Preparation and Identification of some new Compounds Derived from Isonicotonic Acid Hydrazide (Isoniazid INH)

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Abstract : This work involves a preparation of some new derivatives of INH . The prepared derivatives are classified into two types . The first type includes three Schiff bases while the second type includes three amides. The derivatives are identified by FT-IR , mass and proton nuclear magnetic resonance spectroscopic methods .

Introduction:

Isoniazid is the most effective antituberculosis drug currently available [1] .So that many studies give especially importance for the synthesis of INH derivatives. Such as the study which included the formation of hydrazones between the INH and α- ketoglutaric acid , Pyruvic acid and Vit B_6[2]. Also INH is used with some famous drugs , for example rifampin , ethambutol streptomycine and pyrazinamide as mixture to treat tuberculosis[3].Francisco et.al [4] synthesized the antituberculosis hydrazones derivative from 6-amino-5 formal -1,3-dimethyl uracil and nicotinic acid hydrazide .Nayyar et.al [5] found that some of hydrazine derivatives appeared high activity (99%) antituberculosis (type H_{37}).In general hydrazones have wide spectrum of biological activities ,such as anticonvulsant [6], antidepressant[7], analgesis [8] ,antimalaria [9], antitumoral [10]and antiviral[11].The other reviews which enclosed our subject are [12-17].

The aim of this work was a preparation and identification of some new INH derivatives which may help us to obtain derivatives with high biological activities .

Experimental:

Melting points were measured using Electrothermal – 6500 digital melting point apparatus at the Chemistry Department Labs of Education College/ Basrah University .IR spectra were recorded as KBr disk using FTIR – 8400S Schimadzu at the Chemistry Department Labs of Science College / Basrah University . Mass spectra were recorded using Hewlett Packord , EI, 70 ev at the micro- analytical Center – Cairo University, Giza , Egypt and GCMS , QP5050A Schimadzu at University of Ahel Al-Bait , Jordan .

^{1}H- NMR spectra were recorded using Varian Gemini (200 MH_Z) at micro –analytical Center , Cairo University, Egypt

and FTNMR – Ultrashield (300 MH_Z), Bruker at University Of Ahel Al-Bait , Jordan by using
DMSO – d_6 as solvent and TMS as internal reference.
The chemicals were provided by Merck , Fluka , BDH and Riedel – de Haen companies .

Preparation of Schiff Bases(10,11,12):[18]

INH (1.5 gm,0.01 mol.)was dissolved in the ethanol (20ml).On the other hand a determinative β- diketone (0.01 mol) also was dissolved in ethanol (20 ml). The β- diketone solution and few drops of glacial acetic acid were added to the INH solution .The mixture were stirred and refluxed for 4 hour and T.L.C (ethanol: chloroform 1: 9) test reveals no further reaction . The mixture was cooled in ice bath and filtered .The crystals were washed with cool ethanol ,then the separated derivative was recrystallized from ethanol (95 %) and dried under vacuo at 50^5C for 1 hour to obtain white crystals [(10):75%,352-355 ^{5}C,(11): 24%, 135-137 ^{5}C,(12):69%,132-134 ^{5}C] as shown inTable 1.

Preparation of Derivative (13):[19]

INH (2.74 gm ,0.02 mol) was dissolved in dry pyridine(80 ml) and then was added to it 1- naphthoyl chloride (7.6 gm,0.04 mol.) gradually.The mixture was stirred for 7 hour at room temperature and the T.L.C. (ethanol chloroform 1:9) showed no further reaction .The mixture was washed with 50 ml of 10% HCL until the medium became neutral . The mixture was cooled and filtered , then the product was recrystallized from H_2O and dried under vacuo at 50 ^{5}C for 1 hour to obtain white crystals (36%, 197-198 ^{5}C).

Preparation of phenylisothiocynate:

Phenylisothiocynate was prepared according to the review [20].

Preparation of derivative (14):[18]

INH (4.247 gm ,0.031 mole) was dissolved in absolute ethanol (150 ml) and then added to it (4.20 gm, 0.031 mol.)

of phenylisothiocynate gradually .The mixture was stirred and refluxed for 3 hour and T.L.C. test (ethanol: chloroform 2:8) reveals no further reaction . The mixture was cooled and filtered .The separated derivative was recrystalized from ethanol and dried under vacuo at 50^5C for 1 hr to obtain white crystals (63%,191-192^5C).

Preparation of the derivative (15):

This derivative was prepared according to the same procedure followed as compound (14) , instead of the molar ratio of mixing of (0.247 gm, 0.02 mol) of INH with (2.0 gm ,0.02 mol.) of allylisothiocynate to obtain white crystals (75%, 218-220 ^{5}C).

Results and Discussion :

Some physical properties of the prepared compounds are summarized in Table 1 . The isoniazed derivatives are identified by FT-IR ,mass and ^{1}H-NMR spectroscopic methods . The IR spectral data of the products [Table 2 and Figs(1-6)] showed two principal stretching vibration bands ,the first in the region 3251-3120 cm^{-1} which was attributed to the –NH group of the hydrazide , whereas the second one in the region 1677-1625 cm^{-1} which is attributed to the C=O group. The compounds (Schiff bases 10,11,12) are showed of the stretching vibration bands at the region 1600-1544 cm^{-1} due to the C=N group. The disappearance of the $–NH_2$ band and the appearance of the C=N band confirmed the correct of the expected structures of the Schiff bases compounds. The FT-IR spectra of compounds 11,12 and 15 are characterized with appearance of the stretching bands of the alephatic C-H at 2925,2785 and 2927cm^{-1} due to the presence of the $–CH_3$,-CH_2 and CH groups in their structures . The amide compounds (14 and 15) showed the stretching vibration bands at 3255 and 3267 cm^{-1}respectively resulted from the –NHgroup in the -C-N-H- fragment ,as well as the

appearance of stretching band at the 1247and 1267 cm^{-1} respectively due to the thiocarbonyl group (C=S).

The mass spectral data of the prepared derivatives are gathered in the Figs(7-12). Mass spectra of the products show a molecular ion M^+peak.The molecular ion peaks are good agreement with their empirical formulas .The relative intensity(R.I)of M^+ range is from 20 to 50% .The base peak at 78 m/z is attributed to $[C_5H_4N]^+$ which is observed in all prepared compounds with variable relative intensity, also the peak at 106 m/z is observed in the spectra of the products expect the compound (13) with high R.I which is ascribed to the fragment $[C_6H_4NO]^+$. The compounds 10 and 12 appeared peak at 371 m/z (1.8%) and 272 m/z (4.7%) respectively due to the$[M-H]^+$. Mass spectrum of 11 compound reveals peak at 204 m/z (8%)resulted from the lossing of $-CH_3$ group, whereas the base peak appeared at 66 m/z ascribed to $[C_4H_4N]^+$. Compound 13 reveals two significance peaks ,the
first at 155 m/z ascribed to$[C_{11}H_7O]^+$ and the second at 127 m/z (54%) resulted from the lossing of CO group ascribed to $[C_{10}H_7]^+$. Whereas the mass spectrum of compound 14 has peak at 135 m/z attributed to $[C_6H_5N_3O]^+$.The spectrum of compound 15 appeared the peaks, 237 m/z (17%), 238 m/z (6%) and 115 m/z due to the [M+1] ,[M+2] and $[C_4H_7N_2S]^+$ respectively.

^{1}H-NMR spectral data of the products are shown in Figs(13-18) . DMSO-d_6 appeared two signals, the first is ascribed to non-deuterated solvent (2.5 ppm) and the second is due to water in the solvent(3.3 ppm) . The prepared derivatives show two doublet signals are attributed to the aromatic protons of pyridyl moiety . The first signal is ascribed to the chemical shift value of H-2 and H-6 which appeared within the range 8.65 – 8.82 ppm, whereas the second signal is ascribed to the chemical shift value of H-3

and H- 5 which appeared within the range 7.45-7.89 ppm. The spectra of products give singlet signal at 6.62-12.19 ppm resulted from the proton of –NH group which is disappeared after addition of D_2O, indicating that the signal is due to the –NH group . Compound 12 reveals singlet signal at 8.50ppm attributed to the proton of the azomethine (CH=N). The ^{1}H-NMR spectra of compound 11,12 and 15 are characterized with appearance of signals resulted from -CH_3 and –CH_2 groups. Also we noticed compounds 10 ,13 and 14 showed multiplet signals due to aromatic system protons. The multiplet signal at 5.89 ppm of compound 15 is explained by its homo cosy spectrum(Fig. 18). Also this spectrum was appeared cross peaks between the doublet signal of NCH_2 (4.10 ppm) and the singlet signal of NH-11(8.36 ppm).

References :

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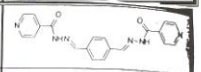
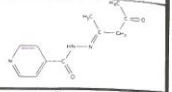
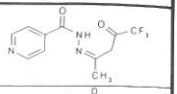
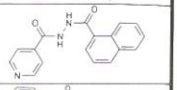
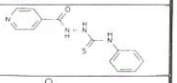
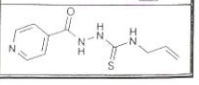
Table 1:Names,Molecular weight and the Molecular structure of the products

No. of Compound	Name (IUPAC)	Mol.weight gm/mol	Molecular structure
10	*N',N''*-[1,4-phenylenedimethylylidene] Bis isonicotinohydrazide	372	
11	Isonicotinic acid [1-methyl-3-oxo-butylidene]-hydrazide	219	
12	*N'*-(5,5,5-trifluoro-4-oxopentan-2-ylidene)isonicotinohydrazide	273	
13	*N'*-(1-naphthoyl)isonicotinohydrazide	291	
14	2-isonicotinoyl-*N*-phenylhydrazine carbothioamide	272	
15	*N*-allyl-2-isonicotinoylhydrazine carbothioamide	236	

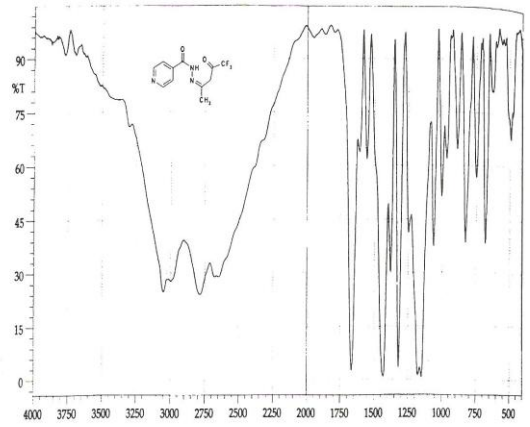


Fig.3: IR spectrum of compound 12.

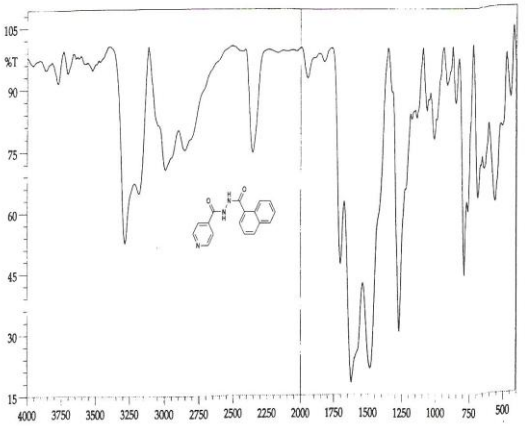


Fig.4: IR spectrum of compound 13.

Table 2: IR spectral data of the products .

Compounds	$\bar{\nu}$ (C=N) (C=C) St.	(C=O) $\bar{\nu}$ Hydrazide St.	$\bar{\nu}$ (OH) St.	$\bar{\nu}$ (CH) aliphatic St.	$\bar{\nu}$ (CH) aromatic St.	$\bar{\nu}$ (NH) St.
INH	-	1662 s	-	-	3010 s	3112 s
10	1600 m	1665 vs	-	-	3074 m	3251 s
11	1544 s	1625 vs	-	2925 w	3000 vw	3134 w
12	1554	1666 vs	-	2785 m	3051 w	3150 br
13	-	1703 m	-	-	3040 w	3182 m

Compounds	$\bar{\nu}$ (C=S) St.	$\bar{\nu}$ (C=C) St.	$\bar{\nu}$ (C=O) hydrazide	$\bar{\nu}$ (CH) aliphatic St.	$\bar{\nu}$ (CH) aromatic St.	$\bar{\nu}$ (NH) St.	$\bar{\nu}$ (NH) St.
14	1247s	1500s	1674s	—	3050sh	3255br	3120 br
15	1267s	1542vs	1677s	2999asy 2927sym	3066w	3267vs	3224vs

s : strong , m : medium , w: weak , vs : very strong , br : broad , sh : shoulder

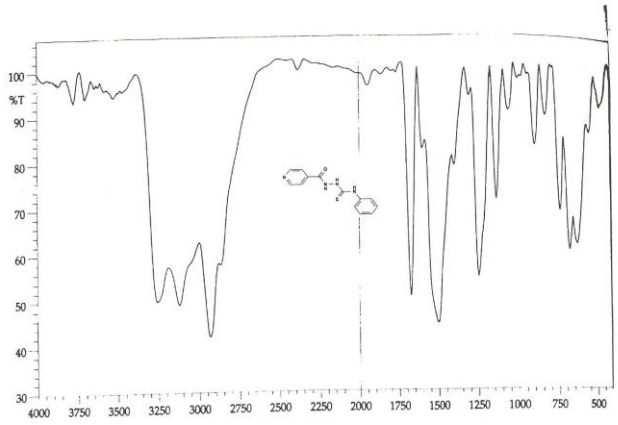


Fig.5: IR spectrum of compound 14.

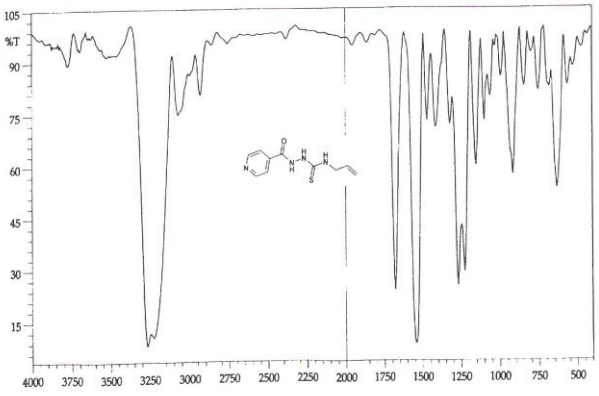
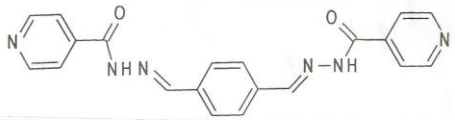
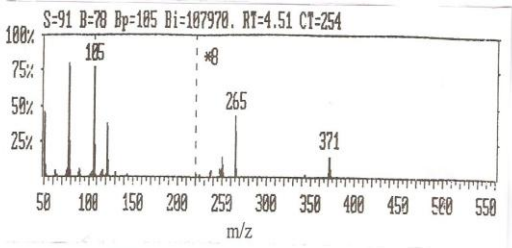


Fig.6: IR spectrum of compound 15.

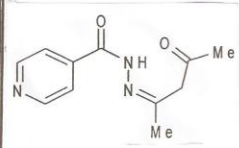
Fragment	m/z	Intensity%
$[M]^+$ ($C_{20}H_{16}N_6O_2$)	372	1.7
$[M-H]^+$	371	1.8
$[C_6H_4NO]^+$	106	96.1
$[C_6H_3NO]^+$	105	100
$[C_5H_4N]^+$	78	76.9

Fig.7: Mass spectrum of compound 10.





Fragment	m/z	Intensity%
$[M]^+$ ($C_{11}H_{13}N_3O_2$)	219	12.0
$[M-CH_3]^+$	204	8.0
$[C_6H_4NO]^+$	106	67
$[C_5H_4N]^+$	78	57
$[C_4H_4N]^+$	66	100



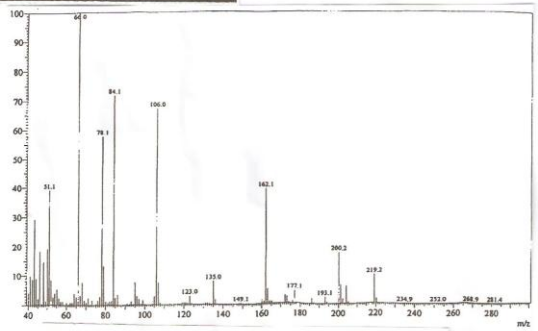
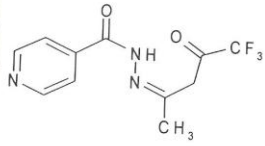
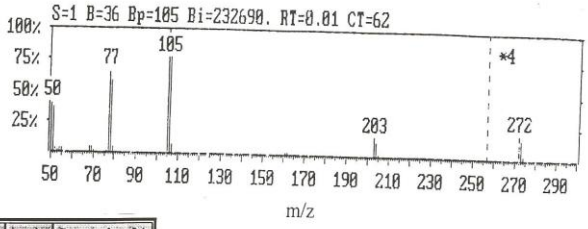


Fig.8: Mass spectrum of compound 11.

Fragment	m /z	Intensity %
$[M]^+$ ($C_{11}H_{10}N_3O_2F_3$)	273	4.0
$[M-H]^+$	272	4.7
$[M-CF_3]^+$	204	11.3
$[C_6H_4NO]^+$	106	85.4
$[C_6H_3N]^+$	105	100
$[C_5H_4N]^+$	78	57.4

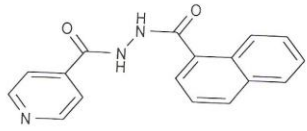
Fig.9:Mass spectrum of compound 12.

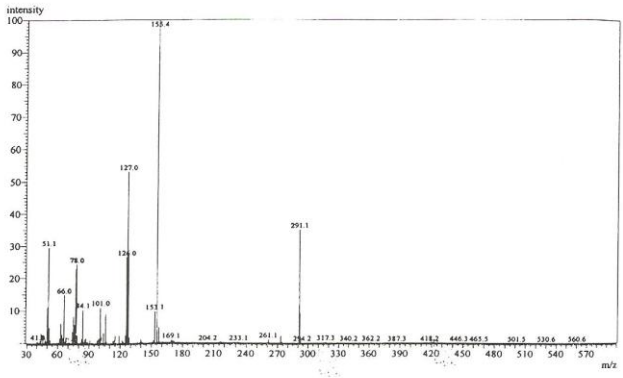




Fragment	m /z	Intensity %
$[M]^+$ ($C_{17}H_{13}N_3O_2$)	291	37.0
$[C_{11}H_7O]^+$	155	100
$[C_{10}H_7]^+$	127	54.0
$[C_5H_4N]^+$	78	25.0
$[C_4H_4N]^+$	66	15

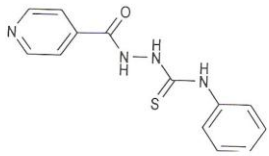
Fig.10:Mass spectrum of compound 13.

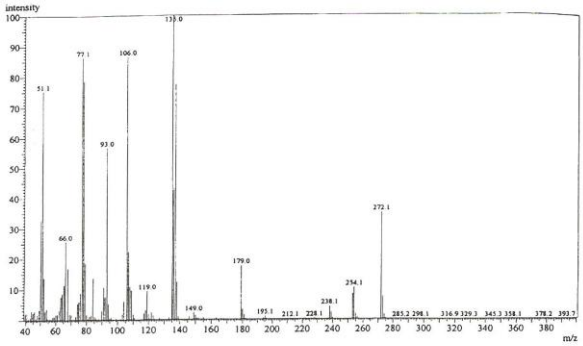




Fragment	m /z	Intensity %
$[M]^+$ ($C_{13}H_{12}N_4OS$)	272	34.0
$[C_6H_5N_3O]^+$	135	100
$[C_6H_4NO]^+$	106	88.0
$[C_5H_4N]^+$	78	79.0
$[C_4H_4N]^+$	66	36.0

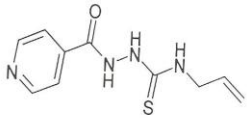
Fig.11:Mass spectrum of compound 14.

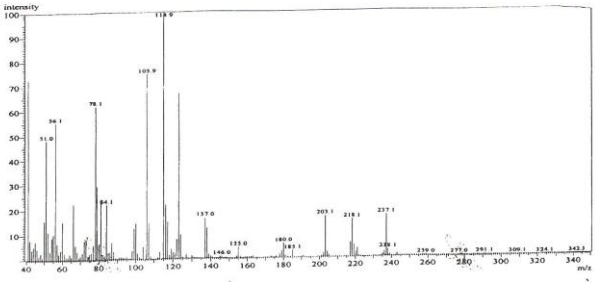




Fragment	m /z	Intensity %
$[M]^+$ ($C_{10}H_{12}N_4OS$)	236	4.0
$[M+1]^+$	237	17.0
$[M+2]^+$	238	6.0
$[C_4H_7N_2S]^+$	115	100
$[C_6H_4NO]^+$	106	75.0
$[C_5H_4N]^+$	78	64.0

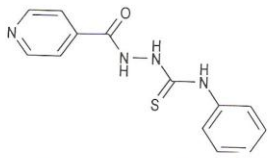
Fig.12:Mass spectrum of compound 15.

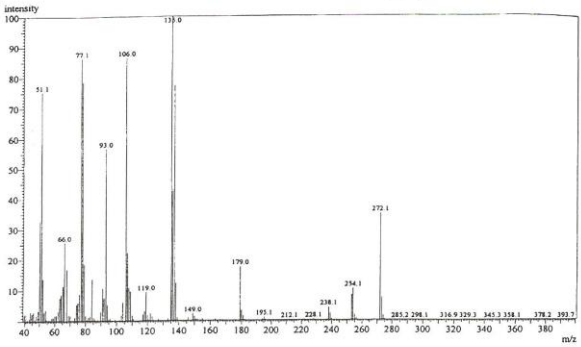




Fragment	m /z	Intensity %
$[M]^+$ ($C_{13}H_{12}N_4OS$)	272	34.0
$[C_6H_5N_3O]^+$	135	100
$[C_6H_4NO]^+$	106	88.0
$[C_5H_4N]^+$	78	79.0
$[C_4H_4N]^+$	66	36.0

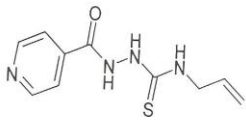
Fig.11:Mass spectrum of compound 14.

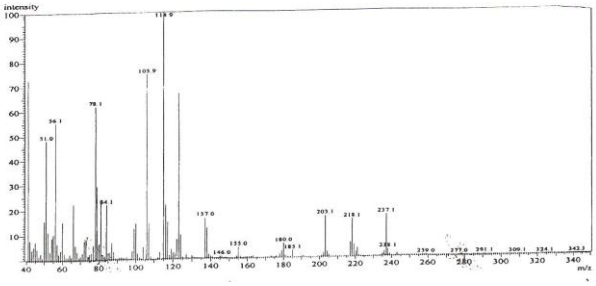




Fragment	m /z	Intensity %
$[M]^+$ ($C_{10}H_{12}N_4OS$)	236	4.0
$[M+1]^+$	237	17.0
$[M+2]^+$	238	6.0
$[C_4H_7N_2S]^+$	115	100
$[C_6H_4NO]^+$	106	75.0
$[C_5H_4N]^+$	78	64.0

Fig.12:Mass spectrum of compound 15.





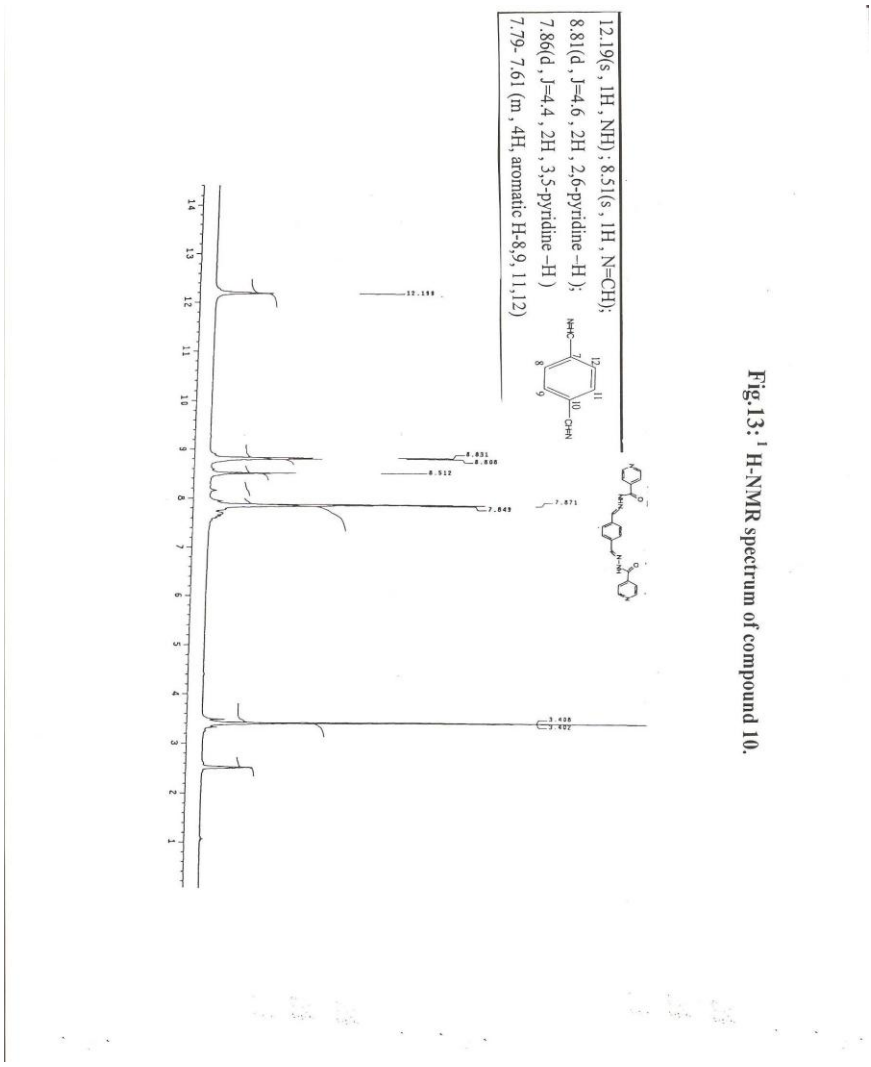


Fig.13: ^{1}H-NMR spectrum of compound 10.

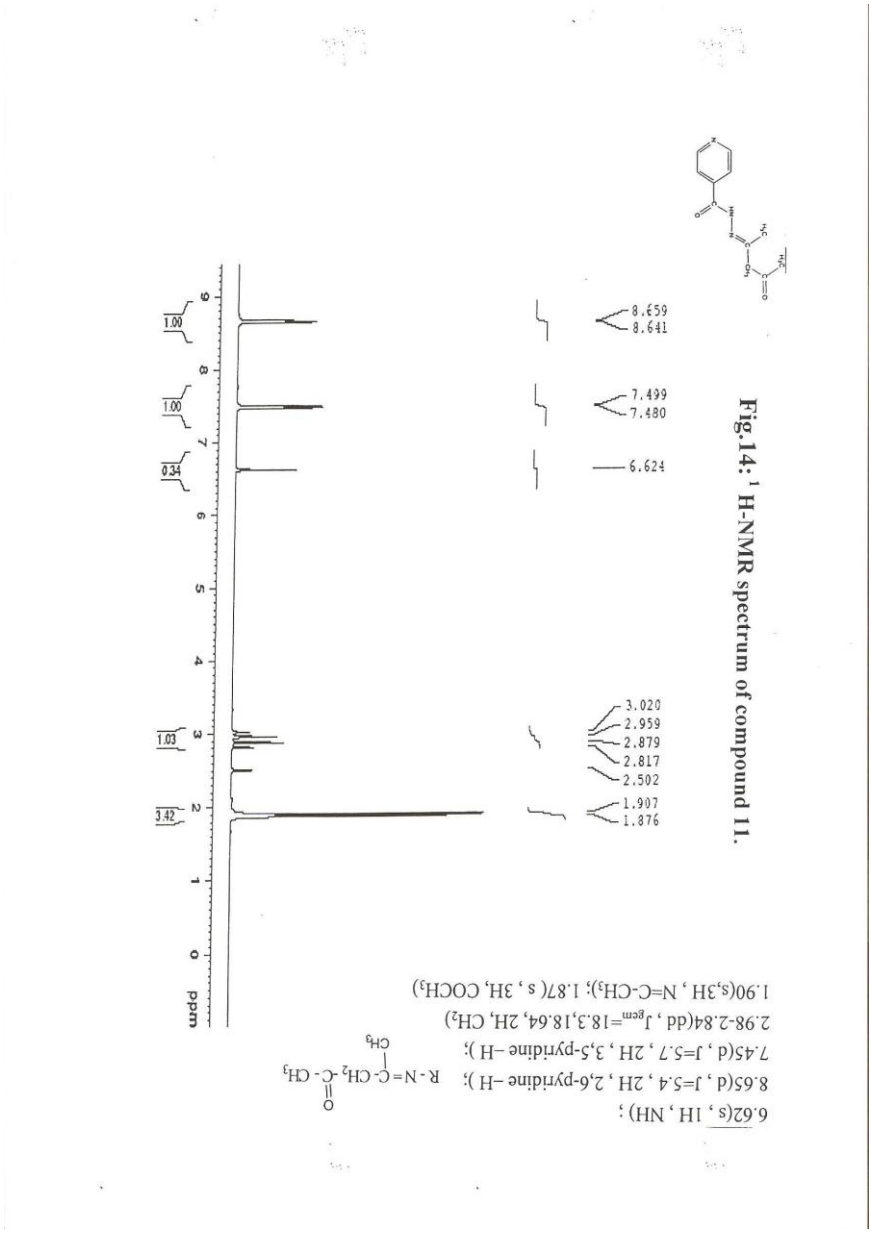


Fig.14: ^{1}H-NMR spectrum of compound 11.

6.62(s , 1H , NH) ;
8.65(d , J=5.4 , 2H , 2,6-pyridine –H);
7.45(d , J=5.7 , 2H , 3,5-pyridine –H);
2.98-2.84(dd , J_{gem}=18.3,18.64, 2H, CH_2)
1.90(s,3H , N=C-CH_3); 1.87(s , 3H, $COCH_3$)

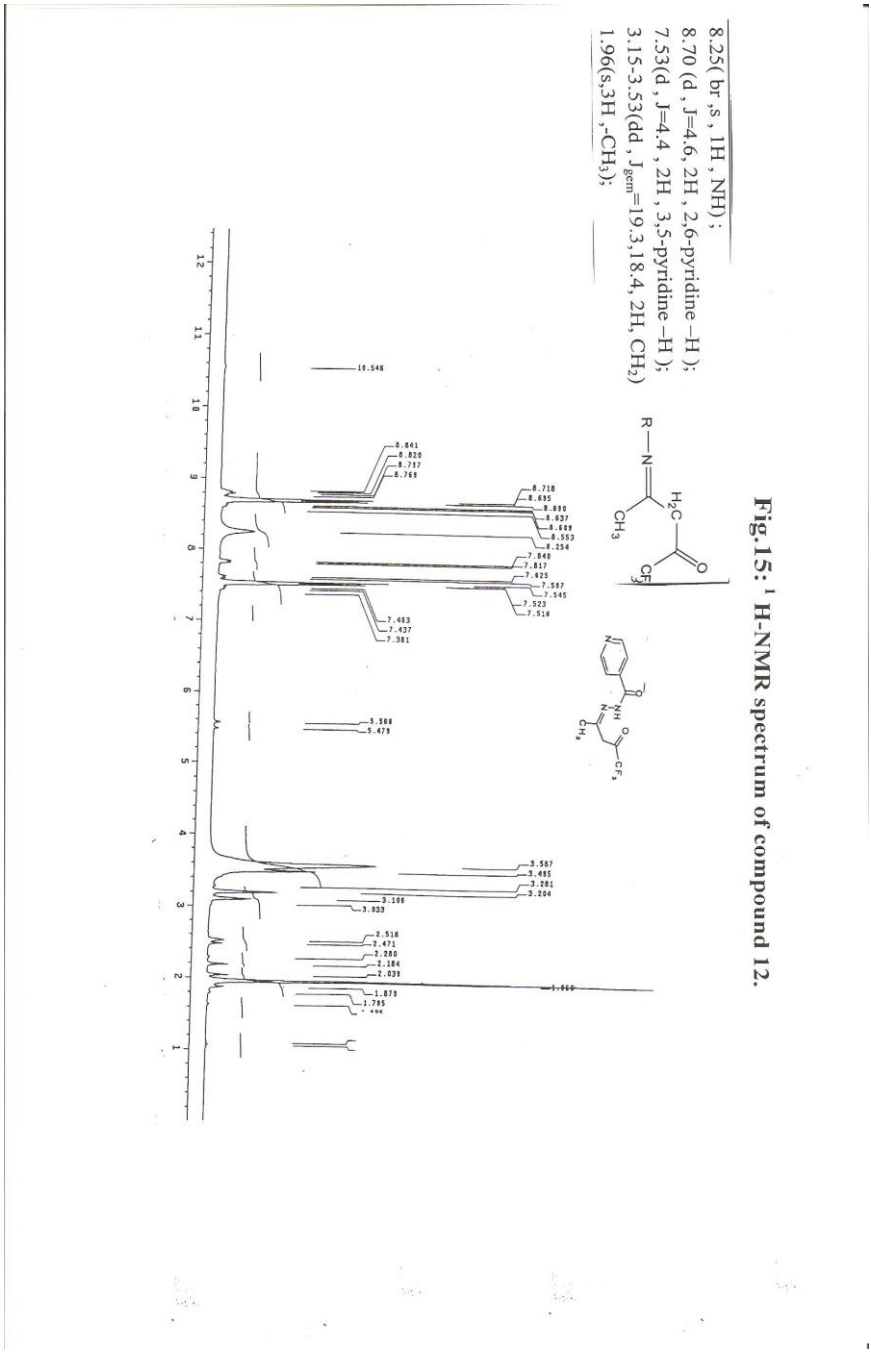


Fig.15: ^{1} H-NMR spectrum of compound 12.

10.97(s, 1H, NH-8)
10.62 (s , 1H , NH-9)
8.82 (d , J =5.7 , 2H, 2,6-pyridine-H
7.89(d , J= 5.7 , 2H, 3,5-pyridine-H
8.42,(d , J=8.4,1H, aromatic H-14);
8.09,(d , J=8.1,1H, aromatic H-12);
8.02,(d ,J=7.2 ,2H, aromatic H-20);
7.73,(d , J=6.9,1H, aromatic H-17);
7.66-7.59,(m , 3H, aromatic H-13,18,19);

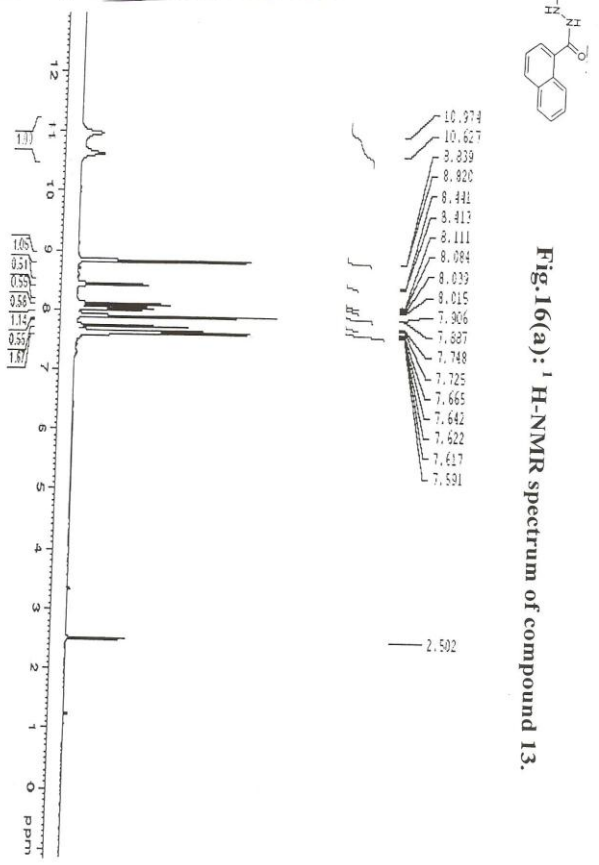


Fig.16(a): ^{1}H-NMR spectrum of compound 13.

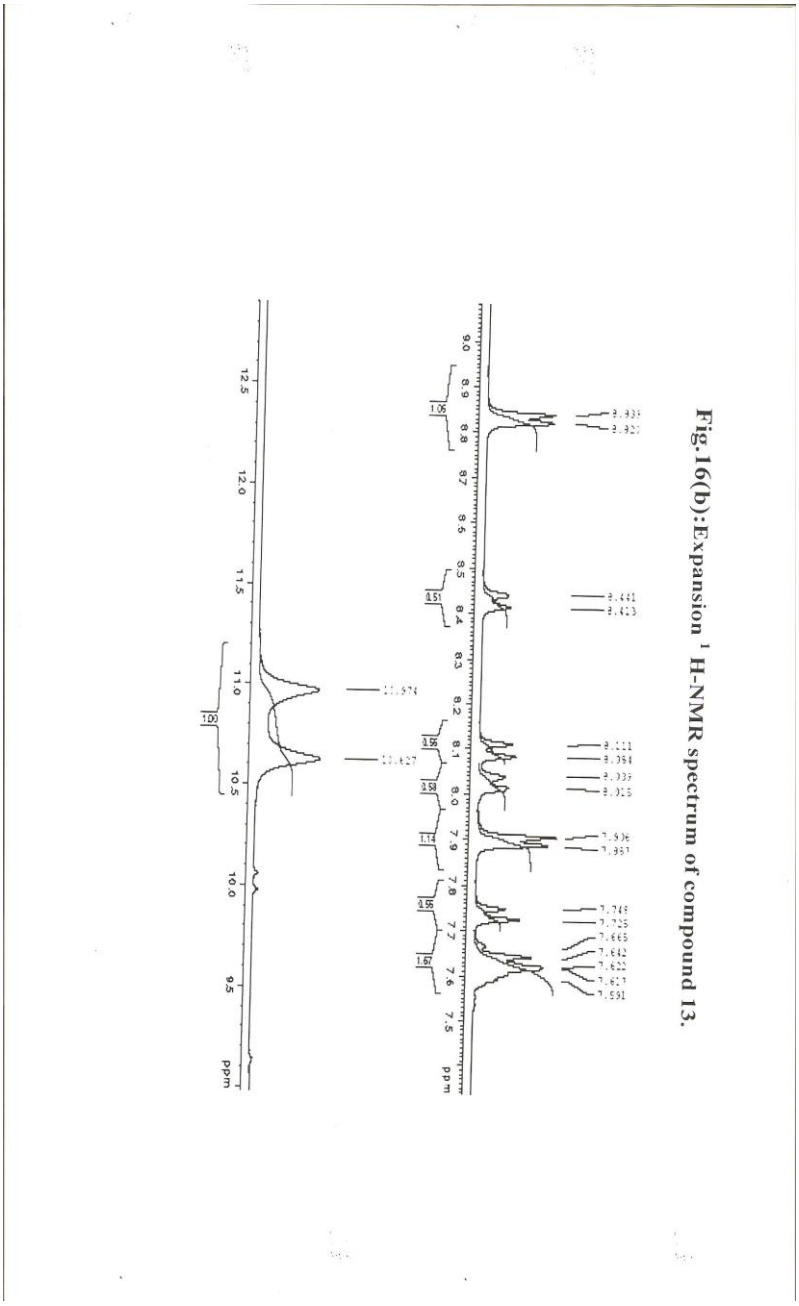


Fig.16(b):Expansion ^{1} H-NMR spectrum of compound 13.

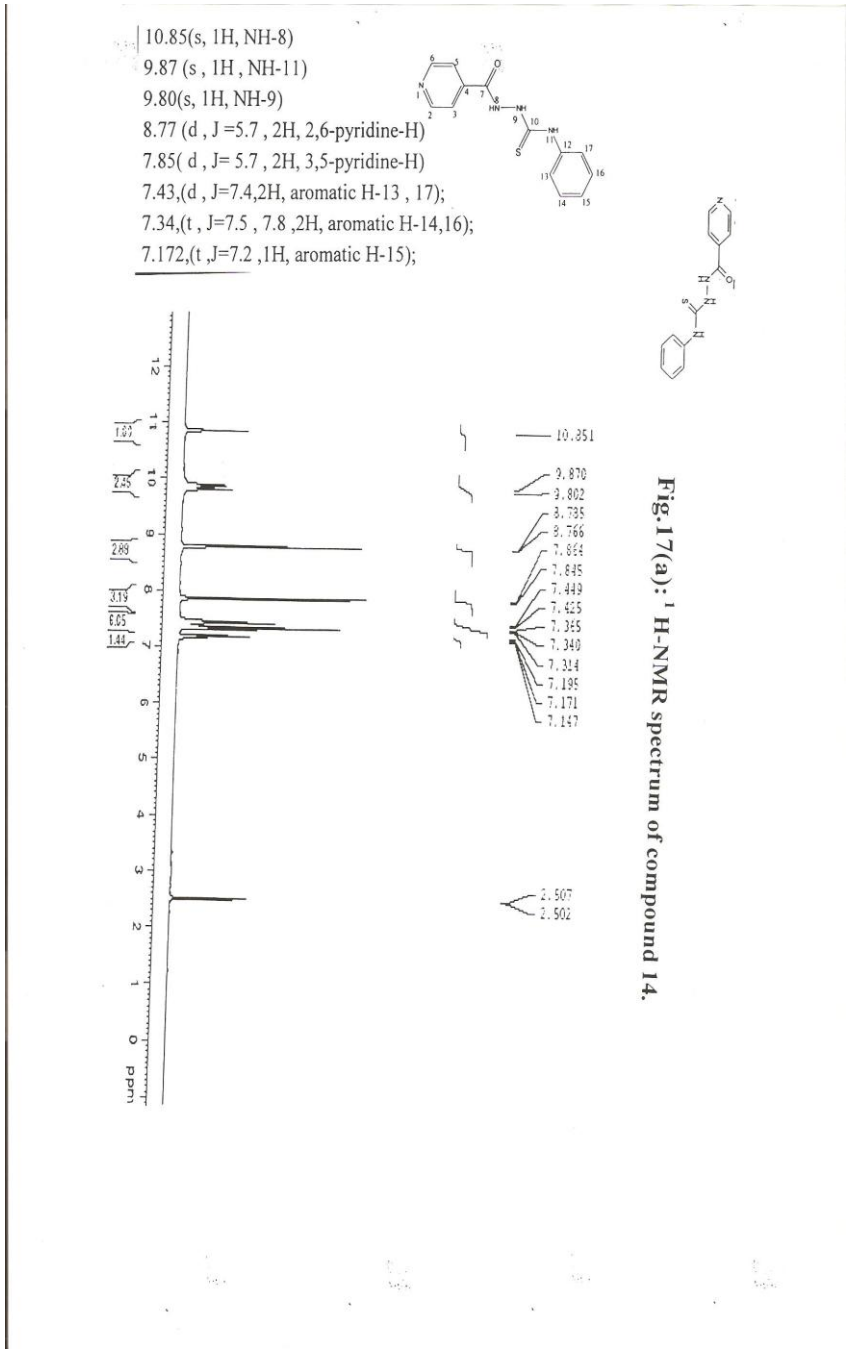


Fig.17(a): ^{1}H-NMR spectrum of compound 14.

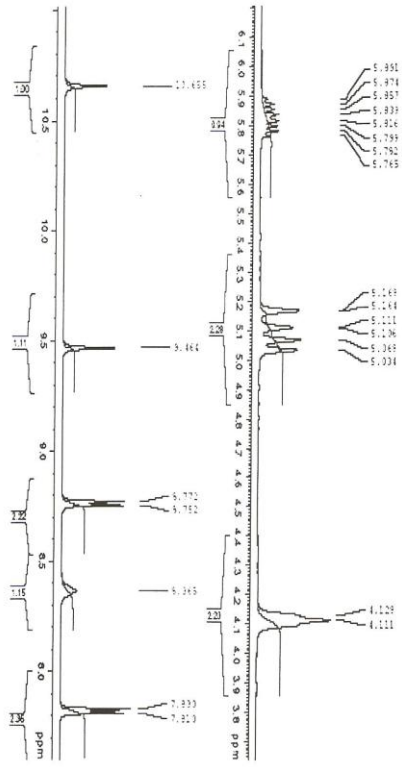


Fig.18(b): Expansion ^{1}H-NMR spectrum of compound 15.

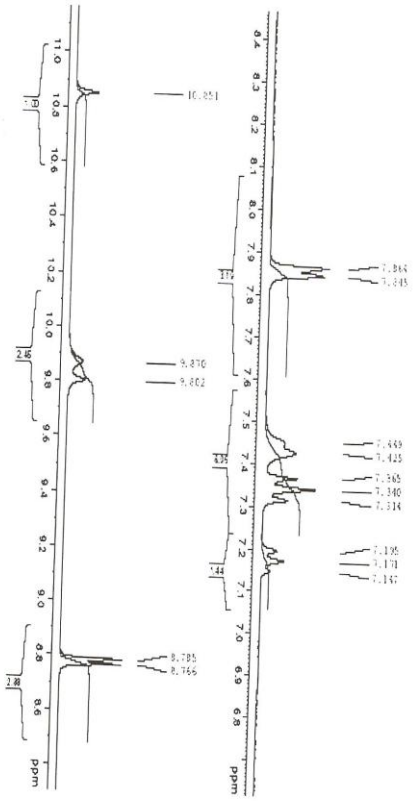


Fig.17(b): Expansion ^{1}H-NMR spectrum of compound 14.

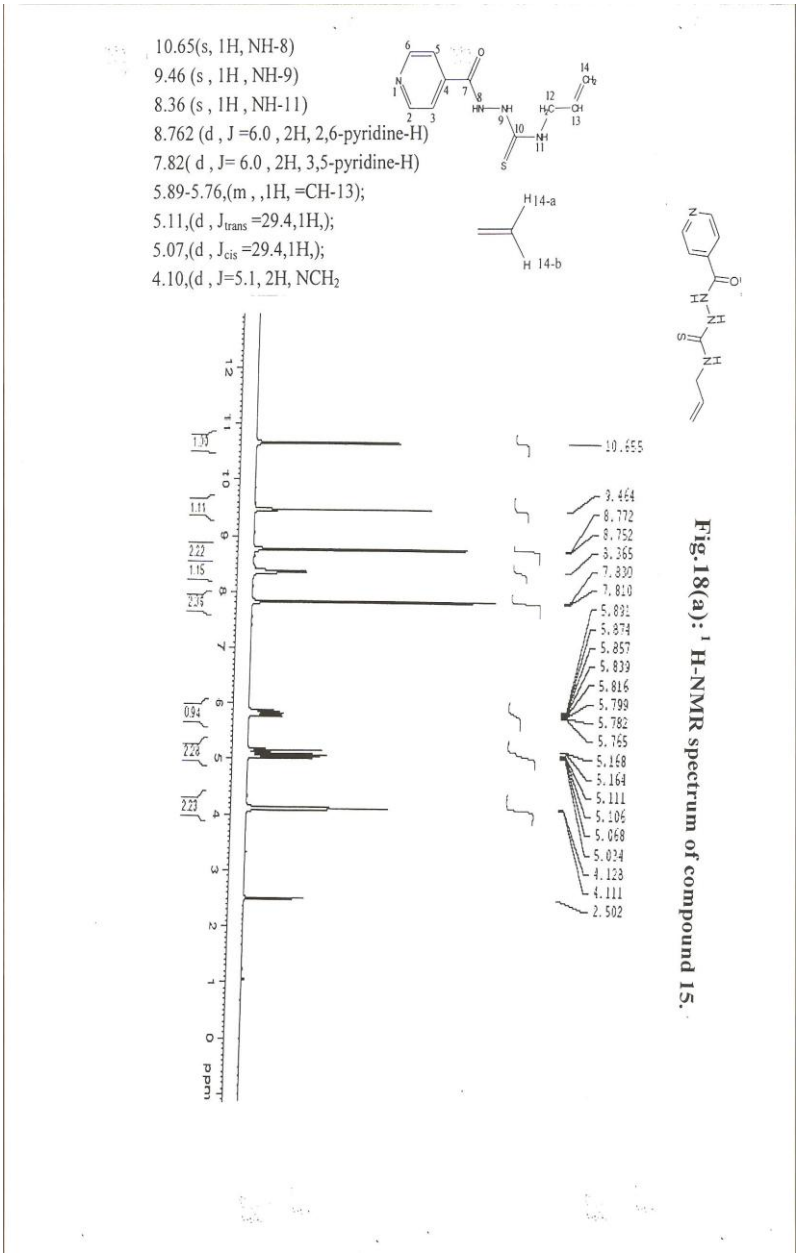


Fig.18(a): ^{1}H-NMR spectrum of compound 15.

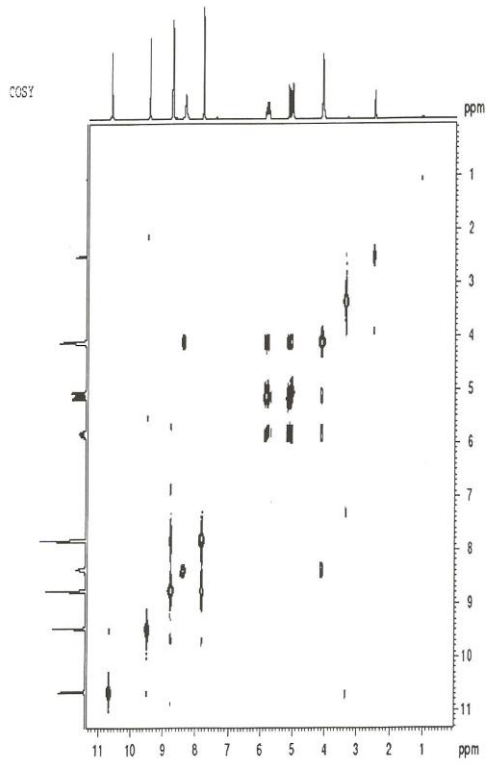


Fig.18(c):2D-cosy ^{1} H-NMR spectrum of compound 15.

تحضير وتشخيص بعض المركبات الجديدة المشتقة من حامض الايزونايكوتينك (ايزونايزايد).

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المستخلص : يتضمن العمل تحضير بعض المشتقات الجديدة للايزونايزايد والتي تشمل نوعين، الأول يمثل ثلاث قواعد شف للايزونايزايد والثاني يمثل ثلاث اميدات للايزونايزايد، شخصت المشتقات المحضرة بواسطة مطيافيات تحت الحمراء والكتلة والرنين النووي المغناطيسي للبروتون .