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Effect of New Derivatives of Isoniazid on *Mycobacterium Tuberculosis*

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ABSTRACT

Derivatives of Isoniazid with Cinnamaldehyde, Furfuraldehyde and Acetophenone were synthesized which were characterized by elemental analysis and spectral studies. Effect of newly synthesized compounds was studied against mycobacterium tuberculosis. The antibacterial behaviour of the synthesized compounds clearly reflect that 2 (1-Isonicotinyl 2-furfurylidene Hydrazone) is more potent than the compound 1 (1-Isonicotinyl 2-Cinnamylidene Hydrazone) and 3 (1-Isonicotinyl 2-Methylphenyl ketone hydrazone) and order of the antibacterial potential of resulted new derivatives is in the order 2 >1> 3 to inhibit the growth of Mycobacterium Tuberculosis. This work leads to new frontiers in drug industry and many more applications.

Keywords: Isoniazid, Cinnamaldehyde, Mycobacterium, Furfuraldehyde, Acetophenone, Reframpin.

INTRODUCTION

Tuberculosis, a disease that has been with mankind since antiquity, remains an important health problem and a major cause of human misery even today. Mycobacterium tuberculosis is an organism belonging to the family of mycobacteriaceae and the order actinomycetals. It is slowly growing organism. The most common form of tuberculosis in man is a chronic infection of lungs, but virtually every organ of the body may be involved. Streptomycin was established as the first effective anti tuberculous drug. A few years later introduction of Isoniazid revolutionized the treatment of all forms of tuberculosis but it does not produce immediate inhibition of the growth of Mycobacterium tuberculosis [**1-3**]. Tuberculosis, regardless of the concentration. Recently the other antitubercular drugs have been developed such as Pyrazinamide, Rifampicin and ethambutol [**4-6**]. The organism however can develop resistance to these drugs therefore the work is still continued to develop a safe drug which may prove more potent as compared to the previous drugs. Susceptibility of mycobacterium tuberculosis against Isoniazid and its derivatives was reported by Suriyati Mohammad [**7**]. Advanced anti Mycobacterial screening of Isoniazid related hydrazones and hydrazides has been reported recently [**8, 9**]. Hence the present studies are carried out to synthesize some new derivatives of Isoniazid with some aldehydes and Ketones, as mentioned in the paper, which are characterised by elemental analysis and spectral studies and their effect of on antimycobacterium tuberculosis is studied by Lowenstein-Jensen medium to test these compounds as antitubercular agents [**10, 11**].

MATERIALS AND METHODS

Melting points were measured by capillary method. Elemental analysis of C, H, N, IR spectra and ^{1}HNMR spectra were carried out in research laboratory of CDRI, Lucknow. Purity of compounds was monitored by TLC on Silica gel coated plates.

1-Isonicotinyl 2-Cinnamylidene Hydrazone, (1): Equimolar proportion of Isoniazid (1gm.) and Cinnamaldehyde (0.96 gm.) were mixed and mixture was refluxed on water bath for about half an hour at the temperature between 60-65 °C.The solid compound so formed separated on cooling, which was then washed and recrystallized with alcohol to furnish compound (1) Yield 1.8 gm. Per 1 gm. Of Isoniazid, M.P. 198-200 °C. Anal. Caled for C_{15}, $H_{13,}$ N_3 , O: C, 71.72; H.5.17;N, 16.72. Found: C, 70.64; H, 4.99; N, 16.86%; IR: Cm 1631.8 [C=C], 1600.1 [C=N], 1580.2 [C=O], 3232.9 aromatic CH -stretching], 3413.3 [NH-Stretching]; 'HNMR δ8.701 [py-C=O]; 7.587 [HN-C=O]; 4.889 [N=C-C]; 7.372 [HC-Ar].

1-Isonicotinyl 2-furfurylidene Hydrazone, (2): Isoniazid and fururaldehyde in equimolar proportion i.e. 0.70 gm. of furfuraldehyde per gm. of Isoniazid were mixed and mixture was refluxed in a round bottom flask on water bath with thermostat device for one hour at the temperature between 40-45°C. The solid compound so formed separated on cooling which was washed and recrystallized with alcohol. Yield 1.25 gm per 1gm. of Isoniazid, M.P. 190°C. anal. Calcd. For C_{11}, H_9, N_3 O_2: C, 61.41; H, 4.18; N, 19.53. Found: C, 61.31; H, 3.99; N, 20.19%; IR: cm^{-1} 949.6 [Furon ring], 1619.9 [C=N], 1650.3 [C-0], 3121.2 [Aromatic CH- Stretching], 3271.6 [NH-Stretching]; ^{1}HNMR: δ8.693 [Py-C=O]: 7.587 [HN-C=O]; 3.331 [HC-fur]; 6.623 [furfuryl ring).

1-Isonicotinyl 2-Methylphenyl ketone hydrazone, (3): The equimolar proportion of the isoniazid(Igm.) and acetophenone was refluxed on water bath with thermostat device for about an hour in the range temperature between 90-95°C. The obtained compound was filtered and washed and thereafter re-crystallized with alcohol. Yield 1.3 gm per 1 gm. of Isoniazid, M.P. 165-171°C. Anal. Calcd. For C_{14} H_{13} N_3 O: C, 70.30; H, 5.43; N, 17.56. Found: C, 69.50; H, 5.25; N, 17.70%; IR: cm^{-1} 1407.6 [Banding vibration frequency for CH_3 group], 1601.2 [C=N]; 1687.5 [C=O]; 3120.5 [aromatic CH-Stretching], 3188.0 [NH-Stretching]; ^{1}HNMR: δ8.680 [Py-C=O]; 7.614 [HN-C=-O bond]: 2.416(Ar-C-R). Characterization data of these compounds are presented in table 1.

Table 1. Characteristics and elemental analysis of Isoniazid Derivatives

Compound	Yield	M.P. (^{0}C)	Mol. Formula	Found (%) [Calcd]		
	Gm./1gm. of INH			C	H	N
1	1.8	198-200	C_{15} H_{13} N_3 O	70.64 [71.72]	4.99 [5.17]	16.86 [16.72]
2	1.25	190	C_{11} H_9 N_3 O_2	61.31 [61.41]	3.99 [4.18]	20.19 [19.53]
3	1.3	165-171	C_{14} H_{13} N_3 O	69.50 [70.30]	5.25 [5.43]	17.70 [17.56]

RESULTS AND DISCUSSION

The derivatives of Isoniazid were screened for their antibacterial behaviour against mycobacterium tuberculosis. "Proportion method" was used for the antibacterial activity. The method was based on Lowenstein-Jensen medium [**11, 12**]. The observations regarding the sensitivity of the compounds are based on the growth of the bacteria in different suspensions prepared by adding varying concentration of the compound and the days to inhibit the growth. Five suspensions (S_1, S_2, S_3, S_4, S_5, as indicated in table 2) were used for all proportion sensitivity tests (Where 4mg/ml of moist bacteria is present in the first suspension S_1 and the ratio of concentration in others suspension as compared to S_1, is 1: 10:100:1000:10000 in terms of dilutions.) Standard antibacterial Isoniazid was also tested under similar conditions for comparison. On the basis of the observations as shown in Table 2, synthesized derivative 2 (1- Isonicotinyl 2 furfurylidene Hydrazone) was found more potent against bacteria in

comparison to compound 1 (1-Isonicotinyl 2-Cinnamylidene Hydrazone) and 3 (1-Isonicotinyl 2 Methylphenyl ketone hydrazone) as it inhibit the growth for the longest period at S_4 and S_5, levels. Compound 3 (1-Isonicotinyl 2-Methylphenyl ketone hydrazone) is least effective as compared to 1(1-Isonicotinyl 2-Cinnamylidene Hydrazone) and 2 (1Isonicotinyl 2-furfurylidene Hydrazone). Compound 3(1-Isonicotinyl 2-Methylphenyl ketone hydrazone) as this compound inhibit the growth of bacteria only at S_5 level and that too for three weeks only, where the compound no.1(1-Isonicotinyl 2-Cinnamylidene Hydrazone) inhibit the growth up to four weeks at same level of concentration.

Table 2. Antibacterial activity data of Isoniazid Derivatives (Invitro sensitivity of Derivatives of Isoniazid on L-J medium [drug containing L-J]

Compound	Suspension	Observation Days					
		7	14	21	28	35	42
INH*	S_1	-	+	++	++±	++±	++++
	S_2	-	+	++	++±	+++	++++
	S_3	-	+	+	+±	++	+++
	S_4	-	+	±	+	+	++
	S_5	-	-	-	-	+	+
1	S_1	-	+	++	+++	++++	++++
	S_2	-	+	+	++±	+++	+++
	S_3	-	+	+	++	++±	+++
	S_4	-	-	-	+	++	++
	S_5	-	-	-	-	+	+
2	S_1	-	+	++	+++	+++±	++++
	S_2	-	+	++	++	++±	+++
	S_3	-	-	+	+	+	++
	S_4	-	-	-	-	+	++
	S_5	-	-	-	-	-	+
3	S_1	-	+	++	+++	+++	++++
	S_2	-	+	+	+±	++	+++
	S_3	-	-	-	-	++	+++
	S_4	-	-	-	+	+	++
	S_5	-	-	-	+	+	+

Growth was recorded as +++ confluent growth, ++ more than 100 colonies, 1-99 the actual number of colonies, INH* [Control, Drug fee, L-J]

APPLICATION

Isoniazid with Cinnamaldehyde, Furfuraldehyde and Acetophenone were synthesized which were characterized by elemental analysis and spectral studies. This organism can develop resistance to certain drugs, therefore the work is still continued to develop a safe drug which may prove more potent as compared to the previous drugs in this field. It is also noticed thatsusceptibility of mycobacterium tuberculosis against Isoniazid and its derivatives are much useful in drug industry.On the basis of the observations it is found that bacteria in comparison to certain compounds under study as it inhibit the growth for the longest period for three weeks only, where the compounds like1-Isonicotinyl 2-Cinnamylidene Hydrazone inhibit the growth up to four weeks at same level of concentration. This work is in agreement with the work of other coworks [**13**]. Certain more applications can be recorded using more potential values. This work leads to new frontier in the drug Industry and Biochemistry etc.

CONCLUSION

Result of the studies pertaining to the antibacterial behaviour of the synthesized compounds clearly reflect that 2 (1-Isonicotinyl 2-furfurylidene Hydrazone) is more potent than the compound 1 (1-Isonicotinyl 2-Cinnamylidene Hydrazone) and 3 (1-Isonicotiny! 2-Methylphenyl ketone hydrazone) and order of the antibacterial potential of resulted new derivatives is in the order 2 >1> 3 to inhibit the growth of Mycobacterium Tuberculosis.

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