Research Article **www.ijcps.com**

International Journal of
Chemical and Pharmaceutical Sciences
2015, June., Vol. 6 (2)

ISSN: 0976-9390
IJCPS

Characterization of famciclovir by physico-chemical methods

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Received: 23 July 2015, Revised and Accepted: 30 July 2015

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

Keywords: Synthesis, Famciclovir, Characterization, ^{1}H NMR, ^{13}C NMR, Mass spectra, Electronic spectra and IR spectra.

1. INTRODUCTION

Famciclovir, an *anti-viral agent* (acyclic guanine derivative), chemically it is 2-[2-(2-amino-9H-purin-9-yl) ethyl]-1, 3-propanediol diacetate. Famciclovir is a guanine analogue used for the treatment of various herpes viral infections, most commonly for herpes zoster (shingles). It is a prodrug form of penciclovir undergoes rapid biotransformation to the active antiviral compound penciclovir, which has inhibitory activity against herpes simplex virus types 1 (HSV- 1) and 2 (HSV-2) and varicella zoster virus (VZV). 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 regio selective 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. Famciclovir is indicated for the treatment of herpes zoster (shingles) [5], treatment of herpes simplex virus 2 (genital herpes) [6], herpes labialis (cold sores) in immunocompetent patients [7] and for the suppression of recurring episodes of herpes simplex virus 2. It is also indicated for treatment of recurrent episodes of herpes simplex in HIV patients.

2. MATERIAL AND METHODS

All the Chemicals and reagents used were of Analytical Grade and were purchased from Merck.

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

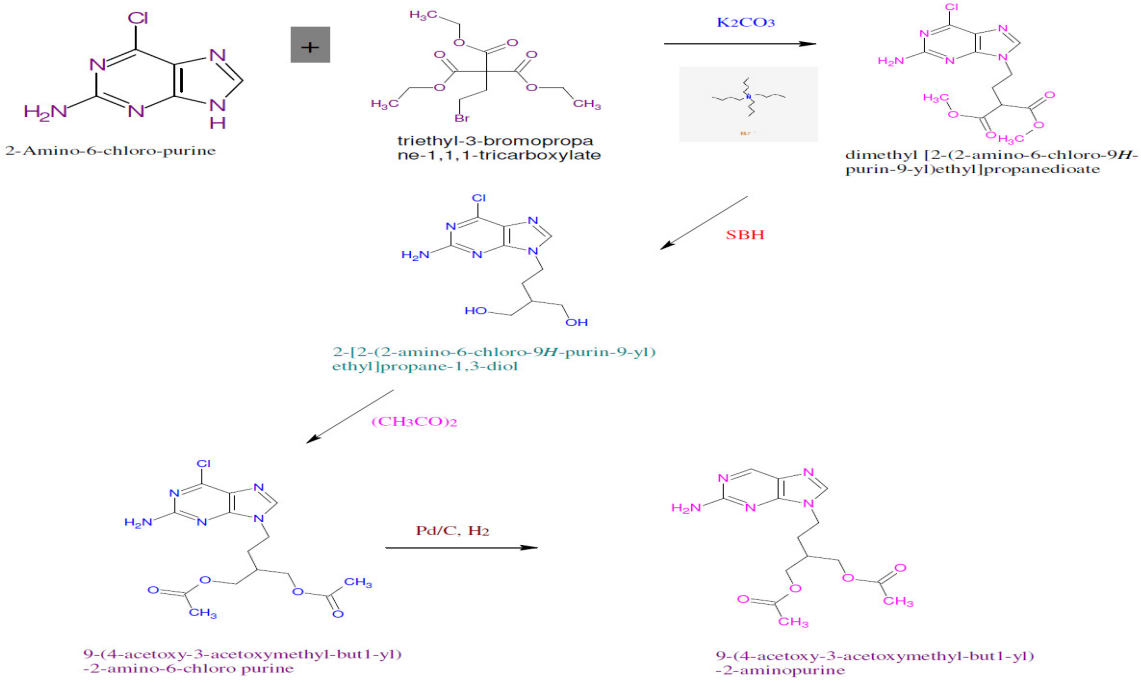
The preparation of Famciclovir utilizes 2-Amino-6-Chloropurine as a starting material (available commercially). Synthesis involves Esterification, peptide coupling between 2-Amino-6-Chloropurine and Triethyl 3-bromopropane 1, 1, 1-tricarboxylate using Potassium Carbonate as a catalyst gives Dimethyl 2-(2-amino-6-chloro 9H-purin-9-yl)malanoate (FCV-I).This (FCV-I) on further reduction with Sodium borohydride gives 2-[2-(2-amino-6-Chloro-9H-purin-9-yl) ethyl]

propane-1, 3-diol(FCV-II). By acetylation of FCV-II 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 (FCV-IV). Physical state of the compound is white amorphous. Melting point is 102-104^{0}C. Percentage of yield is 90.

The detailed procedure for the synthesis of all the four compounds is shown in the following table 1.

Table – 1: A detailed procedure for the synthesis

Compound	Reactants	Catalyst/ Medium	Conditions
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^{0}C for 16 hours , the residue obtained to cooled to 20^{0}C, stirred for one hour and dried in hot air oven at 60^{0}C.
FCV-II	FCV-I and methylene dichromate	Sodium borohydride	The reaction mixture is cooled to 20^{0}C, added methanol, pH is adjusted to 6.5, distilled at 60^{0}C and the resultant solid obtained is dried at 50^{0}C
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^{0}C
FCV-IV	FCV-III and isopropyl alcohol	Carbon, palladium (5%) and sodium acetate	Stirred well, heated to 60^{0}C 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^{0}C



Scheme – 1: Steps involved in the synthesis of Famciclovir

3. RESULTS

3.1. Physical properties

The physical properties of the final compound as well as intermediates are shown in table 2.

Table - 2: Physical properties of the Compounds synthesized

Compound	Molecular Formula	Molecular Weight	Physical State	Color
FCV-I	$C_{12}H_{14}ClN_5O_4$	327.72	Amorphous	White
FCV-II	$C_{10}H_{14}ClN_5O_2$	271.70	Amorphous	White
FCV-III	$C_{14}H_{18}ClN_5O_4$	355.78	Amorphous	Pale Yellow
FCV-IV	$C_{14}H_{19}N_5O_4$	321.33	Amorphous	White

3.2. Elemental analysis

The compounds were analysed for carbon, hydrogen and nitrogen and the results are shown in table 3.

Table - 3: Analytical data for the compounds

Compound	Molecular Weight	Found (Calculated) %		
		C	H	N
FCV-I	327.72	43.89 (43.98)	4.22 (4.31)	21.28 (21.37)
FCV-II	271.70	44.10 (44.21)	5.10 (5.19)	25.69 (25.78)
FCV-III	355.78	47.19 (47.26)	4.99 (5.10)	19.59 (19.68)
FCV-IV	321.33	52.24 (52.33)	5.89 (5.96)	21.71 (21.79)

3.3. ^{1}H NMR Spectral data:

The ^{1}H NMR Spectra of all the compounds is taken and the data obtained is tabulated in table 4 and the spectra are shown in figure 2 and 3.

Table - 4: ^{1}H NMR Spectral data for the compounds

Compound	Proton Number	Multiplicity	Chemical shift (ppm)
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
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
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
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

3.4. ^{13}C NMR Spectral Data:

The ^{1}H NMR Spectra of all the compounds is taken and the data obtained is tabulated in table 5.

Table - 5: ^{13}C NMR Spectral Data for the compounds

Compound	Carbon Number	Chemical Shift (ppm)
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
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
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
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

3.5. Mass spectrum

The mass Spectra of all the compounds is taken and the data obtained is tabulated in table 5 and the spectrum is shown in figure 4

Table - 5: Mass spectral data for the compounds

Compound	m/z	Fragment
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	$C_7H_{11}O_4$
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)	$C_{10}H_{14}ClN_5O_2$
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)	$C_{14}H_{18}ClN_5O_4$
FCV-IV	343.95 (M+Na)	$C_{14}H_{19}N_5O_4Na$
	321.96 (M+1)	$C_{14}H_{19}N_5O_4$

3.6. 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

Compound	Wave length (nm)	Band
FCV-I	223.20	K band of aromatic ring
	247.99	B band of aromatic ring
	310.24	β band of aromatic ring
FCV-II	223.72	K band of aromatic ring
	310.27	β band of aromatic ring
FCV-III	223.46	K band of aromatic ring
	248.24	B band of aromatic ring
	310.50	β band of aromatic ring
FCV-IV	223.00	K band of aromatic ring
	310.37	β band of aromatic ring

3.7. Infrared Spectral data:

The IR Spectral data of all the compounds is taken and tabulated in table 7 and the spectrum is shown in figure 6

Table - 7: IR Spectral data for the compounds

Compound	Frequency (cm^{-1})	Assignment
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
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
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
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

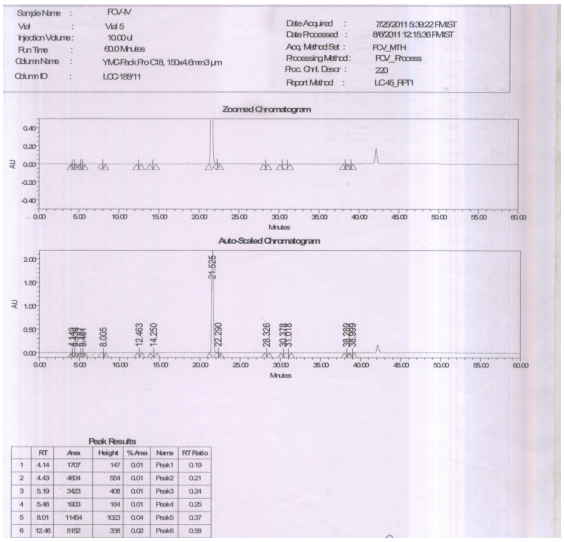


Figure – 1: HPLC for FCV-4

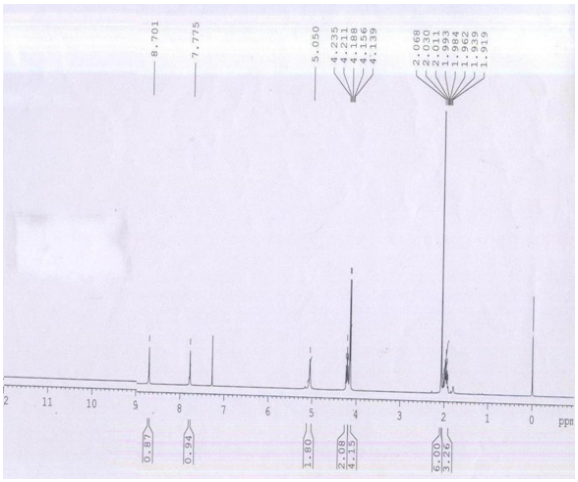


Figure – 2: ^{1}H NMR Spectrum for FCV-4

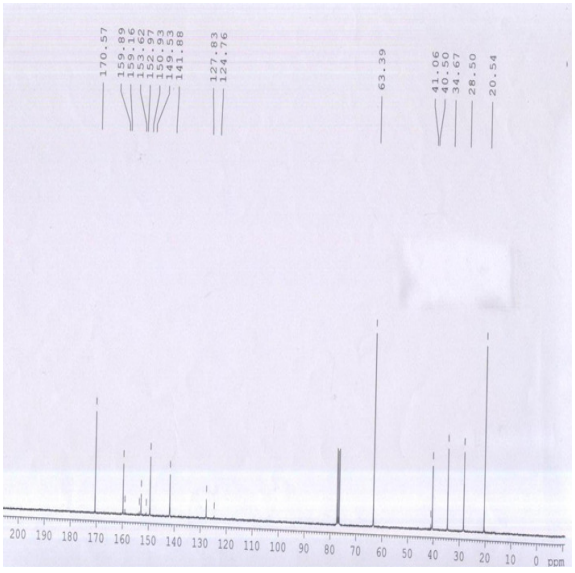


Figure – 3: ^{13}C NMR Spectrum for FCV-4

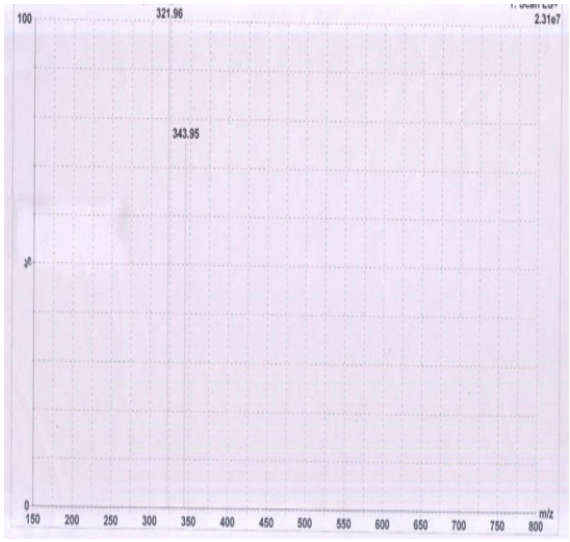


Figure – 4: Mass spectrum for FCV-4

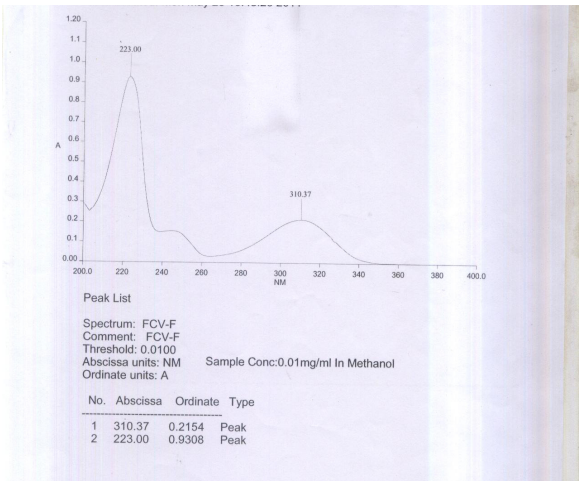


Figure – 5: Electronic Spectrum of FCV-4

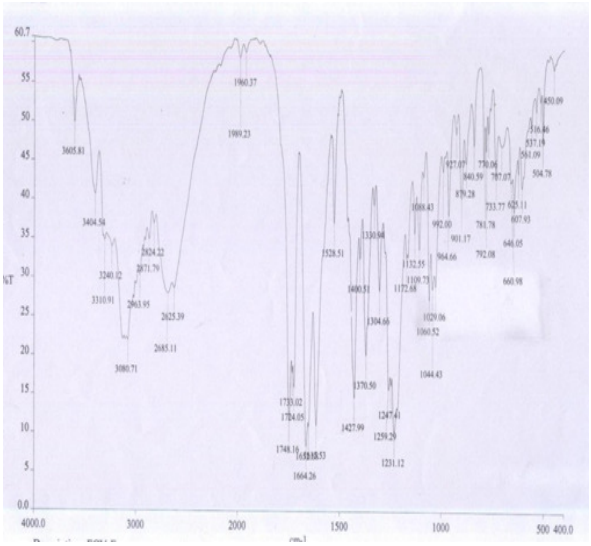


Figure – 6: IR Spectrum of FCV-4

4. DISCUSSION

The elemental analysis data, 1H-NMR, C^{13} NMR, Mass, Electronic, IR Spectral data confirm the synthesis of the compound Famciclovir as well as proposed structure for the compound. The purity of the compound is confirmed by HPLC

5. 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 for all the compounds.

6. REFERENCES

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