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Synthesis and Antimicrobial Activity of Some Novel 1, 3,4-Thiadiazole derivatives.

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ABSTRACT

The earlier sources of drugs were from plant, animal and mineral sources, but due to the lack of potential action and definitive cure and sometimes more toxicity, the discovery of new drugs that are more potential and less toxic is essential. The synthesis of derivatives has been an important part and is aimed at modifying the action of drugs, particularly to reduce the side effects and to potentiate the drug action. Today more than 60% drugs used in practice are synthesized derivatives and day-by-day the scope of synthetic medicinal chemistry is broadening. The substituted 1,3,4-thiadiazole moieties are already known for different biological activities. Here we have synthesized some novel 1,3,4-thiadiazole analogues combining with different substituted aromatic and aliphatic system with view to get a good antibacterial activity withless toxicity and side effects. All the synthesized compounds were screened for antibacterial activity. As expected 1,3,4thiadiazole derivatives exhibited significant and moderately antibacterial when compared with standard drugs. Therefore in search of new generation of the active compounds, it maybe worthwhile to explore the possibility in this area by introducing different Functional groups or by cyclization as substitutions which may result into better pharmacological agent.

Keywords : Antibacterial activity, Thiadiazole, Aromatic system, Aliphatic system

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INTRODUCTION

The treatment of infectious disease still remains an important and challenging problem because of combination factors including emerging infectious diseases and increasing number of multi-drug resistant microbial pathogens with particular relevance for gram-positive bacteria. In split of the large number of antibiotics and chemotherapeutics available for medical use, the emergence of old and new antibiotic resistant bacterial strains in the last decades constitutes a substantial need for the new class of antibacterial agents[2,,32,7,71,72].

The varied biological activities of 1,3,4-thiadiazole and there analogues have been known from the beginning of 20th century. 1,3,4-thiadiazole have become a pharmacologically important class of Heterocyclic compounds since the introduction of various clinical use for the treatment of type II diabetes and diabetic complications.

Chemical modification of these heterocycles has constantly resulted in compounds with broad spectrum of pharmacological activities. 1,3,4-thiadiazole derivatives constitute an important class of heterocyclic compounds for which divers biological properties such as antifungal[64], antibacterial[15], antimycobacterium[14], anticonvulsants[13], antitumor[27], CNS depressants[32], herbicidal[9], antiviral[40], and anti-inflammatory activity[51]. In view of the facts mentioned above and as part of our initial efforts to discover potentially active new agents, we report herein the synthesis of 1,3,4-thiadiazole derivatives and evaluation of their antibacterial activities.

MATERIAL AND METHOD

Materials and Reagents:

The chemicals and reagents used in the present project were of AR grade and LR grade, purchased from Lancaster, Sigma, Qualigens, NR Chem., Rolex, S.D. Fine Chem. Ltd., Merck, Loba and Hi-media. And used without further purification.

Synthesis:

***Step 1: Synthesis of thiosemicarbazones[33]* (MY1a-c):**

Aromatic aldehyde (0.2 M) in warm alcohol (300 ml) and thiosemicarbazide (0.2 M) in warm water (300 ml) were mixed slowly with continuous stirring. The product separated immediately on cooling which was filtered with suction, dried and recrystalized in 75% ethanol to yield thiosemicarbazone.

Step-2: Synthesis of 5-phenyl-1, 3, 4-thiadiazole-2-amine[33] (MY2a-c):

Thiosemicarbazone (0.05 M) was suspended in 300 ml warm water, FeCl3 (0.15 M) in 300 ml water was added quantitatively, slowly with constant stirring. The contents were heated at 80-90

^{0}C for 45 min. Solution was filtered while hot and then citric acid (0.11 M) and sodium citrate (0.05M) were added. The resulting mixture was divided into 4 parts and each part was neutralized separately with ammonia (10 %). The required amine separated out, filtered with suction, dried and recrystallized with appropriate solvent.

Step-3: Synthesis of N-benzylidene-5-phenyl-1,3,4-thiaadiazole -2-amine, (MY3a-i)

To a stir solution of compound (0.02mol, 5g) in methanol (50 ml) containing

glacial acetic acid (2 ml) was added appropriate aromatic aldehyde (0.02 mol) and the mixture refluxed for 6-8 hours on a water bath the separated solvent was distilled off at reduced pressure and the resulting solids was cooled , dried and recrystallised from benzene-chloroform mixture to give the compound.

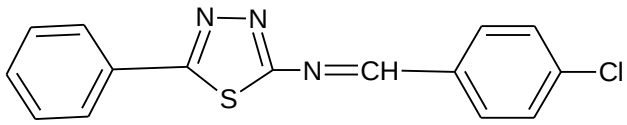
EXPERIMENTAL

Melting points of the synthesized compounds were determined using Thiel's melting point apparatus and were found uncorrected. Purity of the compounds was checked by thin layer chromatography using silica gel G as stationary phase and various combinations of chloroform and methanol are used as mobile phase. The spots resolved were visualized as brown coloured spots by using iodine chamber. The techniques employed for the characterization of the synthesized compounds were IR spectra, ^{1}H-NMR, and Mass spectra.

The IR spectra of the synthesized compounds were recorded using dry KBr pellets in Range of 4000-400 cm^{-1} on a BRUKER α-Fourier transform IR spectrometer at Sipra labs ltd. Hyderabad and frequencies were recorded in wave numbers.^{1}H-NMR spectra were recorded in BRUKER (200 MHz) using $CDCL_3$ as solvent at Sipra labs ltd. Hyderabad. Mass spectra were done by LC-MS technique at Sipra labs pvt. ltd Hyderabad.

SPECTRAL DATA INTERPRETATION

Compound MY3-b



N-(4-chlorobenzylidene)-5-phenyl-1,3,4-thiadiazol-2-amine

IR (KBr cm^{-1}): 3058 (NH) , 2855 (Ar-H) , 1702 (C=N) ,

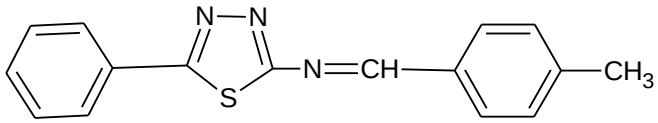
1590- 1614 (C=C) , 687 (C-S)

^{1}HNMR (DMSO , ppm δ): 726 – 798 (m for 9H for Ar-H)

LCMS (m/z) Molecular ion peak appear at 300 (as M+1 100%)

Mol. Formula: $C_{15}H_{10}ClN_3S$, Mol . wt. 299.77 Melting point 285 ^{0}C.

Compound MY3-c



N-(4-methylbenzylidene)-5-phenyl-1,3,4-thiadiazol-2-amine

IR (KBr cm^{-1}): 3276 (NH), 3061 (Ar-H), 2964 (C-H, in CH_3), 1686-1687 (C=N), 1633 (C=C), 688 (C-S)

^{1}HNMR (DMSO , ppm δ): 2.45-2.7 Singlet (3H of CH_3) 7.26-8.96 (9H of Ar-H)

LCMS (m/z) Molecular ion peak appear at280 (M+1 100%)

Mol. Formula: $C_{16}H_{13}N_3S$Mol . wt. 279.35Melting point 290-292

Antimicrobial activity:

The synthesized compounds were screened for antibacterial activity at a concentration of 100µg/ml using DMSO as a controlled against B. subtilis, B. pumilus, p. aeruginosa and E. coli by disc diffusion method on nutrient agar media, **Ciprofloxacin** was used as standard against Gram +ve and Gram –ve bacteria. The results are tabulated in table 1.

RESULTS AND DISCUSSION

All the synthesized compounds were screened for in vitro antibacterial activity. The data in the **table 1 indicates** that compounds **MY3-b, MY3-c, MY3-d,** and **MY3-I** were exhibited a broad spectrum antibacterial activity. While other synthesized compounds of this series shown moderate antibacterial activity. All the synthesized compounds were screened for antibacterial activity against Bacillus subtilis, bacillus pumilus, Escherichia coli and Pseudomonas aureginosa by disc diffusion method using Ciprofloxacin as a standard against gram positive and Gram negative bacteria.

Table 1: Antibacterial activity of synthesized compound (MY3a-i)

Compound code	***Inhibition of zone diameter in mm**			
	B.subtilis	**B.pumillis**	**E.coli**	**P.aeriginosa**
	100 ug	**100ug**	**100ug**	**100ug**
MY3-a	6	7	10	9
MY3-b	12	14	13	13
MY3-c	11	12	13	12
MY3-d	12	14	13	13
MY3-e	10	11	9	11
MY3-f	9	8	10	9
MY3-g	10	10	9	9
MY3-h	9	9	10	8

MY3-i	11	12	13	14
Standard	17	17	18	17
DMSO	-	-	-	-

Standard: ciprofloxacin

*Each value is an average of three independent determination Standard deviation.

Note: '-' denotes no activity, 8-12mm poor activity, 13-17mm moderate activity, 18-20 mm good activity.

CONCLUSION:

We have synthesized series of novel 1,3,4-thiadiazole derivatives the result of antimicrobial screening revealed the discovery of new compounds series of antibacterial agents the mode of action of these compounds was unknown this observation my promote a further development of this group of 1,3,4,-thiadiazole may leads to better pharmacological profile than standard antibacterial drugs From the above results one can establish that the synthesized substituted 1,3,4-thiadiazole can be rich source for the exploitation. Therefore in search of new generation of the active compounds, it may be worthwhile to explore the possibility in this area by introducing different functional groups or by cyclization as substitutions. Which may results into better pharmacological agents?

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