

Triazinane Derivatives as Possible Antimicrobial Agents

Bajarang Bali Lal Srivastava*

Department of Chemistry, School Of Physical Science, College of Natural and Mathematical science,
University of Dodoma, Tanzania. Post box 259

Abstract: *s*-Triazines (3) were synthesized by the reaction of formaldehyde with substituted benzoic hydrazides (2). Structural assignments of newly synthesized compounds are based on the analytical and spectral data. The final compound (3) were screened against various bacteria viz *Staphylococcus aureus* (Sa) *Enterococcus faecalis* (Ef) and *Escherichia Coli* (Ec) involving two strains of (Sa) and (Ef) and only one of (Ec) as recommended by NCCLS, Moxifloxacin and linezolid were taken as reference standard.

Keywords: Synthesis, Triazines, Hydrazides, Antibacterial activity. Moxifloxacin, linezolid.

I. Introduction

A number of triazines derivatives containing pharmacological groups have been synthesized possess significant antibacterial activity both in vivo and in vitro. Various triazine derivatives such as 2-amino-4-morpholinyl triazine were found outstanding, more recently, some of the triazines derivatives were screened for their antiviral activity² against Encephalomyocarditis virus (EMCV) and Japanese encephalitis virus (JEV) in vivo and in vitro. S-triazines are an important group of heterocyclic compounds. Several derivatives of heterocyclic compounds have been marketed as biologically active agents. We now wish to report our studies on the synthesis of some new S-triazines containing benzamides moiety for improved therapeutic results. The final compound (3) were screened against various bacteria viz *Staphylococcus aureus* (Sa) *Enterococcus faecalis* (Ef) and *Escherichia Coli* (Ec) involving two strains of (Sa) and (Ef) and only one of (Ec) as recommended by NCCLS, Moxifloxacin and linezolid were taken as reference standard.

II. Material And Methods

Melting point was determined in open capillaries and is uncorrected. IR spectra were recorded on a Perkin Elmer Spectrum RXI (4000-450 cm⁻¹) spectrophotometer (cm⁻¹) and ¹H NMR spectra in CDCl₃, on a Bruker DPX 300 instrument using TMS as internal standard (chemical shift in ppm.)

Synthesis of Substituted Phenyl Hydrazides

Substituted phenyl benzoate 1 (0.1 mol) was dissolved in ethanol and hydrazine hydrate (0.15 mol) was added to it with continuous stirring. The reaction mixture was refluxed for 5 hours. Excess ethanol was distilled off. The crystals obtained were filtered and dried in vacuo. Compounds of this category thus prepared.

Synthesis Of N, N', N''-1,3,5-Triazinane-1,3,5-Triyl Tribenzamide (3a)

Substituted benzoic hydrazides 2a (0.01 mol) was dissolved in ethanol (15 ml) by slow warming. The solution was cooled at room temperature and 37% formaldehyde solution (0.025 mol) was added to it. The resultant mixture was allowed to stand at room temperature for one hour a solid appeared which was filtered and washed with cold ethanol. The product was triturated with petroleum ether. The purified product was filtered and dried in vacuum desiccator. Compound of this category thus prepared along with their characterization data are listed in Table 1.

Biological Activity

All the compounds were screened against three bacteria namely *Staphylococcus aureus* (Sa), *Enterococcus faecalis* (Ef), *Escherichia coli* (Ec) in the Dr. Reddy Laboratory, Hyderabad. The Antibacterial activity shown in table II

III. Result And Discussion

Eight compounds belonging to the type N, N', N''-1,3,5-Triazinane-1,3,5-Triyl Tribenzamide (3) were evaluated against two strains of *Staphylococcus aureus*, two strains of *Enterococcus faecalis* and one strain of *Escherichia coli* using the broth dilution technique as recommended by National Committee for Clinical Laboratory Standards (NCCLS). Antimicrobial activity data incorporated in Table II reveal that such compounds are not promising, chemical candidate molecules as far as antimicrobial activity is concerned since only one such compound out of eight, which were screened, displayed moderate order of activity. Thus,

compound no. 4 having Ar = m-nitro phenyl caused inhibition of bacterial inhibition. This compound was found antibacterially active against *Staphylococcus aureus* and *Enterococcus faecalis* to a moderate degree when compared with standard drug moxifloxacin and linezolid. However, anti-bacterial activity was found to be more pronounced on comparison with linezolid. Antibacterial activity of all the compounds was determined against two strains of *Staphylococcus aureus* viz., methicillin susceptible *Staphylococcus aureus* (MSSA) and methicillin-resistant *Staphylococcus aureus* (MRSA); two strains of *Enterococcus faecalis* viz. Vancomycin susceptible *Enterococcal* infection and Vancomycin resistant *enterococcal* (VRE) infection and only one strain of *Escherichia coli*. Some interesting observations have become known regarding the antibacterial effect caused by compound No. 4. This compound was found more active against methicillin resistant *Staphylococcus aureus* (MRSA) than methicillin susceptible *Staphylococcus aureus* (MSSA) since MIC value was found to be 8.0 in the former case and 32 in the latter case. A compound showing activity against resistant strain of bacteria warrants more investigations since a majority of available antibiotics have developed resistance or are developing resistance. In MRSA and some penicillin resistant enterococci, an additional low affinity PBP (penicillin binding protein) is found, that is absent in sensitive strains and which can take over the function of the normal high molecular weight PBPs which have been inhibited by β -lactam action. However, the same compound was found to show the same order of antibacterial activity against both the strains of *Enterococcus faecalis*. It had a MIC value of 32 against both the Vancomycin susceptible *Streptococcal* (VSE) strain and Vancomycin resistant *enterococcal* (VRE) strain. The potential of this compound cannot be disputed since it is showing greater – magnitude of antibacterial activity against MRSA and equal degree of activity against VRE infection. This compound also showed antibacterial activity moderately if compared with standard linezolid (MIC = 256/32 = 8) but not with moxifloxacin. Interestingly, the compound no. 8 having one more nitro group (Ar = 3,5-di-nitrophenyl) was found completely inactive against both the strains of *Staphylococcus aureus* and *Enterococcus faecalis* since MIC values were >256. It seems quite reasonable to interpret that compound no.4 having Ar = m-nitro group finds better fit at the receptor site than the compound no.8 bearing Ar = 3,5-dinitrophenyl group. However, in order to select new chemical agents and to predict their *in vitro* activity against several strains of bacteria quantitative structure activity relationship (QSAR) models need to be developed. This can be done by linear discriminant analysis (LDA) and multilinear regression analyses (MLRA) by using topological indices (TI) as descriptors. In QSAR a large number of compounds of the same series having bioactivity are required but QSAR does not address the lead molecule. In the present case although eight compounds were screened for their antimicrobial activity, only one compound displayed a moderate order of activity. In order to find out a better correlation between the antimicrobial activity and the structural features, synthesis of more such compounds having additional and different substituent's not only at one position of the molecular architecture but at other positions (at least two or three) is desirable.

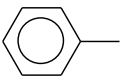
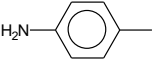
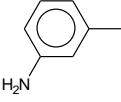
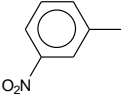
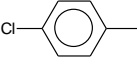
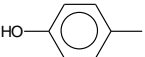
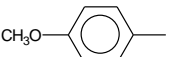
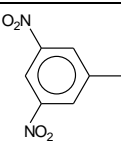
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Table I

Compd.	R	M. P. oC	Yield%	Mol. Formula	Mol. Wt.	Elemental Analysis found (Calculated)		
						C	H	N
3a	H	135	80	C ₂₄ H ₂₄ N ₆ O ₃	444.49	64.82(64.85)	5.47 (5.44)	18.92(18.91)
3b	p-cl	145	75	C ₂₄ H ₂₁ N ₆ O ₃ Cl ₃	547.82	52.65 (52.62)	3.82(3.86)	15.30(15.34)
3e	p-NH ₂	125	70	C ₂₇ H ₃₂ N ₄ O ₁	489.53	59.62(58.8)	6.25 (5.56)	25.1(25.75)
3d	m-NH ₂	138	82	C ₂₄ H ₂₄ N ₄ O ₄	489.53	57.71 (58.8)	5.63 (5.56)	25.72(25.75)
3e	m-NO ₂	136	80	C ₂₄ H ₂₁ N ₉ O ₉	579.48	49.71(49.74)	3.63 (3.65)	21.72(21.75)
3f	3,5-diNO ₂	148	85	C ₂₄ H ₁₈ N ₁₂ O ₁₅	714.47	40.32(40.35)	2.563 (2.54)	23.50(23.53)
3g	p-OH	150	65	C ₂₄ H ₂₄ N ₆ O ₆	492.48	56.50(58.53)	4.88(4.91)	17.10(17.06)
3h	-OCH ₃	153	60	C ₂₇ H ₃₀ N ₆ O ₆	534.56	60.61 (60.66)	5.63 (5.63)	15.68(15.72)

Table II

Compound No.	Ar	Minimum Inhibitory Concentration (MIC) in µg/ml				
		Sa		Ef		Ec
		DRCC035 MSSA	DRCC018 MRSA	DRCC034 VSE	DRCC153 VRE	DRCC018
1		>256	128	>256	>256	>256
2		256	128	>256	>256	>256
3		>256	256	>256	>256	>256
4		32	8	32	32	>256
5		>256	256	>256	>256	>256
6		>256	>256	>256	>256	>256
7		>256	>256	>256	>256	>256
8		256	>256	>256	>256	>256
	Moxifloxacin	0.6	0.6	0.25	0.25	0.03
	Linezolid	2.0 (2.4)	1.0 (1.2)	2.0 (2.4)	1.0 (2.4)	>32

Sa = *Staphylococcus aureus*; Ef = *Enterococcus faecalis*; Ec = *Escherichia coli*