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Original Research Article

# Synthesis, characterization and pharmacological evaluation of certain sulfonamide containing heterocyclic motifs

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ABSTRACT

*Introduction:* Heterocycles containing nitrogen, oxygen and sulphur have diverse and exceptional therapeutical and industrial significance. Particularly sulfonamides containing pyrrolidine and thiophene moieties constitute an important class of drugs and display a variety of pharmacological activities.

*Aim:* To design, synthesize and characterize substituted sulfonamides and evaluate their *in vitro* antimicrobial activity and *in silico* HMG-CoA reductase inhibitory activity.

*Material and methods:* The synthetic investigations have been well supported by elemental analysis data and standard modern spectroscopic techniques. The compounds were evaluated for their *in vitro* antimicrobial activity against *Staphylococcus aureus* NCCS 2079, *Bacillus cereus* NCCS 2106, *Escherichia coli* NCCS 2065, *Aspergillus niger* NCCS 1196 and *Candida albicans* NCCS 2106. *In silico* studies were done against 3VKK (PDB Id). Pharmacophore mapping studies were reported to analyze the important pharmacophore features and to predict the quantitative structure-activity relationship.

*Results and discussion:* The antibacterial activity data revealed that compounds of 8 series were more active than the compounds of 7 series followed by compounds of series 6. *In silico* studies revealed that HMG-CoA reductase inhibitory activity of these drugs is of the order 'a > b > c > d > e > f'.

*Conclusions:* Antibacterial activity studies indicate that nitro and halo substituted sulfonamides of each series were more active than the other members. A detailed analysis from virtual screening data led to the conclusion that all these compounds are potential HMG-CoA

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reductase inhibitors and within each series, nitro substituted sulfonamide has demonstrated least drug score.



## 1. Introduction

An exhaustive range of heterocycles containing nitrogen, oxygen and sulphur are currently in use due to their diverse therapeutical and industrial significance. Particularly sulfonamides containing these heterocyclic moieties namely pyrrolidine[1–5] and thiophene[6–10] constitute an important class of drugs and display a variety of activities including antibacterial, antifungal, anticancer, antitumor, anti HIV, anti viral, anti inflammatory, enzyme inhibitory, etc.

HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase catalyzes the biosynthesis of cholesterol. Cholesterol synthesis has been the subject of recent research as high levels of cholesterol or hypercholesterolemia is an important factor for the development of cardiovascular diseases (coronary heart disease). HMG-CoA reductase inhibitors are effective and safe drugs and are prescribed for the treatment of hypercholesterolemia i.e. to block the pathway for the synthesis of cholesterol in the liver.[11–14] The therapy by HMG-CoA reductase inhibitors has an added advantage of targeting coronary risks.[15,16] Compared to other HMG-CoA reductase inhibitors, it has been reported that sulfonamides possess advantageous pharmacological properties, hydrophilicity and highest bonding interactions with HMG-CoA reductase, resulting in the most potent inhibition of cholesterol synthesis.[17–19]

## 2. Aim

This article demonstrates the antimicrobial activity and significant HMG-CoA reductase inhibitory activity of sulfonamides containing pyrrolidine and thiophene moieties. To design, synthesize and characterize substituted sulfonamides and evaluate their *in vitro* antimicrobial activity and *in silico* HMG-CoA reductase inhibitory activity.

## 3. Material and methods

All chemicals and reagents were procured from Merck India Ltd. Melting points were determined using X-6 digital display binocular microscope. Infrared spectra were taken on a nicolet nexus 470 FT-IR spectrometer using smear KBr crystal or KBr plate. NMR spectra were recorded on a Bruker Avance (300 MHz) spectrometer. The standard bacterial and fungal stains were procured from National Centre for Cell Science, Pune, India. The antimicrobial activity was expressed in terms of minimum inhibitory concentration (MIC). MIC was found out by broth dilution method.[20] Docking was carried out using GOLD (Genetic Optimization of Ligand Docking) software. The compounds were docked to the active site of the HMG-CoA reductase. The crystal structure of the protein was taken from the Protein Data Bank (PDB Id: 3VKK). The parameters used for genetic algorithm (GA) were: population size (100), selection pressure (1.1), number of operations (10 000), number of island (1) and niche size (2). Operator parameters for crossover, mutation and migration were set to 100, 100 and 10, respectively.

### 3.1. *Synthesis of title compounds*

The sequence of reactions corresponding to the synthesis of title compounds is shown in Fig. 1.

#### 3.1.1. *Synthesis of ethyl 2-((3S,4S)-3,4-diazidopyrrolidin-1-yl) acetate (2)*[21]

A mixture of ethyl 2-((3R,4R)-3,4-bis((methylsulphonyl)oxy) pyrrolidin-1-yl)acetate (**1**) (4.3 g, 1.22 mmol) and aqueous sodium azide (3.43 g, 7.35 mmol) in DMF (40 mL) was heated to 120°C for 18 hours. After completion of reaction as indicated by TLC, the reaction mixture was poured onto crushed ice and extracted with ethylacetate. The ethylacetate extract was subjected to flash chromatography to give **2** (yield: 68%; melting point: 176°C–177°C).

#### 3.1.2. *Synthesis of ethyl 2-((3S,4S)-3,4-diaminopyrrolidin-1-yl)acetate (3)*[22]

A mixture of ethyl 2-((3R,4R)-3,4-diazidopyrrolidin-1-yl)acetate (**2**) (2.39 g, 10 mM), 10% Pd/C (5 g) and methanol (20 mL) was hydrogenated for 10 hours in a pressure reactor. After completion of reaction, catalyst was filtered through celite and washed with methanol. Filtrate was concentrated under reduced pressure to get colorless solid (yield: 77%; melting point: 154°C–155°C).

#### 3.1.3. *Synthesis of ethyl 2-((3S,4S)-3,4-bis(thiophene-2-sulphonamido)pyrrolidin-1-yl)acetate (4)*

A mixture of (**3**) (1.2 g, 25 mM) and thiophen-2-sulphonyl chloride (0.91 g, 5 mM) and 5 mL of pyridine was refluxed for 3 hours. The reaction mixture was poured into cold water (25 mL) and stirred well to crystallize the product. The solid so obtained was filtered and recrystallized from ethanol (yield: 82%; melting point: 184°C–185°C).

#### 3.1.4. *Synthesis of [3-(1-Mercapto-prop-1-ene-1-sulfonylamino)-4-(thiophene-2-sulfonylamino)-pyrrolidin-1-yl]-acetic acid (5)*[23]

A solution of ester (4.79 g, 10 mM) in tetrahydrofuran, MeOH, and $H_2O$ (1:1:1) and LiOH (9.6 g, 4 mM) or aqueous NaOH (2 N) were stirred at room temperature or refluxed for 4–16 hours.