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Synthesis, Characterization and Antimicrobial Activity of Bifunctional Sulfonamide-Amide Derivatives

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ABSTRACT. A convenient synthesis of bifunctional sulfonamide-amide derivatives was reported. Amide coupling of 4-methyl benzoic acid **1** followed by reaction with chlorosulfonic acid produce ethyl-4-(3-(chlorosulfonyl)-4-methylbenzoyl)piperazine-1-carboxylate **4**. The resulted compound on further treatment with various anilines produces the title sulfonamide-amide derivatives **5a–n**. The configurations of these compounds were established by elemental analysis, IR, ^{1}H NMR, mass spectra, and by their preparation from the corresponding 4-methyl benzoic acid **1** and chlorosulfonic acid. All these new compounds demonstrate significant in vitro antibacterial and antifungal activities against all bacterial and fungal strains.

Key words: Sulfonamide-amide, 4-Methyl benzoic acid, Chlorosulfonic, Antibacterial and antifungal activities

INTRODUCTION

The development of simple and efficient methods for synthesis of bifunctional derivatives from readily available reagents is one of the major challenges in peptide chemistry. Among bifunctional derivatives, sulfonamide and amide bonds are represent the key functional group in peptides, polymers, many natural products and pharmaceuticals and most significant linkages in organic chemistry.[1] Molecules that are having both sulfonamide and amide functional groups are an important class of pharmaceutical compounds with a broad spectrum of biological activities. Some of these compounds reveal various types of biological properties such as histone deacetylase,[2] hepatitis C virus,[3] HIV-protease,[4] β-secretase (BACE1) inhibitors,[5] $\alpha\nu\beta3$ integrin,[6] glycine transporter 1(GlyT1),[7] matriptase,[8] and as a cholecystokinin type 2 receptor (CCK2R).[9] Moreover, bifunctional sulfonamide-amide compounds have played important role in synthetic chemistry to promising their in the field of biomedicinal chemistry.[10] Bifunctional sulfonamide-amide containing compounds have been synthesized via multistep approaches in the presence of expensive catalysts under sensitive conditions.[11,12] For instance, the sulfonamide derivatives are promisingly important in modern medicinal chemistry and agriculture. Many sulfonamide derivatives have been reported in the literature as antimicrobial, and antibiotic drugs,[13,14] anticonvulsants, and diuretics,[15] analgetics and antimigraine remedies.[15] Furthermore, a large variety of sulfonamide derivatives were reported to posses powerful inhibitors of proteases,[15] carbonic anhydrase,[16] COX-2,[17] caspase,[18] as well as osteogenic agents,[19] and antitumor drugs.[20] Some sulfonamides also exhibit a herbicidal activity.[21] Amide bond formation is one of the most important and regularly utilized reactions in organic synthesis.[22,23] These derivatives were associated with broad spectrum of biological activities including antituberculosis,[25] anticonvulsant,[26] analgesic-antiinflammatory,[27] insecticidal,[28] antifungal,[29] and antitumor,[30] properties. These outcome promoted us as part of my research respect to *N*-heterocycles,[31] and peptide chemistry,[32] we planned to synthesize the compounds that contain both amide and sulfonamide functional groups and evaluate for their antibacterial and antifungal activities.

EXPERIMENTAL

Melting points of synthesized compounds were determined in open capillary tubes on Mel-Temp apparatus and are uncorrected. Infrared spectra (νmax in cm^{-1}) were recorded as KBr pellets on a Perkin-Elmer 283 double beam spectrophotometer. ^{1}H NMR spectra were recorded on an ABX 400 MHz spectrophotometer operating at 400 MHz, using DMSO-d_6 as solvent. The ^{1}H NMR chemical shifts were referenced to tetramethylsilane (TMS).

Preparation of Ethyl-4-(4-methylbenzoyl)piperazine-1-carboxylate (3)

To a ice-cold stirred solution of the 4-methyl benzoic

acid **1** (2.0 g, 14.7 mmol) in dry CH_2Cl_2 (50 mL) was added EDC (4.2 g, 22.0 mmol) followed by HOBT (2.7 g, 17.6 mmol) and then the resulting mixture was stirred vigorously for 30 min. Compound **2** (2.8 g, 17.6 mmol) was added slowly in the presence of triethylamine (1 eqv.) and the mixture stirred for 5 h. After completion of the reaction, the content was washed with water (10 mL × 3) and drying to concentration in vacuo yielded the crude product **3** as off-white solid (*R_f value:* 0.5; *Yield*: 2.1 g (51%)). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.32 (3H, t, J = 6.8 MHz, CH_3–C), 2.32 (3H, s, CH_3), 2.71 (3H, s, CH_3), 3.21 (4H, t, J = 8.4 MHz, –CH_2–N–CH_2–), 3.75 (4H, t, J = 6.4 MHz, –CH_2–N–CH_2–), 4.20 (2H, q, C–CH_2–O), 7.48 (2H, d, J = 4.8 MHz, Ar–H), 7.96 (2H, d, J = 4.4 MHz, Ar–H); IR (KBr) ν (cm^{-1}): 1681 (C=O ester), 1703 (C=O amide); [M^+]: 276.33. Calcd. (%) for $C_{15}H_{20}N_2O_3$: C, 65.20; H, 7.31; N, 10.14. Found: C, 65.21; H, 7.34; N, 10.16.

Preparation of Compound Ethyl-4-(3-(chlorosulfonyl)-4-methylbenzoyl)piperazine-1-carboxylate (4)

To a stirred solution of chlorosulfonic acid (10 mL) was added to the compound **3** (1.0 g, 3.6 mmol) in portion wise and then the mixture was heated for 6 h at 100 ºC. The mixture was cooled, poured in to crushed ice and extracted with CH_2Cl_2. The extract was washed with ice water, dried over anhydrous Na_2SO_4 and concentrated to yield compound 4 as brown oil (*R_f value*: 0.4; *Yield:* 0.6 g (44%)).^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.38 (3H, t, CH_3–C, J = 8.8 MHz), 2.32 (3H, s, CH_3), 2.77 (3H, s, CH_3), 3.26 (4H, t, J = 6.6 MHz, –CH_2–N–CH_2–), 3.78 (4H, t, J = 12.8 MHz, –CH_2–N–CH_2–), 4.22 (2H, q, C–CH_2–O), 7.42 (1H, d, J = 8.0 MHz, Ar–H), 7.86 (1H, d, J = 12.4 MHz, Ar–H), 8.05 (1H, s, Ar–H); IR (KBr) ν (cm^{-1}): 1685 (C=O ester), 1704 (C=O amide), 1357, 1170 (SO_2); [M^+]: 374.84. Calcd. (%) for $C_{15}H_{19}ClN_2O_5S$: C, 48.06; H, 5.11; Cl, 9.46; N, 7.47; S, 8.55. Found: C, 48.05; H, 5.15; Cl, 9.44; N, 7.46; S, 8.51.

General Procedure for Synthesis of Compounds (5a–n)

To a solution of respective anilines (1.0 eq.) in CH_2Cl_2 (15 mL) was added pyridine at 0 ºC and the mixture stirred for 5 min. Compound **4** (1.0 eq.) in CH_2Cl_2 (10 mL) was added and the mixture stirred at room temperature for 12–48 h. The mixture was diluted with CH_2Cl_2 (25 mL) and washed with diluted HCl and water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated to obtain crude was subjected to column chromatography on silica gel to yield title compounds **5**.

Preparation of Compound 3-(Chlorosulfonyl)-4-methylbenzoic Acid (6)

To a well-stirred solution of chlorosulfonic acid was added to the compound **1** (3.0 g, 22.0 mmol) in portion wise. The mixture was heated for 3 h at 100 ºC. The mixture was cooled, poured into crushed ice and extracted with CH_2Cl_2. The organic layer was washed with ice water, dried over anhydrous Na_2SO_4 and concentrated to yield compound **6** as off white solid (*R_f value:* 0.4; *Yield:* 3.0 g (58%)). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.48 (1H, d, J = 5.6 MHz, Ar–H), 7.96 (1H, d, J = 6.4 MHz, Ar–H), 7.95 (1H, s, Ar–H); IR (KBr)ν (cm^{-1}): 1681 (C=O acid), 1354, 1173 (SO_2); [M^+]: 233.66. Calcd. (%) for $C_8H_7ClO_4S$: C, 40.95; H, 3.01; Cl, 15.11; S, 13.66. Found: C, 40.94; H, 3.03; Cl, 15.12; S, 13.66.

General Procedure for Synthesis of Compounds (7a–n)

To a solution of anilines (1.2 eq.) in acetonitrile (15 mL) was added compound **5** (1.0 eq.) and the mixture stirred at room temperature for 16 h. The solid formed was filtered and washed with acetonitrile (5 mL). The filtrate was concentrated to afford residue was subjected to column chromatography on silica gel to yield compound **7** (Yield: 47–78%).

General Procedure for Synthesis of Compound (5a–n)

To a solution of Compound **7** (1.0 eq.) in CH_2Cl_2 (15 mL) was added HOBT. H_2O (1.2 eq.) at 0 ºC and stirred for 5 min at the 0 ºC temperature. Compound **2** (1.2 eq.) in CH_2Cl_2 (10 mL) was added followed by the addition of EDC.HCl (1.5 eq.) portion wise. NEt_3 was added drop wise (to adjust pH ~8) and the mixture stirred at room temperature for another 2 h. The mixture was diluted with CH_2Cl_2 (25 mL), washed with water, dried over anhydrous Na_2SO_4 and concentrated to obtain residue was purified by column chromatography on silica gel to yield title compounds **5a–n.**

Ethyl-4-(4-methyl-3-(*N-p*-tolylsulfamoyl)benzoyl)piperazine-1-carboxylate (5a)

Light brown solid; Yield: 68%, m.p. 186 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.38 (3H, t, J = 12.8 MHz, CH_3–C), 2.54 (3H, s, CH_3), 2.87 (3H, s, CH_3), 3.15 (4H, t, J = 2.4 MHz, –CH_2–N–CH_2–), 3.86 (4H, t, J = 4.8 MHz, –CH_2–N–CH_2–), 4.26 (2H, q, C–CH_2–O), 7.05 (2H, d, J = 6.0 MHz, Ar–H), 7.14 (2H, d, J = 6.4 MHz, Ar–H), 7.73 (1H, d, J = 2.8 MHz, Ar–H), 7.98 (1H, d, J = 4.4 MHz, Ar–H), 8.45 (1H, s, Ar–H); IR (KBr) ν (cm^{-1}): 3345 (NH), 1685 (C=O ester), 1708 (C=O amide), 1354, 1173 (SO_2); [M^+]: 445.21. Calcd. (%) for $C_{22}H_{27}N_3O_5S$: C, 59.32; H, 6.12; N,

9.43, S, 7.21. Found: C, 59.33; H, 6.14; N, 9.46, S, 7.20.

Ethyl-4-(4-methyl-3-(*N*-*m*-tolylsulfamoyl)benzoyl)piperazine-1-carboxylate (5b)

Light brown solid; Yield: 51%, m.p. 145–146 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.24 (3H, t, J = 8.8 MHz, CH_3–C), 2.58 (3H, s, CH_3), 2.64 (3H, s, CH_3), 3.17 (4H, t, J = 4.4 MHz, –CH_2–N–CH_2–), 3.77 (4H, t, J = 4.8 MHz, –CH_2–N–CH_2–), 4.21 (2H, q, C–CH_2–O), 7.01 (1H, d, J = 8.8 MHz, Ar–H), 7.18 (1H, t, J = 9.6 MHz Ar–H), 7.42 (1H, d, J = 2.8 MHz, Ar–H), 7.62 (1H, s, Ar–H), 7.83 (1H, d, J = 2.4 MHz, Ar–H), 8.01 (1H, d, J = 2.8 MHz, Ar–H), 8.42 (1H, s, Ar–H); IR (KBr) ν (cm^{-1}): 3348 (NH), 1689 (C=O ester), 1702 (C=O amide), 1351, 1157 (SO_2); [M^+]: 445.21. Calcd. (%) for $C_{22}H_{27}N_3O_5S$: C, 59.32; H, 6.12; N, 9.43, S, 7.21. Found: C, 59.31; H, 6.15; N, 9.43, S, 7.21.

Ethyl-4-(3-(N-(4-methoxyphenyl)sulfamoyl)-4-methylbenzoyl)piperazine-1-carboxylate (5c)

Off white solid; Yield: 65%, m.p. 162–163 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.38 (3H, t, J = 1.6 MHz, CH_3–C), 2.76 (3H, s, CH_3), 3.23 (4H, t, J = 4.4 MHz, –CH_2–N–CH_2–), 3.67 (3H, s, OCH_3), 3.82 (4H, t, J = 4.8 MHz, –CH_2–N–CH_2–), 4.21 (2H, q, C–CH_2–O), 6.94 (2H, d, J = 7.1 MHz, Ar–H), 7.05 (2H, d, J = 7.2 MHz, Ar–H), 7.52 (1H, d, J = 8.8 MHz, Ar–H), 7.97 (1H, d, J = 4.0 MHz, Ar–H), 8.38 (1H, s, Ar–H); IR (KBr) ν (cm^{-1}): 3355 (NH), 1688 (C=O ester), 1703 (C=O amide), 1314, 1134 (SO_2); [M^+]: 461.52. Calcd. (%) for $C_{22}H_{27}N_3O_6S$: C, 57.27; H, 5.90; N, 9.10, S, 6.95. Found: C, 57.23; H, 5.92; N, 9.12, S, 6.95.

Ethyl-4-(3-(N-(3-methoxyphenyl)sulfamoyl)-4-methylbenzoyl)piperazine-1-carboxylate (5d)

Off white solid; Yield: 68%, m.p. 186–187 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.35 (3H, t, J = 3.6 MHz, CH_3–C), 2.72 (3H, s, CH_3), 3.18 (4H, t, J = 4.8 MHz, –CH_2–N–CH_2–), 3.64(3H, s, OCH_3), 3.78 (4H, t, J = 4.4 MHz, –CH_2–N–CH_2–), 4.23 (2H, q, C–CH_2–O), 6.95 (1H, d, J = 4.8 MHz, Ar–H), 7.09 (1H, t, J = 7.2 MHz, Ar–H), 7.34 (1H, d, J = 7.2 MHz, Ar–H), 7.55 (1H, s, Ar–H), 7.86 (1H, d, J = 2.8 MHz, Ar–H), 7.99 (1H, d, J = 7.6 MHz, Ar–H), 8.35 (1H, s, Ar–H); IR (KBr) ν (cm^{-1}): 3344 (NH), 1685 (C=O ester), 1703 (C=O amide), 1357, 1154 (SO_2); [M^+]: 461.52. Calcd. (%) for $C_{22}H_{27}N_3O_6S$: C, 57.27; H, 5.90; N, 9.10, S, 6.95. Found: C, 57.24; H, 5.91; N, 9.12, S, 6.93.

Ethyl-4-(3-(N-(4-chlorophenyl)sulfamoyl)-4-methylbenzoyl)piperazine-1-carboxylate (5e)

White solid; Yield: 91%, m.p. 154 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.33 (3H, t, J = 2.8 MHz, CH_3–C), 2.78 (3H, s, CH_3), 3.23 (4H, t, J = 4.4 MHz, –CH_2–N–CH_2–), 3.83 (4H, t, J = 4.0 MHz, –CH_2–N–CH_2–), 4.22 (2H, q, C–CH_2–O), 7.08 (2H, d, J = 7.2 MHz, Ar–H), 7.16 (2H, d, J = 7.2 MHz, Ar–H), 7.55 (1H, d, J = 7.6 MHz, Ar–H), 7.94 (1H, d, J = 6.4 MHz, Ar–H), 8.35 (1H, s, Ar–H); IR (KBr) ν (cm^{-1}): 3352 (NH), 1687 (C=O ester), 1704 (C=O amide), 1312, 1134 (SO_2); [M^+]: 465.11. Calcd. (%) for $C_{21}H_{24}ClN_3O_5S$: C, 54.13; H, 5.19; Cl, 7.61; N, 9.02, S, 6.88. Found: C, 54.13; H, 5.12; Cl, 7.63; N, 9.03, S, 6.85.

Ethyl-4-(3-(N-(3-chlorophenyl)sulfamoyl)-4-methylbenzoyl)piperazine-1-carboxylate (5f)

White solid; Yield: 82%, m.p. 162–165 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.34 (3H, t, J = 2.4 MHz, CH_3–C), 2.77 (3H, s, CH_3), 3.19 (4H, t, J = 4.0 MHz, –CH_2–N–CH_2–), 3.78 (4H, t, J = 4.8 MHz, –CH_2–N–CH_2–), 4.21 (2H, q, C–CH_2–O), 7.05 (1H, d, J = 6.4 MHz, Ar–H), 7.18 (1H, t, J = 7.2 MHz, Ar–H), 7.35 (1H, d, J = 7.6 MHz, Ar–H), 7.58 (1H, s, Ar–H), 7.83 (1H, d, J = 7.2 MHz, Ar–H), 7.92 (1H, d, J = 6.4 MHz, Ar–H), 8.31 (1H, s, Ar–H); IR (KBr) ν (cm^{-1}): 3344 (NH), 1687 (C=O ester), 1701 (C=O amide), 1352, 1157 (SO_2); [M^+]: 465.11. Calcd. (%) for $C_{21}H_{24}ClN_3O_5S$: C, 54.13; H, 5.19; Cl, 7.61; N, 9.02, S, 6.88. Found: C, 54.14; H, 5.19; Cl, 7.62; N, 9.03, S, 6.88.

Ethyl-4-(3-(N-(4-fluorophenyl)sulfamoyl)-4-methylbenzoyl)piperazine-1-carboxylate (5g)

White solid; Yield: 77%, m.p. 123–124 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.28 (3H, t, J = 4.0 MHz, CH_3–C), 2.71 (3H, s, CH_3), 3.19 (4H, t, J = 4.8 MHz, –CH_2–N–CH_2–), 3.81 (4H, t, J = 4.4 MHz, –CH_2–N–CH_2–), 4.20 (2H, q, C–CH_2–O), 7.07 (2H, d, J = 7.2 MHz, Ar–H), 7.18 (2H, d, J = 7.1 MHz, Ar–H), 7.54 (1H, d, J = 7.6 MHz, Ar–H), 7.93 (1H, d, J = 6.2 MHz, Ar–H), 8.31 (1H, s, Ar–H); IR (KBr) ν (cm^{-1}): 3353 (NH), 1688 (C=O ester), 1701 (C=O amide), 1345, 1136 (SO_2); [M^+]: 449.51. Calcd. (%) for $C_{21}H_{24}FN_3O_5S$: C, 56.11; H, 5.39; F, 4.23; N, 9.35, S, 7.13. Found: C, 56.13; H, 5.40; F, 4.23; N, 9.36, S, 7.15.

Ethyl-4-(3-(N-(3-fluorophenyl)sulfamoyl)-4-methylbenzoyl)piperazine-1-carboxylate (5h)

White solid; Yield: 78%, m.p. 194–196 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.31 (3H, t, J = 4.4 MHz, CH_3–C), 2.72 (3H, s, CH_3), 3.14 (4H, t, J = 4.8 MHz, –CH_2–N–CH_2–), 3.73 (4H, t, J = 4.0 MHz, –CH_2–N–CH_2–), 4.20 (2H, q, C–CH_2–O), 7.05 (1H, d, J = 7.2 MHz, Ar–H), 7.18 (1H, t, J = 6.8 MHz, Ar–H), 7.31 (1H, d, J = 7.2 MHz, Ar–H), 7.59 (1H, s, Ar–H), 7.84 (1H, d, J = 6.4 MHz, Ar–H), 7.99

(1H, d, J = 6.8 MHz, Ar–H), 8.31 (1H, s, Ar–H); IR (KBr) ν (cm^{-1}): 3344 (NH), 1687 (C=O ester), 1701 (C=O amide), 1352, 1157 (SO_2); [M^+]: 449.51. Calcd. (%) for $C_{21}H_{24}FN_3O_5S$: C, 56.11; H, 5.39; F, 4.23; N, 9.35, S, 7.13. Found: C, 56.13; H, 5.40; F, 4.23; N, 9.36, S, 7.15.

Ethyl-4-(4-methyl-3-(N-(4-(trifluoromethyl)phenyl)sulfamoyl)-4-methylbenzoyl)piperazine-1-carboxylate (5i)

White solid; Yield: 54%, m.p. 169–171 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.33 (3H, t, J = 4.0 MHz, CH_3–C), 2.77 (3H, s, CH_3), 3.23 (4H, t, J = 4.2 MHz, –CH_2–N–CH_2–), 3.86 (4H, t, J = 4.4 MHz, –CH_2–N–CH_2–), 4.26 (2H, q, C–CH_2–O), 7.12 (2H, d, J = 4.8 MHz, Ar–H), 7.34 (2H, d, J = 7.1 MHz, Ar–H), 7.58 (1H, d, J = 6.8 MHz, Ar–H), 7.99 (1H, d, J = 6.4 MHz, Ar–H), 8.34 (1H, s, Ar–H); IR (KBr) ν (cm^{-1}): 3353 (NH), 1685 (C=O ester), 1701 (C=O amide), 1334, 1142 (SO_2); [M^+]: 499.21. Calcd. (%) for $C_{22}H_{24}F_3N_3O_5S$: C, 52.90; H, 4.84; F, 11.41; N, 8.41, S, 6.42. Found: C, 52.91; H, 4.84; F, 11.43; N, 8.41, S, 6.42.

Ethyl-4-(4-methyl-3-(N-(3-(trifluoromethyl)phenyl)sulfamoyl)-4-methylbenzoyl)piperazine-1-carboxylate (5j)

White solid; Yield: 59%, m.p. 175–177 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.34 (3H, t, J = 12.8 MHz, CH_3–C), 2.79 (3H, s, CH_3), 3.19 (4H, t, J = 4.8 MHz, –CH_2–N–CH_2–), 3.72 (4H, t, J = 4.0 MHz, –CH_2–N–CH_2–), 4.23 (2H, q, C–CH_2–O), 7.08 (1H, d, J = 4.4 MHz, Ar–H), 7.19 (1H, t, J = 7.2 MHz, Ar–H), 7.39 (1H, d, J = 7.6 MHz, Ar–H), 7.62 (1H, s, Ar–H), 7.80 (1H, d, J = 6.4 MHz, Ar–H), 7.99 (1H, d, J = 8.4 MHz, Ar–H), 8.33 (1H, s, Ar–H); IR (KBr) ν (cm^{-1}): 3342 (NH), 1688 (C=O ester), 1703 (C=O amide), 1356, 1153 (SO_2); [M^+]: 499.21. Calcd. (%) for $C_{22}H_{24}F_3N_3O_5S$: C, 52.90; H, 4.84; F, 11.41; N, 8.41, S, 6.42. Found: C, 52.92; H, 4.84; F, 11.43; N, 8.42, S, 6.43.

Ethyl-4-(4-methyl-3-(N-(2-(trifluoromethyl)phenyl)sulfamoyl)-4-methylbenzoyl)piperazine-1-carboxylate (5k)

White solid; Yield: 61%, m.p. 140–143 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.28 (3H, t, J = 4.0 MHz, CH_3–C), 2.64 (3H, s, CH_3), 3.16 (4H, t, J = 4.4 MHz, –CH_2–N–CH_2–), 3.72 (4H, t, J = 4.0 MHz, –CH_2–N–CH_2–), 4.24 (2H, q, C–CH_2–O), 7.09 (1H, d, J = 7.1 MHz, Ar–H), 7.20 (1H, t, J = 7.1 MHz, Ar–H), 7.31 (1H, t, J = 7.3 MHz, Ar–H), 7.48 (1H, d, J = 6.4 MHz, Ar–H), 7.82 (1H, d, J = 8.4 MHz, Ar–H), 7.99 (1H, d, J = 7.6 MHz, Ar–H), 8.34 (1H, s, Ar–H); IR (KBr) ν (cm^{-1}): 3346 (NH), 1684 (C=O ester), 1705 (C=O amide), 1357, 1163 (SO_2); [M^+]: 499.21. Calcd. (%) for $C_{22}H_{24}F_3N_3O_5S$: C, 52.90; H, 4.84; F, 11.41; N, 8.41, S, 6.42. Found: C, 52.90; H, 4.84; F, 11.43; N, 8.42, S, 6.41.

Ethyl-4-(4-methyl-3-(N-(4-(trifluoromethoxy)phenyl)sulfamoyl)-4-methylbenzoyl)piperazine-1-carboxylate (5l)

White solid; Yield: 68%, m.p. 186–187 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.35 (3H, t, J = 4.0 MHz, CH_3–C), 2.78 (3H, s, CH_3), 3.35 (4H, t, J = 4.8 MHz, –CH_2–N–CH_2–), 3.87 (4H, t, J = 4.4 MHz, –CH_2–N–CH_2–), 4.25 (2H, q, C–CH_2–O), 6.78 (2H, d, J = 7.2 MHz, Ar–H), 6.99 (2H, d, J = 6.4 MHz, Ar–H), 7.58 (1H, d, J = 4.8 MHz, Ar–H), 7.92 (1H, d, J = 6.8 MHz, Ar–H), 8.30 (1H, s, Ar–H); IR (KBr) ν (cm^{-1}): 3352 (NH), 1687 (C=O ester), 1704 (C=O amide), 1348, 1137 (SO_2); [M^+]: 515.12. Calcd. (%) for $C_{22}H_{24}F_3N_3O_6S$: C, 51.25; H, 4.69; F, 11.06; N, 8.15, S, 6.22. Found: C, 51.23; H, 4.70; F, 11.05; N, 8.16, S, 6.23.

Ethyl-4-(4-methyl-3-(N-(3-(trifluoromethoxy)phenyl)sulfamoyl)-4-methylbenzoyl)piperazine-1-carboxylate (5m)

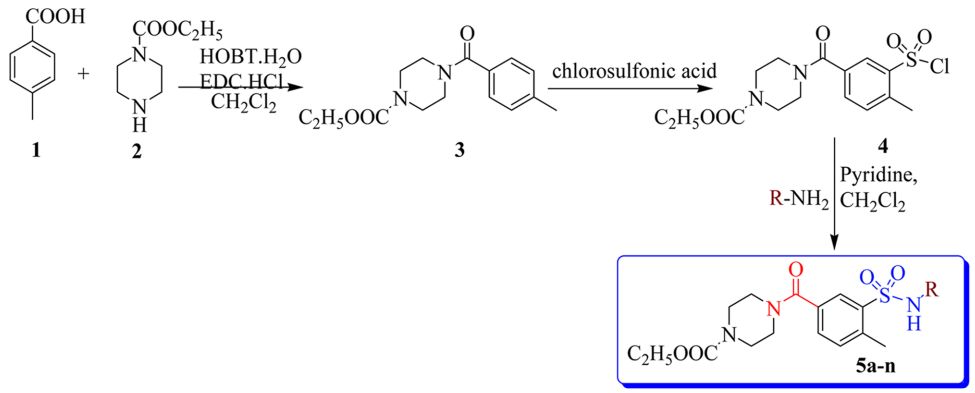
White solid; Yield: 72%, m.p. 175–176 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.32 (3H, t, J = 4.4 MHz, CH_3–C), 2.73 (3H, s, CH_3), 3.17 (4H, t, J = 4.0 MHz, –CH_2–N–CH_2–), 3.78 (4H, t, J = 4.0 MHz, –CH_2–N–CH_2–), 4.26 (2H, q, C–CH_2–O), 6.78 (1H, d, J = 6.4 MHz, Ar–H), 6.95 (1H, t, J = 7.1 MHz, Ar–H), 7.05 (1H, d, J = 7.6 MHz, Ar–H), 7.25 (1H, s, Ar–H), 7.83 (1H, d, J = 4.8 MHz, Ar–H), 8.02 (1H, d, J = 7.2 MHz, Ar–H), 8.33 (1H, s, Ar–H); IR (KBr) ν (cm^{-1}): 3348 (NH), 1685 (C=O ester), 1703 (C=O amide), 1354, 1156 (SO_2); [M^+]: 515.12. Calcd. (%) for $C_{22}H_{24}F_3N_3O_6S$: C, 51.25; H, 4.69; F, 11.06; N, 8.15, S, 6.22. Found: C, 51.24; H, 4.73; F, 11.05; N, 8.13, S, 6.22.

Ethyl-4-(4-methyl-3-(N-(2-(trifluoromethoxy)phenyl)sulfamoyl)-4-methylbenzoyl)piperazine-1-carboxylate (5n)

White solid; Yield: 648%, m.p. 138–140 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.32 (3H, t, J = 12.8 MHz, CH_3–C), 2.70 (3H, s, CH_3), 3.18 (4H, t, J = 4.4 MHz, –CH_2–N–CH_2–), 3.73 (4H, t, J = 4.8 MHz, –CH_2–N–CH_2–), 4.24 (2H, q, C–CH_2–O), 6.86 (1H, d, J = 4.0 MHz, Ar–H), 6.97 (1H, t, J = 7.1 MHz, Ar–H), 7.11 (1H, t, J = 7.3 MHz, Ar–H), 7.34 (1H, d, J = 6.4 MHz, Ar–H), 7.82 (1H, d, J = 7.2 MHz, Ar–H), 7.99 (1H, d, J = 8.0 MHz, Ar–H), 8.34 (1H, s, Ar–H); IR (KBr) ν (cm^{-1}): 3342 (NH), 1684 (C=O ester), 1703 (C=O amide), 1356, 1162 (SO_2); [M^+]: 515.12. Calcd. (%) for $C_{22}H_{24}F_3N_3O_6S$: C, 51.25; H, 4.69; F, 11.06; N, 8.15, S, 6.22. Found: C, 51.25; H, 4.71; F, 11.06; N, 8.16, S, 6.23.

RESULTS AND DISCUSSION

Bifunctional sulfonamide-amide derivaties (**5a–n**) were synthesized by expedient synthetic route is outlined in *Scheme* 1. The compound **3** was obtained by the reaction



***Scheme* 1.** Ra = 4-$CH_3C_6H_4$, b = 3-$CH_3C_6H_4$, c = 4-$OCH_3C_6H_4$, d = 3-$OCH_3C_6H_4$, e = 4-ClC_6H_4, f = 3-ClC_6H_4, g= 4-FC_6H_4, h = 3-FC_6H_4, i = 4-$CF_3C_6H_4$, j = 3-$CF_3C_6H_4$, k = 2-$CF_3C_6H_4$, l = 4-$OCF_3C_6H_4$, m = 3-$OCF_3C_6H_4$, n = 2-$OCF_3C_6H_4$.

of 4-methylbenzoic acid (**1**) with ethylpiperazine-1-carboxylate (**2**) by a standard amide (Et_3N-HOBT-EDC) coupling procedure,[33] which was consequently converted into ethyl-4-(3-(chlorosulfonyl)-4-methylbenzoyl)piperazine-1-carboxylate (**4**), by adding chlorosulfonic acid. This compound was permitted to react with various anilines in CH_2Cl_2 to afford the title compounds **5a**–**n**. The completion of the reaction was monitored by TLC (hexane-ethyl acetate, 70:30). Under these conditions, several anilines were effectively and quantitatively coupled with 4-methyl benzoic acid proving the efficiency of this method. Simple workup, along with the good yields of the products and also the mild reaction conditions pramoted us to apply this method for the synthesis of bifunctional sulfonamide-amide derivaties (**5a**–**n**). All synthesized compounds were deduced from their elemental analyses, IR, ^{1}H NMR and Mass spectral data.

Characteristic IR absorption bands were observed for (NH), (C=O) and (SO_2) at 3345, 1735, 1354 and 1145 cm^{-1}, respectively. The aromatic hydrogens resonated at d 6.78–8.45. The structure was further confirmed by mass spectral studies.

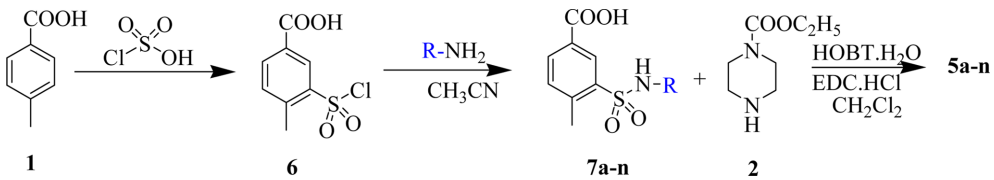
The title compounds **5a**–**n** was further confirmed by the treatment of 4-methylbenzoic acid with chlorosulfonic acid to yielded sulfonyl chloride **6**. Reaction of **6** with varies anilines under standard conditions to give **7a–n** and finally the **7a–n** converted into sulfonamide-amide derivatives with ethylpiperazin-1-carboxylate (**2**) (*Scheme* 2).

ANTIBACTERIAL ACTIVITY

The sulfonamide and amide derivatives known to be more potent antimicrobial agents.[10,23,24] All the compounds synthesized in the current study (**5a** through **5n**) were, therefore, screened for their antibacterial activity with respect to human pathogenic bacteria such as *Pseudomonas aeruginosa*, *Staphylococcus aureus, Escherichia coli, Streptococcus faecalis*, and *Propionibacterium acnes*. The minimum inhibition concentration was determined using the dilution method.[34] DMF was used as a blank and ciprofloxacin as standard, and the results are presented in *Table* 1. An examination of the data expose that all the compounds showed antibacterial activity ranging from 0.14 to 6.74 μg/mL^{-1}. Of the compounds **5d** to **5f** and **5l** to **5n** exhibited potent antimicrobial activity followed the order: **5n > 5m > 5l > 5e > 5f > 5d**. The results clearly indicate that the existence of methoxy/chloro/trifluoromethoxy group at the phenyl ring enhances the antimicrobial activity.

ANTIFUNGAL ACTIVITY

The compounds **5a**–**n** were screened also for their antifungal activity (*Table* 1) against *Candida albicans* and *Aspergillus niger* using fungicide fuuconazole in DMF as the standard.[35] All the compounds exhibited diffident to high-antifungal activity when compared with that of the



***Scheme* 2.**

***Table* 1.** In vitro antimicrobial activity of compounds **5a–n**

Comp.	Minimum inhibitory concentrations (MIC) mg/mL						
	P. aeruginosa	*S. aureus*	*E. coli*	*S. faecalis*	*P. acnes*	*C. albicans*	*A. niger*
5a	2.35	2.15	2.82	3.42	6.74	2.51	3.12
5b	5.64	2.34	3.14	3.15	1.75	1.5	2.4
5c	0.8	0.8	0.8	0.8	0.8	0.6	0.6
5d	0.8	1.0	0.9	0.8	1.24	0.4	0.4
5e	0.6	0.6	0.5	0.4	0.6	0.4	0.5
5f	0.8	0.8	0.6	0.7	0.4	0.72	0.44
5g	1.74	1.54	1.68	1.37	0.8	0.97	0.45
5h	0.99	0.6	0.8	0.8	0.75	0.36	0.87
5i	2.31	0.8	0.8	0.7	0.42	1.57	0.99
5j	1.66	0.97	1.54	1.56	0.55	0.88	0.96
5k	2.13	22.3	0.8	0.7	0.65	1.24	1.125
5l	0.5	0.8	0.6	0.8	0.6	0.6	0.8
5m	0.6	0.9	0.8	0.6	0.4	0.6	1.12
5n	0.54	0.14	0.87	0.9	0.8	1.85	0.94
Ciprofloxacin	0.0012	0.009	0.016	0.009	0.014	–	–
Fluconazole	–	–	–	–	–	0.078	0.007

reference compound. Most of the compounds exerted high activity against the tested fungi.

CONCLUSIONS

We have synthesized original derivatives of bifunctional sulfonamide-amide analogues by predictable methods. Among the synthesized compounds, almost all compounds showed good activity against bacteria and fungi and emerged as potential molecules for advance development.

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