ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 18, Issue 8, 2025

Online - 2455-3891
Print - 0974-2441

Research Article

SYNTHESIS OF 1-(3,4-BIS(BENZYLOXY)PHENYL)-2-(4(SUBSTITUTEDSULFONYL)PIPERAZIN-1-YL)ETHANONES: MOLECULAR DOCKING AND ANTIBACTERIAL PROPERTIES

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Received: 12 April 2025, Revised and Accepted: 16 June 2025

ABSTRACT

Objectives: The aim of the study was to prepare a series of piperazine sulfonamide analogs (7a-l) and to perform *in silico* and *in vitro* antibacterial studies to determine their antibacterial activity.

Methods: All the synthesized sulfonamides are characterized by different spectroscopic techniques. Further, the antibacterial screening results revealed that the synthesized sulfonamides exhibit good antibacterial activities.

Results: Among the synthesized compounds, 7c and 7f displayed noteworthy antibacterial activity. The piperazine sulfonamide 7c exhibited superior inhibition of *Enterobacter aerogenes* and *Bacillus subtilis* pathogens with minimum inhibitory concentration (MIC) values of 81±0.78 and 49±1.02 µg/mL, respectively. The molecule 7f is most effective against *E. aerogenes* and *B. subtilis* with consecutive MIC's of 86±0.58 µg/mL and 67±0.76 µg/mL. Moreover, the molecular docking studies were performed to comprehend the compounds binding interactions. Using *in silico* studies, the designed molecules were effectively screened as *Escherichia coli* deoxyribonucleic acid gyrase enzyme (PDB: 4BAE) inhibitors. The molecular docking studies for all the synthesized piperazine sulfonamide analogs (7a-l) were carried out using Maestro 11.2 and geometry optimized by Macro model program v9.1 (GLIDE, Schrodinger, LLC). In addition, to categorize the ligands accountable for the anti-bacterial activity, the molecular docking simulations were performed with software AutoDock Vina of PyRx and the Discovery studio. The obtained piperazine sulfonamide hybrids 7c and 7f gained superior molecular docking scores of −5.62 and −5.70, respectively. The structure activity relationships of the target sulfonamides were established.

Conclusion: The *in vitro* antibacterial screening outcomes revealed that the molecules 7f and 7c showed potent anti-bacterial activity and good binding energy in docking analysis.

Keywords: Piperazine, Sulfonamide, Anti-microbial, Structure activity relationship, Molecular docking, AutoDock.

 DOI: http://dx.doi.org/10.22159/ajpcr.2025v18i8.54852. Journal homepage: https://innovareacademics.in/journals/index.php/ajpcr

INTRODUCTION

Since the 20th century, antibiotics have significantly improved the management of infectious diseases. The use of antibacterial agents as a common drug in a variety of treatments has increased their use worldwide. In addition to the rapidly increasing drug resistance, the current state of bacterial infection treatments is subpar, which limits the use of various antibacterial agents. The approval of new antibiotics has been steadily declining, which has added to the ongoing threat to human health posed by bacterial resistance development [1,2]. Today, one of the biggest therapeutic challenges is resistance to the current antibacterial agents. It led to a pressing need to find novel, safe compounds with a variety of modes of action that likely target both sensitive and resistant bacterial strains simultaneously [3] and is one of the most promising strategies in antimicrobial research [4,5].

Heterocycles that contain nitrogen are essential building blocks for a variety of commercially available medications and bioactive natural products [6-8]. Piperazine derivatives exhibited extensive range of pharmacological activities such as anti-malarial [9], anticancer [10], antibacterial [11], antidepressant [12], anthelmintic [13], anticonvulsant [14], antifungal [15], and antimycobacterial [16]. This heterocycle is present in a number of well-known drugs, belonging to diverse pharmacological classes [17]. Many drug moieties with a piperazine scaffold (Fig. 1) are used to treat a variety of disorders, including trimetazidine as antianginal [18], cyclizine as antihistamine [19], and fluphenazine as antipsychotic [20]. Sulfonyl derivatives also exhibited numerous pharmacological activities such as analgesic and antitumor activities [21], anti-inflammatory [22], anticancer [23], and antidiabetic [24] activities.

Undeniably, sulfonamides represent a significant class of drugs (Fig. 2), having diverse types of pharmacological properties such as antiobesity [25], antimicrobial [26-29], antithyroid [30], anti-oxidant [31], anti-hypoglycemic [32], diuretic [33], antineuropathic pain [34], antitumor [35-36], anti-protozoal [37], and anti-inflammatory [38] activities.

The widespread chemical motifs present in the heterocyclic/aromatic/amino acid/sugar sulfonamides endowed with such capabilities is thus associated with a multitude of biological activities, and many other motifs are being frequently discovered, such as, among others: Human immunodeficiency virus (HIV) protease inhibitors [39], non-nucleoside HIV reverse transcriptase or HIV integrase inhibitors [40,41], matrix metalloproteinase and bacterial protease inhibitors [42,43], carbonic anhydrase inhibitors [44], translation initiation inhibitors [45], dual PI3K/mTOR inhibitors [46] and β-secretase inhibitors [47], 11β-HSD [48], histone deacetylase inhibitors [49], etc., additionally known to act as, 5-HT6, 5-HT7 receptor antagonists [50], A2B and CXCR3 antagonists [51]. They are also efficient for the treatment of ulcerative colitis, urinary, and ophthalmic and infections [52], rheumatoid arthritis [53], male erectile dysfunction as the phosphodiesterase-5 inhibitor sildenafil better known under its commercial name, Viagra [54]. More recently, sulfonamides are used as an anticancer

agent [55], as the antiviral HIV protease inhibitor amprenavir [56] and in Alzheimer's disease [57]. This is perhaps due to the unique features of the -SO_2NH- or -OSO_2NH-, -or $NHSO_2$NH- moieties, which can interact with a variety of biomolecules acting as therapeutic targets, including amino acid residues, metal ions, deoxyribonucleic acid (DNA), and ribonucleic acid moieties [58,59]. Moreover, sulfonamides and their isosteres are normally stable, simple to prepare and bioavailable, which may explain the need of incorporation these motifs in huge number of drugs [21-38].

Due to great biological importance of piperazine and sulfonyl derivatives and in continuation of our efforts toward the development of potent bioactive heterocycles [60-62], we have planned to synthesized hybrid derivatives of both of these moieties and their evaluation of their antibacterial properties.

EXPERIMENTAL

The chemicals have all been carried forward without additional purification; they were all bought from SRL-India, Merck, and Finar. Using a JASCO FT/IR-5300, IR spectra of potassium bromide pellets were captured. We used deuterated dimethyl sulfoxide (DMSO) as a solvent to record ^{1}H NMR spectras on a Varian 300 MHz spectrometer. Mass spectra were captured using the electro spray ionization mode on an LC-MSD-Trap-SL device. Using silica gel plates that had already been coated, thin layer chromatography was used to track each reaction (60F 254; Merck). Ten to twenty fold excess (by weight) of the crude reaction product was used for column chromatography on 100–200 mesh silica gel (SRL, India). Over anhydrous sodium sulfate, the organic extracts were dried.

Synthesis of 2-chloro-1-(3,4-dihydroxyphenyl)ethan-1-one (2)
To the stirred solution of 10 g (0.5 moL) of catechol **1** to the mixture of $AlCl_3$ (30 g, 0.25 moL) and dichloromethane (90 mL) at 0–10°C followed by gradual addition of chloroacetyl chloride (11 g, 0.1 moL) and then the reaction mixture was stirred at 50°C for 3 h. Then, after cooling to room temperature, the reaction mixture was diluted with 100 mL of water and then taken out using of ethyl acetate (3 × 100 mL). Later to obtain 2-chloro-1-(3,4-dihydroxyphenyl)ethan-1-one **(2)**, the organic layer was removed, doused with 50 mL of brine solution, dried with Na_2SO_4, filtered, and concentrated in vacuum.

White solid; Yield: 9.4 g, 92%; M.P: 184–186°C.

Synthesis of 1-(3,4-bis(benzyloxy)phenyl)-2-chloroethan-1-one (3)
To a stirred solution of 18.6 g (10 mmoL) of 2-chloro-1-(3,4-dihydroxyphenyl)ethan-1-one **2** in CH_2Cl_2 (20 mL), K_2CO_3 (27.6 g, 20 mmoL) and 13 g (10 mmoL) of benzyl chloride was added and then stirred for 3 h. Next, it was diluted with 100 mL water and extracted thrice each time with 50 mL ethyl acetate. Next, the 1*1*-(3,4-bis(benzyloxy) phenyl)-2-chloroethan-1-one **(3)** was obtained by washing the organic layer with 50 mL water and 50 mL brine solution consecutively. Then, it was taken out and dried up on Na_2SO_4, filtered and concentrated in vacuum.

White solid; Yield: 14 g, 82%; M.P: 214–216°C.

Synthesis of 1-(3,4-bis(benzyloxy)phenyl)-2-(piperazin-1-yl) ethan-1-one (5)
To a stirred solution of 10 g (27.7 mmoL) of 1-(3,4-bis(benzyloxy)phenyl)-2-chloroethan-1-one 3 in 12 g (13.90 mmoL) of piperazine, $Pd(OAc)_2$ (10 moL%, 22.4 mg), K_2CO_3 K_2CO_3 (27.6 g, 20 mmoL) was added and then heated to 100°C for 4 h. After bringing the crude mixture down to R.T, it was diluted with 50 mL water and extracted thrice each time with 50 mL ethyl acetate. Next, the 1-(3,4-bis(benzyloxy)phenyl)-2-(piperazin-1-yl) ethan-1-one (5) was obtained by washing the organic layer with 50 mL water and 50 mL brine solution consecutively. Then, it was taken out and dried up on Na_2SO_4, filtered and concentrated in vacuum.

White solid; Yield: 9.2 g, 92%; M.P: 222–224°C.

General procedure for the Synthesis of 1-(3,4-bis(benzyloxy) phenyl)-2-(4-(substitutedsulfonyl)piperazin-1-yl)ethanone (7a-j)
149 mg (0.36 mmoL) of 1-(3,4-bis(benzyloxy)phenyl)-2-(piperazin-1-yl)ethan-1-one **(5)** was solvated in 10 mL Et_3N at and added 1 mmol sulfonyl chlorides (6a-j). The overall mixture was stirred at R.T for 18 h, and then, it was quenched with H_2O and extracted thrice with 10 mL ethyl acetate. Finally, the titled molecules 7a-j were obtained after rinsing the organic with 10 mL brine solution, drying with Na_2SO_4 and concentration in vacuum.

1-(3,4-bis(phenoxymethyl)phenyl)-2-(4-(pyridin-4-ylsulfonyl)piperazin-1-yl)ethan-1-one (7a)

Pale yellow solid; Yield: 85%; M.P: 222–224 C; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 9.01(1H, d, ArN=C-H),8.8 (1H, d, ArH) 8.13 (1H, t, ArH), 7.65–7.25 (13H, m, ArH), 6.93 (1H, t, ArH), 5.22 (4H, s), 3.75 (2H, s), 3.18 (4H, t), 2.68 (4H, t); m/z (ESI–MS) 558.20 $[M+H]^+$.

1-(3,4-bis(phenoxymethyl)phenyl)-2-(4-((2-fluorophenyl)sulfonyl) piperazin-1-yl)ethan-1-one (7b)

Off white solid; Yield: 73%; M.P: 194–196°C;.^{1}H NMR (400 MHz, $CDCl_3$): 7.83–7.46(m, 4H, ArH), 7.48–7.24 (m, 12H, ArH), 6.90(1H, d, ArH), 5.21(s, 4H), 3.76 (2H, s), 3.28 (t, 4H), 2.67(d, 4H); m/z (ESI–MS) 574.1 $[M+H]^+$.

1-(3,4-bis(phenoxymethyl)phenyl)-2-(4-(ethylsulfonyl)piperazin-1-yl) ethan-1-one (7c)

Pale brown solid; Yield: 79%; M.P: 198–200°C; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.41 (m, 4H, ArH), 7.36 (m, 5H, ArH), 6.91 (1H, d, ArH), 7.6 (1H, d, ArH), 7.5 (1H, d, ArH), 5.25 (4H, s), 3.78 (2H, s), 3.3 (4H, t), 2.8 (2H, d), 2.7 (4H, t), 2.3 (1H, m), 1.19 (t,3H); m/z (ESI–MS) 509.1 $[M+H]^+$.

1-(3,4-bis(phenoxymethyl)phenyl)-2-(4-(quinolin-7-ylsulfonyl)piperazin-1-yl)ethan-1-one (7d)

Off white solid; Yield: 72%; M.P: 214–216°C; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 9.41(d, 1H, ArN=C-H), 8.8–8.3 (4H, m, ArH), 7.9 (1H, t, ArH), 7.6–7.1 (13H, m, ArH), 5.16 (4H, s), 3.9 (2H, S), 3.1 (4H, t), 2.42 (4H, d); m/z (ESI–MS) 608.3$[M+H]^+$.

1-(3,4-bis(phenoxymethyl)phenyl)-2-(4-(phenylsulfonyl)piperazin-1-yl) ethan-1-one (7e)

Pale yellow solid; Yield: 87%; M.P:176–178°C; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.81–7.65 (5H, m, ArH), 7.5 (3H, d, ArH), 7.41 (m, 4H, ArH), 7.83–7.55 (m, 5H, ArH), 6.92 (1H, d, ArH), 5.25 (4H, s), 3.8 (2H, s), 3.3 (4H, t), 2.9 (4H, t); m/z (ESI–MS) 557.27$[M+H]^+$.

1-(3,4-bis(phenoxymethyl)phenyl)-2-(4-((3-chlorophenyl)sulfonyl) piperazin-1-yl)ethan-1-one (7f)

Pale brown solid; Yield: 75%; M.P: 242–244°C; ^{1}H NMR (400 MHz, $CDCl_3$): 7.80–7.48(m, 4H, ArH), 7.49–7.26 (m, 12H, ArH), 6.91(1H, d, ArH), 5.22(s, 4H), 3.75 (2H, s), 3.26 (t, 4H), 2.65(d, 4H); ESI. MS: *m/z* 592.21 $(M+H)^+$.

1-(3,4-bis(phenoxymethyl)phenyl)-2-(4-((2-bromophenyl)sulfonyl) piperazin-1-yl)ethan-1-one (7g)

Pale pink solid; Yield: 76%; M.P: 218–220°C; 7.83–7.46 (m, 4H, ArH), 7.47–7.23 (m, 12H, ArH), 6.92(1H, d, ArH), 5.23(s, 4H), 3.78 (2H, s), 3.29 (t, 4H), 2.66(d, 4H); m/z (ESI–MS) 636.18 $[M+H]^+$.

2-(4-((4-aminophenyl)sulfonyl)piperazin-1-yl)-1-(3,4-bis(phenoxymethyl)phenyl)ethan-1-one (7h)

Off white solid; Yield: 81%; M.P: 242–244°C; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.41 (m, 4H, ArH), 7.36 (m, 6H, ArH), 6.91 (1H, d, ArH),

7.6 (1H, d, ArH), 7.5 (1H, d, ArH), 5.25 (4H, s), 3.8 (2H, s), 3.3 (4H, t), 2.8 (2H, d), 2.7 (4H, t), 2.3 (1H, m), 1.1 (s,6H); m/z (ESI–MS) 537.2[M+H]$^+$.

2-(4-((4-aminophenyl)sulfonyl)piperazin-1-yl)-1-(3,4-bis(phenoxymethyl)phenyl)ethan-1-one (7i)

Off white solid, Yield: 85%; M.P: 232–234°C.^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.24 (2H, br s), 7.70 (2H, d, ArH), 7.55 (3H, d, ArH), 7.45 (3H, d, ArH), 7.39 (d, 2H, ArH), 7.33 (m, 6H, ArH), 6.91 (1H, d, ArH), 5.22 (4H, s), 3.78 (2H, s), 3.32 (4H, t), 2.72 (4H, t); m/z (ESI–MS) 572.26 [M+H]$^+$

1-(3,4-bis(phenoxymethyl)phenyl)-2-(4-tosylpiperazin-1-yl)ethan-1-one (7j)

Off white solid; Yield: 87%; M.P: 224–226°C; δ: 7.71 (2H, d, ArH), 7.6 (3H, d, ArH), 7.5 (3H, d, ArH), 7.41(d, 2H, ArH), 7.36 (m, 6H, ArH), 6.91 (1H, d, ArH), 5.25 (4H, s), 3.8 (2H, s), 3.3 (4H, t), 2.7 (4H, t), 2.3 (3H, s); m/z (ESI–MS) 571. 24 [M+H]$^+$.

1-(3,4-bis(phenoxymethyl)phenyl)-2-(4-(methylsulfonyl)piperazin-1-yl)ethan-1-one (7k)

Off white solid; Yield: 83%; M.P: 234–236°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.62 (3H, d, ArH), 7.48 (5H, d, ArH), 7.44(m, 4H, ArH), 6.91 (1H, d, ArH), 5.23 (4H, s), 3.76 (2H, s), 3.32 (4H, t), 2.71 (4H, t), 3.43 (s, 3H); m/z (ESI–MS) 495. 21 [M+H]$^+$.

1-(3,4-bis(phenoxymethyl)phenyl)-2-(4-(m-tolylsulfonyl)piperazin-1-yl)ethan-1-one (7l)

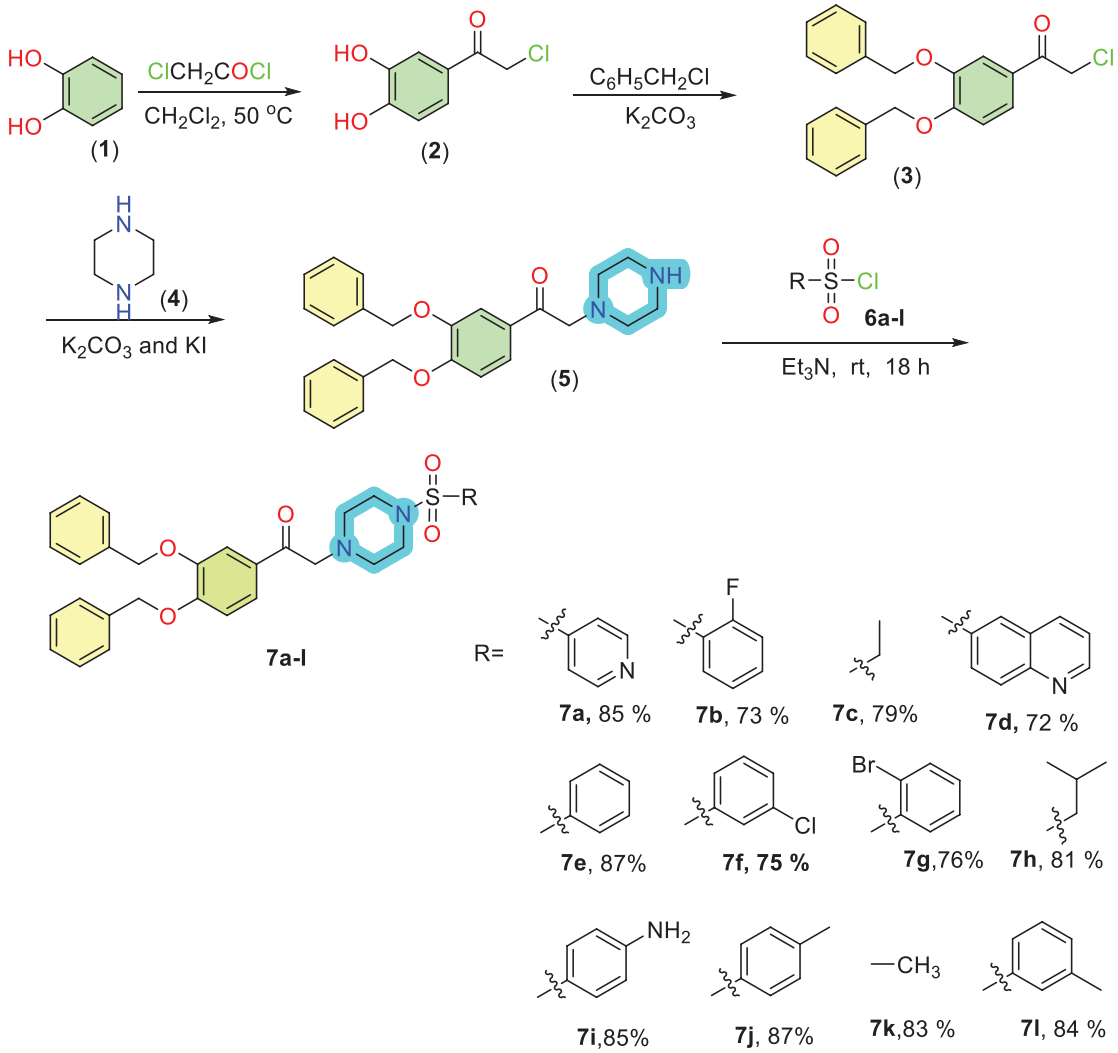
Off white solid; Yield: 84%; M.P: 254–256°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.6 (3H, d, ArH), 7.5 (3H, d, ArH), 7.41(m, 4H, ArH), 7.36(m, 6H, ArH), 6.91 (1H, d, ArH), 5.25 (4H, s), 3.8 (2H, s), 3.3 (4H, t), 2.7 (4H, t), 2.1 (3H, s); m/z (ESI–MS) 571. 27 [M+H]$^+$.

RESULTS AND DISCUSSION

Chemistry

The synthesis of 1-(3,4-bis(benzyloxy)phenyl)-2-(4-(sulfonyl) piperazin-1-yl)ethanone derivatives is carried out by the reaction of pyrocatechol (1) with 2-chloroacetyl chloride in dichloromethane at 50°C to produce 2-chloro-1-(3,4-dihydroxyphenyl)ethanone (2), this on treatment with benzyl chloride in the presence of K_2CO_3 procured the key intermediate 1-(3,4-bis(benzyloxy)phenyl)-2-chloroethanone (3). The intermediate (3) participate in on reaction with piperazine (4) in the presence of K_2CO_3/KI delivered the precursor 1-(3,4-bis(benzyloxy) phenyl)-2-(piperazin-1-yl)ethanone (5). Finally, in the presence of base Et_3N the intermediate (5) on reaction with various sulfonyl chlorides (6a-l) at room temperature for about 18 h yielded target sulfonamides 7a-l in 72–87% yields (Scheme 1).

Furthermore, in the characterization of title compound 7h, the ^{1}H-NMR spectra of the compound 7h (Scheme 1) showed proton signals at 7.41 (m, 4H, ArH), 7.36 (m, 6H, ArH), 6.91 (1H, d, ArH), 7.6 (1H, d,



Scheme 1: Synthetic route for the 1-(3,4-bis(benzyloxy)phenyl)-2-(4-(sulfonyl)piperazin-1-yl)ethanone motifs 7a-l

ArH), 7.5 (1H, d, ArH) corresponds to aromatic protons of bis phenoxy and phenyl ring of phenyl ethanone groups. The ^{1}H-NMR signals at 5.25 (4H, s) represent –O-CH_2- protons of bis phenoxymethyl group. The ^{1}H-NMR signals at 3.3 ppm (4H, t) and 2.7 ppm (4H, t) indicates –CH_2 protons of piperazine ring and signal at 3.8 (2H, s) indicates the methylenic protons (–CO-CH_2-N-). The proton signals δ 2.3 ppm (1H, m) and 1.1 ppm (s,6H) represent the isopropyl (-$CH(CH_3)_2$) group and the signal at δ 2.8 ppm (doublet, 2H) corresponds to –CH_2 group attached to sulfonyl group. The mass spectra of the compound showed a $(M+H)^+$ peak at 537.2 and corresponding to molecular formula $C_{30}H_{36}N_2O_5S$. The observed spectroscopic data characterized the title molecule 7h as 2-(4-((4-aminophenyl)sulfonyl)piperazin-1-yl)-1-(3,4-bis(phenoxymethyl)phenyl)ethan-1-one. In the same way, remaining title compounds of the series were also adequately characterized.

Anti-bacterial screening

The designed 1-(3,4-bis(benzyloxy)phenyl)-2-(4-(sulfonyl)piperazin-1-yl)ethanone derivatives (7a-l) were investigated for *in vitro* anti-bacterial properties on the Gram-negative bacterial strains *Enterobacter aerogenes*, *Pseudomonas aeruginosa*, and *Escherichia coli* and Gram-positive bacterial strains *Bacillus subtilis*, *Bacillus cereus*, and *Staphylococcus aureus* by well-diffusion method [62,63]. Ciprofloxacin was used as a standard antibacterial reference compound. The outcomes of antibacterial screening were tabulated in Table 1 with zone of inhibition.

The antibacterial screening outcomes revealed that the titled compounds 7f, 7c 7g, 7b, 7a, 7e, 7d and 7h are active on all the six bacterial pathogens examined. The titled molecules 7f and 7c exhibited potent inhibition against *E. aerogenes and P. aeruginosa and E. coli* strains with zone of inhibition values 24±0.6–18±0.9 mm. Similarly, the molecules 7f, and 7c, displayed fine inhibition on Gram-positive pathogens *S. aureus, B. cereus*, and *B. subtilis* with zone of inhibition values between with zone of inhibition values 21±1.2–19±0.8 mm. The zone of inhibition investigation reveals that compounds 7c and 7f are most potent with higher zone of inhibition values among the tested of piperazine sulfonamide derivatives (7a-l).

After evaluation of zone of inhibition values, next molecules with prominent growth inhibition zones (7c and 7f) were further investigated for their minimum inhibitory concentration (MIC) value (μg/mL) by serial dilution technique and the outcomes were presented in Table 2.

The investigation outcomes specify that many of the examined molecules exhibited erratic inhibitory properties on bacterial strain growth. The MIC was calculated from the Clinical and Laboratory Standards Institute method and guidelines (Table 2). In the present work, the MIC was evaluated for the selected most effective 7c, and 7f molecules. Compound 7f exhibited excellent inhibition against *E. aerogenes* and *B. subtilis* pathogens with MIC values of 81 μg/mL and 49 μg/mL, respectively. Moreover, the molecule 7c exhibited good activity against the *E. aerogenes* and *B. subtilis* pathogens by MIC values of 86 μg/mL and 67 μg/mL, respectively, whereas the reference drug ciprofloxacin shows the MIC values of 25 μg/mL and 17 μg/mL against the pathogens *E. aerogenes* (–) and *B. subtilis* (+), respectively, indicating that the molecules 7f and 7c are less potent than the reference streptomycin.

From the outcomes of the antibacterial investigation, it was assumed that (i) existence of halo unit –Cl unit on the third position of the phenyl ring in molecule 7f is accountable for the potent activity on the examined bacterial pathogens; (ii) the -I effect of the units on phenyl ring system is responsible for the antibacterial potency by augmenting the lipophilicity and consequently improve cell penetration rate; (iii) the ethyl group on the sulfur of the sulfonamide is responsible for the potent anti-bacterial activity of compound 7c; (iv) presence of halo units such as -Br, -F on phenyl ring is responsible for the activity of compounds 7g and 7b; (v) presence of pyridine, tolyl, and naphthyl ring is responsible for the activity of compounds 7a, 7e, and 7d, respectively.

Procedure for antibacterial activity

Every compound was dissolved at a 1 mg/mL concentration in DMSO. In sterile Mueller–Hinton medium, each one bacterial species was inoculated at 37°C for a full day to build up an inoculum. To get the turbidity to meet the 0.5 McFarland standards, the bacterial suspension was diluted with sterile saline. On sterile Mueller–Hinton agar plates, a 200 μL diluted suspension of each one pathogen was inoculated. Next, in the agar medium, wells were punched. Each compound solution was divided into 100 μL wells using a micropipette. To assess its effectiveness against the pathogenic culture, a well was additionally filled with 100 μL of DMSO solution without any compound. Then, every petri dish was incubated at 37°C for 1 day (24 h). Positive outcomes were regarded as a clear zone surrounding the well. Following the full incubation period, the produced compounds' antibacterial activity was assessed and noted the zone of inhibition in millimeters (mm).

Table 1: Antibacterial activity of the final compounds 7a-l in Zone of inhibition (mm)

Molecule	Microorganism					
	Gram (–)			Gram (+)		
	Enterobacter aerogenes (–)	*Pseudomonas aeruginosa* (–)	*Escherichia coli* (–)	*Bacillus subtilis* (+)	*Bacillus cereus* (+)	*Staphylococcus aureus* (+)
7a	12±1.5	14±1.4	12±1.7	10±1.1	11±1.2	11±0.9
7b	15±0.9	17±1.4	15±1.7	11±0.7	13±1.2	14±1.1
7c	22±0.9	21±1.1	18±0.9	21±1.2	20±1.5	19±1.2
7d	10±1.7	15±1.7	14±0.7	16±1.1	17±0.6	16±0.7
7e	12±1.1	12±1.3	10±0.6	11±1.1	09±1.1	09±0.6
7f	24±0.6	21±1.6	19±0.9	20±1.4	19±0.8	19±1.9
7g	19±1.8	18±1.7	16±1.4	17±1.7	18±1.7	16±1.2
7h	10±1.1	13±1.8	11±0.7	10±1.8	14±1.1	12±0.8
7i	10±0.2	–	11±1.2	–	15±1.2	10±0.5
7j	10±0.6	12±0.6	–	10±1.1	–	11±1.1
7k	10±0.8	–	11±1.4	10±0.7	17±1.7	–
7l	10±0.4	–	10±0.3	–	–	10±0.2
Ciprofloxacin	29±1.8	23±3.1	25±2.3	23±3.7	24±3.1	21±3.2

–: No inhibition; Zone of inhibition diameter is presented in mm, Mean±Standard deviation of three replicates was expressed as results

Molecular docking

Further, molecular docking studies for all the newly synthesized hybrids were carried out using Maestro 11.2 and geometry optimized by the Macro model program v9.1 (GLIDE, Schrodinger, LLC) [64]. The X-ray crystal structure of DNA Gyrase B subunit (PDB ID: 4BAE) derived from *E. coli* in complex with co-crystalized ligand (2-[(3S,4R)-4-[(3-bromanyl-4-chloranyl-5-methyl-1H-pyrrol-2-yl) carbonylamino]-3-methoxy-piperidin-1-yl]-4-(2-methyl-1,2,4-triazol-3-yl)-1,3-thiazole-5-arboxylic acid)obtained from the Protein Data Bank (PDB) was used to model the protein structure in this study.

Next, the crystallized water molecules were removed from the complex, and the protein was optimized for docking using the protein preparation and refinement utility provided by Schrodinger LLC. Partial atomic charges were assigned according to the OPLS_2005 force field. The PDB structure 4BAE bound to the inhibitor represents an accurate binding site. An essential feature of the binding site is the conservation of hydrogen bonding and the aromatic π-π stacking interactions. Hence, to identify other residual interactions of the tested compounds, a grid box (including residues within a 10.0 Å radius) large enough to accommodate the active site was constructed. The 2D structures of the synthesized hybrids were converted to energy-minimized 3D structures and used for *in silico* protein-ligand docking calculations.

Table 2: MIC values of most potent titled compounds (µg/mL)

Entry	*Enterobacter aerogenes* (−)	*Bacillus subtilis* (+)
7c	81±0.78	49±1.02
7f	86±0.58	67±0.76
Ciprofloxacin	25±1.20	17±0.79

Docking evaluation of synthesized compounds with the *E. coli* DNA gyrase enzyme displayed well-conserved hydrogen bonds with one or more amino acid residues of the active pocket. Table 3 represents the docking scores of the synthesized compound and also reference drug ciprofloxacin. Compound 7f presented the best docking score (−5.70) and glide energy (−53.16) and compound 7c displayed its docking score (−5.62) and glide energy (−59.80), whereas the reference drug displayed the docking score (−5.43) and glide energy (−37.23). A comparison of the different docking poses of the compounds suggests that these compounds adopt similar binding modes with the H-bonding network. Fig. 3 shows a docked model of the reference drug. Fig. 4 represents the compounds 7f and 7c into the active site of DNA gyrase. The phenyl ring binds in the active catalytic site through hydrogen bonds. The phenyl ring of both compounds reported one hydrogen bonds with ARG 82 (d1=2.02 Å). The molecular docking investigation of these compounds exposed conserved hydrogen bonding with the residues ARG82 which is essential for inhibiting *E. coli* DNA gyrase B. These results provide strong evidence that the novel sulfonamide hybrids play a vital role in binding, leading to effective inhibition of *E. coli* DNA gyrase B.

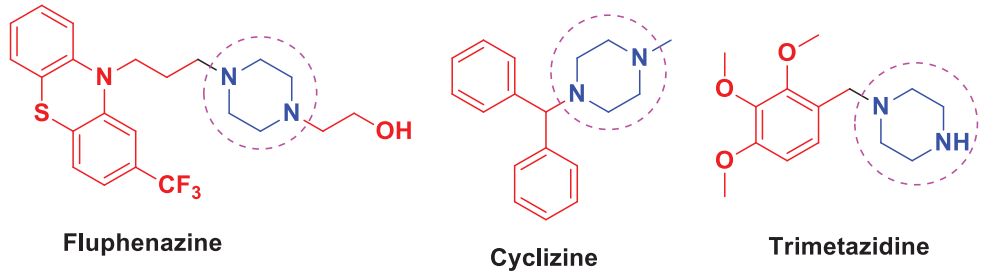


Fig. 1: Various drugs with piperazine scaffold

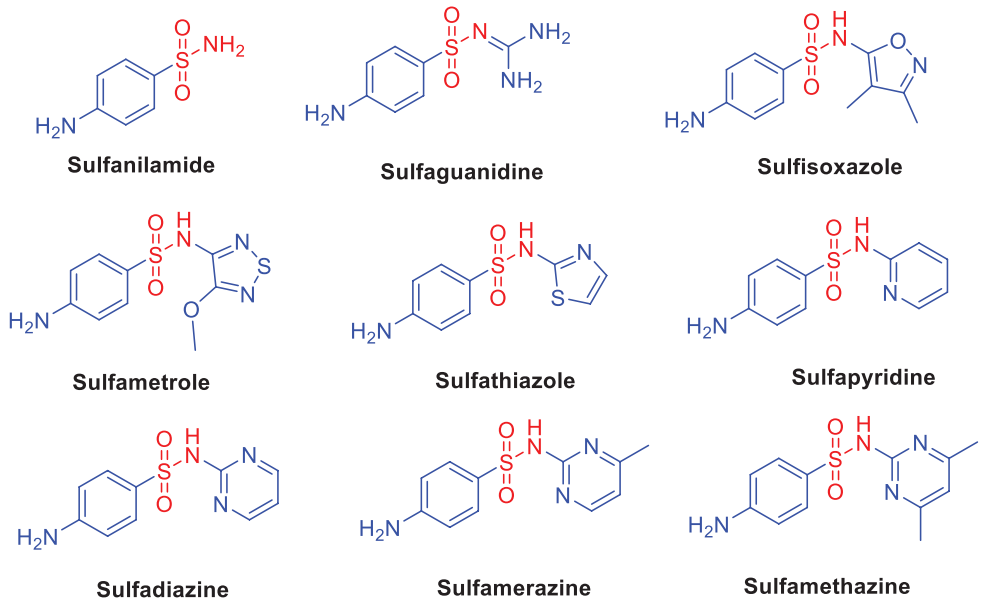


Fig. 2: Structure of several sulfonamide antimicrobial drugs [38]

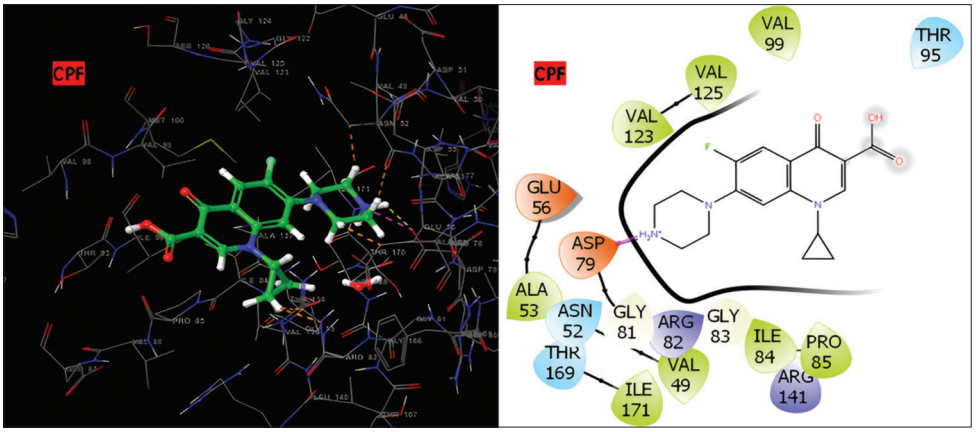


Fig. 3: 2D representation of the complex between the reference drug ciprofloxacin and the protein

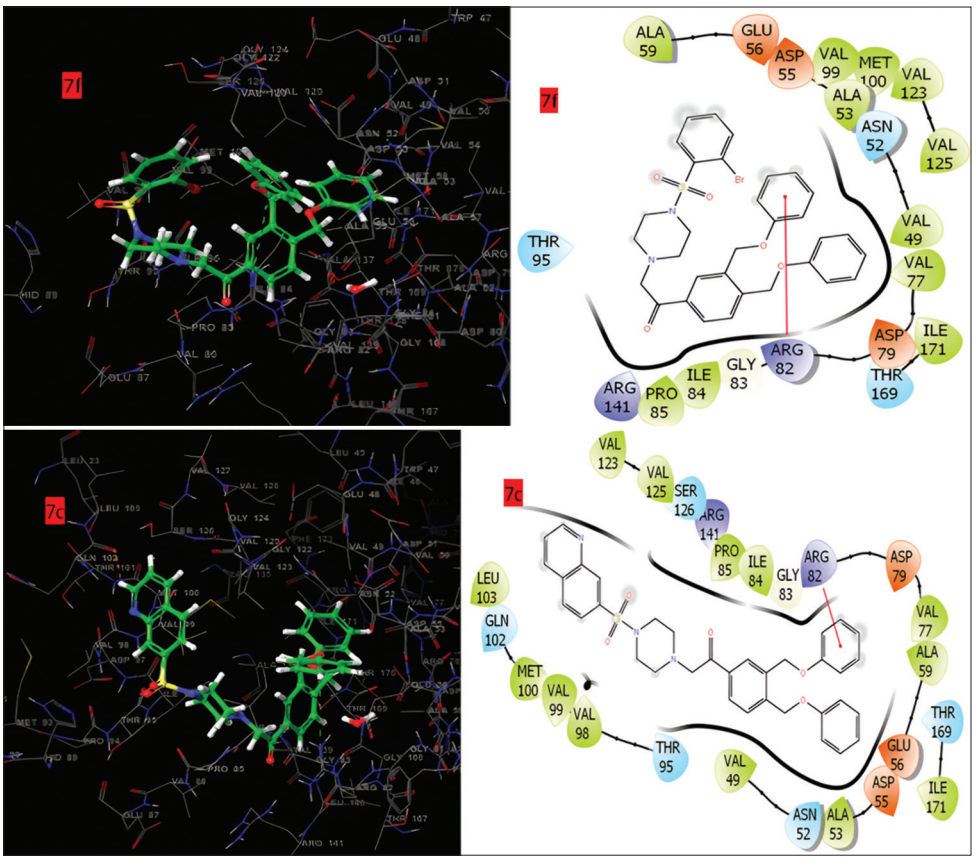


Fig. 4: 2D representation of the complex between the highest binding score ligands 7f and 7c. The binding mode of compounds in the adenosine triphosphate binding site of *Escherichia coli* DNA gyrase B. Hydrogen bonds are indicated as red dotted lines

Table 3: Molecular docking scores for newly synthesized title compounds 7a-j

Compound	Docking score	Glide energy
7a	−5.22	−56.05
7b	−5.32	−50.36
7c	−5.62	−59.80
7d	−4.66	−48.53
7e	−5.04	−52.76
7f	−5.70	−53.16
7g	−5.49	−52.70
7h	−4.49	−48.62
7i	−4.31	−48.36
7j	−4.42	−49.56
7k	−4.38	−48.61
7l	−4.26	−47.89
Ciprofloxacin (Reference)	−5.43	−37.23

CONCLUSION

A series of new 1-(3,4-bis(benzyloxy)phenyl)-2-(4-(sulfonyl) piperazin-1-yl)ethanone motif derivatives 7a-l have been synthesized and evaluated for antibacterial properties. The *in vitro* antibacterial screening outcomes revealed that the molecules 7f and 7c inhibited the majority antibacterial growth of all the tested pathogens. Further, the docking analysis indicated that compounds 7f and 7c showed the highest binding energy. The *in silico* docking scores are in good correlation with the *in vitro* MIC values of the prepared molecules. As a result, medicinal chemists who work with antibacterial agents should consider the synthesized piperazine sulfonamide scaffolds as a potential, favorable alternative. However, further lead optimization is needed to get a wide spectrum of activity.

ACKNOWLEDGMENTS

The authors are thankful to Shri Venkateshwara University, Gajraula, Amroha, Uttar Pradesh, India, for constant support and encouragement.

AUTHOR'S CONTRIBUTION

The manuscript was written through contributions from all the authors. The authors have given approval to the final version of the manuscript. Durgarao Kantheti: Conceptualization, investigation, methodology, validation, writing; Pawanjeet Kaur: Formal analysis, visualization; writing-review and editing, supervision; SN Murthy Boddapati: Conceptualization, Writing-review, Molecular Docking.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

AUTHOR'S FUNDING

There is no author funding.

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