Supporting Information

Hip to be square: oxetanes as design elements to alter metabolic pathways.

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In vitro enzyme assays and metabolite identification section

Incubation mixtures were analyzed by ultra-high performance liquid chromatography/high resolution quadrupole time-of-flight mass spectrometry (UHPLC-QTOF-MS) as described previously.[1] MSMS spectra of (**13**) were recorded at *m/z* 481.20 using a collision energy ramp from 15-35eV on a Synapt G2 Q-TOF (Waters).

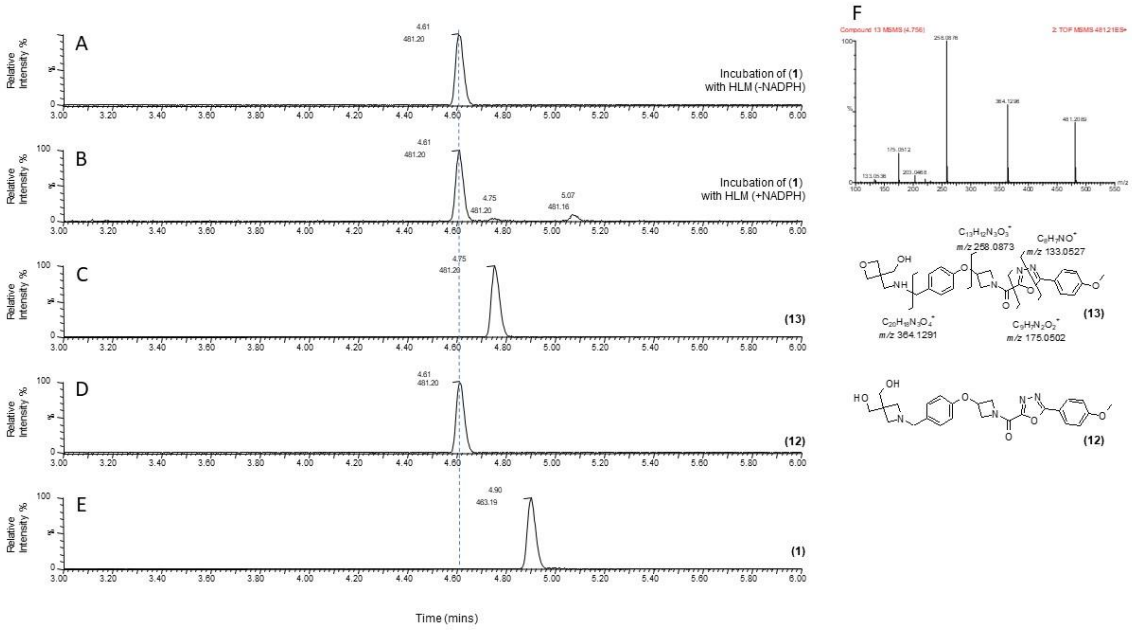


Figure S1 UPLC-MS analysis of (**1**) incubated with HLM in the absence (A) and presence (B) of NADPH. Chromatograms C, D, E are synthetic standards of (**13**), (**12**) and (**1**) respectively. A-D are extracted ion chromatograms at *m/z* 481.20. Chromatogram E is an extracted ion chromatogram at *m/z* 463.19 ($M+H^+$, **1**). Peak at 5.07 mins in B is the 2-^{13}C isotope of the N-oxide metabolite of (**1**) at *m/z* 481.19. F) MSMS spectrum and assigned fragmentation pattern of **13**.

Computational Section

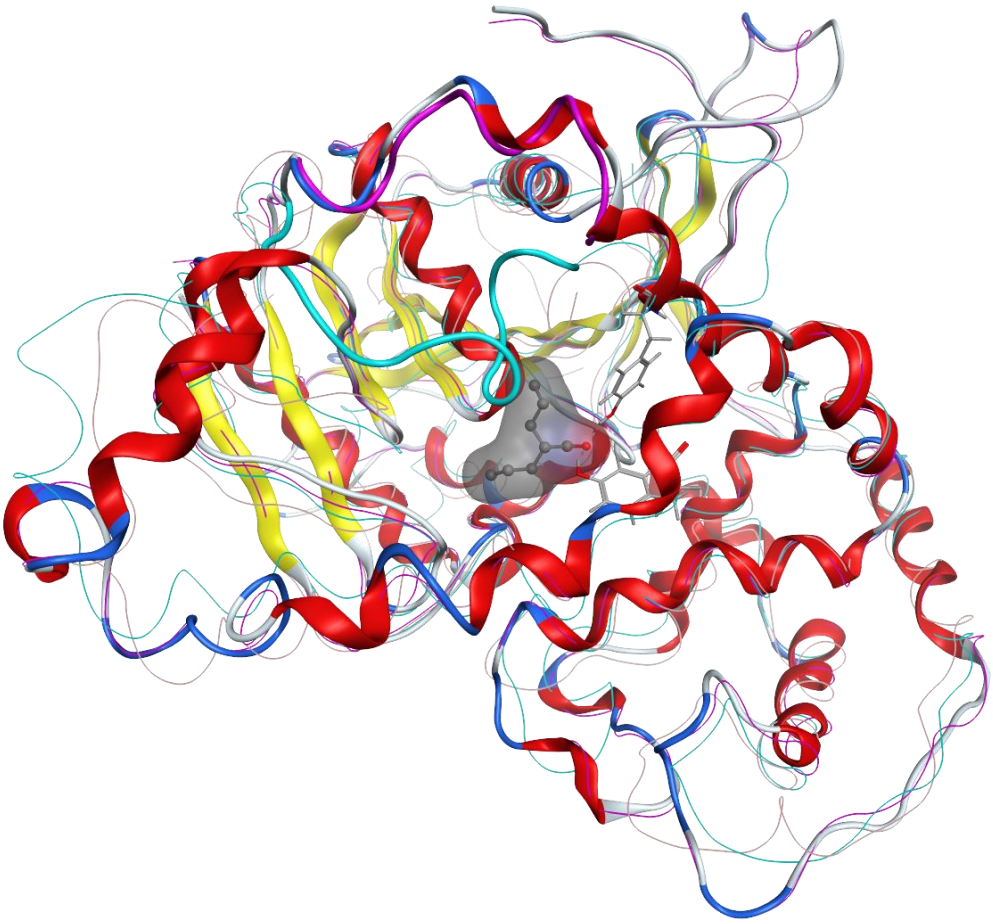
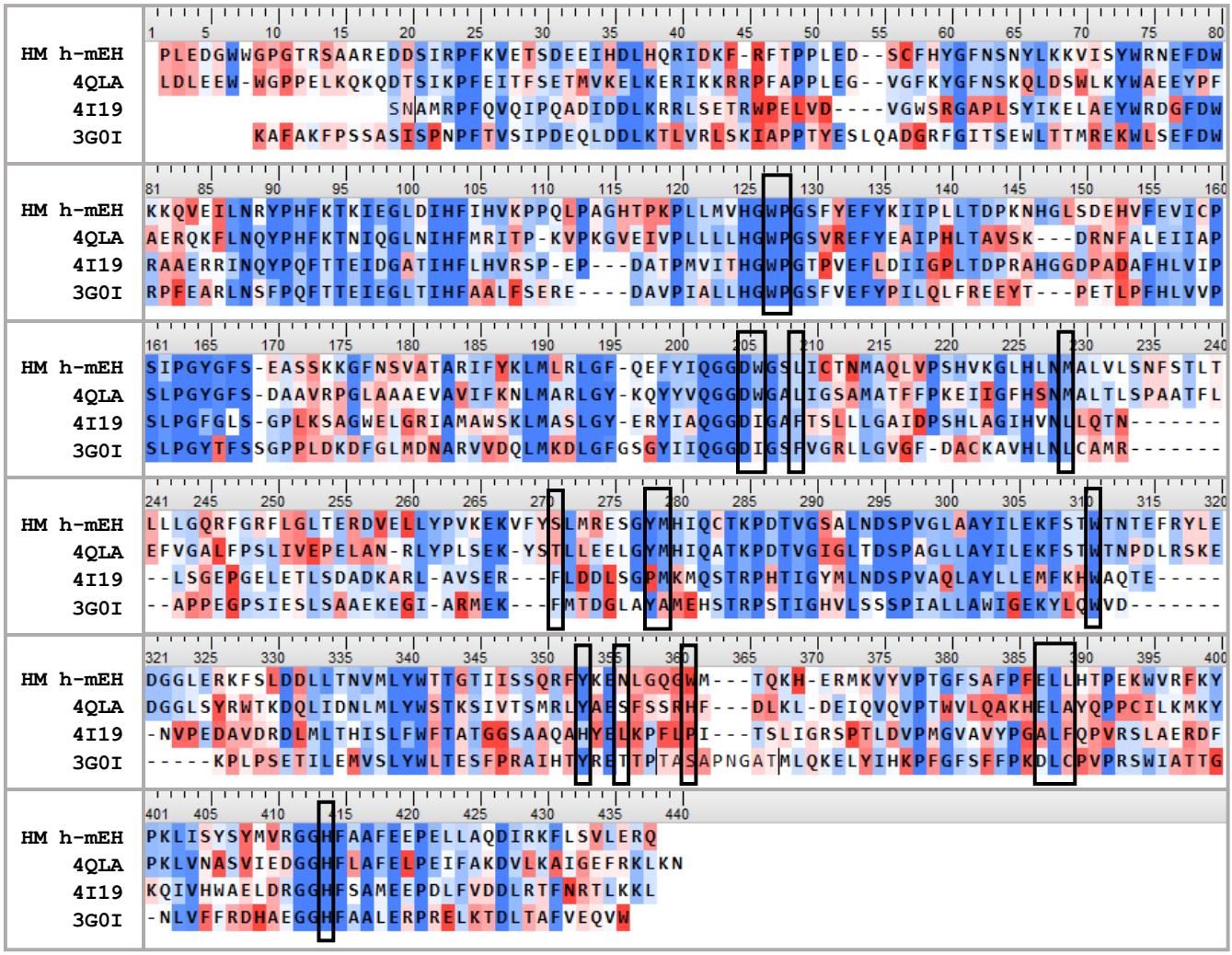


Figure S2 Homology model of human microsomal epoxide hydrolase (mEH) with backbone structure represented as thick ribbon with both shape and color indicating secondary structure elements (red: alfa-helix, yellow: beta-sheet: blue: turn). The three crystal structures are superposed based on sequence alignment and 3D structure overlap and are shown as thin wire representations of the backbone structure. The template structure (PDB ID 4QLA) in purple, PDB id 4I19 in turquoise, and PDB ID 3G0I in grey. The ligand represented by an atom colored shaded molecular surface represents the superposed enzyme inhibitor valpromide (2-propylpentanamide) from the *Asperillus niger* structure complex (3G0I). The largest structural difference between the crystal structures is indicated in the picture by thicker representations for the template (purple) and the structure 4I19 (turquoise). This part of the structure defines the entrance in to the substrate binding site (this sequence stretch corresponds to the alignment positions 358-372 in Figure S3a). Sequence similarity and identity matrices are shown in Figure S3b. All similarity measures strongly indicate the improvement of the homology model of the human mEH using the silkworm *Bombyx mori* X-ray crystal structure (PDB ID: 4QLA) compared to the templates used in earlier models in the literature. Authors will release the atomic coordinates upon article publication

a



b

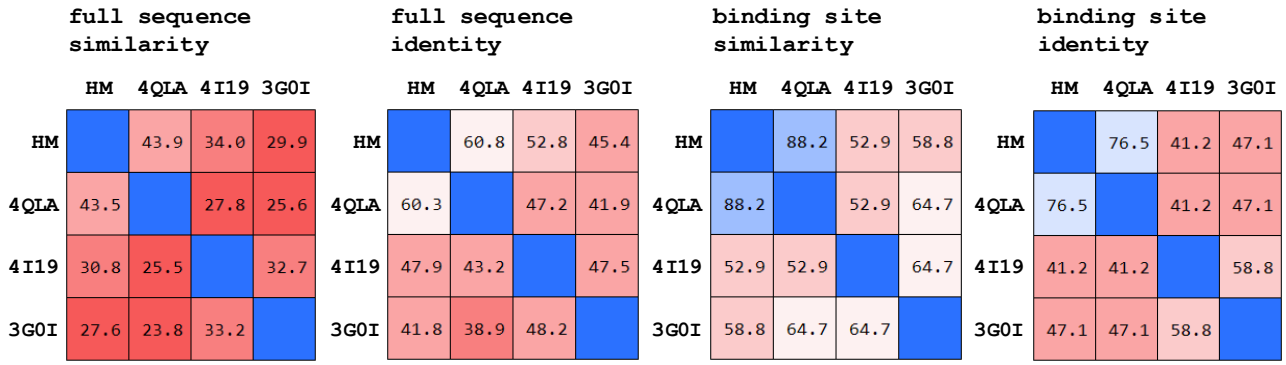


Figure S3 a) sequence alignment between the homology model of human mEH and the three crystal structures identified with their corresponding PDB ID. Residues are color coded according to amino acid similarity in each alignment position. Binding site residues (indicated in black rectangles) are defined as all residues with one atom within 4.5 Å from any atom in valpromide (3G0I) in all 4 superposed structures in Fig S2, extended to the corresponding residues in all proteins for each such alignment position. b) sequence similarity and identity matrices for the full sequence and for the binding site are shown.

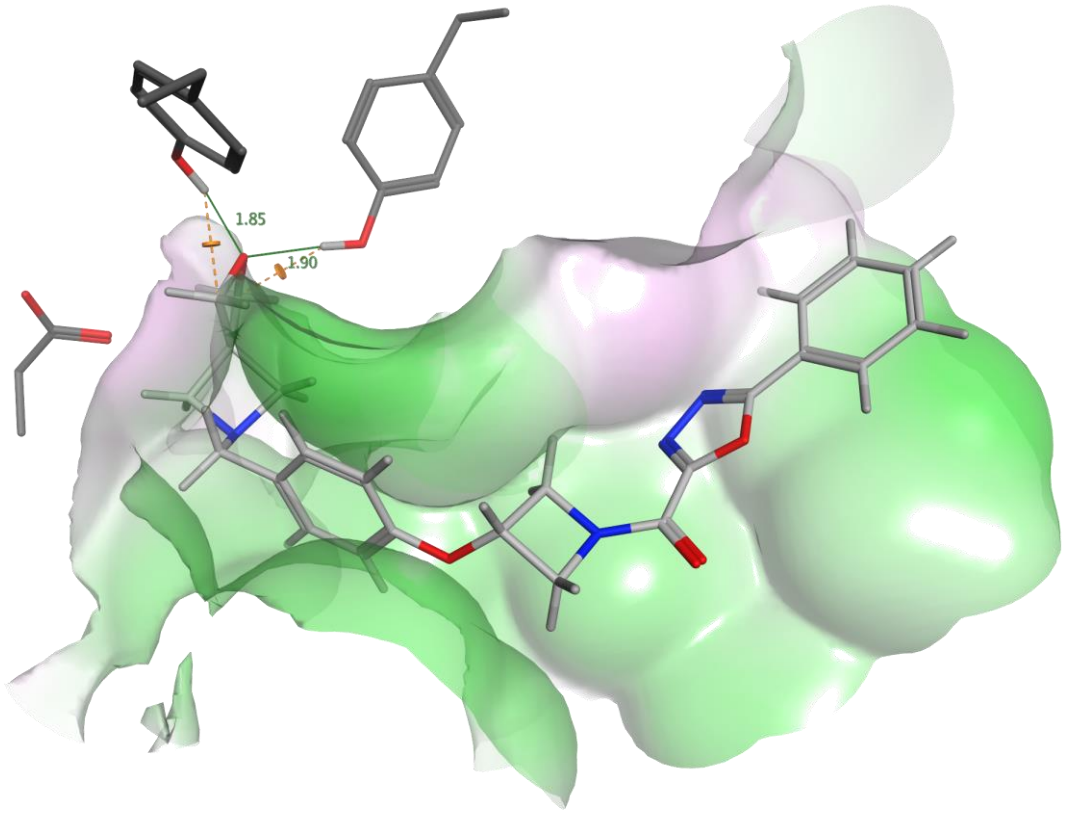


Figure S4 Docking poses in the active site of the mEH protein structure model of **2**. The accessible surface of the protein, represented by how close a oxygen atom in a water molecule could be without any steric repulsion, is shown for the parts of the protein that is in close proximity to the ligand. Green color: hydrophobic areas and purple: hydrophilic areas. The two tyrosines in the active site coordinating with the ring oxygen in the ligand (Y299 & Y374, O···H distances in Å) and the catalytic Aspartic acid (D226) are shown. Yellow dashed lines with discs indicate moderate sterical clashes (1.2 kcal/mol).

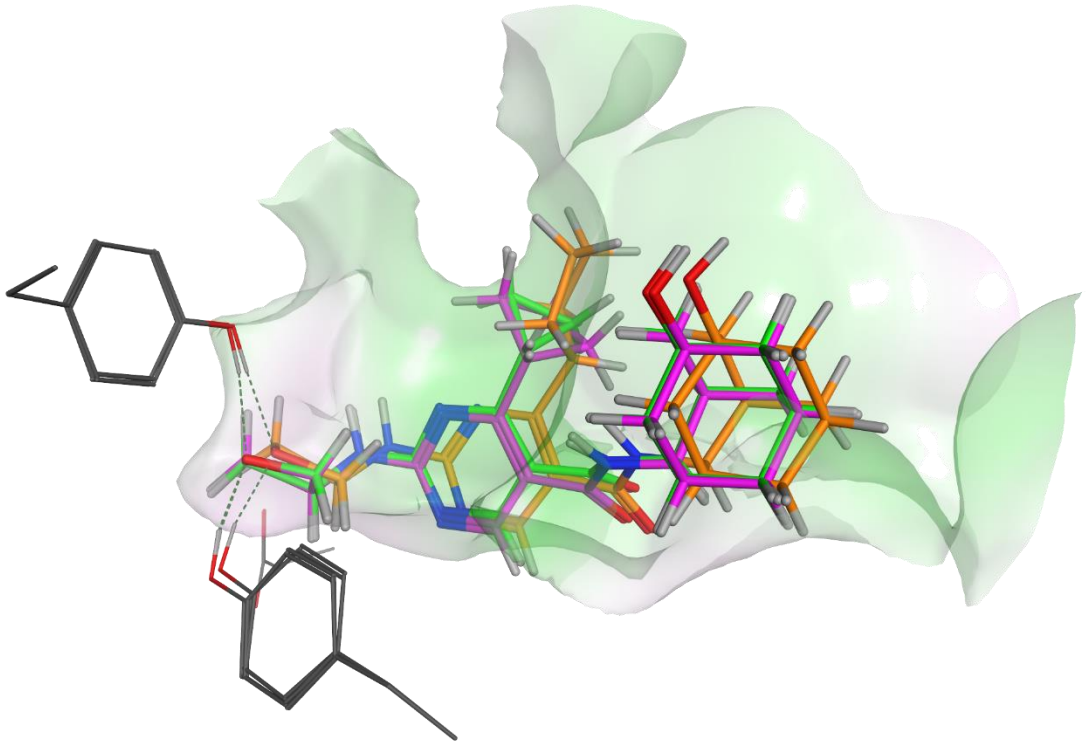
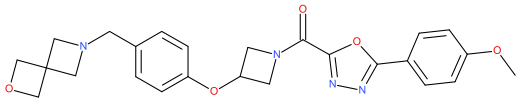


Figure S5 Overlaid docking poses of **29** (green), **31** (purple) and **33** (orange) in the active site of the mEH protein structure model. The accessible surface of the protein, represented by how close an oxygen atom in a water molecule could be without any steric repulsion, is shown for the parts of the protein that is in close proximity to the ligand. Green color: hydrophobic areas and purple: hydrophilic areas. The two tyrosines in the active site coordinating with the ring oxygen in the ligand (Y299 & Y374) and the catalytic Aspartic acid (D226) are shown. The viewpoint is chosen for best view of the difference in binding pose between the analogues.

Purity analysis

Analytical ultra high-performance liquid chromatography/mass spectrometry (UPLC/MS) was conducted on a QTOF mass spectrometer using a UV detector monitoring either at (a) 210 nm with a BEH C18 column (2.1 × 100 mm, 1.7 µm, 0.7 mL/min flow rate) or XBridge C18 column (3.0x50mm, 5 µm, 1.0ml/min flow rate) using a gradient of 2% v/v CH_3CN in H_2O (ammonium carbonate buffer pH 11) to 98% v/v CH_3CN in H_2O, or at (b) 230 nm with an HSS C18 column (2.1 × 100 mm, 1.8 µm, 0.7 mL/min flow rate), using a gradient of 2% v/v CH_3CN in H_2O (ammonium formate buffer pH 3) to 98% v/v CH_3CN in H_2O. All compounds (**1**-**36**) studied were determined to be ≥95% pure except **5**, **7**, **10**, **17** and **20** which were ≥91% using the analytical method (a) or (b) described above based on the peak area percentage. Compound **32** contained ca 9% of a diol impurity but was not a substrate for mEH. Diol **28** (83%) proved difficult to purify and was used only as a chromatographic standard.

Compound **1**



Openlynx Report - 1030277240 Page 1
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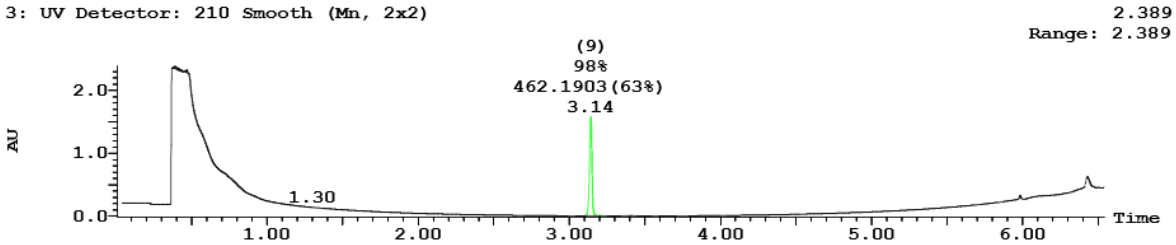
Sample Report:



Peak Number	Compound	Time	AreaAbs	Area %Total	Height	Mass Found
1		1.30	3e+001	0.10		
6		2.67	2e+001	0.06	7e+002	
8		3.01	2e+001	0.07	9e+002	
9	Found	3.14	3e+004	97.82	2e+006	462.1903
9	Found	3.22	1e+002	0.35	5e+003	462.1903
10		3.37	8e+001	0.24	4e+003	
11		3.39	6e+001	0.20	4e+003	
12		3.41	2e+002	0.70	1e+004	
13		3.57	3e+001	0.08	1e+003	
15		3.73	3e+001	0.09	1e+003	
16		3.77	1e+001	0.04	7e+002	
17		4.03	1e+001	0.04	6e+002	
21		4.57	2e+001	0.06	2e-002	
23		5.72	2e+001	0.05	3e-002	
24		5.87	3e+001	0.09	3e-002	

Peak ID	Compound	Time	Target	Error PPM	Error mDa
9	Found	3.13	463.1981	3.0	1.4

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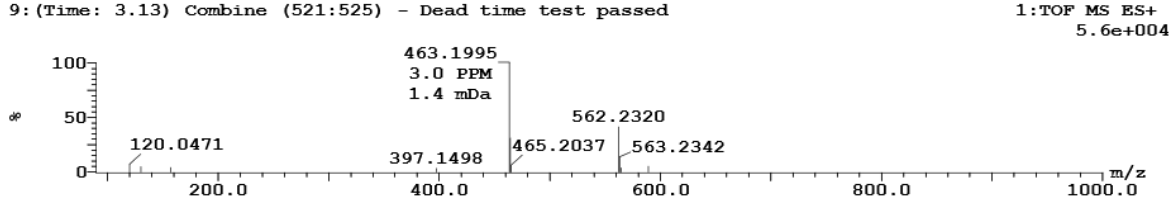
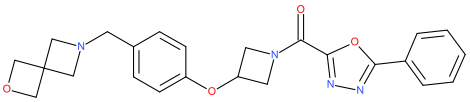


Compound **2**



Openlynx Report - 1030075938 Page 1

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Date:21-Jan-2009 Vial:6:21

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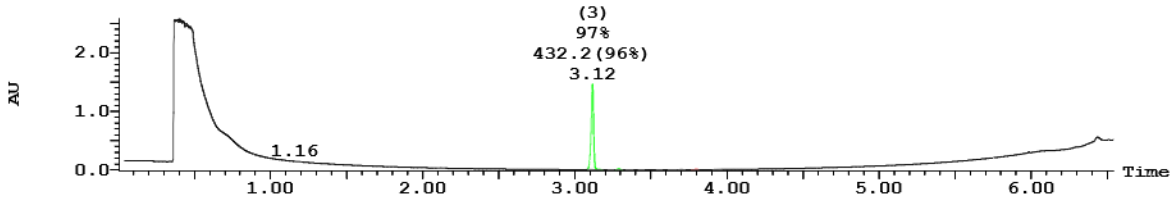

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1		1.18	1e+002	0.40	6e+003	
2		2.12	1e+002	0.37	5e+003	
3	Found	3.12	3e+004	96.73	1e+006	432.18
4		3.24	4e+001	0.14	2e+003	
5	Found	3.29	3e+002	1.03	2e+004	432.18
6		3.36	4e+001	0.12	1e+003	
7		3.44	2e+001	0.06	7e+002	
8		3.55	3e+001	0.10	1e+003	
9		3.66	6e+001	0.21	2e+003	
10		3.70	1e+002	0.41	5e+003	
11		3.80	8e+001	0.30	4e+003	
12		3.93	4e+001	0.13	1e+003	

Peak ID	Compound	Time	Target	Error PPM	Error mDa
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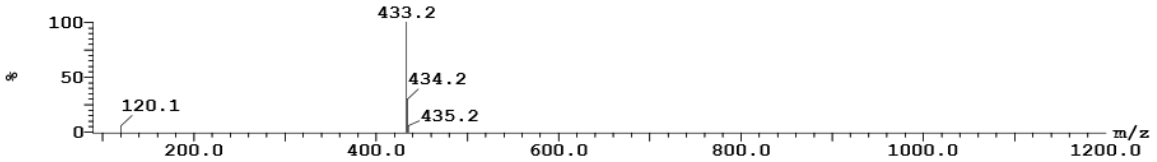
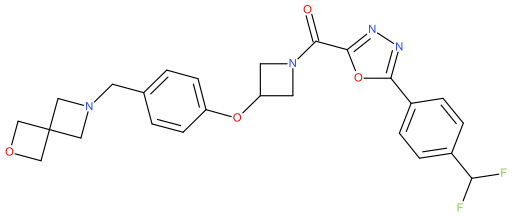


Compound **3**



Openlynx Report - 1030826974 Page 1
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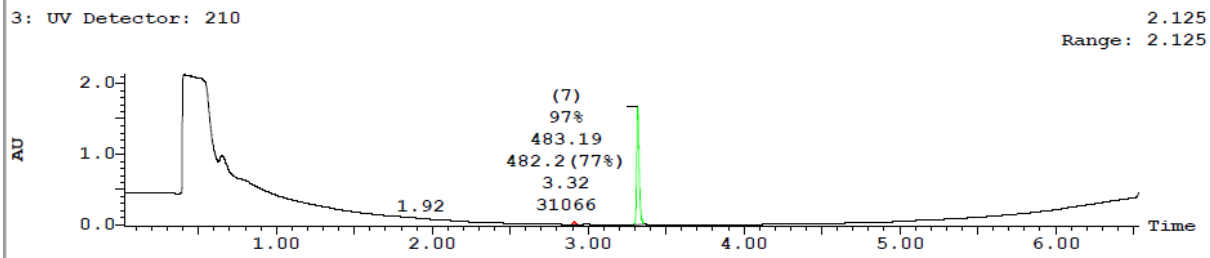
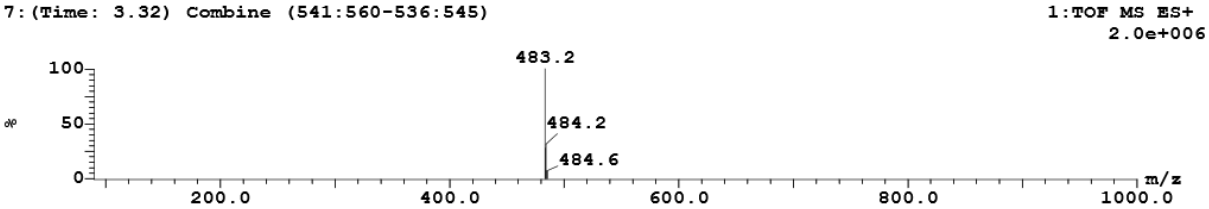


Peak Number	Compound	Time	AreaAbs	Area %Total	Height	Mass Found
2		1.92	2e+001	0.07	2e+003	
3		2.91	7e+002	2.27	4e+004	
5	Found	3.22	9e+001	0.27	6e+003	482.18
7	Found	3.32	3e+004	97.02	2e+006	482.18
8		3.48	7e+001	0.23	3e+003	
11	Found	3.88	5e+001	0.14	2e+003	482.18

Peak ID	Compound	Time	Target	Error PPM	Error mDa
7	Found	3.32	483.1844	8.3	4.0



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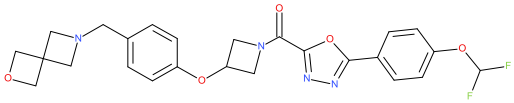

Openlynx Report - 1030169903 Page 1
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Date:03-Apr-2009 Vial:4:18

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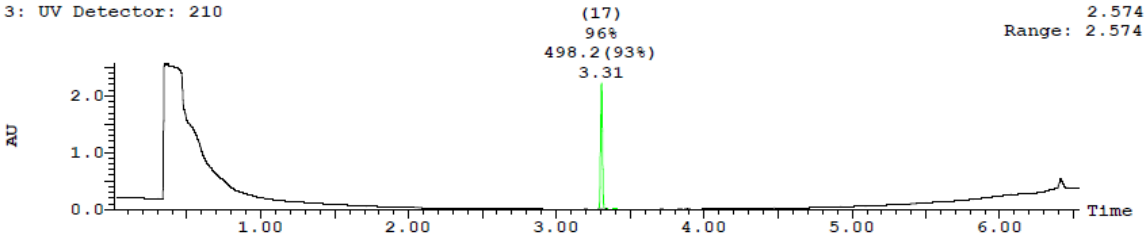

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11		2.26	3e+001	0.10	3e+003	
13		3.00	3e+001	0.09	1e+003	
16		3.20	1e+002	0.42	7e+003	
17	Found	3.31	3e+004	96.45	2e+006	498.17
17	Found	3.34	4e+001	0.11	3e+003	498.17
17	Found	3.40	2e+002	0.58	1e+004	498.17
20		3.49	4e+001	0.11	3e+003	
23		3.71	1e+002	0.38	8e+003	
24		3.76	4e+001	0.13	3e+003	
25		3.84	2e+002	0.71	2e+004	
26		3.88	5e+001	0.17	4e+003	
27		3.90	6e+001	0.19	4e+003	
30		4.46	6e+001	0.17	4e+003	
32		5.41	7e+001	0.23	5e+003	

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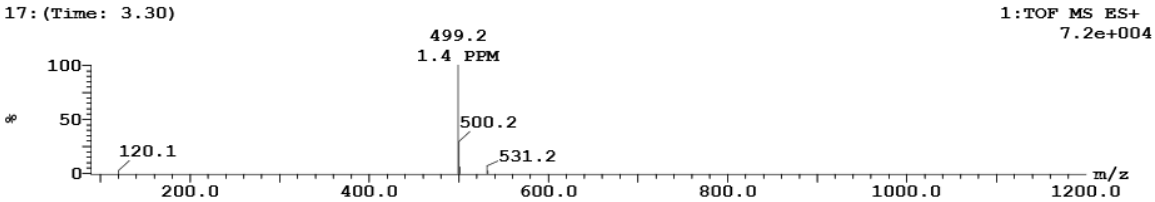

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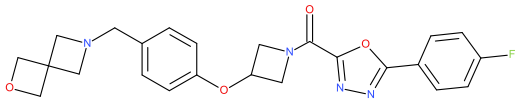

Openlynx Report - 1030169903 Page 1

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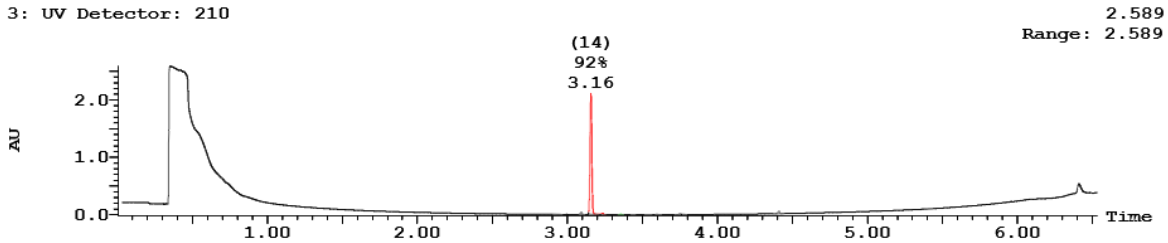

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13		3.09	6e+002	1.77	4e+004	
14		3.16	3e+004	92.41	2e+006	
14		3.20	1e+002	0.37	6e+003	
14		3.23	3e+002	0.82	2e+004	
17	Found	3.36	9e+001	0.27	6e+003	450.17
18		3.44	2e+001	0.05	8e+002	
19		3.55	2e+001	0.07	1e+003	
20		3.60	1e+002	0.32	7e+003	
21		3.73	2e+001	0.06	2e+003	
22		3.75	2e+002	0.77	2e+004	
23		3.77	1e+002	0.42	9e+003	
26		4.38	3e+001	0.10	2e+003	
27		4.41	6e+002	2.04	4e+004	
30		5.41	9e+001	0.28	6e+003	

Peak ID	Compound	Time	Target	Error PPM	Error mDa
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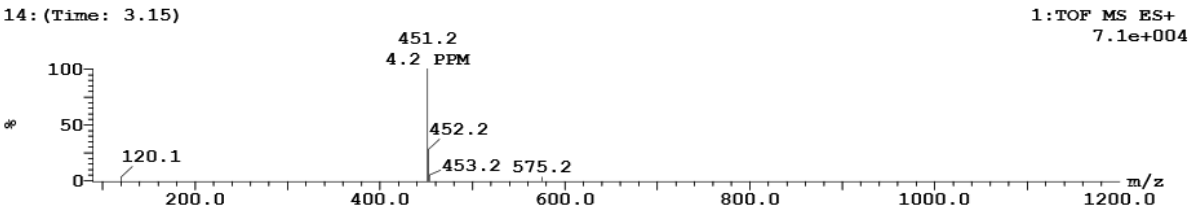

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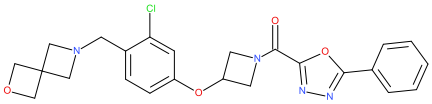
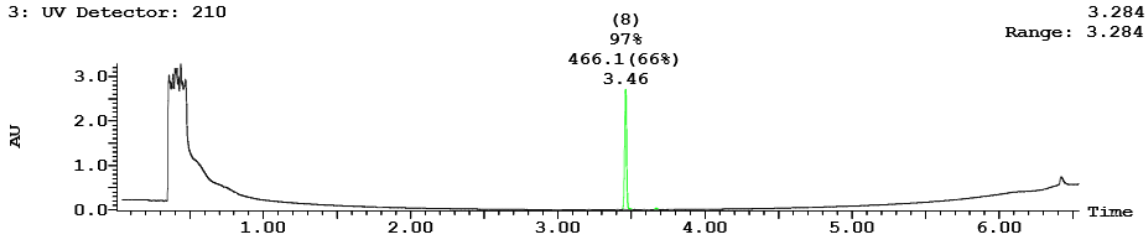


Openlynx Report - 1030142241 Page 1

Purity & Accurate mass File:20090310_LCTP_183

Date:11-Mar-2009 Vial:4:74

Sample Report:



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4		2.98	2.02e+001	0.05	1.3e+003	
5		3.01	4.07e+001	0.09	1.4e+003	
6		3.21	9.82e+001	0.23	5.6e+003	
7		3.41	9.95e+001	0.23	6.9e+003	
8	Found	3.46	4.24e+004	97.43	2.7e+006	466.14
9		3.59	5.63e+001	0.13	3.4e+003	
10		3.61	1.79e+001	0.04	1.4e+003	
11	Found	3.67	5.29e+002	1.22	3.7e+004	466.14
12		3.76	4.75e+001	0.11	2.1e+003	
14		4.01	1.89e+001	0.04	1.2e+003	
16		4.73	1.82e+001	0.04	1.0e+003	
20		5.42	1.05e+002	0.24	6.5e+003	
23		5.66	1.85e+001	0.04	5.7e+002	
25		5.74	2.44e+001	0.06	2.0e-002	

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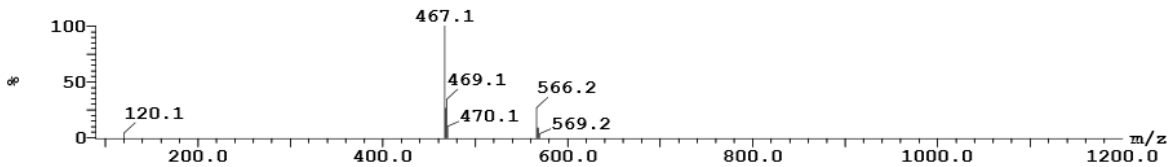
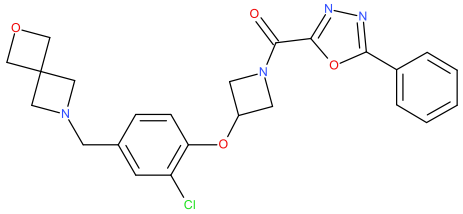


Compound **7**



Openlynx Report - 1030173757 Page 1

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Date:08-Apr-2009 Vial:5:72

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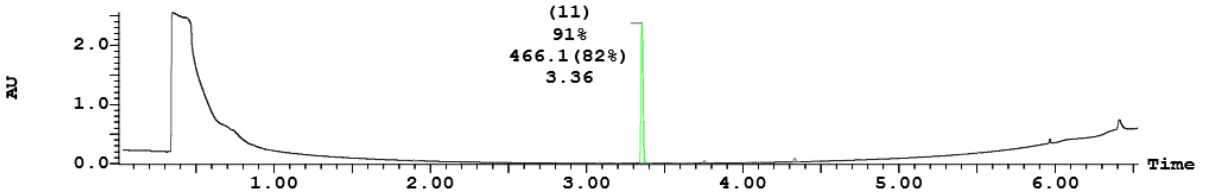
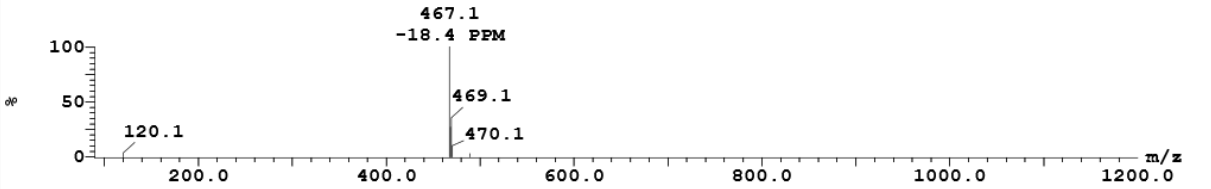
Range: 2.555



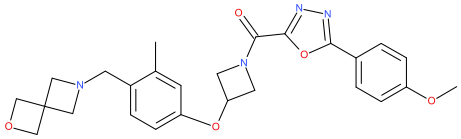
Peak Number	Compound	Time	AreaAbs	Area %Total	Height	Mass Found
3		1.89	2e+002	0.47	1e+004	
7		3.08	3e+002	0.68	2e+004	
9		3.20	2e+002	0.40	9e+003	
11	Found	3.35	3e+004	91.41	2e+006	466.14
14		3.57	2e+002	0.47	1e+004	
15		3.62	1e+002	0.27	7e+003	
16		3.66	2e+002	0.50	1e+004	
17		3.75	6e+002	1.56	4e+004	
18		3.80	1e+002	0.27	6e+003	
21		4.03	7e+001	0.18	4e+003	
22		4.12	2e+002	0.41	1e+004	
24		4.33	1e+003	2.72	7e+004	
26		4.44	9e+001	0.23	5e+003	
28		4.78	6e+001	0.16	4e+003	
30		5.41	1e+002	0.27	7e+003	

Peak ID	Compound	Time	Target	Error PPM	Error mDa
11	Found	3.36	467.1486	-9.0	-4.2

11:(Time: 3.36) 5.9e+004



Compound **8**



Openlynx Report - 1030701240 Page 1

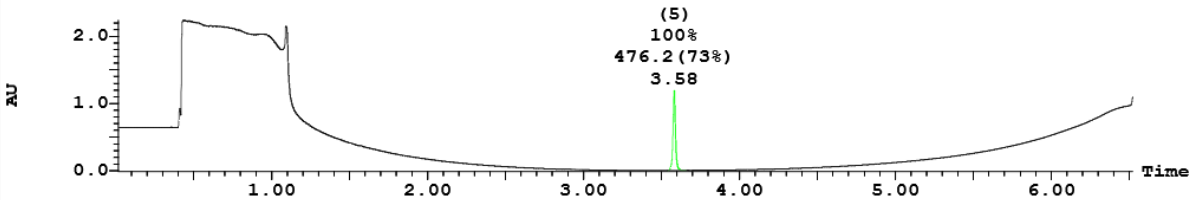
Purity & Accurate mass File:20100921_Xevo_116

Date:21-Sep-2010 Vial:6:12

Sample Report:

3: UV Detector: 210 2.237

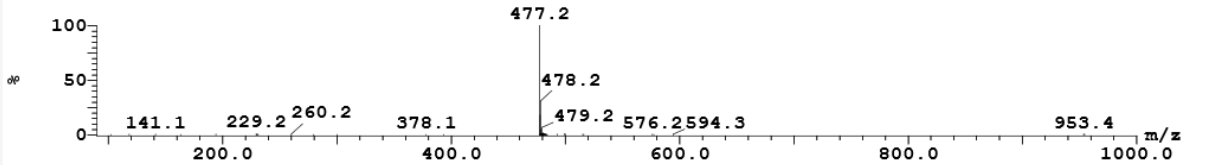
Range: 2.237



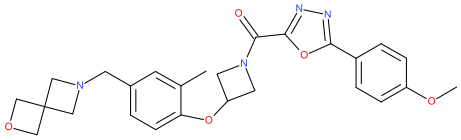
Peak Number	Compound	Time	AreaAbs	Area %Total	Height	Mass Found
4		2.94	9e+001	0.39	6e+003	
5	Found	3.58	2e+004	99.61	1e+006	476.21

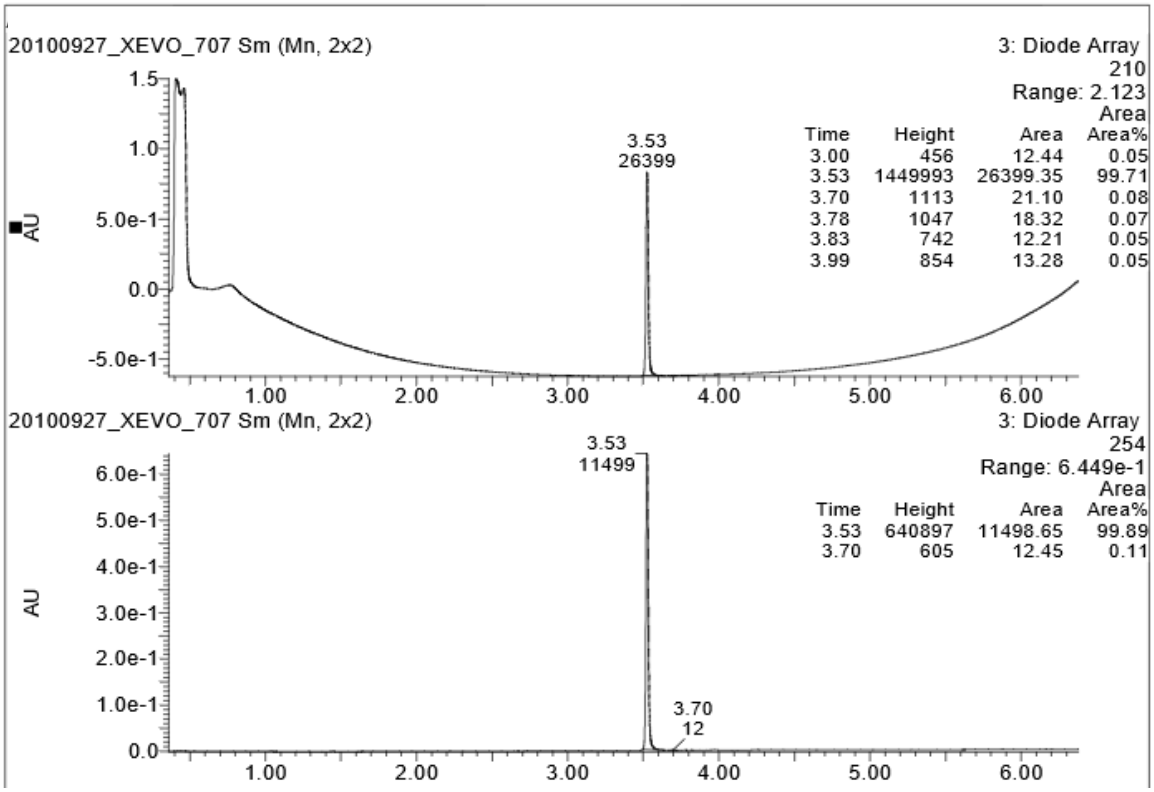
Peak ID	Compound	Time	Target	Error PPM	Error mDa
5	Found	3.59	477.2138	-0.2	-0.1

5:(Time: 3.59) Combine (604:608) 1:TOF MS ES+ 3.8e+004

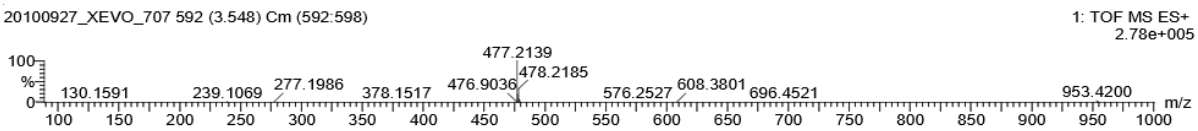


Compound **9**



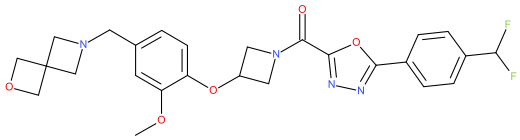


Monoisotopic Mass, Even Electron Ions
1 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 26-26 H: 28-29 N: 4-4 O: 5-5



Minimum:				-1.5			
Maximum:		5.0	10.0	50.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
477.2139	477.2138	0.1	0.2	14.5	284.3	0.0	C26 H29 N4 O5

Compound **10**

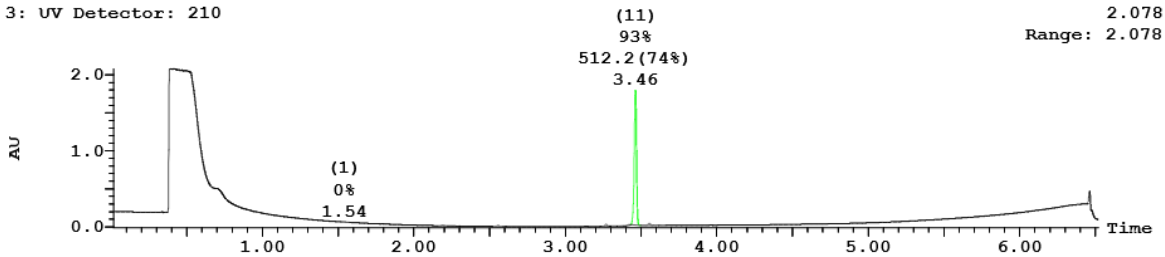


Openlynx Report - 1042663550 Page 1

Purity & Mass ID File:20110414_LCTP2_CARS3697_134

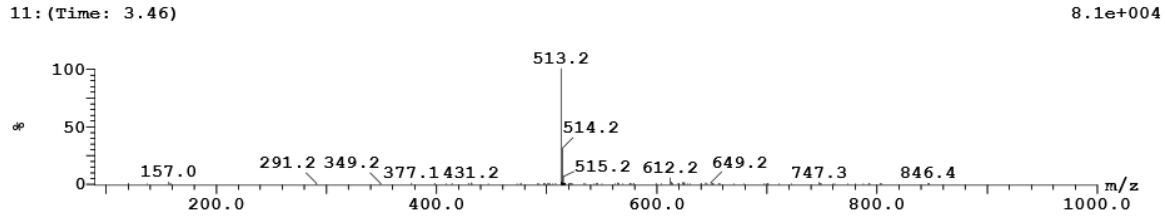
Date:14-Apr-2011 Vial:7:34

Sample Report:

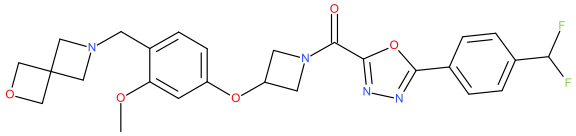


Peak Number	Compound	Time	AreaAbs	Area %Total	Height	Mass Found
1		1.54	6e+001	0.19	4e+003	
2		2.19	2e+002	0.47	1e+004	
3		2.56	3e+002	0.91	2e+004	
4		3.27	5e+002	1.48	3e+004	
5		3.29	7e+001	0.21	5e+003	
6		3.31	1e+002	0.37	6e+003	
8		3.36	9e+001	0.26	4e+003	
10		3.42	1e+002	0.30	7e+003	
11	Found	3.46	3e+004	92.85	2e+006	512.19
12		3.55	7e+002	1.97	3e+004	
13		3.61	2e+002	0.47	8e+003	
14		3.63	2e+002	0.54	9e+003	

Peak ID	Compound	Time	Target	Error PPM	Error mDa
11	Found	3.46	513.19	-0	-0



Compound **11**

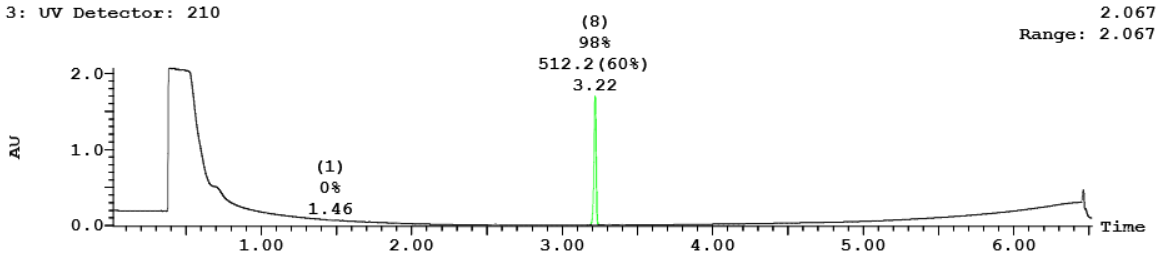


Openlynx Report - 1042663550 Page 1

Purity & Mass ID File:20110414_LCTP2_CARS3697_159

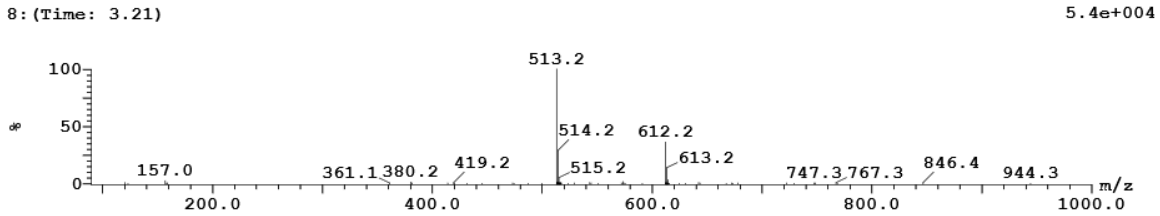
Date:15-Apr-2011 Vial:7:59

Sample Report:

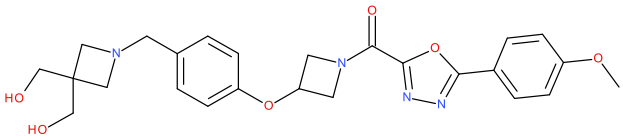


Peak Number	Compound	Time	AreaAbs	Area %Total	Height	Mass Found
1		1.46	7e+001	0.25	5e+003	
3		1.92	7e+001	0.25	6e+003	
5		2.56	3e+002	0.96	2e+004	
8	Found	3.22	3e+004	97.80	2e+006	512.19
10		3.31	1e+002	0.43	6e+003	
12		3.40	9e+001	0.31	6e+003	

Peak ID	Compound	Time	Target	Error PPM	Error mDa
8	Found	3.21	513.19	-1	-0



Compound **12**



Openlynx Report - 1051151888 Page 1

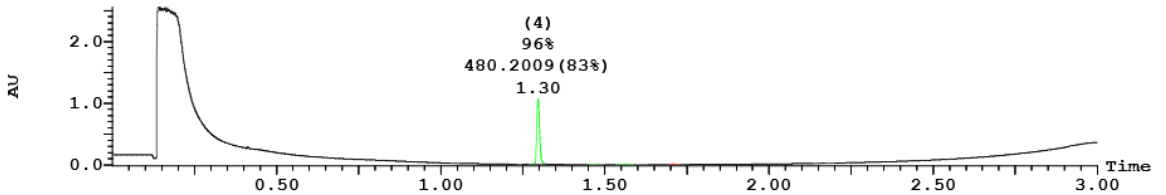
Purity & Accurate mass File:20120217_LCTp_Cars4447_8074

Date:17-Feb-2012 Vial:8:72

Sample Report:

3: UV Detector: 210 2.559

Range: 2.559

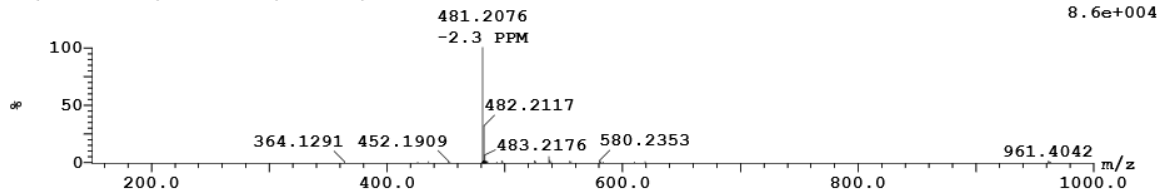


Peak Number	Compound	Time	AreaAbs	Area %Total	Height	Mass Found
1		1.05	8.57e+001	0.79	8.0e+003	
2		1.25	1.18e+001	0.11	1.1e+003	
3		1.26	2.64e+001	0.24	3.2e+003	
4	Found	1.30	1.03e+004	95.52	1.1e+006	480.2009
5	Found	1.47	3.36e+001	0.31	2.7e+003	480.2009
6		1.49	1.56e+001	0.14	1.4e+003	
7	Found	1.54	5.36e+001	0.49	4.9e+003	480.2009
7	Found	1.58	2.18e+001	0.20	1.8e+003	480.2009
8		1.61	5.83e+001	0.54	4.0e+003	
10		1.71	1.24e+002	1.15	1.1e+004	
11		2.14	3.82e+001	0.35	3.1e+003	
12		2.20	1.62e+001	0.15		

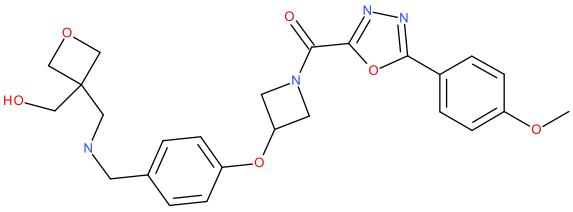
Peak ID	Compound	Time	Target	Error PPM	Error mDa
4	Found	1.31	481.2087	-2.29	-1.10

4:(Time: 1.31) Combine (152:156) 1:TOF MS ES+

8.6e+004



Compound **13**

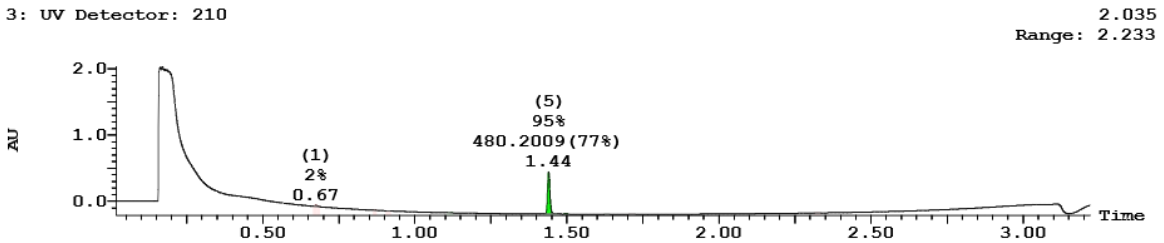


Openlynx Report -
Purity & Accurate mass
Date:26-Sep-2017
SampleType:0

File:Vind-24052_A2_17-09-26_072332_01bb
Vial:4:1,A
Submitter:

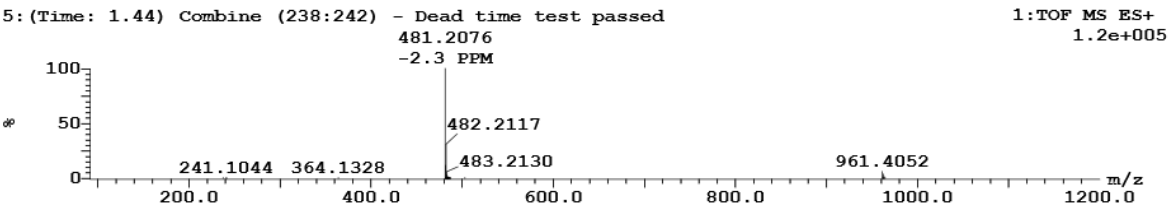
Page 1

Sample Report:

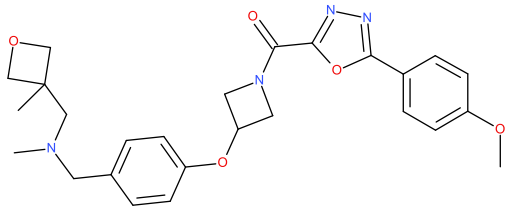


Peak Number	Compound	Time	AreaAbs	Area %Total	Height	Mass Found
1		0.67	1e+002	2.31	2e+004	
2		0.87	7e+000	0.11	9e+002	
3		0.91	1e+001	0.17	1e+003	
4	Found	1.11	3e+001	0.45	3e+003	480.20
5	Found	1.44	6e+003	95.30	6e+005	480.20
6	Found	1.50	3e+001	0.55	4e+003	480.20
7	Found	1.63	2e+001	0.34	2e+003	480.20
8		1.71	3e+001	0.43	3e+003	
9		2.33	2e+001	0.33	2e+003	

Peak ID	Compound	Time	Target	Error PPM	Error mDa
5	Found	1.44	481.2087	-2.3	-1.1



Compound **14**



Openlynx Report walk-up LC/MS Page 1

JobCode (batch):
UserName:
Vial:2,1:68
Method:C:\MassLynx\IS_3min standard.olp

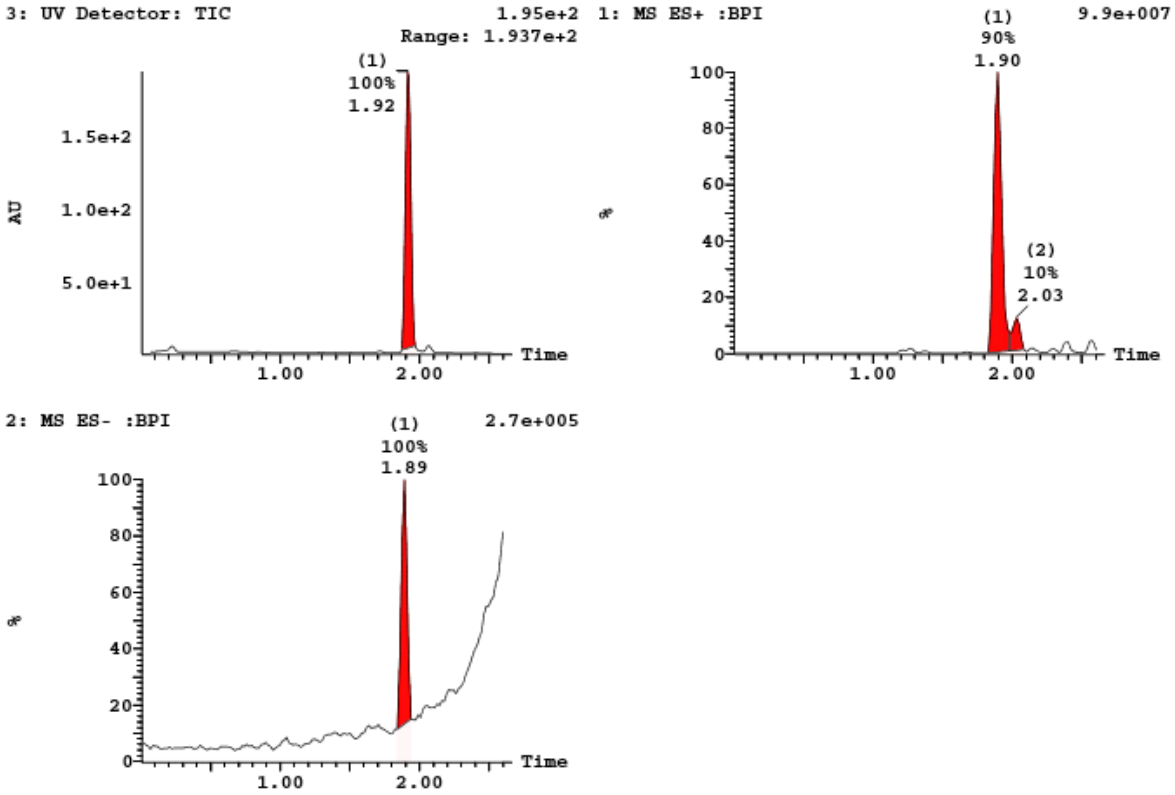
Sample: 2
Sample ID:
Instrument:OA_ZQ_LAA1007
pH: 11

Date:26-Apr-2010
Description:370880001
Location: KK230
Column: XBridge C18 5.0µm 3.0x50mm

Printed: Mon Apr 26 14:02:29 2010

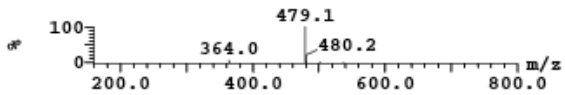
Sample Report:

Sample ID **Description 370880001**



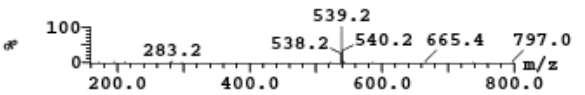
Peak ID	Time	Mass Found
1	1.90	

1:(Time: 1.92) 1:MS ES+ 5.4e+007

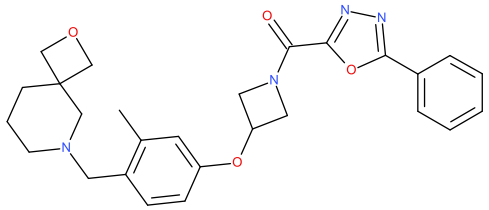


Peak ID	Time	Mass Found
1	1.90	

1:(Time: 1.89) 2:MS ES- 1.2e+005



Compound **15**



Openlynx Report - ALK95_1609 Page 1

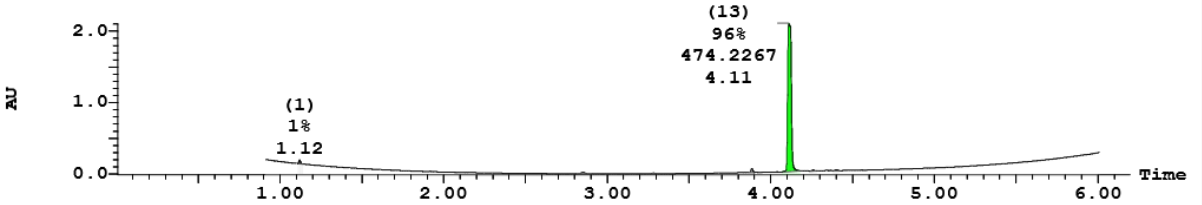
Purity & Mass ID File:1125_alk95_1609_after_13

Date:25-Nov-2009 Vial:4:4,C

Sample Report:

3: UV Detector: 210 2.102

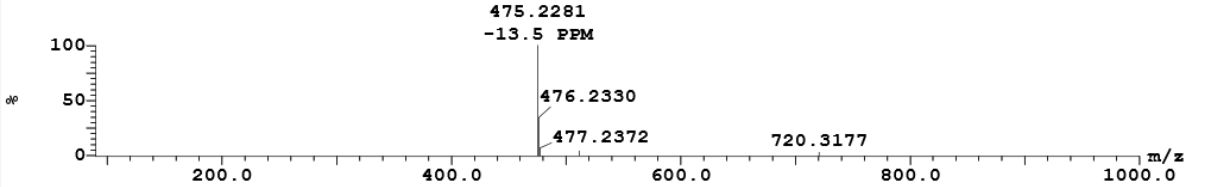
Range: 2.102



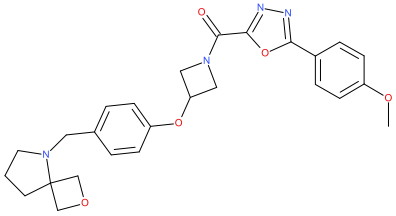
Peak Number	Compound	Time	AreaAbs	Area %Total	Height	Mass Found
1		1.12	6e+002	1.10	6e+004	
3		2.85	6e+002	1.02	2e+004	
6		3.28	2e+002	0.29	1e+004	
10		3.88	8e+002	1.34	6e+004	
13	Tentative	4.11	5e+004	95.66	2e+006	474.23
14		4.26	2e+002	0.31	1e+004	
16		4.40	2e+002	0.27	1e+004	

Peak ID	Compound	Time	Target	Error PPM	Error mDa
13	Tentative	4.12	475.23	-13	-6

13:(Time: 4.11) Combine (685:689) 1.1e+005



Compound **16**



Openlynx Report - ALK92_3124 Page 1

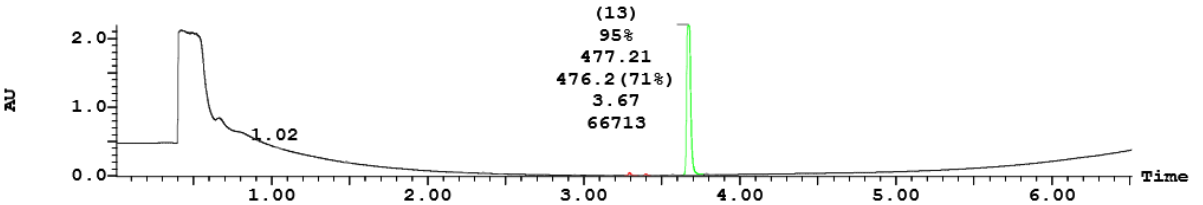
Purity & Accurate mass File:0304_alk92_3124_after_01

Date:04-Mar-2011 Vial:2:1,A

Sample Report:

3: UV Detector: 210 2.194

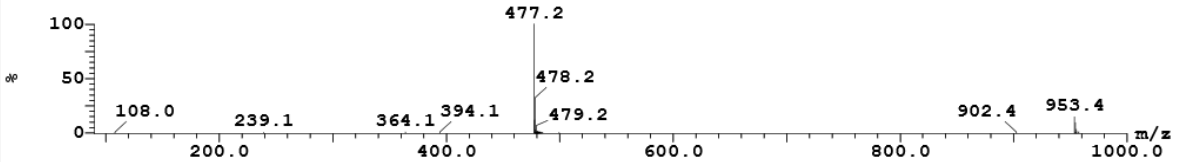
Range: 2.194



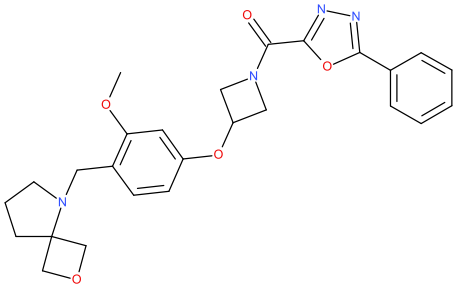
Peak Number	Compound	Time	AreaAbs	Area %Total	Height	Mass Found
1		1.02	2e+001	0.03	3e-002	
1		1.04	2e+001	0.03	1e+003	
2		1.48	3e+002	0.38	2e+004	
3		2.16	2e+002	0.29		
4		2.35	3e+002	0.41	2e+004	
5		2.46	2e+001	0.02	9e+002	
6		2.94	1e+002	0.19	7e+003	
7		3.15	7e+001	0.10	3e+003	
8		3.29	8e+002	1.21	4e+004	
9		3.36	3e+001	0.04	2e+003	
10		3.40	4e+002	0.59	2e+004	
11		3.46	1e+002	0.20	7e+003	
12		3.57	3e+002	0.48	1e+004	
13	Found	3.67	7e+004	95.32	2e+006	476.21
14		3.78	5e+002	0.71	2e+004	

Peak ID	Compound	Time	Target	Error PPM	Error mDa
13	Found	3.69	477.2138	1.7	0.8

13:(Time: 3.69) Combine (612:616) 1:TOF MS ES+ 3.7e+005



Compound **17**



Openlynx Report - ALK92_3214 Page 1

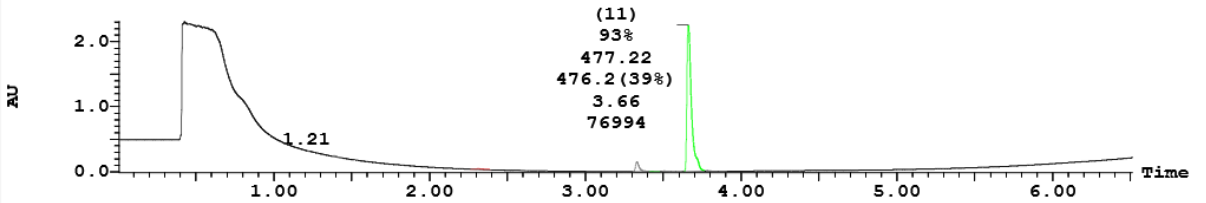
Purity & Accurate mass File:0412_alk92_3214_after_09_04

Date:13-Apr-2011 Vial:2:3,A

Sample Report:

3: UV Detector: 210 2.306

Range: 2.306

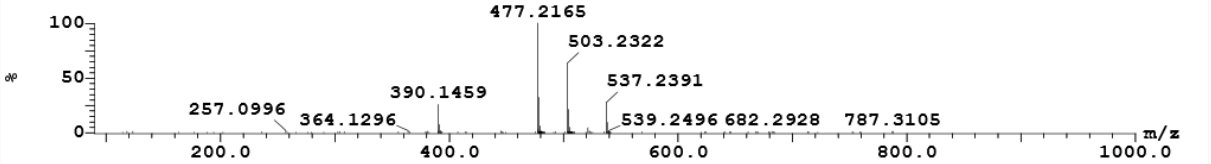


Peak Number	Compound	Time	AreaAbs	Area %Total	Height	Mass Found
1		1.21	4e+000	0.00	3e-002	
2		1.39	4e+002	0.44	2e+004	
4		2.31	5e+002	0.60	9e+003	
5		2.58	1e+001	0.02	1e-002	
6		3.33	4e+003	5.33	2e+005	
7	Found	3.43	1e+002	0.13	4e+003	476.21
8		3.51	3e+002	0.34	1e+004	
9		3.56	2e+001	0.02	1e+003	
10		3.59	1e+001	0.01	6e+002	
11	Found	3.66	8e+004	92.54	2e+006	476.21
12		3.78	4e+002	0.51	1e+004	
13		3.87	5e+001	0.06	2e+003	

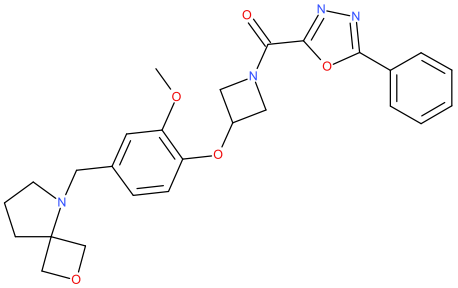
Peak ID	Compound	Time	Target	Error PPM	Error mDa
11	Found	3.71	477.2138	5.7	2.7

11:(Time: 3.71) Combine (634:638) - Dead time test passed 1:TOF MS ES+

1.5e+005



Compound **18**



Openlynx Report - 1042677304 Page 1

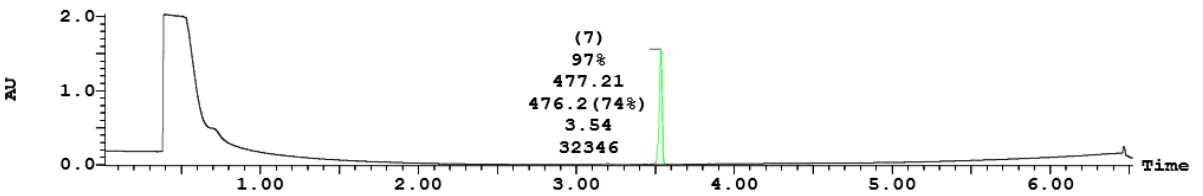
Purity & Accurate mass File:20110420_LCTP_CARS3717_610

Date:20-Apr-2011 Vial:6:10

Sample Report:

3: UV Detector: 210 2.03

Range: 2.03

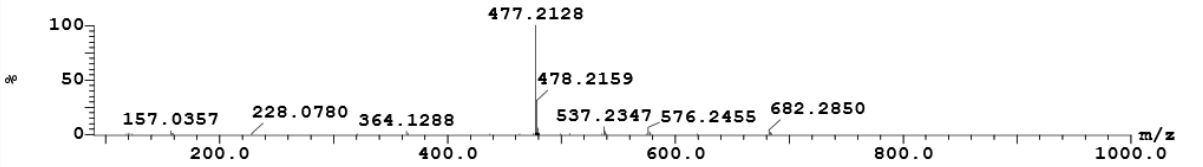


Peak Number	Compound	Time	AreaAbs	Area %Total	Height	Mass Found
2		3.20	5e+002	1.43	3e+004	
3		3.26	8e+001	0.24	5e+003	
4		3.31	1e+002	0.39	6e+003	
7	Found	3.54	3e+004	97.17	2e+006	476.21
8		3.61	2e+002	0.57	1e+004	
9		3.65	7e+001	0.20	4e+003	

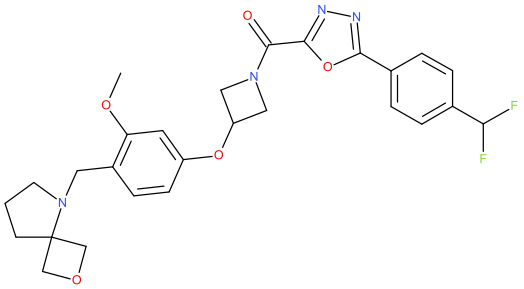
Peak ID	Compound	Time	Target	Error PPM	Error mDa
7	Found	3.52	477.2138	-2.1	-1.0

7:(Time: 3.53) Combine (480:484) 1:TOF MS ES+

5.6e+004



Compound **19**



Openlynx Report - ALK92_3214 Page 1

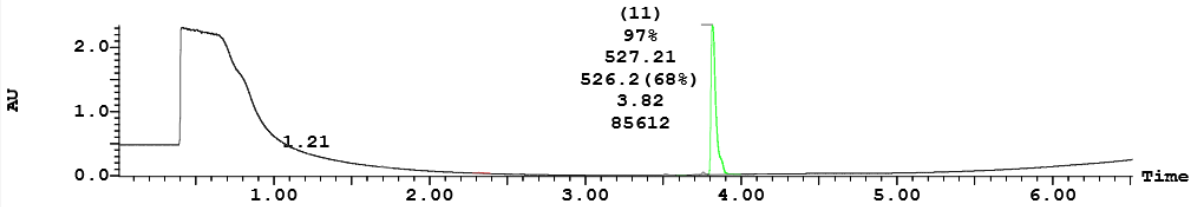
Purity & Accurate mass File:0412_alk92_3214_after_11

Date:12-Apr-2011 Vial:2:3,C

Sample Report:

3: UV Detector: 210 2.342

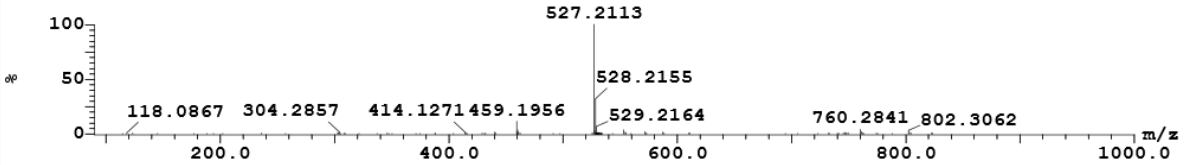
Range: 2.342



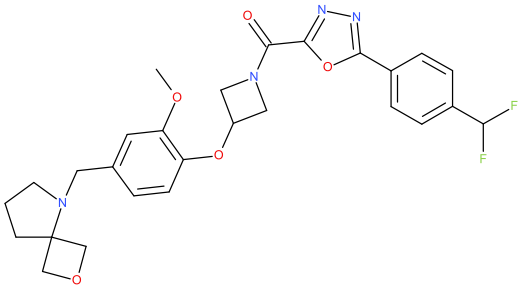
Peak Number	Compound	Time	AreaAbs	Area %Total	Height	Mass Found
1		1.21	5e+000	0.01	2e-002	
2		1.69	3e+002	0.39	1e+004	
4		2.32	5e+002	0.53	9e+003	
5		2.54	2e+001	0.02	8e+002	
6		3.51	6e+002	0.69	2e+004	
7	Found	3.60	8e+001	0.09	3e+003	526.20
8		3.71	3e+001	0.04	1e+003	
9		3.72	2e+001	0.03	1e+003	
10		3.76	1e+003	1.14	4e+004	
11	Found	3.82	9e+004	97.01	2e+006	526.20
12		4.12	5e+001	0.05	2e+003	
13		5.96	1e+000	0.00	1e-002	

Peak ID	Compound	Time	Target	Error PPM	Error mDa
11	Found	3.83	527.2106	1.3	0.7

11:(Time: 3.83) Combine (662:665) - Dead time test passed 1:TOF MS ES+ 1.4e+005



Compound **20**



Openlynx Report - ALK92_3214 Page 1

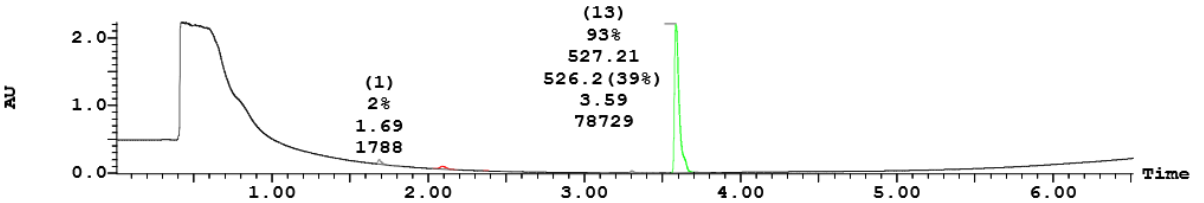
Purity & Accurate mass File:0412_alk92_3214_after_10_04

Date:13-Apr-2011 Vial:2:3,B

Sample Report:

3: UV Detector: 210 2.228

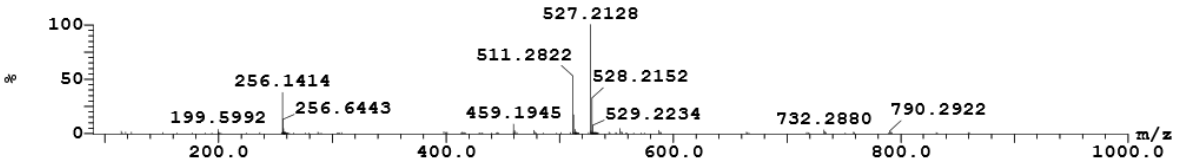
Range: 2.228



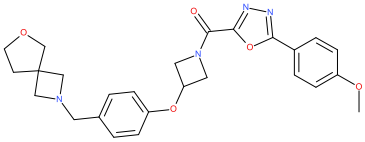
Peak Number	Compound	Time	AreaAbs	Area %Total	Height	Mass Found
1		1.69	2e+003	2.12	7e+004	
2		1.76	5e+001	0.06		
3		2.09	2e+003	2.48	4e+004	
4		2.35	2e+001	0.02	1e-002	
5		2.49	1e+002	0.12	3e+003	
6		2.55	9e+001	0.11	3e+003	
7		3.13	3e+001	0.03	9e+002	
8		3.30	9e+002	1.10	3e+004	
9		3.38	3e+001	0.04	1e+003	
10		3.43	3e+001	0.04	2e+003	
11		3.44	3e+001	0.04	1e+003	
12		3.54	9e+001	0.11	6e+003	
13	Found	3.59	8e+004	93.28	2e+006	526.20
14		3.71	4e+002	0.44	1e+004	
15		3.86	2e+001	0.02	9e+002	

Peak ID	Compound	Time	Target	Error PPM	Error mDa
13	Found	3.62	527.2106	4.2	2.2

13:(Time: 3.62) Combine (621:625) - Dead time test passed 1:TOF MS ES+ 1.4e+005



Compound **21**



Openlynx Report walk-up LC/MS Page 1

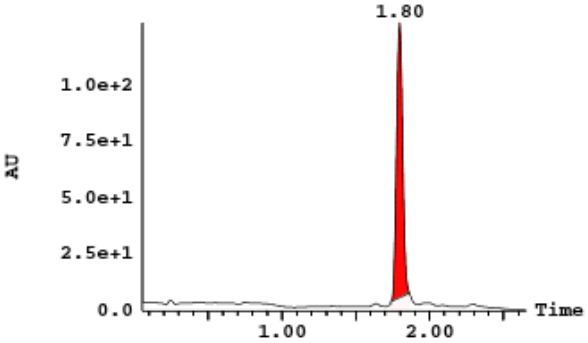
JobCode (batch): Sample: 2 Date:22-Jul-2011
UserName: Sample ID: Description:exp.80
Vial:2,1:71 Instrument:ZQ_LAA1645 Location: KJ338
Method:C:\MassLynx\IS_3min standard.olp pH: 11 Column: XBridge C18 5µ 3.0x50mm

Printed: Fri Jul 22 09:26:27 2011

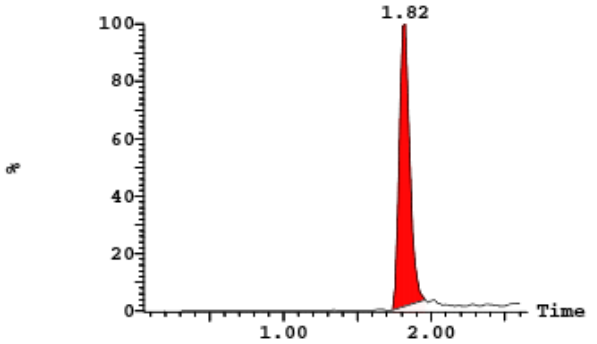
Sample Report:

Sample ID kgvj18226-2 Description exp.80

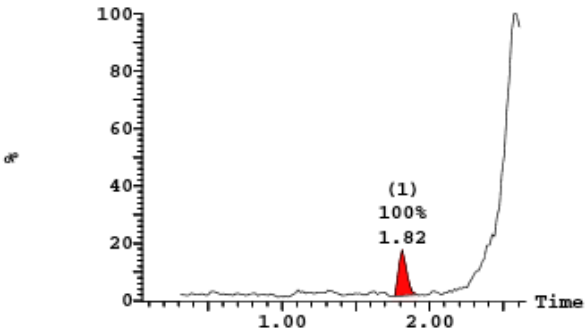
3: UV Detector: TIC (1) 1.27e+2
100%Range: 1.27e+2
1.80



1: MS ES+ :BPI (1) 3.1e+007
100%
1.82

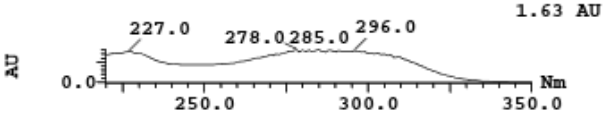


2: MS ES- :BPI 1.5e+005



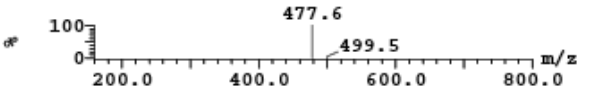
Peak ID	Time	Mass Found
1	1.82	

1:(Time: 1.80) 3:UV Detector 1.63 AU



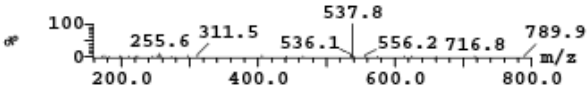
Peak ID	Time	Mass Found
1	1.82	

1:(Time: 1.80) 1:MS ES+ 1.8e+007

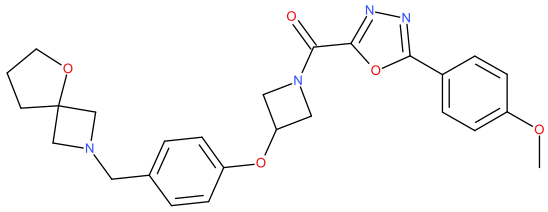


Peak ID	Time	Mass Found
1	1.82	

1:(Time: 1.80) 2:MS ES- 1.4e+004



Compound **22**



Openlynx Report - 1051193307 Page 1

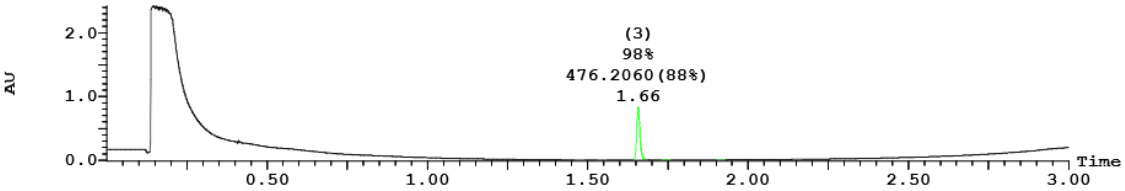
Purity & Accurate mass File:20120322_LCTP_509

Date:2 -ar -012 Vial:12:9

Sample Report:

3: UV Detector: 210 2.425

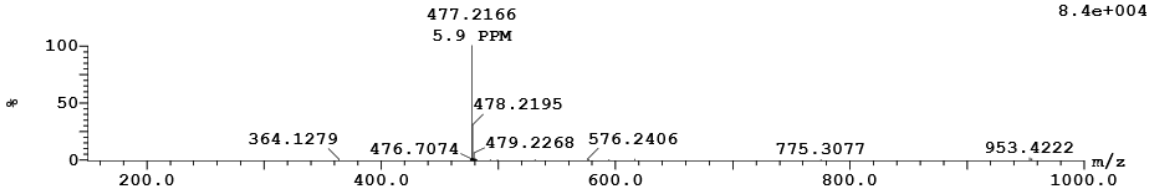
Range: 2.425



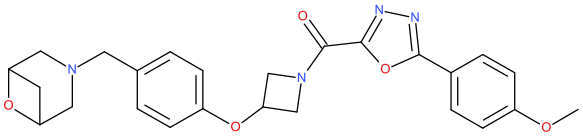
Peak Number	Compound	Time	AreaAbs	Area %Total	Height	Mass Found
1		1.47	3.06e+001	0.30	2.3e+003	
2		1.55	5.14e+001	0.50	3.3e+003	
3	Found	1.66	9.97e+003	97.67	8.4e+005	476.2060
4	Found	1.74	9.85e+001	0.96	8.6e+003	476.2060
6	Found	1.91	2.49e+001	0.24	2.1e+003	476.2060
7		2.15	3.28e+001	0.32	2.2e+003	

Peak ID	Compound	Time	Target	Error PPM	Error mDa
3	Found	1.67	477.2138	5.87	2.80

3:(Time: 1.67) Combine (209:213) 1:TOF MS ES+ 8.4e+004



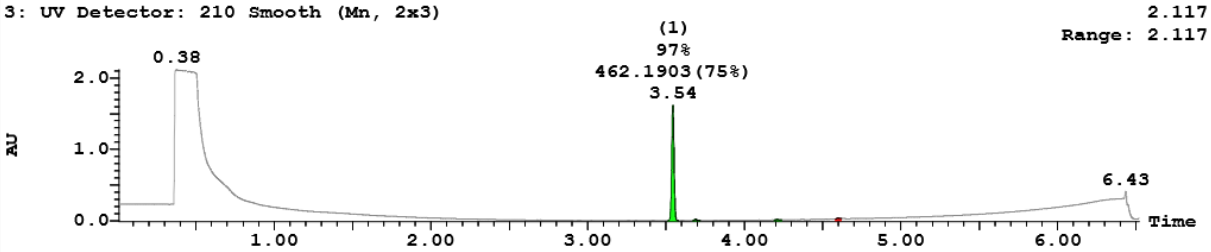
Compound **23**



Openlynx Report - 1051118454
Purity & Mass ID
Date:19-Jan-2012

File:20120119_LCTP_809
Vial:11:9

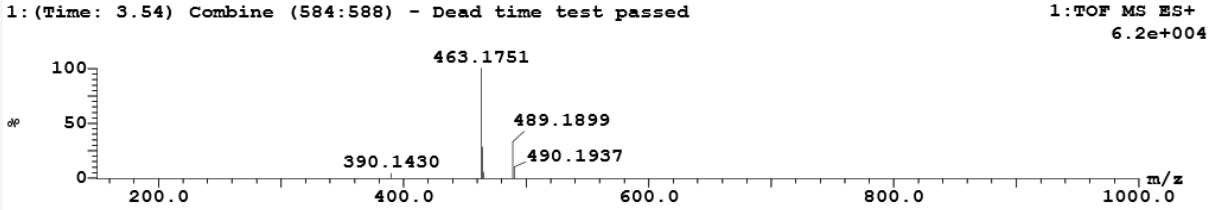
Sample Report:



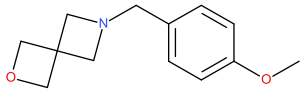
Peak Number	Compound	Time	AreaAbs	Area %Total	Height	Mass Found
1	Found	3.54	3e+004	97.46	2e+006	462.19
3	Found	3.69	4e+002	1.32	2e+004	462.19
5	Found	4.21	1e+002	0.48	8e+003	462.19
6		4.60	2e+002	0.74	1e+004	

Peak ID	Compound	Time	Target	Error PPM	Error mDa
1	Found	3.54	463.20	-50	-23

1:(Time: 3.54) Combine (584:588) - Dead time test passed



Compound **24**

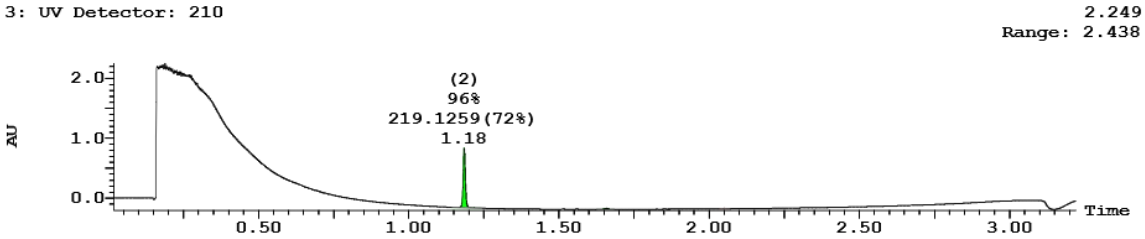


Openlynx Report -
Purity & Accurate mass
Date:11-May-2017
SampleType:0

File:20170511_CM_3076_003b
Vial:9:5
Submitter:1050683076

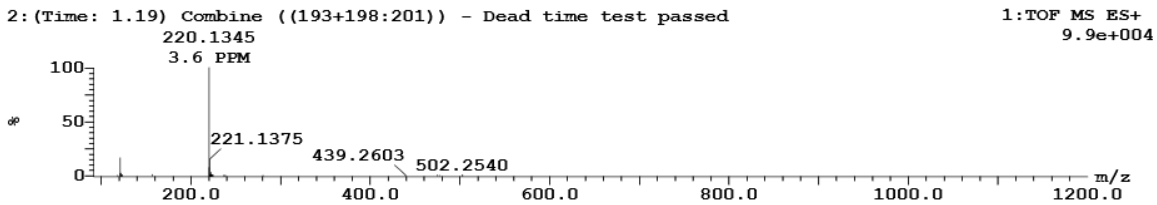
Page 1

Sample Report:

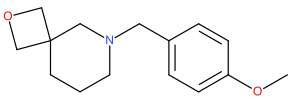


Peak Number	Compound	Time	AreaAbs	Area %Total	Height	Mass Found
2	Found	1.18	9e+003	96.33	1e+006	219.13
3	Found	1.66	2e+002	2.67	2e+004	219.13
5		2.05	9e+001	1.00	9e+003	

Peak ID	Compound	Time	Target	Error PPM	Error mDa
2	Found	1.19	220.1337	3.6	0.8



Compound **25**



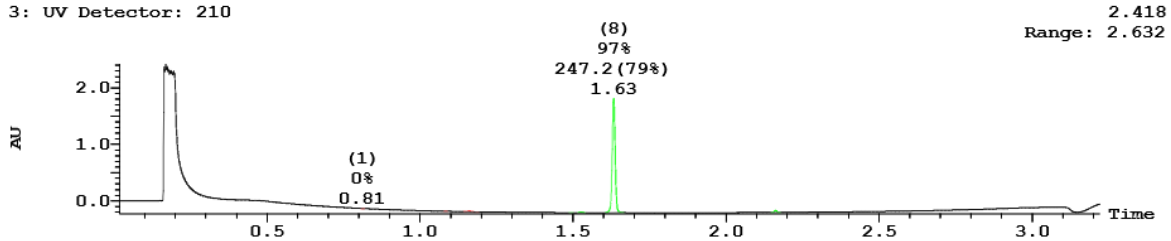
Openlynx Report -
Purity & Accurate mass
Date:13-Mar-2017
SampleType:0

File:Nebulosa-22612_A2_17-03-13_082607_02x
Vial:6:1,B
Submitter:Fredenwall, Marlene

Page 1

Sample Report:

3: UV Detector: 210

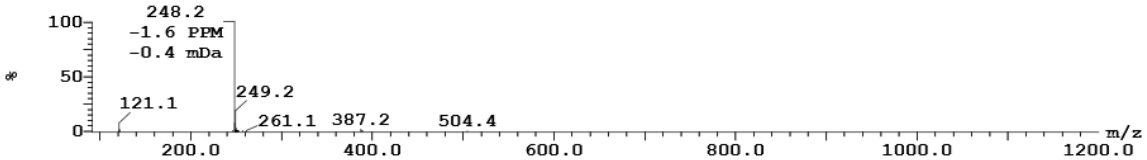


Peak Number	Compound	Time	AreaAbs	Area %Total	Height	Mass Found
1		0.81	2e+001	0.07	2e+003	
2		1.08	1e+001	0.05	2e+003	
3		1.16	1e+002	0.45	1e+004	
4		1.18	6e+000	0.02	5e+002	
6	Found	1.50	1e+001	0.05	1e+003	247.16
7	Found	1.52	1e+002	0.61	1e+004	247.16
8	Found	1.63	2e+004	97.23	2e+006	247.16
10	Found	2.16	4e+002	1.52	4e+004	247.16

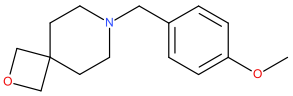
Peak ID	Compound	Time	Target	Error PPM	Error mDa
8	Found	1.63	248.1650	-1.6	-0.4

8:(Time: 1.63) Combine ((267:268+273:275)) - Dead time test passed

1:TOF MS ES+
1.3e+005



Compound **26**



Openlynx Report -

Page 1

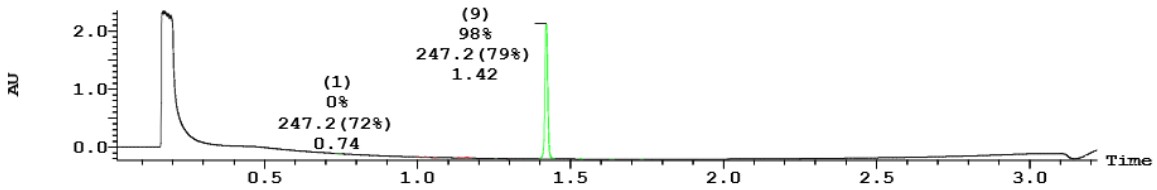
Purity & Accurate mass
Date:13-Mar-2017
SampleType:0

File:Nebulosa-22612_A2_17-03-13_082607_03x
Vial:6:1,C
Submitter:Fredenwall, Marlene

Sample Report:

3: UV Detector: 210

2.353
Range: 2.567

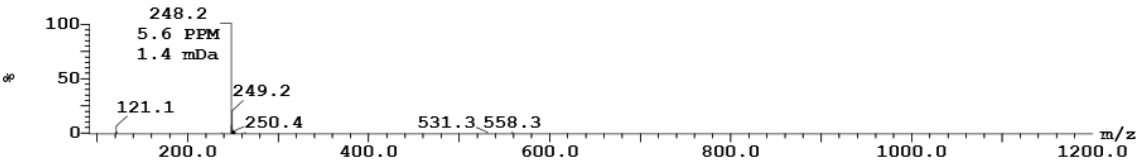


Peak Number	Compound	Time	AreaAbs	Area %Total	Height	Mass Found
1	Found	0.74	4e+001	0.15	4e+003	247.16
3		1.00	1e+001	0.05	1e+003	
4		1.02	6e+001	0.24	6e+003	
5		1.05	8e+000	0.03	9e+002	
6		1.13	3e+001	0.11	3e+003	
7		1.16	2e+002	0.76	2e+004	
8	Found	1.25	4e+000	0.02	8e+002	247.16
9	Found	1.42	3e+004	98.47	2e+006	247.16
10	Found	1.53	2e+001	0.06	2e+003	247.16
11	Found	1.63	1e+001	0.06	1e+003	247.16
12	Found	1.73	1e+001	0.05	1e+003	247.16

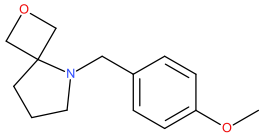
Peak ID	Compound	Time	Target	Error PPM	Error mDa
9	Found	1.42	248.1650	5.6	1.4

9:(Time: 1.42) Combine ((233:234+238:240)) - Dead time test passed

1:TOF MS ES+
9.9e+004



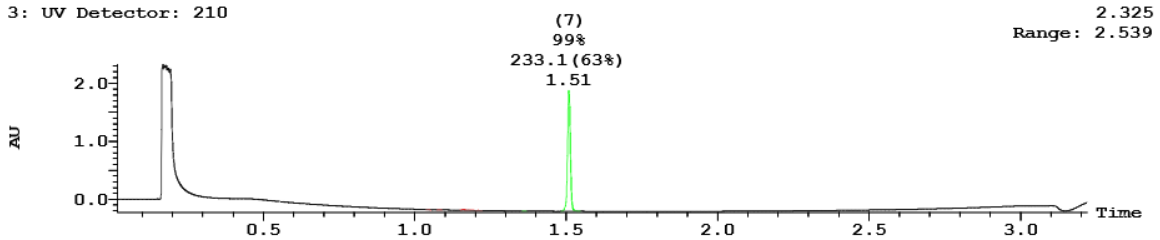
Compound **27**



Openlynx Report -
Purity & Accurate mass
Date:13-Mar-2017
SampleType:0

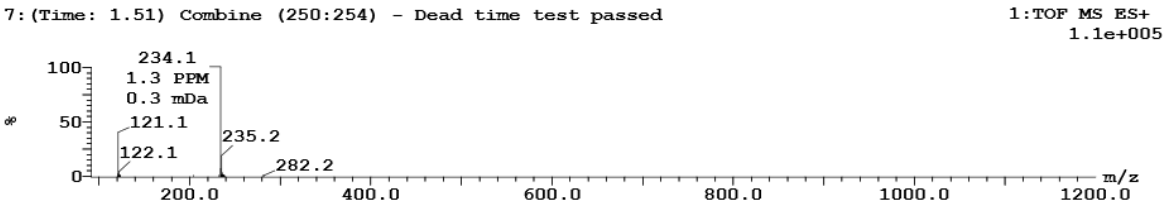
File:Nebulosa-22612_A2_17-03-13_082607_04x
Vial:6:1,D
Submitter:Fredenwall, Marlene

Sample Report:

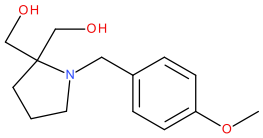


Peak Number	Compound	Time	AreaAbs	Area %Total	Height	Mass Found
1		1.04	1e+001	0.06	1e+003	
2		1.08	2e+001	0.10	3e+003	
3		1.16	2e+002	0.71	2e+004	
4		1.18	2e+001	0.09	2e+003	
5		1.21	2e+001	0.09	2e+003	
6	Found	1.36	9e+000	0.04	1e+003	233.14
7	Found	1.51	2e+004	98.92	2e+006	233.14

Peak ID	Compound	Time	Target	Error PPM	Error mDa
7	Found	1.51	234.1494	1.3	0.3



Compound **28**



Openlynx Report - 5003084577
Sample: 18
File:20170530 XEVO 056 b
Description:

Vial:8:41
Date:01-Jun-2017

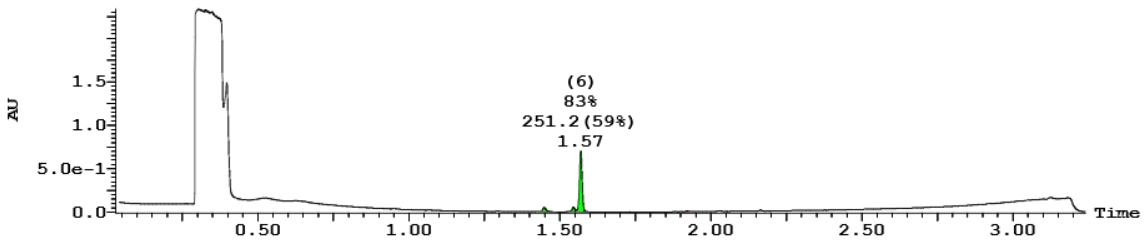
Page 1

Printed: Fri Jun 09 09:48:34 2017

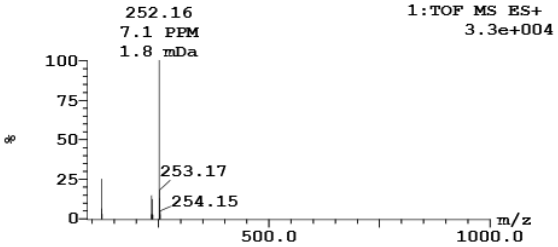
Sample Report:

3: UV Detector: 210 Smooth (Mn, 2x3)

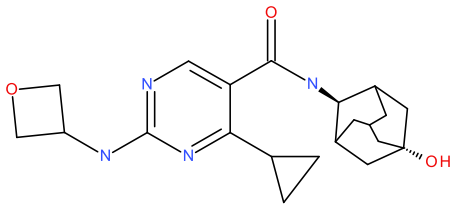
2.336
Range: 2.336



Peak ID	Compound	Time	Mass Found
6	Found	1.57	252.16



Compound **29**

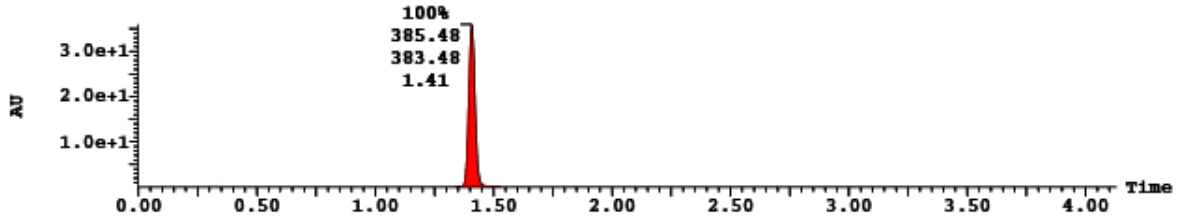


Openlynx Report - 166243 Page 1

Sample: 1 Vial:3:41 ID:EN01334-81-1
File: Date:11-Jun-2008 Method:C:\MassLynx\MONITORbase.olp
Time:13:43:42 Description: 3s11blcms

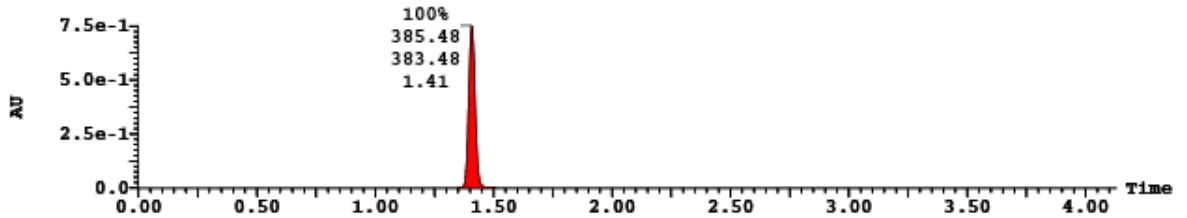
Printed: Wed Jun 11 13:49:45 2008

3: UV Detector: TIC 3.589e+1
Range: 3.584e+1

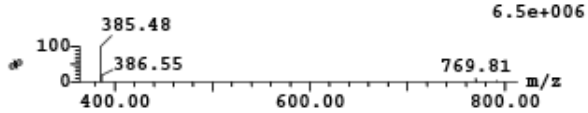


Peak Number	Compound	Time	AreaAbs	Area %Total	Mass Found
1		1.41	1e+006	100.00	

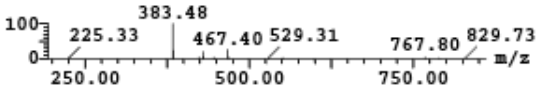
3: UV Detector: 254 7.515e-1
Range: 7.514e-1



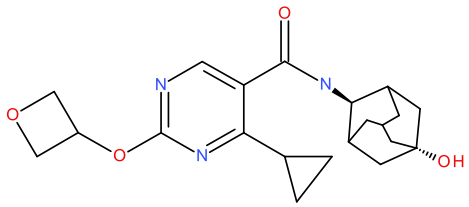
Peak ID
1
Combine (68:73-(55:57+86:89)) 1:MS ES+
6.5e+006



Peak ID
1
Combine (67:72-(54:57+86:88)) 2:MS ES-
2.9e+005



Compound **30**

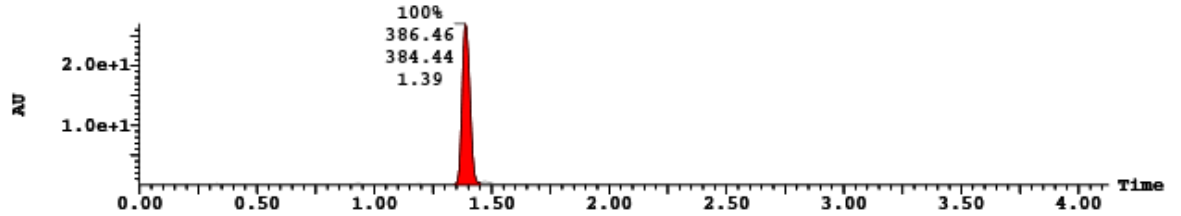


Openlynx Report - 166243 Page 1

Sample: 1 Vial:1:40 ID:en01334-82-1
File: Date:12-Jun-2008 Method:C:\MassLynx\MONITORbase.olp
Time:13:19:24 Description: 3s11blcms

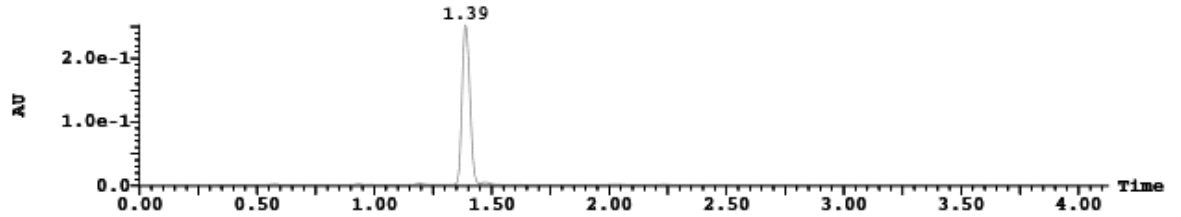
Printed: Thu Jun 12 13:26:29 2008

3: UV Detector: TIC 2.699e+1
Range: 2.693e+1

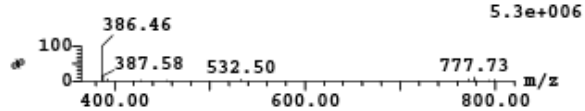


Peak Number	Compound	Time	AreaAbs	Area %Total	Mass Found
1		1.39	1e+006	100.00	

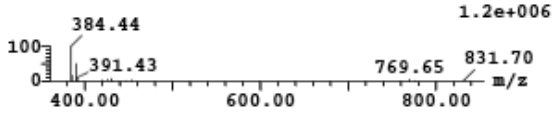
3: UV Detector: 254 2.527e-1
Range: 2.526e-1



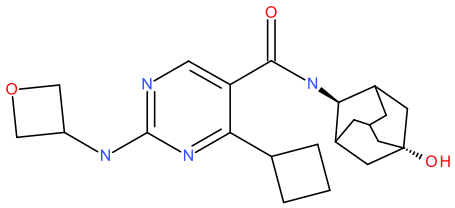
Peak ID
1
Combine (67:72-(54:57+82:85)) 1:MS ES+
5.3e+006



Peak ID
1
Combine (66:71-(54:56+82:84)) 2:MS ES-
1.2e+006



Compound **31**

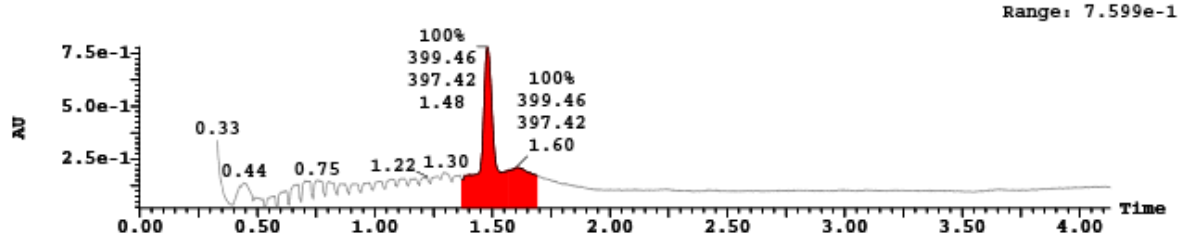


Openlynx Report - 166243 Page 1

Sample: 1 Vial:1:41 ID:en01837-08-1
File: Date:12-Jun-2008 Method:C:\MassLynx\MONITORbase.olp
Time:13:26:28 Description: 3s11blcms

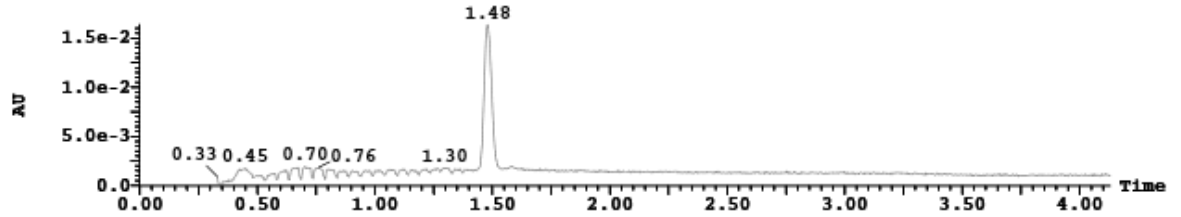
Printed: Thu Jun 12 13:32:31 2008

3: UV Detector: TIC 7.801e-1
Range: 7.599e-1

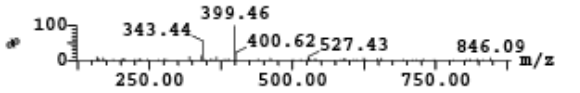


Peak Number	Compound	Time	AreaAbs	Area %Total	Mass Found
1		1.48	3e+004	100.00	

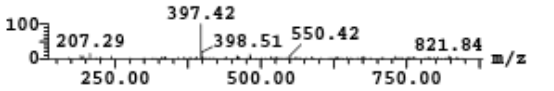
3: UV Detector: 254 1.638e-2
Range: 1.635e-2



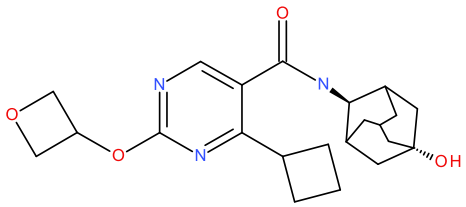
Peak ID
1
Combine (71:76-(56:59+94:97)) 1:MS ES+
2.4e+005



Peak ID
1
Combine (71:76-(56:58+94:96)) 2:MS ES-
8.8e+004



Compound **32** (contains ca.9% of +18Da impurity)

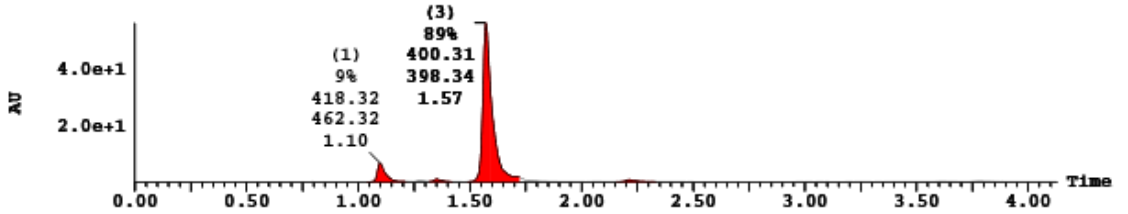


Openlynx Report - knpk467 Page 1

Sample: 1 Vial:2:30 ID:EN01837-10
File: Date:12-Jun-2008 Method:C:\MassLynx\MONITORbase.olp
Time:14:23:23 Description: 3S11lcms

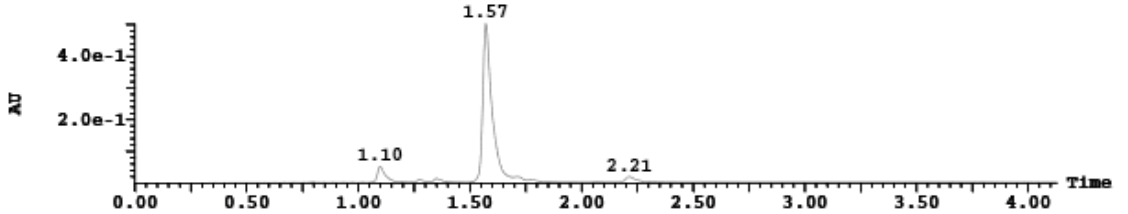
Printed: Thu Jun 12 14:29:33 2008

3: UV Detector: TIC 5.656e+1
Range: 5.652e+1

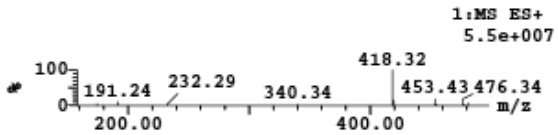


Peak Number	Compound	Time	AreaAbs	Area %Total	Mass Found
1		1.10	3e+005	9.17	
2		1.35	3e+004	1.00	
3		1.57	3e+006	88.56	
4		2.21	4e+004	1.26	

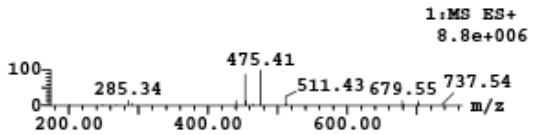
3: UV Detector: 254 5.023e-1
Range: 5.019e-1



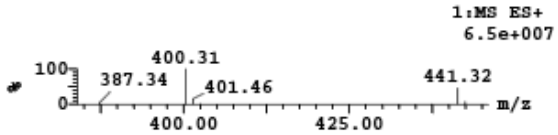
Peak ID
1



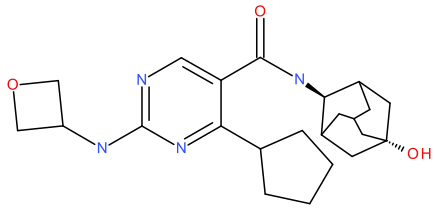
Peak ID
2



Peak ID
3



Compound **33**

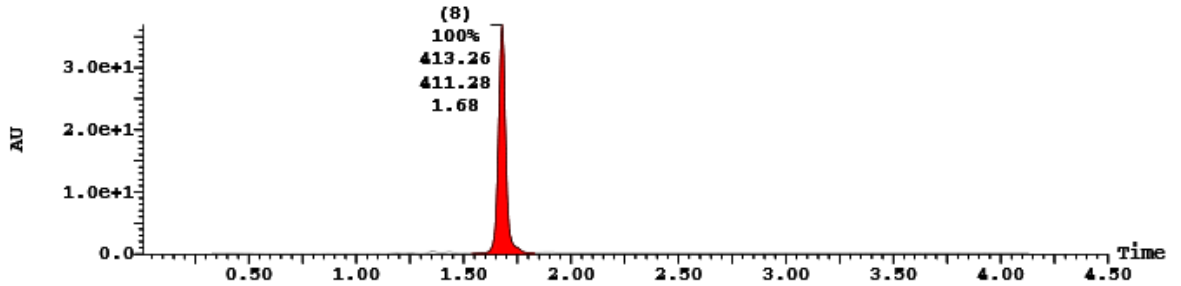


Openlynx Report - 173463 Page 1

Sample: 1 Vial:2:41 ID:EN1504-36
File:(Method:C:\MassLynx\5MINbase.olp Date:14-May-2008
Time:12:18:48 SIGNED BY Description:
3S29B LCMS

Printed: Wed May 14 12:24:50 2008

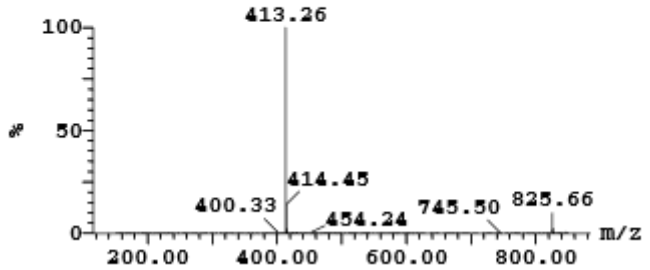
3: UV Detector: TIC 3.687e+1
Range: 3.687e+1



Peak Number	Compound	Time	AreaAbs	Area %Total	Mass Found
8		1.68	1e+006	100.00	

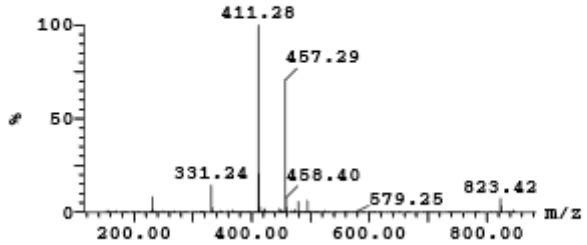
Peak ID	Time	Mass Found
8	1.67	

Combine (81:85-(64:66+100:102)) 1:MS ES+
5.9e+007

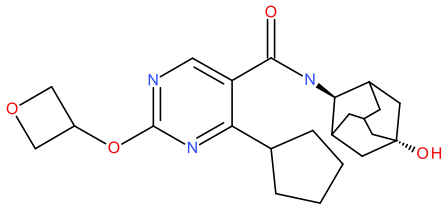


Peak ID	Time	Mass Found
8	1.67	

Combine (81:85-(67:69+100:102)) 2:MS ES-
2.0e+006



Compound **34**



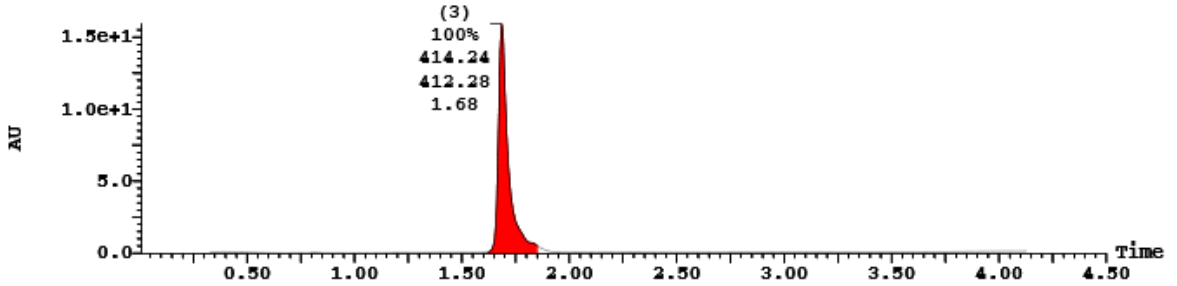
Openlynx Report - 173463 Page 1

Sample: 1 Vial:3:27 ID:EN1504-41
File: Method:C:\MassLynx\5MINbase.olp Date:15-May-2008
Time:11:49:13 SIGNED BY Description:
3S29B LCMS

Printed: Thu May 15 11:55:21 2008

Sample Report:

3: UV Detector: TIC 1.593e+1
Range: 1.592e+1

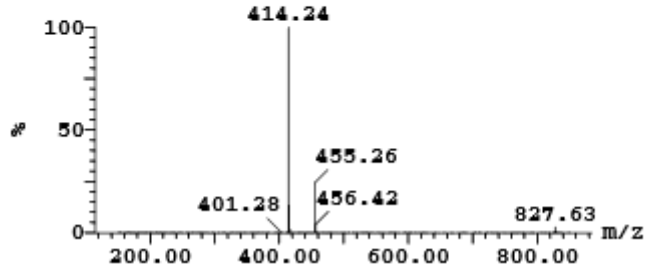


Peak Number	Compound	Time	AreaAbs	Area %Total	Mass Found
3		1.69	8e+005	100.00	

Sample Report (continued):

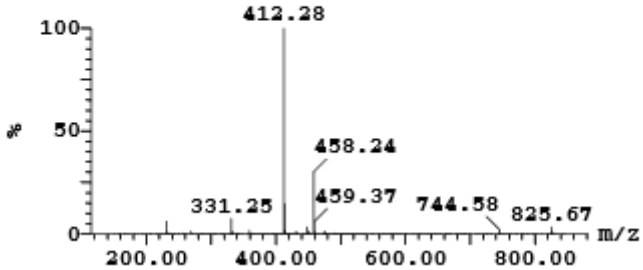
Peak ID	Time	Mass Found
3	1.67	

Combine (81:85-(65:67+96:98)) 1:MS ES+
2.6e+007

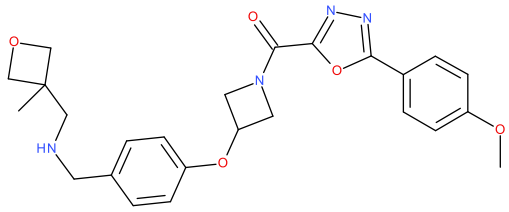


Peak ID	Time	Mass Found
3	1.67	

Combine (81:85-(65:67+105:107)) 2:MS ES-
1.2e+007



Compound **35**



Openlynx Report -
Purity & Accurate mass
Date:22-Sep-2016
Submitter:5003074678

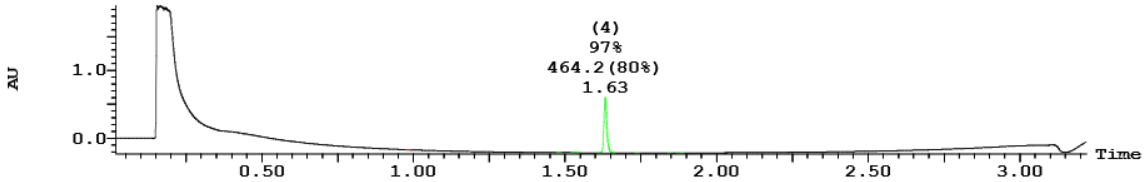
File:20160921_CM4678_011x
Vial:11:37
Inlet Method:Standard_3min_col2_alk

Page 1

Sample Report:

3: UV Detector: 210

1.957
Range: 2.179

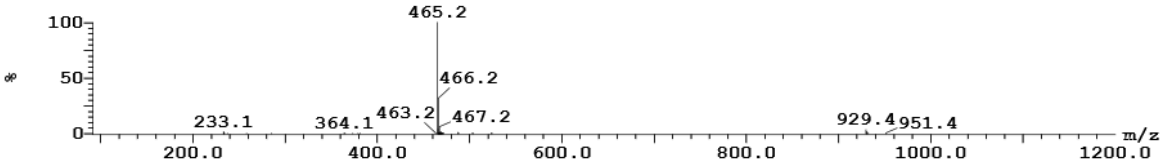


Peak Number	Compound	Time	AreaAbs	Area %Total	Height	Mass Found
1		0.98	3e+001	0.35	3e+003	
2	Found	1.48	2e+001	0.18	2e+003	464.21
3	Found	1.53	1e+002	1.17	8e+003	464.21
4	Found	1.63	9e+003	97.49	8e+005	464.21
5	Found	1.74	3e+001	0.29	3e+003	464.21
6	Found	1.84	2e+001	0.21	2e+003	464.21
7	Found	1.88	3e+001	0.31	2e+003	464.21

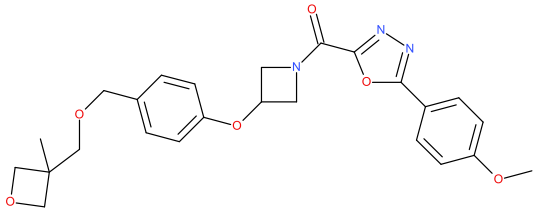
Peak ID	Compound	Time	Target	Error PPM	Error mDa
4	Found	1.63	465.2138	2.4	1.1

4:(Time: 1.63) Combine ((268+274:277)) - Dead time test passed

1:TOF MS ES+
9.2e+004



Compound **36**

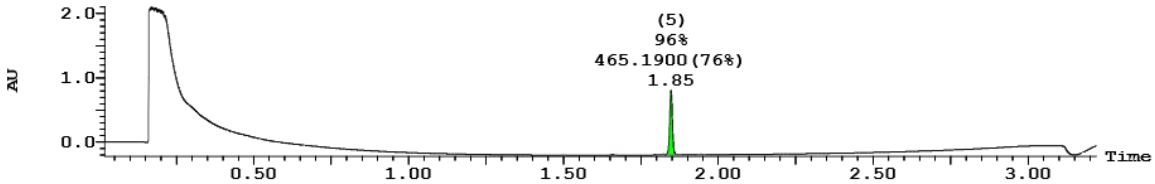


Openlynx Report - Page 1

Purity & Accurate mass File:20170511_CM_3076_001
Date:11-May-2017 Vial:9:1
SampleType:0 Submitter:1050683076 TaskCode:

Sample Report:

3: UV Detector: 210 2.11
Range: 2.316



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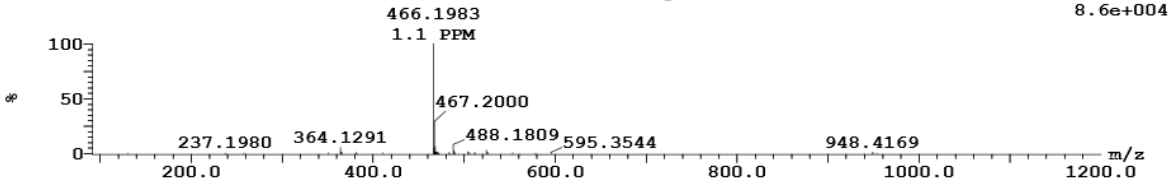
2		1.66	6e+001	0.58	5e+003	
3	Found	1.80	9e+001	0.85	9e+003	465.19
4	Found	1.82	1e+002	1.28	1e+004	465.19
5	Found	1.85	1e+004	96.13	1e+006	465.19
7	Found	1.94	1e+002	1.02	1e+004	465.19

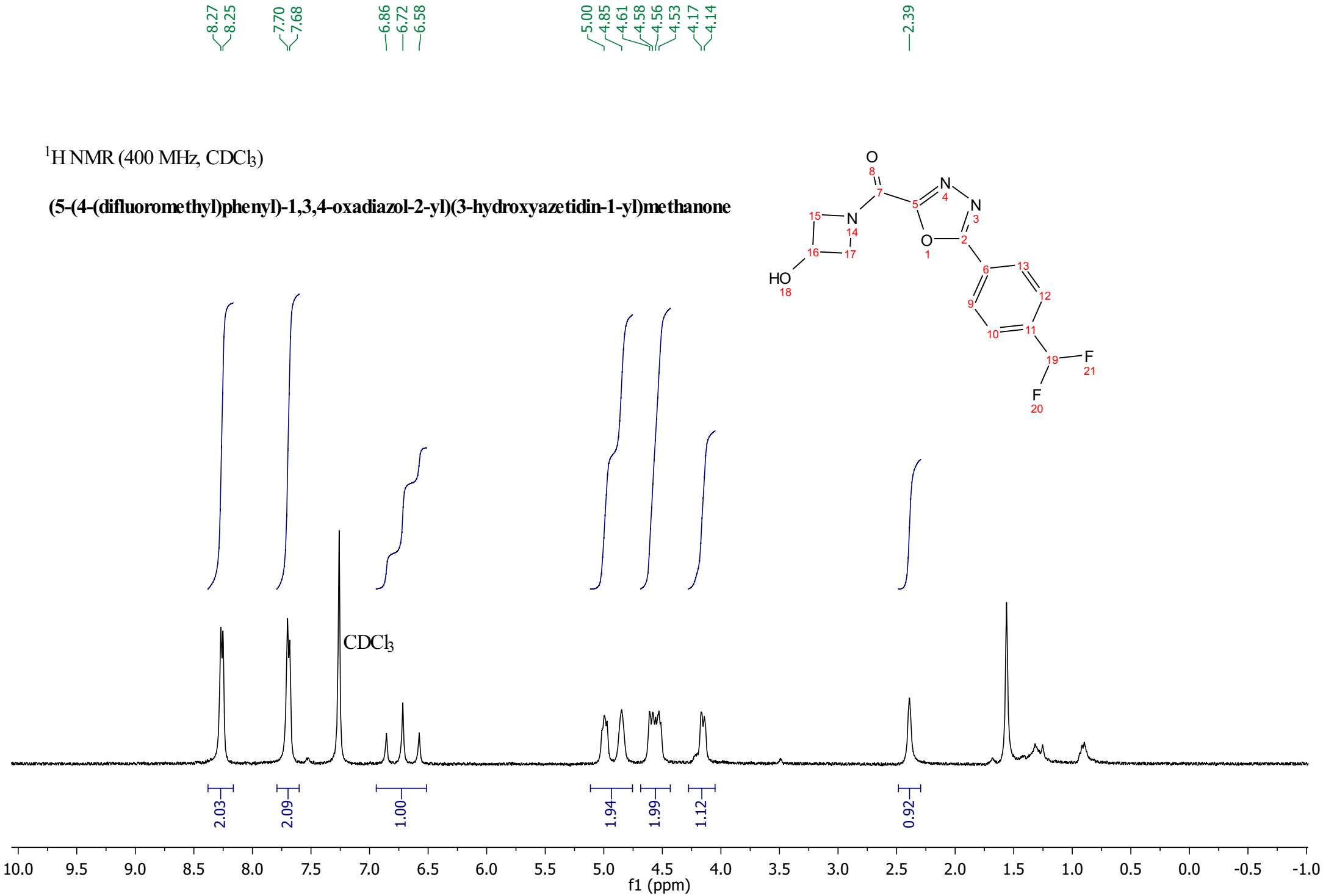
Peak ID	Compound	Time	Target	Error PPM	Error mDa
3	Found	1.80	466.1978	1.1	0.5

3:(Time: 1.80) Combine ((305+309:312)) - Dead time test passed 1:TOF MS ES+
8.6e+004



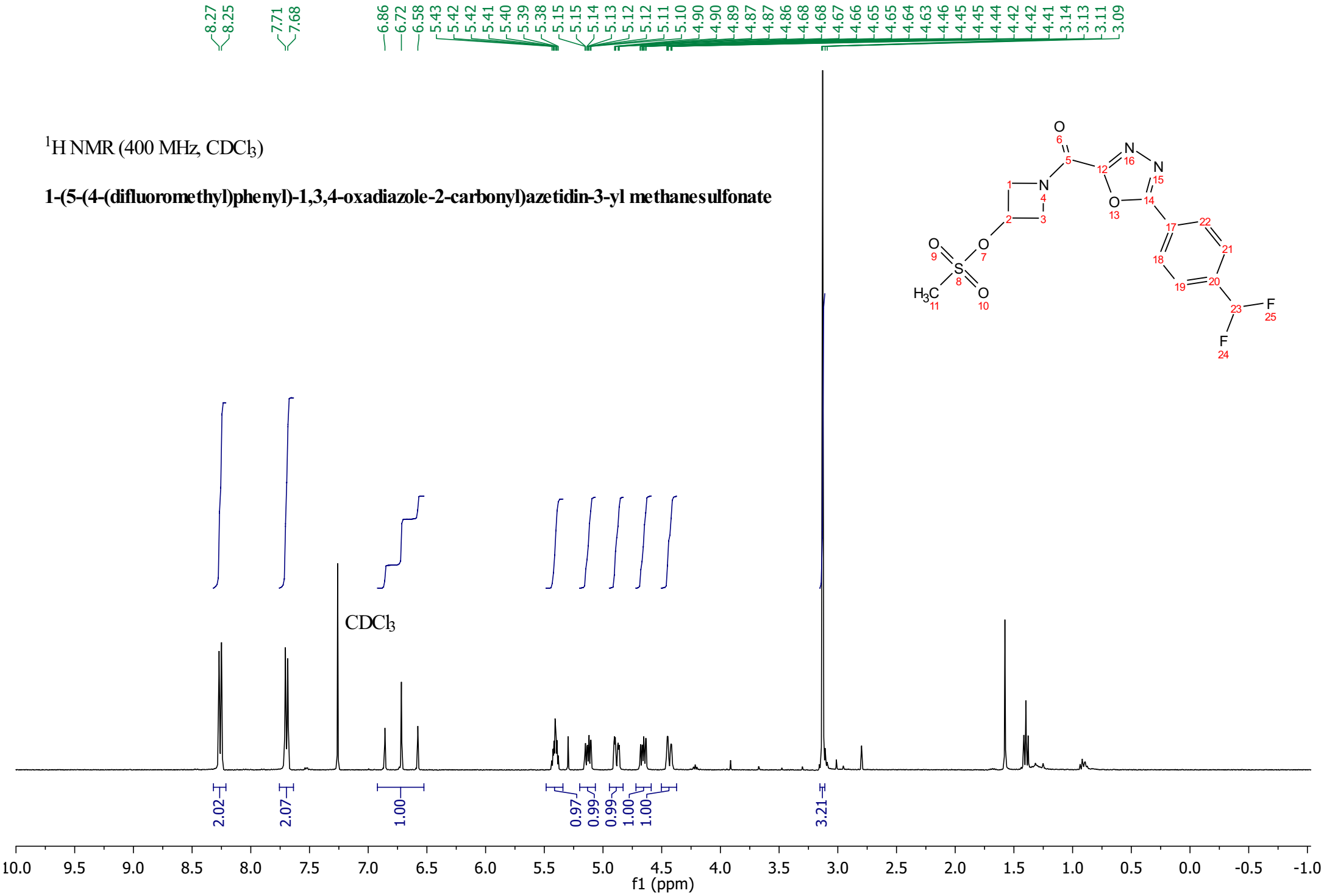
^{1}H NMR (400 MHz, $CDCl_3$)

(5-(4-(difluoromethyl)phenyl)-1,3,4-oxadiazol-2-yl)(3-hydroxyazetidin-1-yl)methanone



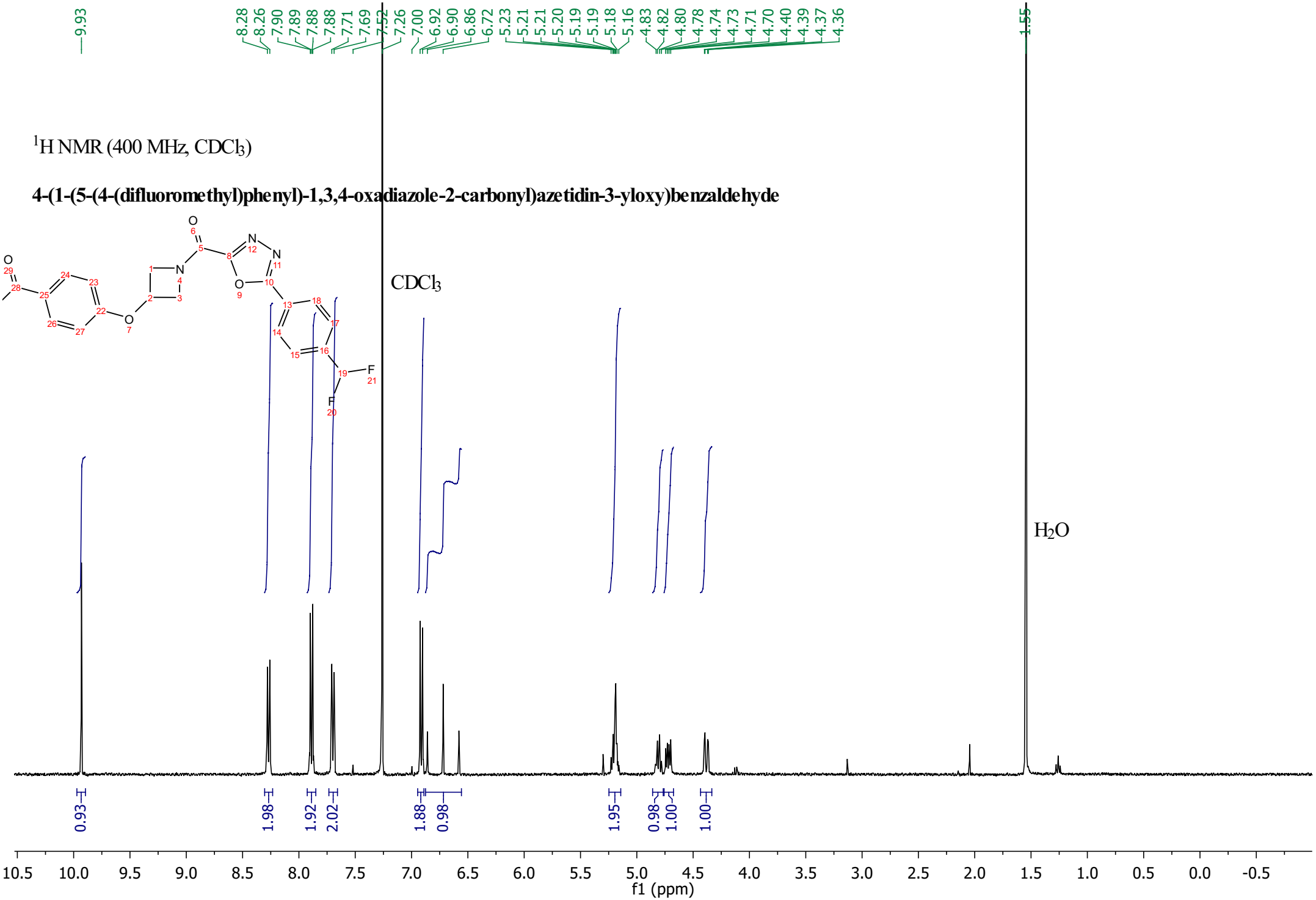
^{1}H NMR (400 MHz, $CDCl_3$)

1-(5-(4-(difluoromethyl)phenyl)-1,3,4-oxadiazole-2-carbonyl)azetidin-3-yl methanesulfonate



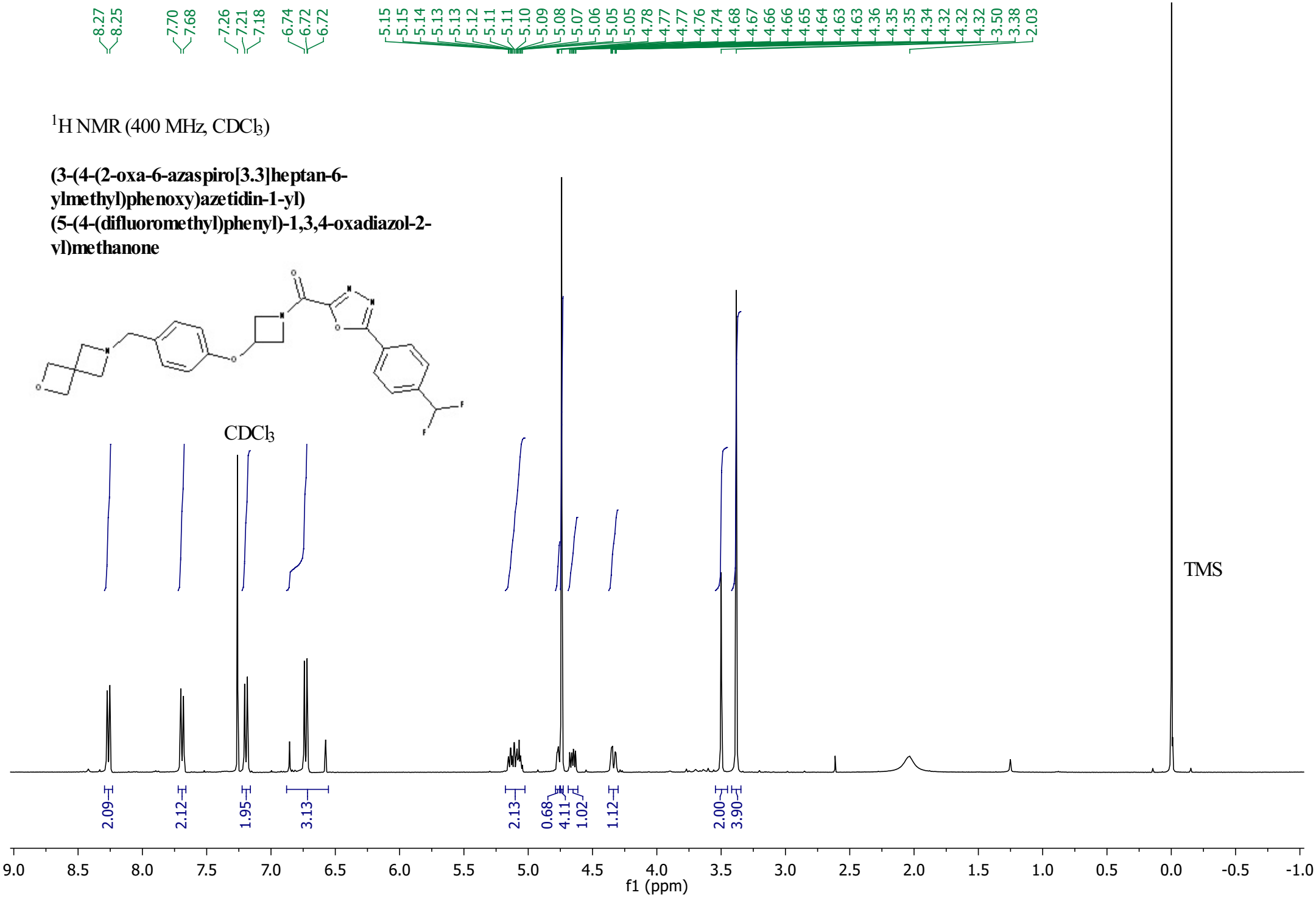
^{1}H NMR (400 MHz, $CDCl_3$)

4-(1-(5-(4-(difluoromethyl)phenyl)-1,3,4-oxadiazole-2-carbonyl)azetidin-3-yloxy)benzaldehyde



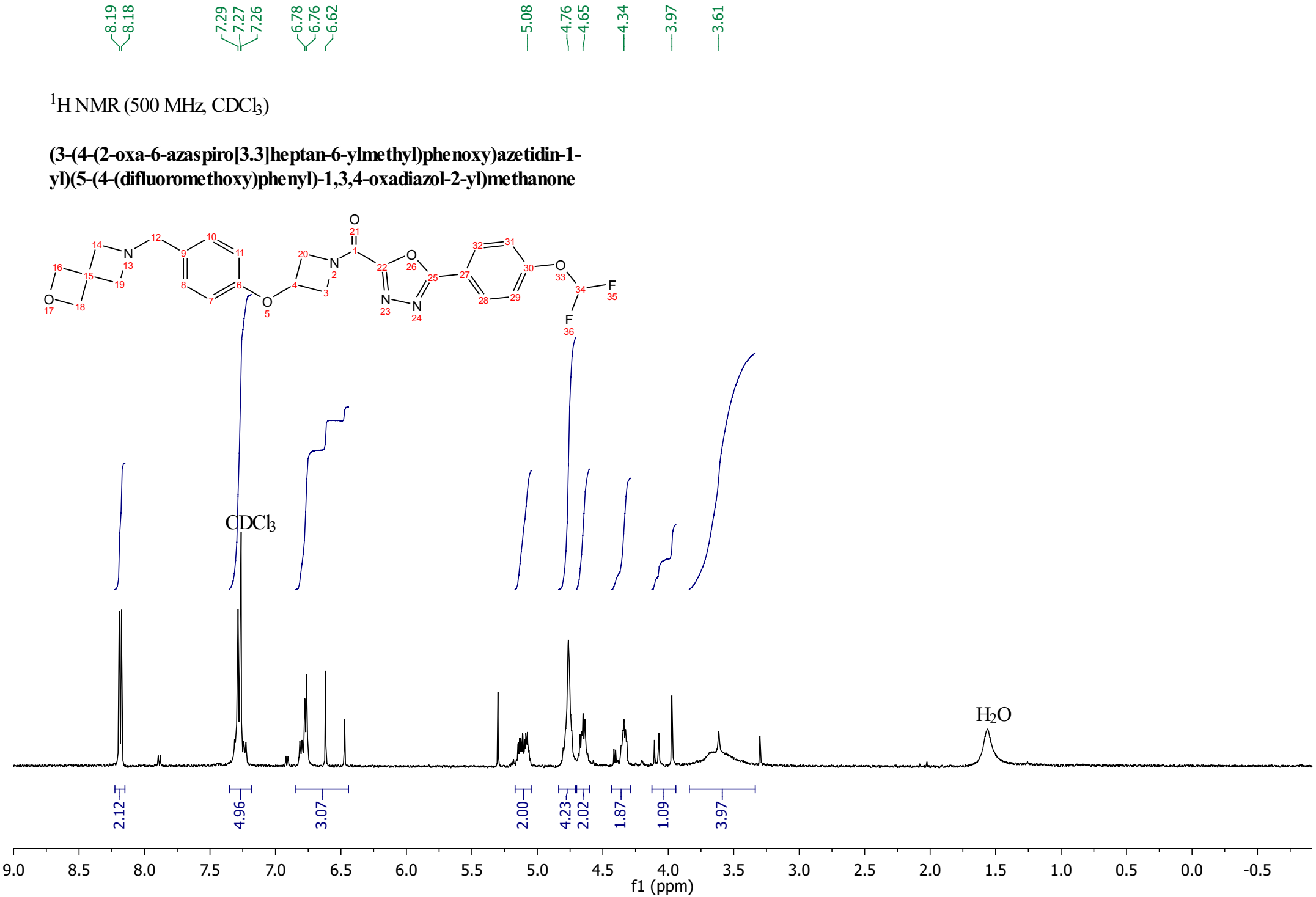
^{1}H NMR (400 MHz, $CDCl_3$)

(3-(4-(2-oxa-6-azaspiro[3.3]heptan-6-ylmethyl)phenoxy)azetidin-1-yl)(5-(4-(difluoromethyl)phenyl)-1,3,4-oxadiazol-2-yl)methanone



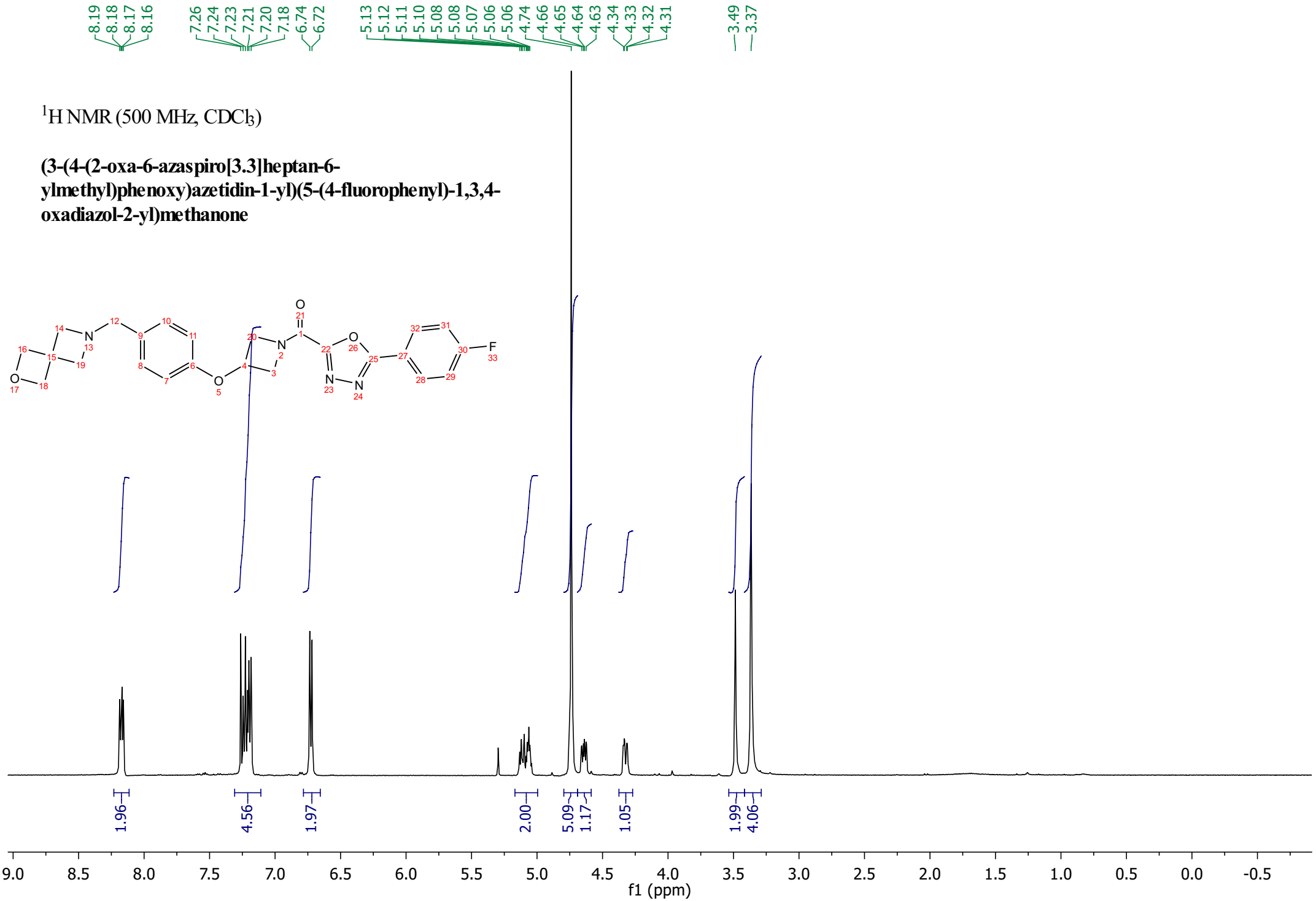
^{1}H NMR (500 MHz, $CDCl_3$)

(3-(4-(2-oxa-6-azaspiro[3.3]heptan-6-ylmethyl)phenoxy)azetidin-1-yl)(5-(4-(difluoromethoxy)phenyl)-1,3,4-oxadiazol-2-yl)methanone



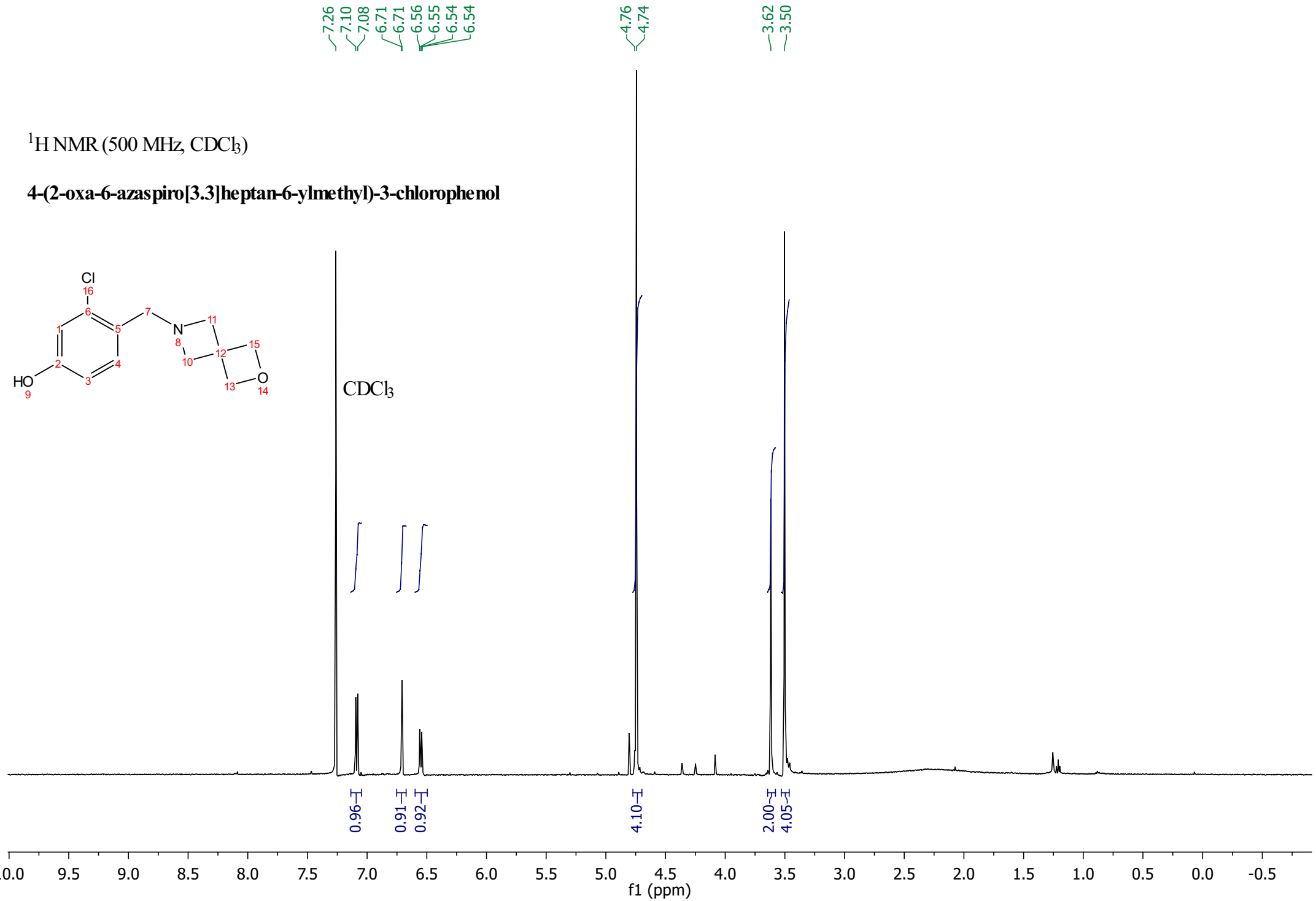
^{1}H NMR (500 MHz, $CDCl_3$)

(3-(4-(2-oxa-6-azaspiro[3.3]heptan-6-ylmethyl)phenoxy)azetidin-1-yl)(5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl)methanone



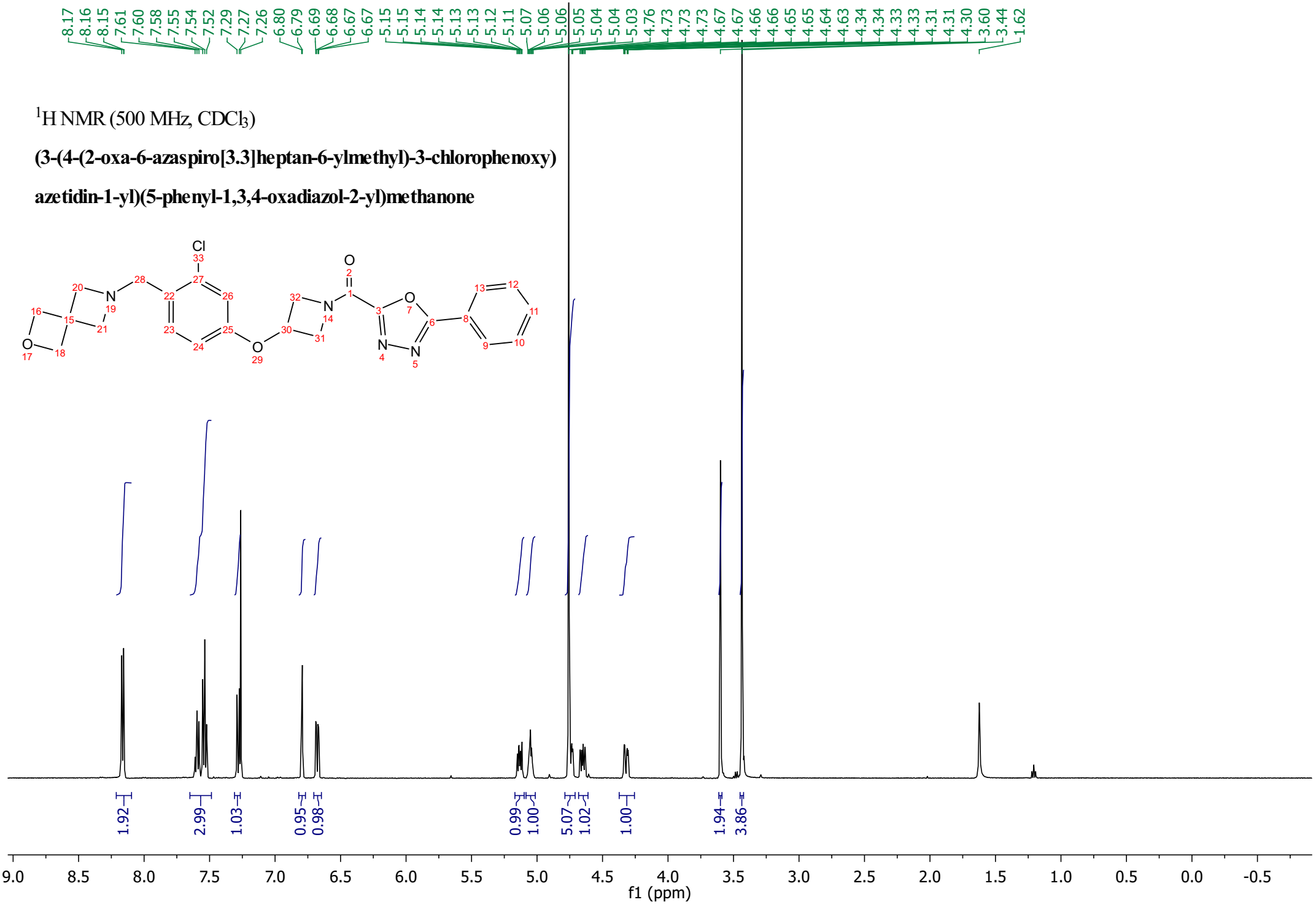
^{1}H NMR (500 MHz, $CDCl_3$)

4-(2-oxa-6-azaspiro[3.3]heptan-6-ylmethyl)-3-chlorophenol



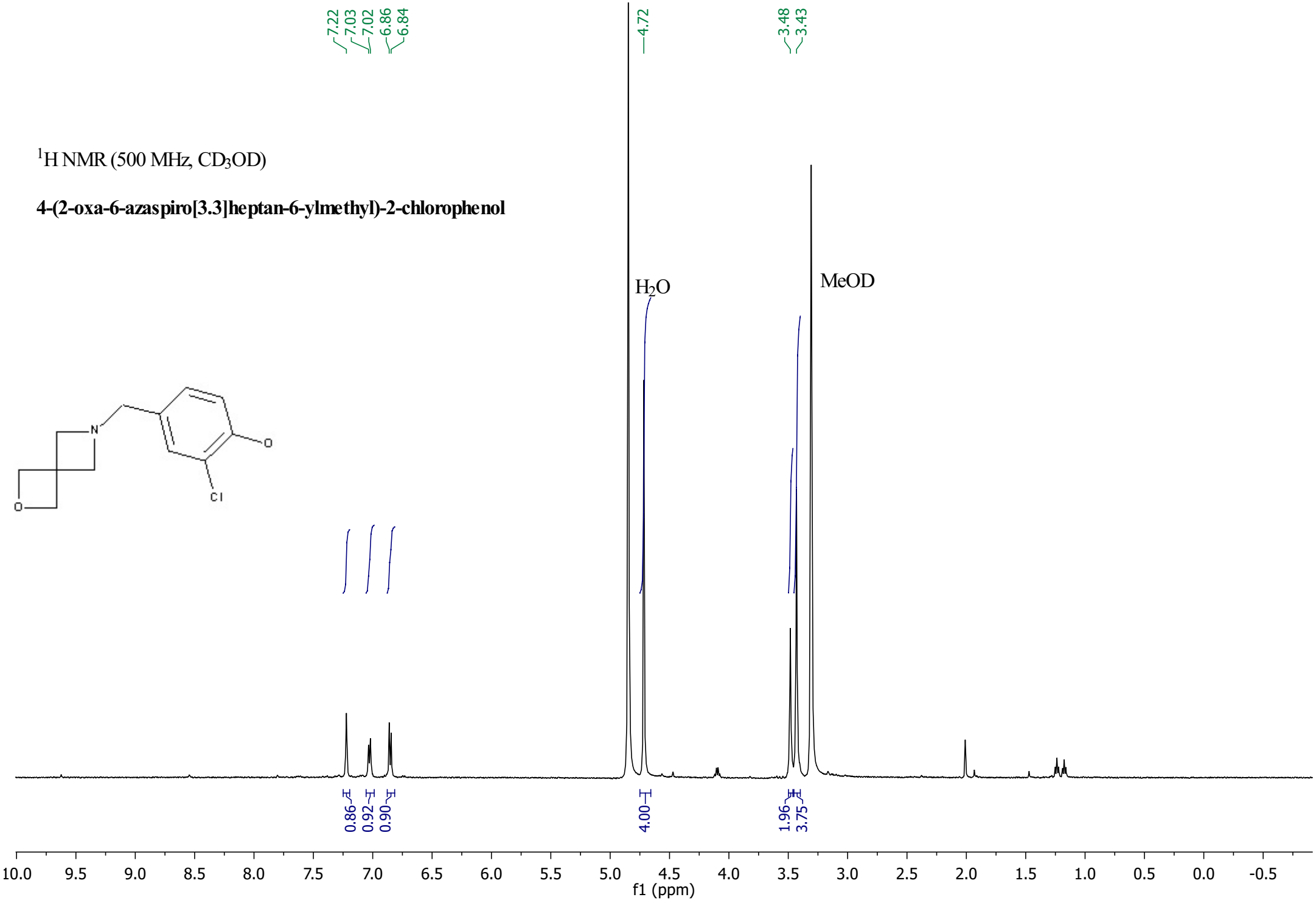
^{1}H NMR (500 MHz, $CDCl_3$)

(3-(4-(2-oxa-6-azaspiro[3.3]heptan-6-ylmethyl)-3-chlorophenoxy) azetidin-1-yl)(5-phenyl-1,3,4-oxadiazol-2-yl)methanone



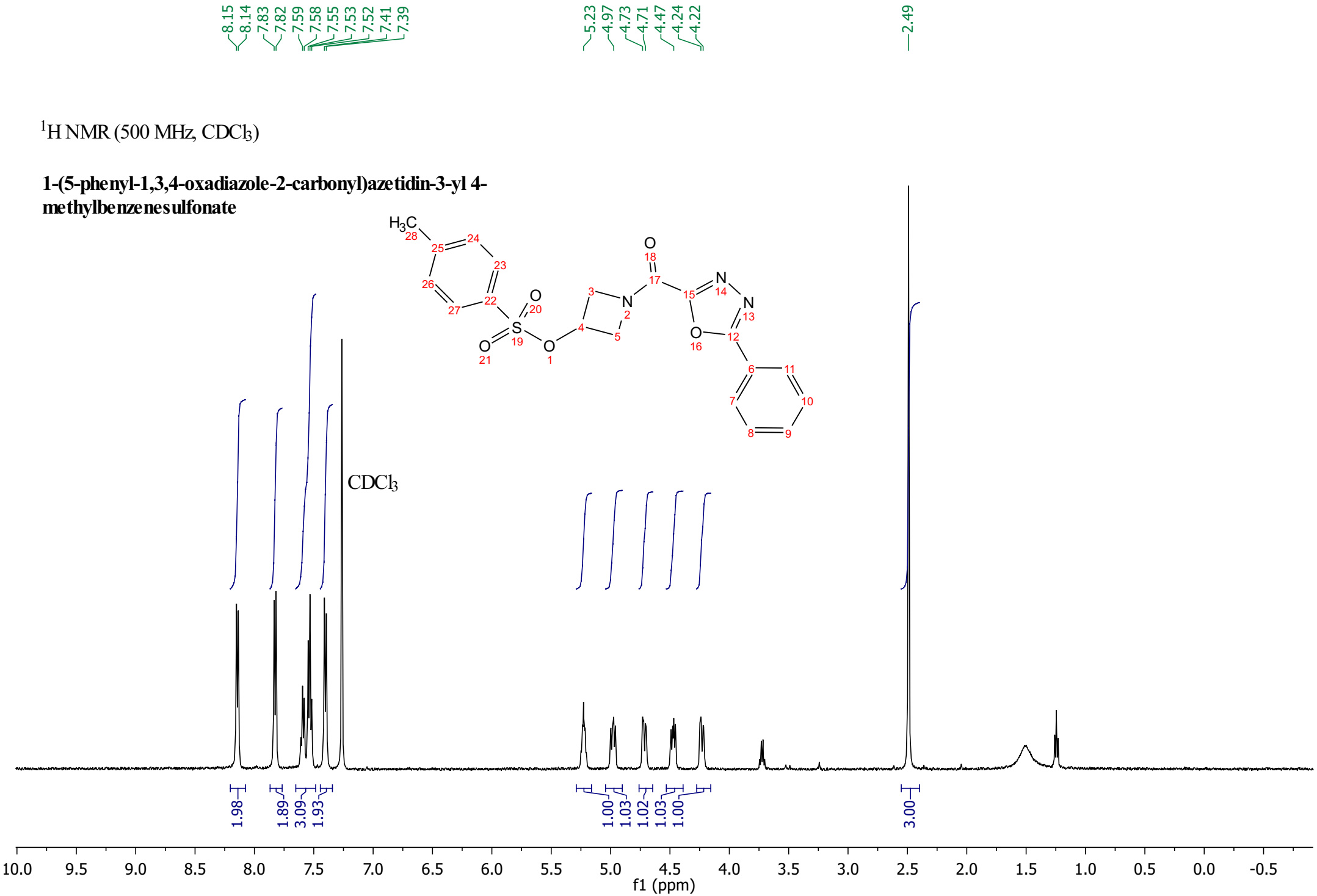
^{1}H NMR (500 MHz, CD_3OD)

4-(2-oxa-6-azaspiro[3.3]heptan-6-ylmethyl)-2-chlorophenol



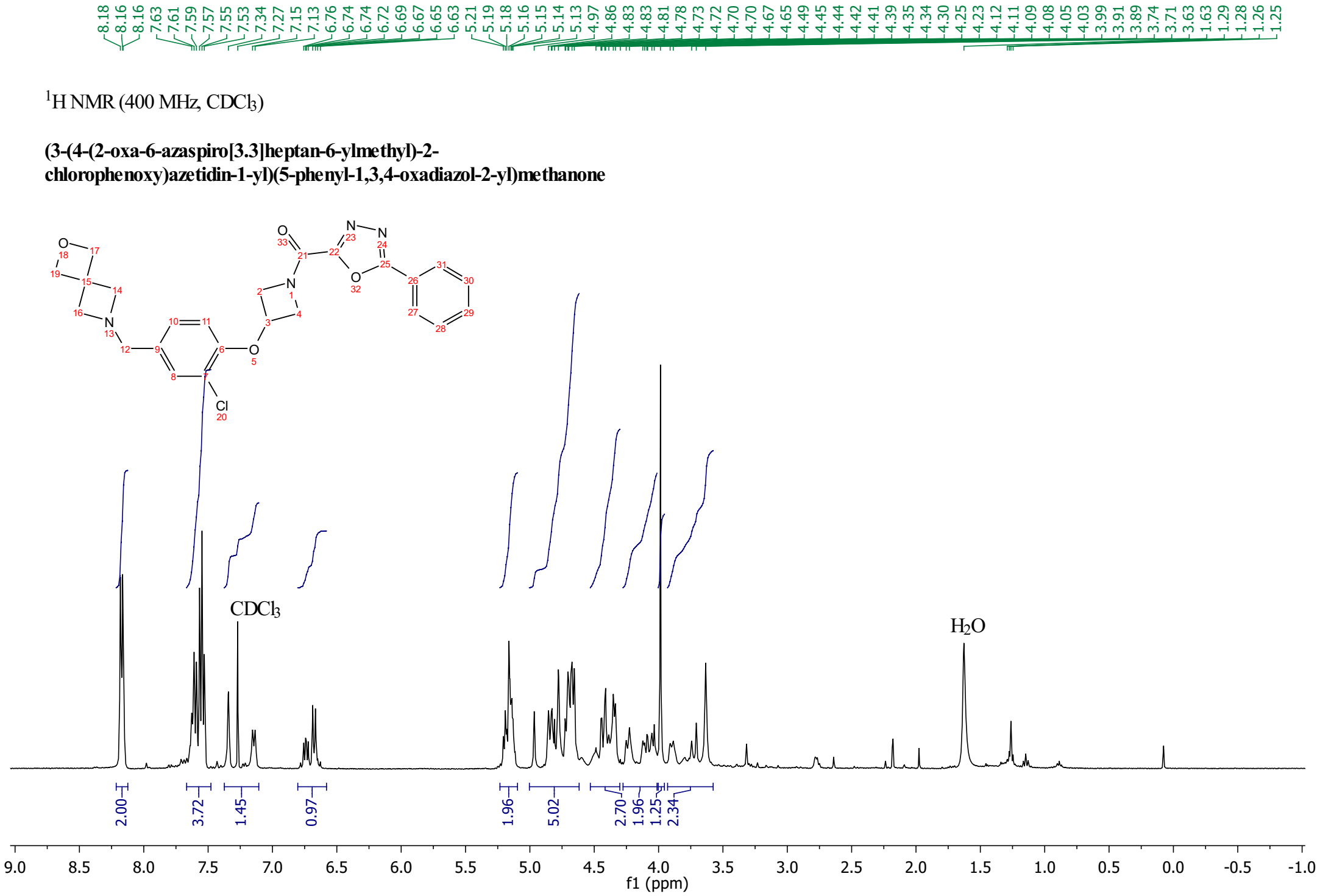
^{1}H NMR (500 MHz, $CDCl_3$)

1-(5-phenyl-1,3,4-oxadiazole-2-carbonyl)azetidin-3-yl 4-methylbenzenesulfonate



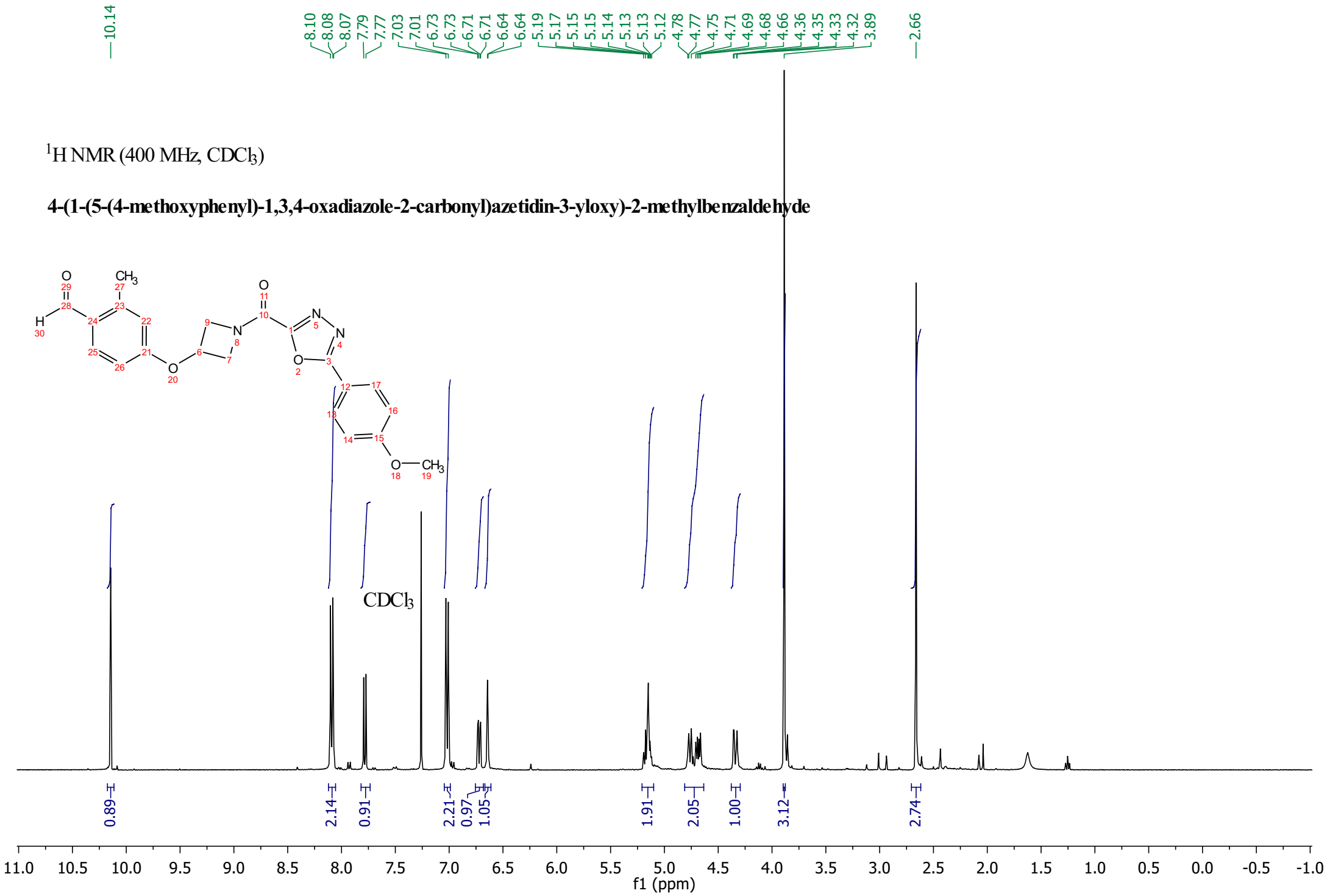
^{1}H NMR (400 MHz, $CDCl_3$)

(3-(4-(2-oxa-6-azaspiro[3.3]heptan-6-ylmethyl)-2-chlorophenoxy)azetidin-1-yl)(5-phenyl-1,3,4-oxadiazol-2-yl)methanone



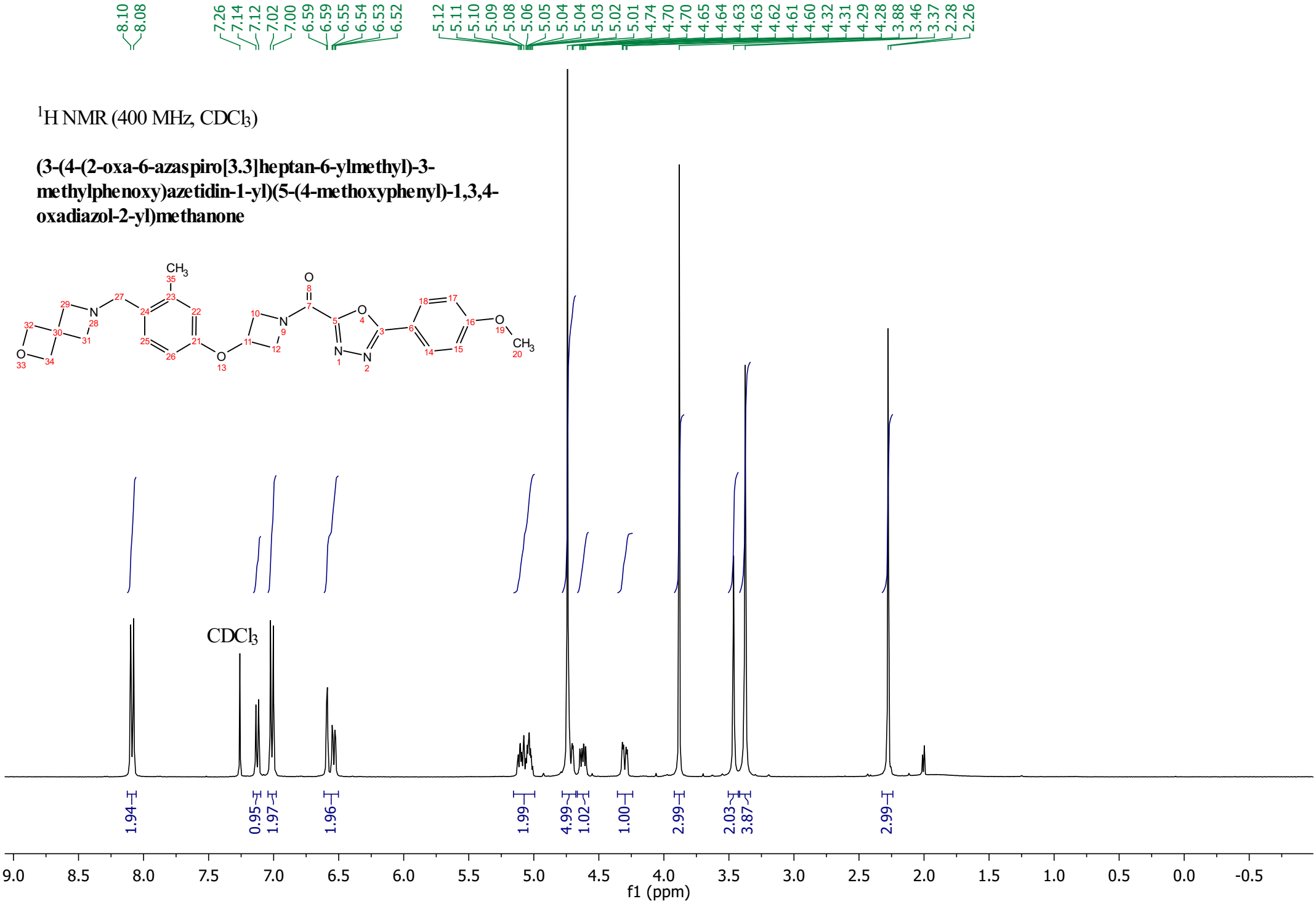
^{1}H NMR (400 MHz, $CDCl_3$)

4-(1-(5-(4-methoxyphenyl)-1,3,4-oxadiazole-2-carbonyl)azetidin-3-yloxy)-2-methylbenzaldehyde



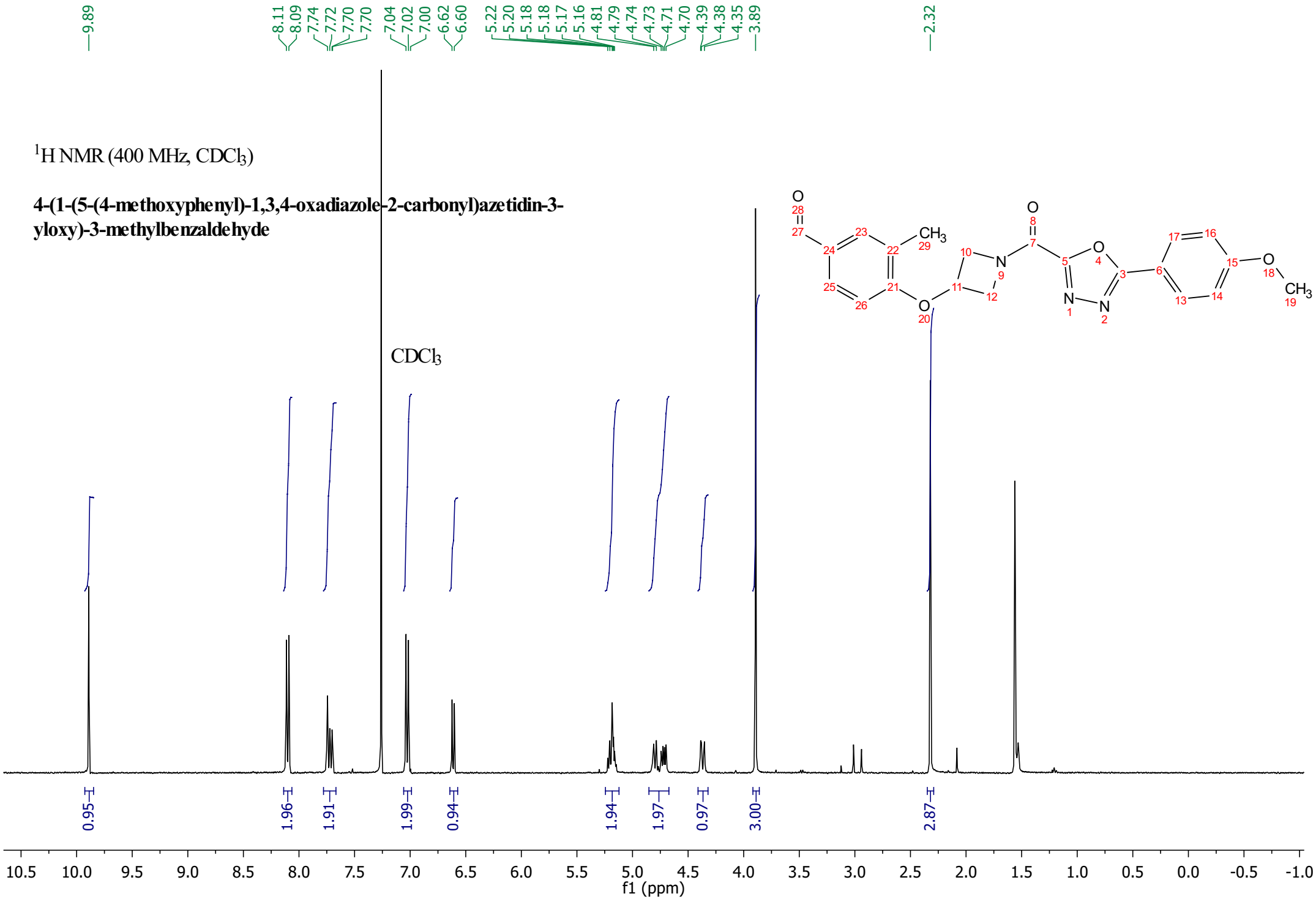
^{1}H NMR (400 MHz, $CDCl_3$)

(3-(4-(2-oxa-6-azaspiro[3.3]heptan-6-ylmethyl)-3-methylphenoxy)azetidin-1-yl)(5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl)methanone



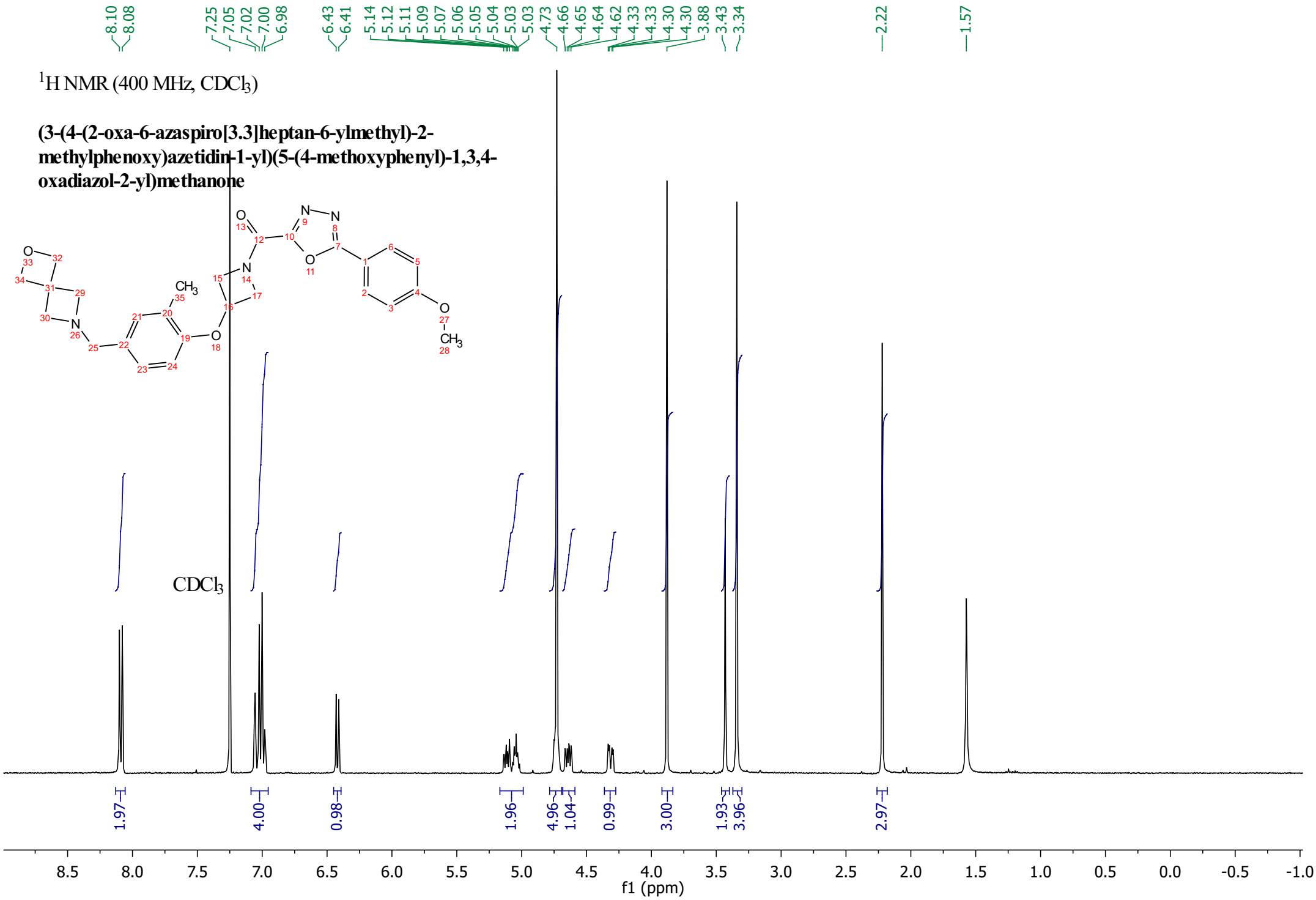
^{1}H NMR (400 MHz, $CDCl_3$)

4-(1-(5-(4-methoxyphenyl)-1,3,4-oxadiazole-2-carbonyl)azetidin-3-yloxy)-3-methylbenzaldehyde



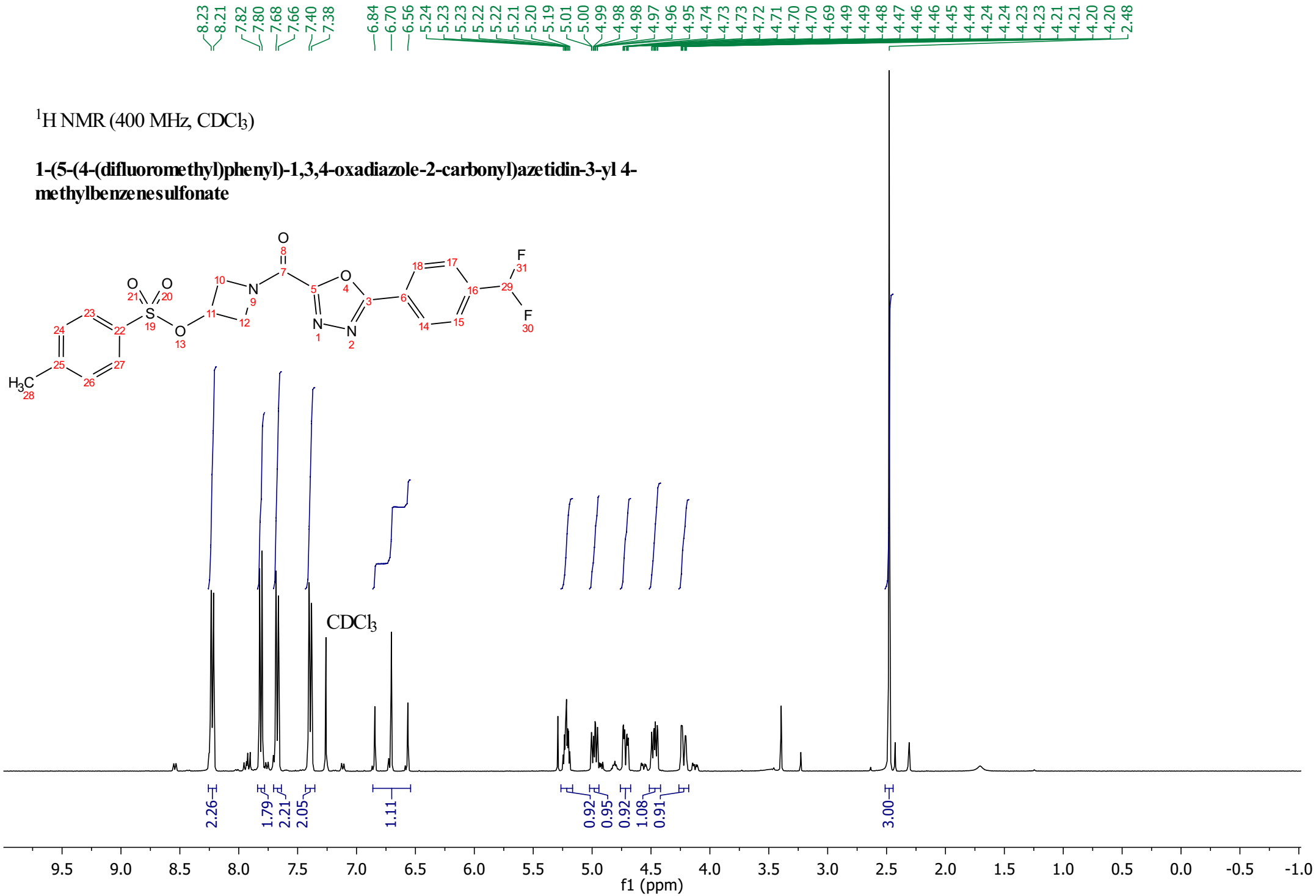
^{1}H NMR (400 MHz, $CDCl_3$)

(3-(4-(2-oxa-6-azaspiro[3.3]heptan-6-ylmethyl)-2-methylphenoxy)azetidin-1-yl)(5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl)methanone



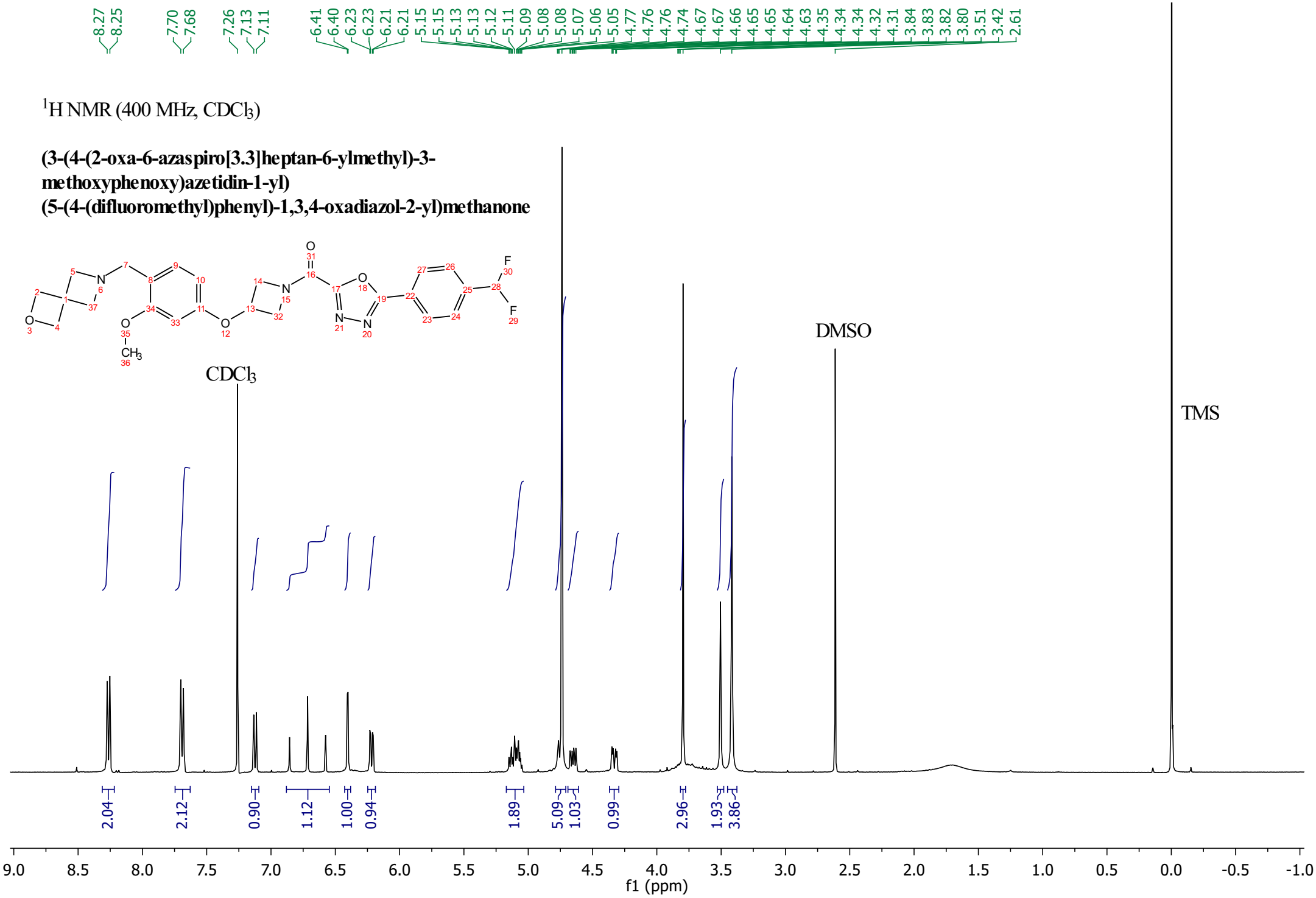
^{1}H NMR (400 MHz, $CDCl_3$)

1-(5-(4-(difluoromethyl)phenyl)-1,3,4-oxadiazole-2-carbonyl)azetidin-3-yl 4-methylbenzenesulfonate



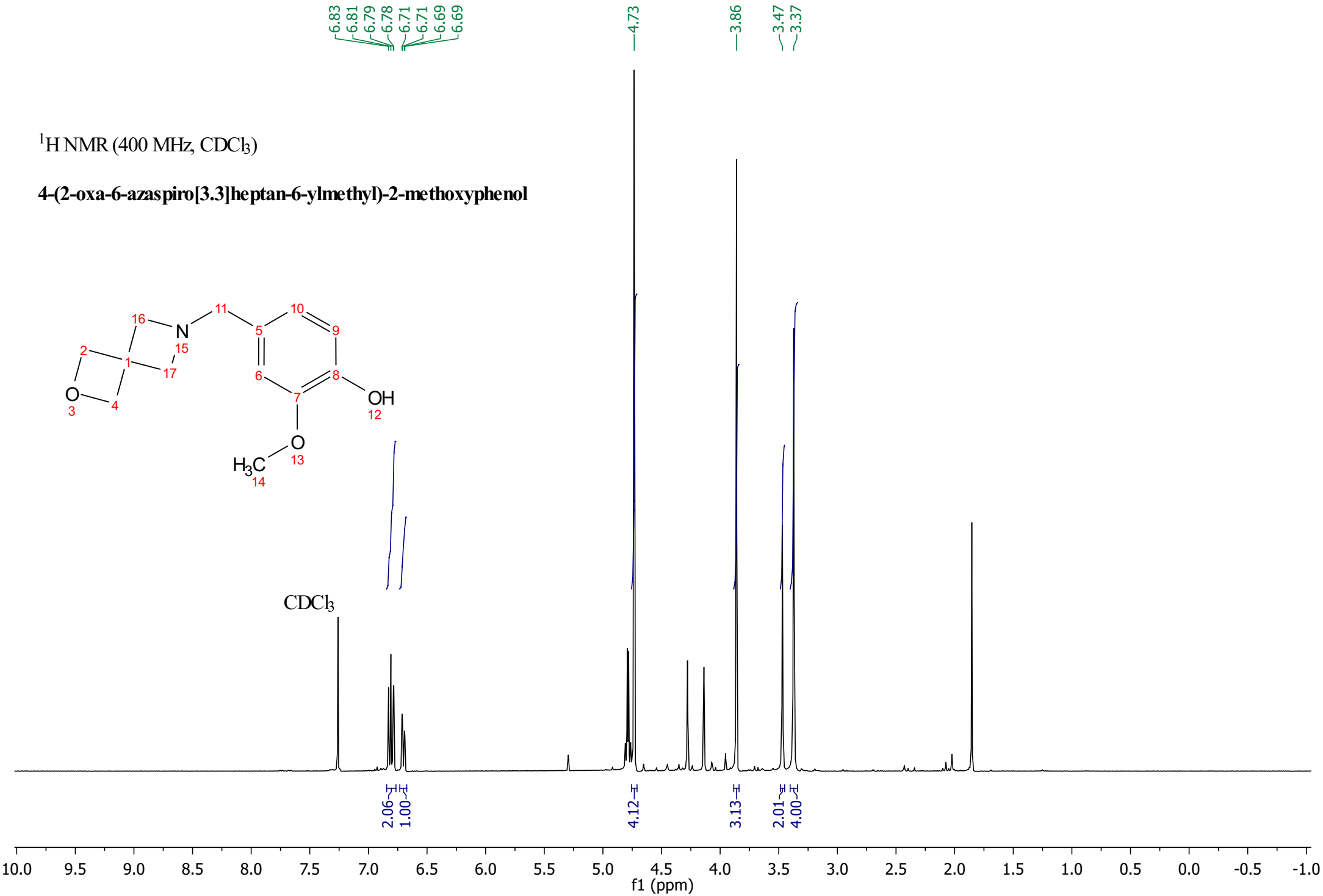
^{1}H NMR (400 MHz, $CDCl_3$)

(3-(4-(2-oxa-6-azaspiro[3.3]heptan-6-ylmethyl)-3-methoxyphenoxy)azetidin-1-yl)(5-(4-(difluoromethyl)phenyl)-1,3,4-oxadiazol-2-yl)methanone



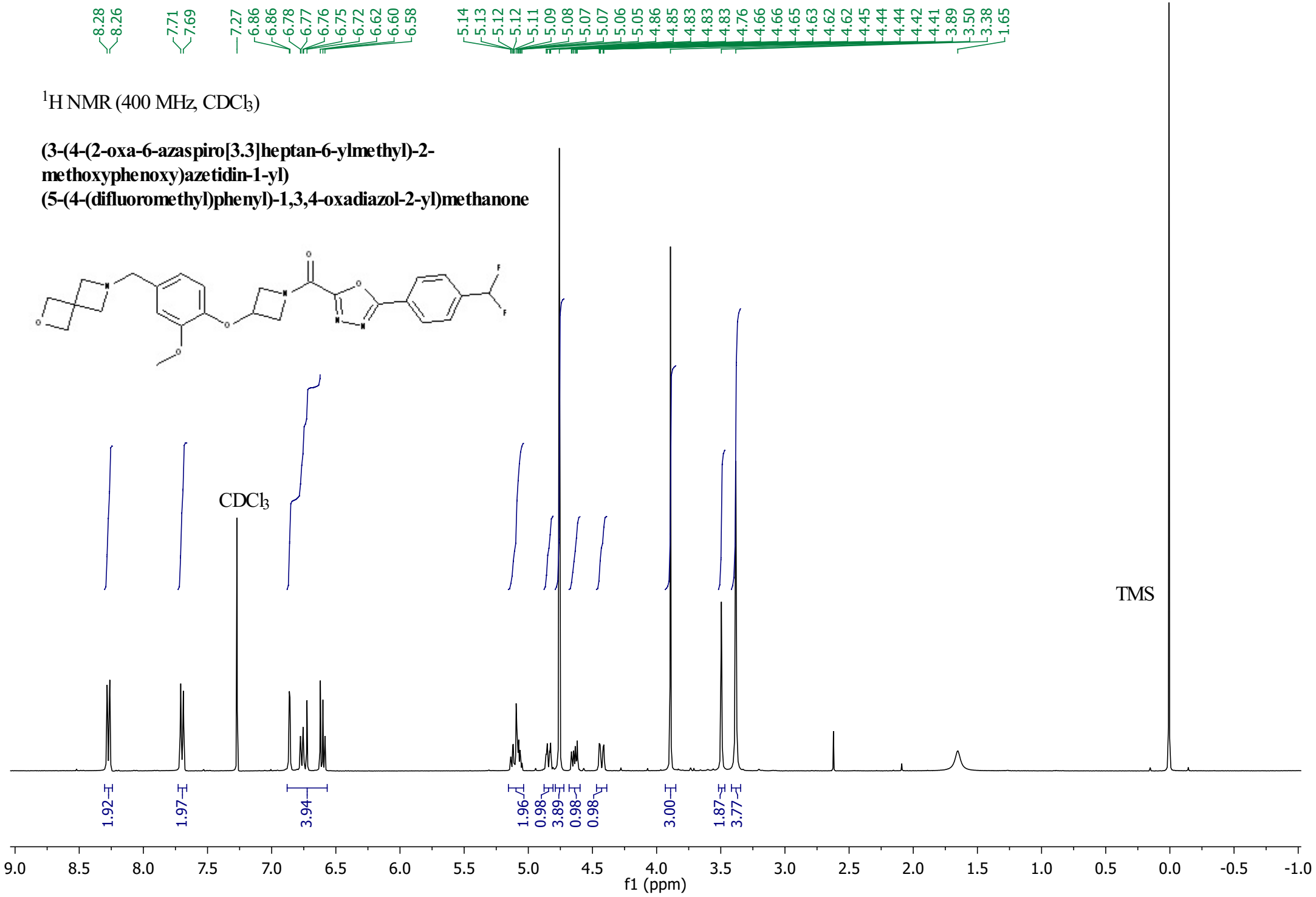
^{1}H NMR (400 MHz, $CDCl_3$)

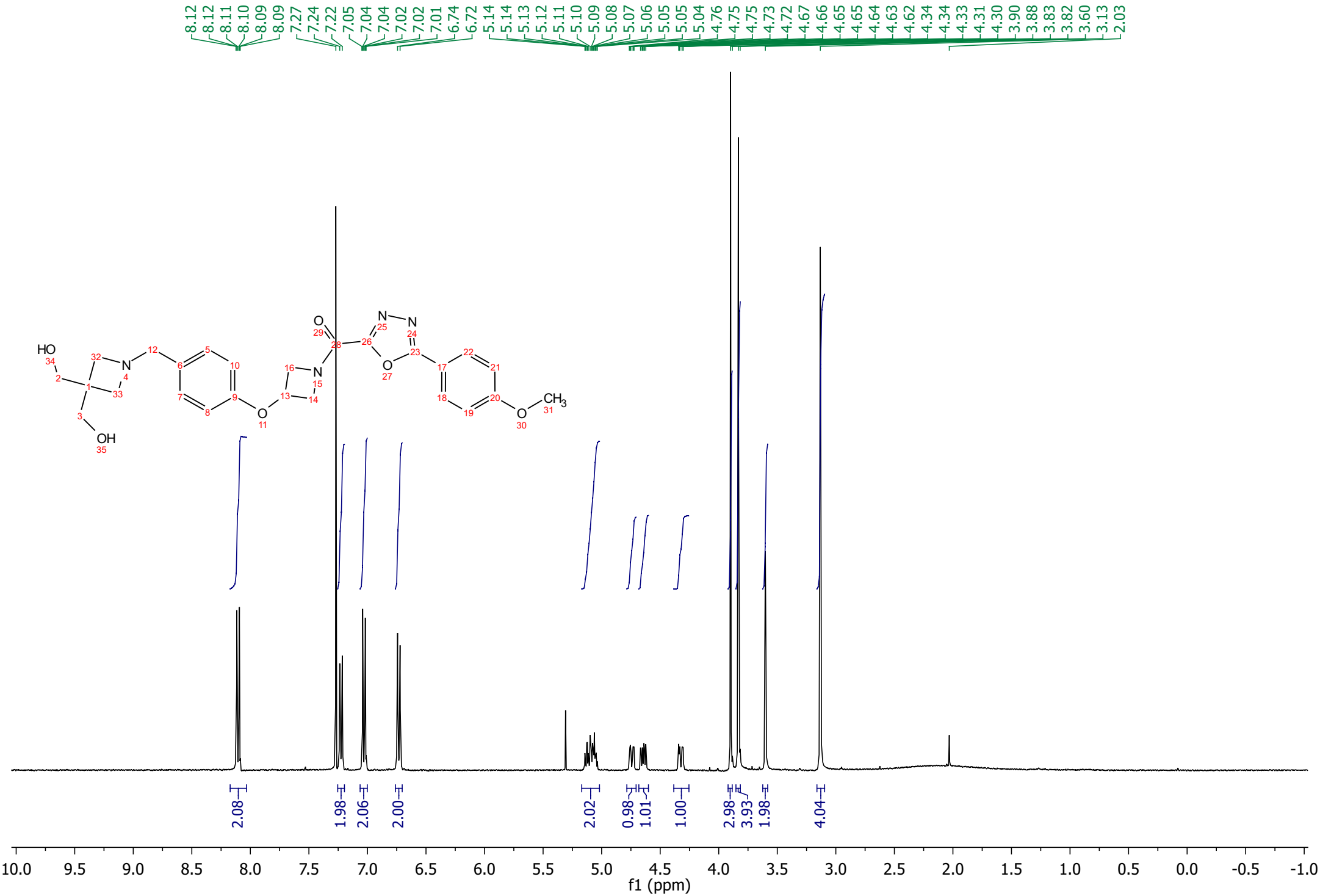
4-(2-oxa-6-azaspiro[3.3]heptan-6-ylmethyl)-2-methoxyphenol



^{1}H NMR (400 MHz, $CDCl_3$)

(3-(4-(2-oxa-6-azaspiro[3.3]heptan-6-ylmethyl)-2-methoxyphenoxy)azetidin-1-yl)(5-(4-(difluoromethyl)phenyl)-1,3,4-oxadiazol-2-yl)methanone

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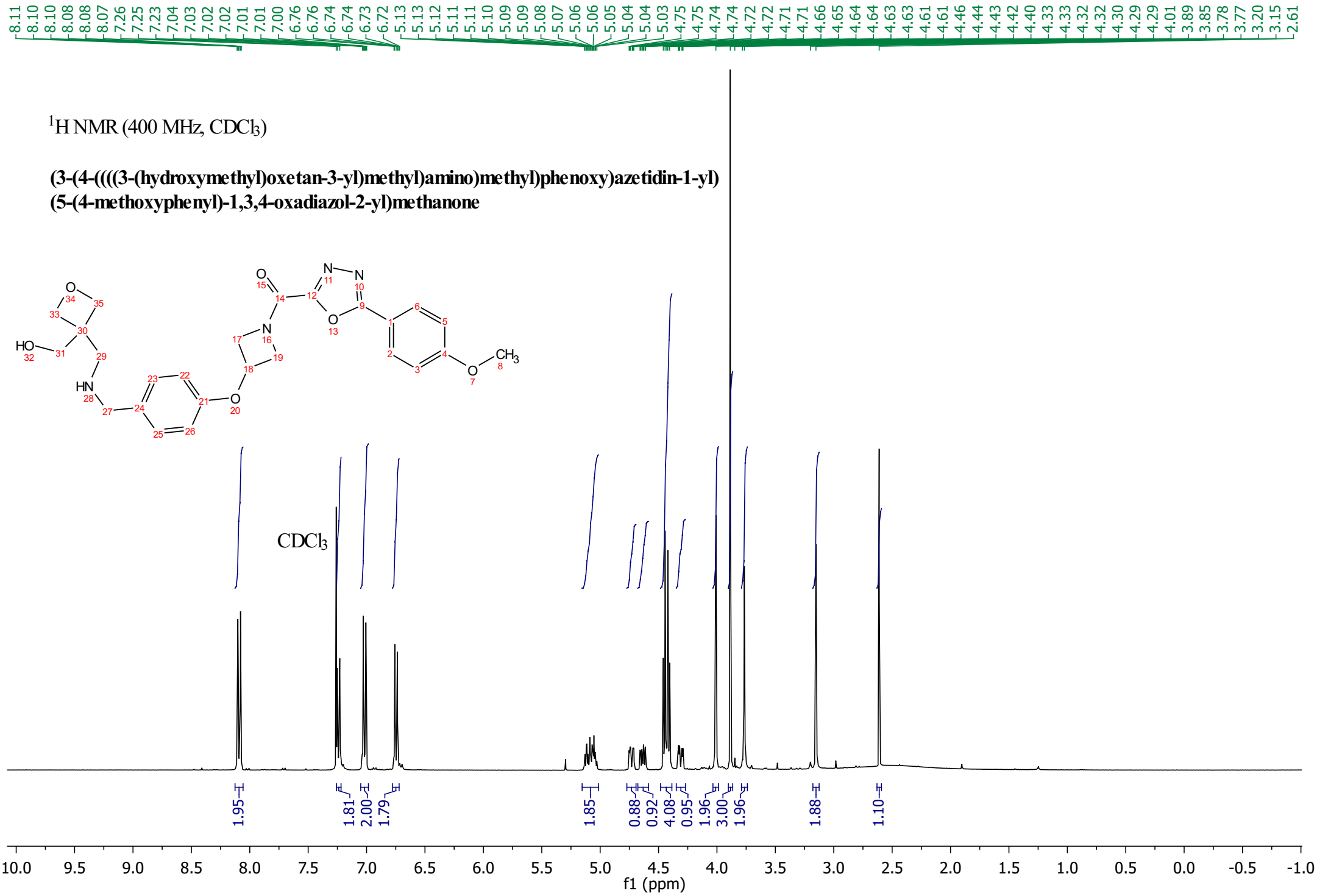
HO
OH
CH3
2.08
1.98
2.06
2.00
2.02
0.98
1.01
1.00
2.98
3.93
1.98
4.04
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

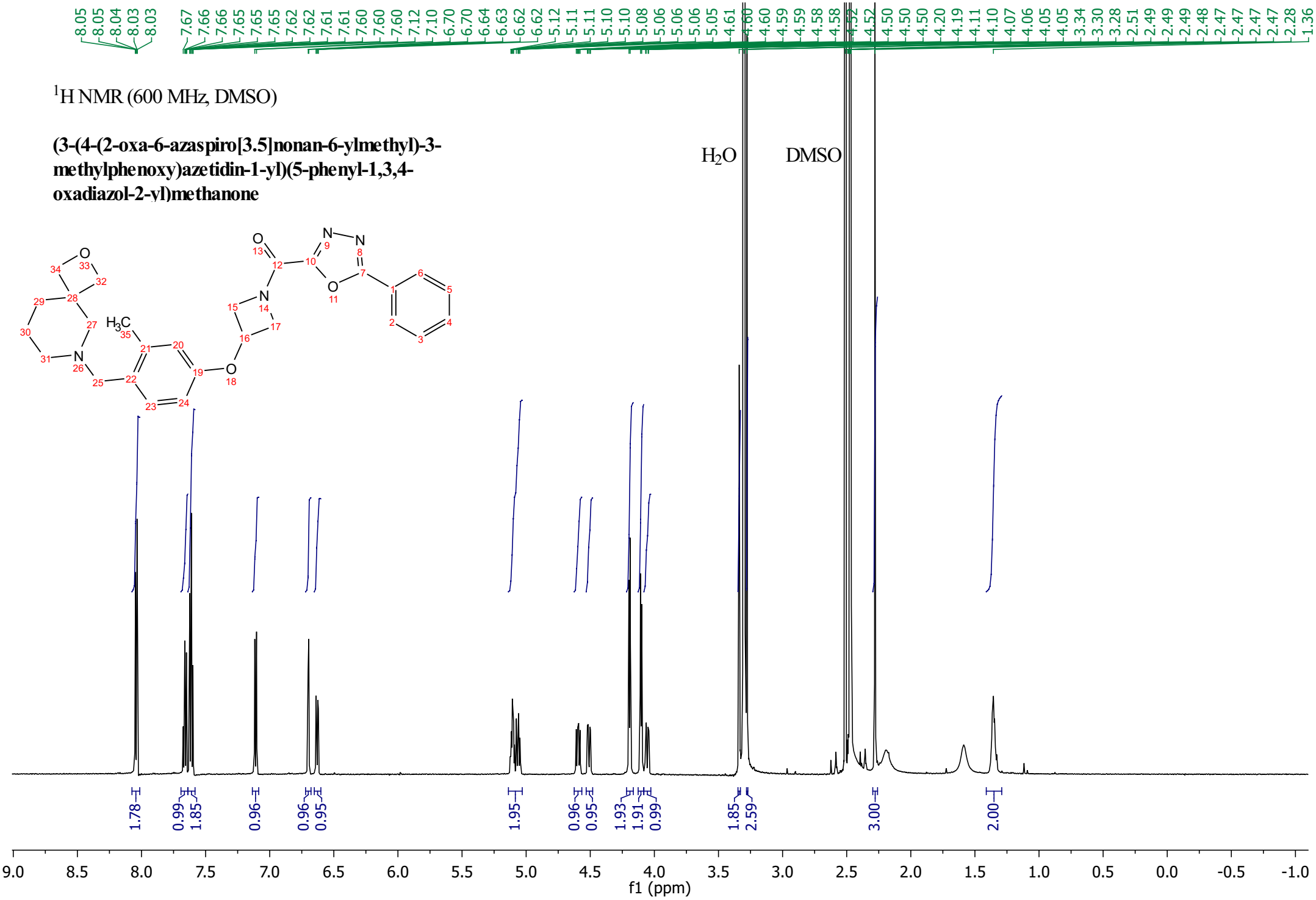
^{1}H NMR (400 MHz, $CDCl_3$)

(3-(4-((((3-(hydroxymethyl)oxetan-3-yl)methyl)amino)methyl)phenoxy)azetidin-1-yl)(5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl)methanone



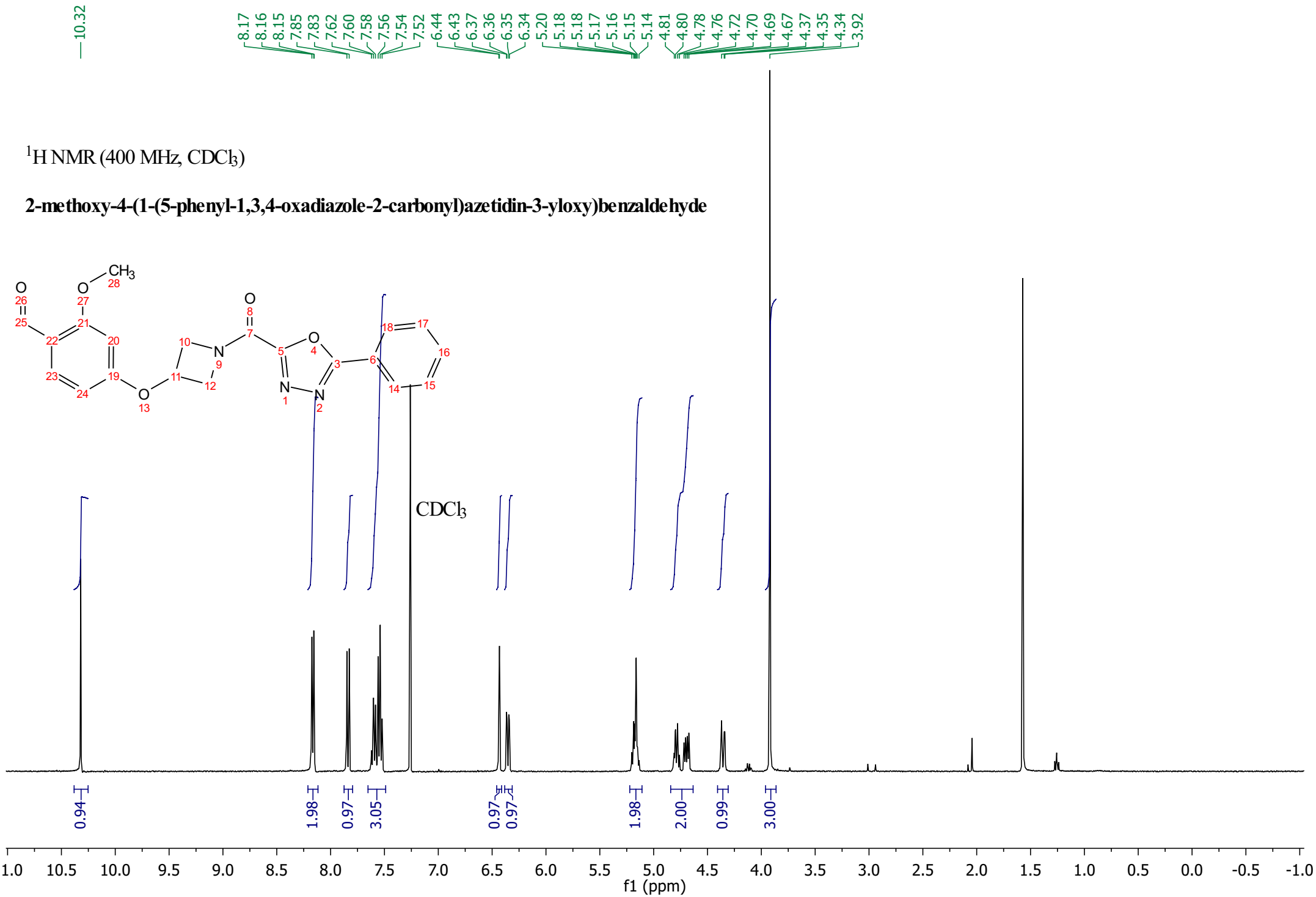
^{1}H NMR (600 MHz, DMSO)

(3-(4-(2-oxa-6-azaspiro[3.5]nonan-6-ylmethyl)-3-methylphenoxy)azetidin-1-yl)(5-phenyl-1,3,4-oxadiazol-2-yl)methanone



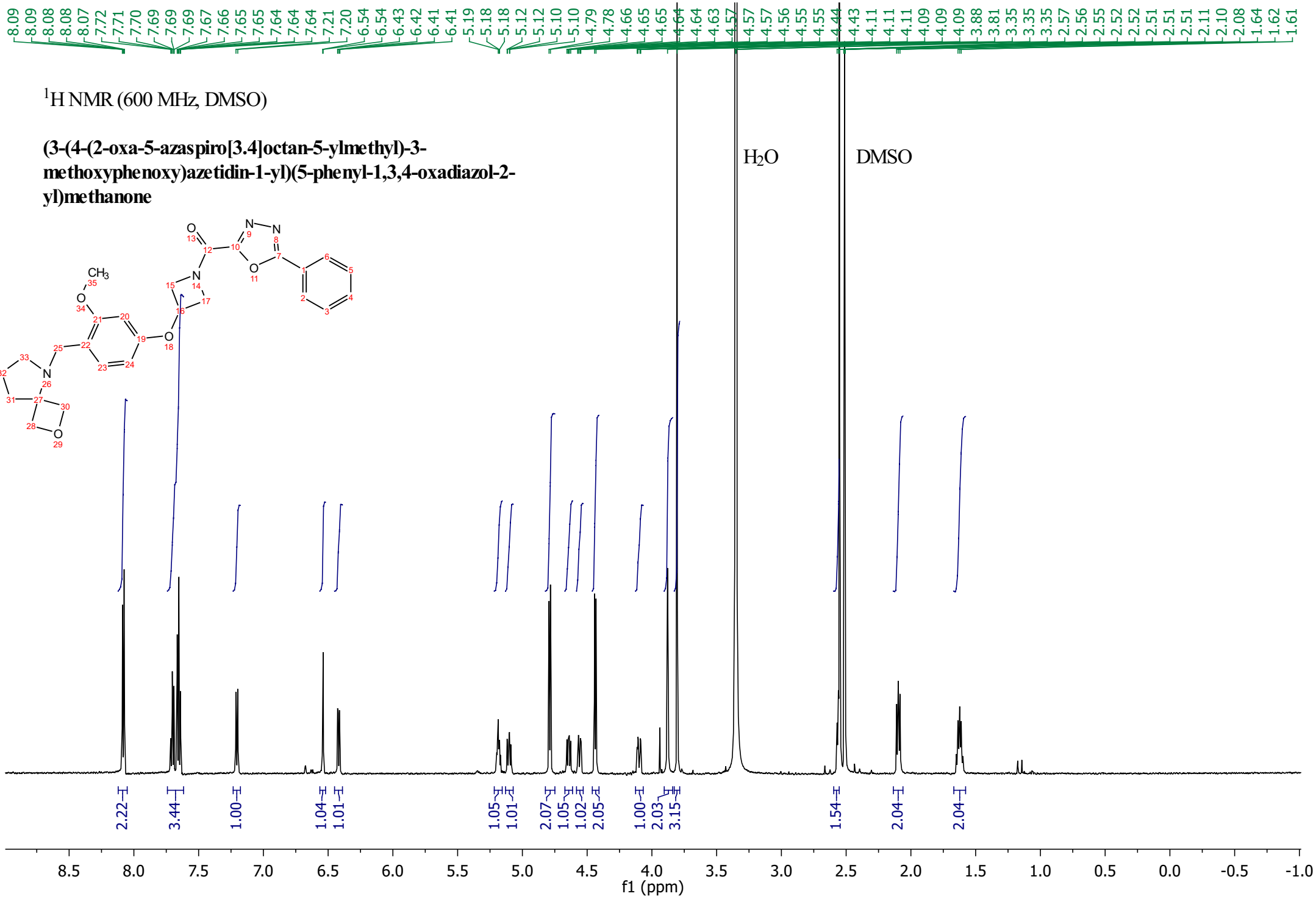
^{1}H NMR (400 MHz, $CDCl_3$)

2-methoxy-4-(1-(5-phenyl-1,3,4-oxadiazole-2-carbonyl)azetidin-3-yloxy)benzaldehyde



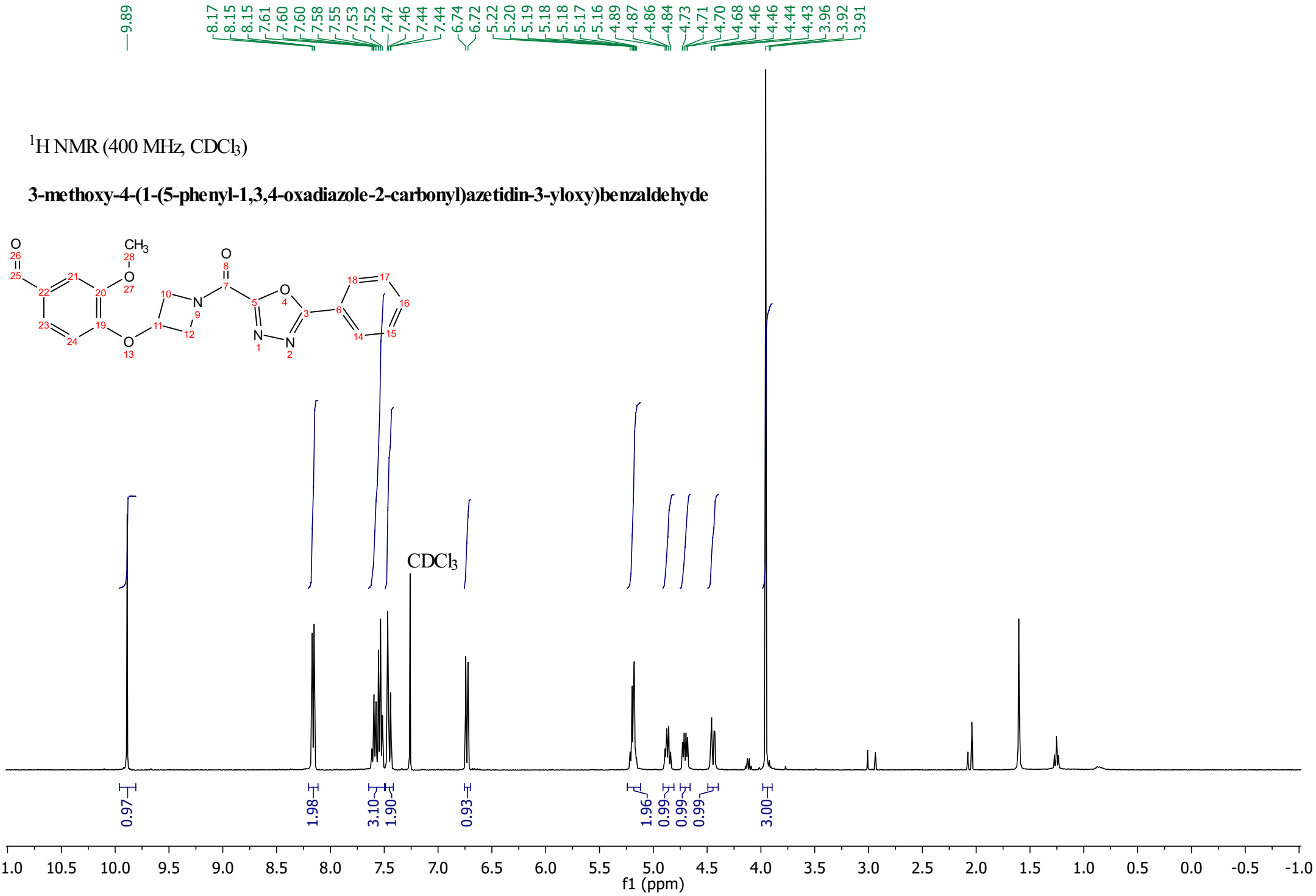
^{1}H NMR (600 MHz, DMSO)

(3-(4-(2-oxa-5-azaspiro[3.4]octan-5-ylmethyl)-3-methoxyphenoxy)azetidin-1-yl)(5-phenyl-1,3,4-oxadiazol-2-yl)methanone



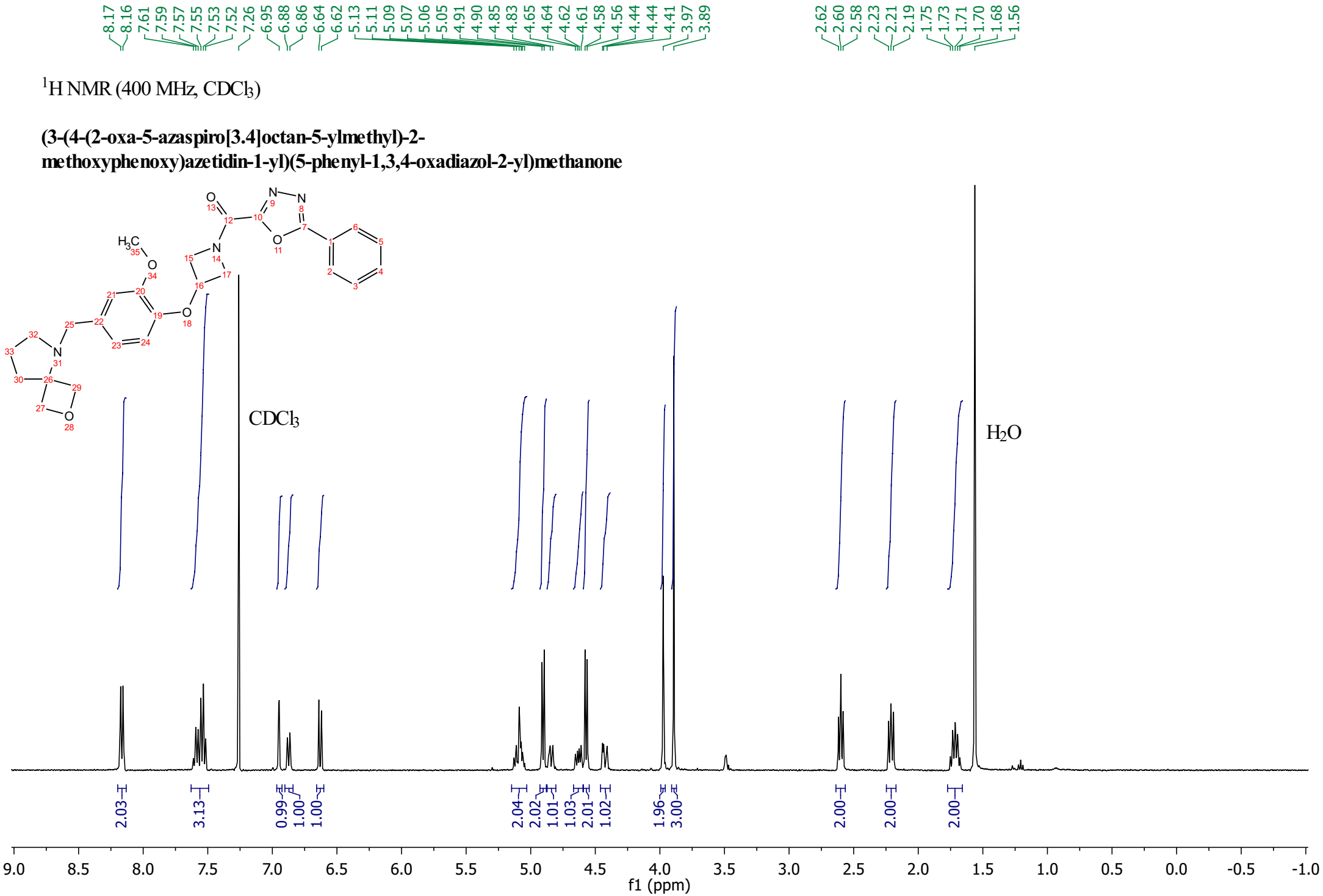
^{1}H NMR (400 MHz, $CDCl_3$)

3-methoxy-4-(1-(5-phenyl-1,3,4-oxadiazole-2-carbonyl)azetidin-3-yloxy)benzaldehyde



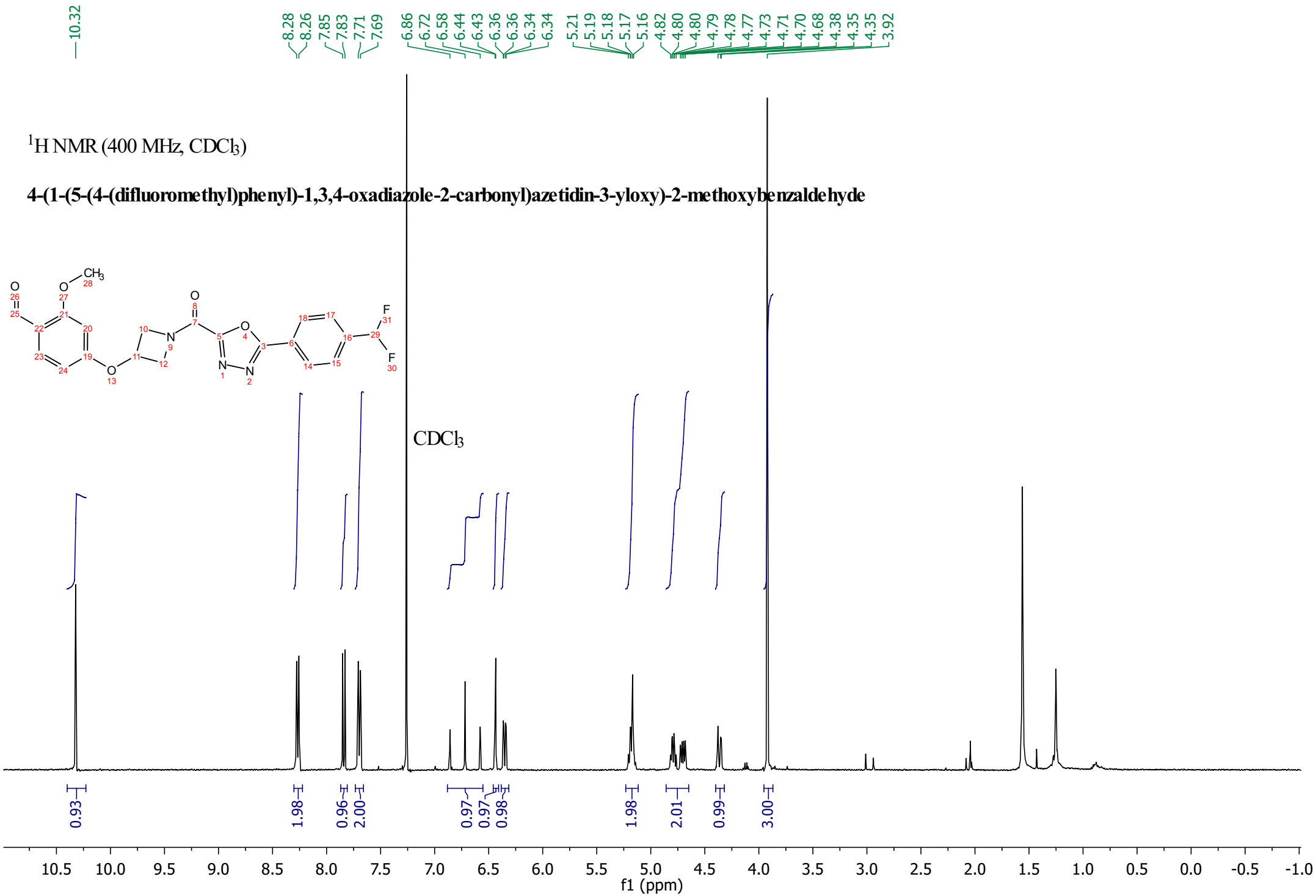
^{1}H NMR (400 MHz, $CDCl_3$)

(3-(4-(2-oxa-5-azaspiro[3.4]octan-5-ylmethyl)-2-methoxyphenoxy)azetidin-1-yl)(5-phenyl-1,3,4-oxadiazol-2-yl)methanone



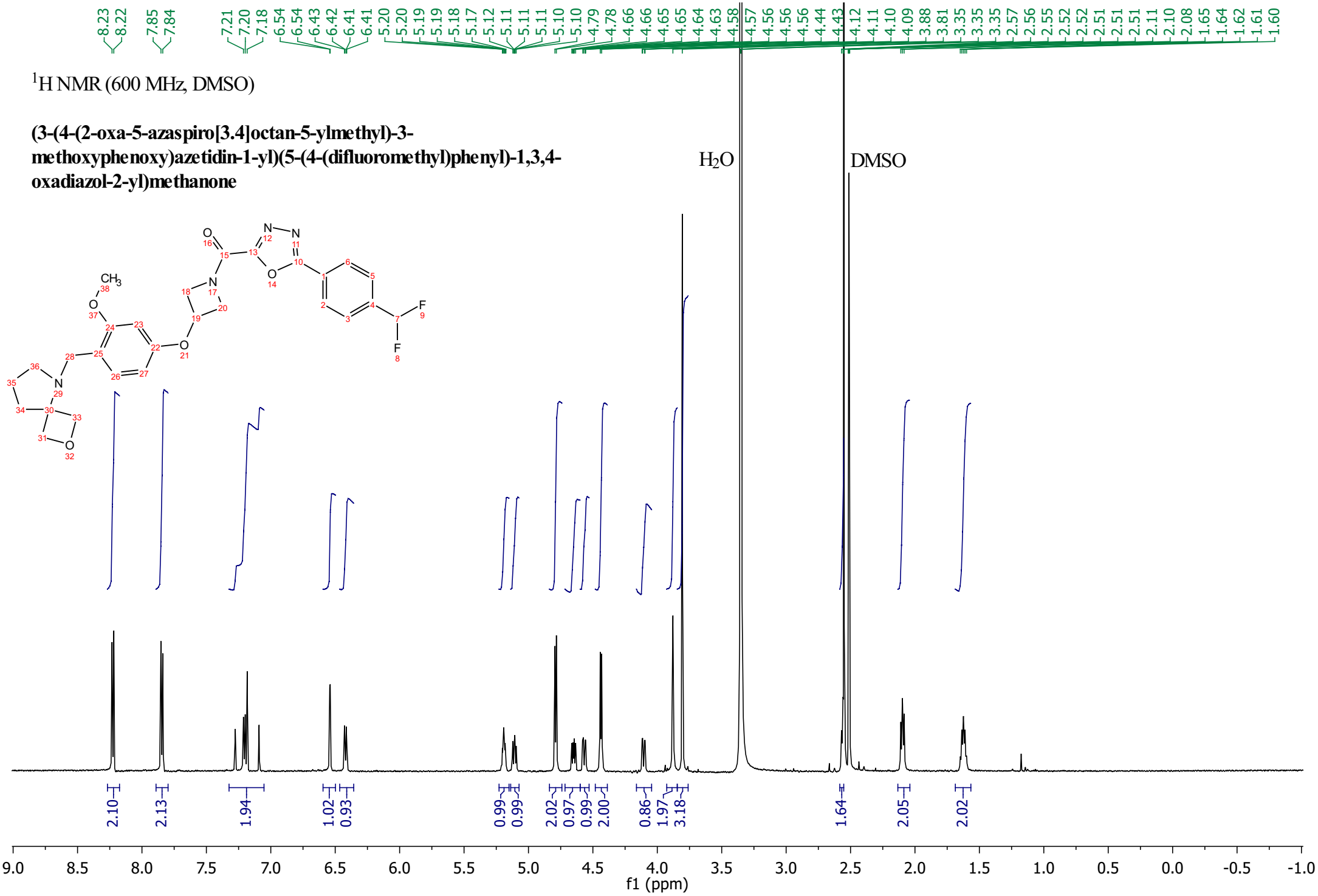
^{1}H NMR (400 MHz, $CDCl_3$)

4-(1-(5-(4-(difluoromethyl)phenyl)-1,3,4-oxadiazole-2-carbonyl)azetidin-3-yloxy)-2-methoxybenzaldehyde



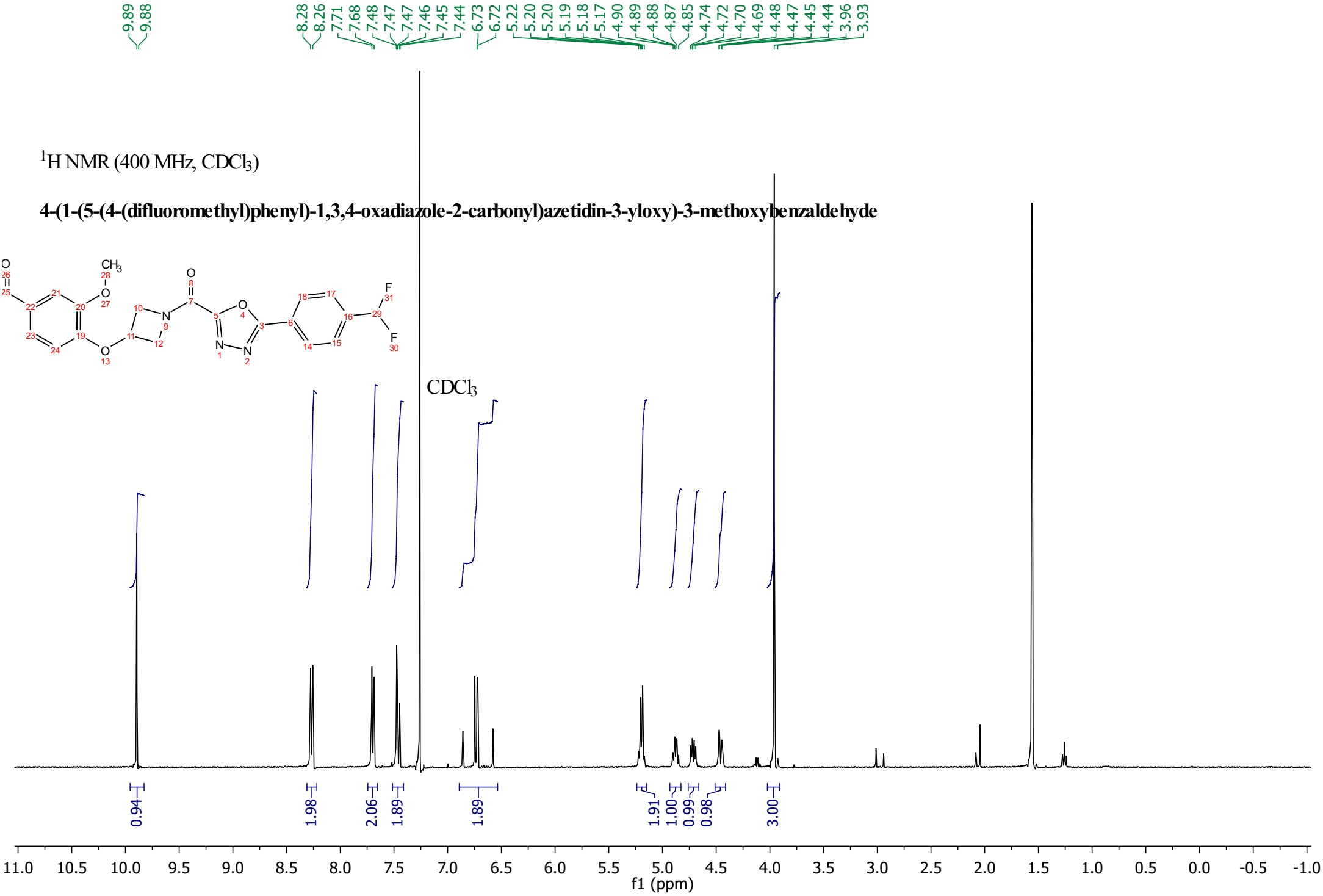
^{1}H NMR (600 MHz, DMSO)

(3-(4-(2-oxa-5-azaspiro[3.4]octan-5-ylmethyl)-3-methoxyphenoxy)azetidin-1-yl)(5-(4-(difluoromethyl)phenyl)-1,3,4-oxadiazol-2-yl)methanone



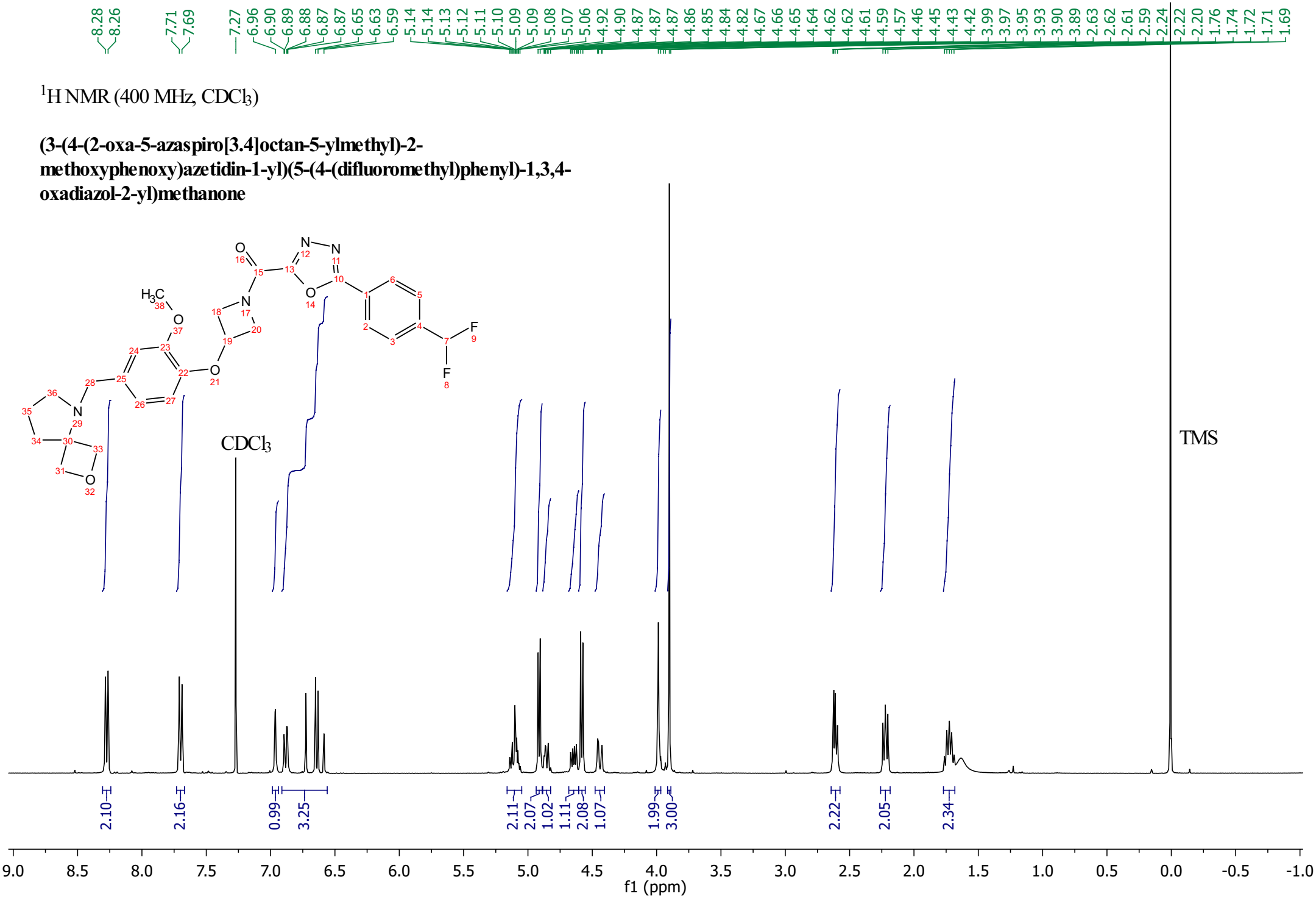
^{1}H NMR (400 MHz, $CDCl_3$)

4-(1-(5-(4-(difluoromethyl)phenyl)-1,3,4-oxadiazole-2-carbonyl)azetidin-3-yloxy)-3-methoxybenzaldehyde



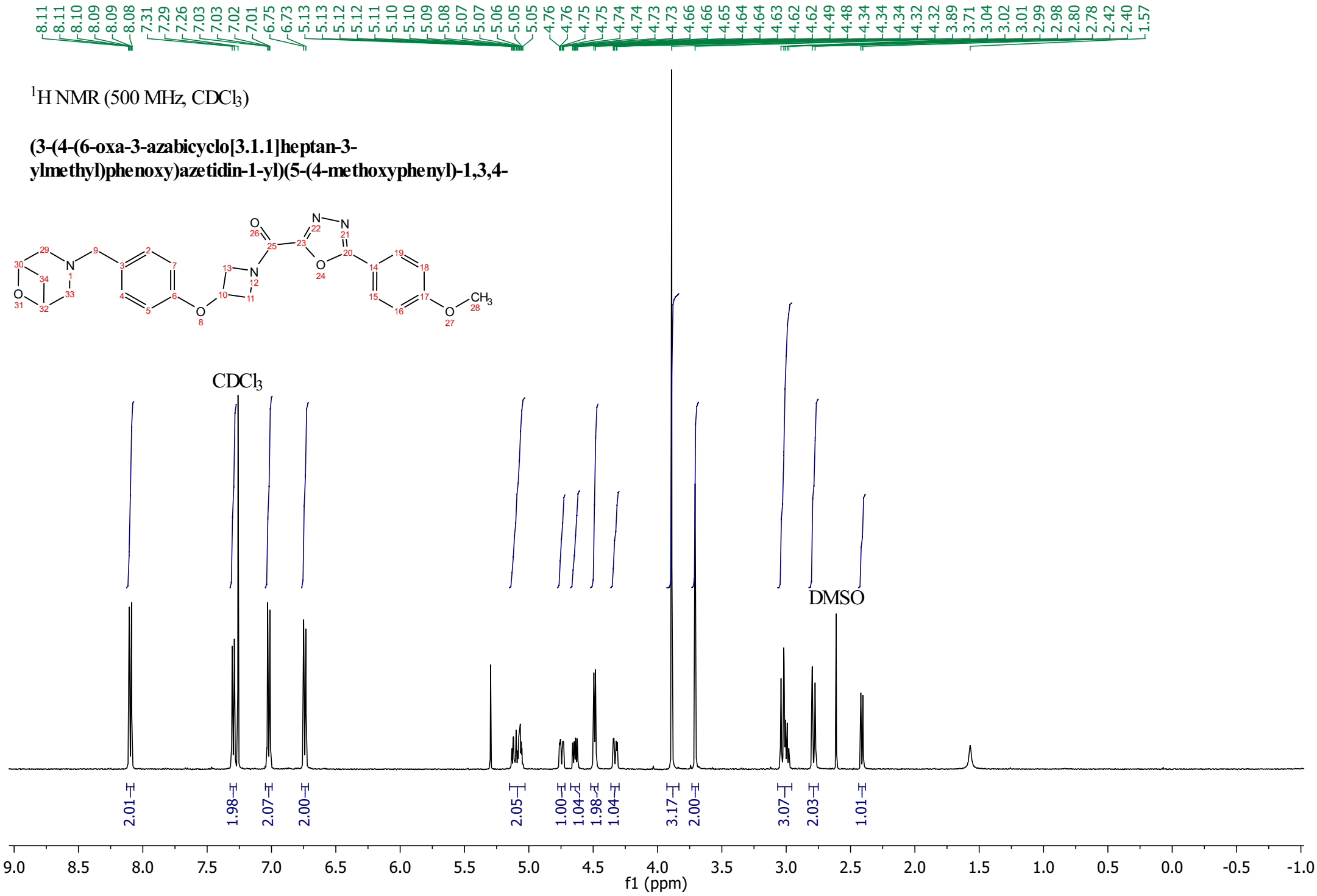
^{1}H NMR (400 MHz, $CDCl_3$)

(3-(4-(2-oxa-5-azaspiro[3.4]octan-5-ylmethyl)-2-methoxyphenoxy)azetidin-1-yl)(5-(4-(difluoromethyl)phenyl)-1,3,4-oxadiazol-2-yl)methanone



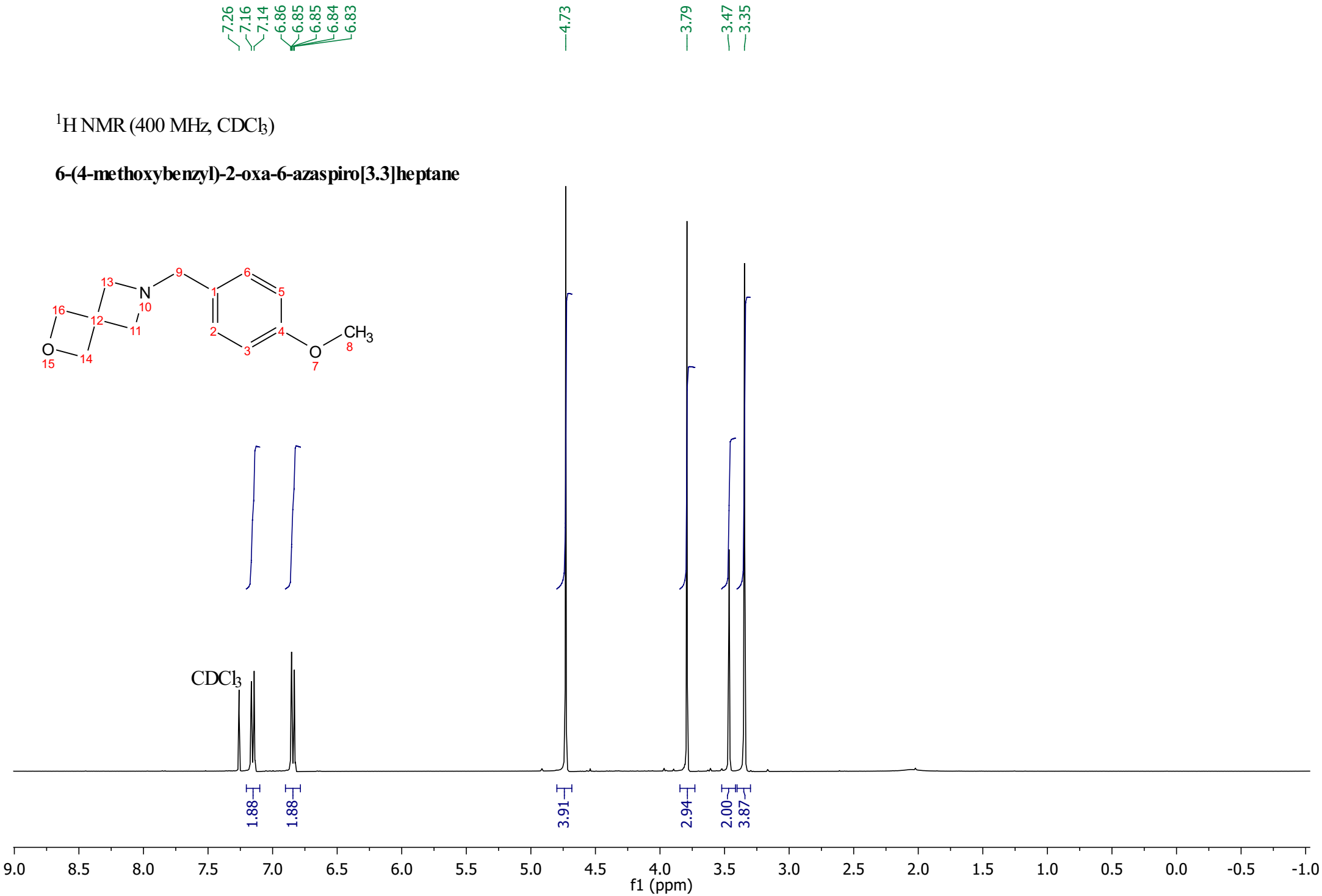
^{1}H NMR (500 MHz, $CDCl_3$)

(3-(4-(6-oxa-3-azabicyclo[3.1.1]heptan-3-ylmethyl)phenoxy)azetidin-1-yl)(5-(4-methoxyphenyl)-1,3,4-



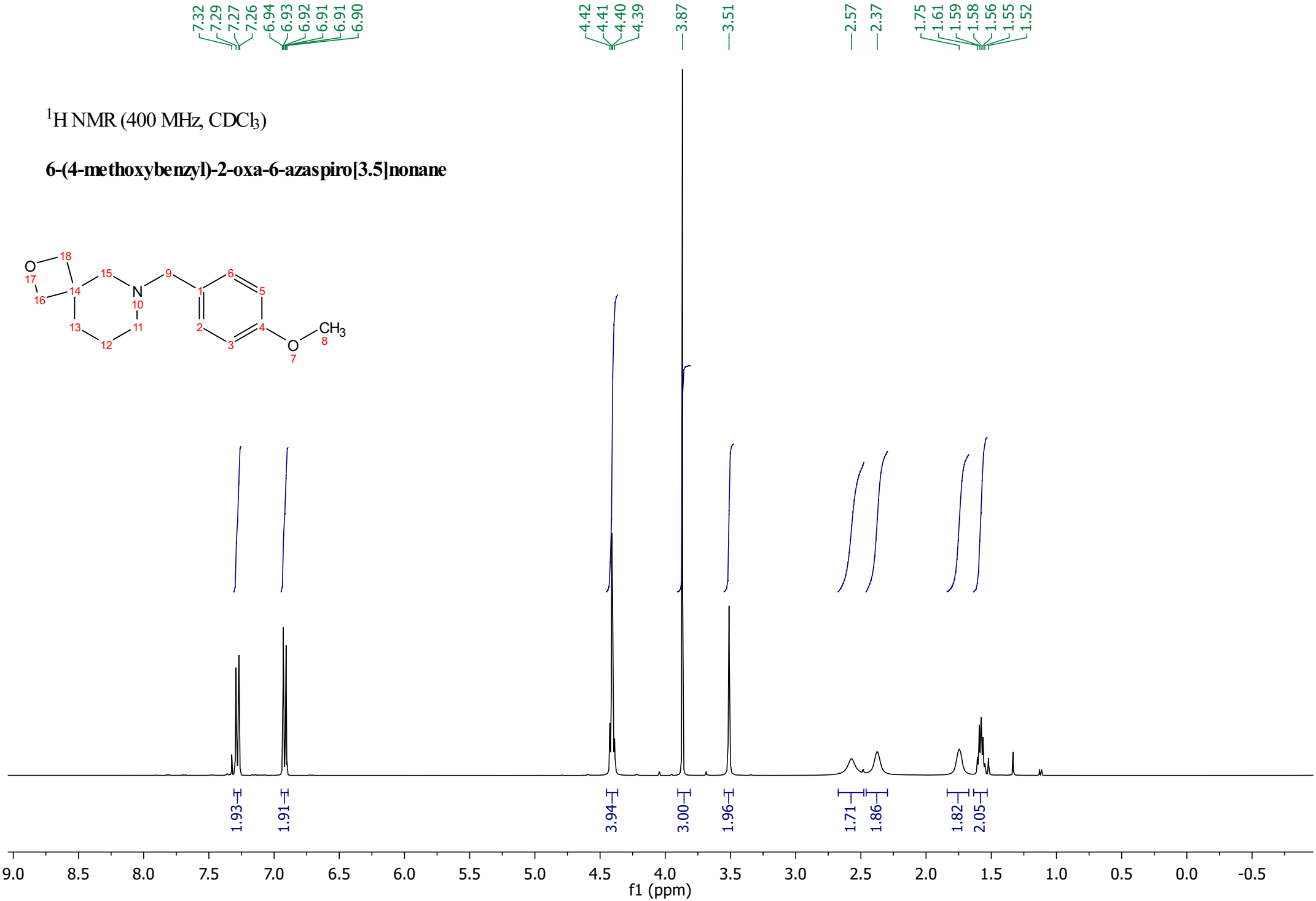
^{1}H NMR (400 MHz, $CDCl_3$)

6-(4-methoxybenzyl)-2-oxa-6-azaspiro[3.3]heptane



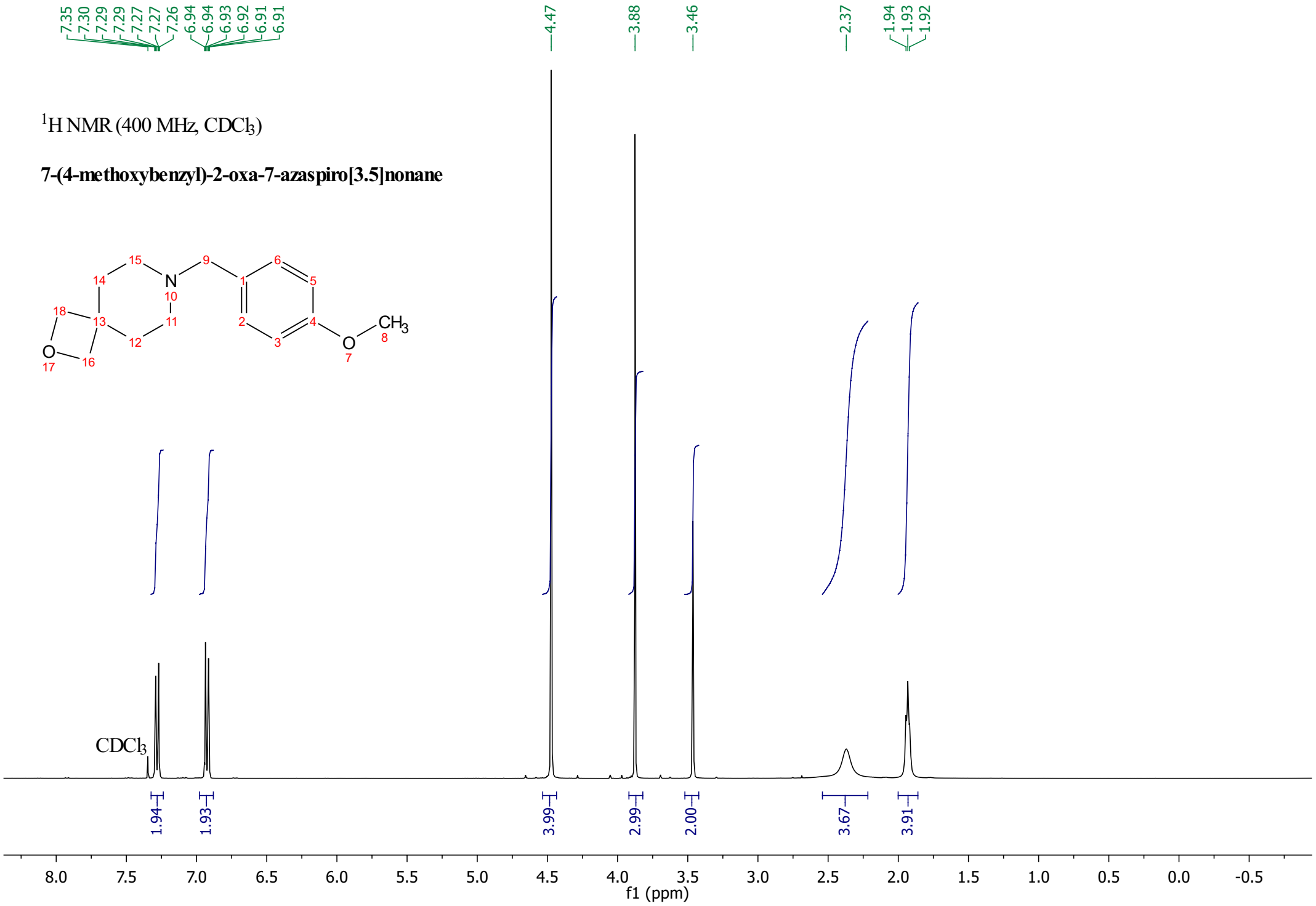
^{1}H NMR (400 MHz, $CDCl_3$)

6-(4-methoxybenzyl)-2-oxa-6-azaspiro[3.5]nonane



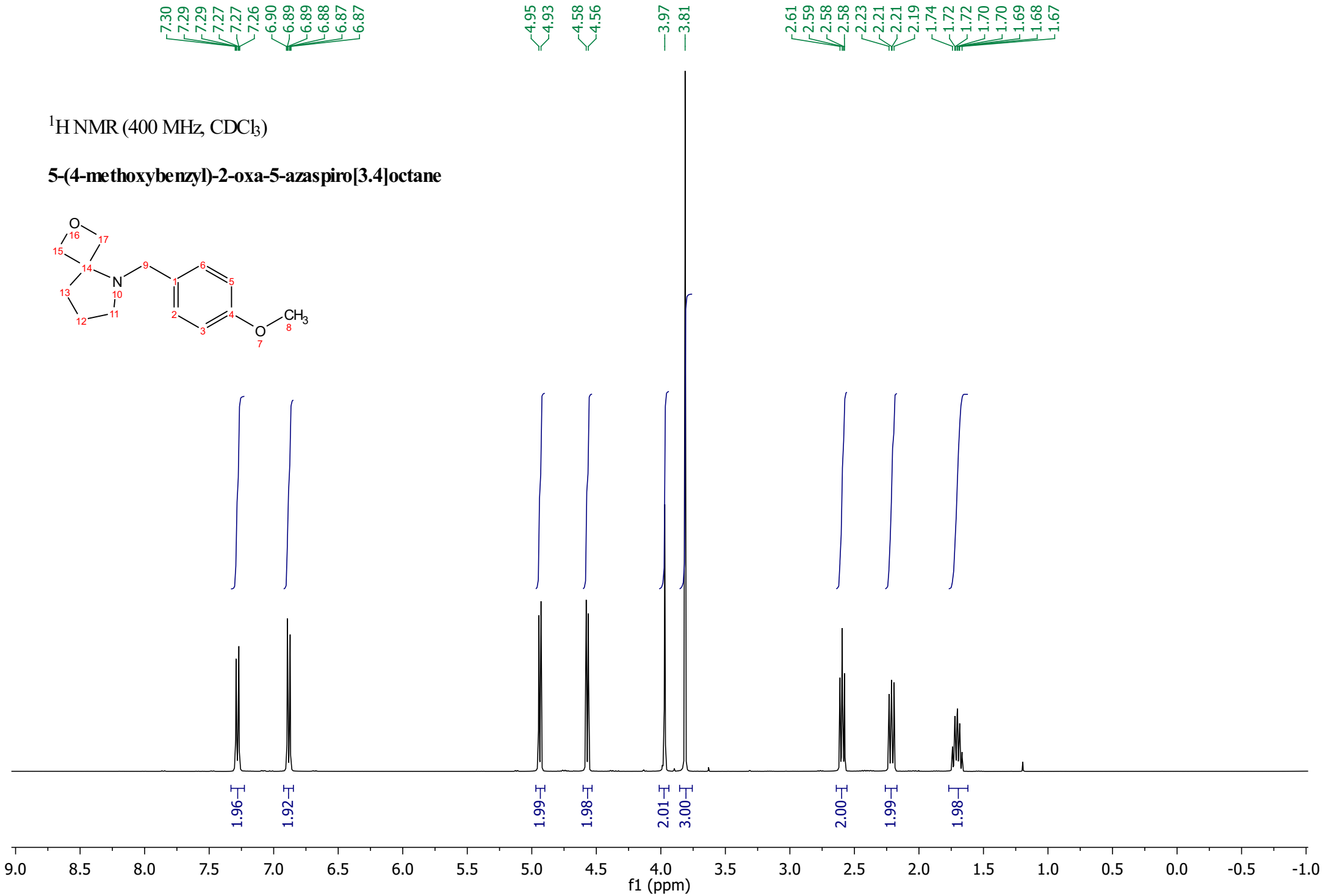
^{1}H NMR (400 MHz, $CDCl_3$)

7-(4-methoxybenzyl)-2-oxa-7-azaspiro[3.5]nonane



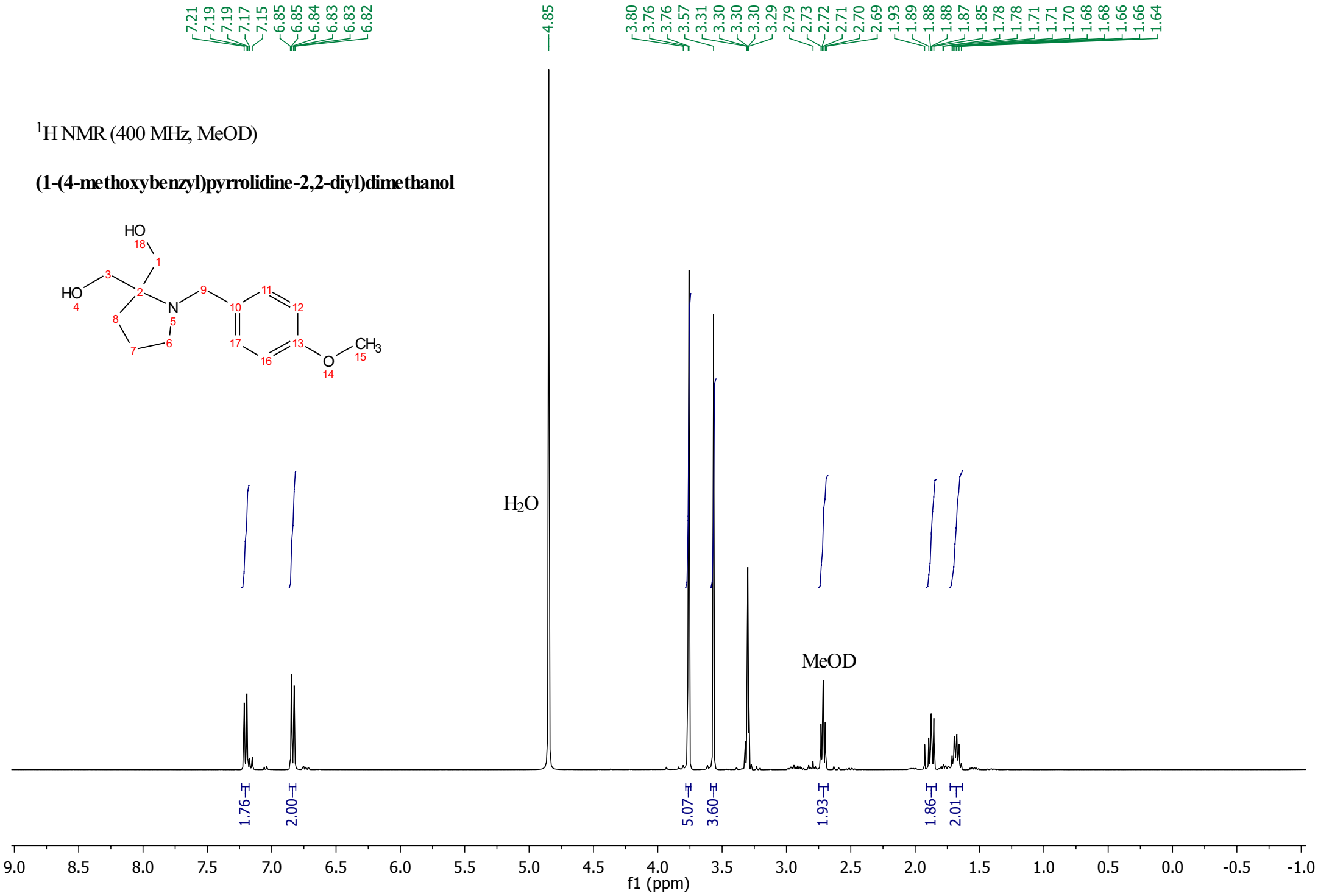
^{1}H NMR (400 MHz, $CDCl_3$)

5-(4-methoxybenzyl)-2-oxa-5-azaspiro[3.4]octane



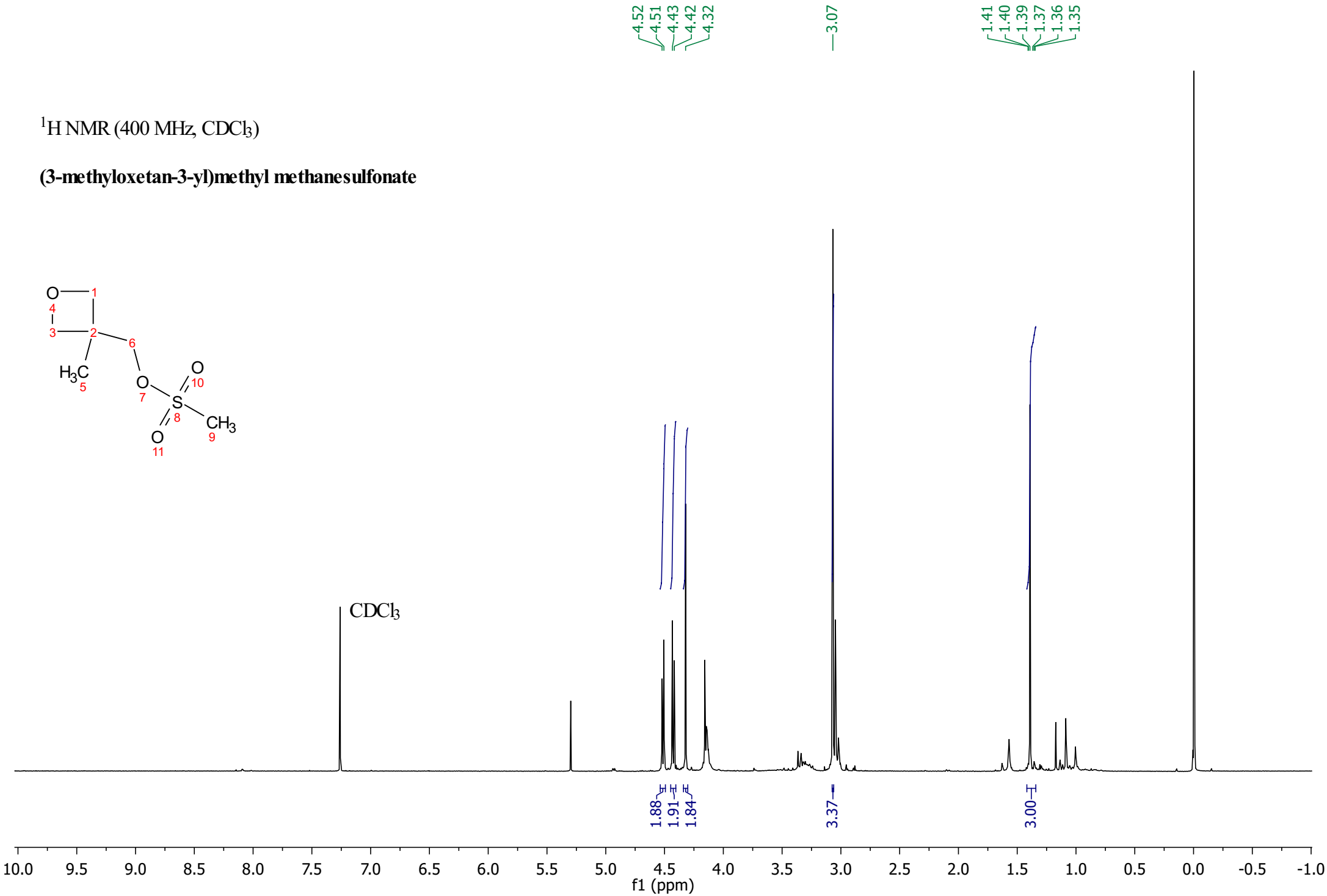
^{1}H NMR (400 MHz, MeOD)

(1-(4-methoxybenzyl)pyrrolidine-2,2-diyl)dimethanol



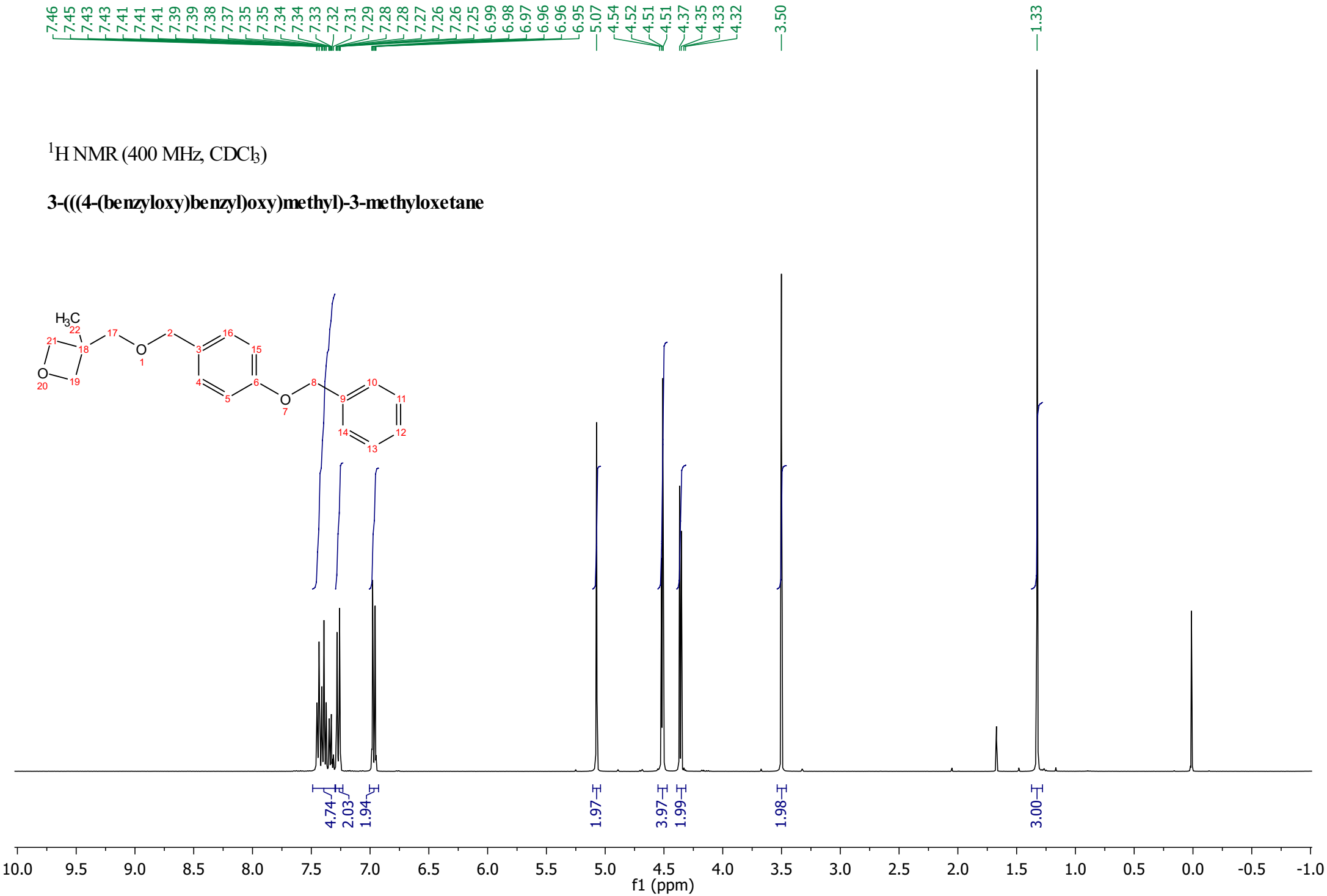
^{1}H NMR (400 MHz, $CDCl_3$)

(3-methyloxetan-3-yl)methyl methanesulfonate



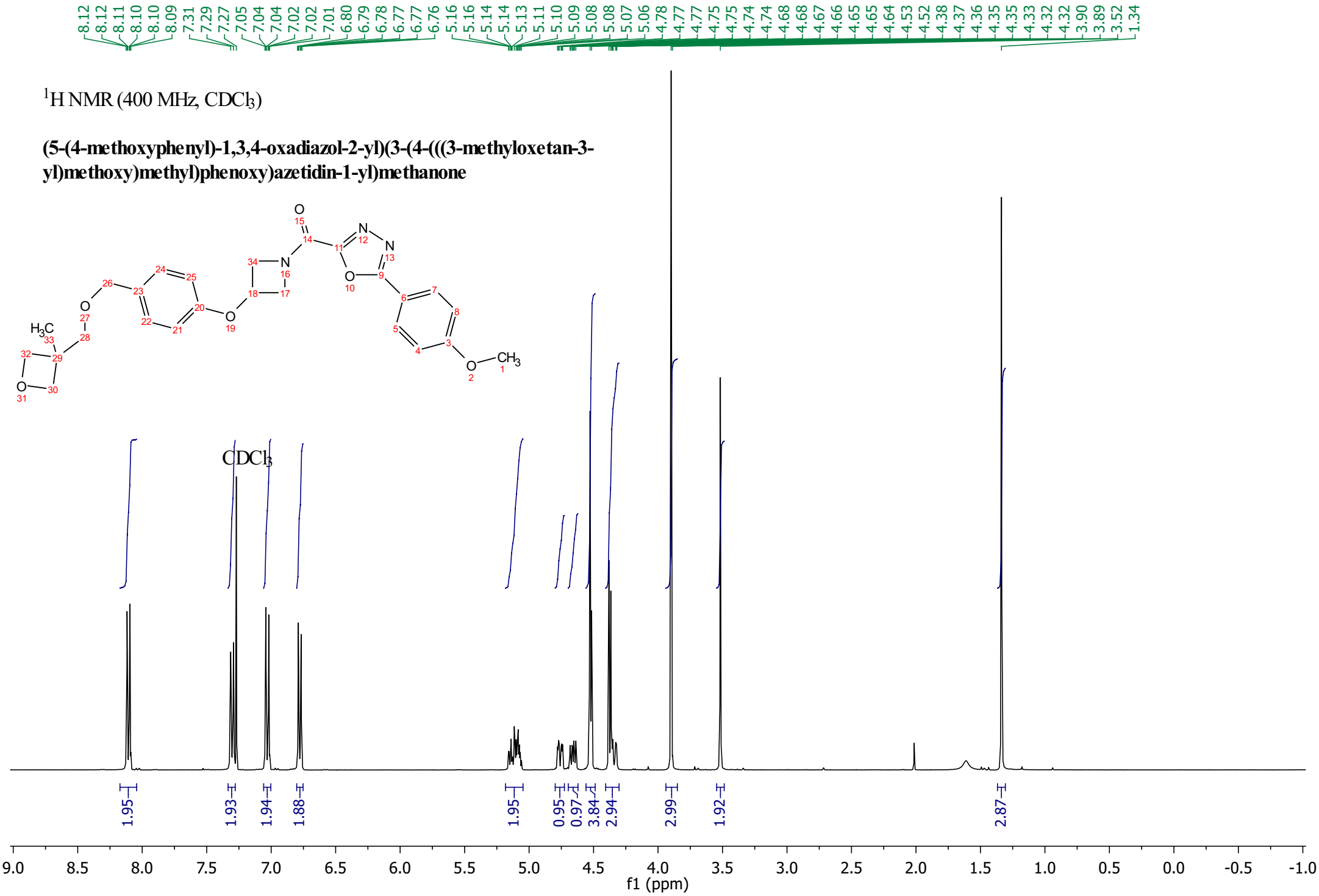
^{1}H NMR (400 MHz, $CDCl_3$)

3-(((4-(benzyloxy)benzyl)oxy)methyl)-3-methyloxetane



^{1}H NMR (400 MHz, $CDCl_3$)

(5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl)(3-(4-(((3-methyloxetan-3-yl)methoxy)methyl)phenoxy)azetidin-1-yl)methanone



References

1) Toselli, F.; Fredenwall, M.; Svensson, P.; Li, X. Q.; Johansson, A.; Weidolf, L.; Hayes, M. A., Oxetane Substrates of Human Microsomal Epoxide Hydrolase. *Drug Metab. Dispos.* **2017,** *45* (8), 966-973.