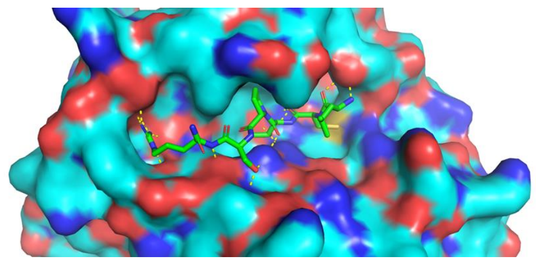
Lead Optimisation of Small Molecule Sulfatase Reactivators for MSD

Niama Ezzaidi,*[a] Lars Schlotawa,[b] Matthias Baud†[a]

[a] School of Chemistry, University of Southampton, Southampton, UK. [b] University Medical Center Goettingen Department of Paediatrics, Goettingen, Germany.

1. Introduction

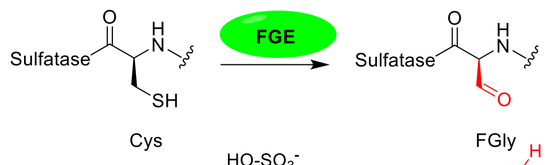
Multiple sulfatase deficiency (MSD) is a rare lysosomal autosomal recessive disease. It results from one or several mutations of the SUMF1 gene, which encodes for the formylglycine generating enzyme (FGE) responsible for post-translationally activating 17 cellular sulfatases. We aim to develop treatments that operate by the reactivation of sulfatases using small-molecule reactivators.

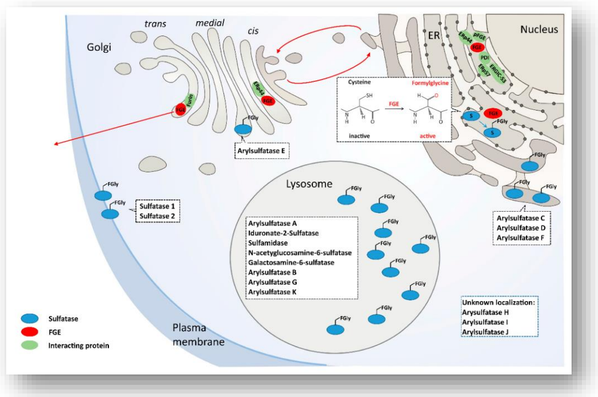


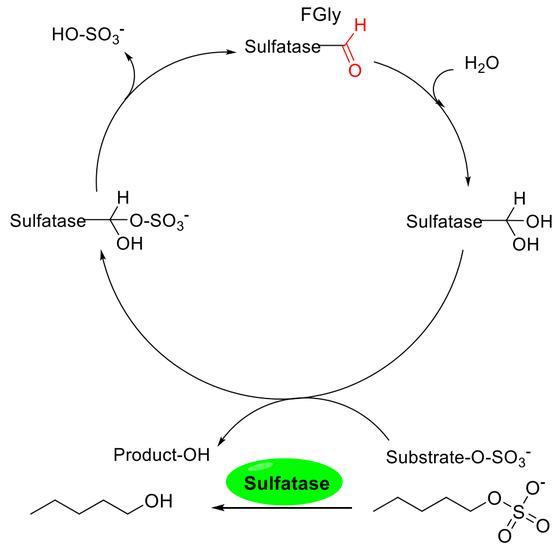
FGE C336S mutant covalently bound to substrate peptide.

2. FGE

Absence of FGE mediated PTM leads to reduced sulfate ester hydrolysis leading to build-up of cytotoxic by-products



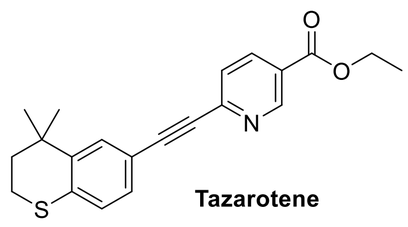




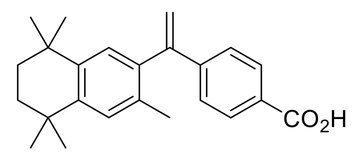
3. Drug Repurposing Screening Assay

High throughput screen of 785 FDA approved drugs on immortalized MSD patient derived fibroblasts → rescue of Arylsulfatase A

Secondary screens and analysis in MSD cell lines confirmed that the 3rd generation retinoids Tz and Bx led to a dose- and time-dependent increase of multiple sulfatase activities at low micromolar concentrations



Tazarotene



Bexarotene

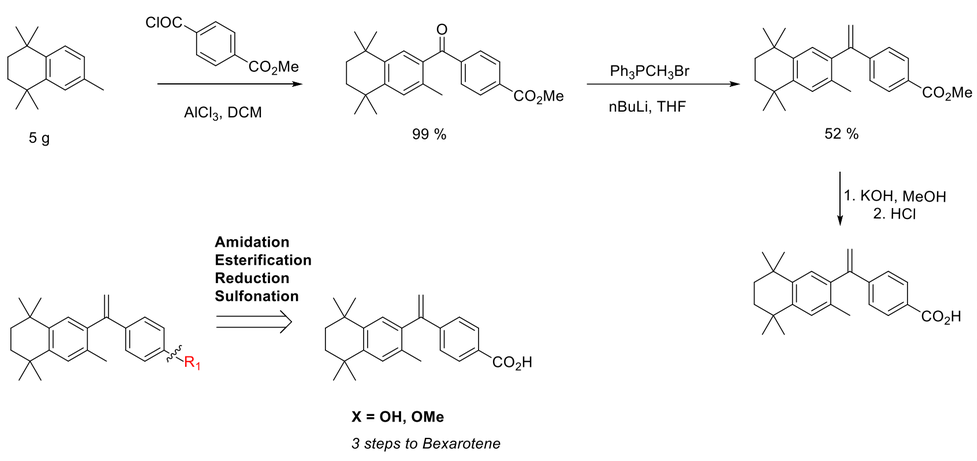
Molecular mechanisms underlying the upregulation of sulfatase activities by Taz/Bex still not understood

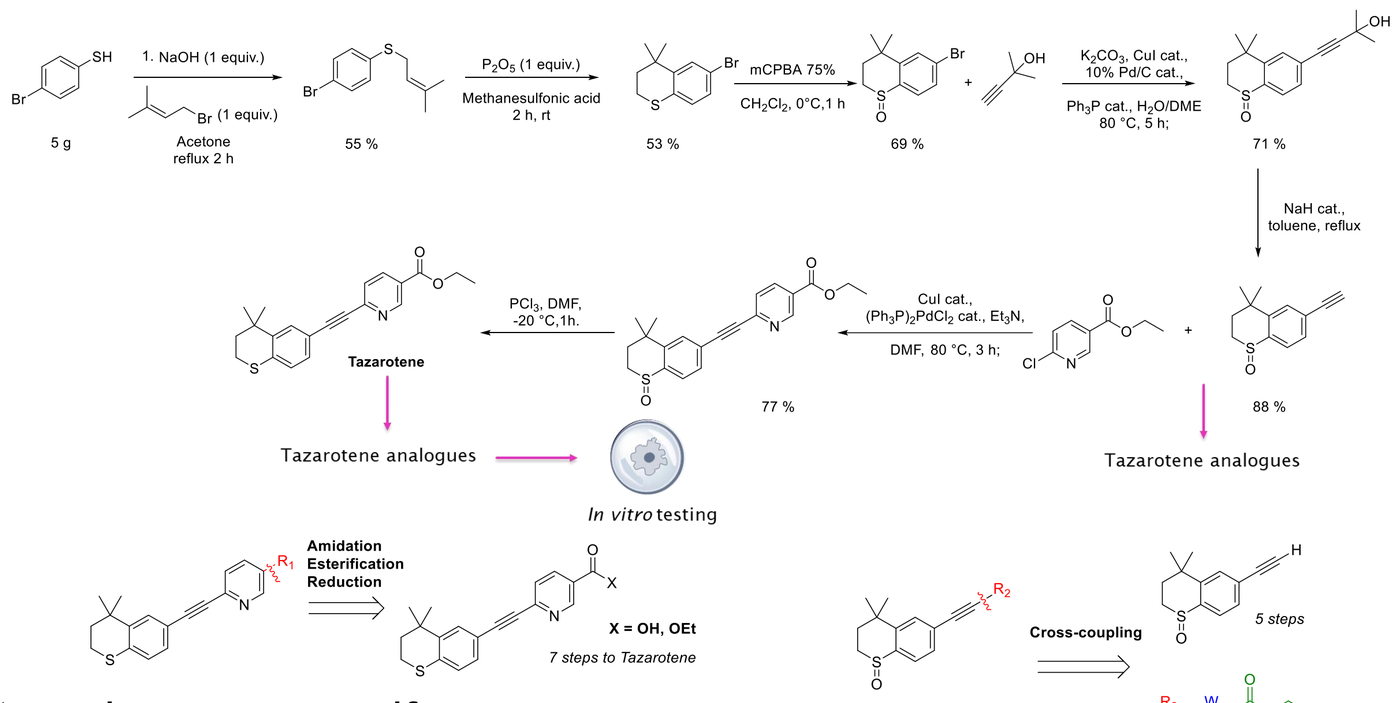
→ Through activation of members of the Retinoic acid receptor (RAR) and Retinoid X receptor (RXR) families

4. Objectives

MedChem: rational SAR based design and chemical synthesis of retinoid derivatives targeting RAR/RXR receptors, aided by available crystal structures and computational docking tools; development of suitable synthetic routes to access them synthetically.
Cell biology: evaluation of their therapeutic effect in MSD patient derived cell lines and identification of structural features correlating enhanced sulfatase activity

5. Synthesis





Bx/Tz analogues synthesised are tested (complementary sulfatase assays, immunofluorescence, cell growth and toxicity assays) to evaluate the effects of structural modification to the scaffolds on bioactivity

6. Conclusions and Future Work

A series of derivatives of Tazarotene and Bexarotene were synthesised for the first time and later tested on MSD cells. Following-up and building on biological results, we propose to investigate new synthetic derivatives of tazarotene/bexarotene exerting enhanced therapeutic effect in MSD fibroblasts as potential future drug candidates for MSD.

7. References

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2. L. Schlotawa, E. C. Ennemann, K. Radhakrishnan, B. Schmidt, A. Chakrapani, H.-J. Christen, H. Moser, B. Steinmann, T. Dierks and J. Gärtner, Eur J Hum Genet, 2011, 19, 253–261.

Author contact details
*N.Ezzaidi@soton.ac.uk
†m.baud@soton.ac.uk
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