

*Crystallization control of droperidol solid forms using templates and cross-seeding*Agris Berzins¹, Aija Trimdale¹, Andris Actiņš¹¹Faculty Of Chemistry, University Of Latvia, Riga, Latvia

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Droperidol and benperidol are neuroleptic pharmaceuticals used as antipsychotics. Molecular structures of both compounds are very similar and differs only by the order of a C-C bond in the middle of the molecule (see Scheme below), resulting in benperidol having a piperidine moiety, whereas droperidol – 1,2,3,6-tetrahydropyridine moiety. In our previous studies [1-2] we have shown that both of these compounds are able to form multiple polymorphs and numerous solvates.

Despite the similarity of the molecular structure, there are no known droperidol polymorph or solvate isostructural to those of benperidol. In detailed comparison of the crystal structures of these pharmaceuticals it was identified that the most important difference between both molecules was the weak intermolecular interactions formed by the central ring which therefore was responsible for the formation of different crystal structures.

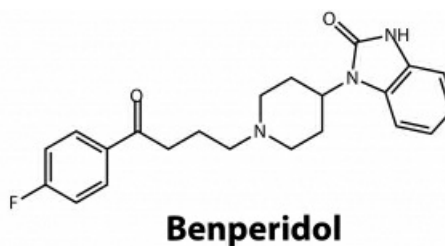
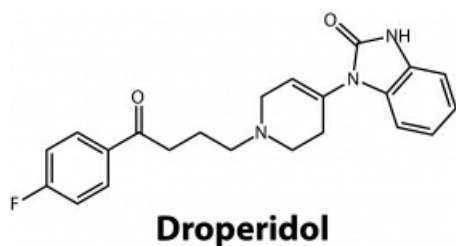
Cross-seeding experiments were performed to check the possibility for the formation of mutually isostructural phases, and theoretical calculations were performed to compare the stability of experimentally observed phases and theoretical isostructural phases by therefore rationalizing the results of the cross-seeding experiments. In cross-seeding crystallizations, three new droperidol phases – an ethanol monosolvate, a dihydrate and a new polymorph, all three isostructural to already known phases of benperidol – were obtained [3]. Therefore, it was proven that the cross-seeding can be used to control the crystallization outcome in cases when the resulting phase has favourable or similar energy to the phase forming in the absence of the seeds.

Additionally, crystal structure analysis and ab initio calculations were used to design templates potentially possible to control the crystallization outcome of droperidol ethanol solvate / polymorph I system. Crystallization experiments in the presence of the designed templates were performed by studying the effect of these templates on the crystallization process and outcome. Molecular self-association studies in the presence and absence of the selected templates were performed to identify the possible associates present in the solution and their role on the phase obtained in the crystallization experiment.

[1] Bērziņš, A. et al. (2015). *Cryst. Growth Des.* 15, 2337-2351.

[2] Bērziņš, A. et al. (2014). *Cryst. Growth Des.* 14, 2654-2664.

[3] Bērziņš, A. & Actiņš, A. (2016). *Cryst. Growth Des.* 16, 1643-1653.



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