Supplementary Information

Multi-target weapons: diaryl-pyrazoline thiazolidinediones simultaneously targeting VEGFR-2 and HDAC cancer hallmarks

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1. In-vitro HUVEC assay

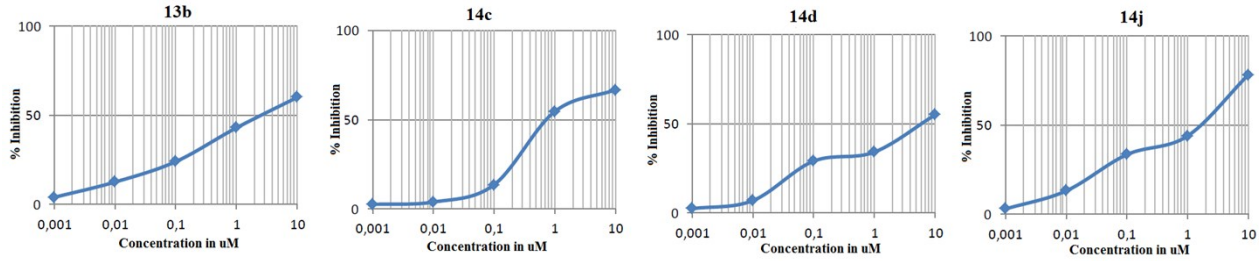


Figure S1. Graphical representation of % inhibition of HUVECs proliferation against different concentration of compounds 13b, 14c, 14d and 14j.

Table S1. HUVECs IC_{50} evaluation table.

Code	Concentrations					IC_{50} (µM)
	10^{1}	10^{0}	10^{-1}	10^{-2}	10^{-3}	
13b	59.66	42.59	23.65	12.25	3.69	2
13d	41.25	35.29	23.62	14.75	2.69	>10
13j	32.15	25.68	15.22	3.65	1.28	>10
14a	48.95	43.3	31.7	10.23	1.85	>10
14c	66.59	54.28	13.26	3.65	2.36	0.7
14d	54.6	33.84	28.74	6.65	2.15	6
14e	41.25	32.69	12.58	3.36	3.58	>10
14j	77.84	43.62	33.18	12.84	2.71	2
15g	36.56	12.58	13.85	1.41	2.36	>10
STS[a]	-	-	-	-	-	0.5

[a]STS represents Staurosporine.

2. VEGFR-2 Inhibition Assay

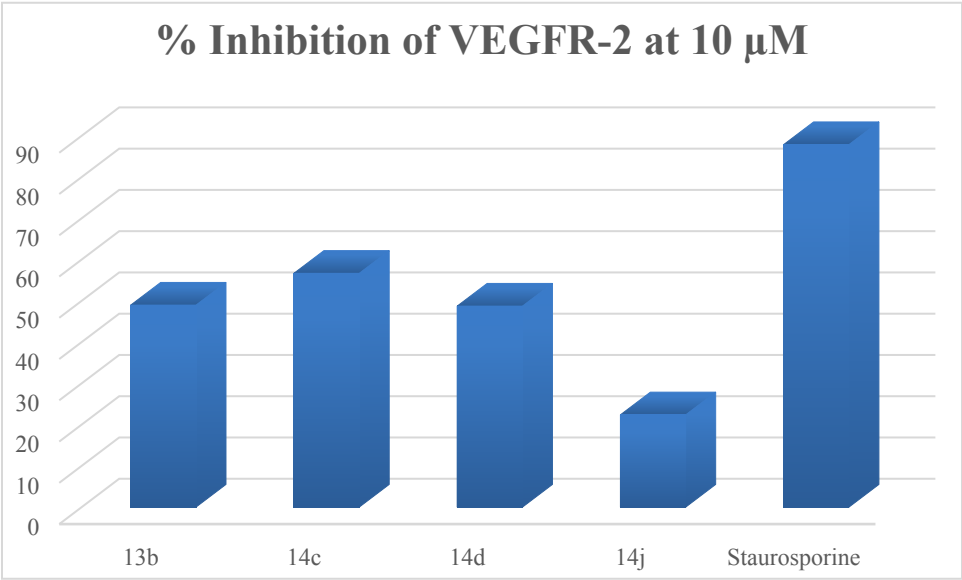


Figure S2. % Inhibition of VEGFR-2 at 10 µM concentration of compounds 13b, 14c, 14d, and 14j.

3. HUVEC Tube Formation Assay

Table S2. Tube formation assay of compound 14c and statistical significance.

Tube formation assay						p-value (student's unpaired t-test)
Intersection counts						
	Field 1	Field 2	Field 3	Avg	Std. Dev.	
Untreated	26	28	32	28.7	3.1	-
Staurosporine	6	8	11	8.3	2.5	<0.0001
14c	25	28	26	26.3	1.5	0.3

4. Cellular Migration Assay (HUVEC)

Table S3. Migration assay of compound 14c and statistical significance.

Migration Assay						p-value (student's unpaired t-test)
% Wound Healing						
	Field 1	Field 2	Field 3	Avg	Std. Dev.	
Untreated	84.32	88.19	79.25	83.9	3.7	-
Staurosporine	32.19	18.65	16.47	22.4	7.0	<0.0001
14c	77.85	71.28	68.22	72.5	4.0	<0.01

5. CAM Assay

Table S4. CAM assay of compound 14c and statistical significance.

Group	Conc. (µg)	Score				Avg.	Std. dev.	p-value (student's unpaired t-test)
UT	8	7	8	6	8	7.3	1.0	-
14c	1	2	0	1	2	1.3	1.0	<0.0001

6. MTT Cell Viability Assay

Table S5. Cell viability of compound 14c.

Mean Cell Viability				
Concentration µM/mL	MCF-7	K562	A549	HT-29
100	28.33	25.00	25.53	22.99
75	32.48	27.35	27.63	23.99
50	44.30	48.90	30.00	27.44
25	49.84	71.87	42.63	34.05
10	74.46	94.36	67.37	64.08
2.5	86.59	95.53	79.34	96.98
Negative control	100			

7. Molecular Docking

7.1 VEGFR-2 (PDB ID: 1YWN)

Table S6: Docking results of indicated TZD-analogs into VEGFR-2 (PDB-ID: 1YWN)

Cpd	GBVI/WSA dG score
(S)-14c	-9.3
(R)-14c	-10.6
(S)-14j	-10.2
(R)-14j	-10.8
Redocked ligand	-11.2

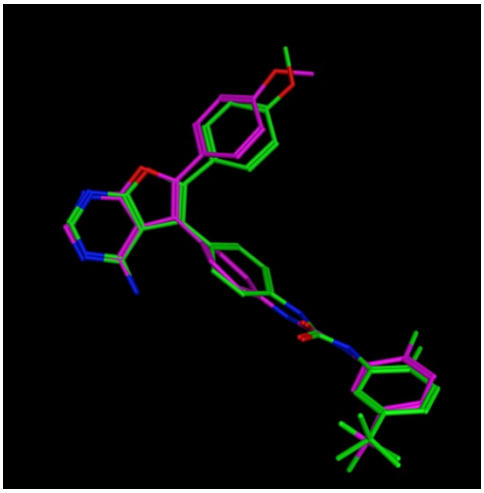


Figure S3: Redocking of ligand from x-ray structure of VEGFR-2 (PDB-ID: 1YWN). Redocked ligand is shown in green and crystallized ligand in magenta.

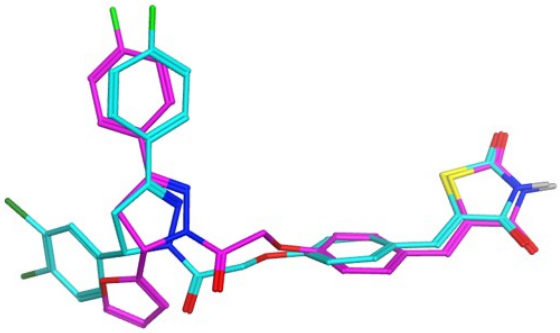


Figure S4: Overlay of (S)-14c and (R)-14j having the same absolute configuration at the pyrazole ring docked into the binding channel of VEGFR-2.

7.2 HDAC4 (PDB ID: 4CBY)

Table S7: Docking results of different TZD-analogs into the active site pocket of HDAC4 (PDB-ID: 4CBY) using Amber 14 force field.

Cpd	GBVI/WSA dG score
(S)-14c	-9.3
(R)-14c	-8.7
(S)-14j	-11.7
(R)-14j	-9.2
Cpd 31[2]	-13.6

[2] Burli, R. W., 2013 Journal of Medicinal Chemistry 56(24): 9934-9954.

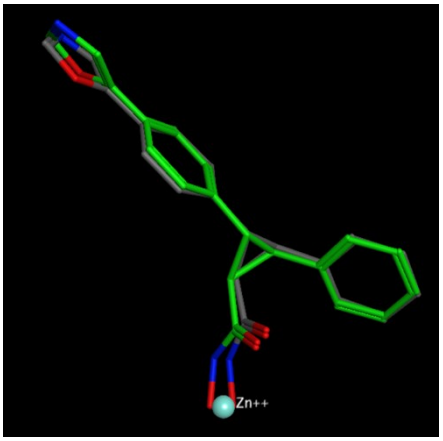


Figure S5: Redocking of ligand "Cpd31" into the crystal structure of the binding pocket of the catalytic domain of HDAC4 (PDB-ID: 4CBY) shows perfect overlap between the docked ligand and the x-ray binding pose. Green: ligand of crystal structure, Grey: redocked ligand.

8. Spectral data –

All the structural characterization data has been presented here in detail

5-(4-(2-(3,5-diphenyl-4,5-dihydro-1H-pyrazol-1-yl)-2-oxoethoxy)benzylidene)thiazolidine-2,4-dione **(13a).** Pale yellow colour. Yield 0.48 g (54%). M.P. 254.6 °C. FTIR (cm^{-1}) 3375, 1735, 1678, 1587, 1504, 1442, 1263, 839. ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm 3.18 (dd, J= 4.8, 18.2 Hz, 1H, pyrazoline CH_2), 3.85-3.93 (m, 1H, pyrazoline CH_2), 5.25 (d, J= 16.2 Hz, 1H, CH_2), 5.39 (d, J= 16.2 Hz, 1H, CH_2), 5.59 (dd, J= 4.8, 11.6 Hz, 1H, pyrazoline CH), 7.04 (d, J= 8.8 Hz, 2H, aromatic), 7.24-7.27 (m, 3H, aromatic), 7.32-7.36 (m, 2H, aromatic), 7.47–7.53 (m, 5H, aromatic), 7.74 (s, 1H, benzylidene), 7.83–7.86 (m, 2H, aromatic), 12.53 (bs, 1H, NH proton). ^{13}C-NMR (100 MHz, DMSO-d_6) δ 41.04, 59.44, 65.57, 115.47, 115.48, 115.74, 115.96, 120.41, 125.73, 127.77, 127.87, 129.31, 129.39, 131.74, 131.75, 137.84, 154.64, 159.78, 162.17, 162.56, 164.49, 167.74, 167.94. Theoretical mass: 483.54, LC-MS (m/z, I%): 482.1 [$(M-H)^+$, 100%]. HPLC Purity: % Area 96.36, Retention Time 4.89 mins.

5-(4-(2-(5-(2-chlorophenyl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)-2-oxoethoxy)benzylidene) thiazolidine-2,4-dione **(13b).** Cream colour. Yield 0.6 g (56%). M.P. 258.0 °C. FTIR (cm^{-1}) 3365, 1734, 1678, 1589, 1568, 1508, 1273, 825, 748. ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm 3.14 (dd, J= 4.8, 18.0 Hz, 1H, pyrazoline CH_2), 3.95-4.03 (m, 1H, pyrazoline CH_2), 5.27 (d, J= 16.4 Hz, 1H, CH_2), 5.46 (d, J= 16.4 Hz, 1H, CH_2), 5.80 (dd, J= 4.8, 11.6 Hz, 1H, pyrazoline CH), 7.11 (d, J= 8.4 Hz, 2H, aromatic), 7.23-7.24 (m, 1H, aromatic), 7.31-7.33 (m, 2H, aromatic), 7.48-7.49 (m, 4H, aromatic), 7.53 (d, J= 8.4 Hz, 2H, aromatic), 7.74 (s, 1H, benzylidene), 7.84 (d, J= 6.4 Hz, 2H, aromatic), 12.52 (bs, 1H, NH proton). ^{13}C-NMR (100 MHz, DMSO-d_6) δ 40.64, 57.71, 65.48, 115.48, 120.41, 125.76, 126.69, 126.93, 127.66, 128.77, 129.15, 129.67, 130.55, 130.70, 130.79, 131.76, 131.87, 138.35, 155.66, 159.80, 164.59,

167.32, 167.88. Theoretical mass: 517.98, LC-MS (m/z, I%): 516.1 [$(M-H)^+$, 100%]. HPLC Purity: % Area 95.49, Retention Time 5.45 mins.

5-(4-(2-oxo-2-(3-phenyl-5-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1H-pyrazol-1-yl)ethoxy) benzylidene)thiazolidine-2,4-dione **(13d).** Cream colour. Yield 0.55 g (52%). M.P. 265.4 °C. FTIR (cm^{-1}) 3354, 1734, 1676, 1585, 1533, 1508, 1263, 1180, 798. ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm 3.23-3.28 (m, 1H, pyrazoline CH_2), 3.90-3.98 (m, 1H, pyrazoline CH_2), 5.27 (d, J= 16.0 Hz, 1H, CH_2), 5.41 (d, J= 16.0 Hz, 1H, CH_2), 5.70 (dd, J= 4.0, 11.6 Hz, 1H, pyrazoline CH), 7.08 (d, J= 8.4 Hz, 2H, aromatic), 7.51-7.54 (m, 7H, aromatic), 7.70-7.74 (m, 3H, benzylidene and aromatic), 7.85-7.86 (m, 2H, aromatic), 12.51 (bs, 1H, NH proton). ^{13}C-NMR (100 MHz, DMSO-d_6) δ 41.52, 59.58, 65.49, 115.43, 120.45, 125.60, 125.64, 125.77, 126.55, 126.96, 128.77, 130.54, 130.72, 131.71, 131.86, 146.22, 155.61, 159.75, 164.66, 167.35, 167.89. Theoretical mass: 551.54, LC-MS (m/z, I%): 549.9 [$(M-H)^+$, 100%]. HPLC Purity: % Area 97.37, Retention Time 5.93 mins.

5-(4-(2-(5-(4-fluorophenyl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)-2-oxoethoxy)benzylidene) thiazolidine-2,4-dione **(13e).** Pale yellow colour. Yield 0.6 g (58%). M.P. 258.4 °C. FTIR (cm^{-1}) 3400, 1734, 1678, 1585, 1506, 1456, 1263, 1143, 1176, 817. ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm 3.20 (dd, J= 3.8, 18.4 Hz, 1H, pyrazoline CH_2), 3.86-3.93 (m, 1H, pyrazoline CH_2), 5.24 (d, J= 16.4 Hz, 1H, CH_2), 5.37 (d, J= 16.0 Hz, 1H, CH_2), 5.60 (dd, J= 4.4, 11.6 Hz, 1H, pyrazoline CH), 7.07 (d, J= 8.4 Hz, 2H, aromatic), 7.16 (t, J= 8.8 Hz, 2H, aromatic), 7.29-7.33 (m, 2H, aromatic), 7.49-7.53 (m, 5H, aromatic), 7.74 (s, 1H, benzylidene), 7.85 (d, J= 4.8 Hz, 2H, aromatic), 12.52 (bs, 1H, NH proton). ^{13}C-NMR (100 MHz, DMSO-d_6) δ 41.68, 59.29, 65.52, 115.27, 115.440, 115.49, 120.44, 125.74, 126.92, 127.70, 127.79, 128.77, 130.66, 131.74, 131.86, 137.89, 155.56, 159.79, 160.14, 162.56, 164.50, 167.36, 167.91. Theoretical mass: 501.53, LC-MS (m/z, I%): 500.1 [$(M-H)^+$, 100%]. HPLC Purity: % Area 99.44, Retention Time 4.31 mins.

5-(4-(2-(5-(2,4-difluorophenyl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)-2-oxoethoxy)benzylidene) thiazolidine-2,4-dione **(13f).** Pale yellow colour. Yield 0.63 g (62%). M.P. 253.2 °C. FTIR (cm^{-1}) 3406, 1734, 1678, 1591, 1508, 1447, 1269, 1151, 1138, 827. ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm 3.27 (dd, J= 5.2, 18.4 Hz, 1H, pyrazoline CH_2), 3.88-3.96 (m, 1H, pyrazoline CH_2), 5.24 (d, J= 16.4 Hz, 1H, CH_2), 5.36 (d, J= 16.4 Hz, 1H, CH_2), 5.70 (dd, J= 5.2, 12.0 Hz, 1H, pyrazoline CH), 7.06 (d, J= 8.4 Hz, 3H, aromatic), 7.23-7.28 (m, 1H, aromatic), 7.31-7.37 (m, 1H, aromatic), 7.50-7.53 (m, 5H, aromatic), 7.74 (s, 1H, benzylidene), 7.84 (d, J= 4.8 Hz, 2H, aromatic), 12.51 (s, 1H, NH proton). ^{13}C-NMR (100 MHz, DMSO-d_6) δ 40.46, 54.47, 65.44, 104.11, 111.49, 115.42, 120.46, 125.76, 126.91, 128.78, 130.57, 130.70, 131.72, 131.85, 155.78, 159.76, 164.55, 167.36, 167.90. Theoretical mass: 519.52, LC-MS (m/z, I%): 518.1 [$(M-H)^+$, 100%]. HPLC Purity: % Area 96.28, Retention Time 4.67 mins.

5-(4-(2-oxo-2-(3-phenyl-5-(p-tolyl)-4,5-dihydro-1H-pyrazol-1-yl)ethoxy)benzylidene)thiazolidine-2,4-dione **(13g).** Pale yellow colour. Yield 0.67 g (61%). M.P. 272.3 °C. FTIR (cm^{-1}) 3390, 3036, 1732, 1678,

1581, 1504, 1452, 1257, 804. ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm 2.27 (s, 3H, CH_3), 3.16 (dd, J= 4.8, 18.0 Hz, 1H, pyrazoline CH_2), 3.85-3.92 (m, 1H, pyrazoline CH_2), 5.24 (d, J= 16.0 Hz, 1H, CH_2), 5.37 (d, J= 16.4 Hz, 1H, CH_2), 5.55 (dd, J= 4.4, 11.6 Hz, 1H, pyrazoline CH), 7.07 (d, J= 8.8 Hz, 2H, aromatic), 7.49-7.53 (m, 5H, aromatic), 7.74 (s, 1H, benzylidene), 7.83-7.86 (m, 6H, aromatic), 12.55 (bs, 1H, NH proton). ^{13}C-NMR (100 MHz, DMSO-d_6) δ 20.60, 41.77, 59.73, 65.56, 115.45, 120.42, 125.47, 125.73, 126.88, 128.78, 129.18, 130.61, 130.75, 131.77, 131.86, 136.55, 138.82, 155.56, 159.83, 164.37, 167.34, 167.91. Theoretical mass: 497.56, LC-MS (m/z, I%): 496.0 [$(M-H)^+$, 100%]. HPLC Purity: % Area 97.76, Retention Time 5.54 mins.

5-(4-(2-(5-(3,4-dichlorophenyl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)-2-oxoethoxy)benzylidene) thiazolidine-2,4-dione **(13j).** Cream colour. Yield 0.7 g (69%). M.P. 272.7 °C. FTIR (cm^{-1}) 3389, 1730, 1681, 1591, 1512, 1469, 1271, 825, 688, 632. ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm 3.17 (dd, J= 5.6, 18.4 Hz, 1H, pyrazoline CH_2), 3.94-4.01 (m, 1H, pyrazoline CH_2), 5.26 (d, J= 16.4 Hz, 1H, CH_2), 5.44 (d, J= 16.4 Hz, 1H, CH_2), 5.77 (dd, J= 5.6, 12.0 Hz, 1H, pyrazoline CH), 7.10 (d, J= 8.8 Hz, 2H, aromatic), 7.27 (d, J= 8.4 Hz, 1H, aromatic), 7.40 (dd, J= 2.0, 8.4 Hz, 1H, aromatic), 7.48-7.50 (m, 3H, aromatic), 7.54 (d, J= 8.4 Hz, 2H, aromatic), 7.66 (d, J= 1.6 Hz, 1H, aromatic), 7.74 (s, 1H, benzylidene), 7.83 (m, 2H, aromatic), 12.53 (bs, 1H, NH proton). ^{13}C-NMR (100 MHz, DMSO-d_6) δ 40.37, 57.34, 65.45, 115.45, 120.47, 125.78, 126.95, 127.78, 28.34, 128.78, 129.09, 130.47, 130.76, 131.75, 131.87, 132.74, 137.51, 155.74, 159.76, 164.67, 167.35, 167.91. Theoretical mass: 552.43, LC-MS (m/z, I%): 550.0 [$(M-2H)^+$, 100%]. HPLC Purity: % Area 96.92, Retention Time 6.40 mins.

5-(4-(2-(5-(4-bromophenyl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)-2-oxoethoxy)benzylidene) thiazolidine-2,4-dione **(13k).** Cream colour. Yield 0.68 g (59%). M.P. 273.0 °C. FTIR (cm^{-1}) 3406, 1732, 1680, 1591, 1568, 1508, 1273, 825, 601. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.20 (dd, J= 4.4, 18.4 Hz, 1H, pyrazoline CH_2), 3.86-3.94 (m, 1H, pyrazoline CH_2), 5.24 (d, J= 16.0 Hz, 1H, CH_2), 5.38 (d, J= 16.0 Hz, 1H, CH_2), 5.58 (dd, J= 4.4, 11.6 Hz, 1H, pyrazoline CH), 7.07 (d, J= 8.4 Hz, 2H, aromatic), 7.23 (d, J= 8.0 Hz, 2H, aromatic), 7.49-7.50 (m, 2H, aromatic), 7.51-7.52 (m, 2H, aromatic), 7.53-7.54 (m, 3H, aromatic), 7.74 (s, 1H, benzylidene), 7.83-7.85 (d, J= 5.2 Hz, 2H, aromatic), 12.50 (bs, 1H, NH proton). ^{13}C-NMR (100 MHz, DMSO-d_6) δ 41.53, 59.41, 65.49, 115.43, 120.40, 120.47, 125.75, 126.93, 127.97, 128.78, 130.60, 130.69, 131.53, 131.73, 131.87, 141.08, 155.58, 159.77, 164.53, 167.38, 167.92. Theoretical mass: 562.43, LC-MS (m/z, I %): 561.0 [$(M-H)^+$, 100%]. HPLC Purity: % Area 98.65, Retention Time 5.83 mins.

5-(4-(2-(3-(4-fluorophenyl)-5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)-2-oxoethoxy)benzylidene) thiazolidine-2,4-dione **(14a).** Off white colour. Yield 0.74 g (55%). M.P. 248.0 °C. FTIR (cm^{-1}) 3365, 1732, 1676, 1647, 1585, 1506, 1456, 1425, 1263, 1143, 833. ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm 3.20 (d, J= 15.48 Hz, 1H, pyrazoline CH_2), 3.88 (s, 1H, pyrazoline CH_2), 5.23-5.40 (m, 2H, CH_2), 5.59 (s, 1H,

pyrazoline CH), 7.07 (s, 2H, aromatic), 7.26-7.34 (m, 7H, aromatic), 7.51 (s, 2H, aromatic), 7.31 (s, 1H, benzylidene), 7.91 (s, 2H, aromatic), 12.57 (bs, 1H, NH proton). ^{13}C-NMR (100 MHz, DMSO-d_6) δ 40.46, 54.52, 65.37, 104.05, 115.34, 115.71, 115.92, 120.45, 125.27, 127.27, 129.23, 129.31, 131.62, 131.78, 154.81, 159.68, 162.21, 164.49, 167.14, 167.81. Theoretical mass: 501.53, LC-MS (m/z, I%): 500.1 [$(M-H)^+$, 100%]. HPLC Purity: % Area 95.03, Retention Time 4.66 mins.

5-(4-(2-(5-(2-chlorophenyl)-3-(4-fluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)-2-oxoethoxy) benzylidene)thiazolidine-2,4-dione **(14b).** Off white colour. Yield 0.71 g (58%). M.P. 269.3 °C. FTIR (cm^{-1}) 3365, 1735, 1678, 1579, 1504, 1446, 1338, 1271, 833, 746. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.14 (dd, J= 5.2, 18.1 Hz, 1H, pyrazoline CH_2), 3.93-4.0 (m, 1H, pyrazoline CH_2), 5.27 (d, J= 16.2 Hz, 1H, CH_2), 5.46 (d, J= 16.3 Hz, 1H, CH_2), 5.80 (dd, J= 5.2, 12.0 Hz, 1H, pyrazoline CH), 7.10 (d, J= 8.8 Hz, 2H, aromatic), 7.22-7.25 (m, 1H, aromatic), 7.29-7.34 (m, 4H, aromatic), 7.47-7.51 (m, 1H, aromatic), 7.53 (d, J= 8.8 Hz, 2H, aromatic), 7.74 (s, 1H, benzylidene), 7.88–7.91 (m, 2H, aromatic), 12.52 (bs, 1H, NH proton). ^{13}C-NMR (100 MHz, DMSO-d_6) δ 40.45, 57.47, 65.69, 115.44, 115.77, 115.98, 120.64, 125.83, 127.17, 127.78, 128.36, 129.08, 129.37, 129.45, 131.67, 131.86, 132.77, 137.45, 154.85, 159.73, 164.69, 168.01. Theoretical mass: 535.97, LC-MS (m/z, I%): 533.9 [$(M-H)^+$, 100%]. HPLC Purity: % Area 96.36, Retention Time 5.11 mins.

5-(4-(2-(3-(4-fluorophenyl)-5-(furan-2-yl)-4,5-dihydro-1H-pyrazol-1-yl)-2-oxoethoxy)benzylidene) thiazolidine-2,4-dione **(14c).** Off white colour. Yield 0.73 g (60%). M.P. 252.7 °C. FTIR (cm^{-1}) 3406, 1734, 1683, 1585, 1508, 1456, 1338, 1259, 833. ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm 3.43 (dd, J= 4.4, 18.1 Hz, 1H, pyrazoline CH_2), 3.72-3.80 (m, 1H, pyrazoline CH_2), 5.20 (d, J= 15.9 Hz, 1H, CH_2), 5.28 (d, J= 16.2 Hz, 1H, CH_2), 5.70 (dd, J= 4.4, 11.6 Hz, 1H, pyrazoline CH), 6.39 (d, J= 7.7 Hz, 2H, aromatic), 7.06 (d, J= 8.4 Hz, 2H, aromatic), 7.35 (t, J= 8.6 Hz, 2H, aromatic), 7.52 (d, J= 8.4 Hz, 2H, aromatic), 7.59 (s, 1H, aromatic), 7.74 (s, 1H, benzylidene), 7.9-7.95 (m, 2H, aromatic), 12.57 (bs, 1H, NH proton). ^{13}C-NMR (100 MHz, DMSO-d_6) δ 40.57, 57.54, 65.45, 115.44, 120.47, 125.78, 126.95, 127.78, 128.34, 128.78, 129.09, 130.43, 130.76, 131.75, 131.87, 132.74, 137.51, 155.74, 159.76, 164.67, 167.35, 167.94. Theoretical mass: 491.49, LC-MS (m/z, I%): 490.0 [$(M-H)^+$, 100%]. HPLC Purity: % Area 97.50, Retention Time 4.41 mins.

5-(4-(2-(3-(4-fluorophenyl)-5-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1H-pyrazol-1-yl)-2-oxoethoxy)benzylidene)thiazolidine-2,4-dione **(14d).** Off white colour. Yield 0.72 g (64%). M.P. 263.6 °C. FTIR (cm^{-1}) 3302, 1734, 1678, 1637, 1583, 1541, 1506, 1456, 1423, 1261, 1180, 827. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.26 (dd, J= 5.2, 18.8 Hz, 1H, pyrazoline CH_2), 3.89-3.96 (m, 1H, pyrazoline CH_2), 5.26 (d, J= 16.4 Hz, 1H, CH_2), 5.39 (d, J= 16.0 Hz, 1H, CH_2), 5.69 (d, J= 6.8 Hz, 1H, pyrazoline CH), 7.07 (d, J= 8.0 Hz, 2H, aromatic), 7.34 (t, J= 8.4 Hz, 2H, aromatic), 7.51 (t, J= 8.4 Hz, 4H, aromatic), 7.70-7.73 (m, 3H, benzylidene and aromatic), 7.90 (m, 2H, aromatic), 12.55 (bs, 1H, NH

proton). ^{13}C-NMR (100 MHz, DMSO-d_6) δ 41.59, 59.69, 65.48, 115.43, 115.76, 115.98, 120.48, 125.63, 125.77, 126.57, 127.22, 129.36, 129.45, 131.70, 131.86, 146.16, 154.71, 159.74, 162.23, 164.66, 167.38, 167.91. Theoretical mass: 569.53, LC-MS (m/z, I%): 568.1 [$(M-H)^+$, 100%]. HPLC Purity: % Area 96.38, Retention Time 4.69 mins.

5-(4-(2-(3,5-bis(4-fluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)-2-oxoethoxy)benzylidene) thiazolidine-2,4-dione **(14e).** Cream colour. Yield 0.76 g (62%). M.P. 248.6 °C. FTIR (cm^{-1}) 3387, 1732, 1681, 1583, 1506, 1456, 1419, 1259, 1141, 848. ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm 3.20 (dd, J= 3.6, 18.0 Hz, 1H, pyrazoline CH_2), 3.84-3.92 (m, 1H, pyrazoline CH_2), 5.24 (d, J= 16.4 Hz, 1H, CH_2), 5.36 (d, J= 16.4 Hz, 1H, CH_2), 5.60 (d, J= 7.2 Hz, 1H, pyrazoline CH), 7.06 (d, J= 8.4 Hz, 2H, aromatic), 7.16 (t, J= 8.4 Hz, 2H, aromatic), 7.29-7.36 (m, 4H, aromatic), 7.52 (d, J= 8.0 Hz, 2H, aromatic), 7.74 (m, 1H, benzylidene), 7.89-7.92 (m, 2H, aromatic), 12.51 (bs, 1H, NH proton). ^{13}C-NMR (100 MHz, DMSO-d_6) δ 41.74, 59.40, 65.50, 115.27, 115.42, 115.48, 115.74, 115.96, 120.41, 125.73, 127.72, 127.80, 129.31, 129.39, 131.74, 131.85, 137.84, 154.64, 159.78, 162.19, 162.56, 164.49, 167.34, 167.90. Theoretical mass: 519.52, LC-MS (m/z, I%): 518.0 [$(M-H)^+$, 100%]. HPLC Purity: % Area 96.42, Retention Time 4.47 mins.

5-(4-(2-(5-(2,4-difluorophenyl)-3-(4-fluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)-2-oxoethoxy) benzylidene)thiazolidine-2,4-dione **(14f).** Pale yellow colour. Yield 0.66 g (69%). M.P. 241.6 °C. FTIR (cm^{-1}) 3383, 1730, 1683, 1647, 1583, 1506, 1456, 1425, 1263, 1178, 1143, 854. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.27 (dd, J= 5.6, 18.4 Hz, 1H, pyrazoline CH_2), 3.87-3.95 (m, 1H, pyrazoline CH_2), 5.23 (d, J= 16.4 Hz, 1H, CH_2), 5.35 (d, J= 16.0 Hz, 1H, CH_2), 5.70 (dd, J= 5.2, 12.0 Hz, 1H, pyrazoline CH), 7.06 (d, J= 8.4 Hz, 3H, aromatic), 7.25 (t, J= 9.6 Hz, 1H, aromatic), 7.32 (t, J= 8.8 Hz, 3H, aromatic), 7.52 (d, J= 8.8 Hz, 2H, aromatic), 7.74 (s, 1H, benzylidene), 7.91 (t, J= 7.6 Hz, 2H, aromatic), 12.51 (bs, 1H, NH proton). ^{13}C-NMR (100 MHz, DMSO-d_6) δ 40.46, 54.52, 65.37, 104.05, 115.34, 115.70, 115.92, 120.45, 125.72, 127.27, 129.23, 129.32, 131.62, 131.78, 154.80, 159.68, 162.20, 164.49, 167.34, 167.86. Theoretical mass: 537.51, LC-MS (m/z, I%): 536.0 [$(M-H)^+$, 100%]. HPLC Purity: % Area 97.44, Retention Time 4.47 mins.

5-(4-(2-(3-(4-fluorophenyl)-5-(p-tolyl)-4,5-dihydro-1H-pyrazol-1-yl)-2-oxoethoxy)benzylidene) thiazolidine-2,4-dione **(14g).** Creamish solid. Yield 0.7 g (65%). M.P. 285.1 °C. FTIR (cm^{-1}) 3383, 3117, 1732, 1676, 1637, 1583, 1506, 1458, 1419, 1259, 854. ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm 2.26 (s, 3H, CH_3), 3.16 (dd, J= 4.4, 18.4 Hz, 1H, pyrazoline CH_2), 3.83-3.91 (m, 1H, pyrazoline CH_2), 5.23 (d, J= 16.4 Hz, 1H, CH_2), 5.36 (d, J= 16.0 Hz, 1H, CH_2), 5.54 (dd, J= 4.4, 11.6 Hz, 1H, pyrazoline CH), 7.06 (d, J= 8.4 Hz, 2H, aromatic), 7.13 (s, 4H, aromatic), 7.33 (t, J= 8.8 Hz, 2H, aromatic), 7.52 (d, J= 8.4 Hz, 2H, aromatic), 7.74 (s, 1H, benzylidene), 7.90 (t, J= 7.6 Hz, 2H, aromatic), 12.52 (s, 1H, NH proton). ^{13}C-NMR (100 MHz, DMSO-d_6) δ 20.59, 41.84, 59.83, 65.52, 115.44, 115.97, 120.54, 125.48, 125.71, 129.17, 129.28, 129.36, 131.86, 136.56, 138.77, 154.97, 159.81, 164.37. Theoretical mass: 515.56, LC-MS (m/z, I%): 514.0 [$(M-H)^+$, 100%]. HPLC Purity: % Area 96.65, Retention Time 5.26 mins.

5-(4-(2-(5-(3,4-dichlorophenyl)-3-(4-fluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)-2-oxoethoxy) benzylidene)thiazolidine-2,4-dione **(14j).** Off white solid. Yield 0.56 g (62%). M.P. 252.3 °C. FTIR (cm^{-1}) 3302, 1732, 1683, 1591, 1508, 1444, 1273, 823, 690, 636. ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm 3.17 (dd, J= 5.2, 18.4 Hz, 1H, pyrazoline CH_2), 3.93-4.01 (m, 1H, pyrazoline CH_2), 5.24 (d, J= 16.4 Hz, 1H, CH_2), 5.44 (d, J= 16.4 Hz, 1H, CH_2), 5.77 (d, J= 5.2, 11.6 Hz, 1H, pyrazoline CH), 7.10 (d, J= 8.8 Hz, 2H, aromatic), 7.27 (d, J= 8.4 Hz, 1H, aromatic), 7.33 (t, J= 8.8 Hz, 2H, aromatic), 7.39-7.40 (m, 1H, aromatic), 7.41 (d, J= 8.8 Hz, 2H, aromatic), 7.66 (d, J=1.6 Hz, 1H, aromatic), 7.74 (s, 1H, benzylidene), 7.88-7.92 (m, 2H, aromatic), 12.58 (bs, 1H, NH proton). ^{13}C-NMR (100 MHz, DMSO-d_6) δ 40.45, 46.47, 57.47, 65.69, 115.45, 115.77, 115.98, 120.62, 125.83, 127.18, 127.78, 128.36, 129.08, 129.37, 129.45, 131.67, 131.86, 132.77, 137.45, 154.85, 159.73, 164.69, 168.01. Theoretical mass: 570.42, LC-MS (m/z, I%): 568.0 [$(M-2H)^+$, 100%]. HPLC Purity: % Area 96.08, Retention Time 5.36 mins.

5-(4-(2-(3-(2,4-difluorophenyl)-5-(furan-2-yl)-4,5-dihydro-1H-pyrazol-1-yl)-2-oxoethoxy) benzylidene)thiazolidine-2,4-dione **(15c).** Pale yellow solid. Yield 0.84 g (61%). M.P. 220.6 °C. FTIR (cm^{-1}) 3392, 1730, 1681, 1589, 1566, 1510, 1442, 1413, 1269, 1176, 1151, 819. ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm 3.32–3.42 (m, 1H, pyrazoline CH_2), 3.77–3.85 (m, 1H, pyrazoline CH_2), 5.17 (d, J= 16.2 Hz, 1H, CH_2), 5.25 (d, J= 16.2 Hz, 1H, CH_2), 5.68 (dd, J= 4.8, 11.8 Hz, 1H, pyrazoline CH), 6.38–6.41 (m, 2H, aromatic), 7.04 (d, J= 8.8 Hz, 2H, aromatic), 7.21–7.26 (m, 1H, aromatic), 7.39–7.44 (m, 1H, aromatic), 7.51 (d, J= 8.8 Hz, 2H, aromatic), 7.59 (d, J= 0.8 Hz, 1H, aromatic), 7.73 (s, 1H, benzylidene), 7.99–8.05 (m, 1H, aromatic), 12.56 (bs, 1H, NH proton). ^{13}C-NMR (100 MHz, DMSO-d_6) δ 43.73, 59.45, 65.38, 105.33, 112.40, 115.41, 120.47, 125.49, 125.75, 129.19, 131.72, 131.85, 136.61, 138.63, 151.27, 159.76, 164.51, 167.93. Theoretical mass: 509.48, LC-MS (m/z, I%): 508.1 [$(M-H)^+$, 100%]. HPLC Purity: % Area 97.50, Retention Time 4.41 mins.

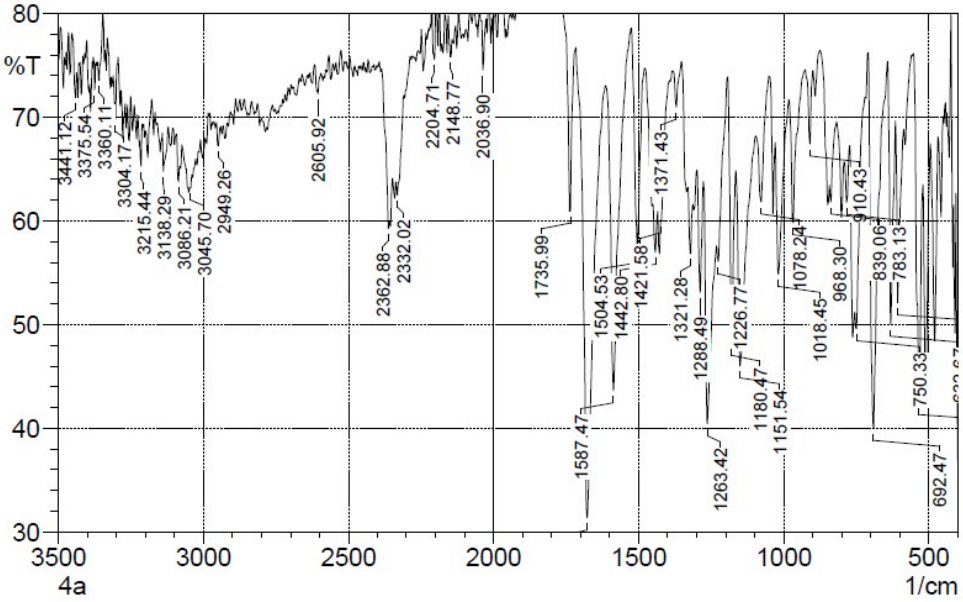
5-(4-(2-(3-(2,4-difluorophenyl)-5-(4-fluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)-2-oxoethoxy) benzylidene)thiazolidine-2,4-dione **(15e).** Cream colour solid. Yield 0.8 g (77%). M.P. 228.2 °C. FTIR (cm^{-1}) 3427, 1734, 1680, 1654, 1585, 1560, 1508, 1429, 1259, 1226, 1180, 1147, 821. ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm 3.08–3.14 (m, 1H, pyrazoline CH_2), 4.00–4.07 (m, 1H, pyrazoline CH_2), 5.25 (d, J= 16.3 Hz, 1H, CH_2), 5.45 (d, J= 16.3 Hz, 1H, CH_2), 5.78 (dd, J= 5.2, 12.0 Hz, 1H, pyrazoline CH), 7.09 (d, J= 8.8 Hz, 2H, aromatic), 7.27–7.22 (m, 2H, aromatic), 7.35–7.30 (m, 2H, aromatic), 7.45–7.41 (m, 1H, aromatic), 7.48–7.50 (m, 1H, aromatic), 7.53 (d, J= 8.8 Hz, 2H, aromatic), 7.73 (s, 1H, benzylidene), 8.01–8.08 (m, 1H, aromatic), 12.55 (bs, 1H, NH proton). ^{13}C-NMR (100 MHz, DMSO-d_6) δ 30.69, 43.80, 50.88, 54.92, 59.04, 65.25, 105.08, 105.33, 109.89, 111.95, 112.28, 112.47, 115.20, 115.42, 119.15, 119.76, 127.76, 127.85, 128.28, 130.93, 137.42, 138.38, 145.60, 151.05, 151.41, 160.17, 160.63, 163.91, 164.22, 167.04, 167.39, 169.72, 175.00. Theoretical mass: 537.51, LC-MS (m/z, I%): 536.0 [$(M-H)^+$, 100%]. HPLC Purity: % Area 97.72, Retention Time 4.40 mins.

5-(4-(2-(3-(2,4-difluorophenyl)-5-(p-tolyl)-4,5-dihydro-1H-pyrazol-1-yl)-2-oxoethoxy)benzylidene) thiazolidine-2,4-dione **(15g).** Off white solid. Yield 0.72 g (63%). M.P. 256.3 °C. FTIR (cm^{-1}) 3394, 3045, 1732, 1680, 1581, 1504, 1452, 1423, 1259, 1178, 1145, 850. ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm 2.26 (s, 3H, CH_3), 3.13 (dd, J= 2.8, 18.4 Hz, 1H, pyrazoline CH_2), 3.90-3.97 (m, 1H, pyrazoline CH_2), 5.22 (d, J= 16.0 Hz, 1H, CH_2), 5.35 (d, J= 16.4 Hz, 1H, CH_2), 5.52 (dd, J= 4.8, 12.0 Hz, 1H, pyrazoline CH), 7.05 (d, J= 8.8 Hz, 2H, aromatic), 7.14 (s, 4H, aromatic), 7.22-7.27 (m, 1H, aromatic), 7.38-7.44 (m, 1H, aromatic), 7.52 (d, J= 8.8 Hz, 2H, aromatic), 7.74 (s, 1H, benzylidene), 8.01-8.07 (m, 1H, aromatic), 12.53 (bs, 1H, NH proton). ^{13}C-NMR (100 MHz, DMSO-d_6) δ 20.60, 43.74, 59.45, 65.48, 105.13, 112.40, 115.42, 120.47, 125.49, 125.75, 129.19, 131.72, 131.85, 136.61, 138.63, 151.03, 159.76, 164.58, 167.91. Theoretical mass: 533.55, LC-MS (m/z, I%): 532.0 [$(M-H)^+$, 100%]. HPLC Purity: % Area 98.38, Retention Time 5.29 mins.

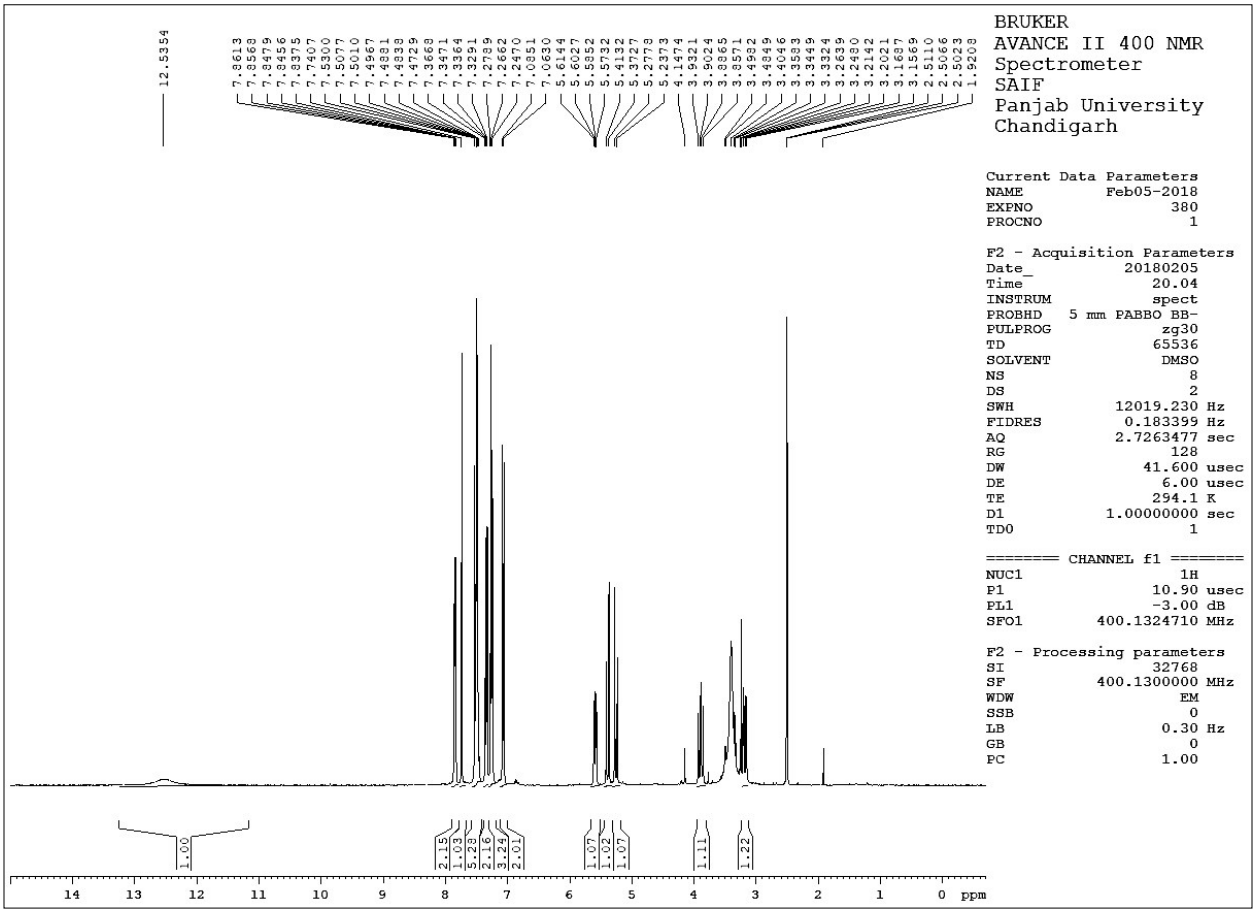
9. Structural characterization data

5-(4-(2-(3,5-diphenyl-4,5-dihydro-1H-pyrazol-1-yl)-2-oxoethoxy)benzylidene)thiazolidine-2,4-dione (13a).

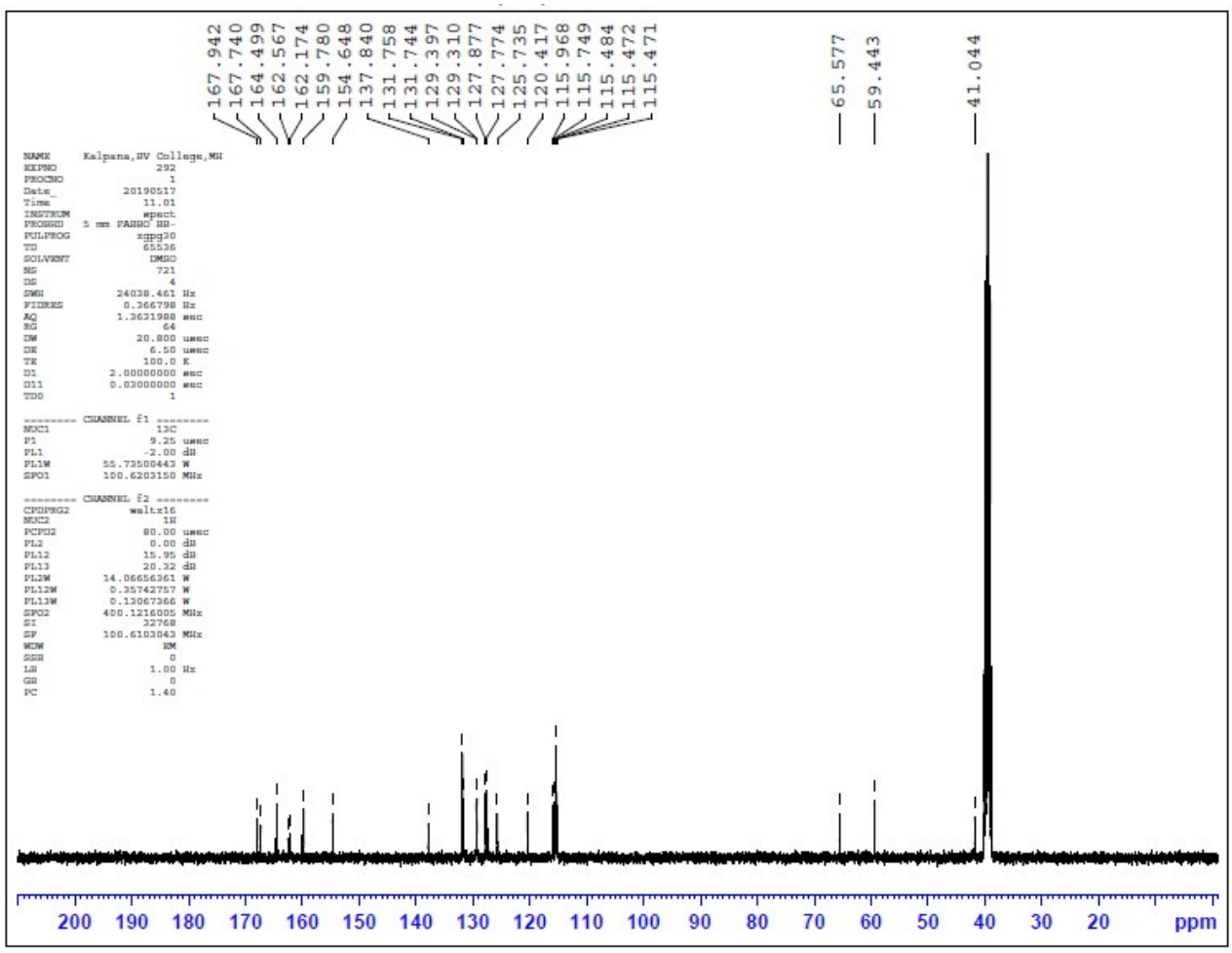
a. FTIR



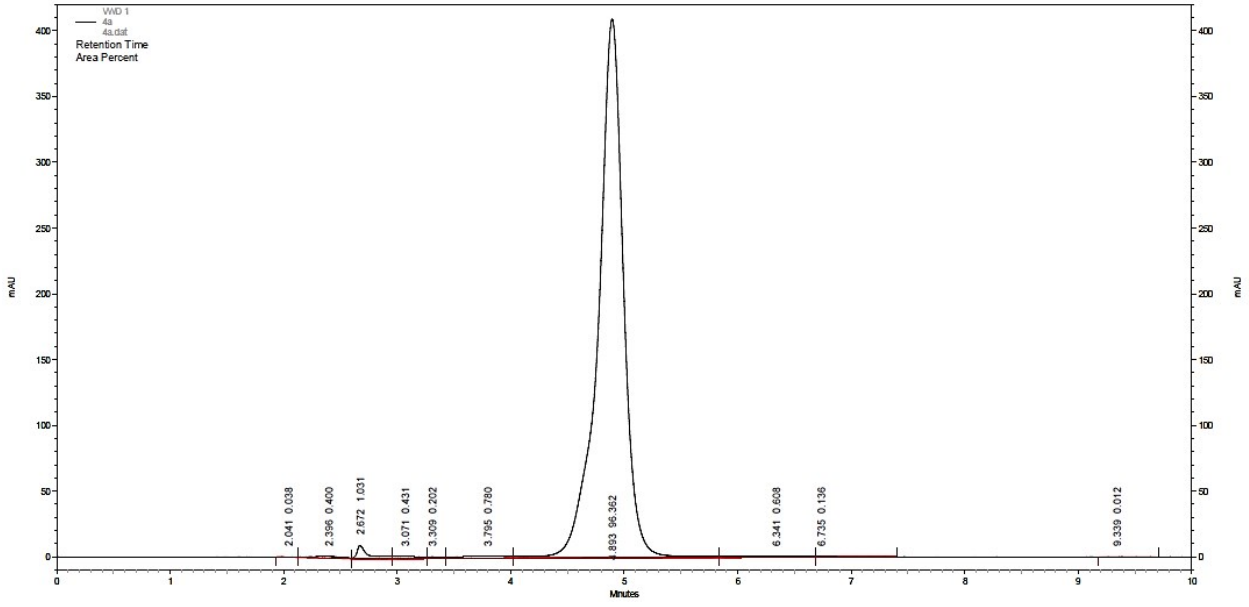
b. ^{1}H-NMR



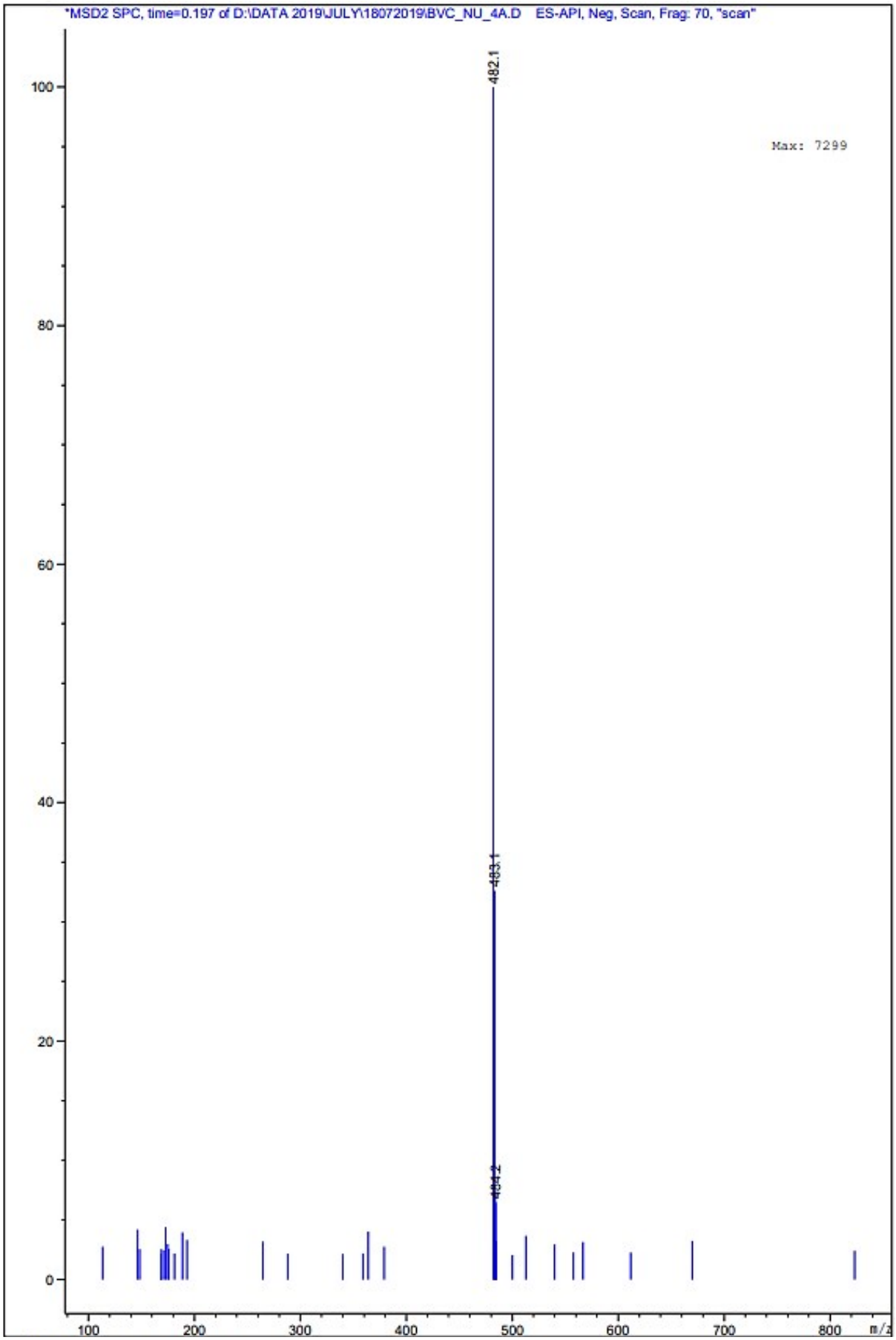
c. ^{13}C-NMR



d. HPLC

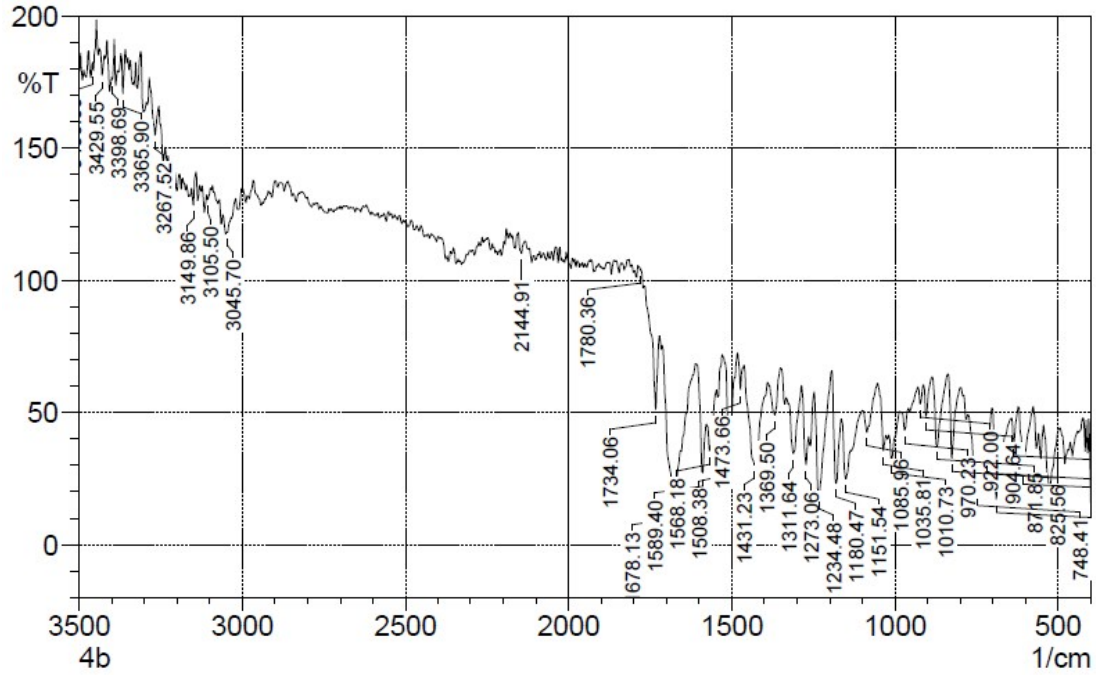


e. Mass spectroscopy

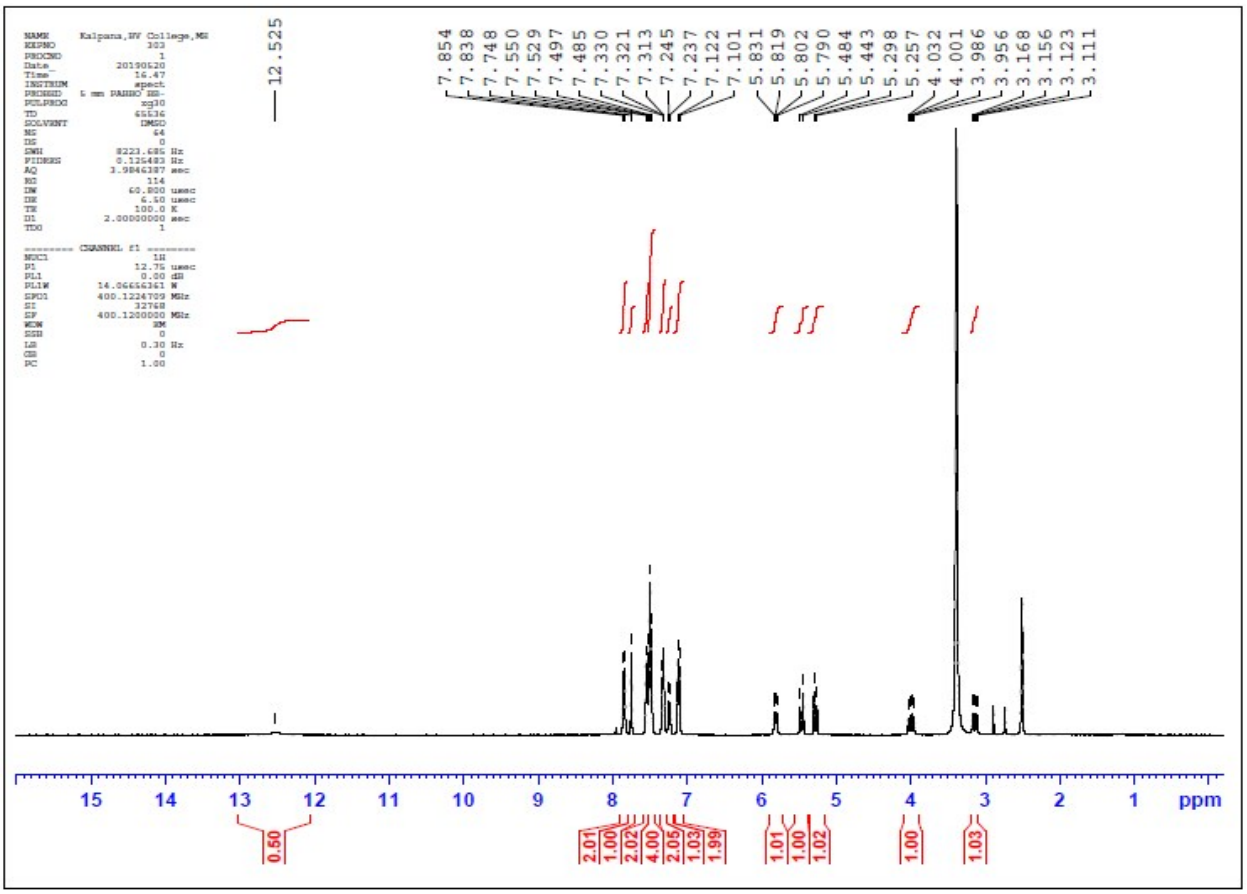


5-(4-(2-(5-(2-chlorophenyl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)-2-oxoethoxy)benzylidene) thiazolidine-2,4-dione (13b).

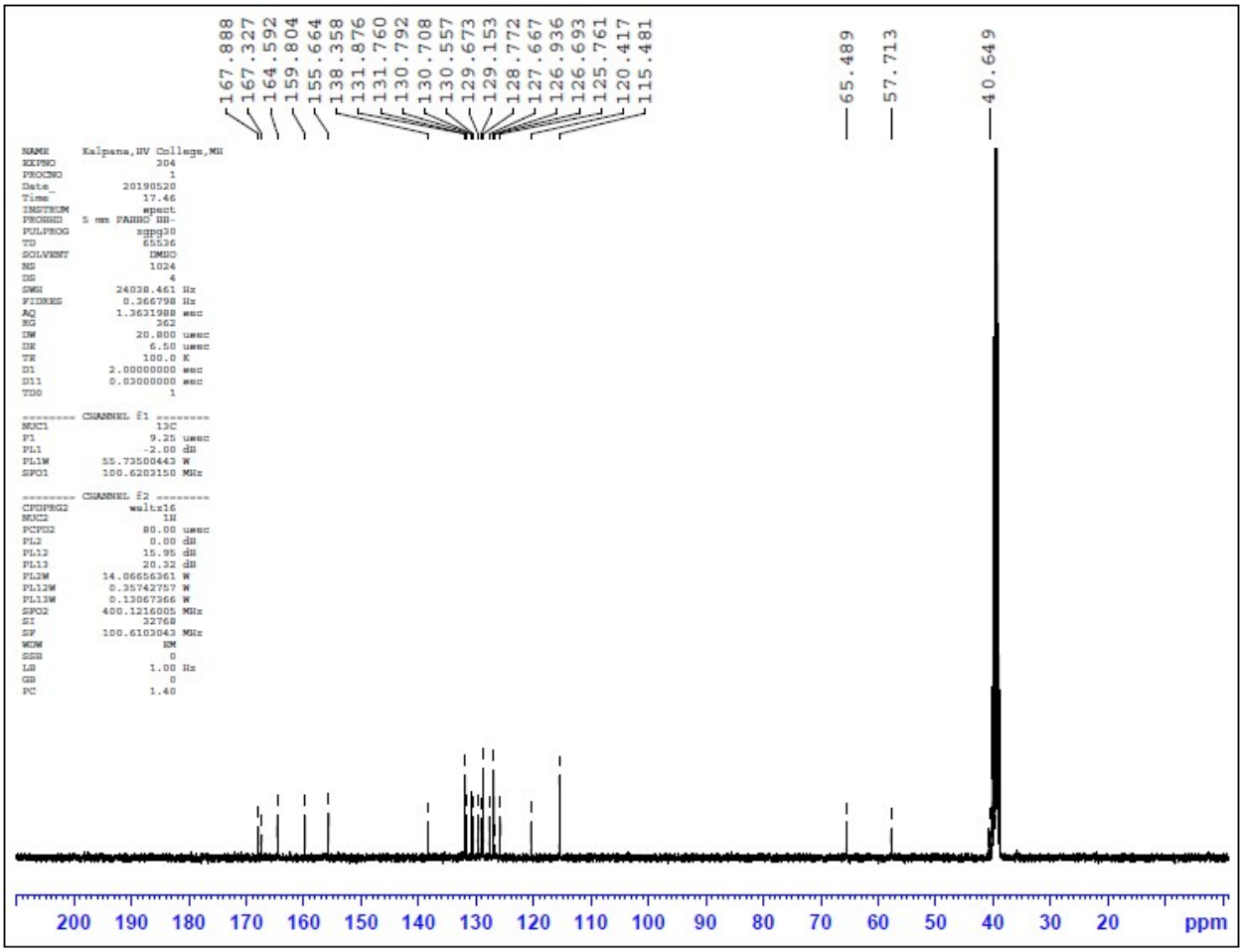
a. FTIR



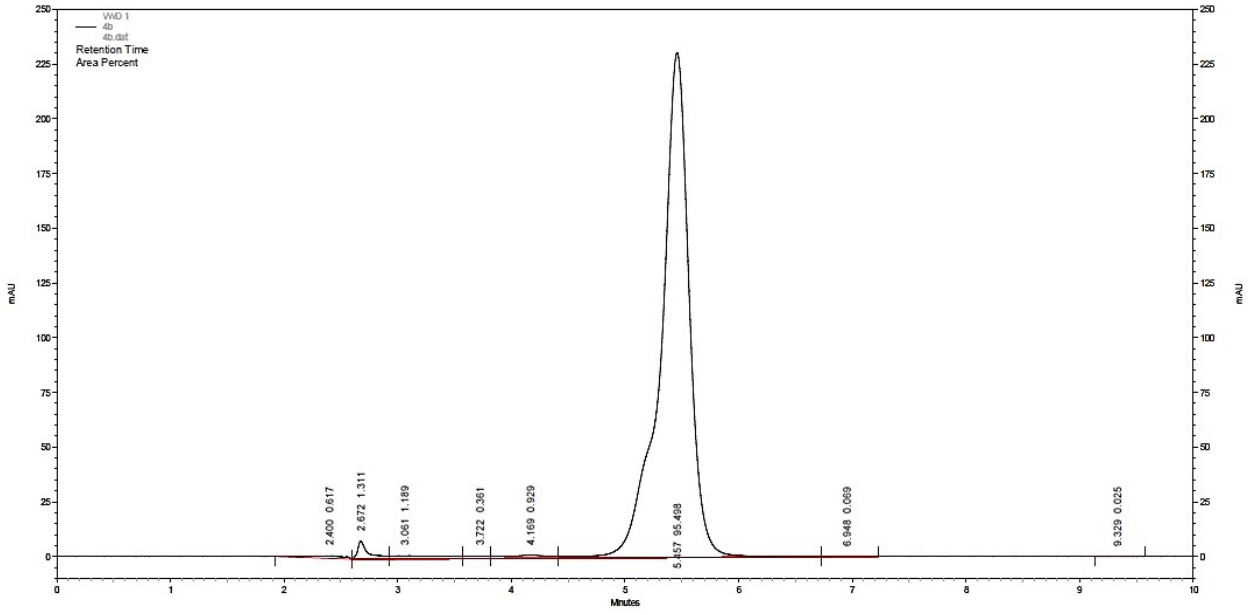
b. ^{1}H-NMR



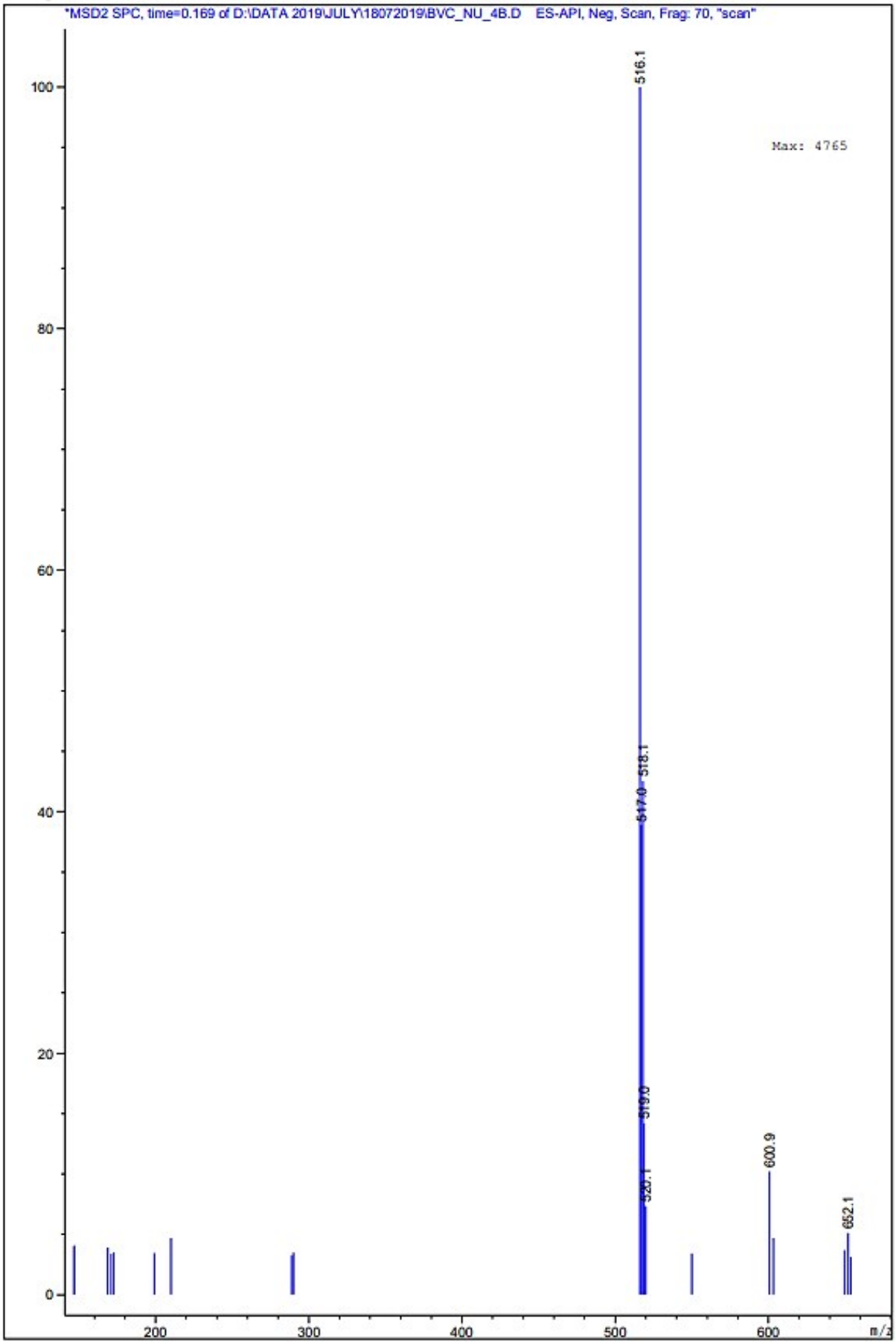
c. ^{13}C-NMR



d. HPLC

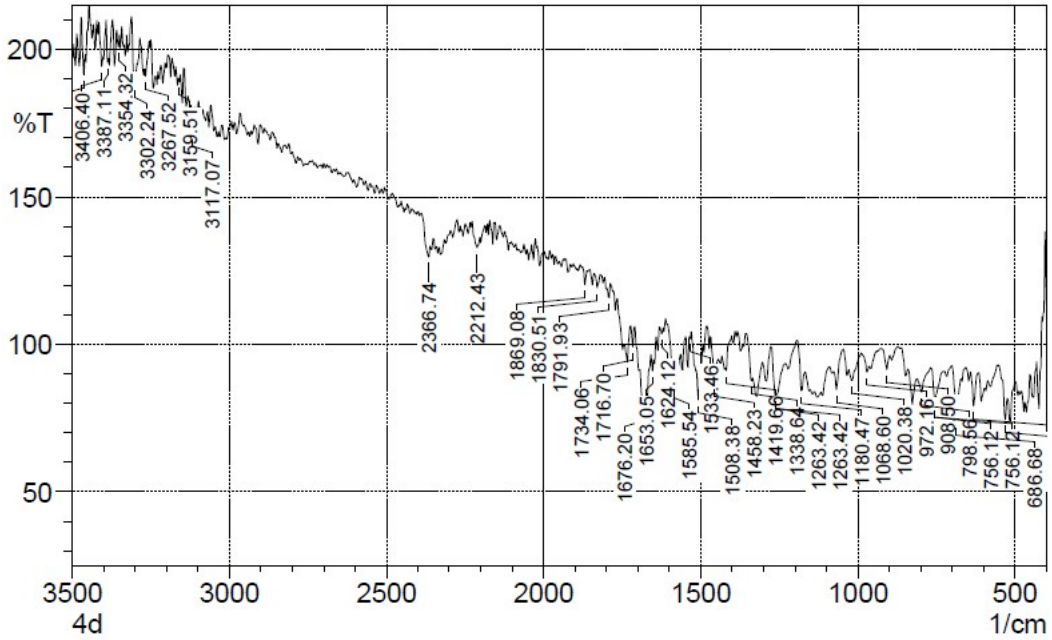


e. Mass spectroscopy

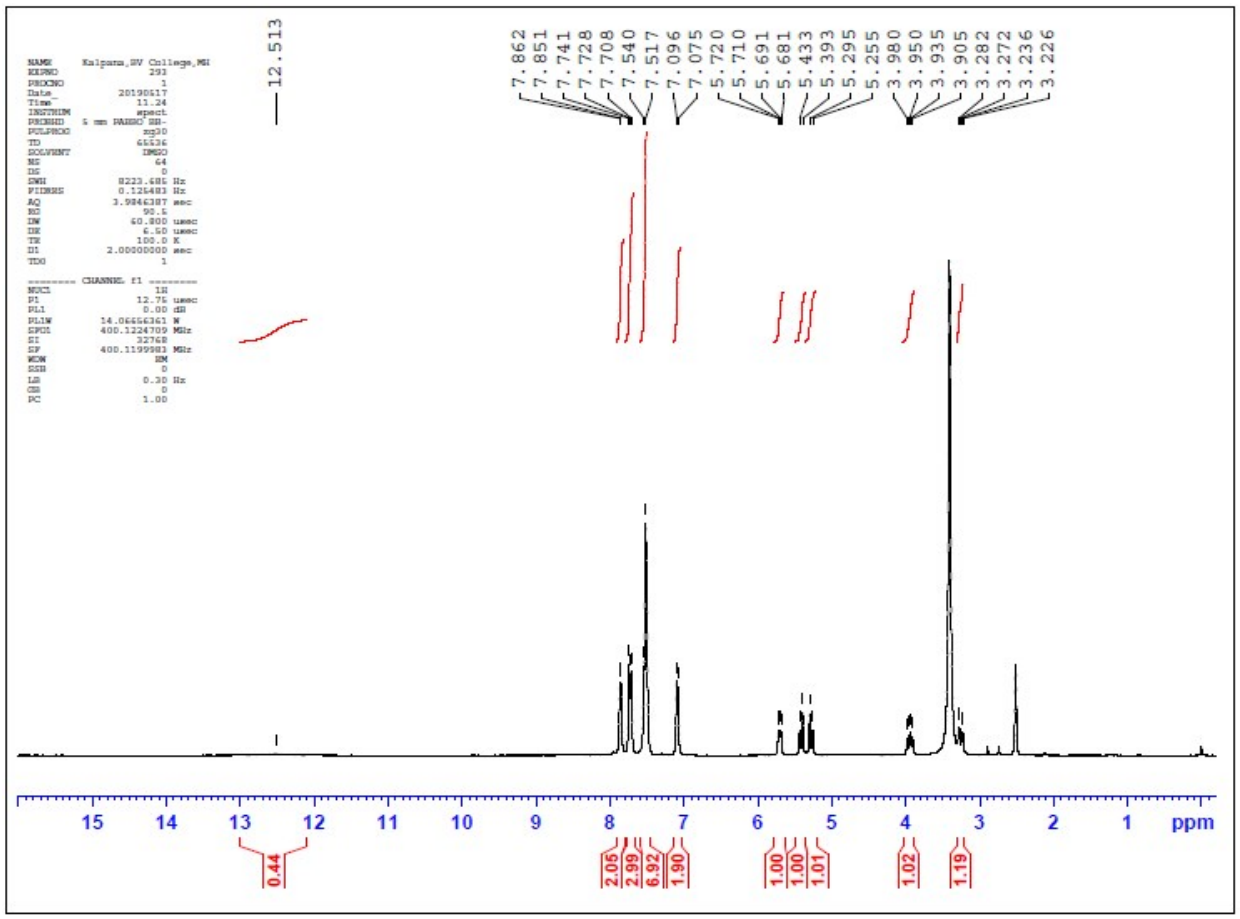


5-(4-(2-oxo-2-(3-phenyl-5-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1H-pyrazol-1-yl)ethoxy)benzylidene) thiazolidine-2,4-dione (13d).

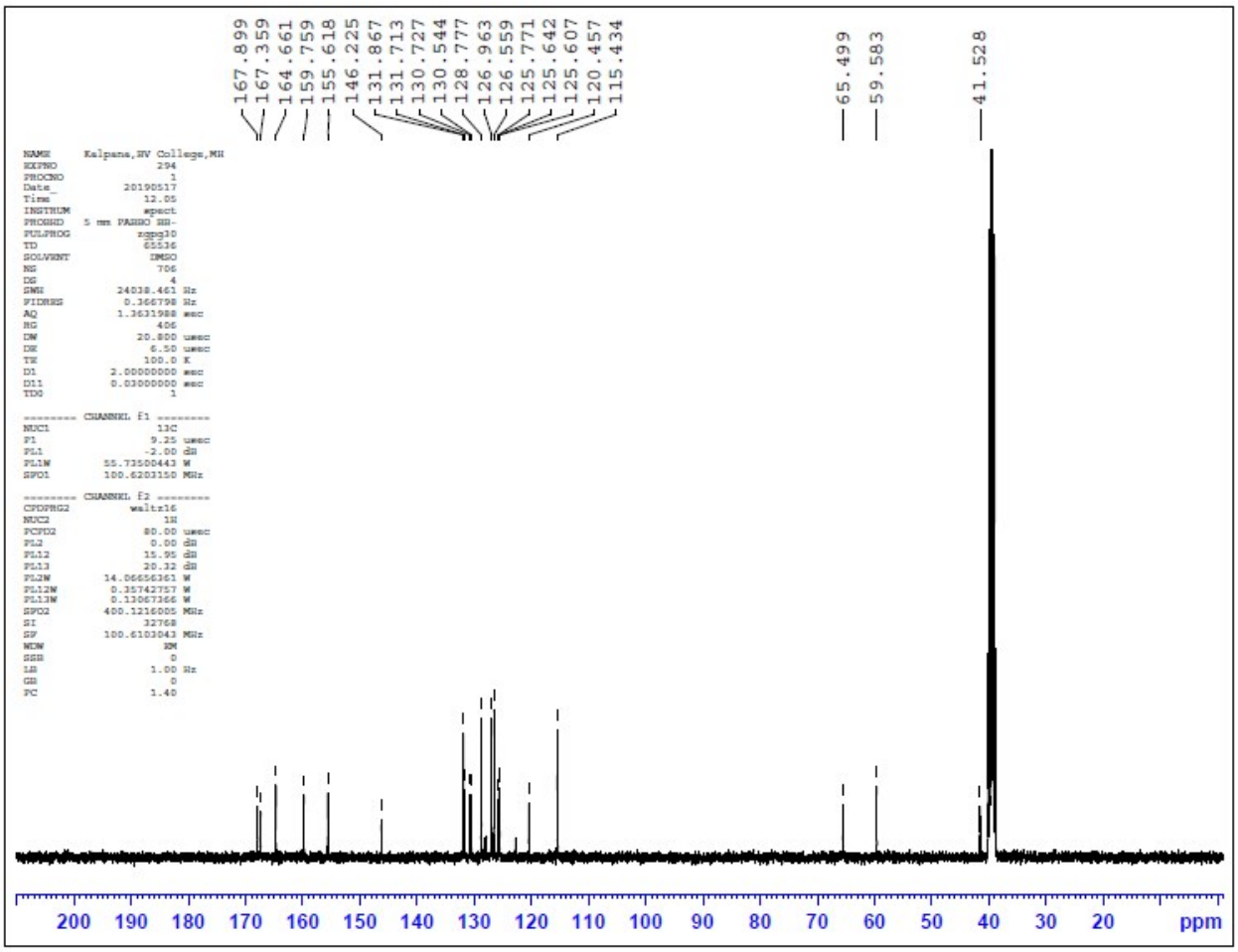
a. FTIR



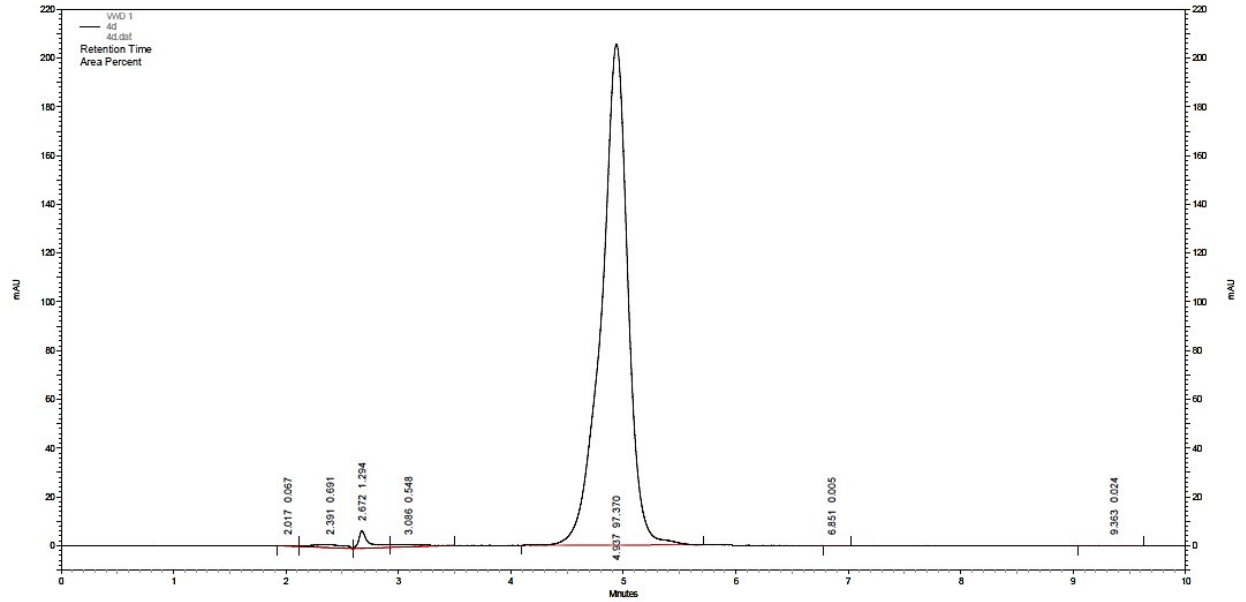
b. ^{1}H-NMR



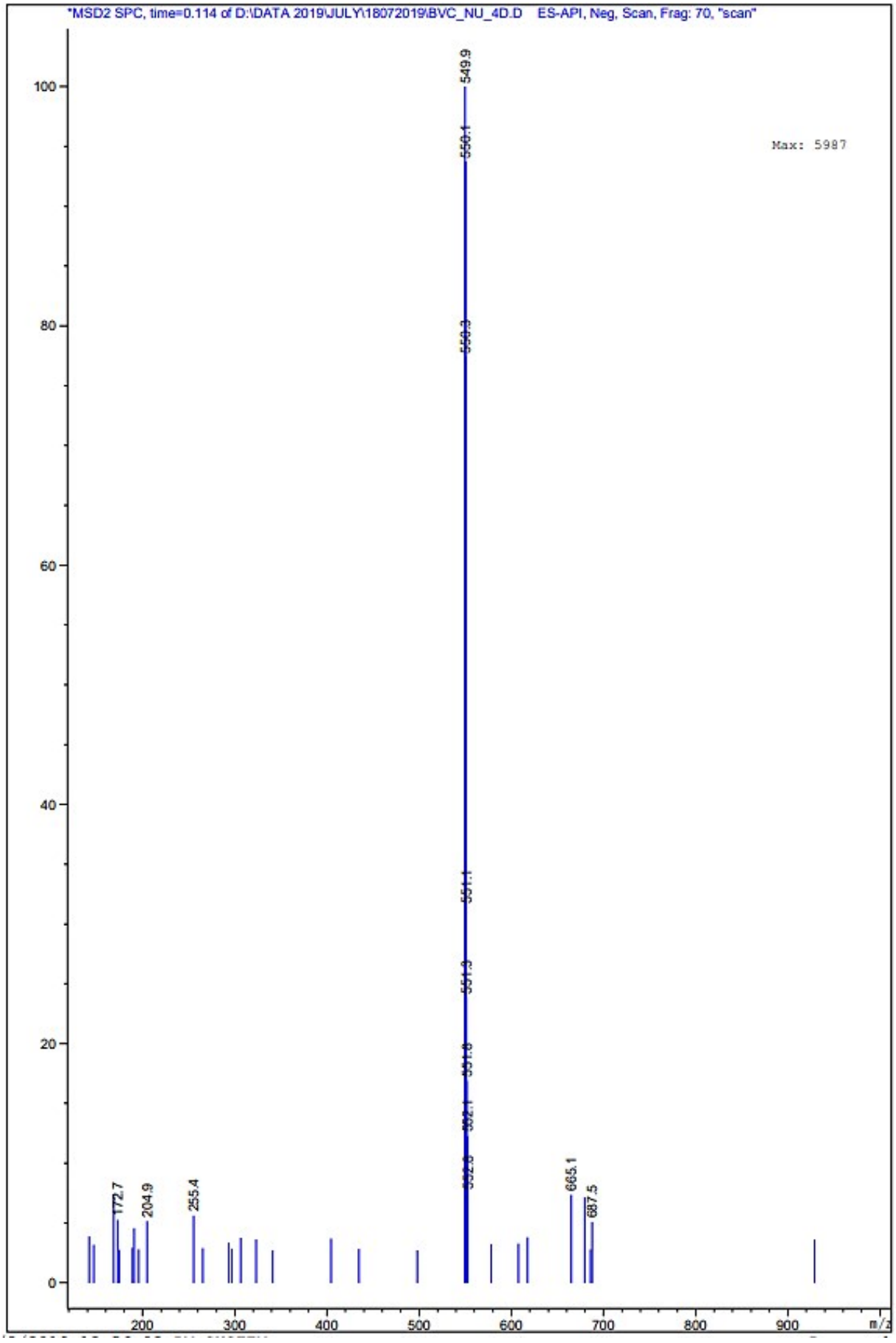
c. ^{13}C-NMR



d. HPLC

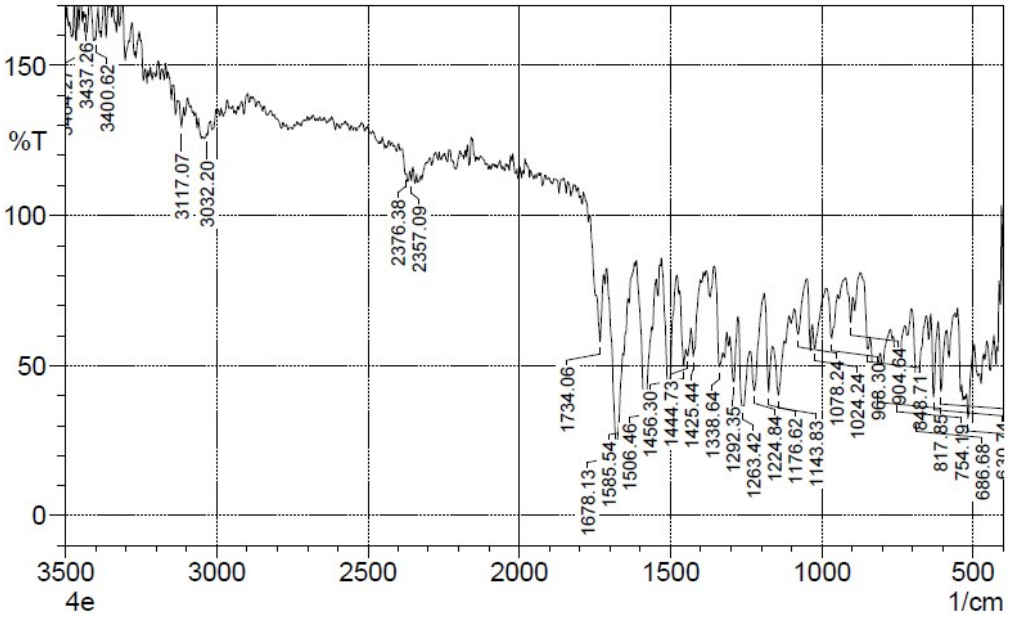


e. Mass spectroscopy

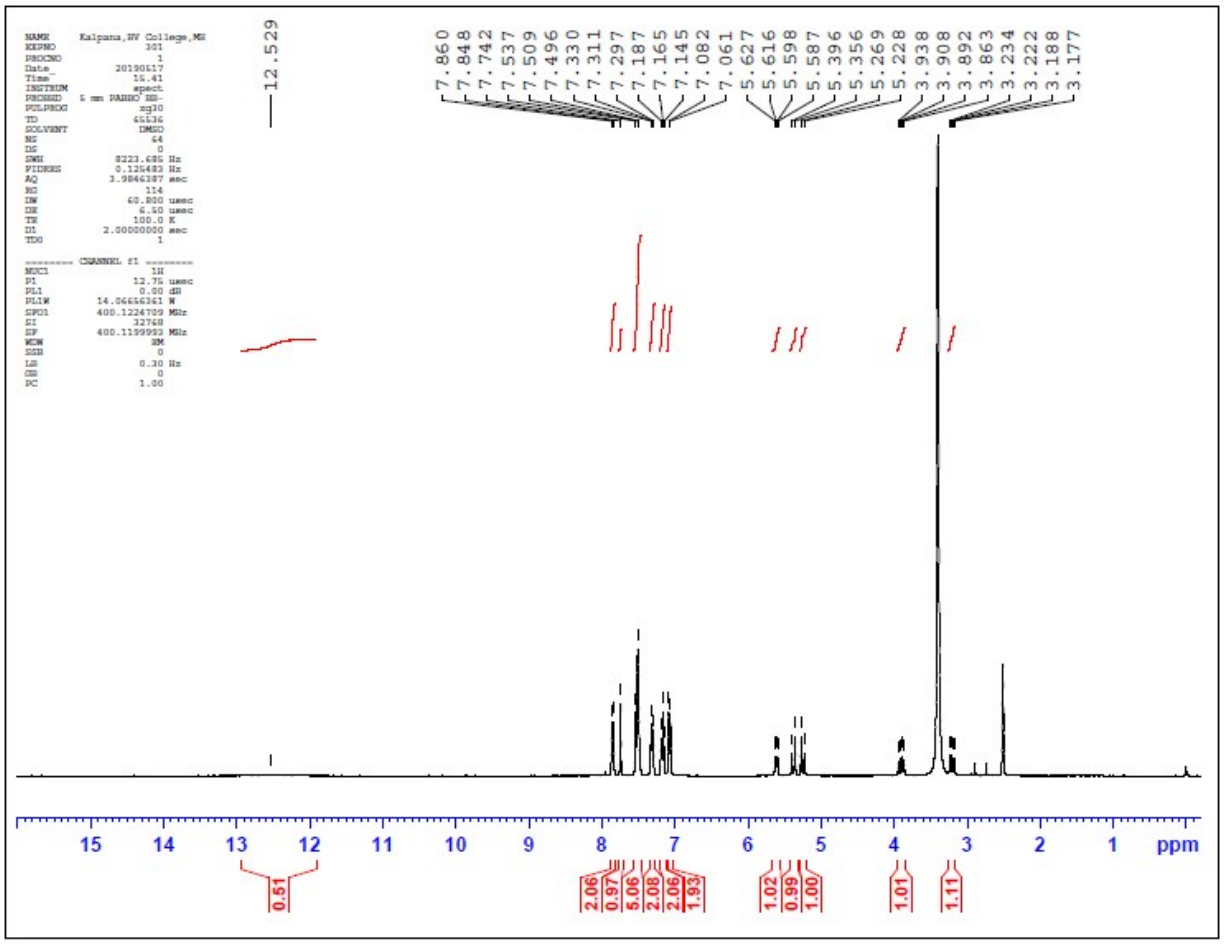


5-(4-(2-(5-(4-fluorophenyl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)-2-oxoethoxy)benzylidene)thiazolidine-2,4-dione (13e).

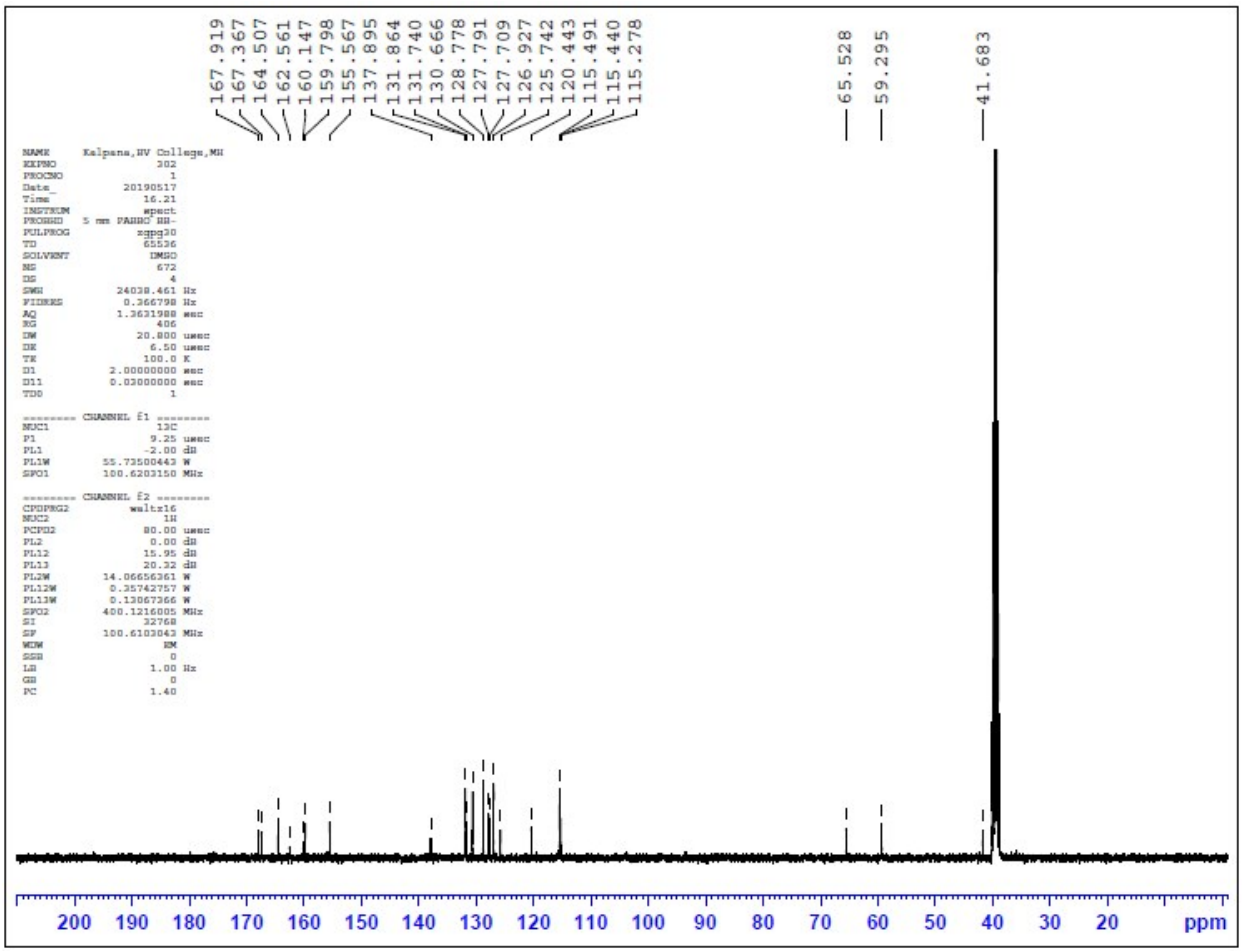
a. FTIR



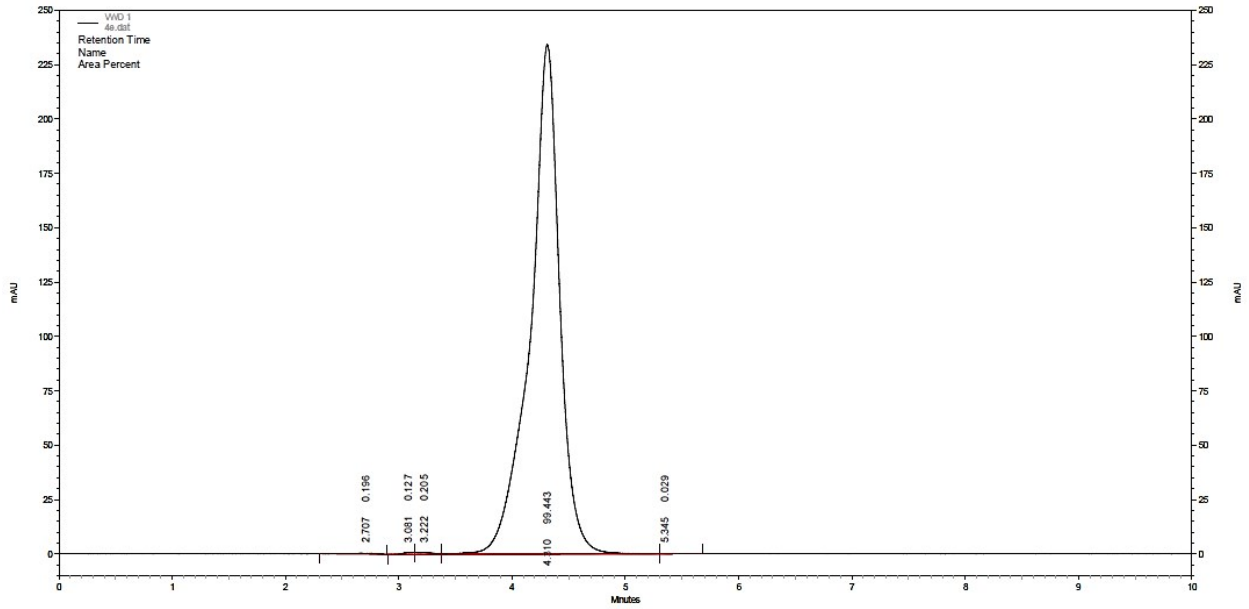
b. ^{1}H-NMR



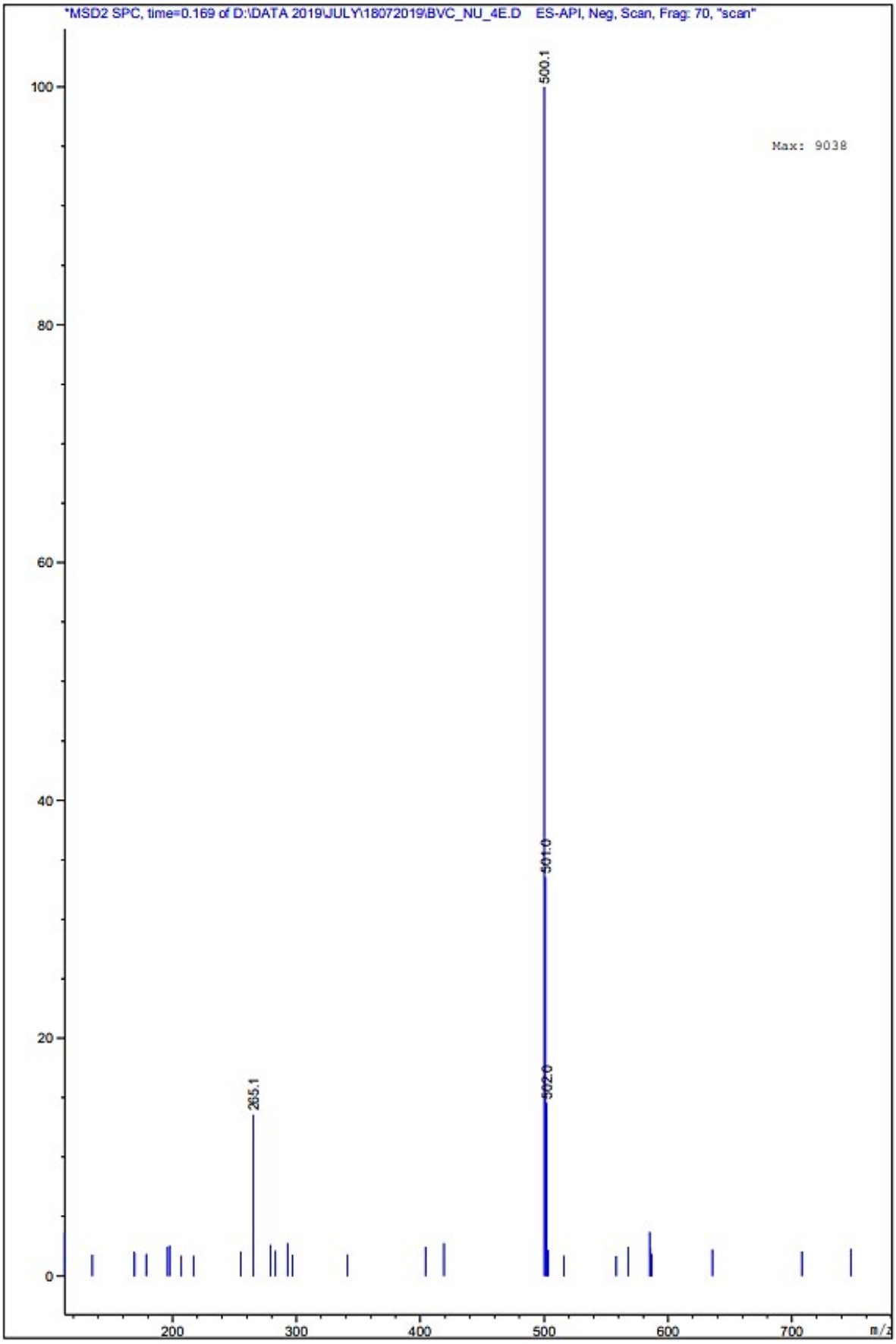
c. ^{13}C-NMR



d. HPLC

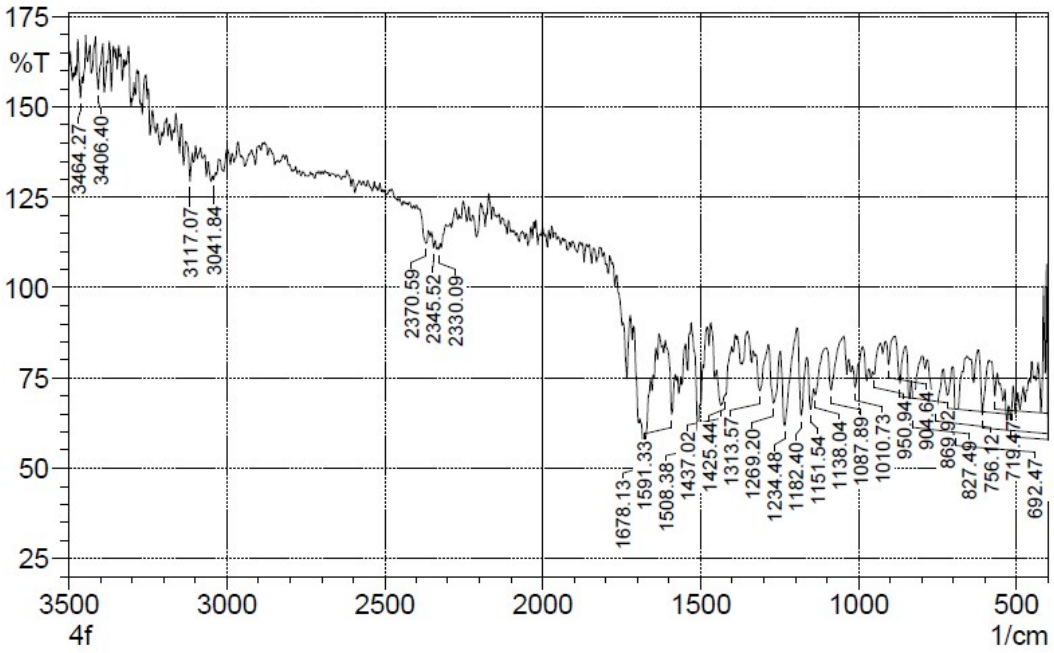


e. Mass spectroscopy

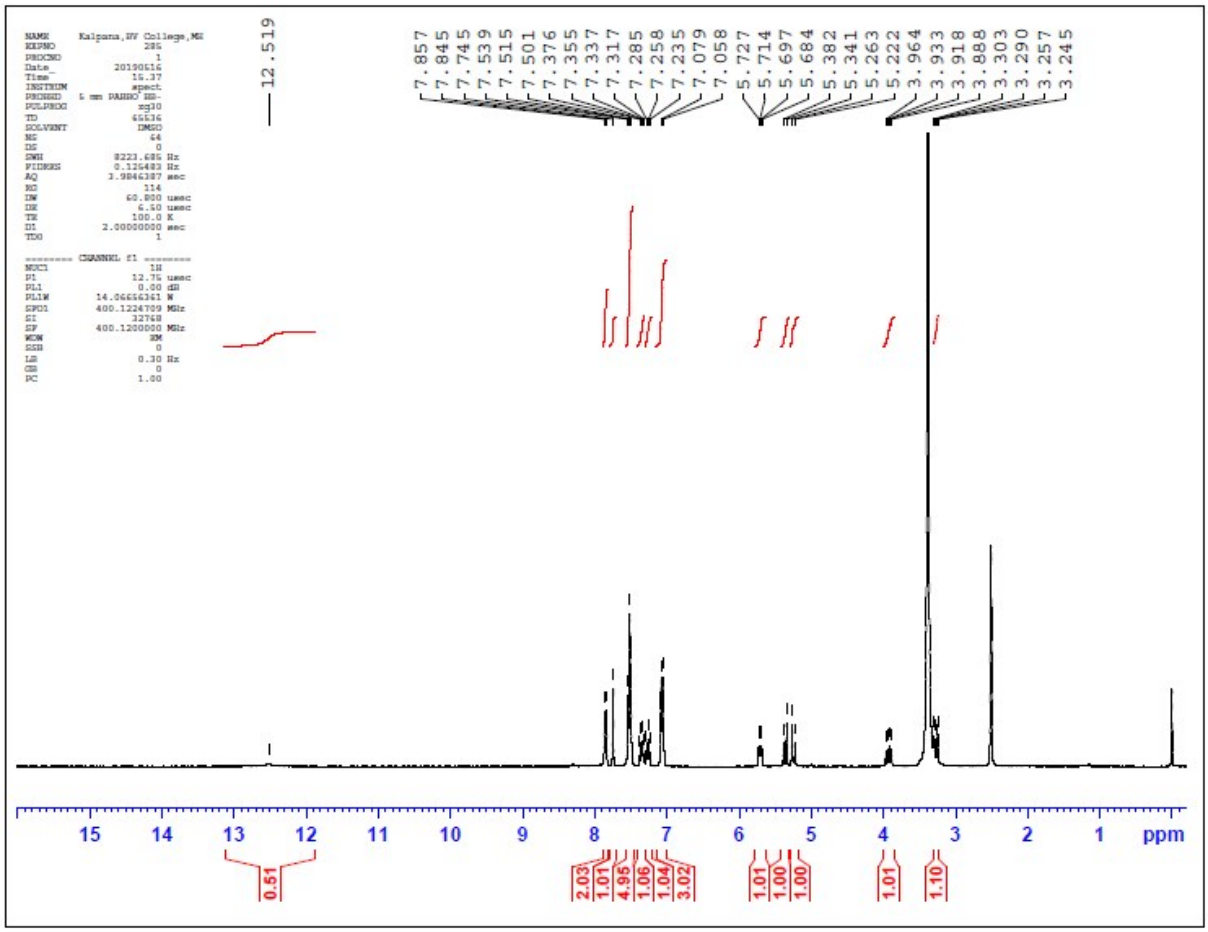


5-(4-(2-(5-(2,4-difluorophenyl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)-2-oxoethoxy)benzylidene) thiazolidine-2,4-dione (13f).

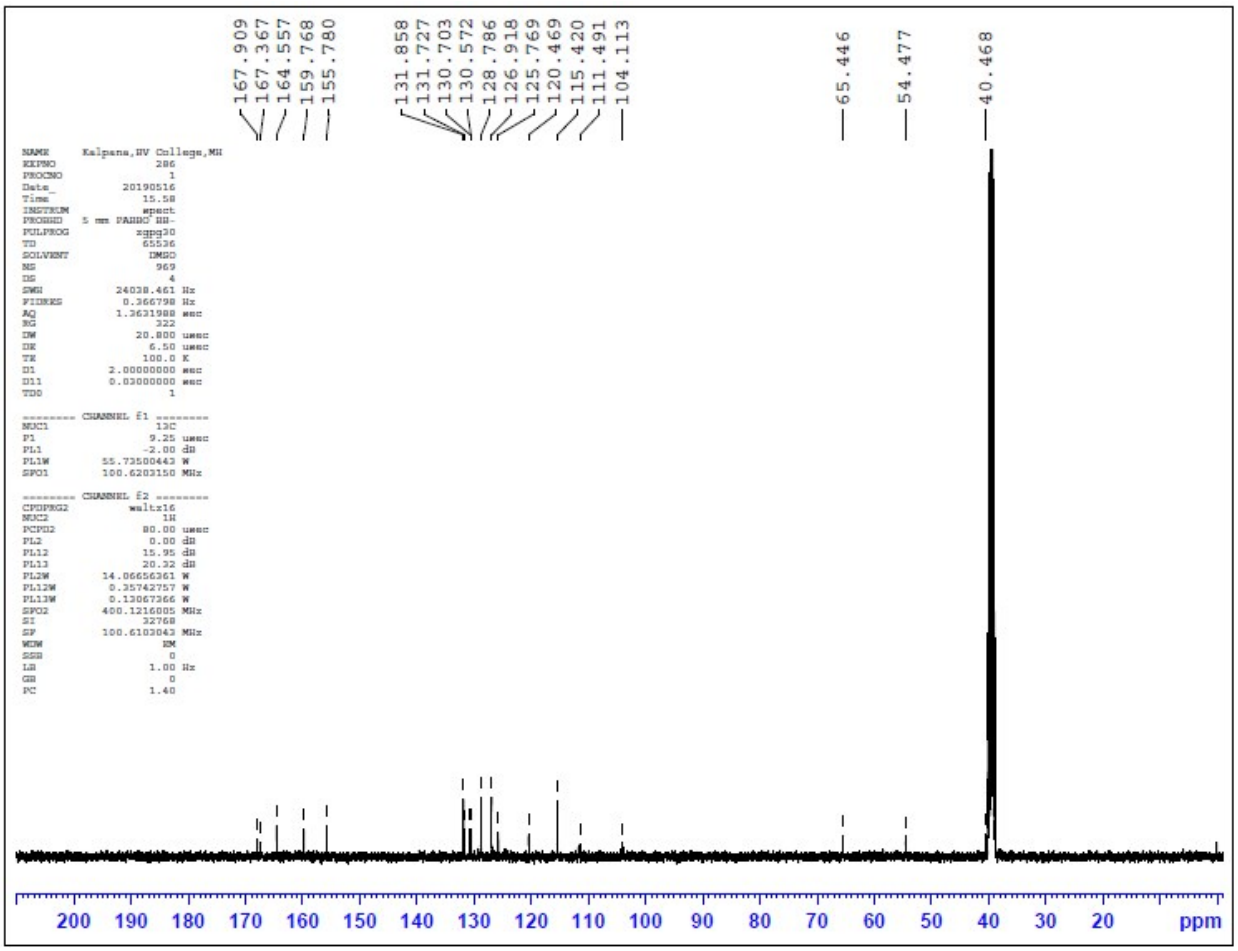
a. FTIR



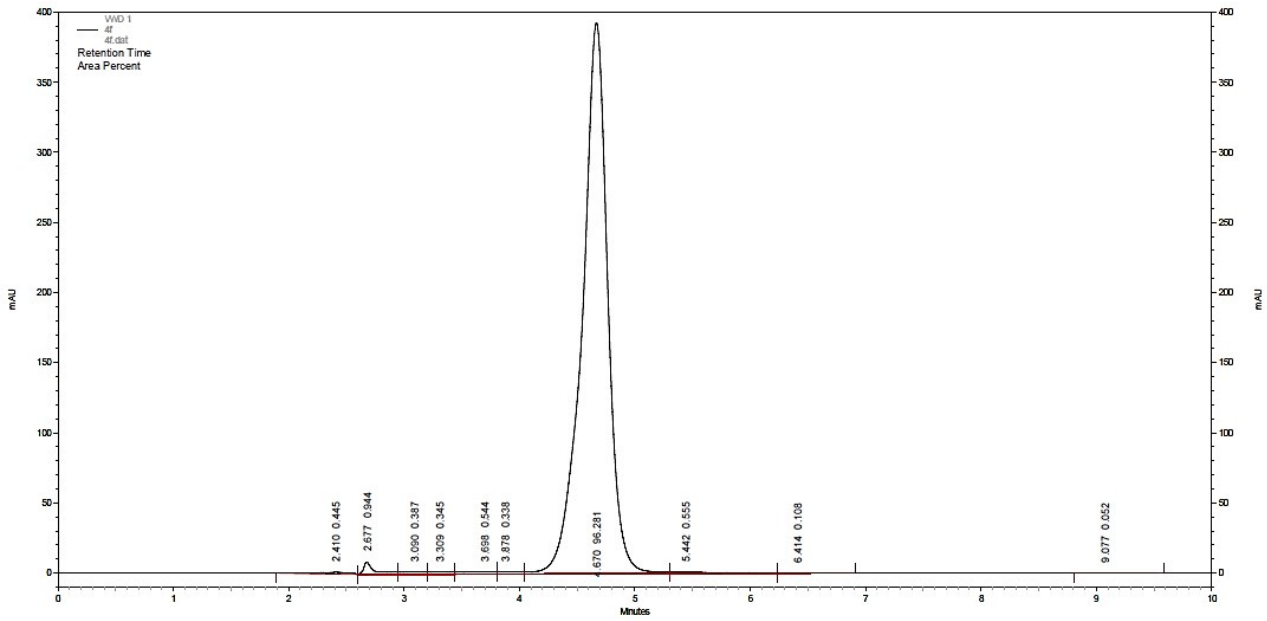
b. ^{1}H-NMR



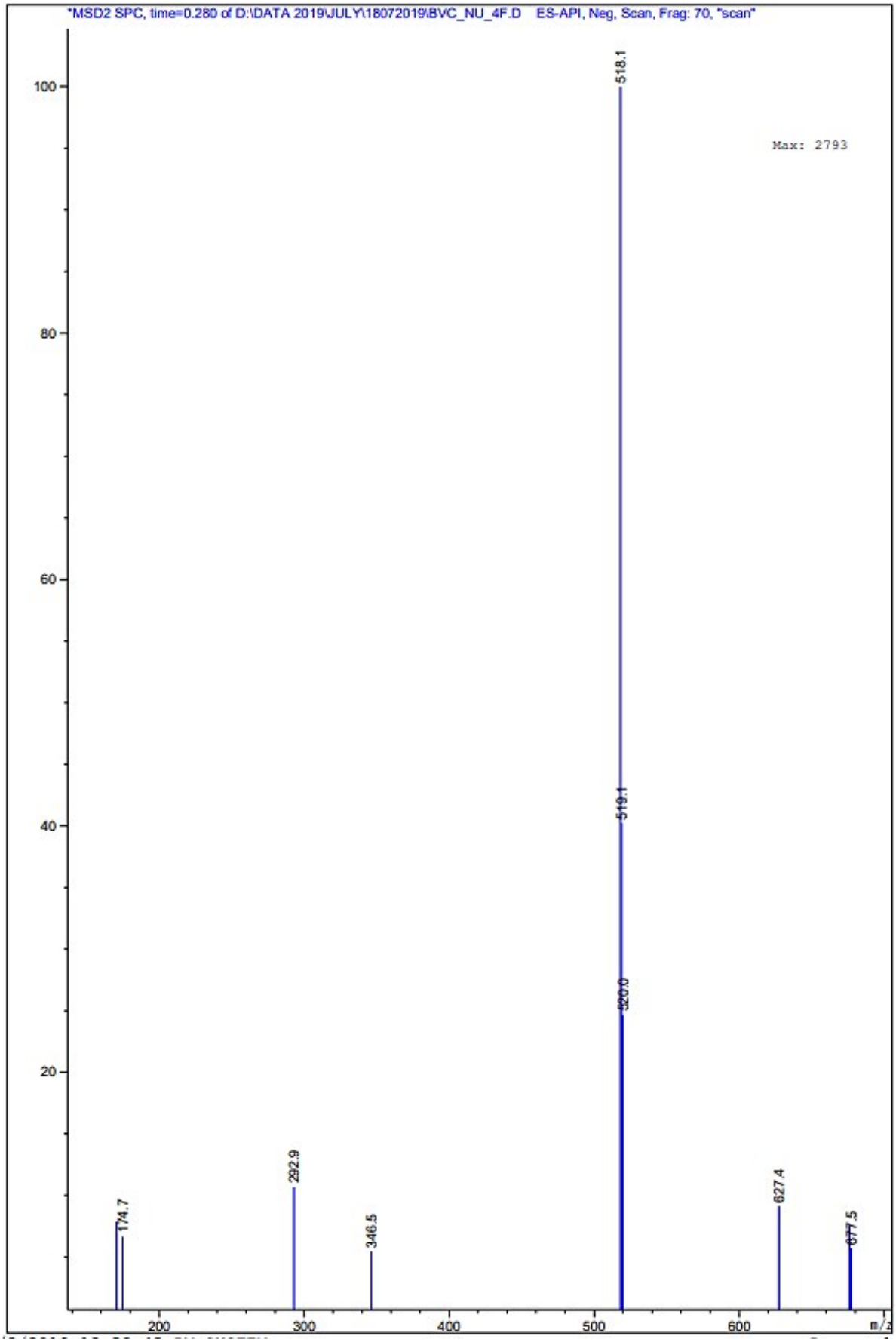
c. ^{13}C-NMR



d. HPLC

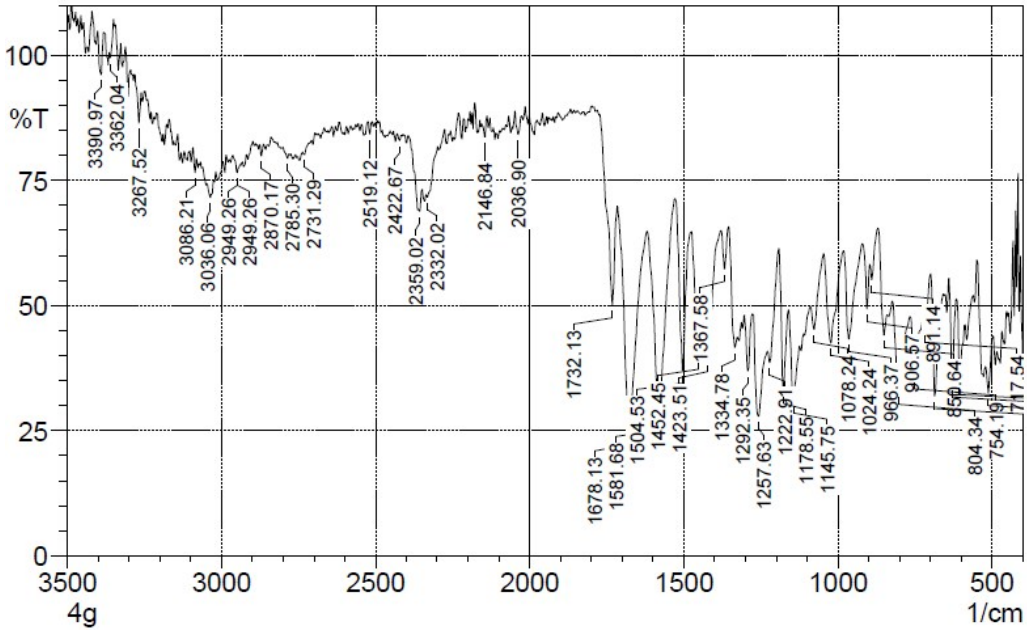


e. Mass spectroscopy

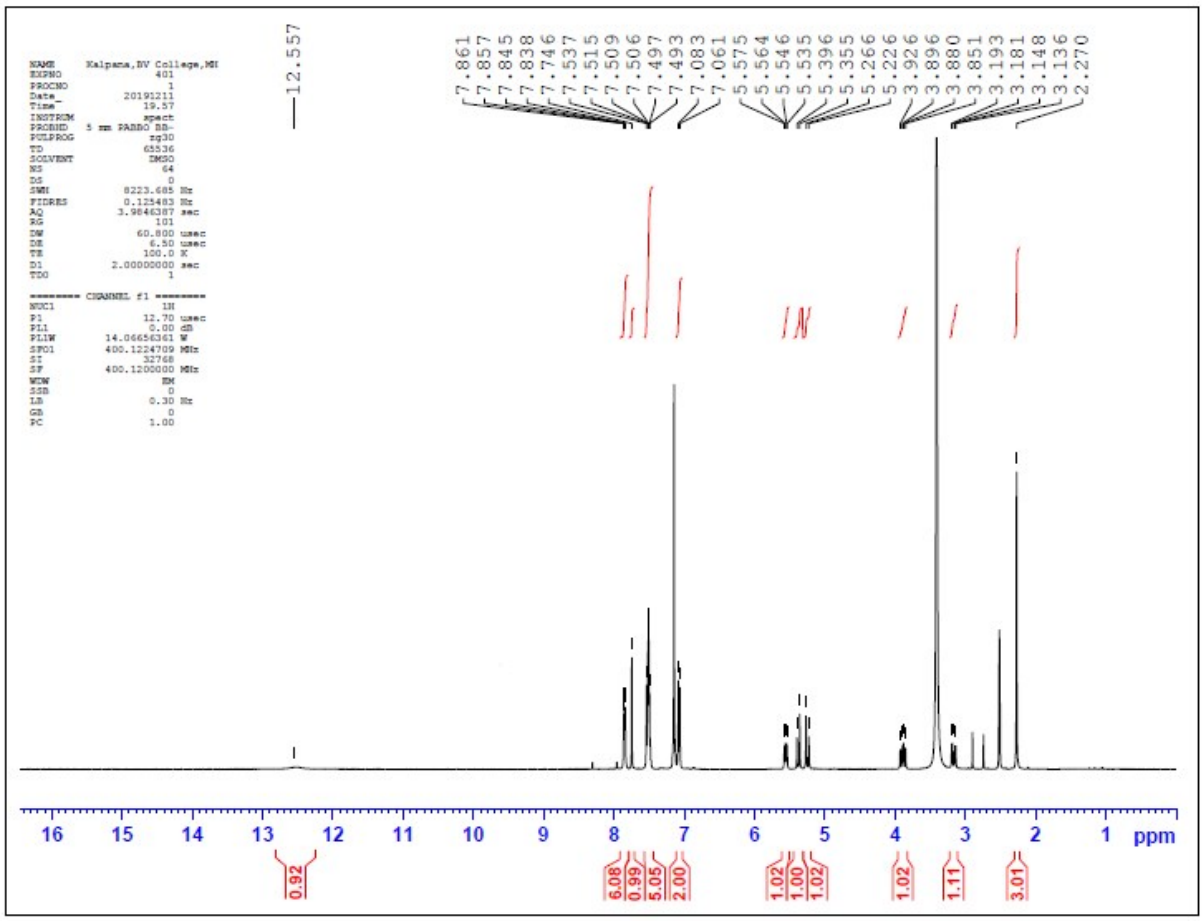


5-(4-(2-oxo-2-(3-phenyl-5-(p-tolyl)-4,5-dihydro-1H-pyrazol-1-yl)ethoxy)benzylidene) thiazolidine-2,4-dione (13g).

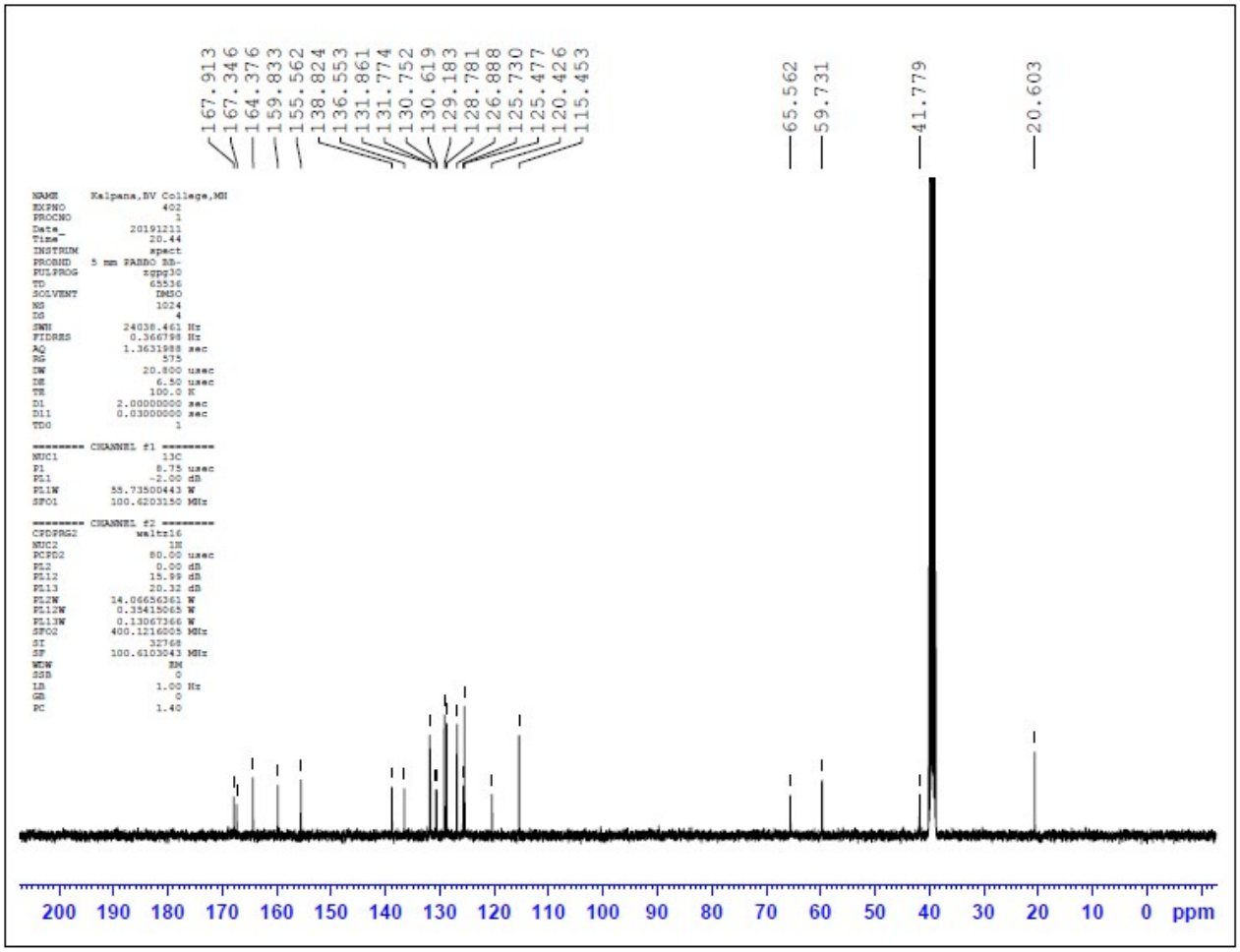
a. FTIR



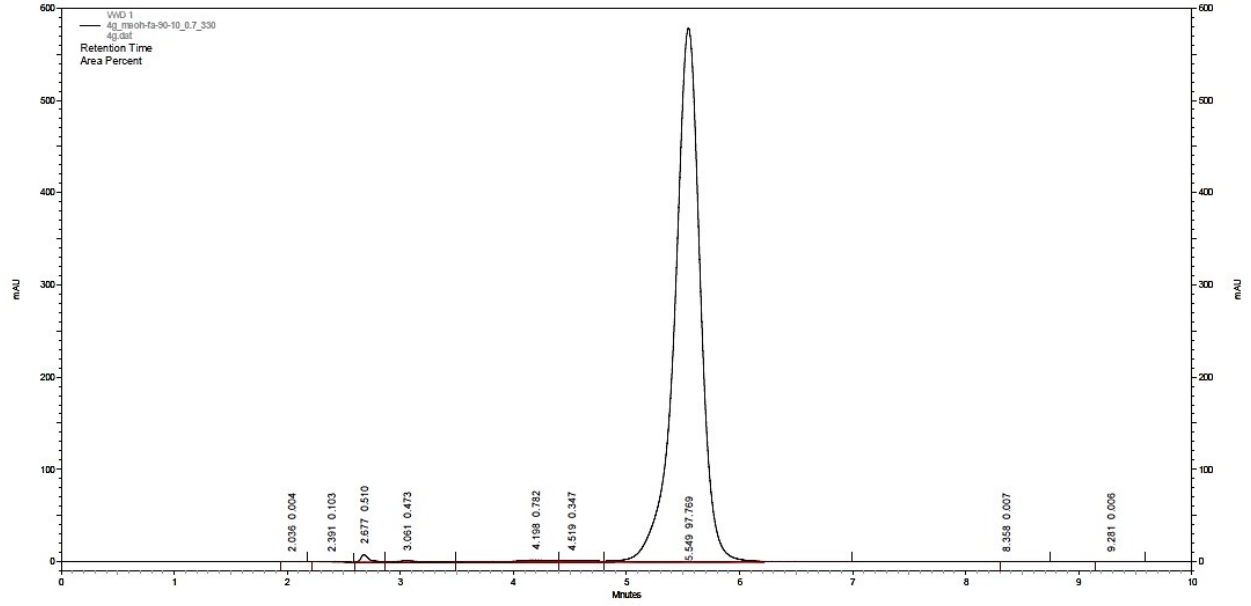
b. ^{1}H-NMR



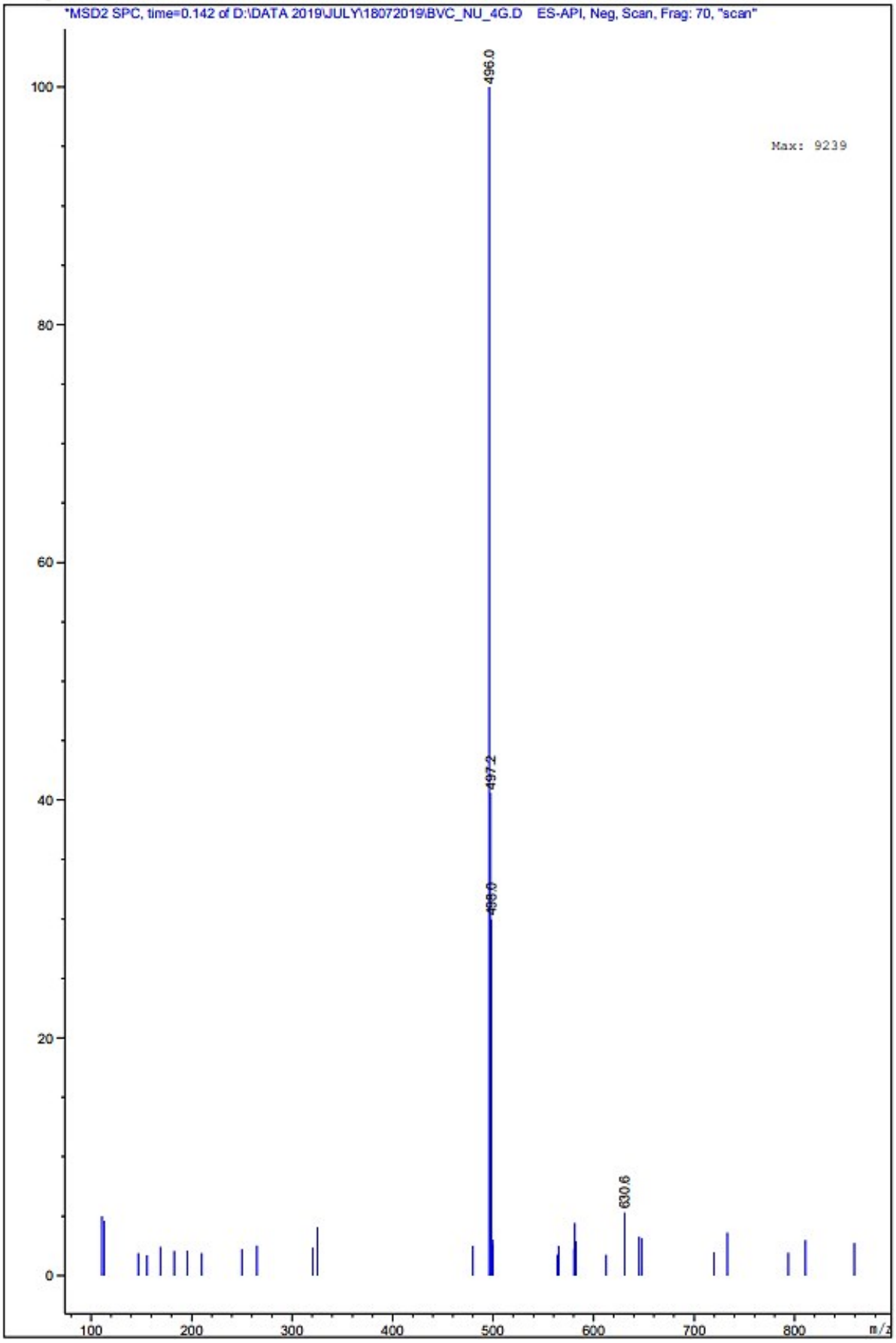
c. ^{13}C-NMR



d. HPLC

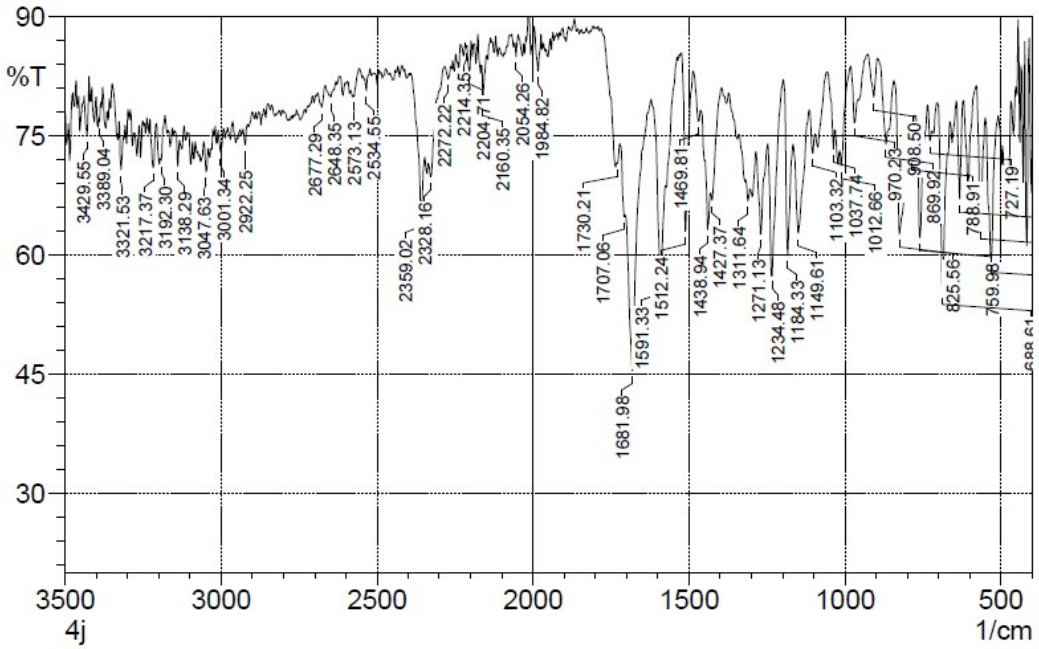


e. Mass spectroscopy

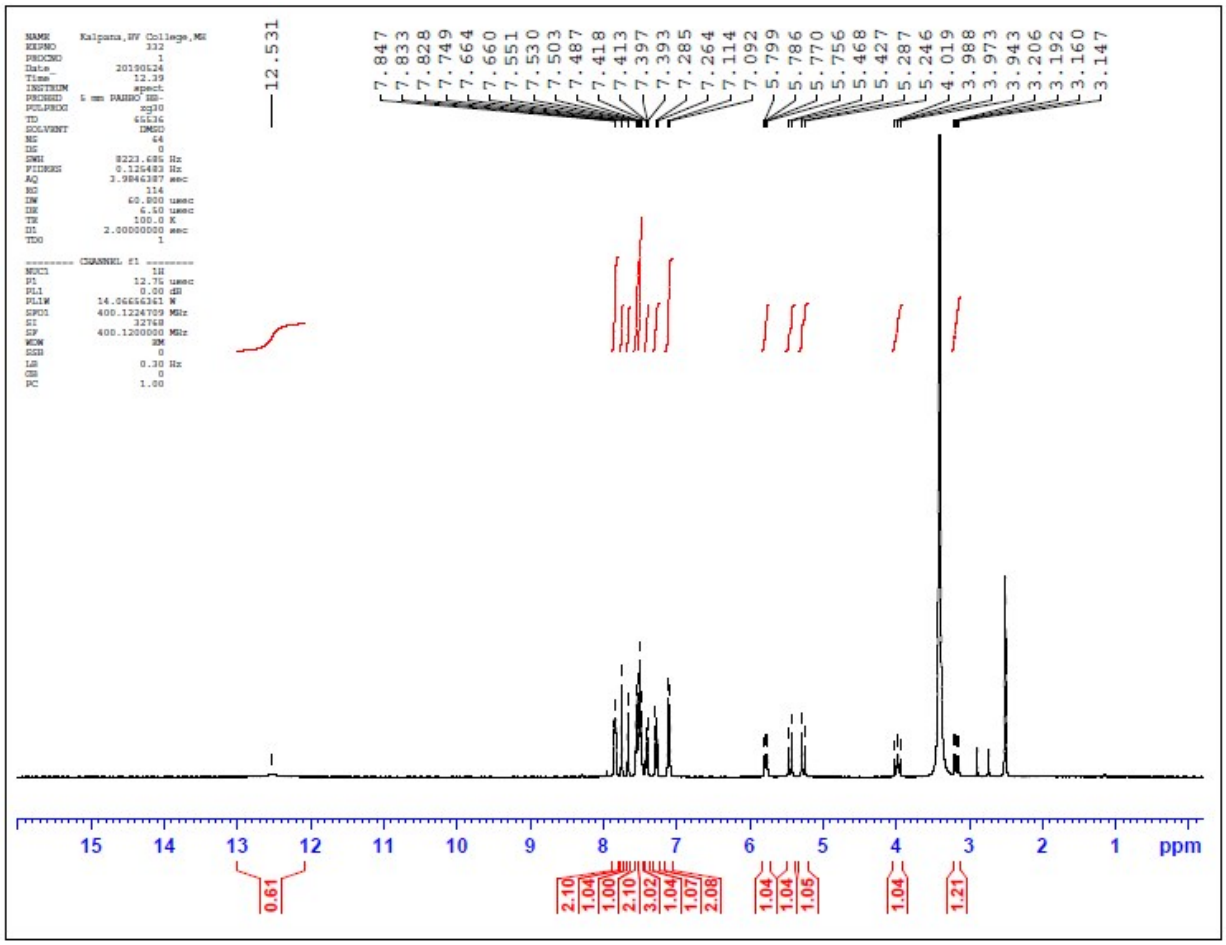


5-(4-(2-(5-(3,4-dichlorophenyl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)-2-oxoethoxy) benzylidene)thiazolidine-2,4-dione (13j).

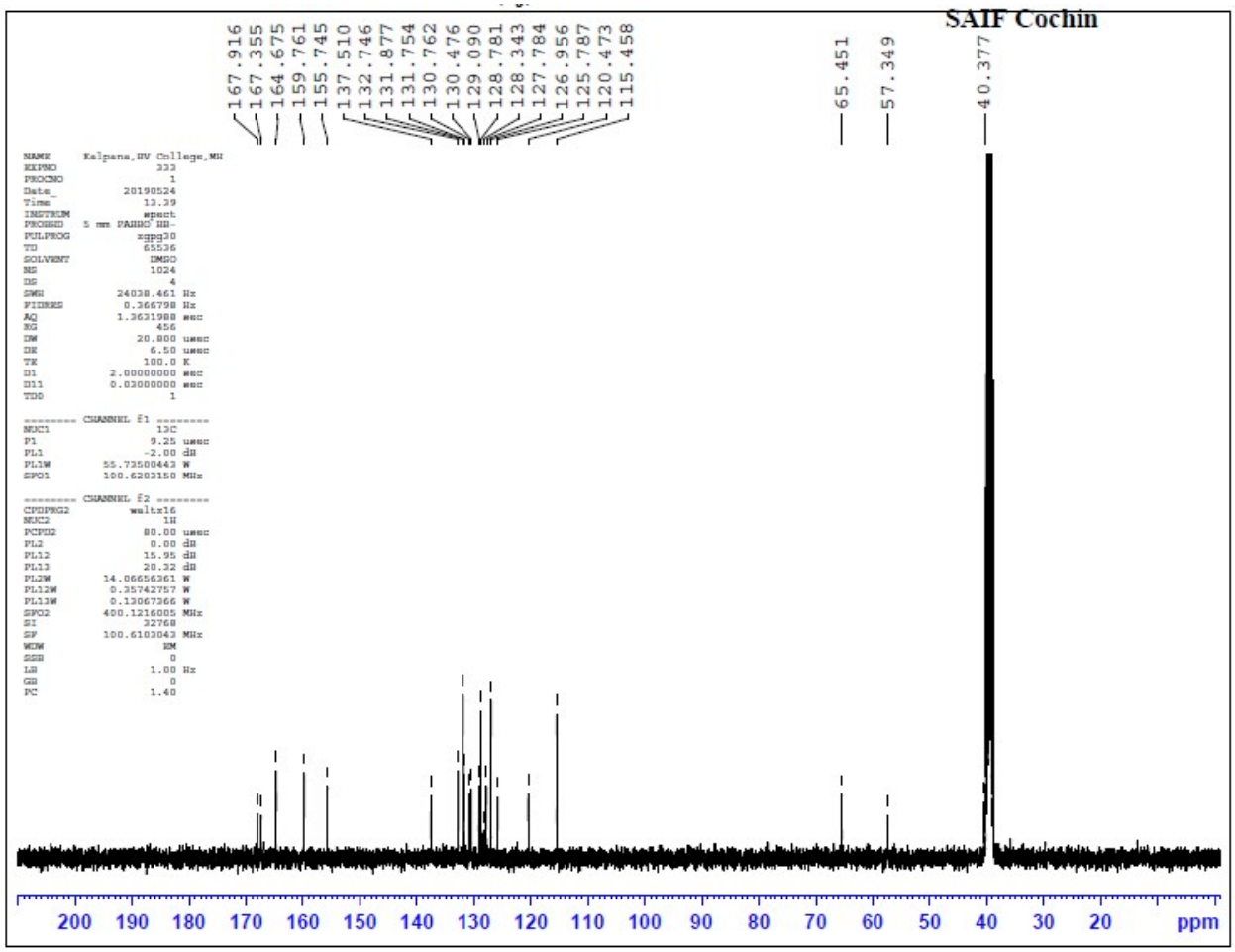
a. FTIR



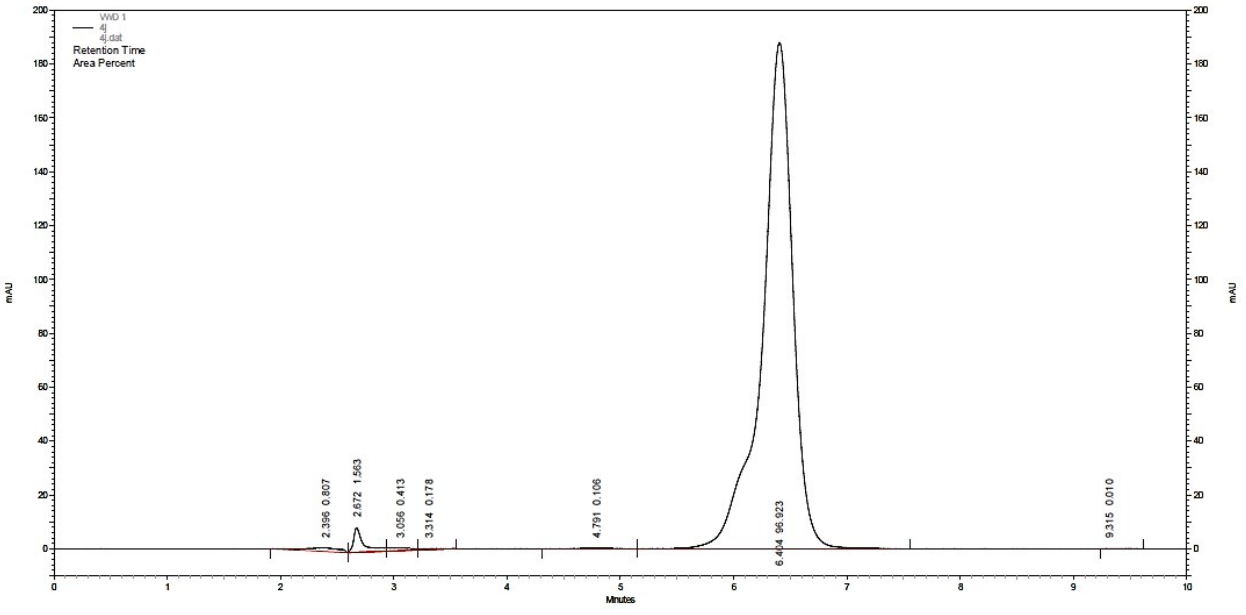
b. ^{1}H-NMR



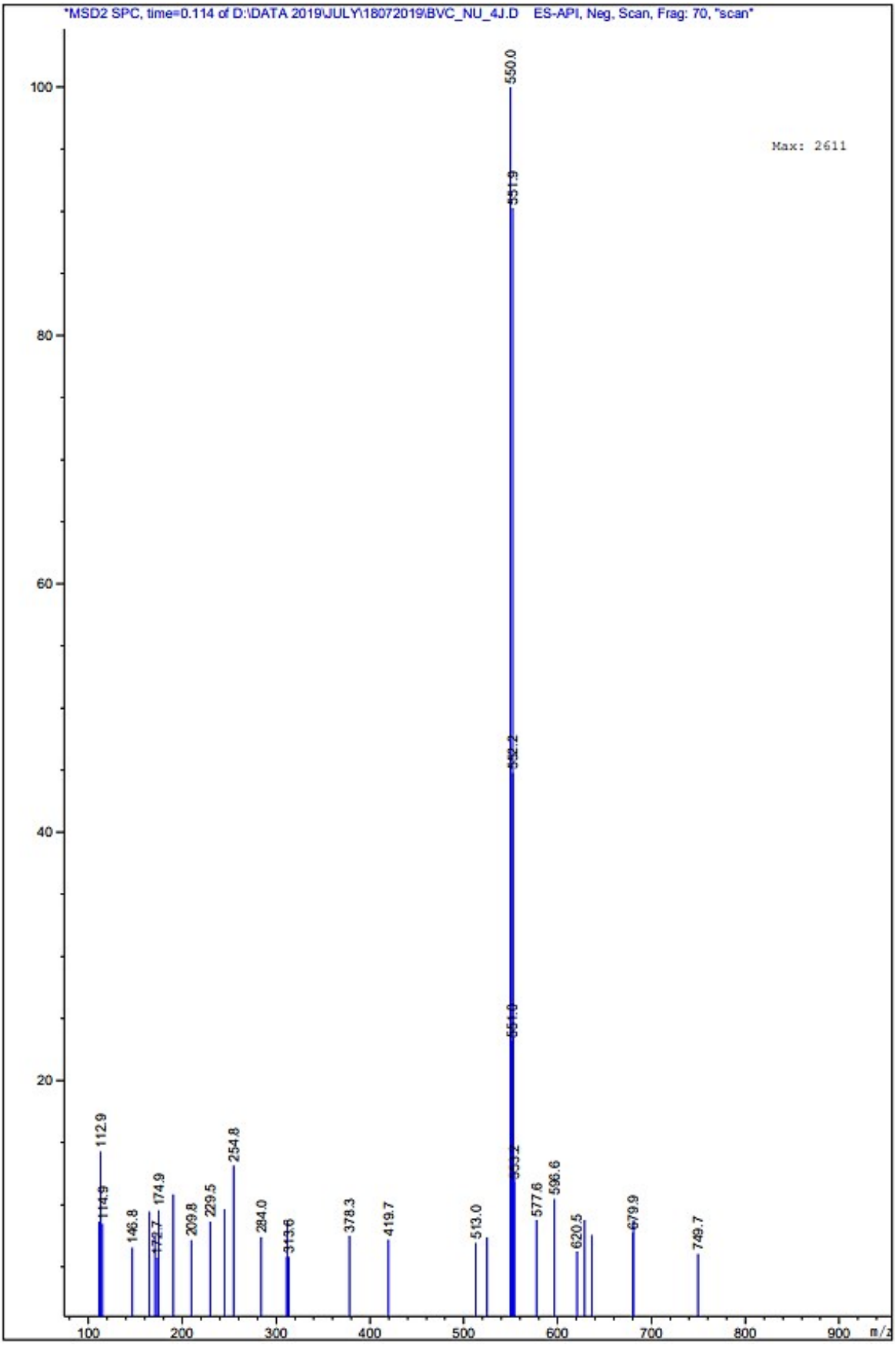
c. ^{13}C-NMR



d. HPLC

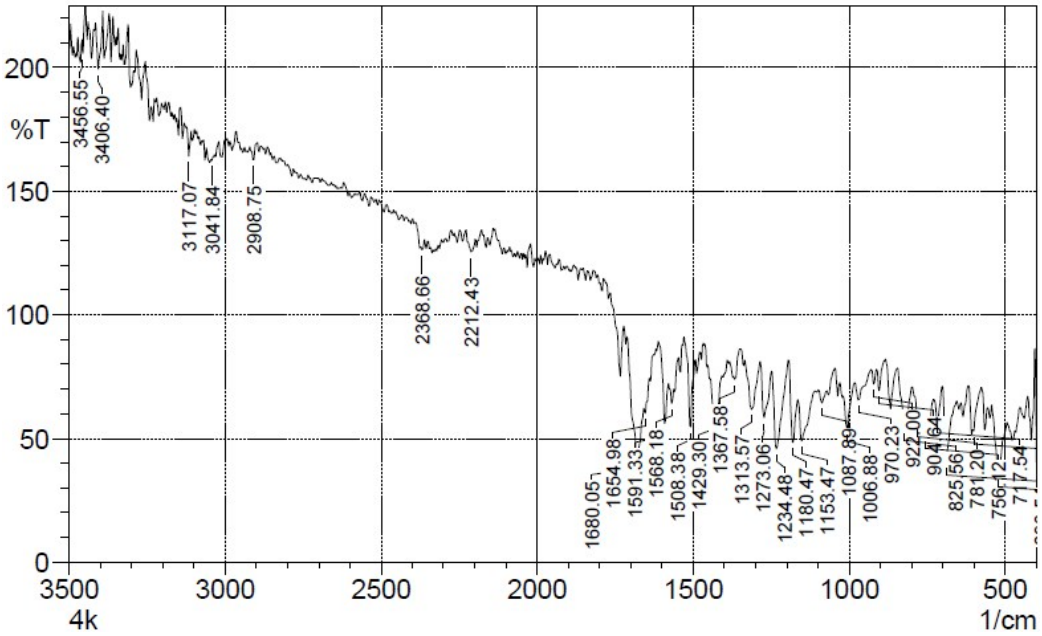


e. Mass spectroscopy

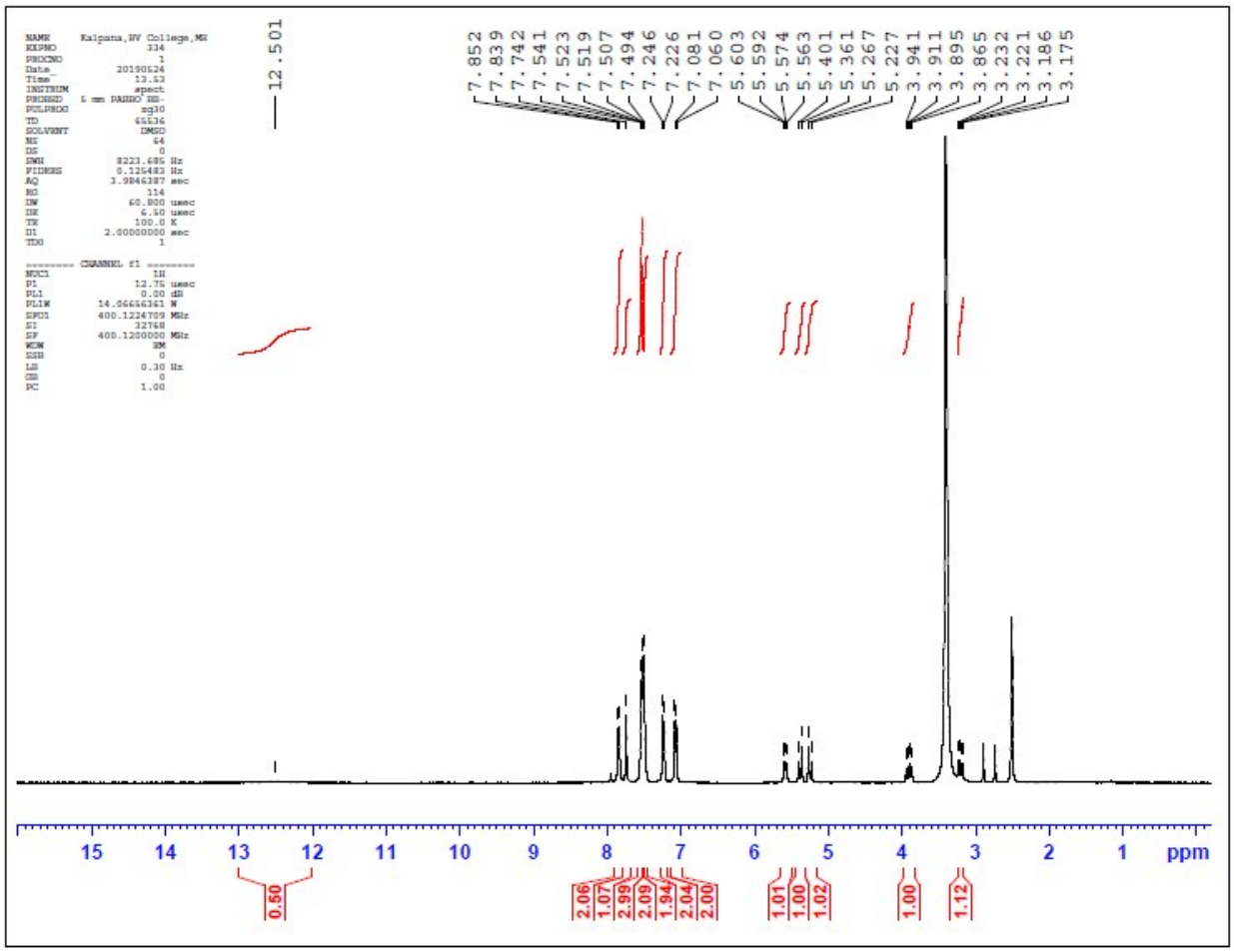


5-(4-(2-(5-(4-bromophenyl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)-2-oxoethoxy)benzylidene) thiazolidine-2,4-dione (13k).

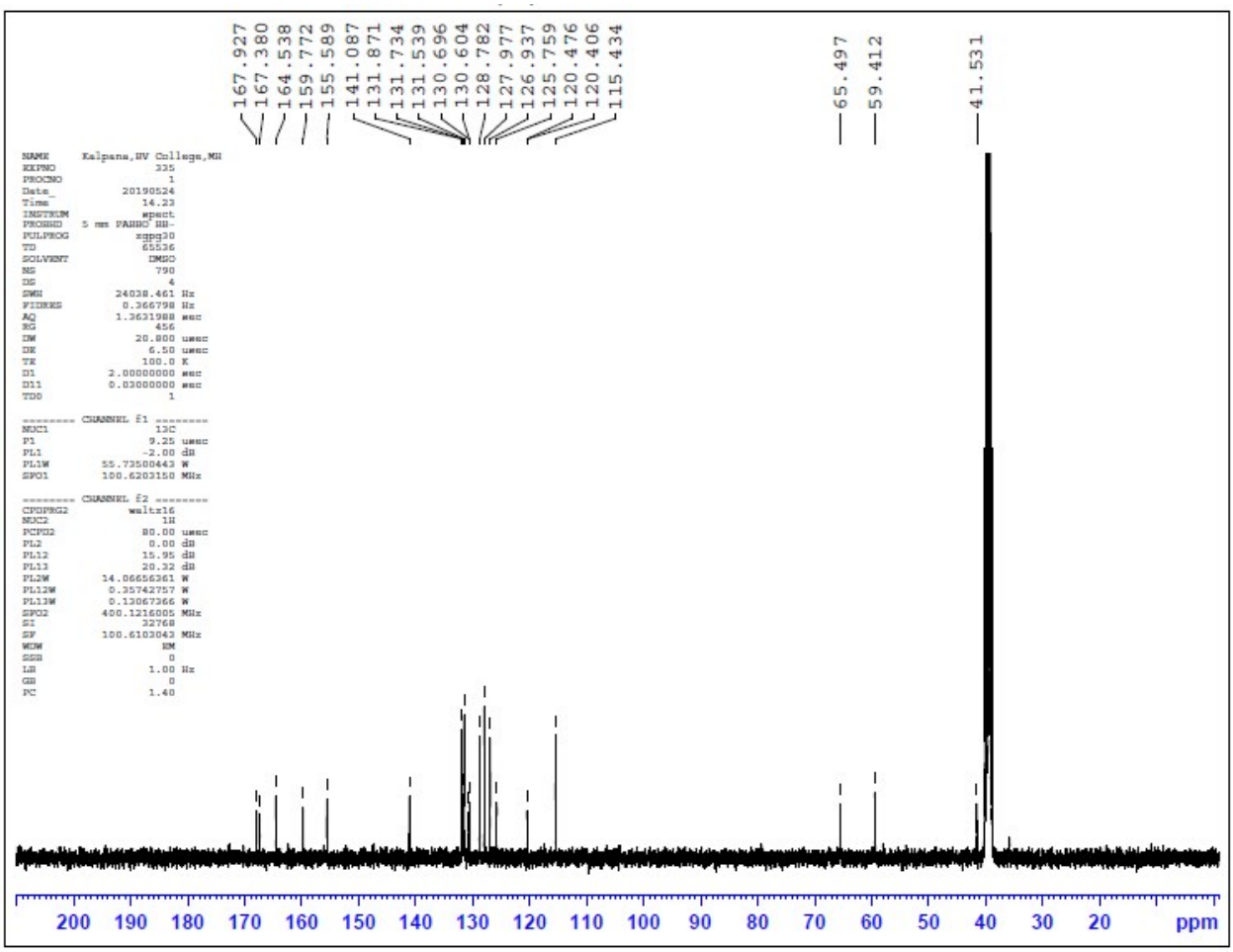
a. FTIR



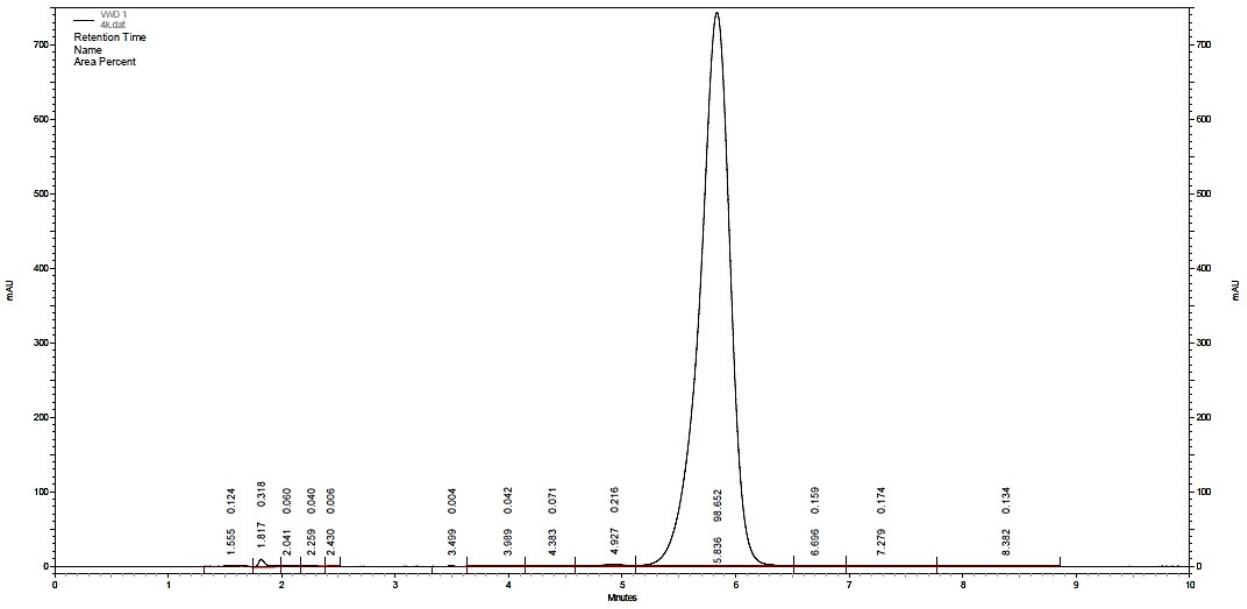
b. ^{1}H-NMR



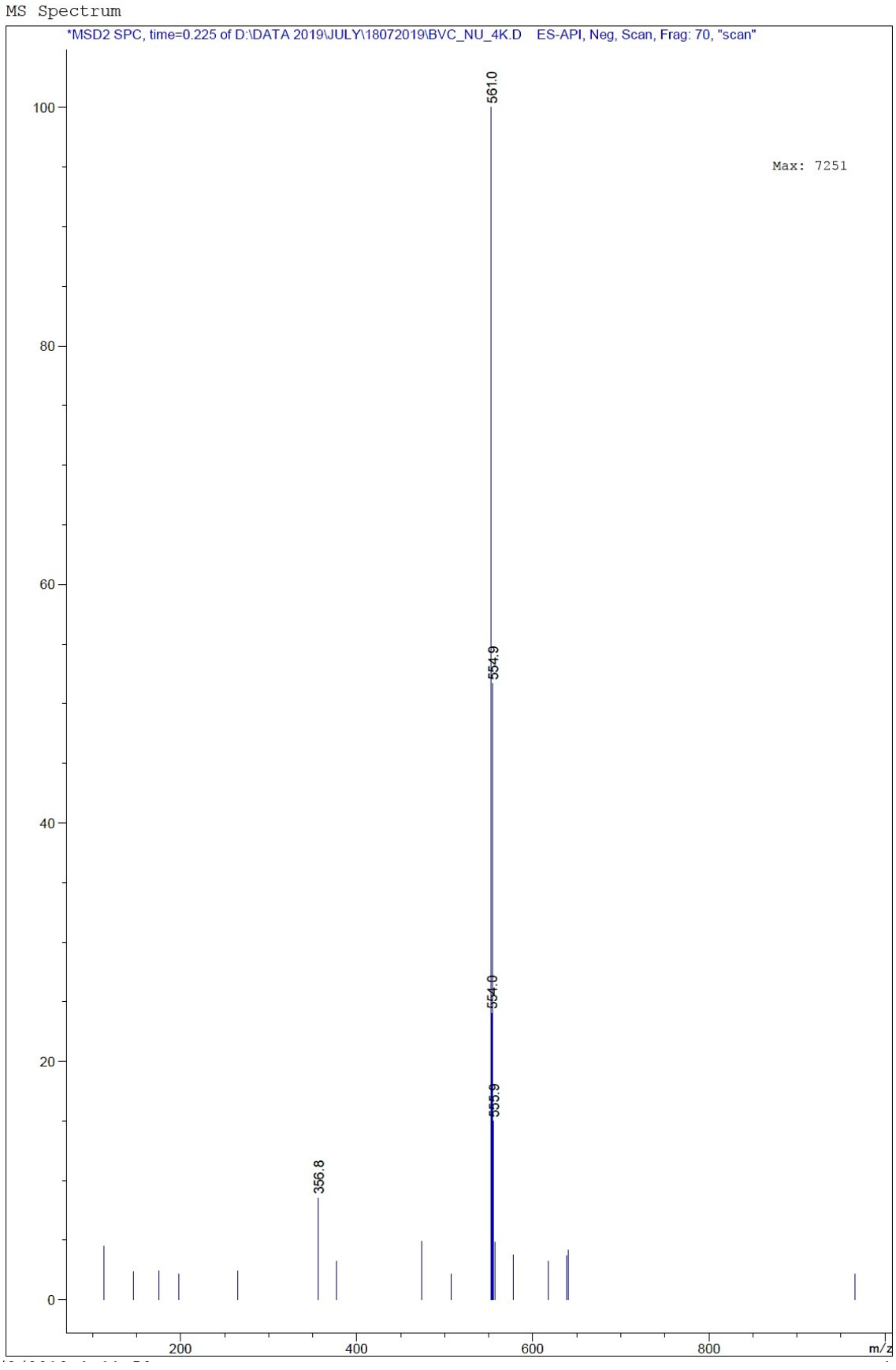
c. ^{13}C-NMR



d. HPLC

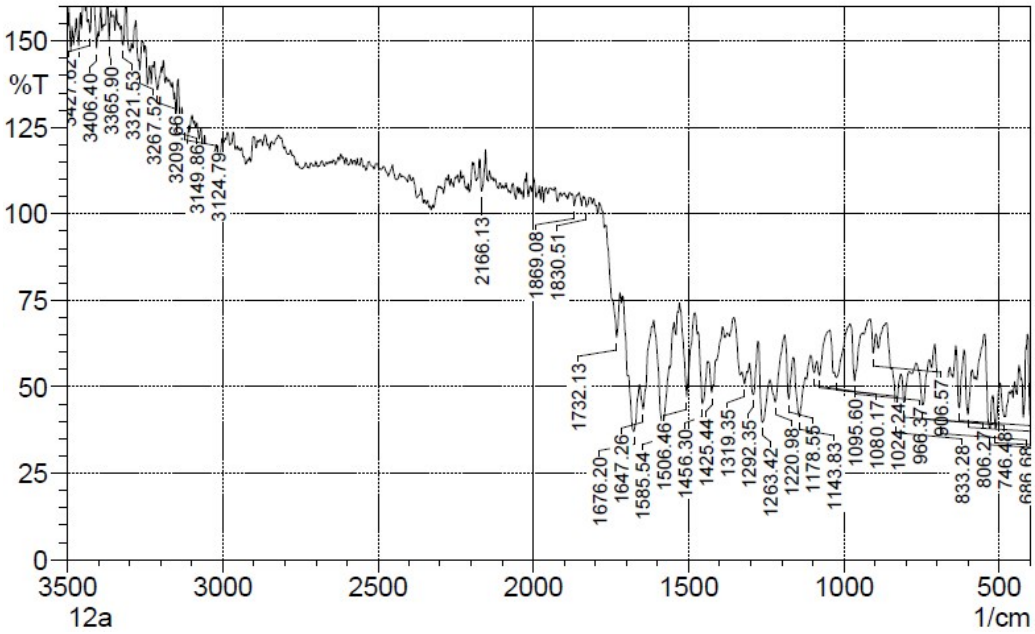


e. Mass spectroscopy

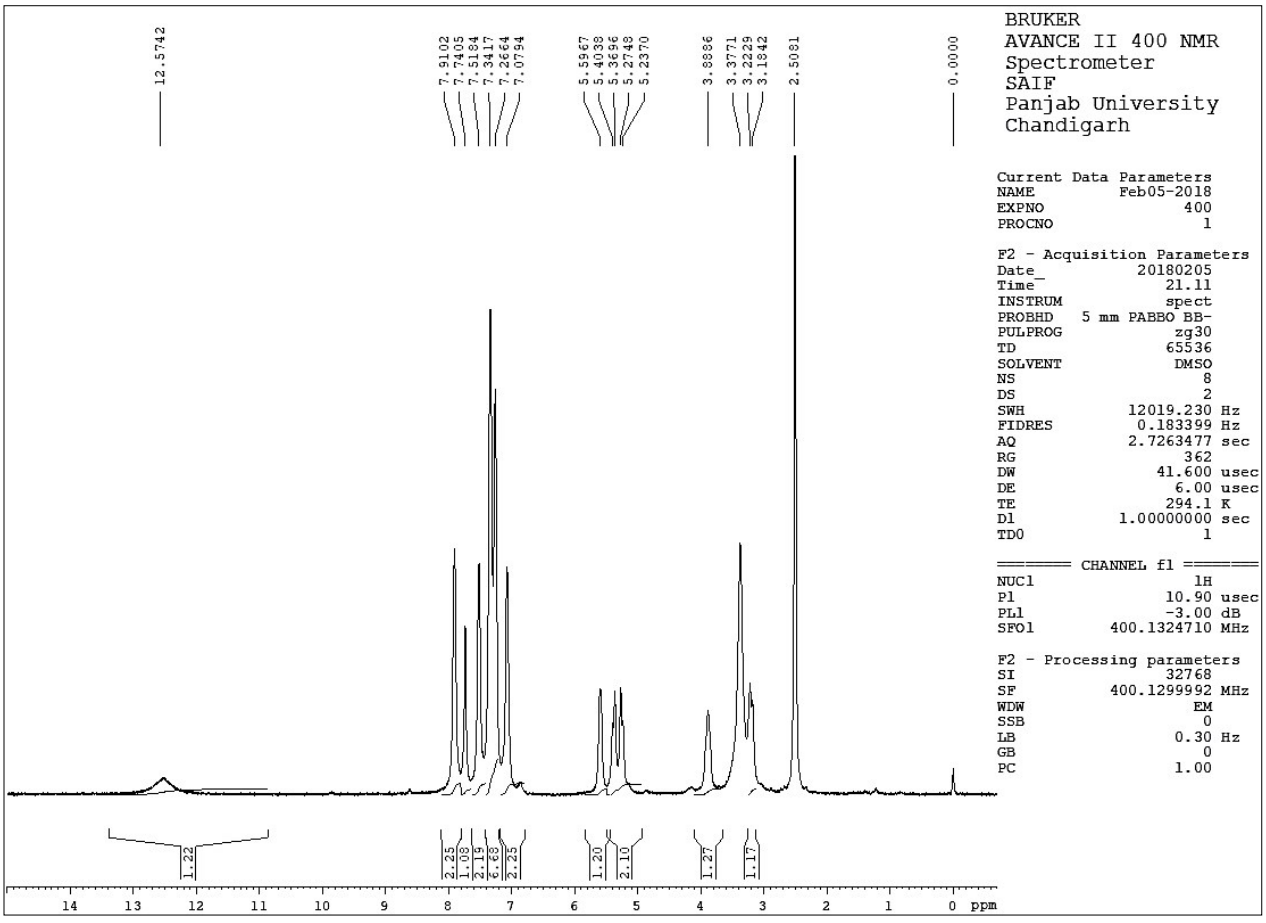


5-(4-(2-(3-(4-fluorophenyl)-5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)-2-oxoethoxy) benzylidene)thiazolidine-2,4-dione (14a).

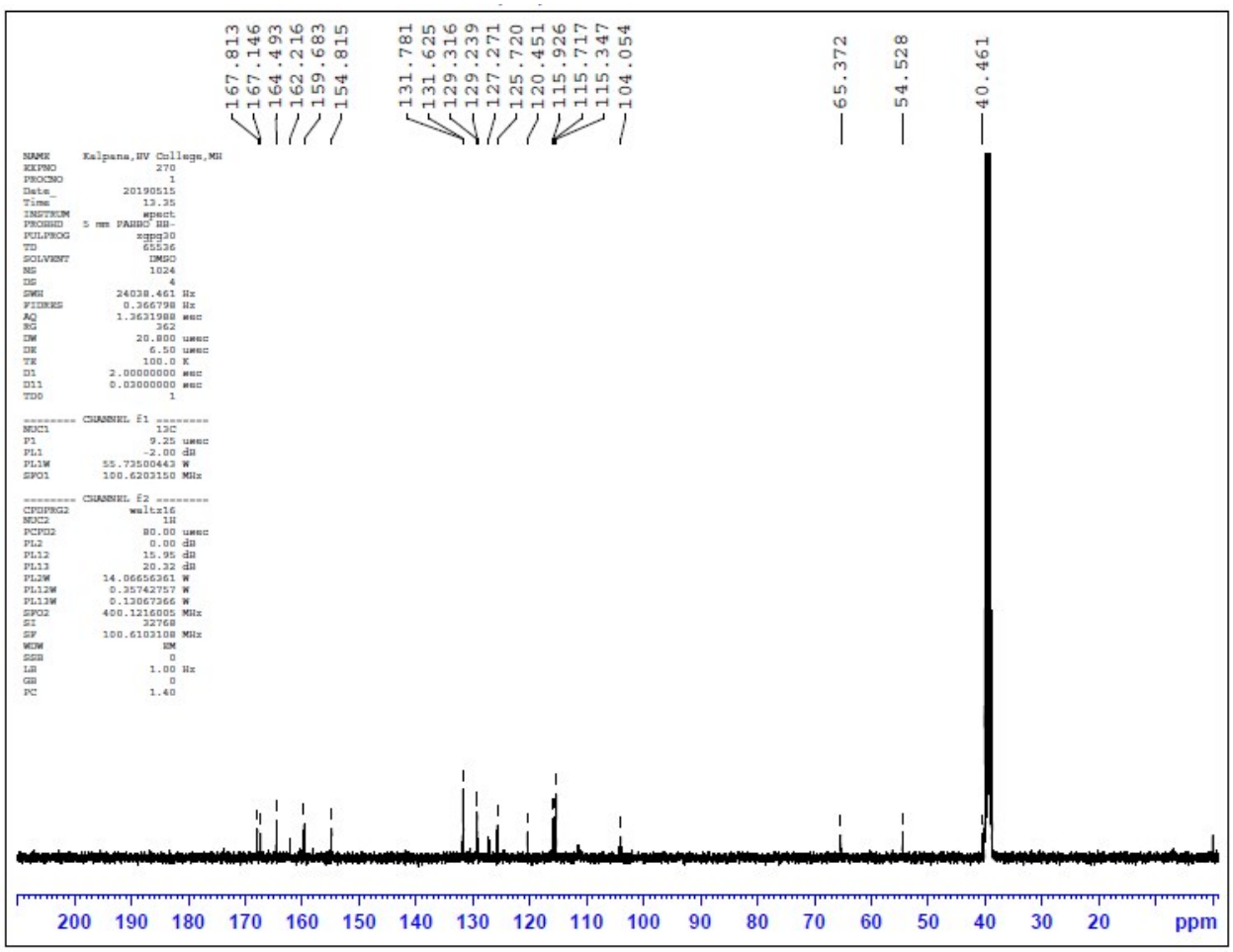
a. FTIR



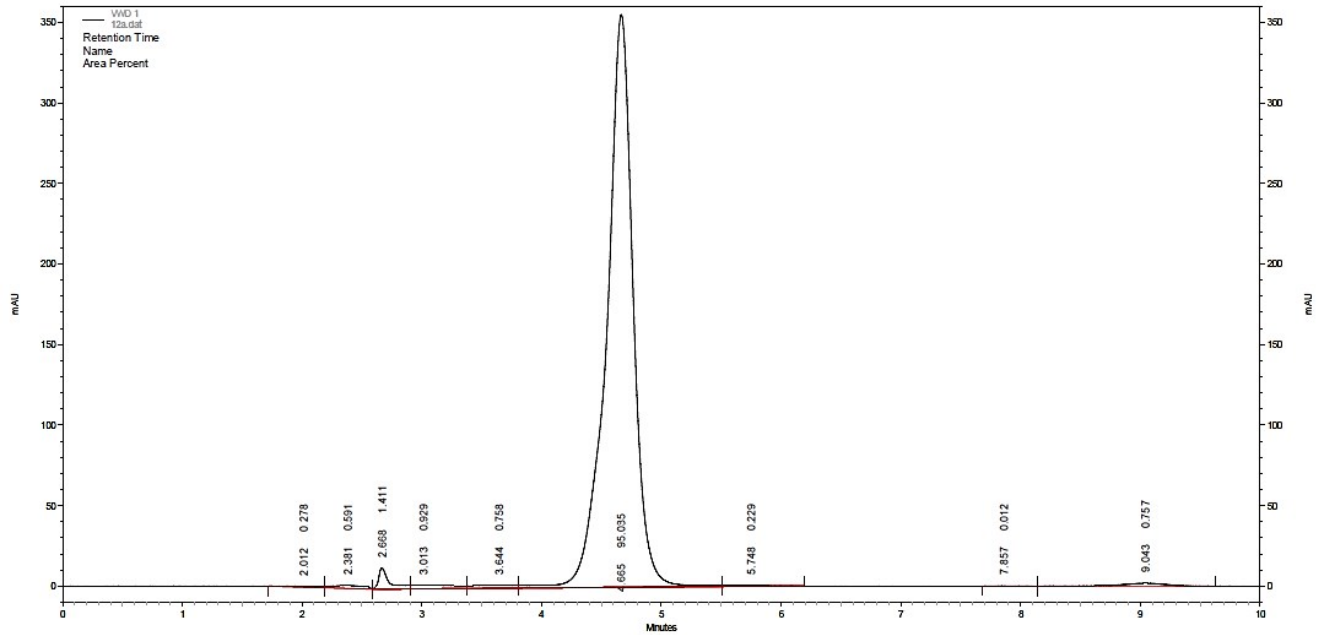
b. ^{1}H-NMR



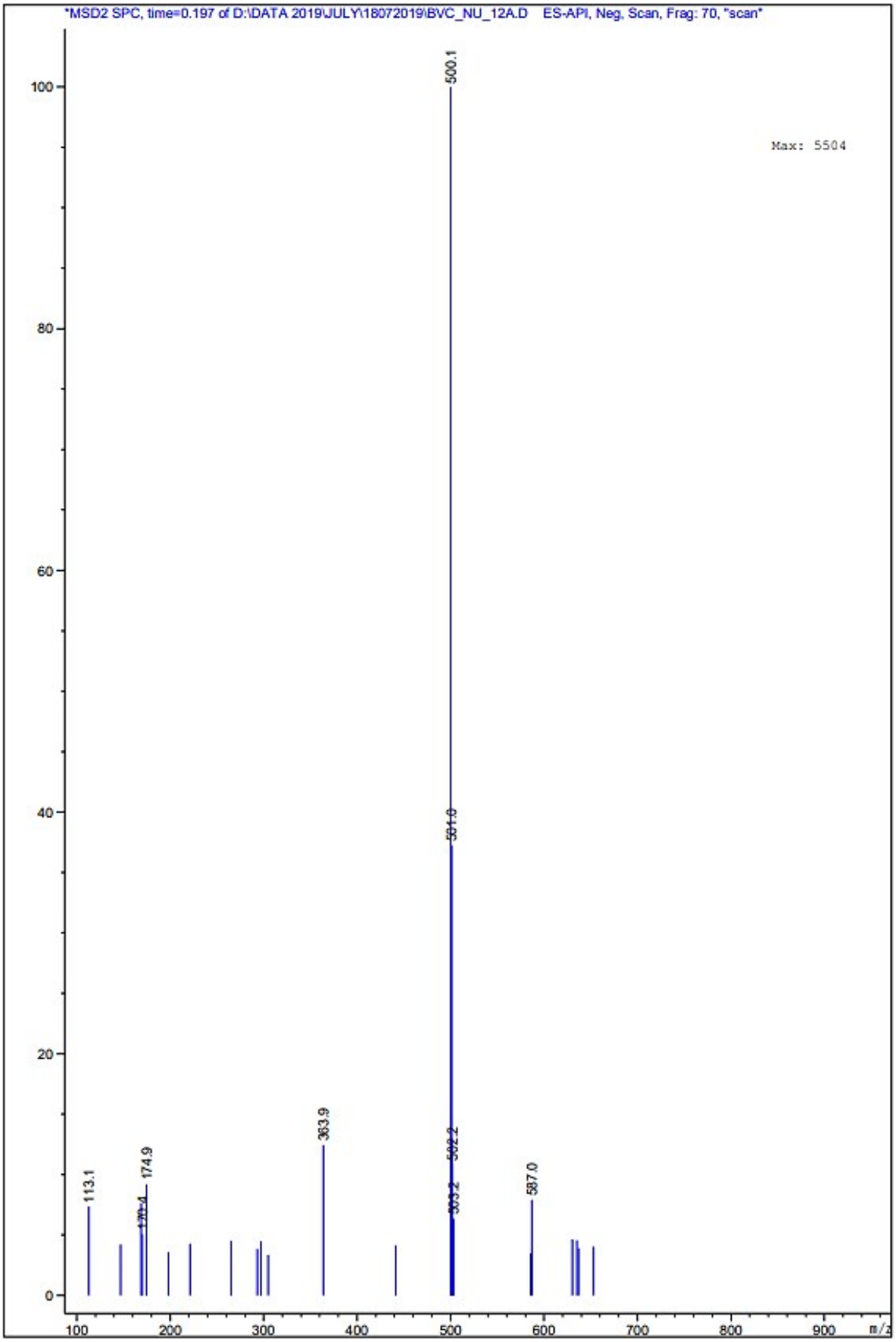
c. ^{13}C-NMR



d. HPLC

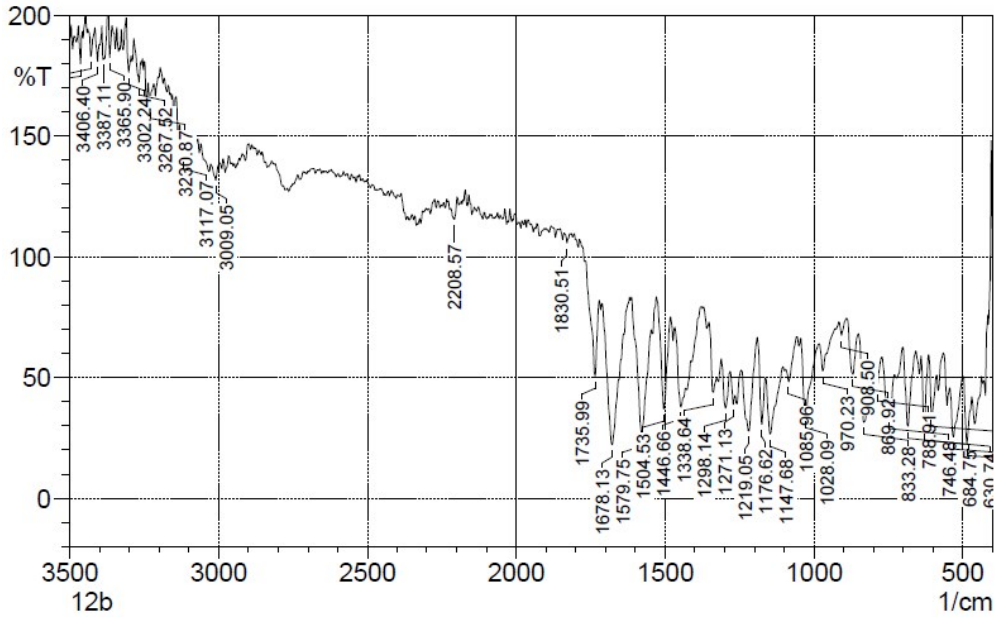


e. Mass spectroscopy

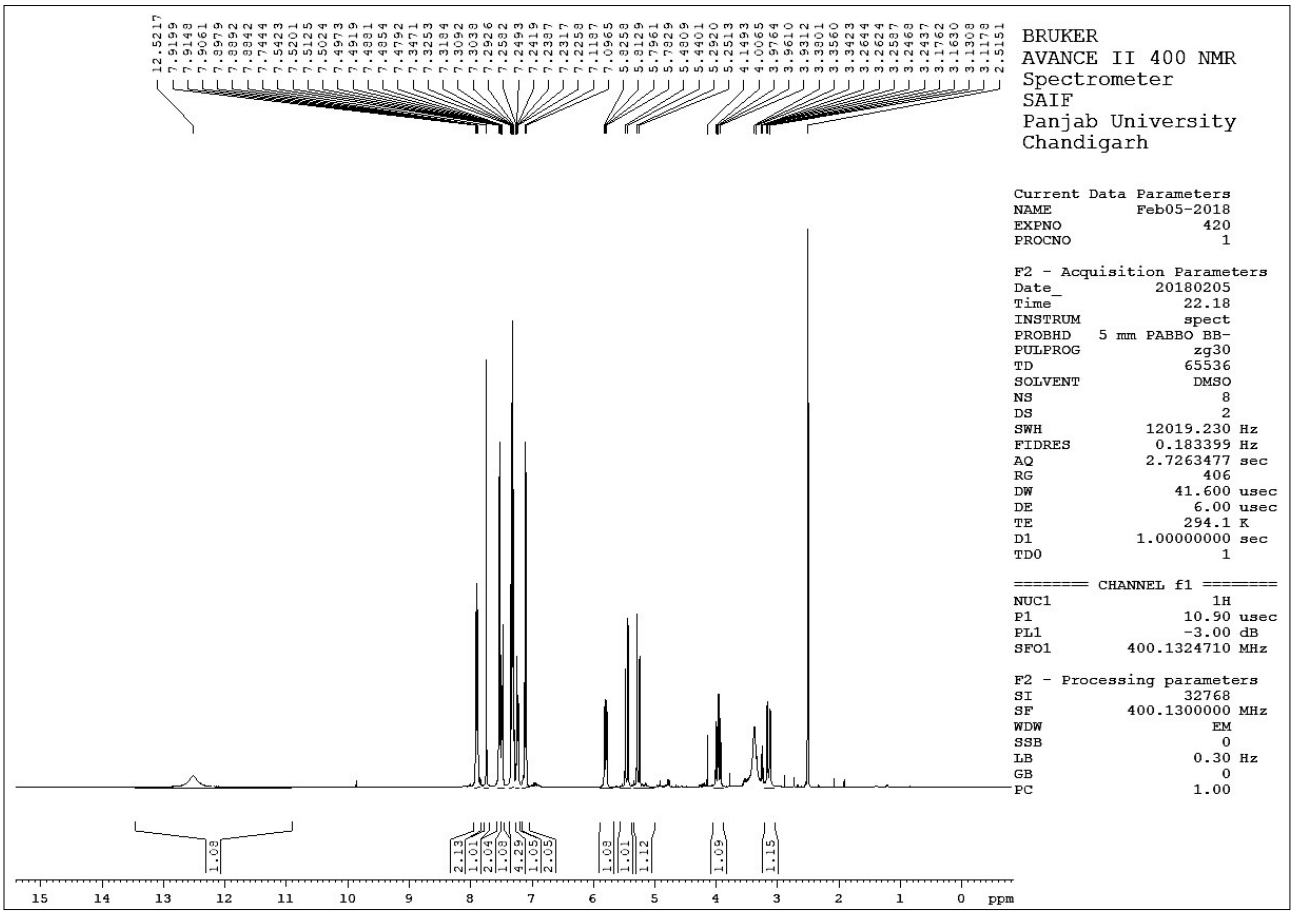


5-(4-(2-(5-(2-chlorophenyl)-3-(4-fluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)-2-oxoethoxy) benzylidene)thiazolidine-2,4-dione (14b).

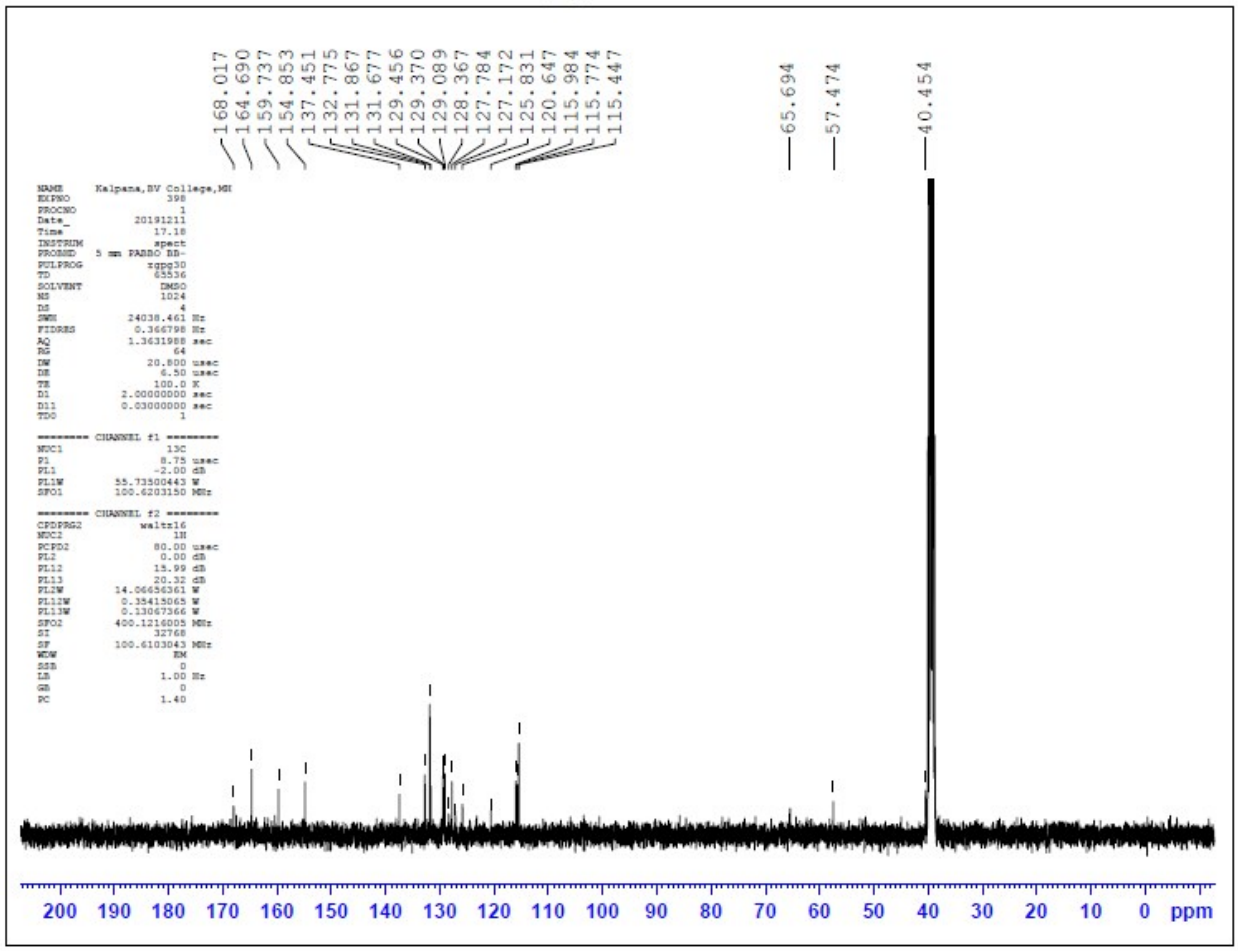
a. FTIR



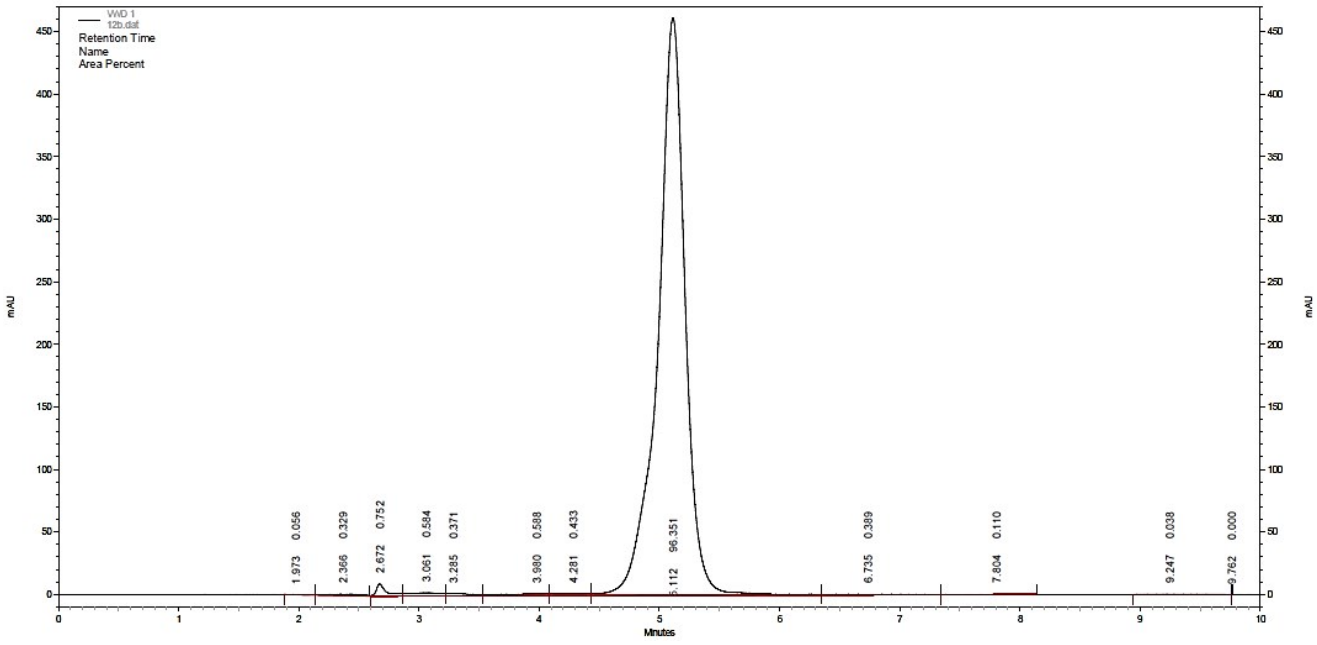
b. ^{1}H-NMR



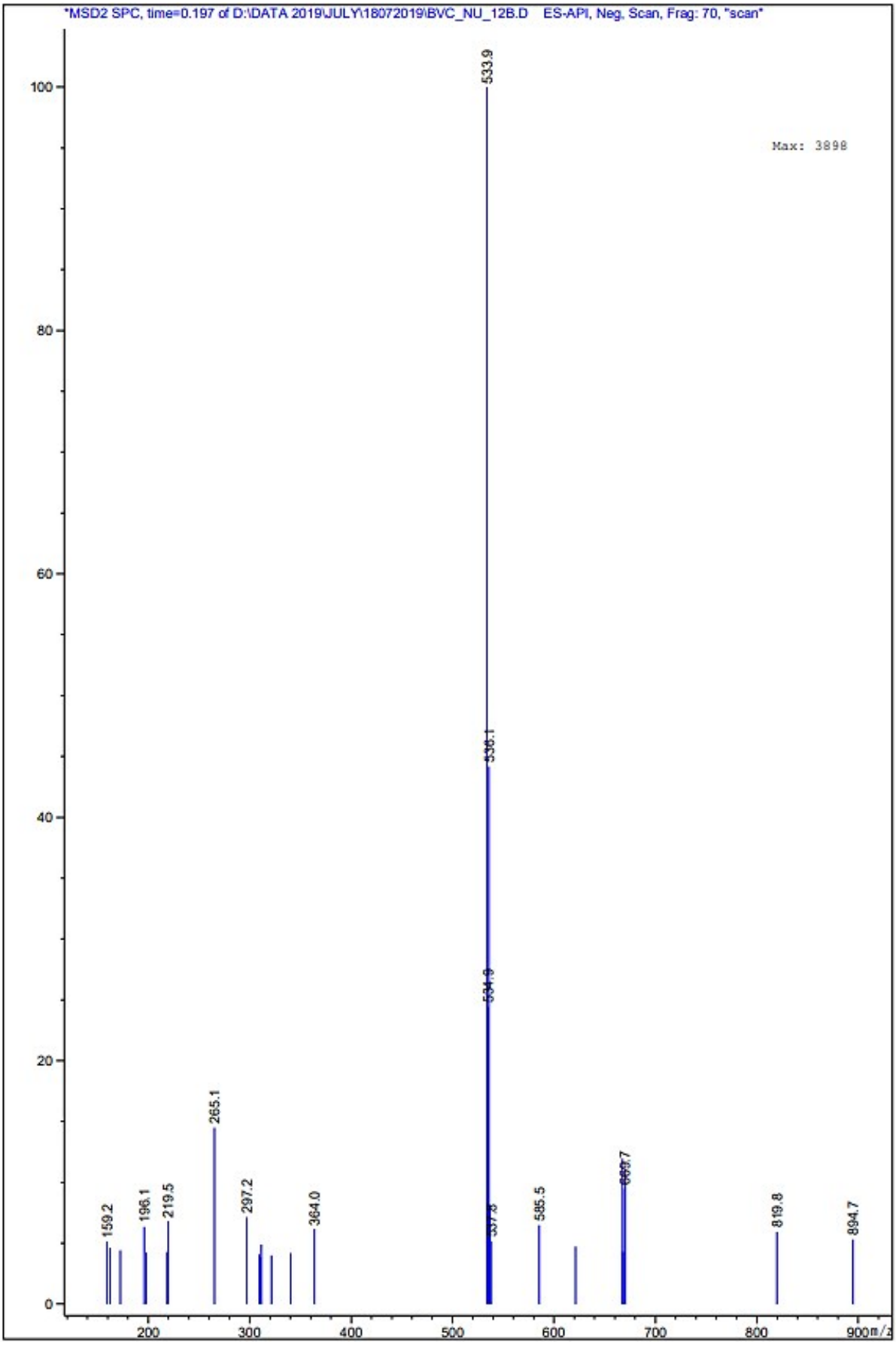
c. ^{13}C-NMR



d. HPLC

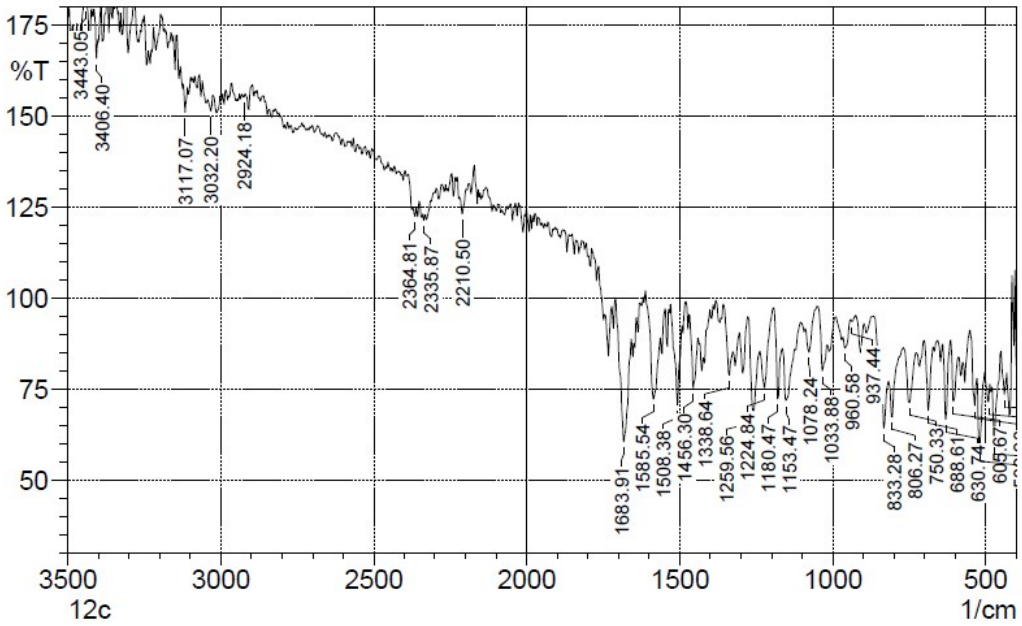


e. Mass spectroscopy

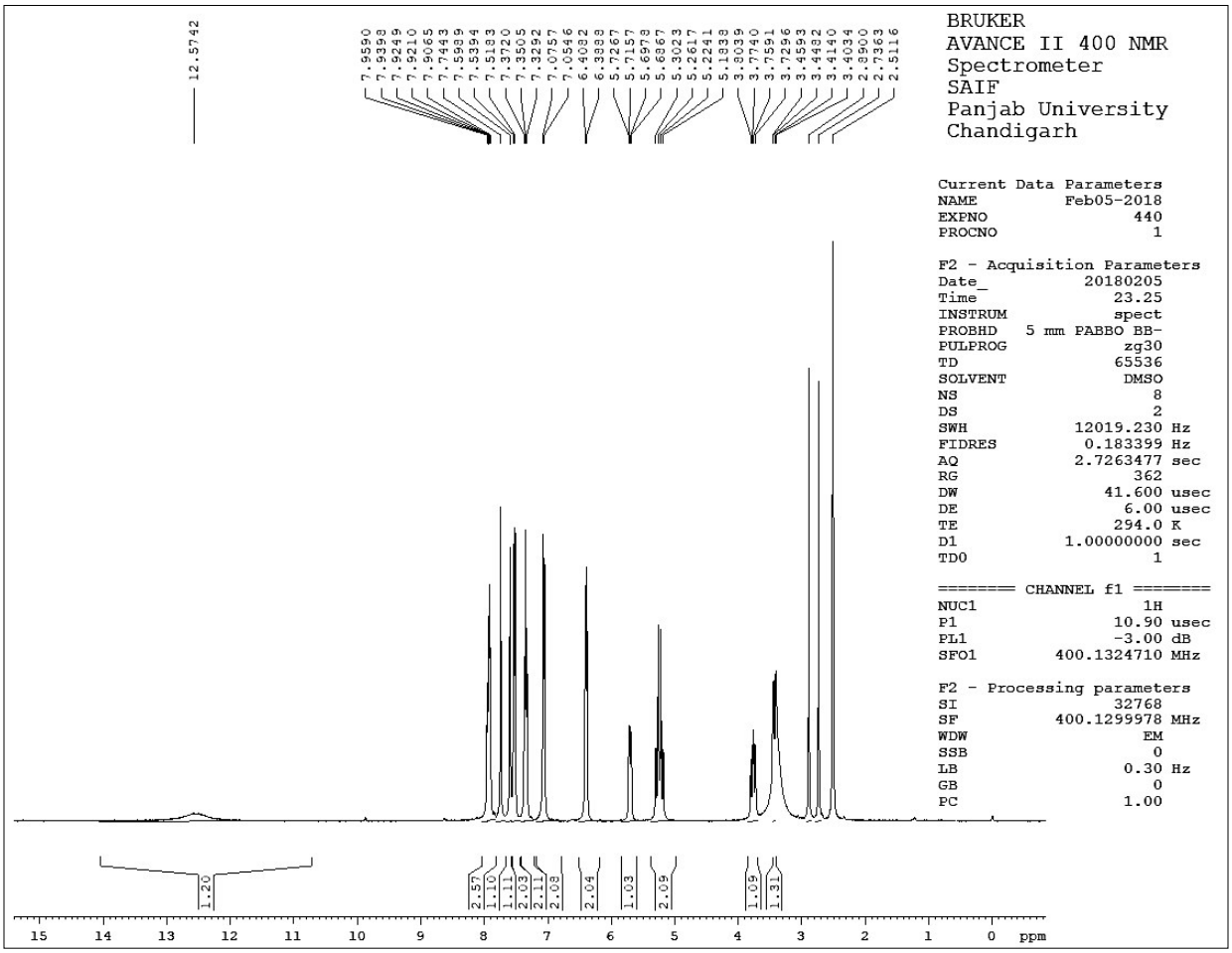


5-(4-(2-(3-(4-fluorophenyl)-5-(furan-2-yl)-4,5-dihydro-1H-pyrazol-1-yl)-2-oxoethoxy) benzylidene)thiazolidine-2,4-dione (14c).

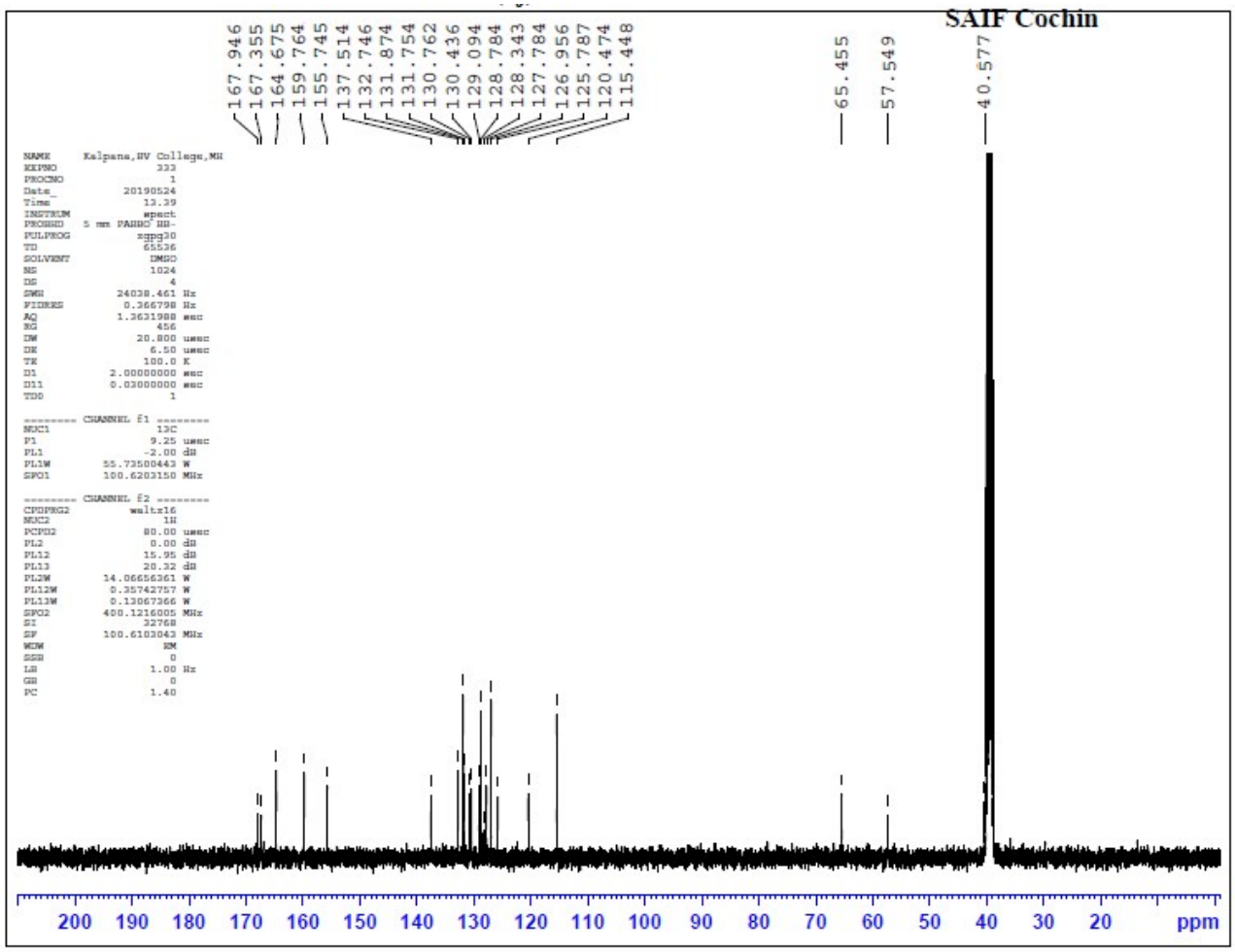
a. FTIR



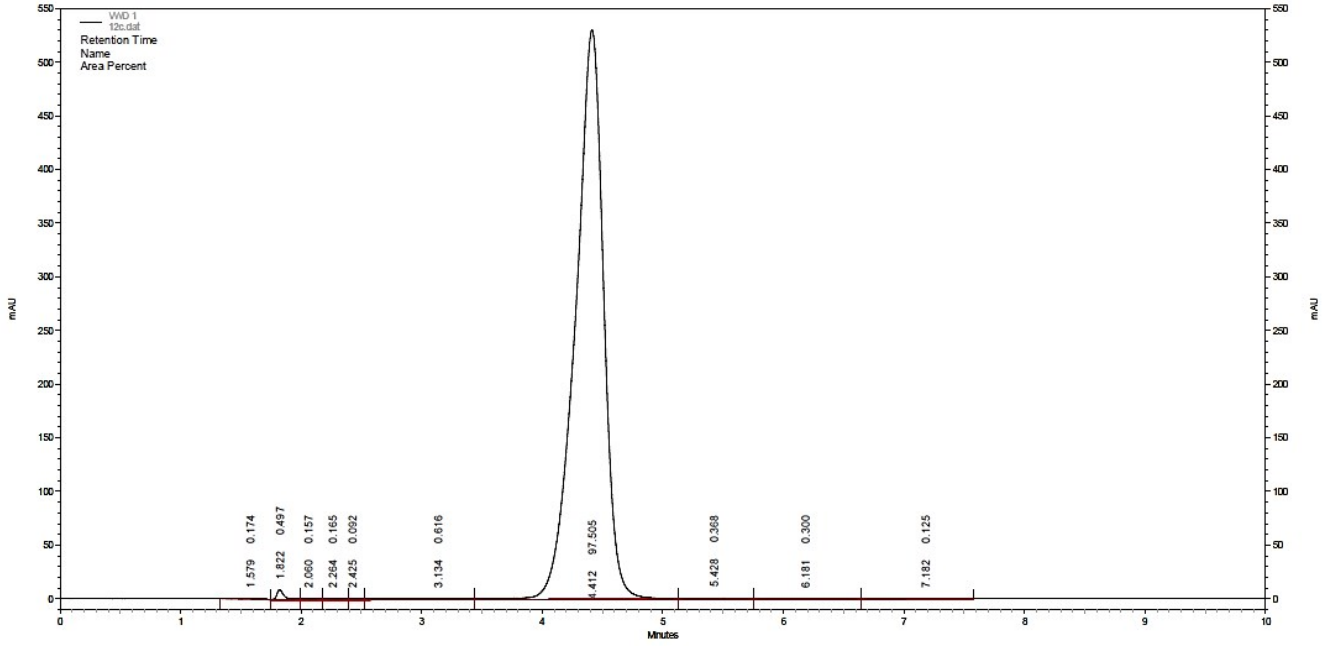
b. ^{1}H-NMR



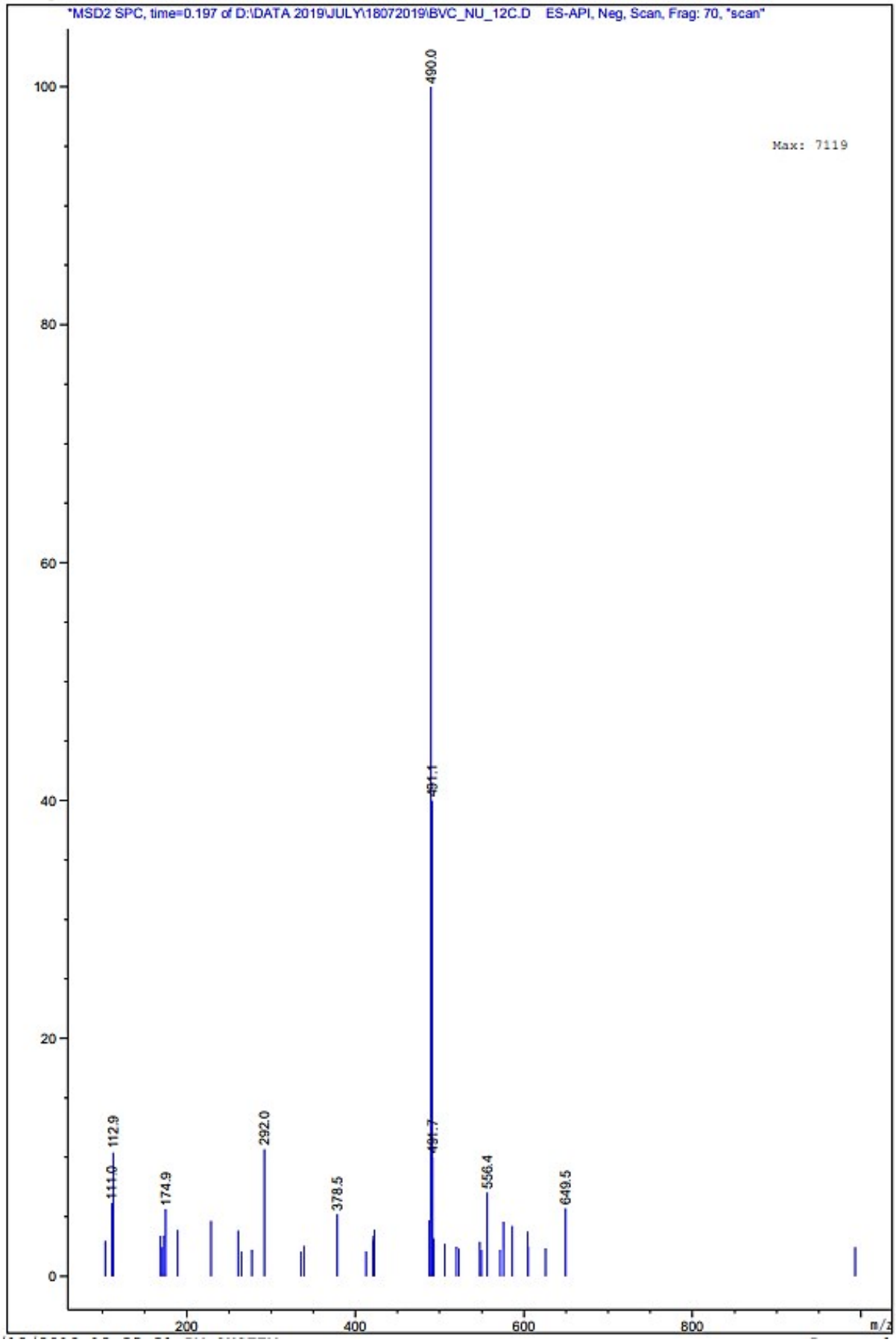
c. ^{13}C-NMR



d. HPLC

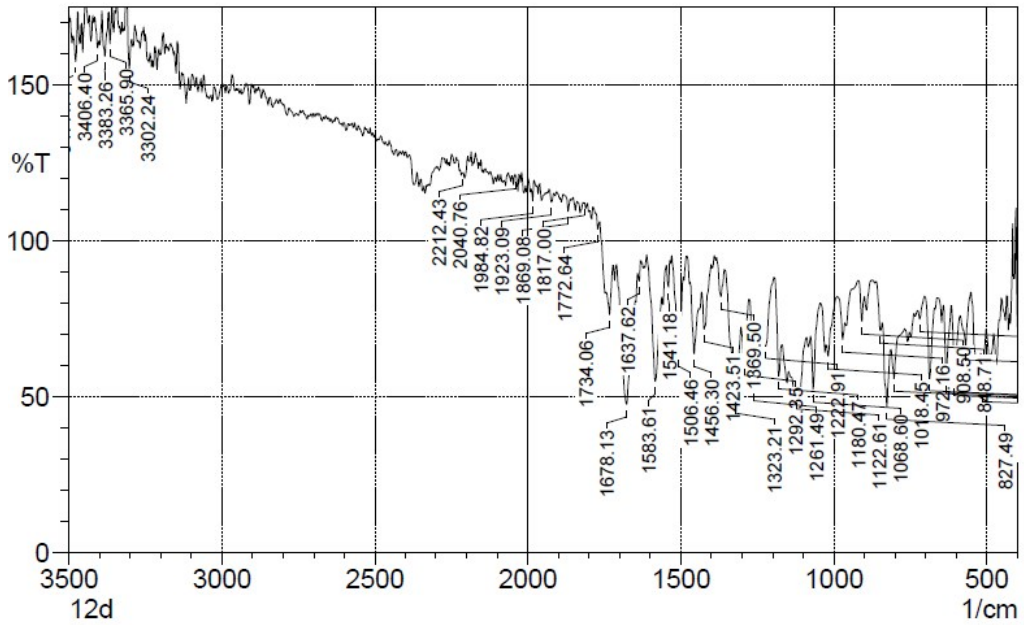


e. Mass spectroscopy

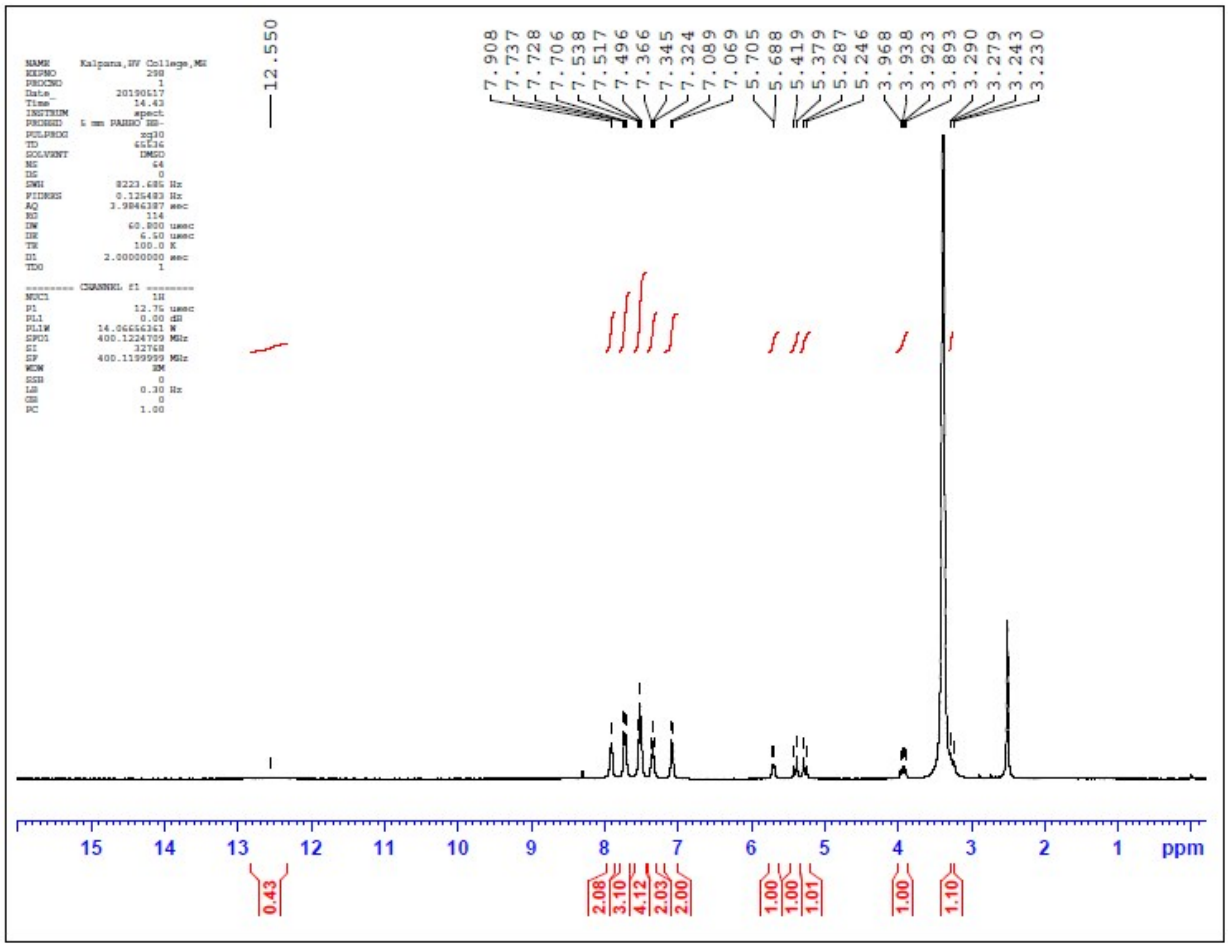


5-(4-(2-(3-(4-fluorophenyl)-5-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1H-pyrazol-1-yl)-2-oxoethoxy)benzylidene)thiazolidine-2,4-dione (14d).

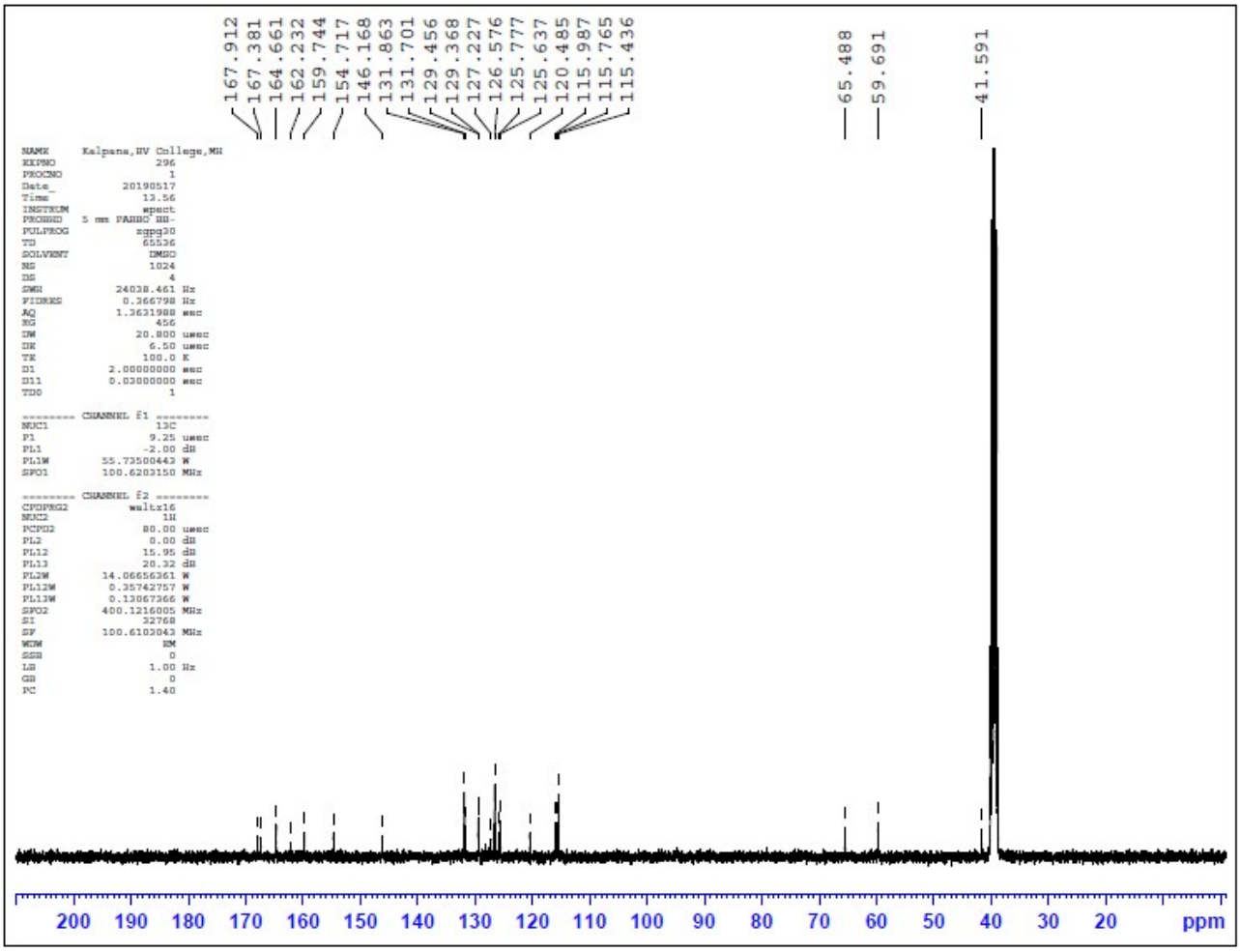
a. FTIR



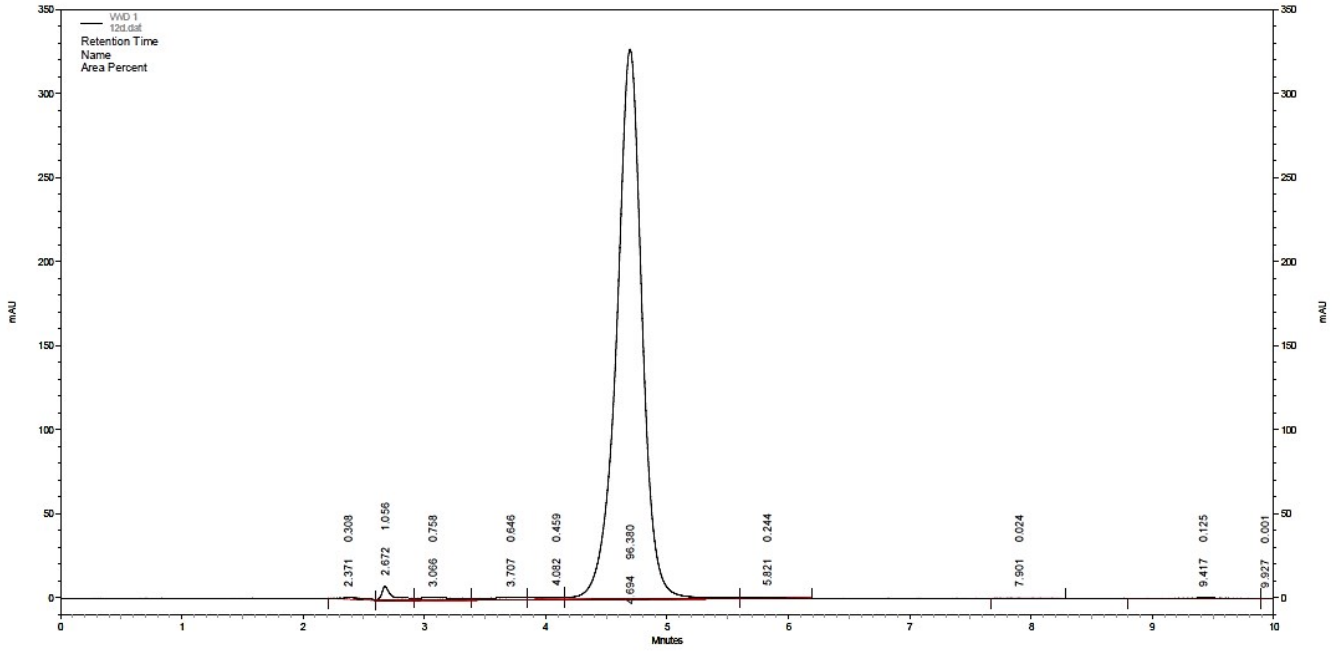
b. ^{1}H-NMR



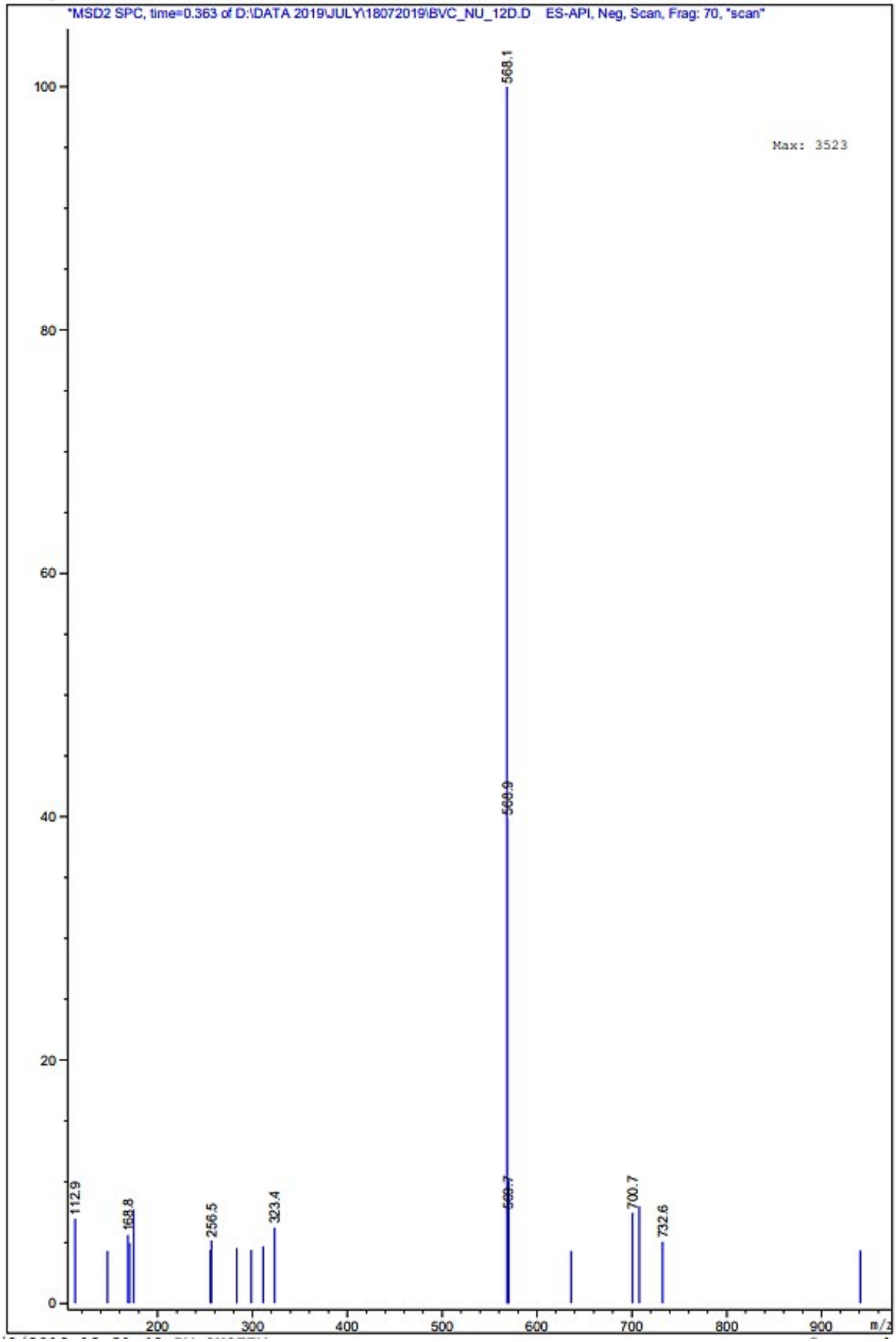
c. ^{13}C-NMR



d. HPLC

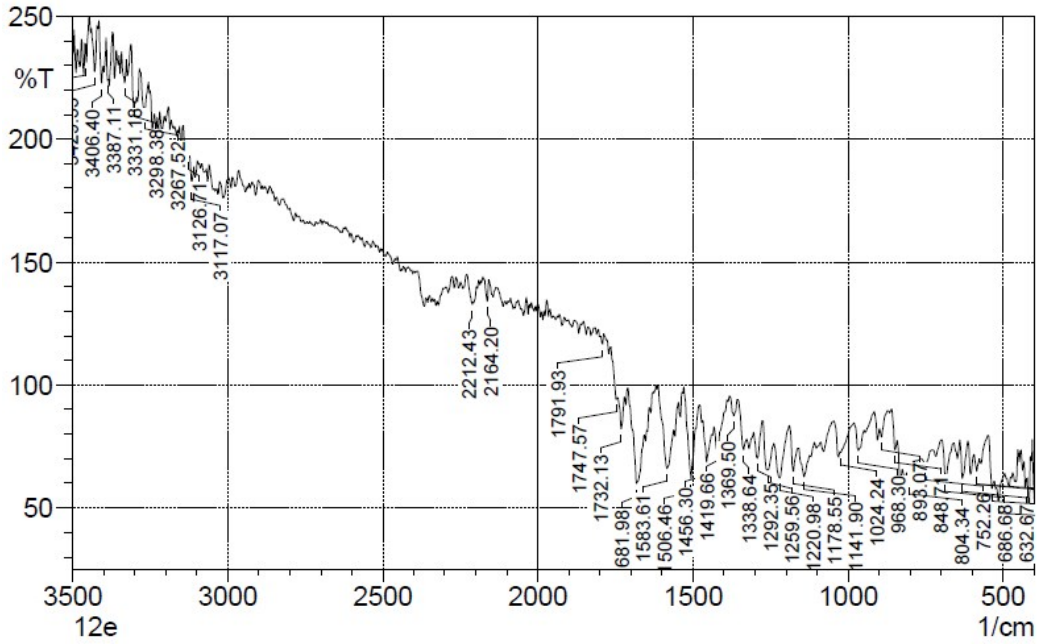


e. Mass spectroscopy

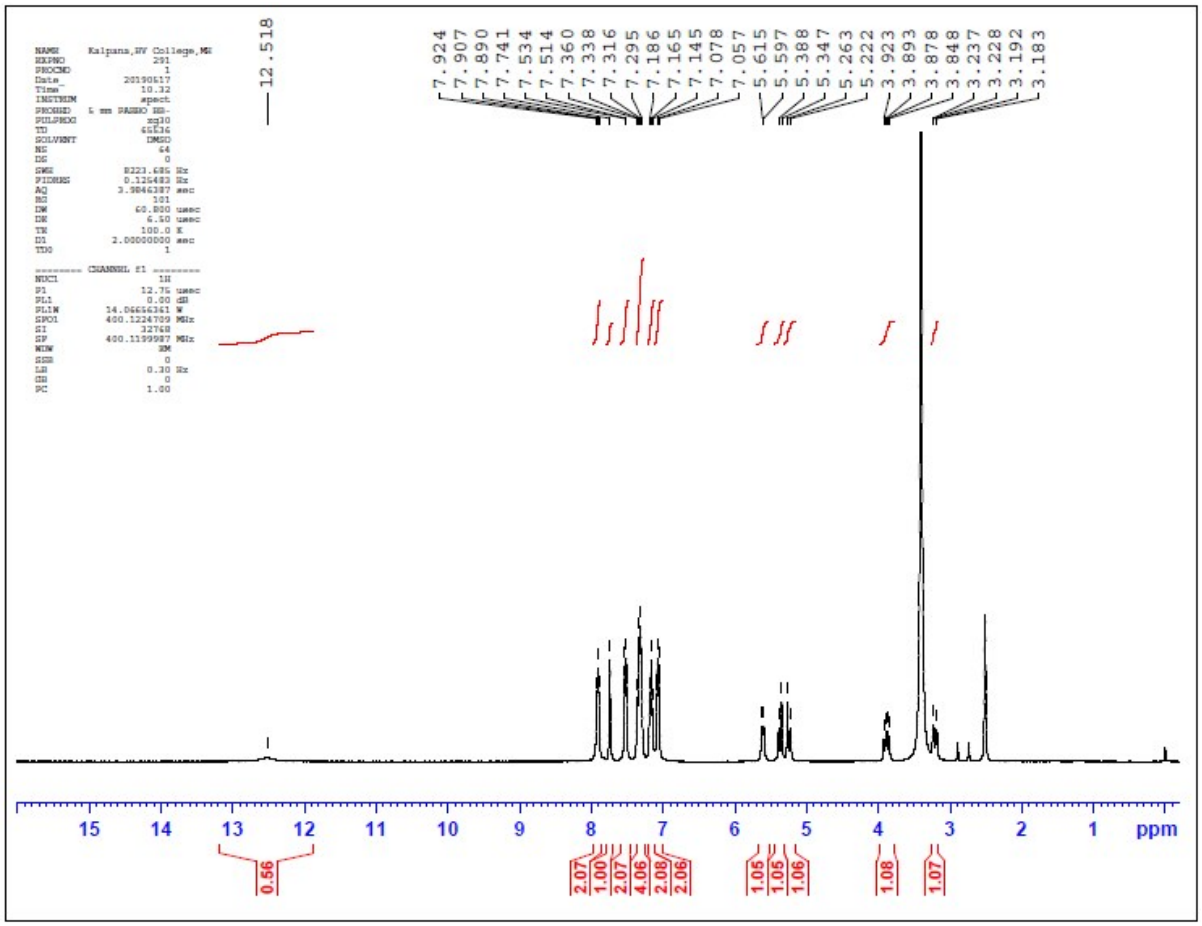


5-(4-(2-(3,5-bis(4-fluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)-2-oxoethoxy)benzylidene) thiazolidine-2,4-dione (14e).

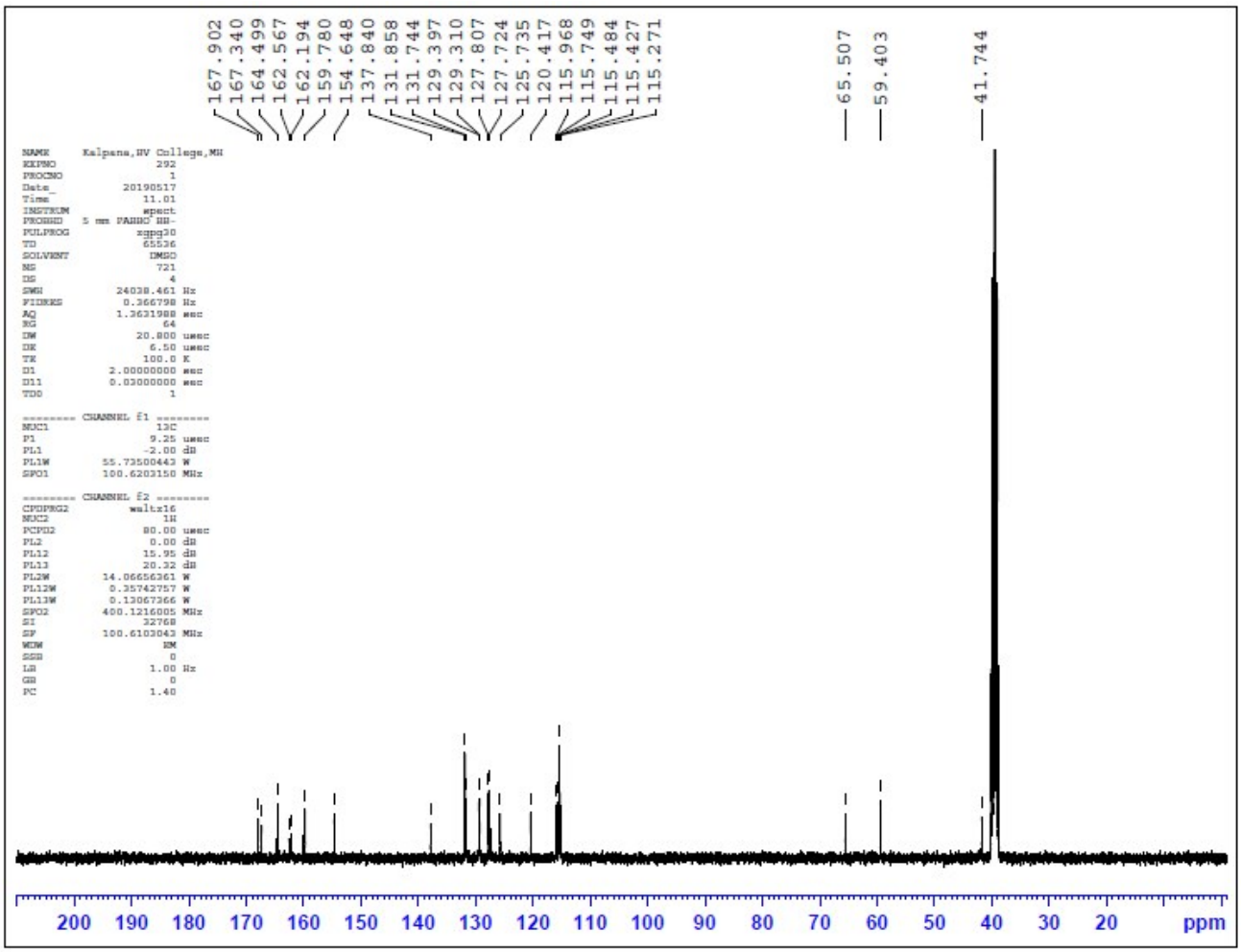
a. FTIR



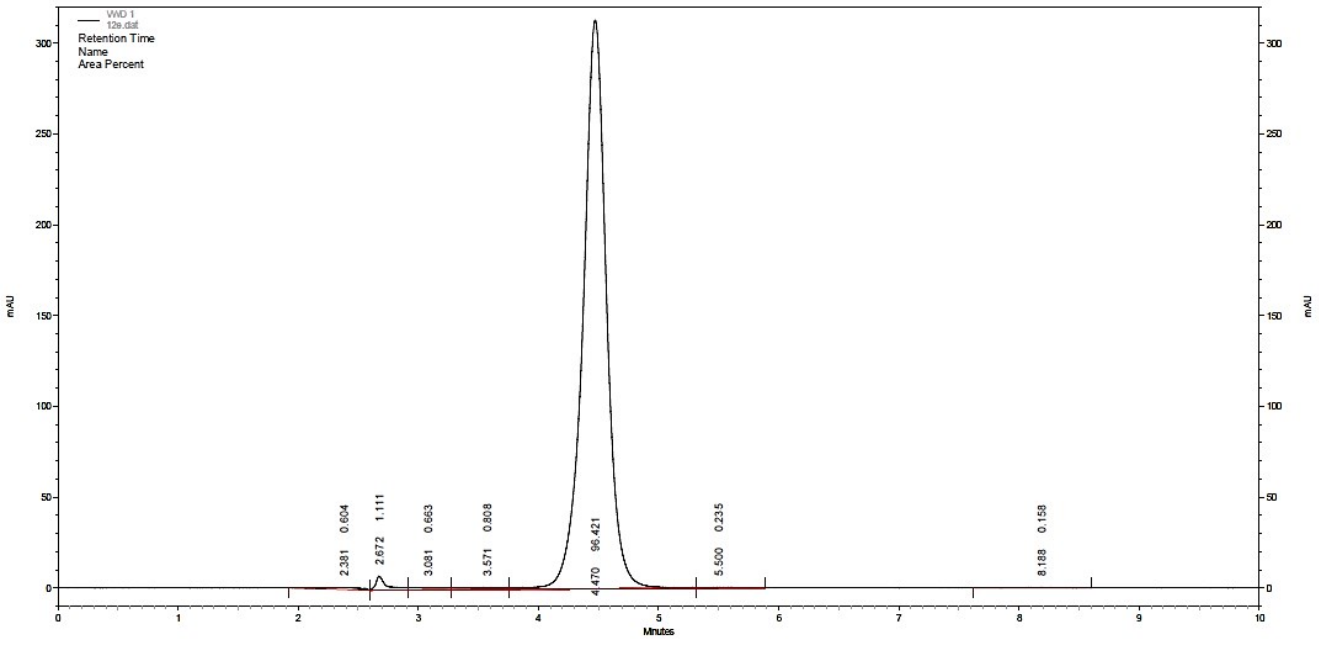
b. ^{1}H-NMR



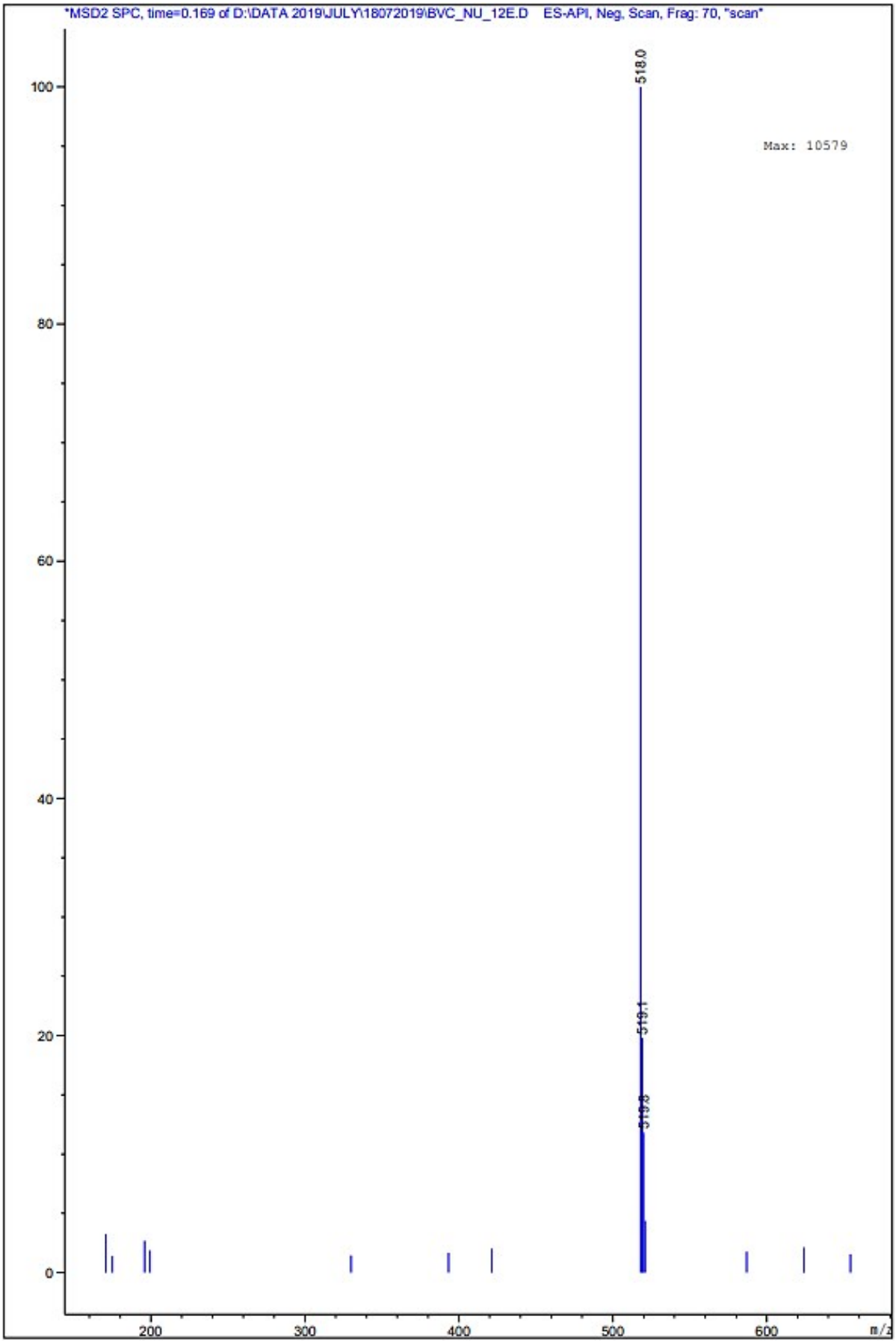
c. ^{13}C-NMR



d. HPLC

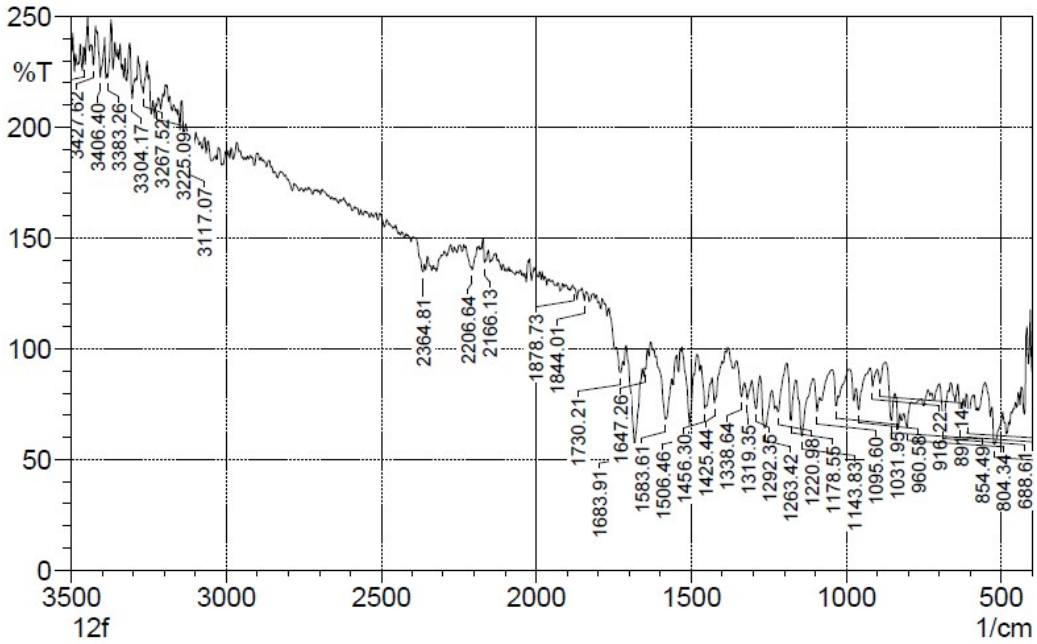


e. Mass spectroscopy

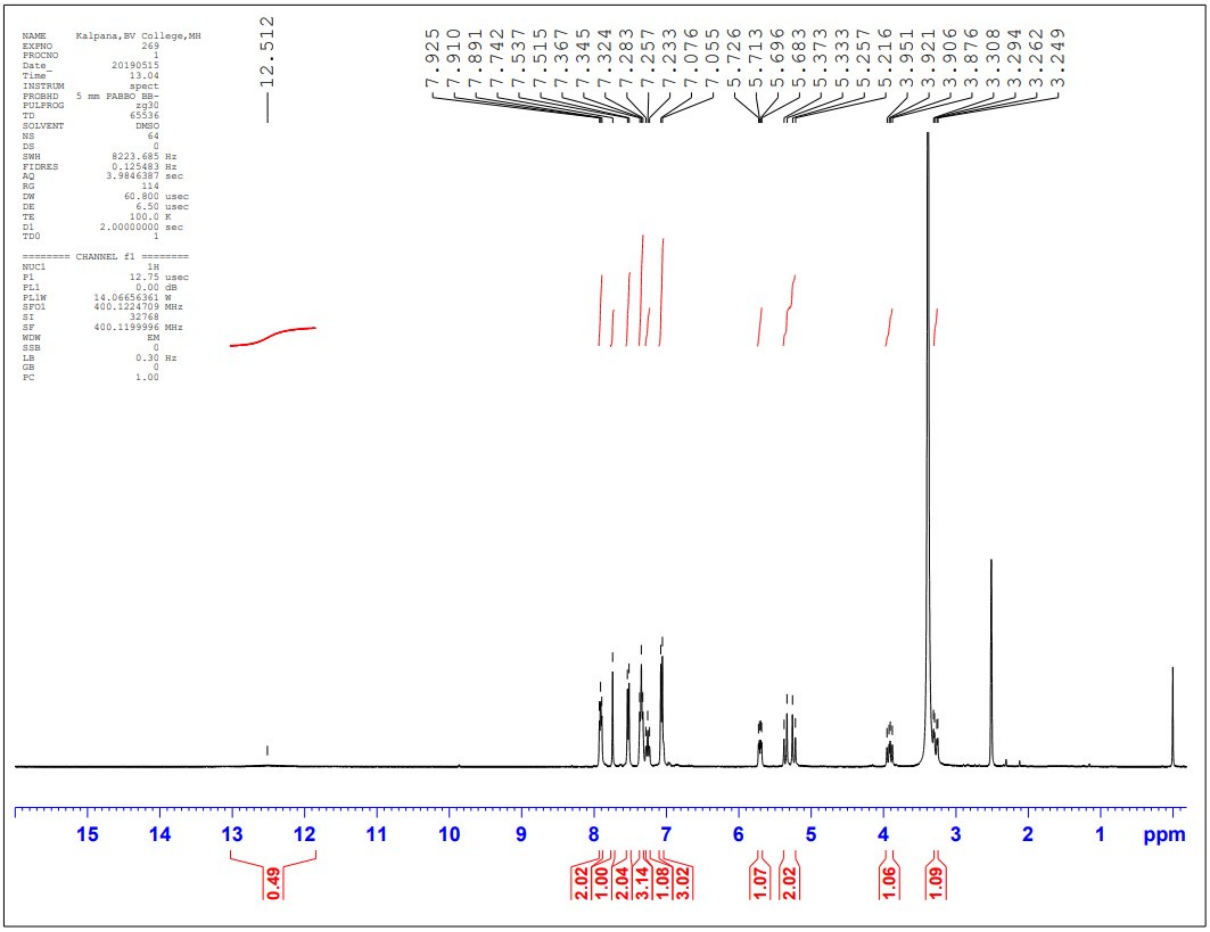


5-(4-(2-(5-(2,4-difluorophenyl)-3-(4-fluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)-2-oxoethoxy)benzylidene) thiazolidine-2,4-dione (14f).

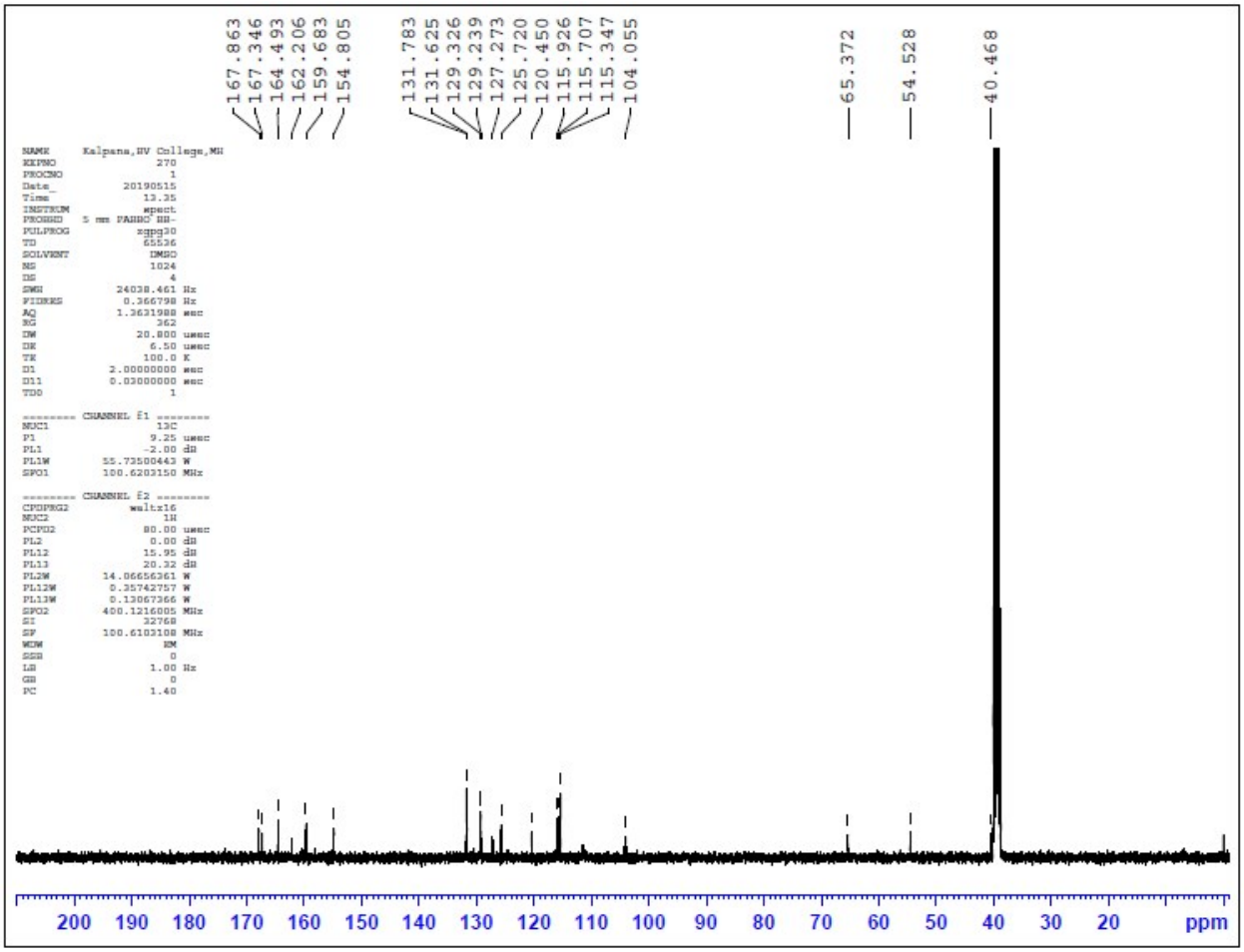
a. FTIR



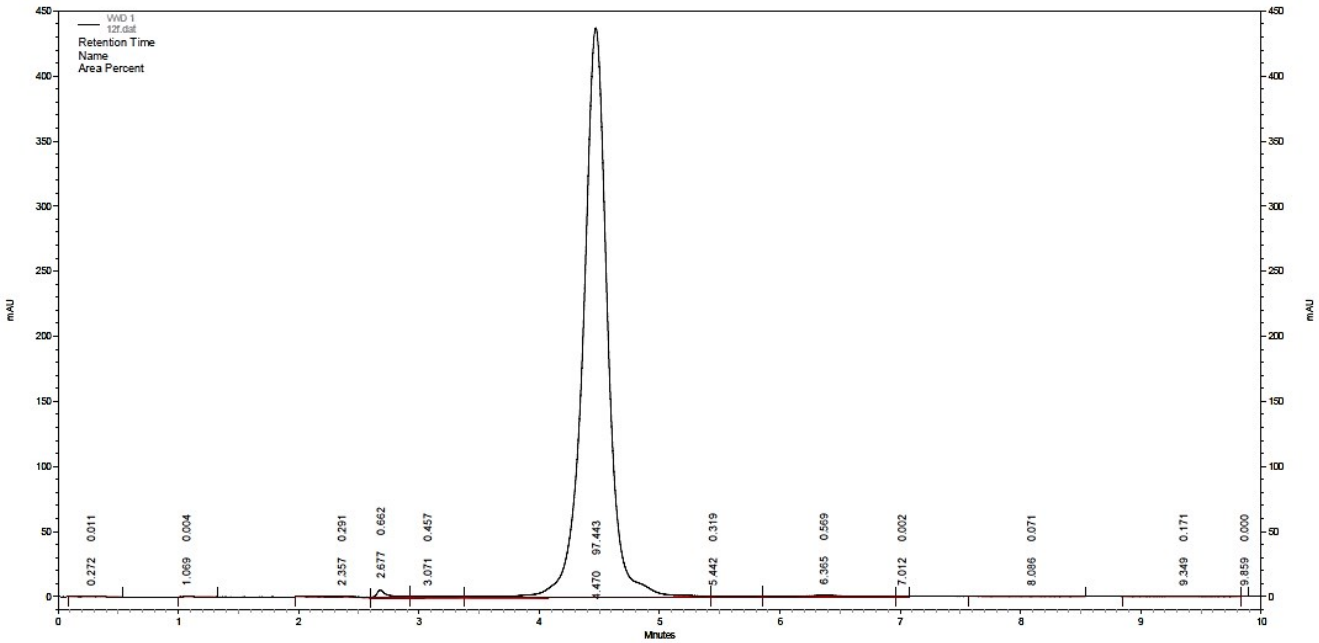
b. ^{1}H-NMR



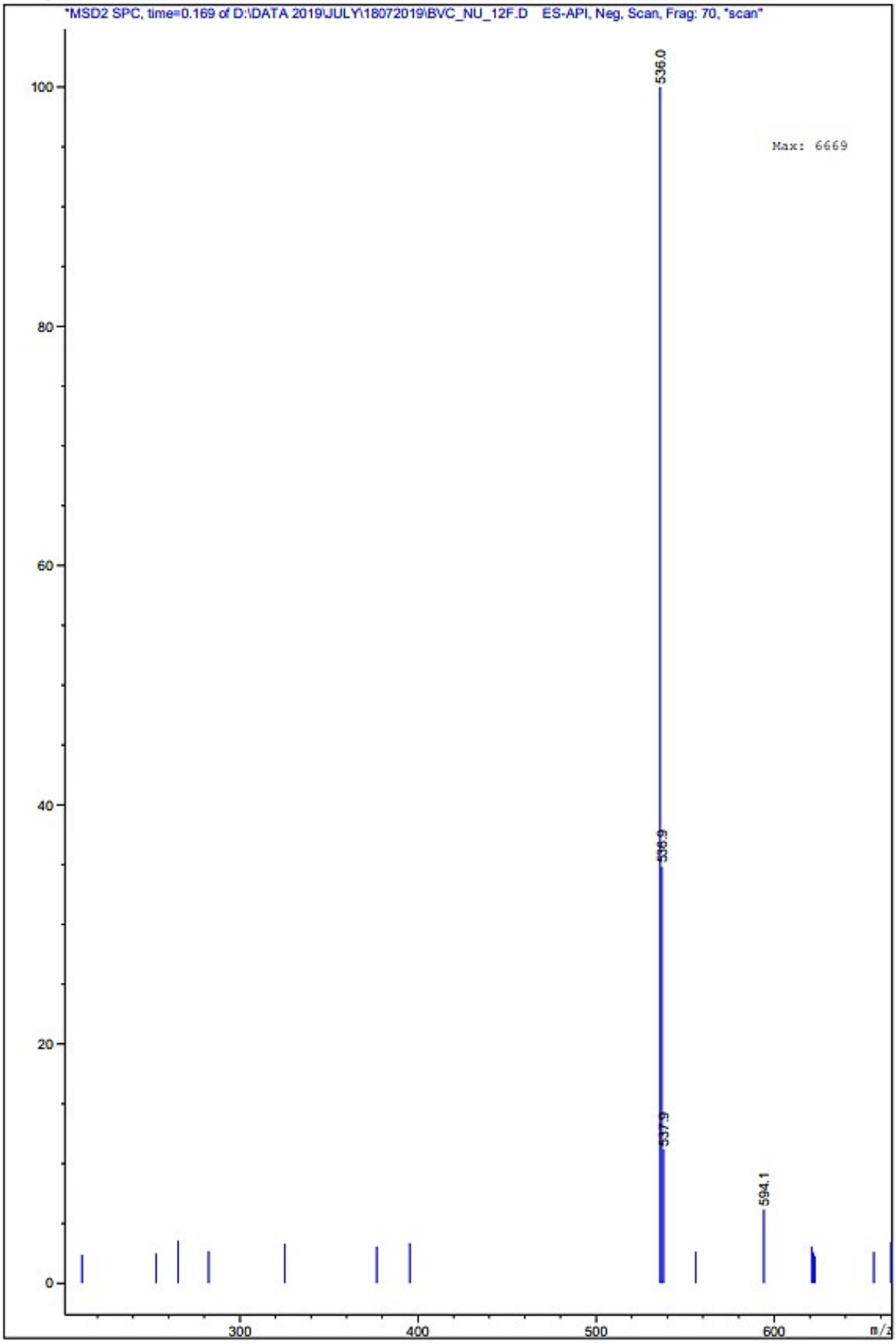
c. ^{13}C-NMR



d. HPLC

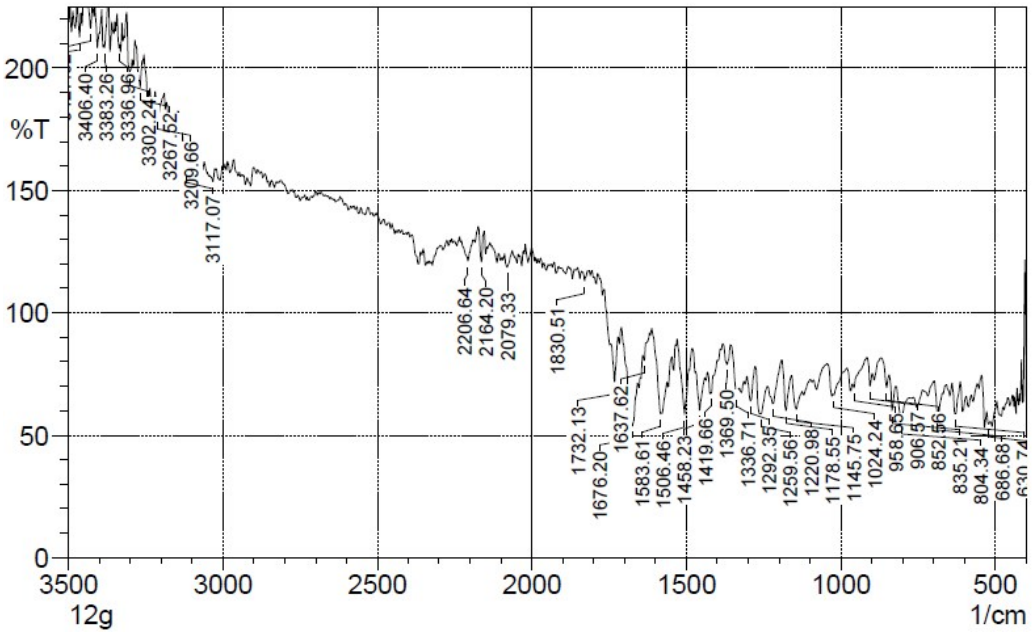


e. Mass spectroscopy

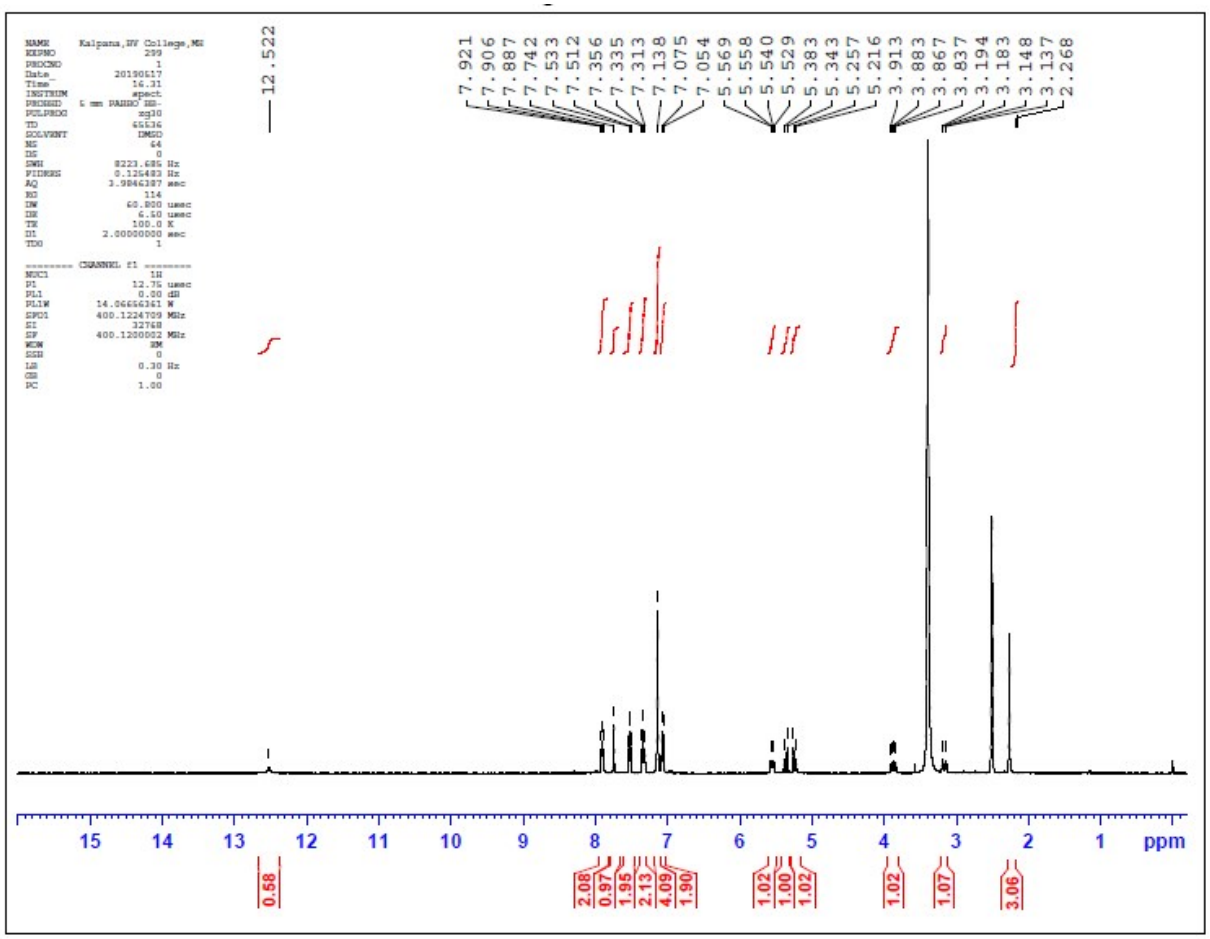


5-(4-(2-(3-(4-fluorophenyl)-5-(p-tolyl)-4,5-dihydro-1H-pyrazol-1-yl)-2-oxoethoxy) benzylidene)thiazolidine-2,4-dione (14g).

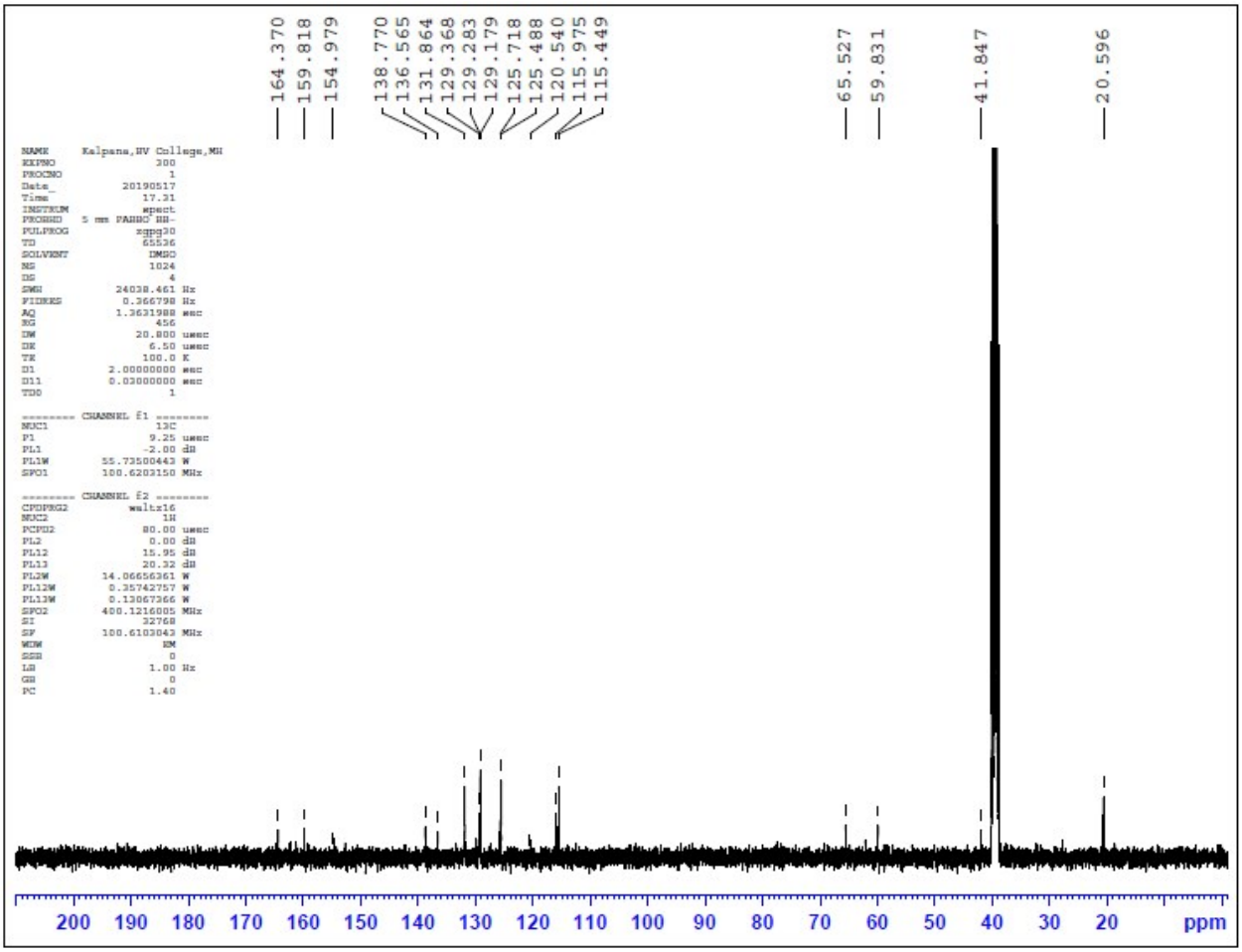
a. FTIR



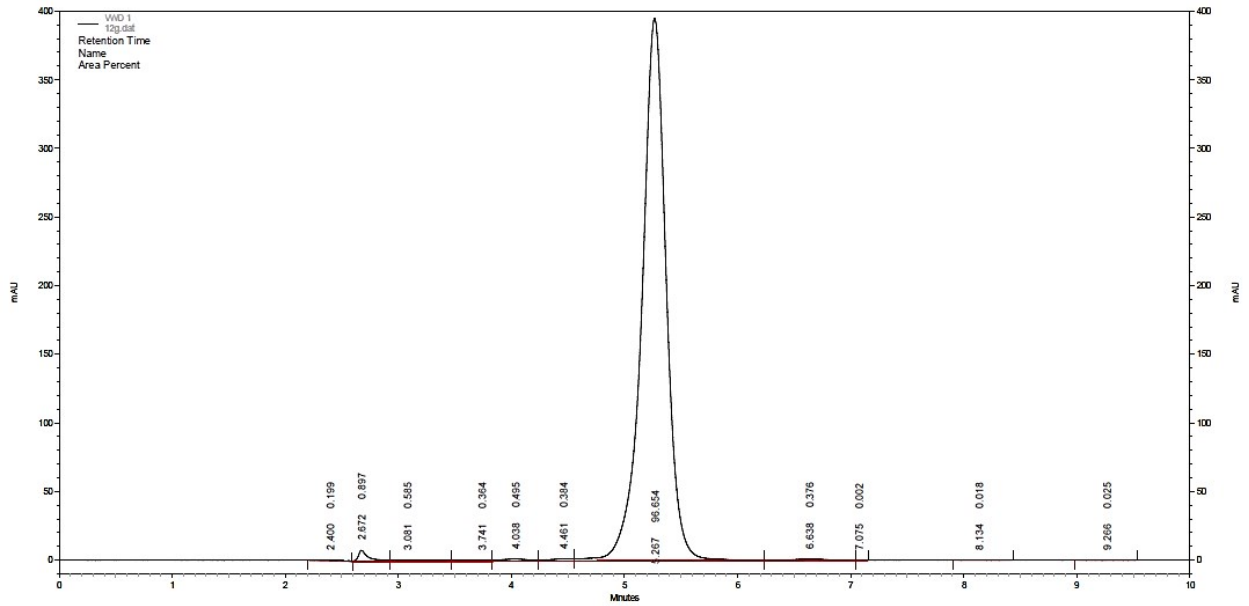
b. ^{1}H-NMR



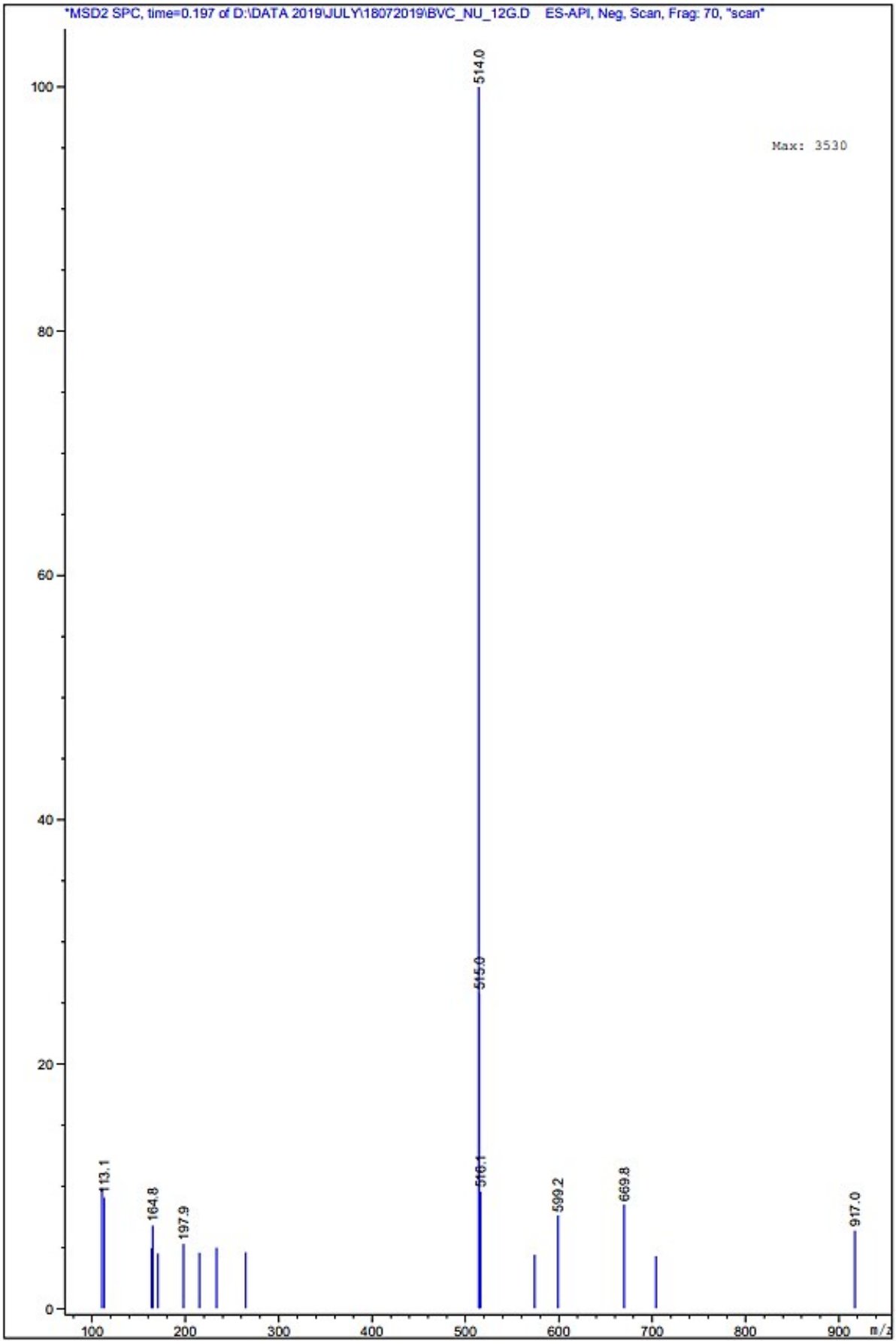
c. ^{13}C-NMR



d. HPLC

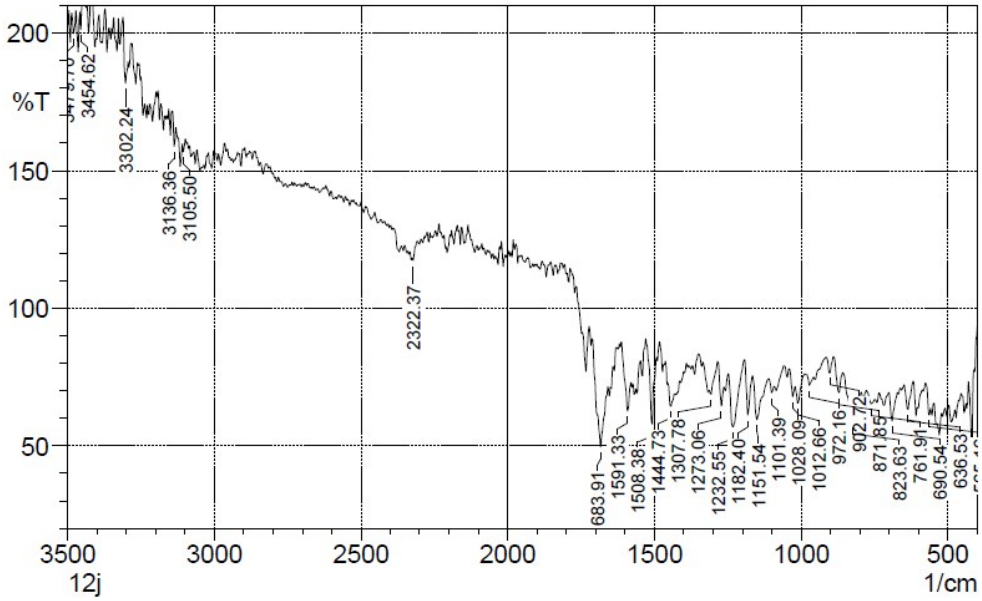


e. Mass spectroscopy

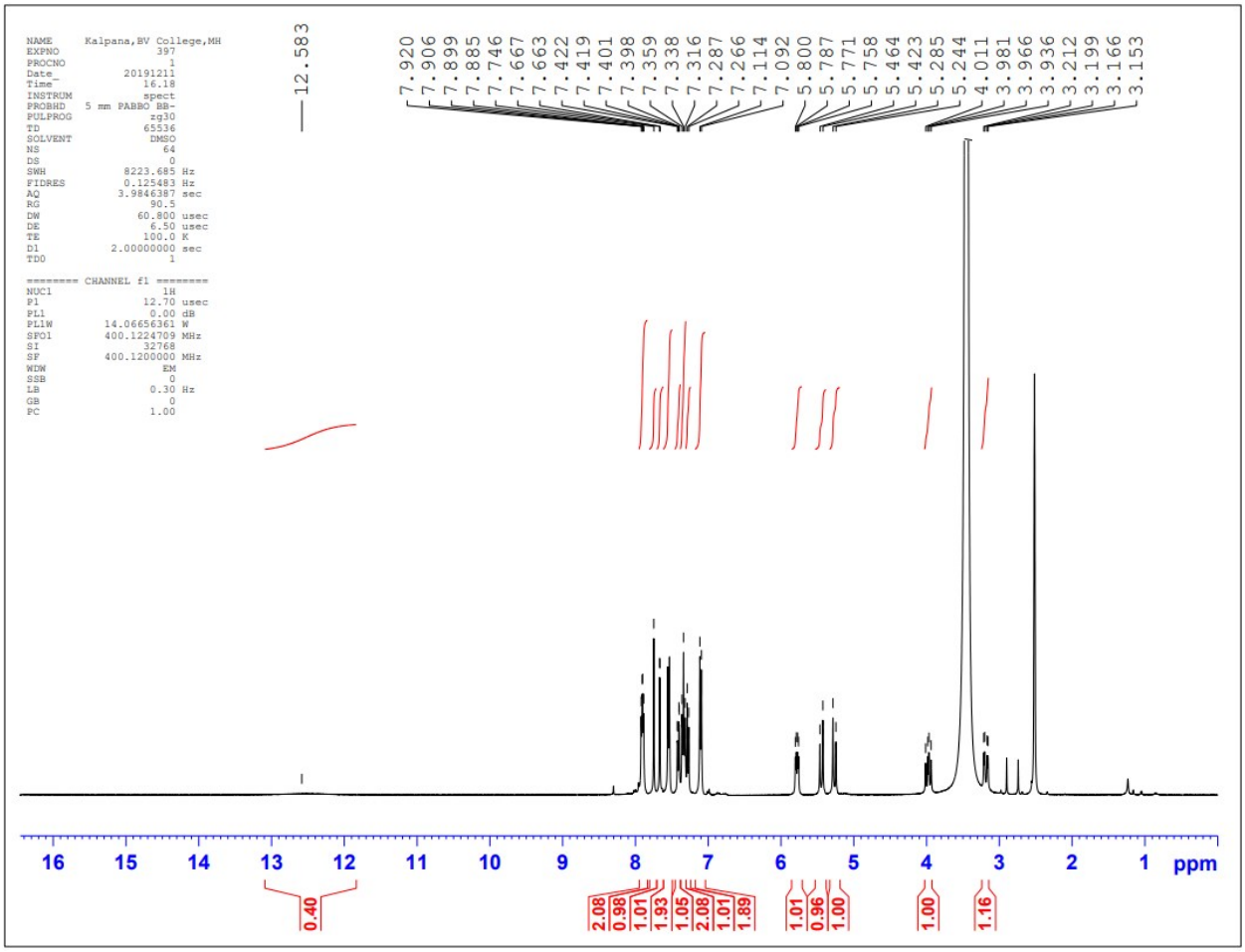


5-(4-(2-(5-(3,4-dichlorophenyl)-3-(4-fluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)-2-oxoethoxy)benzylidene)thiazolidine-2,4-dione (14j).

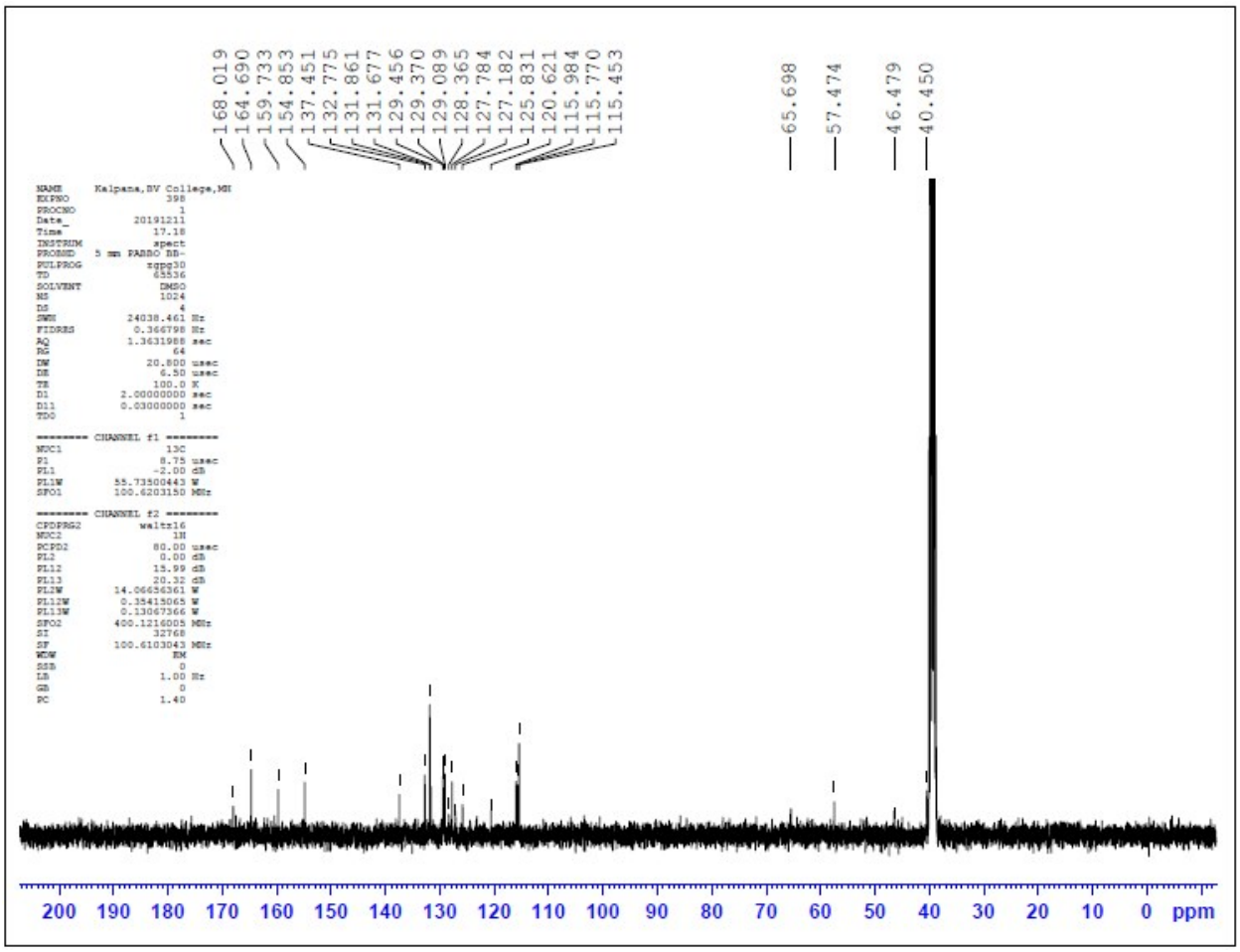
a. FTIR



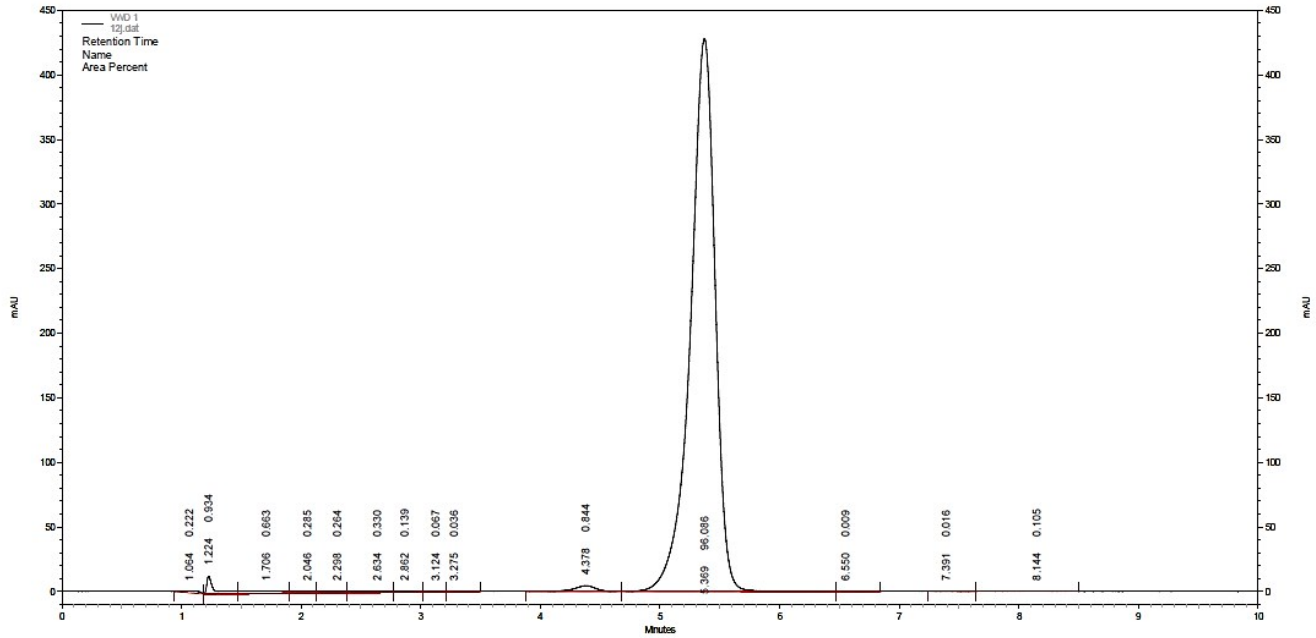
b. ^{1}H-NMR



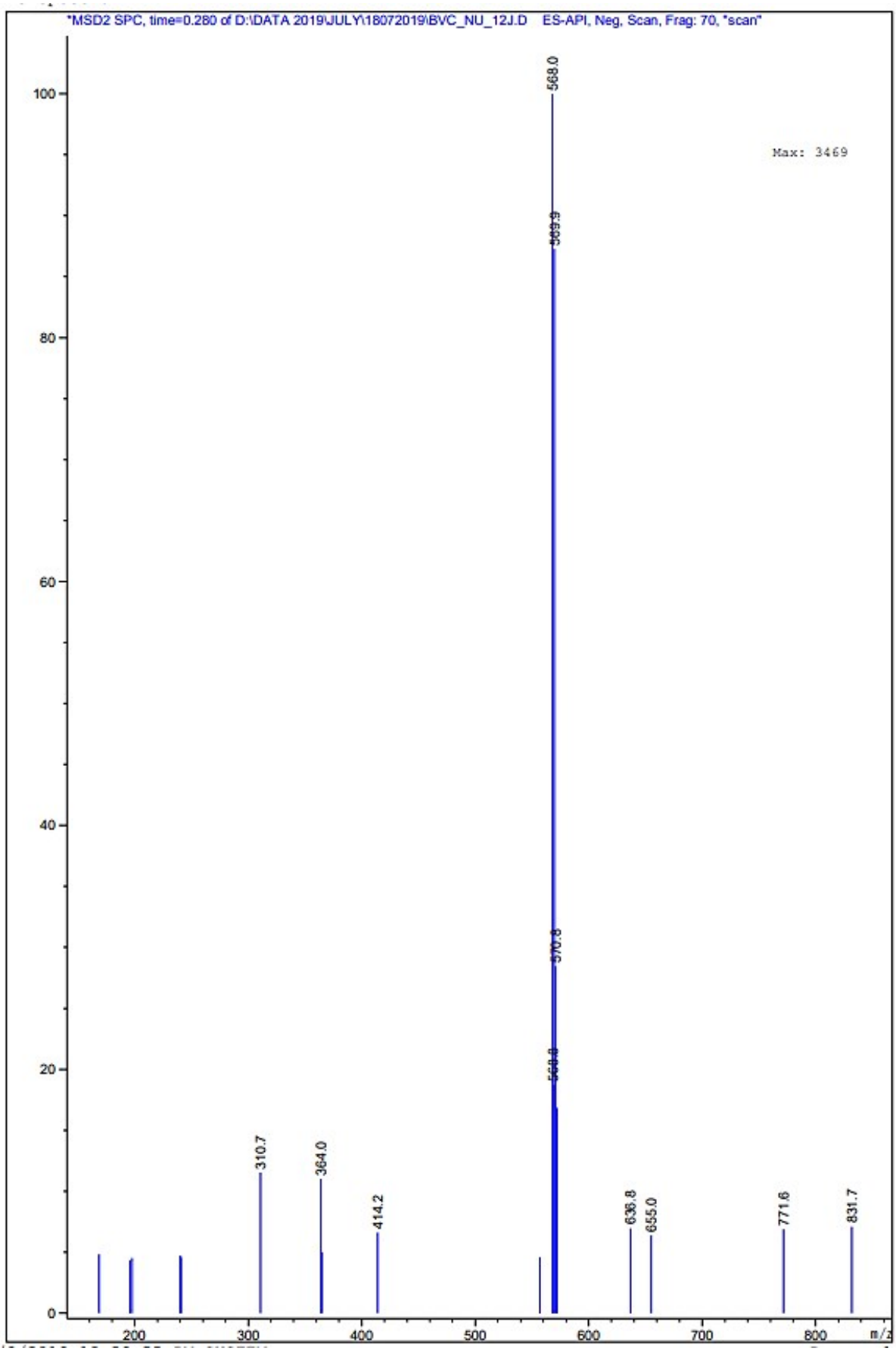
c. ^{13}C-NMR



d. HPLC

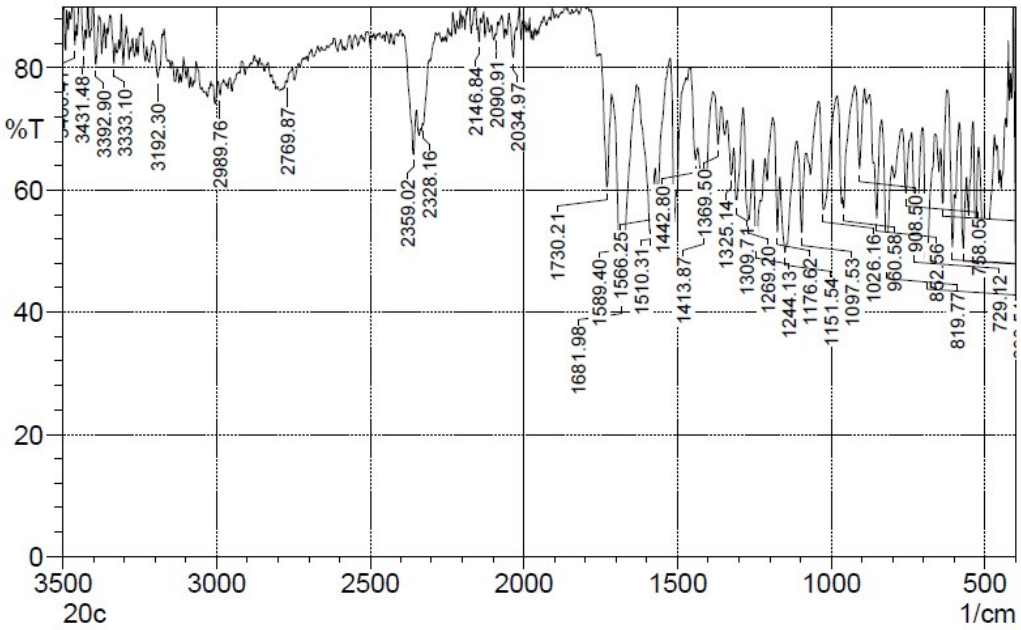


e. Mass spectroscopy

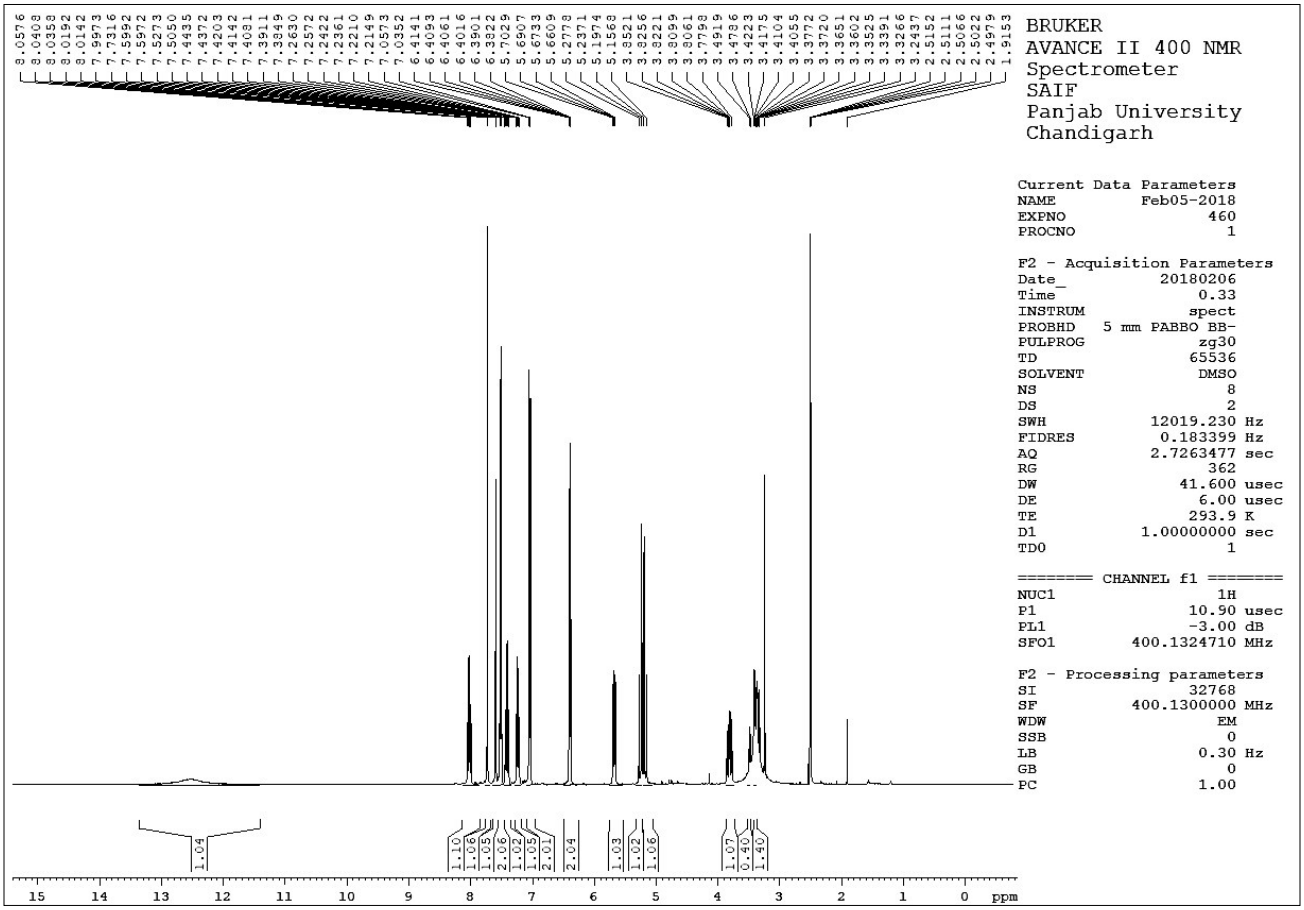


5-(4-(2-(3-(2,4-difluorophenyl)-5-(furan-2-yl)-4,5-dihydro-1H-pyrazol-1-yl)-2-oxoethoxy)benzylidene)thiazolidine-2,4-dione (15c).

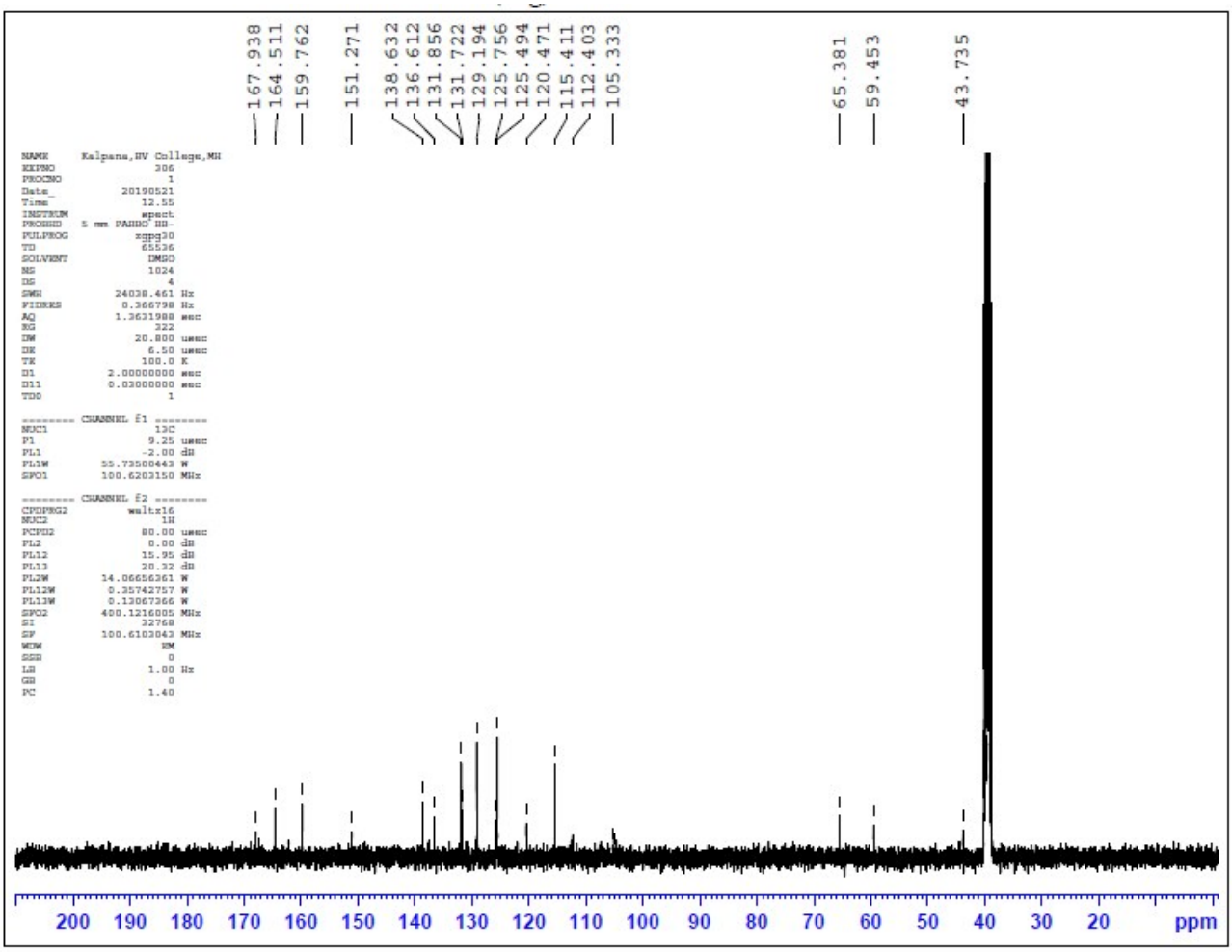
a. FTIR



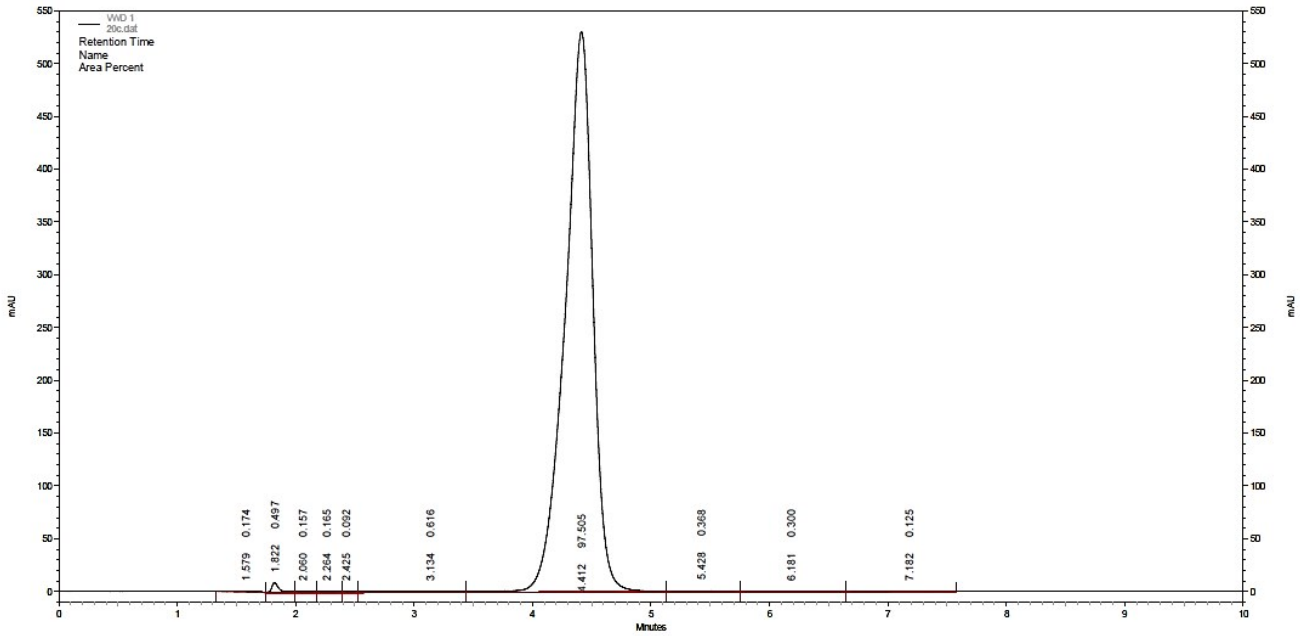
b. ^{1}H-NMR



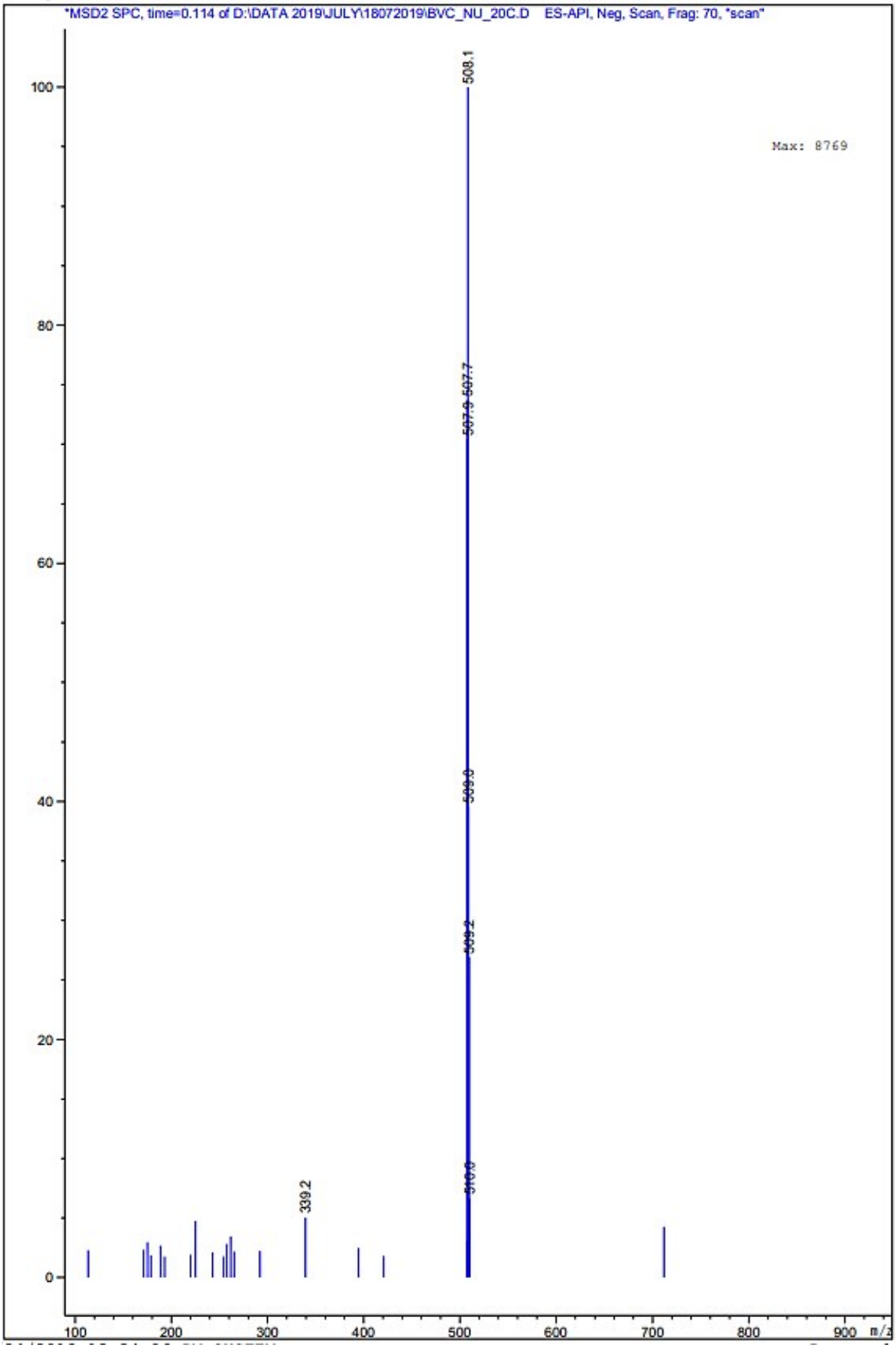
c. ^{13}C-NMR



d. HPLC

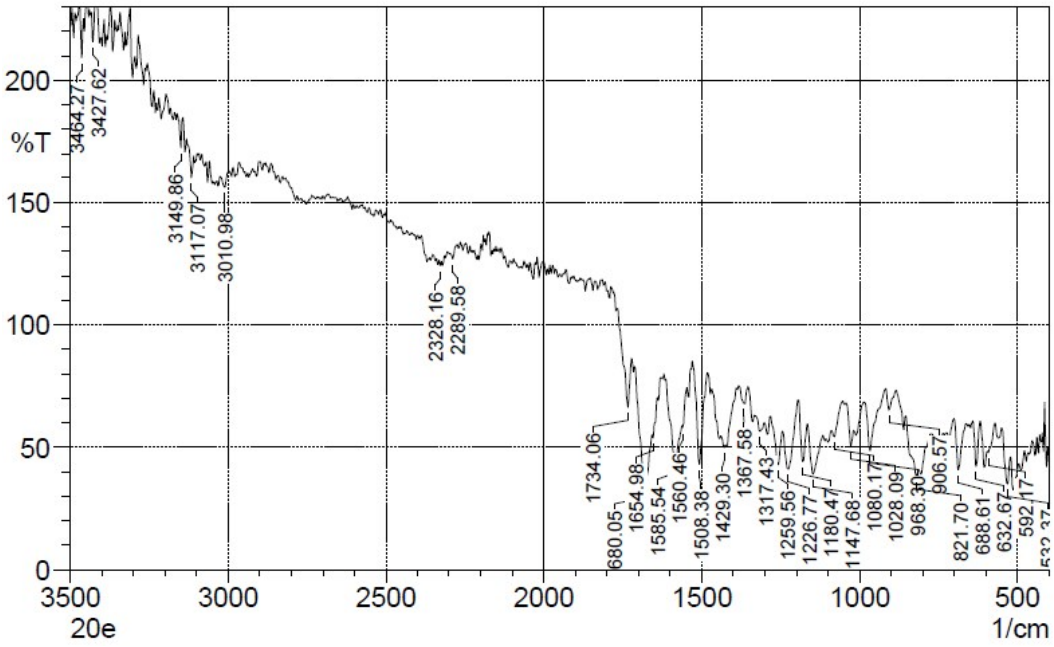


e. Mass spectroscopy

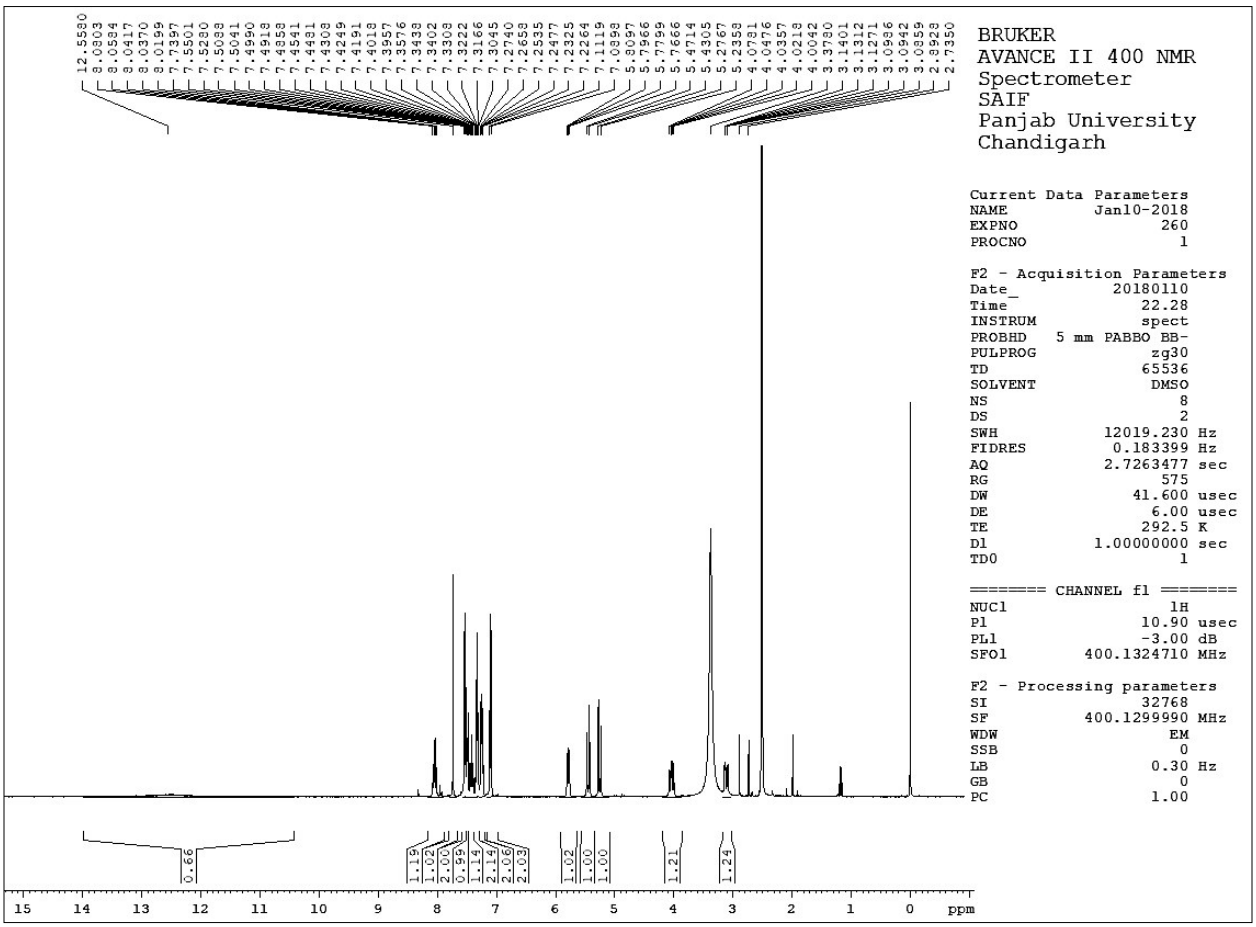


5-(4-(2-(3-(2,4-difluorophenyl)-5-(4-fluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)-2-oxoethoxy)benzylidene)thiazolidine-2,4-dione (15e).

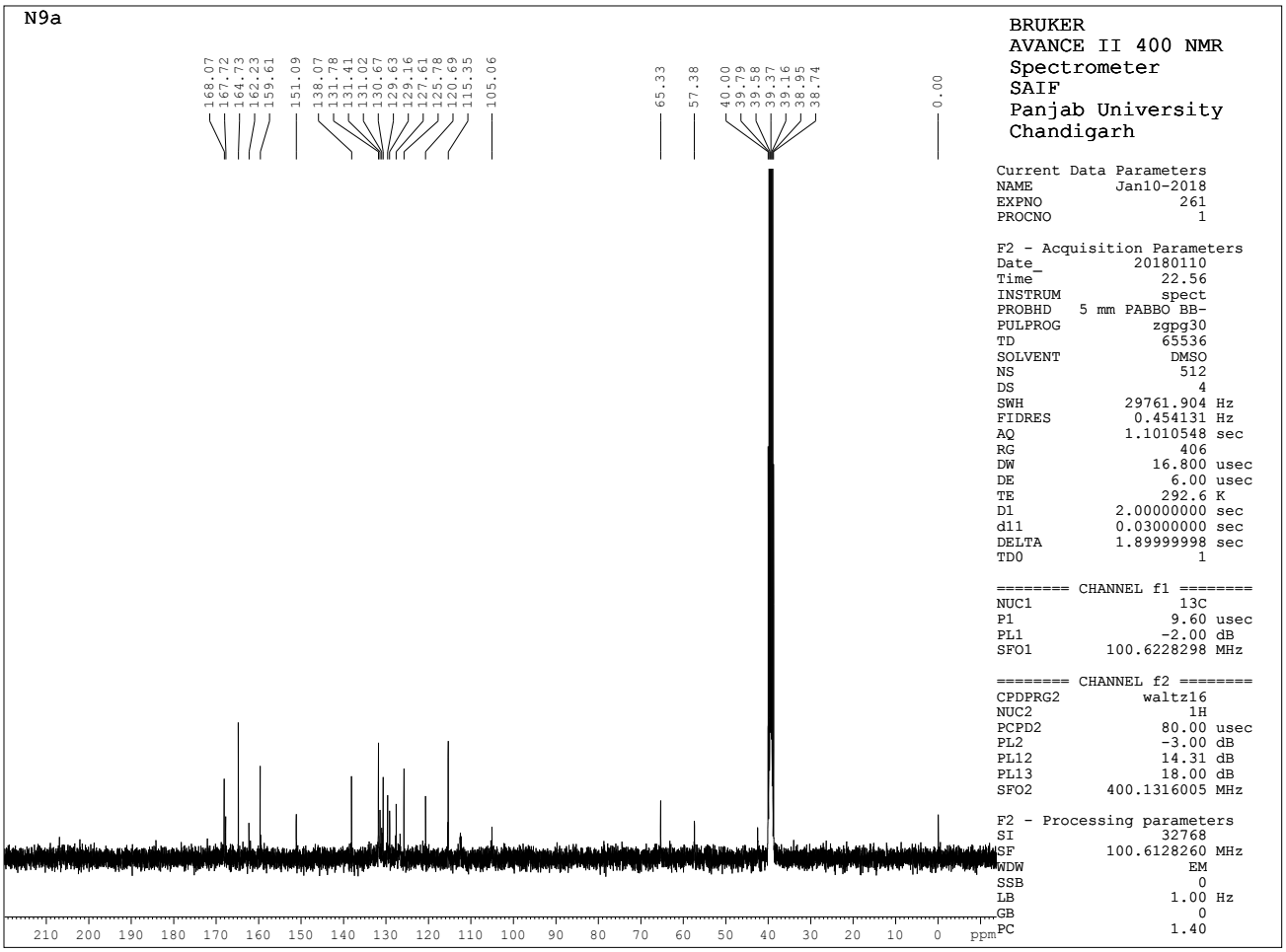
a. FTIR



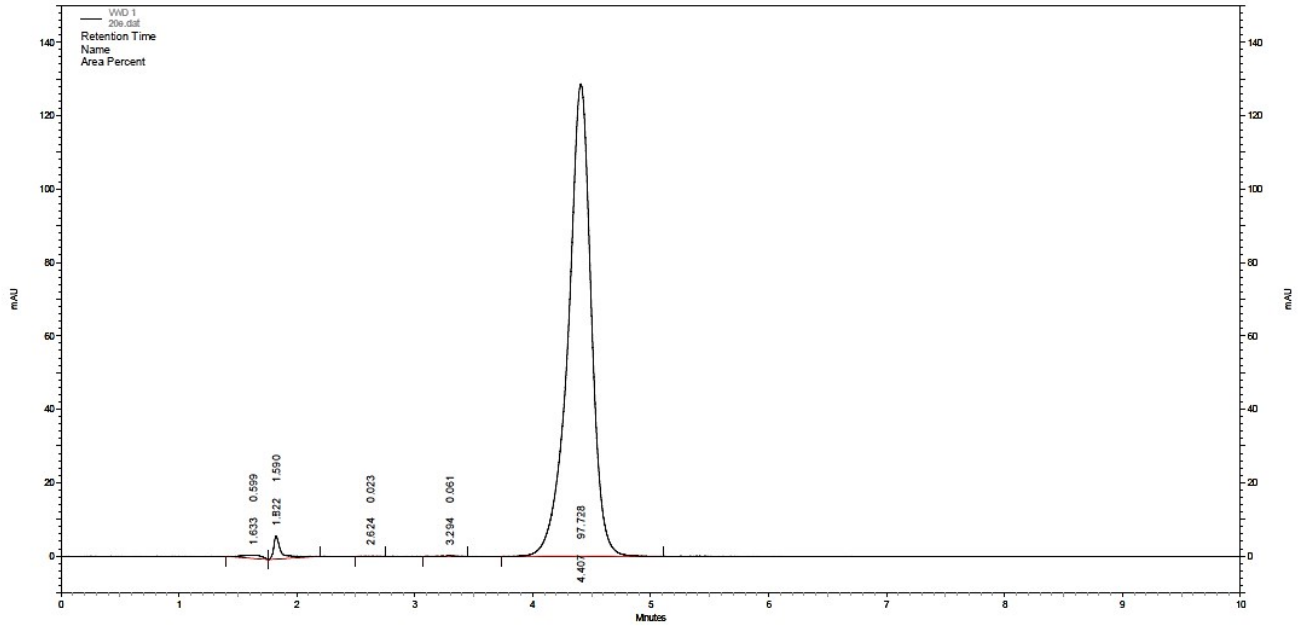
b. ^{1}H-NMR



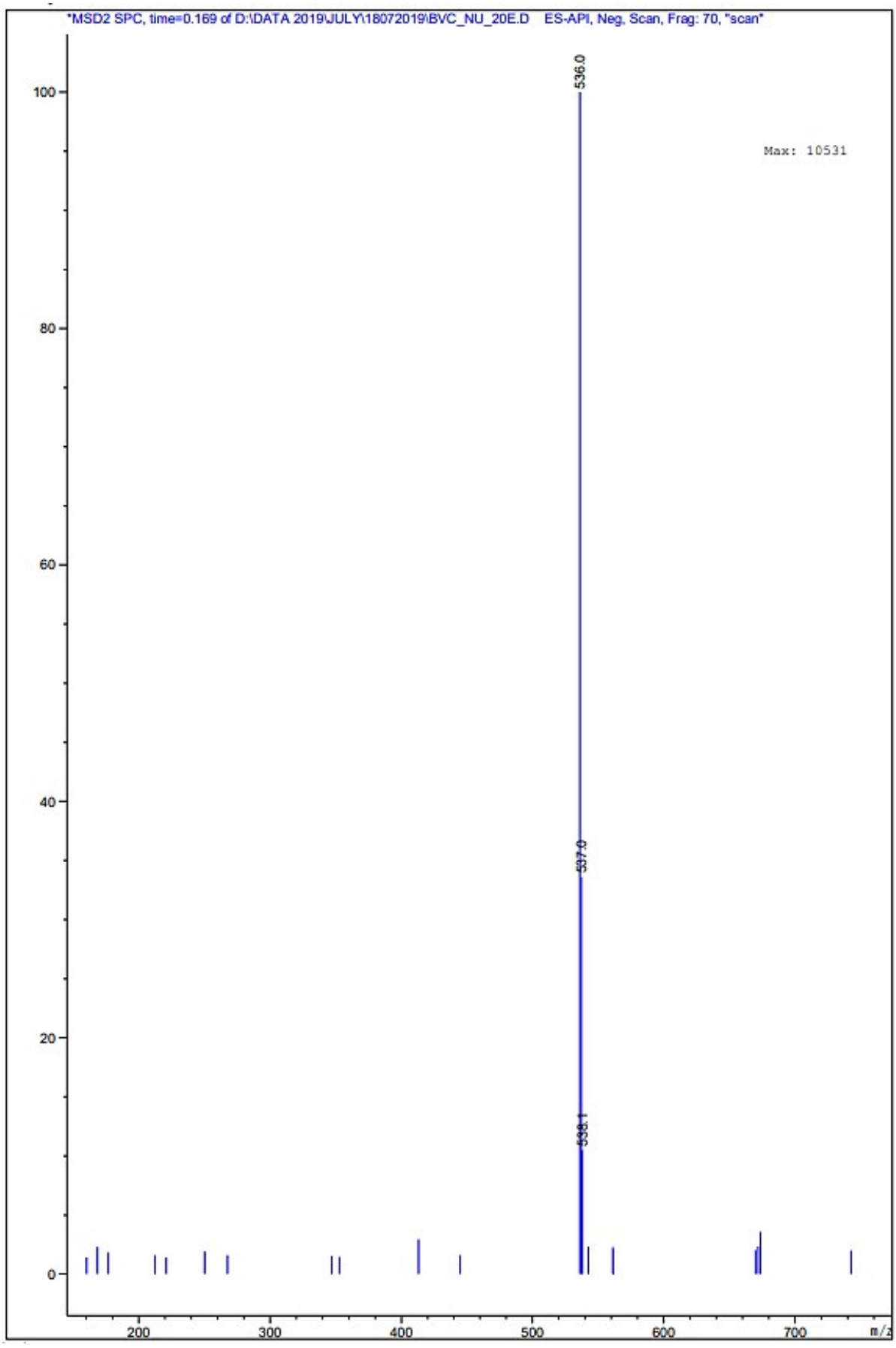
c. ^{13}C-NMR



d. HPLC

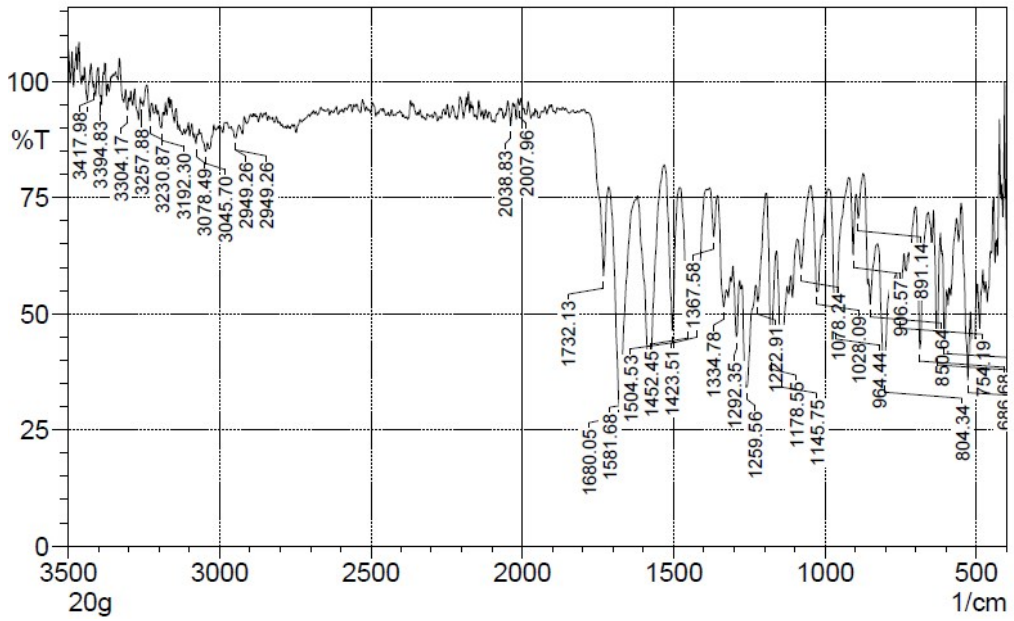


e. Mass spectroscopy

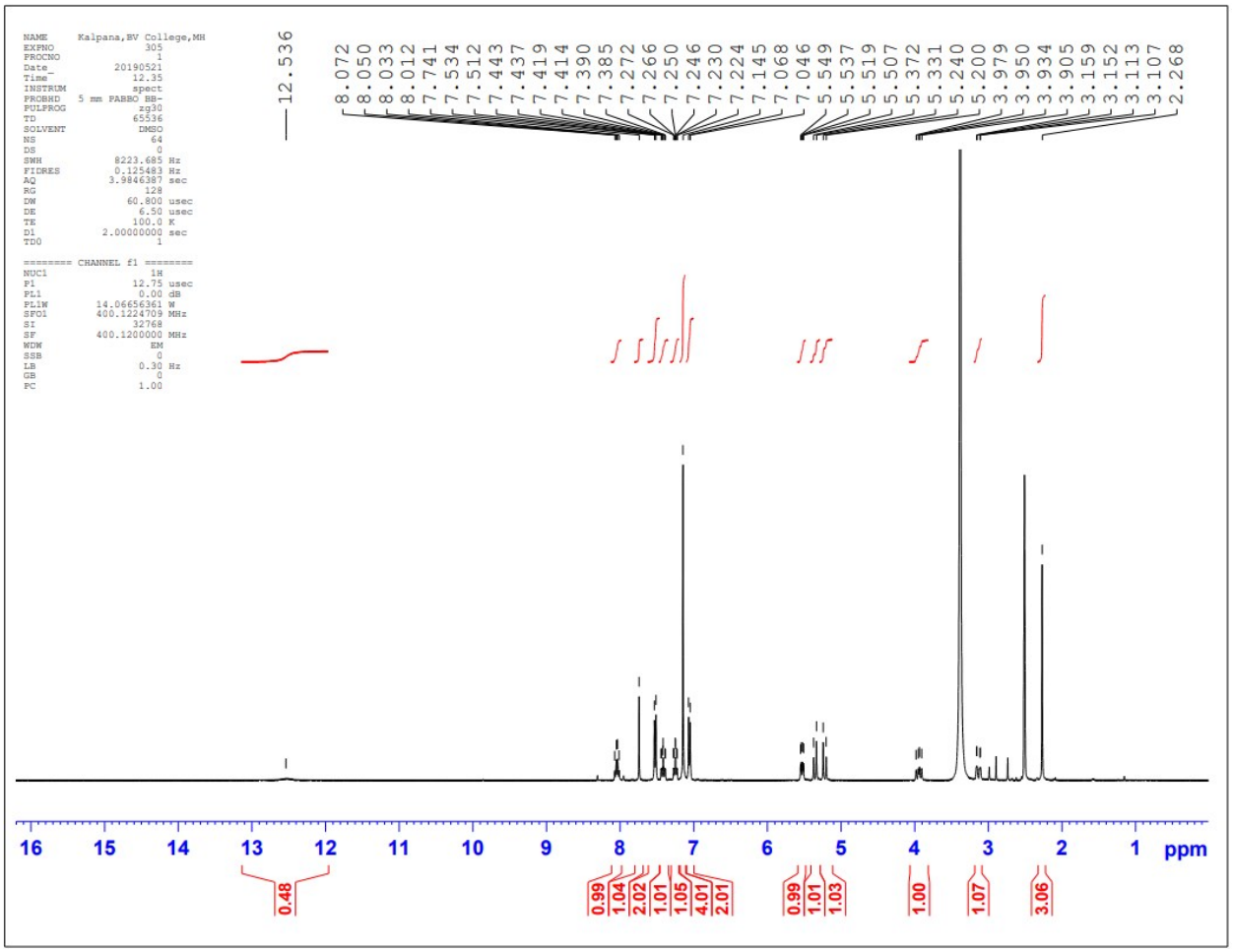


5-(4-(2-(3-(2,4-difluorophenyl)-5-(p-tolyl)-4,5-dihydro-1H-pyrazol-1-yl)-2-oxoethoxy) benzylidene) thiazolidine-2,4-dione (15g).

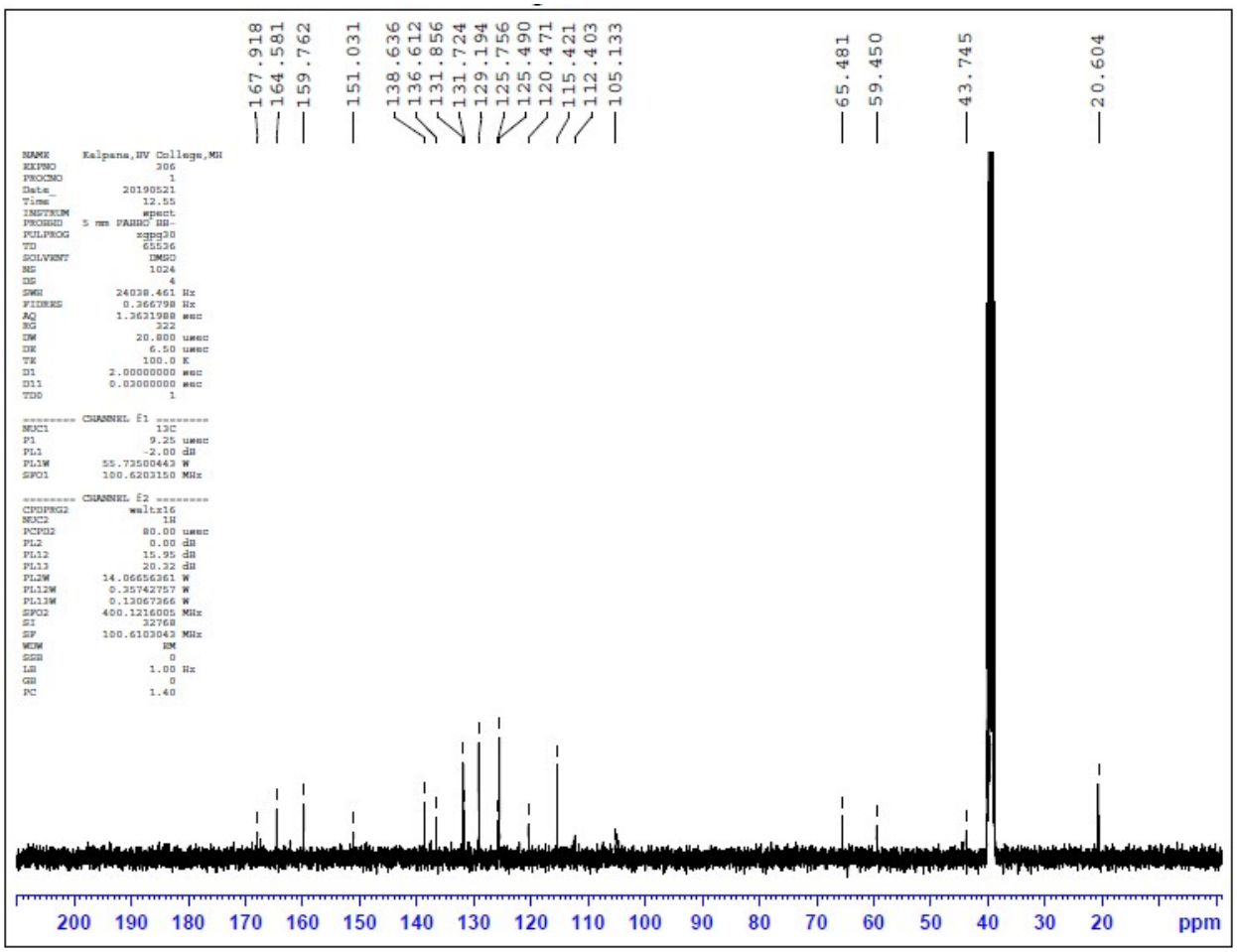
a. FTIR



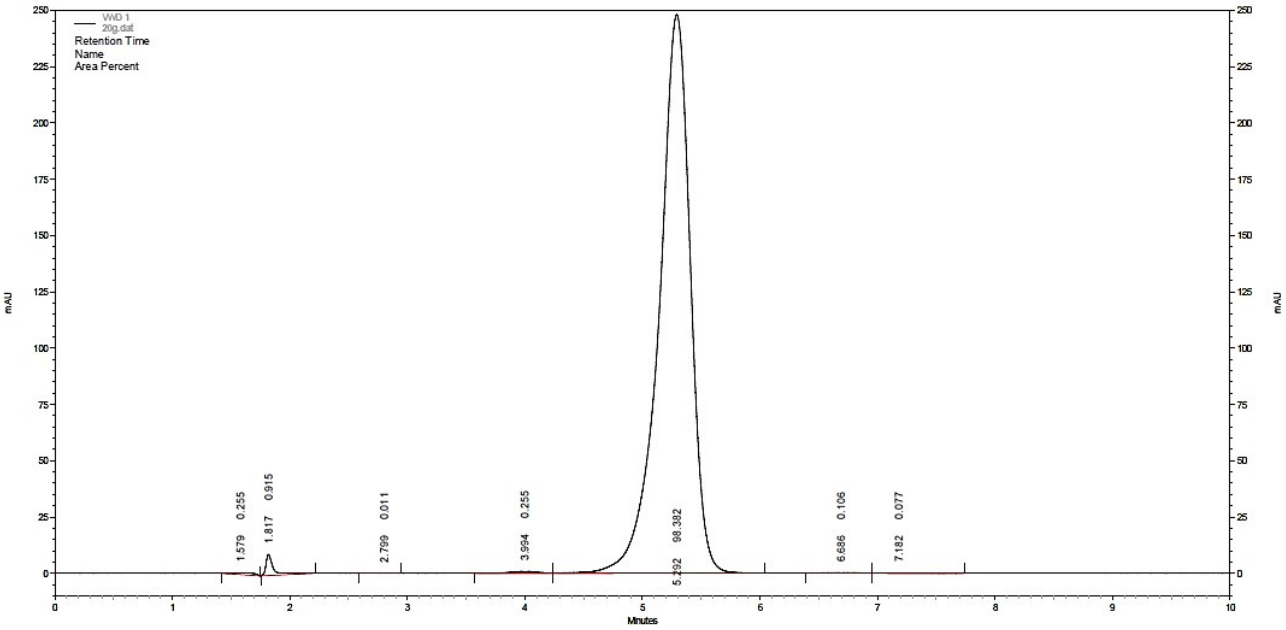
b. ^{1}H-NMR



c. ^{13}C-NMR



d. HPLC



e. Mass spectroscopy