

Ionic liquid mediated one-pot green synthesis of 6-aminouracils

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A. Experimental

Reagents: All the chemicals were purchased from Sigma Aldrich, S. D. Fine chemicals and Spectrochem Pvt. Ltd. India and were used without further purification.

1. Measurement and analysis:

The ionic liquid [TMG] [Ac] was prepared by previously reported method without any modifications and characterized by FTIR, ¹H NMR spectroscopy and physical parameters were matched with reported data¹. The reagents and solvents were commercially available. All

synthesized compounds were identified by spectroscopic data. FTIR spectra were obtained on a Perkin-Elmer infrared spectrometer with KBr discs and ^1H NMR spectra were recorded in DMSO- D_6 on a JEOL 300MHz spectrometer with TMS as internal standard. Mass spectral data were obtained with micromass - Q – Tof (YA105) spectrometer.

B. Typical procedure for synthesis of 1-benzyl-6-aminouracil **5g**:

To a stirred mixture of [TMG] [Ac] (1g) and water (0.3mL) was added amine **1g** (4.6 mmol) followed by cyanate **2g** (4.6 mmol) and the mixture was heated to 60°C for 30min. To this, a solution of cyanoacetic acid (4.6 mmol) in acetic anhydride (9.2 mmol) was added and heated at 60°C for 60min. to get a clear solution, then reaction temperature was raised to 90°C and stirred further for 60min. The progress of the reaction was monitored by TLC. After the completion of reaction, cold water (5 mL) was added and stirred for 5min. The precipitated solid was collected by filtration, washed with water (5 mL) and dried to obtain 6-aminouracil **5g** (0.88g, 88%). The ionic liquid catalyst was recovered by removing water under reduced pressure and reused five times in subsequent runs. Some of the products were further purified by recrystallization from suitable solvent and were characterized by melting point determination, IR and ^1H NMR spectroscopy, according to the literature^{10, 12, 14, 15, 16} and references cited therein.

C. Competitive experiment procedure

To a stirred mixture of [TMG] [Ac] (1g) and water (0.3mL), aniline (10.7 mmol) and n-propylamine (10.7 mmol) was added followed by potassium cyanate (10.7 mmol) and the reaction mixture was heated at 60°C for 30min. The progress of the reaction was monitored by TLC. The cold water (5 mL) was added to reaction mixture and stirred for 5min. The reaction mixture was extracted thrice with ethyl acetate (3x10 mL). The organic layer was separated and passed over sodium sulfate. The produced n-propylurea and phenylurea were separated from

organic layer by preparative TLC. The n-propylurea was obtained in higher yield (29%) as compared to phenylurea (13%).

D. Experimental procedure for synthesis of N-benzylurea

To a stirred mixture of [TMG] [Ac] (1g) and water (0.3mL) was added benzylamine (4.6 mmol) followed by potassium cyanate (4.6 mmol) and the reaction mixture was heated to 60°C for 30min. The progress of the reaction was monitored by TLC. After the completion of reaction, cold water (5 mL) was added and stirred for 5min. The precipitated solid was collected by filtration, washed with water (5 mL) and dried to obtain N-benzylurea (0.53g, 91%).

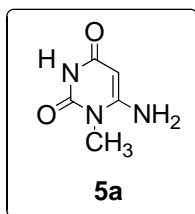
E. Experimental procedure for synthesis of N-benzylcyanoacetylurea

To a solution of cyanoacetic acid (3.9 mmol) in acetic anhydride (7.9 mmol), N-benzylurea (3.9 mmol) and [TMG] [Ac] (1g) was added and heated at 60°C for 60min. to get a clear solution. The progress of the reaction was monitored by TLC. After the completion of reaction, the reaction mixture was cooled to room temperature to get a precipitate. The cold water (3 mL) was added to the reaction mixture and stirred for 5min. The solid was collected by filtration, washed with diethylether (5 mL) and dried to obtain N-benzylcyanoacetylurea (0.77g, 89%).

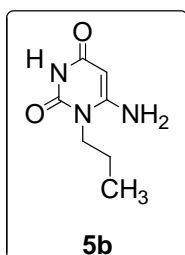
F. Experimental procedure for cyclization of N-benzylcyanoacetylurea to 1-benzyl-6-aminouracil

[TMG] [Ac] (1g) was added to N-benzylcyanoacetylurea (2.3 mmol) and the reaction mixture was heated at 90°C for 60min. The progress of the reaction was monitored by TLC. After the completion of reaction, cold water (5 mL) was added and stirred for 5min. The precipitated solid was collected by filtration, washed with water (5 mL) and dried to obtain 1-benzyl-6-aminouracil (0.86g, 86%).

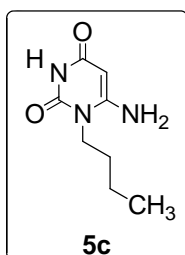
G. Spectral data for 6-aminouracils



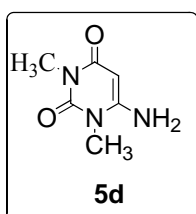
5a: m.p. >300°C (Lit. 305-306°C); ν_{\max} cm^{-1} : 3370, 3175, 1716, 1664 and 1623; ^1H NMR (300 MHz, DMSO- d_6) δ = 3.18 (s, 3H), 4.55 (s, 1H), 6.78 (s, 2H), 10.34 (s, 1H); ESI MS (m/z) = 142 (M+H).



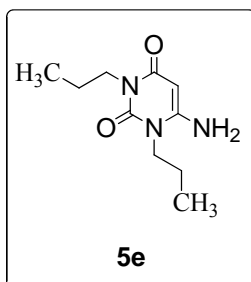
5b: m.p. 273-274°C (Lit. 273-275°C); ν_{\max} cm^{-1} : 3362, 3199, 1700, 1654 and 1602; ^1H NMR (300 MHz, DMSO- d_6) δ = 0.86 (t, 3H), 1.50 (m, 2H), 3.68 (t, 2H), 4.52 (s, 1H), 6.79 (s, 2H), 10.30 (s, 1H); ESI MS (m/z) = 170 (M+H).



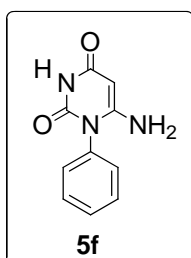
5c: m.p. 265-267°C (Lit. 266-267°C); ν_{\max} cm^{-1} : 3366, 3200, 1700, 1654 and 1597; ^1H NMR (300 MHz, DMSO- d_6) δ = 0.86 (t, 3H), 1.27 (m, 2H), 1.47 (m, 2H), 3.72 (t, 2H), 4.53 (s, 1H), 6.78 (s, 2H), 10.31 (s, 1H), ESI MS (m/z) = 184 (M+H).



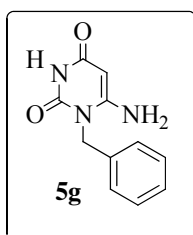
5d: m.p. 289-291°C (Lit. 290-292°C); ν_{\max} cm^{-1} : 3393, 3230, 1677, 1643 and 1580; ^1H NMR (300 MHz, DMSO- d_6) δ = 3.07 (s, 3H), 3.24 (s, 3H), 4.69 (s, 1H), 6.79 (s, 2H); ESI MS (m/z) = 156 (M+H).



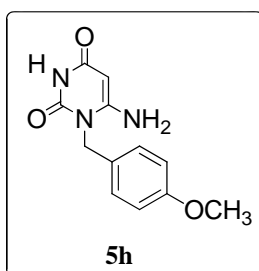
5e: m.p. 135-136°C (Lit. 135-137°C); ν_{\max} cm^{-1} : 3312, 3202, 1705, 1635 and 1570; ^1H NMR (300 MHz, DMSO- d_6) δ = 0.85 (t, 6H), 1.51 (m, 4H), 3.68 (t, 4H), 4.50 (s, 1H), 6.82 (s, 2H); ESI MS (m/z) = 212 (M+H).



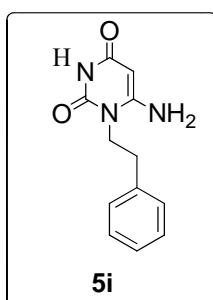
5f: m.p. 285-286°C (Lit. 285-287°C); ν_{\max} cm^{-1} : 3478, 3332, 3196, 1711, 1629 and 1581; ^1H NMR (300 MHz, DMSO-d_6) δ = 4.67 (s, 1H), 6.07 (s, 2H), 7.30-7.49 (m, 5H), 10.44 (s, 1H); ESI MS (m/z) = 204 (M+H).



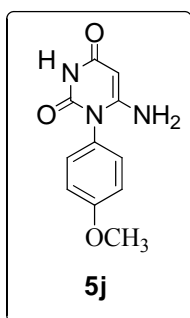
5g: m.p. 285-286°C (Lit. 285-286°C); ν_{\max} cm^{-1} : 3471, 3330, 3251, 1695, 1635 and 1576; ^1H NMR (300 MHz, DMSO-d_6) δ = 4.59 (s, 1H), 5.03 (s, 2H), 6.79 (s, 2H), 7.21-7.35 (m, 5H), 10.49 (s, 1H); ESI MS (m/z) = 218 (M+H).



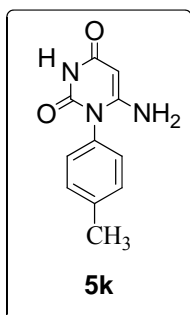
5h: m.p. 275-277°C (Lit. 276-278°C); (EtOH:H₂O = 50:50); ν_{\max} cm^{-1} : 3445, 3331, 1700, 1647 and 1607; ^1H NMR (300 MHz, DMSO-d_6) δ = 3.73 (s, 3H), 4.57 (s, 1H), 4.94 (s, 2H), 6.69 (s, 2H), 6.83 (d, 2H), 7.17 (d, 2H), 10.44 (s, 1H); ESI MS (m/z) = 248 (M+H).



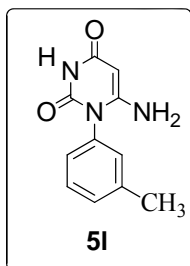
5i: m.p. 265-266°C (Lit. 265-267°C); ν_{\max} cm^{-1} : 3394, 3182, 1711, 1691, 1658 and 1595; ^1H NMR (300 MHz, DMSO-d_6) δ = 2.81 (t, 2H), 3.97 (t, 2H), 4.56 (s, 1H), 6.85 (s, 2H), 7.29 (m, 5H), 10.45 (s, 1H); ESI MS (m/z) = 232 (M+H). ,.



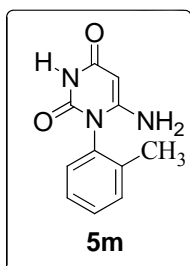
5j: m.p. >300°C (Lit. >300°C); (MeOH:H₂O = 70:30); ν_{\max} cm^{-1} : 3432, 3324, 1713, 1649 and 1571; ^1H NMR (300 MHz, DMSO-d_6) δ = 3.15 (s, 3H), 4.54 (s, 1H), 6.67 (s, 2H), 6.82 (d, 2H), 7.18 (d, 2H), 10.46 (s, 1H); ESI MS (m/z) = 234 (M+H).



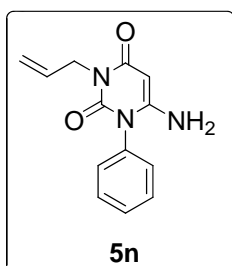
5k: m.p. >300°C (Lit. >300°C); (EtOH:H₂O = 50:50); ν_{\max} cm^{-1} : 3470, 3317, 1701, 1643 and 1576 ; ^1H NMR (300 MHz, DMSO-d_6) δ = 2.37 (s, 3H), 4.64 (s, 1H), 6.09 (s, 2H), 7.12 (d, 2H), 7.32 (d, 2H), 10.43 (s, 1H); ESI MS (m/z) = 218 (M+H).



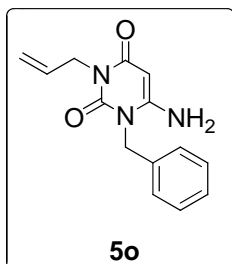
5l: m.p. >300°C (Lit. >300°C); ν_{\max} cm^{-1} : 3413, 3326, 1686, 1648 and 1581; ^1H NMR (300 MHz, DMSO- d_6) δ = 2.38 (s, 3H), 4.65 (s, 1H), 6.11 (s, 2H), 6.81 (d, 1H), 6.95 (m, 1H), 7.14 (d, 1H), 7.34 (m, 1H), 10.40 (s, 1H); ESI MS (m/z) = 218 (M+H).



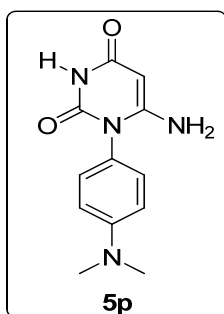
5m: m.p. >300°C (Lit. >300°C); ν_{\max} cm^{-1} : 3394, 3317, 3240, 1711, 1629 and 1571; ^1H NMR (300 MHz, DMSO- d_6) δ = 2.13 (s, 3H), 4.65 (s, 1H), 5.92 (s, 2H), 6.70 (m, 1H), 6.87 (m, 1H), 7.03 (d, 1H), 7.16 (d, 1H), 10.41 (s, 1H); ESI MS (m/z) = 218 (M+H).



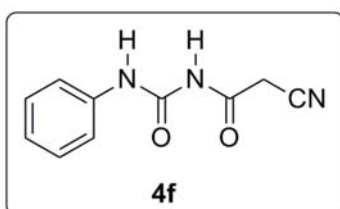
5n: m.p. 191-193°C (Lit. 190-194°C); (EtOH:H₂O = 50:50); ν_{\max} cm^{-1} : 3451, 3394, 1701, 1634 and 1571; ^1H NMR (300 MHz, DMSO- d_6) δ = 3.74 (d, 2H), 4.87 (s, 2H), 5.15 (m, 1H), 5.21 (m, 1H), 6.22 (s, 1H), 6.90 (m, 1H), 7.31 (m, 5H); ESI MS (m/z) = 244 (M+H).



5o: m.p. 218-219°C (Lit. 218-220°C); (EtOH:H₂O = 50:50); ν_{\max} cm⁻¹: 3394, 3220, 1710, 1634, 1605 and 1561; ¹H NMR (300 MHz, DMSO-d₆) δ = 3.83 (d, 2H), 4.55 (s, 1H), 4.89 (s, 2H), 5.09 (s, 2H), 5.15 (m, 1H), 5.21 (m, 1H), 6.84 (m, 1H), 7.30 (m, 5H); ESI MS (*m/z*) = 258 (M+H).

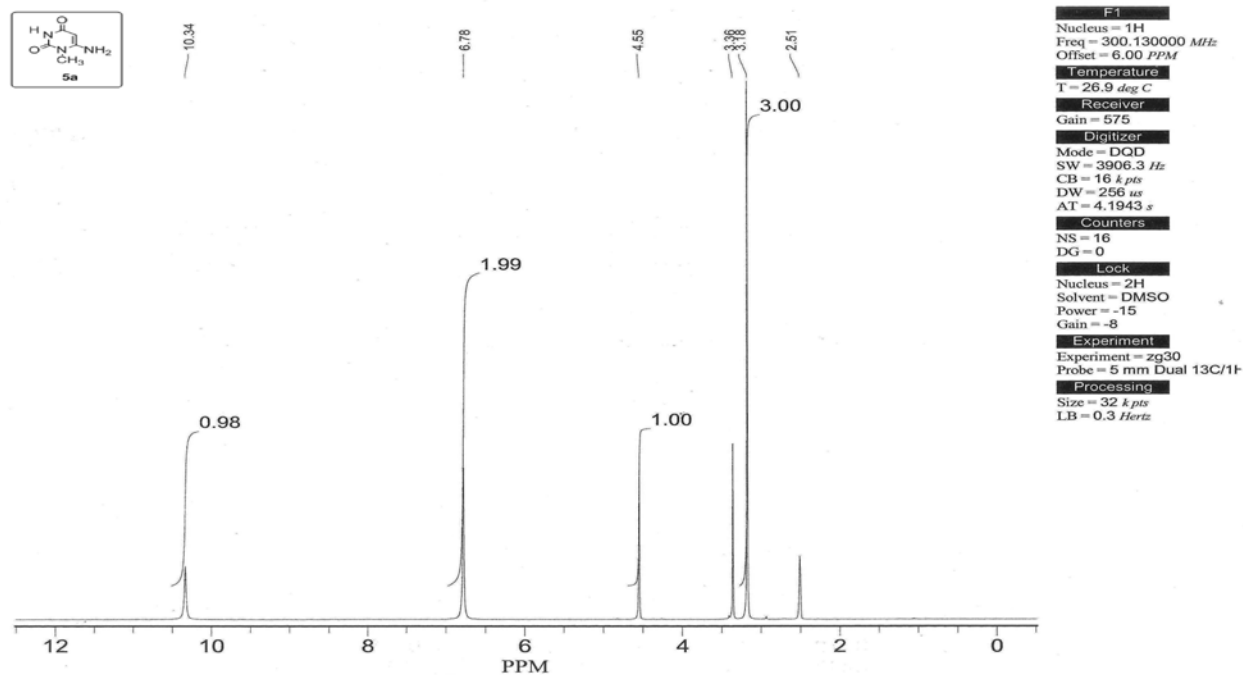


5p: m.p. >300°C (Lit. >300°C); ν_{\max} cm⁻¹: 3394, 3240, 3115, 1696, 1614, 1590 and 1547; ¹H NMR (300 MHz, DMSO-d₆) δ = 3.20 (s, 6H), 4.75 (s, 1H), 6.30 (s, 2H), 7.19 (d, 2H), 7.38 (d, 2H), 10.58 (s, 1H); ESI MS (*m/z*) = 247 (M+H).

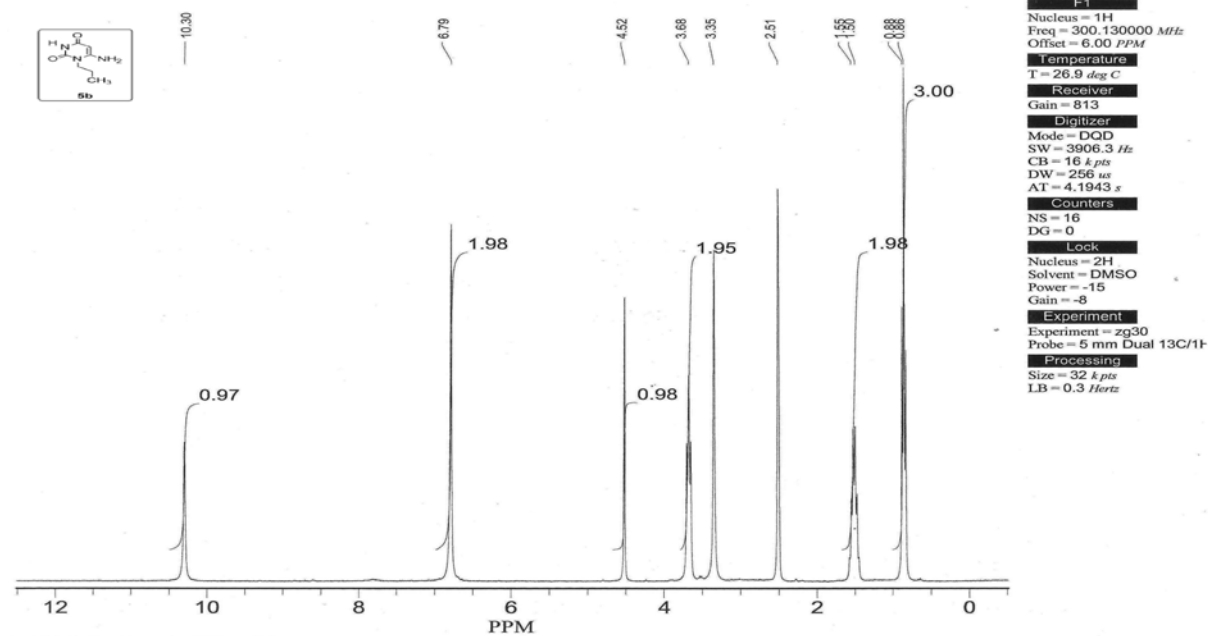


4f: ¹H NMR (300 MHz, DMSO-d₆) δ = 4.01 (s, 2H), 7.09-7.49 (m, 5H), 9.97 (s, 1H), 10.82 (s, 1H).

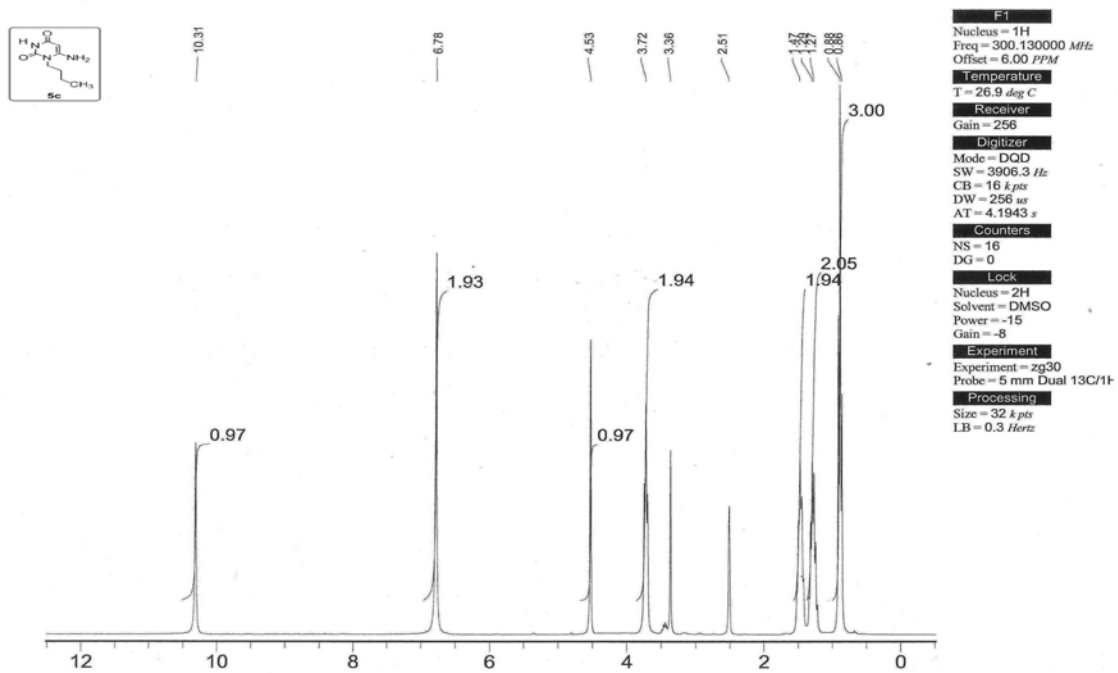
H. Spectra of 6-aminouracils (¹H NMR):



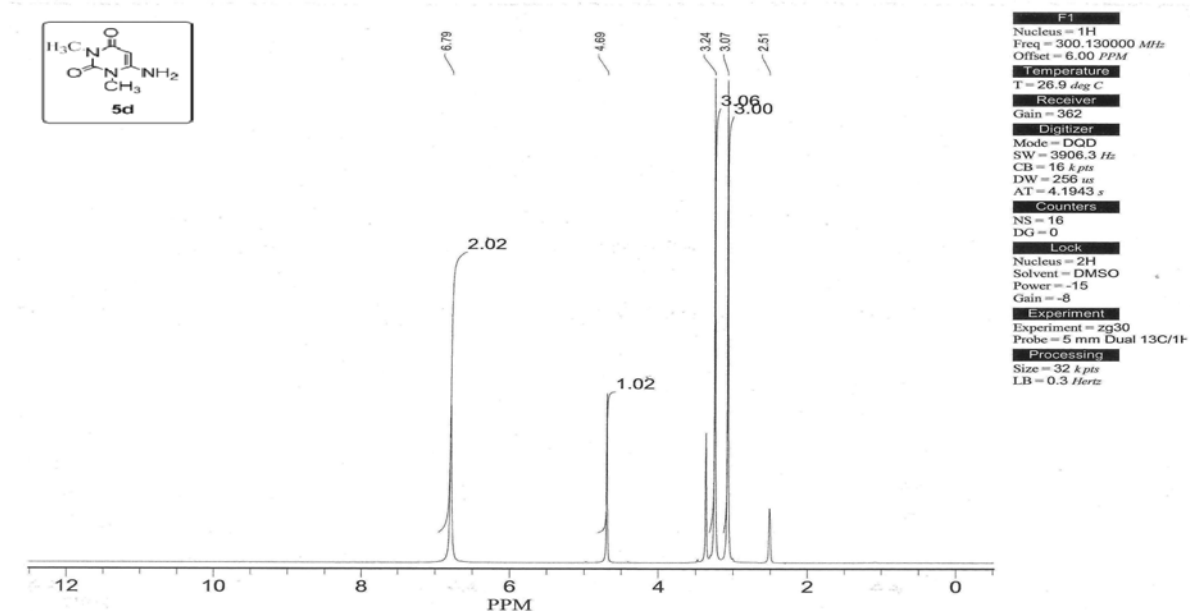
Compound 5a



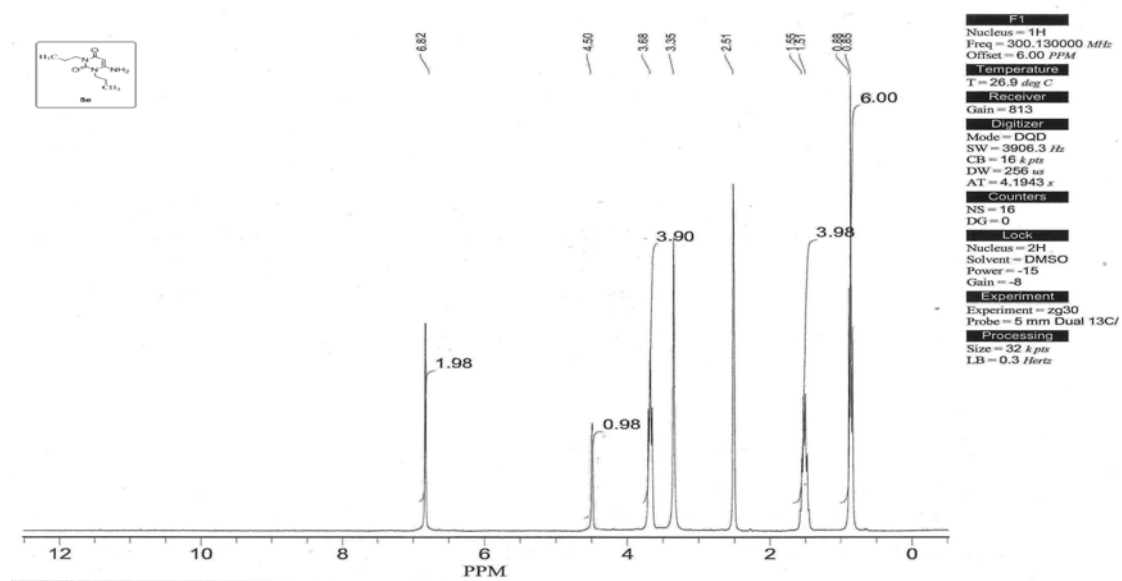
Compound 5b



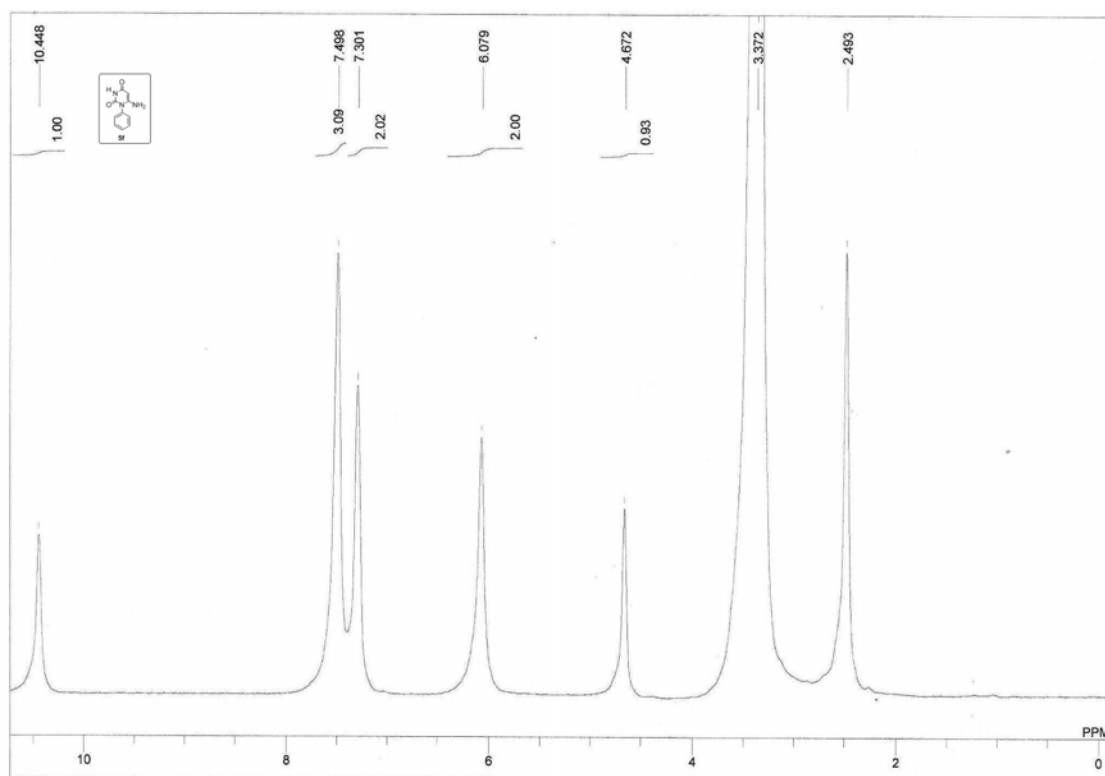
Compound 5c



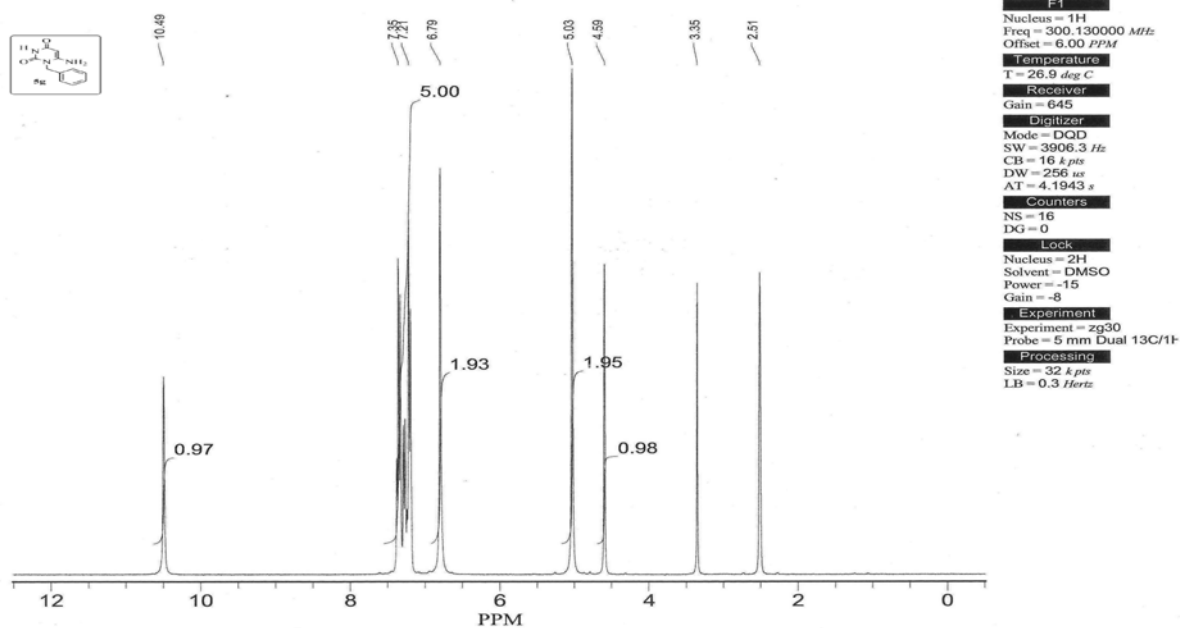
Compound 5d



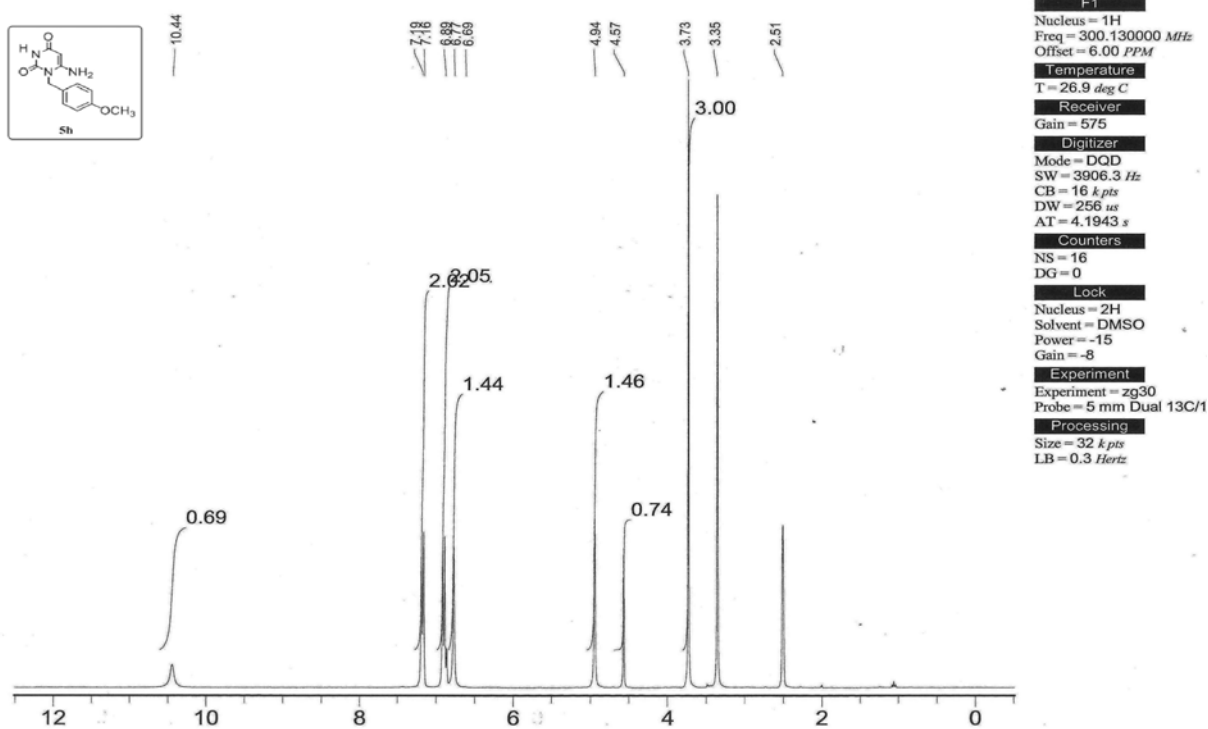
Compound 5e



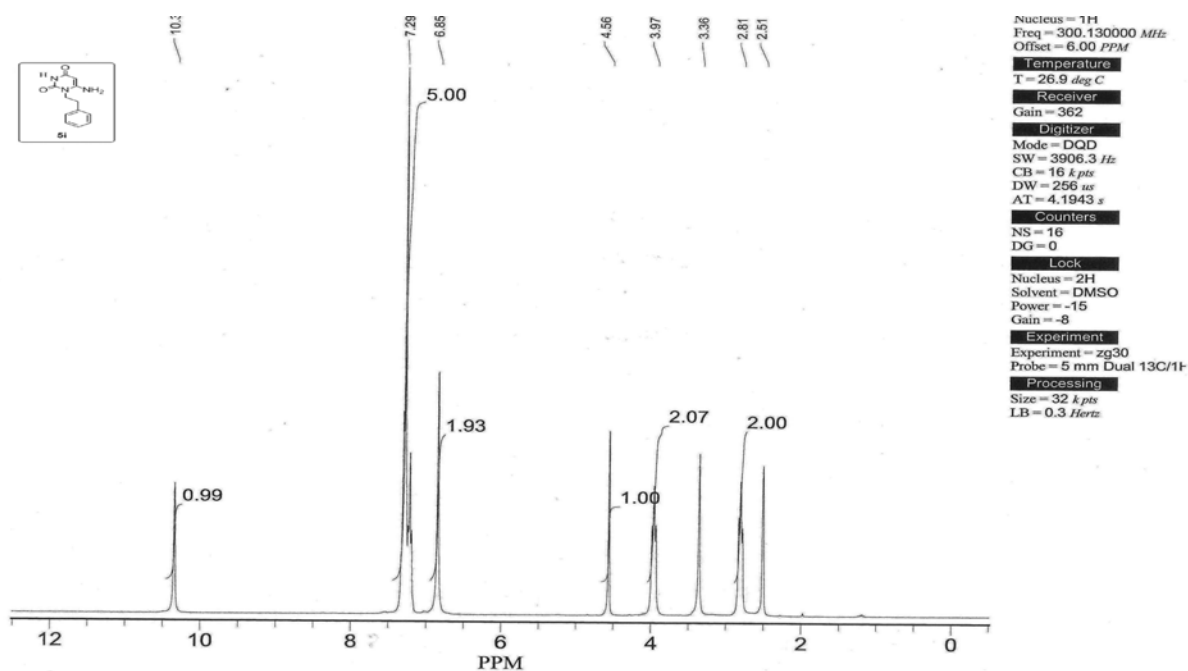
Compound 5f



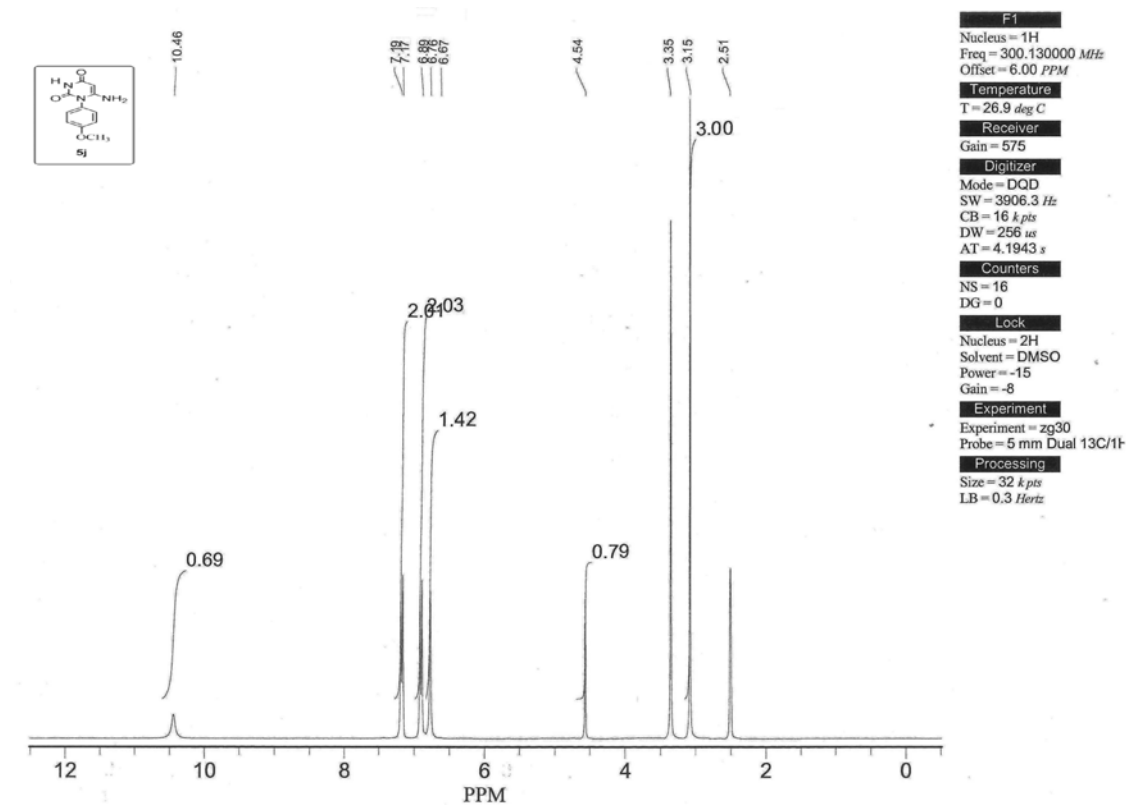
Compound 5g



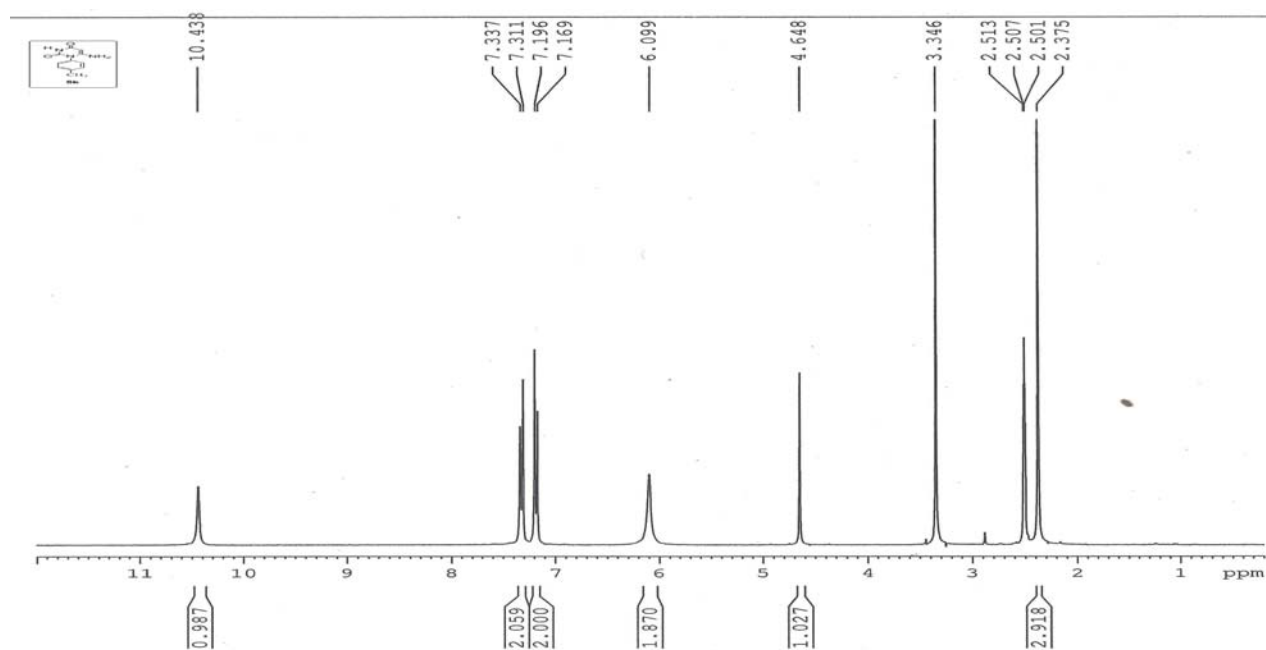
Compound 5h



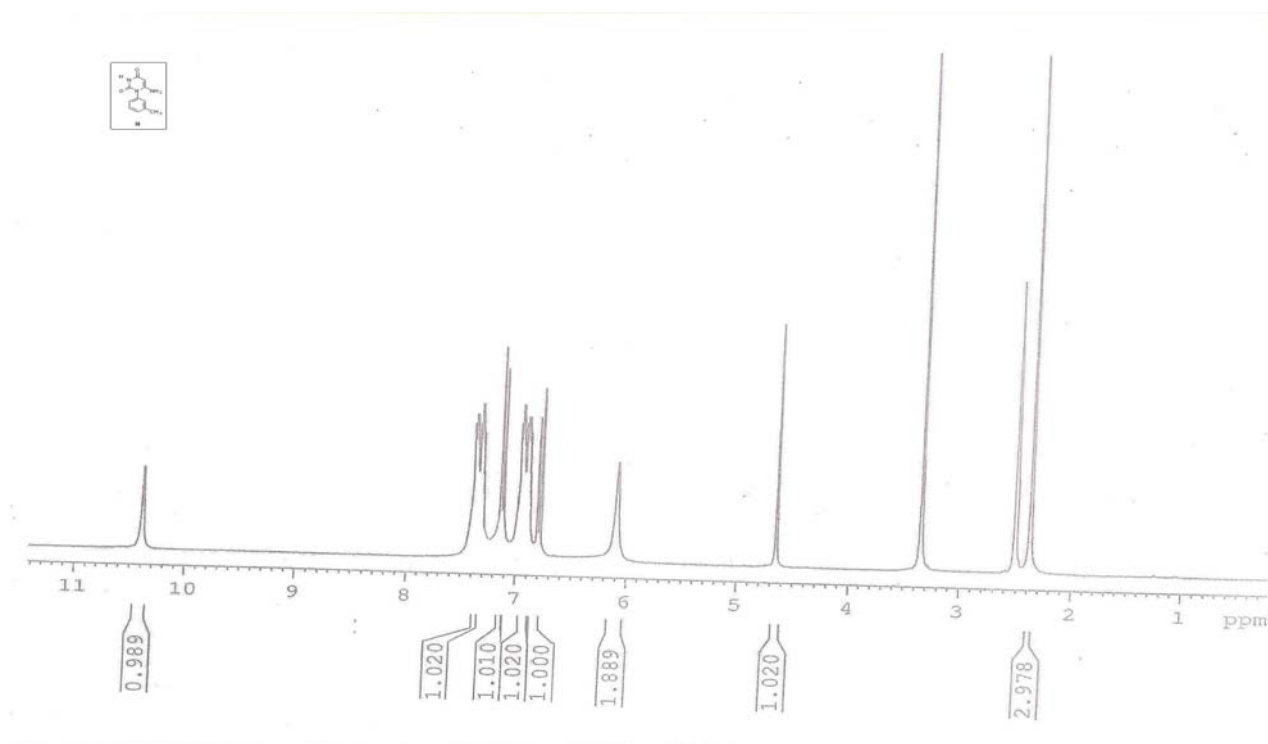
Compound 5i



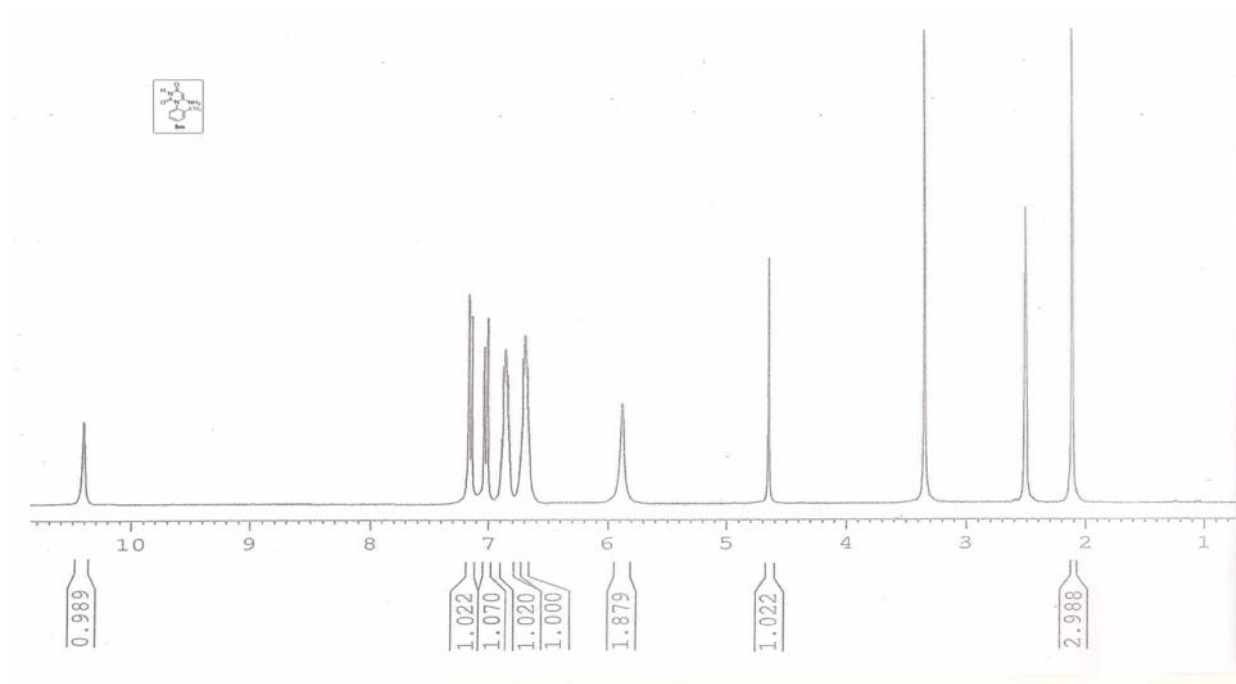
Compound 5j



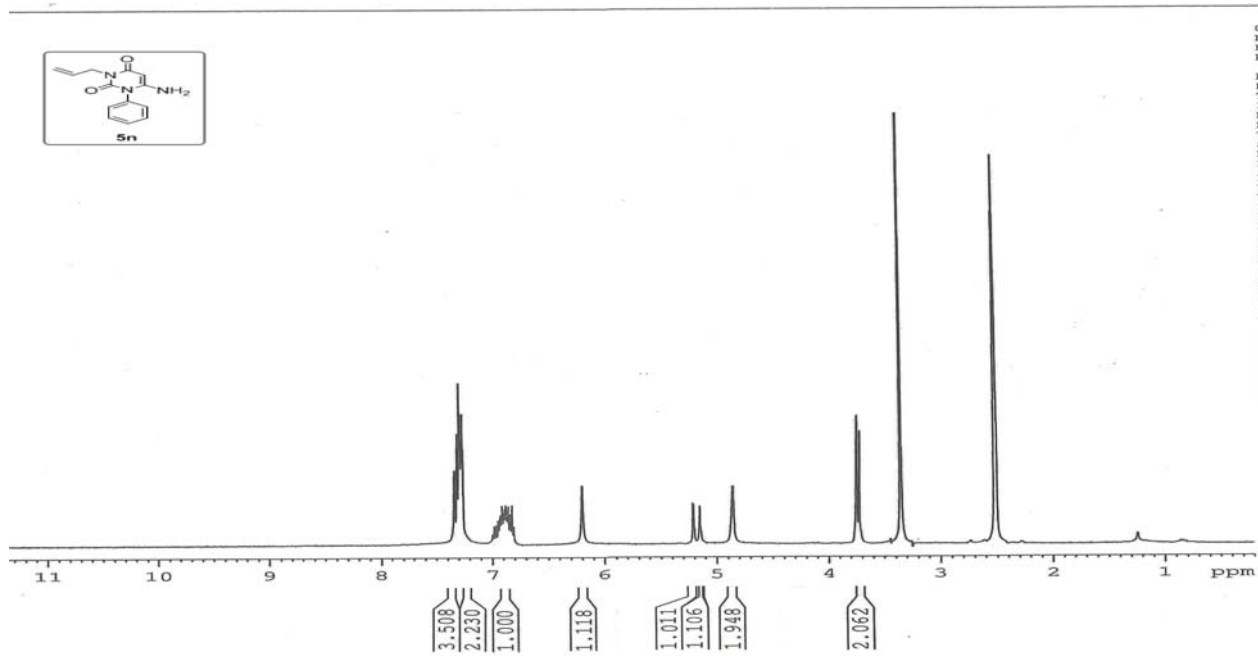
Compound 5k



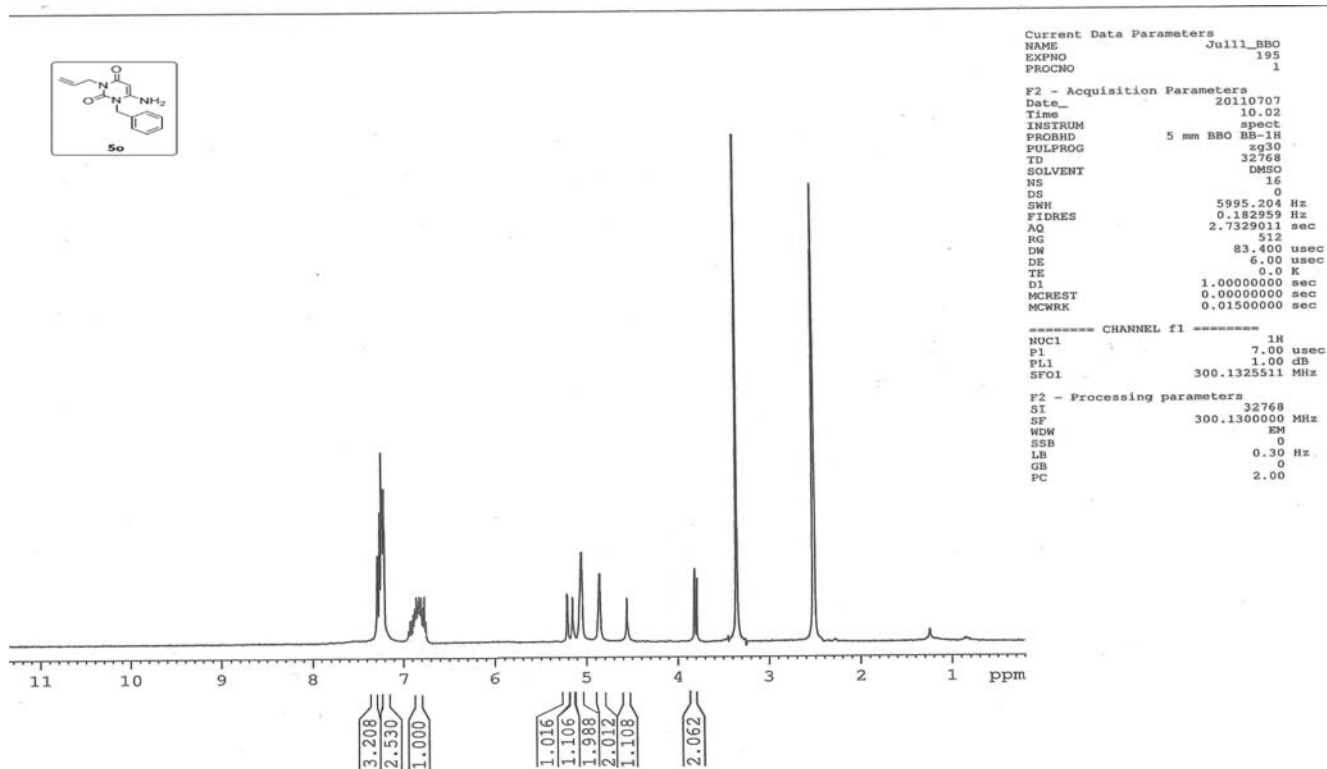
Compound 5l



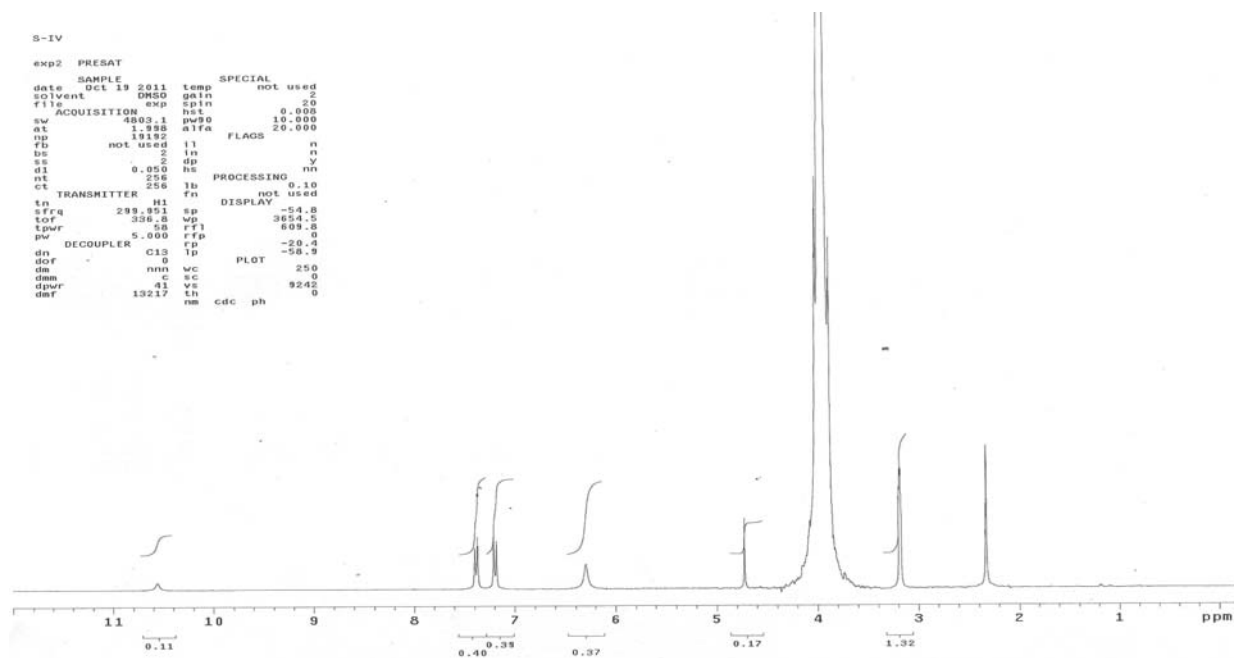
Compound 5m



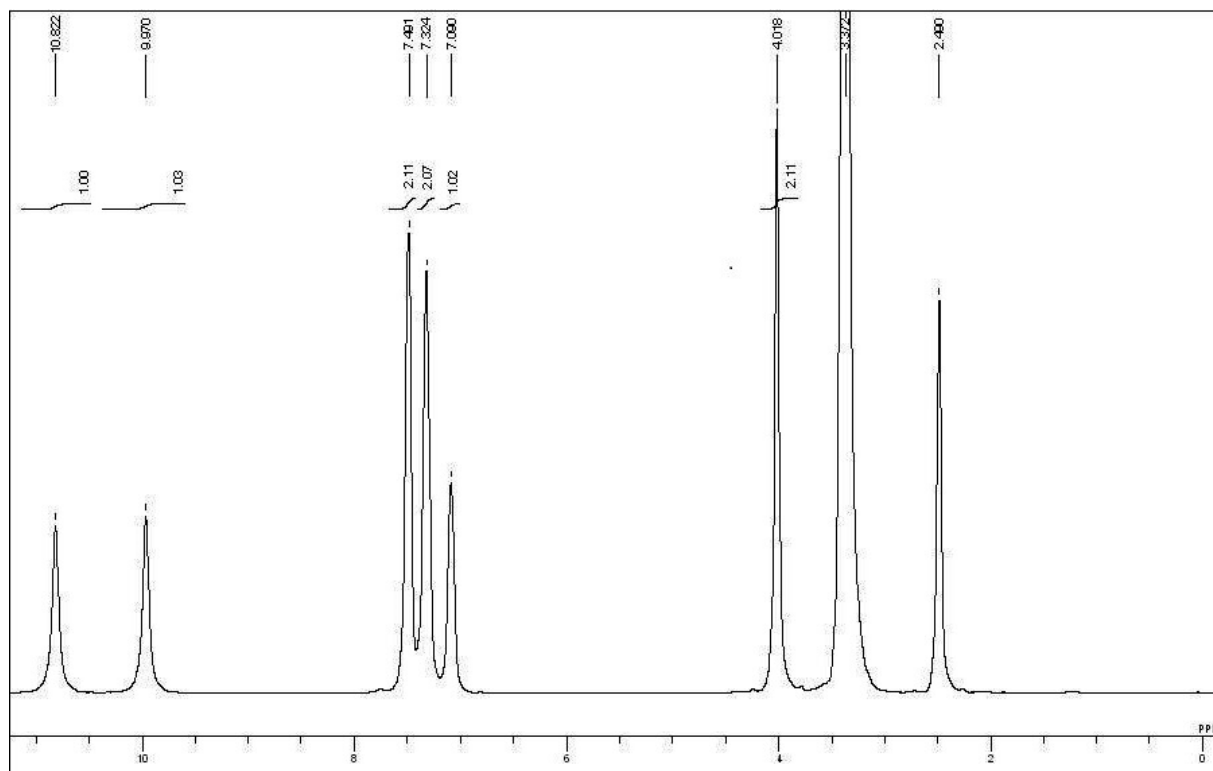
Compound 5n



Compound 5o

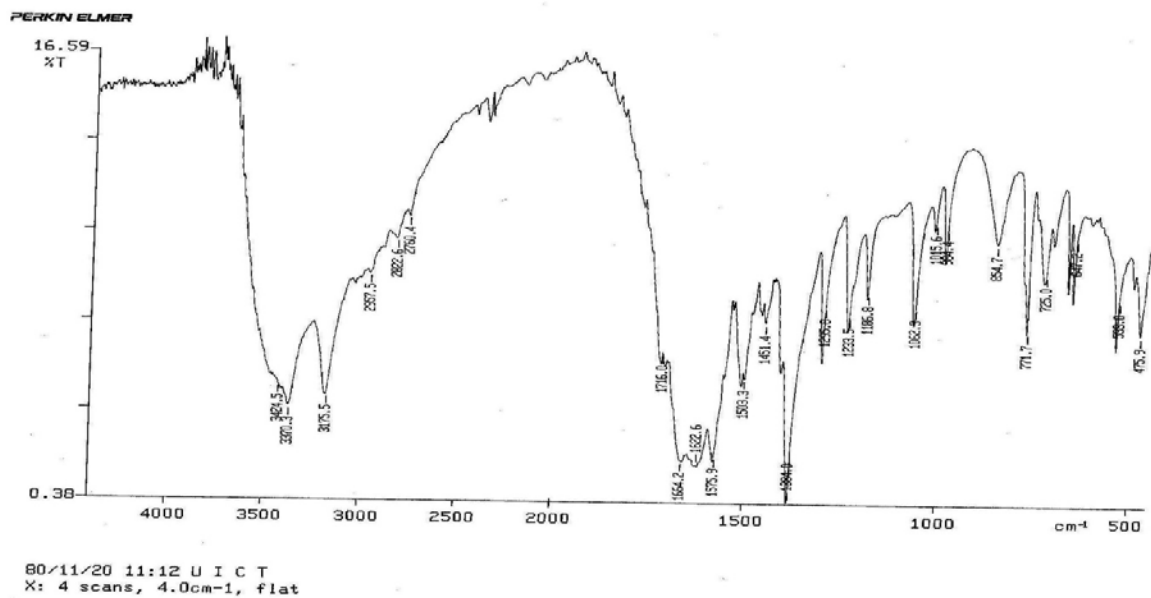


Compound 5p

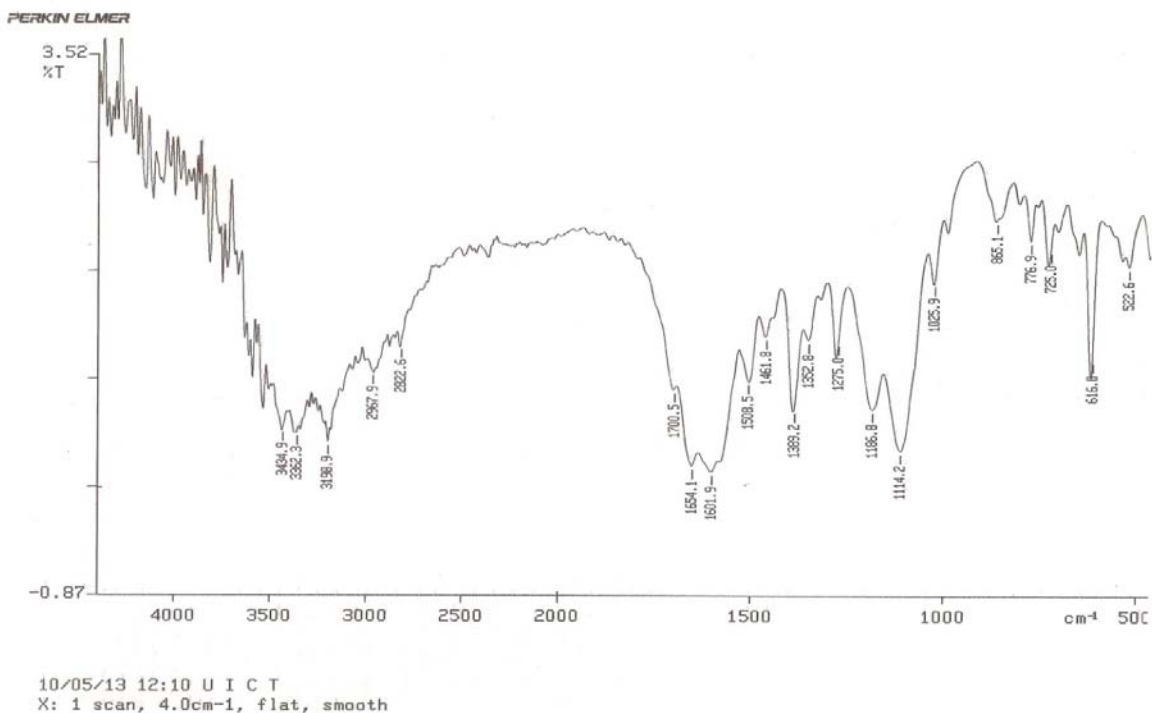


Compound 4f

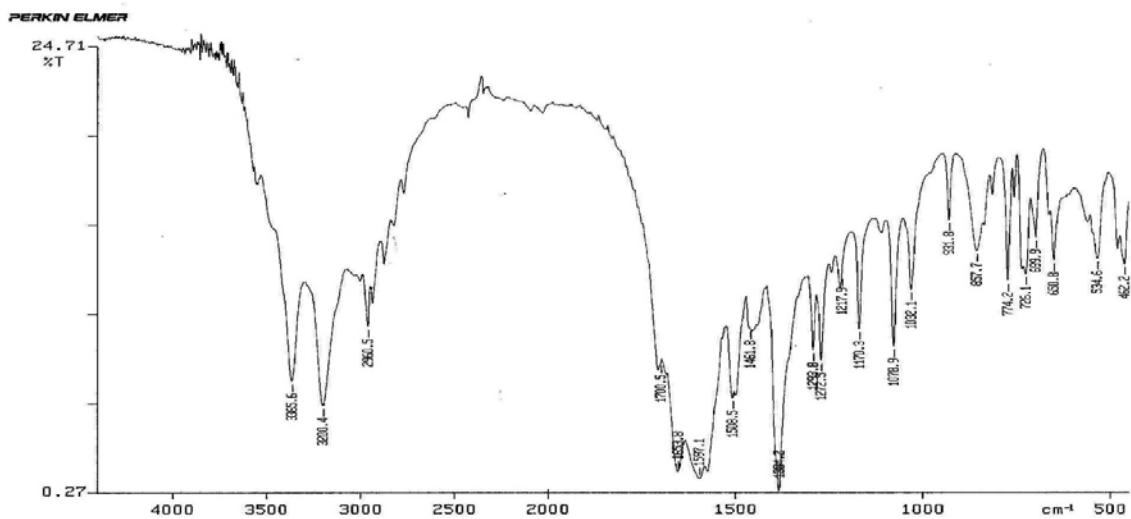
I. IR spectra of 6-aminouracils



Compound 5a

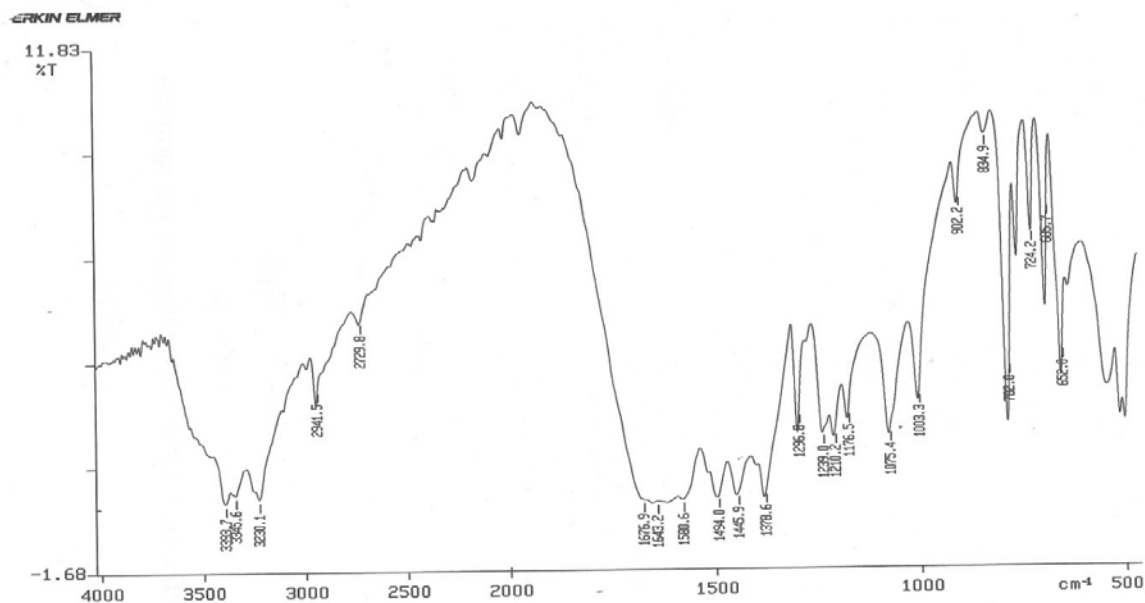


Compound 5b



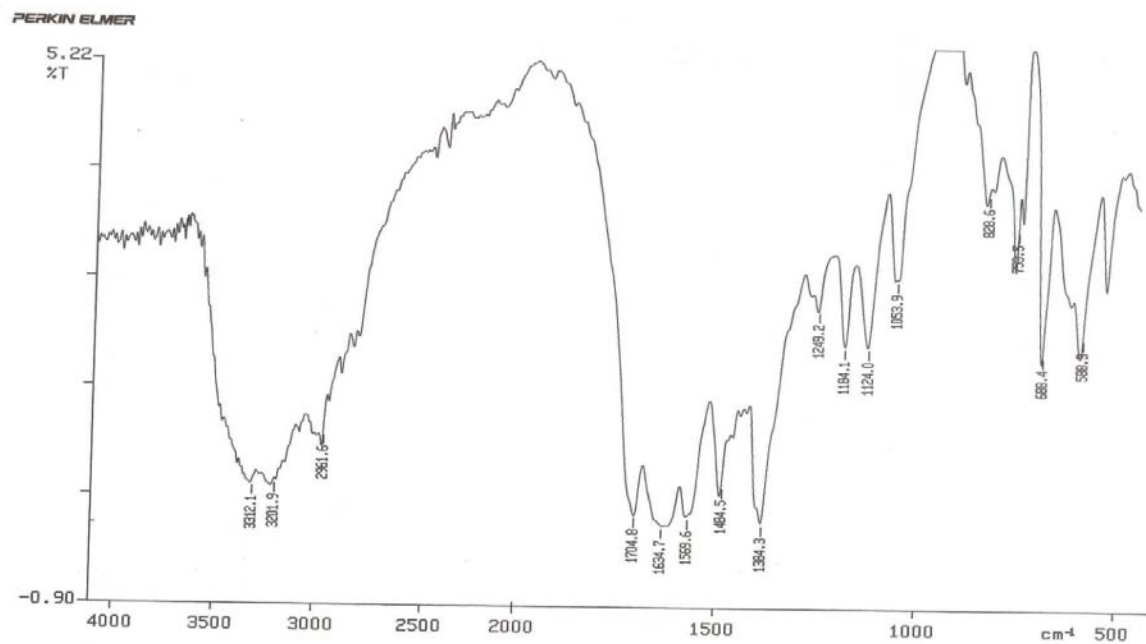
09/01/30 18:15 U I C T
X: 4 scans, 4.0cm⁻¹, flat

Compound 5c



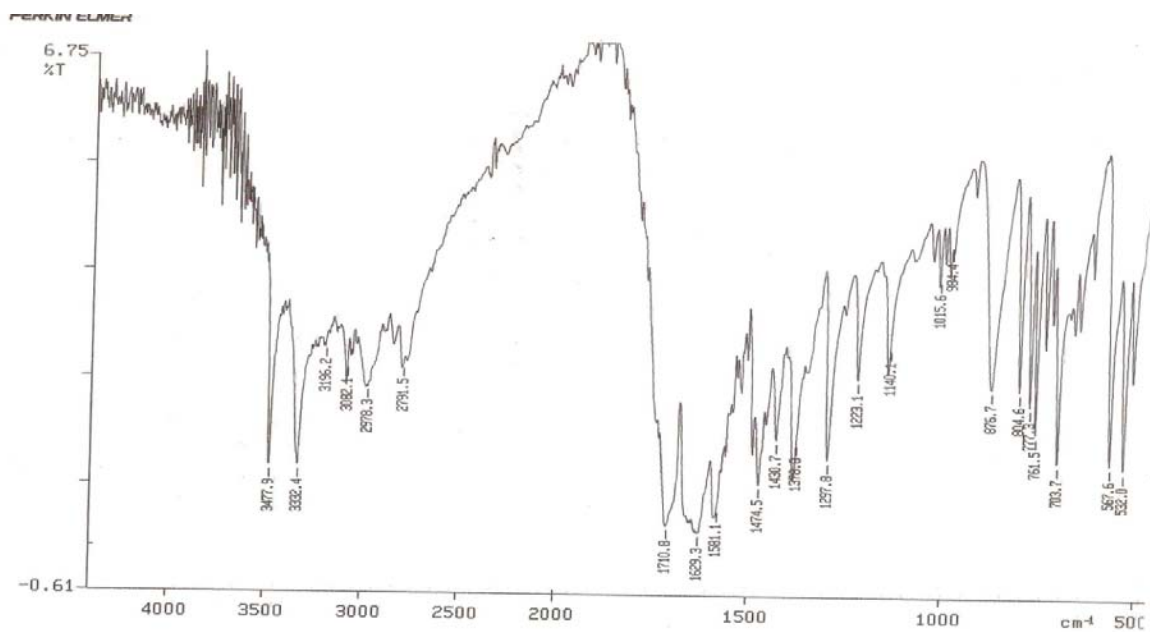
11/03/11 18:25 U I C T
X: 4 scans, 4.0cm⁻¹, flat, smooth

Compound 5d



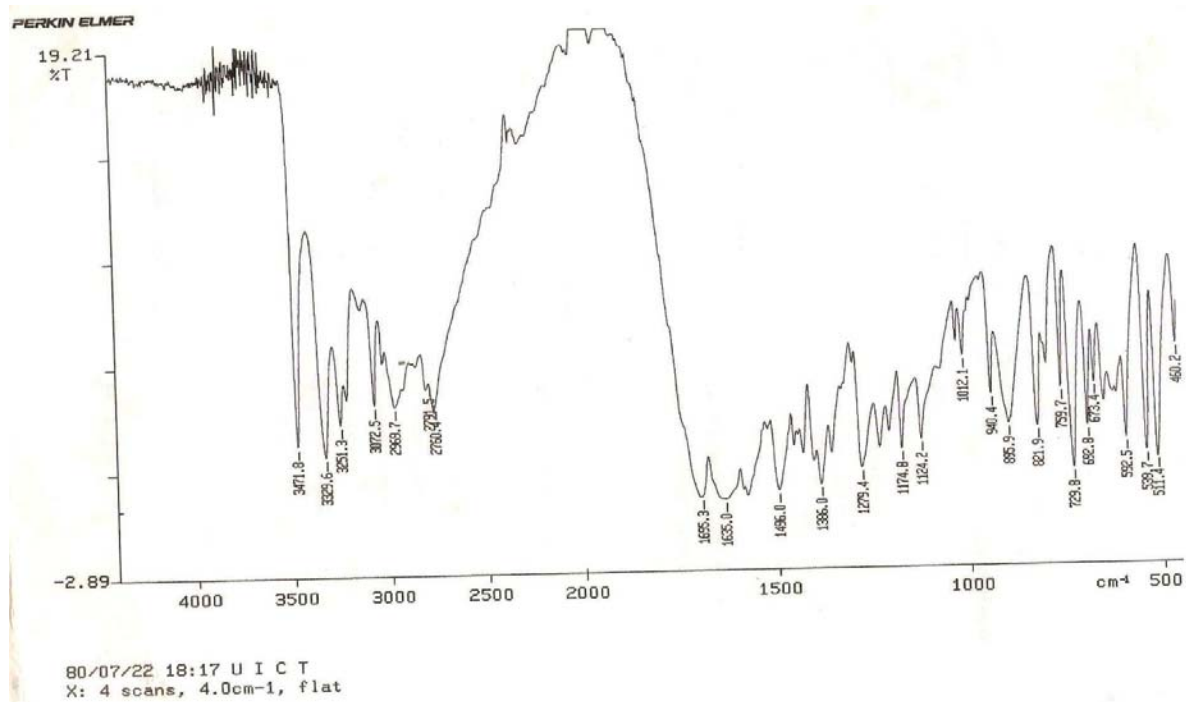
11/03/11 19:00 U I C T
X: 4 scans, 4.0cm⁻¹, flat, smooth

Compound 5e

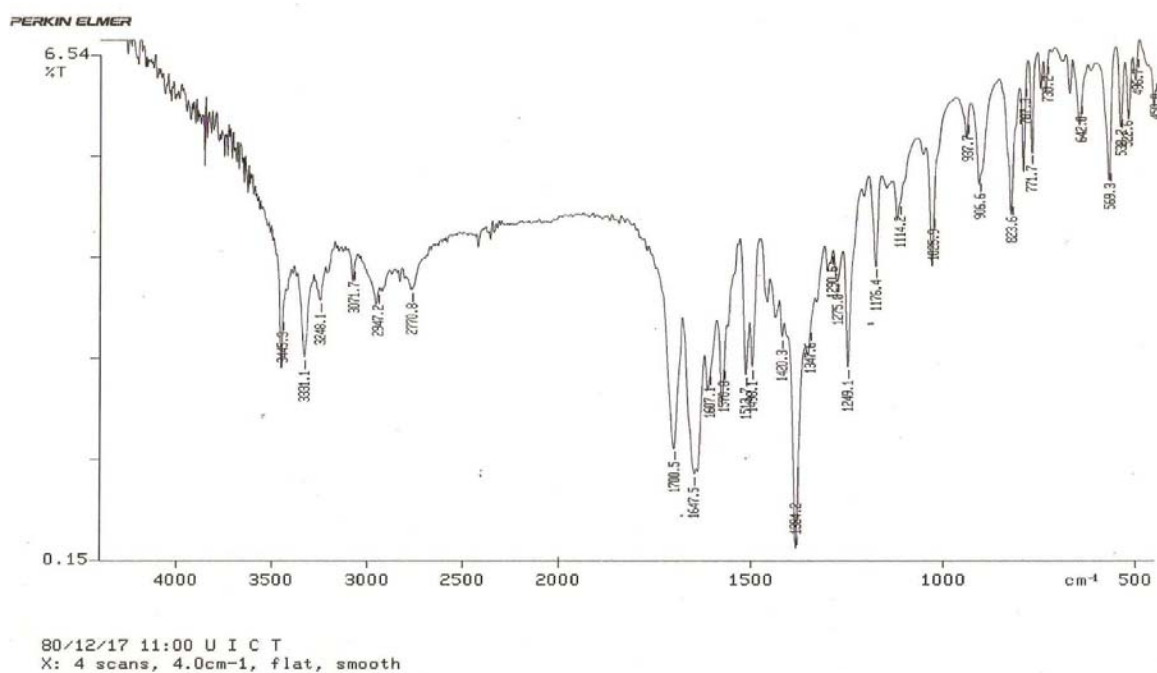


10/05/13 12:28 U I C T
X: 4 scans, 4.0cm⁻¹, flat

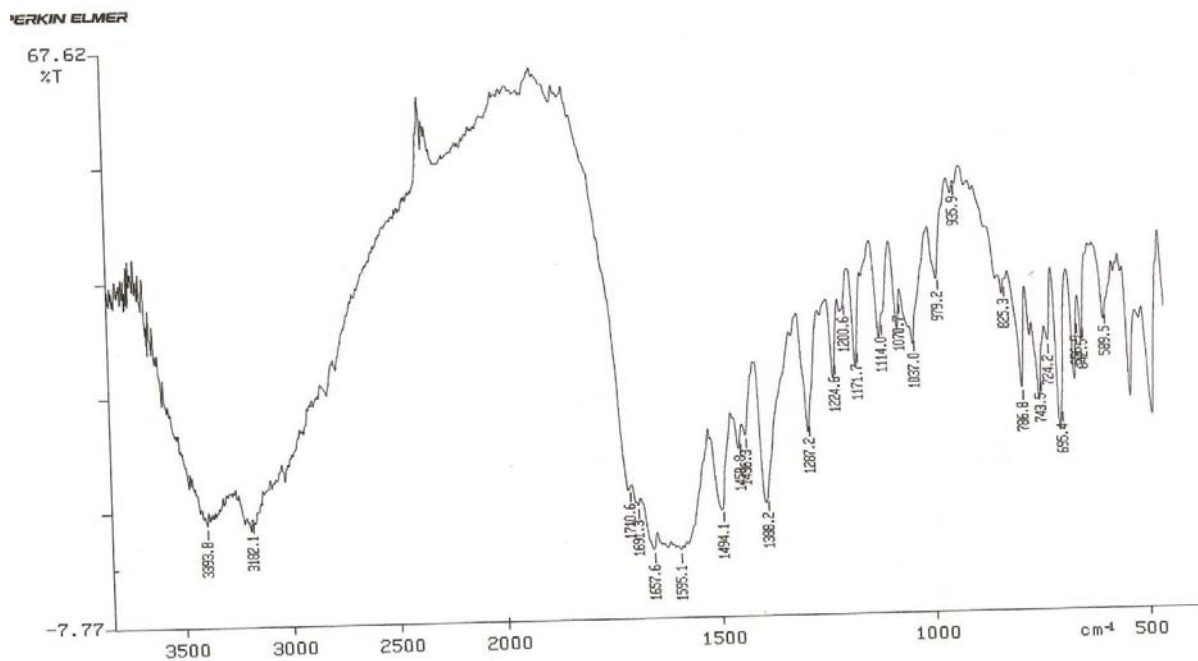
Compound 5f



Compound 5g

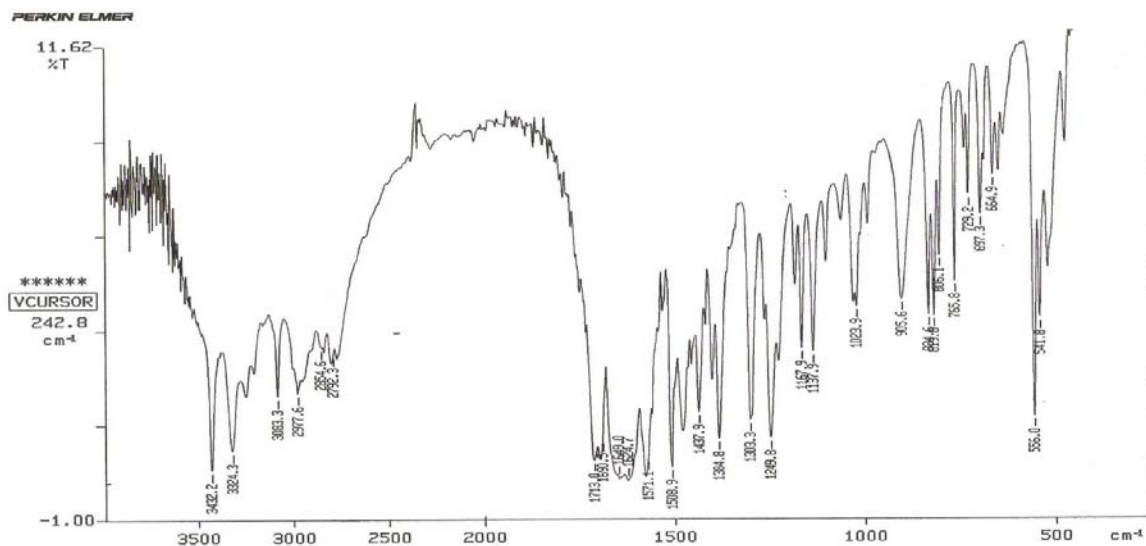


Compound 5h



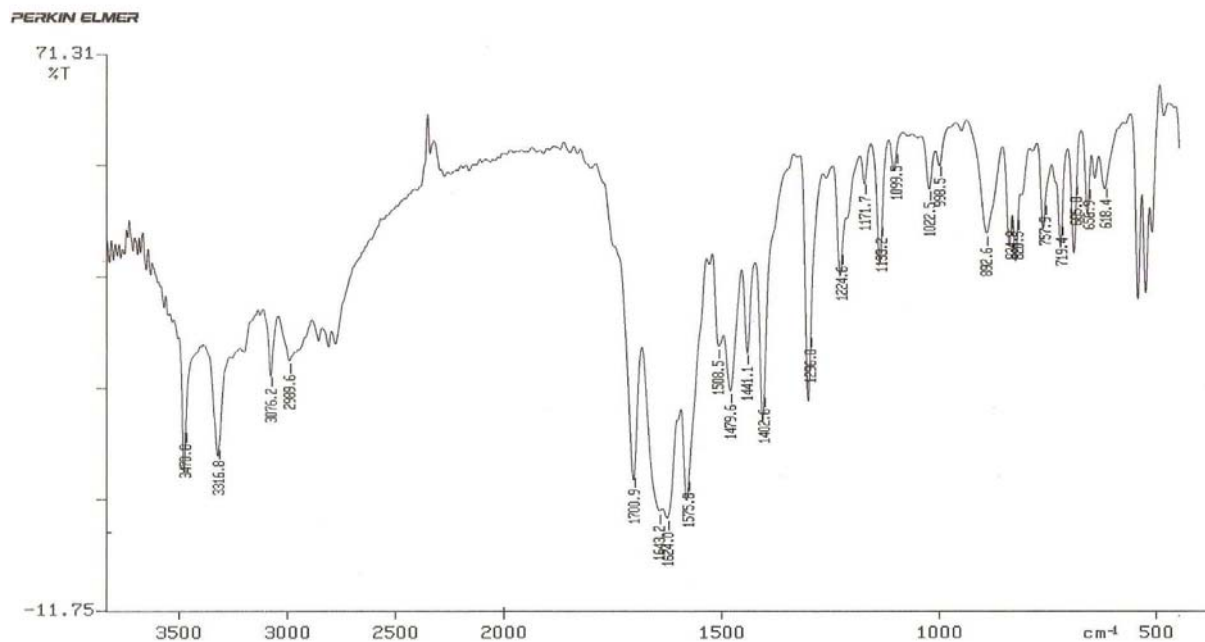
11/09/22 15:40 U I C T
X: 4 scans, 4.0 cm^{-1} , smooth

Compound 5i



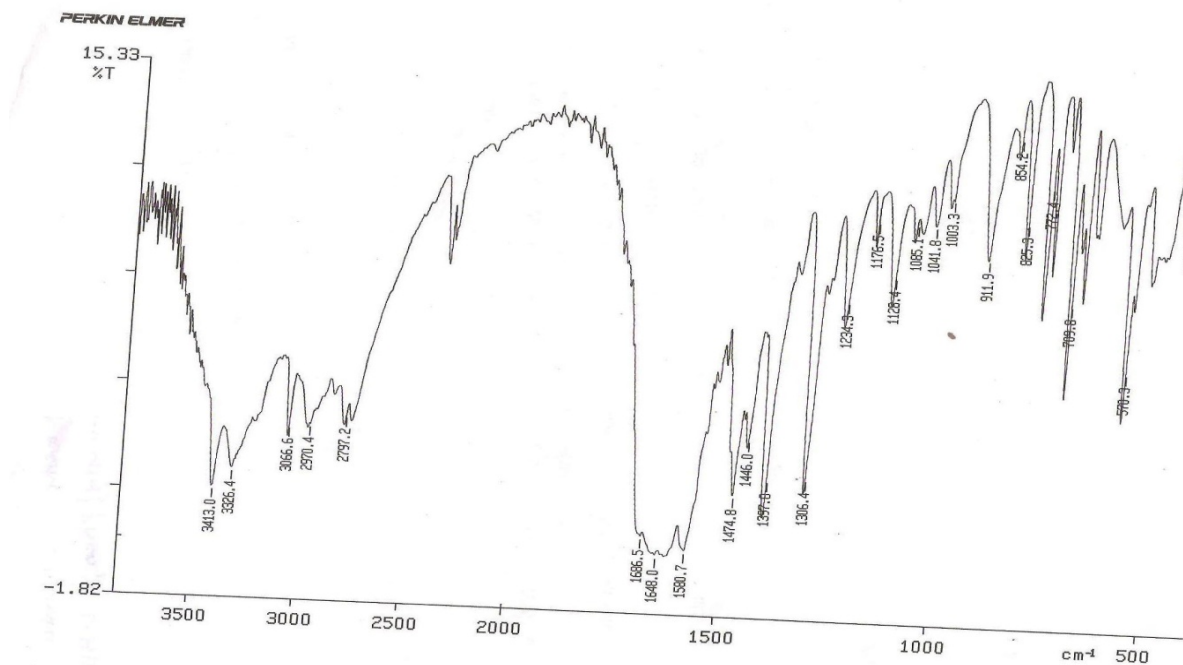
10/03/31 17:47 U I C T
X: 4 scans, 4.0 cm^{-1} , flat

Compound 5j



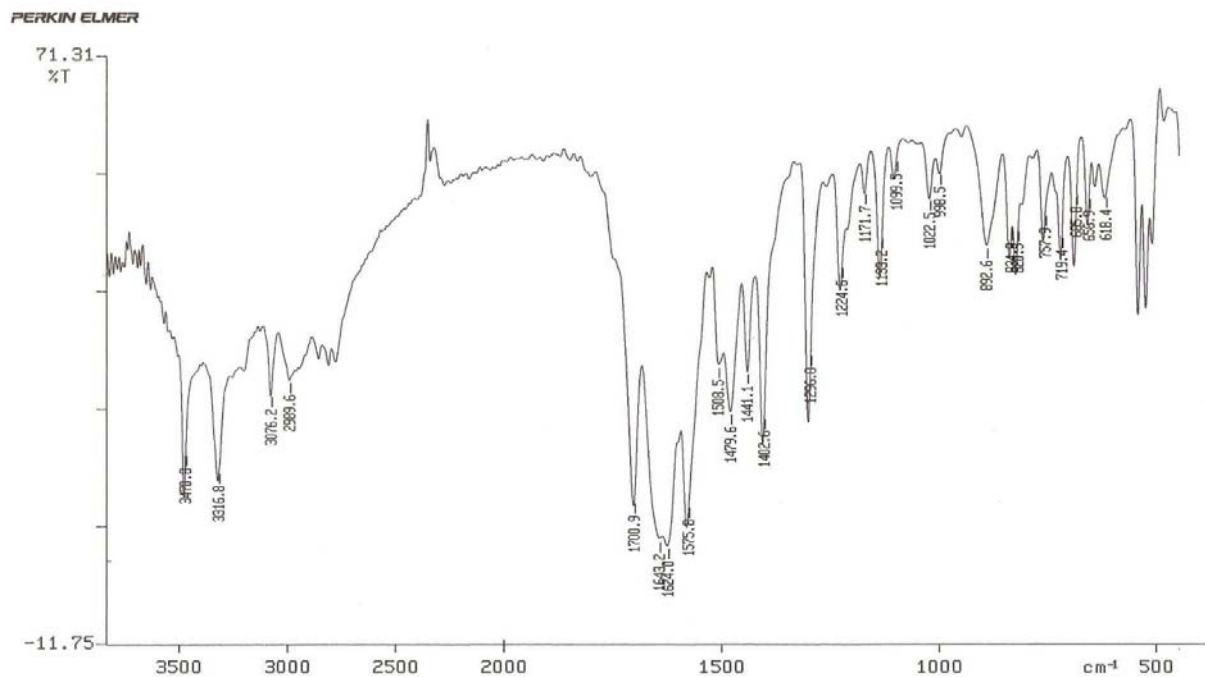
11/09/22 15:21 U I C T
X: 4 scans, 4.0 cm^{-1} , smooth

Compound 5k



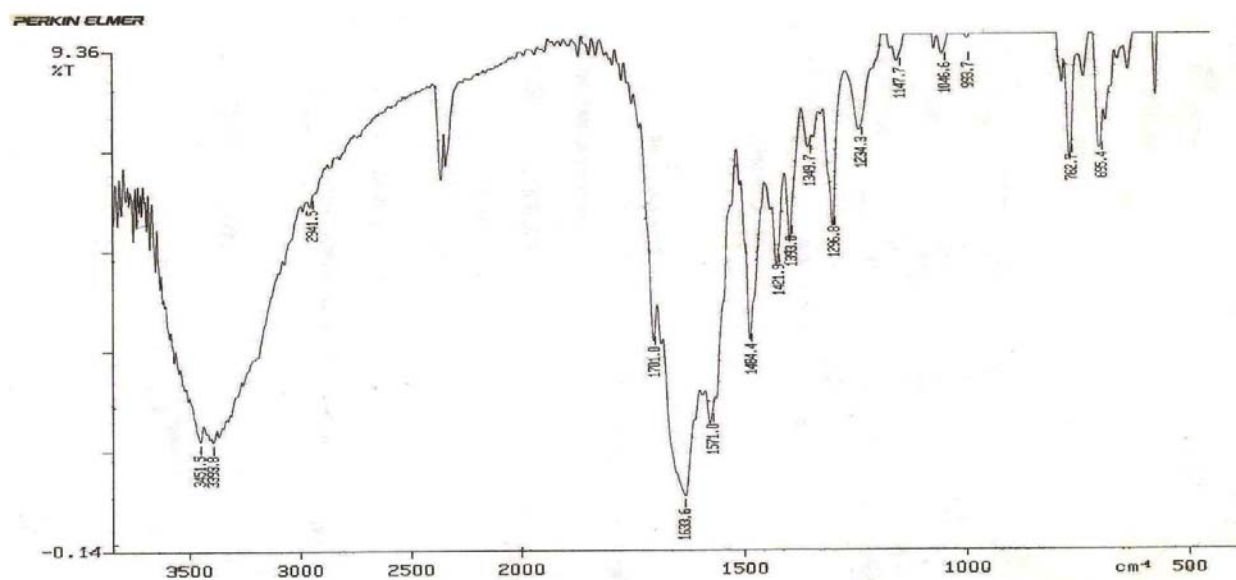
11/07/02 15:01 U I C T
X: 4 scans, 4.0 cm^{-1} , flat, smooth

Compound 5l



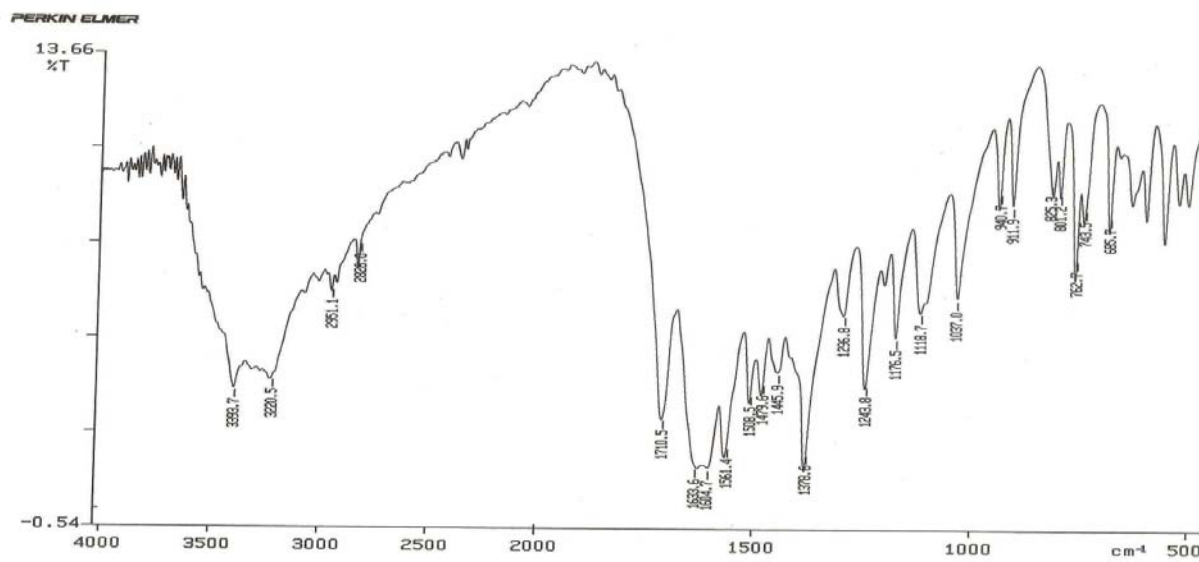
11/09/22 15:21 U I C T
X: 4 scans, 4.0cm⁻¹, smooth

Compound 5m



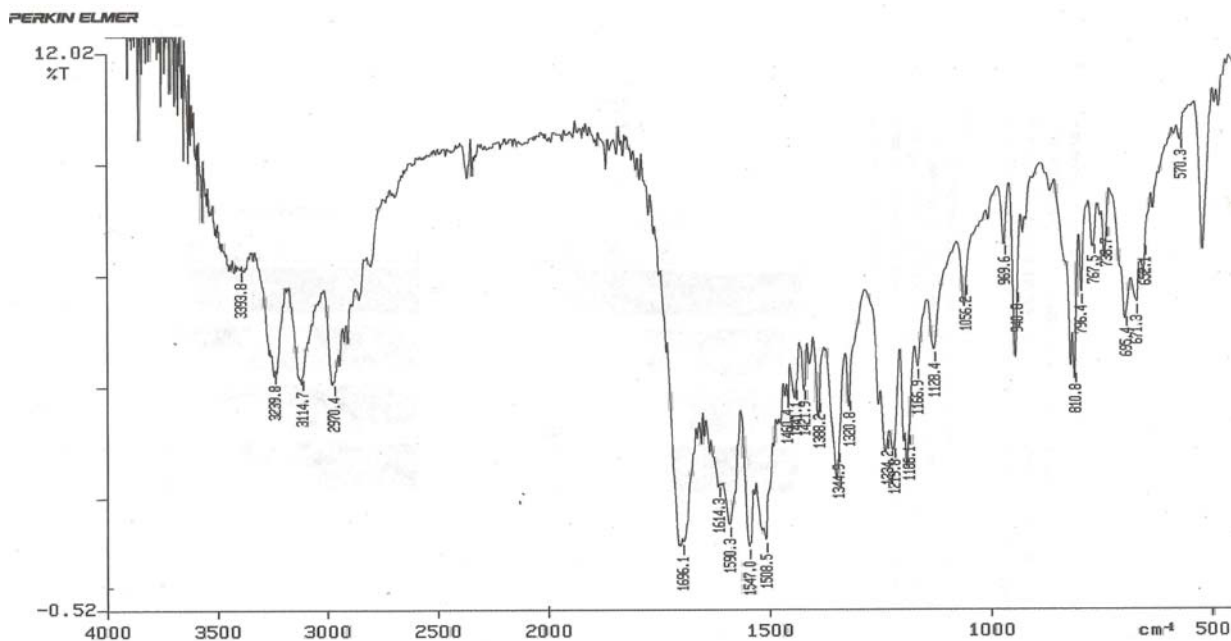
11/07/02 15:08 U I C T
X: 4 scans, 4.0cm⁻¹, flat, smooth

Compound 5n



11/03/11 18:28 U I C T
X: 4 scans, 4.0 cm^{-1} , flat, smooth

Compound 5o



Compound 5p

J. References

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