Achieving Enantiopurity Through Directed Evolution and Crystallization under Non-Equilibrium Conditions

Doctorant·e
PINÈTRE Clément

Direction de thèse
DUPRAY VALÉRIE (Directeur·trice de thèse)
BRANDEL CLEMENT (Co-encadrant·e de thèse)

Date de la soutenance
16/12/2024 à 10:00

Lieu de la soutenance
Amphi Perey - Batiment Blondel

Rapporteurs de la thèse
LEYSSENS TOM LOUVAINS
NOORDUIN WIM L Université d'Amsterdam

Membres du jurys
BAUDEQUIN FERRON CHRISTINE, , Université de Rouen Normandie (URN)
BRANDEL CLEMENT, , Université de Rouen Normandie (URN)
DUPRAY VALÉRIE, , Université de Rouen Normandie (URN)
GOUTAUDIER CHRISTELLE, , Université Claude Bernard - Lyon 1
LEYSSENS TOM, , LOUVAINS
NOORDUIN WIM L, , Université d'Amsterdam

Abstract

Crystallization is widely used for isolating biorelevant enantiopure molecules, which requires enantiomers to self-sort into separate enantiopure crystals. Unfortunately, this behaviour is unpredictable and rare (5-10%), as both enantiomers predominantly crystallize together into racemic crystals, hindering any such chiral sorting. Recognizing that non-equilibrium conditions may overcome these unfavourable statistics, we explored the solid-state landscapes and thermodynamic properties of different series of numerous analogous molecules derived from three distinct chiral cores: Praziquantel, Proxyphylline and Paclobutrazol. Our investigations led to three key approaches for enhancing crystallization-based chiral resolution methods: (i) A directed evolution strategy based on the energy differences between racemic and enantiopure crystal phases, (ii) the identification of specific molecular features favouring the crystallization of enantiopure crystals and (iii) engineering a crystal structure with efficient chiral discrimination capabilities that relies on a host-guest association strategy. These insights relying on the study of chemically related derivatives open new, previously unconsidered possibilities for isolating pure enantiomers that are essential in our daily lives.