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## 1. General Experimental Methods

General Methods: $^{1}H$ NMR and $^{13}C$ NMR spectra were recorded on an Agilent 400 NMR spectrometer. Deuterated chloroform and deuterated dimethyl sulfoxide were used as solvents, unless stated otherwise. The spectra were calibrated against the residual solvent peak or TMS. Chemical shifts (δ) and coupling constants (J) are given in ppm (parts per million) and Hz (Hertz). The following abbreviations were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, bs = broad singlet. Purity of final compounds was assessed using a Thermo Finnigan LCQ Deca with a Thermo Surveyor LCMS system at wavelengths of 214 and 254 nm and confirmed >95%. All commercially available compounds were used without purification.

## 2. Figures and Synthetic Schemes

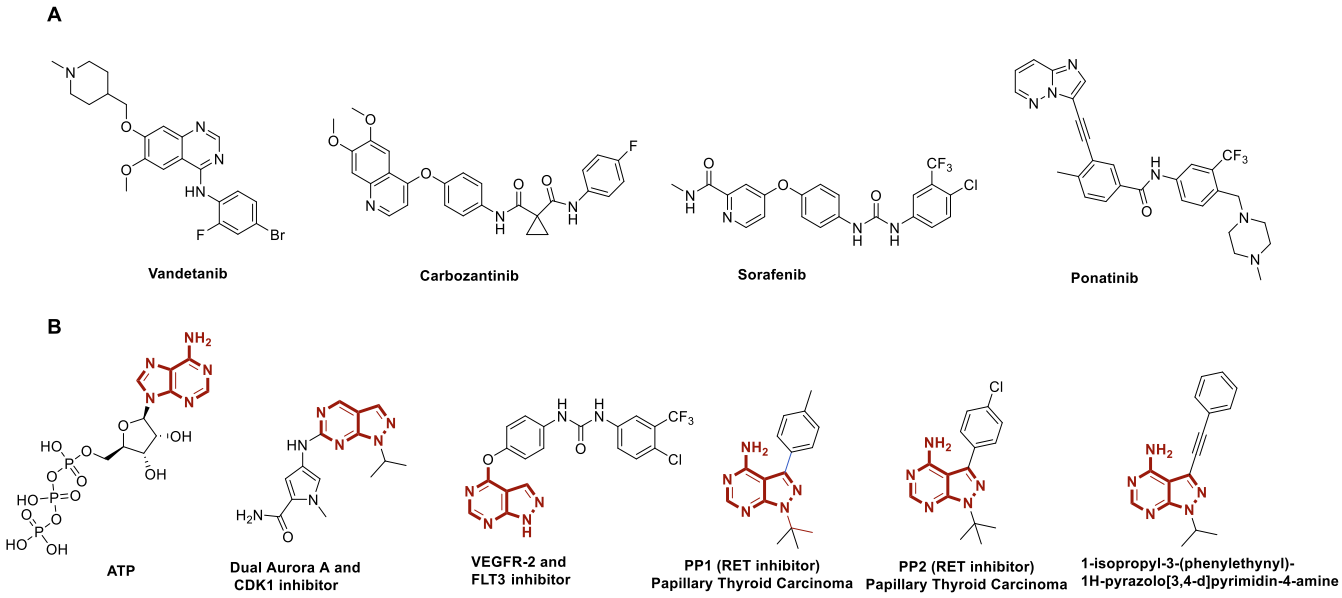



**Figure S1.** (A) Representative RET inhibitors. (B) Structures of ATP and different pyrazoloadenine-based protein kinase inhibitors

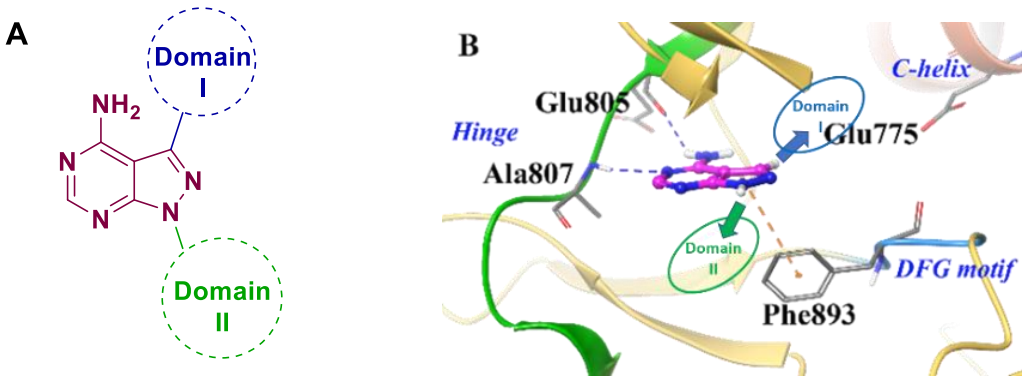



**Figure S2:** (A) Fragment 1 with Domains I and II highlighted. (B) Fragment 1 in the RET active site. Hydrogen bonds are illustrated in blue and π-π stacking interactions in brown.

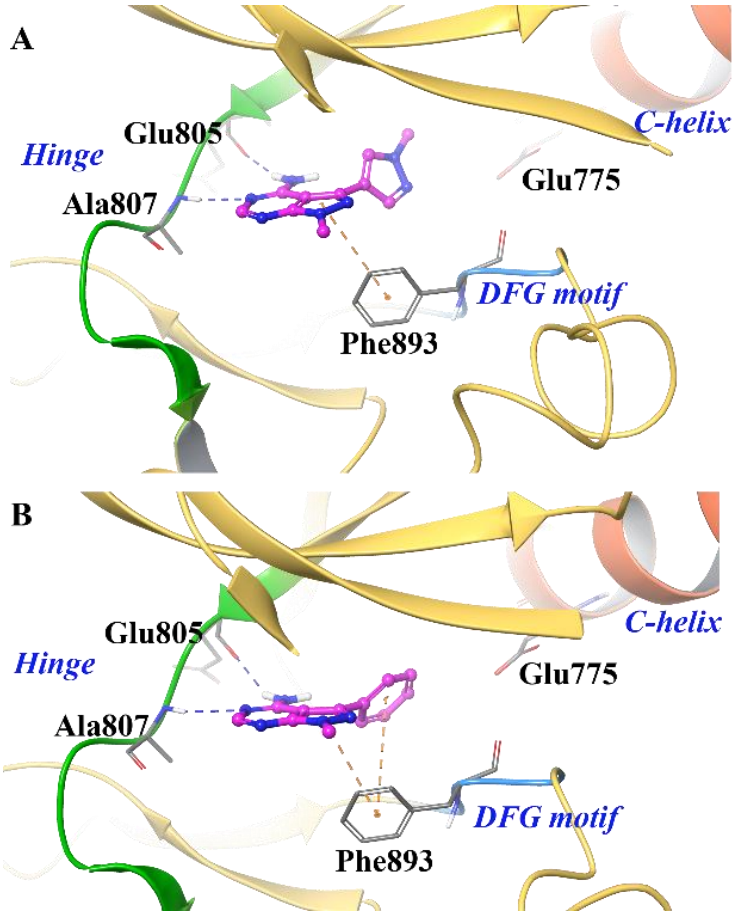
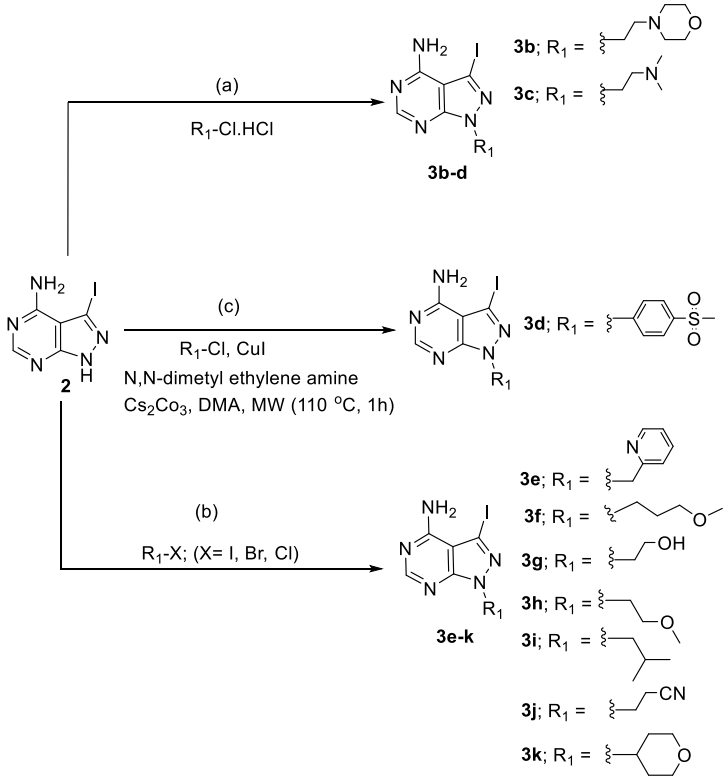


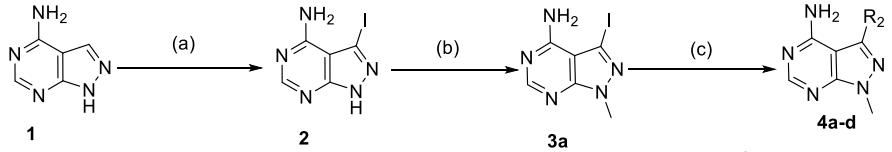

**Figure S3:** (A) Fragment **4d** modelled in the RET active site. The pyrazole does not interact with Phe893 of the DFG motif. (B) Fragment **4a** modelled in the RET active site. The phenyl ring effectively interacts with Phe893 of the DFG motif to gain access into the back pocket. Hydrogen bonds are illustrated in blue and π-π stacking interactions in brown.

## Scheme S1: Synthesis of fragments 3b-d and 3e-k[a]




[a]Reagents and condition: a) NaH (1.08 eq.), dry DMF, inert atm., rt to 80 °C, 24-48 h 48-50%; b) $K_2CO_3$ (1.5 eq.), DMF, rt to 80 °C, 12 h, 56-60%; c) CuI (10 mol%), *N*,*N*-dimetyl ethylene amine (20 mol%), $Cs_2CO_3$ (3.0 eq), DMA, MW (110 °C, 1h)

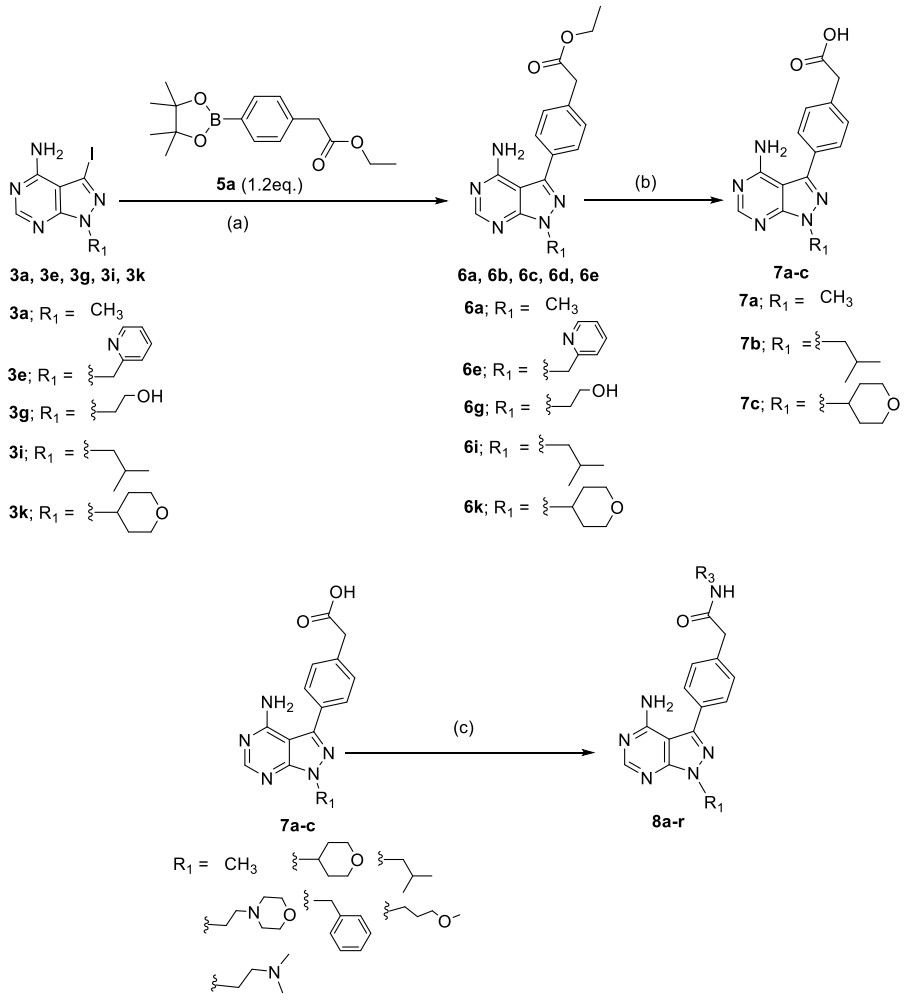
## Scheme S2: Synthesis of fragments 4a-d[a]




**4a**; $R_2$ = phenyl
**4b**; $R_2$ = *p*-fluoro phenyl
**4c**; $R_2$ = pyridin-4-yl
**4d**; $R_2$ = 1-methyl-1*H*-pyrazol-4-yl

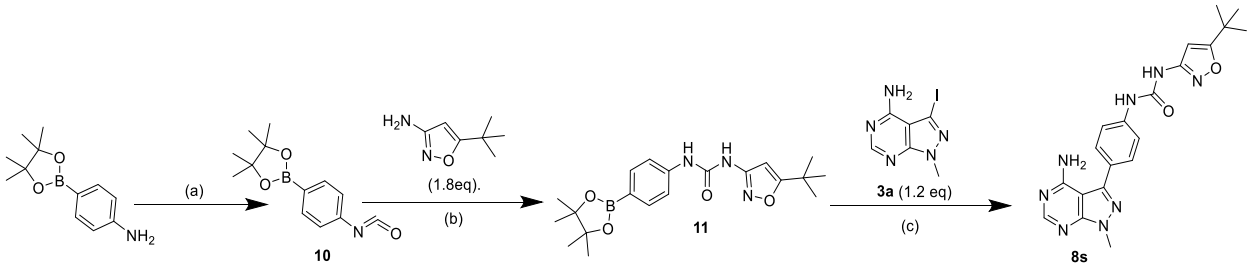
[a]Reagents and condition: a) *N*-iodosuccinimide (1.3 eq.), DMF, $N_2$ atm., 18 h, 92%; b) MeI (1.5 eq.), $K_2CO_3$ (1.5 eq.), DMF, rt to 80 °C, 12 h. 80%; c) $R_1$-$B(OH)_2$ (1.0 eq.), Pd(dppf)$Cl_2$.DCM complex (1.0 eq.), $K_3PO_4$ (2.0 eq.), Dioxne:$H_2O$(4:1), MW (100 °C, 1 h), 45-50%.

## Scheme S3: Synthesis of 6a-e, 7a-c and 8a-r[a]



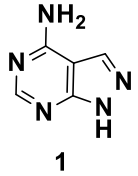

[a]Reagents and condition: a) $Pd_2(dba)_3$ (10 mol%), $PCy_3$ (20mol%), $K_2CO_3$(2eq.), DMF:EtOH (4:1), MW (100 °C, 1 h), 42-56%; b) LiOH (3 eq.), THF:$H_2O$ (1:1), MW (100 °C, 15 min.), 75-88%; c) $R_3$-$NH_2$ (1.5 eq.), HOAt (1 eq.), EDCl (2.5 eq.), DIPEA (1.2 eq.), dry DMF, rt, 24 h, 35-50%.

## Scheme S4: Synthesis of scaffold 8s[a]



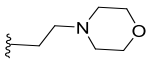
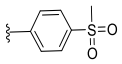
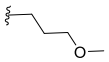
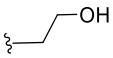
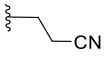
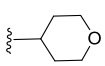

[a]Reagents and condition: a) Triphosgene (0.33 eq.), trimethylamine (0.90 eq.), THF, 0-60 °C, 6 h, 61%; b) DIPEA (2.0 eq.), THF, inert atm., rt, 5 h.60%; c) $Pd_2(dba)_3$(10 mol%), $PCy_3$ (20mol%), $K_2CO_3$ (2.0eq.), DMF:$H_2O$ (4:1), MW (100 °C, 1 h), 38%.

**Table S1. Inhibition values for various *N*-functionalized fragments[a]**



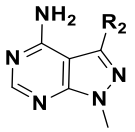
**1**

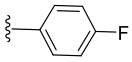
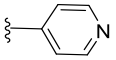
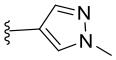
RET $IC_{50}$ = 9.20 $\mu$M
TRKA $IC_{50}$ = 57.07 $\mu$M
LC-2/ad $GI_{50}$ = 1.47 $\mu$M
KM-12 $GI_{50}$ = 1.73 $\mu$M
A549 $GI_{50}$ = 3.02 $\mu$M

| Compound | $R_1$ | RET $IC_{50}$ (µM) | TRKA $IC_{50}$ (µM) | LC-2/ad $EC_{50}$ (µM) | KM-12 $EC_{50}$ (µM) | A549 $EC_{50}$ (µM) |
|---|---|---|---|---|---|---|
| 2 | H | 3.2±0.98 | 16.8±1.48 | 9.68±0.41 | 6.81±0.38 | 9.86±1.98 |
| 3a | $CH_3$ | 3.3±0.80 | 74.7±4.14 | 1 | 1 | 1 |
| 3b |  | 0.73±0.50 | 84.3±0.46 | > 20 | > 20 | > 20 |
| 3c |  | 0.87±0.008 | 42.8±1.20 | > 20 | > 20 | > 20 |
| 3d |  | 1.6±0.6 | 55.8±10.98 | 5.16±1.35 | 7.42±0.30 | 8.56±2.49 |
| 3e |  | 14.7±1.7 | 66.8±3.30 | >20 | >20 | >20 |
| 3f |  | 1.9±2.81 | 88.5±44.23 | 0.36±0.09 | 8.62±1.33 | 32.01±9.05 |
| 3g |  | 1.5±0.61 | >100 | > 10 | > 10 | > 10 |
| 3h |  | 10.1±2.05 | 59.5±2.96 | > 10 | > 10 | > 10 |
| 3i |  | 1.9±2.23 | 25.6±2.64 | > 10 | > 10 | > 10 |
| 3j |  | 28.08±12.97 | -- | > 10 | > 10 | > 10 |
| 3k |  | 1.3±0.60 | 1.374±0.50 | > 10 | > 10 | > 10 |

[a] All data represent mean of at least n = 3 independent experiments.

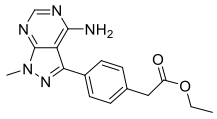
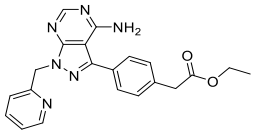
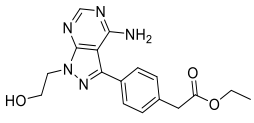
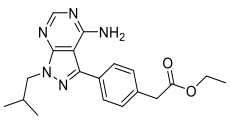
## Table S2. Inhibition values for various C-3 functionalized fragments[a]

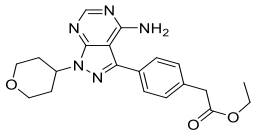
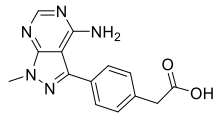
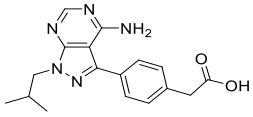
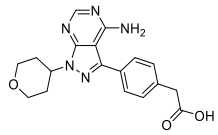


| Compound | $R_2$ | RET $IC_{50}$ (µM) | TRKA $IC_{50}$ (µM) | LC-2/ad $EC_{50}$ (µM) | KM-12 $EC_{50}$ (µM) | A549 $EC_{50}$ (µM) |
|---|---|---|---|---|---|---|
| 4a |  | 6.82±2.22 | 69.1±3.21 | > 20 | > 20 | > 20 |
| 4b |  | 14.62±0.2 | 109±5.42 | > 20 | > 20 | > 20 |
| 4c |  | 27.13±3.11 | > 100 | > 20 | > 20 | > 20 |
| 4d |  | 1.044±0.27 | > 100 | > 20 | > 20 | > 20 |

[a] All data represent mean of at least n = 3 independent experiments.

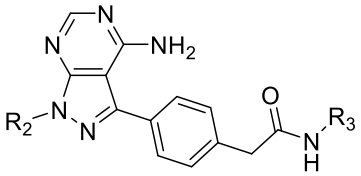
## Table S3. Inhibition values and SAR for various N-1 and C-3 functionalized derivatives[a]

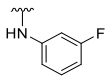
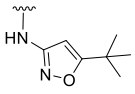
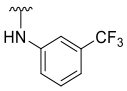
| Code | Compound | RET $IC_{50}$ (µM) | TRKA $IC_{50}$ (µM) | LC-2/ad $EC_{50}$ (µM) | KM-12 $EC_{50}$ (µM) | A549 $EC_{50}$ (µM) |
|---|---|---|---|---|---|---|
| 6a |  | 1.01±0.37 | 2.65 | > 20 | >20 | >20 |
| 6b |  | 14.16±3.2 | --- | > 20 | > 20 | > 20 |
| 6c |  | 10.16±4.2 | 6.43 | > 20 | > 20 | > 20 |
| 6d |  | 12.187±5.84 | 62.116 | > 20 | > 20 | > 20 |

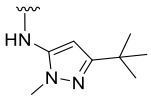
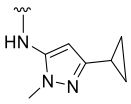
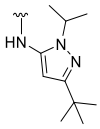
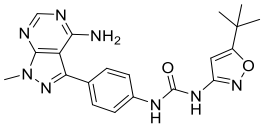
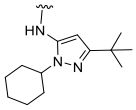
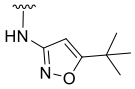
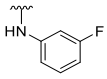
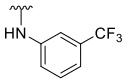
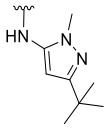
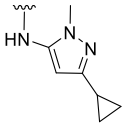
| | | | | | | |
|---|---|---|---|---|---|---|
| 6e |  | 0.27±0.18 | 1.34 | > 20 | > 20 | > 20 |
| 7a |  | 1.02±0.36 | 1.59±0.02 | >20 | >20 | >20 |
| 7b |  | 35.52±1.48 | 40.9±18.09 | > 20 | > 20 | > 20 |
| 7c |  | 10.27±3.5 | 11.1±5.32 | > 20 | > 20 | > 20 |

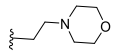
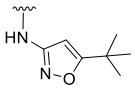
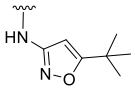
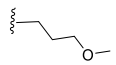
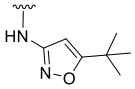
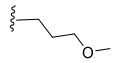
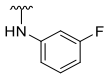
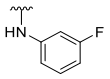
[a] All data represent mean of at least n = 3 independent experiments.

**Table S4. Inhibition values and SAR for various *N*-functionalized substituted phenylacetamides[a]**



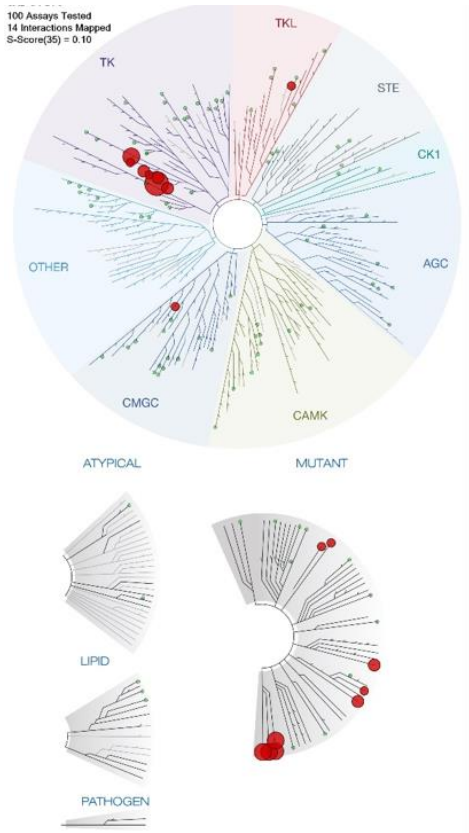
| Code | $R_1$ | $R_3$ | RET $IC_{50}$ (µM) | TRKA $IC_{50}$ (µM) | LC-2/ad $EC_{50}$ (µM) | KM-12 $EC_{50}$ (µM) | A549 $EC_{50}$ (µM) |
|---|---|---|---|---|---|---|---|
| 8a | $CH_3$ |  | 35.52±1.41 | 3.7±0.25 | 1.68±0.45 | 2.11±0.08 | 9.20±3.11 |
| 8b | $CH_3$ |  | 0.00057±0.0000005 | 0.20±0.74 | 0.024±0.02 | 0.71±0.07 | 20.35±0.51 |
| 8c | $CH_3$ |  | 0.0562±0.000004 | 4.03±0.93 | 0.37±0.04 | 2±0.03 | 56.3±5.91 |

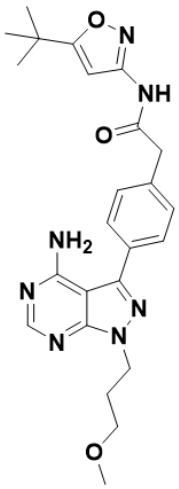
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 8d | $CH_3$ |  | 0.007954±0.02 | 106±22.59 | > 20 | > 20 | > 20 |
| 8e | $CH_3$ |  | 0.25±0.075 | 120±36.4 | > 20 | > 20 | > 20 |
| 8f | $CH_3$ |  | 26.42±0.4 | 47.8±18.05 | > 20 | > 20 | > 20 |
| 8g |  | | 0.449±0.005 | 0.13±0.025 | 0.76±0.35 | 3.42±0.27 | 9.87±3.64 |
| 8h | $CH_3$ |  | 0.109±0.40 | 0.295±0.16 | 1.56±0.36 | 10.46±0.21 | > 20 |
| 8i |  |  | 21.63±4.5 | 98.9±20.7 | > 20 | > 20 | > 20 |
| 8j |  |  | > 20 | > 20 | > 20 | > 20 | > 20 |
| 8k |  |  | 0.13±0.07 | 4.74±1.45 | 0.38±0.03 | 1.12±0.12 | > 20 |
| 8l |  |  | 0.069±0.004 | 3.95±0.8 | 3.0±0.04 | 2.57±0.64 | > 20 |
| 8m |  |  | 2.93±0.5 | 0.49±0.18 | > 20 | > 20 | > 20 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 8n |  |  | 0.08±0.02 | 0.12±0.06 | 7.83±0.80 | > 20 | > 20 |
| 8o |  |  | 16.70±8.95 | 46.60±3.45 | > 20 | > 20 | > 20 |
| 8p |  |  | 0.000326±0.00005 | 0.198±0.067 | 0.016 | 0.3±0.02 | 5.92±1.33 |
| 8q |  |  | 0.25±0.07 | 1.74±0.43 | 2.41±0.16 | 4.38±0.30 | > 20 |
| 8r |  |  | 3.48±0.42 | 2.48±0.83 | > 20 | > 20 | > 20 |

[a] All data represent mean of at least n = 3 independent experiments.

## 3. Kinase Selectivity




| Target Kinase | % Control at 20nM |
|---|---|
| RET | 1.2 |
| RET (M918T) | 1.8 |
| RET (V804L) | 3.0 |
| RET (V804M) | 4.9 |

**Figure S4** . Kinome profiling of **8p** at 20 nM.

## 4. Experimental Details of Final Compounds

**3-iodo-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (3a)** $K_2CO_3$ (3.96 g, 28.74 mmol) and iodomethane (4.07 g, 28.74 mmol) were added to a solution of **2** (5.0 g, 19.16 mmol) in DMF (100 mL). The reaction mixture was stirred at room temperature for 1 h and then heated to 80 °C for 12 h. The suspension was filtered through a pad of Celite® and washed with DMF (15 mL). The filtrate was concentrated and purified by column chromatography (16% petroleum ether in ethyl acetate) to provide **3a** in 80% yield as a white solid. **$^1$H NMR (400 MHz, DMSO)** δ 8.16 (s, 1H), 3.83 (s, 3H); **$^{13}$C NMR (101 MHz, DMSO)** δ 156.41, 150.04, 146.23, 100.71, 91.20, 34.14.Creamish white solid; Yield: 80%; (LCMS): Calculated for $[M+1]^+$ $C_6H_6IN_5$ 276.05, found 276.10.

**3-iodo-1-(2-morpholinoethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (3b)** A suspension of intermediate **2** (75mg, 0.35mmol), 4-(2-chloroethyl)morpholine hydrochloride (l eq) and sodium hydride (1.08 eq) in dry DMF (3mL) was stirred at 80°C for 24-48h under argon atmosphere. Upon completion, the reaction mixture was cooled to room temperature, the reaction mixture was evaporated and subjected to column chromatography (methanol/dichloromethane = 18-20%) to afford **3b** in 45% yield. White solid; Yield: 45%; **$^1$H NMR (400 MHz, DMSO)** δ 8.24 (s, 1H), 4.43 (t, *J* = 6.6 Hz, 2H), 3.53 – 3.50 (m, 4H), 2.77 (t, *J* = 6.6 Hz, 2H), 2.46 (s, 4H); **$^{13}$C NMR (101 MHz, CDCl$_3$)** δ 158.08, 156.35, 154.04, 103.44, 89.23, 66.49, 57.27, 53.38, 44.20; Calculated for $[M+1]^+$ $C_{11}H_{15}IN_6O$ 375.19, found 375.22 .

**1-(2-(dimethylamino)ethyl)-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (3c)** A suspension of intermediate **2** (75mg, 0.35mmol), 2-Chloro-*N*,*N*-dimethylethylamine hydrochloride (l eq) and sodium hydride (1.08 eq) in dry DMF (3mL) was stirred at 80°C for 24-48h under argon atmosphere. Upon completion, the reaction mixture was cooled to room temperature, the reaction

mixture was evaporated and subjected to column chromatography (methanol/dichloromethane = 18-20%) to afford **3c** in 32% yield. White solid; Yield: 32%; **$^{1}$H NMR (400 MHz, DMSO)** δ 8.24 (s, 1H), 4.43 (t, *J* = 6.6 Hz, 2H), 3.53 – 3.50 (m, 4H), 2.77 (t, *J* = 6.6 Hz, 2H), 2.46 (s, 4H); **$^{13}$C NMR (101 MHz, DMSO**) δ 157.35, 156.18, 155.69, 104.01, 86.31, 70.35, 58.84, 47.10. Calculated for $[M+1]^+$ $C_9H_{13}IN_6$ 333.15, found 333.60.

**3-iodo-1-(pyridin-2-ylmethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (3e)** A suspension of intermediate **2** (75mg, 0.35mmol), 2-(chloromethyl)pyridine (l eq) and potassium carbonate (2eq) in DMF (3mL) was stirred at 80°C for 12h. Upon completion, the reaction mixture was cooled to room temperature, the mixture was treated with water and extracted with dichloromethane. The combined organic phase was collected and then concentrated in vacuum, column chromatography (ethyl acetate / petroleum ether = 60-70%) to afford **3e** in 45% yield. Light brown solid; Yield: 45%; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 8.57-8.53 (m, 1H), 8.35 (s, 1H), 7.60 (t, *J* = 7.7 Hz, 1H), 7.19 – 7.15 (m, 1H), 7.05 (d, *J* = 7.9 Hz, 1H), 5.92 (brs, 2H), 5.69 (s, 2H); **$^{13}$C NMR (101 MHz, DMSO**) δ 158.14, 156.70, 156.32, 154.34, 149.64, 137.54, 123.29, 122.07, 103.55, 90.19, 51.98. Calculated for $[M+1]^+$ $C_{11}H_9IN_6$ 353.14, found 353.52.

**3-iodo-1-(3-methoxypropyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (3f)** A suspension of intermediate **2** (75mg, 0.35mmol), 1-bromo-3-methoxypropane (l eq) and potassium carbonate (2eq) in DMF (3mL) was stirred at 80°C for 12h. Upon completion, the reaction mixture was cooled to room temperature, the mixture was treated with water and extracted with dichloromethane. The combined organic phase was collected and then concentrated in vacuo, column chromatography (ethyl acetate / petroleum ether = 60-70%) to afford **3f** in 67% yield. Creamish white solid; Yield: 67%; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 8.34 (s, 1H), 5.94 (brs, 2H), 4.48 (t, *J* = 6.9 Hz, 2H), 3.38 (t, *J* = 6.0 Hz, 2H), 3.31 (s, 3H), 2.15 (quin, *J* = 8.0 Hz, 2H); **$^{13}$C**

**NMR (101 MHz, $CDCl_3$)** δ 157.27, 156.06, 153.84, 103.95, 85.74, 69.35, 58.65, 44.84, 29.73. Calculated for $[M+1]^+$ $C_9H_{12}IN_5O$ 334.13, found 334.52.

**2-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethan-1-ol (3g)** A suspension of intermediate **2** (75mg, 0.35mmol), 2-bromoethan-1-ol (l eq) and potassium carbonate (2eq) in DMF (3mL) was stirred at 80°C for 12h. Upon completion, the reaction mixture was cooled to room temperature, the mixture was treated with water and extracted with dichloromethane. The combined organic phase was collected and then concentrated in vacuum, column chromatography (ethyl acetate / petroleum ether = 60-70%) to afford 3-substituted-1*H*-pyrazolo [3,4-*d*]pyrimidin-4-amines in 56-60% yield. Light yellow solid; Yield: 42%; **$^1$H NMR (400 MHz, DMSO)** δ 8.15 (s, 1H), 4.83 (t, *J* = 5.7 Hz, 1H), 4.27 (t, *J* = 5.8 Hz, 2H), 3.74 (q, *J* = 5.7 Hz, 2H); **$^{13}$C NMR (101 MHz, DMSO)** δ 162.03, 157.59, 155.74, 154.73, 109.44, 91.05, 59.66, 49.86. Calculated for $[M+1]^+$ $C_7H_8IN_5O$ 306.08, found 306.15.

**3-iodo-1-(2-methoxyethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (3h)** A suspension of intermediate **2** (75mg, 0.35mmol), 1-bromo-2-methoxyethane (l eq) and potassium carbonate (2eq) in DMF (3mL) was stirred at 80°C for 12h. Upon completion, the reaction mixture was cooled to room temperature, the mixture was treated with water and extracted with dichloromethane. The combined organic phase was collected and then concentrated in vacuum, column chromatography (ethyl acetate / petroleum ether = 60-70%) to afford 3-substituted-1*H*-pyrazolo [3,4-*d*]pyrimidin-4-amines in 56-60% yield. Creamish white solid; Yield: 62%; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.32 (s, 1H), 6.01 (brs, 2H), 4.54 (t, *J* = 5.2 Hz, 2H), 3.82 (t, *J* = 5.2 Hz, 2H), 3.31 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 157.35, 156.18, 155.69, 104.01, 86.31, 70.35, 58.84, 47.10. Calculated for $[M+1]^+$ $C_8H_{10}IN_5O$ 320.10, found 320.22.

**3-iodo-1-isobutyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (3i)** A suspension of intermediate **2** (75mg, 0.35mmol), 1-bromo-2-methylpropane (l eq) and potassium carbonate (2eq) in DMF (3mL) was stirred at 80°C for 12h. Upon completion, the reaction mixture was cooled to room temperature, the mixture was treated with water and extracted with dichloromethane. The combined organic phase was collected and then concentrated in vacuum, column chromatography (ethyl acetate / petroleum ether = 60-70%) to **3i** in 52% yield. White solid; Yield: 52%; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 8.32 (s, 1H), 6.05 (brs, 2H), 4.18 (d, *J* = 7.4 Hz, 2H), 2.34 (dp, *J* = 14.0, 6.9 Hz, 1H), 0.92 (d, *J* = 6.7 Hz, 6H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 161.50, 160.02, 158.29, 158.14, 89.74, 58.89, 33.25, 23.96. Calculated for $[M+1]^+$ $C_9H_{12}IN_5$ 317.13, found 317.25 .

**3-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)propanenitrile (3j)** A suspension of intermediate **2** (75mg, 0.35mmol), 3-bromopropanenitrile (l eq) and potassium carbonate (2eq) in DMF (3mL) was stirred at 80°C for 12h. Upon completion, the reaction mixture was cooled to room temperature, the mixture was treated with water and extracted with dichloromethane. The combined organic phase was collected and then concentrated in vacuum, column chromatography (ethyl acetate / petroleum ether = 60-70%) to afford **3j** in 35% yield. Light yellow solid; Yield: 35%; **$^{1}$H NMR (400 MHz, DMSO)** δ 8.20 (s, 1H), 4.52 – 4.48 (m, 3H), 3.09 – 3.08 (m, 2H); **$^{13}$C NMR (101 MHz, DMSO)** δ 158.16, 156.68, 156.65, 154.15, 118.74, 103.57, 90.53, 42.63, 18.12. Calculated for $[M+1]^+$ $C_8H_7IN_6$ 315.09, found 315.21.

**3-iodo-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (3k)** A suspension of intermediate **2** (75mg, 0.35mmol), 4-bromotetrahydro-2*H*-pyran (l eq) and potassium carbonate (2eq) in DMF (3mL) was stirred at 80°C for 12h. Upon completion, the reaction mixture was cooled to room temperature, the mixture was treated with water and extracted with dichloromethane. The combined organic phase was collected and then concentrated in

vacuum, column chromatography (ethyl acetate / petroleum ether = 60-70%) to afford **3k** in 40% yield. White solid; Yield: 40%; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 8.30 (s, 1H), 6.03 (brs, 2H), 4.89 (tt, *J* = 11.7, 4.2 Hz, 1H), 4.11 (dd, *J* = 11.4, 4.4 Hz, 2H), 3.57 (t, *J* = 12.0, 2H), 2.36 (dt, *J* = 12.2, 7.8 Hz, 2H), 1.90 (d, *J* = 12.6, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 157.29, 155.74, 153.21, 104.09, 85.84, 66.98, 54.02, 32.20. Calculated for $[M+1]^+$ $C_{10}H_{12}IN_5O$ 346.14, found 346.18.

**1-methyl-3-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (4a)** To a solution of 3-Iodo-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine **(3a)** (0.400 g, 1.53 mmol) in 1,4-dioxane (4.5 mL) and water (1.2 mL) was added phenyl boronic acid (0.260 g, 2.13 mmol), potassium phosphate (1.50 g, 4.60 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.089 g, 0.077 mmol). The mixture was degassed and was subjected to heating at 100 °C for 12h. Upon completion of reaction, the mixture was diluted with water and extracted with ethyl acetate. The organic extracts were combined and concentrated under reduced pressure. The residue was purified by column chromatography (ethyl acetate / petroleum ether = 60-70%) on silica to afford **4a**. Light brown solid; Yield: 45%; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 8.39 (s, 1H), 7.68 (d, *J* = 7.2 Hz, 2H), 7.55-7.50 (t, *J* = 7.5 Hz, 2H), 7.49-7.45 (m, 1H), 5.54 (brs, 2H), 4.07 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 157.7, 155.9, 154.5, 144.1, 133.1, 129.3, 129.0, 128.3, 98.3, 33.8; LCMS (ESI): Calculated for $[M+1]^+$ $C_{12}H_{11}N_5$ 226.25, found 226.35.

**1-methyl-3-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (4b)** 3-Iodo-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine **(3a)** (0.400 g, 1.53 mmol) in 1,4-dioxane (4.5 mL) and water (1.2 mL) was added 4-floro phenyl boronic acid (0.296 g, 2.13 mmol), potassium phosphate (1.50 g, 4.60 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.089 g, 0.077 mmol). The mixture was degassed and was subjected to heating at 100 °C for 12h. Upon completion of reaction, the mixture was diluted with water and extracted with ethyl acetate. The

organic extracts were combined and concentrated under reduced pressure. The residue was purified by column chromatography (ethyl acetate / petroleum ether = 60-70%) on silica to obtain **4b**. Light brown solid; Yield: 45%; **$^{1}$H NMR (400 MHz, DMSO)** δ 8.30 (s, 1H), 7.76-7.70 (m, 2H), 7.44-7.38 (m, 2H), 3.99 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 162.7 (d, *J* = 244 Hz), 161.5, 158.5, 156.2, 154.7, 142.9, 130.78 (d, *J* = 8 Hz), 129.75 (d, *J* = 3.0 Hz), 129.7, 116.4 (d, *J* = 22 Hz), 97.6, 33.9; LCMS (ESI): Calculated for $[M+1]^+$ $C_{12}H_{11}N_5$ 226.25, found 226.32.

**1-methyl-3-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (4d)** 3-Iodo-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine **(3a)** (0.400 g, 1.53 mmol) in 1,4-dioxane (4.5 mL) and water (1.2 mL) was (1-methyl-1*H*-pyrazol-4-yl)boronic acid (0.266 g, 2.13 mmol), potassium phosphate (1.50 g, 4.60 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.089 g, 0.077 mmol). The mixture was degassed and was subjected to heating at 100 °C for 12h. Upon completion of reaction, the mixture was diluted with water and extracted with ethyl acetate. The organic extracts were combined and concentrated under reduced pressure. The residue was purified by column chromatography (ethyl acetate / petroleum ether = 60-70%) on silica to obtain **4d**. Light brown solid; Yield: 22%; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 8.37 (s, 1H), 7.79 (s, 1H), 7.73 (s, 1H), 5.50 (s, 2H), 4.03 (s, 3H), 4.00 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 155.85, 152.13, 142.83, 138.28, 129.35, 123.85, 118.11, 111.19, 109.99, 33.81, 29.68; Calculated for [M+1]+ $C_{10}H_{11}N_7$ 230.25, found 230.57.

**Ethyl 2-(4-(4-amino-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)phenyl)acetate (6a)** Intermediate **3a** (30 mg, 0.11 mmol), $K_2CO_3$ (2eq.), $Pd_2(dba)_3$ (10 mg, 0.01 mmol), tricyclohexylphospine (3.1 mg, 0.02 mol), and ethyl 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate (43.4mg, 0.18 mmol) were stirred in DMF:EtOH (4:1), purged with nitrogen and microwave irradiated at 110 °C for 1 h. After completion, the reaction mixture was

subsequently evaporated, and the residue was purified by chromatography (methanol/dichloromrthane = 10-15%) to afford **6a** in 72% yield. Light brown solid; Yield: 72%; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 8.38 (s, 1H), 7.64 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 8.0 Hz, 2H), 5.58 (brs, 2H), 4.17 (q, *J* = 7.1 Hz, 2H), 4.06 (s, 3H), 4.01 (s, 2H), 1.27 (t, *J* = 8.0 Hz, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 171.21, 157.73, 156.14, 155.91, 143.77, 135.16, 131.96, 130.28, 128.49, 98.34, 61.05, 41.12, 33.88, 14.16; LCMS (ESI): Calculated for $[M+1]^+$ $C_{16}H_{17}N_5O_2$ 312.34, found 312.56.

**Ethyl 2-(4-(4-amino-1-(pyridin-2-ylmethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)phenyl)acetate (6b).** Intermediate **3e** (38.7 mg, 0.11 mmol), $K_2CO_3$ (2eq.), $Pd_2(dba)_3$ (10 mg, 0.01 mmol), tricyclohexylphospine (3.1 mg, 0.02 mol), and ethyl 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate (43.4mg, 0.18 mmol) were stirred in DMF:EtOH (4:1), purged with nitrogen and microwave irradiated at 110 °C for 1 h. After completion, the reaction mixture was subsequently evaporated, and the residue was purified by chromatography (methanol/dichloromrthane = 10-15%) to afford **6b** in 75% yield. Light brown solid; Yield: 75%; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 8.56 (t, *J* = 5.0 Hz, 1H), 8.38 (d, *J* = 22.5 Hz, 2H), 7.66 (d, *J* = 6.7 Hz, 1H), 7.61-7.58 (m, 1H), 7.43 (d, *J* = 7.0 Hz, 2H), 7.18-7.14 (m, 1H), 7.06-7.03 (m, 1H), 5.77 (s, 1H), 5.69 (s, 1H), 5.54 (brs, 2H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.67 (s, 2H), 1.25-1.22 (m, 3H); **$^{13}$C NMR (101 MHz, DMSO)** δ 172.56, 157.96, 156.71, 156.29, 155.67, 155.64, 149.64, 143.36, 138.35, 137.52, 134.76, 134.08, 130.48, 123.26, 122.06, 102.89, 59.11, 59.10, 38.32, 16.44. Calculated for $[M+1]^+$ $C_{21}H_{20}N_6O_2$ 389.43, found 389.57.

**Ethyl 2-(4-(4-amino-1-isobutyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)phenyl)acetate (6d).** Intermediate **3i** (38.4 mg, 0.11 mmol), $K_2CO_3$ (2eq.), $Pd_2(dba)_3$ (10 mg, 0.01 mmol),

tricyclohexylphospine (3.1 mg, 0.02 mol), and ethyl 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate (43.4mg, 0.18 mmol) were stirred in DMF:EtOH (4:1), purged with nitrogen and microwave irradiated at 110 °C for 1 h. After completion, the reaction mixture was subsequently evaporated, and the residue was purified by chromatography (methanol/dichloromrthane = 10-15%) to afford **6d** in 51% yield. Creamish white solid; Yield: 51%; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 8.36 (s, 1H), 7.65 (d, *J* = 8.2 Hz, 2H), 7.44 (d, *J* = 8.0 Hz, 2H), 5.49 (brs, 2H), 4.23 (d, *J* = 7.4 Hz, 2H), 4.16 (q, *J* = 8.2 Hz, 2H), 3.67 (s, 2H), 2.43 – 2.36 (m, 1H), 1.26 (t, *J* = 8.0 Hz, 3H), 0.94 (d, *J* = 6.7 Hz, 6H); **$^{13}$C NMR (101 MHz, $cdcl_3$)** δ 171.19, 157.70, 155.80, 143.59, 140.35, 135.07, 132.13, 130.23, 128.57, 96.90, 61.03, 54.32, 41.13, 29.12, 19.98, 14.16; Calculated for $[M+1]^+$ $C_{19}H_{23}N_5O_2$ 354.43, found 354.50.

**Ethyl 2-(4-(4-amino-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)phenyl)acetate (6e)** Intermediate **3k** (37.9 mg, 0.11 mmol), $K_2CO_3$ (2eq.), $Pd_2(dba)_3$ (10 mg, 0.01 mmol), tricyclohexylphospine (3.1 mg, 0.02 mol), and ethyl 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate (43.4mg, 0.18 mmol) were stirred in DMF:EtOH (4:1), purged with nitrogen and microwave irradiated at 110 °C for 1 h. After completion, the reaction mixture was subsequently evaporated, and the residue was purified by chromatography (methanol/dichloromrthane = 10-15%) to afford **6e** in 52% yield. Creamish white solid; Yield: 52%; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 8.34 (s, 1H), 7.64 (d, *J* = 6.8 Hz, 2H), 7.43 (d, *J* = 7.7 Hz, 2H), 5.67 (brs, 2H), 4.20-4.07 (m, 4H), 3.67 (s, 1H), 3.60 (t, *J* = 11.9 Hz, 2H), 1.97 – 1.88 (m, 4H), 1.21 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 171.26, 157.81, 155.48, 153.78, 143.71, 135.10, 132.12, 130.26, 128.59, 98.54, 67.09, 61.07, 53.25, 41.11, 32.16, 14.17; Calculated for $[M+1]^+$ $C_{20}H_{23}N_5O_3$ 382.44, found 382.70.

**2-(4-(4-amino-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)phenyl)acetic acid (7a):** Intermediates **6a** (365.3 mg, 1.014 mmol) were dissolved in 1:1 THF/Water (8 mL). LiOH monohydrate (128 mg, 3.04 mmol) was then added to the reaction and was heated under microwave irradiation for 15 minutes at 100 °C. Upon completion, the reaction was subsequently acidified to a pH ~3-4 and the obtained solid was vacuum filtered to yield the acids **7a** in 82% yield**.** Light brown solid; Yield: 82%; **$^{1}$H NMR (400 MHz, DMSO)** δ 8.49 (s, 1H), 8.21 (s, 1H), 7.47 (d, *J* = 8.2 Hz, 2H), 7.35 (d, *J* = 8.1 Hz, 2H), 3.91 (s, 3H), 3.25 (s, 2H); **$^{13}$C NMR (101 MHz, DMSO)** δ 171.90, 160.49, 156.11, 152.59, 142.64, 140.13, 133.76, 130.43, 127.79, 46.33, 33.85.; Calculated for $[M+1]^+$ $C_{14}H_{13}N_5O_2$ 284.29, found 284.30.

**2-(4-(4-amino-1-isobutyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)phenyl)acetic acid (7c):** Intermediates **6d** (35.7 mg, 1.014 mmol) were dissolved in 1:1 THF/Water (8 mL). LiOH monohydrate (128 mg, 3.04 mmol) was then added to the reaction and was heated under microwave irradiation for 15 minutes at 100 °C. Upon completion, the reaction was subsequently acidified to a pH ~3-4 and the obtained solid was vacuum filtered to yield the acids **7a** in 77% yield**.** Light brown solid; Yield: 77%; **$^{1}$H NMR (400 MHz, DMSO)** δ 8.43 (s, 1H), 8.20 (s, 1H), 7.52 (d, *J* = 8.0 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 4.11 (d, *J* = 7.2 Hz, 2H), 3.13 (s, 2H), 2.25 – 2.20 (m, 1H), 0.84 (d, *J* = 6.7 Hz, 6H); **$^{13}$C NMR (101 MHz, DMSO)** δ 158.55, 156.07, 154.87, 148.08, 143.89, 130.80, 130.52, 130.46, 128.13, 97.50, 49.01, 31.12, 29.11, 20.29; Calculated for $[M+1]^+$ $C_{17}H_{19}N_5O_2$ 326.37, found 326.55.

**2-(4-(4-amino-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)phenyl)-*N*-(3-fluorophenyl)acetamide (8a):** Anhydrous DMF (1 mL) was added to the intermediate **4a,** followed by EDCl (52.5 mg, 0.338 mmol), HOAt (18.41 mg, 0.135 mmol), and DIPEA (0.028 mL, 0.162 mmol). 3-floroaniline (29.4 mg, 0.203 mmol) were added and the reaction was sealed

under $N_2$ and was reacted for 12 hours or until complete product conversion. The reaction was quenched with water, extracted with DCM, and washed with saturated $NaHCO_3$. The organic layer was collected, dried with $MgSO_4$, adsorbed onto silica, and purified by flash chromatography using DCM/MeOH (10-15%) to generate **8a** in 56% yield. Light brown solid; Yield: 56%; **$^1$H NMR (400 MHz, DMSO)** δ 10.41 (s, 1H), 8.22 (s, 1H), 7.63-7.57 (m, 4H), 7.49-7.45 (m, 2H), 7.31-7.28 (m, 2H), 6.88 – 6.81 (m, 2H), 3.91 (s, 3H), 3.71 (s, 2H); **$^{13}$C NMR (101 MHz, DMSO)** δ 169.66, 161.32 (d, *J* = 4 Hz), 158.34 (d, *J* = 36 Hz), 156.16, 154.69, 143.65, 141.32 (d, *J* = 11 Hz), 136.49, 131.74, 130.82 (d, *J* = 10 Hz), 130.36, 128.55, 115.27, 110.14 (d, *J* = 21 Hz), 110.04, 106.35 (d, *J* = 26 Hz), 97.66, 43.47, 33.91. Calculated for $[M+1]^+$ $C_{20}H_{17}FN_6O$ 377.40, found 377.45.

**2-(4-(4-amino-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)phenyl)-*N*-(5-(*tert* butyl)isoxazol-3-yl)acetamide (8b):** Anhydrous DMF (1 mL) was added to the intermediate **4a**, followed by EDCl (52.5 mg, 0.338 mmol), HOAt (18.41 mg, 0.135 mmol), and DIPEA (0.028 mL, 0.162 mmol). 5-(*tert*-butyl)isoxazol-3-amine (28.4 mg, 0.203 mmol) were added and the reaction was sealed under $N_2$ and was reacted for 12 hours or until complete product conversion. The reaction was quenched with water, extracted with DCM, and washed with saturated $NaHCO_3$. The organic layer was collected, dried with $MgSO_4$, adsorbed onto silica, and purified by flash chromatography using DCM/MeOH (10-15 %) to generate 2-(4-(4-amino-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)phenyl)-*N*-methylacetamides **8b** in 35% yield. Light brown solid; Yield: 35%; **$^1$H NMR (400 MHz, DMSO)** δ 8.22 (s, 1H), 7.59 (d, *J* = 8.2 Hz, 2H), 7.45 (d, *J* = 8.2 Hz, 2H), 6.56 (s, 1H), 3.91 (s, 2H), 3.72 (s, 1H), 1.23 (s, 9H); **$^{13}$C NMR (101 MHz, DMSO)** δ 180.91, 169.61, 158.34, 155.96, 154.60, 143.70, 136.13, 131.76, 130.35, 128.57, 97.63, 93.55, 45.37, 33.93, 32.92; Calculated for $[M+1]^+$ $C_{21}H_{23}N_7O_2$ 406.46, found 406.50.

**2-(4-(4-amino-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)phenyl)-*N*-(3-(trifluoromethyl)phenyl)acetamide (8c):** Anhydrous DMF (1 mL) was added to the intermediate **4a**, followed by EDCl (52.5 mg, 0.338 mmol), HOAt (18.41 mg, 0.135 mmol), and DIPEA (0.028 mL, 0.162 mmol). 3-trifloroaniline (22.5 mg, 0.203 mmol) were added and the reaction was sealed under $N_2$ and was reacted for 12 hours or until complete product conversion. The reaction was quenched with water, extracted with DCM, and washed with saturated $NaHCO_3$. The organic layer was collected, dried with $MgSO_4$, adsorbed onto silica, and purified by flash chromatography using DCM/MeOH (10-15 %) to generate **8c** in 54% yield. Light brown solid; Yield: 54%; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.83 (s, 1H), 8.38 (s, 1H), 7.84 (d, *J* = 8.4 Hz, 2H), 7.69 (d, *J* = 6.5 Hz, 2H), 7.54 (d, *J* = 6.6 Hz, 2H), 7.41 – 7.36 (m, 1H), 7.31 (d, *J* = 6.3 Hz, 1H), 4.07 (s, 3H), 3.84 (s, 2H); **$^{13}$C NMR (101 MHz, DMSO)** δ 169.90, 158.12, 155.60, 154.50, 143.84, 140.35, 136.46, 131.64, 127.13 (q, *J* = 253 Hz), 130.45, 130.40, 129.85 (q, *J* = 31 Hz), 128.56, 123.06, 120.03 (q, *J* = 4 Hz), 115.54 (q, *J* = 4 Hz), 103.85, 97.61, 46.30, 26.38. Calculated for $[M+1]^+$ $C_{21}H_{17}F_3N_6O$ 427.40, found 427.22.

**2-(4-(4-amino-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)phenyl)-*N*-(3-(*tert*-butyl)-1-methyl-1*H*-pyrazol-5-yl)acetamide (8d):** Anhydrous DMF (1 mL) was added to the intermediate **4a**, followed by EDCl (52.5 mg, 0.338 mmol), HOAt (18.41 mg, 0.135 mmol), and DIPEA (0.028 mL, 0.162 mmol). 3-(*tert*-butyl)-1-methyl-1*H*-pyrazol-5-amine (31.0 mg, 0.203 mmol) were added and the reaction was sealed under $N_2$ and was reacted for 12 hours or until complete product conversion. The reaction was quenched with water, extracted with DCM, and washed with saturated $NaHCO_3$. The organic layer was collected, dried with $MgSO_4$, adsorbed onto silica, and purified by flash chromatography using DCM/MeOH (10-15 %) to generate **8d** in 48% yield. Creamish white solid; Yield: 48%; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.37 (s, 1H), 7.72 (d, *J* = 7.9

Hz, 2H), 7.49 (d, *J* = 7.8 Hz, 2H), 7.13 (brs, 1H), 6.05 (s, 1H), 5.61 (brs, 2H), 4.07 (s, 3H), 3.80 (s, 2H), 3.58 (s, 3H), 1.23 (s, 9H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 168.63, 167.72, 157.69, 155.92, 150.65, 134.95, 132.78, 130.34, 129.12, 99.80, 98.34, 96.63, 43.36, 35.27, 33.93, 30.36, 29.23; Calculated for $[M+1]^+$ $C_{22}H_{26}N_8O$ 419.51, found 419.60.

**2-(4-(4-amino-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)phenyl)-*N*-(3-cyclopropyl-1-methyl-1*H*-pyrazol-5-yl)acetamide (8e):** Anhydrous DMF (1 mL) was added to the intermediate **4a**, followed by EDCl (52.5 mg, 0.338 mmol), HOAt (18.41 mg, 0.135 mmol), and DIPEA (0.028 mL, 0.162 mmol). 3-cyclopropyl-1-methyl-1*H*-pyrazol-5-amine (27.8 mg, 0.203 mmol) were added and the reaction was sealed under $N_2$ and was reacted for 12 hours or until complete product conversion. The reaction was quenched with water, extracted with DCM, and washed with saturated $NaHCO_3$. The organic layer was collected, dried with $MgSO_4$, adsorbed onto silica, and purified by flash chromatography using DCM/MeOH (10-15 %) to generate 2-(4-(4-amino-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)phenyl)-*N*-methylacetamides **(8a-r)** in 35-50% yield. Creamish white solid; Yield: 42%; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 8.39 (s, 1H), 7.73 (d, *J* = 8.0 Hz, 2H), 7.50 (d, *J* = 7.9 Hz, 2H), 7.40 (d, *J* = 8.0 Hz, 2H), 5.85 (d, *J* = 5.2 Hz, 1H), 4.08 (s, 3H), 4.05 (s, 3H), 1.82 (d, *J* = 6.2 Hz, 1H), 0.83 (s, 2H), 0.65 (s, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 158.10, 157.66, 155.92, 154.14, 145.67, 139.99, 135.35, 132.81, 130.34, 129.51, 129.17, 96.50, 96.20, 43.73, 34.48, 29.66, 9.33, 7.61; Calculated for $[M+1]^+$ $C_{21}H_{22}N_8O$ 403.46, found 403.52.

**1-(4-(4-amino-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)phenyl)-3-(5-(*tert*-butyl)isoxazol-3-yl)urea (8g):** Intermediate **8** (42mg, 1.2eq.) was treated with **3a** (30mg, 1.0eq.) $K_2CO_3$ (2eq.), $Pd_2(dba)_3$ (10 mg, 0.01 mmol), tricyclohexylphospine (3.1 mg, 0.02 mol), and ethyl 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate (43.4 mg, 0.18 mmol) were stirred in DMF:EtOH (4:1), purged with nitrogen and microwave irradiated at 100 °C for 1 h. After

completion, the reaction mixture was subsequently evaporated, and the residue was purified by chromatography (methanol/dichloromethane = 8-12%) to afford **8g** in 38% yield. Light brown solid; Yield: 38%; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 8.37 (d, *J* = 8.6 Hz, 1H), 7.61 (q, *J* = 8.8 Hz, 2H), 7.45 (d, *J* = 8.5 Hz, 1H), 6.80 (d, *J* = 8.5 Hz, 1H), 5.53 (brs, 2H), 4.06 (d, *J* = 12.5 Hz, 3H), 1.13 (s, 9H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 160.64, 157.85, 157.73, 155.91, 155.78, 153.44, 150.77, 147.28, 129.50, 129.10, 120.43, 115.49, 79.32, 33.87, 33.75, 27.88; Calculated for $[M+1]^+$ $C_{20}H_{22}N_8O_2$ 407.45, found 407.62.

**2-(4-(4-amino-1-(pyridin-2-ylmethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)phenyl)-*N*-(5-(tert-butyl)isoxazol-3-yl)acetamide (8i):** Anhydrous DMF (1 mL) was added to the acid intermediate of **6b**, followed by EDCl (52.5 mg, 0.338 mmol), HOAt (18.41 mg, 0.135 mmol), and DIPEA (0.028 mL, 0.162 mmol). 5-(*tert*-butyl)isoxazol-3-amine (28.4 mg, 0.203 mmol) was added and the reaction was sealed under $N_2$ and was reacted for 12 hours or until complete product conversion. The reaction was quenched with water, extracted with DCM, and washed with saturated $NaHCO_3$. The organic layer was collected, dried with $MgSO_4$, adsorbed onto silica, and purified by flash chromatography using DCM/MeOH (10-15 %) to generate **8i** in 48% yield. Light brown solid; Yield: 48%; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 8.57 (d, *J* = 4.9 Hz, 1H), 8.42 (s, 1H), 8.17 (s, 1H), 7.72 (d, *J* = 8.2 Hz, 2H), 7.59 (td, *J* = 7.7, 1.8 Hz, 1H), 7.46 (d, *J* = 8.2 Hz, 2H), 7.19 – 7.14 (m, 1H), 7.06 (d, *J* = 7.8 Hz, 1H), 6.66 (s, 1H), 5.78 (s, 2H), 5.50 (s, 1H), 3.76 (d, *J* = 28.4 Hz, 2H), 1.31 (s, 9H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 156.37, 155.19, 152.03, 149.55, 147.33, 136.81, 134.81, 134.62, 134.48, 132.69, 130.37, 129.20, 128.66, 124.21, 122.56, 121.61, 98.45, 93.10, 52.36, 33.03, 28.60; Calculated for $[M+1]^+$ $C_{26}H_{26}N_8O_2$ 483.55, found 483.66.

**2-(4-(4-amino-1-(pyridin-2-ylmethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)phenyl)-*N*-(3-fluorophenyl)acetamide (8j):** Anhydrous DMF (1 mL) was added to the acid intermediate of **6b**,

followed by EDCl (52.5 mg, 0.338 mmol), HOAt (18.41 mg, 0.135 mmol), and DIPEA (0.028 mL, 0.162 mmol). 3-Floroaniline (22.5 mg, 0.203 mmol) was added and the reaction was sealed under $N_2$ and was reacted for 12 hours or until complete product conversion. The reaction was quenched with water, extracted with DCM, and washed with saturated $NaHCO_3$. The organic layer was collected, dried with $MgSO_4$, adsorbed onto silica, and purified by flash chromatography using DCM/MeOH (10-15 %) to generate **8j** in 61% yield. Creamish white solid; Yield: 61%; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.55 (d, *J* = 4.6 Hz, 1H), 8.39 (s, 1H), 7.99 (s, 1H), 7.68 (d, *J* = 7.8 Hz, 2H), 7.59 (t, *J* = 8.5 Hz, 1H), 7.45 (d, *J* = 7.9 Hz, 2H), 7.17 (dd, *J* = 13.7, 7.6 Hz, 2H), 7.08 (d, *J* = 7.9 Hz, 2H), 6.77 (t, *J* = 7.9 Hz, 1H), 5.77 (brs, 2H), 5.64 (s, 1H), 3.75 (s, 2H); **$^{13}$C NMR (101 MHz, DMSO)** δ 169.64, 162.50 (d, *J* = 240 Hz), 158.63, 156.58 (d, *J* = 32 Hz), 155.24, 149.59, 144.50, 141.29 (d, *J* = 11 Hz), 137.48, 136.63, 131.60, 130.85, 130.55 (d, *J* = 39 Hz), 128.61, 123.16, 121.94, 115.28, 110.15 (d, *J* = 22 Hz), 106.33 (d, *J* = 26 Hz), 97.77, 56.24, 43.47; Calculated for $[M+1]^+$ $C_{25}H_{20}FN_7O$ 454.48, found 454.23.

**2-(4-(4-amino-1-(pyridin-2-ylmethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)phenyl)-*N*-(3-(trifluoromethyl)phenyl)acetamide (8k):** Anhydrous DMF (1 mL) was added to acid intermediate of **6b**, followed by EDCl (52.5 mg, 0.338 mmol), HOAt (18.41 mg, 0.135 mmol), and DIPEA (0.028 mL, 0.162 mmol). 3-trifloro aniline (32.6 mg, 0.203 mmol) was added and the reaction was sealed under $N_2$ and was reacted for 12 hours or until complete product conversion. The reaction was quenched with water, extracted with DCM, and washed with saturated $NaHCO_3$. The organic layer was collected, dried with $MgSO_4$, adsorbed onto silica, and purified by flash chromatography using DCM/MeOH (10-15 %) to generate **8k** in 53% yield. Light brown solid; Yield: 53%; **$^1$H NMR (400 MHz, DMSO)** δ 8.46 (d, *J* = 4.9 Hz, 1H), 8.25 (d, *J* = 8.3 Hz, 2H), 8.07 (d, *J* = 6.6 Hz, 2H), 7.80 – 7.68 (m, 3H), 7.51 (t, *J* = 8.0 Hz, 1H), 7.38 (d, *J* = 8.3 Hz, 2H),

7.35 (brs, 1H), 7.29 – 7.25 (m, 1H), 7.13 (d, *J* = 7.8 Hz, 1H), 5.62 (s, 2H), 3.69 (s, 2H); **$^{13}$C NMR (101 MHz, DMSO)** δ 170.01, 161.60, 158.18, 156.31, 154.32, 149.71, 148.85, 147.38, 140.41, 140.34, 137.57, 130.43, 129.55, 128.33, 126.36, 126.09, 123.32, 123.08, 122.03, 120.03, 104.06, 52.40, 49.02; Calculated for $[M+1]^+$ $C_{26}H_{20}F_3N_7O$ 504.49, found 504.13.

**2-(4-(4-amino-1-(pyridin-2-ylmethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)phenyl)-*N*-(3-(tert-butyl)-1-methyl-1*H*-pyrazol-5-yl)acetamide (8l):** Anhydrous DMF (1 mL) was added to acid intermediate of **6b**, followed by EDCl (52.5 mg, 0.338 mmol), HOAt (18.41 mg, 0.135 mmol), and DIPEA (0.028 mL, 0.162 mmol). 3-(*tert*-butyl)-1-methyl-1*H*-pyrazol-5-amine (31.0 mg, 0.203 mmol) was added and the reaction was sealed under $N_2$ and was reacted for 12 hours or until complete product conversion. The reaction was quenched with water, extracted with DCM, and washed with saturated $NaHCO_3$. The organic layer was collected, dried with $MgSO_4$, adsorbed onto silica, and purified by flash chromatography using DCM/MeOH (10-15 %) to generate **8l** in 34% yield. Brown solid; Yield: 34%; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.53 (s, 1H), 8.36 (s, 1H), 7.75 (s, 1H), 7.67 (d, *J* = 7.8 Hz, 1H), 7.62 – 7.52 (m, 2H), 7.44 (d, *J* = 7.7 Hz, 2H), 7.22 – 7.11 (m, 2H), 7.09 (d, *J* = 7.9 Hz, 1H), 6.04 (s, 1H), 5.75 (s, 2H), 3.76 (s, 2H), 3.56 (s, 3H), 1.21 (s, 9H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 168.90, 160.61, 157.88, 156.19, 155.99, 155.02, 149.47, 144.41, 136.93, 135.29, 130.24, 129.06, 122.71, 121.84, 98.42, 96.48, 52.28, 43.15, 35.33, 30.37, 29.87; Calculated for $[M+1]^+$ $C_{27}H_{29}N_9O$ 496.59, found 496.65.

**2-(4-(4-amino-1-(pyridin-2-ylmethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)phenyl)-*N*-(3-cyclopropyl-1-methyl-1*H*-pyrazol-5-yl)acetamide (8m):** Anhydrous DMF (1 mL) was added to the acid intermediate of **6b**, followed by EDCl (52.5 mg, 0.338 mmol), HOAt (18.41 mg, 0.135 mmol), and DIPEA (0.028 mL, 0.162 mmol). 3-cyclopropyl-1-methyl-1*H*-pyrazol-5-amine (29.4 mg, 0.203 mmol) was added and the reaction was sealed under $N_2$ and was reacted for 12 hours or

until complete product conversion. The reaction was quenched with water, extracted with DCM, and washed with saturated $NaHCO_3$. The organic layer was collected, dried with $MgSO_4$, adsorbed onto silica, and purified by flash chromatography using DCM/MeOH (10-15 %) to generate **8m** in 31% yield. Light brown solid; Yield: 31%; **$^1$H NMR (400 MHz, cdcl$_3$)** δ 8.55 (d, *J* = 4.8 Hz, 1H), 8.40 (s, 1H), 7.71 (d, *J* = 7.9 Hz, 2H), 7.59 (t, *J* = 7.0 Hz, 2H), 7.46 (d, *J* = 7.9 Hz, 2H), 7.19 – 7.14 (m, 2H), 7.07 (d, *J* = 7.8 Hz, 1H), 5.77 (s, 2H), 5.59 (brs, 2H), 3.78 (s, 2H), 1.82-1.80 (m, 1H), 0.85-0.81 (m, 2H), 0.65-0.61 (m, 2H); **$^{13}$C NMR (101 MHz, CDCl$_3$)** δ 168.68, 162.50, 157.75, 156.35, 156.04, 155.13, 153.86, 149.54, 144.24, 136.86, 135.08, 132.58, 130.25, 129.19, 122.66, 121.72, 98.45, 96.39, 52.33, 43.26, 35.25, 9.33, 7.61; Calculated for $[M+1]^+$ $C_{26}H_{25}N_9O$ 480.55, found 480.68.

**2-(4-(4-amino-1-(3-methoxypropyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)phenyl)-*N*-(5-(tert-butyl)isoxazol-3-yl)acetamide (8p):** Anhydrous DMF (1 mL) was added to the intermediate **3f**, followed by EDCl (52.5 mg, 0.338 mmol), HOAt (18.41 mg, 0.135 mmol), and DIPEA (0.028 mL, 0.162 mmol). 5-(*tert*-butyl)isoxazol-3-amine (27.8 mg, 0.203 mmol) was added and the reaction was sealed under $N_2$ and was reacted for 12 hours or until complete product conversion. The reaction was quenched with water, extracted with DCM, and washed with saturated $NaHCO_3$. The organic layer was collected, dried with $MgSO_4$, adsorbed onto silica, and purified by flash chromatography using DCM/MeOH (10-15 %) to generate **8p** in 76% yield. Light brown solid; Yield: 76%; **$^1$H NMR (400 MHz, DMSO)** δ 11.21 (s, 1H), 8.21 (s, 1H), 7.60 (d, *J* = 8.2 Hz, 2H), 7.45 (d, *J* = 8.2 Hz, 2H), 6.55 (s, 1H), 4.35 (t, *J* = 7.0 Hz, 2H), 3.72 (s, 2H), 3.18 (s, 3H), 2.04 – 2.00 (m, 2H), 1.24 (s, 9H), 1.03 (s, 2H); **$^{13}$C NMR (101 MHz, DMSO)** δ 180.91, 169.62, 158.53, 158.34, 156.10, 154.57, 143.75, 136.12, 131.87, 130.33, 128.61, 97.67, 93.55, 69.45, 58.39, 44.05, 28.74, 25.38; Calculated for $[M+1]^+$ $C_{24}H_{29}N_7O_3$ 464.54, found 464.62.

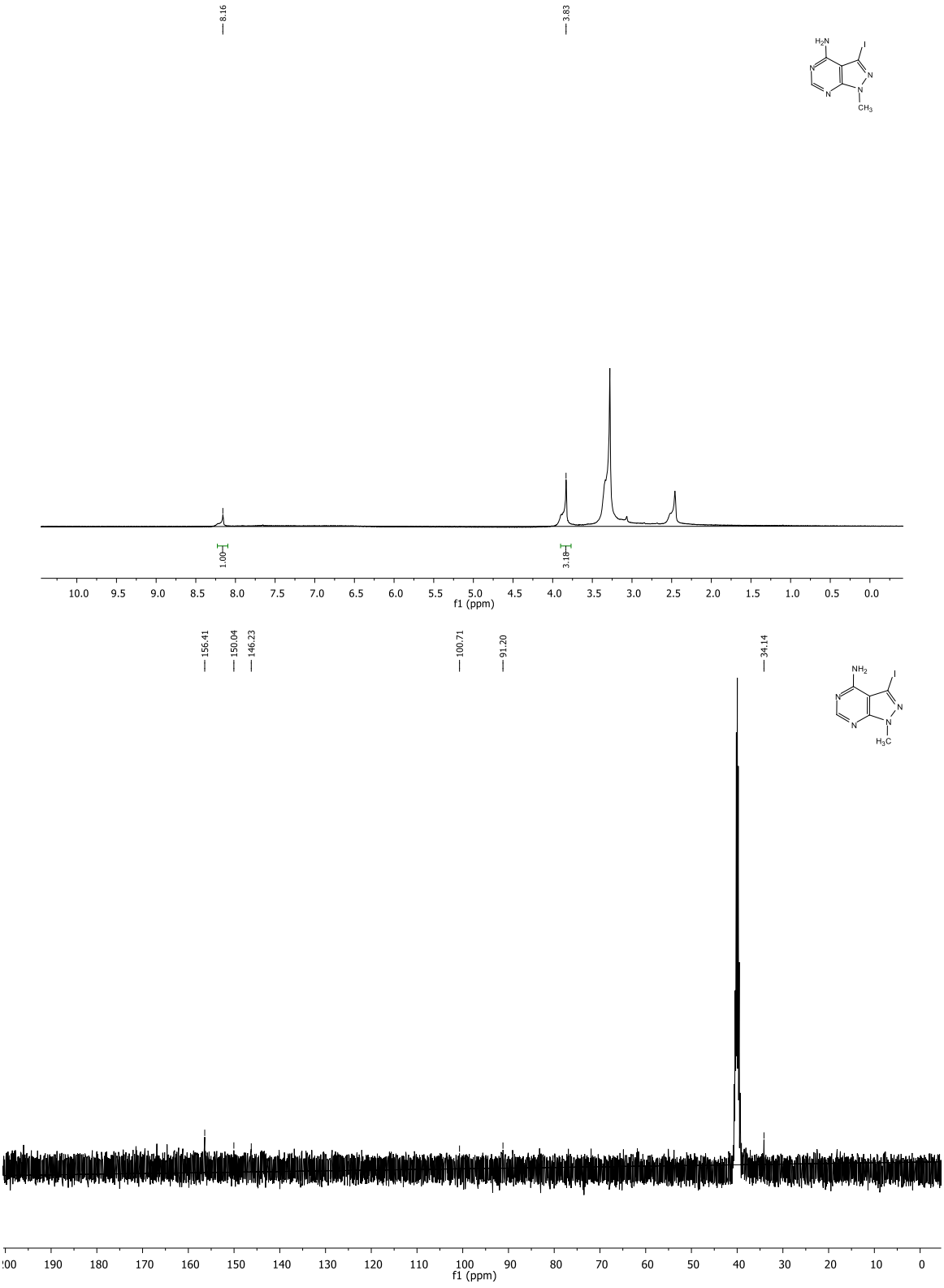
**2-(4-(4-amino-1-(3-methoxypropyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)phenyl)-*N*-(3-fluorophenyl)acetamide (8q):** Anhydrous DMF (1 mL) was added to the acid intermediate of **3f**, followed by EDCl (52.5 mg, 0.338 mmol), HOAt (18.41 mg, 0.135 mmol), and DIPEA (0.028 mL, 0.162 mmol). 3-floroaniline (22.5 mg, 0.203 mmol) was added and the reaction was sealed under $N_2$ and was reacted for 12 hours or until complete product conversion. The reaction was quenched with water, extracted with DCM, and washed with saturated $NaHCO_3$. The organic layer was collected, dried with $MgSO_4$, adsorbed onto silica, and purified by flash chromatography using DCM/MeOH (10-15 %) to generate **8q** in 71% yield. Light brown solid; Yield: 71%; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.38 (s, 1H), 7.71 (d, *J* = 7.5 Hz, 1H), 7.53 – 7.44 (m, 3H), 7.08 (d, *J* = 7.8 Hz, 1H), 6.79 (t, *J* = 8.7 Hz, 1H), 5.53 (s, 2H), 4.53 (t, *J* = 6.8 Hz, 2H), 3.80 (s, 2H), 3.42 (s, 2H), 3.31 (s, 3H), 2.25 – 2.18 (m, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 172.33, 170.24, 168.68, 162.90 (d, *J* = 244 Hz), 157.69, 155.79, 154.47, 143.55, 139.23 (d, *J* = 10 Hz), 135.27, 132.58, 130.37, 130.02, 129.97 (d, *J* = 92 Hz), 129.01, 128.39, 115.00, 111.14 (d, *J* = 21 Hz), 111.04, 107.36 (d, *J* = 26 Hz), 98.34, 69.61, 58.65, 44.38, 29.76, 24.84; Calculated for $[M+1]^+$ $C_{23}H_{23}FN_6O_2$ 435.48, found 435.80 .

**2-(4-(4-amino-1-isobutyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)phenyl)-*N*-(3-fluorophenyl)acetamide (8r):** Anhydrous DMF (1 mL) was added to the acid intermediate of **3i**, followed by EDCl (52.5 mg, 0.338 mmol), HOAt (18.41 mg, 0.135 mmol), and DIPEA (0.028 mL, 0.162 mmol). 3-floroaniline (22.5 mg, 0.203 mmol) was added and the reaction was sealed under $N_2$ and was reacted for 12 hours or until complete product conversion. The reaction was quenched with water, extracted with DCM, and washed with saturated $NaHCO_3$. The organic layer was collected, dried with $MgSO_4$, adsorbed onto silica, and purified by flash chromatography using DCM/MeOH (10-15 %) to generate **8r** in 64% yield. Light brown solid; Yield: 64%; **$^1$H NMR**

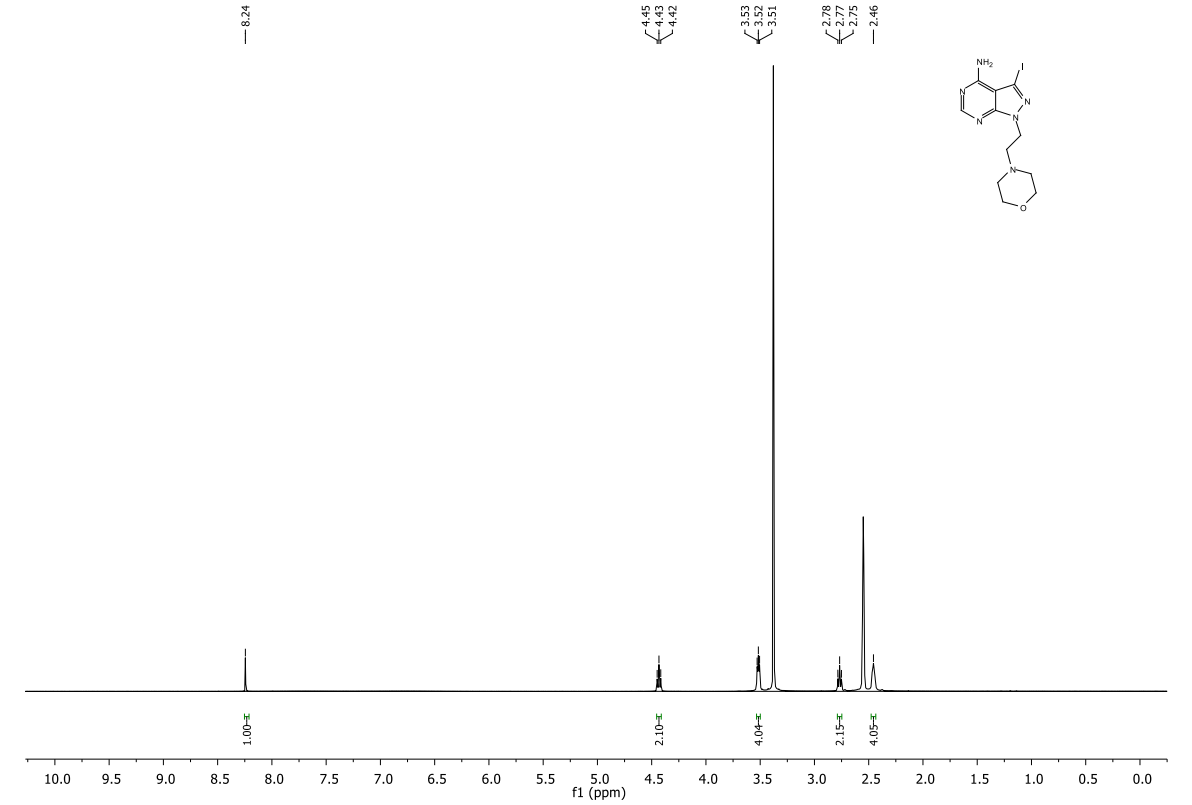
**(400 MHz, $CDCl_3$)** δ 8.28 (s, 1H), 7.69 (d, *J* = 8.1 Hz, 2H), 7.51 (d, *J* = 8.0 Hz, 2H), 7.48 – 7.39 (m, 2H), 7.38 (brs, 1H), 7.24 – 7.16 (m, 2H), 7.08 (d, *J* = 8.1 Hz, 1H), 6.80 – 6.75 (m, 1H), 5.28 (s, 1H), 4.24 (d, *J* = 7.3 Hz, 2H), 3.80 (s, 2H), 2.15 (brs, 1H), 0.94 (d, *J* = 6.7 Hz, 6H); **$^{13}$C NMR (101 MHz, cdcl$_3$)** δ 177.72, 171.12, 168.50, 162.90 (d, *J* = 294 Hz), 156.84, 154.05, 153.04, 144.28, 139.05 (d, *J* = 11 Hz) 135.47, 132.07, 130.53, 130.07 (d, *J* = 4 Hz) 129.26 (d, *J* = 137 Hz), 128.57, 115.02, 111.23 (d, *J* = 22 Hz), 107.37 (d, *J* = 27 Hz), 97.76, 60.36, 44.43, 29.66, 14.16.Calculated for $[M+1]^+$ $C_{23}H_{23}FN_6O$ 419.48, found 419.50.

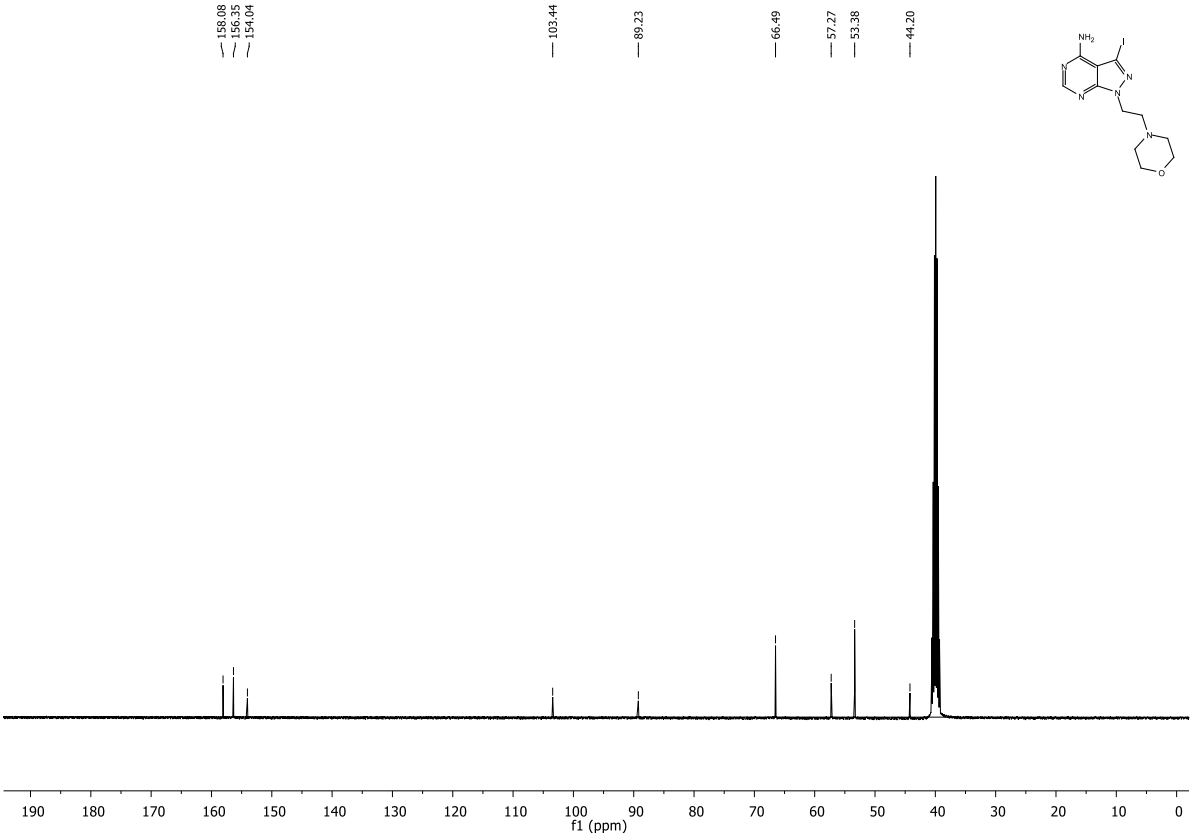
## 5. $^{1}H$ and $^{13}C$ NMR spectra for all Compounds

### 3-iodo-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (3a)

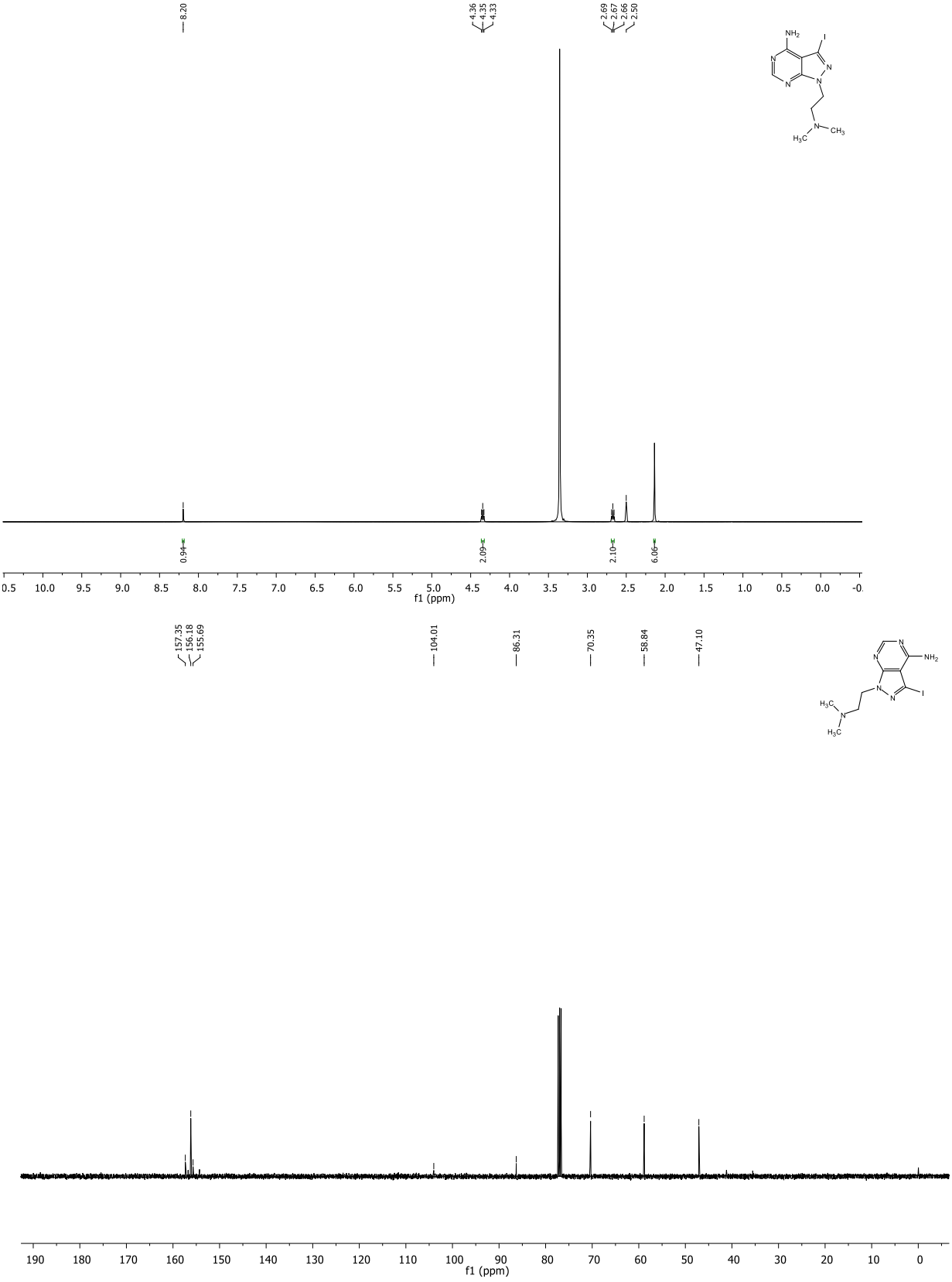


**3-iodo-1-(2-morpholinoethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (3b)**

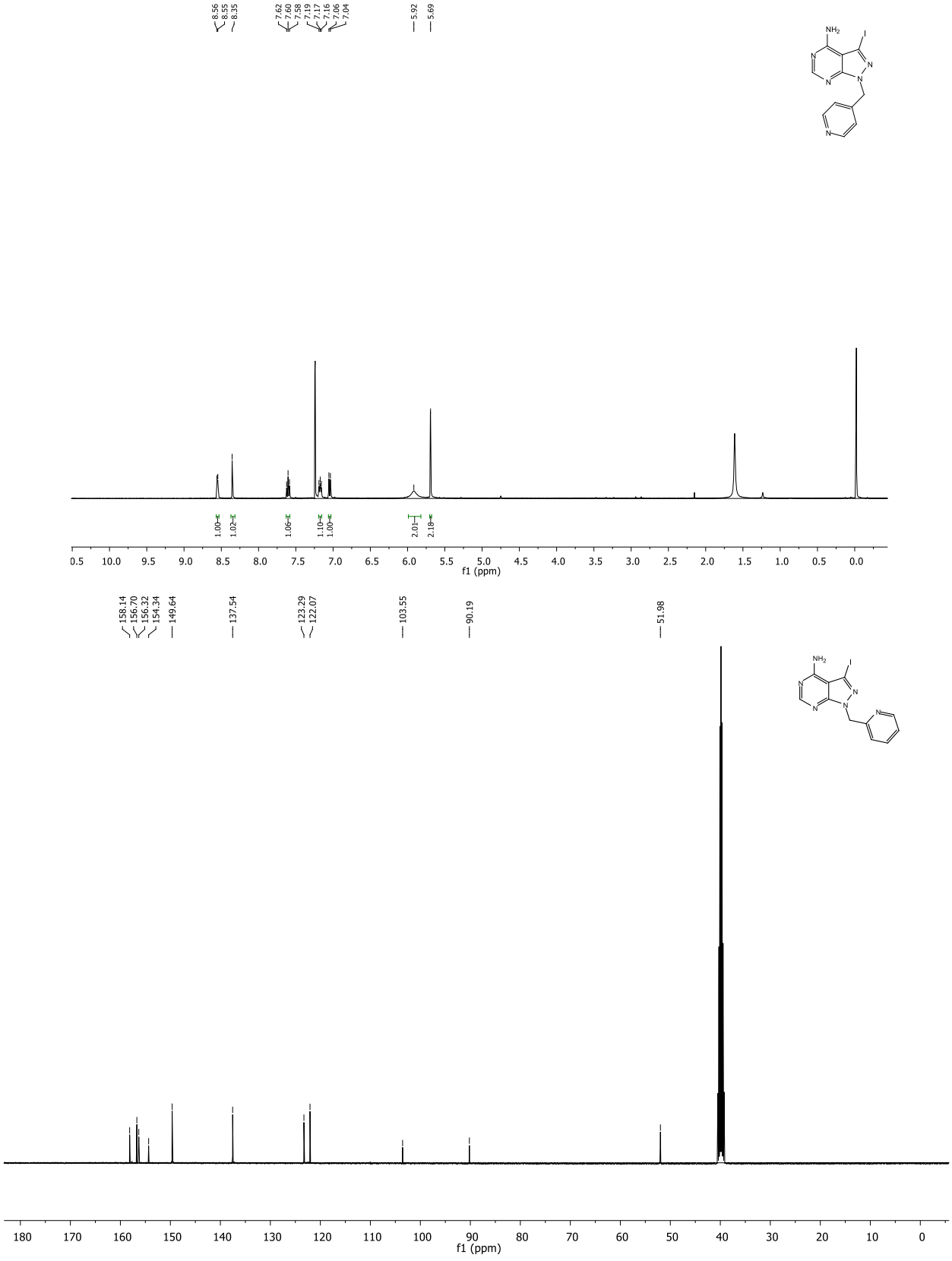


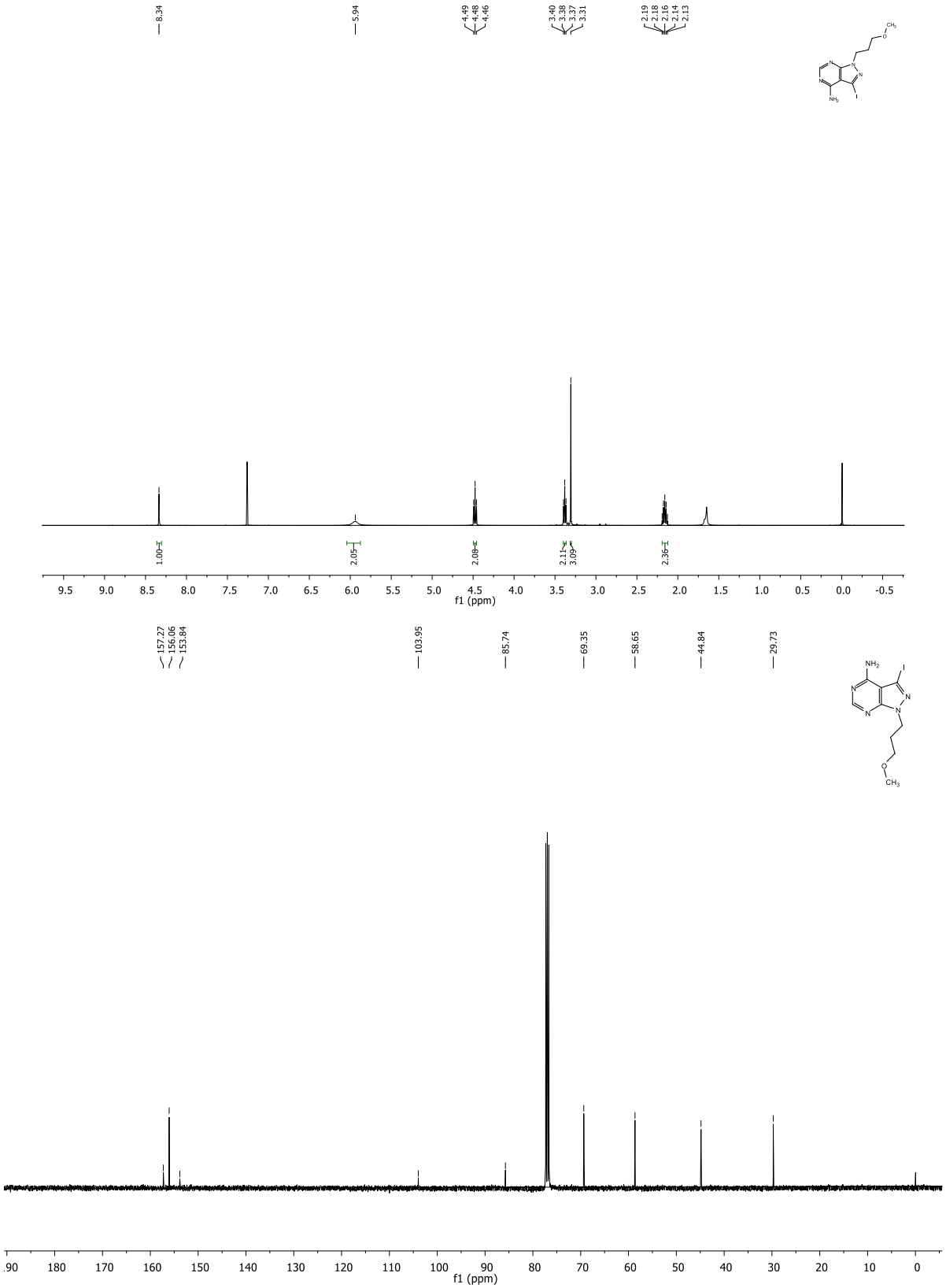
**1-(2-(dimethylamino)ethyl)-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (3c)**



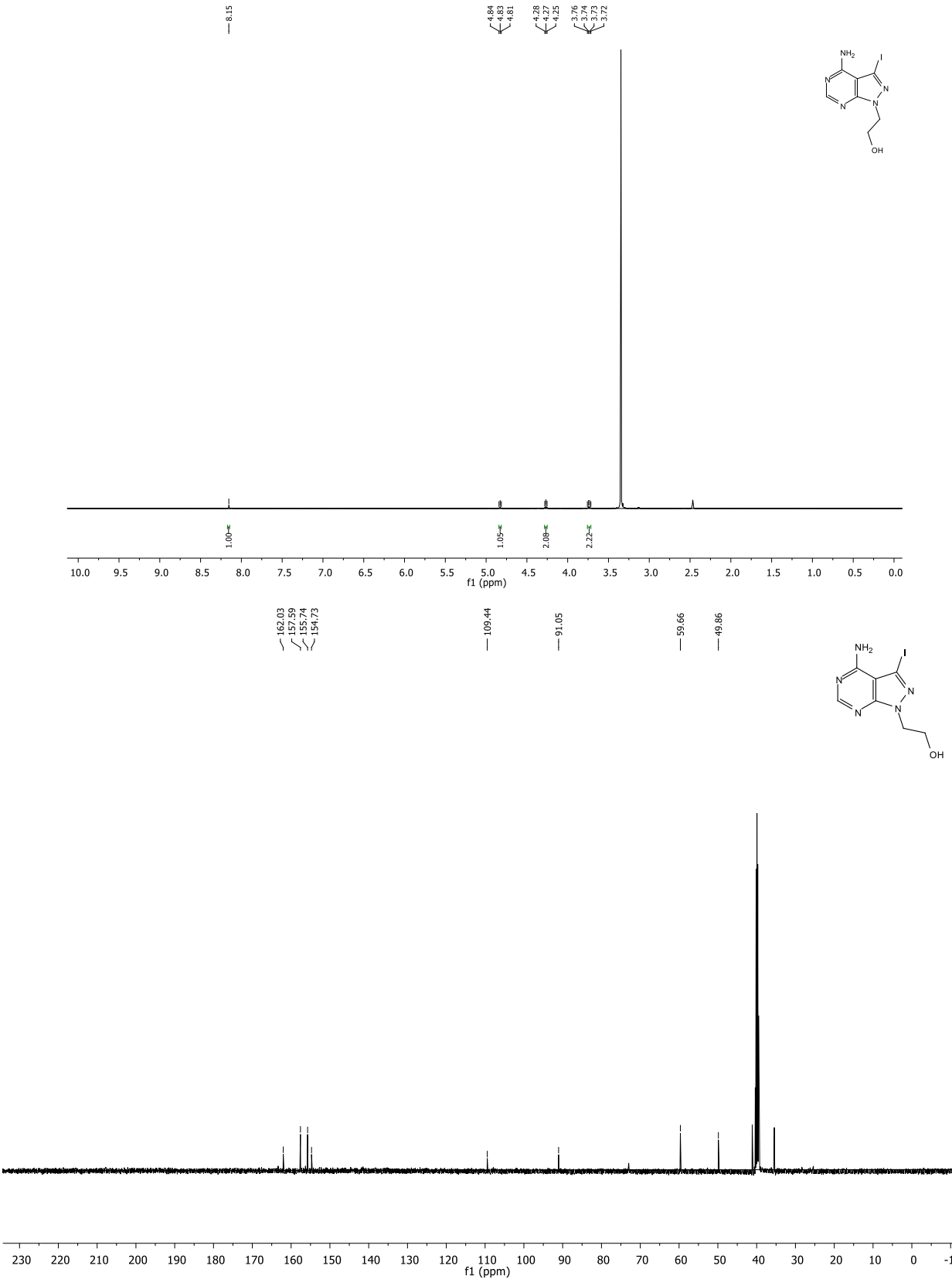
**3-iodo-1-(pyridin-2-ylmethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (3e)**



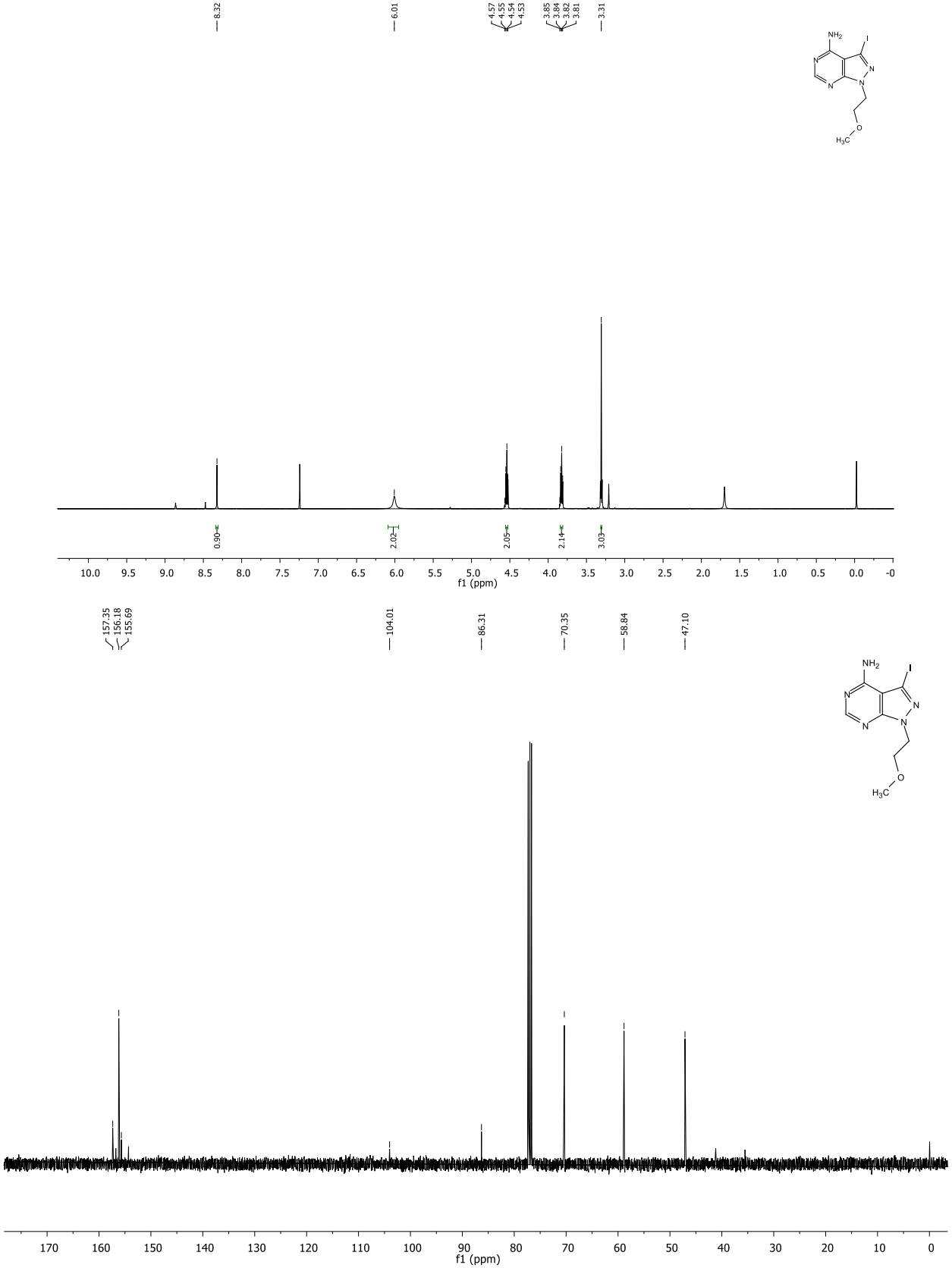
**3-iodo-1-(3-methoxypropyl)-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine (3f)**



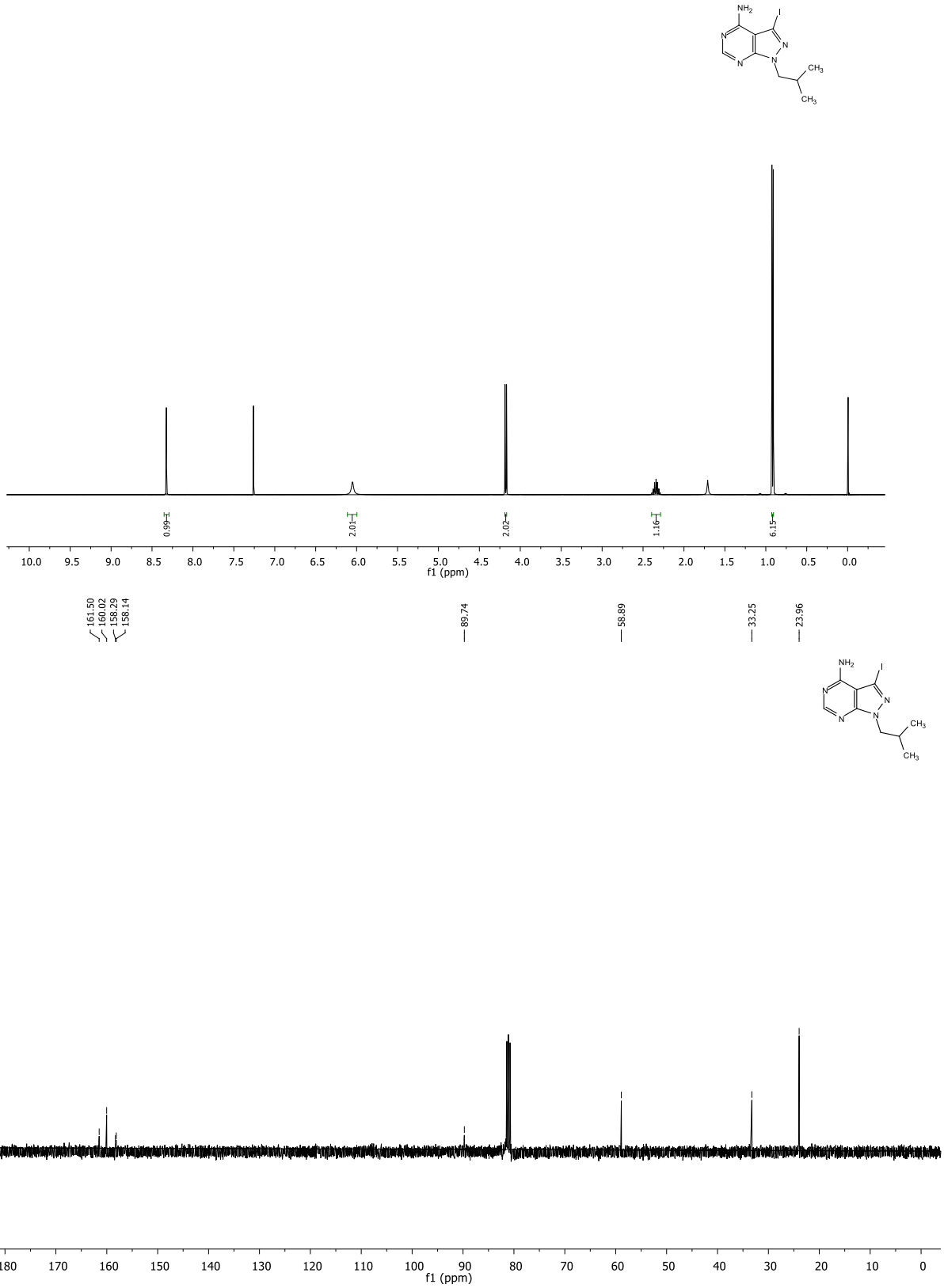
**2-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethan-1-ol (3g)**



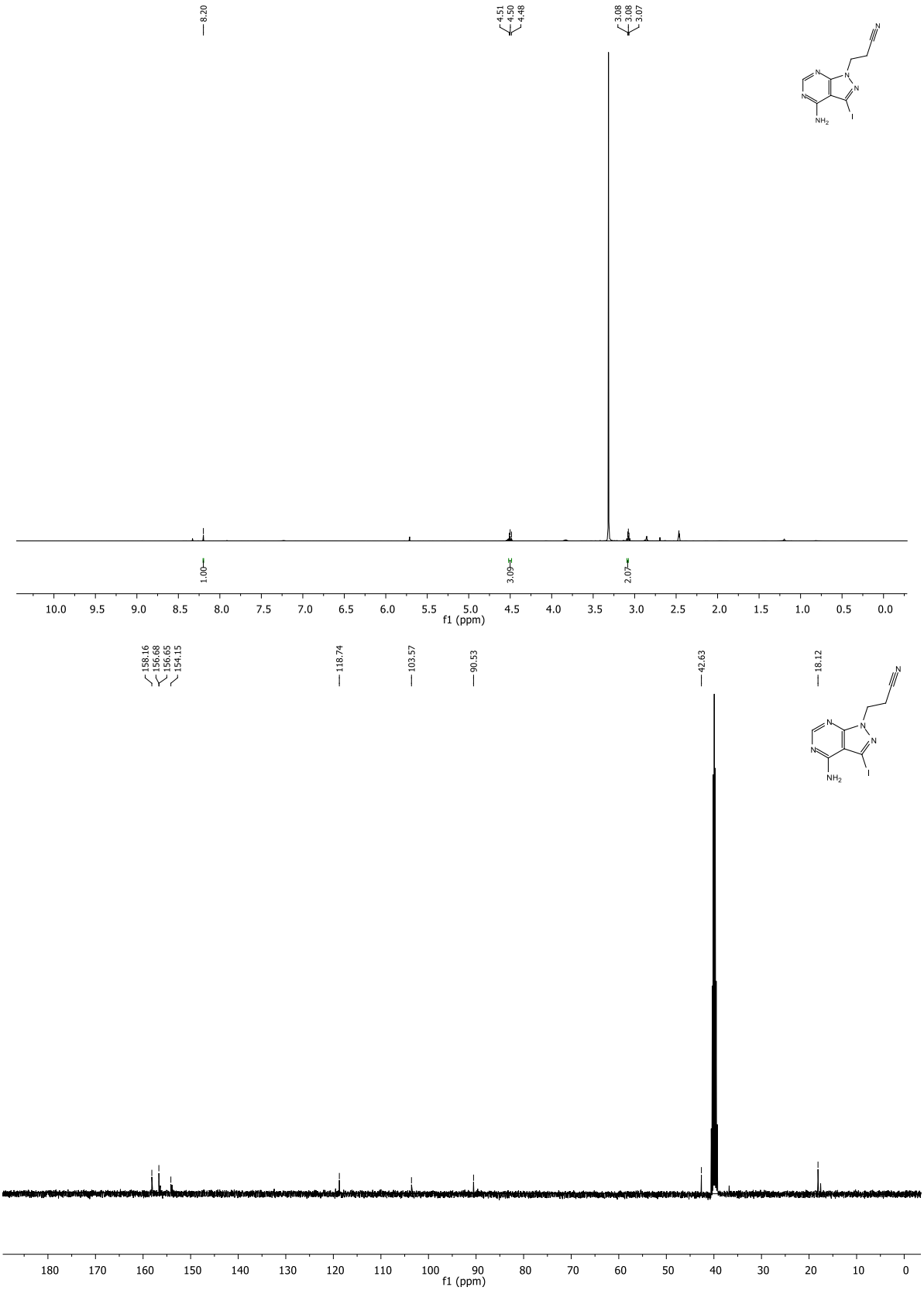
**3-iodo-1-(2-methoxyethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (3h)**



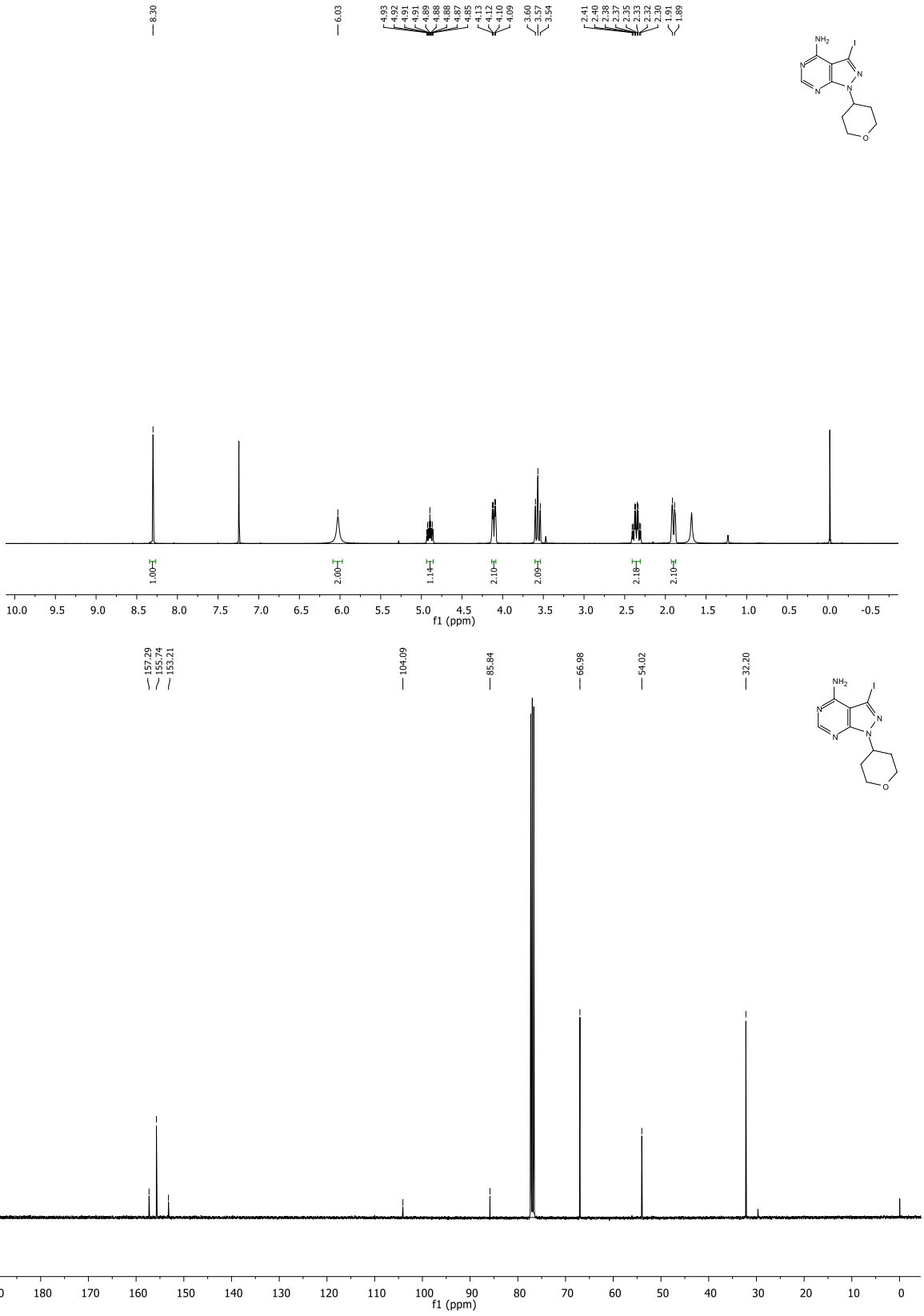
**3-iodo-1-isobutyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (3i)**



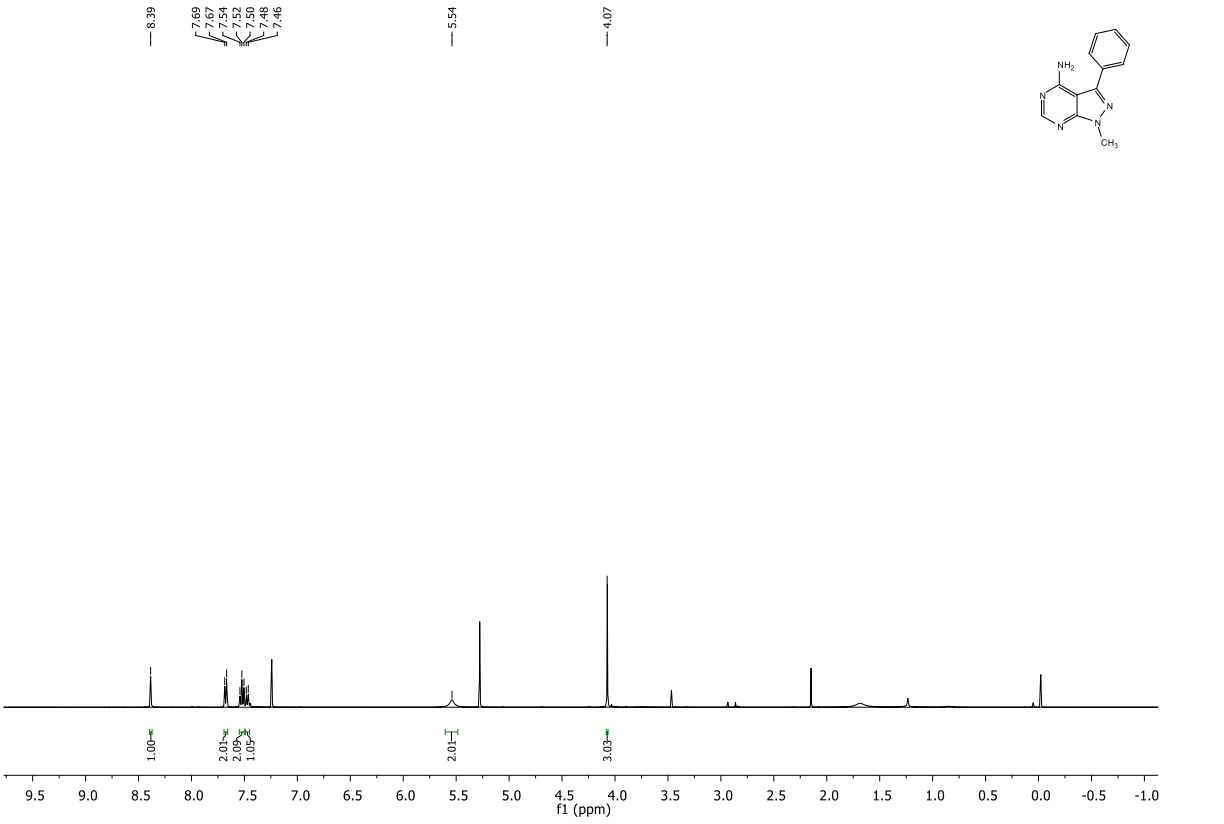
**3-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)propanenitrile (3j)**

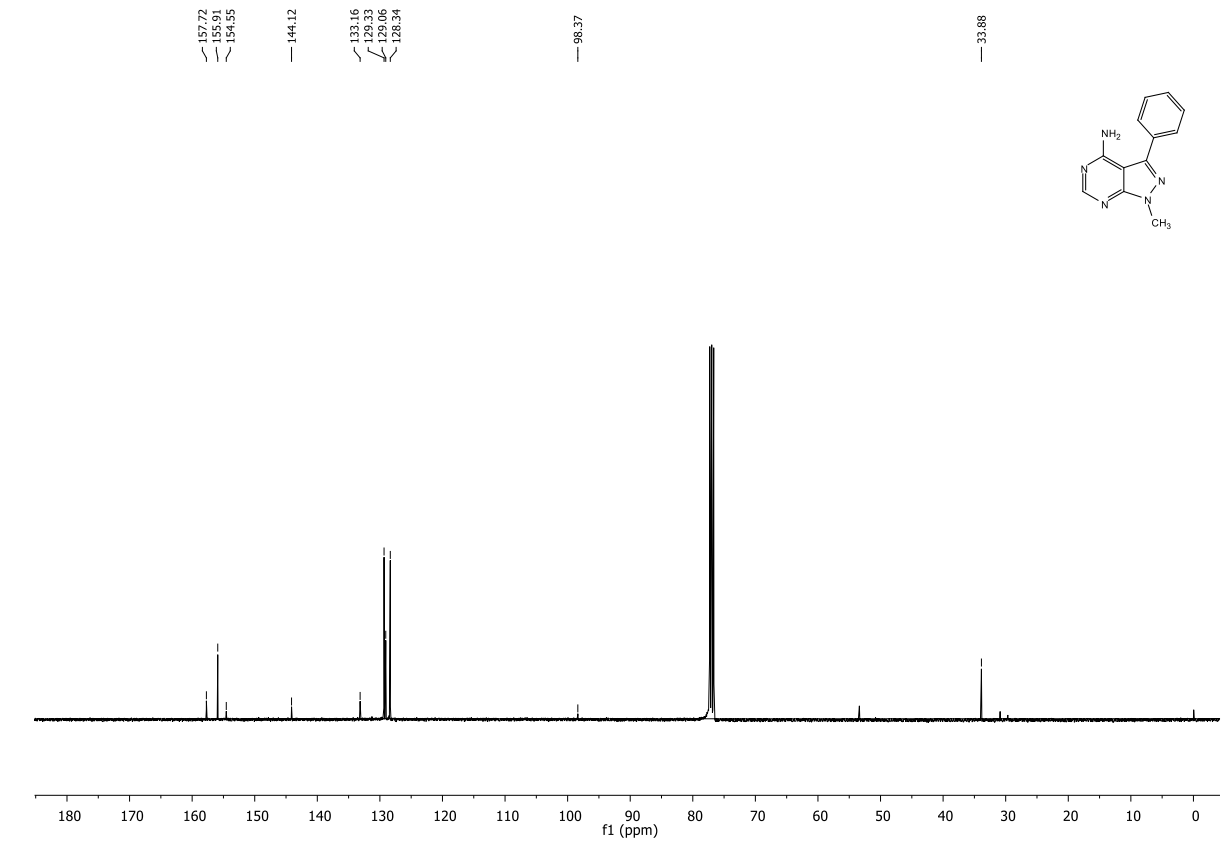


**3-iodo-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (3k)**

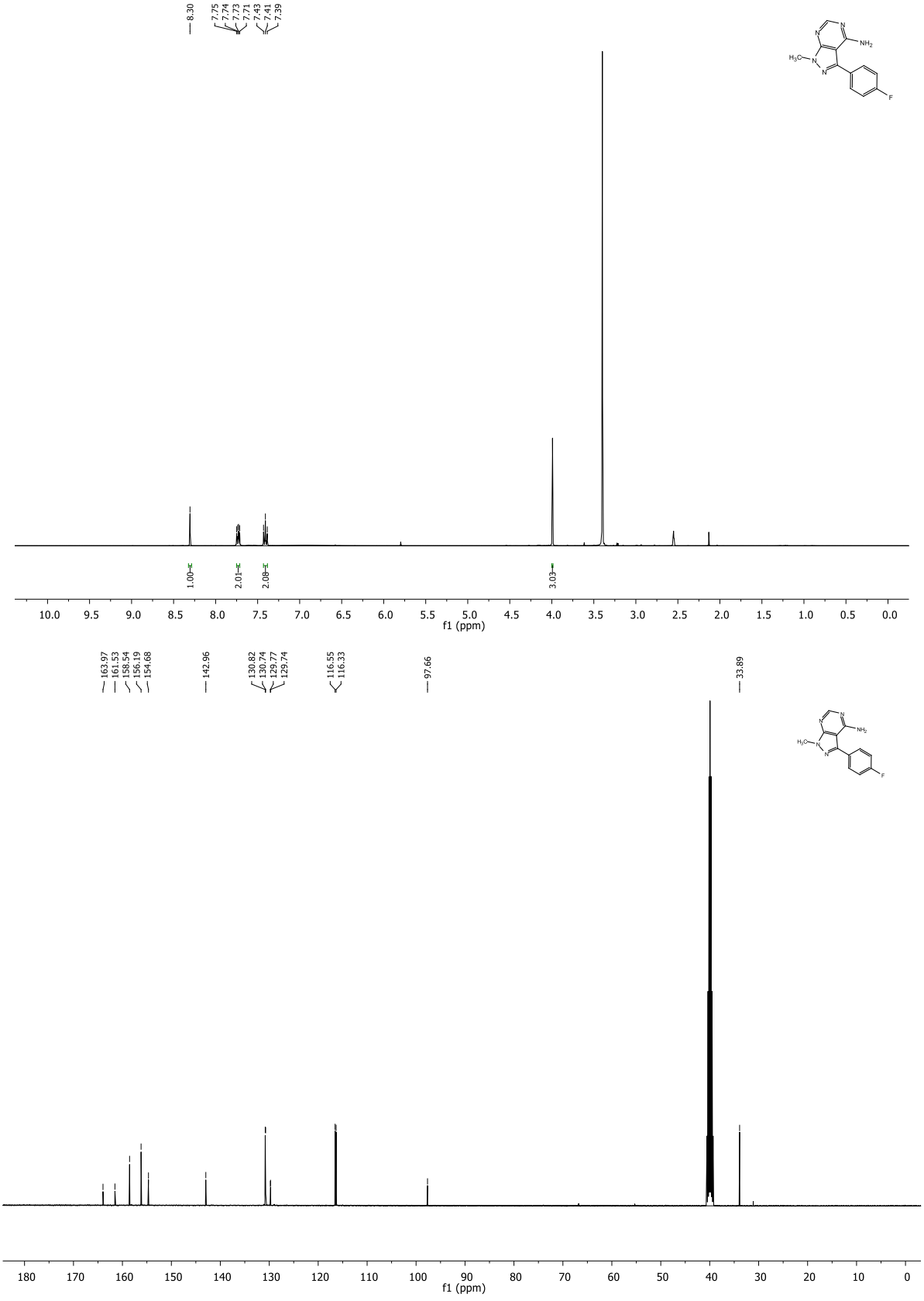


**1-methyl-3-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (4a)**

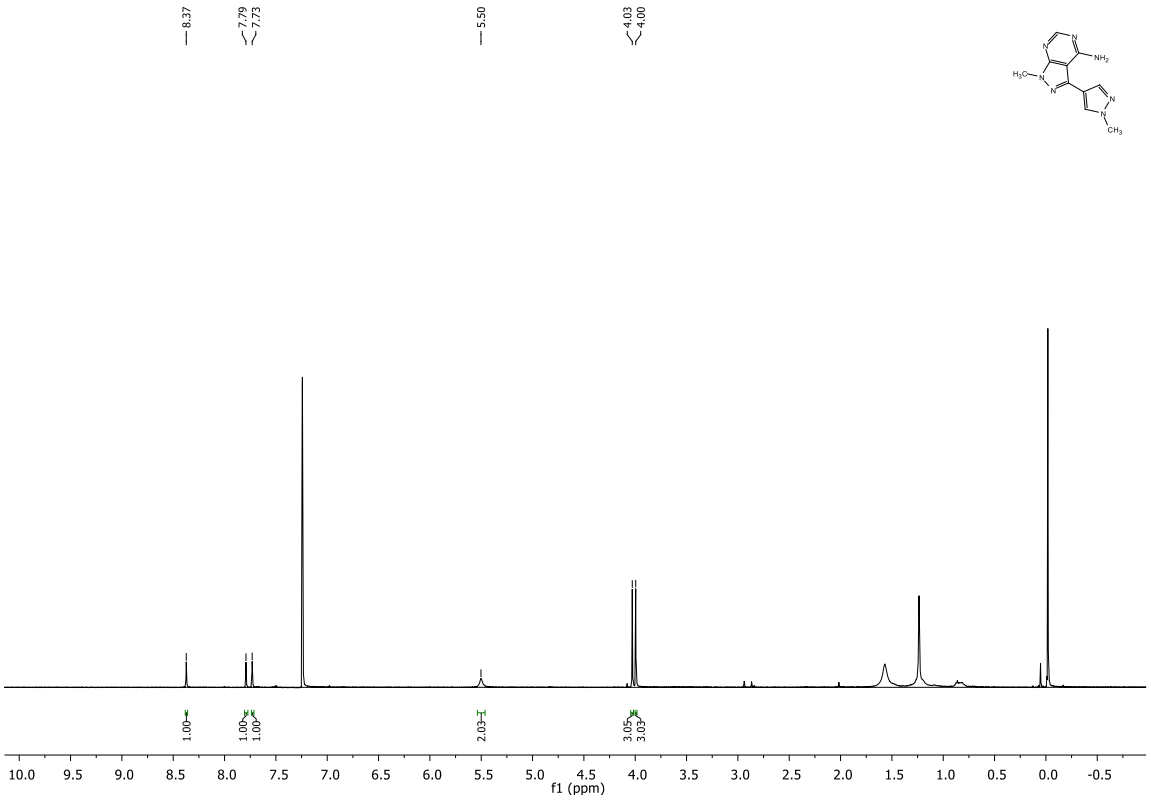


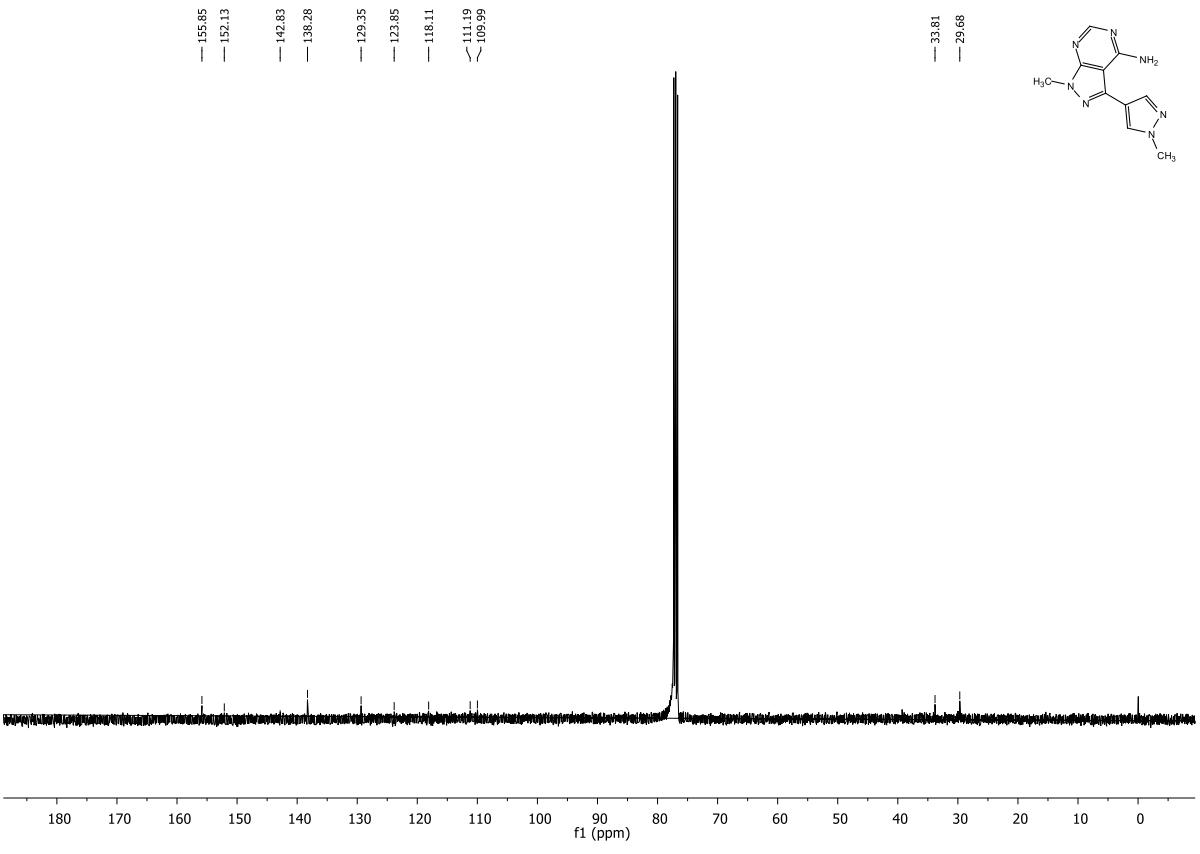



**1-methyl-3-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (4b)**

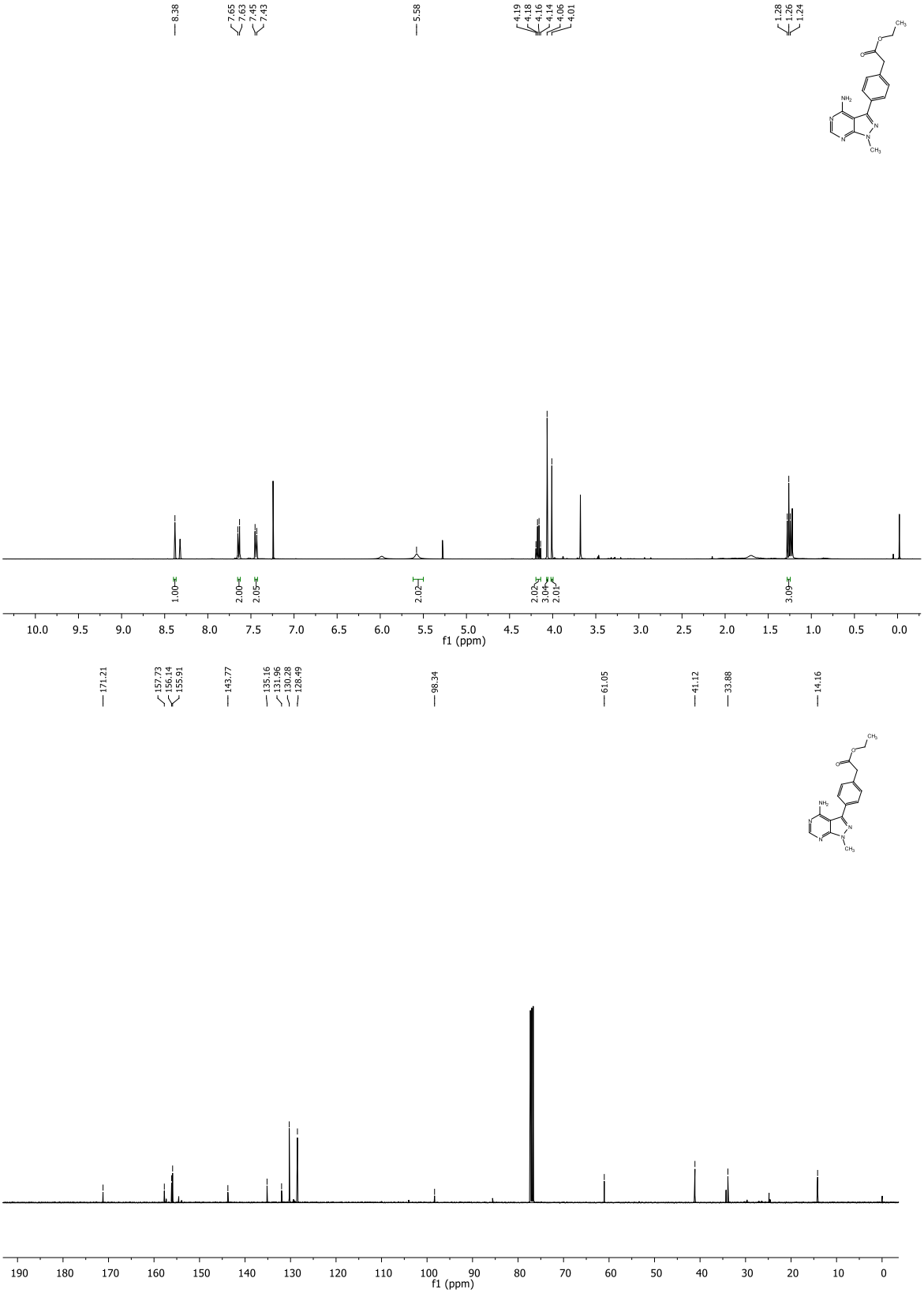


**1-methyl-3-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (4d)**

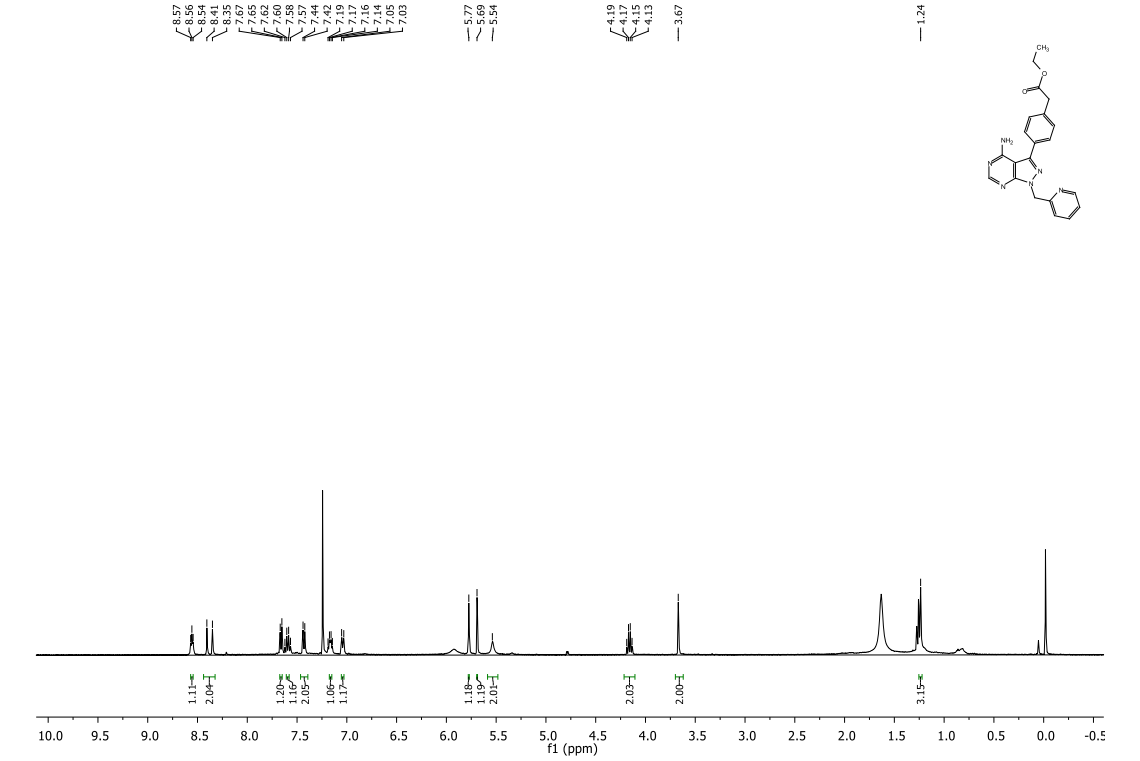


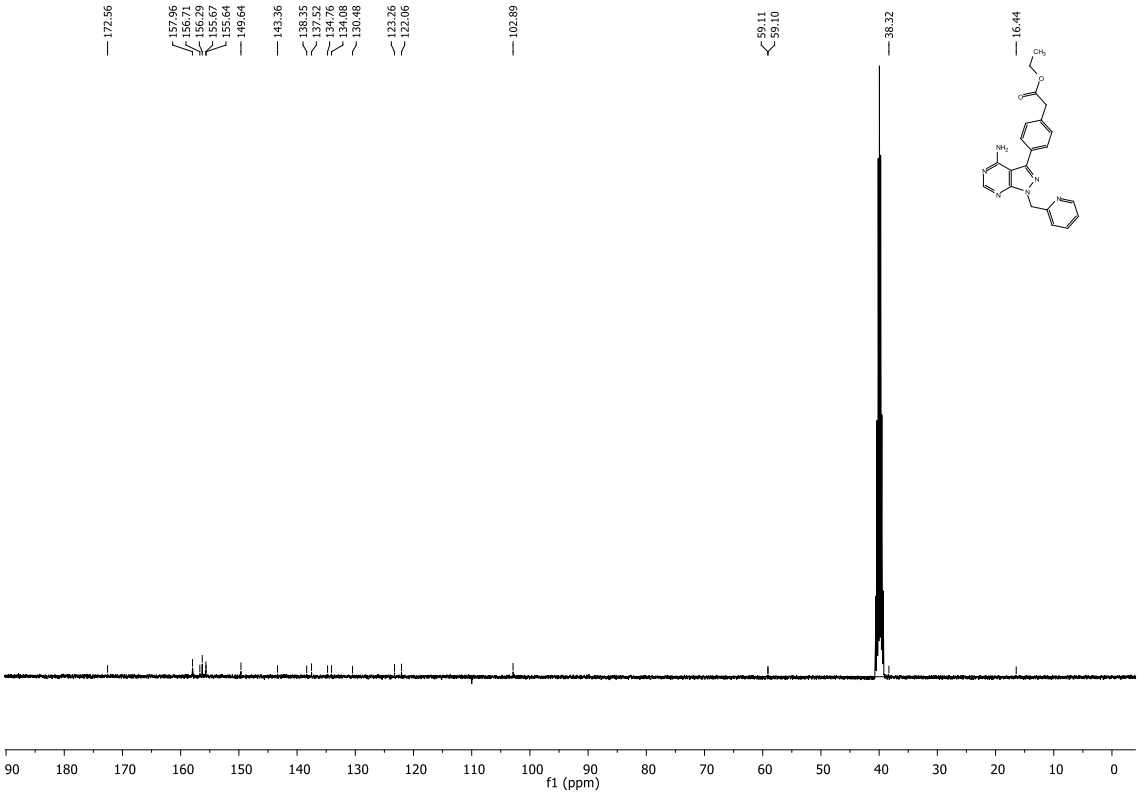



**Ethyl 2-(4-(4-amino-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)phenyl)acetate (6a)**

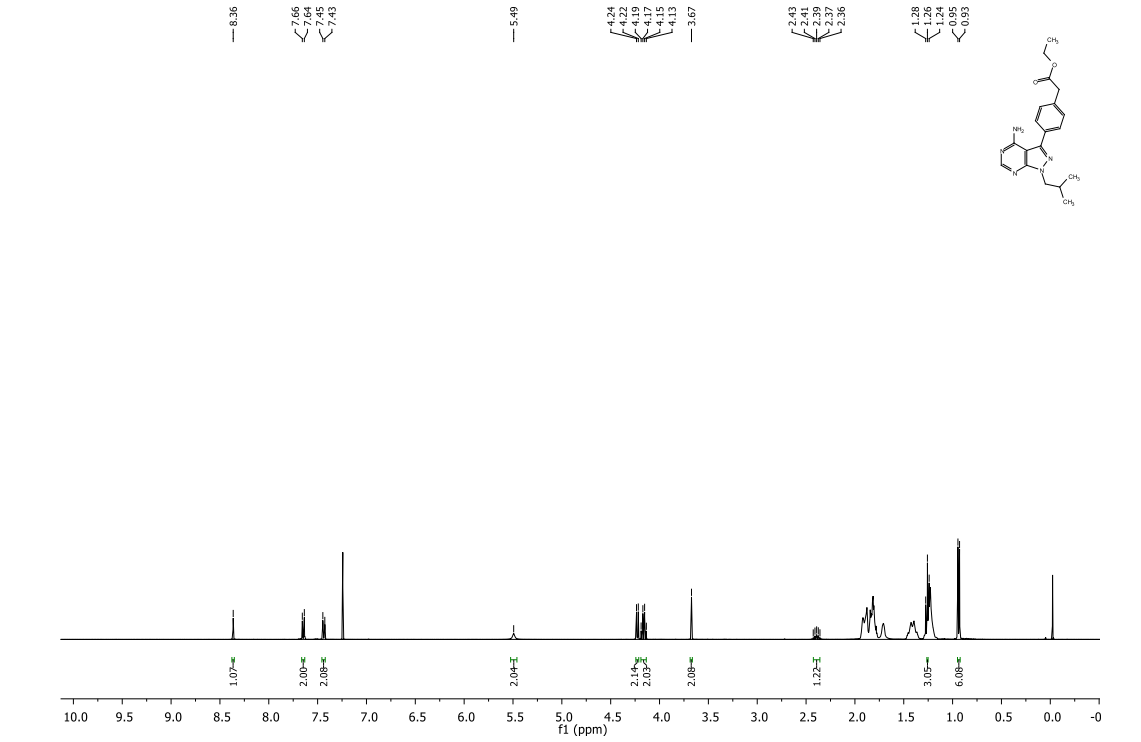


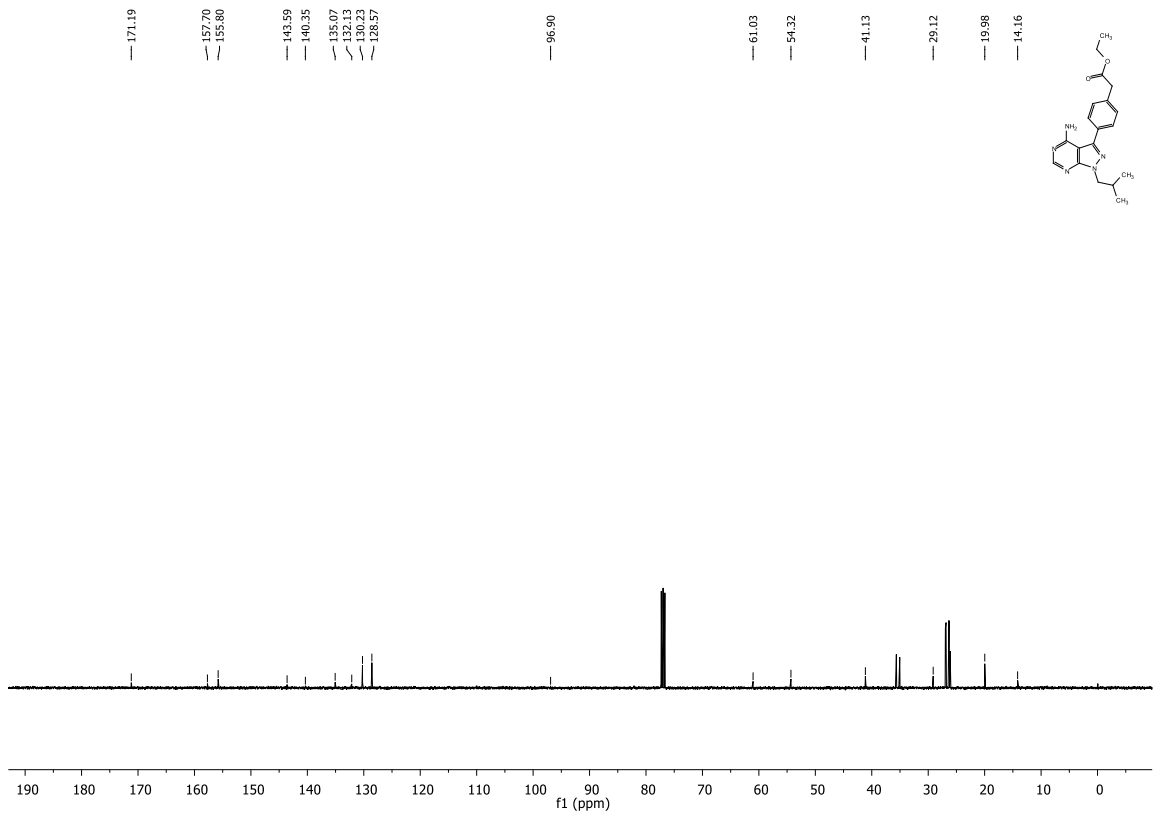
**Ethyl 2-(4-(4-amino-1-(pyridin-2-ylmethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)phenyl)acetate (6b)**



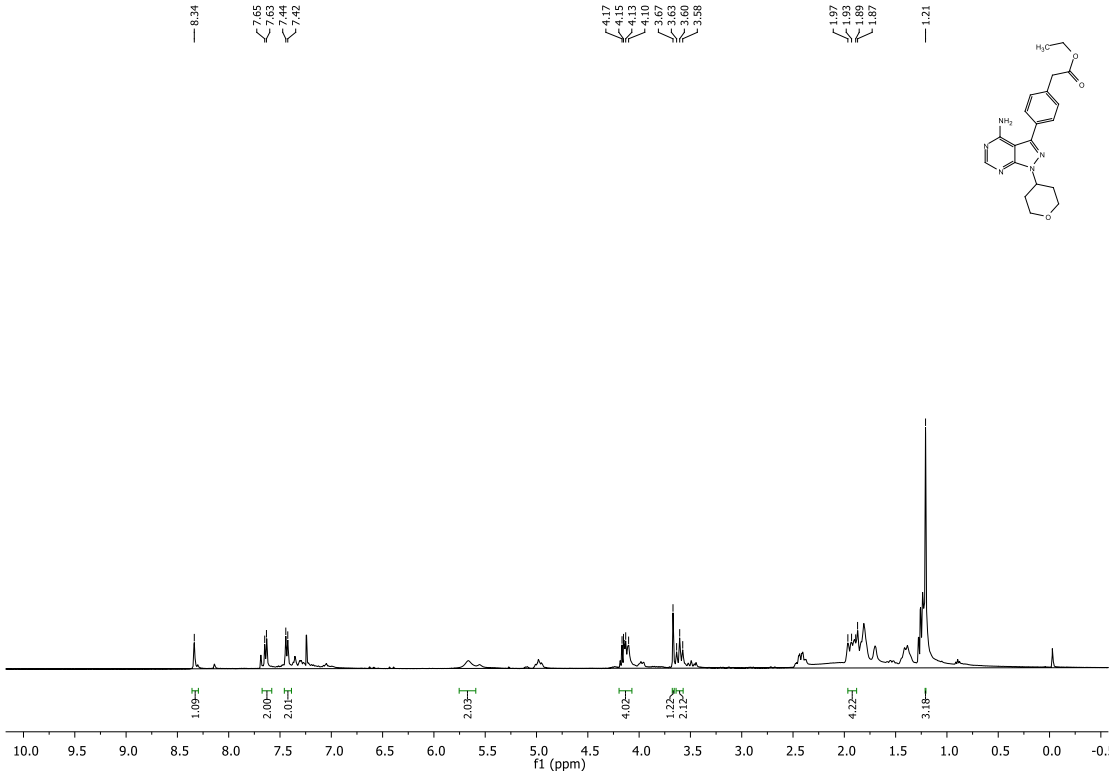



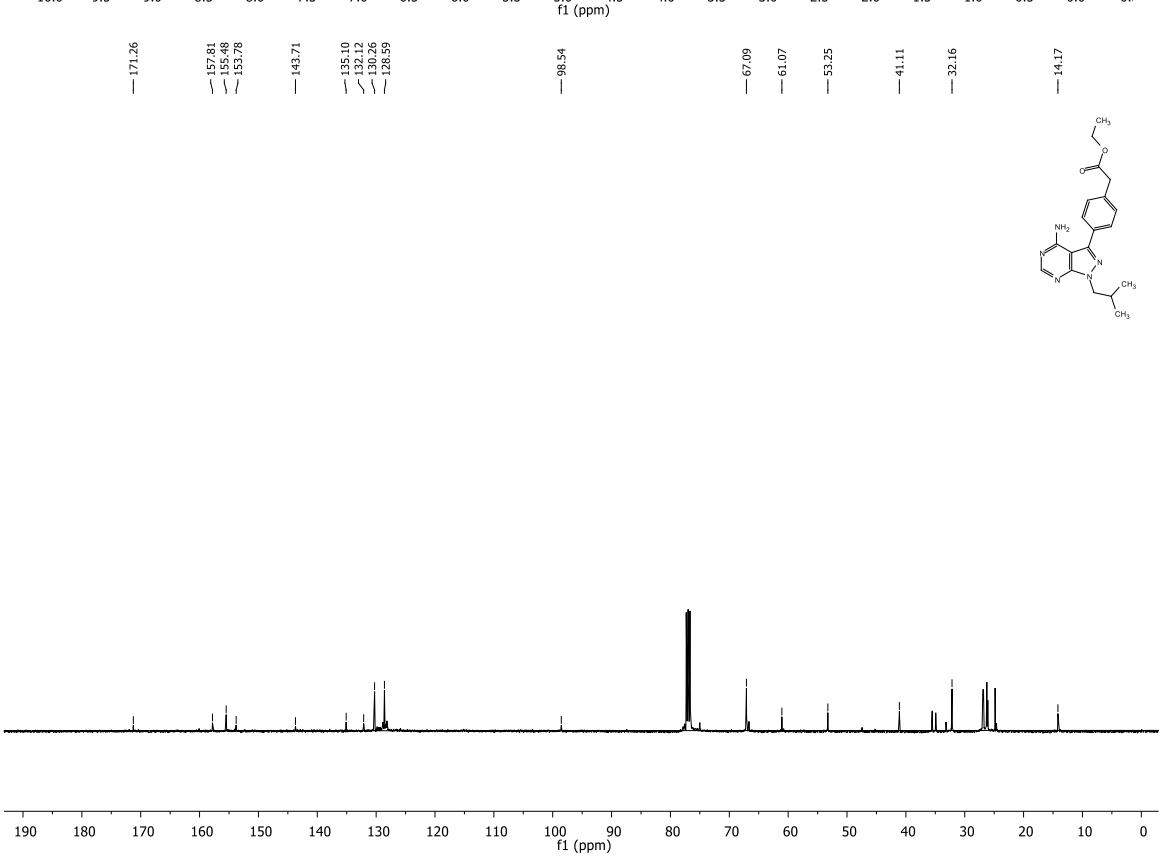
**Ethyl 2-(4-(4-amino-1-isobutyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)phenyl)acetate (6d)**



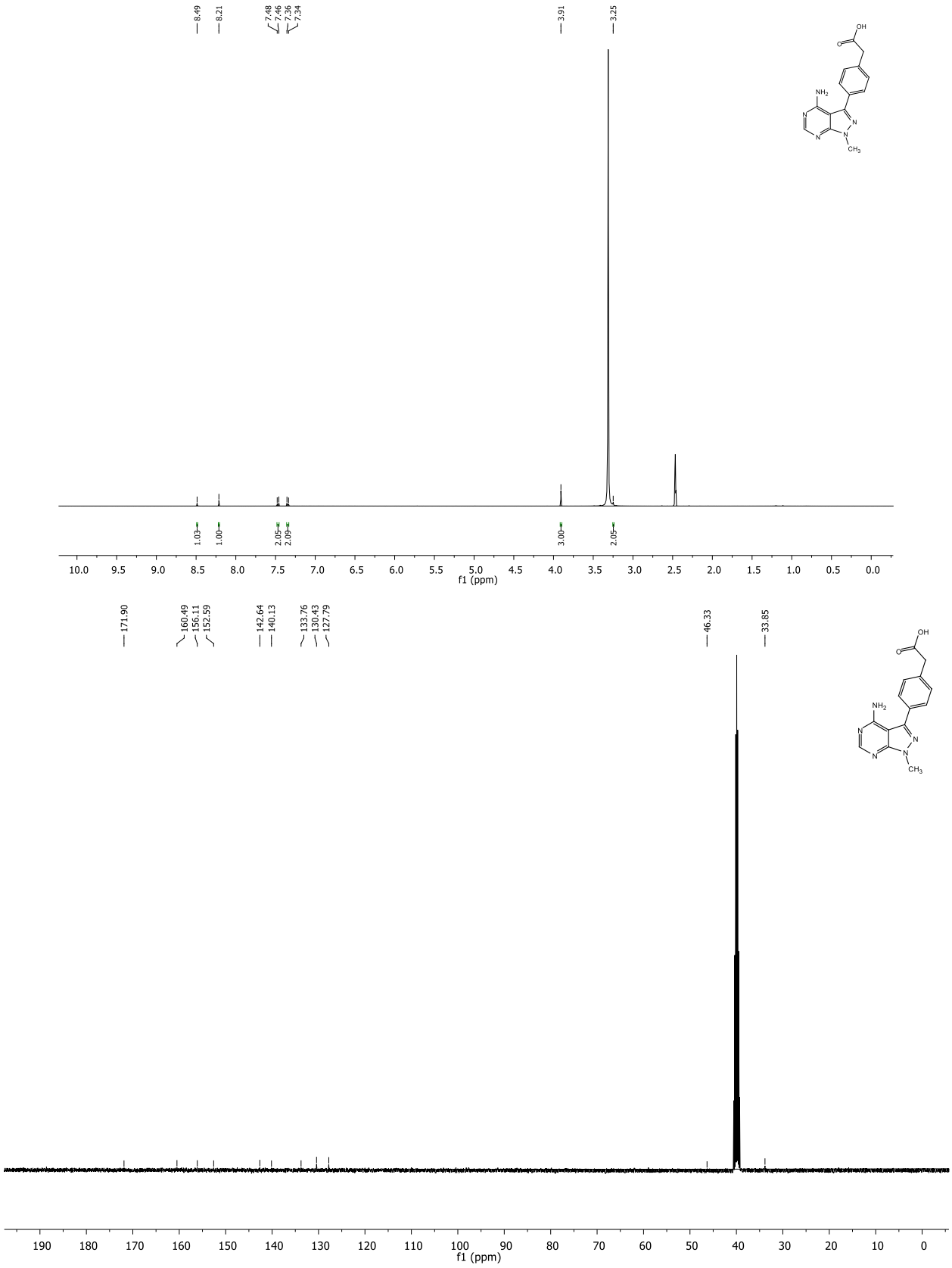



**Ethyl 2-(4-(4-amino-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)phenyl)acetate (6e)**

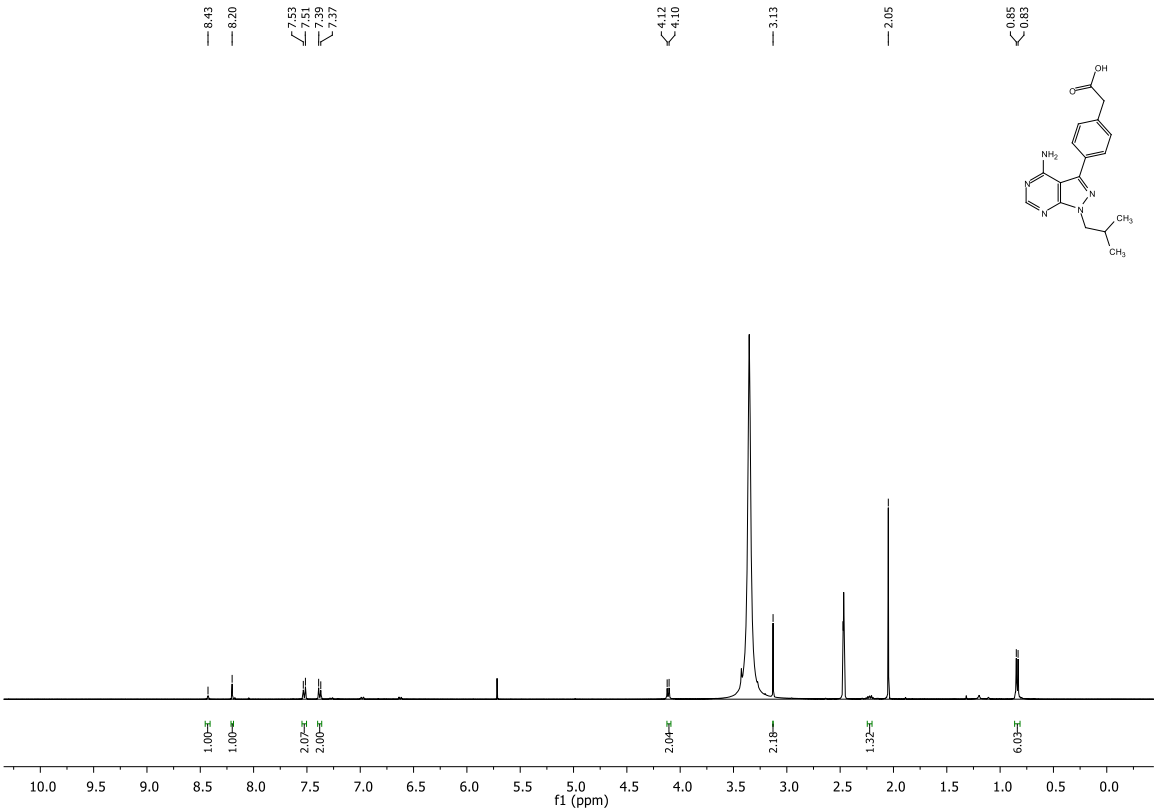


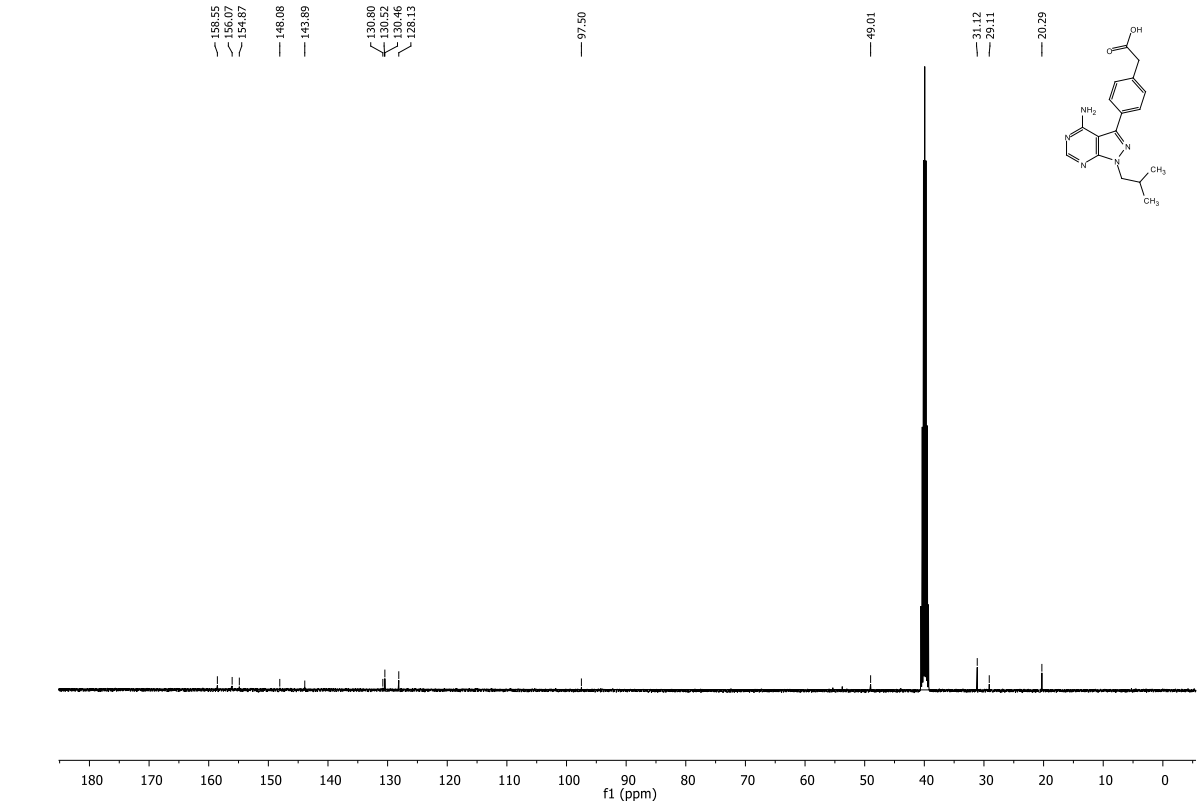



**2-(4-(4-amino-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)phenyl)acetic acid (7a)**

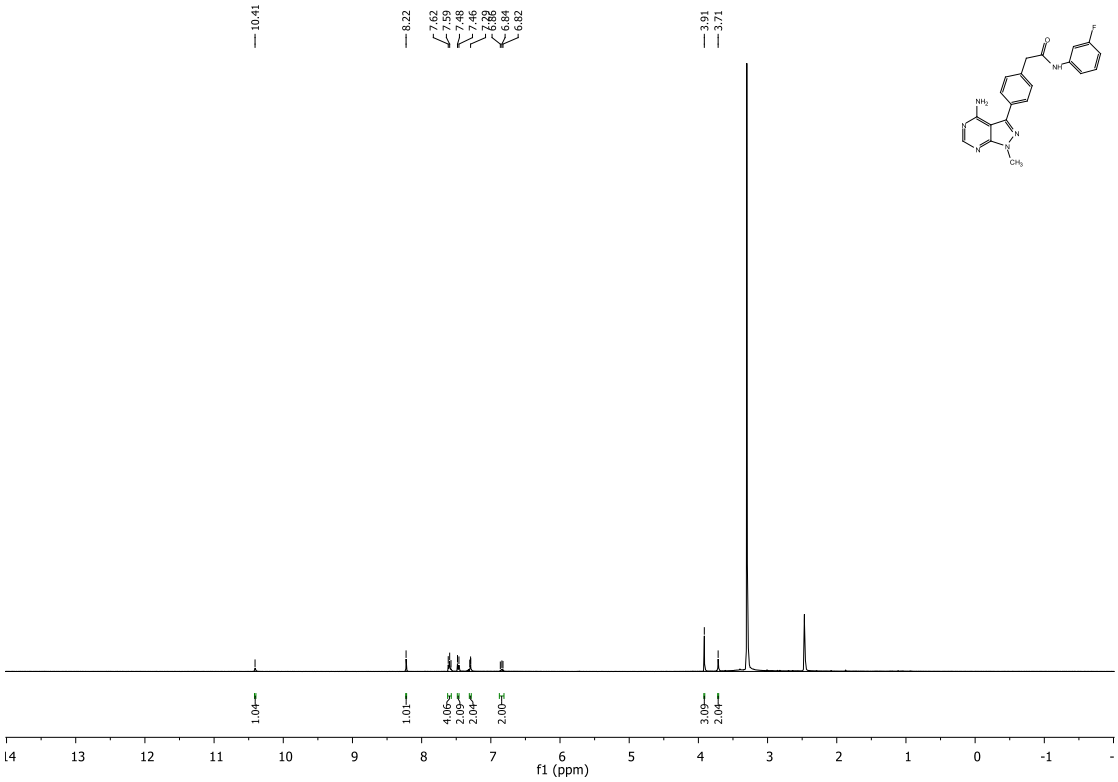


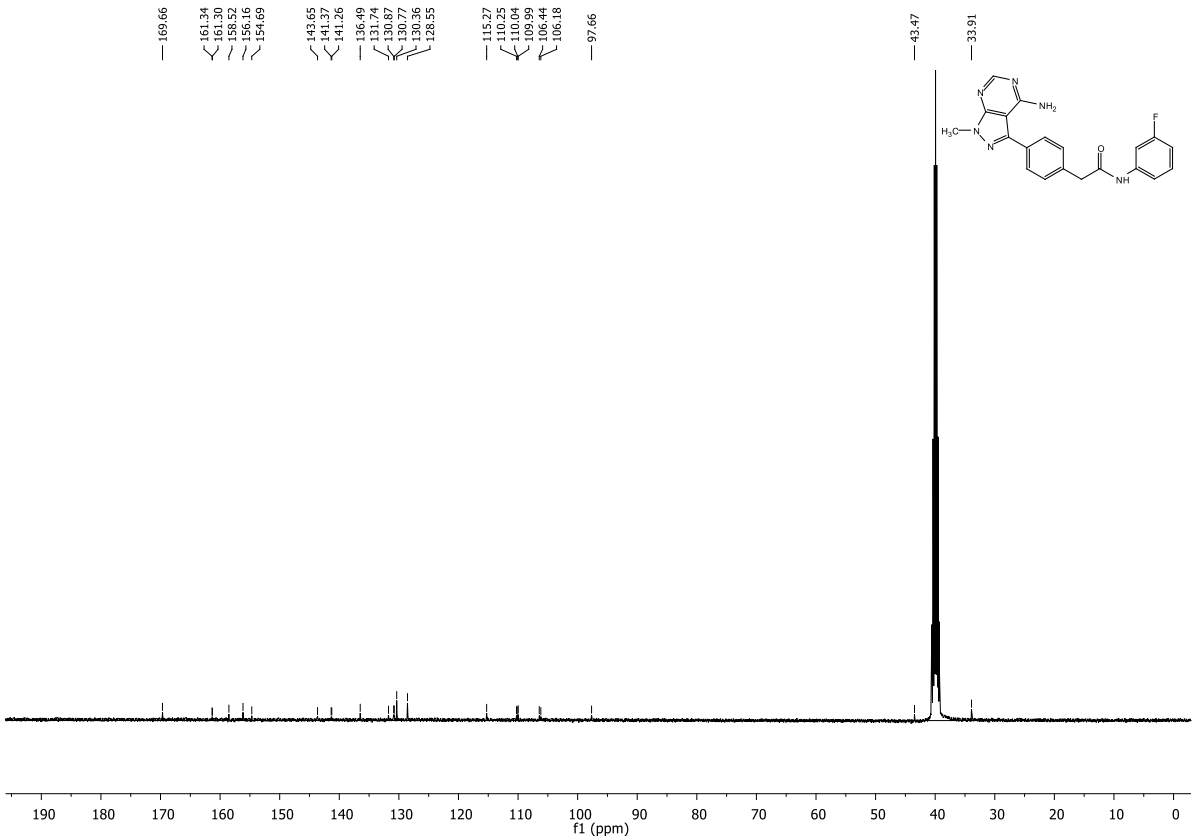
**2-(4-(4-amino-1-isobutyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)phenyl)acetic acid (7c)**



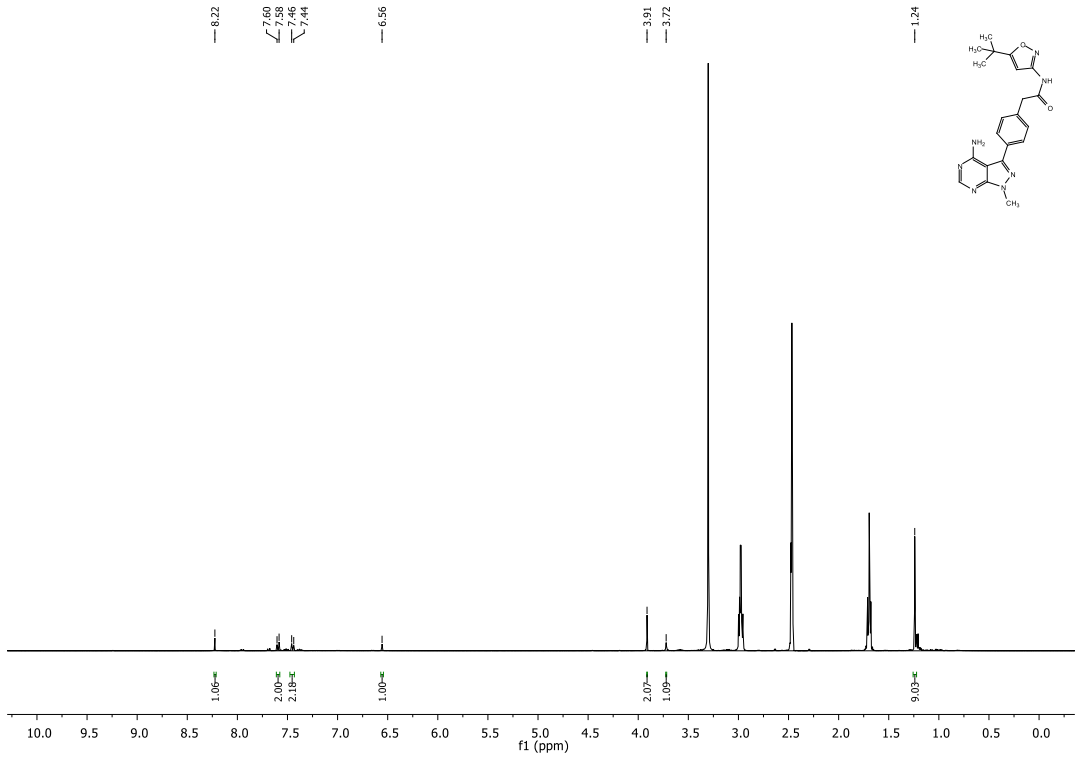



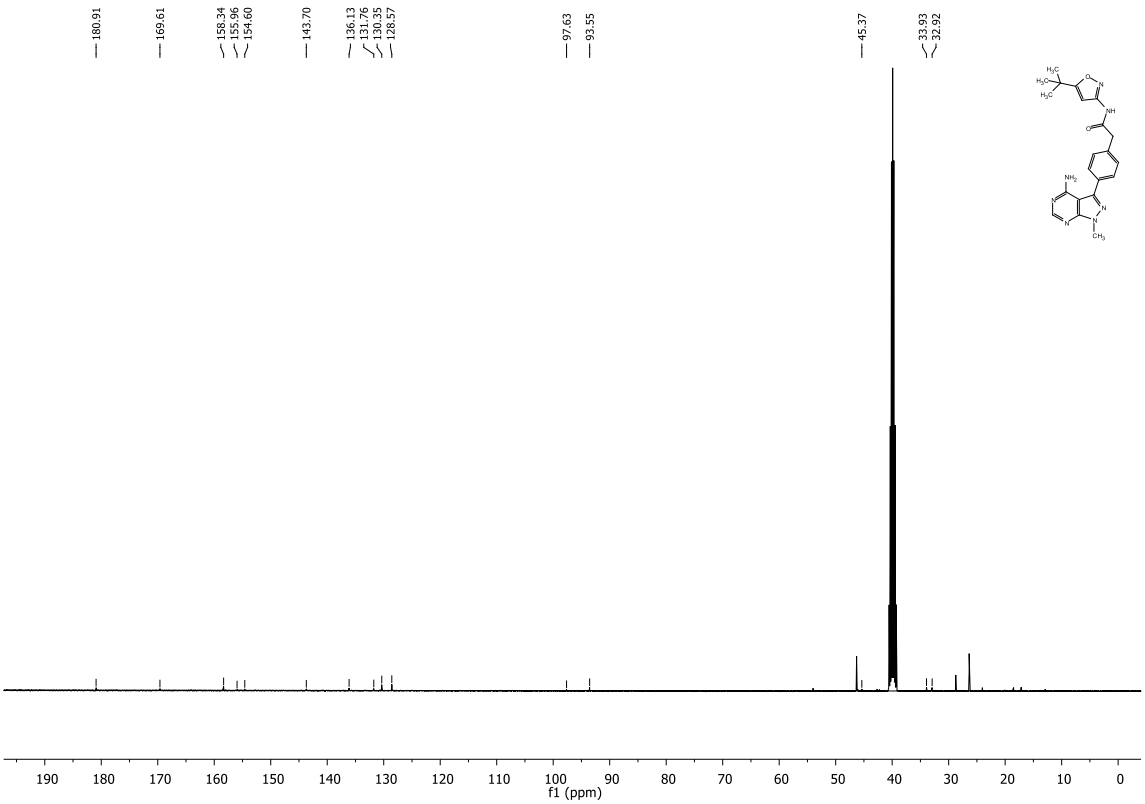
**2-(4-(4-amino-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)phenyl)-*N*-(3-fluorophenyl)acetamide (8a)**



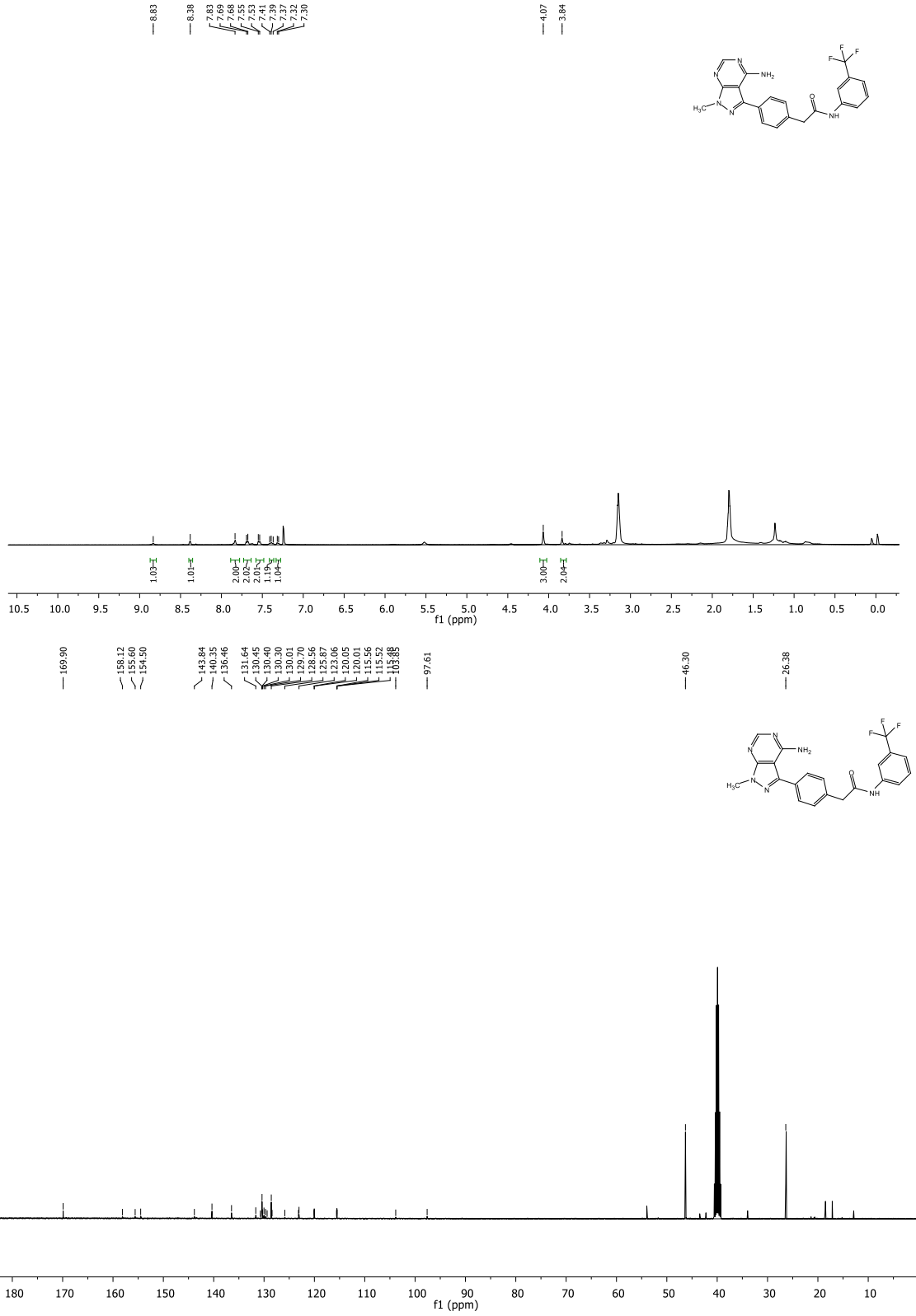



**2-(4-(4-amino-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)phenyl)-*N*-(5-(*tert*-butyl)isoxazol-3-yl)acetamide (8b)**

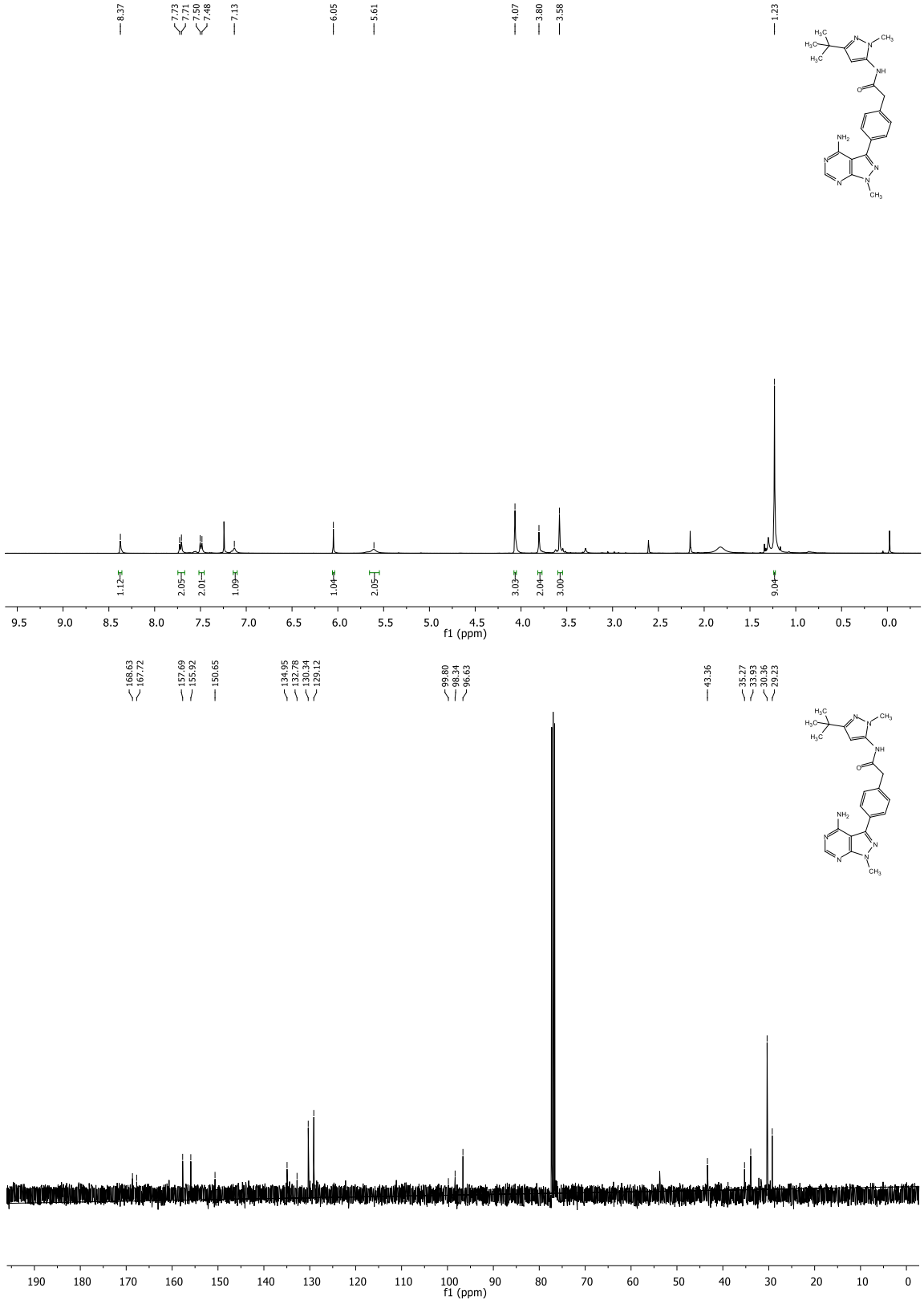



180.91
169.61
158.34
155.96
154.60
143.70
136.13
131.76
130.35
128.57
97.63
93.55
45.37
33.93
32.92
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

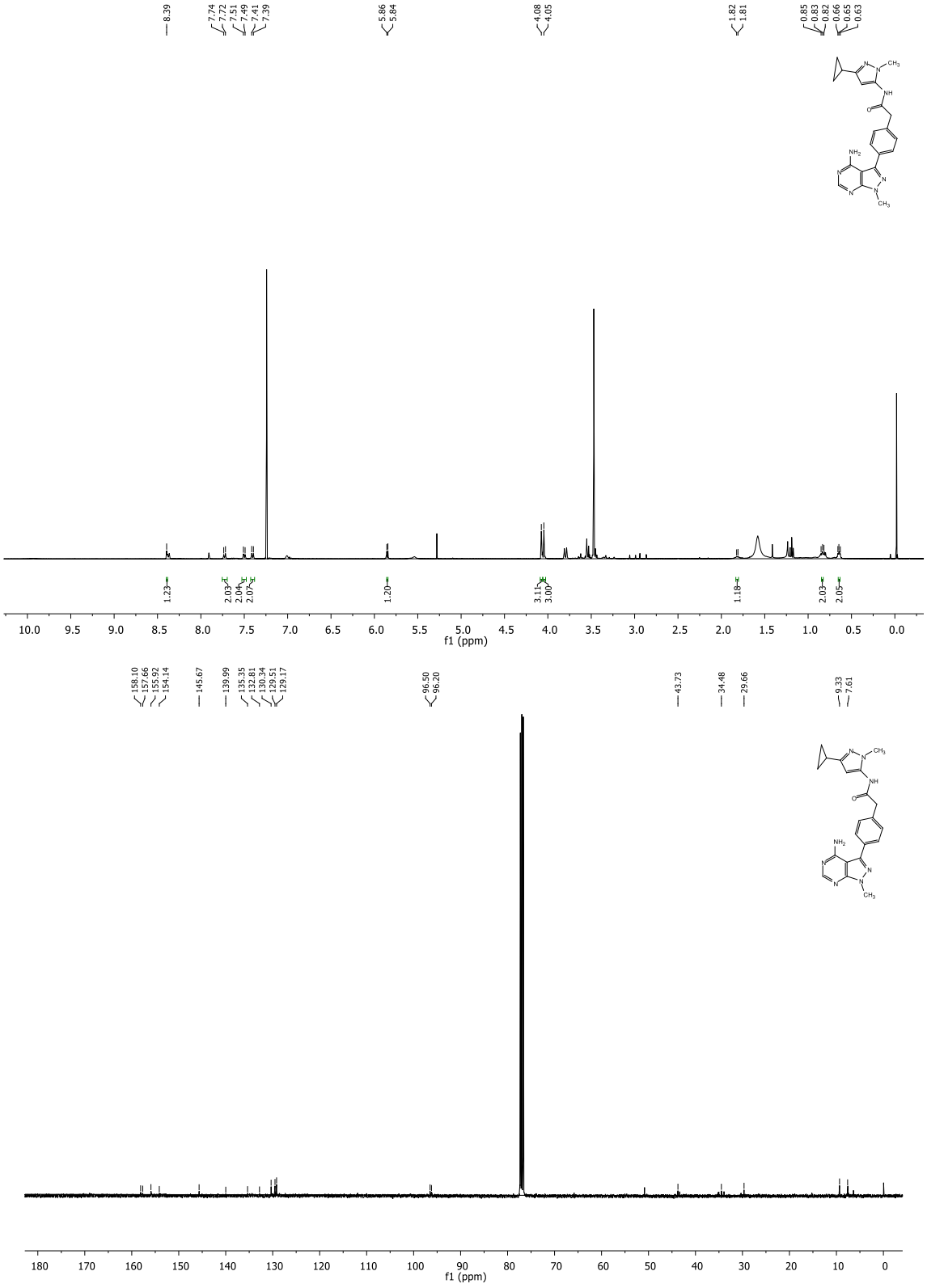
**2-(4-(4-amino-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)phenyl)-*N*-(3-(trifluoromethyl)phenyl)acetamide (8c)**



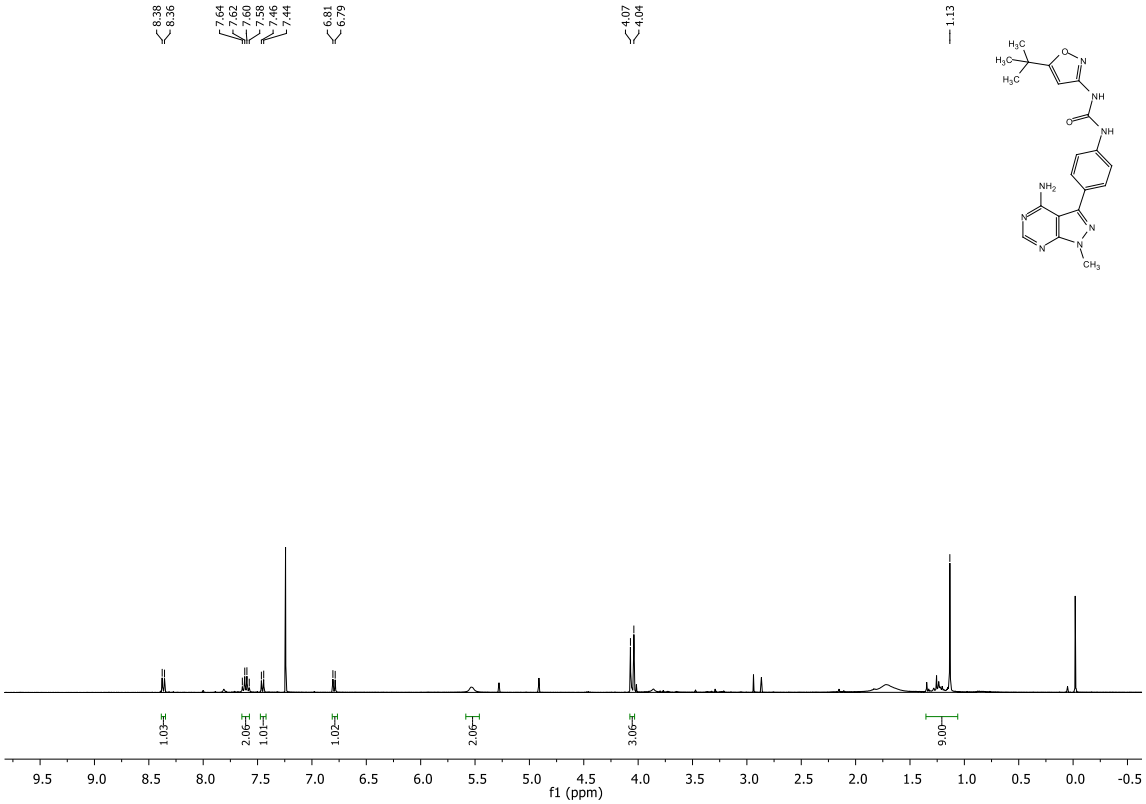
**2-(4-(4-amino-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)phenyl)-*N*-(3-(*tert*-butyl)-1-methyl-1*H*-pyrazol-5-yl)acetamide (8d)**

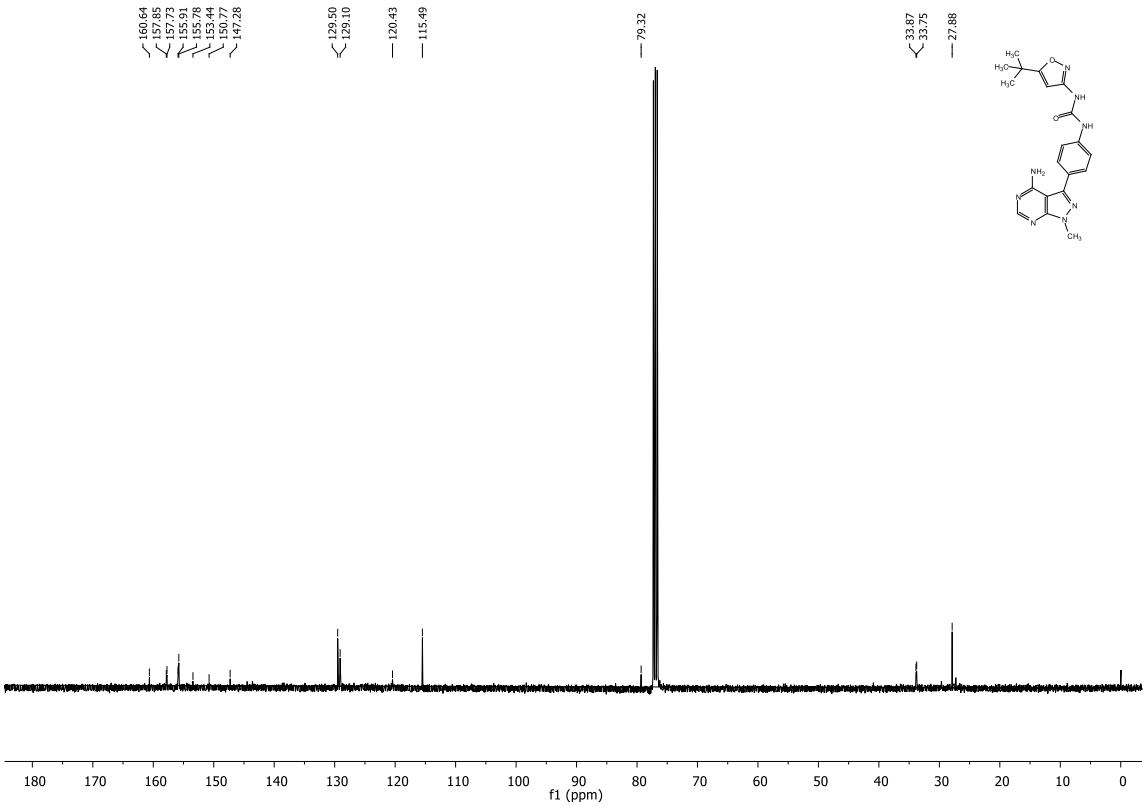


**2-(4-(4-amino-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)phenyl)-*N*-(3-cyclopropyl-1-methyl-1*H*-pyrazol-5-yl)acetamide (8e)**

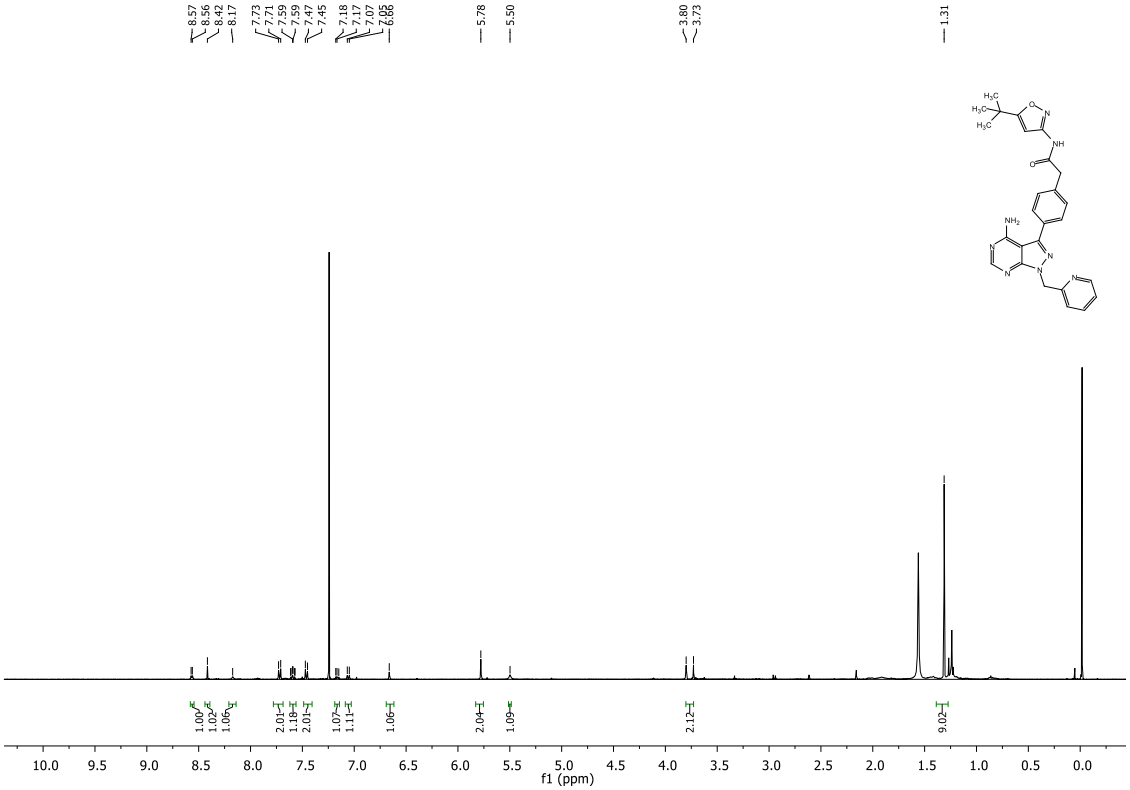


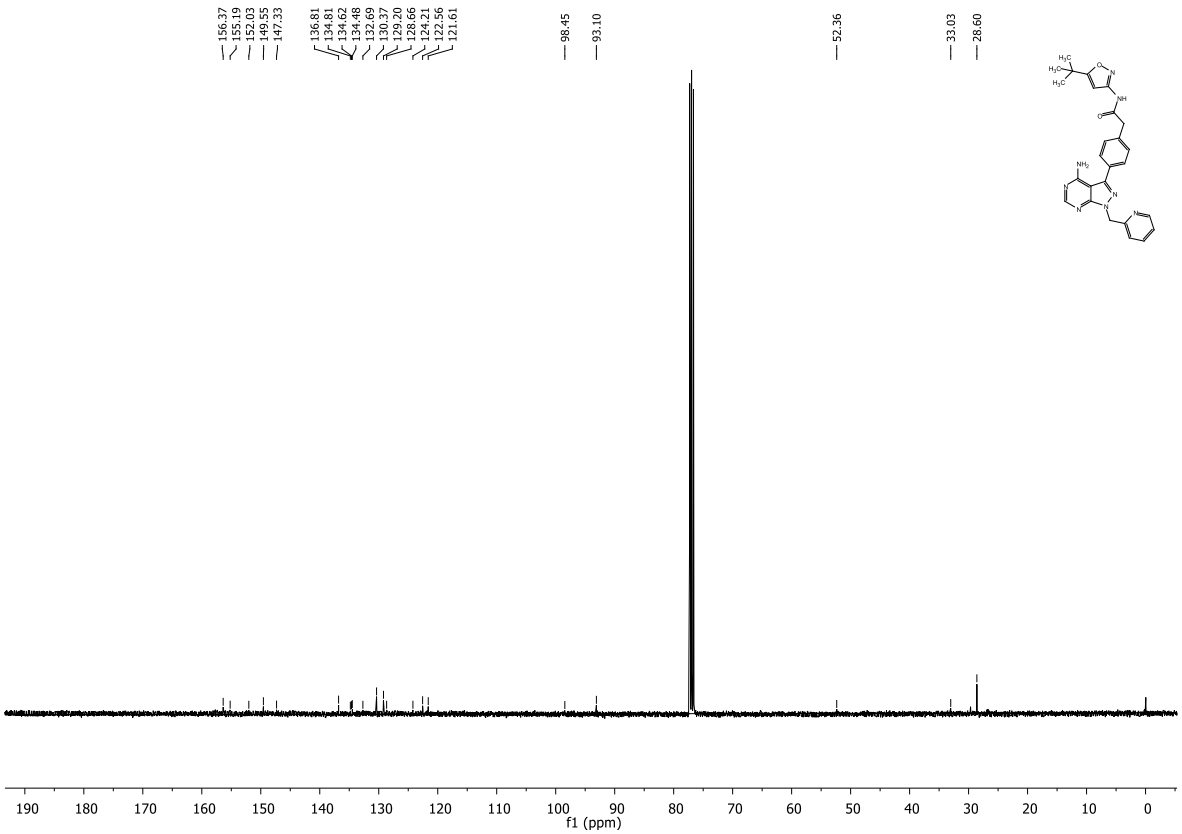
**1-(4-(4-amino-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)phenyl)-3-(5-(*tert*-butyl)isoxazol-3-yl)urea (8g)**



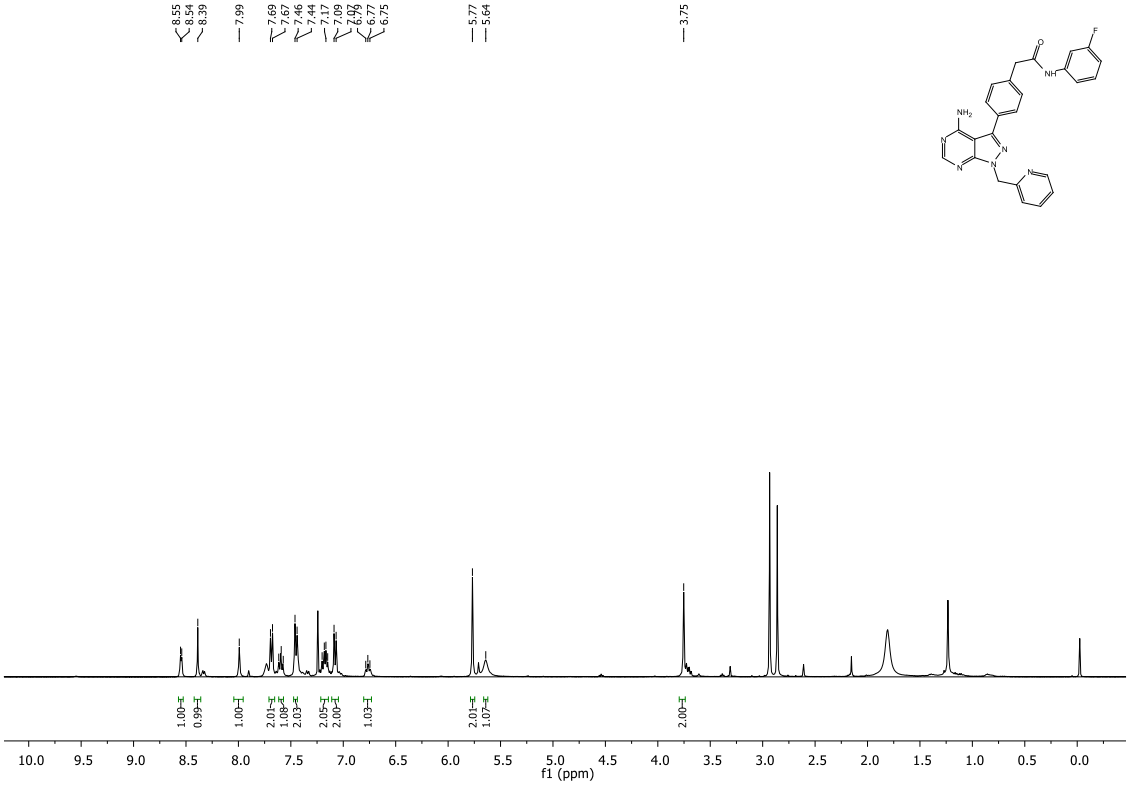



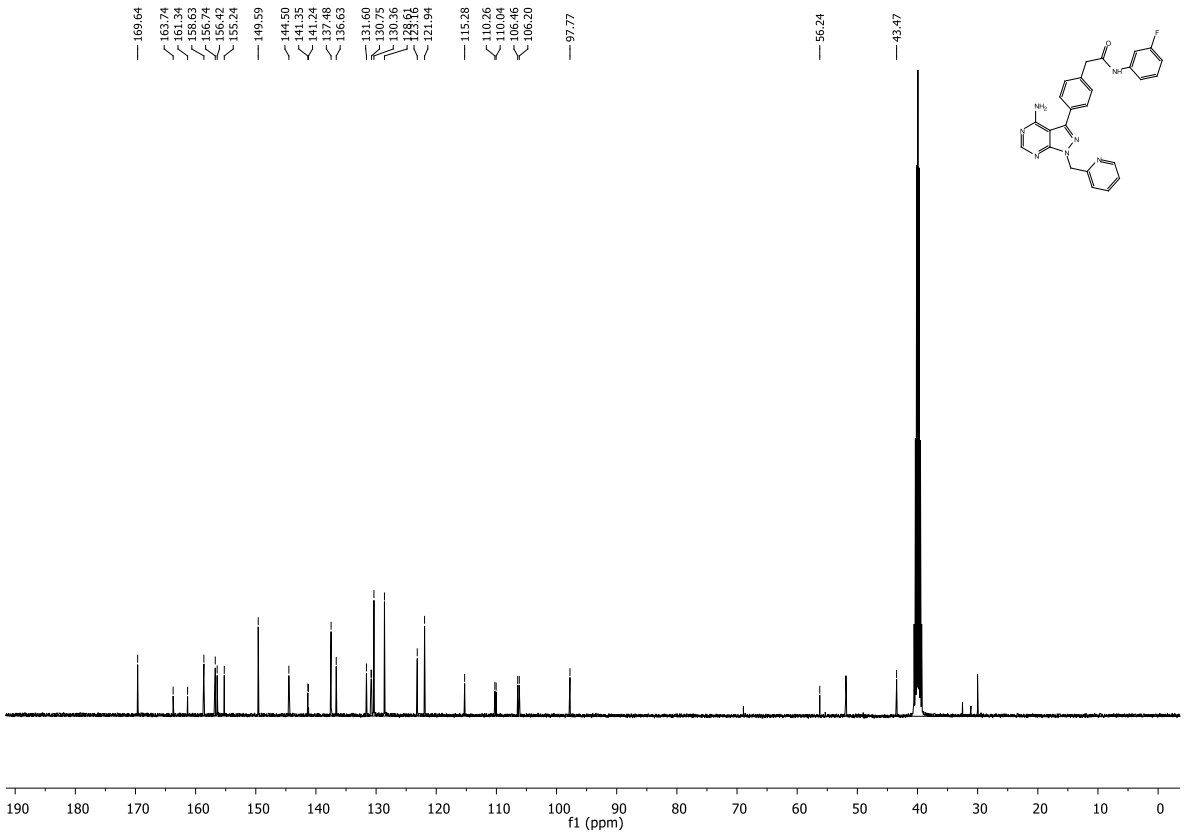
**2-(4-(4-amino-1-(pyridin-2-ylmethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)phenyl)-*N*-(5-(tert-butyl)isoxazol-3-yl)acetamide (8i)**



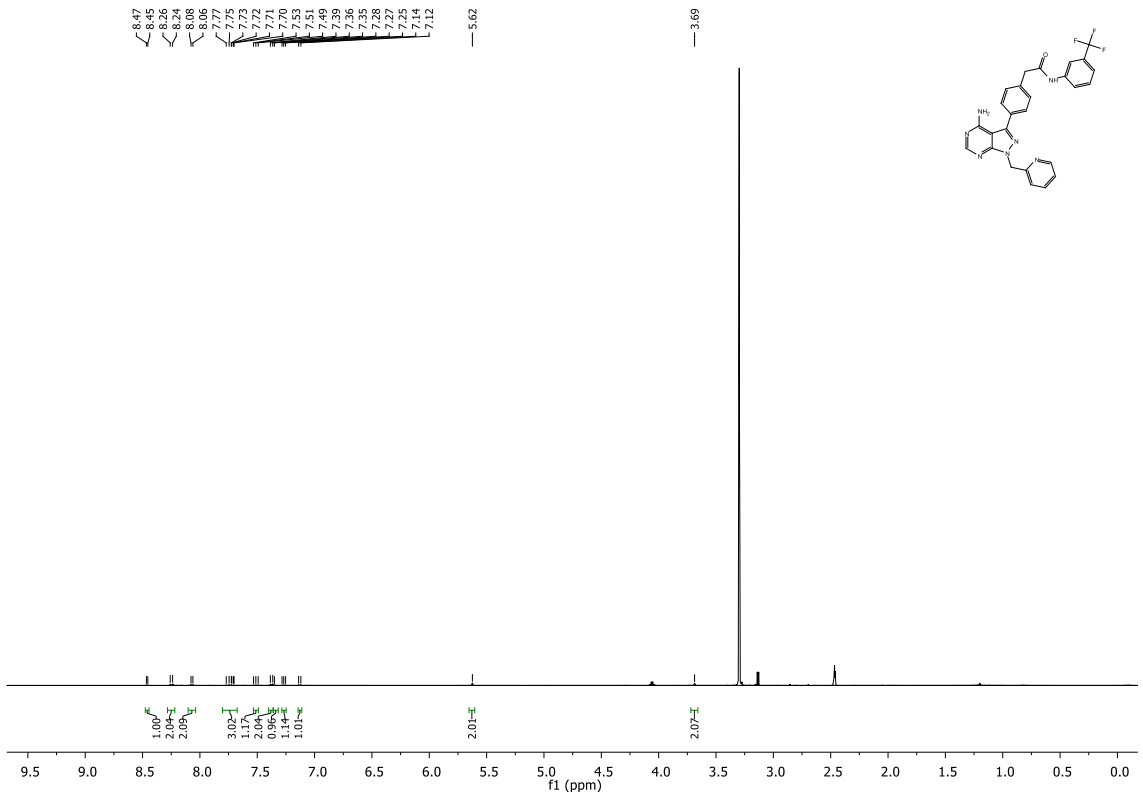


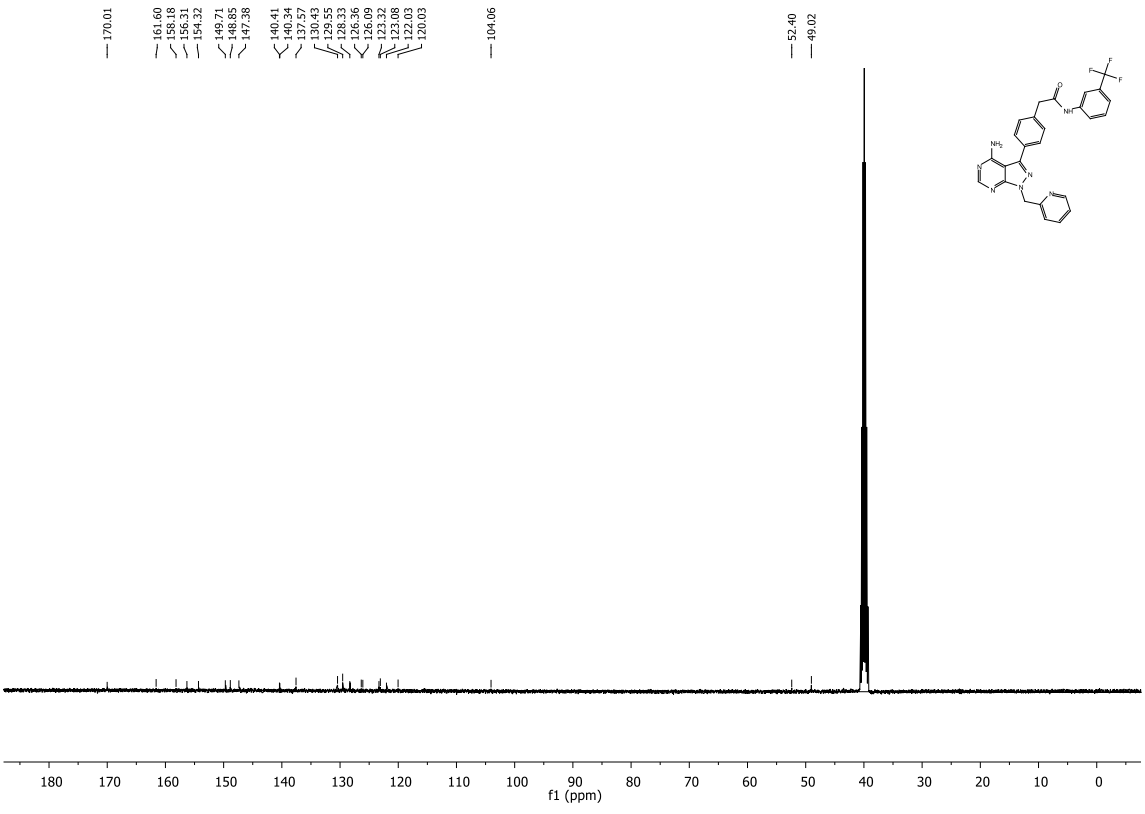

**2-(4-(4-amino-1-(pyridin-2-ylmethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)phenyl)-*N*-(3-fluorophenyl)acetamide (8j)**



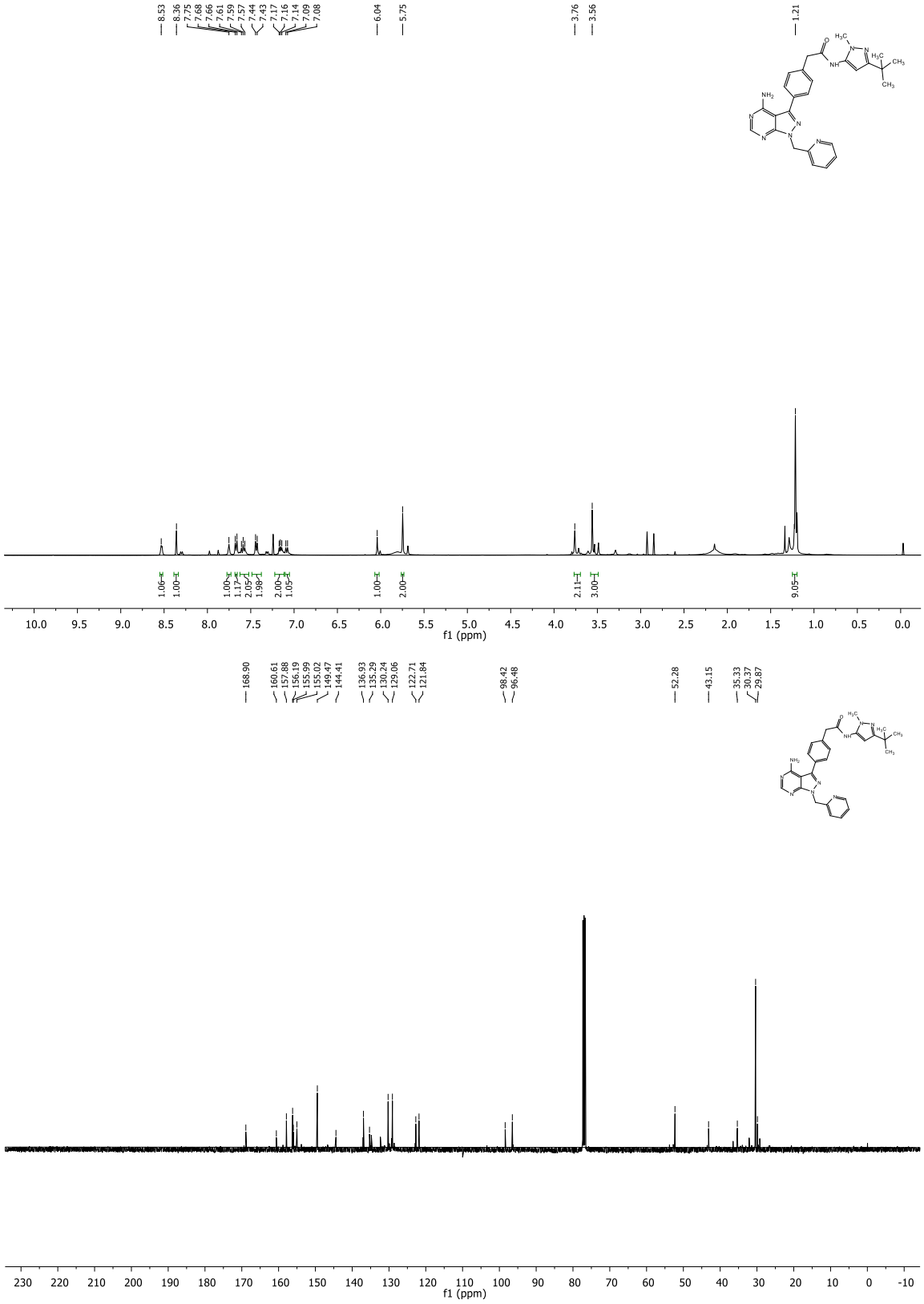



**2-(4-(4-amino-1-(pyridin-2-ylmethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)phenyl)-*N*-(3-(trifluoromethyl)phenyl)acetamide (8k)**

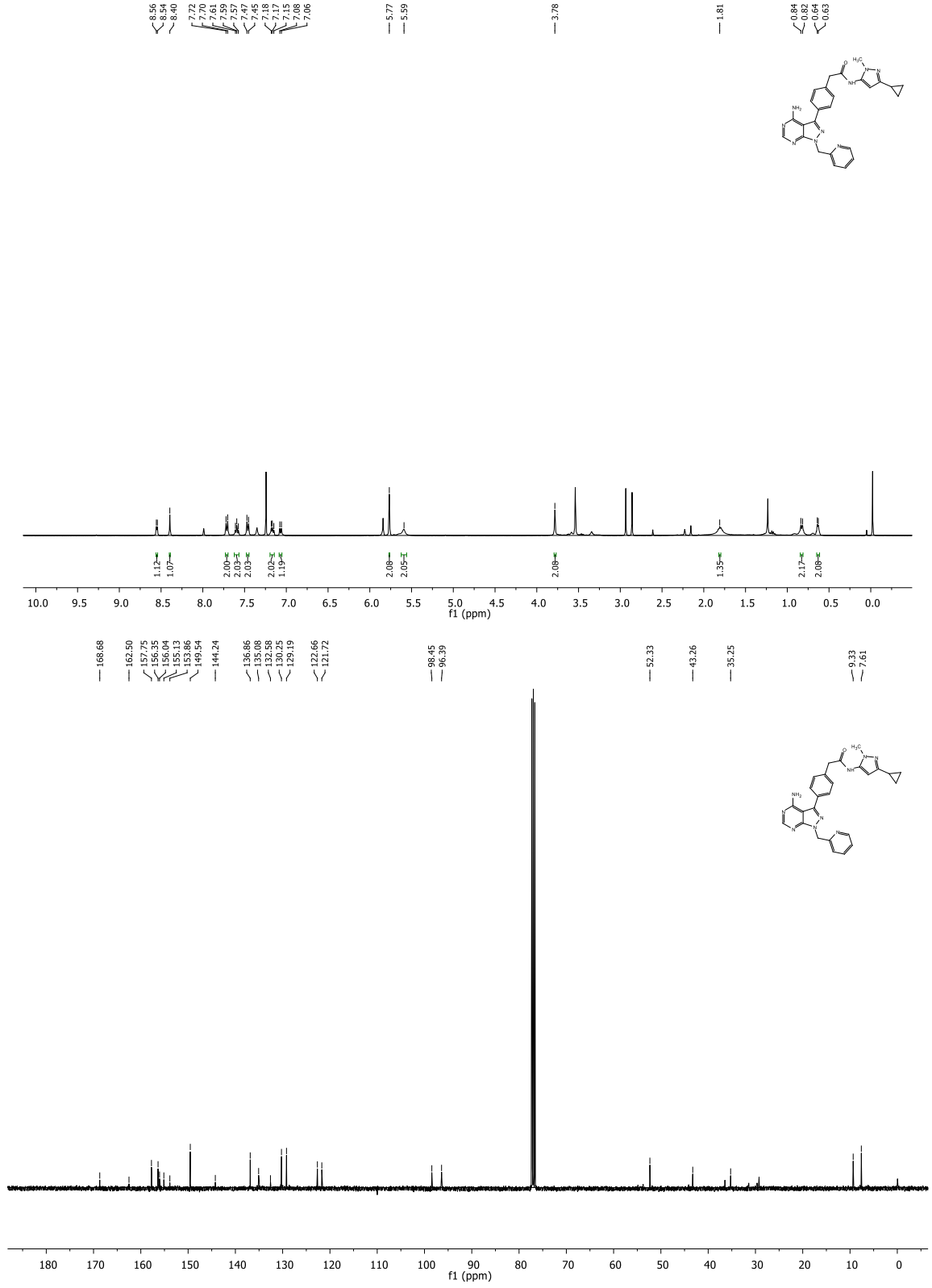

8.47
8.45
8.26
8.24
8.08
8.06
7.77
7.75
7.73
7.72
7.71
7.70
7.53
7.51
7.49
7.39
7.36
7.35
7.28
7.27
7.25
7.14
7.12
5.62
3.69
1.00
2.04
2.09
3.03
1.12
2.04
0.96
1.14
1.01
2.01
2.07
f1 (ppm)


170.01
161.60
158.18
156.31
154.32
149.71
148.85
147.38
140.41
140.24
137.57
130.43
129.55
128.33
126.36
126.09
123.32
123.08
122.03
120.03
104.06
52.40
49.02
f1 (ppm)

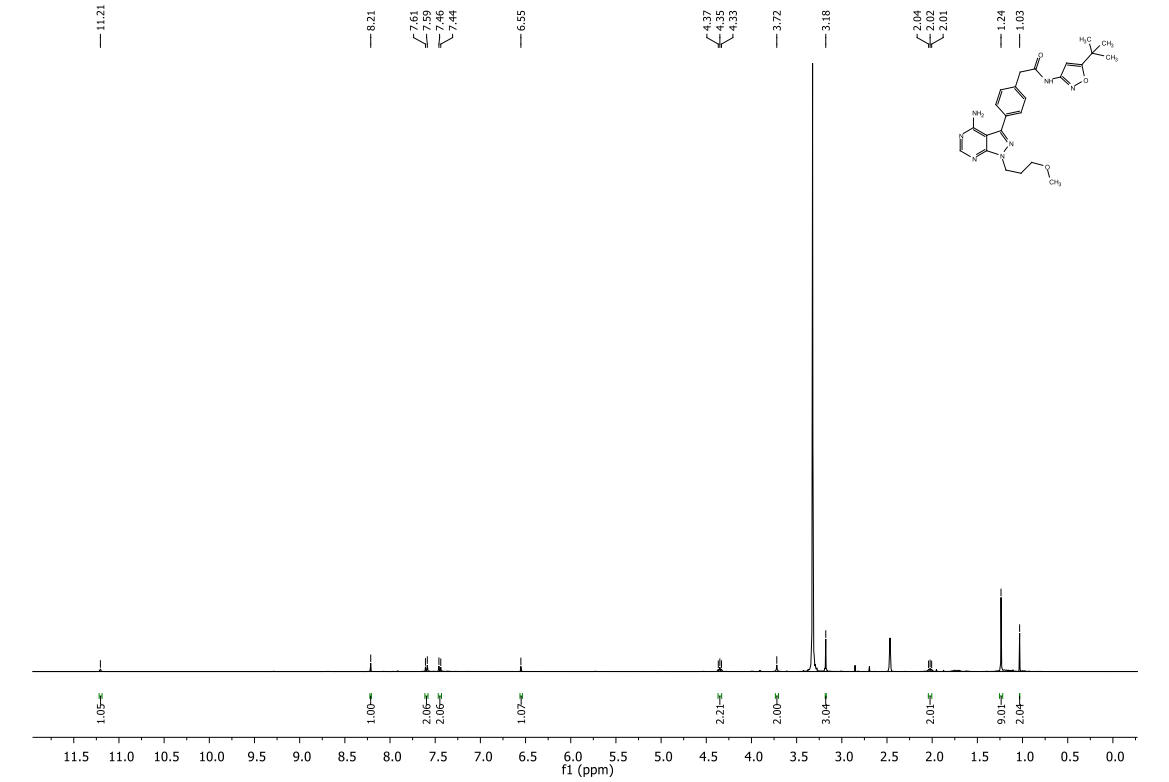
**2-(4-(4-amino-1-(pyridin-2-ylmethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)phenyl)-*N*-(3-(tert-butyl)-1-methyl-1*H*-pyrazol-5-yl)acetamide (8l)**

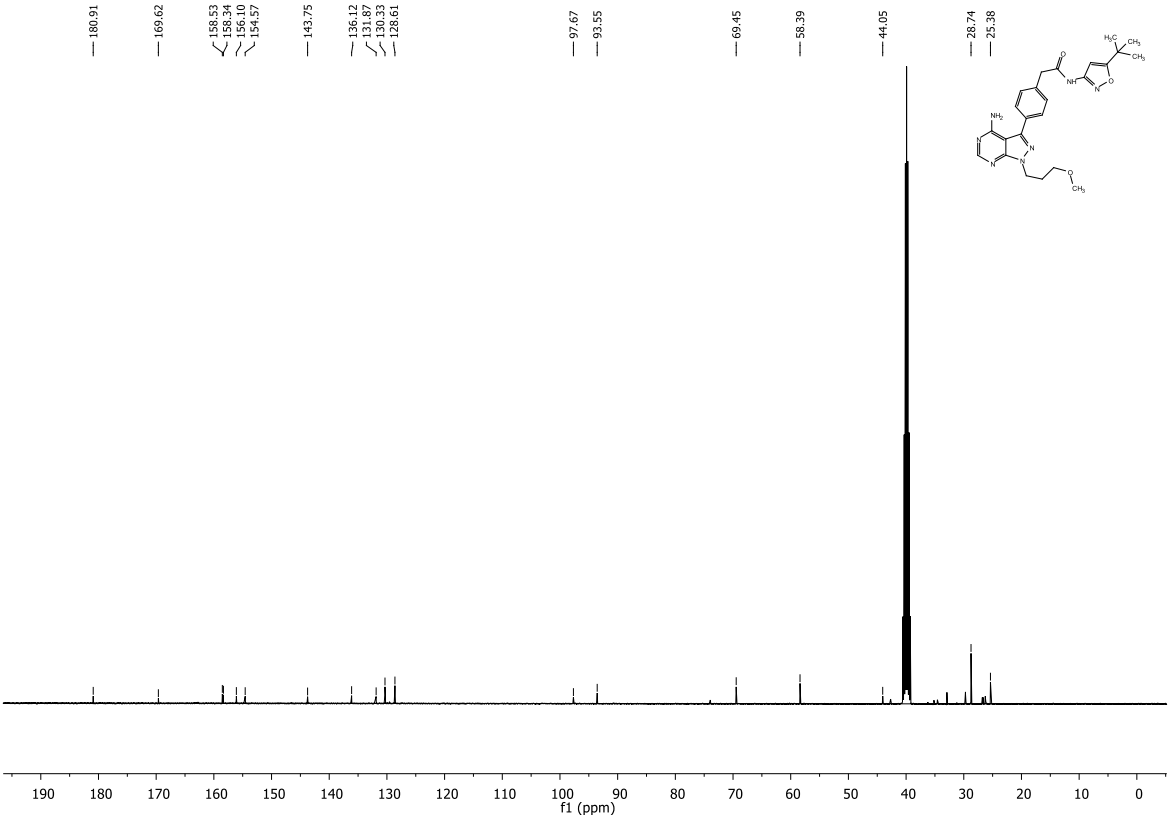


**2-(4-(4-amino-1-(pyridin-2-ylmethyl)-1*H*-pyrazolo[3,4-d]pyrimidin-3-yl)phenyl)-*N*-(3-cyclopropyl-1-methyl-1*H*-pyrazol-5-yl)acetamide (8m)**

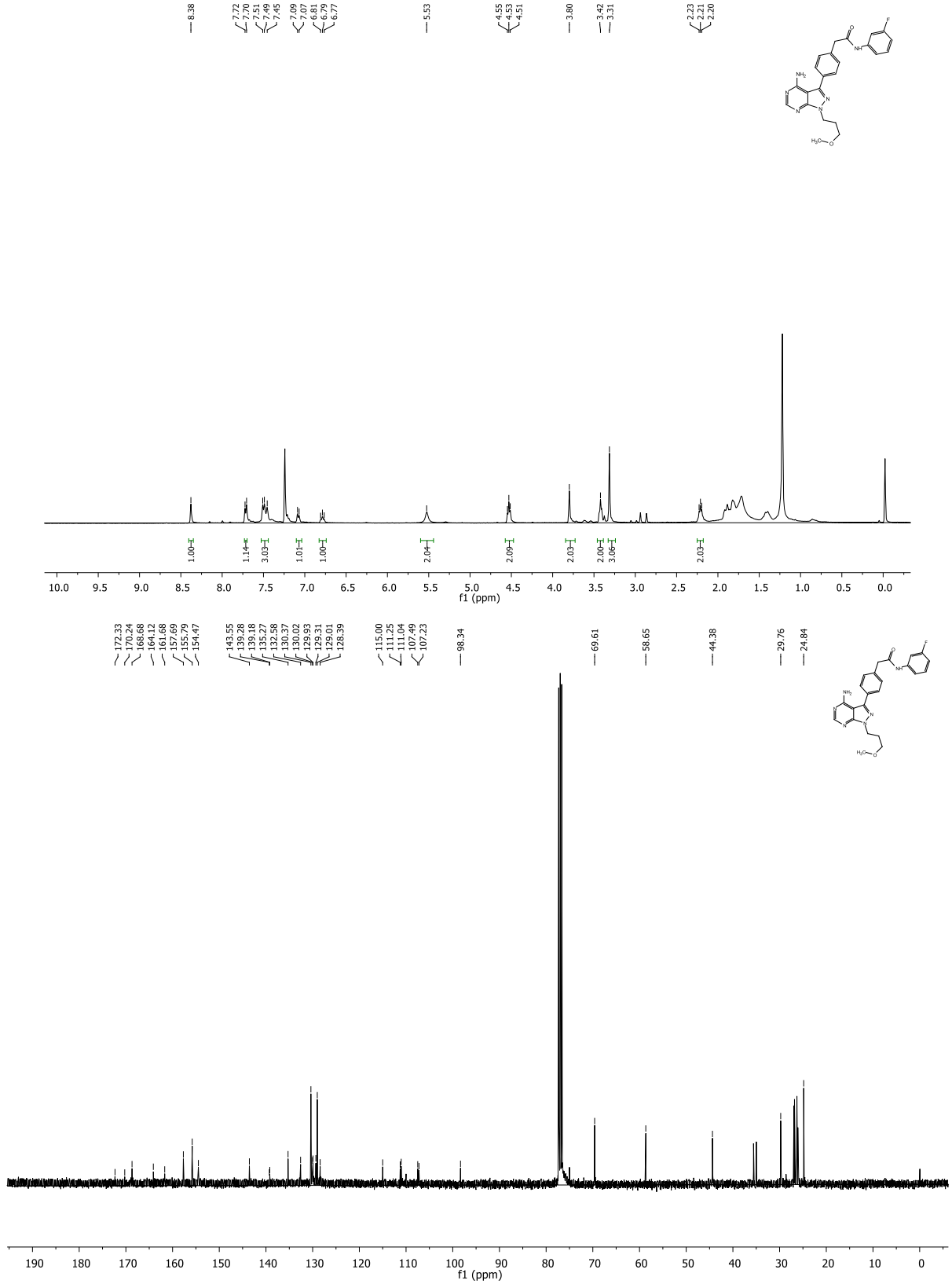


**2-(4-(4-amino-1-(3-methoxypropyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)phenyl)-*N*-(5-(tert-butyl)isoxazol-3-yl)acetamide (8p)**

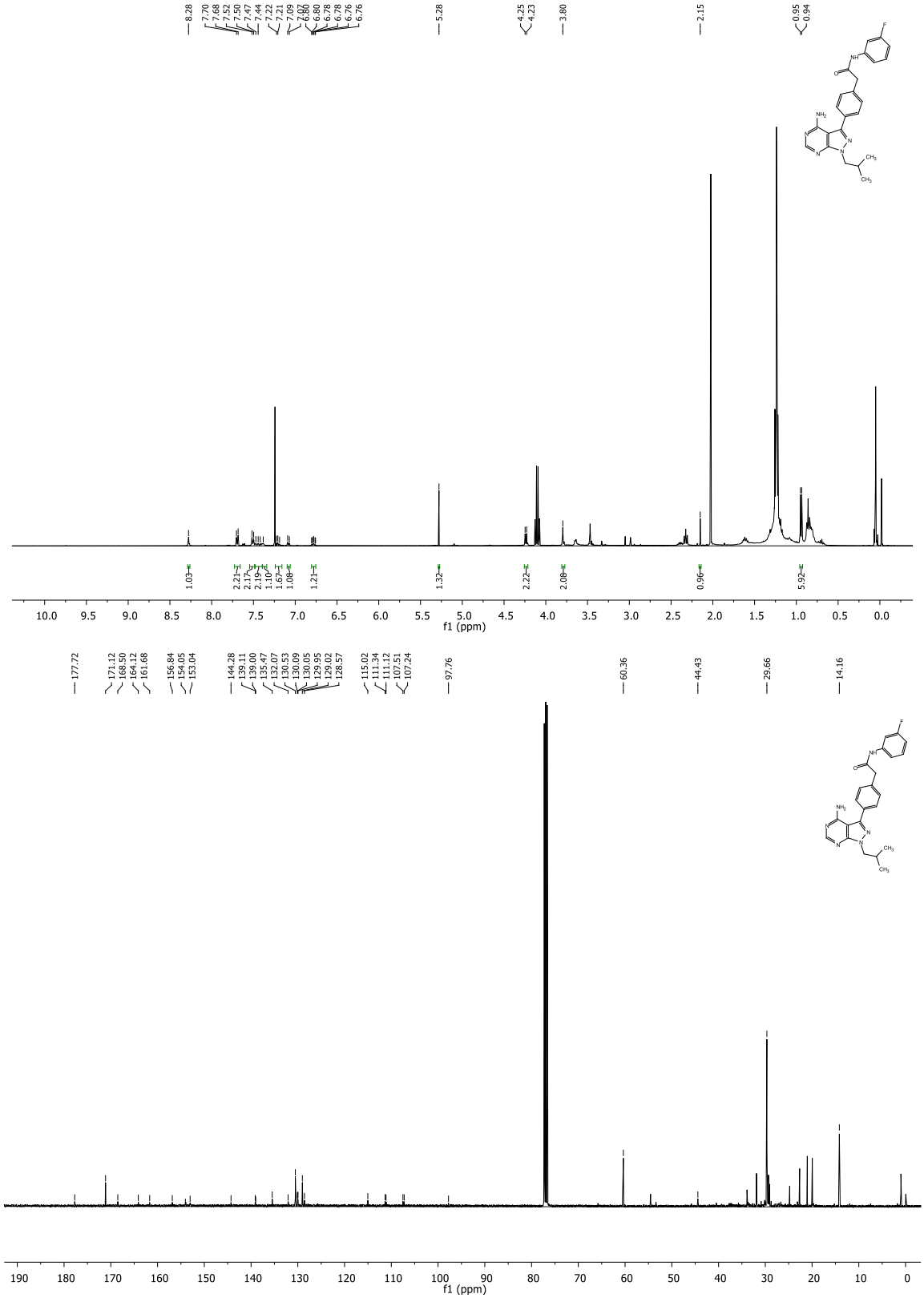


**2-(4-(4-amino-1-(3-methoxypropyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)phenyl)-*N*-(3-fluorophenyl)acetamide (8q)**



**2-(4-(4-amino-1-isobutyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)phenyl)-*N*-(3-fluorophenyl)acetamide (8r)**



**6. Cellular Assay Procedure**

**Cell Culture.** A549 (CCL-185, ATCC), KM12 (JCRB1389, JCRB cell bank) and LC-2/ad (94072247, Millipore Sigma) cell lines were grown in RPMI 1640 GlutaMAX medium (ThermoFisher Scientific, USA) containing 10% heat-inactivated fetal calf serum (Hyclone Laboratories, Utah, USA) in a humidified incubator (37 $^{o}$C, 5% $CO_2$).

**Cell viability assay.** Cell lines were seeded at $5x10^3$ cells/well and treated with either DMSO or compounds (all compounds were reconstituted in DMSO) (full concentration range used 0.001-100 uM, depending on inhibitor and cell line) for 72 h at 37 $^{o}$C. Cell viability was analyzed by performing a CCK8 assays following manufacturer's instructions (Dojindo Inc.). For each assay cells were plated in duplicate/per condition and at least n=3 assays were performed. $EC_{50}$ was generated using nonlinear regression (curve fit) with Log(inhibitor) vs. normalized response with variable slope and interpolation of unknown values on X= log(X) transformed data. Mean $EC_{50}$ was generated from at least n=3 repeats.

**7. Enzymatic Assay Procedure**

Kinase activity was measured by a microfluidic assay that monitors the separation of the phosphorylated product from substrate. The assay was run using a 12-sipper chip on a Caliper EZ Reader II (PerkinElmer®, Walthman, USA) with separation buffer (100 mM HEPES, 10 mM EDTA, 0.015% Brij-35, 0.1% CR-3 PerkinElmer®). In 96-well polypropylene plates (Greiner, Frickenhausen, Germany), compound stocks (20 mM in DMSO) were diluted into kinase buffer (50 mM HEPES, 0.075% Brij-35, 0.1 % Tween 20, 2 mM DTT, 10 mM MgCl2, and 0.02% $NaN_3$) in 12-point ½log dilutions (2 mM–6.32 nM). After, 1 µL was transferred into a 384-well polypropylene assay plate (Greiner). The enzymes (RET, TRKA) (Invitrogen™, Grand Island, USA) were diluted in kinase buffer to a concentration of 2 nM and 5 $\mu$L of the enzyme mixture was transferred to the assay plate. Kinases were pre-incubated with the compound or DMSO control for 60 minutes. A substrate mix was prepared containing ATP (Ambresco®, Solon, USA) and substrate peptide dissolved in kinase buffer, and 5 µL of the substrate mix was added to the assay plate. Running concentrations were as follows: ATP (190 µM), peptide (1.5 µM), compound 12-point ½log dilutions (0.2 mM–0.632 nM). For positive control, no inhibitor was added. For negative control, no enzyme was added. The plate was run until 10-20% conversion, based on the

positive control wells. The following separation conditions were utilized: upstream voltage – 500 V; downstream voltage, -1900 V; chip pressure -0.8. Percent inhibition was measured for each well comparing starting peptide to phosphorylated product peaks relative to the baseline. Dose response curves, spanning the $IC_{50}$ dose, were generated in GraphPad Prism® 7 and fit to an exponential one-phase decay line; $IC_{50}$ values were obtained from the half-life value of the curve. $IC_{50}$ values were generated in triplicate.

**8. Molecular Modelling Procedure**

Molecular docking studies were performed to determine the binding pose and interactions of the ligands in the RET kinase. An RET DFG *'out'* homology model was generated with the VEGFR2 crystal structure (PDB ID: 2OH4) as previously described.[37] Protein preparation and ligand preparation were performed using the Maestro 2018-4 suite obtained with an academic license. Docking studies were performed using Autodock Vina. A grid was defined to include the residues of the hinge region, $\alpha$C-helix, DFG motif, and the P-loop. The designed ligands were docked into this grid box to identify the best binding poses. The results obtained were visualized using Maestro 2018-4 suite.