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HIV-1 MATURATION INHIBITORS DISRUPT CA-SP1-NC GAG JUNCTION DYNAMICS

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PHARMACIE

Santé

Université Paris Cité

ABSTRACT

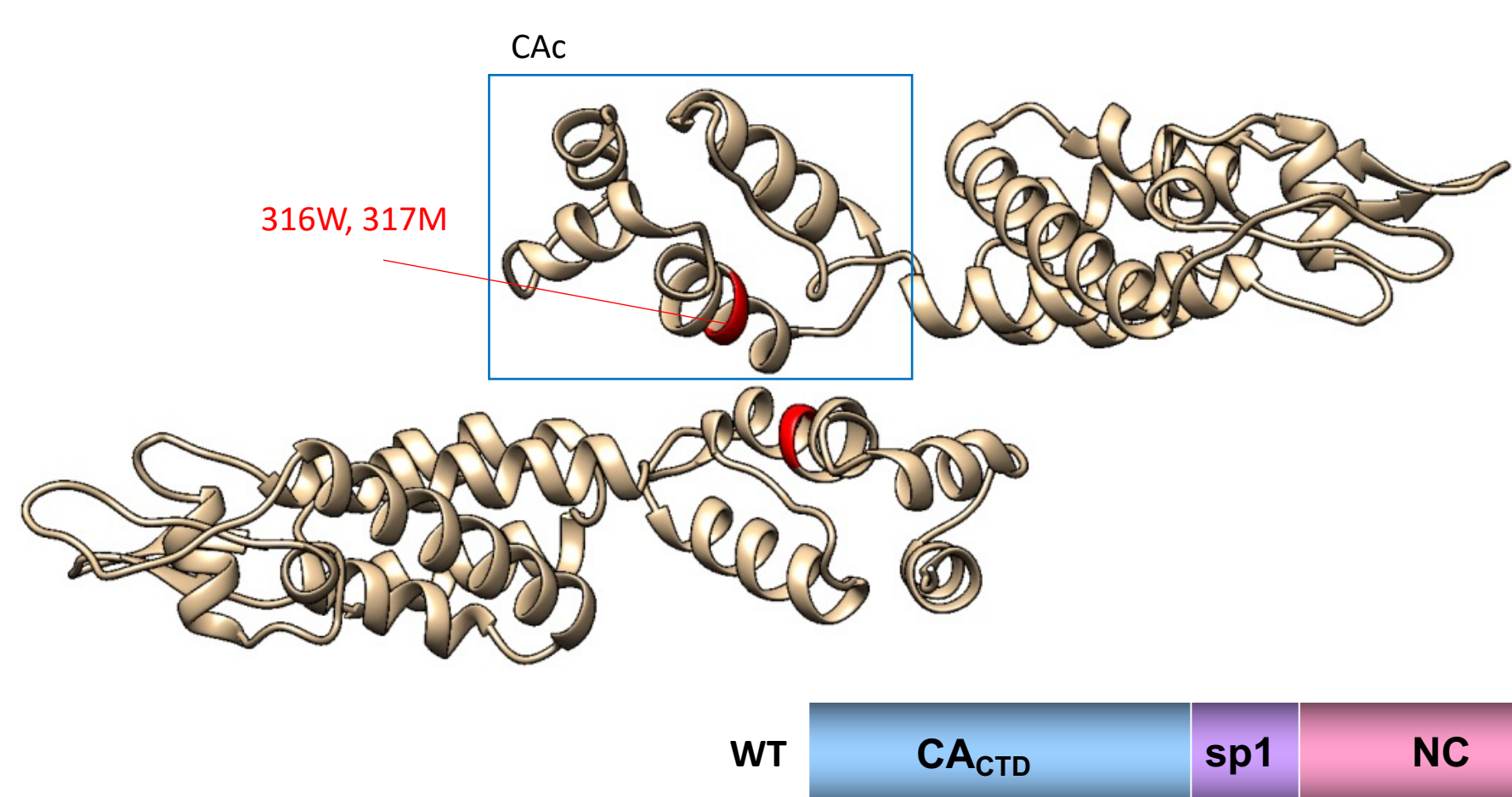
During maturation of the HIV-1 particle, the Gag polyprotein is cleaved into several proteins by the HIV-1 protease (1, 2). After cleavage, the proteins reorganize to form infectious viral particles. The CA-SP1-NC junction in the flexible domain is in dynamic coil-helix equilibrium (3) and final cleavage between CA and SP1 can be blocked by maturation inhibitors (4, 5). Despite recent studies, the mode of interaction between CA-SP1 and maturation inhibitors remains unclear (6). In this study, the solution structure and dynamics of a monomeric domain encompassing the C-terminal of the capsid, the spacer peptide SP1 and the Gag nucleocapsid were characterized by nuclear magnetic resonance in the presence of different maturation inhibitors. We show that although the structure of these inhibitors is different, their action is the same on the dynamics of the CA-SP1-NC junction, notably the QVT motif in SP1. These inhibitors disrupt the natural coil-helix equilibrium on either side of the SP1 domain by stabilizing the transient alpha helical structure (7). Our results provide new insights into the structure and dynamics of the SP1 domain and how HIV-1 maturation inhibitors interfere with this domain. They offer additional avenues for the development of new generation inhibitors targeting HIV-1 maturation.

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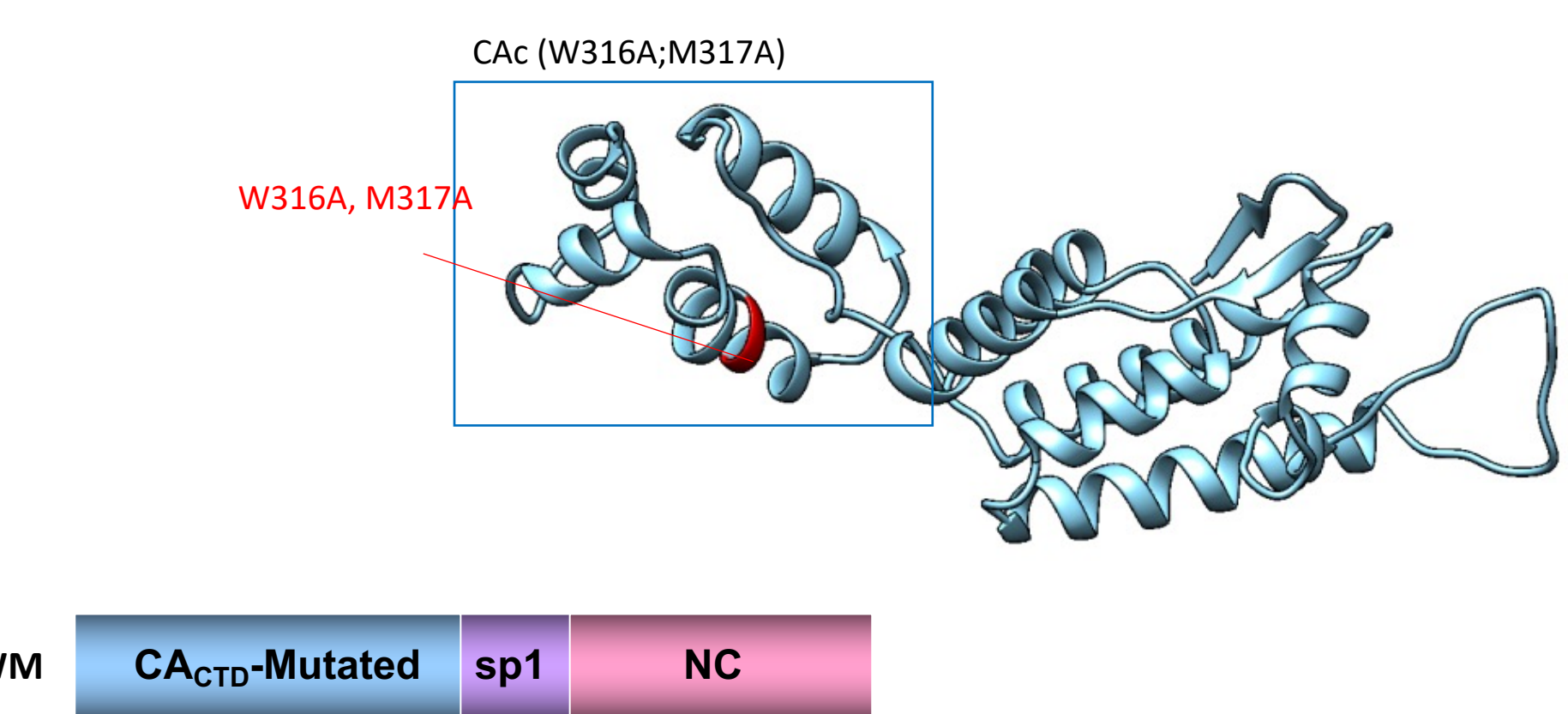
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WILD AND MUTATED CA_{CTD}SP1NC

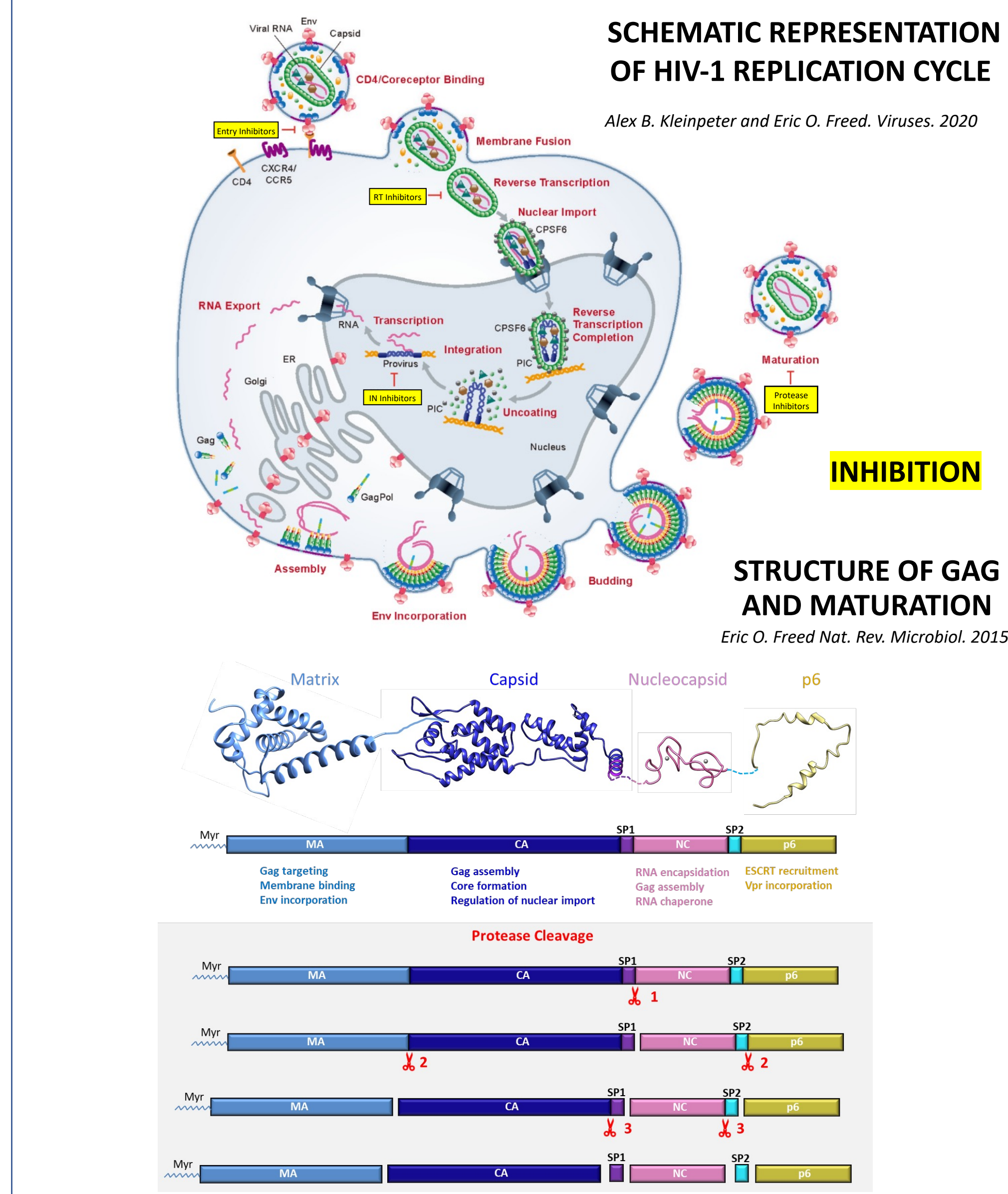
HIV capsid dimer 2M8L Deshmush. L et al. 2013



HIV capsid (W316A, M317A) 2M8P Deshmush. L et al. 2013

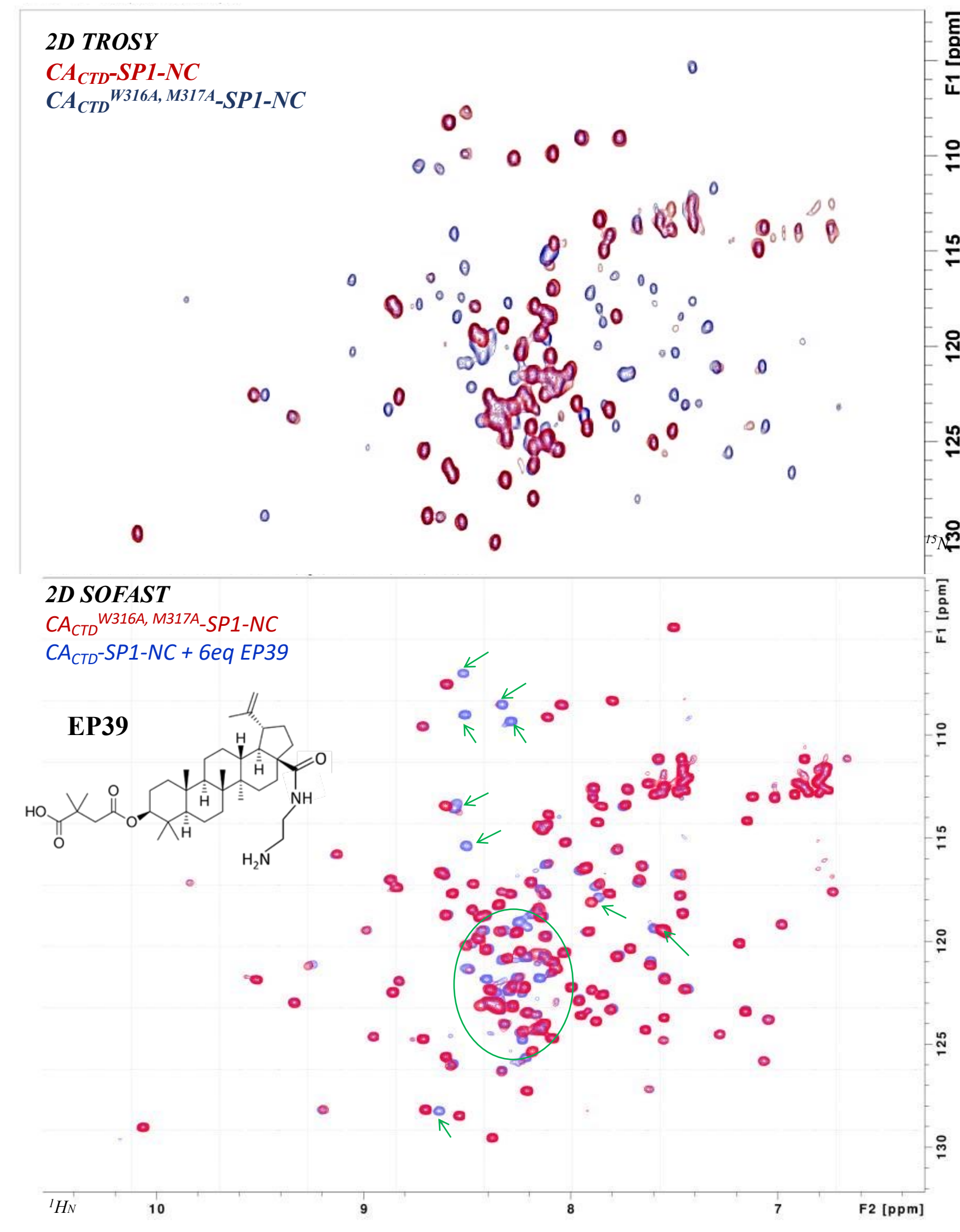


Crystal structure of CA in monomeric form, CANTD in blue, CACTD in orange (PDB ID 2M8N) [6]; solution NMR structure of dimeric CA (code PDB 2M8L).

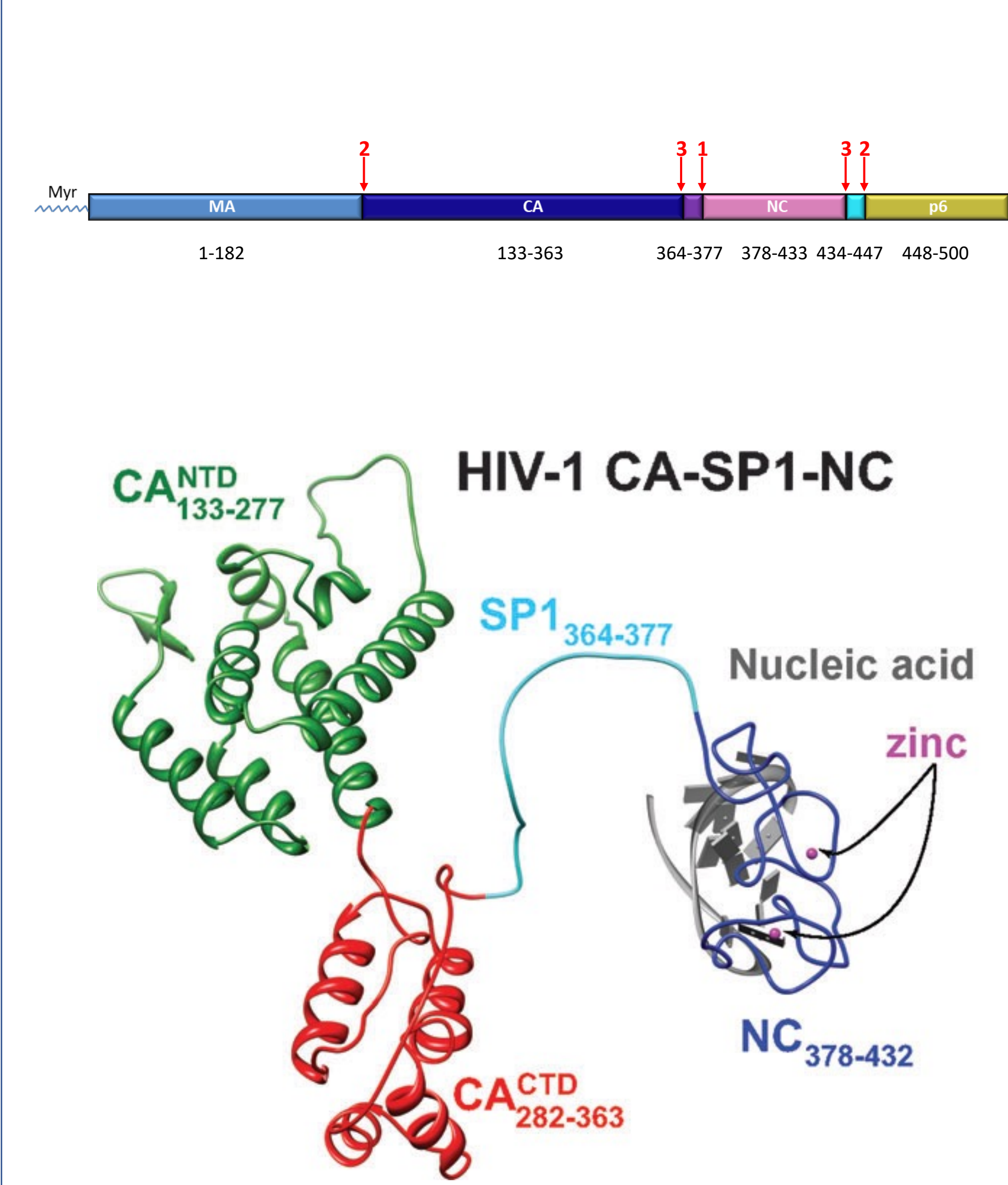


CHEMICAL SHIFT PERTURBATIONS ON WILD AND MUTATED CA_{CTD}SP1NC

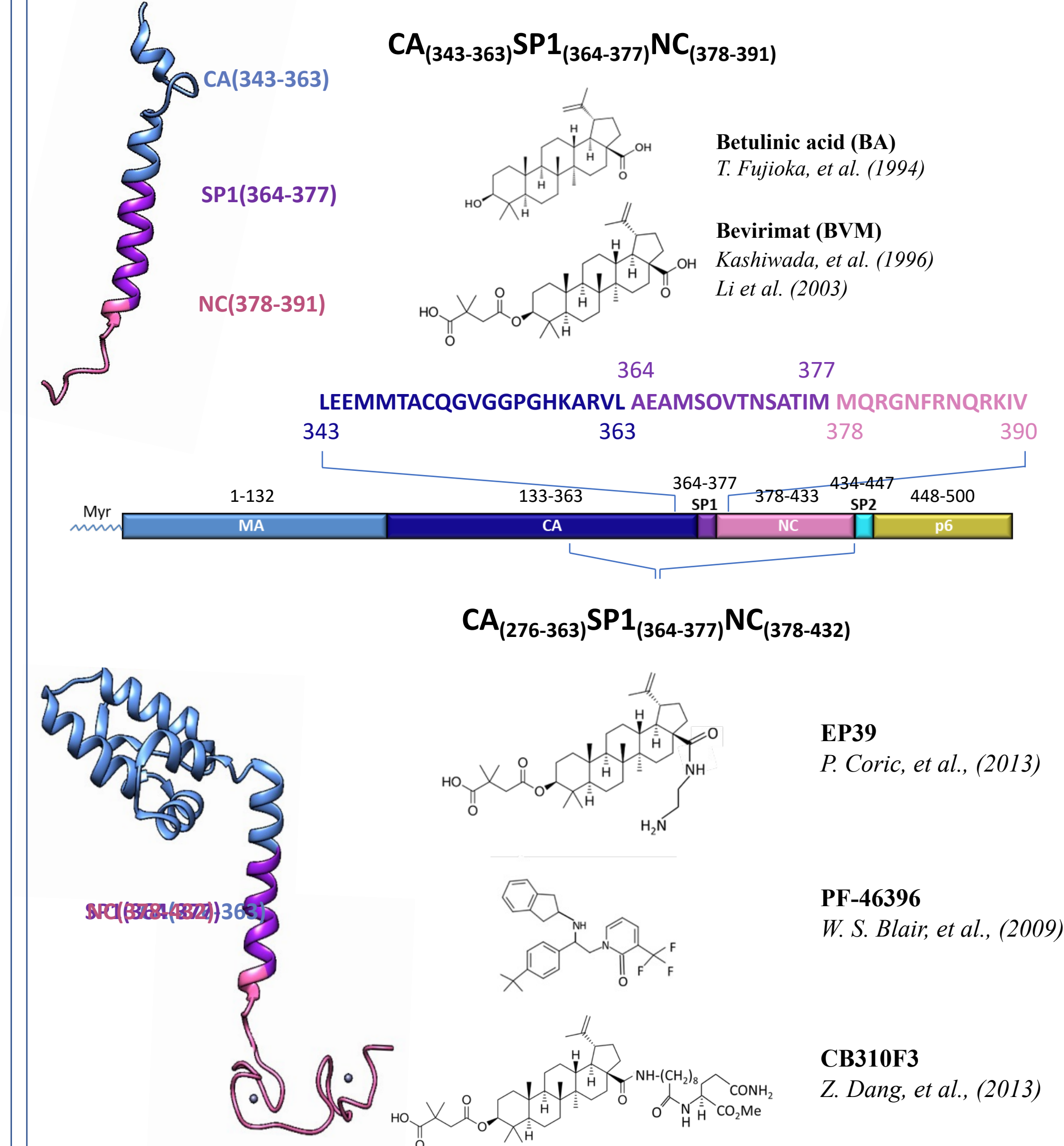
WT and WM with same concentration in Acetate buffer (25mM NaAc, pH 6.5, 25mM NaCl, 0.1mM ZnCl₂, 0.1mM BME)



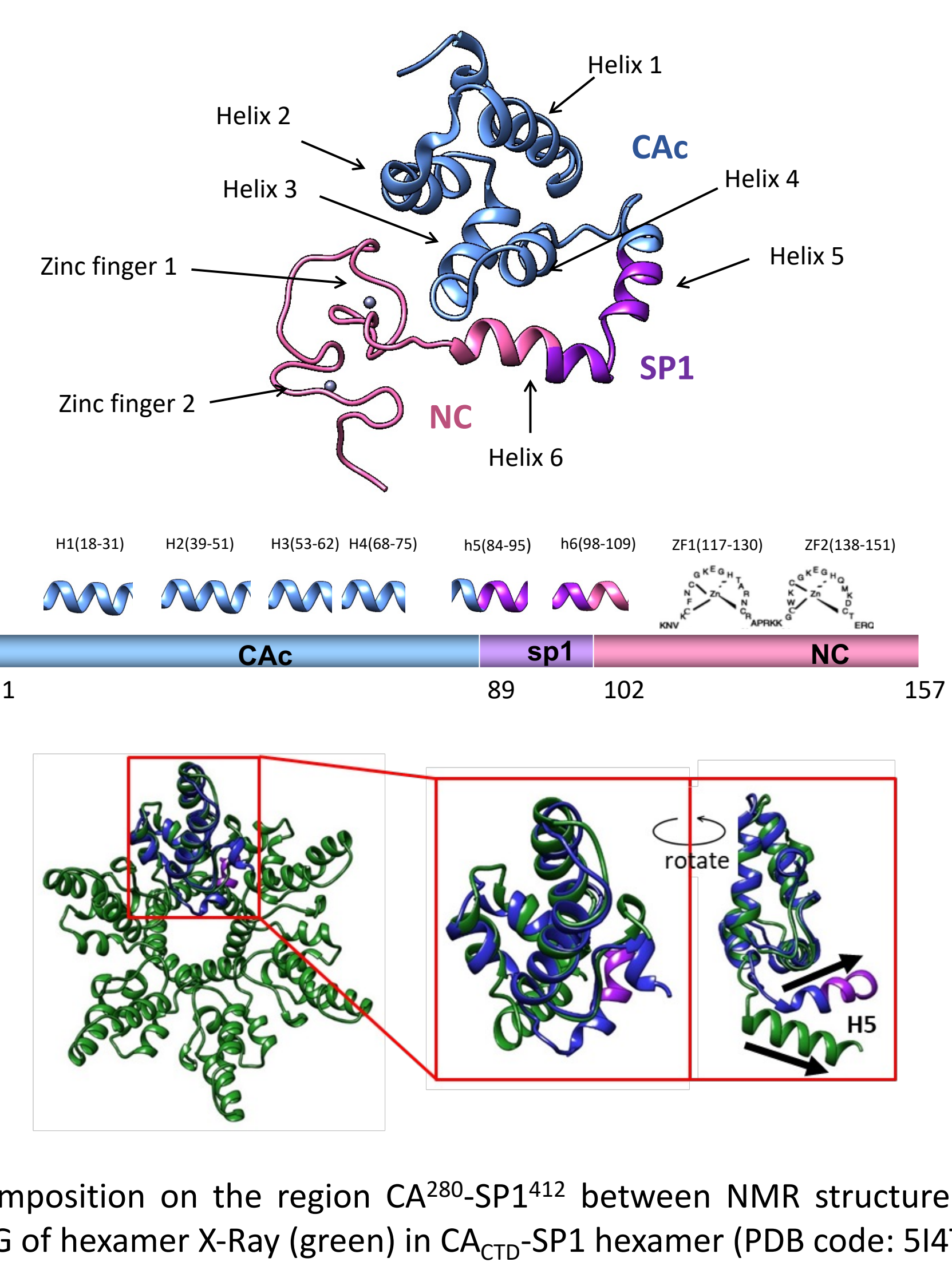
STRUCTURAL STUDIES OF THE SP1 DOMAIN ARE NECESSARY



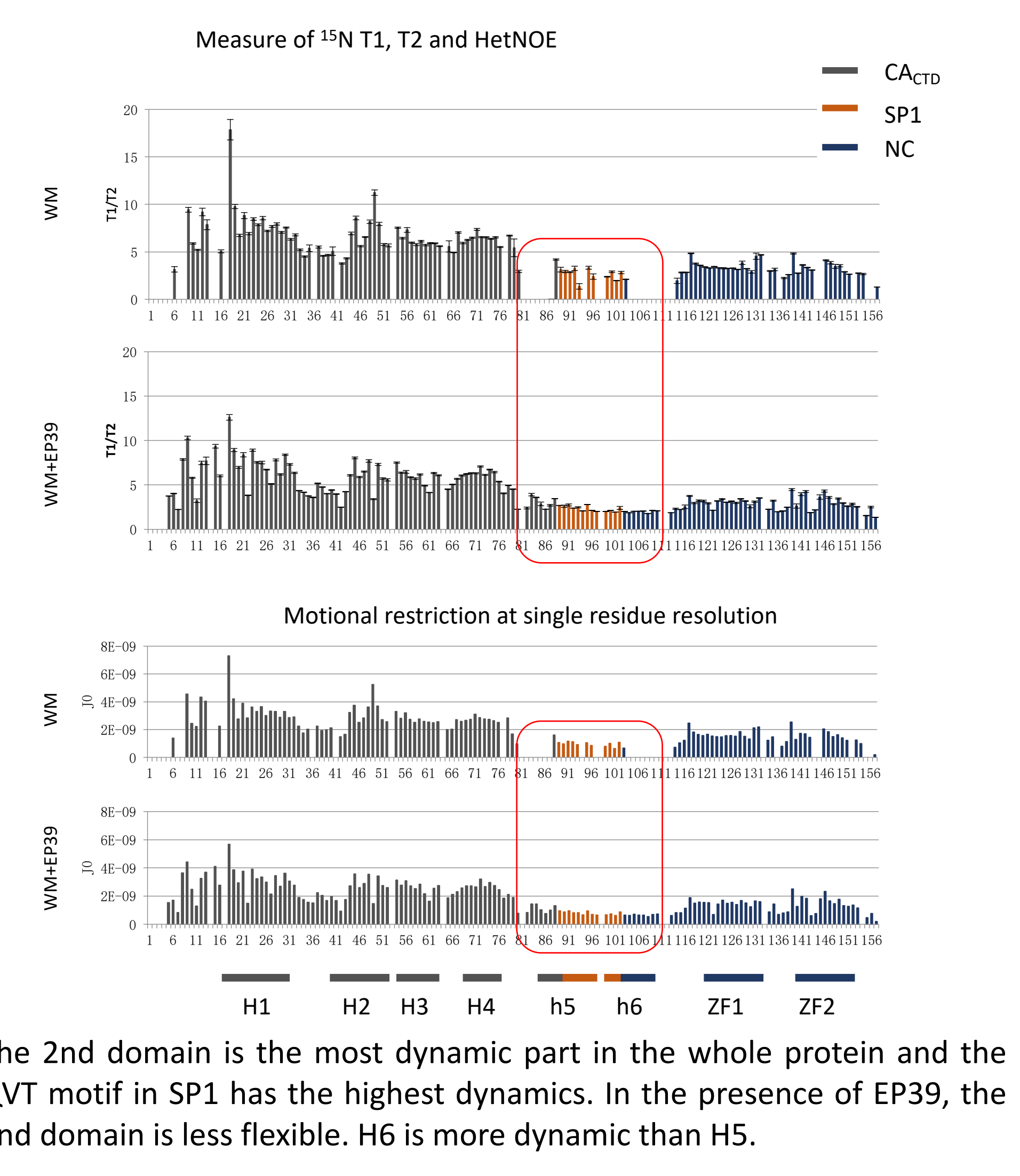
STRUCTURAL STUDIES OF SP1 CONTAINING DOMAINS



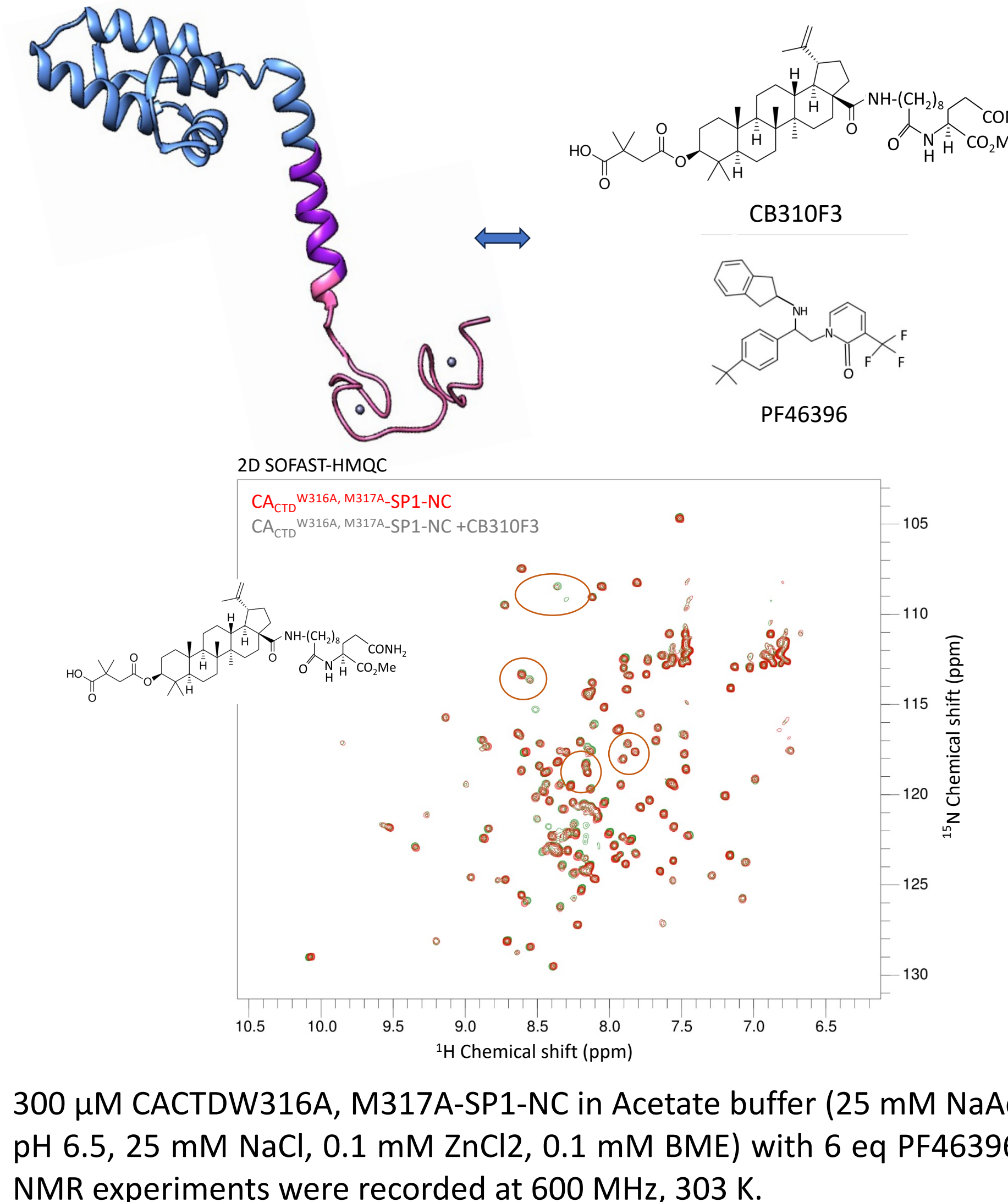
NMR STRUCTURE OF CACSP1NC IN PRESENCE OF EP39 CONTAINS 6 ALPHA HELICES AND 2 ZINC FINGERS



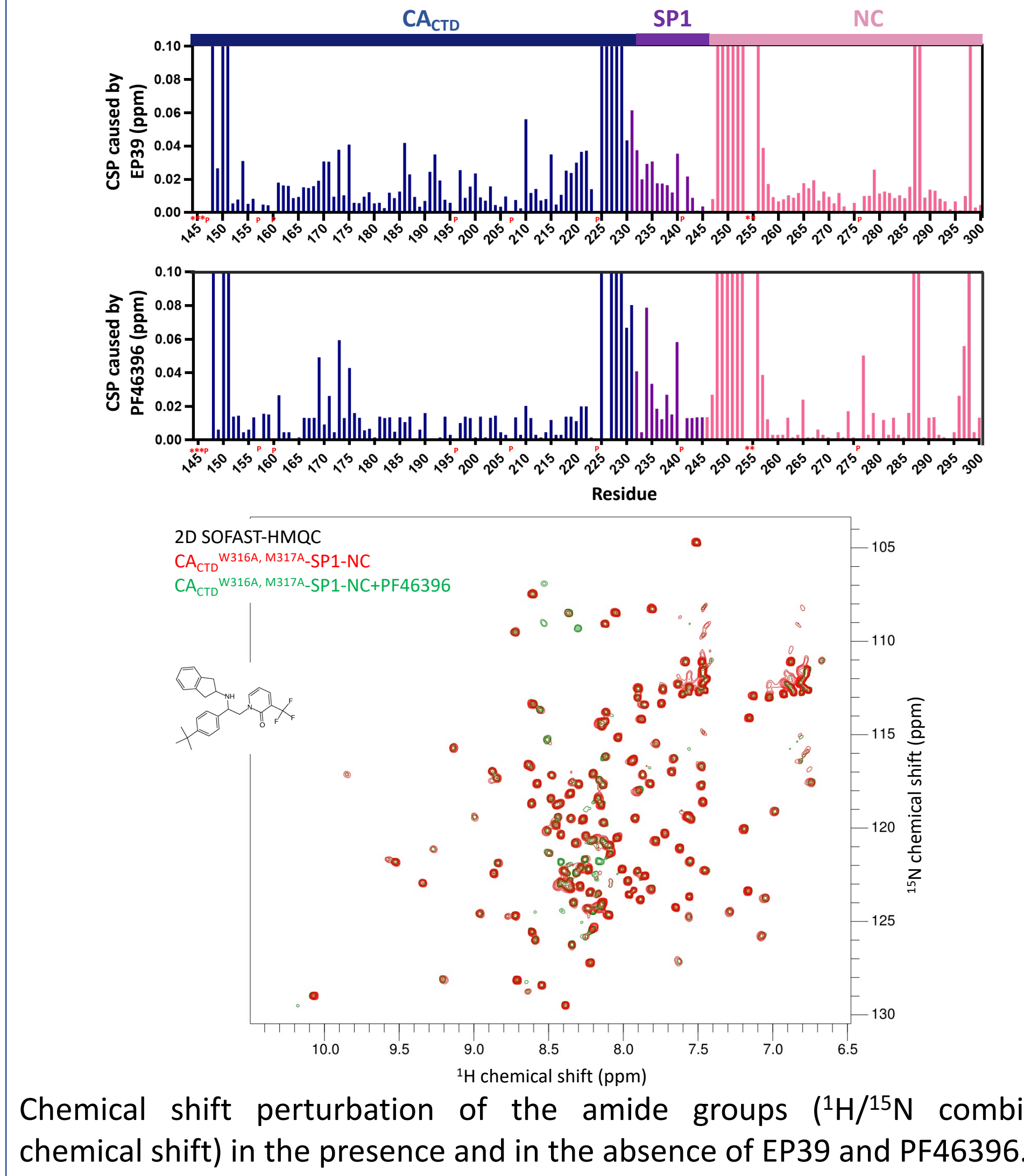
DYNAMICS CHARACTERIZATION OF CA_{CTD}W316A,M317A-SP1-NC IN THE ABSENCE AND PRESENCE OF 6 EQ EP39



STUDY OF THE 2ND GENERATION HIV-1 MATURATION INHIBITORS



PF46396 DECREASES THE DYNAMICS OF SP1 DOMAIN SIMILARLY TO EP39



CONCLUSIONS

- EP39 interacts with the protein firstly at the QVT motif and stabilizes the SP1 domain.
- EP39 binding interferes with the dynamic helix-coil equilibrium of the CA-SP1 junction.
- Due to the low solubility and low affinity of EP39, we failed in building the structure of the complex. So, a new inhibitor with higher affinity to protein CA_{CTD}W316A,M317A-SP1-NC is necessary.
- CB310F3 does not seem to interact with protein CA_{CTD}W316A,M317A-SP1-NC.
- PF46396 stabilizes the SP1 domain in a less efficient way compared to EP39, even they have different structures.
- The structure of the inhibitors seems to be less important than their stabilizing effect.
- The structure and the stabilizing effect of inhibitors should all be considered for the development of new inhibitors.

PERSPECTIVES

- In the future work, it is important to get a new inhibitor that has higher affinity to SP1 domain.
- Synthesize new inhibitors by modifying EP39 to get a higher affinity to protein CA_{CTD}W316A,M317A-SP1-NC compared to EP39.
- Decipher the complex structure of the new inhibitor and N15/C13 labeled CA_{CTD}W316A,M317A-SP1-NC by NMR.
- With the structure of the complex, we can improve the structure of inhibitors.

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