Exploring the binding mechanism of Fibroblast Activation Protein (FAP) inhibitor UAMC-1110 using QM/MM – Drs. Joep Wals

Fibroblast activation protein (FAP) is strongly expressed in cancer-associated fibroblasts and has emerged as an attractive target in oncology. FAP inhibitors (FAPIs) are already applied for tumour imaging by attaching chelators that allow precise localization. Extending this strategy toward theranostics—combining diagnosis and therapy—requires inhibitors with improved tumour retention. To address this need, we investigated the molecular binding mechanism of the in-house FAPI frontrunner UAMC-1110.

Using molecular dynamics simulations, we first established a plausible non-covalent binding pose. Subsequent QM/MM calculations revealed that UAMC-1110 undergoes covalent bond formation with FAP through a proton transfer from Ser624 to His714, followed by a nucleophilic attack of Ser624 on the ligand's nitrile warhead. The resulting covalent intermediate is stabilized through two possible protonation pathways of the imidate anion.

Our findings indicate that UAMC-1110 binds reversibly to FAP, while related compounds may form irreversible covalent complexes. These insights open opportunities to design next-generation FAPIs with prolonged tumour retention, supporting the development of effective theranostic applications.

Curriculum vitae of Drs. Joep Wals

Joep Wals obtained a Bachelor in Pharmaceutical Sciences from Vrije Universiteit Amsterdam (2015–2018), followed by a Master in Drug Discovery and Safety at the same university (2018–2021). During the master program, the focus was on synthetic medicinal chemistry and computational chemistry, with a thesis project dedicated to the design and synthesis of ACKR3 agonists and antagonists, as well as DFT calculations on the half-life of azobenzene derivatives.

Since 2022, Joep has been working as a Graduate Research and Teaching Assistant in (Computational) Medicinal Chemistry at the University of Antwerp. This role combines doctoral research with teaching responsibilities. Research activities centre on computational approaches to medicinal chemistry, supported by an early track record of scientific communication, including an oral presentation at the EuChemS Computational Chemistry Conference in Thessaloniki.