

A rare case of Polymorphism in the Binary System of Enantiomers of a Praziquantel derivative: Crystal Structures and Phase Diagram Determinations.

Clément Pinètre^{1*}, Clément Brandel¹, Loïc Ritou¹, Charline J.J. Gérard¹, Hugo Cercel¹, Michel Leeman², Richard M. Kellogg², Paul Tinnemans³, René de Gelder³, Valérie Dupray¹, Joop H. ter Horst¹.

¹Univ Rouen Normandie, SMS, UR 3233, F-76000 Rouen, France

²Symeres, Kadijk 3, 9747 AT Groningen, The Netherlands

³Institute for Molecules and Materials, Radboud University, Heyendaalseweg 135, 6525 AJ Nijmegen (The Netherlands)

*clement.pinetre1@univ-rouen.fr

Keywords: Polymorphism, Racemic compound, Crystal Structure, Praziquantel, Phase diagram.

Praziquantel is an important chiral anthelmintic drug used to treat schistosomiasis.[1] It crystallizes as a stable racemic compound and is marketed as racemic mixture but the biological activity is mainly due to the (*R*)-enantiomer. It is possible to prepare enantiopure Praziquantel by classical resolution of its precursor Praziquanamine using Dibenzoyl Tartaric Acid as a resolving agent.[2] More recently, a study reported the chiral resolution of a PZQ derivative crystallizing as a conglomerate by Viedma ripening, illustrating the benefit of simple molecular derivation for enantiomeric resolution.[3] In a conglomerate screening context, we prepared numerous derivatives of PZQ, mainly by modification of the moiety linked to the amide function. In this study, we discovered that 2-(cyclopropanecarbonyl)dodecahydro-4H-pyrazino[2,1-a]isoquinolin-4-one (PZQ_CyP hereafter), *i.e.* a PZQ derivative in which the six-membered ring has been substituted by a three-membered ring, exhibits a very rare crystallization behavior with no less than three enantiotropic polymorphs of the racemic compound: low (LT), medium (MT) and high (HT) temperature polymorphs. Although chiral resolution is not possible for this system, we report a unique polymorphic situation between the two enantiomers. The results are in particular supported by the experimental construction of the binary phase diagram between PZQ_CyP enantiomers and the crystal structures of the different polymorphs are presented.

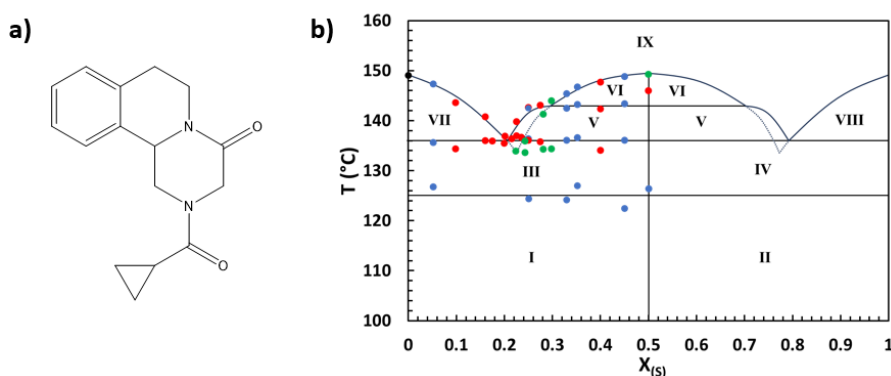


Figure 1. a) Molecular structure of PZQ_CyP and b) Melting phase diagram of PZQ_CyP. Blue, red and green circles stand for experimental data obtained using LT, MT and HT polymorphs respectively. I: <R> + <RS>_{LT}; II: <S> + <RS>_{LT}; III: <R> + <RS>_{MT}; IV: <S> + <RS>_{MT}; V: <RS>_{MT} + Liquide; VI: <RS>_{HT} + Liquide; VII: <R> + Liquide; VIII: <S> + Liquide; IX: Liquide. Bolded lines and dashed lines are respectively for stable and metastable equilibria (guides for the eyes).

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JEEP 2023

October 4-6, 2023

Preferred type of contribution:

☐ **Poster**

☒ **Oral**

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