Supporting Information

Convenient, Functional Group-Tolerant, Transition Metal-Free Synthesis of Aryl and Heteroaryl Trifluoromethyl Ketones with the Use of Methyl Trifluoroacetate

Kazumasa Funabiki,[*a] *Ayaka Hayakawa,*[a] *and Toshiyasu Inuzuka* [b]

[a] Department of Chemsitry and Biomolecular Science, Gifu University, 1-1 Yanagido, Gifu 501-1193, Japan.

[b] Division of Instrumental Analysis, Life Science Research Center, Gifu University, 1-1 Yanagido, Gifu 501-1193, Japan.

(Contents)

Measurement. ^{1}H NMR spectra were measured at 392, 400, 500 or 600 MHz in deuterochloroform ($CDCl_3$), tetradeuteromethanol (CD_3OD) or hexadeuteroacetone ($(CD_3)_2CO$) solutions with tetramethylsilane (Me_4Si) as an internal standard using a JEOL ECS-400, ECX-400P, ECA-500 or ECA-600 FT-NMR spectrometer. ^{13}C NMR spectra were obtained at 99, 101, 126 or 151 MHz in $CDCl_3$, CD_3OD or $(CD_3)_2CO$ solution with Me_4Si as an internal standard using a JEOL ECS-400, ECX-400P, ECA-500 or ECA-600 FT-NMR spectrometer. ^{19}F NMR spectra were recorded at 369, 376, 470 or 564 MHz in $CDCl_3$, CD_3OD or $(CD_3)_2CO$ solutions using $CFCl_3$ as an external standard using a JEOL ECS-400, ECX-400P, ECA-500 or ECA-600 FT-NMR spectrometer. The data are reported as (s = singlet, t = triplet, q = quartet, m = multiplet, br s = broad singlet, coupling constant(s), integration). Melting points were obtained on a Yanagimoto MP-S3 micro melting point apparatus and are uncorrected. IR spectra were recorded on a Shimadzu IR Affinity-1. Electrospray ionization mass spectroscopy (ESI-MS) analysis using MeOH was performed with a Waters Xevo QTof mass spectrometer or JEOL JMS-T100LP (Accu TOF LC-plus).

Materials. Turbo Grignard reagent (*i*-PrMgCl·LiCl complex), *i*-PrMgCl, *i*-PrMgBr, and MeMgCl were purchased from Aldrich Co. Various iodoarenes, iodoheteroarenes, methyl trifluoroacetate, methyl difluoroacetate, methyl chlorodifluoroacetate, methyl pentafluoropropionate, and sodium trifluoroacetate were purchased from TCI Fine Chemicals, Wako Pure Chemicals, and Sigma-Aldrich Co. Pure products were isolated by column chromatography using Silica Gel 60 (spherical, 270–325 mesh, KANTO CHEMICAL CO., INC.). Analytical TLC was performed on Merck precoated (0.25 mm) silica gel 60 F_{254} plates. All chemicals were of reagent grade and, if necessary, purified in the usual manner prior to use. Aryl trifluoromethyl ketones **4a**, **4b**, **4g**, **4h**, **4i**, and **7**, are not new compounds and commercially available from Fluorochem, Matrix Scientitic, Oakwood Chemical, Enamine Building Blocks, Rieke Metals NCS Brand, Aurora Fine Chemicals, and UkrOrgSyntez Led.

Typical procedure for in situ generation of functionalized aromatic Grignard reagents and trifluoroacetylation with methyl trifluoroacetate (2a).

To a THF solution of *i*-PrMgCl·LiCl (1.3 M) (1.05 mmol, 0.81 ml) was added ethyl 4-iodobenzoate (**1a**) (0.294 g, 1.0 mmol) at –25 °C under an argon atmosphere. After the reaction mixture stirred at that temperature for 30 min, methyl trifluoroacetate (**2a**) (0.395 g, 3.1 mmol) was added. The resultant mixture was warmed to 0 °C and stirred for 30 min. The reaction mixture was quenched with NH_4Cl aq solution (20 ml), extracted with diethyl ether (30 ml X 3), dried over anhydrous Na_2SO_4, and concentrated under vacuum to give the residue. After the yields were measured by ^{19}F NMR with benzotrifluoride, the residue was purified by silica gel chromatography (hexane/ethyl acetate = 5/1) to give ethyl 4-(2,2,2-trifluoroacetyl)benzoate (**4a**) and ethyl 4-(2,2,2-trifluoro-1,1-dihydroxyethyl)benzoate (**4a**-hydrate) (0.185 g, k/hyd = 99/1, 71%).

The mixture of ethyl 4-(2,2,2-trifluoroacetyl)benzoate (4a) and 4a-hydrate (4a/4a-hydrate = 99/1)[1]

Yield = 71%; R_f 0.23 (hexane/ethyl acetate = 5/1); mp = 76.2-78.2 °C; IR (KBr) 1694 (ketone C=O, ester C=O), 3229 (OH) cm^{-1}; **ethyl 4-(2,2,2-trifluoroacetyl)benzoate (4a)**; ^1H NMR ($CDCl_3$) δ 1.39 (t, *J* = 6.97 Hz, 3H, OCH_2CH_3), 4.39 (q, *J* = 6.97 Hz, 2H, OCH_2CH_3), 8.08 (d, *J* = 8.30 Hz, 2H, aryl H), 8.15 (d, *J* = 8.30 Hz, 2H, aryl H); ^{13}C NMR ($CDCl_3$) δ 14.2 (s), 61.9 (s), 116.5 (q, *J* = 291.1 Hz), 130.0 (s), 130.1 (s), 132.9 (s), 136.4 (s), 165.2 (s), 180.2 (q, *J* = 36.0 Hz); ^{19}F NMR ($CDCl_3$) δ –71.7 (s, 3F); **ethyl 4-(2,2,2-trifluoro-1,1-dihydroxyethyl)benzoate (4a-hydrate)**; ^{19}F NMR ($CDCl_3$) δ –84.5 (s, 3F).

The mixture of ethyl 3-(2,2,2-trifluoroacetyl)benzoate (4b) and 4b-hydrate (4b/4b-hydrate = 91/9)[1]

Yield = 72%; R_f 0.28 (hexane/ethyl acetate = 5/1); IR (KBr) 1724 (ketone C=O, ester C=O), 3429 (OH) cm^{-1}; **ethyl 3-(2,2,2-trifluoroacetyl)benzoate (4b)**; ^1H NMR ($CDCl_3$) δ 1.39 (t, *J* = 6.99 Hz, 3H, OCH_2CH_3), 4.39 (q, *J* = 6.99 Hz, 2H, OCH_2CH_3), 7.61 (t, *J* = 8.02 Hz, 1H, aryl H), 8.20 (d, *J* = 8.02 Hz,

[1] Ketones **4a** and **4b** are commercially available from Fluorochem Ltd., Matrix Scientific and Oakwood Chemical.

1H, aryl H), 8.33 (d, *J* = 8.02 Hz, 1H, aryl H), 8.67 (s, 1H, aryl H); ^{13}C NMR ($CDCl_3$) δ 14.2 (s), 61.9 (s), 116.6 (q, *J* = 291.6 Hz), 129.5 (s), 130.2 (s), 131.1 (s), 131.8 (s), 133.9 (s), 136.2 (s), 165.2 (s), 180.0 (q, *J* = 35.4 Hz); ^{19}F NMR ($CDCl_3$) δ −71.5 (s, 3F); **ethyl 3-(2,2,2-trifluoro-1,1-dihydroxyethyl)benzoate (4b-hydrate)**; ^{1}H NMR ($CDCl_3$) δ 1.34 (t, *J* = 7.11 Hz, 3H, $OCH_2C\mathit{H}_3$), 4.31 (q, *J* = 7.11 Hz, 2H, $OC\mathit{H}_2CH_3$), 5.12 (br s, 2H, OH), 7.40 (t, *J* = 7.72 Hz, 1H, aryl H), 7.87 (d, *J* = 7.72 Hz, 1H, aryl H), 7.98 (t, *J* = 7.72 Hz, 1H, aryl H), 8.67 (s, 1H, aryl H); ^{13}C NMR ($CDCl_3$) δ 14.2 (s), 61.4 (s), 93.4 (q, *J* = 32.8 Hz), 122.8 (q, *J* = 287.5 Hz), 128.3 (s), 128.4 (s), 130.5 (s), 130.8 (s), 131.8 (s), 137.2 (s), 166.4 (s); ^{19}F NMR ($CDCl_3$) δ −84.5 (s, 3F).

3-Methoxy-3-(trifluoromethyl)isobenzofuran-1(3*H*)-one (5)

Yield = 66%; R_f 0.33 (hexane/diethyl ether = 10/1); IR 1797 (C=O) cm^{-1}; HRMS (ESI) found: *m/z* 233.0443. Calcd for $C_{10}H_8F_3O_3$: $[M+H]^+$, 233.0426; ^{1}H NMR ($CDCl_3$) δ 3.20 (s, 3H, OCH_3), 7.68 (d, *J* = 7.63 Hz, 1H, aryl H), 7.74 (t, *J* = 7.63 Hz, 1H, aryl H), 7.83 (t, *J* = 7.63 Hz, 1H, aryl H), 7.96 (t, *J* = 7.63 Hz, 1H, aryl H); ^{13}C NMR ($CDCl_3$) δ 52.0 (s), 103.5 (q, *J* = 34.8 Hz), 121.2 (q, *J* = 284.7 Hz), 124.3 (s), 126.3 (s), 128.0 (s), 132.7 (s), 135.5 (s), 139.7 (s); ^{19}F NMR ($CDCl_3$) δ −81.5 (s, 3F).

The mixture of 4-(2,2,2-trifluoroacetyl)benzonitrile (4c) and 4c-hydrate (4c/4c-hydrate = 89/11)[2]

Yield = 82%; R_f 0.15 (dichloromethane); mp = 76.2-78.2 °C; IR (KBr) 1728 (C=O), 2241 (C≡N), 3379 (OH) cm^{-1}; **4-(2,2,2-trifluoroacetyl)benzonitrile (4c)**; ^{1}H NMR ($(CD_3)_2CO$) δ 8.09 (d, *J* = 8.30 Hz, 2H, aryl H), 8.26 (d, *J* = 8.30 Hz, 2H, aryl H); ^{13}C NMR ($(CD_3)_2CO$) δ 117.3 (q, *J* = 290.3 Hz), 118.1 (s), 119.4 (s), 131.2 (s), 133.8 (s), 134.0 (s), 180.4 (q, *J* = 36.0 Hz); ^{19}F NMR ($(CD_3)_2CO$) δ −72.6 (s, 3F); **4-(2,2,2-trifluoro-1,1-dihydroxyethyl)benzonitrile (4c-hydrate)**; ^{1}H NMR ($(CD_3)_2CO$) δ 6.91 (s, 2H, OH), 7.84 (d, *J* = 8.30 Hz, 2H, aryl H), 7.93 (d, *J* = 8.30 Hz, 2H, aryl H); ^{13}C NMR ($(CD_3)_2CO$) δ 93.8

[2] W. Wu, Q. Tian, T. Chen and Z. Weng, *Chem. Eur. J.*, **2016**, *22*, 16455–16458.

(q, J = 32.4 Hz), 113.9 (s), 119.0 (s), 124.1 (q, J = 286.7 Hz), 129.4 (s), 132.6 (s), 144.0 (s); ^{19}F NMR ($(CD_3)_2CO$) δ −84.5 (s, 3F).

1-Trifluoroacetylnaphthalene (4d)[3]

Yield = 63%; R_f 0.25 (hexane); IR (KBr) 1708 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.46 (t, J = 8.07 Hz, 1H, aryl H), 7.52-7.60 (m, 1H, aryl H), 7.61-7.70 (m, 1H, aryl H), 7.83 (d, J = 8.07 Hz, 1H, aryl H), 8.02 (d, J = 8.07 Hz, 1H, aryl H), 8.17-8.25 (m, 1H, aryl H), 8.88 (d, J = 8.07 Hz, 1H, aryl H); ^{13}C NMR ($CDCl_3$) δ 116.8 (q, J = 293.1 Hz), 124.0 (s), 125.1 (s), 126.1 (s), 127.0 (s), 129.0 (s), 129.4 (s), 131.1 (s), 131.7 (q, J = 3.8 Hz), 133.9 (s), 136.2 (s), 182.2 (q, J = 33.8 Hz); ^{19}F NMR ($CDCl_3$) δ −69.9 (s, 3F).

9,9-Dimethyl-2-trifluoroacetylfluorene (4e)

Yield = 68%; R_f 0.35 (hexane/dichloromethane = 10/1); IR (KBr) 1709 (C=O) cm^{-1}; HRMS (ESI) found: *m/z* 291.0982. Calcd for $C_{17}H_{14}F_3O$: $[M+H]^+$, 291.0997; ^{1}H NMR ($CDCl_3$) δ 1.56 (s, 6H, CH_3 X 2), 7.39−7.50 (m, 2H, aryl H), 7.52 (d, J = 7.40 Hz, 1H, aryl H), 7.85 (t, J = 7.40 Hz, 2H, aryl H), 8.13 (d, J = 7.40 Hz, 1H, aryl H), 8.21 (s, 1H, aryl H); ^{13}C NMR ($CDCl_3$) δ 26.8 (s), 47.3 (s), 117.1 (q, J = 291.7 Hz), 120.4 (s), 121.7 (s), 123.1 (s), 124.4 (s), 127.6 (s), 128.7 (s), 129.7 (s), 130.2 (s), 137.3 (s), 146.9 (s), 154.3 (s), 155.3 (s), 180.3 (q, J = 34.5 Hz); ^{19}F NMR ($CDCl_3$) δ −70.6 (s, 3F).

The mixture of 2,4-dimethoxy-5-trifluoroacetylpyrimidine (4f) and 4f-hydrate (4f/4f-hydrate = 80/20)

Yield = 67%; R_f 0.30 (hexane/diethyl ether = 3/2); mp = 68.9-70.6 °C; IR (KBr) 1721 (C=O), 3283 (OH) cm^{-1}; HRMS (ESI) found: *m/z* 237.0465. Calcd for $C_8H_8F_3N_2O_3$: $[M+H]^+$, 237.0487; **2,4-dimethoxy-5-trifluoroacetylpyrimidine (4f)**; ^{1}H NMR ($(CD_3)_2CO$) δ 4.09 (s, 3H, OCH_3), 4.13 (s, 3H, OCH_3), 8.81 (br s, 1H, aryl H); ^{13}C NMR ($(CD_3)_2CO$) δ 55.4 (s), 56.3 (s), 108.8 (s), 117.1 (q, J = 290.3 Hz), 164.7 (s), 168.7 (s), 170.8 (s), 178.0 (q, J = 36.6 Hz); ^{19}F NMR δ −74.7 (s, 3F); **1-(2,4-**

[3] T. Konno, T. Takehana, M. Mishima and T. Ishihara, *J. Org. Chem.*, **2006**, *71*, 3545−3550.

dimethoxypyrimidin-5-yl)-2,2,2-trifluoroethane-1,1-diol (4f-hydrate); ^{1}H NMR ($(CD_3)_2CO$) δ 3.96 (s, 1H, OCH_3), 4.04 (s, 3H, OCH_3), 8.57 (br s, 1H, aryl H), Signal derived from OH was not able to be assigned; ^{13}C NMR ($(CD_3)_2CO$) δ 54.6 (s), 55.3 (s), 93.0 (q, *J* = 33.8 Hz), 111.9 (s), 124.4 (q, *J* = 288.4 Hz), 160.8 (s), 166.8 (s), 169.4 (s); ^{19}F NMR ($(CD_3)_2CO$) δ −85.1 (s, 3F).

The mixture of 1,3-dimethyl-5-(2,2,2-trifluoroacetyl)pyrimidine-2,4(1*H*,3*H*)-dione (4g) and 4g-hydrate (4g/4g-hydrate = 4/96)[4]

Yield = 48%; R_f 0.54 (hexane/ethyl acetate = 1/1); mp = 107.0-108.7 °C; IR (KBr) 1624 (amido C=O), 1724 (ketone C=O), 3522 (OH) cm^{-1}; **1,3-dimethyl-5-(2,2,2-trifluoroacetyl)pyrimidine-2,4(1*H*,3*H*)-dione (4g)**; ^{19}F NMR ($(CD_3)_2CO$) δ −74.7 (s, 3F); **1,3-dimethyl-5-(2,2,2-trifluoro-1,1-dihydroxyethyl)pyrimidine-2,4(1*H*,3*H*)-dione (4g-hydrate)**: ^{1}H NMR ($(CD_3)_2CO$) δ 3.28 (s, 3H, CH_3), 3.54 (s, 3H, CH_3), 7.35 (s, 2H, OH), 7.98 (s, 1H, aryl H); ^{13}C NMR ($(CD_3)_2CO$) δ 28.0 (s), 37.7 (s), 93.1 (q, *J* = 33.5 Hz), 106.7 (s), 124.4 (q, *J* = 288.8 Hz), 147.2 (s), 151.5 (s), 165.7 (s); ^{19}F NMR ($(CD_3)_2CO$) δ −86.8 (s, 3F).

The mixture of 2,2,2-trifluoro-1-methoxy-1-(pyridin-4-yl)ethan-1-ol (4h-hemiacetal) and 2,2,2-trifluoro-1-(pyridin-4-yl)ethane-1,1-diol (4h-hydrate) (4h-hemiacetal/4h-hydrate = 96/4)[5]

Yield = 47%; R_f 0.23 (dichloromethane/methaol = 20/1); mp = 110-120 °C (sublimation); IR (KBr) 3271 (OH) cm^{-1}; **2,2,2-trifluoro-1-methoxy-1-(pyridin-4-yl)ethan-1-ol (4h-hemiacetal)**; ^{1}H NMR (CD_3OD) δ 3.24 (s, 3H, OCH_3), 7.66 (d, *J* = 6.30 Hz, 2H, aryl H), 8.64 (d, *J* = 6.30 Hz, 2H, aryl H); ^{13}C NMR (CD_3OD) δ 50.2 (s), 97.0 (d, *J* = 32.0 Hz), 124.0 (q, *J* = 287.5 Hz), 124.7 (s), 146.5 (s), 150.3 (s); ^{19}F NMR (CD_3OD) δ −84.2 (s, 3F); **2,2,2-trifluoro-1-(pyridin-4-yl)ethane-1,1-diol (4h-hydrate)** ; ^{19}F NMR (CD_3OD) δ −85.5 (s, 3F).

[4] Ketone **4g** is commercially available from Aurora Fine Chemicals and UkrOrgSyntez Led.
[5] Ketone **4h** is commercially available from Enamine Building Blocks.

The mixture of 1-(3,5-dimethylisoxazol-4-yl)-2,2,2-trifluoroethan-1-one (4i) and 4i-hydrate (4i/4i-hydrate = 42/58)

Yield = 55%; R_f 0.13 (hexane/diethyl ether = 1/1); mp = 170.8-172.2 °C; IR (KBr) 1709 (C=O), 3260 (OH) cm^{-1}; HRMS (ESI) found: *m/z* 226.0691. Calcd for $C_8H_{11}F_3NO_3$; $[M+MeOH+H]^+$, 226.0691; **1-(3,5-dimethylisoxazol-4-yl)-2,2,2-trifluoroethan-1-one (4i)**; ^1H NMR ($(CD_3)_2CO$) δ 2.28 (s, 3H, CH_3), 2.47 (s, 3H, CH_3); ^{13}C NMR ($(CD_3)_2CO$) δ 11.7 (s), 12.8 (s), 72.1 (q, *J* = 32.0 Hz), 113.0 (s), 126.2 (q, *J* = 284.7 Hz), 159.8 (s), 170.2 (s); ^{19}F NMR ($(CD_3)_2CO$) δ –77.9 (s, 3F); **1-(3,5-dimethylisoxazol-4-yl)-2,2,2-trifluoroethane-1,1-diol (4i-hydrate)**; ^1H NMR ($(CD_3)_2CO$) δ 2.01 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), Signal derived from OH was not able to be assigned; ^{13}C NMR ($(CD_3)_2CO$) δ 11.6 (s), 12.6 (s), 92.2 (q, *J* = 33.9 Hz), 112.4 (s), 124.7 (q, *J* = 286.6 Hz), 160.0 (s), 167.7 (s); ^{19}F NMR ($(CD_3)_2CO$) δ –86.0 (s, 3F).

2,2,2-Trifluoro-1-(1-methyl-1*H*-pyrazol-4-yl)ethan-1-one (4j)[6]

Yield = 50%; R_f 0.44 (dichloromethane); mp = 76.2-78.2 °C; IR (KBr) 1709 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.96 (s, 3H, CH_3), 8.01 (s, 1H, aryl H), 8.04 (s, 1H, aryl H); ^{13}C NMR ($CDCl_3$) δ 39.6 (s), 116.49 (q, *J* = 290.3 Hz), 116.53 (s), 135.1 (s), 142.0 (s), 174.5 (q, *J* = 37.6 Hz); ^{19}F NMR ($CDCl_3$) δ –75.0 (s, 3F).

Ethyl 4-(2,2-difluoroacetyl)benzoate (6)[7]

Yield = 19%; R_f 0.63 (dichloromethane); mp = 58.3-59.5 °C; IR (KBr) 1713 (ketone C=O and ester C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.41 (t, *J* = 7.11 Hz, 3H, OCH_2CH_3), 4.41 (q, *J* = 7.11 Hz, 2H, OCH_2CH_3), 6.29 (t, *J* = 53.40 Hz, 1H, CHF_2), 8.12 (d, *J* = 8.95 Hz, 2H, aryl H), 8.17 (d, *J* = 8.95 Hz,

[6] D. V. Yarmoliuk, V. V. Arhipov, M. V. Stambirskyi, Y. V. Dmytriv, O. V. Shishkin, A. A. Tolmachev and Mykhailiuk, *Synthesis*, **2014**, *46*, 1254–1260.
[7] W. Peng and J. M. Shreeve, *J. Org. Chem.*, **2005**, *70*, 5760–5763.

2H, aryl H); ^{13}C NMR ($CDCl_3$) δ 14.4 (s), 61.8 (s), 111.2 (t, *J* = 253.7 Hz), 129.7 (s), 130.1 (s), 134.5 (s), 135.9 (s), 165.4 (s), 187.4 (t, *J* = 25.8 Hz); ^{19}F NMR ($CDCl_3$) δ −121.9 (d, *J* = 53.4 Hz, 2F).

Ethyl 4-(2,2-difluoro-1,1-dihydroxyethyl)benzoate (6-hydrate)

Yield = 46%; R_f 0.24 (dichloromethane); IR (KBr) 1724 (ketone C=O, ester C=O), 3343 (OH) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.35 (t, *J* = 7.18 Hz, 3H, OCH_2CH_3), 3.92 (br s, 2H, OH), 4.32 (q, *J* = 7.18 Hz, 2H, OCH_2CH_3), 6.22 (t, *J* = 54.95 Hz, 1H, CHF_2), 7.51 (d, *J* = 8.50 Hz, 2H, aryl H), 7.95 (d, *J* = 8.50 Hz, 2H, aryl H); ^{13}C NMR ($CDCl_3$) δ 14.3 (s), 61.3 (s), 78.0 (t, *J* = 21.6 Hz), 116.6 (t, *J* = 250.9 Hz), 127.2 (s), 129.6 (s), 130.4 (s), 144.9 (s), 166.3 (s); ^{19}F NMR ($CDCl_3$) δ −127.1 (d, *J* = 55.0 Hz, 2F).

The mixture of ethyl 4-(2-chloro-2,2-difluoroacetyl)benzoate (7) and 7-hydrate (7/7-hydrate = 94/6)[8]

Yield = 71%; R_f 0.30 (hexane/dichloromethane = 2/3); mp = 57.0-58.0 °C; IR (KBr) 1724 (ketone C=O, ester C=O) cm^{-1}; **ethyl 4-(2-chloro-2,2-difluoroacetyl)benzoate (7)**; ^{1}H NMR ($CDCl_3$) δ 1.38 (t, *J* = 7.11 Hz, 3H, OCH_2CH_3), 4.39 (q, *J* = 7.11 Hz, 2H, OCH_2CH_3), 8.12 (s, 4H, aryl H); ^{13}C NMR ($CDCl_3$) δ 14.2 (s), 61.8 (s), 120.0 (t, *J* = 304.9 Hz), 129.9 (s), 130.4 (s), 132.5 (s), 136.0 (s), 165.2 (s), 180.7 (t, *J* = 29.2 Hz); ^{19}F NMR ($CDCl_3$) δ −61.3 (s, 2F); **ethyl 4-(2-chloro-2,2-difluoro-1,1-dihydroxyethyl)benzoate (7-hydrate)**; ^{19}F NMR ($CDCl_3$) δ −67.8 (s, 2F).

The mixture of ethyl 4-(2,2,3,3,3-pentafluoropropanoyl)benzoate (8) and 8-hydrate (8/8-hydrate = 94/6)

Yield = 51%; R_f 0.43 (hexane/dichloromethane = 1/1); IR (KBr) 1713 (ketone C=O, ester C=O) cm^{-1}; HRMS (ESI) found: *m/z* 329.0813. Calcd for $C_{13}H_{14}F_5O_4$; $[M+MeOH+H]^+$, 329.0812; **ethyl 4-(2,2,3,3,3-pentafluoropropanoyl)benzoate (8)**; ^{1}H NMR ($CDCl_3$) δ 1.40 (t, *J* = 7.08 Hz, 3H,

[8] Ketone **7** is commercially available from UkrOrgSyntez Led.

OCH_2CH_3), 4.41 (q, *J* = 7.08 Hz, 2H, OCH_2CH_3), 8.11 (d, *J* = 8.55 Hz, 2H, aryl H), 8.17 (d, *J* = 8.55 Hz, 2H, aryl H); ^{13}C NMR ($CDCl_3$) δ 14.3 (s), 61.9 (s), 108.6 (tq, *J* = 269.0, 37.3 Hz), 61.9 (s), 118.0 (qt, *J* = 286.5, 33.4 Hz), 130.0 (t, *J* = 2.9 Hz), 130.1 (s), 136.4 (s), 165.2 (s), 183.0 (t, *J* = 12.8 Hz); ^{19}F NMR ($CDCl_3$) δ −81.6 (s, 3F), −115.8 (s, 2F); **ethyl 4-(2,2,3,3,3-pentafluoro-1,1-dihydroxypropyl)benzoate (8-hydrate)**; ^{19}F NMR ($CDCl_3$) δ −78.5 (s, 3F), −125.4 (s, 2F).

Typical procedure for *in situ* generation of functionalized aromatic Grignard reagents and successive reaction with methyl trifluoroacetate (2a) and acetone.

To a THF solution of *i*-PrMgCl·LiCl (1.3 M) (1.05 mmol, 0.81 ml) was added ethyl 4-iodobenzoate (**1a**) (0.293 g, 1.0 mmol) at −25 °C under an argon atmosphere. After the reaction mixture stirred at that temperature for 30 min, methyl trifluoroacetate (**2a**) (0.389 g, 3.0 mmol) was added. The mixture was warmed to 0 °C and stirred for 5 min. Then, to the reaction mixture was added acetone (0.294 g, 5.0 mmol) and stirred at 23 °C for overnight. The reaction mixture was quenched with NH_4Cl aq solution (20 ml), extracted with diethyl ether (30 ml X 3), dried over anhydrous Na_2SO_4, and concentrated under vacuum to give the residue. After the yields were measured by ^{19}F NMR with benzotrifluoride, the residue was purified by silica gel chromatography (hexane/ethyl acetate = 3/1) to give diethyl 4,4'-(1,1,1,7,7,7-hexafluoro-2,6-dihydroxy-4-oxoheptane-2,6-diyl)dibenzoate (**9a**) (0.182 g, 71%).

Diethyl 4,4'-(1,1,1,7,7,7-hexafluoro-2,6-dihydroxy-4-oxoheptane-2,6-diyl)dibenzoate (9a)

Yield = 71%; R_f 0.31 (hexane/ethyl acetate = 3/1); IR (KBr) 1717 (ketone C=O, ester C=O), 3437 (OH) cm^{-1}; HRMS (ESI^+) found: *m/z* 573.1323. Calcd for $C_{25}H_{24}F_6NaO_7$: $[M+Na]^+$, 573.1324;

Major/Minor = 52/48

Major isomer: ^1H NMR ($CDCl_3$) δ 1.380 (t, *J* = 7.18 Hz, 6H, OCH_2CH_3 X 2), 3.28 (d, *J* = 17.40 Hz, 2H,

C*H*$_A$H$_B$ X 2), 3.47 (d, *J* = 17.40 Hz, 2H, CH$_A$*H*$_B$ X 2), 4.37 (q, *J* = 7.18 Hz, 4H, OC*H*$_2$CH$_3$ X 2), 4.79 (s, 2H, OH X 2), 7.54 (d, *J* = 8.55 Hz, 4H, aryl H) , 8.01 (d, *J* = 8.55 Hz, 4H, aryl H); ^{13}C NMR ($CDCl_3$) δ 14.3 (s), 47.2 (s), 61.5 (s), 76.0 (q, *J* = 29.5 Hz), 124.1 (q, *J* = 285.3 Hz), 126.34 (s), 129.77 (s), 131.19 (s), 141.2 (s), 166.15 (s), 208.3 (s); ^{19}F NMR ($CDCl_3$) δ −80.1 (s, 6F).

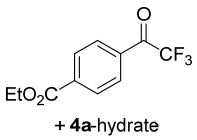
Minor isomer: ^{1}H NMR ($CDCl_3$) δ 1.384 (t, *J* = 7.09 Hz, 6H, OCH$_2$C*H*$_3$ X 2), 3.33 (d, *J* = 17.10 Hz, 2H, C*H*$_A$H$_B$ X 2), 3.42 (d, *J* = 17.10 Hz, 2H, CH$_A$*H*$_B$ X 2), 4.38 (q, *J* = 7.09 Hz, 4H, OC*H*$_2$CH$_3$ X 2), 4.83 (s, 2H, OH X 2), 7.49 (d, *J* = 8.55 Hz, 4H, aryl H) , 7.98 (d, *J* = 8.55 Hz, 4H, aryl H); ^{13}C NMR ($CDCl_3$) δ 14.3 (s), 47.1 (s), 61.5 (s), 76.0 (q, *J* = 29.5 Hz), 124.1 (q, *J* = 285.3 Hz), 126.27 (s), 129.80 (s), 131.17 (s), 141.3 (s), 166.22 (s), 208.7 (s); ^{19}F NMR ($CDCl_3$) δ −80.0 (s, 6F).

Ethyl 4-(1,1,1-trifluoro-2-hydroxy-3-nitropropan-2-yl)benzoate (10a)[9]

Yield = 74%; R_f 0.30 (dichloromethane); IR (KBr) 1365 (NO_2), 1721 (C=O), 3599 (OH) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.37 (t, *J* = 7.19 Hz, 3H, OCH$_2$C*H*$_3$), 4.37 (q, *J* = 7.19 Hz, 2H, OC*H*$_2$CH$_3$), 5.05 (s, 1H, OH), 5.06 (d, *J* = 13.50 Hz, 1H, C*H*$_A$H$_B$), 5.13 (d, *J* = 13.50 Hz, 1H, CH$_A$*H*$_B$), 7.69 (d, *J* = 8.55 Hz, 2H, aryl H) , 8.09 (d, *J* = 8.55 Hz, 2H, aryl H); ^{13}C NMR ($CDCl_3$) δ 14.2 (s), 61.6 (s), 76.3 (q, *J* = 29.7 Hz), 77.5 (s), 123.5 (q, *J* = 286.3 Hz), 126.5 (s), 130.1 (s), 131.9 (s), 137.8 (s), 166.1 (s); ^{19}F NMR ($CDCl_3$) δ −78.4 (s, 3F).

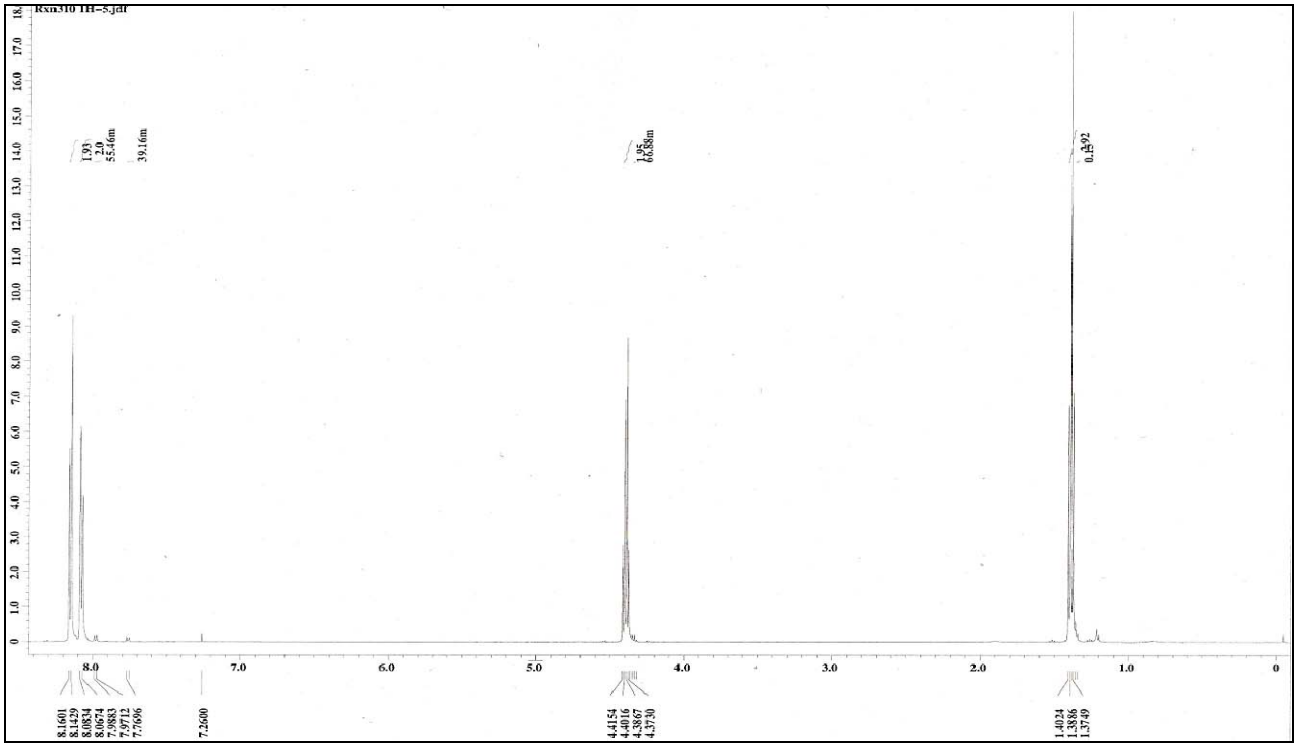
[9] H. Xu and C. Wolf, *Chem. Commun.*, **2010**, *46*, 8026–8028.

Ethyl 4-(2,2,2-trifluoroacetyl)benzoate (**4a**) and
ethyl 4-(2,2,2-trifluoro-1,1-dihydroxyethyl)benzoate (**4a**-hydrate)

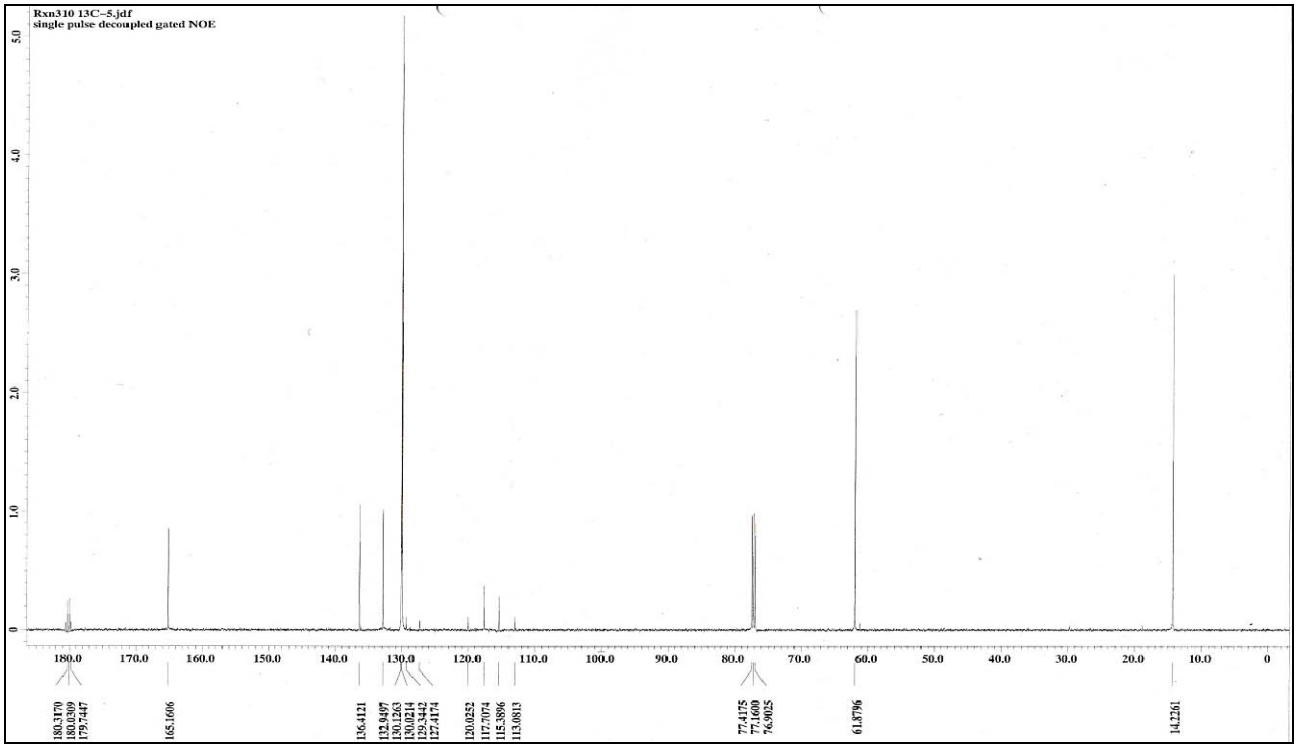


+ **4a**-hydrate

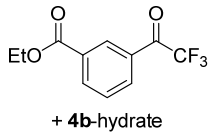
^{1}H NMR



^{13}C NMR

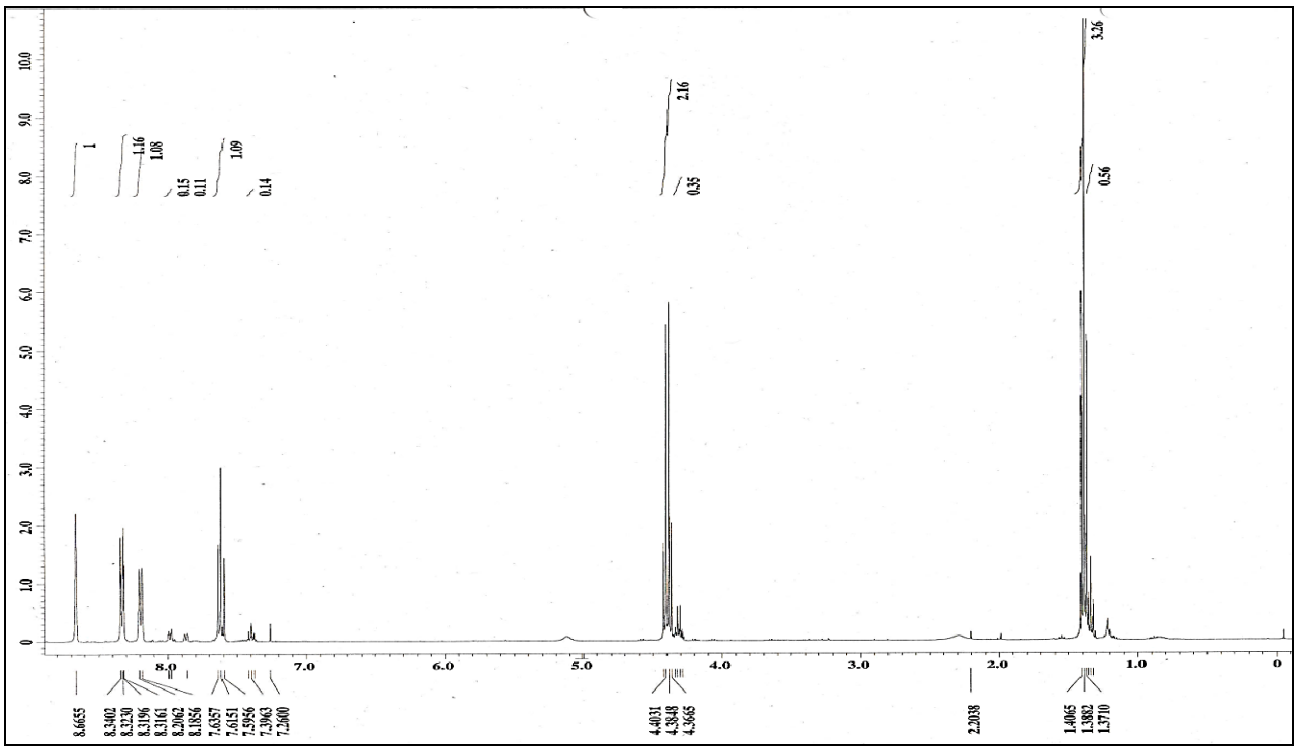


Ethyl 3-(2,2,2-trifluoroacetyl)benzoate (**4b**) and
ethyl 3-(2,2,2-trifluoro-1,1-dihydroxyethyl)benzoate (**4b**-hydrate)

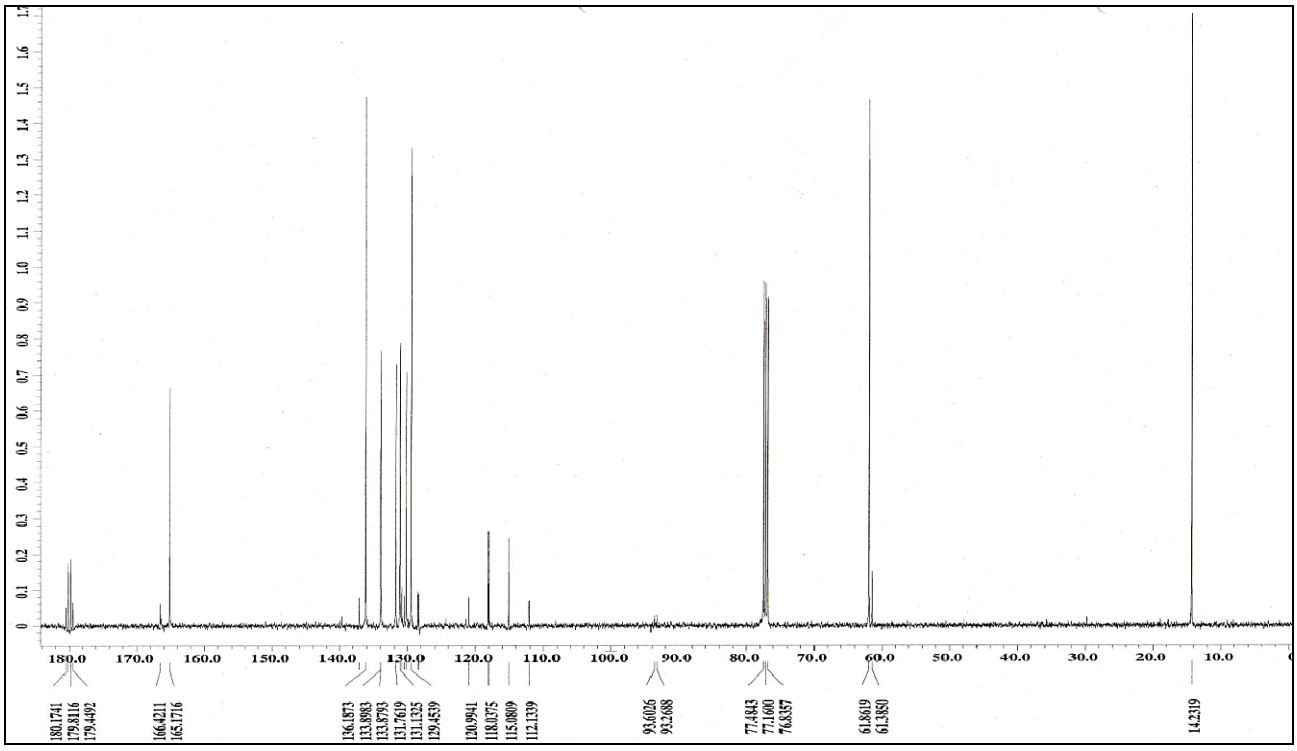


+ **4b**-hydrate

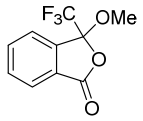
^{1}H NMR



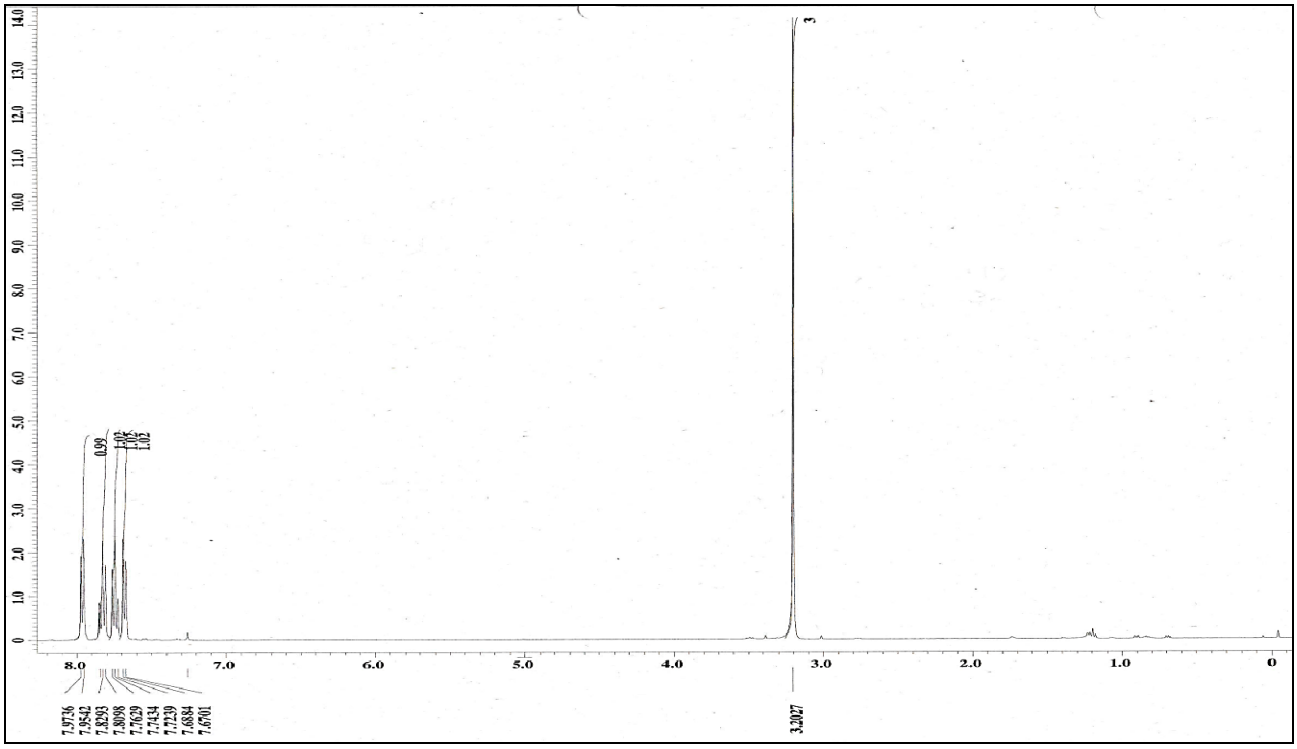
^{13}C NMR



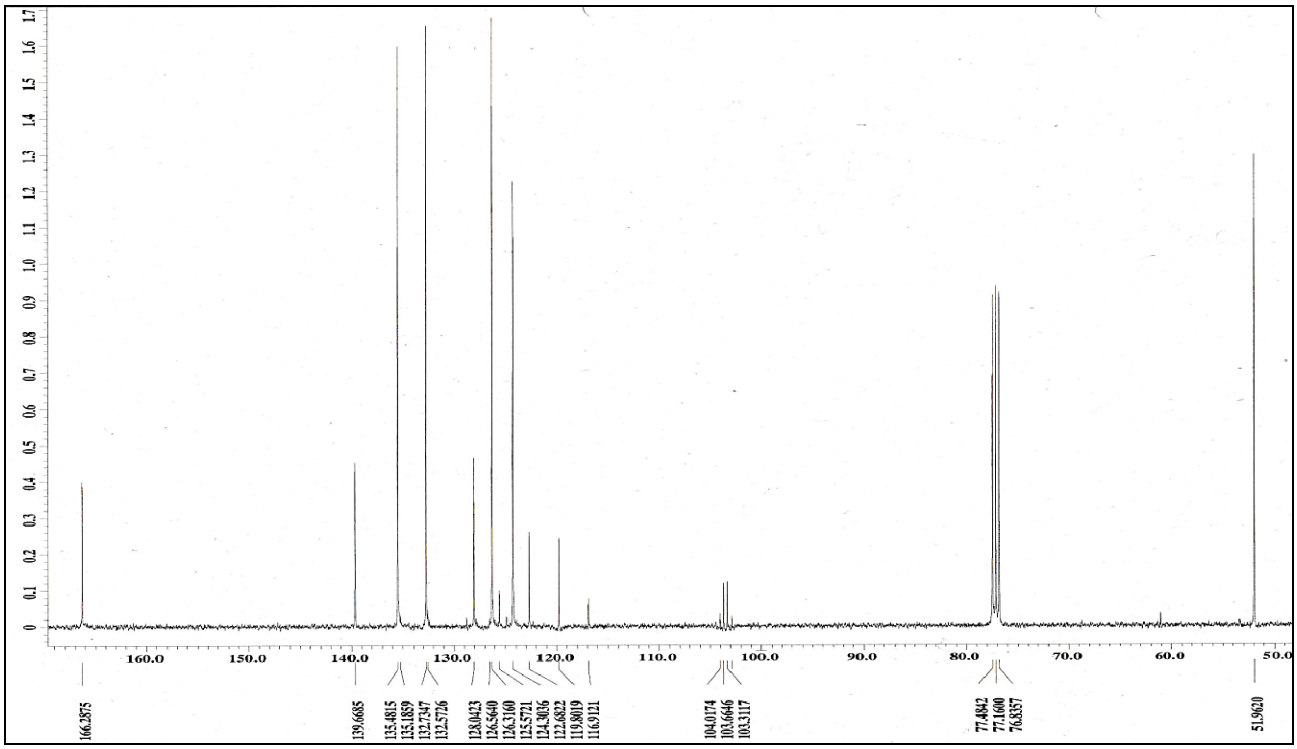
3-Methoxy-3-(trifluoromethyl)isobenzofuran-1(3*H*)-one (5)



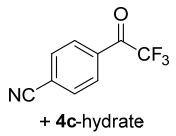
^{1}H NMR



^{13}C NMR

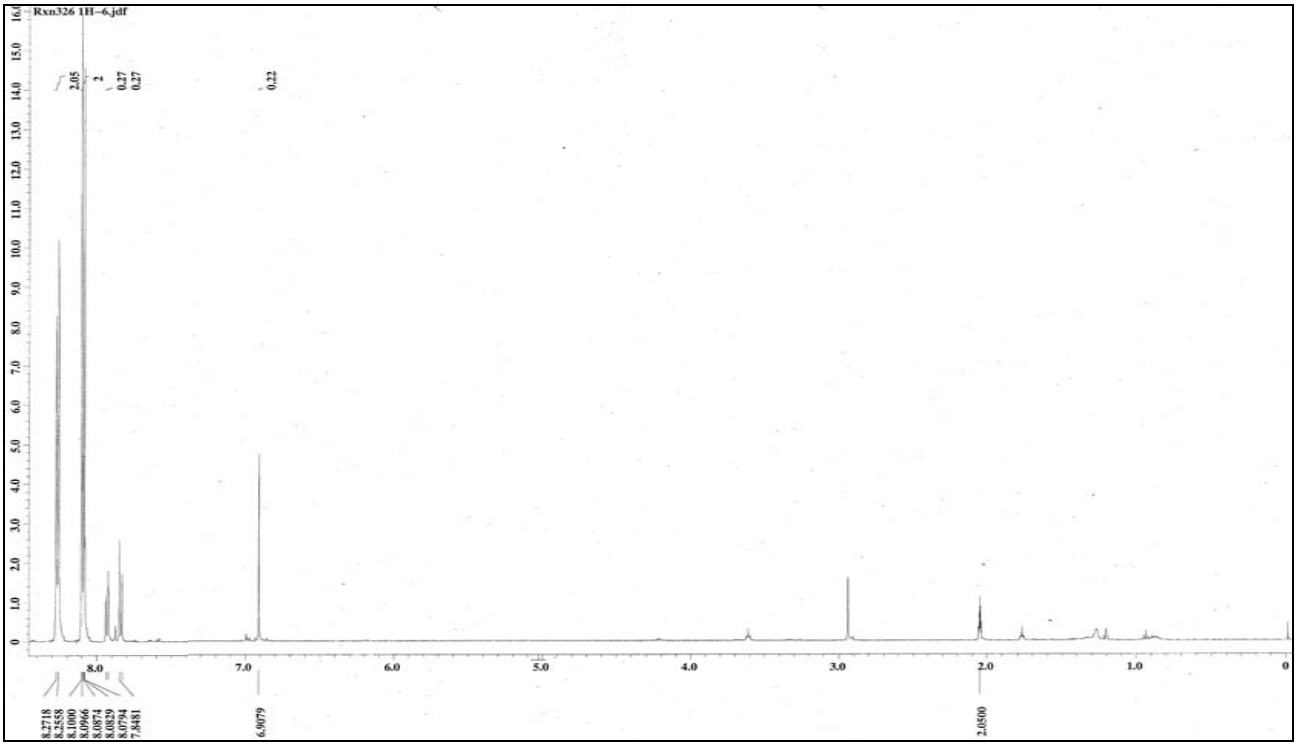


4-(2,2,2-Trifluoroacetyl)benzonitrile (**4c**) and
4-(2,2,2-trifluoro-1,1-dihydroxyethyl)benzonitrile (**4c**-hydrate)

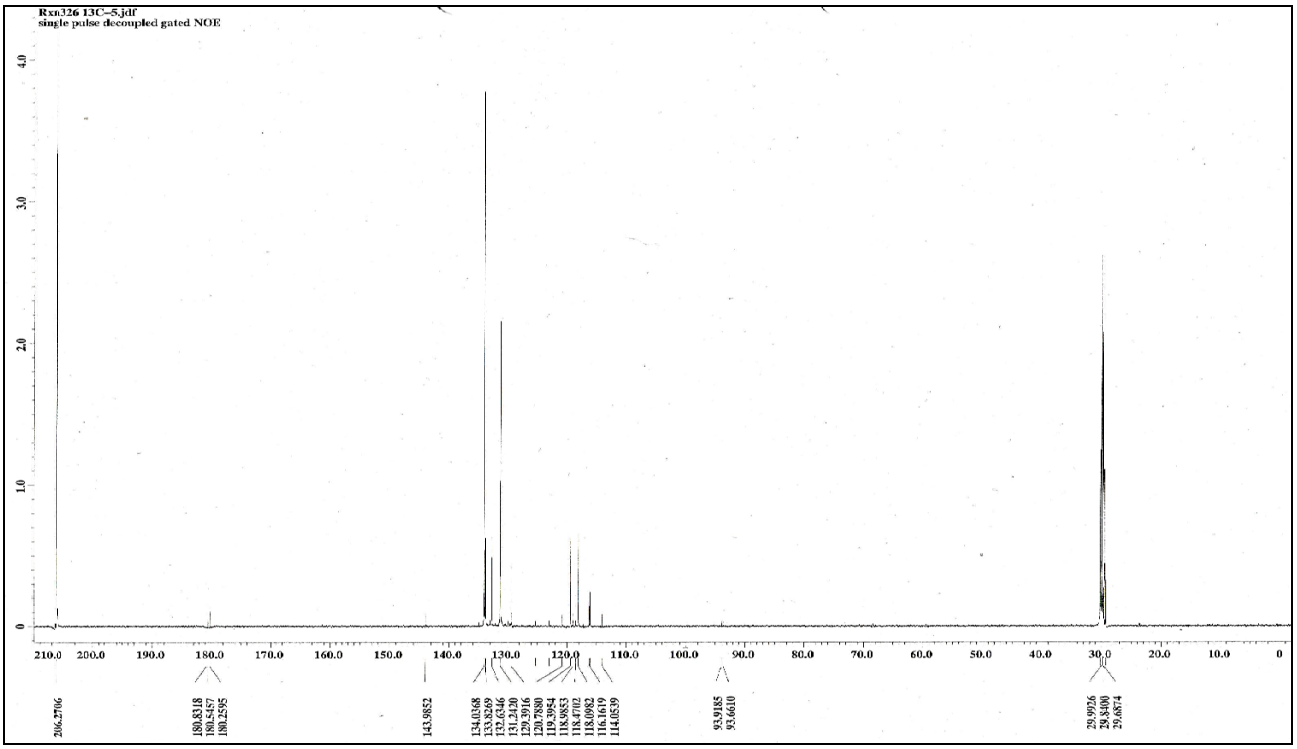


+ **4c**-hydrate

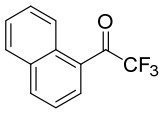
^{1}H NMR



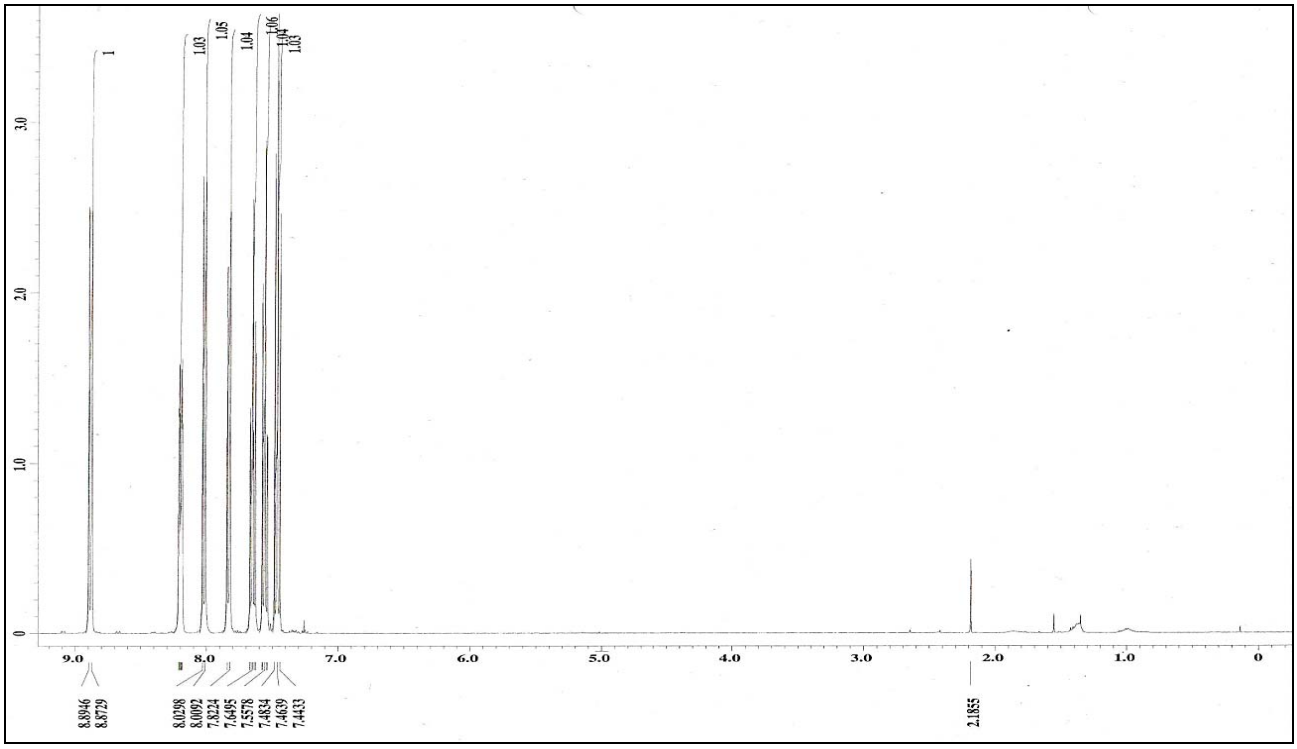
^{13}C NMR



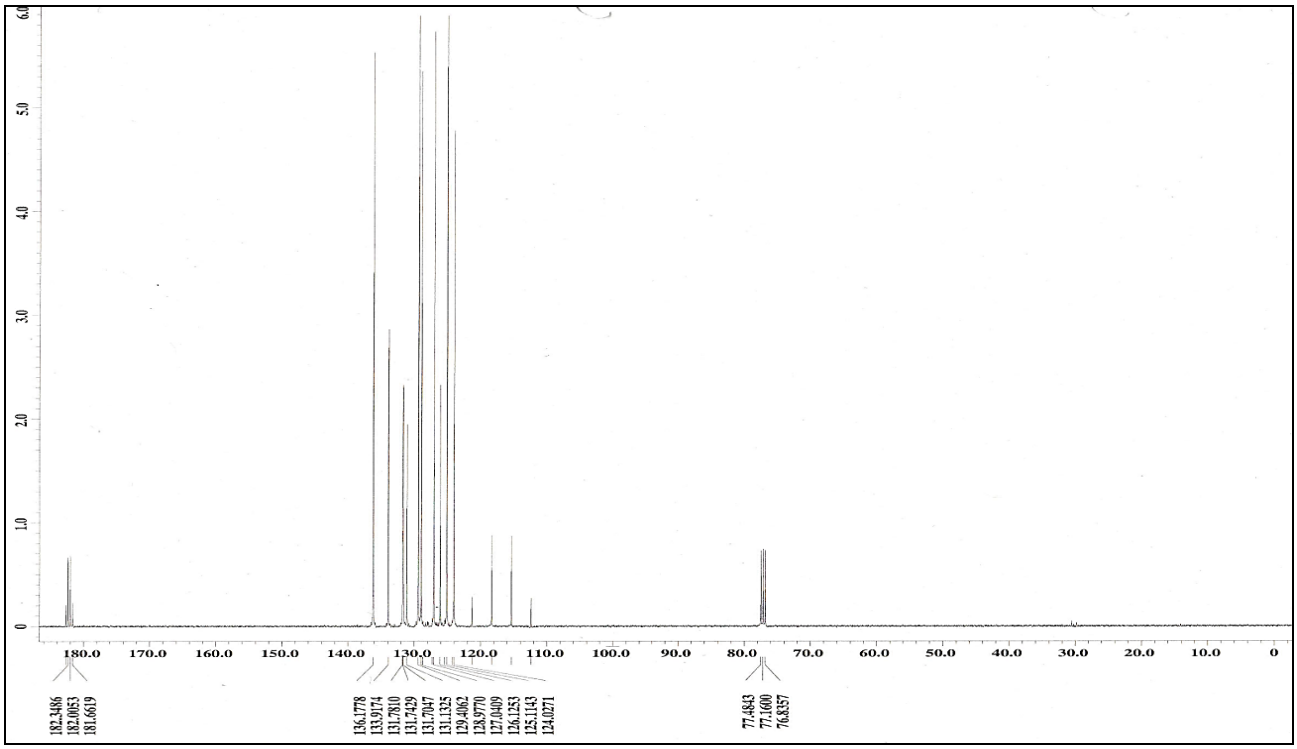
2,2,2-Trifluoro-1-(naphthalen-1-yl)ethan-1-one (4d)



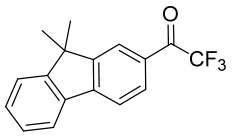
^{1}H NMR



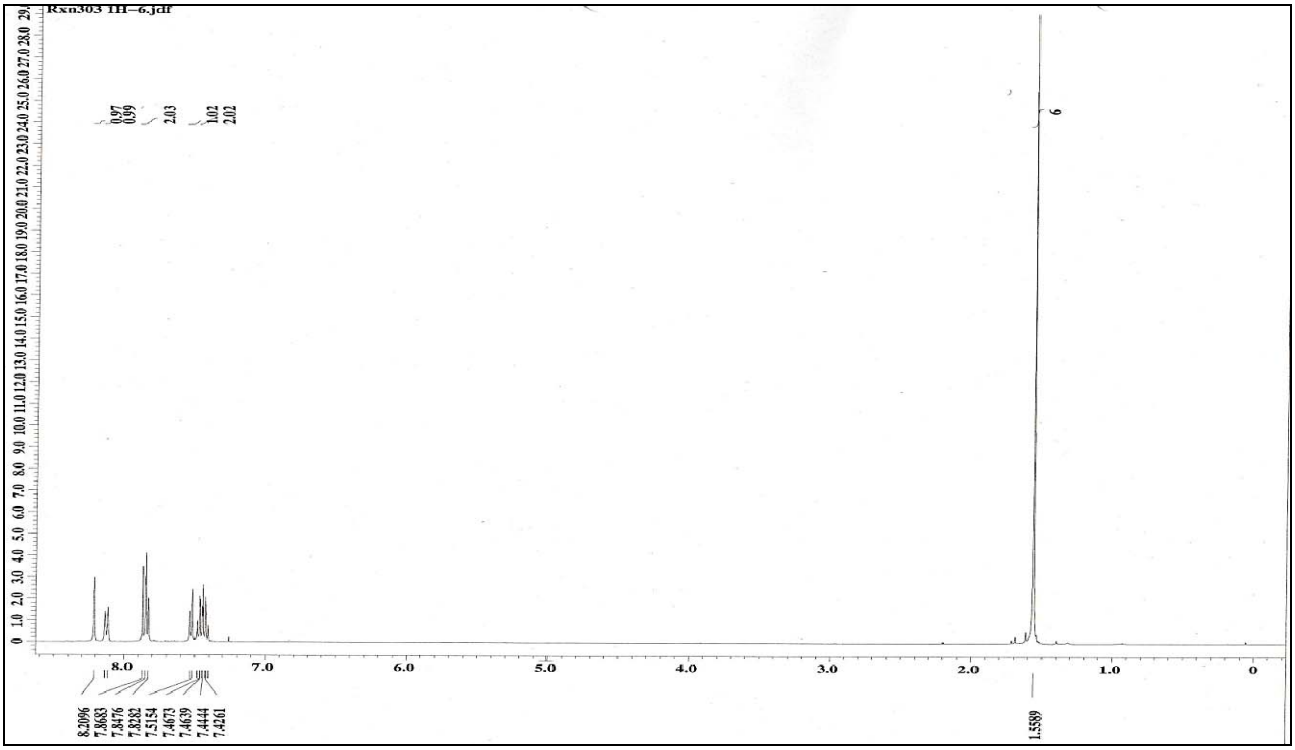
^{13}C NMR



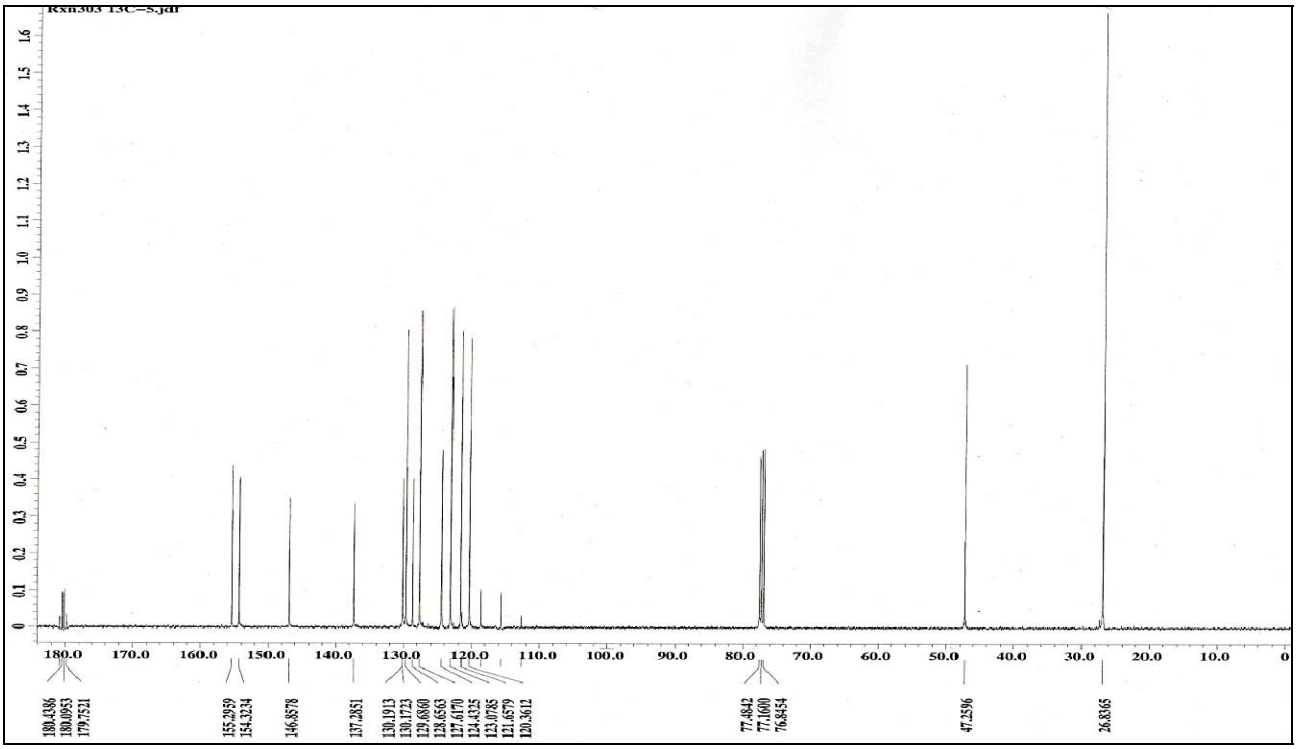
1-(9,9-Dimethyl-9*H*-fluoren-2-yl)-2,2,2-trifluoroethan-1-one (4e)



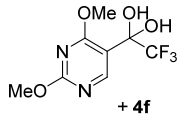
^{1}H NMR



^{13}C NMR

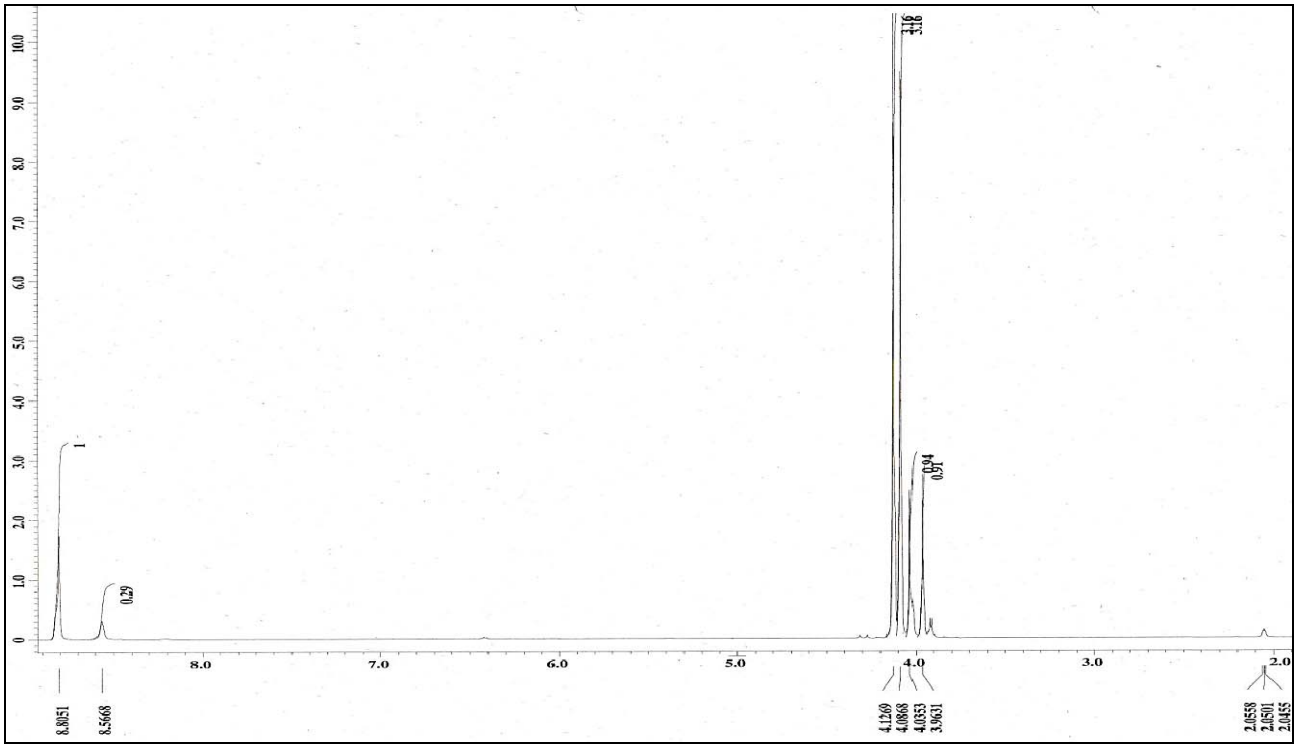


1-(2,4-Dimethoxypyrimidin-5-yl)-2,2,2-trifluoroethan-1-one (**4f**) and
1-(2,4-dimethoxypyrimidin-5-yl)-2,2,2-trifluoroethane-1,1-diol (**4f**-hydrate)

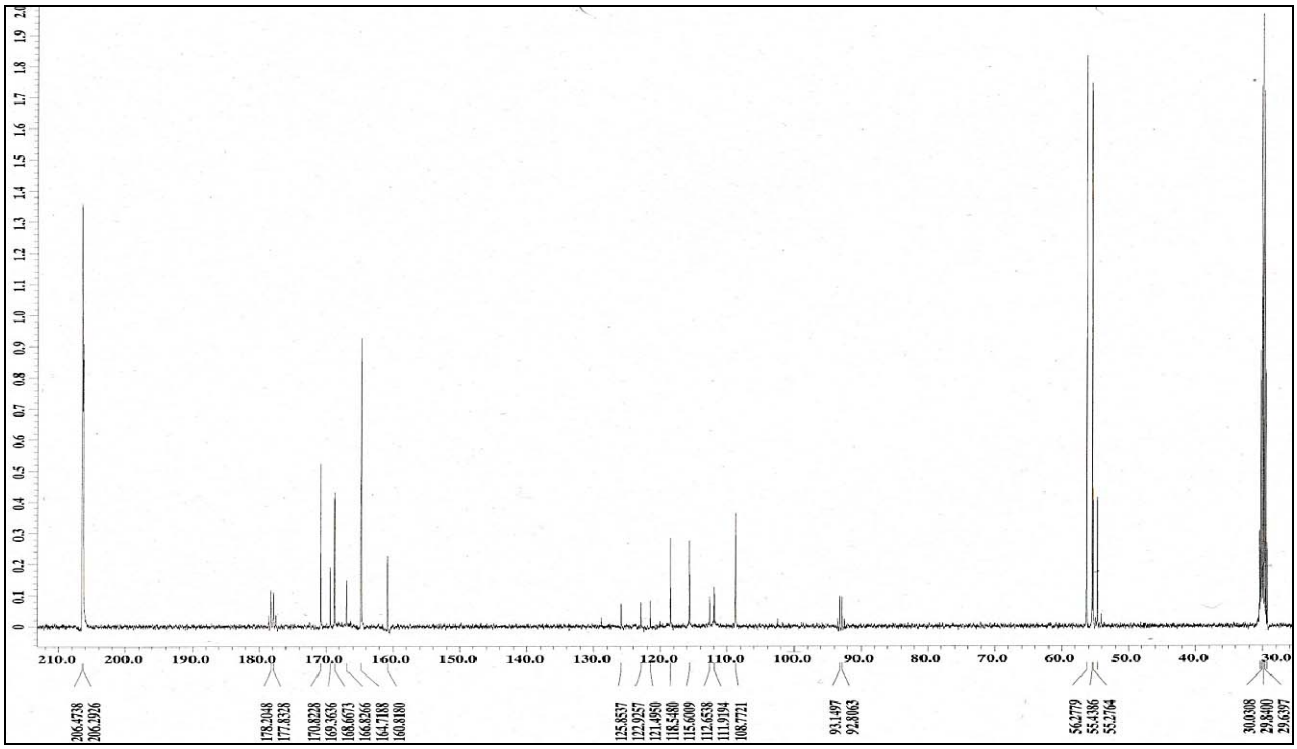


+ **4f**

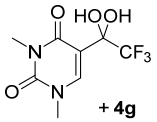
^{1}H NMR



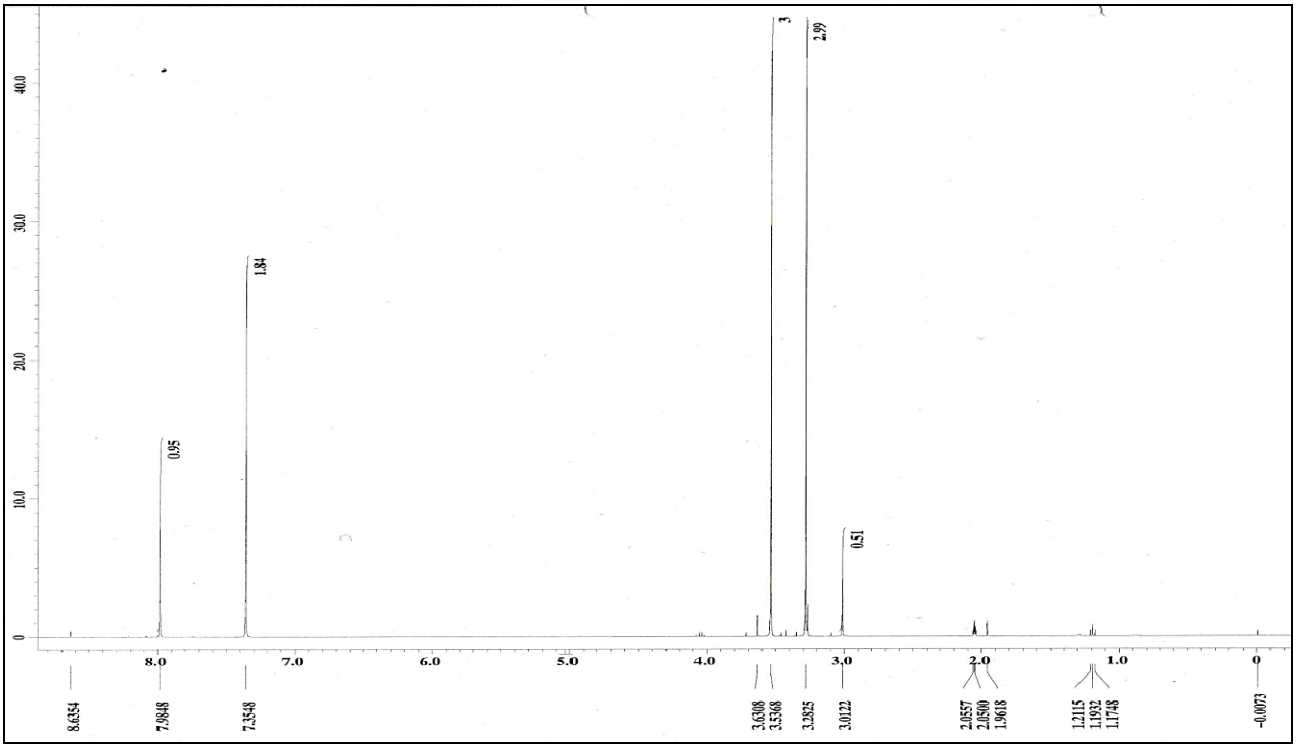
^{13}C NMR



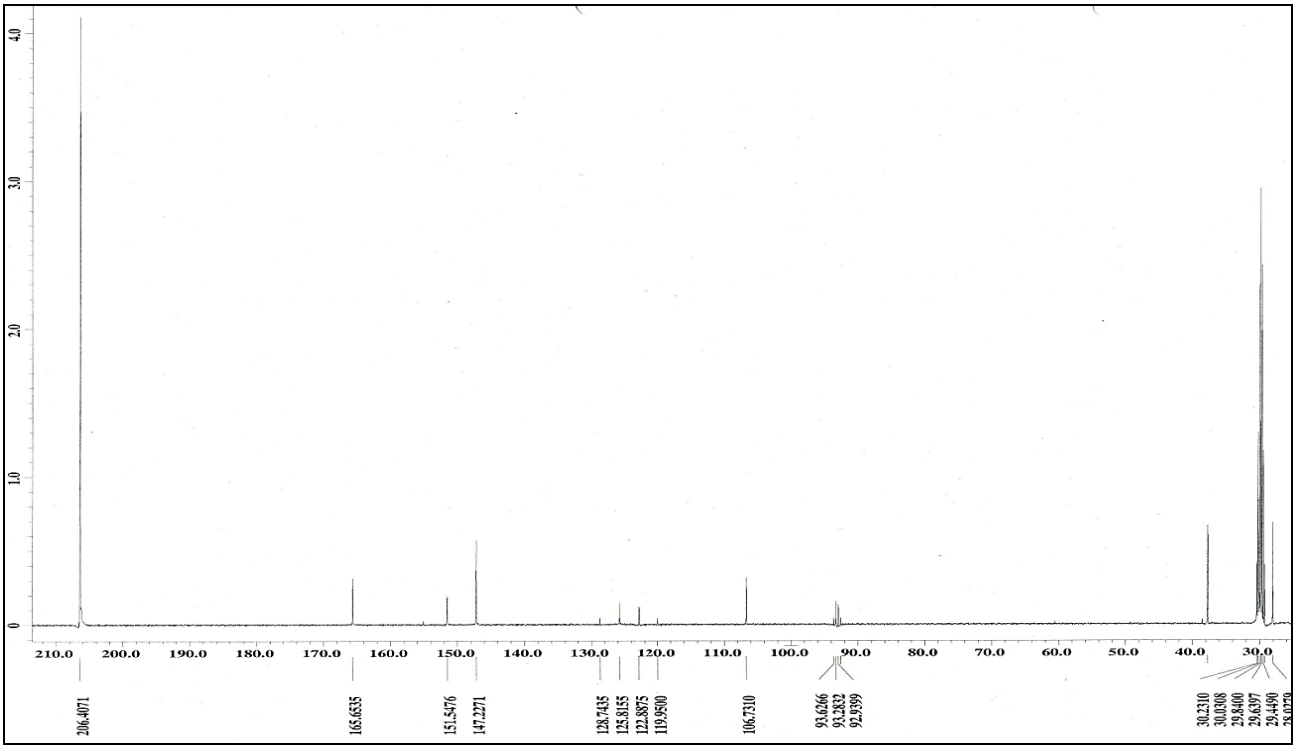
1,3-Dimethyl-5-(2,2,2-trifluoroacetyl)pyrimidine-2,4(1*H*,3*H*)-dione (**4g**) and **1,3-dimethyl-5-(2,2,2-trifluoro-1,1-dihydroxyethyl)pyrimidine-2,4(1*H*,3*H*) -dione** (**4g**-hydrate)



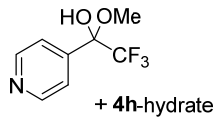
^{1}H NMR



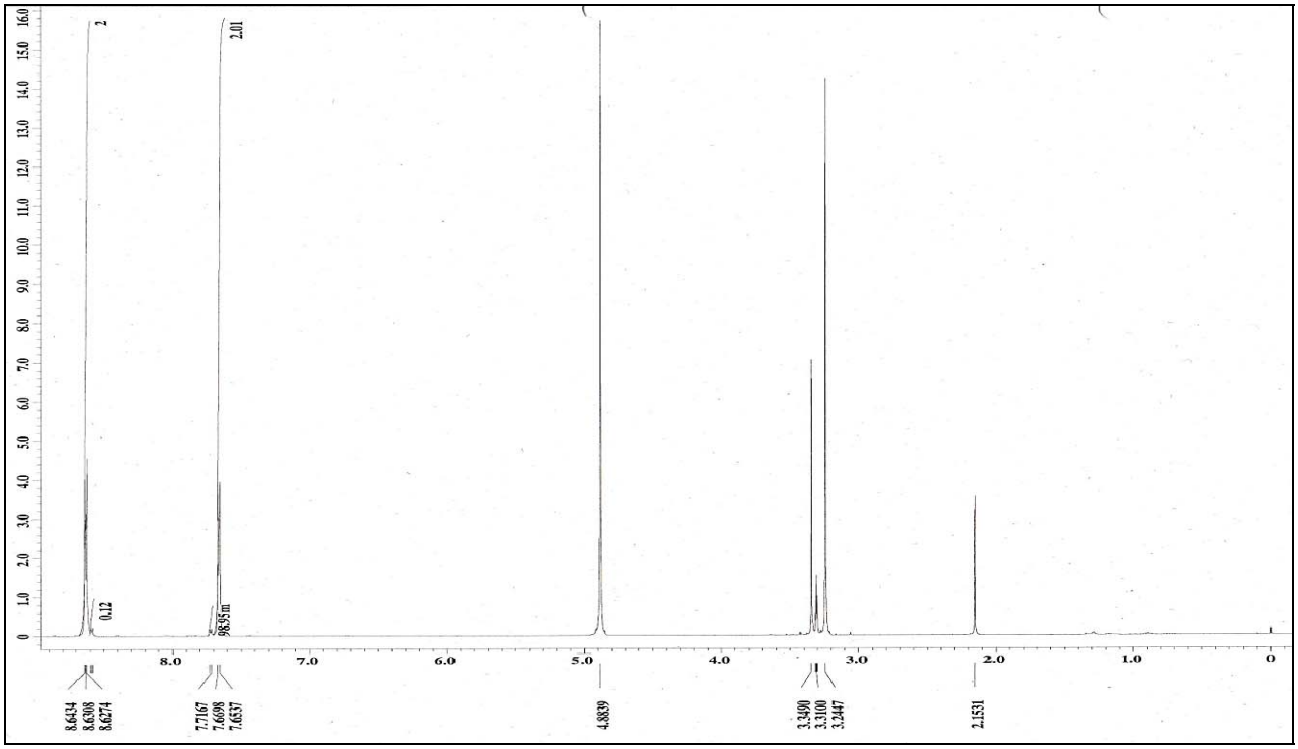
^{13}C NMR



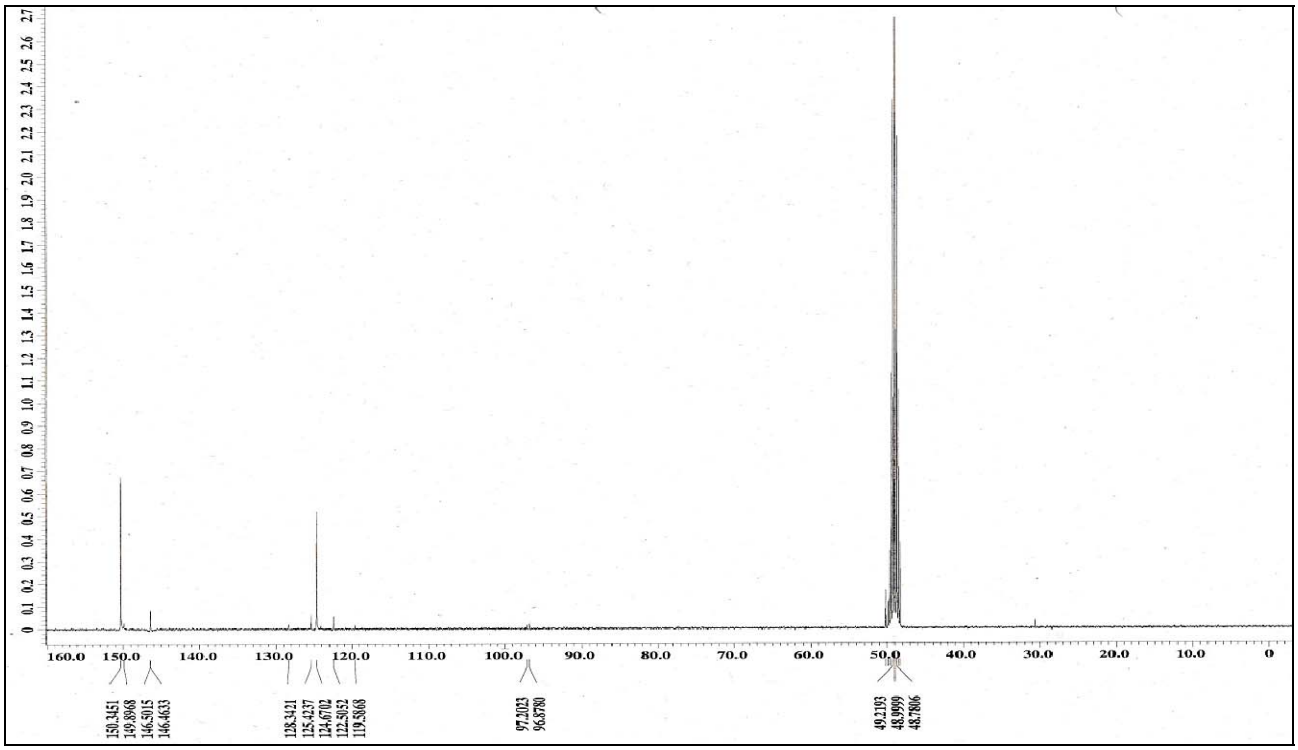
2,2,2-Trifluoro-1-methoxy-1-(pyridin-4-yl)ethan-1-ol (**4h**-hemiacetal) and **2,2,2-trifluoro-1-(pyridin-4-yl)ethane-1,1-diol** (**4h**-hydrate)



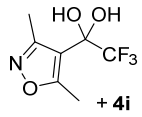
^{1}H NMR



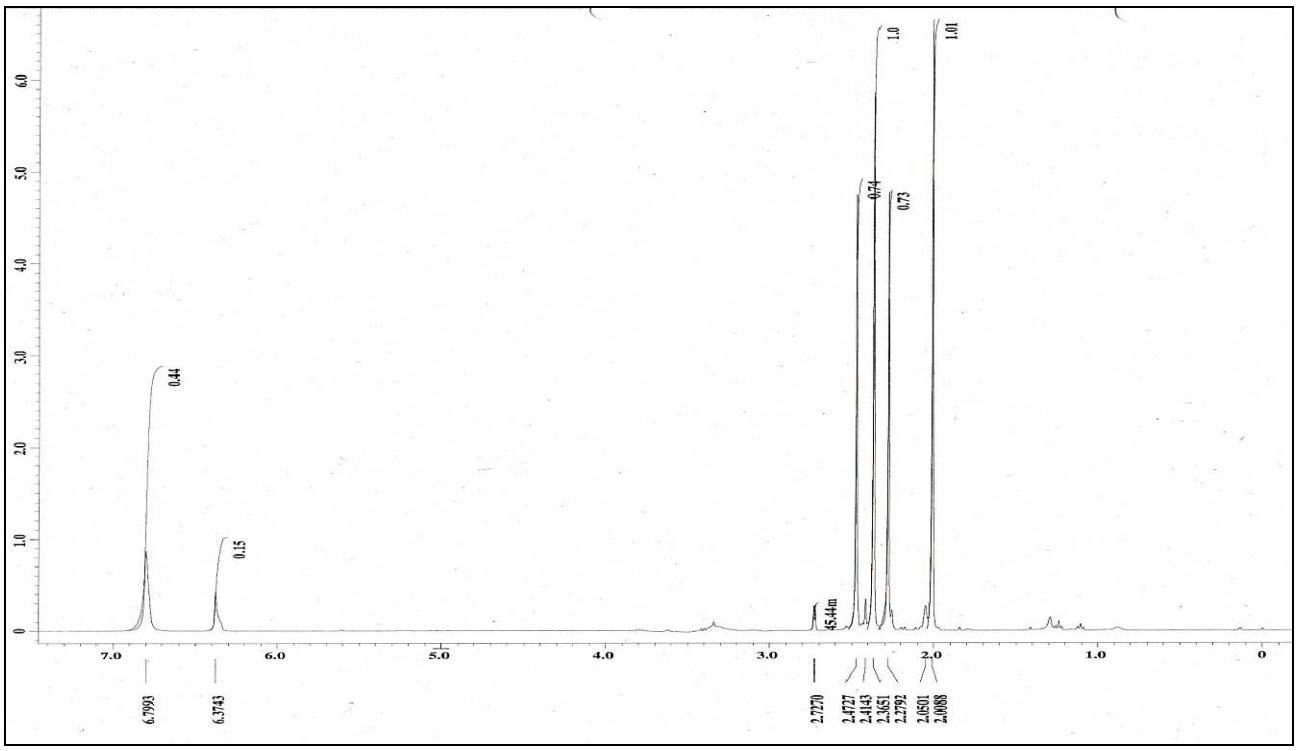
^{13}C NMR



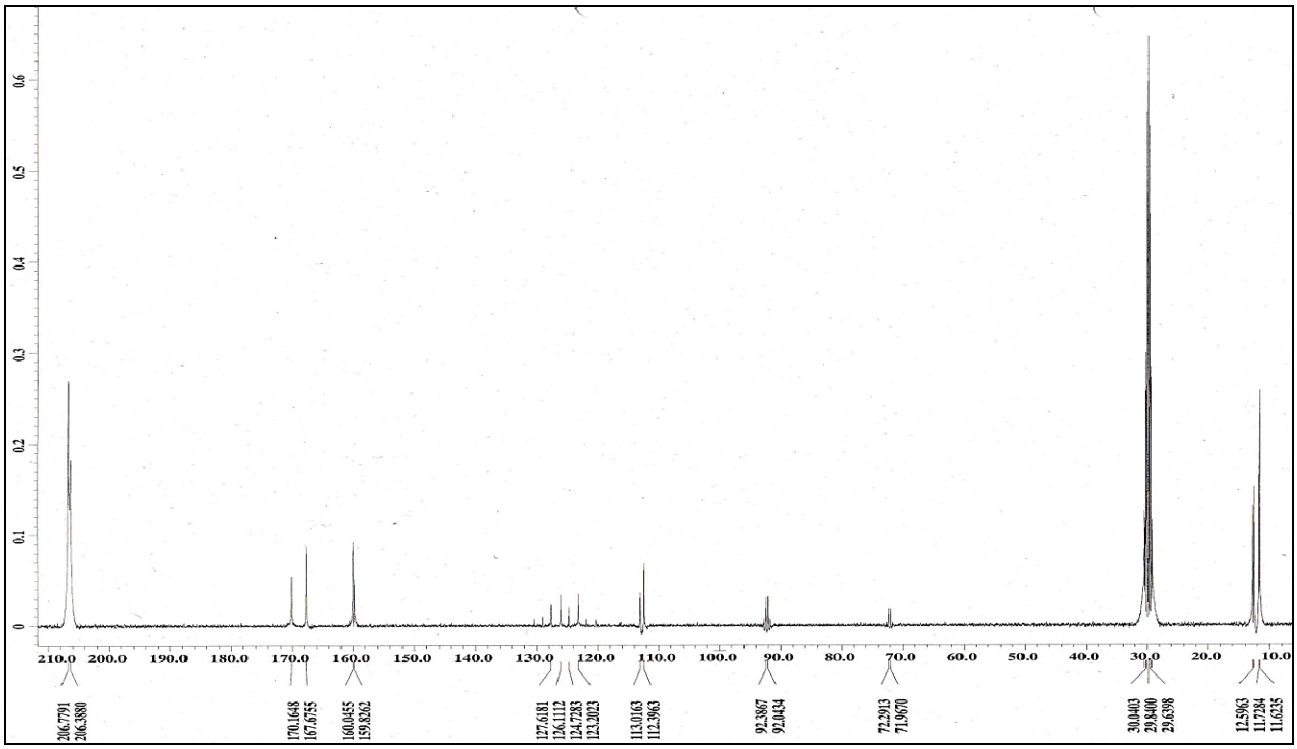
1-(3,5-Dimethylisoxazol-4-yl)-2,2,2-trifluoroethan-1-one (**4i**) and
1-(3,5-dimethylisoxazol-4-yl)-2,2,2-trifluoroethane-1,1-diol (**4i**-hydrate)



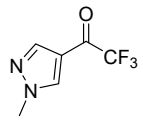
^{1}H NMR



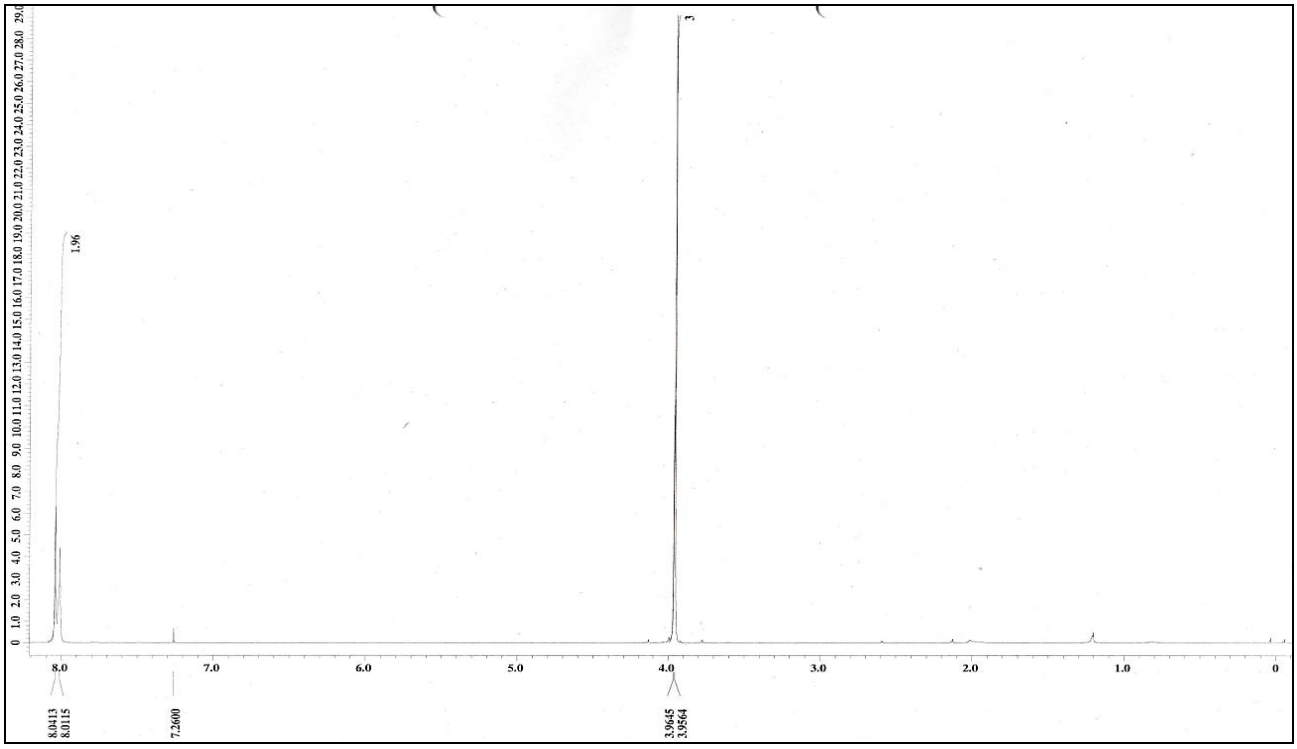
^{13}C NMR



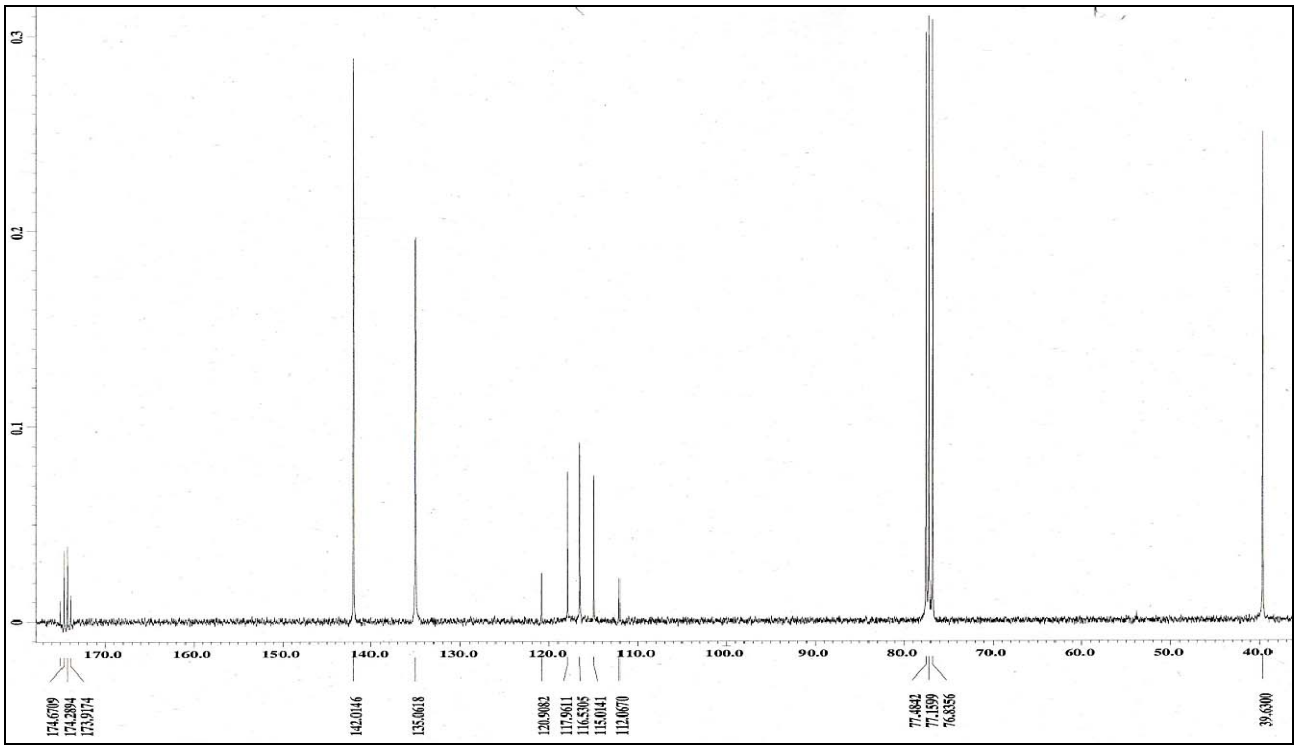
2,2,2-Trifluoro-1-(1-methyl-1*H*-pyrazol-4-yl)ethan-1-one (4j)



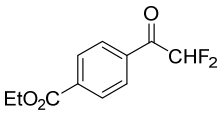
^{1}H NMR



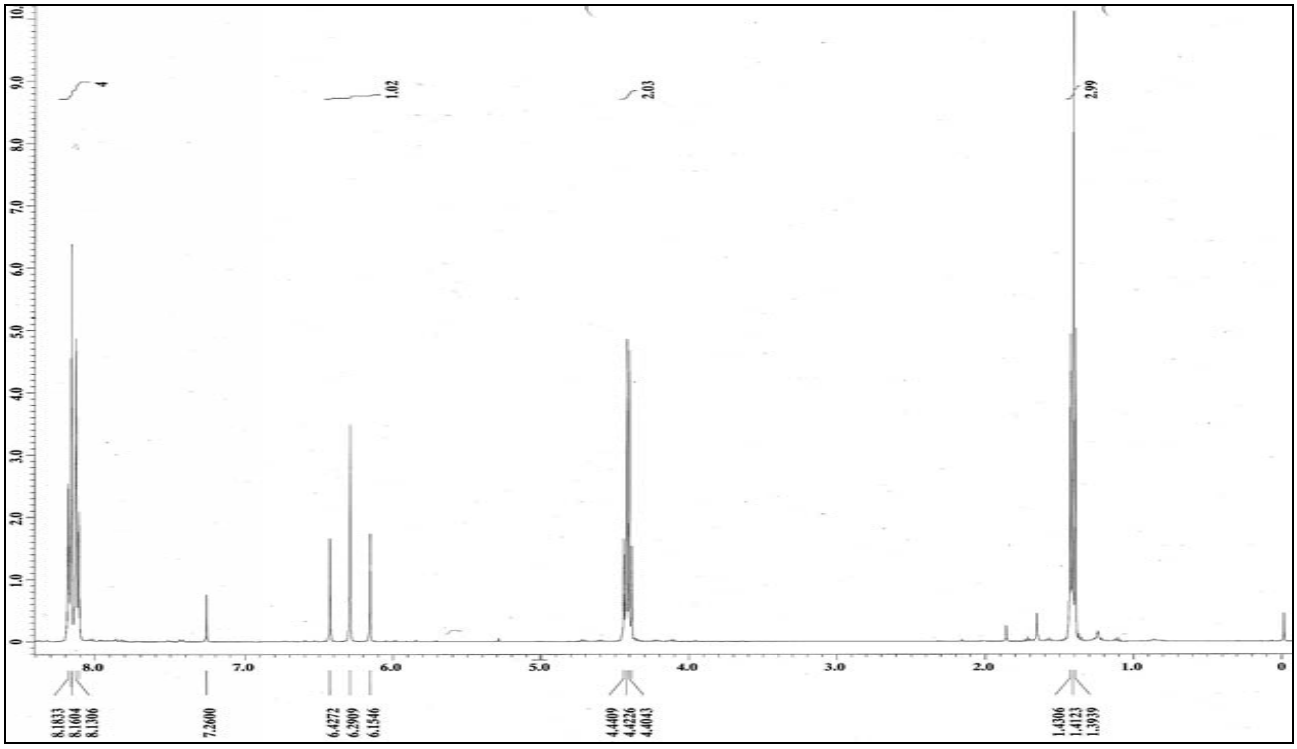
^{13}C NMR



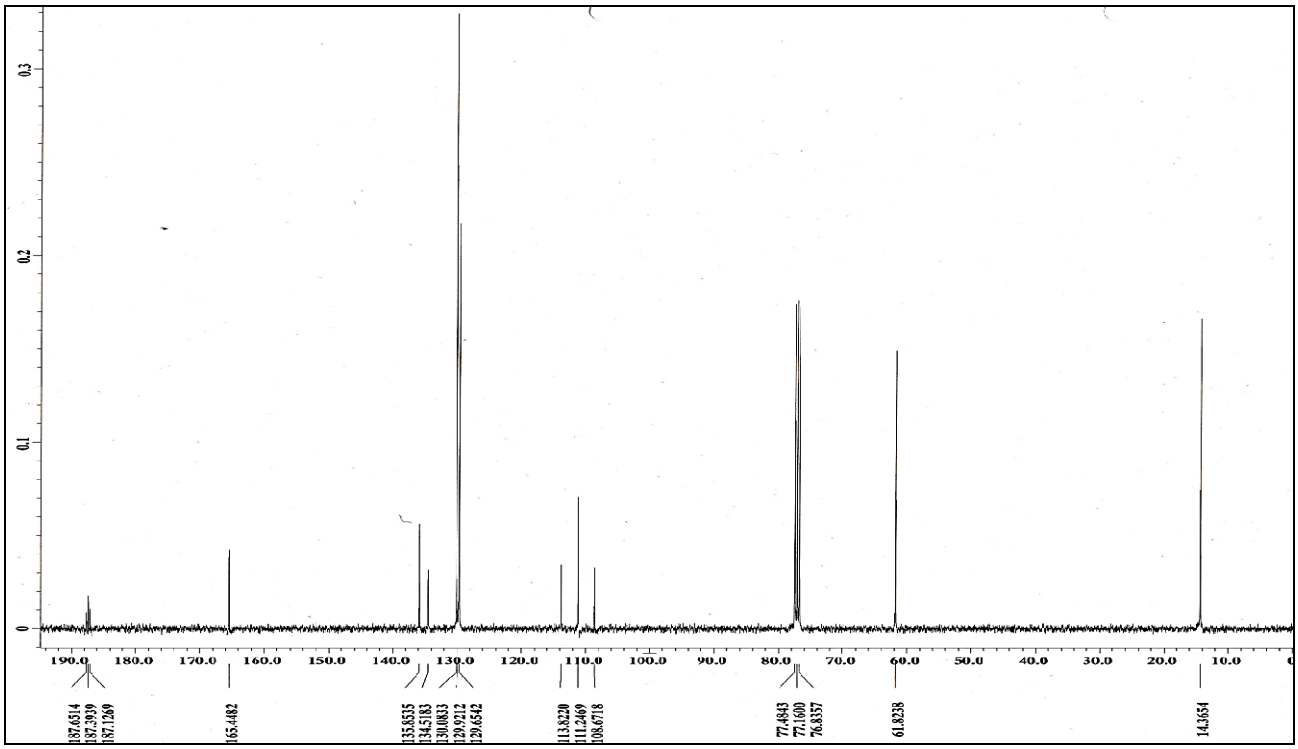
Ethyl 4-(2,2-difluoroacetyl)benzoate (6)



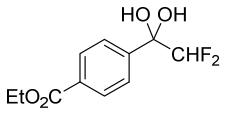
^{1}H NMR



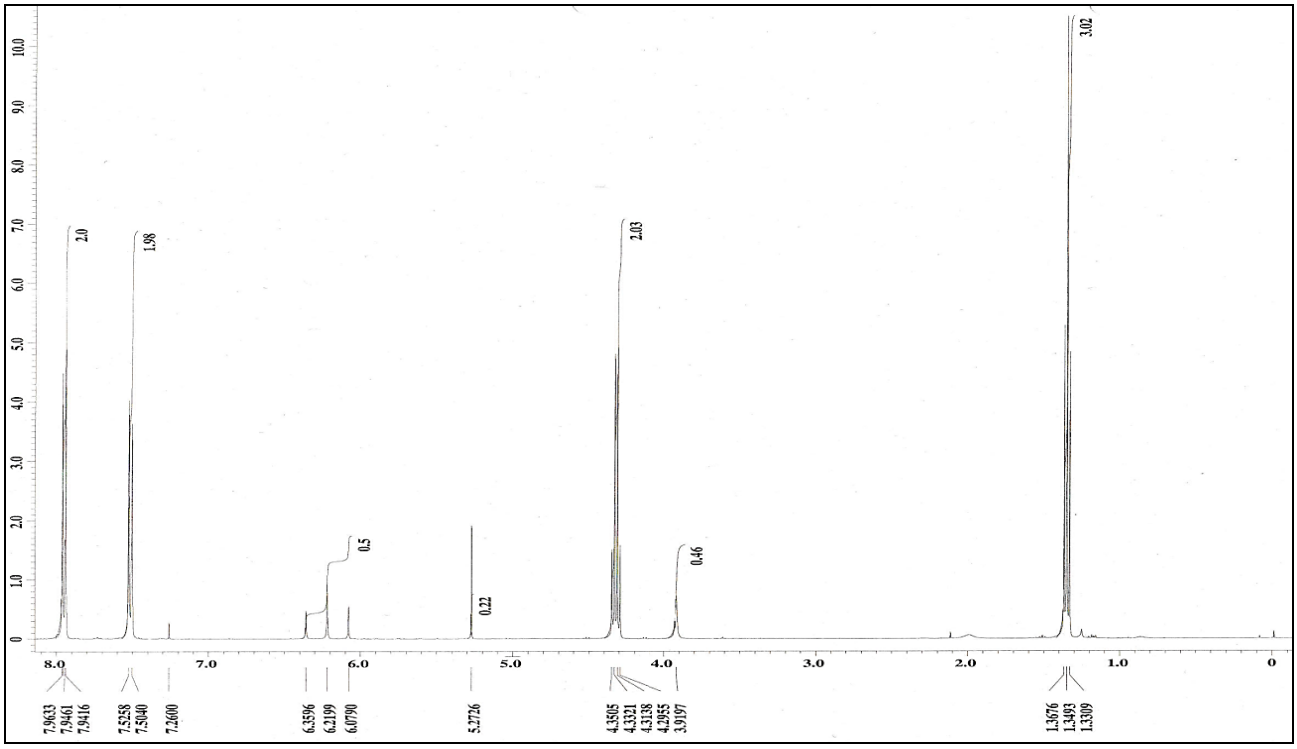
^{13}C NMR



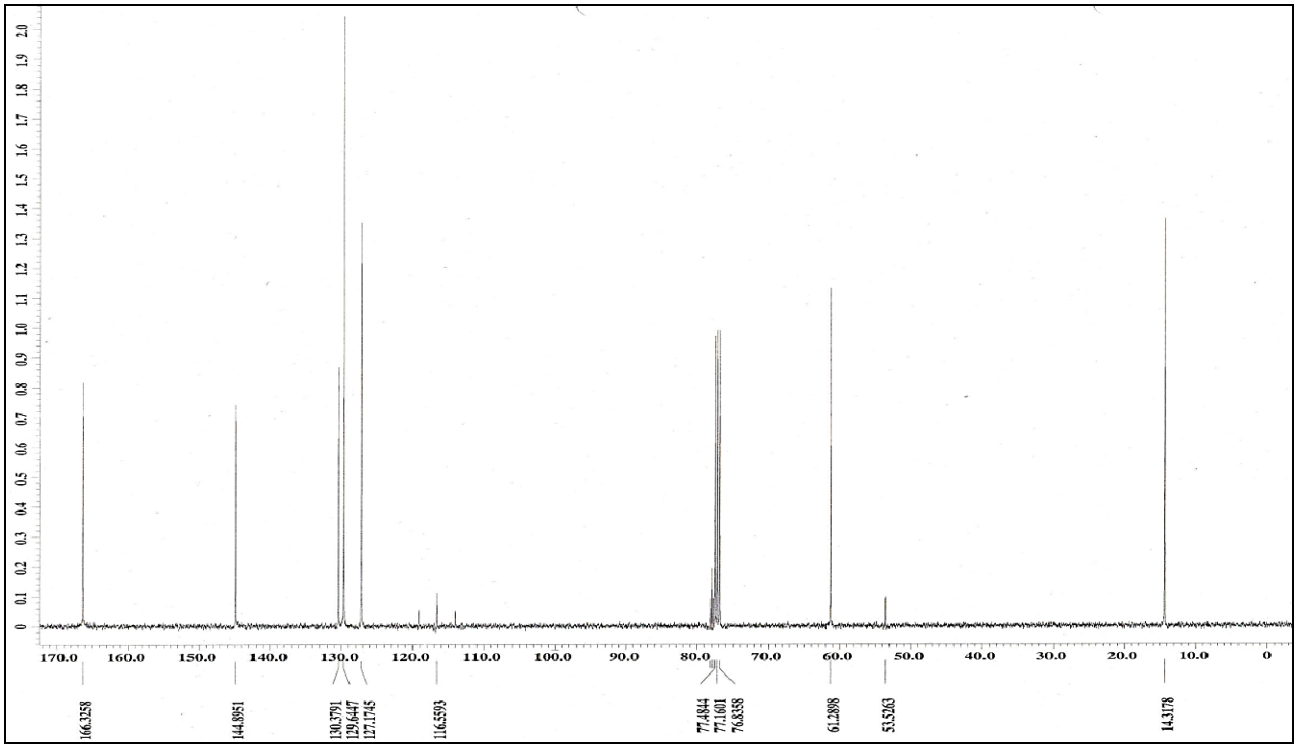
Ethyl 4-(2,2-difluoro-1,1-dihydroxyethyl)benzoate (**6**-hydrate)



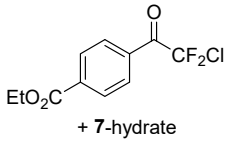
^{1}H NMR



^{13}C NMR

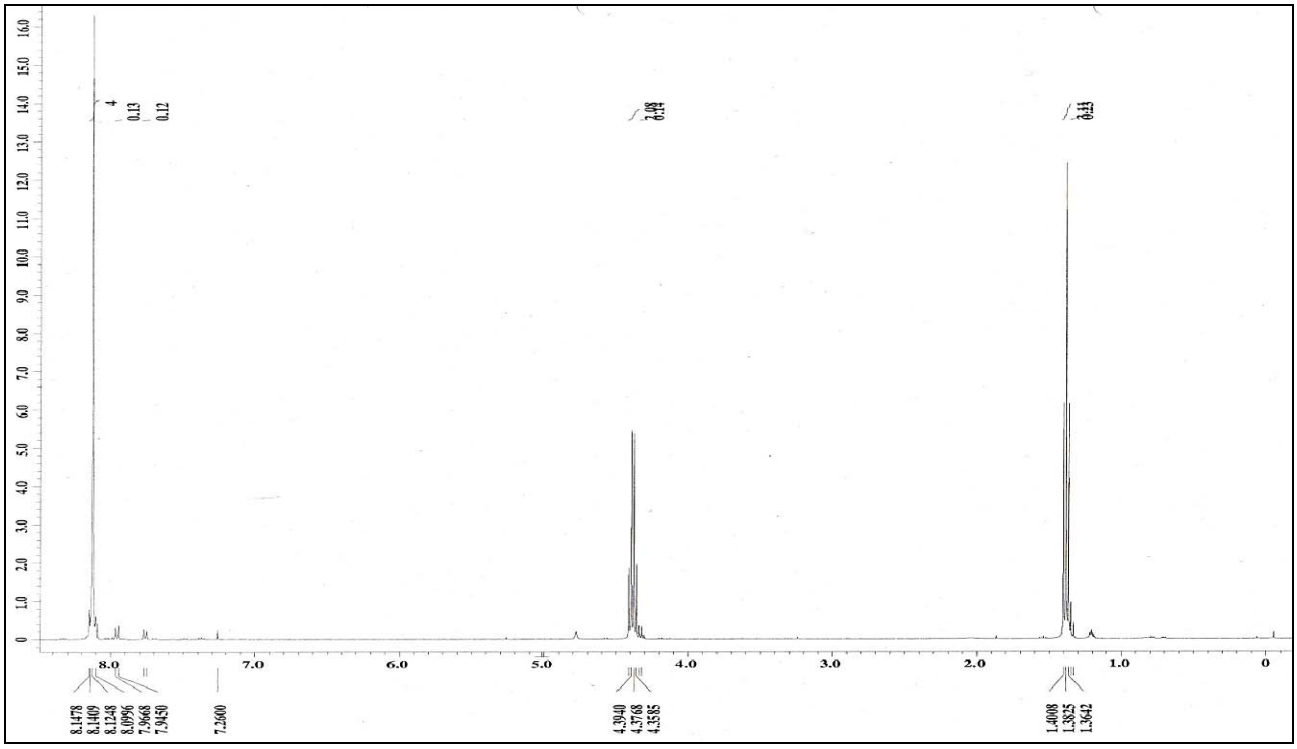


Ethyl 4-(2-chloro-2,2-difluoroacetyl)benzoate (**7**) and
ethyl 4-(2-chloro-2,2-difluoro-1,1-dihydroxyethyl)benzoate (**7**-hydrate)

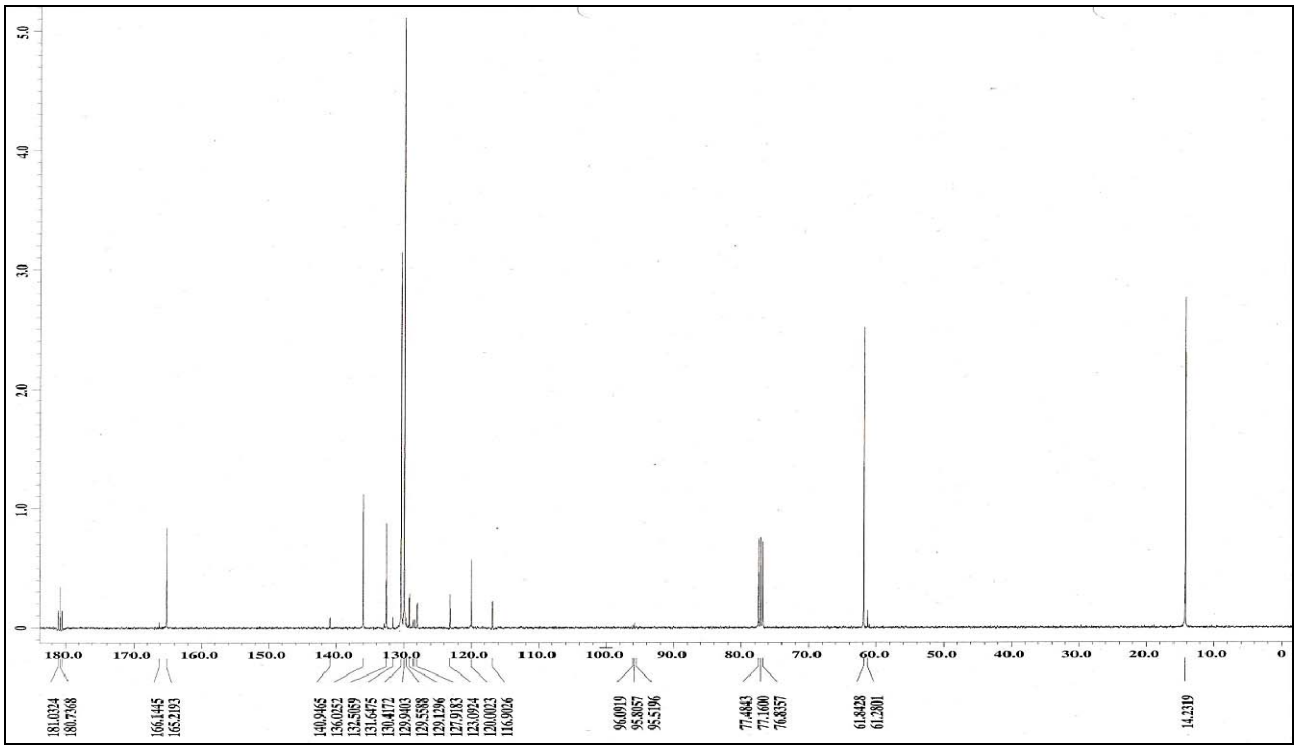


+ **7**-hydrate

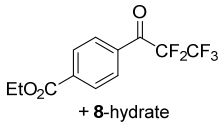
^{1}H NMR



^{13}C NMR

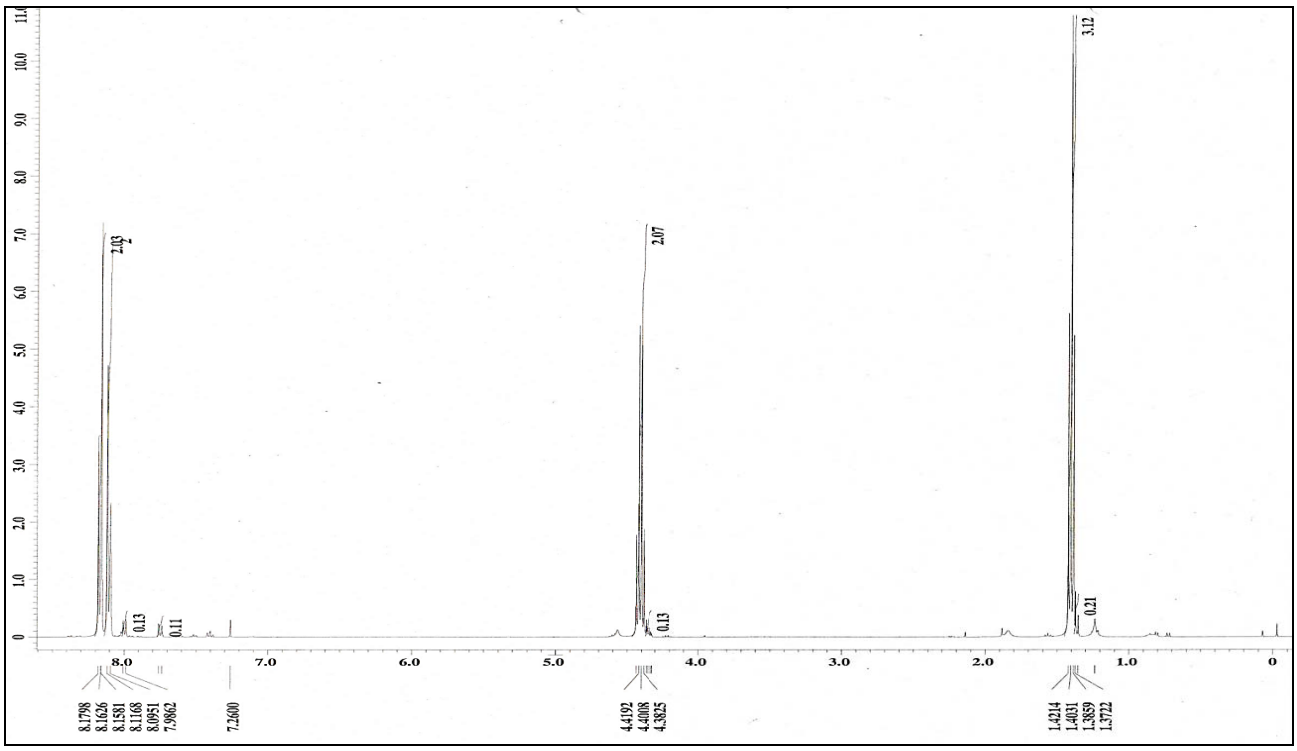


Ethyl 4-(2,2,3,3,3-pentafluoropropanoyl)benzoate (**8**) and
ethyl 4-(2,2,3,3,3-pentafluoro-1,1-dihydroxypropyl)benzoate (**8**-hydrate)

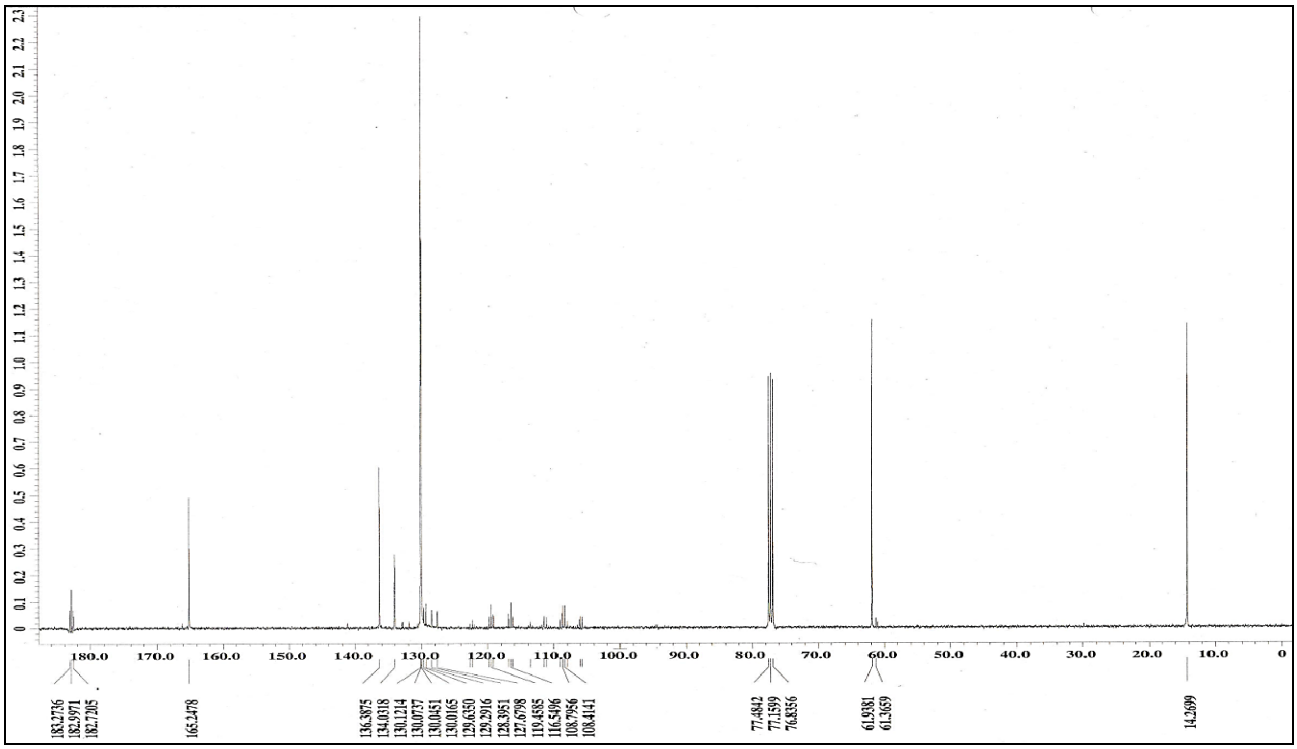


+ **8**-hydrate

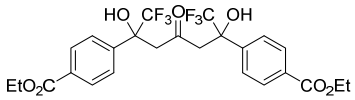
^{1}H NMR



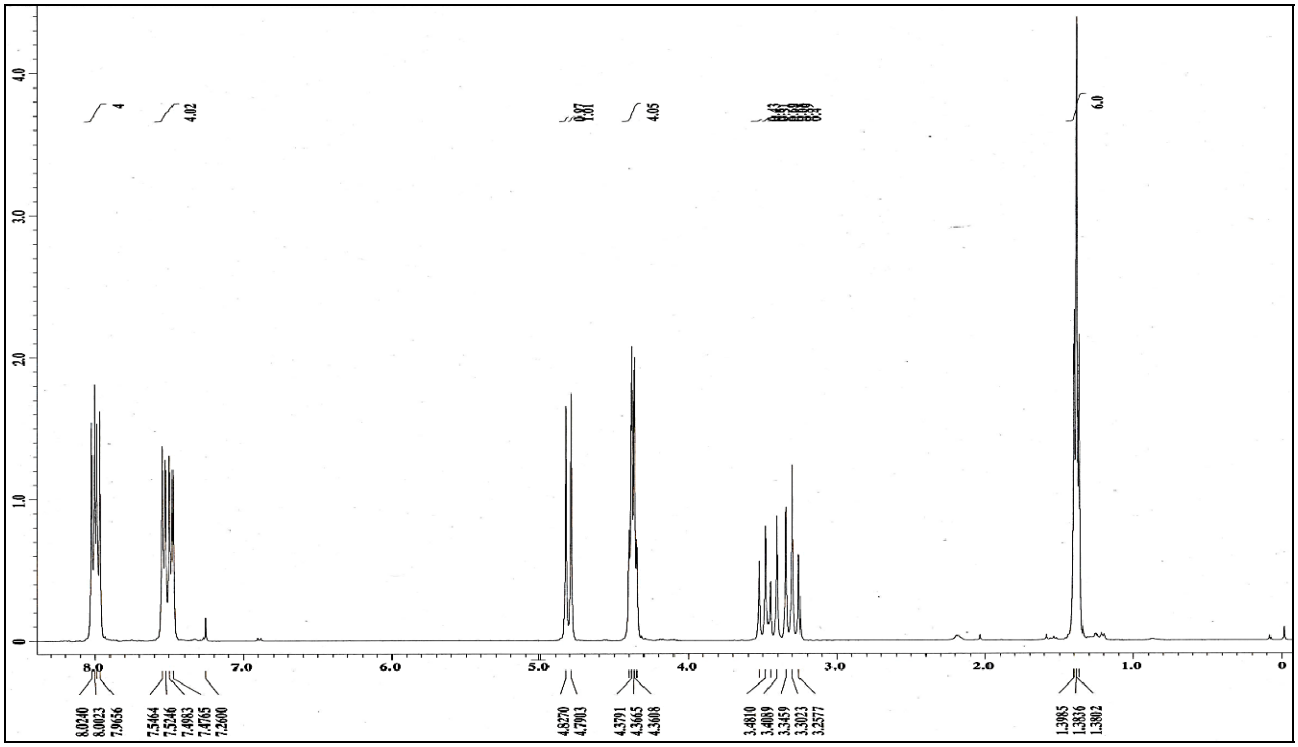
^{13}C NMR



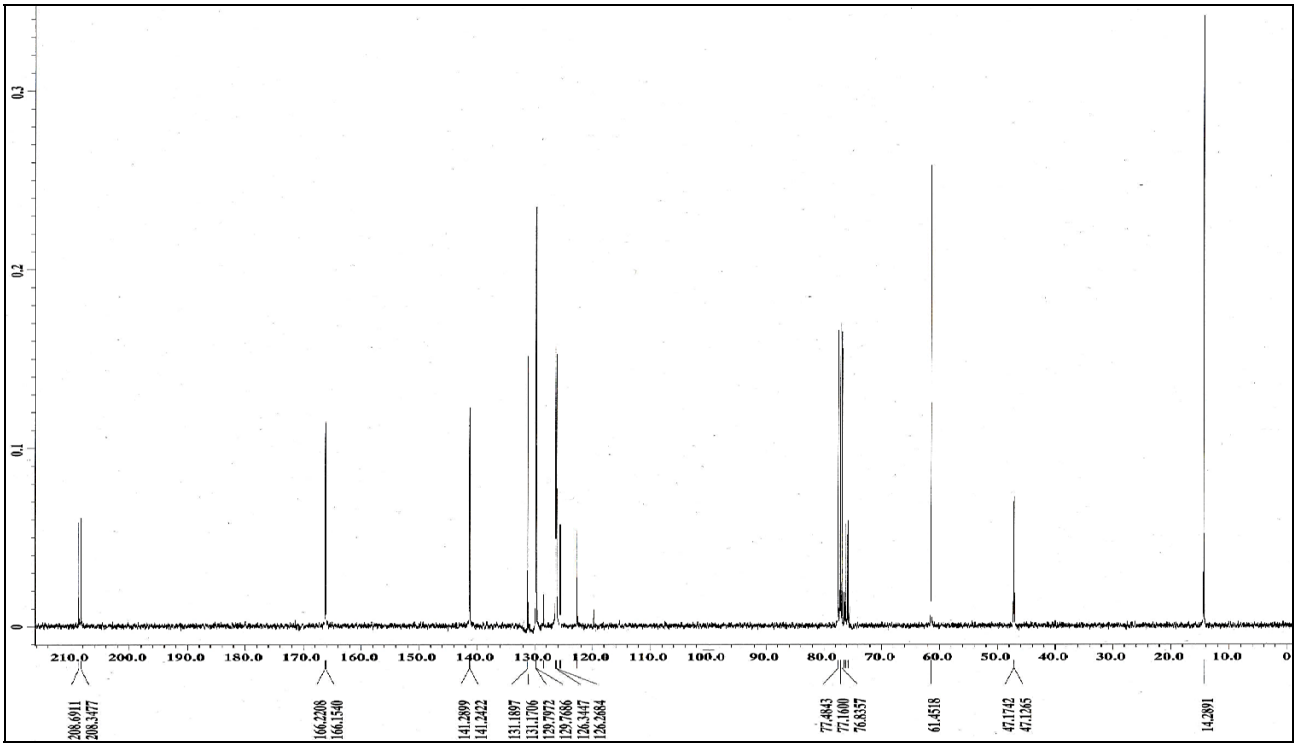
Diethyl 4,4'-(1,1,1,7,7,7-hexafluoro-2,6-dihydroxy-4-oxoheptane-2,6-diyl)dibenzoate (9a)



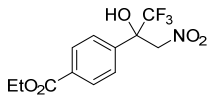
^{1}H NMR



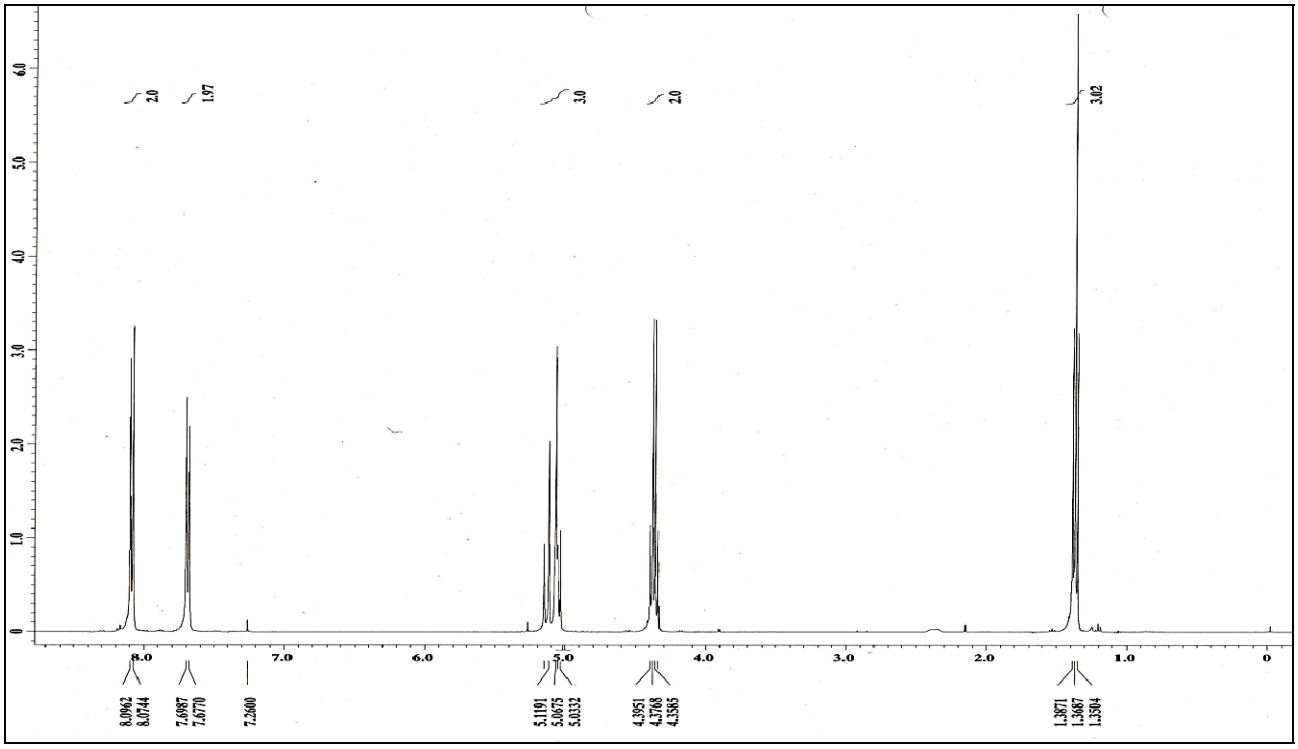
^{13}C NMR



Ethyl 4-(1,1,1-trifluoro-2-hydroxy-3-nitropropan-2-yl)benzoate (10a)



^{1}H NMR



^{13}C NMR