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(RESEARCH ARTICLE)



Synthesis and evaluation of newly 1-substituted-(2H)-2-thio-4-(3-substitutedthiocarbamido-1-yl)-6-(2-imino-4-thio-5-substitutedbiureto-1-yl) 1,2-dihydro-S-triazines as potent antimicrobial agents

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Abstract

The search for novel antibiotics is of immense importance in research areas around the world for agricultural, pharmaceutical, and industrial applications. The s-triazines are widely used as an important biological tool for the production of a wide range of novel secondary metabolites. In the present study, the series of 1-substituted-(2H)-2-thio-4-(3-substitutedthiocarbamido-1-yl)-6-(2-imino-4-thio-5-substitutedbiureto-1-yl) 1,2-dihydro-s-triazine [4a(i) to 4f(iii)] have been obtained by the isomerisation of 2-(2-imino-4-thio-5-substitutedbiureto-1-yl)-4-(3-substitutedthiocarbamido-1-yl)-6-substitutedimino-1,3,5-thiadiazine [3a(i) to 3f(iii)] in presence of ethanolic sodium bicarbonate solution. The later were synthesized by the chemical action of 1, 3-bis-(N-phenylamidinothiocarbamido)-thiocarbamide and aryl/alkylisocyanodichlorides. On the basis of IR, PMR spectrum data and elemental analysis, the structures of all these compounds were established. The synthesized s-triazine were analyzed for antimicrobial activities by cup plate diffusion method and exhibited a broad spectrum of antimicrobial activity against test pathogens. The isolate was tested for the ability to grow in the presence of antibiotic, such as ciprofloxacin at the same concentration. Thus, the study concludes with the eco-friendly route for synthesizing s-triazine with antibacterial activity against clinically important pathogens.

Keywords: Microbial activity; Synthesis; 1, 3, 5-thiadiazines; s-triazines.

1. Introduction

The heterocyclic compounds containing triazine nucleus gain enormous significance in human life due to their applications in pharmaceutical, industrial, medicinal, agricultural values. s-triazines possess potential therapeutic value for several diseases. Some s-triazines act as antibacterial [1-3], anti-inflammatory, antidiabetic, hypoglycemic agent, and muscle relaxant. They are also used as herbicidal, sea water algicidal, insecticidal [4], and bacteriocidal [5-7], some of them have been used as chain lengthening agents in polymerization, paints, plastic and rubber. In the view of the utility of those compounds in various fields. It was thought interesting to investigate the biological activities of synthesized s-triazines.

2. Experimental Section

All chemical used were of analar grade, 1,3-bis (N-phenylamidinothiocarbamido) thiocarbamide [8] and N-aryl/alkylisocyanodichlorides were prepared according to literature method [9]. Melting point of all synthesized compounds was determined by open capillary method. IR spectra were recorded on Perkin-Elmer spectrometer in the

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range 4000-400 cm^{-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 0.3mm. All compounds gave satisfactory C, H, N and S elemental analysis. All Synthesized s- triazine were screened for their antimicrobial activity using cup plate diffusion method [10-11]. Both gram-positive and gram-negative bacterial organisms viz. *S. aureus*, *B. subtilis*, *A. aerogenes*, *E. coli*, and *S. typhi* were used for microbial activities.

2.1. Synthesis of 2-(2-imino-4-thio-5-phenylbiureto-1-yl)-4-(3-phenyl thiocarbamido-1-yl)-6-ethylimino-1,3,5-thiadiazine [3a(iii)]

A mixture of 1,3-bis (N-phenylamidinothiocarbamido) thiocarbamide (2a) and ethylisocyanodichlorides was refluxed in carbontetrachloride medium for 4 hrs. The product was isolated which on basification with dilute ammonium hydroxide solution afforded crystals of [3a(iii)], yield 69%, m.p. 256°C.

Similarly others compounds [3a(i) to 3f(iii)] were synthesized by above stated scheme.

2.2. Synthesis of 1-ethyl-(2H)-2-thio-4-(3-phenylthiocarbamido-1-yl)-6-(2-imino-4-thio-5-phenylbiureto-1-yl)-1,2-dihydro-s-triazine. [4a(iii)]

2-(2-imino-4-thio-5-phenylbiureto-1-yl)-4-(3-phenylthiocarbamido-1-yl)-6-ethylimino-1,3,5-thiadiazine [3a(iii)] was suspended in 5% aqueous ethanolic sodium bicarbonate solution and refluxed for 2 hr crystalline pale yellow solid were separated out. Yield 71% m.p. 243°C and identified as 1-ethyl-(2H)-2-thio-4-(3-phenyl- thiocarbamido-1-yl)-6-(2-imino-4-thio-5-phenylbiureto-1-yl)-1,2-dihydro-s-triazine [4a(iii)].

2.3. Properties of Compound [4a (iii)]

It is crystalline pale yellow solid having m.p. 243°C. From analytical data, the molecular formula of compound [4a(iii)] is $\text{C}_{20}\text{H}_{21}\text{N}_9\text{S}_3$. IR spectra of compound shows $\nu_{3435.6} \text{ cm}^{-1}$ (NH), 2922.6 cm^{-1} (C-H), 1687.8 cm^{-1} (C=N), 1294.5 cm^{-1} (C-N), 1193.6 cm^{-1} (C=S), 776.9 cm^{-1} (C-S), 1648.2 cm^{-1} (C=N) grouping; The PMR spectrum of compound [4a(iii)] was carried out in DMSO- d_6 and CDCl_3 . Ar-NH protons at δ 8.25-8.61 ppm, triazino NH protons at δ 7.89 ppm, Ar-H protons at δ 6.0-6.85 ppm, $-\text{CH}_2$ protons at δ 3.21-3.38 ppm and $-\text{CH}_3$ protons at δ 0.84-1.50 ppm. The signals at δ 2.53 ppm is due to moisture in DMSO and at δ 2.1 ppm is due to DMSO.

Similarly other compounds were synthesized from [3a (i)] to [3f (iii)] and which on isomerizes yielded [4a (i)] to [4f (iv)] by above method and enlisted in table 1.

3. Results and discussion

All the synthesized compounds were effectively characterized by their IR, UV and PMR spectral analysis and elemental analyses. They were also assayed for their antimicrobial activity against both gram-positive and gram-negative human pathogens and found that they possess insecticidal, bactericidal and medicinal values.

All the bacterial organisms studied are human pathogens. The activity is compared with standard drug ciprofloxacin at the same concentration. From the experimental data it has been observed that in case of gram-positive bacteria like *S. aureus* the compound 4a(ii), 4c(i), 4d(i) and 4e(ii) shows highly activity while compound 4a(i), 4a(iii), 4b(i), 4b(ii), 4c(ii), 4d(ii), 4d(iii), 4e(i), 4e(iii) and 4f(ii) shows moderately activity against the same bacteria. *B. subtilis* organisms, the compound 4a(i), 4a(ii), 4a(iii), 4c(i), 4c(ii), 4d(i) and 4e(iii) were highly effective.

While in case of gram-negative bacteria like *E. coli* the compounds compound 4a(i), 4b(i), 4d(i), and 4f(iii) shows moderate activity and remaining compounds shows inactivity against same pathogen. Similarly 4a(i), 4a(iii), 4b(i), 4c(i), 4c(iii), 4f(i) and 4f(iii) shows high activity against *S. typhi* and compounds 4a(ii), 4b(ii), 4b(iii), 4c(i), 4d(ii), 4d(iii), 4e(ii), 4e(iii) and 4f(ii) shows moderate activity while remaining compounds are inactive against same pathogen.

Table 1 Physical data and antimicrobial activity of the compounds [4a(i) to 4f(iii)].

Compound	R	R ₁	Yield %	m.p. (°C)	Gram Positive		Gram Negative		
					<i>S. aureus</i>	<i>B. subtilis</i>	<i>A. aerogenes</i>	<i>E. coli</i>	<i>S. typhi</i>
[4a(i)]	Phenyl	Phenyl	65	236	++	+++	++	++	+++
[4a(ii)]	Phenyl	<i>p</i> -Chlorophenyl	69	261	+++	+++	++	+	++
[4a(iii)]	Phenyl	Ethyl	71	243	++	+++	-	+	+++
[4b(i)]	Ethyl	Phenyl	67	255	++	++	+	++	+++
[4b(ii)]	Ethyl	<i>p</i> -Chlorophenyl	72	258	++	++	++	-	++
[4b(iii)]	Ethyl	Ethyl	71	241	+	++	++	-	++
[4c(i)]	<i>p</i> -Chlorophenyl	Phenyl	68	251	+++	+++	++	+	+++
[4c(ii)]	<i>p</i> -Chlorophenyl	<i>p</i> -Chlorophenyl	62	259	++	+++	++	+	++
[4c(iii)]	<i>p</i> -Chlorophenyl	Ethyl	71	241	+	++	+	+	+++
[4d(i)]	<i>p</i> -Tolyl	Phenyl	65	241	+++	+	+++	++	-
[4d(ii)]	<i>p</i> -Tolyl	<i>p</i> -Chlorophenyl	69	249	++	+++	+	+	++
[4d(iii)]	<i>p</i> -Tolyl	Ethyl	71	219	++	-	+	++	++
[4e(i)]	Methyl	Phenyl	73	223	++	++	+	-	+
[4e(ii)]	Methyl	<i>p</i> -Chlorophenyl	63	235	+++	++	-	+	++
[4e(iii)]	Methyl	Ethyl	74	217	++	+++	-	+	++
[4f(i)]	<i>t</i> -Butyl	Phenyl	61	252	-	++	++	+	+++
[4f(ii)]	<i>t</i> -Butyl	<i>p</i> -Chlorophenyl	76	257	++	-	++	+	++
[4f(iii)]	<i>t</i> -Butyl	Ethyl	65	267	+	-	++	++	+++

* All Compounds gave satisfactory C, H, N, and S analysis

4. Conclusion

As newly s-triazines shows remarkable antimicrobial activity, these compounds can be easily used as alternative drugs for the treatment of various diseases.

Compliance with ethical standards

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Disclosure of conflict of interest

Authors wish to state that there is no conflict of interest on this work.

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