Synthesis And Characterization Of New 2-amino pyridine Derivatives

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Abstract

New series view of ethyl2-(pyridin-2-ylamino) acetate compounds were synthesized by react 2-amino pyridine with ethyl chloro acetate and KOH, then the ethyl2-(pyridin-2-ylamino)acetate react with hydrazine hydrate (99%)to give 2-(pyridin-2-ylamino)acetohydrazide[2], which the 2-(pyridin-2-ylamino) acetohydrazide treated with different substituted aromatic aldehydes formed various substituted arylidine derivatives [3a-d]. These arylidine derivatives on treatment with triethyl amine and chloroacetyl chloride yielded different azetidine derivatives [4a-d].Reaction of 2-aminopyridin with different aromatic aldehyde and CuCN formed various substituted cyanic [5a-c] .Reaction of [5a-c] compound with NaN_3,NH_4Cl and DMF afford tetrazole derivatives [6a-c].Also 2-amino pyridine reacted with 2-mercaptobenzoxazole,2-mercaptopyrimidin and 2-mercapto benzo thiazole to give the new derivatives of compounds[7,8,9].The molecular structure were characterized by FTIR,^{1}HNMR.

Key Worde: amino pyridine, arylidine , tetrazole.

الخلاصة

حضرت سلسلة مركبات جديدة من 1–اثل(2–امينوبريدين–2يل امينو)استيت من تفاعل 2–امينوبريدين مع اثل كلورواستيت بوجود هيروكسيدالبوتاسيوم,بعدما عومل المركب [1] مع الهيدرازين المائي (99%) ليعطي مشتق الهايدرازين [2] والذي تم تفاعله مع بعض الالديهايدات الاروماتية ليعطي مشتقات مختلفة من الاريلادين [3a–c] وعند تفاعل مشتقات اريلايدين مع كلورواستل كلورايد , تراي اثل امين نتجت مشتقات جديدة من ازيتادنيل[4a–c] , 2–امينو بريدين فعل مع بعض الالديهايدات المختلفة التعويض بوجود CuN اعطى مشتقات جديدة من مركبات[5a–c] السيانيد والذي تم معاملة الاخير مع NaN_3NH_4Cl بوجود DMF ليعطي مشتقات التيترازول [6a–c] كذلك تفاعل 2–امينوبريدين مع 2–مركبتوبنزوكزازول,2–مركبتربايرميدين و 2–مركبتوبنزوثايزول ليعطي مشتقات جديدة[7,8,9] وفسرت هذه النواتج بالاعتماد على بعض الخواص الطيفية ^{1}HNMR,FTIR

مفتاح الكلمة: امينوبريدين , اريلايدين, تيترازول.

Introduction

Different 2-amino pyridine derivatives of heterocyclic nuclease have shown potent pharmacological properties like antifungal[1], anti-tubercular[2],anti-microbial[3] and insecticidal activities[4].βlactam (azetidinone) heterocyclic are still the most prescribed antibiotics used in medicine[5]. A large number of β lactam ring are known to exhibit various biological activities like antibiotic [6], antifungal [7] and anti-inflammatory activities[8]. The synthesis of novel tetrazole derivatives and investigation of their chemical and biological behaviors has gained more due to their broad spectrum of biological properties[9] which act as anti-allergic[10], antibiotic,anticonvulsant,analgesic, anti-inflammatory[11] and anticancer activity[12] .On other hand the substituted tetrazoles have long been known for their pharmaceutical activity as stimulants or depressants on the central nervous system. [13]

Experimental

The melting point were determined in open capillary tubes on a Gallen Kamp melting point apparatus and were uncorrected .The FT.IR Spectra of some prepared derivatives were taken on Shimadzu-2N,FTIR-8400 S.and the spectra were recored as KBr discs were recorded with Shimadzu-2N,FTIR-8400 S. ^{1}H-NMR Spectra of some prepared derivatives were recorded on a Varian-Mercury 300MHZ Spectrometer, d6-DMSO use as a solvent in^{1}H-NMR Spectra.

Synthesis of ethyl2-(pyridin-2-ylamino)acetate [1]

Ethyl chloro acetate (0.05 mole) was add drop wise to stirred solution of 2-amino pyridine (5.3g, 0.05mole), KOH(2.8g, 0.05 mole)in 30 ml ethanol. The mixture was refluxed 8 hrs. The filtrated was pourd on crushed ice. The resulting product was recrystallized from chloroform.

Synthesis of 2-(pyridin-2-ylamino)acetohydrazide [2]

To a solution of ethyl2-(pyridin-2-ylamino)acetate [1] (0.01 mole) in 20 ml ethanol ,hydrazine hydrate (0.02 mole) was added and the reaction mixture was refluxed 6hrs.Then filtered off and the product was recrystallized by ethanol.

Synthesis of N/ (arylbenzylidene)-2-pyridine -2-ylamino) acetohydrazide [3a-d]

To a suspension of compound [2] 2-(pyridin-2-ylamino)acetohydrazide. (0.012 mole) in ethanol 30 ml was refluxed with aryl aldehyde (0.012 mole) in the presence of few drops of glacial acetic acid for 7 hrs.After the completion of reaction ,the mixture was allowed to cool and filtered it .The precipitate solid was recrystallized from ethanol.

Synthesis of N-(3-chloro-2-(aryl phenyl)-4-oxoazetidin-1-yl)-2-(pyridine-2-ylamino)acetamide [4a-d][6]

To a stirred solution of compound [3a-c] (0.01 mole)and triethylamin (0.02 mole) in dioxane (15ml), chloracetyl chloride (0.02 mole) was added dropwise at 0-5C°.The reaction mixture was stirred for about 5-7 hours .The mixture was then poured into ice water,the product was recrystallized from different solvent.

Synthesis of 2(arylphenyl) -2-(pyridine-2-ylamino) acetonitrile [5a-c][2]

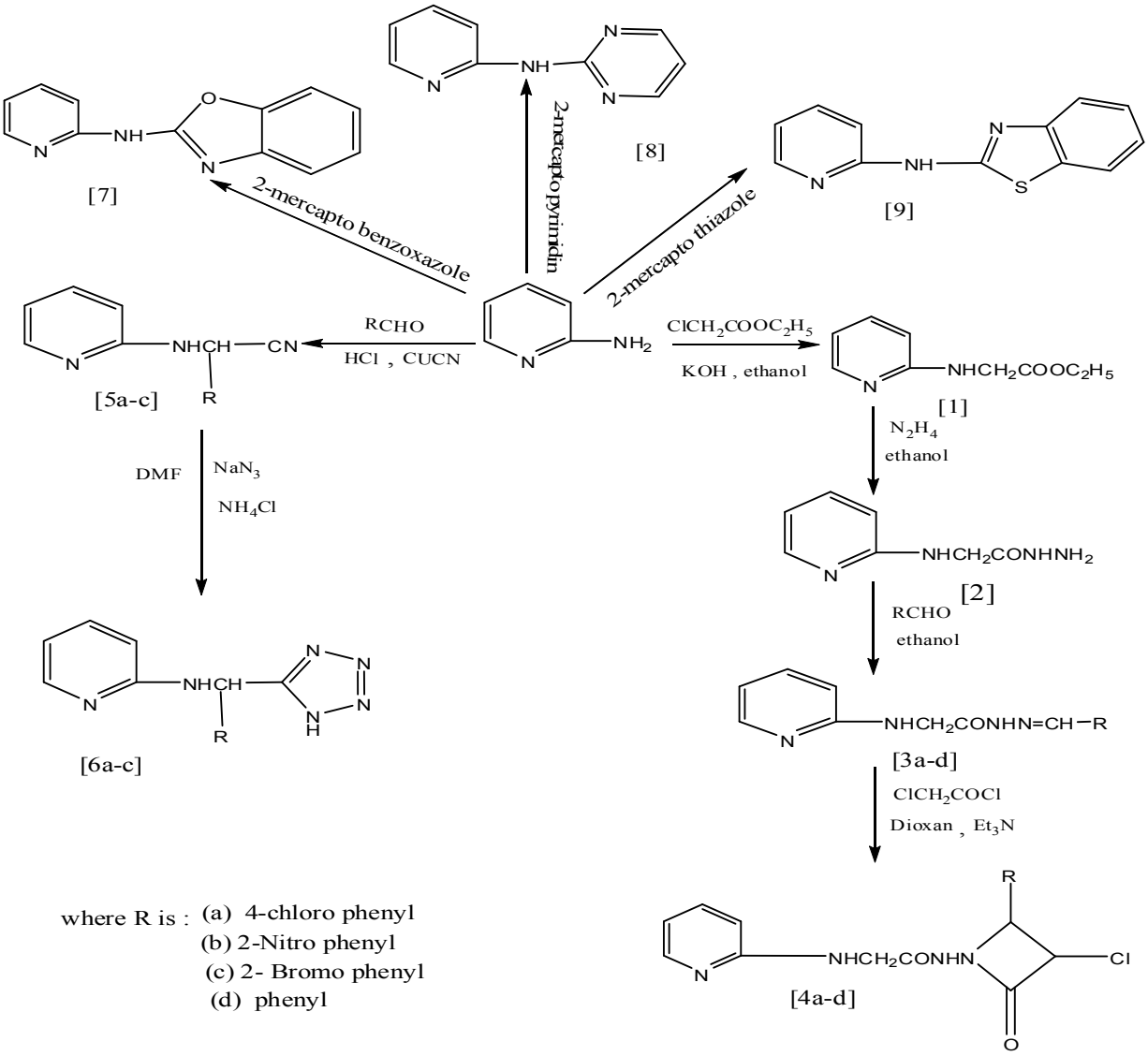
A (0.015 mole) of the different aromatic aldehyds were added to the mixture of 2-amino pyridine (0.015 mole) was mixed with 2.5 ml concentrated HCl and 10g ice water and (0.015 mole)from CuCN in 4 ml water was add ,the reaction mixture was stirred over night at room temperature and filtrated off .

Synthesis of N(aryl phenyl)(1H-tetrazol-5-yl)methyl) pyridine-2-amin [6a-c][9]

A mixture of compound [5a-c] (0.01 mole),(0.01 mole) sodium azid and (0.01 mole) ammonium chloride in 10 ml DMF was refluxed in oil bath 125C° for 7 hrs. The solvent was removed under reduced pressure .The residue was dissolved in 100ml of water then carefully acidified to pH=2 using hydrochloric acid then cooled to 5C°in ice bath and recrystallized from methanol.

General procedure [7,8,9][14]

2-amino pyridine(0.94 g, 0.01 mole) react with 2-mercaptobenzoxazole (1.5g,0.01mole), 2-mercapto pyrimidin (1.12g,0.01mole) and 2-mercaptobenzothiazole (1.67 g , o.o1 mole) respectively in 30 ml ethanol was refluxed for (7-12) hours . The precipitated solid was collected and recrystallized from ethanol.



Scheme(1)

Results and Discussion

The new derivatives of 2-amino pyridine β lactam and tetrazoles were prepared by following the reaction sequences outlined in ***scheme 1***.

The compound [1] ethyl2-(pyridin-2-ylamino) acetate was synthesized by the reaction of 2-amino pyridine with chloro ethyl acetate .The formation of this compound was indicated by presence in their IR spectra of carbonyl group (C=O) of ester at (1741cm^{-1}) table [1]. ^{1}HNMR (DMSO_d_6)ς(ppm)ofcompound[1]:1.23(t,3H,$COOCH_2C\underline{H}_3$) ,4.01 (q,2H, $COOC\underline{H}_2CH_3$) , 4.12 (d, 2H,$NHC\underline{H}_2$) , 7.8 (s, 1H,$N\underline{H}CH_2$), 6.1-7.6 ppm which belonged to aromatic protons.

Reaction between compound [1] and hydrazine hydrate (95%) afforded the acid hydrazid derivatives [2] in good yield. The spectrum showed the appearance of the (C=O)Amide at (1699cm^{-1}) and disappearance the carbonyl group (C=O)of ester at (1741 cm^{-1}), NH stretching absorption near (3385) cm^{-1} table [1].^{1}HNMR (DMSO_ d_6) ς (ppm) of compound [2]: 4.5(d, 2H, $NHNH_2$), 9.1(s, 1H, $NHNH_2$), 3.01(d, 2H, $NHCH_2$), 7.2 (s, 1H, NH CH_2), 6.1-8.07 ppm which belonged to aromatic protons.

Condensation of compound [2] with different substituted aromatic aldehydes in absolute ethanol gave arylidine derivatives [3a-d]. The formation of these azomethines was indicated by the presence in their IR spectra of (CH=N) stretching bands at (1627)cm^{-1}combined with the disappearance of NH_2 stretching band table [1].^{1}HNMR (DMSO_ d_6) ς (ppm) of compound [3a]: 3.5(d, 2H, NH $C\underline{H}_2$), 7.4(s, 1H, $N\underline{H}$ CH_2), 8.4 (s, 1H, N=C$\underline{H}$), 10.1 (s, 1H, NHN=C), 6.2-8.4 ppm which belonged to aromatic protons.

Schiff bases Treatment with tri ethyl amine and chloro acetyl chloride yielded different azetidinyl derivatives [4a-d]. The IR Spectra of these

derivatives showed the disappearance bands of (CH=N) in theregion (1627) cm^{-1} combined with the appearance of Absorption band at (1735) cm^{-1} (C=O β lactam) table [2].^{1}HNMR(DMSO_ d_6) ς (ppm)of compound [4a]: 3.8 (d, 2H, NH $C\underline{H}_2$), 8.1 (s, 1H, $N\underline{H}$ CH_2), 8.4(s, 1H, N$\underline{H}$N-C), 5.7(d, 1H, C$\underline{H}$Cl-CH-Ar), 6.1-8.1 ppm which belonged to aromatic protons.

When the 2-amino pyridine reacts with different aldehydes in presence CUCN that gave compounds derivatives [5a-c]. The IR spectra that appearance the band of (C≡N) at (2166) cm^{-1}table [2].^{1}HNMR (DMSO_ d_6)ς (ppm)of compound [5a]: 5.9(d, 1H, NH C$\underline{H}$), 4.2(s, 1H, NHCH), 6.6-8.1 ppm which belonged to aromatic protons.

Compounds [5a-c] react with sodium azid ,ammonium chloride in DMF gave the new derivatives of tetrazoles compounds [6a-c] .The IR. Spectra show the disappearance the band of (C≡N) at (2166) $cm^{-1}$and appearance the band of tetrazole ring (1192) $cm^{-1}$and (1296) cm^{-1}(N-N=N),table [3].^{1}HNMR (DMSO_ d_6)ς (ppm)of compound [6a]:5.4(d, 1H, NH C$\underline{H}$), 3.98(s, 1H, NHCH), 8.4(s, 1H, N$\underline{H}$-N=N), 6.5-7.9 ppm which belonged to aromatic protons.

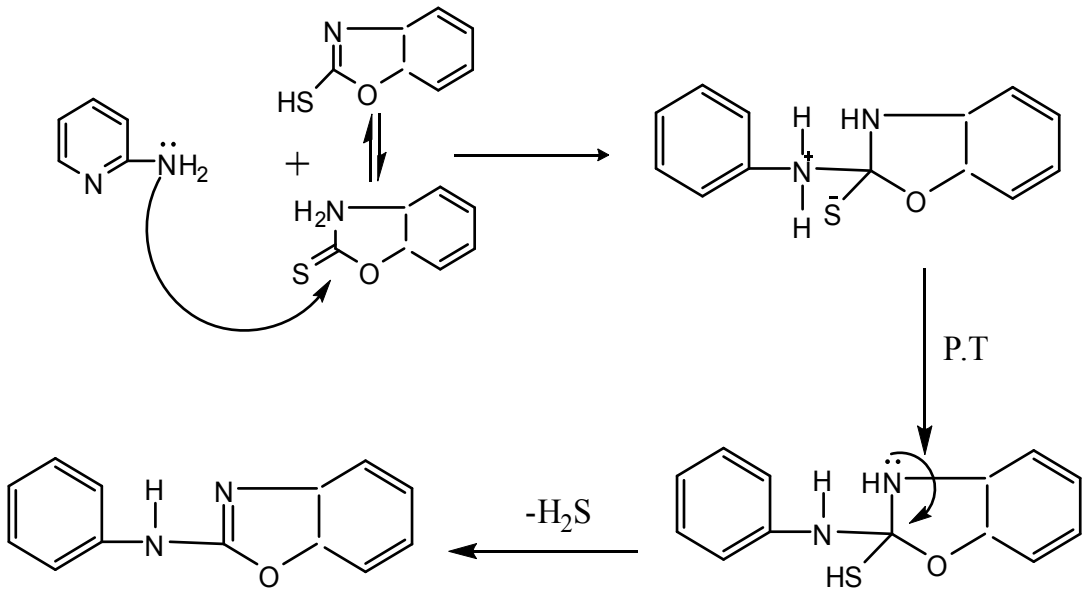
Reaction of 2-amino pyridine with 2-mercaptobenzoxazole, 2-mercapto pyrimidinand 2-mercaptobenzothiazole respectively in ethanol gave new derivatives [7, 8, and 9] respectively .Course of the reaction steps wasfollowed up and make sure it

occurs by use lead acetate paper, which is inferred from blackening the paper and the liberalization of H_2S and occurrence of the reaction according the following equation:

$$(CH_3COO)_2pb + H_2S \rightleftharpoons pbS\downarrow + 2\ CH_3COOH$$

The IR Spectra show the disappearance the H_2S and appearance the stretching band of NH at (3210) cm^{-1}, table [4]. ^{1}HNMR (DMSO_ d_6) ς (ppm) of compound [7]: 4.3(s, 1H, NH), 6.6-8.1 ppm which belonged to aromatic protons.

The reaction may be explained as shown in mechanism[14]:



Scheme (2)

Table [1]:physical properties and Spectral data

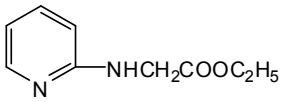
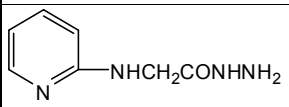
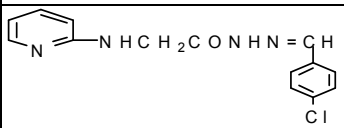
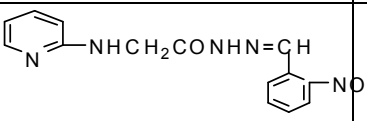
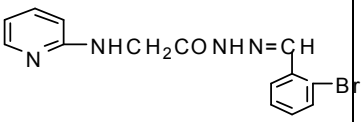
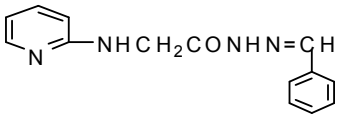
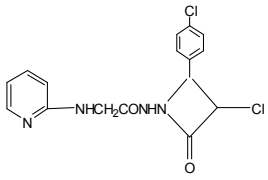
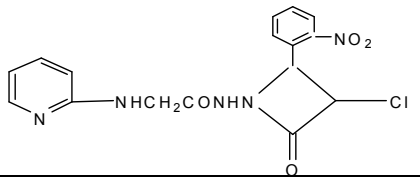
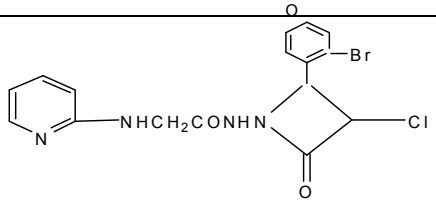
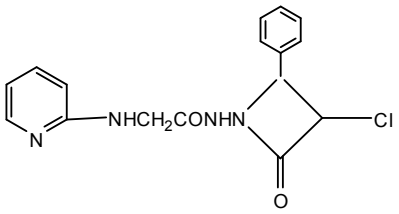
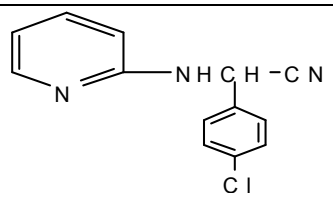
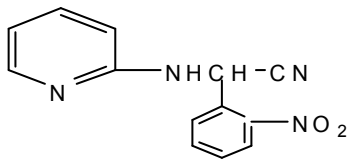
NO	*Compound*	*Yiel %*	*Mp.C°*	*Recrystallize*	*IR.(KBr) cm^{-1}*
1		80	94-96	Chloroform.	1741 (C=O ester), 3043 CH aromatic, 2831CH aliphatic, 3201NH stretching, 1523 (C=C).
2		75	100-102	Ethanol	1699 (C=O amid), 3064CH aromatic, 2829CH aliphatic, 3265NH, 3385 NH_2, 1585 (C=C).
3a		70	180-182	Ethanol	1653(C=O amid),1626 (C=N) ,3043 CH aromatic,2943 CH aliphatic ,3252 NH,1585 (C=C),858 Para substitution
3b		73	195-197	Ethanol	1699(C=O amid), 1627(C=N), 3043 CH aromatic, 2837 CH aliphatic, 3250 NH, 1589(C=C) ,779ortho substitution.
3c		67	200-202	Ethanol	1685(C=O amid),1626 (C=N) ,3090 CH aromatic, 2852 CH aliphatic,3260 NH,1587 (C=C), 758 ortho substitution.
3d		65	178-180	Ethanol	1681(C=O amid),1626(C=N),3153 CH aromatic, 2810 CH aliphatic,3310 NH,1587 (C=C).
4a		65	230-232	Ethanol / water	1735 C=O β Lactam , 1678 C=0 amide , 3064 CH aromatic, 2991 CH aliphatic , 1487 C-N , 1597 C=C aromatic, 844 Para substitution .

Table [2]:physical properties and Spectral data

NO	*Compound*	*Yied%*	*Mp.C°*	*Recrystillize*	*IR.(KBr) cm^{-1}*
4b		60	225-227	Ethanol/ water	1730 C=O β Lactam , 1651 C=0 amide , 3084 CH aromatic, 2955 CH aliphatic , 1425 C-N , 1523 C=C aromatic , 740 ortho substitution
4c		67	240-242	Benzene	1734 C=O β Lactam , 1650 C=0 amide , 3086 CH aromatic, 2950 CH aliphatic , 1487 C-N , 1591 C=C aromatic, 794 ortho substitution
4d		66	202-204	Methanol	1734 C=O β Lactam , 1645 C=0 amide , 3086CH aromatic, 2955 CH aliphatic , 1481 C-N , 1518 C=C aromatic .
5a		70	186-190	Benzene	2166(C≡N),3066CH aromatic,2850 CH aliphatic,3387 NH,1543(C=C) aromatic , 850 Para substitution.
5b		70	220-222	Benzene	2166(C≡N),3045CHaromatic ,2850 CH aliphatic,3387 NH,1585 (C=C) aromatic ,738orthosubstitution.

Table[3]:physical properties and Spectral data

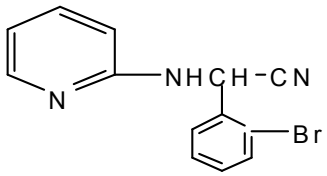
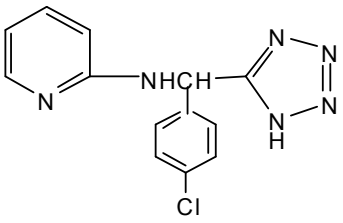
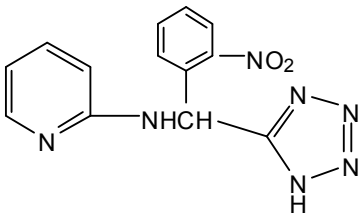
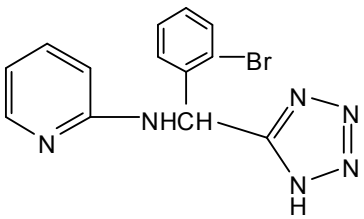
NO	*Compound*	*Yield%*	*Mp.C°*	*Recrystillize*	*IR.(KBr) cm^{-1}*
5c		75	236-240	Benzene	2162(C≡N),3031CH aromatic ,2921 CH aliphatic,3310 NH,1545 (C=C)aromatic,765ortho substitution.
`6a		75	260-262	Methanol	1292(N-N=N),1182(tetrazo ring), 3043(CH-Ar.),2837CH aliphatic, 3250 NH,1589 (C=C) aromatic ,844 Para substitution.
6b		68	270-272	Ethanol	1296(N-N=N),1188(tetrazol ring) ,3080(CH-Ar.),2852CH aliphatic, 3338 NH, 1577 (C=C) aromatic ,758 ortho substitution.
6c		65	235-237	Methanol	1259(N-N=N),1192(tetrazol ring),3174(CH-Ar.), 2929 CH aliphatic,3327 NH,1577 (C=C) aromatic ,754ortho substitution.

Table [4]: physical properties and Spectral data

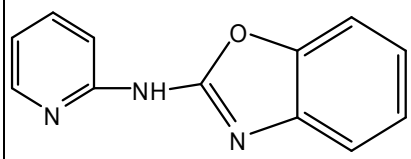
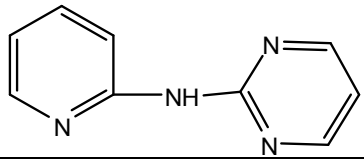
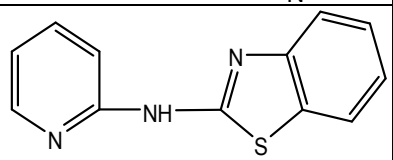
NO	*Compound*	*Yield%*	*Mp.C°*	*Recrystillize*	*IR.(KBr) cm^{-1}*
7		85	199-200	Ethanol	3176 starching NH, 3082 CH aromatic , 2960 CH aliphatic, 1217 C-O-C , 1568 C=C aromatic .
8		80	180-182	Ethanol	3200 starching NH, 3055 CH aromatic , 2962 CH aliphatic , 1564 C=N, 1521 C=C aromatic .
9		75	201-203	Ethanol	3210 starching NH , 3070 CH aromatic , 2981 CH aliphatic ,632 C-S-C , 1570 C=N, 1539 C=C aromatic .

Table [5]: Chemical shifts ^{1}HNMR spectra

NO.	*^{1}HNMR (DMSO_d_6) ς ppm*
1	1.23 (t,3H,COOCH$_2$C<u>H</u>$_3$) , 4.01(q,2H,COOC<u>H</u>$_2$CH$_3$) , 4.12(d, 2H,NHC<u>H</u>$_2$) , 7.8(s, 1H,N<u>H</u>CH$_2$), 6.1-7.6 ppm which belonged to aromatic protons.
2	4.5(d, 2H, NHNH$_2$), 9.1(s, 1H, NHNH$_2$), 3.01(d, 2H, NHCH$_2$), 7.2 (s, 1H, NHCH$_2$), 6.1-8.07 ppm which belonged to aromatic protons.
3a	3.5(d, 2H, NH C<u>H</u>$_2$), 7.4(s, 1H,N<u>H</u>CH$_2$), 8.4 (s,1H, N=C<u>H</u>), 10.1 (s, 1H, NHN=C), 6.2-8.4 ppm which belonged to aromatic protons.
4a	3.8(d, 2H, NH C<u>H</u>$_2$), 8.1 (s, 1H,N<u>H</u>CH$_2$), 8.4(s,1H,N<u>H</u>N-C), 5.7(d, 1H,C<u>H</u>Cl-CH-Ar), 6.4-8.2 ppm which belonged to aromatic protons.
5a	5.9(d, 1H, NH C<u>H</u>), 4.2(s, 1H, NHCH), 6.6-8.1 ppm which belonged to aromatic protons.
6a	5.4(d, 1H, NH C<u>H</u>), 3.9(s, 1H, NHCH), 8.4(s, 1H, N<u>H</u>-N=N), 6.5-7.9 ppm which belonged to aromatic protons.
7	4.3(s, 1H, NH), 6.6-8.1 ppm which belonged to aromatic protons.

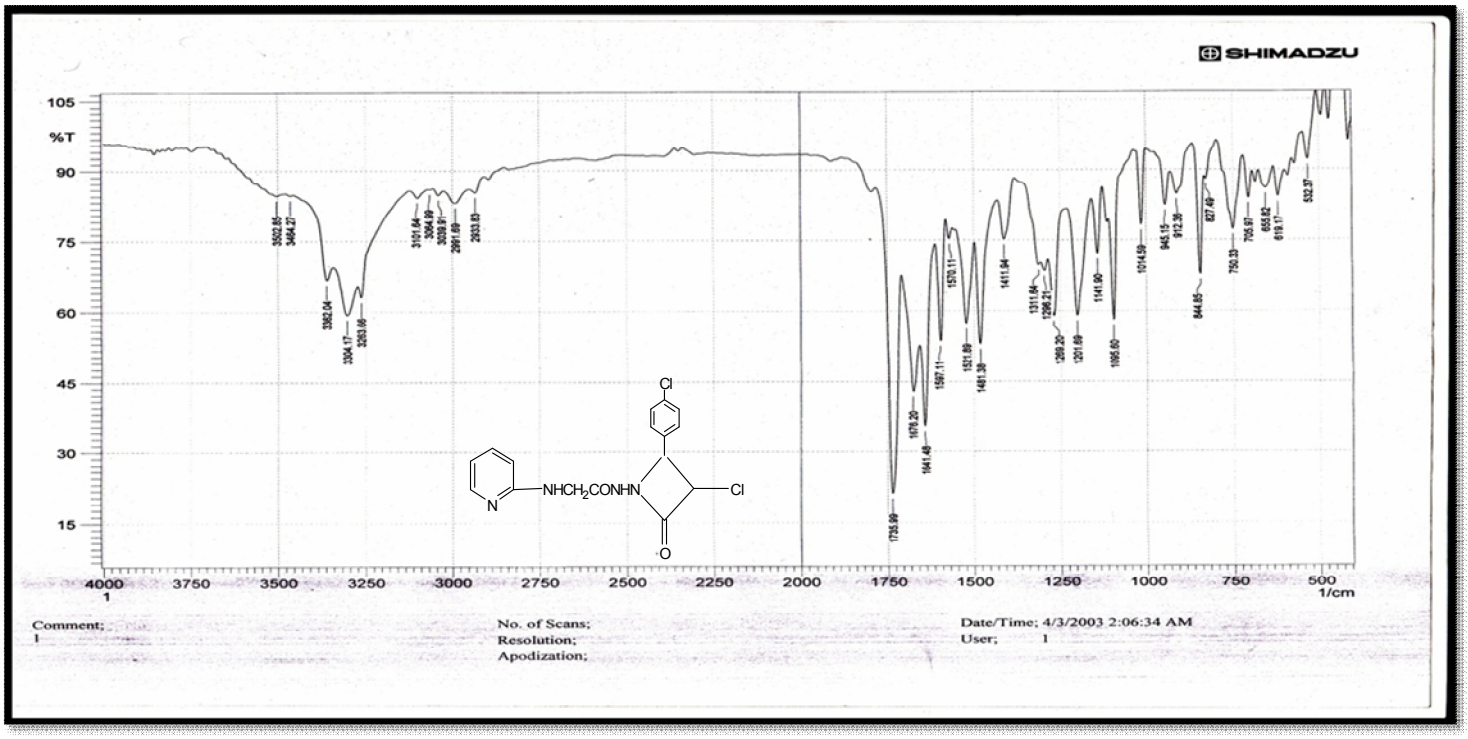


Figure.[1] FT.IR spectrum of compound [4a]

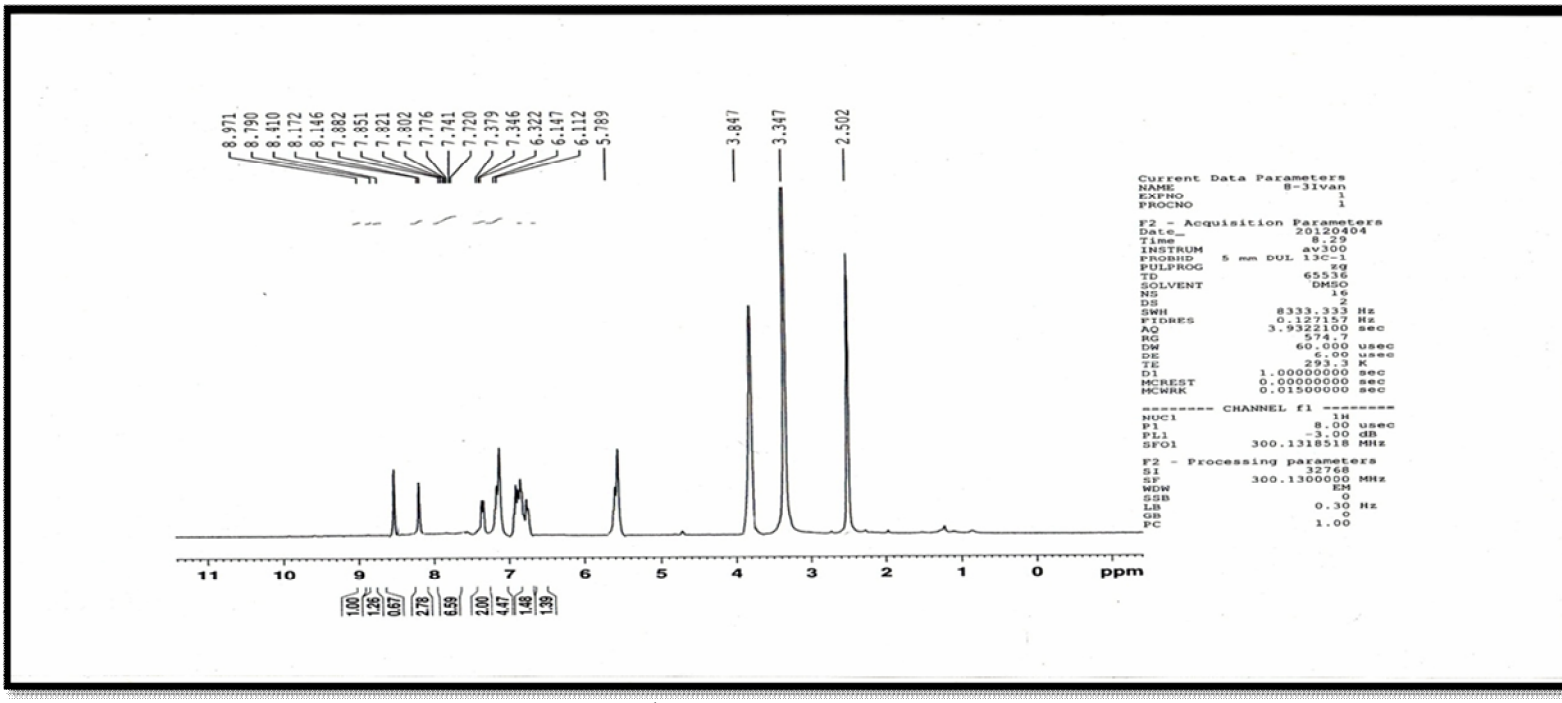


Figure [1] ^{1}HNMR of compound [4a]

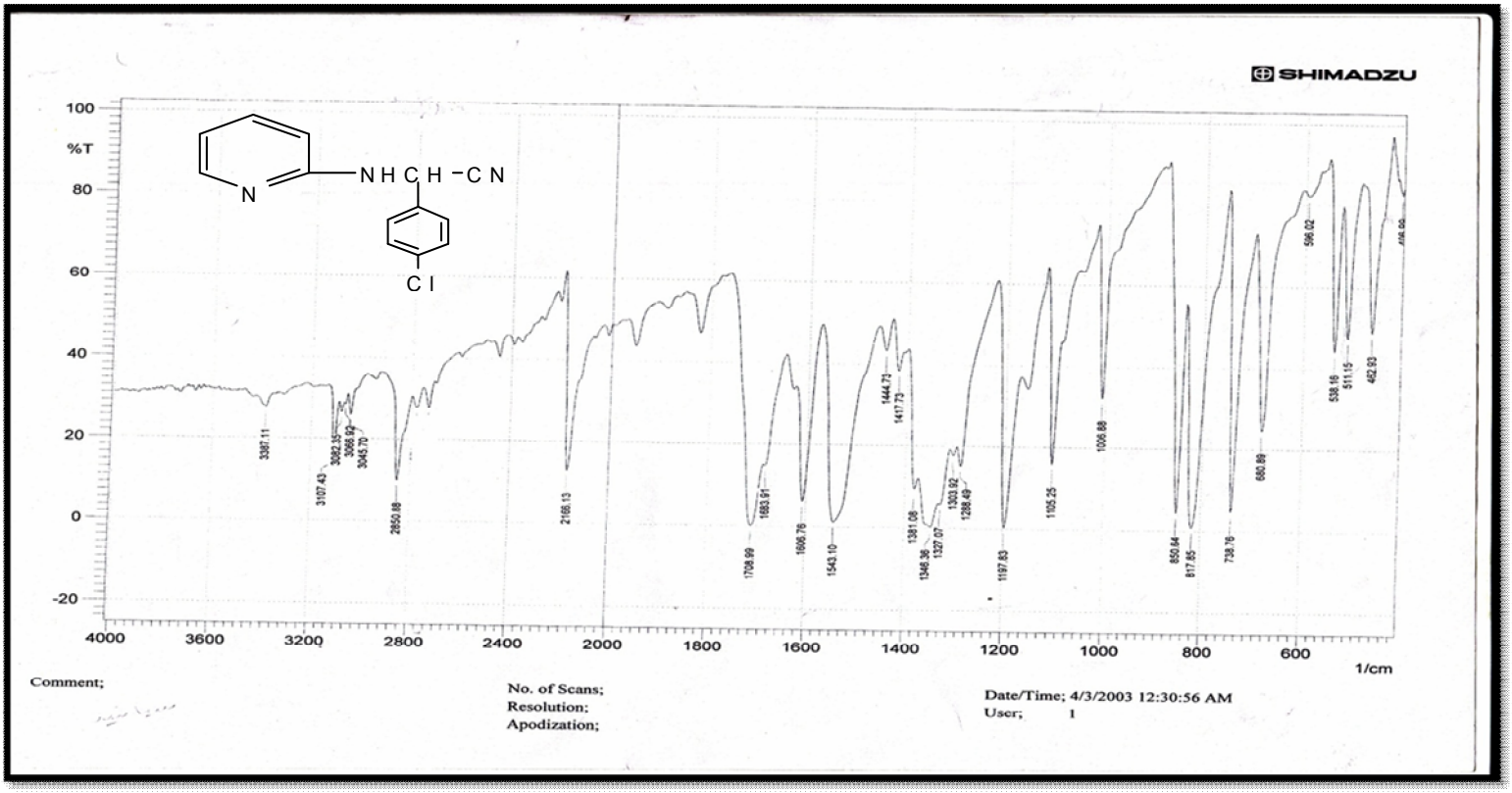


Figure.[2] FT.IR spectrum of compound [5a]

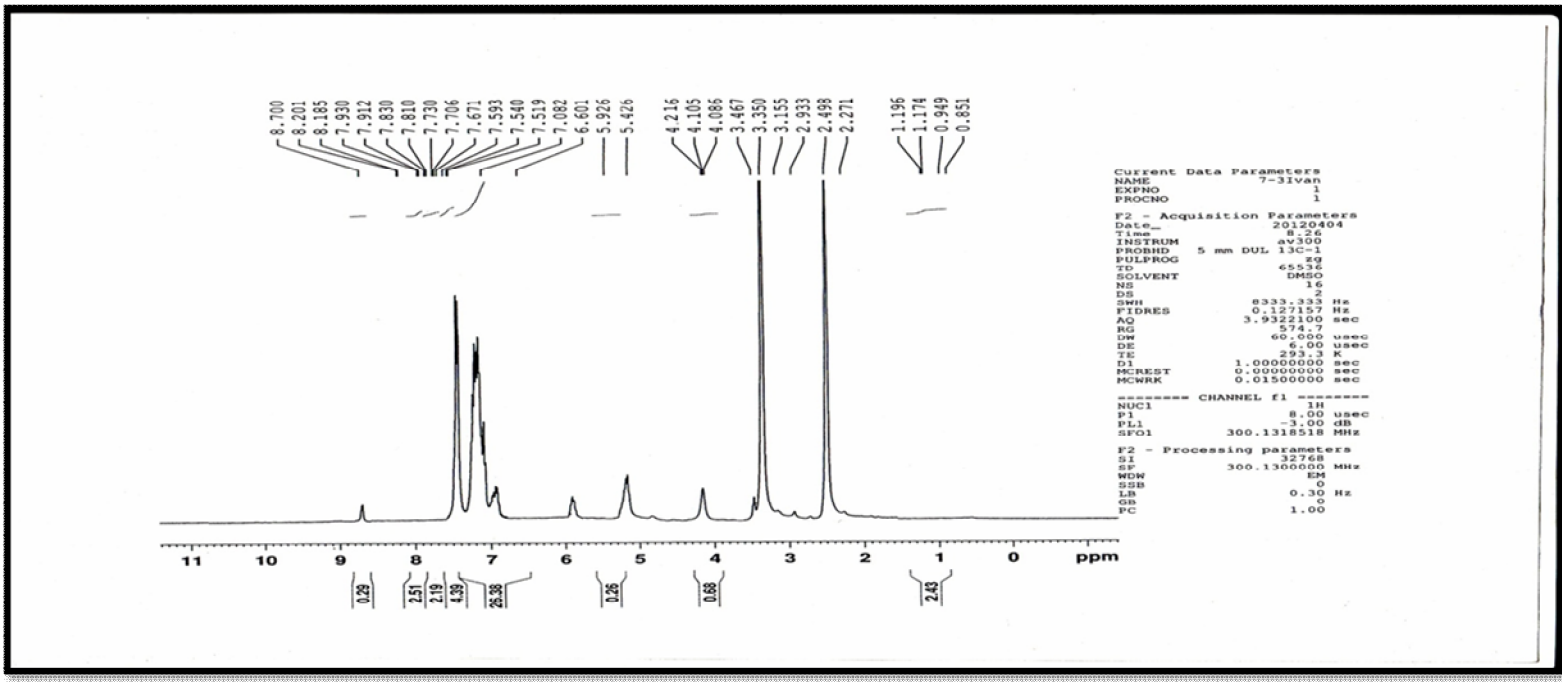


Figure [2] ^{1}HNMR of compound [5a]

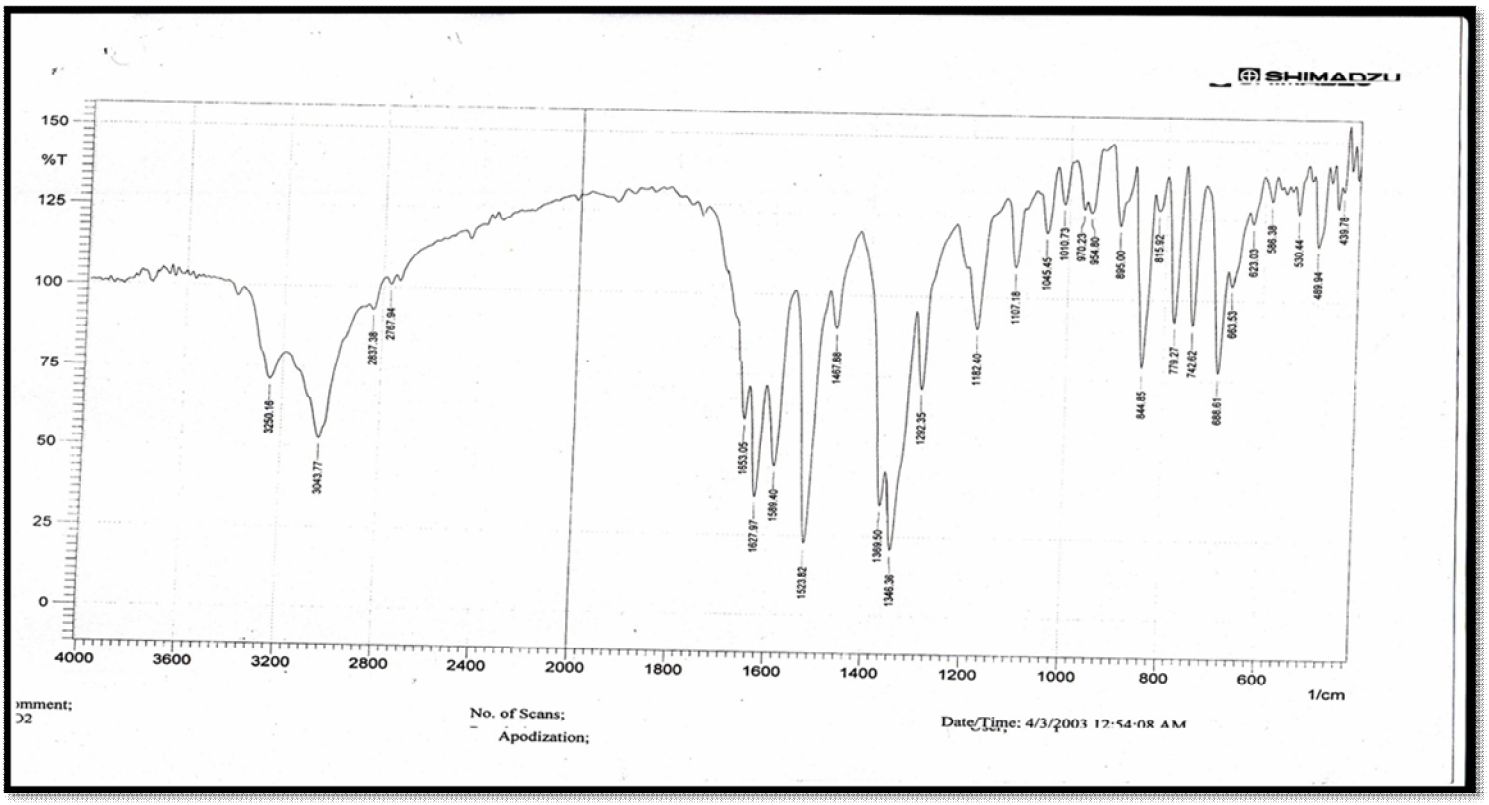


Figure.[3] FT.IR spectrum of compound [6a]

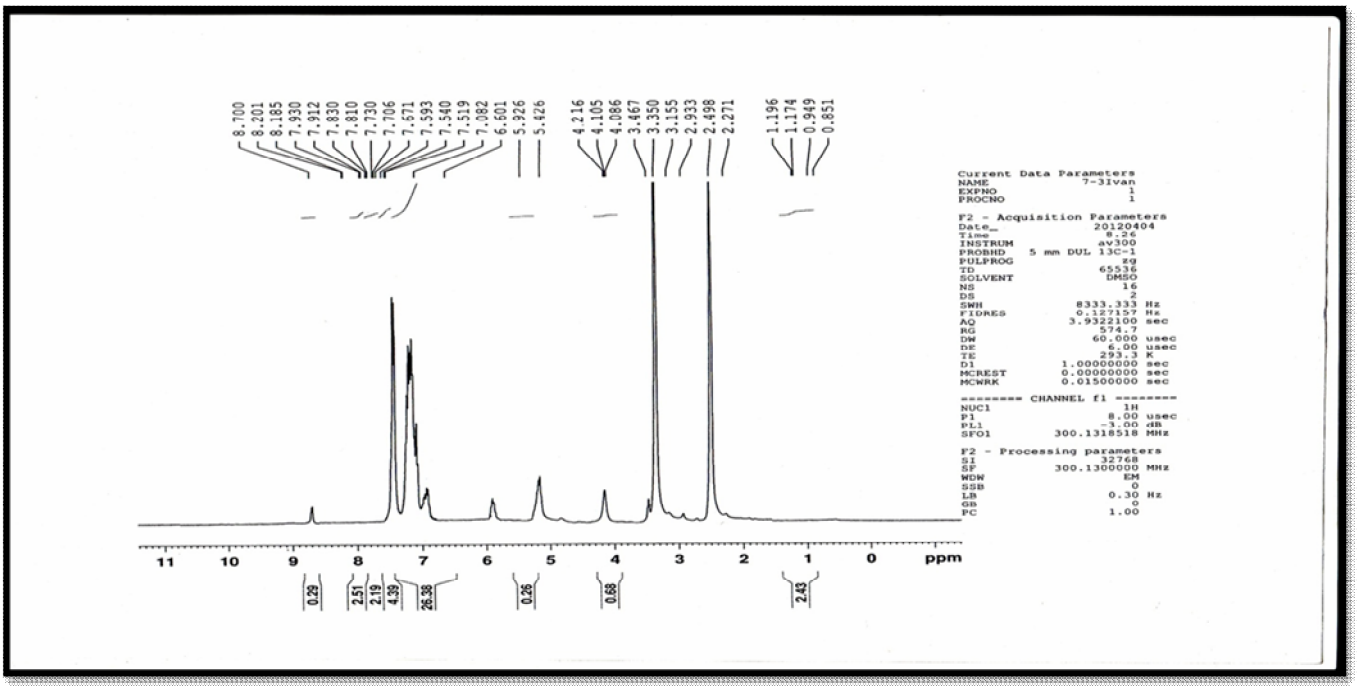


Figure [3] ^{1}HNMR of compound [6a]

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