Secteur des Sciences et Technologies

UCLouvain

Invitation à la soutenance publique de thèse de

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Pour l'obtention du grade de Docteur en sciences

«Development and Optimization of a new general thermodynamic deracemization method: Co-crystallization Induced Spontaneous Deracemization »

qui se déroulera
le vendredi 27 novembre 2020 à 16h
En visioconférence
1348 Louvain-la-Neuve

Jury members :

Prof. Tom Leyssens (UCLouvain), supervisor
Prof. Olivier Riant (UCLouvain), supervisor
Prof. Yann Garcia (UCLouvain), chairperson
Prof. Michael Singleton (UCLouvain), secretary
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In pharmaceutical industry, 50% of the marketed drug compounds contain a chiral center, essential to their functioning. Where one enantiomer has the desired pharmacological effect, the other might be inactive, equally active or have adverse effects. For this reason, development of enantiopure drugs is strongly recommended by regulation authorities to industries. The industrially most prominent way to enantiopure drugs still involves formation of a racemic compound, followed by a chemical or physical resolution. Such a resolution implies a maximum yield of 50%, as the unwanted enantiomer is discarded upon separation. However, if the compound is racemizable, in principle the unwanted enantiomer can be transformed into the desired one, leading to a so-called deracemization process, which finally can lead to a 100% maximum yield. Such processes exist for compounds that either are intermediates (Dynamic Kinetic resolution), can form salts (Crystallization Induced Diastereomer Transformation) or conglomerates (Viedma Ripening). However, there are still a considerable amount of racemizable molecules that don't meet either criteria and therefore cannot be deracemized.

In this work, the aim is to develop a novel tool within the library of deracemization techniques in order to touch a larger range of compounds, with the ultimate goal to develop a physical thermodynamic deracemization technique applicable to all racemizable compounds. To do so, crystal engineering and crystal growth tools are combined to develop a Cocrystallization Induced Spontaneous Deracemization method (CoISD). This process is based on co-crystallization in order to induce an imbalance in solution by precipitation of only one enantiomer while racemizing the excess of the other one in solution. Doing so, we first identified a suitable system on which to develop the CoISD process by synthetizing a series of analog compounds and submitting them to a co-crystal screening. A suitable co-crystal system composed of the synthetized analog (R,S)-4,4-dimethyl-1-(4-fluorophenyl)-2-(1H-1,2,4-triazol-1-yl)-Pentan-3-one ((R,S)-BnFTP) and the identified co-former enantiopure 3-Phenylbutyric acid. This system forms diastereomeric co-crystals that can be separated upon crystallization. Then, this system was submitted to chiral resolution and racemization studies to eventually develop the CoISD process in toluene with 1,8-Diazabicyclo[5.4.0]undéc-7-ène (DBU) as the racemizing agent. The process ran as a two-pot one-step deracemization with a crystallization cell at low temperature and a racemization cell at high temperature. Following the success of the development, the process was optimized in a two-step manner, first studying the kinetics of racemization of BnFTP with DBU with and without the presence of the co-former. Then, incorporating those data, several operational parameters were varied in order to assess their impact on the process yield and overall deracemization. At the end, an efficient process with a yield of 73% and an oval deracemization of 80% was achieved. Finally, the deracemized BnFTP was valorized by the reduction of its ketone function by keeping the stereochemistry of the original chiral center while inducing a favored configuration for the newly formed chiral center. Reduced BnFTP is a closely related analog of Paclobutrazol, a fungicide and growth retardant.