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Research Article

Synthesis and antibacterial activity of synthesized derivative of sulphonamide drug of 1,3-thiazole

Muhammad Shahid Ramzan[a,*], Hafiza Samina Amanat[b]

[a]*Department of Chemistry, Government College University, Lahore, Pakistan.*
[b]*School of Chemistry, University of the Punjab, Lahore, Pakistan.*

Abstract

The amalgamation of two heterocyclic moieties i.e. 1,3-thiazole and 1,3,4-oxadiazole, were carried out in the designed molecules to impart them possible therapeutic properties. The new compounds have been synthesized by encompassing different bioactive moieties including 1,3-thiazole, sulphonyl, alkyl halid. The synthesized molecules have been subjected to evaluation of their antibacterial potential. Furthermore, enzyme inhibition potential results have been supported by computational docking in order to find the types of interactions with the active site of involved enzymes.

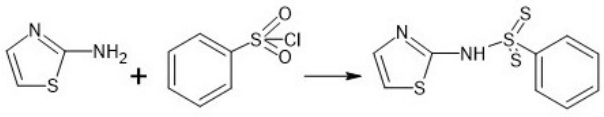
Keywords:
1,3-thiazole, alkyl halide, Sulphonamide, Antibiotic.

1. Introduction

The chemistry of heterocyclic compounds is a vast subject. Out of all the heterocyclic compound 1,3-thiazole is one of the important area of research because of the manifold pharmacological activities. It is used as an intermediate to manufacture synthetic drugs, fungicides, and dyes [1]. Its ring structure is also a useful element in medicinal chemistry. This structure has found applications in drug development for treatment of allergies, hypertension, inflammation, schizophrenia, and bacterial and HIV infections [2]. In the recent years, many thiazole derivatives have been synthesized and subjected to varied biological activities [3]. Naturally, thiazole is available in a large number of terrestrial and marine compounds with different pharmacological activities. Thiazole is also present in the vitamin B1 (Thiamine). It will be exciting to observe that these modifications can be utilized as potent therapeutic agents in future [4].

2. Materials and Methods

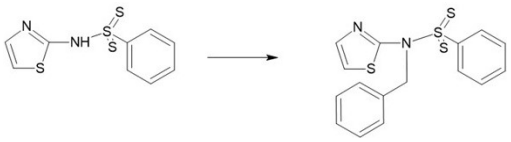
A simple method in aqueous media under dynamic pH control is adopted for synthesis of sulfonamides. Filtration after acidification is involved for isolation of products. All the drugs were weighed accurately and dissolved completely by addition of distilled water by constant stirring using magnetic stirrer. The pH of the reaction contents was strictly monitored and maintained at 8-10 at regular intervals during the experimental reaction using Na_2CO_3 solution (1M). Then benzene sulphonyl chloride was accurately weighed and added carefully into the above solution. Reaction was carried in round bottom flask equipped with magnetic stirrer. Alkaline environment made the removal of hydrogen easier. During stirring benzene sulphonyl chloride initially floats on surface and the completion of reaction was examined by the change in pH value due to formation of HCl by the consumption of p-toluene sulphonyl chloride during the reaction. On completion of reaction pH was adjusted at 2-3 using HCl solution (2M). The precipitates formed were filtered through Whatman Filter Paper No. 42, washed several times with distilled water and recrystallized using methanol, and finally washed with water and acetone (9:1) and dried over anhydrous $MgSO_4$. Products formation was confirmed through TLC (methanol:water:acetone in 60:20:20 ratio).



*Corresponding Author:
sramzan46@gmail.com (Muhammad Shahid Ramzan)

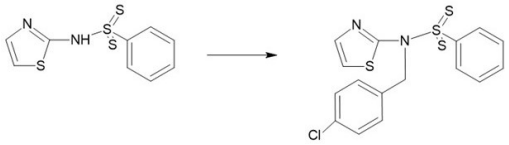
2.1. synthesis of N-benzyl-N-(1,3-thiazol-2-yl) benzenesulfono thioamide

The synthesized compound N-(1,3-thiazol-2-yl) benzene sulfonothioamide was dissolved in N,N-dimethyl formamide (DMF, 5-10 mL) in a 100 mL RB flask. Solid LiH (0.005g) was added and mixture was stirred for half an hour. Then different electrophiles, alkyl/aralkyl halides, were added in equimolar ratios and further stirred for 3-5 hours. The reaction was monitored by TLC using n-hexane and ethyl acetate solvent system (80:20). After completion of reaction,ice cold distilled water was added and the products were collected by filtration or solvent extraction.



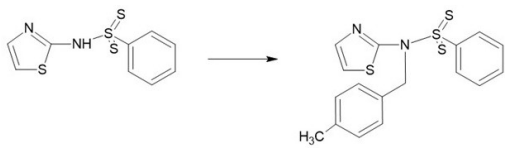
2.2. synthesis of N-[(4-chlorophenyl)methyl]-N-(1,3-thiazol-2-yl)benzenesulfonothioamide

The compound N-(1,3-thiazol-2-yl)benzenesulfonothioamide (17; 0.1g; 0.00047 mol) was dissolved in N,N-dimethyl formamide (DMF, 5-10 mL) in a 100 mL RB flask. Solid LiH (0.005g) was added and mixture was stirred for half an hour. Then different electrophiles, alkyl/aralkyl halides, were added in equimolar ratios and further stirred for 3-5 hours. The reaction was monitored by TLC using n-hexane and ethyl acetate solvent system (80:20). After completion of reaction, ice cold distilled water was added and the products were collected by filtration or solvent extraction



2.3. synthesis of N-[(4-methylphenyl)methyl]-N-(1,3-thiazol-2-yl)benzenesulfonothioamide

The compound N-(1,3-thiazol-2-yl)benzenesulfonothioamide (17; 0.1g; 0.00047 mol) was dissolved in N,N-dimethyl formamide (DMF, 5-10 mL) in a 100 mL RB flask. Solid LiH (0.005g) was added and mixture was stirred for half an hour. Then different electrophiles, alkyl/aralkyl halides, were added in equimolar ratios and further stirred for 3-5 hours. The reaction was monitored by TLC using n-hexane and ethyl acetate solvent system (80:20). After completion of reaction, ice cold distilled water was added and the products were collected by filtration or solvent extraction.



2.4. Antibacterial Assay

Disc diffusion method was used to find out the antibacterial activity of the synthesized compounds. 100 μL suspensions of tested microorganisms was spread on PDA medium for 106 spores/mL of fungi and on NA medium for 107 colony-forming units/mL of bacteria cells. The filter discs of 6 mm diameter were saturated with compound solution and placed on the agar plates inoculated with the tested microorganisms. Filter discs without samples were employed as negative control. Fluconazole (30 μg/disk) and Streptomycin (30 μg/disk) were applied as positive reference for bacterial strains and fungal strains, respectively. Plates were placed 4° C for 2 hours and then incubated at 37° C for 18 hours for bacterial strains. Antimicrobial activity was justified after comparison of diameter of growth inhibition zone measured in mm for organisms and the controls [5, 6].

3. Results

3.1. N-benzyl-N-(1,3-thiazol-2-yl)benzenesulfonothioamide

Light brown solid; yield: 89%; m.p.: 236-237°C; Molecular Formula: $C_{13}H_{12}N_4OS_2$; Mol. Mass: 304$gmol^{-1}$. IR (KBr, cm^{-1}) v: 3350 (N-H), 3052 (C-H of aromatic ring), 2923 (-CH_2- stretching), 1576 (C=C streaching of aromatic ring), 1518(C=N). EI-MS: m/z 304 $[M]^+$ 233 $[C_{17}H_{15}N]^+$, 213$[C_6H_5N_4OS_2]^+$, 170 $[C_7H_8NO_2S]^+$, 155 $[C_7H_7O_2S]^+$, 127 $[C_{10}H_7]^+$, 113 $[C_4H_5N_2S]^+$, 91 $[C_7H_7]^+$

3.2. N-[(4-chlorophenyl)methyl]-N-(1,3-thiazol-2-yl) benzenesulfonothioamide

Dull white solid; yield: 87%; m.p.: 261-262°C; Mol. Formula: $C_{13}H_9ClN_4O_2S_2$; Mol. Mass: 352 $gmol^{-1}$. IR (KBr, cm^{-1}) v: 3345 (N-H), 3175 (C-H stretching of aromatic ring), 2923 (-CH_2- stretching), 1672 (C=C stretching of aromatic ring), 1590 (C=N), 743 (-C-H), 580 (C-Cl stretching). EIMS: m/z 352 $[M]^+$, 253 $[C_{10}H_6ClN_2O_2S]^+$, 226 $[C_9H_6ClN_2OS]^+$, 193 $[C_8H_6N_3OS]^+$, 179 $[C_8H_4ClN_2OS]^+$, 139 $[C_5H_3N_2OS]^+$, 125 $[C_7H_5Cl]^+$, 114 $[C_3H_2N_2OS]^+$, 75 $[C_6H_3]^+$.

3.2.1. N-[(4-methylphenyl)methyl]-N-(1,3-thiazol-2-yl)benzene sulfonothioamide

Light-brown solid; yield: 79%; m.p.: 227-228 oC; Mol. Formula: C15H14N4O2S2; Mol. Mass: 346 g/mol; IR (KBr, cm-1) v: 3358 (N-H stretching), 2977 (C-H stretching of aromatic ring), 1675 (C=N stretching), 1645 (C=O stretching), 1576 (C=C stretching of aromatic ring), 1169 (C-O-C stretching). EI-MS: m/z 346 $[M]^+$, 233 $[C_{11}H_9N_2O_2S]^+$, 206 $[C_{10}H_9N_2OS]^+$, 192 $[C_8H_5N_3OS]^+$, 159 $[C_9H_7N_2O]^+$, 141 $[C_5H_5N_2OS]^+$, 119 $[C_8H_7O]^+$, 104 $[C_7H_4O]^+$, 91 $[C_7H_7]^+$, 65 $[C_5H_5]^+$.

Table 1: % Biofilm inhibition against E. coli and S. aureus of synthesized compounds a-c

Compound	% Inhibition	
	E. coli	*S. aureus*
a	31.278	18.392
b	9.692	40.503
c	30.250	24.673

4. Discussion

A series of three sulfonamides were synthesized in aqueous basic media by simple reaction of six amino group containing drugs; two amino acids and two amino acid analogs with paratoluene sulphonyl chloride with continuous stirring and details of reaction conditions are explained in experimental section. The compounds were obtained in excellent yield (above 80%). Elemental analysis was performed for the conformation of all the compounds and measurement of absorption maximum provided the justification. The synthesized compounds were characterized by FT-IR; the characteristics band at 3263-3371 cm^{-1} of N-H amide stretching and 1174-1127 cm^{-1} for (-N- S=O) and 1072-1010 cm^{-1} (S=O) for all compounds reveals the formation of sulfonamides. $[M + 2]^{+}$ peaks obtained by ESI-MS represented the isolation of sulfonyl group in all synthesized compounds. The structures of all the compounds were also confirmed by 1HNMR and $^{13}CNMR$ by dissolving in MeOD. $^{1}HNMR$ spectra of compounds a,b and c showed a signal at δ 7.03-7.61, while a signal at δ 16.11 and 11.81?ppm for 11b and 11a corresponds to NH group of sulfonamide.

A broad singlet due to -NH group was also obtained for compounds 3a, 3b, 5b, and 13a at δ 8.38, 9.68, 8.01, and 9.51 ppm, respectively. The characteristics C-SO-NH signals at δ 131-139 ppm of all the compounds were shown by $^{13}CNMR$ which identified structures correctly. Synthesized compounds were also screened for their antibacterial activities against gram negative bacterial *E. coli* and gram positive *S. aureus* and *B. subtilis* by following the guidelines of CLSI [7, 8]using ciprofloxacin as reference antibacterial agent. Among the bacterial strains, the compounds 3a and 3b have excellent antibacterial activities against *S. aureus* with zone of inhibition comparable with control drug. Compounds c, b, a, and a showed moderate activities while remaining compounds have no activity against the prescribed bacterial strain. Compounds a and b exhibited excellent activities against *E. coli* almost the same zone of inhibition as by reference ciprofloxacin (MIC 7.81), while 3a and 7a showed no activity.

5. Conclusion

In conclusion, three novel sulfonamides were synthesized; the reactions conditions are easy and excellent yields of compounds were obtained and progress of reaction was monitored by TLC and their structures were confirmed by spectral and elemental analysis. All the synthesized compounds were evaluated for their antibacterial activities and the results of their bioassay indicated that the sulfonamides attached to amino acid (histidine) and antifibrinolytic (tranexamic acid) showed antibacterial activities comparable to ciprofloxacin although these two agents alone have no antibacterial activity. The results confirmed that the compounds which are inactive against bacterial strains showed antibacterial activities after formation of sulfonamides.

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