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SYNTHESIS AND ANTI-TUBERCULAR ACTIVITY- ; N,N'-BIS(BENZOTHIOZOLYL)-2,6-PYRIDINEDICARBOXAMIDE

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Abstract
N,N'-bis(benzothiazolyl)-2,6-pyridinedicarboxamide was synthesized by the condensation of 2,6-Pyridinedicarboxylic acid and thionyl chloride under anhydrous conditions, with benzothiazole ,synthesized compound was characterized by IR (KBr) υ cm $^{-1}$ ^{1}HNMR(DMSO-d_6),^{13}CNMR and mass spectral studies The results show that the substitution of 2-amino-benzothiozolyl group at -OH moiety of carboxylic group of pyridinedicarboxylic acid make this molecule active against Mycobacterium –tuberculosis

Keywords: - *N,N'*-bis(benzothiozolyl)-2,6-pyridinedicarboxamide, M-tuberculosis

Introduction
The amide bond –C(O)NH–of Pyridine-2,6-dicarboxamide has long attracted much attention since it is an essential building unit in proteins. The high stability of the amide linkage towards hydrolysis is of crucial importance to biological systems, since it allows the construction of peptides from relatively simple amino acid precursors[1].

Another derivatives of pyridine- dicarboxamide in which pyridine ring is in the form of 1,4-dihydropyridine are used as anti-allergic[2-4] and anti-inflammatory agents[5-7]. They are also used in the treatment of cardio-vascular diseases[8] as well as potential cardiovascular agents[9-10]. In recent years Pyridine-2,6-dicarboxamide derivatives are used in asymmetric synthesis ,molecular receptor[11-12], & in dendimer synthesis[13]. Pyridine-2,6-dicarboxamide derivatives show their various biological activities. N,N'-2-napthyol-Pyridine-2,6-dicarboxamide exhibit its sedative[14] and anticonvulsants properties [15]. Another derivatives of pyridine dicarboxamide in which Nitrogen atom of pyridine dicarboxamide is substituted with heterocyclic moiety like isoxazoles are used as anti-allergic[16] and anti-inflammatory agents [17]. Sulphonamides substituted pyridine dicarboxamide are also used in the treatment of cardio-vascular diseases[18] as well as they are potential cardiovascular agents[19]. Our outgoing research is to synthesized the benzothiozolyl substituted pyridine dicarboxamide derivatives and evaluate their in-vitro activity against M-tuberculosis which are resistance to Moxifloxacin.

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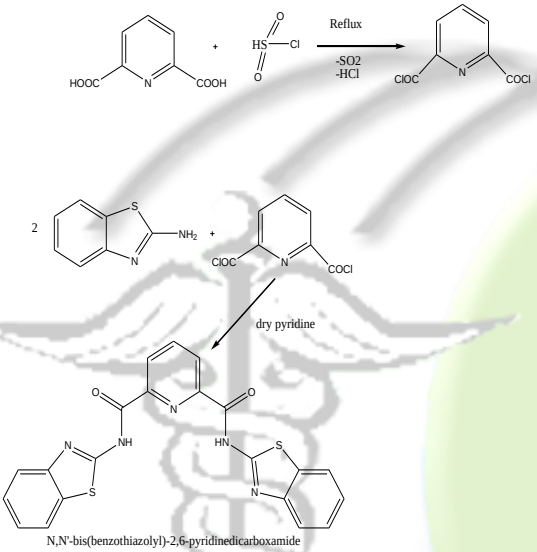
EXPERIMENTAL
MATERIAL AND INSTRUMENTATION
All the solvents used were of analytical grade. The starting materials, 2,6-pyridinedicarboxylic acid, thionyl chloride and 4-amino-benzothiazole were of BDH grade.The carbon, hydrogen and nitrogen contents of the ligand and the complexes were determined using a Heraus C H N rapid analyzer. IR Spectra in the 4000–400 cm^{-1} range were measured on a Thermo Nicolet 320 FTIR spectrometer using KBr discs. ^{1}H-NMR spectra were recorded in DMSO-d6 as a the solvent at 400 MHz on a BRUKER AMX 400 spectrometer using tetramethylsilanes(TMS) as an internal reference.

SYNTHESIS OF THE COMPOUND
2,6-Pyridinedicarboxylic acid (1.67g) and thionyl chloride (20 – 25 ml) were refluxed under anhydrous conditions for 4 – 6 h until a clear solution was

obtained. The excess thionyl chloride was removed under reduced pressure and the remaining mixture was cooled to 0 ºC and dry pyridine (30 – 35 ml) was added followed by 4-amino-benzothiazole (3.0g,) with occasional stirring, until the evolution of HCl had ceased. The solid obtained was poured into ice cold water (200 ml), filtered off and washed with 5 % sodium bicarbonate solution, then with hot water and ethanol. The resulting compound was recrystallized from dioxane. The purity of the compound was controlled by TLC on pre-coated silica gel, which gave a single spot. The synthetic route of N,N'-bis(benzothiazolyl)-2,6-pyridinedicarboxamide (BPD) is given in Scheme 1[20-21].



Scheme-1

Microanalysis

The elemental studies, melting point studies and solubility of synthesized compounds shown by table 1

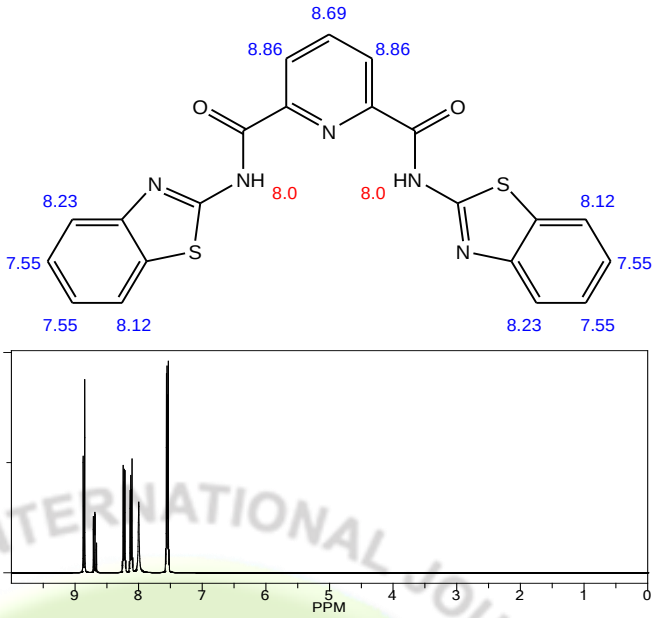
TABLE-1;Elemental analysis of synthesized compound

Compound	C%Calc./found	H% Calc./found	N % Calc./found	Solubility	MP°C
$C_{22}H_{15}N_4S_2O_2$	58.45/58.46	3.03/3.02	16.23/16.27	DMSO	175

SPECTRAL STUDIES

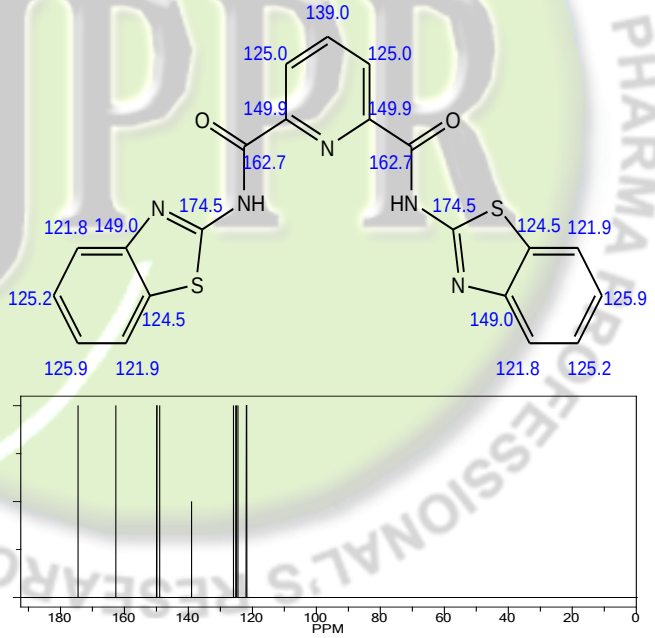
IR (KBr) υ cm $^{-1}$ 3252m *(NH)*, 1696s (Amide-I), 1604s (Benzothiazole*)*, 1610m 1542m 1456m(Pyridine ring stretching),1468(Amide II) ,998 w (Pyridine ring Breathing)

HNMR(DMSO-d_6) N1H and N2H 13.50 (*s*, 2H) H3 and H5 8.53 (*d*, 2H; J = 10.4 Hz) H4 8.25 (*t*, 1H; J = 8.0 Hz H8' and H8" 7.92 (*d*, 2H; J = 11.2 Hz) H5' and H5" 7.82 (*d*, 2H; J = 10.4 Hz) H7' and H7" 7.49 (*t*, 2H; J = 8.80 Hz) H6' and H6" 7.36 (*t*, 2H; J = 8.0 Hz)



^{1}HNMR spectra of *N,N'-bis(benzothiazolyl)-2,6-pyridinedicarboxamide*

^{13}CNMR(DMSO-d_6) 174.5(carbon atom of thiazole ring),124.4,121.9 , 125.9,125.2,121.8,149.0 (Aromatic carbon atom)139,125,149,149.9,125,(Carbon atom of pyridine ring)



^{13}CNMR Specta of *N,N'-bis(benzothiazolyl)-2,6-pyridinedicarboxamide*

MS:m/z(%) (*M*+) *m/z* = 638,

BACTERIAL CULTURE

The strain of bacteria used was MDR resistant Mycobacterium –Tuberculosis. All strains were isolated from L.L.R.M. Medical college, Meerut. The identity of all the strains was confirmed. A bacterial pension was prepared and added to the sterilized medium before solidification .The media with bacteria was poured in to sterilized Petri dishes under aseptic conditions. Different weights of synthesized compounds

(6.250µg/ml, 3.125µg/ml, 1.562µg/ml) were placed in the surface of culture and incubated at 37˚C for 24hours.After incubation the zone of inhibition (mm) recorded in table 2

Table -2 ANTI-TUBERCULAR ACTIVITIES OF SYNTHESISED COMPOUND

Compound	Concentration I	Concentration II	Concentration III
$C_{22}H_{15}N_4S_2O_2$	1.562 µg/ml	3.125µg/ml	6.250µg/ml
Zone of inhibition(mm)	9mm	12-15 mm	22-23mm

Moxifloxacin = Z.I.= 23-25mm

RESULT AND DISCUSSION

The synthesized compound show its maximum activity against M-tuberculosis in 6.25µg/ml concentration in D.M.S.O.At this concentration reported compound show 22-23 mm zone of inhibition which is quietly similar to zone of inhibition of Moxifloxacin standard drug (ZI= 23-25 mm).

These results show that the substitution of 2-amino-benzothiozolyl group at -OH moiety of carboxylic group of pyridinedicarboxylic acid make this molecule active against Mycobacterium – tuberculosis.

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