Inhibition of Thiol-Mediated Cellular Uptake with Hit Inhibitors

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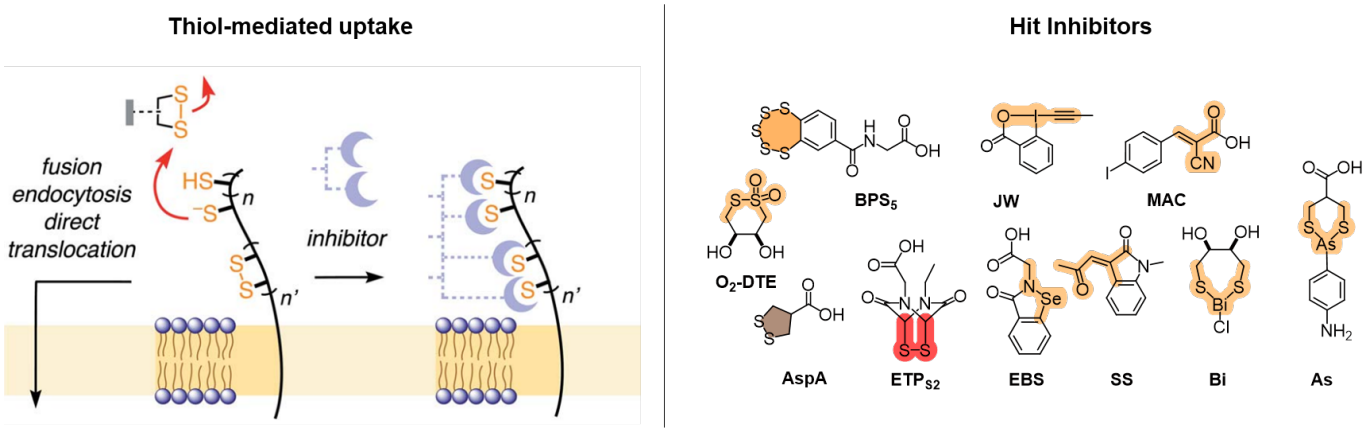
The delivery of biological substrates into the cytosol of cells has always been a challenging yet an intriguing topic. Among the various methods of cell penetration, thiol-mediated uptake is an efficient method for direct cytosolic delivery of molecules of interest, *i.e.* from small molecules to larger objects such as quantum dots or proteins.[1-2] This efficient method relies on a dynamic covalent cascade exchange between a substrate containing a thiol-reactive group, usually a disulfide, and exofacial thiols on cell surface. The covalently bound substrate enters then the cell by either fusion, endocytosis or direct translocation into the cytosol. Lately, thiol-mediated uptake is getting a lot of attention since this thiol-disulfide exchange is involved in viral entries such as HIV or SARS-CoV-2 lentivirus.[3] Although the mechanism of internalization is poorly understood because of the dynamic nature of the process, over the years, excellent candidates have been developed as transporters but also inhibitors of thiol-mediated uptake.[2]



In this study, the activities of the hit inhibitors developed over the years are reported against various fluorescent transporters. This study is expected to provide a deeper understanding of the mechanism of this dynamic covalent cascade exchange.

[1] Q. Laurent, R. Martinent, B. Lim, A.-T. Pham, T. Kato, J. López-Andarias, N. Sakai, S. Matile, *JACS Au* **2021**, *1*, 710-728.

[2] Y. Cheng, A.-T. Pham, T. Kato, B. Lim, D. Moreau, J. López-Andarias, L. Zong, N. Sakai, S. Matile, *Chem. Sci.* **2021**, *12*, 626-631.

[3] (a) T. Kato, B. Lim, Y. Cheng, A.-T. Pham, J. Maynard, D. Moreau, A.I. Poblador-Bahamonde, N. Sakai, S. Matile, *JACS Au* **2022**, *2*, 839-852. (b) B. Lim, T. Kato, C. Besnard, A. I. Poblador Bahamonde, N. Sakai, S. Matile, *JACS Au* **2022**, *2*, 1105-1115.