Biography

ARJUN MALLIK M.S. (RES)

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Research Chemist and Biomedical Scientist – Some highlights

1. **Recipient of Gold Medal** for an outstanding research work on synthesizing several anti-tubercular drugs given by the Department of Organic chemistry, Indian Institute of Science, Bangalore, India.
2. Discoverer of Cobalt as an essential trace nutrient element in higher plants like Tomato and Rubber Plants- Post Graduate Research conducted in Kuala Lumpur, Malaysia.
3. Discoverer of new Pathways to understanding mechanism of implantation of 5-day old Rat blastocyst to the rat uterine wall. Research conducted under the direction Dr.C. Alan B. Clementson MD, FACOG, Director & Head of the Department OBG-GYN at the Methodist Hospital of Brooklyn-NewYork.1968-73
4. Design and redesign of chemical and biochemical equipments at the Methodist Hospital of Brooklyn, New York- 1968-73.
5. Over 40 publications in international and peer reviewed Journals.
6. Established a New Basic Chemicals and Pharmaceutical manufacturing plants in Bangalore, India-1975-79.
7. Project manager in Fisher Scientific Company in the R &D division, Introduced over 200 new products in Biotechnology Division, New Jersey 1980-87.
8. Author and Co-Author of 5 patents at Fisher Scientific Company
9. Administrator of SM medical practice. Optimized The management of the practice for improved productivity and efficiency.1988-2002.

10. Arjun Malik's professional experience can be found in WHO's Who directory [CAMBRIDGE, NY]16TH edition. For details and availability for consultation contact: Arjun-mallik@comcast.net.

Early Development of Antitubercular drugs and their Pharmacological data

By Arjun Mallik, Biomedical Scientist

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Background:

Tuberculosis (TB) is a serious airborne disease caused by *Mycobacterium tuberculosis*[1] , being considered as a global health emergency by the World Health Organization (WHO).[2] Control and prevention of TB are major challenge as one-third of the world's population is infected with Mycobacterium. The use of Penicillin [3-6], sulfa drugs [7] streptomycin[8,] Isonicotinic acid hydrazides (INH) [9-11] and p-aminosalicylic acid (PAS) [12] are important milestones in the progress of chemotherapy treatment for the control of tuberculosis in several countries in the world. In the 50's itself Tuberculosis was ranked as the seventh among the causes of death worldwide and the death rate was 5-6 million each year and dreaded as enemy number 1.

Among the chemotherapeutics used Streptomycin had serious drawbacks leading to serious kidney dysfunction and drug resistance. The problem of drug resistance was overcome by the administration of p-Aminosalicylic acid (PAS), Isonicotinic acid hydrazide (INH) along with Streptomycin. Several other combination drugs were developed since then. Clinical treatments using INH was considered as "wonder drug' in the treatment of tuberculosis. However, INH also developed drug resistance. A class of thiosemicarbazones called 'Tibiones' and related compounds were introduced by Behrnisch and coworkers.[13] Acyl derivatives of thiosemicarbazones and its oxygen analogues were prepared and showed promising antituberculostatic due to their thiosemicarbazone moiety.

Part I. In search of new potent and safe antitubercular agents, the author decided to synthesize a new class of *several* acyl semicarbazides and acylthiosemicarbazides and their pharmacological activities were studied for the treatment of Tuberculosis.

Part II of the investigation concentrates on the isolation of the amino acids in the human hair sample and Silk waste.

Part III describes the N-Acyl derivatives of alpha amino acids (esters and amides) where the acyl groups were the hydrazides described in **Part I**. Pharmacological data included shows the effectivity of these drugs for curing tuberculosis.

In this brief article amongst several other compounds that were synthesized and tested for the pharmacological activity, the most important ones only are described here.

Part I. The following Semicarbazides (or carbazones) and their corresponding thio derivatives were synthesized by novel methods. The following scheme **1** shows the general method for the preparation of semicarbazides starting from the corresponding hydrazides.

General reaction scheme where R the individual semicarbazide structures are shown in **Figure 1** below.

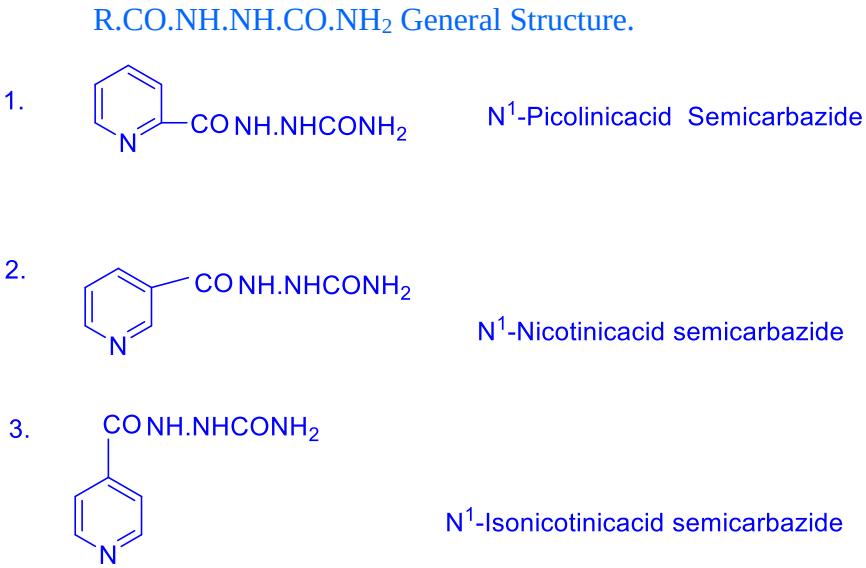


Figure-1- Semicarbazides

Table 1. shows the percent yield and other analysis data for the semicarbazides. The author also prepared the corresponding hydrazides in high yield and they were characterized appropriately.

Table 1. Data for acylsemicarbazides.

RCO-	Solvent of crystallization	Yield (%)	m.p.^{o}C	N_2 found (%)	N_2 Calculated	Solubility in water
Picolinyl	Water	45	190	29.84	31.1	Soluble
Nicotinoyl	Alcohol	20	190-01	-	31.1	Very soluble
Isonicotinyl	Water	55	218-9	30.9	31.1	Soluble
Benzoyl	Water	80	220	-	-	Moderately soluble

The pharmacological properties of the new compounds synthesized by the author along with other hydrazides are shown in Table 2. It is to be noted that picolinic acid hydrazide and Isonicotinylsemicarbazides inhibit the growth of tuberculosis in vitro in the concentration of 10γ and 2 γ respectively though isonicotinic acid hydrazide is far more powerful than either of these.

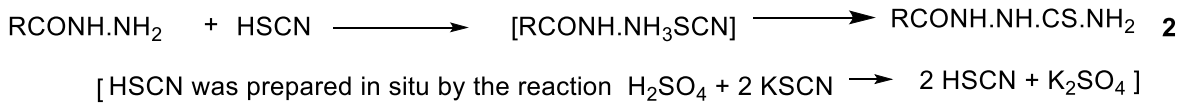
Table 2. The pharmacological data of the newly synthesized compounds. *

Compound	Concentration used		
	Staph. Aureus 1:1000	E. Coli 1:1000	Myco.Tuberc.
Picolinic acid hydrazide	+	+	10 γ -
N^1-Picolinyl semicarbazide	+	+	10 γ +
Nicotinic acid hydrazide	+	+	10 γ +
N^1-Nicotinyl semicarbazide	+	+	10 γ +
Isonioctinic acid hydrazide	+	+	0.05 γ -
N^1-Isonicotinyl semicarbazide	+	+	2 γ -

+ Growth - No Growth

- The data were provided by the pharmacology department of the Indian Institute of Science

It has been found by Behnisch[14] and co- workers that the acyl derivatives of p-acetylamino benzaldehyde thiosemicarbazone known as "Tibione" has antitubercular properties. This semicarbazide itself as well as its alkyl derivatives have been found to be active against BCG strain of Tuberculosis. Based on those studies the author extended his work to prepare several thiosemicarbazones and tested their pharmacological properties. These derivatives are the corresponding thio derivatives of the semicarbazides shown above in Figure **1**. They were all prepared by the general scheme **2** as shown below:



General reaction scheme **2** where R the individual thiosemicarbazide strucures are simila to the one shown in Figure **1, where S replaces the O in - NH-CO-NH_2**

Table 3 shows the data for the compounds along with the elemental analysis and melting point data to prove the formation of the compounds.

Table 3. Data for N^{1-} acyl thiosemicarbazones.

Compound	Yield (%)	m.p. ^oC	N_2 found (%)	N_2 Calculated (%)
N^1-Picolinyl thio-semicarbazides	60	190	28.8	28.6
N^1-Nicotinyl thio-semicarbazides	40	181-2	28.6	28.6
N^1-Isonicotinyl thio-semicarbazides	70	278 (with decom.	28.2	28.2
N^1- Benzoyl thio-semicarbazides	60	220	20.75	20.75

The pharmacological properties of the new compounds synthesized by the author are shown in Table 4. *

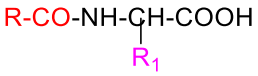
Compound	Concentration used		
	Staph.Auraus 1:1000	E. Coli 1:1000	M. Tuber
N^1-Picolinyl thiosemicarbazone	-	-	10 γ +
N^1-Nicotinyl thiosemicarbazone	-	+	10 γ +
N^1-Isonicotinyl semicarbazide	+	+	10 γ -

- + Growth - No Growth. *The data were provided by the pharmacology department of Indian Institute of Science

The inhibitory action of the picolinoyl derivative on the Staph. Aureus and E. Coli at 1:1000 concentration and that of Nicotinoyl derivative on the Staph. Aureus at 1:1000 concentration and finally that of the iso-nicotinoyl derivative at 10 γ- concentration are noteworthy.

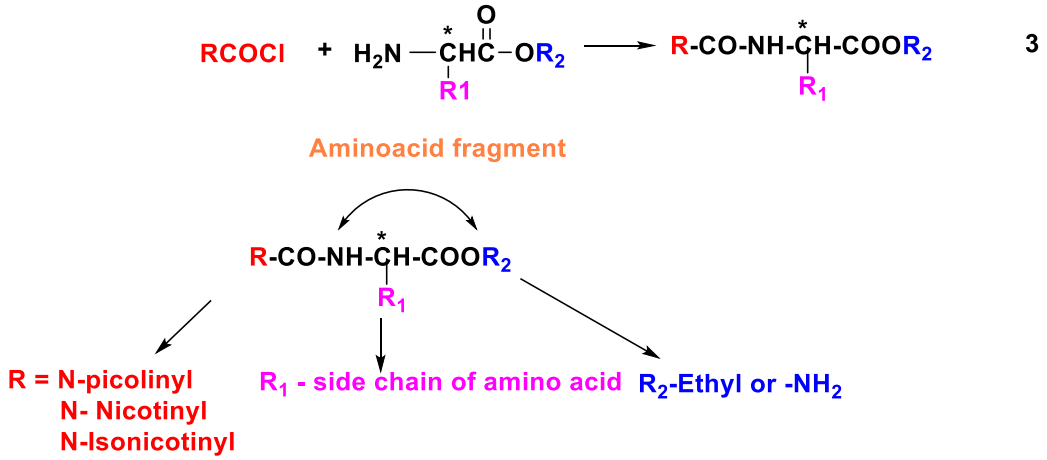
Part II. Isolation of α-amino acids from human hair and silk waste.

The Biological importance of alpha amino acids as essential material for human and animal nutrition and well-being and their occurrence as conjugates in bile acids stimulated the investigation of the authors using amino acids isolated from human hair and silk waste and their Acyl derivatives as potential antibacterial agents against Tuberculosis (shown below). This study lead to new leads in the development of these drugs.



The author spent extensive time in isolating several amino acids from the least expensive raw materials such as human hair and silk waste to prevent the use of high-priced fine chemicals (B.D.H catalogue) using novel methods. Glycine, l (+) alanine, l (-) alanine, l (-) serine, and l (-) Tyrosine, were isolated from the silk waste and l (-) cystine from human hair waste collected from barber shops. All these isolated amines were characterized by their melting points, N_2 contents, specific color reactions using circular chromatography. Optical rotations were determined using Polarimeter (data is not shown here). The author also developed a unique ninhydrin spraying apparatus (Figure not shown here) for the circular chromatography.

The isolated amines were then converted to their acyl derivatives by coupling with different acid chlorides and the ester or the amides of the amino acids, or via azide method (not shown here) as shown by the general scheme 3.



The compounds prepared were characterized by estimating the amino acid content by Van Slyke's method by measuring the amount of Nitrogen after hydrolysis and treatment with nitrous acid. The author used a home-made apparatus for the Van Slyke's method since it was not available, with pieces of broken burettes and separatory funnels see **Figure 2** below. The analysis results are not included in this article.

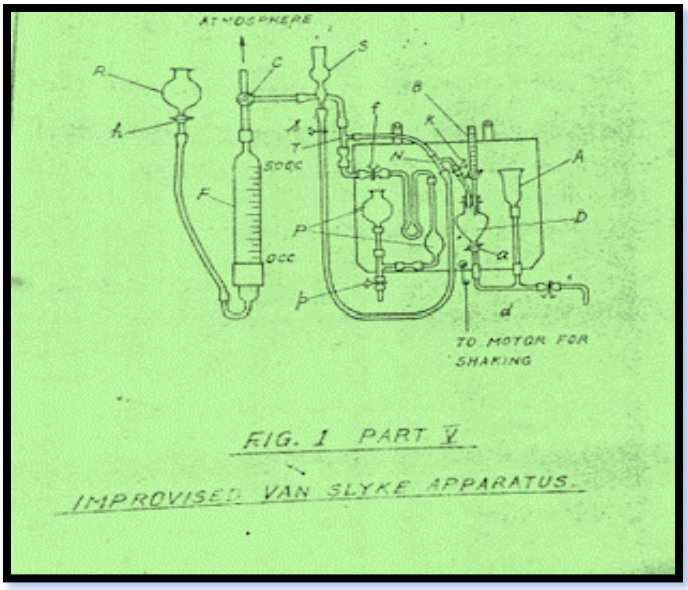


FIG. 1 PART V

IMPROVISED VAN SLYKE APPARATUS.

More than15 different compounds were synthesized and their pharmacological properties* were tested. (*The data were provided by the pharmacology department of The Indian Institute of Science).

Table 5 summarizes the pharmacological data.

Serial Number	Compound	**Minimum inhibitory Concentration**		
		Mycotuberculosis **H_{37} Rv**	E. Coli	Staph. Aureus
1	Picolinyl Glycine	-	-	-
2	Picolinyl amide	-	-	-
3	Picolinyl alanine	-	-	-
4	Picolinyl hydrazide	-	-	-
5	Nicotinoyl alanine	-	-	-
6	Nicotinoyl amide	-	-	-
7	Nicotinoyl ethyl ester	-	-	-
8	Nicotinoylhydrazide	-	-	-
9	Iso-NicotinoyIalanine amide	-	-	-
10	Iso-NicotinoyIalanine hydrazide	1/1 mill.	1/1 mill.	1/1 mill.
11	Isonicotinic acid	-	-	-
12	Nicotinic acid	-	-	-
13	Picolinic acid hydrochloride	1/1000	1/1000	1/1000
14	Glycine	-	-	-
15	Alanine dextrorotatory	-	-	-

Legend- No inhibition in 1/100

Isonicotinyl alanine hydrazide has shown in vitro and in vivo high antitubercular activity. However, it was found that their antitubercular activity was less than that of INH.

The work described by the author is part of the research conducted for Master's dissertation. Complete work will be published elsewhere. In summary, this work describes the synthesis and biological evaluation of several semicarbazones and thiosemicarbazones of Picoline, Nicotinic and Isonicotinic acid hydrazides and *N* -acylhydrazone derivatives of amino acids from different amino acids, such as glycine, l(-)alanine, l(+) alanine l(-)serine, l(-) tyrosine , l(-)cystine and l(-)glutamic acid. The amino acids used were isolated from silk waste and human hair samples. Many of them showed as very promising drugs for the treatment of Tuberculosis.

Even to date INH related[14] and Acyl derivatives of amino acids[15] are being used and they are effective against Mycobacterium Tuberculosis.

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