Supplementary Information for:

Isotope ratio encoding of sequence-defined oligomers

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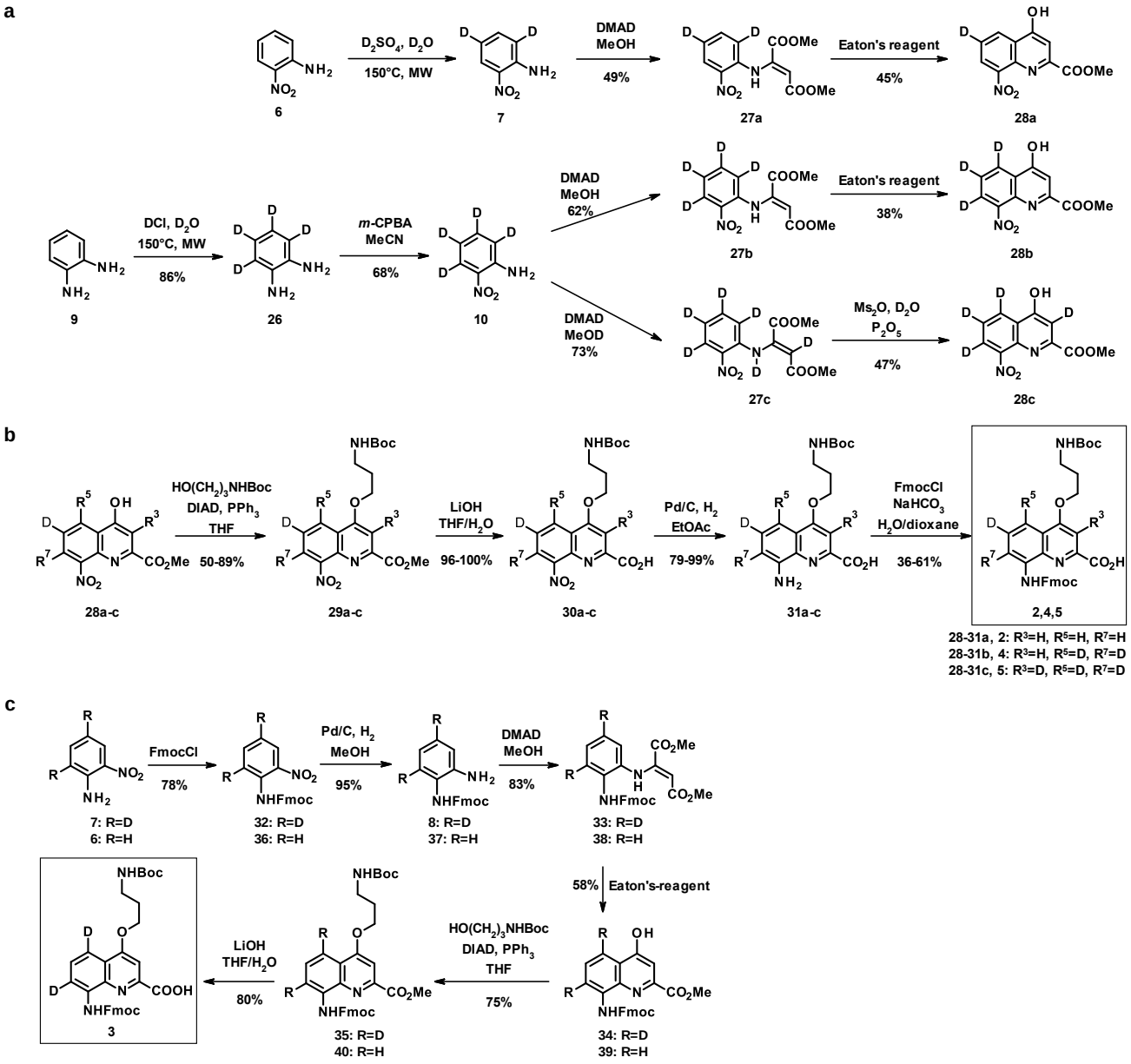
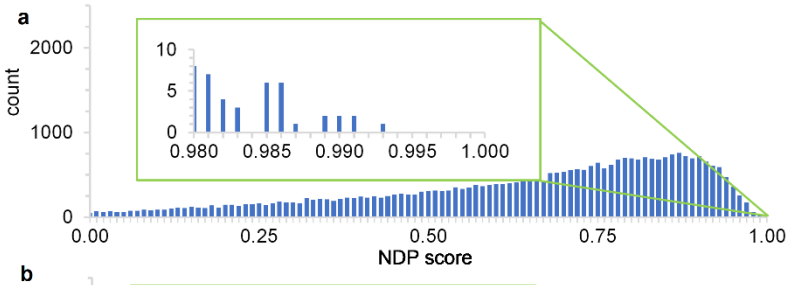


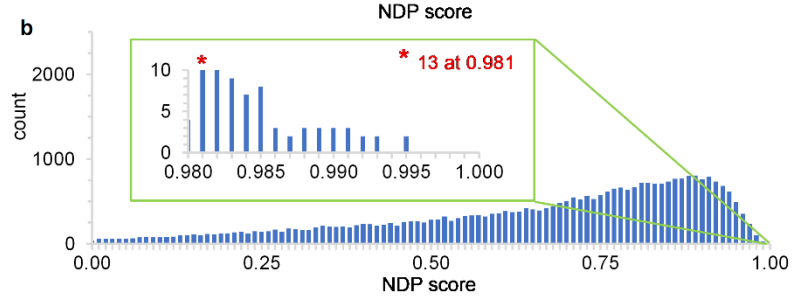
Figure S1. Synthesis of monomers **2**-**5**. (A) Selective deuteration of anilines and construction of labeled quinoline cores **28a-c**; (B) Preparation of monomers **2**, **4**, **5** from key intermediates **28a-c** was accomplished on multigram scale by following the literature route[1,2] described for the non-deuterated analog **1**; (C) Monomer **5** was prepared on a different synthetic route: swapping of the amine protection in **6** shifted deuteration from the future bridgehead position resulting dideuterated quinoline. To provide the necessary analytical references (**36-40**), the reaction sequence was also performed with non-deuterated analogs. Under the reported conditions no significant deuterium erosion was observed at any stage of the syntheses, affording excellent deuterium incorporation in the final products.

a



Monomer	Exact isotopologue content				
	$^2H_0$ %	$^2H_1$ %	$^2H_2$ %	$^2H_3$ %	$^2H_4$ %
D_1	2.3	97.7	0.0	0.0	0.0
D_2	0.0	4.8	95.2	0.0	0.0
D_3	0.0	0.0	2.9	97.1	0.0
D_4	0.0	0.0	0.2	10.6	89.2

b



Monomer	Exact isotopologue content				
	$^2H_0$ %	$^2H_1$ %	$^2H_2$ %	$^2H_3$ %	$^2H_4$ %
D_1	6.3	93.7	0.0	0.0	0.0
D_2	0.0	8.8	91.2	0.0	0.0
D_3	0.0	0.0	6.9	93.1	0.0
D_4	0.0	0.0	0.2	14.6	85.2

c

Code table					
Monomer		A	B	C	D
Isotopologues		D_1 %	D_2 %	D_3 %	D_4 %
Mixing ratio at position	1	100	75	25	50
	2	75	100	50	25
	3	50	25	100	75
	4	25	50	75	100

d

Composition 1				
	C	H	N	O
A	13	13	3	2
B	13	13	3	2
C	13	13	3	2
D	13	13	3	2
non-coding	2	4	0	2

Figure S2. Performance of encoding systems utilizing less efficiently deuterated monomers. (a-b) Abundance of NDP scores when comparing pairwise all 256 tetrameric sequences comprised of units A-D. In each case, a table at right indicates the exact isotopologue content of monomers. $^2H_0$ stands for the non-deuterated, $^2H_1$ for the monodeuterated… isotopologue present in monomers named D_1-D_4; (c) Code table indicates which isotopologues are used and in which proportion (% with respect to D_0) to encode units A, B, C, or D when they are in position 1, 2, 3, or 4 of the sequence; (d) Molecular formula of A-D used in the calculations. In the diagrams, bar width is 0.01 NDP units, and 0.001 NDP units in the inset.

Code table						
Monomer		A	B	C	D	E
Isotopologues		D_1 %	D_2 %	D_3 %	D_4 %	D_5 %
Mixing ratio at position	1	100	0	25	50	75
	2	75	100	0	25	50
	3	50	75	100	0	25
	4	25	50	75	100	0
	5	0	25	50	75	100

Composition 4				
	C	H	N	O
A	13	13	3	2
B	14	15	3	2
C	15	17	3	2
D	16	19	3	2
E	17	21	3	2
non-coding	2	4	0	2

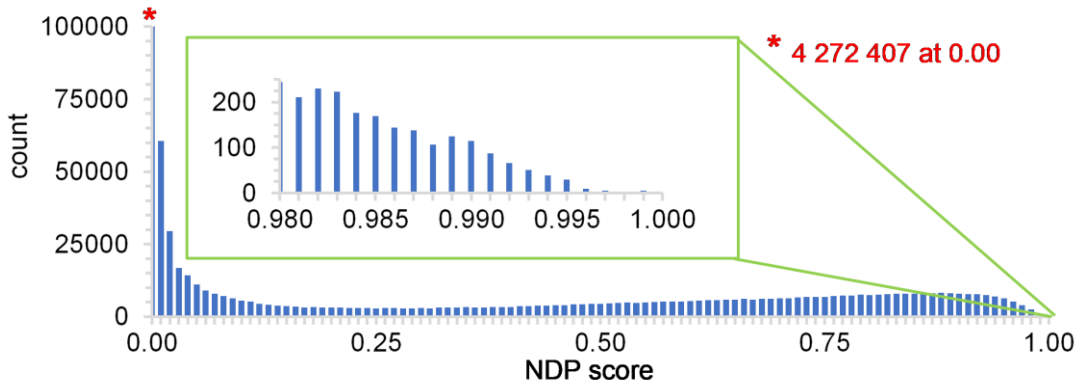
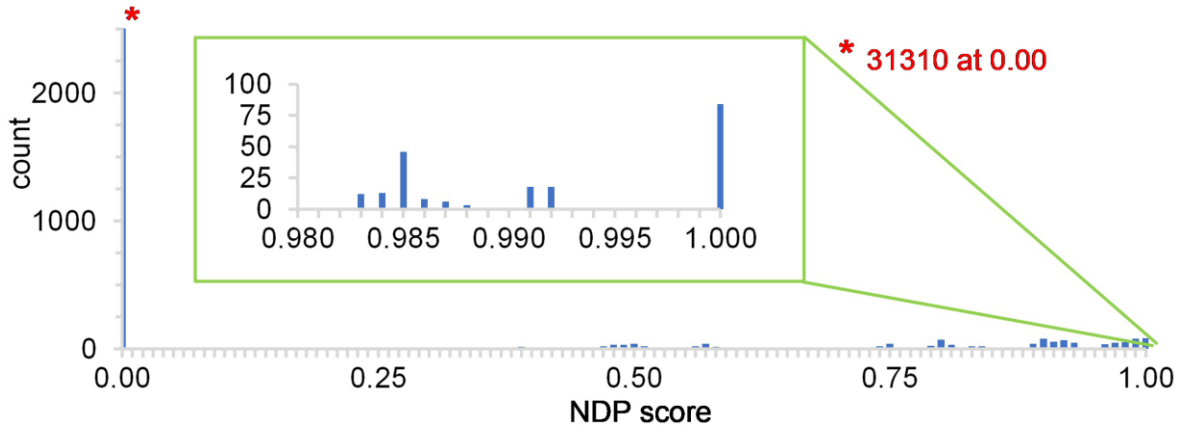


Figure S3. Assessment of the encoding of the 3125 different pentameric sequences of five monomers A-E each differing a single methylene unit (as in composition 4). Monomers A-E contain different proportions of their unlabelled isotopologue and of their mono- (for A), di- (for B), tri- (for C) tetra- (for D) and pentadeuterated (for E) isotopologue, depending on their position in the sequence, as indicated in the code table. The bar diagram shows the NDP score of the pairwise comparison of the isotope envelope of the 3125 sequences. Only 19 pairs of sequences have an NDP score > 0.995

Code table					
Monomer		A	B	C	D
Isotopologues		D_1 %	D_1 %	D_1 %	D_1 %
Mixing ratio at position	1	100	0	33	66
	2	66	100	0	33
	3	33	66	100	0
	4	0	33	66	100

Composition					
	C	H	N	O	F
A	13	13	3	2	0
B	14	15	3	2	0
C	14	13	3	2	2
D	19	13	3	2	4
non-coding	2	4	0	2	0



AABB=BBAA use "100,66,33,0"	1	identical	pair
CCDD=DDCC use "100,66,33,0"	1	identical	pair
CDAB = DCBA use "33,33,0,0"	1	identical	pair
ABDC=BACD use "100,100,66,66"	1	identical	pair
ACDB = BCAD = DACB = DBAC use "100,66,33,33"	6	identical	pairs
CADB = DABC = BDAC = BCDA use "66,66,33,0"	6	identical	pairs
CABD = BDCA = CBDA = ADBC use "100,66,0,0"	6	identical	pairs
ADBC = CBAD = ACBD = DBCA use "100,100,33,0"	6	identical	pairs

Figure S4. Assessment of the encoding of the 256 different tetrameric sequences of four monomers A-D having different chemical composition, as shown in the composition table, with single istope labelling for each monomer using the shown code table. The bar diagram shows shows the NDP scores of the pairwise comparison of all isotope patterns. It indicates that 84 pairs of sequences have a score of 1.00, *i.e.* their isotope patterns are undistinguishable. Many of these are inherent to the degeneracy of the coding. Examples of sequences whose mass and isotope pattern will be identical are shown at the bottom.

2. Supplementary tables cited in the main text S1-S5

Tetramer		DCAB(11)		DCBB(12)	
Measurement		Before storage	After storage	Before storage	After storage
Relative Peak Intensities	M	19.55	23.69	28.74	33.75
	M+1	37.18	39.63	32.65	26.16
	M+2	41.31	47.34	57.11	60.50
	M+3	69.40	72.80	81.71	73.33
	M+4	93.23	91.44	86.68	87.48
	M+5	99.03	98.52	100.00	100.00
	M+6	100.00	100.00	96.18	96.31
	M+7	94.70	95.82	94.10	95.87
	M+8	73.64	73.24	58.98	58.42
	M+9	52.64	55.32	54.49	71.26
	M+10	42.68	46.81	27.65	36.20
	M+11	19.21	21.71	14.95	20.58
	M+12	5.70	6.41	6.36	9.65
	M+13	0.41	0.00	1.82	0.00
	M+14	0.00	0.00	0.52	0.00
NDP		0.99920		0.99529	

Table S1. Changes in the isotope distribution of tetramers on standing for 22 months at +4°C.

Building block	Storage period	Measurement	Composition (%)				
			$^2H_0$	$^2H_1$	$^2H_2$	$^2H_3$	$^2H_4$
2	*54 months*	Before storage	1.3	**98.7**	0.0	0.0	0.0
		After storage	1.6	**98.4**	0.0	0.0	0.0
3	*55 months*	Before storage	0	3.8	**96.2**	0.0	0.0
		After storage	0.0	3.7	**96.3**	0.0	0.0
4	*50 months*	Before storage	0.0	0.0	1.9	**98.1**	0.0
		After storage	0.0	0.1	1.9	**98.0**	0.0
5	*45 months*	Before storage	0.0	0.0	0.2	9.6	**90.2**
		After storage	0.0	0.0	0.2	9.1	**90.7**

Table S2. Changes in the isotope distribution of FmocQD$^{1\text{-}4}$(Boc)OH on standing for at least 45 months at +4°C.

Compound	Composition (%)				
	$^2H_0$	$^2H_1$	$^2H_2$	$^2H_3$	$^2H_4$
5	0.0	0.0	0.0	9.7	**90.3**
21	0.0	0.0	0.0	9.7	**90.3**
22	0.0	0.0	0.0	9.2	**90.8**
23	0.0	0.0	0.0	8.3	**91.7**
24	0.0	0.0	0.0	8.9	**91.1**
25	0.0	0.0	0.0	9.2	**90.8**

Table S3. Isotope labeling erosion during coupling and deprotection.

		Relative peak intensities														
Tetramer		**11**			**12**			**13**			**14**			**15**		
Data source		**Calculated**	**Orbitrap**	**TOF**	**Calculated**	**Orbitrap**	**TOF**	**Calculated**	**Orbitrap**	**TOF**	**Calculated**	**Orbitrap**	**TOF**	**Calculated**	**Orbitrap**	**TOF**
m/z for [M+H]+	**1033.5**	25.8	19.6	12.8	38.8	28.7	25.1	13.3	10.3	7.1	17.9	14.5	18.4	13.7	11.6	10.1
	1034.5	42.6	37.2	26.7	26.8	32.6	19.7	59.9	47.8	40.0	63.4	52.1	45.9	28.1	25.9	20.9
	1035.5	48.7	41.3	36.4	60.5	57.1	50.5	87.5	75.4	66.0	62.7	58.7	50.9	61.4	57.1	50.1
	1036.5	76.4	69.4	60.4	77.7	81.7	69.0	96.9	87.7	85.6	96.6	96.8	86.2	100.0	100.0	91.5
	1037.5	92.9	93.2	87.3	89.2	86.7	84.7	100.0	100.0	100.0	79.9	83.4	74.8	85.7	90.4	100.0
	1038.5	98.4	99.0	99.0	99.9	100.0	93.8	99.8	97.9	97.3	100.0	100.0	100.0	83.8	85.0	86.9
	1039.5	100.0	100.0	100.0	100.0	96.2	100.0	99.4	99.9	89.8	81.3	85.6	79.7	91.6	92.9	87.0
	1040.5	95.8	94.7	94.7	96.3	94.1	88.5	96.6	92.0	81.0	95.6	89.9	87.3	57.6	58.1	52.6
	1041.5	71.4	73.6	67.1	63.9	59.0	61.3	78.1	77.1	63.1	56.5	49.6	49.5	22.1	21.2	20.9
	1042.5	56.1	52.6	48.0	69.9	54.5	56.2	34.7	35.9	26.5	34.7	27.3	24.1	6.0	5.4	3.6
	1043.5	46.6	42.7	34.1	37.7	27.6	26.5	10.4	14.1	9.1	14.4	10.9	11.0	1.3	1.1	0.0
	1044.5	21.3	19.2	15.5	23.3	15.0	16.7	2.3	5.0	1.0	4.2	3.2	3.7	0.2	1.0	0.0
	1045.5	6.5	5.7	3.1	9.9	6.4	5.4	0.4	1.6	0.0	0.9	0.4	0.0	0.0	0.0	0.0
	1046.5	1.5	0.4	0.0	3.0	1.8	0.5	0.1	0.4	0.0	0.2	0.0	0.0	0.0	0.0	0.0
	1047.5	0.3	0.0	0.0	0.7	0.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	1048.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	1049.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	1050.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	1051.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Table S4. Calculated and measured (TOF and Orbitrap) isotopic distributipon of tetramers **11**-**15.**

		Relative peak intensities														
Tetramer		**16**			**17**			**18**			**19**			**20**		
Data source		**Calculated**	**Orbitrap**	**TOF**	**Calculated**	**Orbitrap**	**TOF**	**Calculated**	**Orbitrap**	**TOF**	**Calculated**	**Orbitrap**	**TOF**	**Calculated**	**Orbitrap**	**TOF**
m/z for [M+H]+	**1033.5**	31.2	24.8	20.4	0.0	4.8	0.0	19.7	16.8	0.0	8.0	8.6	4.4	0.0	0.3	0.0
	1034.5	51.5	45.6	41.2	0.0	8.8	0.0	13.3	14.4	0.0	28.0	25.5	22.0	0.0	2.9	0.0
	1035.5	59.1	51.9	54.4	0.5	10.7	0.0	24.0	24.9	17.1	19.7	20.9	16.0	0.1	3.4	0.0
	1036.5	100.0	92.4	88.8	24.9	36.4	22.9	21.7	25.4	17.7	40.6	41.9	38.7	3.7	8.6	2.7
	1037.5	96.5	100.0	100.0	83.7	85.8	71.8	87.3	85.5	71.1	100.0	100.0	95.2	39.4	40.3	27.2
	1038.5	86.6	89.8	91.5	75.1	77.1	73.2	63.3	66.5	56.2	86.7	90.7	99.6	57.4	58.3	45.8
	1039.5	89.0	90.2	85.0	100.0	100.0	99.0	100.0	99.7	94.3	65.6	73.8	80.6	34.2	39.1	33.5
	1040.5	54.0	59.0	51.2	81.2	78.7	92.1	69.7	74.5	71.3	64.3	70.3	79.7	56.3	57.9	55.9
	1041.5	30.7	39.3	26.3	99.2	89.7	100.0	98.7	100.0	100.0	93.0	93.8	100.0	100.0	100.0	100.0
	1042.5	21.5	29.0	19.2	80.9	70.7	84.2	70.0	69.5	72.3	59.2	60.3	64.3	84.4	84.6	85.4
	1043.5	9.4	13.6	5.2	93.1	77.3	80.1	95.6	88.1	88.6	41.7	40.5	43.1	44.4	44.8	50.2
	1044.5	2.8	7.6	0.5	47.3	38.6	38.3	55.7	50.0	53.3	18.4	17.7	18.7	52.1	46.3	46.0
	1045.5	0.6	6.5	0.0	15.1	12.3	7.2	34.8	29.1	32.0	5.5	5.4	3.5	56.3	50.5	45.8
	1046.5	0.1	3.1	0.0	3.5	2.9	0.0	19.7	15.6	16.9	1.3	0.5	0.0	27.4	23.5	18.8
	1047.5	0.0	0.2	0.0	0.6	0.5	0.0	21.5	17.4	16.7	0.2	0.0	0.0	8.5	7.1	0.0
	1048.5	0.0	0.0	0.0	0.1	0.0	0.0	11.0	9.1	6.5	0.0	0.0	0.0	2.0	0.3	0.0
	1049.5	0.0	0.0	0.0	0.0	0.0	0.0	3.5	3.0	1.3	0.0	0.0	0.0	0.4	0.0	0.0
	1050.5	0.0	0.0	0.0	0.0	0.0	0.0	0.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	1051.5	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Table S5. Calculated and measured (TOF and Orbitrap) isotopic distributipon of tetramers **16**-**20.**

3. Supplementary methods

3.1. User's manual for the Excel spreadsheet for calculations (Macro S1.xlsm)

Availability

Macro S1.xlsm is available free of charge directly from the authors or at:
https://drive.google.com/file/d/1Wjkja11cAtREa658TaZPP0MLtMSlM5XD/view?usp=sharing

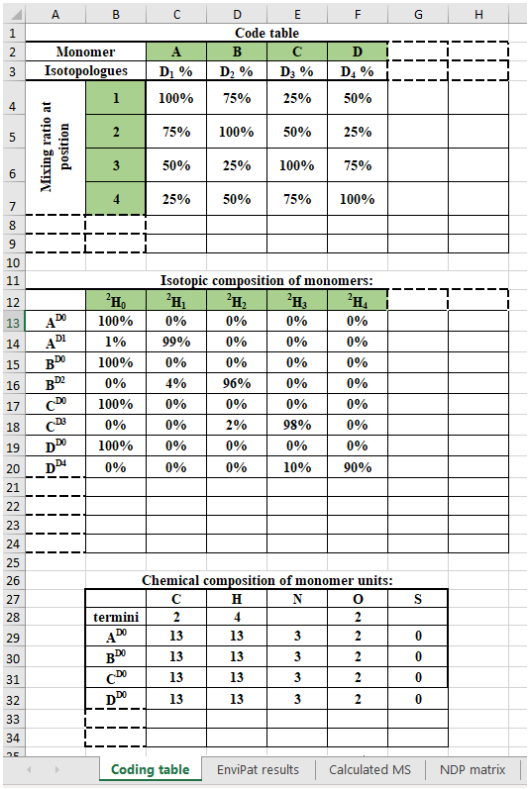
General remarks

The Excel spreadsheet uses macros with fixed cell and sheet references. Shifting cells or renaming sheets will result in uinpredictable errors. Sheets can be added without altering the macros operation.

Defining an encoding system

To define an encoding system, enter the following descriptors to the "***Coding table***" sheet (Figure S5):

- Code table
  The macros can flexibly handle mono- to pentamers, built up from binary mixtures of non-labelled and labelled isotopologues of monomers. Maximum five different monomers can be used. The code table indicates which isotopologues are used and in which proportion (% with respect to D_0) to encode units in each position. ***Headers should be adjusted for the given encoding system***. *(The algorithm checks whether cells are filled-in or blank in the headers (ranges C2:G2 and B4:B8) to determine the size of the entered code table. Filled-in header automatically turns green.)*
- Isotopic composition of monomers
  The macros can flexibly handle mono- to pentadeuterated monomers. Exact isotopologue content not including the natural isotope distribution pattern (*i.e.* deuteration rates) of all labelled and non-labelled monomers should be given. $^2H_0$ stands for the non-deuterated, $^2H_1$ for the monodeuterated… isotopologue present in monomers. ***Header should be adjusted for the given encoding system***. *(The algorithm checks whether cells are filled-in or blank in the header (range B12:G12) to determine the maximal extent of labeling. Filled-in header automatically turns green.)*
- Chemical composition of monomers
  The macros can handle monomers with chemical compositions including C, H, N, O atoms and one extra atom which is user defined (example uses sulfur). Chemical composition of non-labelled monomer units and terminal (non-coding) units within the oligomer should be given. *Do not confuse this with the building blocks (e.g. Fmoc and Boc protected aminoacids) used for oligomer synthesis.*



Code table

Monomer		A	B	C	D
Isotopologues		D_1 %	D_2 %	D_3 %	D_4 %
Mixing ratio at position	1	100%	75%	25%	50%
	2	75%	100%	50%	25%
	3	50%	25%	100%	75%
	4	25%	50%	75%	100%

Isotopic composition of monomers:

	$^2H_0$	$^2H_1$	$^2H_2$	$^2H_3$	$^2H_4$
A^{D0}	100%	0%	0%	0%	0%
A^{D1}	1%	99%	0%	0%	0%
B^{D0}	100%	0%	0%	0%	0%
B^{D2}	0%	4%	96%	0%	0%
C^{D0}	100%	0%	0%	0%	0%
C^{D3}	0%	0%	2%	98%	0%
D^{D0}	100%	0%	0%	0%	0%
D^{D4}	0%	0%	0%	10%	90%

Chemical composition of monomer units:

	C	H	N	O	S
termini	2	4		2	
A^{D0}	13	13	3	2	0
B^{D0}	13	13	3	2	0
C^{D0}	13	13	3	2	0
D^{D0}	13	13	3	2	0

Coding table | EnviPat results | Calculated MS | NDP matrix

Figure S5. Defining an encoding system.

Calculating the mass spectra of oligomers

To calculate the mass spectra of oligomers, the formula and natural isotope distribution pattern of the non-labelled oligomer(s) must be given. As an oligomer library built up from several different monomers might contain oligomers with multiple different chemical compositions, a semi-automated system was developed to help data entry.

- Got to the "***Coding table***" sheet and click on the "***Generate formulas!***" button to get all possible oligomer formulas within the system.
- Copy the obtained, listed formulas to the input window of enviPat from Eawag[3] available at https://envipat.eawag.ch/. Set the parameters shown on Figure S6 for enviPat, run the calculation and save your results as a single ".csv" file.

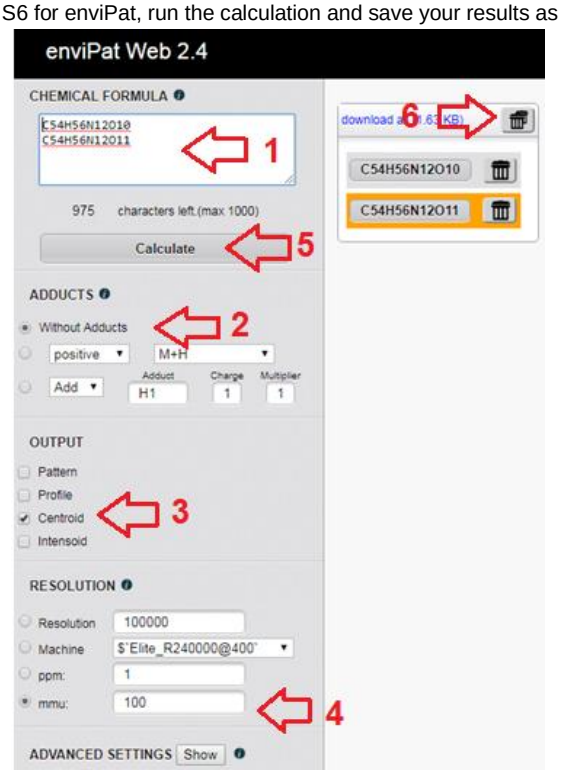


Figure S6. Predicting natural isotope pattern of oligomers with enviPat.

- Go to the "***Envipat results***" sheet and click on "***Import results from file***" button, browse the ".csv" result file and click "OK". The natural isotope distribution pattern and monoisotopic mass of all possible oligomers will appear (Figure S7).

	A	B	C	D	E	F	G	H
1	***Formula***	***Mono Mass***	***Abund. (M)***	***Abund. (M+1)***	***Abund. (M+2)***	***Abund. (M+3)***	***Abund. (M+4)***	***Abund. (M+5)***
2	C54H56N12O10	1032.5	100	63.87588	22.12986	5.430973	1.036897	0.15721
3								
4								

Figure S7. Structure of data imported from enviPat.

- On the "***Envipat results***" sheet click on "***Calculate MS***" button, then click "OK". The sequence No, sequence code and the calculated mass spectra of the oligomers will be written to the "***Calculate MS***" sheet rounded to 1 decimal (Figure S8). *This operation might take long time, pressing the "ESC" button will terminate the process.*

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q
1	No	Coding	1032.5	1033	1033.5	1034	1034.5	1035	1035.5	1036	1036.5	1037	1037.5	1038	1038.5	1039	1039.
2	1	AAAA	0.2		15.3		70.1		100		64.3		24.6		6.7		1.
3	2	AAAB	0.2		14.6		63.2		91.9		100		85.5		38.7		11.
4	3	AAAC	0.1		6.4		27.6		33.9		36.8		88		100		48.
5	4	AAAD	0		0		0		0.1		2.4		27		88.9		10
6	5	AABA	0.3		27.1		100		92.6		68		37		13.6		3.
7	6	AABB	0.2		19.6		67.2		67		100		60.8		38.6		16.

Coding table | EnviPat results | Calculated MS | NDP matrix | Sequence search

Figure S8. Structure of data after mass spectra calculation (detail).

Background. The following cycle is used to generate the mass spectrum of labelled oligomer sequences:

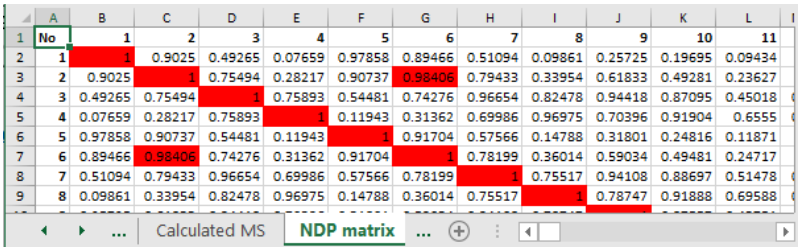
- **Step1:** Calculate the chemical composition (formula) of the oligomer.
- **Step2:** From the formula (*obtained in step1*), calculate the monoisotopic mass and find the natural isotope distribution pattern of the oligomer imported from enviPat.
- **Step3:** From the mixing ratios and the exact isotopic composition of the building block units, calculate the exact isotopic composition of each monomer mixture used to build up the given sequence.
- **Step4:** For each monomer isotopologue combination, which might make up the oligomer, calculate the probability of its presence and the overall number of deuterium atoms it comprises.
- **Step5:** From the linear combination of the several deuteration degree/probability pairs (*obtained in step4*), calculate the isotope pattern resulting from the deuterium labelling.
- **Step6:** Merge the patterns resulting from the natural isotope distribution pattern (*obtained in step2*) and the pattern resulting from the isotope labelling *(obtained in step5*).

- **Step7:** Shift the pattern (*obtained in step6*) with the monoisotopic mass (*obtained in step2*) to get the mass spectrum of the given sequence.
- **Step8:** Record the mass spectrum to a database.
- **Step9:** Go to *step 1*, or end if all sequences are done.

Calculating the NDP matrix and distribution

The similarity of the mass spectra within the coding system is evaluated by pairwise comparisons based on the NDP function.

- Go to the "***Envipat results***" sheet and click on "***NDP Matrix***" button, then click "OK". NDP similarity values will be calculated for all MS fingerprint pairs within the coding system and summarized on the "***NDP matrix***" sheet. Headers contain the sequence No, values are rounded to 5 decimals (Figure S9). *This operation might take long time, pressing the "ESC" button will terminate the process.*



No	1	2	3	4	5	6	7	8	9	10	11
1	1	0.9025	0.49265	0.07659	0.97858	0.89466	0.51094	0.09861	0.25725	0.19695	0.09434
2	0.9025	1	0.75494	0.28217	0.90737	0.98406	0.79433	0.33954	0.61833	0.49281	0.23627
3	0.49265	0.75494	1	0.75893	0.54481	0.74276	0.96654	0.82478	0.94418	0.87095	0.45018
4	0.07659	0.28217	0.75893	1	0.11943	0.31362	0.69986	0.96975	0.70396	0.91904	0.6555
5	0.97858	0.90737	0.54481	0.11943	1	0.91704	0.57566	0.14788	0.31801	0.24816	0.11871
6	0.89466	0.98406	0.74276	0.31362	0.91704	1	0.78199	0.36014	0.59034	0.49481	0.24717
7	0.51094	0.79433	0.96654	0.69986	0.57566	0.78199	1	0.75517	0.94108	0.88697	0.51478
8	0.09861	0.33954	0.82478	0.96975	0.14788	0.36014	0.75517	1	0.78747	0.91888	0.69588

Figure S9. Structure of data after NDP matrix calculation (detail).

- NDP distributionon sheet "***NDP distribution***" is obtained by plotting the number of sequence pairs with a specific NDP value within the matrix, against the corresponding NDP values. Counting the number of sequences with a specific NDP value is done by simpe excel functions which have to be adjusted to the size of the system by the user. *For different resolutions rounding of NDP matrix values was performed on "**Round.00**" and "**Round.000**" sheets. Note that the diagonals should be omitted, and all pairs occur twice in the matrix.*

Background. Normalized dot product (NDP) for mass spectra ***A*** and ***B***, consisting of ***k*** peaks is calculated as following:

$$NDP_{A,B} = \frac{\sum_{i=1}^{k} I_{A,i} \cdot I_{B,i}}{\sqrt{\sum_{i=1}^{k} I_{A,i}^2 \cdot \sum_{i=1}^{k} I_{B,i}^2}}$$

Where

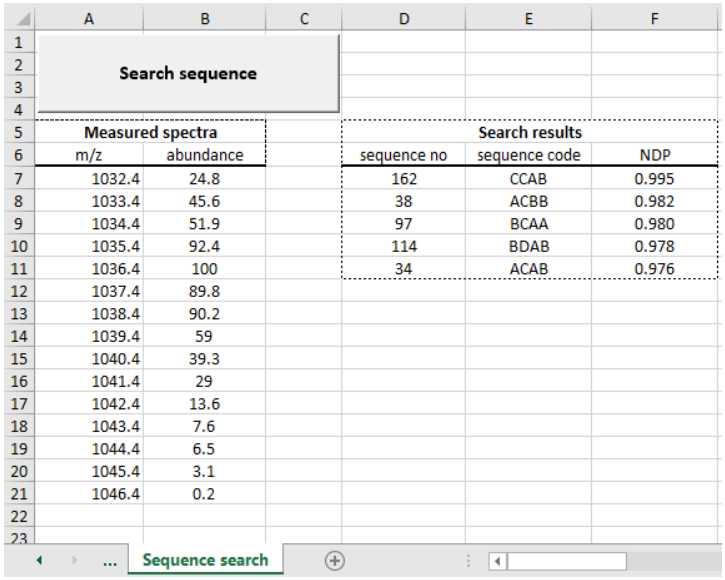
- $I_{A,i}$ describes the relative intensity of the i^{th} peak in spectrum of ***A***
- $I_{B,i}$ describes the relative intensity of the i^{th} peak in spectrum of ***B***

Sequence search tool

A search engine is provided, which can compare a measured spectrum to the calculated spectra based on NDP and list the five best matches along with their sequence No, sequence code and the corresponding NDP values.

- Go to "***Sequence search***" sheet and enter the measured mass spectrum datapoints. Click on "***Search sequence***" button. The results will appear on the right (Figure S10). *The data should be normalized so that the largest peak's abundance is 100. The m/z values should be given without adducts. Number of datapoints is not restricted.*

Performing large number of automated sequence searches (e.g. for OBOC library screening) could be enabled by minimal extension of the macro's code, as today any MS will provide a digital output that could be coupled with our workflow.



Search sequence					
Measured spectra			Search results		
m/z	abundance		sequence no	sequence code	NDP
1032.4	24.8		162	CCAB	0.995
1033.4	45.6		38	ACBB	0.982
1034.4	51.9		97	BCAA	0.980
1035.4	92.4		114	BDAB	0.978
1036.4	100		34	ACAB	0.976
1037.4	89.8				
1038.4	90.2				
1039.4	59				
1040.4	39.3				
1041.4	29				
1042.4	13.6				
1043.4	7.6				
1044.4	6.5				
1045.4	3.1				
1046.4	0.2				

Figure S10. Sequence search tool.

3.2. General experimental details

For monomers

Reagents obtained from commercial sources were used without further purification. Anhydrous solvents were obtained from commercial sources and used without further drying. Nitrogen gas dried on a column of Drierite® was used as inert atmosphere. The reactions were monitored using LC-MS and GC-MS instruments. **Analytical LC-MS:** Agilent HP1200 LC with Agilent 6140 quadrupole MS, operating in positive or negative ion electrospray ionisation mode. Molecular weight scan range was 100 to 1350 m/z. Parallel UV detection was done at 210 nm and 254 nm. Samples were supplied as a 1 mM solution in MeCN or in THF:water (1:1) with 5 µL loop injection. LC-MS analyses were performed on two instruments, one of which was operated with basic, and the other with acidic eluents. Basic LC-MS: Gemini-NX, 3 µm, C18, 50 mm × 3.00 mm i.d. column at 23°C, at a flow rate of 1 mL min^{-1} using 5 mM aq NH_4HCO_3 solution and MeCN as eluents. Acidic LC-MS: ZORBAX Eclipse XDB-C18, 1.8 µm, 50 mm × 4.6 mm i.d. column at 40°C, at a flow rate of 1 mL min^{-1} using water and MeCN as eluents, both containing 0.02 V/V% formic acid. Combination **gas chromatography** and low-resolution mass spectrometry were performed on Agilent 6850 gas chromatograph and Agilent 5975C mass spectrometer using 15 m × 0.25 mm column with 0.25 µm HP-5MS coating and helium as carrier gas. Ion source: EI^+, 70 eV, 230°C, quadrupole: 150°C, interface: 300°C. **Flash chromatography** was performed on ISCO CombiFlash Rf 200i or ISCO CombiFlash Torrent® with pre-packed silica-gel cartridges (Redi*Sep*®*R*$_f$ Gold High Performance). **Preparative HPLC** purifications were performed on an ISCO CombiFlash EZ Prep system with a Gemini-NX® 10 µm C18, 250 mm × 50 mm column running at a flow rate of 118 mL min^{-1} with UV diode array detection. For large size samples a system equipped with Hanbon NP7000 pump, Hanbon DAC-HB100 dynamic axial column (Luna® 10 µm C18 spheric, 265 mm × 100 mm i.d) running at a flow rate of 400 mL min^{-1}, ECOM Flash 14 DAD detector (210 – 400 nm) and ISCO Foxy R2 fraction collector was used.Microwave assisted reactions were carried out in Anton Paar MonoWave or Anton Paar MultiWave Pro microwave reaction systems. **^{1}H NMR, and DEPTQ ^{13}C NMR** measurements were performed on Bruker Avance III 500 MHz spectrometer and Bruker Avance III 400 MHz spectrometer, using DMSO-d_6 or $CDCl_3$ as solvent. ^{1}H and ^{13}C NMR data are in the form of delta values, given in part per million (ppm), using the residual peak of the solvent as internal standard (DMSO-d_6: 2.50 ppm (^{1}H) / 39.5 ppm (^{13}C); $CDCl_3$: 7.26 ppm (^{1}H) / 77.0 ppm (^{13}C)). Splitting patterns are designated as: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sp (septet), m (multiplet), br s (broad singlet), dd (doublet of doublets), td (triplet of doublets), qd (quartet of doublets), dt (doublet of triplets). In some cases, due to tautomers or amide rotamers two sets of signals appear in the spectra. Solvent peaks are marked with a "▼" sign on the spectra, type of solvent is indicated if other than water or the deuterated solvent in the title. **HRMS** were determined on an Agilent 6545 Q-TOF, coupled with an Agilent 1290 Infinity II: UHPLC. Mass resolution 45000. Chromatographic parameters were the following: mobile phase A: 5 mM NH4COO in ultrapure water; mobile phase B: 5 mM NH4COO in acetonitrile:ultrapure water 95:5; gradient: from 0% B to 100% in 5.5 min; flow rate: 0.7ml/min. MS parameters were the following: Dual Agilent Jet Stream ESI ion source; gas temperature: 300°C; drying gas flow: 10 l/min; nebulizer pressure: 40 psi; sheath gas temperature: 300°C; sheath gas flow: 10 l/min; capillary voltage: 2500 V; nozzle voltage: 1000 V; fragmentor voltage: 100 V.Samples were supplied as a 0.1 mM solution in MeCN or in THF:water (1:1) with 5 µL loop injection.

During the synthesis of isotope labeled quinoline carboxylate foldamer building blocks the greatest challenge was to reach high and selective deuterium incorporation and to preserve it throughout the synthesis. Therefore, the deuterium content had to be monitored throughout the whole synthesis. We used different analytical methods, usually in parallel to obtain reliable data. ^{1}H-NMR was used to determine the approximate H/D ratio in a given position using the following formula:

$$D\% = 100 \times \left(1 - \frac{I_{rel,deuterated}}{I_{rel,non-deuterated}}\right)$$

Where

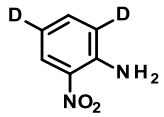
- D% is the deuterium incorporation
- $I_{rel,\ deuterated}$ is the integral of the given proton signal compared to the integral of the reference proton signal in the labeled molecules ^{1}H NMR spectra
- $I_{rel,\ non\text{-}deuterated}$ is the integral of the given proton signal compared to the integral of the reference proton signal in the non-labeled molecules ^{1}H NMR spectra

LC-MS and GC-MS methods allowed the determination of isotopologue ratios regardless of the regioselectivity of labeling. The isotopologue ratios were deconvoluted from the single ion chromatogram integrals of the corresponding isotopologues in a given sample considering the natural isotope abundances. In case of the final products **2-5** and some intermediates, signal overlaps in the ^{1}H-NMR spectra made the quantification of deuterium incorporation difficult, therefore only isotopolgue ratios from LC-MS data are presented. To help analysis, **1** and its intermediates were prepared and used as non-deuterated reference.

For tetramers and compounds 21-24 synthesized for the erosion study

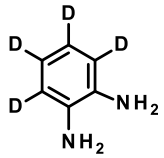
Low loading Wang resin (0.4 mmol/g) was purchased from Novabiochem. 1-chloro-*N*,*N*,2-trimethylpropenylamine (Ghosez reagent) and anhydrous *N*,*N*-dimethylformamide (DMF) were purchased from Sigma Aldrich. *N*,*N*-diisopropylethylamine (DIEA) was distilled over calcium hydride. Analytical grade organic solvents were used for solid phase synthesis. Dry organic solvents for solid phase synthesis were dispensed from a solvent purification system that passes solvents through packed columns (THF, CH_2Cl_2: dry neutral alumina). Milli-Q water was delivered from a PureLab Prima 7/15/20 system. RP-HPLC quality acetonitrile (CH_3CN) and MilliQ water were used for RP-HPLC analysis. **SPS** was carried out manually at atmospheric pressure using a CEM Discover microwave oven and SPS station in the proprietary reactor vessels. The temperature of microwave-assisted reactions was controlled by an optical fiber probe internal to the reaction mixture. **^{1}H NMR** spectra were measured at 300 MHz. Chemical shifts are reported in ppm and are calibrated against residual solvent signals of DMSO-d_6 (δ=2.50 ppm). All coupling constants are reported in Hertz (Hz). Signals were abbreviated as s (singlet), br s (broad singlet), d, (doublet), t (triplet), q (quartet), m (multiplet). **RP-HPLC** analysis were performed with a JASCO HPLC system using a Macherey-Nagel Nucleodur C18 HTEC column (4.6 x 100 mm, 5 µm) at 1.5 mL/min with running solvents: Milli-Q water containing 0.1 V/V% TFA (solvent A), CH_3CN containing 0.1 V/V% TFA (solvent B) with a gradient method 5-100%B in 15min. **LC-MS** analysis were performed on a Agilent 6230 ESI-TOF apparatus operating in positive ion electrospray ionisation mode with acidic eluents water and MeCN both containing 0.01 V/V% formic acid, a Macherey-Nagel Nucleodur C18 HTEC column (2 x 50 mm, 1.8 µm) at 0.4 mL/min with running solvents at 40°C. **HRMS** (ESI+) experiments were performed using a Thermo Fisher Scientific Exactive Orbitrap instrument, HESI-II electrospray source operated in positive ion mode (IECB Mass Spectrometry facility).

3.3. Monomer synthesis



2,4-dideuterio-6-nitroaniline (7)

A 50 mL microwave reaction vial was filled with 11.9 g 2-nitroaniline (86.3 mmol), 23 mL D_2O (15.0 equiv., 1.29 mol) and 3.2 mL D_2SO_4 (0.75 equiv., 64 mmol). The reaction mixture was stirred at 150°C for 90 min, then cooled to rt and extracted with 4x25 mL anhydrous DCM. The combined organic phase was dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The residue was placed in the microwave reaction vial, 38.6 mL D_2O (25.0 equiv., 2.15 mol) and 5.38 mL D_2SO_4 (1.25 equiv., 108 mmol) were added. The reaction mixture was stirred at 150°C for 90 min, then cooled to rt and extracted with 4x25 mL DCM. The combined organic phase was washed with 3x100 mL water, dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo* to afford **7** as a brown, crystalline solid (10.9 g, 87%). ^{1}H NMR (500 MHz, DMSO-d_6) δ=7.95 (d, *J* = 1.3 Hz, 1H), 7.40 (s, 2H), 7.38 ppm (d, *J* = 0.8 Hz, 1H). Based on ^{1}H NMR the D rate at position 4 and 6 is more than 98%. ^{13}C NMR (100 MHz, DMSO-d_6) δ=146.2, 135.5, 130.2, 125.2, 118.9 (t, *J* = 24.8 Hz), 115.2 ppm (t, *J* = 25.6 Hz). According to GC-MS the rate of isotopologues is: <0.1% D_0; 2.9% D_1; 97.1% D_2. HRMS (EI) *m/z* calcd for $C_6D_2H_4N_2O_2$ $[M]^+$: 140.0555; found: 140.0547.

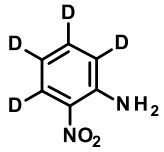


3,4,5,6-tetradeuteriobenzene-1,2-diamine (26)

Prepared by modification of the method described in the literature.[4]

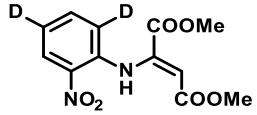
6.78 g benzene-1,2-diamine (62.5 mmol) was added portionwise to 75 mL well stirred and cooled HCl solution (93.8 mmol, 1.50 equiv., 1.25 M in EtOH) at rt and stirred for 15 min.

The following procedure was repeated three times: <The slurry or solution was concentrated under reduced pressure. To remove traces of protic solvents, 25 mL anhydrous THF was added and evaporated under reduced pressure. Another 25 mL portion of anhydrous THF was added and evaporated *in vacuo*. The residue was dissolved in 37.5 mL D_2O (33.6 equiv., 2.10 mol) and transferred to a 50 mL microwave reaction vial. The reaction mixture was stirred at 150°C for 30 min.> The solution was filtered through a pad of Celite®, the filter cake was washed with 62.5 mL 2 M aq. NaOH solution. The filtrate was extracted with DCM, the organic phase was dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo* to afford **26** as a purple, crystalline solid (6.01 g, 86%). ^{1}H NMR (400 MHz, DMSO-d_6) δ=4.39 ppm (s, 4H). Based on ^{1}H NMR the D rate at position 3,4,5 and 6 is more than 98%. ^{13}C NMR (125 MHz, DMSO-d_6) δ=134.8 (d, *J* = 6.0 Hz), 116.7 (t, *J* = 24.2 Hz), 114.1 ppm (t, *J* = 23.3 Hz). HRMS (ESI) *m/z* calcd for $C_6D_4H_5N_2$ $[M+H]^+$: 113.1011; found:113.1005. According to LC-MS the rate of isotopologues is: <0.1% D_0; <0.1% D_1, 0.2% D_2, 4.4% D_3, 95.3% D_4.



2,3,4,5-tetradeuterio-6-nitro-aniline (10)

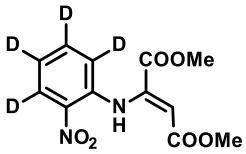
A solution of 398 mmol *m*-CPBA (3.90 equiv.) in 600 mL MeCN was added dropwise to a well stirred solution of 11.5 g **26** (102 mmol) in 500 mL MeCN at 0°C during a 15 min period. The mixture was stirred at 0°C for further 10 min then 100 mL sat. aq. K_2CO_3 solution and 100 mL sat. aq. $Na_2S_2O_3$ solution were added and stirred for 5 min to quench the excess of *m*-CPBA. The organic phase was separated, washed with brine. The combined aq. solutions were extracted with EtOAc. The combined organic phase was dried over Na_2SO_4, filtered. Then 200 g Na_2SO_4 was added to the filtrate and it was concentrated *in vacuo*. The residue was sonicated with 3 × 1000 mL DIPE/heptane 2/1 mixture for 3x30 minutes and filtered. The filtrate was concentrated under reduced pressure to afford **10** as an orange solid (9.90 g, 68%). ^{1}H NMR (500 MHz, DMSO-d_6) δ=7.40 ppm (s, 2H). Based on ^{1}H NMR the D rate at position 2,3,4 and 5 is more than 98%. ^{13}C NMR (125 MHz, DMSO-d_6) δ=146.2, 135.2 (t, *J* = 24.3 Hz), 130.2, 125.0 (t, *J* = 24.9 Hz), 118.8 (t, *J* = 21.2 Hz), 115.0 ppm (t, *J* = 25.4 Hz). HRMS (ESI) *m/z* calcd for $C_6D_4H_3N_2O_2$ $[M+H]^+$: 143.0753; found:143.0753. According to LC-MS the rate of isotopologues is: <0.1% D_0; <0.1% D_1, 0.3% D_2, 1.8% D_3, 97.9% D_4.



Dimethyl (*Z*)-2-(2,4-dideuterio-6-nitro-anilino)but-2-enedioate (27a)

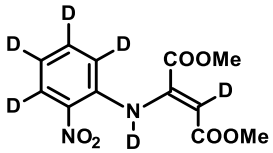
To a well stirred suspension of 28.0 g **7** (197 mmol) in 300 mL anhydrous MeOH 24.2 mL DMAD (1.00 equiv., 197 mmol) was added. The reaction mixture was stirred at 60°C for 72 h, then the formed crystals were filtered at 0°C, washed with MeOH and dried. The mother liquor was concentrated to 100 mL, cooled to 0°C and filtered to give a second crop of crystals. **27a** was obtained as orange crystals (together 27.3 g, 49%). ^{1}H NMR (500 MHz, DMSO-d_6) δ=10.90 (s, 1H), 8.15 (d, *J* = 1.6 Hz, 1H), 7.66 (d, *J* = 1.3 Hz, 1H), 5.77 (s, 1H), 3.74 (s, 3H), 3.72 ppm (s, 3H). Based on ^{1}H NMR the D rate at position 2 and 4 is more than 98%. ^{13}C NMR (125 MHz, DMSO-d_6) δ=167.7, 163.5, 143.9,

137.9, 135.6, 135.1, 125.9, 101.2, 53.4, 51.8 ppm. HRMS (ESI) *m/z* calcd for $C_{12}D_2H_{11}N_2O_6$ $[M+H]^+$: 283.0894; found: 283.0894. According to LC-MS the rate of isotopologues is: 0.1% D_0; 2.5% D_1; 97.5% D_2.



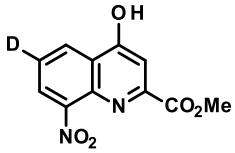
Dimethyl (*Z*)-2-(2,3,4,5-tetradeuterio-6-nitro-anilino)but-2-enedioate (27b)

To a well stirred suspension of 22.9 g **10** (161 mmol) in 250 mL anhydrous MeOH 19.8 mL DMAD (1.00 equiv., 161 mmol) was added. The reaction mixture was stirred at 60°C for 72 h, then the formed crystals were filtered at 0°C, washed with MeOH and dried *in vacuo* to afford **27b** as an orange, crystalline solid (28.5 g, 62%). ^{1}H NMR (500 MHz, DMSO-d_6) δ=10.90 (s, 1H), 5.77 (s, 1H), 3.74 (s, 3H), 3.72 ppm (s, 3H). Based on ^{1}H NMR the D rate at position 2,3,4 and 5 is more than 98%. ^{13}C NMR (125 MHz, DMSO-d_6) δ=167.7, 163.5, 143.9, 137.8, 135.6, 101.2, 53.4, 51.8 ppm. HRMS (ESI) *m/z* calcd for $C_{12}D_4H_9N_2O_6$ $[M+H]^+$: 285.1019; found:285.1021. According to LC-MS the rate of isotopologues is: <0.1% D_0; <0.1% D_1, <0.1% D_2, 1.9% D_3, 98.1% D_4.



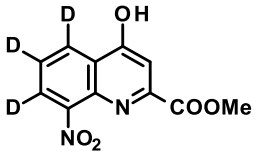
Dimethyl (*Z*)-2-deuterio-3-(*N*,2,3,4,5-pentadeuterio-6-nitro-anilino)but-2-enedioate (27c)

5.00 g **10** (35.2 mmol) was dissolved in 10 mL MeOD, stirred at rt for 10 min then the solvent was removed under reduced pressure. The residue was dissolved in 55 mL MeOD and 4.31 mL DMAD (1.00 equiv., 35.2 mmol) was added. The reaction mixture was stirred under N_2 at 60°C for 72 h, then the formed crystals were filtered at 0°C, washed with MeOD and dried *in vacuo* to afford **27c** as an orange, crystalline solid (7.35 g, 73%). ^{1}H NMR (400 MHz, DMSO-d_6) δ=3.73 (s, 3H), 3.72 ppm (s, 3H). Based on ^{1}H NMR the D rate at position 2,3,4 and 5 is more than 98%. The vinyl and amine deuteriums (D rate >96%) exchange in protic media, thus exact H/D ratio could not be determined in these positions. ^{13}C NMR (100 MHz, DMSO-d_6) δ=167.6, 163.5, 143.6, 137.8, 135.5, 134.8 (t, *J* = 24.9 Hz), 125.6 (t, *J* = 25.0 Hz), 122.6 (t, *J* = 25.8 Hz), 120.8 (t, *J* = 24.2 Hz), 101.0 (t, *J* = 26.8 Hz), 53.4; 51.7 ppm. HRMS (ESI) *m/z* calcd for $C_{12}D_5H_8N_2O_6$ $[M-D+H]^+$: 286.1082; found: 286.1081 (Deuterium on the nitrogen was replaced by H in the eluent).



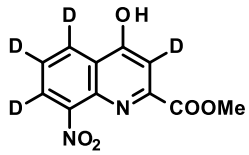
Methyl 6-deuterio-4-hydroxy-8-nitro-quinoline-2-carboxylate (28a)

25.9 g **27a** (91.7 mmol) was added to 365 mL of Eaton's reagent at 50°C while stirring vigorously. Stirring was continued for 30 min at 50°C, then the reaction mixture was poured into 700 mL ice cold MeCN and during a 10 min period 350 g crushed ice was added in small portions. The solution was diluted with 1.50 L water and extracted with DCM. The combined organic phase was washed with sat. aq. $NaHCO_3$ solution, dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography (750 g column, DCM/MeOH, gradient elution: 0-10%) to afford **28a** as an orange solid (10.3 g, 45%). ^{1}H NMR (400 MHz, DMSO-d_6) δ=12.58/11.50 (br s/br s, 1H), 8.75/8.29 (br s/br s, 1H), 8.54/8.41 (br s/br s, 1H), 7.58/6.79 (br s/br s, 1H), 4.02/3.92 ppm (br s/br s, 3H). Presence of tautomers at rt. Due to line broadening in the ^{1}H NMR spectra the exact D rate can not be given. ^{13}C NMR (100 MHz, DMSO-d_6) δ=176.8, 170.6, 164.7, 162.1, 146.9, 140.5, 137.6, 136.5, 134.8, 133.7, 131.2, 128.9, 127.3, 125.9, 124.2, 123.0, 111.6, 105.6, 102.2, 54.2, 53.0, 52.4 ppm. HRMS (ESI) *m/z* calcd for $C_{11}DH_8N_2O_5$ $[M+H]^+$: 250.0569; found: 250.0578. According to LC-MS the rate of isotopologues is: 1.2% D_0; 98.8% D_1.



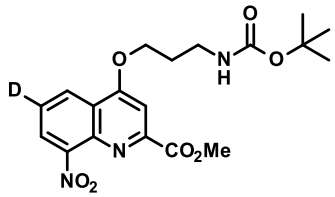
Methyl 5,6,7-trideuterio-4-hydroxy-8-nitro-quinoline-2-carboxylate (28b)

28.4 g **27b** (100 mmol) was added to 400 mL of Eaton's reagent at 50°C while stirring vigorously. Stirring was continued for 30 min at 50°C, then the reaction mixture was poured into 800 mL ice cold MeCN and during a 10 min period 400 g crushed ice was added in small portions. The solution was diluted with 1.50 L water and extracted with DCM. The combined organic phase was washed with sat. aq. $NaHCO_3$ solution, dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography (750 g column, DCM/MeOH, gradient elution: 0-10%) to afford **28b** as an orange solid (9.45 g, 38%). ^{1}H NMR (500 MHz, DMSO-d_6) δ=11.52 (s, 1H). 6.81 (s, 1H), 4.02 ppm (s, 3H). Based on ^{1}H NMR the D rate at position 5, 6 and 7 is more than 98%. ^{13}C NMR (125 MHz, DMSO-d_6) δ=162.1, 127.3, 111.7, 54.2 ppm. HRMS (ESI) *m/z* calcd for $C_{11}D_3H_6N_2O_5$ $[M+H]^+$: 252.0694; found:252.0694. According to LC-MS the rate of isotopologues is: <0.1% D_0; <0.1% D_1, 1.3% D_2, 98.7% D_3.



Methyl 3,5,6,7-tetradeuterio-4-hydroxy-8-nitro-quinoline-2-carboxylate (28c)

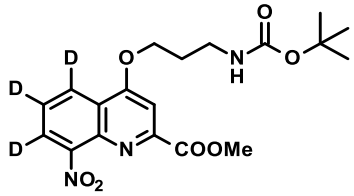
In a glovebox 121 g methanesulfonic anhydride (692 mmol) and 12.4 mL D_2O (692 mmol) were mixed and heated to 50°C for 10 min, then 20.2 g P_2O_5 was added and the stirring was continued until a clear solution was obtained (30 min). To this mixture 6.90 g **27c** (24.1 mmol) was added at 50°C while stirring vigorously. Stirring was continued for 30 min at 50°C, then the reaction mixture was cooled in an ice bath, 200 mL ice cold MeCN and then 100 mL water was added. After 10 min stirring, the solution was diluted with 400 mL water and extracted with DCM. The combined organic phase was dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography (220 g column, DCM/MeOH, gradient elution: 0-10%) to afford **28c** as an orange solid (2.84 g, 47%). ^{1}H NMR (500 MHz, DMSO-d_6) δ=3.99 ppm (s, 3H). Based on ^{1}H NMR the D rate at position 5, 6 and 7 is more than 98%, while D rate at position 3 cannot be determined due to line broadening/tautomers. ^{13}C NMR (125 MHz, DMSO-d_6) δ: 53.9 ppm. HRMS (ESI) *m/z* calcd for $C_{11}D_4H_5N_2O_5$ $[M+H]^+$: 253.0757; found:253.0758. According to LC-MS the rate of isotopologues is: <0.1% D_0; <0.1% D_1, 0.1% D_2, 9.5% D_3, 90.4% D_4.



Methyl 4-[3-(*tert*-butoxycarbonylamino)propoxy]-6-deuterio-8-nitro-quinoline-2-carboxylate (29a)

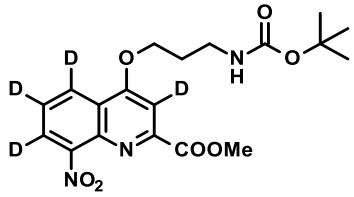
A 250 mL pear-shaped flask was filled with 10.1 g **28a** (40.5 mmol), 13.8 mL *tert*-butyl *N*-(3-hydroxypropyl)carbamate (2.00 equiv., 80.7 mmol) and 18.3 g PPh_3 (1.73 equiv., 69.9 mmol). The flask was closed and flushed with nitrogen then 100 mL anhydrous THF was added. 13.8 mL DIAD (1.73 equiv., 69.9 mmol) was added dropwise at 0°C during a 10 min period. After stirring at 0°C for 30 min the reaction mixture was left stirred at rt overnight. The mixture was concentrated *in vacuo* to a volume of 70 mL then the product was crystallized at -15°C by adding 50 mL MeOH. (*Note: In certain cases crystallization takes 15-20 min to begin. Adding a few drops of water can accelerate this slow process.*) The crystals were filtered, washed with cold MeOH and dried *in vacuo* to afford **29a** as a white solid (9.22 g, 56%).

^{1}H NMR (400 MHz, DMSO-d_6) δ=8.45 (d, *J* = 1.3 Hz, 1H), 8.35 (d, *J* = 1.3 Hz1 1H), 7.66 (s, 1H), 6.99/6.62 (t/s, *J* = 5.6 Hz, 1H), 4.40 (t, *J* = 6.0 Hz, 2H), 3.95 (s, 3H), 3.20 (q, *J* = 6.3 Hz, 2H), 2.01 (quint, *J* = 5.8 Hz, 2H), 1.34 ppm (s, 9H). Based on ^{1}H NMR the D rate at position 6 is more than 98%. ^{13}C NMR (100 MHz, DMSO-d_6) δ=164.8, 162.3, 155.6, 150.9, 148.3, 138.7, 125.5, 124.3, 122.3, 102.6, 77.5, 67.3, 53.0, 36.7, 28.7, 28.2 ppm. HRMS (ESI) *m/z* calcd for $C_{19}DH_{23}N_3O_7$ $[M+H]^+$: 407.1672; found: 407.1671. According to LC-MS the rate of isotopologues is: 0.1% D_0; 99.9% D_1.



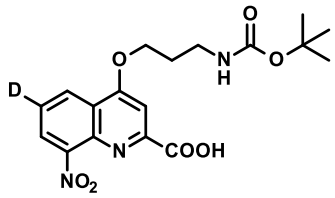
Methyl 4-[3-(*tert*-butoxycarbonylamino)propoxy]-5,6,7-trideuterio-8-nitro-quinoline-2-carboxylate (29b)

A 250 mL pear-shaped flask was filled with 9.41 g **28b** (37.5 mmol), 11.0 mL *tert*-butyl *N*-(3-hydroxypropyl)carbamate (1.71 equiv., 64.1 mmol) and 14.6 g PPh_3 (1.48 equiv., 55.5 mmol). The flask was closed and flushed with nitrogen then 85.0 mL anhydrous THF was added. 11.0 mL DIAD (1.48 equiv., 55.5 mmol) was added dropwise at 0°C during a 10 min period. After stirring at 0°C for 30 min the reaction mixture was left stirred at rt for 90 min. The mixture was concentrated *in vacuo* to a volume of 45 mL then the product was crystallized at -15°C by adding 100 mL MeOH. (*Note: In certain cases crystallization takes 15-20 min to begin. Adding a few drops of water can accelerate this slow process.*) The crystals were filtered, washed with cold MeOH and dried *in vacuo* to afford **29b** as a white solid (20.6 g, 58%). ^{1}H NMR (500 MHz, DMSO-d_6) δ=7.66 (s, 1H), 6.99 (t, *J* = 5.6 Hz, 1H), 4.41 (t, *J* = 6.1 Hz, 2H), 3.95 (s, 3H), 3.20 (q, *J* = 6.3 Hz, 2H), 2.01 (quint, *J* = 6.5 Hz, 2H), 1.34 ppm (s, 9H). Based on ^{1}H NMR the D rate at position 5, 6 and 7 is more than 98%. ^{13}C NMR (125 MHz, DMSO-d_6) δ=164.9, 162.4, 155.6, 150.9, 148.2, 138.7, 122.2, 102.6, 77.5, 67.3, 53.0, 36.7, 28.7, 28.2 ppm. HRMS (ESI) *m/z* calcd for $C_{19}D_3H_{21}N_3O_7$ $[M+H]^+$: 409.1797; found:409.1801. According to LC-MS the rate of isotopologues is: <0.1% D_0; <0.1% D_1, 1.5% D_2, 98.5% D_3.



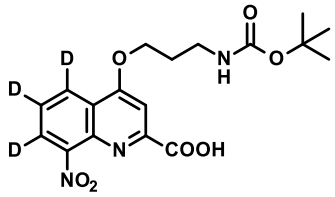
Methyl 4-[3-(*tert*-butoxycarbonylamino)propoxy]-3,5,6,7-tetradeuterio-8-nitro-quinoline-2-carboxylate (29c)

A 50 mL pear-shaped flask was filled with 2.81 g **28c** (11.2 mmol), 2.86 mL *tert*-butyl *N*-(3-hydroxypropyl)carbamate (1.50 equiv., 16.7 mmol) and 3.80 g PPh_3 (1.30 equiv., 14.5 mmol). The flask was closed and flushed with nitrogen then 22.0 mL anhydrous THF was added. 2.86 mL DIAD (1.30 equiv., 14.5 mmol) was added dropwise at 0°C during a 10 min period. After stirring at 0°C for 30 min the reaction mixture was left stirred at rt overnight. The solvent was removed under reduced pressure then the product was crashed out at -15°C by adding 30 mL MeOH. (*Note: In certain cases crystallization takes 15-20 min to begin. Adding a few drops of water can accelerate this slow process.*) The crystals were filtered, washed with cold MeOH and dried *in vacuo* to afford **29c** as a white solid (2.32 g, 50%). ^{1}H NMR (500 MHz, DMSO-d_6) δ=6.99/6.62 (t/s, *J* = 5.6 Hz, 1H), 4.41 (t, *J* = 6.1 Hz, 2H), 3.95 (s, 3H), 3.20 (q, *J* = 6.3 Hz, 2H), 2.01 (quint, *J* = 6.3 Hz, 2H), 1.34 ppm (s, 9H). Based on ^{1}H NMR the D rate at position 5, 6 and 7 is more than 98% and at position 3 it is 93%. ^{13}C NMR (125 MHz, DMSO-d_6) δ=164.8, 162.3, 155.7, 150.9, 148.2, 138.7, 126.5, 125.3, 124.1, 122.2, 102.4, 77.5, 67.4, 53.0, 36.7, 28.7, 28.2 ppm. HRMS (ESI) *m/z* calcd for $C_{19}D_4H_{20}N_3O_7$ $[M+H]^+$: 410.1860; found: 410.1855. According to LC-MS the rate of isotopologues is: <0.1% D_0; <0.1% D_1, 0.2% D_2, 9.2% D_3, 90.6% D_4.



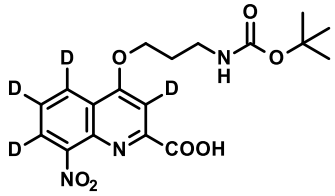
4-[3-(*tert*-butoxycarbonylamino)propoxy]-6-deuterio-8-nitro-quinoline-2-carboxylic acid (30a)

A 1 L round-bottom flask was filled with 9.14 g **29a** (22.5 mmol) and 670 mL THF. The flask was closed, flushed with nitrogen and a solution of 1.42 g LiOH•H_2O (1.50 equiv., 33.8 mmol) in 175 mL water was added. The reaction mixture was stirred for 1 h at rt then acidified to pH=4 by adding 1 M aq. HCl solution and extracted with DCM. The organic phase was washed with water and brine, then the combined washing solutions were extracted with DCM. The combined organic phase was dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo* to afford **30a** as a yellow solid (8.70 g, 98%). ^{1}H NMR (500 MHz, DMSO-d_6) δ=13.71 (br s, 1H), 8.44 (d, *J* = 1.3 Hz, 1H), 8.33 (d, *J* = 1.4 Hz, 1H), 7.65 (s, 1H), 6.99 (t, *J* = 5.7 Hz, 1H), 4.40 (t, *J* = 6.1 Hz, 2H), 3.20 (q, *J* = 6.3 Hz, 2H), 2.01 (quint, *J* = 6.5 Hz, 2H), 1.34 ppm (s, 9H). Based on ^{1}H NMR the D rate at position 6 is 98%. ^{13}C NMR (125 MHz, DMSO-d_6) δ=165.9, 162.2, 155.6, 152.1, 148.3, 138.8, 126.4, 125.5, 124.2, 122.2, 102.5, 77.5, 67.2, 36.7, 28.7, 28.2 ppm. HRMS (ESI) *m/z* calcd for $C_{18}DH_{21}N_3O_7$ $[M+H]^+$: 393.1515; found: 393.1514. According to LC-MS the rate of isotopologues is: 1.3% D_0; 98.7% D_1.



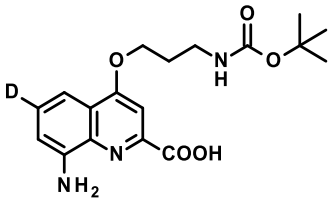
4-[3-(*tert*-butoxycarbonylamino)propoxy]-5,6,7-trideuterio-8-nitro-quinoline-2-carboxylic acid (30b)

A 1 L round-bottom flask was filled with 8.89 g **29b** (21.8 mmol) and 550 mL THF. The flask was closed, flushed with nitrogen and a solution of 1.37 g LiOH•H_2O (1.50 equiv., 32.7 mmol) in 140 mL water was added. The reaction mixture was stirred for 1 h at rt then acidified to pH=4 by adding 1 M aq. HCl solution and extracted with DCM. The organic phase was washed with water and brine, then the combined washing solutions were extracted with DCM. The combined organic phase was dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo* to afford **30b** as a yellow solid (8.60 g, 100%). ^{1}H NMR (400 MHz, DMSO-d_6) δ=13.69 (br s, 1H), 7.65 (s, 1H), 6.99/6.61 (t/s, *J* = 5.7 Hz, 1H), 4.40 (t, *J* = 6.1 Hz, 2H), 3.20 (q, *J* = 6.3 Hz, 2H), 2.01 (quint, *J* = 6.3 Hz, 2H), 1.34 ppm (s, 9H). Based on ^{1}H NMR the D rate at position 5, 6 and 7 is more than 98%. ^{13}C NMR (100 MHz, DMSO-d_6) δ=165.9, 162.2, 155.6, 152.1, 148.3, 138.8, 122.2, 102.5, 77.5, 67.2, 36.7, 28.7, 28.2 ppm. HRMS (ESI) *m/z* calcd for $C_{18}D_3H_{19}N_3O_7$ $[M+H]^+$: 395.1640; found:395.1642. According to LC-MS the rate of isotopologues is: <0.1% D_0; <0.1% D_1, 1.5% D_2, 98.5% D_3.



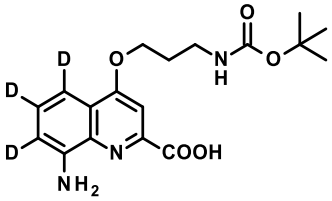
4-[3-(*tert*-butoxycarbonylamino)propoxy]-3,5,6,7-tetradeuterio-8-nitro-quinoline-2-carboxylic acid (30c)

A 1 L round-bottom flask was filled with 2.30 g **29c** (5.62 mmol) and 135 mL THF. The flask was closed, flushed with nitrogen and a solution of 354 mg LiOH•H_2O (1.50 equiv., 8.43 mmol) in 35.0 mL water was added. The reaction mixture was stirred for 1 h at rt then acidified to pH=4 by adding 1 M aq. HCl solution and extracted with DCM. The organic phase was washed with water and brine, then the combined washing solutions were extracted with DCM. The combined organic phase was dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo* to afford **30c** as a yellow solid (2.14 g, 96%). ^{1}H NMR (500 MHz, DMSO-d_6) δ=13.72 (br s, 1H), 6.99/6.62 (t/s, *J* = 5.6 Hz, 1H), 4.40 (t, *J* = 6.1 Hz, 2H), 3.20 (q, *J* = 6.3 Hz, 2H), 2.01 (quint, *J* = 6.3 Hz, 2H), 1.34 ppm (s, 9H). Based on ^{1}H NMR the D rate at position 5, 6 and 7 is more than 98% and at position 3 it is 93%. ^{13}C NMR (125 MHz, DMSO-d_6) δ=165.9, 162.2, 155.6, 152.1, 148.3, 138.8, 126.1, 125.2, 123.9, 122.2, 102.3, 77.5, 67.2, 36.7, 28.7, 28.2 ppm. HRMS (ESI) *m/z* calcd for $C_{18}D_4H_{18}N_3O_7$ $[M+H]^+$: 396.1703; found: 396.1702. According to LC-MS the rate of isotopologues is: <0.1% D_0; <0.1% D_1, 0.1% D_2, 9.3% D_3, 90.6% D_4.



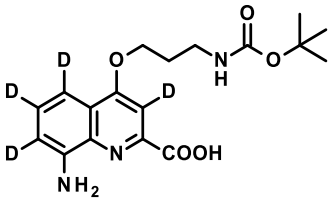
8-amino-4-[3-(*tert*-butoxycarbonylamino)propoxy]-6-deuterio-quinoline-2-carboxylic acid (31a)

A 1 L round-bottom flask was filled with 8.65 g **30a** (22.0 mmol), 920 mg Pd/C (10 m/m%) catalyst and 275 mL EtOAc. The reaction mixture was stirred vigorously under 1 atm. H_2 at rt overnight. 100 mL MeOH was added to dissolve the precipitated product then the catalyst was filtered and washed with MeOH. The filtrate was dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo* to afford **31a** as an orange solid (7.43 g, 93%). ^{1}H NMR (500 MHz, DMSO-d_6) δ=12.78 (br s, 1H), 7.46 (s, 1H), 7.22 (d, *J* = 1.1 Hz, 1H), 6.97 (t, *J* = 5.5 Hz, 1H), 6.87 (d, *J* = 1.1 Hz, 1H), 6.50 (br s, 2H), 4.29 (t, *J* = 6.2 Hz, 2H), 3.17 (q, *J* = 6.4 Hz, 2H), 1.97 (quint, *J* = 6.5 Hz, 2H), 1.36 ppm (s, 9H). Based on ^{1}H NMR the D rate at position 6 is 98%. ^{13}C NMR (100 MHz, DMSO-d_6) δ=166.1, 162.0, 155.6, 146.4, 145.4, 136.4, 128.6, 122.4, 109.4, 106.4, 99.4, 77.5, 66.3, 36.9, 29.0, 28.2 ppm. HRMS (ESI) *m/z* calcd for $C_{18}DH_{23}N_3O_5$ $[M+H]^+$: 363.1773; found: 363.1776. According to LC-MS the rate of isotopologues is: 1.3% D_0; 98.7% D_1.



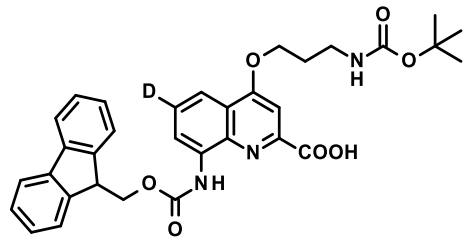
8-amino-4-[3-(*tert*-butoxycarbonylamino)propoxy]-5,6,7-trideuterio-quinoline-2-carboxylic acid (31b)

A 1 L round-bottom flask was filled with 8.60 g **30b** (21.8 mmol), 900 mg Pd/C (10 m/m%) catalyst and 250 mL EtOAc. The reaction mixture was stirred vigorously under 1 atm. H_2 at rt overnight. 100 mL MeOH was added to dissolve the precipitated product then the catalyst was filtered and washed with MeOH. The filtrate was dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo* to afford **31b** as an orange solid (7.64 g, 96%). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 12.78 (br s, 1H), 7.46 (s, 1H), 6.97 (t, *J* = 5.7 Hz, 1H), 6.50 (s, 2H), 4.29 (t, *J* = 6.2 Hz, 2H), 3.17 (q, *J* = 6.4 Hz, 2H), 1.97 (quint, *J* = 6.4 Hz, 2H), 1.36 ppm (s, 9H). Based on ^{1}H NMR the D rate at position 5, 6 and 7 is more than 98%. ^{13}C NMR (100 MHz, DMSO-d_6) δ=165.8, 162.2, 155.6, 146.4, 144.3, 136.2, 128.8, 122.5, 109.2, 106.0, 99.2, 77.5, 66.4, 36.9, 28.9, 28.2 ppm. HRMS (ESI) *m/z* calcd for $C_{18}D_3H_{21}N_3O_5$ $[M+H]^+$: 3665.1899; found: 365.1902. According to LC-MS the rate of isotopologues is: <0.1% D_0; <0.1% D_1, 2.0% D_2, 97.9% D_3.



8-amino-4-[3-(*tert*-butoxycarbonylamino)propoxy]-3,5,6,7-tetradeuterio-quinoline-2-carboxylic acid (31c)

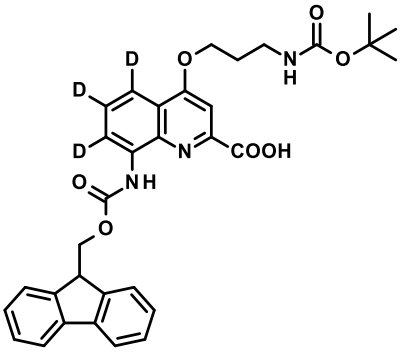
A 1 L round-bottom flask was filled with 2.14 g **30c** (5.41 mmol), 218 mg Pd/C (10 m/m%) catalyst, 20.0 mL MeOH and 55.0 mL EtOAc. The reaction mixture was stirred vigorously under 1 atm. H_2 at 35°C for 2 h. The catalyst was filtered and washed with MeOH. The filtrate was dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo* to afford **31c** as an orange solid (1.96 g, 99%). ^{1}H NMR (500 MHz, DMSO-d_6) δ=12.77 (br s, 1H), 6.97 (t, *J* = 5.6 Hz, 1H), 6.50 (br s, 2H), 4.29 (t, *J* = 6.2 Hz, 2H), 3.17 (q, *J* = 6.4 Hz, 2H), 1.97 (quint, *J* = 6.5 Hz, 2H), 1.36 ppm (s, 9H). Based on ^{1}H NMR the D rate at position 5, 6 and 7 is more than 98% and at position 3 it is 93%. ^{13}C NMR (125 MHz, DMSO-d_6) δ=165.8, 162.1, 155.6, 146.4, 144.3, 136.2, 128.7, 122.5, 109.2, 106.1, 99.0, 77.5, 66.4, 36.9, 28.9, 28.2 ppm. HRMS (ESI) *m/z* calcd for $C_{18}D_4H_{20}N_3O_5$ $[M+H]^+$: 366.1962; found: 366.1961. According to LC-MS the rate of isotopologues is: <0.1% D_0; <0.1% D_1, 0.2% D_2, 9.7% D_3, 90.1% D_4.



4-[3-(*tert*-butoxycarbonylamino)propoxy]-6-deuterio-8-(9*H*-fluoren-9-ylmethoxycarbonylamino)quinoline-2-carboxylic acid (2)

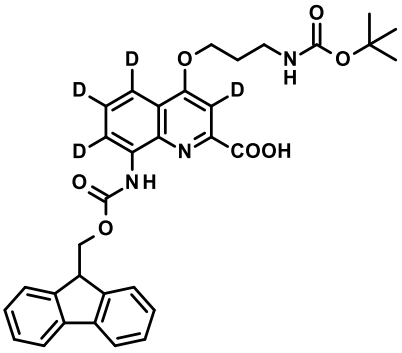
A 2 L round-bottom flask was filled with 7.31 g **31a** (20.2 mmol), 10.0 g $NaHCO_3$ (6.00 equiv., 120 mmol), 150 mL 1,4-dioxane and 450 mL water. The headspace of the flask was flushed with N_2 and fitted with a dropping funnel. The reaction mixture was cooled to 0°C and a solution of 9.20 g FmocCl (1.75 equiv., 35.6 mmol) in 1,4-dioxane (450 mL) was added dropwise during a 1 h period. The mixture was stirred for further 1 h at 0°C then at rt overnight. 800 mL water was added and the pH was adjusted to 4 by adding 2 M aq. HCl solution. The product was extracted with DCM, the combined organic phase was washed with water, dried over Na_2SO_4, filtered and the filtrate was

concentrated *in vacuo*. The crude product was purified by normal phase flash chromatography (330 g column, DCM/MeOH, gradient elution: 0-7%) then reversed phase preparative HPLC (Hanbon system, eluent: 25 mM aq. NH_4HCO_3/MeCN, gradient: 40-65%) to afford **2** as an off-white solid (4.29 g, 36%). HPLC-UV purity: 99.9%. ^{1}H NMR (500 MHz, DMSO-d_6) δ=13.52 (br s, 1H), 10.46 (br s, 1H), 8.36 (br s, 1H), 7.93 (d, *J* = 7.6 Hz, 2H), 7.82 (d, *J* = 1.1 Hz, 1H), 7.78 (d, *J* = 7.5 Hz, 2H), 7.62 (s, 1H), 7.44 (t, *J* = 7.4 Hz, 2H), 7.37 (td, *J* = 7.4 Hz, *J* = 1.1 Hz, 2H), 6.99 (t, *J* = 5.5 Hz, 1H), 4.61 (d, *J* = 6.7 Hz, 2H), 4.45 (t, *J* = 6.8 Hz, 1H), 4.37 (t, *J* = 6.1 Hz, 2H), 3.19 (q, *J* = 6.3 Hz, 2H), 2.00 (quint, *J* = 6.4 Hz, 2H), 1.35 ppm (s, 9H). The exact D ratios can not be given due to signal overlap. ^{13}C NMR (125 MHz, DMSO-d_6) δ=165.5, 162.7, 155.6, 153.5, 146.7, 143.7, 140.8, 137.5, 135.7, 128.1, 127.8, 127.2, 125.2, 121.9, 120.3, 116.4, 114.6, 100.4, 77.5, 66.9, 66.4, 46.6, 36.8, 28.9, 28.2 ppm. HRMS (ESI) *m/z* calcd for $C_{33}DH_{33}N_3O_7$ $[M+H]^+$: 585.2454; found: 585.2454. According to LC-MS the rate of isotopologues is: 1.3% D_0; 98.7% D_1.



4-[3-(*tert*-butoxycarbonylamino)propoxy]-5,6,7-trideuterio-8-(9*H*-fluoren-9-ylmethoxycarbonylamino)quinoline-2-carboxylic acid (4)

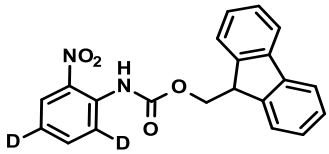
A 2 L round-bottom flask was filled with 7.64 g **31b** (21.0 mmol), 9.23 g $NaHCO_3$ (5.24 equiv., 110 mmol), 130 mL 1,4-dioxane and 390 mL water. The headspace of the flask was flushed with N_2 and fitted with a dropping funnel. The reaction mixture was cooled to 0°C and a solution of 8.51 g FmocCl (1.57 equiv., 33.0 mmol) in 1,4-dioxane (390 mL) was added dropwise during a 1 h period. The mixture was stirred for further 1 h at 0°C then at rt overnight. 750 mL water was added and the pH was adjusted to 4 by adding 2 M aq. HCl solution. The product was extracted with DCM, the combined organic phase was washed with water, dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The crude product was purified by normal phase flash chromatography (330 g column, DCM/MeOH, gradient elution: 0-7.0%) then reversed phase preparative HPLC (Hanbon system, eluent: 25 mM aq. NH_4HCO_3/MeCN, gradient: 40-65%) to afford **4** as an off-white solid (6.39 g, 52%). HPLC-UV purity: 99.9%. ^{1}H NMR (500 MHz, DMSO-d_6) δ=13.52 (br s, 1H), 10.45 (br s, 1H), 7.93 (d, *J* = 7.6 Hz, 2H), 7.78 (d, *J* = 7.4 Hz, 2H), 7.62 (s, 1H), 7.44 (t, *J* = 7.4 Hz, 2H), 7.36 (td, *J* = 7.5Hz, *J* = 1.1 Hz, 2H), 6.99 (t, *J* = 5.6 Hz, 1H), 4.61 (d, *J* = 6.9 Hz, 2H), 4.45 (t, *J* = 6.8 Hz, 1H), 4.37 (t, *J* = 6.1 Hz, 2H), 3.19 (q, *J* = 6.4 Hz, 2H), 2.00 (quint, *J* = 6.4 Hz, 2H), 1.35 ppm (s, 9H). Based on ^{1}H NMR the D rate at position 5, 6 and 7 is more than 98%. ^{13}C NMR (125 MHz, DMSO-d_6) δ=165.5, 162.7, 155.6, 153.5, 146.8, 143.7, 140.8, 137.4, 135.6, 127.8, 127.2, 125.2, 121.8, 120.3, 100.4, 77.5, 66.9, 66.4, 46.6, 36.8, 28.8, 28.2 ppm. HRMS (ESI) *m/z* calcd for $C_{33}D_3H_{31}N_3O_7$ $[M+H]^+$: 587.2580; found: 587.2580. According to LC-MS the rate of isotopologues is: <0.1% D_0; <0.1% D_1, 1.9% D_2, 98.1% D_3.



4-[3-(*tert*-butoxycarbonylamino)propoxy]-3,5,6,7-tetradeuterio-8-(9*H*-fluoren-9-ylmethoxycarbonylamino)quinoline-2-carboxylic acid (5)

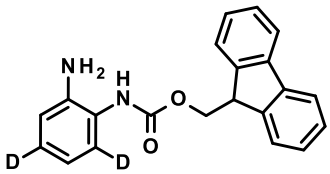
A 2 L round-bottom flask was filled with 1.96 g **31c** (5.36 mmol), 2.25 g $NaHCO_3$ (5.00 equiv., 26.8 mmol), 30.0 mL 1,4-dioxane and 100 mL water. The headspace of the flask was flushed with N_2 and fitted with a dropping funnel. The reaction mixture was cooled to 0°C and a solution of 2.08 g FmocCl (1.50 equiv., 8.04 mmol) in 1,4-dioxane (100 mL) was added dropwise during a 1 h period. The mixture was stirred for further 30 min at 0°C then at rt for 1 h. 200 mL water was added and the pH was adjusted to 4 by adding 2 M aq. HCl solution. The product was extracted with DCM, the combined organic phase was washed with water, dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The crude product was purified by normal phase flash chromatography (80 g column, DCM/MeOH, gradient elution: 0-7%) then reversed phase preparative HPLC (Hanbon system, eluent: 25 mM aq. NH_4HCO_3/MeCN, gradient: 40-65%) to afford **5** as an off-white solid (1.93 g, 61%). HPLC-UV purity: 99.9% ^{1}H NMR (500 MHz, DMSO-d_6) δ=13.53 (br s, 1H), 10.45 (br s, 1H), 7.93 (d, *J* = 7.6 Hz, 2H), 7.78 (d, *J* = 7.5 Hz, 2H), 7.44 (t, *J* = 7.4 Hz, 2H), 7.36 (td, *J* = 7.5Hz, *J* = 1.1 Hz, 2H), 6.99 (t, *J* = 5.6 Hz, 1H), 4.61 (d, *J* = 6.6 Hz, 2H), 4.44 (t, *J* = 6.8 Hz, 1H), 4.36 (t, *J* = 6.1 Hz, 2H), 3.19 (q, *J* = 6.3 Hz, 2H), 2.00 (quint, *J* = 6.4 Hz, 2H), 1.35 ppm (s, 9H). Based on ^{1}H NMR the D rate at position 5, 6 and 7 is more than 98% and at position 3 it is 90%. ^{13}C NMR (125 MHz, DMSO-d_6) δ=165.5, 162.6, 155.6, 153.5, 146.7, 143.7, 140.8, 137.4, 135.6, 127.8, 127.2, 125.2, 121.8, 120.3, 77.5, 66.9, 66.4, 46.6, 36.8, 28.8, 28.2 ppm. HRMS (ESI) *m/z*

calcd for $C_{33}D_4H_{30}N_3O_7$ $[M+H]^+$: 588.2642; found: 588.2640. According to LC-MS the rate of isotopologues is: <0.1% D_0; <0.1% D_1, 0.2% D_2, 9.6% D_3, 90.2% D_4.



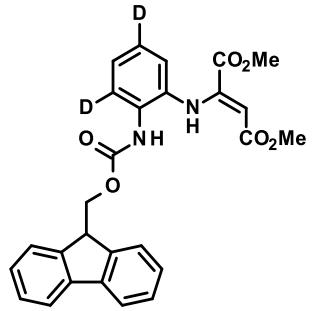
9*H*-fluoren-9-ylmethyl *N*-(2,4-dideuterio-6-nitro-phenyl)carbamate (32)

A 50 mL microwave reaction vial was filled with a finely ground mixture of 3.55 g **7** (25.0 mmol) and 7.10 g FmocCl (1.10 equiv., 27.5 mmol). The reaction mixture was stirred and heated to 110°C by MW irradiation at a rate of 5.0°C/min to avoid overheating then stirred at 110°C for 30 min. The vial was cooled to rt, vented carefully and the content was dissolved in 30 mL DCM. The solution was washed with water, dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The residue was recrystallized from EtOAc and dried *in vacuo* to afford **32** as pale yellow crystals (7.09 g, 78%). ^{1}H NMR (500 MHz, DMSO-d_6) δ=9.95 (s, 1H), 7.95 (d, *J* = 1.6 Hz, 1H), 7.91 (d, *J* = 7.5 Hz, 2H), 7.73 (dd, *J* = 7.5 Hz, *J* = 0.7 Hz, 2H), 7.67 (d, *J* = 1.5 Hz, 1H), 7.43 (t, *J* = 7.3 Hz, 2H), 7.35 (td, *J* = 7.4 Hz, *J* = 1.1 Hz, 2H), 4.46 (d, *J* = 6.9 Hz, 2H), 4.31 ppm (t, *J* = 6.8 Hz, 1H). Based on ^{1}H NMR the D rate at position 4 and 6 is more than 98%. ^{13}C NMR (125 MHz, DMSO-d_6) δ=153.5, 143.5, 141.8, 140.8, 133.8, 131.7, 127.8, 127.2, 125.2, 125.1, 120.2, 66.4, 46.4 ppm. HRMS (ESI) *m/z* calcd for $C_{21}D_2H_{14}N_2O_4Na$ $[M+Na]^+$: 385.1128; found: 385.1128. According to LC-MS the rate of isotopologues is: 0.1% D_0; 3.1% D_1, 96.8% D_2. NH_4^+ adduct was used for quantification.



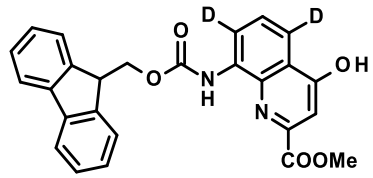
9*H*-fluoren-9-ylmethyl *N*-(2-amino-4,6-dideuterio-phenyl)carbamate (8)

A 2 L round-bottom flask was filled with 28.3 g **32** (78.1 mmol), 2.08 g Pd/C (10 m/m%) catalyst and 780 mL MeOH. The reaction mixture was stirred vigorously under 1 atm. H_2 at rt for 2 h. 750 mL DCM was added to dissolve the precipitated product then the catalyst was filtered and washed with DCM. The filtrate was dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo* to afford **8** as an orange solid (24.7 g, 95%). ^{1}H NMR (500 MHz, DMSO-d_6, T=343K) δ=8.52 (s, 1H), 7.89 (d, *J* = 7.6 Hz, 2H), 7.72 (d, *J* = 7.5 Hz, 2H), 7.42 (t, *J* = 7.1 Hz, 2H), 7.33 (td, *J* = 7.5 Hz, *J* = 1.0 Hz, 2H), 6.73 (d, *J* = 1.5 Hz, 1H), 6.54 (d, *J* = 1.2 Hz, 1H), 4.80 (br s, 2H), 4.41 (d, *J* = 7.0 Hz, 2H), 4.28 ppm (t, *J* = 7.0 Hz, 1H). Based on ^{1}H NMR the D rate at position 4 and 6 is more than 98%. ^{13}C NMR (125 MHz, DMSO-d_6, T=343K) δ=154.1, 143.6, 141.5, 140.5, 127.3, 126.7, 124.9, 122.9, 119.7, 115.8, 115.4, 65.5, 46.6 ppm. HRMS (ESI) *m/z* calcd for $C_{21}D_2H_{17}N_2O_2$ $[M+H]^+$: 333.1566; found: 333.1568. According to LC-MS the rate of isotopologues is: 0.1% D_0; 3.1% D_1, 96.8% D_2.



Dimethyl (*Z*)-2-[3,5-dideuterio-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)anilino]but-2-enedioate (33)

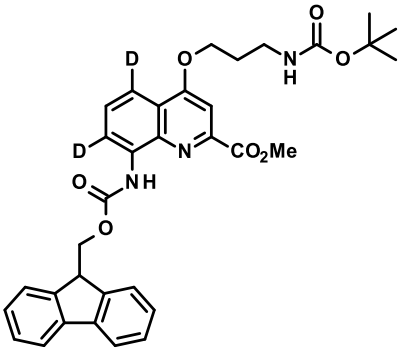
To a well stirred suspension of 25.4 g **8** (76.4 mmol) in 150 mL anhydrous MeOH 10.3 mL DMAD (1.10 equiv., 84.1 mmol) was added at rt. After 2 h stirring at rt the solvent was removed *in vacuo* and the residue was purified by normal phase flash chromatography (750 g column, heptane/EtOAc, gradient elution: 20-50%) to give **33** as a bright yellow solid (30.2 g, 83%). ^{1}H NMR (500 MHz, DMSO-d_6) δ=9.46 (s, 1H), 9.29 (s, 1H), 7.88 (dd, *J* = 7.6 Hz, *J* = 0.8 Hz, 2H), 7.69 (d, *J* = 7.8 Hz, 2H), 7.44-7.39 (m, 2H), 7.33-7.29 (m, 2H), 7.22 (s, 1H), 7.12 (d, *J* = 1.3 Hz, 1H), 6.83 (d, *J* = 0.9 Hz, 1H), 5.27 (s, 1H), 4.45 (d, *J* = 7.2 Hz, 2H), 4.34 (t, *J* = 7.2 Hz, 1H), 3.59 (s, 3H), 3.58 ppm (s, 3H). The exact D ratios can not be given due to signal overlap. ^{13}C NMR (125 MHz, DMSO-d_6) δ=167.8, 163.8, 154.2, 147.6, 143.5, 140.5, 134.6, 130.2, 127.3, 126.7, 124.8, 124.4, 122.1, 119.7, 92.8, 66.0, 52.3, 50.4, 46.4 ppm. HRMS (ESI) *m/z* calcd for $C_{27}D_2H_{23}N_2O_6$ $[M+H]^+$: 475.1833; found: 475.1834. According to LC-MS the rate of isotopologues is: <0.1% D_0; 3.1% D_1, 96.9% D_2.



Methyl 5,7-dideuterio-8-(9*H*-fluoren-9-ylmethoxycarbonylamino)-4-hydroxy-quinoline-2-carboxylate (34)

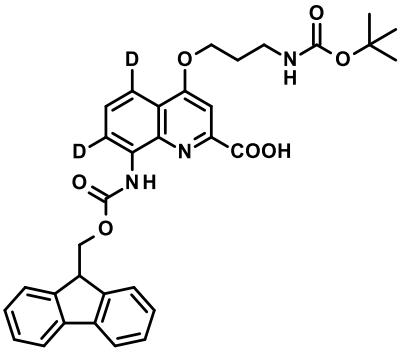
30.1 g **33** (63.4 mmol) was added to 280 mL of Eaton's reagent at rt while stirring vigorously. Stirring was continued for 3 h at 50°C, then the reaction mixture was poured into 600 mL ice cold MeCN and during a 10 min period 300 g crushed ice was added in small portions.

The solution was diluted with 900 mL water and extracted with DCM. The combined organic phase was washed with sat. aq. $NaHCO_3$ solution, dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography (330 g column, DCM/MeOH, gradient elution: 0-30%) to afford **34** as an orange solid (16.2 g, 58%). ^{1}H NMR (500 MHz, DMSO-d_6) δ=12.13 (br s, 1H), 9.10 (br s, 1H), 7.93 (d, *J* = 7.6 Hz, 2H), 7.74 (d, *J* = 7.4 Hz, 2H), 7.54 (br s, 2H), 7.44 (t, *J* = 7.4 Hz, 2H), 7.36 (d, *J* = 7.3 Hz, 2H), 4.63 (d, *J* = 5.6 Hz, 2H), 4.42 (t, *J* = 5.7 Hz, 1H), 3.94 ppm (s, 3H). Based on ^{1}H NMR the D rate at position 5 and 7 is more than 98%. ^{13}C NMR (125 MHz, DMSO-d_6) δ=165.0, 162.6, 152.6, 146.7, 143.7, 140.8, 138.4, 134.3, 127.7, 127.2, 125.0, 121.4, 120.2, 115.0, 104.9, 66.3, 52.8, 46.6 ppm. HRMS (ESI) *m/z* calcd for $C_{26}D_2H_{19}N_2O_5$ $[M+H]^+$: 443.1570; found: 443.1569. According to LC-MS the rate of isotopologues is: <0.1% D_0; 3.6% D_1, 96.3% D_2.



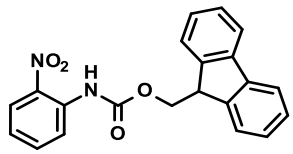
Methyl 4-[3-(*tert*-butoxycarbonylamino)propoxy]-5,7-dideuterio-8-(9*H*-fluoren-9-ylmethoxycarbonylamino)quinoline-2-carboxylate (35)

A 250 mL pear-shaped flask was filled with 16.1 g **34** (36.6 mmol), 8.4 mL *tert*-butyl *N*-(3-hydroxypropyl)carbamate (1.32 equiv., 48.3 mmol) and 12.1 g PPh_3 (1.26 equiv., 46.1 mmol). The flask was closed and flushed with nitrogen then 90 mL anhydrous THF was added. 9.1 mL DIAD (1. 26 equiv., 46.1 mmol) was added dropwise at 0°C during a 10 min period. After stirring at 0°C for 30 min the reaction mixture was left stirred at rt for 1 h. The product was crashed out at 0°C by adding 420 mL MeOH. The crystals were filtered, washed with cold MeOH and dried *in vacuo*. The mother liquor was concentrated to 40 mL, diluted with 150 mL MeOH, cooled to 0°C and filtered to give a second crop of crystals. **35** was obtained as a white crystalline solid (together 16.5 g, 75%). ^{1}H NMR (500 MHz, DMSO-d_6) δ=9.11 (br s, 1H), 7.94 (d, *J* = 7.6 Hz, 2H), 7.75 (dd, *J* = 7.4 Hz, *J* = 0.6 Hz, 2H), 7.61 (br s, 1H), 7.58 (s, 1H), 7.44 (t, *J* = 7.4 Hz, 2H), 7.36 (td, *J* = 7.5 Hz, *J* = 1.1 Hz, 2H), 6.98 (t, *J* = 5.7 Hz, 1H), 4.64 (d, *J* = 6.3 Hz, 2H), 4.42 (t, *J* = 6.3 Hz, 1H), 4.35 (t, *J* = 6.1 Hz, 2H), 3.97 (s, 3H), 3.19 (q, *J* = 6.3 Hz, 2H), 2.00 (quint, *J* = 6.3 Hz, 2H), 1.35 ppm (s, 9H). Based on ^{1}H NMR the D rate at position 5 and 7 is more than 98%. ^{13}C NMR (125 MHz, DMSO-d_6) δ=165.0, 162.5, 155.6, 152.6, 147.1, 143.7, 140.8, 137.8, 134.5, 128.0, 127.8, 127.2, 125.0, 121.4, 120.2, 101.6, 77.5, 66.9, 66.4, 52.9, 46.5, 36.8, 28.8, 28.2 ppm. HRMS (ESI) *m/z* calcd for $C_{34}D_2H_{34}N_3O_7$ $[M+H]^+$: 600.2673; found: 600.2668. According to LC-MS the rate of isotopologues is: <0.1% D_0; 3.6% D_1, 96.3% D_2.



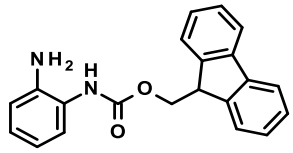
4-[3-(*tert*-butoxycarbonylamino)propoxy]-5,7-dideuterio-8-(9*H*-fluoren-9-ylmethoxycarbonylamino)quinoline-2-carboxylic acid (3)

A 1 L round-bottom flask was filled with 16.4 g **35** (27.4 mmol), 385 mL THF and 190 mL water. The headspace of the flask was flushed with N_2 and fitted with a dropping funnel. A solution of 1.27 g LiOH•H_2O (1.10 equiv., 30.1 mmol) in 190 mL water was added dropwise at rt during a 30 min period. The reaction mixture was stirred for 2 h at rt then acidified to pH=5 by adding glacial acetic acid and extracted with DCM. The combined organic phase was dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo* and purified by reversed phase preparative HPLC (Hanbon system, eluent: 25 mM aq. NH_4HCO_3/MeCN, gradient: 5-90%) to afford **3** as an off-white solid (12.9 g, 80%). HPLC-UV purity: 99.7%. ^{1}H NMR (500 MHz, DMSO-d_6) δ=13.52 (br s, 1H), 10.45 (br s, 1H), 7.93 (d, *J* = 7.5 Hz, 2H), 7.78 (d, *J* = 7.5 Hz, 2H), 7.62 (br s, 2H), 7.44 (t, *J* = 7.4 Hz, 2H), 7.36 (td, *J* = 7.4 Hz, *J* = 0.8 Hz, 2H), 6.99 (t, *J* = 5.6 Hz, 1H), 4.61 (d, *J* = 6.7 Hz, 2H), 4.45 (t, *J* = 6.8 Hz, 1H), 4.37 (t, *J* = 6.1 Hz, 2H), 3.19 (q, *J* = 6.3 Hz, 2H), 2.00 (quint, *J* = 6.4 Hz, 2H), 1.35 ppm (s, 9H). Based on ^{1}H NMR the D rate at position 5 and 7 is more than 98%. ^{13}C NMR (125 MHz, DMSO-d_6) δ=165.5, 162.7, 155.6, 153.5, 146.7, 143.7, 140.8, 137.4, 135.6, 128.2, 127.8, 127.2, 125.2, 121.8, 120.3, 100.4, 77.5, 66.9, 66.4, 46.6, 36.8, 28.8, 28.2 ppm. HRMS (ESI) *m/z* calcd for $C_{33}D_2H_{32}N_3O_7$ $[M+H]^+$: 586.2517; found: 586.2510. According to LC-MS the rate of isotopologues is: <0.1% D_0; 3.8% D_1, 96.2% D_2.



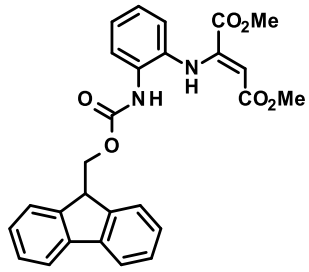
9*H*-fluoren-9-ylmethyl *N*-(2-nitrophenyl)carbamate (36)

A 10 mL microwave reaction vial was filled with a finely ground mixture of 691 mg 2-nitroaniline (5.00 mmol) and 1.42 g FmocCl (1.10 equiv., 5.5 mmol). The reaction mixture was stirred and heated to 110°C by MW irradiation at a rate of 5.0°C/min to avoid overheating then stirred at 110°C for 30 min. The vial was cooled to rt, vented carefully and the content was dissolved in 5 mL DCM. The solution was washed with water, dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The residue was sonicated with 15 mL DIPE, filtered, washed with 3x2 mL DIPE and dried *in vacuo* to afford **36** as pale yellow crystals (800 mg, 44%). ^{1}H NMR (500 MHz, DMSO-d_6) δ=9.96 (s, 1H), 7.95 (dd, *J* = 8.2 Hz, *J* = 1.5 Hz, 1H), 7.91 (d, *J* = 7.5 Hz, 2H), 7.73 (d, *J* = 7.5 Hz, 2H), 7.67 (ddd, *J* = 8.2 Hz , *J* = 7.3 Hz *J* = 1.5 Hz, 1H), 7.59 (dd, *J* = 8.2 Hz, *J* = 1.2 Hz, 1H), 7.43 (t, *J* = 4.9 Hz, 2H), 7.36-7.31 (m, 3H), 4.46 (d, *J* = 6.9 Hz, 2H), 4.31 ppm (t, *J* = 6.8 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ=153.5, 143.6, 141.8, 140.8, 134.0, 131.8, 127.8, 127.2, 125.2, 124.81, 124.79, 120.2, 66.4, 46.4. HRMS (ESI) *m/z* calcd for $C_{21}H_{20}N_3O_4$ $[M+NH_4]^+$: 378.1448; found: 378.1449.



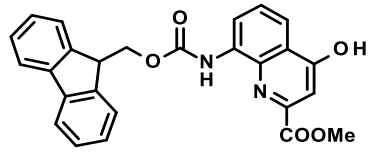
9*H*-fluoren-9-ylmethyl *N*-(2-aminophenyl)carbamate (37)

A 100 mL round-bottom flask was filled with 780 mg **36** (2.16 mmol), 57.6 mg Pd/C (10 m/m%) catalyst and 21.6 mL MeOH. The reaction mixture was stirred vigorously under 1 atm. H_2 at rt for 2 h. 20 mL DCM was added to dissolve the precipitated product then the catalyst was filtered and washed with DCM. The filtrate was dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The crude product was purified by normal phase flash chromatography (40 g column, DCM/MeOH, gradient elution: 0-10%) to afford **37** as a yellow solid (620 mg, 87%). ^{1}H NMR (500 MHz, DMSO-d_6) δ=8.74 (br s, 1H), 7.91 (d, *J* = 7.6 Hz, 2H), 7.75 (br s, 2H), 7.43 (t, *J* = 7.4 Hz, 2H), 7.34 (br t, 2H), 7.13 (br s, 1H), 6.88 (td, *J* = 7.6 Hz, *J* = 1.2 Hz, 1H), 6.69 (dd, *J* = 8.0 Hz, *J* = 1.4 Hz, 1H), 6.52 (t, *J* = 7.4 Hz, 1H), 4.87 (s, 2H), 4.39 (d, *J* = 7.0 Hz, 2H), 4.29 ppm (br t, 1H). 1H-NMR spectra is in agreement with the one reported in the literature.[5] ^{13}C NMR (125 MHz, DMSO-d_6) δ=154.4, 143.8, 140.8, 127.7, 127.1, 125.61, 125.59, 125.3, 120.2, 116.2, 115.6, 65.7, 46.7 ppm. HRMS (ESI) *m/z* calcd for $C_{21}H_{19}N_2O_2$ $[M+H]^+$: 331.1441; found: 331.1441.



Dimethyl (*Z*)-2-[2-(9*H*-fluoren-9-ylmethoxycarbonylamino)anilino]but-2-enedioate (38)

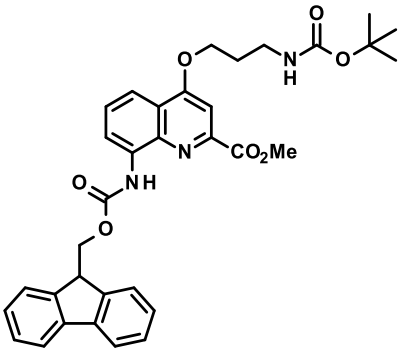
To a well stirred suspension of 500 mg **37** (1.51 mmol) in 3.00 mL anhydrous MeOH, 205 µL DMAD (1.10 equiv., 1.67 mmol) was added at rt. After 2 h stirring at rt the solvent was removed *in vacuo* and the residue was purified by normal phase flash chromatography (40 g column, heptane/EtOAc, gradient elution: 0-60%) to give **38** as a bright yellow solid (380 mg, 53%). ^{1}H NMR (500 MHz, DMSO-d_6) δ=9.56/8.84 (br s/br s, 1H), 9.54/8.76 (s/s, 1H), 7.91 (d, *J* = 7.6 Hz, 2H), 7.71 (br , 2H), 7.50 (br s, 1H), 7.44-7.40 (m, 2H), 7.35-7.28 (m, 2H), 7.23 (br s, 1H), 7.18/6.80 (m/m, 1H), 7.15-7.10 (m, 1H), 5.26/4.70 (s/s, 1H); 4.45/4.40 (d/d, *J* = 7.1 Hz/*J* = 7.1 Hz, 2H), 4.34/4.30 (t/t, *J* = 6.3 Hz/ *J* = 6.3 Hz, 1H), 3.568/3.43 (s/s, 3H), 3.570/3.76 ppm (s/s, 3H). Presence of amide rotamers at rt. ^{13}C NMR (125 MHz, DMSO-d_6) δ= 168.1, 164.2, 154.5, 153.9, 147.9, 143.7, 140.7, 134.9, 130.1, 127.7, 127.1, 125.6, 125.2, 125.0, 122.4, 120.2, 93.1, 66.2, 52.8, 50.9, 46.5 ppm. HRMS (ESI) *m/z* calcd for $C_{27}H_{25}N_2O_6$ $[M+H]^+$: 473.1707; found: 473.1711.



Methyl 8-(9*H*-fluoren-9-ylmethoxycarbonylamino)-4-hydroxy-quinoline-2-carboxylate (39)

333 mg **38** (0.70 mmol) was added to 2.79 mL of Eaton's reagent at rt while stirring vigorously. Stirring was continued for 3 h at 50°C, then the reaction mixture was poured into 10.0 mL ice cold MeCN and during a 10 min period 5.00 g ice was added in portions. The solution was diluted with 30 mL water and extracted with DCM. The combined organic phase was washed with sat. aq. $NaHCO_3$ solution, dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography (40 g column, heptane/EtOAc, gradient elution: 0-60%) to afford **39** as an orange solid (64.1 mg, 21%). ^{1}H NMR (400 MHz, DMSO-d_6) δ=12.13 (br s, 1H), 9.11 (br s, 1H), 8.13 (br s, 1H), 7.93 (d, *J* = 7.5 Hz, 2H), 7.80 (d, *J* = 7.8 Hz, 1H), 7.74 (d, *J* = 7.4 Hz, 2H), 7.54 (br s, 2H), 7.44 (t, *J* = 7.4 Hz, 2H), 7.36 (t, *J* = 7.0 Hz, 2H), 4.63 (d, *J* = 6.1 Hz, 2H), 4.42 (t, *J* = 5.9 Hz, 1H), 3.94 ppm (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ=165.0, 162.6, 152.6,

146.7, 143.7, 140.8, 138.4, 134.4, 127.7, 127.4, 127.2, 125.0, 121.4, 120.2, 115.5, 115.2, 104.9, 66.3, 52.8, 46.6 ppm. HRMS (ESI) *m/z* calcd for $C_{26}H_{21}N_2O_5$ $[M+H]^+$: 441.1445; found: 441.1449.



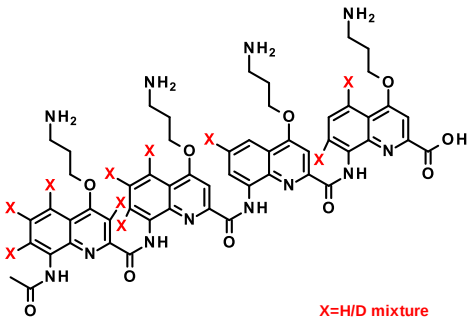
Methyl 4-[3-(*tert*-butoxycarbonylamino)propoxy]-8-(9*H*-fluoren-9-ylmethoxycarbonylamino)quinoline-2-carboxylate (40)
A 4 mL screw-cap vial was filled with 49.0 mg **39** (0.11 mmol), 21.0 µL *tert*-butyl *N*-(3-hydroxypropyl)carbamate (1.10 equiv., 0.12 mmol) and 30.6 mg PPh_3 (1.05 equiv., 0.12 mmol). The vial was closed and flushed with nitrogen then 0.25 mL anhydrous THF was added. 23.0 µL DIAD (1.05 equiv., 0.12 mmol) was added dropwise at 0°C during a 10 min period. After stirring at 0°C for 30 min the reaction mixture was left stirred at rt for 18 h. The product was crashed out at 0°C by adding 1.00 mL MeOH. The crystals were filtered, washed with cold MeOH and dried *in vacuo* to afford **40** as a white crystalline solid (46.8 mg, 70%). ^{1}H NMR (500 MHz, DMSO-d_6) δ=9.11 (s, 1H), 8.17 (br s, 1H), 7.94 (d, *J* = 7.6 Hz, 2H), 7.82 (d, *J* = 7.6 Hz, 1H), 7.75 (d, *J* = 7.5 Hz, 2H), 7.61 (t, *J* = 7.9 Hz, 1H), 7.58 (s, 1H), 7.44 (t, *J* = 7.4 Hz, 2H), 7.36 (td, *J* = 7.4 Hz, *J* = 70.8 Hz, 2H), 6.98/6.61 (t/s, 1H, *J* = 5.5 Hz), 4.64 (d, *J* = 6.2 Hz, 2H), 4.42 (t, *J* = 6.2 Hz, 1H), 4.35 (t, *J* = 6.1 Hz, 2H), 3.97 (s, 3H), 3.19 (q, *J* = 6.3 Hz, 2H), 2.00 (quint, *J* = 6.4 Hz, 2H), 1.35 ppm (s, 9H). ^{13}C NMR (125 MHz, DMSO-d_6) δ= 165.0, 162.5, 152.6, 147.1, 143.7, 140.8, 137.8, 134.5, 128.2, 127.8, 127.2, 125.0, 121.5, 120.2, 117.0, 115.9, 114.9, 101.6, 77.5, 66.9, 66.4, 52.9, 46.5, 36.8, 28.8, 28.2 ppm. HRMS (ESI) *m/z* calcd for $C_{34}H_{36}N_3O_7$ $[M+H]^+$: 598.2548; found: 598.2550.

3.4. Tetramer synthesis

General procedure

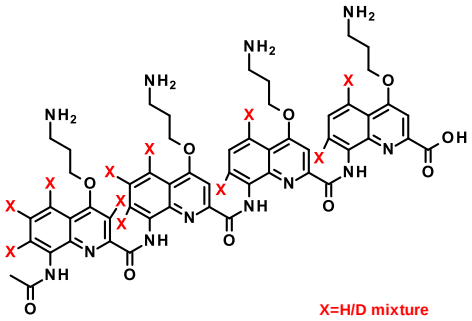
The solid phase synthesis of the amine common precursor of oligomers **11**-**20** as well as the final *N*-terminal acetylation to give oligomers **11**-**20** were carried out on a 12.0 µmol scale using reported methods[6,7] using defined mixtures of monomer isotopologues **1**-**5**. Cleavage of tetramers **11-20** from the resin was performed following reported method[6] then crude products were precipitated in cold ether, dried under vacuum and analyzed directly by LCMS and HRMS. Given yields are based on the obtained mass of the crude compound and their purity shown by HPLC.

Synthesis of compound 11 (DCAB)



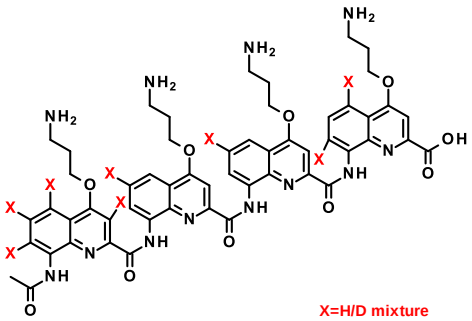
Synthesis was performed according to the general procedure. The first coupled monomer mixture contained 50 n/n% **3** and 50 n/n% **1**. The second coupled monomer mixture contained 50 n/n% **2** and 50 n/n% **1**. The third coupled monomer mixture contained 25 n/n% **4** and 75 n/n% **1**. The fourth coupled monomer mixture contained 25 n/n% **5** and 75 n/n% **1**. Yield: 96%. ^{1}H NMR (300 MHz, DMSO-d_6) δ=12.54 (br s, 1H), 12.20 (s, 1H), 11.76 (s, 1H), 11.68 (s, 1H), 9.08(s, 1H), 8.97 (t, *J* = 3.2 Hz, 1H*), 8.44 (d, *J* = 7.5 Hz, 1H*), 8.10-7.74 (m, 17H), 7.45 (t, *J* = 7.0 Hz, 1H*), 7.37 (t, *J* = 7 Hz, 1H*), 7.26 (s, 1H*), 6.76 (s, 1H), 6.64 (s, 1H), 4.69-4.52 (m, 4H), 4.38-4.10 (m, 4H), 3.29-3.11 (m, 11H), 2.44-2.19 (m, 7H) ppm. * corresponds to protons lower in concentration due to D /H mixtures.

Synthesis of compound 12 (DCBB)



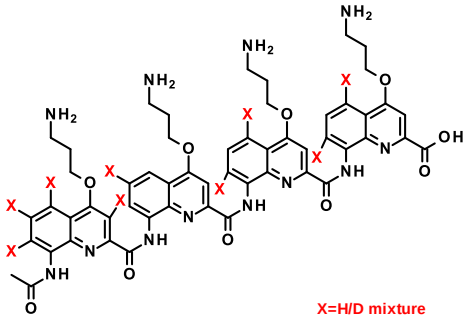
Synthesis was performed according to the general procedure. The first coupled monomer mixture contained 50 n/n% **3** and 50 n/n% **1**. The second coupled monomer mixture contained 25 n/n% **3** and 75 n/n% **1**. The third coupled monomer mixture contained 25 n/n% **4** and 75 n/n% **1**. The fourth coupled monomer mixture contained 25 n/n% **5** and 75 n/n% **1**. Yield: 80%. ^{1}H NMR (300 MHz, DMSO-d_6) δ=12.54 (br s, 1H), 12.20 (s, 1H), 11.76 (s, 1H), 11.69 (s, 1H), 9.08 (s, 1H), 8.98 (t, *J* = 3.2 Hz, 1H*), 8.44 (d, *J* = 7.5 Hz, 1H*), 8.10-7.74 (m, 17H), 7.45 (t, *J* = 7.0 Hz, 1H*), 7.37 (t, *J* = 7 Hz, 1H*), 7.26 (s, 1H*), 6.75 (s, 1H), 6.64 (s, 1H), 4.69-4.52 (m, 4H), 4.38-4.10 (m, 4H), 3.29-3.11 (m, 11H), 2.44-2.19 (m, 7H) ppm. * corresponds to protons twice lower in concentration due to D /H mixtures.

Synthesis of compound 13 (DAAB)



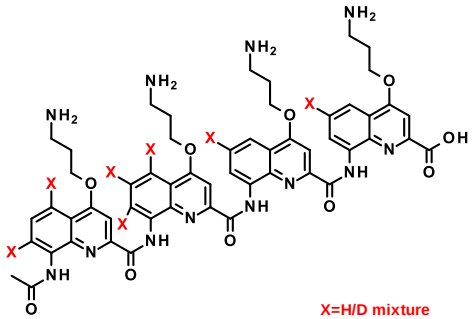
Synthesis was performed according to the general procedure. The first coupled monomer mixture contained 50 n/n% **3** and 50 n/n% **1**. The second coupled monomer mixture contained 50 n/n% **2** and 50 n/n% **1**. The third coupled monomer mixture contained 75 n/n% **2** and 25 n/n% **1**. The fourth coupled monomer mixture contained 25 n/n% **5** and 75 n/n% **1**. Yield: 72%.

Synthesis of compound 14 (DABB)



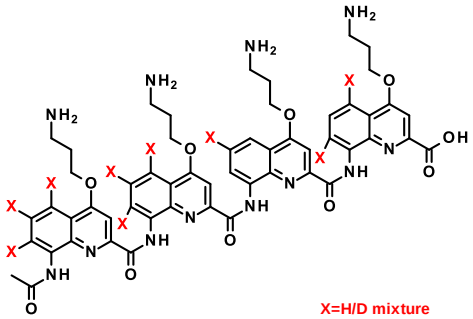
Synthesis was performed according to the general procedure. The first coupled monomer mixture contained 50 n/n% **3** and 50 n/n% **1**. The second coupled monomer mixture contained 25 n/n% **3** and 75 n/n% **1**. The third coupled monomer mixture contained 75 n/n% **2** and 25 n/n% **1**. The fourth coupled monomer mixture contained 25 n/n% **5** and 75 n/n% **1**. Yield: 69%. ^{1}H NMR (300 MHz, DMSO-d_6) δ=12.19 (s, 1H), 11.76 (s, 1H), 11.68 (s, 1H), 9.07 (s, 1H*), 8.97 (d, *J* = 7.2 Hz, 1H*), 8.44 (d, *J* = 7.1 Hz, 1H*), 8.00-7.73 (m, 13H*), 7.79 (s, 1H*), 7.74 (s, 1H*), 7.45 (t, *J* = 7.0 Hz, 1H*), 7.37 (t, *J* = 7.0 Hz, 1H*), 7.28-7.26 (m, 1H*), 7.25 (s, 1H*), 6.74 (s, 1H*), 6.64 (s, 1H), 4.71-4.50(m, 4H), 4.37-4.11 (m, 4H), 3.28-3.11 (m, 8H*), 2.74-2.71 (m, 1H*), 2.43-2.20 (m, 7H) ppm. * corresponds to protons lower in concentration due to D /H mixtures.

Synthesis of compound 15 (BCAA)



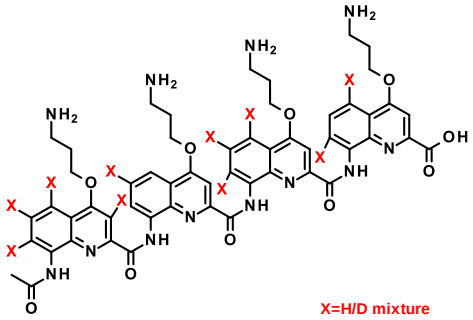
Synthesis was performed according to the general procedure. The first coupled monomer mixture contained 25 n/n% **2** and 75 n/n% **1**. The second coupled monomer mixture contained 50 n/n% **2** and 50 n/n% **1**. The third coupled monomer mixture contained 25 n/n% **4** and 75 n/n% **1**. The fourth coupled monomer mixture contained 75 n/n% **3** and 25 n/n% **1**. Yield: 78%. ^{1}H NMR (300 MHz, DMSO-d_6) δ=12.54 (br s, 1H), 12.20 (s, 1H), 11.77 (s, 1H), 11.68 (s, 1H), 9.087 (s, 1H), 8.96 (t, *J* = 3.2 Hz, 1H*), 8.44 (d, *J* = 7.5 Hz, 1H*), 8.10-7.66 (m, 17H), 7.48-7.30 (m, 1H*), 7.37 (s, 1H), 7.26 (s, 1H), 6.75 (s, 1H), 6.64 (s, 1H), 4.69-4.49 (m, 4H), 4.39-4.11 (m, 4H), 3.30-3.09 (m, 11H), 3.02-2.99 (m, 1H*), 2.74-2.71 (m, 1H*), 2.43-2.18 (m, 7H) ppm. * corresponds to protons lower in concentration due to D /H mixtures.

Synthesis of compound 16 (CCAB)



Synthesis was performed according to the general procedure. The first coupled monomer mixture contained 50 n/n% **3** and 50 n/n% **1**. The second coupled monomer mixture contained 50 n/n% **2** and 50 n/n% **1**. The third coupled monomer mixture contained 25 n/n% **4** and 75 n/n% **1**. The fourth coupled monomer mixture contained 40 n/n% **4** and 50 n/n% **1**. Yield: 71%. ^{1}H NMR (300 MHz, DMSO-d_6) δ=12.54 (br s, 1H), 12.20 (s, 1H), 11.76 (s, 1H), 11.68 (s, 1H), 9.08(s, 1H), 8.97 (t, *J* = 3.2 Hz, 1H*), 8.45 (d, *J* = 7.5 Hz, 1H*), 8.13-7.74 (m, 17H), 7.46 (t, *J* = 7.0 Hz, 1H*), 7.38 (t, *J* = 7 Hz, 1H*), 7.26 (s, 1H*), 6.76 (s, 1H), 6.65 (s, 1H), 4.69-4.53 (m, 4H), 4.38-4.10 (m, 4H), 3.29-3.11 (m, 11H), 2.74-2.71 (m, 1H), 2.44-2.19 (m, 7H) ppm. * corresponds to protons lower in concentration due to D /H mixtures.

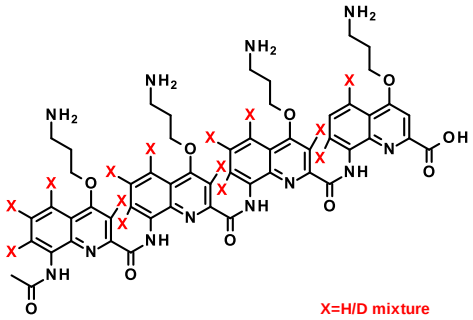
Synthesis of compound 17 (DACB)



X=H/D mixture

Synthesis was performed according to the general procedure. The first coupled monomer mixture contained 50 n/n% **3** and 50 n/n% **1**. The second coupled monomer was 100 n/n% **4**. The third coupled monomer mixture contained 75 n/n% **2** and 25 n/n% **1**. The fourth coupled monomer mixture contained 25 n/n% **5** and 75 n/n% **1**. Yield: 68%. ^{1}H NMR (300 MHz, DMSO-d_6) δ=12.50 (br s, 1H), 12.20 (s, 1H), 11.77 (s, 1H), 11.68 (s, 1H), 9.07 (s, 1H*), 8.44 (d, *J* = 7.1 Hz, 1H*), 8.05-7.72 (m, 12H*), 7.88 (s, 1H*), 7.79 (s, 1H*), 7.74 (s, 1H*), 7.45 (t, *J* = 7.0 Hz, 1H*), 7.37 (t, *J* = 7.0 Hz, 1H*), 7.28-7.26 (m, 1H*), 7.25 (s, 1H*), 6.87 (s, 1H*), 6.75 (s, 1H*), 6.64 (s, 1H), 4.72-4.50(m, 4H), 4.38-4.12 (m, 4H), 3.26-3.11 (m, 8H*), 3.05-2.99 (m, 1H*), 2.74-2.71 (m, 1H*), 2.40-2.19 (m, 7H) ppm. * corresponds to protons lower in concentration due to D /H mixtures.

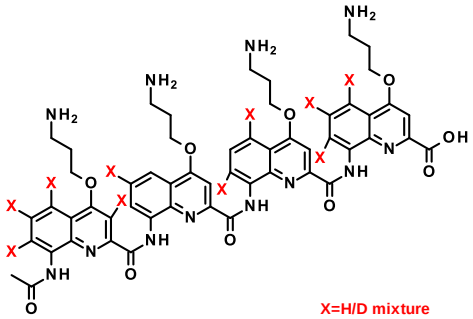
Synthesis of compound 18 (DDDB)



X=H/D mixture

Synthesis was performed according to the general procedure. The first coupled monomer mixture contained 50 n/n% **3** and 50 n/n% **1**. The second coupled monomer mixture contained 75 n/n% **5** and 25 n/n% **1**. The third coupled monomer mixture contained 50 n/n% **5** and 50 n/n% **1**. The fourth coupled monomer mixture contained 25 n/n% **5** and 75 n/n% **1**. Yield: 73%. ^{1}H NMR (300 MHz, DMSO-d_6) δ=12.50 (br s, 1H), 12.20 (s, 1H), 11.76 (s, 1H), 11.68 (s, 1H), 9.09 (s, 1H*), 8.97 (d, *J* = 7.3 Hz, 1H*), 8.45 (d, *J* = 7.1 Hz, 1H*), 8.05-7.74 (m, 14H*), 7.79 (s, 1H*), 7.74 (s, 1H*), 7.45 (t, *J* = 7.0 Hz, 1H*), 7.37 (t, *J* = 7.0 Hz, 1H*), 7.26 (s, 1H*), 6.75 (s, 1H), 6.65 (s, 1H*), 4.71-4.52 (m, 4H), 4.38-4.12 (m, 4H), 3.29-3.10 (m, 9H), 2.74-2.71 (m, 1H*), 2.44-2.19 (m, 7H) ppm. * corresponds to protons lower in concentration due to D /H mixtures.

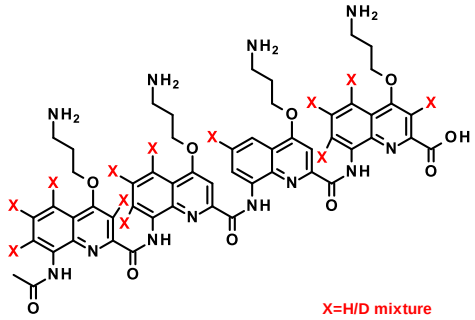
Synthesis of compound 19 (DABC)



X=H/D mixture

Synthesis was performed according to the general procedure. The first coupled monomer mixture contained 75 n/n% **4** and 25 n/n% **1**. The second coupled monomer mixture contained 25 n/n% **3** and 75 n/n% **1**. The third coupled monomer mixture contained 75 n/n% **2** and 25 n/n% **1**. The fourth coupled monomer mixture contained 25 n/n% **5** and 75 n/n% **1**. Yield: 65%. ^{1}H NMR (300 MHz, DMSO-d_6) δ=12.52 (br s, 1H), 12.20 (s, 1H), 11.76 (s, 1H), 11.68 (s, 1H), 9.08 (s, 1H*), 8.97 (d, *J* = 7.3 Hz, 1H*), 8.44 (d, *J* = 7.1 Hz, 1H*), 8.05-7.71 (m, 12H*), 7.78 (s, 1H*), 7.89 (s, 1H*), 7.88 (s, 1H*), 7.75 (s, 1H*), 7.45 (t, *J* = 7.0 Hz, 1H*), 7.38 (t, *J* = 7.0 Hz, 1H*), 7.25 (s, 1H*), 6.75 (s, 1H), 6.64 (s, 1H*), 4.71-4.52 (m, 4H), 4.38-4.12 (m, 4H), 3.29-3.10 (m, 9H), 2.74-2.71 (m, 1H*), 2.44-2.19 (m, 7H) ppm. * corresponds to protons lower in concentration due to D /H mixtures.

Synthesis of compound 20 (DCAD)

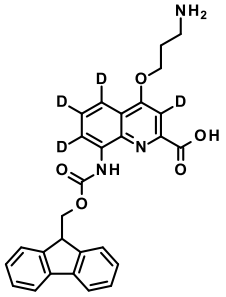


Synthesis was performed according to the general procedure. The first coupled monomer was 100 n/n% **5**. The second coupled monomer mixture contained 50 n/n% **2** and 50 n/n% **1**. The third coupled monomer mixture contained 25 n/n% **4** and 75 n/n% **1**. The fourth coupled monomer mixture contained 25 n/n% **5** and 75 n/n% **1**. Yield: 72%. ^{1}H NMR (300 MHz, DMSO-d_6) δ=12.20 (s, 1H), 11.77 (s, 1H), 11.68 (s, 1H), 9.08 (s, 1H), 8.97 (t, *J* = 3.2 Hz, 1H*), 8.10-7.72 (m, 16H), 7.74 (s, 1H), 7.45 (t, *J* = 7.0 Hz, 1H*), 7.37 (t, *J* = 7 Hz, 1H*), 7.26 (s, 1H*), 6.75 (s, 1H), 4.69-4.52 (m, 4H), 4.40-4.11 (m, 4H), 3.29-3.09 (m, 9H), 3.01 (t, *J* = 6.0 Hz, 1H*), 2.73-2.72 (m, 1H*), 2.44-2.19 (m, 7H) ppm. * corresponds to protons twice lower in concentration due to D /H mixtures.

3.5. Oligomer synthesis for erosion studies

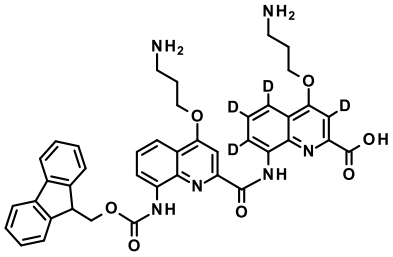
Compounds **21**-**25** were obtained by solid phase synthesis following the general procedure described in **section 3.4**. Compounds were cleaved from the resin and analyzed as Fmoc-protected amines.

Synthesis of compound 21



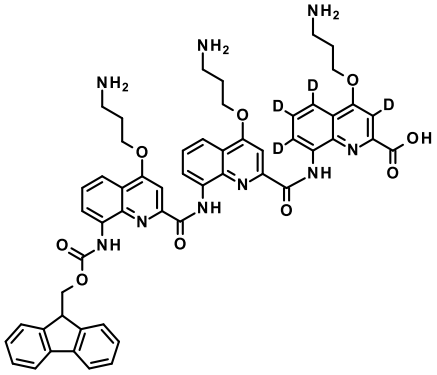
^{1}H NMR (300 MHz, DMSO-d_6) δ=10.11 (s, 1H), 7.93 (d, *J* = 7.3 Hz, 2H), 7.76 (d, *J* = 7.2 Hz, 2H), 7.43 (t, *J* = 7.3 Hz, 2H), 7.35 (t, *J* = 7.3 Hz, 2H), 4.61 (d, *J* = 6.2 Hz, 2H), 4.43 (br s, 2H), 3.09 (br s, 2H), 2.19 (br s, 2H) ppm. HRMS (ESI) *m/z* calcd for $C_{28}H_{22}D_4N_3O_5$ $[M+H]^+$: 488.2118; found: 488.2121. HPLC: rt = 13.8 min.

Synthesis of compound 22



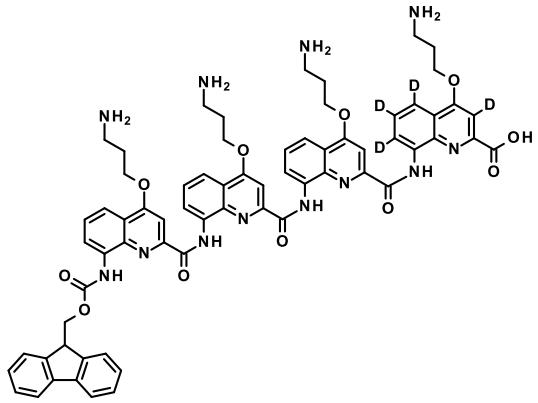
^{1}H NMR (300 MHz, DMSO-d_6) δ=12.38 (s, 1H), 9.31 (s, 1H), 8.36 (d, *J* = 6.9 Hz, 2H), 7.97-7.67 (m, 3H), 7.81 (d, *J* = 7.5 Hz, 2H), 7.57 (d, *J* = 7.5 Hz, 2H), 7.28 (t, *J* = 7.4 Hz, 2H), 6.93 (t, *J* = 7.4 Hz, 2H), 4.54 (br s, 2H), 4.44 (d, *J* = 7.5 Hz, 2H), 4.36 (br s, 2H), 4.30 (t, *J* = 7.3 Hz, 1H), 3.14-3.08 (m, 4H), 2.27-2.17 (m, 4H) ppm. HRMS (ESI) *m/z* calcd for $C_{41}H_{35}D_4N_6O_7$ $[M+H]^+$: 731.3126; found: 731.3122. HPLC: rt = 8.5 min.

Synthesis of compound 23



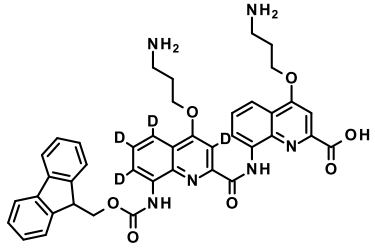
^{1}H NMR (300 MHz, DMSO-d_6) δ=12.32 (br s, 1H), 12.24 (br s, 1H), 8.97 (br s, 1H), 8.60 (br s, 1H), 8.14-7.62 (m, 7H), 7.80 (d, *J* = 7.5 Hz, 2H), 7.50-7.23 (m, 6H), 6.94 (br s, 2H), 4.60 (br s, 2H), 4.44 (br s, 2H), 4.14-4.04 (m, 5H), 3.17-3.08 (m, 6H), 2.28-2.17 (m, 6H) ppm. HRMS (ESI) *m/z* calcd for $C_{54}H_{48}D_4N_9O_9$ $[M+H]^+$: 974.4134; found: 974.4120. HPLC: rt = 8.0 min.

Synthesis of compound 24



^{1}H NMR (300 MHz, DMSO-d_6) δ=12.18 (s, 1H), 11.84 (s, 1H), 11.75 (s, 1H), 9.09 (br s, 1H), 8.47 (br s, 1H), 8.18-7.78 (m, 8H), 7.74 (d, *J* = 7.6 Hz, 2H), 7.63-7.57 (m, 2H), 7.50-7.05 (m, 6H), 6.76-6.71 (m, 2H), 4.70-4.55 (m, 3H), 4.45 (br s, 1H), 4.34 (br s, 1H), 4.25-4.11 (m, 4H), 4.00-3.91 (m, 1H), 3.30-3.10 (m, 8H), 2.44-2.17 (m, 8H) ppm. HRMS (ESI) *m/z* calcd for $C_{67}H_{61}D_4N_{12}O_{11}$ $[M+H]^+$: 1217.5141; found: 1217.5101.HPLC: rt = 7.5 min.

Synthesis of compound 25



^{1}H NMR (300 MHz, DMSO-d_6) δ=12.39 (s, 1H), 9.30 (s, 1H), 8.34 (d, *J* = 7.1 Hz, 2H), 8.00-7.32 (m, 3H), 7.81 (d, *J* = 7.8 Hz, 2H), 7.57 (d, *J* = 7.5 Hz, 2H), 7.27 (t, *J* = 7.4 Hz, 2H), 6.93 (t, *J* = 7.4 Hz, 2H), 4.52 (br s, 2H), 4.44 (d, *J* = 7.3 Hz, 2H), 4.38-2.28 (m, 3H), 3.17-3.05 (m, 4H), 2.28- 2.14 (m, 4H) ppm. HRMS (ESI) *m/z* calcd for $C_{41}H_{35}D_4N_6O_7$ $[M+H]^+$: 731.3126; found: 731.3147. HPLC: rt = 8.5 min.

3.6. Mass spectrometric analysis of compounds 11-25

The experiments were performed with the Thermo Fisher Scientific Exactive Orbitrap instrument in positive ion mode. The capillary voltage was 70V, the capillary temperature was 280 °C, the skimmer voltage was 46 V, the tube lens offset was 170 V. The samples were dissolved in 2mM aqueous NH_4OAc solution.

For the MS analysis on one bead of resin, one bead of resin was isolated under the microscope and put in a small eppendorf tube. 5µL of TFA was added and cleavage was run for 1 hour. TFA was then evaporated under vacuum and 100µL of 2mM aqueous NH_4OAc solution was added to the tube. Bead was removed under microscope and the solution analyzed by HRMS by direct injection.

Note1: In some of the recorded mass spectra of oligomers, a low intensity, secondary set of peaks (isotope envelope) appear due to $[2M+2H]^{2+}$ adducts. The adduct formation depends on experimental conditions and might be suppressed by adjusting ionization parameters. Unless extremely high adduct formation is observed, this effect has negligible bias on the mass fingerprint recognition.
Note2: For isotope code comparison, m/z values were rounded to the nearest 0.1 amu. More accurate values are unnecessary for low values of z.

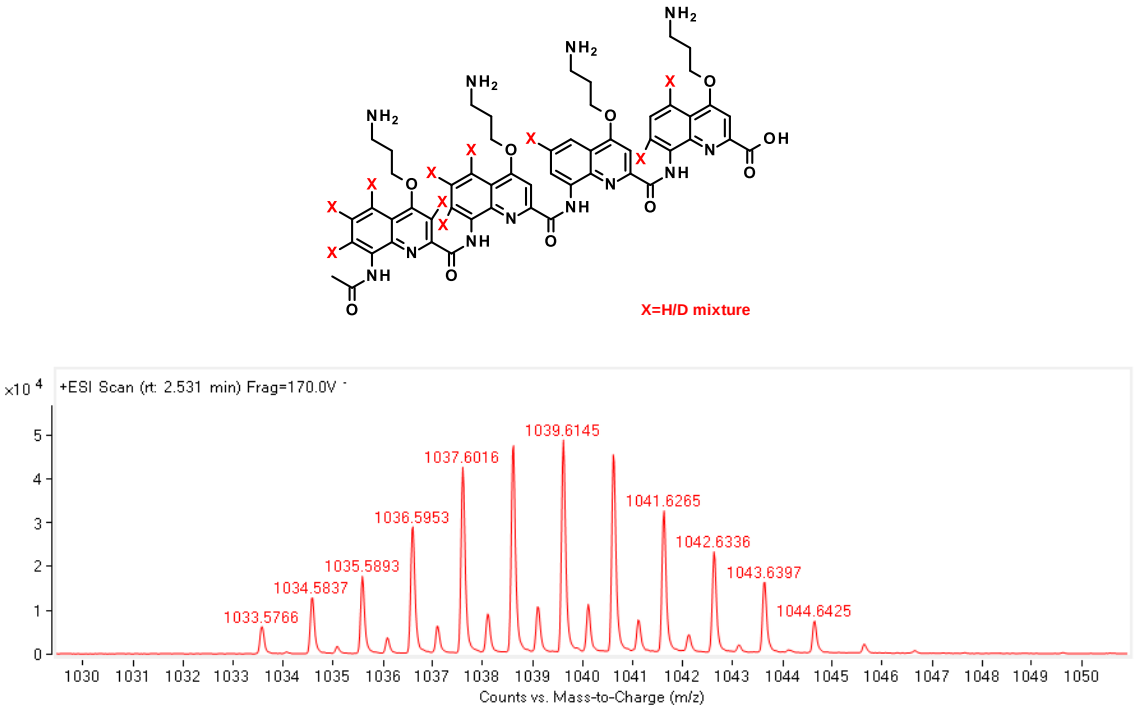


Figure S11 TOF HRMS spectrum of compound **11**.

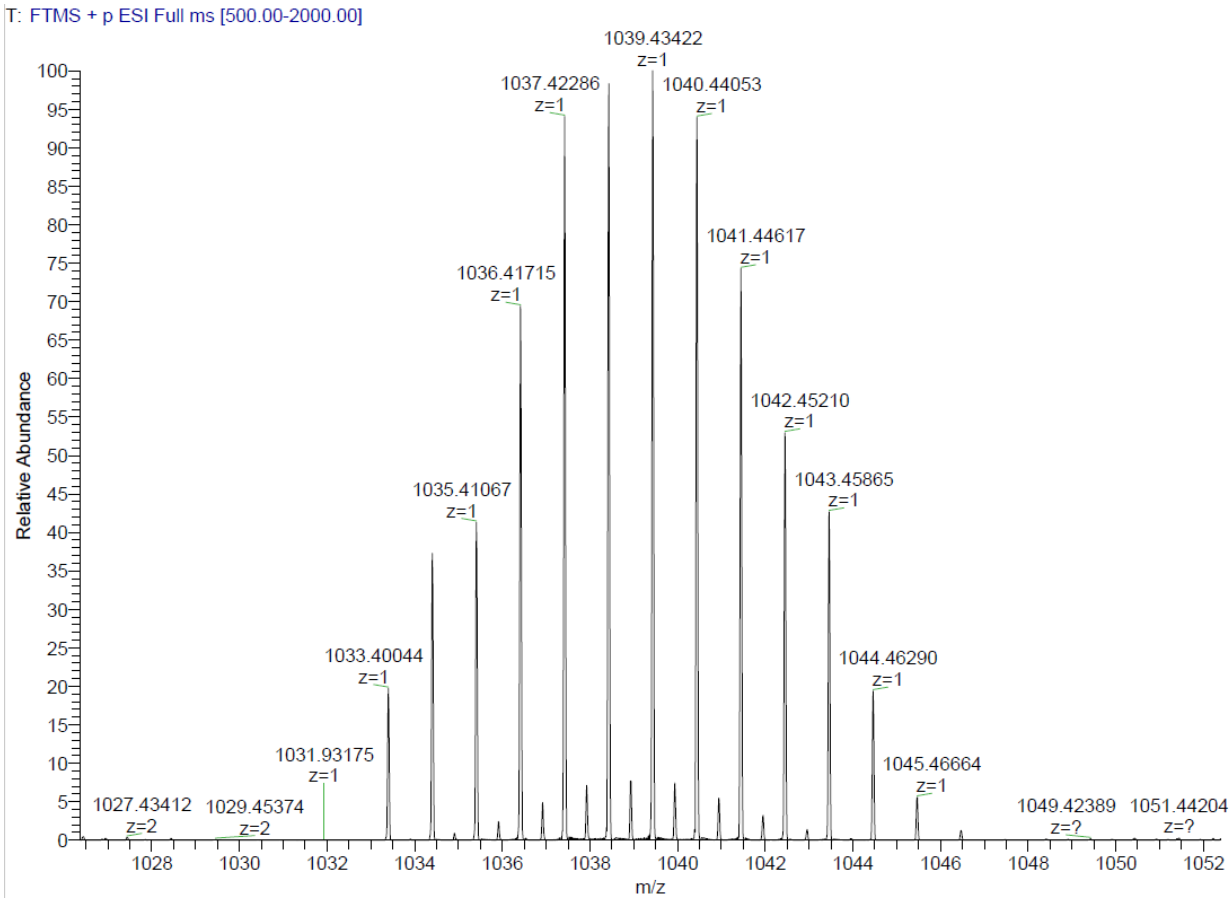
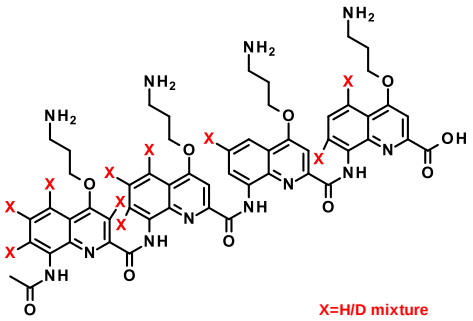


Figure S12. Orbitrap HRMS spectrum of compound **11**.



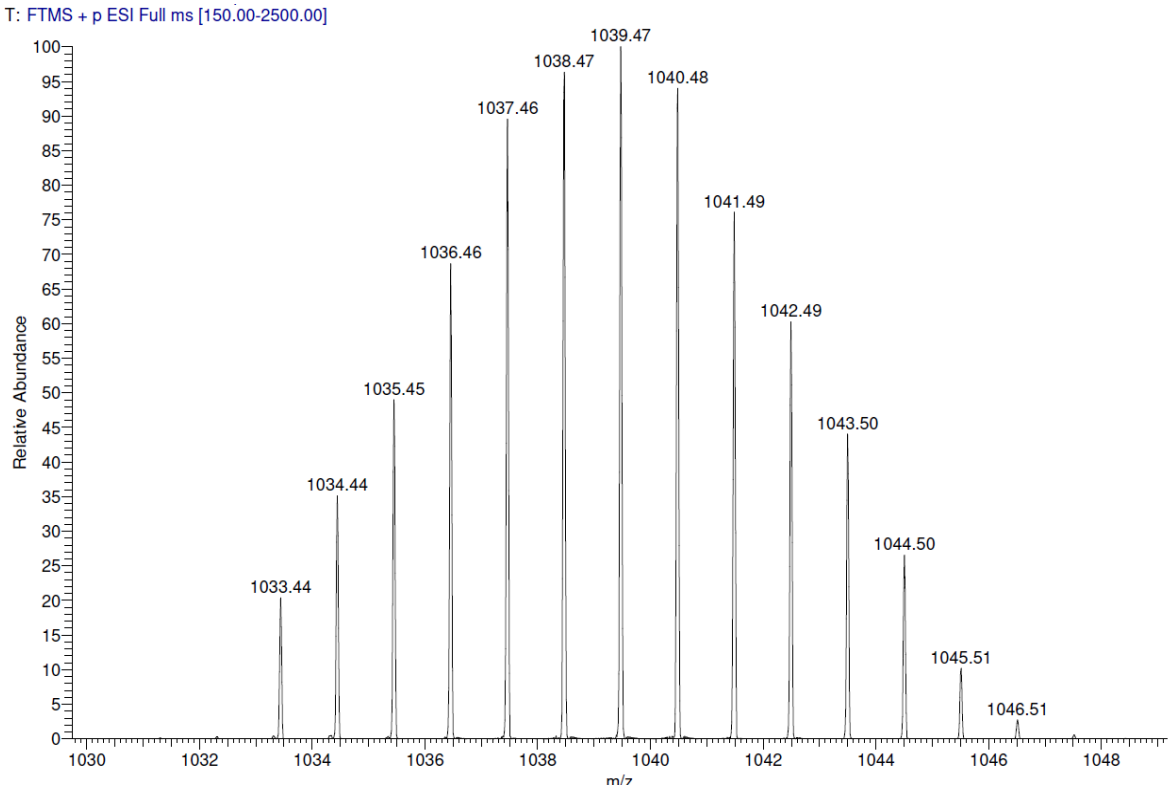


Figure S13. Orbitrap HRMS spectrum of compound **11** (solution obtained from the cleavage of one bead of resin).

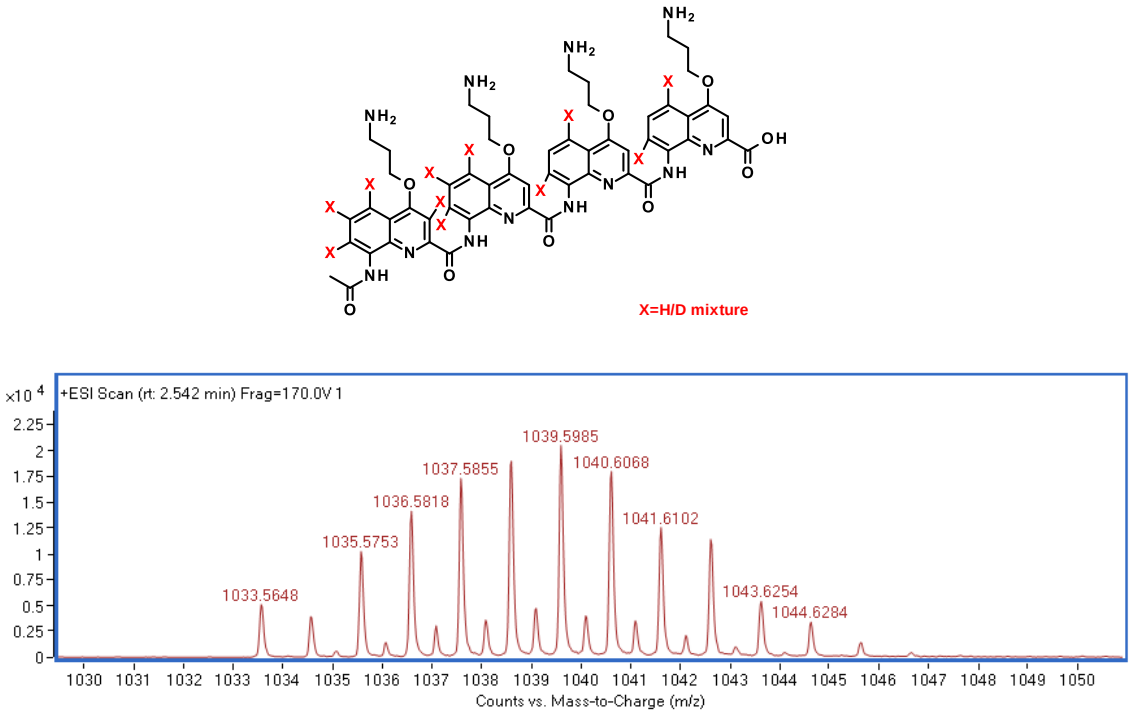


Figure S14. TOF HRMS spectrum of compound **12**.

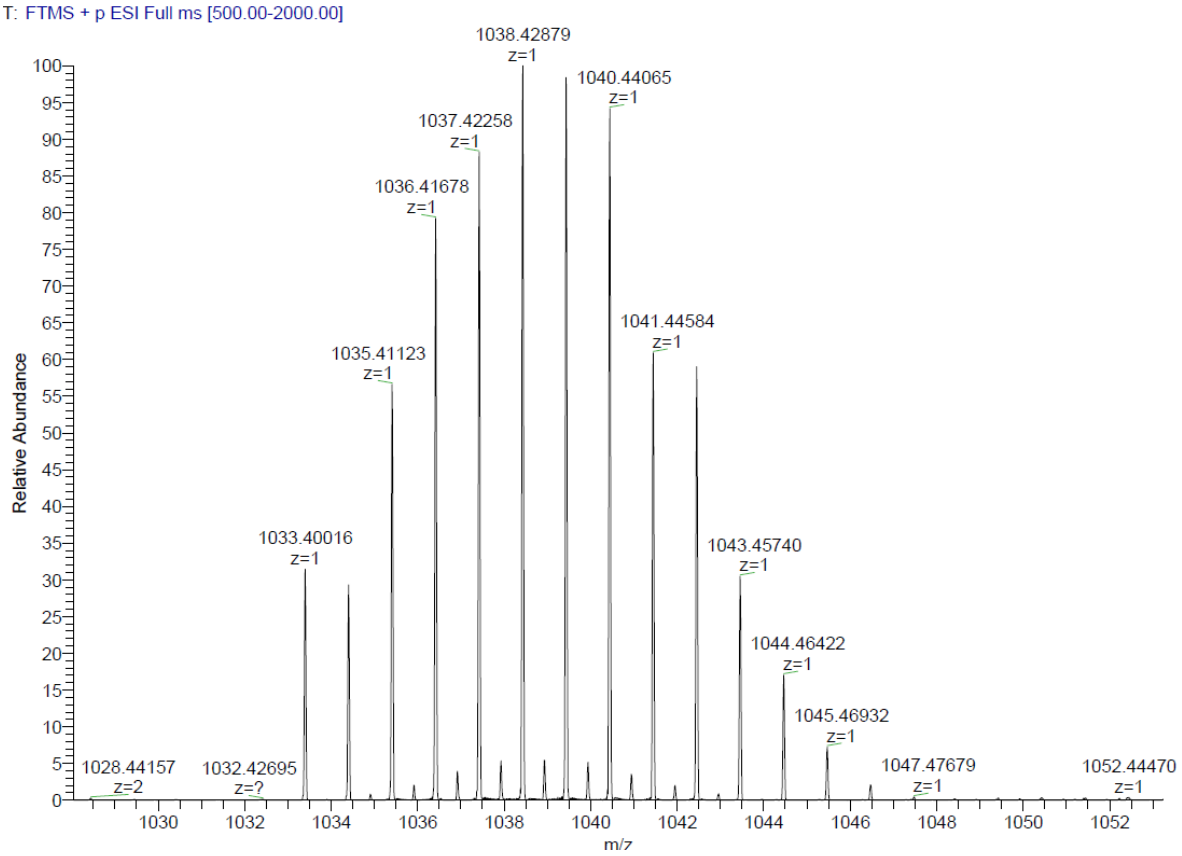


Figure S15. Orbitrap HRMS analysis of compound **12**.

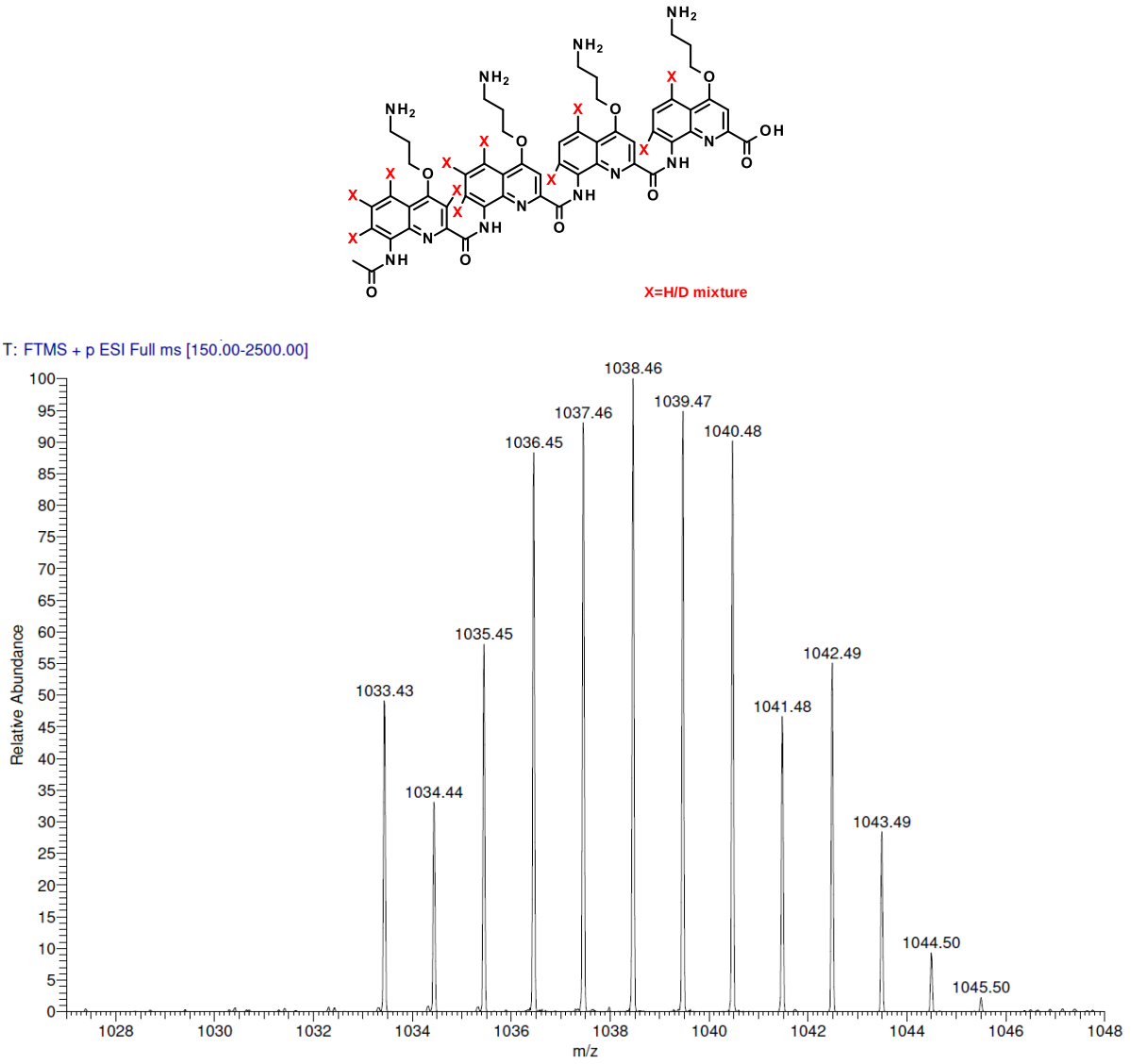


Figure S16. Orbitrap HRMS spectrum of compound **12** (solution obtained from the cleavage of one bead of resin).

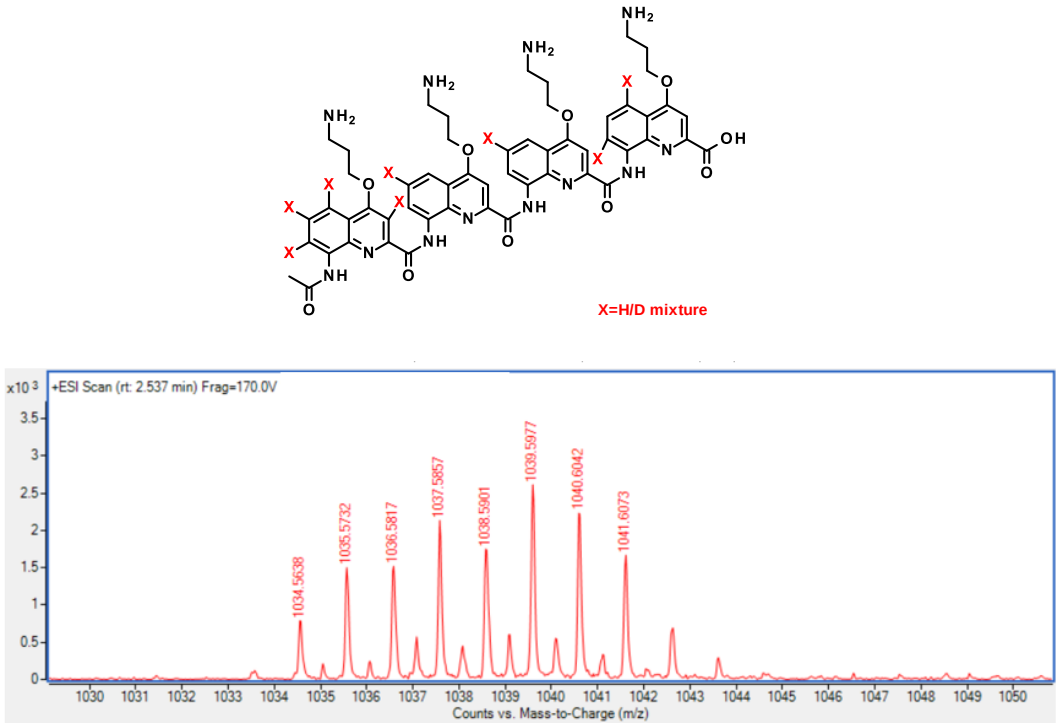


Figure S17. TOF HRMS spectrum of compound **13**.

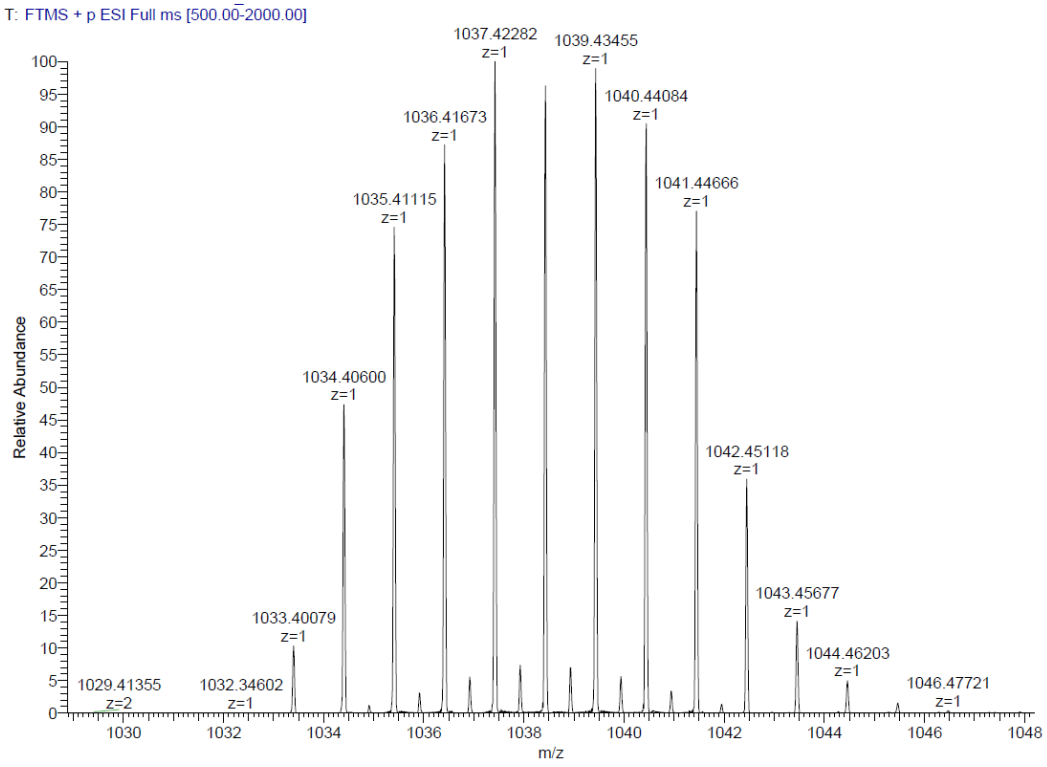


Figure S18. Orbitrap HRMS analysis of compound **13**.

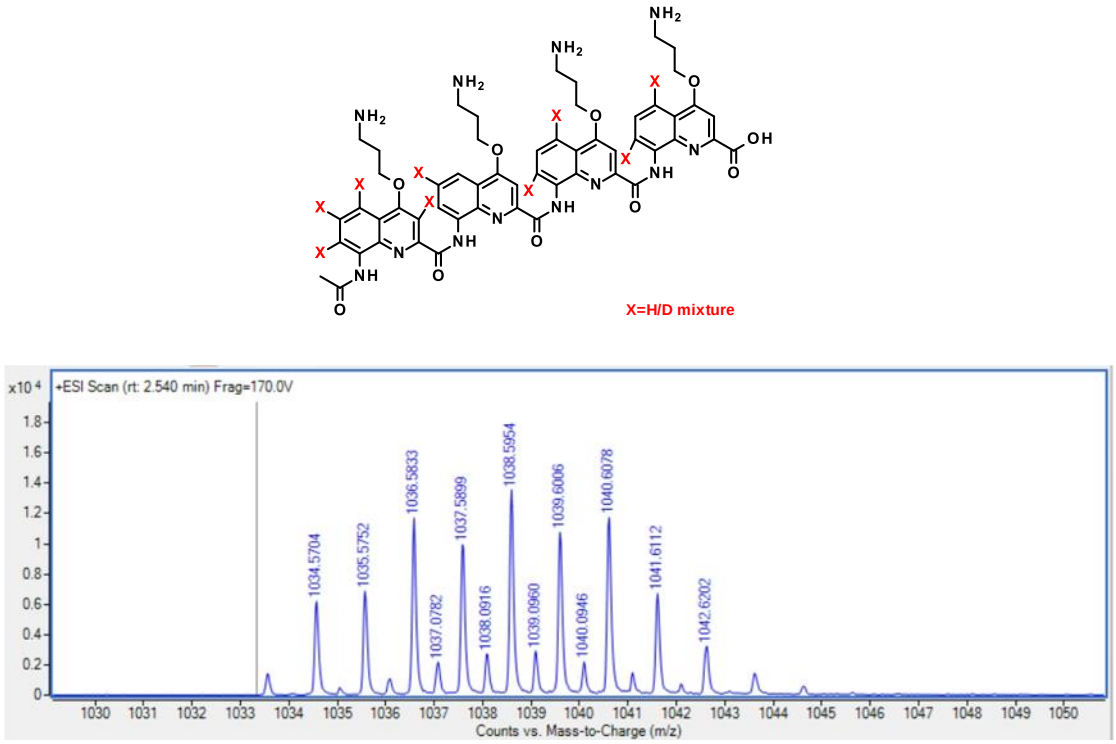


Figure S19. TOF HRMS spectrum of compound **14**.

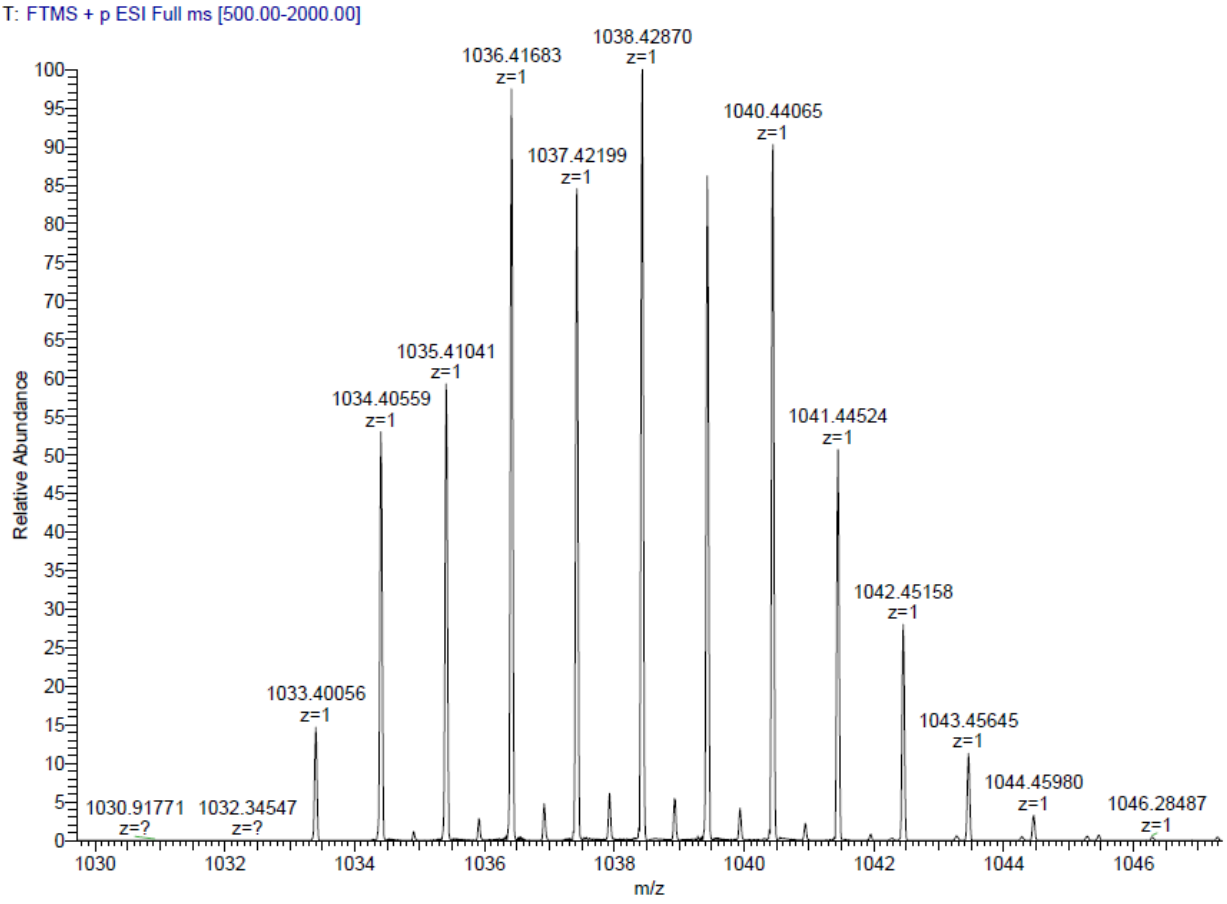


Figure S20 Orbitrap HRMS spectrum of compound **14**.

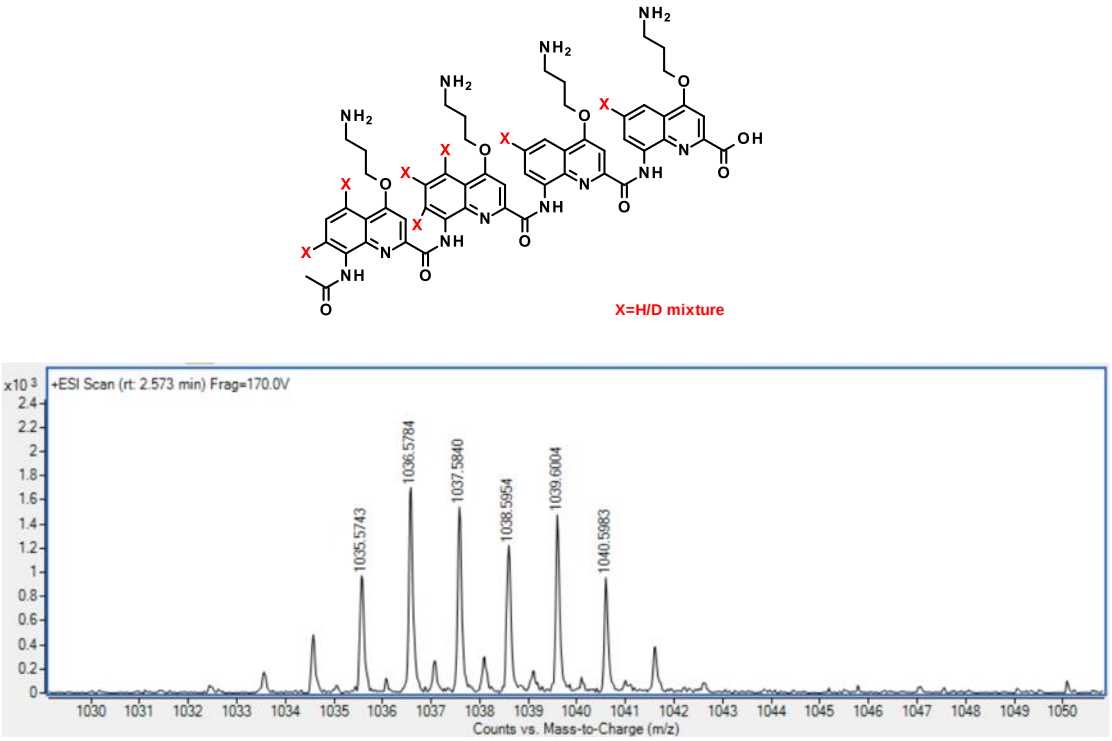


Figure S21. TOF HRMS spectrum of compound **15**.

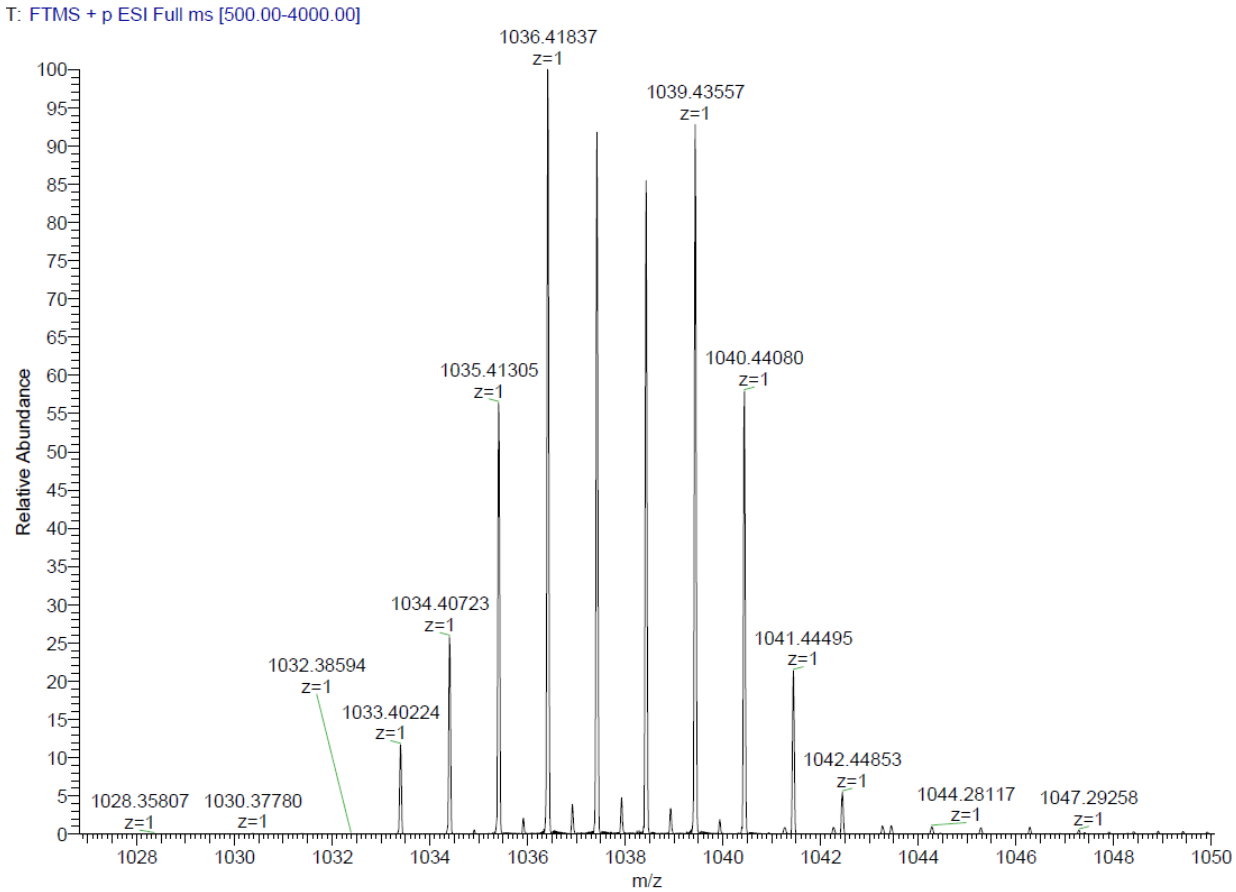


Figure S22. Orbitrap HRMS spectrum of compound **15**.

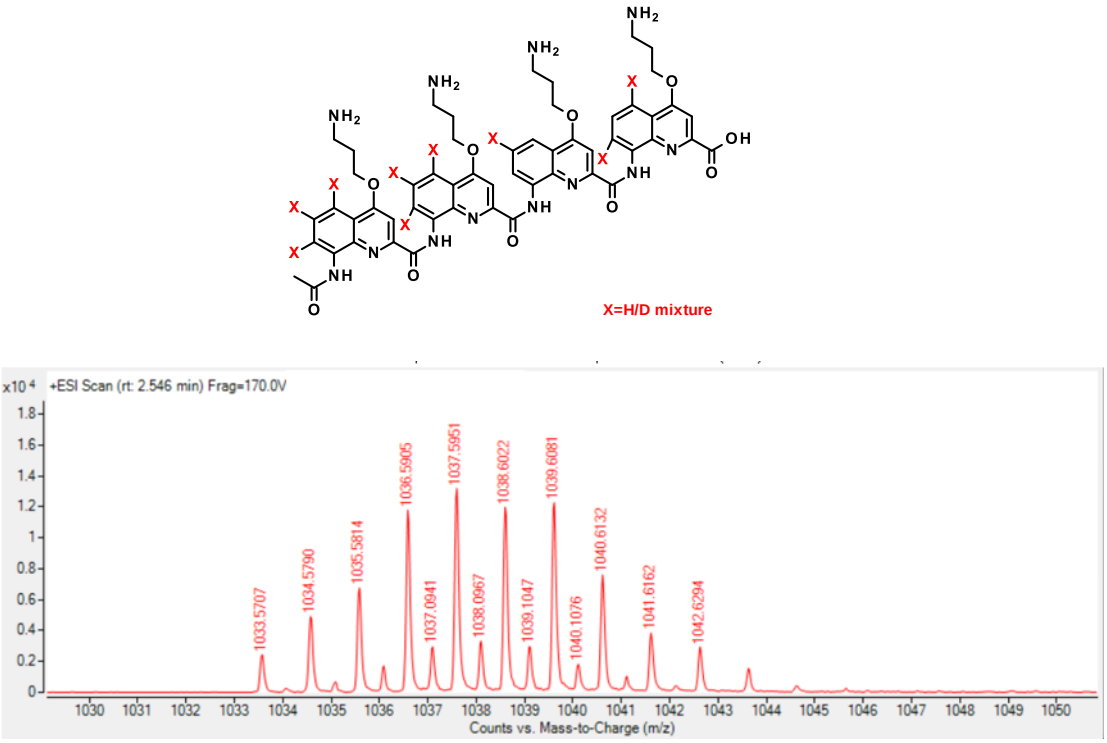


Figure S23. TOF HRMS spectrum of compound **16**.

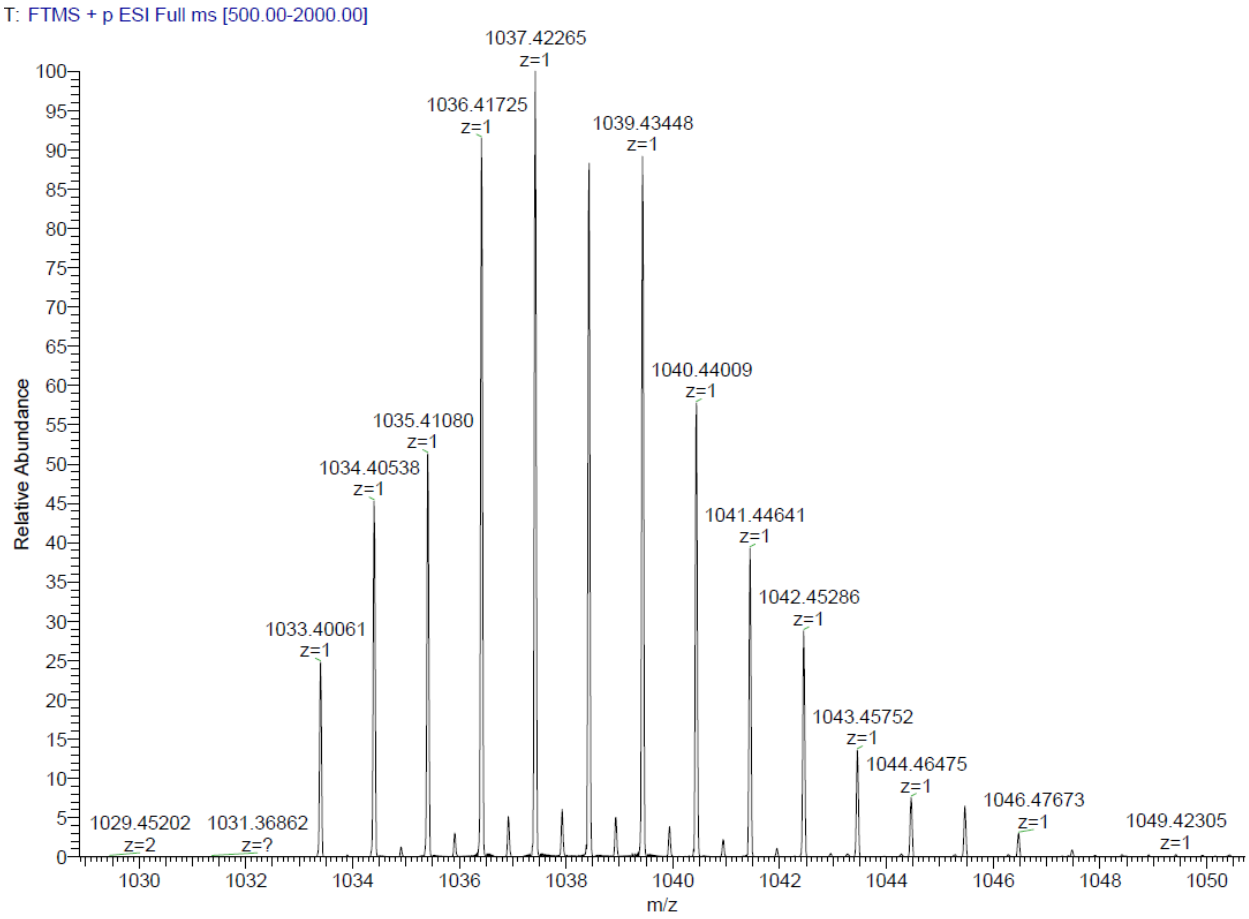


Figure S24. Orbitrap HRMS spectrum of compound **16**.

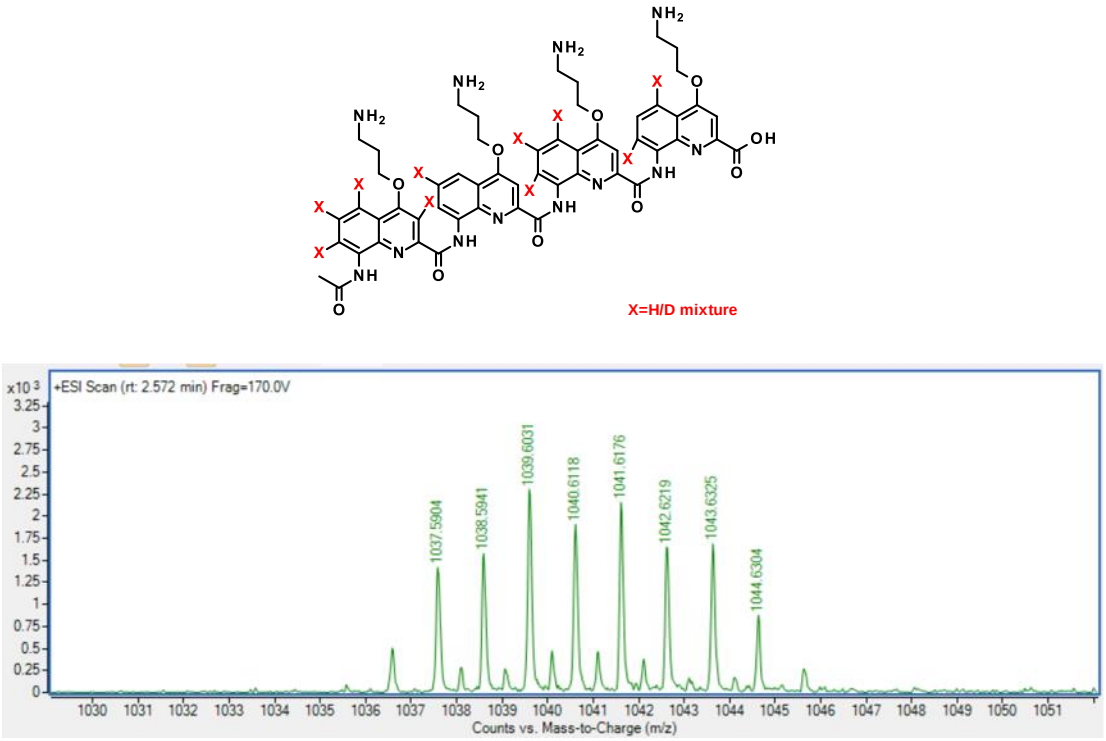


Figure S25. TOF HRMS spectrum of compound **17**.

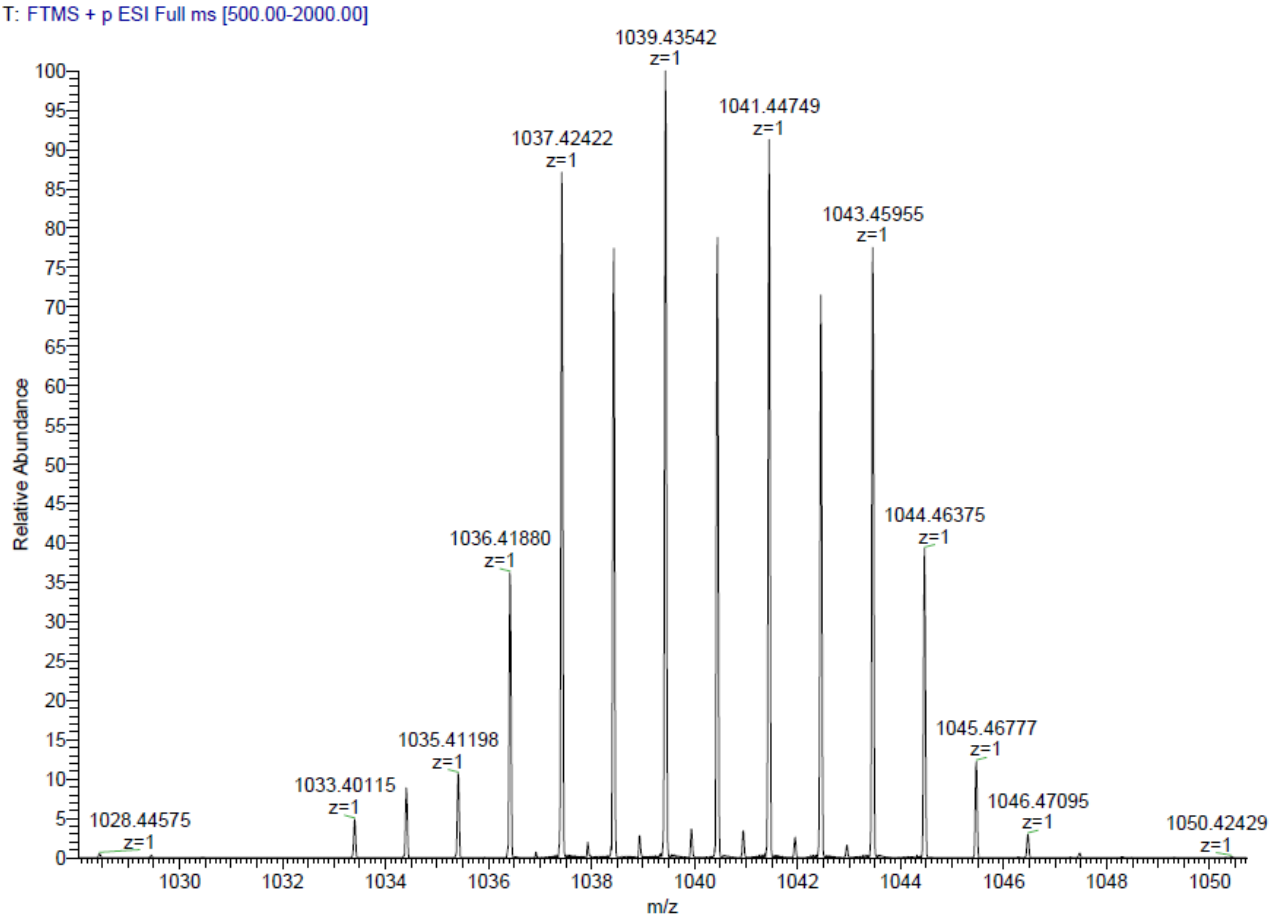


Figure S26. Orbitrap HRMS spectrum of compound **17**.

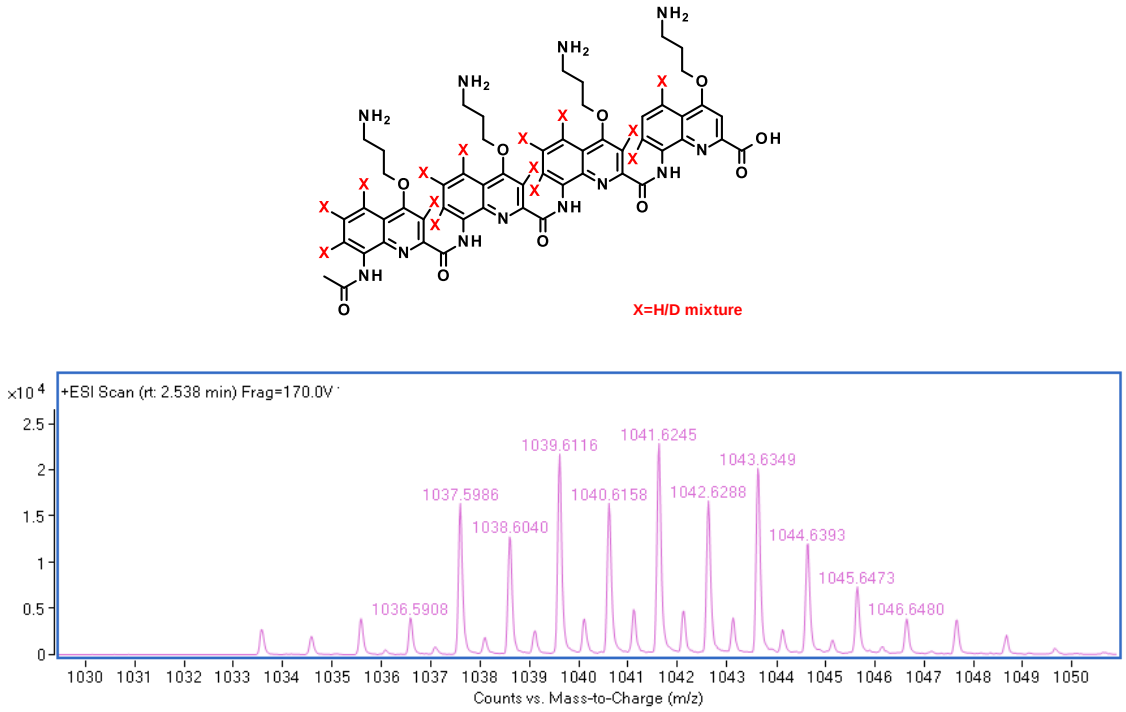


Figure S27. TOF HRMS spectrum of compound **18**.

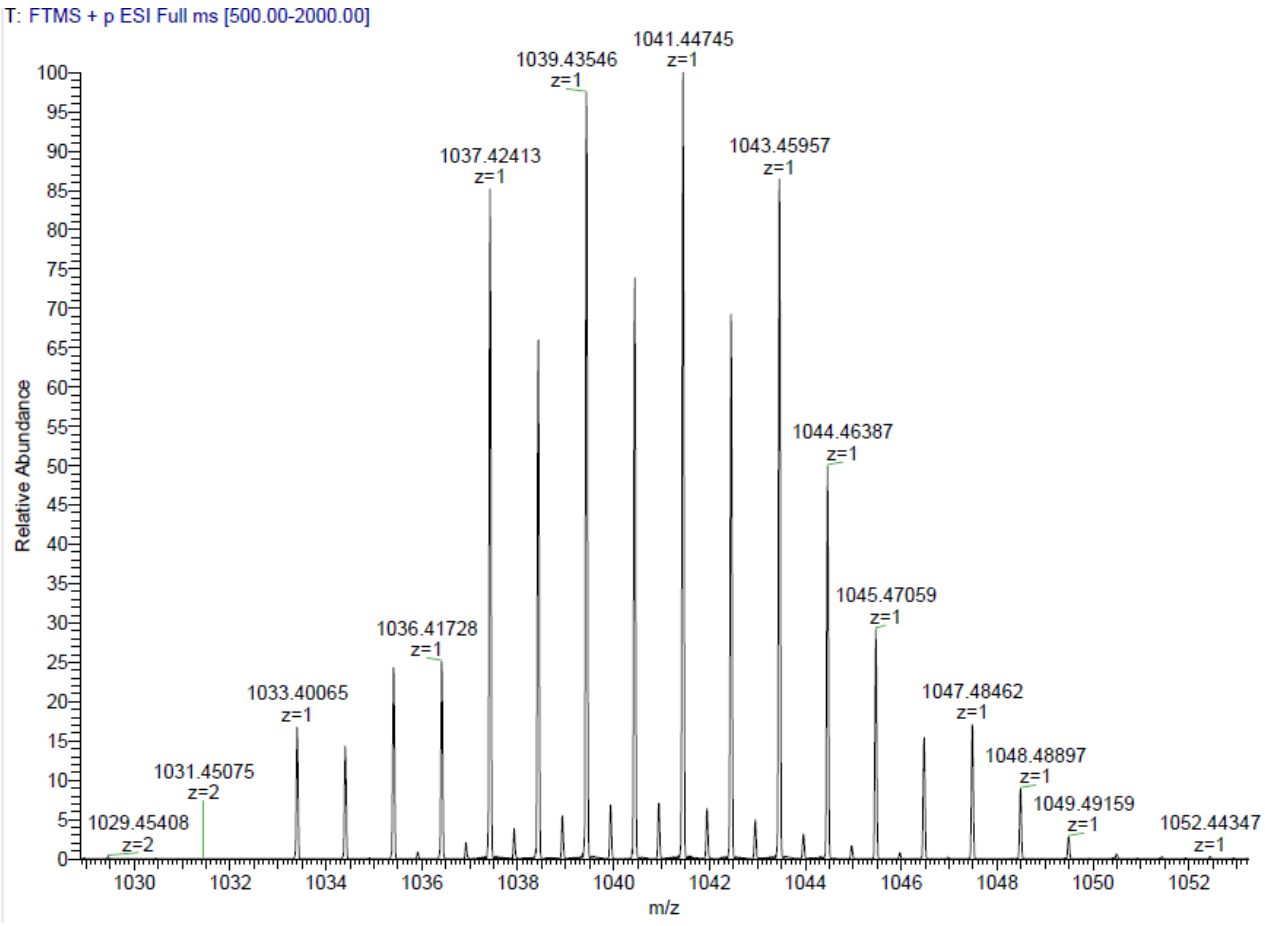


Figure S28. Orbitrap HRMS spectrum of compound **18**.

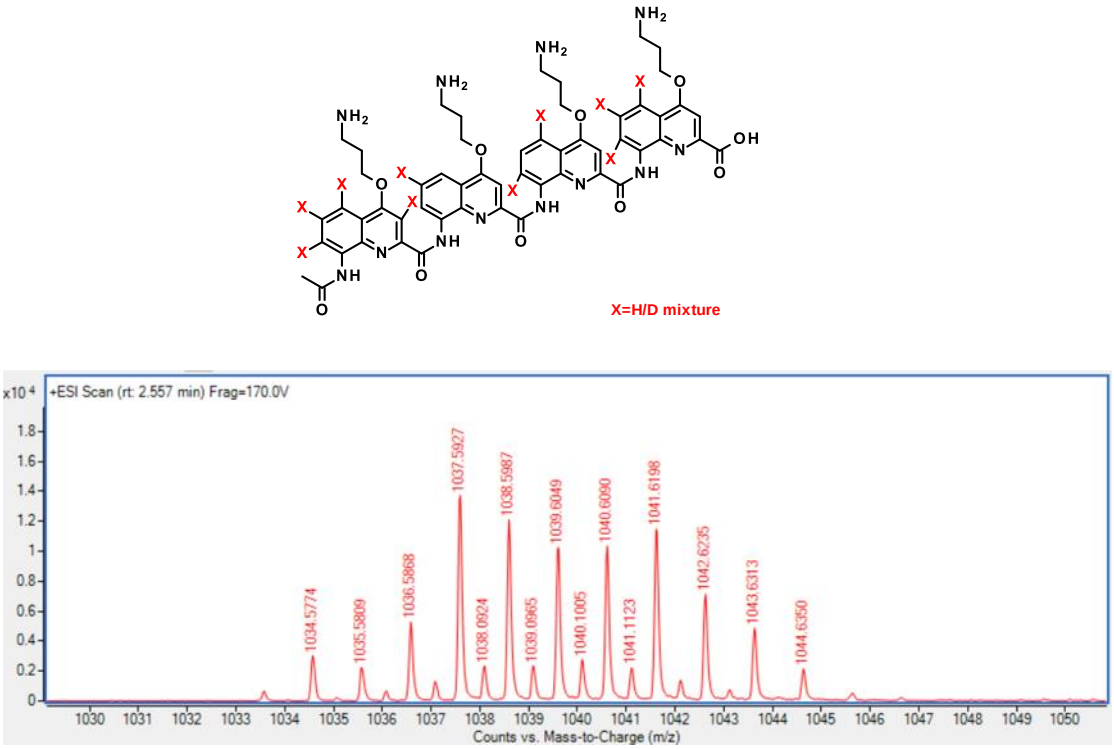


Figure S29. TOF HRMS spectrum of compound **19**.

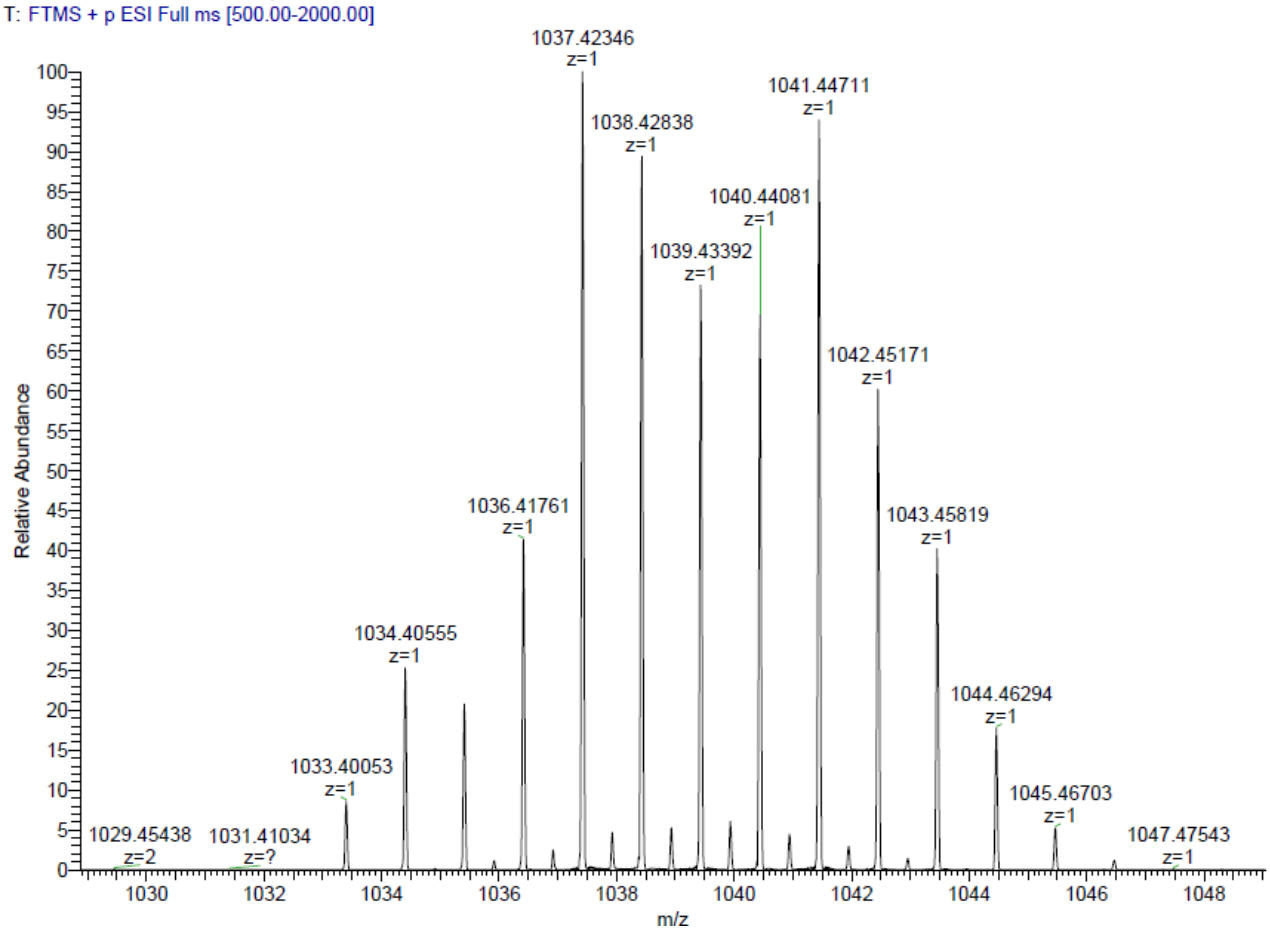


Figure S30. Orbitrap HRMS spectrum of compound **19**.

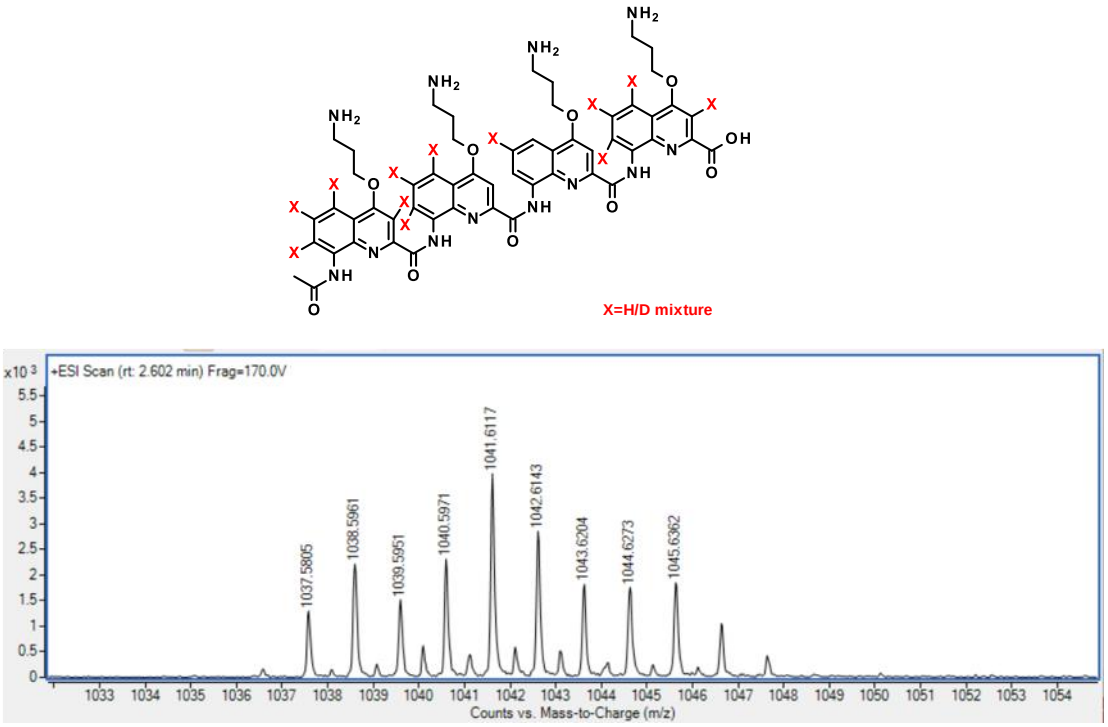


Figure S31. TOF HRMS spectrum of compound **20**.

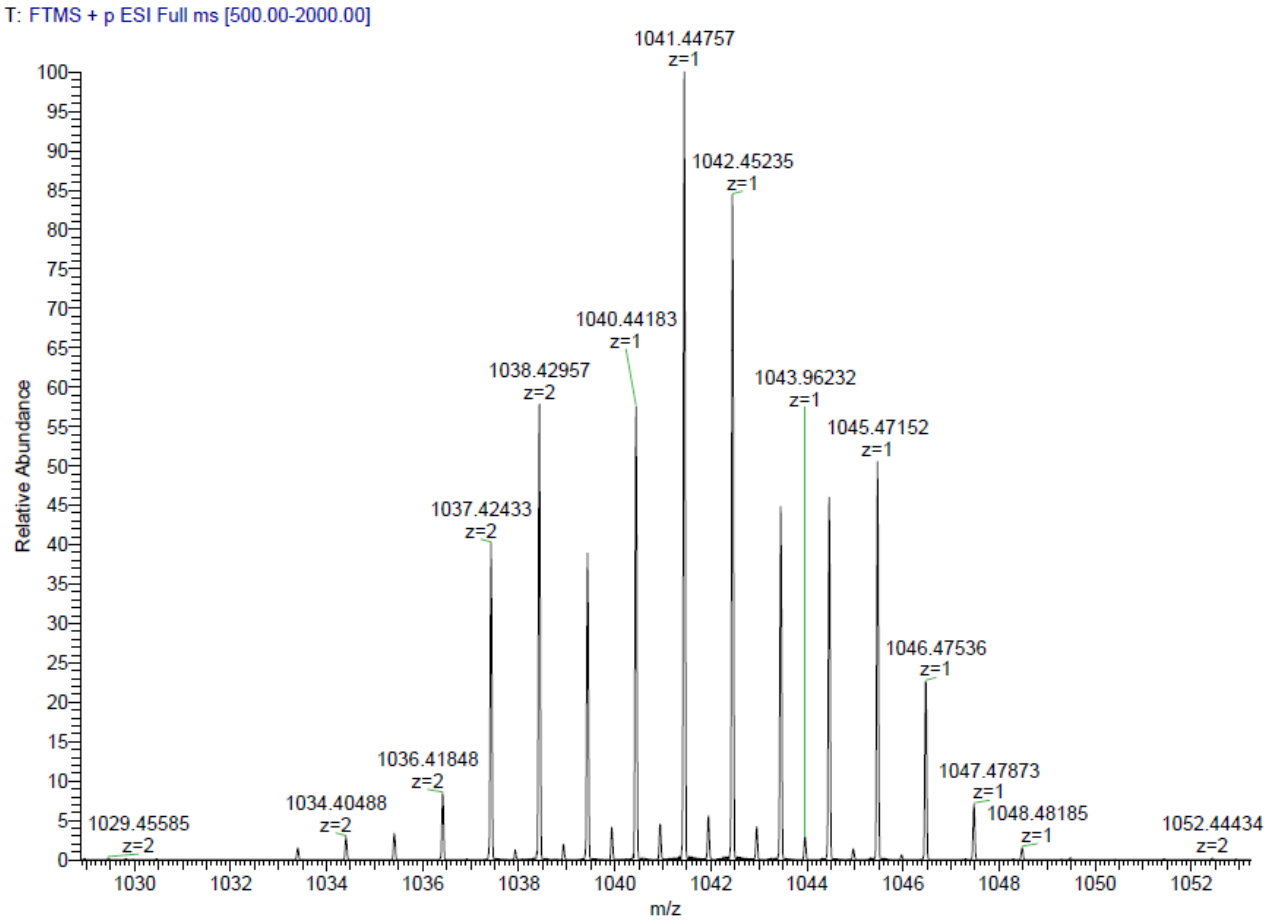


Figure S32. Orbitrap HRMS spectrum of compound **20**.

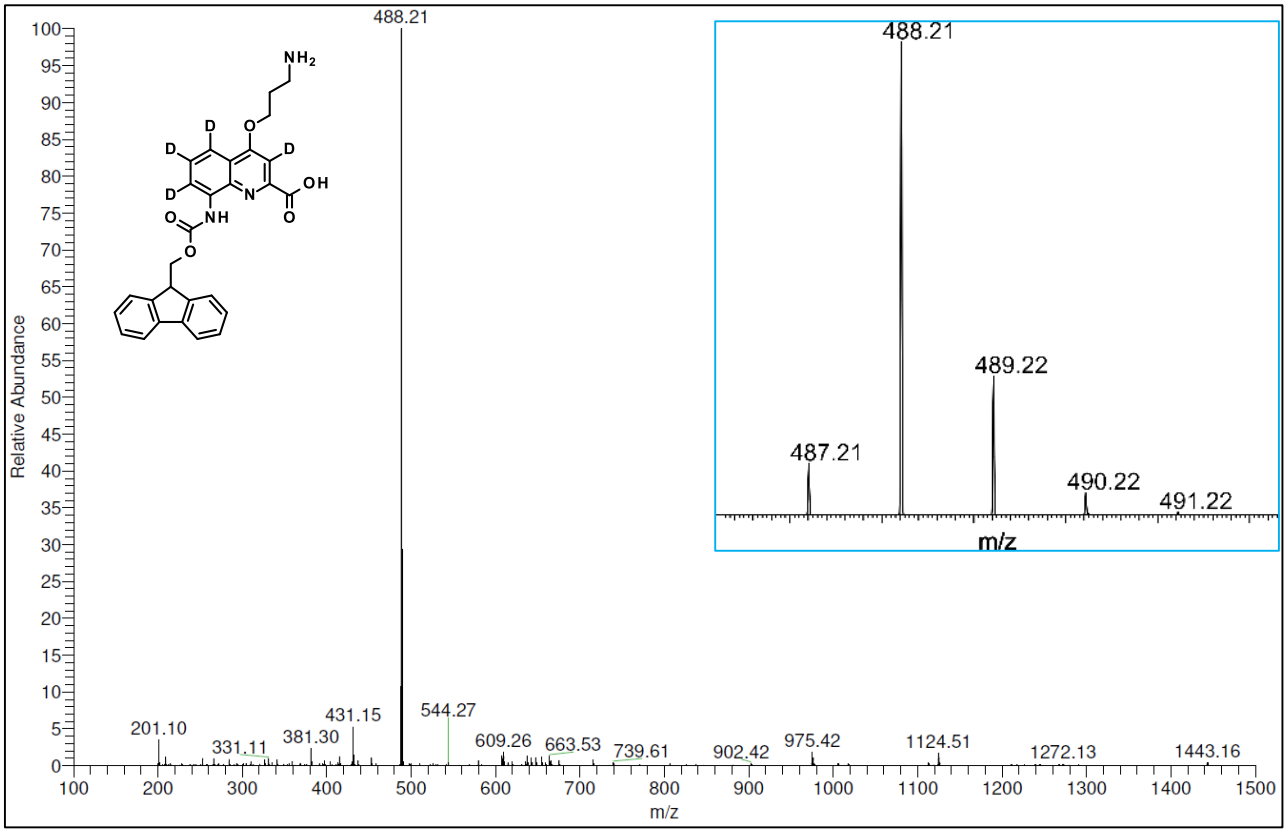


Figure S33. Orbitrap HRMS spectrum and zoom of compound **21**.

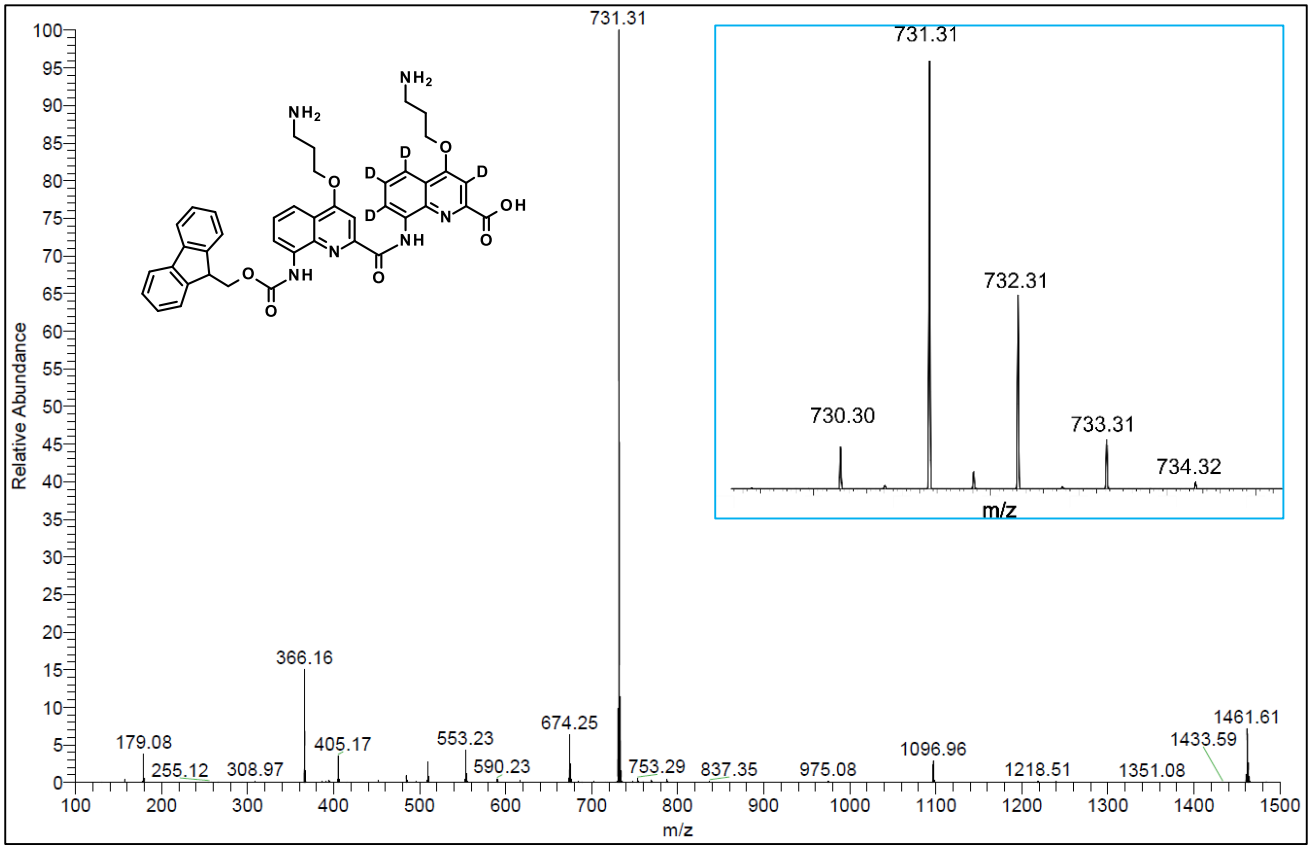


Figure S34. Orbitrap HRMS spectrum and zoom of compound **22**.

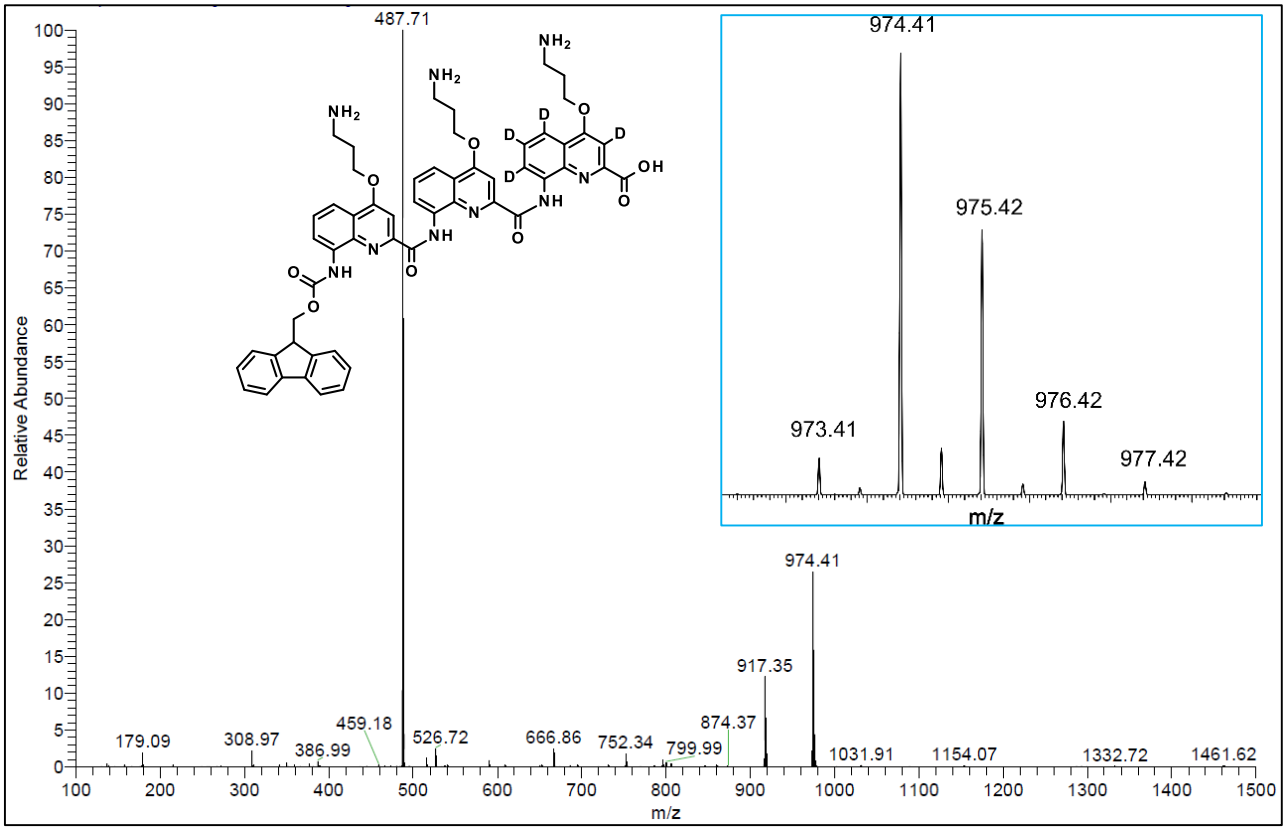


Figure S35. Orbitrap HRMS spectrum and zoom of compound **23**.

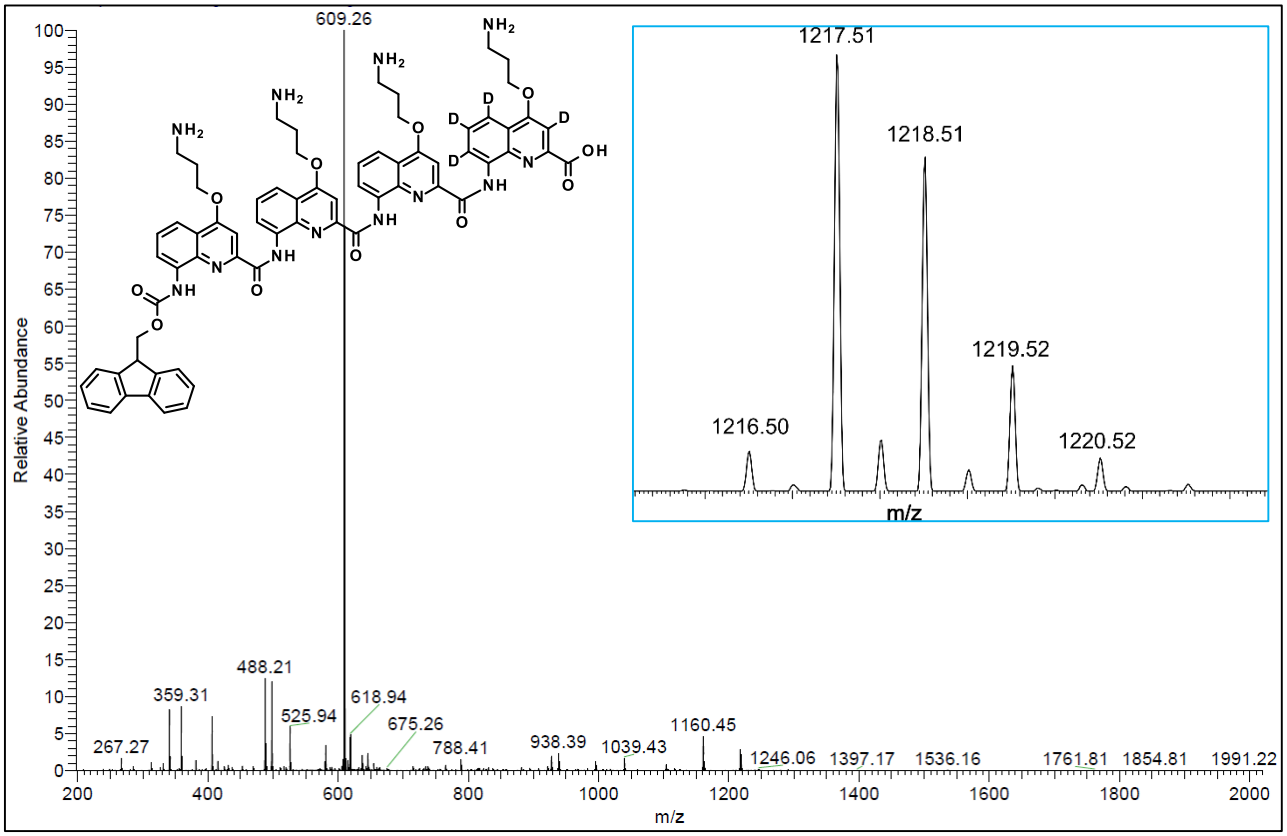


Figure S36. Orbitrap HRMS spectrum and zoom of compound **24**.

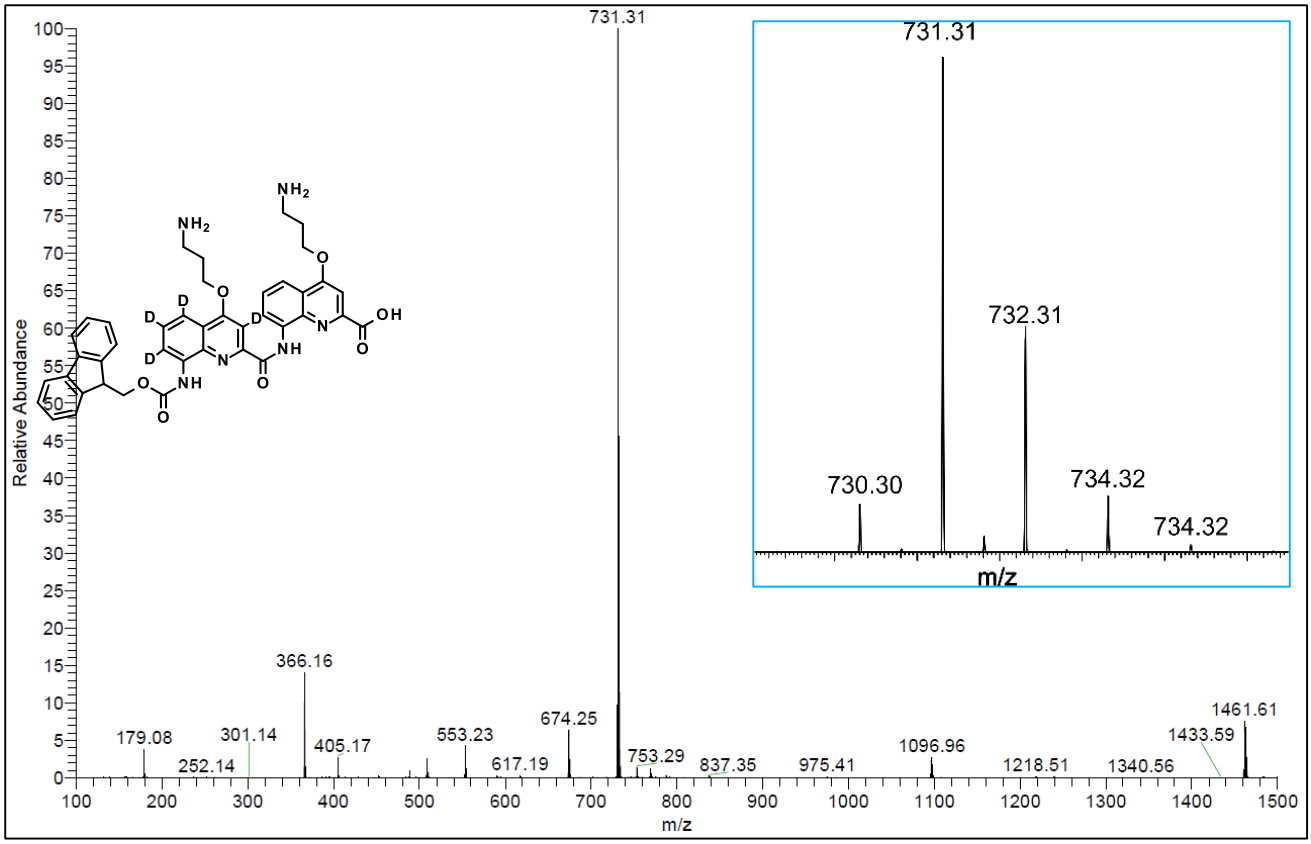


Figure S37. Orbitrap HRMS spectrum and zoom of compound **25**.

3.7. NMR spectra and chromatograms for new compounds

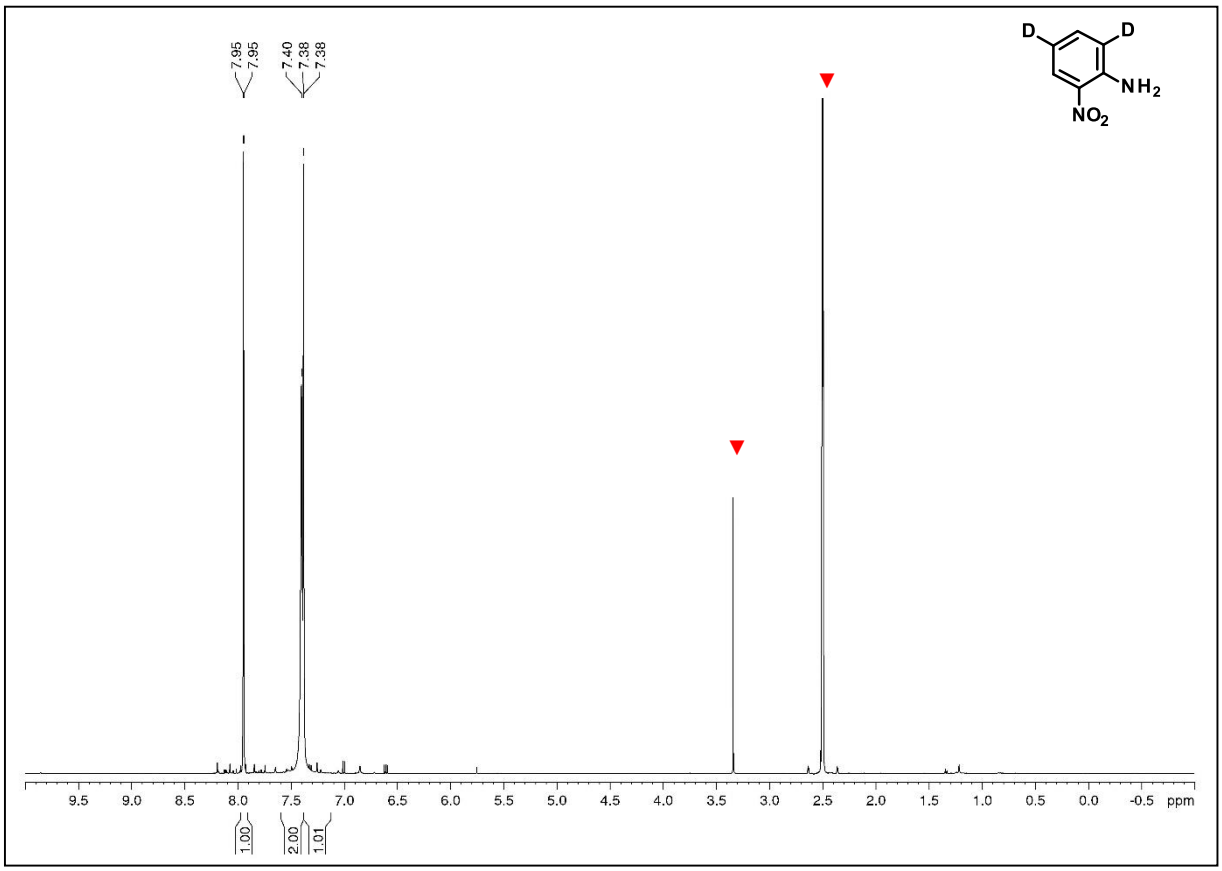


Figure S38 ^{1}H NMR (500 MHz, DMSO-d_6) of compound **7**.

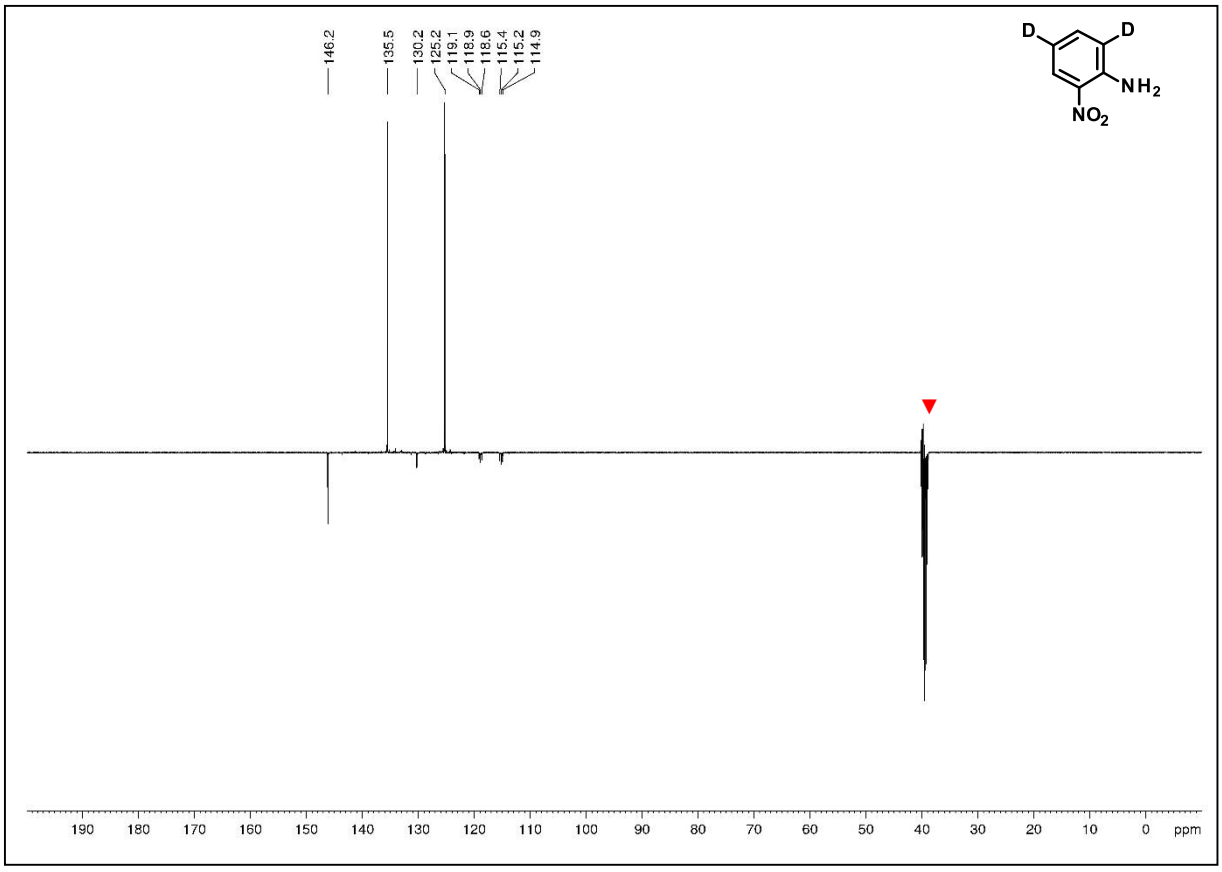


Figure S39. ^{13}C NMR (100 MHz, DMSO-d_6) of compound **7**.

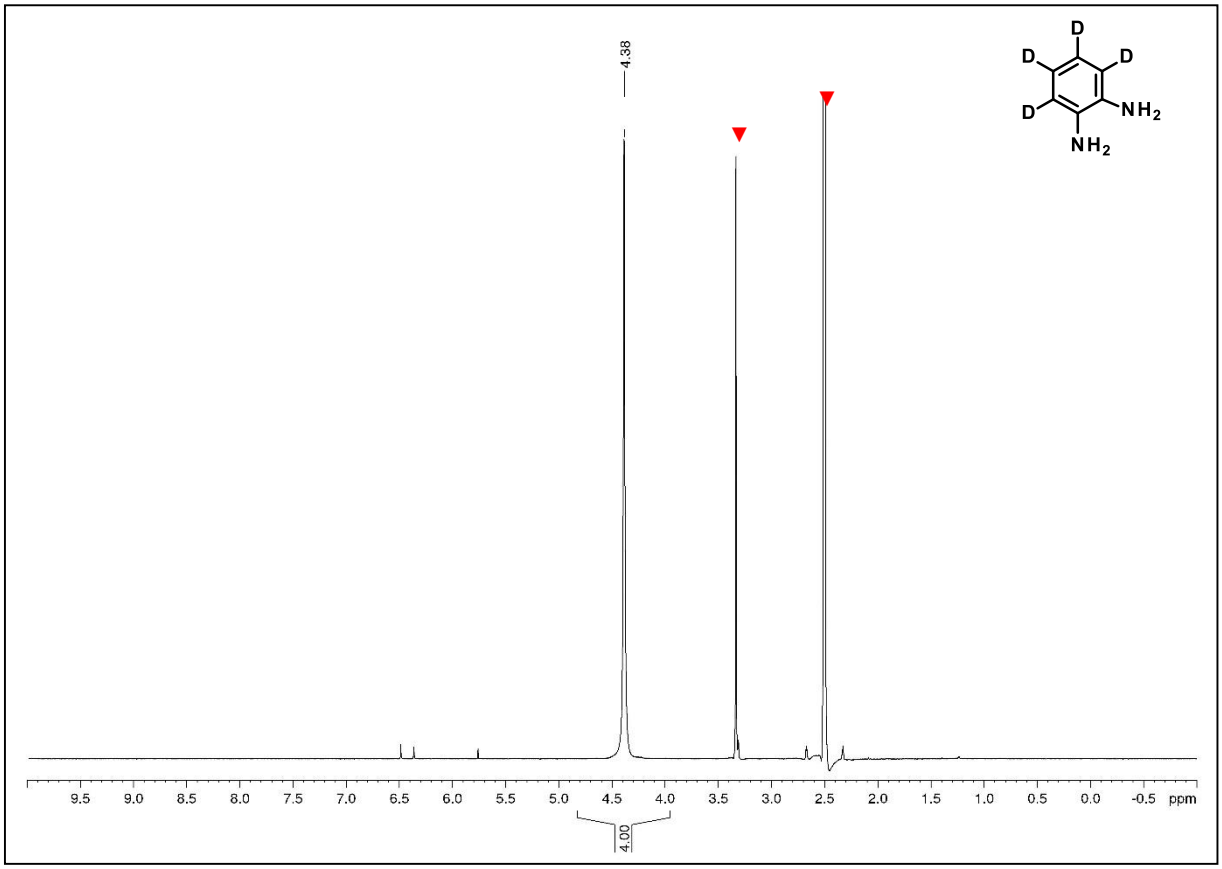


Figure S40. ^{1}H NMR (400 MHz, DMSO-d_6) of compound **26**.

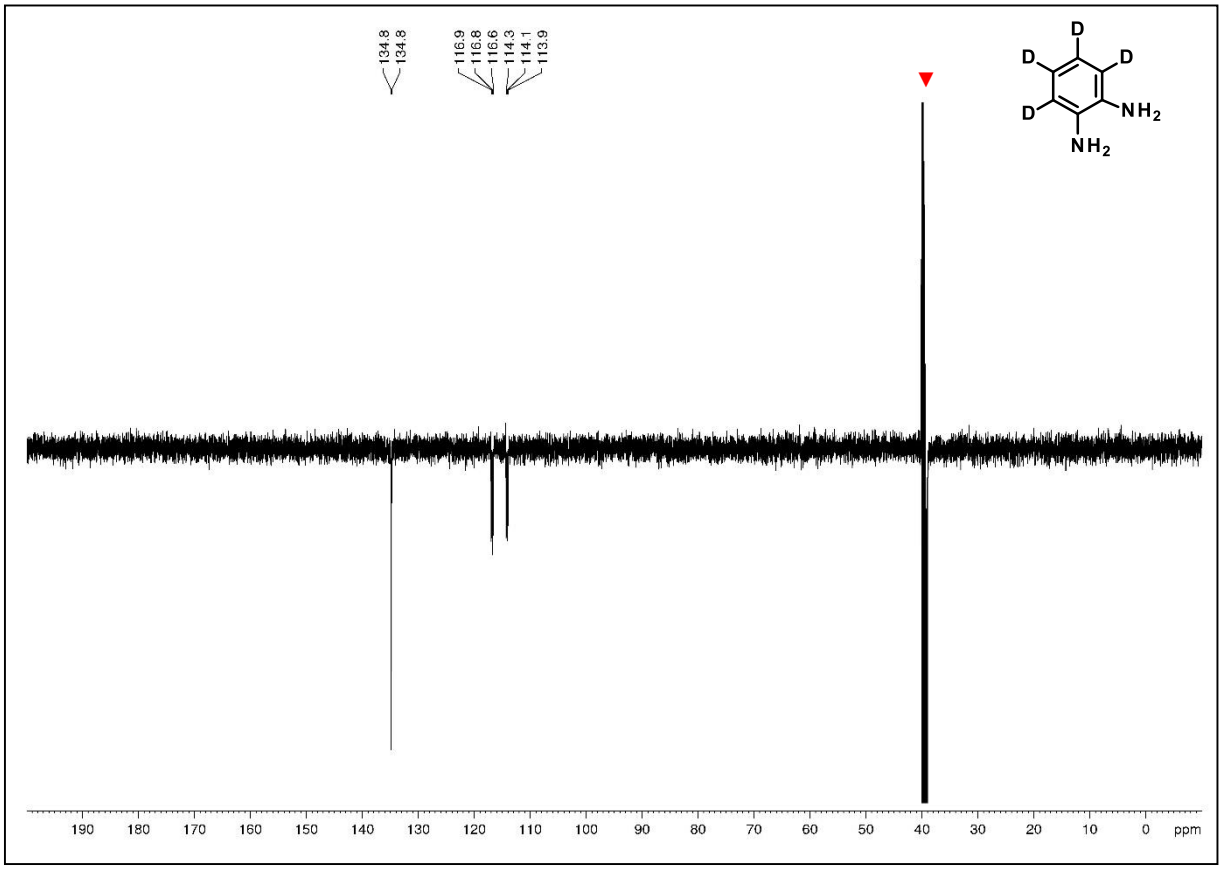


Figure S41. ^{13}C NMR (125 MHz, DMSO-d_6) of compound **26**.

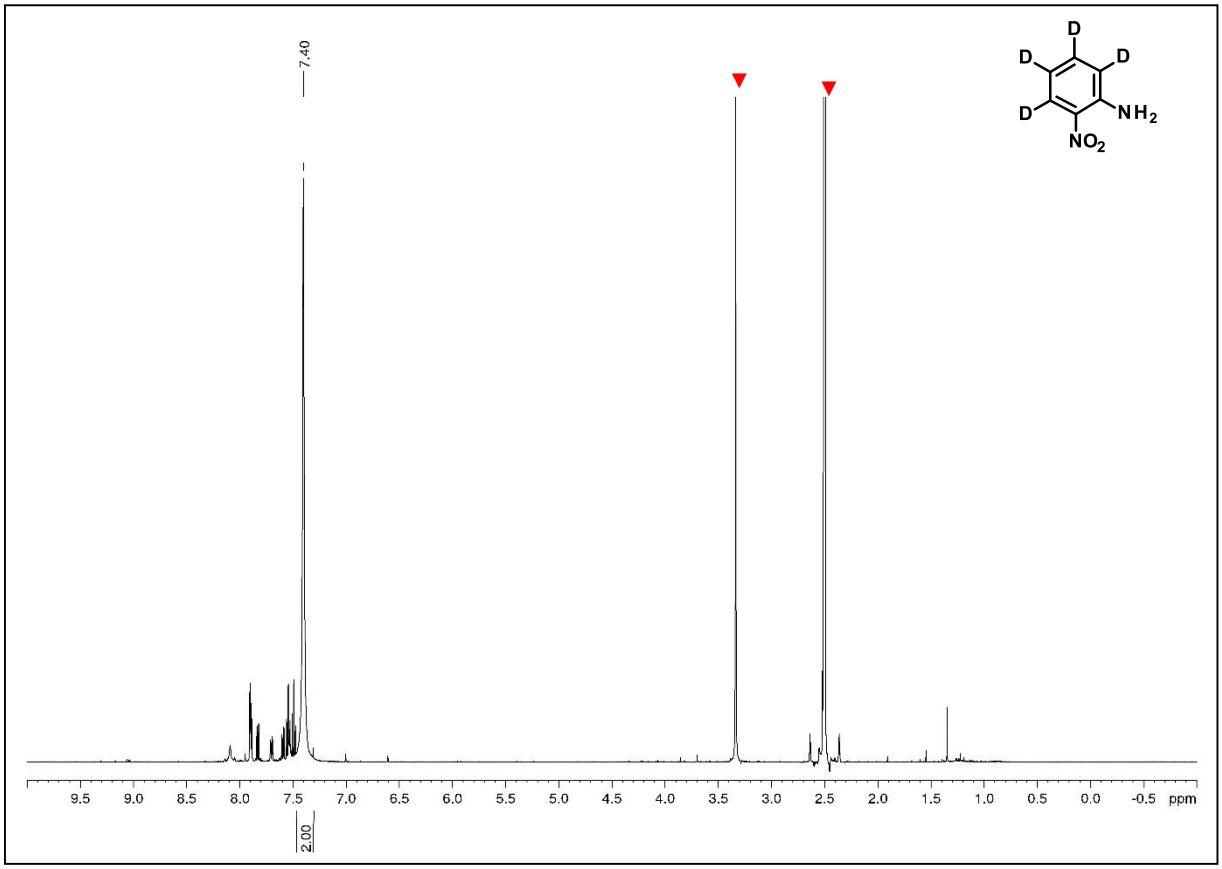


Figure S42. ^{1}H NMR (500 MHz, DMSO-d_6) of compound **10**.

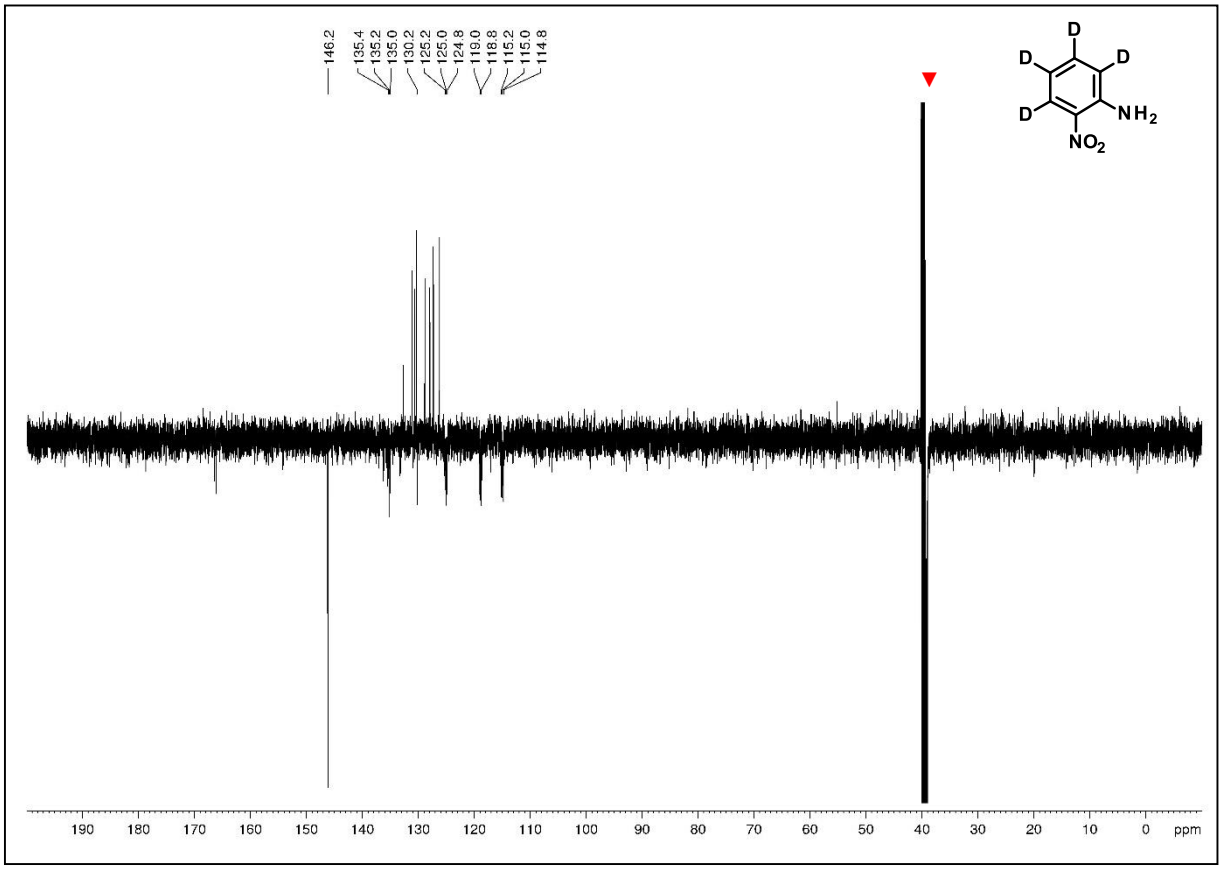


Figure S43. ^{13}C NMR (125 MHz, DMSO-d_6) of compound **10**.

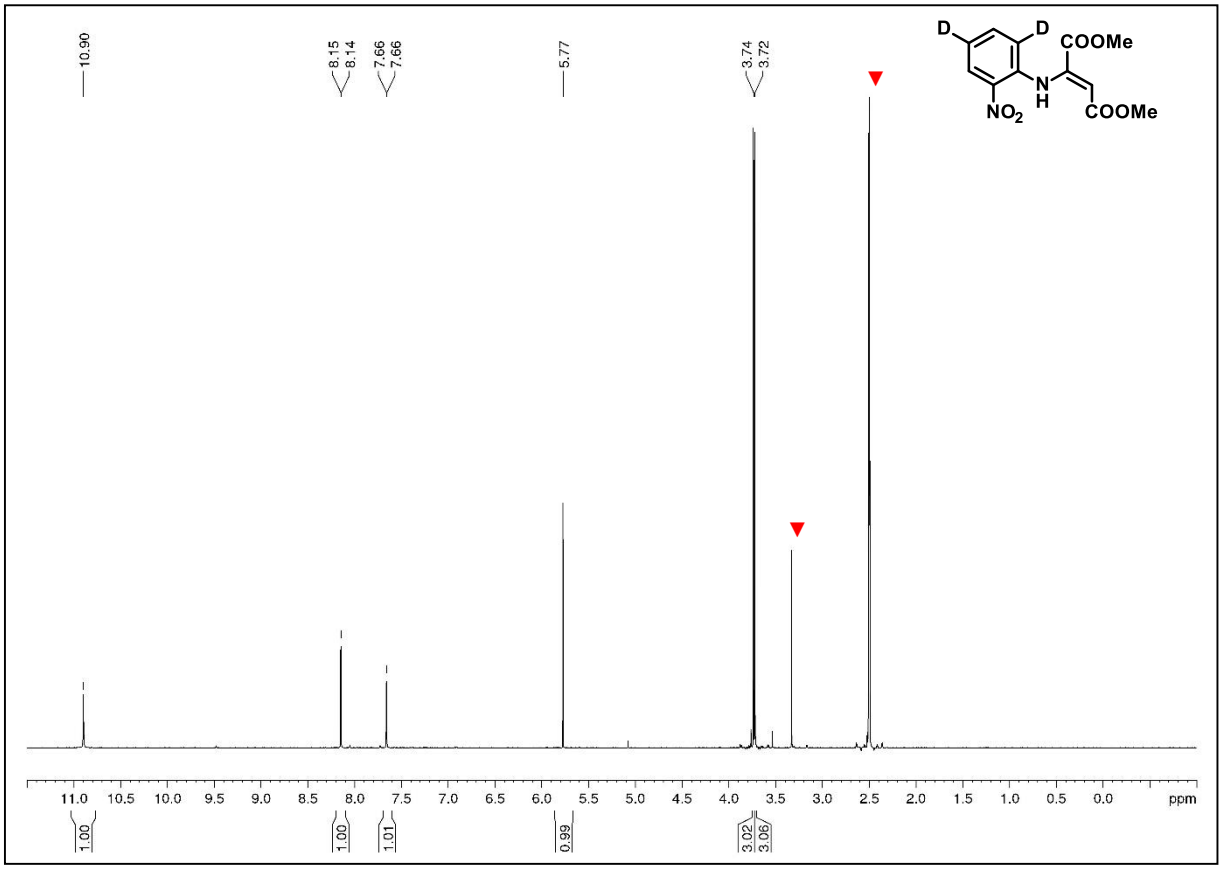


Figure S44. ^{1}H NMR (500 MHz, DMSO-d_6) of compound **27a**.

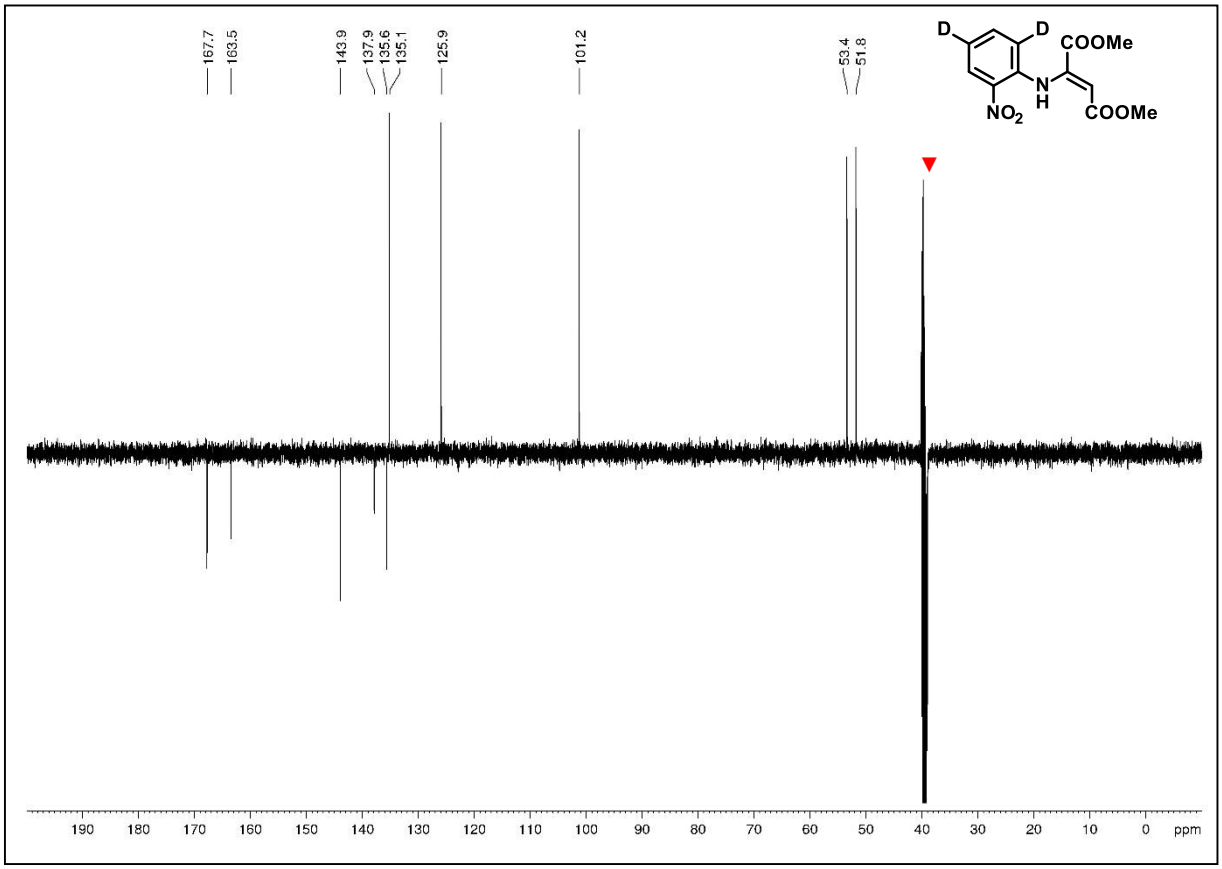


Figure S45. ^{13}C NMR (125 MHz, DMSO-d_6) of compound **27a**.

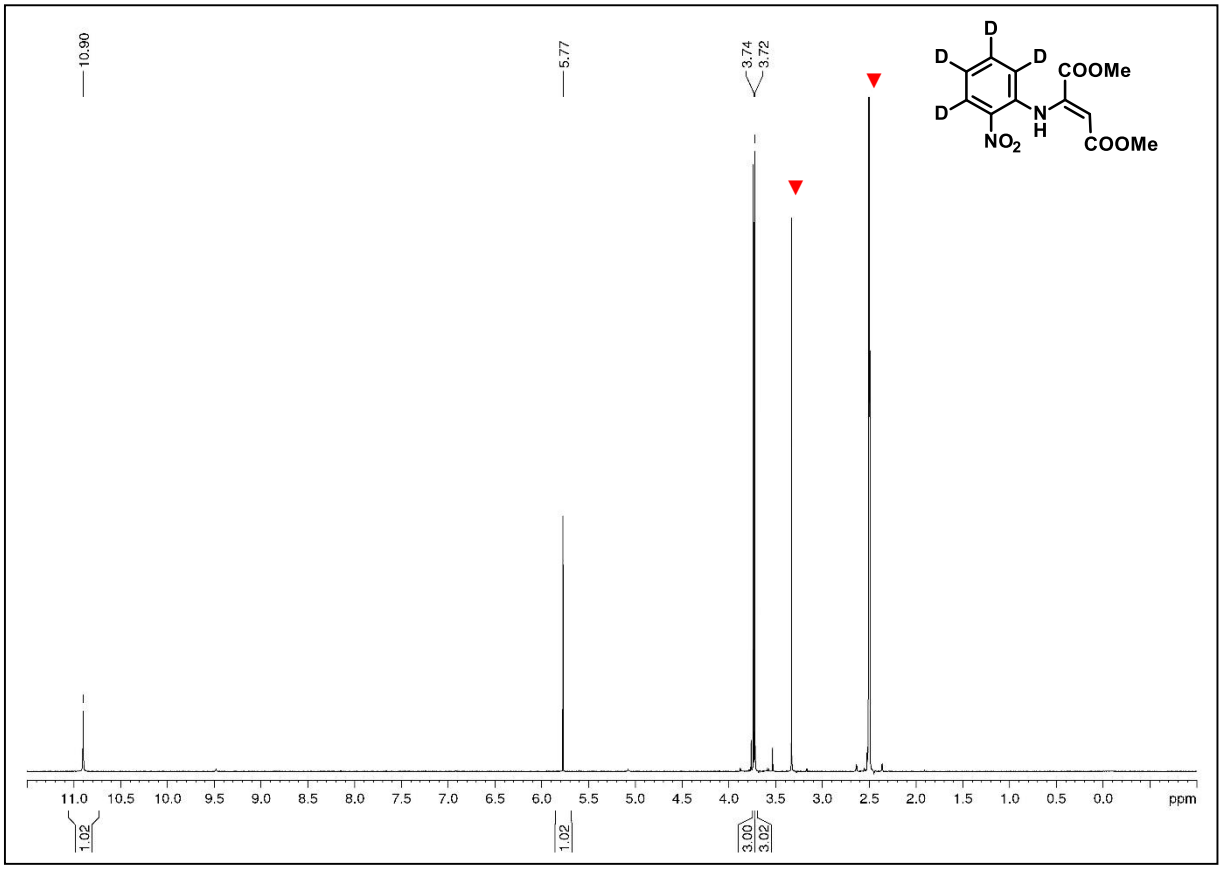


Figure S46. ^{1}H NMR (500 MHz, DMSO-d_6) of compound **27b**.

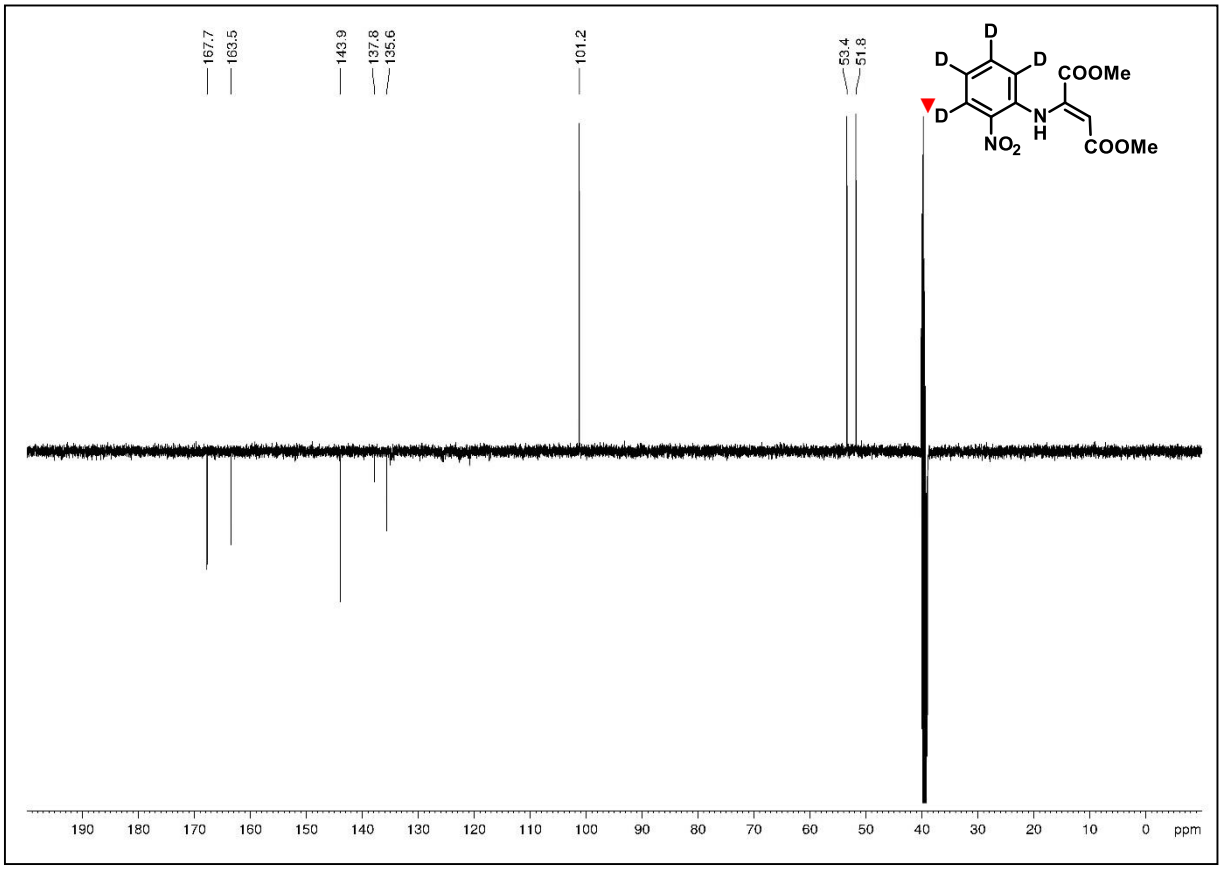


Figure S47. ^{13}C NMR (125 MHz, DMSO-d_6) of compound **27b**.

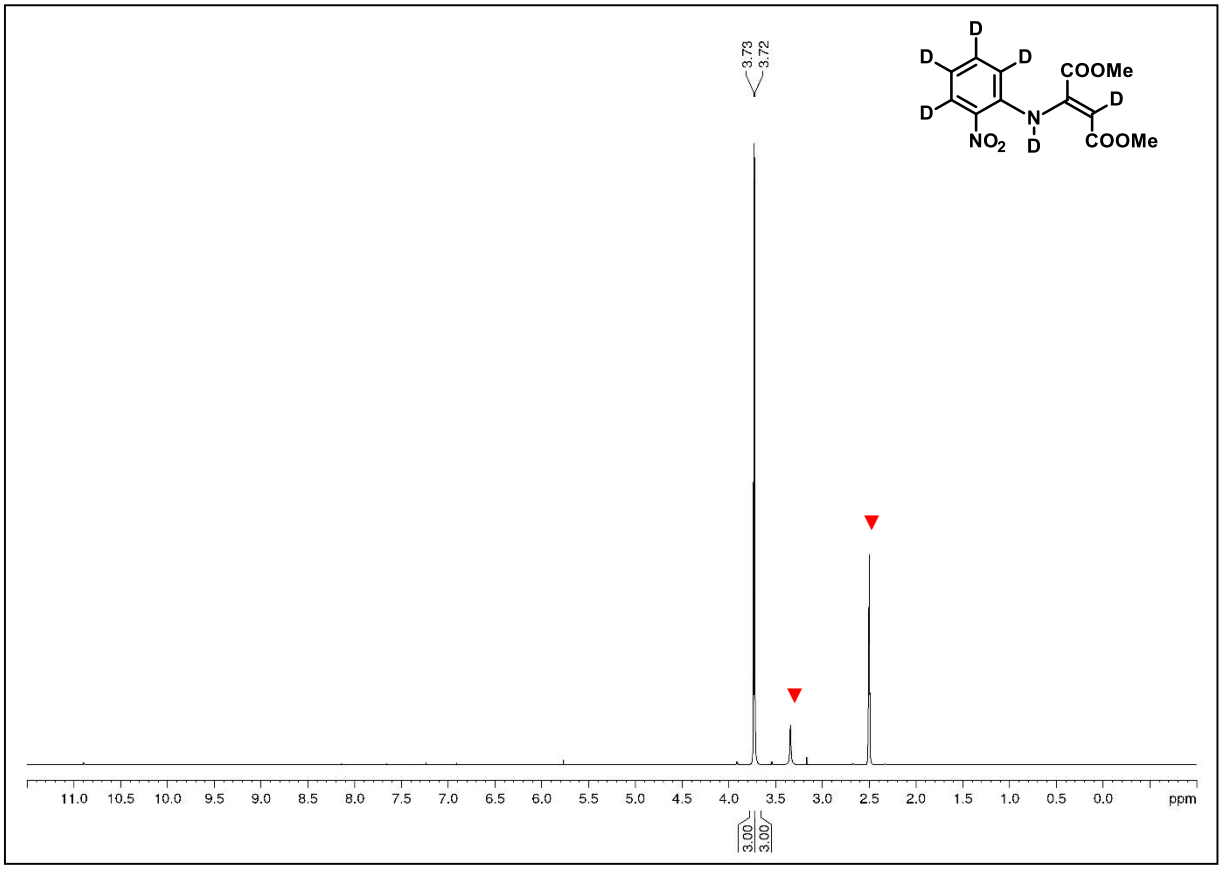


Figure S48. ^{1}H NMR (400 MHz, DMSO-d_6) of compound **27c**.

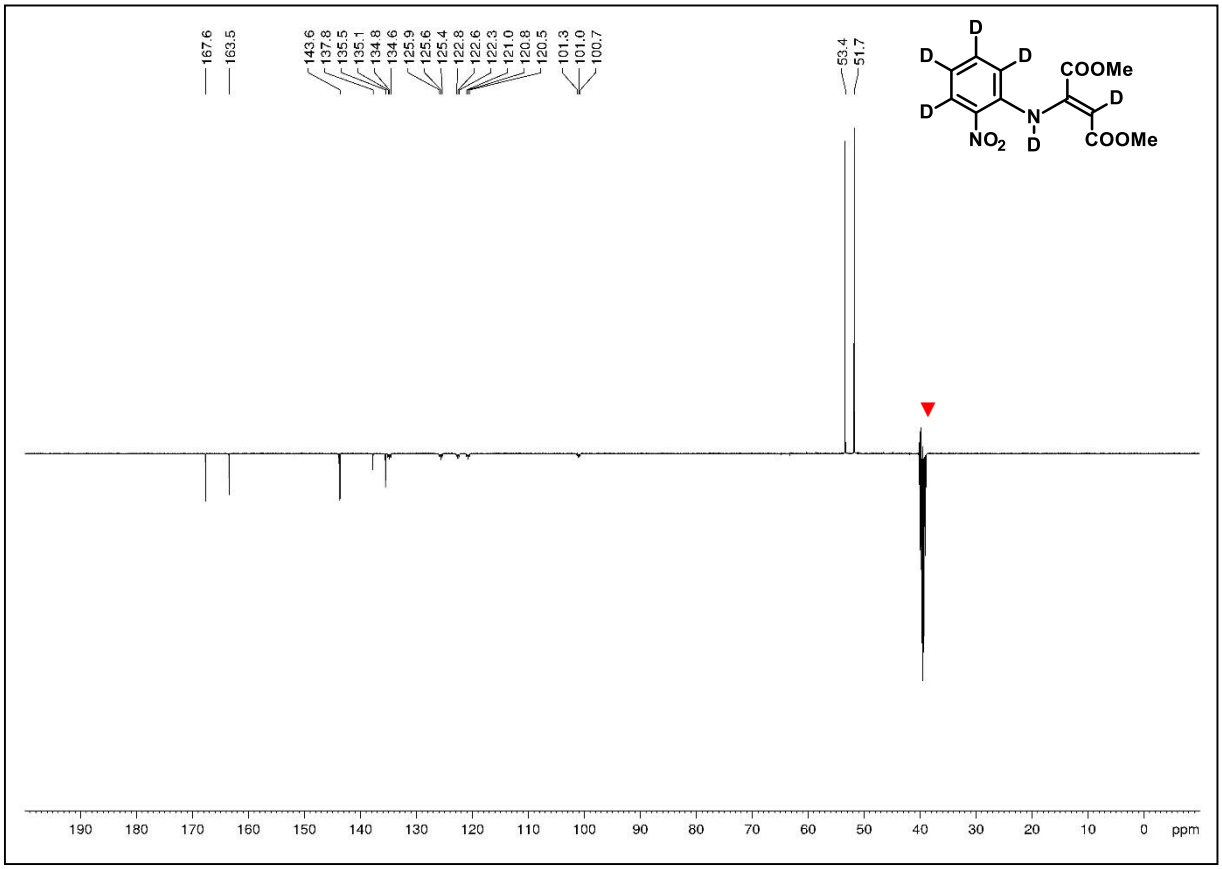


Figure S49. ^{13}C NMR (100 MHz, DMSO-d_6) of compound **27c**.

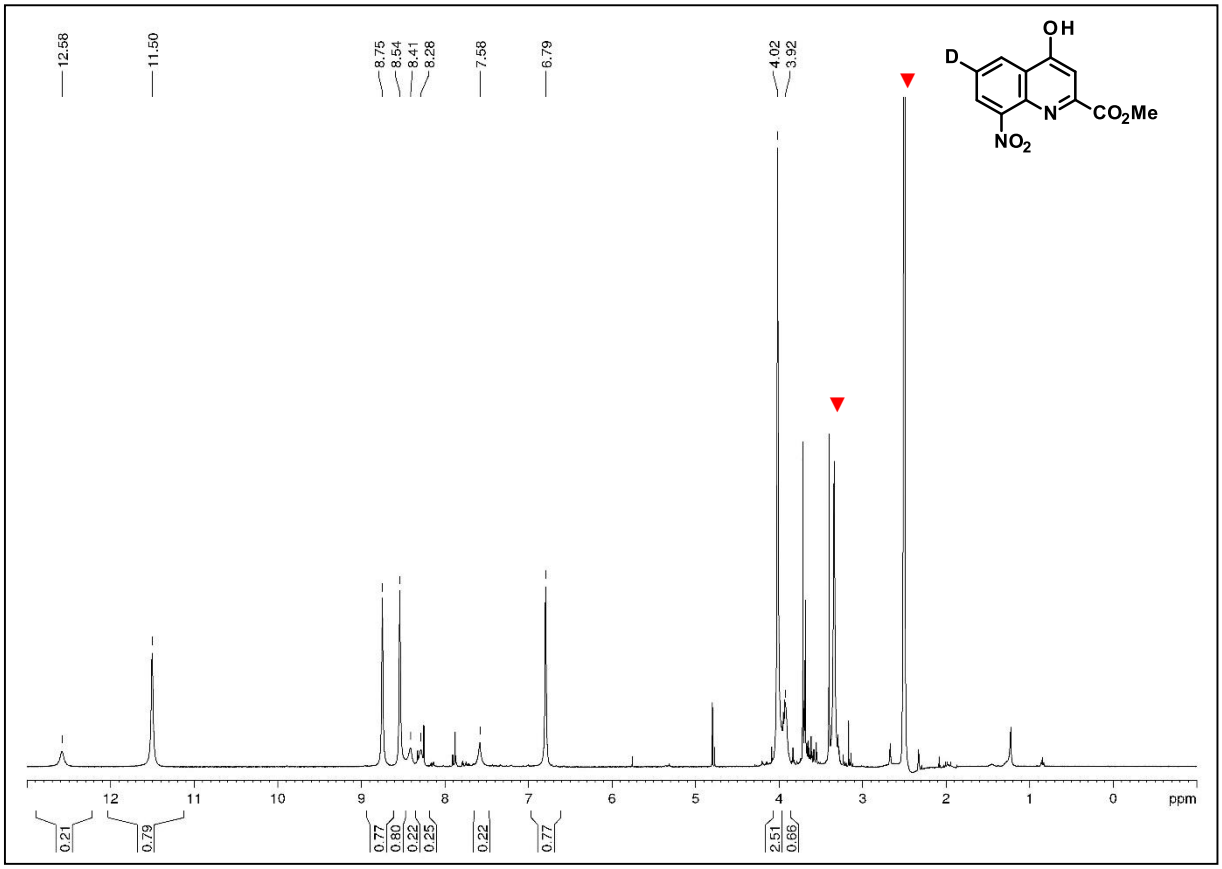


Figure S50. ^{1}H NMR (400 MHz, DMSO-d_6) of compound **28a**.

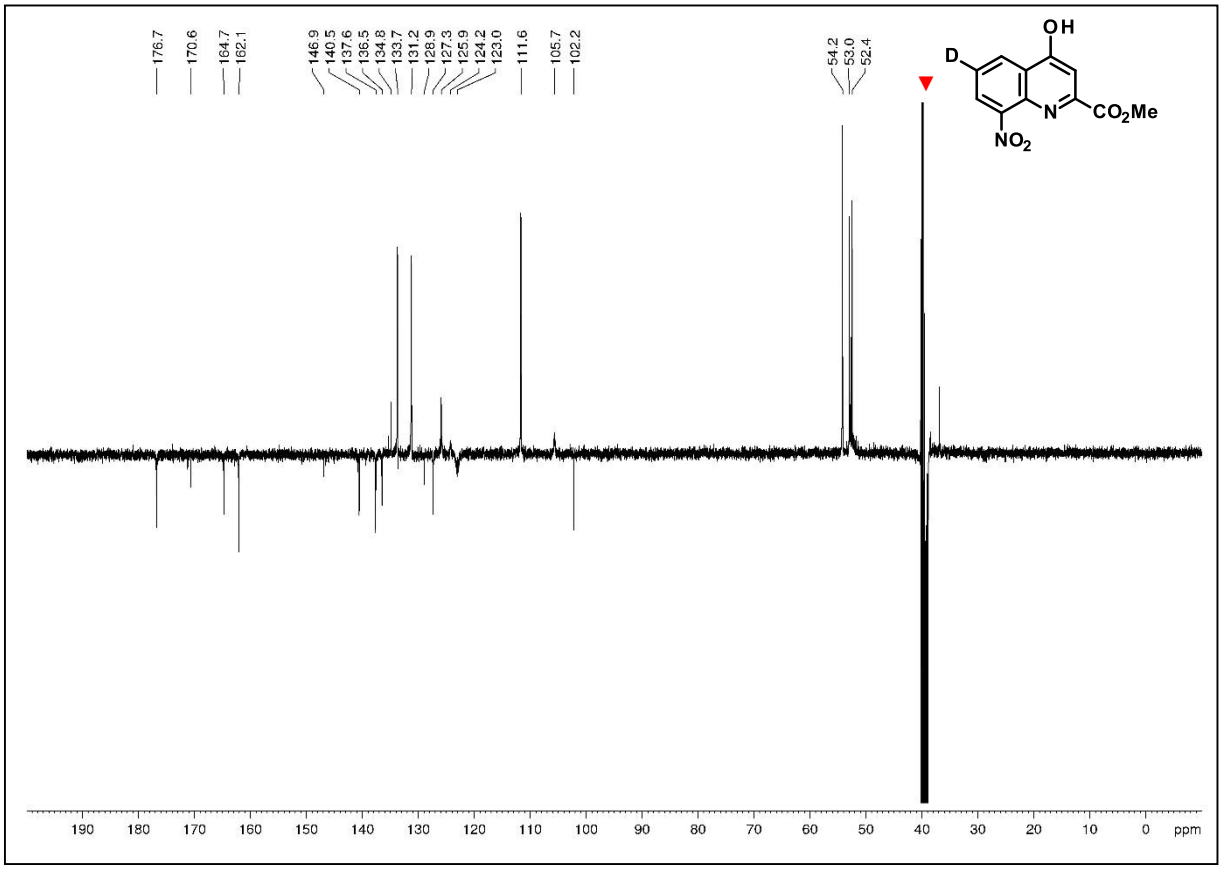


Figure S51. ^{13}C NMR (100 MHz, DMSO-d_6) of compound **28a**.

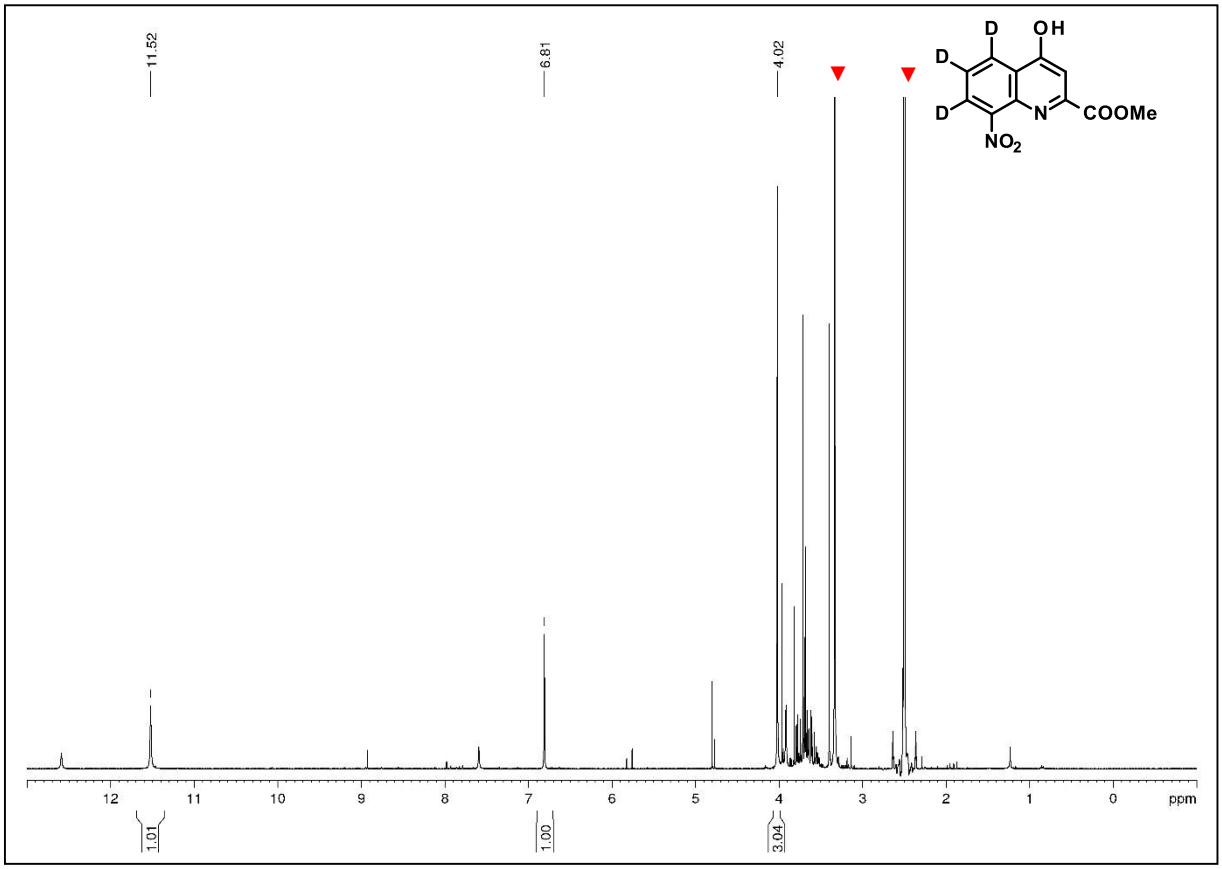


Figure S52. ^{1}H NMR (500 MHz, DMSO-d_6) of compound **28b**.

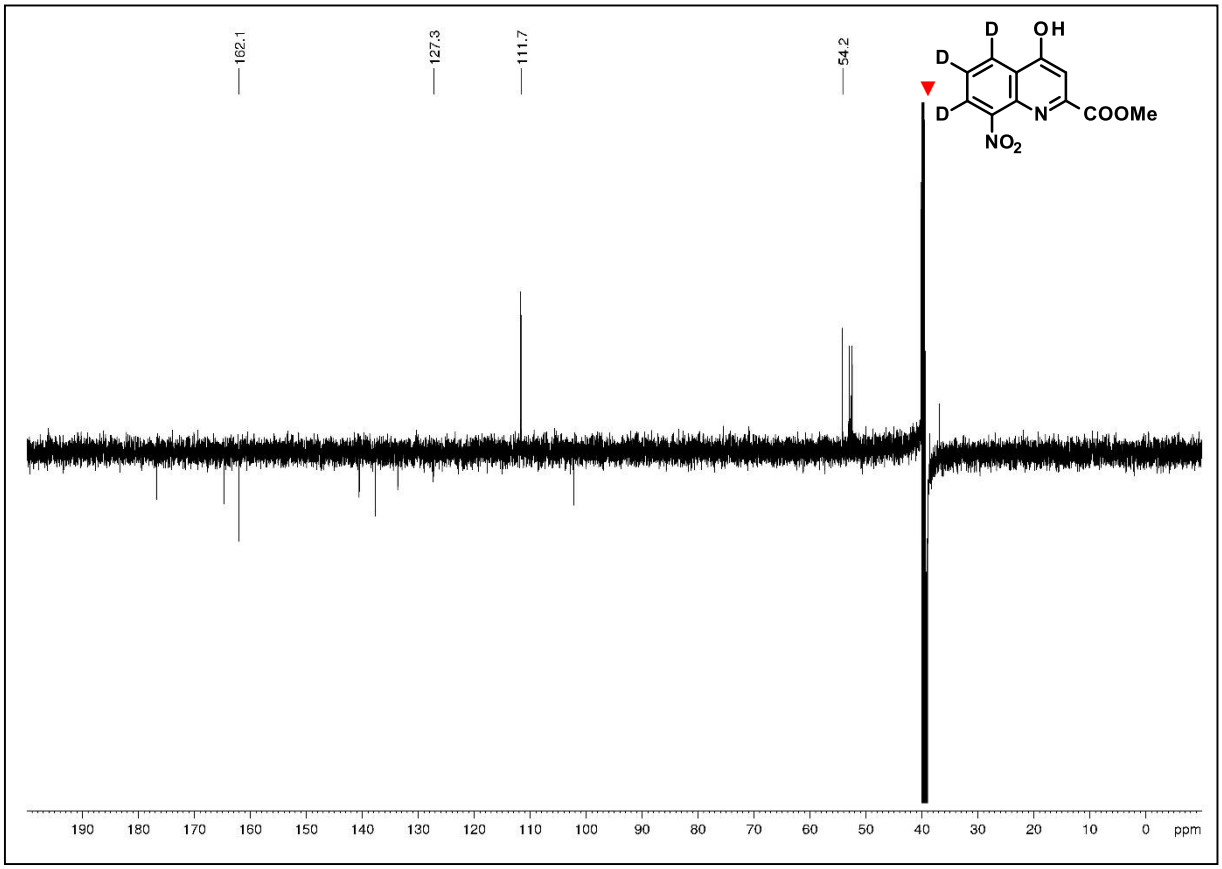


Figure S53. ^{13}C NMR (125 MHz, DMSO-d_6) of compound **28b**.

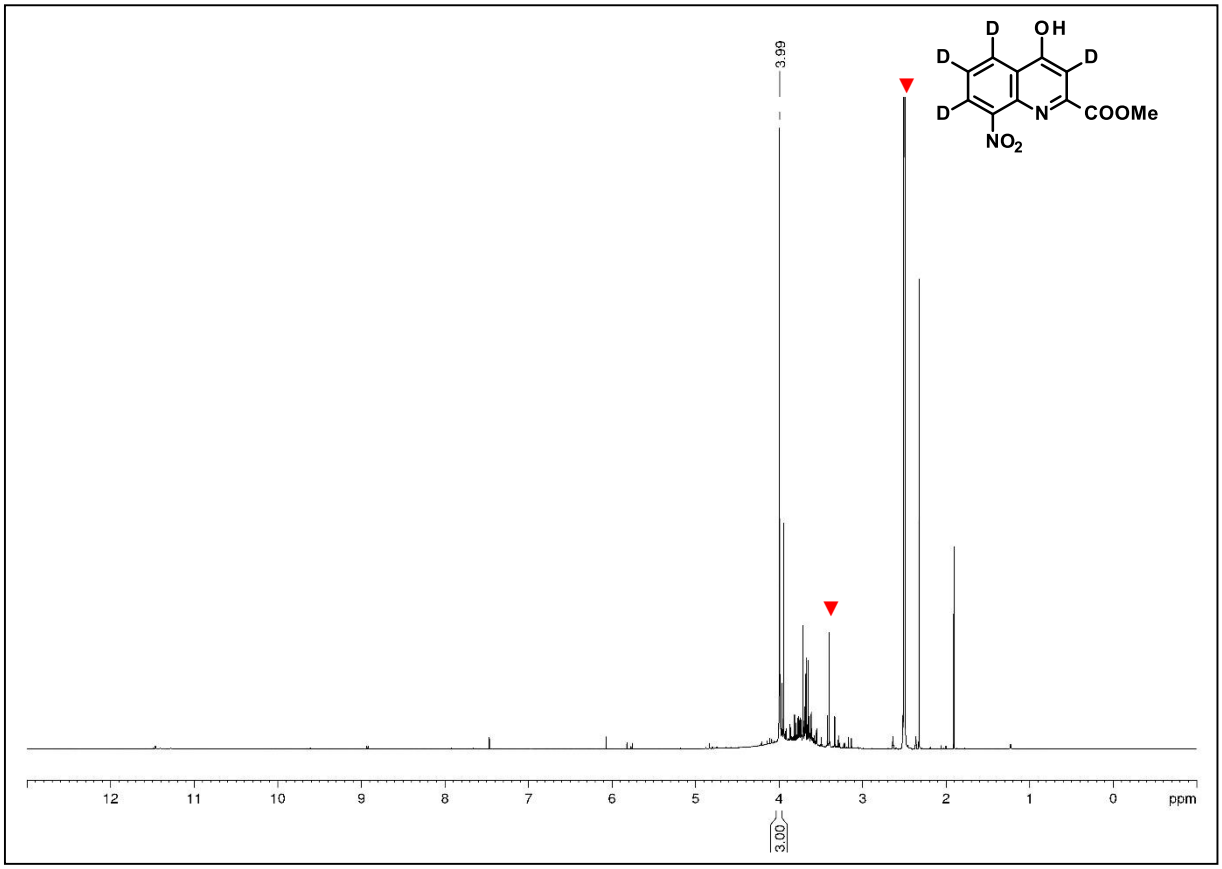


Figure S54. ^{1}H NMR (500 MHz, DMSO-d_6) of compound **28c**.

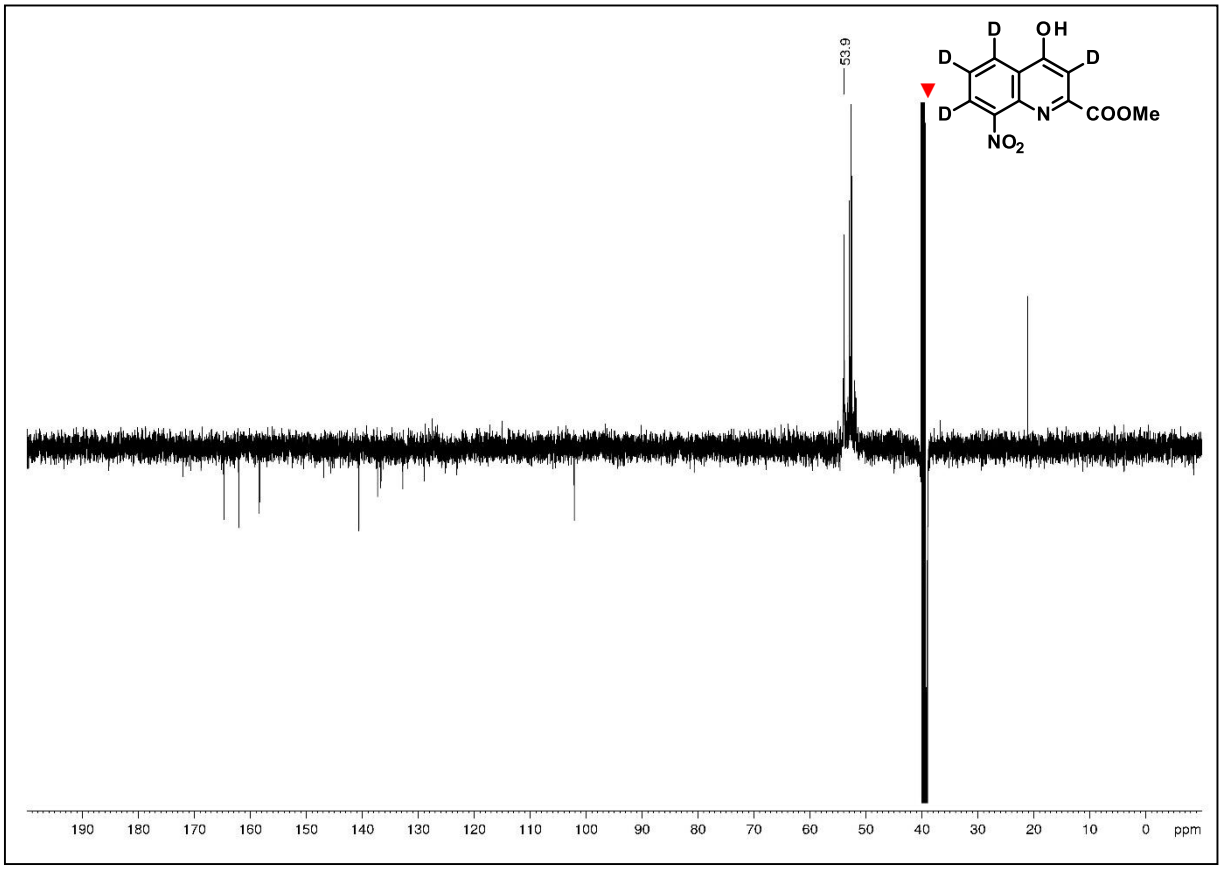


Figure S55. ^{13}C NMR (125 MHz, DMSO-d_6) of compound **28c**.

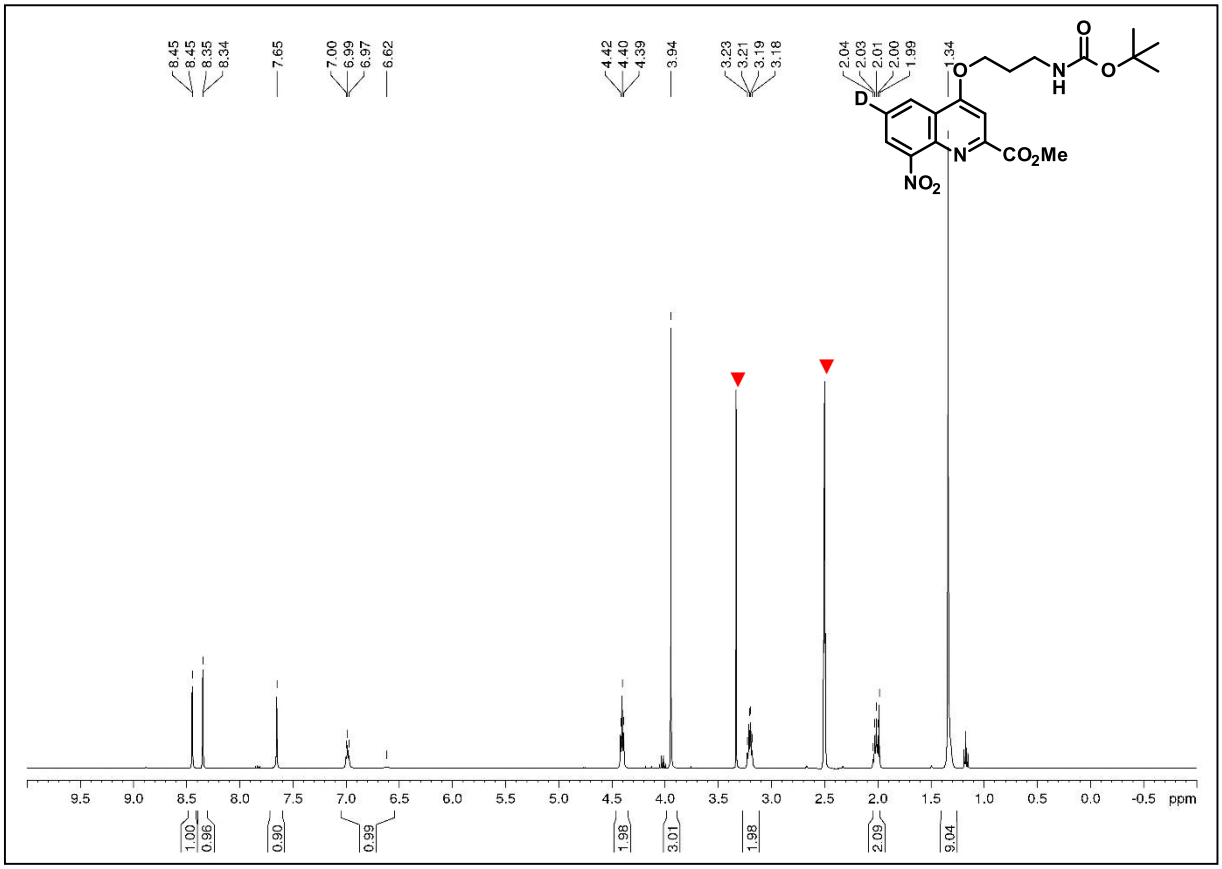


Figure S56. ^{1}H NMR (400 MHz, DMSO-d_6) of compound **29a**.

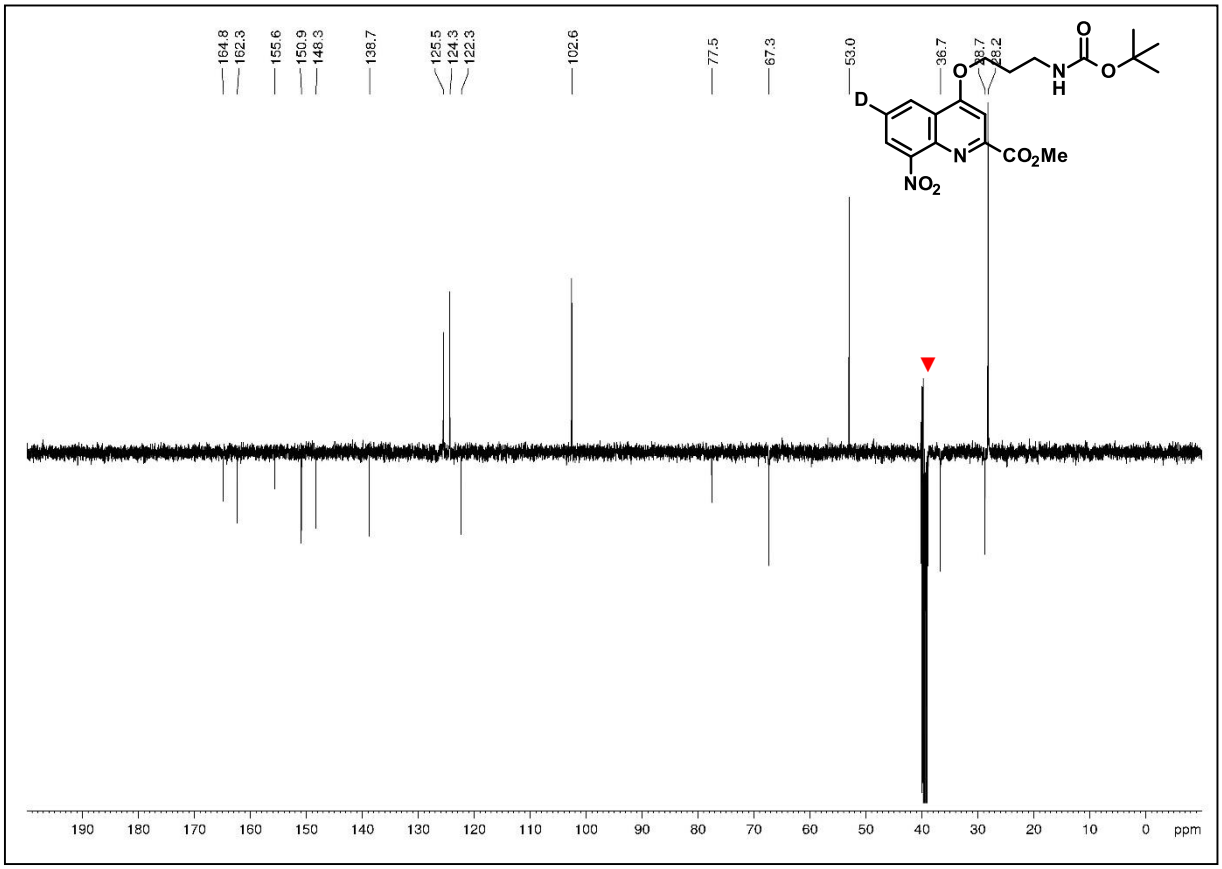


Figure S57. ^{13}C NMR (100 MHz, DMSO-d_6) of compound **29a**.

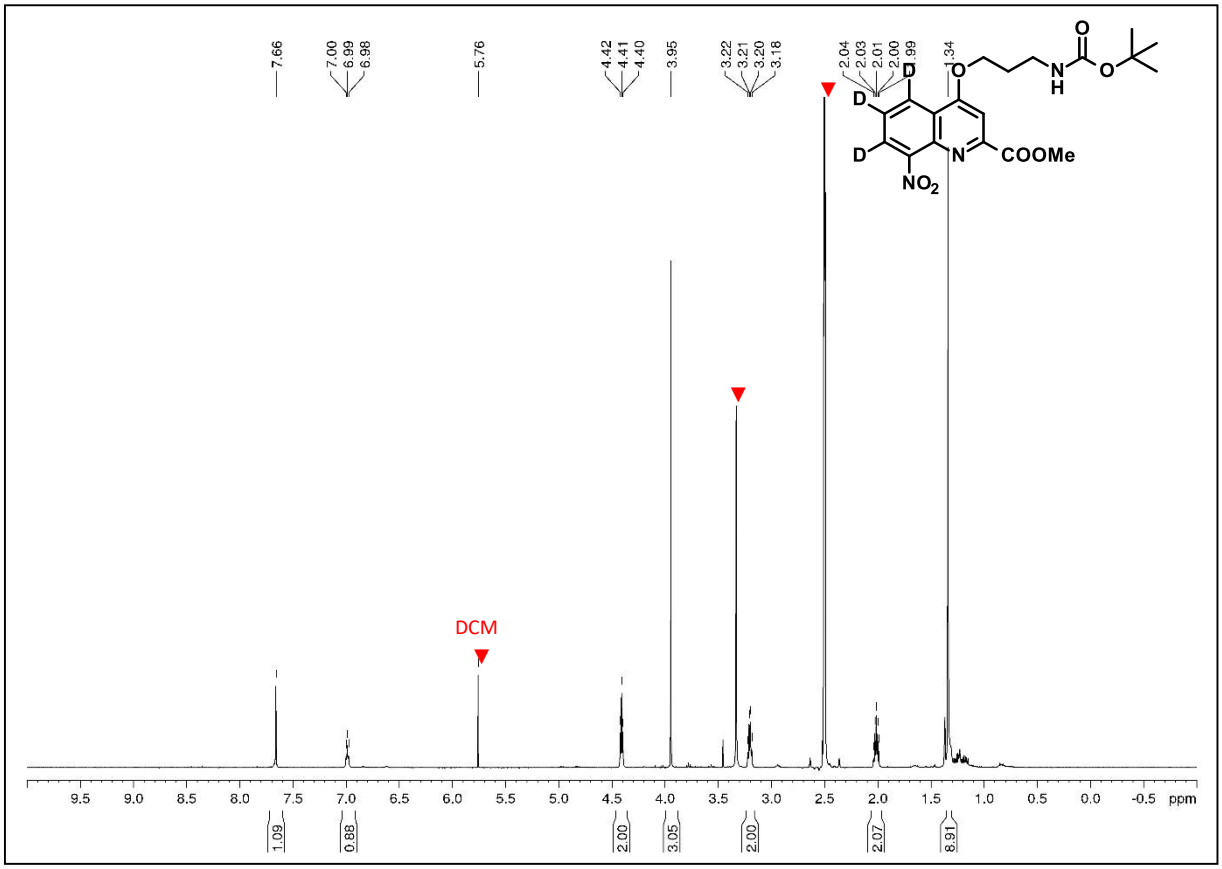


Figure S58. ^{1}H NMR (500 MHz, DMSO-d_6) of compound **29b**.

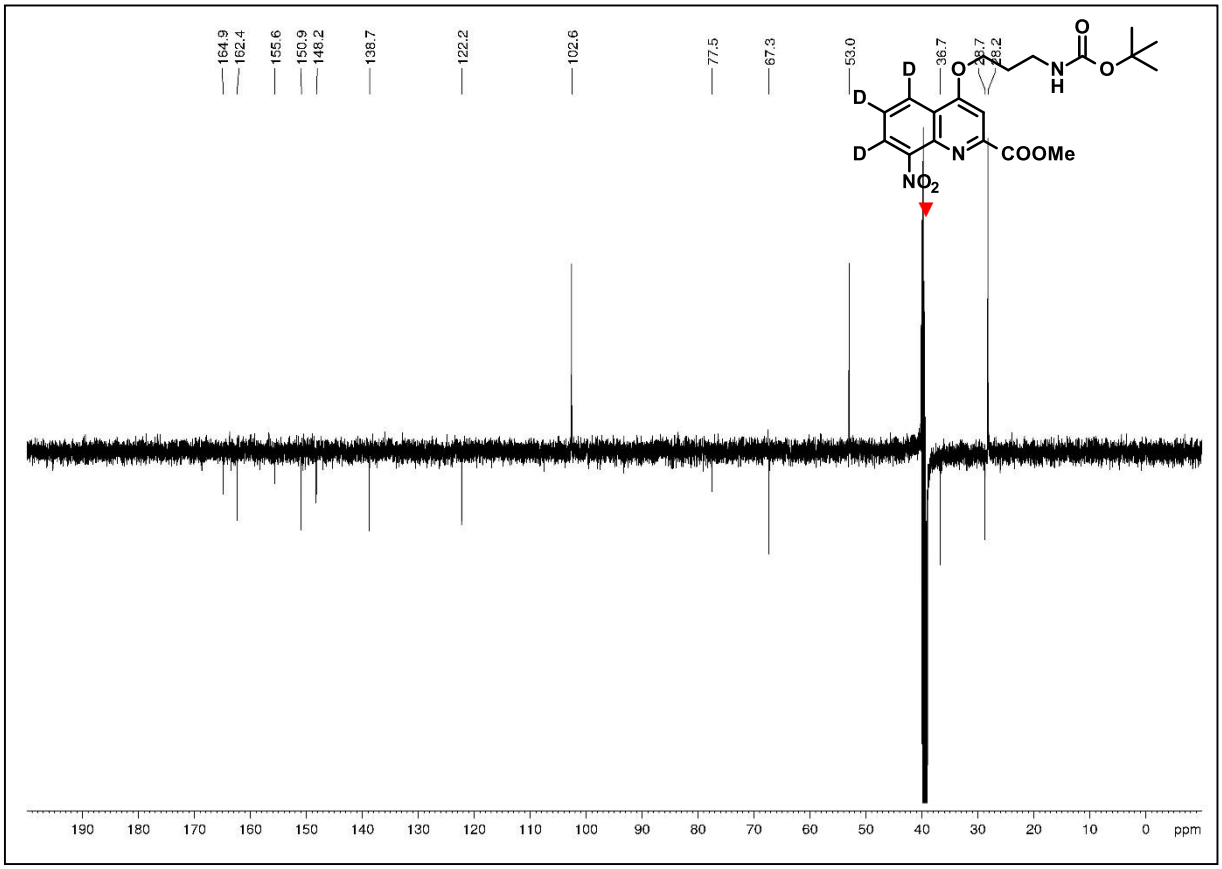


Figure S59. ^{13}C NMR (125 MHz, DMSO-d_6) of compound **29b**.

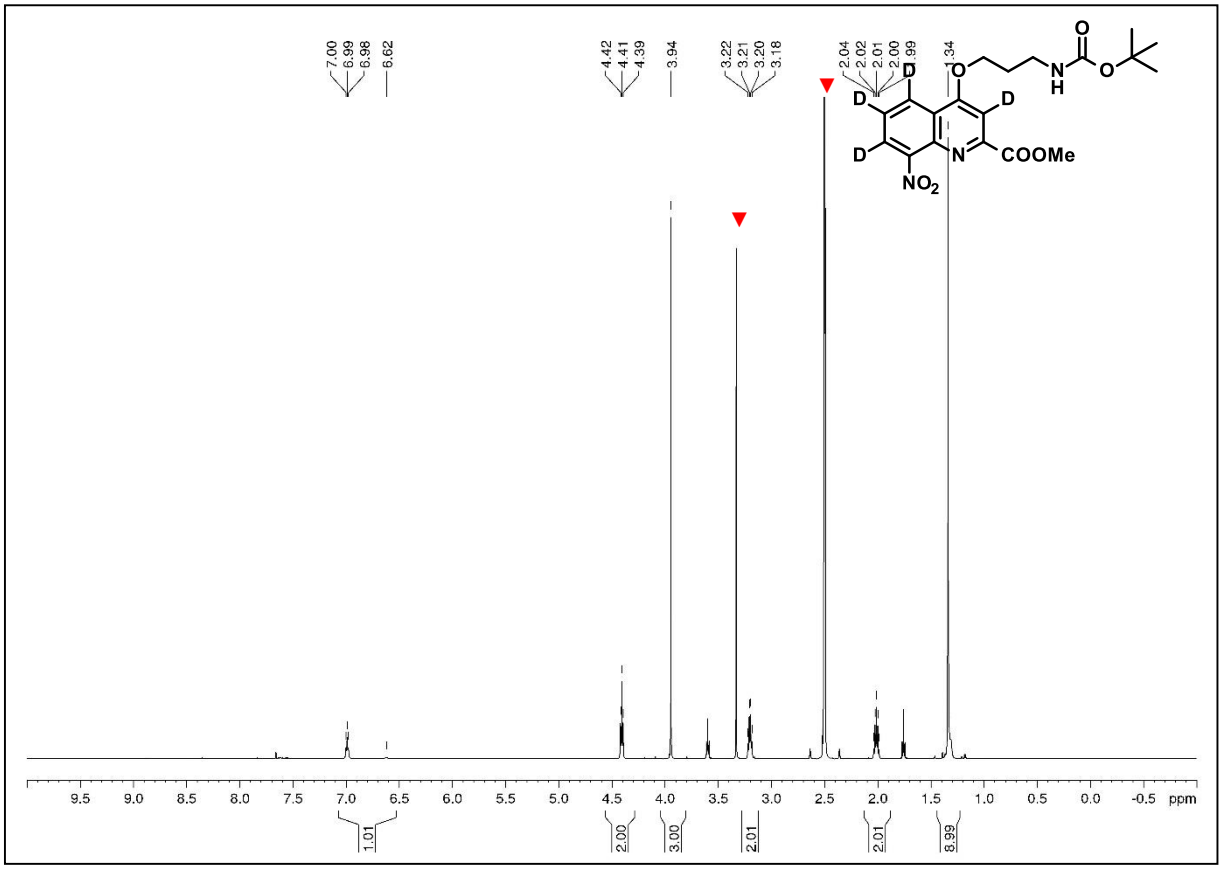


Figure S60. ^{1}H NMR (500 MHz, DMSO-d_6) of compound **29c**.

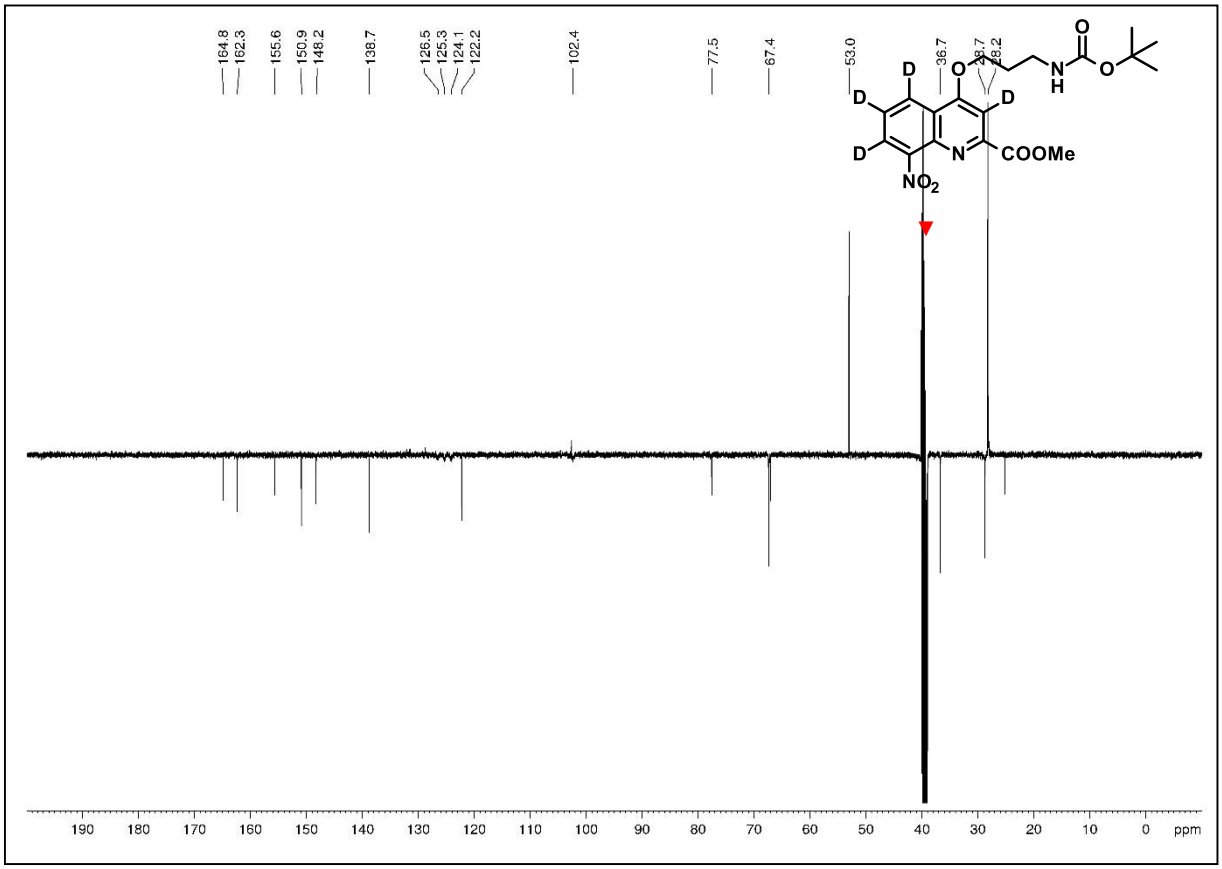


Figure S61. ^{13}C NMR (125 MHz, DMSO-d_6) of compound **29c**.

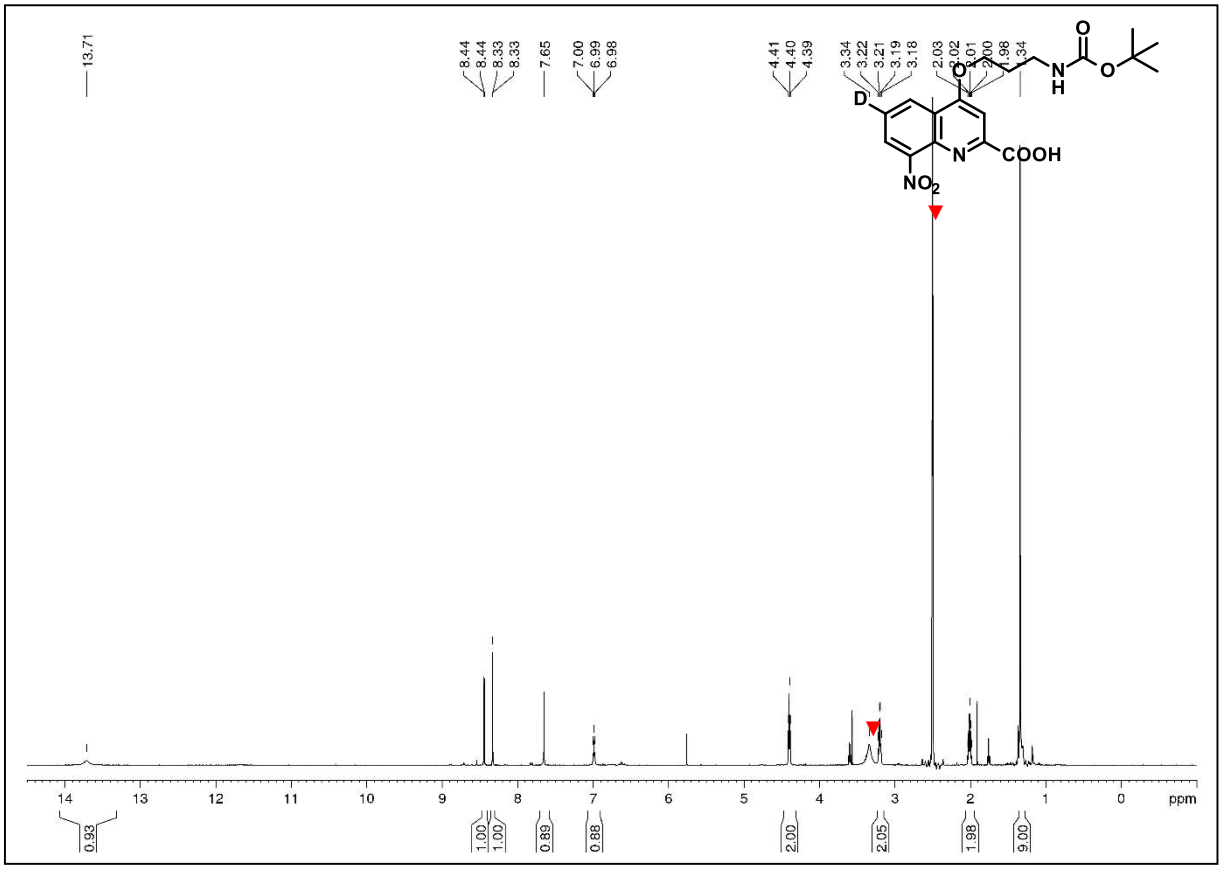


Figure S62. ^{1}H NMR (500 MHz, DMSO-d_6) of compound **30a**.

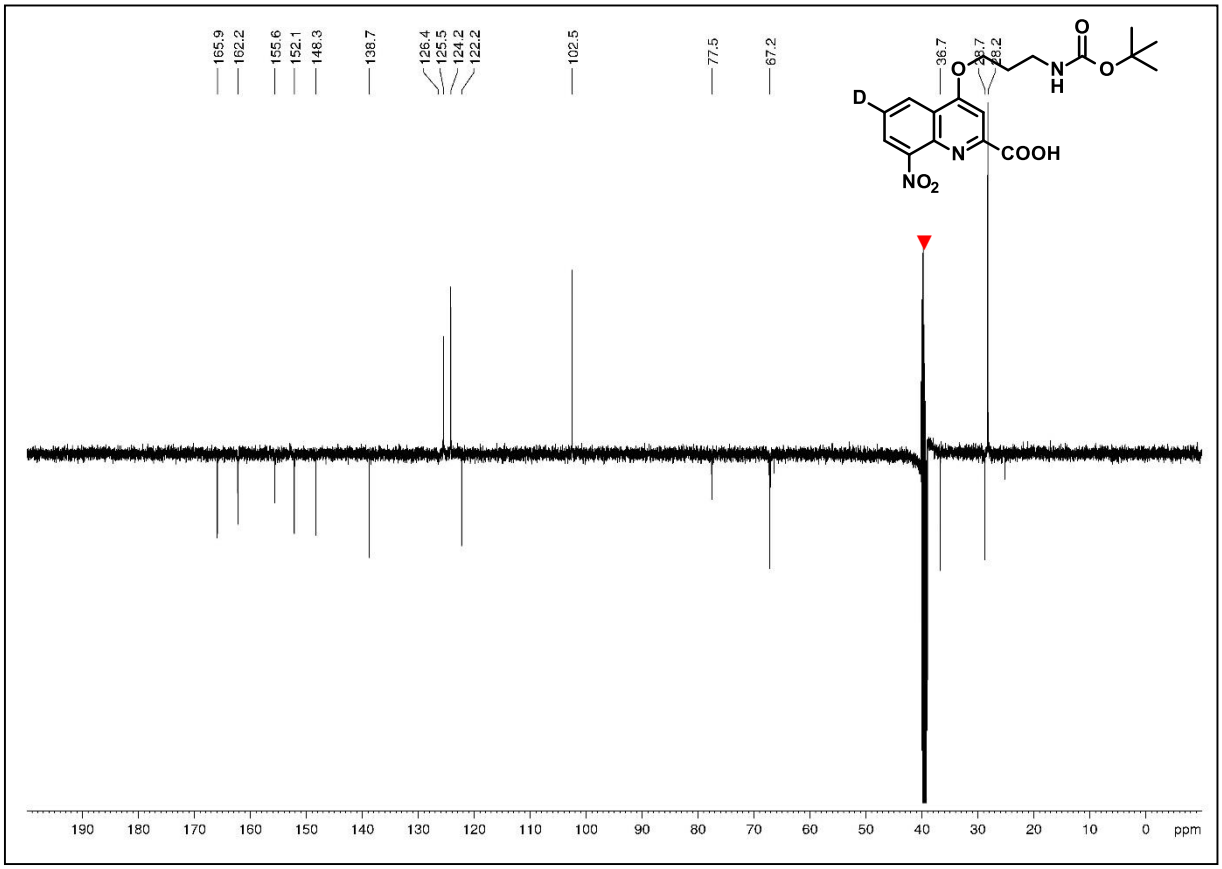


Figure S63. ^{13}C NMR (125 MHz, DMSO-d_6) of compound **30a**.

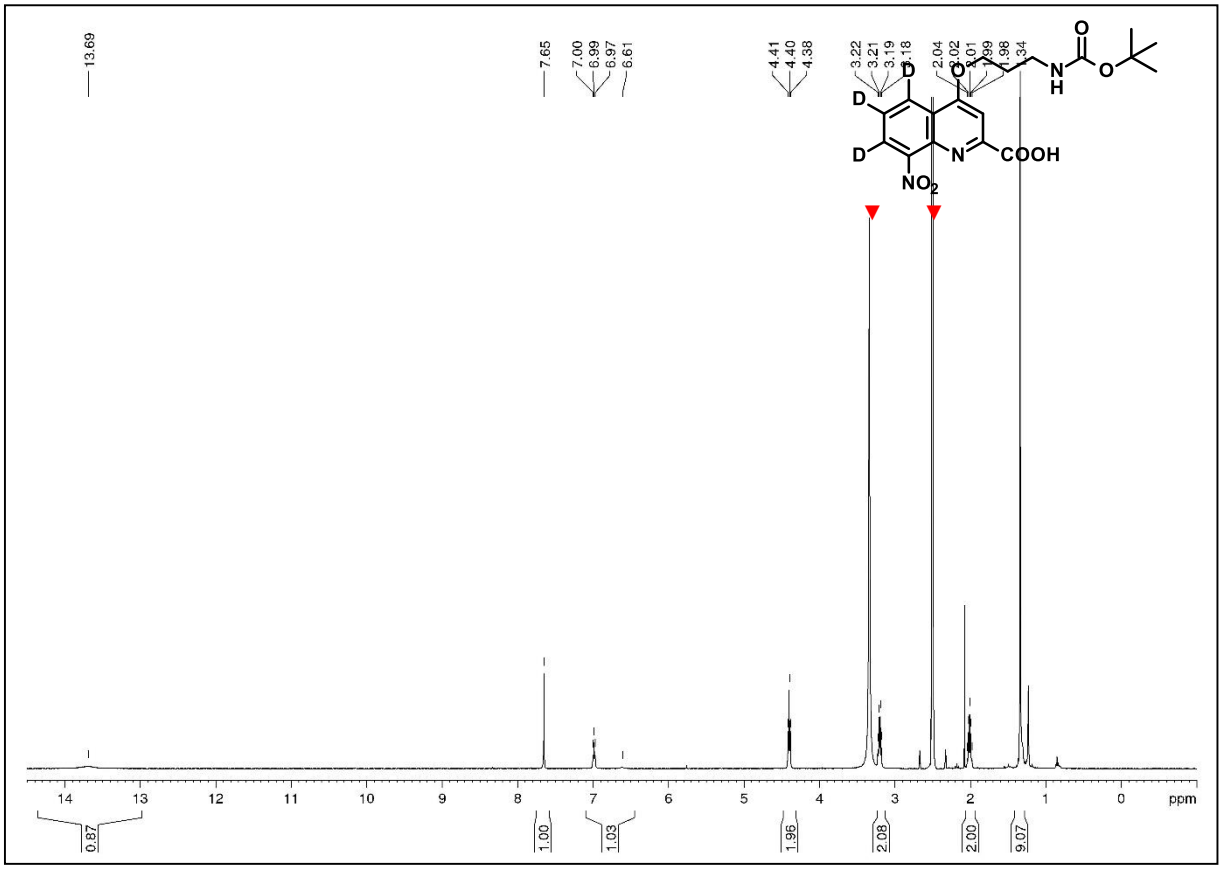


Figure S64. ^{1}H NMR (400 MHz, DMSO-d_6) of compound **30b**.

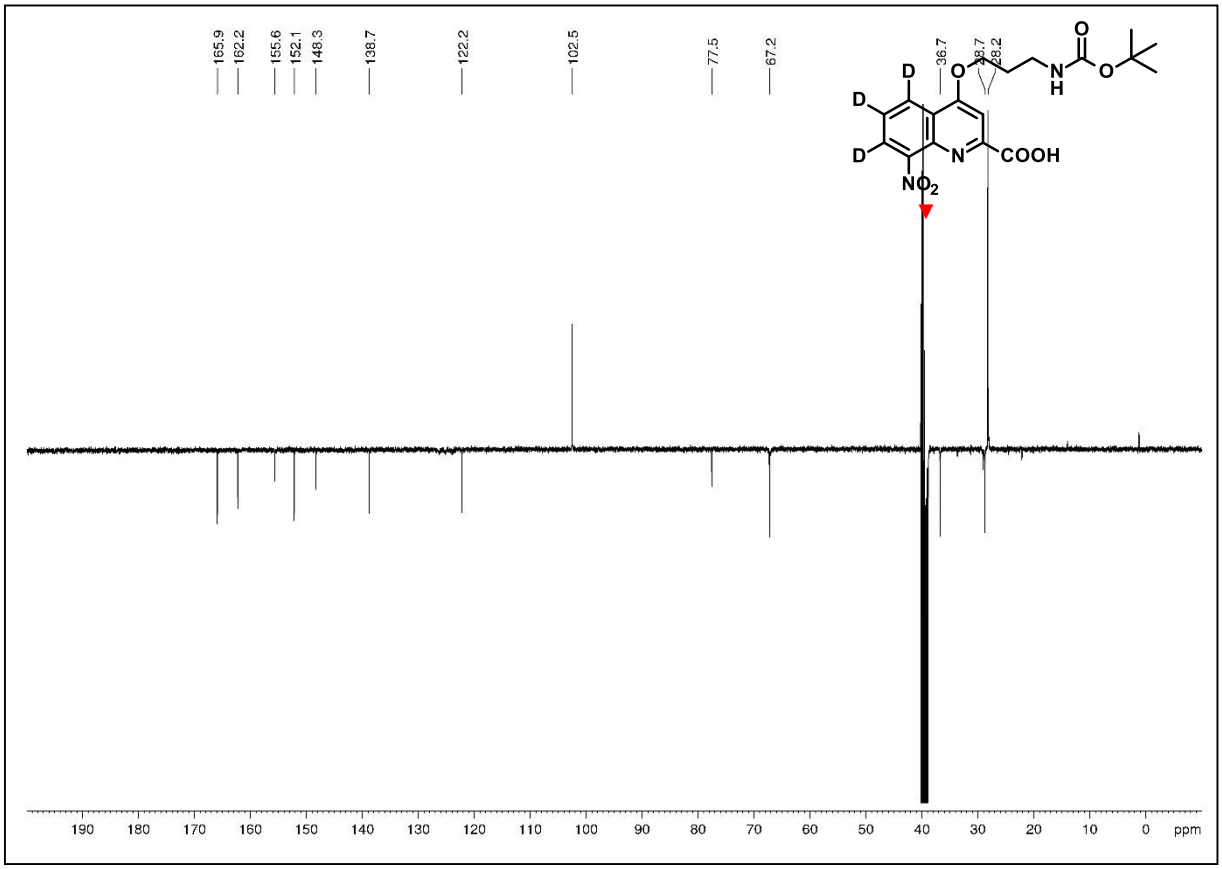


Figure S65. ^{13}C NMR (100 MHz, DMSO-d_6) of compound **30b**.

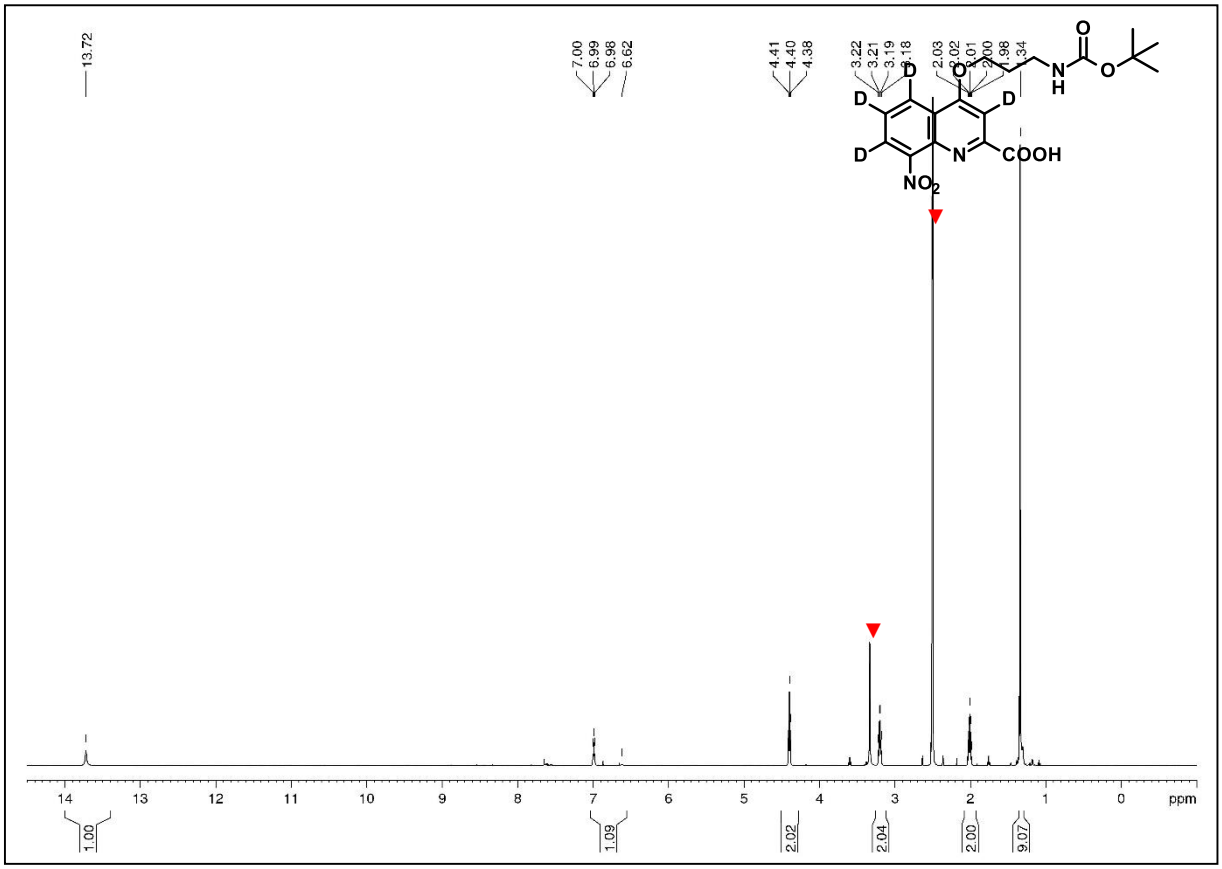


Figure S66. ^{1}H NMR (500 MHz, DMSO-d_6) of compound **30c**.

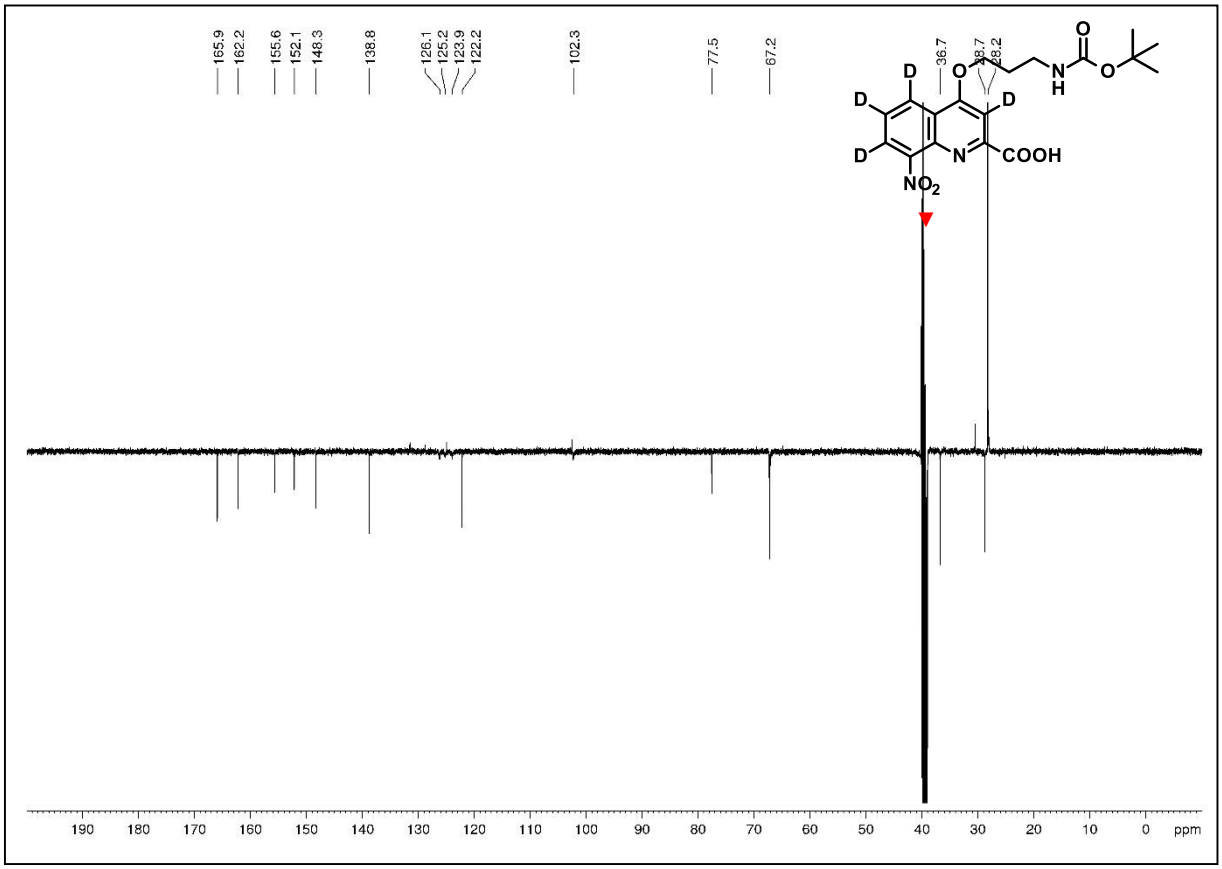


Figure S67. ^{13}C NMR (125 MHz, DMSO-d_6) of compound **30c**.

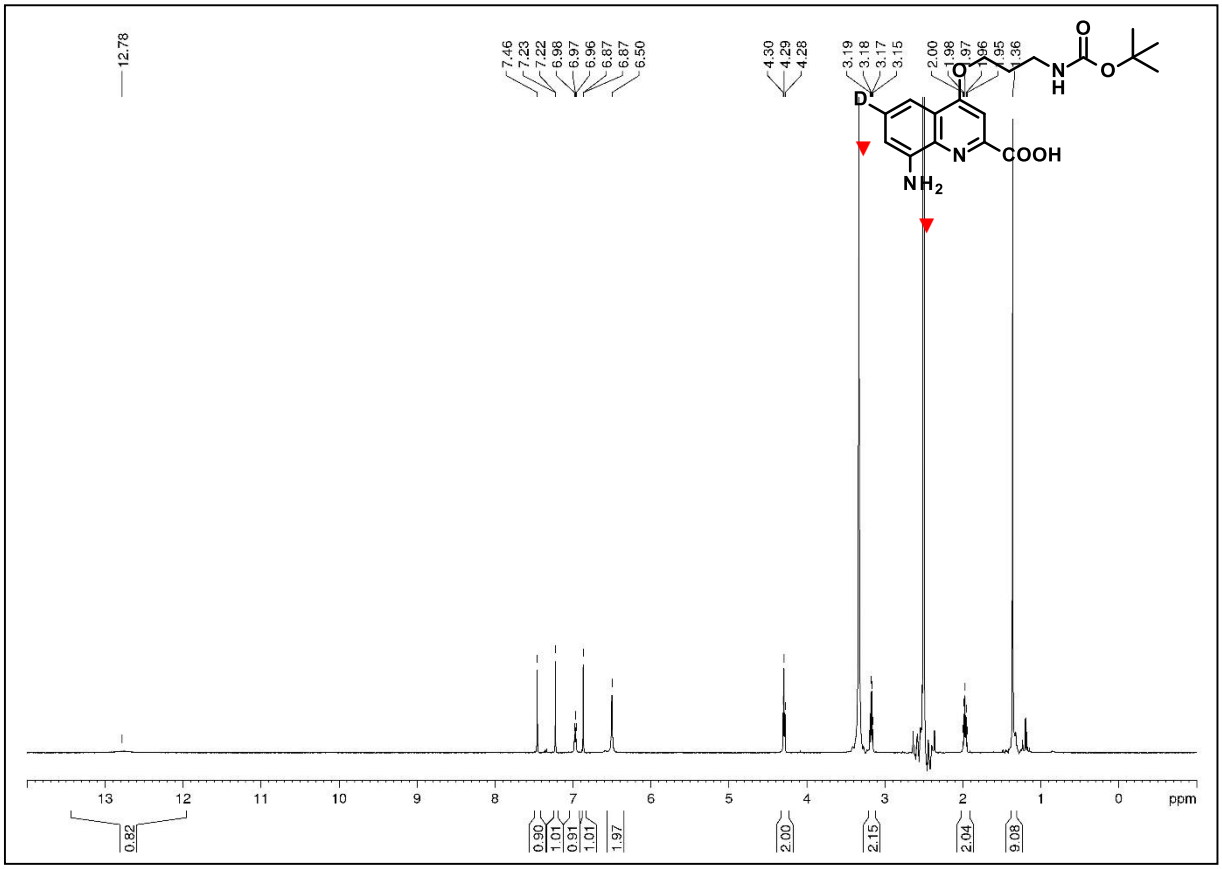


Figure S68. ^{1}H NMR (500 MHz, DMSO-d_6) of compound **31a**.

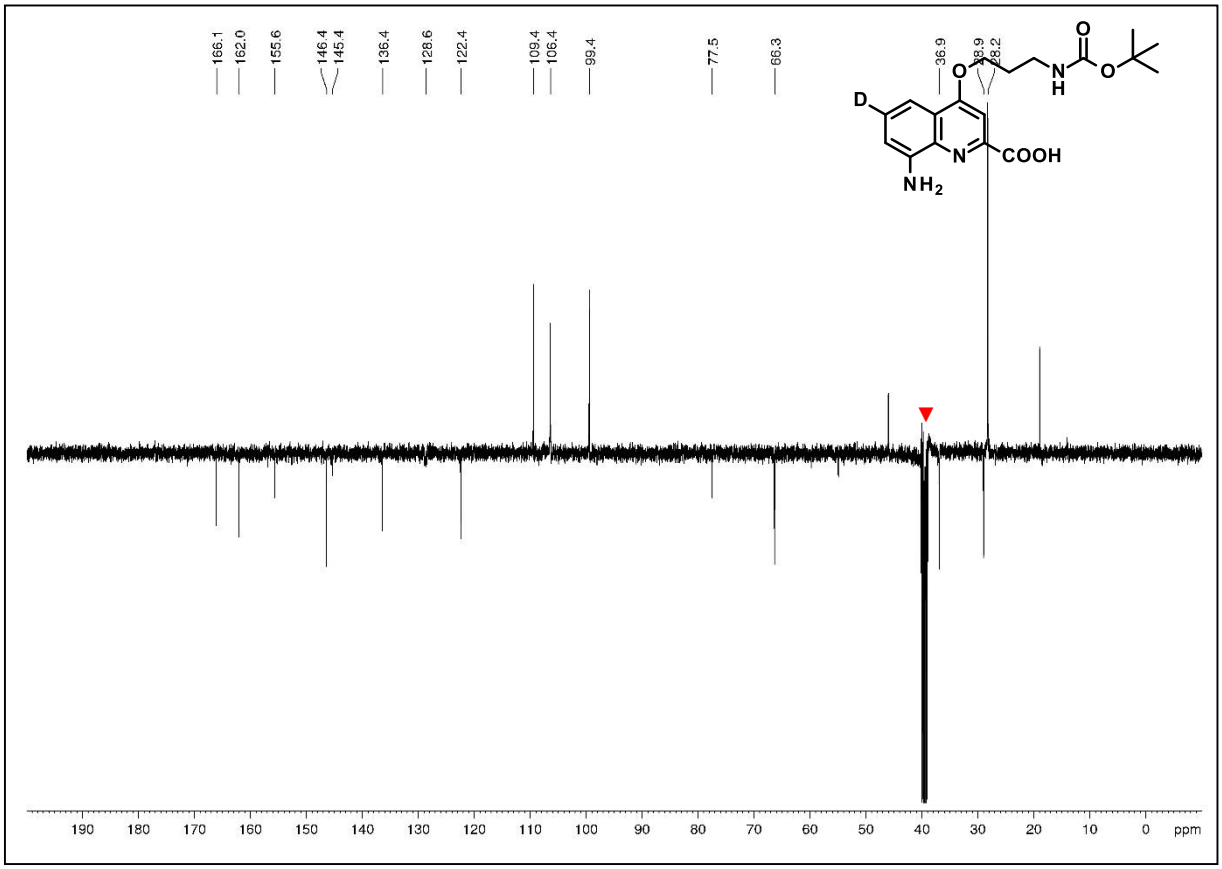


Figure S69. ^{13}C NMR (100 MHz, DMSO-d_6) of compound **31a**.

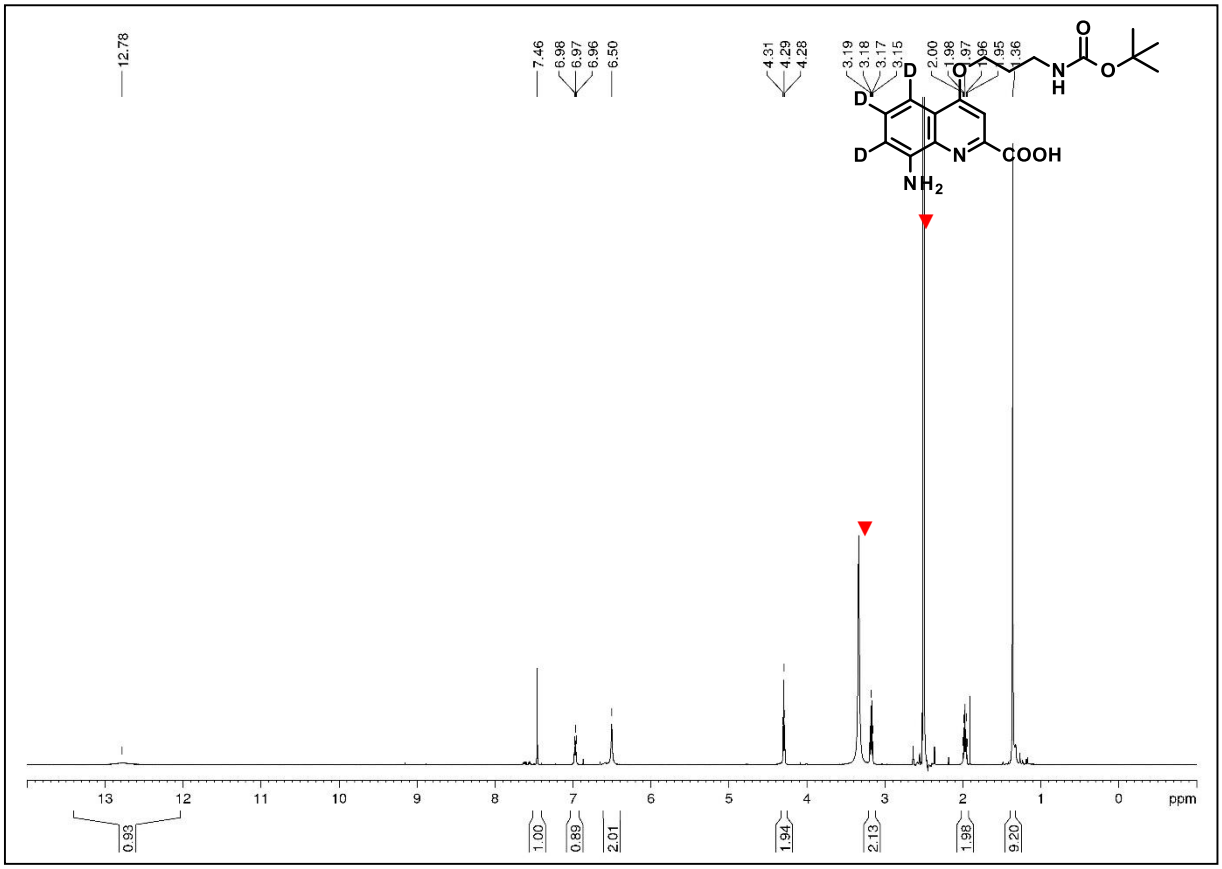


Figure S70. ^{1}H NMR (500 MHz, DMSO-d_6) of compound **31b**.

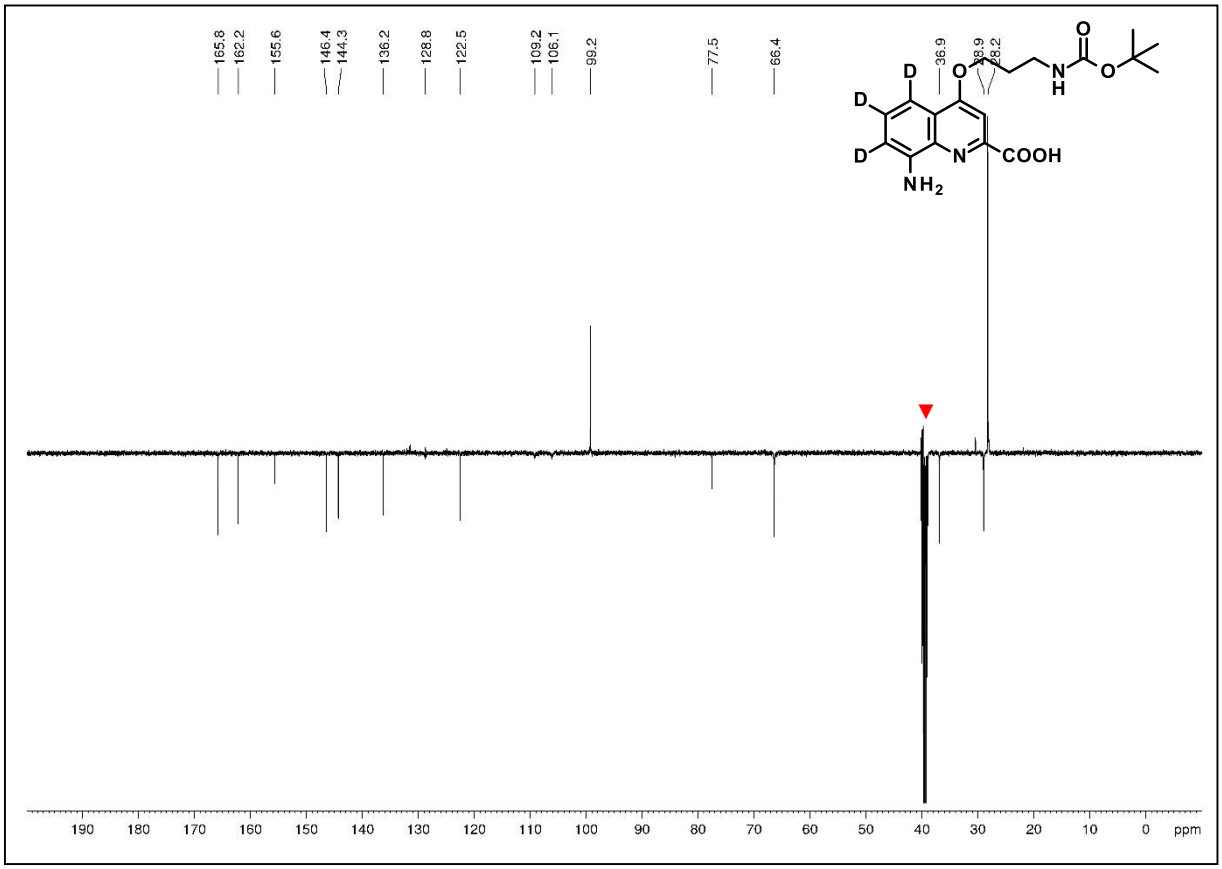


Figure S71. ^{13}C NMR (100 MHz, DMSO-d_6) of compound **31b**.

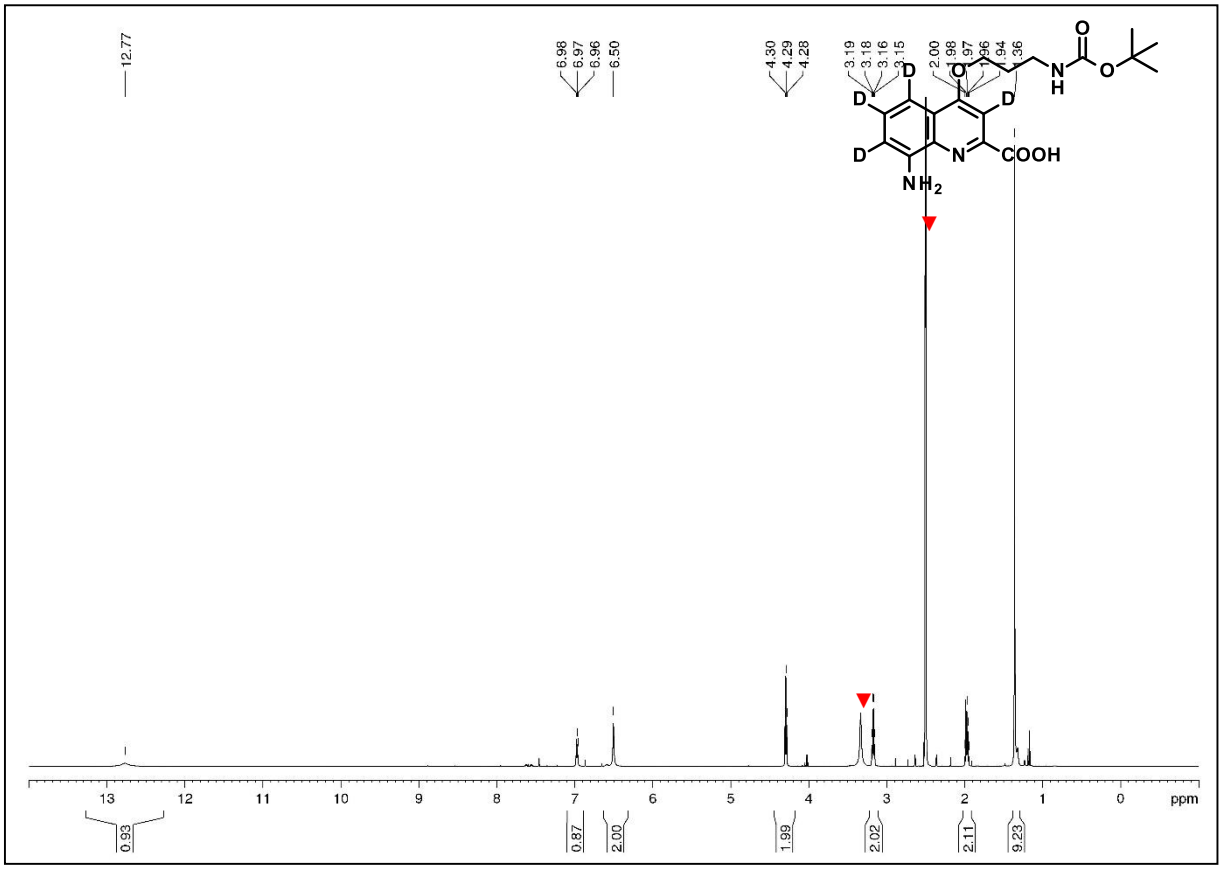


Figure S72. ^{1}H NMR (500 MHz, DMSO-d_6) of compound **31c**.

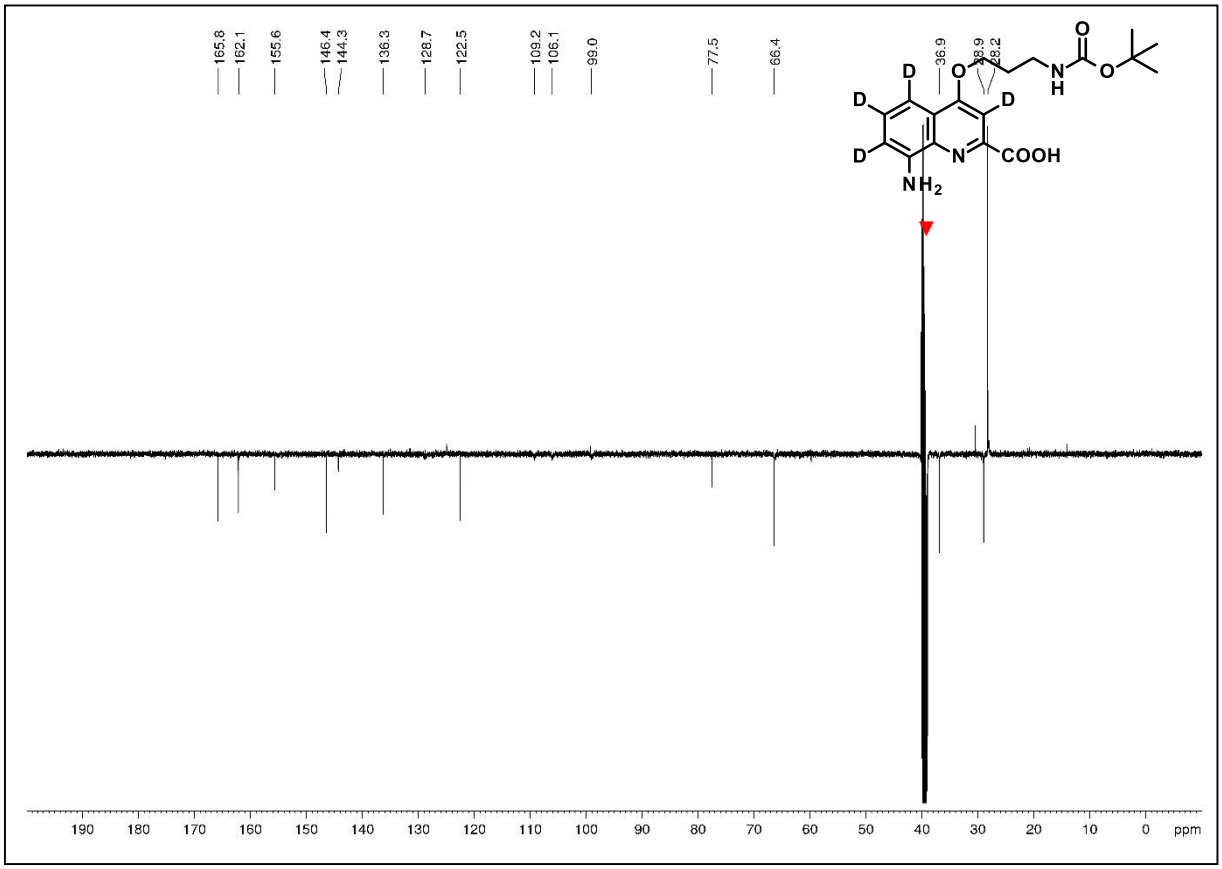


Figure S73. ^{13}C NMR (125 MHz, DMSO-d_6) of compound **31c**.

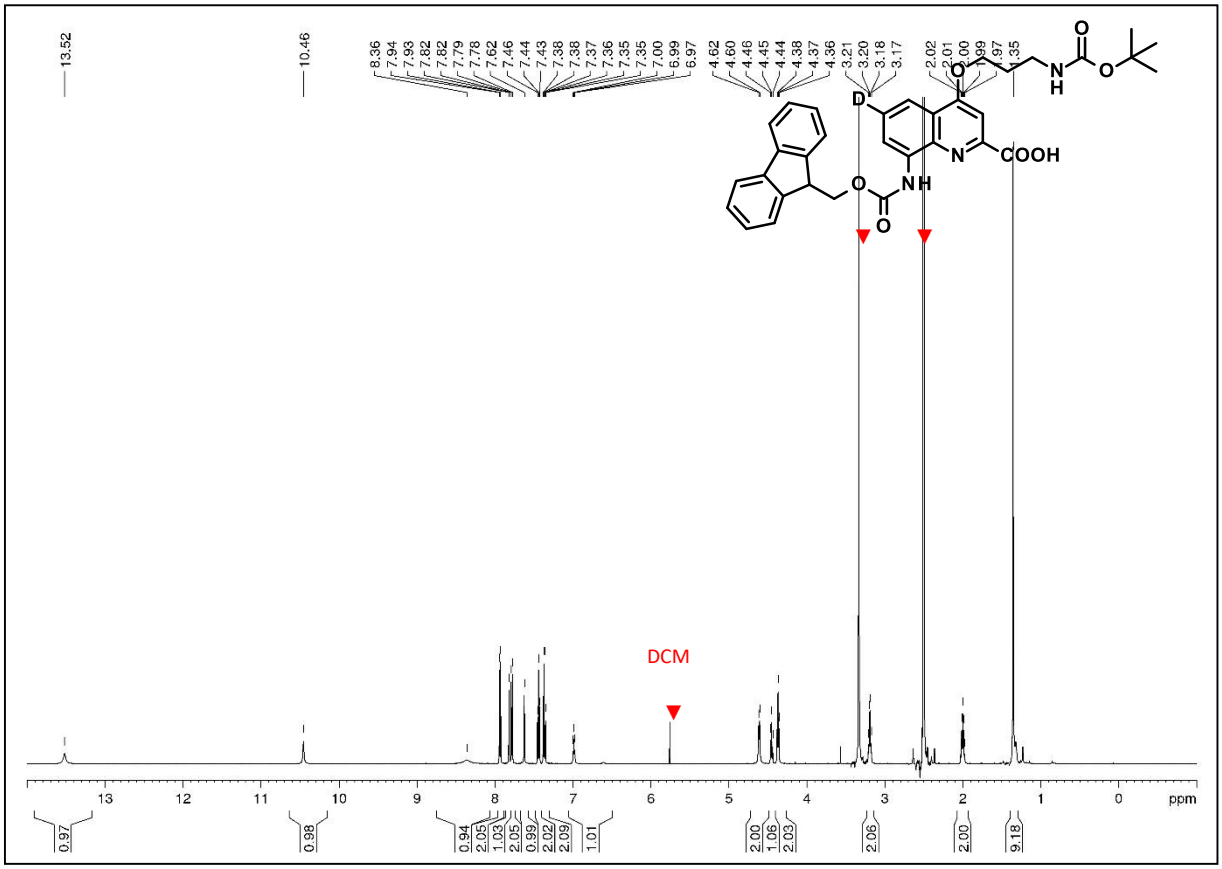


Figure S74. ^{1}H NMR (500 MHz, DMSO-d_6) of compound **2**.

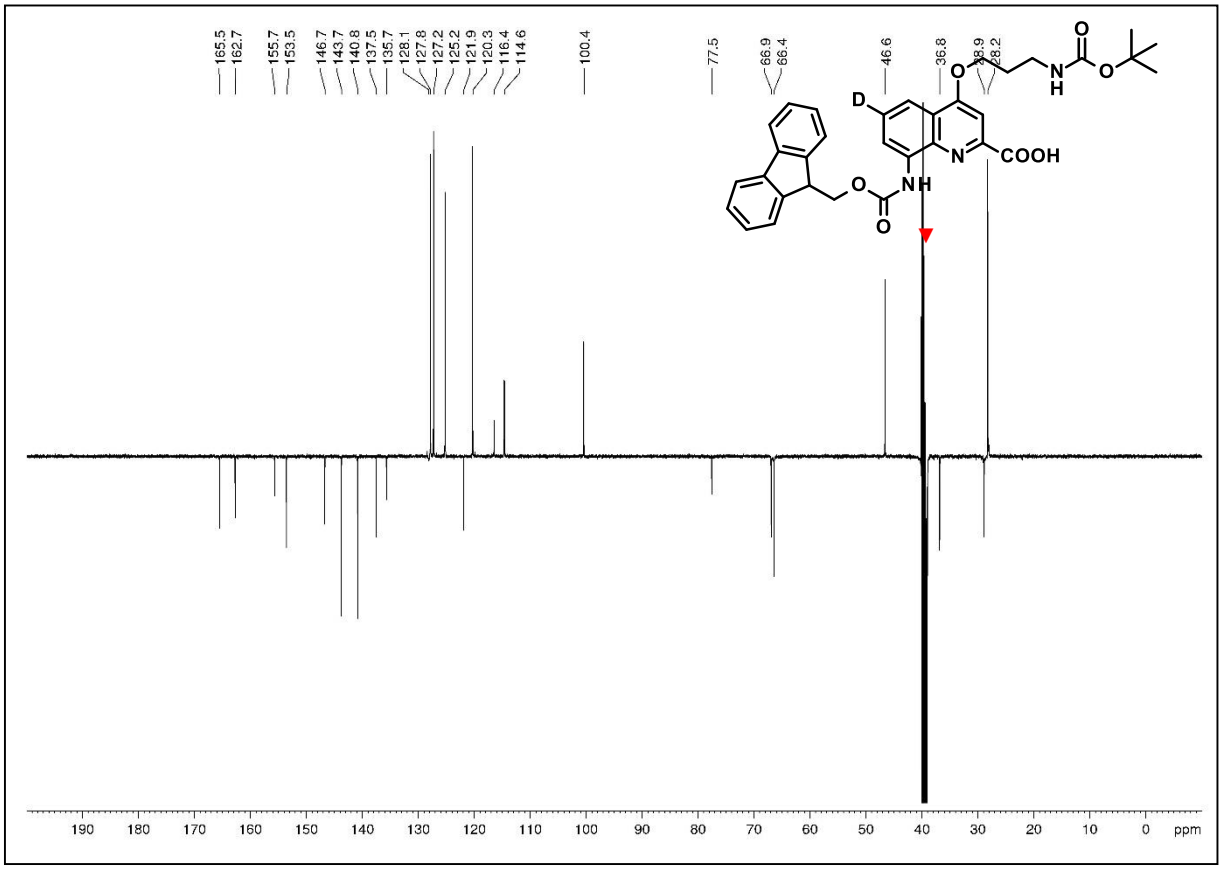


Figure S75. ^{13}C NMR (125 MHz, DMSO-d_6) of compound **2**.

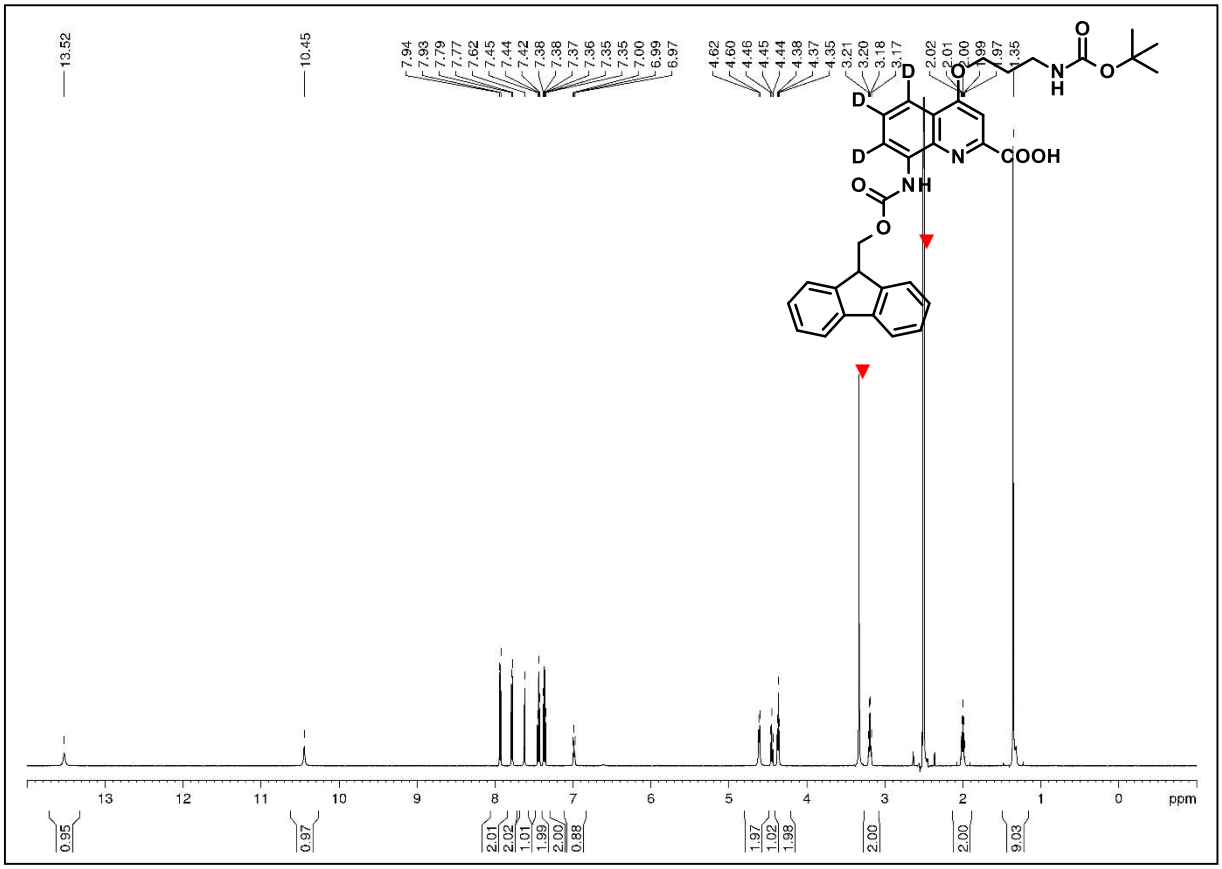


Figure S76. ^{1}H NMR (500 MHz, DMSO-d_6) of compound **4**.

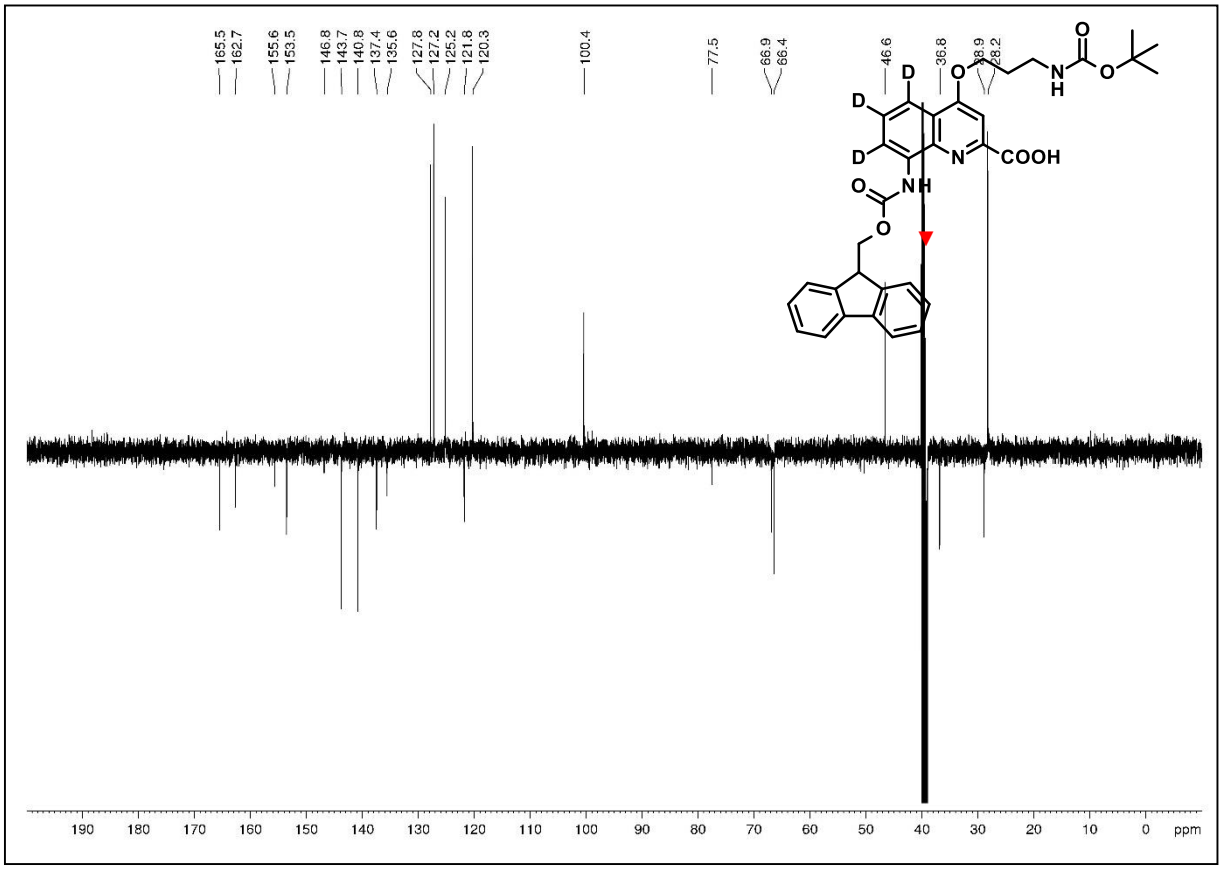


Figure S77. ^{13}C NMR (125 MHz, DMSO-d_6) of compound **4**.

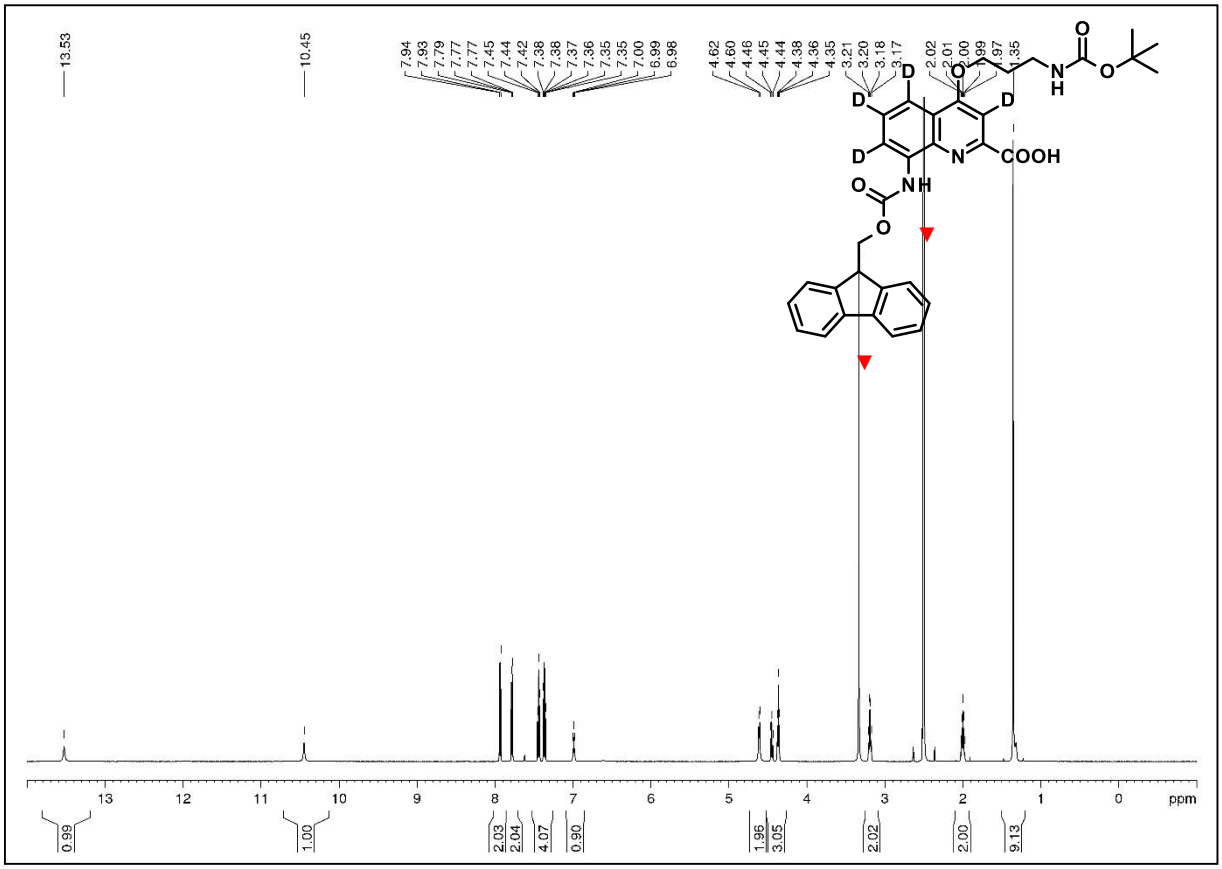


Figure S78. ^{1}H NMR (500 MHz, DMSO-d_6) of compound **5**.

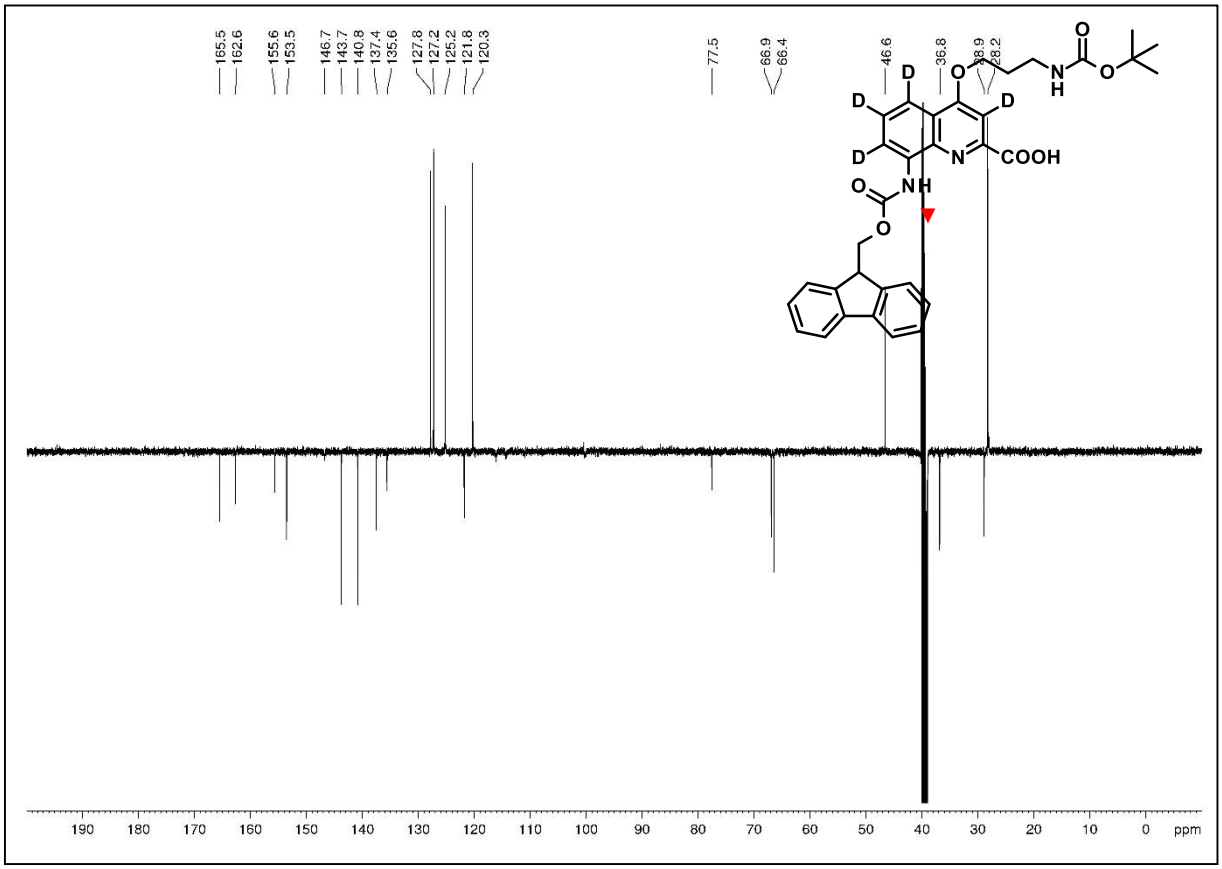


Figure S79. ^{13}C NMR (125 MHz, DMSO-d_6) of compound **5**.

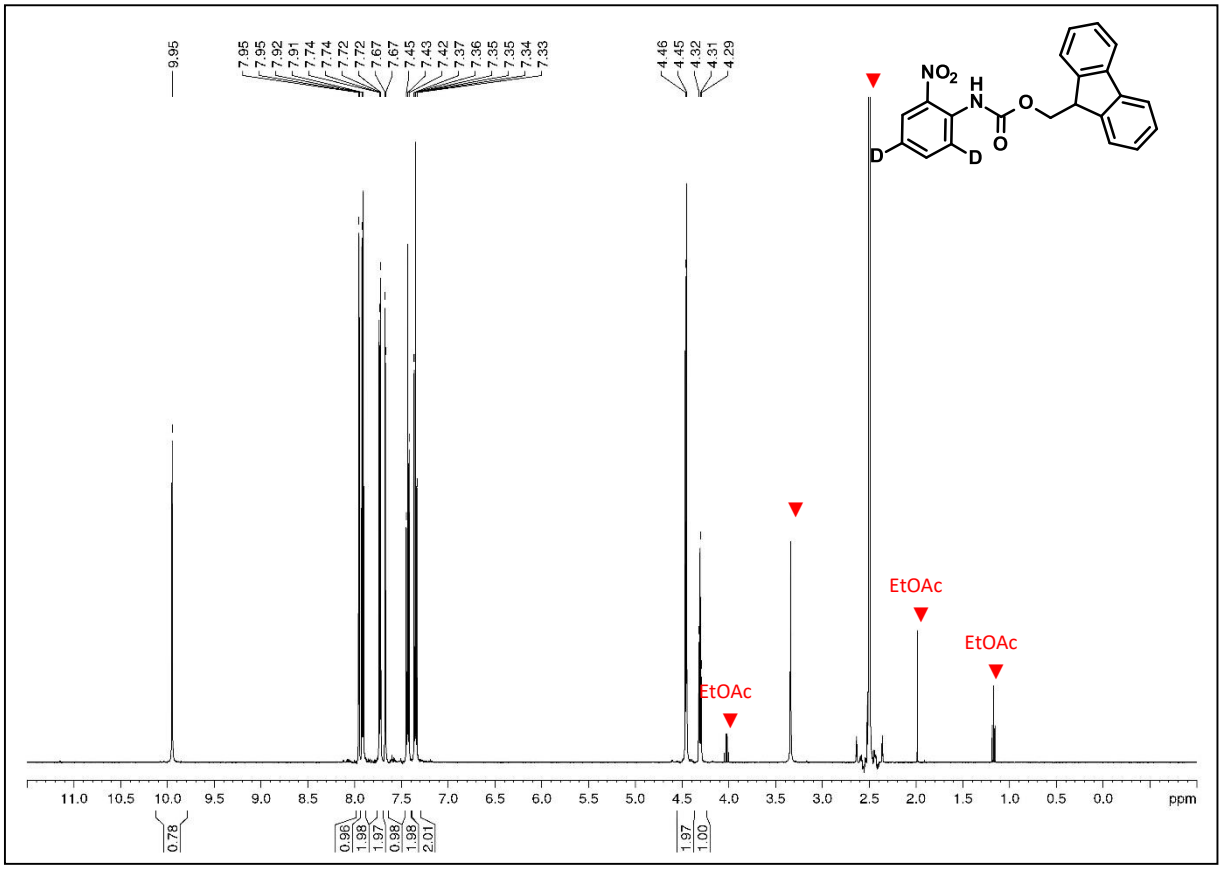


Figure S80. ^{1}H NMR (500 MHz, DMSO-d_6) of compound **32**.

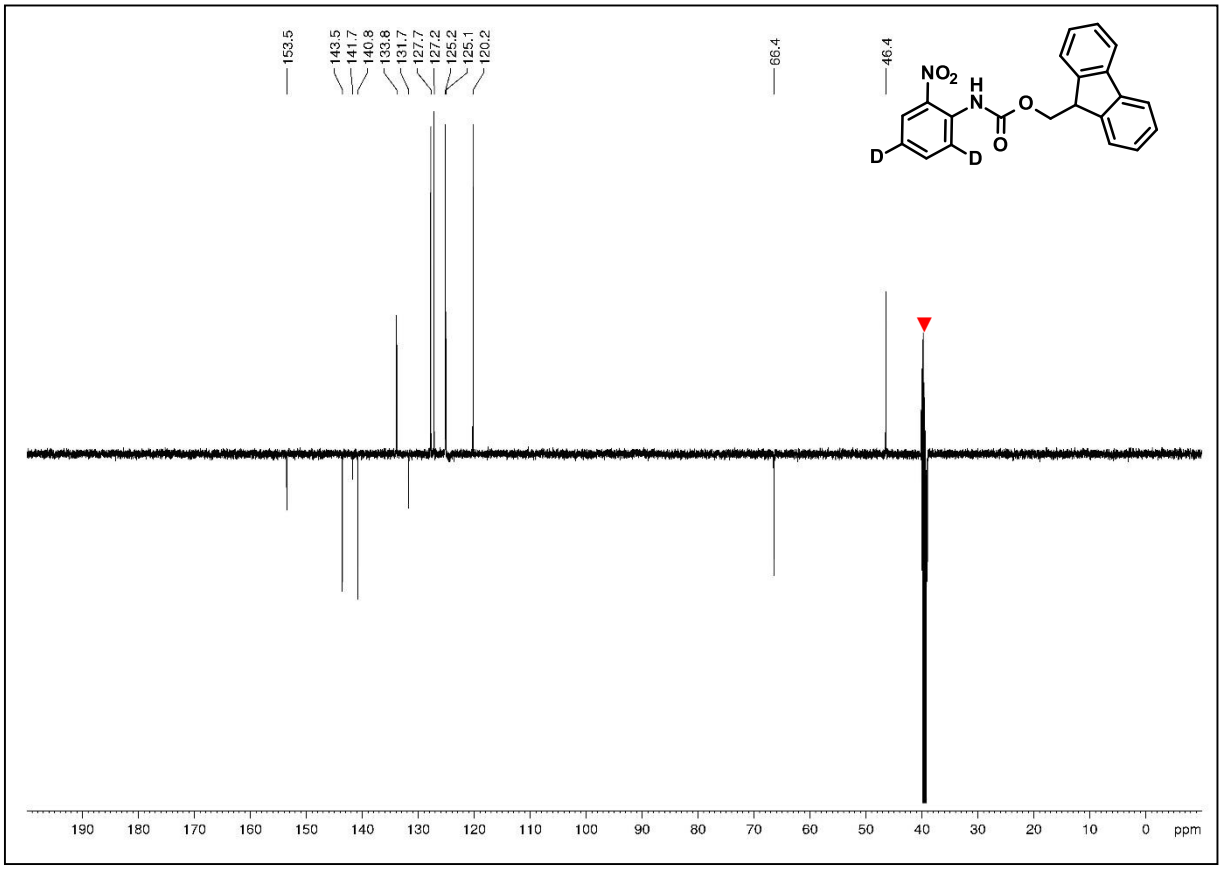


Figure S81. ^{13}C NMR (125 MHz, DMSO-d_6) of compound **32**.

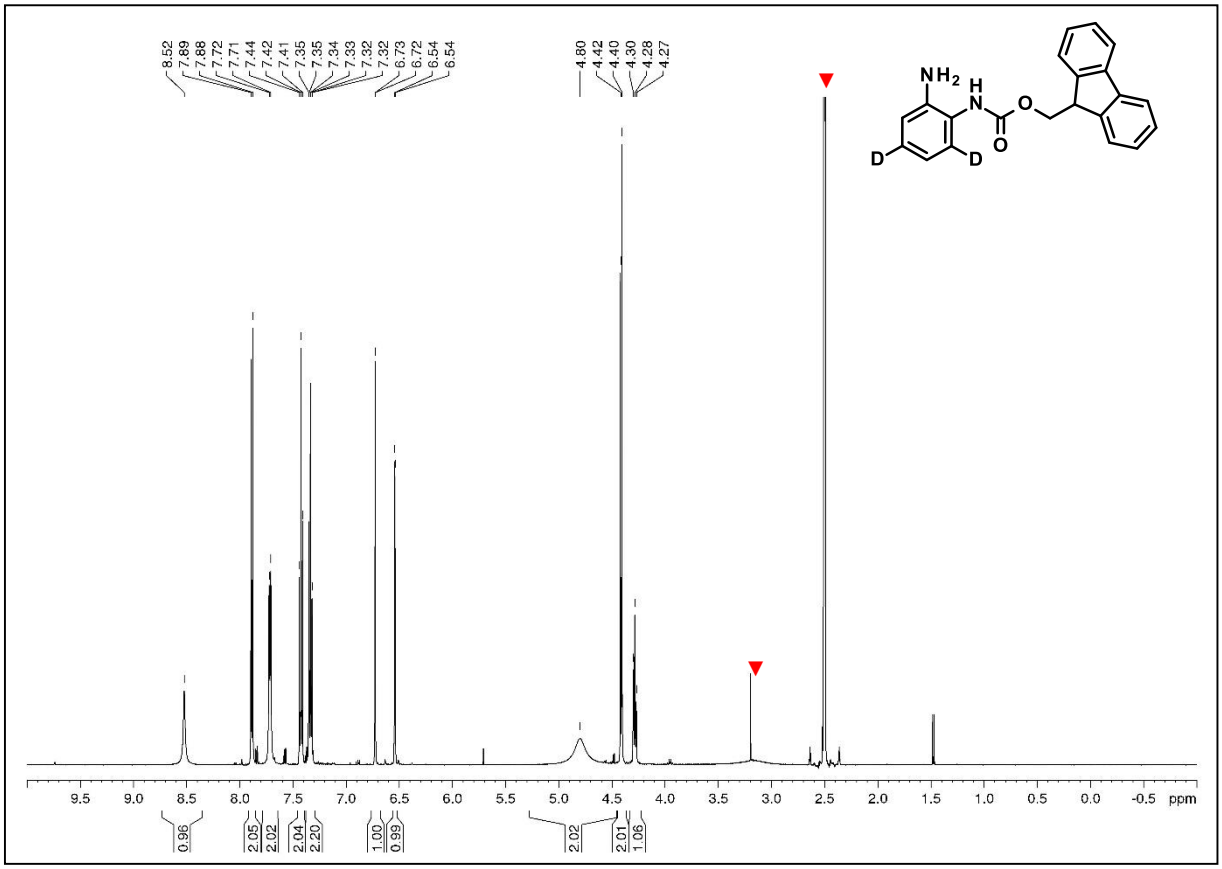


Figure S82. ^{1}H NMR (500 MHz, DMSO-d_6) of compound **8**.

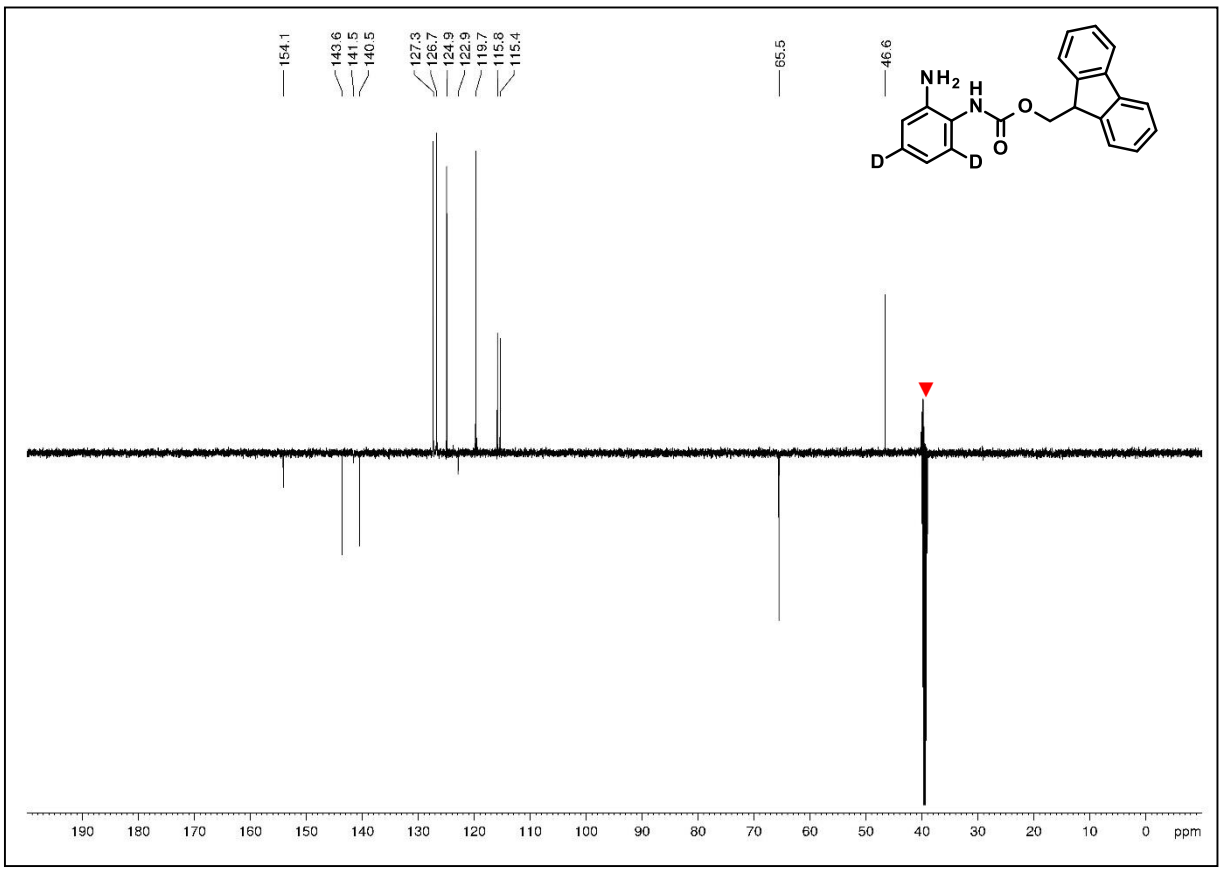


Figure S83. ^{13}C NMR (125 MHz, DMSO-d_6) of compound **8**.

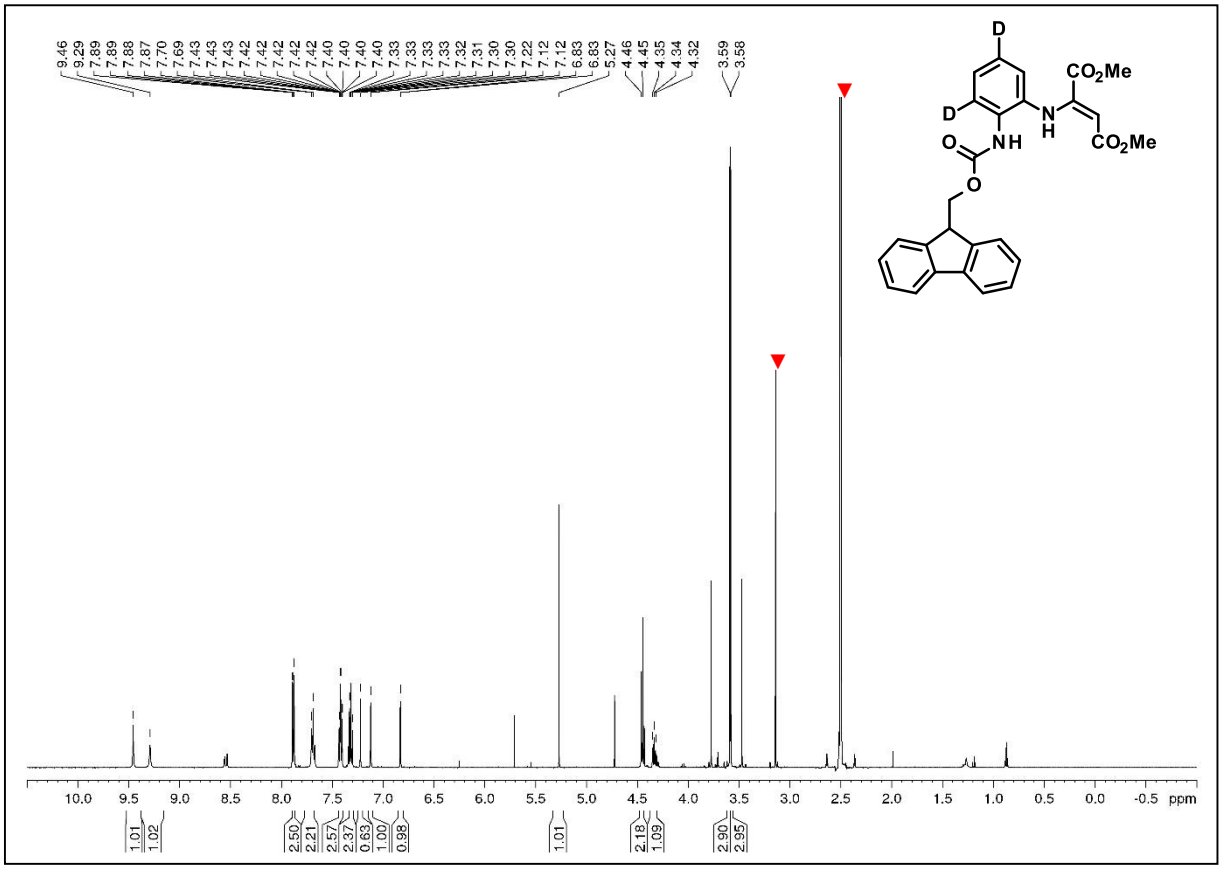


Figure S84. ^{1}H NMR (500 MHz, DMSO-d_6) of compound **33**.

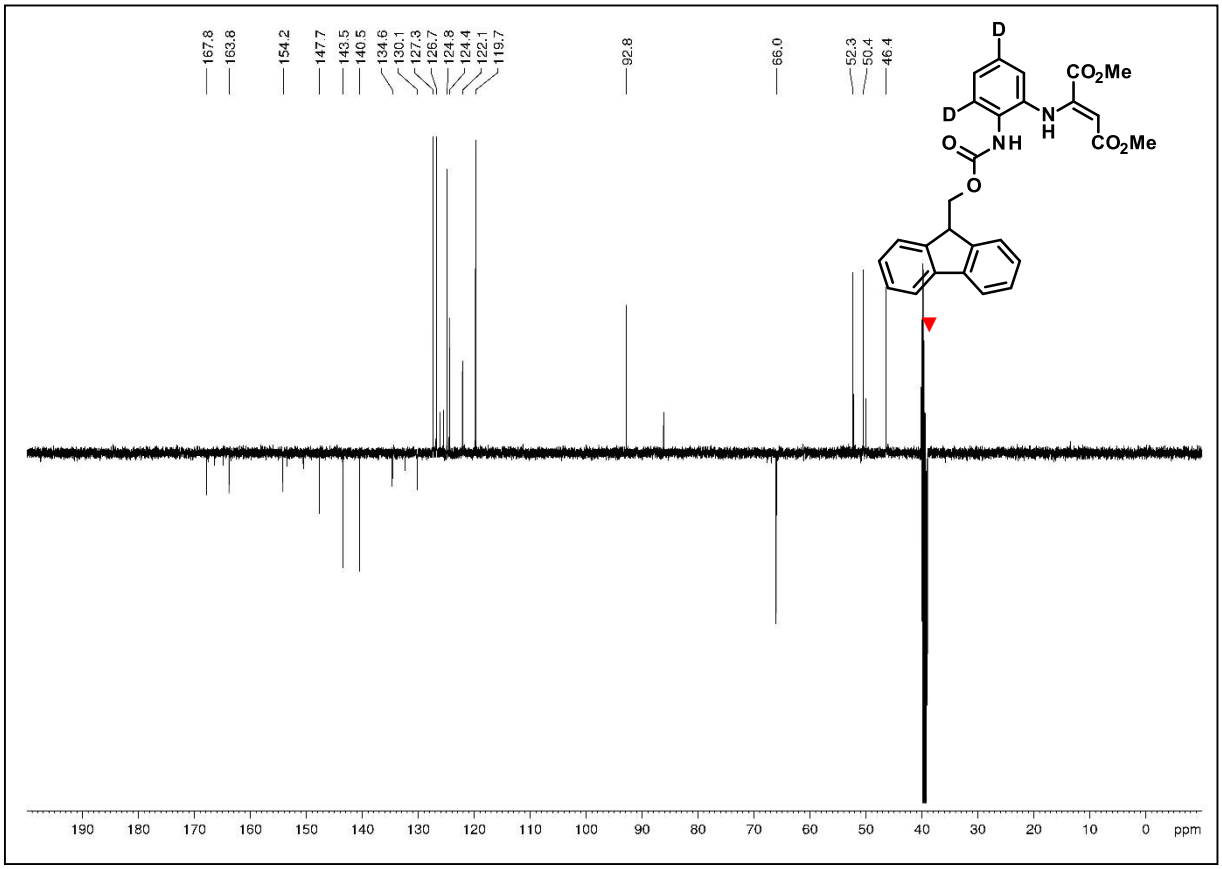


Figure S85. ^{13}C NMR (125 MHz, DMSO-d_6) of compound **33**.

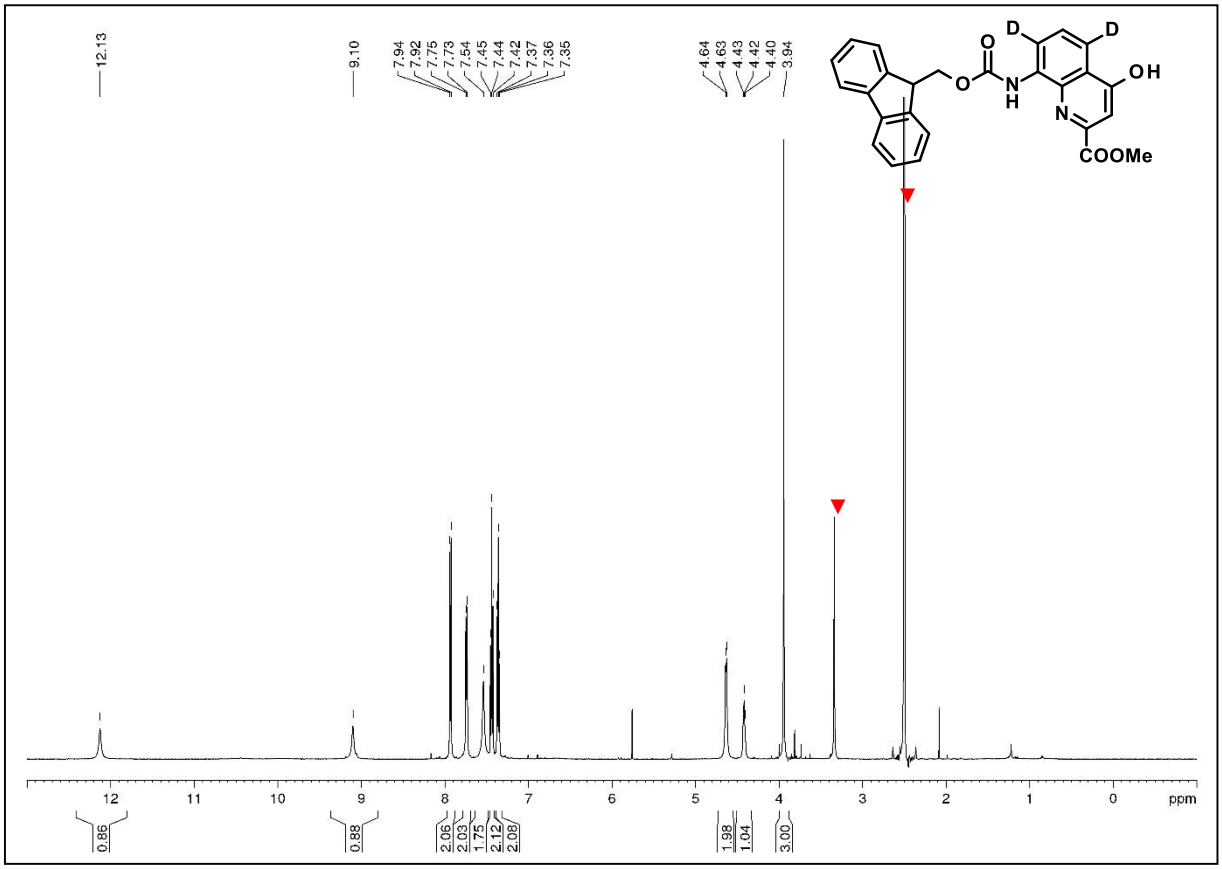


Figure S86. ^{1}H NMR (500 MHz, DMSO-d_6) of compound **34**.

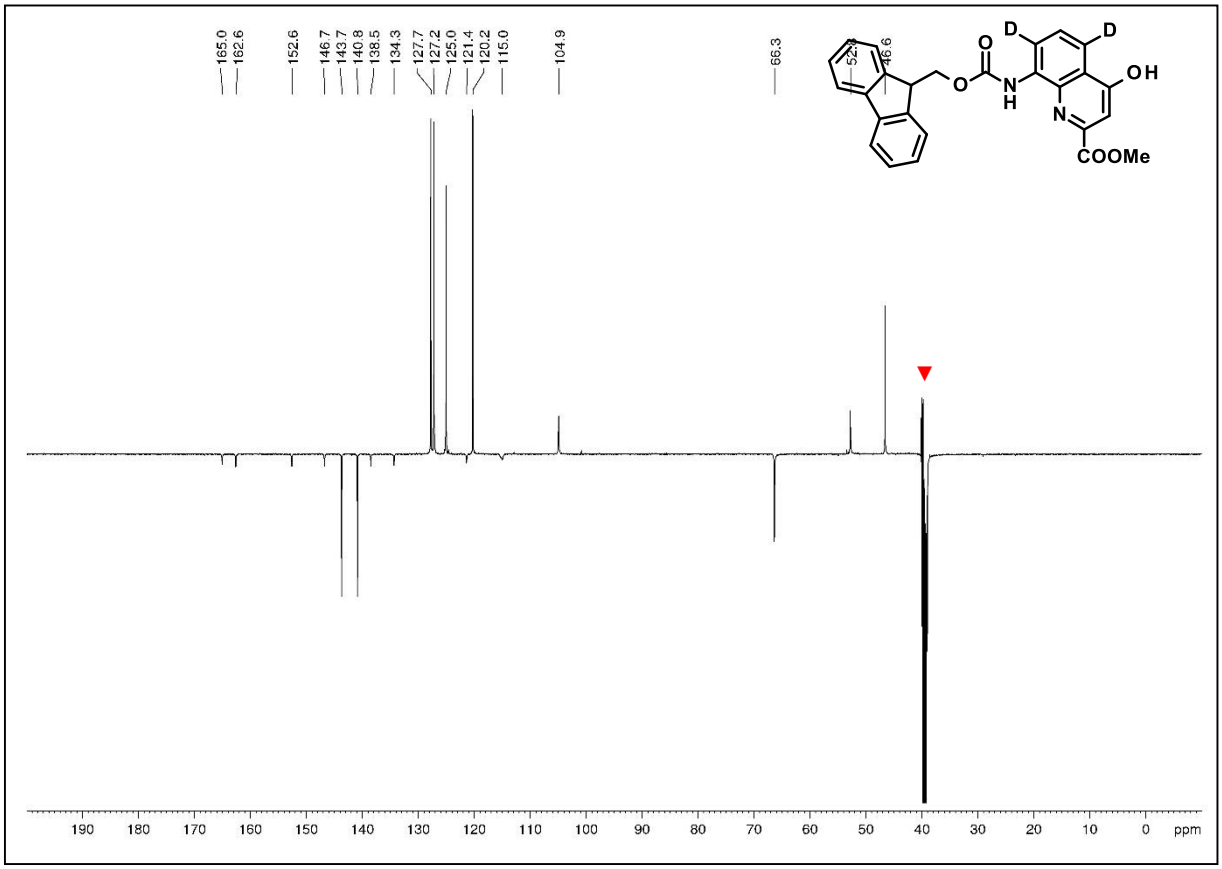


Figure S87. ^{13}C NMR (125 MHz, DMSO-d_6) of compound **34**.

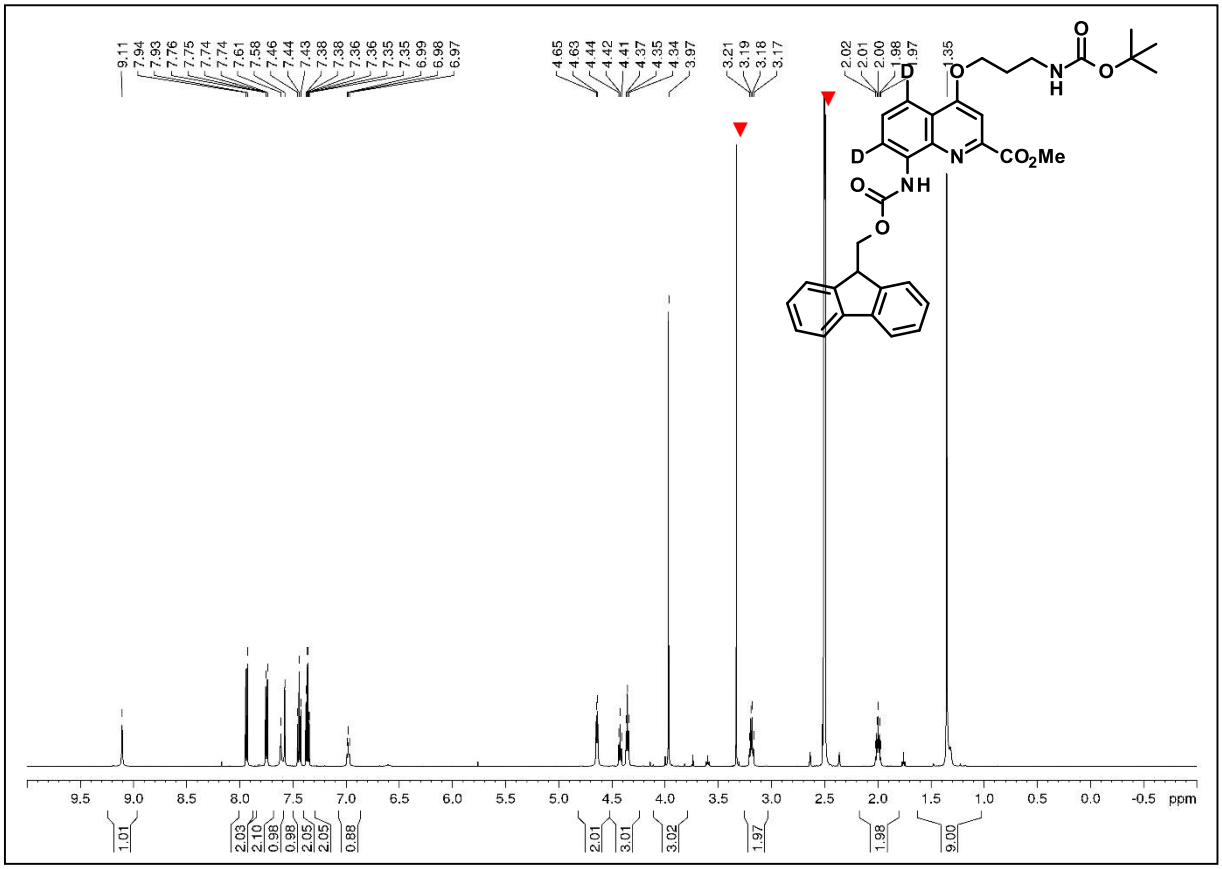


Figure S88. ^{1}H NMR (500 MHz, DMSO-d_6) of compound **35**.

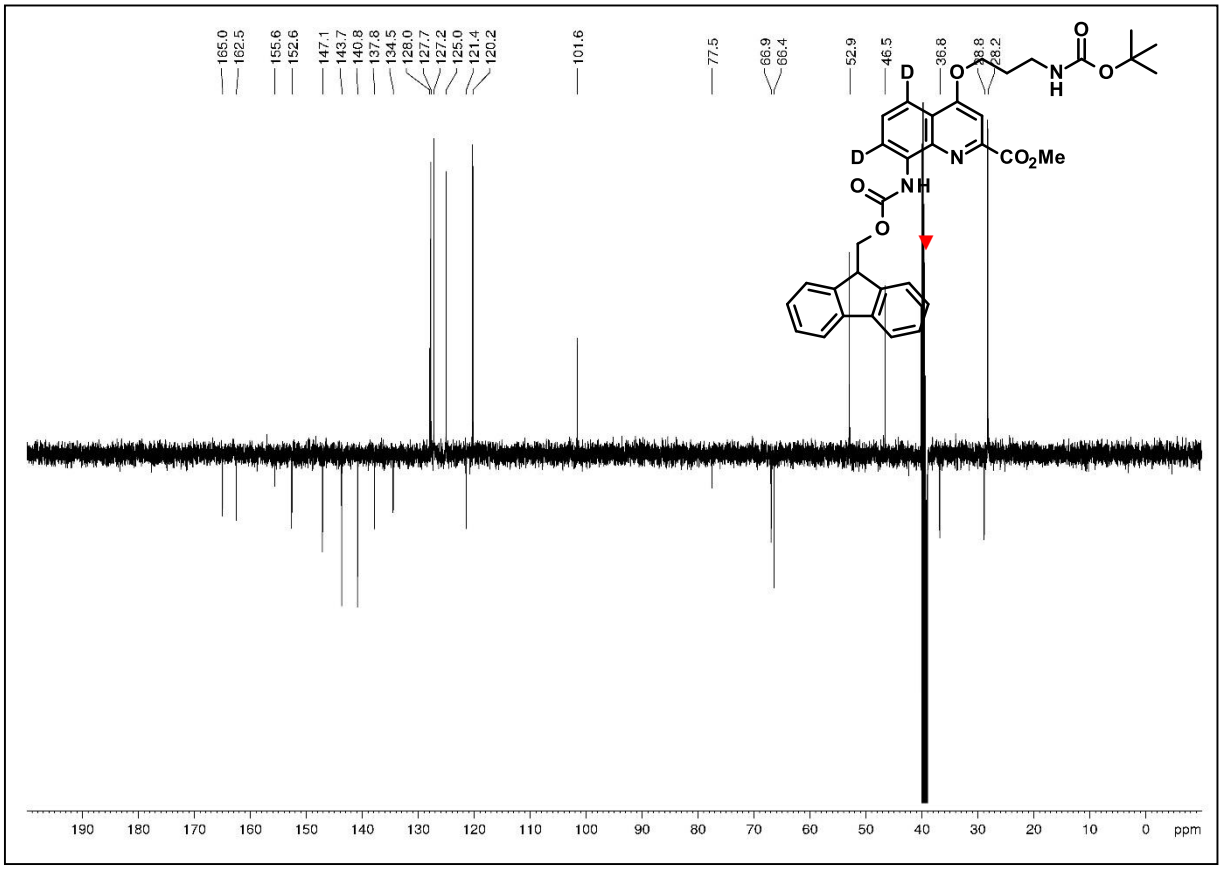


Figure S89. ^{13}C NMR (125 MHz, DMSO-d_6) of compound **35**.

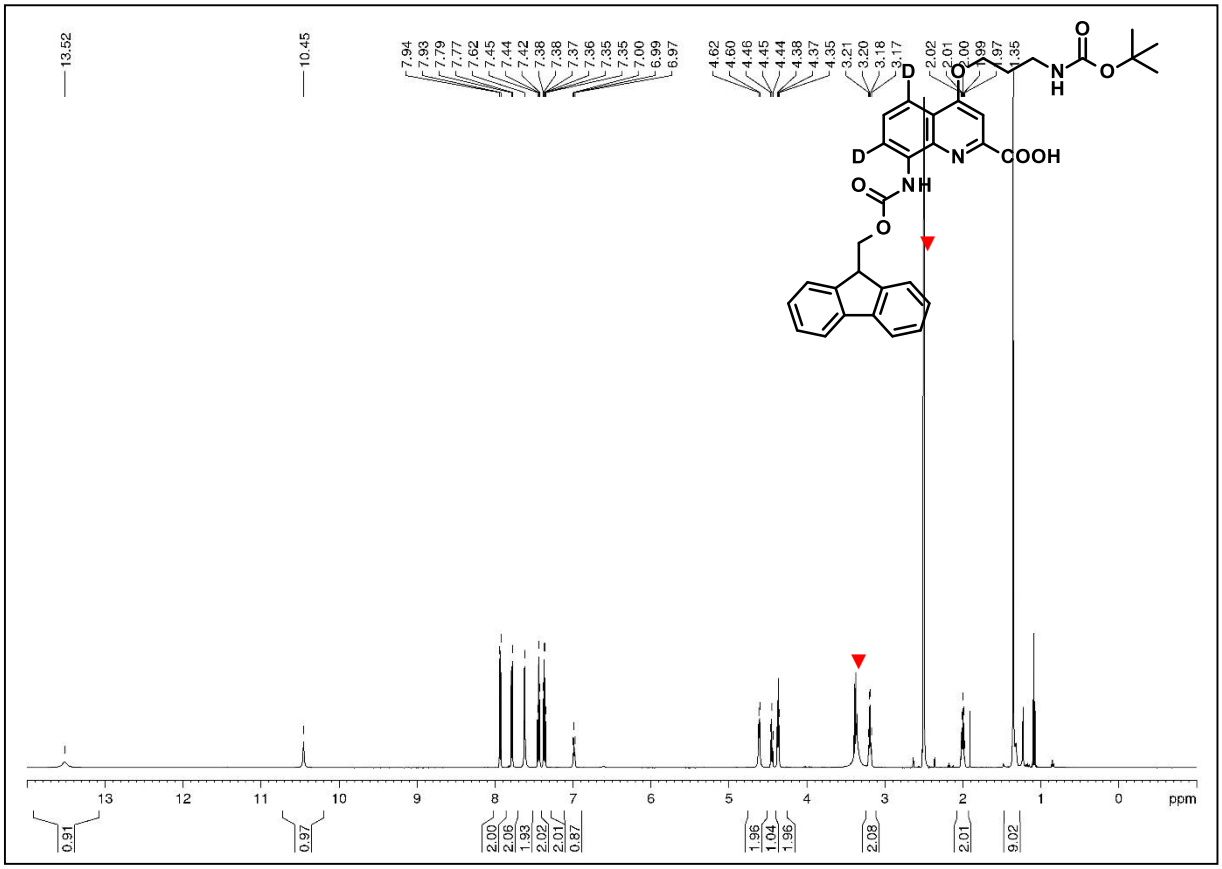


Figure S90. ^{1}H NMR (500 MHz, DMSO-d_6) of compound **3**.

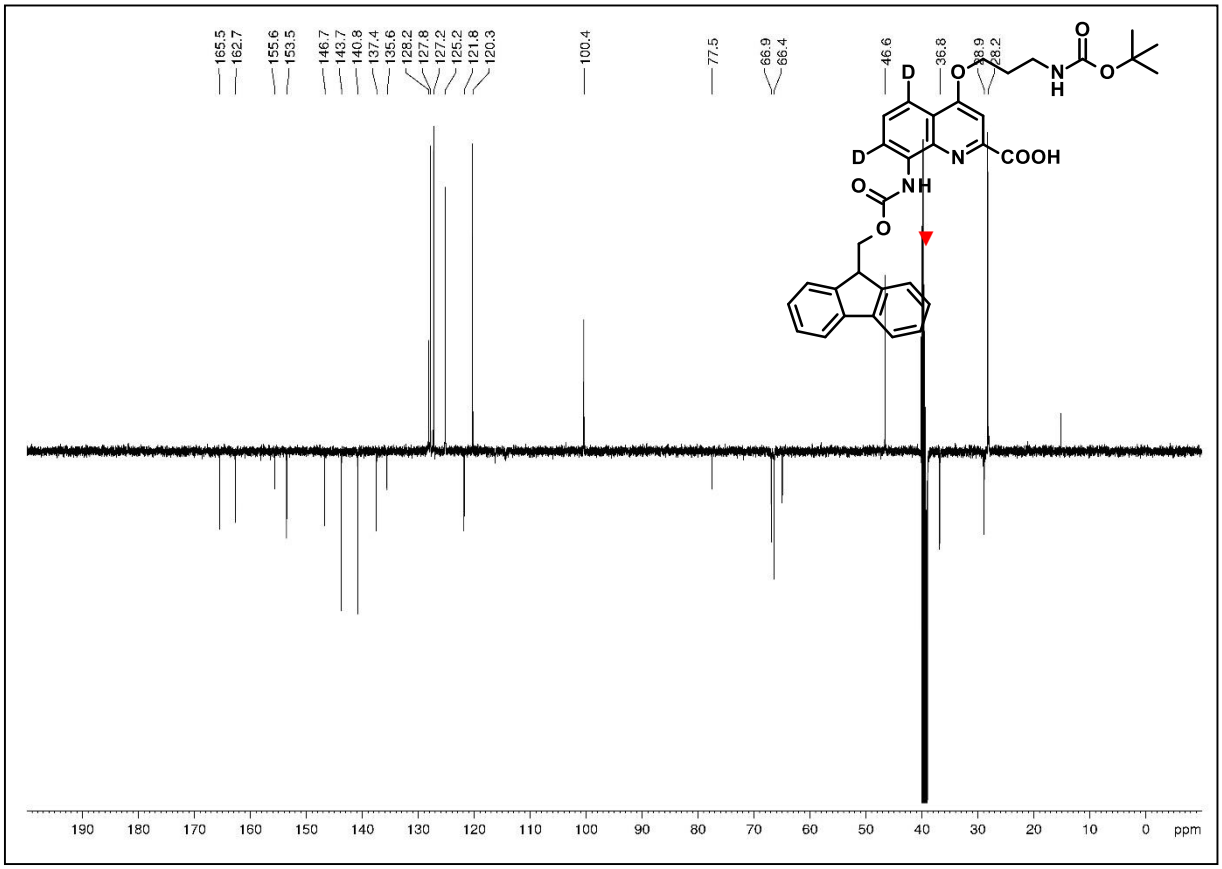


Figure S91. ^{13}C NMR (125 MHz, DMSO-d_6) of compound **3**.

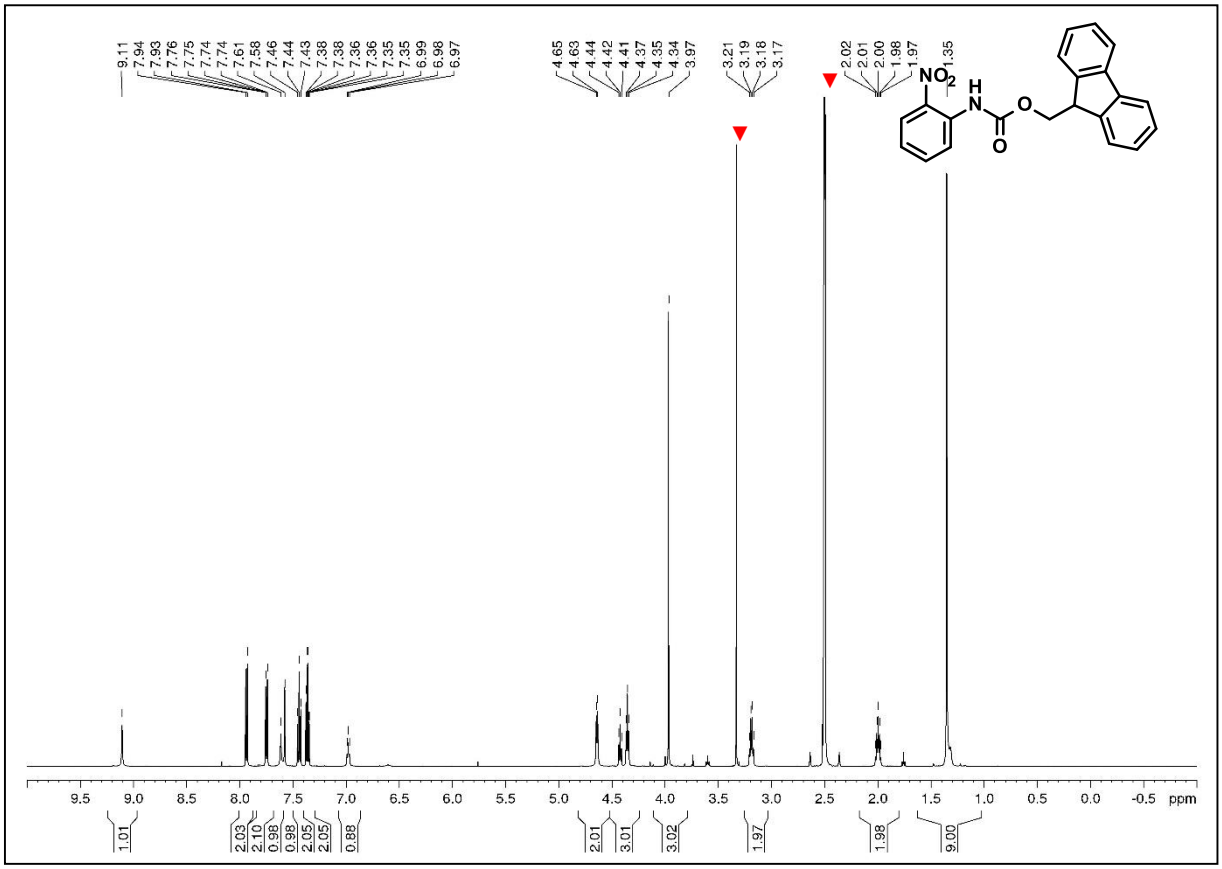


Figure S92. ^{1}H NMR (500 MHz, DMSO-d_6) of compound **36**.

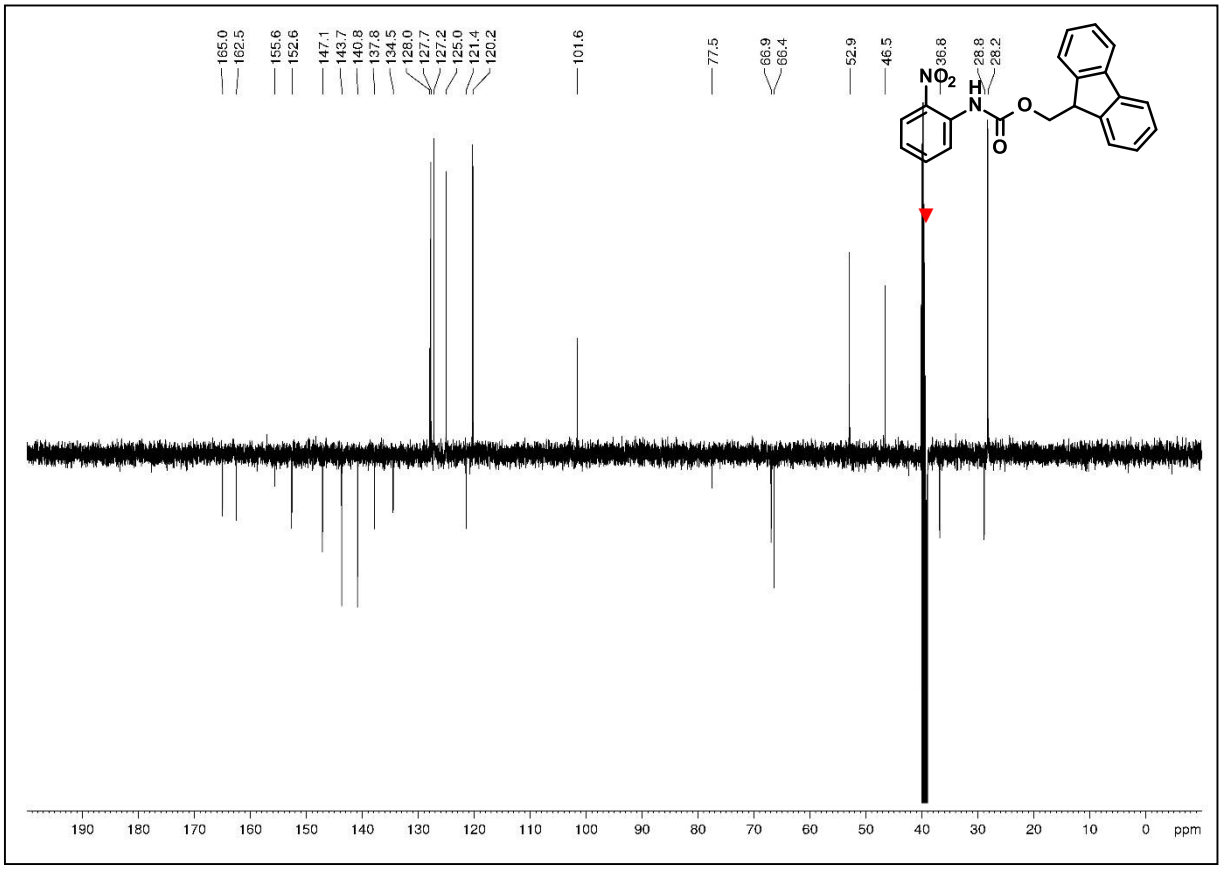


Figure S93. ^{13}C NMR (125 MHz, DMSO-d_6) of compound **36**.

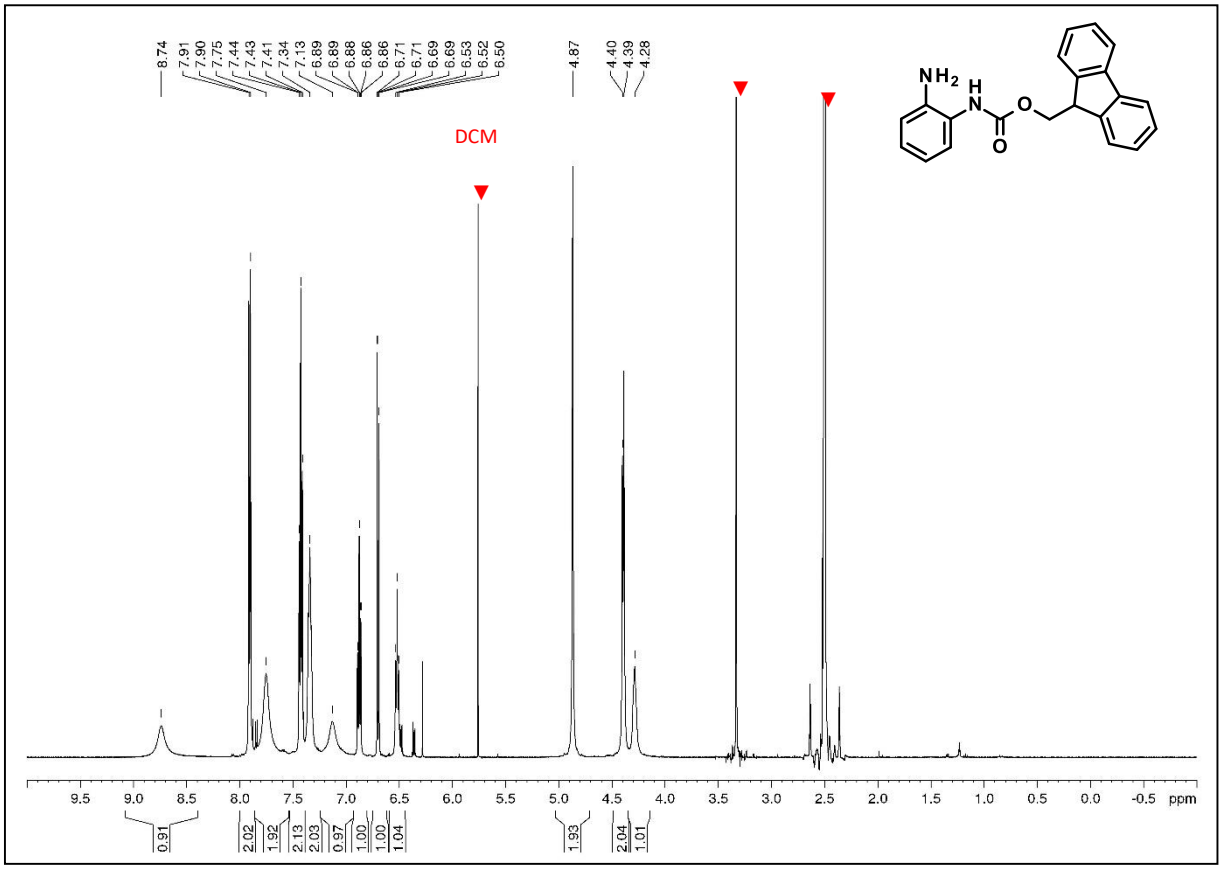


Figure S94. ^{1}H NMR (500 MHz, DMSO-d_6) of compound **37**.

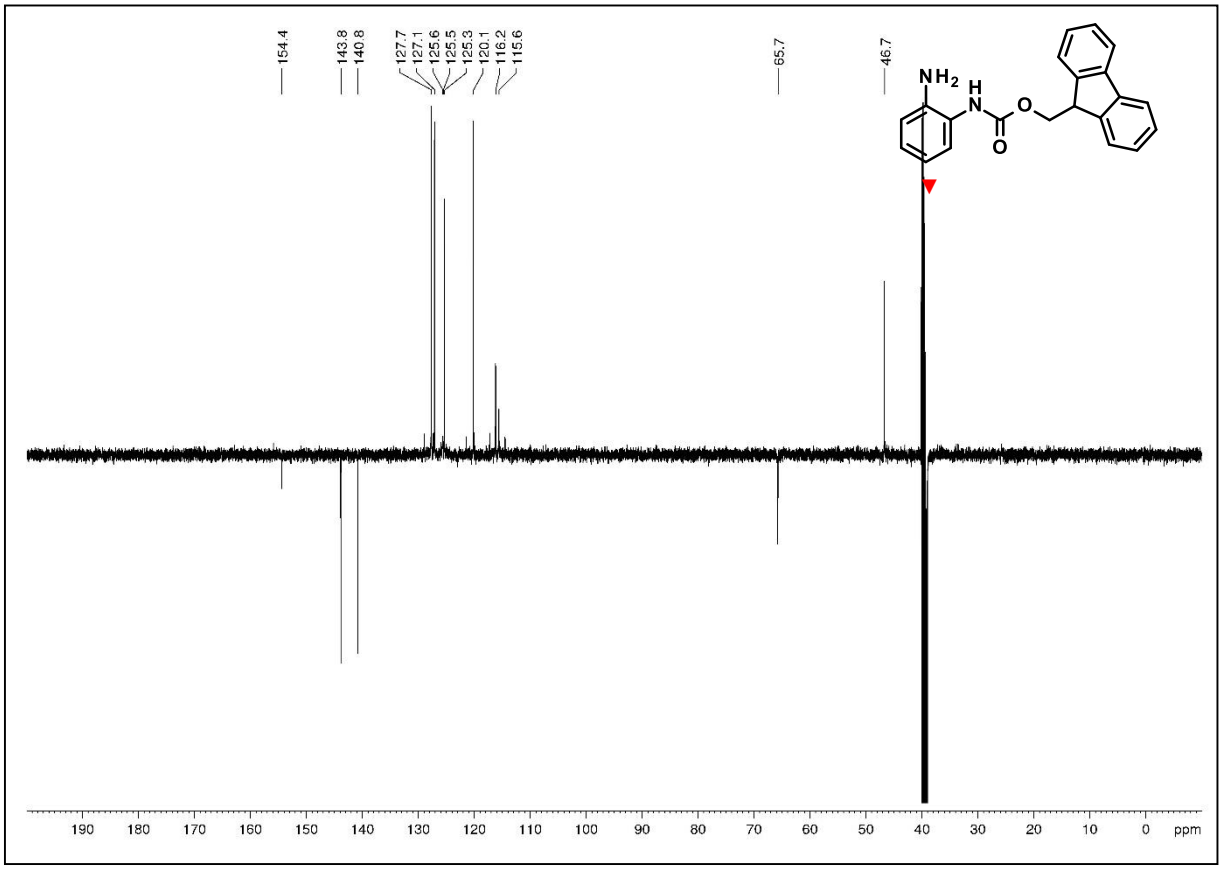


Figure S95. ^{13}C NMR (125 MHz, DMSO-d_6) of compound **37**.

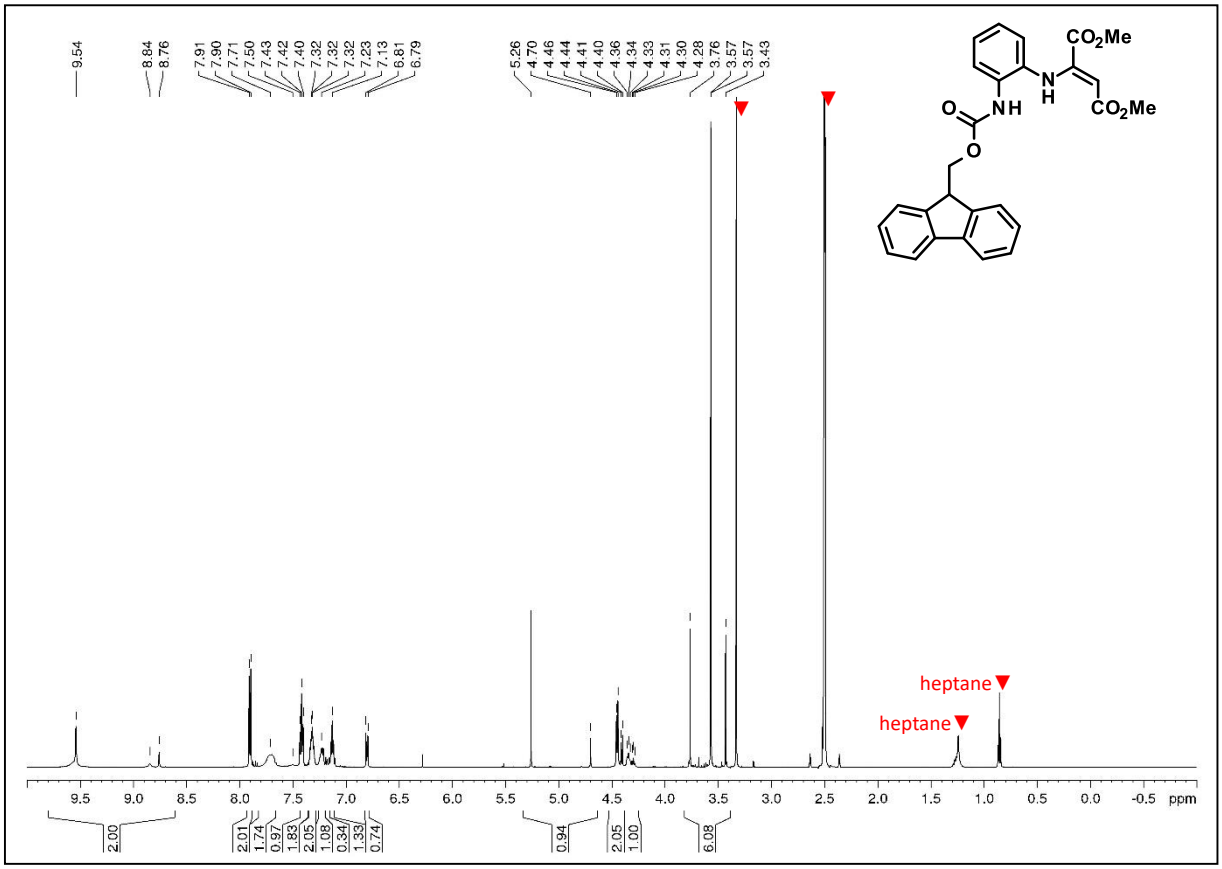


Figure S96. ^{1}H NMR (500 MHz, DMSO-d_6) of compound **38**.

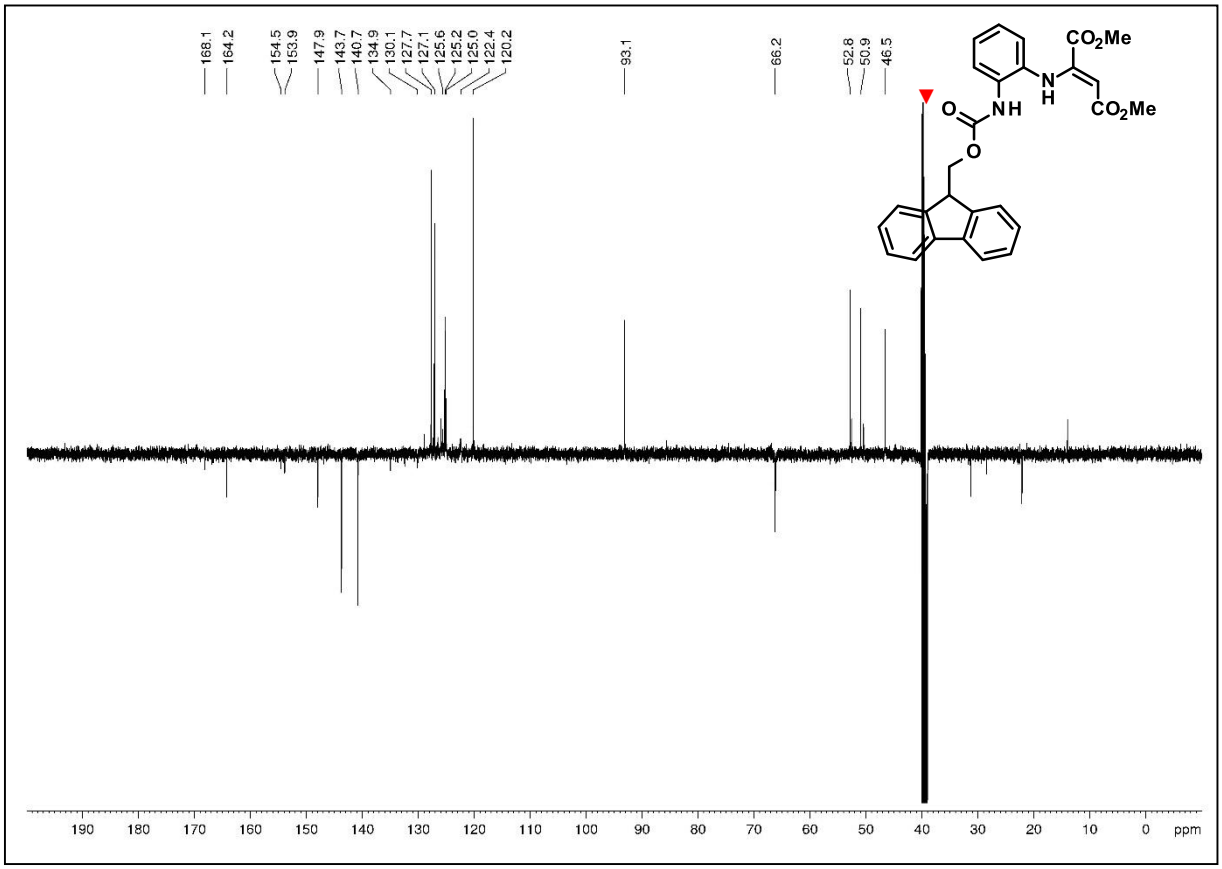


Figure S97. ^{13}C NMR (125 MHz, DMSO-d_6) of compound **38**.

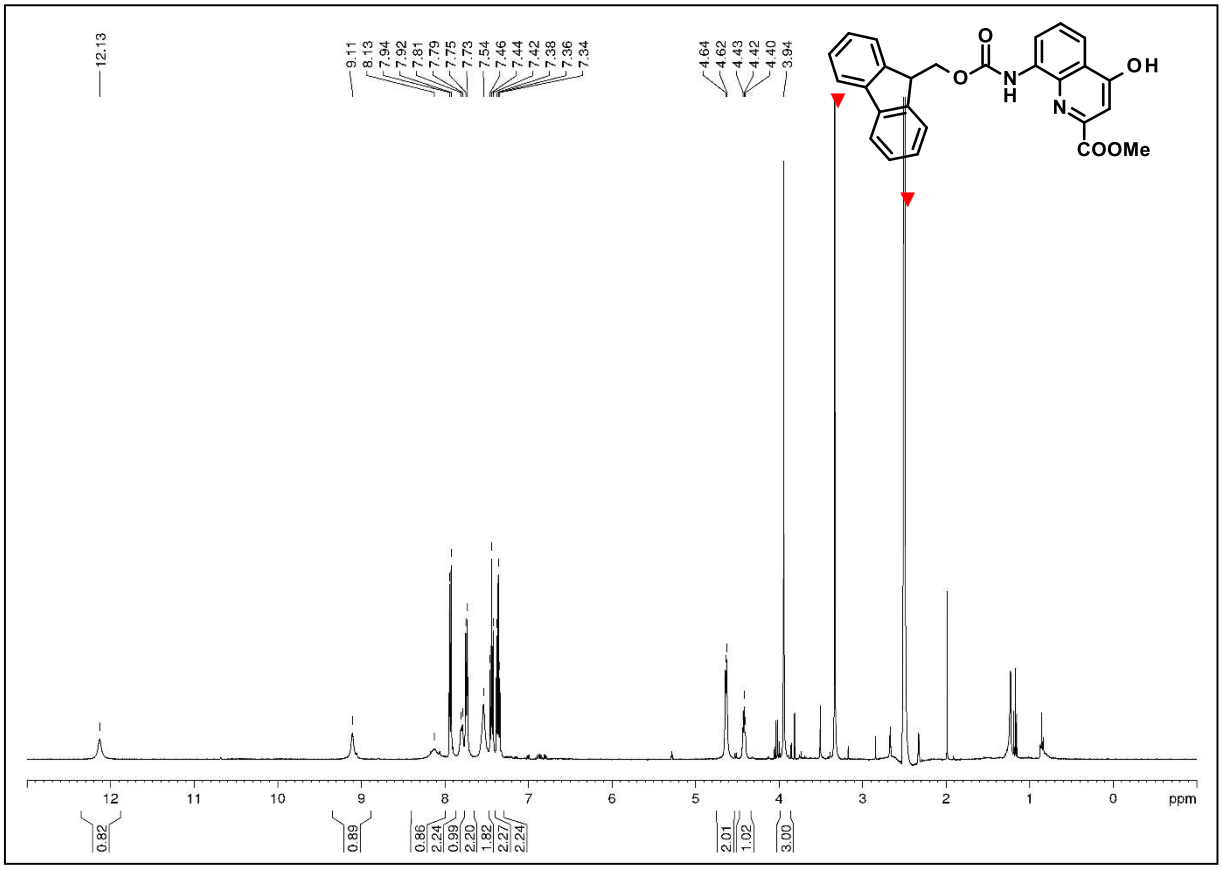


Figure S98. ^{1}H NMR (400 MHz, DMSO-d_6) of compound **39**.

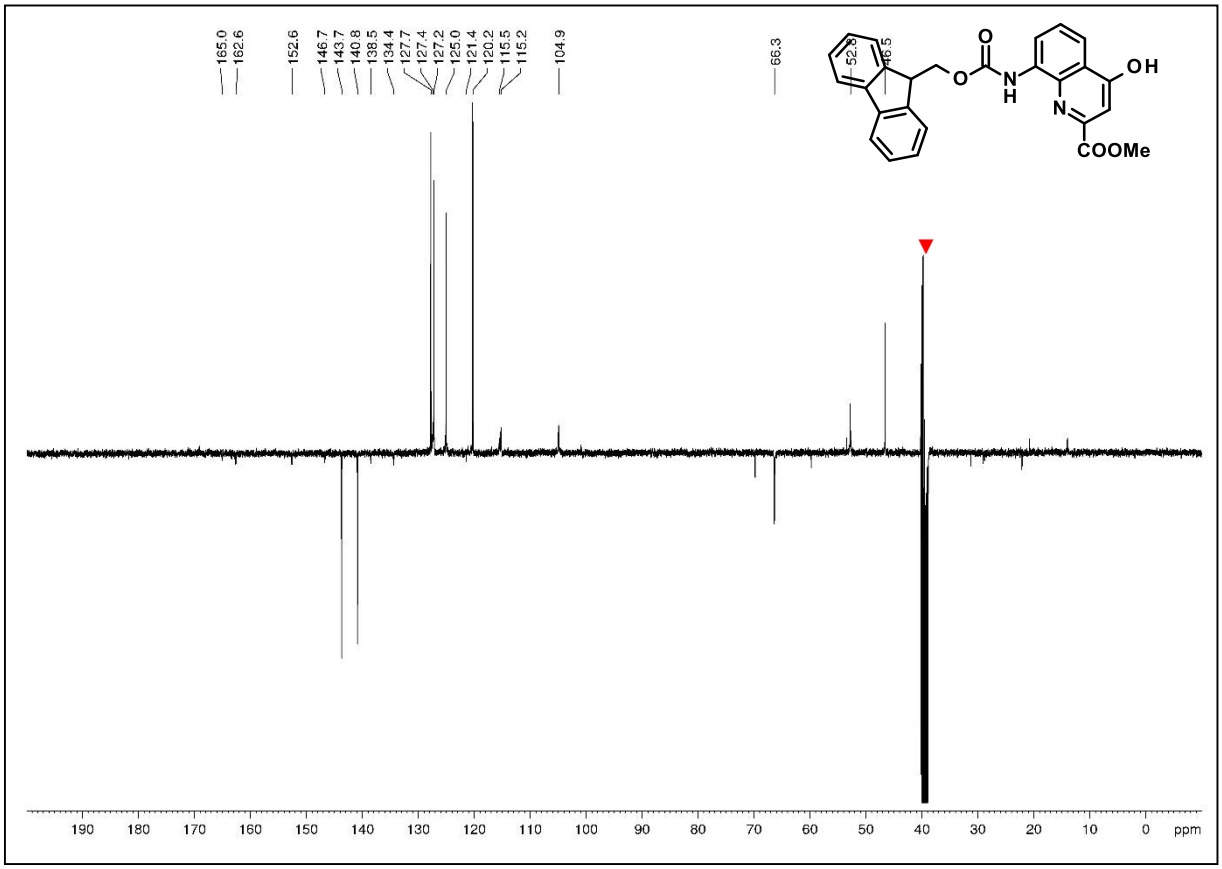


Figure S99. ^{13}C NMR (100 MHz, DMSO-d_6) of compound **39**.

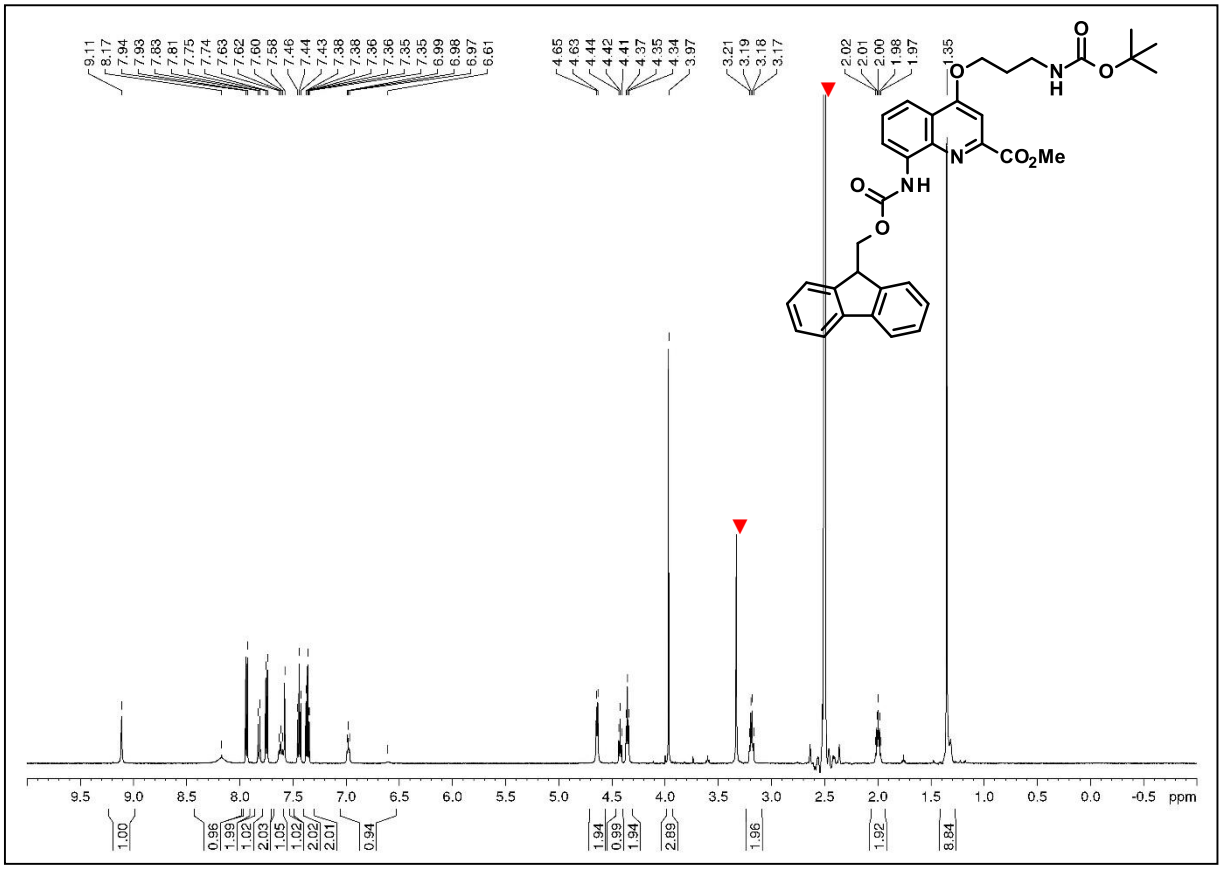


Figure S100. ^{1}H NMR (500 MHz, DMSO-d_6) of compound **40**.

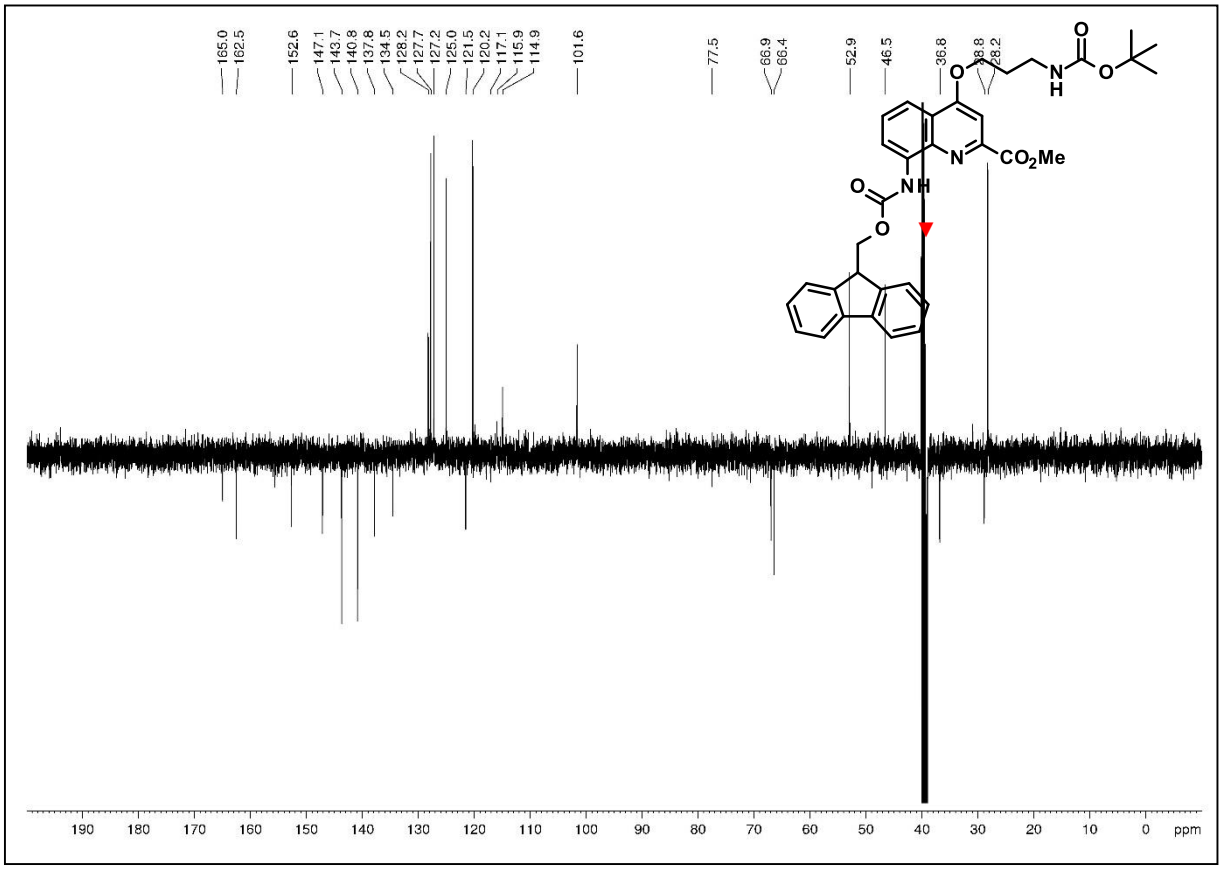


Figure S101. ^{13}C NMR (125 MHz, DMSO-d_6) of compound **40**.

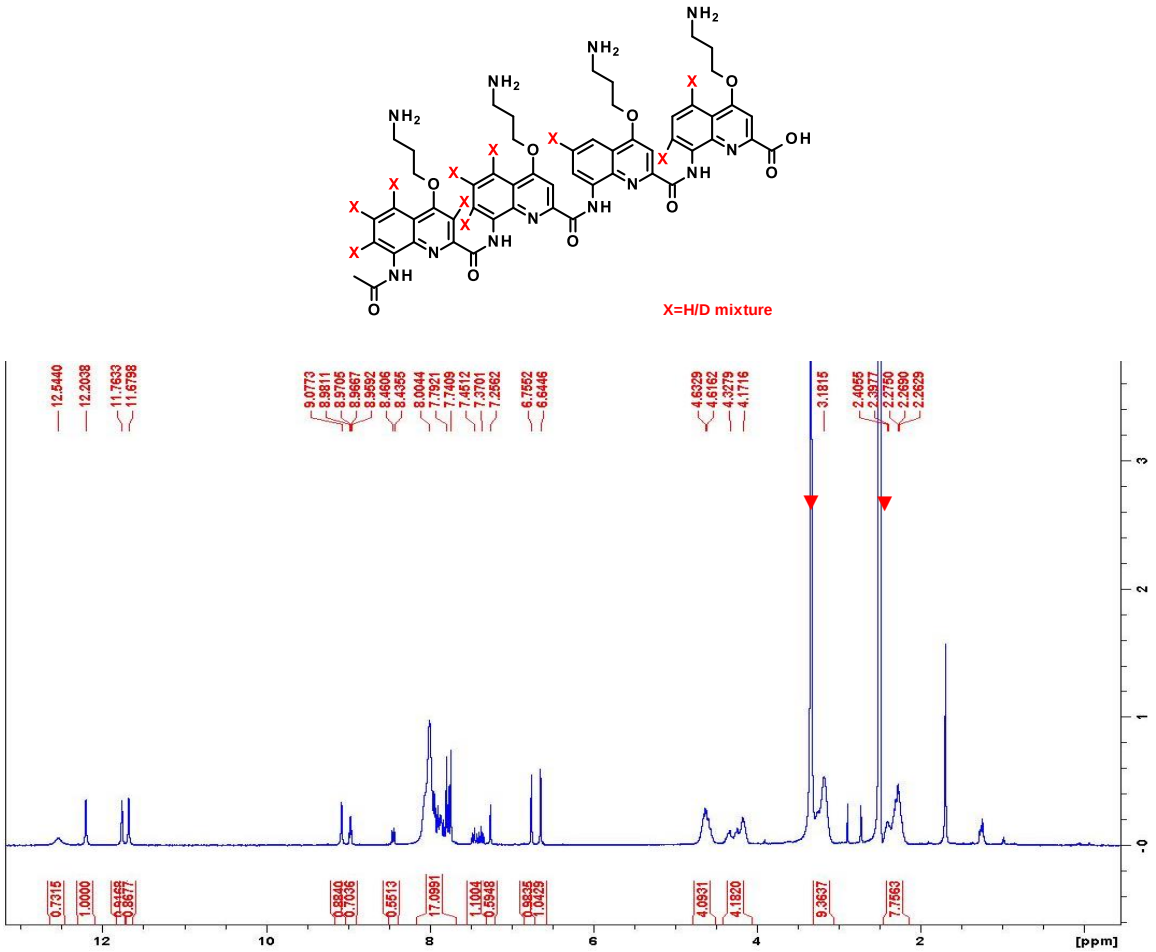


Figure S102. ^{1}H NMR (300 MHz, DMSO-d_6) of compound **11**.

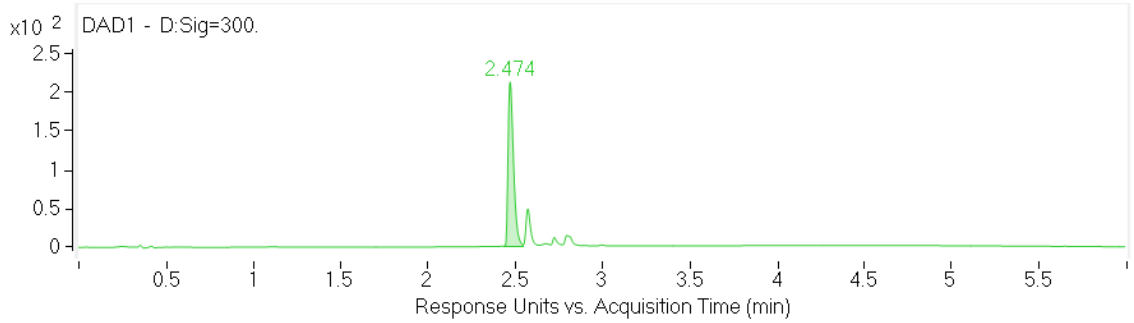


Figure S103. LCMS analysis (HPLC-UV chromatogram) of compound **11**.

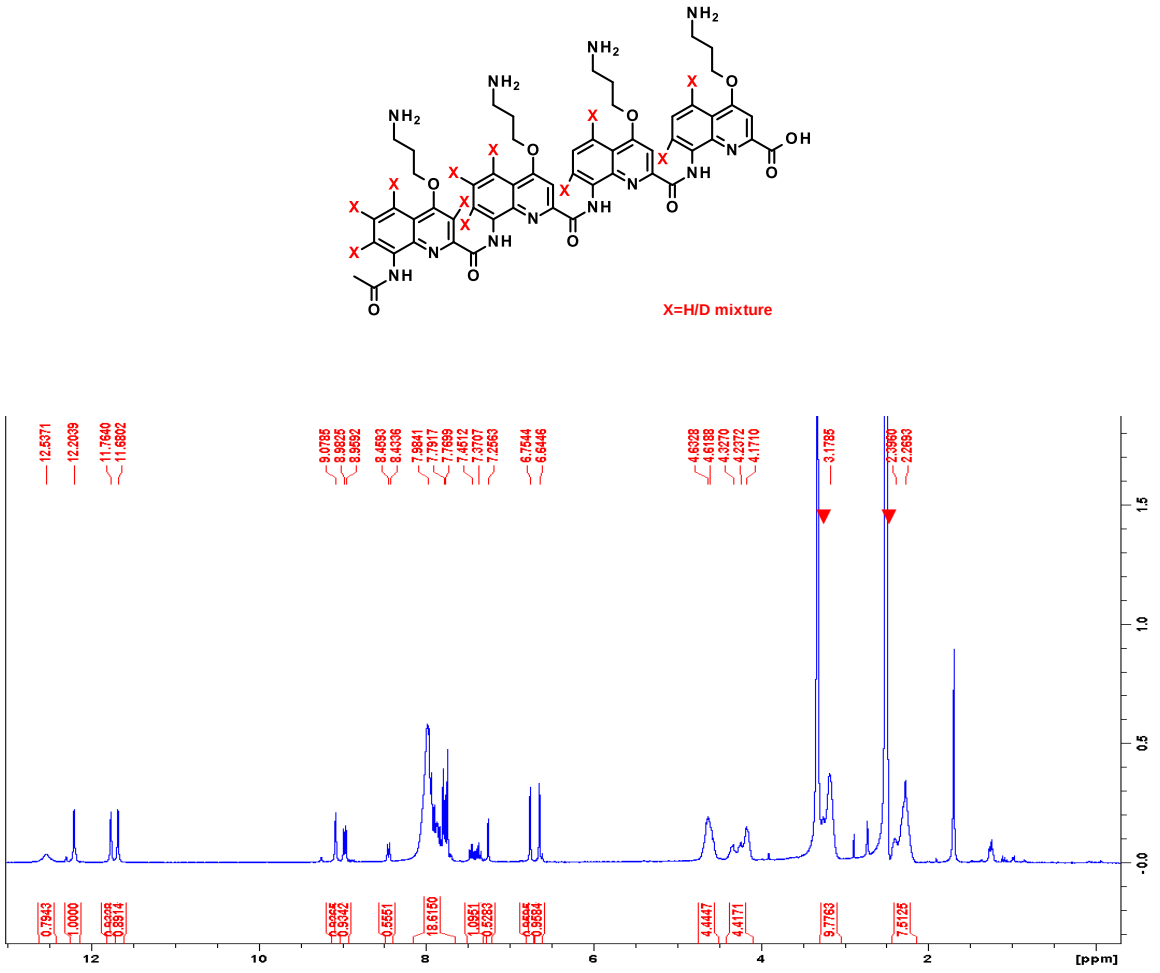


Figure S104. ^{1}H NMR (300 MHz, DMSO-d_6) of compound **12**.

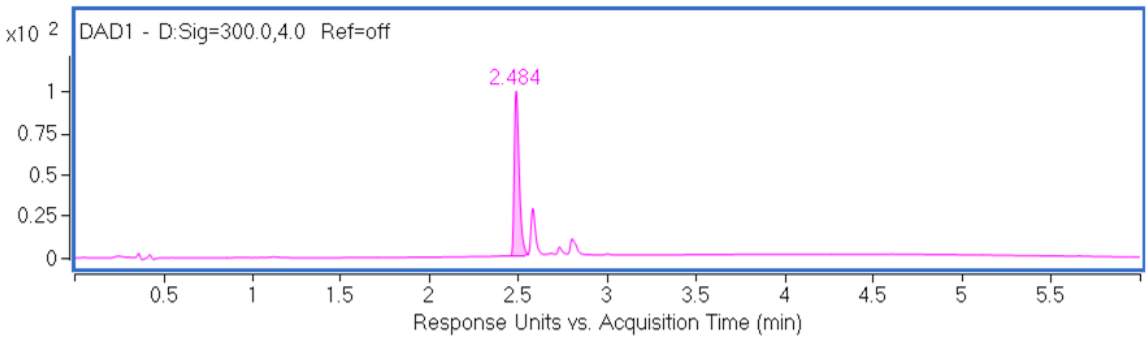


Figure S105. LCMS analysis (HPLC-UV chromatogram) of compound **12**.

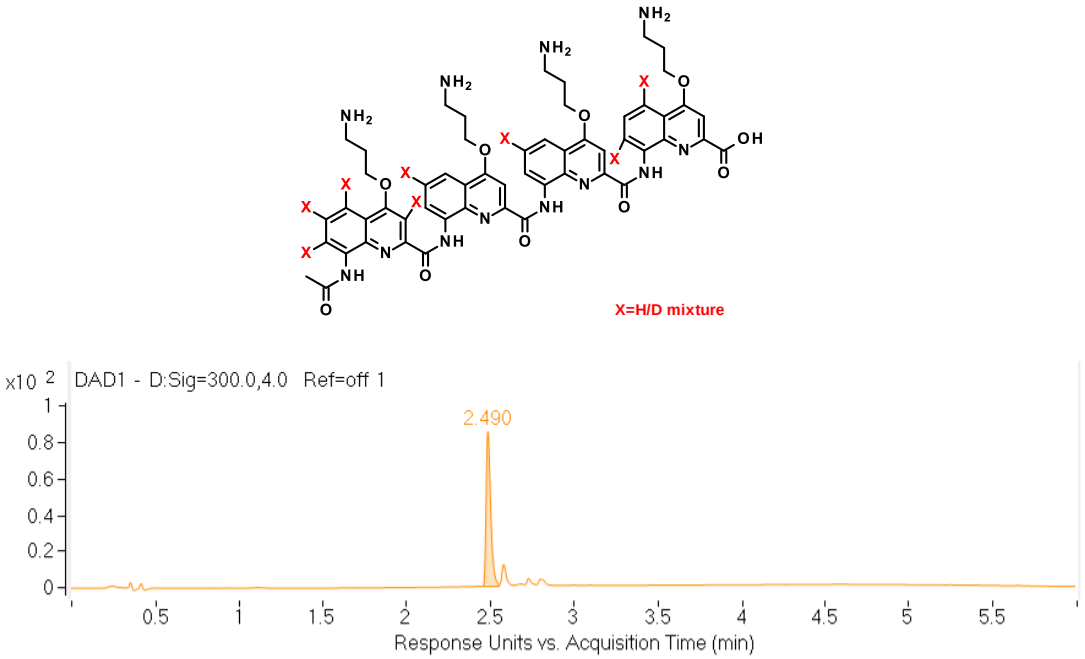


Figure S106. LCMS analysis (HPLC-UV chromatogram) of compound **13**.

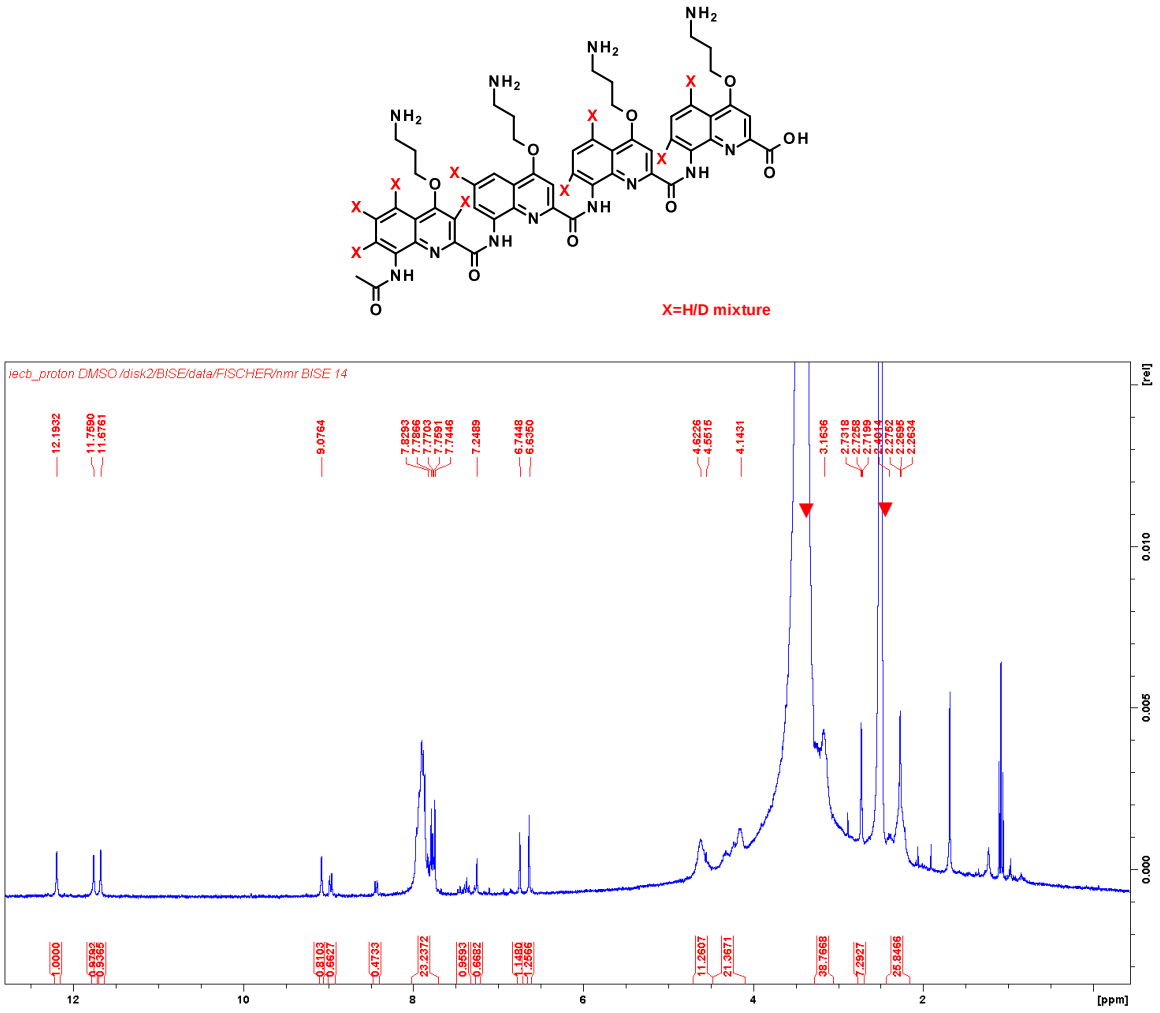


Figure S107. ^{1}H NMR (300 MHz, DMSO-d_6) of compound **14**.

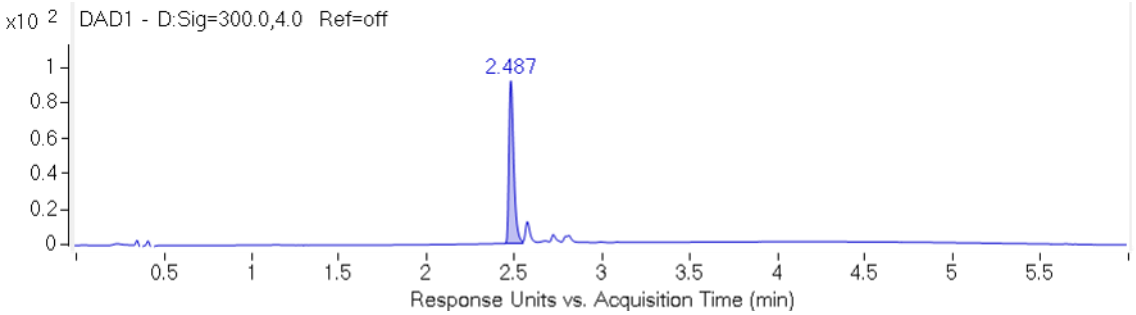


Figure S108. LCMS analysis (HPLC-UV chromatogram) of compound **14**.

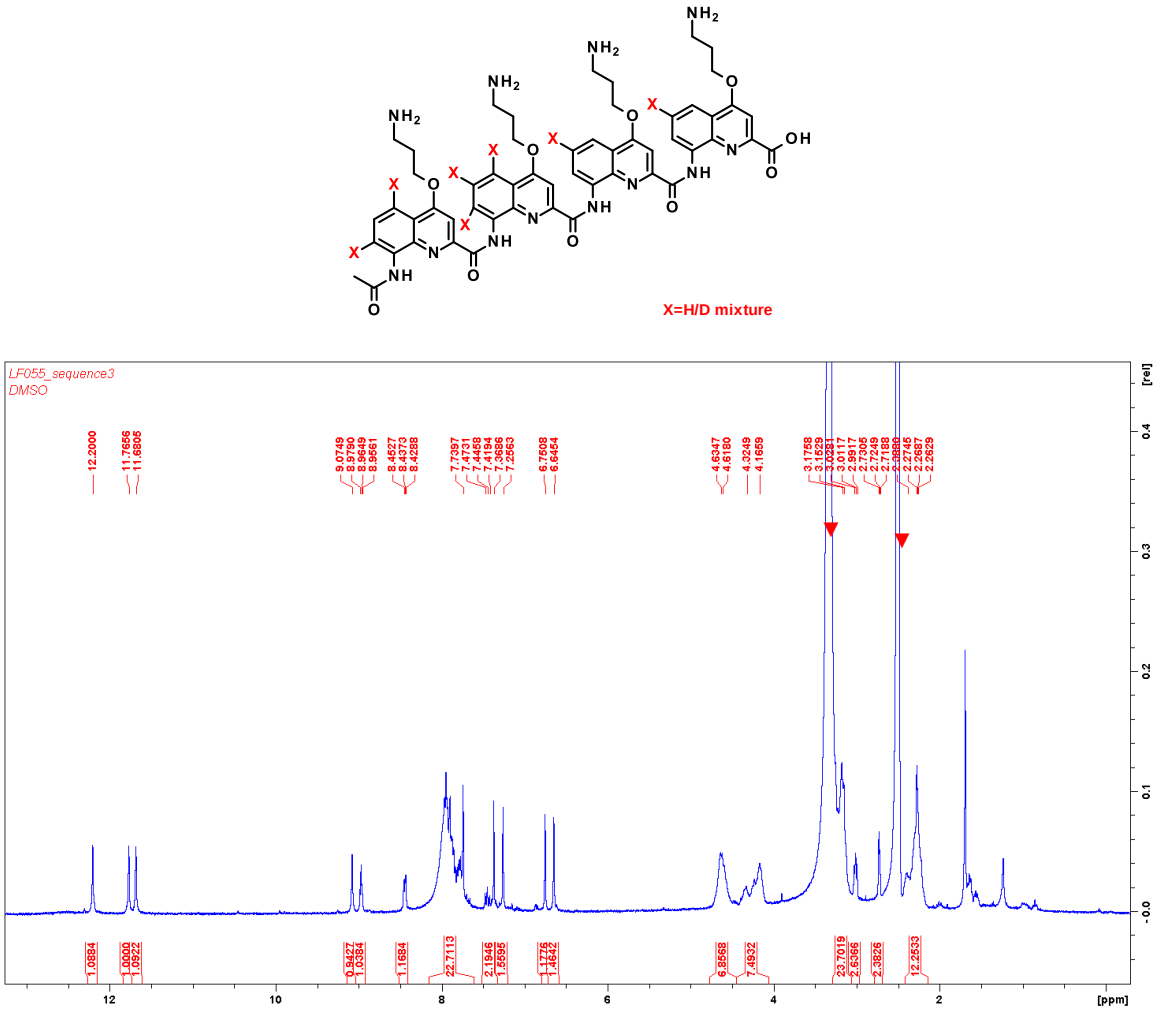


Figure S109. ^{1}H NMR (300 MHz, DMSO-d_6) of compound **15**.

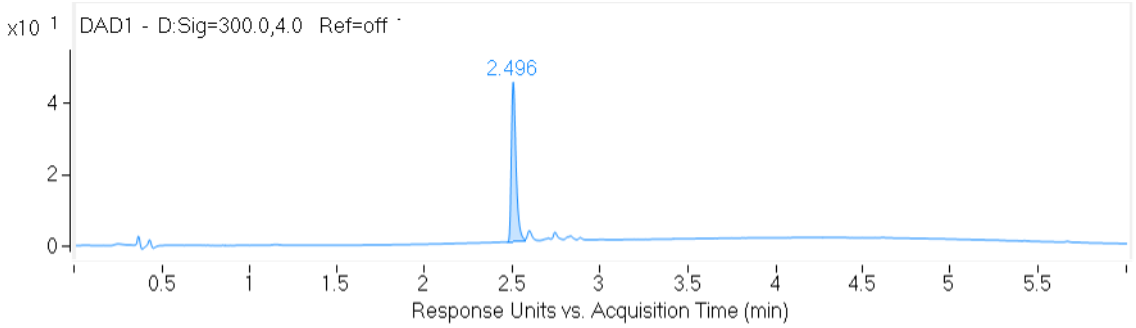


Figure S110. LCMS analysis (HPLC-UV chromatogram) of compound **15**.

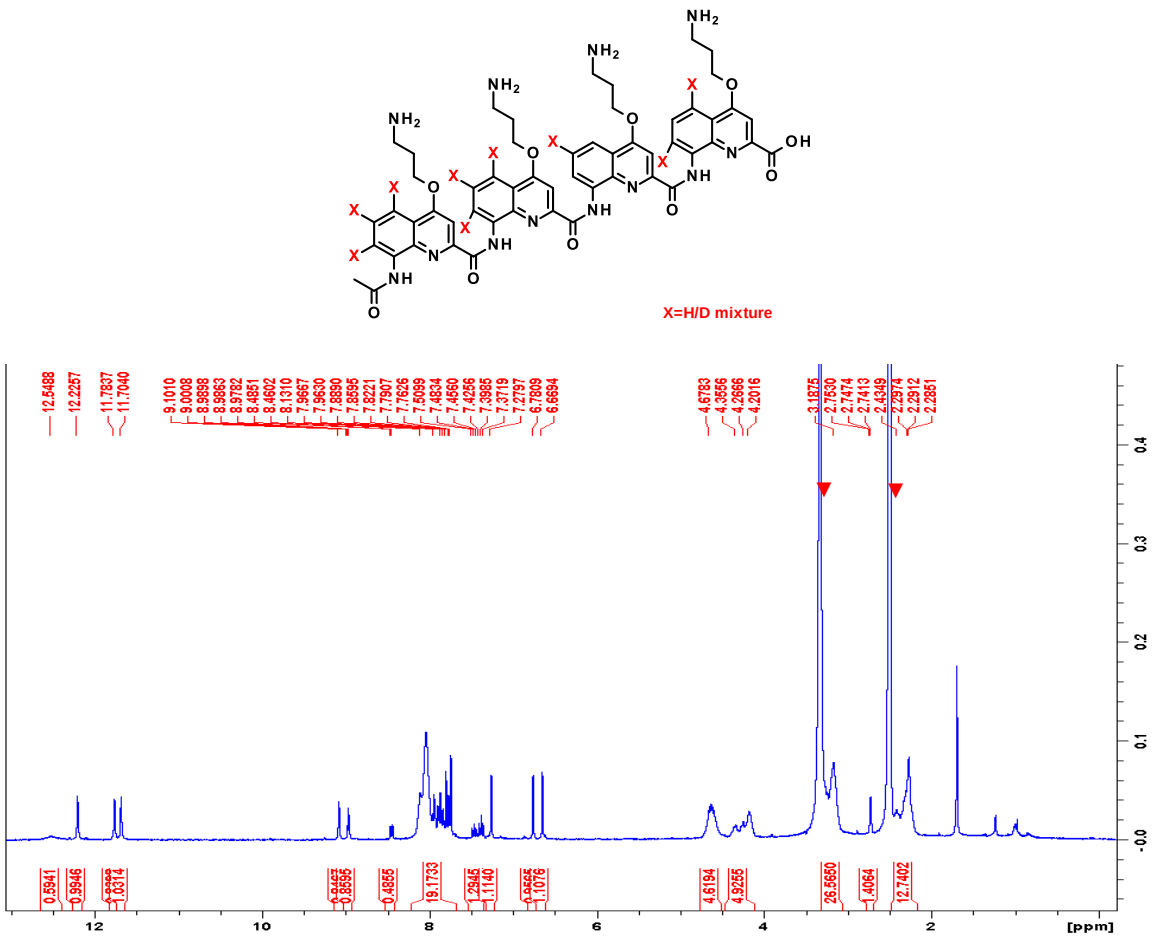


Figure S111. ^{1}H NMR (300 MHz, DMSO-d_6) of compound **16**.

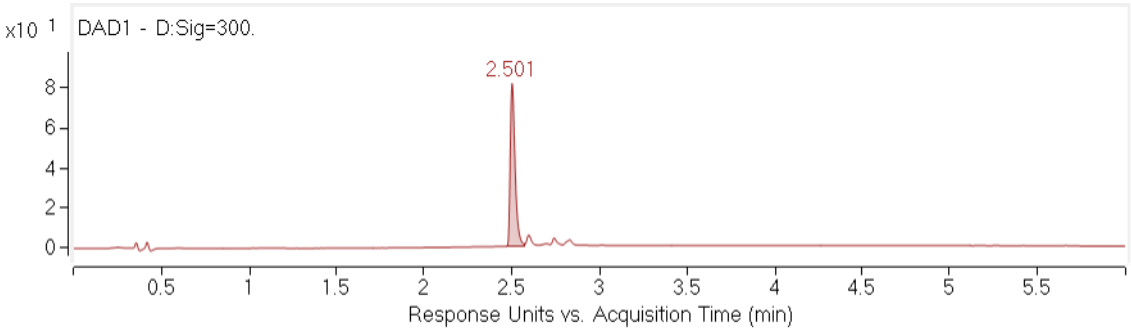


Figure S112. LCMS analysis (HPLC-UV chromatogram) of compound **16**.

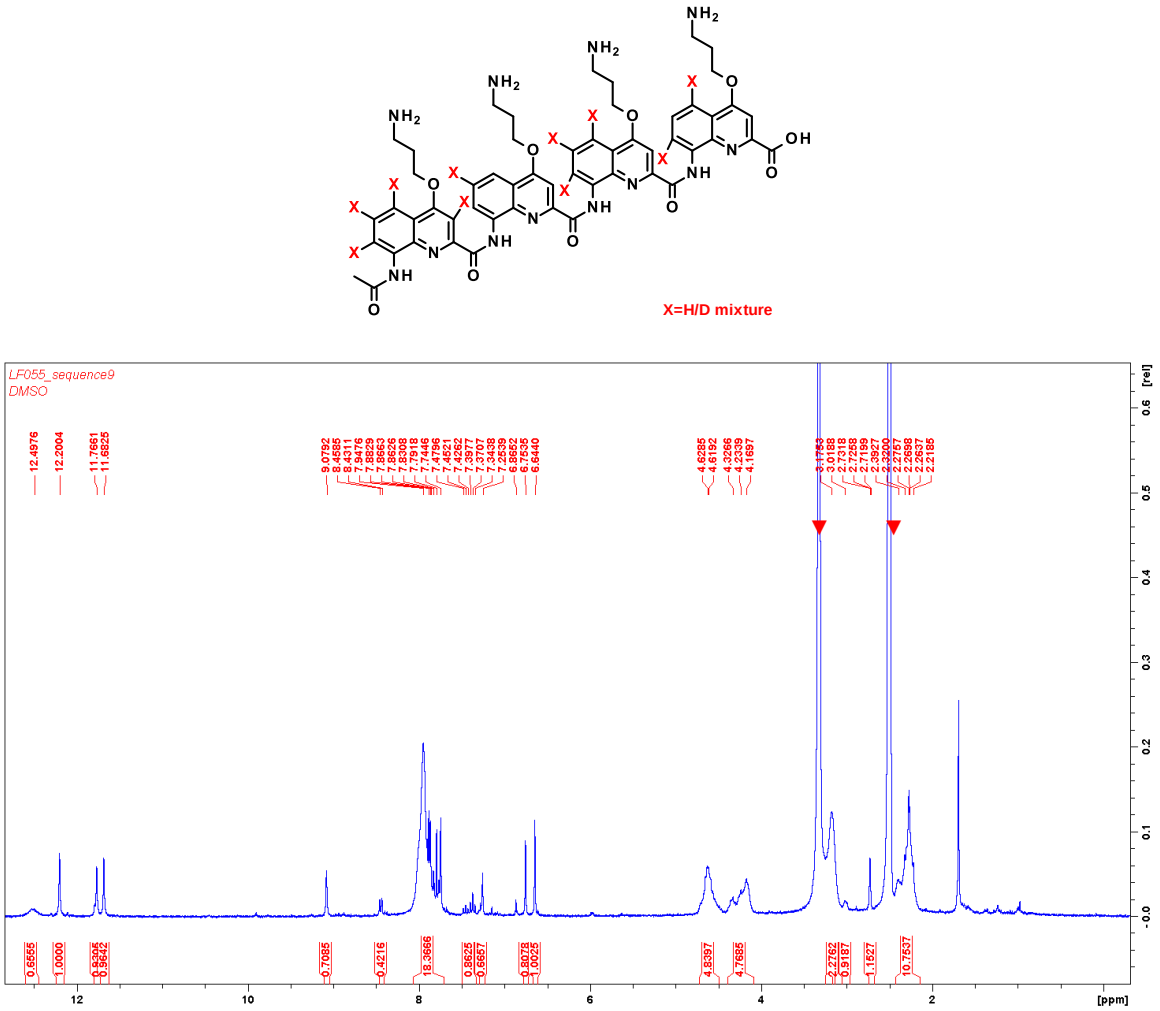


Figure S113. ^{1}H NMR (300 MHz, DMSO-d_6) of compound **17**.

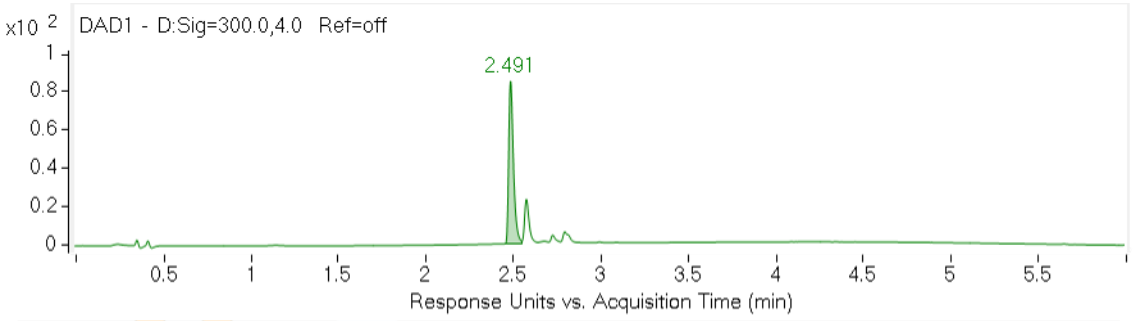


Figure S114. LCMS analysis (HPLC-UV chromatogram) of compound **17**.

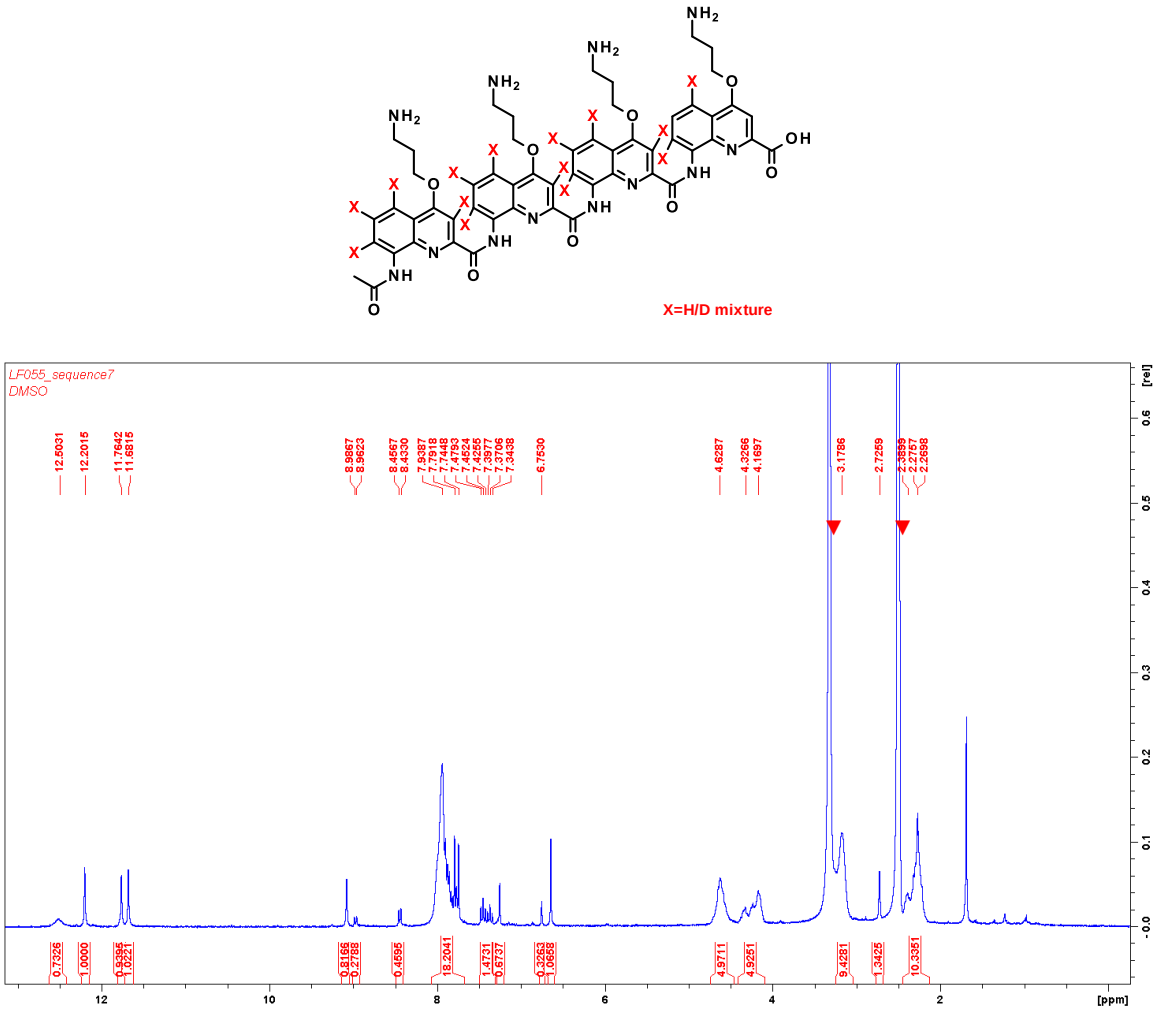


Figure S115. ^{1}H NMR (300 MHz, DMSO-d_6) of compound **18**.

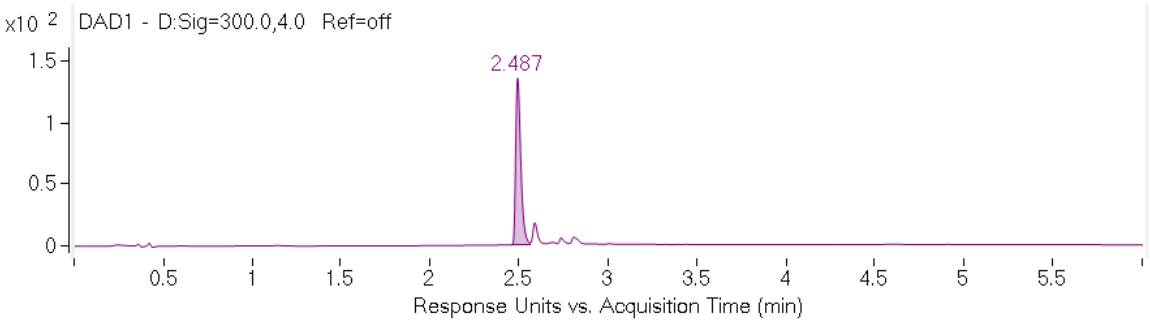


Figure S116. LCMS analysis (HPLC-UV chromatogram) of compound **18**.

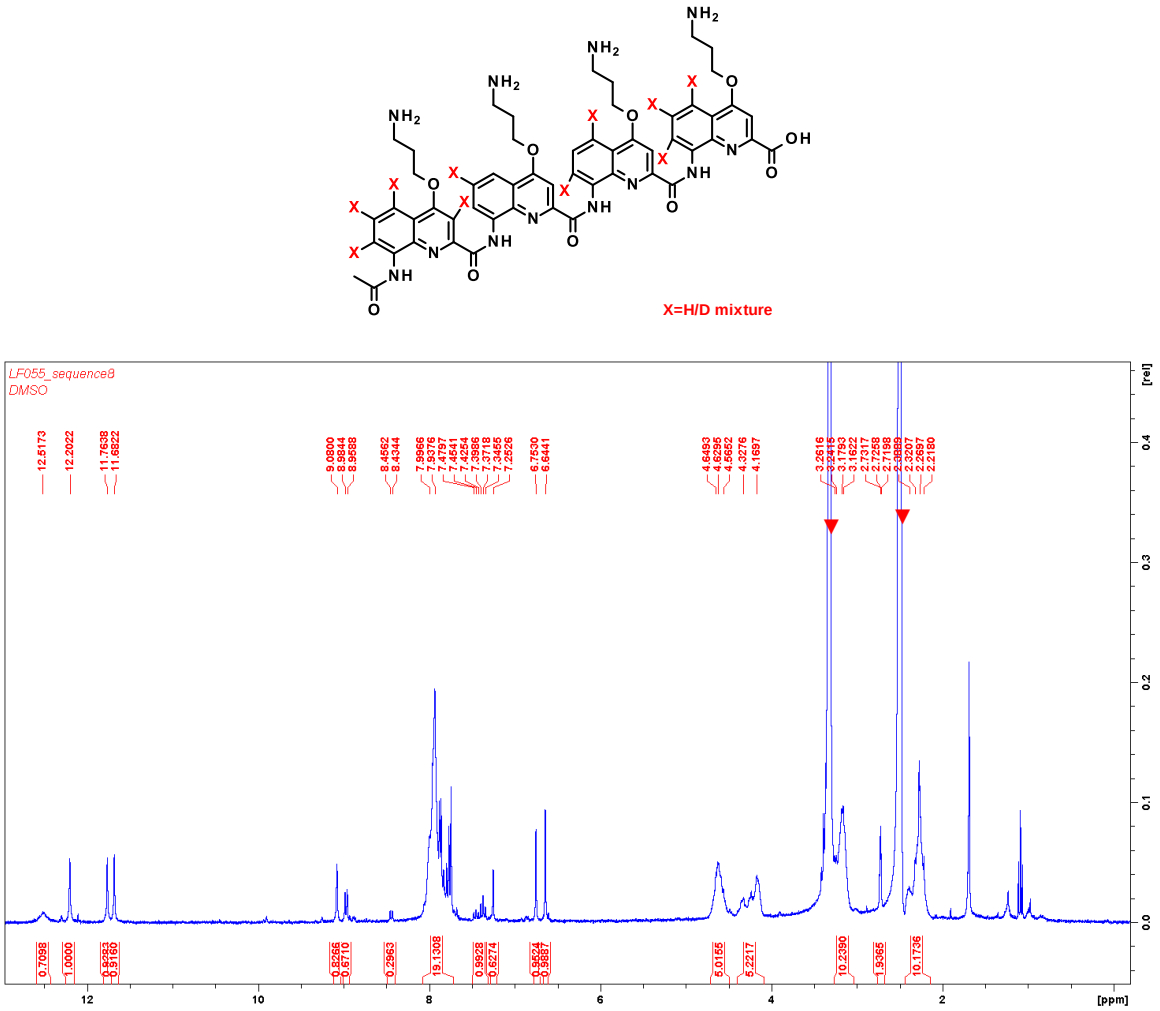


Figure S117. ^{1}H NMR (300 MHz, DMSO-d_6) of compound **19**.

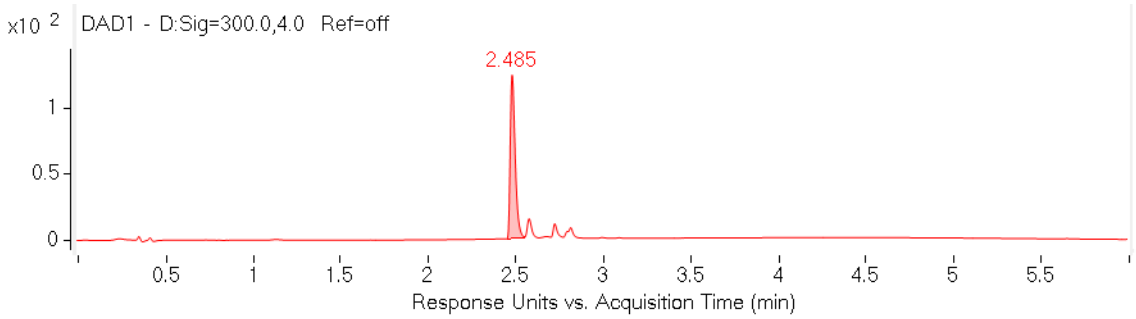


Figure S118. LCMS analysis (HPLC-UV chromatogram) of compound **19**.

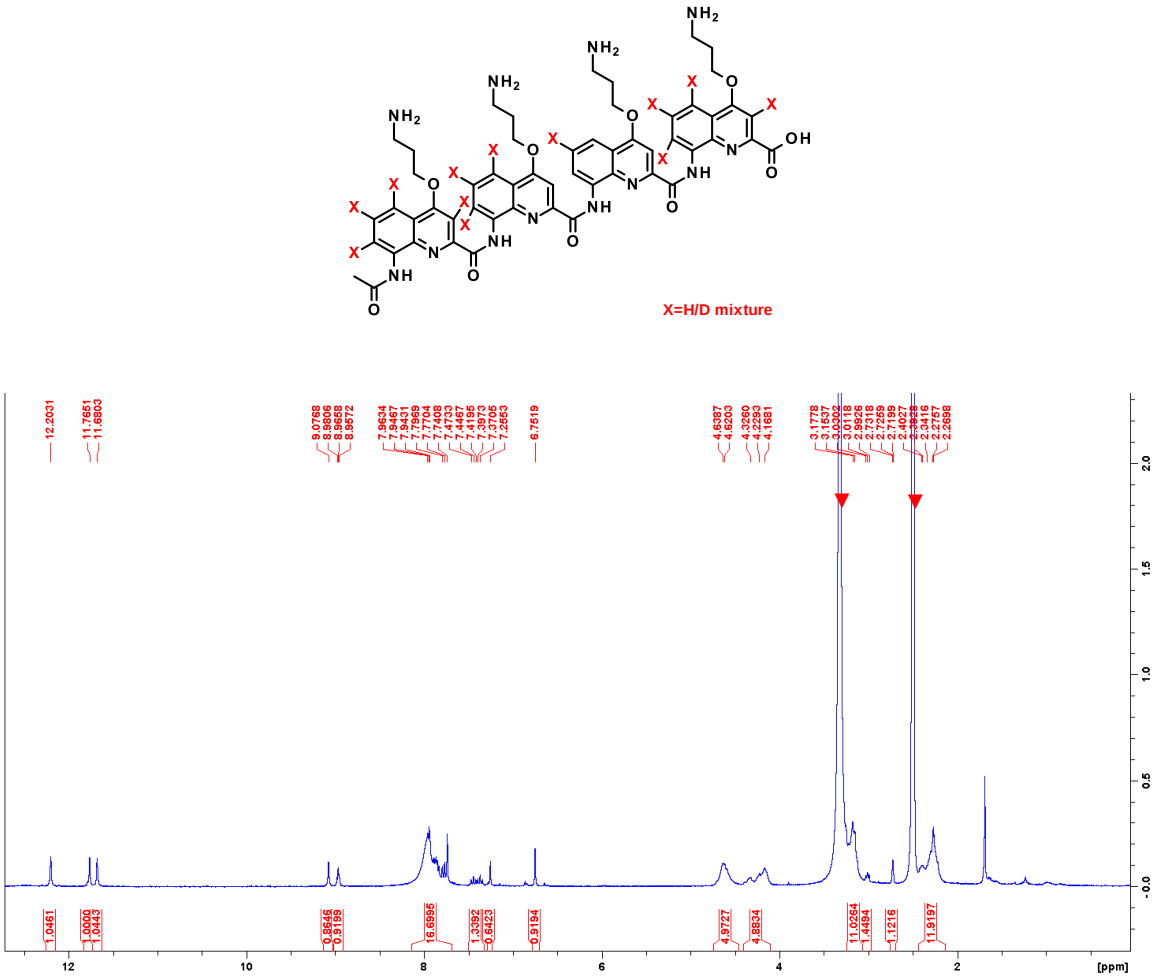


Figure S119. ^{1}H NMR (300 MHz, DMSO-d_6) of compound **20**.

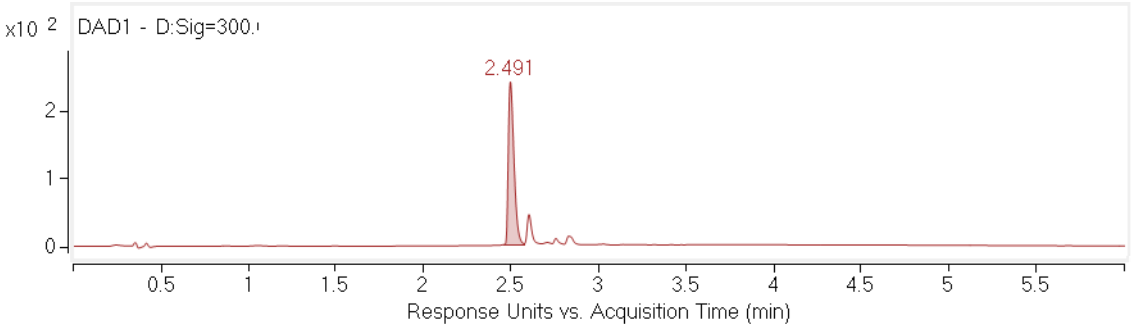


Figure S120. LCMS analysis (HPLC-UV chromatogram) of compound **20**.

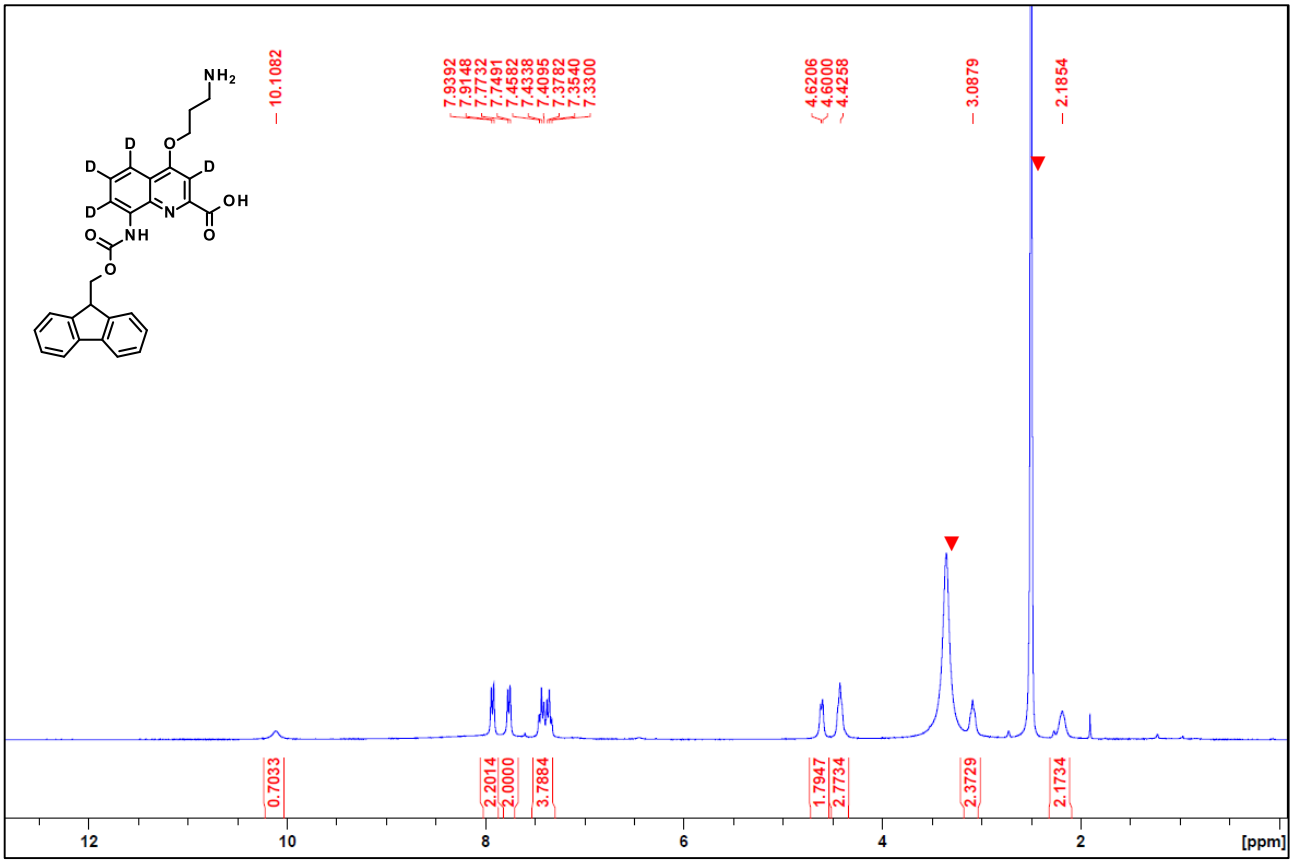


Figure S121. ^{1}H NMR (300 MHz, DMSO-d_6) of compound **21**.

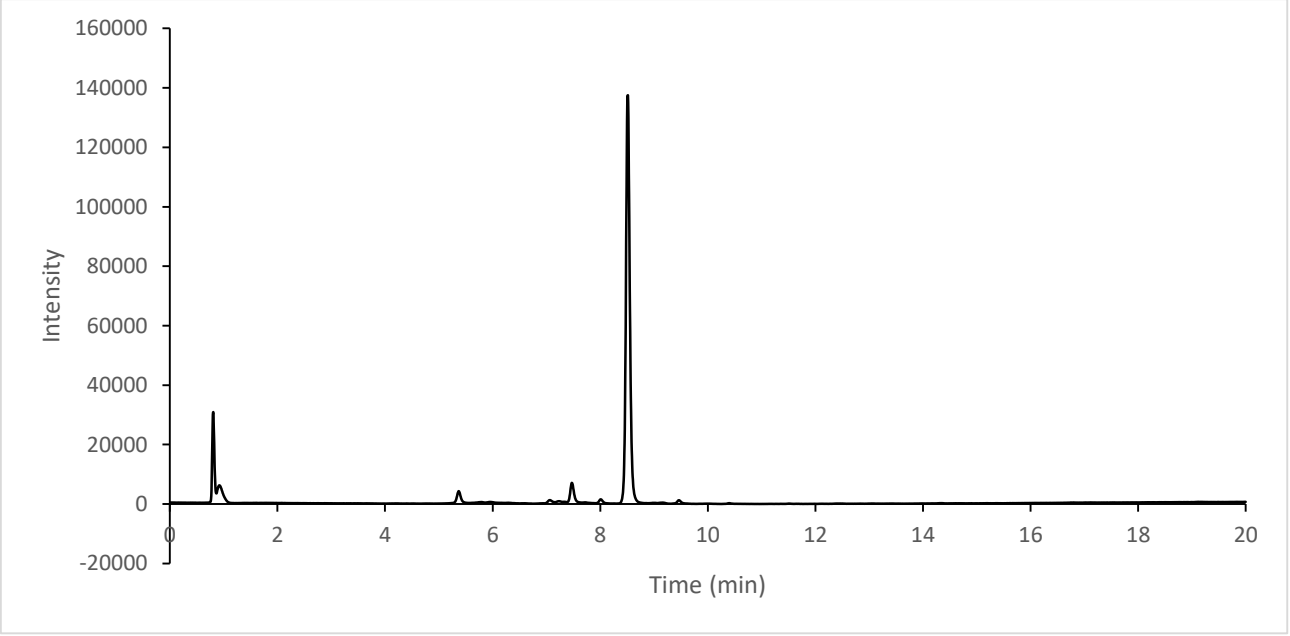


Figure S122. HPLC-UV chromatogram of compound **21**.

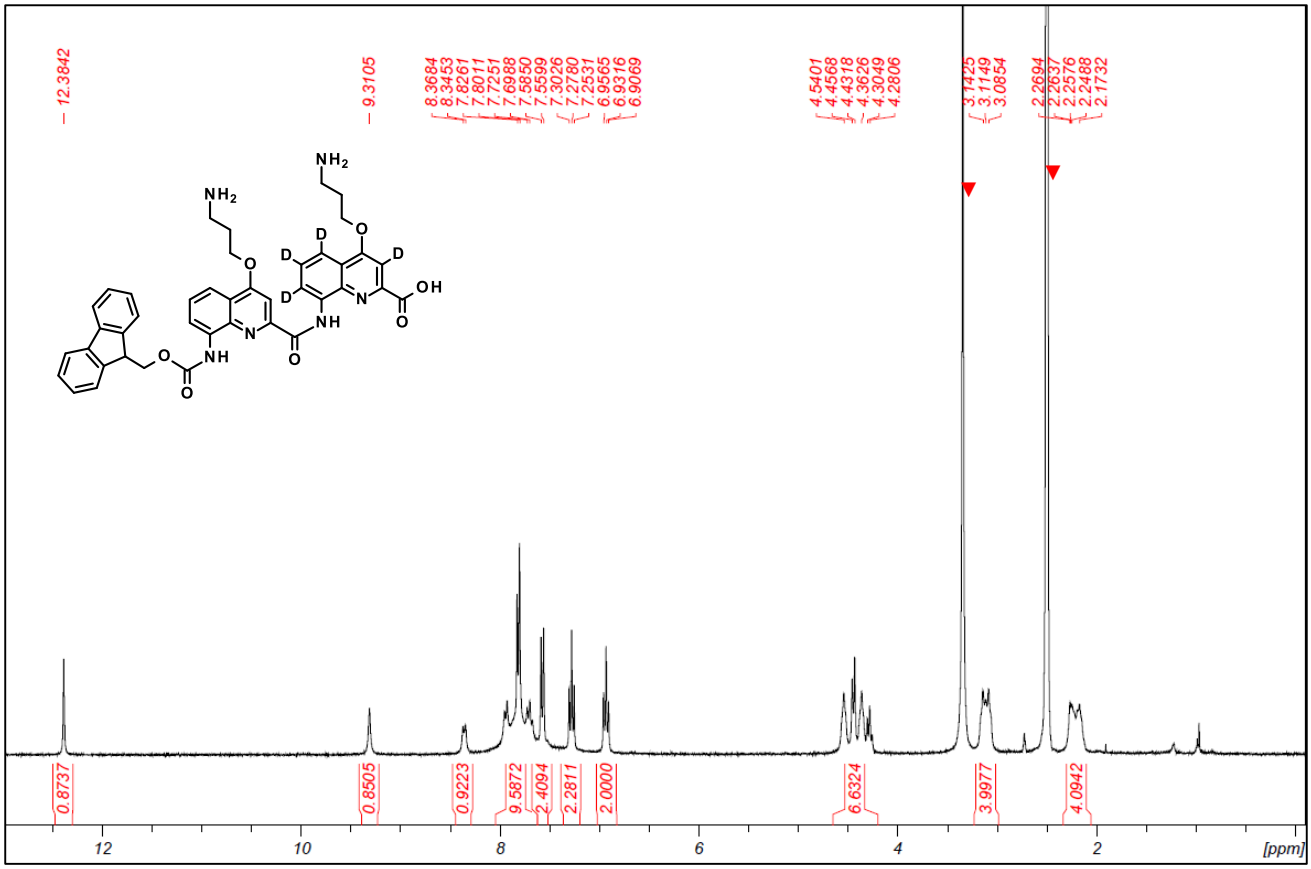


Figure S123. ^{1}H NMR (300 MHz, DMSO-d_6) of compound **22**.

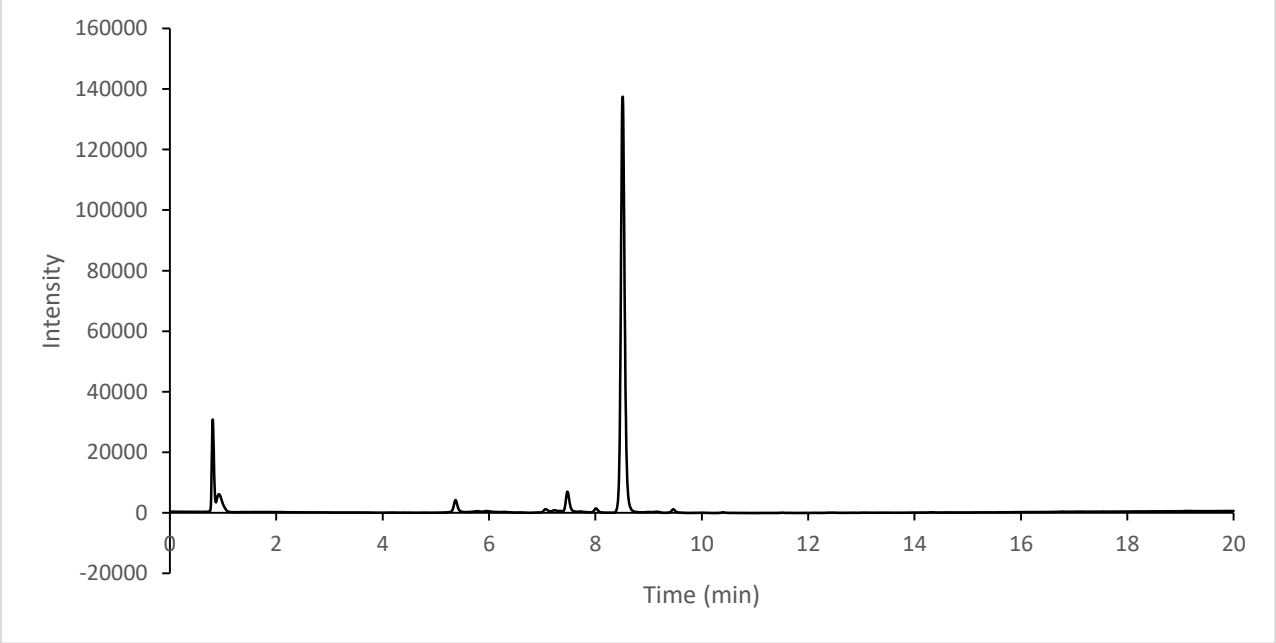


Figure S124. HPLC-UV chromatogram of compound **22**.

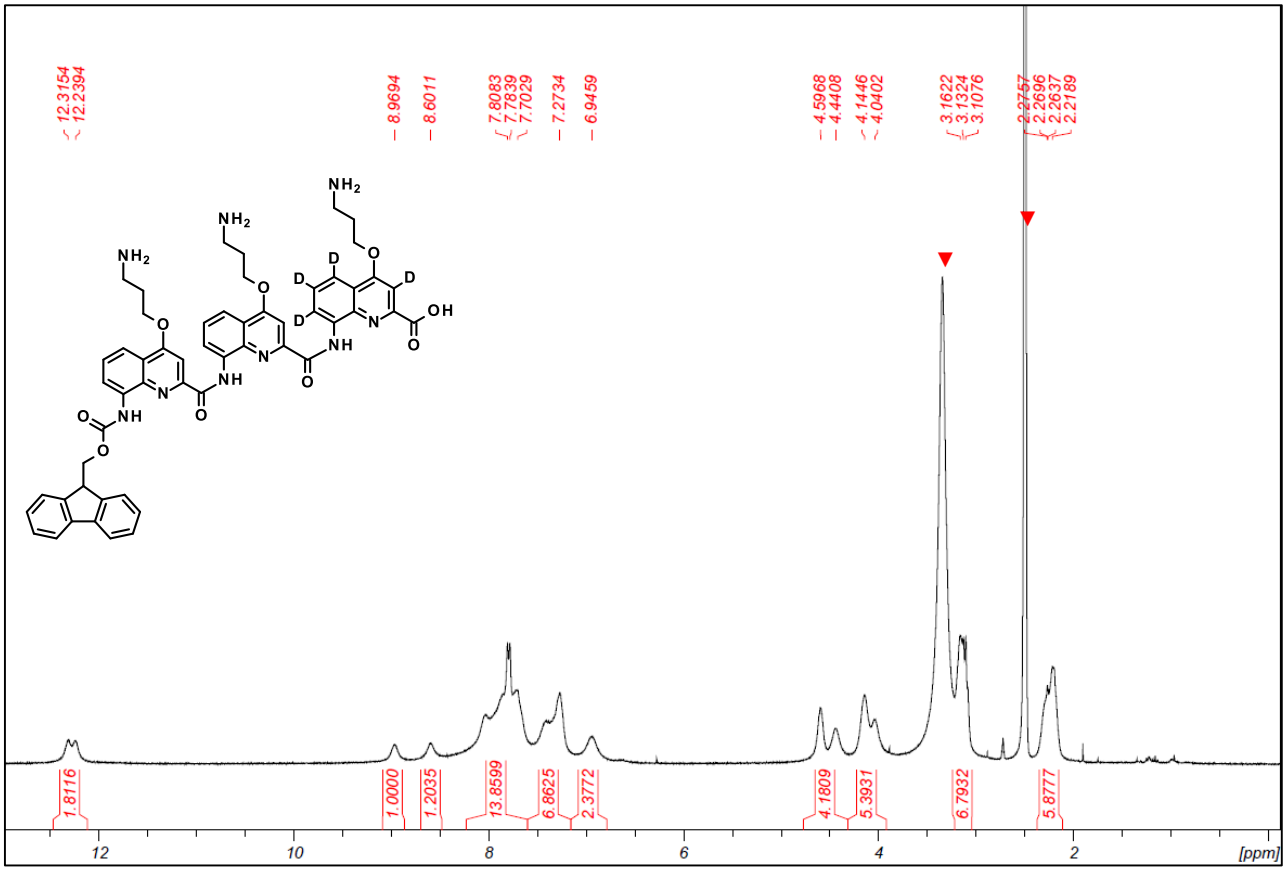


Figure S125. ^{1}H NMR (300 MHz, DMSO-d_6) of compound **23**.

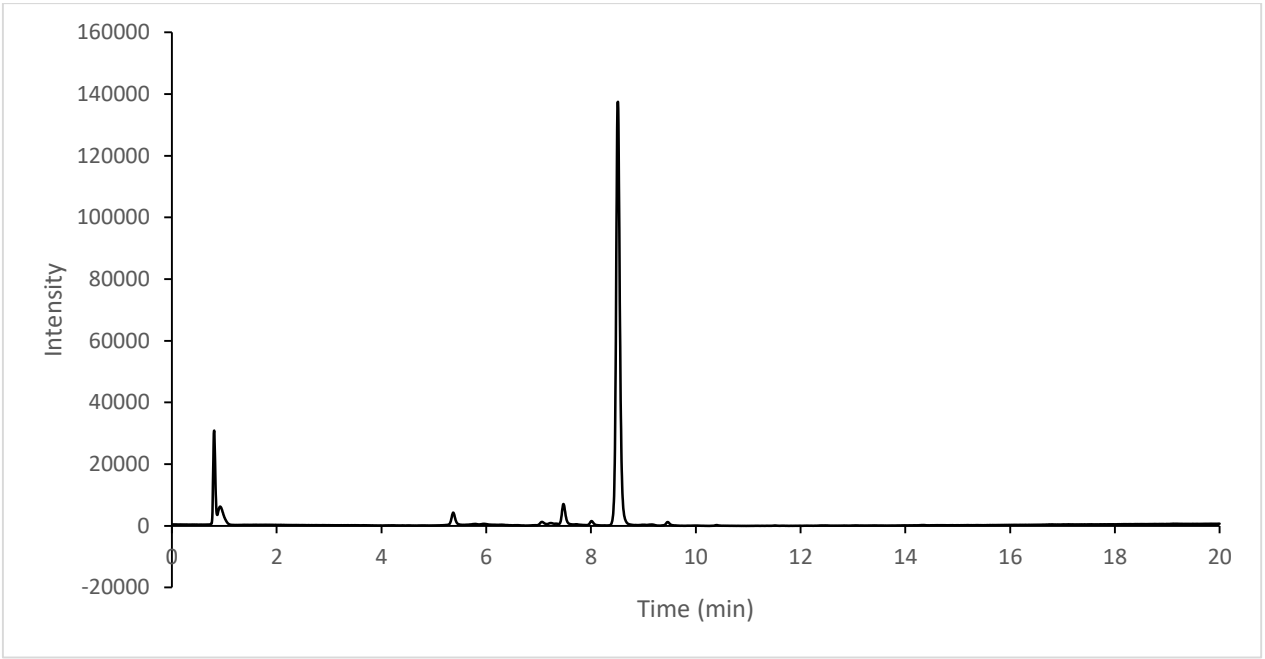


Figure S126. HPLC-UV chromatogram of compound **23**.

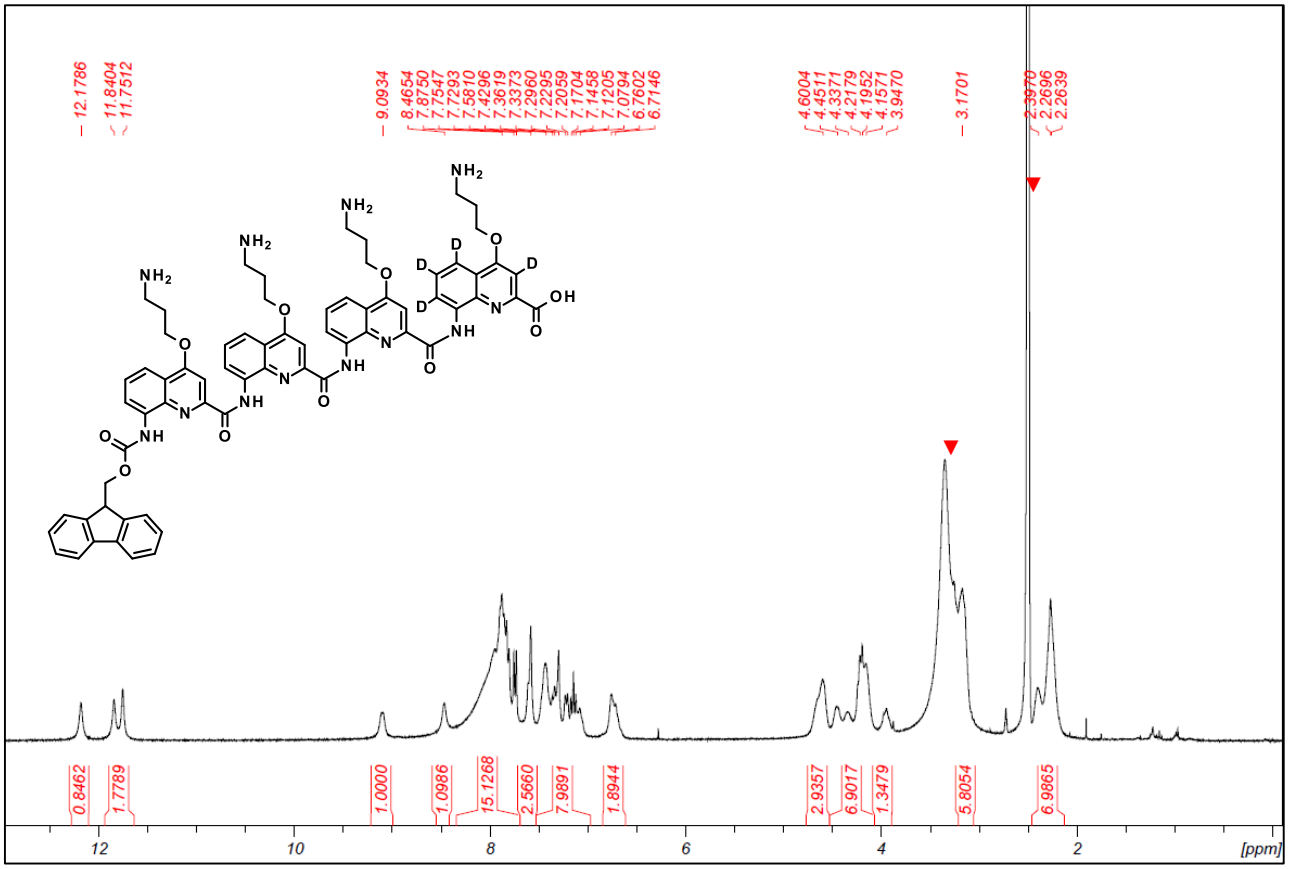


Figure S127. ^{1}H NMR (300 MHz, DMSO-d_6) of compound **24**.

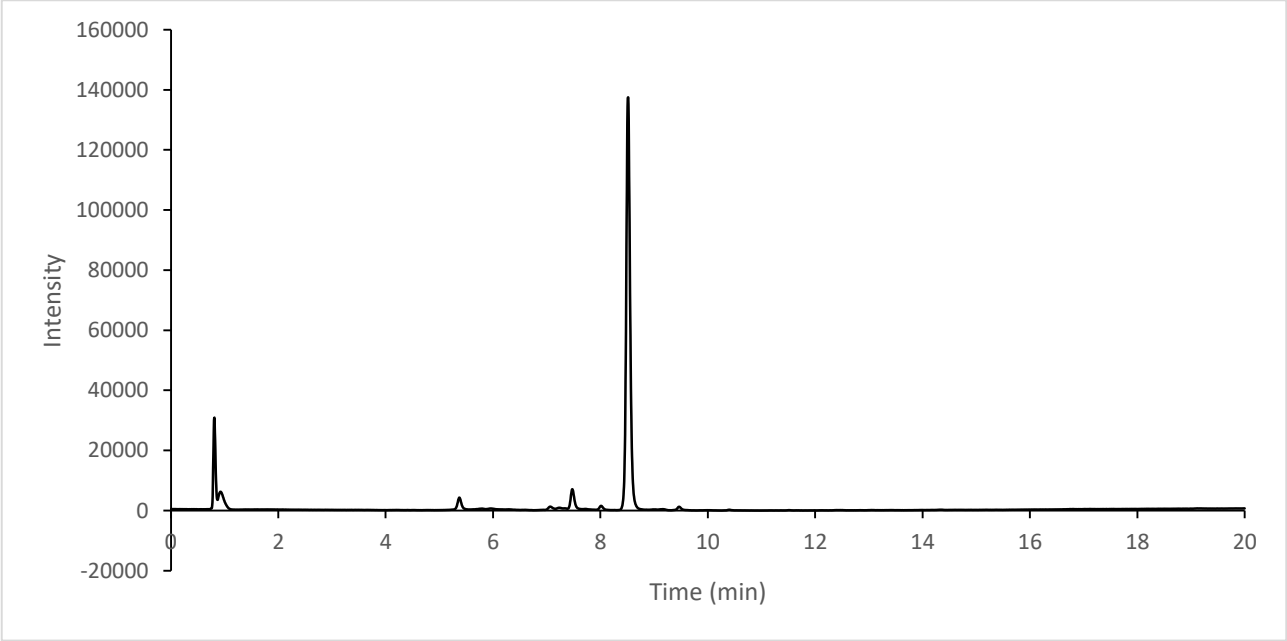


Figure S128. HPLC-UV chromatogram of compound **24**.

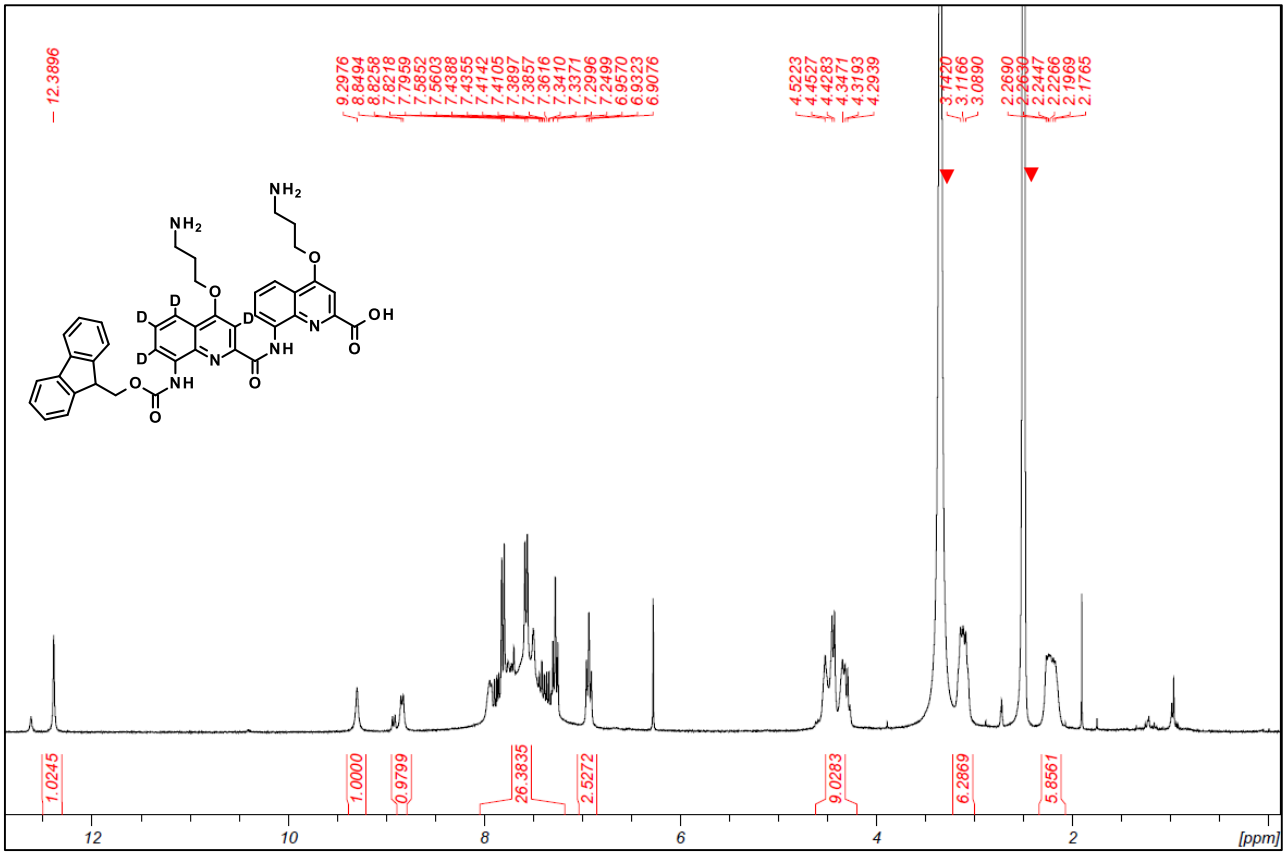


Figure S129. ^{1}H NMR (300 MHz, DMSO-d_6) of compound **25**.

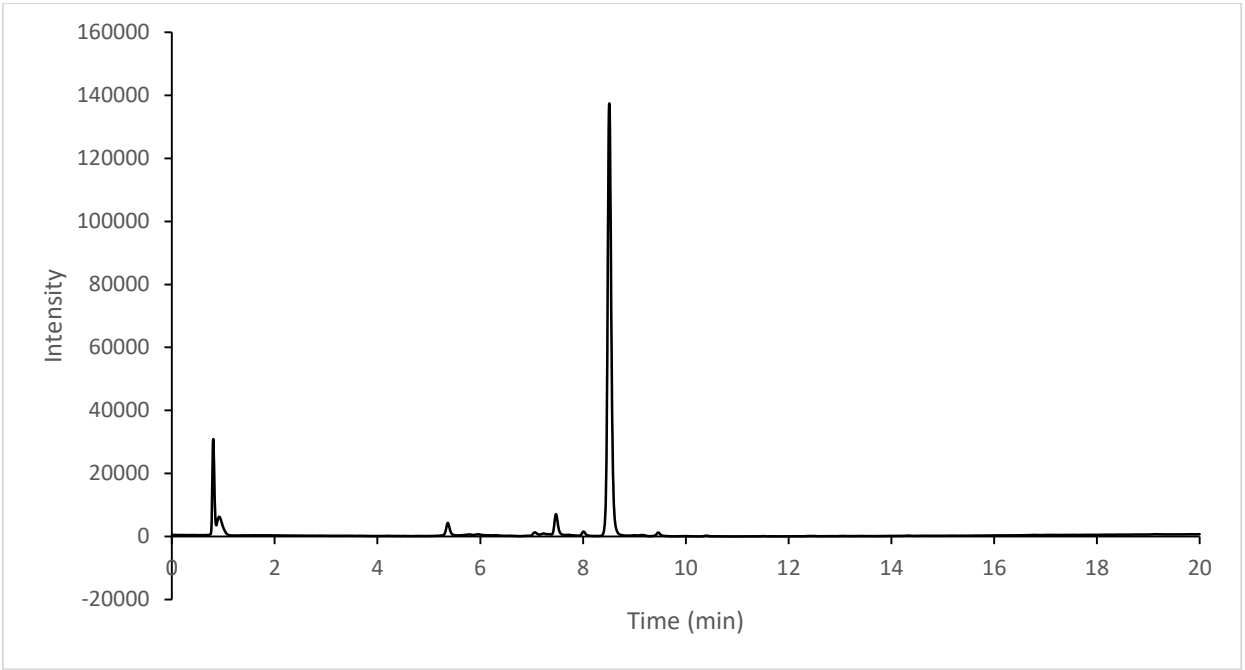


Figure S130. HPLC-UV chromatogram of compound **25**.

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