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Supporting Information

Isothiazolo[4,3-*b*]pyridines as inhibitors of cyclin G associated kinase : synthesis, structure-activity relationship studies and antiviral activity

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Experimental section

General

For all reactions, analytical grade solvents were used. All moisture-sensitive reactions were carried out in oven-dried glass-ware (135 °C). ^{1}H and ^{13}C NMR spectra: *Bruker Avance 300 Mhz* (^{1}H-NMR: 300 MHz, ^{13}C-NMR: 75 MHz), *500 MHz* (^{1}H-NMR: 500 MHz, ^{13}C-NMR: 125 MHz) using tetramethylsilane as internal standard for ^{1}H-NMR spectra and (D_6)-DMSO (39.5 ppm) or $CDCl_3$ (77.2 ppm) and CD_3OD (49.0 ppm) for ^{13}C-NMR spectra. Abbreviations used are: *s* = singlet, *d* = doublet, *t* = triplet, *q* = quartet, *m* = multiplet, br = broad. Coupling constants are expressed in Hz. Mass spectra are obtained with a Finnigan LCQ Advantage Max (ion trap) mass spectrophotometer from Thermo Finnigan, San Jose, CA, USA. High resolution mass spectrometry spectra were acquired on a quadrupole orthogonal acceleration time-of-flight mass spectrometer (Synapt G2 HDMS, Waters, Milford, MA). Samples were infused at 3 µL/min and spectra were obtained in positive (or negative) ionization mode with a resolution of 15000 (FWHM) using leucine enkephalin as lock mass. Precoated aluminum sheets (*Fluka* Silica gel/TLC-cards, 254 nm) were used for TLC. Column chromatography (CC) was performed on *ICN* silica gel 63-200, 60 Å.

Compounds **3** and **6** have been synthesized according to known procedures.[1]

N-(6-Bromo-isothiazolo[4,3-*b*]pyridin-3-yl)isobutyramide (4c)

To a stirred suspension of 6-bromo-isothiazolo[4,3-*b*]pyridin-3-amine (1.74 mmol, 400 mg), isobutyric acid (2.17 mmol, 0.2 ml) and DIPEA (2.72 mmol, 0.45 ml) in DMF (45 ml), was added TBTU (2.11 mmol, 680 mg) in one portion. The mixture was stirred at room temperature for 12 hours, then at 75°C for 10 hours. After this time, the solvents were evaporated and the crude residue was purified by silicagel flash chromatography using a mixture of cyclohexane/ethyl acetate in a ratio of 4:1. The title compound was obtained in 38 % yield (0.67 mmol, 201 mg).

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.19 (d, *J* = 6.84 Hz, 6H, $2CH_3$), 3.14 (m, 1H, CH), 8.37 (d, *J* = 2.01 Hz, 1H, arom H), 8.65 (d, *J* = 2.04 Hz, 1H, arom H), 12.86 (s, 1H, NH) ppm.

^{13}C-NMR (75 MHz, DMSO-d_6): δ = 19.76 (CH_3), 33.44 (CH), 120.48 (arom C), 130.62 (arom CH), 134.52 (arom C), 148.08 (arom CH), 151.42 (arom C), 158.75 (arom C), 176.82 (CO) ppm.

Synthesis of 3-substituted-6-bromo-isothiazolo[4,3-*b*]pyridines (4g, 4h, 4i, 4j)

General procedure

To a stirred suspension of 6-bromo-isothiazolo[4,3-*b*]pyridin-3-amine in DMF (10 mL) was added an appropriate carboxylic acid (1.2 eq), DIPEA (1.5 eq) and HATU (1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium-3-oxide

hexafluorophosphate ; 1.2 eq). The reaction mixture was stirred at room temperature. After completion of reaction, solvents were evaporated and the crude residue was purified by silicagel flash chromatography affording the titled compounds. The following compounds were made according to this procedure:

N-(6-Bromo-isothiazolo[4,3-*b*]pyridin-3-yl)cyclopent-3-enecarboxamide (4g)

This compound was prepared from 6-bromo-isothiazolo[4,3-*b*]pyridin-3-amine (230 mg, 1 mmol) using cyclopent-3-enecarboxylic acid (124 µL, 1.2 mmol), DIPEA (247 µL, 1.5 mmol) and HATU (456 mg, 1.2 mmol). The crude product was purified using a mixture of cyclohexane/ethyl acetate in a ratio of 5:1, affording the title compound 89 % yield (290 mg, 0.89 mmol).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.84 (m, 4H, 2xCH_2), 3.46 (m, 1H, CH), 5.79 (s, 2H, 2xCH), 8.22 (d, *J* = 1.98 Hz, 1 arom H), 8.53 (d, *J* = 1.98 Hz, 1 arom H), 9.91 (bs, 1H, NH) ppm.

N-(6-Bromo-isothiazolo[4,3-*b*]pyridin-3-yl)cycloheptanecarboxamide (4h)

This compound was prepared from 6-bromo-isothiazolo[4,3-*b*]pyridin-3-amine (230 mg, 1 mmol) using cycloheptanecarboxylic acid (165 µL, 1.2 mmol), DIPEA (247 µL, 1.5 mmol) and HATU (456 mg, 1.2 mmol). The crude product was purified using a mixture of cyclohexane/ethyl acetate in a ratio of 1:1, affording the title compound in in 46 % yield (163 mg, 0.46 mmol).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.65-1.68 (m, 6H, 3xCH_2), 1.89 (m, 4H, 2xCH_2), 2.11 (m, 2H, CH_2), 2.81 (m, 1H, CH), 8.25 (d, *J* = 1.92 Hz, 1 arom H), 8.57 (d, *J* = 1.92 Hz, 1 arom H), 9.73 (bs, 1H, NH) ppm.

N-(6-Bromoisothiazolo[4,3-*b*]pyridin-3-yl)tetrahydro-2H-pyran-4-carboxamide (4i)

This compound was prepared from 6-bromo-isothiazolo[4,3-*b*]pyridin-3-amine (230 mg, 1 mmol) using tetrahydro-2H-pyran-4-carboxylic acid (156 mg, 1.2 mmol), DIPEA (247 µL, 1.5 mmol) and HATU (456 mg, 1.2 mmol). The crude residue was purified using a mixture of cyclohexane/ethyl acetate in a ratio of 5:2, affording the title compound in 88 % yield (301 mg, 0.88 mmol).

^{1}H-NMR (300 MHz, CD_3OD): δ = 1.72 (m, 2H, CH_2), 2.56 (m, 1H, CH), 3.08 (m, 1H, CH), 3.56 (m, 2H, CH_2), 4.08 (m, 2H, CH_2), 8.23 (d, *J* = 1.98 Hz, 1 arom H), 8.65 (d, *J* = 1.98 Hz, 1 arom H) ppm.

N-(6-bromoisothiazolo[4,3-*b*]pyridin-3-yl)benzamide (4j)

This compound was prepared from 6-bromo-isothiazolo[4,3-*b*]pyridin-3-amine (143 mg, 0.621 mmol) using benzoic acid (91 mg, 0.747 mmol), DIPEA (153 µL, 0.931 mmol) and HATU (284 mg, 0.745 mmol). The crude product was purified using a mixture of

cyclohexane/ethyl acetate in a ratio of 3:2, affording the title compound in 45 % yield (94 mg, 0.281 mmol).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.57-7.60 (m, 2H, arom H), 7.65 (m, 1H, arom H), 7.93 (m, 2H, arom H), 8.45 (bs, 1H, NH), 8.51 (d, *J* = 2.01 Hz, 1 arom H), 9.28 (d, *J* = 2.01 Hz, 1 arom H) ppm.

N-(6-(3,4-Dimethoxyphenyl)isothiazolo[4,3-*b*]pyridin-3-yl)acetamide (5a)

To a solution of 3,6-dibromo-isothiazolo[4,3-*b*]pyridine (100 mg, 0.341 mmol) in DMF (10 ml) was added acetic acid (20 mg, 0.682 mmol), DIPEA (153 µL, 0.931 mmol) and HATU (259 mg, 0.682 mmol). The mixture was stirred at room temperature for 6 hours. Then, the solvent was removed and the crude residue was purified by silica gel flash chromatography, affording pure **4a**. The pure product was dissolved in 1,4-dioxane (2 mL) and 3,4-dimethoxyphenylboronic acid (62 mg, 0.341 mmol), 2M K_2CO_3 (300 µL), $Pd(PPh_3)_4$ (20 mg, 0.017 mmol) were added. The mixture was stirred under MW irradiation at 80^{o}C for 60 minutes. The crude product was purified using a mixture of cyclohexane/ethyl acetate in a ratio of 1:5, affording the title compound in 19 % yield (21 mg, 0.064 mmol).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.45 (s, 3H, CH_3), 3.95 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 6.98 (d, *J* = 8.4 Hz, 1H, arom H), 7.15-7.28 (m, 2H, arom H), 8.07 (d, *J* = 1.8 Hz, 1H, arom H), 8.78 (d, *J* = 2.1 Hz, 1H, arom H), 10.27 (brs, 1H, NH) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 22.64 (CH_2), 56.17 (OCH_3), 56.20 (OCH_3), 110.62 (CH), 111.88 (CH), 120.19 (CH), 125.29 (CH), 130.04 (C_q), 135.02 (C_q), 136.58 (C_q), 148.13 (CH), 149.76 (C_q), 149.91 (C_q), 151.93 (C_q), 155.79 (C_q), 167.79 (C_q) ppm.

HR-MS $[M+H]^+$ calcd for $C_{16}H_{16}N_3O_3S$ 330.09068 , found 330.0905.

N-(6-(3,4-Dimethoxyphenyl)isothiazolo[4,3-*b*]pyridin-3-yl)propionamide (5b)

To a solution of 3,6-dibromo-isothiazolo[4,3-*b*]pyridine (100 mg, 0.341 mmol) in DMF (10 ml) was added propionic acid (50 mg, 0.682 mmol), DIPEA (153 µL, 0.931 mmol) and HATU (259 mg, 0.682 mmol). The mixture was stirred at room temperature for 6 hours. Then, the solvent was removed and the crude residue was purified by silica gel flash chromatography, affording compound **4b**. The pure product was dissolved in 1,4-dioxane (2 mL) and 3,4-dimethoxyphenylboronic acid (62 mg, 0.341 mmol), 2M K_2CO_3 (300 µL), $Pd(PPh_3)_4$ (20 mg, 0.017 mmol) was added. The mixture was stirred under MW irradiation at 80^{o}C for 60 minutes. The crude product was purified using a mixture of cyclohexane/ethyl acetate in a ratio of 1:5, affording the title compound in 25 % yield (29 mg, 0.085 mmol).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.38 (t, *J* = 7.5, 6H, $2CH_3$), 2.69-2.77 (m, 1H, CH), 3.97 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 7.0 (d, *J* = 8.4 Hz, 1H, arom H), 7.17-7.28 (m, 2H, arom H), 8.08 (d, *J* = 2.1 Hz, 1H, arom H), 8.80 (d, *J* = 2.1 Hz, 1H, arom H), 10.34 (brs, 1H, NH) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 8.83 (CH_3), 26.76 (CH_2), 55.51 (OCH_3), 55.57 (OCH_3), 110.17 (CH), 111.38 (CH), 119.52 (CH), 124.14 (CH), 129.93 (C_q), 135.61 (C_q), 136.56 (C_q), 146.58 (CH), 149.10 (C_q), 151.23 (C_q), 154.34 (C_q), 157.38 (C_q), 172.76 (C_q) ppm.
HR-MS $[M+H]^+$ calcd for $C_{17}H_{18}N_3O_3S$ 344.10633, found 344.0912.

N-(6-(3,4-Dimethoxyphenyl)isothiazolo[4,3-*b*]pyridin-3-yl)isobutyramide (5c)

This compound was prepared starting from N-(6-Bromo-isothiazolo[4,3-*b*]pyridin-3-yl)isobutyramide (4c) and 3,4-dimethoxyphenylboronic acid. The crude residue was purified using a mixture of cyclohexane/ethyl acetate in a ratio of 1:1, affording the title compound in 32 % yield.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.42 (d, 6H, 2xCH_3(iPr)), 2.91 (m, 1H, CH(iPr)), 3.97 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 7.03 (d, *J* = 8.31 Hz, 1H, arom H), 7.18 (d, *J* = 1.98 Hz, 1H, arom H), 7.24-7.27 (m, 1H, arom H), 8.09 (d, *J* = 1.86 Hz, 1H, arom H), 8.23 (d, *J* = 1.86 Hz, 1H, arom H), 9.83 (br s, 1H, NH) ppm.

N-(6-(3,4-Dimethoxyphenyl)isothiazolo[4,3-*b*]pyridin-3-yl)pivalamide (5d)

To a solution of 3,6-dibromo-isothiazolo[4,3-*b*]pyridine (100 mg, 0.341 mmol) in DMF (10 ml) was added pivalic acid (69 mg, 0.682 mmol), DIPEA (153 µL, 0.931 mmol) and HATU (259 mg, 0.682 mmol). The mixture was stirred at room temperature for 6 h. Then, the solvent was removed and the crude residue was purified by silica gel flash chromatography, affording pure compound **4d**. The pure product was dissolved in 1,4-dioxane (2 mL) and then 3,4-dimethoxyphenylboronic acid (62 mg, 0.341 mmol), 2M K_2CO_3 (300 µL), $Pd(PPh_3)_4$ (20 mg, 0.017 mmol) was added. The mixture was stirred under MW irradiation at 80^{o}C for 60 minutes. The crude product was purified using a mixture of cyclohexane/ethyl acetate in a ratio of 1:5, affording the title compound in 12 % yield (15 mg, 0.04 mmol).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.48 (s, 9H, 3CH_3), 1.93 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 4.00 (s, 3H, CH_3), 7.0 (d, *J* =8.1 Hz, 1H, arom H), 7.19 (d, *J* = 2.1 Hz, 1H, arom H), 7.25-7.28 (m, 2H, arom H), 8.09 (d, *J* =1.8 Hz, 1H, arom H), 8.83 (d, *J* = 1.8 Hz, 1H, arom H), 9.86 (brs, 1H, NH) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 27.55 (3CH_3), 39.00 (C_q), 56.22 (2OCH_3), 110.70 (CH), 111.94 (CH), 112.72 (C_q), 120.23 (CH), 125.35 (CH), 130.25 (CH), 136.65 (CH), 147.99 (C_q), 149.81 (C_q), 149.93 (C_q), 151.96 (C_q), 155.91 (C_q), 158.86 (C_q), 176.46 (C_q) ppm.
HR-MS $[M+H]^+$ calcd for $C_{19}H_{22}N_3O_3S$ 372.1376, found 372.1373.

N-(6-(3,4-Dimethoxyphenyl)isothiazolo[4,3-*b*]pyridin-3-yl)-2-ethylbutanamide (5e)

To a solution of 3,6-dibromo-isothiazolo[4,3-*b*]pyridine (100 mg, 0.341 mmol) in DMF (10 ml) was added 2-ethylbutanoic acid (79 mg, 0.682 mmol), DIPEA (153 µL, 0.931 mmol) and

HATU (259 mg, 0.682 mmol). The mixture was stirred at room temperature for 6 hours. Then the solvent was removed and the crude residue was purified by silica gel flash chromatography, affording pure **4e**. The pure product was dissolved in 1,4-dioxane (2 mL) and 3,4-dimethoxyphenylboronic acid (62 mg, 0.341 mmol), 2M K_2CO_3 (300 µL), $Pd(PPh_3)_4$ (20 mg, 0.017 mmol) was added.The mixture was stirred under MW irradiation at 80°C for 60 minutes. The crude residue was purified using a mixture of cyclohexane/ethyl acetate in a ratio of 1:5, affording the title compound in 20 % yield (26 mg, 0.068 mmol).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.02 (t, J = 8.0 Hz 6H, $2CH_3$), 1.64-1.84 (m, 4H, $2CH_2$), 2.22-2.32 (m, 1H, CH), 3.94 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 6.9 (d, J = 8.4 Hz, 1H, arom H), 7.13 (d, J =2.1 Hz, 1H, arom H), 7.22-7.28 (m, 1H, arom H), 7.81 (brs, 1H, NH), 8.62 (d, J =2.1 Hz, 1H, arom H), 9.00 (d, J =2.1 Hz, 1H, arom H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 12.06 ($2CH_3$), 25,74 ($2CH_2$), 52.35 (CH), 56.16 (OCH_3), 56.28 (OCH_3), 110.42 (CH), 111.82 (CH), 115.36(C_q), 120.37 (CH), 125.85 (CH), 138.89 (C_q), 140.78 (C_q), 144.36 (CH), 149.08 (C_q), 150.61 (C_q), 175.62 (C_q) ppm.

N-(6-(3,4-dimethoxyphenyl)isothiazolo[4,3-*b*]pyridin-3-yl)cyclopropanecarboxamide (5f)

To a solution of 3,6-dibromo-isothiazolo[4,3-*b*]pyridine (100 mg, 0.341 mmol) in DMF (10 ml) was added cyclopropanecarboxylic acid (59 mg, 0.682 mmol), DIPEA (153 µL, 0.931 mmol) and HATU (259 mg, 0.682 mmol). The mixture was stirred at room temperature for 6 h. Then solvent was removed and the crude residue was purified by silica gel flash chromatography. The pure product was dissolved in 1,4-dioxane (2 mL) and then 3,4-dimethoxyphenylboronic acid (62 mg, 0.341 mmol), 2M K_2CO_3 (300 µL), $Pd(PPh_3)_4$ (20 mg, 0.017 mmol) were added.The mixture was stirred under MW irradiation at 80°C for 60 minutes. Product was purified using a mixture of cyclohexane/ethyl acetate in a ratio of 1:5, affording the title compound in 22 % yield (27 mg, 0.075 mmol).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.02-1.01 (m, 2H, CH_2), 1.16-1.22 (m, 2H, CH_2), 1.69-1.77 (m, 1H, CH), 3.95 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 6.97 (d, *J* = 8.4 Hz, 1H, arom H), 6.99 (s, 1H, arom CH), 7.17-7.24 (m, 1H, arom H), 7.99 (brs, 1H, NH), 8.61 (d, *J* = 2.1 Hz, 1H, arom H), 9.00 (d, *J* = 2.1 Hz, 1H, arom H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 9.37 (CH_2), 16.30 (CH_2), 27.50 (CH), 56.18 (OCH_3), 56.29 (OCH_3), 110.45 (CH), 111.86 (CH), 115,.48 (C_q), 119,.88(C_q), 120.64 (CH), 125.54 (CH), 128.61(C_q), 139.14 (C_q), 140.78 (C_q), 144.16 (CH), 149.85 (C_q), 150.65 (C_q), 173.19 (C_q) ppm.

Synthesis of N-(6-(3,4-dimethoxyphenyl)isothiazolo[4,3-*b*]pyridin-3-yl) (5g, 5h, 5i, 5j)

General procedure

To a solution of a 3-substituted-6-bromo-isothiazolo[4,3-*b*]pyridine (0.2 mmol) in DME was added an appropriate boronic acid (1.5 eq) and potassium carbonate (2 eq). Mixture was degassed and $Pd(PPh_3)_4$ (10 mol %) was added. The reaction was heated at 80°C overnight or irradiated in microwave reactor (140 °C, 150 W, 30-180 minutes). After the completion of reaction, solvents were evaporated. The crude residue was purified by silicagel flash chromatography, yielding the pure title compounds.

The following compounds were made according to this procedure :

N-(6-(3,4-Dimethoxyphenyl)isothiazolo[4,3-*b*]pyridin-3-yl)cyclopent-3-enecarboxamide (5g)

This compound was prepared from N-(6-bromo-isothiazolo[4,3-*b*]pyridin-3-yl)cyclopent-3-enecarboxamide **4g** (48.6 mg, 0.15 mmol) using 3,4-dimethoxyphenylboronic acid (41 mg, 0.225 mmol), 2M K_2CO_3 (150 µL) and $Pd(PPh_3)_4$ (17 mg, 0.015 mmol) in DME (2 mL) by MW irradiation for 30 minutes. The product was purified using a mixture of cyclohexane/ethyl acetate in a ratio of 1:1, affording the title compound in 38 % yield (21.7 mg, 0.0569 mmol).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.86 (m, 4H, 2xCH_2), 3.47 (m, 1H, CH), 3.97 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 5.80 (s, 2H, 2xCH), 7.01 (d, *J* = 8.34 Hz, 1H, arom H), 7.17 (d, *J* = 2.07 Hz, 1H, arom H), 7.24-7.27 (m, 1H, arom H), 8.08 (d, *J* = 1.98 Hz, 1 arom H), 8.82 (d, *J* = 1.98 Hz, 1 arom H), 10.22 (bs, 1H, NH) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 36.59 (2xCH_2), 42.44 (CH), 55.74 (2xOCH_3), 110.18 (CH), 111.44 (CH), 119.75 (CH), 124.86 (CH), 128.75 (2xCH), 129.68 (C_q), 134.67 (C_q), 136.16 (C_q), 147.61 (CH), 149.32 (C_q), 149.45 (C_q), 151.52 (C_q), 155.45 (C_q), 173.25 (C_q) ppm.

HR-MS $[M+H]^+$ calcd for $C_{20}H_{20}N_3O_3S$ 382.1219, found 382.1217.

N-(6-(3,4-dimethoxyphenyl)isothiazolo[4,3-*b*]pyridin-3-yl)cycloheptanecarboxamide (5h)

This compound was prepared from N-(6-bromoisothiazolo[4,3-*b*]pyridin-3-yl)cycloheptanecarboxamide **4h** (53 mg, 0.15 mmol) using 3,4-dimethoxyphenylboronic acid (41 mg, 0.225 mmol), 2M K_2CO_3 (150 µL), $Pd(PPh_3)_4$ (17 mg, 0.015 mmol) in DME (2 mL) by MW irradiation for 45 minutes. The product was purified using a mixture of cyclohexane/ethyl acetate in a ratio of 1:1, affording the title compound in 33 % yield (20.7 mg, 0.05 mmol).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.61-1.68 (m, 6H, 3xCH_2), 1.89 (m, 4H, 2xCH_2), 2.08 (m, 2H, CH_2), 2.78 (m, 1H, CH), 3.97 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 7.02 (d, *J* = 8.38 Hz, 1H, arom H), 7.4 (d, *J* = 2.01 Hz, 1H, arom H), 7.24-7.27 (m, 1H, arom H), 8.08 (d, *J* = 1.92 Hz, 1 arom H), 8.81 (d, *J* = 1.92 Hz, 1 arom H), 9.76 (bs, 1H, NH) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 26.08 (2xCH_2), 27.90 (2xCH_2), 30.98 (2xCH_2), 46.04 (CH), 55.74 (2xOCH_3), 110.19 (CH), 111.44 (CH), 119.75 (CH), 124.95 (CH), 129.69 (C_q), 134.18

(C_q), 136.10 (C_q), 147.45 (CH), 149.32 (C_q), 149.45 (C_q), 151.47 (C_q), 155.55 (C_q), 174.50 (C_q) ppm.
HR-MS $[M+H]^+$ calcd for $C_{22}H_{26}N_3O_3S$ 412.1689, found 412.1685.

N-(6-(3,4-Dimethoxyphenyl)isothiazolo[4,3-*b*]pyridin-3-yl)tetrahydro-2H-pyran-4-carboxamide (5i)

This compound was prepared from N-(6-bromo-isothiazolo[4,3-*b*]pyridin-3-yl)tetrahydro-2H-pyran-4-carboxamide **4i** (51 mg, 0.15 mmol) using 3,4-dimethoxyphenylboronic acid (41 mg, 0.225 mmol), 2M K_2CO_3 (150 µL), $Pd(PPh_3)_4$ (17 mg, 0.015 mmol) in DME (2 mL) by MW irradiation for 30 minutes. Product was purified using a mixture of cyclohexane/ethyl acetate in a ratio of 1:7, affording the title compound in 42 % yield (25 mg,0.062 mmol).
^{1}H-NMR (300 MHz, CD_3OD): δ = 1.90 (m, 4H, 2xCH_2), 2.98 (m, 1H, CH), 3.55 (m, 2H, CH_2), 3.87 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 6.98 (d, *J* = 8.04 Hz, 1H, arom H), 7.18-7.21 (m, 2H, arom H), 7.84 (d, *J* = 1.98 Hz, 1 arom H), 8.79 (d, *J* = 1.98 Hz, 1 arom H) ppm.
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 28.58 (CH_2), 41.20 (CH), 55.74 (2xOCH_3), 66.62 (CH_2), 110.19 (CH), 111.45 (CH), 119.77 (CH), 124.84 (CH), 129.62 (C_q), 134.87 (C_q), 136.25 (C_q), 147.79 (CH), 149.34 (C_q), 149.49 (C_q), 154.97 (C_q), 171.55 (C_q) ppm.

N-(6-(3,4-Dimethoxyphenyl)isothiazolo[4,3-*b*]pyridin-3-yl)benzamide (5j)

Title compound was prepared from N-(6-bromo-isothiazolo[4,3-*b*]pyridin-3-yl)benzamide **4j** (90 mg, 0.269 mmol) using 3,4-dimethoxyphenylboronic acid (74 mg, 0.403 mmol), 2M K_2CO_3 (269 µL) and $Pd(PPh_3)_4$ (31 mg, 0.0269 mmol) by heating at 80°C in DME (3 mL). Product was purified using a mixture of cyclohexane/ethyl acetate in a ratio of 7:3, affording the title compound in 40 % yield (42 mg, 0.107 mmol).
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 3.97 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 6.99 (d, *J* = 8.37 Hz, 1H, arom H), 7.18 (d, *J* = 2.1 Hz, 1H, arom H), 7.28 (dd, *J* = 2.1 Hz, *J* = 8.37 Hz, 1H, arom H), 7.56-7.60 (m, 3H, arom H), 7.67 (m, 2H, arom H), 7.96 (bs, 1H, NH), 8.49 (d, *J* = 2.01 Hz, 1 arom H), 9.20 (d, *J* = 2.01 Hz, 1 arom H), 9.76 (bs, 1H, NH) ppm.
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 54.73 (OCH_3), 54.82 (OCH_3), 109.98 (CH), 111.43 (CH), 114.99 (CH), 120.20 (CH), 125.06 (CH), 126.92 (2xCH), 128.05 (C_q), 128.91 (2xCH), 132.77 (C_q), 136.13 (C_q), 138.65 (C_q), 140.06 (C_q), 144.06 (CH), 149.33 (2xC_q), 150.23 (C_q), 165.63 (C_q) ppm.

Synthesis of 6-bromo-3-substituted-isothiazolo[4,3-*b*]pyridines (7l, 7m, 7n, 7o, 7p, 7q, 7r, 7s, 7t)

General procedure

To a solution of 3,6-di-bromo-isothiazolo[4,3-*b*]pyridine in ethanol (10 ml) was added an appropriate nitrogen nucleophile (1.1 eq or 3.0 eq). The reaction was stirred at 75°C. After completion of reaction, solvent was evaporated in vacuo and the crude residue was purified by silicagel flash chromatography yielding the pure title compounds.

The following compounds were made according to this procedure:

6-Bromo-3-(4-isopropylpiperazin-1-yl)isothiazolo[4,3-*b*]pyridine (7l)

This compound was prepared from 3,6-di-bromo-isothiazolo[4,3-*b*]pyridine (146 mg, 0.5 mmol) and N-isopropylpiperazine (192 mg, 1.5 mmol) in EtOH (10 ml). The crude product was purified using a mixture of DCM/MeOH in a ratio of 95:5, affording the title compound in 49 % yield (84 mg, 0.246 mmol).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.09 (d, *J* = 6.54 Hz, 6H, 2xCH_3), 2.76 (m, 4H, 2xCH_2), 3.96 (m, 4H, 2xCH_2), 7.93 (d, *J* = 2.07 Hz, 1H, arom H), 8.29 (d, *J* = 2.04 Hz, 1 arom H) ppm.

6-Bromo-3-(4-butylpiperazin-1-yl)isothiazolo[4,3-*b*]pyridine (7m)

This compound was prepared from 3,6-di-bromo-isothiazolo[4,3-*b*]pyridine (146 mg, 0.5 mmol) and N-butylpiperazine (78 mg, 0.55 mmol) in EtOH (10 ml). The product was purified using a mixture of cyclohexane/ethyl acetate in a ratio of 1:4, affording the title compound in 69 % yield (124 mg, 0.349 mmol).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.99 (t, *J* = 7.26 Hz, 3H, CH_3), 1.34-1.53 (m, 6H, 3xCH_2), 2.70 (m, 4H, 2xCH_2), 3.94 (m, 4H, 2xCH_2), 7.93 (d, *J* = 2.01 Hz, 1H, arom H), 8.29 (d, *J* = 2.01 Hz, 1 arom H) ppm.

6-Bromo-3-(4-(pyridin-4-yl)piperazin-1-yl)isothiazolo[4,3-*b*]pyridine (7n)

This compound was prepared from 3,6-di-bromo-isothiazolo[4,3-*b*]pyridine (146 mg, 0.5 mmol) and 1-(pyridin-4-yl)piperazine (90 mg, 0.55 mmol) in EtOH (10 ml). A yellow precipitate was formed during the reaction. The solids were filtered off, affording the title compound in 59 % yield (112 mg, 0.297 mmol).

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 3.68 (m, 4H, 2xCH_2), 4.10 (m, 4H, 2xCH_2), 6.79 (d, *J* = 6.39 Hz, 2H, arom H), 7.94 (m, 1H, arom H), 8.30 (m, 2H, arom H) ppm.

1-(4-(6-Bromo-isothiazolo[4,3-*b*]pyridin-3-yl)piperazin-1-yl)ethanone (7o)

This compound was prepared from 3,6-di-bromo-isothiazolo[4,3-*b*]pyridine (146 mg, 0.5 mmol) and *N*-acetylpiperazine (69 µL, 0.55 mmol) in EtOH (10 ml). The crude product was

purified using a mixture of cyclohexane/ethyl acetate in a ratio of 3:7, affording the title compound in 59 % yield (102 mg, 0.299 mmol).
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.16 (s, 3H, CH_3), 3.72 (m, 2H, CH_2), 3.83 (m, 4H, 2xCH_2), 4.06 (s, 2H, CH_2), 7.94 (d, *J* = 2.07 Hz, 1H, arom H), 8.30 (d, *J* = 2.07 Hz, 1 arom H) ppm.

Ethyl 4-(6-bromoisothiazolo[4,3-*b*]pyridin-3-yl)piperazine-1-carboxylate (7p)
This compound was prepared from 3,6-di-bromo-isothiazolo[4,3-*b*]pyridine (146 mg, 0.5 mmol) and ethyl N-piperazinecarboxylate (219 µL, 1.5 mmol) in EtOH (10 ml). Product was purified using a mixture of cyclohexane/ethyl acetate in a ratio of 8:2, affording the title compound in 97 % yield (181 mg, 0.486 mmol).
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.27 (t, *J* = 7.64 Hz, 3H, CH_3), 3.75 (m, 4H, 2xCH_2), 3.95 (m, 4H, 2xCH_2), 4.22 (q, 2H, CH_2), 7.97 (d, *J* = 2.07 Hz, 1 arom H), 8.33 (d, *J* = 2.04 Hz, 1H, arom H) ppm.

(4-(6-Bromoisothiazolo[4,3-*b*]pyridin-3-yl)piperazin-1-yl)(phenyl)methanone (7q)
This compound was prepared from 3,6-di-bromo-isothiazolo[4,3-*b*]pyridine (146 mg, 0.5 mmol) and *N*-benzoylpiperazine (105 mg, 0.55 mmol) in EtOH (10 ml). The crude product was purified using a mixture of cyclohexane/ethyl acetate in a ratio of 1:1, affording the title compound in 57 % yield (115 mg, 0.285 mmol).
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 3.99 (m, 8H, 4xCH_2), 7.47 (m, 5H, arom H), 7.98 (d, *J* = 1.47 Hz, 1H, arom H), 8.31 (d, *J* = 1.52 Hz, 1 arom H) ppm.

6-Bromo-3-(4-methyl-1,4-diazepan-1-yl)isothiazolo[4,3-*b*]pyridine (7r)
This compound was prepared from 3,6-di-bromo-isothiazolo[4,3-*b*]pyridine (146 mg, 0.5 mmol) and 1-methyl-1,4-diazepane (192 mg, 1.5 mmol) in EtOH (10 ml). The product was purified using a mixture of DCM/MeOH in a ratio of 95:5, affording the title compound in 31 % yield (51 mg, 0.155 mmol).
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.16 (m, 2H, CH_2), 2.42 (s, 3H, CH_3), 2.67 (m, 2H, CH_2), 2.83 (m, 2H, CH_2), 3.82 (m, 2H, CH_2), 4.36 (m, 2H, CH_2), 7.89 (d, *J* = 2.01 Hz, 1H, arom H), 8.22 (d, *J* = 2.01 Hz, 1 arom H) ppm.

6-Bromo-N-(piperidin-4-yl)isothiazolo[4,3-*b*]pyridin-3-amine (7s)
This compound was prepared from 3,6-di-bromo-isothiazolo[4,3-*b*]pyridine (584 mg, 2 mmol) and *tert*-butyl 4-amino-1-piperidinecarboxylate (219 µL, 1.5 mmol) in EtOH (10 mL). After completion of the reaction, the solvent was evaporated affording crude *tert*-butyl 4-(6-bromoisothiazolo[4,3-*b*]pyridin-3-ylamino)piperidine-1-carboxylate as a yellow powder, which was used as such in the next step. Crude *tert*-butyl 4-(6-bromoisothiazolo[4,3-*b*]pyridin-3-

ylamino)piperidine-1-carboxylate was treated with 20% TFA in DCM (40 mL) at room temperature. After completion of reaction, the mixture was carefully neutralized with solid K_2CO_3. The solids were filtered off and filtrate was evaporated. The crude product was purified on silicagel using a mixture of DCM/MeOH in a ratio of 8:2, affording the title compound in 34 % yield (212 mg, 0.67 mmol).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.61 (m, 2H, CH_2), 2.22 (m, 2H, CH_2), 2.79 (m, 2H, CH_2), 3.21 (m, 2H, CH_2), 3.39 (m, 1H, CH), 6.29 (bs, 1H, NH), 7.96 (d, *J* = 1.89 Hz, 1H, arom H), 8.28 (d, *J* = 1.89 Hz, 1 arom H) ppm.

6-Bromo-3-(4-methylpiperidin-1-yl)isothiazolo[4,3-*b*]pyridine (7t)

This compound was prepared from 3,6-di-bromo-isothiazolo[4,3-*b*]pyridine (146 mg, 0.5 mmol) and 4-methylpiperidine (176 µL, 1.5 mmol) in EtOH (10 ml). The product was purified using a mixture of cyclohexane/ethyl acetate in a ratio of 4:6, affording the title compound in 35 % yield (55 mg, 0.175 mmol).

^{1}H-NMR (300 MHz, CD_3OD): δ = 1.02 (d, *J* = 6.39 Hz, 3H, CH_3), 1.47 (m, 2H, CH_2), 1.74 (m, 1H, CH), 1.82 (m, 2H, CH_2), 3.22 (m, 2H, CH_2), 4.62 (m, 2H, CH_2), 7.91 (d, *J* = 2.07 Hz, 1H, arom H), 8.27 (d, *J* = 2.01 Hz, 1 arom H) ppm.

Synthesis of 3-substituted-6-(3,4-dimethoxyphenyl)isothiazolo[4,3-*b*]pyridines (8l, 8m, 8n, 8o, 8p, 8q, 8r, 8s, 8t)

General procedure

To a solution of 3-substituted-6-bromo-isothiazolo[4,3-*b*]pyridine (0.2 mmol) in DME was added an appropriate boronic acid (1.5 eq) and potassium carbonate (2 eq). Mixture was degassed and $Pd(PPh_3)_4$ (10 mol %) was added. The reaction was heated at 80°C overnight or irradiated in microwave reactor (140 °C, 150 W, 30-180 minutes). After the completion of reaction, solvents were evaporated. The crude residue was purified by silicagel flash chromatography, yielding the pure title compounds.

The following compounds were made according to this procedure :

6-(3,4-Dimethoxyphenyl)-3-(4-isopropylpiperazin-1-yl)isothiazolo[4,3-*b*]pyridine (8l)

This compound was prepared from 6-bromo-3-(4-isopropylpiperazin-1-yl)isothiazolo[4,3-*b*]pyridine (51 mg, 0.15 mmol) using 3,4-dimethoxyphenylboronic acid (41 mg, 0.225 mmol), 2M K_2CO_3 (150 µL), $Pd(PPh_3)_4$ (17 mg, 0.015 mmol) in DME (2 mL) by MW irradiation for 30 minutes. The crude product was purified using a mixture of DCM/MeOH in a ratio of 95:5, affording the title compound in 60 % yield (36 mg, 0.09 mmol).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.09 (d, *J* = 6.54 Hz, 6H, 2xCH_3), 2.78 (m, 4H, 2xCH_2), 3.93-3.98 (m, 10H, 2xCH_2, 2xOCH_3), 6.98 (d, *J* = 8.28 Hz, 1H, arom H), 7.17 (d, *J* = 2.04 Hz, 1H,

arom H), 7.22 (dd, *J* = 8.28 Hz, *J* = 2.04 Hz, 1H, arom H), 7.85 (d, *J* = 2.07 Hz, 1H, arom H), 8.52 (d, *J* = 2.04 Hz, 1 arom H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 18.04 (CH_3), 47.60 (CH_2), 50.38 (CH_2), 54.43 (CH), 55.68 (2xOCH_3), 110.08 (CH), 111.37 (CH), 119.53 (CH), 124.43 (CH), 130.10 (C_q), 133.64 (C_q), 135.09 (C_q), 143.71 (CH), 149.17 (2xC_q), 155.98 (C_q), 172.83 (C_q) ppm.

HR-MS $[M+H]^+$ calcd for $C_{21}H_{27}N_4O_2S$ 399.1849, found 399.1844.

3-(4-Butylpiperazin-1-yl)-6-(3,4-dimethoxyphenyl)isothiazolo[4,3-*b*]pyridine (8m)

This compound was prepared from 6-bromo-3-(4-butylpiperazin-1-yl)isothiazolo[4,3-*b*]pyridine (53 mg, 0.15 mmol) using 3,4-dimethoxyphenylboronic acid (41 mg, 0.225 mmol), 2M K_2CO_3 (150 µL), $Pd(PPh_3)_4$ (17 mg, 0.015 mmol) in DME (3 mL) by MW irradiation for 30 minutes. Product was purified using a mixture of cyclohexane/ethyl acetate in a ratio of 2:8, affording the title compound in 32 % yield (20 mg, 0.048 mmol).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.01 (t, *J* = 7.26 Hz, 3H, CH_3), 1.44 (m, 1H, CH), 3.42-3.47 (m, 7H, CH, 3xCH_2), 3.95 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 4.28 (m, 2H, CH_2), 4.59 (m, 2H, CH_2), 7.98 (d, *J* = 8.40 Hz, 1H, arom H), 7.16 (d, *J* = 2.01 Hz, 1H, arom H), 7.23 (dd, *J* = 2.04 Hz, *J* = 8.22 Hz, 1H, arom H), 7.89 (d, *J* = 2.01 Hz, 1H, arom H), 8.67 (d, *J* = 2.01 Hz, 1 arom H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 13.49 (CH_3), 19.72 (CH_2), 23.81 (CH_2), 44.71 (2xCH_2), 55.71 (2xOCH_3), 62.43 (2xCH_2), 71.38 (CH_2), 110.09 (CH), 111.42 (CH), 119.61 (CH), 124.61 (CH), 129.73 (C_q), 133.92 (C_q), 135.39 (C_q), 144.91 (CH), 149.25 (C_q), 149.37 (C_q), 156.01 (C_q), 171.41 (C_q) ppm.

6-(3,4-Dimethoxyphenyl)-3-(4-(pyridin-4-yl)piperazin-1-yl)isothiazolo[4,3-*b*]pyridine (8n)

This compound was prepared from 6-bromo-3-(4-(pyridin-4-yl)piperazin-1-yl)isothiazolo[4,3-*b*]pyridine (56 mg, 0.15 mmol) using 3,4-dimethoxyphenylboronic acid (41 mg, 0.225 mmol), 2M K_2CO_3 (150 µL), $Pd(PPh_3)_4$ (17 mg, 0.015 mmol) in DME (2 mL) by MW irradiation for 30 minutes. The crude product was purified using a mixture of cyclohexane/ethyl acetate in a ratio of 3:2, affording the title compound 29 % yield (19 mg, 0.043 mmol).

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 3.65 (m, 4H, 2xCH_2), 3.82 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 4.07 (m, 4H, 2xCH_2), 6.90 (d, *J* = 6.45 Hz, 2H, arom H), 7.10 (d, *J* = 9.03 Hz, 1H, arom H), 7.38 (m, 2H, arom H), 8.01 (d, *J* = 2.04 Hz, 1H, arom H), 8.20 (d, *J* = 6.27 Hz, 1H, arom H), 8.78 (d, *J* = 2.07 Hz, 1 arom H) ppm.

^{13}C-NMR (75 MHz, DMSO-d_6): δ = 44.71 (2xCH_2), 49.19 (2xCH_2), 55.76 (OCH_3), 55.82 (OCH_3), 108.59 (CH), 110.92 (CH), 112.39 (CH), 119.82 (CH), 124.00 (CH), 129.26 (C_q), 133.26 (C_q), 134.84 (C_q), 144.21 (CH), 149.43 (C_q), 149.54 (C_q), 149.81 (CH), 154.30 (C_q), 155.79 (C_q), 172.23 (C_q) ppm.

HR-MS $[M+H]^+$ calcd for $C_{23}H_{24}N_5O_2S$ 434.1645, found 434.1638.

1-(4-(6-(3,4-Dimethoxyphenyl)isothiazolo[4,3-*b*]pyridin-3-yl)piperazin-1-yl)ethanone (8o)

This compound was prepared from 4-(6-bromo-isothiazolo[4,3-*b*]pyridin-3-ylamino)-N-ethylpiperidine-1-carboxamide (51 mg, 0.15 mmol) using 3,4-dimethoxyphenylboronic acid (41 mg, 0.225 mmol), 2M K_2CO_3 (150 µL) and $Pd(PPh_3)_4$ (17 mg, 0.015 mmol) in DME (3 mL) by MW irradiation for 30 minutes. The crude product was purified using a mixture of cyclohexane/ethyl acetate in a ratio of 1:4, affording the title compound in 28 % yield (17 mg, 0.042 mmol).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.20 (s, 3H, CH_3), 3.76 (m, 2H, CH_2), 3.78 (m, 4H, 2xCH_2), 3.89 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 4.11 (m, 2H, CH_2), 7.00 (d, *J* = 8.37 Hz, 1H, arom H), 7.17 (d, *J* = 2.07 Hz, 1H, arom H), 7.24 (m, 1H, arom H), 7.89 (d, *J* = 2.07 Hz, 1H, arom H), 8.67 (d, *J* = 2.07 Hz, 1 arom H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 20.99 (CH_3), 40.26 (CH_2), 45.27 (CH_2), 49.54 (CH_2), 50.05 (CH_2), 55.71 (2xOCH_3), 110.10 (CH), 111.42 (CH), 119.59 (CH), 124.55 (CH), 129.85 (C_q), 134.10 (C_q), 135.37 (C_q), 144.51 (CH), 149.23 (C_q), 149.34 (C_q), 156.03 (C_q), 168.86 (C_q), 172.32 (C_q) ppm.

HR-MS $[M+H]^+$ calcd for $C_{20}H_{22}N_4O_3S$ 399.1485, found 399.1487.

Ethyl 4-(6-(3,4-dimethoxyphenyl)isothiazolo[4,3-*b*]pyridin-3-yl)piperazine-1-carboxylate (8p)

This compound was prepared from (4-(6-bromo-isothiazolo[4,3-*b*]pyridin-3-yl)piperazin-1-yl)(phenyl)methanone (92 mg, 0.25 mmol) using 3,4-dimethoxyphenylboronic acid (68 mg, 0.375 mmol), 2M K_2CO_3 (250 µL) and $Pd(PPh_3)_4$ (29 mg, 0.025 mmol) by heating at 80°C in DME (3 mL). The crude product was purified using a mixture of cyclohexane/ethyl acetate in a ratio of 7:3, affording the title compound in 25 % yield (27 mg, 0.063 mmol).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.28 (t, *J* = 7.28 Hz, 3H, CH_3), 3.69 (m, 4H, 2xCH_2), 3.96-3.98 (m, 10H, 2xCH_2, 2xOCH_3), 4.19 (q, 2H, CH_2), 6.97 (d, *J* = 8.40 Hz, 1H, arom H), 7.16 (d, *J* = 2.07 Hz, 1H, arom H), 7.22 (dd, *J* = 2.04 Hz, *J* = 8.40, 1H, arom H), 7.86 (d, *J* = 2.07 Hz, 1 arom H), 8.64 (d, *J* = 2.07 Hz, 1H, arom H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.32 (CH_3), 42.65 (CH_2), 49.74 (CH_2), 55.69 (2xOCH_3), 61.48 (CH_2), 110.06 (CH), 111.38 (CH), 119.55 (CH), 124.48 (CH), 129.89 (C_q), 133.68 (C_q), 135.25 (C_q), 144.27 (CH), 149.20 (C_q), 149.26 (C_q), 155.04 (C_q), 156.01 (CO), 172.56 (C_q) ppm.

HR-MS $[M+H]^+$ calcd for $C_{21}H_{25}N_4O_4S_1$ 429.1590, found 429.1588.

(4-(6-(3,4-Dimethoxyphenyl)isothiazolo[4,3-*b*]pyridin-3-yl)piperazin-1-yl)(phenyl)methanone (8q)

This compound was prepared from (4-(6-bromoisothiazolo[4,3-*b*]pyridin-3-yl)piperazin-1-yl)(phenyl)methanone (61 mg, 0.15 mmol) using 3,4-dimethoxyphenylboronic acid (41 mg, 0.225 mmol), 2M K_2CO_3 (150 µL), $Pd(PPh_3)_4$ (17 mg, 0.015 mmol) in DME (3 mL) by MW irradiation for 30 minutes. The crude residue was purified using a mixture of cyclohexane/ethyl acetate in a ratio of 3:2, affording the title compound in 23 % yield (16 mg, 0.034 mmol).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 3.95 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 4.01 (m, 8H, $4CH_2$), 6.99 (d, *J* = 8.31 Hz, 1H, arom H), 7.17 (d, *J* = 1.86 Hz, 1H, arom H), 7.25 (dd, *J* = 1.86 Hz, *J* = 8.31 Hz, 1H, arom H), 7.47 (m, 5H, arom H), 7.88 (d, *J* = 1.47 Hz, 1H, arom H), 8.65 (d, *J* = 1.52 Hz, 1 arom H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 50.05 ($4xCH_2$), 55.71 ($2xOCH_3$), 110.08 (CH), 111.39 (CH), 119.61 (CH), 124.47 (CH), 126.82 (2xCH), 128.37 (2xCH), 129.88 (C_q), 134.71 (C_q), 135.44 (C_q), 144.56 (CH), 149.23 (C_q), 149.35 (C_q), 155.94 (C_q), 164.80 (C_q), 170.38 (C_q), 172.35 (C_q) ppm.

HR-MS $[M+H]^+$ calcd for $C_{25}H_{25}N_4O_3S$ 461.1641, found 461.1637.

6-(3,4-dimethoxyphenyl)-3-(4-methyl-1,4-diazepan-1-yl)isothiazolo[4,3-*b*]pyridine (8r)

This compound was prepared from 6-bromo-3-(4-methyl-1,4-diazepan-1-yl)isothiazolo[4,3-*b*]pyridine (49 mg, 0.15 mmol) using 3,4-dimethoxyphenylboronic acid (41 mg, 0.225 mmol), 2M K_2CO_3 (150 µL), $Pd(PPh_3)_4$ (17 mg, 0.015 mmol) in DME (2 mL) by MW irradiation for 30 minutes. The crude product was purified using a mixture of DCM/MeOH in a ratio of 95:5, affording the title compound in 26 % yield (15 mg, 0.039 mmol).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.21 (m, 2H, CH_2), 2.45 (s, 3H, CH_3), 2.71 (m, 2H, CH_2), 2.89 (m, 2H, CH_2), 2.90 (m, 2H, CH_2), 3.96 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 4.43 (m, 2H, CH_2), 6.99 (d, J = 8.37 Hz, 1H, arom H), 7.18 (d, *J* = 2.01 Hz, 1H, arom H), 7.24 (dd, *J* = 8.37 Hz, *J* = 2.01 Hz, 1H, arom H), 7.83 (d, *J* = 2.01 Hz, 1H, arom H), 8.57 (d, *J* = 2.01 Hz, 1 arom H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 26.89 (CH_2), 46.20 (CH_2), 50.79 (CH_2), 52.86 (CH_2), 55.67 (OCH_3), 55.69 (OCH_3), 57.30 (CH_2), 57.68 (CH_2), 110.10 (CH), 111.37 (CH), 119.48 (CH), 124.16 (CH), 130.27 (C_q), 132.55 (C_q), 135.00 (C_q), 142.71 (CH), 149.14 ($2xC_q$), 155.82 (C_q), 171.55 (C_q) ppm.

HR-MS $[M+H]^+$ calcd for $C_{20}H_{25}N_4O_2S_1$ 385.1692, found 385.1692.

6-(3,4-Dimethoxyphenyl)-3-(4-methylpiperidin-1-yl)isothiazolo[4,3-*b*]pyridine (8s)

This compound was prepared from 6-bromo-3-(4-methylpiperidin-1-yl)isothiazolo[4,3-*b*]pyridine (49 mg, 0.15 mmol) using 3,4-dimethoxyphenylboronic acid (41 mg, 0.225 mmol),

2M K_2CO_3 (150 µL) and $Pd(PPh_3)_4$ (17 mg, 0.015 mmol) in DME (2 mL) by MW irradiation for 30 minutes. The crude product was purified using a mixture of DCM/MeOH in a ratio of 95:5, affording the title compound in 43 % yield (24 mg, 0.065 mmol).

^{1}H-NMR (300 MHz, CD_3OD): δ = 1.02 (d, *J* = 6.39 Hz, 3H, CH_3), 1.50 (m, 2H, CH_2), 1.73 (m, 1H, CH), 1.75 (m, 2H, CH_2), 3.22 (m, 2H, CH_2), 3.95 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 4.67 (m, 2H, CH_2), 6.99 (d, *J* = 8.34 Hz, 1H, arom H), 7.18 (d, *J* = 2.04 Hz, 1H, arom H), 7.23 (dd, *J* = 8.37 Hz, *J* = 2.04 Hz, 1H, arom H), 7.84 (d, *J* = 2.07 Hz, 1H, arom H), 8.31 (d, *J* = 2.01 Hz, 1 arom H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 21.42 (CH_3), 30.13 (CH), 33.10 (2xCH_2), 50.88 (2xCH_2), 55.67 (OCH_3), 55.69 (OCH_3), 110.05 (CH), 111.35 (CH), 119.50 (CH), 124.20 (CH), 130.08 (C_q), 133.31 (C_q), 135.09 (C_q), 143.21 (CH), 149.14 (C_q), 149.16 (C_q), 155.81 (C_q), 173.01 (C_q) ppm.

HR-MS $[M+H]^+$ calcd for $C_{19}H_{23}N_4O_2S_1$ 371.1536 , found 371.1528.

6-(3,4-Dimethoxyphenyl)-3-(4-methylpiperidin-1-yl)isothiazolo[4,3-*b*]pyridine (8t)

This compound was prepared from 6-bromo-3-(4-methylpiperidin-1-yl)isothiazolo[4,3-b]pyridine (49 mg, 0.15 mmol) using 3,4-dimethoxyphenylboronic acid (41 mg, 0.225 mmol), 2M K_2CO_3 (150 µL), $Pd(PPh_3)_4$ (17 mg, 0.015 mmol) in DME (2 mL) by MW irradiation for 30 minutes. The crude product was purified using a mixture of DCM/MeOH in a ratio of 95:5, affording the title compound in 43 % yield (24 mg, 0.065 mmol).

^{1}H-NMR (300 MHz, CD_3OD): δ = 1.02 (d, *J* = 6.39 Hz, 3H, CH_3), 1.50 (m, 2H, CH_2), 1.73 (m, 1H, CH), 1.75 (m, 2H, CH_2), 3.22 (m, 2H, CH_2), 3.95 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 4.67 (m, 2H, CH_2), 6.99 (d, *J* = 8.34 Hz, 1H, arom H), 7.18 (d, *J* = 2.04 Hz, 1H, arom H), 7.23 (dd, *J* = 8.37 Hz, *J* = 2.04 Hz, 1H, arom H), 7.84 (d, *J* = 2.07 Hz, 1H, arom H), 8.31 (d, *J* = 2.01 Hz, 1 arom H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 21.42 (CH_3), 30.13 (CH), 33.10 (2xCH_2), 50.88 (2xCH_2), 55.67 (OCH_3), 55.69 (OCH_3), 110.05 (CH), 111.35 (CH), 119.50 (CH), 124.20 (CH), 130.08 (C_q), 133.31 (C_q), 135.09 (C_q), 143.21 (CH), 149.14 (C_q), 149.16 (C_q), 155.81 (C_q), 173.01 (C_q) ppm.

Synthesis of 3-alkoxy-6-bromo-isothiazolo[4,3-*b*]pyridines (7i, 7j)

General procedure

To a solution of 3,6-dibromo-isothiazolo[4,3-*b*]pyridine (0.68 mmol) in the appropriate alcohol (10 ml) was added carefully at 0°C the appropriate sodium alcoxide (3 eq). The resulting reaction mixture was stirred overnight at room temperature and then heated at 55°C for 8 hours. The reaction was cooled down to room temperature, neutralized with a 5% HCl solution and evaporated *in vacuo*. The residue was divided between ethyl acetate (250 ml)

and water (150 ml). The organic phase was dried and evaporated. The crude residue was purified by silica gel flash chromatography, the mobile phase being a mixture of cyclohexane and ethylacetate (in a ratio gradually ranging from 5:1 to 4:1), yielding the pure title compound.

The following compounds were made according to this procedure :

3-Ethoxy-6-bromo-isothiazolo[4,3-*b*]pyridine (7i)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.70 (t, *J* = 7.02 Hz, 3H, CH_3), 4.54 (q, *J* = 7.02 Hz, 2H, CH_2), 8.09 (d, *J* = 1.98 Hz, 1 H, arom H), 8.56 (d, *J* = 2.01 Hz, 1 H, arom H) ppm.

3-Isopropoxy-6-bromo-isothiazolo[4,3-*b*]pyridine (7j)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.63 (d, *J* = 6.09 Hz, 6H, 2 x CH_3), 4.88 (sept, *J* = 6.09 Hz, 1 H, CH), 8.08 (d, *J* = 2.01 Hz, 1 H, arom H), 8.54 (d, *J* = 2.01 Hz, 1 H, arom H) ppm.

Synthesis of 3-alkoxy-6-(3-thienyl)isothiazolo[4,3-*b*]pyridines (8i, 8j)

General procedure

These compounds were synthesized according to the general procedure for the synthesis of compounds **8l-t**, using 3-thiophene boronic acid instead of 3,4-dimethoxyphenylboronic acid.

The following compounds were made according to this procedure :

3-Ethoxy-6-(3-thienyl)-isothiazolo[4,3-*b*]pyridine (8i)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.67 (t, *J* = 7.02 Hz, 3H, CH_3), 4.51 (q, *J* = 7.02 Hz, 2H, CH_2), 7.45 (d, *J* = 2.01 Hz, 2 H, arom H), 7.65 (t, 1 H, arom H), 7.95 (d, *J* = 1.89 Hz, 1 H, arom H), 8.85 (d, *J* = 1.89 Hz, 1 H, arom H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.49 (CH_3), 72.51 (OCH_2), 122.81 (CH), 124.56 (CH), 126.22 (CH), 127.36(CH), 131.59 (C_q), 138.48 (C_q), 148.11 (C_q), 145.92 (C_q), 181.96 (C_q).

HR-MS $[M+H]^+$ calcd for $C_{12}H_{11}N_2OS_2$ 263.03072, found 263.0312.

3-Isopropoxy-6-(3-thienyl)-isothiazolo[4,3-*b*]pyridine (8j)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.60 (d, *J* = 6.09 Hz, 6H, 2 x CH_3), 4.86 (sept, *J* = 6.09 Hz, 1 H, CH), 7.45 (d, *J* = 2.01 Hz, 2 H, arom H), 7.65 (t, *J* = 2.01 Hz, 1 H, arom H), 7.95 (d, *J* = 1.83 Hz, 1 H, arom H), 8.85 (d, *J* = 1.86 Hz, 1 H, arom H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 22.08 (CH_3), 81.32 (OCH), 122.80 (CH), 124.61 (CH), 126.27 (CH), 127.38 (CH), 131.23 (C_q), 134.39 (C_q), 138.73 (C_q), 148.01 (CH), 155.12 (C_q), 181.45 (C_q).

HR-MS $[M+H]^+$ calcd for $C_{13}H_{13}N_2OS_2$ 277.04637, found 277.0467.

6-(3,4-Dimethoxyphenyl)-3-isopropoxyisothiazolo[4,3-*b*]pyridine (8b)

To a solution of propan-2-ol (81 mg, 1.76 mmol) in toluene (10 ml) was added NaH (16 mg, 0.682 mmol) and 3,6-dibromo-isothiazolo[4,3-*b*]pyridine (100 mg, 0.341 mmol) at room temperature. The mixture was stirred under MW irradiation at 50°C for 60 minutes. Then, the solvent was removed and the crude residue was purified by silica gel flash chromatography, affording pure **7b**. The pure product was dissolved in 1,4-dioxane (2 mL), then 3,4-dimethoxyphenylboronic acid (62 mg, 0.341 mmol), 2M K_2CO_3 (300 µL) and $Pd(PPh_3)_4$ (20 mg, 0.017 mmol) were added. The mixture was stirred under MW irradiation at 80°C for 60 minutes. Product was purified using a mixture of cyclohexane/ethyl acetate in a ratio of 1:5, affording the title compound in 30 % yield (33 mg, 0.10 mmol).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.63 (d, *J* = 6.3, 6H, $2CH_3$), 3.96 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 4.86-4.95 (m, 1H, OCH), 6.99 (d, *J* = 8.4 Hz, 1H, arom H), 7.17-7.28 (m, 2H, arom H), 7.92 (d, *J* = 2.1 Hz, 1H, arom H), 8.83 (d, *J* = 2.1 Hz, 1H, arom H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 22.05 (CH_3), 56.15 (OCH_3), 56.17 (OCH_3), 81.23 (OCH), 110.60 (CH), 111.83 (CH), 120.20 (C_q), 125.13 (C_q), 130.15 (C_q), 133.96 (C_q), 136.60 (C_q), 148.50 (CH), 149.69 (C_q), 149.86 (C_q), 155.02 (C_q),181.23 (C_q).

HR-MS $[M+H]^+$ calcd for $C_{17}H_{18}N_2O_3S$ 331.11108, found 331.1107.

3-sec-Butoxy-6-(3,4-dimethoxyphenyl)isothiazolo[4,3-*b*]pyridine (8c)

To a solution of butan-2-ol (130 mg, 1.76 mmol) in toluene (10 ml) was added NaH (16 mg, 0.682 mmol) and 3,6-dibromo-isothiazolo[4,3-*b*]pyridine (100 mg, 0.341 mmol) at room temperature. The mixture was stirred under MW irradiation at 50°C for 60 minutes. The solvent was removed and the crude residue was purified by silica gel flash chromatography. The pure product was dissolved in 1,4-dioxane (2 mL), and 3,4-dimethoxyphenylboronic acid (62 mg, 0.341 mmol), 2M K_2CO_3 (300 µL) and $Pd(PPh_3)_4$ (20 mg, 0.017 mmol) were added. The mixture was stirred under MW irradiation at 80°C for 60 minutes. The crude product was purified using a mixture of cyclohexane/ethyl acetate in a ratio of 1:5, affording the title compound in 33 % yield (41 mg, 0.11 mmol).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.07 (t, *J* = 7.5, 3H, CH_3), 1.56 (d, *J* = 6.3, 3H, CH_3), 1.80-2.15 (m, 2H, CH_2), 3.93 (s, 3H,OCH_3), 3.96 (s, 3H, OCH_3), 4.65 (t, *J* = 6.2, 1H, OCH), 6.86 (d, *J* = 8.7 Hz, 1H, arom H), 6.97 (s, 1H, arom H), 7.21-7.28 (m, 1H, arom H), 7.92 (d, *J* = 1.8 Hz, 1H, arom H), 8.81 (d, *J* = 1.8 Hz, 1H, arom H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 9.14 (CH_3), 19.21(CH_2), 29.15 (CH_3), 56.01 (OCH_3), 56.03 (OCH_3), 86.63 (OCH), 110.40 (CH), 111.70 (CH), 120.09 (CH), 125.02 (CH), 129.85 (C_q), 133.26 (C_q), 136.62 (C_q), 148.30 (CH), 149.54 (C_q), 149.74 (C_q), 152.28 (C_q), 154.91(C_q), 181.65 (C_q) ppm.

HR-MS $[M+H]^+$ calcd for $C_{18}H_{21}N_2O_3S$ 345.12673, found 345.1271.

3-Butoxy-6-(3,4-dimethoxyphenyl)isothiazolo[4,3-*b*]pyridine (8d)

To a solution of butan-1-ol (130 mg, 1.76 mmol) in toluene (10 ml) was added NaH (16 mg, 0.682 mmol) and 3,6-dibromo-isothiazolo[4,3-*b*]pyridine (100 mg, 0.341 mmol) at room temperature. The mixture was stirred under MW irradiation at 50°C for 60 minutes. The solvent was removed and the crude residue was purified by silica gel flash chromatography. The pure product was dissolved in 1,4-dioxane (2 mL), and then 3,4-dimethoxyphenylboronic acid (62 mg, 0.341 mmol), 2M K_2CO_3 (300 µL) and $Pd(PPh_3)_4$ (20 mg, 0.017 mmol) were added. The mixture was stirred under MW irradiation 80°C for 60 minutes. The crude product was purified using a mixture of cyclohexane/ethyl acetate in a ratio of 1:5, affording the title compound in 23 % yield (27 mg, 0.078 mmol).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.03 (t, *J* = 7.3, 6H, CH_3), 1.58-1.68 (m, 2H, CH_2), 1.99-2.08 (m, 2H, CH_2), 3.96 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 4.47 (t, *J* = 6.5, 2H, OCH_2), 6.99 (d, *J* = 8.4 Hz, 1H, arom H), 7.16 (s, 1H, arom H), 7.23-7.28 (m, 1H, arom H), 7.94 (d, *J* = 2.1 Hz, 1H, arom H), 8.84 (d, *J* = 2.1 Hz, 1H, arom H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 13.75 (CH_3), 19.13 (CH_2), 31.21 (CH_2), 56.13 (OCH_3), 56.15 (OCH_3), 76.58 (OCH_2), 110.58 (CH), 111.81 (CH), 120.19 (CH), 125.11 (CH), 130.08 (C_q), 133.29 (C_q), 148.57 (CH), 149.68 (C_q), 149.85 (C_q), 155.01 (C_q), 182.34 (C_q) ppm.

HR-MS $[M+H]^+$ calcd for $C_{18}H_{21}N_2O_3S$345.12673, found 345.1261.

6-(3,4-Dimethoxyphenyl)-3-(pentyloxy)isothiazolo[4,3-*b*]pyridine (8e)

To a solution of pentan-1-ol (154 mg, 1.76 mmol) in toluene (10 ml) was added NaH (16 mg, 0.682 mmol) and 3,6-dibromo-isothiazolo[4,3-*b*]pyridine (100 mg, 0.341 mmol) at room temperature. The mixture was stirred under MW irradiation 50°C for 60 minutes. Then, the solvent was removed and the crude residue was purified by silica gel flash chromatography. The pure product was dissolved in 1,4-dioxane (2 mL), then 3,4-dimethoxyphenylboronic acid (62 mg, 0.341 mmol), 2M K_2CO_3 (300 µL) and $Pd(PPh_3)_4$ (20 mg, 0.017 mmol) were added. The mixture was stirred under MW irradiation 80°C for 60 minutes. The crude product was purified using a mixture of cyclohexane/ethyl acetate in a ratio of 1:5, affording the title compound in 18 % yield (32 mg, 0.092 mmol).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 7.2, 6H, CH_3), 1.43-1.60 (m, 4H, $2CH_2$), 2.02-2.11 (m, 2H, CH_2), 3.96 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 4.47 (t, *J* = 6.5, 2H, OCH_2), 6.99 (d, *J* = 8.1 Hz, 1H, arom H), 7.17 (s, 1H, arom H), 7.24-7.28 (m, 1H, arom H), 7.94 (d, *J* = 1.8 Hz, 1H, arom H), 8.84 (d, *J* = 1.8 Hz, 1H, arom H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 13.98 (CH_3), 22.40 (CH_2), 27.98 (CH_2), 28.95 (CH_2), 56.12 (OCH_3), 56.14 (OCH_3), 76.70 (OCH_2), 110.58 (CH), 111.81 (CH), 120.18 (CH), 125.11 (CH), 130.09 (C_q), 133.30 (C_q), 148.57 (CH), 149.68 (C_q), 149.(C_q), 155.01 (C_q), 182.34 (C_q) ppm.

HR-MS $[M+H]^+$ calcd for $C_{19}H_{22}N_2O_3S$ 359.14238, found 359.1415.

6-(3,4-Dimethoxyphenyl)-3-(isopentyloxy)isothiazolo[4,3-*b*]pyridine (8f)

To a solution of 4-methylpentan-1-ol (179 mg, 1.76 mmol) in toluene (10 ml) was added NaH (16 mg, 0.682 mmol) and 3,6-dibromo-isothiazolo[4,3-*b*]pyridine (100 mg, 0.341 mmol) at room temperature. The mixture was stirred under MW irradiation at 50°C for 60 minutes. Then, the solvent was removed and the crude residue was purified by silica gel flash chromatography. The pure product was dissolved in 1,4-dioxane (2 mL), then 3,4-dimethoxyphenylboronic acid (62 mg, 0.341 mmol), 2M K_2CO_3 (300 µL) and $Pd(PPh_3)_4$ (20 mg, 0.017 mmol) were added. The mixture was stirred under MW irradiation at 80°C for 60 minutes. The crude product was purified using a mixture of cyclohexane/ethyl acetate in a ratio of 1:5, affording the title compound in 27 % yield (32 mg, 0.092 mmol).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.03 (d, *J* = 6.0 Hz, 6H, $2CH_3$), 1.92-2.00 (m, 2H, CH_2), 3.96 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 4.47 (t, *J* = 6.3 Hz, 2H, OCH_2), 7.00 (d, *J* = 8.4 Hz, 1H, arom H), 7.17 (s, 1H, arom H), 7.24-7.28 (m, 1H, arom H), 7.95 (d, *J* = 1.8 Hz, 1H, arom H), 8.85 (d, *J* = 1.8 Hz, 1H, arom H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 22.47 ($2CH_3$), 24.89 (CH), 37.76 (CH_2), 56.10 (OCH_3), 56.12 (OCH_3), 75.29 (OCH_2), 110.54 (CH), 111.79 (CH), 120.17 (CH), 125.08 (CH), 130.044 (C_q), 133.26 (C_q), 136.54 (C_q), 148.55 (CH), 149.65 (C_q), 149.83 (C_q), 154.99 (C_q), 182.29 (C_q) ppm.

HR-MS $[M+H]^+$ calcd for $C_{19}H_{23}N_2O_3S$ 359.14238, found 359.1420.

6-(3,4-Dimethoxyphenyl)-3-(cyclohexyloxy)isothiazolo[4,3-*b*]pyridine (8g)

To a solution of cyclohexanol (176 mg, 1.76 mmol) in 10 ml toluene added NaH (16 mg, 0.682 mmol) and 3,6-dibromoisothiazolo[4,3-*b*]pyridine (100 mg, 0.341 mmol) at room temperature. The mixture was stirred under MW irradiation 50°C for 60 minutes. Then solvent was removed and the crude residue was purified by silica gel flash chromatography. The pure product was dissolved in 1,4-dioxane (2 mL), then added 3,4-dimethoxyphenylboronic acid (62 mg, 0.341 mmol), 2M K_2CO_3 (300 µL), $Pd(PPh_3)_4$ (20 mg, 0.017 mmol).The mixture was stirred under MW irradiation 80°C for 60 minutes. Product was purified using a mixture of cyclohexane/ethyl acetate in a ratio of 1:5, affording the title compound in 20 % yield (12 mg, 0.034 mmol).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.87-0.89 (m, 2H, CH_2), 1.27-2.29 (m, 8H, $4CH_2$), 3.97 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 4.56-4.65 (m, 1H, OCH), 7.01 (d, *J* = 8.4 Hz, 1H, arom H), 7.17 (s, 1H, arom H), 7.25-7.28 (m, 1H, arom H), 7.93 (d, *J* = 2.1 Hz, 1H, arom H), 8.84 (d, *J* = 2.1 Hz, 1H, arom H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 23.85 (CH_2), 25.28 ($2CH_2$), 31.68 ($2CH_2$), 56.21 ($2OCH_3$), 86.46 (OCH), 110.66 (CH), 111.89 (CH), 120.24 (CH), 125.18 (CH), 130.25 (C_q), 136.62 (C_q), 148.51 (CH), 149.75 (C_q), 149.90 (C_q), 155.08 (C_q), 181.59 (C_q).

HR-MS $[M+H]^+$ calcd for $C_{19}H_{23}N_2O_3S$ 371.14238, found 371.1408.

Cells

Huh-7.5 cells were grown in Dulbecco's modified Eagle medium (Life Technologies) supplemented with 10% fetal bovine serum (Omega Scientific), nonessential amino acids (Gibco), 1% L-glutamine (Gibco), and 1% penicillin-streptomycin (Gibco), and maintained in 5% CO_2 at 37°C.

HCVcc generation

pFL-J6/JFH(p7-Rluc2A) was a gift from Dr. C.M. Rice.[2] HCV RNA was generated and delivered into Huh-7.5 cells, as previously described.[3,4] Viral titers were determined by limiting dilution and immunohistochemical staining, as described.[3,4]

HCVcc infection

$6x10^3$ Huh-7.5 cells seeded in 96-well plates were infected in triplicates with HCVcc J6/JFH(p7-Rluc2A) at MOI (multiplicity of infection) of 0.1 in the presence of serial dilutions of the compounds. Culture medium was replaced daily with medium containing serial dilutions of the inhibitors. HCVcc infection was measured by standard luciferase assays at 72 hours postinfection, using a *Renilla* luciferase substrate and Tecan M1000 (Tecan) according to the manufacturers' protocols.

Viability assay

Following treatment with GAK inhibitors, Huh-7.5 cells infected with HCVcc were incubated for 2-4 hours with media supplemented with 10% AlamarBlue reagent (Life Technologies) at 37°C. Fluorescence at 560nm was measured via Tecan M1000 (Tecan) as readout of cellular metabolic activity.

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(2) Murray, C.L.; Jones, C.T.; Tassello, J.; Rice, C.M. *J. Virol*. **2007**, *81*, 10220-10231.

(3) Lindenbach, B.D.; Evans, M.J.; Syder, A.J.; Wölk, B.; Tellinghuisen, T.L.; Liu, C.C.; Maruyama, T.; Hynes, R.O.; Burton, D.R.; McKeating, J.A.; Rice C.M. *Science* **2005**, *309*, 623-626.

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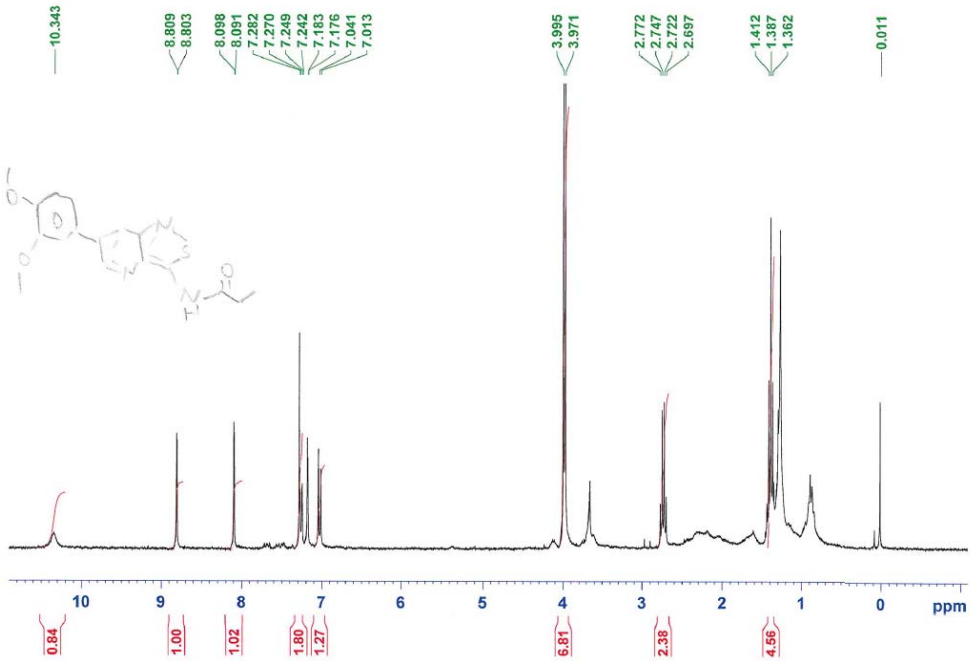
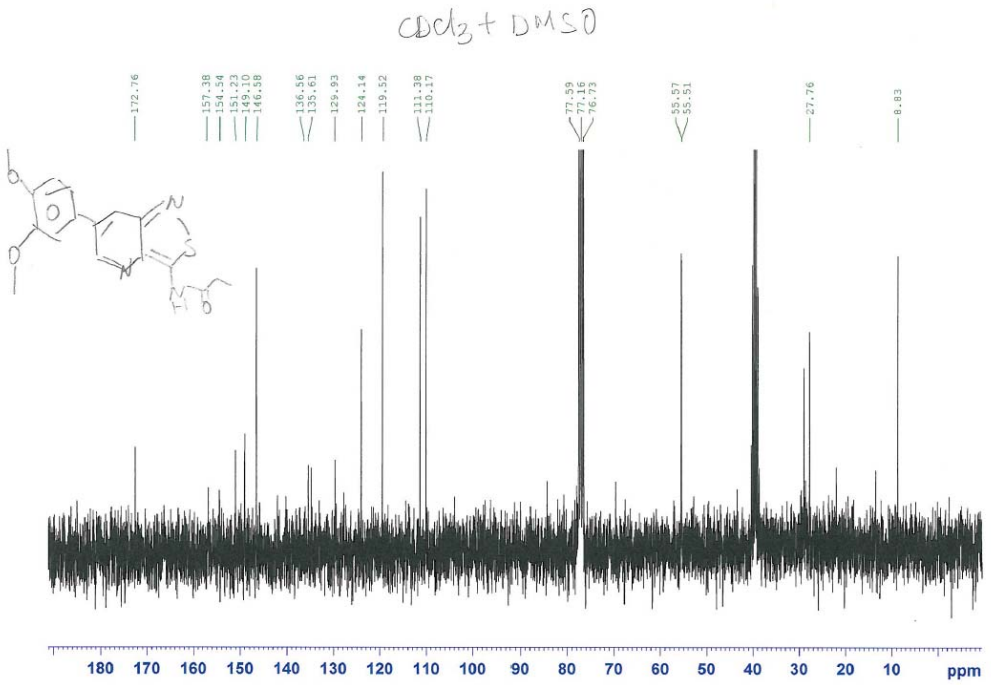
NMR spectra of final compounds

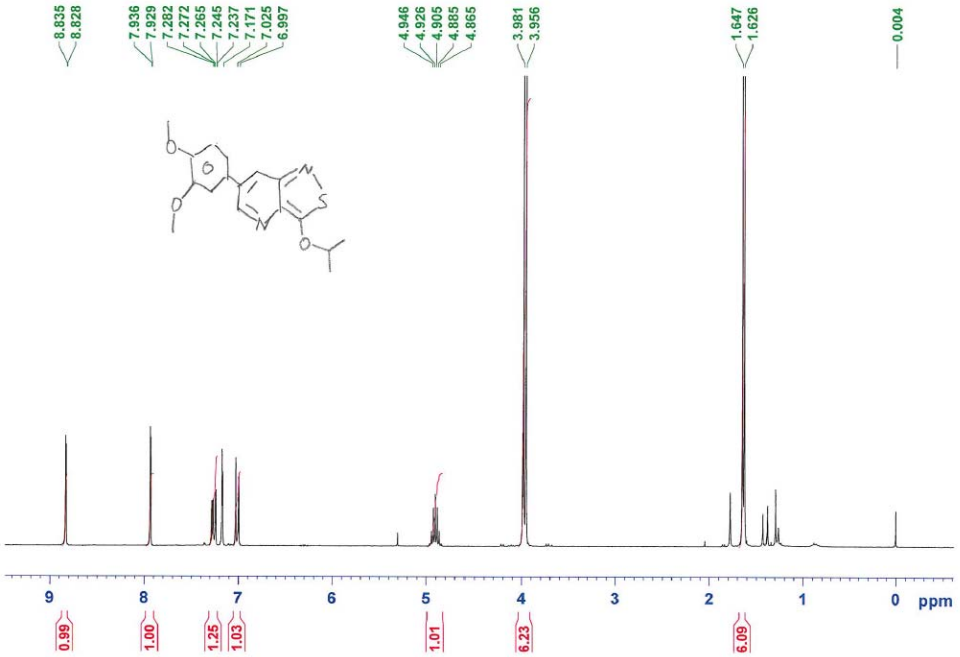
Compound **5b** - ^{1}H NMR spectrum



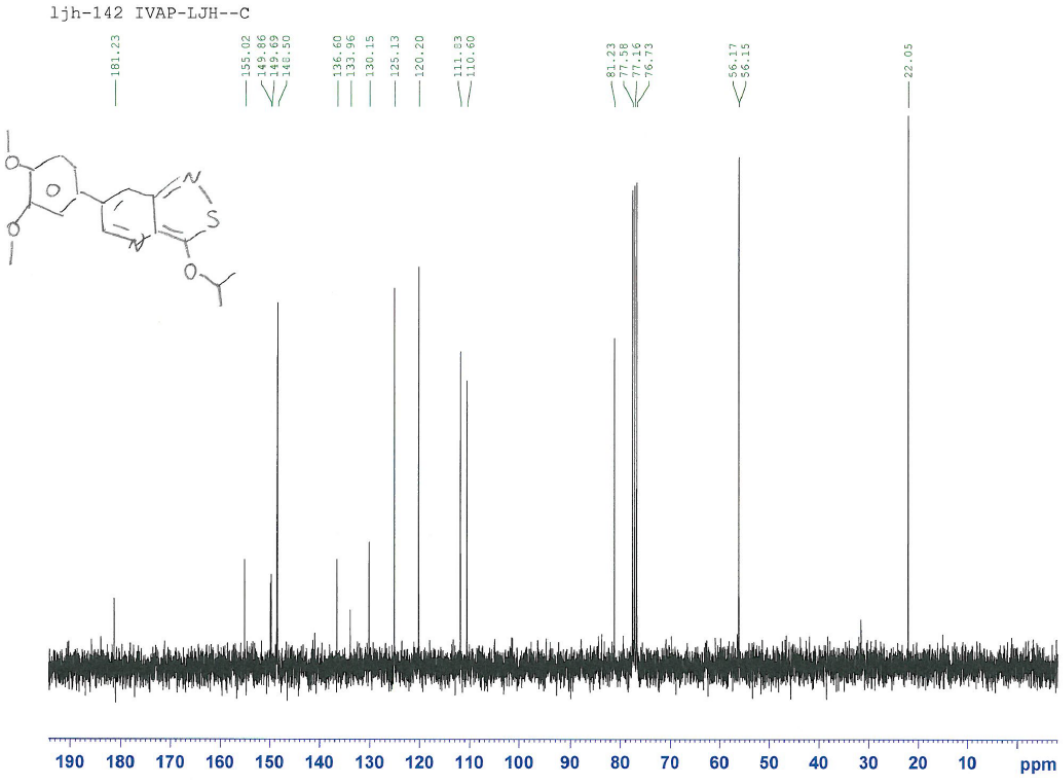
Compound **5b** – ^{13}C NMR spectrum



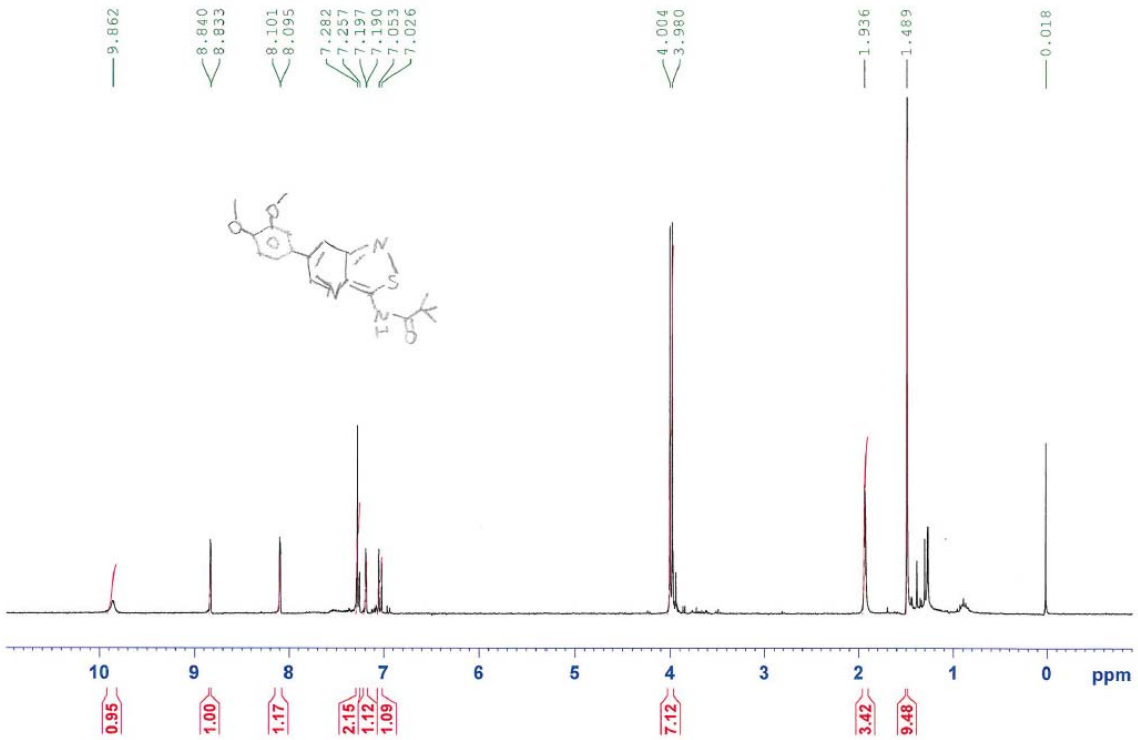
Compound **5c** - ^{1}H NMR spectrum



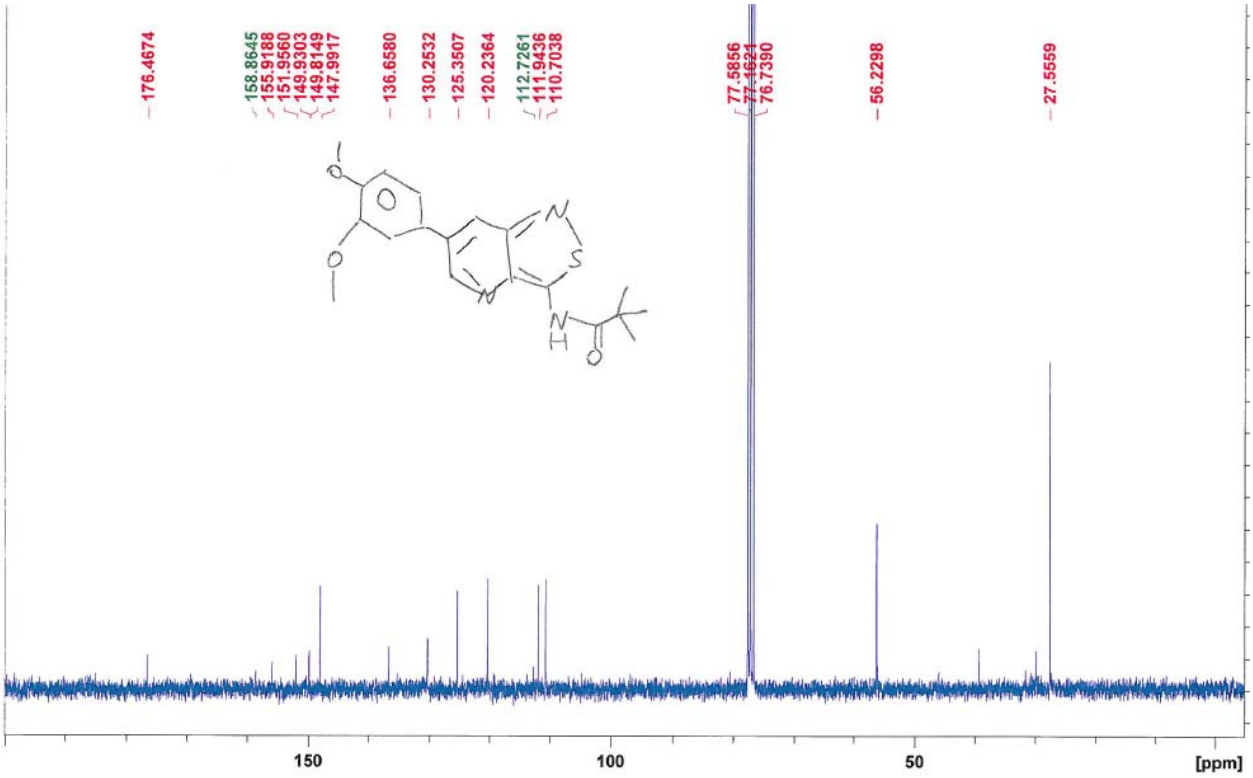
Compound **5c** – ^{13}C NMR spectrum



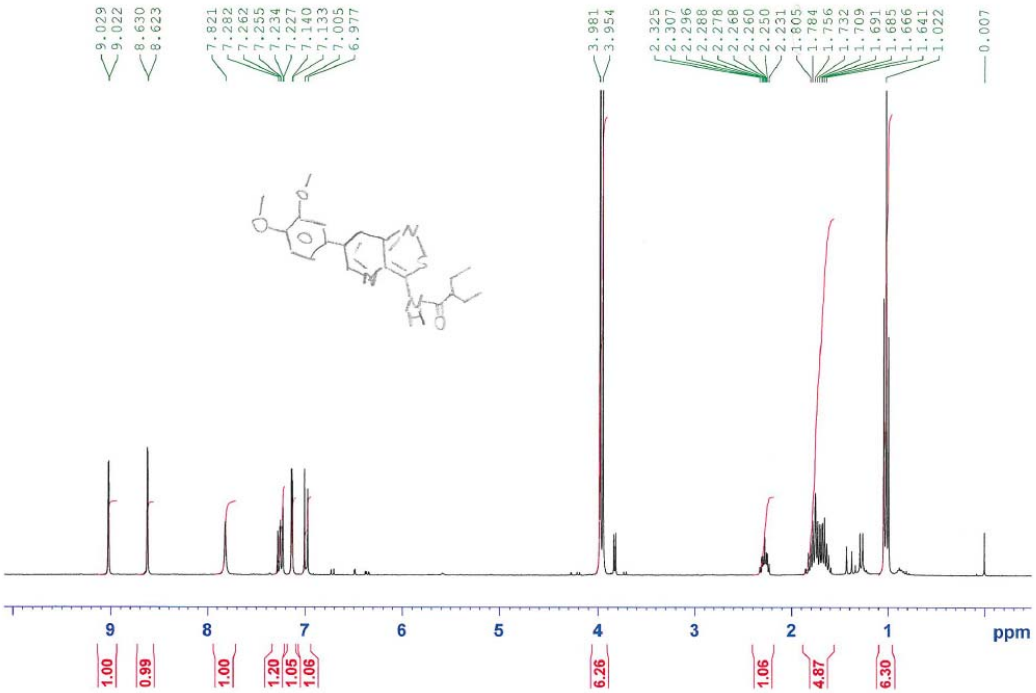
Compound **5d** - ^{1}H NMR spectrum



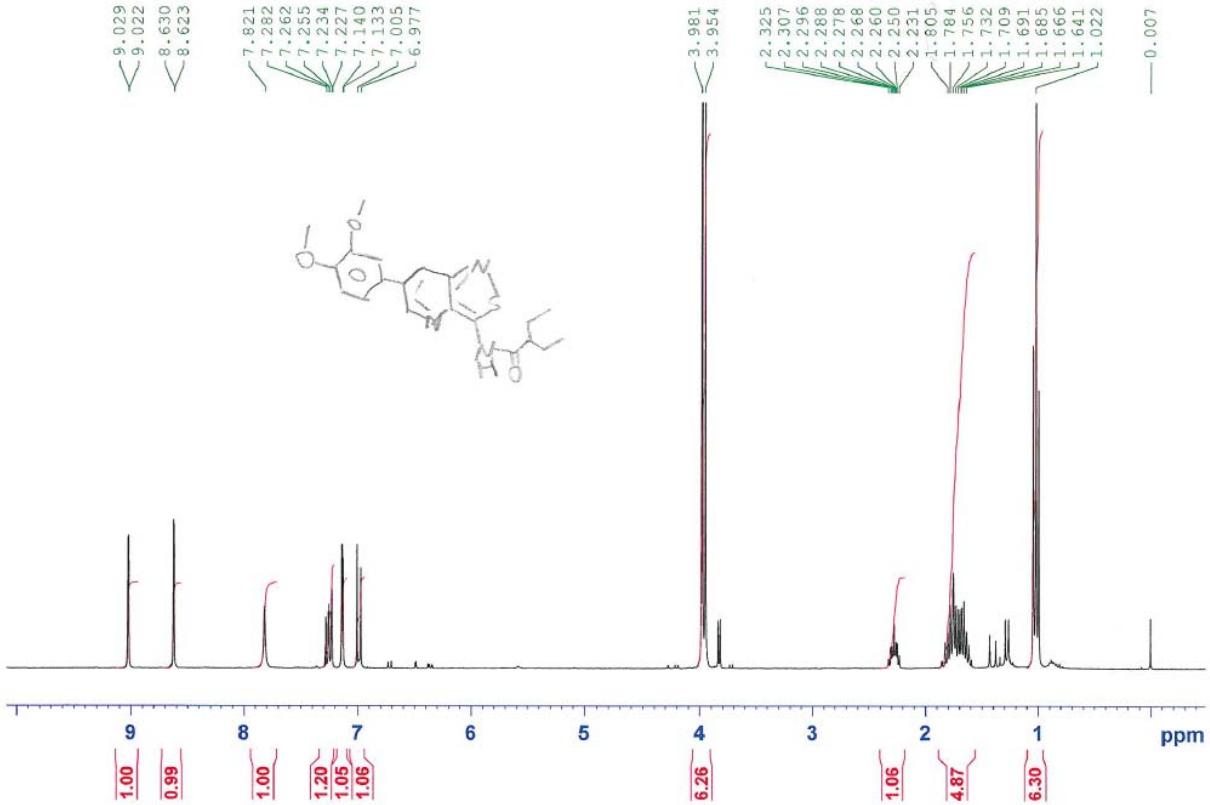
Compound **5d** – ^{13}C NMR spectrum



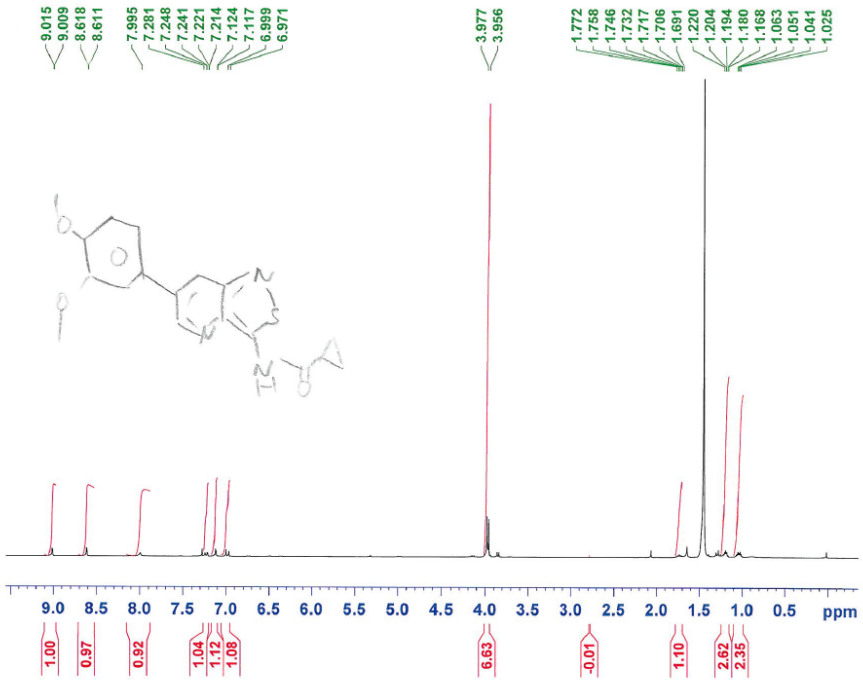
Compound **5e** - ^{1}H NMR spectrum



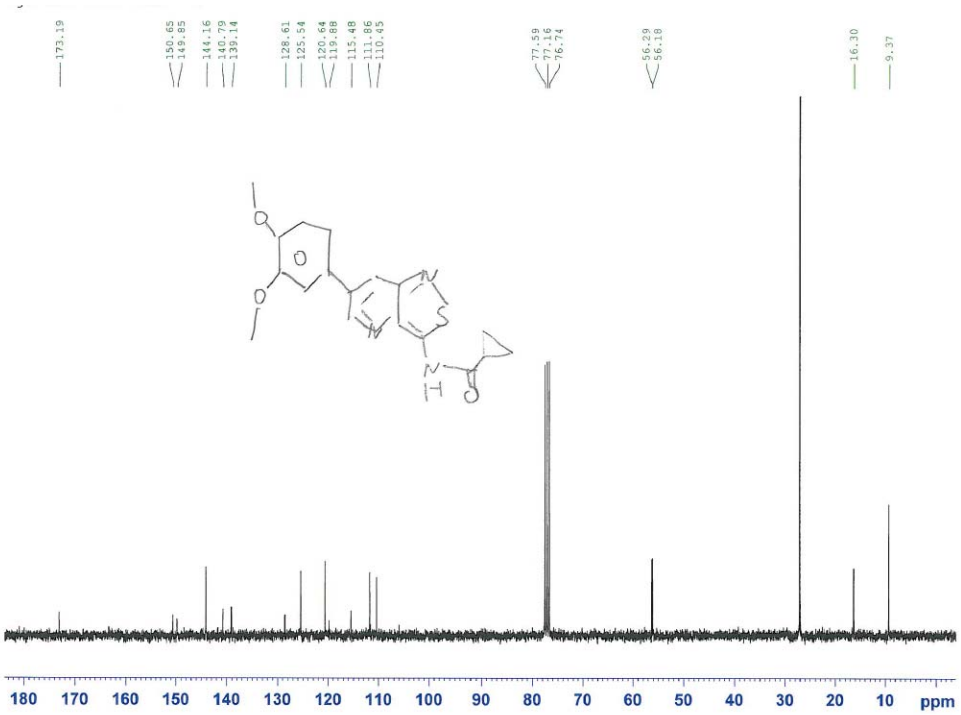
Compound **5e** – ^{13}C NMR spectrum



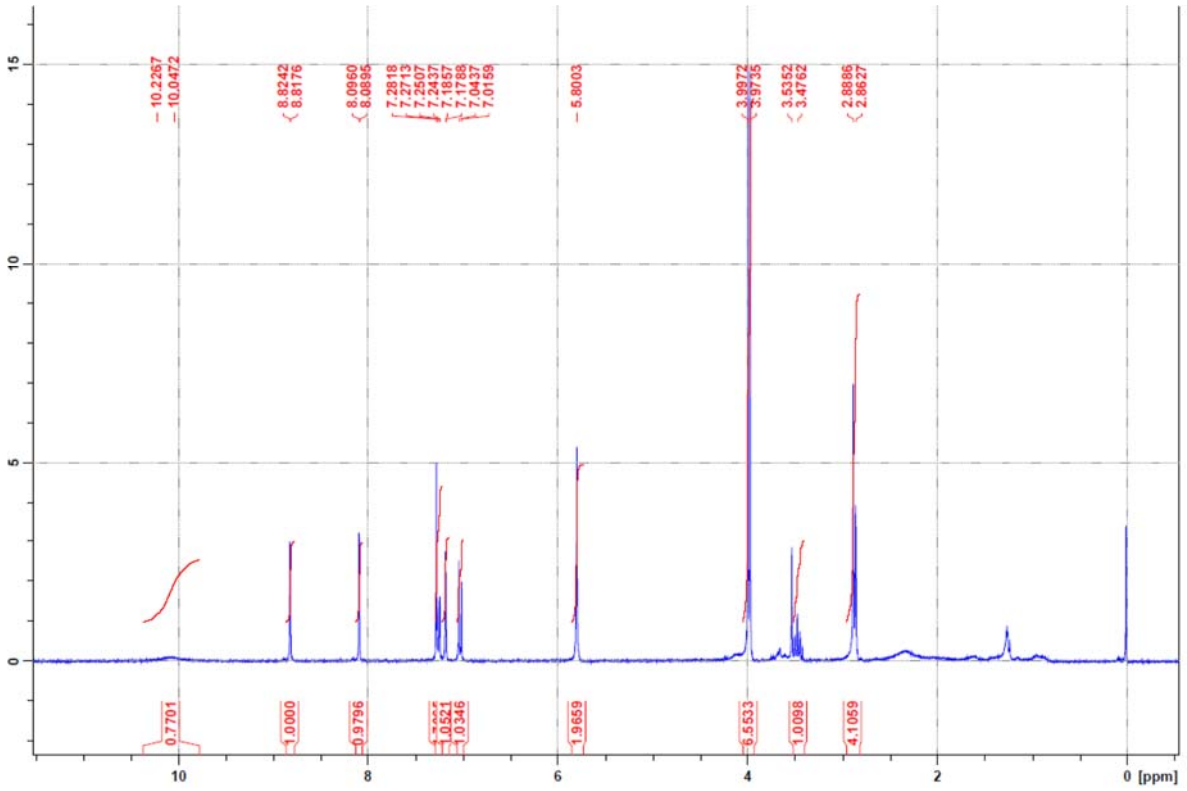
Compound **5f** - ^{1}H NMR spectrum



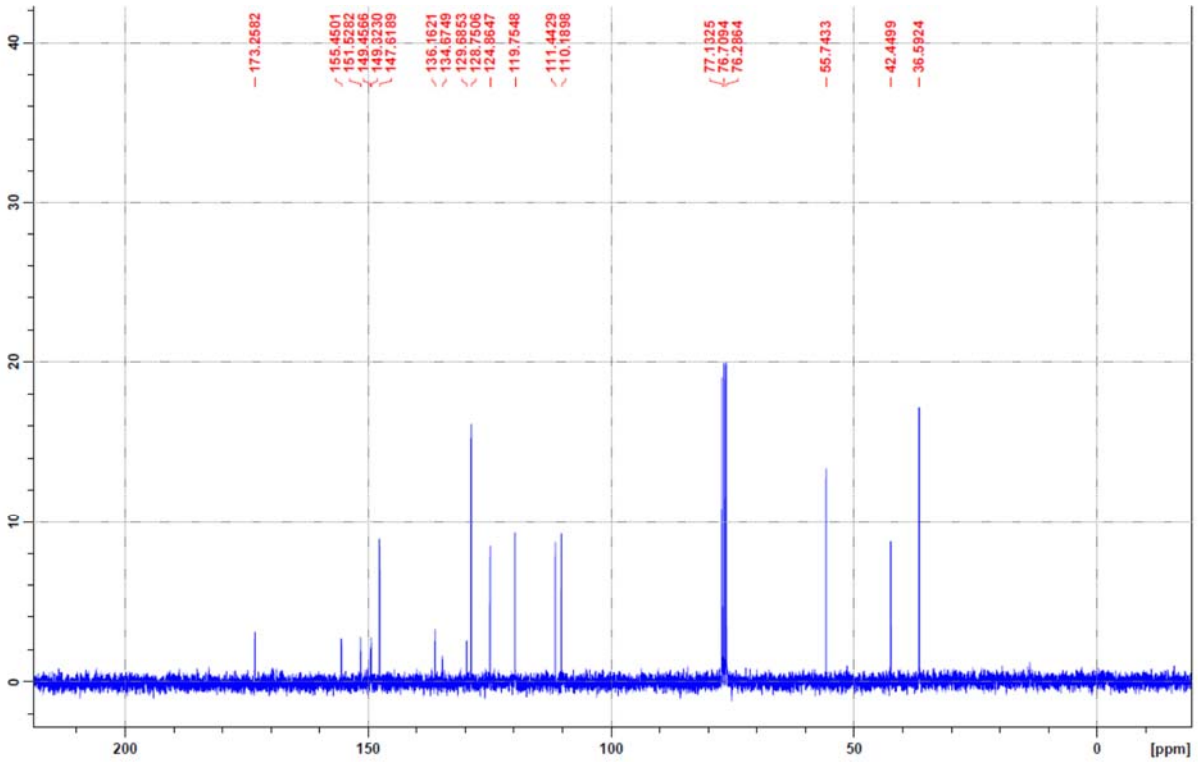
Compound **5f** – ^{13}C NMR spectrum



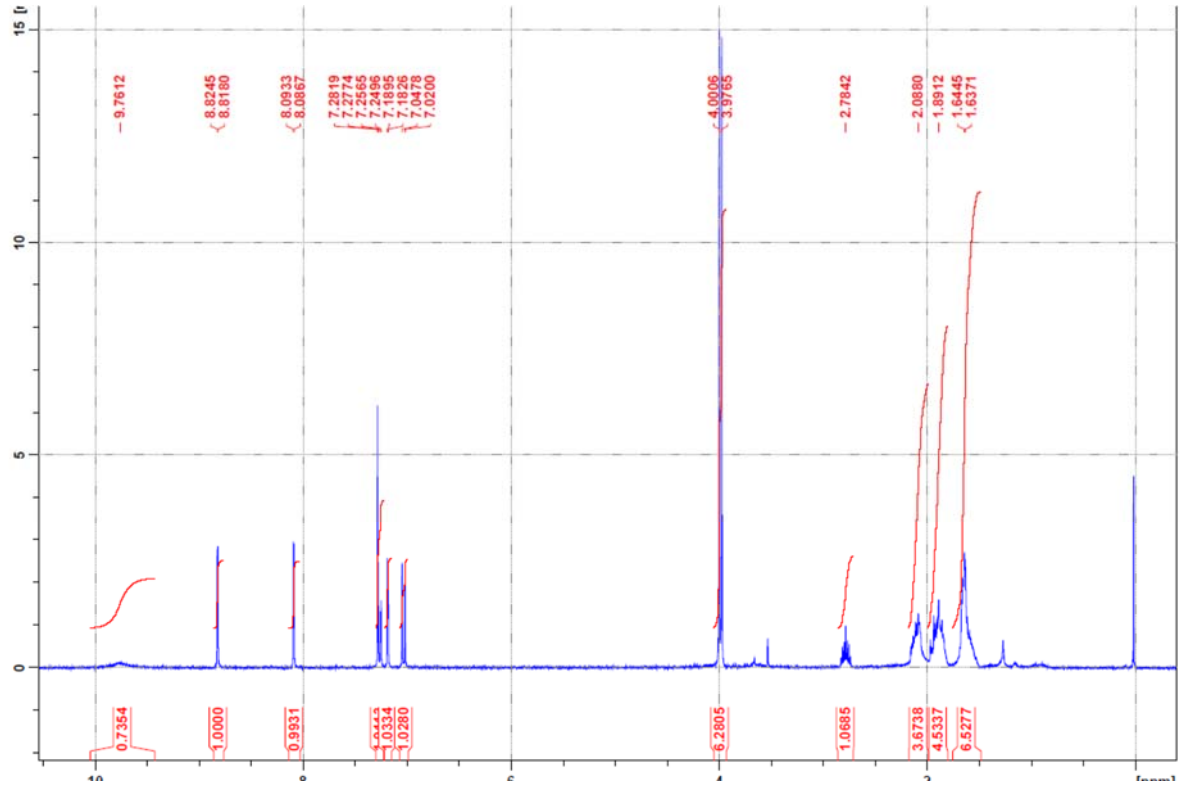
Compound **5g** - ^{1}H NMR spectrum



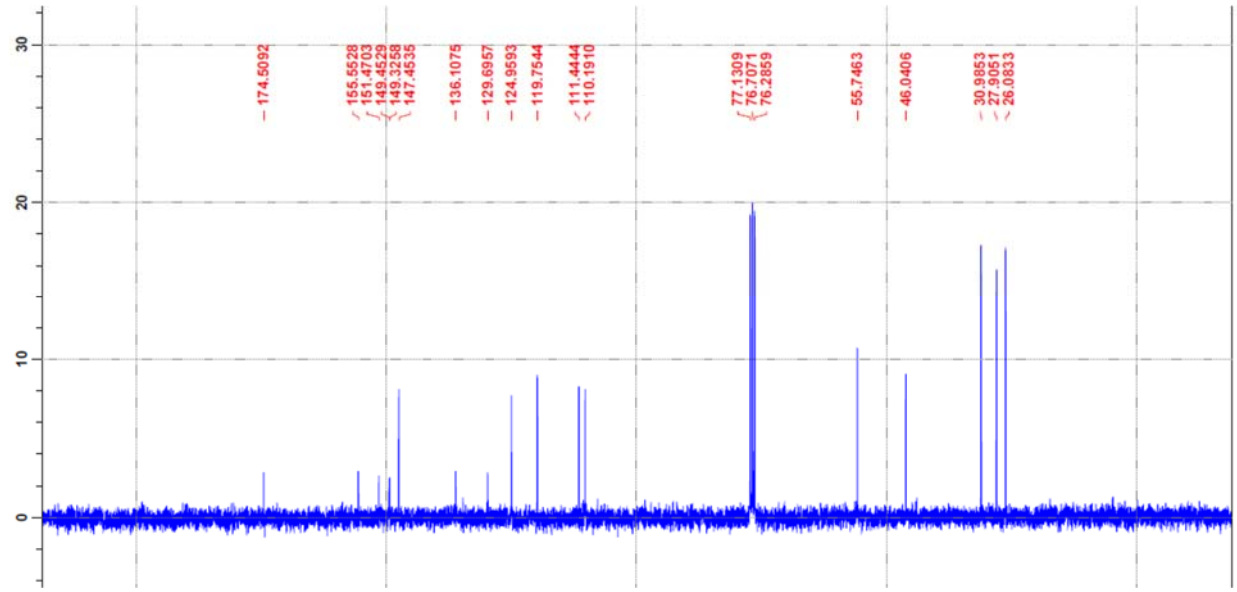
Compound **5g** – ^{13}C NMR spectrum



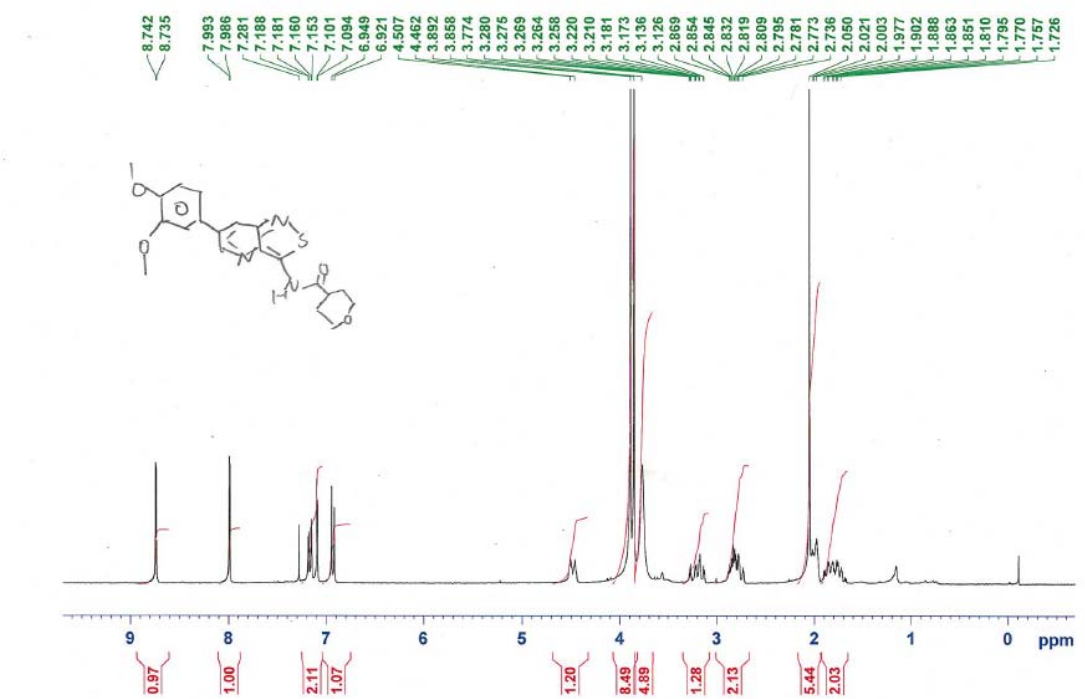
Compound **5h** - ^{1}H NMR spectrum



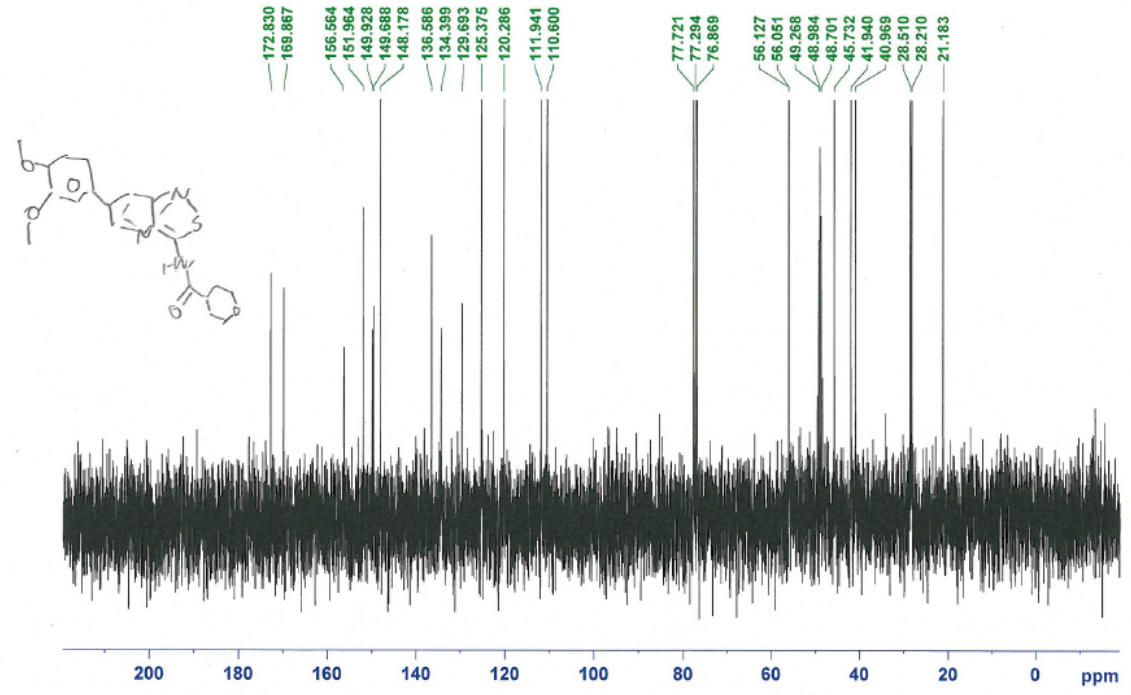
Compound **5h** – ^{13}C NMR spectrum



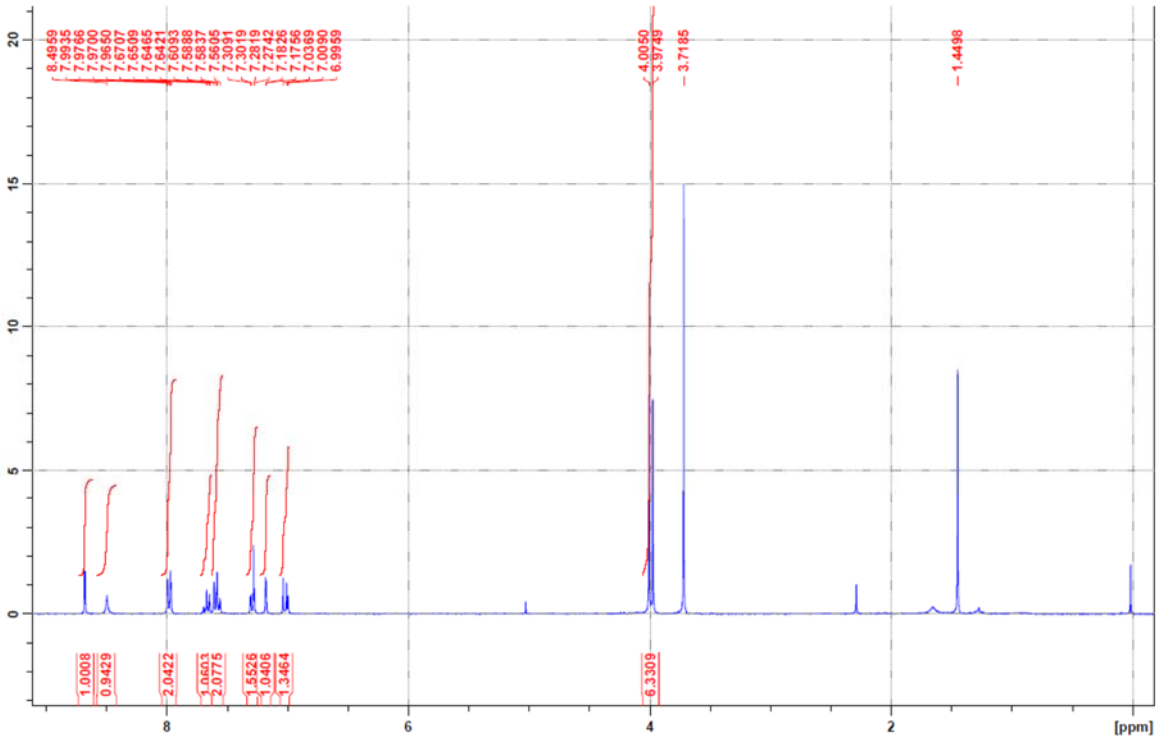
Compound **5i** – ^{1}H NMR spectrum



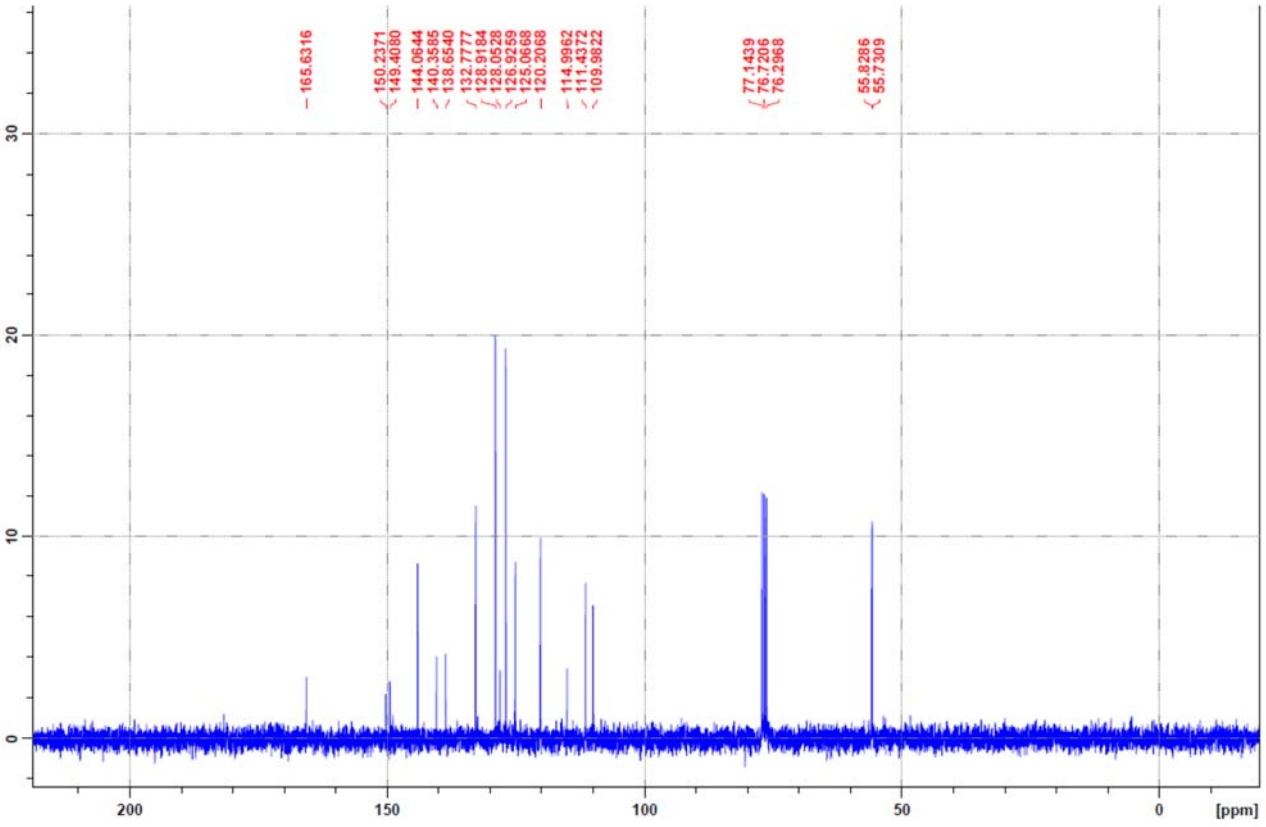
Compound **5i** – ^{13}C NMR spectrum



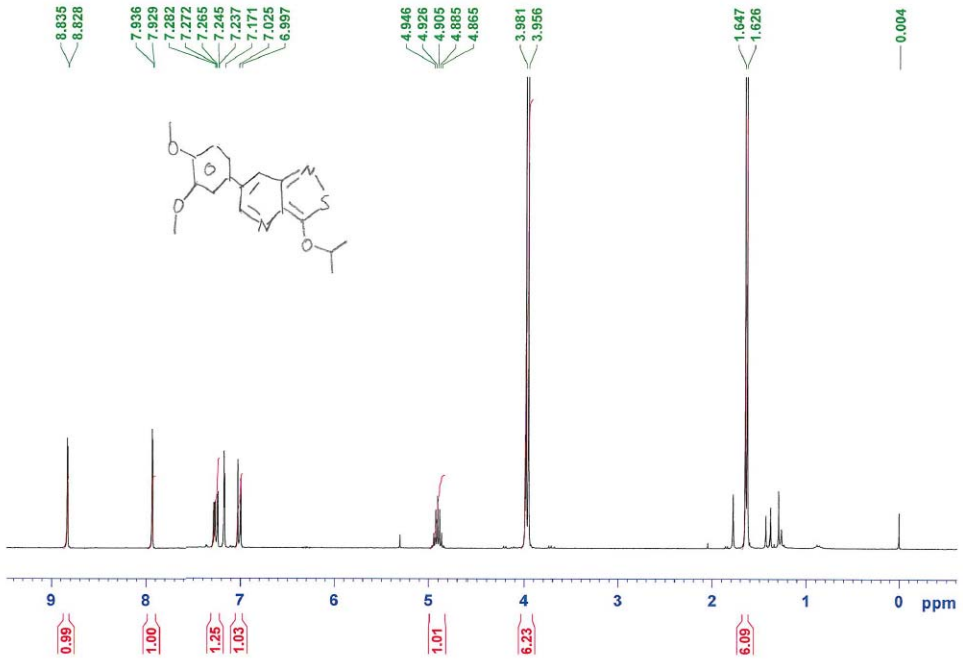
Compound **5j** - ^{1}H NMR spectrum



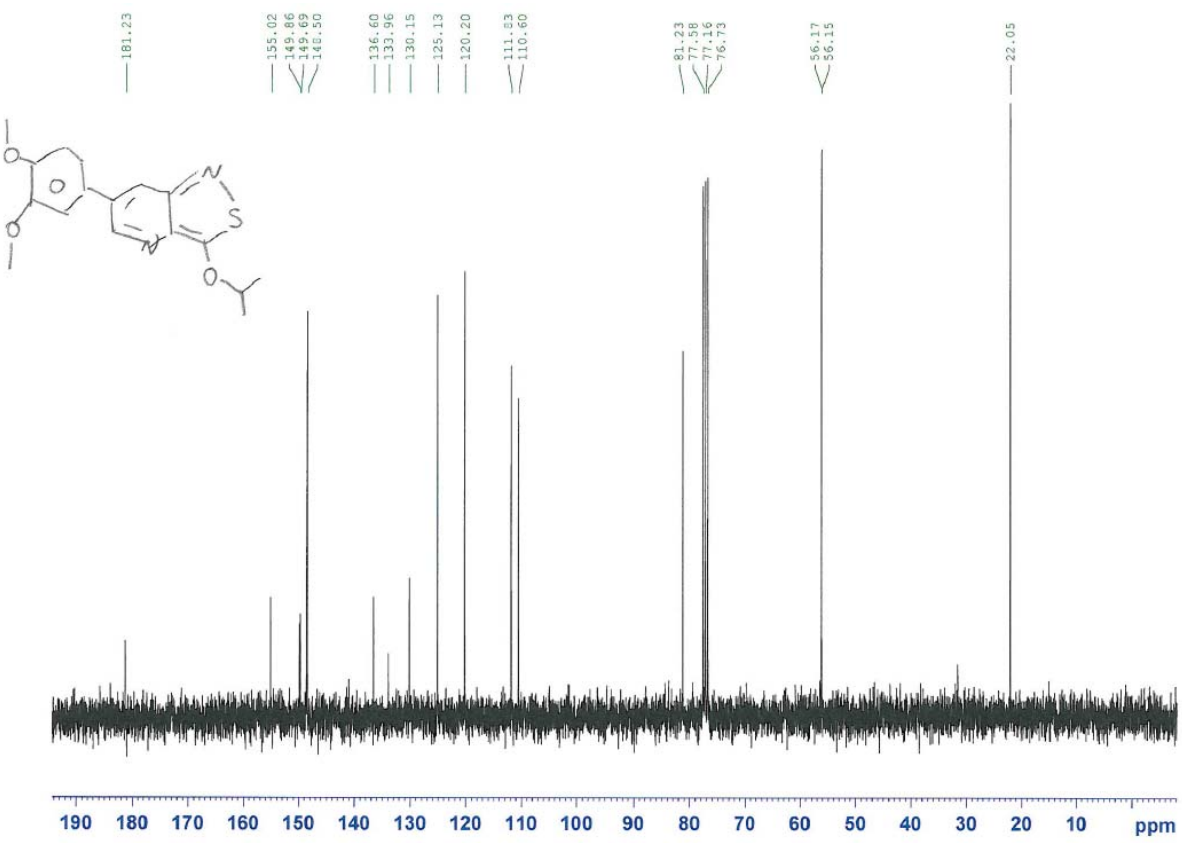
Compound **5j** – ^{13}C NMR spectrum



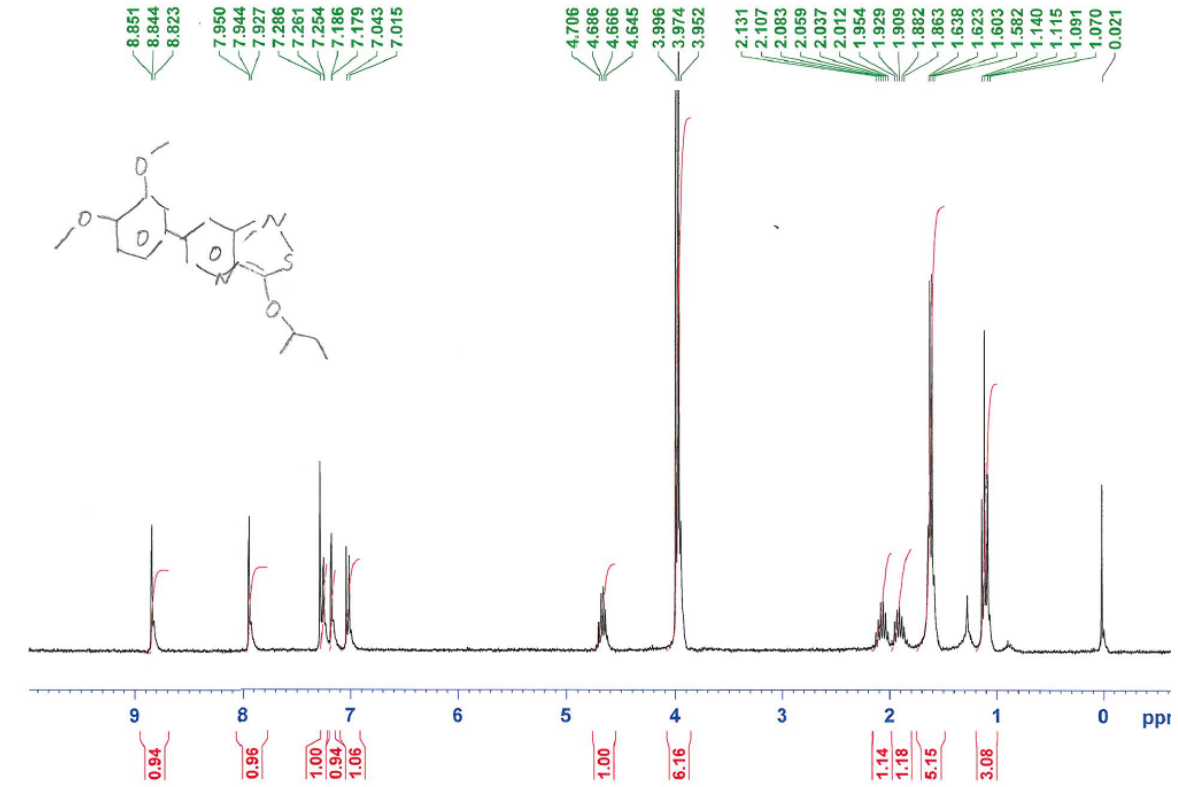
Compound **8b** - ^{1}H NMR spectrum



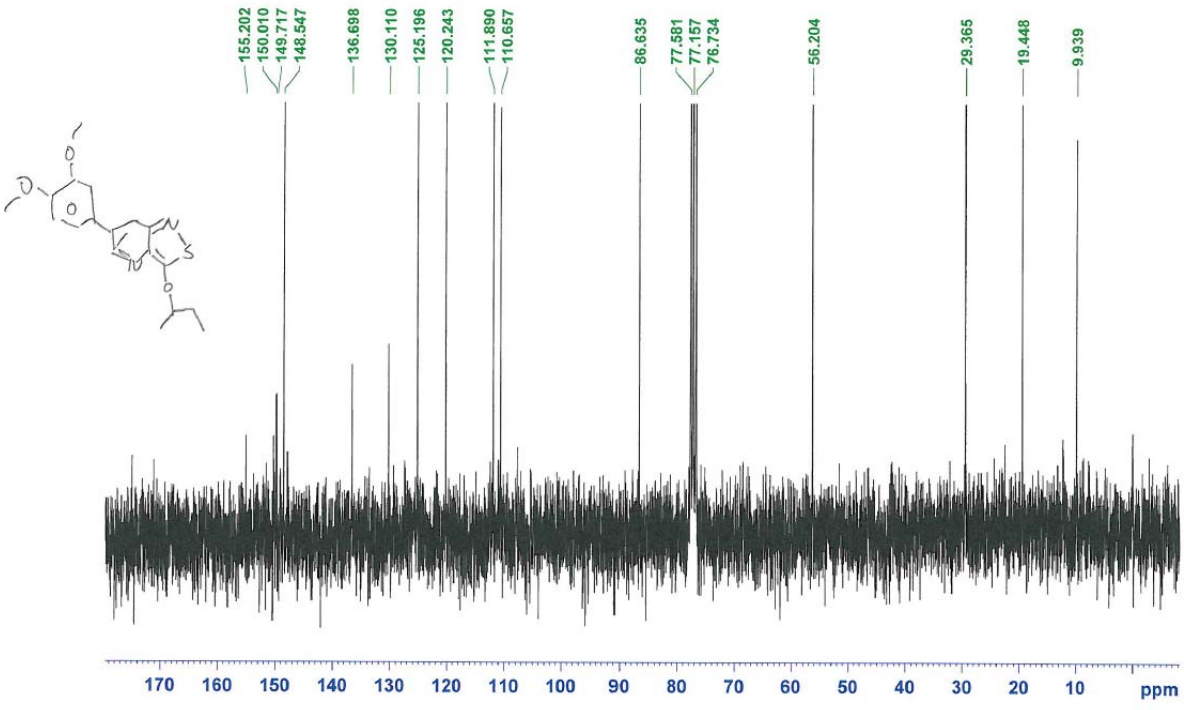
Compound **8b** – ^{13}C NMR spectrum



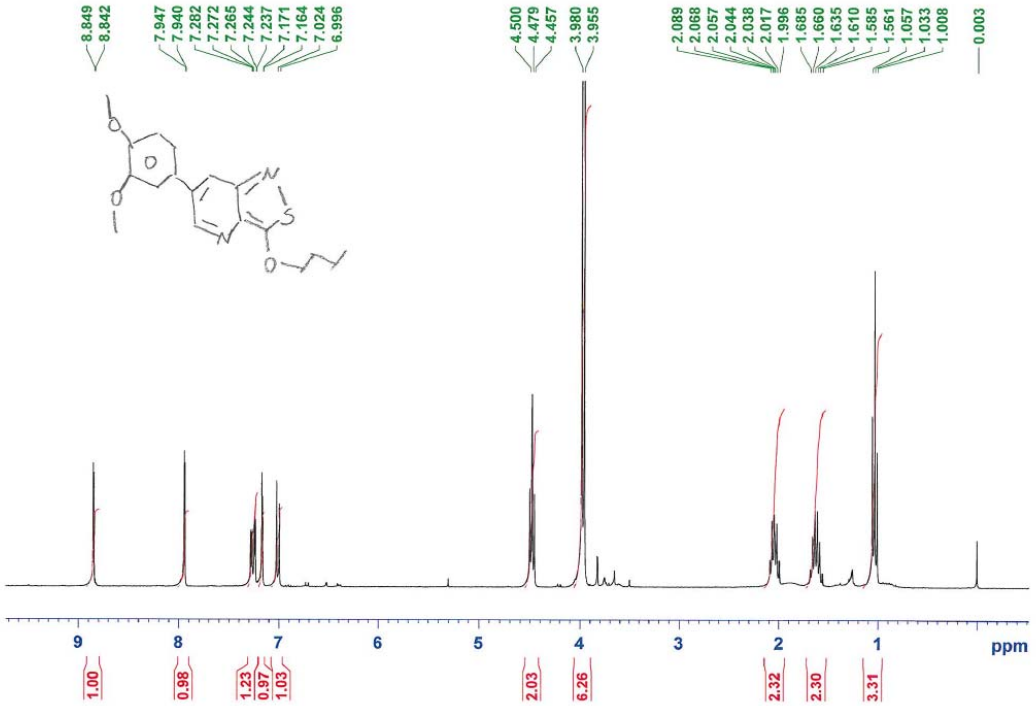
Compound **8c** - ^{1}H NMR spectrum



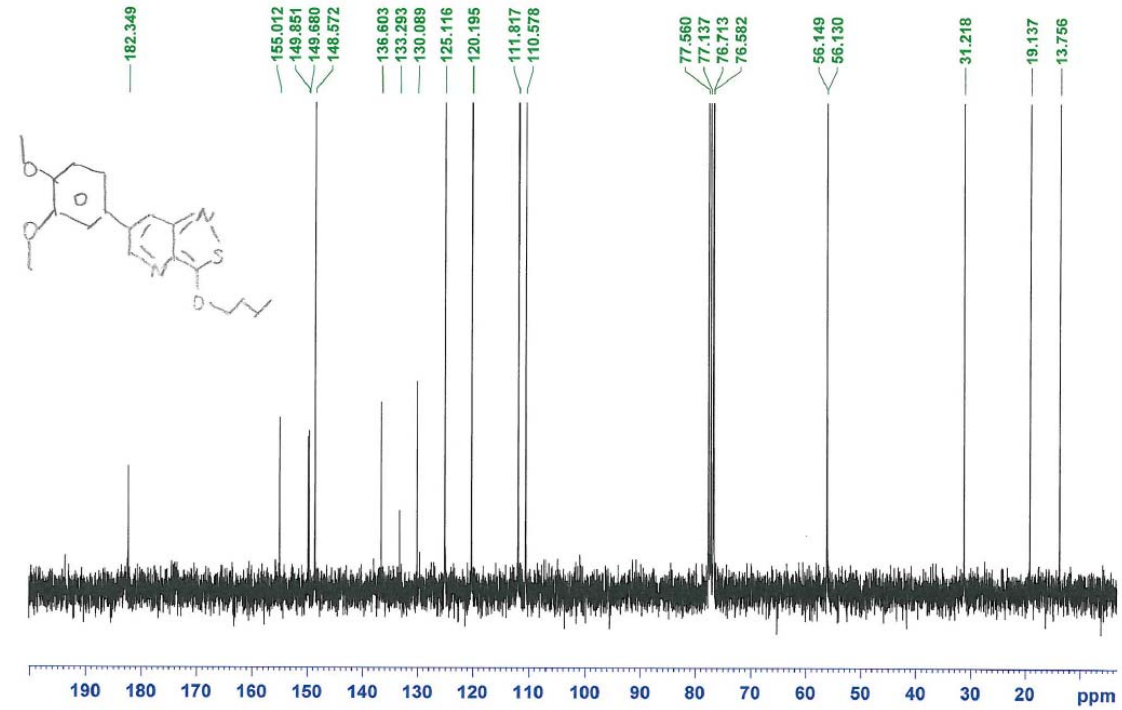
Compound **8c** – ^{13}C NMR spectrum



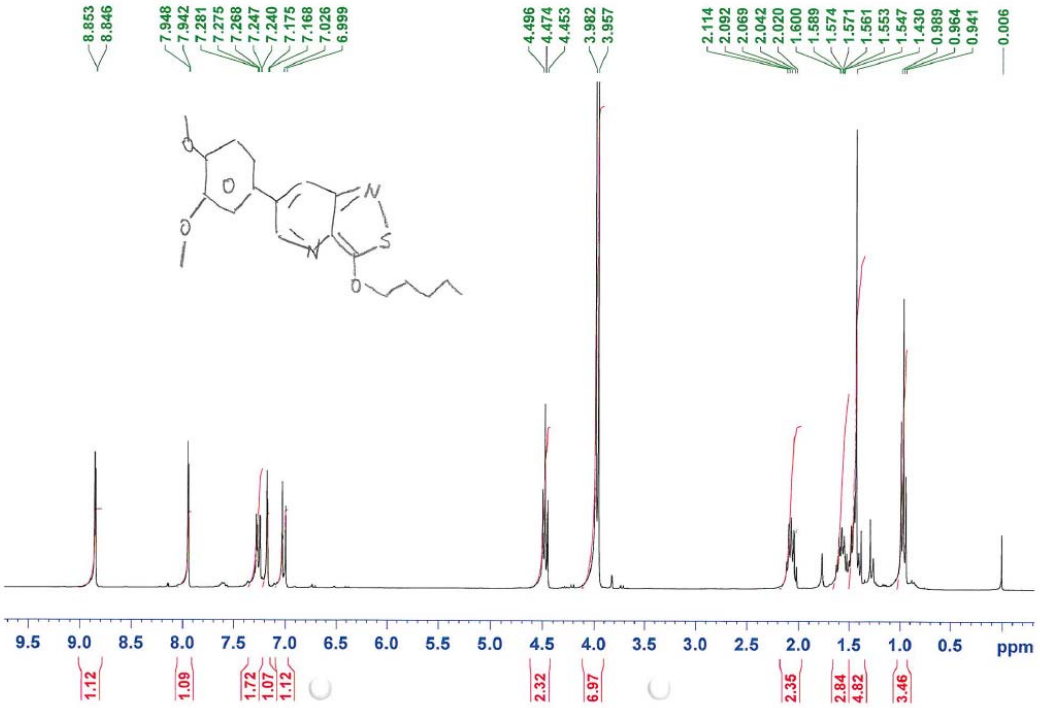
Compound **8d** - ^{1}H NMR spectrum



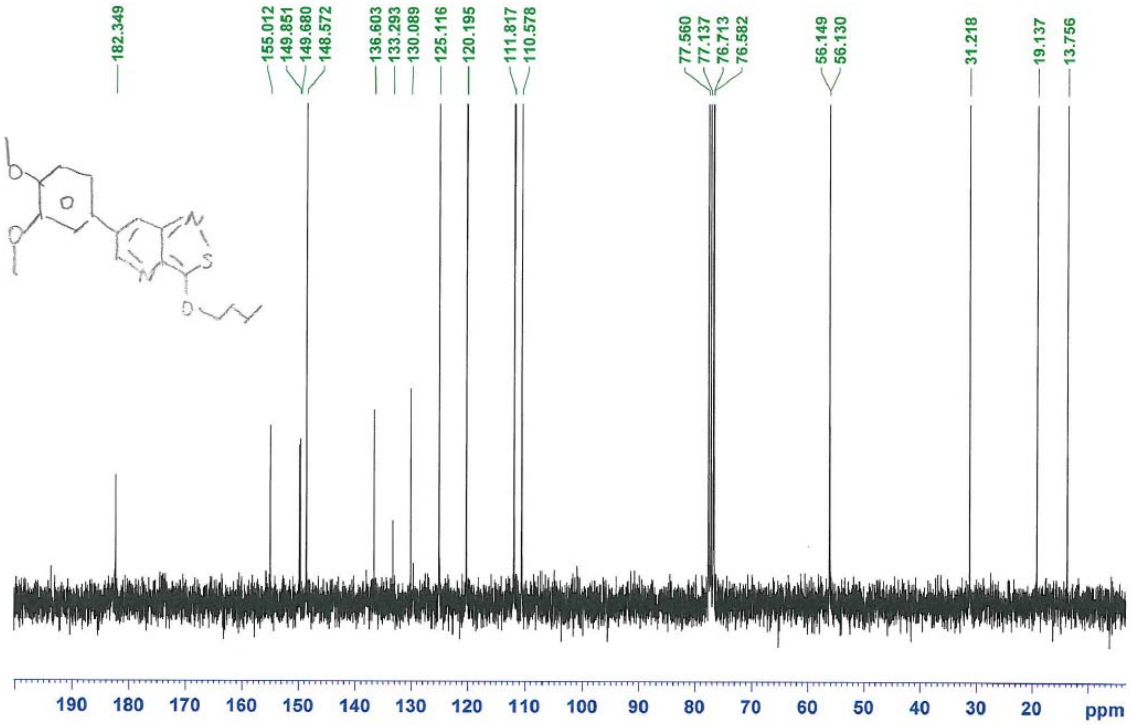
Compound **8d** – ^{13}C NMR spectrum



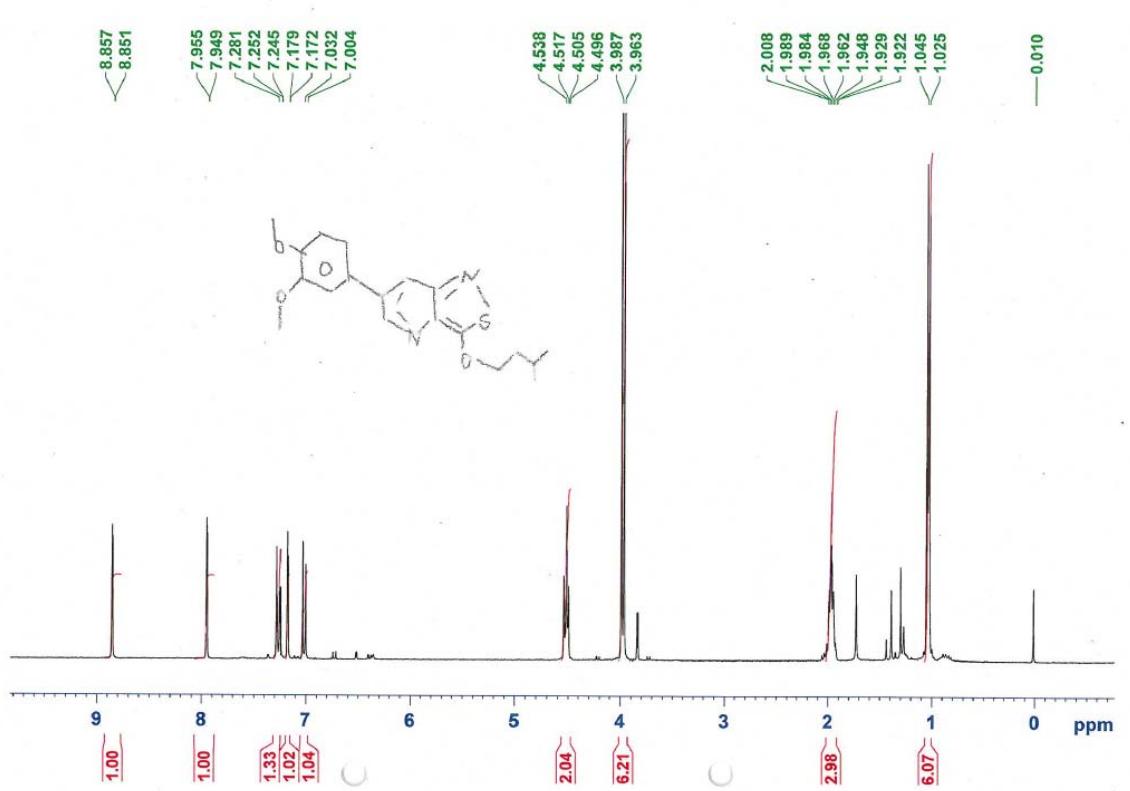
Compound **8e** - ^{1}H NMR spectrum



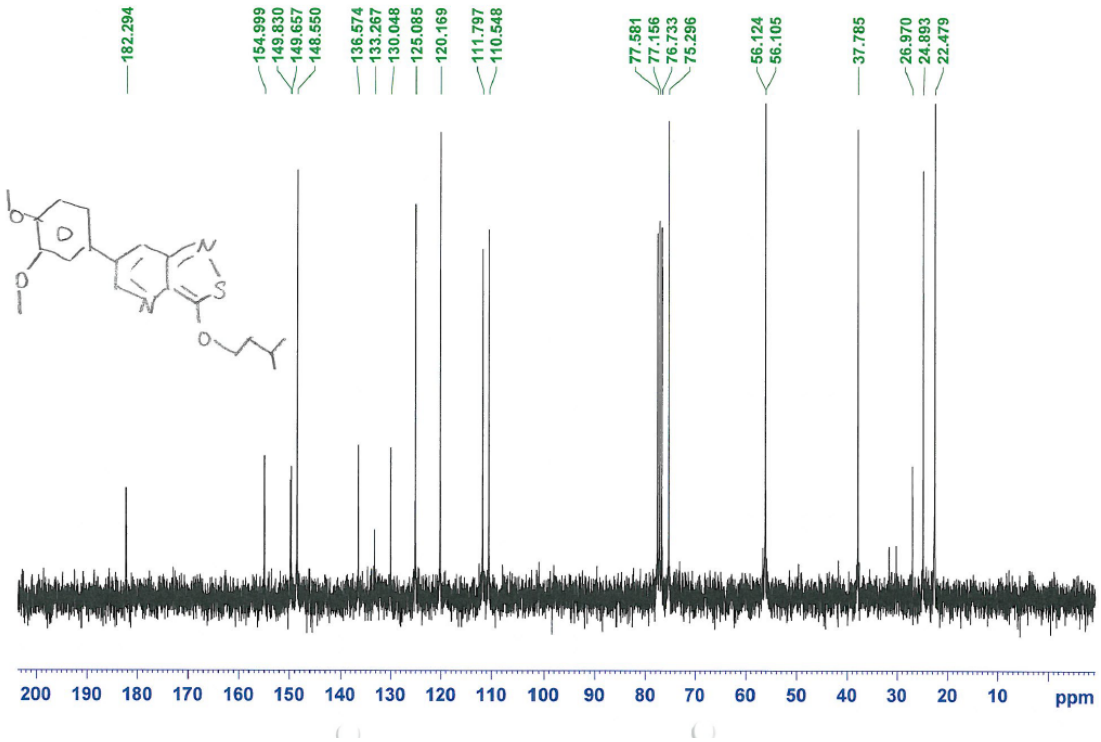
Compound **8e** – ^{13}C NMR spectrum



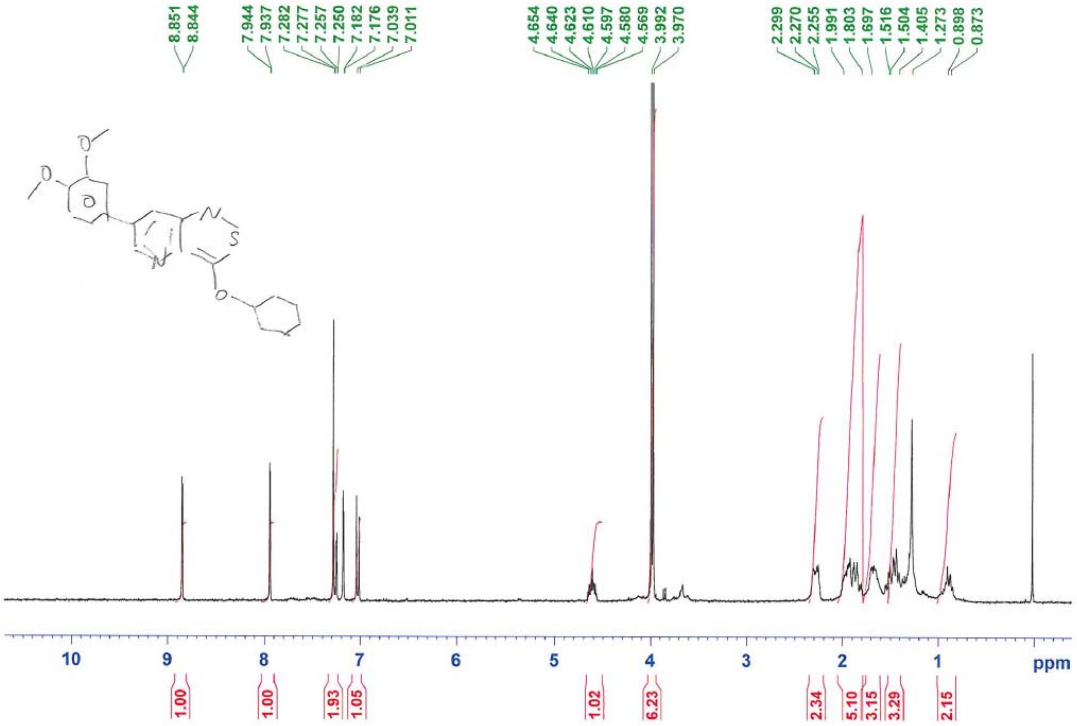
Compound **8f** - ^{1}H NMR spectrum



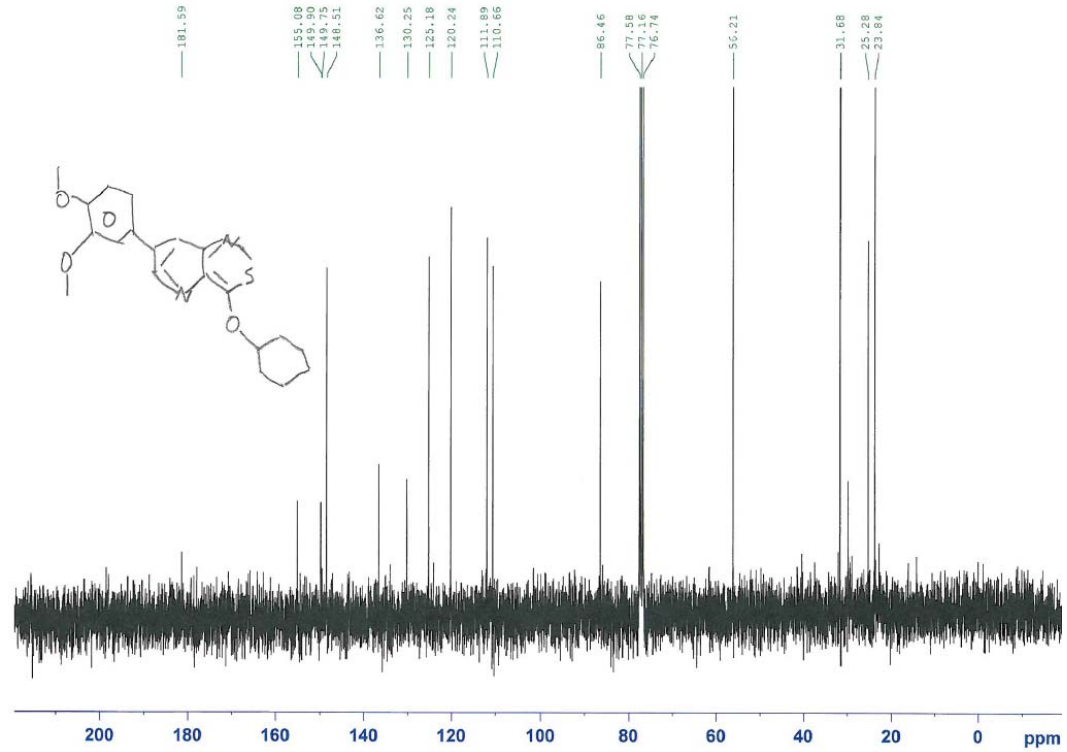
Compound **8f** – ^{13}C NMR spectrum



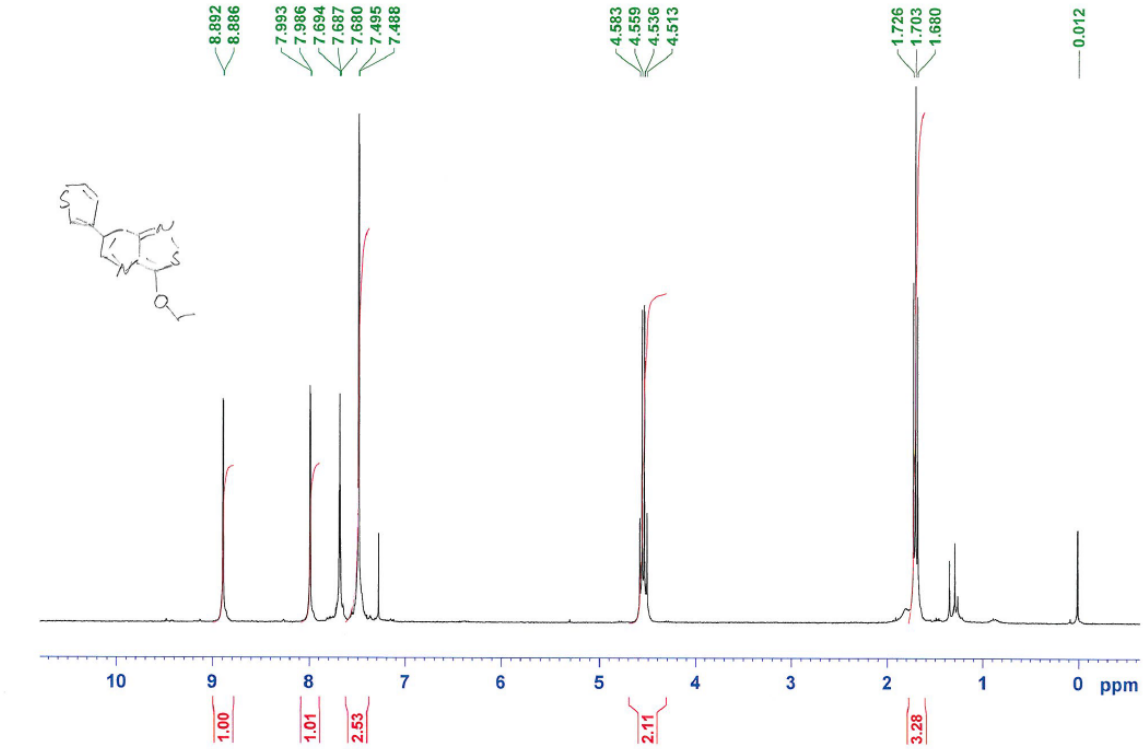
Compound **8g** - ^{1}H NMR spectrum



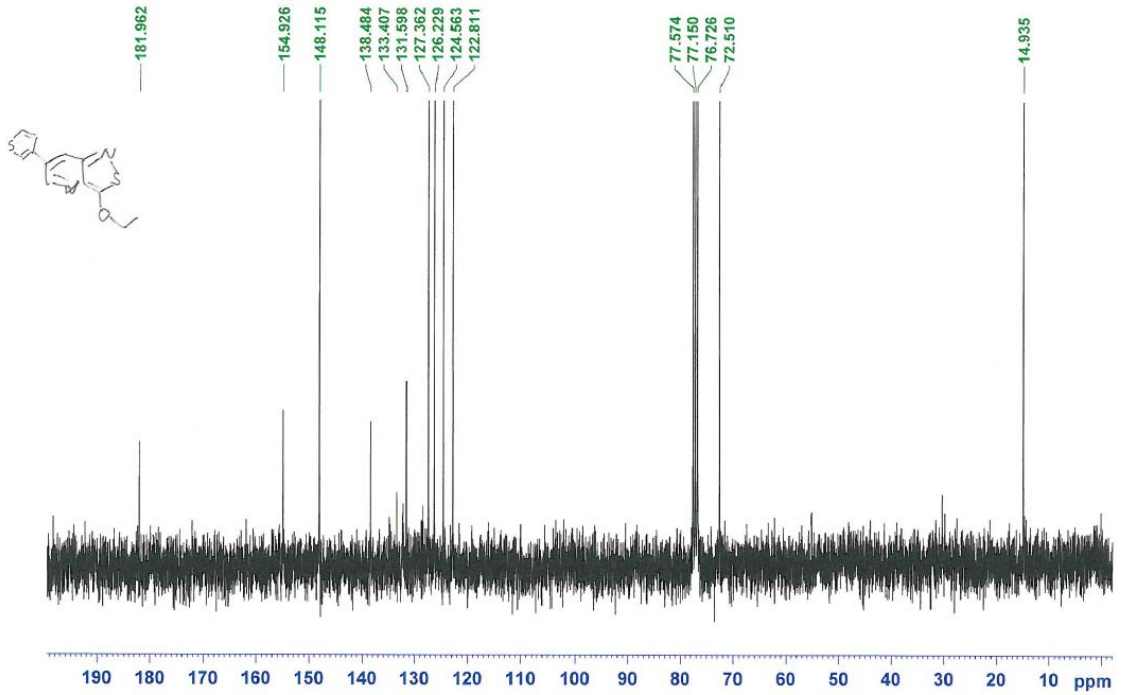
Compound **8g** – ^{13}C NMR spectrum



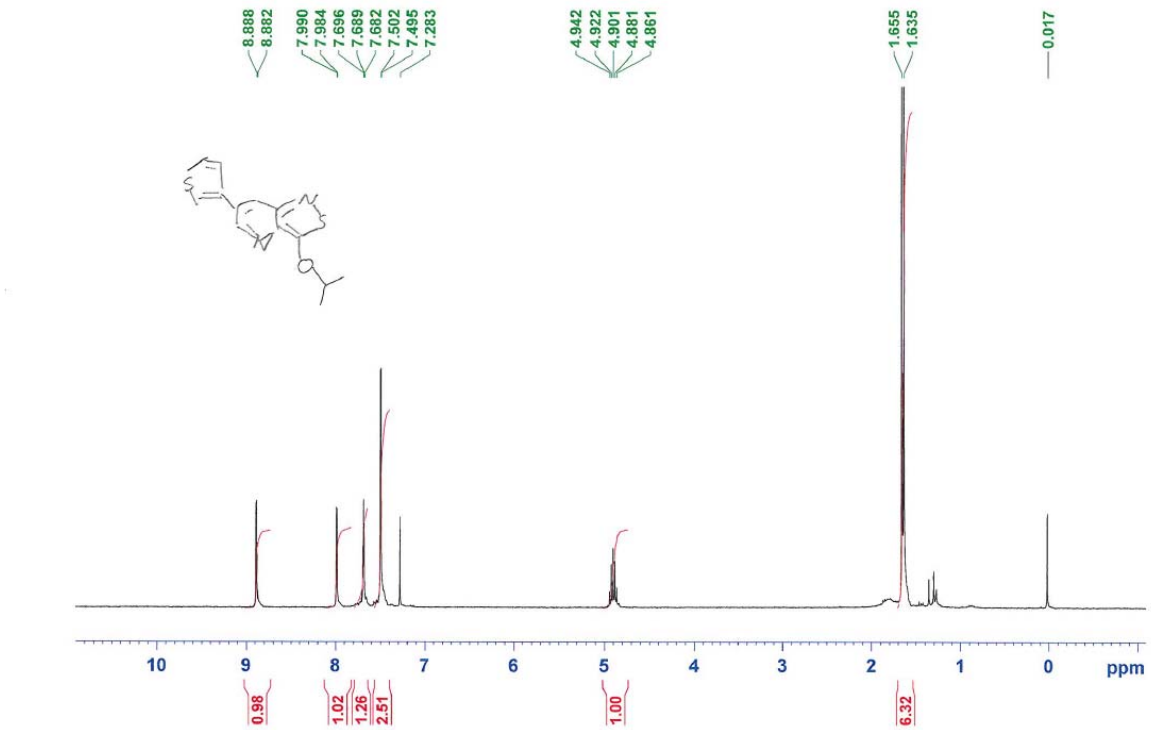
Compound **8i** - ^{1}H NMR spectrum



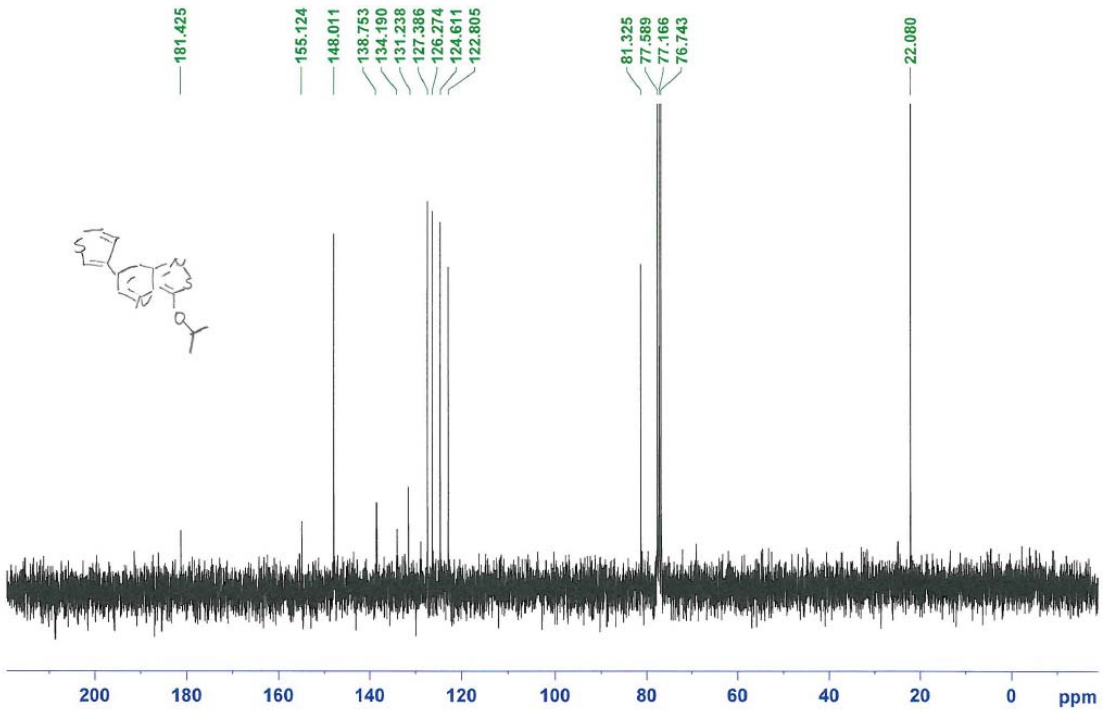
Compound **8i** – ^{13}C NMR spectrum



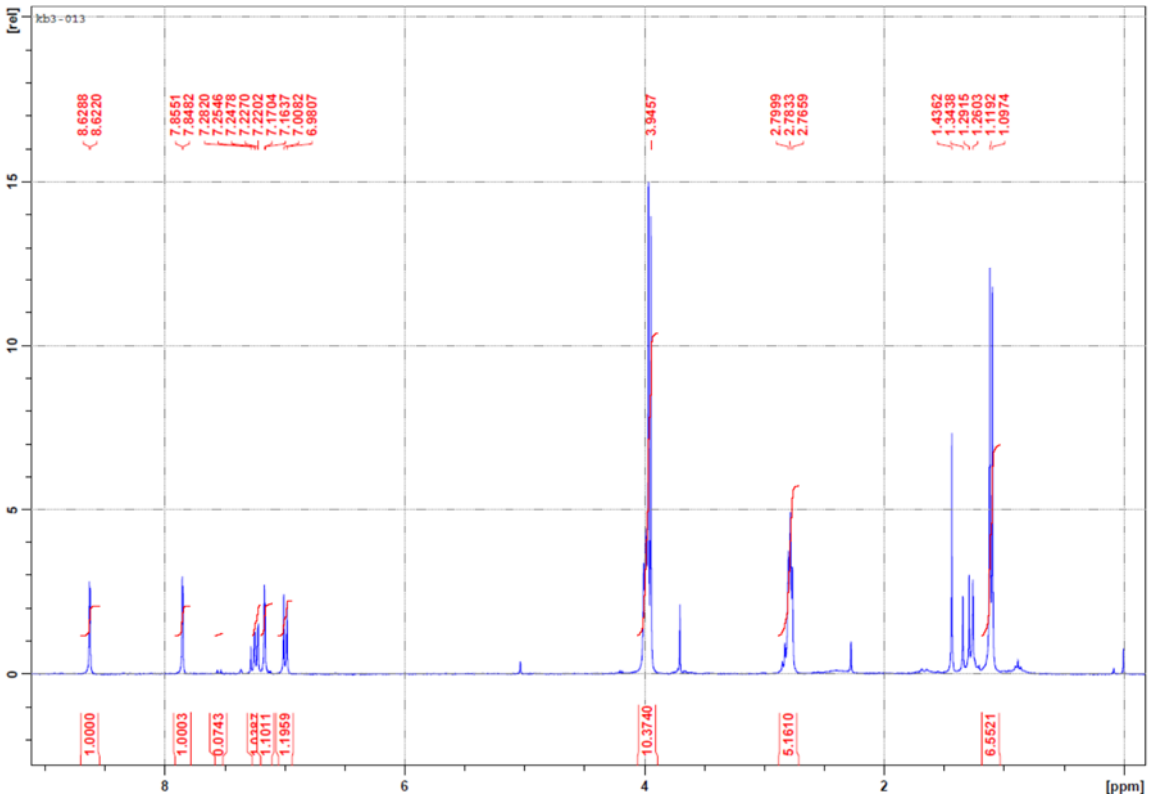
Compound **8j** - ^{1}H NMR spectrum



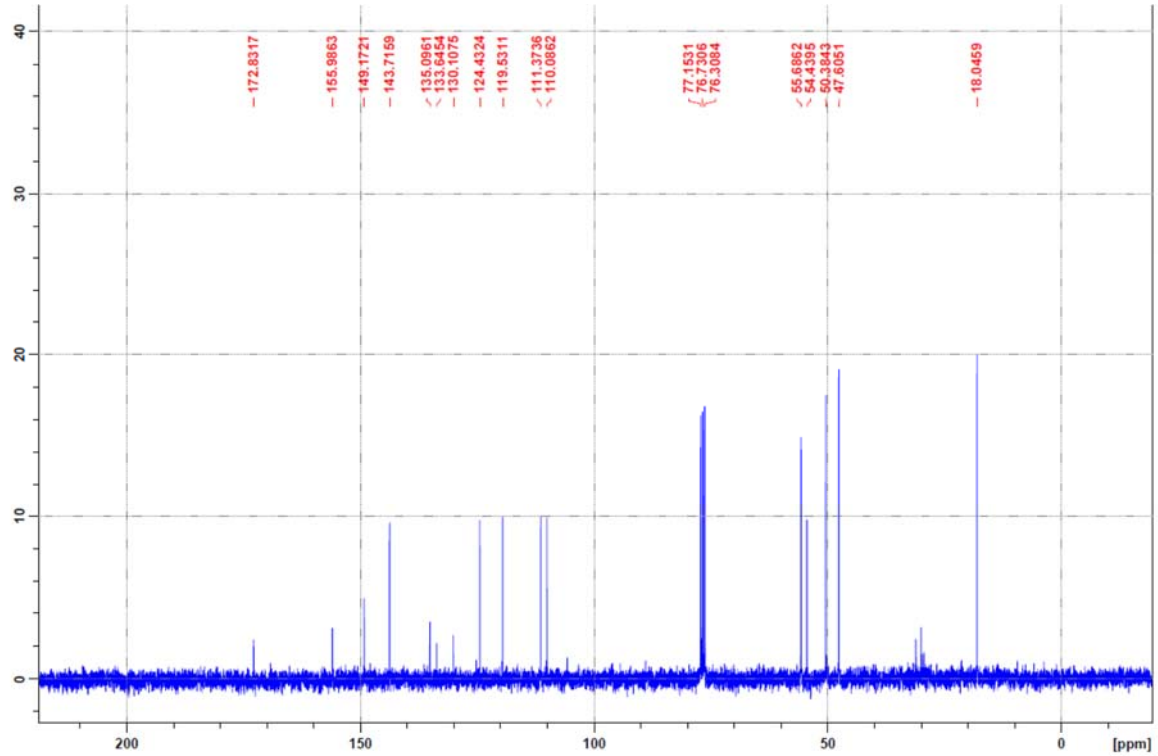
Compound **8j** – ^{13}C NMR spectrum



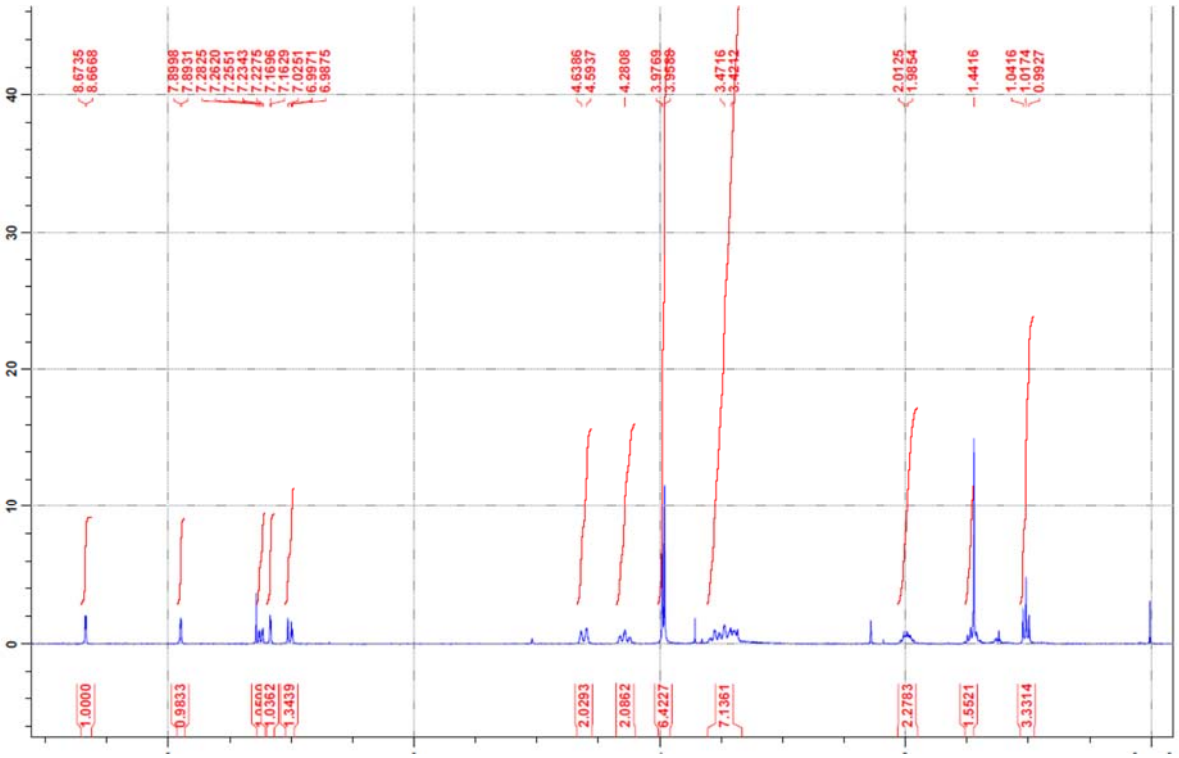
Compound **8l** - ^{1}H NMR spectrum



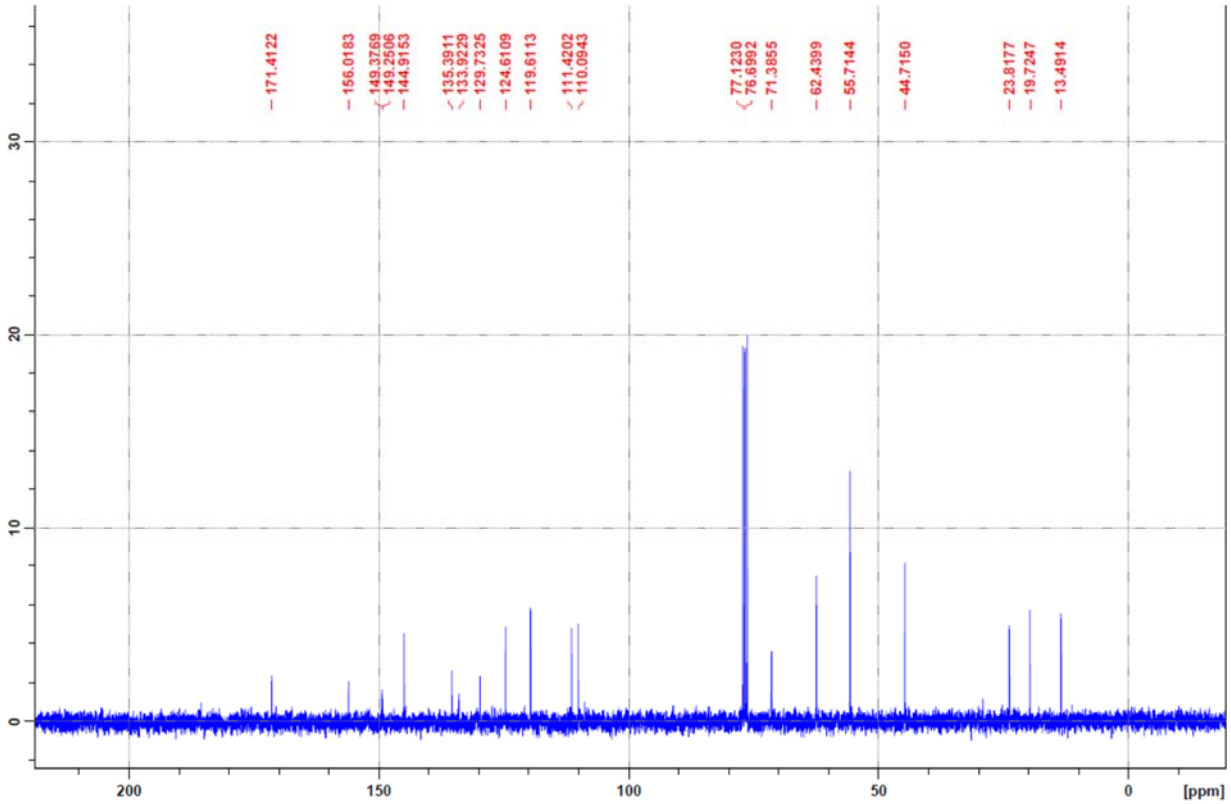
Compound **8l** – ^{13}C NMR spectrum



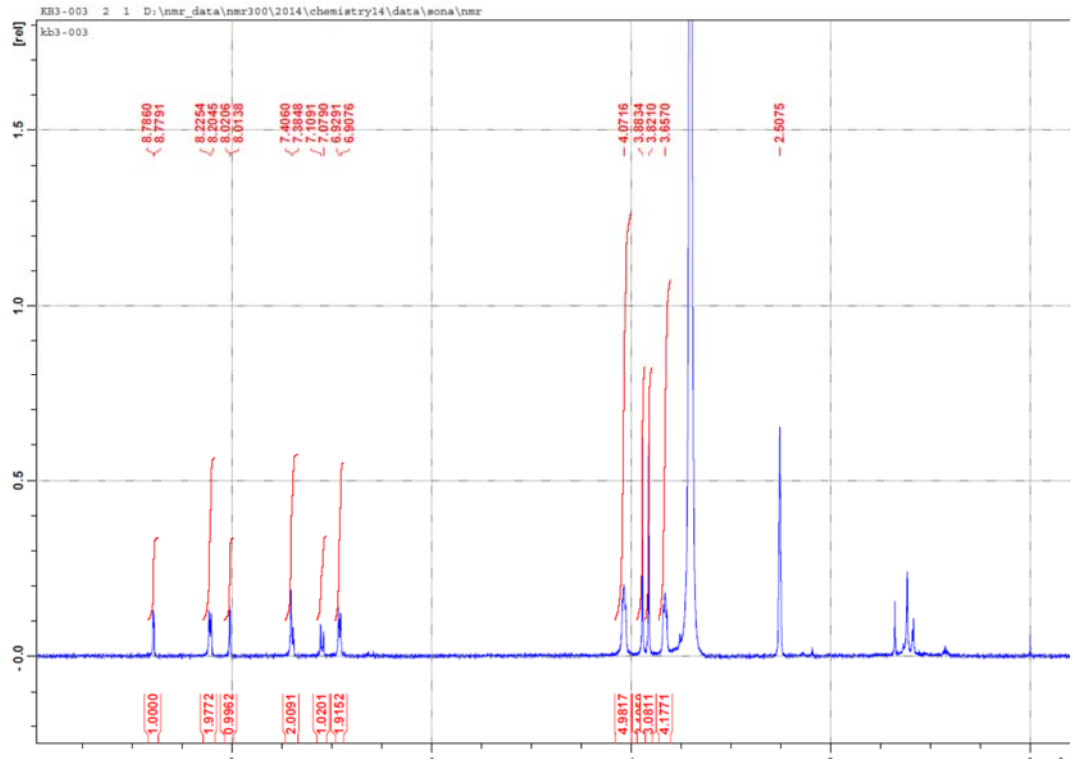
Compound **8m** - ^{1}H NMR spectrum



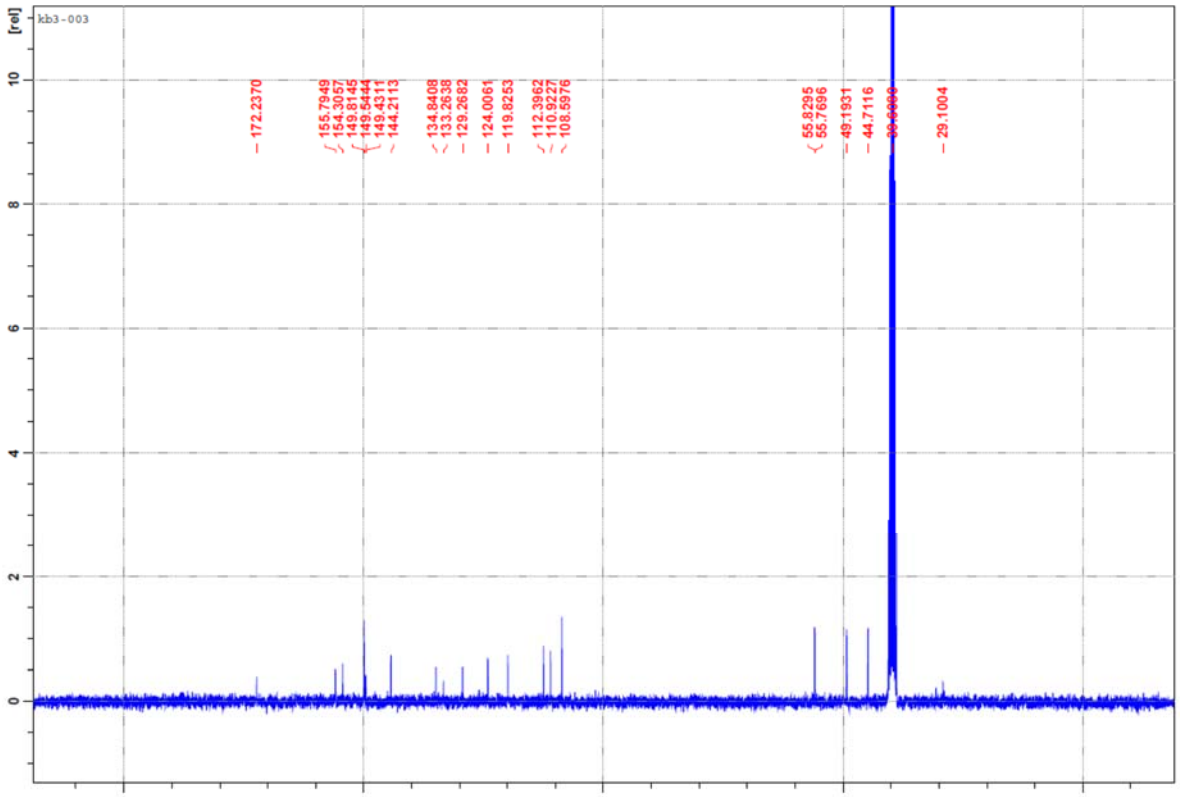
Compound **8m** – ^{13}C NMR spectrum



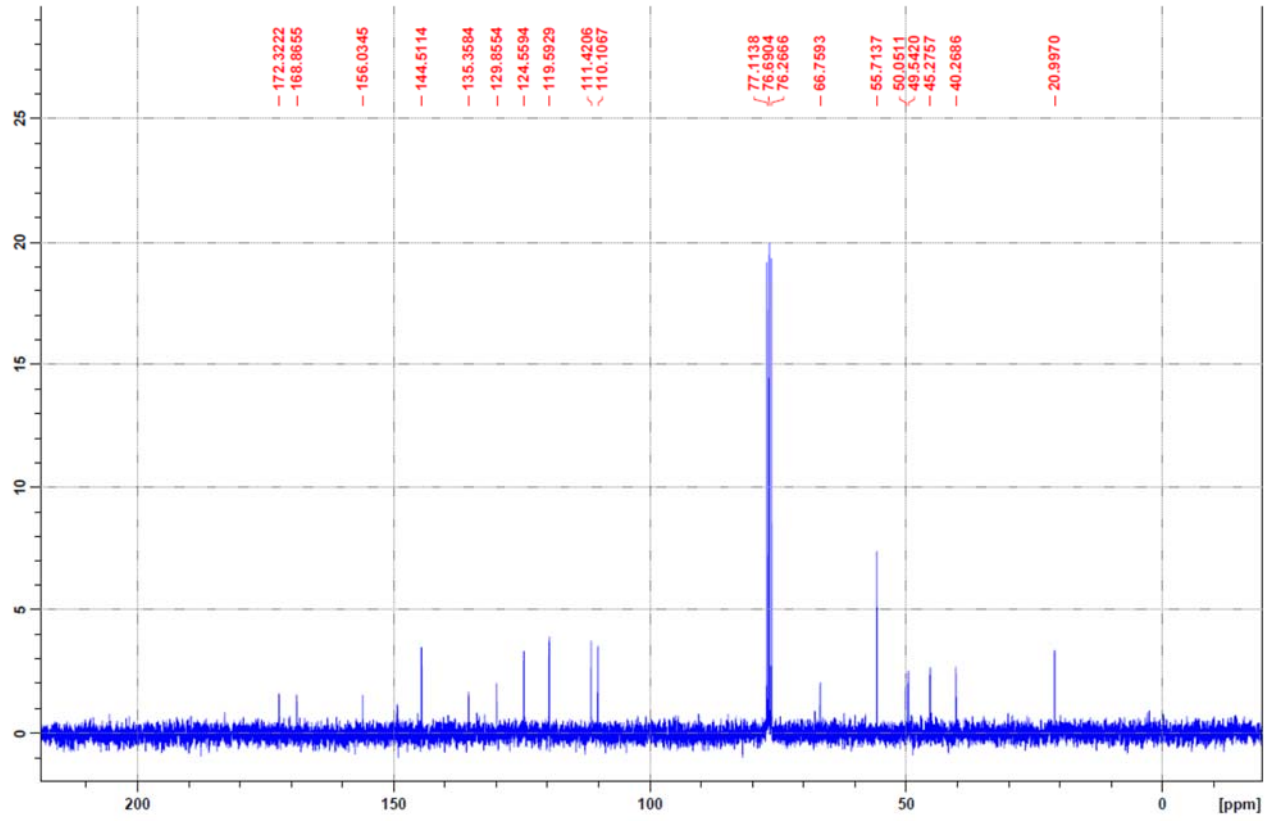
Compound **8n** - ^{1}H NMR spectrum



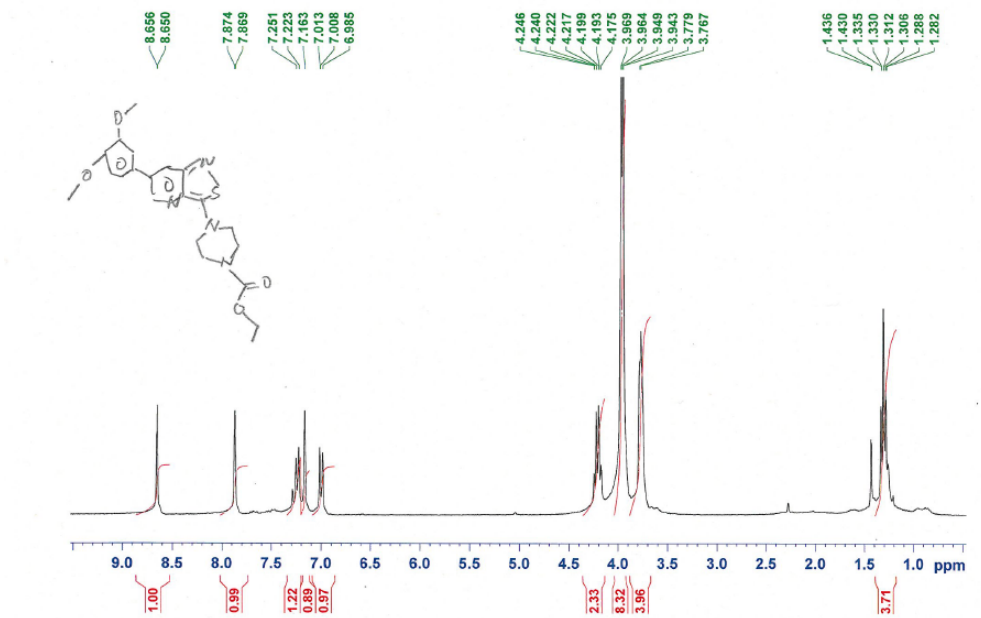
Compound **8n** – ^{13}C NMR spectrum



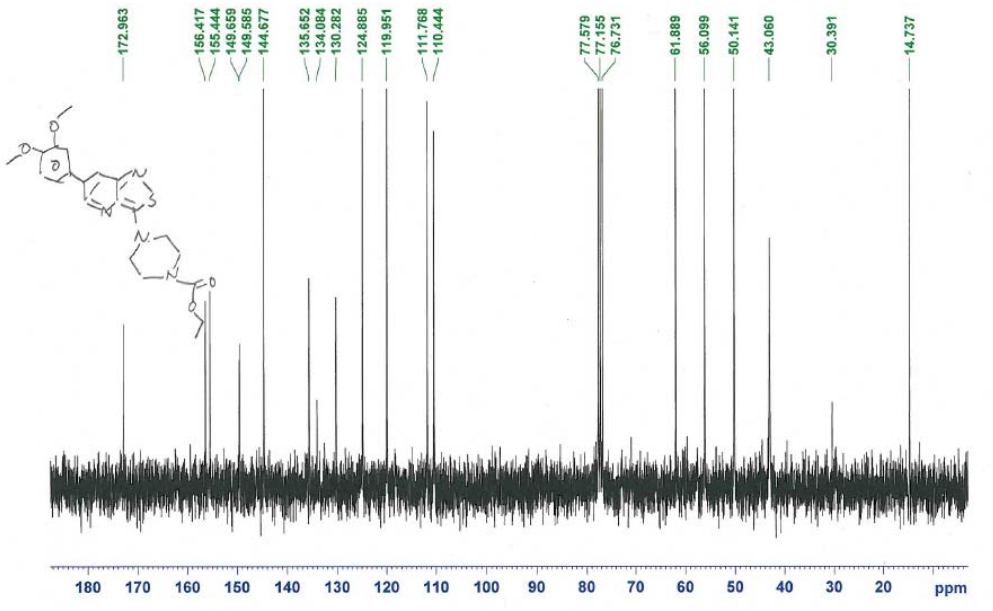
Compound **8o** – ^{13}C NMR spectrum



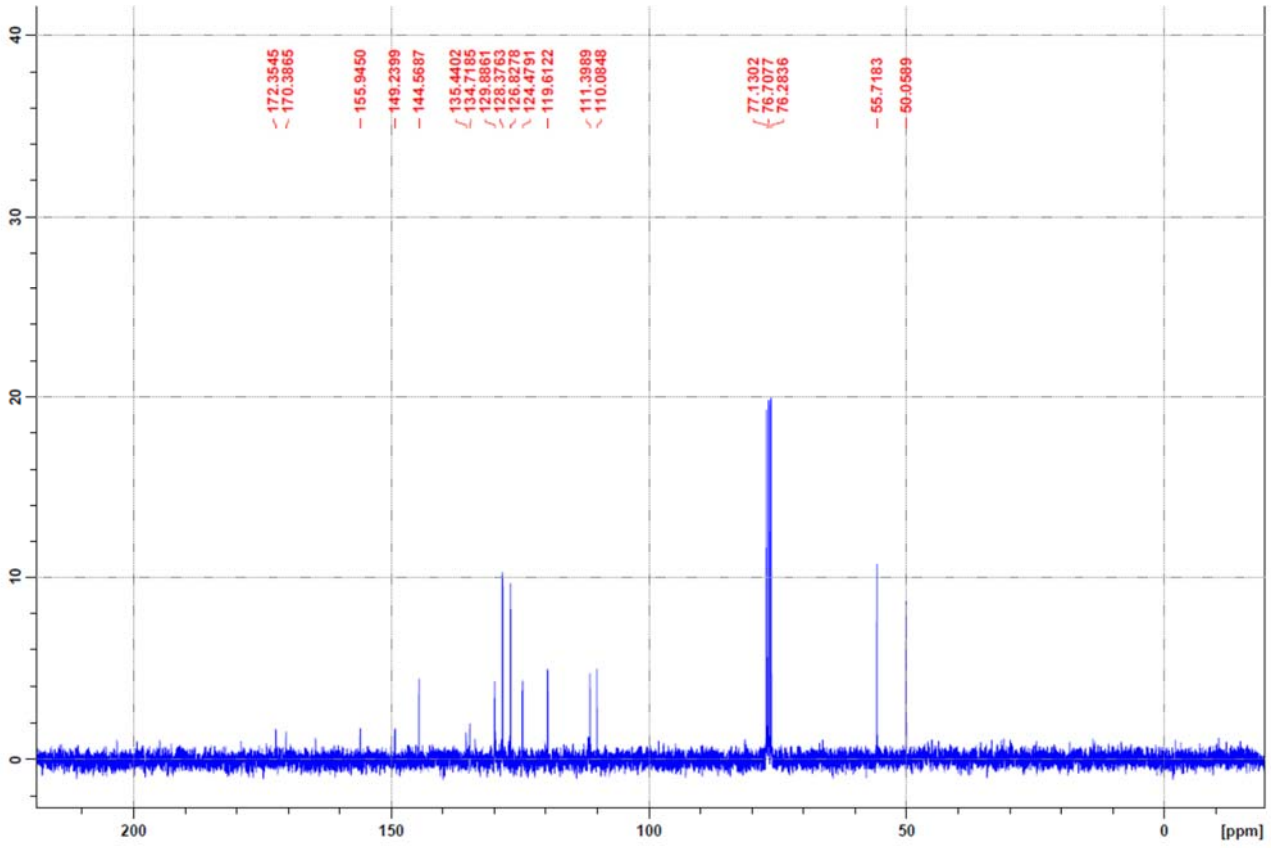
Compound **8p** - ^{1}H NMR spectrum



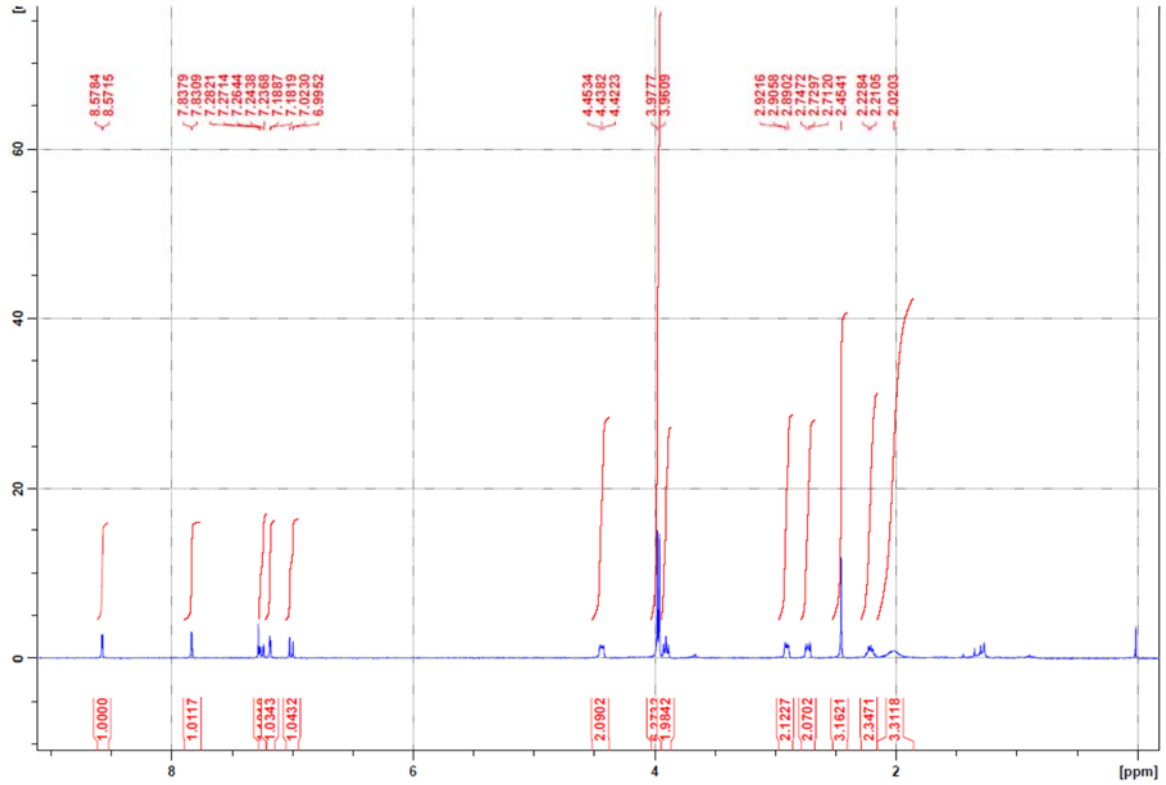
Compound **8p** – ^{13}C NMR spectrum



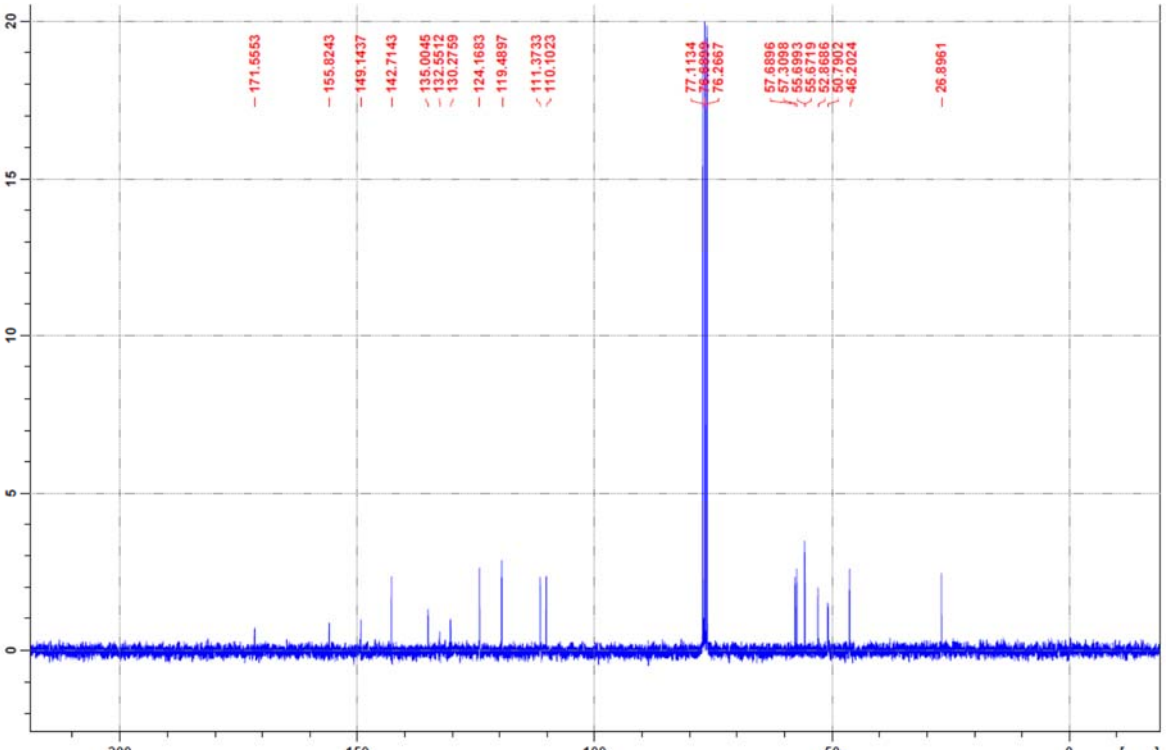
Compound **8q** – ^{13}C NMR spectrum



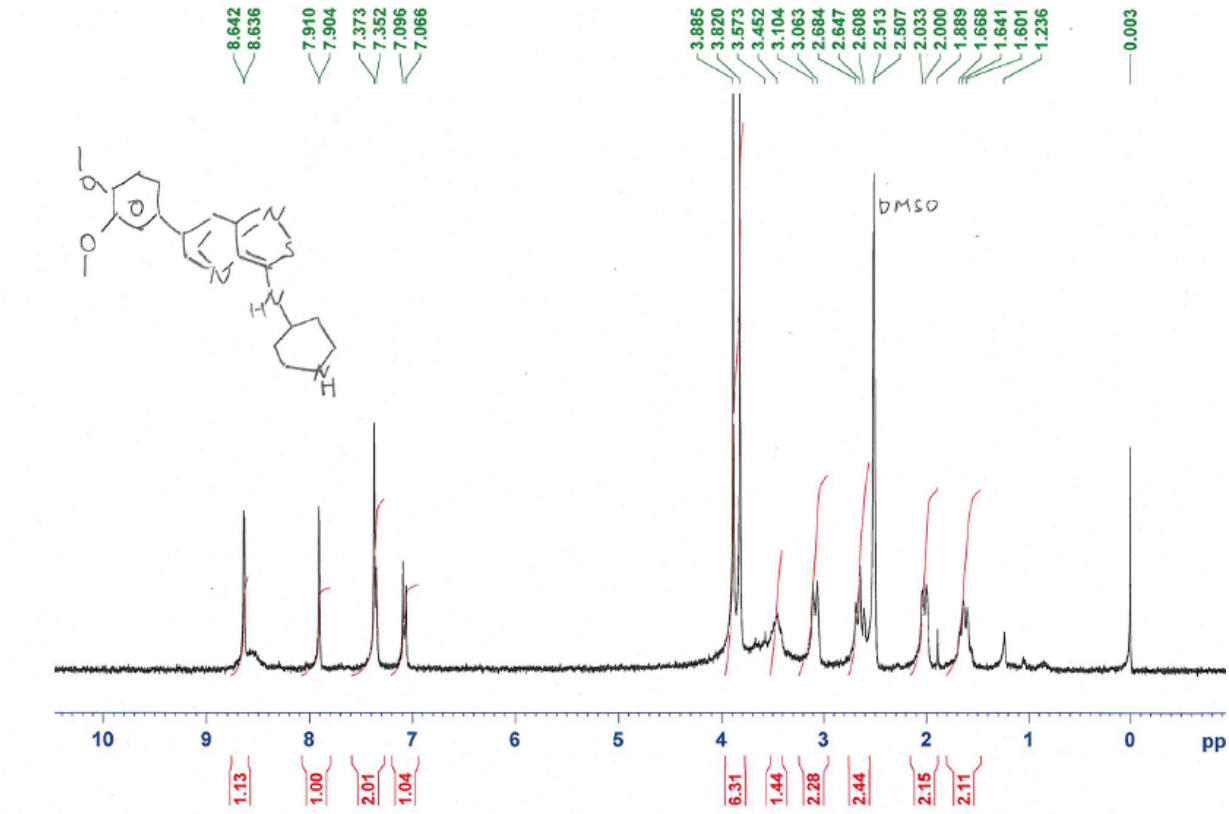
Compound **8r** - ^{1}H NMR spectrum



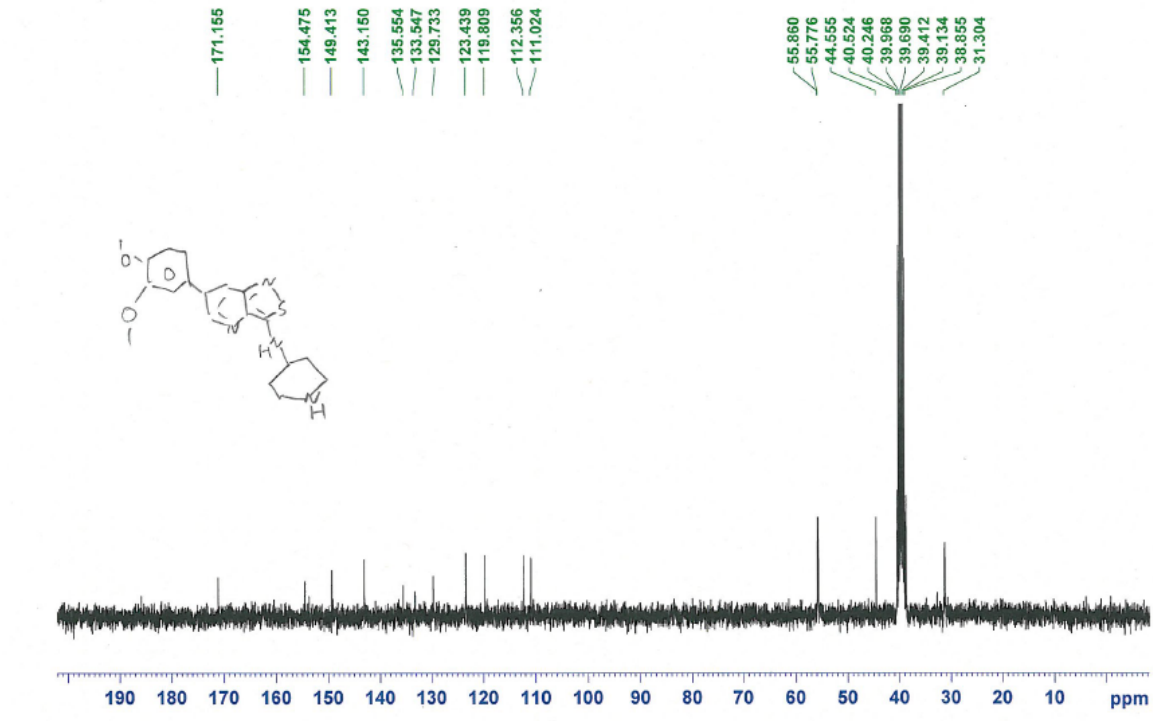
Compound **8r** – ^{13}C NMR spectrum



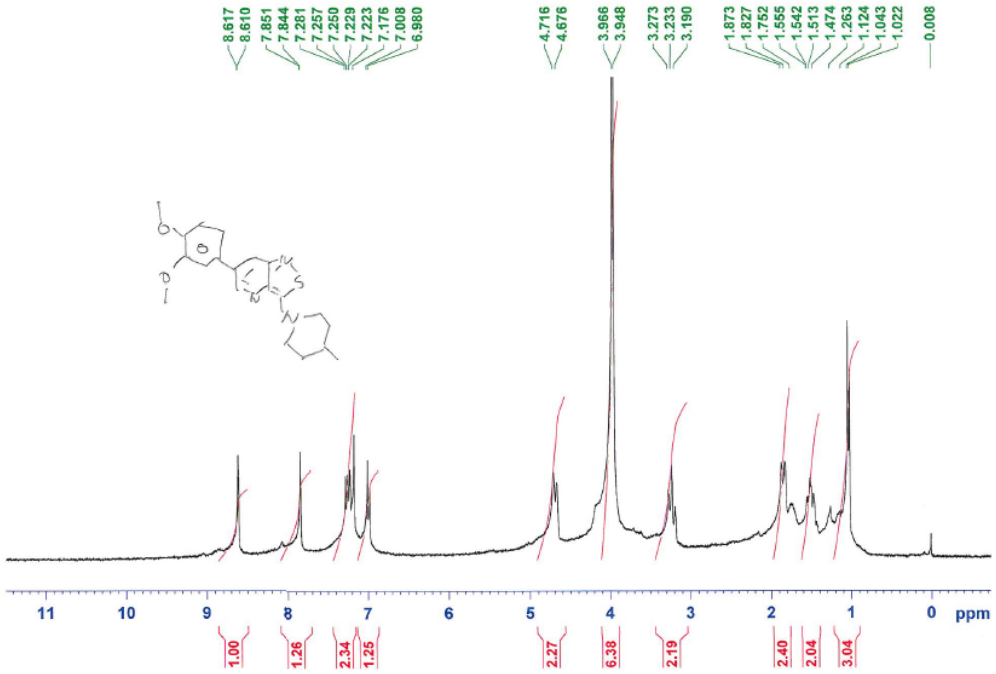
Compound **8s** - ^{1}H NMR spectrum



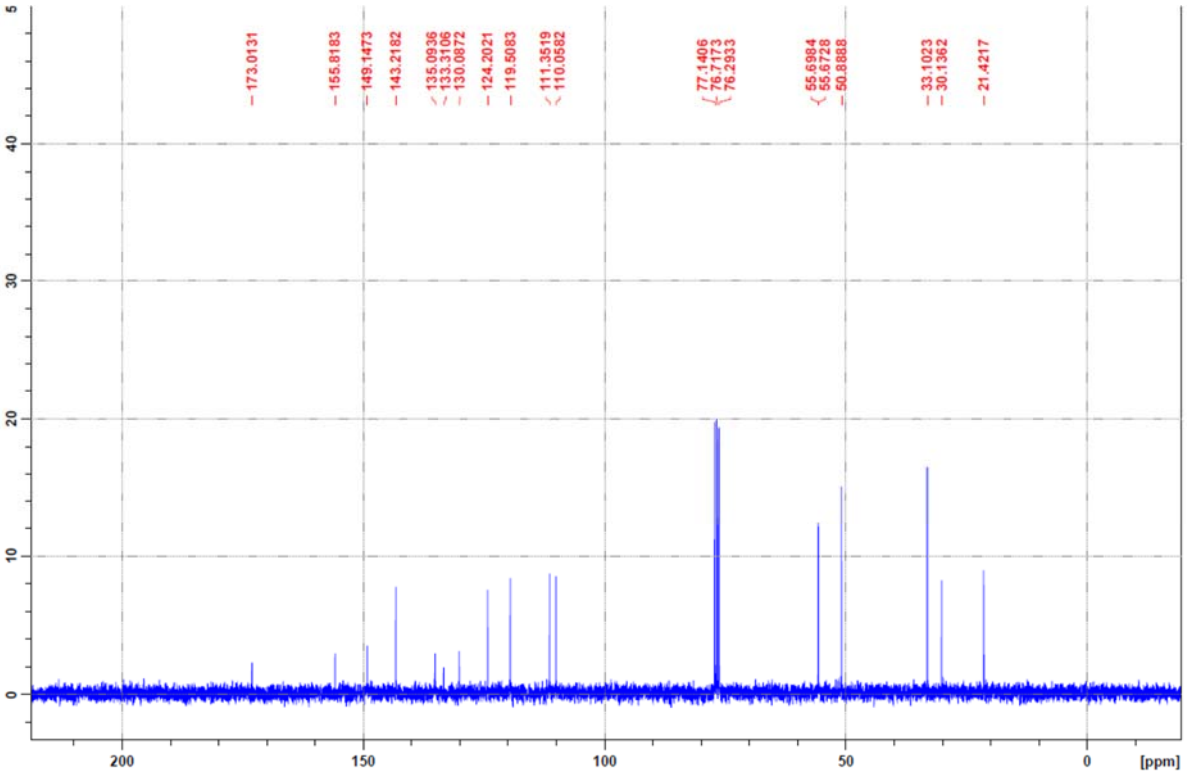
Compound **8s** – ^{13}C NMR spectrum



Compound **8t** - ^{1}H NMR spectrum



Compound **8t** – ^{13}C NMR spectrum



HPLC purity data of final compounds

Purity of final compounds was determined by analytical RP-HPLC analysis on a XBridge column (C-18, 5 µm, 4.6 mm × 150 mm) in combination with a Waters 600 HPLC system and a Waters 2996 photodiode array detector from Waters, Milford, Massachusetts, USA. Elution was done using a gradient mixture of H_2O containing 0.2% (vol) of TFA (A) and Acetonitrile (B) as indicated in Table S1.

Table S1: Gradient table for RP-HPLC purity check.

	Time (min)	Flow (mL/min)	%A	%B
1	0	1.0	100	0
2	5	1.0	100	0
3	20	1.0	0	100
4	30	1.0	0	100

Compound#	Rf (min)	Purity (%)
5a	24.0	99
5b	22.4	99
5c	23.0	99
5d	23.3	97
5e	23.6	99
5f	21.9	99
5g	23.7	99
5h	25.6	99
5i	21.0	99
5j	23.1	97
8b	24.0	99
8c	24.6	99
8d	24.8	99
8e	25.9	99
8f	25.6	99
8g	25.5	99
8h	25.6	99
8i	23.0	98
8j	23.9	99
8l	19.2	97

8m	20.3	99
8n	19.6	96
8o	22.3	99
8p	23.0	99
8q	22.8	96
8r	18.9	99
8s	18.4	98
8t	23.5	93