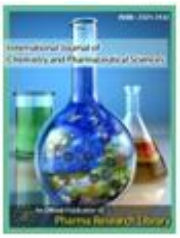
International Journal of Chemistry and Pharmaceutical Sciences
ISSN: 2321-3132 | CODEN (USA): IJCPNH
Available online at:http://www.pharmaresearchlibrary.com/ijcps



Design Synthesis and Characterization of Novel Deuterated Heterocyclic Compounds as Antimycobacterials

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ABSTRACT

The Isoniazid- D was synthesized by using deuterium oxide and the percentage yield was calculated as 67%. The yield obtained was good. The deuterated Isoniazid was characterized by using IR Spectroscopy. The physiochemical properties were determined by Molinspiration Cheminformatics software. NMR Spectroscopic studies were carried out on a Bruker DRX Avance spectrometer equipped with a triple resonance inverse.

Keywords: Moringa oleifera, inhibitory activity, diabetes and hyperlipidemia

ARTICLE HISTORY: Received 11 March 2022, **Accepted** 15 April 2022, **Available Online 2**4 May 2022

Citation: Dhayalan.M, *et al. Design Synthesis and Characterization of Novel Deuterated Heterocyclic Compounds as Antimycobacterials, Int. J. of Chem. and Pharm. Sci., 10(1), 2022: 32-40.*

CONTENTS:

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1. Introduction

Deuterium is used in heavy water moderated fission reactors, usually as liquid D_2O, to slow neutrons without the high neutron absorption of ordinary hydrogen. In research reactors, liquid D_2 is used in cold sources to moderate neutronsto very low energies and wavelength appropriate for scattering experiments. The deuterated drug has lower rates of metabolism and longer half life because of its kinetic isotope effect. In 2017, deutetrabenazine became the first deuterated drug to receive FDA approval. Deuterated polyunsaturated fatty acids, such as linoleic acid, slow down the chain reaction of lipid peroxidation that damage living cells.

Kinetic isotope effect:

Due to the greater atomic mass if deuterium cleavage of the carbon deuterium(C-D) covalent bond requires greater energy than the carbon hydrogen(C-H). C-D bond have a lower vibrational frequency and lower zero point energy that corresponds C-H bonds. The lower zero point energy results in a higher activation energy and a slower rate for C-D bond cleavage. This rate effect is the primary deuterium isotope effect and is expressed as k_H/k_D. The deuterium isotope effect could potentially affect the pharmacokinetics of many drugs that are metabolized by pathways involving C-H bond. The metabolic reaction is

often masked which means that it can be much smaller than k_H/k_D or absent in some cases.

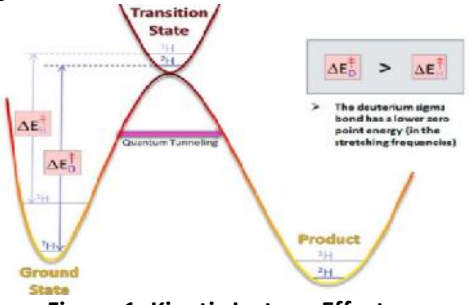


Figure-1: Kinetic Isotope Effect

Deuterium effects on pharmacokinetics:

Deuterium incorporation can sometimes significantly alter the metabolic profile of a molecule, thereby resulting in change in the amount of metabolite formed. The reduced rates of metabolism and metabolic switching, where the ratio of the metabolite change. These changes in the exposure to parent drug and metabolites can have important ramifications with respect to the pharmacodynamic, tolerability and efficacy of a deuterated drug

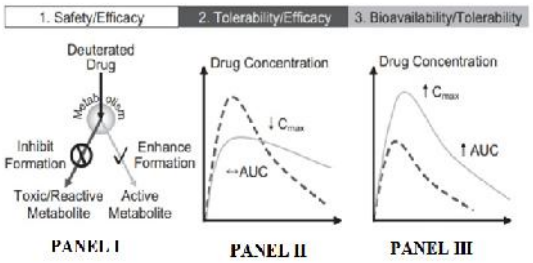


Figure-2: Deuterium Effects on Pharmacokinetics

In panel I, Nevirapine is an example of metabolites shunting in which a deuterated analogue that showed effect upon both the metabolic clearance and toxicity. Nevirapine is non nucleoside reverse transcriptase inhibitor for the treatment of HIV infection that is associated with skin rashes and hepatotoxicity in humans. The deuterium substitution of nevirapine significantly reduces the covalent binding to hepatic proteins. After oral dosing of deuterated nevirapine was rapidly cleared and resulting on plasma level that were much lower than the same dose of the nevirapine. Therefore the metabolic shunting in which deuterium substitution reduce the formation of an undesired or toxic metabolite as well as enhancing the formation of a desired metabolite.

In panel II, Indiplon is an example to reduce the rate of systemic clearance on the effect of deuteration, resulting the compound to increase the biological half life. Indiplon is a $GABA_A$ agonist sleep agent which provides improved pharmacokinetic property. Replacements of N-CH3 with N-CD3 results increase half life. Individual oral dosing of indiplon or deuterated indiplon in rat shows a distinct pharmacokinetic advantage for the deuterated molecule since the half-life increased 2-fold and the exposure increased 2.6 fold.

In panel III, Rofecoxib is an example of reduced rates of metabolism result in an increase in exposure of the drug without changing the rate of systemic clearance. Rofecoxib is a COX-2 selective non-steroidal anti-inflammatory drug and of safety concerns about the increased rate of heart attack and stroke. Deuterated rofecoxib improves the pharmacokinetic profile. After oral dosing in rat the mean C_{max} value of deuterated compound increased 1.6 fold. No improvement in oral half life was observed. The deuterated compound significantly shows impact on pharmacokinetics of the compound without changing the intrinsic pharmacology.

Problems Arising From Formulations Of Deuterated Drugs: P^D is different from P^H while the value of P^D is not equal to the P^H the correction factor is $P^D = P^H$ (PH meter reading) +0.4. The deuterated buffer will be made by carrying out isotopic exchange of aqueous solution with deuterium oxide. The compound would be deuterated at different rate like carboxylic acid, alcohols, amino compounds is instantaneously deuterated. Hydrogen α carbonyl group is exchange slowly with deuterium. Proteins and polynucleotide are deuterated much slower. Deuterated position will exchange back with hydrogen at the same relative rate following dilution and administration into the body.

Deuterium undergoes exchange reaction in the body when it deuterate the organic molecule in the body for example glucose, amino acid. The deuterium oxide administered would be distributed and excreted rapid with water turnover rate. The extra burden should be taken for deuterium oxide in small parenterals should be harmless to human. The transitory enrichment of body water with deuterium oxide would not exceed the toxic threshold. Further investigation and clinical trials are necessary.

Mycobacterium Avium Complex:

The mycobacterium intracellulare causes pulmonary diseases often in immunocompetent individuals. The infection is difficult to treat, mainly due to three barriers

Cell wall:

The cell wall composition of the mycobacterium appears like waxy. More than 60% of the cell wall is lipid, mainly mycolic acids composed of 2- branched, 3- hydroxyl fatty acids with chains made of 76-90 carbon atoms. This prevents many pharmacological compounds from getting to the bacterial cell membrane or inside the cytosol.

Efflux pumps:

A second layer of defense comes from an abundance of efflux pumps in the cell membrane. These transport proteins pumps out potentially harmful chemicals from the bacterial cytoplasm back into the extracellular space and are responsible for the native resistance of mycobacteria to many standard antibiotics.

Location in host: A third barrier is the propensity of some of the bacilli to hide inside the patient's cells, thereby surrounding themselves with an extra physicochemical barrier that antimicrobial agents must cross to be effective.

Tuberculosis:

Tuberculosis is a contagious disease which is caused by mycobacterium tuberculosis. Mycobacterium tuberculosis is not a single species but a complex of species with 99.9% similarity of nucleotide level. The complex includes mycobacterium tuberculosis, M.africanum, M.bovis and M.microti. They are slow growing, intracellular, resistant to single agents and have rich lipid cell wall.

Extrapulmonary tuberculosis:

Tuberculosis that affects any organ outside the pulmonary parenchyma is designated extrapulmonary tuberculosis. In addition to all the sites of the body outside the chest affected by tuberculosis that are clearly extrapulmonary, certain forms of tuberculosis occurring in sites that are fully or partially within the chest are also considered extrapulmonary

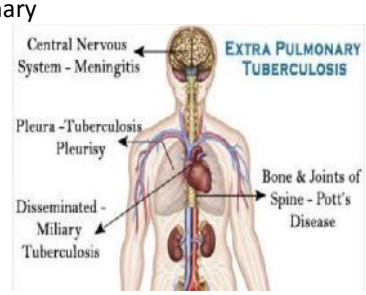


Figure-3: Extrapulmonary tuberculosis

Pleural tuberculosis:

Primary tuberculosis pleurisy occurs within the first month after primary infection, and is not accompanied by active pulmonary tuberculosis. Pleural biopsy yields a yellow liquid, an exudates showing a protein level of more than 30g/l and clear lymphocytosis. Biopsy of pleura can be done by two specimen, one for histological examination, and the other for culture in which case the diagnosis of tuberculosis can be confirmed in more than 70% of cases.

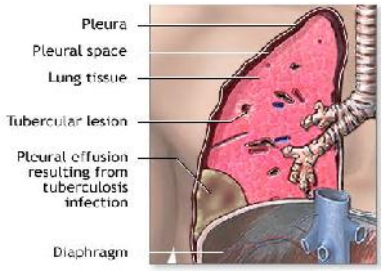


Figure-4: Pleural Tuberculosis

Tuberculous lymphadenitis:

Tuberculous lymphadenitis most frequently affects the lymph nodes in the neck. This form of tuberculosis, which occurs relatively early after primary infection with mycobacterium tuberculosis, often affects young people in countries with a high prevalence of tuberculosis. Adenopathy usually occurs in a single lymph node or chain. At first the enlarged lymph nodes are small, firm and painless then increased in size, become fluctant and may suppurate and drain in a chronic fistula. Within several months a permanent, irregular, dark red scar appears.

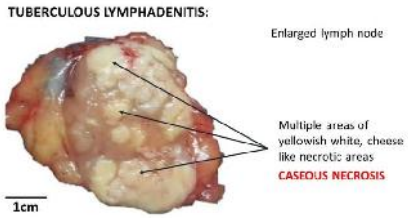


Figure-5: Lymph Tuberculosis

Tuberculosis of the abdomen:

Peritoneal tuberculosis may present with ascites, with no signs of portal hypertension. Aspiration yields a yellow fluid that is rich in protein and lymphocytes. If possible, laparoscopy will show the presence of necrotising granulomata on the peritoneal surface, and histology will confirm the diagnosis of tuberculosis. Intestinal tuberculosis usually occurs in the ileo- caecal area, although it can affect the oesophagus, the stomach and the duodenum. It often presents with intestinal obstruction, fistula formation or an abdominal mass.

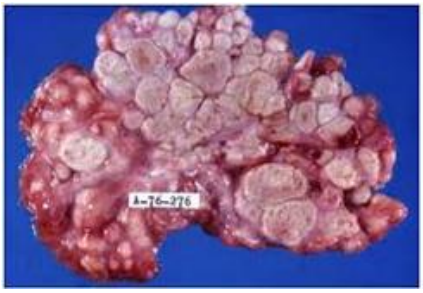


Figure-6: Peritoneal Tuberculosis

Tuberculosis of the pericardium:

Tuberculosis of the pericardium is an infrequent form of tuberculosis of the serous membrane, it is nevertheless more frequent among HIV- infected individuals. The clinical symptoms are those associated with pericardial effusion progressively worsening dyspnoea, paradoxical rapid pulse, low blood pressure, quiet heart beat, high fever, general listlessness. Restrictive pericarditis is accompanied by signs of peripheral stasis (hepatomegaly, ascites, oedema of the legs) reduce heart sounds, and on X-ray the heart shadow may be reduced in size with an immobile margin.

Tuberculosis of the bones and joints:

Tuberculosis of the spine can be a severe form of tuberculosis when there are neurological sequelae. In many cases more than one intervertebral disc space is involved. As the diseases develops, the vertebral body adjacent to the disc space is affected, an abscess is formed and spreads either forward towards the mediastinum or the retroperitoneal space, to the vertebral body with compression of the spinal chord, or back along the vertebral column, eventually appearing as a subcutaneous

"cold" abscess. Collapse of adjacent vertebral bodies affected by tuberculosis may lead to angulated kyphosis. Tuberculosis of the joints primarily affects the large joints (hip, knees, shoulders and elbows) but can affect any joint, including those of the fingers and the small bones of feet. It is usually monoarticular arthritis which presents first as limitations in movement, then painless swelling of the joint after creation of an abscess, but without redness or heat. Late manifestations typical of tuberculosis are draining sinuses from the joints, destruction of the joints and chronic disability.

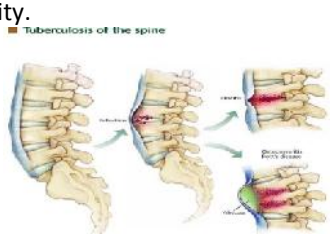


Figure-7: Spine Tuberculosis

Mortality of tuberculosis:

In 2019, an estimated 10 million people fell ill with tuberculosis worldwide and a total of 1.4 million people died from tuberculosis (including 208000 people with HIV). In 2020, the total death of tuberculosis was estimated as 1.66 million. Tuberculosis cases was decreased by an average of 25%.

Life cycle of tuberculosis:

Onset of infection:

The first stage takes place after the inhalation of TB bacillus. If the macrophage is not able to resist the TB bacilli they can reproduce in the macrophage. This leads to the destruction of the macrophage and the infection begins. It takes place between 1-7 days.

Symbiosis:

The TB bacilli start reproducing exponentially and replicate the new emerge ones. This leads to rapid expansion of initial TB bacilli. This stage leads to the third week of infection.

Initial caseous necrosis:

They kill the surrounding non- activated macrophage and run out of cells to divide. The bacteria produce the anoxic condition and reduce the ph. The bacteria can't reproduce anymore but can still live for long time.

Interplay of Tissue: Macrophages surround the tubercule but some may be inactive. The turbecule can break off and spread around. If it spread in the blood it can develop tuberculosis outside the lungs, this is called miliary tuberculosis.

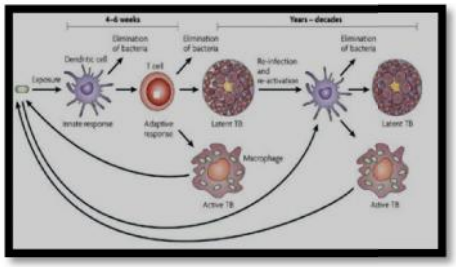


Figure-8: Life Cycle of Tuberculosis

Liquification and cavity formation:

The tubercule at one point will liquify, which will make the diseases spread faster, only a few will get into this stage.

AIM: To design, synthesis and characterization of novel deuterated heterocyclic compound as antimycobacterials.

Objective:

- ❖ To synthesis the novel deuterated heterocyclic compound
- ❖ To determine the characterization of novel drug by spectral analysis
- ❖ To evaluate the novel deuterated compound as anti mycobacterials

Drug profile:

Isoniazid:

Isoniazid is an important drug for the chemotherapy of drug-susceptible tuberculosis. The use of combination therapy (Isoniazid + Pyrazinamide + rifampin) provides the basis for short- course therapy and improved cure rates.

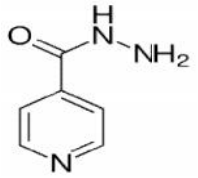


Figure-9: Structure of Isoniazid

Mechanism of action:

Isoniazid enters bacilli by passive diffusion. The drug is not directly toxic to the bacillus but it is activated by KatG, a multifunctional catalase- peroxidase. KatG catalyse the production from Isoniazid of an isonicotinoyl radical that interact with NAD and NADP. A nicotinoyl- NAD isomer, inhibits the activation of enoyl acyl carrier protein reductase. Inhibition of the enzymes inhibits the synthesis of mycolic acid, an essential component of the mycobacterial cell wall, leading to bacterial cell death. Another adduct, a nicotinoyl-NADP isomer, potently inhibits mycobacterial dihydrofolate reductase, thereby interfering with nucleic acid synthesis.

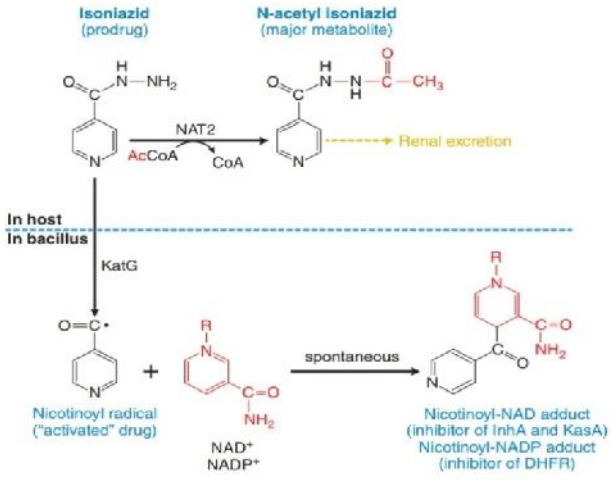


Figure-10: Metabolism and Activation of Isoniazid

Therapeutic uses:

Isoniazid is available as a pill, as an elixir and for parenteral administration. The recommended dose of Isoniazid is maximum of 300 mg administered daily two or three times a week; oral and intra-muscular doses are identical.

Isoniazid Overdose:

As little as 1.5g of Isoniazid can be toxic. Isoniazid overdose has been associated with the clinical trial of

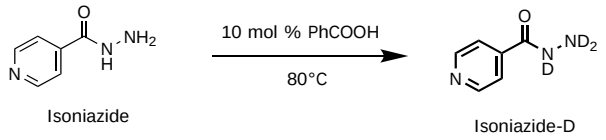
- Seizures refractory to treatment with phenytoin and barbiturates
- Metabolic acidosis with an anion gap that is resistant to treatment with sodium bicarbonate
- Coma

The common symptoms appear within 0.5-3 hours of ingestion include ataxia, peripheral neuropathy, dizziness and slurred speech. When patients ingest 30mg/kg or more of the drug lead to grand mal seizures and coma. If the dose of ingested Isoniazid is unknown, then a pyridoxine dose of 70mg/kg should be used.

2. Materials and Methods

Deuterium oxide (D_2O, 99.9 atom % D) manufactured by Sigma Aldrich and purchased from local vendors. Benzoic acid was purchased from Nice Chemicals Pvt Ltd. Isoniazid were purchased freely from pharmaceutical industry. All reagents used were of laboratory grade.

Figure-11: Schematic Diagram of Isoniazid using Deuterium oxide:



Sythensis:

A mixture of 10mmol of isoniazide (pyridine 4 carbohydrazide) in 2ml of deuterium oxide was refluxed at 60°C for 18h in the presence of 5 mol% benzoic acid. The mixture was neutralized with sodium bicarbonate solution and extracted with ethyl acetate.

Figure-12: Reaction setup for the synthesis of Isoniazid using deuterium oxide

Characterization:

IR Spectroscopy:

IR Spectroscopy studies were carried out on a thermo fisher infrared spectroscopy (Nicolet IS5 FTIR). The results are given below.

NMR Spectroscopy:

NMR Spectroscopy studies were carried out on a Bruker DRX Avance spectrometer equipped with a triple resonance inverse.

MASS Spectroscopy:

The samples were analyzed by LC-MS a triple quadrupole tandem mass spectrometer in polarity switching mode.

Anti tuberculosis activity:

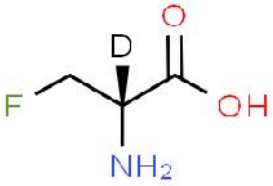
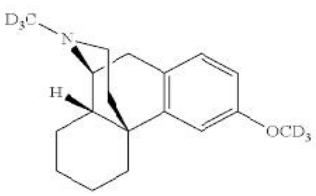
The in vitro anti TB activity of different solvent partitions of the Isoniazid and Isoniazid D was determined against mycobacterium tuberculosis H37Rv using a tetrazolium colorimetric micro dilution assay.

Chemistry:

Synthesis:

The isoniazide - D was synthized by using the above procedure and extarcted with ethyl acteate and the ethyl layer was evaporated, solid were obtained. The percentage yield of isoniazide–D were calculated as 67%. The deuterated isoniazide were characterized by using NMR Spectroscopy, IR Spectroscopy, Mass Spectroscopy and anti-tuberculosis activity.

Table No: 1 Clinical Development of Deuterated Compounds

CHEMICAL STRUCTURE	COMPOUND	STATUS	DEUTERIUM EFFECT
	Fludalnine (MK-0641)	First deuterated drug candidate to enter clinic (1970s) Discontinued	Reduce toxic metabolite, 3-fluorolactate
	D_6 detromethorphan (AVP- 786)	Phase III	Reduce formation of toxic metabolite by CYP2D6

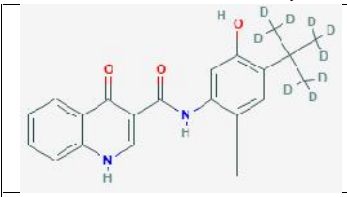
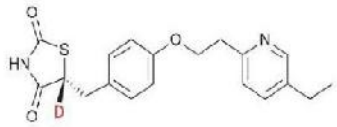
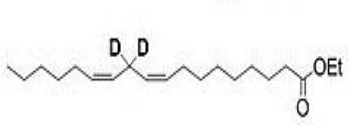
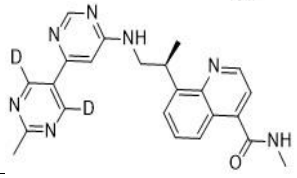
	D_9–ivacaftor	Phase II	Reduce rate of tert- butyl group oxidation and *in vivo* clearance by CYP3A4
	D_1(R)- Pioglitazone	Phase I	Stabilize preferred R-enantiomer obtain mitochondrial function modulation without affected by S- isomer
	D_2 linoleic acid ethyl ester (RT001)	Phase ½	Limit lipid peroxidation
	VX-984	Phase I	Reduce aldehyde oxidase (AO)- driven metabolism

Table: 2 Mycobacterial species and their drugs

MYCOBACTERIALS SPECIES	DRUGS
Mycobacterium kansaii	Isoniazid + rifampin+ Ethambutol
Mycobacterium fortuitum complex	Amickacin + doxycycline
Mycobacterium marinum	Rifampin + Ethambutol
Mycobacterium ulcerans	Rifampin + streptomycin
Mycobacterium abscessus	Cefoxitin (or) imipenem+ Amickacin + clarithromycin
Mycobacterium malmoense	Rifampin + Ethambutol ± clarithromycin

3. Results and Discussion

IR SPECTROSCOPY:

The interperatation of IR Spectroscopy

ISONIAZID- D

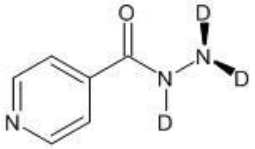


Figure-13: STRUCTURE OF ISONIAZID- D

WAVE NUMBER(cm^-1)	FUNCTIONAL GROUP
2915	Armatic CH Stretching
1678	C=O
1600	C=N

Table:3-: Wave Number and Functional Group of Isoniazide D

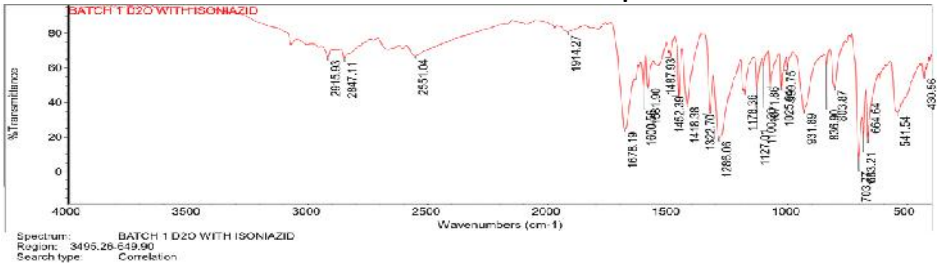


Figure-14: FTIR SPECTRUMOF ISONIAZID-D

ISONIAZIDE:

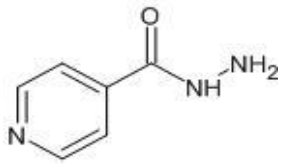


Figure-15: STRUCTURE OF ISONIAZID

Table: 4 Wave Number and Functional Group of Isoniazide

WAVE NUMBER(cm^{-1})	FUNCTIONAL GROUP
3302	NH Stretching (NH_2 Group)
3102	NH Stretching (CONH Group)
3008	Aromatic (CH Stretching)
2849	CH_2 Stretching
1661	C=O Stretching
1602	C=N Stretching

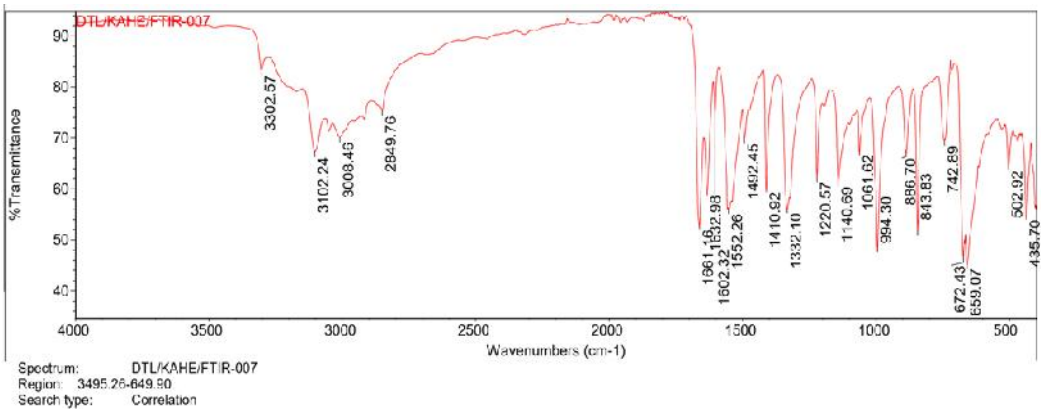
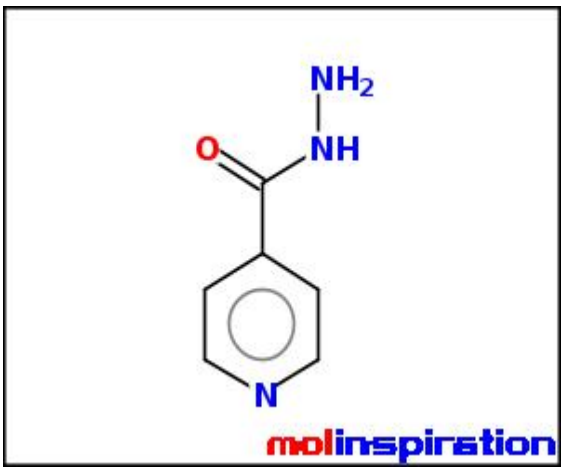


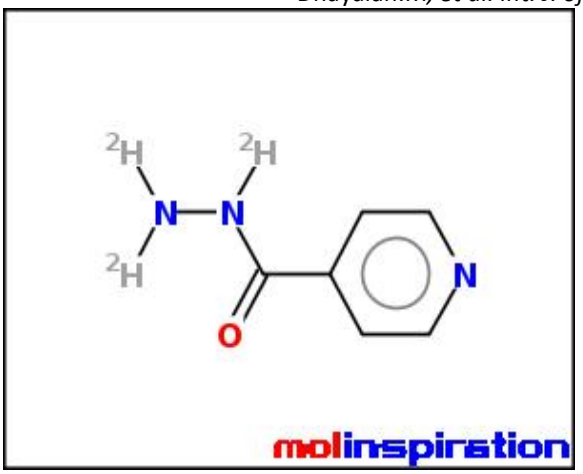
Figure-16: FTIR SPECTRUM OF ISONIAZID

In the structure of Isoniazid the spectrum of 3302 (NH Stretching of NH_2 Group) and 3102 (NH Stretching of CONH Group) were not observed in the spectrum of isoniazide - D. Hence it is confirmed that the deuterated compound of isoniazid were formed.



MOLINSPIRATION:
Mol inspiration of Isoniazid

Log P	0.97
TPSA	68.01
N atoms	10
MW	137.14
No N	4
No NHN	3
n violations	0
N rotb	1
Volume	122.56



Mol inspiration of Isoniazid D

Log P	0.97
TPSA	68.01
N atoms	10
MW	140.12
No N	4
No NHN	3
n violations	0
N rotb	1
Volume	122.56

Physicochemical properties were determined by mol inspiration and the value of log P was -0.97 were same for both the compound and there were difference in the molecular weight.

4. References

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