Supporting Information

Three Berkeleyones and Related Meroterpenes From a Deep Water Acid Mine Waste Fungus That Inhibit the Production of Interleukin 1-β from Induced Inflammasomes

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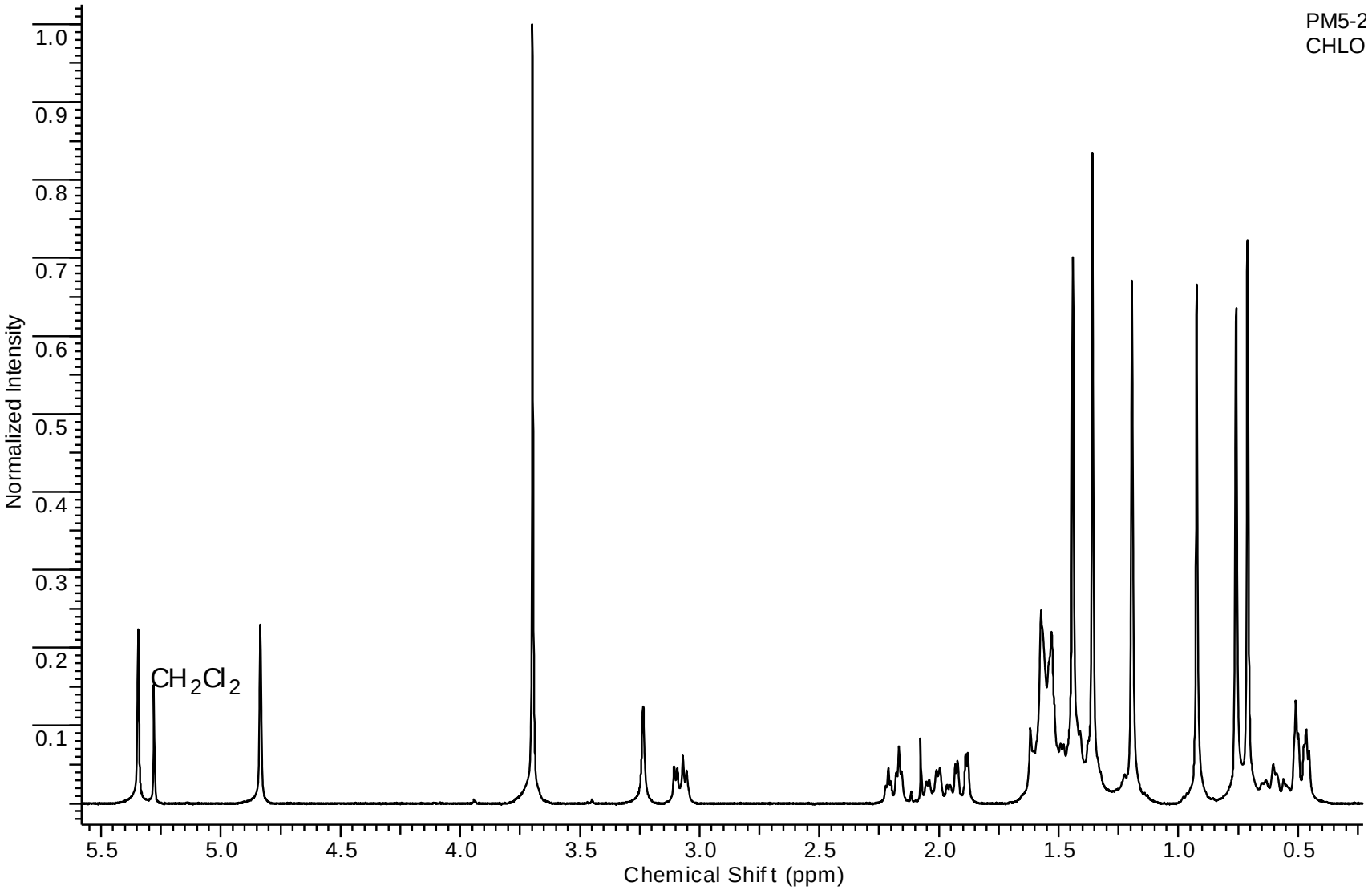
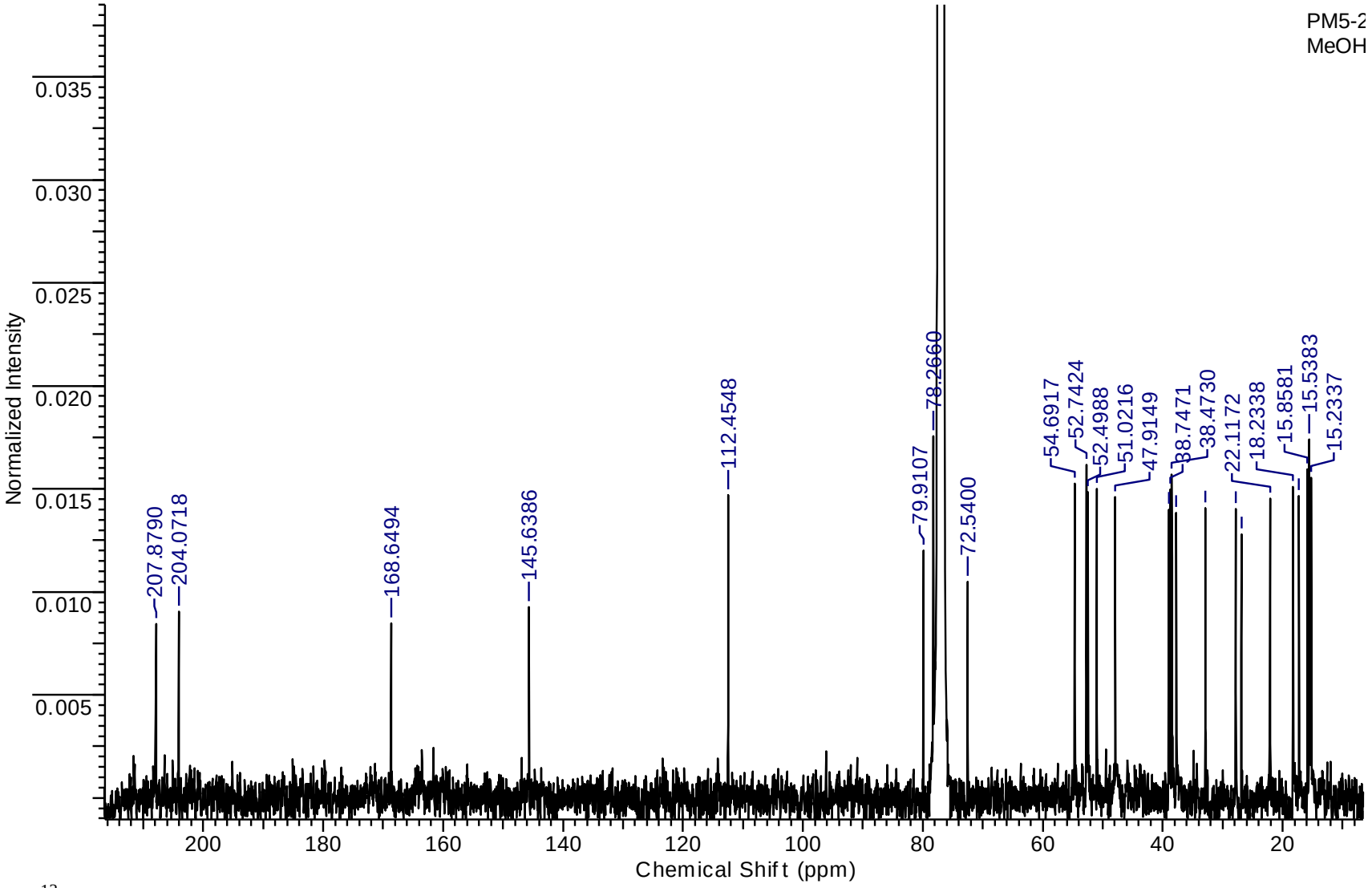
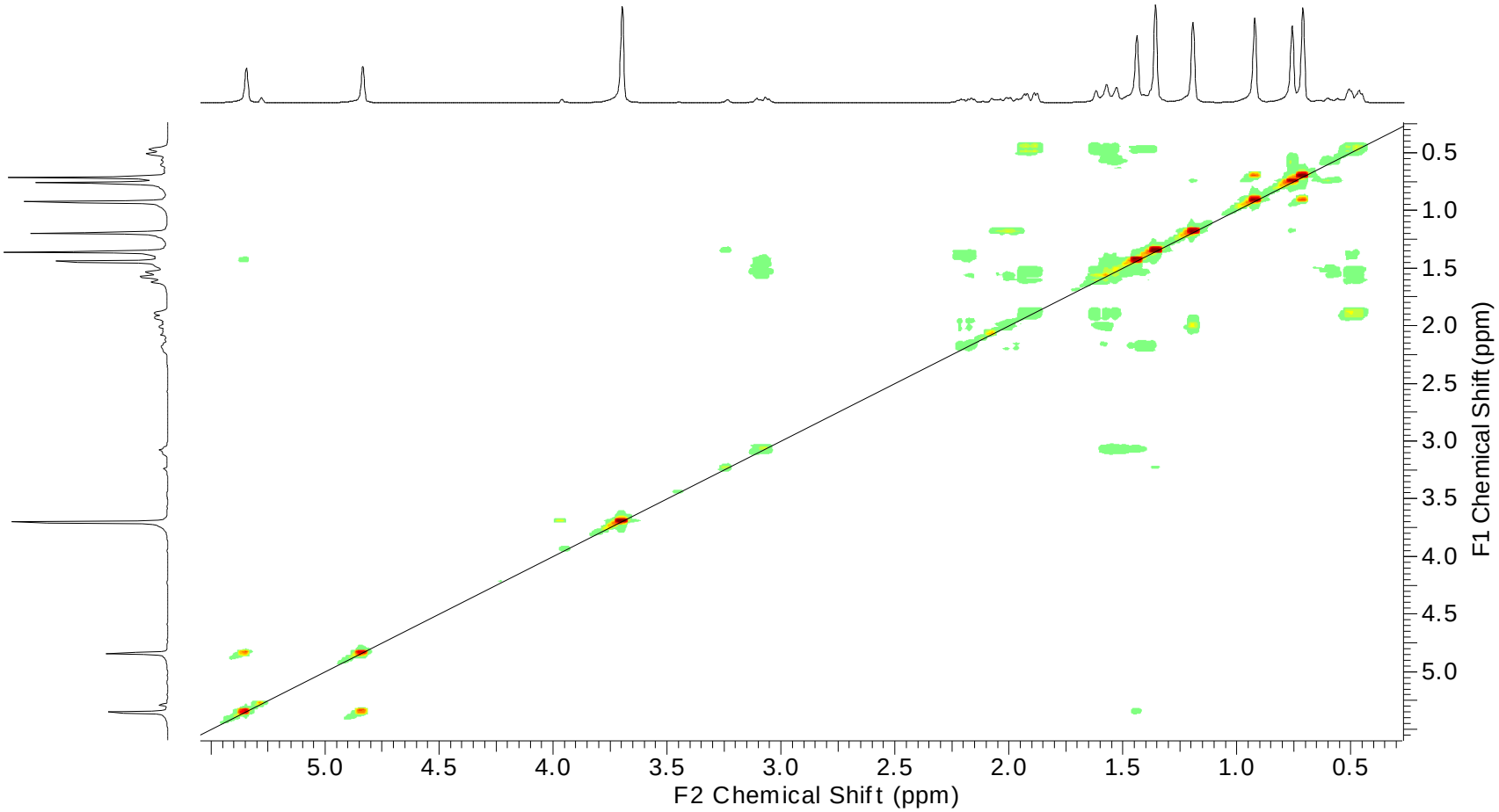


S3-^{1}H NMR of Berkeleyone A(**4**), 300 MHz, $CDCl_3$



S4- ^{13}C NMR of Berkeleyone A(**4**) , 75 MHz, $CDCl_3$



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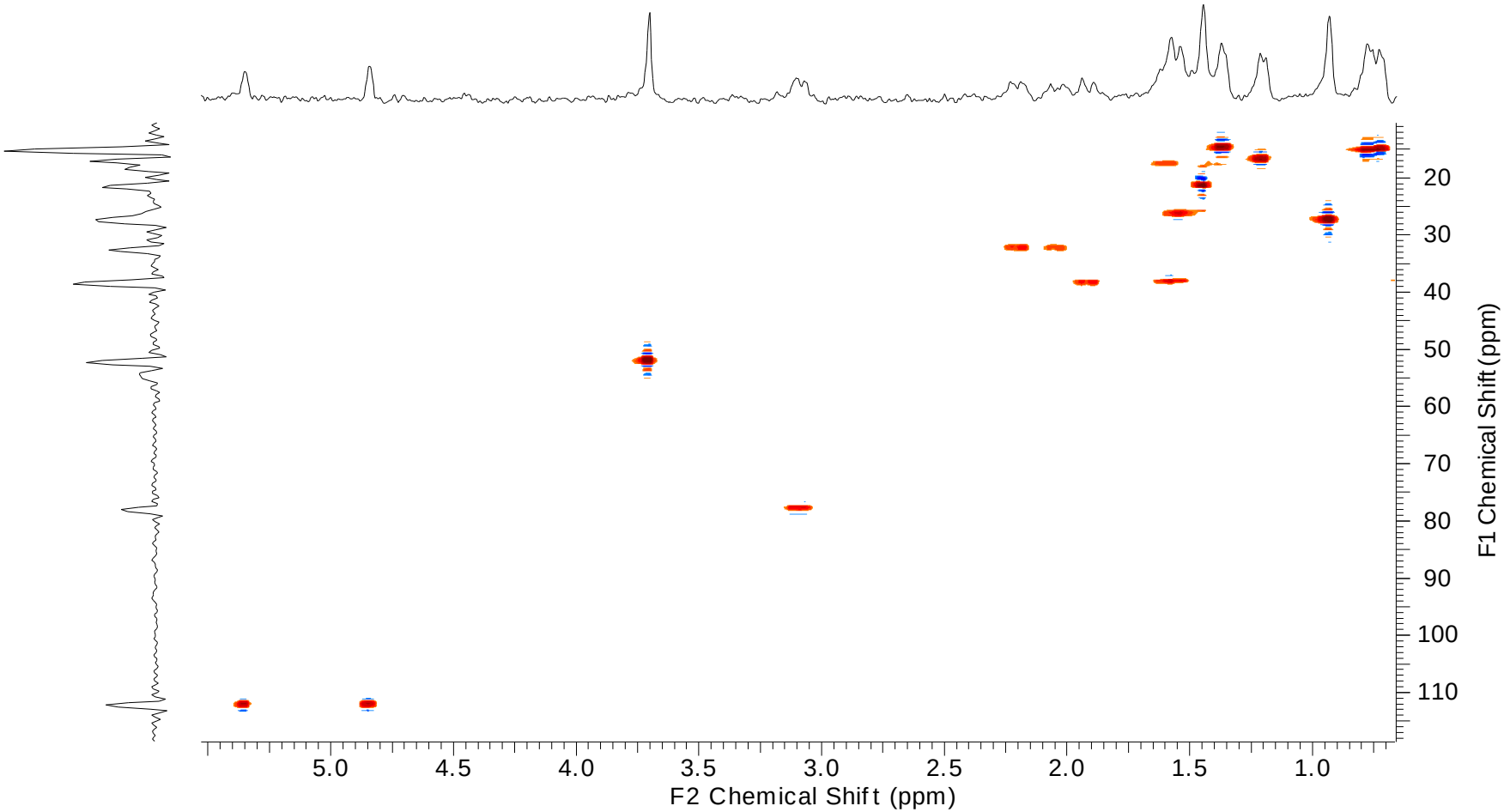
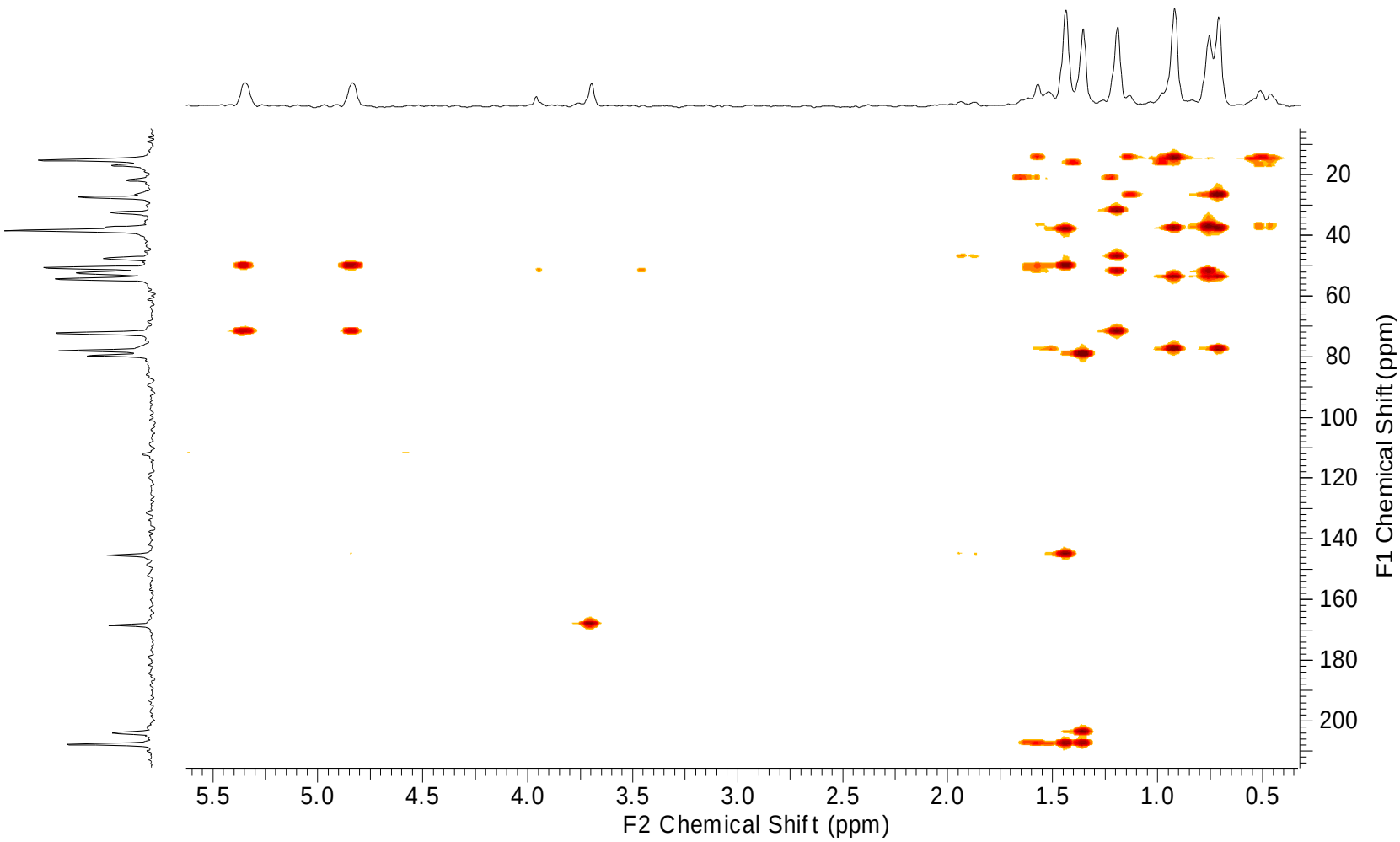
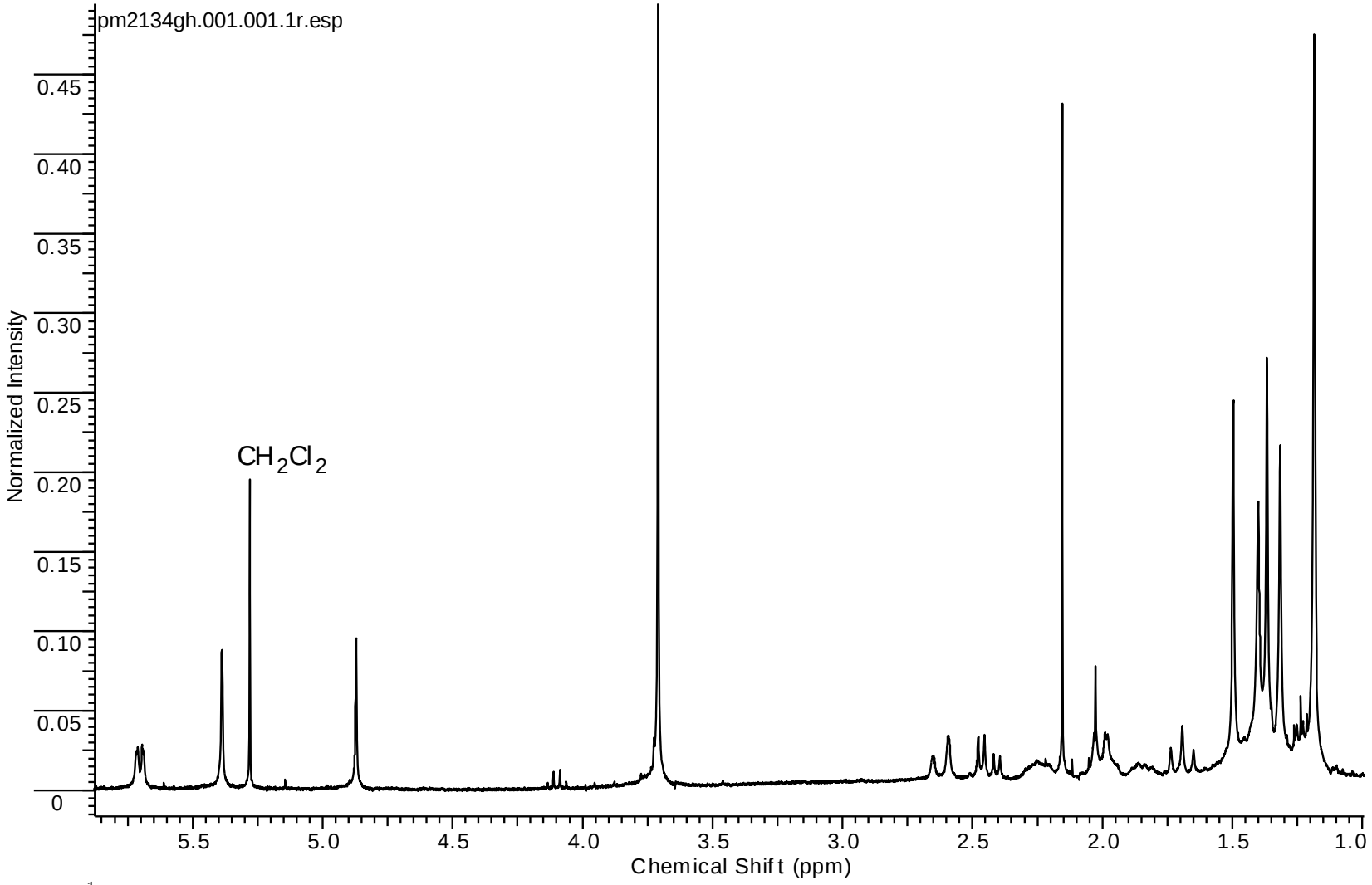


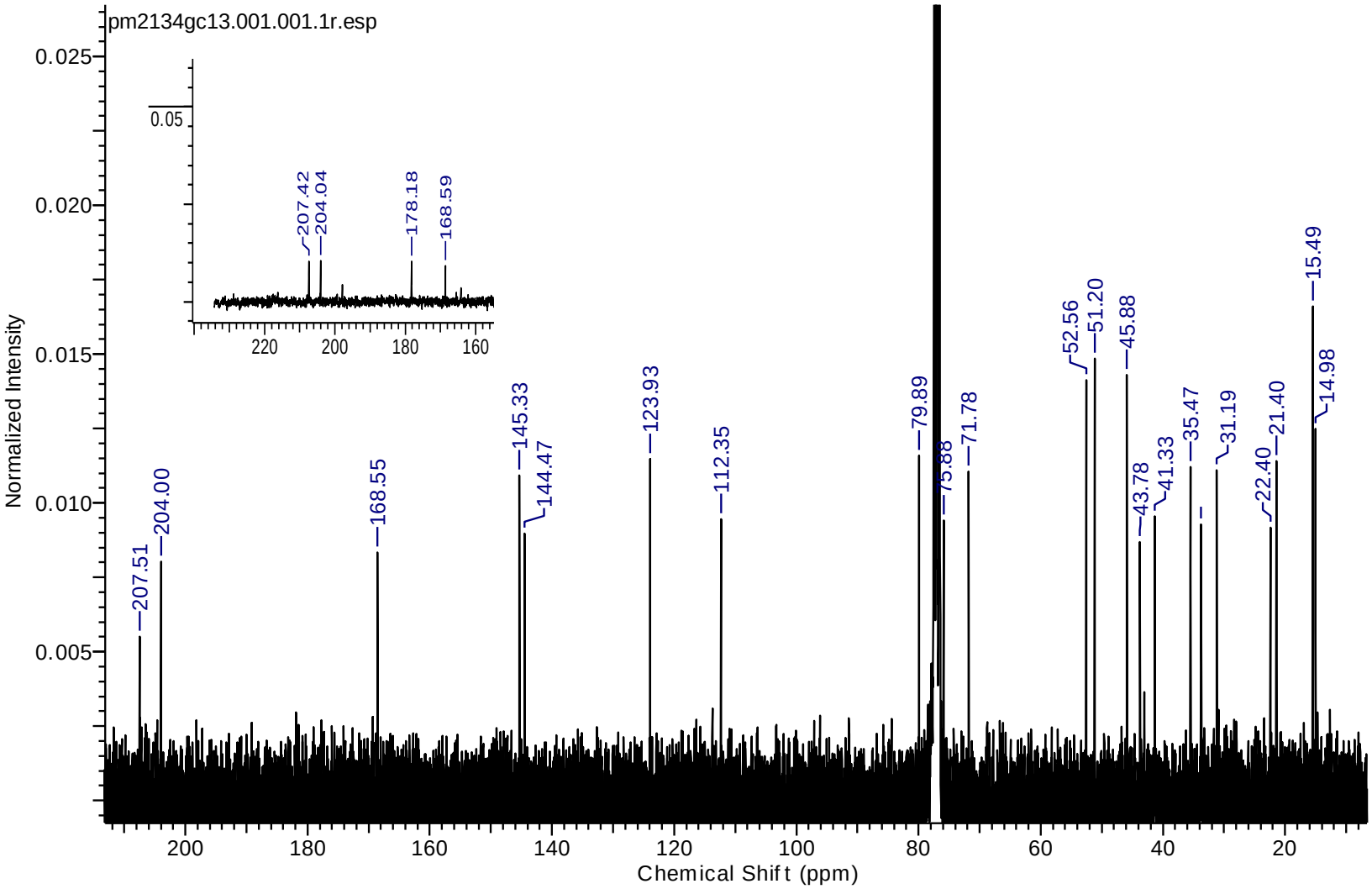
S6 HSQC of Berkeleyone A(**4**)



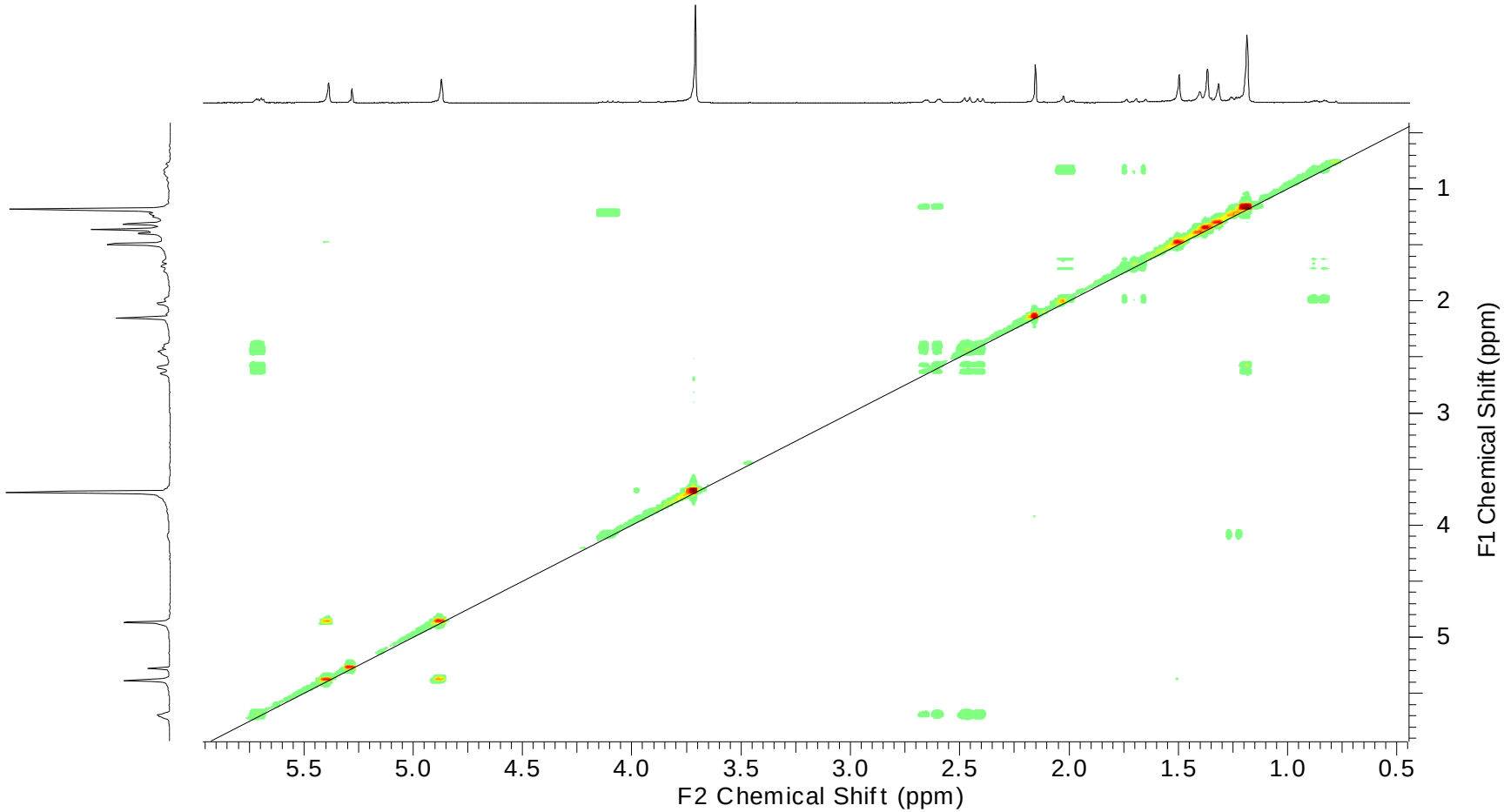
S7 HMBC of Berkeleyone A(**4**)



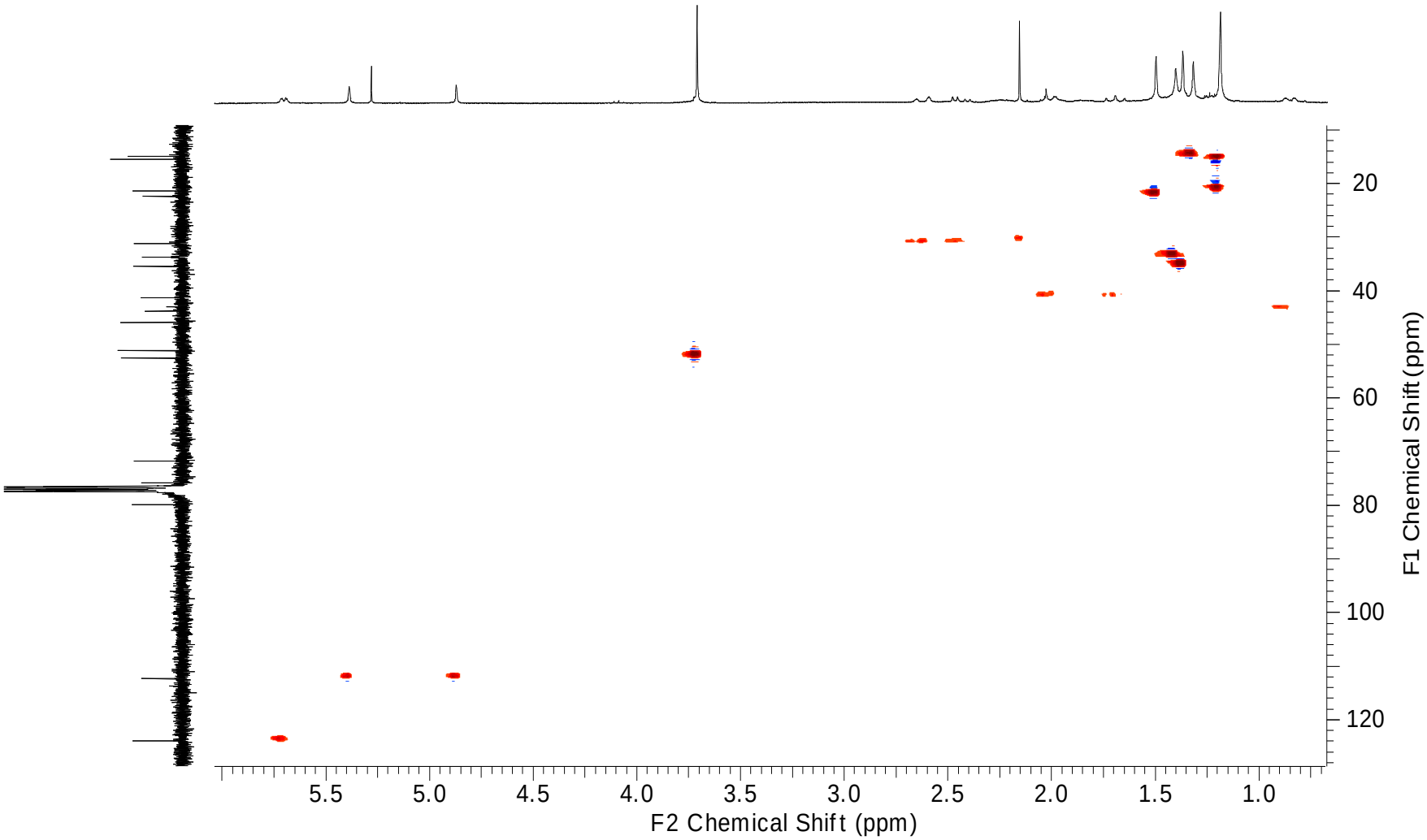
S8 ^{1}H NMR of Berkeleyone B(**5**) , 300 MHz, $CDCl_3$, CH_2Cl_2 impurity



S9- ^{13}C NMR of Berkeleyone B(**5**), 75 MHz, $CDCl_3$; inset with longer D1



S10 COSY of Berkeleyone B(**5**)



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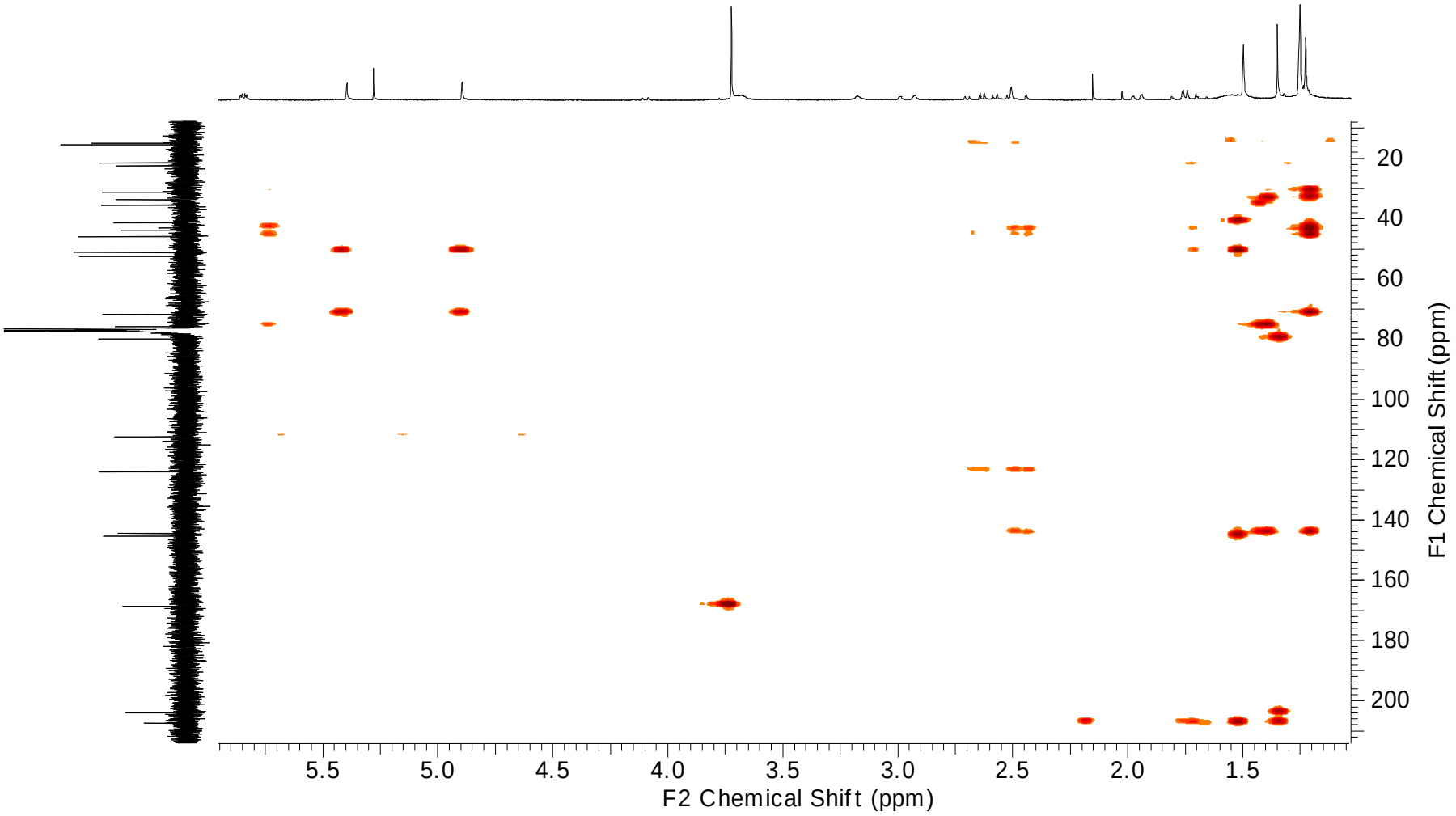

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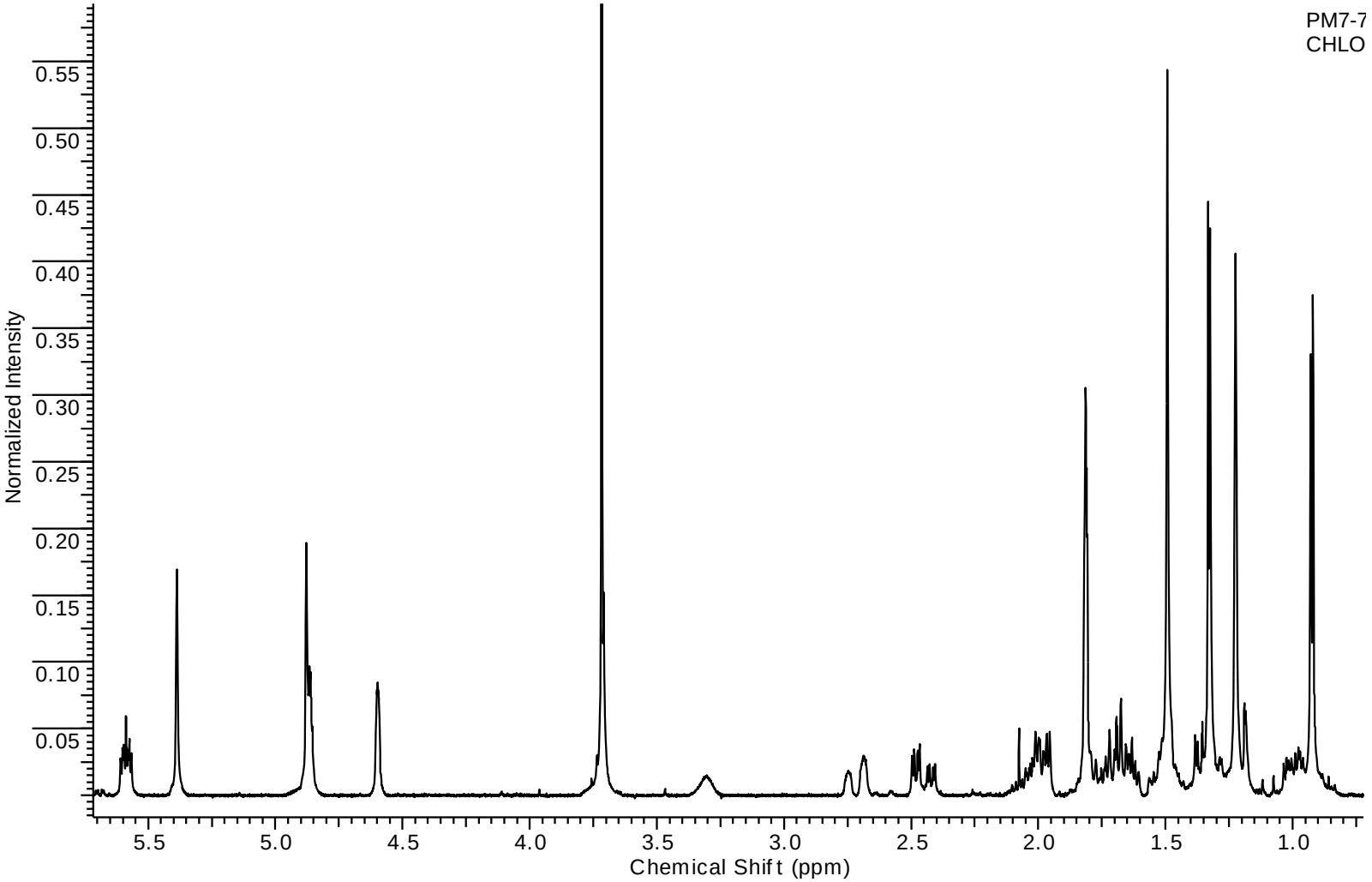
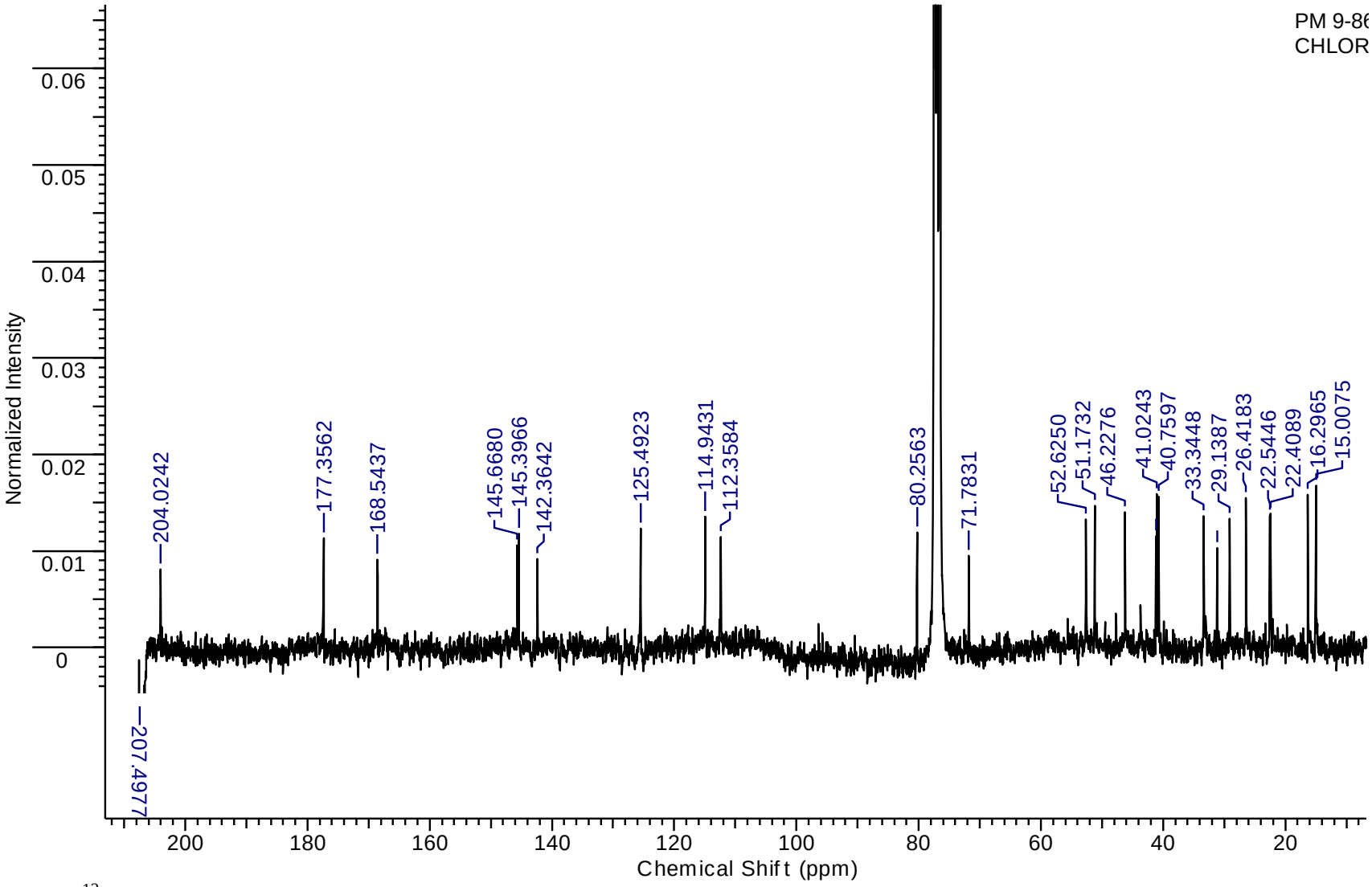
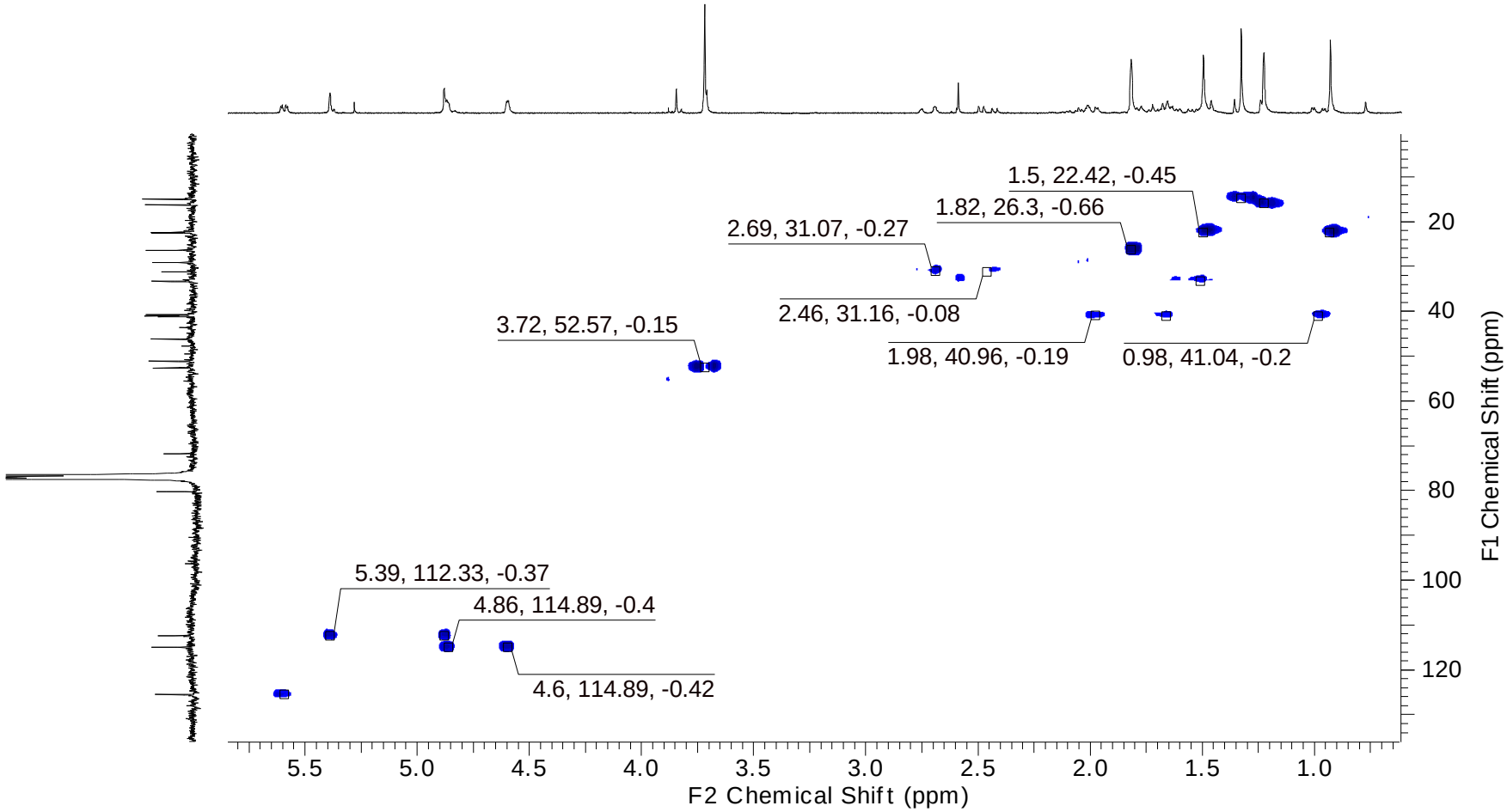


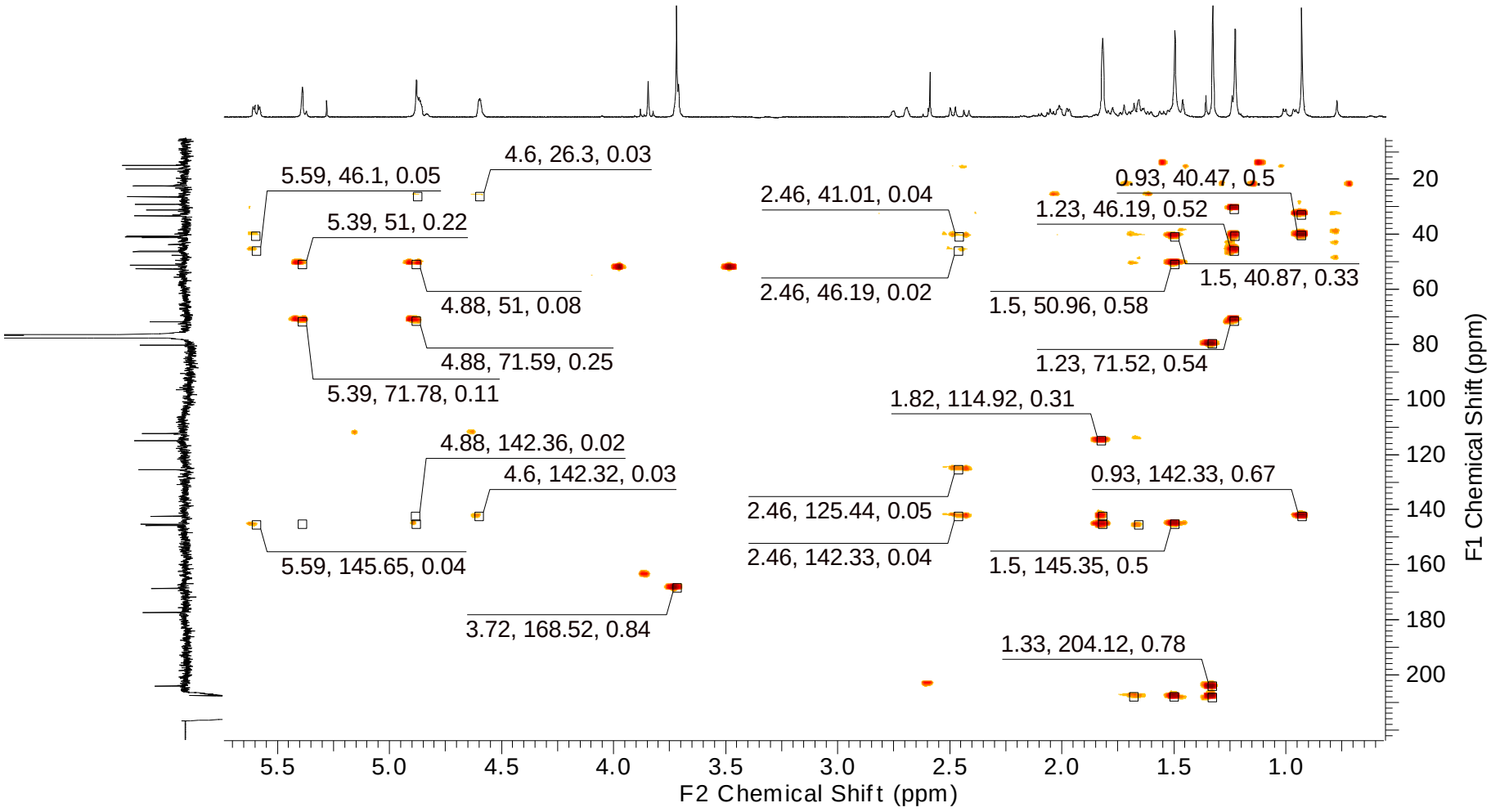
S13- ^{1}H NMR of Berkeleyone C(**7**) , 300 MHz, $CDCl_3$



S14 ^{13}C NMR of Berkeleyone C(**7**), 75 MHz, $CDCl_3$



S15 HSQC of Berkeleyone C(**7**)

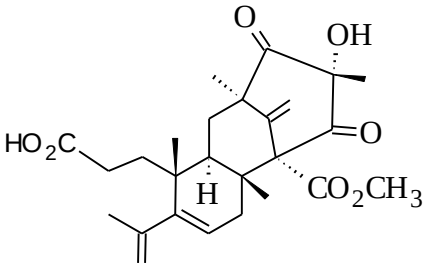


S16 HMBC of Berkeleyone C(**7**)

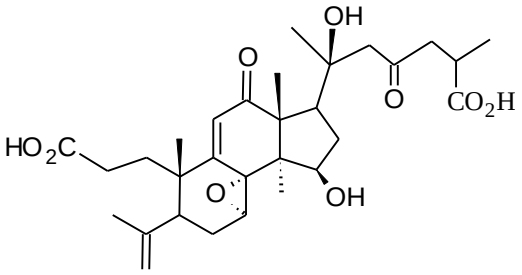
S17-Selected ^{13}C signals for berkeleyone C (**7**) and elfvingic acid H.[a]

No.	berkeleyone C (**7**)[b] δ_C	elfvingic acid H[c] δ_C
1	177.4	176.1
2	29.1	30.1
3	33.3	37.9
4	40.8	44.4
15	142.4	
16	145.4	145.6
17	26.4	23.8
18	114.9	115.5

[a] numbering system is based on the berkeleyone skeleton.
[b] recorded in $CDCl_3$.
[c] recorded in pyridine-d_5.



berkeleyone C, **7**



elfvingic acid H

S 18 Docking Studies for Compounds 1-7

Docking studies were carried out to examine the possible interactions between caspase-1 and compounds **1**-**7**. Given the substantial conformational change observed upon ligand binding,[1] the *apo* structure was not investigated for docking. A variety of wild-type *holo* crystal structures were used in an ensemble fashion in order to avoid ligand tuning. These were selected from the PDB[2] based on structural diversity of the co-crystallized ligand: 1RWX,[3] 1ICE,[4] 2HBQ,[5] 1RWK**Error! Bookmark not defined.**,[6] 1RWV, 1BMQ,[7] and 1ICE.[8] The fluorinated assay substrate control molecule Ac-YVAD-AMC was docked against the same ensemble. The top-scoring pose showed the same interactions and motif as the co-crystallized YVAD (1ICE), with the exception being the fluorescent tag, which is too large to fit into the catalytic pocket of caspase-1. The correct pose predicted a different crystal structure of caspase-1 lends support to the predictive capabilities of the ensemble methodology.

Analysis of the top scoring clusters of poses across the family suggests a common site of potential binding. The berkeleydione analog sets are very conformationally restrained, and cannot access the catalytic pocket when static docking structures are used. However, there is substantial opportunity for interactions along the active site groove and at the opening of the catalytic site. Docked analogs interact primarily with His237 and Arg341 of the active site, and other residues along the groove (such as Val288, Ser339, or lipophilic interactions with Trp340 and Val338). Binding motifs were examined for compounds **1**-**7**, including both enantiomers of berkeleydione. Figure 1A (manuscript) demonstrates such binding motifs, of berkeleydione (configuration shown) and

preaustinoid A. Both of these poses represent the collection of top scoring poses, which form interactions along the groove and at the opening to the catalytic site.

Several poses also existed along the active site groove in a region occupied by the Tyr of YVAD (as shown in Figure 1B). While this would not directly inhibit the catalytic site, binding in this region could prevent the binding of the native substrate, which would occupy the same space during the enzymatic activity. This pocket is also rich in binding opportunities. Figure 1B demonstrates the enantiomeric configuration of berkeleydione making contacts with Arg352, Arg383, and lipophilic contacts with Val348, Phe377, and Arg383.

Ligands were also docked to the crystal structure of caspase-1 bound to an allosteric inhibitor to explore potential binding modes to the allosteric site (PDB: 2FQQ).[4] Generally speaking, more poses were returned at the active site, with higher fitness scores and greater energies of interaction (hydrogen bonding and van der waal's) than at the allosteric site. Only two analogs returned ten poses at the allosteric site, while the other five returned three or fewer. At the active site, two analogs returned fewer than five poses, while the remaining five found at least 10 possible poses of positive interaction. The top ranked poses for all analogs were lower at the allosteric site than at the active site. This suggests that the crystallographic structure of the active-site bound ligand presents more positive binding opportunities to the berkeleyone family than the allosteric-bound *holo* structure.

A soft scoring potential was also explored in the ensemble docking exercise in an attempt to account for residue flexibility. While this yielded poses with higher scores -

often in the catalytic pocket, we felt this did not represent the binding potential any better than the static receptor case, given the degree of ligand-protein interpenetration.

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