SYNTHESIS, CHARACTERIZATION AND IN-VITRO ANTIMICROBIAL STUDY OF SERIES OF 1-((SUBSTITUTED ARYL/ALKYL)SULFONYL)-4-TOSYLPIPERAZINES

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ARTICLE INFO

ABSTRACT

A new series of bis-sulfonl piperazines were taken up for synthesis by inserting two sulfonl groups at 1st and 4th position of piperazine in search of potent antimicrobial agents. An imperative intermediate 1-tosylpiperazine was accomplished through deprotection of di-tert-butyl dicarbonate group from 4-tosylpiperazine-1-carboxylate by using trifluoroacetic acid. Further 1-tosylpiperazine upon electrophilic substitution reaction using appropriate substituted sulfonyl chlorides gave 1-((substituted aryl/alkyl)sulfonyl)-4-tosylpiperazines 8a-k as targeted series of bis-sulfonl piperazines. The design, synthesis, FT-IR, ¹H NMR, ¹³C NMR, LC-MS spectral characterizations, elemental analysis and their in-vitro antimicrobial potency is discussed in this communication. Compounds 8f, 8j and 8k are proved to be potent antimicrobial agents.

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Please cite this article in press as Mohan N R et al., Synthesis, characterization and in-vitro antimicrobial study of series of 1-((substituted aryl/alkyl)sulfonyl)-4-tosylpiperazines. Indo American Journal of Pharm Research. 2013:3(12).
INTRODUCTION

In the field of chemotherapeutic drug discovery, search for novel, potent, selective and less toxic compounds is still very intense. Sulfonamides have been an important class of functionality which has been integrated with wide range of aromatic and heterocycles for their biological importance.[1-3] In combination with certain heterocycles sulfonamides are used for the treatment of various infectious diseases. Because of piperazine structural rigidity and attractive pharmacological results, it is evident that they are ideal scaffold in several proven drugs successful in the market. Biological study of various heterocycles possessing piperazine and sulfonamide as one of the functionality and their synchronized performance is of considerable interest in research.[4,] Derivatives with these functionalists alone are known to possess vital biological activities such as anticancer,[5,6,7] antidepressant,[8] antipsychotic,[8] antibacterial,[9] antifungal,[10] anti-inflammatory,[11] antidiabetic,[12] and anthelmintic[13] activities and additionally known to act as 5-HT₆[14] A2B and CXCR3 antagonists,[15, 16] 11β-HSD,[17] histone deacetylase (HDAC) inhibitor,[18] β-secretase (BACE1) inhibitor[19] and dual PI3K/mTOR inhibitor[20].

Despite of major efforts to improve the mode of action of sulfonamides in modern medications, over the time sulfonamides have remained to be bacteriostatic in nature. Along with this most of the classical antimicrobial sulfa drugs are of mono-sulfonyl group and are proven to be potent agents and an attractive target of modern day organic synthesis. Encouraged by these findings, we designed to achieve bis-sulfonyl substituted piperazine derivatives and examined their antifungal activity against Chrysosporium indicum, Microsporum gypseum, Trichophyton equinum, and Candida albicans fungal strains and antibacterial activity against Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa bacterial strains. Out of all the compounds screened for antimicrobial activity compounds 8f, 8j and 8k were proved to be potent pharmacophores.

MATERIALS AND METHODS

All the chemicals were purchased from Aldrich, Spectrochem, SD Fine chemicals and were used without further purification. Melting points (mp) were established using open capillary tubes and are uncorrected. Purification of the newly synthesized substituted sulfonyl-4-tosylpiperazine derivatives was carried out by column chromatography using silica gel 60-120 mesh size and petroleum ether/ethyl acetate (7:3) as solvent system. Nuclear magnetic resonance spectra were acquired at 400 MHz for ¹H-NMR, and 100 MHz for ¹³C-NMR on JEOL ECX NMR spectrometer using CDCl₃ as solvent and tetramethylsilane (TMS) as internal standard. Chemical shifts were expressed in δ ppm and are abbreviated as s = singlet, d = doublet, dd = doublet of doublet, t = triplet and m = multiplet. Infrared spectra were recorded on Jasco FT-IR spectrometer using KBr pellet. Reactions were monitored on thin layer chromatography (TLC) using precoated silica gel plates (Merck Kiesel gel 60F254, layer thickness 0.25 mm). LC-MS chromatogram was recorded on Waters Alliance 2795 separations module and Waters Micromass LCT mass detector.

Experimental

Scheme: Reagents and conditions: a) = MDC, 0 °C, r.t, 5h; b) = TEA / MDC, Δ, 2h; c)= TFA / EDC, Δ, 8h; d) = TEA/MDC, Δ, 2h

Synthesis of tert-butyl piperazine-1-carboxylate (3)

A mixture of piperazine (10 mM, 0.86 g) 1 was taken in 10 mL dichloromethane. To this reaction mixture di-tert-butyl dicarbonate (5 mM, 1.1 mL) 2 was added and stirred for 5 hours at room temperature. Reaction was monitored by thin layer chromatography, after the completion of reaction acetonitrile was removed under reduced pressure. Crude solid obtained was dissolved in methylene dichloride; organic layer was washed with water and then with brine solution, further dried over anhydrous sodium sulphate. Solvent was removed under reduced pressure and crude tert-Butyl piperazine-1-carboxylate 3 obtained was purified using neutral alumina column, (7:3) petroleum ether / ethyl acetate as eluent and yield obtained was about 44%, the structure was well
established and matched with the literature [21]. MP: 46-48 °C. 1H NMR, δ ppm: 8.91 (s, 1H, NH), 3.75-3.8 (m, 4H, CH2), 3.67-3.69 (m, 4H, NCH2), 1.3 (s, 9H, 3CH3). 13C NMR, δ ppm: 154.0, 79.8, 51.1 (2C), 47.1 (2C), 28.4 (3C). LCMS: 187.3 (M+1)

Synthesis of tert-butyl 4-tosylpiperazine-1-carboxylate (5)

Synthesis was carried out with reference to literature,[22] tert-Butyl piperazine-1-carboxylate (10 mM, 1.862 g) 3 in dichloromethane 10 mL. was taken in round bottom flask and cooled to 0 °C, triethylamine (30 mM, 4.184 mL) was added under stirring at 0 °C. To this mixture 4-methylbenzene-1-sulfonyl chloride (10 mM, 1.722 g) 4 was added and stirring was continued for 2 hours at room temperature, completion of the reaction was monitored by thin layer chromatography (TLC). Reaction mixture was diluted with dichloromethane and quenched with ice cold water. Organic layer was separated, washed with brine solution and dried over anhydrous sodium sulphate and concentrated to obtain crude tert-butyl 4-tosylpiperazine-1-carboxylate 5. Crude compound was purified by column chromatography using silica gel 60-120 mesh size and (7:3) petroleum ether / ethyl acetate as a eluent. mp: 210 – 213°C. 1H NMR, δ ppm: 7.64-7.62 (d, 2H, Ar-H, = 8.29 Hz), 7.34-7.32 (d, 2H, Ar-H, = 8.17), 3.51-3.48 (t, 4H, H2C-N-CH2), 2.97-2.94 (t, 4H, H2C-N-CH2), 2.43 (s, 3H, CH3), 1.40 (s, 9H, C(CH3)3). 13C NMR, δ: 153.87, 143.68, 132.21, 129.56 (2C), 127.53 (2C), 80.01, 45.65 (2C), 43.40 (2C), 28.04 (3C), 21.27. LCMS: 341 (M+1) peak

Synthesis of 1-tosylpiperazine (6)

tert-butyl 4-tosylpiperazine-1-carboxylate (10 mM, 2 g) 5 was taken in ethylene dichloride (10 mL) and the reaction mixture was cooled to 0 °C, to this reaction mixture trifluoroacetic acid (80 mM, 6.121 mL) was added and stirred at room temperature for 8 hours. Reaction was monitored for completion by TLC. Excess trifluoroacetic acid and ethylene dichloride were removed under reduced pressure. Without purification crude 1-tosylpiperazine 6 was taken for next step. The crude product was found to be brown gummy and the yield obtained was about 96%. mp: 244-246°C according to the literature [23]; 1H NMR, δ ppm: 8.94 (s, 1H, N-H) 7.66-7.64 (d, 2H, Ar-H, = 8.29 H2), 7.49-7.47 (d, 2H, H Ar, = 8.29), 3.18-3.17 (t, 4H, H2C-N-CH2), 2.40-2.40 (s, 3H, CH3). 13C NMR, δ ppm: 144.46 (C2), 131.36 (C12), 130.13 (C1b, C11), 127.86 (C5, C9), 40.31 (C2, C6), 34.17 (C3, C5), 20.99 (C13). LCMS: 241 (M+1) peak

General procedure for the synthesis of 1-((substituted aryl/alkyl)sulfonyl)-4-tosylpiperazines (8a-k)

An equimolar mixture of 1-tosylpiperazine 6 (10 mM, 2.403 g) and appropriate substituted sulfonyl chlorides 7a-k (10 mM) along with triethylamine (Et3N) (30 mM, 4.18 mL) in ethylene dichloride (5 mL) was refluxed for 3 hours. Reaction mixture was cooled to room temperature diluted with ethylene dichloride and washed with water. Organic layer separated was dried over sodium sulphate and concentrated to get crude compounds 8a-k. Crude compound obtained was further purified by column chromatography using petroleum ether: ethyl acetate (7:3) as eluent to get the pure 1-((Substituted Aryl/Alkyl)Sulfonyl)-4-Tosylpiperazine derivatives 8a-k in good yield Table 1.

1-(methylsulfonyl)-4-tosylpiperazine (8a)

1H NMR (400 MHz, CDCl3) δ ppm: 7.64 (d, J = 6.19 Hz, 2H, Ar-H); 7.43 (d, J = 0.7 Hz, 2H, Ar-H); 3.27 (t, 4H, H2C-N-CH2), 2.93 (s, 3H, S-CH3), 2.56 (t, 4H, H2C-N-CH2), 2.39 (s, 3H, Ar-CH3).

1-((4,4-dichlorophenyl)sulfonyl)-4-tosylpiperazine (8b)

1H NMR (400 MHz, CDCl3) δ ppm: 7.90 (s, 1H, Ar-H); 7.75 (d, J = 0.7 Hz, 3H, Ar-H); 7.50 (dd, J = 7.9 Hz and 1.5 Hz, 1H, Ar-H); 7.44 (d, J = 1.5 Hz, 2H, Ar-H); 3.75 (t, 4H, H2C-N-CH2), 3.63 (t, 4H, H2C-N-CH2), 2.39 (s, 3H, Ar-CH3).

1-((3,3-dichlorophenyl)sulfonyl)-4-tosylpiperazine (8c)

1H NMR (400 MHz, CDCl3) δ ppm: 7.74-7.65 (m, 4H, Ar-H); 7.57 (t, 1H, Ar-H); 7.42 (d, J = 7.99 Hz, 2H, Ar-H); 3.48 (t, 4H, H2C-N-CH2); 3.40 (t, 4H, H2C-N-CH2), 2.45 (s, 3H, Ar-CH3).

1-((2,6-dichlorophenyl)sulfonyl)-4-tosylpiperazine (8d)

IR: vmax/cm⁻¹: C=H: 2920.6 cm⁻¹, C=C: 1424.1 cm⁻¹, S=O: 1345.1 cm⁻¹ (Asymmetric), 1171.5 cm⁻¹ (Symmetric). 1H NMR (400 MHz, CDCl3) δ ppm: 7.64 (d, J = 5.5 Hz, 2H, Ar-H); 7.46 (d, J = 0.7 Hz, 2H, Ar-H); 7.39 - 7.30 (m, 3H, Ar-H); 3.52 (t, 4H, H2C-N-CH2); 3.11 (t, 4H, H2C-N-CH2), 2.45 (s, 3H, Ar-CH3). 13C NMR (100 MHz, CDCl3) δ ppm: 144.18, 135.41, 134.44, 132.73, 132.20, 131.68, 129.86 (2C), 129.59 (4C), 45.97 (2C), 45.34 (2C). CHNS (Calculated, Found): C% 45.44 (45.45), H% 4.04 (4.05), N% 6.23 (6.24), S% 14.27 (14.28). LCMS (M+1): 450.3

1-((3-fluoro-4-methylphenyl)sulfonyl)-4-tosylpiperazine (8e)

IR: vmax/cm⁻¹: C=H: 2917.8 cm⁻¹, C=C: 1430.5 cm⁻¹, S=O: 1333.2 cm⁻¹ (Asymmetric), 1161.3 cm⁻¹ (Symmetric). 1H NMR (400 MHz, CDCl3) δ ppm: 7.64 (d, J = 8.7 Hz, 2H, Ar-H); 7.41 - 7.33 (m, 5H, Ar-H); 3.78 (t, 4H, H2C-N-CH2); 3.31 (t, 4H, H2C-N-CH2), 2.45 (s, 3H, Ar-CH3), 2.37 (s, 3H, Ar-CH3). 13C NMR (100 MHz, CDCl3) δ ppm: 161.61, 143.13, 138.42, 137.1, 130.76, 129.54 (2C), 128.17 (2C), 127.01, 124.04, 113.60, 45.62 (2C), 45.33 (2C), 21.56, 14.52. CHNS (Calculated, Found): C% 52.41 (52.41), H% 4.61 (4.62), N% 6.79 (6.81), S% 15.55 (15.48). LCMS (M+1): 413.1

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1-((fluorosulfonyl)-4-tosylpiperezine (8f)

$^1$H NMR (400 MHz, CDCl$_3$) δ ppm: 7.95 (d, J = 1.9 Hz, 2H, Ar-H); 7.79 (d, J = 1.5 Hz, 2H, Ar-H); 7.45 – 7.41 (m, 4H, Ar-H); 3.73 (t, 4H, H$_2$C-N-CH$_2$); 3.39 (t, 4H, H$_2$C-N-CH$_2$); 2.48 (s, 3H, Ar-CH$_3$).

5-methyl-1-(4-(tosylperazin-1-yl)sulfonyl)isoxazole (8h)

$^1$H NMR (400 MHz, CDCl$_3$) δ ppm: 8.10 (s, 1H, Isoxazole proton), 7.78 (d, J = 7.9, 2H, Ar-H), 7.52 (d, J = 1.5 Hz, 2H, Ar-H), 3.43 (t, 4H, CH$_2$-N-CH$_2$), 3.25 (s, 3H, Isoxazole-CH$_3$), 3.17 (t, 4H, CH$_2$-N-CH$_2$), 2.47 (s, 3H, Ar-CH$_3$).

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Table 1: Physical and analytical data

In vitro Antimicrobial Activity

Antifungal Activity:

_Invitro_ antifungal study of 8a-k was carried out on different fungal strains Chrysosporium indicum (MTCC-4266), Microsporum gypseum (MTCC-2157), Trichophyton equinum (ATCC-6275), and Candida albicans (ATCC-10231), which were procured from Institute of Microbial Technology (IMTECH), Chandigarh, India. Fungi cultures were prepared on fresh potato dextrose agar media and stored at 4°C. Testing was done by adopting agar well diffusion technique.[24] The fungal spore suspension was prepared by taking a loop full of spores in 6 mL solution of sterilized distilled water and Tween 20 in 5:1 ratio. Then fungal spore suspension was spread evenly on the sterile petri plate containing 20 mL of solidified potato dextrose agar. Four wells of equal diameter were bored by using sterile cork borer of 6 mm diameter with a capacity of holding 50 µL volumes in each well. Samples were loaded in to the wells using sterile micropipette tips in 2 different concentrations i.e., 250 µg/50mL and 500µg/50µL dimethyl sulfoxide (DMSO) a negative control respectively, which showed no zone of inhibition and Ketoconazole(10µg/50µL) a positive control (standard) purchased from Himedia, Mumbai. Concentrations of 250 and 500 µg/50 µL in different wells were used to measure the dose dependent activity. Plates were incubated at 25°C, zone of inhibition was measured in mm after 5 days of incubation.
After the incubation period, the diameter of the zone of inhibition of each well was measured in mm; tests were conducted in triplicates to achieve concordant results which are illustrated in Figure 1 and Figure 2 for the two different concentrations.

Antibacterial Activity:

*In vitro* antibacterial activity of 8a-k was studied against *Staphylococcus aureus* (NCIM-5022), *Escherichia coli* (NCIM-5051), *Pseudomonas aeruginosa* (NCIM-2242) Gram positive and Gram negative bacterial strains respectively. Bacterial strains for the study were procured from CSIR-National Chemical Laboratory (NCL) Pune. Agar well diffusion technique was incorporated for the study.[25] bacterial broth cultures were incubated for 24 hours and were uniformly smeared on sterilized nutrient agar medium in petri plates using sterile L-Shaped glass rod. Four uniform wells with 6 mm diameter were bored using cork borer to accommodate 50 µL of volumes in each well. Samples were dissolved in DMSO a negative control which showed no zone of inhibition and Ciprofloxacin (5µg/50µL) was taken as standard drug a positive control procured from Himedia, Mumbai. Concentrations of 200 and 400 µg/50 µL in different wells were used to assess the dose dependent activity. Plates were incubated at 37 °C for 36 hours. After the incubation period, the diameter of the zone of inhibition of each well was measured in mm, the experiment was performed in triplicates and the average values which are illustrated in Figure 3 and Figure 4.

RESULTS AND DISCUSSION

Synthesis of 1-((substituted aryl/alkyl)sulfonyl)-4-tosylpiperazines 8a-k was carried out as described in Scheme. Initial tert-butyl piperazine-1-carboxylate (N-BOC piperazine) 3 was prepared by reacting piperazine 1 with di-tert-butyl dicarbonate 2, in presence of dichloromethane and nitrogen atmosphere. Reacting N-BOC piperazine 3 with 4-methylbenzene-1-sulfonyl chloride 4 in dichloromethane using base triethylamine yielded 4-tosylpiperazine-1-carboxylate 5 in good yield. Deprotection of BOC group of 4-tosylpiperazine-1-carboxylate 5 was achieved by refluxing it with trifluoroacetic acid to obtain 1-tosylpiperazine 6 as a key intermediate for our final step, compound 6 was treated with appropriate substituted aryl/alkyl/heterosulfonyl chlorides 7a-k to get 1-((Substituted Aryl/Alkyl) Sulfonyl)-4-Tosylpiperazines 8a-k in good yield as given in Table 1. All the synthesized derivatives 8a-k has proven to be potent antibacterial and antifungal agents.

Initial examination of antifungal activity results showed that all tested compounds 8a-k exhibited no activity against *C. indicum* fungal strain. Moderated activity against *M. gypseum* and showed significant activity against *T. equinum*. Further the compounds were screened at higher concentrations (250µg/50µLand 500µg/50µL). Minimum Inhibitory Concentrations (MIC) obtained from micro dilution method for *T. equinum* and *C. albicans* were 100µg and 210 µg respectively.

**Figure 1: Zone of Inhibition results of 8a-kat 250 µg/ 50µL concentration, Keto: Ketoconazole**

Compounds 8c, 8e, 8f and 8k were found to be less active against *M. gypseum* and remaining all the compounds 8a-k showed moderate activity against *T. equinum* and *C. albicans* compared to standard drug ketoconazole respectively at 250µg/50µL concentration (Figure 1).

**Figure 2: Zone of Inhibition results of 8a-kat 500 µg/50µL concentration, Keto: Ketoconazole**

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Compounds tested for activity at 500µg/50µL concentration 8d was found to be less active, compounds 8c, 8e and 8f were moderately active and 8k showed significant activity against M. gypseum and compounds 8a-ε, 8g, 8h, 8i and 8k showed moderate activity against T. equinum and C. albicans compounds 8f and 8j showed significant activity against T. equinum compared to standard drug ketoconazole respectively (Figure 2).

Investigation of antibacterial screening data initially revealed tested compounds 8a-k were inactive against S. aureus but moderate to significant activity was observed against E. coli and P. aeruginosa. Furthermore compounds were screened at higher concentrations (200µg/µL and 400µg/µL). The Minimum Inhibitory Concentrations (MIC) assessed for compounds 8a-k against P. aeruginosa and E. coli is 85µg and 110µg respectively which were obtained by micro dilution method.

**Figure 3:** Zone of Inhibition results of 8a-kat 200 µg/ 50µl concentration, Cipro: Ciprofloxacin

Compounds tested at 200µg/50µL concentration 8a, 8d and 8h / 8a, 8c, 8e and 8g were found to be less active against P. aeruginosa and E. coli. Compounds 8c, 8e, 8g and 8i / 8b, 8d, 8h and 8i were found to be moderately active against P. aeruginosa and E. coli. Compounds 8b, 8f, 8j and 8k / 8f, 8j and 8k showed significant activity against P. aeruginosa and E. coli compared to standard drug ciprofloxacin respectively (Figure 3).

**Figure 4:** Zone of Inhibition results of 8a-kat 400 µg/ 50µl concentration, Cipro: Ciprofloxacin

Compounds tested at 400µg/50µL concentration 8e and 8h / 8a, 8c, 8d, 8e and 8g were found to be less potent against P. aeruginosa and E. coli. Compounds 8a, 8c, 8d, 8g and 8i / 8b, 8h and 8i were found to be moderately potent against P. aeruginosa and E. coli respectively. Compounds 8b, 8f, 8j and 8k / 8f, 8j and 8k showed significant activity against P. aeruginosa and E. coli compared to standard drug ciprofloxacin respectively (Figure 4).

**CONCLUSION**

Synthesis of 1-((substituted aryl/alkyl)sulfonyl)-4-tosylpiperazines by synchronizing piperazine and sulfonyl moiety resulted in potent antifungal and antibacterial agents. Compounds 8f, 8j and 8k proven to be potent antimicrobial pharmacophores. Anti-inflammatory and analgesic activities of these potent molecules are under study for these molecules, functional group modifications and detailed toxicity studies will be taken up in future.

**ACKNOWLEDGMENTS**

The authors thank Tumkur University for providing laboratory facilities. Authors thank Sri Siddaganga college of Pharmacy for biological studies and Sapala Organics Private Limited for spectral data.

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List of abbreviations

- 13C NMR: Carbon-13 Nuclear Magnetic Resonance Spectrometry
- BOC: Di-tert-butyl dicarbonate
- DMSO: Dimethyl Sulfoxide
- FT-IR: Fourier Transform Infrared Spectroscopy
- HDAC: Histone Deacetylase
- LC-MS: Liquid Chromatography–Mass Spectrometry
- MDC: Methylene Dichloride
- MIC: Minimum Inhibitory Concentrations
- 1H NMR: Proton Nuclear Magnetic Resonance Spectrometry
- TMS: Tetramethylsilane
- TLC: Thin Layer Chromatography
- Et3N: Triethylamine

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