JOURNAL OF PURE AND APPLIED MICROBIOLOGY, April 2007. Vol. **1**(1), p. 133-135

Biological activity of 2-(1- substitutedguanidino-3-yl)-4-(3-phenylthiocarbamido-1-yl)-6- substituted imino-1,3,5-thiadiazine

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(Received: 12 February 2007; accepted: 17 March 2007)

Novel series 2-(1-substitutedguanidino-3-yl)-4-(3-phenylthiocarbamido-1-yl)-6- substituted imino-1,3,5-thiadiazine [3a(i) to 3f(ii)] **have been obtained by basification of their hydrochlorides** [2a(i) to 2f(ii)] **in presence of ammonium hydroxide solution, which are synthesized by the interaction of 1-Formamidino- (N-_substitutedthioamido)-5-phenyl-2-thio-4-iminobiuret** (1a-f) **and N-aryl/alkylisocyanodichlorides. The latter were prepared initially by the condensation of substitutedisothiocyanate with N-phenylformamidinoformamidinothiocarbamide. 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 antimicrobial 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: N-phenylformamidinoformamidinothiocarbamide, 1,3,5-thiadiazines, antimicrobial activity.

The literature survey reveals that the heterocyclic compounds containing nitrogen and nitrogen and sulphur have gain immense importance in human life due to their variety of applications in agricultural, medicinal, pharmacological and industrial value. It has also found that the heterocyclic compounds containing 1,3,5-thiadiazine in the nucleus have been successfully tested against several pathogens and found that they possess fungicidal, insecticidal, industrial, medicinal, pharmaceutical[1], agricultural and bactericidal[2-3] properties.

MATERIAL AND METHODS

"Any chemical moiety which inhibit the growth of microorganism or kill it is called as antimicrobial activity".

All S-triazine compounds were screened for their antibacterial activity using cup plate diffusion method.[4-5] 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 synthesized compounds. Plane DMF solvent was used as control. The plates were

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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. Substituted isothiocyanates were prepared according to literature method.[6] melting points of 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-(1-phenylguanidino-3-yl)-4-(3-phenylthiocarbamido-1-yl)-6-phenylimino-1,3,5-thiadiazine [3a(i)].

1-Formamidino-(N-phenylthioamido)-5-phenyl-2-thio-4-iminobiuret. (0.01m) (1a) was suspended in carbon tetrachloride medium (25ml). To this a solution of phenylisocyano-dichlorides (0.01m) was added. The reaction mixture was refluxed on water bath for 4 hr. During heating evolution of hydrogen chloride gas was observed. The reaction mixture was filtered and after distillation of filtrate needle shape crystals were separated out. It was crystallized from aqueous ethanol. Yield 82 %; m.p.272^{0}C and identified as of 2-(1-phenylguanidino-3-yl)-4-(3-phenylthio-carbamido-1-yl)-6-phenylimino-1,3,5-thiadiazine hydrochloride [2a(i)], which on basification with ammonium hydroxide solution afforded free base [3a(i)]. It was recrystallised from aqueous ethanol. Yield 72% m.p.265^{0}C.IR spectra of compound shows ν(N-H) 3396.6 cm^{-1}, ν(CH-Ar) 2924 cm^{-1}, ν(C=N) 1661.1 cm^{-1}, ν(C=S) grouping 1101.1 cm^{-1}, ν(C-S) 778.2 cm^{1}. The PMR spectra of compound showed signals due to Ar-NH protons at δ 6.1605 ppm, N-H protons at δ 4.00925 ppm and Ar-H protons at δ 7.226 ppm. Similarly others compounds [2a(ii) to 2f(ii)] and [3a(ii) to 3f(ii)] were synthesized by above mention method and enlisted in Table 1.

Table 1. Physical data and antimicrobial activity of the compounds [3a(i) to 3f(ii)]*

Compd.	R	R_1	Yield	m.p. (^{0}C)	Gram Positive			Gram Negative	
					S. aureus	*B. subtilis*	*A. aerogenes*	*E. coli*	*S. typhi*
[3a(i)]	Phenyl	Phenyl	72	265	++	+	+++	+++	+++
[3a(ii)]	Phenyl	Ethyl	68	254	+++	++	++	-	+++
[3b(i)]	*p*-Chlorophenyl	Phenyl	56	262	+	+++	-	+	+++
[3b(ii)]	*p*-Chlorophenyl	Ethyl	61	257	++	+	+	++	-
[3c(i)]	*p*-Tolyl	Phenyl	68	271	++	-	++	+	++
[3c(ii)]	*p*-Tolyl	Ethyl	77	269	+	+	+++	-	++
[3d(i)]	Ethyl	Phenyl	79	248	+++	++	+++	+	++
[3d(ii)]	Ethyl	Ethyl	59	242	++	++	++	-	+++
[3e(i)]	Methyl	Phenyl	62	242	++	-	+	+	+++
[3e(ii)]	Methyl	Ethyl	72	238	+++	+	+++	++	-
[3f(i)]	*t*-Butyl	Phenyl	77	213	++	++	-	-	+++
[3f(ii)]	*t*-Butyl	Ethyl	72	267	+	-	++	++	++

* 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)

RESULTS AND DISCUSSION

All the bacterial organisms studied are 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 3a(i), 3a(ii), 3b(i), 3d(ii), 3e(i) and 3f(i) shows highly activity against *S. typhi* and compounds 3b(i), 3c(ii), 3d(i) and 3f(ii) shows moderately activity while remaining compounds are inactive against same pathogen. Similarly compound 3a(i), 3c(ii) 3d(i) and 3e(ii) shows highly activity against *A.aerogenes* and compound 3a(ii), 3c(ii), 3d(ii) and 3f(ii) shows moderately activity against same pathogen. In case of *E. coli* the compound 3b(ii), 3e(ii) and 3f(ii) show moderately activity while compound 3a(i), shows highly activity against the same bacteria. In case of Gram-positive bacteria like the compounds 3a(ii), 3d(i) and 3e(i) shows highly activity against *S. aureus* while 3a(ii), 3b(ii), 3d(i), 3e(i) and 3f(i) shows moderately activity against *S. aureus* while the compound 3a(ii), 3d(i), 3d(ii) and 3f (i) were effective against the *B. subtilis* organisms. As newly 1,3,5-thiadiazine shows remarkable antimicrobial activity, these compounds can be easily used as alternative drugs for the treatment of diseases like typhoid.

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