Synthesis of Phenyl-1,3-thiazole Substituted Amino s-triazines as Antibacterial Agents

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ABSTRACT: Amino s-triazines are widely believed to exert their antibacterial effects by nonspecific mechanisms. We assessed the extent to which physicochemical properties can be exploited to promote discriminative activity. In a wide search program towards new and efficient antibacterial agents, a series of amino substituted s-triazines were synthesized and subsequently screened for their *in-vitro* antibacterial activity against three Gram positive (*Bacillus subtilis, B. cereus, Staphylococcus aureus)* and three Gram-negative microorganism (*Salmonella typhi, Escherichia coli, Klebsiella aerogenes*) by the broth dilution technique, recommended by European Committee for antimicrobial susceptibility testing (EUCAST) with reference to streptomycin. The phenyl-1,3-thiazole substituted amino-s-triazine derivatives showed good antibacterial activity.

Key words: Antibacterial activity, Bacterial resistance, Broth dilution technique, Physicochemical properties, s-Triazine.

INTRODUCTION

The extraordinary progress represented by the arrival of antibiotics has changed the medical prognosis of minor and major infections.[1] Any bacterial species acquired resistance to the most common classes of antibiotics. Bacterial resistance continues to develop and pose a significant threat both in hospitals and more recently in the community.[2] A relevant report on resistant antibacterial agents for human medicine is provided by World Health Organization**.** The panel agreed that the list of Critically Important antibacterial agents should be updated regularly as new information becomes available, including data on resistance patterns, new and emerging diseases and the development of new drugs.[3]

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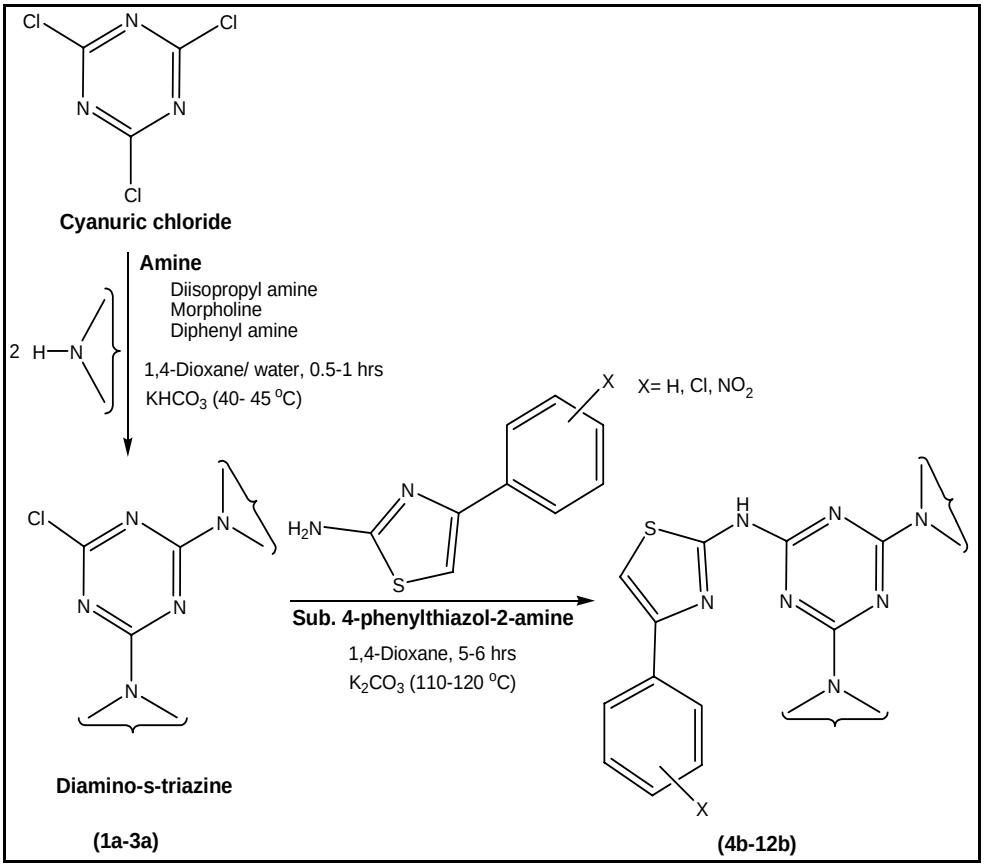
During the last few years the potential of s-triazine derivatives in agrochemical and medicinal properties have been subjected to investigation. Literature survey reveals that amino substituted s-triazine derivatives are associated with number of pronounced antibacterial activities[4-7] against gram positive (*B. subtilis, B. sphaericus, S. aureus* etc) and gram negative organism (*E. coli, K. aerogenes, P. aeruginosa* etc). The biological activity is a function of physicochemical properties of the targeted molecule and this assessment is made of the sorts of chemicals that might fit into an active site.[8,9] To randomly explore the novel compounds, our idea was to combine, cyanuric chloride and various amines with good antibacterial properties. The substituted phenylthiazole-2-amine derivatives remain attractive, with their significant biological activities[10,11] and further incorporation of these derivatives, could give access to a wide array of structures, which can be expected to show interesting antibacterial activities.

In this program we demonstrate various amines mediated substitution in cyanuric chloride and subsequently with 4-sustituted phenylthiazole-2-amine to synthesize series of phenyl-1,3-thiazole substituted amino s-triazine.

MATERIALS AND METHODS

Phenyl- 4-chlorophenyl- and 4-nitrophenyl thiazole-2-amine derivatives were synthesized according to literature procedures[12,13] with the help of corresponding acetophenone, thiourea, thionyl chloride and bromine. The designed compounds were prepared in two step reaction, first step consists of nucleophilic substitution of two chlorines in cyanuric chloride in presence of aq. dioxane with various amines like diisopropylamine, morpholine and diphenyl amine to synthesize (**1a**-**3a**) diamino-s-triazine[14] (0.5-1 hour) and second step involves further substitution of third chlorine in presence of 1,4-dioxane[15] with synthesized phenyl-1,3-thiazole-2-amine to obtain a series (Scheme 1) of (**4b**-**12b**) phenyl-1,3-thiazole substituted amino s-triazine (5-6 hours).



Scheme 1: Synthesis of phenyl-1,3-thiazole substituted amino-[1,3,5]-triazine (4b- 12b)

Synthesized compounds (Figure 1) were subsequently screened for their *in-vitro* antibacterial activity (MIC) against three Gram positive (*Bacillus subtilis, Bacillus cereus, Staphylococcus aureus)* and three Gram-negative microorganism (*Salmonella typhi, Escherichia coli, Klebsiella aerogenes*) by the broth dilution technique, recommended by European Committee for antimicrobial susceptibility testing (EUCAST) E. Dis 5.1[16] with reference to streptomycin. Nutrient agar (M090) and Nutrient broth (M002) were procured from Himedia Laboratories, Mumbai.

RESULTS AND DISCUSSION

The MIC values of synthesized compounds against tested organism displayed a significant activity with wide degree of variation (Table 1).

Data from these experiments was combined for MIC over control Streptomycin (Figure 2). This series of compounds have displayed good antibacterial results against *B. subtilis*, among them

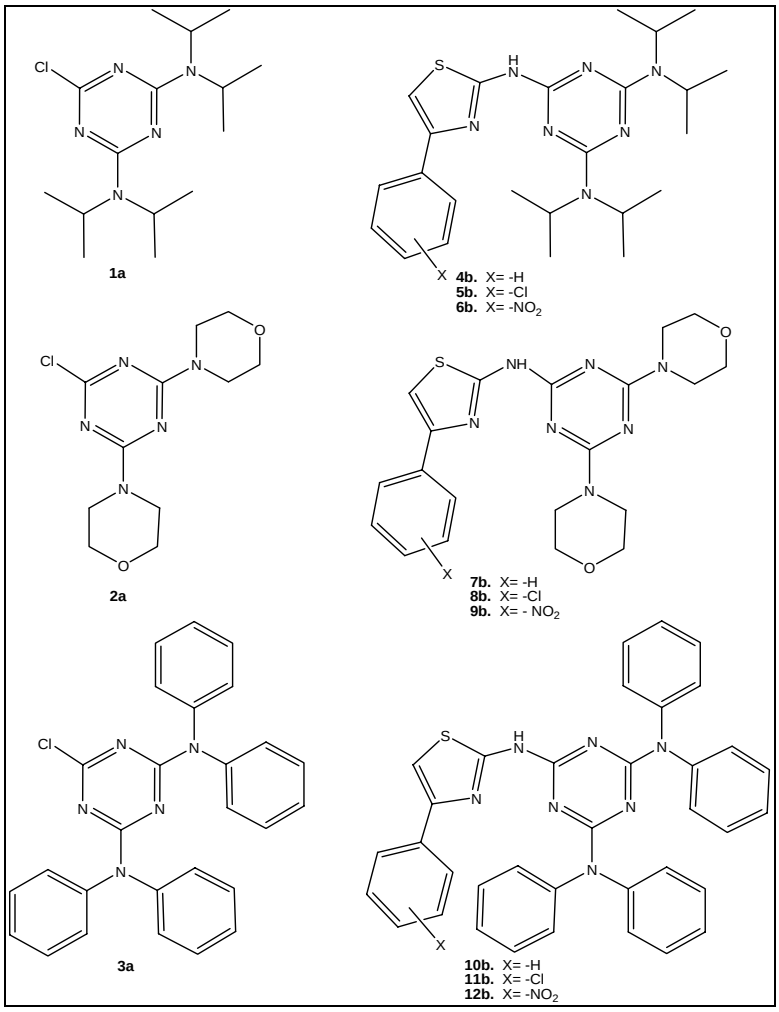


Figure 1. Structure of synthesized compounds (**1a**-**12b**)

Table 1. *In-vitro* antibacterial activity of the synthesized compounds

Compound	MIC (µg /ml)					
	B. subtilis	*B. cereus*	*S. aureus*	*S. typhi*	*E. coli*	*K. aerogenes*
1a	64	128	64	32	16	32
2a	128	128	128	128	64	128
3a	32	64	64	64	16	64
4b	16	16	16	32	16	8
5b	32	64	16	32	16	16
6b	8	8	8	16	8	32
7b	64	16	16	64	16	32
8b	4	16	16	16	4	32
9b	8	8	16	16	8	8
10b	16	32	4	32	8	32
11b	32	8	32	8	16	16
12b	4	8	8	16	4	32
Streptomycin	8	4	8	< 2	< 2	< 2

* DMSO as negative control.

compounds **6b** and **9b** were found equipotent to streptomycin, whereas compounds 8b and 12b have shown comparatively greater activity for the same strain. A comparatively decreased activity have been achieved against *B. cereus*, compounds **6b**, **9b**, **11**b and **12b** exhibited significant activity and rest of the other derivatives showed substantial to weak activity. Similarly greater to moderate activity is achieved by all s-triazine derivatives against *S. aereus,* compound **10b** has shown comparatively greater activity for the same strain. Against *S. typhi*, only compound **11b** has been found to possess significant activity, comparatively weak activity has been reported by remaining compounds. *E. coli* was found to be more susceptible than rest of the other strains of bacteria, among them compounds **6b**, **8b**, **9b**, **10b** and **12b** were showing great to significant activity for the same strain. **4b** and **9b** exhibit significant activity against *K. aerogenes*, remaining other compounds were found to possess substantial to moderate activity.

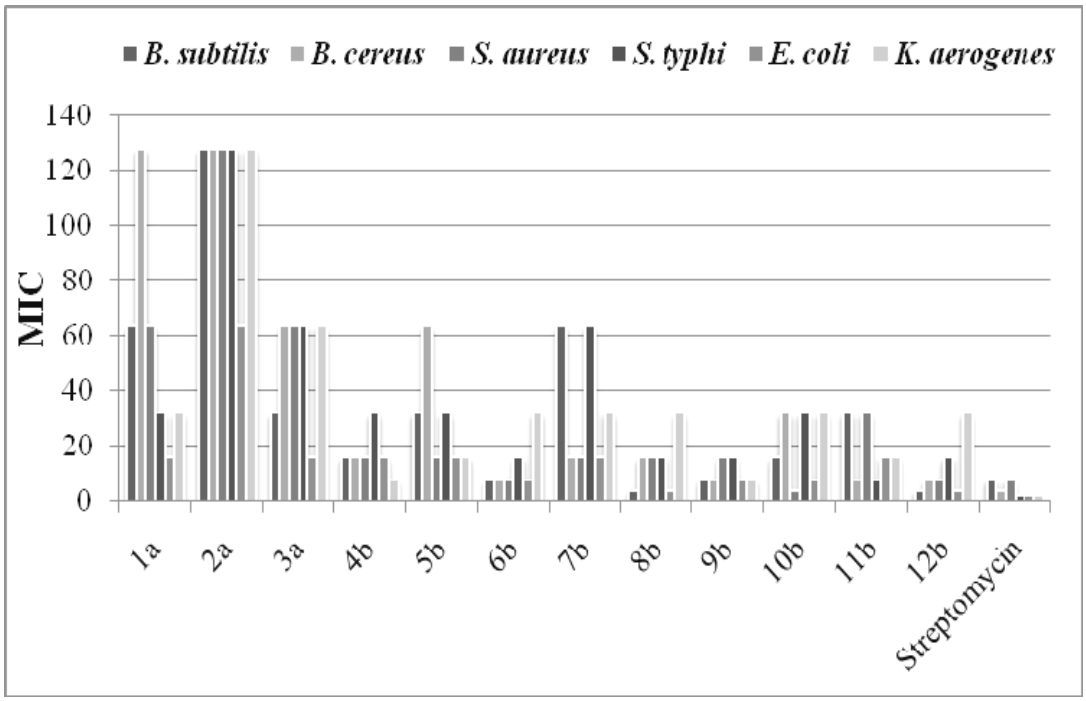


Figure 2. MIC value of synthesized compounds over control (Streptomycin)

A perusal of data in table 1 indicates that the compounds having a nitro group in thiazole skeleton showed maximum antibacterial activity (MIC 4-8 µg/ml) for gram positive bacteria, this is probably due to facilitated binding by nitro groups with the targets. The preliminary antibacterial results showed that substituted (**1a**-**3a**) diamino-s-triazine derivatives were significantly less active, among them (**3a**) diphenylamine substituted s-triazine were more efficient substituent for the entire tested microorganisms, A considerable difference in antibacterial activity between (**1a**-**3a**) di-substituted amino s-triazine derivatives (MIC= 16-128 µg/ml) and (**4b**-**12b**) phenyl-1,3-thiazole substituted tri-amino s-triazine derivatives (MIC= 4-64 µg/ml), emphasized the importance of incorporating lipophilic groups. All of the biologically active substituted amino-s-triazine derivatives show lipophilic traits.

We have presented a new economical synthesis of a series of phenyl-1,3-thiazole substituted amino s-triazine. The operational simplicity very short reaction times can impose this procedure as useful and attractive

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