SUPPORTING INFORMATION

Novel selective inhibitors of the plasmodial zinc aminopeptidase M1 as potential antimalarial agents.

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Table of purities for target compounds, analyzed by 2 different HPLC techniques.

	Method 1[a]		Method 2[b]	
Compound	**t_R1**	**Purity (215nm)**	**t_R2**	**Purity (215 nm)**
32	3.90	100	1.24	100
33	4.11	100	1.75	100
34	4.63	100	2.40	100
37	4.71	100	2.57	100
38	4.13	95	1.38	100
39	4.74	95	2.14	100
40	5.03	95	2.92	100
41	5.32	100	6.29	100
42	5.47	99	8.20	100
43	5.90	99	19.44	100
44	6.26	99	14.32	100
47	5.82	99	17.44	100
48	6.05	99	26.44	100
49	4.25	100	1.47	100
50	4.31	100	1.95	100
51	4.82	98	2.95	100
52	5.20	99	5.15	100
53	4.92	99	2.34	100
54	5.46	95	8.27	97
55	3.16	96	1.57	100
56	4.53	100	2.29	97
57	4.31	100	1.67	100
58	4.80	97	2.69	100
59	4.53	97	2.02	100
60	4.89	99	3.75	95
61	5.45	99	8.62	100
62	5.43	99	8.14	95
63	5.49	98	8.23	100
66	4.23	99	1.42	100
68	4.41	99	1.98	99
71	5.10	99	2.90	100
72	6.01	99	8.90	96

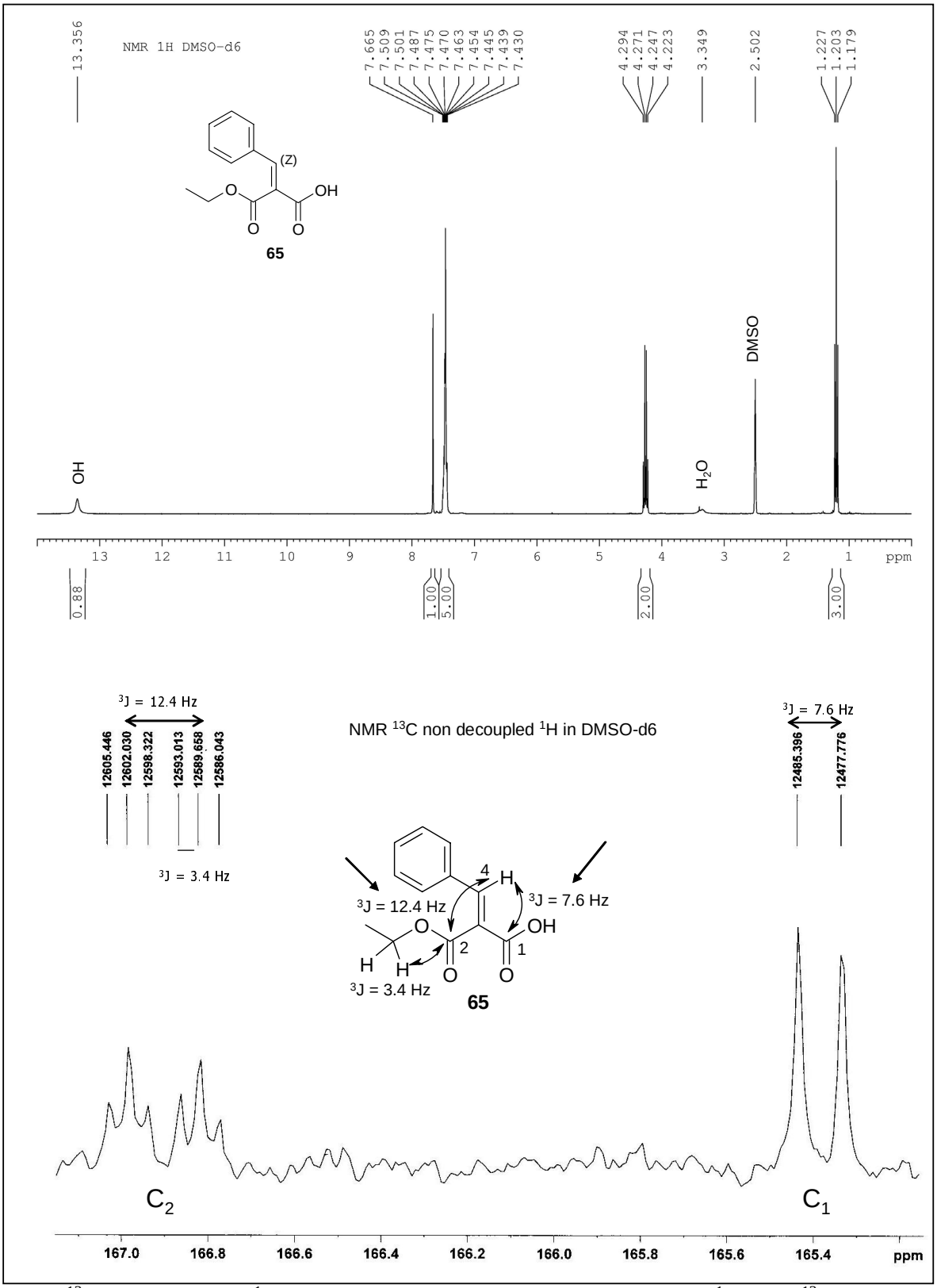
[a] HPLC analysis was performed on a LCMS-MS triple-quadrupole system (Varian 1200ws) using a C18 TSK-GEL Super ODS 2 µm particle size column, dimensions 50 * 4.6 mm. A gradient starting from 100% H_2O / 0.1% formic acid and reaching 20% H_2O / 80% CH_3CN / 0.08% formic acid within 10 min at a flow rate of 1 mL/min was used.

[b] HPLC analysis was performed on a HPLC (Shimadzu SP-10A) using a C18 ACE 3 µm particle size column, dimensions 50 * 4.6 mm. The analysis was performed under isocratic conditions (70% sodium acetate buffer 10 mM pH=5 adjusted with glacial acetic acid / 30 % acetonitrile) within 30 min at a flow rate of 1.5 mL/min.

Inhibition results at 10 µM of PfA-M1 and APN for each member of the library

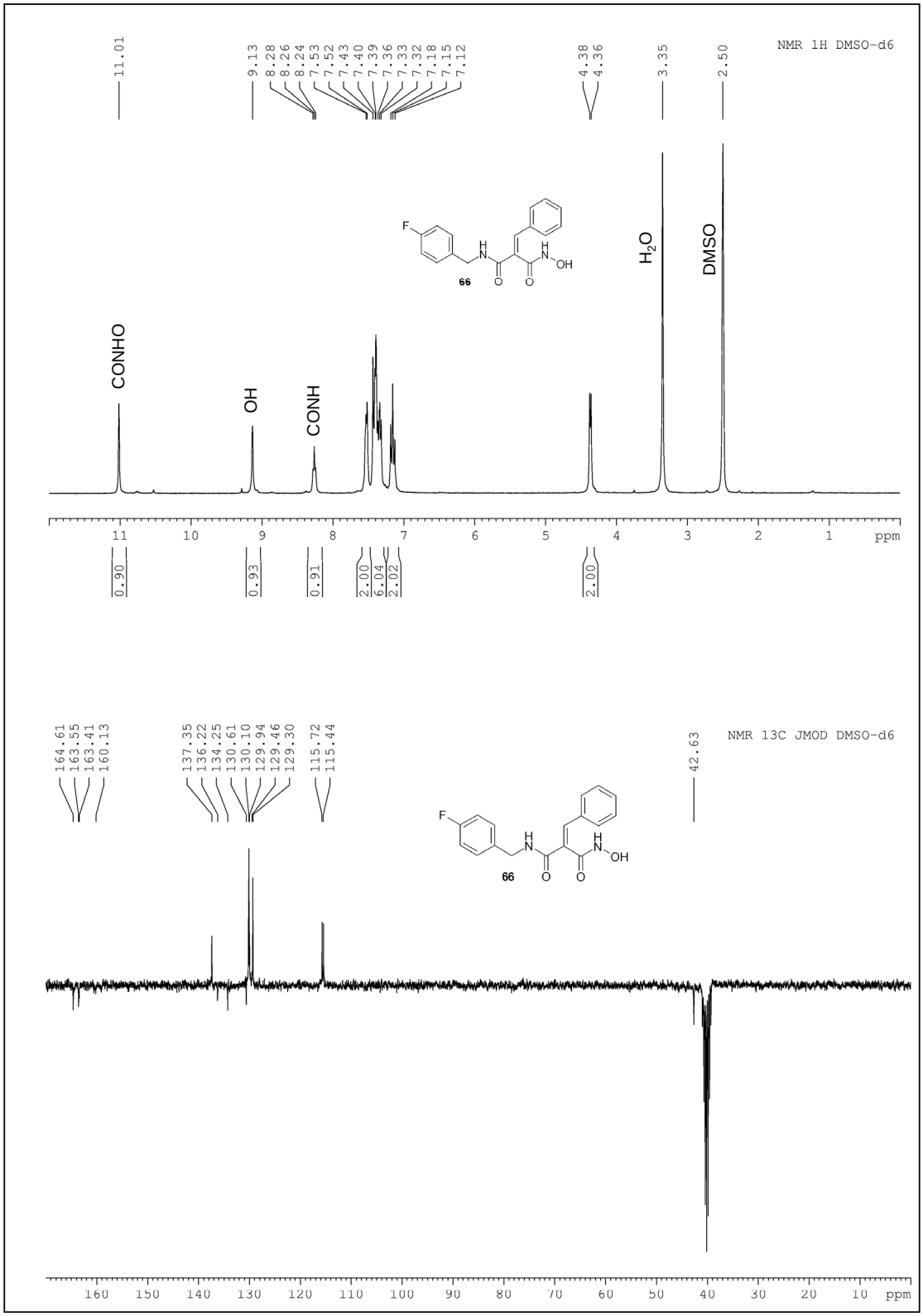
R_1	NH_2	H	m-PhO-benzyl	i-butyl	benzyl	NH_2	H	m-PhO-benzyl	i-butyl	benzyl
Amine	PfA-M1 (% inhibition at 10 µM)					APN (% inhibition at 10 µM)				
1	10	2	96	19	94	77	19	79	39	69
2	5	10	96	90	93	54	13	76	99	80
3	9	6	35	85	91	18	16	22	92	72
4	6	1	102	24	67	55	40	84	45	75
5	-6	3	99	-4	-6	24	18	85	30	15
6	9	32	99	88	95	23	17	86	98	85
7	-1	-4	86	23	45	29	9	89	37	36
8	-8	-2	98	74	82	25	27	88	105	70
9	-7	-2	67	30	29	22	16	85	86	47
10	20	-2	43	61	26	36	12	72	93	61
11	2	0	66	42	59	16	14	78	93	76
12	64	2	93	98	94	8	15	89	95	84
13	56	19	96	87	94	42	36	84	92	81
14	12	-4	80	2	76	10	11	95	20	53
15	37	22	36	42	45	-1	45	52	60	28
16	2	-3	41	58	43	37	19	86	86	28
17	3	22	77	66	67	18	32	83	81	46
18	-4	-2	5	3	3	25	14	72	57	21
19	-2	-9	38	38	20	11	11	63	103	46
20	49	-3	100	74	84	32	19	84	90	50
21	-3	7	97	21	53	23	11	31	19	29
22	18	8	84	29	75	-5	23	47	28	21
23	45	7	97	100	92	39	23	65	68	34
24	-6	5	65	7	40	43	19	70	26	22
25	12	6	74	15	-1	34	19	76	54	56
26	-4	-5	48	16	7	9	27	81	21	32
27	8	50	50	76	65	62	87	59	102	83
28	4	5	38	42	75	34	32	67	105	56
29	-5	21	-6	-2	0	10	14	41	19	14
30	35	28	41	69	71	62	66	81	95	90
31	51	44	68	88	87	31	55	69	96	83

^{1}H NMR spectrum and excerpt of ^{13}C non decoupled ^{1}H spectrum of compound 65



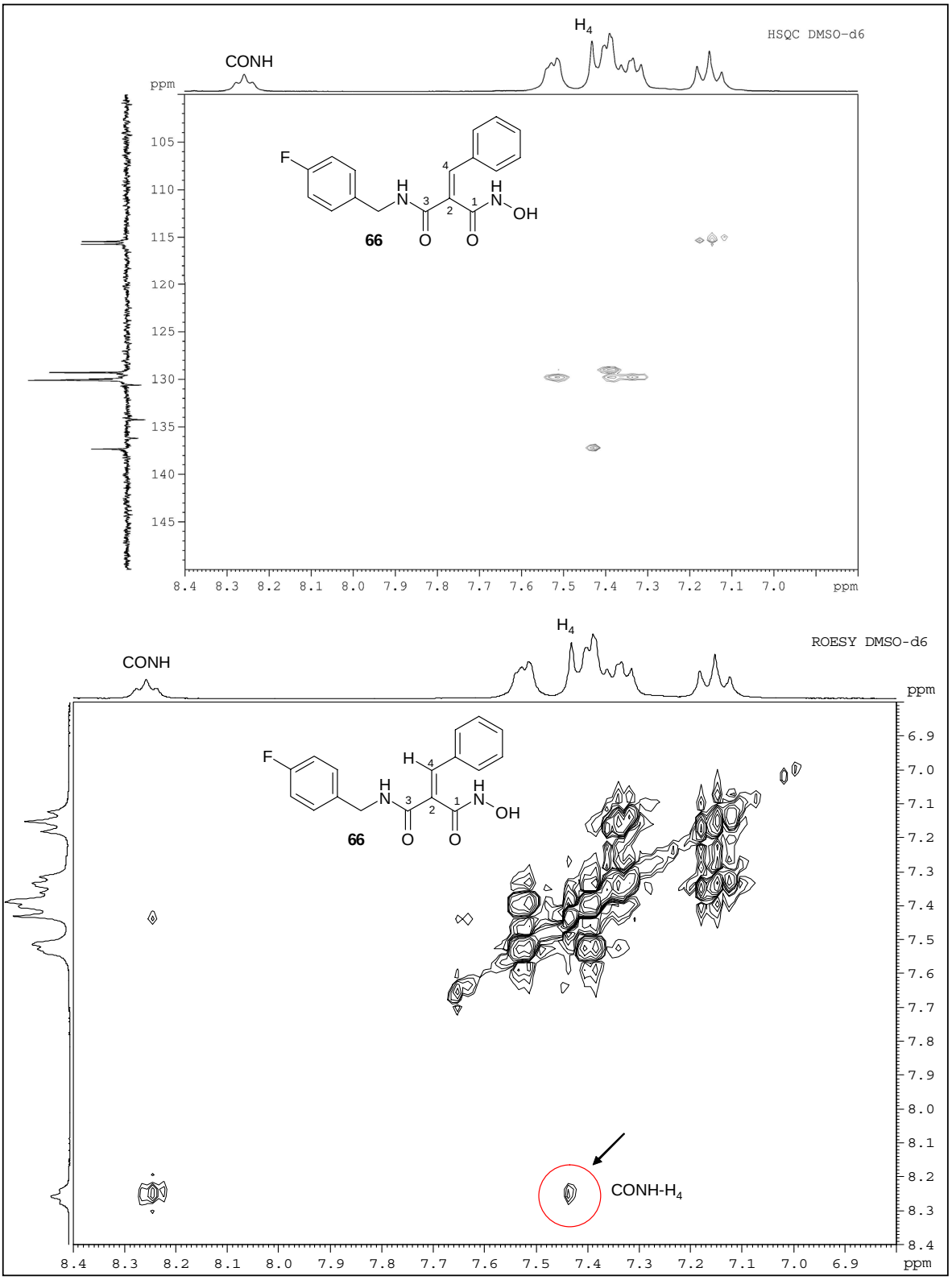
The ^{13}C non decoupled ^{1}H NMR experiment was used for determining ^{1}H-C=C-^{13}C coupling constants of compound **65**. The *trans* coupling constant of alkenes is always larger than the corresponding *cis* coupling constant. This experiment allows thus to attribute an *E* configuration to compound **65**.

^{1}H NMR and ^{13}C NMR spectra of compound 66



The J-modulated ^{13}C NMR experiment is useful to differentiate primary and tertiary carbons (that are above the spectrum) from secondary and quaternary carbons (that are under the spectrum).

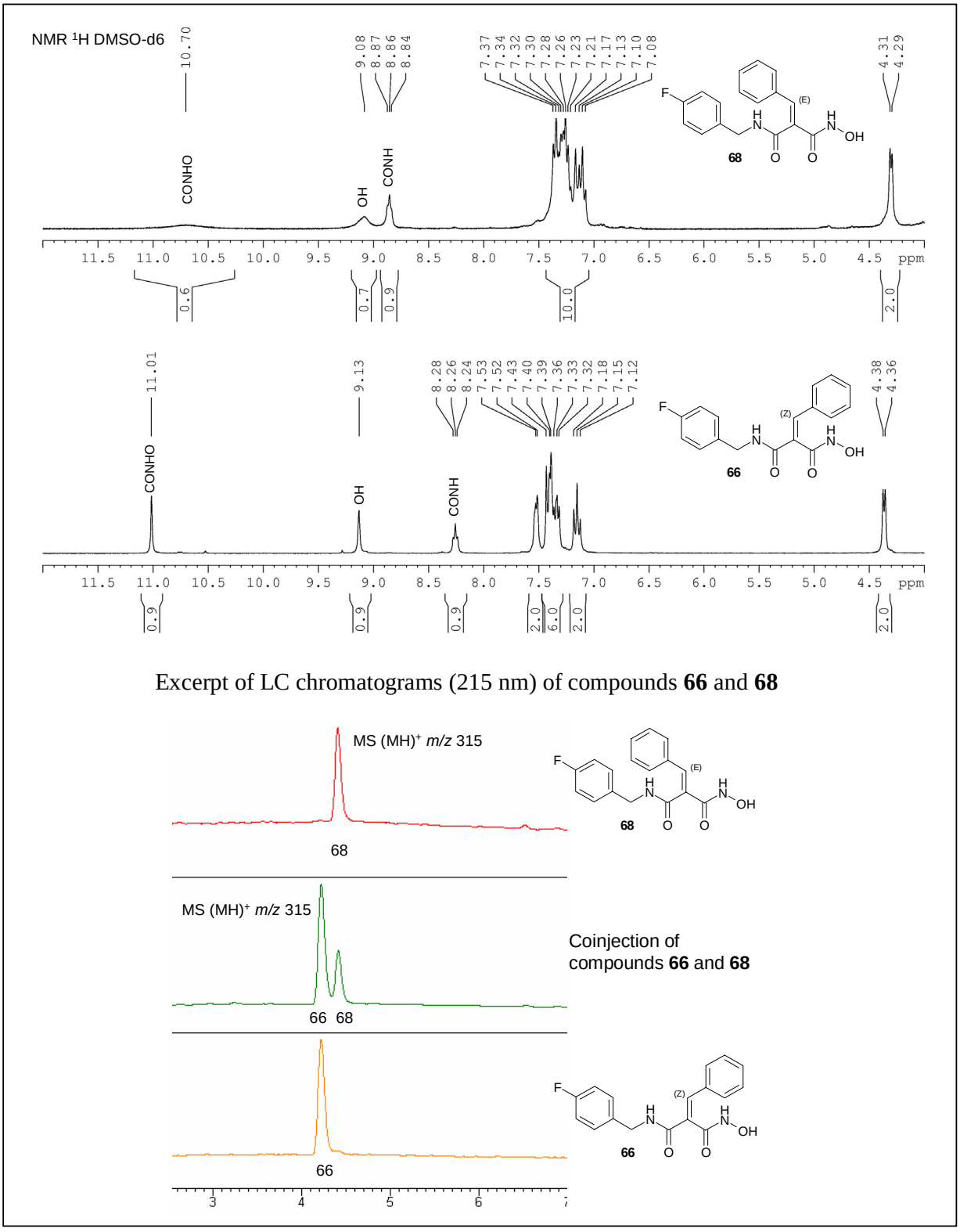
Excerpt of HSQC and ROESY NMR spectra of compound 66



ROESY NMR spectrum shows that H_4 interacts with the hydrogen of the amide function thus these two proton are close in space. This allows us to attribute a *Z* configuration to compound **66**.

Comparison of analytical data of compound 68 to those of compound 66

66 and **68**, were obtained from the same intermediate **65** by reversing the sequence of introduction of amine and protected hydroxylamine. Comparison of ^{1}H NMR spectra and LC chromatograms proves that compounds **68** and **66** are two isomers respectively *E* and *Z*.



Excerpt of LC chromatograms (215 nm) of compounds **66** and **68**