Supporting Information

3-Aryl-1,2,4-Oxadiazole Derivatives Active Against Human Rhinovirus

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1. Experimental Procedures for Biological Assays

Cells, Viruses, and Chemicals

H1HeLa cells (ATCC CRL-1958) were purchased from ATCC and cultured in Minimum Essential Medium (MEM) supplemented with 10% fetal bovine serum (Hyclone). Human rhinovirus type 14 (ATCC VR-284), type 21 (ATCC VR-496) and type 71 (ATCC VR-1181) were obtained from ATCC and expanded in H1HeLa cells. Virus titers were measured using end-point dilution assay. Pleconaril (Sigma SML-0307) was purchased and dissolved in DMSO used as control compounds.

Antiviral Assay

To test the antiviral activity of the compounds on human rhinoviruses, a cytopathic effect (CPE) reduction assay was performed using 3-(4,5-dimethylthiazol-2yl)-2,5-diphenyltetrazolium bromide (MTT; Sigma) as previously described (Kang, H.; Kim, C.; Kim, D.-e.; Song, J.-H.; Choi, M.; Choi, K.; Kang, M.; Lee, K.; Kim, H. S.; Shin, J. S.; Kim, J.; Han, S.-B.; Lee, M.-Y.; Lee, S. U.; Lee, C.-K.; Kim, M.; Ko, H.-J.; van Kuppeveld, F. J. M.; Cho, S. Synergistic antiviral activity of gemcitabine and ribavirin against enteroviruses. *Antiviral Res.* **2015**, *124*, 1-10). H1HeLa cells were plated in 96-well plates 1 d before the assays were performed. Equal volumes of virus and compounds were added and incubated at 33 ºC for 3 d in CO_2 incubator. After removing the cell culture supernatant, MTT solution was added and the resulting mixture was incubated for 1 h at 33 ºC. Formazan products were dissolved using organic solvent and absorbance at 540 nm (main) and at 690 nm (reference) were measured using a microplate reader (Synergy H1, Biotek). Wells without viral infection and chemical treatment were considered as having a 100% survival rate and wells only infected with virus were considered as having a 0% survival rate. The 50% cytotoxic concentration (CC_{50}) and 50% effective concentration (EC_{50}) of the compound were calculated based on the survival rates of wells treated with compounds

CYP450 Assay

Luminogenic hCYP450 inhibition assay was carried out using P450-Glo Screening system from Promega (Promega Inc., Madison, WI, USA) according to the manufacturer's instructions. Appropriate luminogenic substrates of CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 were incubated with test compound (10 μM) under the NADPH regeneration system with respective recombinant CYP enzyme for 20 min at 37ºC (Shake incubation, 350-360 rpm). After incubation, luciferin detection reagent (50 μL) was added to the plate and stored for 20 min in the dark to initiate a luminescent reaction. Then, luminescence signal was read using Infinite M1000 PRO (Tecan, Switzerland) and the data was expressed as percentage inhibition of signals compared to vehicle control.

Compd.	1A2	2C9	2C19	2D6	3A4
2d	16.29	65.9	71.8	6.24	30.45
3j	89.24	53.4	76.6	2.80	1.32
3k	82.21	<1	65.02	9.50	9.40
3l	28.72	67.5	65.5	4.42	2.37
Inhibitor[a]	99.4	95.9	93.8	97.8	99.2

Table S1. Human CYP isozyme inhibition of selected compounds. Percent inhibition of human CYP isozymes at 10 μM concentration. [a]1A2: α-naphthoflavone (10 μM), 2C9: sulfaphenazole (10 μM), 2C19: amitriptyline (100 μM), 2D6: quinidine (10 μM), 3A4: ketoconazole (10 μM).

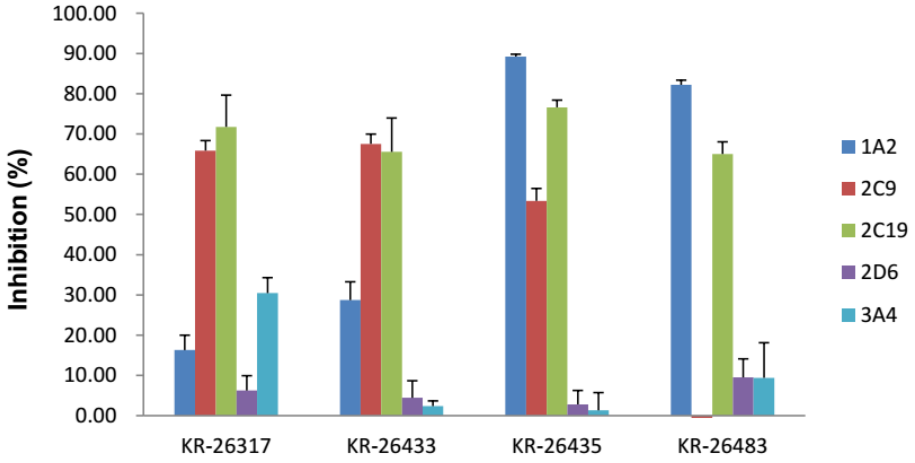


Figure S1. Percent Inhibition of human CYP isozymes at 10 μM.
KR-26317: **2d**, KR-26433: **3l**, KR-26435: **3j**, KR-26483: **3k**.

In vitro Metabolic Stability Assay

NADPH-dependent oxidative metabolism of the test compounds in human and rat liver microsomes was evaluated. Pooled liver microsomes were purchased from Corning Gentest (Tewksbury, MA, USA). The reaction mixture was composed of liver microsomes (0.5 mg protein/mL) in 100 mM PBS (pH 7.4) and the final concentration of a test compound was 1 μM. The metabolic reaction was initiated by the addition of NADPH-regenerating solution, containing 1.3 mM $NADP^+$, 3.3 mM glucose-6-phosphate, 0.4 U/mL glucose-6-phosphate dehydrogenase, and 3.3 mM $MgCl_2$. After the 30 min incubation of sample at 30 °C with mild shaking, the reaction was stopped by the addition of ice-cold acetonitrile containing an internal standard (5 ng/mL disopyramide) for quantification. Subsequently, the samples were then centrifuged at 13000 g for 10 min and supernatant was stored at -20 °C until the analysis. The concentrations of test compounds were determined by LC/MS/MS on an Agilent 1200 HPLC system coupled to an Agilent 6460 triple quadrupole mass spectrometer equipped

with ESI source (Agilent, Santa Clara, CA, USA). The peak areas for all components were automatically integrated using Agilent 6460 Quantitative Analysis processing software.

In vivo Rat Pharmacokinetic Study

In vivo Pharmacokinetics of compounds was examined in male Sprague Dawley rats (6-7 weeks, 250-280 g, OrientBio, Kyunggi-do, South Korea). Rats were anesthetized with zoletil at 10 mg/kg (Virbac S.A., Carros, France) and xylazine at 5 mg/kg (Bayer Korea, Seoul, Korea) via intramuscular injection and subjected to catheter surgery of the femoral vein. Then, the test compound was administered intravenously or orally. Dosing vehicles were composed of 5% DMSO and 40% PEG400 in water and dosing volume was 2 mL/kg. Blood samples were collected at different time points (n = 3 rats per time point) from the femoral vein. After centrifugation (13000 g, 3 min, 37 °C, the plasma samples were obtained and were stored at -20 °C until the analysis. The sample analysis was performed by LC/MS/MS as described in the above section. Pharmacokinetic and statistical analyses of plasma concentrations and statistical analysis of pharmacokinetic parameters were performed using non-compartmental analysis with Phoenix WinNonlin (v6.4; Pharsight Corp., Mountain View, CA, USA). The area under the plasma concentration-time curve from time 0 to infinity (AUC_{inf}) was calculated by the trapezoidal rule with extrapolation to time infinity. The terminal $T_{1/2}$ was calculated as $\ln 2/\lambda_z$, where λ_z was the first-order rate constant associated with the terminal (log-linear) portion of the curve. Plasma clearance (CL) was calculated as dose/AUC_{inf}. The C_{max} and the time when it occurred (T_{max}) were obtained by visual inspection of the plasma concentration-time curve. The apparent volume of distribution at steady-state (Vd_{ss}) was calculated by $CL \times MRT_{inf}$ where MRT is the mean residence time extrapolated to infinity calculated as $AUMC_{inf}/AUC_{inf}$, where $AUMC_{inf}$ is the area under the first moment curve extrapolated to infinity. The bioavailability (F) was calculated as $(AUC_{non\text{-}intravenous} \times dose_{i.v.})/(AUC_{i.v} \times dose_{non\text{-}intravenous})$.

Time (hr)	#1	#2	#3	Mean	S.D.
0.033	17268	14521	18169	16653	1900
0.167	12662	12310	14418	13130	1129
0.5	6822	8475	8444	7914	945
1	5571	5113	5879	5521	385
2	4023	4100	3898	4007	102
4	2047	2538	2774	2453	371
6	1112	1234	895	1080	172
8	432	744	619	598	157
24	49.1	87.3	88.7	75.0	22.4

Table S2. Plasma concentrations of **3k** after intravenous administration in male rats.

Time (hr)	1	2	3	Mean	S.D.
0.25	934	824	878	879	55
0.5	1153	1710	1262	1375	295
1	3201	2594	1602	2466	807
2	6603	2598	1881	3694	2545
4	2203	1270	2402	1958	604
6	1052	557	962	857	264
8	420	285	459	388	91
24	21.3	13.40	9.72	14.8	5.92

Table S3. Plasma concentrations of **3k** after oral administration in male rats.

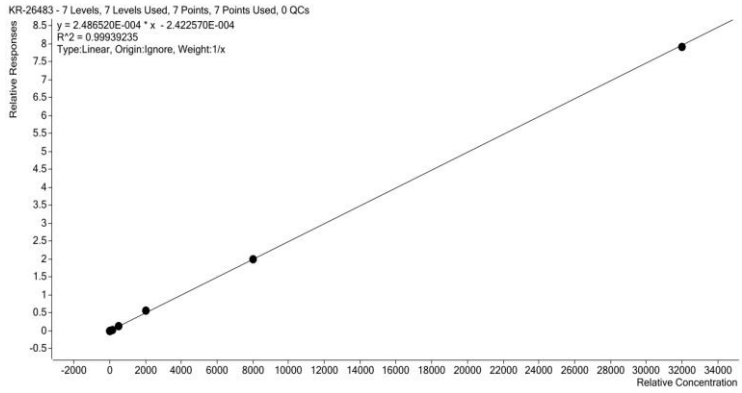


Figure S2. Calibration curve of **3k**.

Subject	T_{max} (h)	C_{max} (μg/mL)	$T_{1/2}$ (h)	AUC_t (μg·h/mL)	AUC_∞ (μg·h/mL)	CL (L/h/kg)	Vss (L/kg)
1	NA	NA	3.35	28.4	28.6	0.175	0.583
2	NA	NA	4.87	32.8	33.4	0.150	0.640
3	NA	NA	5.52	32.6	33.3	0.150	0.612
Mean	NA	NA	4.58	31.2	31.8	0.158	0.611
SD	NA	NA	1.12	2.50	2.75	0.014	0.029

Table S4. Pharmacokinetic parameters after intravenous administration in male rats.

Subject	$T_{1/2}$ (h)	T_{max} (h)	C_{max} (μg/mL)	AUC_t (μg·h/mL)	AUC_∞ (μg·h/mL)	CL (L/h/kg)	Vss (L/kg)
1	3.37	2.00	6.60	23.4	23.5	NA	NA
2	3.42	2.00	2.60	13.0	13.1	NA	NA
3	2.79	4.00	2.40	15.7	15.7	NA	NA
Mean	3.19	2.67	3.87	17.4	17.4	NA	NA
SD	0.35	1.15	2.37	5.41	5.44	NA	NA

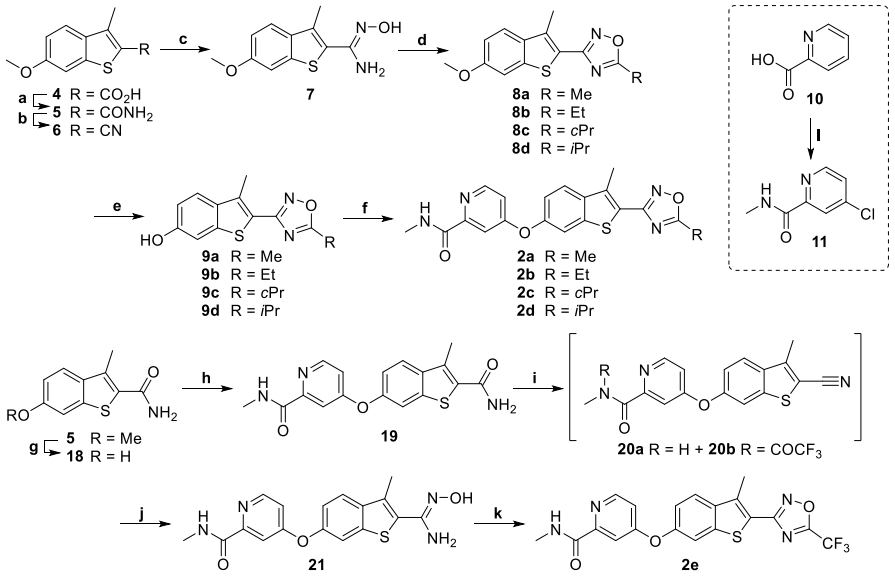
Table S5. Pharmacokinetic parameters after oral administration in male rats.

2. Synthetic Procedures for Key Compounds

General Procedures

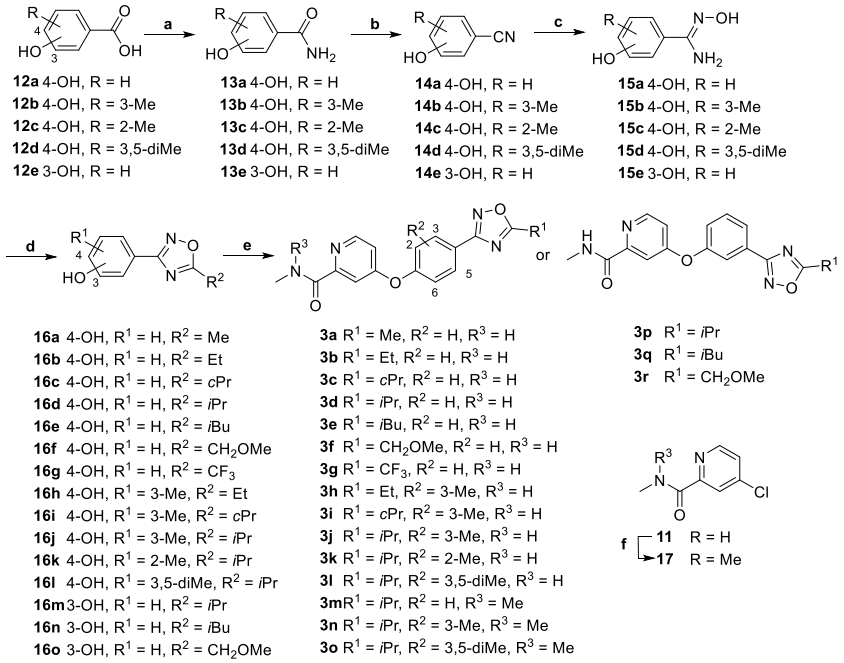
Unless otherwise stated, all commercially available reagents and solvents were used without further purification. DMF, CH_3CN, CH_2Cl_2, and THF were dried by using a JC Meyer solvent purification system prior to use. Analytical thin layer chromatography (TLC) was performed on Merck silica gel 60 F_{254} plates. Column chromatography was performed on silica gel 60 (230-400 mesh) using proper eluent systems. ^{1}H NMR spectra were recorded on Bruker 300 instrument at 300 MHz. Chemical shifts were quoted in parts per million (ppm) referenced to the appropriate solvent peak or 0.0 ppm for tetramethylsilane. The following abbreviations were used to describe peak splitting patterns when appropriate: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet, td = triplet of doublet, ddd = doublet of doublet of doublet, m = multiplet. Coupling constants, *J*, were reported in hertz unit (Hz). ^{13}C NMR spectra were recorded on Bruker 500 instrument at 126 MHz and fully decoupled by broad band proton decoupling. Chemical shifts are given in ppm referenced to the center of a triplet at 77.0 ppm of $CDCl_3$ or appropriate solvent peaks. Infrared (IR) spectra were recorded on Smiths Detection IdentifyIR FT-IR Spectrometer. Frequencies are given in reciprocal centimeters (cm^{-1}) and only selected absorbances are reported. High resolution mass spectra (HRMS) were obtained from the Korea Research Institute of Chemical Technology by using EI ionization method. All compounds assayed were >95% pure, as determined by UPLC analysis conducted on Waters Acquity UPLC H-Class system with photodiode array (PDA) detector using a reverse-phase column with a linear H_2O/CH_3CN gradient system, 10 % to 90 % CH_3CN in H_2O.

Synthetic Schemes for Key Compounds

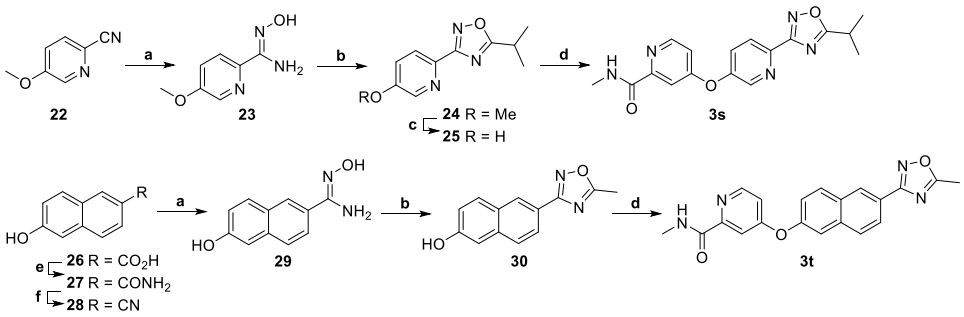


Scheme S1. Preparation of benzo[*b*[thiophenenyl oxadiazole derivatives. Reagents and conditions: (a) DMF, $SOCl_2$, 80 °C, 4 h then NH_3, H_2O, THF, 0 °C to 25 °C, 16 h; (b) TFAA, pyridine, $ClCH_2CH_2Cl$, 25 °C, 1.5 h; (c) NH_2OH, H_2O, EtOH, 90 °C, 48 h; (d) ROCl, pyridine, 0 °C to 120 °C, 16 h; (e) BBr_3, CH_2Cl_2, -78 °C to 25 °C,

16 h; (f) **11**, neat, 150 °C, 60 h; (g) NH_2OH, H_2O, 85 °C, 24 h; (h) TFAA, pyridine, 120 °C, 16 h then NaOH, THF, H_2O, 25 °C, 2 h; (l) DMF, $SOCl_2$, 45 °C then 75 °C, 72 h then CH_3NH_2, H_2O, THF, 0 °C then 25 °C, 4 h.



Scheme S2. Preparation of phenyl oxadiazole derivatives. Reagents and conditions: (a) DMF, $SOCl_2$, 70 °C, 5 h then NH_3, H_2O, THF, 0 °C to 25 °C, 16 h; (b) TFAA, pyridine, THF, 0 °C to 25 °C, 16 h; (c) NH_2OH, H_2O, EtOH, 90 °C, 16 h; (d) RCOCl or TFAA (for **16g**), pyridine, 0°C to 120 °C, 16 h; (e) **11** or **17** (for **3m–o**), neat, 150 °C, 90 h; (f) MeI, NaH, DMF, 0 °C then 25 °C, 3 h.



Scheme S3. Preparation of pyridyl and naphthyl oxadiazole derivatives. Reagents and conditions: (a) NH_2OH, H_2O, EtOH, 90 °C, 16 h; (b) RCOCl, pyridine, 0°C to 120 °C, 16 h; (c) BBr_3, CH_2Cl_2, -78 °C to 25 °C, 16 h; (d) **11**, neat, 150 °C, 90 h; (e) DMF, $SOCl_2$, 70 °C, 5 h then NH_3, H_2O, THF, 0 °C to 25 °C, 16 h; (f) TFAA, pyridine, THF, 0 °C to 25 °C, 16 h

Purities of Key Compounds

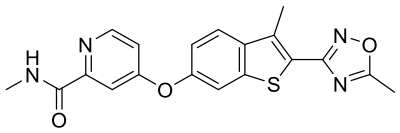
Compound	purity (%)
2a	99.99
2b	99.25
2c	98.73

Compound	purity (%)
3i	99.99
3j	95.89
3k	99.99

2d	99.14	**3l**	96.96
2e	99.04	**3m**	99.01
3a	98.53	**3n**	99.99
3b	99.99	**3o**	97.86
3c	99.99	**3p**	99.99
3d	96.03	**3q**	99.99
3e	95.52	**3r**	97.88
3f	96.82	**3s**	99.99
3g	99.99	**3t**	97.12
3h	99.99		

Table S6. UPLC purity of key compounds. The purity was determined by an UPLC analysis on Waters Acquity UPLC H-Class system with photodiode array (PDA) detector using a reverse-phase column with a linear H_2O/CH_3CN gradient system, 10 % to 90 % CH_3CN in H_2O

Synthetic Procedures for Key Compounds



N-Methyl-4-((3-methyl-2-(5-methyl-1,2,4-oxadiazol-3-yl)benzo[*b*]thiophen-6-yl)oxy)picolinamide (**2a**)

Step 1. 6-Methoxy-3-methylbenzo[*b*]thiophene-2-carboxamide (**5**)

6-Methoxy-3-methylbenzo[*b*]thiophene-2-carboxylic acid (**4**, 1.56 g, 7.01 mmol) and DMF (47.2 mg, 0.646 mmol) was taken into $SOCl_2$ (14 mL) sequentially and the mixture was stirred at 80 °C for 4 h. The mixture was cooled to 25 °C, concentrated under reduced pressure, and remaining $SOCl_2$ was removed by adding toluene (20 mL) and evaporating the solvents three times. The residue was taken into THF (20 mL) and 30% aq. NH_3 was added dropwise at 0 °C. After stirring at 25 °C for 16 h, the mixture was neutralized to pH=7 with 2 N aq. HCl and the aqueous layer was extracted with EtOAc (50 mL x 3). The combined organic layer was washed with 0.05 N aq. HCl (10 mL) and brine (10 mL) sequentially, dried over $MgSO_4$, and concentrated to obtain **5** (1.17 g, 75%), which was used for the next reaction without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (dd, *J* = 8.9, 0.5 Hz, 1H), 7.28 (s, 1H), 7.08 (dd, *J* = 8.9, 2.4 Hz, 1H), 5.74 (s, 2H), 3.92 (s, 3H), 2.73 (s, 3H).

Step 2. 6-Methoxy-3-methylbenzo[*b*]thiophene-2-carbonitrile (**6**)

Trifluoroacetic anhydride (3.33 g, 15.8 mmol) was added to a suspension of **5** (1.17 g, 5.28 mmol) in $ClCH_2CH_2Cl$ (25 mL). After stirring for 3 min at 25 °C, pyridine (2.09 g, 26.4 mmol) was added and the mixture was stirred at 25 °C for 1.5 h. The mixture was diluted with CH_2Cl_2 (30 mL) and 1 N aq. HCl (50 mL), and the aqueous layer was extracted with CH_2Cl_2 (50 mL x 3). The combined organic layer was washed with brine (10 mL), dried over $MgSO_4$, concentrated, and the residue was purified by SiO_2 column chromatography (EtOAc/Hx = 1:10) to obtain **6** (758 mg, 71%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.9 Hz, 1H), 7.27 (d, *J* = 3.8 Hz, 1H), 7.11 (dd, *J* = 8.9, 2.4 Hz, 1H), 3.92 (s, 3H), 2.62 (s, 3H).

Step 3. (*Z*)-*N*'-hydroxy-6-methoxy-3-methylbenzo[*b*]thiophene-2-carboximidamide (**7**)

6 (830 mg, 4.08 mmol) was taken into a mixture of 50% aq. NH_2OH (15 mL) and EtOH (5 mL). After stirring at 90 °C for 48 h, the mixture was cooled to 25 °C and concentrated under reduced pressure to obtain **7** (956 mg, 99%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.80 (s, 1H), 7.67 (d, J = 8.8 Hz, 1H), 7.49 (d, J = 2.4 Hz, 1H), 7.02 (dd, J = 8.8, 2.4 Hz, 1H), 5.81 (s, 2H), 3.83 (s, 3H), 2.48 (s, 3H).

Step 4. 3-(6-Methoxy-3-methylbenzo[*b*]thiophen-2-yl)-5-methyl-1,2,4-oxadiazole (**8a**)

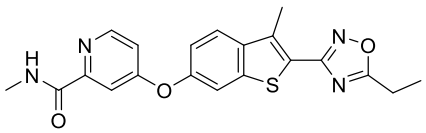
Acetyl chloride (99.7 mg, 1.27 mmol) was added to a solution of **7** (250 mg, 1.06 mmol) in pyridine (3 mL) at 0 °C and the reaction mixture was stirred at 120 °C for 16 h. The mixture was cooled to 25 °C and concentrated under reduced pressure. The residue was taken into a mixture of EtOAc (30 mL) and H_2O (30 ml) and the aqueous layer was extracted with EtOAc (20 mL x 3). The combined organic layer was washed with brine, dried over $MgSO_4$, concentrated, and the residue was purified by SiO_2 column chromatography (EtOAc/Hx = 1:5) to obtain **8a** (135 mg, 49%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, J = 8.9 Hz, 1H), 7.33 (d, J = 2.4 Hz, 1H), 7.06 (dd, J = 8.9, 2.4 Hz, 1H), 3.92 (s, 3H), 2.78 (s, 3H), 2.68 (s, 3H).

Step 5. 3-Methyl-2-(5-methyl-1,2,4-oxadiazol-3-yl)benzo[*b*]thiophen-6-ol (**9a**)

A solution of BBr_3 (1.0 M in CH_2Cl_2, 1.4 mL, 1.4 mmol) was added to a suspension of **8a** (124 mg, 0.478 mmol) in CH_2Cl_2 (4 mL) at -78 °C and the mixture was stirred at 25 °C for 16 h. The mixture was poured into ice-cooled biphasic mixture of H_2O (30 mL) and CH_2Cl_2 (40 mL). The aqueous layer was neutralized to pH=8 with satd. aq. $NaHCO_3$ and extracted with CH_2Cl_2 (50 mL x 3). The combined organic layer was washed with brine (10 mL), dried over $MgSO_4$, concentrated, and the residue was purified by SiO_2 column chromatogrpahy (CH_2Cl_2/acetone = 30:1) to obtain **9a** (108 mg, 92%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, J = 8.7 Hz, 1H), 7.30 (d, J = 2.4 Hz, 1H), 7.00 (dd, J = 8.7, 2.3 Hz, 1H), 5.05 (s, 1H), 2.78 (s, 3H), 2.69 (s, 3H).

Step 6. *N*-Methyl-4-((3-methyl-2-(5-methyl-1,2,4-oxadiazol-3-yl)benzo[*b*]thiophen-6-yl)oxy)picolinamide (**2a**)

A mixture of **9a** (98.0 mg, 0.398 mmol) and **11** (67.9 mg, 0.398 mmol) were stirred at 150 °C for 60 h. The mixture was cooled to 25 °C and diluted in a mixture of CH_2Cl_2 (50 mL) and H_2O (30 mL). The aqueous layer was extracted with CH_2Cl_2 (30 mL x 3). The combined organic layer was dried over $MgSO_4$, concentrated, and the residue was purified by SiO_2 column chromatography (CH_2Cl_2/acetone = 10:1) to obtain **2a** (42.6 mg, 28%) as off-white solid; mp 204–206 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 (dd, J = 5.6, 0.6 Hz, 1H), 8.02 (br. s, 1H), 7.86 (dd, J = 8.7, 0.5 Hz, 1H), 7.76 (dd, J = 2.6, 0.5 Hz, 1H), 7.60 (dd, J = 2.2, 0.5 Hz, 1H), 7.20 (dd, J = 8.7, 2.2 Hz, 1H), 7.02 (dd, J = 5.6, 2.6 Hz, 1H), 3.03 (d, J = 5.1 Hz, 3H), 2.83 (s, 3H), 2.70 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.16, 166.22, 165.10, 164.46, 152.43, 152.35, 149.81, 141.31, 138.40, 135.30, 124.67, 123.28, 118.44, 114.35, 114.31, 110.48, 26.15, 13.70, 12.34. IR (diamond) 3401, 3070, 2927, 1668, 1529, 1227 cm^{-1}. HRMS (EI) *m*/*z* calcd for $C_{19}H_{16}N_4O_3S$ $[M]^+$ 380.0943, found 380.0942.



4-((2-(5-Ethyl-1,2,4-oxadiazol-3-yl)-3-methylbenzo[*b*]thiophen-6-yl)oxy)-*N*-methylpicolinamide (**2b**)

Step 1. 5-Ethyl-3-(6-methoxy-3-methylbenzo[*b*]thiophen-2-yl)-1,2,4-oxadiazole (**8b**)

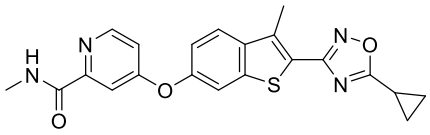
Following the same procedure used to prepare **8a**, **7** (251 mg, 1.06 mmol), propionyl chloride (118 mg, 1.27 mmol) and pyridine (3 mL) were used to obtain **8b** (758 mg, 71%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.9 Hz, 1H), 7.33 (d, *J* = 2.4 Hz, 1H), 7.06 (dd, *J* = 8.9, 2.4 Hz, 1H), 3.92 (s, 3H), 3.01 (q, *J* = 7.6 Hz, 2H), 2.78 (s, 3H), 1.48 (t, *J* = 7.6 Hz, 3H).

Step 2. 2-(5-Ethyl-1,2,4-oxadiazol-3-yl)-3-methylbenzo[*b*]thiophen-6-ol (**9b**)

Following the same procedure used to prepare **9a**, **8b** (138 mg, 0.503 mmol), BBr_3 (1.0 M in CH_2Cl_2, 1.5 mL, 1.5 mmol) and CH_2Cl_2 (4 mL) were used to obtain **9b** (117 mg, 89%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.7 Hz, 1H), 7.30 (d, *J* = 2.3 Hz, 1H), 7.00 (dd, *J* = 8.7, 2.4 Hz, 1H), 5.01 (s, 1H), 3.02 (q, *J* = 7.6 Hz, 2H), 2.78 (s, 3H), 1.48 (t, *J* = 7.6 Hz, 3H).

Step 3. 4-((2-(5-Ethyl-1,2,4-oxadiazol-3-yl)-3-methylbenzo[*b*]thiophen-6-yl)oxy)-*N*-methylpicolinamide (**2b**)

Following the same procedure used to prepare **2a**, **9b** (100 mg, 0.384 mmol) and **11** (65.5 mg, 0.384 mmol) were used to obtain **2b** (36.2 mg, 21%) as white solid; mp 162–164 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (dd, *J* = 5.6, 0.6 Hz, 1H), 8.03 (br. s, 1H), 7.86 (dd, *J* = 8.7, 0.5 Hz, 1H), 7.76 (dd, *J* = 2.6, 0.5 Hz, 1H), 7.60 (dd, *J* = 2.3, 0.5 Hz, 1H), 7.20 (dd, *J* = 8.7, 2.2 Hz, 1H), 7.02 (dd, *J* = 5.6, 2.6 Hz, 1H), 3.10 – 2.96 (m, 5H), 2.84 (s, 3H), 1.50 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 180.30, 166.21, 164.95, 164.46, 152.40, 152.30, 149.80, 141.29, 138.39, 135.21, 124.62, 123.44, 118.38, 114.31, 114.28, 110.46, 26.15, 20.27, 13.67, 10.82. IR (diamond) 3404, 3061, 2994, 2929, 1673, 1529, 1296 cm^{-1}. HRMS (EI) *m*/*z* calcd for $C_{20}H_{18}N_4O_3S$ $[M]^+$ 394.1100, found 394.1101.



4-((2-(5-Cyclopropyl-1,2,4-oxadiazol-3-yl)-3-methylbenzo[*b*]thiophen-6-yl)oxy)-*N*-methylpicolinamide (**2c**)

Step 1. 5-Cyclopropyl-3-(6-methoxy-3-methylbenzo[*b*]thiophen-2-yl)-1,2,4-oxadiazole (**8c**)

Following the same procedure used to prepare **8a**, **7** (161 mg, 0.682 mmol), cyclopropanecarbonyl chloride (85.6 mg, 0.819 mmol) and pyridine (3 mL) were used to obtain **8c** (81.6 mg, 39%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (dd, *J* = 8.9, 0.5 Hz, 1H), 7.31 (d, *J* = 2.3 Hz, 1H), 7.06 (dd, *J* = 8.9, 2.4 Hz, 1H), 3.92 (s, 3H), 2.76 (s, 3H), 2.30 (tt, *J* = 8.2, 5.0 Hz, 1H), 1.43 – 1.20 (m, 4H).

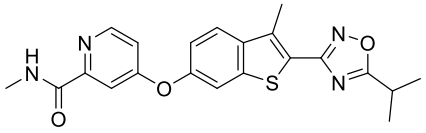
Step 2. 2-(5-Cyclopropyl-1,2,4-oxadiazol-3-yl)-3-methylbenzo[*b*]thiophen-6-ol (**9c**)

Following the same procedure used to prepare **9a**, **8c** (81.6 mg, 0.285 mmol), BBr_3 (1.0 M in CH_2Cl_2, 850 μL, 0.85 mmol) and CH_2Cl_2 (10 mL) were used to obtain **9c** (45.1 mg, 58%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.7 Hz, 1H), 6.99 (dd, *J* = 8.7, 2.4 Hz, 1H), 4.97 (s, 1H), 2.76 (s, 3H), 2.36 – 2.24 (m, 1H), 1.40 – 1.24 (m, 4H).

Step 3. 4-((2-(5-Cyclopropyl-1,2,4-oxadiazol-3-yl)-3-methylbenzo[*b*]thiophen-6-yl)oxy)-N-methylpicolinamide (**2c**)

Following the same procedure used to prepare **2a**, **9c** (45.1 mg, 0.166 mmol) and **11** (84.9 mg, 0.497 mmol) were used to obtain **2c** (11.9 mg, 21%) as white solid; mp 169–171 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 (d, *J* = 5.6 Hz, 1H), 8.03 (br. s, 1H), 7.85 (d, *J* = 8.7 Hz, 1H), 7.76 (d, *J* = 2.5 Hz, 1H), 7.59 (d, *J* = 2.2 Hz, 1H), 7.19 (dd, *J* = 8.7, 2.2 Hz, 1H), 7.02 (dd, *J* = 5.6, 2.6 Hz, 1H), 3.03 (d, *J* = 5.1 Hz, 3H), 2.82 (s, 3H), 2.32 (tt, *J* = 8.2,

5.0 Hz, 1H), 1.42 – 1.24 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 181.14, 166.25, 164.93, 164.47, 152.42, 152.27, 149.80, 141.30, 138.41, 135.13, 124.61, 123.51, 118.37, 114.33, 114.27, 110.49, 26.15, 13.66, 10.30, 7.79. IR (diamond) 3401, 3017, 2919, 2850, 1665, 1519, 1286 cm^{-1}. HRMS (EI) *m*/*z* calcd for $C_{21}H_{18}N_4O_3S$ $[M]^+$ 406.1100, found 406.1100.



4-((2-(5-Isopropyl-1,2,4-oxadiazol-3-yl)-3-methylbenzo[*b*]thiophen-6-yl)oxy)-*N*-methylpicolinamide (**2d**)

Step 1. 5-Isopropyl-3-(6-methoxy-3-methylbenzo[*b*]thiophen-2-yl)-1,2,4-oxadiazole (**8d**)

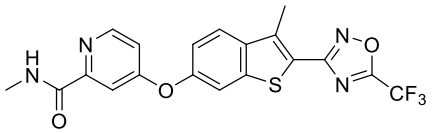
Following the same procedure used to prepare **8a**, **7** (251 mg, 1.06 mmol), isobutyryl chloride (129 mg, 1.21 mmol) and pyridine (3 mL) were used to obtain **8d** (235 mg, 81%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.9 Hz, 1H), 7.32 (d, *J* = 2.4 Hz, 1H), 7.06 (dd, *J* = 8.9, 2.4 Hz, 1H), 3.92 (s, 3H), 3.43 – 3.25 (m, 1H), 2.78 (s, 3H), 1.49 (d, *J* = 7.0 Hz, 6H).

Step 2. 2-(5-Isopropyl-1,2,4-oxadiazol-3-yl)-3-methylbenzo[*b*]thiophen-6-ol (**9d**)

Following the same procedure used to prepare **9a**, **8d** (190 mg, 0.657 mmol), BBr_3 (1.0 M in CH_2Cl_2, 2.0 mL, 2.0 mmol), and CH_2Cl_2 (4 mL) were used to obtain **9d** (119 mg, 66%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.7 Hz, 1H), 7.30 (d, *J* = 2.5 Hz, 1H), 6.99 (dd, *J* = 8.7, 2.3 Hz, 1H), 5.09 (s, 1H), 3.41 – 3.25 (m, 1H), 2.78 (s, 3H), 1.49 (d, *J* = 7.0 Hz, 6H).

Step 3. 4-((2-(5-Isopropyl-1,2,4-oxadiazol-3-yl)-3-methylbenzo[*b*]thiophen-6-yl)oxy)-*N*-methylpicolinamide (**2d**)

Following the same procedure used to prepare **2a**, **9d** (109 mg, 0.396 mmol) and **11** (67.5 mg, 0.396 mmol) were used to obtain **2d** (38.8 mg, 24%) as off-white solid; mp 60–62 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 (dd, *J* = 5.6, 0.5 Hz, 1H), 8.03 (br. s, 1H), 7.95 – 7.80 (m, 1H), 7.76 (dd, *J* = 2.6, 0.5 Hz, 1H), 7.68 – 7.51 (m, 1H), 7.19 (dd, *J* = 8.7, 2.2 Hz, 1H), 7.02 (dd, *J* = 5.6, 2.6 Hz, 1H), 3.34 (hept, *J* = 7.0 Hz, 1H), 3.03 (d, *J* = 5.1 Hz, 3H), 2.84 (s, 3H), 1.50 (d, *J* = 7.0 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 183.48, 166.22, 164.88, 164.47, 152.42, 152.29, 149.80, 141.31, 138.40, 135.16, 124.60, 123.56, 118.35, 114.31, 114.27, 110.47, 27.53, 26.14, 20.17, 13.65. IR (diamond) 3394, 3054, 2975, 2934, 1665, 1524, 1289 cm^{-1}. HRMS (EI) *m*/*z* calcd for $C_{21}H_{20}N_4O_3S$ $[M]^+$ 408.1256, found 408.1257.



N-Methyl-4-((3-methyl-2-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzo[*b*]thiophen-6-yl)oxy)picolinamide (**2e**)

Step 1. 6-Hydroxy-3-methylbenzo[*b*]thiophene-2-carboxamide (**18**)

A solution of BBr_3 (3.40 g, 13.6 mmol) in CH_2Cl_2 (5 mL) was added to a suspension of **5** (1.00 g, 4.52 mmol) in CH_2Cl_2 (10 mL) dropwise at -78 °C and the reaction mixture was stirred at 20 °C for 16 h. The reaction was quenched by adding 30% aq. NH_3 (5 mL) dropwise over 20 min at 0 °C. The mixture was then diluted with a

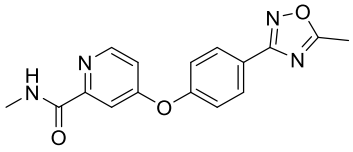
mixture of EtOAc (100 mL) and H_2O (100 mL) and the aqueous layer was extracted with EtOAc (50 mL x 3). The combined organic layer was dried over $MgSO_4$ and concentrated. The obtained product was used for the next reactions without further purification (615 mg, 66%). ^{1}H NMR (300 MHz, acetone-d_6) δ 8.93 (s, 1H), 7.72 (dd, J = 8.8, 0.5 Hz, 1H), 7.32 (d, J = 0.5 Hz, 1H), 7.03 (dd, J = 8.8, 2.3 Hz, 1H), 6.85 (s, 2H), 2.66 (s, 3H).

Step 2. 4-((2-Carbamoyl-3-methylbenzo[*b*]thiophen-6-yl)oxy)-*N*-methylpicolinamide (**19**)

A mixture of **18** (300 mg, 1.45 mmol) and **11** (247 mg, 1.45 mmol) was stirred at 150 °C for 60 h. The mixture was cooled to 25 °C and dissolved in a mixture of $CHCl_3$ (100 mL) and H_2O (100 mL). The aqueous layer was extracted with $CHCl_3$ (100 mL x 3) and the combined organic layer was dried over $MgSO_4$, concentrated. The residue was purified by SiO_2 column chromatography (CH_2Cl_2/acetone = 1:4) to obtain **19** (63.3 mg, 13%). ^{1}H NMR (300 MHz, acetone-d_6) δ 8.51 (d, J = 5.6 Hz, 1H), 8.33 (s, 1H), 8.04 (d, J = 8.8 Hz, 1H), 7.85 (d, J = 2.3 Hz, 1H), 7.60 (d, J = 2.6 Hz, 1H), 7.34 (dd, J = 8.8, 2.3 Hz, 1H), 7.15 (dd, J = 5.6, 2.6 Hz, 1H), 7.02 (s, 2H), 2.94 (d, J = 5.0 Hz, 3H), 2.76 (s, 3H).

Step 3. *N*-Methyl-4-((3-methyl-2-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzo[*b*]thiophen-6-yl)oxy)picolinamide (**2e**)

Trifluoroacetic anhydride (158 mg, 0.752 mmol) was added to a suspension of **19** (63.3 mg, 0.188 mmol) in CH_2Cl_2 (2 mL) at 0 °C. After stirring at 25 °C for 10 min, the mixture was cooled to 0 °C and pyridine (74.3 mg, 0.940 mmol) was added. After further stirring at 25 °C for 2 h, the mixture was diluted with CH_2Cl_2 (30 mL) and water (30 mL) sequentially. The aqueous layer was extracted with CH_2Cl_2 (50 mL x 3). The combined organic layer was washed with brine (10 mL), dried over $MgSO_4$, concentrated, and the residue was purified by SiO_2 column chromatography (CH_2Cl_2/acetone = 1:2) to obtain mixture of 4-((2-cyano-3-methylbenzo[*b*]thiophen-6-yl)oxy)-*N*-methylpicolinamide (**20a**) and 4-((2-cyano-3-methylbenzo[*b*]thiophen-6-yl)oxy)-*N*-methyl-N-(2,2,2-trifluoroacetyl)picolinamide (**20b**). The mixture was taken into 50% aq. NH_2OH (3 mL) and stirred at 85 °C for 24 h. The mixture was cooled to 25 °C and concentrated under reduced pressure to obtain crude (*Z*)-4-((2-(*N*'-hydroxycarbamimidoyl)-3-methylbenzo[*b*]thiophen-6-yl)oxy)-*N*-methylpicolinamide (**21**). The crude **21** was taken into pyridine (3 mL) and trifluoroacetic anhydride (74.1 mg, 0.353 mmol) was added. After stirring at 120 °C for 16 h, the mixture was concentrated under reduced pressure and the residue was dissolved in a mixture of THF (2 mL) and H_2O (5 mL). 1 N aq. NaOH (0.5 mL) was added and to the mixture and after stirring at 25 °C for 2 h, the reaction was quenched by adding 2 N aq. HCl (1 mL). The mixture was diluted with CH_2Cl_2 (50 mL) and H_2O (30 mL) and the aqueous layer was extracted with CH_2Cl_2 (30 mL x 3). The combined organic layer was washed with brine (5 mL), dried over $MgSO_4$, concentrated, and the residue was purified by SiO_2 column chromatography (EtOAc/Hx = 1:1) to obtain **2e** (18.2 mg, 22%) as off-white solid; mp 157–159 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (dd, J = 5.6, 0.6 Hz, 1H), 8.04 (s, 1H), 7.91 (dd, J = 8.8, 0.6 Hz, 1H), 7.75 (dd, J = 2.6, 0.5 Hz, 1H), 7.62 (dd, J = 2.2, 0.5 Hz, 1H), 7.24 (dd, J = 8.8, 2.2 Hz, 1H), 7.06 (dd, J = 5.6, 2.6 Hz, 1H), 3.04 (d, J = 5.1 Hz, 3H), 2.88 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.01, 165.85, 165.34 (q, J = 43.2 Hz), 164.44, 152.97, 152.42, 149.86, 141.71, 138.00, 137.58, 125.09, 120.93, 118.76, 115.93 (q, J = 274.0 Hz), 114.51, 114.31, 110.44, 26.17, 13.82. IR (diamond) 3387, 3066, 2919, 2852, 1668, 1531, 1150 cm^{-1}. HRMS (EI) *m/z* calcd for $C_{19}H_{13}F_3N_4O_3S$ $[M]^+$ 434.0660, found 434.0662.



N-Methyl-4-(4-(5-methyl-1,2,4-oxadiazol-3-yl)phenoxy)picolinamide (**3a**)

Step 1. (*Z*)-*N*',4-Dihydroxybenzimidamide (**15a**)

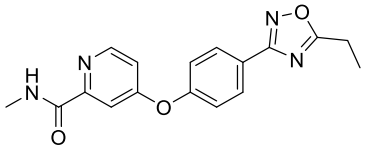
4-Cyanophenol (1.04 g, 8.76 mmol) was taken into a mixture of 50% aq. NH_2OH (8 mL) and EtOH (2 mL) and the reaction mixture was stirred at 90 °C for 16 h. The mixture was cooled to 20 °C, concentrated under reduced pressure, and dried under vacuum to obtain **15a** (1.32 g, 99%). ^{1}H NMR (300 MHz, acetone-d_6) δ 7.58 (d, J = 8.8 Hz, 1H), 6.83 (d, J = 8.9 Hz, 1H), 5.38 (s, 1H).

Step 2. 4-(5-Methyl-1,2,4-oxadiazol-3-yl)phenol (**16a**)

Acetyl chloride (155 mg, 1.97 mmol) was added to a solution of **15a** (250 mg, 1.64 mmol) in pyridine (4 mL) at 0 °C and the reaction mixture was stirred at 120 °C for 16 h. The mixture was cooled to 25 °C and concentrated under reduced pressure. The residue was taken into a mixture of EtOAc (30 mL) and H_2O (30 ml) and the aqueous layer was extracted with EtOAc (20 mL x 3). The combined organic layer was washed with brine, dried over $MgSO_4$, concentrated, and the residue was purified by SiO_2 column chromatography (EtOAc/Hx = 1:3) to obtain **16a** (187 mg, 65%). ^{1}H NMR (300 MHz, acetone-d_6) δ 9.02 (s, 1H), 7.92 (d, J = 8.7 Hz, 2H), 6.99 (d, J = 8.7 Hz, 2H), 2.63 (s, 3H).

Step 3. *N*-Methyl-4-(4-(5-methyl-1,2,4-oxadiazol-3-yl)phenoxy)picolinamide (**3a**)

A mixture of **16a** (100 mg, 0.566 mmol) and **11** (96.8 mg, 0.566 mmol) was stirred at 150 °C for 90 h. The mixture was cooled to 25 °C and diluted in a mixture of CH_2Cl_2 (50 mL) and H_2O (30 mL). The aqueous layer was extracted with CH_2Cl_2 (30 mL x 3). The combined organic layer was dried over $MgSO_4$, concentrated, and the residue was purified by SiO_2 column chromatography (CH_2Cl_2/acetone = 10:1) to obtain **3a** (57.6 mg, 33%) as white solid; mp 96–98 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (dd, J = 5.6, 0.5 Hz, 1H), 8.16 (d, J = 6.7 Hz, 2H), 8.03 (br. s, 1H), 7.80 (dd, J = 2.6, 0.5 Hz, 1H), 7.22 (d, J = 8.8 Hz, 2H), 7.04 (dd, J = 5.6, 2.5 Hz, 1H), 3.04 (d, J = 5.1 Hz, 3H), 2.69 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.71, 167.54, 165.40, 164.35, 156.21, 152.49, 149.90, 129.56, 124.18, 120.90, 114.61, 110.78, 26.13, 12.38. IR (diamond) 3322, 3070, 2927, 2879, 1668, 1531, 1236 cm^{-1}. HRMS (EI) *m*/*z* calcd for $C_{16}H_{14}N_4O_3$ $[M]^+$ 310.1066, found 310.1056.



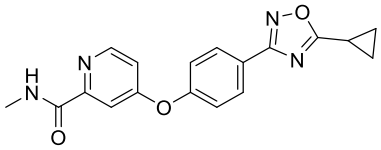
4-(4-(5-Ethyl-1,2,4-oxadiazol-3-yl)phenoxy)-*N*-methylpicolinamide (**3b**)

Step 1. 4-(5-Ethyl-1,2,4-oxadiazol-3-yl)phenol (**16b**)

Following the same procedure used to prepare **16a**, **15a** (248 mg, 1.63 mmol), propionyl chloride (181 mg, 1.95 mmol), and pyridine (4 mL) were used to obtain **16b** (245 mg, 79%). ^{1}H NMR (300 MHz, acetone-d_6) δ 9.02 (s, 1H), 7.93 (d, J = 8.7 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 2.98 (q, J = 7.6 Hz, 2H), 1.41 (t, J = 7.6 Hz, 3H).

Step 2. 4-(4-(5-Ethyl-1,2,4-oxadiazol-3-yl)phenoxy)-*N*-methylpicolinamide (**3b**)

Following the same procedure used to prepare **3a**, **16b** (102 mg, 0.534 mmol) and **11** (91.0 mg, 0.54 mmol) were used to obtain **3b** (36.2 mg, 21%) as white solid; mp 80–82 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (dd, *J* = 5.6, 0.6 Hz, 1H), 8.16 (d, *J* = 8.8 Hz, 2H), 8.03 (br. s, 1H), 7.85 – 7.75 (m, 1H), 7.21 (d, *J* = 8.7 Hz, 2H), 7.02 (dd, *J* = 5.6, 2.6 Hz, 1H), 3.08 – 2.93 (m, 5H), 1.48 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 180.91, 167.43, 165.44, 164.36, 156.16, 152.50, 149.89, 129.62, 124.34, 120.89, 114.57, 110.79, 26.13, 20.30, 10.80. IR (diamond) 3346, 3066, 2984, 2934, 2886, 1658, 1416, 1231 cm^{-1}. HRMS (EI) *m*/*z* calcd for $C_{17}H_{16}N_4O_3$ $[M]^+$ 324.1222, found 324.1219.



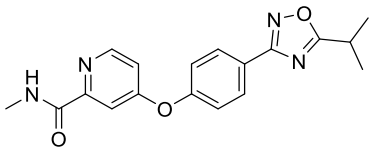
4-(4-(5-Cyclopropyl-1,2,4-oxadiazol-3-yl)phenoxy)-*N*-methylpicolinamide (**3c**)

Step 1. 4-(5-Cyclopropyl-1,2,4-oxadiazol-3-yl)phenol (**16c**)

Following the same procedure used to prepare **16a**, **15a** (297 mg, 1.95 mmol), cyclopropanecarbonyl chloride (245 mg, 2.34 mmol), and pyridine (6 mL) were used to obtain **16c** (238 mg, 53%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.9 Hz, 2H), 6.93 (d, *J* = 8.9 Hz, 2H), 5.34 (br. s, 1H), 2.26 (tt, *J* = 8.2, 5.0 Hz, 1H), 1.37 – 1.21 (m, 4H).

Step 2. 4-(4-(5-Cyclopropyl-1,2,4-oxadiazol-3-yl)phenoxy)-*N*-methylpicolinamide (**3c**)

Following the same procedure used to prepare **3a**, **16c** (101 mg, 0.500 mmol) and **11** (85.2 mg, 0.500 mmol) were used to obtain **3c** (29.6 mg, 18%) as white solid; mp 104–106 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 (d, *J* = 5.6 Hz, 1H), 8.13 (d, *J* = 8.7 Hz, 2H), 8.02 (br. s, 1H), 7.80 (d, *J* = 2.6 Hz, 1H), 7.20 (d, *J* = 8.7 Hz, 2H), 7.02 (dd, *J* = 5.6, 2.5 Hz, 1H), 3.04 (d, *J* = 5.1 Hz, 3H), 2.29 (tt, *J* = 8.2, 5.0 Hz, 1H), 1.41 – 1.22 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 181.76, 167.39, 165.49, 164.38, 156.12, 152.49, 149.89, 129.62, 124.40, 120.87, 114.56, 110.82, 26.15, 10.19, 7.78. IR (diamond) 3329, 3078, 2922, 2850, 1656, 1526, 1416, 1236 cm^{-1}. HRMS (EI) *m*/*z* calcd for $C_{18}H_{16}N_4O_3$ $[M]^+$ 336.1222, found 336.1221.



4-(4-(5-Isopropyl-1,2,4-oxadiazol-3-yl)phenoxy)-*N*-methylpicolinamide (**3d**)

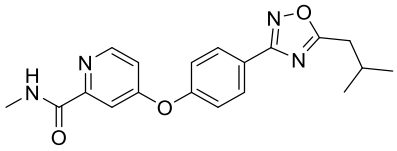
Step 1. 4-(5-Isopropyl-1,2,4-oxadiazol-3-yl)phenol (**16d**)

Following the same procedure used to prepare **16a**, **15a** (193 mg, 1.27 mmol), isobutyryl chloride (163 mg, 1.53 mmol), and pyridine (4 mL) were used to obtain **16d** (204 mg, 79%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.9 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 5.67 (s, 1H), 3.30 (hept, *J* = 7.0 Hz, 1H), 1.47 (d, *J* = 7.0 Hz, 6H).

Step 2. 4-(4-(5-Isopropyl-1,2,4-oxadiazol-3-yl)phenoxy)-*N*-methylpicolinamide (**3d**)

Following the same procedure used to prepare **3a**, **16d** (101 mg, 0.496 mmol) and **11** (83.5 mg, 0.490 mmol) were used to obtain **3d** (48.2 mg, 29%) as off-white solid; mp 78–80 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 (dd, *J* = 5.6, 0.6 Hz, 1H), 8.18 (d, *J* = 8.9 Hz, 2H), 8.02 (br. s, 1H), 7.80 (dd, *J* = 2.6, 0.6 Hz, 1H), 7.22 (d, *J* =

8.8 Hz, 2H), 7.02 (dd, *J* = 5.5, 2.6 Hz, 1H), 3.32 (hept, *J* = 7.0 Hz, 1H), 3.04 (d, *J* = 5.1 Hz, 3H), 1.50 (d, *J* = 7.0 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.13, 167.38, 165.51, 164.38, 156.15, 152.52, 149.89, 129.69, 124.49, 120.90, 114.56, 110.85, 27.55, 26.15, 20.20. IR (diamond) 3346, 3085, 2972, 2936, 1658, 1526, 1287 cm^{-1}. HRMS (EI) *m*/*z* calcd for $C_{18}H_{18}N_4O_3$ $[M]^+$ 338.1379, found 338.1378.



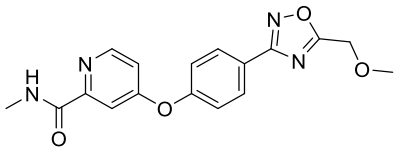
4-(4-(5-Isobutyl-1,2,4-oxadiazol-3-yl)phenoxy)-*N*-methylpicolinamide (**3e**)

Step 1. 4-(5-Isobutyl-1,2,4-oxadiazol-3-yl)phenol (**16e**)

Following the same procedure used to prepare **16a**, **15a** (150 mg, 0.986 mmol), isovaleryl chloride (143 mg, 1.18 mmol), and pyridine (3 mL) were used to obtain **16e** (190 mg, 88%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.9 Hz, 2H), 6.94 (d, *J* = 8.9 Hz, 2H), 5.41 (s, 1H), 2.84 (d, *J* = 7.2 Hz, 2H), 2.39 – 2.19 (m, 1H), 1.07 (d, *J* = 6.7 Hz, 6H).

Step 2. 4-(4-(5-Isobutyl-1,2,4-oxadiazol-3-yl)phenoxy)-*N*-methylpicolinamide (**3e**)

Following the same procedure used to prepare **3a**, **16e** (105 mg, 0.483 mmol) and **11** (82.3 mg, 0.483 mmol) were used to obtain **3e** (52.1 mg, 31%) as off-white solid; mp 72–74 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (d, *J* = 5.5 Hz, 1H), 8.17 (d, *J* = 8.8 Hz, 2H), 8.03 (br. s, 1H), 7.79 (d, *J* = 2.5 Hz, 1H), 7.21 (d, *J* = 6.9 Hz, 2H), 7.02 (dd, *J* = 5.6, 2.5 Hz, 1H), 3.03 (d, *J* = 5.0 Hz, 3H), 2.86 (d, *J* = 7.1 Hz, 2H), 2.40 – 2.21 (m, 1H), 1.08 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 179.54, 167.41, 165.49, 164.36, 156.18, 152.52, 149.88, 129.65, 124.40, 120.91, 114.57, 110.81, 35.34, 27.44, 26.13, 22.29. IR (diamond) 3358, 3066, 2960, 2929, 2876, 1660, 1529, 1246 cm^{-1}. HRMS (EI) *m*/*z* calcd for $C_{19}H_{20}N_4O_3$ $[M]^+$ 352.1535, found 352.1531.



4-(4-(5-(Methoxymethyl)-1,2,4-oxadiazol-3-yl)phenoxy)-*N*-methylpicolinamide (**3f**)

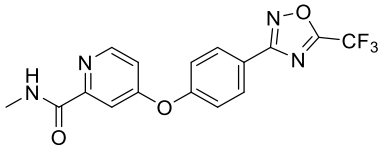
Step 1. 4-(5-(Methoxymethyl)-1,2,4-oxadiazol-3-yl)phenol (**16f**)

Following the same procedure used to prepare **16a**, **15a** (150 mg, 0.986 mmol), methoxyacetyl chloride (112 mg, 1.04 mmol), and pyridine (3 mL) were used to obtain **16f** (140 mg, 69%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.9 Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 5.98 – 5.74 (m, 1H), 4.76 (s, 2H), 3.58 (s, 3H).

Step 2. 4-(4-(5-(Methoxymethyl)-1,2,4-oxadiazol-3-yl)phenoxy)-*N*-methylpicolinamide (**3f**)

Following the same procedure used to prepare **3a**, **16f** (98.2 mg, 0.476 mmol) and **11** (81.2 mg, 0.476 mmol) were used to obtain **3f** (49.7 mg, 31%) as off-white solid; mp 98–100 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (d, *J* = 5.5 Hz, 1H), 8.20 (d, *J* = 8.8 Hz, 2H), 8.02 (br. s, 1H), 7.80 (d, *J* = 2.5 Hz, 1H), 7.23 (d, *J* = 8.8 Hz, 2H), 7.04 (dd, *J* = 5.6, 2.6 Hz, 1H), 4.79 (s, 2H), 3.60 (s, 3H), 3.04 (d, *J* = 5.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.10, 167.58, 165.37, 164.34, 156.45, 152.53, 149.92, 129.78, 123.79, 120.91, 114.67, 110.83, 65.14, 59.63,

26.13. IR (diamond) 3325, 3066, 2934, 2826, 1660, 1524, 1239 cm^{-1}. HRMS (EI) *m/z* calcd for $C_{17}H_{16}N_4O_4$ $[M]^+$ 340.1172, found 340.1169.



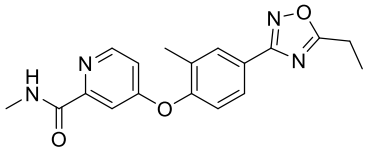
N-Methyl-4-(4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)phenoxy)picolinamide (**3g**)

Step 1. 4-(5-(Trifluoromethyl)-1,2,4-oxadiazol-3-yl)phenol (**16g**)

Following the same procedure used to prepare **16a**, **15a** (300 mg, 1.97 mmol), trifluoroacetic anhydride (620 mg, 2.96 mmol), and pyridine (6 mL) were used to obtain **16g** (329 mg, 73%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.8 Hz, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 5.56 (s, 1H).

Step 2. *N*-Methyl-4-(4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)phenoxy)picolinamide (**3g**)

Following the same procedure used to prepare **3a**, **16g** (102 mg, 0.444mmol) and **11** (75.2 mg, 0.444 mmol) were used to obtain **3g** (33.2 mg, 17%) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.47 (dd, *J* = 5.6, 0.6 Hz, 1H), 8.21 (d, *J* = 8.8 Hz, 2H), 8.03 (s, 1H), 7.80 (dd, *J* = 2.6, 0.5 Hz, 1H), 7.26 (d, *J* = 8.8 Hz, 2H), 7.07 (dd, *J* = 5.6, 2.5 Hz, 1H), 3.04 (d, *J* = 5.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.37, 165.94 (q, *J* = 44.5 Hz), 165.10, 164.29, 157.31, 152.62, 150.03, 130.08, 122.10, 121.06, 115.96 (q, *J* = 273.8 Hz), 114.95, 110.95, 26.17. IR (diamond) 3396, 2952, 2924, 2849, 1675, 1471, 1161 cm^{-1}. HRMS (EI) *m/z* calcd for $C_{16}H_{11}F_3N_4O_3$ $[M]^+$ 364.0783, found 364.0776.



4-(4-(5-Ethyl-1,2,4-oxadiazol-3-yl)-2-methylphenoxy)-*N*-methylpicolinamide (**3h**)

Step 1. 4-Hydroxy-3-methylbenzamide (**13b**)

4-Hydroxy-3-methylbenzoic acid (**12b**, 1.00 g, 6.59 mmol) and DMF (47.2 mg, 0.646 mmol) were sequentially added to $SOCl_2$ (13 mL) and the reaction mixture was stirred at 70 °C for 5 h. The mixture was cooled to 25 °C and concentrated under reduced pressure. Remaining $SOCl_2$ was removed by adding toluene (10 mL) and evaporating the solvents under reduced pressure three times. The residue was taken into THF (10 mL), cooled to 0 °C, and 30 % aqueous NH_3 (3 mL) was added dropwise. After stirring at 25 °C for 16 h, the mixture was concentrated and the residue was diluted with EtOAc (30 mL) and H_2O (30 mL). The aqueous layer was extracted with EtAOc (20 mL x 3). The combined organic layer was washed with brine (5 mL), dried over $MgSO_4$ and concentrated to obtain **13b**, which was used for the next reaction without further purification (241 mg, 24%). ^{1}H NMR (300 MHz, acetone-d_6) δ 8.85 (s, 1H), 7.74 (s, 1H), 7.67 (d, *J* = 8.4 Hz, 1H), 7.24 (s, 1H), 6.87 (d, *J* = 8.3 Hz, 1H), 6.41 (s, 1H).

Step 2. 4-Hydroxy-3-methylbenzonitrile (**14b**)

Pyridine (984 mg, 12.4 mmol) was added to a solution of **13b** (376 mg, 2.49 mmol) in THF (7.5 mL) and the mixture was cooled to 0 °C. Trifluoroacetic anhydride (1.57 g, 7.46 mmol) was added and the mixture was

stirred at 25 °C for 16 h. After dilution with EtOAc (100 mL) and H_2O (50 mL), the aqueous layer was extracted with EtOAc (50 mL x 3). The combined organic layer was washed with brine(10 mL), dried over $MgSO_4$, concentrated, and the residue was purified by SiO_2 column chromatography (CH_2Cl_2) to obtain **14b** (268 mg, 81%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 – 7.59 (m, 2H), 7.33 (d, *J* = 8.3 Hz, 1H), 2.30 (s, 3H).

Step 3. (*Z*)-*N*',4-Dihydroxy-3-methylbenzimidamide (**15b**)

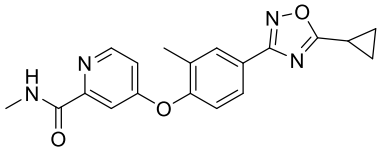
Following the same procedure used to prepare **15a**, **14b** (352 mg, 2.64 mmol) and 50% aq. NH_2OH (8 mL) were used to obtain **15b** (423 mg, 96%). ^{1}H NMR (300 MHz, acetone-d_6) δ 9.32 (s, 1H), 7.48 (s, 1H), 7.39 (dd, *J* = 8.4, 2.3 Hz, 1H), 6.81 (d, *J* = 8.4 Hz, 1H), 5.37 (s, 2H), 2.21 (s, 3H).

Step 4. 4-(5-Ethyl-1,2,4-oxadiazol-3-yl)-2-methylphenol (**16h**)

Following the same procedure used to prepare **16a**, **15b** (78.5 mg, 0.460 mmol), propionyl chloride (51.1 mg, 0.552 mmol) and pyridine (1.5 mL) were used to obtain **16h** (45.2 mg, 48%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.78 (dd, *J* = 8.3, 2.0 Hz, 1H), 6.85 (d, *J* = 8.3 Hz, 1H), 6.43 (s, 1H), 2.99 (q, *J* = 7.6 Hz, 2H), 2.31 (s, 3H), 1.46 (t, *J* = 7.6 Hz, 3H).

Step 2. 4-(4-(5-Ethyl-1,2,4-oxadiazol-3-yl)-2-methylphenoxy)-*N*-methylpicolinamide (**3h**)

Following the same procedure used to prepare **3a**, **16h** (45.2 mg, 0.221 mmol) and **11** (113.1 mg, 0.663 mmol) were used to obtain **3h** (29.7 mg, 40%) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (d, *J* = 5.6 Hz, 1H), 8.06 (s, 1H), 8.05 – 8.01 (br. s, 1H), 7.99 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.71 (d, *J* = 2.5 Hz, 1H), 7.13 (d, *J* = 8.4 Hz, 1H), 6.93 (dd, *J* = 5.6, 2.6 Hz, 1H), 3.07 – 2.96 (m, 5H), 2.25 (s, 3H), 1.49 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 180.89, 167.58, 165.56, 164.46, 154.02, 152.48, 149.85, 131.33, 131.11, 127.00, 124.68, 121.54, 113.58, 110.02, 26.15, 20.35, 16.02, 10.85. IR (diamond) 3387, 2985, 2929, 1677, 1568, 1295 cm^{-1}. HRMS (EI) *m*/*z* calcd for $C_{18}H_{18}N_4O_3$ $[M]^+$ 338.1379, found 338.1373.



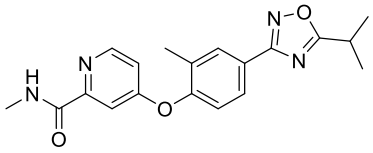
4-(4-(5-Cyclopropyl-1,2,4-oxadiazol-3-yl)-2-methylphenoxy)-*N*-methylpicolinamide (**3i**)

Step 1. 4-(5-Cyclopropyl-1,2,4-oxadiazol-3-yl)-2-methylphenol (**16i**)

Following the same procedure used to prepare **16a**, **15b** (78.5 mg, 0.460 mmol), cyclopropanecarbonyl chloride (57.7 mg, 0.460 mmol) and pyridine (1.5 mL) were used to obtain **16i** (58.3 mg, 59%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, *J* = 1.3 Hz, 1H), 7.76 (dd, *J* = 8.3, 1.9 Hz, 1H), 6.84 (d, *J* = 8.3 Hz, 1H), 6.13 (s, 1H), 2.39 – 2.17 (m, 4H), 1.42 – 1.18 (m, 4H).

Step 2. 4-(4-(5-Cyclopropyl-1,2,4-oxadiazol-3-yl)-2-methylphenoxy)-*N*-methylpicolinamide (**3i**)

Following the same procedure used to prepare **3a**, **16i** (58.3 mg, 0.270 mmol) and **11** (138.2 mg, 0.810 mmol) were used to obtain **3i** (40.3 mg, 43%) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (d, *J* = 5.6 Hz, 1H), 8.07 – 7.99 (m, 2H), 7.95 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.70 (d, *J* = 2.5 Hz, 1H), 7.11 (d, *J* = 8.4 Hz, 1H), 6.91 (dd, *J* = 5.6, 2.6 Hz, 1H), 3.03 (d, *J* = 5.1 Hz, 3H), 2.36 – 2.14 (m, 4H), 1.43 – 1.22 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 182.99, 168.01, 165.67, 164.43, 155.34, 152.45, 149.82, 141.22, 132.34, 123.86, 123.15, 118.01, 114.49, 110.81, 27.44, 26.15, 22.29, 20.23. IR (diamond) 3398, 3030, 2936, 1677, 1532, 1293 cm^{-1}. HRMS (EI) *m*/*z* calcd for $C_{19}H_{18}N_4O_3$ $[M]^+$ 350.1379, found 350.1379.



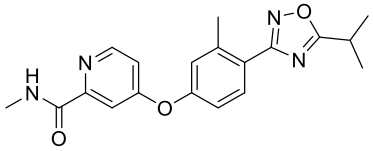
4-(4-(5-Isopropyl-1,2,4-oxadiazol-3-yl)-2-methylphenoxy)-*N*-methylpicolinamide (**3j**)

Step 1. 4-(5-Isopropyl-1,2,4-oxadiazol-3-yl)-2-methylphenol (**16j**)

Following the same procedure used to prepare **16a**, **15b** (300 mg, 1.81 mmol), isobutyryl chloride (231 mg, 2.17 mmol), and pyridine (10 mL) were used to obtain **16j** (304 mg, 52%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, *J* = 1.3 Hz, 1H), 7.80 (dd, *J* = 8.3, 1.8 Hz, 1H), 6.85 (d, *J* = 8.3 Hz, 1H), 5.97 (s, 1H), 3.30 (hept, *J* = 7.0 Hz, 1H), 2.31 (s, 3H), 1.47 (d, *J* = 7.0 Hz, 6H).

Step 2. 4-(4-(5-Isopropyl-1,2,4-oxadiazol-3-yl)-2-methylphenoxy)-*N*-methylpicolinamide (**3j**)

Following the same procedure used to prepare **3a**, **16j** (100 mg, 0.458 mmol) and **11** (78.2 mg, 0.458 mmol) were used to obtain **3j** (26.9 mg, 17%) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (d, *J* = 5.6 Hz, 1H), 8.06 (s, 1H), 8.05 – 7.88 (m, 2H), 7.71 (d, *J* = 2.5 Hz, 1H), 7.13 (d, *J* = 8.4 Hz, 1H), 6.92 (dd, *J* = 5.6, 2.6 Hz, 1H), 3.42 – 3.24 (m, 1H), 3.03 (d, *J* = 5.1 Hz, 3H), 2.26 (s, 3H), 1.50 (d, *J* = 7.0 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.09, 167.49, 165.58, 164.47, 153.98, 152.46, 149.84, 131.29, 131.14, 127.04, 124.79, 121.52, 113.54, 110.05, 27.56, 26.15, 20.21, 16.01. IR (diamond) 3392, 2978, 2926, 1674, 1525, 1293, 924 cm^{-1}. HRMS (EI) *m*/*z* calcd for $C_{19}H_{20}N_4O_3$ $[M]^+$ 352.1535, found 352.1536.



4-(4-(5-Isopropyl-1,2,4-oxadiazol-3-yl)-3-methylphenoxy)-*N*-methylpicolinamide (**3k**)

Step 1. 4-Hydroxy-2-methylbenzamide (**13c**)

Following the same procedure used to prepare **13b**, 4-hydroxy-2-methylbenzoic acid (3.00 g, 19.7 mmol), DMF (100 μL), $SOCl_2$ (20 mL), THF (30 mL) and 30% aq. NH_3 (15 mL) were used to obtain **13c** (301 mg, 10%). ^{1}H NMR (300 MHz, acetone-d_6) δ 8.86 (s, 1H), 7.41 (d, *J* = 8.3 Hz, 1H), 6.70 (s, 1H), 6.66 (d, *J* = 8.3 Hz, 1H), 7.17 – 6.04 (m, 2H), 2.42 (s, 3H).

Step 2. 4-Hydroxy-2-methylbenzonitrile (**14c**)

Following the same procedure used to prepare **14b**, **13c** (381 mg, 2.52 mmol), trifluoroacetic anhydride (1.59 g, 7.56 mmol), pyridine (997 mg, 12.6 mmol) and THF (7.5 mL) were used to obtain **14c** (206 mg, 61%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.4 Hz, 1H), 6.80 (s, 1H), 6.78 – 6.73 (m, 1H), 6.05 (s, 1H), 2.51 (s, 3H).

Step 3. (*Z*)-*N*',4-Dihydroxy-2-methylbenzimidamide (**15c**)

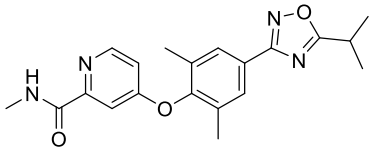
Following the same procedure used to prepare **15a**, **14c** (195 mg, 1.47 mmol) and 50% aq. NH_2OH (5 mL) were used to obtain **15c** (216 mg, 89%). ^{1}H NMR (300 MHz, acetone-d_6) δ 7.16 (d, *J* = 8.2 Hz, 1H), 6.69 (d, *J* = 2.3 Hz, 1H), 6.65 (dd, *J* = 8.2, 2.4 Hz, 1H), 5.64 (s, 2H), 4.92 (s, 1H), 2.32 (s, 3H).

Step 4. 4-(5-Isopropyl-1,2,4-oxadiazol-3-yl)-3-methylphenol (**16k**)

Following the same procedure used to prepare **16a**, **15c** (100 mg, 0.657 mmol), isobutyryl chloride (84.0 mg, 0.788 mmol) and pyridine (2.0 mL) were used to obtain **16k** (65.3 mg, 46%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.2 Hz, 1H), 6.82 – 6.68 (m, 2H), 6.02 (s, 1H), 3.31 (hept, *J* = 7.0 Hz, 1H), 2.57 (s, 3H), 1.48 (d, *J* = 7.0 Hz, 6H).

Step 5. 4-(4-(5-Isopropyl-1,2,4-oxadiazol-3-yl)-3-methylphenoxy)-*N*-methylpicolinamide (**3k**)

Following the same procedure used to prepare **3a**, **16k** (65.3 mg, 0.299 mmol) and **11** (153.0 mg, 0.897 mmol) were used to obtain **3k** (34.3 mg, 33%) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (d, *J* = 5.6 Hz, 1H), 8.10 (d, *J* = 9.0 Hz, 1H), 8.02 (s, 1H), 7.79 (d, *J* = 2.5 Hz, 1H), 7.08 – 7.03 (m, 2H), 7.01 (dd, *J* = 5.6, 2.6 Hz, 1H), 3.33 (hept, *J* = 7.0 Hz, 1H), 3.04 (d, *J* = 5.1 Hz, 3H), 2.66 (s, 3H), 1.50 (d, *J* = 7.0 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 182.99, 168.01, 165.67, 164.43, 155.34, 152.45, 149.82, 141.22, 132.34, 123.86, 123.15, 118.01, 114.49, 110.81, 27.44, 26.15, 22.29, 20.23. IR (diamond) 3390, 2973, 2934, 1674, 1527, 1293, 1231 cm^{-1}. HRMS (EI) *m*/*z* calcd for $C_{19}H_{20}N_4O_3$ $[M]^+$ 352.1535, found 352.1536.



4-(4-(5-Isopropyl-1,2,4-oxadiazol-3-yl)-2,6-dimethylphenoxy)-*N*-methylpicolinamide (**3l**)

Step 1. (*Z*)-*N*',4-Dihydroxy-3,5-dimethylbenzimidamide (**15d**)

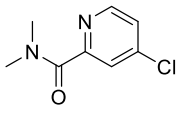
Following the same procedure used to prepare **15a**, 4-hydroxy-3,5-dimethylbenzonitrile (1.00 g, 6.81 mmol) and 50% aq. NH_2OH (13 mL) were used to obtain **15d** (1.31 g, 100%). ^{1}H NMR (300 MHz, acetone-d_6) δ 7.33 (s, 2H), 5.36 (s, 2H), 2.24 (s, 6H).

Step 2. 4-(5-Isopropyl-1,2,4-oxadiazol-3-yl)-2,6-dimethylphenol (**16l**)

Following the same procedure used to prepare **16a**, **15d** (500 mg, 2.78 mmol), isobutyryl chloride (355 mg, 3.33 mmol), and pyridine (10 mL) were used to obtain **16l** (232 mg, 36%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 – 7.59 (m, 2H), 3.29 (hept, *J* = 7.0 Hz, 1H), 2.32 (s, 6H), 1.47 (d, *J* = 7.0 Hz, 6H).

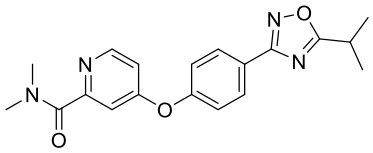
Step 3. 4-(4-(5-Isopropyl-1,2,4-oxadiazol-3-yl)-2,6-dimethylphenoxy)-*N*-methylpicolinamide (**3l**)

Following the same procedure used to prepare **3a**, **16l** (100 mg, 0.431 mmol) and **11** (73.5 mg, 0.453 mmol) were used to obtain **3l** (13.1 mg, 8%) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (d, *J* = 5.6 Hz, 1H), 8.03 (s, 1H), 7.88 (s, 2H), 7.65 (d, *J* = 2.5 Hz, 1H), 6.81 (dd, *J* = 5.6, 2.6 Hz, 1H), 3.47 – 3.20 (m, 1H), 3.03 (d, *J* = 5.1 Hz, 3H), 2.18 (s, 6H), 1.50 (d, *J* = 7.0 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.06, 167.61, 165.04, 164.54, 152.52, 151.85, 149.89, 131.71, 128.50, 124.80, 112.26, 109.08, 27.57, 26.14, 20.22, 16.20. IR (diamond) 3390, 2975, 2928, 2771, 1677, 1532, 1190, 924 cm^{-1}. HRMS (EI) *m*/*z* calcd for $C_{20}H_{22}N_4O_3$ $[M]^+$ 366.1692, found 366.1689.



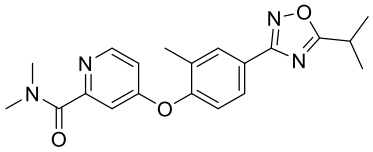
4-Chloro-*N*,*N*-dimethylpicolinamide (**17**)

NaH (60% in mineral oil, 235 mg, 5.86 mmol) was added to a solution of 4-chloro-*N*-methylpicolinamide (1.00 g, 5.86 mmol) in DMF (20 mL) at 0 °C and the mixture was stirred at 0 °C for 25 min. MeI (1.66 g, 11.7 mmol) was added to the suspension at 0 °C and the mixture was stirred at 25 °C for 3 h. Reaction completion was observed by TLC analysis. The mixture was concentrated under reduced pressure and the residue was diluted with EtOAc (100 ml) and H_2O (100 mL). The aqueous layer was extracted with EtOAc (50 mL x 3). The combined organic layer was washed with H_2O (10 mL) and brine (5 mL) sequentially, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by SiO_2 column chromatography (CH_2Cl_2/acetone = 30:1) to obtain the product (887 mg, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (d, *J* = 5.3 Hz, 1H), 7.75 – 7.60 (m, 1H), 7.45 – 7.32 (m, 1H), 3.15 (s, 3H), 3.10 (s, 3H).



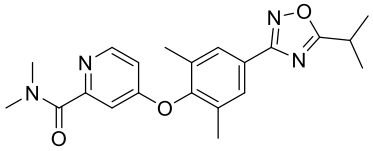
4-(4-(5-Isopropyl-1,2,4-oxadiazol-3-yl)phenoxy)-*N*,*N*-dimethylpicolinamide (**3m**)

Following the same procedure used to prepare **3a**, **16d** (100 mg, 0.490 mmol) and **17** (90.5 mg, 0.490 mmol) were used to obtain **3m** (26.3 mg, 15%) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.49 (d, *J* = 5.7 Hz, 1H), 8.18 (d, *J* = 8.8 Hz, 2H), 7.26 – 7.17 (m, 3H), 6.94 (dd, *J* = 5.7, 2.5 Hz, 1H), 3.41 – 3.24 (m, 1H), 3.12 (d, *J* = 8.5 Hz, 6H), 1.49 (d, *J* = 7.0 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.17, 168.39, 167.35, 165.07, 156.67, 155.96, 150.18, 129.68, 124.56, 121.09, 112.97, 112.03, 38.95, 35.69, 27.55, 20.20. IR (diamond) 3488, 2929, 2852, 1641, 1566, 1282 cm^{-1}. HRMS (EI) *m*/*z* calcd for $C_{19}H_{20}N_4O_3$ $[M]^+$ 352.1535, found 352.1521.



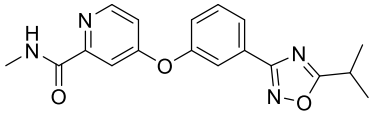
4-(4-(5-Isopropyl-1,2,4-oxadiazol-3-yl)-2-methylphenoxy)-*N*,*N*-dimethylpicolinamide (**3n**)

Following the same procedure used to prepare **3a**, **16j** (100 mg, 0.458 mmol) and **17** (84.6 mg, 0.458 mmol) were used to obtain **3n** (mg, %) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (d, *J* = 5.7 Hz, 1H), 8.04 (s, 1H), 7.97 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.12 (d, *J* = 4.6 Hz, 1H), 7.11 (s, 1H), 6.82 (dd, *J* = 5.7, 2.5 Hz, 1H), 3.39 – 3.20 (m, 1H), 3.10 (s, 3H), 3.07 (s, 3H), 2.25 (s, 3H), 1.47 (d, *J* = 7.0 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.11, 168.44, 167.46, 165.03, 156.64, 153.85, 150.15, 131.37, 131.10, 127.01, 124.81, 121.60, 112.03, 111.25, 38.93, 35.67, 27.55, 20.20, 16.03. IR (diamond) 2973, 2926, 2854, 1640, 1566, 1280 cm^{-1}. HRMS (EI) *m*/*z* calcd for $C_{20}H_{22}N_4O_3$ $[M]^+$ 366.1692, found 366.1693.



4-(4-(5-Isopropyl-1,2,4-oxadiazol-3-yl)-2,6-dimethylphenoxy)-*N*,*N*-dimethylpicolinamide (**3o**)

Following the same procedure used to prepare **3a**, **16l** (150 mg, 0.646 mmol) and **17** (119 mg, 0.646 mmol) were used to obtain **3o** (46.1 mg, 19%) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (d, *J* = 5.7 Hz, 1H), 7.88 (s, 2H), 7.06 (d, *J* = 2.4 Hz, 1H), 6.73 (dd, *J* = 5.7, 2.5 Hz, 1H), 3.42 – 3.24 (m, 1H), 3.10 (d, *J* = 12.5 Hz, 6H), 2.19 (s, 6H), 1.49 (d, *J* = 7.0 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.07, 168.46, 167.56, 164.41, 156.67, 151.75, 150.23, 131.73, 128.46, 124.79, 110.83, 110.21, 38.90, 35.65, 27.55, 20.20, 16.25. IR (diamond) 3480, 2975, 2926, 1641, 1566, 1195 cm^{-1}. HRMS (EI) *m*/*z* calcd for $C_{21}H_{24}N_4O_3$ $[M]^+$ 380.1848, found 380.1848.



4-(3-(5-Isopropyl-1,2,4-oxadiazol-3-yl)phenoxy)-*N*-methylpicolinamide (**3p**)

Step 1. 3-Hydroxybenzamide (**13e**)

Following the procedure used to prepare **13b**, 3-hydroxybenzoic acid (**12b**, 3.01 g, 21.8 mmol), DMF (77.4 mg, 1.06 mmol), $SOCl_2$ (20 mL), THF (20 mL), and 30% aq. NH_3 (10 mL) were used to obtain 13e (2.65 g, 89%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.88 – 6.92 (m, 1H), 7.20 – 7.24 (m, 1H), 7.24 – 7.30 (m, 3H), 7.86 (s, 1H), 9.60 (s, 1H);

Step 2. (*Z*)-*N*',3-Dihydroxybenzimidamide (**15e**)

Trifluoroacetic anhydride (12.1 g, 57.5 mmol) was added to a suspension of **13e** (2.65 g, 19.2 mmol) in THF (100 mL) at 0 °C. After stirring at 25 °C for 30 min, pyridine (7.58 g, 95.9 mmol) was added dropwise and the mixture was stirred at 25 °C for 16 h. The mixture was concentrated and diluted with EtOAc (100 mL) and H_2O (100 mL). The aqueous layer was extracted with EtOAc (100 mL x 3) and combined organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by SiO_2 column chromatography (EtOAc/Hx = 1:2, R_f=0.5) to obtain a mixture containing 3-hydroxybenzonitrile (**14e**) and its polymeric form. The mixture was taken into 50% aq. NH_2OH (20 mL) and stirred at 90 °C for 16 h. The mixture was cooled to 25 °C and concentrated to obtain (*Z*)-*N*',3-Dihydroxybenzimidamide (**15e**,1.73 g, 53%), which was used for the next reaction without further purification. ^{1}H NMR (300 MHz, acetone-d_6) δ 7.24 (s, 1H), 7.22 (d, *J* = 2.5 Hz, 1H), 6.97 – 6.88 (m, 1H), 5.97 (s, 1H).

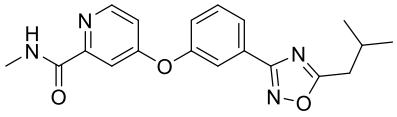
Step 3. 3-(5-Isopropyl-1,2,4-oxadiazol-3-yl)phenol (**16m**)

Following the same procedure used to prepare **16a**, **15e** (150 mg, 0.986 mmol), isobutyryl chloride (125 mg, 1.18 mmol) and pyridine (3 mL) were used to obtain **16m** (92.5 mg, 46%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (ddd, *J* = 7.7, 1.5, 1.0 Hz, 1H), 7.58 (dd, *J* = 2.7, 1.5 Hz, 1H), 7.43 – 7.33 (m, 1H), 7.01 (ddd, *J* = 8.2, 2.7, 1.0 Hz, 1H), 5.39 (s, 1H), 3.32 (hept, *J* = 7.0 Hz, 1H), 1.48 (d, *J* = 7.0 Hz, 6H).

Step 4. 4-(3-(5-Isopropyl-1,2,4-oxadiazol-3-yl)phenoxy)-*N*-methylpicolinamide (**3p**)

Following the same procedure used to prepare **3a**, **16m** (92.5 mg, 0.453 mmol) and **11** (77.3 mg, 0.453 mmol) were used to obtain **3p** (31.8 mg, 21%) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (dd, *J* = 5.6, 0.6 Hz, 1H), 8.08 – 7.94 (m, 2H), 7.85 – 7.83 (m, 1H), 7.75 (d, *J* = 2.4 Hz, 1H), 7.63 – 7.51 (m, 1H), 7.25 (ddd, *J* = 8.2, 2.5, 1.0 Hz, 1H), 7.02 (dd, *J* = 5.6, 2.6 Hz, 1H), 3.30 (hept, *J* = 7.1 Hz, 1H), 3.03 (d, *J* = 5.1 Hz, 3H), 1.47 (d, *J* = 7.0 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.25, 167.32, 165.93, 164.45, 154.23, 152.43, 149.81, 130.88,

129.49, 124.67, 123.39, 119.88, 114.34, 110.46, 27.55, 26.12, 20.17. IR (diamond) 3389, 3070, 2972, 2924, 1673, 1526, 1296 cm^{-1}. HRMS (EI) *m/z* calcd for $C_{18}H_{18}N_4O_3$ $[M]^+$ 338.1379, found 338.1380.



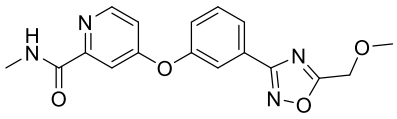
4-(3-(5-Isobutyl-1,2,4-oxadiazol-3-yl)phenoxy)-*N*-methylpicolinamide (**3q**)

Step 1. 3-(5-Isobutyl-1,2,4-oxadiazol-3-yl)phenol (**16n**)

Following the same procedure used to prepare **16a**, **15e** (150 mg, 0.986 mmol), isovaleryl chloride (143 mg, 1.18 mmol), and pyridine (3 mL) were used to obtain **16n** (110 mg, 51%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.7 Hz, 1H), 7.58 (ddd, *J* = 2.1, 1.6, 0.8 Hz, 1H), 7.42 – 7.34 (m, 1H), 7.01 (dd, *J* = 8.0, 2.6 Hz, 1H), 5.23 (s, 1H), 2.86 (dd, *J* = 7.2, 0.7 Hz, 2H), 2.39 – 2.19 (m, 1H), 1.07 (dd, *J* = 6.7, 0.7 Hz, 6H).

Step 2. 4-(3-(5-Isobutyl-1,2,4-oxadiazol-3-yl)phenoxy)-*N*-methylpicolinamide (**3q**)

Following the same procedure used to prepare **3a**, **16n** (110 mg, 0.504 mmol) and **11** (85.9 mg, 0.504 mmol) were used to obtain **3q** (44.7 mg, 25%) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 (dd, *J* = 5.6, 0.5 Hz, 1H), 8.09 – 7.96 (m, 2H), 7.84 (dd, *J* = 2.5, 1.5 Hz, 1H), 7.75 (dd, *J* = 2.6, 0.5 Hz, 1H), 7.63 – 7.51 (m, 1H), 7.26 (ddd, *J* = 8.2, 2.5, 1.0 Hz, 1H), 7.02 (dd, *J* = 5.6, 2.6 Hz, 1H), 3.03 (d, *J* = 5.1 Hz, 3H), 2.85 (d, *J* = 7.2 Hz, 2H), 2.38 – 2.21 (m, 1H), 1.06 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 179.69, 167.38, 165.92, 164.44, 154.27, 152.44, 149.82, 130.90, 129.40, 124.64, 123.43, 119.83, 114.36, 110.48, 35.34, 27.45, 26.12, 22.29. IR (diamond) 3396, 3063, 2958, 2929, 2874, 1673, 1529, 1296 cm^{-1}. HRMS (EI) *m/z* calcd for $C_{19}H_{20}N_4O_3$ $[M]^+$ 352.1535, found 352.1534.



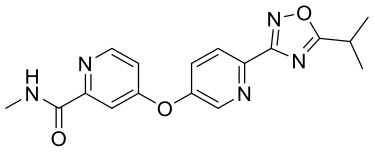
4-(3-(5-(Methoxymethyl)-1,2,4-oxadiazol-3-yl)phenoxy)-*N*-methylpicolinamide (**3r**)

Step 1. 4-(5-(Methoxymethyl)-1,2,4-oxadiazol-3-yl)phenol (**16o**)

Following the same procedure used to prepare **16a**, **15e** (150 mg, 0.986 mmol), methoxyacetyl chloride (112 mg, 1.04 mmol), and pyridine (3 mL) were used to obtain **16o** (115 mg, 56%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (ddd, *J* = 7.7, 1.5, 1.0 Hz, 1H), 7.60 (dd, *J* = 2.6, 1.5 Hz, 1H), 7.44 – 7.33 (m, 1H), 7.03 (ddd, *J* = 8.2, 2.6, 1.0 Hz, 1H), 5.64 (s, 1H), 4.78 (s, 2H), 3.58 (s, 3H).

Step 2. 4-(3-(5-(Methoxymethyl)-1,2,4-oxadiazol-3-yl)phenoxy)-N-methylpicolinamide (**3r**)

Following the same procedure used to prepare **3a**, **16o** (96.1 mg, 0.466 mmol) and **11** (79.5 mg, 0.466 mmol) were used to obtain **3r** (41.5 mg, 26%) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (d, *J* = 5.6 Hz, 1H), 8.10 – 7.97 (m, 2H), 7.91 – 7.82 (m, 1H), 7.75 (d, *J* = 2.5 Hz, 1H), 7.64 – 7.52 (m, 1H), 7.33 – 7.23 (m, 1H), 7.02 (dd, *J* = 5.6, 2.6 Hz, 1H), 4.77 (s, 2H), 3.58 (s, 3H), 3.03 (d, *J* = 5.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.24, 167.55, 165.83, 164.43, 154.33, 152.44, 149.85, 131.00, 128.82, 124.71, 123.72, 119.91, 114.41, 110.47, 65.11, 59.65, 26.13. IR (diamond) 3459, 3394, 3063, 2922, 2855, 1673, 1524, 1296 cm^{-1}. HRMS (EI) *m/z* calcd for $C_{17}H_{16}N_4O_4$ $[M]^+$ 340.1172, found 340.1171.



4-((6-(5-Isopropyl-1,2,4-oxadiazol-3-yl)pyridin-3-yl)oxy)-*N*-methylpicolinamide (**3s**)

Step 1. (*Z*)-*N*'-Hydroxy-5-methoxypicolinimidamide (**23**)

Following the same procedure used to prepare **15a**, 5-methoxypicolinonitrile (450 mg, 3.36 mmol) and 50% aq. NH_2OH (10 mL) were used to obtain **23** (547 mg, 98%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.72 (s, 1H), 8.26 (d, J = 2.9 Hz, 1H), 7.80 (d, J = 8.8 Hz, 1H), 7.43 (dd, J = 8.8, 3.0 Hz, 1H), 5.75 (s, 2H).

Step 2. 5-Isopropyl-3-(5-methoxypyridin-2-yl)-1,2,4-oxadiazole (**24**)

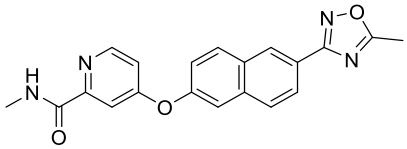
Following the same procedure used to prepare **16a**, **23** (500 mg, 2.99 mmol), isobutyryl chloride (382 mg, 3.59 mmol), and pyridine (10 mL) were used to obtain **24** (551 mg, 84%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48 (dd, J = 3.0, 0.7 Hz, 1H), 8.08 (dd, J = 8.7, 0.6 Hz, 1H), 7.31 (dd, J = 8.8, 3.1 Hz, 1H), 3.94 (s, 3H), 3.33 (hept, J = 7.0 Hz, 1H), 1.48 (d, J = 7.0 Hz, 6H).

Step 3. 6-(5-Isopropyl-1,2,4-oxadiazol-3-yl)pyridin-3-ol (**25**)

Following the same procedure used to prepare **9a**, **24** (500 mg, 2.28 mmol) and BBr_3 (1.71 g, 6.84 mmol) were used to obtain **25** (322 mg, 69%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.42 (br. s, 1H), 8.36 (d, J = 2.3 Hz, 1H), 8.02 (d, J = 8.6 Hz, 1H), 7.38 (dd, J = 8.6, 2.8 Hz, 1H), 3.27 (h, J = 7.0 Hz, 1H), 1.43 (d, J = 7.0 Hz, 6H).

Step 4. 4-((6-(5-Isopropyl-1,2,4-oxadiazol-3-yl)pyridin-3-yl)oxy)-*N*-methylpicolinamide (**3s**)

Following the same procedure used to prepare **3a**, **25** (150 mg, 0.731 mmol) and **11** (125 mg, 0.731 mmol) were used to obtain **3s** (118 mg, 48%) as white solid; mp 71–73 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (d, J = 2.7 Hz, 1H), 8.48 (d, J = 5.6 Hz, 1H), 8.23 (d, J = 8.5 Hz, 1H), 8.02 (br. s, 1H), 7.81 (d, J = 2.5 Hz, 1H), 7.58 (dd, J = 8.6, 2.8 Hz, 1H), 7.05 (dd, J = 5.6, 2.6 Hz, 1H), 3.36 (hept, J = 7.0 Hz, 1H), 3.04 (d, J = 5.1 Hz, 3H), 1.51 (d, J = 7.0 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 185.00, 167.33, 164.87, 164.07, 152.87, 151.98, 150.18, 143.48, 143.34, 128.37, 124.39, 114.54, 110.79, 27.67, 26.19, 20.20. IR (diamond) 3353, 3051, 2984, 2922, 1660, 1519, 1229 cm^{-1}. HRMS (EI) *m/z* calcd for $C_{17}H_{17}N_5O_3$ $[M]^+$ 339.1331, found 339.1329.



N-Methyl-4-((6-(5-methyl-1,2,4-oxadiazol-3-yl)naphthalen-2-yl)oxy)picolinamide (**3t**)

Step 1. 6-Hydroxy-2-naphthonitrile (**28**)

Following the same procedure used to prepare **14b**, 6-hydroxy-2-naphthoic acid (**26**, 2.00 g, 10.6 mmol) in DMF (77.4 mg, 1.06 mmol), $SOCl_2$ (30 mL), THF (20 mL), 50% aq. NH_3 (10 mL) were used to obtain crude 6-hydroxy-2-naphthamide (**27**, 1.018 g with 30% remaining **26**). Using the crude mixture, following the same procedure used to prepare **15b**, TFAA (3.27 g, 16.0 mmol), pyridine (2.11 g, 26.7 mmol), and THF (25 mL) were used to obtain **28** (447.3 mg, 2.644 mmol), ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.18 (d, J = 1.5 Hz, 1H), 7.84 (d, J = 8.7 Hz, 1H), 7.77 (d, J = 8.6 Hz, 1H), 7.58 (dd, J = 8.5, 1.7 Hz, 1H), 7.27 – 7.18 (m, 2H), 5.37 (s, 1H).

. ^{1}H NMR (300 MHz, acetone-d_6) δ 8.91 (br. s, 2H), 8.12 (d, J = 1.8 Hz, 1H), 7.91 – 7.73 (m, 2H), 7.66 (d, J = 8.7 Hz, 1H), 7.22 (d, J = 2.4 Hz, 1H), 7.17 (dd, J = 8.8, 2.5 Hz, 1H), 5.56 (s, 1H).

Step 2. (*Z*)-*N*',6-Dihydroxy-2-naphthimidamide (**29**)

Following the same procedure used to prepare **15b**, **28** (447 mg, 2.644 mmol) and 50% aq. NH_2OH (15 mL) were used to obtain **29** (534 mg, 99%). ^{1}H NMR (300 MHz, Acetone-d_6) δ 8.91 (br. s, 2H), 8.12 (d, J = 1.8 Hz, 1H), 7.91 – 7.73 (m, 2H), 7.66 (d, J = 8.7 Hz, 1H), 7.22 (d, J = 2.4 Hz, 1H), 7.17 (dd, J = 8.8, 2.5 Hz, 1H), 5.56 (s, 1H).

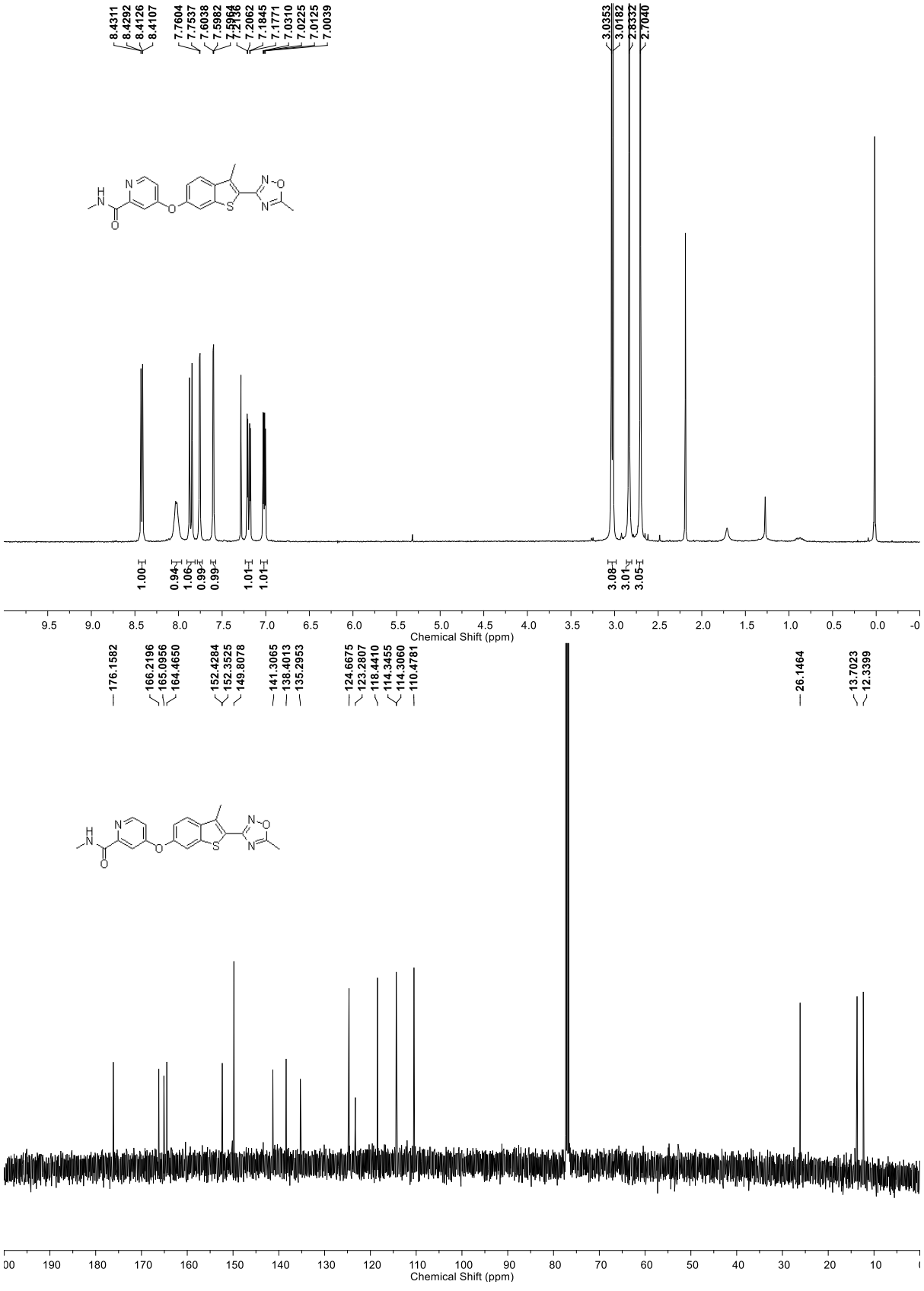
Step 3. 6-(5-Methyl-1,2,4-oxadiazol-3-yl)naphthalen-2-ol (**30**)

Following the same procedure used to prepare **16a**, **29** (150 mg, 0.742 mmol), acetyl chloride (61.2 mg, 0.779 mmol) and pyridine (2.5 mL) were used to obtain **30** (64.4 mg, 38%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 (s, 1H), 8.10 (dd, J = 8.6, 1.7 Hz, 1H), 7.88 (d, J = 8.7 Hz, 1H), 7.79 (d, J = 8.6 Hz, 1H), 7.23 – 7.14 (m, 2H), 5.16 (s, 1H), 2.71 (s, 3H).

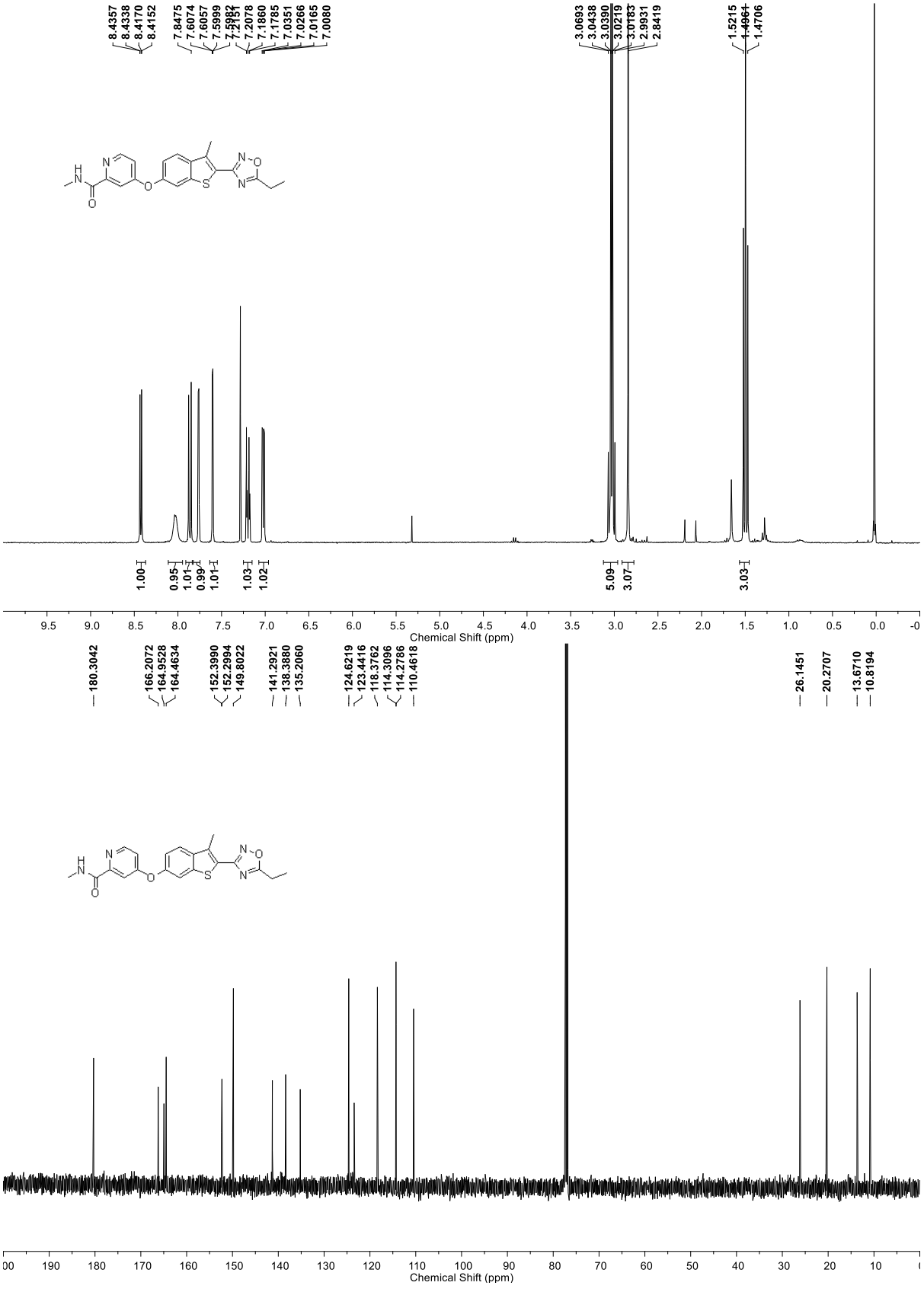
Step 3. *N*-Methyl-4-((6-(5-methyl-1,2,4-oxadiazol-3-yl)naphthalen-2-yl)oxy)picolinamide (**3t**)

Following the same procedure used to prepare **3a**, **30** (64.4 mg, 0.285 mmol) and **11** (48.6 mg, 0.285 mmol) were used to obtain **3t** (21.8 mg, 21%) as white solid; mp 161–163 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.45 (dd, J = 5.6, 0.6 Hz, 1H), 8.20 (dd, J = 8.6, 1.7 Hz, 1H), 8.10 – 7.98 (m, 2H), 7.90 (d, J = 8.6 Hz, 1H), 7.81 (d, J = 2.4 Hz, 1H), 7.58 (d, J = 2.4 Hz, 1H), 7.32 (dd, J = 8.9, 2.4 Hz, 1H), 7.06 (dd, J = 5.6, 2.6 Hz, 1H), 3.04 (d, J = 5.1 Hz, 3H), 2.74 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.70, 168.27, 165.89, 164.45, 152.85, 152.49, 149.86, 135.55, 131.56, 130.89, 128.29, 127.72, 124.91, 124.20, 121.17, 117.37, 114.59, 110.76, 26.14, 12.45. IR (diamond) 3241, 3056, 2929, 1680, 1519, 1287 cm^{-1}. HRMS (EI) *m*/*z* calcd for $C_{20}H_{16}N_4O_3$ $[M]^+$ 360.1222, found 360.1224.

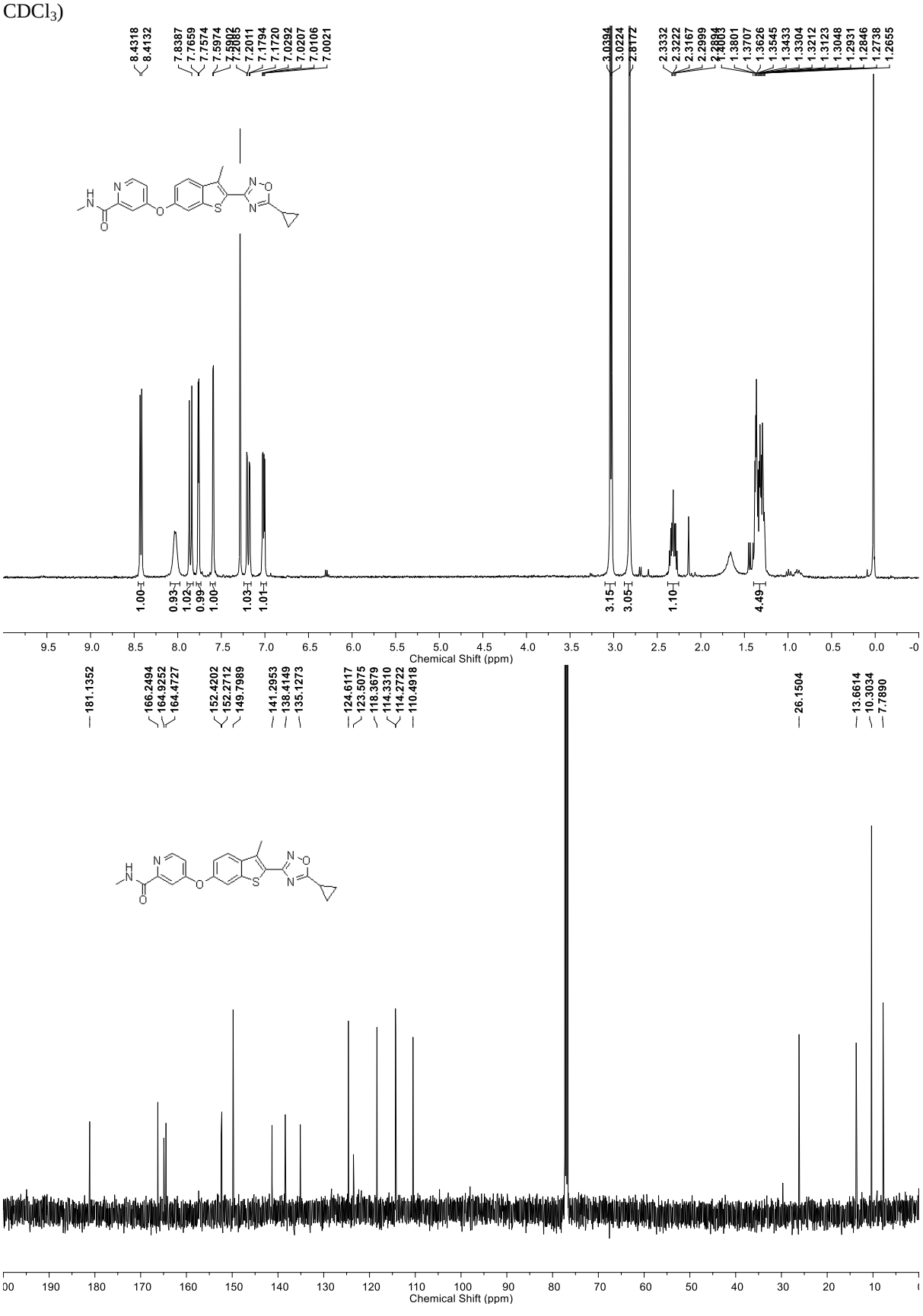
N-Methyl-4-((3-methyl-2-(5-methyl-1,2,4-oxadiazol-3-yl)benzo[*b*]thiophen-6-yl)oxy)picolinamide (**2a**, $CDCl_3$)



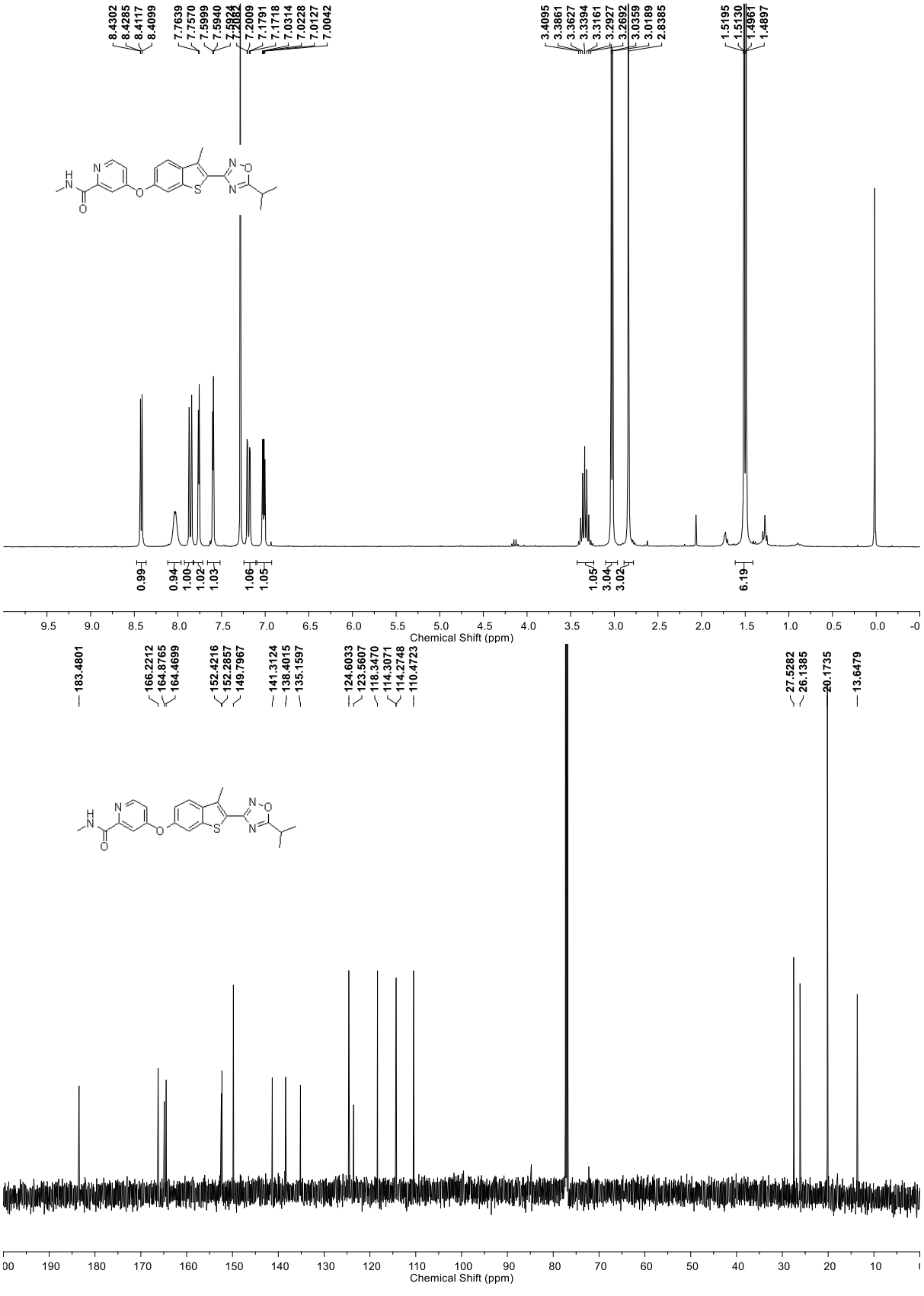
4-((2-(5-Ethyl-1,2,4-oxadiazol-3-yl)-3-methylbenzo[*b*]thiophen-6-yl)oxy)-*N*-methylpicolinamide (**2b**, $CDCl_3$)



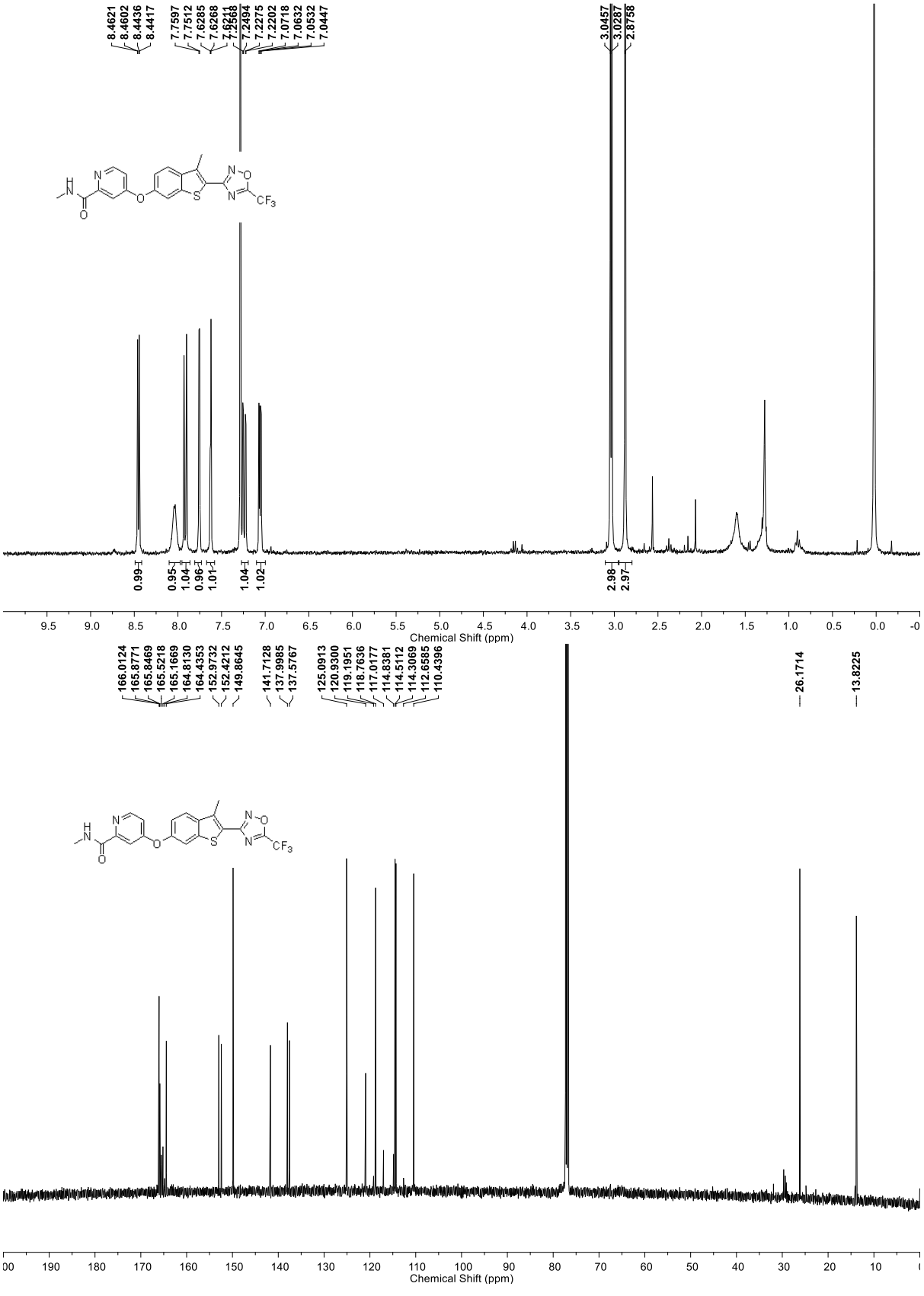
4-((2-(5-Cyclopropyl-1,2,4-oxadiazol-3-yl)-3-methylbenzo[*b*]thiophen-6-yl)oxy)-*N*-methylpicolinamide (**2c**, $CDCl_3$)



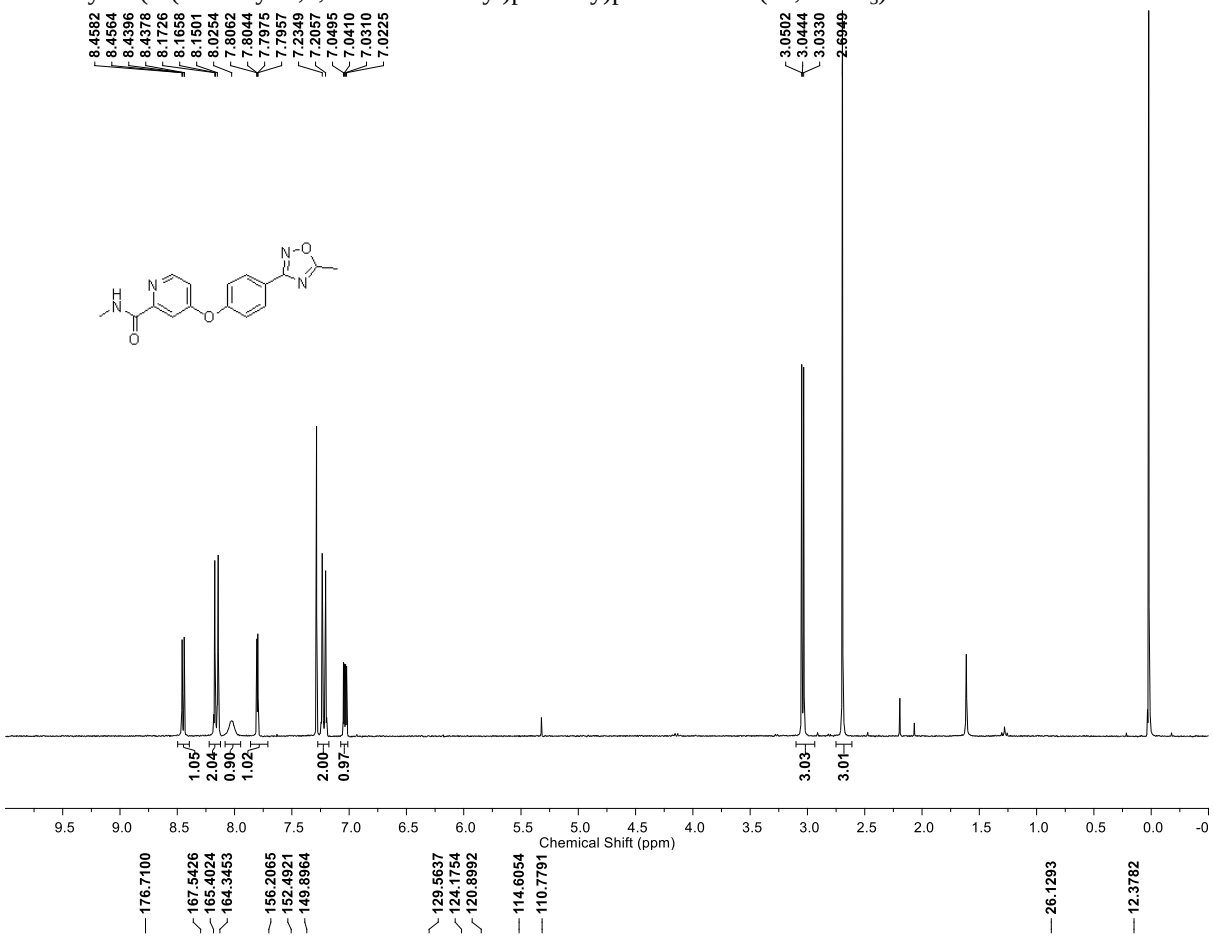
4-((2-(5-Isopropyl-1,2,4-oxadiazol-3-yl)-3-methylbenzo[*b*]thiophen-6-yl)oxy)-*N*-methylpicolinamide (**2d**, $CDCl_3$)

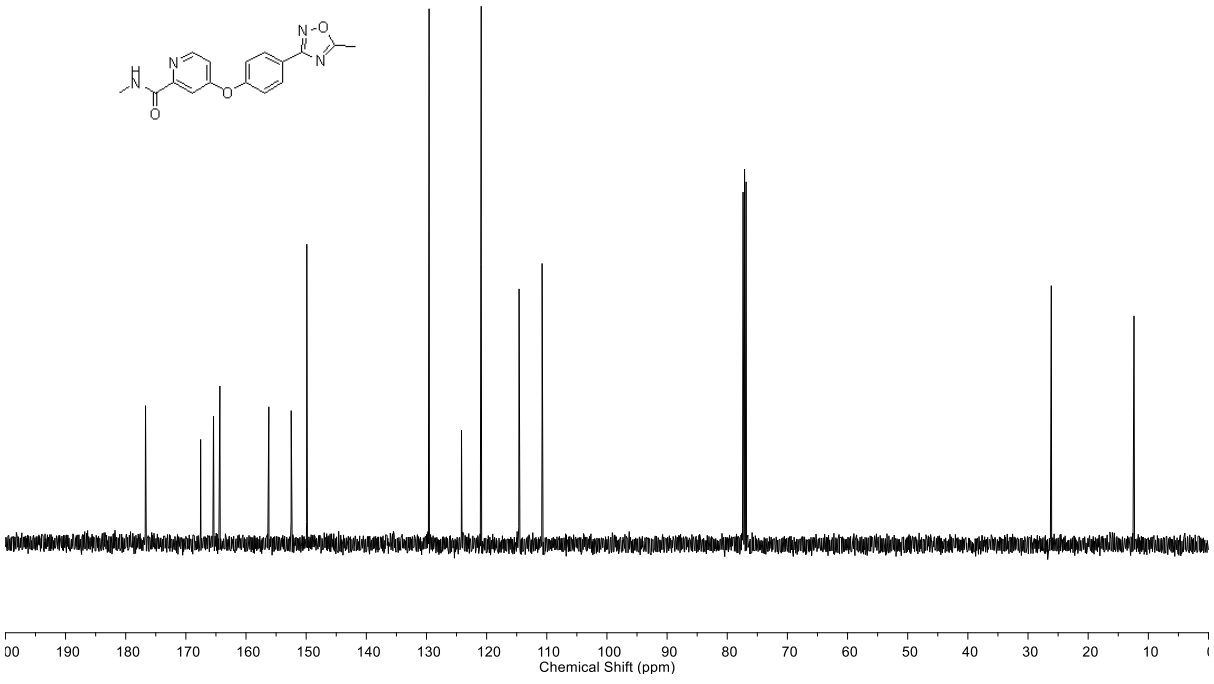


N-Methyl-4-((3-methyl-2-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)benzo[*b*]thiophen-6-yl)oxy)picolinamide (**2e**, $CDCl_3$)

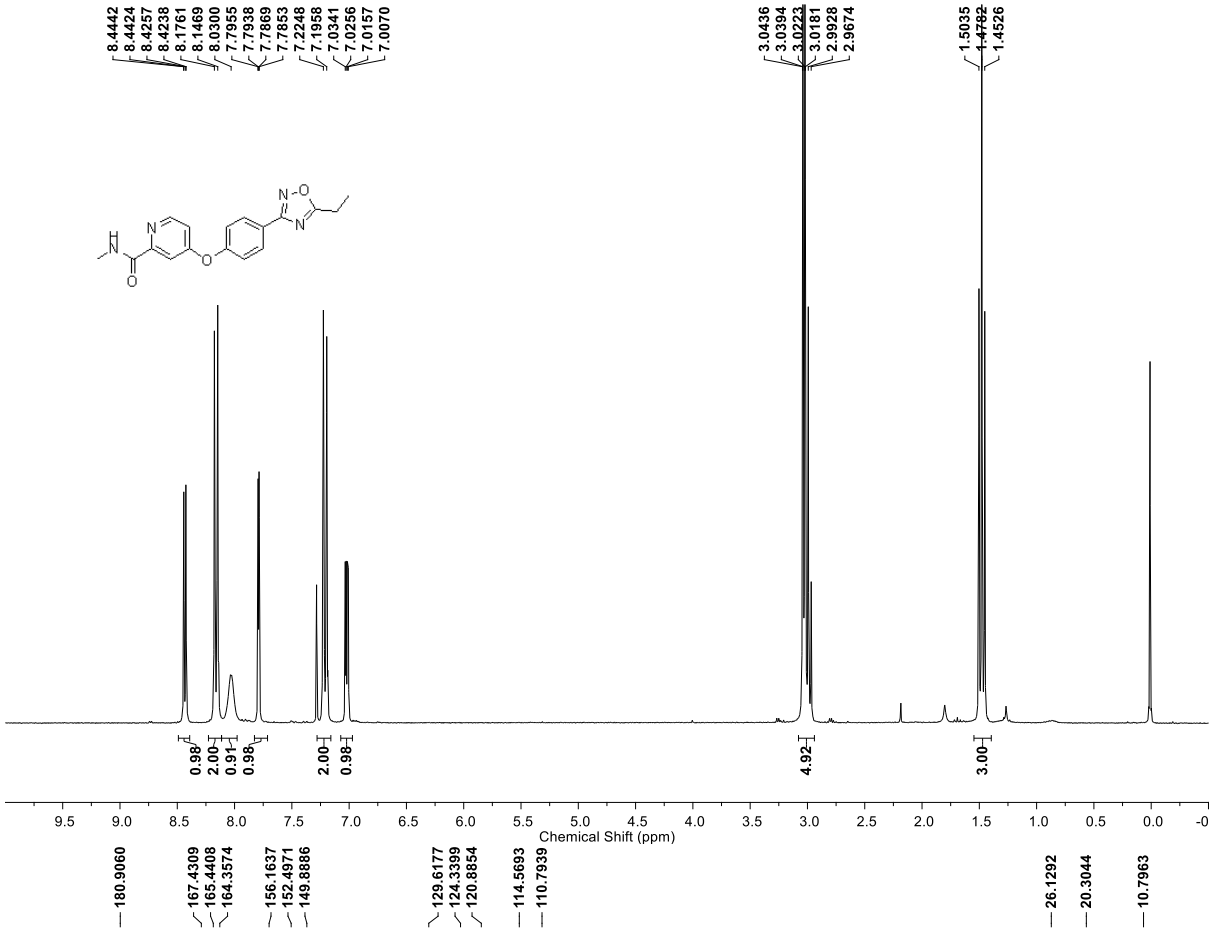


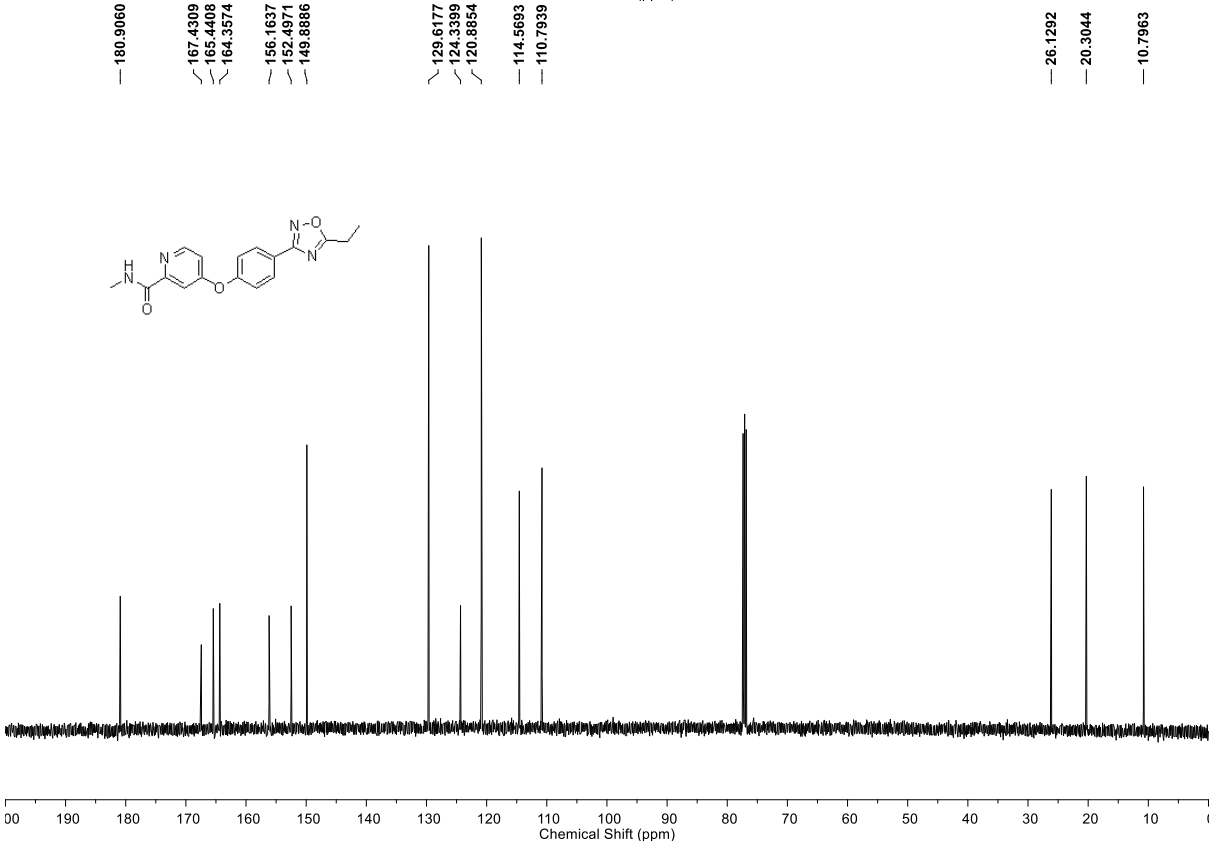
N-Methyl-4-(4-(5-methyl-1,2,4-oxadiazol-3-yl)phenoxy)picolinamide (**3a**, $CDCl_3$)



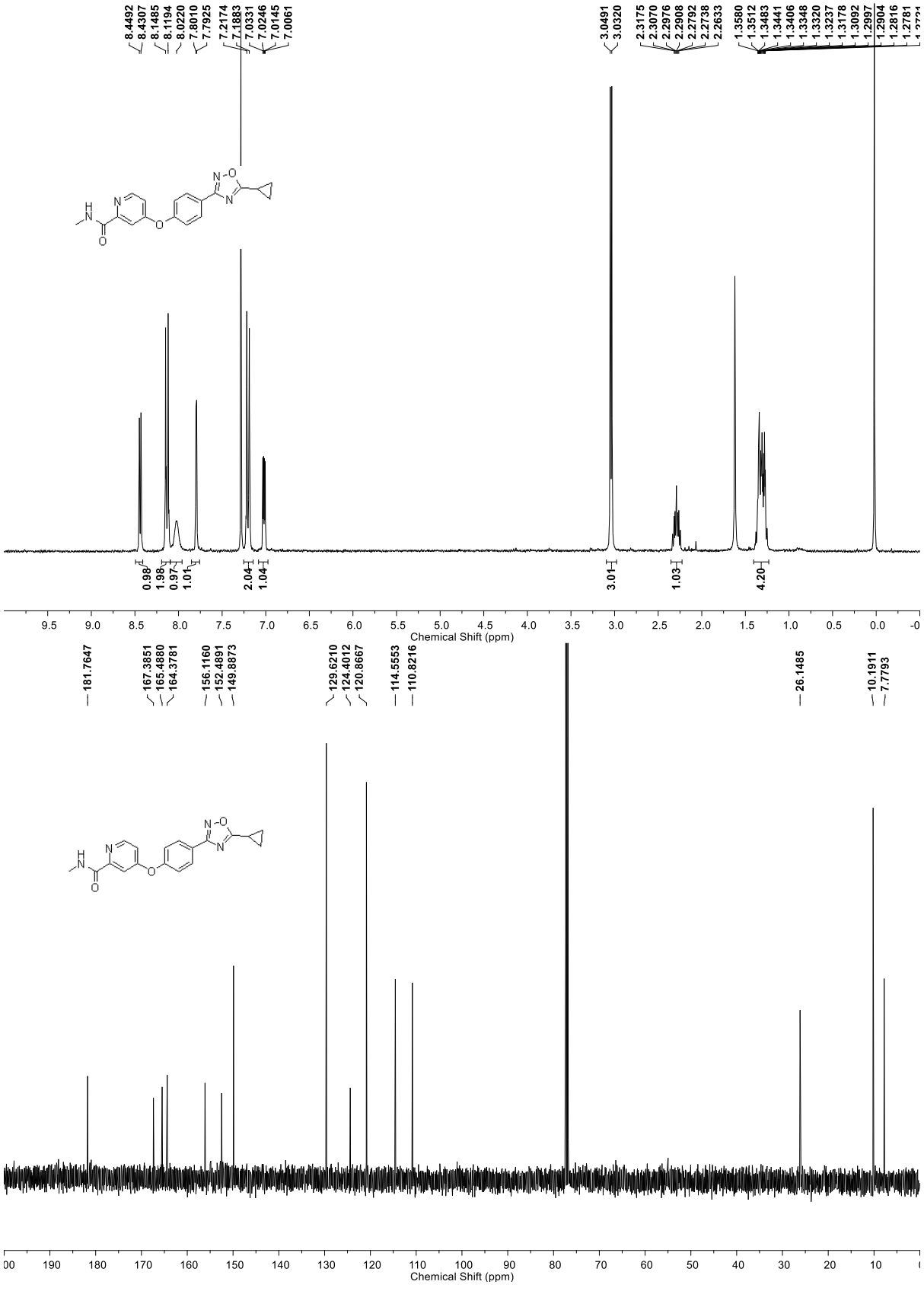


4-(4-(5-Ethyl-1,2,4-oxadiazol-3-yl)phenoxy)-*N*-methylpicolinamide (**3b**, $CDCl_3$)

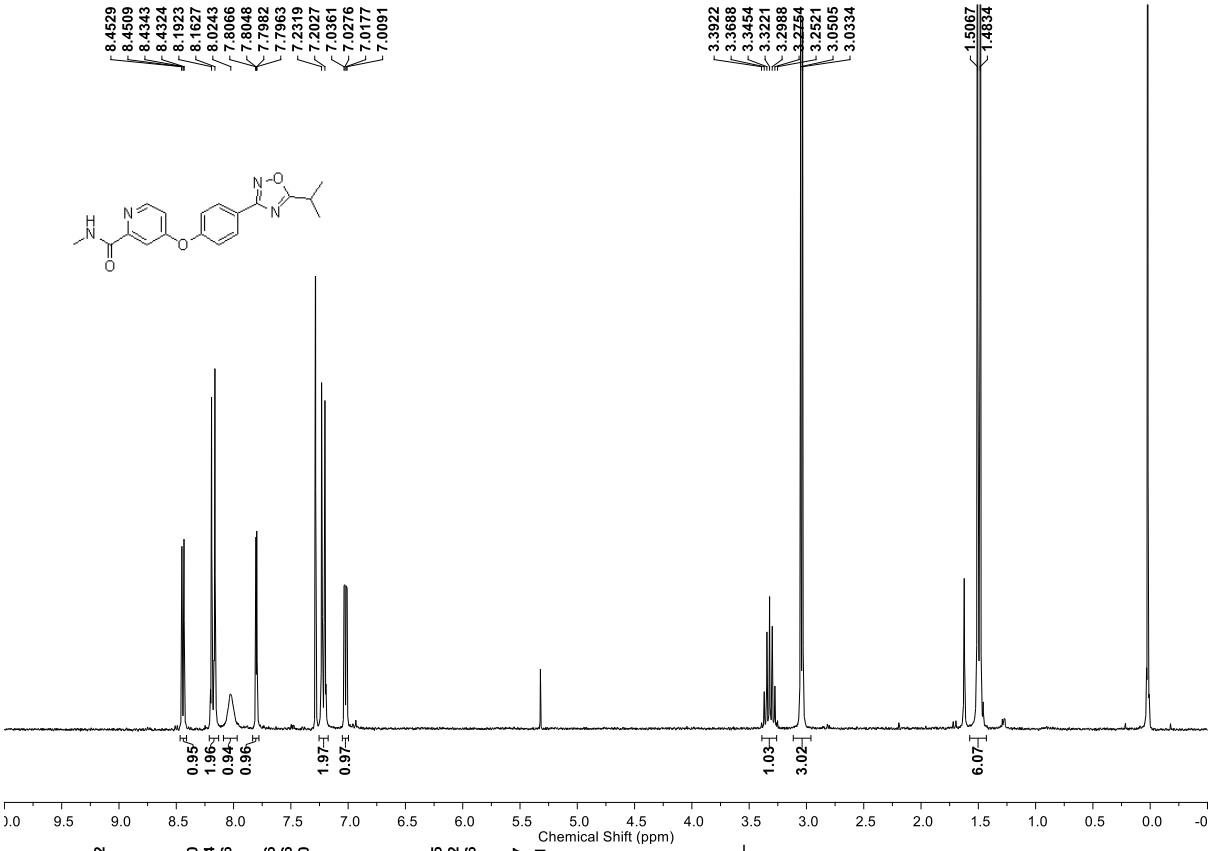


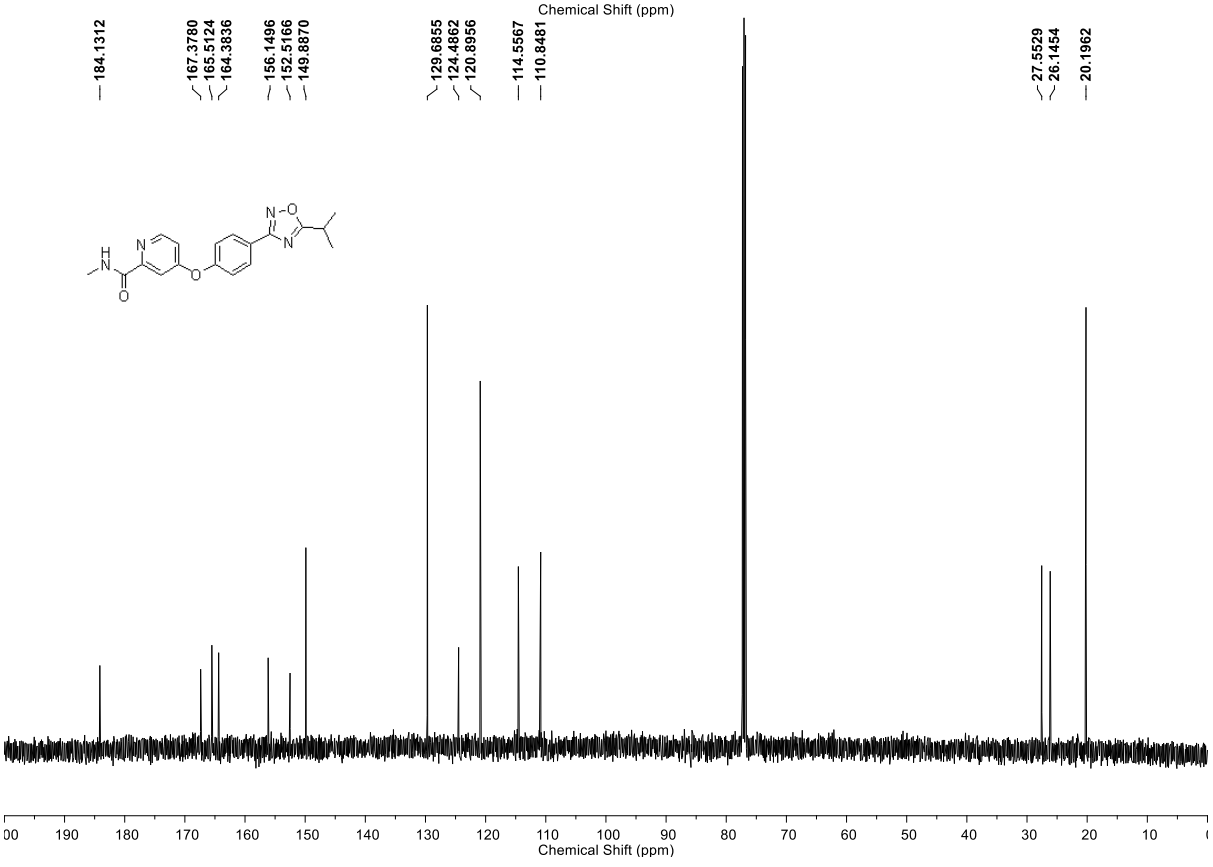


4-(4-(5-Cyclopropyl-1,2,4-oxadiazol-3-yl)phenoxy)-*N*-methylpicolinamide (**3c**, $CDCl_3$)

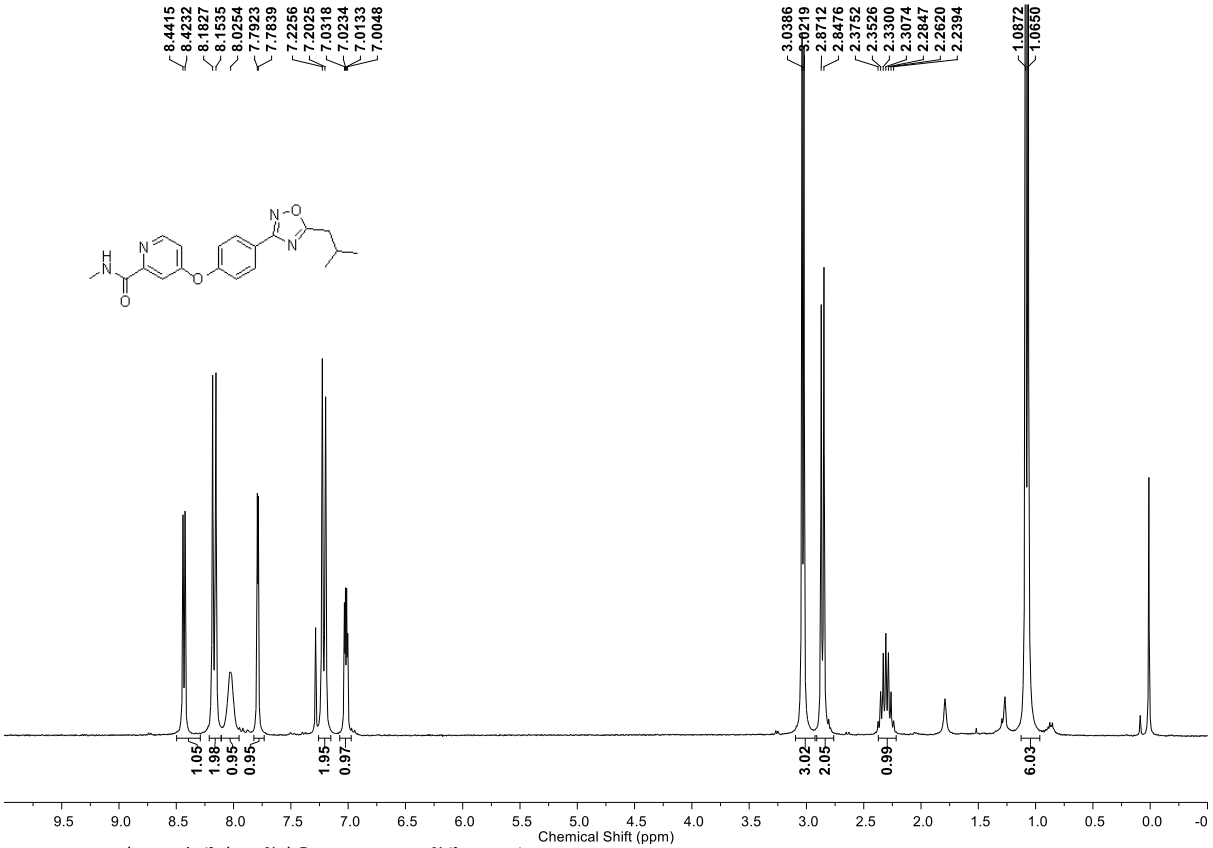


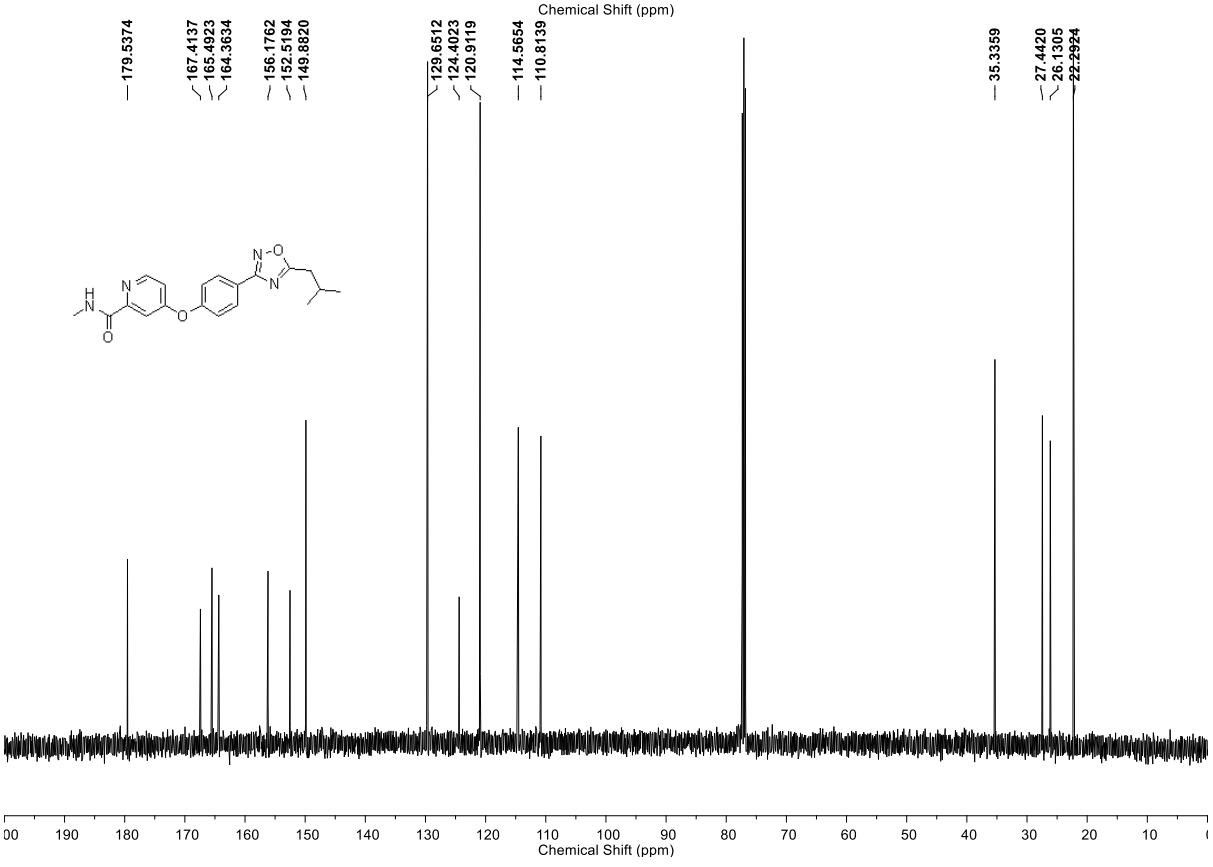
4-(4-(5-Isopropyl-1,2,4-oxadiazol-3-yl)phenoxy)-*N*-methylpicolinamide (**3d**, $CDCl_3$)



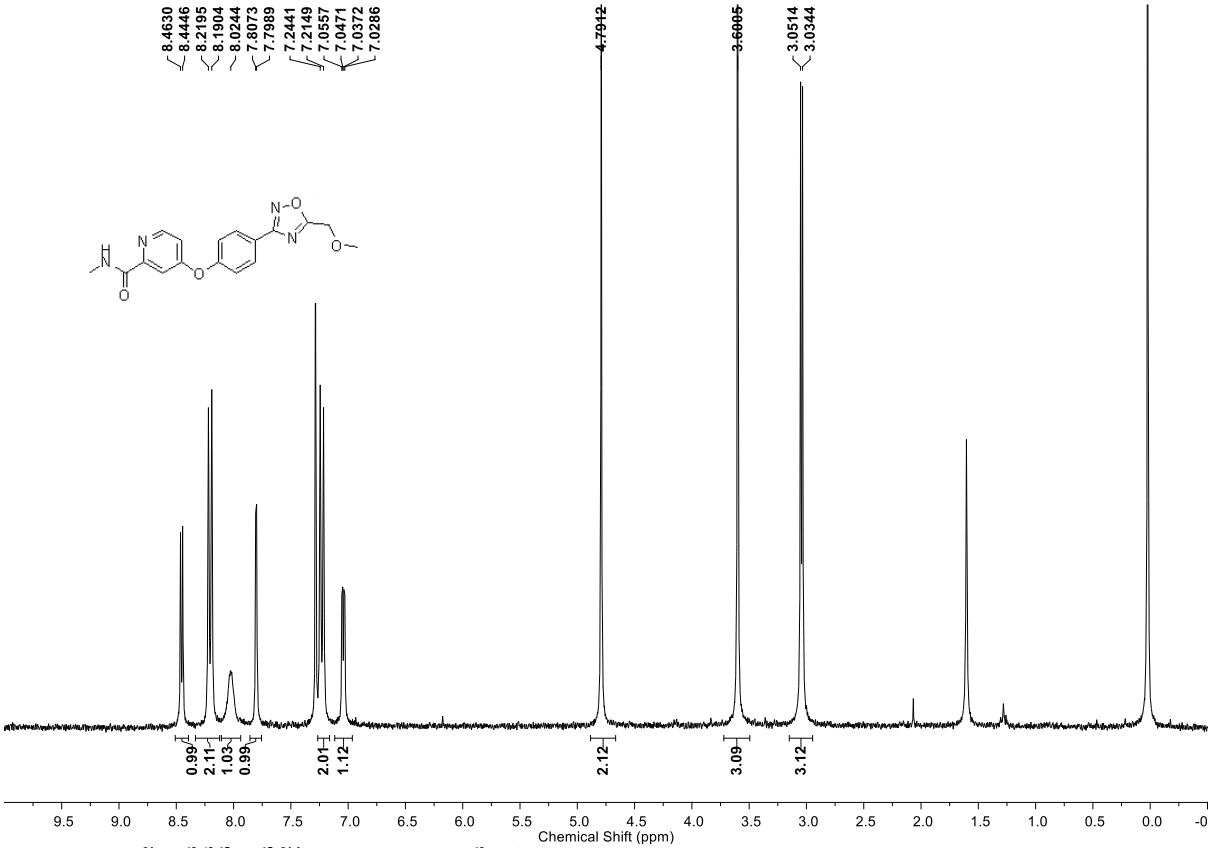


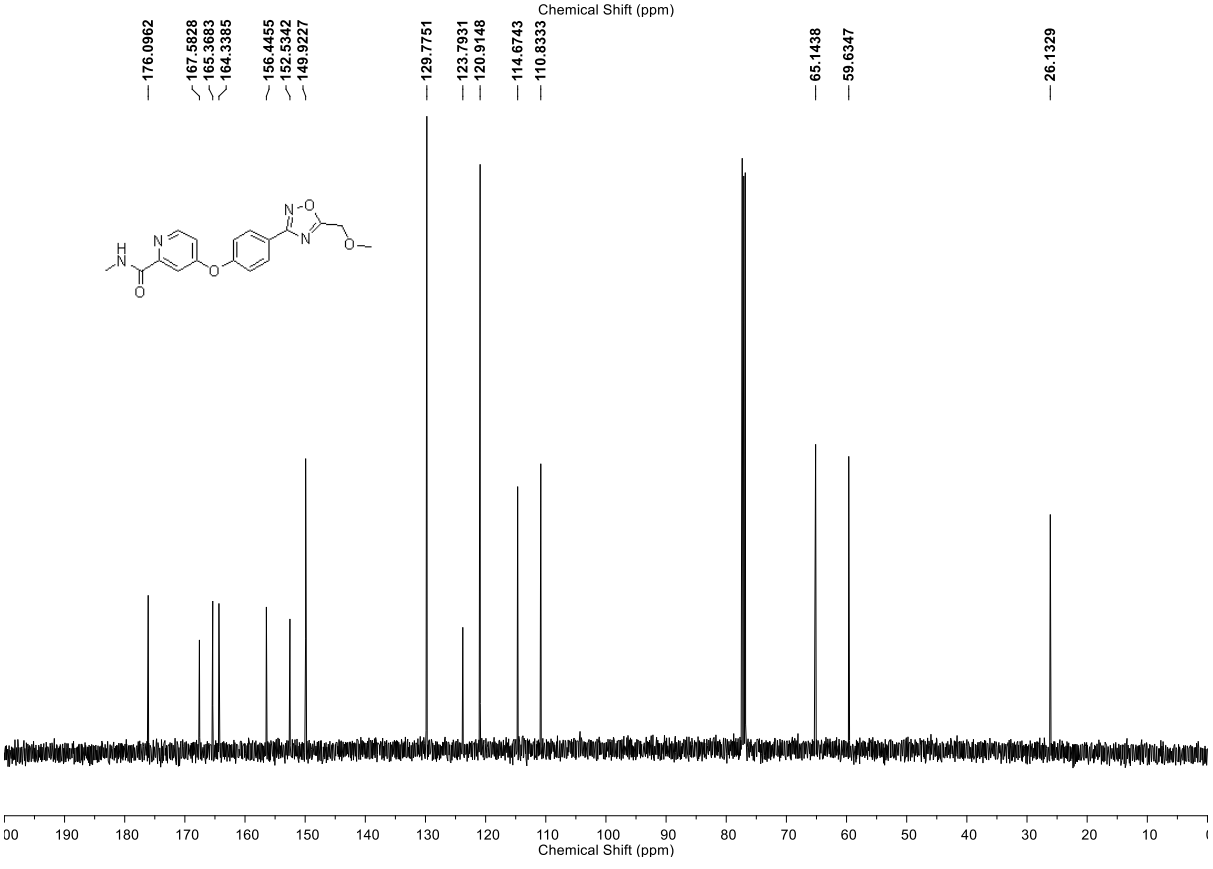
4-(4-(5-Isobutyl-1,2,4-oxadiazol-3-yl)phenoxy)-*N*-methylpicolinamide (**3e**, $CDCl_3$)



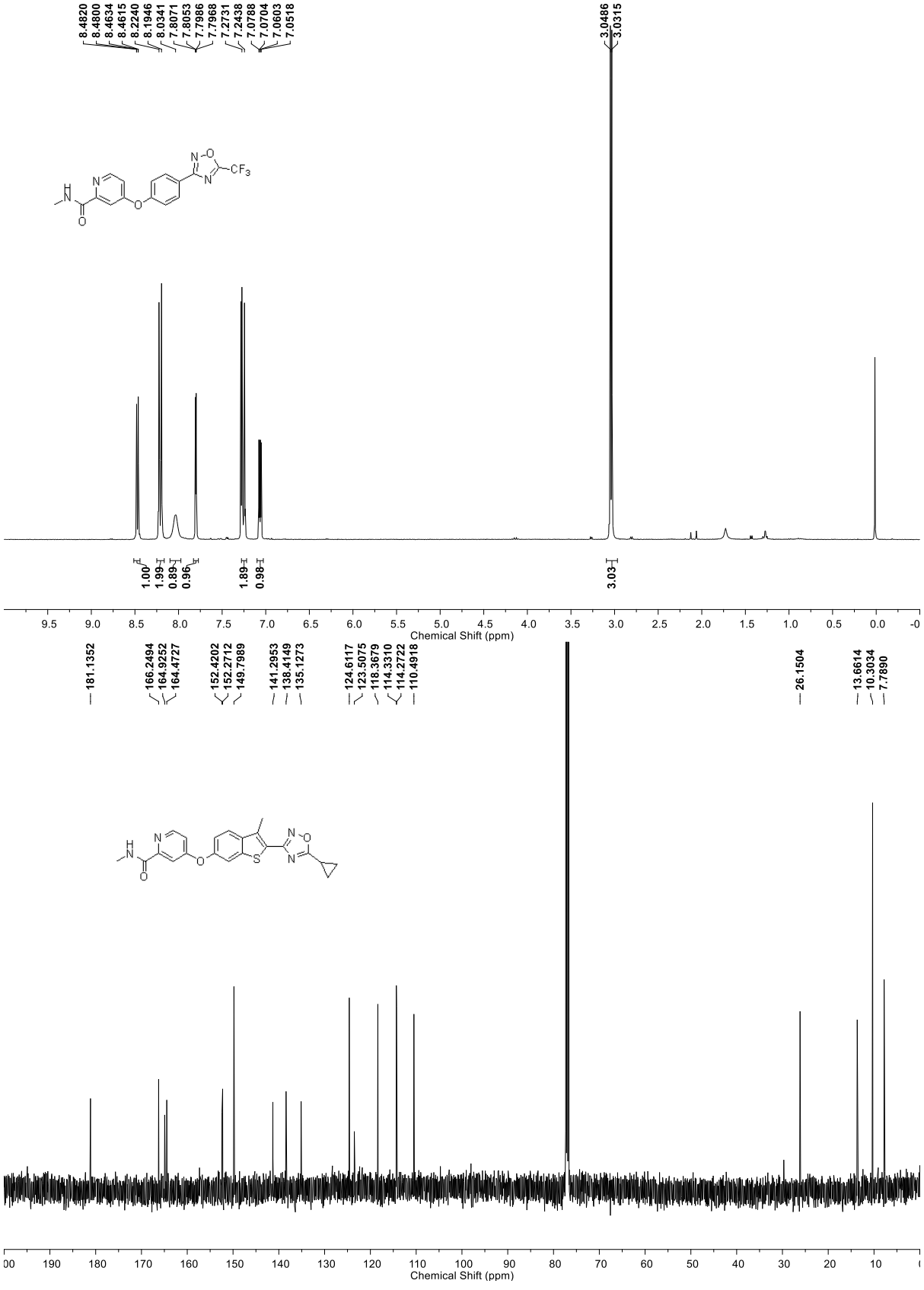


4-(4-(5-(Methoxymethyl)-1,2,4-oxadiazol-3-yl)phenoxy)-*N*-methylpicolinamide (**3f**, $CDCl_3$)

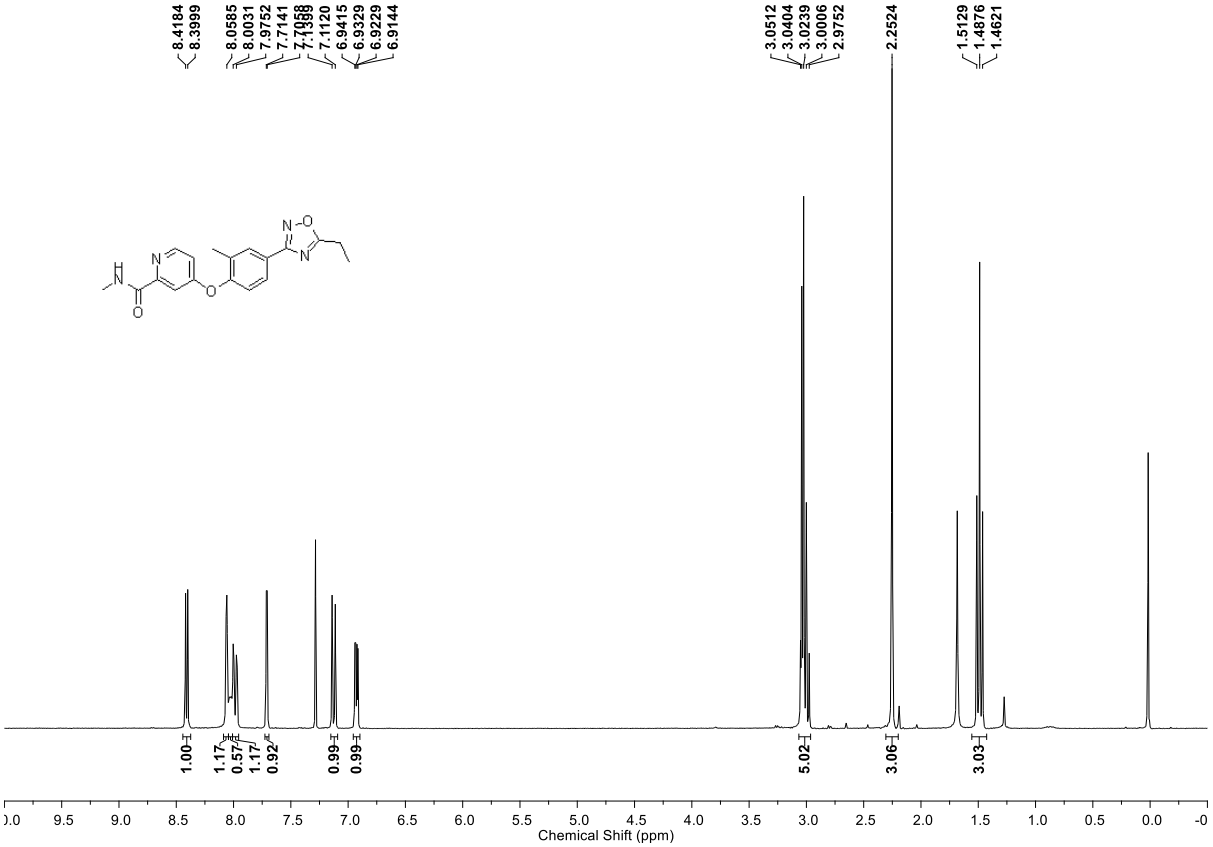


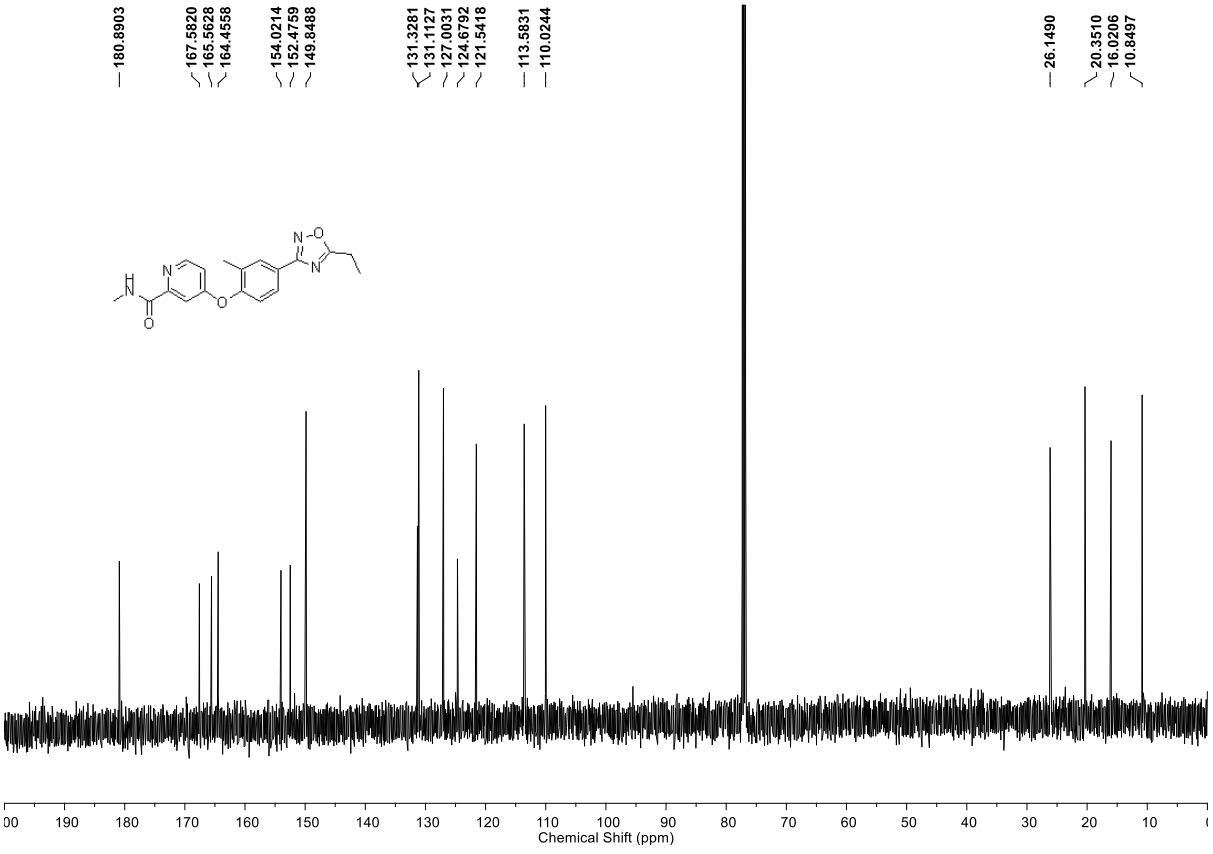


N-Methyl-4-(4-(5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)phenoxy)picolinamide (**3g**, $CDCl_3$)

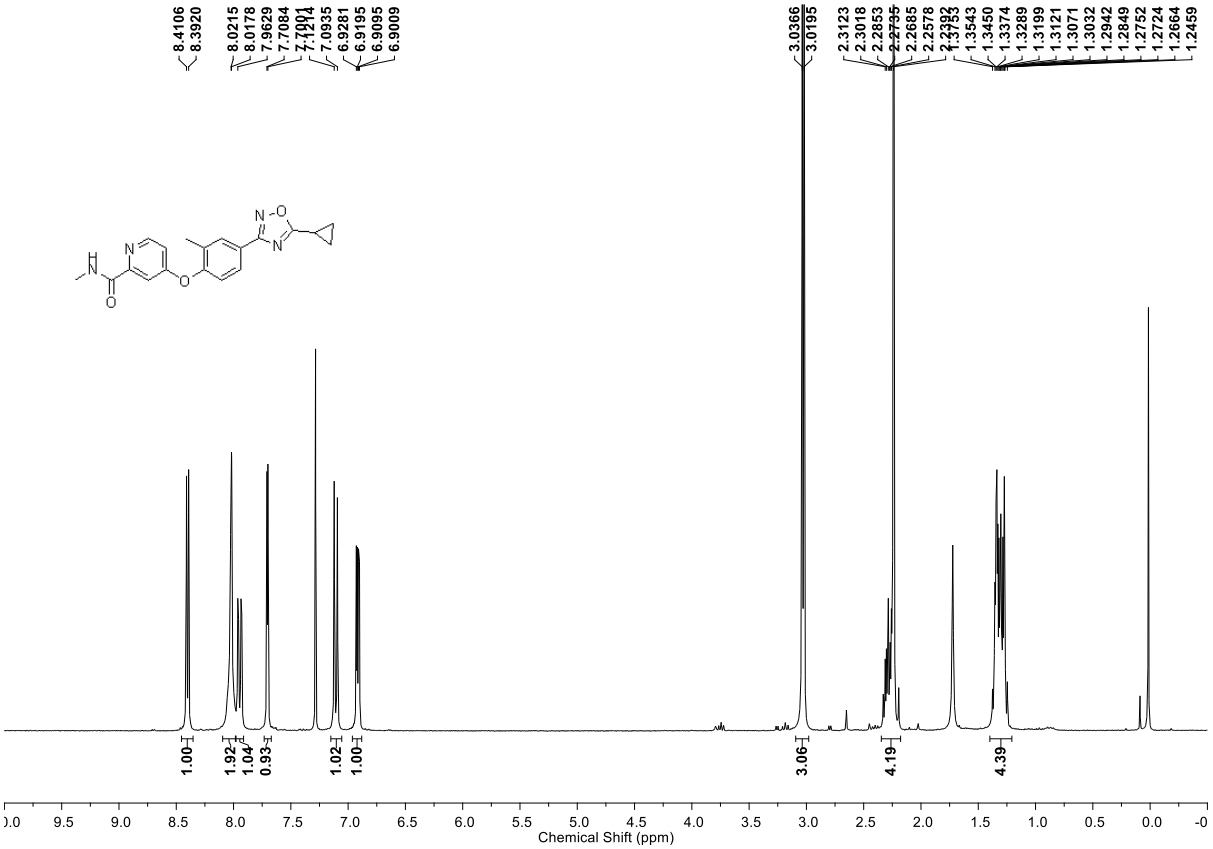


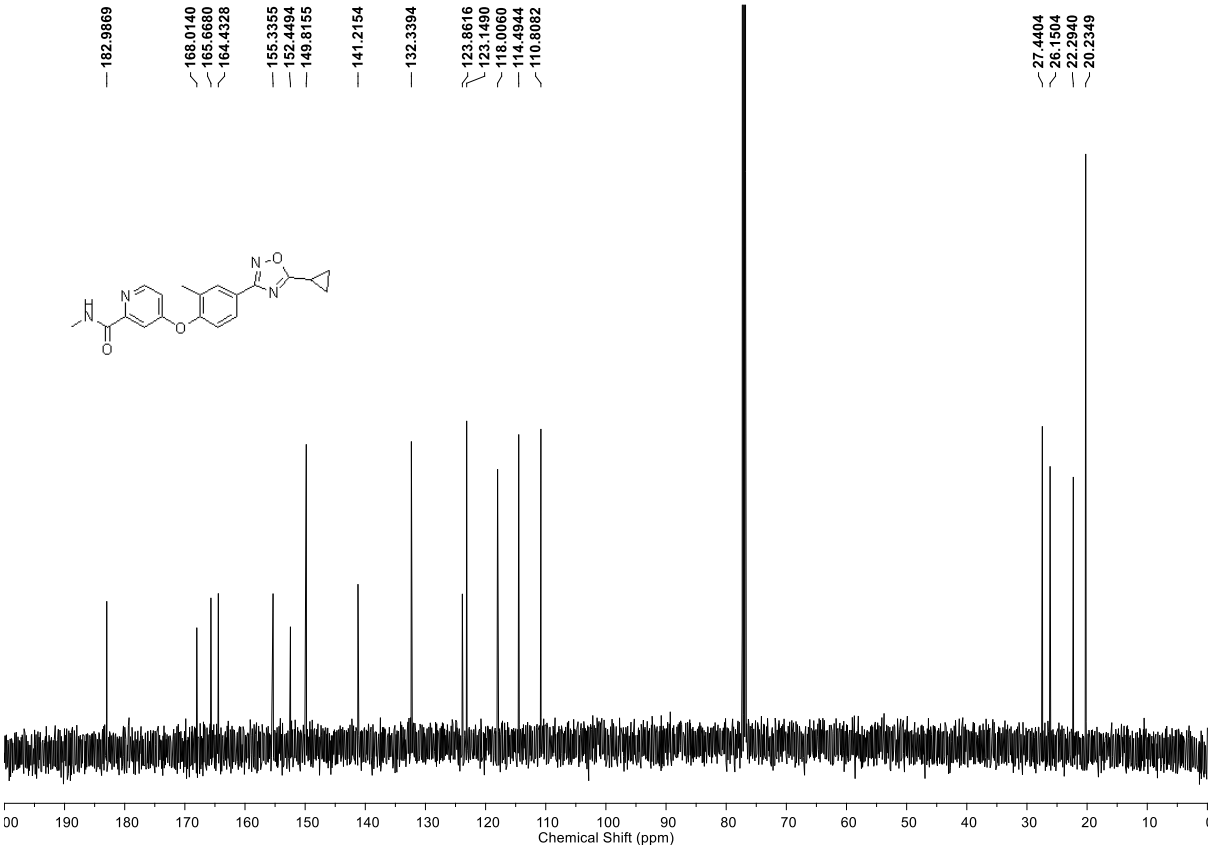
4-(4-(5-Ethyl-1,2,4-oxadiazol-3-yl)-2-methylphenoxy)-*N*-methylpicolinamide (**3h**, $CDCl_3$)



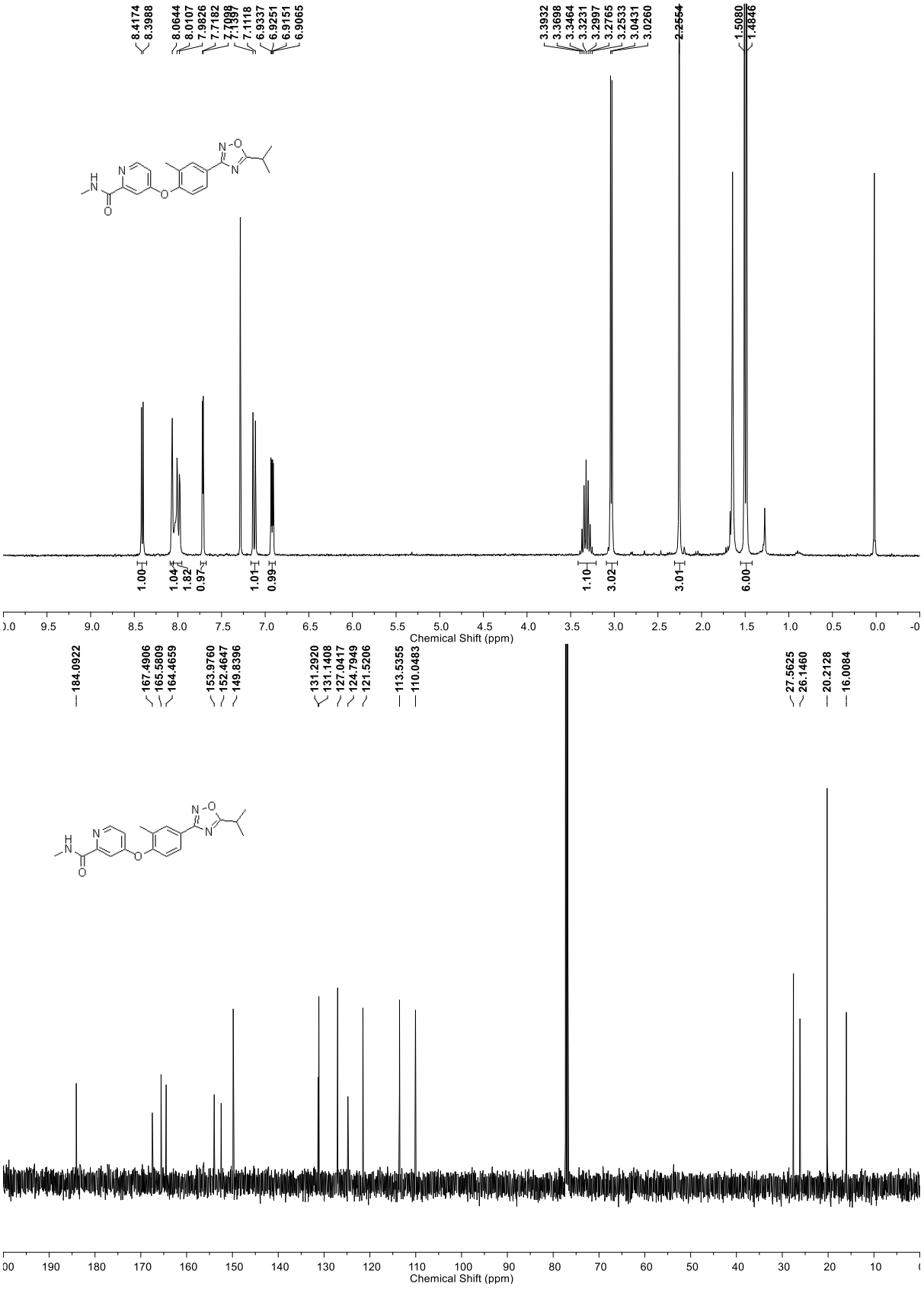


4-(4-(5-Cyclopropyl-1,2,4-oxadiazol-3-yl)-2-methylphenoxy)-*N*-methylpicolinamide (**3i**, $CDCl_3$)

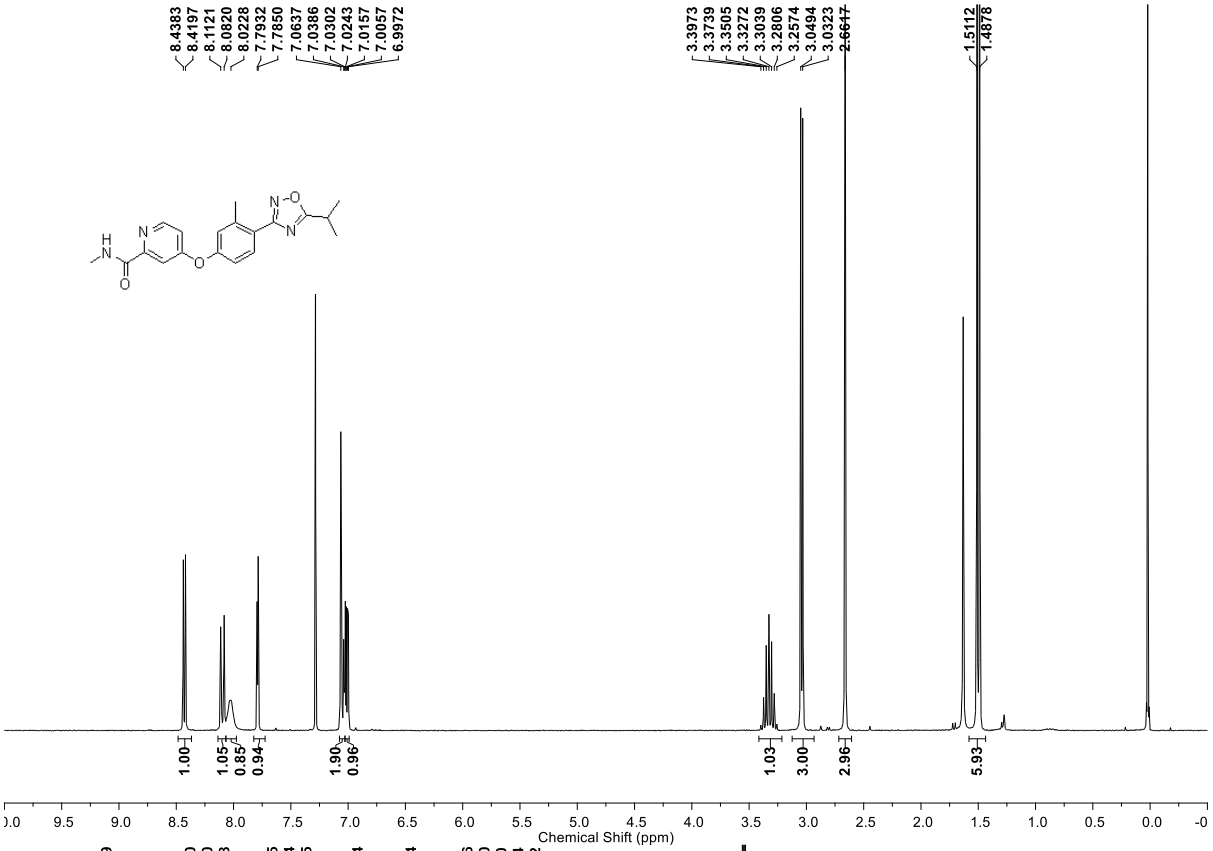


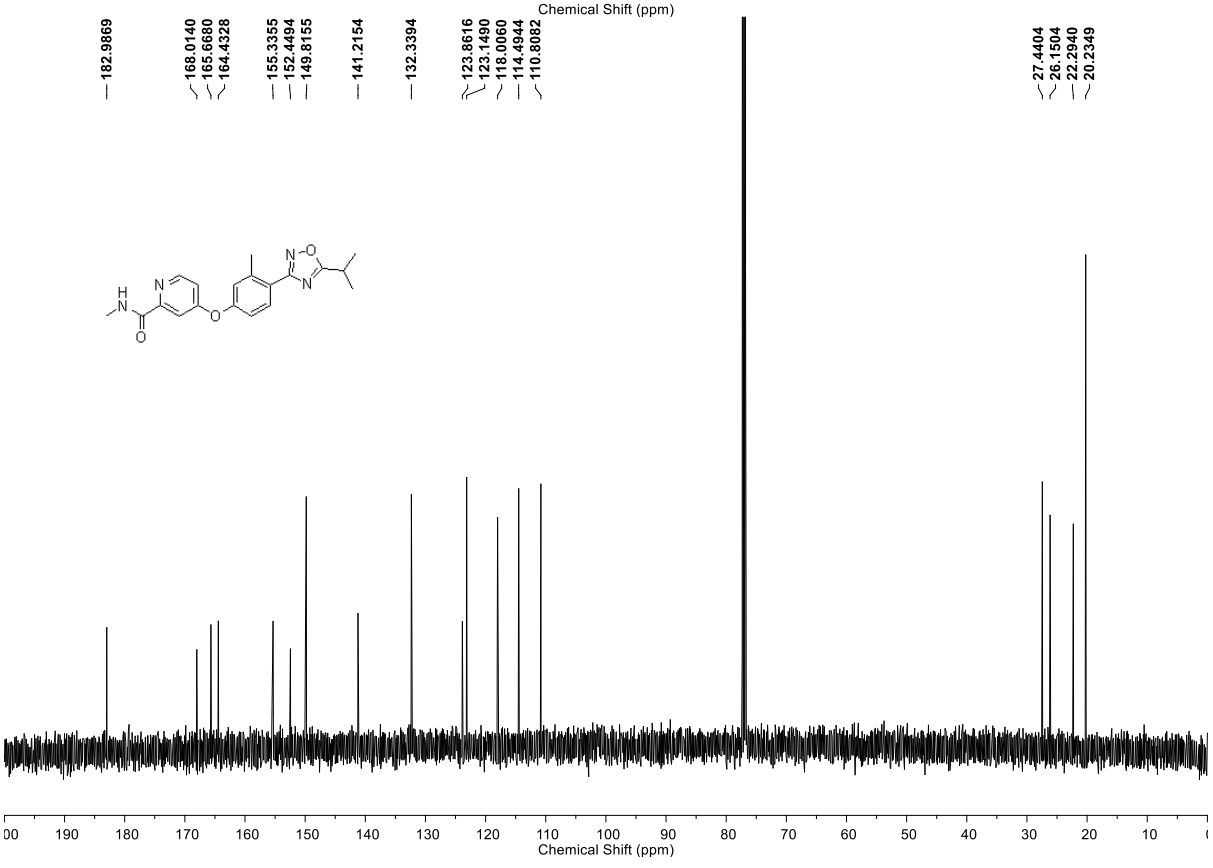


4-(4-(5-Isopropyl-1,2,4-oxadiazol-3-yl)-2-methylphenoxy)-*N*-methylpicolinamide (**3j**, $CDCl_3$)

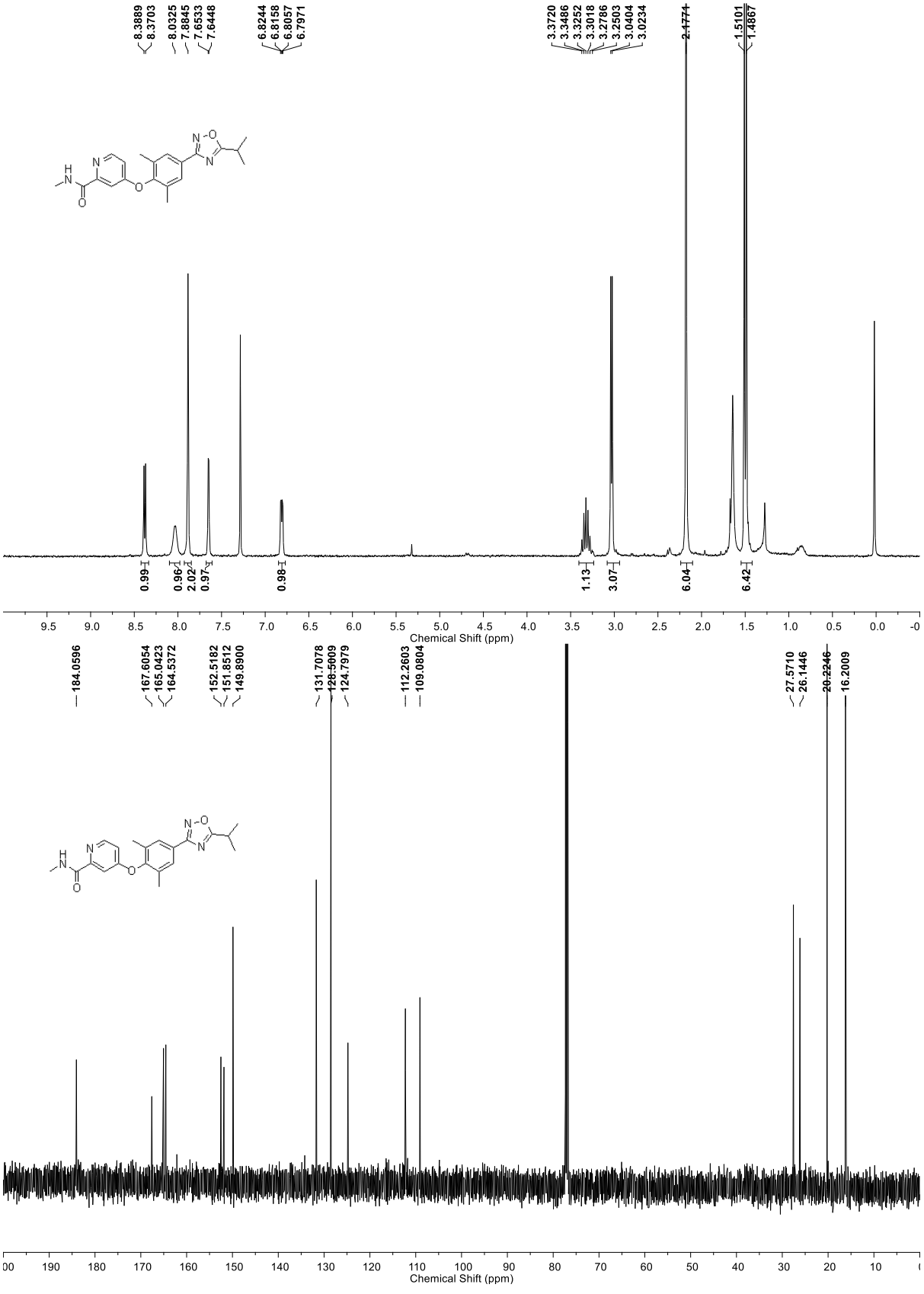


4-(4-(5-Isopropyl-1,2,4-oxadiazol-3-yl)-3-methylphenoxy)-*N*-methylpicolinamide (**3k**, $CDCl_3$)

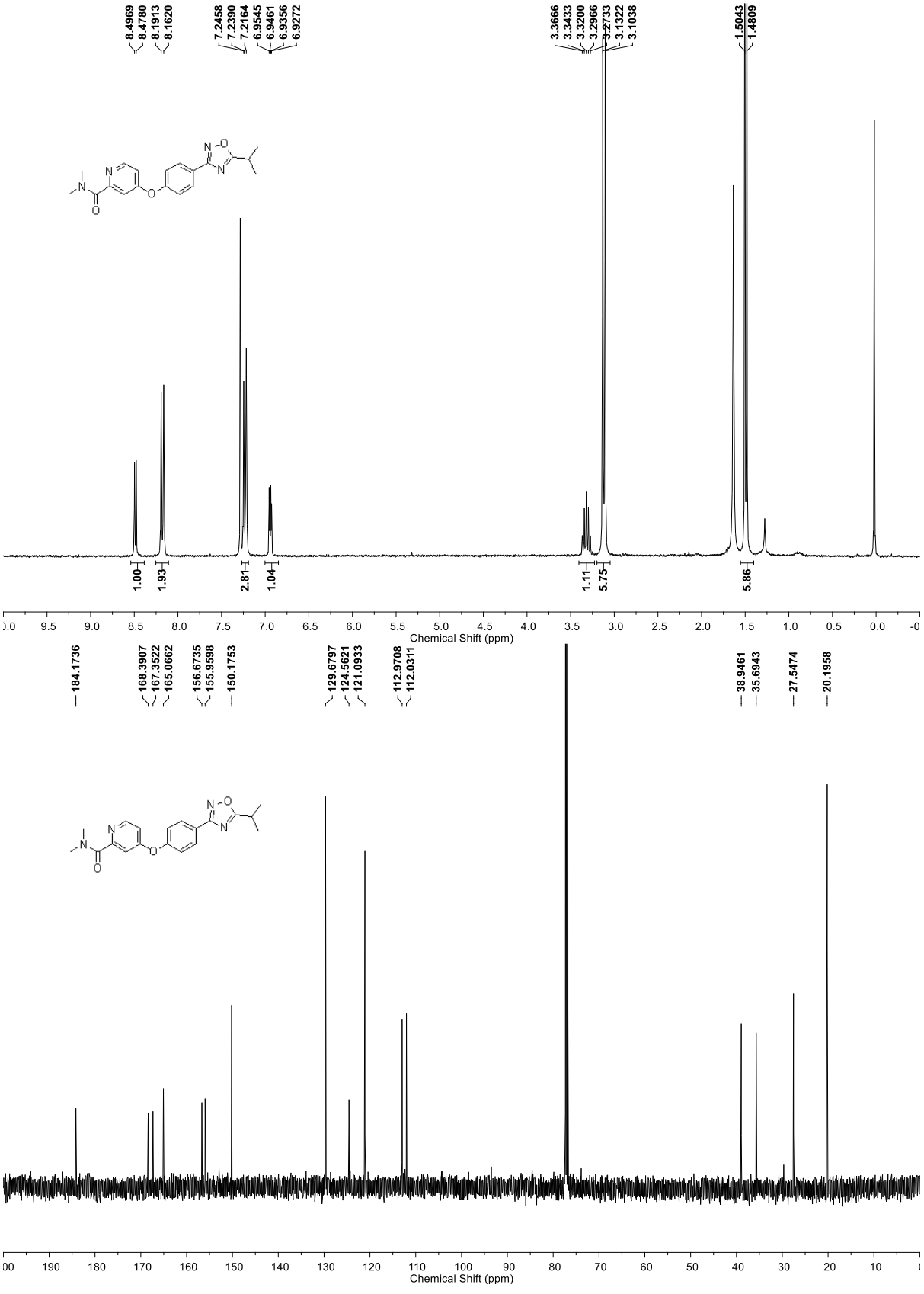




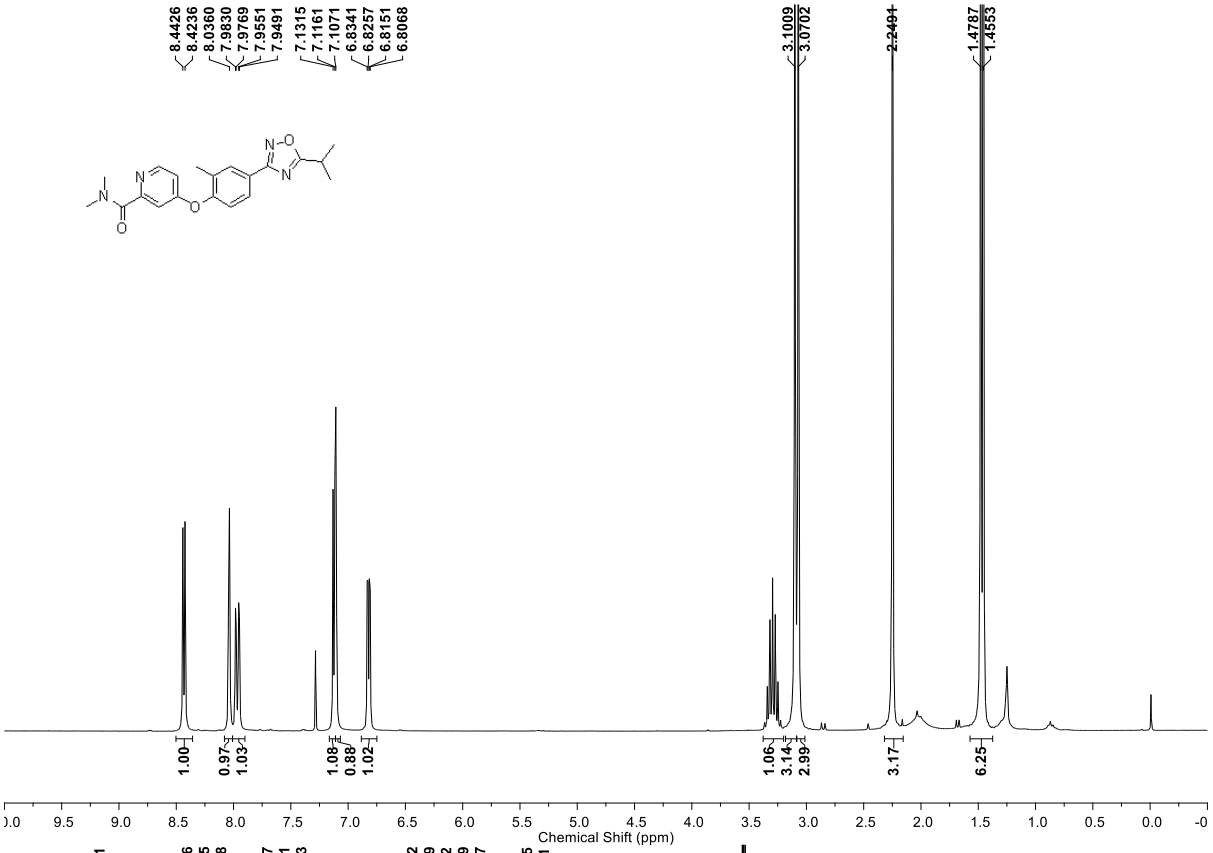
4-(4-(5-Isopropyl-1,2,4-oxadiazol-3-yl)-2,6-dimethylphenoxy)-*N*-methylpicolinamide (**3l**, $CDCl_3$)

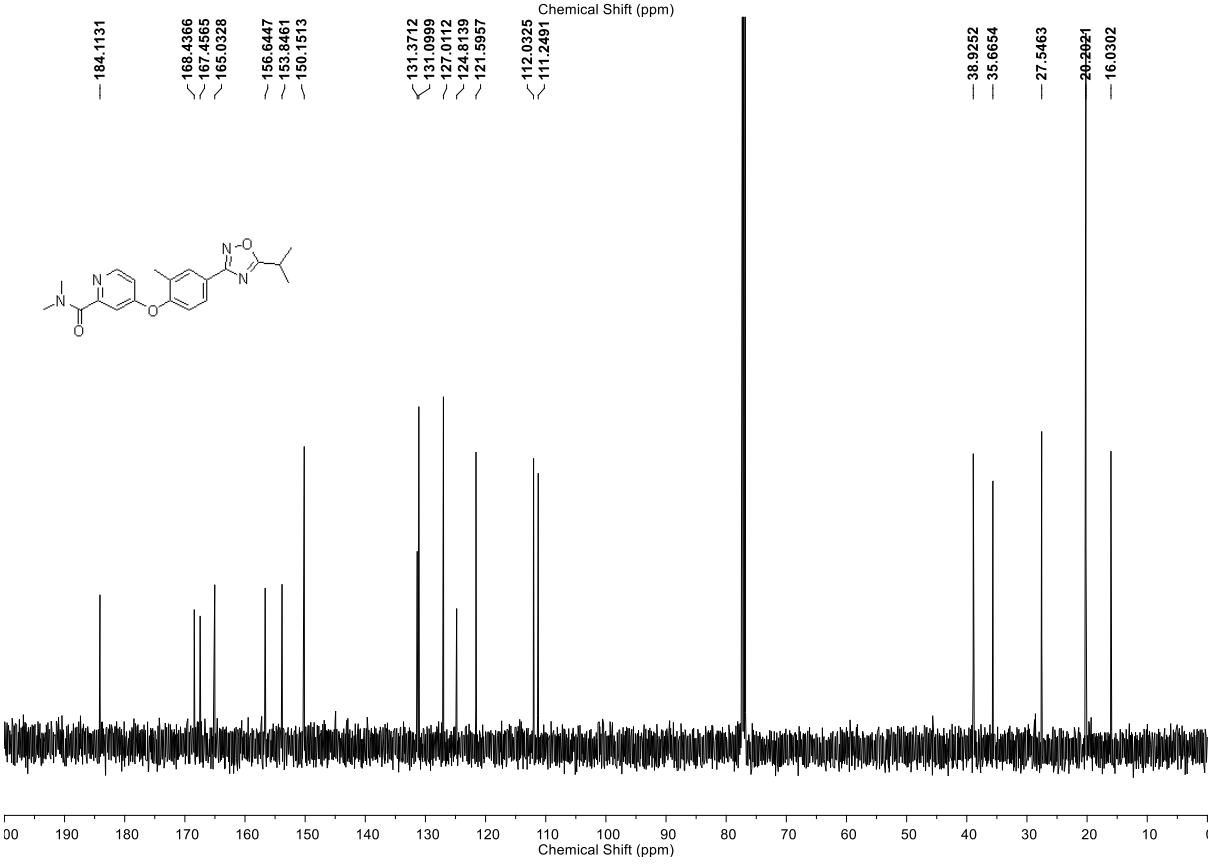


4-(4-(5-Isopropyl-1,2,4-oxadiazol-3-yl)phenoxy)-*N*,*N*-dimethylpicolinamide (**3m**, $CDCl_3$)

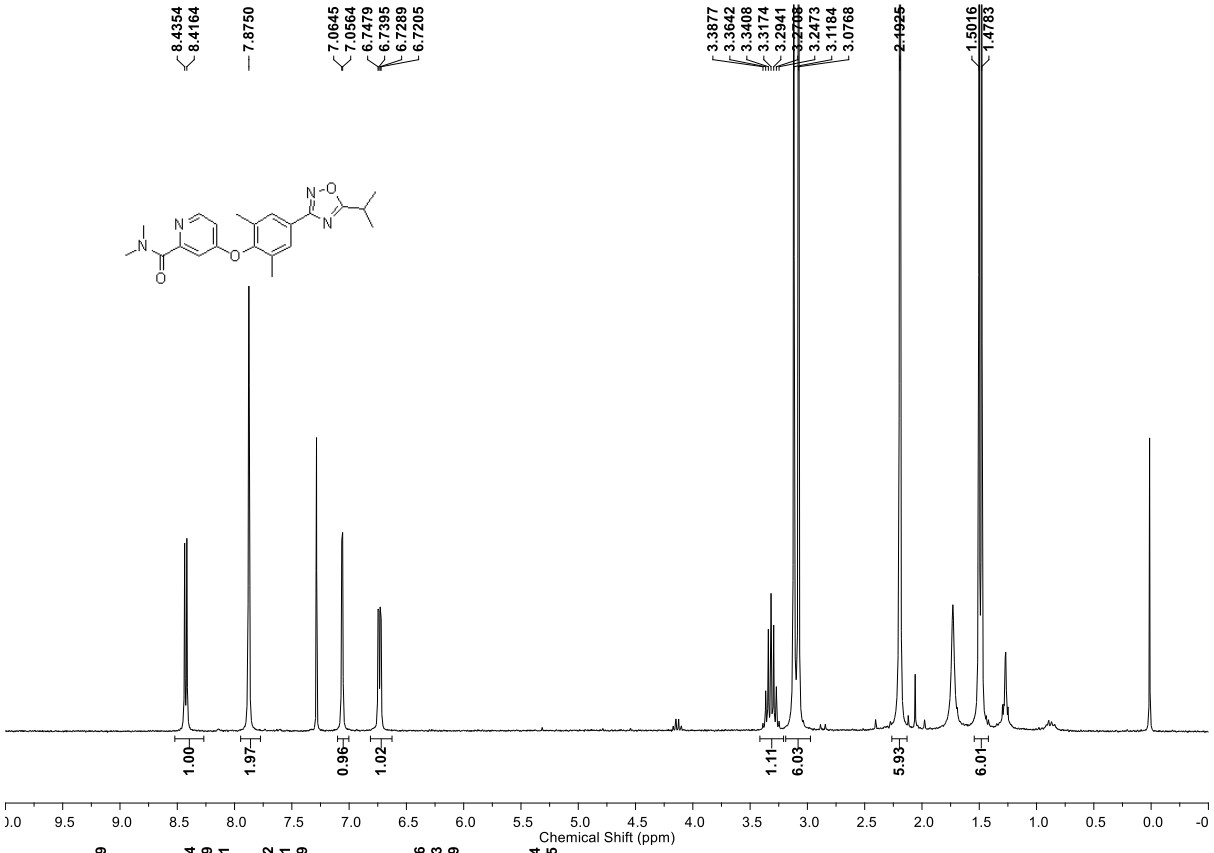


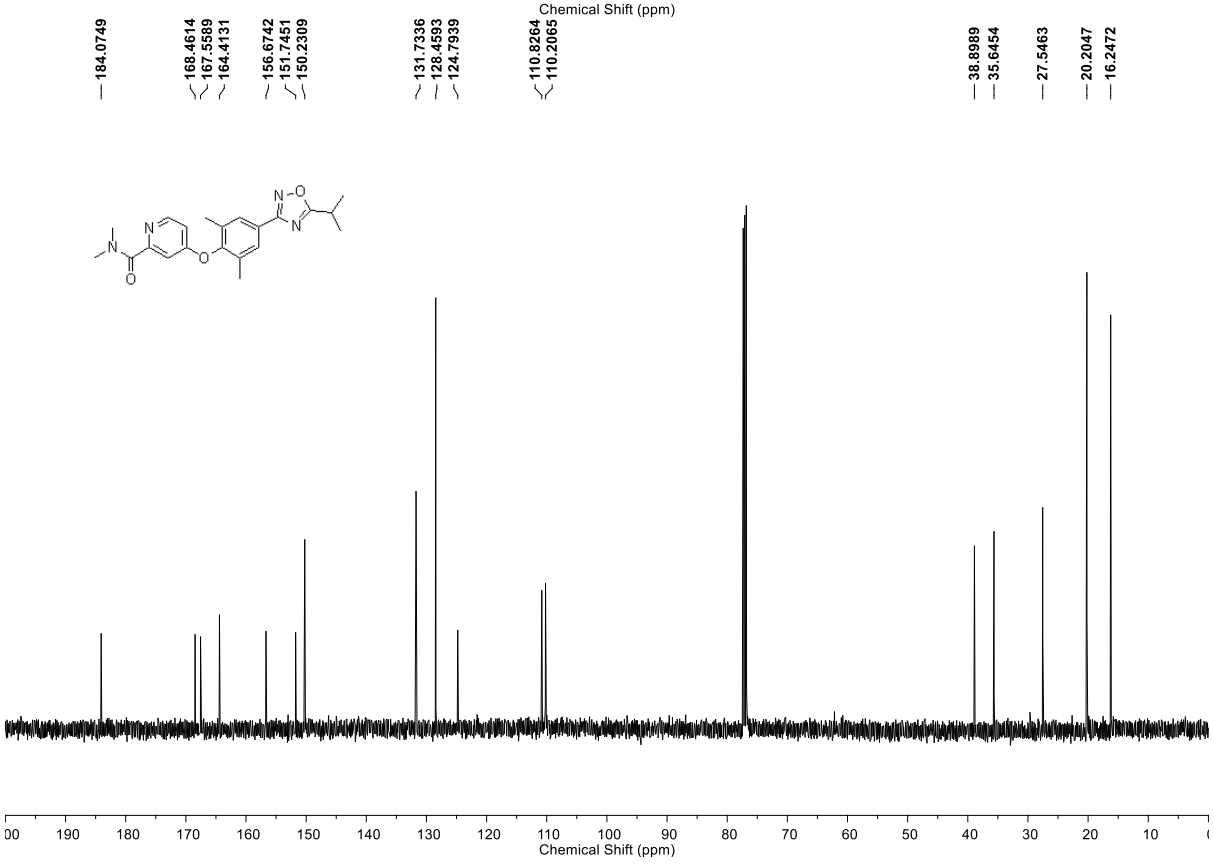
4-(4-(5-Isopropyl-1,2,4-oxadiazol-3-yl)-2-methylphenoxy)-*N*,*N*-dimethylpicolinamide (**3n**, $CDCl_3$)



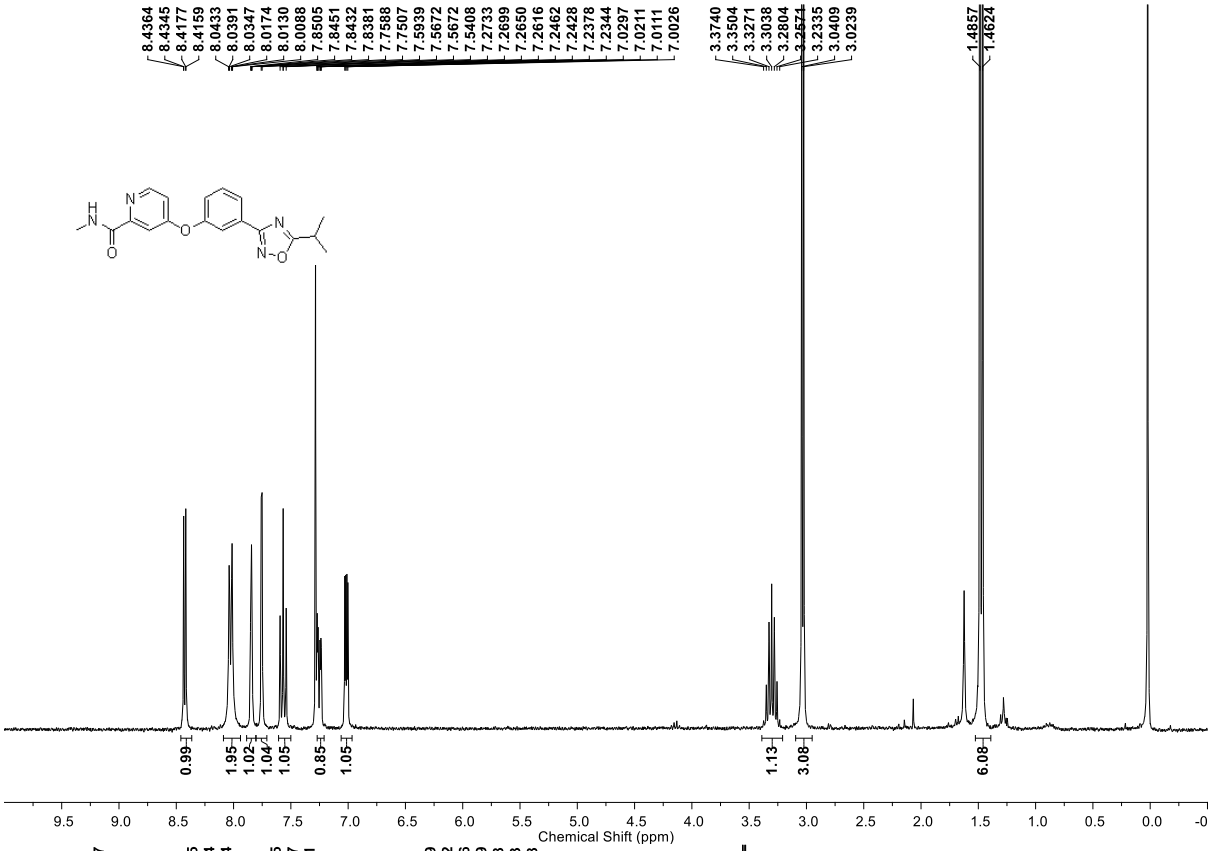


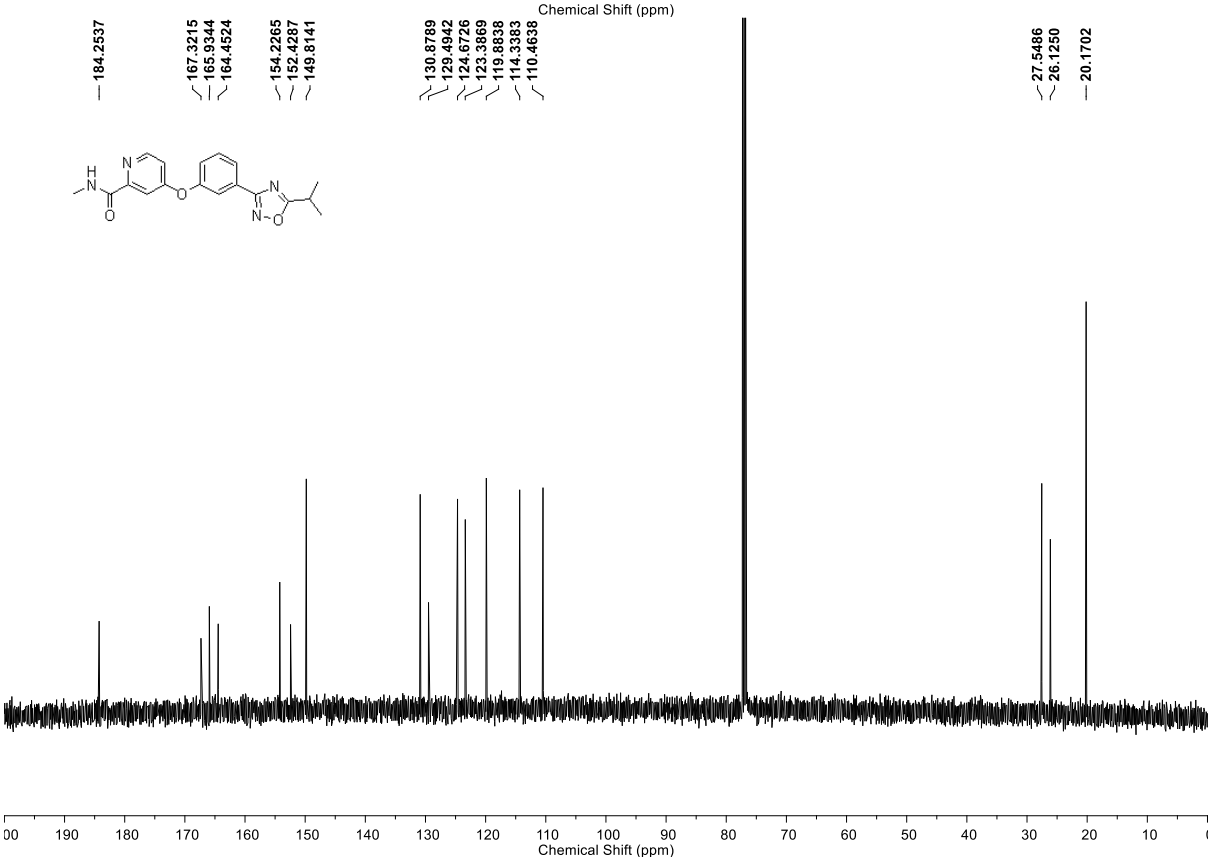
4-(4-(5-Isopropyl-1,2,4-oxadiazol-3-yl)-2,6-dimethylphenoxy)-*N*,*N*-dimethylpicolinamide (**3o**, $CDCl_3$)



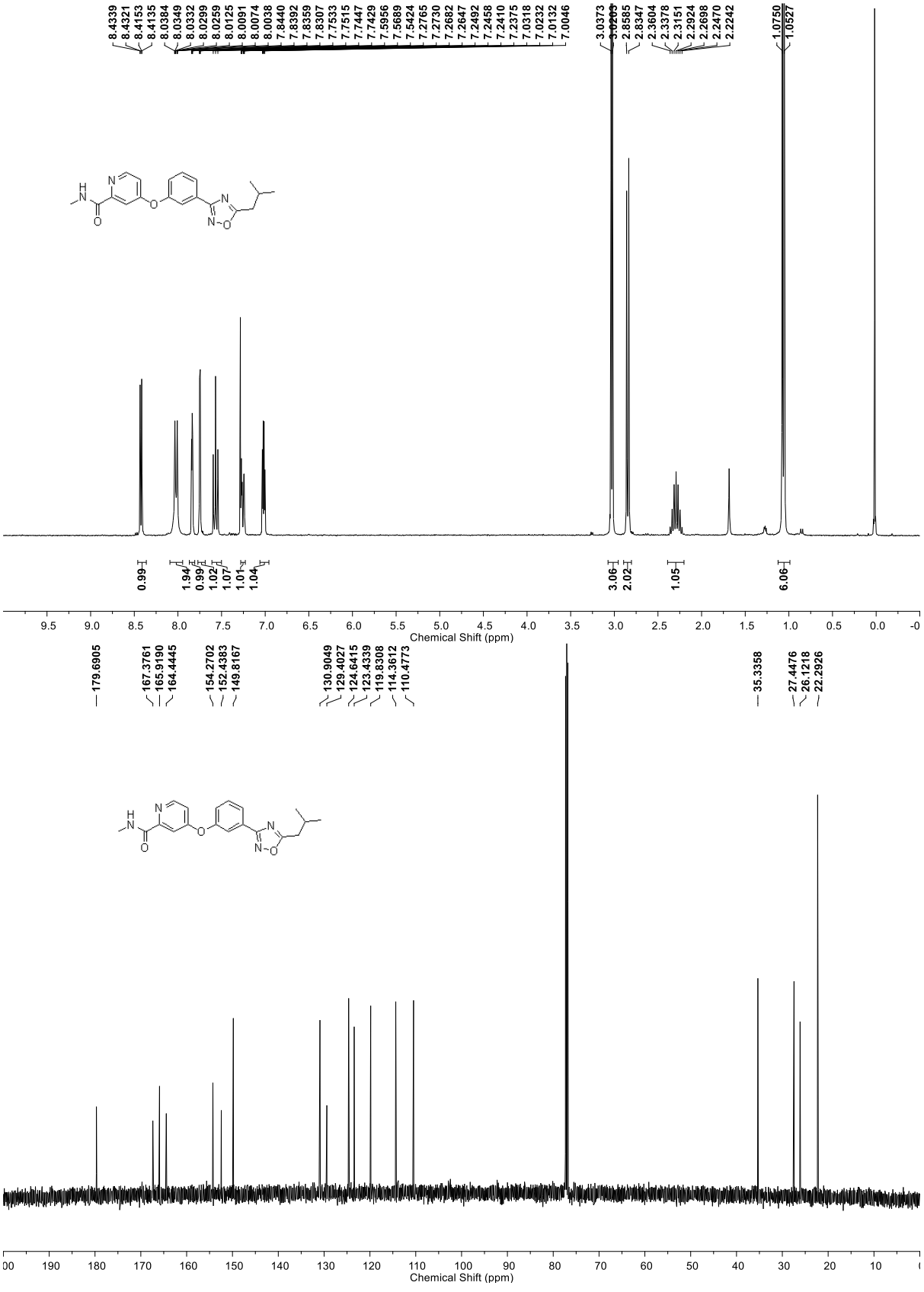


4-(3-(5-Isopropyl-1,2,4-oxadiazol-3-yl)phenoxy)-*N*-methylpicolinamide (**3p**, $CDCl_3$)

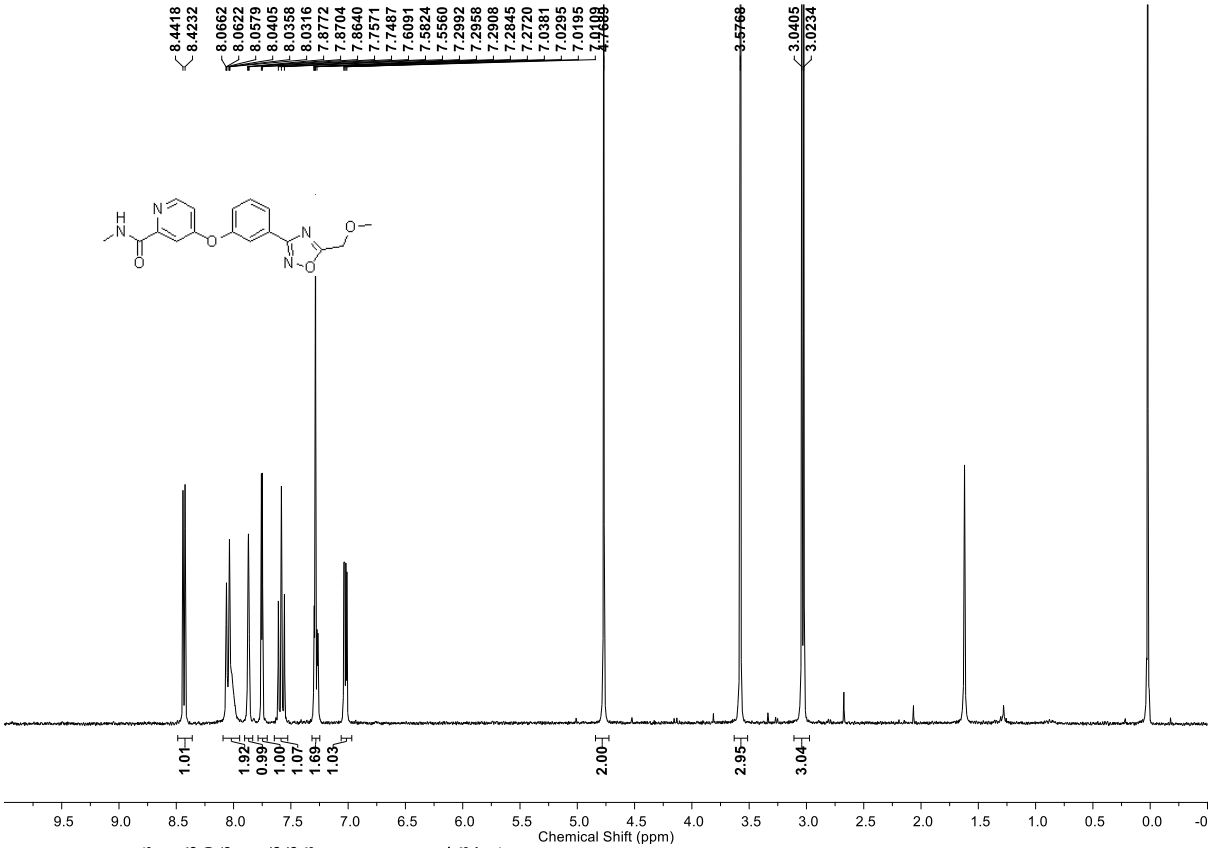


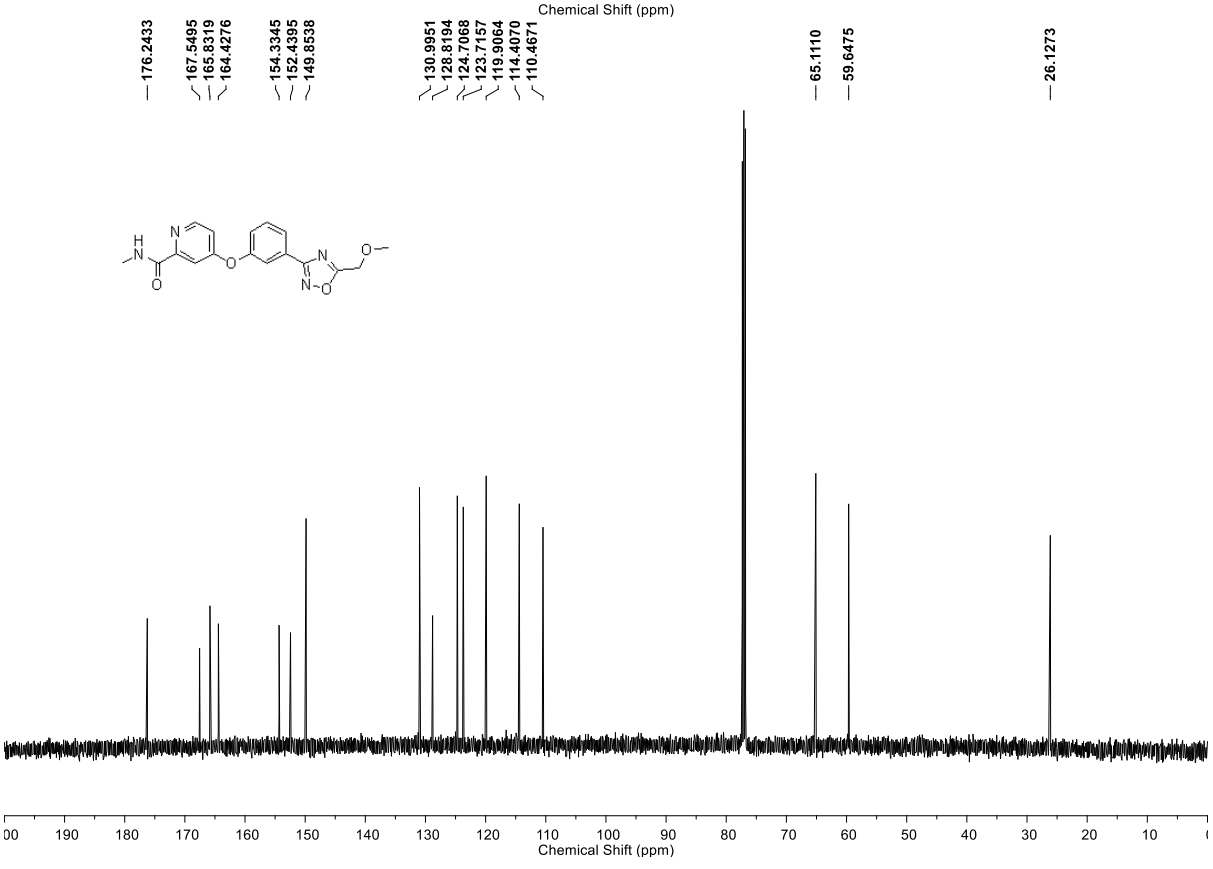


4-(3-(5-Isobutyl-1,2,4-oxadiazol-3-yl)phenoxy)-*N*-methylpicolinamide (**3q**, $CDCl_3$)

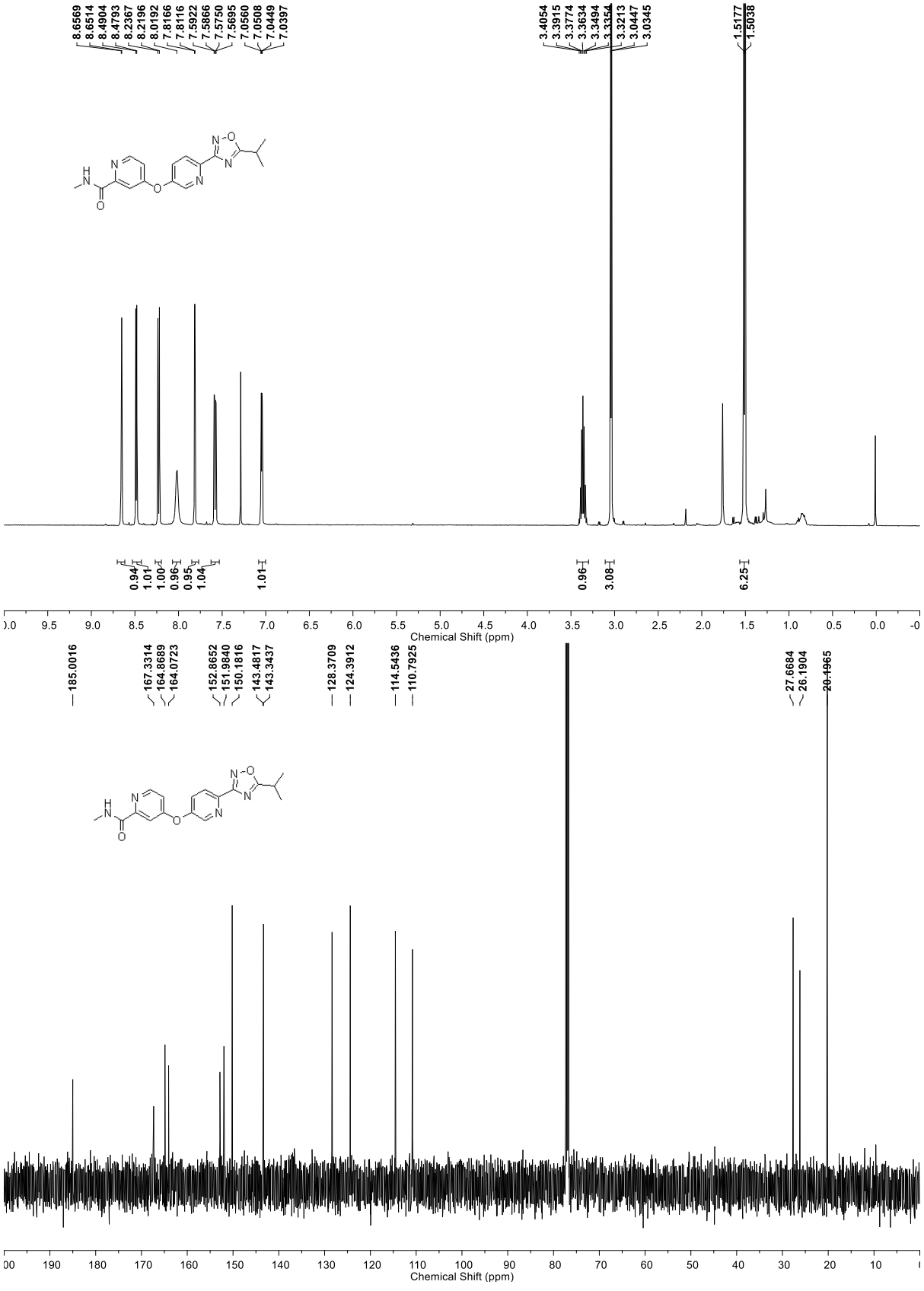


4-(3-(5-(Methoxymethyl)-1,2,4-oxadiazol-3-yl)phenoxy)-*N*-methylpicolinamide (**3r**, $CDCl_3$)





4-((6-(5-Isopropyl-1,2,4-oxadiazol-3-yl)pyridin-3-yl)oxy)-*N*-methylpicolinamide (**3s**, $CDCl_3$)



N-Methyl-4-((6-(5-methyl-1,2,4-oxadiazol-3-yl)naphthalen-2-yl)oxy)picolinamide (**3t**, $CDCl_3$)