Supporting Information for:

A combined crystallographic and molecular dynamics study of cathepsin L retro-binding inhibitors

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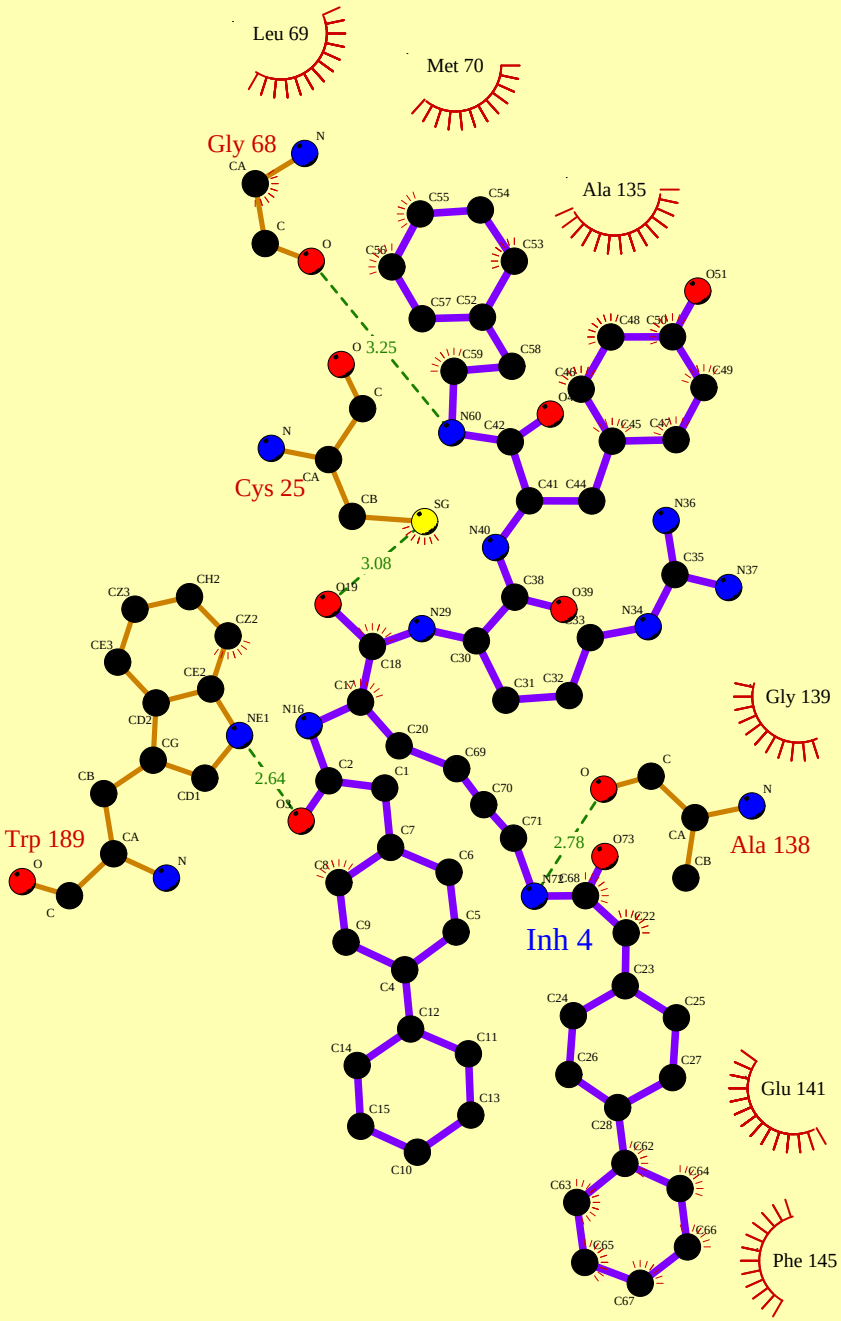
Contents:

(A)

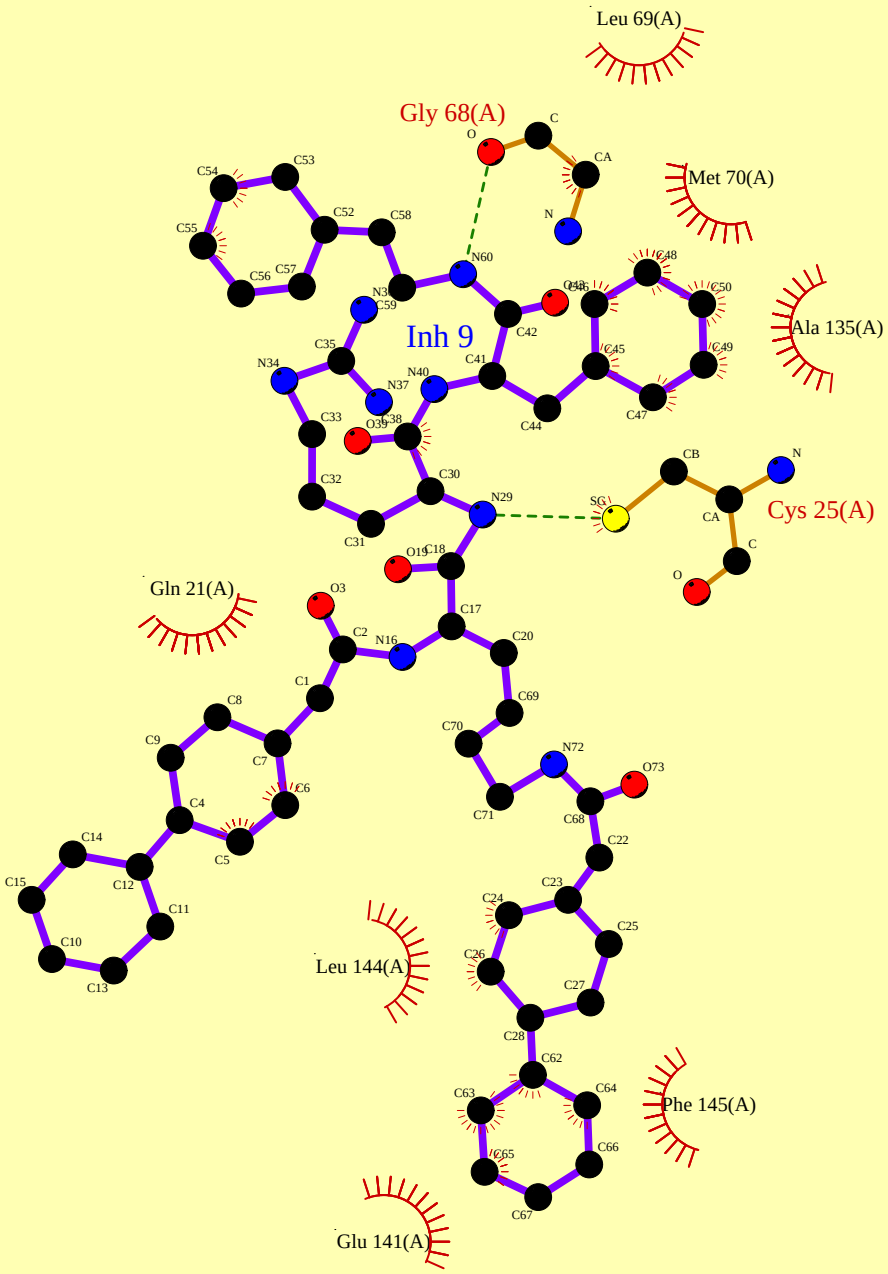


Key

- Ligand bond
- Non-ligand bond
- Hydrogen bond and its length
- His 53 — Non-ligand residues involved in hydrophobic contact(s)
- Corresponding atoms involved in hydrophobic contact(s)

Inhibitor 4

(B)

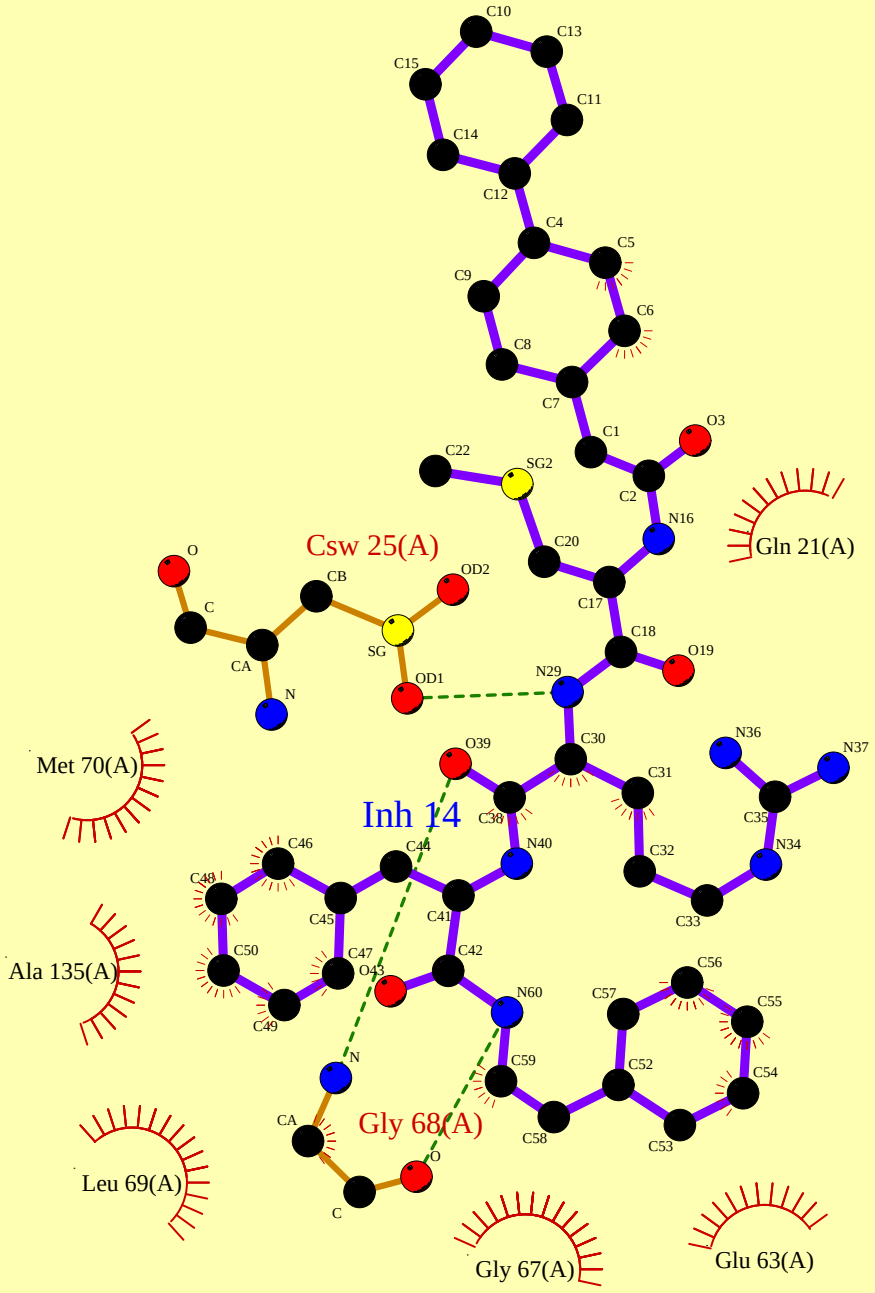


Key

- Ligand bond
- Non-ligand bond
- Hydrogen bond (3.0)
- His 53 — Non-ligand residues involved in hydrophobic contact(s)
- Corresponding atoms involved in hydrophobic contact(s)

Inhibitor 9

(C)



Key

Ligand bond

Non-ligand bond

3.0 Hydrogen bond

His 53 Non-ligand residues involved in hydrophobic contact(s)

Corresponding atoms involved in hydrophobic contact(s)

Inhibitor 14

Figure S1. Schematic view of cathepsin L – inhibitor interactions for **(a)** cathepsin L with inhibitor **4**, **(b)** cathepsin L with inhibitor **9** and **(c)** cathepsin L with inhibitor **14**. Hydrogen bonds between cathepsin L and the inhibitors (less than or equal to 3.2 Å) are indicated by broken lines. These figures were prepared with the program LIGPLOT.[1]

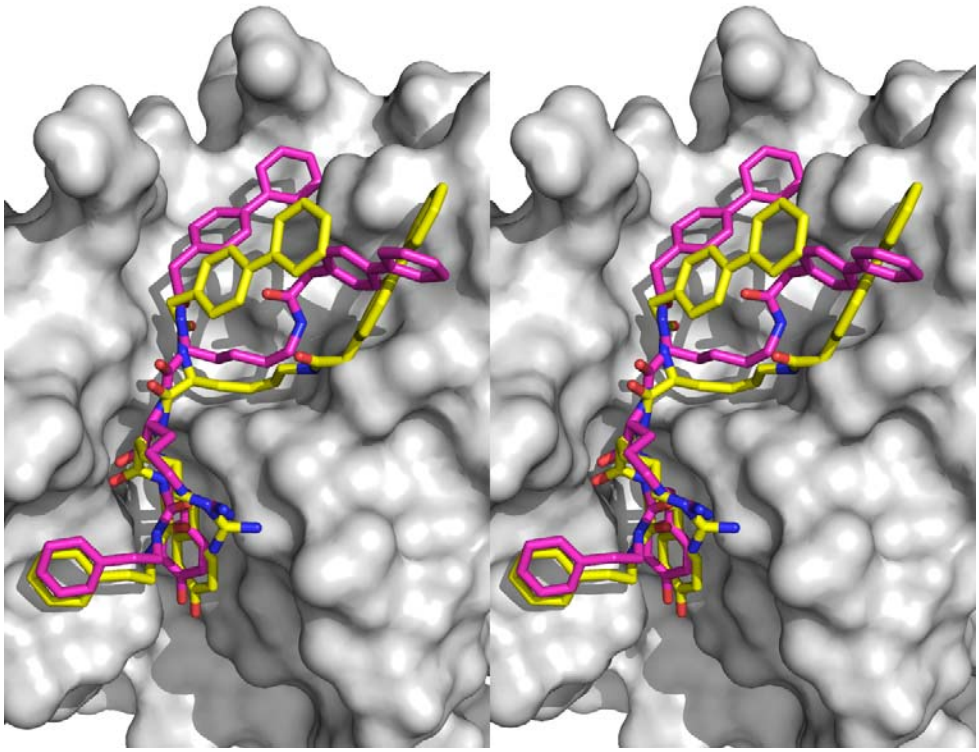


Figure S2. Stereo view of superposition of an MD snapshot of inhibitor **4** and the crystal structure binding mode. The magenta-colored carbon chains correspond to the MD snapshot.

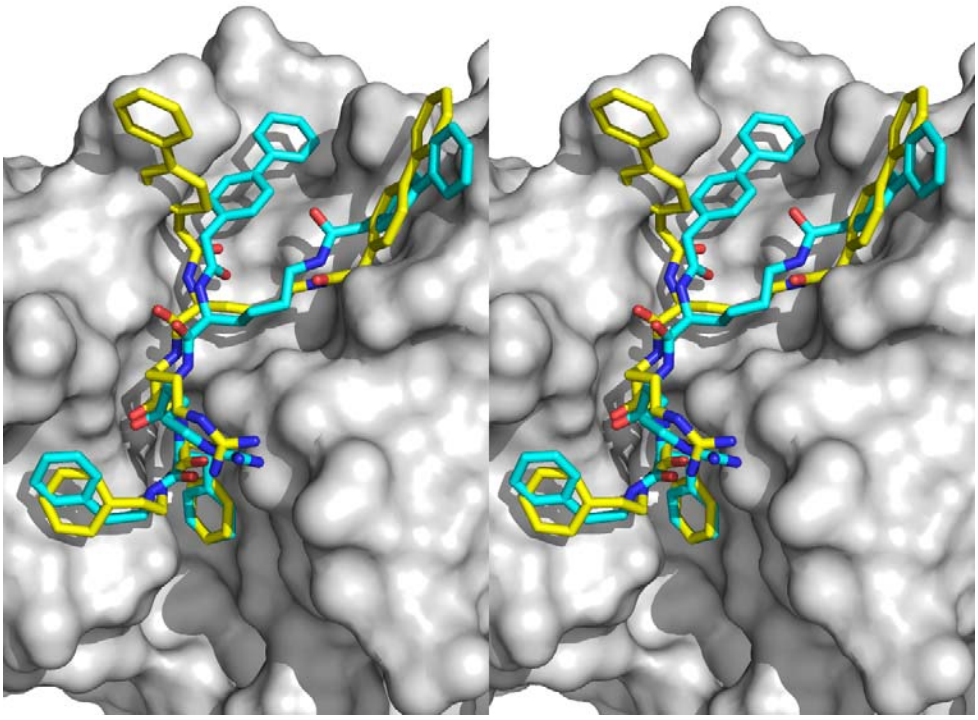


Figure S3. Stereo view of superposition of an MD snapshot of inhibitor **9** and the crystal structure binding mode. The cyan-colored carbon chains correspond to the MD snapshot.

Figure S4. Intentionally left blank.

Figures S5 to S7 below are based on a duplicate MD simulation carried out to verify the reproducibility of the results from the original MD run. They are the equivalent of Figures 5 to 7 in the main text.

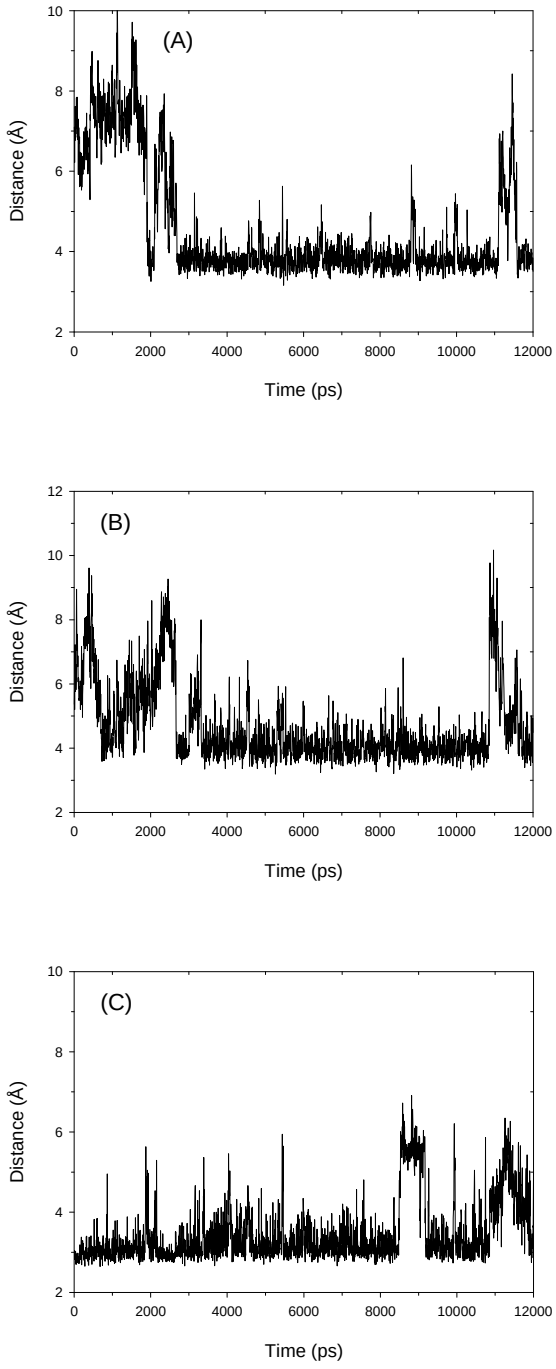


Figure S5. Interatomic distance fluctuations between cathepsin L and inhibitor **4**. *(a)* Trp184 CG – Inhibitor C4. This tracks the interaction of the backbone biphenyl with the Trp184 indole ring. *(b)* Leu144 CD2 – Inhibitor C28. This tracks the interaction of the side chain biphenyl with a nonpolar binding site represented by the Leu144 side chain. *(c)* Ala138 carbonyl O – Inhibitor Lys Nε. This tracks the locking of the inhibitor Lys side chain by formation of a hydrogen bond. See Figure S1a for atom numbering of inhibitor **4**. Together these distances provide an indication of the disposition and mobility of the biphenyl groups.

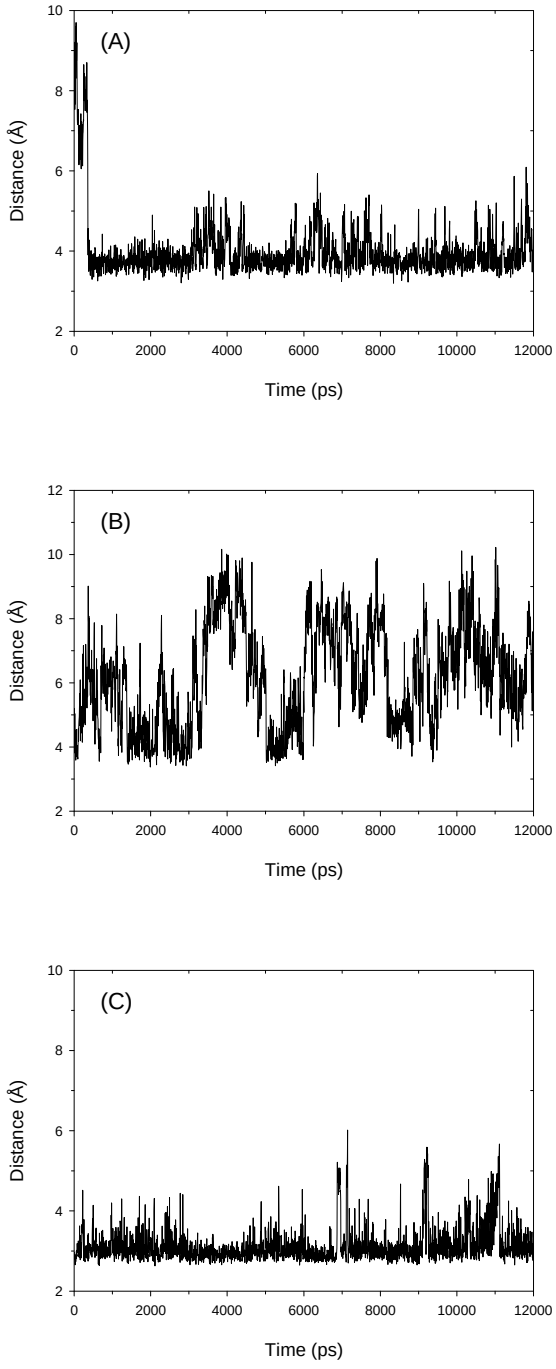


Figure S6. Interatomic distance fluctuations between cathepsin L and inhibitor **9**. *(a)* Trp184 CG – Inhibitor C4, *(b)* Leu144 CD2 – Inhibitor C28, *(c)* Ala138 carbonyl O – Inhibitor Lys Nε. See Figure S1b for atom numbering of inhibitor **4**. The significance of the various tracked distances is as in Figure S5.

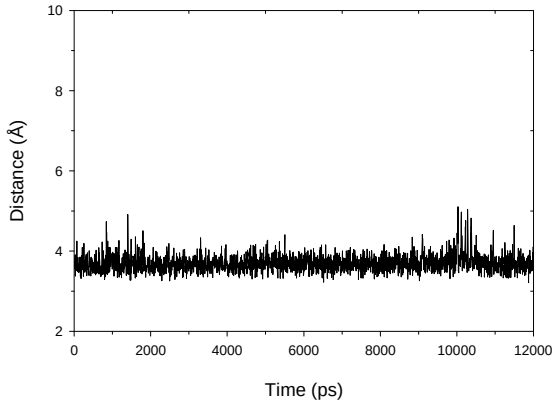


Figure S7. Interatomic distance fluctuations between cathepsin L and inhibitor **14**. Trp184 CG – Inhibitor C4. See Figure S1c for atom numbering of inhibitor **14**. This tracks the interaction of the backbone biphenyl with the Trp184 indole ring.

References

1. Wallace, A. C., Laskowski, R. A. & Thornton, J. M. (1995). LIGPLOT: a program to generate schematic diagrams of protein-ligand interactions. *Protein Eng.* **8**, 127-134.