The mechanism of aquaporin inhibition by gold compounds elucidated by Molecular Dynamics simulations

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Aquaporins (AQPs) are a family of membrane proteins involved in the transport of water and glycerol in cells.[1] [2] The AQP3 isoform has been shown to be over-expressed in several cancer types and to have a crucial role in tumour progression, making it an important target for cancer therapeutics.[1]

Recently, Au(III) compounds have been found to selectively inhibit glycerol permeation via AQP3.[3] To disclose the mechanisms of AQP3 inhibition by Au(III) compounds at a molecular level, molecular dynamics (MD) were used to investigate AQP3 inhibition by the most potent compound $[Au(PbImMe)Cl_2]PF_6$ (Fig. 1). For the first time, important structural changes leading to pore closure upon gold binding were identified.[4]

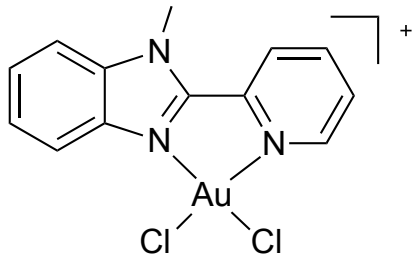

Fig.1. Structure of a Au(III) compound studied as selective AQP3 inhibitor.

[1] Aquaporins in health and disease: new molecular targets for drug discovery, G Soveral, S Nielsen and A Casini, eds. CRC Press, Taylor & Francis Group, 2016.
[2] S. Verkman, M. O. Anderson and M. C. Papadopoulos, Nat. Rev. Drug Discov., 2014, **13**, 259–77.
[3] A. P. Martins, A. Ciancetta, A. deAlmeida, A. Marrone, N. Re, G. Soveral and A. Casini, ChemMedChem, 2013, **8**, 1086–1092.
[4] A. De Almeida, A. F. Mósca, D. Wragg, M. Wenzel, P. Kavanagh, G. Barone, S. Leoni, G. Soveral and A. Casini, Chemical Communications, 2017, **53**, 3830-3033.