SUPPORTING INFORMATION

SAR study of 4-arylazo-3,5-diamino-1H-pyrazoles: Identification of small molecule that induce dispersal of Pseudomonas aeruginosa biofilms

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GENERAL METHODOLOGIES

All solvents were of HPLC quality from either Sigma Aldrich or VWR Chemicals these and other commercially available reagents were used without further purification. The dry DCM was obtained from a PureSolve^{TM} MD-7 Solvent Purification System, from Innovative Technology were Al_2O_3 was used as the stationary phase. Dry MeOH was purchased from Sigma Aldrich.

^{1}H-NMR, ^{13}C-NMR, COSY spectra were recorded on Bruker Ascend spectrometer with a Prodigy cryoprobe operating at 400 MHz for ^{1}H-NMR and 101 MHz for ^{13}C-NMR. The specific deuterated solvent is stated for each compound. Chemical shifts (δ) are reported in ppm downfield from TMS (δ = 0) using solvent resonance as the internal standard (chloroform-d, ^{1}H: 7.26 ppm, ^{13}C: 77.16 ppm; dimethylsulfoxide-d6, ^{1}H: 2.50 ppm, ^{13}C: 39.52 ppm). Coupling constants (J) are reported in Hz and the field is reported in each case. Multiplicities are reported as singlet (s), broad singlet (br. s), doublet (d), doublet of doublets (dd), doublet of triplets (dt), doublet of doublet of doublets (ddd), doublet of doublet of triplets (ddt), triplet (t), triplet of doublets (td), quartet (q), pentet (p), septet (sep) and multiplets (m).

Evaporation of the solvents were performed using a Heidolph Laborota 4000 efficient under reduced pressure (*in vacuo*) at different temperatures depending on the boiling point of the solvents.

N_2 atmosphere was used in experiments for obtaining an inert atmosphere in reactions that would otherwise react with water or oxygen resulting in undesired side-reactions. N_2 atmosphere was achieved by applying a rubber septum to the reagent flask and hereafter applying a constant N_2 inlet through a Schlenk line.

Flash chromatography was performed using Merck Geduran Silica gel 60 Å (particle size 40-63 μm) as the stationary phase. The chromatography method being used, followed the general method developed by Still *et al.* The eluent systems used are specified for each product in the following subsections. These eluent systems are given as a volume ratio.

TLC was performed using Merck Aluminum Sheets which were precoated with silica gel 60 F_{254}. By placing spots on the TLC plates containing the different compounds/products in solution, then the compounds could be separated. The spots were developed using UV-light or a suitable staining agent.

UPLC/MS analysis was run on Waters ACQUITY UPLC system equipped with PDA and either a SQD or a SQD2 electrospray MS detector. Column: Thermo accucore C18 2.6 μm, 2.1 × 50 mm. Column temp: 50^{o}C. Flow rate: 0.6 mL/min. Acid run: Solvent A1 - 0.1% formic acid in water, Solvent B1 - 0.1% formic acid in ACN. Base run: Solvent A2 - 15 mM NH_4Ac in water, Solvent B2 - 15 mM NH_4Ac in ACN/water 9:1. Gradient: (short run) 5% B to 100% B in 2.4 min., hold 0.1 min., total run time 2.6 min. (long run) 5% B to 100% B in 3 min., hold 0.1 min., total run time 5 min.

Preparative HPLC purification was performed on a Waters auto purification system consisting of a 2767 Sample Manager, 2545 Gradient Pump and 2998 PDA detector. Column: XBridge Peptide BEH C18 OBD Prep Column, 130 Å, 5 μm, 19 mm × 100 mm. Column temp: Ambient. Flow rate: 20 mL/min. Solvent A2 - 15 mM NH_4Ac in water, Solvent B2 - 15 mM NH_4Ac in MeCN/water 9:1. Gradient: 5% B to 20% B in min., hold min., gradient: 20% B to 50% B in min., hold min., gradient: 50% B to 70% B in min., hold min., gradient: 70% B to 100% B in min., hold min., run min., recalibrating the column for min. Total run time – 18 min.

General Procedure A1 – Diazotation with malononitrile

In a 250 mL conical flask, a solution of the aniline (0.01 mol, 1 eq.) in H_2O/ice (50 mL) and conc. HCl (3 mL) was cooled to 0°C. Then, a cold solution of sodium nitrite (0.01 mol, 1 eq.) in 10 mL H_2O was added dropwise with stirring. The mixture was allowed to stir for 30 min.,

before slow addition of an aqueous cold solution of malononitrile (0.015 mol, 1.5 eq.) and sodium acetate (25g) in 85 mL H_2O. After stirring the reaction mixture at 0°C for 1 h, the formed solid product was collected by filtration and washed with ice-cold water. For those compounds that did not precipitate, the product was isolated by extraction with EtOAc. dried with $MgSO_4$ and concentrated under vacuum. The product was dried under high vacuum overnight.

General Procedure A2 – Diazotation with ethyl-2-cyanoacetate

In a 250 mL conical flask, a solution of the aniline (0.01 mol, 1 eq.) in H_2O/ice (50 mL) and conc. HCl (3 mL) was cooled to 0°C. Then, a cold solution of sodium nitrite (0.01 mol, 1 eq.) in H_2O (10 mL) was added dropwise under stirring. The reaction was allowed to stir for 30 min., before slow addition of an aqueous cold solution of ethyl-2-cyanoacetate (0.015 mol, 1.5 eq.) and sodium acetate (25g) in H_2O (85 mL). After stirring the reaction mixture at 0°C for 1 h, the precipitated product was collected by filtration and washed with ice-cold water. For those compounds that did not precipitate, the product was isolated by extraction with EtOAc. dried with $MgSO_4$ and concentrated under vacuum. The product was dried under high vacuum overnight.

General Procedure A3 – Diazotation with diethyl malonate

In a 250 mL conical flask, a solution of the aniline (0.01 mol, 1 eq.) in H_2O/ice (50 mL) and conc. HCl (3 mL) was cooled to 0°C. Then, a cold solution of sodium nitrite (0.01 mol, 1 eq.) in H_2O (10 mL) was added dropwise with stirring. The reaction was allowed to stir for 30 min., before slow addition of an aqueous cold solution of diethyl malonate (0.015 mol, 1.5 eq.) and sodium acetate (25g) in 85 mL H_2O. After stirring the reaction mixture at 0°C for 1 h, the precipitated product was collected by filtration and washed with ice-cold water. For those compounds that did not precipitate, the product was isolated by extraction with EtOAc, dried with $MgSO_4$ and concentrated under vacuum. The product was dried under high vacuum overnight.

General Procedure B1 – Cyclization with hydrazine/hydrazide

The product from procedure A1→3 (1 mmol, 1 eq) was dissolved in EtOH (2.9 mL/mmol), followed by addition of the appropriate hydrazine/hydrazide derivative (1.15 eq). Upon completion of the reaction, the product was isolated by filtration. For those compounds that did not precipitate, the solvent and hydrazine was removed by evaporation at high vacuum to give the product. If purification was needed, it was done with either flash chromatography or preparative HPLC.

General Procedure B2 – Cyclization with hydrazine/hydrazide

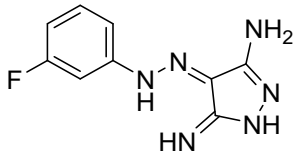
The product from procedure A1→3 (1 mmol, 1 eq) was dissolved in EtOH (2.9 mL/mmol), followed by addition of the appropriate hydrazine/hydrazide derivative (1.15 eq). The reaction was refluxed until completion of the reaction. Afterwards the mixture was cooled to room temperature, and the precipitated product isolated by filtration. For those compounds that did not precipitate, the solvent and hydrazide was removed by evaporation under vacuum to give the product. If purification was needed, it was done with either flash chromatography or preparative HPLC.

General Procedure B3 – Cyclization with hydroxylamine

The product from procedure A1→3 (1 mmol, 1 eq) was dissolved in methanol (6.5 mL/mmol) and added a solution of 10% NaOtBu in methanol (0.5 mL/mmol), followed by hydroxylamine hydrochloride (1.15 eq). The mixture was refluxed overnight. The solvent was removed in vacuo and afterwards purified by flash chromatography or preparative HPLC.

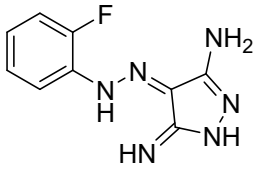
EXPERIMENTAL AND ANALYTICAL DATA

(E)-4-(2-(3-fluorophenyl)hydrazineylidene)-5-imino-4,5-dihydro-1H-pyrazol-3-amine (1)



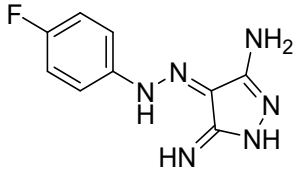
General procedure A1 followed by B1. Yield: 81%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.79 (s, 1H), 7.53 (dt, J = 11.2, 2.2 Hz, 1H), 7.49 (dt, J = 8.0, 1.3 Hz, 1H), 7.40 (td, J = 8.0, 6.3 Hz, 1H), 7.00 (tdd, J = 8.4, 2.7, 1.0 Hz, 1H), 6.44 (s, 1H), 5.90 (s, 1H), 5.27 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.52 (d, J = 242.9 Hz), 156.28 (d, J = 7.1 Hz), 130.70 (d, J = 9.2 Hz), 118.77, 115.07, 113.14 (d, J = 22.1 Hz), 105.50 (d, J = 22.5 Hz). HRMS (ESI) *m/z*: $[C_9H_9FN_6 + H]^+$ Calcd 221.0945; Found 221.0960.

(E)-4-(2-(2-fluorophenyl)hydrazineylidene)-5-imino-4,5-dihydro-1H-pyrazol-3-amine (2)



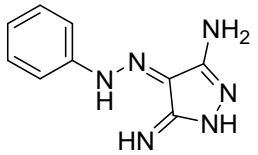
General procedure B1 using N-(2-fluorophenyl)carbonohydrazonoyl dicyanide (35). Yield: 84%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.80 (m, 1H), 7.32 – 7.13 (m, 3H), 6.45 (s, 2H), 6.02 (s, 2H), NH protons not observed. ^{13}C NMR (100 MHz, DMSO-d_6): δ 157.48(d, *J*=248.8 Hz), 141.79(d, *J*=6.4 Hz), 127.77(d, *J*=7.9 Hz), 124.84(d, *J*=3.6 Hz), 117.30, 116.69(d, *J*=19.6 Hz), 116.33. HRMS (ESI) *m/z*: $[C_9H_9FN_6 + H]^+$ Calcd 221.0945; Found 221.0952.

(E)-4-(2-(4-fluorophenyl)hydrazineylidene)-5-imino-4,5-dihydro-1H-pyrazol-3-amine (3)



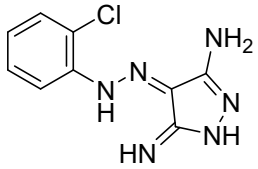
General procedure A1 followed by B1. Yield: 87%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.92 (s, 1H), 7.96 (d, J = 8.2 Hz, 1H), 7.70 (dd, J = 7.9, 1.5 Hz, 1H), 7.63 (td, J = 7.8, 1.4 Hz, 1H), 7.33 (t, J = 7.6 Hz, 1H), 6.60 (s, 1H), 6.04 (s, 1H), 5.37 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 151.38(d, J=243.2 Hz), 133.40(d, J=3.6 Hz), 126.17, 116.89(d, J=21.3 Hz), 116.27(d, J=6.9 Hz). HRMS (ESI) *m/z*: $[C_9H_9FN_6 + H]^+$ Calcd 221.0945; Found 221.0950.

(E)-5-imino-4-(2-phenylhydrazineylidene)-4,5-dihydro-1H-pyrazol-3-amine (4)



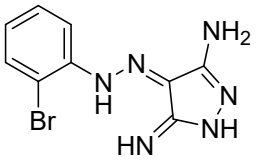
General procedure A1 followed by B1. Yield: 76%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.73 (s, 1H), 7.67 (dd, J = 8.3, 1.4 Hz, 2H), 7.39 (t, J = 7.8 Hz, 2H), 7.25 – 7.16 (m, 1H), 6.29 (s, 1H), 5.84 (s, 1H), 5.16 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 153.53, 128.77, 126.57, 120.46, 114.20. HRMS (ESI) *m/z*: $[C_9H_{10}N_6 + H]^+$ Calcd 203.1040; Found 203.1051.

(E)-4-(2-(2-chlorophenyl)hydrazineylidene)-5-imino-4,5-dihydro-1H-pyrazol-3-amine (5)



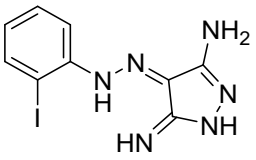
General procedure A1 followed by B1. Yield: 55%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.88 (s, 1H), 7.84 (d, J = 8.1, 1H), 7.50 (d, J = 8.0, 1H), 7.33 (t, J = 7.6 Hz, 1H), 7.23 – 7.15 (m, 1H), 6.52 (s, 1H), 6.11 (s, 1H), 5.31 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 149.39, 130.31, 127.92, 127.68, 117.05, 116.79. HRMS (ESI) *m/z*: $[C_9H_9ClN_6 + H]^+$ Calcd 237.0650; Found 237.0659.

(E)-4-(2-(2-bromophenyl)hydrazineylidene)-5-imino-4,5-dihydro-1H-pyrazol-3-amine (6)

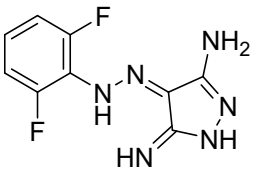


General procedure A1 followed by B1. Yield: Quant. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.90 (s, 1H), 7.82 (ddd, J = 10.0, 8.0, 1.5 Hz, 1H), 7.67 (dd, J = 7.9, 1.4 Hz, 1H), 7.37 (td, J = 8.3, 7.7, 1.4 Hz, 1H), 7.12 (td, J = 7.6, 1.7 Hz, 1H), 6.67 (s, 1H), 6.04 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 152.76, 150.25, 133.29, 128.53, 128.09, 121.58, 117.26, 116.64. HRMS (ESI) *m/z*: $[C9H9BrN6 + H]^+$ Calcd 281.0145; Found 281.0145.

(E)-5-imino-4-(2-(2-iodophenyl)hydrazineylidene)-4,5-dihydro-1H-pyrazol-3-amine (7)



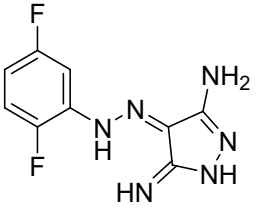
General procedure A1 followed by B1. Yield: Quant. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.84 (s, 1H), 7.90 (d, J = 7.8 Hz, 1H), 7.76 (dd, J = 8.2, 1.5 Hz, 1H), 7.38 (t, J = 7.6 Hz, 1H), 7.26 (s, 0H), 6.98 (td, J = 7.4, 1.6 Hz, 1H), 6.77 – 6.68 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 152.31, 139.28, 129.22, 128.62, 116.82, 115.99, 99.73. HRMS (ESI) *m/z*: $[C9H9IN6 + H]^+$ Calcd 329.0006; Found 329.0090.



(E)-4-(2-(2,6-difluorophenyl)hydrazineylidene)-5-imino-4,5-dihydro-1H-pyrazol-3-amine (8)

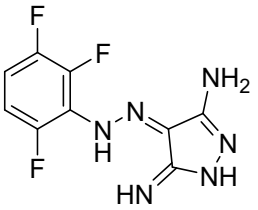
General procedure A1 followed by B1. Yield: 51%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.90 – 10.84 (m, 2H), 7.26 – 7.17 (m, 1H), 7.22 – 7.06 (m, 4H), 6.10 (s, 4H), 3.35 (s, 1H), 2.53 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 155.41 (dd, J = 250.7, 5.6 Hz), 132.35 (t, J = 11.0 Hz), 126.51 (t, J = 10.0 Hz), 117.24, 112.70 (dd, 18.1, 5.6 Hz). HRMS (ESI) *m/z*: $[C9H8F2N6 + H]^+$ Calcd 239.0851; Found 239.0863.

(E)-4-(2-(2,5-difluorophenyl)hydrazineylidene)-5-imino-4,5-dihydro-1H-pyrazol-3-amine (9)



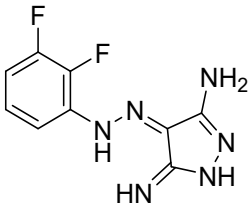
General procedure A1 followed by B1. Yield: 73%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.93 (s, 1H), 7.67 (ddd, J = 10.0, 6.4, 3.3 Hz, 1H), 7.30 (ddd, J = 10.7, 9.0, 4.9 Hz, 1H), 7.01 (ddt, J = 9.0, 7.2, 3.5 Hz, 1H), 6.43 (s, 3H), 6.27 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 10.93 (s, 1H), 7.68 (ddd, J = 10.0, 6.4, 3.3 Hz, 1H), 7.30 (ddd, J = 10.6, 9.0, 4.9 Hz, 1H), 7.05 – 6.95 (m, 1H), 6.47 (s, 2H), 6.25 (s, 2H). HRMS (ESI) *m/z*: $[C9H8F2N6 + H]^+$ Calcd 239.0851; Found 239.0870.

(E)-5-imino-4-(2-(2,3,6-trifluorophenyl)hydrazineylidene)-4,5-dihydro-1H-pyrazol-3-amine (10)



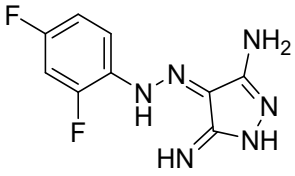
General procedure A1 followed by B1. Yield: 67%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.08 (s, 1H), 7.31 – 7.10 (m, 2H), 6.46 (s, 2H), 5.90 (s, 2H). Due to low electron density of the polyfluorinated compound, it was not possible to obtain a good quality ^{13}C NMR spectrum. HRMS (ESI) *m/z*: $[C9H7F3N6 + H]^+$ Calcd 257.0757; Found 257.0761.

(E)-4-(2-(2,3-difluorophenyl)hydrazineylidene)-5-imino-4,5-dihydro-1H-pyrazol-3-amine (11)



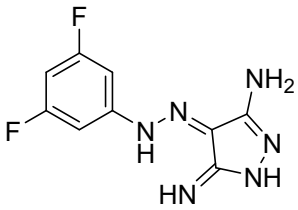
General procedure A1 followed by B1. Yield: 83%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.89 (s, 1H), 7.68 – 7.59 (m, 1H), 7.26 – 7.10 (m, 2H), 6.67 (s, 1H), 6.08 (s, 2H), 5.46 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 151.08 (dd, J = 243.5, 11.3 Hz), 145.29 (dd, J = 250.2, 13.5 Hz), 143.73 (dd, J = 3.6, 1.5 Hz), 124.29 (dd, J = 8.0, 4.8 Hz), 116.92, 114.13 (d, J = 17.2 Hz), 112.76 (d, J = 3.1 Hz). HRMS (ESI) *m/z*: [C9H8F2N6 + H]$^{+}$ Calcd 239.0851; Found 239.0874.

(E)-4-(2-(2,4-difluorophenyl)hydrazineylidene)-5-imino-4,5-dihydro-1H-pyrazol-3-amine (12)



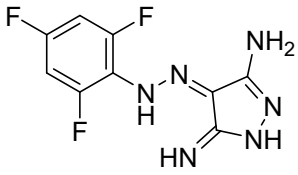
General procedure A1 followed by B1. Yield: 72%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.84 (s, 2H), 7.85 (td, J = 9.1, 6.4 Hz, 2H), 7.30 (ddd, J = 11.7, 9.2, 2.8 Hz, 2H), 7.18 (s, 1H), 7.08 (dddd, J = 9.3, 8.2, 2.8, 1.3 Hz, 2H), 6.46 (s, 2H), 5.90 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.79 (dd, J = 245.5, 11.7 Hz), 157.18 (dd, J = 251.9, 12.3 Hz), 138.90 (dd, J = 6.7, 3.7 Hz), 118.32 (dd, J = 9.5, 2.7 Hz), 116.12, 111.99 (dd, J = 22.1, 3.6 Hz), 104.94 (dd, J = 26.5, 24.1 Hz). HRMS (ESI) *m/z*: [C9H8F2N6 + H]$^{+}$ Calcd 239.0851; Found 239.0862.

(E)-4-(2-(3,5-difluorophenyl)hydrazineylidene)-5-imino-4,5-dihydro-1H-pyrazol-3-amine (13)



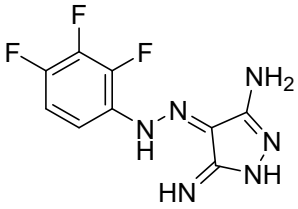
General procedure A1 followed by B1. Yield: 23%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.86 (s, 1H), 7.45 – 7.35 (m, 2H), 7.01 – 6.91 (m, 1H), 6.61 (s, 1H), 5.97 (s, 1H), 5.36 (s, 1H). Due to low electron density of the polyfluorinated compound, it was not possible to obtain a good quality ^{13}C NMR spectrum. HRMS (ESI) *m/z*: [C9H8F2N6 + H]$^{+}$ Calcd 239.0851; Found 239.0861.

(E)-5-imino-4-(2-(2,4,6-trifluorophenyl)hydrazineylidene)-4,5-dihydro-1H-pyrazol-3-amine (14)



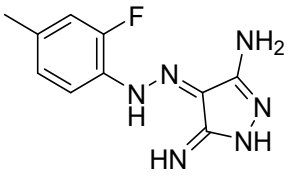
General procedure A1 followed by B1. Yield: 43%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.06 (s, 1H), 7.29 – 7.16 (m, 1H), 6.82 (ddd, J = 11.7, 9.2, 2.8 Hz, 1H), 6.61 (ddd, J = 10.6, 2.8, 1.7 Hz, 1H), 6.37 (s, 2H), 6.16 (s, 2H), 5.80 (s, 1H). Due to low electron density of the polyfluorinated compound, it was not possible to obtain a good quality ^{13}C NMR spectrum. HRMS (ESI) *m/z*: [C9H7F3N6 + H]$^{+}$ Calcd 257.0757; Found 257.0762.

(E)-5-imino-4-(2-(2,3,4-trifluorophenyl)hydrazineylidene)-4,5-dihydro-1H-pyrazol-3-amine (15)



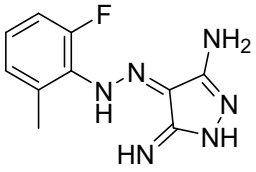
General procedure A1 followed by B1. Yield: 56%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.80 (s, 1H), 7.72 – 7.61 (m, 1H), 7.36 – 7.22 (m, 1H), 6.29 (s, 4H). Due to low electron density of the polyfluorinated compound, it was not possible to obtain a good quality ^{13}C NMR spectrum. HRMS (ESI) *m/z*: [C9H7F3N6 + H]$^{+}$ Calcd 257.0757; Found 257.0758.

(E)-4-(2-(2-fluoro-4-methylphenyl)hydrazineylidene)-5-imino-4,5-dihydro-1H-pyrazol-3-amine (16)



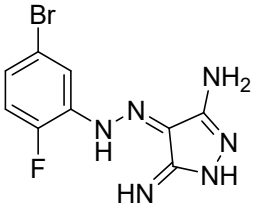
General procedure A1 followed by B1. Yield: 51%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.80 (s, 1H), 7.70 (t, J = 8.4 Hz, 1H), 7.09 (dd, J = 12.4, 1.8 Hz, 1H), 6.99 (dd, J = 8.4, 1.8 Hz, 1H), 6.37 (s, 1H), 5.90 (s, 1H), 5.22 (s, 1H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 157.35 (d, J = 249.0 Hz), 139.44 (d, J = 6.7 Hz), 138.15 (d, J = 7.7 Hz), 125.50, 116.99 (d, J = 19.5 Hz), 116.97, 115.82, 21.07. HRMS (ESI) *m/z*: [C10H11FN6 + H]$^{+}$ Calcd 235.1102; Found 235.1108.

(E)-4-(2-(2-fluoro-6-methylphenyl)hydrazineylidene)-5-imino-4,5-dihydro-1H-pyrazol-3-amine (17)



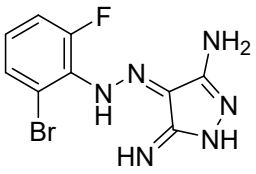
General procedure A1 followed by B1. Yield: 86%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.29 – 7.16 (m, 1H), 7.21 – 7.13 (m, 1H), 7.18 – 7.08 (m, 2H), 7.09 (d, J = 2.8 Hz, 2H), 7.11 – 7.00 (m, 4H), 7.04 – 6.93 (m, 2H), 2.44 (s, 2H), 2.40 (s, 2H), 2.40 – 2.30 (m, 1H), 2.32 (s, 6H), 2.23 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 155.66, 153.19, 141.37, 141.29, 134.13, 133.77, 133.40, 127.36, 126.86, 126.82, 126.78, 126.51, 126.48, 116.92, 115.03, 114.64, 114.42, 114.21, 114.01, 19.22, 18.86, 18.83, 18.25, 18.22. HRMS (ESI) *m/z*: [C10H11FN6 + H]$^{+}$ Calcd 235.1102; Found 235.1118.

(E)-4-(2-(5-bromo-2-fluorophenyl)hydrazineylidene)-5-imino-4,5-dihydro-1H-pyrazol-3-amine (18)



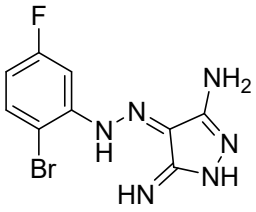
General procedure A1 followed by B1. Yield: 63%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.92 (s, 1H), 8.01 (dd, J = 7.2, 2.6 Hz, 1H), 7.38 – 7.29 (m, 1H), 7.29 – 7.20 (m, 1H), 6.75 (s, 2H), 6.10 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 156.43 (d, J = 249.3 Hz), 143.09 (d, J = 7.6 Hz), 129.42 (d, J = 8.0 Hz), 119.79, 118.82 (d, J = 21.4 Hz), 117.53 (d, J = 3.2 Hz), 117.09. HRMS (ESI) *m/z*: [C9H8BrFN6 + H]$^{+}$ Calcd 299.0051; Found 299.0053.

(E)-4-(2-(2-bromo-6-fluorophenyl)hydrazineylidene)-5-imino-4,5-dihydro-1H-pyrazol-3-amine (19)



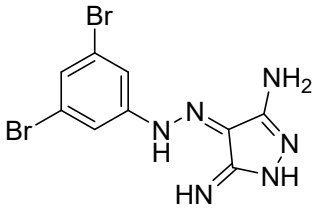
General procedure A1 followed by B1. Yield: Quant. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.91 (s, 1H), 7.52 (dt, J = 8.0, 1.3 Hz, 1H), 7.33 – 7.23 (m, 1H), 7.17 – 7.07 (m, 1H), 6.51 (s, 1H), 5.80 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 153.75 (d, J = 255.3 Hz), 140.78, 128.90 (d, J = 3.5 Hz), 127.39 (d, J = 8.8 Hz), 120.10 (d, J = 3.5 Hz), 117.07 (d, J = 2.1 Hz), 116.88. HRMS (ESI) *m/z*: [C9H8BrFN6 + H]$^{+}$ Calcd 299.0051; Found 299.0052.

(E)-4-(2-(2-bromo-5-fluorophenyl)hydrazineylidene)-5-imino-4,5-dihydro-1H-pyrazol-3-amine (20)



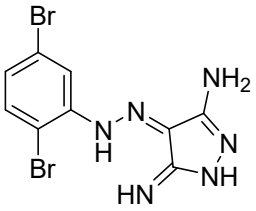
General procedure A1 followed by B1. Yield: 98%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.99 (s, 1H), 7.74 – 7.64 (m, 2H), 7.04 – 6.93 (m, 1H), 6.73 (s, 1H), 6.26 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.81 (d, J = 244.5 Hz), 152.19 (d, J = 6.1 Hz), 134.34 (d, J = 8.8 Hz), 117.20, 115.65 (d, J = 2.9 Hz), 114.44 (d, J = 24.2 Hz), 103.74 (d, J = 24.6 Hz). HRMS (ESI) *m/z*: $[C_9H_8BrFN_6 + H]^+$ Calcd 299.0051; Found 299.0052.

(E)-4-(2-(3,5-dibromophenyl)hydrazineylidene)-5-imino-4,5-dihydro-1H-pyrazol-3-amine (21)



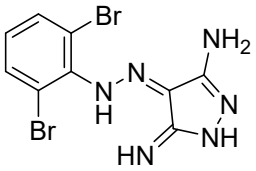
General procedure A1 followed by B1. Yield: 91%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.83 (s, 1H), 7.90 (d, J = 1.8 Hz, 2H), 7.54 (t, J = 1.8 Hz, 1H), 6.19 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 156.73, 130.21, 123.30, 122.57, 116.16. HRMS (ESI) *m/z*: $[C_9H_8Br_2N_6 + H]^+$ Calcd 358.9250; Found 358.9250.

(E)-4-(2-(2,5-dibromophenyl)hydrazineylidene)-5-imino-4,5-dihydro-1H-pyrazol-3-amine (22)



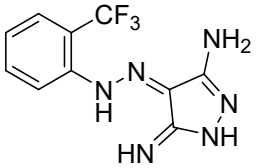
General procedure A1 followed by B1. Yield: 63%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.62 (s, 1H), 8.02 (d, J = 2.4 Hz, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.30 – 7.21 (m, 1H), 6.75 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 151.60, 134.81, 134.20, 129.72, 122.26, 119.93 (d, J = 5.2 Hz), 119.72, 117.59. HRMS (ESI) *m/z*: $[C_9H_8Br_2N_6 + H]^+$ Calcd 358.9250; Found 358.9253.

(E)-4-(2-(2,6-dibromophenyl)hydrazineylidene)-5-imino-4,5-dihydro-1H-pyrazol-3-amine (23)



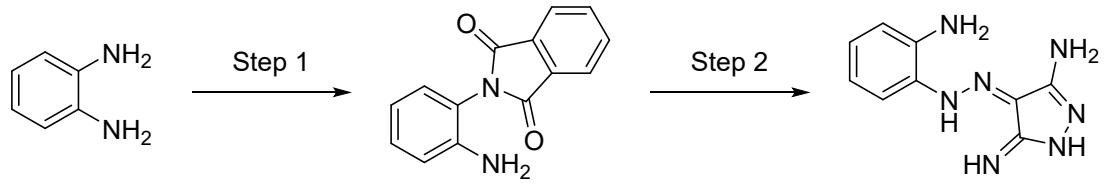
General procedure A1 followed by B1. Yield: Quant. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.88 (s, 1H), 7.68 (d, J = 8.0 Hz, 2H), 7.03 (t, J = 7.9 Hz, 1H), 6.36 (s, 1H), 5.81 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 150.28, 133.19, 128.10, 116.97, 115.70. HRMS (ESI) *m/z*: $[C_9H_8Br_2N_6 + H]^+$ Calcd 358.9250; Found 358.9249.

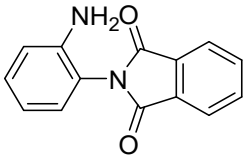
(E)-5-imino-4-(2-(2-(trifluoromethyl)phenyl)hydrazineylidene)-4,5-dihydro-1H-pyrazol-3-amine (24)



General procedure A1 followed by B1. Yield: 78%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.82 (m, 1H), 7.41 – 7.22 (m, 3H), 6.63 (s, 2H), 6.20 (s, 2H), NH protons not observed. Due to low electron density of the polyfluorinated compound, it was not possible to obtain a good quality ^{13}C NMR spectrum. HRMS (ESI) *m/z*: $[C_{10}H_9F_3N_6 + H]^+$ Calcd 271.0914; Found 271.0922.

(E)-4-(2-(2-aminophenyl)hydrazineylidene)-5-imino-4,5-dihydro-1H-pyrazol-3-amine (25)

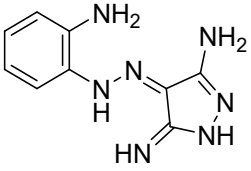




Step 1

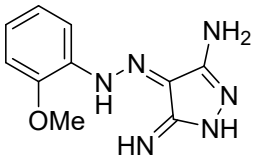
O-Phenylenediamine (1 g, 9.25 mmol, 1 eq) was dissolved in 0.1 M phosphate buffer (2.2 mL/mmol) and N-hydroxyphthalimide was added (1 eq). The reaction was stirred overnight at rt. The product was isolated by filtration and washed with water. Yield: 85%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.98 – 7.82 (m, 4H), 7.18 – 7.09 (m, 1H), 7.02 (dd, J = 7.8, 1.5 Hz, 1H), 6.77 (dd, J = 8.2, 1.3 Hz, 1H), 6.58 (td, J = 7.5, 1.4 Hz, 1H), 5.37 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.02, 146.96, 134.57, 132.96, 130.47, 130.16, 123.53, 116.42, 115.81, 115.77.

Step 2



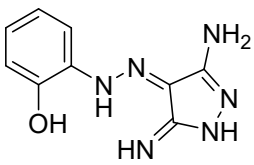
General procedure A1 followed by B1. Yield: Quant. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.58 (s, 1H), 7.48 (dd, J = 8.0, 1.5 Hz, 1H), 6.96 – 6.87 (m, 1H), 6.73 (dd, J = 8.1, 1.3 Hz, 1H), 6.57 – 6.48 (m, 1H), 5.72 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 143.51, 138.54, 127.99, 120.14, 116.44, 116.03, 114.13. HRMS (ESI) *m/z*: $[C_9H_{11}N_7 + H]^+$ Calcd 218.1149; Found 218.1150.

(E)-5-imino-4-(2-(2-methoxyphenyl)hydrazineylidene)-4,5-dihydro-1H-pyrazol-3-amine (26)



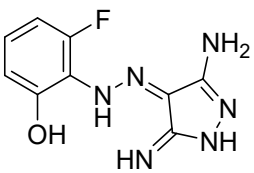
General procedure A1 followed by B1. Yield: 33%. ^{1}H NMR (400 MHz, DMSO-d_6):δ 7.65 (dd, J = 8.0, 1.7 Hz, 1H), 7.24 – 7.11 (m, 1H), 7.14 – 7.05 (m, 1H), 6.97 – 6.89 (m, 1H), 5.80 (s, 0H), 3.86 (s, 3H). NH protons not observed. ^{13}C NMR (100 MHz, DMSO-d_6): δ 155.21, 154.60, 153.01, 142.69, 128.14, 120.88, 115.78, 113.05, 56.29. HRMS (ESI) *m/z*: $[C_{10}H_{12}N_6O + H]^+$ Calcd 233.1145; Found 233.1159.

(E)-2-(2-(3-amino-5-imino-1,5-dihydro-4H-pyrazol-4-ylidene)hydrazineyl)phenol (27)



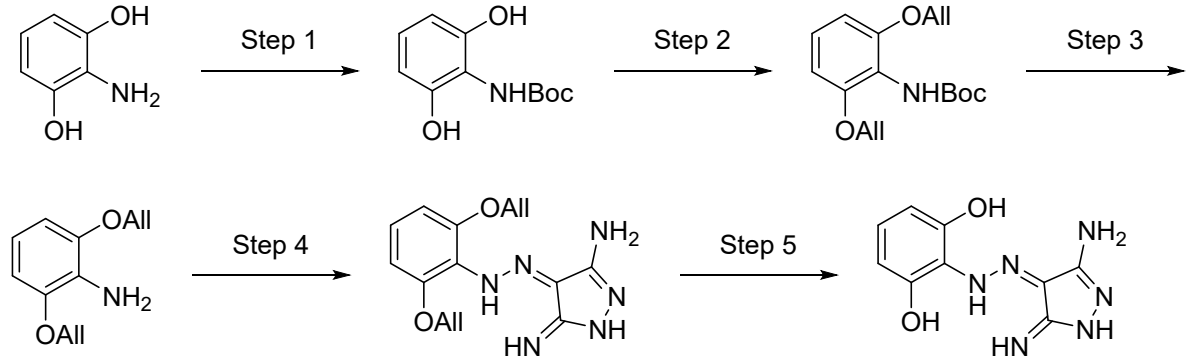
General procedure A1 followed by B1. Yield: 30%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.71 (s, 1H), 10.28 (s, 1H), 7.62 (dd, J = 7.9, 1.7 Hz, 1H), 7.13 – 7.02 (m, 1H), 6.94 – 6.79 (m, 1H), 6.04 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 152.02, 139.79, 135.81, 128.18, 122.01, 119.71, 117.53, 113.92. HRMS (ESI) *m/z*: $[C_9H_{10}N_6O + H]^+$ Calcd 219.0989; Found 219.0990.

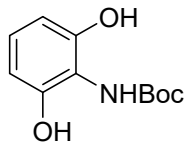
(E)-2-(2-(3-amino-5-imino-1,5-dihydro-4H-pyrazol-4-ylidene)hydrazineyl)-3-fluorophenol (28)



General procedure A1 followed by B1. Yield: 25%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.68 (s, 1H), 10.93 (s, 1H), 7.13 – 7.03 (m, 1H), 6.82 – 6.72 (m, 1H), 6.72 – 6.65 (m, 1H), 6.14 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 158.27 (d, J = 249.1 Hz), 152.26 (d, J = 2.2 Hz), 128.21 (d, J = 10.7 Hz), 126.75 (d, J = 8.2 Hz), 114.39, 113.59 (d, J = 3.1 Hz), 106.73 (d, J = 20.1 Hz). HRMS (ESI) *m/z*: $[C_9H_9FN_6O + H]^+$ Calcd 237.0895; Found 237.0920.

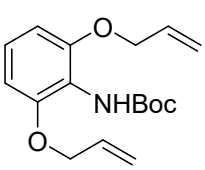
(E)-2-(2-(3-amino-5-imino-1,5-dihydro-4H-pyrazol-4-ylidene)hydrazineyl)benzene-1,3-diol (29)





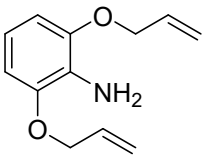
Step 1

2-Aminoresorcinol (589.2 mg, 4.71 mmol, 1 eq) was dissolved in water (5 mL) and added boc-anhydride (1.13 g, 1.1 eq). Upon completion of the reaction, the product was isolated by filtration as a black solid. Yield: 98%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.07 (s, 2H), 7.65 (s, 1H), 6.81 (t, J = 8.1 Hz, 1H), 6.30 (d, J = 8.1 Hz, 2H), 1.42 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 154.98, 154.39, 146.68, 126.92, 113.67, 107.24, 86.08, 78.75, 28.65.



Step 2

tert-butyl (2,6-dihydroxyphenyl)carbamate (1 eq) and K_2CO_3 (3 eq) was dissolved in DMF (1 mL/mmol) and allylbromide (2.3 eq) was added. The reaction was left with stirring overnight at rt. The mixture was filtered and the filtrate was washed with water. The aqueous phase was extracted with Et_2O twice. The combined organic phase was washed with brine and dried over Na_2SO_4. After removal of the solvent under vacuum, two immiscible oils were obtained, which could be separated to give the product as a black oil. The intermediate was used without further purification in the next step.

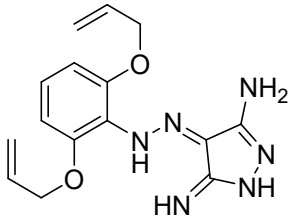


Step 3

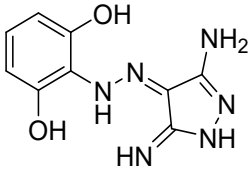
tert-butyl (2,6-bis(allyloxy)phenyl)carbamate was dissolved in DCM:TFA (4:1, 25mL). The TFA and DCM was removed under vacuum, followed by co-evaporating with heptane, to the 2,6-bis(allyloxy)aniline. Yield: 71% over the two steps. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.28 (s, 6H), 7.18 (t, J = 8.4 Hz, 1H), 6.74 (d, J = 8.5 Hz, 2H), 6.02 (ddt, J = 17.4, 10.5, 5.2 Hz, 2H), 5.43 (dq, J = 17.4, 1.7 Hz, 2H), 5.25 (dq, J = 10.5, 1.5 Hz, 2H), 4.65 (dt, J = 5.2, 1.7 Hz, 4H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 151.82, 133.41, 128.07, 118.22, 111.13, 106.32, 69.78.

Step 4

General procedure A1 followed by B1, to give the crude (E)-4-(2-(2,6-bis(allyloxy)phenyl) hydrazineylidene)-5-imino-4,5-dihydro-1H-pyrazol-3-amine. Yield: Crude 96%. Used without further purification in the next step.



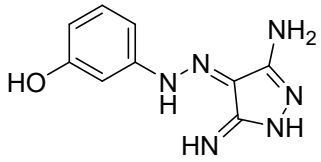
Step 5



The (E)-4-(2-(2,6-bis(allyloxy)phenyl) hydrazineylidene)-5-imino-4,5-dihydro-1H-pyrazol-3-amine (1 eq) was dissolved in dry MeOH (10.8 mL/mmol) and Pd(PPh3)4 (0.02 eq) added, followed by K_2CO_3 (6 eq). The reaction was allowed to stir overnight under nitrogen. The mixture was filtered, conc. in vacuo, and purified by preparative HPLC. Yield: Quant. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.68 – 7.51 (m, 3H). ^{13}C NMR (100 MHz, Deuterium Oxide): δ 146.34,

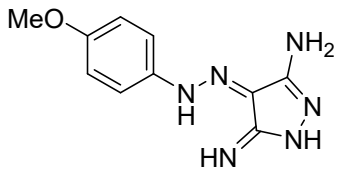
121.54, 121.11, 119.26, 109.3. HRMS (ESI) *m/z*: [C9H9N6O2 - H]$^-$ Calcd 233.0792; Found 233.0791.

(E)-3-(2-(3-amino-5-imino-1,5-dihydro-4H-pyrazol-4-ylidene)hydrazineyl)phenol (30)



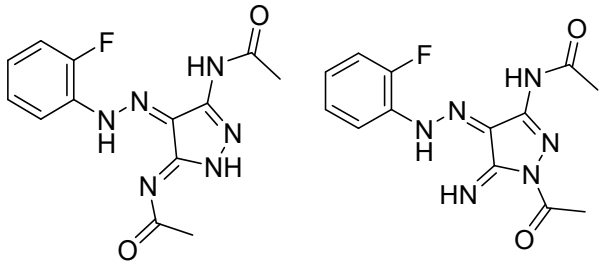
General procedure A1 followed by B1. Yield: 34%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.42 (s, 1H), 7.20 – 7.02 (m, 3H), 6.63 (ddd, J = 7.8, 2.5, 1.2 Hz, 1H), 6.29 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.43, 158.51, 155.44, 129.69, 114.52, 114.25, 112.59, 107.08. HRMS (ESI) *m/z*: [C9H10N6O + H]$^+$ Calcd 219.0989; Found 219.0987.

(E)-5-imino-4-(2-(4-methoxyphenyl)hydrazineylidene)-4,5-dihydro-1H-pyrazol-3-amine (31)



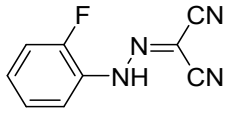
General procedure A1 followed by B1. Yield: 64%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.65 (s, 1H), 7.69 – 7.60 (m, 2H), 7.00 – 6.92 (m, 2H), 3.79 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 158.86, 148.05, 122.16, 114.45, 113.84, 55.75. HRMS (ESI) *m/z*: [C10H12N6O + H]$^+$ Calcd 233.1145; Found 233.1149.

N-((3Z,4E)-5-acetamido-4-(2-(2-fluorophenyl)hydrazineylidene)-2,4-dihydro-3H-pyrazol-3-ylidene)acetamide (32) and (Z)-N-(1-acetyl-4-(2-(2-fluorophenyl)hydrazineylidene)-5-imino-4,5-dihydro-1H-pyrazol-3-yl)acetamide (33)

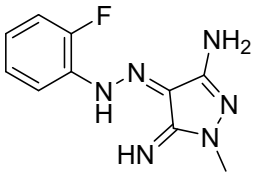


(E)-4-(2-(2-fluorophenyl)hydrazineylidene) -5-imino-4,5-dihydro-1H-pyrazol-3-amine (255.8 mg, 1.16 mmol, 1 eq) was added to a solution of sodium acetate (0.46 mg/mmol) in acetic anhydride (22 eq.) and heated to 100^{o}C until full conversion. The mixture was poured into an ice-water mixture (100 mL), resulting in precipitation of the product. The product was isolated by filtration, followed by recrystallization in ethanol to give the product mixture as black needles, yield 175.8 mg. Initial biological testing was performed on the mixture. Yield: 50%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.39 (s, 0H), 8.34 (s, 2H), 7.93 – 7.80 (m, 0H), 7.71 (td, J = 8.0, 1.7 Hz, 1H), 7.62 – 7.21 (m, 4H), 2.89 (s, 0H), 2.76 – 2.69 (m, 0H), 2.58 (s, 3H), 2.54 (s, 1H), 2.32 (s, 6H), 2.29 (d, J = 2.8 Hz, 1H), 2.19 (d, J = 6.1 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.53, 173.45, 172.02, 159.74, 157.23, 140.86, 140.79, 131.33, 131.25, 125.22, 125.19, 117.83, 117.41, 117.33, 117.13, 117.00, 26.02, 25.96, 23.36, 23.26. HRMS (ESI) *m/z*: [C13H13FN6O2 - H]$^-$ Calcd 303.1011; Found 303.1006 and 303.0902.

N-(2-fluorophenyl)carbonohydrazonoyl dicyanide (34)



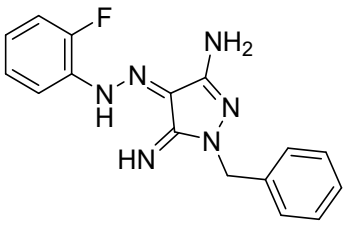
General Procedure A1. Yield: 98%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.56 – 7.46 (m, 1H), 7.41 – 7.29 (m, 1H), 7.34 – 7.21 (m, 2H), NH proton not observed. ^{13}C NMR (100 MHz, DMSO-d_6): δ 157.5 (d, J=253.1 Hz), 127.9, 125.73, 125.70, 120.9, 117.2, 117.0, 110.4, 84.4. HRMS (ESI) *m/z*: [C9H5FN4 - H]$^-$ Calcd 187.0425; Found 187.0429.



(Z)-4-(2-(2-fluorophenyl)hydrazineylidene)-5-imino-1-methyl-4,5-dihydro-1H-pyrazol-3-amine (35)

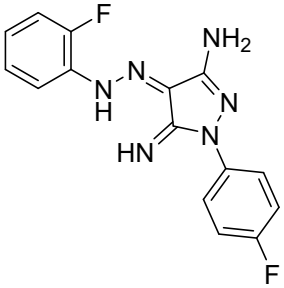
General procedure A1 followed by B1. Yield: 71%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.83 (d, J = 10.1 Hz, 1H), 7.37 – 7.32 (m, 1H), 7.31 – 7.17 (m, 3H), 7.22 – 7.13 (m, 1H), 6.64 (s, 2H), 6.06 (s, 2H), 5.38 (s, 1H), 3.38 (s, 4H), 2.54 – 2.47 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 158.69, 141.79, 127.80, 124.84, 117.33, 116.79, 116.60, 116.20, 34.25. HRMS (ESI) *m/z*: $[C10H11FN6 + H]^+$ Calcd 235.1102; Found 235.1108.

(Z)-1-benzyl-4-(2-(2-fluorophenyl)hydrazineylidene)-5-imino-4,5-dihydro-1H-pyrazol-3-amine (36)



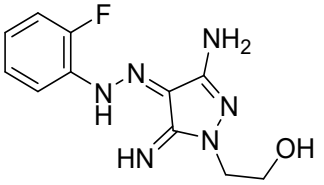
General procedure A1 followed by B2. Yield: 70%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.83 (s, 2H), 7.42 – 7.11 (m, 9H), 6.86 (s, 1H), 6.09 (s, 1H), 5.43 (s, 1H), 4.98 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 157.50 (d, J = 249.7 Hz), 148.92, 147.12, 141.75, 137.68, 128.84, 127.88 (d, J = 7.25 Hz), 127.71, 124.84, 117.37, 116.72 (d, J = 19.5 Hz), 116.13. HRMS (ESI) *m/z*: $[C16H15FN6 + H]^+$ Calcd 311.1415; Found 311.1424.

(Z)-1-(4-fluorophenyl)-4-(2-(2-fluorophenyl)hydrazineylidene)-5-imino-4,5-dihydro-1H-pyrazol-3-amine (37)



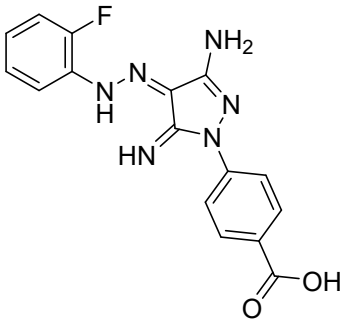
General procedure A1 followed by B2. Yield: 47%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.91 (s, 1H), 7.66 – 7.51 (m, 2H), 7.44 – 7.14 (m, 6H), 6.90 (s, 1H), 6.25 (s, 1H), 5.75 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.54 (d, J = 243.4 Hz), 157.72 (d, J = 249.7 Hz), 141.47, 128.57 (d, J = 7.9 Hz), 125.14 (d, J = 9.0 Hz), 124.95 (d, J = 3.5 Hz), 117.49, 116.81 (d, J = 19.5 Hz), 116.57, 116.53 (d, J = 22.8 Hz). HRMS (ESI) *m/z*: $[C15H12F2N6 + H]^+$ Calcd 315.1164; Found 315.1177.

(Z)-2-(3-amino-4-(2-(2-fluorophenyl)hydrazineylidene)-5-imino-4,5-dihydro-1H-pyrazol-1-yl)ethan-1-ol (38)

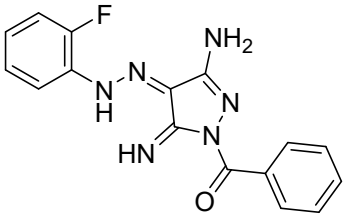


General procedure A1 followed by B2. Yield: 87%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.83 (s, 1H), 7.36 – 7.13 (m, 4H), 6.57 (s, 1H), 6.08 (s, 1H), 5.40 (s, 1H), 4.89 (t, J = 5.2 Hz, 1H), 3.78 (d, J = 6.2 Hz, 2H), 3.67 (q, J = 5.6 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 157.45 (d, J = 249.0 Hz), 149.06, 146.49, 141.80, 127.74 (d, J = 7.8 Hz), 124.84, 117.34, 116.68 (d, J = 19.6 Hz), 116.32, 59.45, 49.17. HRMS (ESI) *m/z*: $[C11H13FN6O + H]^+$ Calcd 265.1208; Found 265.1211.

(Z)-4-(3-amino-4-(2-(2-fluorophenyl)hydrazineylidene)-5-imino-4,5-dihydro-1H-pyrazol-1-yl)benzoic acid (39)



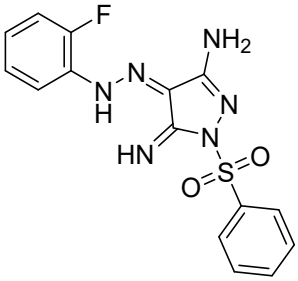
General procedure A1 followed by B2. Yield: 81%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.81 (s, 1H), 8.09 – 7.94 (m, 3H), 7.77 – 7.68 (m, 2H), 7.43 – 6.95 (m, 3H), 6.28 (s, 1H), 5.98 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.20, 157.82 (d, J = 250.2 Hz), 142.42, 141.35, 131.00, 128.89 (d, J = 8.1 Hz), 127.86, 124.96 (d, J = 3.65 Hz), 121.51, 117.52, 116.88 (d, J = 15.3 Hz), 116.77. HRMS (ESI) *m/z*: $[C_{16}H_{13}FN_6O_2 + H]^+$ Calcd 341.1157; Found 341.1162.



(Z)-(3-amino-4-(2-(2-fluorophenyl)hydrazineylidene)-5-imino-4,5-dihydro-1H-pyrazol-1-yl)(phenyl)methanone (40)

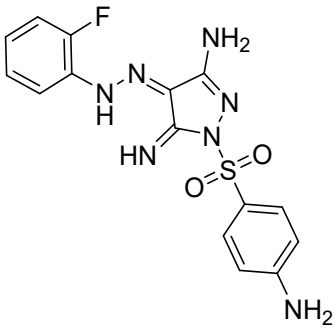
General procedure A1 followed by B2. Yield: 47%. ^{1}H NMR (400 MHz, DMSO-d_6):δ 8.52 (s, 1H), 8.02 – 7.89 (m, 3H), 7.68 – 7.57 (m, 1H), 7.56 – 7.48 (m, 2H), 7.45 – 7.31 (m, 2H), 7.30 – 7.21 (m, 1H), 6.34 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.47, 158.05 (d, J = 250.9 Hz), 141.13 (d, J = 6.4 Hz), 133.62, 132.37, 130.58, 129.81 (d, J = 8.0 Hz), 128.21, 125.06 (d, J = 3.6 Hz), 117.57, 117.01 (d, J = 19.5 Hz), 115.19. HRMS (ESI) *m/z*: $[C_{16}H_{13}FN_6O + H]^+$ Calcd 325.1208; Found 325.1213.

(Z)-4-(2-(2-fluorophenyl)hydrazineylidene)-5-imino-1-(phenylsulfonyl)-4,5-dihydro-1H-pyrazol-3-amine (41)



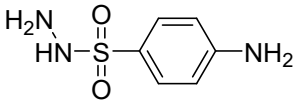
General procedure A1 followed by B1. Yield: 81%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.06 (s, 1H), 7.96 – 7.74 (m, 3H), 7.73 – 7.57 (m, 2H), 7.38 – 7.17 (m, 4H), 6.30 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 158.11 (d, J = 251.4 Hz), 140.77 (d, J = 6.5 Hz), 136.52, 135.33, 133.07, 130.25 (d, J = 8.6 Hz), 129.47, 127.96 (d, J = 13.7 Hz), 125.05 (d, J = 3.6 Hz), 117.52, 117.02 (d, J = 19.5 Hz), 114.89. HRMS (ESI) *m/z*: $[C_{15}H_{13}FN_6O_2S + H]^+$ Calcd 361.0877; Found 361.0835.

(Z)-1-((4-aminophenyl)sulfonyl)-4-(2-(2-fluorophenyl)hydrazineylidene)-5-imino-4,5-dihydro-1H-pyrazol-3-amine (42)



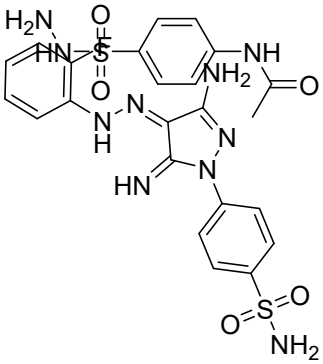
General procedure A1 followed by B1 using 4-aminobenzenesulfonohydrazide (SI1). Yield: 28%. ^{1}H NMR (400 MHz, Methanol-d^4): δ 7.63 – 7.52 (m, 2H), 7.33 – 7.20 (m, 7H). NH proton not observed. ^{13}C NMR (100 MHz, Methanol-d_4): δ 152.31 (d, J = 247.7 Hz), 129.20 (d, J = 9.5 Hz), 126.94 (d, J = 7.4 Hz), 124.98 (d, J = 3.7 Hz), 118.90, 115.93 (d, J = 18.7 Hz), 112.83, 108.22. HRMS (ESI) *m/z*: $[C_{15}H_{14}FN_7O_2S - H^+ + Na^+]$ Calcd 397.0733; Found 397.0748.

4-aminobenzenesulfonohydrazide (SI1)



N-(4-(hydrazineylsulfonyl)phenyl)acetamide (SI2) (923.7 mg, 4.03 mmol, 1 eq.) was dissolved in 40 wt% NaOH (40 mL) and refluxed until LCMS showed completion. When the reaction was complete, the cooled mixture was added ethyl acetate and made slightly acidic with conc. HCl before extraction. The organic phase was evaporated and used as crude salt without further purification. Yield: Quant. ^{1}H NMR (400 MHz, Deuterium Oxide): δ 7.72 – 7.62 (m, 2H), 7.52 – 7.38 (m, 2H). NH proton not observed. ^{13}C NMR (100 MHz, Deuterium Oxide): δ 173.13, 140.95, 136.69, 128.08, 126.40, 121.37, 23.09.

N-(4-(hydrazineylsulfonyl)phenyl)acetamide (SI2)

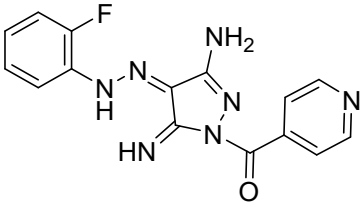


4-acetamidobenzenesulfonyl chloride (3g, 12.84 mmol, 1 eq.) was dissolved in DCM (1.95 mL/mmol) and hydrazine hydrate (50%, 5 eq.) was added under nitrogen. The reaction was followed by TLC and upon completion, the product was isolated by filtration and dried under vacuum. Yield: 52%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.40 (s, 1H), 8.24 (s, 1H), 7.82 – 7.66 (m, 4H), 7.52 (s, 1H), 4.04 (s, 2H), 2.09 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.50, 143.49, 132.03, 129.22, 118.93, 24.60.

(Z)-4-(3-amino-4-(2-(2-fluorophenyl)hydrazineylidene)-5-imino-4,5-dihydro-1H-pyrazol-1-yl)benzenesulfonamide (43)

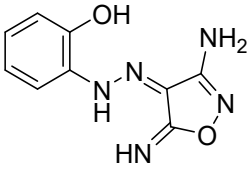
General procedure A1 followed by B2. Yield: Quant. ^{1}H NMR (400 MHz, DMSO-d_6):δ 10.46 (s, 2H), 8.88 (s, 1H), 7.97 – 7.88 (m, 1H), 7.81 – 7.74 (m, 1H), 7.74 – 7.67 (m, 2H), 7.46 (s, 1H), 7.37 – 7.20 (m, 1H), 7.20 (s, 2H), 7.08 – 7.00 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 157.81 (d, J = 249.9 Hz), 148.88, 141.35 (d, J = 6.8 Hz), 141.23, 136.59, 128.94 (d, J = 7.9 Hz), 127.38 (d, J = 2.1 Hz), 124.99 (d, J = 3.5 Hz), 121.97, 117.52, 116.97, 116.74 (d, J = 6.2 Hz), 113.74. HRMS (ESI) *m/z*: $[C15H14FN7O2S + H]^+$ Calcd 376.0986; Found 376.0988.

(Z)-(3-amino-4-(2-(2-fluorophenyl)hydrazineylidene)-5-imino-4,5-dihydro-1H-pyrazol-1-yl)(pyridin-4-yl)methanone (44)



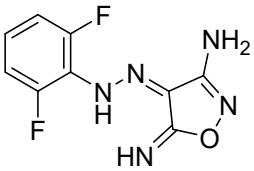
General procedure A1 followed by B1. Yield: 40%. ^{1}H NMR (400 MHz, DMSO-d_6):δ 8.80 – 8.74 (m, 2H), 8.54 (s, 1H), 7.97 – 7.89 (m, 1H), 7.85 – 7.79 (m, 2H), 7.45 – 7.20 (m, 4H), 7.04 (s, 1H), 6.42 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.85, 158.09 (d, J = 251.1 Hz), 153.03, 150.03, 141.23, 141.05 (d, J = 6.3 Hz), 130.00 (d, J = 8.1 Hz), 123.53, 118.17, 117.56, 117.03 (d, J = 19.5 Hz), 115.14. HRMS (ESI) *m/z*: $[C15H12FN7O + H]^+$ Calcd 326.1160; Found 326.1151.

(Z)-2-(2-(3-amino-5-iminoisoxazol-4(5H)-ylidene)hydrazineyl)phenol (45)



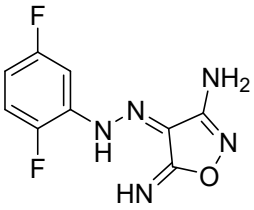
General procedure A1 followed by B3. Yield: Quant. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.12 (s, 1H), 8.03 (s, 1H), 7.72 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.46 (s, 1H), 7.27 (ddd, *J* = 8.7, 7.3, 1.7 Hz, 1H), 7.07 (dd, *J* = 8.3, 1.4 Hz, 1H), 6.98 (ddd, *J* = 8.4, 7.4, 1.4 Hz, 1H), 6.00 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 146.73, 128.42, 123.46, 121.15, 119.63, 116.23, 115.52. HRMS (ESI) *m/z*: $[C9H9N5O2 + H]^+$ Calcd 220.0829; Found 220.0829.

(Z)-4-(2-(2,6-difluorophenyl)hydrazineylidene)-5-imino-4,5-dihydroisoxazol-3-amine (46)



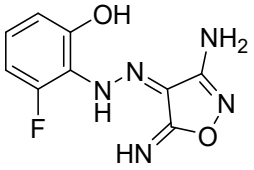
General procedure A1 followed by B3. Yield: 41%. ^{1}H NMR (400 MHz, Methanol-d_4): δ 7.44 – 7.24 (m, 2H), 7.26 (s, 1H), 7.28 – 7.20 (m, 2H), 7.24 – 6.99 (m, 8H). Due to low electron density of the polyfluorinated compound, it was not possible to obtain a good quality ^{13}C NMR spectrum. HRMS (ESI) *m/z*: $[C_9H_7F_2N_5O + H]^+$ Calcd 240.0691; Found 240.0697.

(Z)-4-(2-(2,5-difluorophenyl)hydrazineylidene)-5-imino-4,5-dihydroisoxazol-3-amine (47)



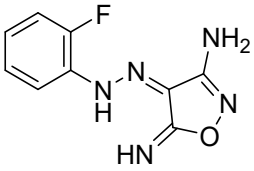
General procedure A1 followed by B3. Yield: 52%. ^{1}H NMR (400 MHz, Methanol-d_4): δ 7.61 – 7.52 (m, 1H), 7.29 – 7.18 (m, 1H), 7.11 – 6.99 (m, 1H). ^{13}C NMR (100 MHz, Methanol-d_4): δ 159.20 (dd, J = 241.0, 2.0 Hz), 154.10 (dd, J = 246.7, 2.3 Hz), 142.33 (dd, J = 23.7, 8.9 Hz), 118.29 (dd, J = 22.6, 9.3 Hz), 115.26 (dd, J = 25.3, 8.2 Hz), 110.21, 103.71 (d, J = 25.6, 8.3 Hz). HRMS (ESI) *m/z*: $[C_9H_7F_2N_5O + H]^+$ Calcd 240.0691; Found 240.0690.

(Z)-2-(2-(3-amino-5-iminoisoxazol-4(5H)-ylidene)hydrazineyl)-3-fluorophenol (48)



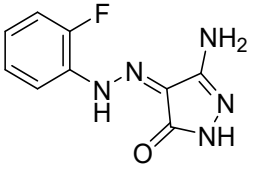
General procedure A1 followed by B3. Yield: 2%. ^{1}H NMR (400 MHz, Chloroform-d): 1δ 11.27 (s, 1H), 11.04 (q, J = 8.5, 7.7 Hz, 0H), 10.76 (s, 1H), 10.60 (dh, J = 17.5, 8.9, 8.3 Hz, 2H), 7.65 (s, 9H), 5.16 (s, 3H), 4.82 – 4.72 (m, 1H), 3.98 (d, J = 4.0 Hz, 4H). ^{13}C NMR (100 MHz, Chloroform-d): δ 53.50, 53.29, 53.08, 52.87, 52.65, 52.44, 52.23, 4.82. HRMS (ESI) *m/z*: $[C_9H_8FN_5O_2 - H]^-$ Calcd 236.0589; Found 236.0587.

(Z)-4-(2-(2-fluorophenyl)hydrazineylidene)-5-imino-4,5-dihydroisoxazol-3-amine (49)



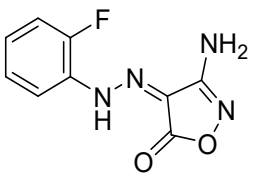
General procedure A1 followed by B3. Yield: 12%. ^{1}H NMR (400 MHz, Acetone-d_6): δ 13.15 (s, 1H), 7.83 (td, J = 8.2, 1.7 Hz, 1H), 7.39 – 7.24 (m, 2H), 7.19 – 7.08 (m, 1H), 5.97 (s, 2H). ^{13}C NMR (100 MHz, Acetone-d_6): δ 159.34, 150.95 (d, J = 242.5 Hz), 150.08, 130.39 (d, J = 9.2 Hz), 126.48, 125.89 (d, J = 3.5 Hz), 124.92 (d, J = 7.2 Hz), 116.31 (d, J = 17.6 Hz), 115.70. HRMS (ESI) *m/z*: $[C_9H_8FN_5O + H]^+$ Calcd 222.0786; Found 222.0790.

(Z)-5-amino-4-(2-(2-fluorophenyl)hydrazineylidene)-2,4-dihydro-3H-pyrazol-3-one (50)



General procedure A2 giving ethyl (E)-2-cyano-2-(2-(2-fluorophenyl)hydrazineylidene)acetate (**57**) from ethyl 2-cyanoacetate (**55**), followed by B1. Yield: 38%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.78 (td, J = 7.9, 7.4, 1.2 Hz, 1H), 7.39 – 7.26 (m, 2H), 7.23 (ddd, J = 8.4, 5.3, 3.4 Hz, 1H), 6.28 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 158.54, 149.05(d, J = 245.43 Hz), 148.97, 129.54(d, J = 9.7 Hz), 124.96(d, J = 3.7 Hz), 124.83(d, J = 7.2 Hz) 117.52. HRMS (ESI) *m/z*: $[C_9H_8FN_5O + H]^+$ Calcd 222.0786; Found 222.0763.

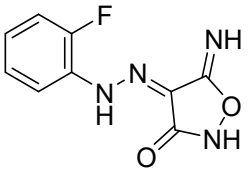
(Z)-3-amino-4-(2-(2-fluorophenyl)hydrazineylidene)isoxazol-5(4H)-one (51)



General procedure A2 giving ethyl (E)-2-cyano-2-(2-(2-fluorophenyl)hydrazineylidene)acetate (**57**) from ethyl 2-cyanoacetate (**55**), followed by B3. Yield: 77%. ^{1}H NMR (400 MHz, Methanol-d_4): δ 7.71 (td, J = 8.1, 1.7 Hz, 1H), 7.21 – 7.08 (m, 2H), 7.07 – 6.97 (m, 1H).

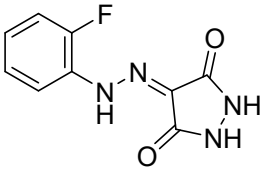
NH protons not observed. ^{13}C NMR (100 MHz, Methanol-d_4): δ 165.64, 151.38, 151.21 (d, J = 242.5 Hz), 131.23 (d, J = 9.5 Hz), 124.70 (d, J = 3.5 Hz), 122.94 (d, J = 7.2 Hz), 119.59, 115.27 (d, J = 2.0 Hz), 114.89 (d, J = 18.0 Hz). HRMS (ESI) *m/z*: [C9H7FN4O2 + H]$^+$ Calcd 223.0626; Found 223.0672.

(Z)-4-(2-(2-fluorophenyl)hydrazineylidene)-5-iminoisoxazolidin-3-one (52)



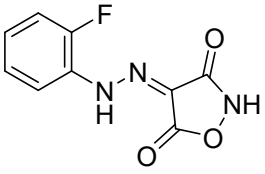
General procedure A2 giving ethyl (E)-2-cyano-2-(2-(2-fluorophenyl)hydrazineylidene)acetate (**57**) from ethyl 2-cyanoacetate (**55**), followed by B3. Yield: 8%. ^{1}H NMR (400 MHz, Methanol-d_4): δ 7.89 (td, J = 7.9, 1.5 Hz, 1H), 7.34 – 7.22 (m, 3H). NH protons not observed. ^{13}C NMR (100 MHz, Methanol-d_4): δ 164.03, 158.74, 150.51(d, J = 245.71 Hz), 125.93 (d, J = 7.5 Hz), 125.13 (d, J = 3.5 Hz), 116.00, 115.47 (d, J = 18.0 Hz), 114.90 (d, J = 18.1 Hz). HRMS (ESI) *m/z*: [C9H7FN4O2 + H]$^+$ Calcd 223.0626; Found 223.0625.

4-(2-(2-fluorophenyl)hydrazineylidene)pyrazolidine-3,5-dione (53)



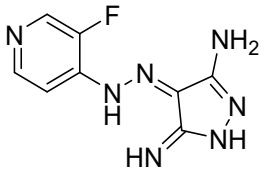
General procedure A3 giving diethyl 2-(2-(2-fluorophenyl)hydrazineylidene)malonate (**58**) from diethyl malonate (**56**), followed by B1. Yield: 42%. ^{1}H NMR (400 MHz, Methanol-d_4): δ 7.88 (td, J = 7.9, 1.6 Hz, 1H), 7.34 – 7.20 (m, 3H). NH protons not observed. ^{13}C NMR (100 MHz, Methanol-d_4): δ 161.59, 151.68 (d, J = 244.7 Hz), 129.50 (d, J = 8.9 Hz), 125.92 (d, J = 7.4 Hz), 125.28 (d, J = 3.6 Hz), 122.62, 115.86, 115.52 (d, J = 18.0 Hz). HRMS (ESI) *m/z*: [C9H7FN4O2 + H]$^+$ Calcd 223.0626; Found 223.0623.

(Z)-4-(2-(2-fluorophenyl)hydrazineylidene)isoxazolidine-3,5-dione (54)



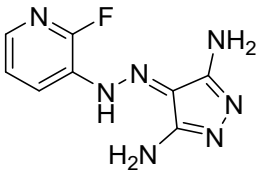
General procedure A3 giving diethyl 2-(2-(2-fluorophenyl)hydrazineylidene)malonate (**58**) from diethyl malonate (**56**), followed by B3. Yield: Quant. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.35 (s, 1H), 7.89 – 7.75 (m, 1H), 7.19 – 7.01 (m, 3H). ^{13}C NMR (100 MHz, DMSO): δ 154.51(d, J = 245.7 Hz), 131.76(d, J = 10.1 Hz), 125.3(d, J = 2.1 Hz), 123.45(d, J = 8.2 Hz), 121.71, 117.98(d, J = 7.8 Hz), 116.43 (d, J = 18.1 Hz). HRMS (ESI) *m/z*: [C9H6FN3O3 + H]$^+$ Calcd 224.0466; Found 224.0468.

(E)-4-(2-(3-fluoropyridin-4-yl)hydrazineylidene)-5-imino-4,5-dihydro-1H-pyrazol-3-amine (59)



General procedure A1 followed by B1. Yield: Quant. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.06 (d, J = 3.7 Hz, 1H), 7.86 (dd, J = 5.3, 0.8 Hz, 1H), 7.41 (s, 9H), 6.68 (dd, J = 8.1, 5.3 Hz, 1H), 6.18 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.46, 148.87 (d, J = 244.3 Hz), 146.17 (d, J = 4.3 Hz), 143.10 (d, J = 10.7 Hz), 136.12 (d, J = 19.2 Hz), 110.96 (d, J = 3.0 Hz). HRMS (ESI) *m/z*: [C8H8FN7 + H]$^+$ Calcd 222.0898; Found 222.0903.

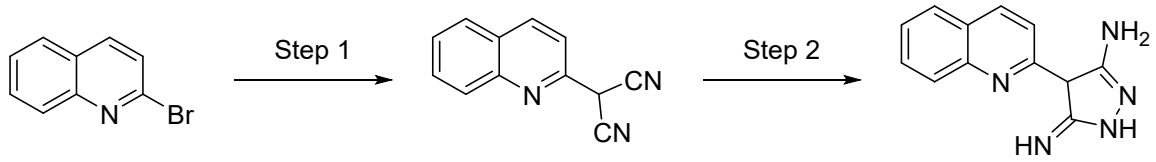
(E)-4-(2-(2-fluoropyridin-3-yl)hydrazineylidene)-5-imino-4,5-dihydro-1H-pyrazol-3-amine (60)

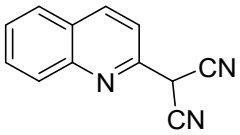


General procedure A1 followed by B1. Yield: 91%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.62 (dd, J = 7.2, 2.0 Hz, 1H), 7.28 (dd, J = 6.4, 2.0 Hz, 1H), 6.60 (s, 2H), 6.23 (dd, J = 7.2, 6.3 Hz, 1H), 5.78 (s, 2H). Due to low electron density of the polyfluorinated compound, it was not

possible to obtain a good quality ^{13}C NMR spectrum. HRMS (ESI) *m/z*: $[C8H6FN7 + H]^+$ Calcd 220.0741; Found 220.0956.

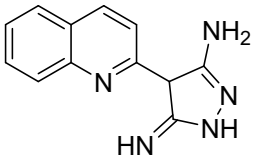
5-imino-4-(quinolin-2-yl)-4,5-dihydro-1H-pyrazol-3-amine (61)





Step 1

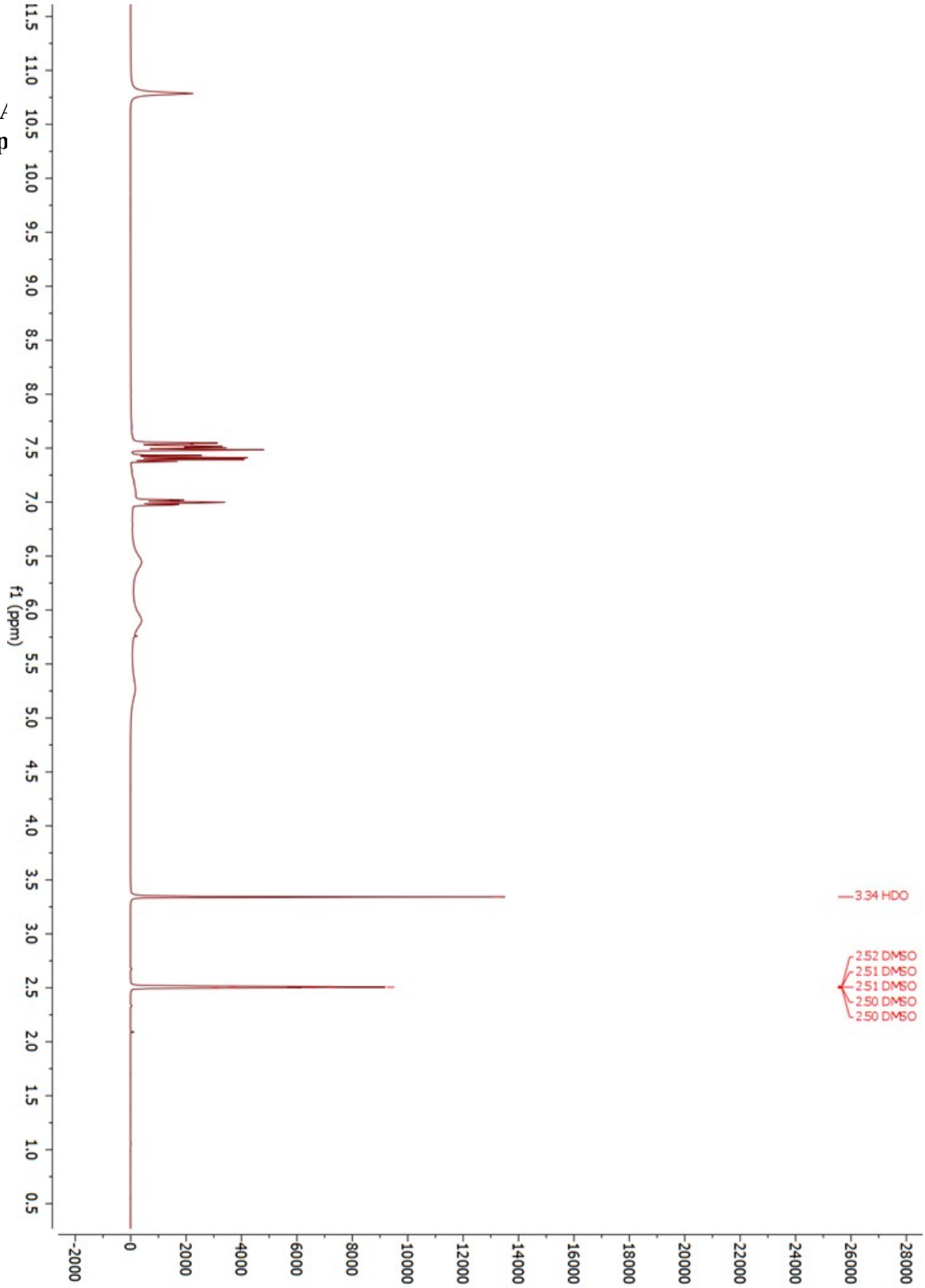
In a dry round bottom flask was added malonitrile (1.7 eq) to a solution of NaH (4.5 eq, 60% in oil) in HMPA (2.1 mL/mmol quinoline). The solution was cooled in an ice bath for 30 min before addition of 2-bromoquinoline (1 eq), afterwards the reaction was allowed to heat to rt before being heated to 100°C until full conversion. The reaction was poured into ice/water (80 mL) and neutralized with acetic acid. The precipitate was isolated by vacuum filtration and washed with toluene. The crude product was used without further purification. Yield: Quant. ^1H NMR (400 MHz, DMSO-d_6): δ 12.61 (s, 1H), 8.11 (d, J = 9.3 Hz, 1H), 7.92 (d, J = 8.4 Hz, 1H), 7.81 (dd, J = 7.9, 1.4 Hz, 1H), 7.75 – 7.50 (m, 2H), 7.41 (ddd, J = 8.2, 7.2, 1.1 Hz, 1H), 7.16 (d, J = 9.3 Hz, 1H), 3.43(s, H1). ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.36, 147.82, 134.67, 129.87, 128.32, 127.84, 126.73, 125.92, 122.04, 111.74.



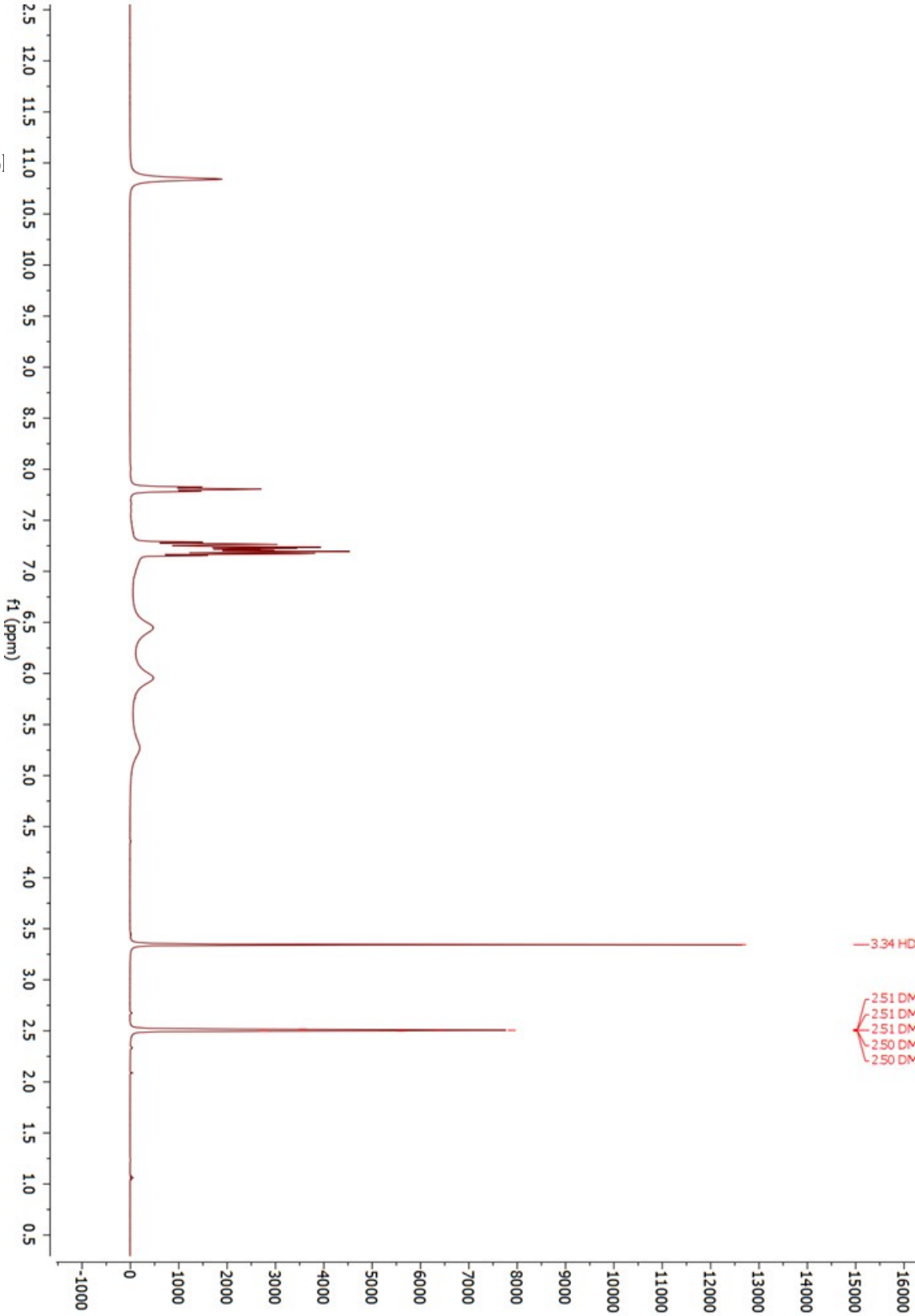
Step 2

General procedure B2. Yield: 3%. ^1H NMR (400 MHz, DMSO-d_6): δ 10.64 (s, 1H), 8.14 (d, J = 8.9 Hz, 1H), 7.85 – 7.76 (m, 3H), 7.69 – 7.58 (m, 1H), 7.38 (t, J = 7.4 Hz, 1H), 5.69 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 155.93, 147.55, 135.78, 129.70, 127.95, 127.67, 125.04, 124.34, 119.23, 90.47. HRMS (ESI) *m/z*: $[C12H11N5 + H]^+$ Calcd 226.1087; Found 226.1085.

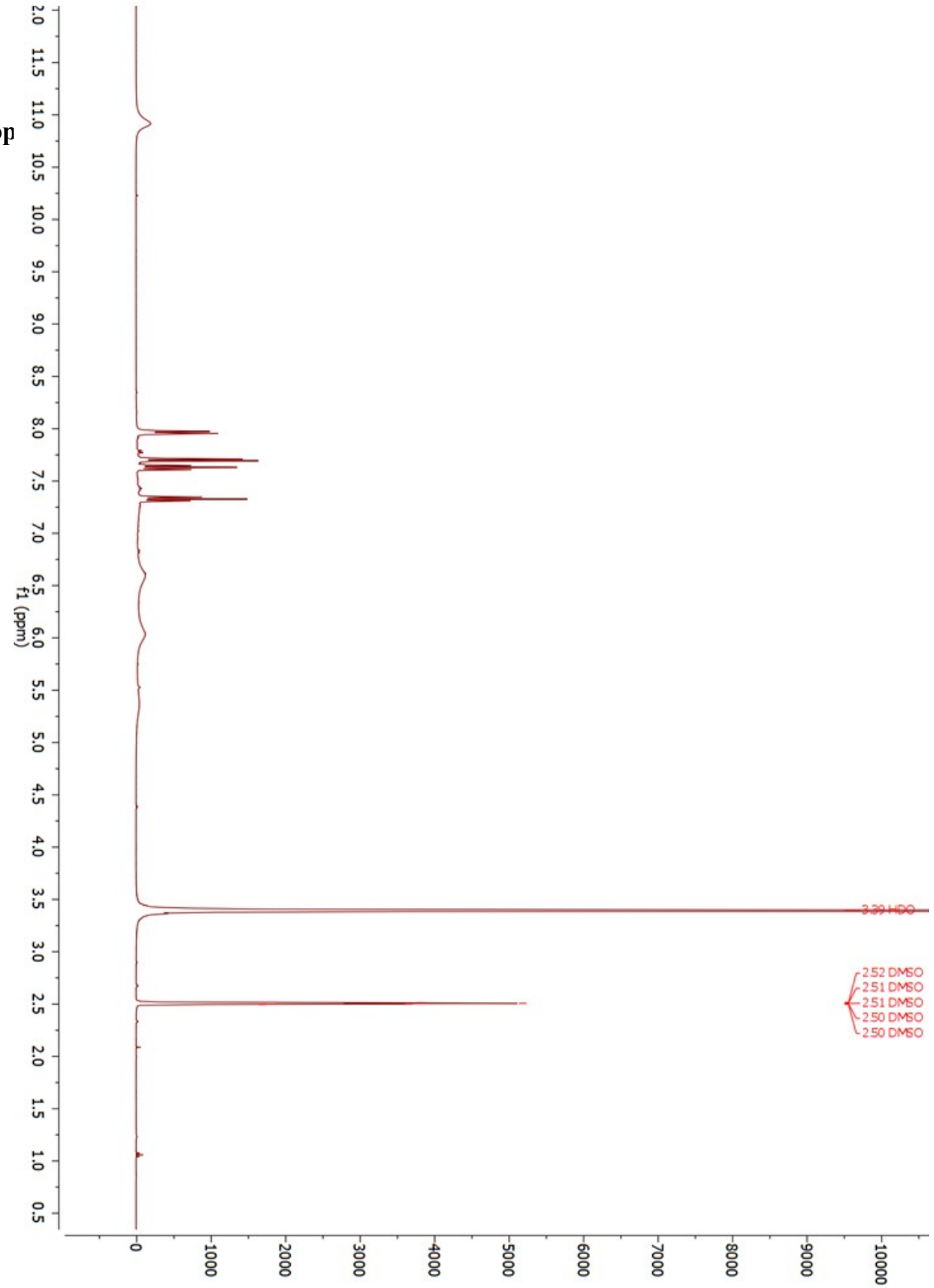
^{1}H-NMR SPECTRA
(E)-4-(2-(3-fluorop



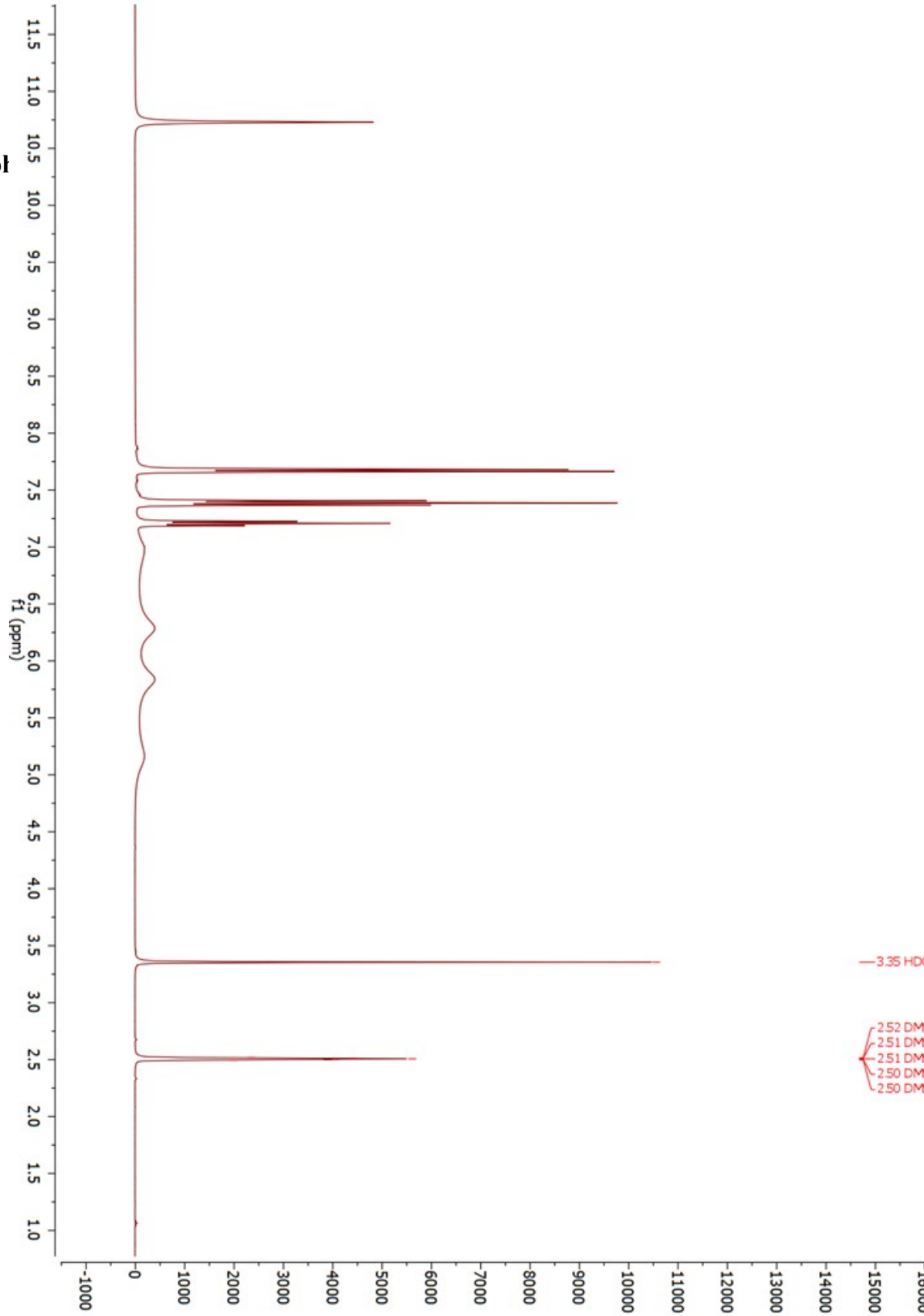
(E)-4-(2-(2-fluorop



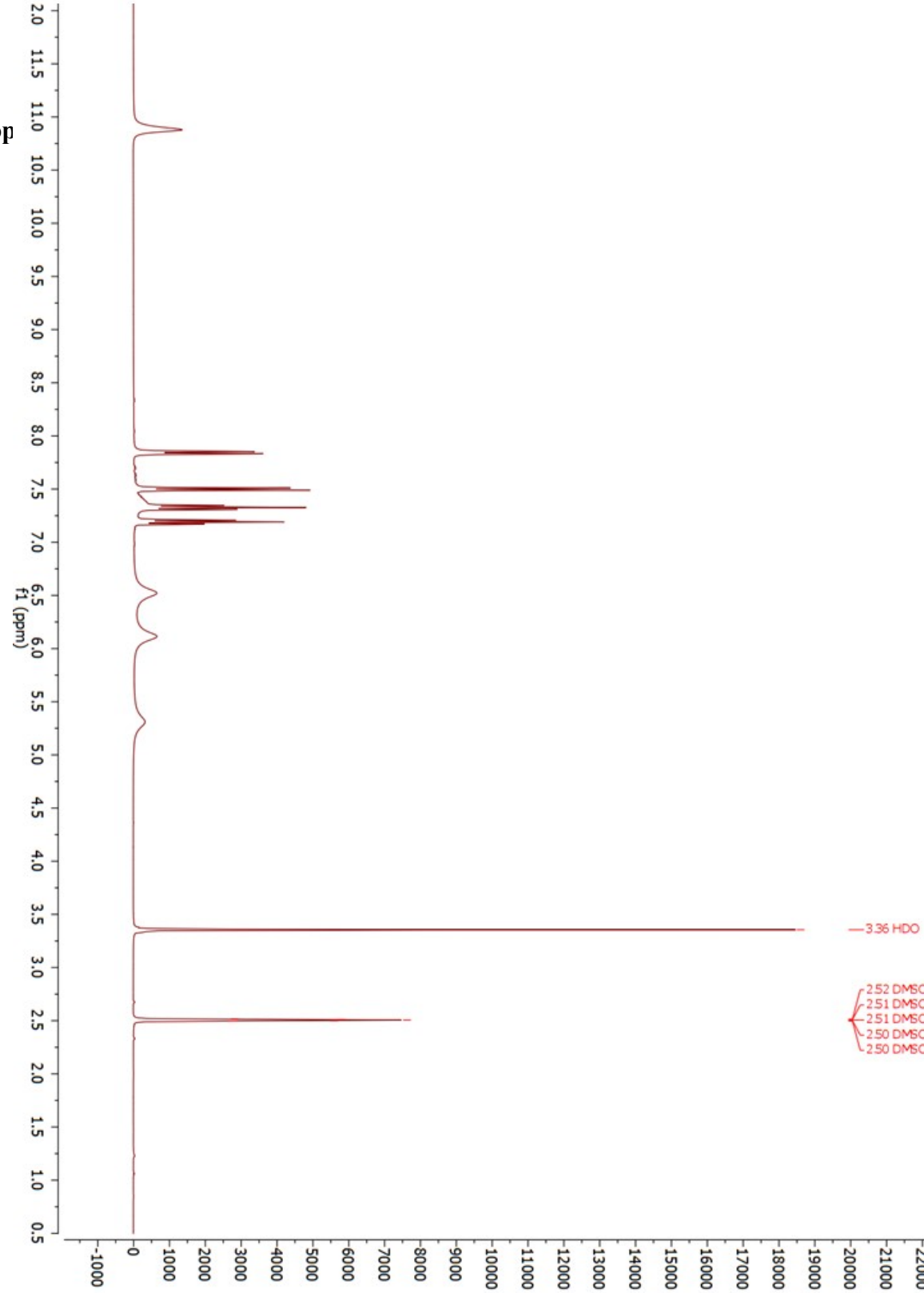
(E)-4-(2-(4-fluorop
(3)



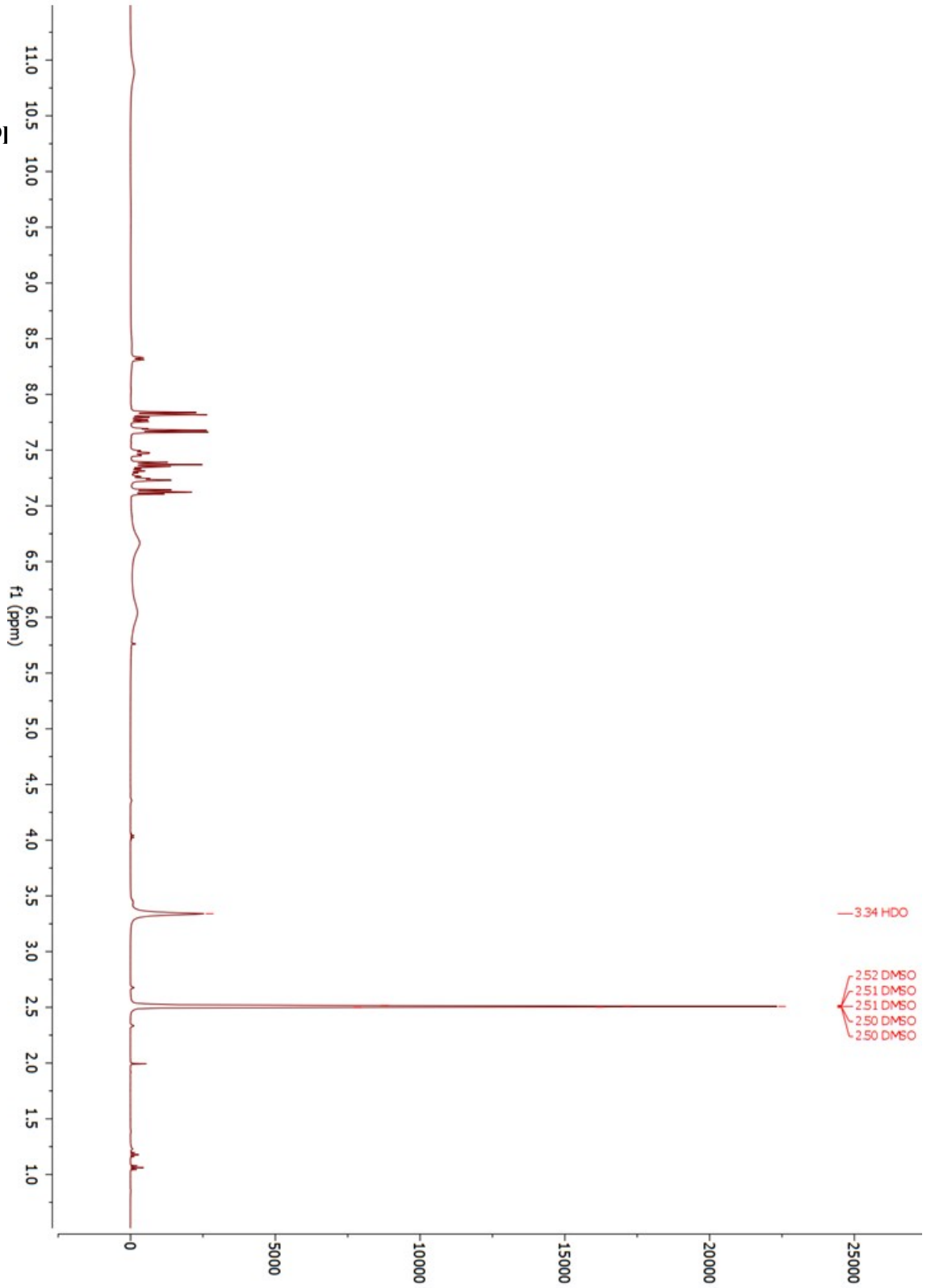
(E)-5-imino-4-(2-pł



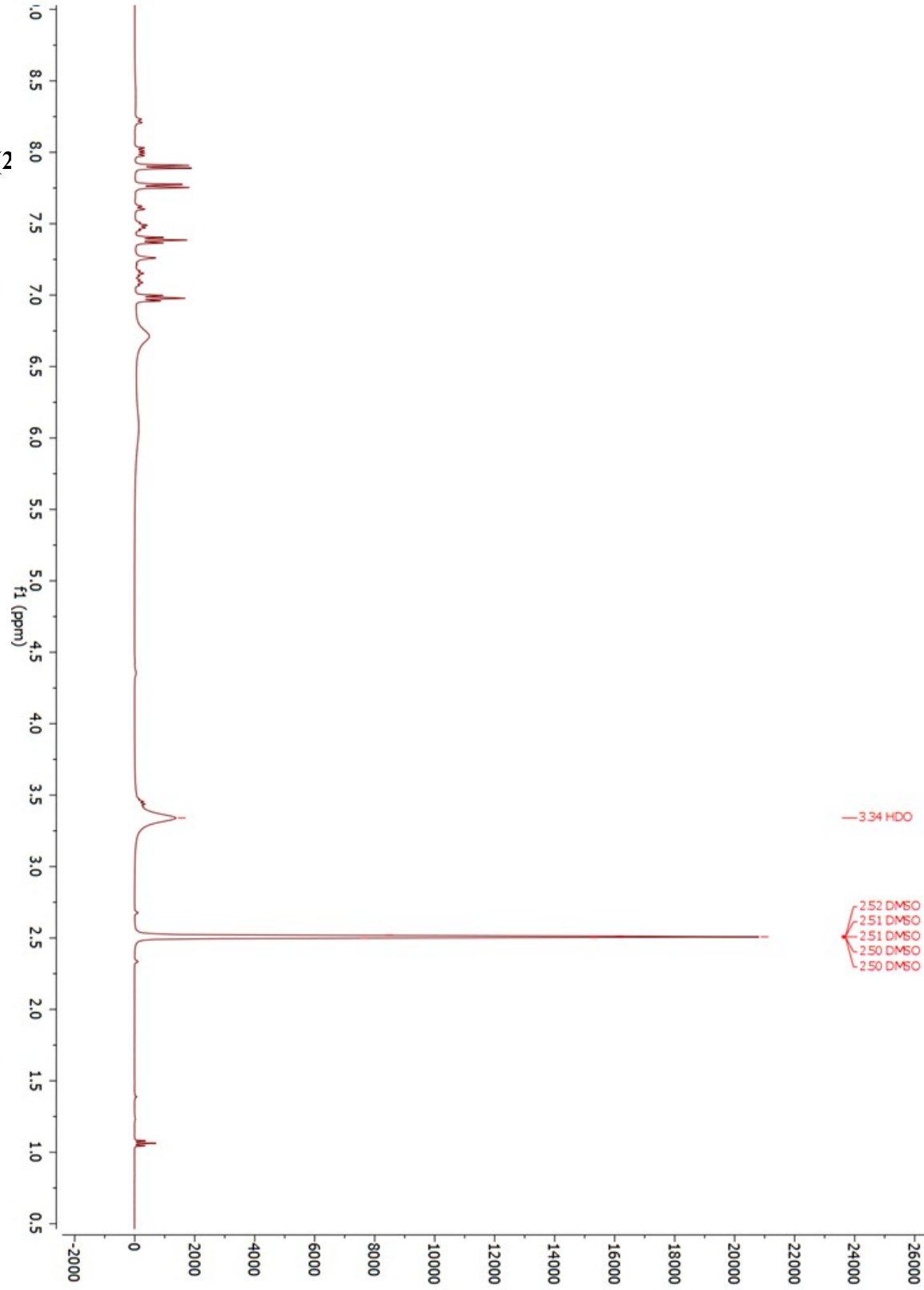
(E)-4-(2-(2-chlorop
(5)



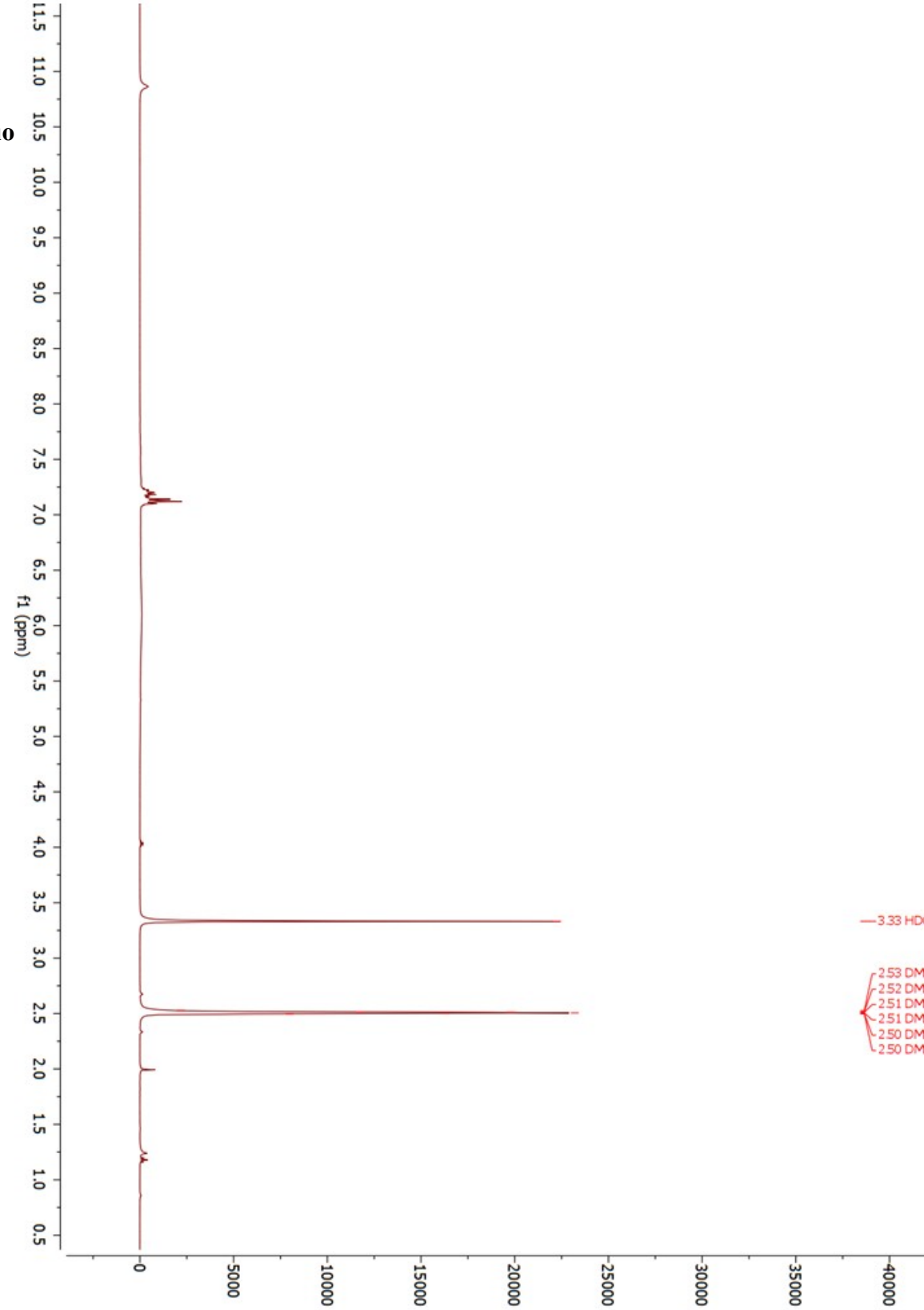
(E)-4-(2-(2-bromo
(6)



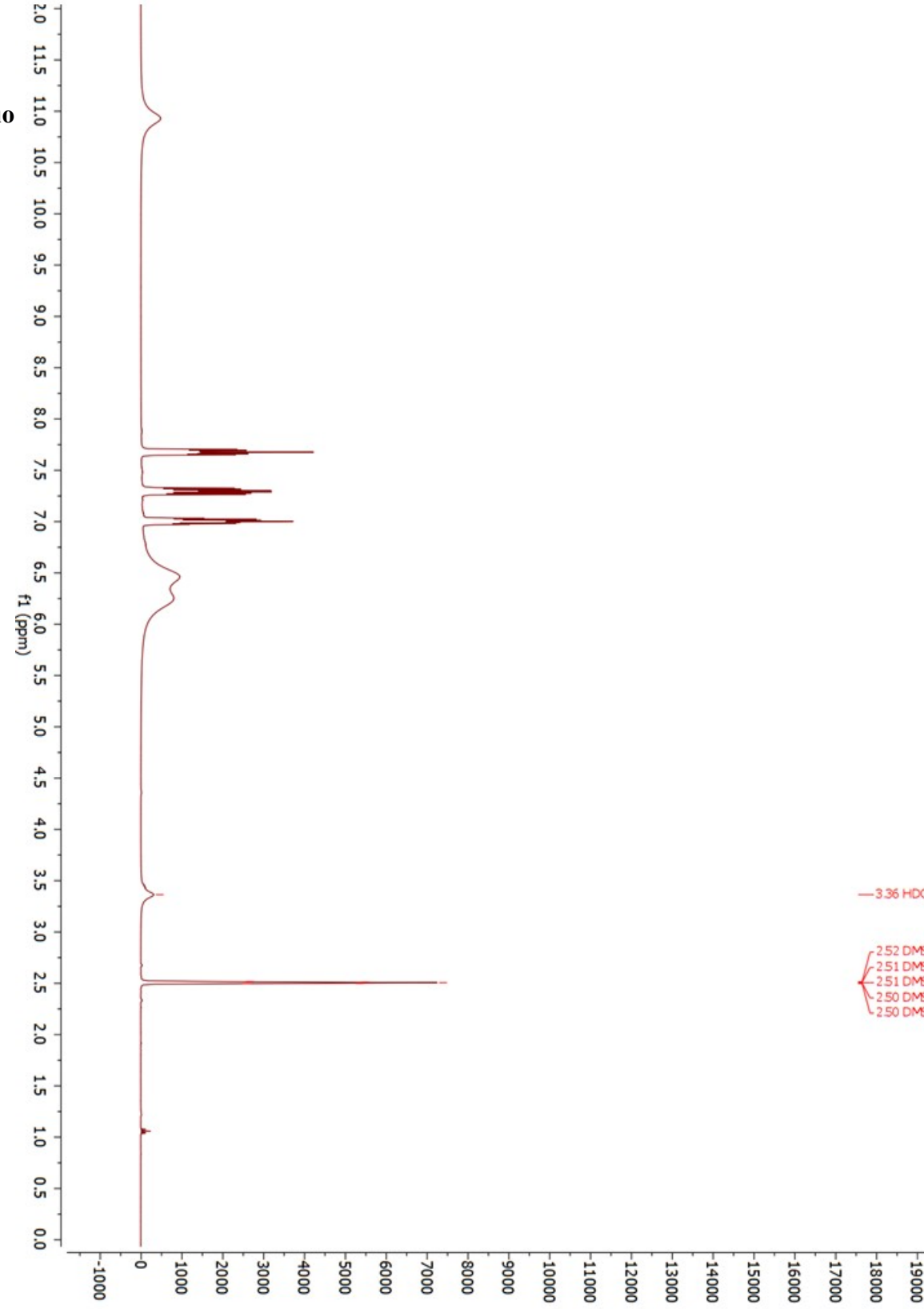
(E)-5-imino-4-(2-(2



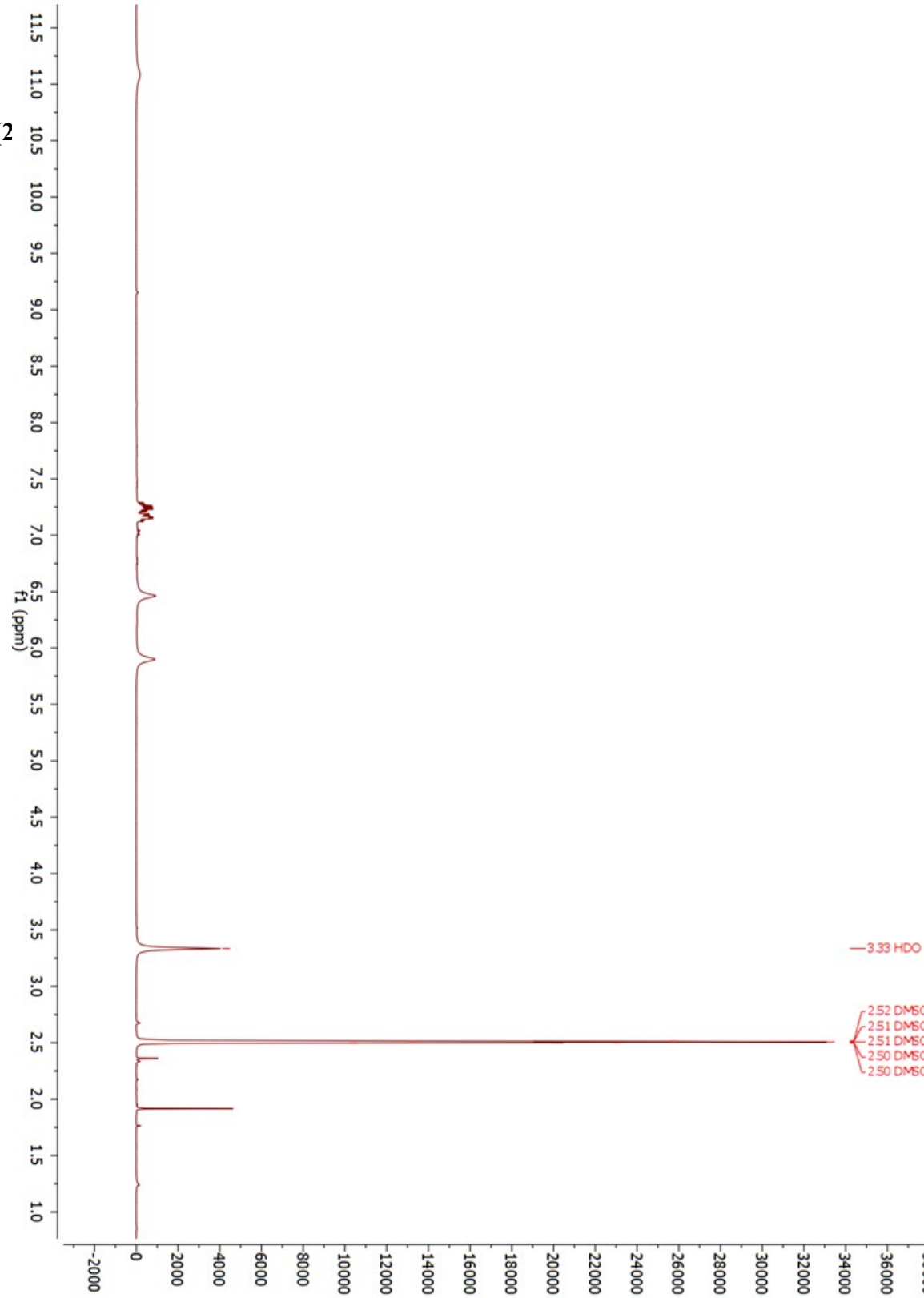
(E)-4-(2-(2,6-difluo amine (8)



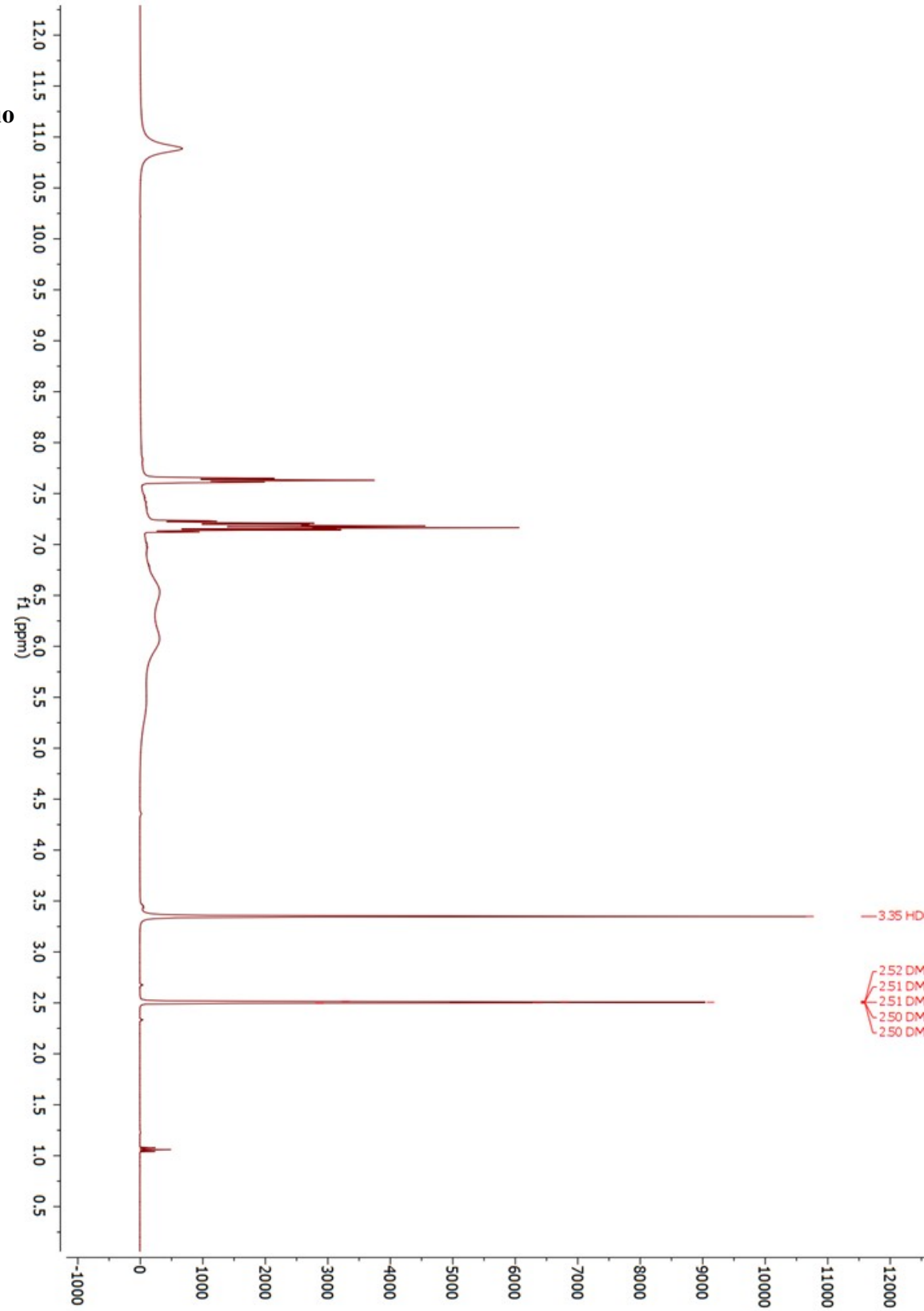
(E)-4-(2-(2,5-difluo amine (9)



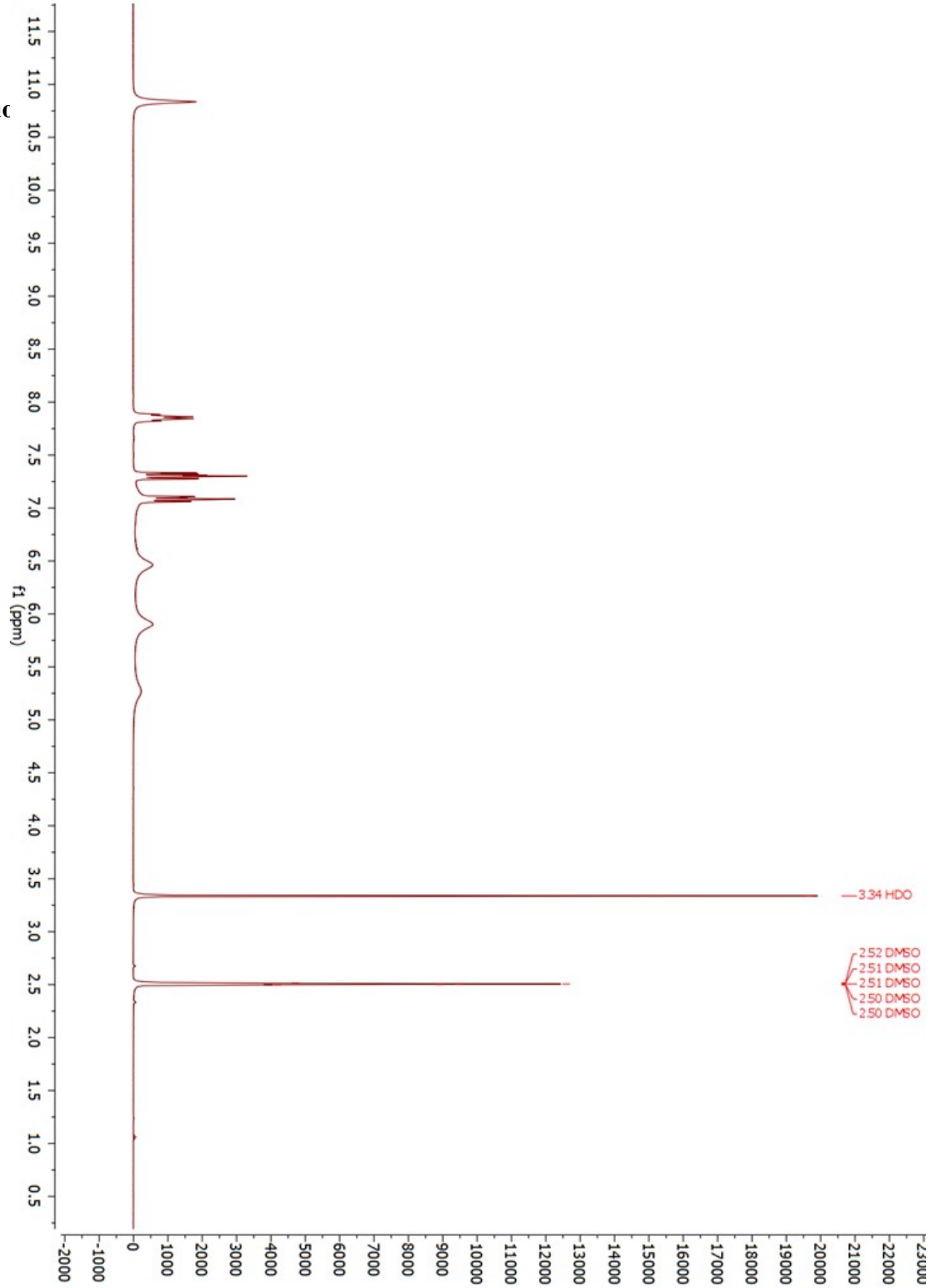
(E)-5-imino-4-(2-(2
amine (10)



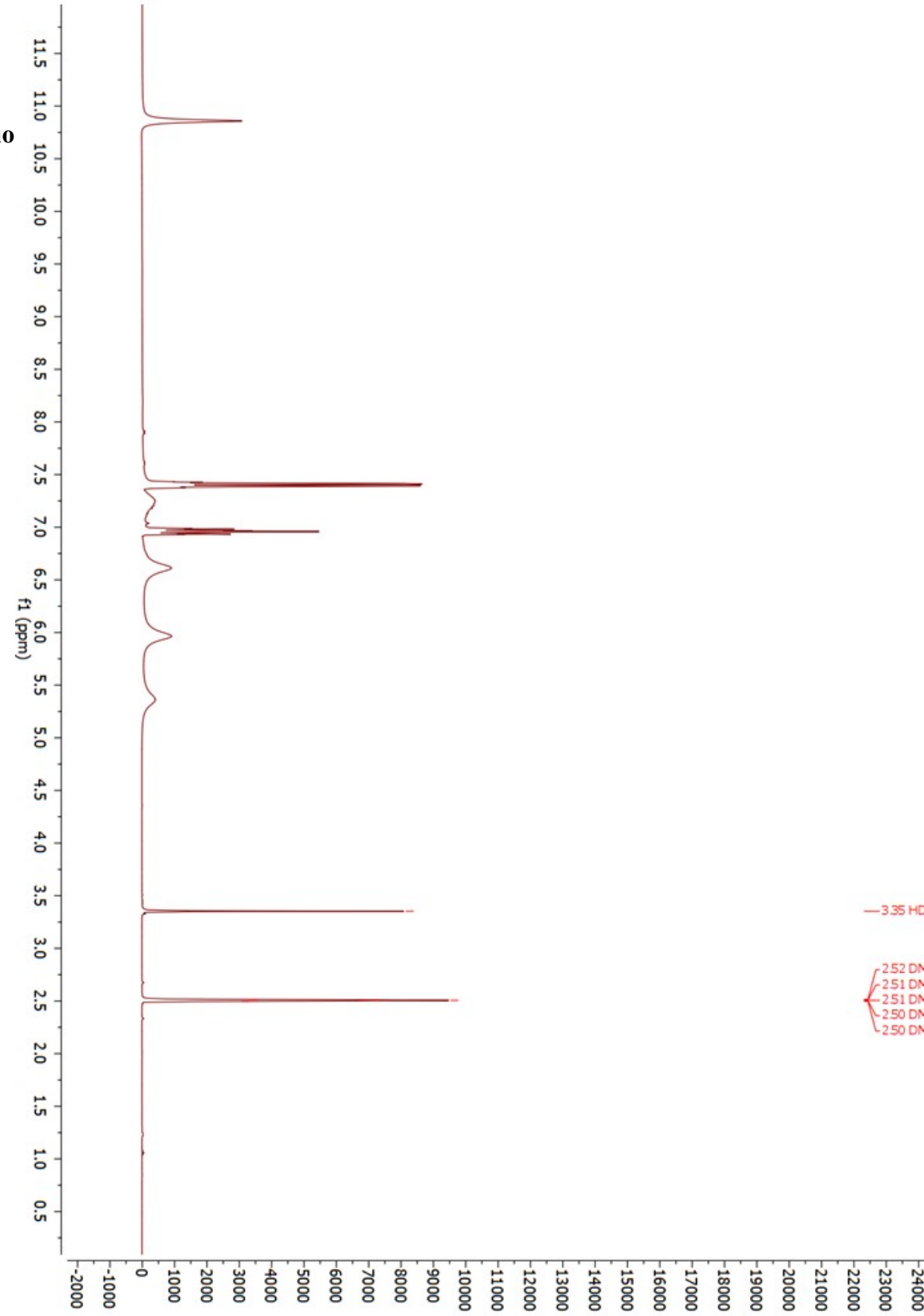
(E)-4-(2-(2,3-difluo amine (11)



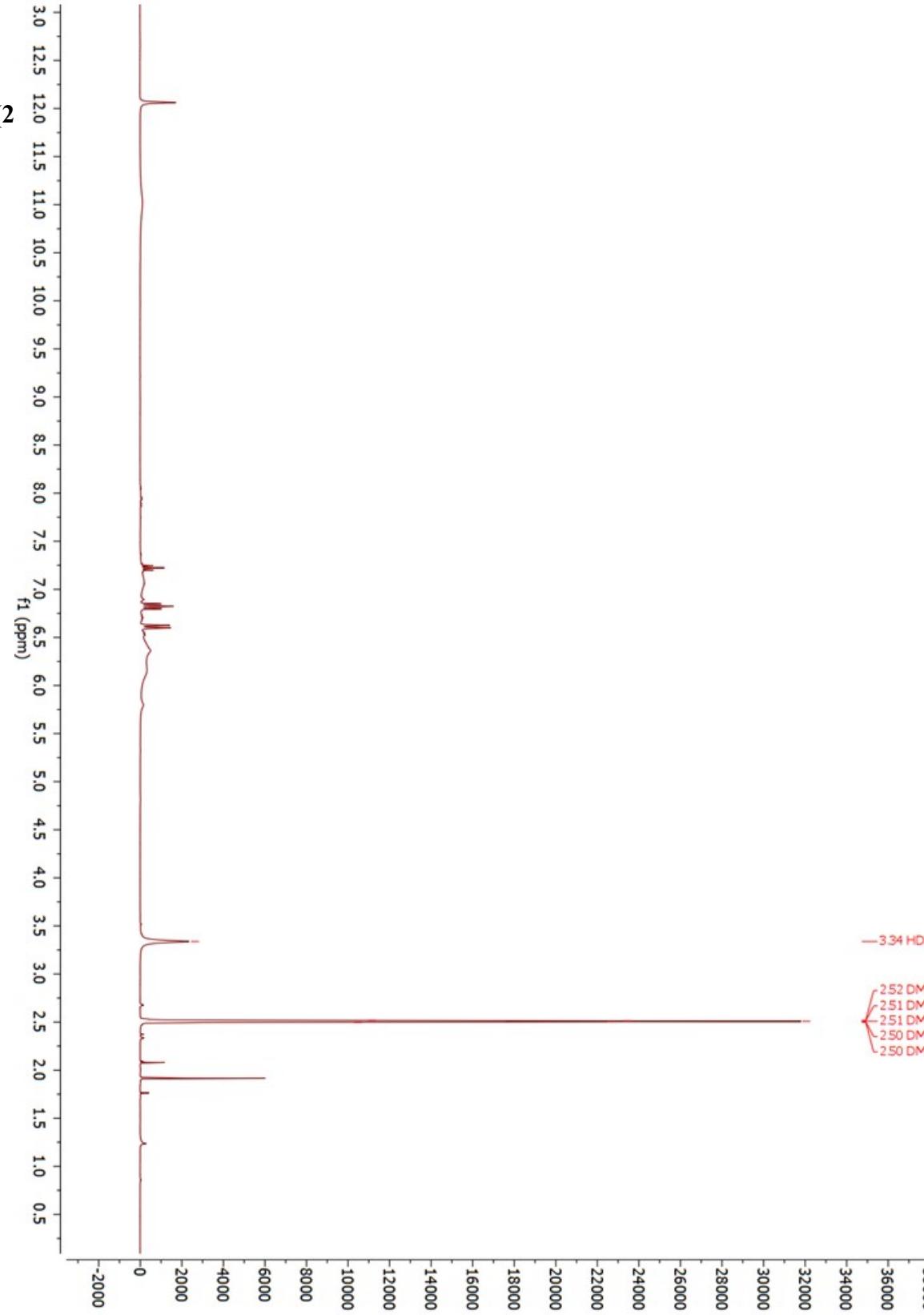
(E)-4-(2-(2,4-difluc
amine (12)



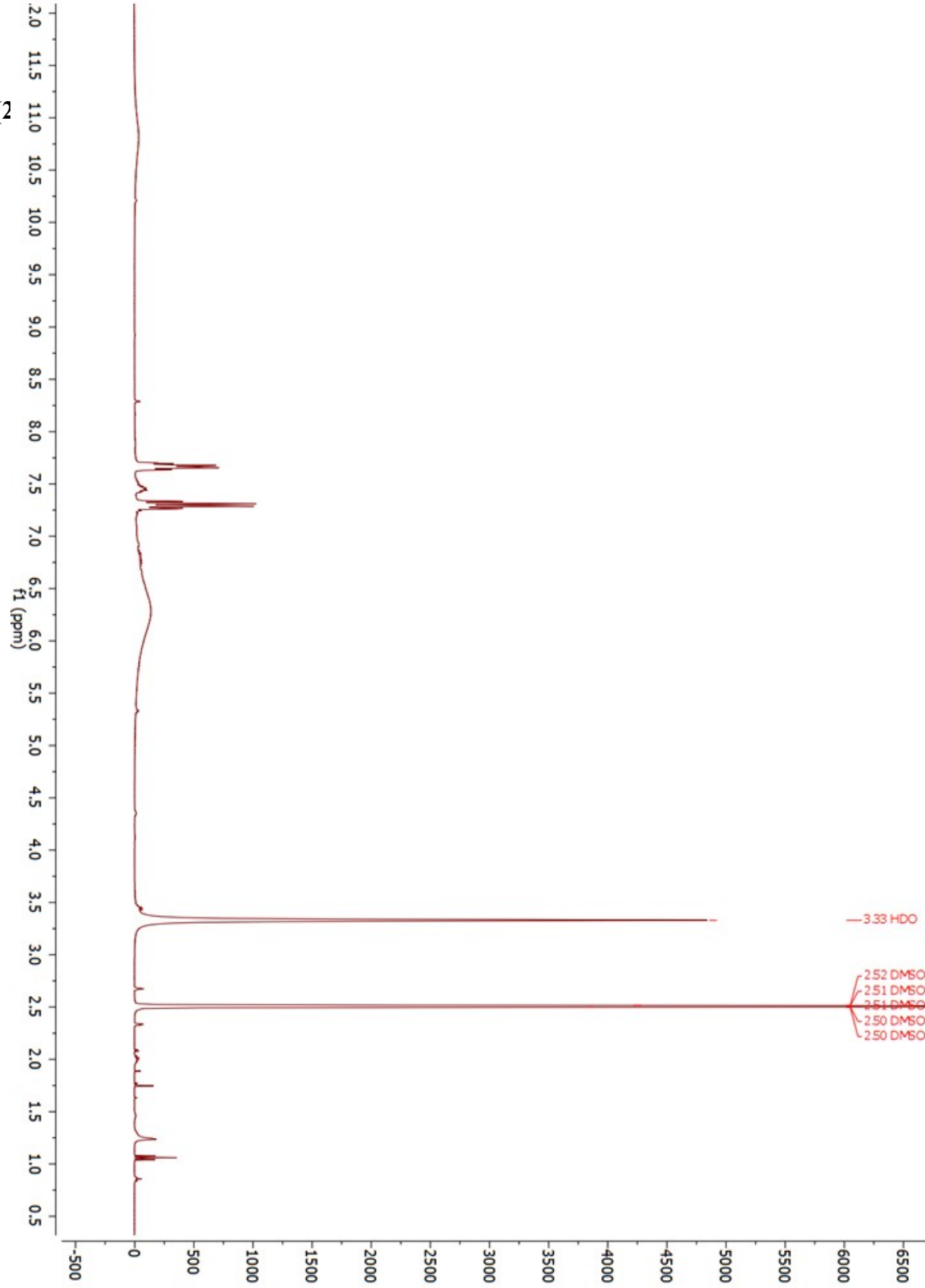
(E)-4-(2-(3,5-difluo amine (13)



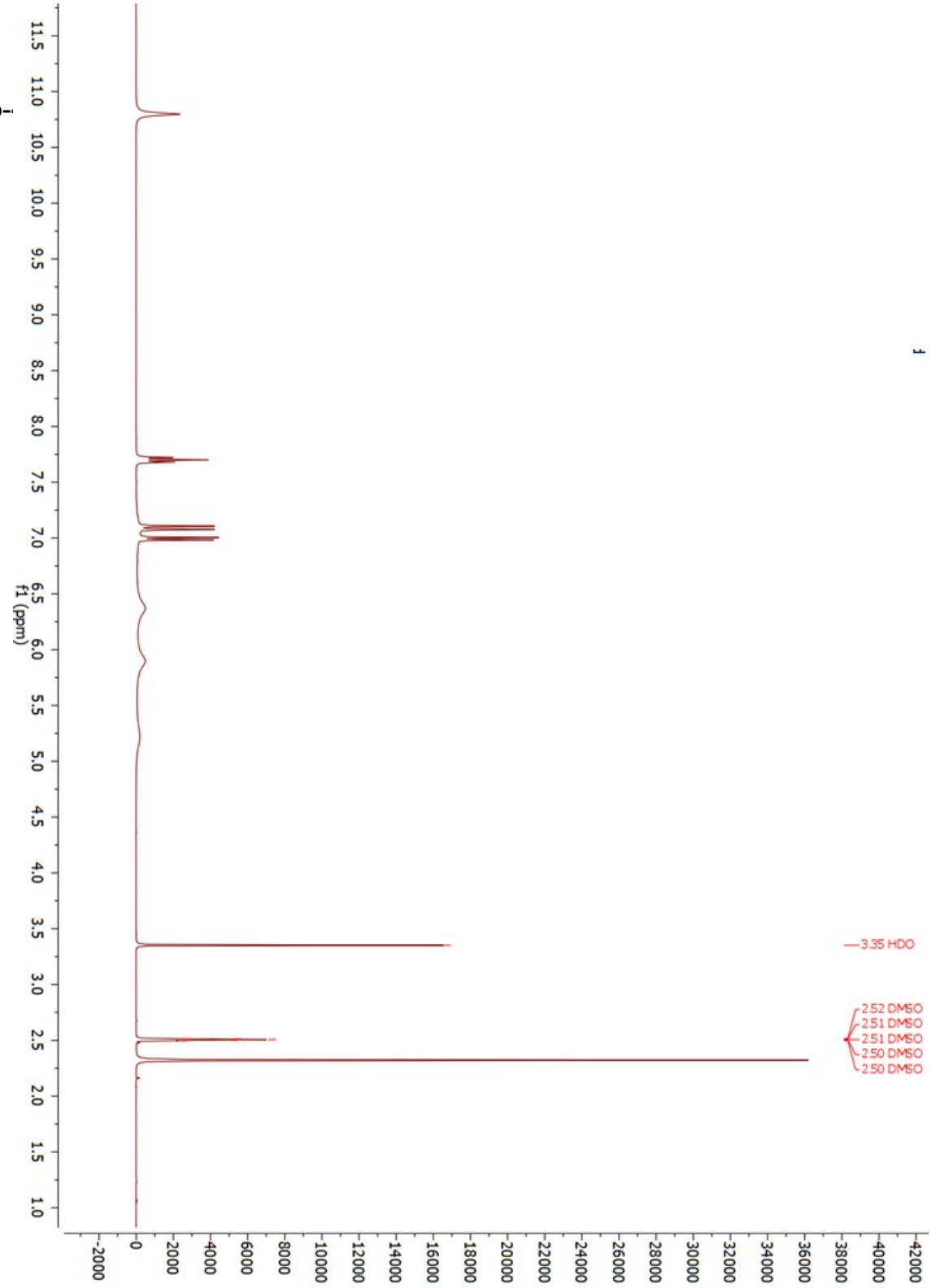
(E)-5-imino-4-(2-(2 amine (14)



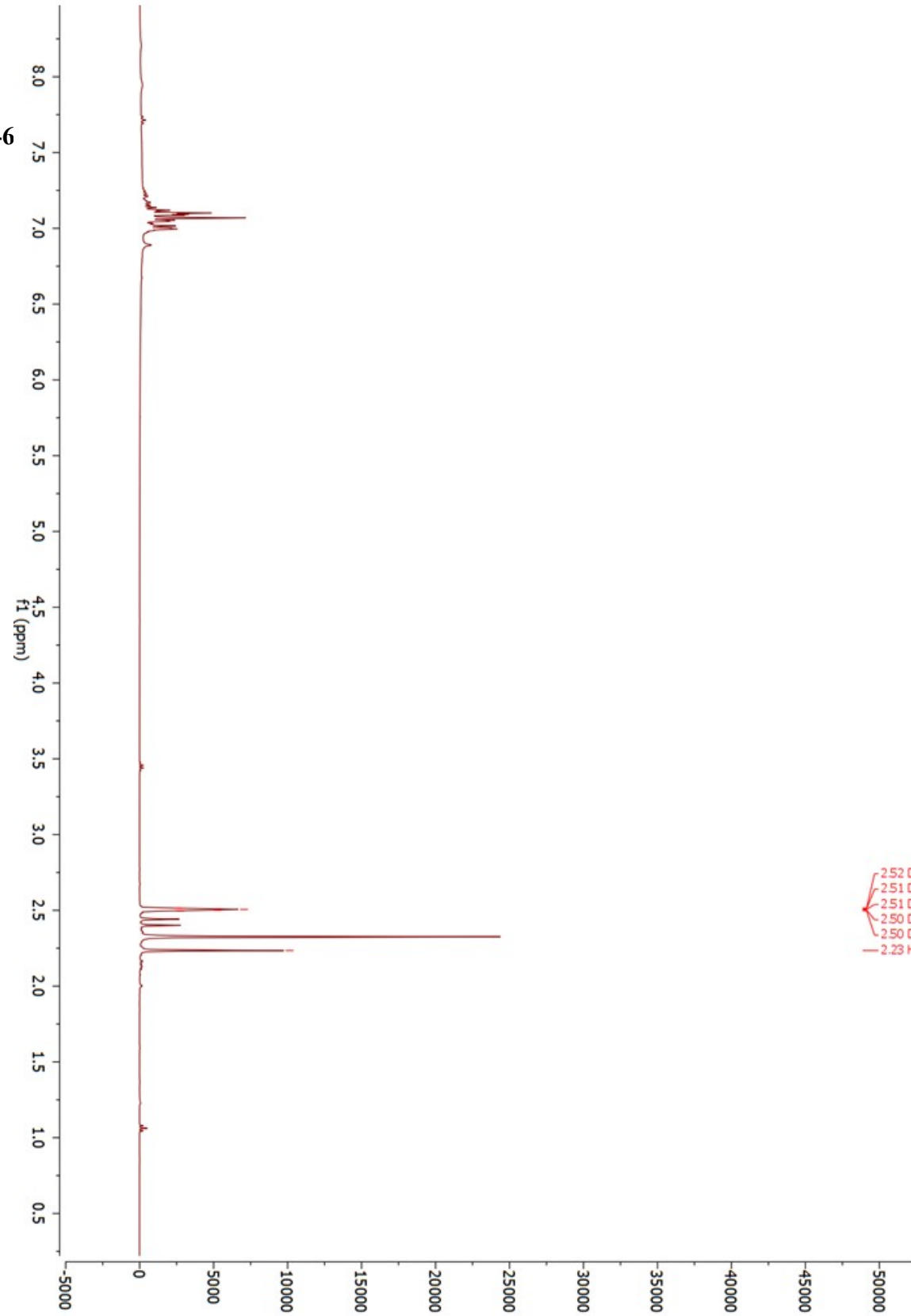
(E)-5-imino-4-(2-(2
amine (15)



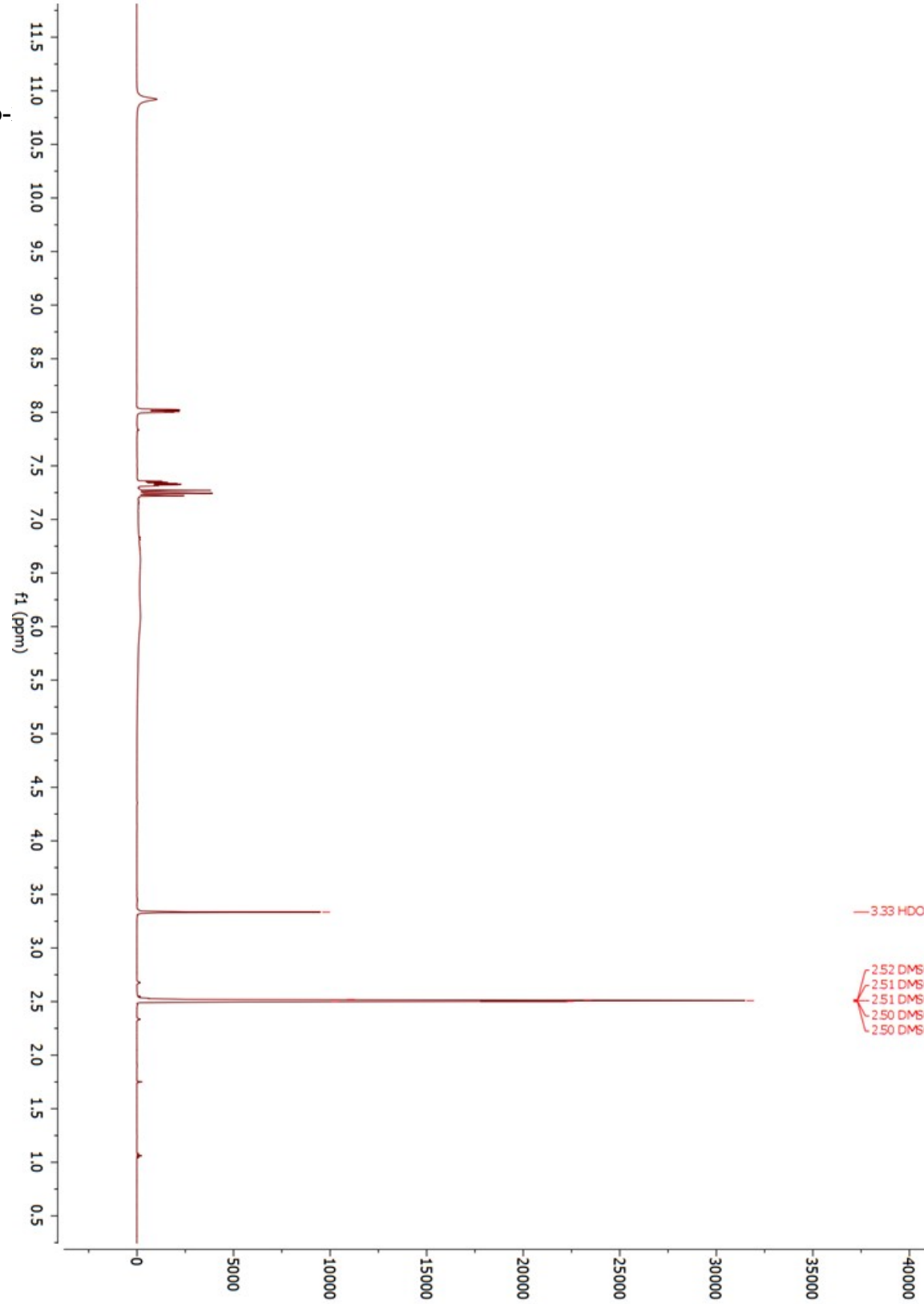
(E)-4-(2-(2-fluoro-
3-amine (16)



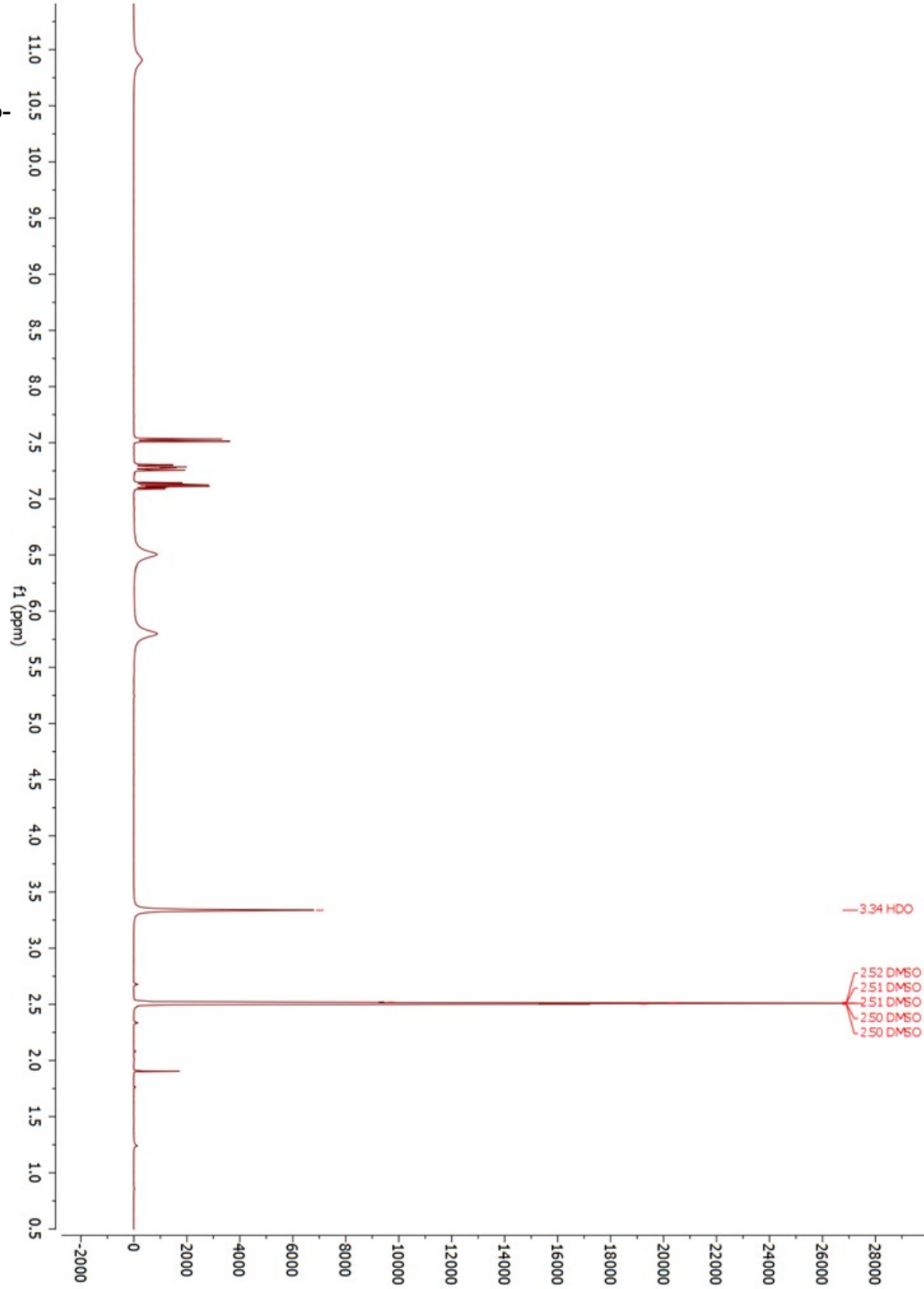
(E)-4-(2-(2-fluoro-6
3-amine (17)



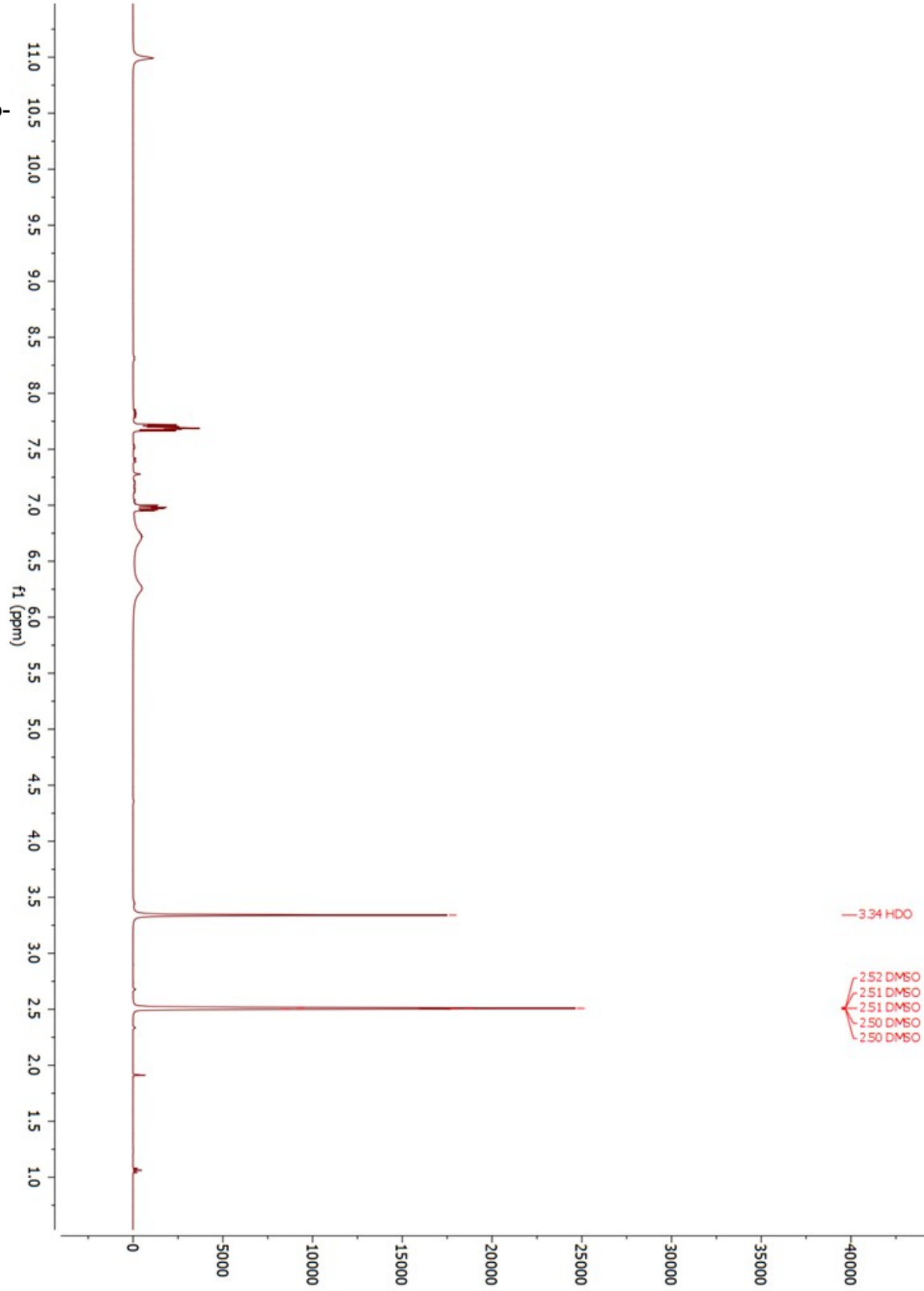
(E)-4-(2-(5-bromo-
amine (18)



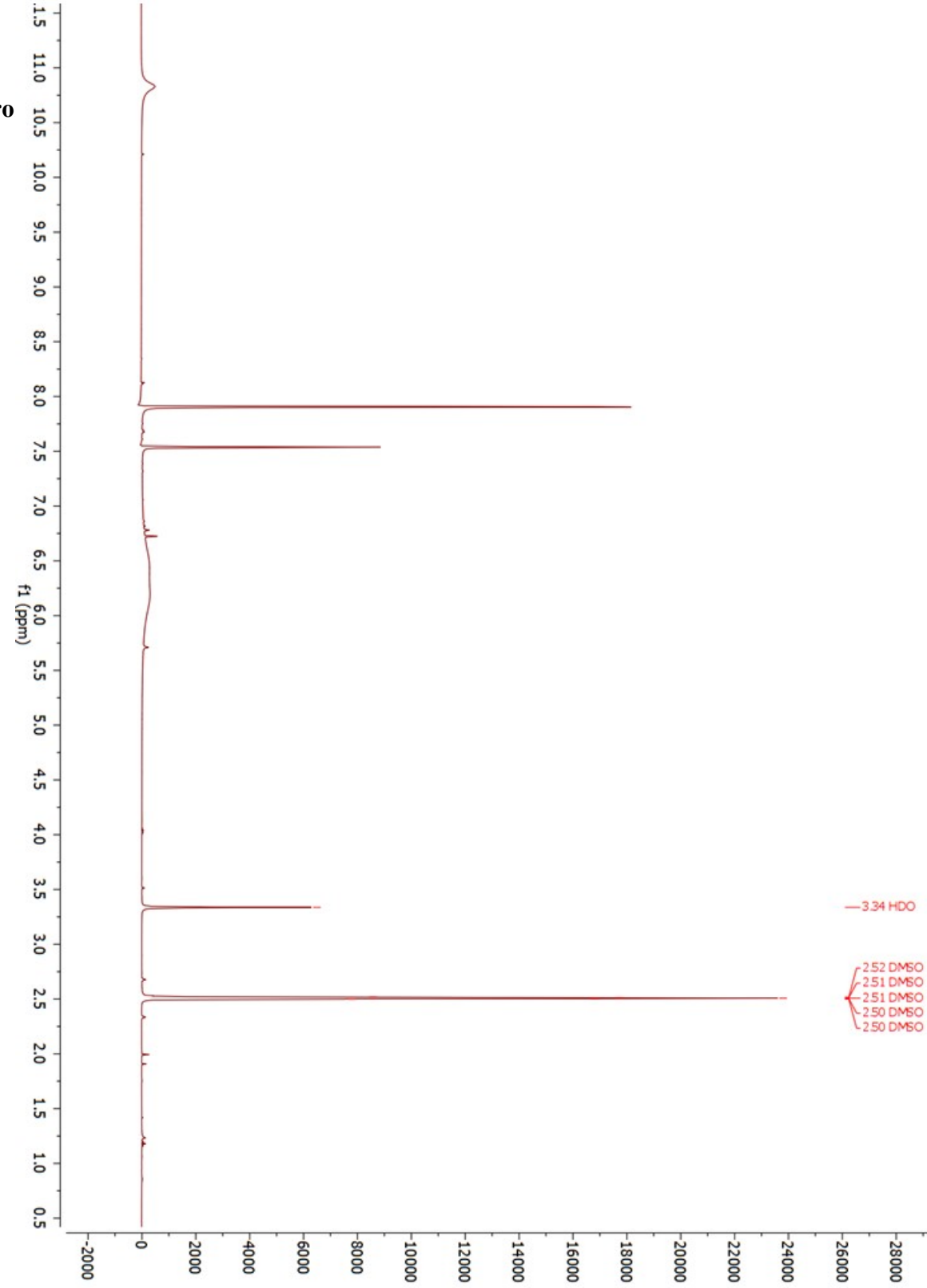
(E)-4-(2-(2-bromo-amine (19)



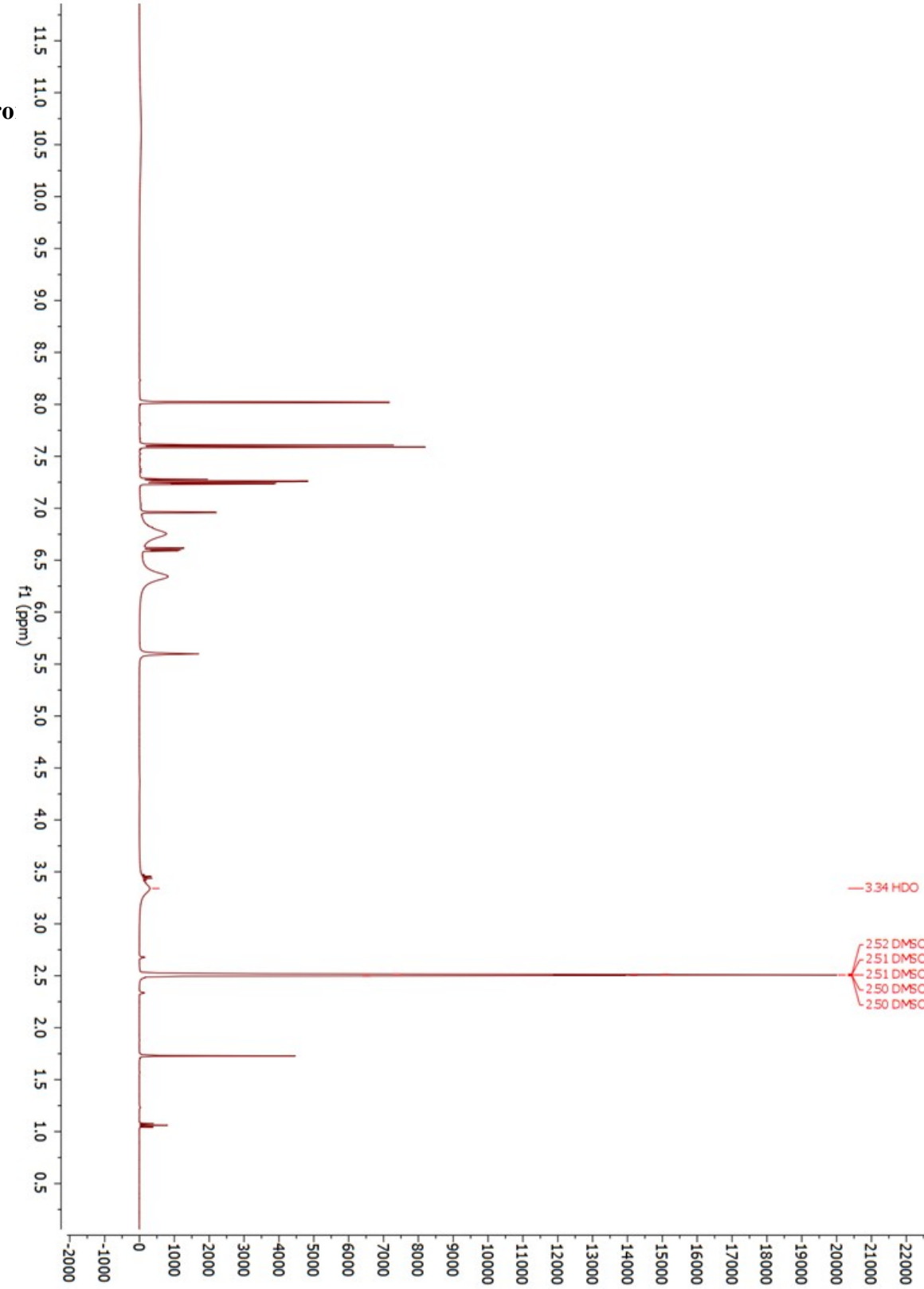
(E)-4-(2-(2-bromo-amine (20)



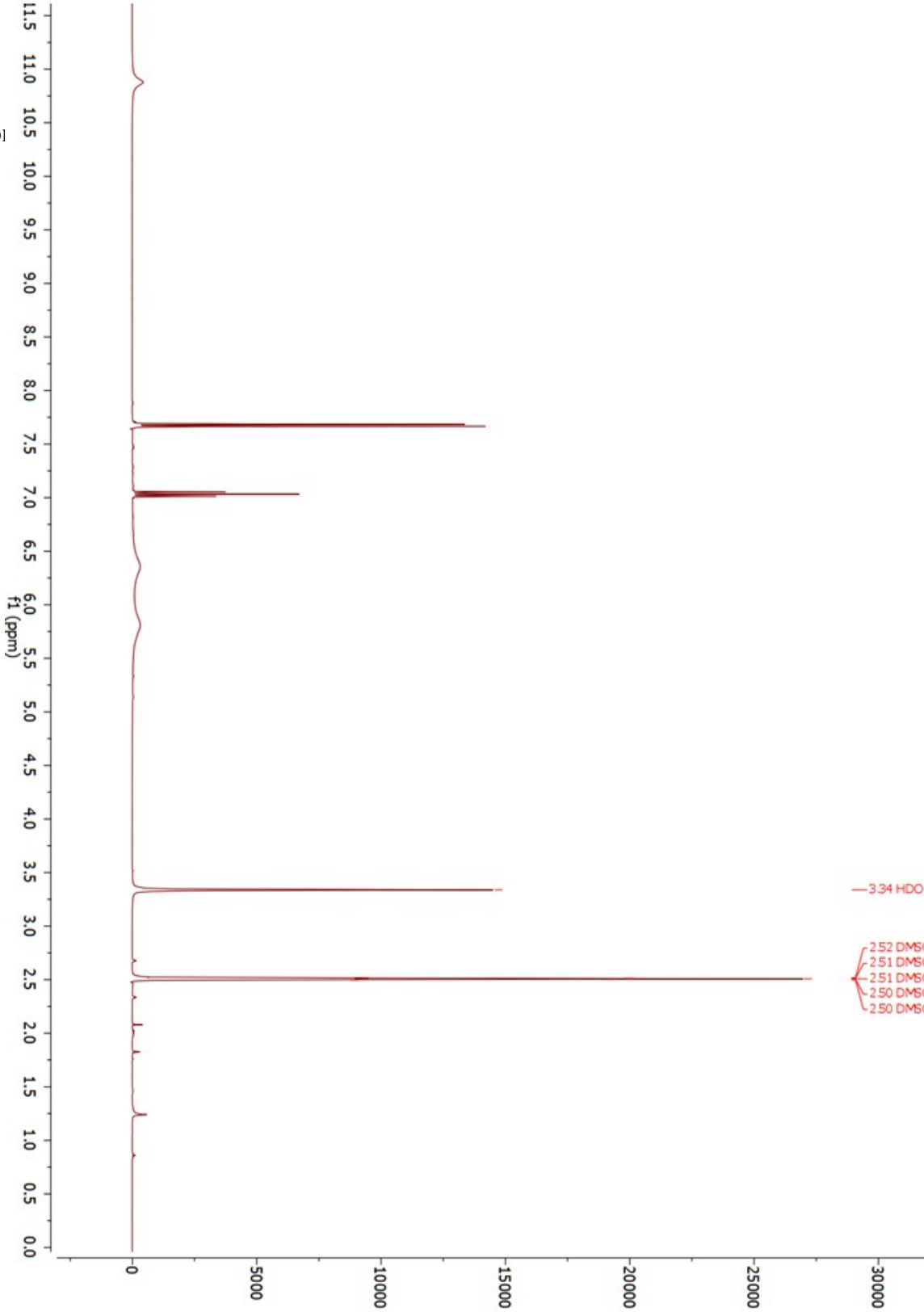
(E)-4-(2-(3,5-dibro amine (21)



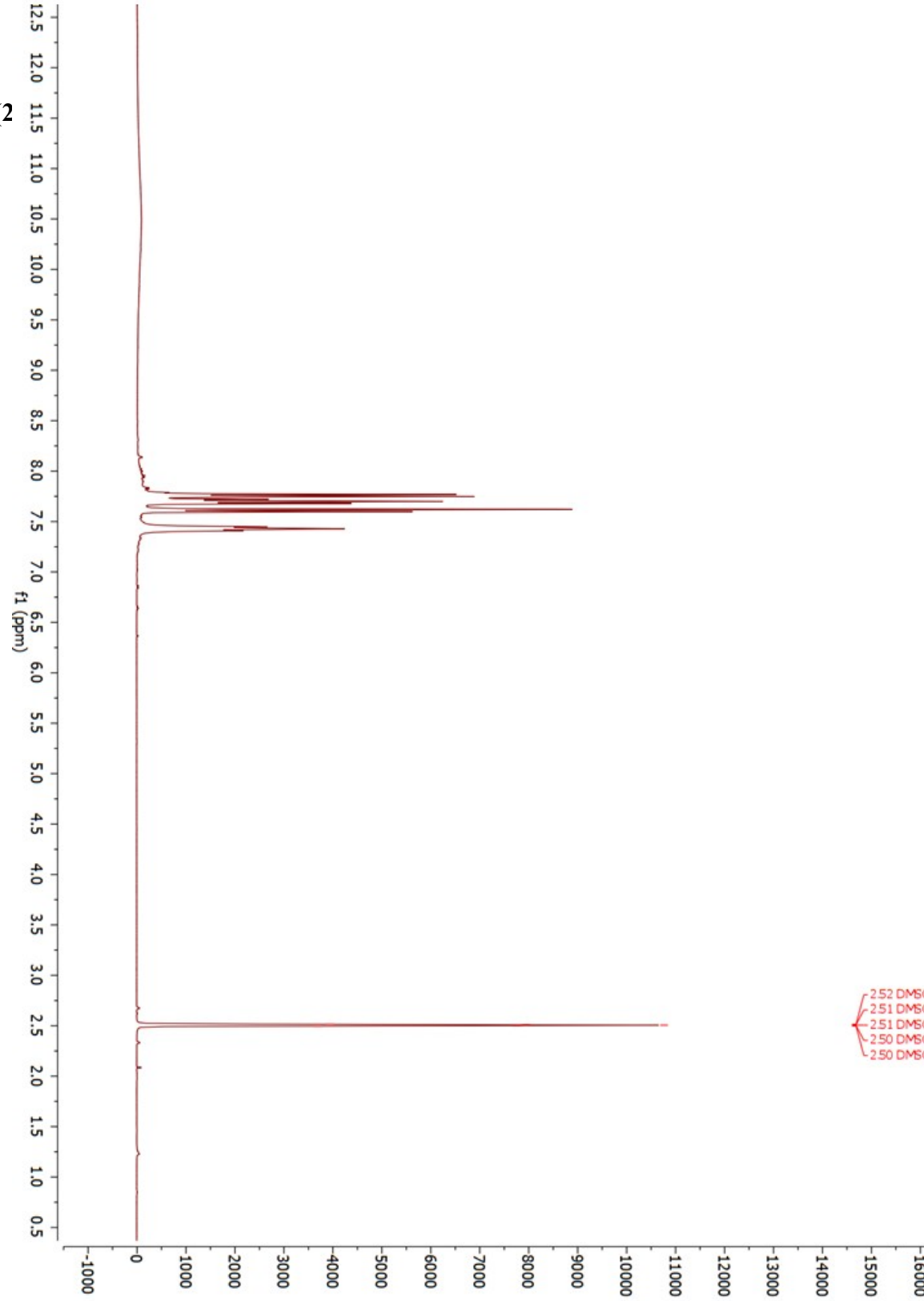
(E)-4-(2-(2,5-dibro amine (22)



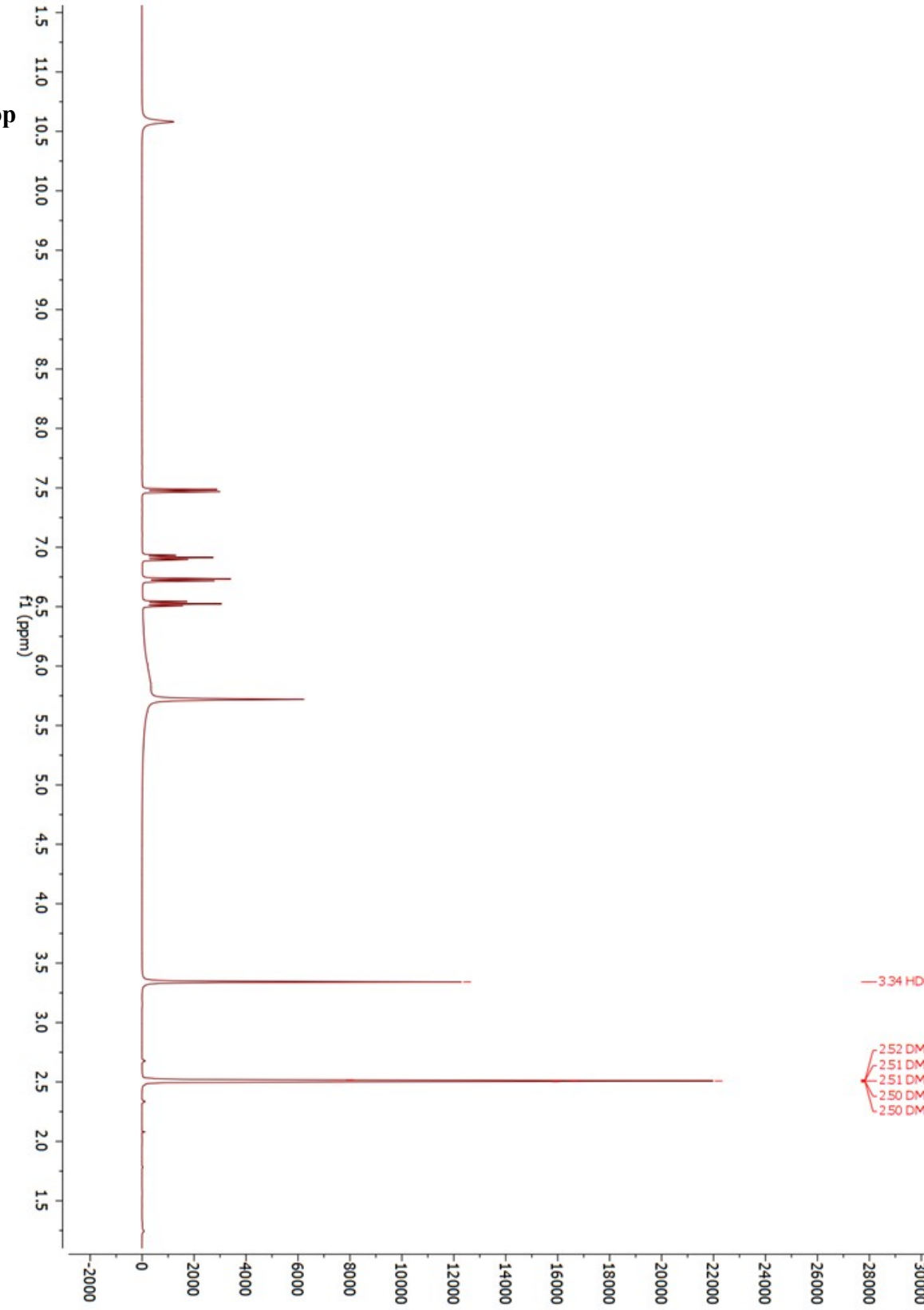
(E)-4-(2-(2,6-dibro
amine (23)



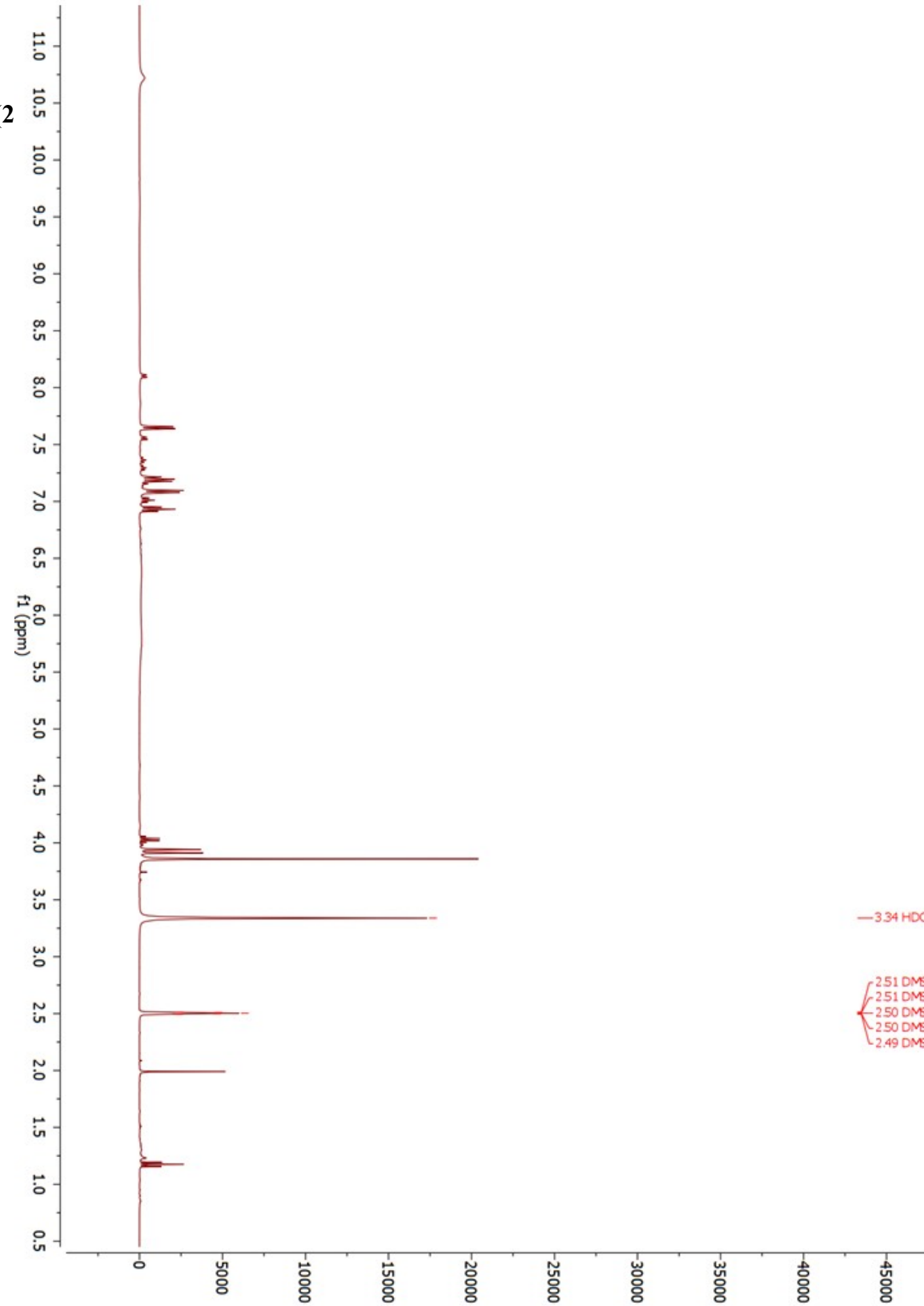
(E)-5-imino-4-(2-(2
3-amine (24)



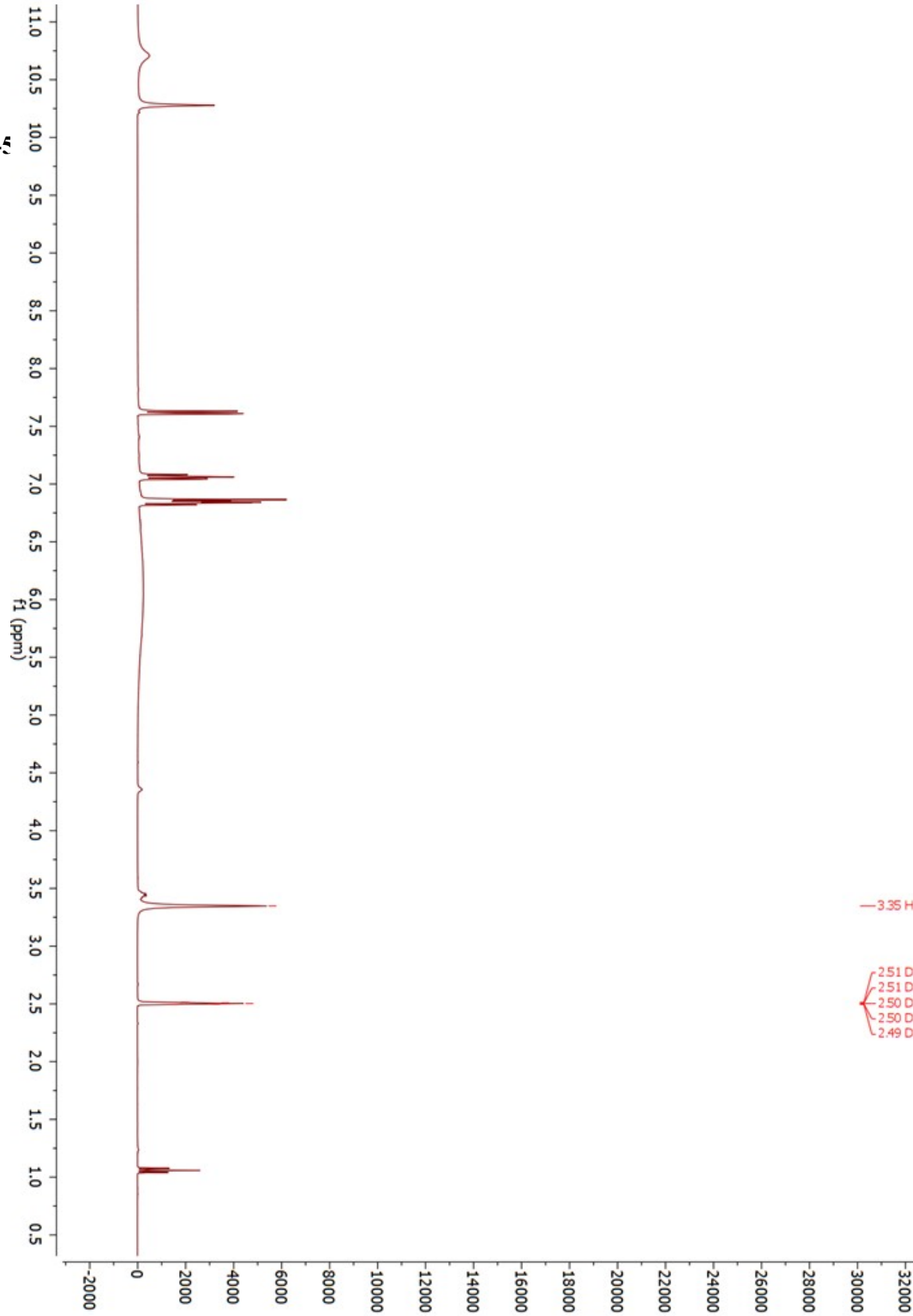
(E)-4-(2-(2-aminop
(25)



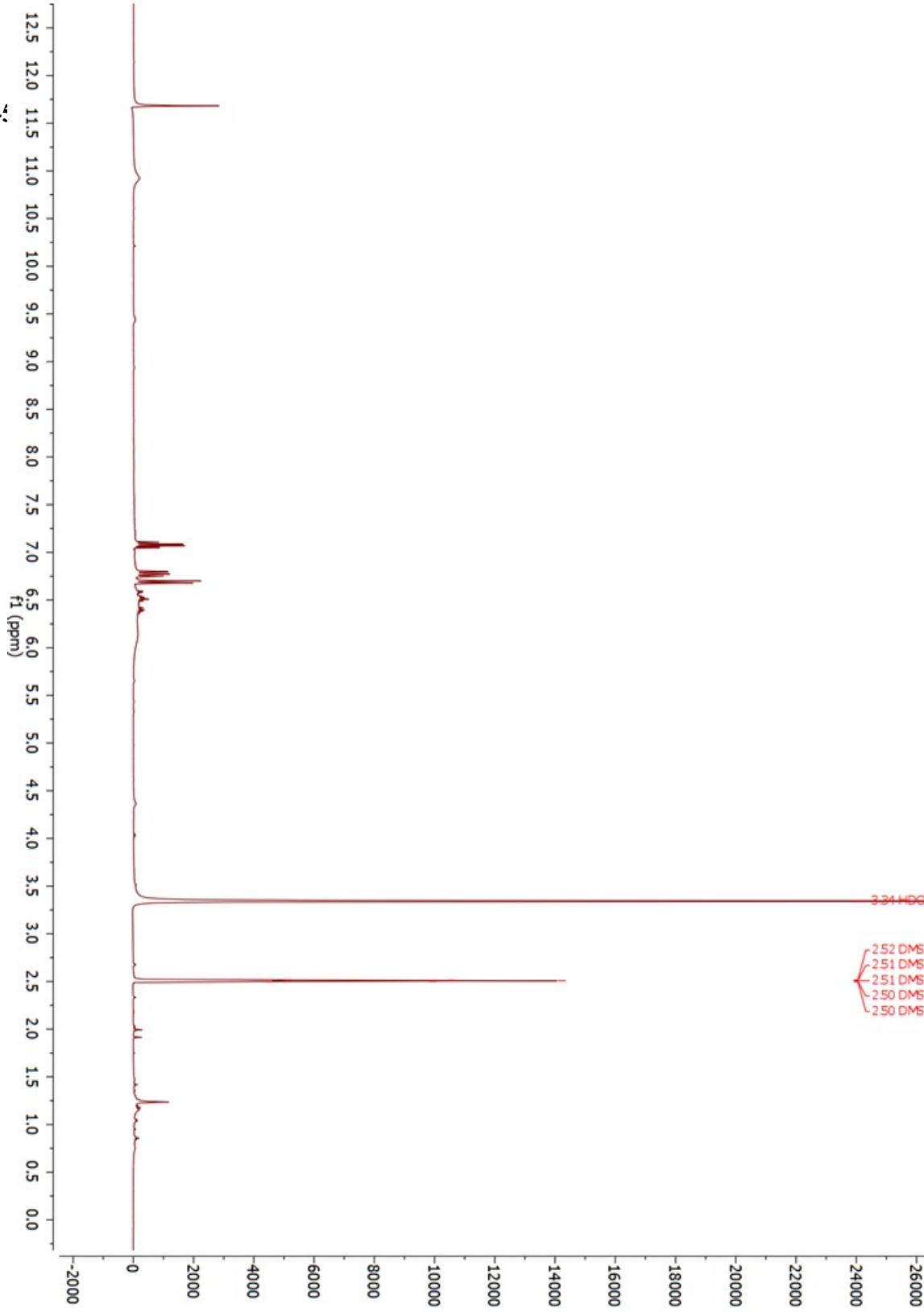
(E)-5-imino-4-(2-(2
(26)



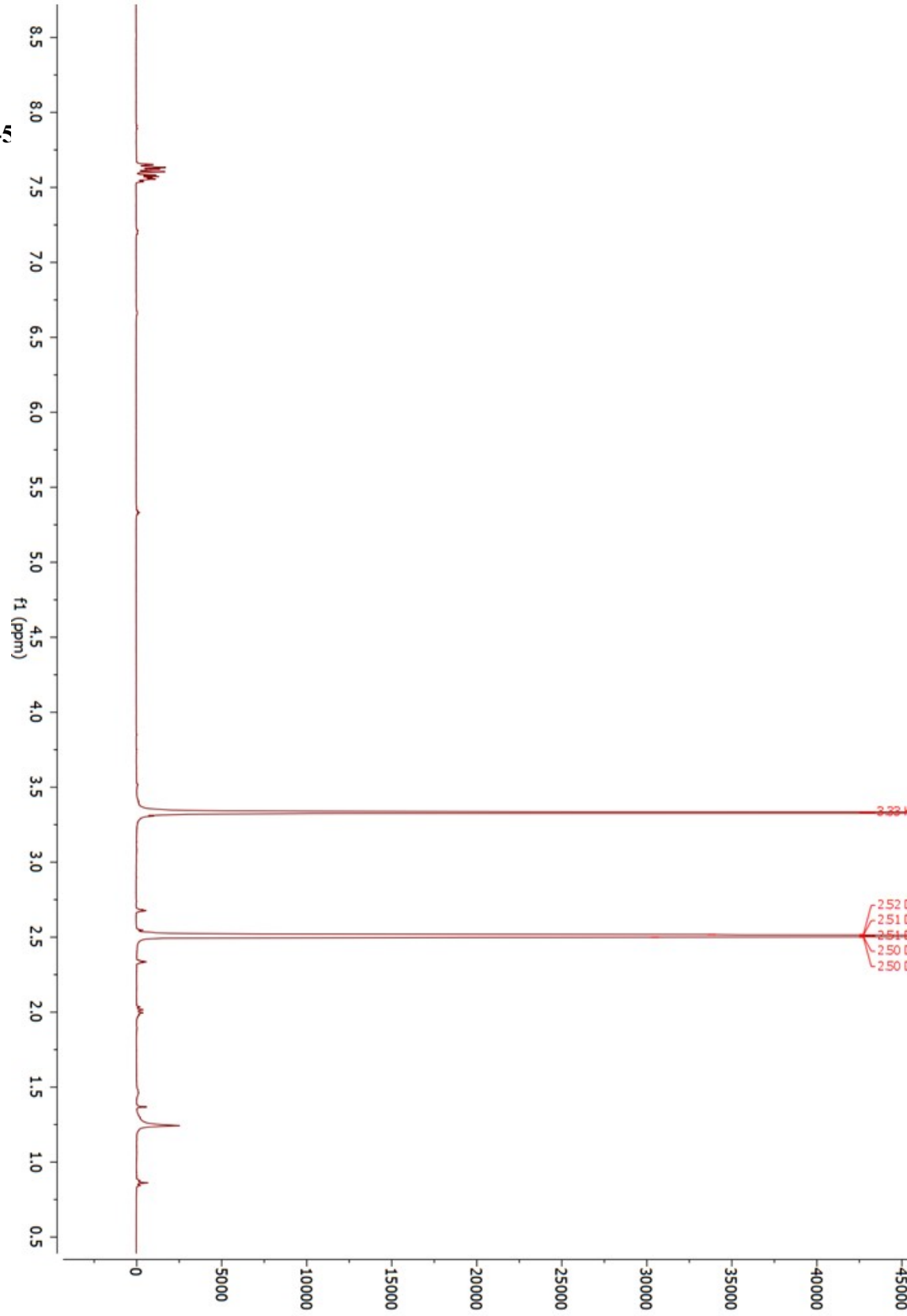
(E)-2-(2-(3-amino-5



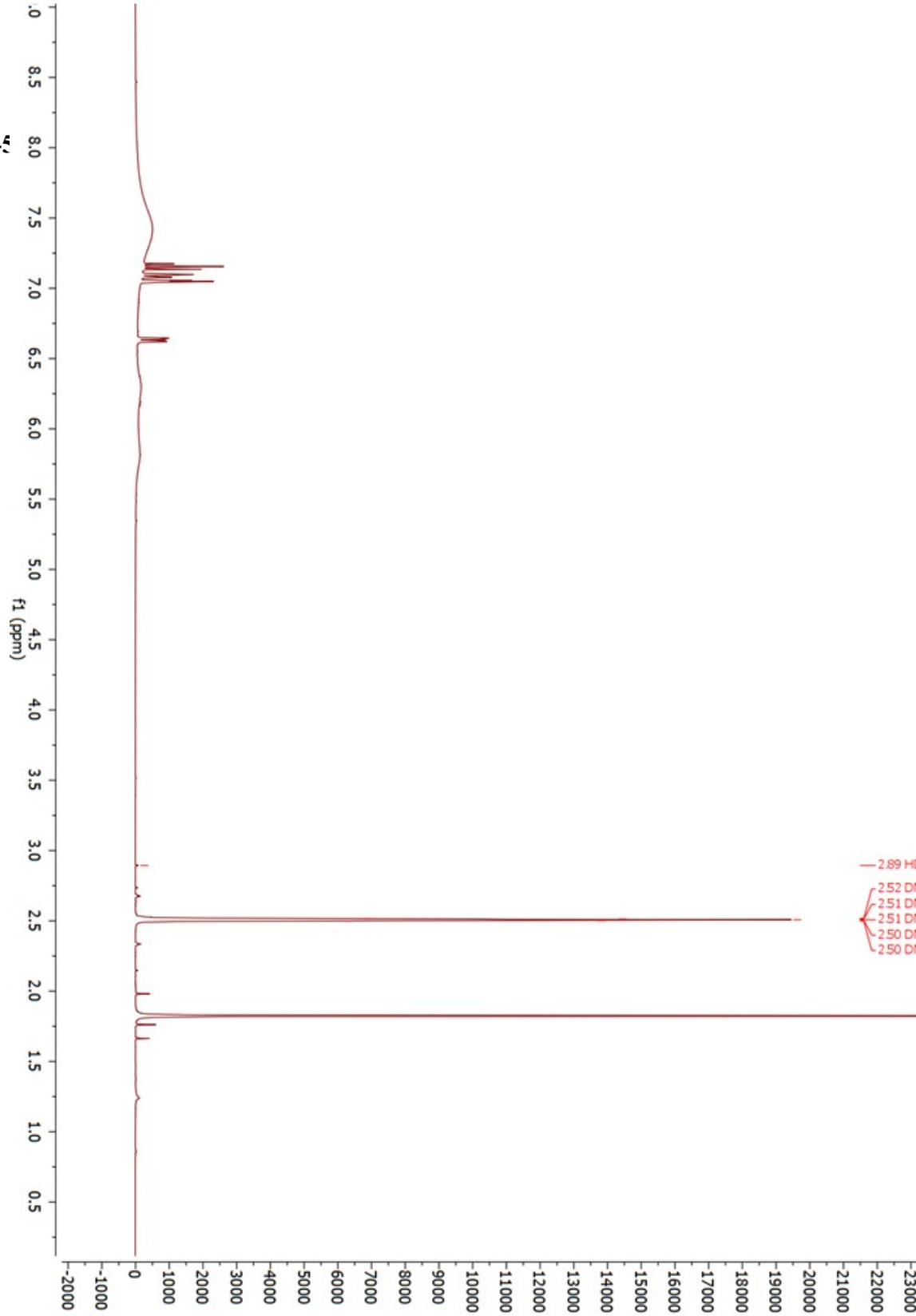
(E)-2-(2-(3-amino-5
fluorophenol (28)



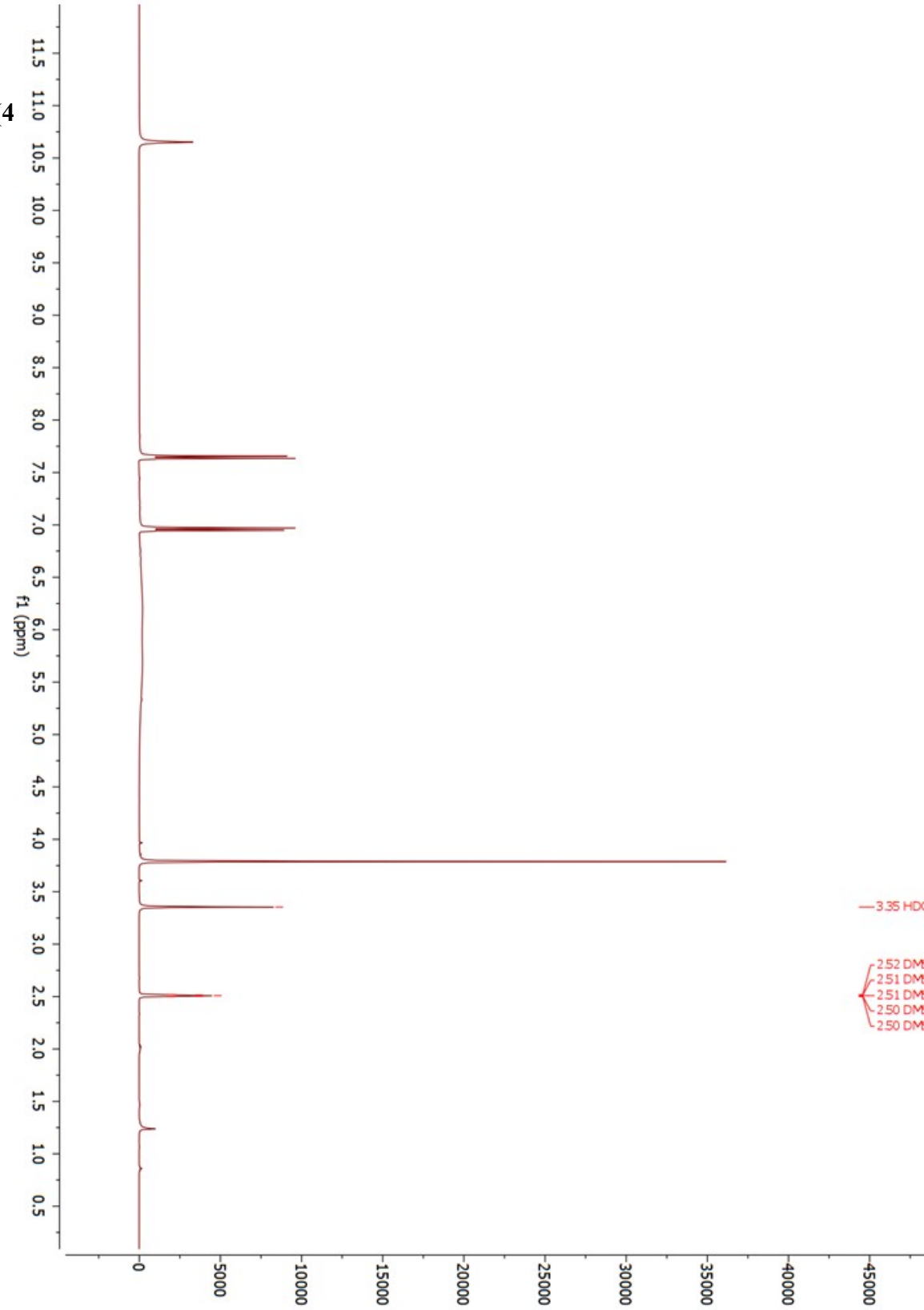
(E)-2-(2-(3-amino-5
diol (29)



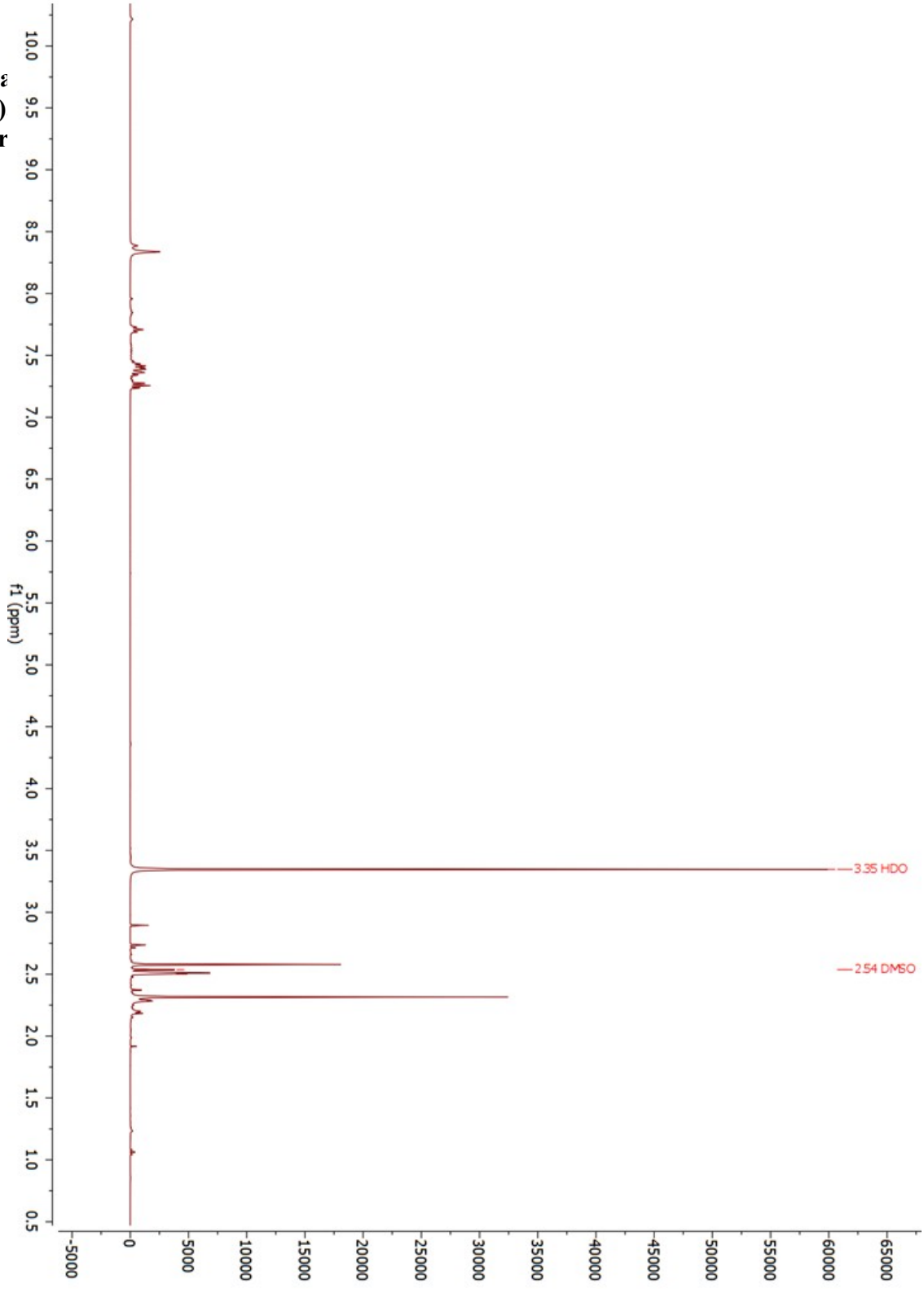
(E)-3-(2-(3-amino-5



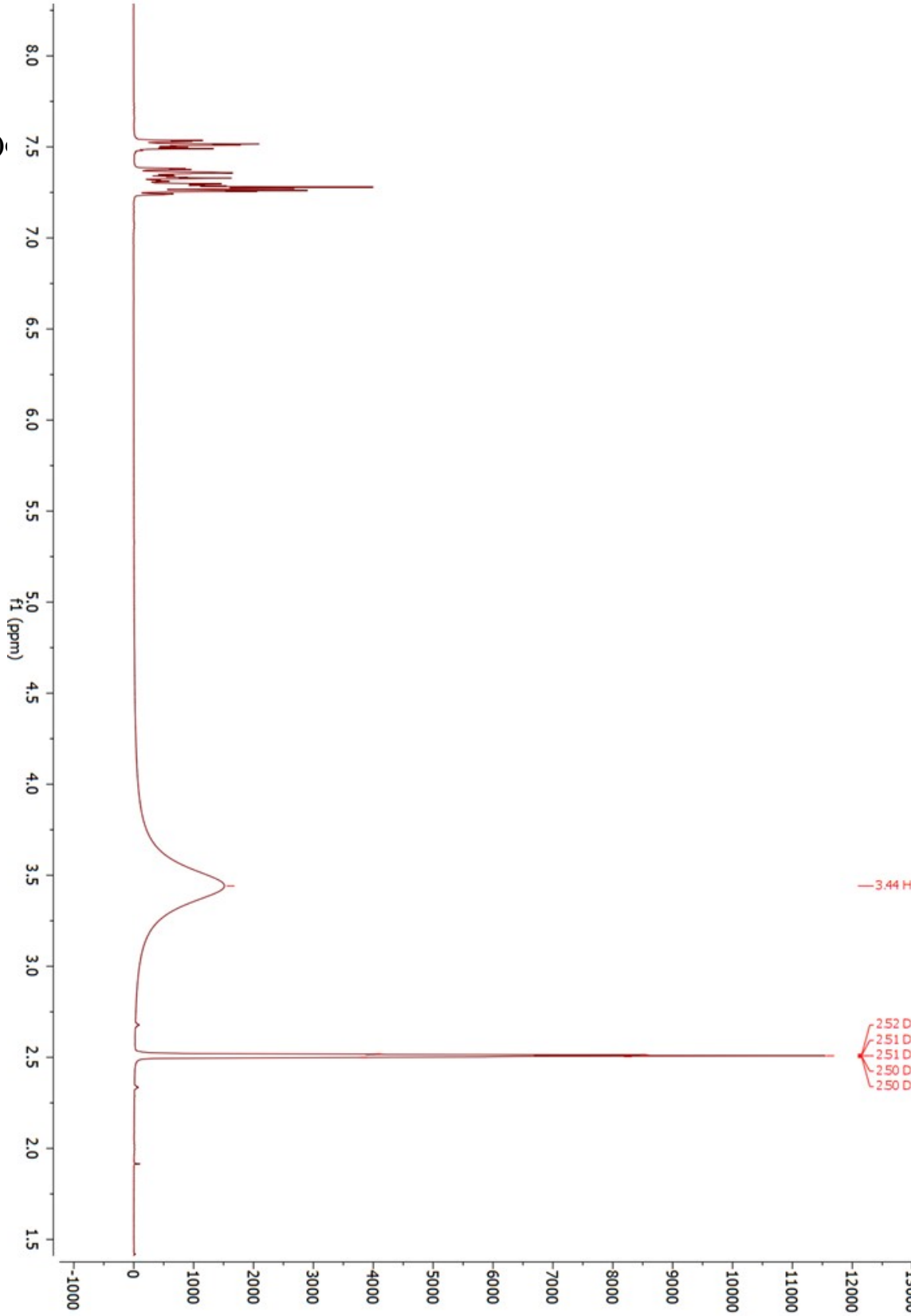
(E)-5-imino-4-(2-(4
(31)



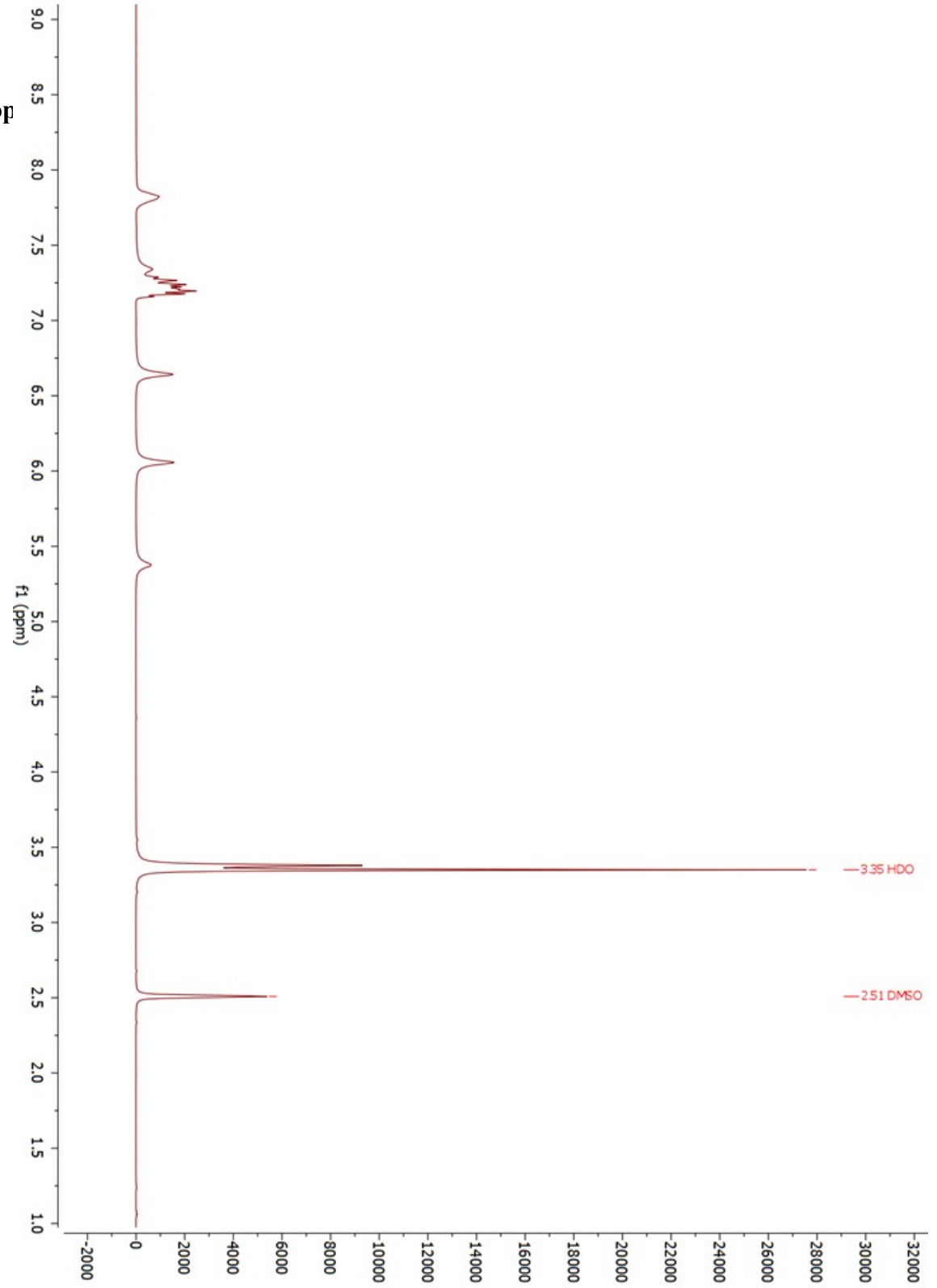
N-((3Z,4E)-5-aceta
pyrazol-3-ylidene)
fluorophenyl)hydr



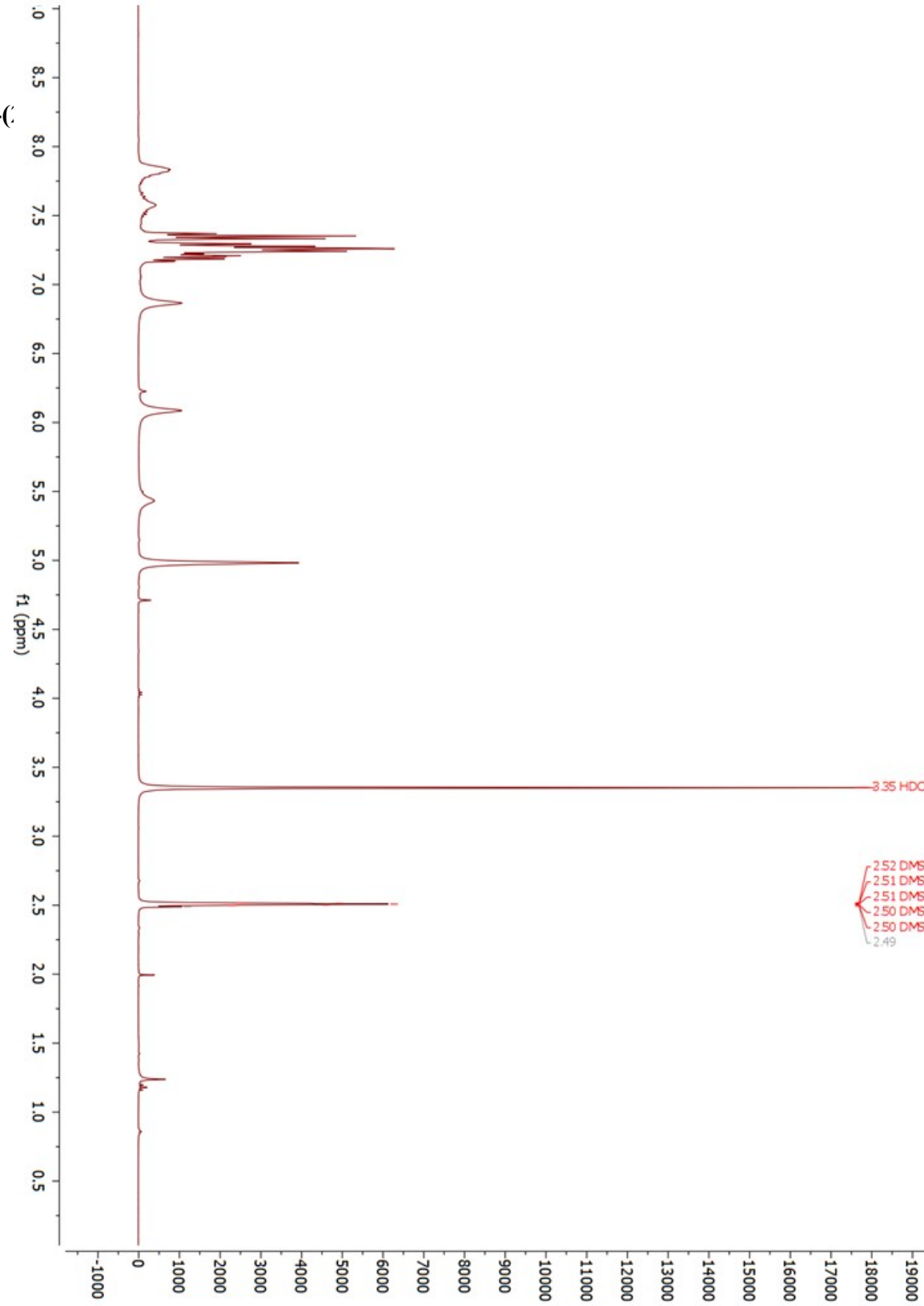
N-(2-fluorophenyl)



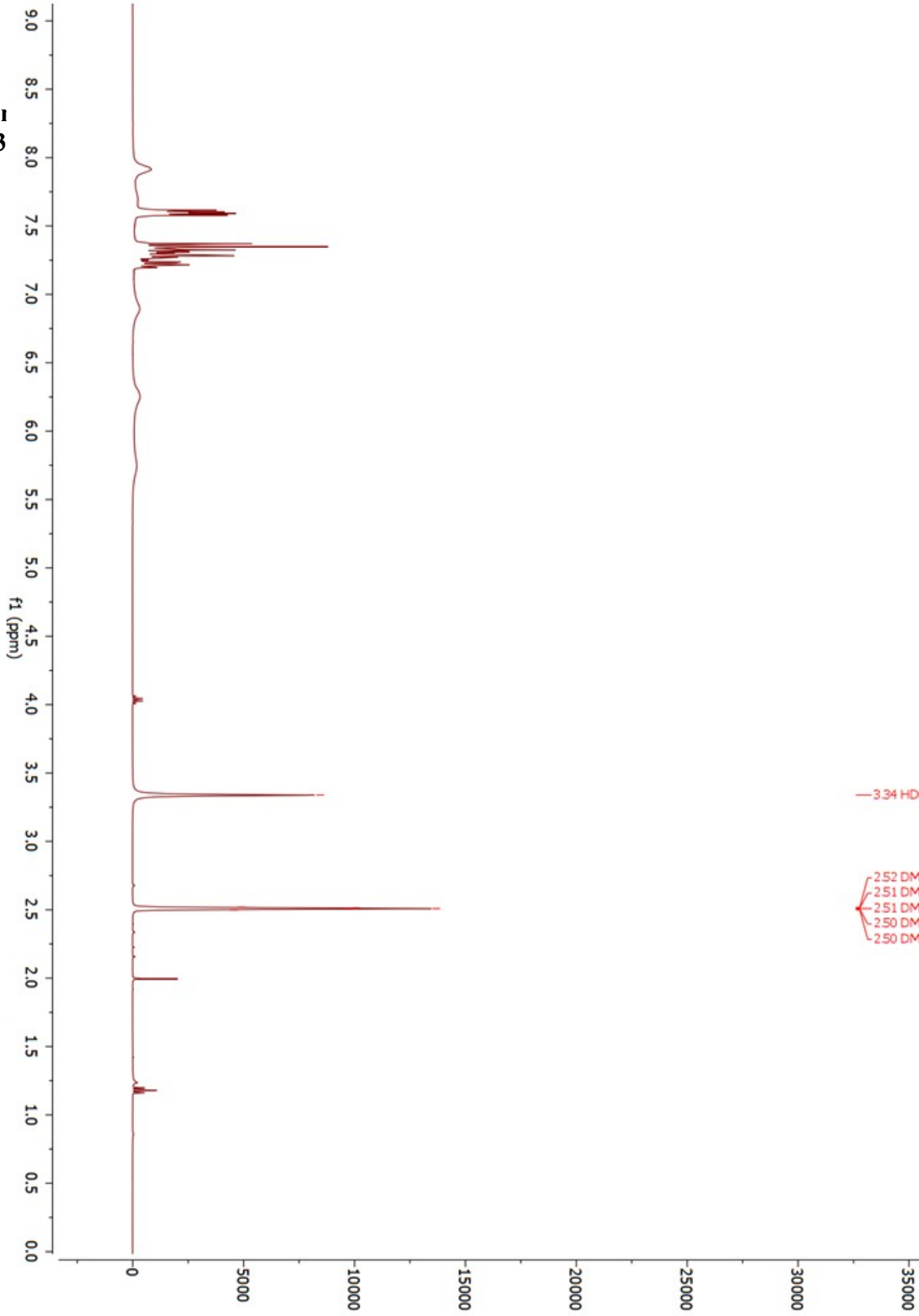
(Z)-4-(2-(2-fluorop
3-amine (35)



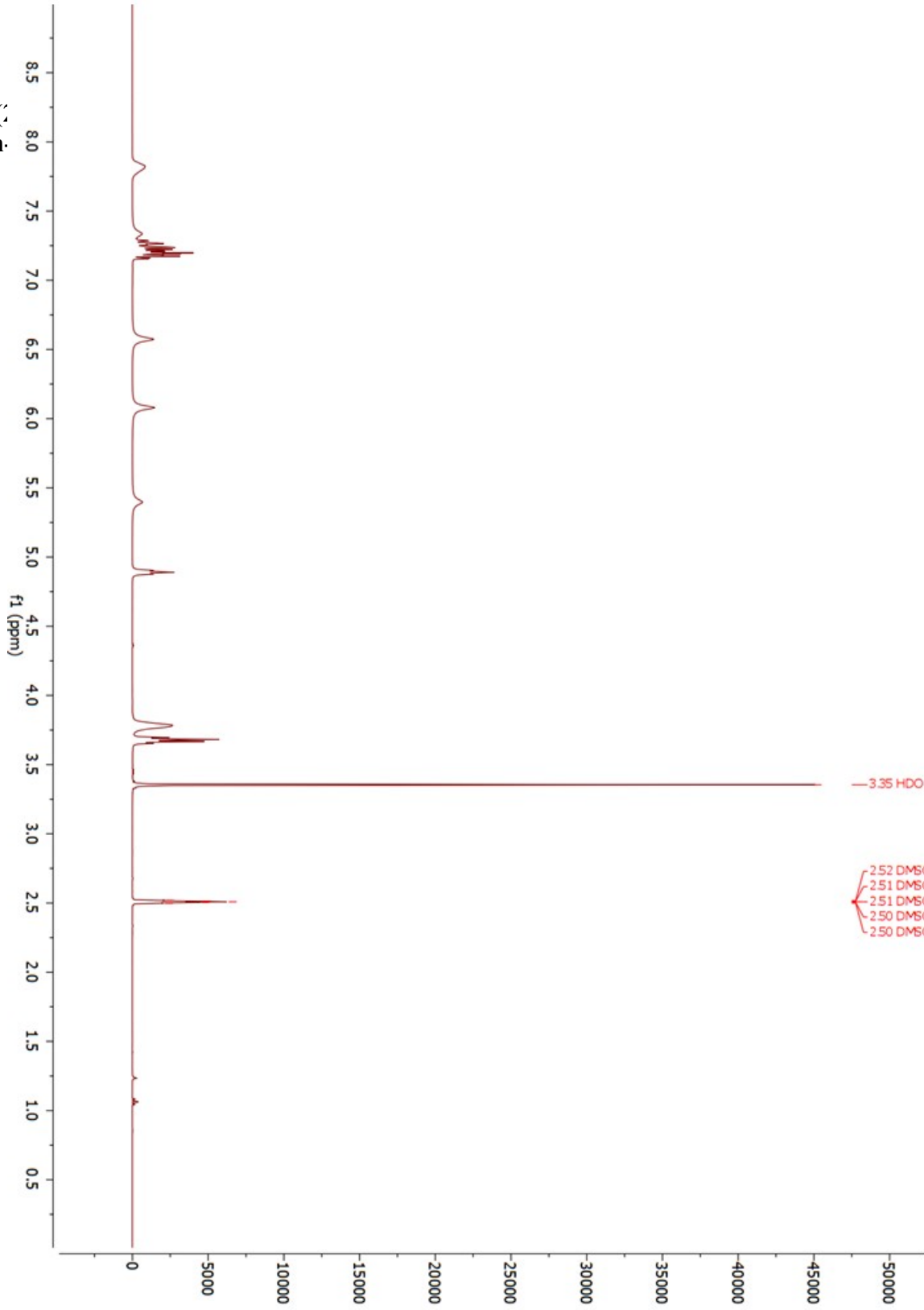
(Z)-1-benzyl-4-(2-(
amine (36)



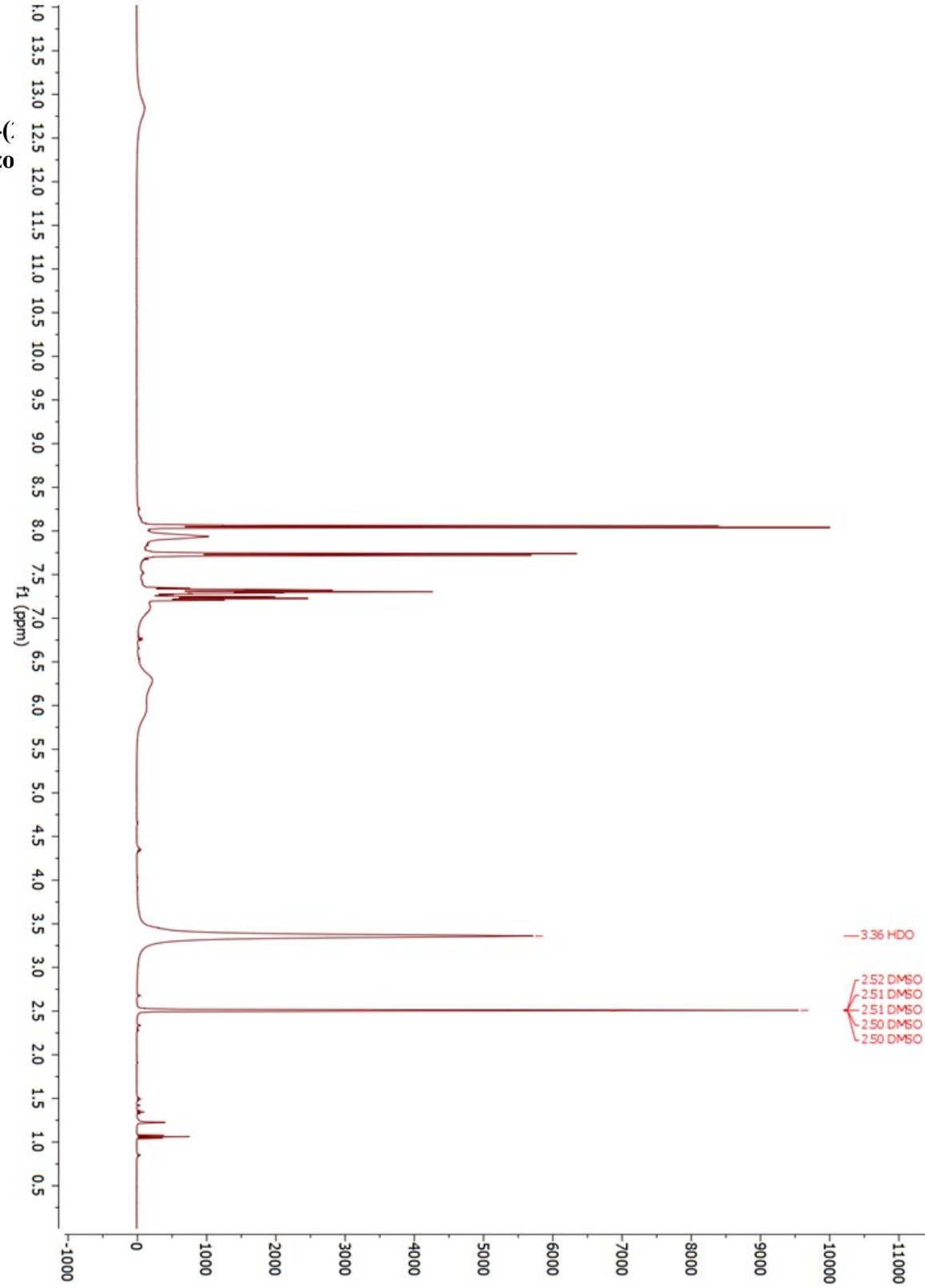
(Z)-1-(4-fluorophe
pyrazol-3-amine (3



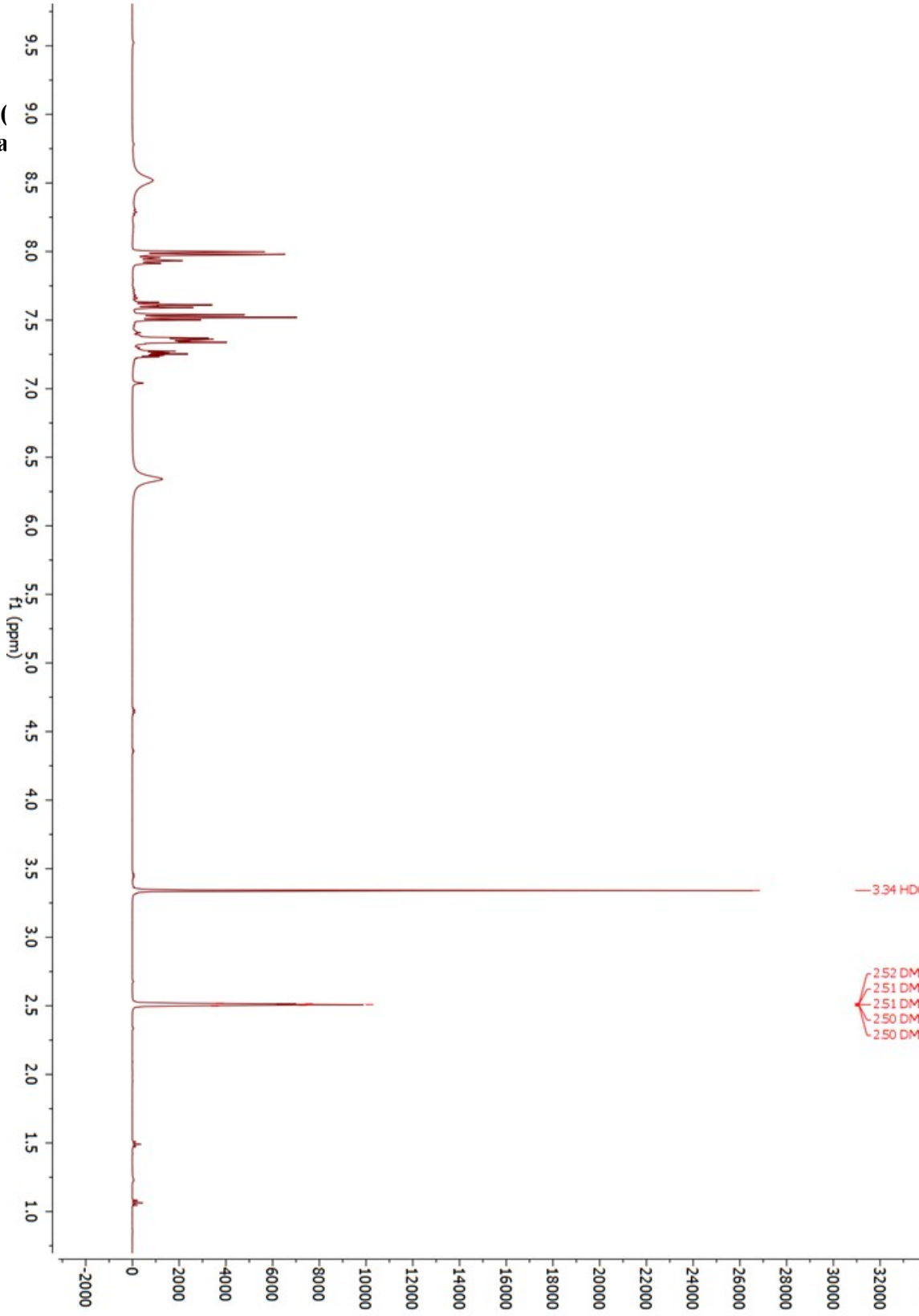
(Z)-2-(3-amino-4-(
pyrazol-1-yl)ethan



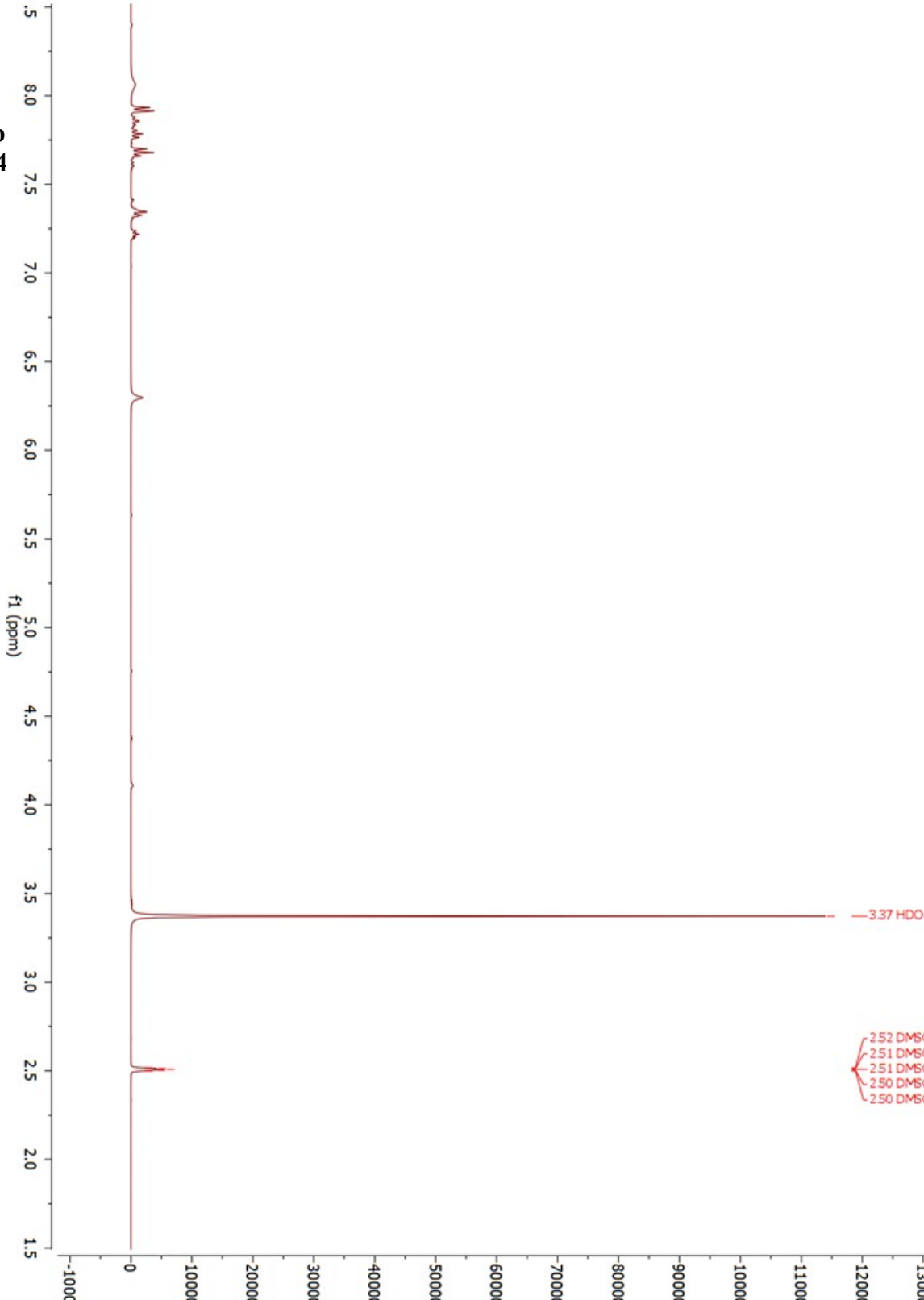
(Z)-4-(3-amino-4-(
pyrazol-1-yl)benzo



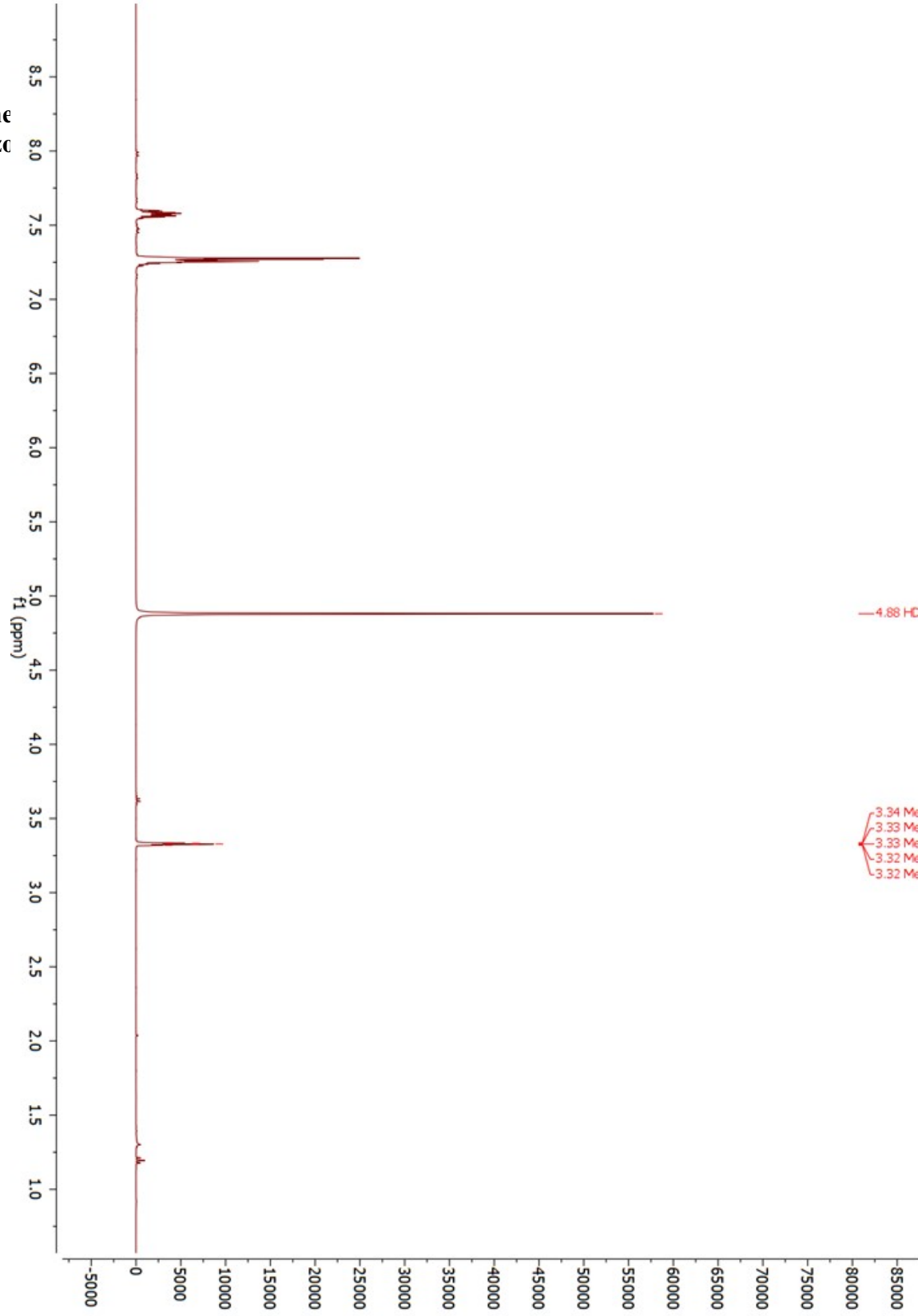
(Z)-(3-amino-4-(2-(
1-yl)(phenyl)metha



(Z)-4-(2-(2-fluorop
pyrazol-3-amine (4



(Z)-1-((4-aminophe
dihydro-1H-pyrazo



(Z)-4-(3-amino-4-(
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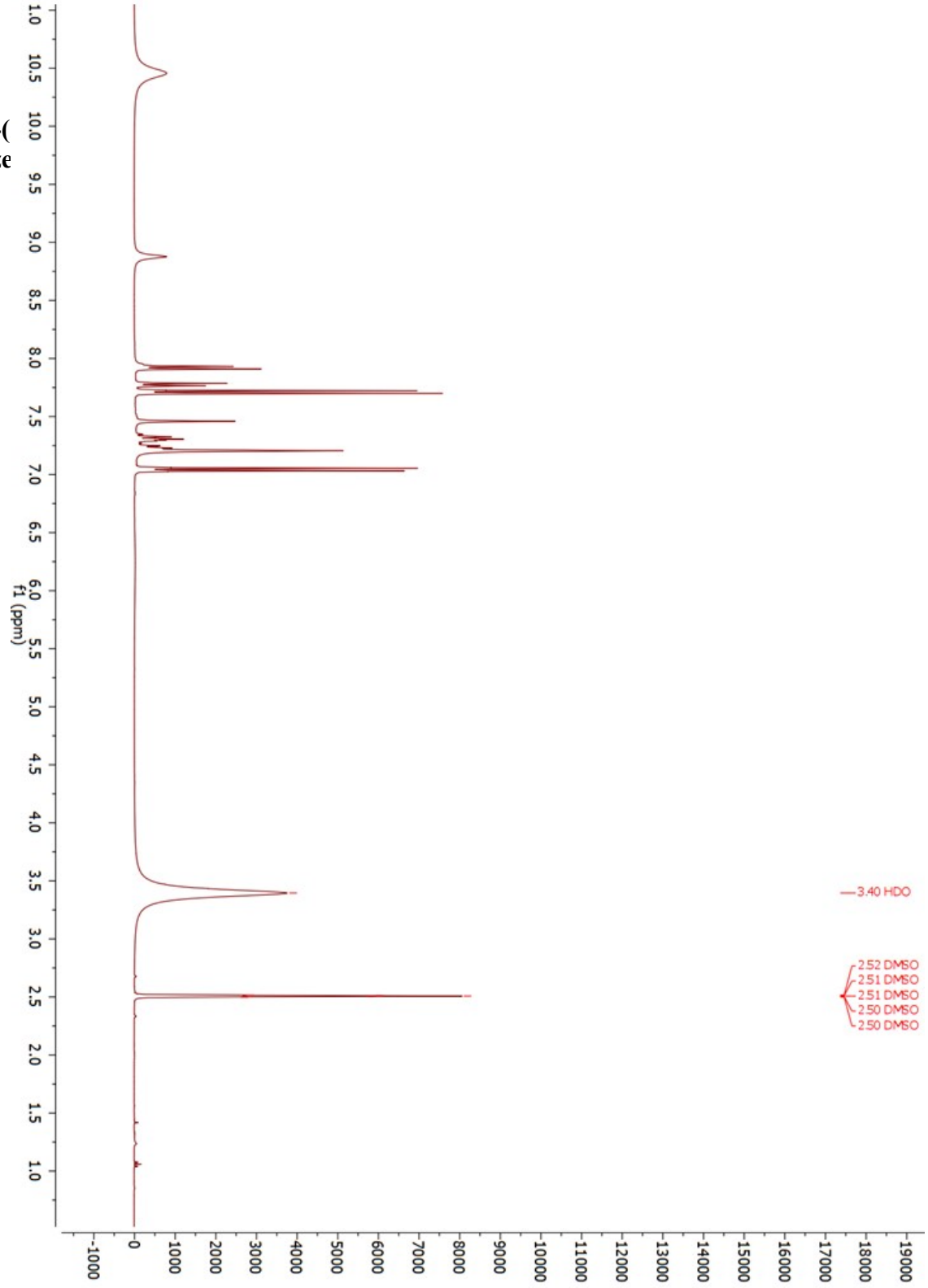
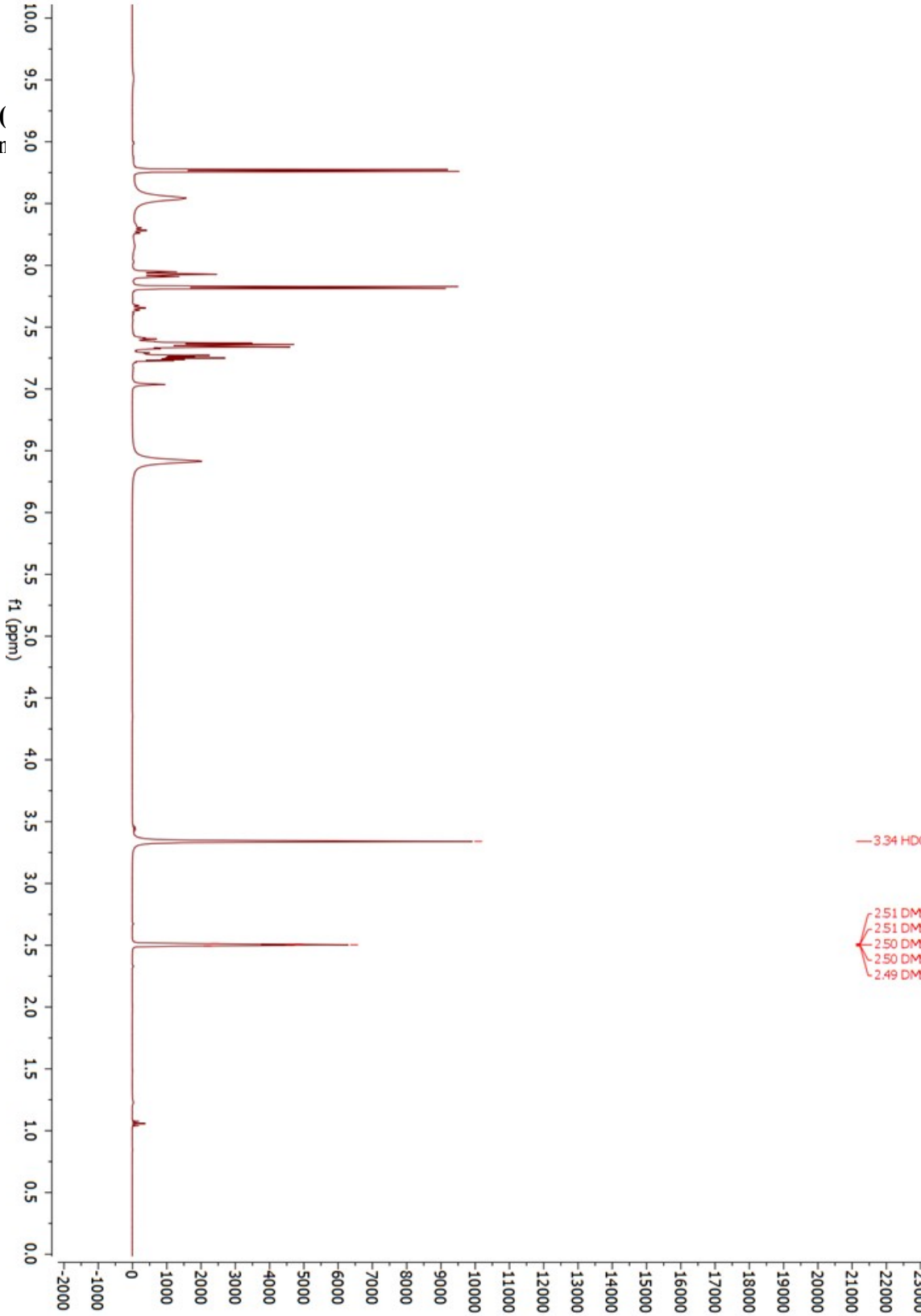
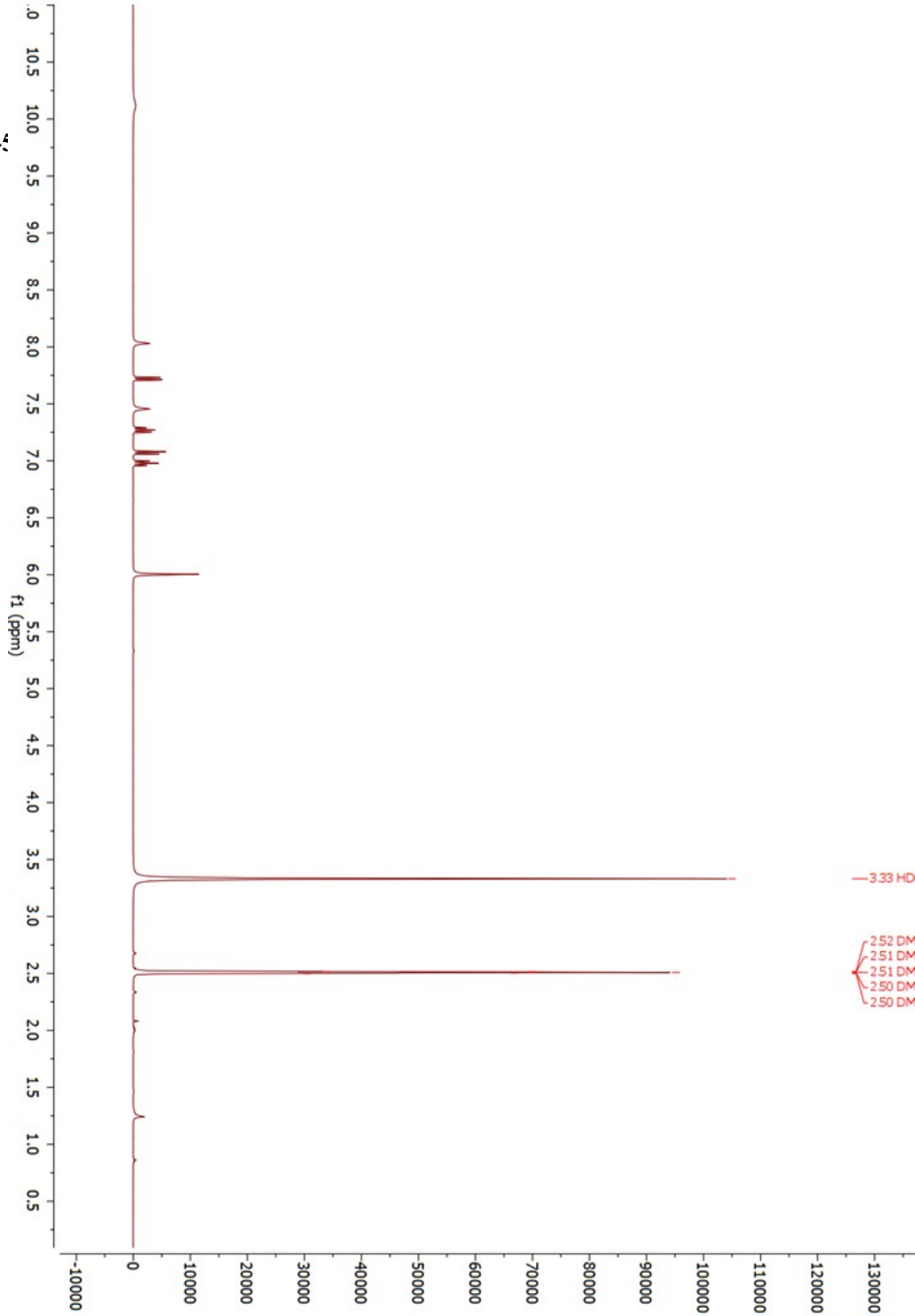


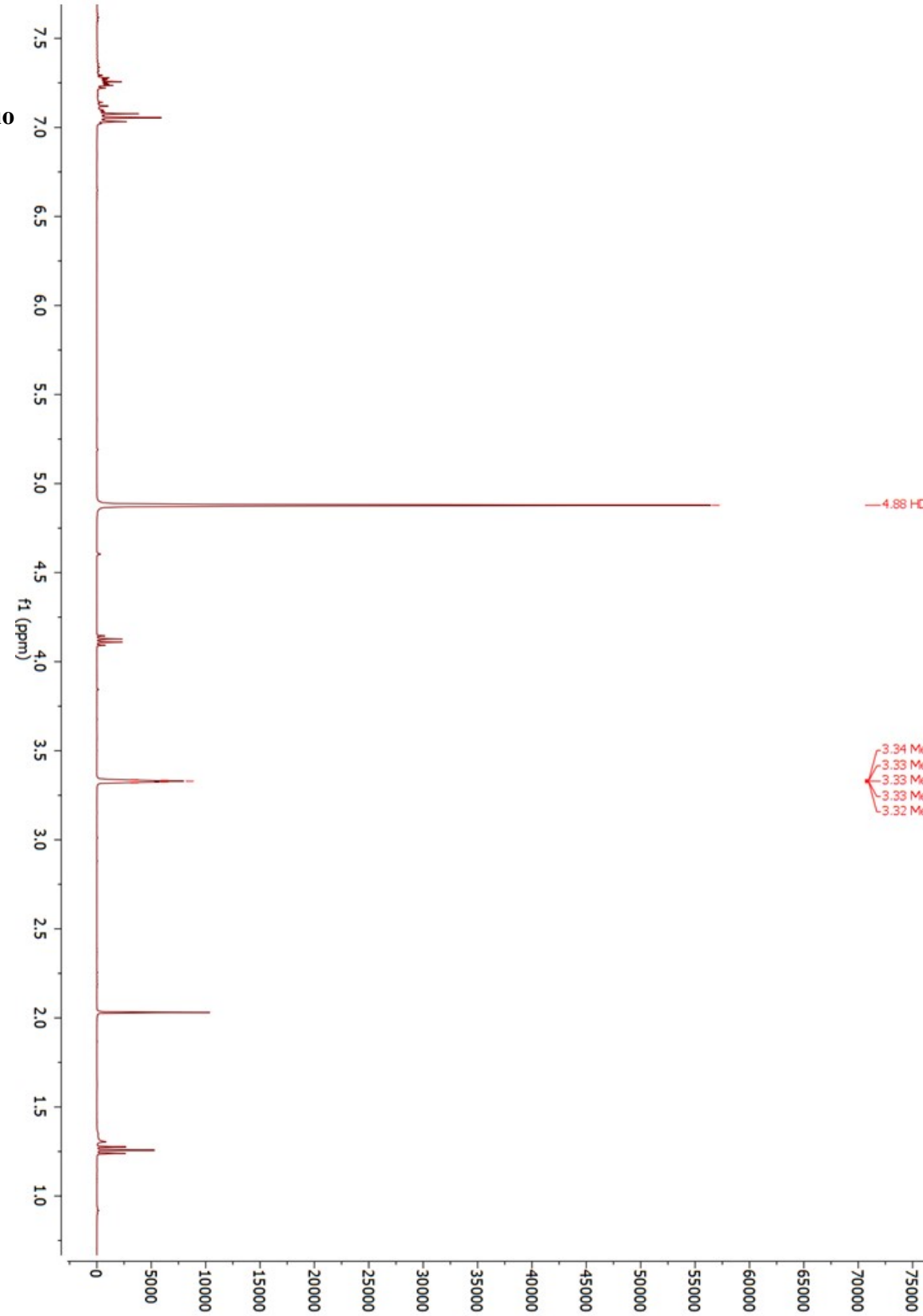
(Z)-(3-amino-4-(2-(
1-yl)(pyridin-4-yl)r



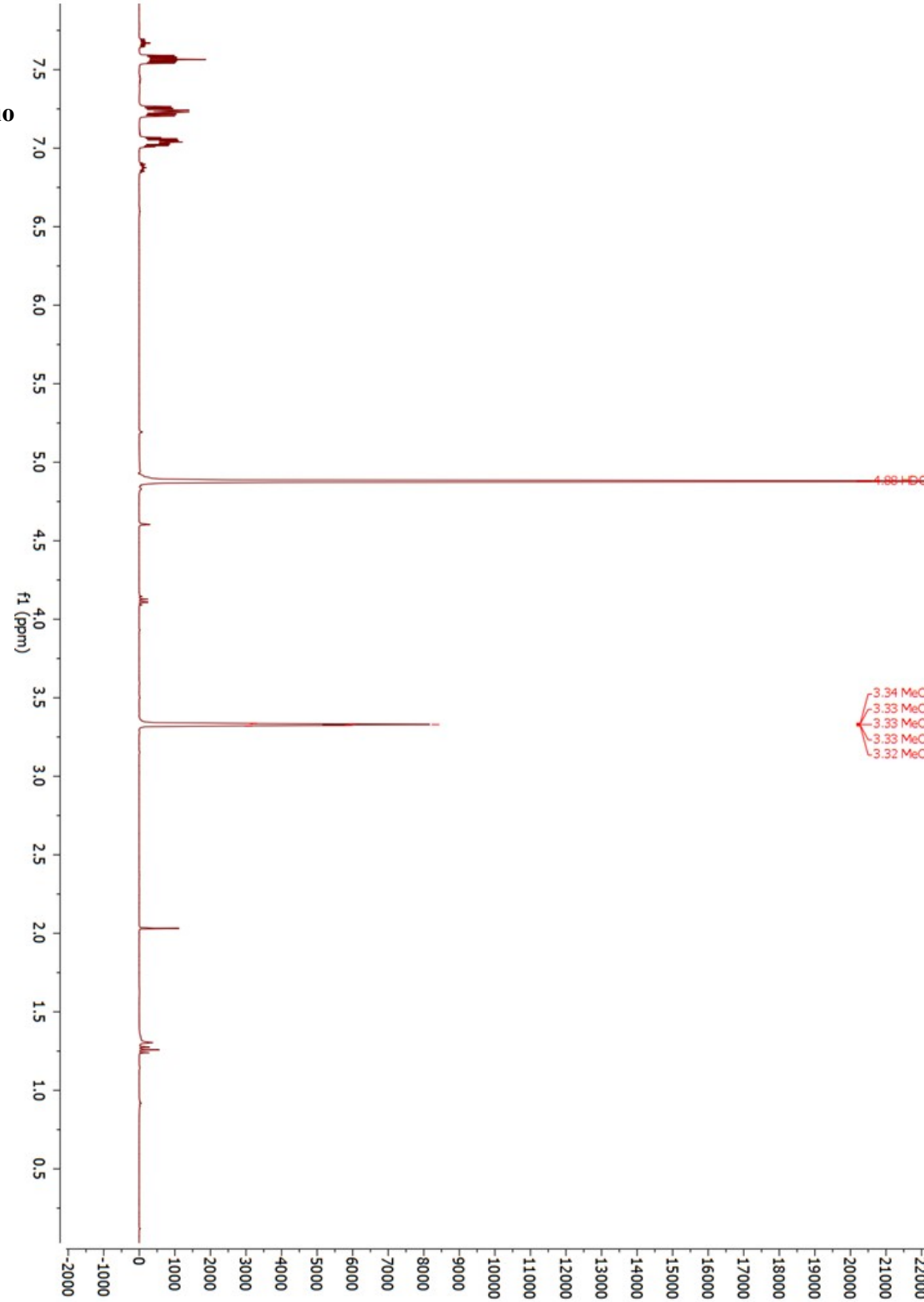
(Z)-2-(2-(3-amino-5



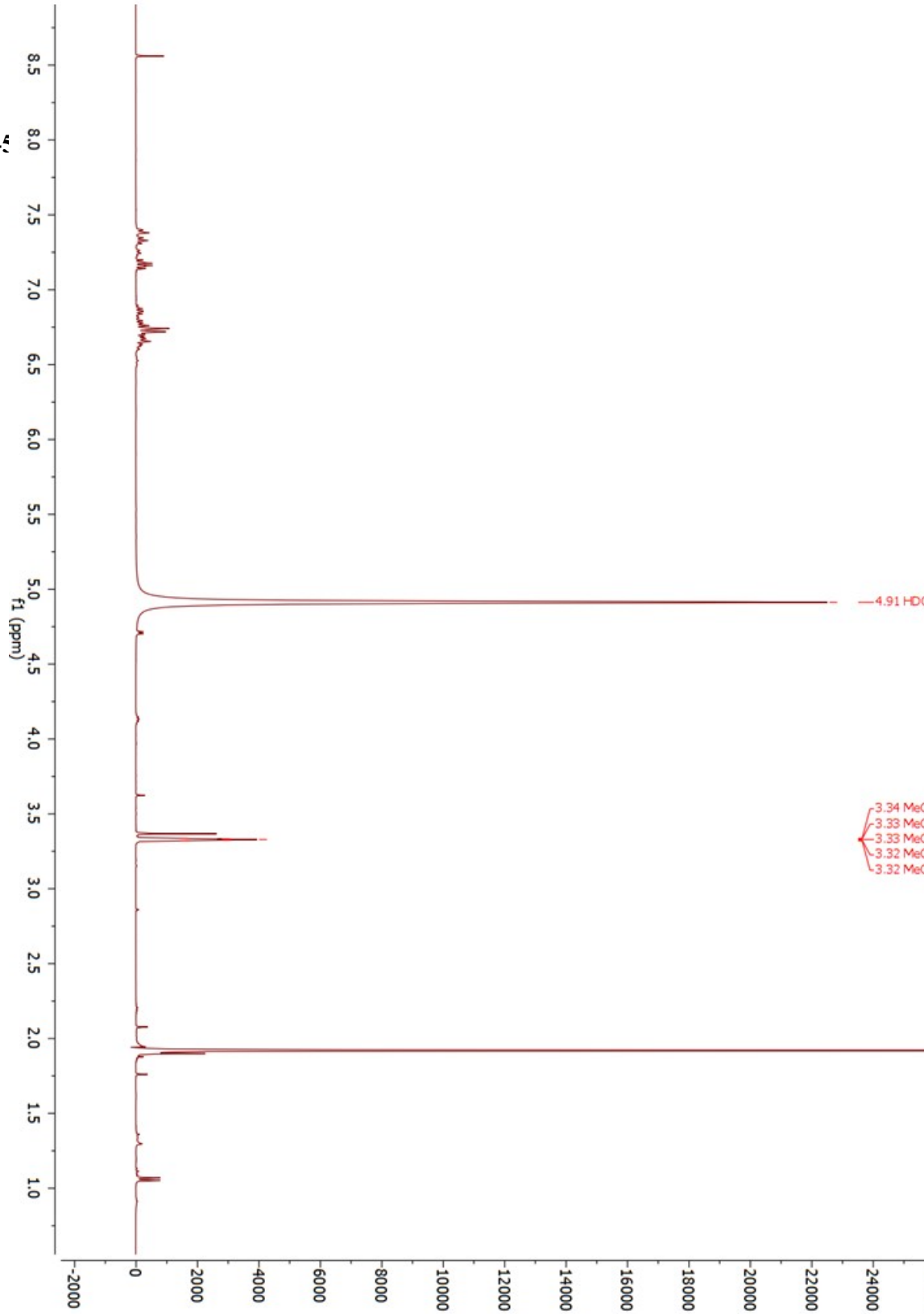
(Z)-4-(2-(2,6-difluo
(46)



(Z)-4-(2-(2,5-difluo
(47)



(Z)-2-(2-(3-amino-5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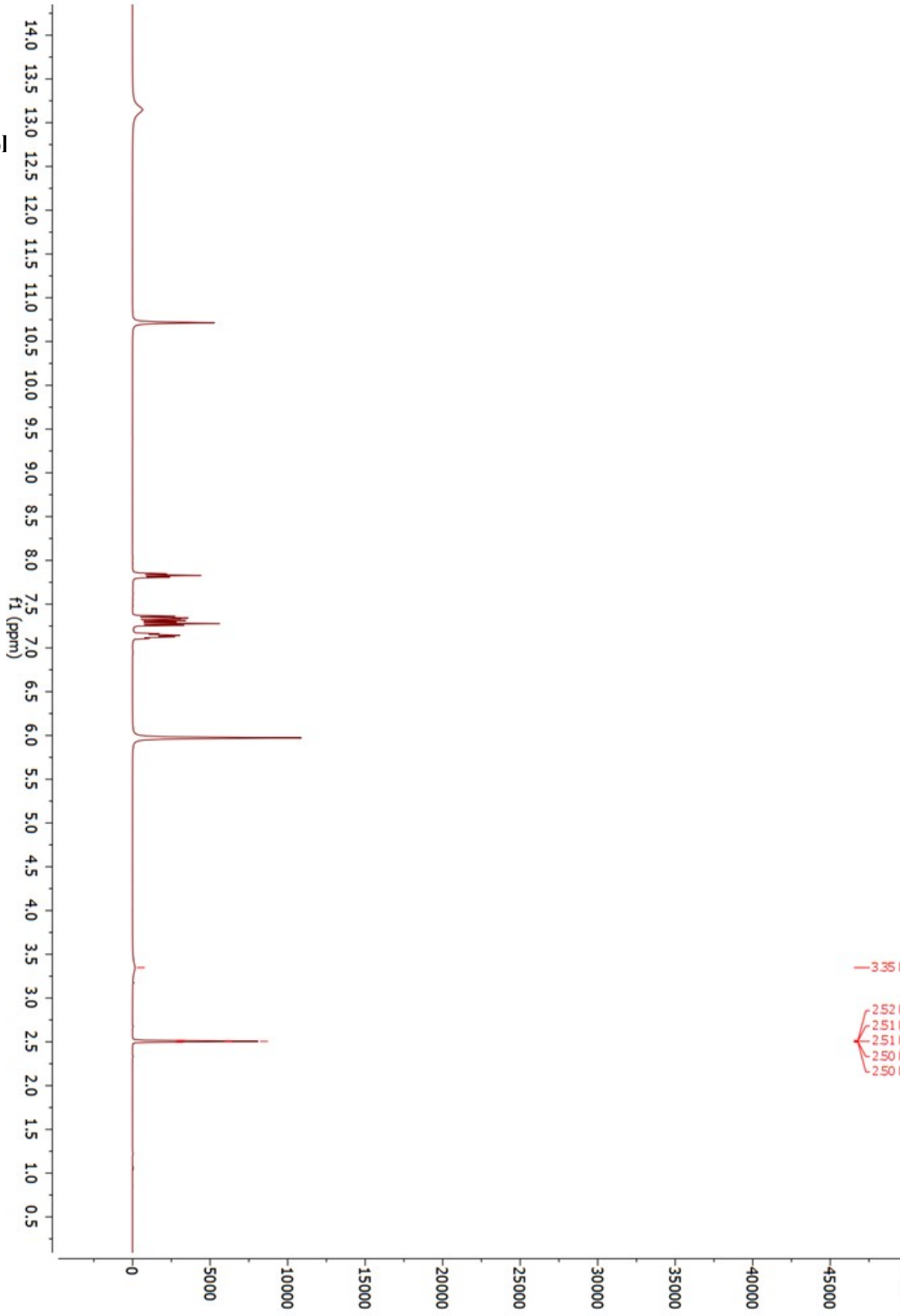
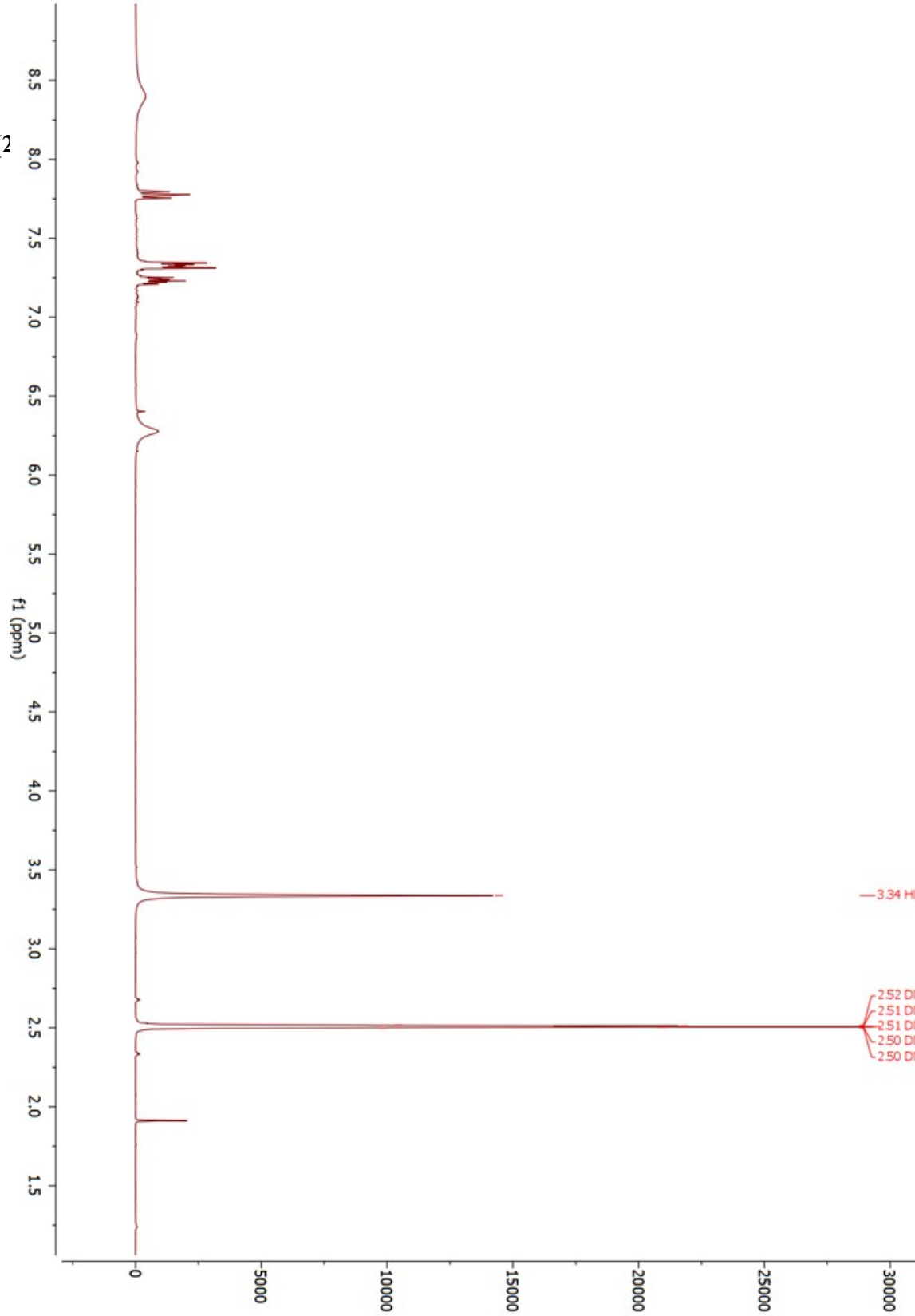
4.0
3.5
3.0
2.5
2.0
1.5
1.0
4.91 HDO
3.34 MeO
3.33 MeO
3.33 MeO
3.32 MeO
3.32 MeO
-2000
0
2000
4000
6000
8000
10000
12000
14000
16000
18000
20000
22000
24000

(Z)-4-(2-(2-fluoropl



(Z)-5-amino-4-(2-(2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4.5
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3.0
2.5
2.0
1.5
0
5000
10000
15000
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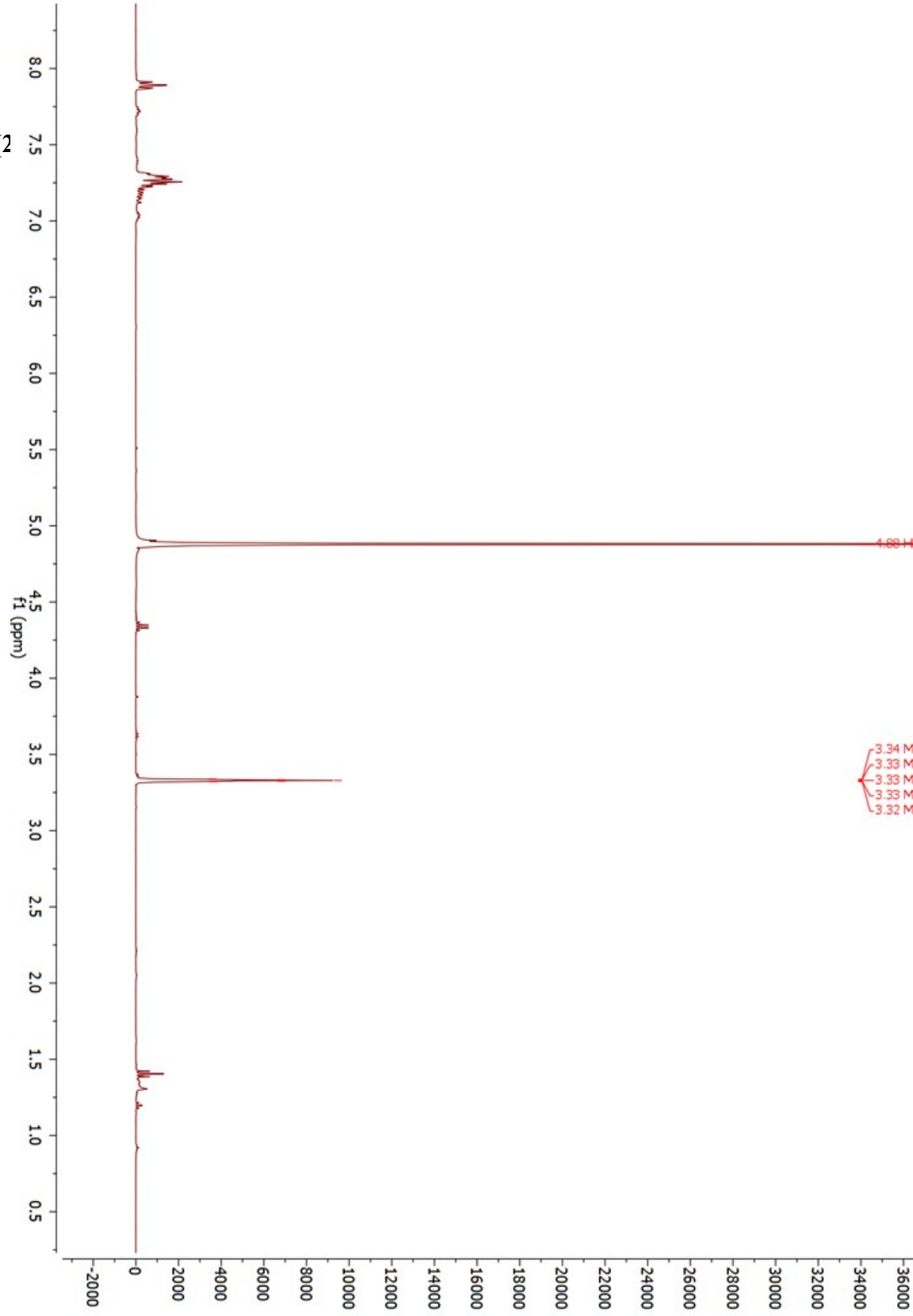
2.52 D
2.51 D
2.51 D
2.50 D
2.50 D

(Z)-3-amino-4-(2-(2


f1 (ppm)
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3.5
3.0
2.5
2.0
1.5
1.0
0.5
-2000
0
2000
4000
6000
8000
10000
12000
14000
16000
18000
20000
22000
24000
26000
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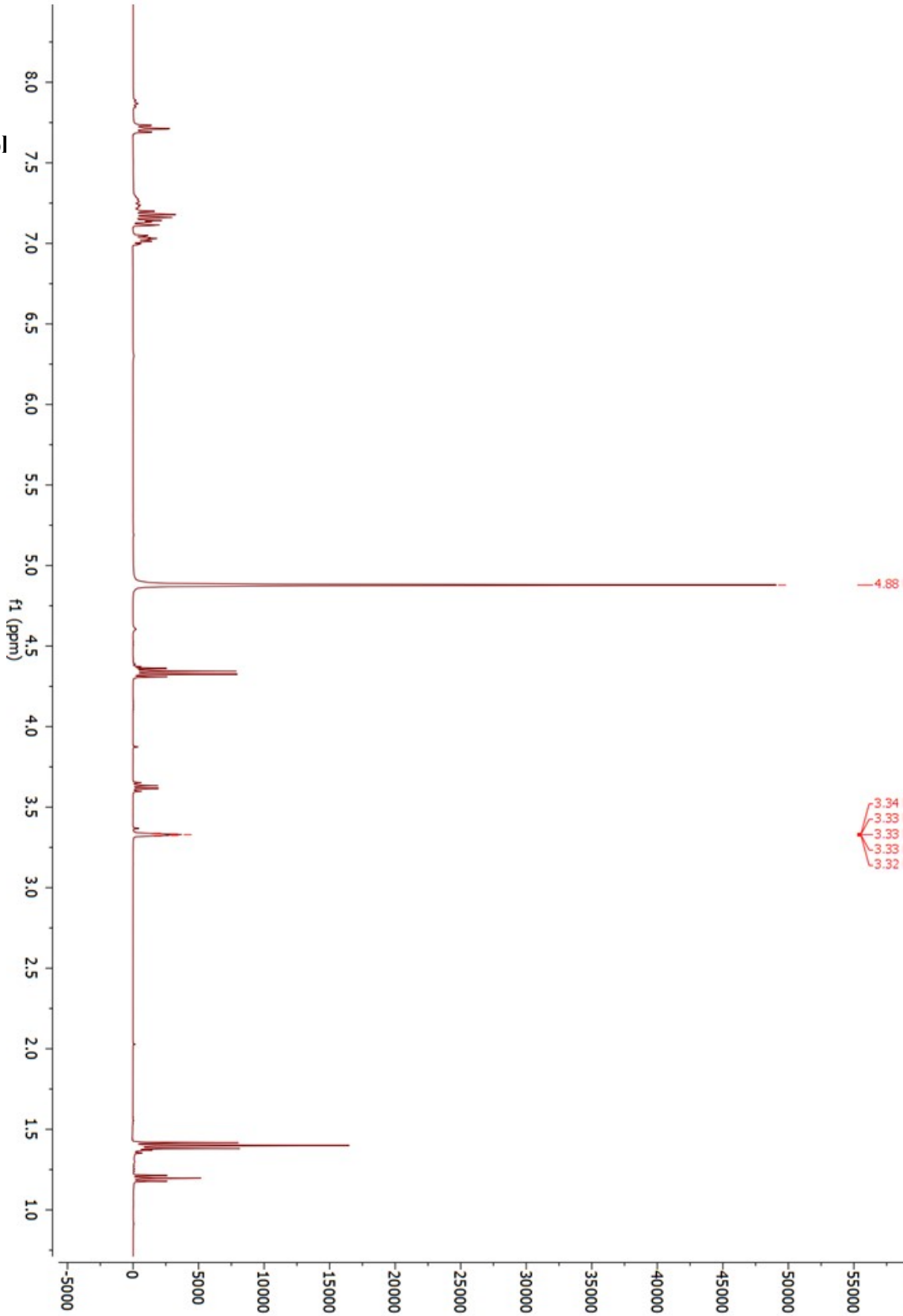
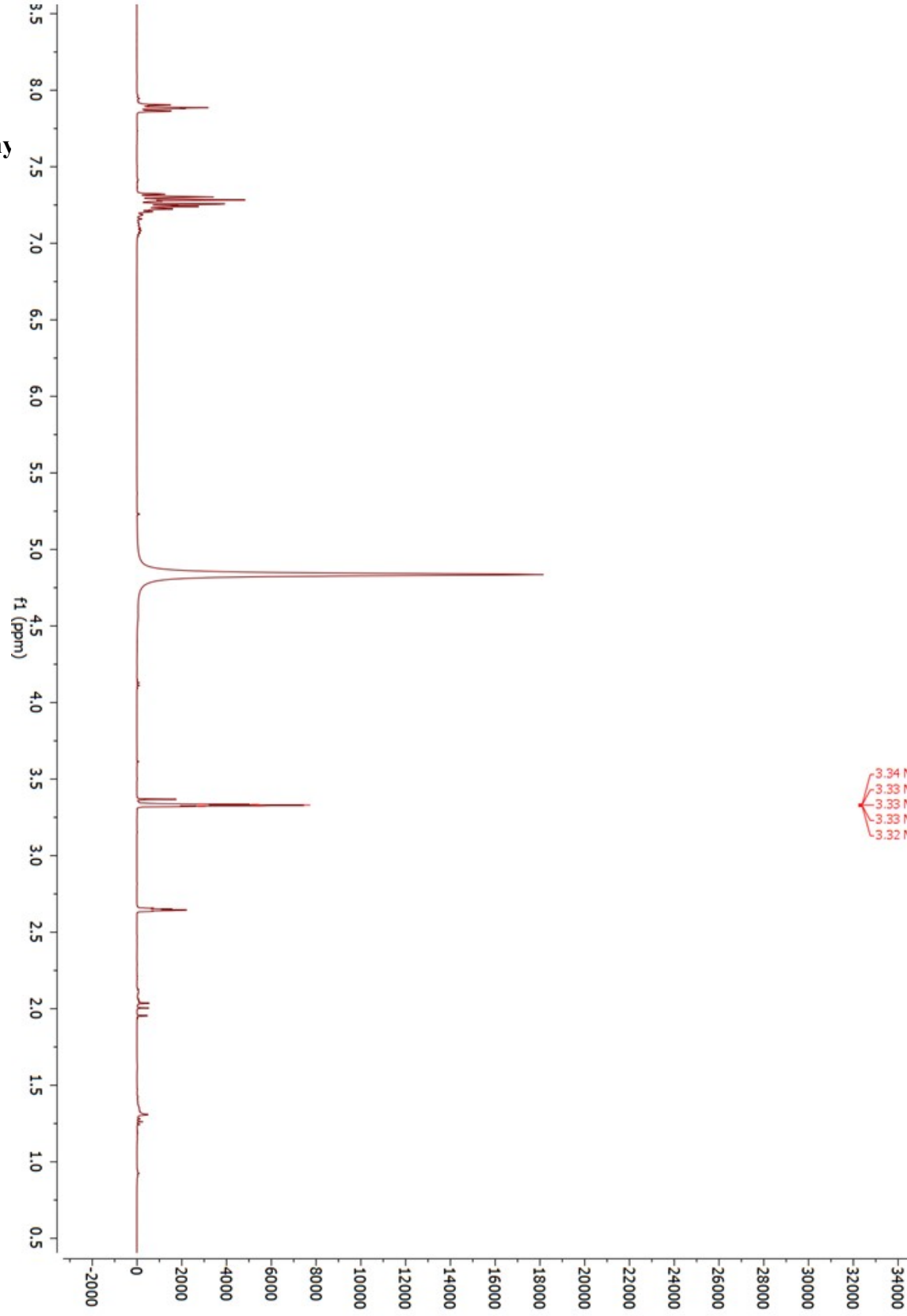
3.34 M
3.33 M
3.33 M
3.33 M
3.32 M

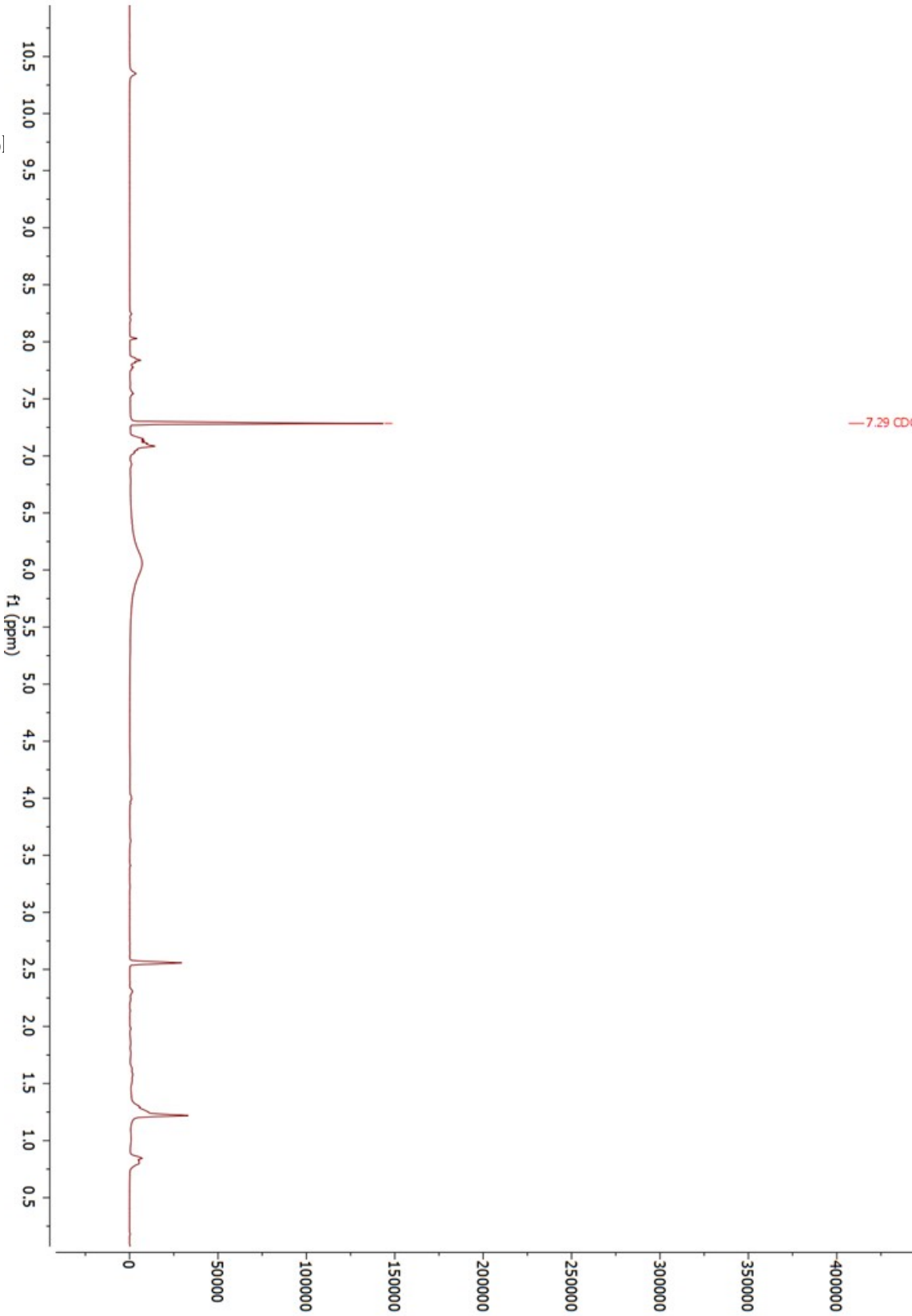
(Z)-4-(2-(2-fluoropl



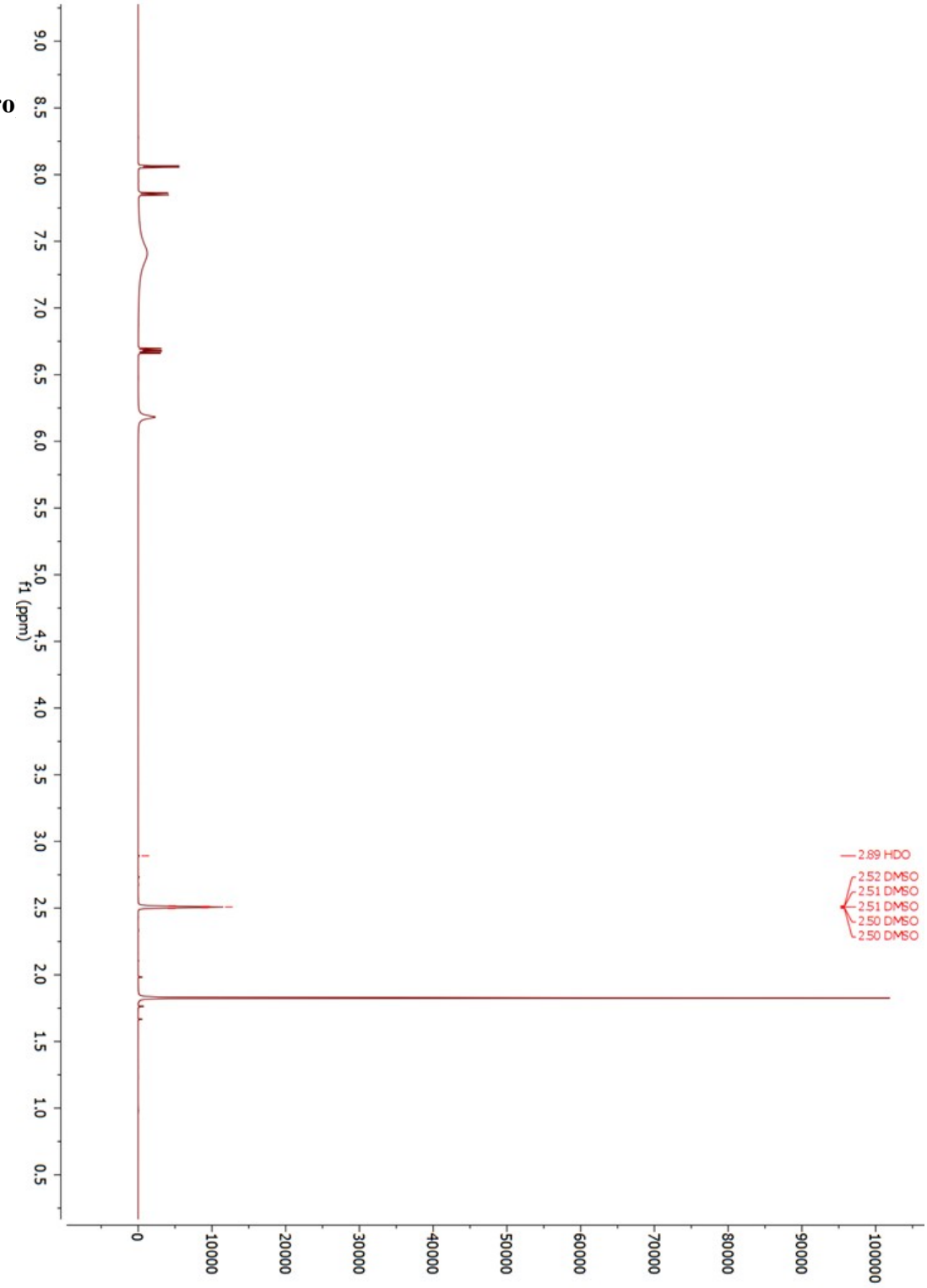
4-(2-(2-fluorophenyl



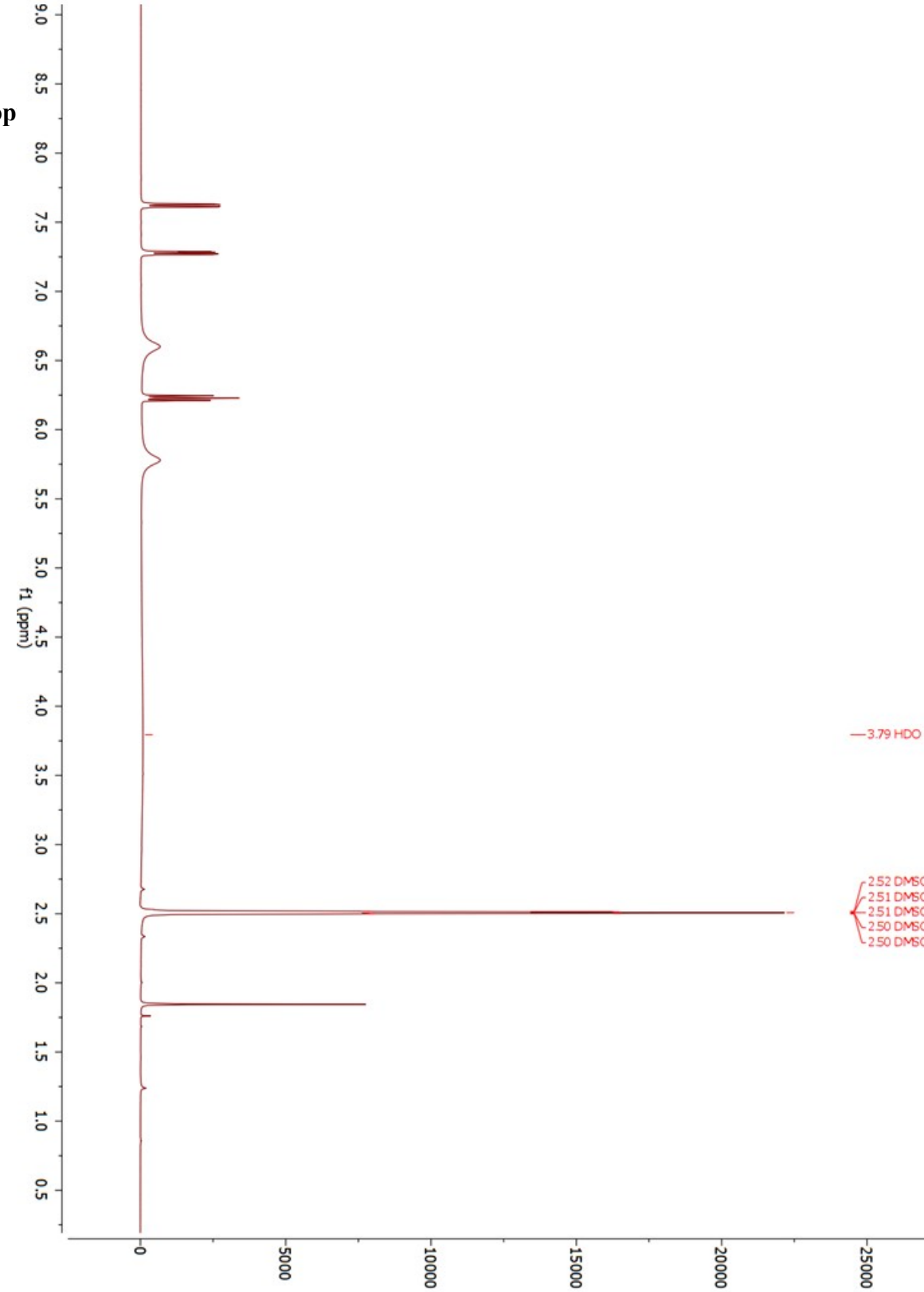
(Z)-4-(2-(2-fluorop



(E)-4-(2-(3-fluoro amine (59)



(E)-4-(2-(2-fluorop amine (60)



5-imino-4-(quinolin