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Synthesis and biological evaluation of hydrazone derivatives as potential antibacrerial agents

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Abstract
A number of hydrazone derivatives were synthesized, and were purified by crystallization or by column chromatography. Structures of all the synthesized compounds are supported by correct IR, 1H NMR, mass spectral and analytical data. The synthesised compounds were tested for their antibacterial activity. Two strains each of gram positive (*Staphylococcus aureusNCIM 2901* and *Bacillus subtilis MTCC 441*) and gram negative species of bacteria (*Escherichia coliNCIM 2563* and *Proteus vulgaris MTCC 1771)* were used for the study Antibacterial activity evaluation was carried out by using agar plate method. Therefore many researchers have synthesized these compounds as target structures and evaluated their biological activities. These observations have been guiding for the development of new hydrazones that possess varied biological activities.

Keywords: hydrazone, antibacterial activity and column chromatography

Introduction

Hydrazones have been demonstrated to possess, among other, antimicrobial, anticonvulsant, analgesic, antiinflammatory, antiplatelet, antitubercular and antitumoral activities (Figure No.1). For example, isonicotinoyl hydrazones are antitubercular; 4-hydroxybenzoic acid [(5-nitro-2-furyl)methylene]- hydrazide (nifuroxazide) is an intestinal antiseptic; 4-fluorobenzoic acid [(5-nitro-2-furyl)methylene]- hydrazide1 and 2, 3, 4- hydrazone 2, which were synthesized in our Department, have antibacterial activity against both Staphylococcus aureus ATCC 29213 and Mycobacterium tuberculosis H37Rv at a concentration of 3.13 µg/mL. N1-(4 Methoxy benzamido) benzoyl]-N2-[(5-nitro-2-furyl) methylene] hydrazine, which was also synthesized in our Department 3, demonstrated antibacterial activity. In addition, some of the new hydrazide-hydrazones that we have recently synthesized were active against the same strain of M. tuberculosis H37Rv between the concentrations of 0.78-6.25 µg/mL4. Hydrazones containing an azometine -NHN=CHproton are synthesized by heating the appropriate substituted hydrazines/hydrazides with aldehydes and ketones in solvents like ethanol, methanol, tetrahydrofuran, butanol, glacial acetic acid, ethanolglacial acetic acid. Another synthetic route for the synthesis of hydrazones is the coupling of aryldiazonium salts with active hydrogen compounds. In addition, 4-acetylphenazone isonicotinoylhydrazones was prepared by Amal and Ergen5 by exposing an alcohol solution of 4- acetylphenazone and INH to sunlight or by mixing them with a mortar in the absence of the solvent. Many effective compounds, such as iproniazide (Figure No. 1) and isocarboxazide (Figure No. 1), are synthesized by reduction of hydrazide-hydrazones. Iproniazide, like INH, is used in the treatment of tuberculosis. It has also displays an antidepressant effect and patients appear to have a better mood during the treatment. Another clinically effective hydrazide-hydrazones is nifuroxazide, which is used as an intestinal antiseptic.

Experimental Work

Reaction Scheme

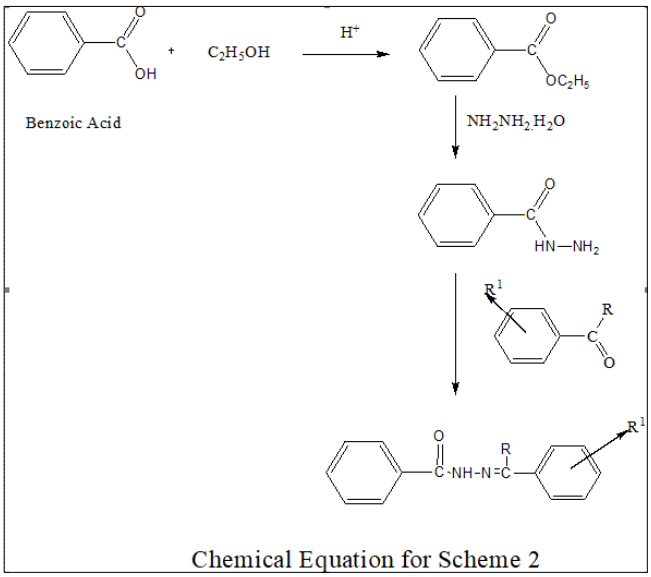

Fig 1

Table 1: Physical caharacterisation data of synthesised compounds

Code	Aldehyde/ Ketone rected	R	R^1	% yield	Melting Point	Physical state	Colour
1a	Benzaldehyde	H	H	82%	206 - 208 ^{0}C	Solid	Pale Yellow
1b	4-Nitrobenzaldehyde	H	4-NO_2	85%	250 - 252 ^{0}C	Solid	Yellowish white
1c	4-Methoxybenzaldehyde	H	4-OCH_3	86%	216 - 218 ^{0}C	Solid	Cream
1d	Phenyl methyl ketone	CH_3	H	92%	196 - 198 ^{0}C	Solid	Reddish Brown
1e	4-Nitro phenyl methyl ketone	CH_3	4-NO_2	80%	248 - 250 ^{0}C	Solid	Cream

Procedure

1. Initially esters were prepared from benzoic acid by using the method reported by S.D. Bhardwaj.The refluxion on these acids with absolute methanol and conc. H_2SO_4 on steam bath formed corresponding methyl substituted benzoates.
2. The methyl esters on refluxing in water bath with hydrazine hydrate dissolved in methanol formed corresponding benzhydrazides.
3. Aldehydes and ketones (0.02 mol) in 15 mL of ethanol was taken in a Round Bottomed Flask
4. Then to the flask aqueous solution of benzhydrazides (0.03 mol) and 2 drops of Acetic acid was added slowly.
5. The mixture was heated at 80-90 ^oC for 4 h and then left to cool.
6. The precipitate was collected and purified by crystallization from ethanol to give compounds as crystals and the physical characterization data will be given in table-1

Anti microbial Studies

Antibacterial Studies

The synthesised compounds were tested for their antibacterial activity. Two strains each of gram positive (*Staphylococcus aureusNCIM 2901* and *Bacillus subtilis MTCC 441*) and gram negative species of bacteria (*Escherichia coliNCIM 2563* and *Proteus vulgaris MTCC 1771)* were used for the study. Tetracycline and Chloramphenicol were used as standards. This method evaluates the effectiveness of the compound in comparison with the zones of inhibition formed in solid agar medium caused by the inhibition of growth of bacteria by the compound and the results were given in table 2.

Table 2: Inhibition Zone diameters of various concentrations of 1a-1e on various species of bacteria

Organism	Concentration (µg/ml)	Inhibition Zone diameter (cm)				
		1a	1b	1c	1d	1e
Sa NCIM 2901	Standard (10 µg/ml)	1.2	1.2	1.2	1.2	1.2
	10 µg/ml	0.0	0.0	0.2	0.2	0.2
	20 µg/ml	0.0	0.0	0.4	0.4	0.4
	30 µg/ml	1.0	0.6	0.6	0.6	0.6
	40 µg/ml	1.5	0.8	0.7	0.7	0.7
	50 µg/ml	1.8	0.9	0.9	0.9	0.9
Bs MTCC 441	Standard (10 µg/ml)	1.4	1.4	1.4	1.4	1.4
	10 µg/ml	0.0	0.0	0.0	0.0	0.0
	20 µg/ml	0.2	0.3	0.5	0.5	0.5
	30 µg/ml	0.8	0.6	0.6	0.6	0.6
	40 µg/ml	1.1	0.8	0.9	0.9	0.9
	50 µg/ml	1.3	1.1	1.1	1.1	1.1
Ec MTCC 441	Standard (10 µg/ml)	1.2	1.1	1.1	1.1	1.1
	10 µg/ml	0.0	0.0	0.0	0.0	0.0
	20 µg/ml	0.4	0.4	0.3	0.3	0.3
	30 µg/ml	0.7	0.6	0.5	0.5	0.5
	40 µg/ml	1.0	0.9	0.7	0.7	0.7
	50 µg/ml	1.5	1.2	1.0	1.0	1.0
PsMTCC 1771	Standard (10 µg/ml)	1.0	1.0	1.0	1.0	1.0
	10 µg/ml	0.0	0.0	0.2	0.2	0.2
	20 µg/ml	0.0	1.3	0.6	0.6	0.6
	30 µg/ml	0.5	1.6	1.0	1.0	1.0
	40 µg/ml	0.6	2.2	1.3	1.3	1.3
	50 µg/ml	0.8	2.5	1.6	1.6	1.6

Conclusion

Literature review reveals that many hydrazones derivatives were reported for antimicrobial activity. However because of the developing resistance of microbes to the drugs, newer derivatives were needed to combat this resistance. Hence various derivatives of hydrazones were developed.The designed compounds are synthesized as per procedures reported in various articles and journals. The carbonyl compounds i.e Aldehydes and Ketones were condensed with hydrazine derivatives to get various hydrazones derivatives. These compounds tested for Antimicrobial activity.All the synthesised compounds of the two series were evaluated for their antibacterial activity by cup-plate method. Various concentrations of the synthesised compounds were tested for their activity over 2 strains each of gram-positive and gram negative bacteria and four strains of fungi. The compounds showed good anti-bacterial activity.

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