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Synthesis and structural elucidation of Famciclovir

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ABSTRACT

The compound Famciclovir is synthesized and characterized by elemental analysis, ^{1}H NMR, ^{13}C NMR, mass spectra, electronic spectra and IR spectra. This confirms the proposed structure for the compound Famciclovir.

Key words: Synthesis, elucidation, famciclovir, ^{1}H NMR, ^{13}C NMR, mass spectra, electronic spectra and IR spectra.

INTRODUCTION

Famciclovir is a guanine analogue ANTI VIRAL DRUG used for the treatment of various herpes viral infections, most commonly for herpes zoster (shingles). It is a prodrug form of penciclovir with inproved oral bioavailability. Torii et al.,[1] have established practical methods for the synthesis of Famciclovir (FCV) from readily available N2-acetyl-7-benzylguanine. Chiodini et al.,[2] have reported the manufacture of Famciclovir using phase-transfer catalysts. Kobe et al.,[3] have reported a new process for the preparation of alkyl substituted purine derivatives. Wang et al.,[4] have established a new method for the preparation of Famciclovir with 21% yield via regioselective alkylation of 2-amino purine with 5-(2-bromoethyl)-2,2-dimethyl-1,3-dioxan as a pivotal step. Based on the above literature the authors proposed to synthesize the compound with good quality and economy.

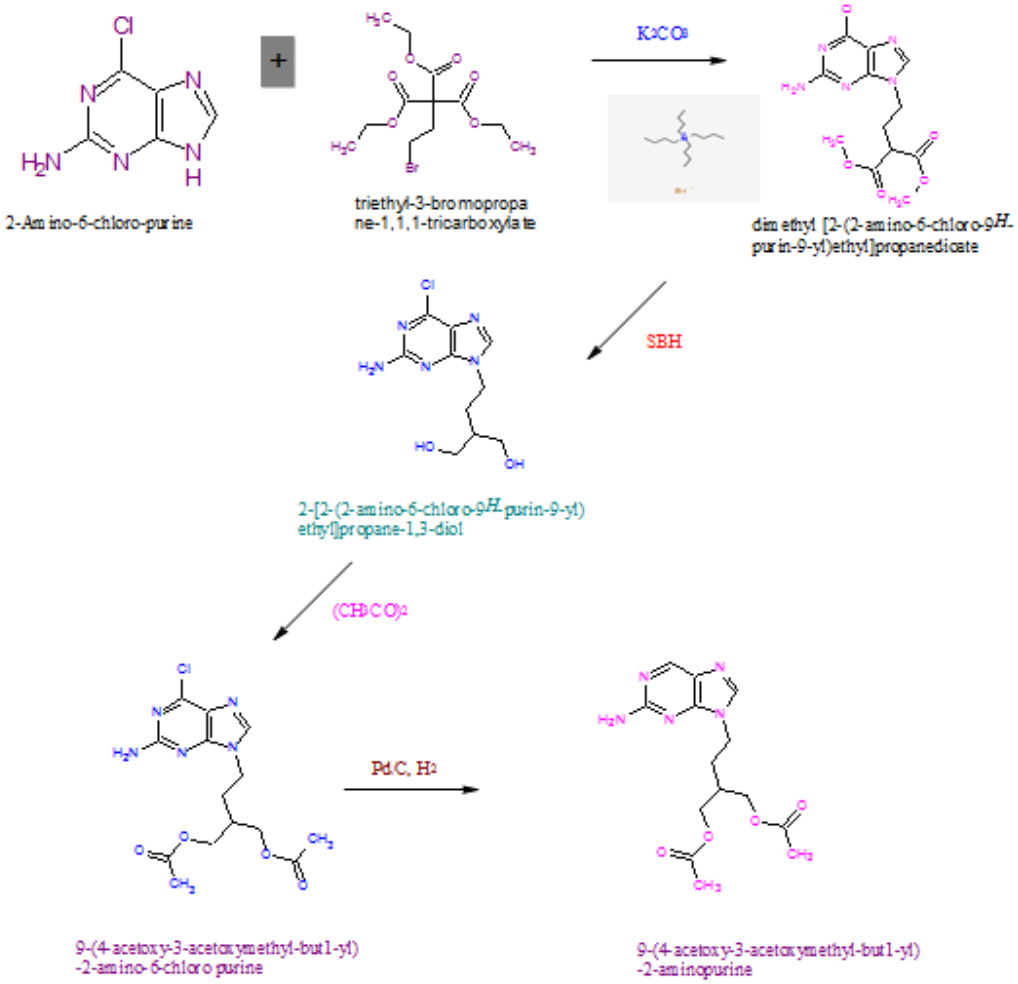
MATERIALS AND METHODS

The ^{1}H Nuclear Magnetic Resonance Spectrum of the compounds I & II are recorded in DMSO-d_6 at $27^{0}C$ on Bruker Avance NMR Spectrometer (300MHz) and the compounds III & IV are recorded in $CDCl_3$ at $27^{0}C$ on Bruker Avance NMR Spectrometer (300MHz).

The ^{13}C Nuclear Magnetic Resonance Spectrum are recorded for compound I in DMSO-d_6, for compound II in DMSO-d_6 + D_2O and for compounds III & IV in $CDCl_3$ at $27^{0}C$ on Bruker Avance NMR Spectrometer (300MHz).

The mass spectra of all the compounds are recorded on Waters Quattro Micro Mass Spectrophotometer.

The infrared spectra of all the compounds are recorded in a KBr pellet on Perkin Elmer infrared Spectrophotometer. The Ultra-Violet spectra of all the compounds in methanol are scanned from 200 to 400 nm on Perkin Elmer Lambda 35 UV/Vis Spectrophotometer



The preparation of Famciclovir, the antiviral drug utilizes 2-Amino-6-Chloropurine as a starting material (available commercially). Synthesis involves Esterification, peptide coupling between 2-Amino-6-Chloropurine and Triethyl 3-bromopropane 1, 1, 1-tricarboxylate using Potassium Carbonate as a catalyst gives Dimethyl 2-(2-amino-6-chloro 9H-purin-9-yl)malanoate (FCV-I).This (FCV-I) on further reduction with Sodium borohydrate gives 2-[2-(2-amino-6-Chloro-9H-purin-9-yl) ethyl] propane-1, 3-diol(FCV-II). By acetylation of 2-[2-(2-amino-6-Chloro-9H-purin-9-yl) ethyl] propane-1, 3-diol using Acetic anhydride and Triethyl amine as a solvent, 9-(4-acetoxy-3-acetoxy methyl-but-1-yl)-2-amino-6-Chloropurine (FCV-III) is formed. FCV-III on reductive acylation using 5% palladium on carbon and sodium acetate in triethyl amine under hydrogen atmosphere at room temperature gave

Famciclovir. Physical state of the compound is white amorphous. Melting point is 102-104^{0}C. % of yield is 90.

The detailed procedure for the synthesis of all the four compounds is shown in the following table:

S. No	Compound	Reactants	Catalyst/ Medium	Conditions
1	FCV-I	2-amino-6-chloro purine and Triethyl 3-bromopropane-1,1,1-tricarboxylate	Potassium carbonate and tetrabutyl ammonium bromide	The reaction mixture is heated to 60^0C for 16 hours , the residue obtained to cooled to 20^0C, stirred for one hour and dried in hot air oven at 60^0C
2	FCV-II	FCV-I and methylene dichromate	Sodium borohydride	The reaction mixture is cooled to 20^0C, added methanol, pH is adjusted to 6.5, distilled at 60^0C and the resultant solid obtained is dried at 50^0C
3	FCV-III	FCV-II, methylene dichromate and triethyl amine	Acetic anhydride	Heated slowly for one hour, cooled to room temperature, pH is adjusted to 7, organic layer is separated, dried with Na_2SO_4, distillation followed by the addition of di-isopropylate (DIP) and finally dried in hot air oven at 60^0C
4	FCV-IV	FCV-III and isopropyl alcohol	Carbon, palladium and sodium acetate	Stirred well, heated to 60^0C till a clear solution is obtained, filtered, pH is adjusted to 7, organic layer is separated , dried with Na_2SO_4 to remove water and finally dried in hot air oven at 65^0C

RESULTS AND DISCUSSION

The physical properties of the final compound as well as intermediates is represented in Table-1

Table-1 Physical properties of the Compounds synthesized

S. No	Compound	Molecular Formula	Molecular Weight	Physical State	Color	Yield (in g)
1	FCV-I	$C_{12}H_{14}ClN_5O_4$	327.72	Amorphous	White	32.0
2	FCV-II	$C_{10}H_{14}ClN_5O_2$	271.70	Amorphous	White	33.0
3	FCV-III	$C_{14}H_{18}ClN_5O_4$	355.78	Amorphous	Pale Yellow	32.5
4	FCV-IV	$C_{14}H_{19}N_5O_4$	321.33	Amorphous	White	33.0

Elemental Analysis:
The compounds were analysed for carbon, hydrogen and nitrogen and the results are shown in Table-2.

Table-2 Analytical data for the compounds

S. No	Compound	Molecular Weight	Found (Calculated) %		
			C	H	N
1	FCV-I	327.72	43.89 (43.98)	4.22 (4.31)	21.28 (21.37)
2	FCV-II	271.70	44.10 (44.21)	5.10 (5.19)	25.69 (25.78)
3	FCV-III	355.78	47.19 (47.26)	4.99 (5.10)	19.59 (19.68)
4	FCV-IV	321.33	52.24 (52.33)	5.89 (5.96)	21.71 (21.79)

^{1}H NMR Spectral data:
The ^{1}H NMR Spectra of all the compounds is taken and the data obtained is tabulated in Table-3

Table-3 ^{1}H NMR Spectral data for the compounds

S.No	Compound	Proton Number	Multiplicity	Chemical shift (ppm)
1	FCV-I	H-8 (1H)	s	8.08
		H-10 (2H)	s	6.09
		H-2" (2H)	t	4.09-4.13
		H-4',5' (6H)	s	3.60
		H-2' (1H)	t	3.51-3.55
		H-1" (2H)	m	2.26-2.36
2	FCV-II	H-8 (1H)	s	8.16
		H-10 (2H)	s	6.90
		H-4',5' (2H)	m	4.51
		H-2" (2H)	t	4.08-4.13
		H-1',3' (4H)	m	3.36-3.45
		H-1" (2H)	q	1.71-1.78
		H-2' (1H)	m	1.39-1.47
3	FCV-III	H-8 (1H)	s	7.79
		H-10 (2H)	s	5.11
		H-1' (2H)	t	4.17-4.22
		H-4',5' (4H)	d	4.13-4.15
		H-7',9' (6H)	s	2.07
		H-2',3' (3H)	m	1.92-1.99
4	FCV-IV	H-6 (1H)	s	8.70
		H-8 (1H)	s	7.77
		H-10 (2H)	s	5.05
		H-1' (2H)	t	4.18-4.23
		H-4',5' (4H)	d	4.13-4.15
		H-7',9' (6H)	s	2.06
		H-2',3' (3H)	m	1.91-2.03

^{3}C NMR Spectral Data:

The ^{1}H NMR Spectra of all the compounds is taken and the data obtained is tabulated in Table-4

Table-4 ^{13}C NMR Spectral Data for the compounds

S.No	Compound	Carbon Number	Chemical Shift (ppm)
1	FCV-I	C-1',3'	168.77
		C-2	159.74
		C-4	154.13
		C-6	149.34
		C-8	143.09
		C-5	123.39
		C-4',5'	52.50
		C-2"	48.46
		C-2'	40.97
		C-1"	27.92
2	FCV-II	C-2	160.01
		C-4	154.38
		C-6	149.88
		C-8	143.94
		C-5	123.78
		C-1',3'	61.62
		C-2"	42.00
		C-2'	40.92
		C-1"	28.66
3	FCV-III	C-6'8'	170.73
		C-2	159.11
		C-4	153.73
		C-6	151.12
		C-8	141.97
		C-5	124.99
		C-4'5'	63.48
		C-1'	41.22
		C-3'	34.80
		C-2'	28.67
		C-7',9'	20.68

4	FCV-IV	C-6'8'	170.57
		C-2	159089
		C-4	152.97
		C-6	149.53
		C-8	141.88
		C-5	127.83
		C-4'5'	63.39
		C-1'	40.50
		C-3'	34.67

Mass Spectrum:
The mass Spectra of all the compounds is taken and the data obtained is tabulated in Table-5

Table-5 Mass spectral data for the compounds

S. No	Compound	m/z	Fragment
1	FCV-I	349.89 (M+Na)	$C_{12}H_{14}ClN_5O_4Na$
		327.92 (m/z)	$C_{12}H_{14}ClN_5O_4$
		158.83	$C_7H_{11}O_4$
2	FCV-II	295.91 (M+2+Na)	$C_{10}H_{14}ClN_5O_2Na$
		293.88 (M+Na)	$C_{10}H_{14}ClN_5O_2Na$
		271.95 (m/z)	$C_{10}H_{14}ClN_5O_2$
3	FCV-III	379.84 (M+2+Na)	$C_{14}H_{18}ClN_5O_4Na$
		377.86 (M+Na)	$C_{14}H_{18}ClN_5O_4Na$
		355.88 (m/z)	$C_{14}H_{18}ClN_5O_4$
4	FCV-IV	343.95 (M+Na)	$C_{14}H_{19}N_5O_4Na$
		321.96 (M+1)	$C_{14}H_{19}N_5O_4$

Electronic Spectral Data:
The electronic spectral data of all the compounds is taken and tabulated in Table-6

Table-6 Electronic spectral data for the compounds

S. No	Compound	Wave length (nm)	Band
1	FCV-I	223.20	K band of aromatic ring
		247.99	B band of aromatic ring
		310.24	β band of aromatic ring
2	FCV-II	223.72	K band of aromatic ring
		310.27	β band of aromatic ring
3	FCV-III	223.46	K band of aromatic ring
		248.24	B band of aromatic ring
		310.50	β band of aromatic ring
4	FCV-IV	223.00	K band of aromatic ring
		310.37	β band of aromatic ring

Infrared Spectral data: (IR Spectral Data)
The IR Spectral data of all the compounds is taken and tabulated in Table-7

Table-7 IR Spectral data for the compounds

S. No	Compound	Frequency (cm^{-1})	Assignment
1	FCV-I	3465 & 3313	NH stretching
		3109 & 3013	C-H stretching in aromatic ring
		2960, 2947 & 2853	C-H stretching in CH_2, CH_3
		1741 & 1717	C=O stretching
		1633 & 1611	C=N stretching
		1562 & 1523	C=C stretching
		1473, 1444 & 1411	NH bending
		1358 & 1337	CH bending in CH_2, CH_3
		1312 & 1301	C-N stretching
		1283 & 1260	C-O stretching
		1228 & 1213	C-Cl stretching
		1195, 1168 & 1153	C-C stretching
		1047, 998 & 962	In plane bending vibrations of C-H in aromatic ring
		913, 886 & 783	Out of plane bending vibrations of C-H in aromatic ring
2	FCV-II	3327 & 3206	NH, OH stretching
		3090	C-H stretching in aromatic ring
		2934 & 2881	C-H stretching in CH_2, CH_3
		1639 & 1611	C=N stretching
		1569 &1526	C=C stretching
		1473 & 1411	NH, OH bending
		1379 & 1358	CH bending in CH_2, CH_3
		1315	C-N stretching
		1283 & 1315	C-Cl stretching
		1166 & 1105	C-C stretching
		1076, 1040 & 1020	In plane bending vibrations of C-H in aromatic ring
		985, 918 & 783	Out of plane bending vibrations of C-H in aromatic ring
3	FCV-III	3484 & 3303	NH stretching
		3195 & 3117	C-H stretching in aromatic ring
		2064, 2944 & 2926	C-H stretching in CH_2, CH_3
		1748 & 1731	C=O stretching
		1652 & 1623	C=N stretching
		1558 & 1520	C=C stretching
		1472 &1446	NH bending
		1410 & 1382	CH bending in CH_2, CH_3
		1367 & 1358	C-N stretching
		1326 & 1309	C-O stretching
		1242	C-Cl stretching
		1171 & 1148	C-C stretching
		1070, 1035 & 1023	In plane bending vibrations of C-H in aromatic ring
		988, 907 & 880	Out of plane bending vibrations of C-H in aromatic ring
4	FCV-IV	3404 & 3310	NH stretching
		3080	C-H stretching in aromatic ring
		2963, 2871 & 2824	C-H stretching in CH_2, CH_3
		1748, 1733 & 1724	C=O stretching
		1664 & 1636	C=N stretching
		1615 & 1528	C=C stretching
		1427	NH bending
		1400 & 1370	CH bending in CH_2, CH_3
		1330 & 1304	C-N stretching
		1259, 1247 & 1231	C-O stretching
		1172, 1132 & 1109	C-C stretching
		1088, 1060 & 1029	In plane bending vibrations of C-H in aromatic ring
		964, 901 & 792	Out of plane bending vibrations of C-H in aromatic ring

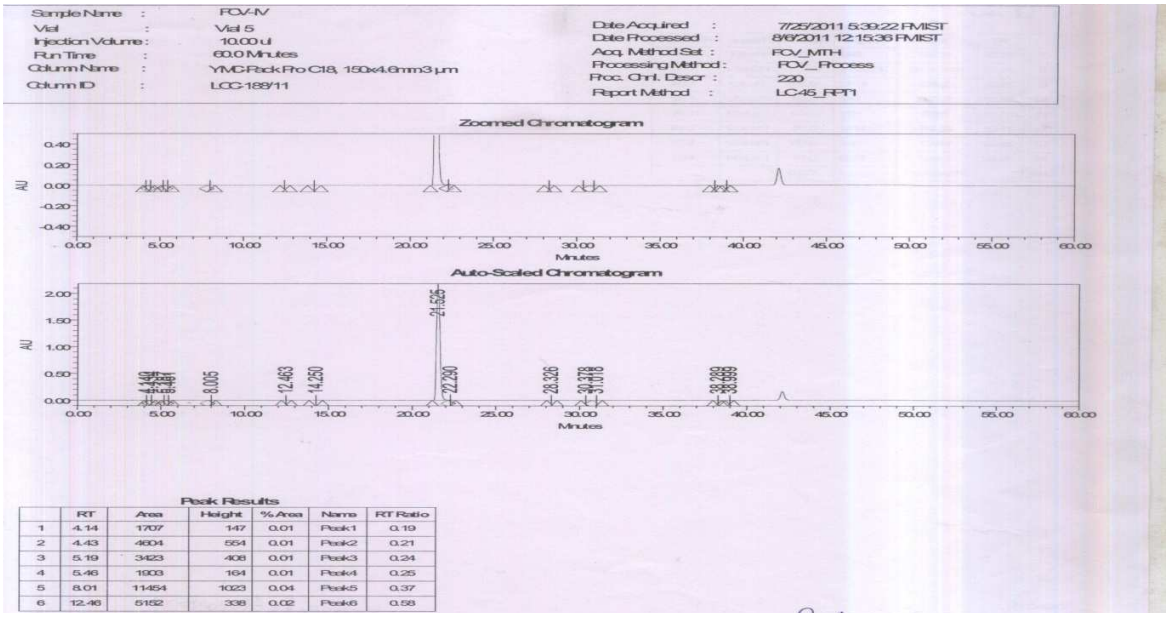


Fig-1 HPLC for FCV-4

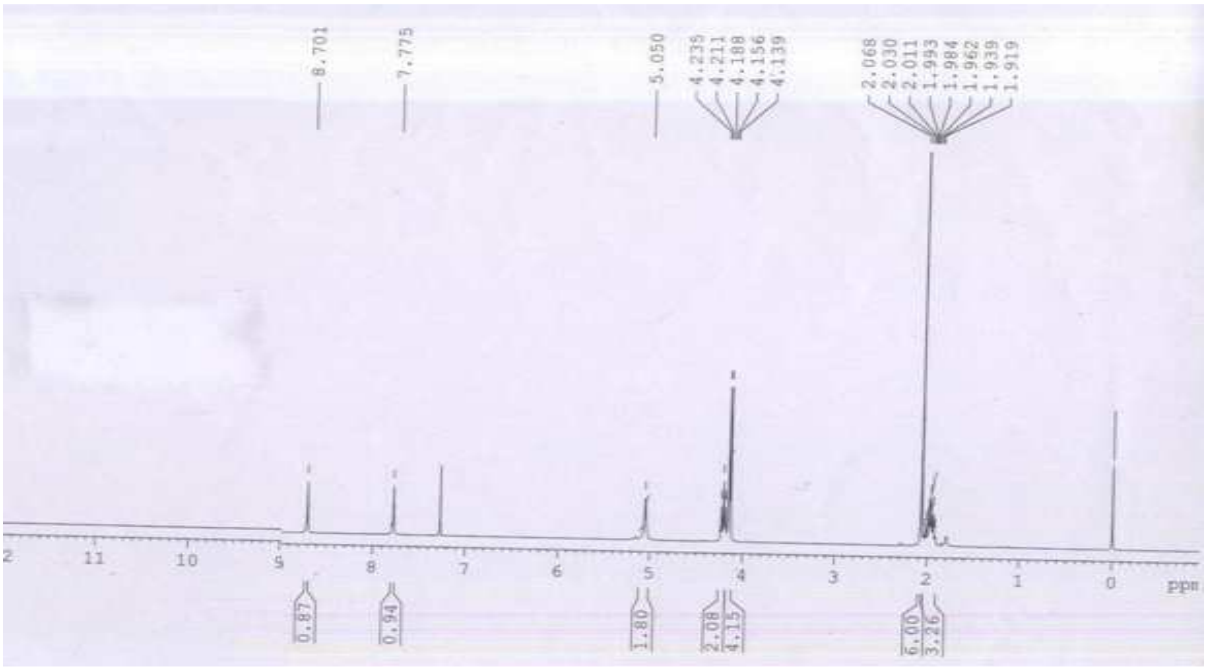


Fig-2 ^{1}H NMR Spectrum for FCV-4

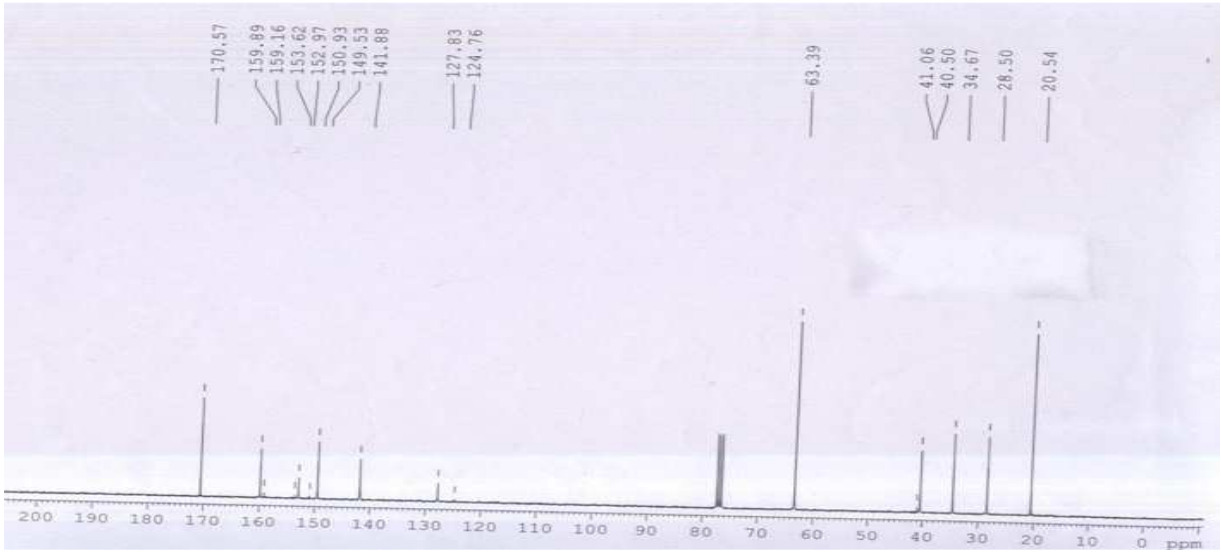


Fig-3 ^{13}C NMR Spectrum for FCV-4

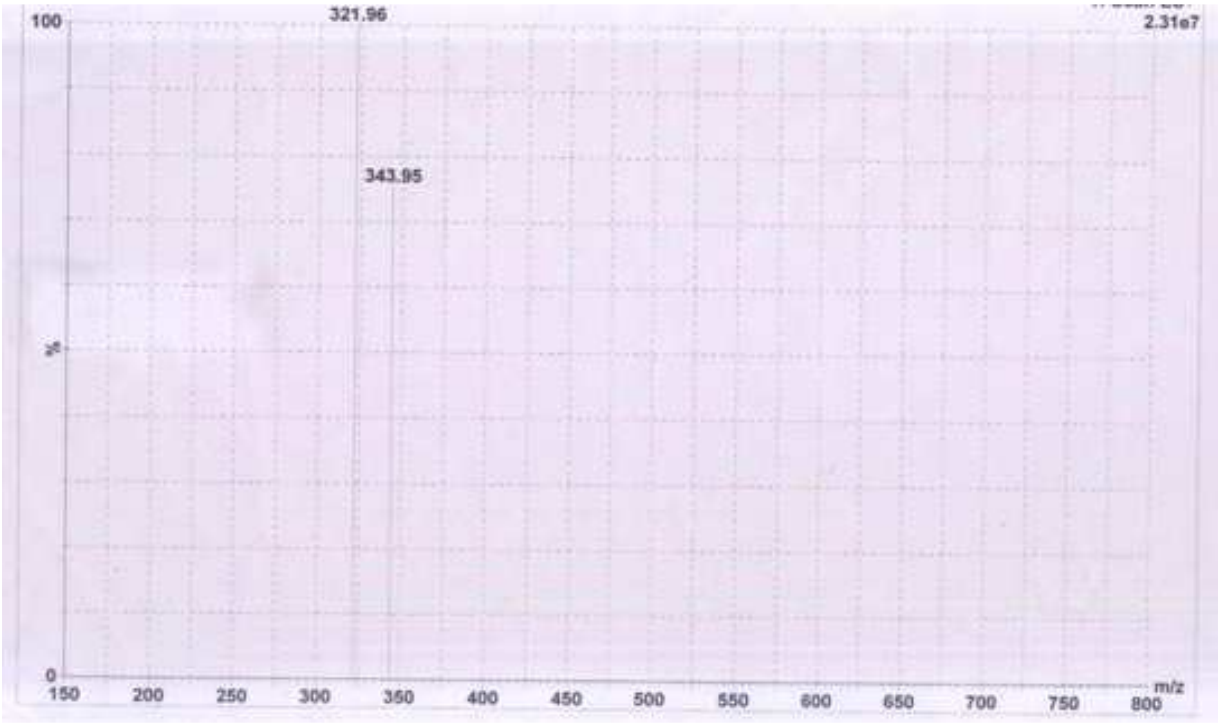


Fig-4 Mass spectrum for FCV-4

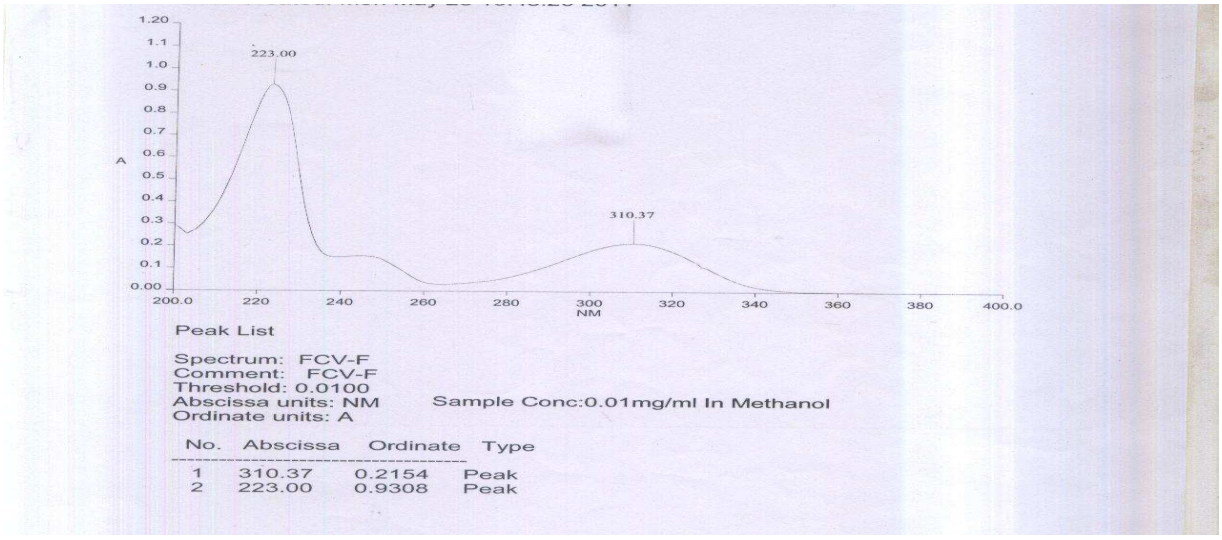


Fig-5 Electronic Spectrum of FCV-4

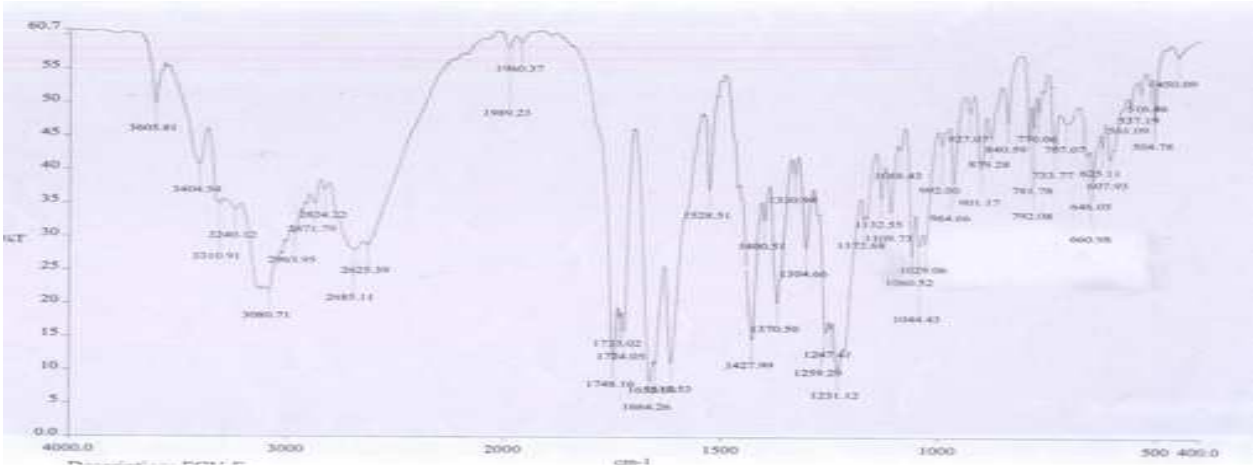


Figure-6: IR Spectrum of FCV-4

CONCLUSION

The compounds (FCV-I to FCV-IV) were synthesized and characterized by elemental analysis, ^{1}H NMR, ^{13}C NMR, mass, electronic and IR spectra. The spectra confirmed the proposed structures of all the compounds.

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