Synthesis, antimicrobial study of novel (E)-4-chloro-N-(4-(3-(4-((substituted)sulfonyl) piperazin-1-yl)-3-oxoprop-1-en-yl)phenyl)-2-methylbenzamide derivatives

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Abstract

A series of novels (E)-4-chloro-N-(4-(3-(4-((substituted) sulfonyl) piperazin-1-yl)-3-oxoprop-1-en-yl) phenyl)-2-methyl benzamide (**9a-9l)** derivatives were synthesized via reduction, amide, and sulfonamide couplings. We have modified the amide and sulfonamide conditions to have strongly electron-donating and electron-withdrawing substituent's, along with a piperazine core, with good yields and simple reaction steps. ^{1}H NMR, ^{19}F, ^{13}C NMR, LCMS, and HPLC analytical techniques characterized the synthesized compounds. The synthesized compounds were tested for in vitro antimicrobial activities by agar diffusion assay and broth micro dilution assay. All the compounds exhibited moderate to good antimicrobial activities against the tested micro organisms. The compounds **9a** and **9e** showed significant antimicrobial activities against antibacterial strains.

Keywords: Piperazine, Sulfanamide; Benzamide; Antimicrobial.

Introduction

The cyclic organic compounds that contain at least one heteroatom are termed for heterocyclic compounds. The atoms like nitrogen, oxygen, and sulfur incorporated in ring makes the heterocyclic compounds which varied medicinal properties depending on the heteroatom. Heterocyclic motifs play a important part in medicinal chemistry research due to their wide spectrum of biological activities and have always emerge with higher therapeutic efficiency. Nitrogen bearing heterocyclic play importance with a good track record of therapeutic advances in the recent drug discovery as lead molecules. Antimicrobial resistance is an alarming concern for humankind as it emerge due to excess use of medicines. WHO had taken new initiatives towards control of antimicrobial resistance by celebrating antimicrobial awareness week, prevention of antimicrobial resistance, spreading awareness globally, and avoiding excess use of medicine to avoid drug resistance etc. since 2015 in world wide. [1 & 2] WHO alerted about deaths of 350 million humans by 2050 by antimicrobial drug resistance occurred from infections

like methicillin-resistant staphylococcus aureus (MRSA), vancomycin-resistant enterococcus (VRE), multi-drug-resistant mycobacterium tuberculosis (MDR-TB), carbapenem-resistant Enterobacteriaceae (CRE), multidrug-resistant Neisseria gonorrhoeae and Escherichia coli etc. The diseases like cancer, HIV, parkinsons, Alzheimer, chronic diseases, diabetic, and central nervous system, etc required longer duration for treatments and there emerge the high possibility of drug resistance. These drug-resistance occurs mainly due to physical health of human, weaker immunity, etc which develops infections and later resulted in weaker immunity. [3 & 4] There is always a competition between bacterial developments towards the drugs, as it is never ending. Recently we have witnessed severe infections like COVID-19 pandemic and many humans lost their lives globally. Along with that in last 10 years we have witnessed Zika virus, Ebola virus, Swine flu, etc causes many deaths to specific parts of world which affected morbidity and mortality of human kind worldwide. Research needed to align with global threat of infectious diseases and to tacking the rapidly increasing newer strains of viruses. [5]

Nitrogen heterocyclic compounds containing piperazine sulfonamide have been of significant interest in the field of medicinal chemistry research for scientists due to their varied pharmacological activities. [6]

The molecules compromising piperazine and sulfonamide are well known in drug discovery for their medicinal activities. The piperazine and sulfonamide act as antimicrobial, anticancer, anti-diabetic, sigma receptor ligands, and antibacterial.[7-10].The piperazine nuclei forma key component of many biologically active molecules and drugs, as the basic nature of nitrogen involved in the piperazine ring plays an important role in biological activity. The drugs containing Oxatomide used for the treatment of muscular dystrophy; Almitrine used for the treatment of respiratory disorders; Hydroxyzine, Buclizine, and Meclizine used as antihistamine drugs; Lomerizine used for the treatment of migraines all having piperazine core.[11]

The derivatization of cinnamic acid like their esters, amides, alcohols, aldehydes, hydroxyl amines etc reported for their varied biological activities like anticancer, antimicrobial, antifungal, antioxidant, anti-tubercular, ant diabetic, antithrombotic, anti-inflammatory etc. [12-17] The cinnamic acid derivatives are mostly used in cosmetics industry, polymer and food as its structure contains acrylic acid, which is present in cis or trans configurations and its natural availability.[18-20] The presence of terminal acid functional groups makes its as a fascinating fragment to link with other bioactive fragments. Some heterocyclic acrylic acid showed lipoxygenase and cyclooxygenase-1 inhibitors with potent antioxidant and anti-inflammatory activity. [21 & 22] The incorporation of piperazine and cinnamic acid by involving amide and sulfonamide coupling ware incorporated in one nuclei with the hope to get promising antimicrobial activity, we have synthesized (E)-4-chloro-N-(4-(3-(4-((substituted)sulfonyl) piperazin-1-yl)-3-oxoprop-1-en-yl)phenyl)-2-methylbenzamide (**9a-9l)** derivatives. The detailed experimental procedures were incorporated in experimental section.

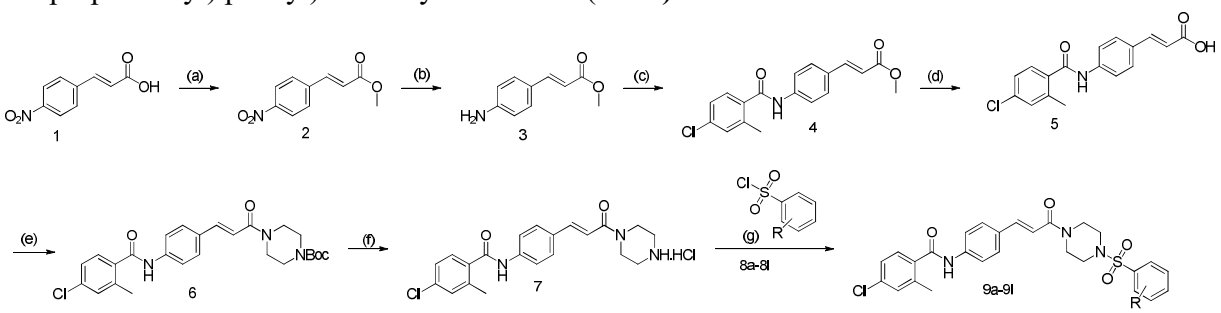
Result and Discussion:

The synthesis of substituted acrylic acid was well documented by Knoevenagel condensation by using aldehyde and malonic acid in the presence of base. [9] The synthesis of (E)-4-chloro-N-(4-

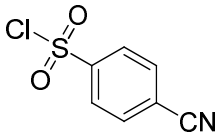
(3-(4-((substituted)sulfonyl) piperazin-1-yl)-3-oxoprop-1-en-yl)phenyl)-2-methylbenzamide (**9a-9l)** was achieved staring from readily available (E)-3-(4-nitrophenyl)acrylic acid (**1**) (Cas No-619-89-6) on esterification by using thionyl chloride in methanol to afford methyl(E)-3-(4-nitrophenyl)acrylate (Cas No-1608-36-2) with ≥93% yield. The obtained methyl ester was further subjected for reduction in the presence of double bond to afforded methyl (E)-3-(4-aminophenyl) acrylate (Cas No- 65198-02-9) with ≥95% yield. This amino acrylate is a key scaffold as we hooked head end with peptide coupling by using 4-chloro-2-methyl benzoic acid (Cas No-7499-07-2) to access amide coupling product methyl(E)-3-(4(4-chloro-2-methylbenzamide)phenyl)acrylate as product with ≥95% yield. The detailed synthesis of (E)-4-chloro-N-(4-(3-(4-((substituted) sulfonyl) piperazin-1-yl)-3-oxoprop-1-en-yl) phenyl)-2-methylbenzamide (**9a-9m)** involving amide and sulfonamide via esterification, reduction, amide, hydrolysis and sulfonamide coupling reactions.

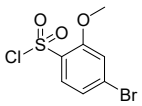
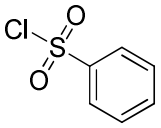
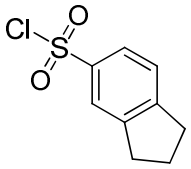
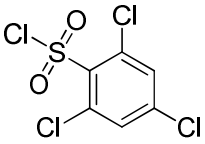
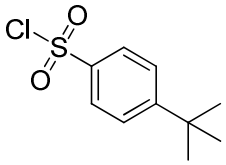
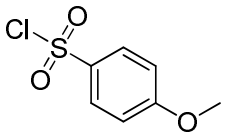
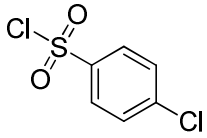
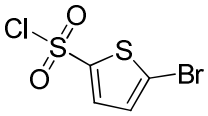
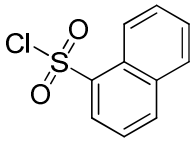
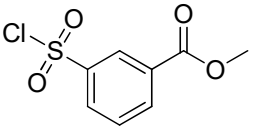
The derivatives involving aromatic, heterocyclic and aliphatic substituents. The reaction scheme for the synthesis of targets ware depicted in below scheme **1**. We have also developed simplified reaction conditions for all the steps so we can avoid costly reagents, tedious purifications, and all the synthesized compounds also have good purity. We here report the synthesis of new substituted sulfonamide derivatives with the aim of investigating their antimicrobial activity via agar diffusion assay and broth micro dilution assay. The synthetic methods adopted for the preparation of the title compounds (**9a-9l**) are depicted in the scheme presented below.

Scheme 1: Synthesis of (E)-4-chloro-N-(4-(3-(4-((substituted) sulfonyl) piperazin-1-yl)-3-oxoprop-1-en-yl) phenyl)-2-methylbenzamide (**9a-9l):**



Reagents and conditions: (a): SOCl2, MeOH, 60°C, 1h; (b) Zn, NH_4CHOO, MeOH, 0°C-90°C, 2h. (c) 4-chloro-2-methyl benzoic acid, HATU, DIPEA, DMF, 0°C to RT, 2h (d) LiOH, THF, H2O, 2h; (e) Boc piperazine, HATU, DIPEA, DMF, 0°C to RT, 2h (f) 4M HCl in 1,4-dioxane, DCM, 0°C to RT, 1h (g) Substituted sulfonyl chloride (8a-8m), pyridine, DCM, 0°C-RT, 6 h.

No.	R	No.	R
8a		8g	

8b		8h	
8c		8i	
8d		8j	
8e		8k	
8f		8l	

The reduction of 4-substituted nitrobenzene was achieved in step b; literature reveals use of sodium dithionate, H2, Pd/C in EtOH or MeOH at room temperature in 16h. [23] The reduction was completed in 2h with ≥ 85% yields by using Fe, ammonium format, EtOH, water and heating with 90°C.

The step c and d involved acid amine coupling reactions and deprotection reaction. The step c was achieved by using literature condition using HATU, DIPEA and DMF as solvent the compound 4-(tert-butyl)-N-(2-(piperazin-1-yl) phenyl) benzamide (6) was isolated by using cold water treatment. The solid precipitates out after aqueous treatment of reactions mixture involving DMF. The compound (**7**) isolated with ≥90% purity with 85% yields. The step d was done with 4M HCl in 1, 4-dioxane in 2h, to isolate compound (7) with ≥90% purity with 95% yields. [24]

In step e the compound 7 reacted with different aromatic aliphatic and heterocyclic sulfonyl chloride (8a-8m), to obtained the desired compounds sulfonamides (9a-9l) with good yields. We varied different bases and solvents for the optimization of sulphonamide coupling as reported previously. [25] The structure of the intermediates were confirmed by 1H NMR spectroscopy, the alkenyl protons got deshielded due to movement of electrons in the pi bond as the coupling

constant was 15 Hz for all the intermediates and final compounds confirms the all the derivatives are having trans configurations. The detailed synthetic procedure for the synthesis of (**9a-9m**) was incorporated in below experimental procedure.

Experimental Details:

Material and methods:

All chemicals, unless otherwise specified, ware purchased from commercial sources and ware used without further purification. The major chemicals purchased from Sigma Aldrich and Avra labs. The development of reactions were monitored by thin layer chromatography (TLC) analysis on Merck pre-coated silica gel 60 F254 aluminum sheets, visualized by UV light. All reactions carried out under inert atmosphere. Melting points recorded on Casia-Siamia (VMP-AM) melting point apparatus and all are uncorrected. The purity of intermediates ware assessed by TLC, NMR, and HRMS. The purity of final compounds checked by NMR, HRMS, and HPLC and all structures are consistent with proposed structures characterization. The 1H NMR spectra were recorded on a 400 MHz Varian NMR spectrometer. The 13C recorded on a 100 MHz Varian NMR spectrometer. The chemical shifts ware reported as NMR spectra δppm units. The following abbreviations are used; singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m) and broad (br). Mass spectra were taken with Micromass-QUATTRO-II of produced by WATERS Corporation.

Experimental procedure for synthesis of (E)-4-chloro-N-(4-(3-(4-((substituted)sulfonyl) piperazin-1-yl)-3-oxoprop-1-en-yl)phenyl)-2-methylbenzamide (9a-9m):

Step a: Synthesis of methyl (E)-3-(4-nitrophenyl) acrylate (2; CAS No-1608-36-2):

To a stirred solution of (E)-3-(4-nitrophenyl) acrylic acid (5 g, 25.8 mmol) in MeOH (50 mL) wad added thionyl chloride (3.75 mL, 51.7 mmol) drop wise at 0°C. The reaction mixture was stirred at 60°C for 1h. Progress of the reaction was monitored by TLC. After completion, the reaction mixture was evaporated under reduced pressure and obtained crude gummy material. The obtained crude was triturated with diethyl ether (50 mL) and cold pentane (50 mL) to obtain precipitate. The obtained precipitated was filtered and dried to afford methyl (E)-3-(4-nitrophenyl) acrylate (2) (5 g, 93.2%) as yellow solid which is used for next reaction.

Step b: **Synthesis of methyl (E)-3-(4-aminophenyl) acrylate (3; CAS No-65198-02-9):**

To a stirred solution of methyl (E)-3-(4-nitrophenyl)acrylate (2) (5 g, 24.1 mmol) in methanol (50 mL) was added zinc (3.17 g, 48.8 mmol) at 0°C followed by addition of ammonium formate (3.07 g, 48.8 mmol).The reaction mixture was stirred at RT for 4h, while monitored by TLC. After completion, the reaction mixture was diluted with ethyl acetate (50 mL) and filter through celite bed. The obtained filtrate was evaporated under reduced pressure to afford yellow semisolid. The crude was diluted with cold DCM (20 mL) to it and then kept at 0°C for 30 min. Then ammonium formate precipitated, decan DCM and concentrated to afforded methyl (E)-3-(4-aminophenyl) acrylate (3) (4 g, 93.6%) as light brown solid as such used for next reaction.

Step c: **Synthesis of** methyl (E)-3-(4-(4-chloro-2-methylbenzamide) phenyl) acrylate **(5):**

To a stirred solution of methyl (E)-3-(4-aminophenyl)acrylate (3) (4 g, 22.5 mmol) in DMF was added 4-chloro-2-methyl benzoic acid (4.62 g, 27.0 mmol) at 0°C followed by addition of HATU (12.8 g, 33.8 mmol) and DIPEA (11.8 mL, 67.7 mmol). The reaction mixture was stirred at RT for 4h. Progress of the reaction was monitored by TLC. After completion of starting material add crushed ice to it. There is solid precipitation, filter it dry it to afford methyl (E)-3-(4-(4-chloro-2-methylbenzamide)phenyl)acrylate (5) (7.1 g, 95.4%) as off white solid used for next reaction.

Step d: Synthesis of methyl (E)-3-(4-(4-chloro-2-methylbenzamide) phenyl) acrylic acid (6; CAS No- 1840739-64-1)):

To a stirred solution of methyl (E)-3-(4-(4-chloro-2-methylbenzamide)phenyl)acrylate (5) (7 g, 21.2 mmol) in THF (35 mL), ethanol (17 mL) and water (8 mL) was added lithium hydroxide (1.52 g, 63.6 mmol) and stirred reaction mixture at room temperature for 2h. Progress reaction was monitored by TLC and LCMS. After completion, the reaction mixture was evaporated under reduced pressure to obtained gummy material. Added (30 mL) of water in it and extracted it with diethyl ether (30 mL). The separated aqueous layer was collected and its pH was adjusted to 4 by using 6N aqueous HCl to obtain precipitate. The obtained precipitate was filtered and washed it with water (100 mL), cold diethyl ether (50 mL) and cold pentane (50 mL) to afforded methyl (E)-3-(4-(4-chloro-2-methylbenzamide)phenyl)acrylic acid **(6)** (6.5 g, 97%) as white solids. (Yield- 80% to 90%).

Step-e: Synthesis of tert-butyl (E)-4-(3-4-(4-chloro-2-methylbenzamide) phenyl) acryloyl) piperazine-1-carboxylate (8)

Experimental procedure same as used for synthesis in step-c. The reaction was done on 6.5 g to afforded tert-butyl (E)-4-(3-4-(4-chloro-2-methylbenzamide) phenyl) acryloyl) piperazine-1-carboxylate (8) (9 g, 91%) as white solid.

Step-f: **Synthesis of (E)-4-chloro-2-methyl-N-(4-(3-oxo-3-(piperazin-1-yl) prop-1-en-1-yl) phenyl) benzamide (9):**

To a stirred solution of tert-butyl (E)-4-(3-4-(4-chloro-2-methylbenzamide) phenyl) acryloyl) piperazine-1-carboxylate (**8)** (9 g, 18.6 mmol) in DMC (50 mL) wad added 4M HCl in 1, 4-dioxane (45 mL) at 0°C. The reaction mixture was stirred at room temperature for 1h. Progress of the reaction was monitored by TLC. After completion the reaction mixture was evaporated under reduced pressure to obtained crude. The obtained crude was triturated with pentane (2 x 30 mL) to afforded (E)-4-chloro-2-methyl-N-(4-(3-oxo-3-(piperazin-1-yl) prop-1-en-1-yl) phenyl) benzamide (**9**) ((6.5 g, 91%) as an off white solid. The obtained compound was used for amide coupling without further purification.

Step g: General procedure for the synthesis of (E)-4-chloro-N-(4-(3-(4-((substituted) sulfonyl) piperazin-1-yl)-3-oxoprop-1-en-yl) phenyl)-2-methylbenzamide (9a-9m):

To a stirred solution of (E)-4-chloro-2-methyl-N-(4-(3-oxo-3-(piperazin-1-yl) prop-1-en-1-yl) phenyl) benzamide (**9**) (1eq) in DMF (10 Vol) wad added DIPEA (3 eq). The reaction mixture was cooled to 0°C and added different sulfonyl chloride (8a-8n) (1.2 eq) portion wise. The reaction mixture was stirred at room temperature for 16h. Progress of the reaction was monitored

by TLC. After consumption of starting material the reaction mixture was diluted with crushed ice to get precipitated which was filtered to obtained different derivatives.

In some derivatives we have extracted aqueous layer with ethyl acetate to afford crude material which was purified by column chromatography silica 100 to 200 mesh using 50% to 80 % ethyl acetate in hexane as an eluent to afford final product as an off white solid.

Analytical data of (E)-4-chloro-N-(4-(3-(4-((substituted) sulfonyl) piperazin-1-yl)-3-oxoprop-1-en-yl) phenyl)-2-methylbenzamide (9a-9m):

1] (E)-4-chloro-N-(4-(3-(4-((4-cyanophenyl) sulfonyl) piperazin-1-yl)-3-oxoprop-1-en-yl) phenyl)-2-methylbenzamide (9a):

^{1}H NMR (400 MHz, DMSO-D_6, ppm) δ 10.50 & 10.25 (s, 1H, NH), 8.19 – 8.09 (m, 2H), 8.01 – 7.87 (m, 2H), 7.77 (d, *J* = 5.6 Hz, 1H), 7.73 (d, *J* = 6.4 Hz, 1H), 7.59 (d, *J* = 5.6 Hz, 1H), 7.54 – 7.35 (m, 4H), 7.18 (d, *J* = 14.8 Hz, 1H), 3.54 (bs, 2H), 3.11 – 2.87 (m, 4H), 2.78 (m, 2H), 2.39 (s, 3H); ^{13}C NMR (DMSO-D_6, 100 MH_Z, ppm) δ 170.62, 167.51, 165.24, 142.29, 140.99, 139.92, 139.78, 138.59, 137.23, 136.64, 136.27, 134.82, 134.56, 134.25, 130.82, 130.73, 129.77, 129.67, 129.35, 129.14, 128.86, 126.15, 120.32, 120.14, 118.23, 116.77, 116.41, 46.44, 44.73, 40.36, 40.15, 39.94, 34.55, 30.56, 19.67; Calculated MS (ESI) *m/z*: 548.1, Found, *m/z*: 549.1 $[M + H]^+$; Elemental analysis for $C_{28}H_{25}ClN_4O_4S$ calcd: C, 61.25; H, 4.59; N, 10.2; Found: C, 61.3; H, 4.55; N, 10.24.

2] (E)-N-(4-(3-(4-((4-bromo-2-methoxyphenyl) sulfonyl) piperazin-1-yl)-3-oxoprop-1-en-1-yl) phenyl)-4-chloro-2-methylbenzamide (9b)

^{1}H NMR (400 MHz, DMSO-D_6, ppm) δ 10.5 & 10.24 (s, 1H, NH), 7.87 – 7.73 (m, 3H), 7.79 (d, *J* = 5.6 Hz, 1H), 7.61 (d, *J* = 6.4 Hz, 1H), 7.52 – 7.33 (m, 4H), 7.27 (d, *J* = 5.6 Hz, 2H), 7.18 (d, *J* = 14.8 Hz, 1H), 3.90 (s, 3H), 3.48 (m, 4H), 3.22 – 3.17 (m, 4H), 2.38 (s, 3H); ^{13}C NMR (DMSO-D_6, 100 MH_Z, ppm) δ 170.65, 167.46, 167.18, 165.28, 156.57, 142.17, 140.90, 138.68, 138.52, 138.04, 137.51, 137.21, 136.55, 136.19, 134.77, 134.51, 133.05, 130.94, 130.74, 130.65, 129.71, 129.59, 129.28, 129.11, 127.87, 127.77, 126.09, 120.25, 120.13, 116.86, 116.31, 111.70, 57.02, 40.24, 40.03, 39.82, 30.58, 19.62; Calculated MS (ESI) *m/z*: 631.1, Found, *m/z*: 632.1 $[M + H]^+$; Elemental analysis for $C_{28}H_{27}BrClN_3O_5S$ calcd: C, 53.13; H, 4.30; N, 6.64; Found: C, 53.12; H, 4.35; N, 6.70.

3] (E)-4-chloro-N-(4-(3-(4-((2, 3-dihydro-1H-inden-5-yl) sulfonyl) piperazin-1-yl)-3-oxoprop-1-en-1-yl) phenyl)-2-methylbenzamide (9c):

^{1}H NMR (400 MHz, DMSO-D_6, ppm) δ 10.25 (s, 1H, NH), 7.73 – 7.69 (m, 6H), 7.67 (d, *J* = 5.6 Hz, 2H), 7.57 – 7.33 (m, 3H), 7.17 (d, *J* = 14.8 Hz, 2H), 3.55 (bs, 3H), 3.93 – 3.65 (m, 4H), 3.57 (bs, 2H), 2.94 (bs, 4H), 2.53 (s, 3H), 2.39 (s, 2H), 2.09 (s, 2H); ^{13}C NMR (DMSO-D_6, 100 MH_Z, ppm) δ 170.54, 167.45, 167.17, 165.18, 150.67, 145.98, 142.22, 140.94, 138.69, 138.54, 137.52, 137.19, 136.59, 136.21, 134.78, 134.51, 133.12, 132.91, 130.90, 130.76, 129.73, 129.62, 129.30, 129.07, 126.46, 126.10, 125.57, 123.89, 120.24, 120.09, 116.75, 46.96, 46.62, 44.65, 41.46, 40.73, 39.47, 34.47, 32.89, 32.67, 30.52, 25.47, 19.63; Calculated MS (ESI) *m/z*: 563.1, Found,

m/z: 564.1 $[M + H]^+$; Elemental analysis for $C_{30}H_{30}ClN_3O_4S$ calcd: C, 63.86; H, 5.36; N, 7.45; Found: C, 63.80; H, 5.42; N, 7.56.

4] (E)-N-(4-(3-(4-((4-(tert-butyl) phenyl) sulfonyl) piperazin-1-yl)-3-oxoprop-1-en-1-yl) phenyl)-4-chloro-2-methylbenzamide (9d):

^{1}H NMR (400 MHz, DMSO-D_6, ppm) δ 10.25 (s, 1H, NH), 7.73 – 7.69 (m, 6H), 7.67 (d, *J* = 5.6 Hz, 2H), 7.57 – 7.33 (m, 3H), 7.17 (d, *J* = 14.8 Hz, 2H), 3.55 (bs, 4H), 2.88 (m, 4H), 2.39 (s, 3H), 1.33 (s, 9H); ^{13}C NMR (DMSO-D_6, 100 MH_Z, ppm) δ 170.60, 167.17, 156.96, 138.57, 137.56, 137.19, 136.60, 134.54, 132.62, 130.70, 129.63, 129.30, 129.10, 128.08, 126.87, 126.1, 120.27, 46.58, 46.32, 44.67, 40.75, 40.54, 40.33, 40.12, 39.91, 39.70, 39.50, 35.50, 34.54, 31.32, 30.55, 19.64; Calculated MS (ESI) *m/z*: 579.2, Found, *m/z*: 580.2 $[M + H]^+$; Elemental analysis for $C_{31}H_{34}ClN_3O_4S$ calcd: C, 64.18; H, 5.91; N, 7.24; Found: C, 64.17; H, 5.88; N, 7.20.

5] (E)-4-chloro-N-(4-(3-(4-((4-chlorophenyl) sulfonyl) piperazin-1-yl)-3-oxoprop-1-en-1-yl) phenyl)-2-methylbenzamide (9e):

^{1}H NMR (400 MHz, DMSO-D_6, ppm) δ 10.51 & 10.26 (s, 1H, NH), 7.86 – 7.68 (m, 6H), 7.64 (d, *J* = 5.6 Hz, 1H), 7.53 (d, *J* = 6.4 Hz, 1H), 7.51 – 7.37 (m, 3H), 7.22 – 7.11 (m, 2H), 3.88 – 3.64 (m, 4H), 3.08 - 2.87 (m, 4H), 2.39 (s, 3H); ^{13}C NMR (DMSO-D_6, 100 MH_Z, ppm) δ 170.68, 167.57, 165.33, 142.31, 141.01, 139.08, 138.78, 136.30, 134.87, 134.61, 134.44, 134.32, 131.00, 130.85, 130.32, 130.11, 129.82, 129.71, 129.39, 129.19, 126.20, 120.38, 120.21, 116.84, 46.53, 44.81, 40.35, 40.15, 39.94, 34.57, 30.61, 19.73; Calculated MS (ESI) *m/z*: 557.1, Found, *m/z*: 558.1 $[M + H]^+$; Elemental analysis for $C_{27}H_{25}Cl_2N_3O_4S$ calcd: C, 58.07; H, 4.51; N, 7.52; Found: C, 58.01; H, 4.55; N, 7.44.

6] (E)-4-chloro-2-methyl-N-(4-(3-(4-(naphthalen-1-ylsulfonyl) piperazin-1-yl)-3-oxoprop-1-en-1-yl) phenyl) benzamide (9f):

^{1}H NMR (400 MHz, DMSO-D_6, ppm) δ 10.22 (s, 1H, NH), 8.49 (s, 1H), 8.28 – 8.16 (m, 2H), 8.07 (d, *J* = 5.6 Hz, 1H), 7.78 – 7.69 (m, 4H), 7.61 (d, *J* = 6.4 Hz, 1H), 7.56 (d, *J* = 5.6 Hz, 1H), 7.52 – 7.33 (m, 4H), 7.22 – 7.11 (d, *J* = 16.6 Hz, 2H), 3.55 (bs, 4H), 3.06 - 2.92 (m, 4H), 2.39 (s, 3H); ^{13}C NMR (DMSO-D_6, 100 MH_Z, ppm) δ 170.51, 167.40, 167.11, 165.17, 142.16, 140.88, 138.63, 138.47, 137.46, 137.10, 136.53, 136.15, 135.33, 135.19, 134.71, 134.46, 133.89, 130.84, 130.70, 130.62, 130.00, 129.67, 129.55, 129.24, 129.01, 128.05, 128.02, 126.08, 126.04, 120.18, 120.03, 116.70, 46.52, 46.27, 44.61, 40.03, 34.40, 30.47, 19.59, 19.56; Calculated MS (ESI) *m/z*: 573.1, Found, *m/z*: 574.1 $[M + H]^+$; Elemental analysis for $C_{31}H_{28}ClN_3O_4S$ calcd: C, 64.86; H, 4.92; N, 7.32; Found: C, 64.93; H, 4.87; N, 7.28.

7] (E)-4-chloro-2-methyl-N-(4-(3-(4-(methylsulfonyl) piperazin-1-yl)-3-oxoprop-1-en-1-yl) phenyl) benzamide (9g):

^{1}H NMR (400 MHz, DMSO-D_6, ppm) δ 10.50 & 10.25 (s, 1H, NH), 8.19 – 8.09 (m, 1H), 8.01 – 7.87 (m, 1H), 7.77 (d, *J* = 5.6 Hz, 1H), 7.73 (d, *J* = 6.4 Hz, 1H), 7.59 (d, *J* = 5.6 Hz, 1H), 7.54 – 7.35 (m, 3H), 7.18 (d, *J* = 14.8 Hz, 1H), 3.54 (bs, 2H), 3.11 – 2.87 (m, 4H), 2.88 (s, 3H), 2.78 (m, 2H), 2.39 (s, 3H); ^{13}C NMR (DMSO-D_6, 100 MH_Z, ppm) δ 170.61, 167.42, 165.24, 142.25, 140.88, 138.62, 138.46, 137.50, 137.11, 136.16, 134.71, 134.46, 130.90, 130.70, 130.61, 129.67, 129.55, 129.29, 129.15, 126.09, 126.05, 120.27, 120.08, 116.75, 46.02, 45.73, 44.99, 40.44,

40.23, 40.02, 39.81, 39.60, 34.63, 34.48, 30.73, 19.58, 19.55; Calculated MS (ESI) *m/z*: 461.1, Found, *m/z*: 462.1 $[M + H]^+$; Elemental analysis for $C_{22}H_{24}ClN_3O_4S$ calcd: C, 57.20; H, 5.24; N, 9.10; Found: C, 57.30; H, 5.15; N, 9.18.

8] **(E)-4-chloro-2-methyl-N-(4-(3-oxo-3-(4-(phenylsulfonyl) piperazin-1-yl) prop-1-en-1 yl) phenyl) benzamide (9h):**

^{1}H NMR (400 MHz, DMSO-D_6, ppm) δ 10.50 & 10.25 (s, 1H, NH), 8.19 – 8.09 (m, 2H), 8.01 – 7.87 (m, 2H), 7.77 (d, *J* = 5.6 Hz, 2H), 7.73 (d, *J* = 6.4 Hz, 1H), 7.59 (d, *J* = 5.6 Hz, 1H), 7.54 – 7.35 (m, 4H), 7.18 (d, *J* = 14.8 Hz, 1H), 3.54 (bs, 4H), 3.11 – 2.87 (m, 4H), 2.39 (s, 3H); ^{13}C NMR (DMSO-D_6, 100 MH_Z, ppm) δ 170.51, 167.40, 167.11, 165.17, 142.16, 140.88, 138.47, 137.46, 137.10, 136.53, 136.15, 135.33, 135.19, 134.71, 134.46, 133.89, 130.84, 130.70, 130.62, 130.00, 129.67, 129.55, 129.24, 129.01, 128.05, 128.02, 126.08, 126.04, 120.18, 120.03, 116.70, 46.52, 46.27, 44.61, 34.40, 30.47, 19.59; Calculated MS (ESI) *m/z*: 523.1, Found, *m/z*: 524.1 $[M + H]^+$; Elemental analysis for $C_{27}H_{26}ClN_3O_4S$ calcd: C, 61.66; H, 5.00; N, 6.02; Found: C, 61.71; H, 4.97; N, 6.07.

9] (E)-4-chloro-2-methyl-N-(4-(3-oxo-3-(4-((2, 4, 6-trichlorophenyl) sulfonyl) piperazin-1-yl) prop-1-en-1-yl) phenyl) benzamide (9i):

^{1}H NMR (400 MHz, DMSO-D_6, ppm) δ 10.50 & 10.25 (s, 1H, NH), 8.19 – 8.09 (m, 2H), 8.01 – 7.87 (m, 2H), 7.77 (d, *J* = 5.6 Hz, 2H), 7.73 (d, *J* = 6.4 Hz, 1H), 7.59 (d, *J* = 5.6 Hz, 2H), 7.54 – 7.35 (m, 4H), 7.18 (d, *J* = 14.8 Hz, 1H), 3.54 (bs, 2H), 3.11 – 2.87 (m, 4H), 2.78 (m, 2H), 2.39 (s, 3H); ^{13}C NMR (DMSO-D_6, 100 MH_Z, ppm) δ 170.65, 167.46, 167.18, 165.28, 156.57, 142.17, 140.90, 138.68, 138.52, 138.04, 137.51, 137.21, 136.55, 136.19, 134.77, 134.51, 133.05, 130.94, 130.74, 130.65, 129.71, 129.59, 129.28, 129.11, 127.87, 127.77, 126.09, 120.25, 120.13, 116.86, 116.31, 111.70, 57.02, 40.24, 40.03, 39.82, 30.58, 19.62; Calculated MS (ESI) *m/z*: 625.2, Found, *m/z*: 627.2 $[M + H]^+$; Elemental analysis for $C_{27}H_{23}Cl_4N_3O_4S$ calcd: C, 51.69; H, 3.70; N, 6.70; Found: C, 51.64; H, 3.70; N, 6.77.

10] (E)-4-chloro-N-(4-(3-(4-((4-methoxyphenyl) sulfonyl) piperazin-1-yl)-3-oxoprop-1-en-1-yl) phenyl)-2-methylbenzamide (9j):

^{1}H NMR (400 MHz, DMSO-D_6, ppm) δ 10.5 & 10.24 (s, 1H, NH), 7.87 – 7.73 (m, 3H), 7.79 (d, *J* = 5.6 Hz, 1H), 7.61 (d, *J* = 6.4 Hz, 2H), 7.52 – 7.33 (m, 4H), 7.27 (d, *J* = 6.4 Hz, 2H), 7.18 (d, *J* = 14.8 Hz, 1H), 3.90 (s, 3H), 3.48 (m, 4H), 3.22 – 3.17 (m, 4H), 2.38 (s, 3H); ^{13}C NMR (DMSO-D_6, 100 MH_Z, ppm) δ 170.55, 167.40, 167.12, 165.19, 142.18, 140.89, 138.64, 138.48, 137.49, 137.15, 136.54, 136.27, 136.17, 136.14, 134.72, 134.52, 134.44, 132.65, 130.88, 130.71, 130.62, 129.68, 129.57, 129.26, 129.04, 126.09, 126.05, 120.34, 120.30, 120.22, 120.06, 116.76; Calculated MS (ESI) *m/z*: 553.1, Found, *m/z*: 554.1 $[M + H]^+$; Elemental analysis for $C_{28}H_{28}ClN_3O_5S$ calcd: C, 60.70; H, 5.09; N, 7.58; Found: C, 60.77; H, 5.02; N, 7.55.

10] (E)-N-(4-(3-(4-((5-bromothiophen-2-yl) sulfonyl) piperazin-1-yl)-3-oxoprop-1-en-1-yl) phenyl)-4-chloro-2-methylbenzamide (9k):

^{1}H NMR (400 MHz, DMSO-D_6, ppm) δ 10.50 & 10.25 (s, 1H, NH), 8.19 – 8.09 (m, 2H), 8.01 – 7.87 (m, 2H), 7.77 (d, *J* = 5.6 Hz, 2H), 7.73 (d, *J* = 6.4 Hz, 1H), 7.59 (d, *J* = 5.6 Hz, 2H), 7.54 – 7.35 (m, 4H), 7.18 (d, *J* = 14.8 Hz, 1H), 3.54 (bs, 2H), 3.11 – 2.87 (m, 4H), 2.78 (m, 2H), 2.39

(s, 3H); ^{13}C NMR (DMSO-D_6, 100 MHz, ppm) δ 170.69, 167.54, 167.23, 165.33, 142.33, 141.03, 138.78, 138.63, 137.62, 137.29, 136.28, 134.85, 134.57, 132.78, 131.01, 130.84, 130.76, 129.82, 129.70, 129.39, 129.18, 126.18, 120.37, 120.19, 116.88, 46.51, 46.34, 44.59, 40.39, 40.18, 39.97, 34.59, 30.62, 19.72; Calculated MS (ESI) *m/z*: 607.1, Found, *m/z*: 609.1 $[M + H]^+$; Elemental analysis for $C_{25}H_{23}BrClN_3O_4S_2$ calcd: C, 49.31; H, 3.81; N, 6.90; Found: C, 49.30; H, 3.85; N, 6.84.

11] (E)-Methyl 3-((4-(3-(4-(4-chloro-2-methylbenzamido) phenyl) acryloyl) piperazin-1 yl) sulfonyl) benzoate (9l):

^{1}H NMR (400 MHz, DMSO-D_6, ppm) δ 10.5 & 10.24 (s, 1H, NH), 7.87 – 7.73 (m, 3H), 7.79 (d, *J* = 5.6 Hz, 1H), 7.61 (d, *J* = 6.4 Hz, 1H), 7.52 – 7.33 (m, 5H), 7.27 (d, *J* = 6.4 Hz, 2H), 7.18 (d, *J* = 14.8 Hz, 1H), 3.90 (s, 3H), 3.48 (m, 4H), 3.22 – 3.17 (m, 4H), 2.38 (s, 3H); ^{13}C NMR (DMSO-D_6, 100 MHz, ppm) δ 170.50, 167.40, 167.11, 165.44, 165.12, 142.12, 140.83, 138.60, 138.45, 137.42, 137.11, 136.50, 136.11, 135.95, 134.70, 134.44, 134.22, 132.40, 131.38, 131.36, 130.96, 130.82, 130.68, 130.59, 129.65, 129.53, 129.21, 128.99, 128.20, 126.07, 126.02, 120.18, 120.03, 116.68, 53.19, 46.42, 46.21, 44.57, 40.20, 39.99, 39.78, 19.56, 19.53; Calculated MS (ESI) *m/z*: 581.1, Found, *m/z*: 582.1 $[M + H]^+$; Elemental analysis for $C_{29}H_{28}ClN_3O_6S$ calcd: C, 59.84; H, 4.85; N, 7.22; Found: C, 59.90; H, 4.88; N, 7.24.

Biological activity:

Antimicrobial activity

All the synthesized compounds were investigated for the in vitro antimicrobial studies. The zone of inhibition corresponding to the MIC values were recorded (**Table 1 & 2**) and the results were assessed by the development of zone of inhibition in mm (Resistant: < 12mm; sensitive: 16–25mm; highly sensitive: >25mm). [26 & 27] The synthesized compounds **9a-9l** exhibit a wide range of antimicrobial activities towards Gram-positive bacteria such as *Staphylococcus aureus* (ATCC 11632, Sa), *Streptococus faecalis* (ATCC 14506, Sf), *Bacillus subtilis* (ATCC 60511, Bs) and Gram-negative bacteria such as *Klebsiella penumoniae* (ATCC 10031, Kp), *Escherichia coli* (ATCC 10536, Ec) and *Pseudomonas aeruginosa* (ATCC 10145, Pa) which are shown in table-**1.** The activities of bactericides **9a-9l** were measured by Agar-disk diffusion method. [28 & 29] for the targeted Gram-positive and Gram-negative bacteria by using ciprofloxacin and norfloxacin as the standard. The efficacy of chemical agents was assessed by the increase in the size of the zone of inhibition and represented in table-**1**.

Table-1: Antimicrobial activity of synthesized compounds **9a-9l[a]:**

S.No	Compounds*	*Gram-Positive organisms***			*Gram-Negative organisms***		
		Sa[a]	***Sf[a]***	***Bs[a]***	***Kp[a]***	***Ec[a]***	***Pa[a]***
1	**9a**	6	5	4	2	4	8
2	**9b**	8	12	12	16	10	8
3	**9c**	16	31.25	62.5	8	8	16

4	**9d**	31.25	31.25	8	31.25	4	16
5	**9e**	4	4	4	16	4	16
6	**9f**	31.25	31.25	8	31.25	8	16
7	**9g**	12	16	12	16	8	16
8	**4h**	31.25	31.25	8	31.25	4	16
9	**9i**	16	31.25	62.5	12	8	16
10	**9j**	16	12	16	8	4	2
11	**9k**	8	4	8	12	12	16
12	**9l**	16	8	8	8	4	2
Std	**Ciprofloxacin**	≤5	≤5	≤1	≤1	≤1	>5
Std	**Norfloxacin**	<5	<5	≤1	≤1	≤1	>5

*antimicrobial activity was studied at the concentrations of 0.5 mg/mL of compounds 4(a-j), ** bacteria as micro-organism, [a] Zone of inhibition (mm) by Agar-Disk method. It was noticed that the synthesized compound **9a, 9e,** and **9k** exhibited overall remarkable anti-bacterial activity towards Gram-positive bacteria such as Staphylococcus aureus (*Sa*), Streptococcus faecalis (*Sf*), and Gram-negative bacteria such as Klebsiella pneumonia (*Kp*), Pseudomonas aeruginosa (*Pa*). The compounds **9a, 9b** and **9j** were found to be more efficient bactericidal agents towards Streptococcus faecalis (*Sf*) and Bacillus subtilis (*Bs*) respectively. Interestingly, the compounds **9e** & **9k** displayed significant bactericidal activity towards Bacillus subtilis (*Bs*) and consequently moderate responses towards Klebsiella penumoniae (*Kp*), Escherichia coli (*Ec*) and Pseudomonas aeruginosa (*Pa*). The compounds **9a, 9c, 9j,** and **4l** revealed minimal antimicrobial activities towards all target micro-organisms. The target Escherichia coli (*Ec*) have shown an overall minimum response with all bactericidal agents (**9a-9l**) among synthesized compounds.

Antifungal activity

The synthesized compounds (**9a-9l)** were further investigated for the fungicidal activities towards the yeasts: Saccharo-myces cerevisiae (ATCC 9763, Sc), Candida tropicalis (ATCC 1369, Ct), Aspergillus niger (ATCC 6275, An) and the results are summarized in table-**2.**

Table-2: Antifungal activity of synthesized compound (**9a-9l)[a]:**

		Fungi		
S. No	Compounds*	*Scedosporium (Sc)*[a]	*Candida tenuis (Ct)*[a]	*Aspergillus niger (An)*[a]
1	**9a**	31.25	31.25	31.25
2	**9b**	125	16	31.25
3	**9c**	4	16	16
4	**9d**	4	16	16

5	**9e**	31.25	31.25	31.25
6	**9f**	16	4	2
7	**9g**	125	16	31.25
8	**9h**	8	16	16
9	**9i**	16	8	8
10	**9j**	8	31.25	16
11	**9k**	31.25	31.25	31.25
12	**9l**	4	16	16
Standard	Fluconazole	≤1	≤1	≤1

*antifungal activity was observed at the concentrations of 5 µg/mL of compounds 4(a-j), [a] Zone of inhibition (mm) by Agar-Disk diffusion method.

It was observed from the **Table-2** that the compounds **9a, 9e** and **9k** have shown significant antifungal efficacy with all the targets such as *Scedosporium(Sc). Candida tenuis (Ct) and Aspergillus Niger (An).* The compounds **9b** and **9g** exhibited remarkable fungicidal sensitivity over *Scedosporium (Sc).* The compounds **9b, 9f, 9g** and **9i** have shown moderate resistant towards the entire target fungi. The compounds **9c, 9d, 9h, 9j,** and **9l** were found to be low resistant across all the fungi.

Effect of substituent's and biological activities

The antimicrobial activity data incorporated in table-**1** and table-**2,** the effect of substituent's on piperazine ring linked via sulfonamide were analyzed and concluded the results. The substituent's having electron withdrawing groups in **9a, 9b, 9e,** and **9k** have shown very promising antimicrobial and antifungal activities towards all the targets. The presence of heterocyclic substituent like thiophene **9k,** and methyl **9g** were found to exhibit enhanced antibacterial and antifungal activities compared to all the other synthesized compounds. The compounds substituted with electron donating tendency like **9c, 9d, 9f, 9h, 9j** and **9l** showed lower response for all the tested strains. The derivatives bearing unsubstituted phenyl **9h** and naphthalene **9f** showed lower resonance for antibacterial and antifungal strains. The derivative bearing aliphatic substituent's like methyl **9g** showed promising antifungal and antibacterial activity. The antimicrobial activity data reveals that among the synthesized compounds **9a, 9e, 3f, 9g** and **9k** are found to be most active and potent antimicrobial agents among the series when compared with the standard. The compound **9f** as well as **9h** containing the naphthalene and phenyl moiety on the piperazine ring showed reduced antimicrobial activity. The compounds **9b, 9i,** and **9l** containing 4-bromo along with 2-methoxy, 2,4,6-trichloro, and 3methyl ester as electron withdrawing substituent's linked to piperazine ring showed intermediate antibacterial activity. The structure-activity relationship of the series can be explained as follows. The electron donating tendency of the substituent's increases the antimicrobial activity decreases and vice versa.

Conclusion:

A series of novel molecules containing substituted sulfonyl piperazine ring structure were designed and synthesized via amide and sulfonamide couplings. The structures of the synthesized compounds were elucidated and confirmed by ^{1}H NMR, ^{13}CNMR, Mass spectrum and the purity was checked through HPLC analysis. These synthesized compounds, **9a-9l** were tested for their antimicrobial activity (minimum inhibitory concentration). The results of the antimicrobial screening data revealed that most of the tested compounds showed moderate to good microbial inhibitions. The derivatives bearing electron withdrawing substituents like cyano, bromo, Chloro, methyl ester on the phenyl ring display prominent antibacterial and antifungal activity compared with standard.

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