**Supporting Information for**

**Multicomponent synthesis and anticancer activity studies of novel 6-(trifluoromethyl)-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate derivatives**

Anil Valeru,a Zhi-Bin Luo,a \*Imran Khan,a Bin Liu,a Bhavanarushi Sngepu,aNarender Reddy Godumagadda,b Yin Xu,aJimin Xie, a \*

a*School of Chemistry and Chemical Engineering, Jiangsu University, Zhenjiang, 212013,P.R.China.*

*b Medicinal Chemistry and Pharmacology Division, CSIR-Indian Institute of Chemical Technology, Tarnaka, Hyderabad–500007, India.*

(E-mail: luozb@ujs.edu.cn, xiejm@ujs.edu.cn)

**General information:**

Melting points were recorded on Casia-Siamia (VMP-AM) melting point apparatus and are uncorrected. 1H NMR spectra were recorded on Bruker AV 300MHz in CDCl3 & DMSO-d6 using TMS as internal standard. ESI spectra were recorded on Micro mass, Quattro LC using ESI+ software with capillary voltage 3.98 kV and ESI mode positive ion trap detector. All high-resolution spectra were recorded on QSTARXL hybrid MS/MS system (Applied Biosystems, USA) under Electrospray ionization. All the reactions were monitored by thin layer chromatography (TLC) on precoated silica gel 60 F254; spots were visualized with UV light. Merck silica gel (60-120 mesh) was used for column chromatography.

**General Procedure:**

A mixture of aryl aldehyde (0.1 mol), urea (0.1 mol) and trifluoromethyl 1,3-dicarbonyl compound (0.1 mol) in aq HF (40%) were charged in polypropelene bottle and stirred at ambient temperature for a period of 60 min. The reaction progress was monitored by thin-layer chromatography (TLC). After completion of the reaction, the reaction mixture was poured into crushed ice, and the resulted solid was filtered. The solid was washed with water and then sodium bicarbonate solution and dried to afford the product.

***Ethyl-2-oxo-4-phenyl-6-(trifluoromethyl)-1,2,3,4-tetrahydro-5-pyrimidine carboxylate (4a):***

Yield: 90%. m.p. 203-205 ºC; 1H NMR (300 MHz, CDCl3+ DMSO-d6): δ 1.21 (3H, t, *J* = 7.2 Hz, OCH2CH3), 4.12 (2H, q, *J* = 7.2 Hz, CH2), 5.13 (1H, d, *J* = 3.1),7.21-7.29 (5H, m), 9.44(1H, bs, N-H), 9.29 (1H, bs, N-H); 13C NMR (75 MHz, CDCl3+ DMSO-d6): δ 171.5, 168.1, 156.0, 152.2, 143.6, 138.6, 131.8, 126.2, 125.8, 124.7, 112.1, 70.8, 58.4, 15.2; MS (ESI): m/z [(M+H)+]: 315. HRMS m/z Calcd. for C14H13F3N2O3 [(M+H)+]: 315.0878, Found 315.0876.

***Ethyl 2-oxo-4-(p-tolyl)-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4b):***

Yield: 87%. m.p. 223-225 ºC; 1H NMR (300 MHz, CDCl3+ DMSO-d6): δ 1.25 (3H, t, *J =* 7.2 Hz, OCH2CH3), 2.34 (3H, s, ArCH3), 4.11 (2H, q, *J* = 7.2 Hz, CH2),5.31 (1H, s, CH), 5.50 (1H, bs, NH),7.28 (2H, d, *J =* 8.4 Hz, ArH), 7.41 (2H, d, *J =* 8.4 Hz, ArH), 7.59 (1H, bs, NH); 13C NMR (75 MHz, CDCl3+ DMSO-d6): δ 170.4, 165.2, 153.4, 151.0, 144.5, 138.1, 132.6, 128.4, 126.8, 124.1, 120.5, 75.3, 60.4, 22.5, 16.2; MS (ESI): m/z [(M+H)+]: 329. HRMS m/z Calcd. for C15H15F3N2O3 [(M+H)+]: 329.1068, Found 329.1066.

***Ethyl 4-(4-chlorophenyl)-2-oxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4c):***

Yield: 91%. m.p. 201-203 ºC; 1H NMR (300 MHz, CDCl3+ DMSO-d6): δ 1.23 (3 H, t, *J =* 7.2 Hz, OCH2CH3), 4.12 (2H, q, *J* = 7.2 Hz, CH2),5.29 (1H, s, CH), 5.53 (1H, bs, NH), 7.29 (2H, d, *J =* 8.4 Hz, ArH), 7.51 (2H, d, *J =* 8.4 Hz, ArH), 7.62 (1H, bs, NH); 13C NMR (75 MHz, CDCl3+DMSO-d6): δ 172.3, 166.2, 154.4, 152.5, 144.8, 136.2, 132.5, 128.6, 125.6, 123.7, 119.1, 72.8, 59.2, 16.2; MS (ESI): m/z [(M+H)+]: 349. HRMS m/z Calcd. for C14H12ClF3N2O3 [(M+H)+]: 349.0489, Found 349.0491.

***Ethyl 4-(4-bromophenyl)-2-oxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4d):***

Yield: 92%. m.p. 241-243 ºC; 1H NMR (300 MHz, CDCl3+ DMSO-d6): δ 1.21 (3 H, t, *J =* 7.2 Hz, OCH2CH3), 4.11 (2H, q, *J* = 7.2 Hz, CH2),5.31 (1H, s, CH), 5.52 (1H, bs, NH), 7.31 (2H, d, *J =* 8.4 Hz, ArH), 7.54 (2H, d, *J =* 8.4 Hz, ArH), 7.65 (1H, bs, NH); 13C NMR (75 MHz, CDCl3+DMSO-d6): δ 171.2, 165.7, 152.1, 149.5, 143.4, 136.1, 133.5, 126.1, 124.4, 122.7, 120.1, 68.2, 56.1, 16.8; MS (ESI): m/z [(M+H)+]: 394. HRMS m/z Calcd. for C14H12BrF3N2O3 [(M+H)+]: 394.1559, Found 394.1560.

***Ethyl 4-(4-methoxyphenyl)-2-oxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4e):***

Yield: 86%. m.p. 209-212 ºC; 1H NMR (300 MHz, CDCl3+ DMSO-d6): δ 1.22 (3H, t, *J =* 7.2 Hz, OCH2CH3), 3.84 (3H, s, ArOCH3), 4.12 (2H, q, *J* = 7.2 Hz, CH2),5.28 (1H, s, CH), 5.52 (1H, bs, NH), 7.29 (2H, d, *J =* 8.4 Hz, ArH), 7.65 (2H, d, *J =* 8.4 Hz, ArH), 7.71 (1H, bs, NH); 13C NMR (75 MHz, CDCl3+DMSO-d6): δ 169.1, 164.6, 156.1, 150.4, 143.2, 138.6, 132.7, 128.1, 124.6, 122.3, 120.8, 73.6, 55.4, 59.2, 16.2; MS (ESI): m/z [(M+H)+]: 345. HRMS m/z Calcd. for C15H15F3N2O4 [(M+H)+]: 345.0984, Found 345.0982.

***Ethyl 2-oxo-4-(o-tolyl)-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4f):***

Yield: 86%. m.p. 215-217 ºC; 1H NMR (300 MHz, CDCl3+DMSO-d6): δ 1.26 (3H, t, *J =* 7.2 Hz, OCH2CH3), 2.34 (3H, s, ArCH3), 4.15 (2H, q, *J* = 7.2 Hz, CH2),5.32 (1H, s, CH), 5.53 (1H, bs, NH), 7.16-7.28 (4H, m, ArH), 7.61 (1H, bs, NH); 13C NMR (75 MHz, CDCl3+ DMSO-d6): δ 171.3, 166.1, 158.9, 152.5, 146.5, 138.4, 135.2, 127.3, 123.3, 124.7, 121.7, 76.6, 61.7, 21.6, 16.8; MS (ESI): m/z [(M+H)+]: 329. HRMS m/z Calcd. for C15H15F3N2O3 [(M+H)+]: 329.1035, Found 329.1032.

***Ethyl 4-(4-fluorophenyl)-2-oxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4g):***

Yield: 89%. m.p. 189-192 ºC; δ 1H NMR (300 MHz, CDCl3): δ 1.21 (3H, t, *J =* 7.2 Hz, OCH2CH3), 4.18 (2H, q, *J* = 7.2 Hz, CH2),5.32 (1H, s, CH), 5.51 (1H, bs, NH), 7.26 (2H, d, *J =* 8.4 Hz, ArH), 7.58 (2H, d, *J =* 8.4 Hz, ArH), 7.69 (1H, bs, NH); 13C NMR (75 MHz, CDCl3+DMSO-d6): δ 170.3, 166.8, 155.2, 148.3, 144.1, 138.3, 132.7, 128.6, 124.9, 121.3, 119.1, 70.2, 57.2, 16.7; MS (ESI): m/z [(M+H)+]: 333. HRMS m/z Calcd. for C14H12F4N2O3 [(M+H)+]: 333.0784, Found 333.0782.

***Ethyl 4-(4-nitrophenyl)-2-oxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4h):***

Yield: 85%. m.p. 210-212 ºC; 1H NMR (300 MHz, CDCl3+ DMSO-d6): δ 1.18 (3 H, t, *J =* 7.2 Hz, OCH2CH3), 4.11 (2H, q, *J* = 7.2 Hz, CH2),5.25 (1H, s, CH), 5.62 (1H, bs, NH), 7.25 (2H, d, *J =* 8.4 Hz, ArH), 7.58 (2H, d, *J =* 8.4 Hz, ArH), 7.68 (1H, bs, NH); 13C NMR (75 MHz, CDCl3+DMSO-d6): δ 171.2, 168.5, 156.3, 151.8, 145.7, 135.9, 131.4, 127.5, 124.7, 122.8, 120.3, 73.9, 59.2, 15.8; MS (ESI): m/z [(M+H)+]: 360. HRMS m/z Calcd. for C14H12F3N3O5 [(M+H)+]: 360.0729, Found 360.0726.

***Ethyl 2-oxo-6-(trifluoromethyl)-4-(3-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4i):***

Yield: 82%. m.p. 231-233 ºC; 1H NMR (300 MHz, CDCl3+DMSO-d6): δ 1.25 (3H, t, *J =* 7.2 Hz, OCH2CH3), 4.15 (2H, q, *J* = 7.2 Hz, CH2),5.34 (1H, s, CH), 5.51 (1H, bs, NH), 7.29 (1H, s, ArH), 7.42-7.48 (3H, m, ArH), 7.68 (1H, bs, NH); 13C NMR (75 MHz, CDCl3+DMSO-d6): δ 168.3, 162.3, 156.7, 151.4, 145.8, 137.1, 136.1, 128.1, 126.4, 123.2, 121.1, 120.3, 71.6, 60.2, 15.8; MS (ESI): m/z [(M+H)+]: 383. HRMS m/z Calcd. for C15H12F6N2O3 [(M+H)+]: 383.0752, Found 383.0755.

***Ethyl 4-(4-cyanophenyl)-2-oxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4j):***

Yield: 82%. m.p. 210-212 ºC; 1H NMR (300 MHz, CDCl3+DMSO-d6): δ 1.23 (3H, t, *J =* 7.2 Hz, OCH2CH3), 4.12 (2H, q, *J* = 7.2 Hz, CH2),5.31 (1H, s, CH), 5.51 (1H, bs, NH), 7.28 (2H, d, *J =* 8.4 Hz, ArH), 7.56 (2H, d, *J =* 8.4 Hz, ArH), 7.69 (1H, bs, NH); 13C NMR (75 MHz, CDCl3+DMSO-d6): δ 171.6, 165.1, 158.5, 152.6, 148.8, 136.5, 132.4, 129.4, 124.6, 122.7, 121.3, 118.2, 71.8, 58.3, 17.1; MS (ESI): m/z [(M+H)+]: 340. HRMS m/z Calcd. for C15H12F3N3O3 [(M+H)+]: 340.0831, Found 340.0833.

***Ethyl 4-(furan-2-yl)-2-oxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4k):***

Yield: 85%. m.p. 184-186 ºC; 1H NMR (300 MHz, CDCl3+DMSO-d6): δ 1.20 (3H, t, *J =* 7.2 Hz, OCH2CH3), 4.10 (2H, q, *J* = 7.2 Hz, CH2),5.32 (1H, s, CH), 5.51 (1H, bs, NH), 7.31-7.39 (3H, m, ArH), 7.71 (1H, bs, NH); 13C NMR (75 MHz, CDCl3+DMSO-d6): δ 171.4, 168.1, 152.5, 135.2, 131.6, 128.7, 125.4, 122.4, 120.5, 72.5, 60.2, 16.1; MS (ESI): m/z [(M+H)+]: 305. HRMS m/z Calcd. for C12H11F3N2O4 [(M+H)+]: 305.0671, Found 305.0668.

***Ethyl 2-oxo-4-(thiophen-2-yl)-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4l):***

Yield: 80%. m.p. 167-168 ºC; 1H NMR (300 MHz, CDCl3+DMSO-d6): δ 1.21 (3H, t, *J =* 7.2 Hz, OCH2CH3), 4.12 (2H, q, *J* = 7.2 Hz, CH2),5.31 (1H, s, CH), 5.51 (1H, bs, NH), 7.33-7.41 (3H, m, ArH), 7.69 (1H, bs, NH); 13C NMR (75 MHz, CDCl3+DMSO-d6): δ 170.2, 166.2, 151.4, 136.6, 132.8, 129.4, 126.7, 122.3, 121.7, 71.1, 61.6, 16.8; MS (ESI): m/z [(M+H)+]: 321. HRMS m/z Calcd. for C12H11F3N2O3S [(M+H)+]: 321.0441, Found 321.0443.

***Ethyl 4-(2,4-difluorophenyl)-2-oxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4m):***

Yield: 88%. m.p. 162-164 ºC; δ 1H NMR (300 MHz, CDCl3+DMSO-d6): δ 1.19 (3H, t, *J =* 7.2 Hz, OCH2CH3), 4.18 (2H, q, *J* = 7.2 Hz, CH2),5.30 (1H, s, CH), 5.52 (1H, bs, NH), 7.12-7.23 (4H, m, ArH), 7.61 (1H, bs, NH); 13C NMR (75 MHz, CDCl3+DMSO-d6): δ 170.1, 162.4, 151.6, 146.1, 142.4, 137.2, 132.4, 128.6, 123.7, 121.2, 120.1, 68.1, 57.6, 16.2; MS (ESI): m/z [(M+H)+]: 351. HRMS m/z Calcd. for C14H11F5N2O3 [(M+H)+]: 351.0690, Found 351.0693.

***Ethyl 4-(3-nitrophenyl)-2-oxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4n):***

Yield: 79%. m.p. 248-250 ºC; 1H NMR (300 MHz, CDCl3+ DMSO-d6): δ 1.20 (3 H, t, *J =* 7.2 Hz, OCH2CH3), 4.12 (2H, q, *J* = 7.2 Hz, CH2),5.23 (1H, s, CH), 5.66 (1H, bs, NH), 7.26 (1H, s, ArH), 7.34-7.41(3H, m, ArH), 7.61 (1H, bs, NH); 13C NMR (75 MHz, CDCl3+DMSO-d6): δ 170.1, 166.3, 154.1, 152.1, 146.1, 132.9, 130.2, 128.5, 123.6, 121.8, 119.2, 71.9, 59.1, 15.5; MS (ESI): m/z [(M+H)+]: 360. HRMS m/z Calcd. for C14H12F3N3O5 [(M+H)+]: 360.0711, Found 360.0709.

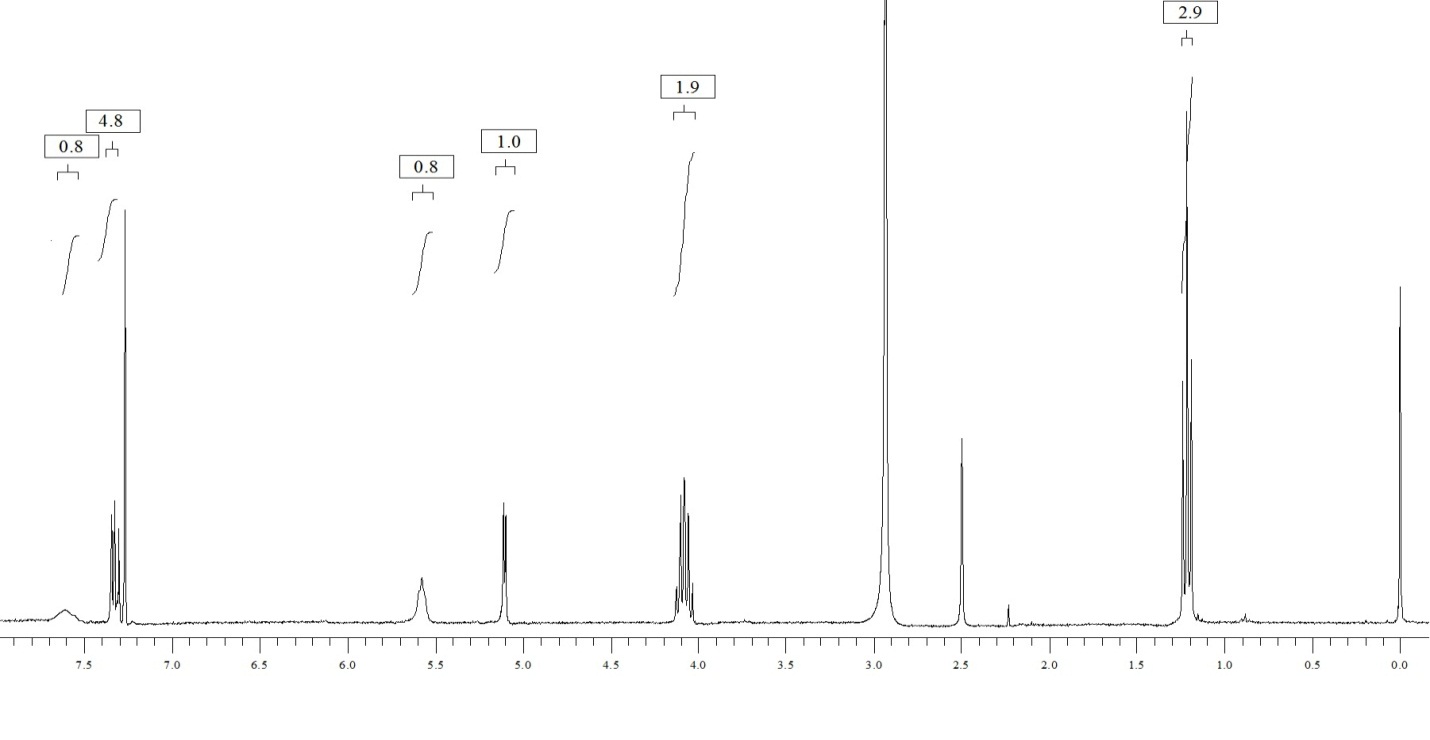
***(E)-ethyl 2-oxo-4-styryl-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4o):***

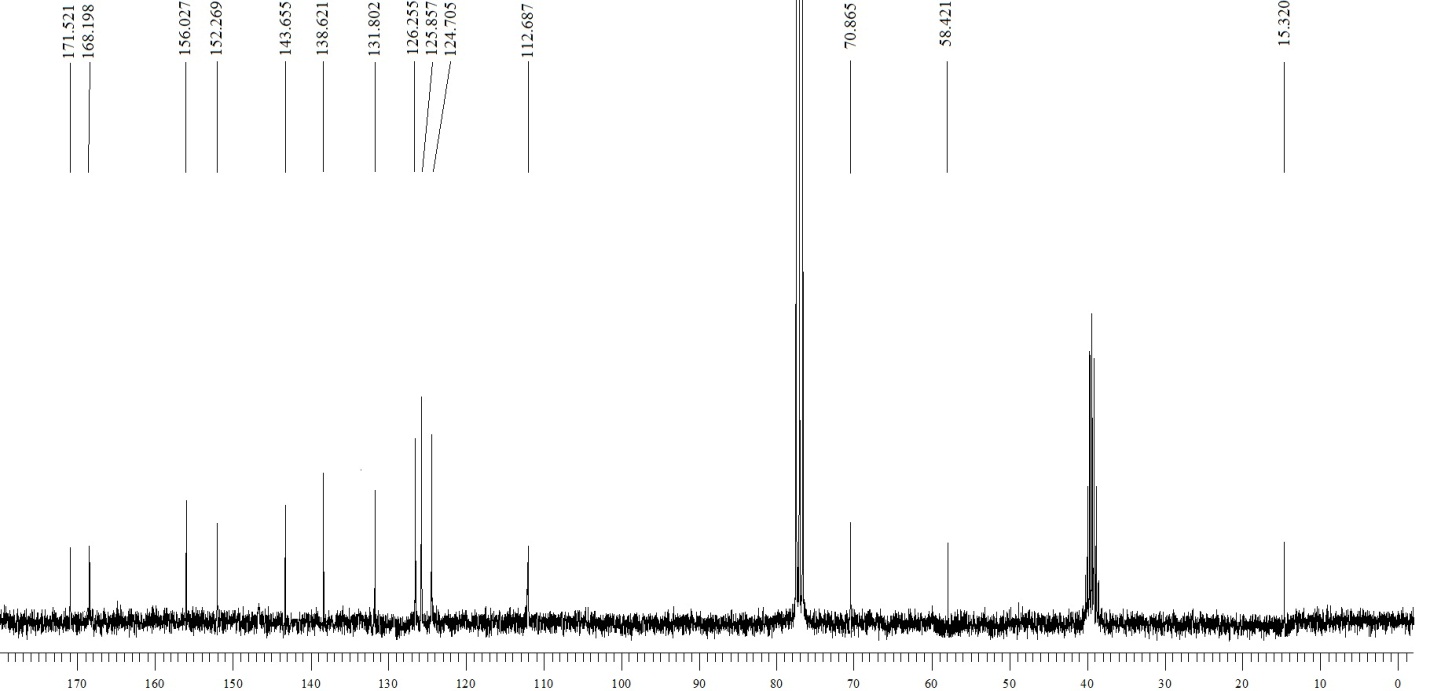
Yield: 81%. m.p. 228-230 ºC; 1H NMR (300 MHz, CDCl3+ DMSO-d6): δ 1.22 (3H, t, *J =* 7.2 Hz, OCH2CH3), 4.18 (2H, q, *J* = 7.2 Hz, CH2),5.22 (1H, s, CH), 5.65 (1H, bs, NH), 7.12 (1H, s, ‒CH=), 7.18 (1H, s, ‒CH=), 7.34-7.41(5H, m, ArH), 7.82 (1H, bs, NH); 13C NMR (75 MHz, CDCl3+ DMSO-d6): δ 170.6, 166.2, 158.8, 151.4, 148.4, 142.6, 139.6, 134.7, 131.9, 127.2, 126.4, 124.3, 120.1, 70.8, 58.4, 15.2; MS (ESI): m/z [(M+H)+]: 341. HRMS m/z Calcd. for C16H15F3N2O3 [(M+H)+]: 341.1032, Found 341.1035.

***Ethyl 4-(naphthalen-2-yl)-2-oxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4p):***

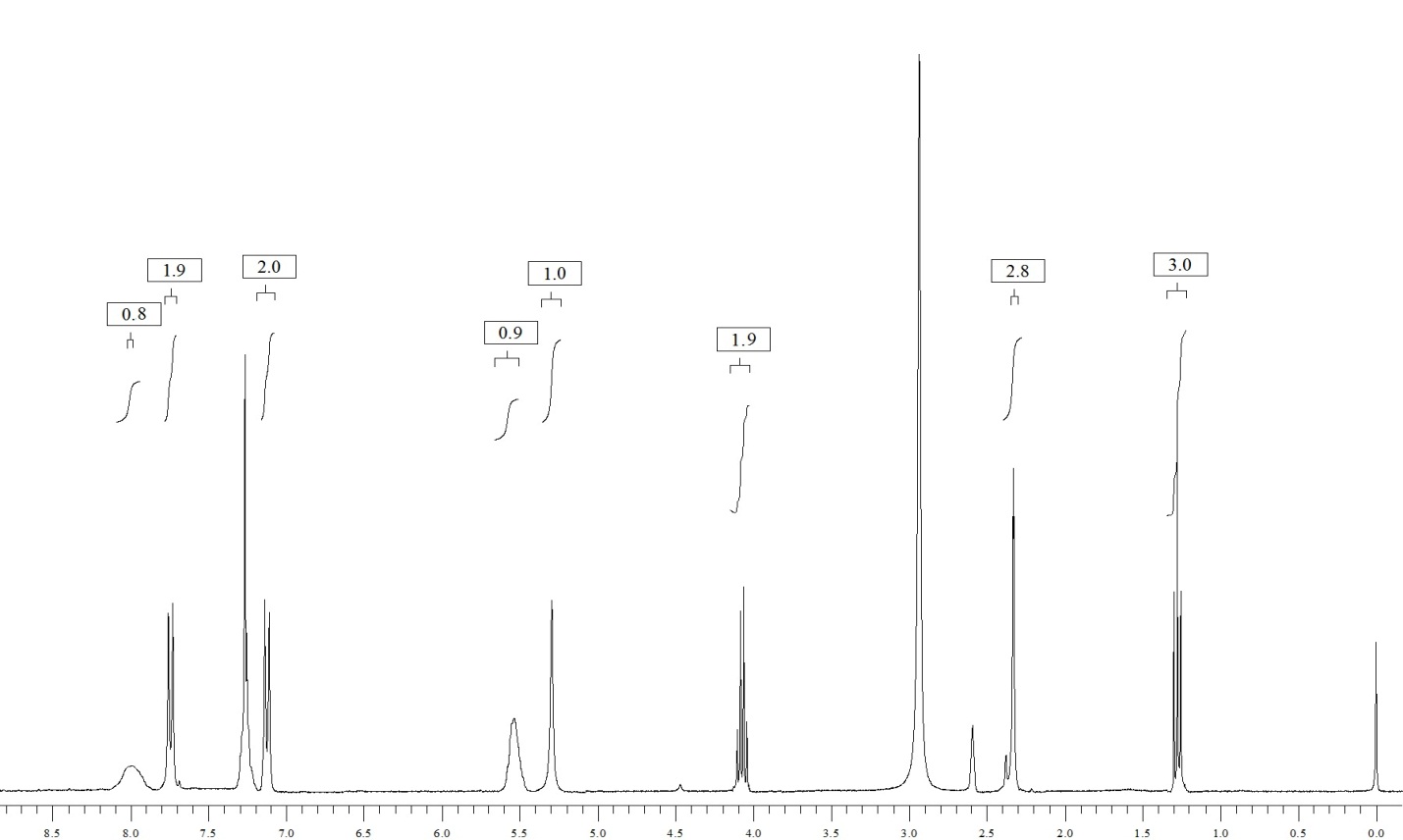
Yield: 80%. m.p. 245-247 ºC; 1H NMR (300 MHz, CDCl3+ DMSO-d6): δ 1.24 (3H, t, *J =* 7.2 Hz, OCH2CH3), 4.22 (2H, q, *J* = 7.2 Hz, CH2),5.23 (1H, s, CH), 5.62 (1H, bs, NH), 7.46-7.79(7H, m, ArH), 7.84 (1H, bs, NH); 13C NMR (75 MHz, CDCl3+ DMSO-d6): δ 170.5, 168.1, 162.5, 158.2, 151.3, 142.5, 139.3, 136.2, 132.5, 128.7, 128.2, 125.8, 124.7, 122.5, 118.7, 71.4, 59.3, 16.2; MS (ESI): m/z [(M+H)+]: 365. HRMS m/z Calcd. for C18H15F3N2O3 [(M+H)+]: 365.1035, Found 365.1032.

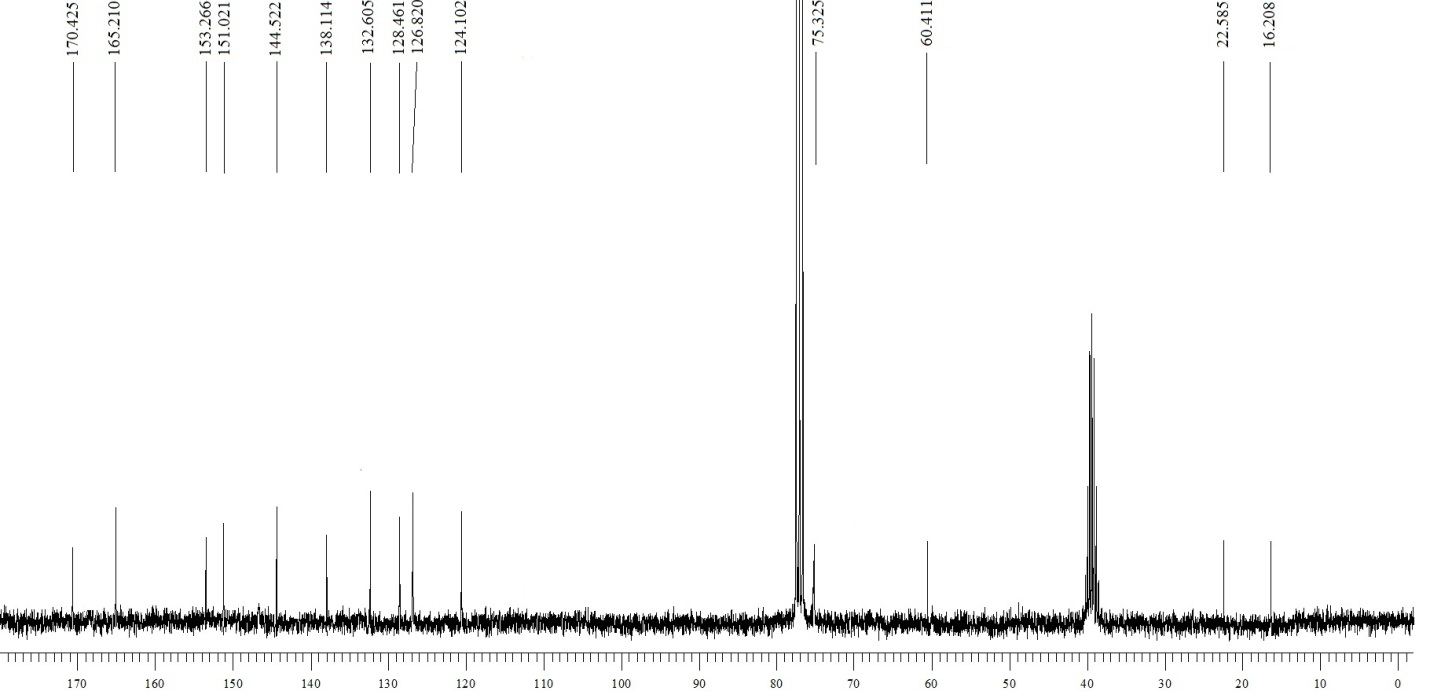
***Ethyl-2-oxo-4-phenyl-6-(trifluoromethyl)-1,2,3,4-tetrahydro-5-pyrimidine carboxylate (4a):***



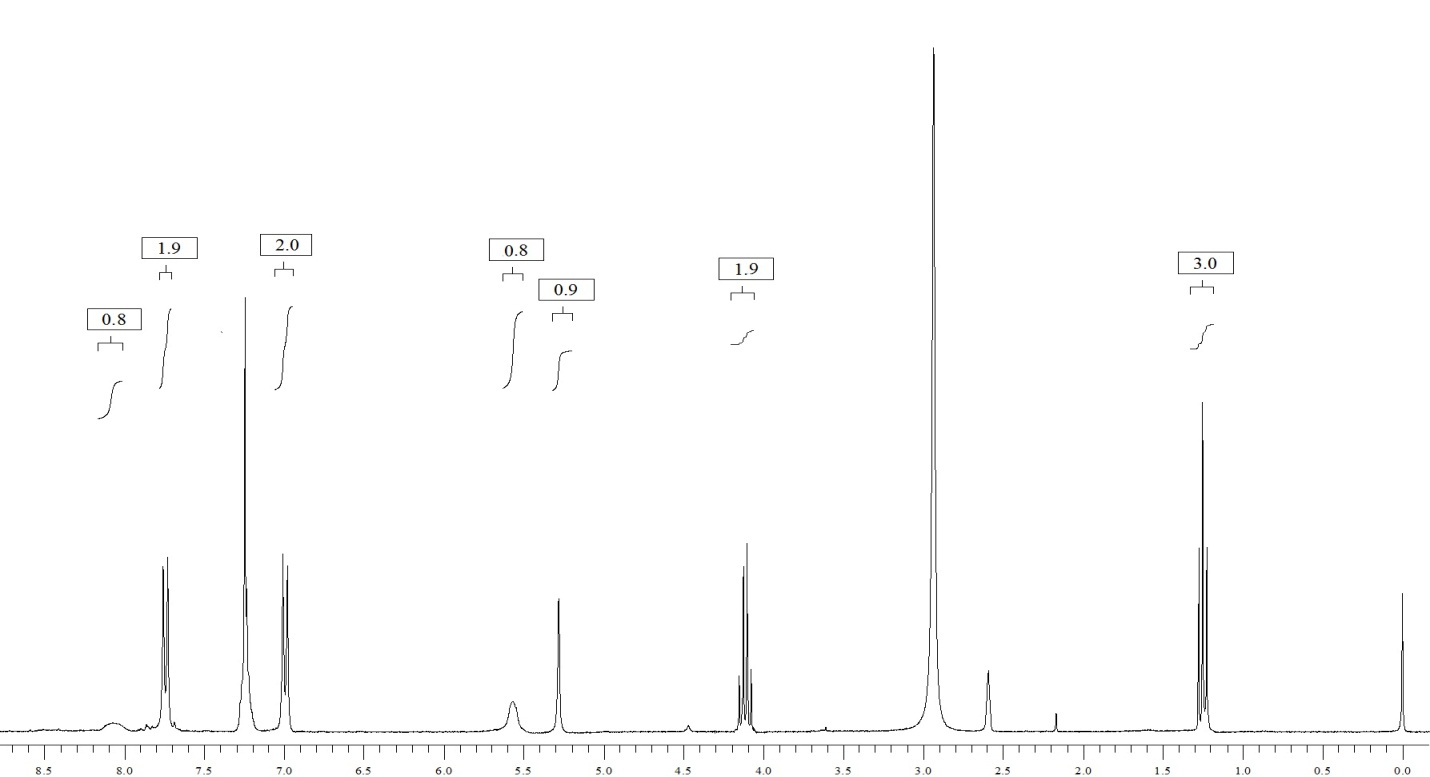
******

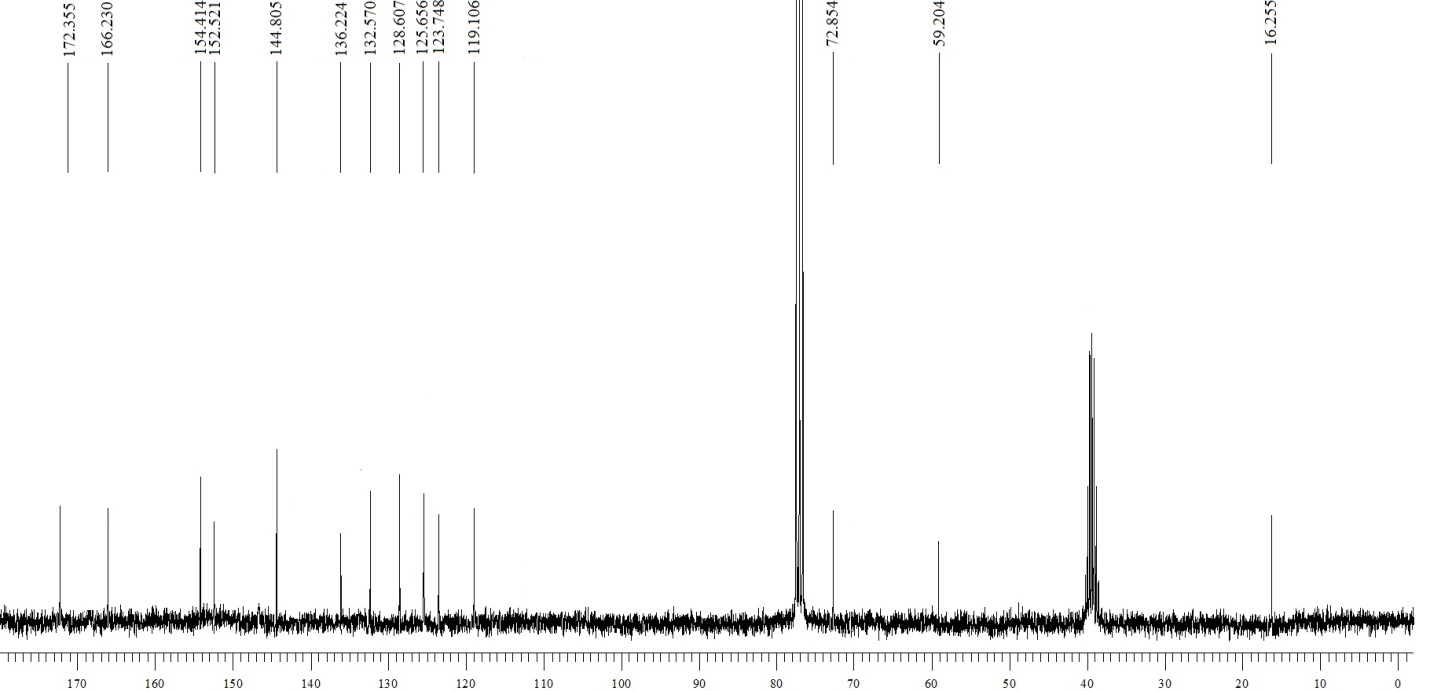
***Ethyl 2-oxo-4-(p-tolyl)-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4b):***



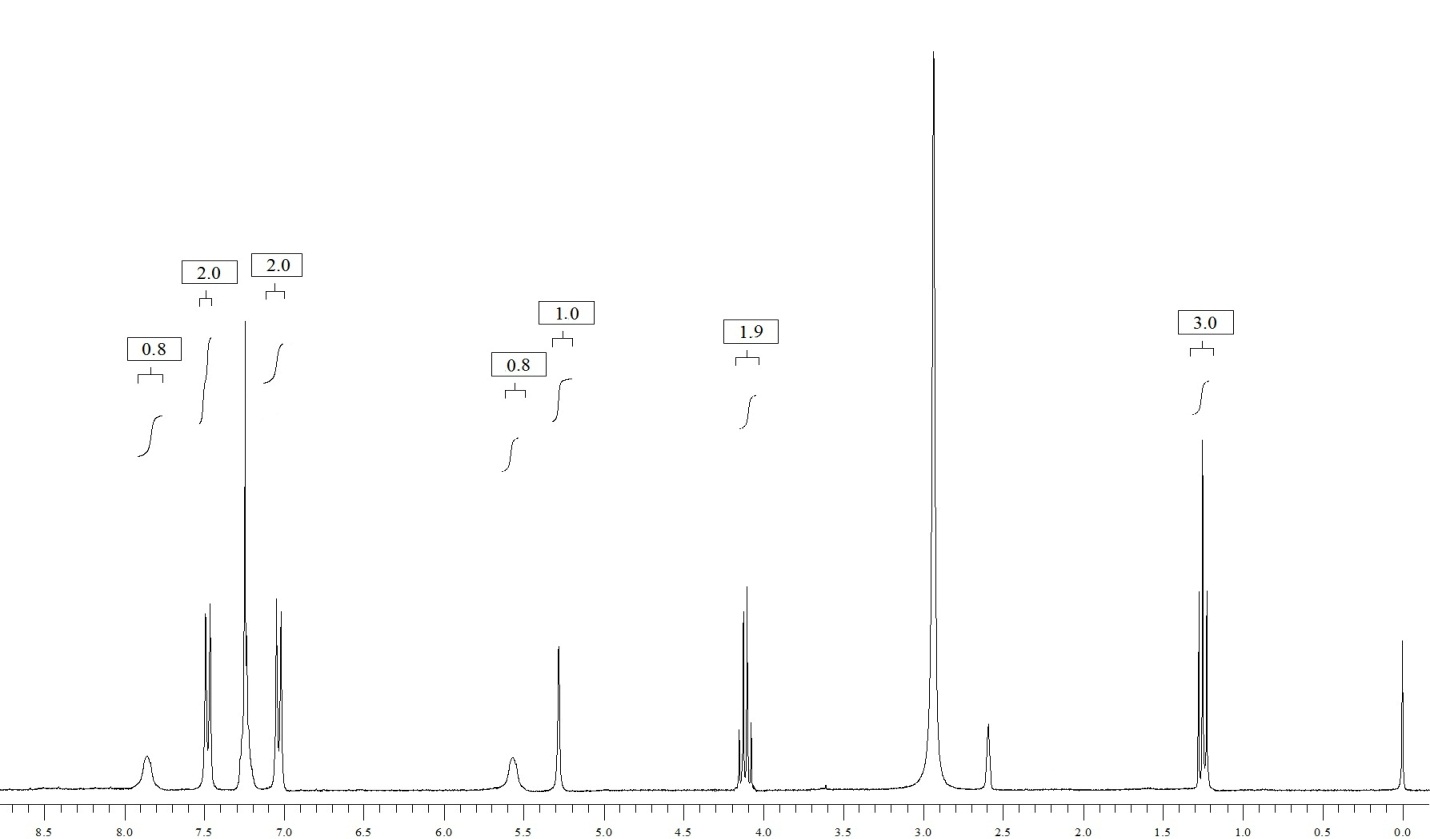
******

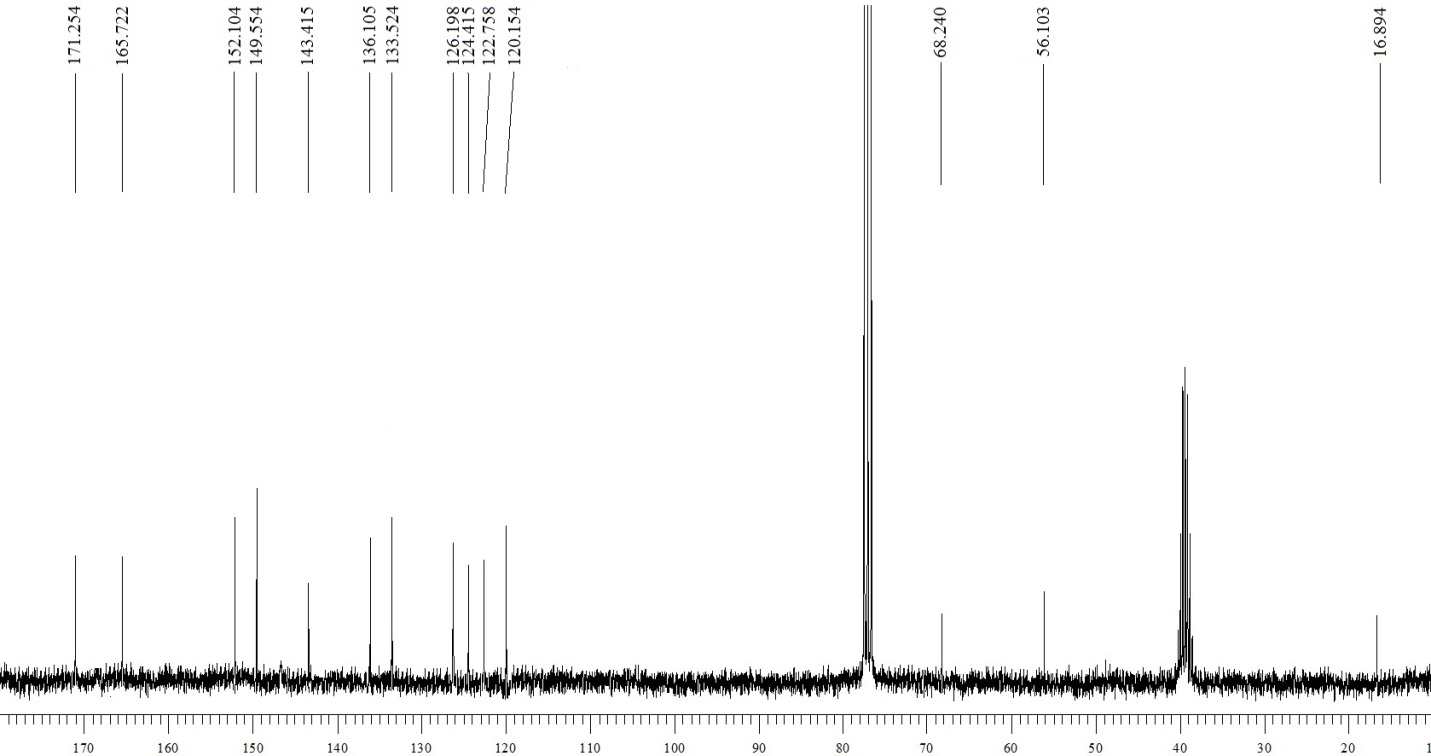
***Ethyl 4-(4-chlorophenyl)-2-oxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4c):***



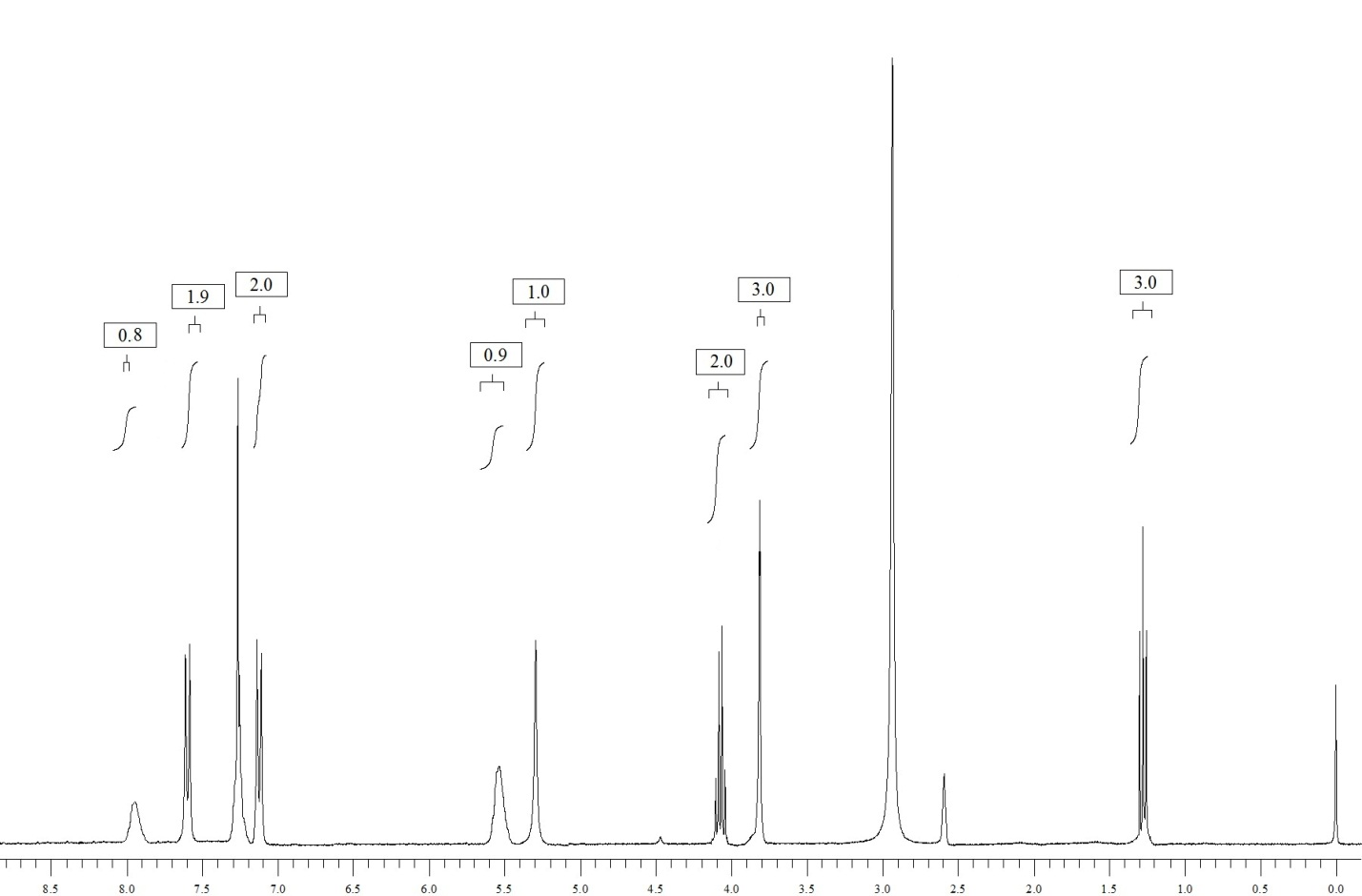
******

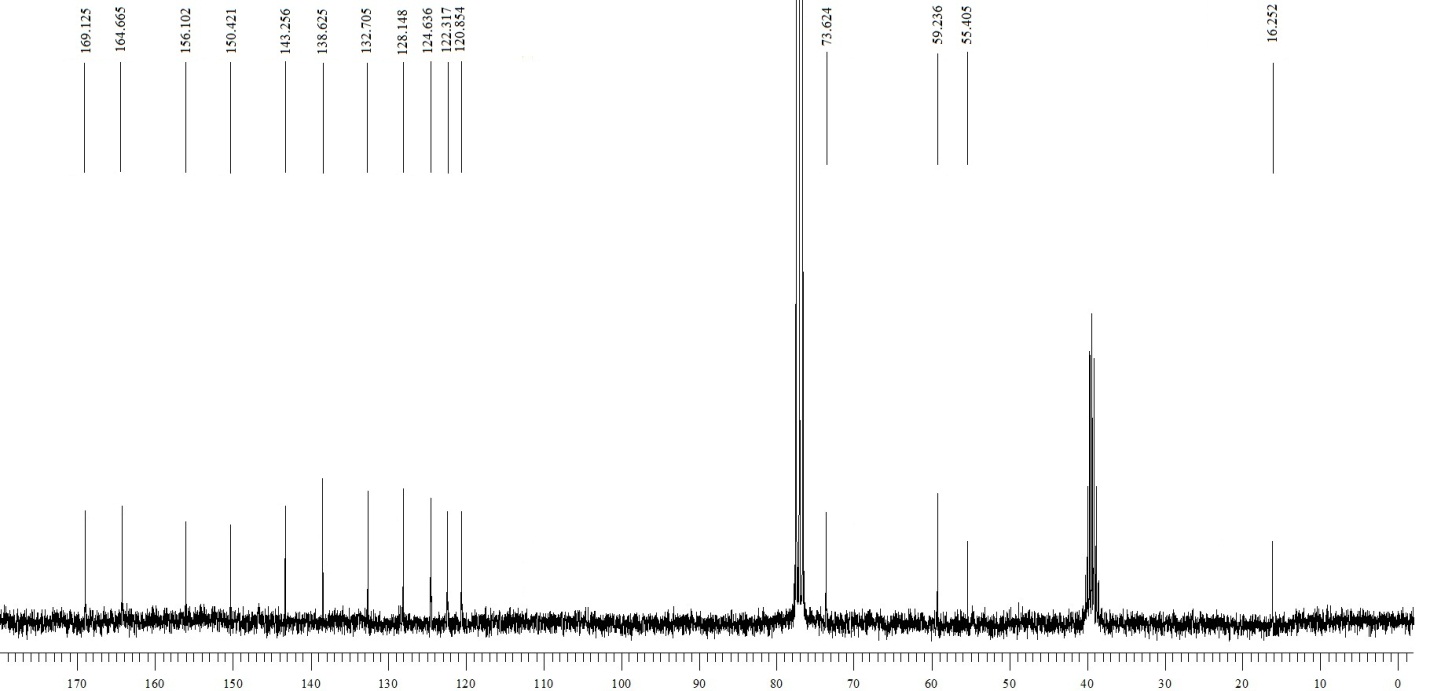
***Ethyl 4-(4-bromophenyl)-2-oxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4d):***



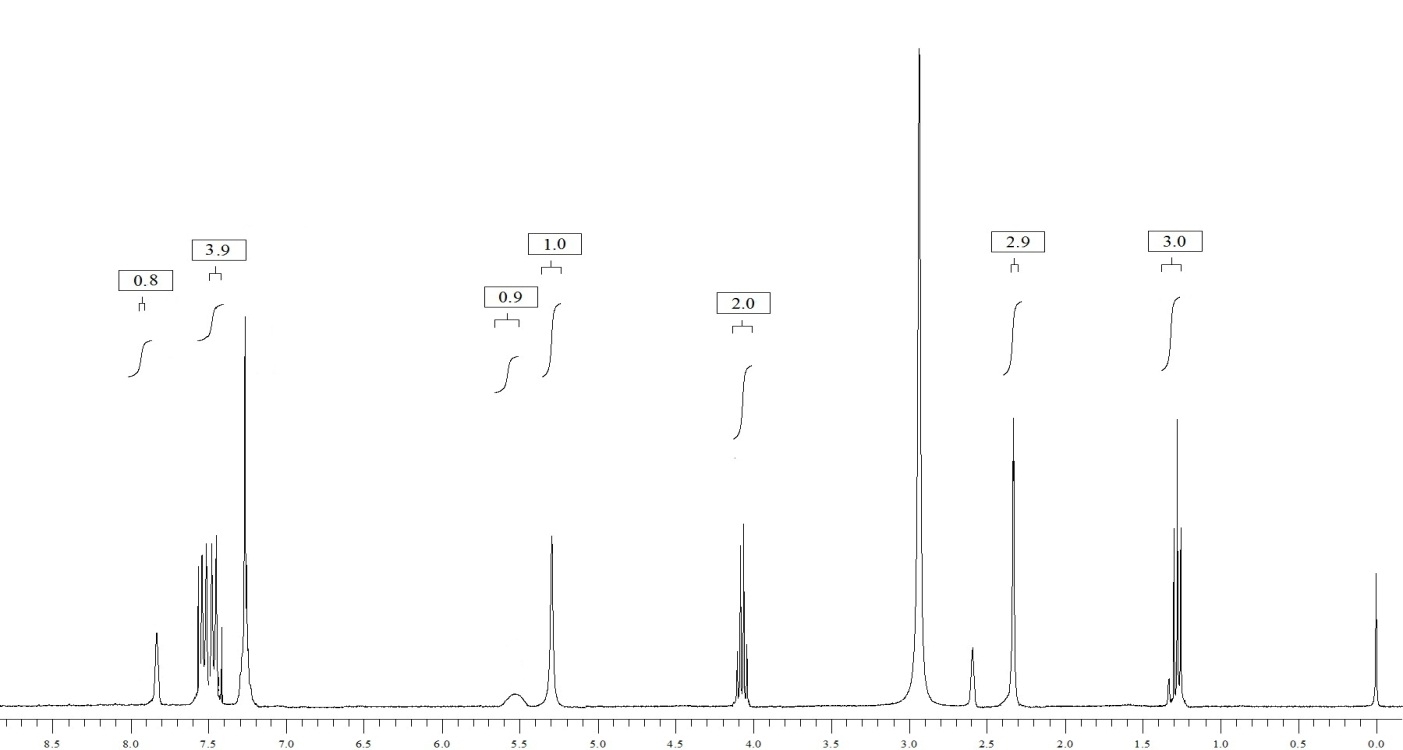


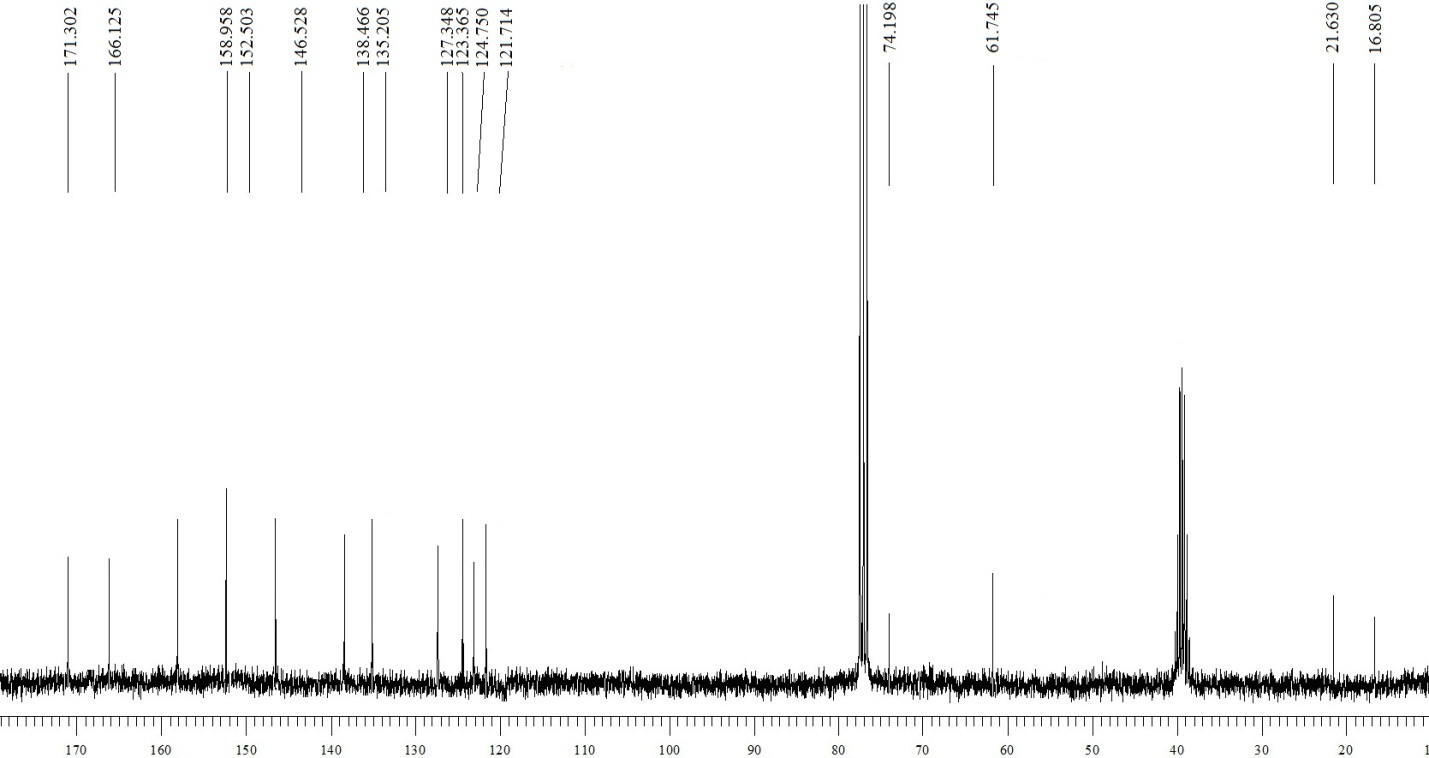
***Ethyl 4-(4-methoxyphenyl)-2-oxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4e):***



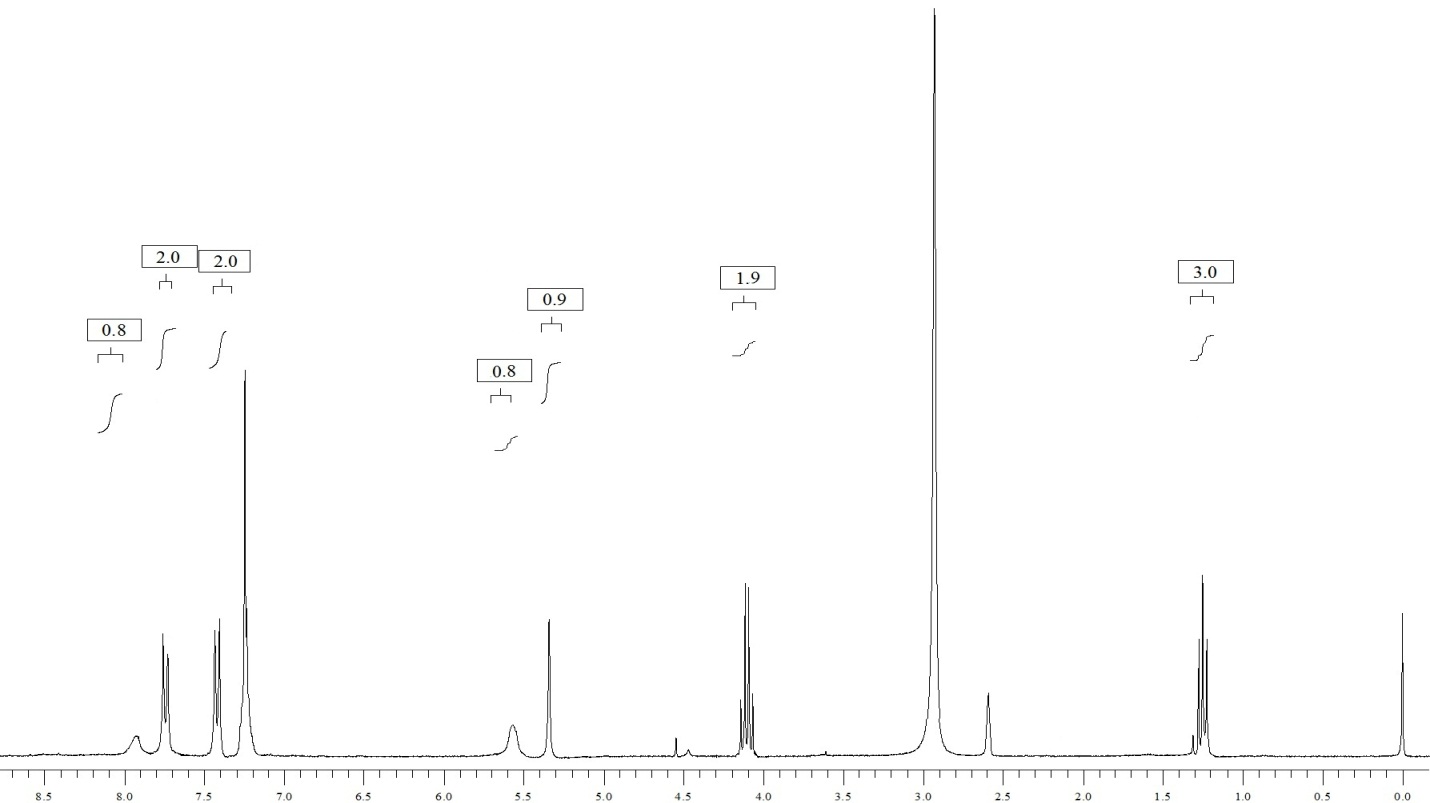
******

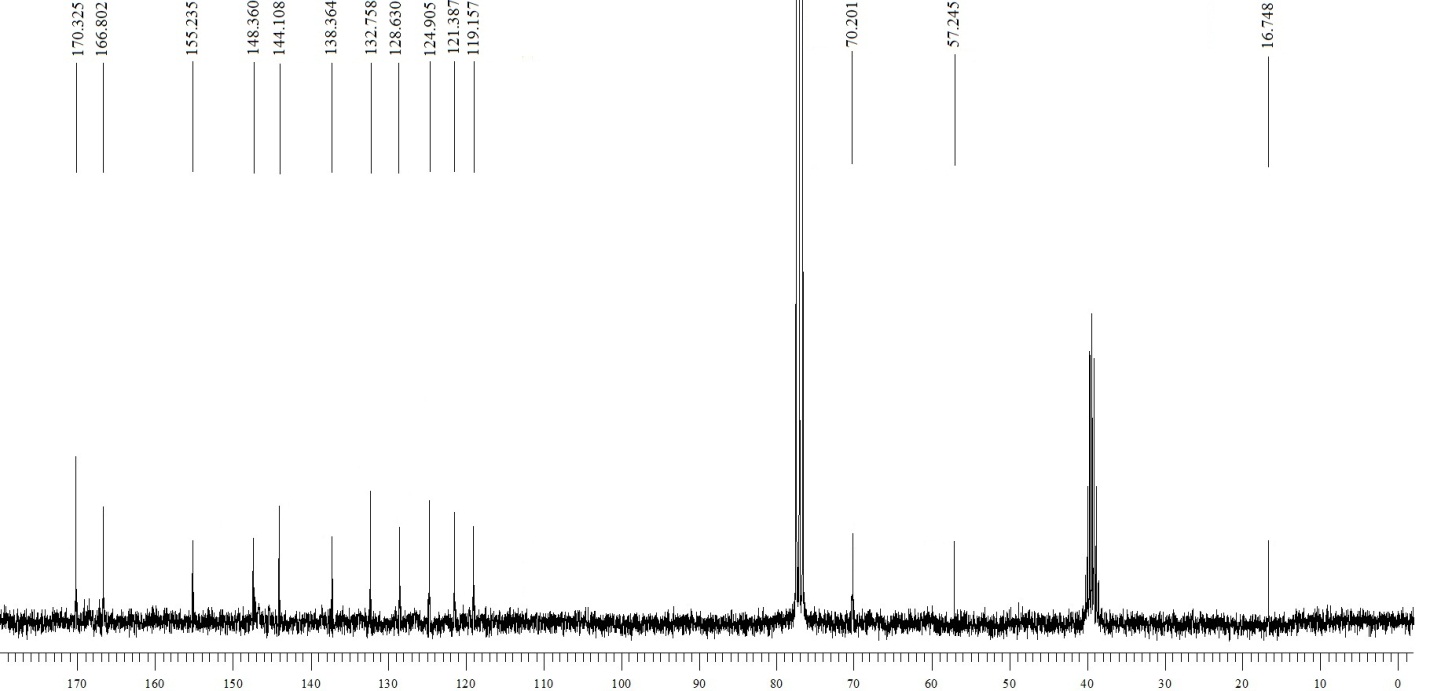
***Ethyl 2-oxo-4-(o-tolyl)-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4f):***



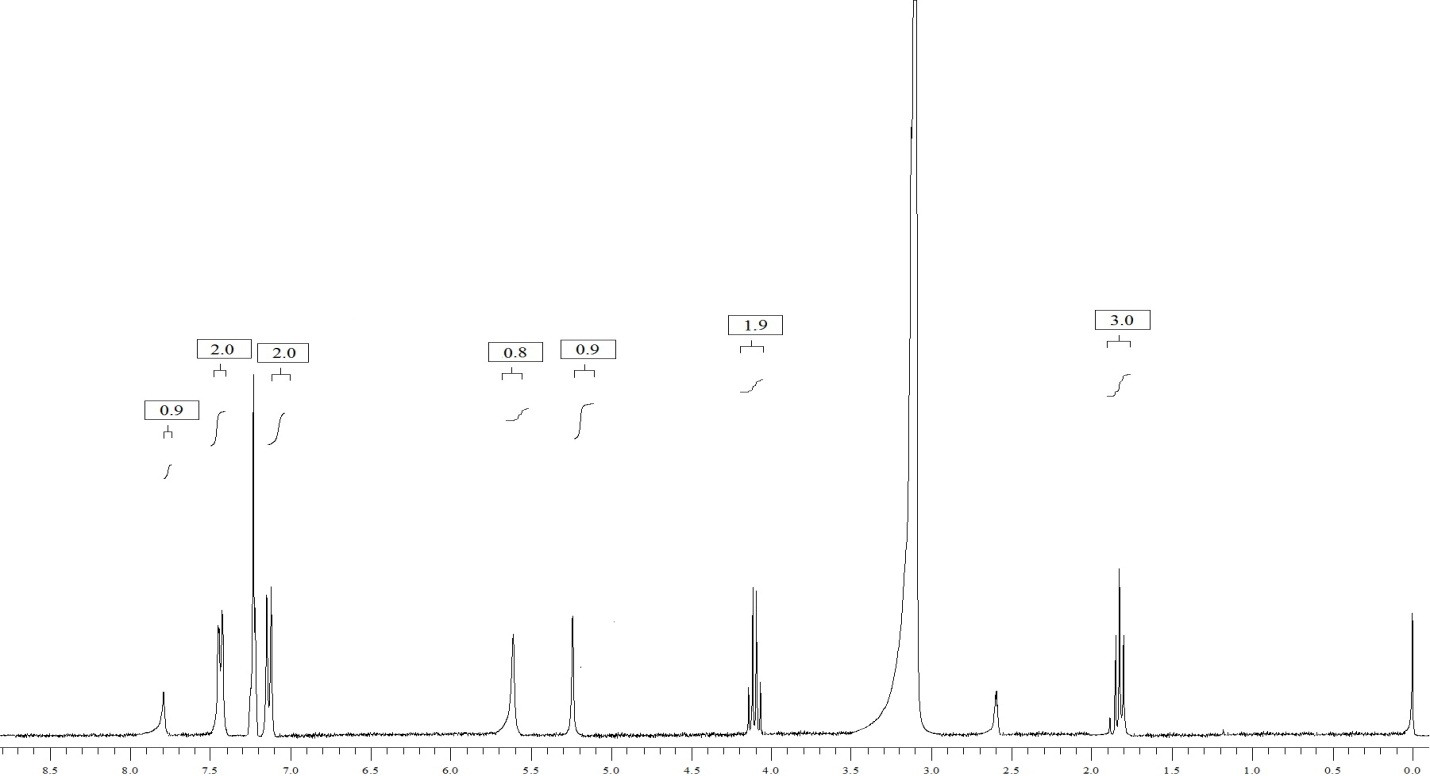
******

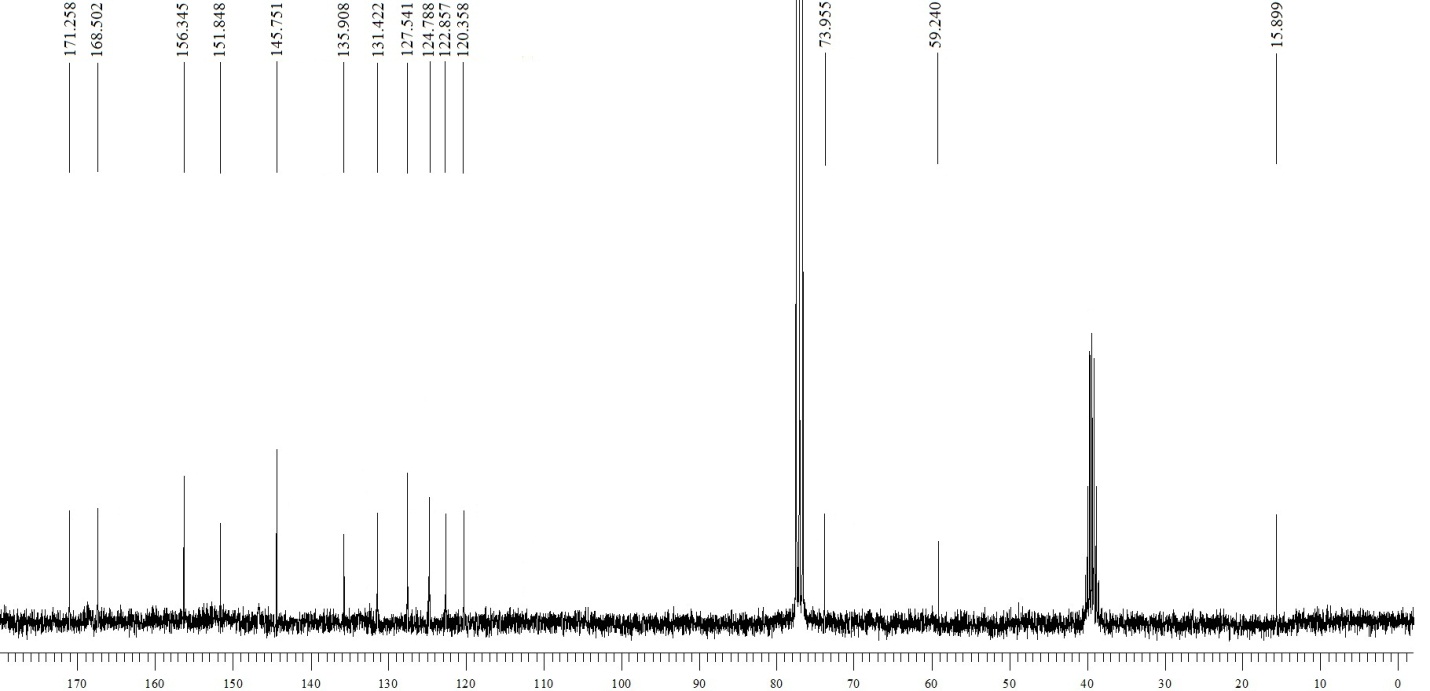
***Ethyl 4-(4-fluorophenyl)-2-oxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4g):***



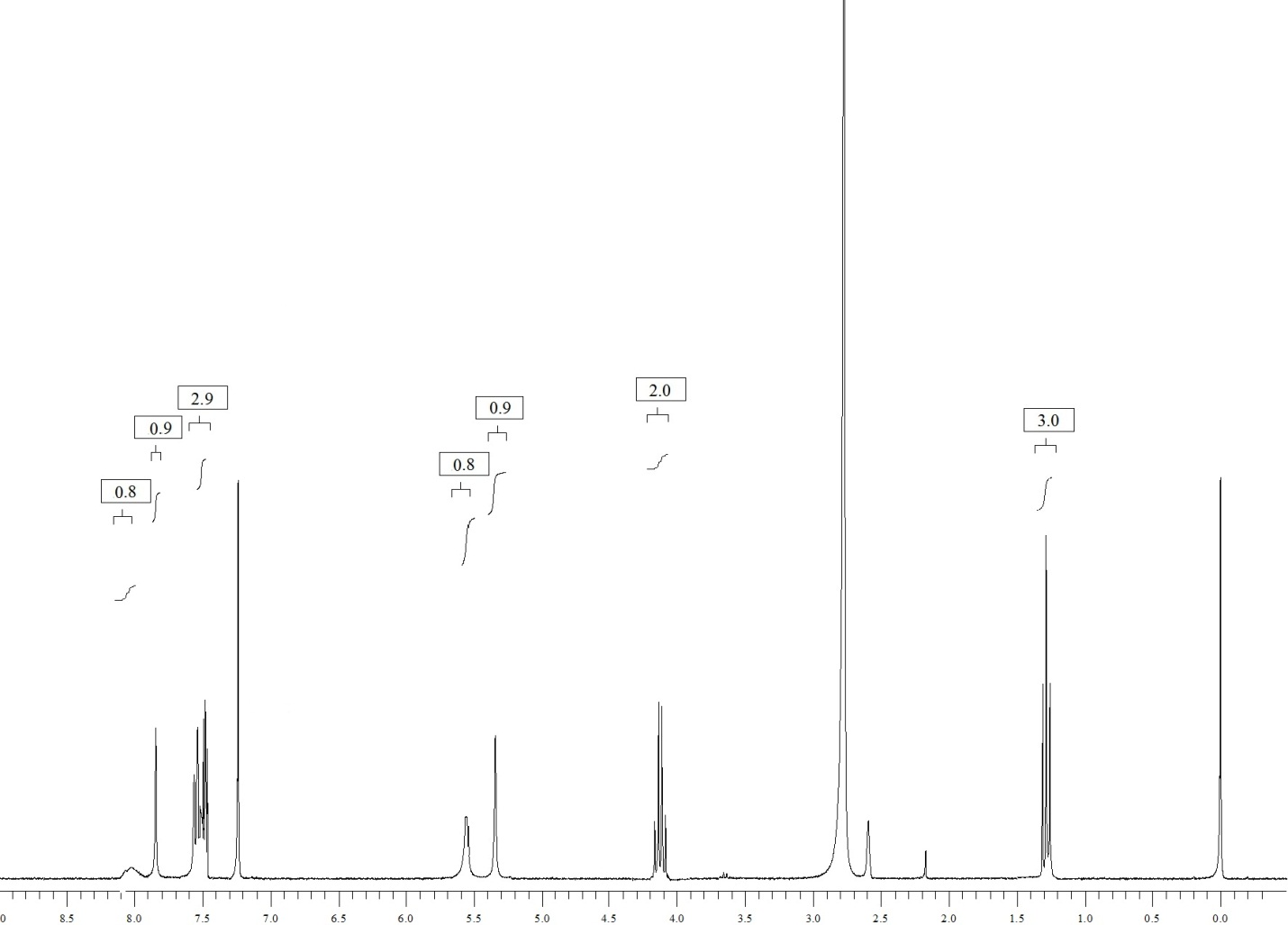


***Ethyl 4-(4-nitrophenyl)-2-oxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4h):***

******

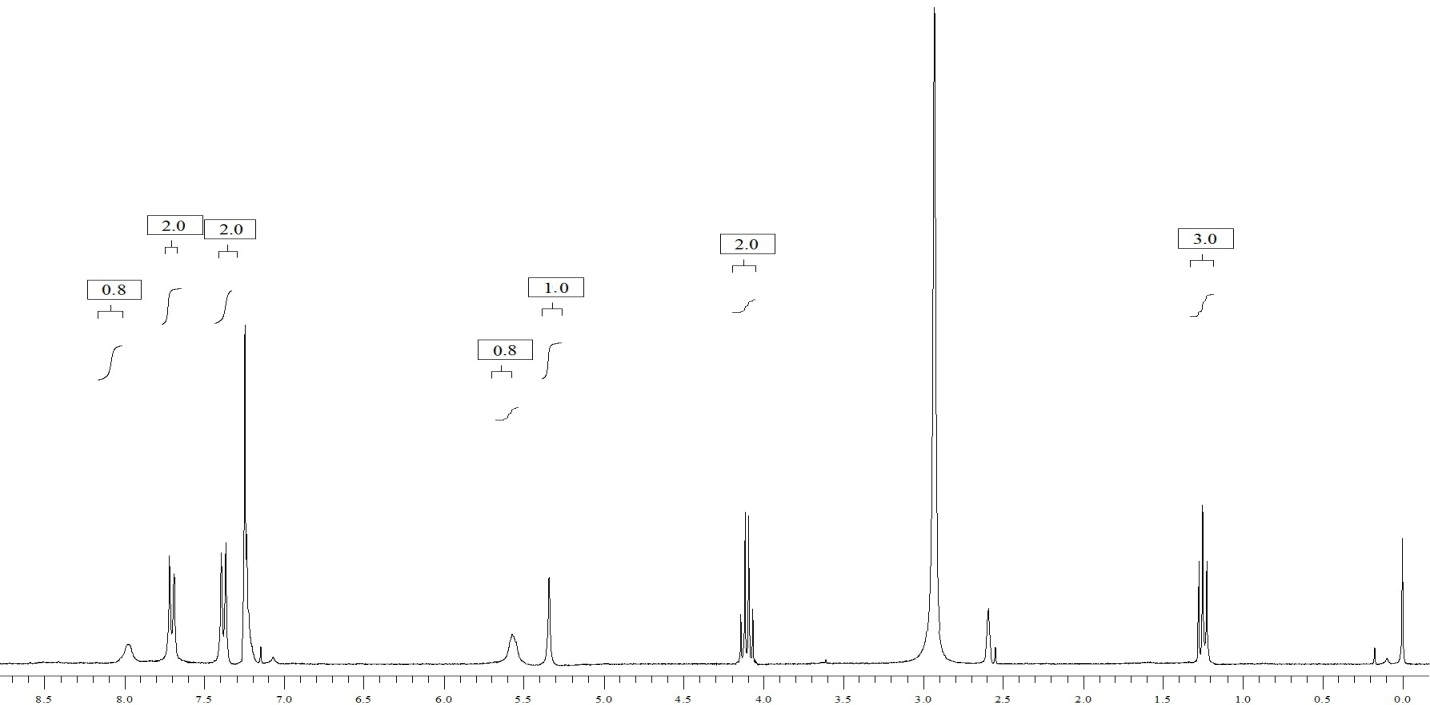
******

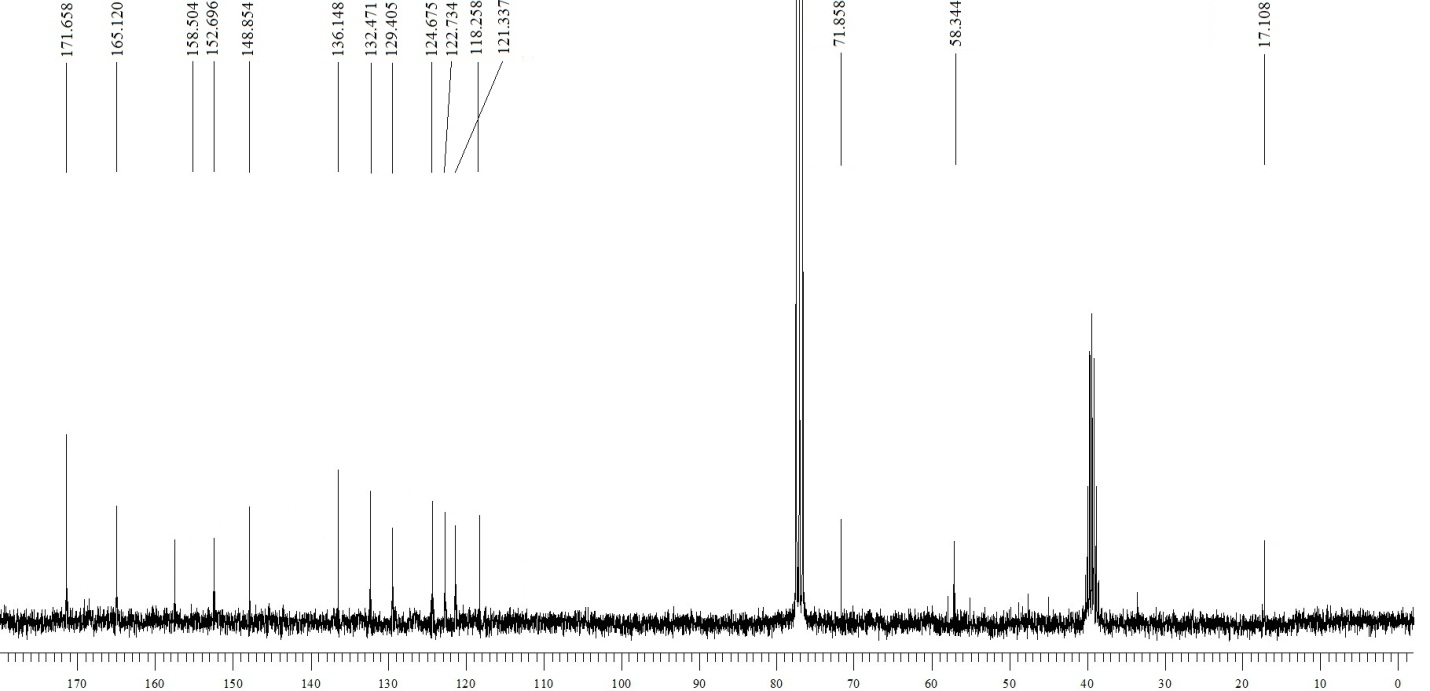
***Ethyl 2-oxo-6-(trifluoromethyl)-4-(3-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4i):***

******

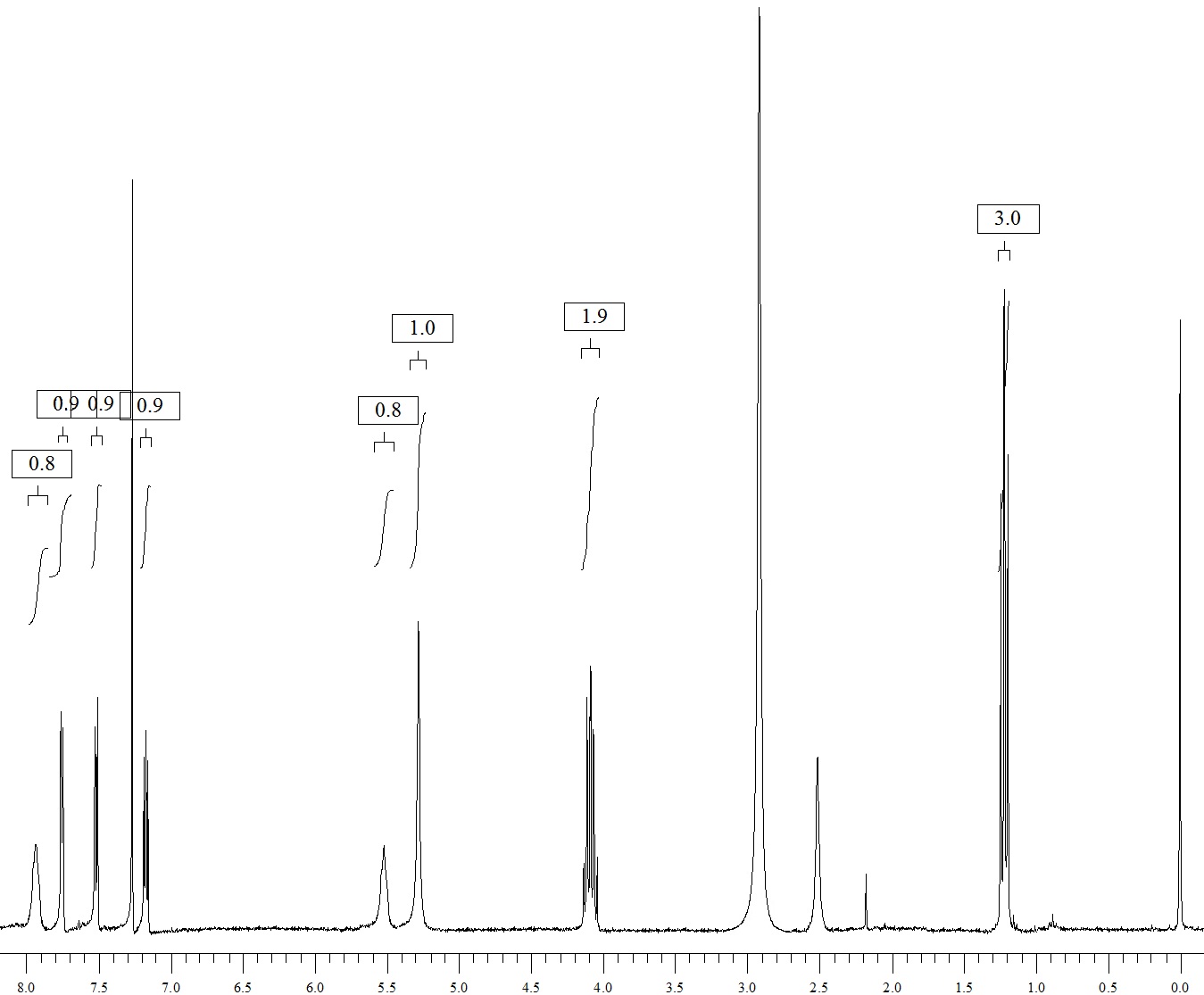
******

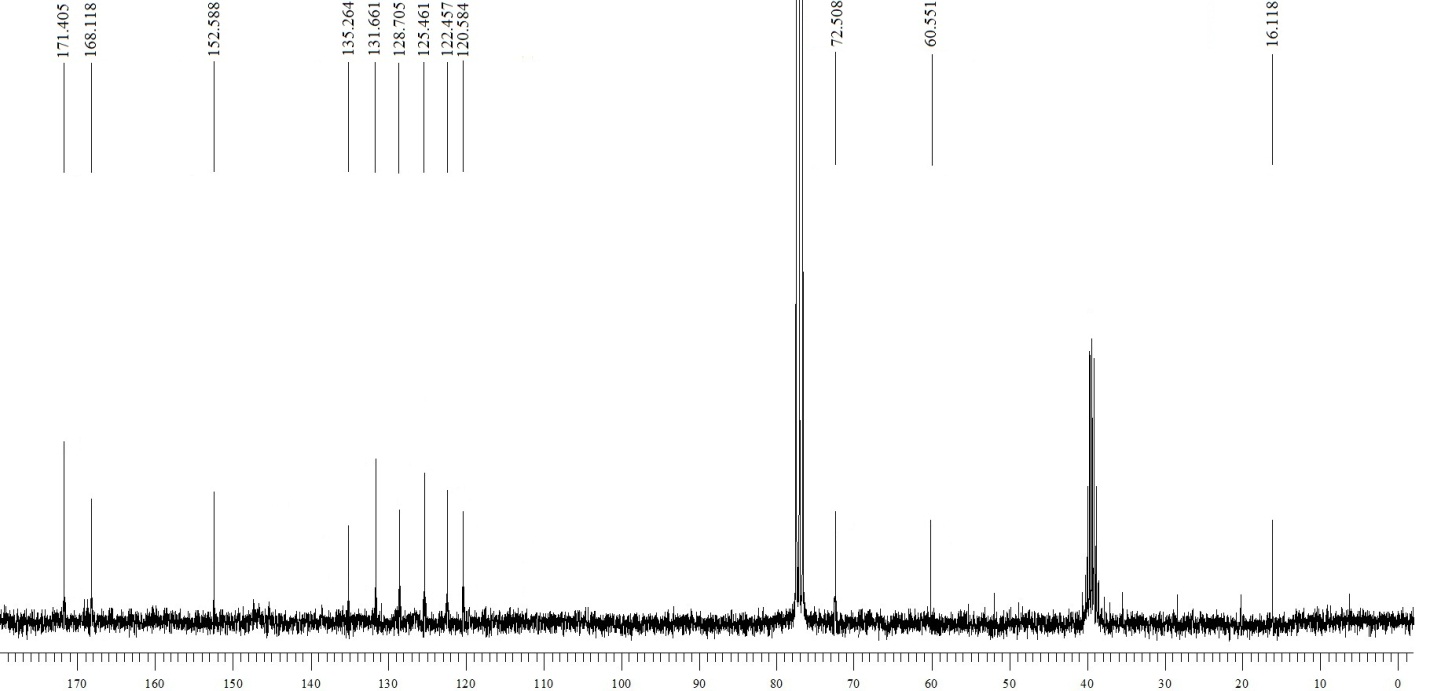
***Ethyl 4-(4-cyanophenyl)-2-oxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4j):***



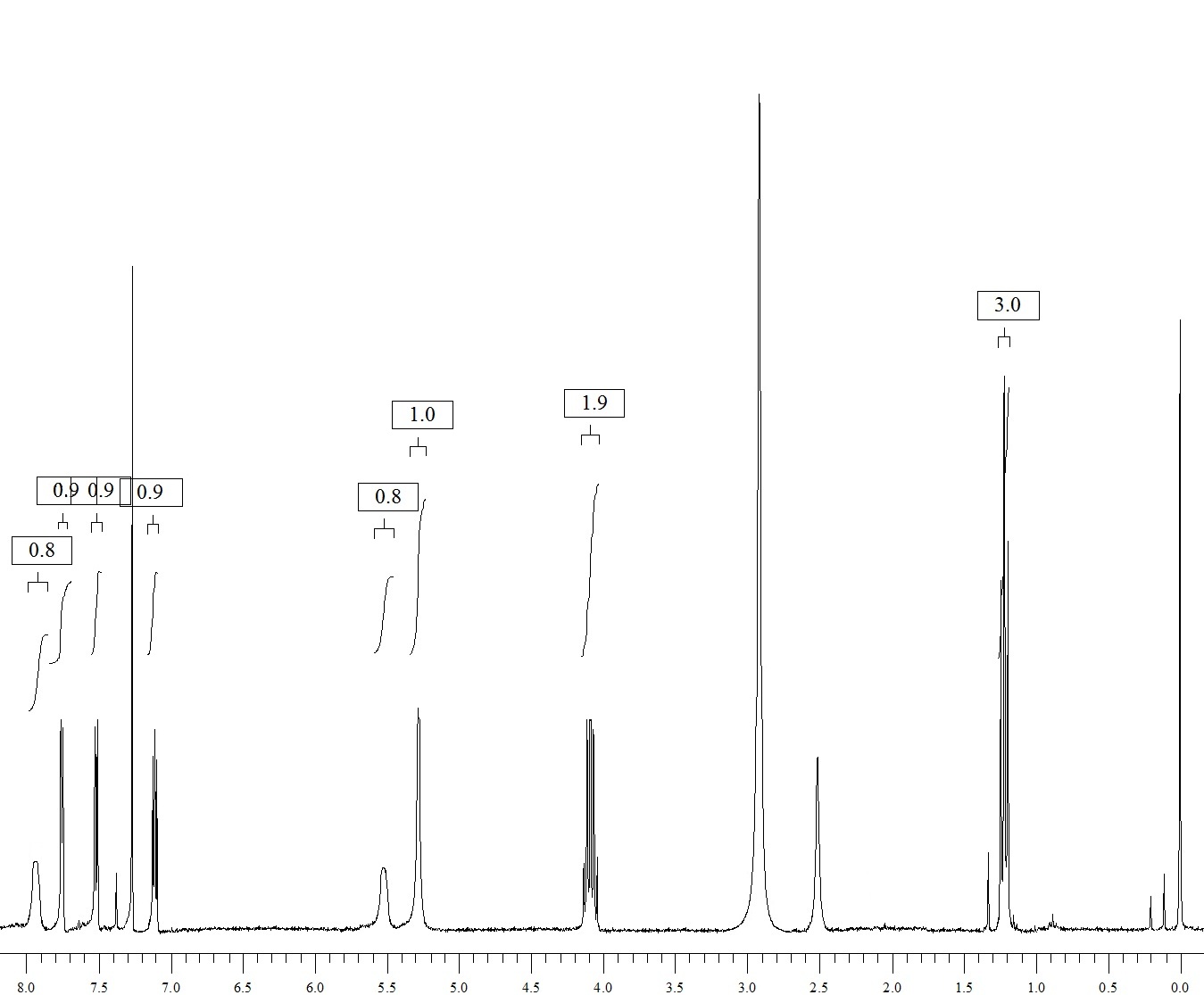
******

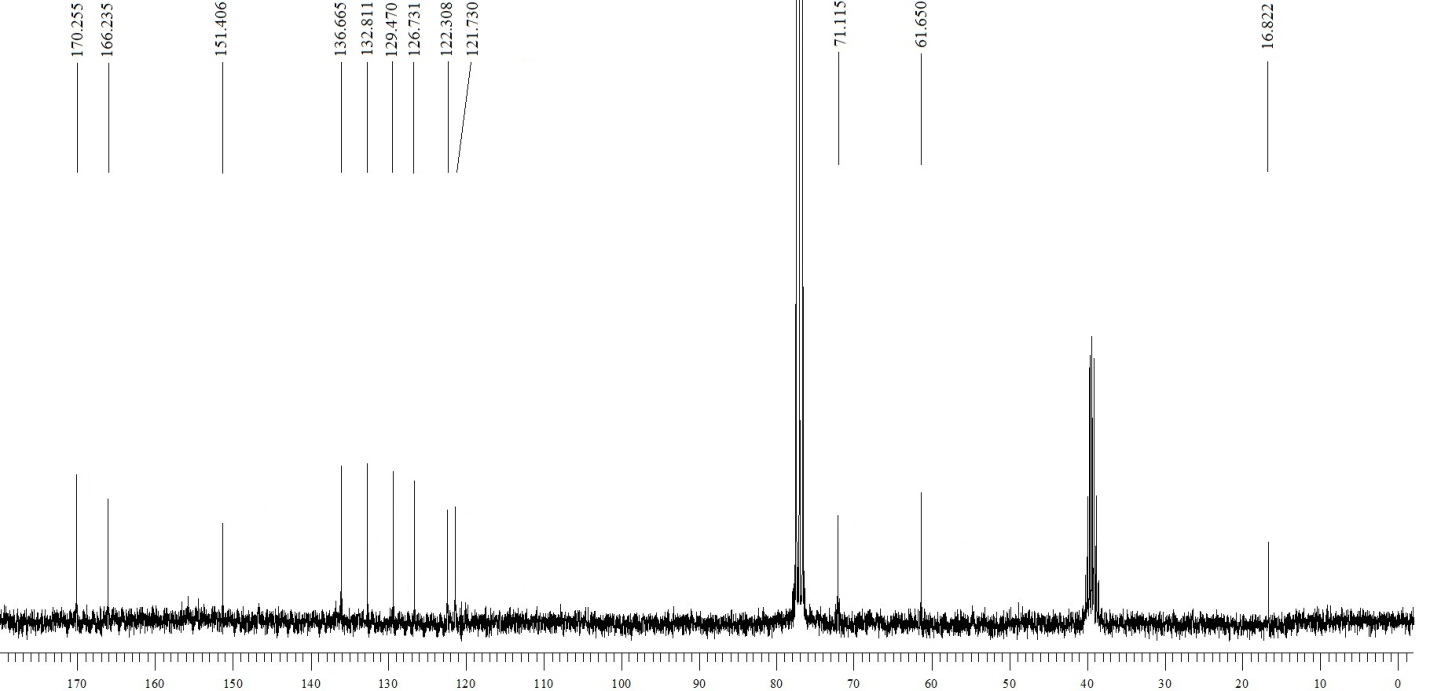
***Ethyl 4-(furan-2-yl)-2-oxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4k):***



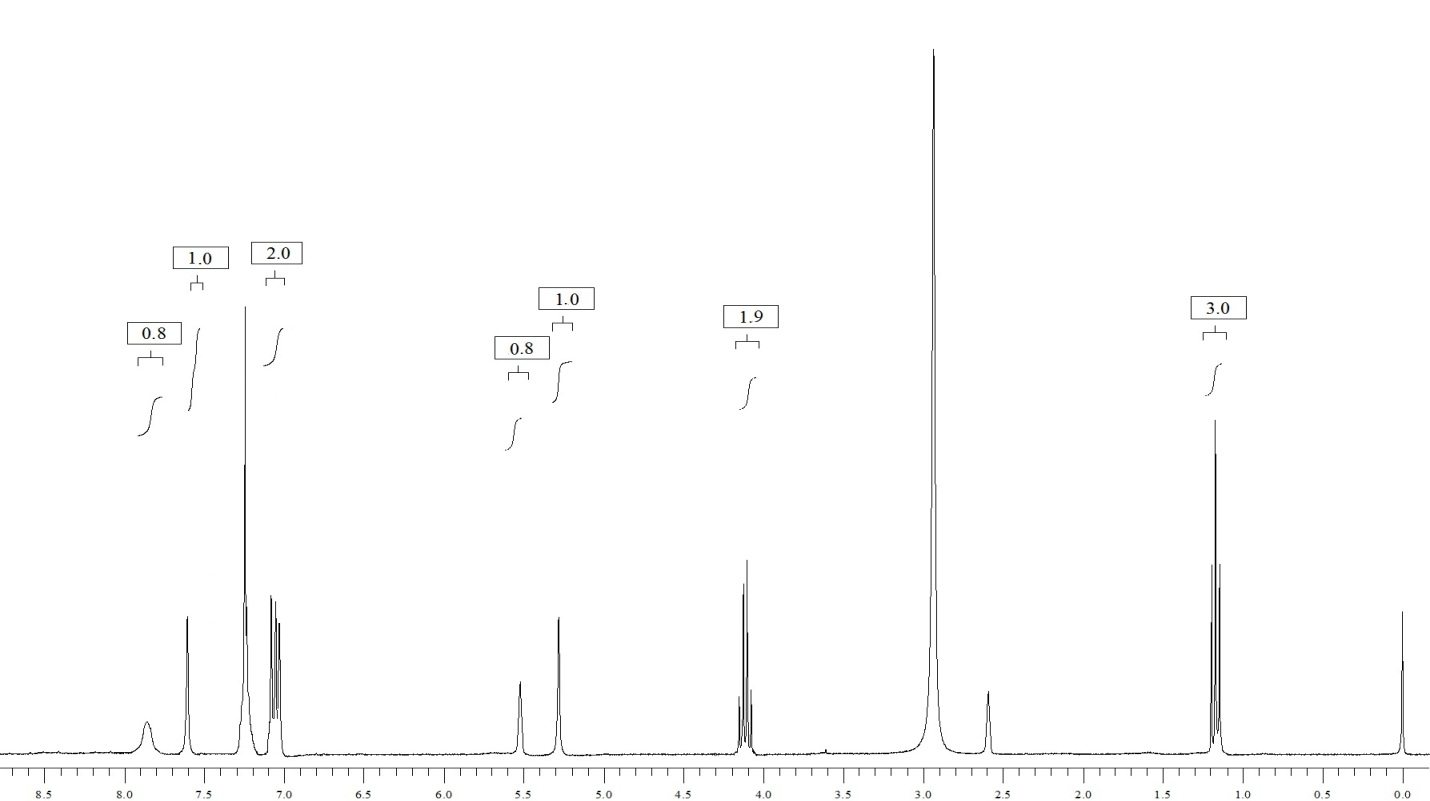
******

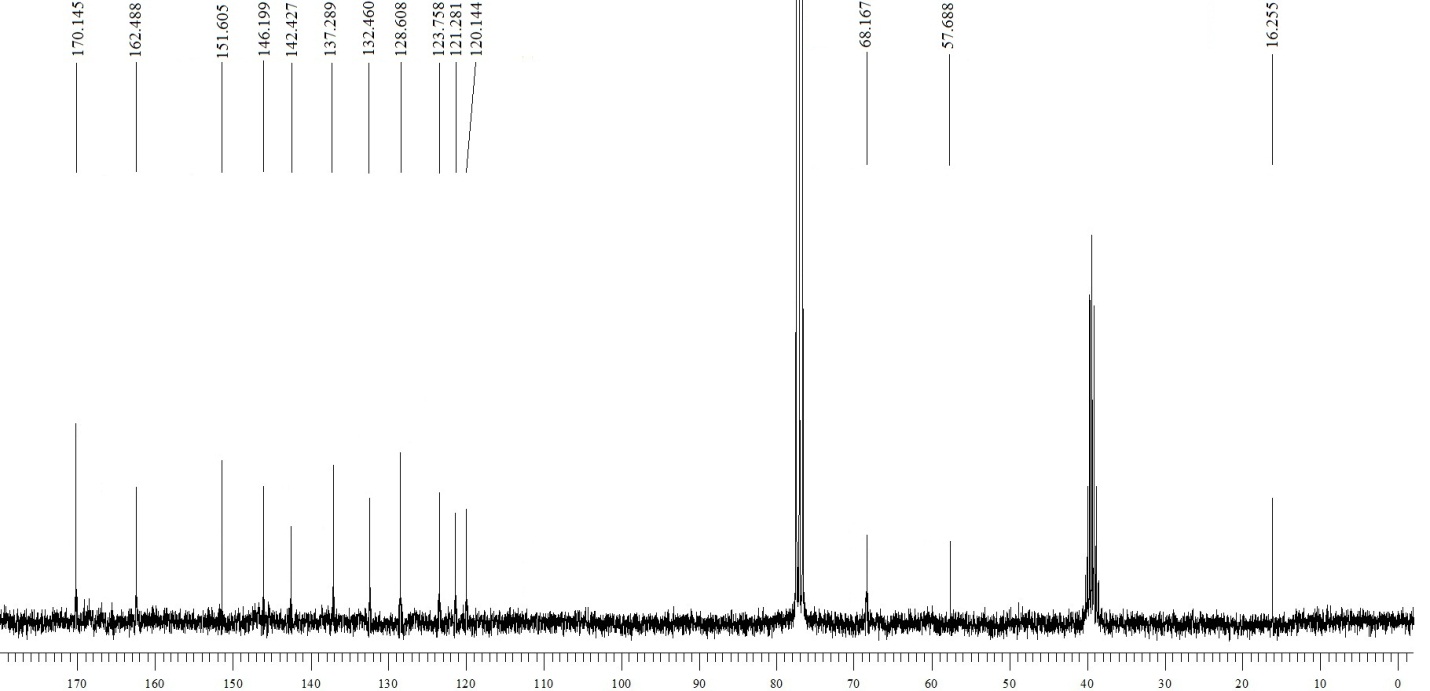
***Ethyl 2-oxo-4-(thiophen-2-yl)-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4l):***



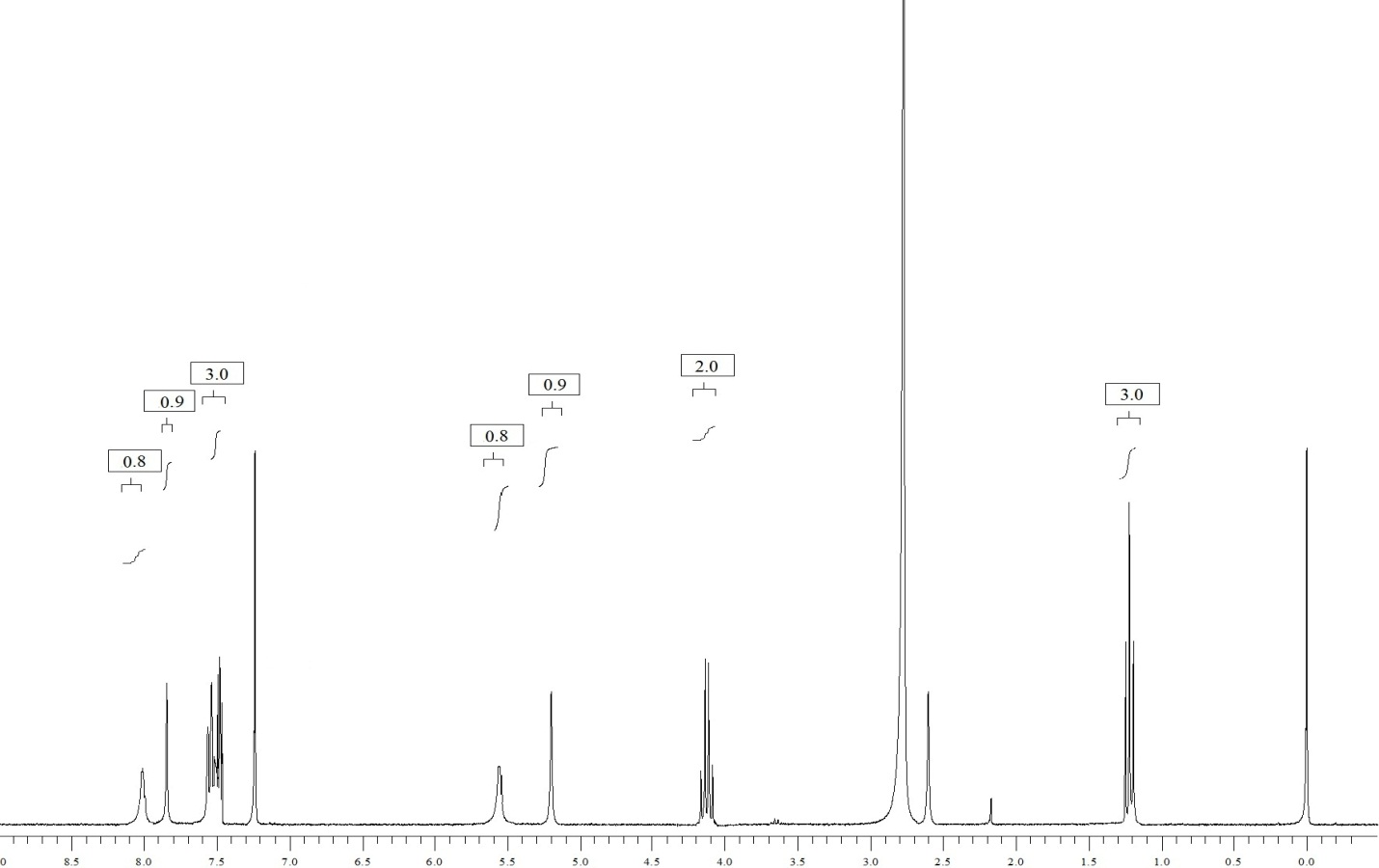
******

***Ethyl 4-(2,4-difluorophenyl)-2-oxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4m):***



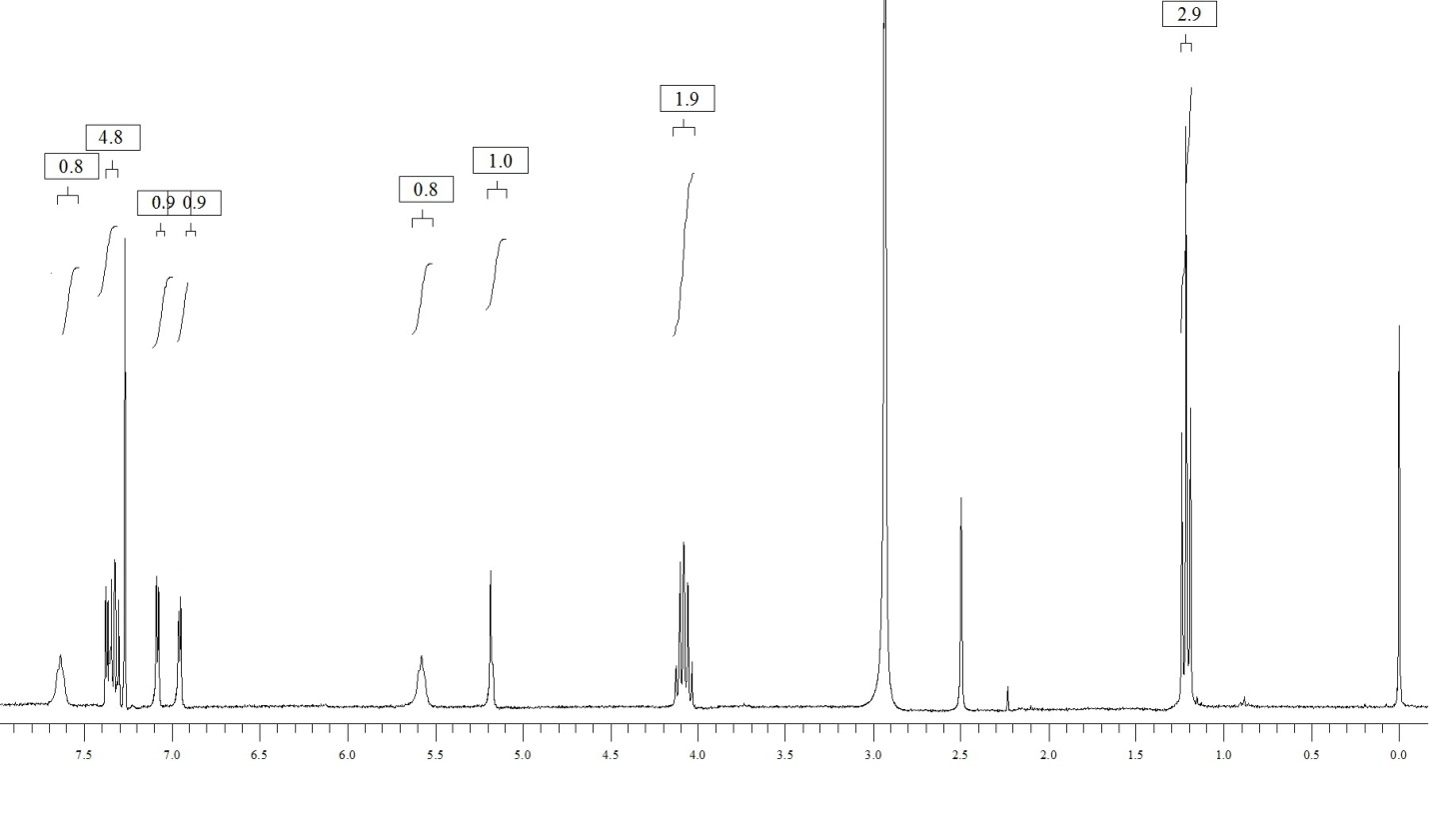
******

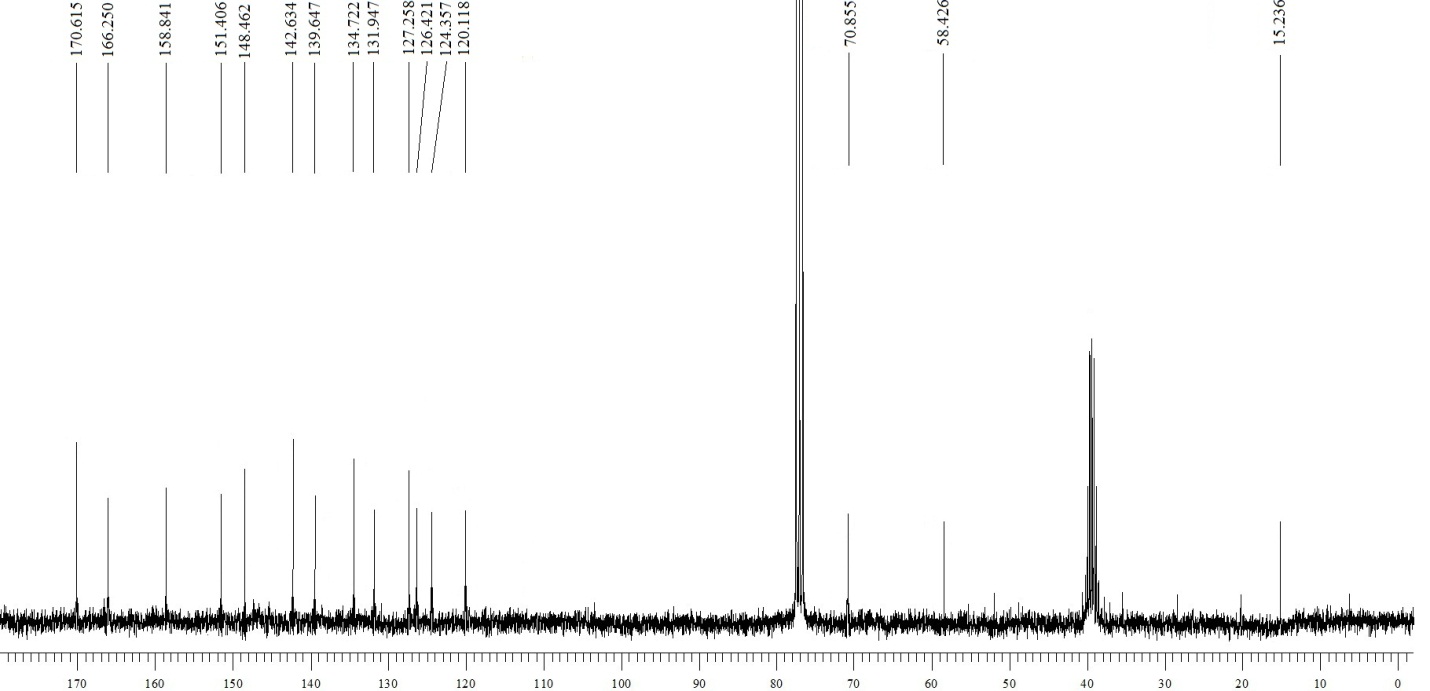
***Ethyl 4-(3-nitrophenyl)-2-oxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4n):***



******

***(E)-ethyl 2-oxo-4-styryl-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4o):***





***Ethyl 4-(naphthalen-2-yl)-2-oxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4p):***

