Introduction

Cyclophilins (Cyp) are member of the Peptidyl Proline Isomerases (PPIases) superfamily, which catalyze the cis/trans isomerization of the peptide bond at proline residues. They are involved in numerous biological processes with key roles in cancer, neurodegeneration, psychiatric disorders and viruses life cycle\(^1\). So far, potent Cyp inhibitors used in clinic or tested in human are all macrocyclic peptides. A first campaign of high-throughput screening involving the EMD Serono compound library failed to deliver validated hits. Here we disclose the results obtained from the identification of original 3D-fragments and the merging strategy that led to a non-peptidic highly active Cyclophilin D inhibitors.

3D-fragments inspired by natural products

Edelris has developed an unique collection of fragments inspired by natural products. The underneath 2-ABN scaffold illustrates the design and synthetic efforts to build a 3D-fragments inspired by natural products.

Figure 1: 3D-Fragments inspired by natural products

Cyclophilin D inhibitors

Cyclophilin D (CypD) act as a key regulator of the mitochondrial permeability transition pore (mPTP), which plays a major role in calcium efflux from mitochondria to the cytosol and can lead to mitochondrial swelling or cell death\(^2\). Calcineurin binding domain

Immunosuppressive activity

Cyclophilin A (CsA) organ transplant, psoriasis, RA

Figure 2: Isomerization of peptide bond via PPIase and Cyclophilin A bindings domain

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Primary Screening of fragment collection

Screening of the EMD Serono fragment collection (2,500 cpds) led to the identification of 58 hits (K\(_{50}<60\)\(\mu\)M) of which 6 were resolved with X-Ray structures\(^3\). Structural information revealed a new binding pocket explored by two fragments from Edelris collection. These 2 fragments share in common an aniline residue leading to a similar binding mode.

Figure 3: FBDD process and structure of 3D-fragments identified as hits

References:
2. Javadov et al., Front. Physiol. 2013, 4, 76
3. X-Ray crystallography performed by Proteos biostructures GmbH
6. I. S. Yadav, Synthesis 2006, 17, 2923–2926