548, 1449 (Ar—C=C str), 1335 (S=O str), 1226 (Ar—C—O str), 1159 (ester—C—O str), 772 (C—H ben) cm^{-1}; ^{1}H NMR spectrum (300 MHz, $CDCl_3$,) δ, ppm (J, Hz): 8.0 (1H, s, Furan—H), 6.6 (1H, s, Furan—H), 4.65 (2H, d, J = 7.12 Hz, —CH_2-hydroxy), 4.3 (2H, q, J = 7.12 Hz, —CH_2—ester), 1.4 (3H, t, J = 7.12 Hz, —CH_3); ^{13}C NMR spectrum (200 MHz, $CDCl_3$) δ, ppm: 163.1 (C=O), 155.3 (Furan—C), 147.5 (Furan—C, 120.0 (Furan—C), 107.5 (Furan—C), 60.9 (—CH_2—ester), 57.1(—CH_2—hydroxy), 14.2 (—CH_3); Mass spectrum (EI, 70 eV): Found, m/z: 170 [M]$^+$, 171 [M +H]$^+$. $C_8H_{10}O_4$. Calculated, m/z: 170.06.

3.3.3. Ethyl 5-((methyl amino)methyl)furan-3-carboxylate (**5**)

A Pale yellow syrupy liquid, b.p. 292–295 °C IR spectrum (KBr), ν, cm^{-1}: 3349 (N—H str), 2870 (C—H str), 1715 (C=O str), 1549, 1447 (Ar—C=C str), 1021 (C—O str), 863 (furan—C—H ben) cm^{-1}; ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) δ, ppm (J, Hz): 8.1 (1H, s, Furan—H), 6.6 (1H, s, Furan—H), 4.5 (2H, s, CH_2—N), 4.3 (2H, q, J = 7.8 Hz, —CH_2—ester), 1.4 (3H, t, J = 7.8 Hz, —CH_3); ^{13}C NMR spectrum ($CDCl_3$, 100 MHz) δ, ppm: 160.5 (C=O), 149.8 (Furan—C), 146.0 (Furan—C), 118.9 (Furan—C), 106.7 (Furan—C), 60.9 (—CH_2—ester), 52.4 (—N—CH_2—), 33.4 (—N—CH_3), 14.1 (—CH_3); Mass spectrum (EI, 70 eV): Found, m/z: 183 [M]$^+$. $C_9H_{13}NO_3$. Calculated, m/z: 183.2.

3.3.4. Ethyl 5-[(Benzene sulfonyl-methyl-amino)-methyl]-furan-3-carboxylate (**6**)

A white solid, m.p. 116–119 °C. IR spectrum (KBr), ν, cm^{-1}: 3076 (Ar—C—H str), 2985, 2944 (C—H str), 1717, 1702 (C=O str), 1548, 1449 (Ar—C=C str), 1335 (S=O str), 1226 (Ar—C—O str), 1159 (ester—C—O str), 772 (C—H ben) cm^{-1}; ^{1}H NMR spectrum (DMSO-d_6) δ, ppm (J, Hz): 8.0 (1H, s, Furan—H), 7.6 (2H, d, J = 7.2 Hz, S—Ar—H), 7.2 (1H, t, J = 7.6 Hz, S—Ar—H), 6.6 (1H, s, Furan—H), 4.3 (2H, d, J = 8 Hz, —N—CH_2—), 2.8 (3H, s, —N—CH_3); ^{13}C NMR spectrum ($CDCl_3$, 100 MHz) δ, ppm: 162.7 (C=O), 150.5 (Furan—C), 147.5 (Furan—C), 137.5 (S—Ar—C), 132.7 (S—Ar—C), 129.0 (S—Ar—C), 127.3 (S—Ar—C), 120.2 (Furan—C), 109.3 (Furan—C), 60.4 (—CH_2—ester), 46.4 (—N—CH_2—), 34.6 (—N—CH_3), 14.2 (—CH_3); Mass spectrum (EI, 70 eV): Found, m/z: 323 [M]$^+$. $C_{15}H_{17}NO_5$. Calculated, m/z: 323.3.

3.3.5. 5-[(Benzene sulfonyl-methyl-amino)-methyl]-furan-3-carboxylic acid (**7**)

A white solid, m.p. 199–201 °C. IR spectrum (KBr), ν, cm^{-1}: 3442 (O—H str), 3158, 3067 (Ar—C—H str), 2927, 2820 (C—H str), 1692, 1677 (C=O str), 1605, 1551 (Ar—C=C str), 1225 (Ar—C—O str), 1161 (C—O str), 934 (Ar—C—H ben) cm^{-1}; ^{1}H NMR spectrum (DMSO-d_6) δ, ppm (J, Hz): 8.2 (1H, s, Furan—H); 7.8 (2H, d, J = 7.2 Hz, S—Ar—H); 7.7 (1H, t, J = 7.6 Hz, S—Ar—H), 7.65 (2H, m, J = 7.55 Hz, S—Ar—H), 6.6 (1H, s, Furan—H), 4.3 (2H, d, J = 8 Hz, —N—CH_2—), 2.4 (3H, s, —N—CH_3); ^{13}C NMR spectrum ($CDCl_3$, 100 MHz) δ, ppm: 166.5 (C=O), 151.2 (Furan—C), 148.9 (Furan—C), 137.6 (S—Ar—C), 132.8 (S—Ar—C), 129.1 (S—Ar—C), 127.4 (S—Ar—C), 119.1 (Furan—C), 109.3 (Furan—C), 46.5 (—N—CH_2—), 34.7 (—N—CH_3); Mass spectrum (EI, 70 eV): Found, m/z: 294 [M]$^-$. $C_{13}H_{13}NO_5S$. Calculated, m/z: 295.05.

3.3.6. 5-[(Benzene sulfonyl-methyl-amino)-methyl]-furan-3-carboxylic acid phenyl amide (**8A**)

Yield: 63%, a pale yellow solid, m.p. 191–193 °C. IR spectrum (KBr), ν, cm^{-1}: 3379 (N—H str), 2923 (C—H str), 1646 (C=O str), 1547, 1443 (Ar—C=C str), 1334 (S=O str), 1162 (C—O str), 936 (Ar—C—H ben) cm^{-1}; ^{1}H NMR spectrum (DMSO-d_6) δ, ppm (J, Hz): 9.90 (1H, br. s, N—H); 8.30 (1H, s, Furan—H); 7.80 (2H, d, J = 7.2 Hz, N—Ar—H); 7.80–7.60 (5H, m, J = 8.6 Hz, S—Ar—H); 7.40 (2H, t, J = 7.6 Hz, N—Ar—H); 7.10 (1H, t, J = 8 Hz, N—Ar—H); 6.90 (1H, s, Furan—H); 4.30 (2H, s, —N—CH_2—); 2.67 (3H, s, —N—CH_3). ^{13}C NMR spectrum (DMSO-d_6, 100 MHz) δ, ppm: 160.0 (C=O); 150.3 (Furan—C); 145.9 (Furan—C); 138.7 (N—Ar—C); 136.8 (S—Ar—C); 133.0 (S—Ar—C); 129.3 (S—Ar—C); 128.6 (Furan—C); 127.2 (S—Ar—C); 123.5 (N—Ar—C); 123.5 (N—Ar—C); 120.1 (N—Ar—C); 108.9 (Furan—C); 46.1 (—N—CH_2—); 34.6 (—N—CH_3); Mass spectrum (EI, 70 eV): Found, m/z: 371.1 [M+H]$^+$. $C_{19}H_{18}N_2O_4$-S. Calculated, m/z: 370.1.

3.3.7. 5-[(Benzene sulfonyl-methyl-amino)-methyl]-furan-3-carboxylic acid (2-methoxy-phenyl)-amide (**8B**)

Yield: 63%, a pale yellow solid, m.p. 153–155 °C. IR spectrum (KBr), ν, cm^{-1}: 3323.9 (N—H str), 3130 (Ar—C—H str), 2935 (C—H str), 1652 (C=O str), 1546, 1487, 1460 (Ar—C=C str), 1340 (S=O str), 1156 (C—O str), 938 (Ar—C—H ben) cm^{-1}; ^{1}H NMR spectrum (DMSO-d_6) (J, Hz): 9.20 (1H, br. s, N—H), 8.32 (1H, s, Furan—H), 7.80 (2H, d, J = 7.6 Hz, S—Ar—H), 7.70 (1H, t, J = 7.6 Hz, N—Ar—H), 7.68–7.6 (3H, m, J = 3 Hz, S—Ar—H), 7.20 (1H, t, J = 8 Hz, N—Ar—H), 7.10 (1H, d, J = 5.2 Hz, N—Ar—H), 6.90 (1H, t, J = 8.8 Hz, N—Ar—H), 6.85 (1H, s, Furan—H), 4.30 (2H, s, —N—CH_2—), 3.80 (3H, s, —O—CH_3), 2.68 (3H, s, —N—CH_3); ^{13}C NMR spectrum ($CDCl_3$, 100 MHz) δ, ppm: 160.0 (C=O), 151.4 (Furan—C), 150.2 (N—Ar—C), 145.8 (Furan—C), 136.8 (S—Ar—C), 133.0 (S—Ar—C), 129.3 (S—Ar—C), 127.2 (N—Ar—C), 126.2 (S—Ar—C), 125.7 (Furan—C), 124.7 (N—Ar—C), 123.3 (N—Ar—C), 120.1 (N—Ar—C), 111.3 (N—Ar—C), 108.9 (Furan—C), 55.6 (—O—CH_3), 46.0 (—N—CH_2—), 34.6 (—N—CH_3); Mass spectrum (EI, 70 eV): Found, m/z: 401.1 [M +H]$^+$. $C_{20}H_{20}N_2O_5S$. Calculated, m/z: 400.1.

3.3.8. 5-[(Benzene sulfonyl-methyl-amino)-methyl]-furan-3-carboxylic acid (4-methoxy-phenyl)-amide (**8C**)

Yield: 60%, a pale yellow solid, m.p. 132–135 °C. IR spectrum (KBr), ν, cm^{-1}: 3323.9 (N—H str), 3130 (Ar—C—H str), 2935 (C—H str), 1652 (C=O str), 1546, 1487, 1460 (Ar—C=C str), 1340 (S=O str), 1156 (C—O str), 938 (Ar—C—H ben) cm^{-1}; ^{1}H NMR spectrum (DMSO-d_6) δ, ppm (J, Hz): 9.79 (1H, br. s, N—H), 8.25 (1H, s, Furan—H), 7.8 (2H, d, J = 6.8 Hz, S—Ar—H), 7.65 (2H, m, J = 8.3 Hz, N—Ar—H), 7.60–7.50 (3H, m, J = 8.03 Hz, S—Ar—H), 6.90 (2H, m, J = 8.82 Hz, N—Ar—H), 4.30 (2H, s, —N—CH_2—), 3.74 (3H, s, —O—CH_3), 2.68 (3H, s, —N—CH_3); ^{13}C NMR spectrum (DMSO-d_6, 100 MHz) δ, ppm: 159.1 (C=O), 155.3 (N—Ar—C), 150.2 (Furan—C),

145.8 (Furan—C), 136.8 (S—Ar—C), 133.03 (S—Ar—C), 129.3 (S—Ar—C), 127.2 (N—Ar—C), 126.2 (S—Ar—C), 125.7 (Furan—C), 124.7 (N—Ar—C), 123.3 (N—Ar—C), 120.1 (N—Ar—C), 111.3 (N—Ar—C), 106.9 (Furan—C), 55.6 (—O—CH_3), 46.05 (—N—CH_2—), 34.6 (—N—CH_3); Mass spectrum (EI, 70 eV): Found, *m*/*z*: 401.2 [M+H]$^+$. $C_{20}H_{20}N_2O_5S$. Calculated, *m*/*z*: 400.1.

3.3.9. 5-[(Benzene sulfonyl-methyl-amino)-methyl]-furan-3-carboxylic acid (3-methoxy-phenyl)-amide (**8D**)

Yield: 64%, a pale yellow solid, m.p. 166–167 °C. IR spectrum (KBr), *v*, cm^{-1}: 3363.9 (N—H str), 3145 (Ar—C—H str), 2924 (C—H str), 1728, 1660 (C=O str), 1543, 1453 (Ar—C=C str), 1328 (S=O str), 1216 (S=O str), 1160 (C—O str), 936 (Ar—C—H ben) cm^{-1}; ^{1}H NMR spectrum (DMSO-d_6) δ, ppm (*J*, Hz): 9.87 (1H, br. s, N—H), 8.29 (1H, s, Furan—H), 7.80 (2H, d, *J* = 7.2 Hz, S—Ar—H), 7.70 (1H, d, *J* = 7.2 Hz, S—Ar—H), 7.60 (2H, t, *J* = 7.6 Hz, S—Ar—H), 7.4 (1H, s, N—Ar—H), 7.30–7.20 (2H, m, *J* = 1.6 Hz, N—Ar—H), 6.90 (1H, s, Furan—H), 6.68 (1H, dd, *J* = 1.6, 8 Hz, N—Ar—H), 4.3 (2H, s, N—CH_2—), 3.74 (3H, s, —O—CH_3), 2.68 (3H, s, —N—CH_3); ^{13}C NMR spectrum (DMSO-d_6, 100 MHz) δ, ppm: 160.1 (C=O), 159.4 (N—Ar—C), 150.3 (Furan—C), 145.9 (Furan—C), 139.9 (N—Ar—C), 136.8 (S—Ar—C), 133.0 (S—Ar—C), 129.3 (S—Ar—C), 127.2 (S—Ar—C), 123.5 (N—Ar—C), 112.3 (N—Ar—C), 109.0 (N—Ar—C), 108.8 (N—Ar—C), 105.8 (Furan—C), 54.5(—O—CH_3), 46.098 (—N—CH_2—), 34.621 (—N—CH_3); Mass spectrum (EI, 70 eV): Found, *m*/*z*: 401.2 [M+H]$^+$. $C_{20}H_{20}N_2O_5S$. Calculated, *m*/*z*: 400.1.

3.3.10. 5-[(Benzene sulfonyl-methyl-amino)-methyl]-furan-3-carboxylic acid (2,5,-dimethoxy-phenyl)-amide (**8E**)

Yield: 72%, a pale yellow solid, m.p. 102–105 °C. IR spectrum (KBr), *v*, cm^{-1}: 3322 (N—H str), 3123 (Ar—C—H str), 2960 (C—H str), 1651 (C=O str), 1600, 1547, 1485 (Ar—C=C str), 1328 (S=O str), 1224 (S=O str), 1161 (C—O str), 936 (Ar—C—H ben) cm^{-1}; ^{1}H NMR spectrum (DMSO-d_6) δ, ppm (*J*, Hz): 9.30 (1H, br. s, N—H), 8.30 (1H, s, Furan—H), 7.8 (2H, d, *J* = 7.2 Hz, S—Ar—H), 7.70 (1H, t, *J* = 7.2 Hz, S—Ar—H), 7.60 (2H, t, *J* = 7.6 Hz, S—Ar—H), 7.39 (1H, dd, *J* = 2, 6.8 Hz, N—Ar—H), 7.0 (1H, d, *J* = 12 Hz, N—Ar—H), 6.80 (1H, s, Furan—H), 6.70 (1H, dd, *J* = 1.8, 8 Hz, N—Ar—H), 4.3 (2H, s, —N—CH_2—), 3.8 (3H, s, —O—CH_3), 3.74 (3H, s, —O—CH_3), 2.68 (3H, s, —N—CH_3); ^{13}C NMR spectrum (DMSO-d_6, 100 MHz) δ, ppm: 160 (C=O), 159 (N—Ar—C), 150 (Furan—C), 145.8 (N—Ar—C), 136.8 (S—Ar—C), 133.03 (S—Ar—C), 129.368 (Furan—C), 127.2 (S—Ar—C), 126.22 (S—Ar—C), 125.7 (Furan—C), 124.7 (N—Ar—C), 123.3 (N—Ar—C), 120.1 (N—Ar—C), 111.36 (N—Ar—C), 106.9 (Furan—C), 55.6 (—O—CH_3), 46.05 (—N—CH_2—), 34.6 (—N—CH_3); Mass spectrum (EI, 70 eV): Found, *m*/*z*: 431.2 [M+H]$^+$. $C_{21}H_{22}N_2O_6$-S. Calculated, *m*/*z*: 430.12.

3.3.11. 5-[(Benzene sulfonyl-methyl-amino)-methyl]-furan-3-carboxylic acid (2,6-dimethoxy-phenyl)-amide (**8F**)

Yield: 74%, a pale yellow solid, m.p. 164-166 °C. IR spectrum (KBr), *v*, cm^{-1}: 3454 (N—H str), 3307.8 (N—H str), 2929 (C—H str), 1729 (C=O str), 1654, 1474 (Ar—C=C str), 1332 (S=O str), 1257 (S=O str), 1115 (C—O str), 938 (Ar—C—H ben) cm^{-1}; ^{1}H NMR spectrum (DMSO-d_6) δ, ppm (*J*, Hz): 9.0 (1H, s, br, N—H), 8.18 (1H, br. S, Furan—H), 7.80 (2H, d, *J* = 7.2 Hz, S—Ar—H), 7.70 (3H, m, *J* = 8.03 Hz, S—Ar—H), 7.20 (1H, m, *J* = 8.18 Hz, N—Ar—H), 6.80 (1H, m, *J* = 8.18 Hz) 6.70 (2H, d, *J* = 7.2 Hz, N—Ar—H), 4.20 (2H, s, —N—CH_2—), 3.70 (6H, s, —O—CH_3), 2.68 (3H, s, —N—CH_3); ^{13}C NMR spectrum (DMSO-d_6,100 MHz) δ, ppm: 160.0 (C=O), 156.2 (N—Ar—C), 150.0 (Furan—C), 145.6 (Furan—C), 136.8 (S—Ar—C), 133.0 (S—Ar—C), 129.3 (S—Ar—C), 127.8 (S—Ar—C), 127.2 (Furan—C), 123.3 (N—Ar—C), 114.1 (N—Ar—C), 109.1 (Furan—C), 104.3 (N—Ar—C), 55.6 (—O—CH_3), 46.1 (—N—CH_2—), 34.6 (—N—CH_3); Mass spectrum (EI, 70 eV): Found, *m*/*z*: 431.2 [M+H]$^+$. $C_{21}H_{22}N_2O_6S$. Calculated, *m*/*z*: 430.12.

3.3.12. 5-[(Benzene sulfonyl-methyl-amino)-methyl]-furan-3-carboxylic acid (2,4,-dimethoxy-phenyl)-amide (**8G**)

Yield: 76%, a pale yellow solid, m.p. 131-133 °C. IR spectrum (KBr), *v*, cm^{-1}: 3322 (N—H str), 3123 (Ar—C—H str), 2960 (C—H str), 1651 (C=O str), 1600, 1547, 1485 (Ar—C=C str), 1328 (S=O str), 1224 (S=O str), 1161 (C—O str), 936 (Ar—C—H ben) cm^{-1}; ^{1}H NMR spectrum (DMSO-d_6) δ, ppm (*J*, Hz): 9.0 (1H, br. S, N—H), 8.30 (1H, s, Furan—H), 7.80 (2H, d, *J* = 7.2 Hz, S—Ar—H), 7.60 (2H, t, *J* = 7.6 Hz, S—Ar—H), 7.40 (1H, d, *J* = 8 Hz, S—Ar—H), 6.90 (1H, d, *J* = 7.2, N—Ar—H), 6.60 (1H, d, *J* = 6.8 Hz, N—Ar—H), 6.70 (1H, dd, *J* = 2.4, 8.77 Hz, N—Ar—H), 6.42 (1H, s, Furan—H), 4.30 (2H, s, —N—CH_2—), 3.8 (3H, s, —O—CH_3), 3.74 (3H, s, —O—CH_3), 2.68 (3H, s, —N—CH_3); ^{13}C NMR spectrum (DMSO-d_6, 100 MHz) δ, ppm: 160.3 (C=O), 159.1 (N—Ar—C), 150.5 (N—Ar—C), 145.8 (Furan—C), 139.1 (N—Ar—C), 136.8 (S—Ar—C), 133.03 (S—Ar—C), 129.3 (S—Ar—C), 127.2 (S—Ar—C), 126.2 (S—Ar—C), 125.7 (Furan—C), 124.7 (N—Ar—C), 123.3 (N—Ar—C), 120.1 (N—Ar—C), 111.36 (Furan—C), 106.9 (Furan—C), 55.6 (—O—CH_3), 46.05 (—N—CH_2—), 34.6 (—N—CH_3); Mass spectrum (EI, 70 eV): Found, *m*/*z*: 431.2 [M+H]$^+$. $C_{21}H_{22}N_2O_6S$. Calculated, *m*/*z*: 430.12.

3.3.13. 5-[(Benzene sulfonyl-methyl-amino)-methyl]-furan-3-carboxylic acid (3,4,5,-trimethoxy-phenyl)-amide (**8H**)

Yield 78%, a yellow solid, m.p. 165–167 °C. IR spectrum (KBr), *v*, cm^{-1}: 3351 (N—H str), 2937 (C—H str), 1655 (C=O str), 1603 (Ar—C=C str), 1335 (S=O str), 1224 (S=O str), 1151 (C—O str), 939 (Ar—C—H ben) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ, ppm (*J*, Hz): 9.80 (1H, br. S, N—H), 8.30 (1H, s, Furan—H), 7.80 (2H, d, *J* = 7.2 Hz, S—Ar—H), 7.70 (1H, t, *J* = 7.2, S—Ar—H), 7.65 (2H, t, *J* = 7.6 Hz, S—Ar—H), 7.16 (2H, s, N—Ar—H), 6.90 (1H, s, N—Ar—H), 4.30 (2H, s, —N—CH_2—), 3.76 (3H, s, —O—CH_3), 3.71 (3H, s, —O—CH_3), 3.60 (3H, s, —O—CH_3), 2.6 (3H, s, —N—CH_3); ^{13}C NMR spectrum (DMSO-d_6, 100 MHz) δ, ppm: 160.2 (C=O), 152.5 (N—Ar—C), 150.8 (Furan—C), 146.3 (Furan—C), 136.6 (N—Ar—C), 135.2 (S—Ar—C), 134.4 (S—Ar—C), 130.7 (S—Ar—C), 128.3 (N—Ar—C), 125.7 (Furan—C), 108.6 (Furan—C), 60.3 (—O—CH_3), 55.6 (—O—CH_3), 46.0 (—N—CH_2—), 34.6(—N—CH_3); Mass spectrum (EI, 70 eV): Found, *m*/*z*: 461.2 [M+H]$^+$. $C_{22}H_{24}N_2O_7S$. Calculated, *m*/*z*: 460.13.

3.3.14. 5-[(Benzene sulfonyl-methyl-amino)-methyl]-furan-3-carboxylic acid (4-hydroxy-phenyl)-amide (**8I**)

Yield: 67%, a yellow solid, m.p. 225–227 °C. IR spectrum (KBr), *v*, cm^{-1}: 3454 (O—H str), 3378 (N—H str), 3124 (Ar—C—H str), 1647 (C=O str), 1548 (Ar—C=C str), 1205 (S=O str), 1149 (C—O str), 938 (Ar—C—H ben) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ, ppm (*J*, Hz): 9.70 (1H, br. S, N—H), 9.2 (1H, br. S, Ar—O—H), 8.30 (1H, s, Furan—H), 7.80 (2H, d, *J* = 7.2 Hz, S—Ar—H), 7.65 (3H, m, *J* = 7.2 Hz, S—Ar—H), 7.40 (2H, m, *J* = 8.8 Hz, N—Ar—H), 6.90 (1H, m, *J* = 8.7 Hz, N—Ar—H), 6.70 (1H, m, *J* = 8.7 Hz, N—Ar—H), 4.30 (2H, s, —N—CH_2—), 2.68 (3H, s, —N—CH_3); ^{13}C NMR spectrum (DMSO-d_6, 100 MHz) δ: 159.5 (C=O), 153.6 (N—Ar—C), 150.1 (Furan—C), 145.5 (Furan—C), 136.8 (S—Ar—C), 133.03 (S—Ar—C), 130.2 (N—Ar—C), 129.3 (S—Ar—C), 127.2 (S—Ar—C), 123.6 (Furan—C), 122.1 (N—Ar—C), 115.0 (N—Ar—C), 108.8 (Furan—C), 46.1 (—N—CH_2—), 34.6 (—N—CH_3); Mass spectrum (EI, 70 eV): Found, *m*/*z*: 387.1 [M+H]$^+$. $C_{19}H_{18}N_2O_5$-S. Calculated, *m*/*z*: 386.09.

3.3.15. 5-[(Benzene sulfonyl-methyl-amino)-methyl]-furan-3-carboxylic acid (2-chloro-4-hydroxy-phenyl)-amide (**8J**)

Yield: 63%, a thick yellow solid, m.p. 124–125 °C. IR spectrum (KBr), *v*, cm^{-1}: 3460 (O—H str), 3369 (N—H str), 1727 (C=O str), 1626, 1499 (Ar—C=C str), 1342 (S=O str), 1196 (C—O str), 575 (C—S str) cm^{-1}; ^{1}H NMR spectrum (DMSO-d_6) δ, ppm (*J*, Hz): 8.50 (1H, s, Furan—H), 7.80 (2H, d, *J* = 7.2 Hz, S—Ar—H), 7.72 (1H, t, *J* = 8.0 Hz, S—Ar—H), 7.66 (2H, t, *J* = 7.2 Hz, S—Ar—H), 7.13 (1H,

d, J = 5.4 Hz, N—Ar—H), 6.90 (1H, dd, J = 2.8, 8.8 Hz, N—Ar—H), 6.8 (1H, d, J = 8.8 Hz, N—Ar—H), 6.75 (1H, br. S, Furan—H), 4.29 (2H, s, —N—CH_2—), 2.65 (3H, s, —N—CH_3); ^{13}C NMR spectrum (DMSO-d_6, 100 MHz) δ, ppm: 161.0 (C=O), 151.2 (N—Ar—C), 149.6 (Furan—C), 142.8 (Furan—C), 139.8 (S—Ar—C), 136.7 (S—Ar—C), 133.0 (S—Ar—C), 129.4 (N—Ar—C), 127.1 (S—Ar—C), 122.2 (Furan—C), 121.2 (N—Ar—C), 118.5 (N—Ar—C), 116.3 (N—Ar—C), 115.1 (N—Ar—C), 109.4 (Furan—C), 45.8 (—N—CH_2—), 34.6 (—N—CH_3); Mass spectrum (EI, 70 eV): Found, m/z: 421.1 $[M+H]^+$. $C_{19}H_{17}N_2O_5S$. Calculated, m/z: 420.05.

3.3.16. 5-[(Benzene sulfonyl-methyl-amino)-methyl]-furan-3-carboxylic acid (2-chloro-5-methoxy-phenyl)-amide (**8K**)

Yield: 81%, a thick yellow solid, m.p. 136–140 °C. IR spectrum (KBr), ν, cm^{-1}: 3446, 3231 (N—H str), 2929 (C—H str), 1649 (Ar—C=C str), 1340 (S=O str), 1223 (S=O str), 1163 (C—O str), 933 (Ar—C—H ben) cm^{-1}; ^{1}H NMR spectrum (DMSO-d_6) δ, ppm (J, Hz): 8.16 (1H, s, Furan—H), 7.9–7.80 (2H, d, J = 7.2 Hz, S—Ar—H), 7.60 (1H, m, J = 7.5 Hz, S—Ar—H), 7.56 (2H, t, J = 7.6 Hz, S—Ar—H), 7.28 (1H, t, J = 8.2 Hz, N—Ar—H), 6.67 (1H, dd, J = 4, 12 Hz, N—Ar—H), 6.50 (s, 1H, Furan—H), 4.30 (2H, s, —N—CH_2—), 3.80 (3H, s, —O—CH_3), 2.80 (3H, s, —N—CH_3); ^{13}C NMR spectrum (DMSO-d_6, 100 MHz) δ, ppm: 159.9 (C=O), 158.9 (N—Ar—C), 151.5 (Furan—C), 145.3 (Furan—C), 137.5 (S—Ar—C), 134.8 (S—Ar—C), 132.8 (N—Ar—C), 129.1 (S—Ar—C), 127.3 (S—Ar—C), 123.6 (Furan—C), 113.8 (N—Ar—C), 111.3 (N—Ar—C), 107.4 (N—Ar—C), 106.3 (Furan—C), 55.6 (—O—CH_3), 46.5 (—N—CH_2—), 34.9 (—N—CH_3); Mass spectrum (EI, 70 eV): Found, m/z: 452. $C_{19}H_{18}N_2O_4S$. Calculated, m/z: 449.9.

3.3.17. 5-[(Benzene sulfonyl-methyl-amino)-methyl]-furan-3-carboxylic acid (2-hydroxy-4-fluoro-phenyl)-amide (**8L**)

Yield: 71%, a light brown solid, m.p. 200–203 °C. IR spectrum (KBr), ν, cm^{-1}: 3343 (N—H str), 3115 (Ar—C—H str), 2924 (C—H str), 1651 (C=O str), 1608 (Ar—C=C str), 1325 (S=O str), 1161 (C—O str), 933 (Ar—C—H ben) cm^{-1}; ^{1}H NMR spectrum (DMSO-d_6) δ, ppm (J, Hz): 10.21 (1H, br. S, Ar—O—H), 9.29 (1H, br. S, N—H), 8.30 (1H, s, Furan—H), 7.80 (2H, d, J = 7.6 Hz, S—Ar—H), 7.70 (1H, t, J = 7.6 Hz, S—Ar—H), 7.66 (2H, t, J = 8 Hz, S—Ar—H), 7.49 (1H, t, J = 6.8 Hz, N—Ar—H), 6.80 (1H, s, Furan—H), 6.72–6.61 (2H, m, J = 5.0 Hz, N—Ar—H), 4.30 (s, 2H, (—N—CH_2—), 2.74 (3H, s, —N—CH_3); ^{13}C NMR spectrum (DMSO-d_6, 100 MHz) δ, ppm: 161.0 (C=O), 160.4 (N—Ar—C), 158.6 (N—Ar—C), 151.5 (N—Ar—C), 150.2 (Furan—C), 145.9 (Furan—C), 136.8 (S—Ar—C), 133.0 (S—Ar—C), 129.3 (S—Ar—C), 127.2 (S—Ar—C), 126.5 (Furan—C), 121.6 (N—Ar—C), 108.9 (Furan—C), 105.2 (N—Ar—C), 103.1 (N—Ar—C), 46.0(—N—CH_2—), 34.6 (—N—CH_3); Mass spectrum (EI, 70 eV): Found, m/z: 420.1 $[M+H]^+$. $C_{20}H_{20}FN_2O_5S$. Calculated, m/z: 419.1.

3.3.18. 5-[(Benzene sulfonyl-methyl-amino)-methyl]-furan-3-carboxylic acid (2,4,6-trifluoro-phenyl)-amide (**8M**)

Yield: 59%, a brown solid, m.p. 84–860 C. IR spectrum (KBr), ν, cm^{-1}: 3379 (N—H str), 3122 (Ar—C—H str), 2923 (C—H str), 1664 (C=O str), 1601, 1547, 1443 (Ar—C=C str), 1162 (C—O str), 936 (Ar—C—H ben) cm^{-1}; ^{1}H NMR spectrum (DMSO-d_6) δ, ppm (J, Hz): 9.22 (1H, br. S, N—H), 8.25 (1H, s, Furan—H), 7.80 (2H, d, J = 7.6 Hz, S—Ar—H), 7.65 (1H, t, J = 8 Hz, S—Ar—H), 7.16 (2H, s, S—Ar—H), 6.90 (2H, s, N—Ar—H), 6.45 (1H, s, Furan—H), 4.30 (2H, s, —N—CH_2—), 2.62 (3H, s, —N—CH_3); ^{13}C NMR spectrum (DMSO-d_6, 100 MHz) δ, ppm: 166.5 (C=O), 164.3 (N—Ar—C), 160.3 (N—Ar—C), 150.7 (Furan—C), 136.5 (S—Ar—C), 134.2 (S—Ar—C), 130.2 (S—Ar—C), 129.2 (N—Ar—C), 127.3 (S—Ar—C), 125.2 (Furan—C) 108.26 (Furan—C), 48.2 (—N—CH_2—), 34.2 (—N—CH_3); Mass spectrum (EI, 70 eV): Found, m/z: 424.9 $[M]^+$. $C_{19}H_{15}F_3N_2O_4S$. Calculated, m/z: 424.07.

3.4. Screening of antibacterial activity

All the synthesized compounds of present study were screened for *in vitro* anti bacterial activity by agar well diffusion method (Murray et al., 1995; Olurinola, 1996). The medium (prepared by dissolving Peptone-5.0 g, Sodium chloride-5.0 g, Beef extract-1.5 g, Agar-15.0 g into 1 litre of distilled water) was poured into petri dishes under aseptic conditions in a laminar flow chamber. When the medium in the plates solidified, 100 µl of the inoculum (1×10^8 cfu/ml) of 24 h old culture of test organism. Gram (+) organisms (*Bacillus Cereus* MTCC-1305, *Corynebacterium glutamicum* MTCC-1529, *Staphylococcus aureus* MTCC-6908, *Streptococcus pyogenes* MTCC-1926) and Gram (–) organisms (Proteus *vulgaris* MTCC-744, *Pseudomonas putida* MTCC-1194, *Pseudomonas aeruginosa* MTCC-10636, *Escherichia coli* MTCC-9537) were inoculated into the petri plate. After inoculation, cups were scooped out with 6 mm sterile cork borer and the lids of the dishes were replaced. All the synthesized compounds with a concentration of 1000 µg/ml (1 mg/ml) were added. DMSO is maintained as negative control, ampicillin (1000 µg/ml) was used as positive control. The treated and the controls were kept in an incubator at 37 °C for 24 h. Inhibition zones were measured to nearest millimeter. Inhibitory zones of negative control were almost negligible compared to the inhibition zones of the samples. The antibacterial activities were carried out in triplicate and average values were compiled.

4. Results and discussion

4.1. Chemistry of synthesis

Furan-4-carboxylic acid ethyl ester (Compound 1) is converted to 5-Formayl-furan-3-carboxylic acid ethyl ester (compound 2) by formylation by using Vilsmeier-Haack (VH) reagent (*N,N*-dimethylformamide/phosphorus oxychloride – $POCl_3$/DMF) because for formylation of substrates (like reactive aromatic and heteroaromatic compounds), VH is a mild reagent, economical and efficient (Khan and Shoeb, 1985). $POCl_3$/DMF generates a halomethyleniminium salt which is used in the synthesis of aromatic aldehydes (Quiroga et al., 2010). Though these reactions are carried out generally either at room temperature or between 60 and 80 °C, sometimes at temperature above 120 °C is also used (Rajput and Girase, 2012; Tang and Shi, 2008). In the present case, reactions are carried out in the temperature range of 127–133 °C. The role of the solvent in different steps of synthesis scheme was investigated. Out of the various solvents tested, THF resulted in maximum yields which can be explained based on the fact that reactions of current category are more efficient in polar solvents. THF is a popular solvent as it dissolves organic molecule as well as a large number of inorganic reagents (Hultin, 2002). Similar to other popular solvent like diethyl ether, THF is highly alkaline (Lucht and Collum, 1999) and it forms stronger complexes with Li^+, Mg^{2+}, and boranes. For reactions involving hydroboration and organometallic compounds (like organolithium and Grignard reagents), THF is a well known as a reagent or a solvent/co-solvent (Elschenbroich and Salzer, 1992).

To convert 5-Formayl-furan-3-carboxylic acid ethyl ester (compound 2) to 5-Hydroxy methyl-furan-3-carboxylic acid ethyl ester (Compound 3), a wide variety of reducing agents are available (Burke and Danheiser, 1999). Out of the available powerful and mild reducing agents, the most commonly used reagents are Lithium aluminum hydride ($LiAlH_4$) and sodium borohydride ($NaBH_4$). As $LiAlH_4$ is a powerful reducing agent capable of reducing all most all functional groups present and hence usage of this reagent is difficult for selective reduction in a multifunctional molecule. However, relatively $NaBH_4$ is mild reducing agent and

Table 1
Anti – bacterial activity of 2, 4-disubstituted furan derivatives.

S. No	Compound Code	Antibacterial activity (in mm)*							
		Staphylococcus aureus MTCC – 6908	*Bacillus cereus* MTCC – 1305	*Corynebacterium glutamicum* MTCC – 1529	*Streptococcus pyogenes* MTCC – 1926	*Pseudomonas aeruginosa* MTCC – 10636	*Pseudomonas putida* MTCC – 1194	*Escherichia coli* MTCC – 9537	*Proteus vulgaris* MTCC – 744
1.	8A	15	17	22	20	10	11	16	15
2.	8B	12	15	19	17	11	12	19	22
3.	8C	12	11	13	10	12	11	18	23
4.	8D	11	10	16	12	11	10	25	20
5.	8E	10	11	11	10	12	13	20	26
6.	8F	15	11	15	13	14	19	26	26
7.	8G	15	10	10	12	11	10	20	15
8.	8H	11	12	17	19	10	13	15	20
9.	8I	10	10	15	23	10	12	20	24
10.	8J	11	12	15	15	12	10	13	26
11.	8K	15	11	15	12	10	19	14	23
12.	8L	11	19	12	20	12	10	16	27
13.	8M	12	10	22	10	10	11	19	17
	Ampicillin	28	28	45	45	16	40	47	37
	Control (DMSO)	–	–	–	–	–	–	–	–

(–) indicates No zone of inhibition and *indicates average of triplicate.

Table 2
Minimum Inhibitory Concentration of 2, 4-disubstituted furan derivatives against different bacteria (μg/ml).

S. No	Compound Code	*Staphylococcus aureus* MTCC – 6908	*Bacillus cereus* MTCC – 1305	*Corynebacterium glutamicum* MTCC – 1529	*Streptococcus pyogenes* MTCC – 1926	*Pseudomonas aeruginosa* MTCC – 10636	*Pseudomonas putida* MTCC – 1194	*Escherichia coli* MTCC – 9537	*Proteus vulgaris* MTCC – 744
1.	8A	500	500	250	250	750	750	500	500
2.	8B	750	500	250	500	750	750	250	250
3.	8C	750	750	750	750	750	750	250	250
4.	8D	750	750	500	750	750	750	100	250
5.	8E	750	750	750	750	750	750	250	100
6.	8F	500	750	500	750	750	250	100	100
7.	8G	500	750	750	750	750	750	250	500
8.	8H	750	750	500	250	750	750	500	250
9.	8I	750	750	500	250	750	750	250	250
10.	8J	750	750	500	500	750	750	750	26
11.	8K	500	750	500	750	750	250	750	250
12.	8L	750	250	750	250	750	750	500	100
13.	8M	750	750	250	750	750	750	250	500
	Ampicillin	100	100	50	50	500	50	50	50

hence used for the reduction of reactive functional groups in polar solvents (Seyden, 1997; Naimi-Jamal et al., 2007). Different aspects of sodium borohydride like ready availability, high stability, mild reaction conditions, ease of workup, and high yields attribute to the spectrum of sodium borohydride use for the reduction of aldehydes and ketones (Ward and Rhee, 1988). Hence sodium borohydride is used in the present case for reduction of 2–3 and reaction time was one hour because $NaBH_4$ is a "nucleophilic" reagent, hence, the rate of reduction depends on the electrophilicity of the carbonyl group. For conversion of to 5-Hydroxy methyl-furan-3-carboxylic acid ethyl ester (Compound 3) into Ethyl 5-((methyl amino)methyl)furan-3-carboxylate (Compound 5), the former is treated with methane sulfonyl chloride (MsCl) because alcohols can be converted to sulfonates which are very good leaving groups (Koo et al., 2000). As the reactions involving MsCl are very sensitive to temperature, the reaction was carried out at a temperature 0 °C (Tayebee, 2012). Conversion of Ethyl 5-((methyl amino)methyl)furan-3-carboxylate (Compound 5) to Ethyl 5-[(Benzene sulfonyl-methyl-amino)-methyl]-furan-3-carboxylate (Compound 6) was carried out in the presence of triethylamine, an organic base which maintains alkaline pH conditions throughout the reaction (Montalbetti and Falque, 2005) to facilitate the removal of hydrochloride formed in the reaction. In this reaction, dichloromethane (DCM) is used as another "workhorse" organic solvent and is stable to weak and medium Bronsted bases (Hultin, 2002).

4.2. In-vitro antibacterial activity and relation to structure

Pathogenic bacteria are selected in the present studies to evaluate the antibacterial nature of the synthesized compounds as these bacteria are responsible for main threats to public health in the developing countries. The zones of inhibitions (mm) and MIC values of tested compounds against bacterial strains were shown in Tables 1 and 2, and the experimental result indicated variable degree of efficacy of the compounds against different strains of bacteria. 8F, 8E, 8D and 8J were found to be effective against Gram (−) bacteria whereas, 8A and 8L were effective against Gram (+) bacteria. Least MIC value was found as 100 μg/ml against *E. coli* (for 8D and 8F), and *P. vulgaris* (for 8E and 8F). Antibacterial activities of the synthesized organic compounds depend on different parameters like nature/type/position/molecular weight of substituent and presence of aromatic moiety. Antimicrobial activity of Benzofuran derivatives was influenced by the substitution on furan ring than that of aromatic moiety (Raj et al., 2012). Out of all tested eight bacteria, better antibacterial activities of synthe-

sized compounds were observed against *S. pyogenes, P. vulgaris, and E. coli*. In the present study, the synthesised compounds exhibited relatively low antibiotic activity compared to Ampicillin, a commercially popular antibiotic compound. The order of antibacterial activity of synthesized compounds with respect to the substituents present on phenyl group (aromatic ring which is connected to amide nitrogen) is given below:

- 2,6-dimethoxy > 2-methoxy > 3,4,5-tri methoxy > unsubstituted > 2,5-dimethoxy > 3 methoxy > 2,4-dimethoxy > 4 methoxy.
- 2-Chloro, 4-hydroxy > 4-hydroxy
- 2-Chloro, 5-methoxy > 2,5-di methoxy
- 2-Hydroxy, 4-fluoro > 2,4,6-tri fluoro

In the present case, the presence of methoxy-, chloro-, and fluoro groups on phenyl group improved the antibacterial activity of synthesized compounds and a similar observation was reported in isoxazoline derivatives (Shah and Desai, 2007). Poor activity was shown by 5-[(Benzene sulfonyl-methyl-amino)-methyl]-furan-3-carboxylic acid (4-methoxy-phenyl)-amide (8C) against tested bacteria compared to the reference compound.

Exceptionally high antibacterial activity was shown by 5-[(Benzene sulfonyl-methyl-amino)-methyl]-furan-3-carboxylic acid-(2,6,-dimethoxy-phenyl)-amide (8F) compared to the other compounds which can be attributed to the two ortho substitutions of methoxy on phenyl groups. The methoxy group affects the charge distribution which confers significant improvement in biological effect. The enhanced inhibition observed in the presence of methoxy group is then more likely due to its interaction with some intracellular target. The presence of a strong electron-withdrawing group must alter the nature of the compound in such a way as to promote binding to the target(s) (Waring et al., 2002). Faqroddin et al., (2012) reported that electron releasing groups such as methoxy and naphthyl groups on 1-(2″,4″-dichlorophenyl)-3-(substituted aryl)-2-propene-1-ones exhibited maximum anti bacterial activity having against gram positive bacteria (*Bacillus subtilis*) and gram negative bacteria (*Escherichia coli*). Similarly, electron- releasing substitutions present in 1,4-naphthoquinones at position 2 or 3 increased (Riffel et al., 2002). Alkoxy substitution (viz., 4-OCH_3 and 3,4,5-$(OCH_3)_3$) on (4-Oxo-thiazolidinyl) quinazolin-4(3*H*) ones of 2-[(2,6-Dichlorophenyl)amino]phenylacetic acid exhibited good antibacterial activity (Patel and Patel, 2007).

In most of the biologically important derivatives of furans, substitutions at 2- and 5-positions are commonly observed in nature (Salem, 2016). Out of the synthesized 2,5-disubstituted compounds on phenyl group in the present case, better antibacterial activity of 5-[(Benzene sulfonyl-methyl-amino)-methyl]-furan-3-carboxylic acid (2-chloro,5-methoxy-phenyl)-amide (8K) compared to 5-[(Benzene sulfonyl-methyl-amino)-methyl]-furan-3-carboxylic acid (2,5-dimethoxy-phenyl)-amide (8E) might be due to the attachment of chloro group to phenyl. This result suggested that the introduction of halogen substituent increased the hydrophobicity of the synthesized compounds leading to the increase of the antibacterial activity (Wan et al., 2010). Electron withdrawing groups like halogens will increase bactericidal potential. According to Prasad et al. (2008) designing the compounds bearing electron withdrawing substituents and with high degree of binding linearity with groups results in high molecular weights which increase antibacterial activity. Literature survey reveals that lipophilicity of the test compounds is amended by the presence of electron withdrawing or donating groups, which in turn alters permeability across the bacterial cell membrane. 4-Amino-*N*-(1,3-Benzothiazol-2-yl)benzene sulphonamide derivatives with electron withdrawing substituents like chloro/carboxy substitutions have shown prominent antibacterial activity (Bhusari et al., 2008) Moreover, the presence of electron withdrawing groups reduces electron density and hence helps the faster diffusion through the bacterial body leading to an increased antimicrobial activity (Hania, 2009). Wan et al. (2010) demonstrated that halogen substitution on the benzotriazoylpropanone improved the hydrophobicity and hence showed higher antibacterial activity against *B. subtilis*. Electron withdrawing functional groups like halo groups on the phenyl group possess antibacterial activity in the case of (*Z*)-1-benzo[*b*]furan-2-yl-3-(Substituted phenyl)prop-2-en-1-one derivatives (Raj et al., 2012), 1-phenyl-3-(4-(4-butanoloxy)phenyl)-5-aryl-1*H*-pyrazoles (Goyal and Jain, 2012), chalcones (Zangade et al., 2011), 4-Substituted-imino-methyltetrazolo[1,5-α]quinoline derivatives (Bawa and Kumar, 2009) and benzotriazoles (Muvvala and Ratnakaram, 2014). Earlier studies reveal that the presence of electron withdrawing functional groups on the phenyl group at para position exhibit enhanced antibacterial activity in (*Z*)-1-benzo[*b*]furan-2-yl-3-(Substituted phenyl)prop-2-en-1-one derivatives (Raj et al., 2012)], 1-phenyl-3-(4-(4-butanoloxy) phenyl)-5-aryl-1*H*-pyrazoles (Goyal and Jain, 2012), 2-Amino-4-(substituted)-6-(3″-thienyl)pyrimidines and 1,3,5-Tri substituted-2-pyrazolines (Anupama et al., 2012a, 2012b). However in the present case, higher activity is observed with chlorine substituent at ortho position

4.3. Higher activity towards Gram (+) bacteria

In the present study it is observed that inhibition displayed by synthetised 2,4-disubstituted furans against all the studied Gram (+) bacteria is higher than Gram (−) bacteria (Tables 1 and 2). The differential activities of the synthesized compounds against these two types of bacteria can be elucidated taking into account of their cell outer layers. In the case of Gram (+) bacteria, cell outer barrier is made up of peptidoglycan layer which is ineffective and permeable. Hence, drug constituents are permeable through the cell wall of Gram (+) bacteria. However, in Gram (−) bacteria, cell wall is made up of multilayered peptidoglycan and phospholipidic membrane which is impermeable to drug constituents (Ravikumar et al., 2011). Hence, 2,4-disubstituted furans have preferable activity against Gram (+) bacteria.

5. Conclusion

In conclusion, the proposed methodology provides better yields compared to previous reports in synthesis of 2,4-di substituted furans. Highest antibacterial activity was exhibited by the compound having methoxy substitution on two ortho positions. Both electron withdrawing and donating groups on phenyl group have shown improved antimicrobial activity on Gram (−) bacteria. Better antibacterial activities of synthesized compounds were observed against *Streptococcus pyogenes, Proteus vulgaris, and Escherichia coli*.

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