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Synthesis and *In Vitro* Antibacterial Screening of some New 2,4,6-Trisubstituted-1,3,5-Triazine Derivatives

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Abstract: With an objective to evaluate the antibacterial activity of triazine derivatives, a series of 2,4,6-trisubstituted-1,3,5-triazine were synthesized and characterized by FTIR, ^{1}H-NMR, ^{13}C-NMR, mass spectroscopy and elemental analysis. The minimum inhibitory concentration (MIC) of the compounds that displayed favourable zone of inhibition was determined by broth microdilution method. Derivatives with morpholinyl substituent (**4a** and **4i**) demonstrated good *in vitro* activities against Gram-positive organisms, whereas two of the compound bearing a diethylamino side chain exhibited moderate (**4e**) to broad spectrum (**4j**) activity comparable to streptomycin. The promising activity of the latter maybe attributed to the substitution of electron releasing group at *para* position of phenyl rings.

Keywords: Antibacterial activity, Cyanuric chloride, 1,3,5-triazine, Morpholine, Minimum inhibitory concentration.

INTRODUCTION

Antimicrobial resistance has become an impending threat globally and necessitates urgent and concerted efforts to avoid relapse to the pre-antibiotic era. Extremely resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci accounts for a high percentage of hospital acquired infections. Evidence from literature suggests that antibiotic resistance is rapidly becoming a global health concern [1]. Contemplating on the scenario, the World Health Organization has selected combating antimicrobial resistance as the theme for World Health Day 2011 [2]. Most of the currently used antibiotics are either incompetent to combat bacterial resistance satisfactorily or are having unfavourable side-effect profile. Therefore, the synthesis of new and effective antimicrobials will soon become the part of the thrust areas of new drug design and discovery programme. The mono-, di-, and tri-substituted 1,3,5-triazine derivatives are of particular interest in synthetic medicinal chemistry. They have been extensively exploited due to the ease of synthesis *via* displacement of chlorine atoms in cyanuric chloride by various nucleophiles, in the presence of a hydrochloride acceptor (usually sodium carbonate, bicarbonate, hydroxide or tertiary amines) [3,4]. Triazine as scaffold provides the basis for the design and development of various biologically significant molecules that include compounds that possess potent antiretroviral [5], antimalarial and antileishmanial [6, 7], anticancer [8], antimicrobial activity [9] and additionally some are also found to be effective against autoimmune diseases [10]. In recent years, Sunduru *et al.* for the first time identified a number of 2,4,6-trisubstituted-1,3,5-triazines that showed potent antitubercular properties active against *Mycobacterium tuberculosis* H37Rv [11].

With regard to their antibacterial potency, Srinivas *et al.* reported the activity of various 1,3,5-triazines having benzyl, benzyloxy and benzylamino substitution at position 2,4,6 of *s*-triazine. They observed that triazine bearing unsubstituted benzyl substitution exhibited broad spectrum antibacterial activity. The *para* methoxy substituted benzyloxy triazine derivatives showed improved activity against Gram negative bacteria while the benzylamine derivatives showed low activity against all the tested organisms [12]. Zhou *et al.* demonstrated interesting results based on the recent screening of three combinatorial libraries. Library with amantadine substituted *s*-triazine was found to be more effective against *Bacillus subtilis* to library with 2,2′-(ethylenedioxy)bis(ethylamine) side chain. They suggested that an increase in the bulkiness on one side chain of the triazine compounds enhanced their antimicrobial activity [13].

In view of the above mentioned findings we report herein the synthesis and antibacterial activity of some new 2,4,6-trisubstituted-1,3,5-triazine derivatives. On the basis of the symmetrical nature of *s*-triazine and in conformity with the pharmacophoric requirements, various substituents have been utilized to observe the affect on triazine scaffold with respect to the antibacterial activity.

MATERIALS AND METHODS

Experimental

All the chemicals used in the experiment were of analytical grade and procured from Merck (India) and Hi-Media (India). Cyanuric chloride was obtained from Lonza Ltd., Switzerland as a gift sample. Melting points were determined in open capillaries using Veego VMP1 melting point apparatus, Veego Instruments Corporation (Mumbai, India) and are uncorrected. The progress of the reaction was monitored by thin layer chromatography developed with n-hexane/diethyether (1:1) and performed on Merck silica gel 60 F254 aluminium sheets and products were purified

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