Supporting information

SYNTHESIS OF TRIFLUOROMETHYL DERIVATES OF QUINOLINE AND ISOQUINOLINE

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N-(2-(2-BROMOETHYL)PHENYL)-2,2,2-TRIFLUOROACETAMIDE (**3a**)

Under a nitrogen atmosphere, a solution of 2-(2-aminophenyl)ethanol **1** (5.4 g, 40 mmol) and Et_3N (4.4 mL, 32 mmol) in CH_2Cl_2/Et_2O (150 mL) was cooled to -20 °C and stirred for 15 min. Then, $(CF_3CO)_2O$ (3.3 mL, 24 mmol) was added dropwise to the reaction mixture and stirred at RT for 2 h. Subsequent to the addition of ice and water to the mixture, the liquid layers thus obtained were shaken and separated. The organic layer was washed with 5% aqueous HCl, saturated $NaHCO_3$ solution, and brine; then, it was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was used directly, without further purification, for the next step. To a stirred solution of crude and CBr_4 (6.0 g, 18 mmol) in Et_2O (30 mL), PPh_3 (4.8 g, 18 mmol) was added at RT for 2 h. After the dilution of the mixture with CH_2Cl_2, the organic layer was washed with water, saturated $NaHCO_3$ solution, and brine; dried over Na_2SO_4; and concentrated under reduced pressure. The residue thus obtained was purified by silica gel column chromatography (hexane/ethyl acetate = 20/1) to yield **3a** (1.5 g, 33%) as a pale pink solid. Mp: 88-90 °C; ^{1}H-NMR ($CDCl_3$) δ: 3.18 (2H, t, *J* = 6.6 Hz), 3.63 (2H, t, *J* = 6.6 Hz), 7.26-7.35 (3H, m), 7.59 (1H, d, *J* = 8.2 Hz), 8.28 (1H, brs); ^{13}C-NMR ($CDCl_3$) δ: 33.4, 34.0, 111.6, 114.5, 117.3, 120.2, 125.5, 128.0, 128.2, 130.3, 132.4, 132.8, 155.5, 155.9, 156.3. HRMS (ESI) calcd for $C_{10}H_9BrF_3NNaO$ $[M + Na]^+$ 317.9712; found 317.9398.

N-(2-(2-BROMOETHYL)PHENYL)-2,2,3,3,3-PENTAFLUOROPROPANAMIDE (**3b**)

Under a nitrogen atmosphere, a solution of 2-(2-aminophenyl)ethanol **1** (1.2 g, 9.1 mmol) and Et_3N (2.8 mL, 20 mmol) in CH_2Cl_2/Et_2O (150 mL) was cooled to -20 °C and stirred for 15 min. Then, $(CF_3CF_2CO)_2O$ (2.0 mL, 10 mmol) was added dropwise to the reaction mixture and stirred at RT for 19 h. Subsequent to the addition of ice and water to the mixture, the liquid layers thus obtained were shaken and separated. The organic layer was washed with 5% aqueous HCl, saturated $NaHCO_3$ solution, and brine; dried over Na_2SO_4; and concentrated under reduced pressure. The residue was used directly, without further purification, for the next step. To a stirred solution of crude and CBr_4 (3.0 g, 8.9 mmol) in Et_2O (18 mL), PPh_3 (3.0 g, 8.9 mmol) was added at RT for 3 h. After dilution of the mixture with CH_2Cl_2, the organic layer was washed with water, saturated $NaHCO_3$ solution, and brine; dried over Na_2SO_4; and concentrated under reduced pressure. The residue thus obtained was purified by silica gel column chromatography (hexane/ethyl acetate = 20/1) to yield **3b** (1.6 g, 51%) as a pale pink solid. Mp: 59-61 °C; ^{1}H-NMR ($CDCl_3$) δ: 3.15 (2H, t, *J* = 6.6 Hz), 3.61 (2H, t, *J* = 6.6 Hz), 7.26-7.36 (3H, m), 7.56 (1H, dd, *J* = 8.4 Hz, 1.6 Hz), 8.39 (1H, brs); ^{13}C-NMR ($CDCl_3$) δ: 33.4, 34.1, 107.0, 117.8, 125.7, 128.1, 128.2, 130.3, 132.4, 132.9, 156.3. HRMS (ESI) calcd for $C_{11}H_9BrF_5NNaO$ $[M + Na]^+$ 367.9680; found 367.9206.

N-(2-(2-BROMOETHYL)PHENYL)ACETAMIDE (**3c**)

Under a nitrogen atmosphere, a solution of 2-(2-aminophenyl)ethanol **1** (4.5 g, 33 mmol) and Et_3N (9.1 mL, 66 mmol) in CH_2Cl_2/Et_2O (150 mL) was cooled to -20 °C and stirred for 15 min. Then, acetic anhydride (3.5 mL, 36 mmol) was added dropwise to the reaction mixture and stirred at RT for 3 h. Following the addition of ice and water to the mixture, the liquid layers thus obtained were shaken and separated. The organic layer was washed with 5% aqueous HCl, saturated $NaHCO_3$ solution, and brine; dried over Na_2SO_4;

and concentrated under reduced pressure. The residue was used directly, without further purification, for the next step. To a stirred solution of crude and CBr_4 (7.8 g, 23 mmol) in CH2Cl2 (50 mL), PPh_3 (6.2 g, 23 mmol) was added at RT for 3 h. After dilution of the mixture with CH_2Cl_2, the organic layer was washed with water, saturated $NaHCO_3$ solution, and brine; dried over Na_2SO_4; and concentrated under reduced pressure. The residue thus obtained was purified by silica gel column chromatography (hexane/ethyl acetate = 2/1) to yield **3c** (2.3 g, 60%) as a light brown solid. Mp: 135-136 °C; ^{1}H-NMR ($CDCl_3$) δ: 2.16 (3H, s), 3.13 (2H, t, *J* = 7.4 Hz), 3.56 (2H, t, *J* = 7.2 Hz), 7.16-7.31 (3H, m), 7.48 (1H, d, *J* = 8.0 Hz), 7.61 (1H, brs); ^{13}C-NMR ($CDCl_3$) δ: 23.8, 32.7, 34.7, 126.2, 126.5, 127.7, 129.8, 132.8, 135.2, 169.2. HRMS (ESI) calcd for $C_{10}H_{12}BrNNaO$ $[M + Na]^+$; 263.9994; found 263.9659.

N-(2-(2-BROMOETHYL)PHENYL)BENZAMIDE (**3d**)

Under a nitrogen atmosphere, a solution of 2-(2-aminophenyl)ethanol **1** (740 mg, 5.4 mmol) and Et_3N (1.1 mL, 8.1 mmol) in CH_2Cl_2/Et_2O (30 mL) was cooled to -20 °C and stirred for 15 min. Then, benzoyl chloride (0.63 mL, 5.4 mmol) added dropwise to the reaction mixture and stirred at RT for 1 h. Subsequent to the addition of ice and water to the mixture, the liquid layers thus obtained were shaken and separated. The organic layer was washed with 5% aqueous HCl, saturated $NaHCO_3$ solution, and brine; dried over Na_2SO_4; and concentrated under reduced pressure. The residue was used directly, without further purification, for the next step. To a stirred solution of crude and CBr_4 (1.8 g, 5.4 mmol) in Et_2O (25 mL), PPh_3 (1.4 g, 5.4 mmol) was added at RT for 1 h. After dilution of the mixture with CH_2Cl_2, the organic layer was washed with water, saturated $NaHCO_3$ solution, and brine; dried over Na_2SO_4; and concentrated under reduced pressure. The residue thus obtained was purified by silica gel column chromatography (hexane/ethyl acetate = 3/1) to yield **3d** (590 mg, 43%) as a light brown solid. Mp: 143-144 °C; ^{1}H-NMR ($CDCl_3$) δ: 3.21 (2H, t, *J* = 7.2 Hz), 3.63 (2H, t, *J* = 7.2 Hz), 7.20-7.32 (3H, m), 7.45-7.57 (3H, m), 7.65 (1H, d, *J* = 8.4 Hz), 7.90 (2H, d, *J* = 7.6 Hz), 8.19 (1H, brs); ^{13}C-NMR ($CDCl_3$) δ: 33.6, 34.6, 126.1, 126.5, 127.2, 127.9, 128.8, 129.9, 131.9, 132.7, 134.3, 135.3, 166.2. HRMS (ESI) calcd for $C_{15}H_{14}BrNNaO$ $[M + Na]^+$ 326.0151; found 325.9731.

N-(2-(BROMOMETHYL)BENZYL)-2,2,2-TRIFLUOROACETAMIDE (**9a**)

Under a nitrogen atmosphere, a solution of (2-(aminomethyl)phenyl)methanol **7a** (1.0 g, 7.3 mmol) and Et_3N (1.2 mL, 8.8 mmol) in CH_2Cl_2/Et_2O (15 mL) was cooled to -20 °C and stirred for 15 min. Then, $(CF_3CO)_2O$ (1.1 mL, 8.0 mmol) was added dropwise to the reaction mixture and stirred at RT for 1 h. Subsequent to the addition of ice and water to the mixture, the liquid layers thus obtained were shake and separated. The organic layer was washed with 5% aqueous HCl, saturated $NaHCO_3$ solution, and brine; dried over Na_2SO_4; and concentrated under reduced pressure. The residue was used directly, without further purification, for the next step. To a stirred solution of crude in CH_2Cl_2 (30 mL), PBr_3 (0.30 mL, 3.2 mmol) was added at 0 °C for 1 h. Subsequent to the addition of ice and water to the mixture, the liquid layers thus obtained were shaken and separated. The organic layer was washed with water, saturated $NaHCO_3$ solution, and brine; dried over Na_2SO_4; and concentrated under reduced pressure. The residue thus obtained was

purified by silica gel column chromatography (hexane/ethyl acetate = 5/1) to yield **9a** (1.4 g, 86%) as a white solid. Mp: 120-123 °C; ^{1}H-NMR ($CDCl_3$) δ: 4.57 (2H, s), 4.67 (2H, d, *J* = 6.0 Hz), 6.76 (1H, brs), 7.32-7.41 (4H, m); ^{13}C-NMR ($CDCl_3$) δ: 29.9, 30.1, 115.7 (q, *J* = 287.5 Hz), 124.5, 127.2, 129.1, 130.0, 130.3, 130.6, 155.2 (q, *J* = 37.4 Hz). HRMS (ESI) calcd for $C_{10}H_9BrF_3NNaO$ $[M + Na]^+$ 317.9712; found 317.9438.

N-(2-(BROMOMETHYL)BENZYL)-2,2,2-TRIFLUORO-N-(4-METHOXYBENZYL)ACETAMIDE (**9b**)

Under a nitrogen atmosphere, a solution of (2-((4-methoxybenzyl)aminomethyl)phenyl)methanol **7b** (590 mg, 2.3 mmol) and Et_3N (1.1 mL, 8.0 mmol) in CH_2Cl_2 (15 mL) was cooled to -20 °C and stirred for 15 min. Then, $(CF_3CO)_2O$ (0.96 mL, 6.9 mmol) was added dropwise to the reaction mixture and stirred at RT for 4 h. Subsequent to the addition of ice and water to the mixture, the liquid layers thus obtained were shake and separated. The organic layer was washed with saturated $NaHCO_3$ solution, water, and brine; dried over Na_2SO_4; and concentrated under reduced pressure. The residue was used directly, without further purification, for the next step. To a stirred solution of crude in CH_2Cl_2 (5 mL), PBr_3 (0.12 mL, 1.3 mmol) was added at 0 °C for 3 h. Following the addition of ice and water to the mixture, the liquid layers obtained were shaken and separated. The organic layer was washed with water, saturated $NaHCO_3$ solution, and brine; dried over Na_2SO_4; and concentrated under reduced pressure. The residue thus obtained was purified by silica gel column chromatography (hexane/ethyl acetate = 20/1) to yield **9b** (420 mg, 43%, diastereomeric mixtures 1/1.3) as a white solid. Mp: 96-98 °C; ^{1}H-NMR ($CDCl_3$) δ: 3.78 (1.3H, s) 3.80 (1.7H, s), 4.32 (0.9H, s) 4.37 (1.1H, s), 4.50 (1.1H, s) 4.54 (0.9H, s), 4.69 (1.1H, s) 4.73 (0.9H, s), 6.85 (0.9H, d, *J* = 8.8 Hz), 6.91 (1.1H, d, *J* = 8.8 Hz), 6.98-7.01 (0.55H, m), 7.09 (1.1H, d, *J* = 8.8 Hz), 7.14-7.17 (0.45H, m), 7.15 (0.9H, d, *J* = 8.8 Hz), 7.26-7.40 (3H, m); ^{13}C-NMR ($CDCl_3$) δ: 30.2, 30.5, 44.8, 45.9, 45.9, 48.9, 49.2, 55.1, 55.2, 114.1, 114.3, 116.5 (q, *J* = 286.5 Hz), 116.7 (q, *J* = 286.5 Hz), 125.8, 126.2, 126.9, 128.1, 128.5, 128.7, 129.1, 129.5, 130.0, 130.8, 131.1, 133.0, 133.5, 135.0, 136.4, 157.3 (q, *J* = 35.4 Hz), 157.9 (q, *J* = 35.4 Hz), 159.5, 159.5. HRMS (ESI) calcd for $C_{18}H_{17}BrF_3NNaO_2$ $[M + Na]^+$ 438.0287; found 438.0284.

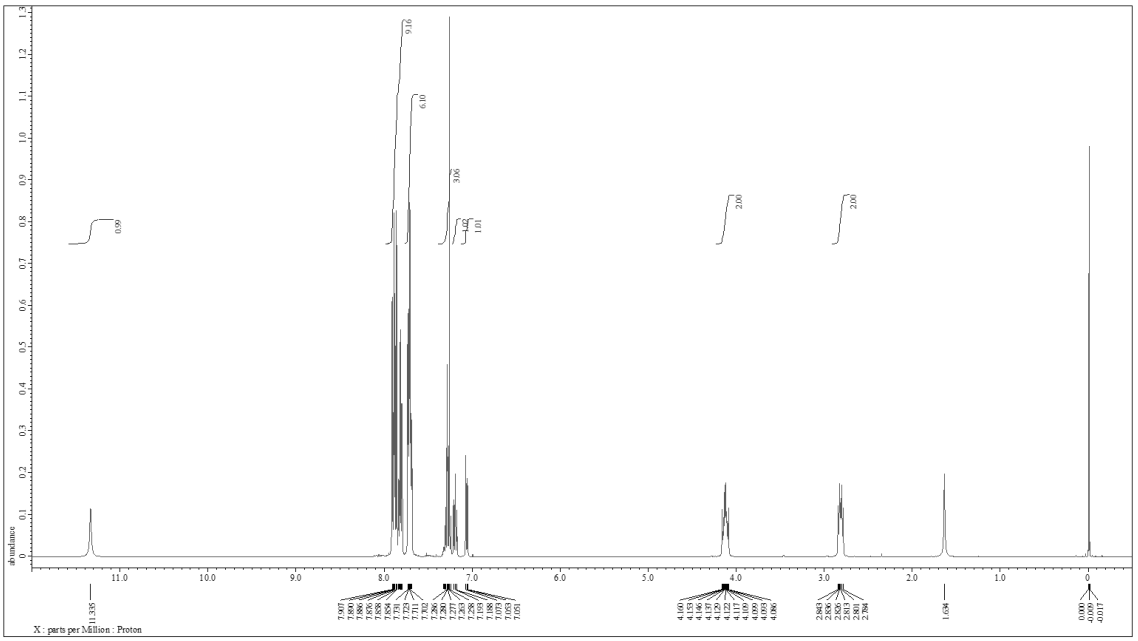
N-(2-(BROMOMETHYL)BENZYL)-2,2,3,3,3-PENTAFLUORO-N-(4-METHOXYBENZYL)PROPENAMIDE (**9c**)

Under a nitrogen atmosphere, a solution of (2-((4-methoxybenzyl)aminomethyl)phenyl)methanol **7b** (930 mg, 3.6 mmol) and Et_3N (1.8 mL, 13 mmol) in CH_2Cl_2 (20 mL) was cooled to -20 °C and stirred for 15 min. Then, $(CF_3CF_2CO)_2O$ (2.1 mL, 11 mmol) was added dropwise to the reaction mixture and stirred at RT for 2 h. Subsequent to the addition of ice and water to the mixture, the liquid layers thus obtained were shaken and separated. The organic layer was washed with saturated $NaHCO_3$ solution, water, and brine; dried over Na_2SO_4; and concentrated under reduced pressure. The residue was used directly, without further purification, for the next step. To a stirred solution of crude and CBr_4 (1.8 g, 5.4 mmol) in Et_2O (15 mL), PPh_3 (1.4 g, 5.4 mmol) was added at RT for 2 h. After dilution of the mixture with CH_2Cl_2, the organic

layer was washed with water, saturated $NaHCO_3$ solution, and brine; dried over Na_2SO_4; and concentrated under reduced pressure. The residue thus obtained was purified by silica gel column chromatography (hexane/ethyl acetate = 10/1) to yield **9c** (250 mg, 30%, diastereomeric mixtures 1/1.2) as a pale yellow solid. Mp: 67-69 °C; ^{1}H-NMR ($CDCl_3$) δ: 3.34 (2H, s), 3.80 (3H, s), 3.81 (1H, d, J = 9.2 Hz), 4.32 (0.45H, s), 4.37 (0.55H, s), 4.55 (1H, d, J = 9.2 Hz), 4.68 (0.55H, s), 4.77 (0.45H, s), 6.85-6.93 (3H, m), 6.98-7.17 (2H, m), 7.24-7.38 (3H, m); ^{13}C-NMR ($CDCl_3$) δ: 30.3, 30.5, 44.8, 45.7, 49.0, 49.1, 55.2, 57.7, 108.3 (tq, J = 233.8 Hz, 35.4 Hz), 113.7, 114.2, 114.4, 119.5 (qt, J = 284.6 Hz, 33.6 Hz), 125.8, 126.2, 127.0, 128.2, 128.6, 128.6, 128.7, 129.0, 129.1, 129.3, 129.5, 129.6, 130.1, 130.2, 130.8, 131.2, 133.0, 133.7, 134.9, 136.5, 158.1 (t, J = 25.2 Hz), 158.8 (t, J = 25.2 Hz), 159.2, 159.6. HRMS (ESI) calcd for $C_{19}H_{17}BrF_5NNaO_2$ $[M + Na]^+$ 488.0255; found 488.0217.

Compound **4a**

^{1}H-NMR



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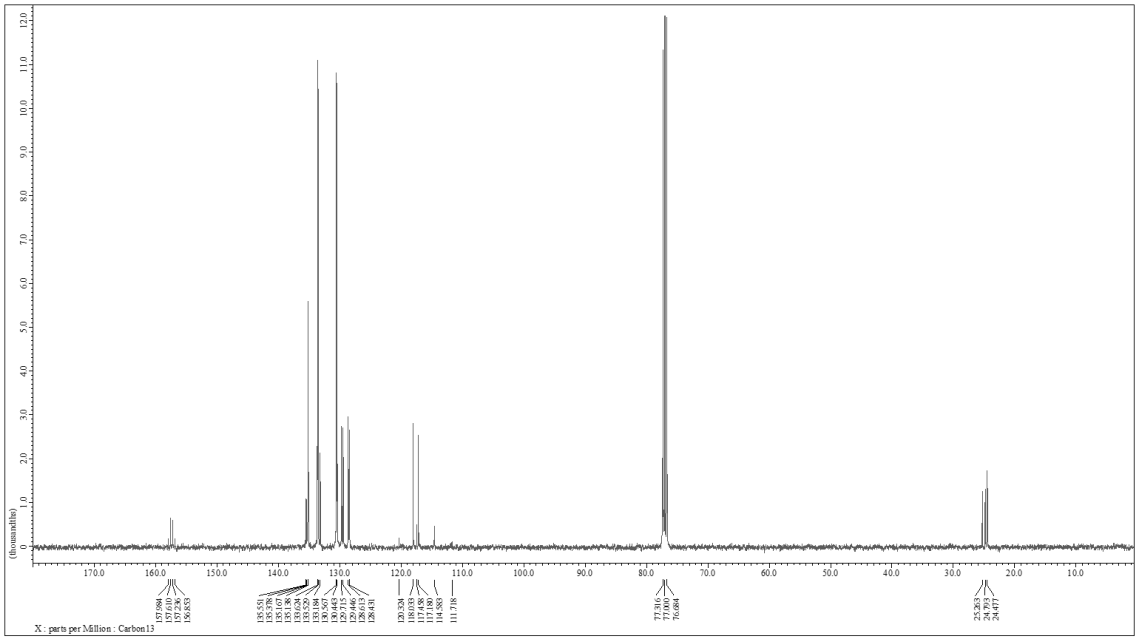

Compound **4b**

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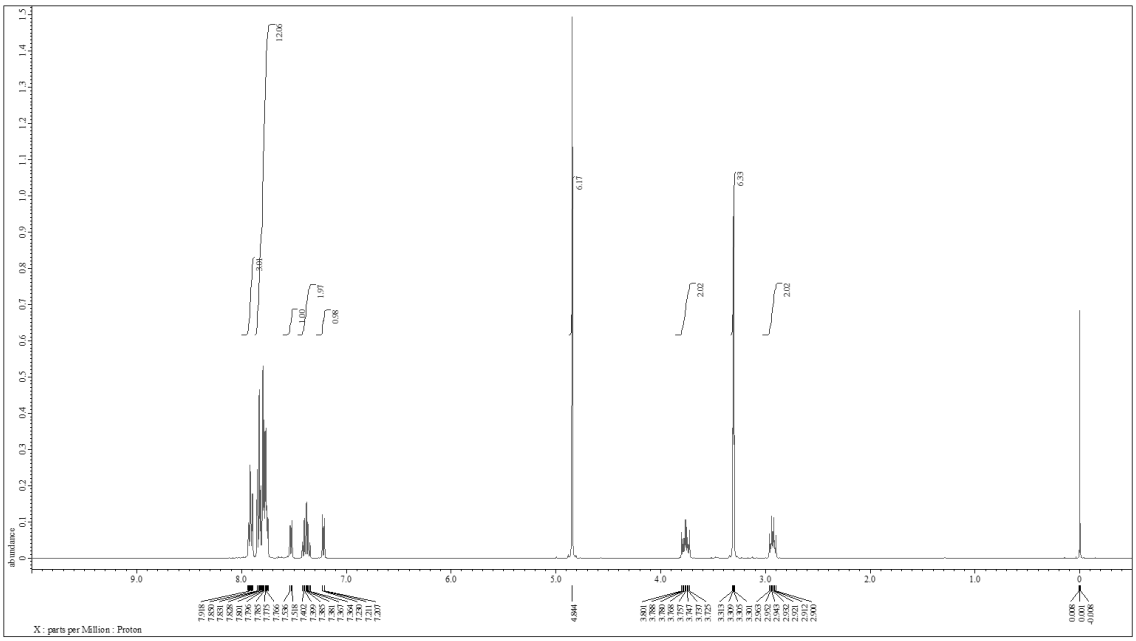

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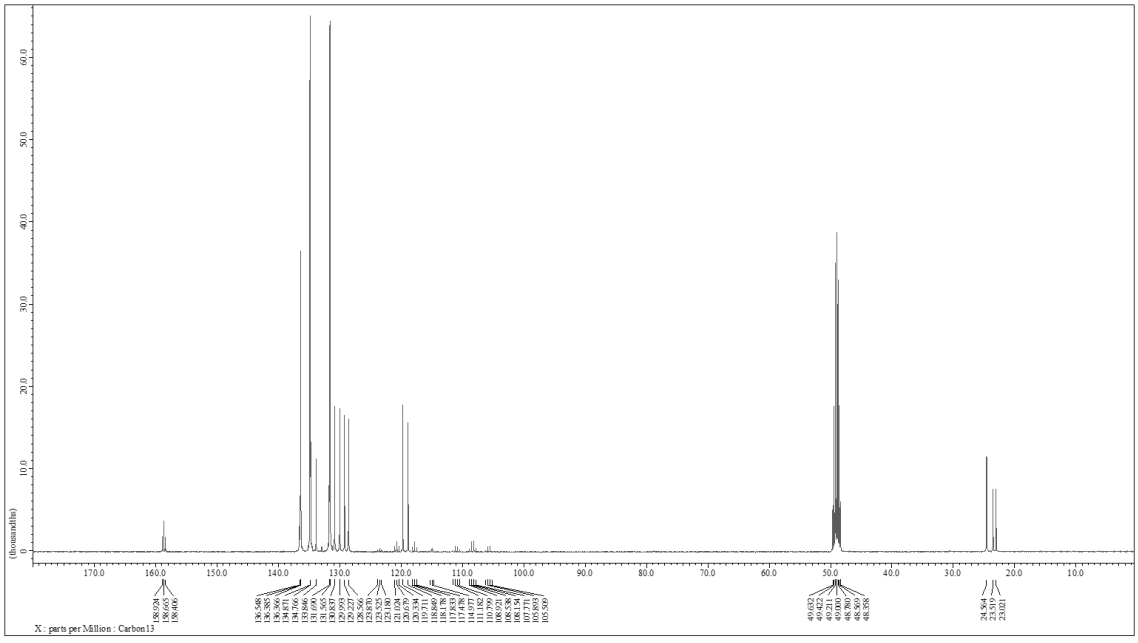

Compound **4c**

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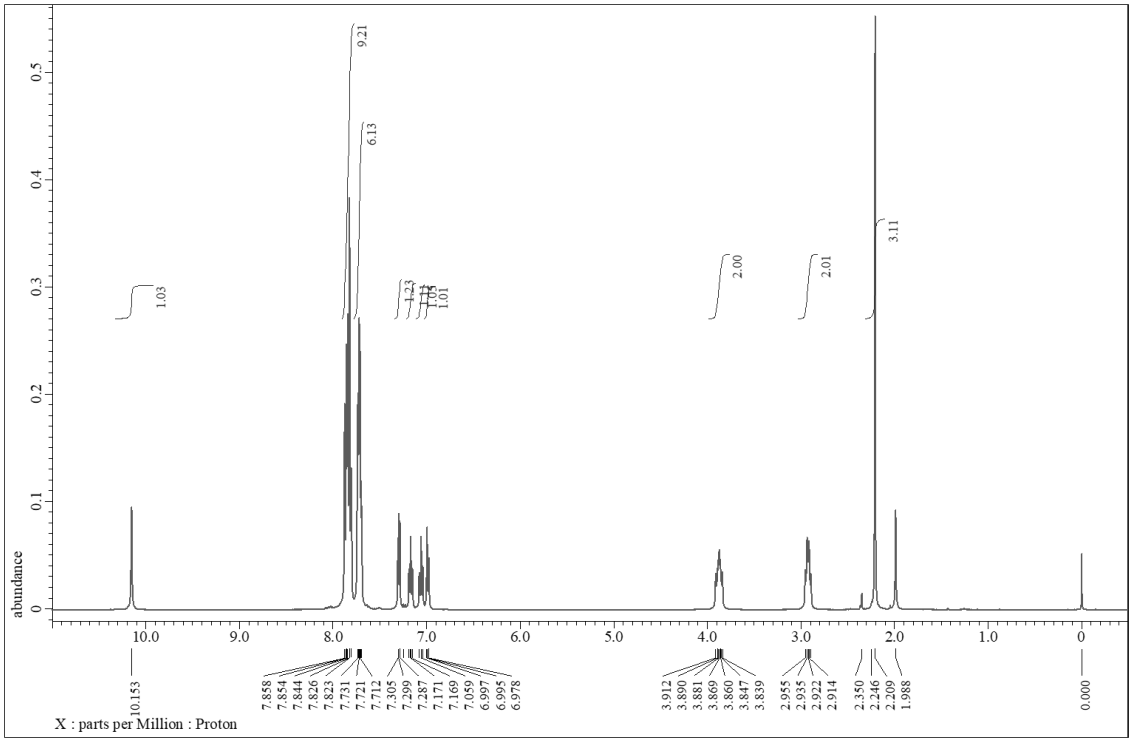

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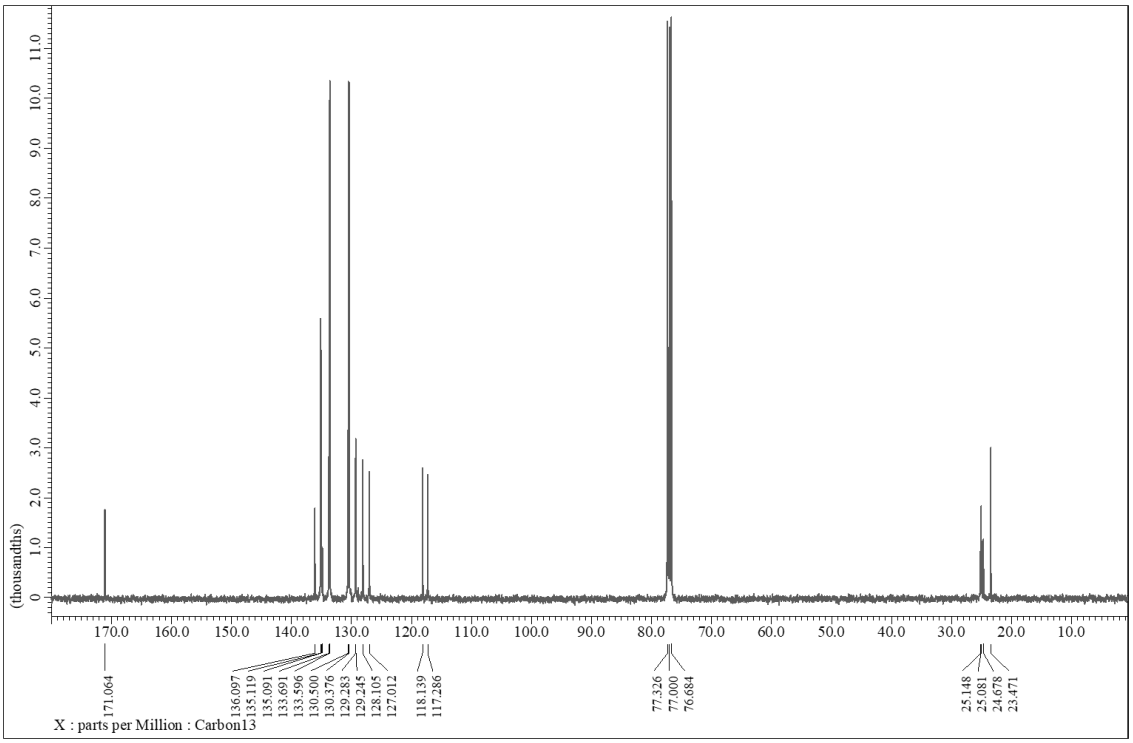

Compound **4d**

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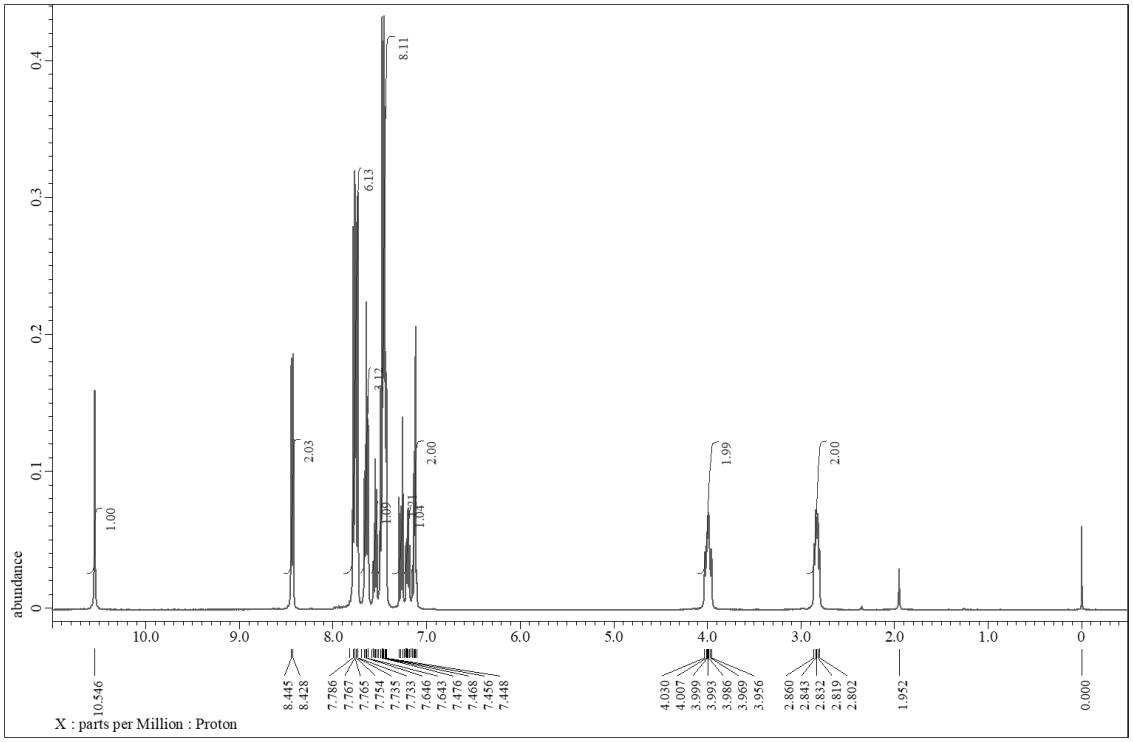

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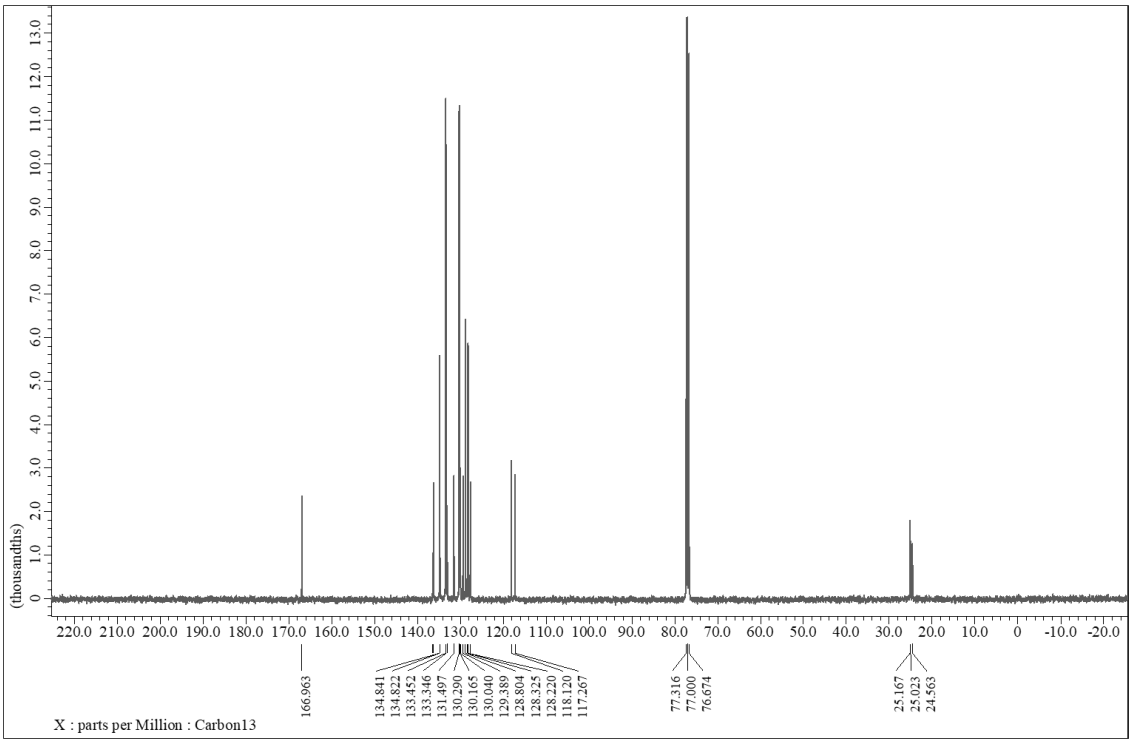

Compound **5a**

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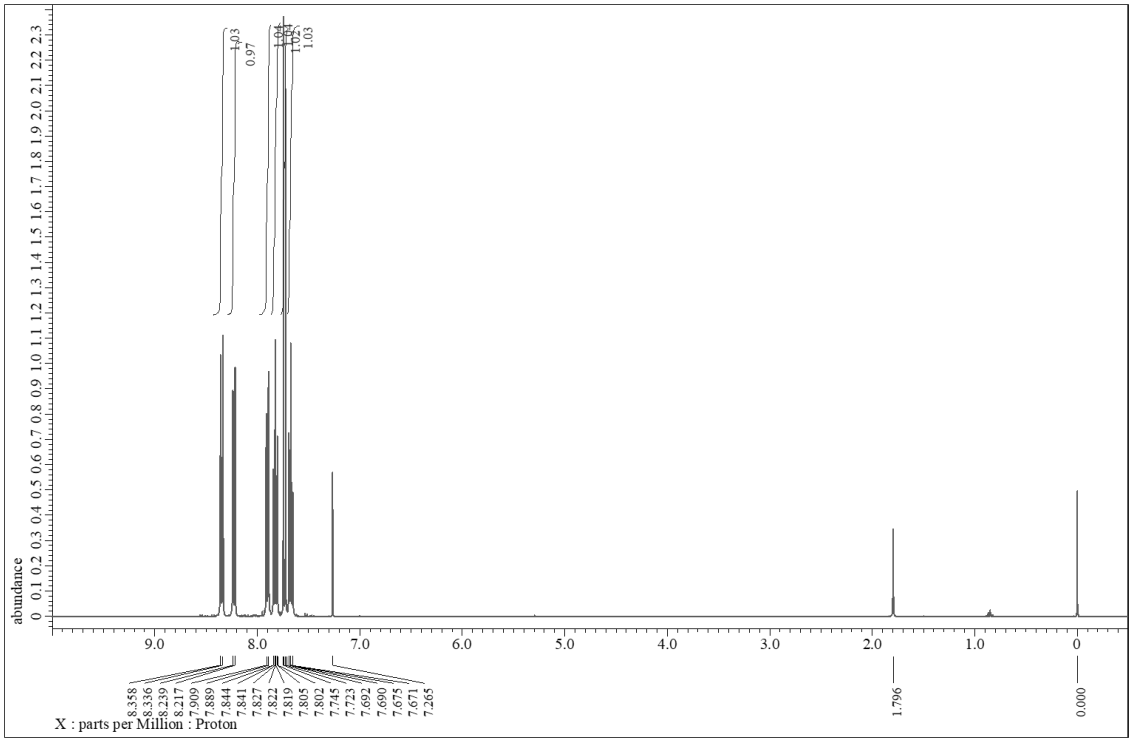

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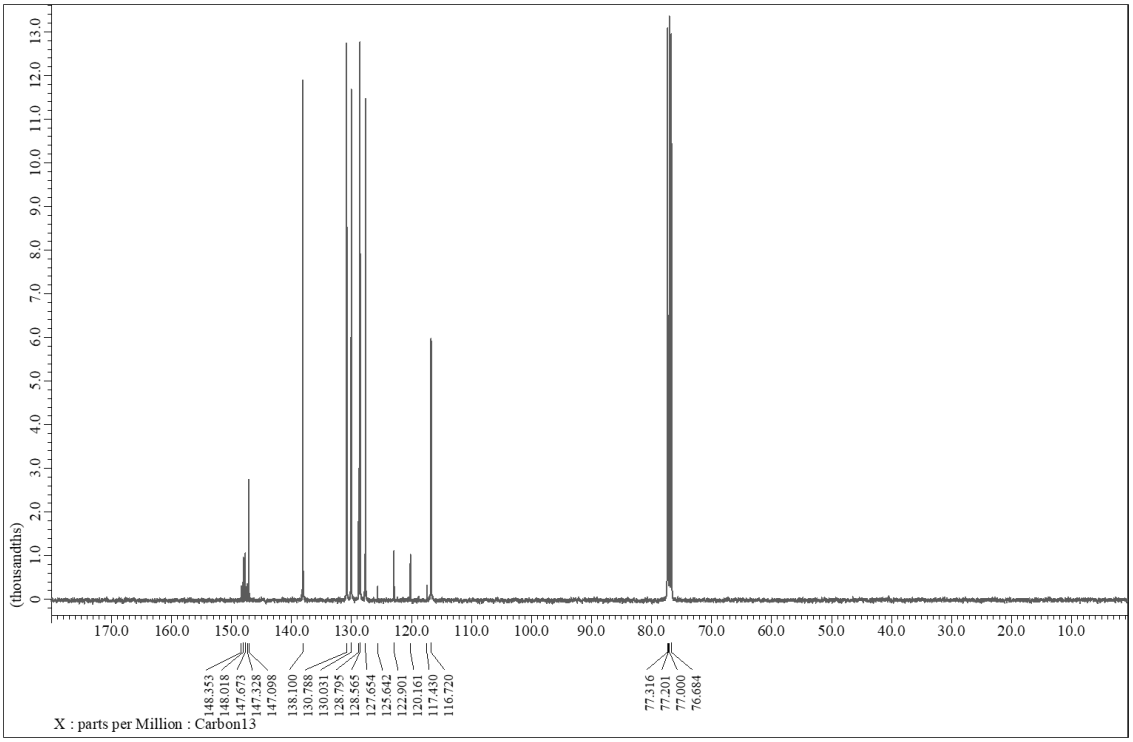

Compound **5a**

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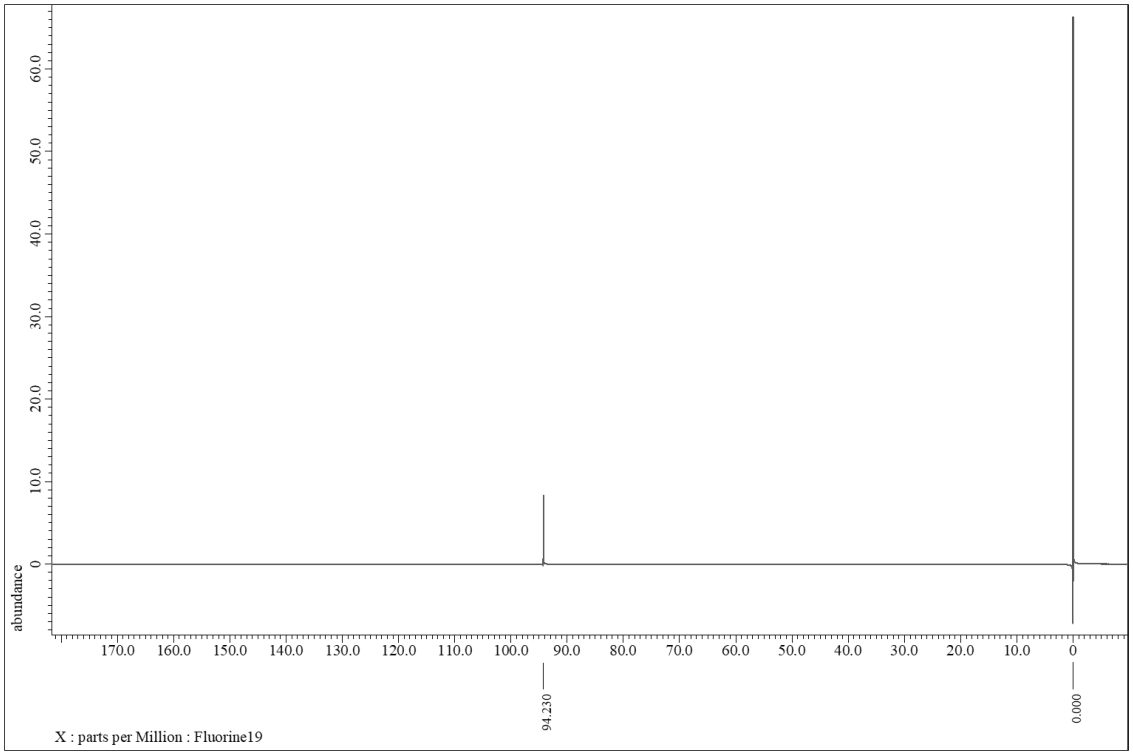
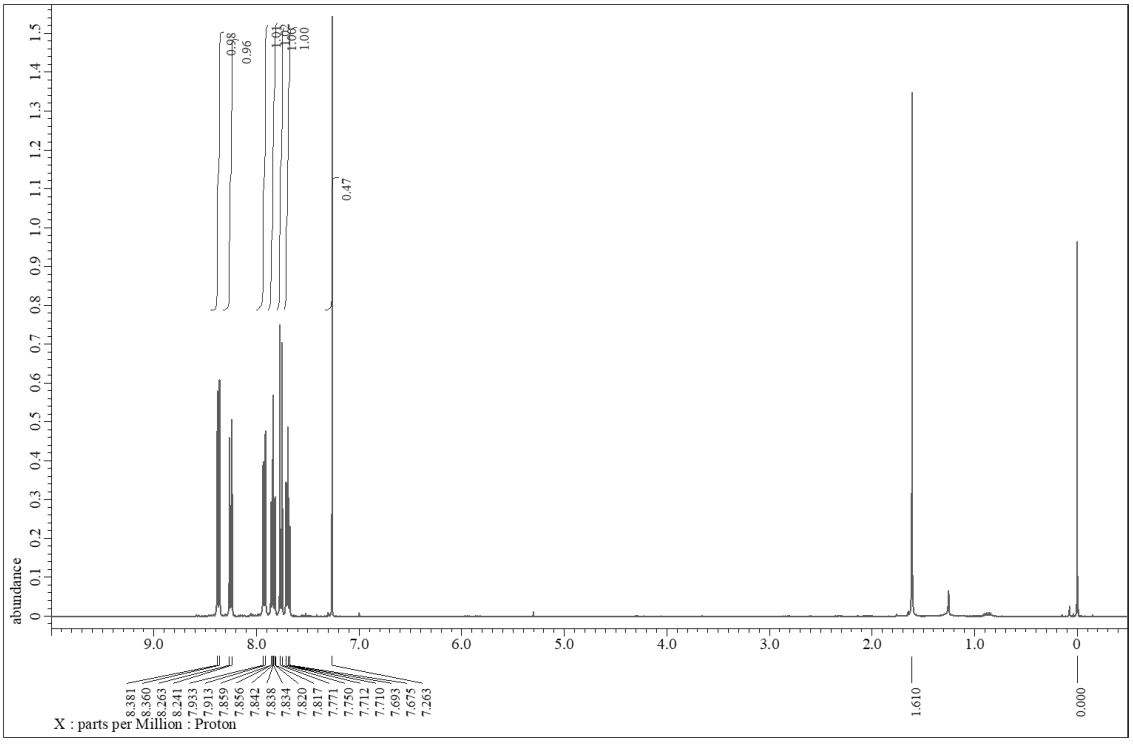


Compound **5b**

^{1}H-NMR



Compound **5b**

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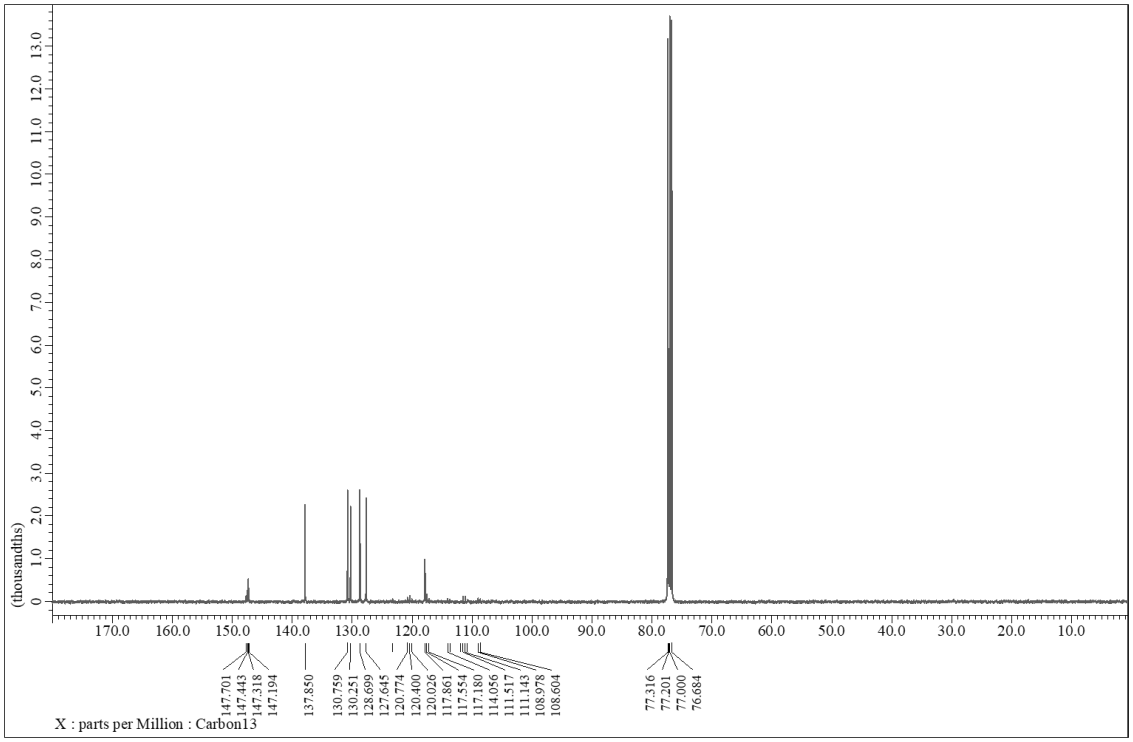

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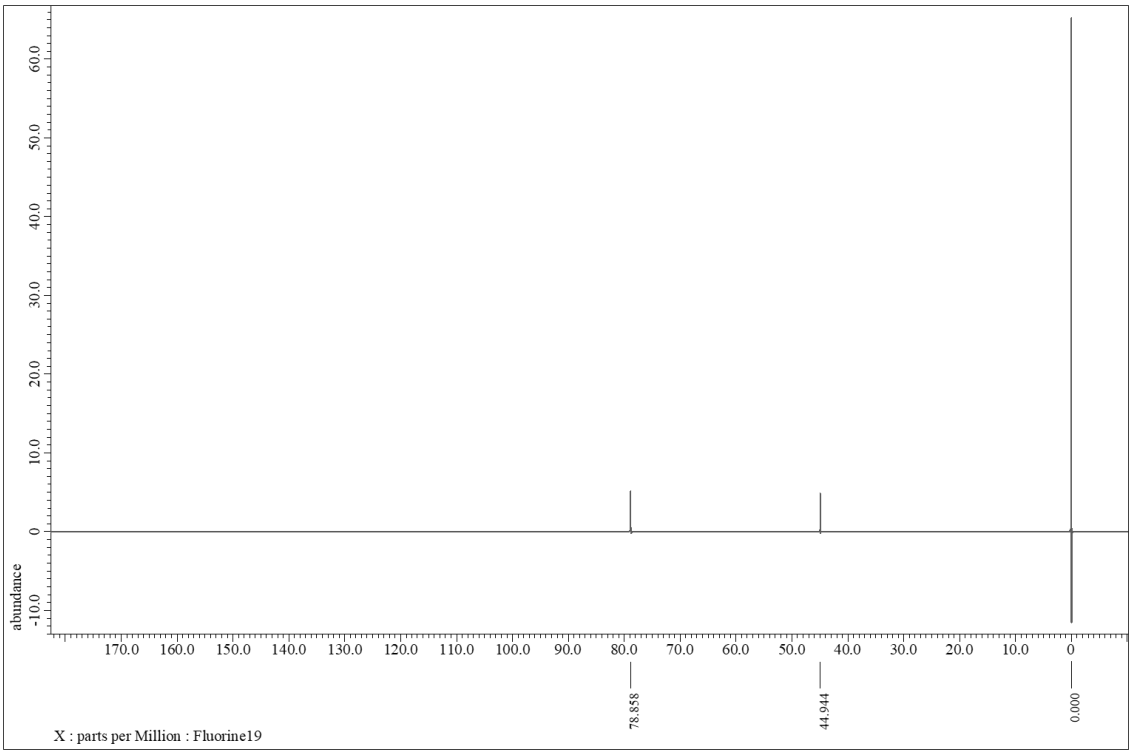
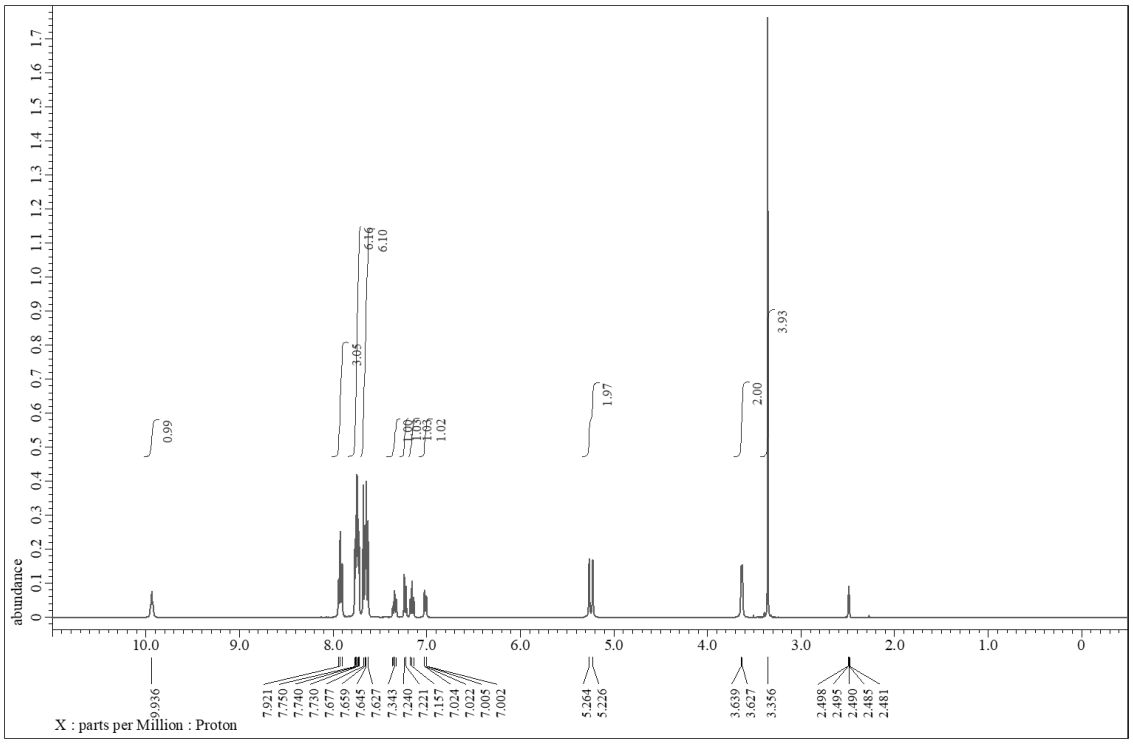


Compound **10a**

^{1}H-NMR



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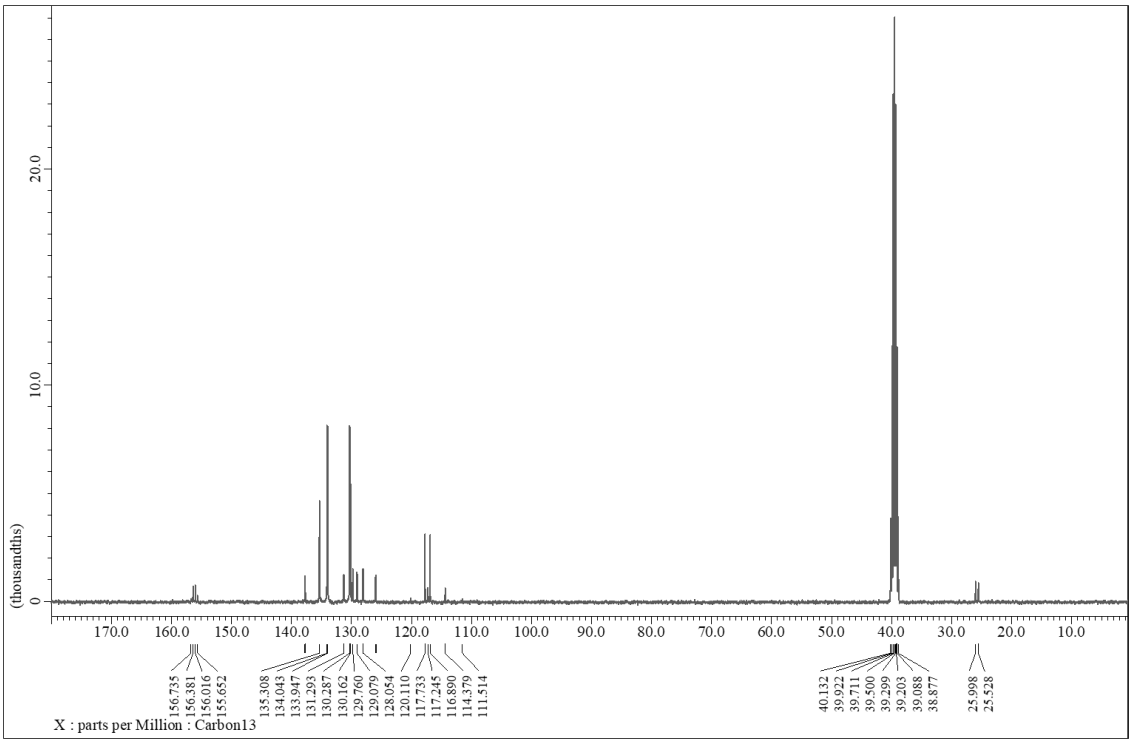
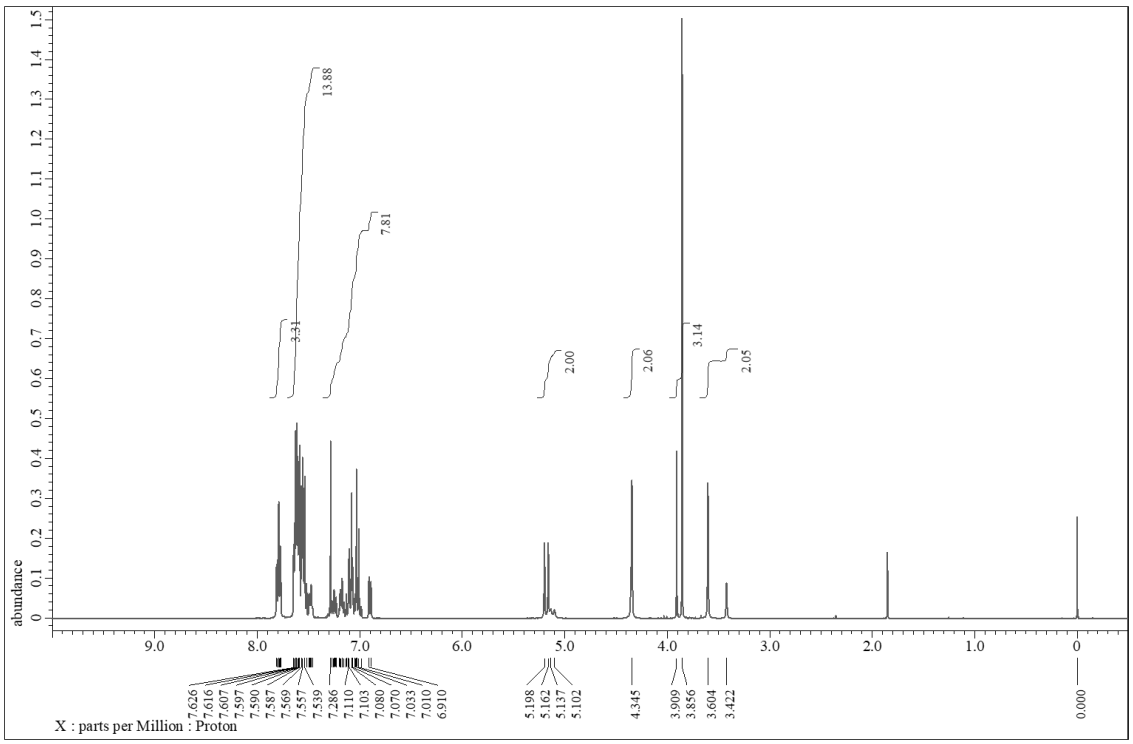


Compound **10b**

^{1}H-NMR



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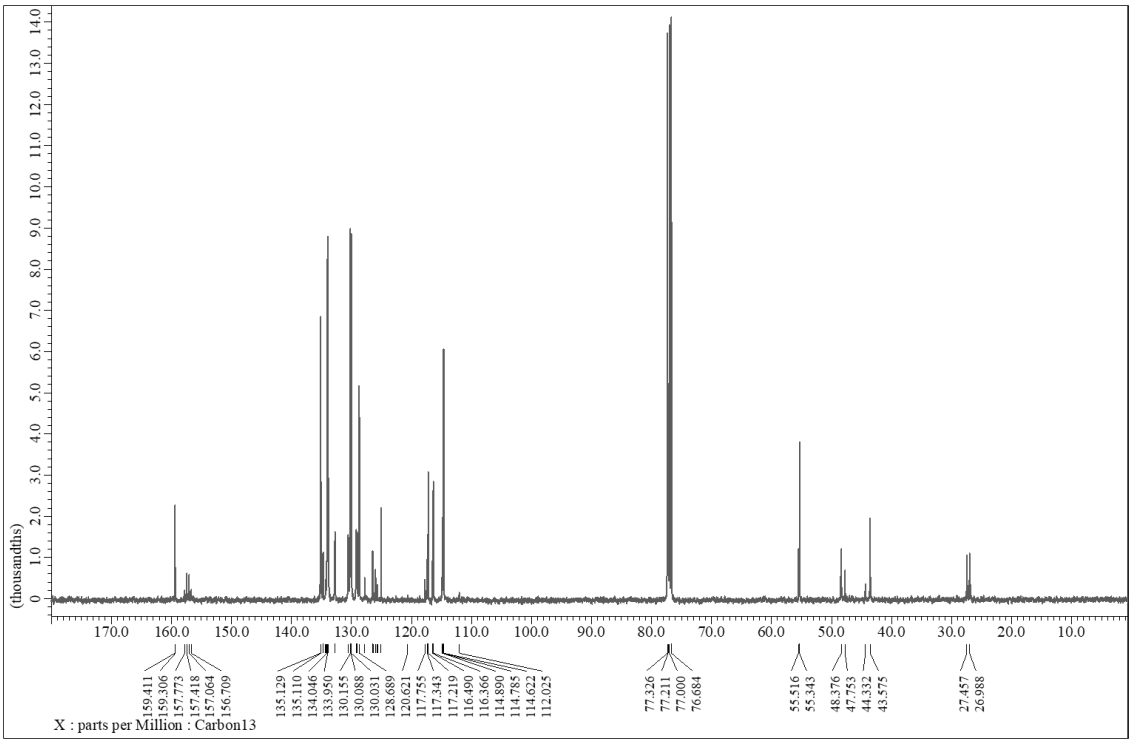

Compound **10c**

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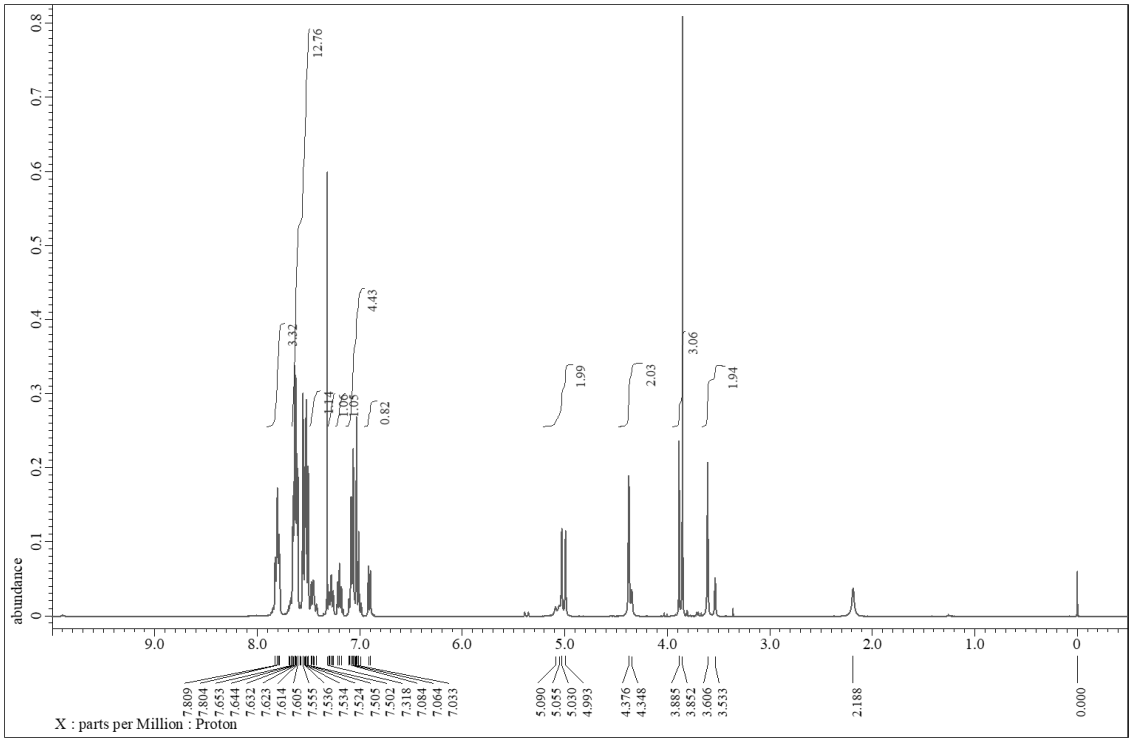

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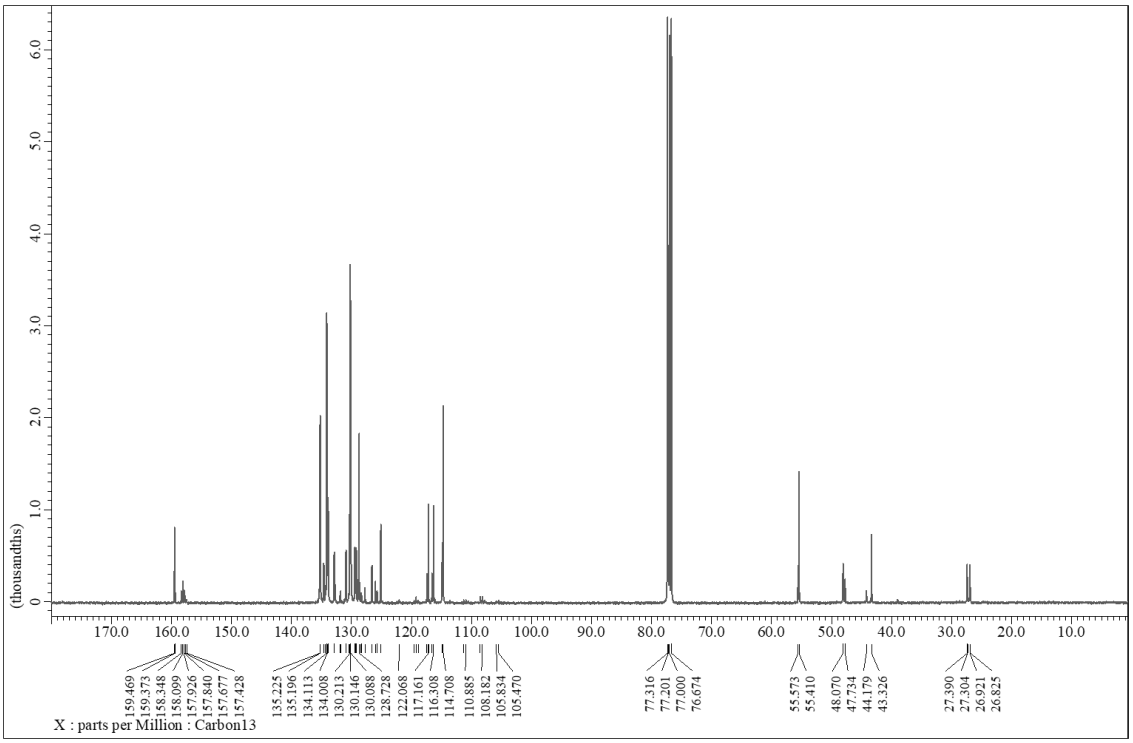
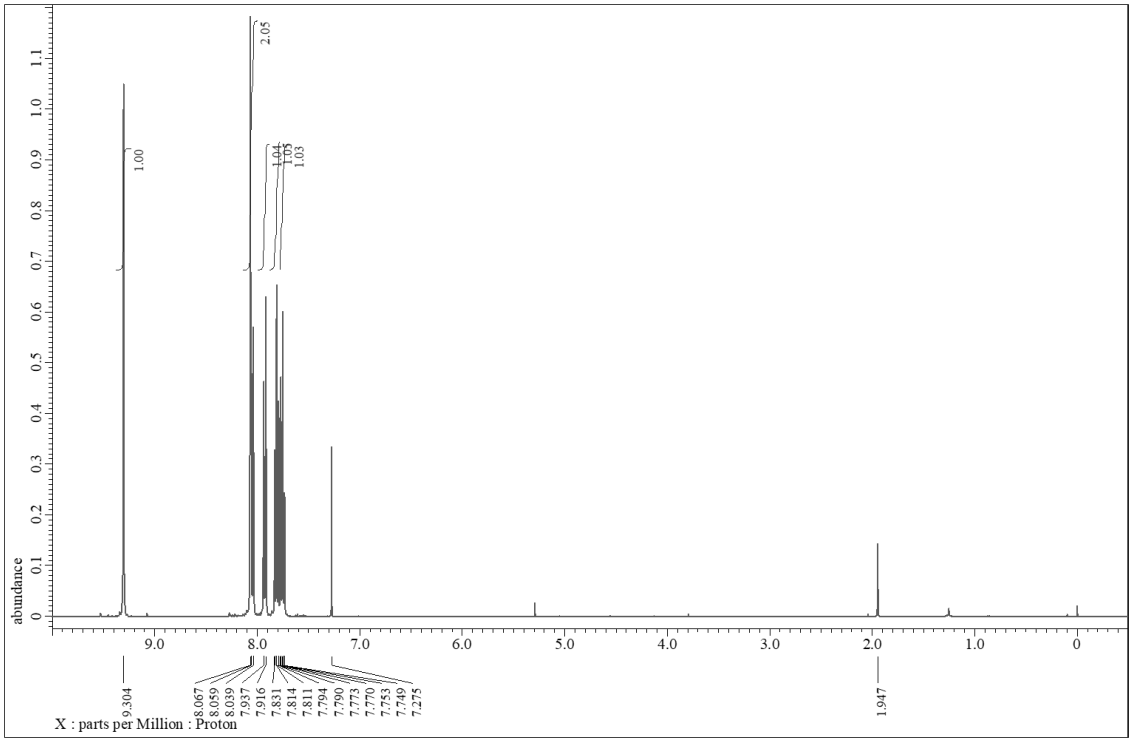


Compound **13**

^{1}H-NMR



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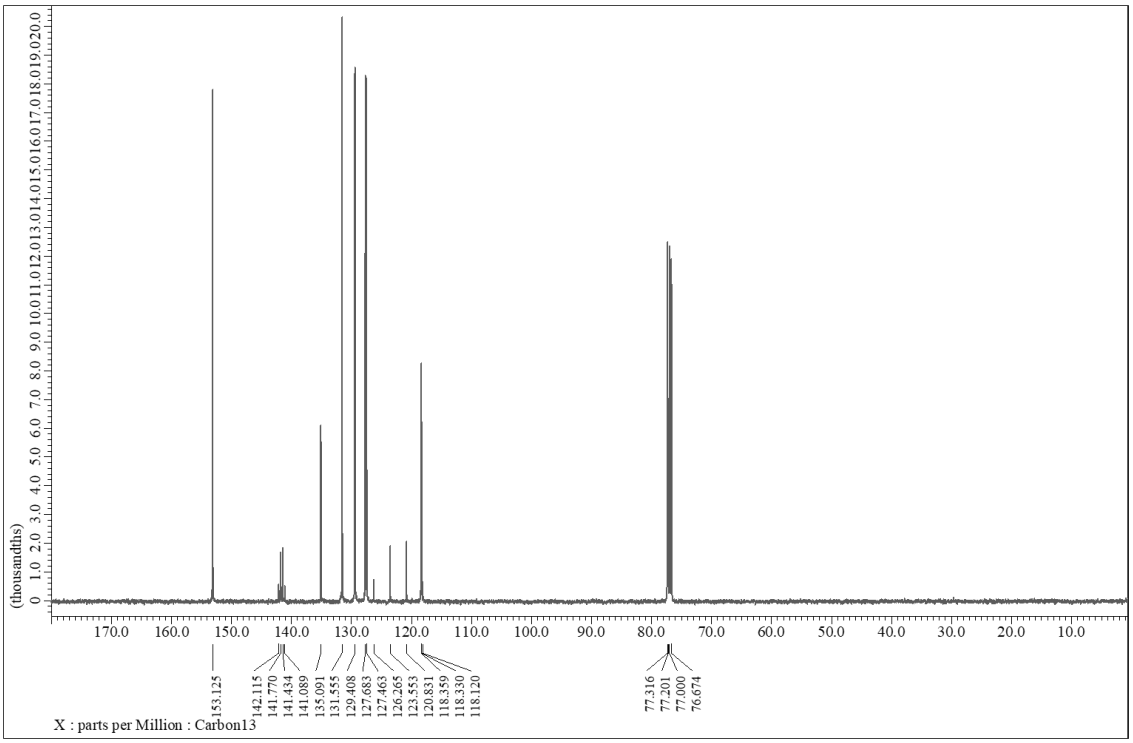
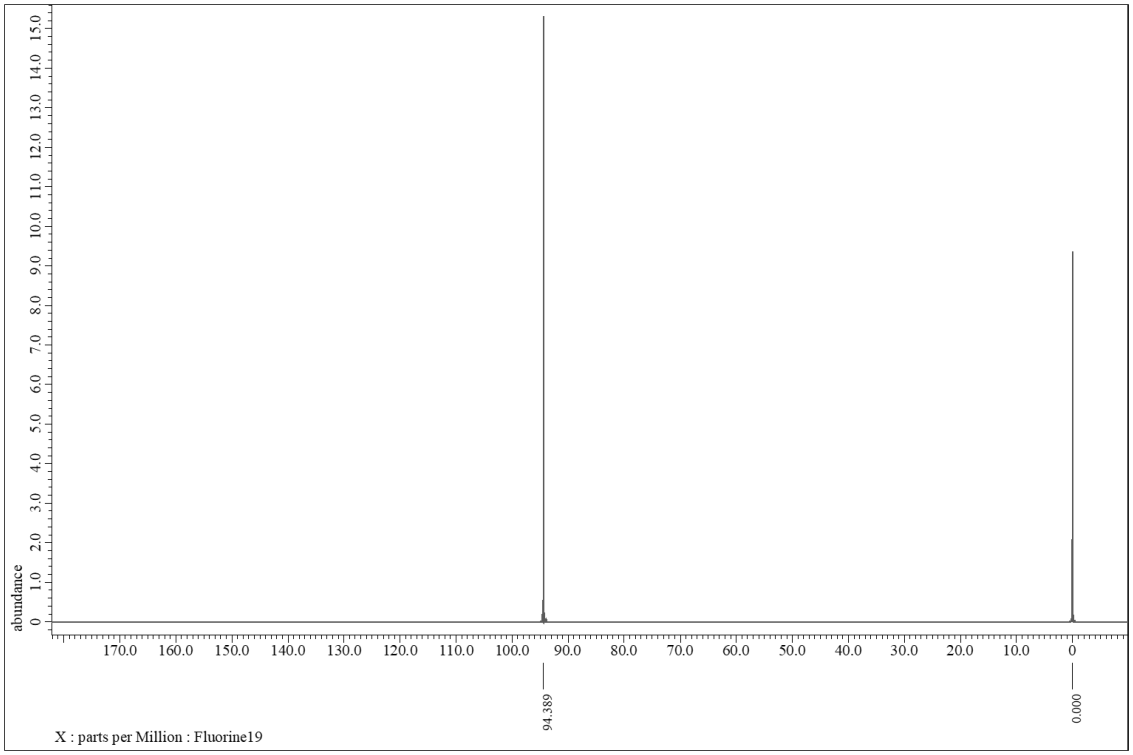


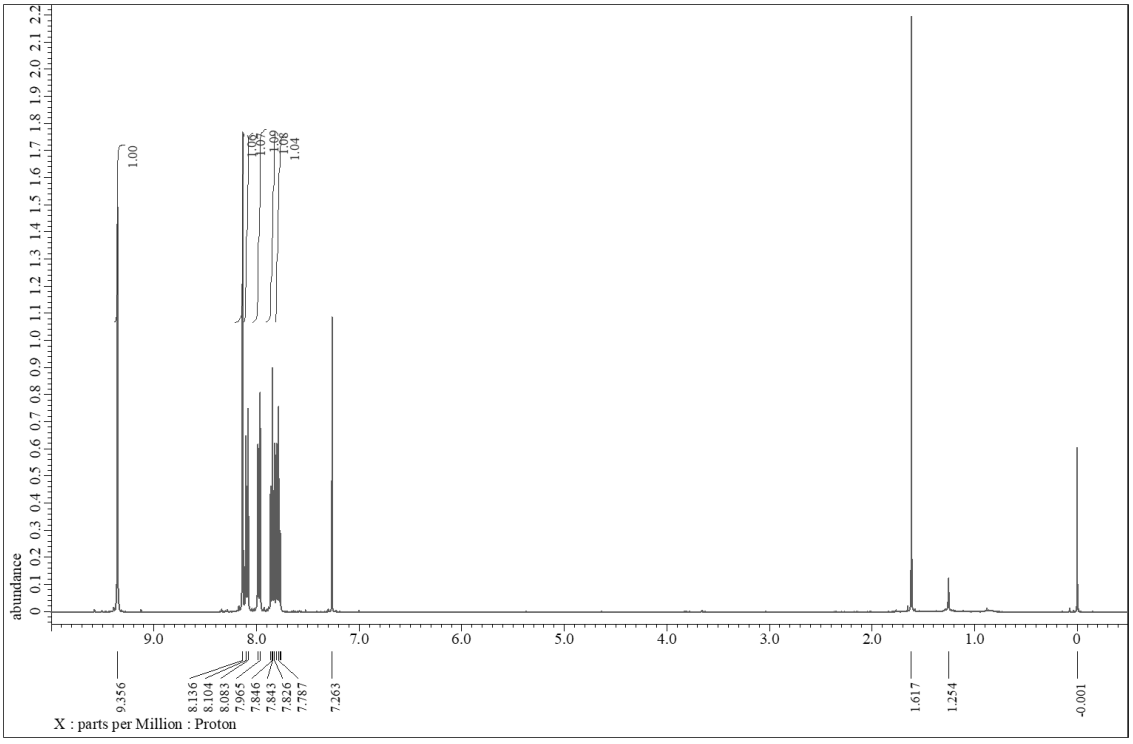
Compound **13**

^{19}F-NMR



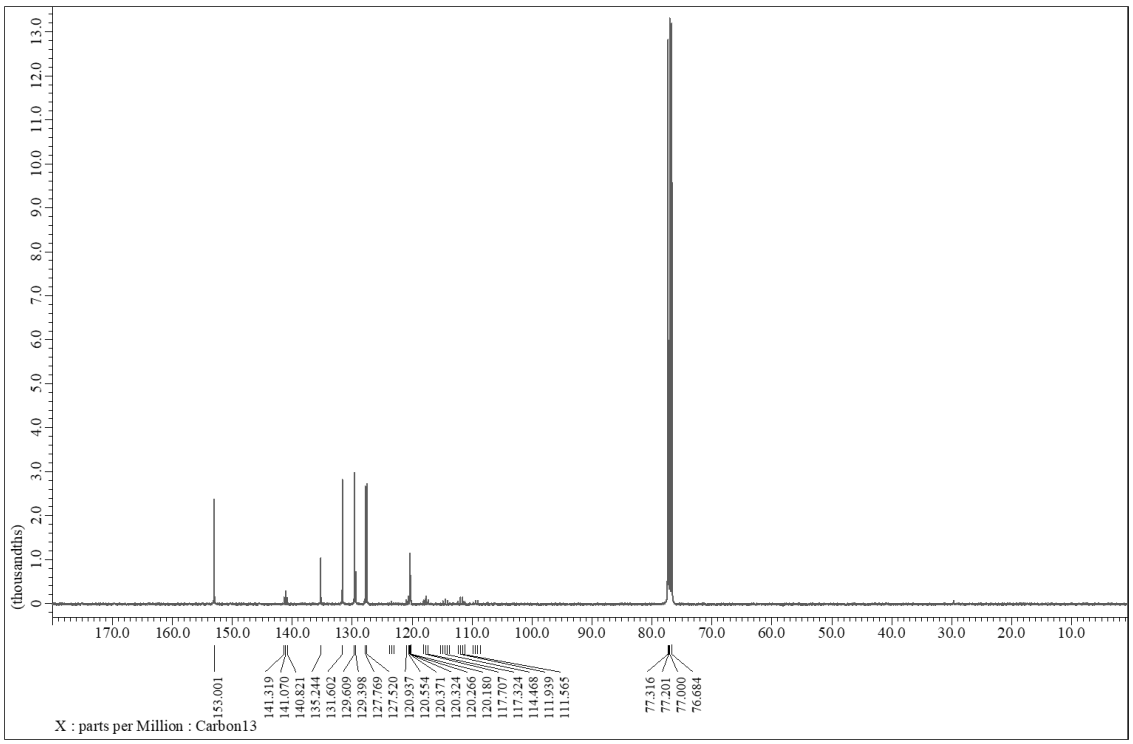
Compound **13'**

^{1}H-NMR

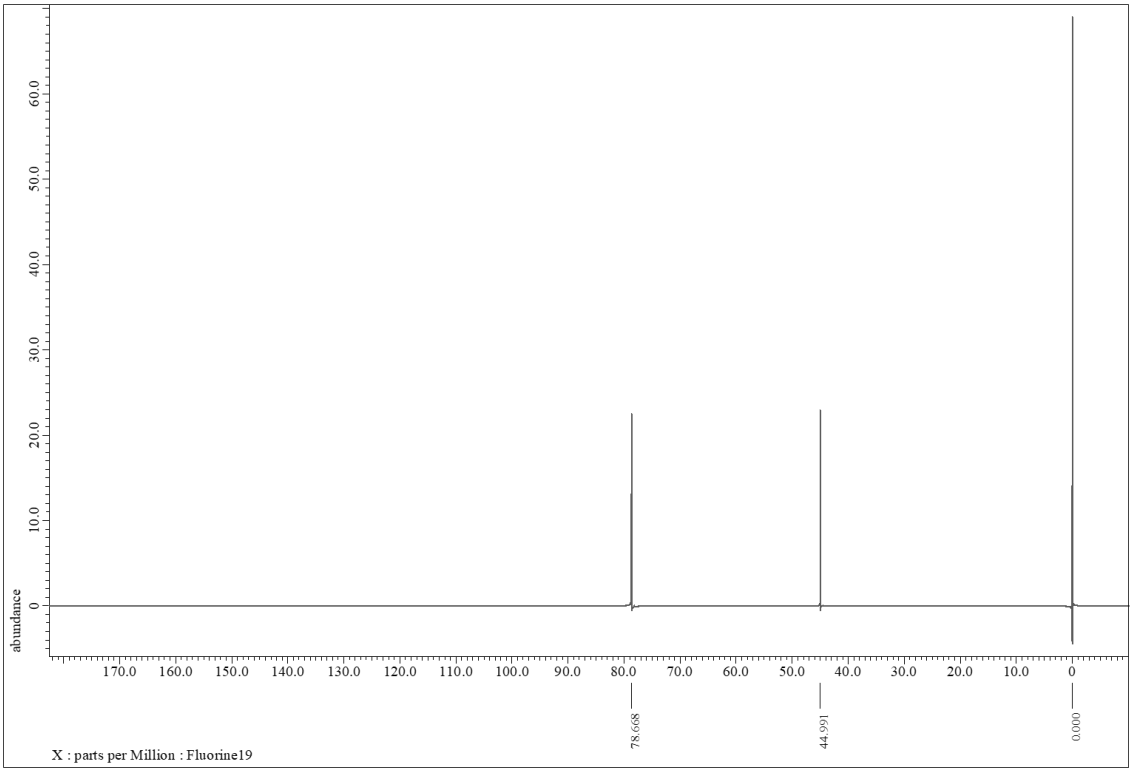


Compound **13'**

^{13}C-NMR

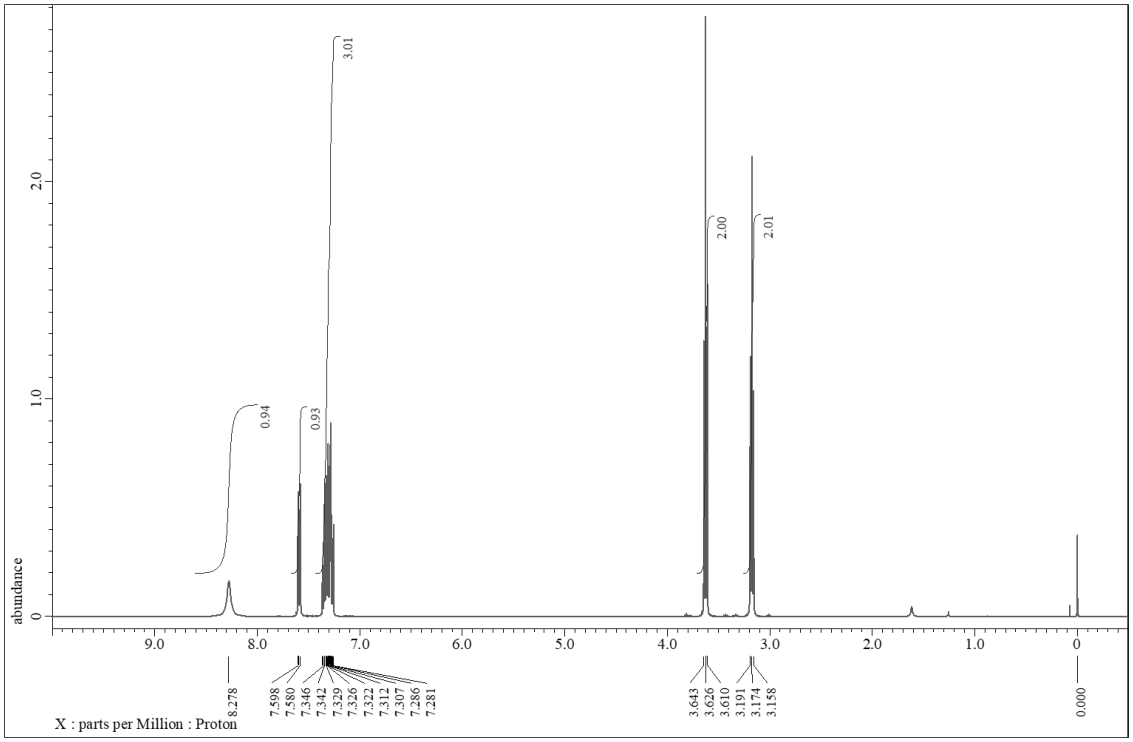


^{19}F-NMR

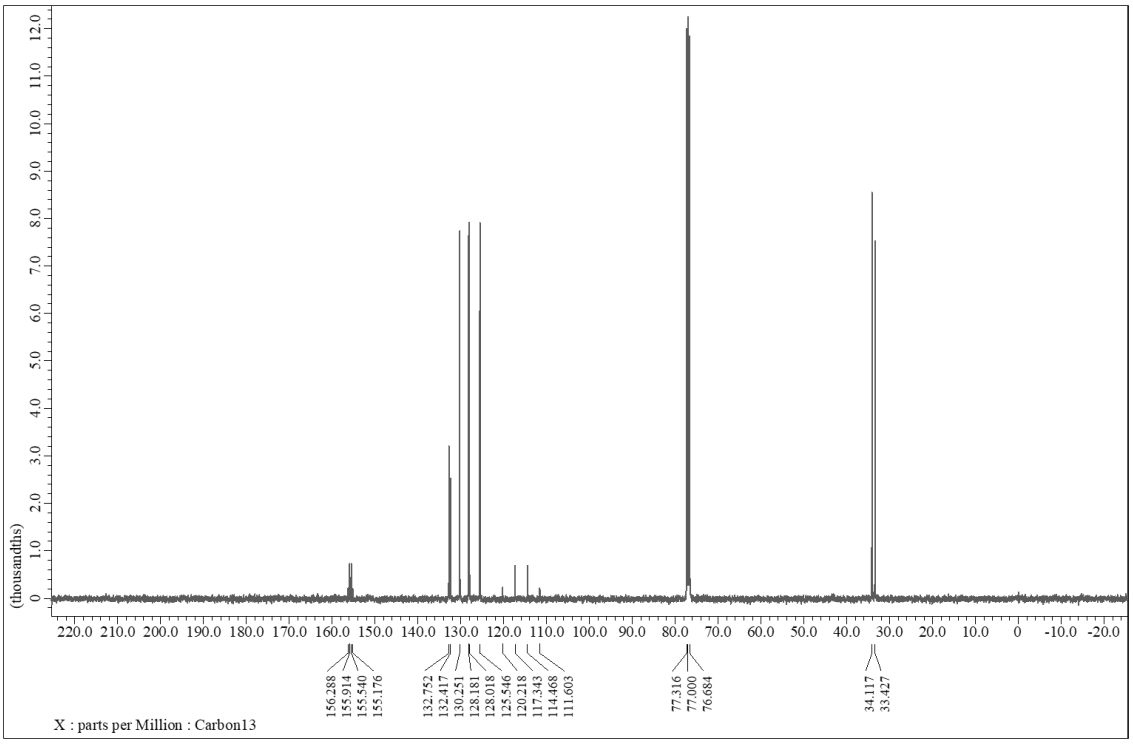


Compound **3a**

^{1}H-NMR

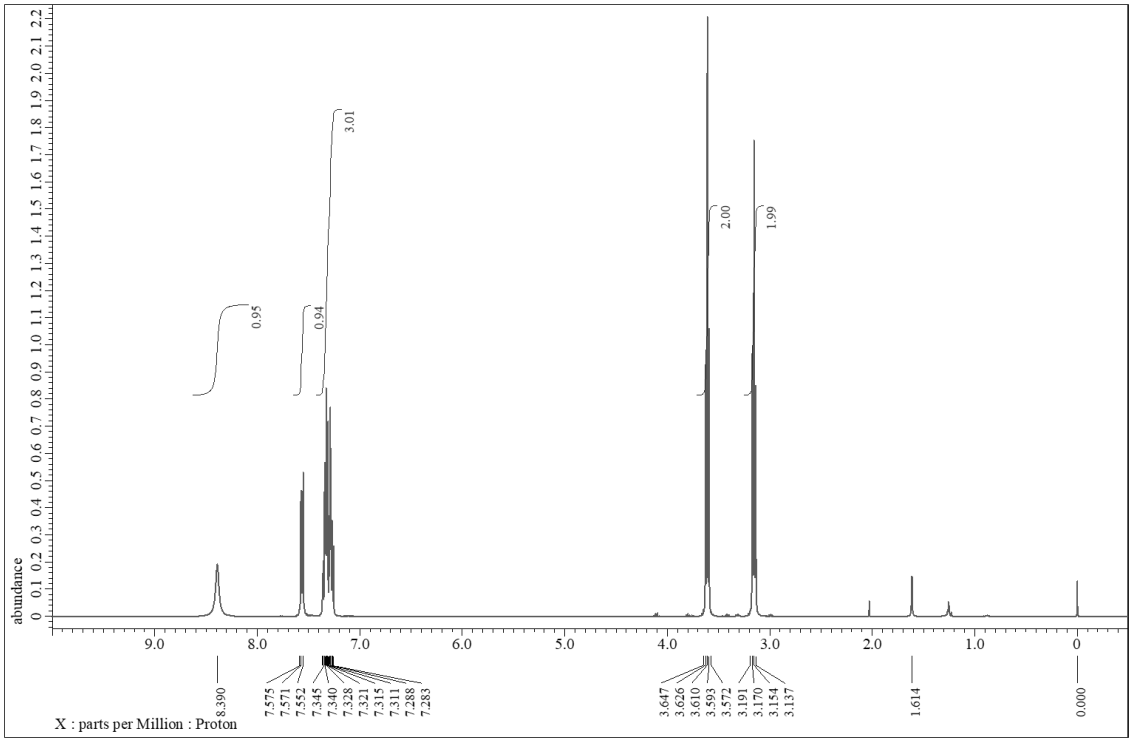


^{13}C-NMR

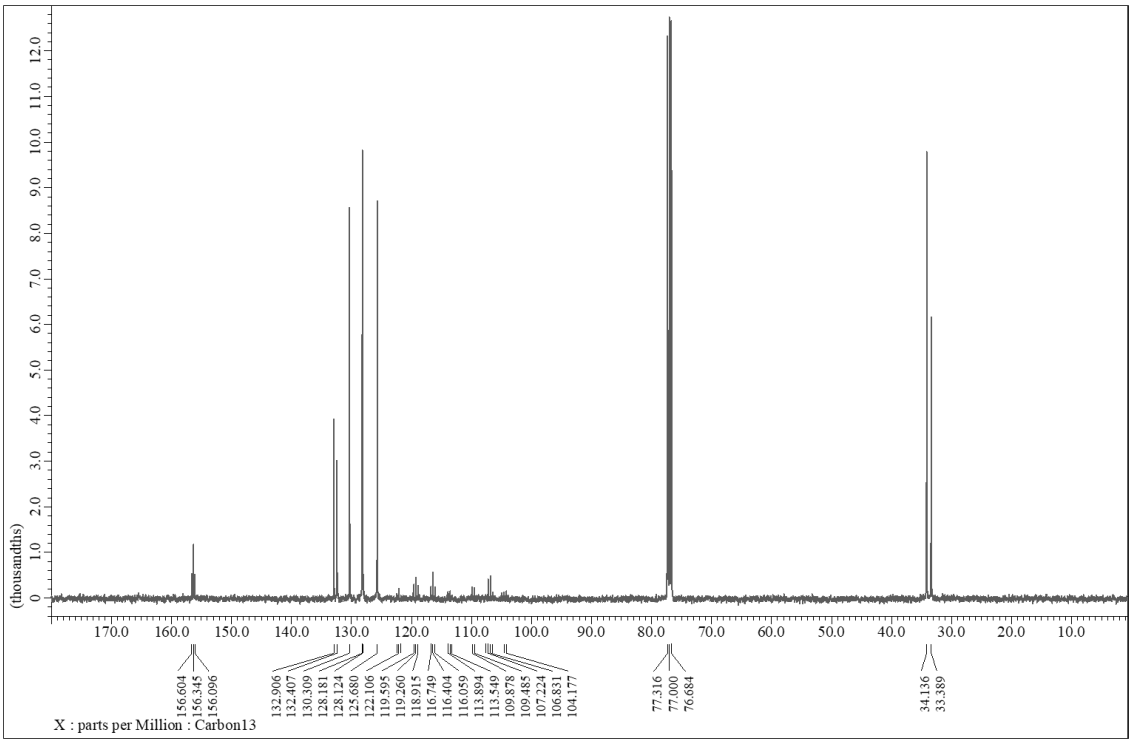


Compound **3b**

^{1}H-NMR

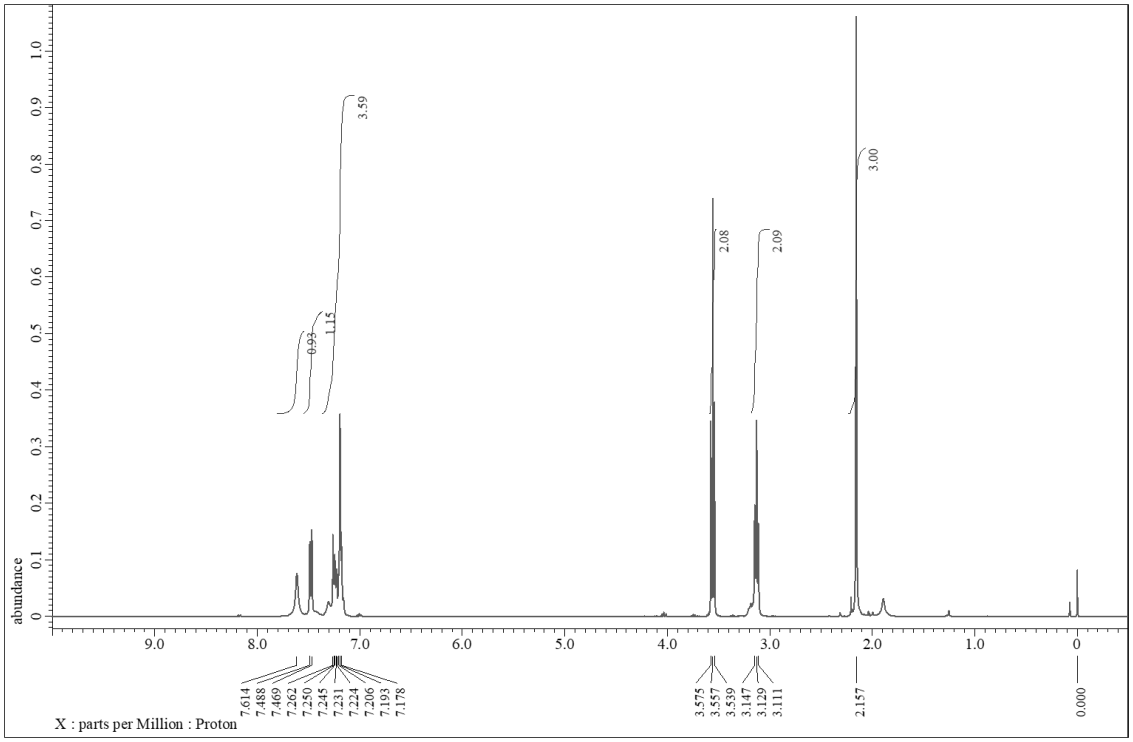


^{13}C-NMR

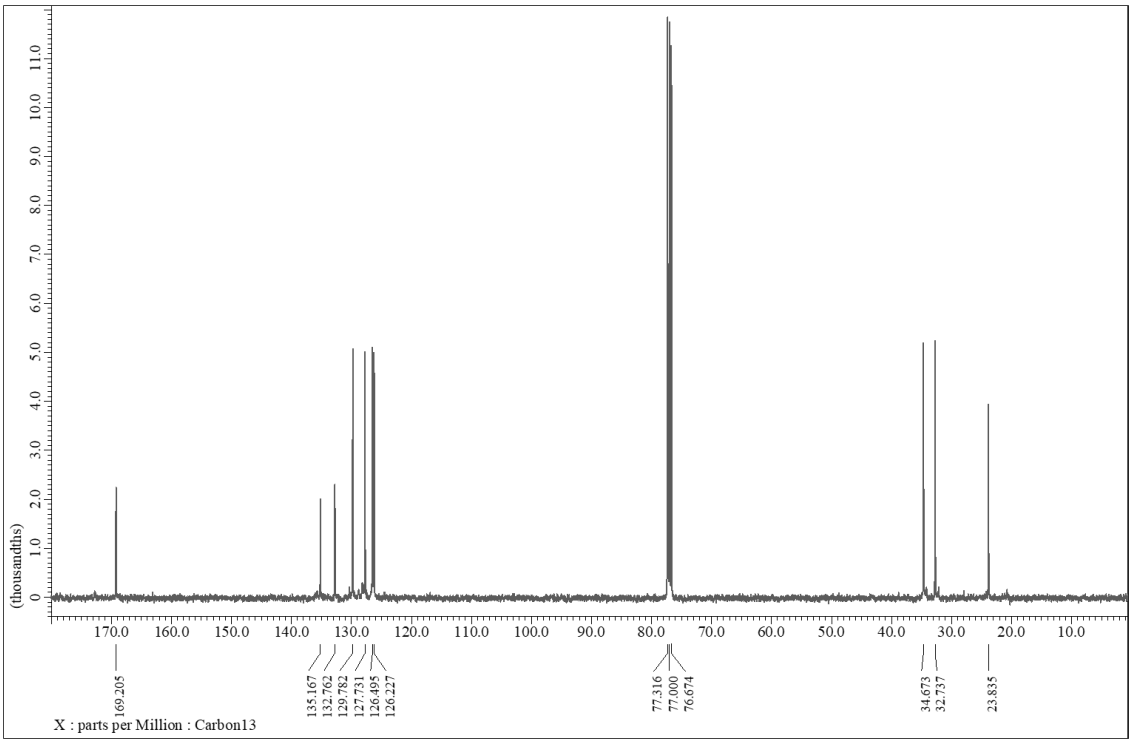


Compound **3c**

^{1}H-NMR

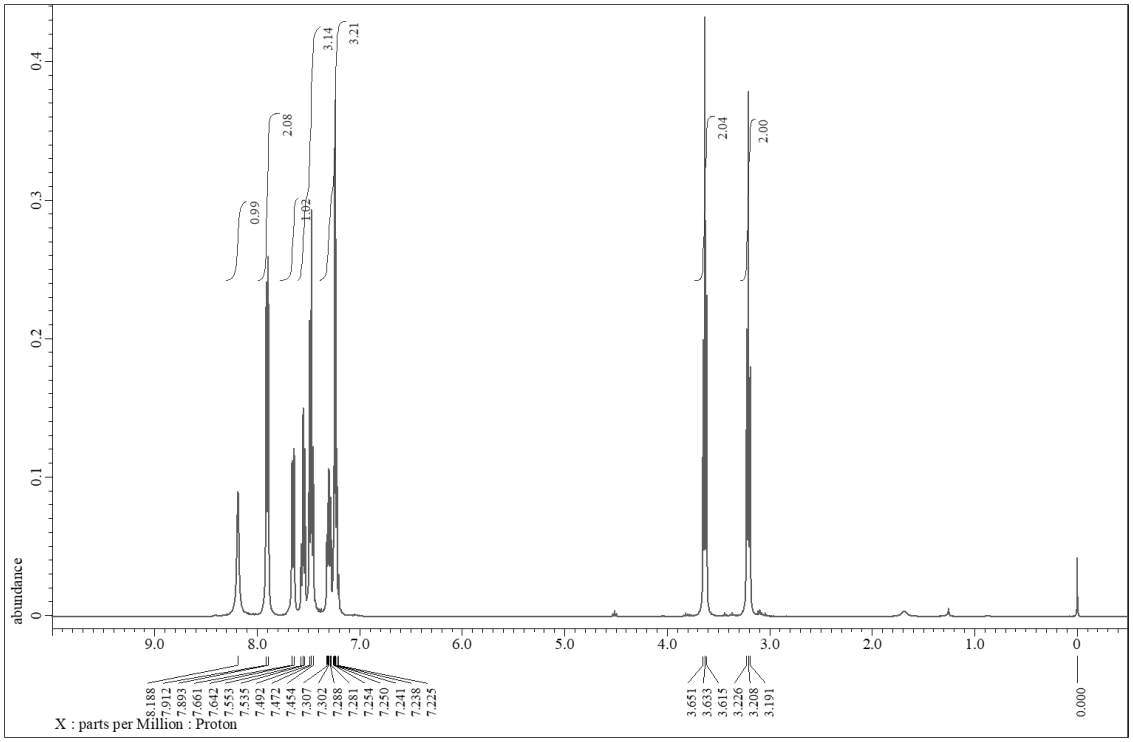


^{13}C-NMR

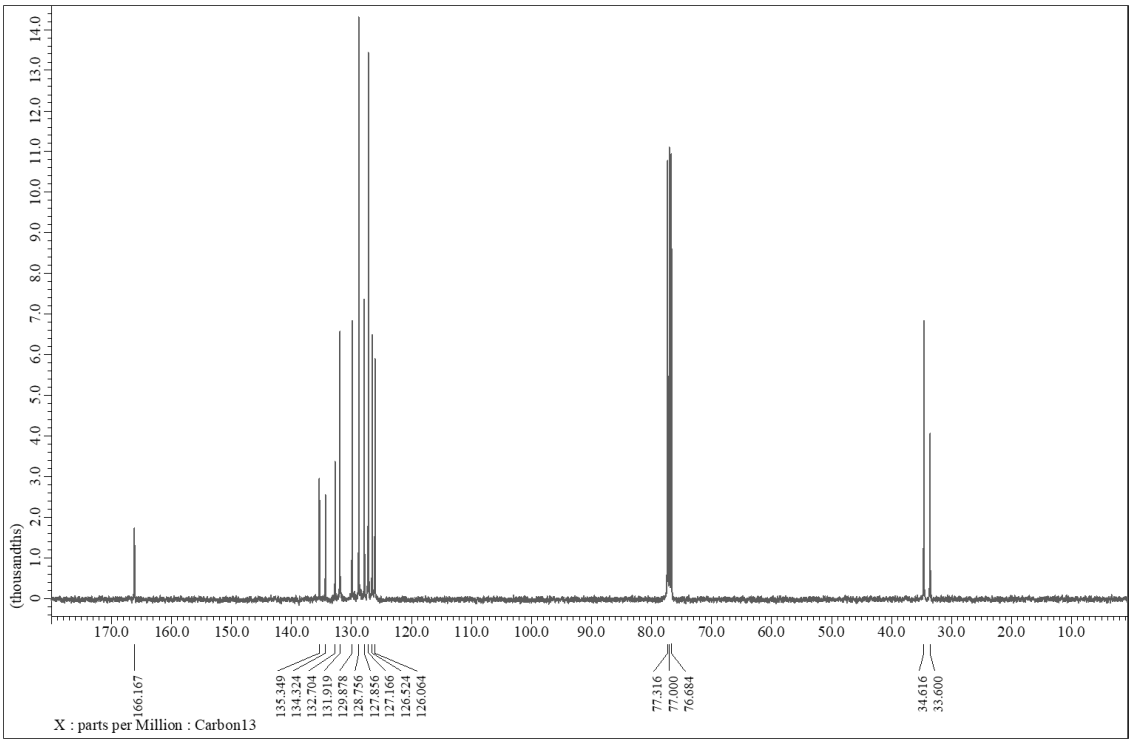


Compound **3d**

^{1}H-NMR

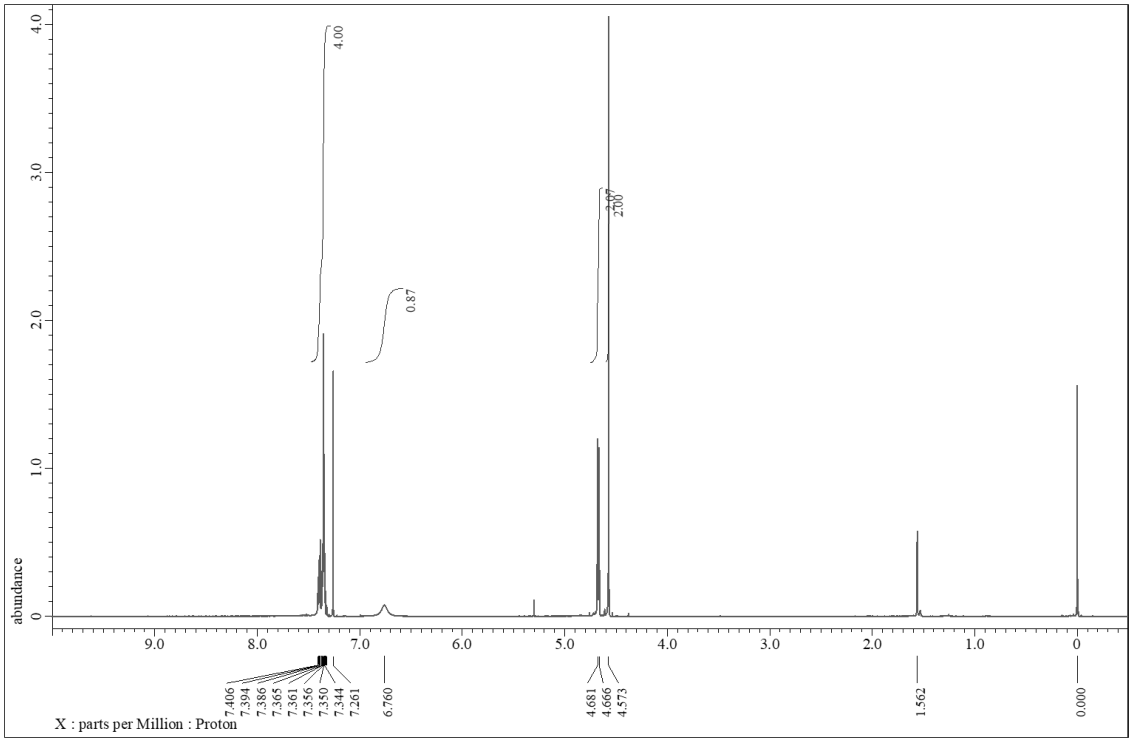


^{13}C-NMR

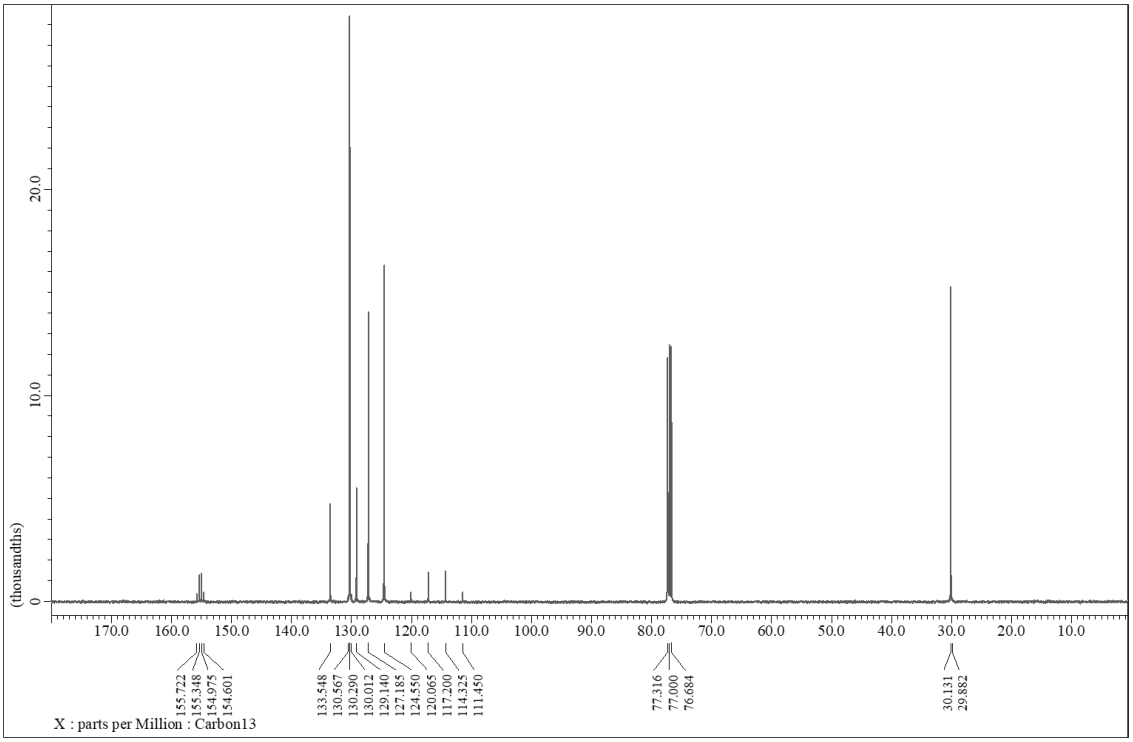


Compound **9a**

^{1}H-NMR

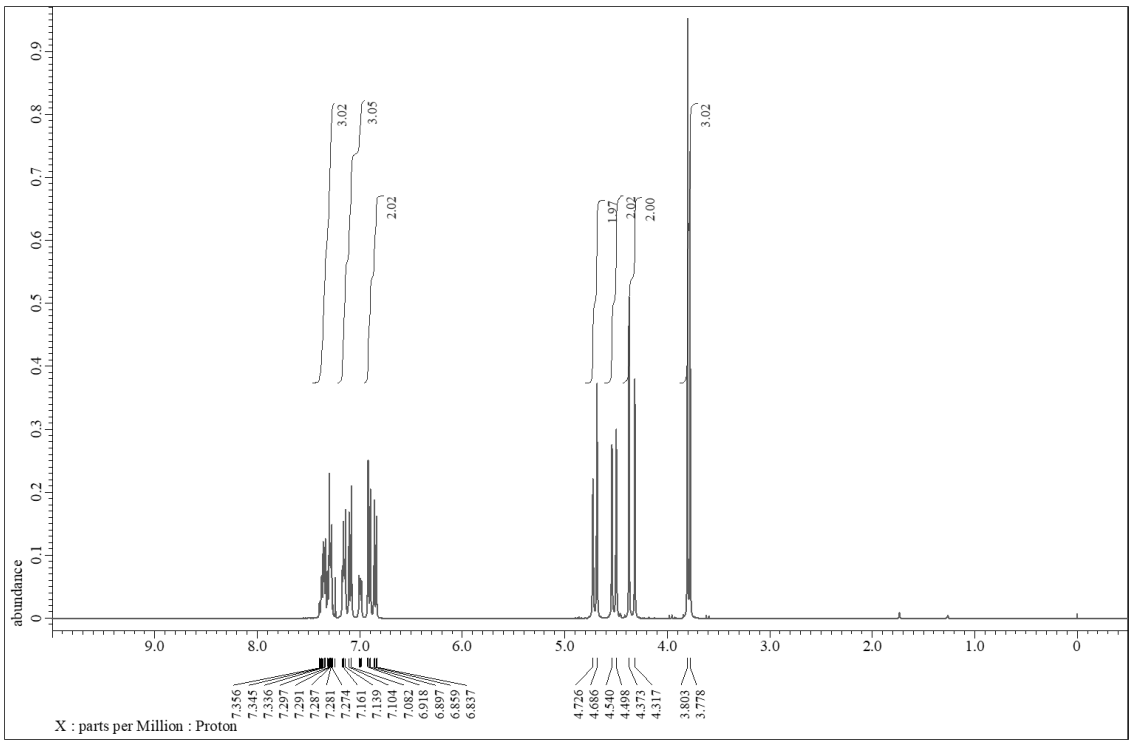


^{13}C-NMR

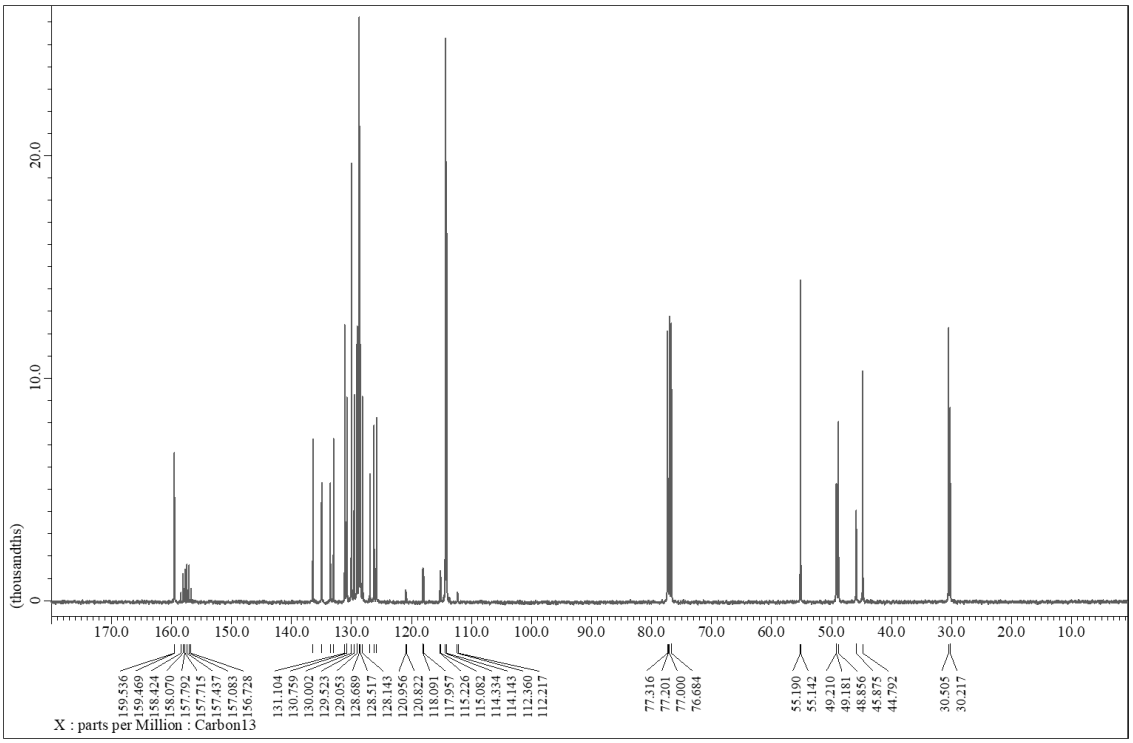


Compound **9b**

^{1}H-NMR

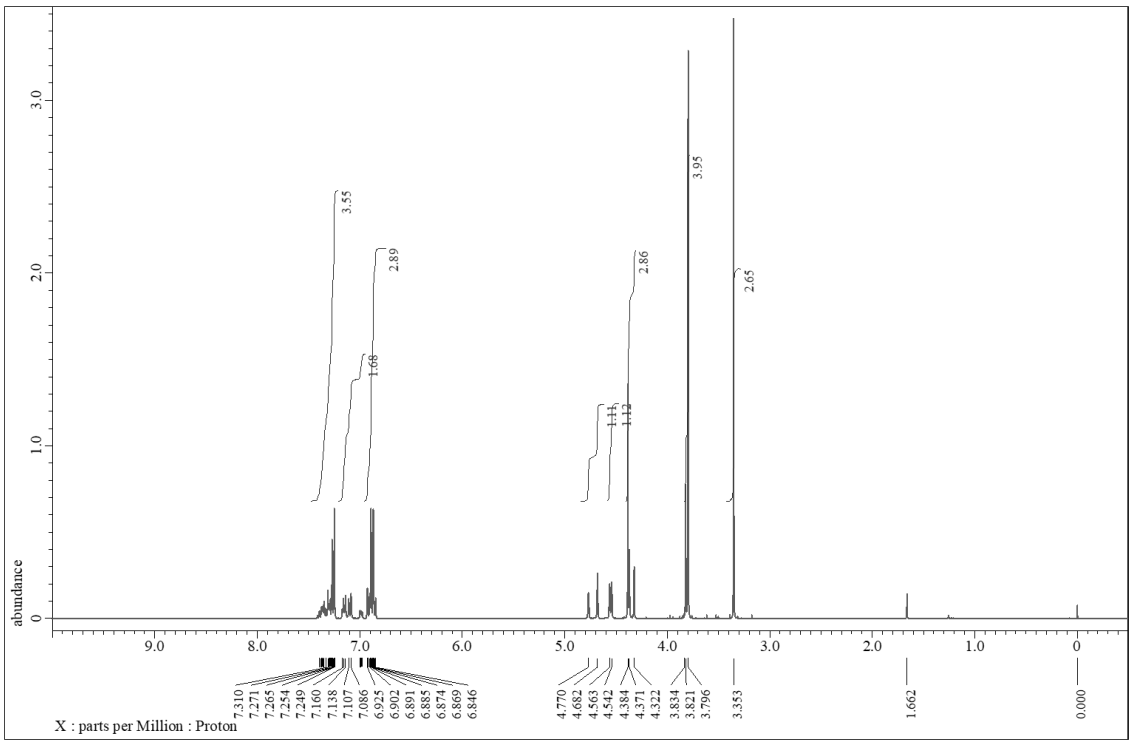


^{13}C-NMR



Compound **9c**

^{1}H-NMR



^{13}C-NMR