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Antibacterial Activity of 2-(2-Imino-4-Thio-5-Substituted Biureto-1-yl)-4-(3-Substituted Thiocarbamido -1-yl)-6-Substituted Imino-1,3,5-Thiadiazine

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Novel series 2-(2-imino-4-thio-5-substitutedbiureto-1-yl)-4-(3-substituted thiocarbamido-1-yl)-6-substitutedimino-1,3,5-thiadiazine [3a(i) to 3f(iii)] **have been obtained by basification of their hydrochlorides** [2a(i) to 2f(iii)] **in presence of ammonium hydroxide solution, which are synthesized by the interaction of 1,3-bis-(N-substitutedamidinothiocarbamido)-thiocarbamide**(1a-1f) **and aryl/alkylisocyanodichlorides. The latter were prepared initially by the condensation of aryl/alkylisothiocyanate with 1,3-Diformamidinothiacarbamide. The structure of all these compounds was established on the basis of IR and PMR spectrum data. All the synthesized compounds have been assayed for their antibacterial activity against both gram-positive and gram-negative human pathogens.**

Key words: 1,3- Diformamidinothiacarbamide, 1,3,5-thiadiazines, Antimicrobial activity.

The literature survey revels that the heterocyclic compounds having 1,3,5-thiadiazines nucleus enhanced pharmaceutical, medicinal, agricultural and industrial values[1-2]. The synthetic applications of N-substitutedisocyanodichlorides have been investigated and shown to have enough potential in the synthesis of nitrogen and sulphur containing heterocyclic compounds[2] thus aim to synthesized 1,3,5-thiadiazines, reaction of aryl/alkylisocyanodichloride have been carried out with 1,3-bis-(N-substitutedamidinothiocarbamido) thiocarbamide in 1:1 molar ratios.

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EXPERIMENTAL

All chemicals used were of analar grade. Aryl/alkylisothiocyanate, Aryl/alkylisocyanodichlorides were prepared according to literature method.[3] Melting points of all synthesized compounds were determined in open capillary. IR spectra were recorded on Perkin-Elmer spectrometer in the range 4000-400 cm^{-1} in 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. All S-triazines compounds were screened for their antimicrobial activity using cup plate diffusion method.[4] The bacterial organisms used included both gram-positive and gram-negative strains viz. *S. aureus, B. subtilis, A. aerogenes, E. coli*, and *S. typhi*. The solvent used was DMF. The media plates were seeded with bacterial inoculums of 1×10^6 CIU/ml having well size 6 mm was loaded with

0.1 ml of test compound solution of variable concentration in DMF. The zone of inhibition was recorded after incubation for 24 h. using vernier calipers and result are cited in Table 1.

Synthesis of 2-(2-imino-4-thio-5-phenylbiureto-1-yl)-4-(3-phenylthio-carbamido-1-yl)-6-phenylimino-1,3,5-thiadiazine [3a(i)]

1-3-Bis-(N-phenylamidino-thiocarbamido)-thiocarbamide (0.01M) (1a) was suspended in carbon tetrachloride medium (25ml). To this a solution of phenylisocyanodichlorides (0.01M) was added in 1:1 molar proportions. The reaction mixture was refluxed on water bath for 4 h. During heating evolution of hydrogen chloride gas was observed and tested with moist blue litmus paper. Cooling the reaction mixture and distilled off excess solvent, needle shape crystals were separated out. And crystallized from aqueous ethanol. Yield 79 %; m.p.276 ^{0}C and identified as of 2-(2-imino-4-thio-5-phenylbiureto-1-yl)-4-(3-phenylthiocarbamido- 1-yl)-6-phenylimino-1,3,5-thiadiazine hydrochloride [2a(i)], which on basification with aqueous ammonium hydroxide solution afforded free base [3a(i)]. It was recrystallised from aqueous ethanol. Yield 72 % m.p.268 ^{0}C. IR spectrum of compound showed ν(N-H) 3273.4 cm^{-1}, ν(CH-Ar) 3118.3 cm^{-1}, ν(C=N) 1695.4 cm^{-1}, ν(C=N) imino grouping 1652.5 cm^{-1}, ν(C-N) 1181.9 cm^{-1}ν, (C=S) grouping 1063.0 cm^{-1}, ν (C-S) 726.6 cm^1. The PMR spectrum of compound showed signals due to Ar-NH protons at δ 7.63 ppm, N-H protons at δ 7.36 ppm and Ar-H protons at δ 6.76 ppm, NH protons at δ 3.0-3.7 ppm. The signal at d 0.87-1.48 ppm is due to moisture DMSO-d_6. Similarly others compounds [2a(ii) to 2f(iii)] and [3a(ii) to 3f(iii)] were synthesized by above mention method.

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

Table 1. Physical data and antibacterial activity of the compounds [3a(i) to 3f(iii)]

Compd.	R	R_1	Yield	m.p.	Gram Positive		Gram Negative		
			%	(°C)	*S. aureus*	*B. subtilis*	*A. aerogenes*	*E. coli*	*S. typhi*
[3a(i)]	Phenyl	Phenyl	72	268	++	+	+++	+++	+++
[3a(ii)]	Phenyl	Ethyl	69	256	+++	++	++	-	+++
[3b(i)]	*p*-Chloro-phenyl	Phenyl	68	273	+	+++	-	+	+++
[3b(ii)]	*p*-Chloro-phenyl	Ethyl	61	252	++	+	+	++	-
[3c(i)]	*p*-Tolyl	Phenyl	67	269	++	-	++	+	++
[3c(ii)]	*p*-Tolyl	Ethyl	64	254	+	+	+++	-	++
[3d(i)]	Ethyl	Phenyl	67	248	+++	++	+++	+	++
[3d(ii)]	Ethyl	Ethyl	77	232	++	++	++	-	+++
[3e(i)]	Methyl	Phenyl	73	231	++	-	+	+	+++
[3e(ii)]	Methyl	Ethyl	62	227	+++	+	+++	++	-
[3f(i)]	*t*-Butyl	Phenyl	59	264	++	++	-	-	+++
[3f(ii)]	*t*-Butyl	Ethyl	67	261	+	-	++	++	++

* 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)

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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