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# Studies in the Antimicrobial activity of 1,3,5-Thiadiazines

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**Novel series of 2-substitutedamino-4-(1-substitutedthiocarbamido-3-yl)-6-substitutedimino-1,3,5-thiadiazines**[2a(i) to 2f(iii)] **have been obtained by basification of their hydrochloride** [1a(1) to 1f(iii)],**which are prepared by the interaction of 1,3-Bis-(N-substitutedthioamido) guanidine and substitutedisocyanodichloride. The latter were prepared initially by the condensation of aryl/alkylisothiocyanate and guanidine carbonate in 1:2 molar ratios. The structure of all these compounds were established on the basis of elemental analysis, IR and PMR spectral data. All the synthesized compounds have been assayed for their antibiological activity against both gram-positive and gram-negative human pathogens and found that they possess insecticidal, and bacteriocidal. Some 1,3,5-thiadiazine compounds show remarkable biological activity.**

**Keywords:** 1,3-Bis-(N- substitutedthioamido) guanidine, 1,3,5-thiadiazines, antimicrobial activity.

Different routes and methods have been reported for the synthesis of 1,3,5-thiadiazines. They posses fungicidal[1-2],insecticidal[3], industrial[4] medicinal[5-6] importance. In view of the utility of those compounds in various fields and as a part of wider programme of these research lab to provide alternative routes for the synthesis of various 6-membered heterocyclic compounds hence the interactions of N-substitutedisocyanodichloride has been carried with different 1,3-Bis-(N-substitutedthioamido) guanidine to synthesize 1,3,5-thiadiazine.

## MATERIAL AND METHODS

All 1,3,5-thiadiazines compounds were screened for their antibacterial activity using cup plate diffusion method.[7-8] bacterial organisms used include both gram positive and gram negative strains like *S. aureus*, *S. typhi, A. aerogenes, E. coli* and *B. subtilis*.

The medium was prepared by dissolving 28 gm of ingredients in one liter of distilled water and was sterilized at 121°C temperature and 15 lbs/inch pressure in an autoclave for 15 minutes.

After sterilization it was cooled down to 50°C and poured into sterile petriplates and allowed to solidify. The media plates were then seeded with 24 hrs old active nutrient growth culture of the test organism in order to obtain lawn culture. The compounds were dissolved in 50% dimethylformamide (DMF) solvent at fix concentration 100 mg/ml . To these added 2 drops of test solutions of synthesised compounds. Plane DMF solvent was used as control. The plates were then incubated at 37°C for 24 hrs. After incubation the zones of inhibition were recorded around the wells and result are cited in Table 1.

## EXPERIMENTAL

All chemicals used were of analar grade. Substitutedisothiocyanates were prepared according to literature method.[9] melting points of

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**Table 1.** Physical data and antimicrobial activity of the compounds [2a(i) to 2f(iii)].

| Compd. | R | $R_1$ | Yield (%) | m.p. (°C) | *Gram Positive* | | *Gram Negative* | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | *S. aureus* | *B. subtilis* | *A. aerogenes* | *E. coli* | *S. typhi* |
| [2a(i)] | Phenyl | Phenyl | 74 | 215 | + | ++ | +++ | ++ | +++ |
| [2a(ii)] | Phenyl | *p*-Chloro -phenyl | 71 | 237 | +++ | ++ | ++ | - | + |
| [2a(iii)] | Phenyl | Ethyl | 79 | 197 | + | +++ | - | + | ++ |
| [2b(i)] | *p*-Chloro phenyl | Phenyl | 73 | 227 | ++ | + | + | ++ | +++ |
| [2b(ii)] | *p*-Chloro phenyl | *p*-Chloro -phenyl | 69 | 242 | ++ | + | ++ | + | ++ |
| [2b(iii)] | *p*-Chloro phenyl | Ethyl | 72 | 212 | + | + | ++ | - | ++ |
| [2c(i)] | *p*-Tolyl | Phenyl | 64 | 227 | +++ | ++ | ++ | + | +++ |
| [2c(ii)] | *p*-Tolyl | *p*-Chloro -phenyl | 69 | 232 | ++ | +++ | ++ | - | ++ |
| [2c(iii)] | *p*-Tolyl | Ethyl | 58 | 198 | ++ | - | + | + | +++ |
| [2d(i)] | Ethyl | Phenyl | 64 | 202 | +++ | + | +++ | ++ | - |
| [2d(ii)] | Ethyl | *p*-Chloro -phenyl | 71 | 192 | ++ | - | + | - | ++ |
| [2d(iii)] | Ethyl | Ethyl | 69 | 177 | + | - | ++ | ++ | +++ |
| [2e(i)] | Methyl | Phenyl | 72 | 170 | ++ | ++ | +++ | - | +++ |
| [2e(ii)] | Methyl | *p*-Chloro -phenyl | 76 | 179 | ++ | + | ++ | ++ | ++ |
| [2e(iii)] | Methyl | Ethyl | 68 | 166 | + | ++ | - | - | +++ |
| [2f(i)] | *t*-Butyl | Phenyl | 79 | 187 | + | + | + | + | - |
| [2f(ii)] | *t*-Butyl | *p*-Chloro -phenyl | 74 | 177 | +++ | - | ++ | ++ | +++ |
| [2f(iii)] | *t*-Butyl | Ethyl | 67 | 172 | - | ++ | +++ | ++ | + |

* All Compounds gave satisfactory C, H, N, and S analysis.
( - ) = Inactive (Less than 10 mm) ( + ) = Weakly Active (10-14 mm)
( ++ ) = Moderately Active (15-18 mm) ( +++ ) = Highly Active (19-35 mm)

all synthesized compounds were determine in open capillary. IR spectra were recorded on Perkin-Elmer spectrometer in the range 4000-400cm$^{-1}$ in Nujol mull as KBr pellets. PMR spectra were recorded with TMS as internal standard using $CDCl_3$ and DMSO-$d_6$. TLC checked the purity of the compounds on silica gel-G plates with layer thickness of 0.3 mm.

**Synthesis of 2-phenylamino-4-(1-phenylthiocar-bamido-3-yl)-6-phenylimino-1,3,5-thiadiazine [2a(i)]**

1,3-Bis- (N- phenylthioamido) guanidine (0.01m) was suspended in carbon tetrachloride medium (25ml). To this a solution of N-phenylisocyanodichloride (0.01m) was added. The reaction mixture was refluxed on water bath for 4hr. During heating evaluation of hydrogen chloride gas was observed. Then excess solvent was distilled off, a needle shape crystal was separated out. It was crystallized from aqueous ethanol. Yield 80% m.p.237°C and identified as 2-phenylamino-4-(1-phenylthiocarbamido-3-yl)-6-phenylimino-1,3,5-thiadiazine hydrochloride [1a(i)] Similarly, other compounds, [1a(ii) to 1f(iii)] were prepared from 1,3-Bis- (N-phenylthioamido) guanidine. On basification of [1a(i)] with aqueous ammonium hydroxide solution afforded free base [2a(i)] was obtained it was crystallized from aqueous ethanol. Yield 74% m.p.215$^0$C IR: 3356.cm$^{-1}$ (NH), 3131.3 cm$^{-1}$ (C-H (Ar)), 1688.4 cm$^{-1}$ C=N), 1294.7 cm$^{-1}$ (C-N), 1197.7 cm$^{-1}$ (C=S), 777.9 cm$^{-1}$ (C-S), 1575.9 cm$^{-1}$ (C=N) grouping; PMR ($CDCl_3$ and DMSO-$d_6$): 7.95 ppm (Ar-NH), 6.87 ppm (Ar-H). Similarly others

compounds [2a(ii) to 2f(iii)] were synthesized by above mention method and enlisted in Table 1.

## RESULTS AND DISCUSSION

All the bacterial strains studied were human pathogens. The activity is compared with standard drug ciprofloxacine at the same concentration. From the experimental data it has been observed that the compounds 2a(i), 2b(i), 2c(i), 2c(iii), 2d(iii), 2e(i), 2e(iii) and 2f(ii) shows high activity against *S. typhi* and compounds 2a(iii), 2b(ii), 2b(iii), 2e(ii), 2d(ii), and 2e(ii) shows moderate activity while remaining compounds are inactive against same pathogen. Similarly compound 2a(i), 2b(i), 2d(i), 2d(iii), 2e(ii), 2f(ii) and 2f(iii) shows moderate activity and remaining compounds shows in activity against *E. coli*. In case of Gram-positive bacteria like *S. aureus* the compound 2a(ii), 2e(ii), 2d(i) and 2f(ii) shows high activity while compound 2b(i), 2b(ii), 2c(ii), 2c(iii), 2d(ii), 2e(i) and 2e(ii) shows moderate activity against the same bacteria. The compound 2a(iii) and 2c(ii) were effective against the *B. subtilis*. As newly thiadiazines shows remarkable antimicrobial activity, these compounds can easily be used as alternative drugs for the treatment of various diseases.

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