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Synthesis, spectral characterization and biological activity of *N*-4-(*N*-2-(trifluoromethylphenyl))sulfamoyl amide derivatives

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Abstract: Synthesis of a series of new *N*-4-(*N*-2-(trifluoromethylphenyl))sulfamoyl amide derivatives **6(a-i)** was accomplished by a sequence of reactions by using aniline as a starting compound **(1)**. The newly synthesized compounds were characterized by the spectral analysis and evaluated their antibacterial activity. 5-Nitro-N-(4-(N-(2-(trifluoromethyl)phenyl)sulfamoyl)phenyl)furan-2-carboxamide (**6b**) exhibited the highest activity.

Keywords: Aniline; trifluoroacetic anhydride; sulfonylchloride; antibacterial activity.

1. Introduction

Sulfonamides were the first antimicrobial drugs[1] that lead to antibiotic evolution in medicine. Generally, sulfonamides are known as sulfa drugs, derived from sulphanilamide which prevents the growth of bacteria.[2]

Prontosil, (4-[(2,4-diaminophenyl)azo]benzenesulfonamide) was the first effective sulfa drug for the treatment of bacterial infections. Initially, the mode of action of this drug was not known as it showed only *in vivo* but not *in vitro* antimicrobial activity. Later, it was discovered that its antibacterial activity is due to the active metabolite, 4-aminobenenesulfonamide or sulfanilamide formed *in vivo* by the reduction of diazyl bond of the prontosil.[3,4] After the therapeutic action of sulfonamide and sulfanilamide was known, its derivatives were used in place of prontosil and this led to the development of second generation of sulfonamides.

The importance of the sulfonamide unit in medicinal chemistry can not be overstated.[5,6] This functional group constitutes the largest class of antimicrobial agents and has been shown to be a transition state mimetic of peptide hydrolysis, and in particular, theoretical motif for potent irreversible inhibitors of cysteine proteases.[7,8] Further, compounds containing sulfonyl groups have long been a research focus as a result of their biological importance, chemical applications and some of the aryl

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sulfonamide derivatives are a common substructure class present in a large number of active pharmaceutical ingredients (APIs).[9,10]

On the other hand, sulfonamides are known to exhibit various potential activities like antitumour,[11] antimicrobial,[12,13] antifungal[14] and anti-inflammatory[15] activities. Recently our research colleagues, have synthesized various sulfonamide derivatives which are of biological importance.[16,17]

Based on overview of the literature and ubiquitous medicinal and biological importance of sulfonamide have led to the great challenge for researchers for designing of these new biological active libraries which may be useful in search of potential drug, drug intermediates and development of new synthetic methodologies. As a part of our research, we have synthesized a series of *N*-4-(*N*-2-(trifluoromethylphenyl))sulfamoyl amide derivatives **6(a-i)** by using 4-amino-*N*-(2-(trifluoromethyl)phenyl)benzenesulfonamide intermediate **(5).** The newly synthesized compounds were screened for their antimicrobial activities and they showed moderate to potent activity against their corresponding pathogens.

2. Experimental

Melting points were recorded in open capillaries and are uncorrected. The progress of the reaction was monitored by using pre-coated silica gel plates (procured from Merck, F_{254}) and visualized using UV lamp and ninhydrin. The purity of the synthesized compounds was checked by performing TLC. FT-IR was recorded on Shimadzu FT-IR model 8400 spectrophotometer using KBr pellets and ^{1}H NMR spectra were recorded on Varian 400 MHz mercury plus spectrophotometer in $CDCl_3$ or using dimethylsulfoxide (DMSO-d_6) as solvents and tetramethylsilane (TMS) as an internal standard at 25 ^{o}C. Peak values are shown in δ (ppm). Mass spectrometry in Electron impact (EI) was recorded on VG 7070 H instrument at 70 eV, using positive and negative scan. Elemental analysis was performed on a Perkin-Elmer analyser.

*2.1. Synthesis of 2,2,2-trifluoro-N-phenylacetamide (**2**)*[18]*:*

Trifluro acetic anhydride (2.0 vol) was added to aniline (3.0 g, 1.0 eq.) at 0-5 ^{o}C slowly with vigorous stirring and the reaction mixture was stirred at room temperature for 1 h. After completion of the reaction, it was cooled to room temperature and the mixture was poured into 50 mL of ice-cold water and stirred for 15 min. The solid formed was filtered, washed with 30 mL of water and dried at 40-45 ^{o}C for 30 min to obtain the title compound **2** as light pink coloured solid. Yield: 91%; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.24-7.37 (m, 1H, Ar-H), 7.39 (t, J = 7.2 Hz, 2H, Ar-H), 7.55-7.57 (d, J = 8.1 Hz, 2H, Ar-H), 7.80-8.05 (bs, 1H, N-H). MS *(m/z):* 188.2 $(M-H)^+$.

*2.2. Synthesis of 4-(2,2,2-trifluoroacetamido)benzene-1-sulfonyl chloride (**3**)*[19]*:*

Chlorosulphonic acid (2.1 vol) was added dropwise carefully to compound **2** (4.0 g, 1.0 eq.) at 5-10 ^{o}C in a round bottomed flask, equipped with reflux condenser. Then, the reaction mixture was heated to reflux for 1 h and the progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature, poured into 40 mL of ice-cold water and stirred at room temperature for 10 min. The solid formed was filtered and washed with 20 mL of water and dried under reduced pressure to obtain the title compound **3** as an off-white solid. Yield 91%; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.61 (s, 4H, Ar-H), 11.31 (s, 1H, N-H). MS (*m/z*): 286.0 $(M-H)^+$.

*2.3. Synthesis of 2,2,2-trifluoro-N-(4-(N-(2-(trifluoromethyl)phenyl) sulfamoyl) phenyl) acetamide (**4**):*

Compound **3** (4.45 g, 1.0 eq.) was added to a solution of 2-(trifluoromethyl)aniline (1.0 eq.) in pyridine (9.0 mL, 2.0 vol) at room temperature. The reaction mixture was stirred at room temperature for 4 h and the progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured into 30 mL of aqueous 1N HCl solution. The solid formed was filtered, purified by

recrystallization from ethylacetate to obtain the title compound **4** as yellowish solid; Yield 79%; ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.54 (d, J = 8.4 Hz, 2H, Ar-H), 7.13 (t, J = 7.2 Hz, 1H, Ar-H), 7.45 (quasi d, J = 4.2 Hz, 2H, Ar-H), 7.52 (d, J = 7.2 Hz, 2H, Ar-H), 7.79 (d, J = 8.6 Hz, 1H, Ar-H), 7.90 (s, 1H, N-H), 8.30 (s, 1H, N-H); ^{13}C NMR(DMSO-d_6): δ 116.8, 116.6, 119.9, 122.3, 125.0, 126.5, 127.5, 158.1, 130.4, 132.3, 133.3, 136.0, 143.1; MS *(m/z):* 411.2 $(M-H)^+$.

*2.4. Synthesis of 4-amino-N-(2-(trifluoromethyl)phenyl)benzenesulfonamide (**5**):*

A mixture of compound **4** (5.1 g, 1.0 eq.), potassium carbonate (3.0 eq.) in a solution of 50 mL of methanol:water (1:1) was stirred at room temperature for 5 h. After completion of the reaction, the solvent was removed under reduced pressure and the aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organic layer was dried over Na_2SO_4 and concentrated to obtain the title compound **5** as a solid, which was recrystallized from methanol to give a brown solid; Yield 88%; ^{1}H NMR (DMSO-d_6): δ 4.14 (s, 2H, NH_2), 6.56 (d, J = 8.4 Hz, 2H, Ar-H), 6.82 (s, 1H, N-H), 7.13 (t, J = 7.2 Hz, 1H, Ar-H), 7.47 (quasi t, J = 4.2 Hz, 2H, Ar-H), 7.54 (d, J = 8.7 Hz, 2H, Ar-H), 7.80 (d, J = 8.7 Hz, 1H, Ar-H); MS *(m/z):* 315.2 $(M-H)^+$.

*2.5. General procedure for the synthesis of N-4-(N-2-(trifluoromethylphenyl))sulfamoyl amide derivatives (**6a-i**)*

Freshly prepared acid chloride (1.2 eq.) from corresponding acid by using oxalyl chloride (1.5 eq.) in 5 mL of dichloromethane (DCM) was added to a solution of compound **5** (200 mg, 1.0 eq.), pyridine (1.5 eq.) in 5 mL of DCM at 0-5 ^{o}C. The reaction mixture was stirred at room temperature for 2 h, the solvent was removed and the resulting residue was dissolved in 20 mL of ice-cold water. The solid formed was filtered and it was further purified by recrystallization from methanol to afford the title compounds **6(a-i)**.

*2.2.1. 2-Methoxy-N-(4-(N-(2-(trifluoromethyl)phenyl)sulfamoyl)phenyl)acetamide (**6a**):*
Yield: 85%, White solid, m.p. 159-161 ^{o}C; IR (KBr): ν 1059, 1317, 1680, 3178, 3346; ^{1}H NMR (DMSO-d_6): δ 3.49 (s, 3H, -CH_3), 4.00 (s, 2H, -OCH_2), 7.20-7.22 (m, 2H, Ar-H), 7.47-7.54 (m, 2H, Ar-H), 7.64-7.75 (m, 4H, Ar-H), 8.41 (s, 1H, N-H), 10.82 (s, 1H, N-H); ^{13}C NMR (DMSO-d_6): δ 59.1, 72.0, 116.2, 119.6, 123.0, 123.6, 125.7, 126.1, 127.0, 129.4, 133.1, 135.3, 141.8, 169.1; MS *(m/z):* 389.2 $(M+H)^+$; Anal. Calcd. For $C_{16}H_{15}F_3N_2O_4S$; C, 49.48; H, 3.89; N, 7.21; Found: C, 49.52; H, 3.88; N, 7.31.

*2.2.2. 5-Nitro-N-(4-(N-(2-(trifluoromethyl)phenyl)sulfamoyl)phenyl)furan-2-carboxamide (**6b**):* Yield: 70%; Yellow solid, m.p. 241-243 ^{o}C; IR (KBr): ν 1060, 1315, 1352, 1666, 3371, 3474; ^{1}H NMR (DMSO-d_6): δ 6.66 (d, J = 8.7 Hz, 1H, Ar-H), 7.08 (t, J = 7.2 Hz, 1H, Ar-H), 7.21 (t, J = 7.8 Hz, 1H, Ar-H), 7.48-7.53 (m, 1H, Ar-H), 7.90 (s, 1H, Ar-H), 7.80-7.86 (m, 2H, Ar-H), 7.96-8.02 (m, 2H, Ar-H), 8.14 (d, J = 6.8 Hz, 1H, Ar-H), 9.94 (s, 1H, N-H), 10.82 (s, 1H, N-H); ^{13}C NMR (DMSO-d_6): δ 112.6, 115.2, 115.7, 118.2, 120.5, 124.8, 125.6, 128.5, 129.3, 131.5, 133.0, 134.6, 145.1, 152.0, 155.3, 162.7; MS *(m/z):* 456.0 $(M+H)^+$; Anal. Calcd. For $C_{18}H_{12}F_3N_3O_6S$; C, 47.48; H, 2.66; N, 9.23; Found: C, 47.28; H, 2.55; N, 9.31.

*2.2.3. 3-(Trifluoromethyl)-N-(4-(N-(2-(trifluoromethyl)phenyl)sulfamoyl)phenyl)benzamide (**6c**):* Yield: 81%; Off-white solid, m.p. 189-191 ^{o}C; IR (KBr): ν 1072, 1321, 1680, 3265, 3350; ^{1}H NMR (DMSO-d_6): δ 7.06 (d, J = 7.6 Hz, 1H, Ar-H), 7.44 (t, J = 7.2 Hz, 1H, Ar-H), 7.58 (t, J = 7.2 Hz, 1H, Ar-H), 7.66-7.88 (m, 4H, Ar-H), 7.99 (d, J = 7.6 Hz, 3H, Ar-H), 8.23-8.31 (m, 2H, Ar-H), 9.92 (s, 1H, N-H), 10.84 (s, 1H, N-H); ^{13}C NMR (DMSO-d_6): δ 116.2, 120.6, 120.8, 124.4, 124.9, 125.0, 127.4, 125.7, 128.8, 129.9, 130.4, 130.8, 132.4, 132.5, 134.8, 135.8, 133.6, 143.2, 165.1; MS *(m/z):* 489.0 $(M+H^+)$; Anal. Calcd. For $C_{21}H_{14}F_6N_2O_3S$; C, 51.64; H, 2.89; N, 5.74; Found: C, 51.49; H, 2.77; N, 5.68.

*2.2.4. 2-Fluoro-N-(4-(N-(2-(trifluoromethyl)phenyl)sulfamoyl)phenyl)benzamide (**6d**):*
Yield: 84%; White solid, m.p. 211-213 ^{o}C; IR (KBr) ν: 1057, 1319, 1668, 3138, 3379; ^{1}H NMR (DMSO-d_6): δ 7.04 (d, *J* = 7.6 Hz, 1H, Ar-H), 7.33-7.42 (m, 4H, Ar-H), 7.45 (t, *J* = 8.0 Hz, 1H, Ar-H), 7.57-7.66 (m, 2H, Ar-H), 7.68-7.74 (m, 2H, Ar-H), 7.92 (d, *J* = 7.6 Hz, 2H, Ar-H), 9.93 (s, 1H, N-H), 10.87 (s, 1H, N-H); ^{13}C NMR (DMSO-d_6): δ 116.6, 116.8, 119.9, 122.3, 124.9, 125.0, 125.1, 127.5, 128.8, 130.4, 132.3, 133.3, 133.7, 134.7, 136.0, 143.1, 160.6, 163.8; MS *(m/z):* 437.1 $(M-H)^{+}$; Anal. Calcd. For $C_{20}H_{14}F_4N_2O_3S$; C, 54.79; H, 3.22; N, 6.39; Found: C, 54.68; H, 3.27; N, 6.26.

*2.2.5. 4-Fluoro-N-(4-(N-(2-(trifluoromethyl)phenyl)sulfamoyl)phenyl)benzamide (**6e**):*
Yield: 87%; White solid, m.p. 223-225 ^{o}C; IR (KBr): ν 1059, 1315, 1660, 3099, 3352; ^{1}H NMR (DMSO-d_6): δ 7.05 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.37-7.48 (m, 3H, Ar-H), 7.58 (t, *J* = 7.6 Hz, 1H, Ar-H), 7.76 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.71 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.98 (d, *J* = 8.8 Hz, 2H, Ar-H), 8.04 (dd, *J* = 5.2 Hz, 2H, Ar-H), 9.90 (s, 1H, N-H), 10.65 (s, 1H, N-H); ^{13}C NMR (DMSO-d_6): δ 116.4, 117.6, 118.7, 123.4, 125.3, 125.5, 126.6, 127.5, 127.6, 131.5, 132.6, 134.5, 134.6, 135.6, 137.2, 144.2, 162.5, 165.8; MS *(m/z):* 439.0 $(M+H)^{+}$; Anal. Calcd. For $C_{20}H_{14}F_4N_2O_3S$; C, 54.79; H, 3.22; N, 6.39; Found: C, 54.72; H, 3.26; N, 6.38.

*2.2.6. N-(4-(N-(2-(Trifluoromethyl)phenyl)sulfamoyl)phenyl)nicotinamide (**6f**):*
Yield: 83%; Off-white solid, m.p. 209-211 ^{o}C; IR (KBr): ν 1057, 1315, 1662, 3124, 3350; ^{1}H NMR (DMSO-d_6): δ 7.05 (d, *J* = 7.6 Hz, 1H, Ar-H), 7.44 (t, *J* = 8.0 Hz, 1H, Ar-H), 7.56-7.64 (m, 2H, Ar-H), 7.71 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.77 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.98 (d, *J* = 7.2 Hz, 2H, Ar-H), 8.31 (d, *J* = 6.4 Hz, 1H, Ar-H), 8.79 (d, *J* = 3.2 Hz, 1H, Ar-H), 9.12 (s, 1H, Ar-H), 9.92 (s, 1H, N-H), 10.83 (s, 1H, N-H); ^{13}C NMR (DMSO-d_6): δ 112.2, 120.4, 120.5, 125.0, 127.5, 128.3, 130.6, 130.7, 133.7, 134.6, 135.2, 136.0, 136.3, 143.2, 149.0, 152.6, 165.0; MS *(m/z):* 422.1 $(M+H)^{+}$; Anal. Calcd. For $C_{19}H_{14}F_3N_3O_3S$; C, 54.15; H, 3.35; N, 9.97; Found: C, 54.31; H, 3.38; N, 9.86.

*2.2.7.4-Nitro-N-(4-(N-(2-(trifluoromethyl)phenyl)sulfamoyl)phenyl)benzamide (**6g**):*
Yield: 48%; Yellow solid, m.p. 223-225 ^{o}C; IR (KBr): ν 1057, 1313, 1666, 3125, 3350; ^{1}H NMR (DMSO-d_6): ^{1}H NMR (DMSO-d_6): δ 7.05 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.39-7.52 (m, 3H, Ar-H), 7.59- (t, *J* = 7.6 Hz, 1H, Ar-H), 7.84 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.96 (d, *J* = 8.0 Hz, 1H, Ar-H), 8.11 (d, *J* = 7.2 Hz, 2H, Ar-H), 8.44 (d, *J* = 8 Hz, 2H, Ar-H), 9.92 (s, 1H, N-H), 10.62 (s, 1H, N-H); ^{13}C NMR (DMSO-d_6): δ 116.3, 118.2, 119.1, 124.0, 125.8, 126.2, 129.6, 128.3, 129.8, 132.2, 132.8, 135.3, 142.2, 151.3, 165.2; MS *(m/z):* 466.0 $(M+H^{+})$; Anal. Calcd. For $C_{20}H_{14}F_3N_3O_5S$; C, 51.61; H, 3.03; N, 9.03; Found: C, 51.59; H, 3.09; N, 9.06.

*2.2.8. 3,5-Difluoro-N-(4-(N-(2-(trifluoromethyl)phenyl)sulfamoyl)phenyl)benzamide (**6h**):*
Yield: 50%; Off-white solid, m.p. 215-217 ^{o}C; IR (KBr) ν: 1055, 1317, 1668, 3136, 3359; ^{1}H NMR (DMSO-d_6): δ 6.93 (t, *J* = 8.8, 1H, Ar-H), 7.38 (t, *J* = 8.4, 2H, Ar-H),7.04 (d, *J* = 7.6 Hz, 1H, Ar-H), 7.42-7.52 (m, 3H, Ar-H), 8.10 (d, *J* = 7.2 Hz, 2H, Ar-H), 8.41 (d, *J* = 8.8 Hz, 2H, Ar-H), 9.90 (s, 1H, N-H), 10.84 (s, 1H, N-H); ^{13}C NMR (DMSO-d_6): δ 108.2, 110.2, 115.3, 118.2, 119.2, 125.0, 125.2, 127.4, 129.6, 132.2, 132.6, 135.4, 141.3, 165.7, 161.2; MS *(m/z):* 457.1 $(M-H)^{+}$; Anal. Calcd. For $C_{20}H_{13}F_5N_2O_3S$; C, 52.63; H, 2.87; N, 6.14; Found: C, 52.67; H, 2.90; N, 6.19.

*2.2.9. N-(4-(N-(2-(Trifluoromethyl)phenyl)sulfamoyl)phenyl)propionamide (**6i**):*
Yield: 55%; White solid, m.p, 211-213 ^{o}C; IR (KBr): ν 1056, 1313, 1669, 3132, 3353; ^{1}H NMR (DMSO-d_6): δ 1.08 (t, *J* = 7.2, 3H, CH_3), 2.45-2.52 (q, 2H, CH_2), 7.04 (d, *J* = 7.6 Hz, 1H, Ar-H), 7.39-7.48 (m, 3H, Ar-H), 7.84 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.64 (d, *J* = 7.6 Hz, 2H, Ar-H), 9.80 (s, 1H, N-H), 10.80 (s, 1H, N-H); ^{13}C NMR (DMSO-d_6): δ 13.2, 30.8, 116.2, 118.4, 119.4, 125.0, 125.3, 127.4, 129.8, 132.6, 132.9, 136.2, 142.9, 169.2,; MS *(m/z):* 372.2 $(M+H)^{+}$ Anal. Calcd. For $C_{16}H_{15}F_3N_2O_3S$; C, 51.61; H, 4.06; N, 7.52; Found: C, 51.65; H, 4.11; N, 7.57.

Antibacterial activity:

The antibacterial activity of the newly synthesized compounds **6(a-f)** was evaluated against two Gram +Ve bacterial strains, *Staphylococcus aureus* and *Pseudomonas aeruginosa*; two Gram –Ve bacterial strains, *Klebsiella pneumoniae* and *Bacillus megaterium;* two Gram –Ve antibiotic resistant bacterial strains, mutant *E. coli* (Streptomycin resistant) and donor *E. coli* (Rifampicin resistant) bacteria, by the agar well diffusion method[20,21] using Amoxicillin as a standard drug. 200 µg of the tested compounds were dissolved in 1 mL of DMSO. Centrifuged pellets of bacteria from 24 h old culture containing approximately 10^4-10^6 colony forming unit (CFU) per mL was spread on the surface of Nutrient Agar (NA) plates. Nutrient agar medium was prepared by suspended nutrient agar 28 g in 1 liter of distilled water, autoclaved and cooled to 45 °C, and then it was seeded with 15 mL of prepared inoculum to have 10^6 CFU/mL. Petri dishes were prepared by pouring 10 mL of seeded nutrient agar. Experimental plates were incubated for 24 h at 37 °C. After incubation, clear inhibition zone was formed around the well and was measured in millimeters (mm).

The minimum inhibitory concentration represents the lowest concentration of the antimicrobial agent preventing the development of visible growth after overnight incubation. MIC measurements were performed using a modified agar well diffusion method.[22] MICs of the test samples are represented in Table 1.

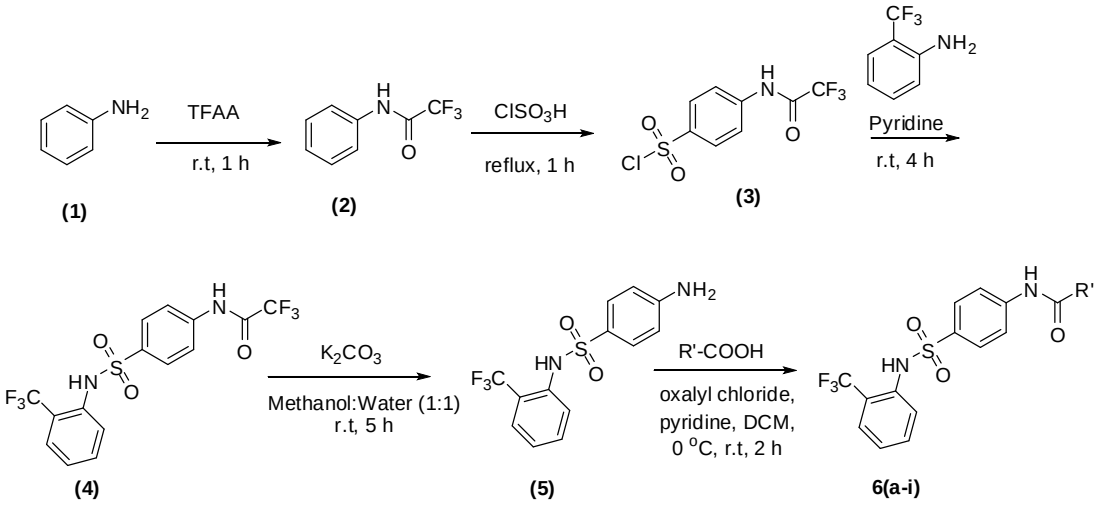
3. Results and Discussion

A new series of *N*-4-(*N*-2-(trifluoromethylphenyl))sulfamoyl amide derivatives **6(a-i)** were synthesized by a sequence of reactions as shown in Figure 1.

In the first step, amino group in aniline was protected by the reaction of trifluoroacetic anhydride at room temperature to afford 2,2,2-trifluoro-*N*-phenylacetamide **(2)** as a pink coloured solid**.** The solid formed was filtered, washed, dried and used for sulfonylation in the second step. To 2,2,2-trifluoro-*N*-phenylacetamide **(2),** chlorosulphonic acid was added and refluxed for 1 h to obtain 4-(2,2,2-trifluoroacetamido)benzene-1-sulfonyl chloride **(3)**, which was followed by the reaction with trifluoromethylaniline in the presence of pyridine at room temperature for 4 h to result in the formation of 2,2,2-trifluoro-*N*-(4-(*N*-(2-(trifluoromethyl)phenyl)sulfamoyl)phenyl) acetamide **(4)**. Initially, this reaction was carried out in the presence of triethylamine and diisopropyl ethylamine in DCM, but we obtained low yields i.e., 30-40%. Compound **4** was hydrolysed in the presence of potassium carbonate, methanol and water (1:1) at room temperature for 5 h to obtain the key intermediate, 4-amino-*N*-(2-(trifluoromethyl)phenyl)benzenesulfonamide **(5)** which was used for the synthesis of the targeted compounds **6(a-i)** by reacting with various carboxylic acids in the presence of oxalyl chloride, DCM and pyridine at 0-5 ^oC to RT for 2 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the solid formed was filtered and it was further purified by recrystallization in methanol to obtain the pure compounds **6(a-i)**.

The newly synthesized compounds **6(a-f)** were characterized by the IR, ^1H NMR, ^{13}C NMR, mass spectral and CHN analysis and for the compounds **6g**, **6h** and **6i** only the mass spectra were recorded due to the very small quantities obtained in column chromatography, possibly due to their unstability.

In ^1H NMR spectra, the chemical shift in the region of δ 10.65-10.87 ppm was assigned to $–SO_2NH$ protons, appeared as a singlet and δ 8.41-9.93 ppm was assigned to -CONH protons, appeared as singlet. The chemical shift in the region of δ 6.56-8.14 ppm was assigned to the aromatic protons. In ^{13}C NMR spectra, the chemical shift in the region δ 162.7-170.2 ppm was assigned to –C=O carbons. Further, the structures of the title compounds **6(a-i)** were confirmed by the appearance of molecular ion peaks in their mass spectra and CHN analysis.



Compound	R′	Compound	R′
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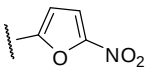
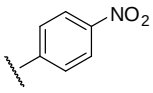
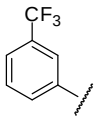
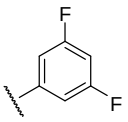
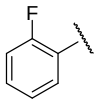
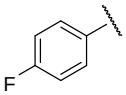
6b		6g	
6c		6h	
6d		6i	
6e			

Figure 1. Synthesis, spectral characterization and biological activity of *N*-4-(*N*-2-(trifluoromethylphenyl))sulfamoyl amide derivatives 6(a-i)

The newly synthesized compounds **6(a-f)** were evaluated for their antibacterial activities against the bacterial strains, *Staphylococcus aureus* and *Pseudomonas aeruginosa* (Gram positive), *Klebsiella pneumoniae* and *Bacillus megaterium* (Gram negative) by the agar well diffusion method. Mutant *E. coli* (Streptomycin resistant, Gram negative), *Donor E. coli* (Rifampin resistant, Gram negative) were also used for screening the antibacterial activity. Amoxicillin was used as a standard drug. Compound **6b** showed potent antibacterial activity against all the tested pathogens. Compound **6c** displayed good activity against *P. aeruginosa.* Compounds **6d** and **6f** exhibited potent activity against *K. pneumoniae.* The results are presented in Table 1**.**

Table 1. MICs of *N*-4-(*N*-2-(trifluoromethylphenyl))sulfamoyl amide derivatives* **6(a-f).**

Compound	*Mutant E. coli*	*Donor E. coli*	*S. aureus*	*P. aeruginosa*	*K. pneumoniae*	*B. megaterium*
6a	50	50	50	50	100	50
6b	5	5	2.5	5	5	5
6c	50	50	50	50	100	50
6d	50	50	50	25	2.5	50
6e	100	100	100	50	100	100
6f	50	100	25	25	2.5	25
Amoxicillin	1.2	0.8	1.2	0.9	0.9	1.2

*MIC values:µg/mL

4. Conclusion

We have synthesized a new series of *N*-4-(*N*-2-(trifluoromethylphenyl))sulfamoyl amide derivatives from a simple starting material aniline through the key intermediate 4-amino-*N*-(2-(trifluoromethyl)phenyl)benzenesulfonamide with various carboxylic acids and evaluated the antibacterial activity. Compound **6b** showed potent activity when compared to the remaining title compounds based on the results obtained in zone of inhibition. This compound might be used as an antibiotic drug in future.

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