Rapid scaffold-hopping for molecular glues: from fragments to cell-active probes targeting the 14-3-3/ERα complex

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1. SUPPLEMENTARY FIGURES

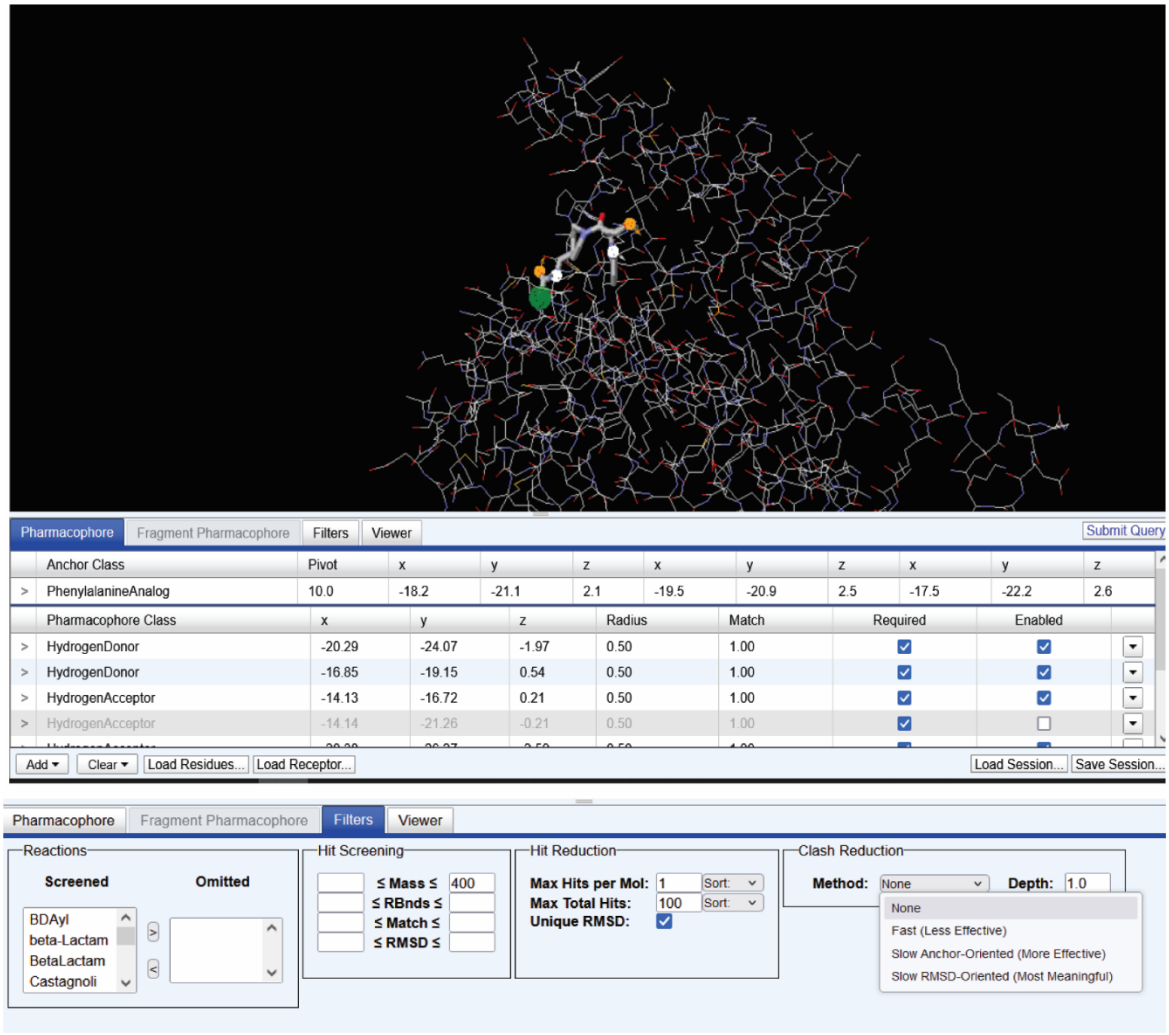


Figure S1. Overview of AnchorQuery™. The crystal structure of compound **127** bound to the 14-3-3σ/ERα complex (PDB 8ALW) was used as a starting point for the design of an MCR scaffold.

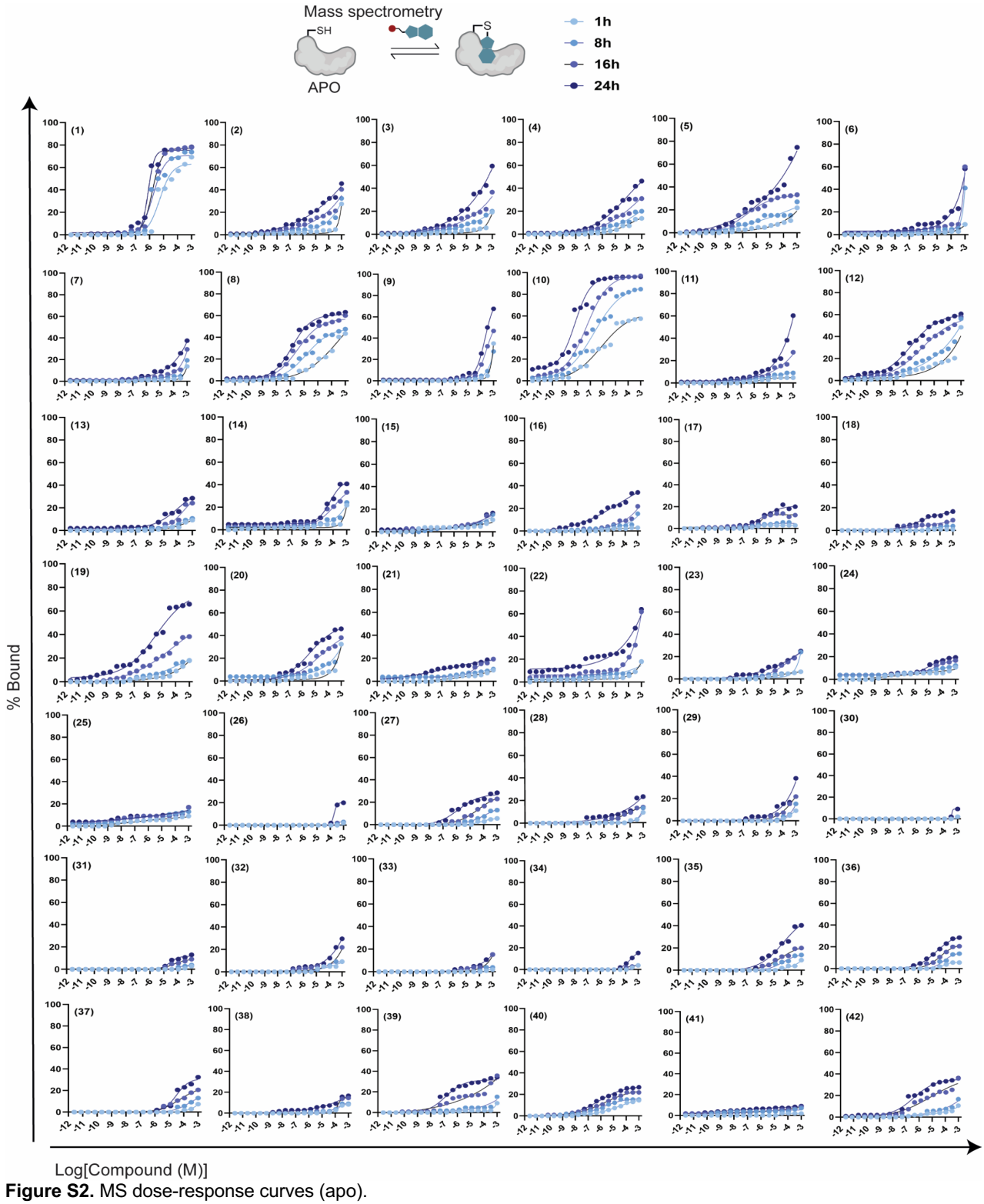


Figure S2. MS dose-response curves (apo).

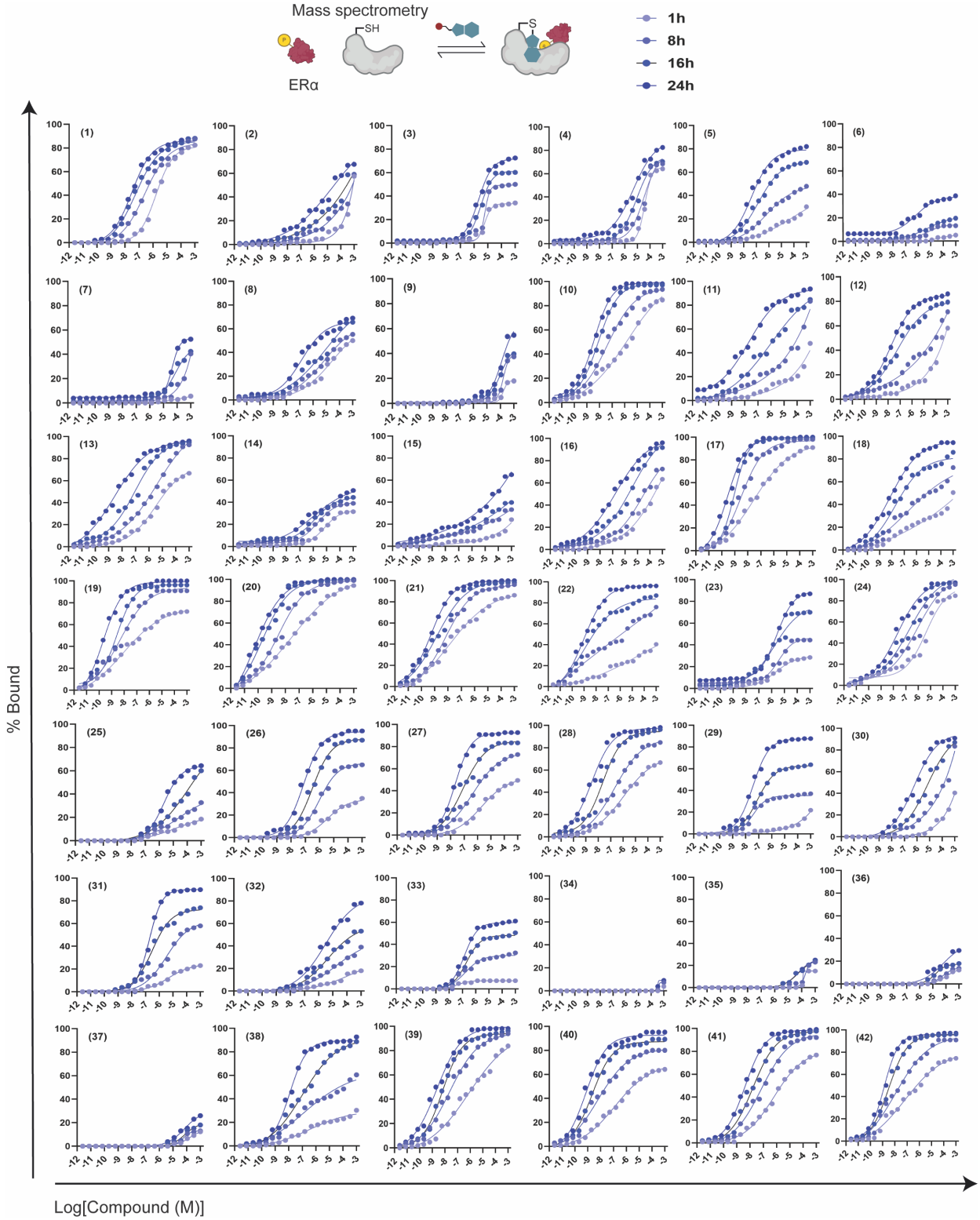


Figure S3. MS dose-response curves (ERα).

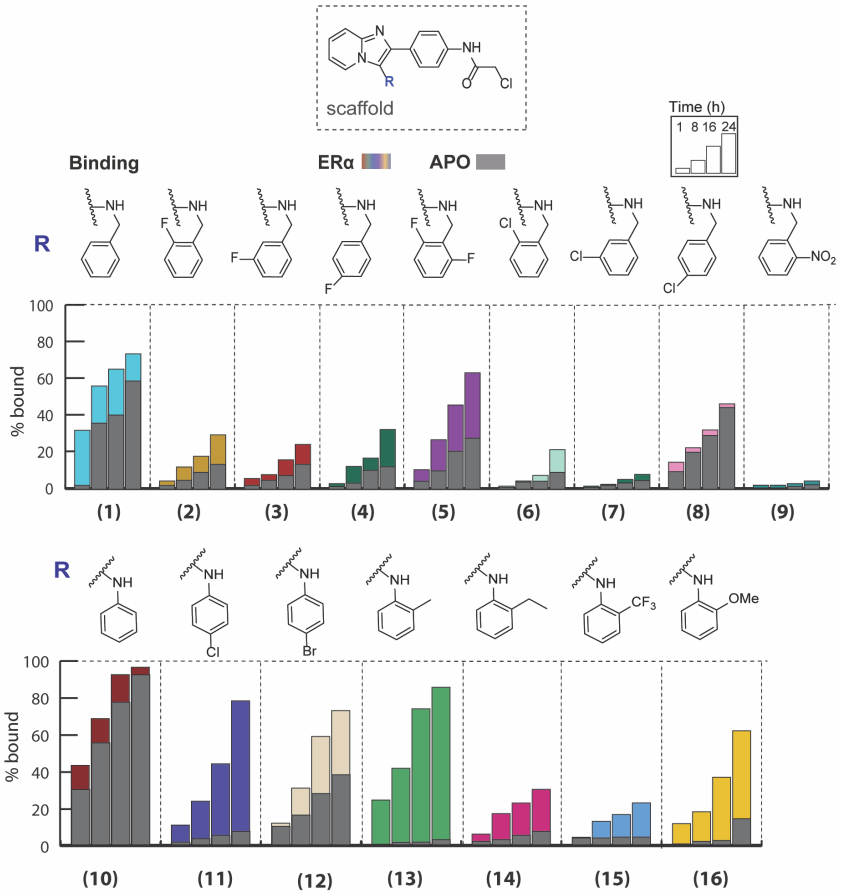


Figure S4. SAR of benzyl and phenyl analogs. MS bar graphs at 1 μM compound. For each compound, time course experiments were performed with measurements at 1h, 8h, 16h and 24h. ERα data are shown with different colors for each compound, and apo data in gray.

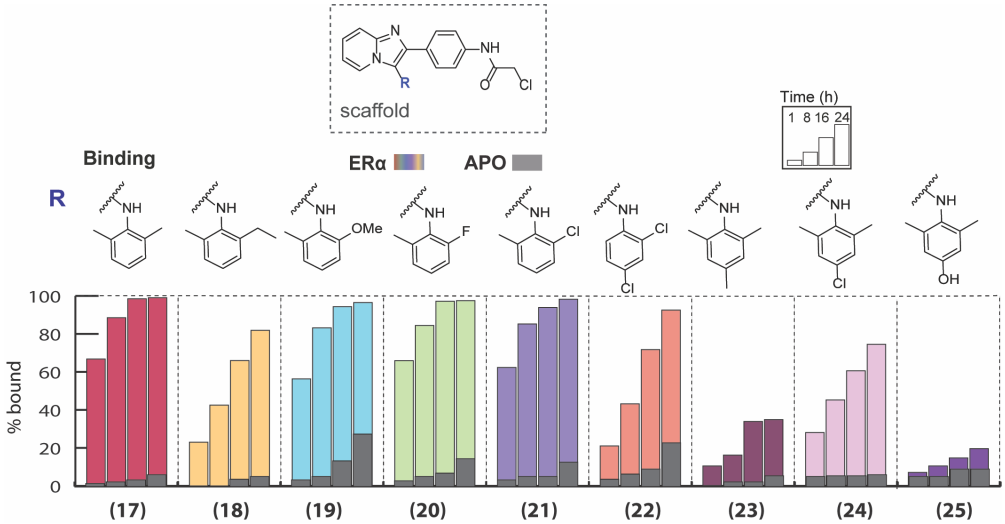


Figure S5. SAR of analogs with double *o*-substitutions. MS bar graphs at 1 μM compound. For each compound, time course experiments were performed with measurements at 1h, 8h, 16h and 24h. ERα data are shown with different colors for each compound, and apo data in gray.

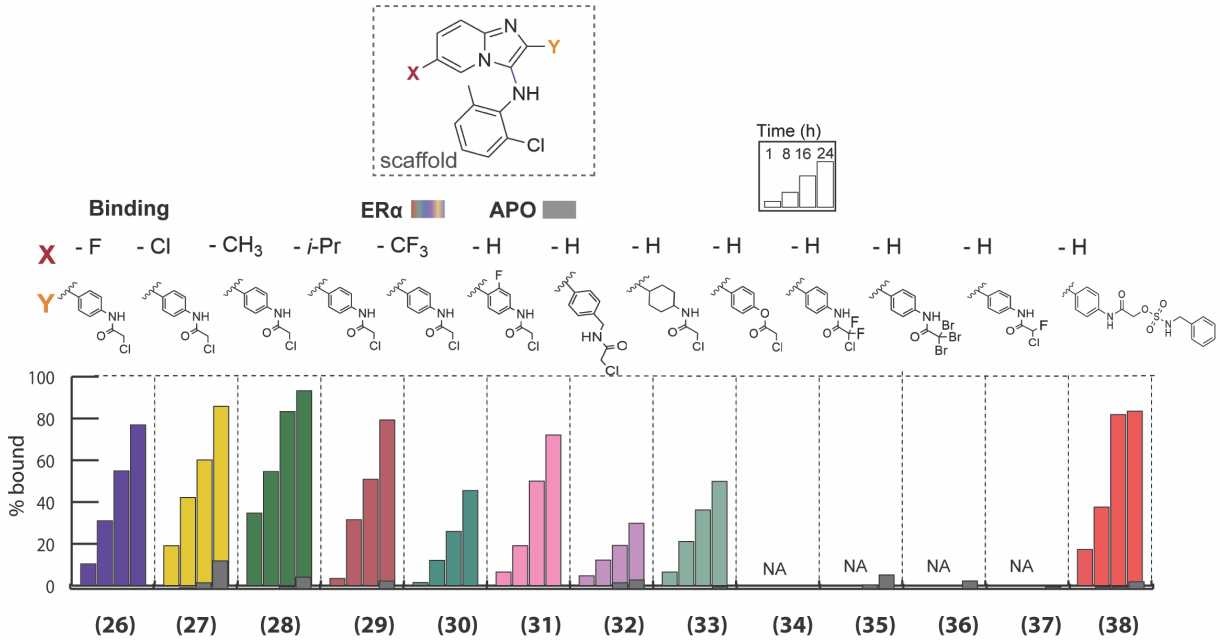


Figure S6. SAR of analogs varying positions X and Y on the scaffold. MS bar graphs at 1 μM compound. For each compound, time course experiments were performed with measurements at 1h, 8h, 16h and 24h. ERα data are shown with different colors for each compound, and apo data in gray.

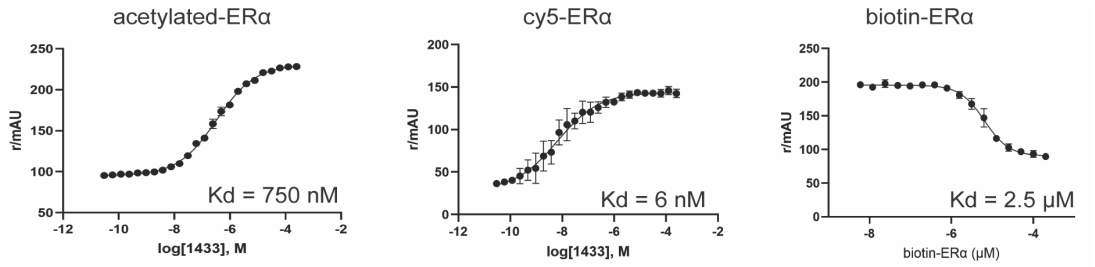


Figure S7. K_D determination for FAM-, cy5- and biotin-labeled ERα peptides.

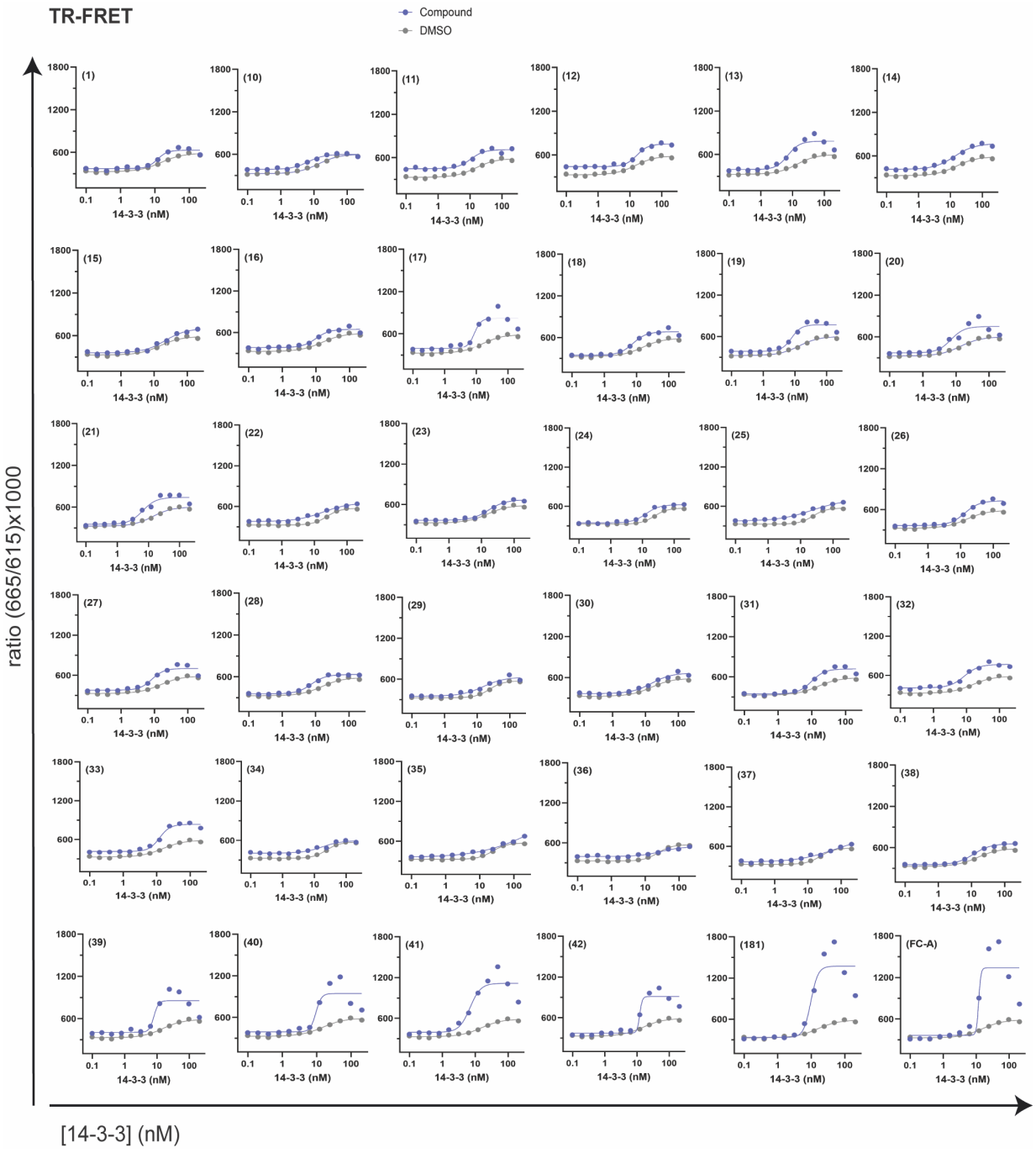


Figure S8. TR-FRET protein titrations.

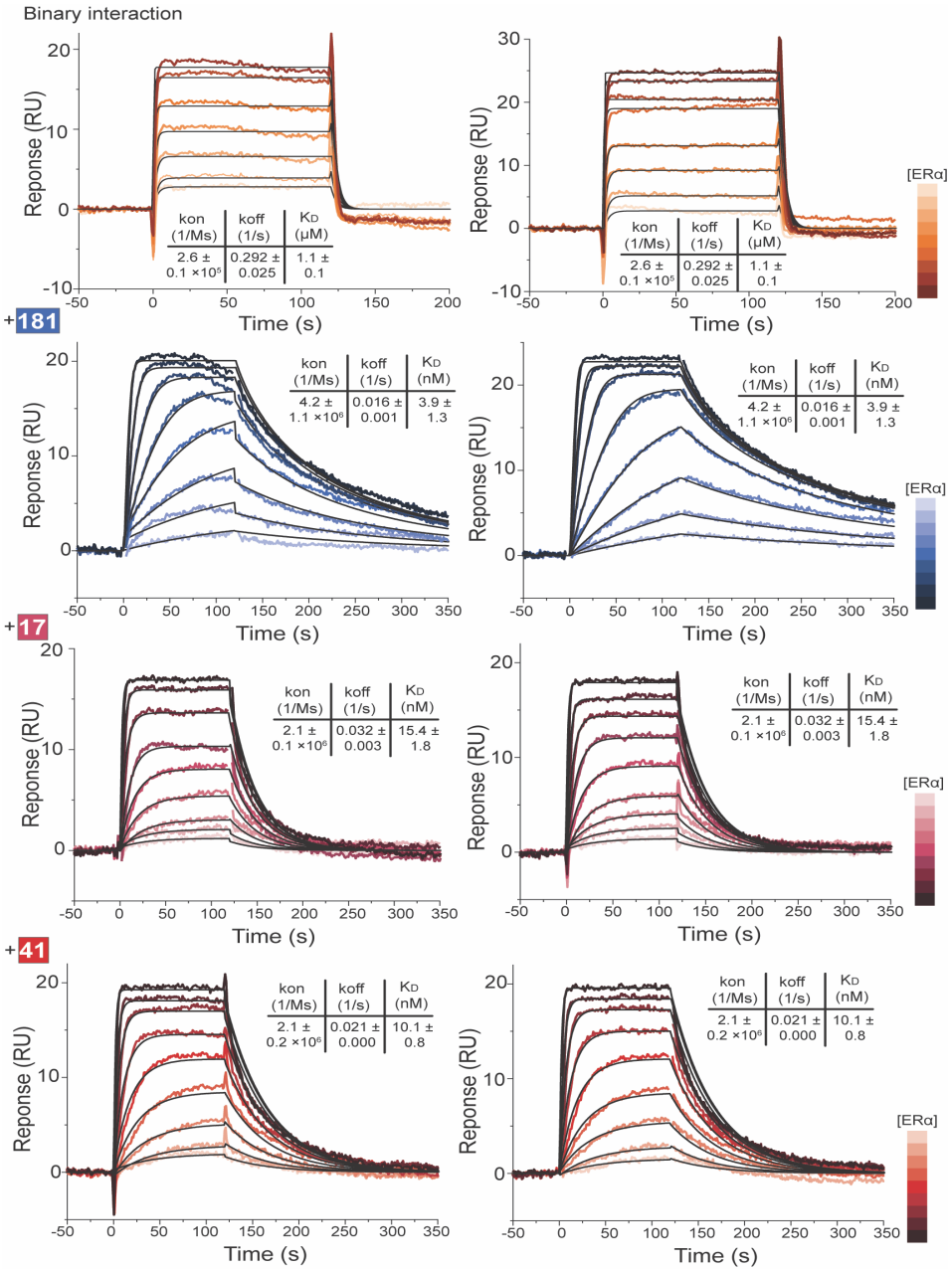


Figure S9. SPR replicates for the binary 14-3-3σ/ERα interaction and ternary interactions with **181**, **17** and **41.**

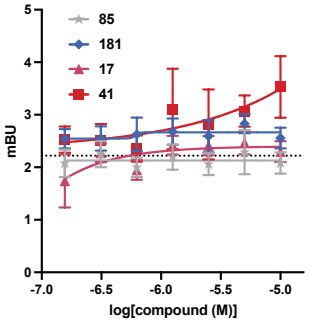


Figure S10. 14-3-3σ^{C38N}/ERα NanoBRET. 1:10 ratio of Nluc- ERα:14-3-3σ^{C38N}-HaloTag plasmids. Cells treated with compound for 24 hours.

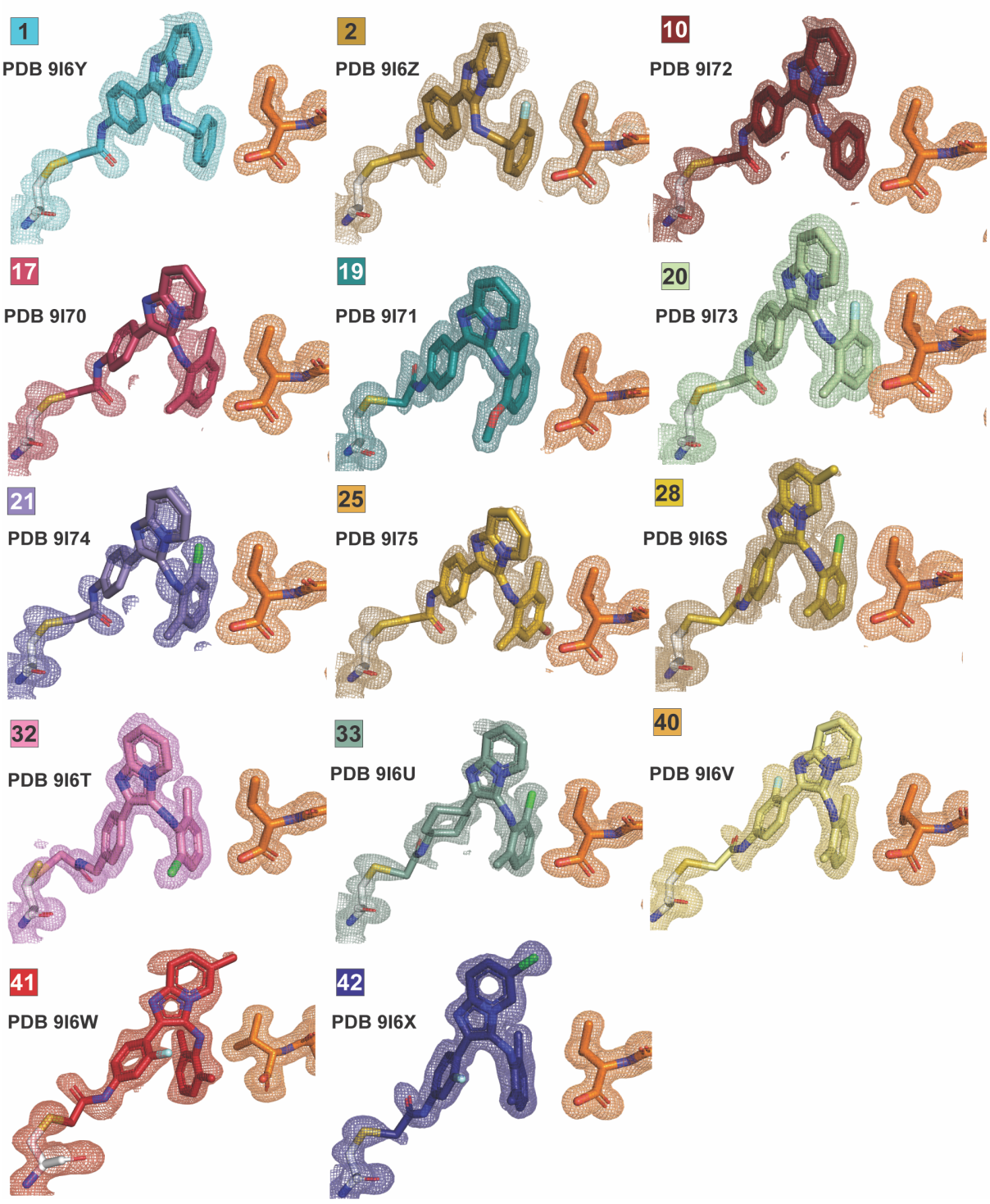
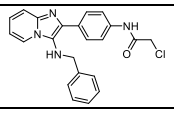
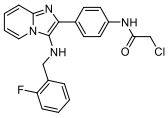
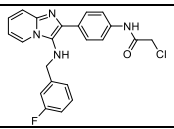
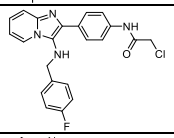
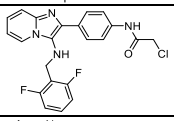
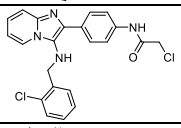
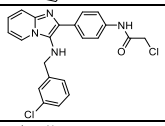
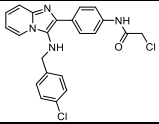
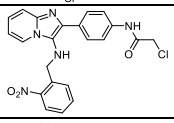
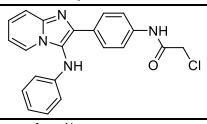
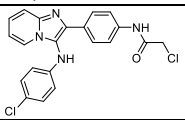
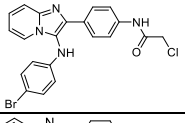
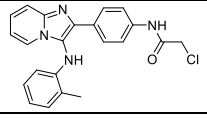
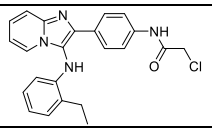
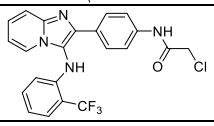
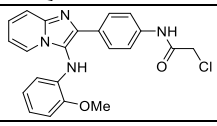
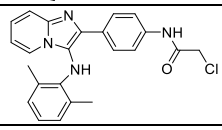
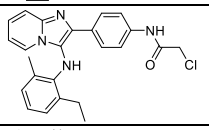
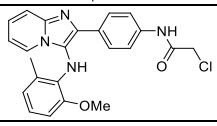
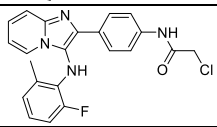
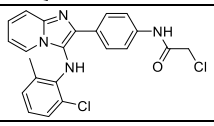
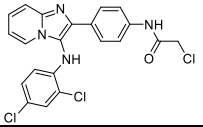
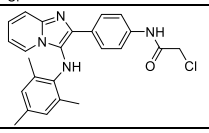
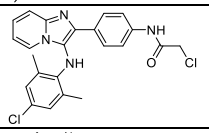
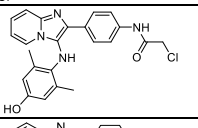
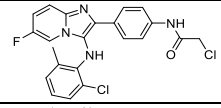
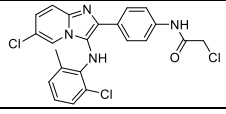


Figure S11. Densities and PDB IDs of MCR molecular glues (represented as sticks, compound number at top left). 2Fo-Fc electron density maps (blue mesh) are contoured at 1σ. Crystallographic statistics are listed in table S5.

2. SUPPLEMENTARY TABLES

Table S1. Molecular structure of compounds, assays performed and table number for the assays.

No.	SMDC ID	STRUCTURE	MS	TR-FRET	Nano-BRET	Crystallography
(1)	**1076388**		S2	S3	-	S5
(2)	**1083860**		S2	-	-	S5
(3)	**1083861**		S2	-	-	-
(4)	**1083857**		S2	-	-	-
(5)	**1084657**		S2	-	-	-
(6)	**1083858**		S2	-	-	-
(7)	**1083859**		S2	-	-	-
(8)	**1084659**		S2	-	-	-
(9)	**1083866**		S2	-	-	-
(10)	**1124905**		S2	S3	S4	S5
(11)	**1083865**		S2	S3	-	-
(12)	**1084656**		S2	S3	-	-
(13)	**1124899**		S2	S3	S4	-

(14)	**1084652**		S2	S3	-	-
(15)	**1124900**		S2	S3	-	-
(16)	**1124902**		S2	S3	-	-
(17)	**1084662**		S2	S3	S4	S5
(18)	**1124901**		S2	S3	-	-
(19)	**1124904**		S2	S3	-	S5
(20)	**1124906**		S2	S3	-	S5
(21)	**1124907**		S2	S3	-	S5
(22)	**1084654**		S2	S3	-	-
(23)	**1124903**		S2	S3	-	-
(24)	**1124908**		S2	S3	-	-
(25)	**1124909**		S2	S3	-	S5
(26)	**1132336**		S2	S3	-	-
(27)	**1132335**		S2	S3	-	-

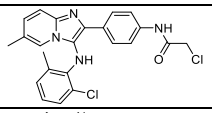
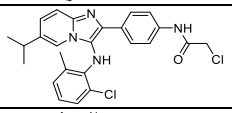
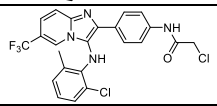
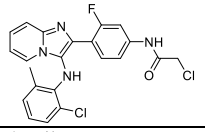
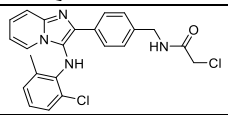
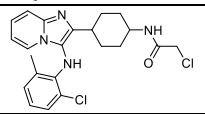
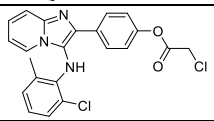
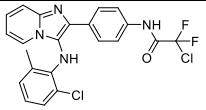
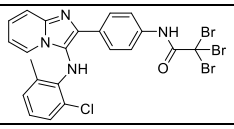
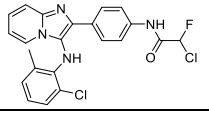
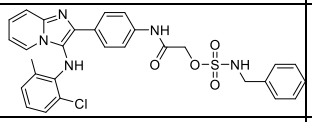
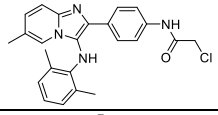
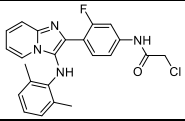
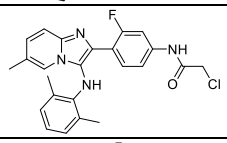
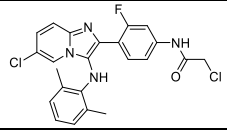
(28)	**1132334**		S2	S3	-	S5
(29)	**1132332**		S2	S3	-	-
(30)	**1132333**		S2	S3	-	-
(31)	**1132337**		S2	S3	-	-
(32)	**1132338**		S2	S3	-	S5
(33)	**1132339**		S2	S3	-	S5
(34)	**1132341**		S2	S3	-	-
(35)	**1132340**		S2	S3	-	-
(36)	**1132342**		S2	S3	-	-
(37)	**1132343**		S2	S3	-	-
(38)	**1133566**		S2	S3	-	-
(39)	**1132364**		S2	S3	-	-
(40)	**1132365**		S2	S3	S4	S5
(41)	**1132366**		S2	S3	S4	S5
(42)	**1132367**		S2	S3	S4	S5

Table S2. Percentage (%) bound of compound (1 μM) to 14-3-3σ (100 nM) measured by mass spectrometry in the absence of peptide (apo) or with ERα peptide (2 μM) after 1, 8, 16 and 24 hours.

		APO				ERα			
No.	**SMDC ID**	**1h**	**8h**	**16h**	**24h**	**1h**	**8h**	**16h**	**24h**
(1)	**1076388**	2	35.7	40.1	58.5	31.5	55.7	64.9	73.2
(2)	**1083860**	2	4.8	9.1	13.4	3.8	11.5	17.3	29
(3)	**1083861**	2	4.8	7.4	13.4	5.2	7.3	15.4	23.8
(4)	**1083857**	1.4	3.3	10.2	12.1	2.4	11.8	16.3	31.9
(5)	**1084657**	4.3	9.9	20.5	27.6	10	26.3	45.3	62.9
(6)	**1083858**	1	3.9	4.3	9.1	1	3.8	6.9	20.9
(7)	**1083859**	1	2	3.4	4.7	1	2	4.7	7.4
(8)	**1084659**	9.5	20	29	44.2	14.1	22	31.7	45.9
(9)	**1083866**	0	0.5	1.5	2.4	1.5	1.5	2.4	3.8
(10)	**1124905**	30.5	56.3	78.8	94	43.6	68.9	92.6	96.6
(11)	**1083865**	1.5	3.4	5.2	7.4	11.4	24.3	44.5	78.5
(12)	**1084656**	10.2	16.4	28.3	38.7	12.4	31.4	59.2	73.2
(13)	**1124899**	0	1.4	1.5	2.9	24.9	42.1	74.2	85.8
(14)	**1084652**	1.9	2.9	5.2	7.4	6.5	17.6	23.3	30.7
(15)	**1124900**	3.8	3.8	4.3	4.3	4.8	13.4	17.1	23.4
(16)	**1124902**	0.5	1.9	2.4	14.4	12.2	18.6	37.2	62.3
(17)	**1084662**	1.5	2.4	3.4	6.1	66.8	88.5	98.5	99
(18)	**1124901**	0	0	3.8	5.2	23	42.5	66	81.9
(19)	**1124904**	3.4	5.2	13.4	27.4	56.3	83.2	94.3	96.5
(20)	**1124906**	2.9	5.2	7	14.5	65.9	84.4	97.2	97.5
(21)	**1124907**	3.4	5.2	5.2	12.7	62.3	85.2	93.9	98.2
(22)	**1084654**	3.8	6.5	9.1	22.8	21	43.2	71.7	92.5
(23)	**1124903**	0.5	2.4	2.4	5.6	10.5	16.2	33.9	34.9
(24)	**1124908**	5.2	5.6	5.6	6.1	28.1	45.2	60.6	74.5
(25)	**1124909**	5.2	5.2	9.1	9.1	7.1	10.5	14.7	19.6
(26)	**1132336**	0	0	0	0	10.4	31	54.9	76.9
(27)	**1132335**	0	0.5	2.9	13.4	19.1	42.2	60.2	85.8
(28)	**1132334**	0	0	1	5.6	34.7	54.6	83.3	93.3
(29)	**1132332**	0	0	0	3.8	3.4	31.5	50.9	79.3
(30)	**1132333**	0	0	0	0	1.5	12.1	25.9	45.5
(31)	**1132337**	0	0	0	0	6.5	19.1	50	72.1
(32)	**1132338**	0	0	2.9	4.3	4.7	12.2	19.2	29.8
(33)	**1132339**	0	0	0	1	6.5	21.1	36.2	49.9
(34)	**1132341**	0	0	0	0	0	0	0	0
(35)	**1132340**	0	0	1.9	6.7	0	0	0	0
(36)	**1132342**	0	0	0	3.8	0	0	0	0
(37)	**1132343**	0	0	0	0.9	0	0	0	0
(38)	**1133566**	0	0.9	0.9	3.4	17.3	37.6	87.9	83.5
(39)	**1132364**	0.9	2.4	14.5	23.6	46.1	70.9	85.4	93.2
(40)	**1132365**	3.4	6.5	9.9	15.2	41.6	67.7	83.3	87.7
(41)	**1132366**	0	3.8	3.8	6.5	47	69	86.3	95.3
(42)	**1132367**	1.9	1.9	14.5	20.2	47	72.2	91.2	93.3

Table S3. TR-FRET protein titrations data. *App*Kd, Emax (at observed protein concentration), fold-increase and fold-stabilization values refer to measurements after 2h-incubation at room temperature. Fold increase = Emax/Emin. Fold stabilization = $AppKd_{(compound)}/AppKd_{(DMSO)}$. NT = not tested in this experiment, NA = not applicable.

No.	SMDC ID	*App*Kd compound (nM)	EMax	Fold increase	Fold stabilization
(1)	**1076388**	NA	-	-	-
(10)	**1124905**	NA	-	-	-
(11)	**1083865**	NA	-	-	-
(12)	**1084656**	NA	-	-	-
(13)	**1124899**	8.1	887.8	2.36	4.19
(14)	**1084652**	NA	-	-	-
(15)	**1124900**	NA	-	-	-
(16)	**1124902**	NA	-	-	-
(17)	**1084662**	7.1	991.6	2.58	4.78
(18)	**1124901**	11.1	742.8	2.14	3.06
(19)	**1124904**	7.7	818.7	2.1	4.41
(20)	**1124906**	7.1	894.0	2.47	4.78
(21)	**1124907**	6.5	772.7	2.28	5.23
(22)	**1084654**	NA	-	-	-
(23)	**1124903**	NA	-	-	-
(24)	**1124908**	16.7	628.6	1.85	2.03
(25)	**1124909**	NA	-	-	-
(26)	**1132336**	13.4	757.7	2.1	2.53
(27)	**1132335**	8.4	761.3	2.1	4.04
(28)	**1132334**	10	627.7	1.73	3.40
(29)	**1132332**	NA	-	-	-
(30)	**1132333**	NA	-	-	-
(31)	**1132337**	9.7	753.5	2.13	3.50
(32)	**1132338**	8.6	810	2	3.95
(33)	**1132339**	12.1	855.8	2.11	2.80
(34)	**1132341**	NA	-	-	-
(35)	**1132340**	NA	-	-	-
(36)	**1132342**	NA	-	-	-
(37)	**1132343**	NA	-	-	-
(38)	**1133566**	NA	-	-	-
(39)	**1132364**	7.8	1017.2	2.61	4.35
(40)	**1132365**	8.4	1184.8	3.12	4.04
(41)	**1132366**	5.2	1359.3	3.71	6.53
(42)	**1132367**	8.8	1036.7	2.97	3.87
(181)	**1083744**	8.6	1725.3	5.52	3.95
-	**FC-A**	11	1715.2	5.52	3.09
-	**DMSO**	34	-	-	-

Table S4. 14-3-3σ-HaloTag/Nluc-ERα NanoBRET data. Calculated EC_{50} values from compound titrations (2-fold dilution series, starting at 40 μM), pEC_{50} values, and the maximum fold-increase in BRET signal for each compound.

No.	SMDC ID	EC_{50} (μM)	pEC_{50}	Fold Increase
(181)	**1083744**	5.19	5.285	1.66
(10)	**1124905**	383	3.417	1.59
(13)	**1124899**	11.7	4.932	1.78
(17)	**1084662**	2.69	5.571	1.84
(40)	**1132365**	7.21	5.142	1.96
(41)	**1132366**	4.97	5.303	2.63
(42)	**1132367**	4.56	5.341	2.01

Table S5: Crystallography

PDB	**9I6Y**	**9I6Z**	**9I72**
Protein	14-3-3σΔC	14-3-3σΔC	14-3-3σΔC
Peptide	ERα pT594	ERα pT594	ERα pT594
Compound	**1 (1076388)**	**2 (1083860)**	**10 (1124905)**
Beam	ESRF ID23-1	DESY PETRA III	ESRF ID30A-3
Data collection			
Wavelength (Å)	0.77490	1.033200	0.967697
Space group	C 2 2 21	C 2 2 21	C 2 2 21
Cell dimensions			
a, b, c (Å)	82.06, 112.31, 62.62	82.14, 112.45, 62.65	81.96, 112.46, 62.48
α, β, γ (°)	90, 90, 90	90, 90, 90	90, 90, 90
Resolution (Å)	45.51 – 1.50 (1.53 – 1.50)	45.55 – 1.40 (1.42 – 1.40)	62.48 – 1.35 (1.37 – 1.35)
I / σ(*I*)	12.0 (3.7)	33.3 (10.3)	20.7 (2.2)
Completeness (%)	100.0 (99.9)	99.5 (98.3)	99.4 (94.7)
Redundancy	12.3 (13.4)	11.4 (9.1)	13.3 (8.8)
$CC_{1/2}$	0.999 (0.940)	0.999 (0.981)	1.000 (0.763)
Refinement			
No. reflections	46592	56783	63101
R_{work}/R_{free}	0.164/0.187	0.150/0.162	0.149/0.172
No. atoms			
Protein	1957	1985	1944
Ligand/ion	33	35	32
Water	314	324	314
B-factors			
Protein	15.03	14.25	16.21
Ligand/ion	22.03	21.53	26.84
Water	26.13	28.48	30.43
R.m.s. deviations			
Bond lengths (Å)	0.185	0.009	0.012
Bond angles (°)	4.62	0.99	1.13
Ramachandran			
favored (%)	98.72	98.72	98.72
outliers (%)	0.00	0.00	0.00

PDB	**9I70**	**9I71**	**9I73**
Protein	14-3-3σΔC	14-3-3σΔC	14-3-3σΔC
Peptide	ERα pT594	ERα pT594	ERα pT594
Compound	**17 (1084662)**	**19 (1124904)**	**20 (1124906)**
Beam	ESRF ID23-1	ESRF ID30A-3	ESRF ID30A-3
Data collection			
Wavelength (Å)	0.885603	0.967697	0.967697
Space group	C 2 2 21	C 2 2 21	C 2 2 21
Cell dimensions			
a, b, c (Å)	82.27, 112.49, 62.65	82.56, 112.85, 62.57	82.36, 112.61, 62.75
α, β, γ (°)	90, 90, 90	90, 90, 90	90, 90, 90
Resolution (Å)	56.24 – 1.40 (1.42 – 1.40)	62.57 – 1.35 (1.37 – 1.35)	41.91 – 1.40 (1.43 – 1.40)
I / σ(I)	18.1 (8.0)	25.2 (3.5)	21.6 (4.4)
Completeness (%)	97.0 (98.9)	99.8 (98.5)	99.9 (99.8)
Redundancy	11.3 (10.6)	13.3 (8.4)	13.8 (13.0)
$CC_{1/2}$	0.996 (0.961)	0.999 (0.897)	0.999 (0.924)
Refinement			
No. reflections	55462	64155	57558
R_{work}/R_{free}	0.139/0.160	0.144/0.176	0.140/0.160
No. atoms			
Protein	1957	1983	1982
Ligand/ion	33	34	32
Water	303	355	343
B-factors			
Protein	18.28	18.88	14.44
Ligand/ion	67.42	20.72	20.92
Water	31.77	31.47	29.14
R.m.s. deviations			
Bond lengths (Å)	0.382	0.014	0.013
Bond angles (°)	5.32	1.24	1.20
Ramachandran			
favored (%)	98.30	98.30	98.72
outliers (%)	0.00	0.00	0.00

PDB	**9I74**	**9I75**	**9I6S**
Protein	14-3-3σΔC	14-3-3σΔC	14-3-3σΔC
Peptide	ERα pT594	ERα pT594	ERα pT594
Compound	**21 (1124907)**	**25 (1124909)**	**28 (1132334)**
Beam	ESRF ID30A-3	ESRF ID30A-3	ESRF ID23-2
Data collection			
Wavelength (Å)	0.967697	0.967697	0.873128
Space group	C 2 2 21	C 2 2 21	C 2 2 21
Cell dimensions			
a, b, c (Å)	82.18, 112.16, 62.51	82.40, 112.44, 62.59	82.96, 113.10, 62.97
α, β, γ (°)	90, 90, 90	90, 90, 90	90, 90, 90
Resolution (Å)	56.08 – 1.50 (1.53 – 1.50)	56.22 – 1.40 (1.42 – 1.40)	66.89 – 1.30 (1.32 - 1.30)
I / σ(I)	21.3 (5.4)	26.2 (6.0)	16.8 (2.1)
Completeness (%)	99.9 (99.9)	99.5 (97.8)	100.0 (99.8)
Redundancy	13.8 (14.1)	13.8 (13.4)	11.3 (11.1)
$CC_{1/2}$	0.999 (0.958)	0.999 (0.962)	0.999 (0.726)
Refinement			
No. reflections	46639	57133	72001
R_{work}/R_{free}	0.143/0.166	0.138/0.160	0.164/0.192
No. atoms			
Protein	1992	1979	1930
Ligand/ion	32	36	32
Water	300	342	279
B-factors			
Protein	16.64	14.85	19.83
Ligand/ion	36.28	33.22	28.23
Water	30.18	29.44	31.75
R.m.s. deviations			
Bond lengths (Å)	0.017	0.011	0.019
Bond angles (°)	1.37	1.08	1.44
Ramachandran			
favored (%)	98.72	98.72	98.30
outliers (%)	0.00	0.00	0.00

PDB	**9I6T**	**9I6U**
Protein	14-3-3σΔC	14-3-3σΔC
Peptide	ERα pT594	ERα pT594
Compound	**32 (1132338)**	**33 (1132339)**
Beam	ESRF ID23-2	ESRF ID23-2
Data collection		
Wavelength (Å)	0.873128	0.873128
Space group	C 2 2 21	C 2 2 21
Cell dimensions		
a, b, c (Å)	82.19, 113.03, 62.89	82.78, 113.12, 62.98
α, β, γ (°)	90, 90, 90	90, 90, 90
Resolution (Å)	62.89 – 1.30 (1.32 – 1.30)	62.98 – 1.30 (1.32 – 1.30)
I / σ(I)	21.7 (3.7)	19.7 (3.0)
Completeness (%)	99.9 (100.0)	100.0 (100.0)
Redundancy	11.8 (11.6)	12.3 (12.1)
$CC_{1/2}$	1.000 (0.881)	0.999 (0.839)
Refinement		
No. reflections	72033	72612
R_{work}/R_{free}	0.145/0.171	0.147/0.175
No. atoms		
Protein	1986	2006
Ligand/ion	33	32
Water	310	285
B-factors		
Protein	27.30	19.45
Ligand/ion	21.26	33.17
Water	31.41	31.63
R.m.s. deviations		
Bond lengths (Å)	0.011	0.013
Bond angles (°)	1.13	1.14
Ramachandran		
favored (%)	98.30	98.72
outliers (%)	0.00	1.28

PDB	**9I6V**	**9I6W**	**9I6X**
Protein	14-3-3σΔC	14-3-3σΔC	14-3-3σΔC
Peptide	ERα pT594	ERα pT594	ERα pT594
Compound	**40 (1132365)**	**41 (1132366)**	**42 (1132367)**
Beam	ESRF ID23-2	ESRF ID23-2	ESRF ID23-2
Data collection			
Wavelength (Å)	0.873128	0.873128	0.873128
Space group	C 2 2 21	C 2 2 21	C 2 2 21
Cell dimensions			
a, b, c (Å)	82.99, 113.07, 62.90	82.88, 113.01, 62.92	82.89, 112.98, 62.86
α, β, γ (°)	90, 90, 90	90, 90, 90	90, 90, 90
Resolution (Å)	66.90 – 1.30 (1.32 – 1.30)	45.81 – 1.30 (1.32 – 1.30)	45.79 – 1.30 (1.32 – 1.30)
I / σ(I)	19.9 (3.5)	13.9 (1.3)	15.3 (1.6)
Completeness (%)	86.0 (84.5)	99.7 (99.4)	99.6 (99.1)
Redundancy	12.4 (11.2)	12.5 (12.5)	10.9 (10.7)
$CC_{1/2}$	0.999 (0.842)	0.999 (0.525)	0.999 (0.599)
Refinement			
No. reflections	62491	72395	72326
R_{work}/R_{free}	0.145/0.175	0.153/0.184	0.149/0.174
No. atoms			
Protein	1984	1973	1967
Ligand/ion	34	35	35
Water	283	297	290
B-factors			
Protein	18.14	21.75	21.46
Ligand/ion	47.55	40.95	30.11
Water	29.66	33.32	33.24
R.m.s. deviations			
Bond lengths (Å)	0.014	0.014	0.016
Bond angles (°)	1.15	1.24	1.40
Ramachandran			
favored (%)	98.72	98.72	98.30
outliers (%)	0.00	0.00	0.00

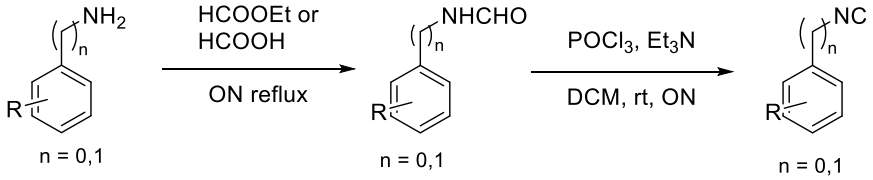
3. SYNTHETIC PROCEDURES

General remarks

All the reagents and solvents were purchased from Sigma-Aldrich, AK Scientific, Fluorochem, Abcr GmbH, Acros, AA blocks, Ambeed, 1PlusChem, Combi-blocks, ChemScene, Enamine and were used without further purification. Thin layer chromatography was performed on Millipore precoated silica gel plates (0.20 mm thick, particle size 25 µm). Nuclear magnetic resonance spectra were recorded on a Bruker Avance 500 spectrometer {^{1}H NMR (500 MHz), ^{13}C NMR (125 MHz)} or on a Bruker Advance-III 400 MHz equipped with a BBFO probe from Bruker {^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz)}. Chemical shifts for ^{1}H-NMR were reported as δ values and coupling constants were in hertz (Hz). The following abbreviations were used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, dd = double of doublets, dt = doublet of triplets, td = triplet of doublets, m = multiplet. Chemical shifts for ^{13}C-NMR were reported in ppm relative to the solvent peak. High resolution mass spectra were recorded using a LTQ-Orbitrap-XL (Thermo) at a resolution of 60000@m/z400.

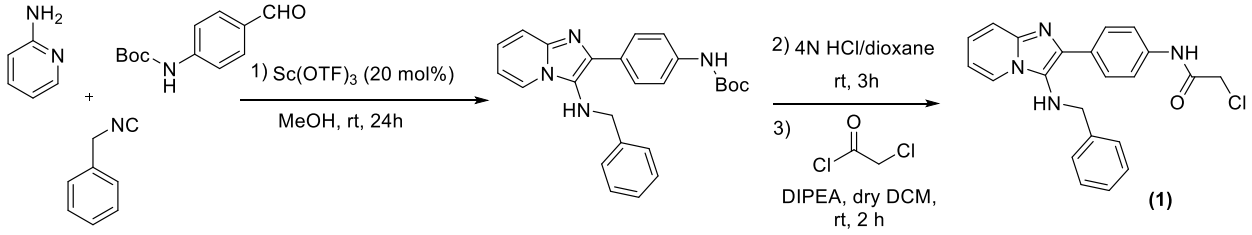
Synthetic routes

Scheme 1



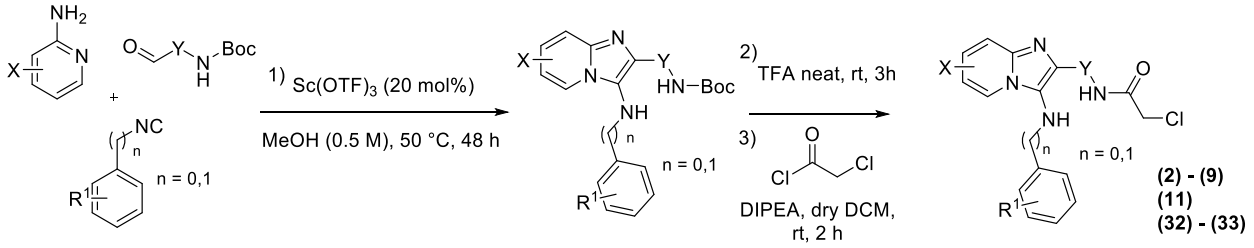
Step 1: In a round bottom flask, the appropriate benzylamine or aniline (1.0 equiv.) was dissolved in ethyl formate or formic acid (6.0 equiv.). Formic acid was used for *ortho*-substituted anilines. The reaction mixture was refluxed overnight. The solvent was removed under reduced pressure. *Step 2:* The intermediate formamide was dissolved in DCM (0.33 M). Triethylamine (5.0 equiv.) was added, and the reaction mixture was cooled at 0°C. $POCl_3$ (1.3 equiv.) was added dropwise over 30 min. The reaction mixture was stirred overnight at room temperature under a $CaCl_2$ tube. The reaction mixture was quenched at 0°C with saturated $NaHCO_3$, and was stirred vigorously for 2h. The mixture was filtered under vacuum and the filtrate was extracted with DCM (x3). The combined organic layers were collected, dried with sodium sulfate, filtered and concentrated under reduced pressure. The crude was purified by filtration over silica under vacuum with ethyl acetate as the eluent. The solvent was removed under reduced pressure. The isocyanides were isolated with yields >80%.

Scheme 2



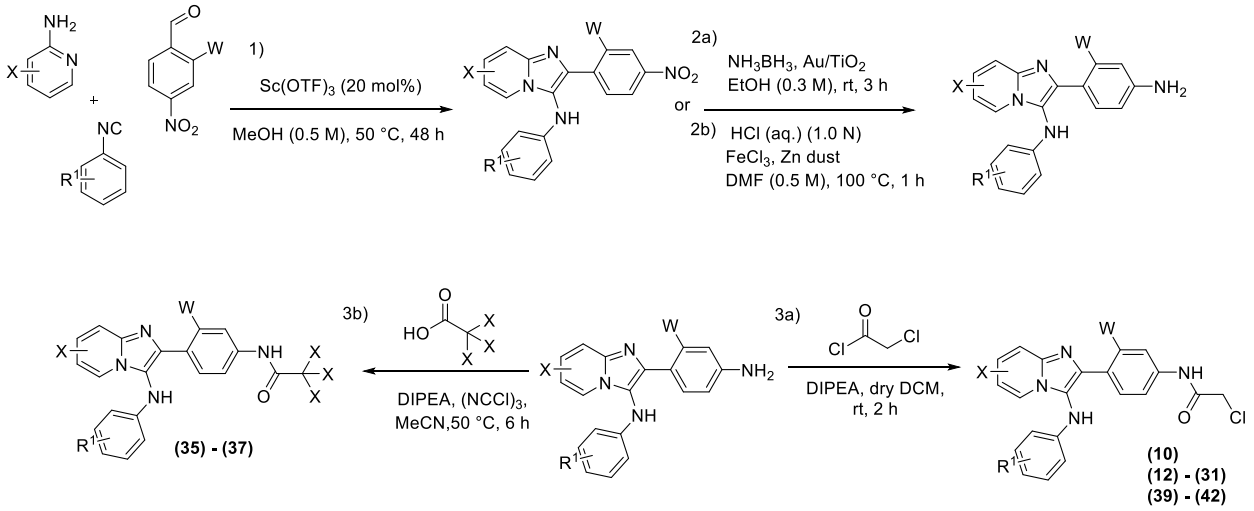
Step 1: In a vial, *tert*-butyl N-(4-formylphenyl)carbamate (0.5 mmol, 1.0 equiv.) and 2-aminopyridine (0.5 mmol, 1.0 equiv) were dissolved in MeOH (0.5M). Scandium triflate (20 mol%) and benzyl isocyanide (0.5 mmol, 1.0 equiv) were added sequentially under stirring. The reaction mixture was stirred at rt overnight. The solvent was removed under reduced pressure and the residue was purified with flash column chromatography [hexane – EtOAc, 0-100% EtOAc in hexane]. The obtained yellow solid was used directly in the next step. *Step 2*: The residue was suspended in 3 ml HCl/dioxane (4N) for Boc-deprotection. Stirring at rt for 3h. The solvent was removed under reduced pressure and the obtained oil was used directly in the next step. *Step 3*: the obtained HCl salt (0.34 mmol, 1.0 equiv.) was suspended in 4 ml dry DCM and cooled at 0 °C. Under stirring, DIPEA (1.4 mmol, 4 equiv.) was added. After 10 min, chloroacetyl chloride (0.52 mmol, 1.5 equiv.) was added slowly. Stirring at rt for 2h. The reaction mixture was diluted with DCM (10 ml), quenched with sat. $NaHCO_3$ (10 ml) and extracted with DCM (3 x 10 ml). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The obtained crude was purified with flash column chromatography [hexane – EA, 0-100% EtOAc in hexane].

Scheme 3



Step 1: To a stirred solution of the appropriate Boc-protected aldehyde (1.2 mmol, 1.0 equiv.) in MeOH (2.4 ml, 0.5M), the appropriate 2-amino pyridine (1.2 mmol, 1.0 equiv.) was added at room temperature. Then, scandium triflate was added (20 mol%) followed by the corresponding isocyanide (1.2 mmol, 1.0 equiv.) and the reaction mixture was stirred vigorously at 50 °C for 48 h. The solvent was removed under reduced pressure and the reaction mixture was diluted with ethyl acetate and washed with water (x3). The organic layer was collected, dried with sodium sulfate, filtered and concentrated under reduced pressure. The crude product was used directly in the next step. *Step 2*: To a stirred solution of the intermediate (1.0-1.2 mmol, 1 equiv.), TFA (10.0-12.0 mmol, 10.0 equiv.) was added at room temperature. The reaction mixture was stirred vigorously for 3 h. TFA was removed under reduced pressure, and the TFA salt was used directly in the next step. *Step 3:* To a stirred solution of the TFA salt (1.0-1.2 mmol, 1.0 equiv) in dry DCM (0.08 M), DIPEA (4.0-4.8 mmol, 4.0 equiv.) was added at 0 °C. The reaction mixture was stirred for 10 min. Then, chloroacetyl chloride was added dropwise (1.5-1.8 mmol, 1.5 equiv.) and the reaction mixture was stirred vigorously at room temperature for 2 h. The reaction mixture was diluted with DCM (10 ml), quenched with sat. $NaHCO_3$ (10 ml) and extracted with DCM (3 x 10 ml). The combined organic layers were collected, dried with sodium sulfate, filtered and concentrated under reduced pressure. The crude was purified with column chromatography (PE-EtOAc 2:1-1:2) to yield compounds **(2)-(9), (11), (32)** and **(33)**.

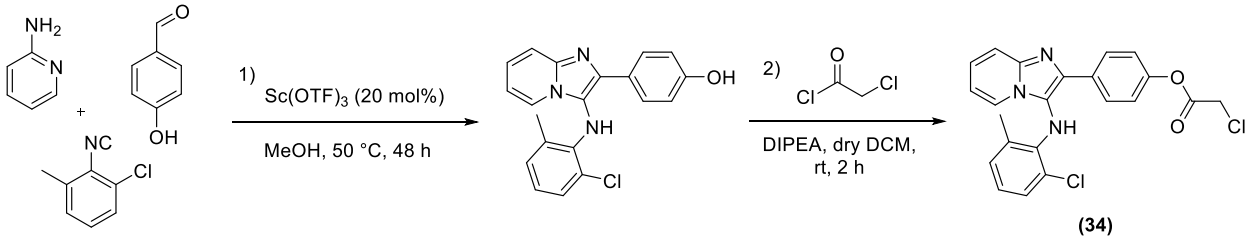
Scheme 4



Step 1: To a stirred solution of the appropriate 4-nitrobenzaldehydes (1.2 mmol, 1.0 equiv.) in MeOH (2.4 ml), the appropriate 2-amino pyridine (1.2 mmol, 1.0 equiv.) was added at room temperature. Then, scandium triflate was added (20 mol%) followed by the corresponding isocyanide (1.2 mmol, 1.0 equiv.). The reaction mixture was stirred vigorously at 50 °C for 48 h. The solvent was removed under reduced pressure and the reaction mixture was diluted with ethyl acetate and washed with water (x3). The organic layer was collected, dried with sodium sulfate, filtered and the solvent was removed under reduced pressure. The crude product was used directly in the next step. Two methods were used for the reduction of the nitro group, leading to quantitative yields. *Step 2*, *method A*: To a stirred solution of the intermediate (1.0-1.2 mmol, 1.0 equiv.) in EtOH (0.3 M), ammoniotrihydroborate (2.5-3.0 mmol, 2.5 equiv.) was added, followed by Au/TiO_2 (2.0-2.4 mmol, 2.0 equiv.). The reaction mixture was stirred vigorously for 3 h at rt. The reaction mixture was filtrated over celite, and the solvent was removed under reduced pressure. This method was used for compounds **(10), (13), (15), (16), (17), (18), (19)** and **(23).** *Step 2*, *method B*: To a stirred solution of the intermediate (1.0-1.2 mmol, 1.0 equiv.) in DMF (0.5 M), HCl (1.0 N, 2.0-2.4 mmol, 2 equiv.) was added followed by iron trichloride (3.0-3.6 mmol, 3.0 equiv.) and Zn dust (10.0-12.0 mmol, 10 equiv.). The reaction mixture was stirred vigorously at 100

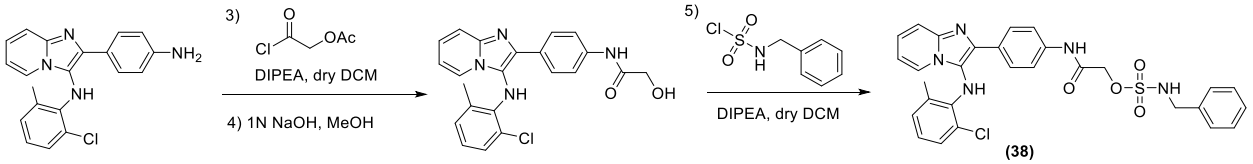
°C for 1 h. The reaction mixture was filtered over celite, and the filtrate was washed with water and sat. $NaHCO_3$. The organic layer was collected, dried with sodium sulfate, filtered and the solvent was removed under reduced pressure. The crude product was used directly in the next step. This method was all remaining compounds. *Step 3, method A*: To a stirred solution of the intermediate (1.0-1.2 mmol, 1.0 equiv) in dry DCM (0.08 M), DIPEA (4.0-4.8 mmol, 4.0 equiv.) was added at 0 °C. The reaction mixture was stirred for 10 min. Then, chloroacetyl chloride was added (1.5-1.8 mmol, 1.5 equiv.) dropwise and the reaction mixture was stirred vigorously at room temperature for 2 h. The reaction mixture was diluted with DCM (10 ml), quenched with sat. $NaHCO_3$ (10 ml) and extracted with DCM (3 x 10ml). The combine organic layers were collected, dried with sodium sulfate and filtered. The solvent was removed under reduced pressure. The crude was purified with column chromatography (PE-EtOAc 2:1-1:2) to yield compounds **(10), (12)-(31), (39)-(42)**. *Step 3, method B*: To a stirred solution of the intermediate (1.0-1.2 mmol, 1.0 equiv.) in MeCN (0.1 M), DIPEA was added (1.2 equiv.), followed by the appropriate carboxylic acid (1.0 equiv.) and cyanuric chloride (0.6 equiv.) The reaction mixture was stirred vigorously at 50 °C for 6 h. Solvent was removed under reduced pressure. The crude was purified with column chromatography (PE-EtOAc 2:1-1:2) to yield compounds **(35)-(37)**.

Scheme 5



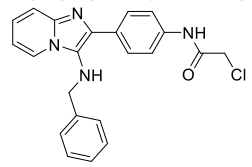
Step 1: To a stirred solution of 4-hydroxybenzaldehyde (1.2 mmol, 1.0 equiv.) in MeOH (2.4 ml), 2-amino pyridine (1.2 mmol, 1.0 equiv.) was added at room temperature. Then, scandium triflate was added (20 mol%) followed by the isocyanide (1.2 mmol, 1.0 equiv.). The reaction mixture was stirred vigorously at 50°C for 48 h. The solvent was removed under reduced pressure and the reaction mixture was diluted with ethyl acetate and washed with water (x3). The organic layer was collected, dried with sodium sulfate, filtered and the solvent was removed under reduced pressure. The crude product was used directly in the next step. *Step 2*: To a stirred solution of the intermediate (1.0 equiv.) in dry DCM (0.08 M), DIPEA (4.0 equiv.) was added at 0 °C. The reaction mixture was stirred for 10 min. Then, chloroacetyl chloride was added dropwise (1.5 equiv.) and the reaction mixture was stirred vigorously at room temperature for 2 h. The reaction mixture was diluted with DCM (10 ml), quenched with sat. $NaHCO_3$ (10 ml) and extracted with DCM (3 x 10 ml). The combined organic layers were collected, dried with sodium sulfate, filtered and concentrated under reduced pressure. The crude was purified with column chromatography (PE-EtOAc 2:1-1:2) to yield compound **(34)**.

Scheme 6



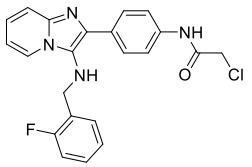
The main intermediate was synthesized following steps 1 and 2 descripted in scheme 4. *Step 3:* To a stirred solution of the intermediate (0.4 mmol, 1.0 equiv.) in dry DCM (0.08 M), DIPEA (4.0 equiv.) was added at 0 °C. The reaction mixture was stirred for 10 min. Then, acetoxyacetyl chloride was added slowly (1.0 equiv.) and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with DCM (10 ml), quenched with sat. $NaHCO_3$ (10 ml) and extracted with DCM (3 x 10 ml). The combined organic layers were collected, dried with sodium sulfate, filtered and concentrated under reduced pressure. *Step 4:* the crude was dissolved in MeOH (2 ml) and NaOH (1N, 1ml) was added to the reaction mixture. The reaction mixture was stirred at rt for 4h. The solvent was removed under reduced pressure and the residue was redissolved in ethyl acetate (10 ml). The organic layer was washed with water (x3). The organic layer was collected, dried with sodium sulfate, filtered and the solvent was removed under reduced pressure. *Step 5:* the crude was dissolved in 3 ml dry DCM and cooled at 0 °C. Under stirring, DIPEA (4 equiv.) was added. After 10 min, benzylsulfamoyl chloride (1.5 equiv.) was added slowly. Stirring at rt for 2h. The reaction mixture was diluted with DCM (10 ml), quenched with sat. $NaHCO_3$ (10 ml) and extracted with DCM (3 x 10 ml). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The obtained crude was purified with flash column chromatography [hexane – EA, 0-100% EtOAc in hexane] to obtain compound **(38)**.

***N*-(4-(3-(benzylamino)imidazo[1,2-a]pyridin-2-yl)phenyl)-2-chloroacetamide (1) 1076388**



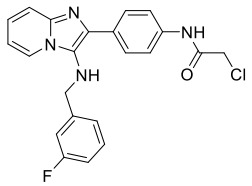
Obtained using scheme 2; 0.5 mmol scale, 71.1 mg, yield 53%, yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (b, 1H), 7.99 (dd, *J* = 10.1, 7.8 Hz, 3H), 7.65 (d, *J* = 8.6 Hz, 2H), 7.54 (d, *J* = 9.0 Hz, 1H), 7.36 – 7.26 (m, 5H), 7.14 (dd, *J* = 11.3, 4.3 Hz, 1H), 6.75 (t, *J* = 6.5 Hz, 1H), 4.21 (s, 2H), 4.19 (d, *J* = 5.1 Hz, 2H), 3.46 (b, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 141.6, 138.8, 135.9, 135.4, 131.1, 128.7, 128.2, 127.7, 127.6, 125.5, 124.2, 122.3, 120.1, 117.4, 111.8, 52.4, 42.9. LCMS (ESI): m/z calcd for $C_{22}H_{19}ClN_4O$; found $[M+H]^+$ 391.24.

2-chloro-*N*-(4-(3-((2-fluorobenzyl)amino)imidazo[1,2-a]pyridin-2-yl)phenyl)acetamide (2) 1083860



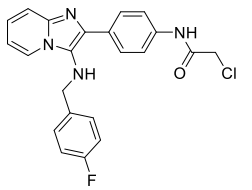
Obtained using scheme 3; 1.2 mmol scale, 236 mg, yield 38%, dark red solid. ^{1}H NMR (500 MHz, $CDCl_3$): 8.48 (s, 1H), 8.01-7.96 (m, 3H), 7.62 (d, *J* = 8.5 Hz, 2H), 7.51 (d, *J* = 9 Hz, 1H), 7.25-7.17 (m, 2H), 7.14-7.10 (m, 1H), 7.05-7.01 (m, 2H), 6.74 (td, *J1* = 6.5 Hz, *J2* = 1 Hz, 1H), 4.21-4.19 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): 163.8, 161.2 (d, J_{C-F} = 244 Hz), 141.6, 136.0, 135.7, 131.0, 130.5 (d, J_{C-F} = 4.5 Hz), 129.6 (d, J_{C-F} = 8 Hz), 127.6, 125.8 (d, J_{C-F} = 15 Hz), 125.1, 124.3 (d, J_{C-F} = 3.5 Hz), 124.2, 122.3, 120.1, 117.3, 115.5 (d, J_{C-F} = 21.5 Hz), 111.8, 46.2 (d, J_{C-F} = 3 Hz), 42.9; HRMS (ESI) m/z: $[M+H]^+$: $C_{22}H_{19}ClFN_4O$, calculated 409.12259; found 409.12319.

2-chloro-*N*-(4-(3-((3-fluorobenzyl)amino)imidazo[1,2-a]pyridin-2-yl)phenyl)acetamide (3) 1083861



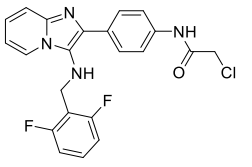
Obtained using scheme 3; 1.2 mmol scale, 152 mg, yield 25%, dark red solid. ^{1}H NMR (500 MHz, $CDCl_3$): 8.34 (s, 1H), 8.00-7.97 (m, 3H), 7.66 (d, *J* = 9 Hz, 2H), 7.55 (dt, J_1 = 9 Hz, J_2= 1 Hz, 1H), 7.29-7.25 (m, 1H), 7.16-7.13 (m, 1H), 7.10-7.07(m, 2H), 6.99-6.95 (m, 1H), 6.77 (td, J_1 = 6.5 Hz, J_2 = 1 Hz, 1H), 4.22 (s, 2H), 4.19 (d, *J* = 5.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): 163.7, 141.7, 141.4 (d, J_{C-F} = 6.5 Hz), 136.0, 135.8, 131.1, 130.2 (d, J_{C-F} = 8.5 Hz), 127.7, 125.1, 124.3, 123.7 (d, J_{C-F} = 3 Hz), 122.2, 120.2, 117.5, 115.0 (d, J_{C-F} = 21 Hz), 114.7, 114.5, 111.9, 51.9, 42.9; HRMS (ESI) m/z: $[M+H]^+$: $C_{22}H_{19}ClFN_4O$, calculated 409.12259; found 409.12316.

2-chloro-*N*-(4-(3-((4-fluorobenzyl)amino)imidazo[1,2-a]pyridin-2 yl)phenyl)acetamide (4) 1083857



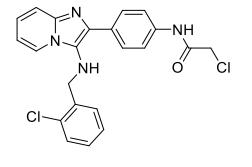
Obtained using scheme 3; 1.2 mmol scale, 291 mg, yield 53%, dark red solid. ^{1}H NMR (500 MHz, $CDCl_3$): 8.54 (s, 1H), 7.97-7.92 (m, 3H), 7.63 (d, *J* = 8 Hz, 2H), 7.54 (d, *J* = 9 Hz, 1H), 7.25-7.22 (m, 2H), 7.17-7.13 (m, 1H), 6.96 (t, *J* = 8.5 Hz, 2H), 6.76 (t, *J* = 6.5 Hz, 1H), 4.21 (s, 2H), 4.12 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): 164.0, 162.3 (d, J_{C-F} = 245 Hz), 141.3, 136.2, 135.2, 134.6 (d, J_{C-F} = 3 Hz), 130.4, 129.9 (d, J_{C-F} = 8 Hz), 127.7, 125.2, 124.8, 122.3, 120.2, 117.0, 115.5 (d, J_{C-F} = 21 Hz), 112.1, 51.6, 43.0; HRMS (ESI) m/z: $[M+H]^+$: $C_{22}H_{19}ClFN_4O$, calculated 409.12259; found 409.12272.

2-chloro-*N*-(4-(3-((2,6-difluorobenzyl)amino)imidazo[1,2-a]pyridin-2-yl)phenyl)acetamide (5) 1084657



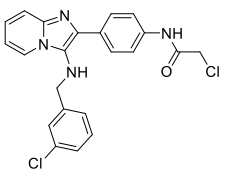
Obtained using scheme 3; 1.2 mmol scale, 160 mg, yield 31%, dark red solid. ^{1}H NMR (500 MHz, $CDCl_3$): 8.43 (s, 1H), 8.11 (d, *J* = 6.5 Hz, 1H), 7.93 (d, *J* = 8.5 Hz, 2H), 7.61 (d, *J* = 8.5 Hz, 2H), 7.57 (d, *J* = 9 Hz, 1H), 7.21-7.17 (m, 2H), 6.85-6.81 (m, 3H), 4.26 (s, 2H), 4.22 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.7, 161.5 (dd, $^1J_{C-F}$ = 246 Hz, $^2J_{C-F}$ = 8 Hz), 141.5, 136.1, 135.5, 129.8 (t, J_{C-F} = 10.5 Hz), 127.6, 127.0, 124.7, 122.4, 120.1, 117.2, 114.4 (t, J_{C-F} = 20 Hz), 112.2, 111.3 (dd, $^1J_{C-F}$ = 20 Hz, $^2J_{C-F}$ = 5.5 Hz), 42.9, 39.1; HRMS (ESI) m/z: $[M+H]^+$: $C_{22}H_{18}ClF_2N_4O$, calculated 427.11317; found 427.11277.

2-chloro-*N*-(4-(3-((2-chlorobenzyl)amino)imidazo[1,2-a]pyridin-2-yl)phenyl)acetamide (6) 1083858



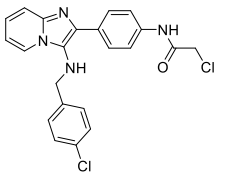
Obtained using scheme 3; 1.2 mmol scale, 234 mg, yield 45%, dark green solid. ^{1}H NMR (500 MHz, $CDCl_3$): 8.38 (s, 1H), 8.00 (dt, J_1 = 7 Hz, J_2 = 1.25 Hz, 1H), 7.92 (d, *J* = 8 Hz, 2H), 7.62-7.59 (m, 3H), 7.33 (dd, J_1 = 8 Hz, J_2 = 1.5 Hz, 1H), 7.20-7.12 (m, 4H), 6.78 (td, J_1 = 7 Hz, J_2 = 1 Hz, 1H), 4.25 (s, 2H), 4.21 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): 174.8, 163.8, 141.2, 136.2, 136.2, 133.9, 130.5, 130.1, 129.7, 129.3, 127.8, 127.1, 125.0, 122.4, 120.1, 116.9, 112.3, 50.1, 42.9; HRMS (ESI) m/z: $[M+H]^+$: $C_{22}H_{19}Cl_2N_4O$, calculated 425.09304; found 425.09382.

2-chloro-*N*-(4-(3-((3-chlorobenzyl)amino)imidazo[1,2-a]pyridin-2-yl)phenyl)acetamide (7) 1083859



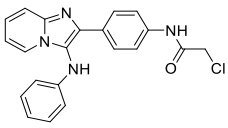
Obtained using scheme 3; 1.2 mmol scale, 397 mg, yield 40%, dark green solid. ^{1}H NMR (500 MHz, $CDCl_3$): 8.42 (s, 1H), 7.98 (d, *J* = 7 Hz, 1H), 7.94 (d, *J* = 8.5 Hz, 2H), 7.64 (d, *J* = 8.5 Hz, 2H), 7.53 (d, *J* = 9 Hz, 1H), 7.34 (s, 1H), 7.24-7.20 (m, 2H), 7.17-7.14 (m, 2H), 6.78 (td, J_1 = 7 Hz, J_2 = 1 Hz, 1H), 4.20 (s, 2H), 4.14 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): 163.9, 141.3, 140.8, 136.2, 135.4, 134.4, 129.9, 128.2, 127.8, 127.7, 127.1, 126.2, 125.1, 124.7, 122.3, 120.2, 117.1, 112.1, 51.7, 42.9; HRMS (ESI) m/z: $[M+H]^+$: $C_{22}H_{19}Cl_2N_4O$, calculated 425.09304; found 425.09353.

2-chloro-*N*-(4-(3-((4-chlorobenzyl)amino)imidazo[1,2-a]pyridin-2-yl)phenyl)acetamide (8) 1084659



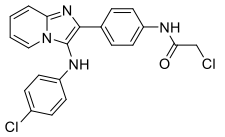
Obtained using scheme 3; 1.2 mmol scale, 197 mg, yield 39%, yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): 8.77 (s, 1H), 7.99 (d, *J* = 6.5 Hz, 1H), 7.88 (d, *J* = 8 Hz, 2H), 7.60 (d, *J* = 8 Hz, 2H), 7.51 (d, *J* = 9 Hz, 1H), 7.22-7.16 (m, 5H), 6.79 (t, *J* = 6.5 Hz), 4.21 (s, 2H), 4.10 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.1, 161.1, 140.9, 137.2, 136.5, 133.4, 129.5, 129.1, 128.8, 128.7, 127.7, 125.2, 122.5, 120.1, 116.6, 112.4, 51.5, 43.0.

2-chloro-*N*-(4-(3-(phenylamino)imidazo[1,2-a]pyridin-2-yl)phenyl)acetamide (10) 1124905



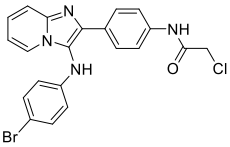
Obtained using scheme 4; 1.2 mmol scale, 189mg, yield 42%, white solid. ^{1}H NMR (500 MHz, $CDCl_3$): 8.27 (s, 1H), 8.01 (d, *J* = 8.5 Hz, 2H), 7.86 (d, *J* = 7 Hz, 1H), 7.65 (d, *J* = 9 Hz, 1H), 7.55 (d, *J* = 8.5 Hz, 2H), 7.25-7.20 (m, 3H), 6.88 (t, *J* = 7.5 Hz, 1H), 6.79 (t, *J* = 7 Hz, 1H), 6.60 (d, *J* = 8Hz, 2H), 5.64 (s, 1H), 4.18 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.7, 144.5, 142.7, 136.8, 130.7, 127.8, 125.5, 123.2, 121.2, 120.1, 120.1, 118.6, 117.6, 114.6, 112.9, 111.9, 43.3.

2-chloro-*N*-(4-(3-((4-chlorophenyl)amino)imidazo[1,2-a]pyridin-2-yl)phenyl)acetamide (11) 1083865



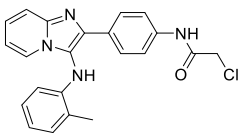
Obtained using scheme 3; 1.2 mmol scale, 225 mg, yield 40%, dark green solid. ^{1}H NMR (500 MHz, $CDCl_3$): 8.52 (s, 1H), 7.84 (d, *J* = 7 Hz, 2H), 7.64 (d, *J* = 9 Hz, 1H), 7.43 (d, *J* = 9 Hz, 2H), 7.28-7.25 (m, 2H), 7.12 (d, *J* = 9 Hz, 2H), 6.84 (t, *J* = 7 Hz, 1H), 6.52 (d, *J* = 9 Hz, 2H), 4.15 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): 164.1, 142.9, 136.9, 129.7, 127.6, 124.8, 122.9, 120.1, 118.1, 116.4, 114.7, 113.4, 43.0; HRMS (ESI) m/z: $[M+H]^+$: $C_{21}H_{17}Cl_2N_4O$, calculated 411.07739; found 411.07805.

***N*-(4-(3-((4-bromophenyl)amino)imidazo[1,2-a]pyridin-2-yl)phenyl)-2-chloroacetamide (12) 1084656**



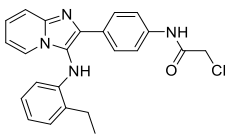
Obtained using scheme 4; 1.2 mmol scale, 96 mg, yield 18%, dark green solid. ^{1}H NMR (500 MHz, MeOD-d_4): 8,33 (d, *J* = 7 Hz, 1H), 7.89-7.86 (m, 4H), 7.74 (d, *J* = 9 Hz, 2H), 7.39-7.37 (m, 1H), 7.31 (d, *J* = 9 Hz, 3H), 6.63 (d, *J* = 9 Hz, 2H), 4.20 (s, 2H); ^{13}C NMR (125 MHz, MeOD-d_4): δ 167.6, 144.9, 141.0, 140.6, 133.7, 133.5, 128.9, 125.8, 124.7, 121.5, 121.2, 117.6, 116.6, 114.3, 113.1, 112.9, 44.0.

2-chloro-*N*-(4-(3-(o-tolylamino)imidazo[1,2-a]pyridin-2-yl)phenyl)acetamide (13) 1124899



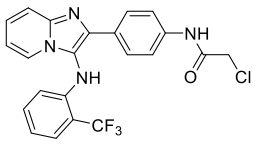
Obtained using scheme 4; 1.2 mmol scale, 105 mg, yield 27%, dark green solid. ^{1}H NMR (500 MHz, $CDCl_3$): 8.29 (s, 1H), 7.96 (d, *J* = 8.5 Hz, 2H), 7.77 (d, *J* = 7 Hz, 1H), 7.64 (d, *J* = 9 Hz, 1H), 7.54 (d, *J* = 8.5 Hz, 2H), 7.25-7.21 (m, 2Hz), 6.97 (t, *J* = 7.5 Hz, 1H), 6.81 (dt, J_1 = 7.5 Hz, J_2 = 1 Hz, 1H), 6.78 (t, *J* = 7.5 Hz, 1H), 6.17 (d, *J* = 1 Hz, 1H), 5.47 (s, 1H), 4.17 (s, 2H), 2.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.7, 142.7, 142.3, 138.4, 136.3, 131.0, 130.3, 127.7, 127.6, 125.2, 122.7, 122.4, 120.1, 119.9, 118.2, 117.5, 112.3, 111.8, 42.9, 17.6; HRMS (ESI) m/z: $[M+H]^+$: $C_{22}H_{20}ClN_4O$, calculated 391.13202; found 391.13157.

2-chloro-*N*-(4-(3-((2-ethylphenyl)amino)imidazo[1,2-a]pyridin-2-yl)phenyl)acetamide (14) 1084652



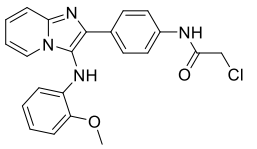
Obtained using scheme 4; 1.2 mmol scale, 160 mg, yield 33%, dark green solid. ^{1}H NMR (500 MHz, $CDCl_3$): 8.43 (s, 1H), 7.92 (d, *J* = 9 Hz, 2H), 7.71 (d, *J* = 6.5 Hz, 1H), 7.60 (d, *J* = 9 Hz, 1H), 7.50 (d, *J* = 8.5 Hz, 2H), 7.24-7.18 (m, 2H), 6.96-6.93 (m, 1H), 6.84 (t, *J* = 8 Hz, 1H), 6.72 (t, *J* = 7 Hz, 1H), 6.13 (d, *J* = 8 Hz, 1H), 5.62 (s, 1H), 4.14 (s, 2H), 2.79 (q, *J* = 7.5 Hz, 2H), 1.41 (t, *J* = 7.5 Hz, 3H), 1.28 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.8, 143.2, 141.6, 136.4, 130.2, 129.0, 128.2, 127.6, 127.4, 125.7, 125.1, 122.7, 120.0, 120.0, 118.1, 117.4, 112.2, 111.9, 42.9, 31.5, 24.1, 13.5.

2-chloro-*N*-(4-(3-((2-(trifluoromethyl)phenyl)amino)imidazo[1,2-a]pyridin-2-yl)phenyl)acetamide (15) 1124900



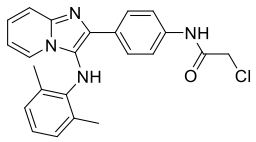
Obtained using scheme 4; 1.2 mmol scale, 85 mg, yield 16%, white solid. ^{1}H NMR (500 MHz, Acetone-d_6): 9.46 (s, 1H), 8.10 (d, J = 8.5 Hz, 2H), 8.00 (d, J = 7 Hz, 1H), 7.70-7.66 (m, 3H), 7.61 (d, J = 9 Hz, 1H), 7.35-7.33 (m, 1H), 7.31-7.27 (m, 1H), 6.96-6.92 (m, 2H), 6.29 (d, J = 8.5 Hz, 1H), 4.23 (s, 2H); ^{13}C NMR (125 MHz, Acetone-d_6): δ 165.4, 144.2, 143.6, 139.7, 139.3, 134.9, 130.9, 128.2, 127.8, 127.8, 127.0, 126.4, 123.8, 120.4, 119.8, 118.2, 117.8, 114.9, 113.4, 44.3.

2-chloro-*N*-(4-(3-((2-methoxyphenyl)amino)imidazo[1,2-a]pyridin-2-yl)phenyl)acetamide (16) 1124902



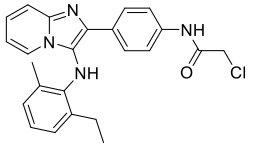
Obtained using scheme 4; 1.2 mmol scale, 51 mg, yield 13%, brown solid. ^{1}H NMR (500 MHz, $CDCl_3$): 8.49 (s, 1H), 7.98 (d, J = 8.5 Hz, 2H), 7.86 (d, J = 6.5 Hz, 1H), 7.70 (d, J = 9 Hz, 1H), 7.55 (d, J = 8.5 Hz, 2H), 7.29 (t, J = 7.5 Hz, 1H), 6.95 (dd, J_1 = 8.5 Hz, J_2 = 1.5 Hz, 1H), 6.85-6.81 (m, 2H), 6.70 (td, J_1 = 7.5 Hz, J_2 = 1.5 Hz, 1H), 6.16-6.15 (m, 2H), 4.17 (s, 2H), 4.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.9, 147.1, 142.0, 137.3, 136.7, 133.6, 129.0, 127.7, 126.2, 122.9, 121.4, 120.0, 119.7, 118.0, 116.9, 112.9, 111.7, 110.5, 55.7, 42.9; HRMS (ESI) m/z: $[M+H]^+$: $C_{22}H_{20}ClN_4O_2$, calculated 407.12693; found 407.12653.

2-chloro-*N*-(4-(3-((2,6-dimethylphenyl)amino)imidazo[1,2-a]pyridin-2-yl)phenyl)acetamide (17) 1084662



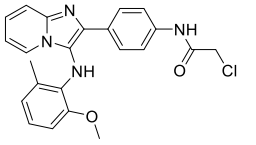
Obtained using scheme 4; 1.2 mmol scale, 260 mg, yield 54%, white solid. ^{1}H NMR (500 MHz, $CDCl_3$): 8.33 (s, 1H), 8.09 (d, J = 8.5 Hz, 2H), 7.66 (d, J = 6.5 Hz, 1H), 7.62 (d, J = 9 Hz, 1H), 7.55 (d, J = 8.5 Hz, 2H), 7.20-7.17 (m, 1H), 6.97 (d, J = 7.5 Hz, 2H), 6.81 (t, J = 7.5 Hz, 1H), 6.74 (t, J = 7 Hz, 1H), 5.48 (s, 1H), 4.19 (s, 2H), 2.00 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.7, 141.1, 140.1, 136.1, 129.9, 127.8, 125.4, 124.9, 122.4, 121.3, 120.8, 119.9, 117.2, 112.7, 42.9, 18.5.

2-chloro-*N*-(4-(3-((2-ethyl-6-methylphenyl)amino)imidazo[1,2-a]pyridin-2-yl)phenyl)acetamide (18) 1124901



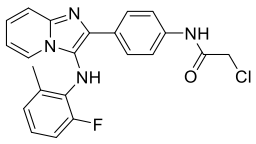
Obtained using scheme 4; 1.2 mmol scale, 140 mg, yield 28%, yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): 8.29 (s, 1H), 8.13 (d, J = 8.5 Hz, 2H), 7.60-7.56 (m, 4H), 7.16-7.13 (m, 1H), 7.07 (dd, J_1 = 7.5 Hz, J_2 = 2 Hz, 1H), 6.94 (dd, J_1 = 7.5 Hz, J_2 = 2 Hz, 1H), 6.87 (t, J = 7 Hz, 1H), 6.68 (td, J_1 = 7 Hz, J_2 = 1.5 Hz, 1H), 5.46 (s, 1H), 4.19 (s, 2H), 2.53 (q, J = 7.5 Hz, 2H), 1.86 (s, 3H), 1.13 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.7, 141.3, 139.5, 136.3, 135.9, 131.5, 130.6, 130.0, 127.7, 127.4, 125.8, 124.2, 122.3, 121.5, 121.1, 119.8, 117.4, 112.2, 42.9, 24.5, 18.5, 13.8.

2-chloro-*N*-(4-(3-((2-methoxy-6-methylphenyl)amino)imidazo[1,2-a]pyridin-2-yl)phenyl)acetamide (19) 1124904



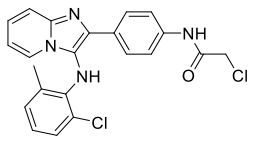
Obtained using scheme 4; 1.2 mmol scale, 135 mg, yield 27%, dark green solid. ^{1}H NMR (500 MHz, $CDCl_3$): 8.45 (s, 1H), 8.07 (d, J = 8.5 Hz, 2H), 7.84 (d, J = 7 Hz, 1H), 7.60 (d, J = 9 Hz, 1H), 7.53 (d, J = 8.5 Hz, 2H), 7.20-7.16 (m, 1H), 6.82-6.74 (m, 3H), 6.56 (d, J = 6.5 Hz, 1H), 6.11 (s, 1H), 4.16 (s, 2H), 3.92 (s, 3H), 1.55 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.7, 148.8, 141.3, 137.0, 136.1, 131.8, 130.0, 127.9, 125.6, 124.8, 124.6, 122.7, 120.6, 120.5, 119.7, 117.0, 112.4, 108.4, 56.0, 42.9, 17.5; HRMS (ESI) m/z: $[M+H]^+$: $C_{23}H_{22}ClN_4O_2$, calculated 421.14258; found 421.14217.

2-chloro-*N*-(4-(3-((2-fluoro-6-methylphenyl)amino)imidazo[1,2-a]pyridin-2-yl)phenyl)acetamide (20) 1124906



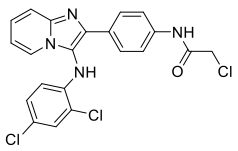
Obtained using scheme 4; 1.2 mmol scale, 52 mg, yield 11%, yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): 8.43 (s, 1H), 7.94 (d, J = 8.5 Hz, 2H), 7.87 (d, J = 7 Hz, 1H), 7.58 (d, J = 9 Hz, 1H), 7.50 (d, J = 8.5 Hz, 2H), 7.20-7.17 (m, 1H), 6.93-6.88 (m, 1H), 6.80-6.72 (m, 3H), 5.69 (d, J = 5 Hz, 1H), 4.14 (s, 1H), 1.82 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.8, 153.0 (d, J_{C-F} = 239 Hz), 141.6, 137.6, 136.2, 130.7 (d, J_{C-F} = 8.5 Hz), 129.9, 127.8, 127.2 (dd, $^1J_{C-F}$ = 9.5 Hz, $^2J_{C-F}$ = 3 Hz), 125.0, 122.5, 120.6 (d, J_{C-F} = 8 Hz), 119.8, 119.5, 117.2, 113.6 (d, J_{C-F} = 20 Hz), 112.4, 42.9, 17.6 (d, J_{C-F} = 3 Hz); HRMS (ESI) m/z: $[M+H]^+$: $C_{22}H_{19}ClFN_4O$, calculated 409.12259; found 409.12223.

2-chloro-*N*-(4-(3-((2-chloro-6-methylphenyl)amino)imidazo[1,2-a]pyridin-2-yl)phenyl)acetamide (21) 1124907



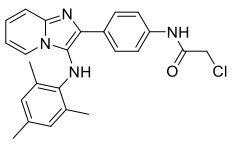
Obtained using scheme 4; 1.2 mmol scale, 294 mg, yield 58%, dark green solid. ^{1}H NMR (500 MHz, $CDCl_3$): 8.32 (s, 1H), 8.04 (d, J = 9 Hz, 2H), 7.82 (dt, J_1 = 7 Hz, J_2 = 1 Hz, 1H), 7.60 (dt, J_1 = 9 Hz, J_2 = 1 Hz, 1H), 7.55 (d, J = 9 Hz, 2H), 7.27 (dd, J_1 = 8 Hz, J_2 = 1.5 Hz, 1H), 7.22-7.18 (m, 1H), 6.84 (d, J = 7 Hz, 1H), 6.79 (td, J_1 = 7 Hz, J_2 = 1 Hz, 1H), 6.76 (t, J = 8 Hz, 1H), 6.14 (s, 1H), 4.17 (s, 2H), 1.55 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.7, 141.7, 138.6, 137.8, 136.2, 131.2, 130.1, 127.9, 127.6, 127.2, 124.8, 122.8, 122.4, 121.4, 119.7, 119.3, 117.5, 112.6, 42.9, 18.2; HRMS (ESI) m/z: $[M+H]^+$: $C_{22}H_{19}Cl_2N_4O$, calculated 425.09304; found 425.09246.

2-chloro-N-(4-(3-((2,4-dichlorophenyl)amino)imidazo[1,2-a]pyridin-2-yl)phenyl)acetamide (22) 1084654



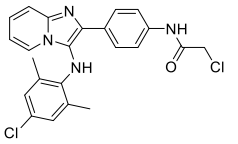
Obtained using scheme 4; 1.2 mmol scale, 117mg, yield 26%, dark green solid. ^{1}H NMR (500 MHz, $CDCl_3$): 8.37 (s, 1H), 7.94 (d, J = 9 Hz, 2H), 7.79 (d, J = 6.5 Hz, 1H), 7.66 (d, J = 9 Hz, 1H), 7.56 (d, J = 9 Hz, 2H), 7.28-7.25 (m, 1H), 6.95 (dd, J_1 = 8.5 Hz, J_2 = 2 Hz, 1H), 6.83 (t, J = 7 Hz, 1H), 6.23 (s, 1H), 6.14 (d, J = 8.5 Hz, 1H), 4.17 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.8, 142.8, 139.4, 138.8, 136.7, 129.5, 129.4, 128.4, 127.6, 125.8, 124.7, 122.3, 120.1, 120.1, 117.6, 116.2, 113.9, 112.8, 42.9.

2-chloro-*N*-(4-(3-(mesitylamino)imidazo[1,2-a]pyridin-2-yl)phenyl)acetamide (23) 1124903



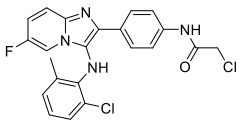
Obtained using scheme 4; 1.2 mmol scale, 184 mg, yield 37%, dark green solid. ^{1}H NMR (500 MHz, $CDCl_3$): 8.35 (s, 1H), 8.09 (d, J = 8.5 Hz, 2H), 7.62 (d, J = 7 Hz, 1H), 7.59 (d, J = 9 Hz, 1H), 7.54 (d, J = 8.5 Hz, 2H), 7.18-7.14 (m, 1H), 6.79 (s, 2H), 6.71 (td, J_1 = 6.5 Hz, J_2 = 1 Hz, 1H), 5.38 (s, 1H), 4.18 (s, 2H), 2.23 (s, 3H), 1.97 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.8, 141.1, 137.5, 136.1, 135.9, 130.5, 130.4, 128.6, 127.7, 125.5, 124.4, 122.4, 121.1, 119.8, 117.2, 112.3, 42.9, 20.3, 18.4; HRMS (ESI) m/z: $[M+H]^+$: $C_{24}H_{24}ClN_4O$, calculated 419.16332; found 419.16279.

2-chloro-*N*-(4-(3-((4-chloro-2,6-dimethylphenyl)amino)imidazo[1,2-a]pyridin-2-yl)phenyl)acetamide (24) 1124908



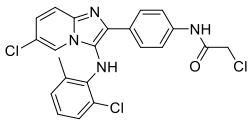
Obtained using scheme 4; 1.2 mmol scale, 73 mg, yield 17%, dark green solid. ^{1}H NMR (500 MHz, $CDCl_3$): 8.39 (s, 1H), 7.92 (d, J = 8.5 Hz, 2H), 7.71-7.68 (m, 2H), 7.51 (d, J = 8.5 Hz, 2H), 7.30-7.25 (m, 1H), 6.94 (s, 2H), 6.83 (t, J = 7 Hz), 5.69 (s, 1H), 4.18 (s, 2H), 1.95 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.9, 140.5, 138.5, 136.5, 130.5, 129.4, 127.9, 127.4, 126.0, 122.5, 120.6, 119.9, 119.1, 116.6, 113.5, 42.9, 18.4; HRMS (ESI) m/z: $[M+H]^+$: $C_{23}H_{21}Cl_2N_4O$, calculated 439.10869; found 439.10839.

2-chloro-*N*-(4-(3-((2-chloro-6-methylphenyl)amino)-6-fluoroimidazo[1,2-a]pyridin-2-yl)phenyl)acetamide (26) 1132336



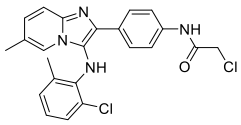
Obtained using scheme 4; 1.2 mmol scale, 77 mg, yield 15%, dark red solid. ^{1}H NMR (500 MHz, $CDCl_3$): 8.33 (s, 1H), 8.25 (s, 1H), 7.91 (d. J = 8.5 Hz, 2H), 7.76 (d, J = 9.5 Hz, 1H), 7.54 (d, J = 8.5 Hz, 2H), 7.37 (dd, J_1 = 9.5 Hz, J_2 = 2 Hz, 1H), 7.28 (dd, J_1 = 8 Hz, J_2 = 2 Hz, 1H), 6.86 (d, J = 7.5 Hz, 1H), 6.79 (t, 7.5 Hz, 1H), 6.13 (s, 1H), 4.18 (s, 2H), 1.58 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.8, 141.1, 138.0, 136.8, 131.1, 129.4, 128.2, 127.8, 127.4, 123.2, 122.2, 121.6, 121.2, 120.7, 119.7, 118.7, 117.8, 117.5, 42.9, 18.3.

2-chloro-*N*-(4-(6-chloro-3-((2-chloro-6-methylphenyl)amino)imidazo[1,2-a]pyridin-2-yl)phenyl)acetamide (27) 1132335



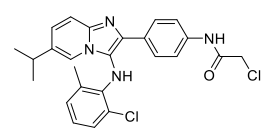
Obtained using scheme 4; 1.2 mmol scale, 252 mg, yield 46%, dark red solid. ^{1}H NMR (500 MHz, DMSO-d_6): 10.72 (s, 1H), 8.92 (s, 1H), 8.01-7.98 (m, 2H), 7.95-7.91 (m, 1H), 7.60 (s, 4H), 7.13 (dd, J_1 = 8 Hz, J_2 = 1.5 Hz, 1H), 7.03 (d, J = 7 Hz, 1H), 6.77 (t, J = 8 Hz, 1H), 4.28 (s, 2H), 2.00 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 164.9, 155.0, 153.1, 139.4, 137.4, 134.7, 130.2, 129.5, 128.1, 127.7, 122.9, 122.9, 122.9, 122.6, 118.9, 114.1, 112.7, 112.4, 43.5, 18.4.

2-chloro-*N*-(4-(3-((2-chloro-6-methylphenyl)amino)-6-methylimidazo[1,2-a]pyridin-2-yl)phenyl)acetamide (28) 1132334



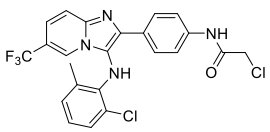
Obtained using scheme 4; 1.2 mmol scale, 164 mg, yield 31%, yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): 8.25 (s, 1H), 8.00 (d, J = 8.5 Hz, 2H), 7.66 (s, 1H), 7.55-7.51 (m, 3H), 7.28 (dd, J_1 = 7.5 Hz, J_2 = 2 Hz, 1H), 7.07 (dd, J_1 = 9.5 Hz, J_2 = 2 Hz, 1H), 6.83 (d, J = 8 Hz, 1H), 6.75 (t, J = 8 Hz, 1H), 6.09 (s, 1H), 4.18 (s, 2H), 2.30 (d, J = 1 Hz, 3H), 1.54 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.6, 140.9, 138.7, 137.8, 136.0, 131.2, 130.2, 128.1, 127.8, 127.5, 126.9, 122.6, 122.4, 121.2, 120.0, 119.7, 118.9, 116.8, 42.9, 18.4, 18.2.

2-chloro-*N*-(4-(3-((2-chloro-6-methylphenyl)amino)-6-isopropylimidazo[1,2-a]pyridin-2-yl)phenyl)acetamide (29) 1132332



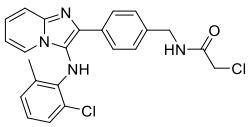
Obtained using scheme 4; 1.2 mmol scale, 213 mg, yield 38%, yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): 8.30 (s, 1H), 7.99 (d, J = 8.5 Hz, 2H), 7.68 (t, J = 1 Hz, 1H), 7.56 (d, J = 9.5 Hz), 7.53 (d, J = 8.5 Hz, 2H), 7.28 (dd, J_1 = 8 Hz, J_2 = 1.5 Hz, 1H), 7.16 (dd, J_1 = 9.5 Hz, J_2 = 2 Hz, 1H), 6.84 (d, J = 8 Hz, 1H), 6.76 (t, J = 8 Hz, 1H), 6.13 (s, 1H), 4.17 (s, 2H), 2.88 (sep, J = 7 Hz, 1H), 1.55 (s, 3H), 1.23 (d, J = 7Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.6, 141.0, 138.8, 137.7, 136.1, 133.3, 131.2, 130.1, 127.8, 127.5, 127.4, 125.9, 123.0, 121.4, 119.7, 119.3, 118.4, 116.9, 42.9, 31.5, 23.3, 18.2; HRMS (ESI) m/z: $[M+H]^+$: $C_{25}H_{25}Cl_2N_4O$, calculated 467.13999; found 467.13969.

2-chloro-*N*-(4-(3-((2-chloro-6-methylphenyl)amino)-6-(trifluoromethyl)imidazo[1,2-a]pyridin-2-yl)phenyl) acetamide (30) 1132333



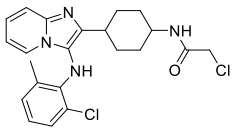
Obtained using scheme 4; 1.2 mmol scale, 21 mg, yield 4%, dark red solid. ^{1}H NMR (500 MHz, $CDCl_3$): 8.33-8.29 (m, 2H), 7.87 (d, J = 8 Hz, 2H), 7.76 (d, J = 9.5 Hz, 1H), 7.51(d, J = 8 Hz, 2H), 7.37 (dd, J_1 = 9.5 Hz, J_2 = 1.5 Hz, 1H), 7.27-7.26 (m, 1H), 6.85 (d, J = 7.5 Hz, 1H), 6.78 (t, J = 8 Hz, 1H), 6.19 (s, 1H), 4.17 (s, 2H), 1.58 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.8, 141.2, 139.0, 137.9, 136.8, 131.1, 129.3, 128.5, 128.1, 127.8, 127.4, 124.5, 123.2, 122.2, 121.6 (d, J_{C-F} = 5 Hz), 121.1, 120.7, 119.7, 118.7, 117.8, 42.9, 18.2.

2-chloro-*N*-(4-(3-((2-chloro-6-methylphenyl)amino)imidazo[1,2-a]pyridin-2-yl)benzyl)acetamide (32) 1132338



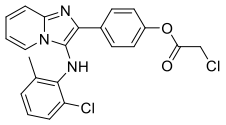
Obtained using scheme 3; 1.2 mmol scale, 185mg, yield 42%, dark green solid. ^{1}H NMR (500 MHz, DMSO-d_6): 8.71 (t, J = 6 Hz, 1H), 8.06 (d, J = 6.5 Hz, 1H), 7.86 (d, J = 8.5 Hz, 2H), 7.59-7.57 (m, 2H), 7.30-7.26 (m, 1H), 7.21-7.18 (m, 3H), 6.97-6.94 (m, 2H), 6.72 (t, J = 7.5 Hz, 1H), 4.28 (d, J = 6 Hz, 2H), 4.12 (s, 2H), 1.72 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): 166.0, 140.6, 139.4, 137.8, 136.6, 132.3, 130.6, 128.1, 127.3, 127.1, 126.6, 124.7, 123.2, 121.5, 120.7, 120.4, 116.6, 112.2, 42.7, 42.2, 18.2.

2-chloro-*N*-(4-(3-((2-chloro-6-methylphenyl)amino)imidazo[1,2-a]pyridin-2-yl)cyclohexyl)acetamide (33) 1132339



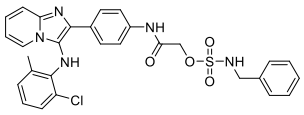
Obtained using scheme 3; 1.2 mmol scale,187 mg, yield 36%, white solid. ^{1}H NMR (500 MHz, $CDCl_3$): 8.04 (d, J = 7 Hz, 1H), 7.55 (d, J = 9 Hz, 1H), 7.28 (dd, J_1 = 8 Hz, J_2 = 1.5 Hz, 1H), 7.19-7.15 (m, 1H), 6.94 (d, J = 7.5 Hz, 1H), 6.85-6.81 (m, 2H), 6.33 (d, J = 8 Hz, 1H), 5.74 (s, 1H), 3.99 (s, 2H), 3.82-3.74 (m, 1H), 2.47-2.41 (m, 1H), 2.02 (m, 2H), 1.83-1.75 (m, 3H), 1.61 (s, 3H), 1.57 (s, 1H), 1.17-1.02 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.8, 144.3, 141.4, 140.2, 130.7, 128.6, 127.4, 124.0, 123.7, 122.1, 121.9, 119.3, 117.1, 112.2, 48.5, 42.6, 35.4, 32.8, 18.1; HRMS (ESI) m/z: $[M+H]^+$: $C_{22}H_{25}Cl_2N_4O$, calculated 431.13999; found 431.13980.

4-(3-((2-chloro-6-methylphenyl)amino)imidazo[1,2-a]pyridin-2-yl)phenyl 2-chloroacetate (34) 1132341



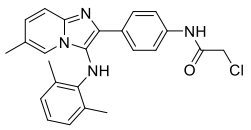
Obtained using scheme 5; 1.2 mmol scale, 316 mg, yield 62%, dark blue solid. ^{1}H NMR (500 MHz, $CDCl_3$): 8.03 (dd, J_1 = 9 Hz, J_2 = 2.5 Hz, 2H), 7.79 (d, J = 5 Hz), 7.62 (d, J = 9 Hz, 1H), 7.26-7.24 (m, 1H), 7.21-7.18 (m, 1H), 7.09 (dd, J_1 = 9 Hz, J_2 = 2.5 Hz, 2H), 6.84 (d, J = 7 Hz, 1H), 6.80-6.73 (m, 2H), 6.24 (s, 1H), 4.27 (s, 2H), 1.57 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.6, 149.8, 141.3, 138.3, 136.7, 131.1, 130.9, 128.3, 127.6, 127.3, 125.3, 122.8, 122.5, 121.5, 120.9, 119.7, 117.2, 112.9, 40.8, 18.2; HRMS (ESI) m/z: $[M+H]^+$: $C_{22}H_{18}Cl_2N_3O_2$, calculated 426.07706; found 426.07670.

2-((4-(3-((2-chloro-6-methylphenyl)amino)imidazo[1,2-a]pyridin-2-yl)phenyl)amino)-2-oxoethyl benzylsulfamate (38) 1133566



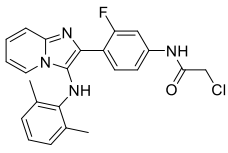
Obtained using scheme 6; 0.4 mmol scale, 23 mg, yield 10%, yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (b, 1H), 8.00 (d, J = 6.7 Hz, 1H), 7.76 – 7.69 (m, 3H), 7.38 – 7.33 (m, 5H), 7.30 – 7.27 (m, 2H), 7.22 – 7.17 (m, 3H), 6.97 (t, J = 6.7 Hz, 1H), 6.85 (d, J = 7.3 Hz, 1H), 6.74 (t, J = 7.8 Hz, 1H), 6.58 (b, 1H), 4.53 (s, 2H), 4.33 (s, 2H), 1.70 (s, 3H). LCMS (ESI): m/z calcd for $C_{29}H_{26}ClN_5O_4S$; found $[M+H]^+$ 576.07.

2-chloro-*N*-(4-(3-((2,6-dimethylphenyl)amino)-6-methylimidazo[1,2-a]pyridin-2-yl)phenyl)acetamide (39) 1132364



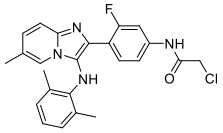
Obtained using scheme 4; 1.2 mmol scale, 243 mg, yield 49%, dark green solid. ^{1}H NMR (500 MHz, $CDCl_3$): 8.25 (s, 1H), 8.04 (d, J = 8.5 Hz, 2H), 7.54-7.49 (m, 4H), 7.02 (dd, J_1 = 9 Hz, J_2 = 1.5 Hz, 1H), 6.97 (d, J = 7.5 Hz, 2H), 6.79 (t, J = 7.5 Hz, 1H), 5.32 (s, 1H), 4.18 (s, 2H), 2.95 (s, 3H), 2.00 (s ,6H); ^{13}C NMR (125 MHz, $CDCl_3$): ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.6, 140.6, 140.5, 135.8, 130.7, 130.0, 127.7, 124.9, 122.1, 120.9, 120.2, 120.0, 119.8, 116.9, 42.9, 18.5; HRMS (ESI) m/z: $[M+H]^+$: $C_{24}H_{24}ClN_4O$, calculated 419.16332; found 419.16289.

2-chloro-*N*-(4-(3-((2,6-dimethylphenyl)amino)imidazo[1,2-a]pyridin-2-yl)-3-fluorophenyl)acetamide (40) 1132365



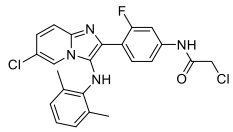
Obtained using scheme 4; 1.2 mmol scale, 316 mg, yield 63%, dark green solid. ^{1}H NMR (500 MHz, $CDCl_3$): 8.49 (s, 1H), 7.69-7.62 (m, 3H), 7.59 (dt, J_1 = 9 Hz, J_2 = 1 Hz, 1H), 7.18-7.15 (m, 2H), 6.88 (d, J = 7.5 Hz, 2H), 6.76-6.72 (m, 2H), 5.55 (d, J = 3.5 Hz, 1H), 4.18 (s, 2H), 1.90 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.8, 159.8 (d, J_{C-F} = 244 Hz), 141.4, 139.7, 137.9 (d, J_{C-F} = 11 Hz), 131.8, 131.2 (d, J_{C-F} = 5 Hz), 129.4, 126.4, 124.1, 123.2, 122.4, 121.4, 117.5, 115.4 (d, J_{C-F} = 3 Hz), 112.4, 107.3 (d, J_{C-F} = 28.5 Hz), 42.8, 18.2; HRMS (ESI) m/z: $[M+H]^+$: $C_{23}H_{21}ClFN_4O$, calculated 423.13824; found 423.13791

2-chloro-*N*-(4-(3-((2,6-dimethylphenyl)amino)-6-methylimidazo[1,2-a]pyridin-2-yl)-3-fluorophenyl)acetamide (41) 1132366



Obtained using scheme 4; 1.2 mmol scale, 382 mg, yield 73%, dark red solid. ^{1}H NMR (500 MHz, $CDCl_3$): 8.89 (s, 1H), 7.61-7.49 (m, 4H), 7.10 (t, J = 8 Hz, 2H), 6.84 (d, J = 7.5 Hz, 2H), 6.70 (t, J = 7 Hz, 1H), 5.68 (s, 1H), 4.17 (s, 2H), 2.27 (s, 3H), 1.89 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.2, 159.7 (d, J_{C-F} = 245 Hz), 139.6, 138.5, 130.9, 129.4, 128.5, 126.3, 123.1, 121.5, 120.3, 119.4, 116.1, 115.2, 107.2, 107.0, 53.7, 43.0, 18.4, 18.2; HRMS (ESI) m/z: $[M+H]^+$: $C_{24}H_{23}ClFN_4O$, calculated 437.15389; found 437.15367.

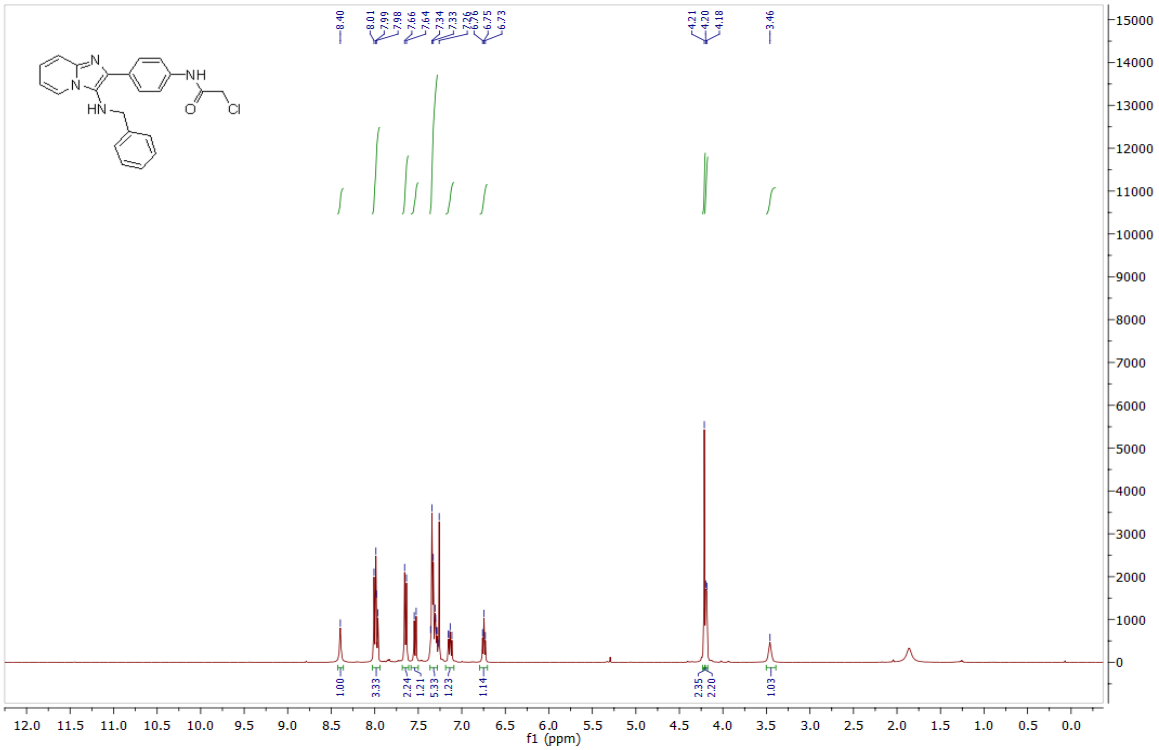
2-chloro-*N*-(4-(6-chloro-3-((2,6-dimethylphenyl)amino)imidazo[1,2-a]pyridin-2-yl)-3-fluorophenyl)acetamide (42) 1132367

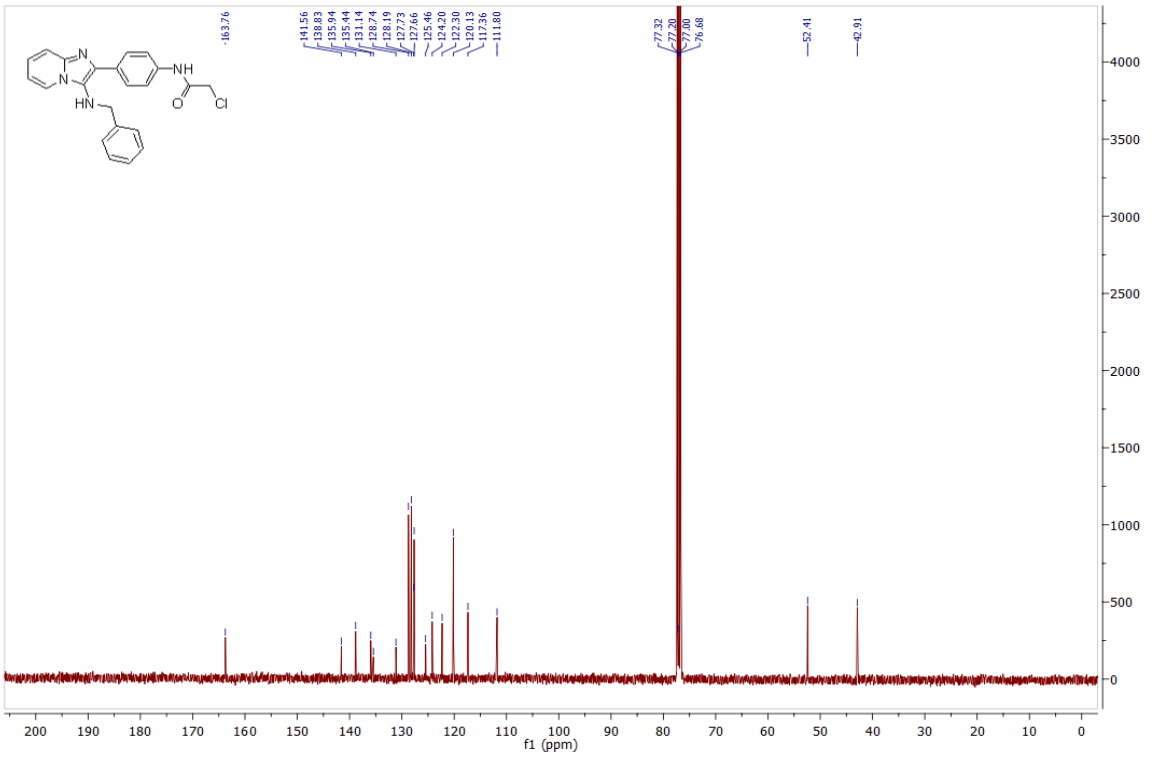


Obtained using scheme 4; 1.2 mmol scale 511 mg, yield 93%, dark red solid. ^{1}H NMR (500 MHz, $CDCl_3$): 8.49 (s, 1H), 7.74 (d, J = 2Hz, 1H), 7.60-7.57 (m, 2H), 7.51 (d, J = 9.5 Hz, 1H), 7.14-7.10 (m, 2H), 6.87 (d, J = 7.5 Hz, 2H), 6.73 (t, J = 7.5 Hz, 1H), 5.56 (d, J = 3 Hz, 1H), 4.15 (s, 2H), 1.90 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.9, 159.7 (d, J_{C-F} = 245 Hz), 139.7, 139.2, 138.1 (d, J_{C-F} = 11.5 Hz), 132.8, 131.0 (d, J_{C-F} = 5 Hz), 129.4, 126.5, 125.4, 123.6, 121.8, 120.7, 120.2, 117.9, 115.3 (d, J_{C-F} = 3 Hz), 107.2 (d, J_{C-F} = 28 Hz), 42.8, 18.1; HRMS (ESI) m/z: $[M+H]^+$: $C_{23}H_{20}Cl_2FN_4O$, calculated 457.09927; found 457.09914.

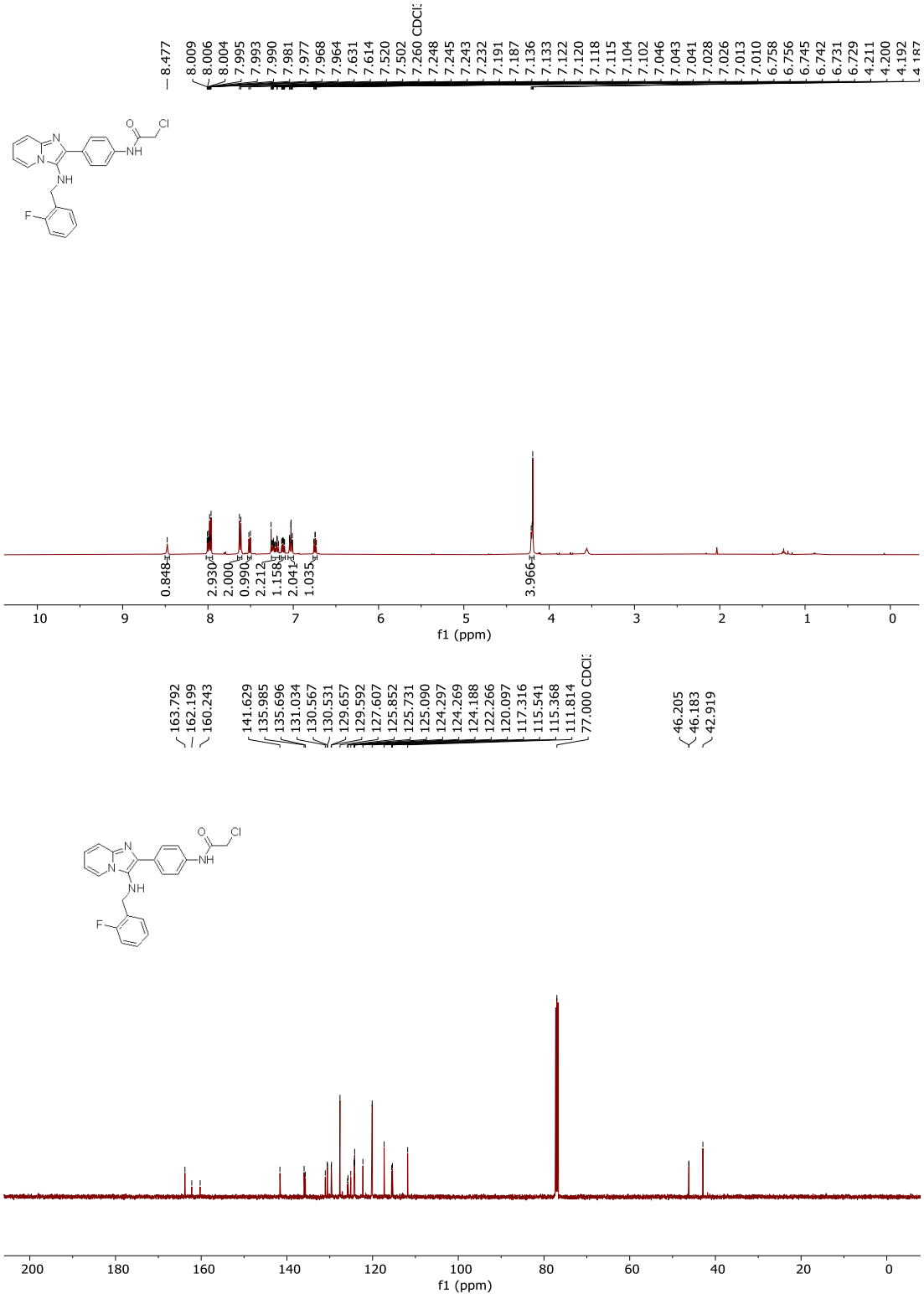
4. REPRESENTATIVE NMR SPECTRA

***N*-(4-(3-(benzylamino)imidazo[1,2-a]pyridin-2-yl)phenyl)-2-chloroacetamide (1) 1076388**

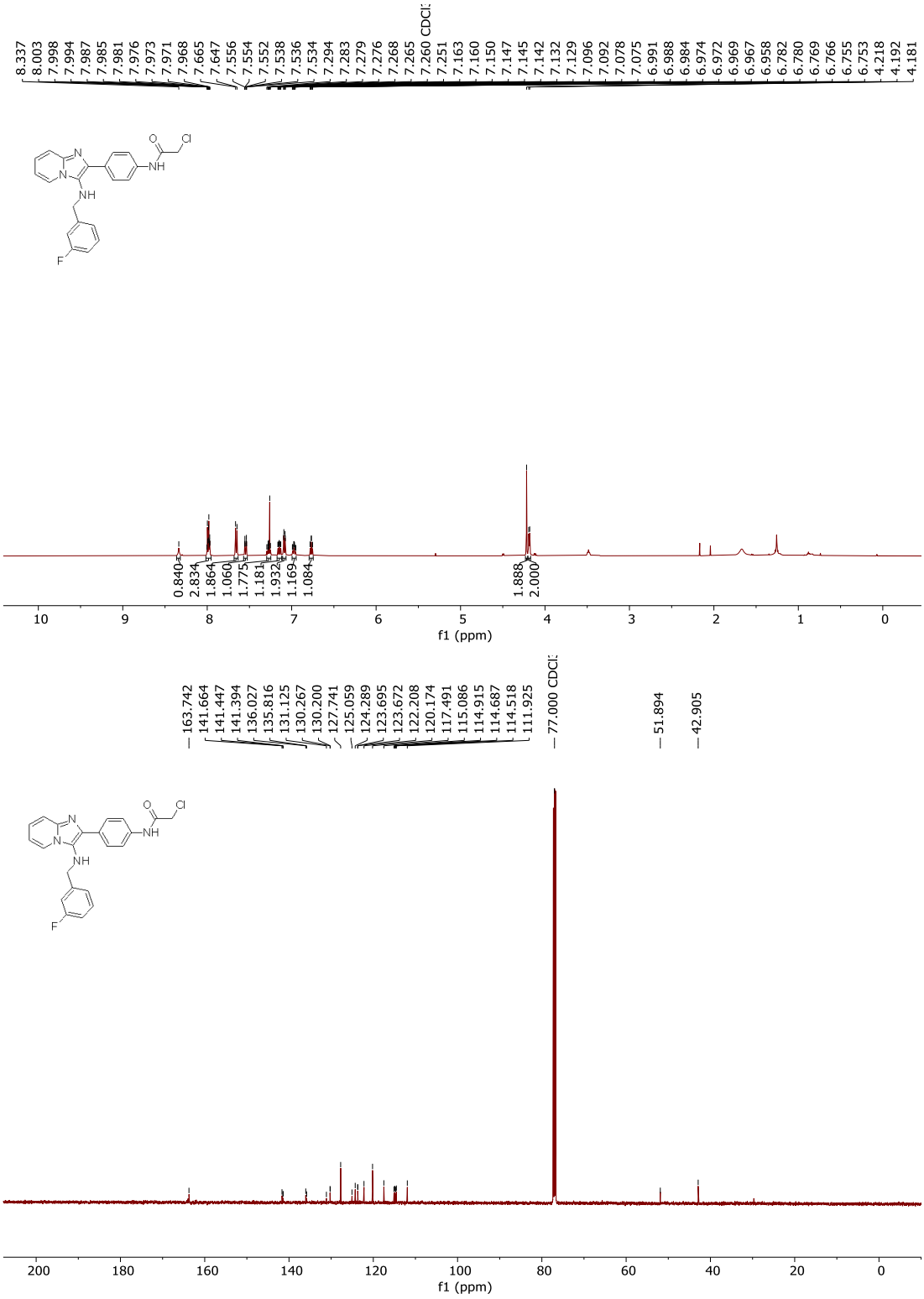




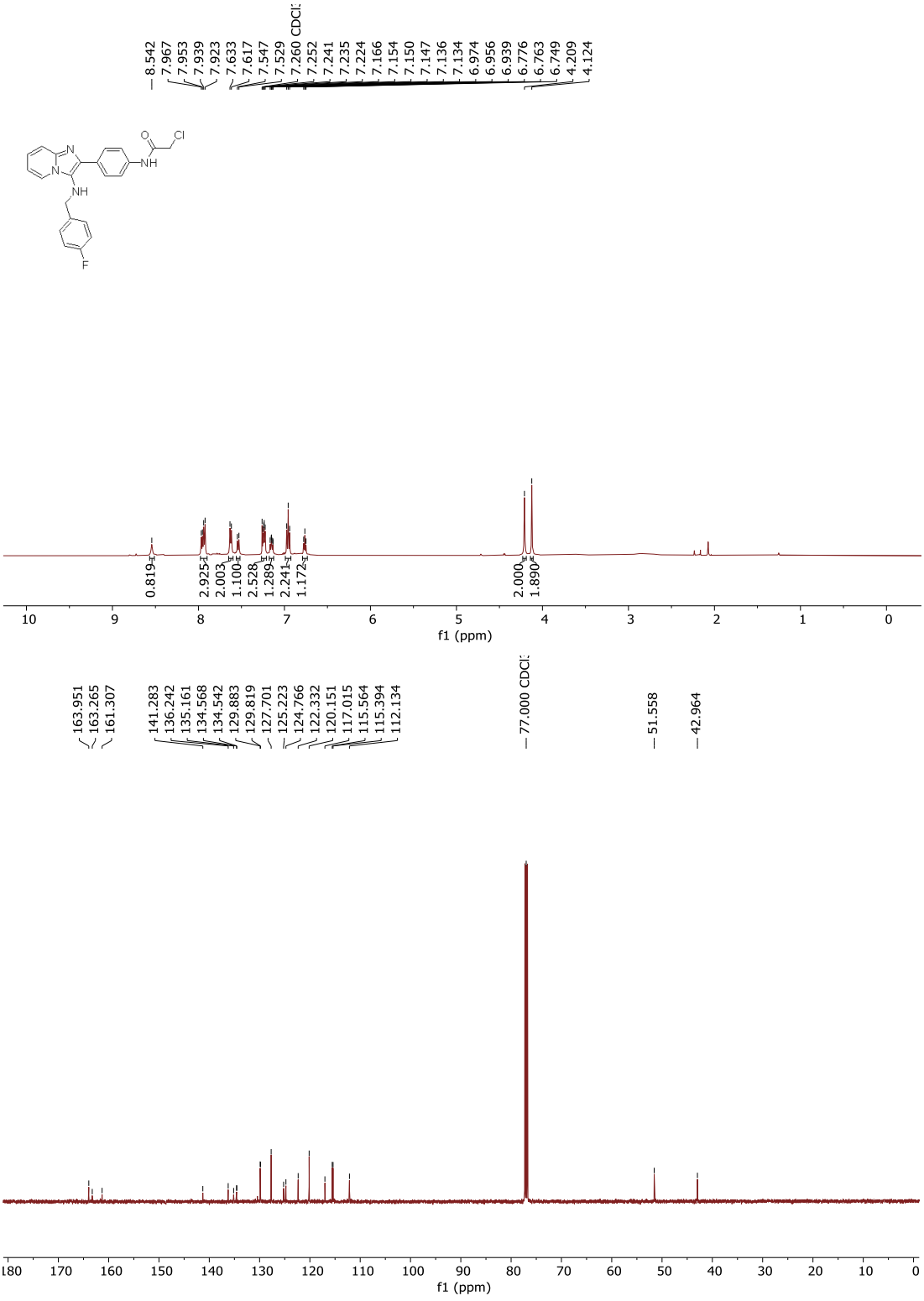
2-chloro-*N*-(4-(3-((2-fluorobenzyl)amino)imidazo[1,2-a]pyridin-2-yl)phenyl)acetamide (2) 1083860



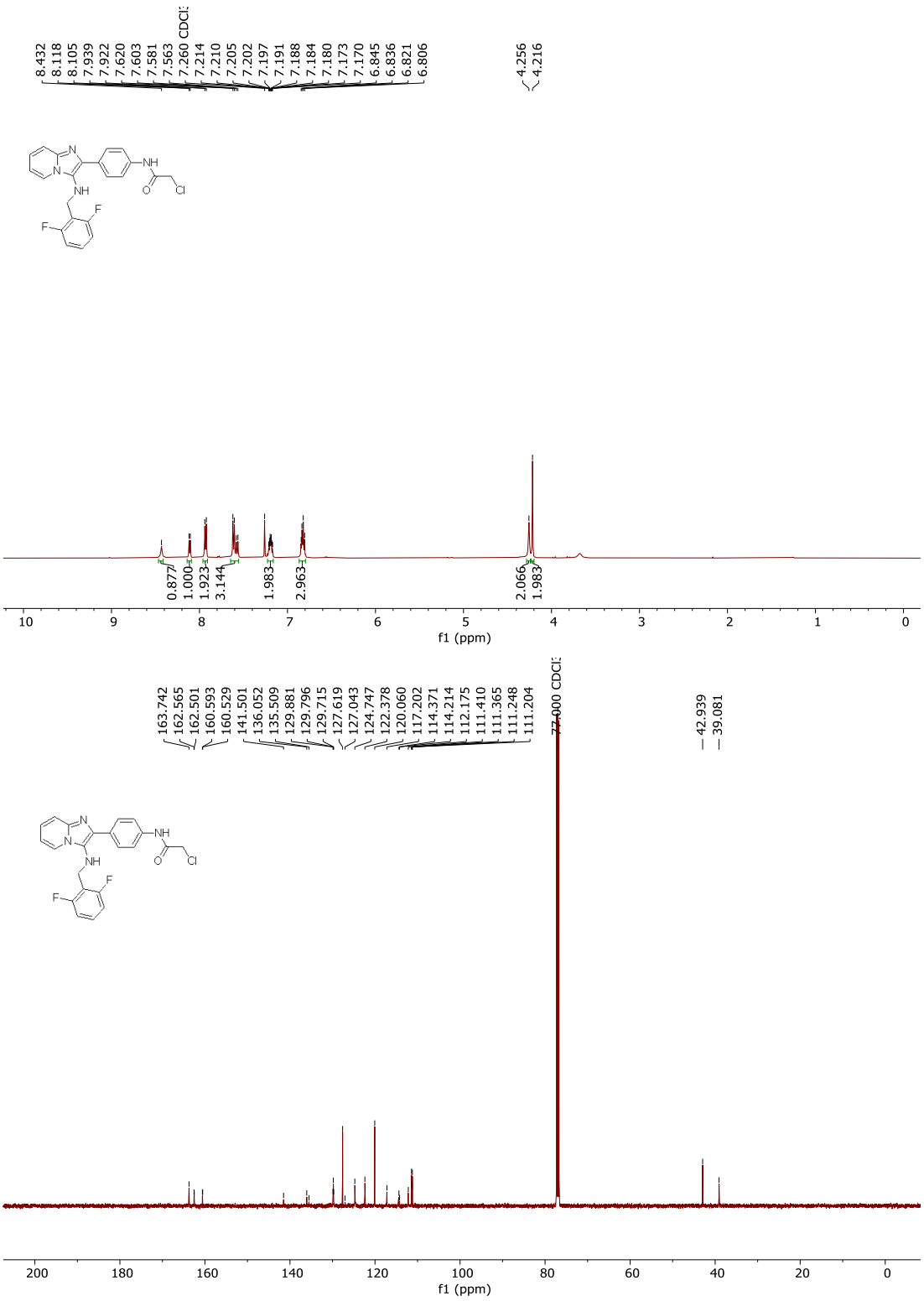
2-chloro-*N*-(4-(3-((3-fluorobenzyl)amino)imidazo[1,2-a]pyridin-2-yl)phenyl)acetamide (3) 1083861



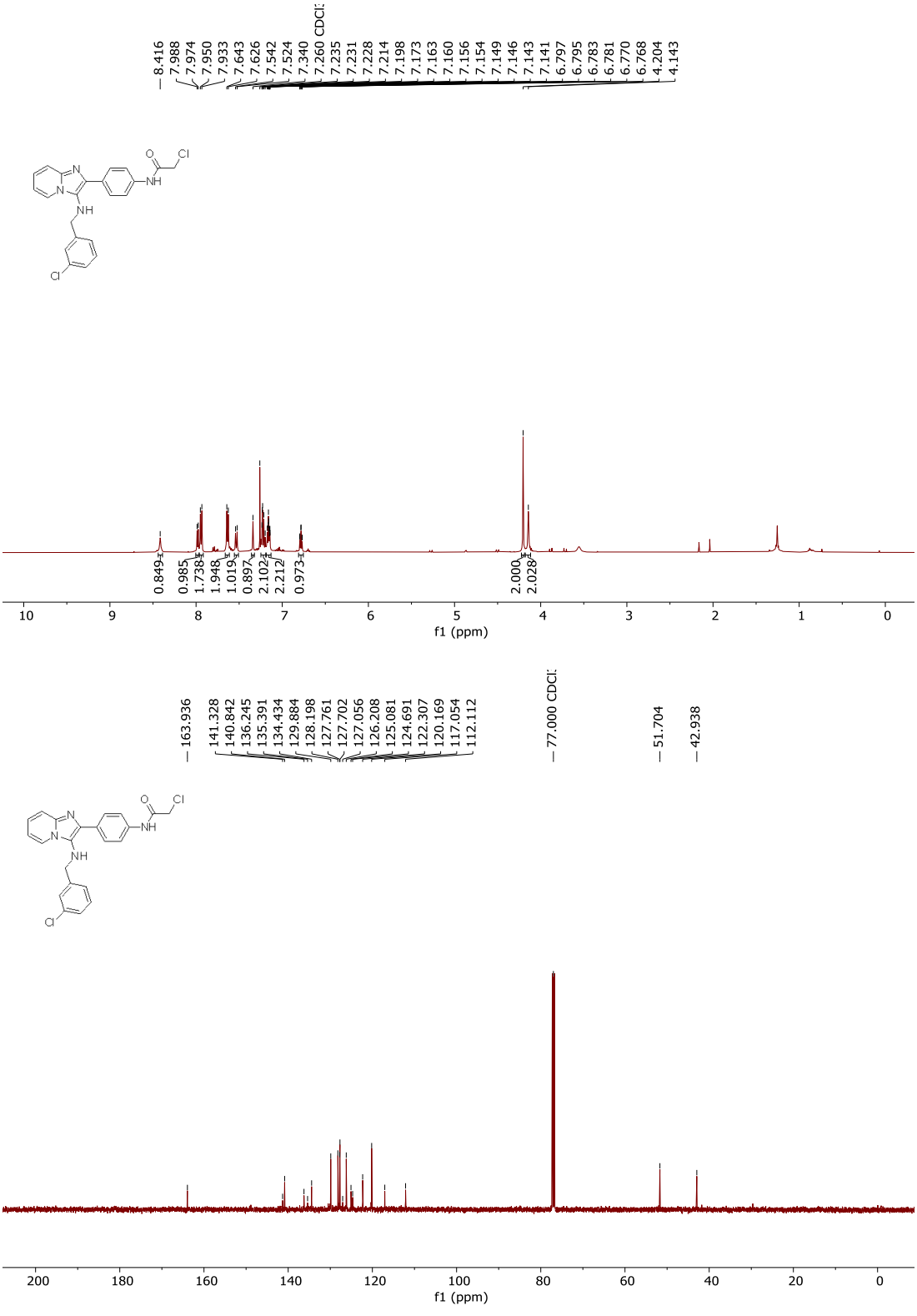
2-chloro-*N*-(4-(3-((4-fluorobenzyl)amino)imidazo[1,2-a]pyridin-2-yl)phenyl)acetamide (4) 1083857



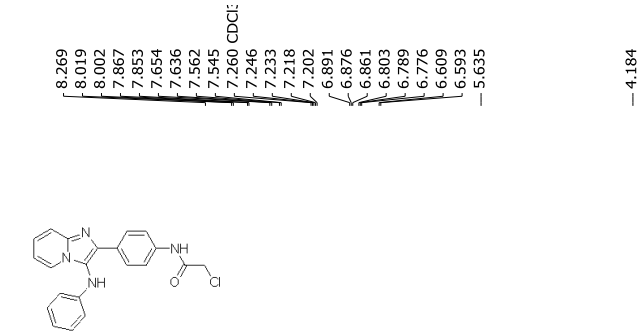
2-chloro-*N*-(4-(3-((2,6-difluorobenzyl)amino)imidazo[1,2-a]pyridin-2-yl)phenyl)acetamide (5) 1084657

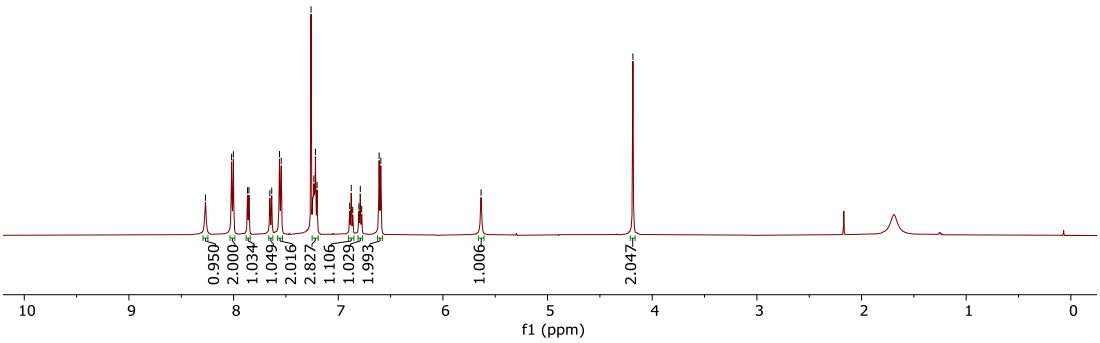


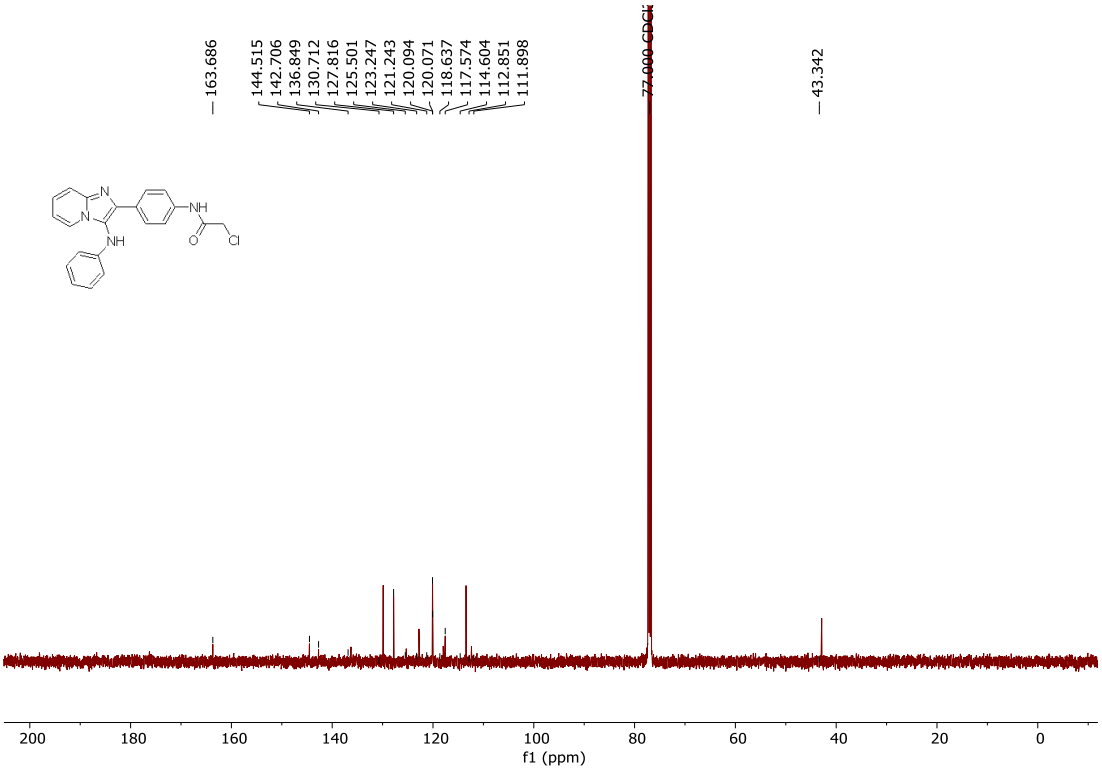
2-chloro-N-(4-(3-((3-chlorobenzyl)amino)imidazo[1,2-a]pyridin-2-yl)phenyl)acetamide (7) 1083859



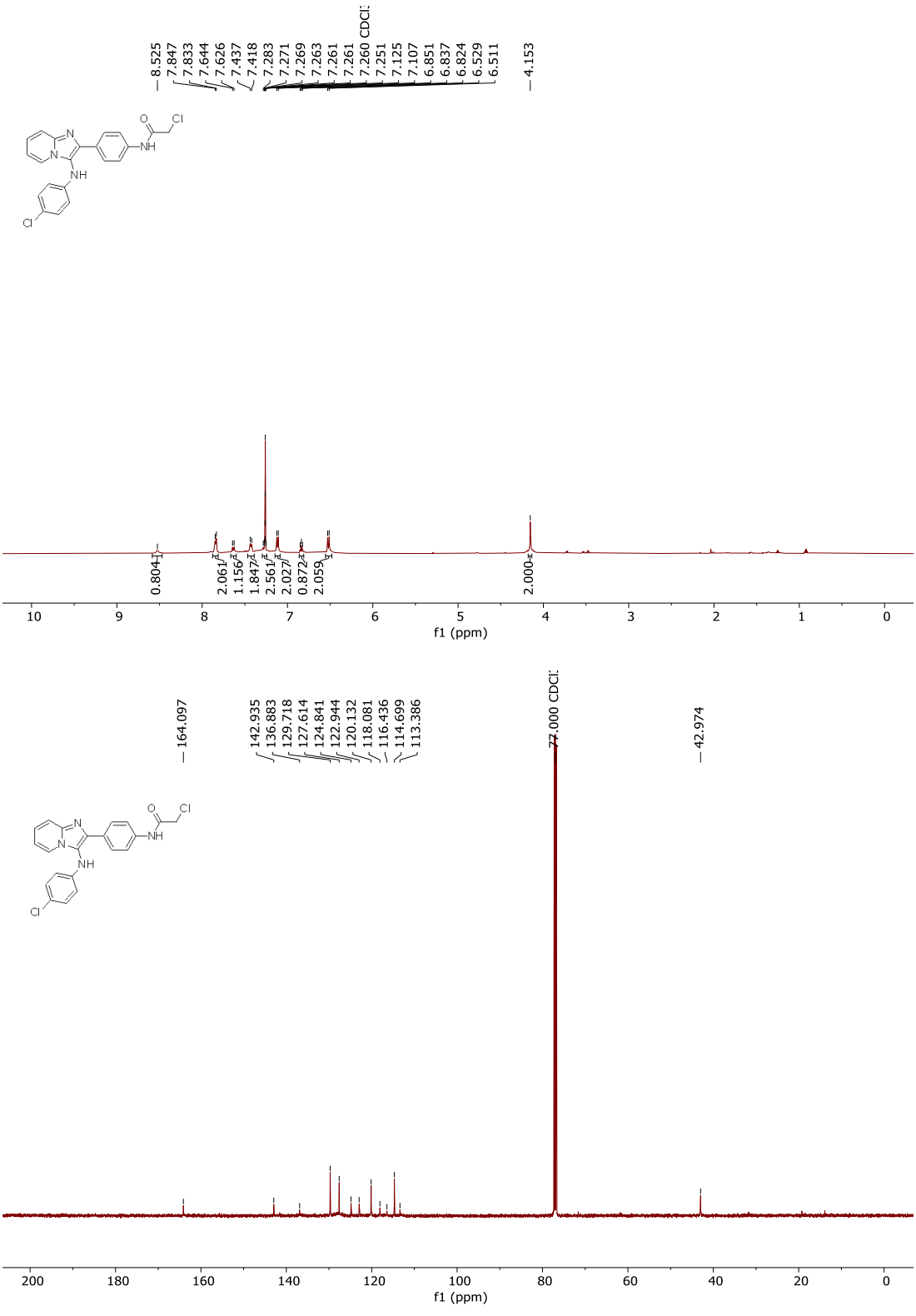
2-chloro-*N*-(4-(3-(phenylamino)imidazo[1,2-a]pyridin-2-yl)phenyl)acetamide (10) 1124905



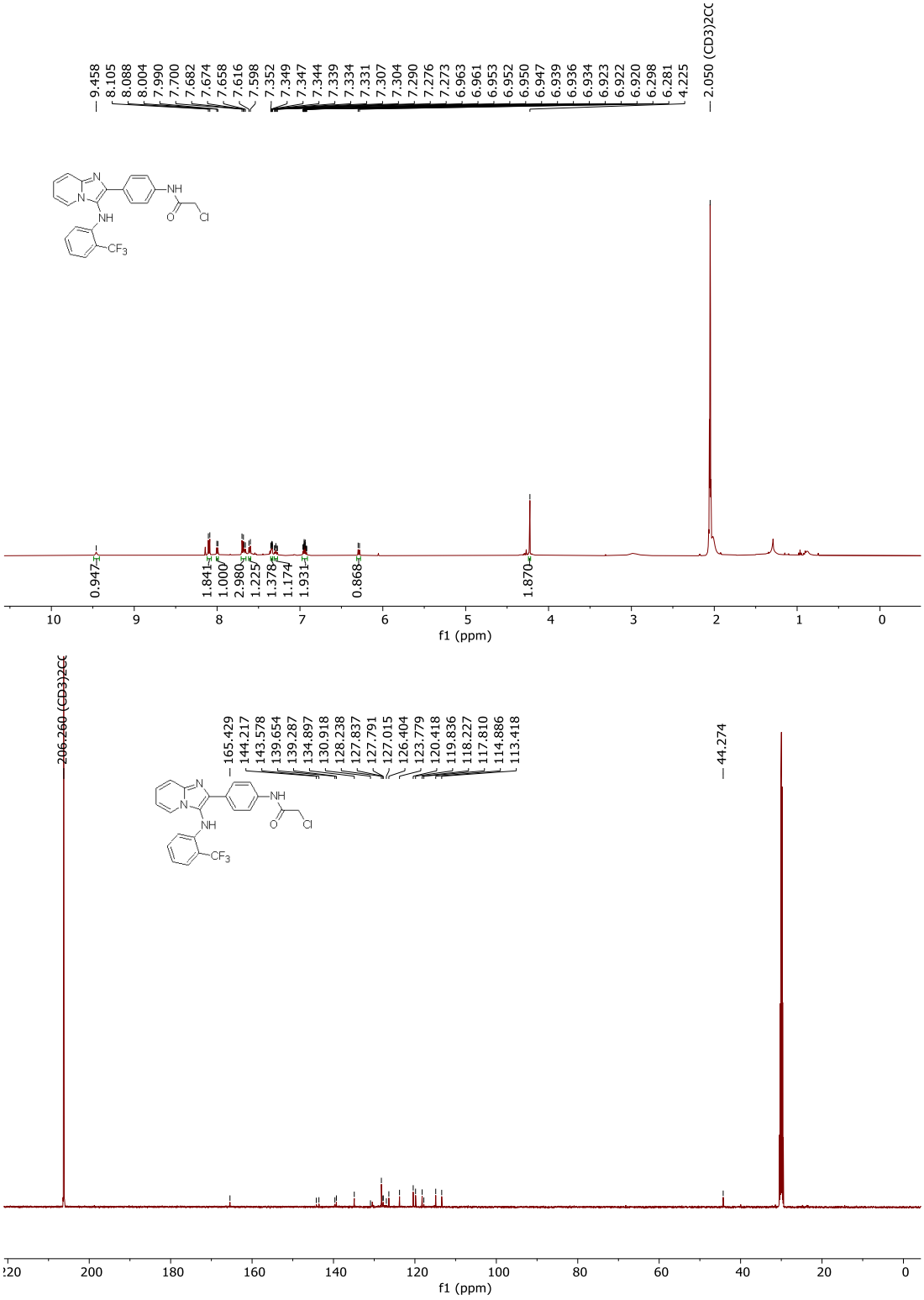




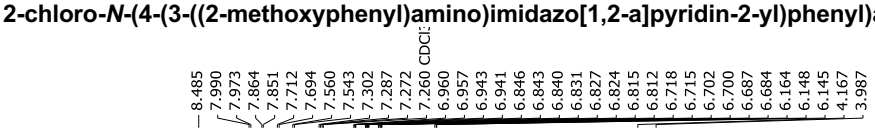
2-chloro-N-(4-(3-((4-chlorophenyl)amino)imidazo[1,2-a]pyridin-2-yl)phenyl)acetamide (11) 1083865

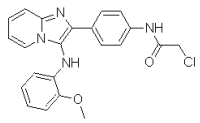


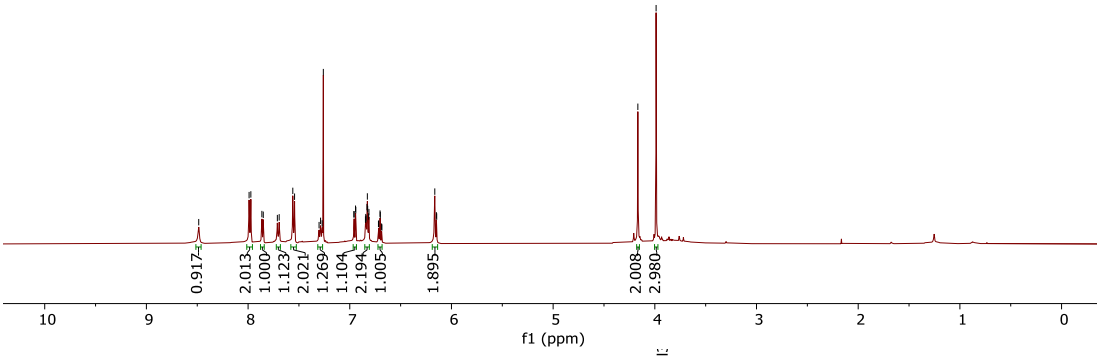
2-chloro-*N*-(4-(3-((2-(trifluoromethyl)phenyl)amino)imidazo[1,2-a]pyridin-2-yl)phenyl)acetamide (15) 1124900

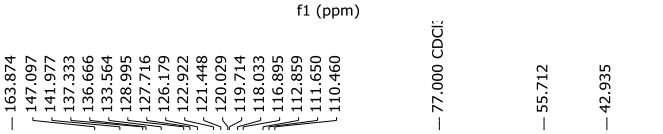


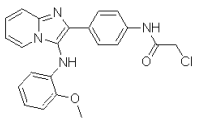
2-chloro-*N*-(4-(3-((2-methoxyphenyl)amino)imidazo[1,2-a]pyridin-2-yl)phenyl)acetamide (16) 1124902



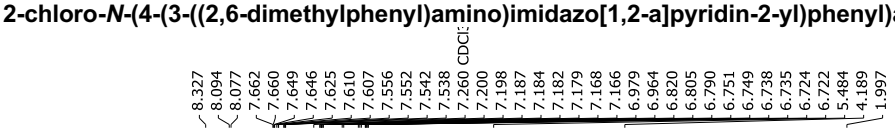


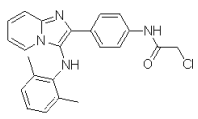


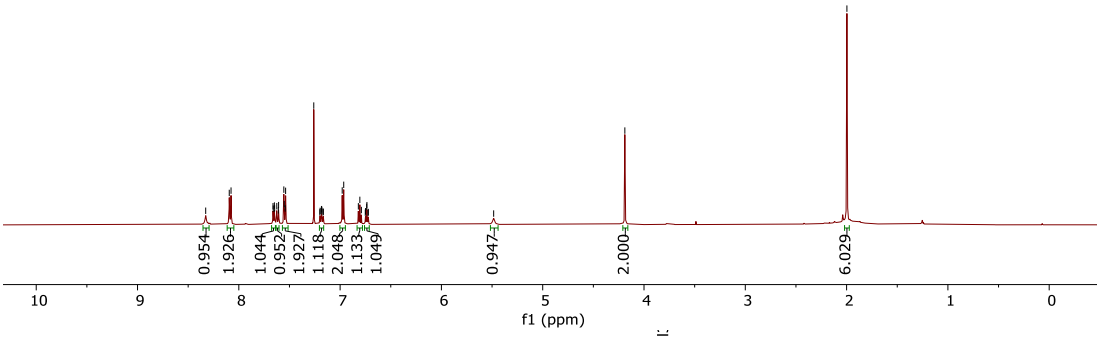


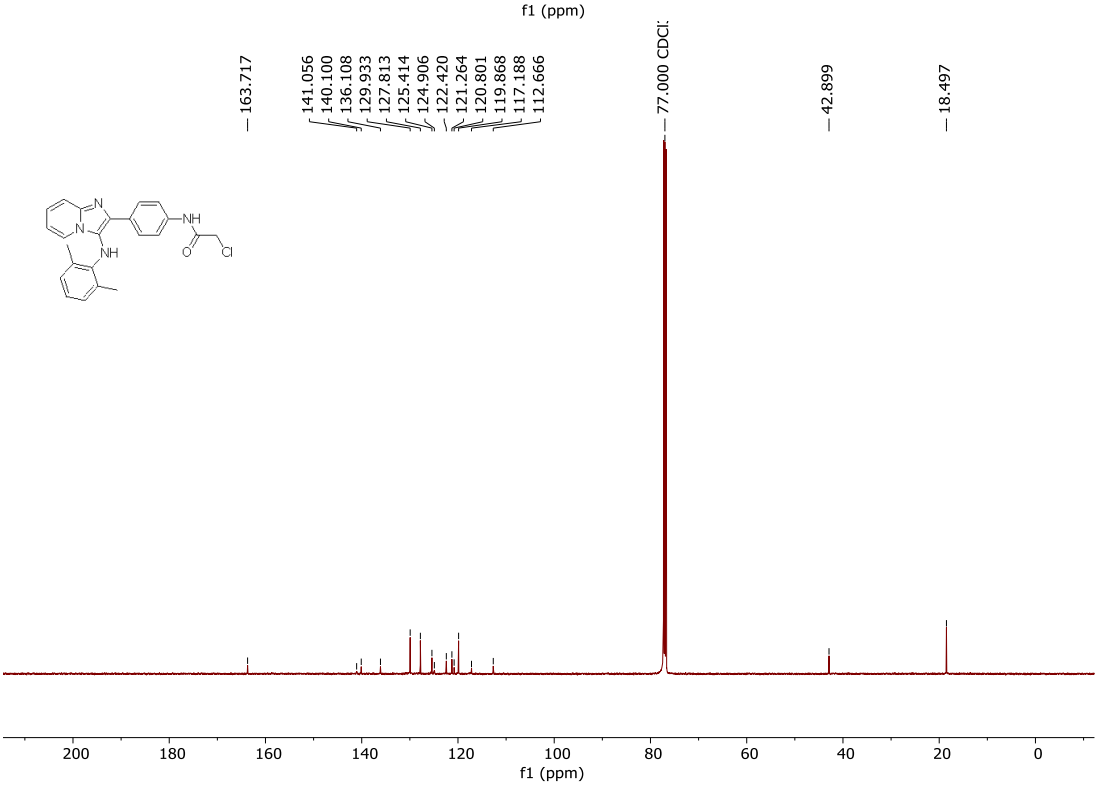


2-chloro-*N*-(4-(3-((2,6-dimethylphenyl)amino)imidazo[1,2-a]pyridin-2-yl)phenyl)acetamide (17) 1084662









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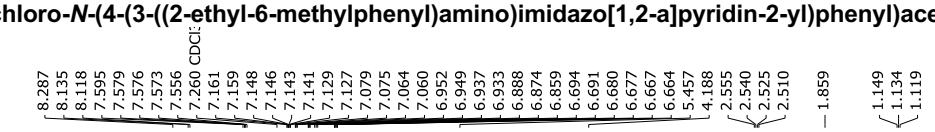

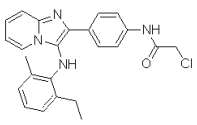

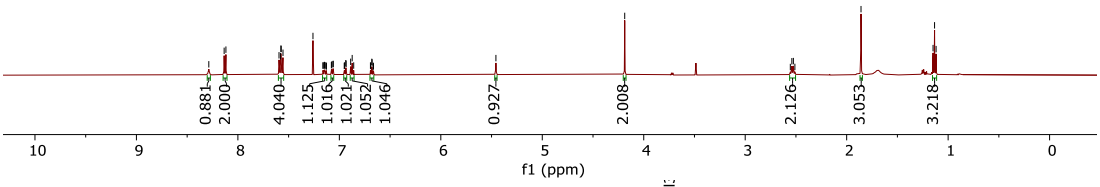

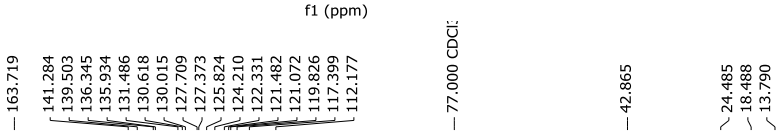

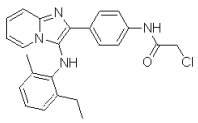

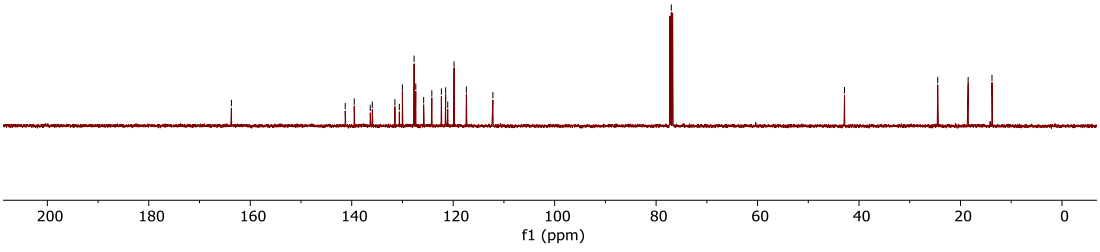

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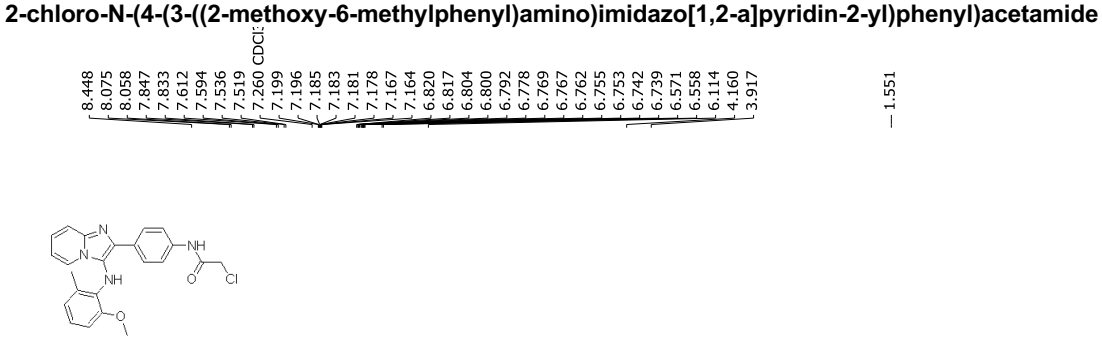
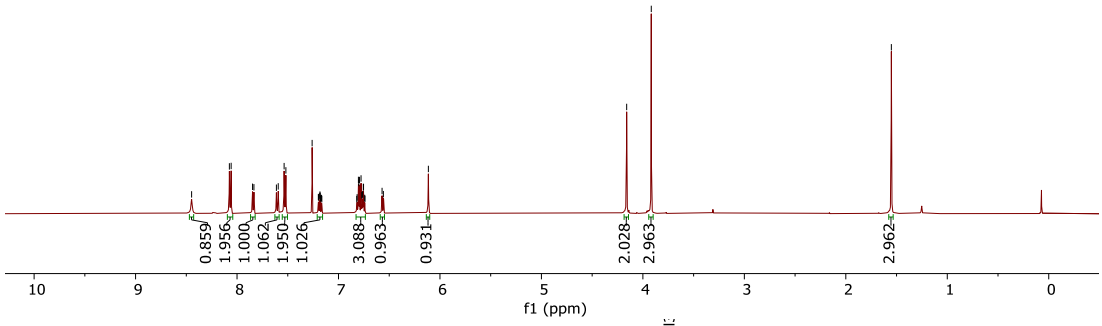
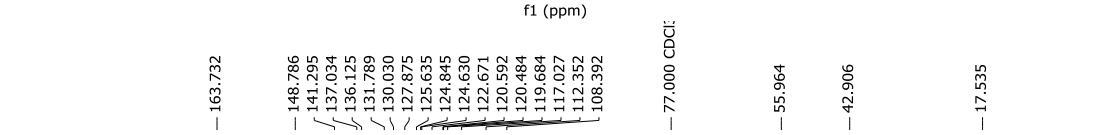
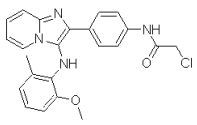
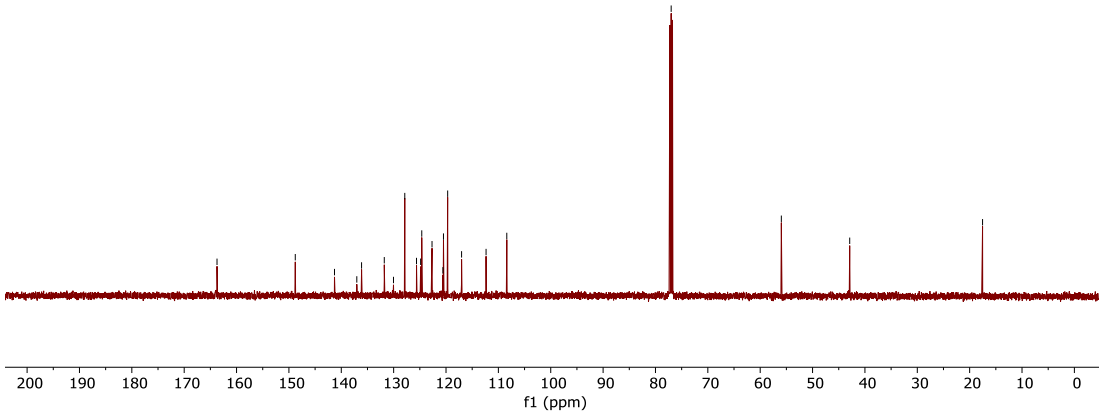


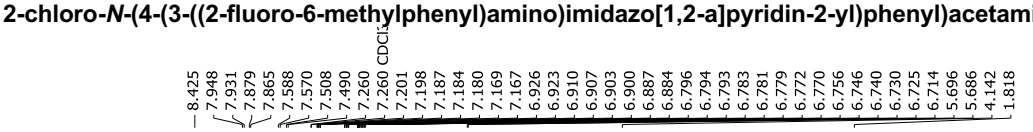


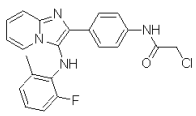


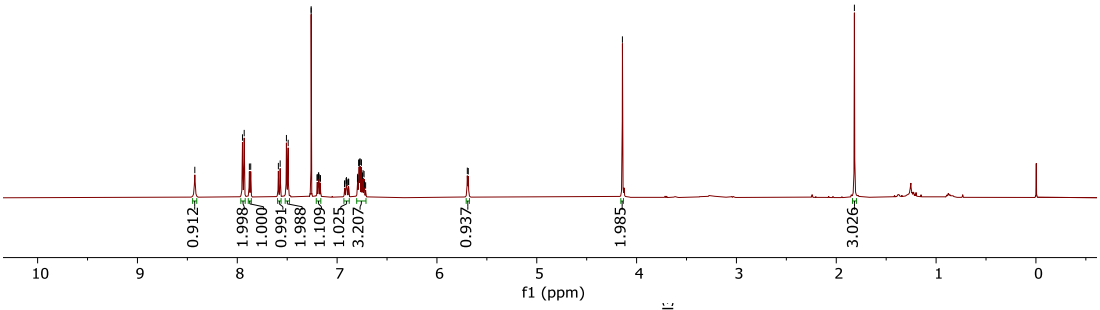


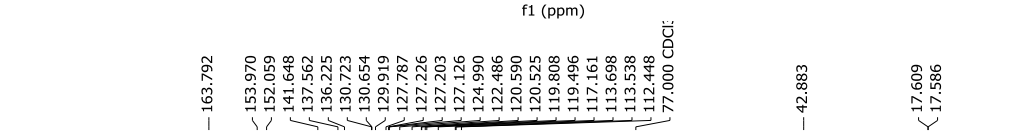


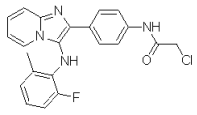
2-chloro-*N*-(4-(3-((2-fluoro-6-methylphenyl)amino)imidazo[1,2-a]pyridin-2-yl)phenyl)acetamide (20) 1124906

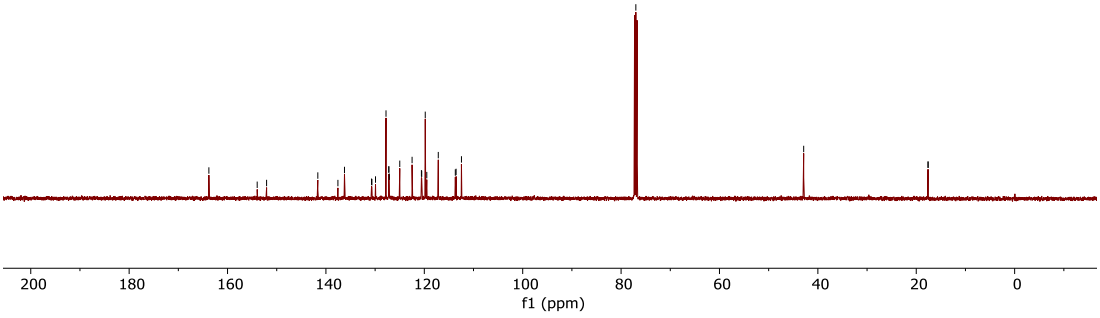




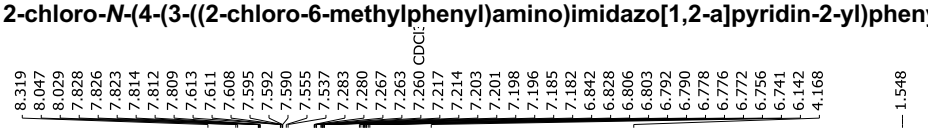


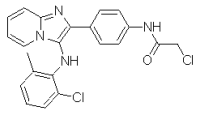


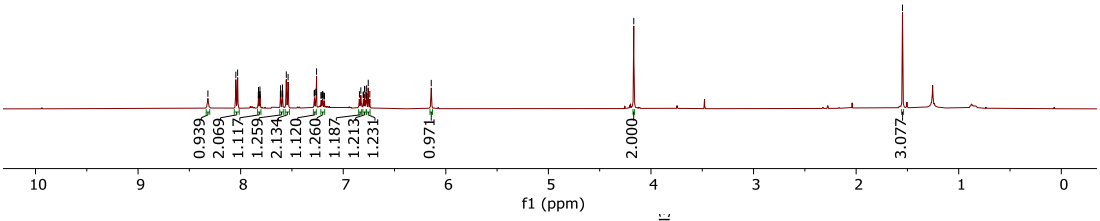


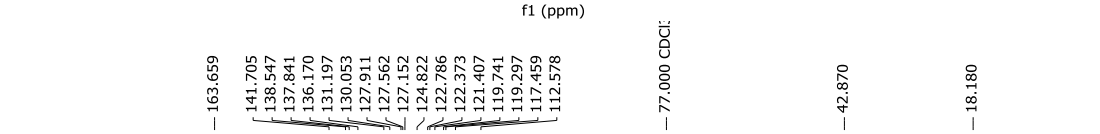


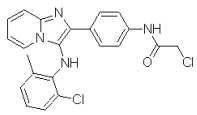
2-chloro-*N*-(4-(3-((2-chloro-6-methylphenyl)amino)imidazo[1,2-a]pyridin-2-yl)phenyl)acetamide (21) 1124907



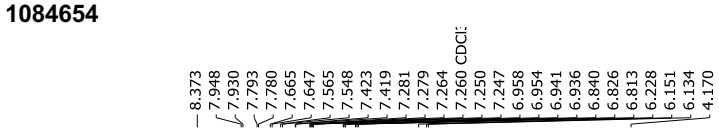


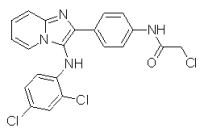


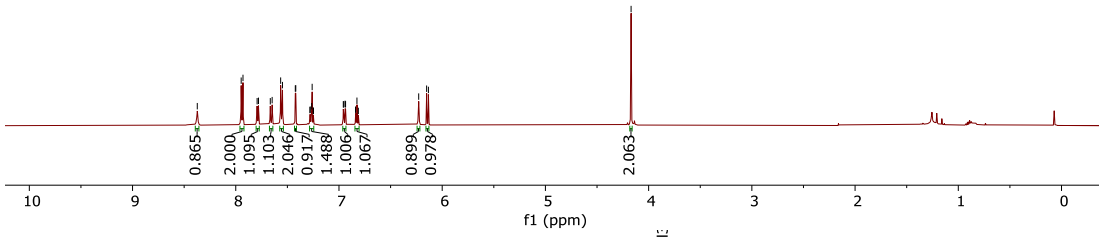


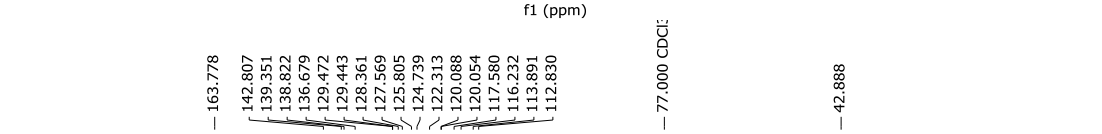


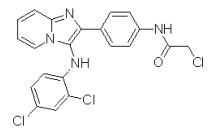
2-chloro-*N*-(4-(3-((2,4-dichlorocyclohexa-2,4-dien-1-yl)amino)imidazo[1,2-a]pyridin-2-yl)phenyl)acetamide (22)
1084654



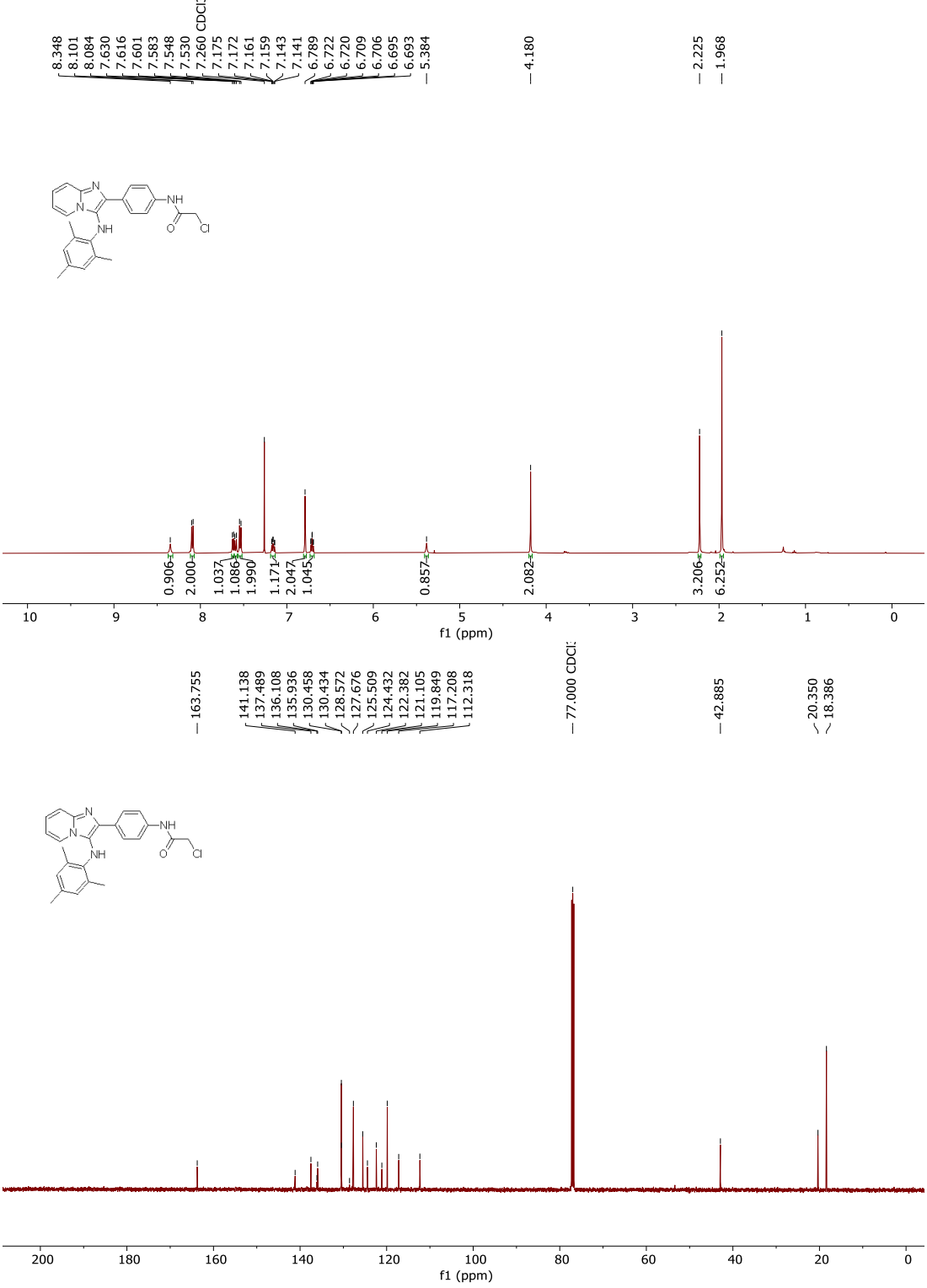




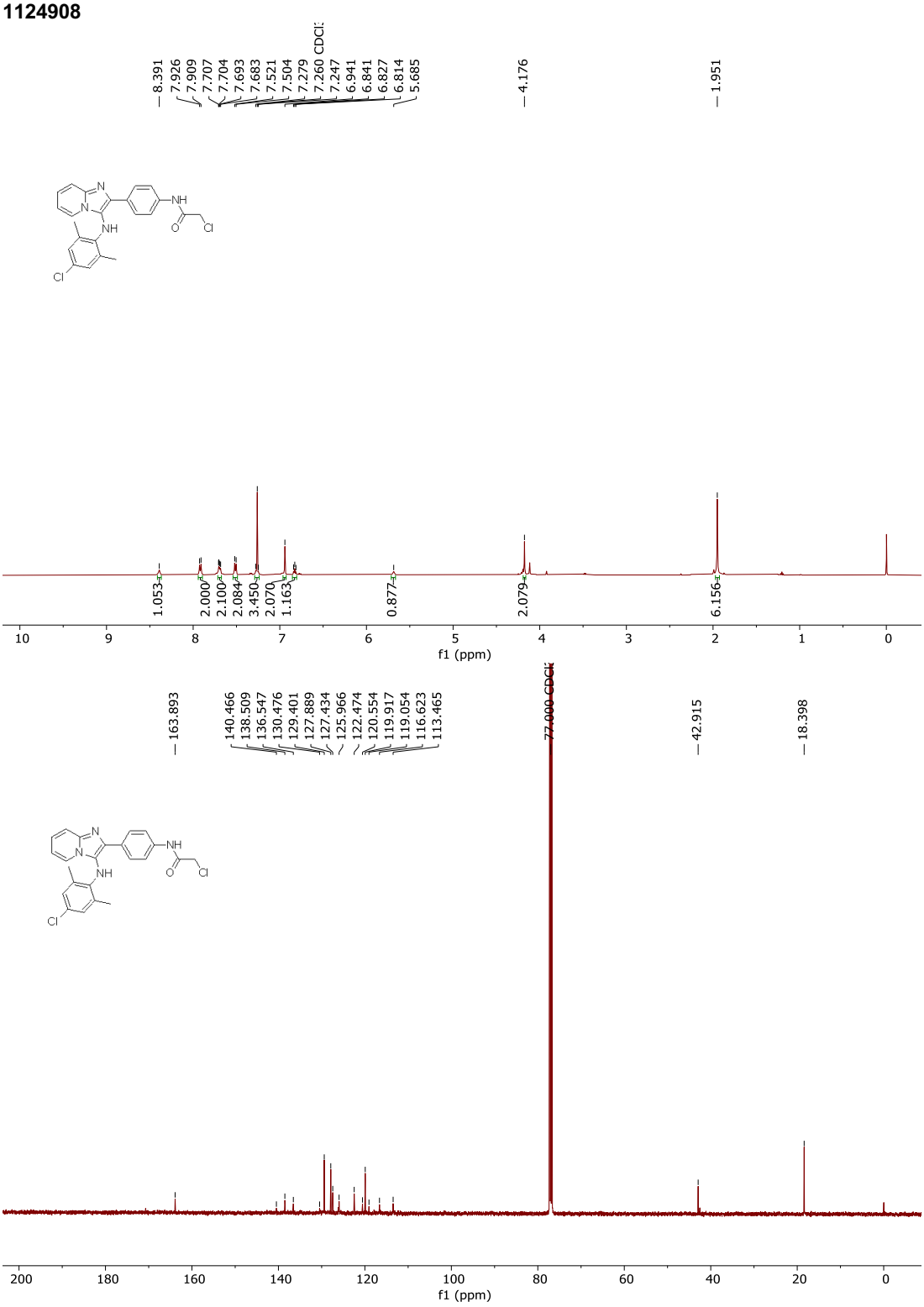




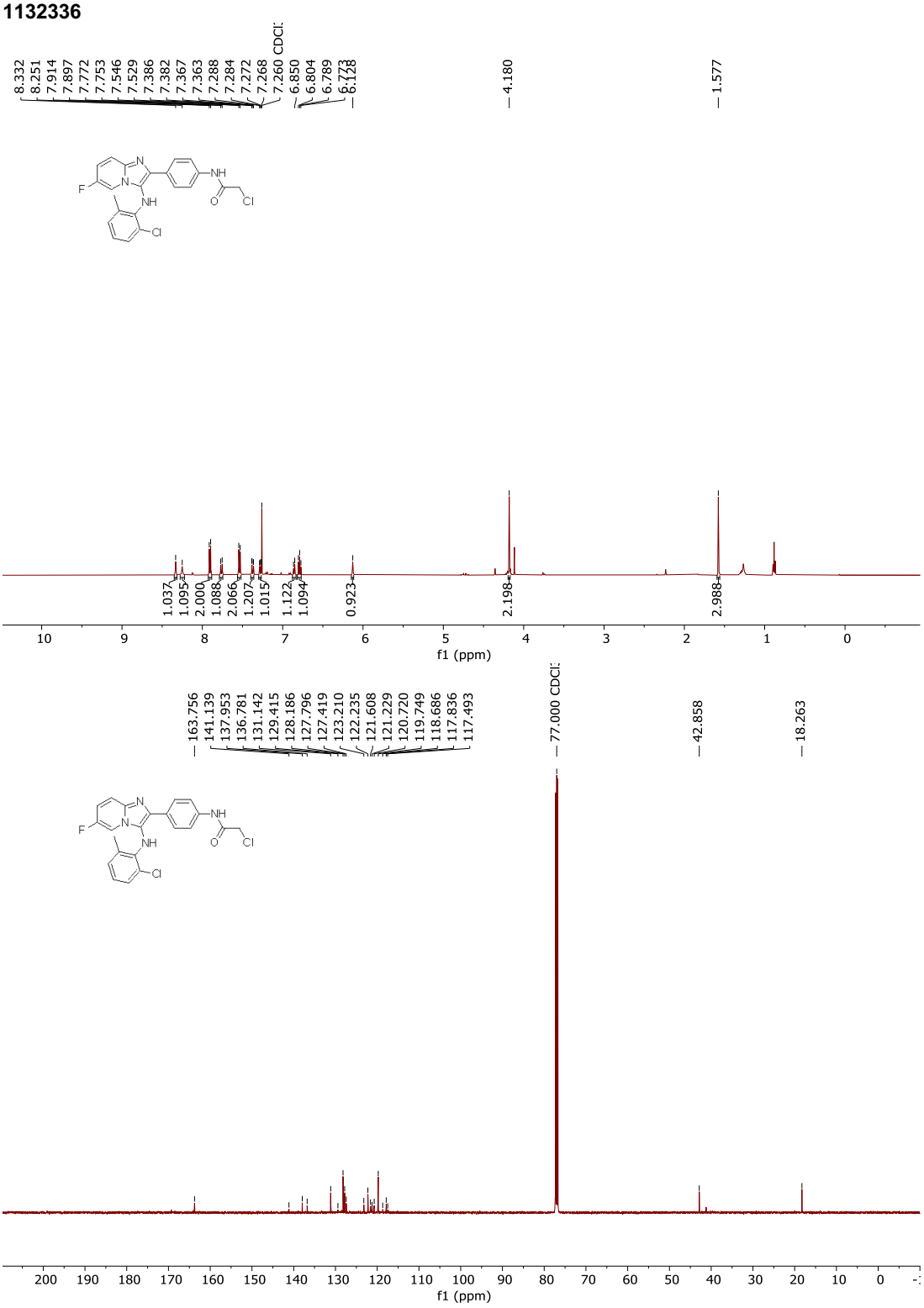
2-chloro-N-(4-(3-(mesitylamino)imidazo[1,2-a]pyridin-2-yl)phenyl)acetamide (23) 1124903



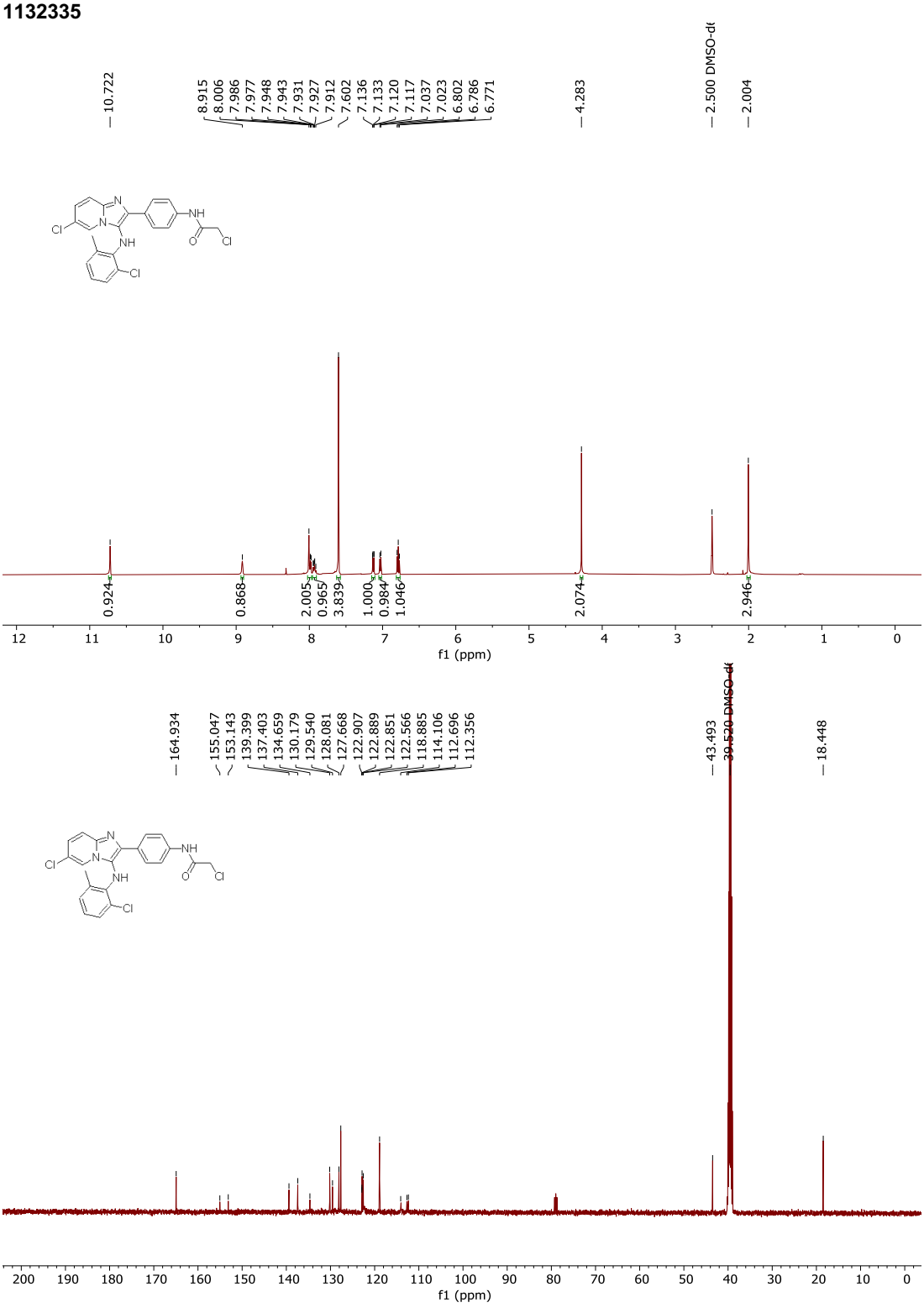
2-chloro-*N*-(4-(3-((4-chloro-2,6-dimethylphenyl)amino)imidazo[1,2-a]pyridin-2-yl)phenyl)acetamide (24)
1124908



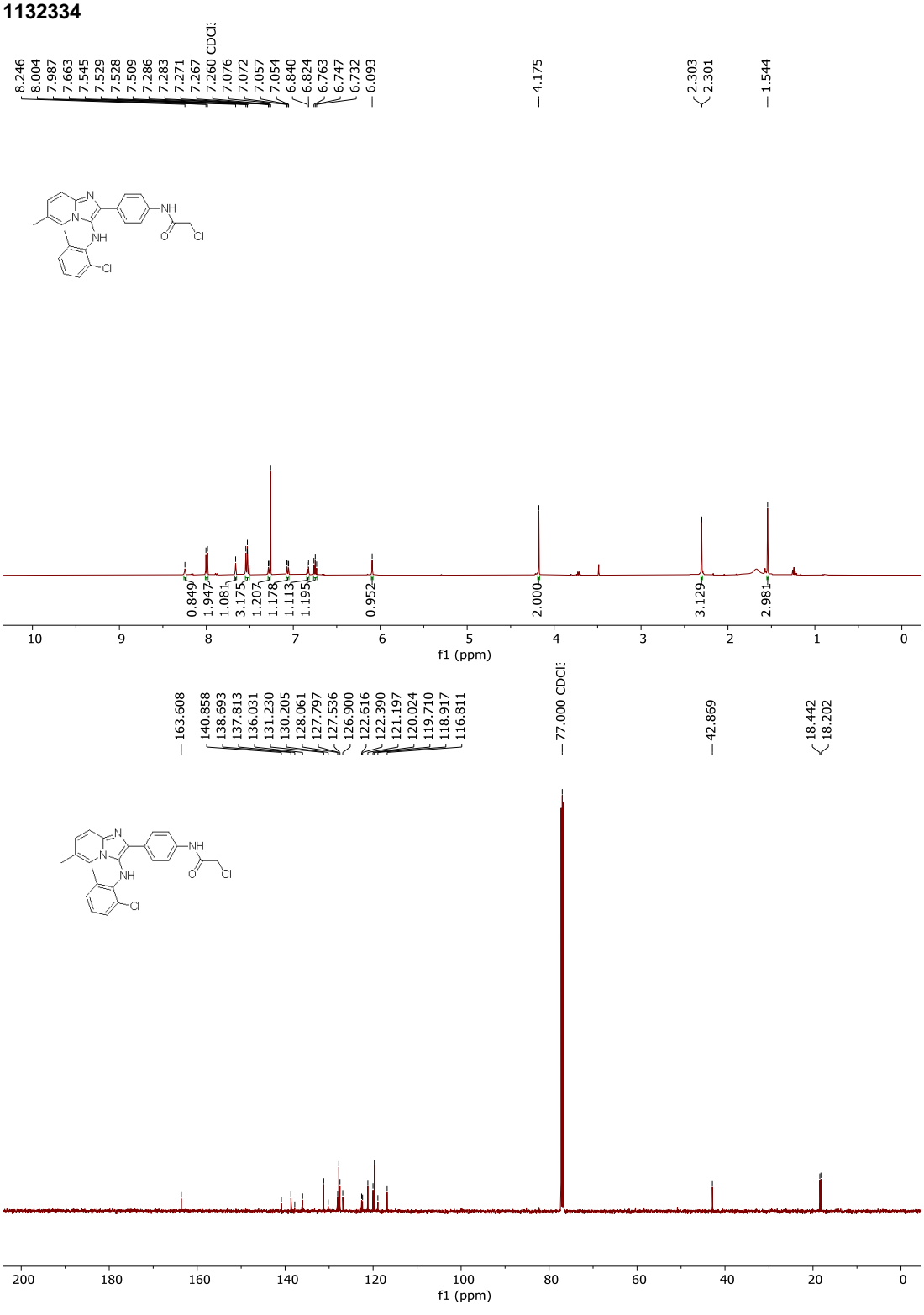
2-chloro-*N*-(4-(3-((2-chloro-6-methylphenyl)amino)-6-fluoroimidazo[1,2-a]pyridin-2-yl)phenyl)acetamide (26)
1132336



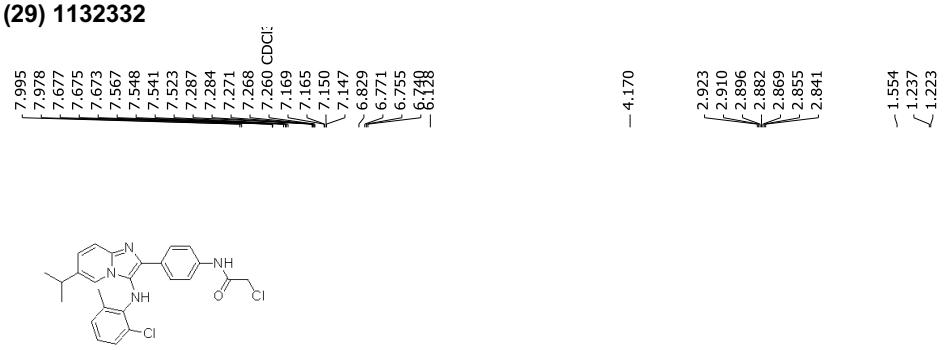
2-chloro-*N*-(4-(6-chloro-3-((2-chloro-6-methylphenyl)amino)imidazo[1,2-a]pyridin-2-yl)phenyl)acetamide (27)
1132335

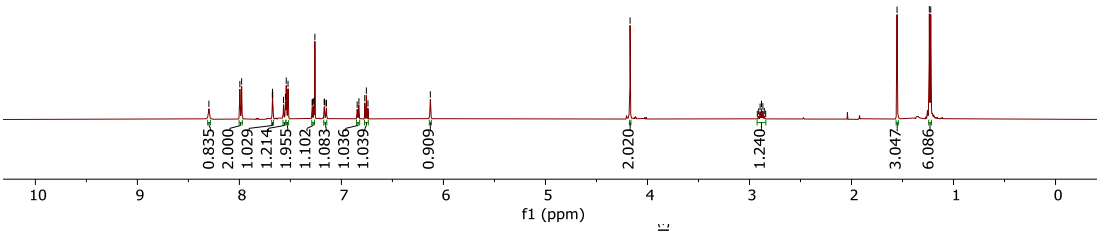


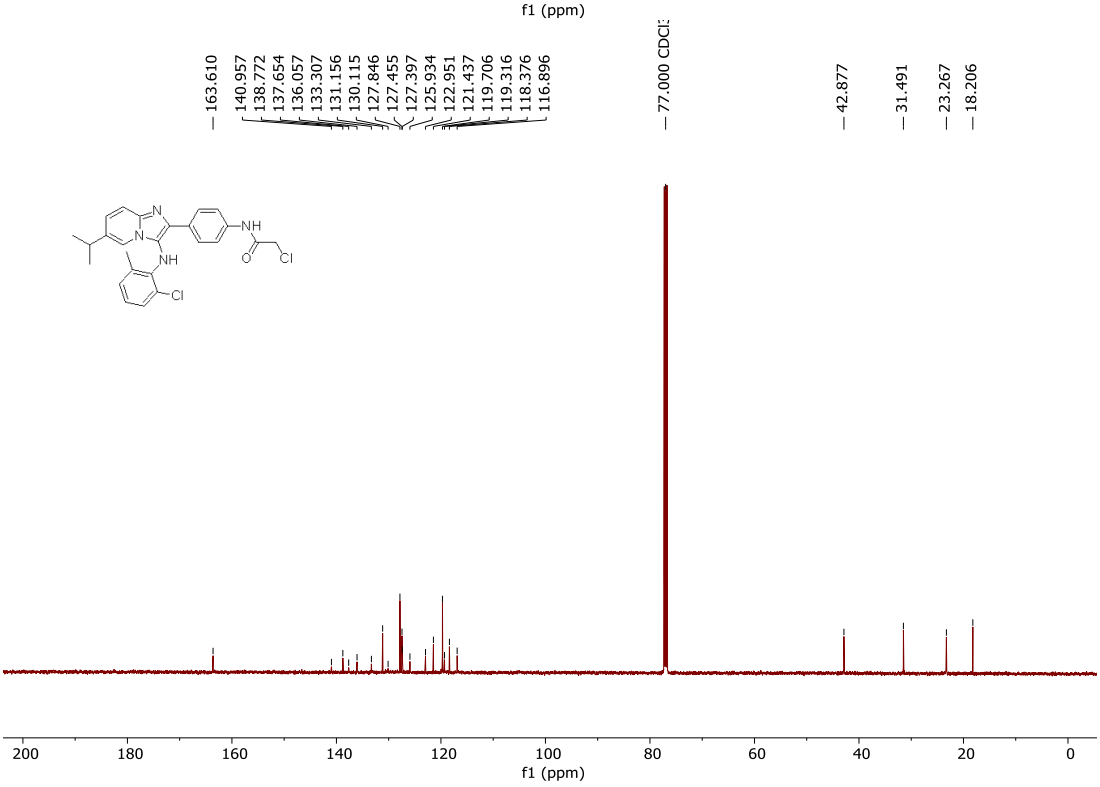
2-chloro-N-(4-(3-((2-chloro-6-methylphenyl)amino)-6-methylimidazo[1,2-a]pyridin-2-yl)phenyl)acetamide (28)
1132334



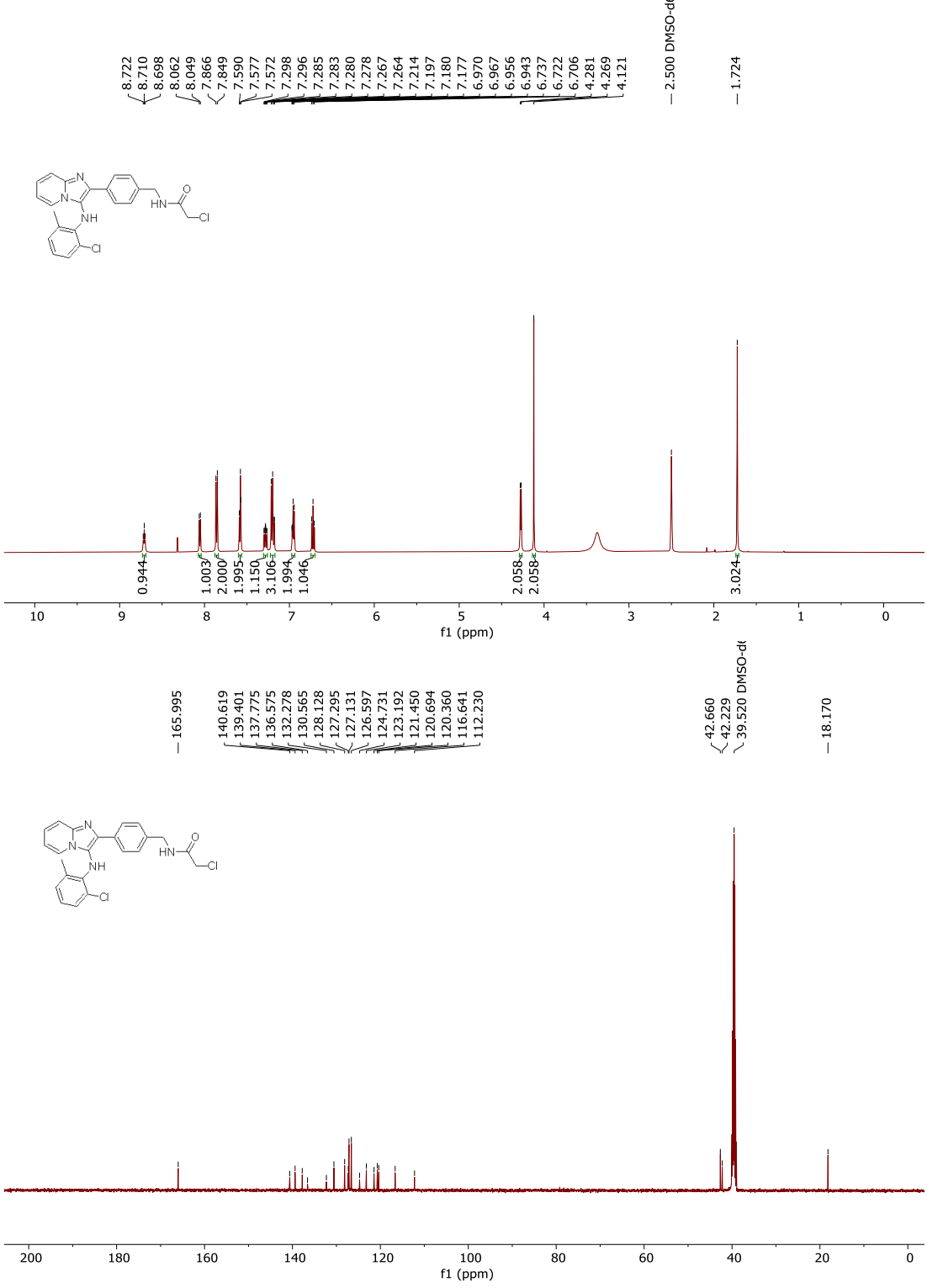
2-chloro-*N*-(4-(3-((2-chloro-6-methylphenyl)amino)-6-isopropylimidazo[1,2-a]pyridin-2-yl)phenyl)acetamide (29) 1132332



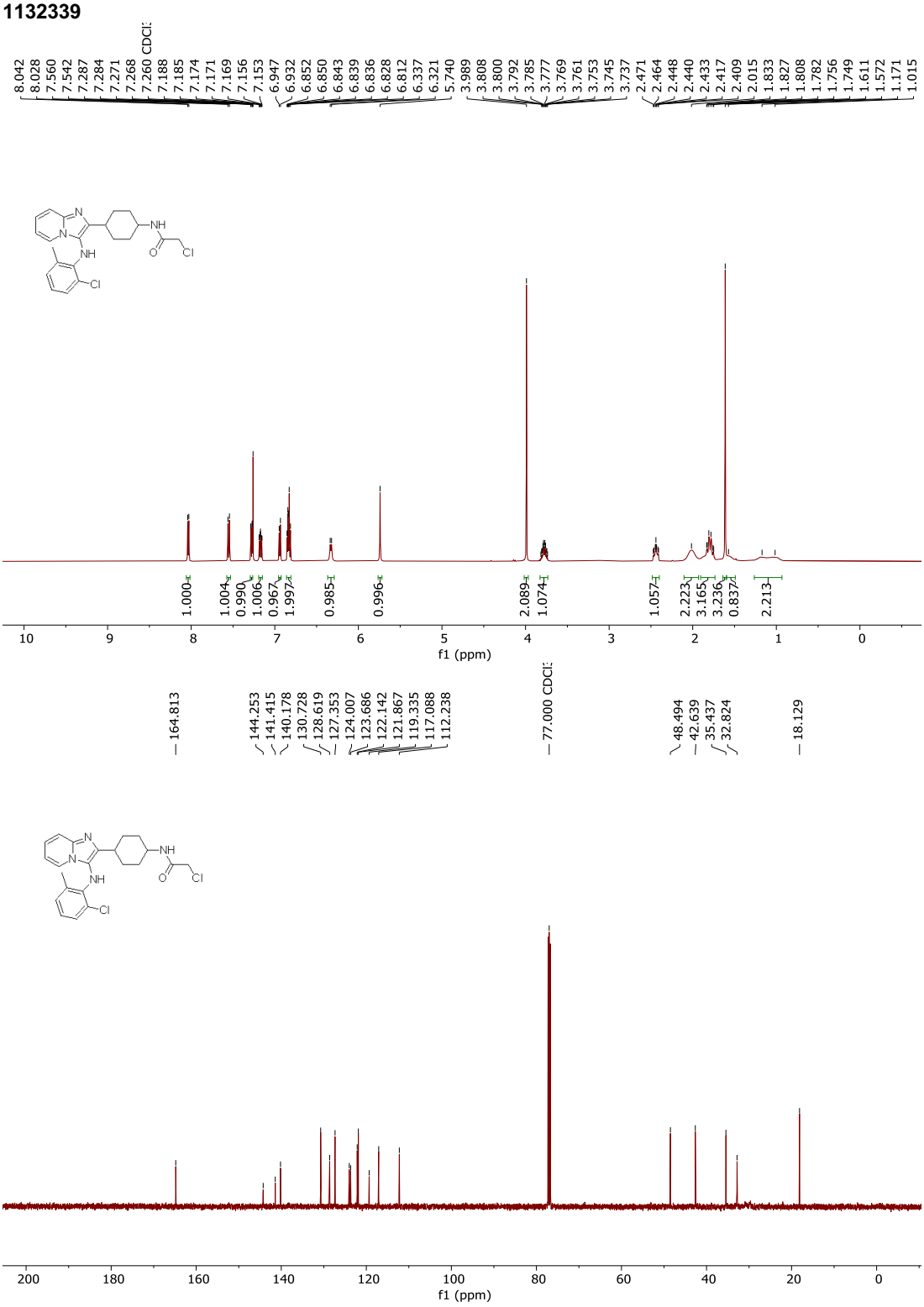




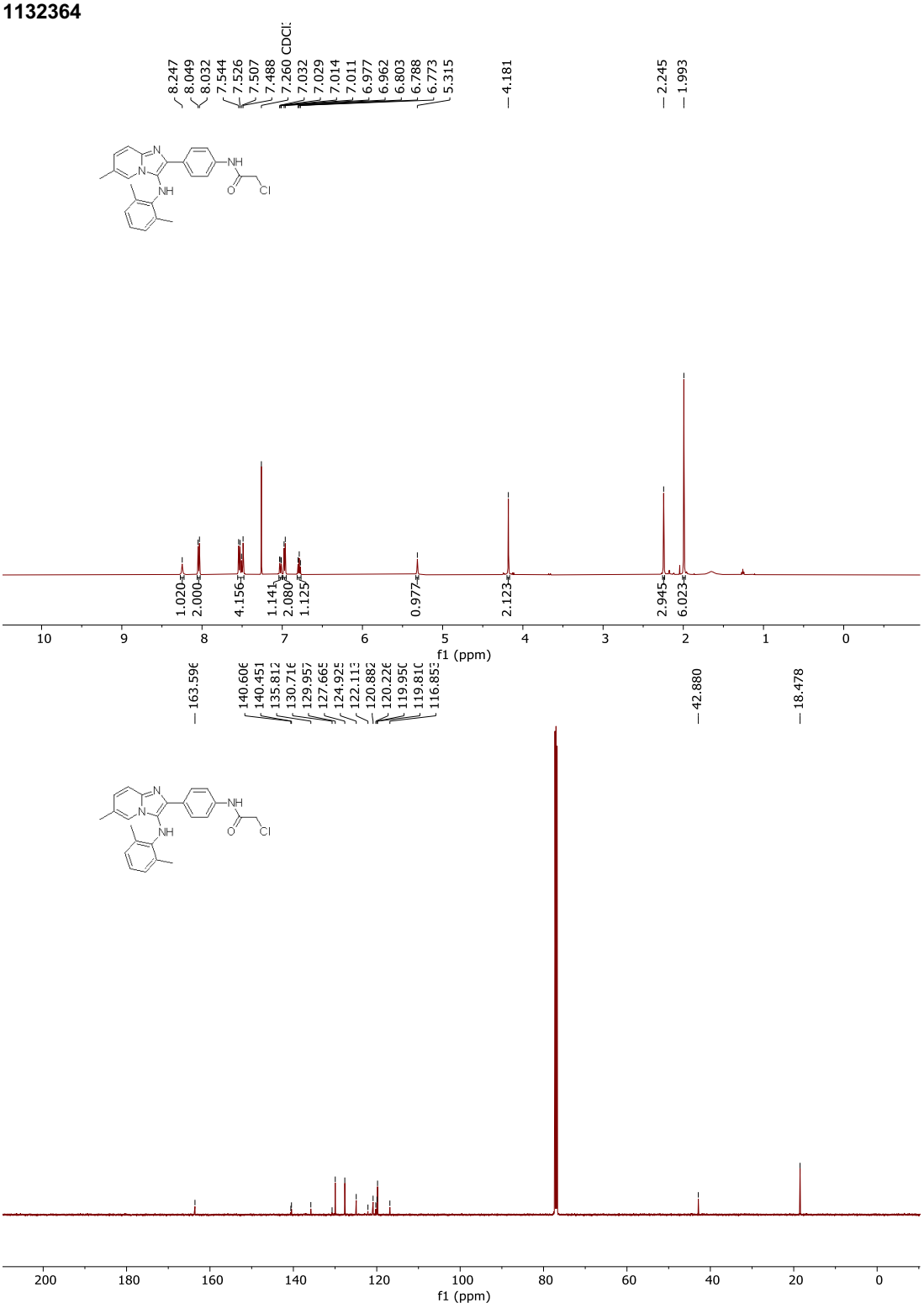
2-chloro-*N*-(4-(3-((2-chloro-6-methylphenyl)amino)imidazo[1,2-a]pyridin-2-yl)benzyl)acetamide (32) 1132338



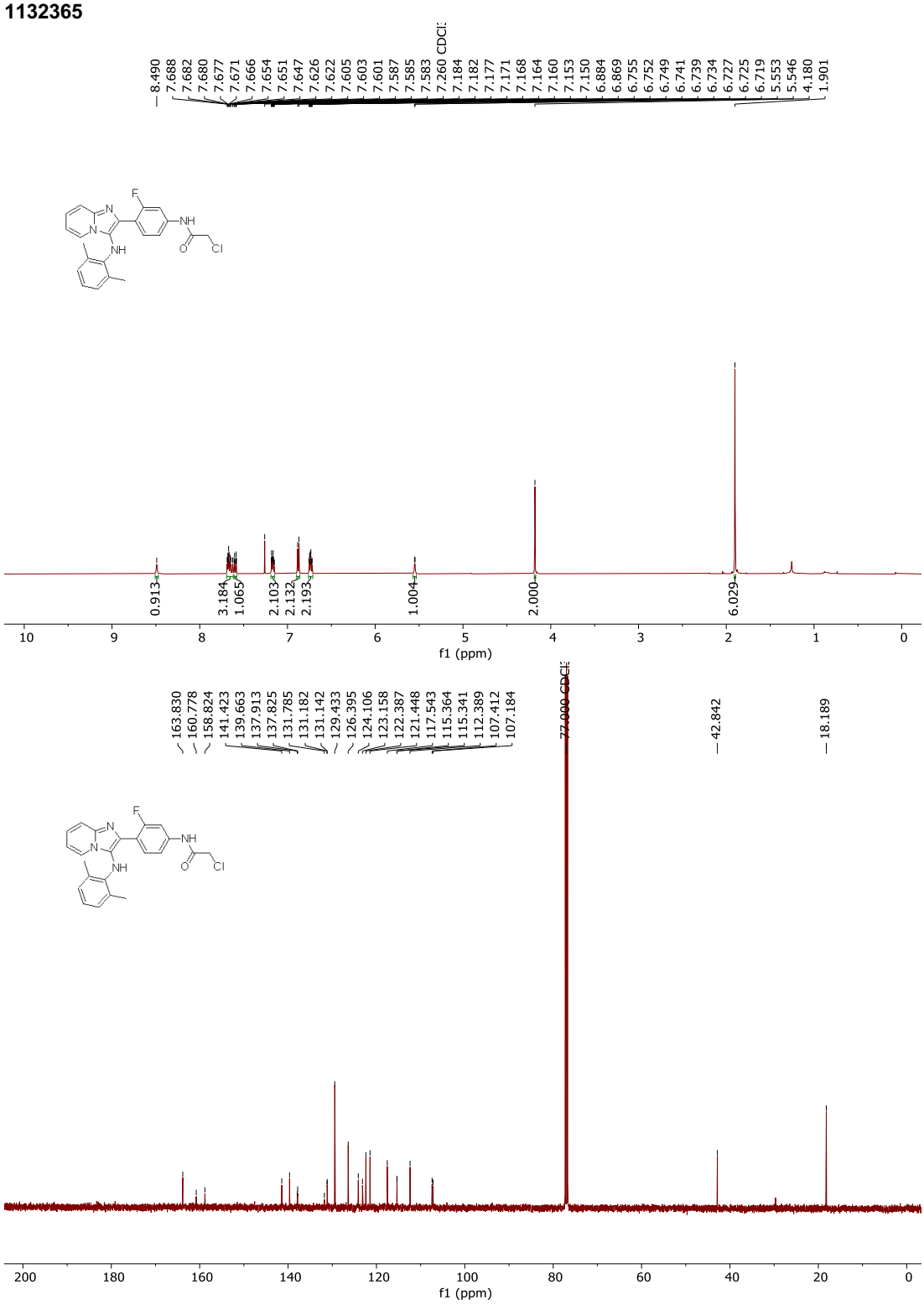
2-chloro-*N*-(4-(3-((2-chloro-6-methylphenyl)amino)imidazo[1,2-a]pyridin-2-yl)cyclohexyl)acetamide (33)
1132339



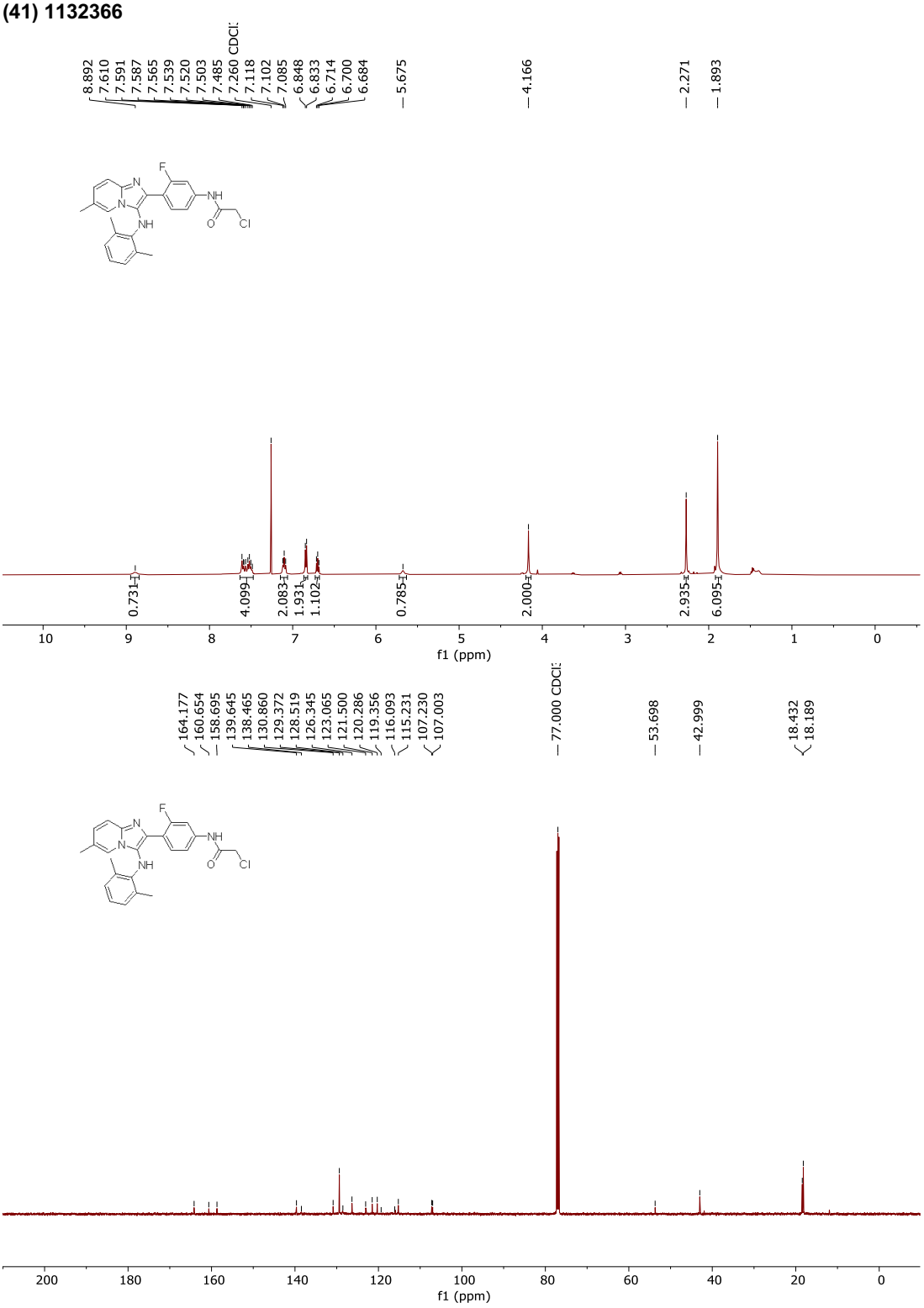
2-chloro-N-(4-(3-((2,6-dimethylphenyl)amino)-6-methylimidazo[1,2-a]pyridin-2-yl)phenyl)acetamide (39)
1132364



2-chloro-N-(4-(3-((2,6-dimethylphenyl)amino)imidazo[1,2-a]pyridin-2-yl)-3-fluorophenyl)acetamide (40)
1132365



2-chloro-N-(4-(3-((2,6-dimethylphenyl)amino)-6-methylimidazo[1,2-a]pyridin-2-yl)-3-fluorophenyl)acetamide (41) 1132366



2-chloro-N-(4-(6-chloro-3-((2,6-dimethylphenyl)amino)imidazo[1,2-a]pyridin-2-yl)-3-fluorophenyl)acetamide (42) 1132367