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Access to several crystalline forms of R-encenicline hydrochloride using desolvation of various solvates

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R-Encenicline (N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-7-chloro-1-benzothiophene-2-carboxamide) hydrochloride (Enc-HCl) is a partial, selective agonist of the α-7 nicotinic acetylcholine receptor. It is being developed for the treatment of cognitive deficits in schizophrenia and Alzheimer's disease. Previously, three monohydrates (I, II and X) were reported in the patent [1], recently we reported fourth polymorph of Enc-HCl monohydrate (III) as well as four dehydrates of all monohydrates (I_D, II_D and III_D) [2].

The solid state landscape of Enc-HCl presents several more nonsolvated polymorphic forms as well as large number of solvates. Almost all of these polymorphic forms (V, VI,VII,VIII,IX) can only be obtained by means of desolvation of different solvates. Moreover, depending on the different desolvation conditions two different polymorphs can be obtained from the same acetic acid disolvate (S_{AA}). Indeed, when the desolvation process is performed in elevated temperature - polymorph VIII is produced, but in dry gas flow - polymorph IX. The only polymorph that is accessible without the parent solvated phase is form IV.

The crystal structures of six polymorphs as well as their precursors have been determined directly from powder diffraction data. The crystal structures of precursors were found to be relatively structurally similar and related to those of desolvated phases, which was consistent with the observed phase transitions among the related pairs. In addition, a comparison of the thermodynamic stability of polymorphs were performed using DFT calculations, differential scanning calorimetry data and solvent mediated slurry-bridging experiments.

References:

[1] Oliver-Shaffer, P. et al. (2014). U.S. Patent 2014/0249179,
[2] Kons, A. et al. (2018) Cryst. Growth Des., 18, 2100–2111.

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Multicomponent crystals of sulfapyridine and sulfadiazine

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Crystal engineering principles were used to cocrystallise sulfa drugs, sulfapyridine (SFP) and sulfadiazine (SFD), with aromatic acids and an amine via solution crystallisation. Sulfapyridine formed cocrystals with 3-nitrobenzoic acid (SFP·3NBA), 5-bromosalicylic acid (SFP·5BSA), 4-dimethylaminopyridine (SFP·4DMAP) and salts with 4-nitrobenzoic acid [SFP^+][$4NBA^-$], 3,5-dinitrosalicylic acid [SFP^+][$DNSA^-$] and 3,5-dibromosalicylic acid [SFP^+][$DBSA^-$], while sulfadiazine formed a salt with 3,5-dinitrosalicylic acid [SFD^+][$DNSA^-$].

The SFP and SFD compounds exhibit tautomerism. In this work it was investigated how the introduction of coformers with varying acidity provides the possibility to form a variety of synthons, and therefore disrupt the common preferred interactions within the sulfonamides. Using selected acids as coformers, the effect on crystal packing of the coformer's substituent position was examined by using the isomers 3NBA and 4NBA. 5BSA and DBSA were employed to analyse the effect of the number of substituents on hydrogen bond formation and crystal packing. In addition, it was investigated how small structural changes in the pharmaceutical compound influences the crystal packing by cocrystallising structurally similar SFP and SFD with the same coformer. Evaluation of the change in coformer acidity was studied by using a pyridine coformer, 4DMAP, and its crystal packing was analysed and compared to structures formed with carboxylic acid coformers.

Finally, we examined how inter-conversion of tautomers promotes crystal formation by conforming to the geometric demands of the different coformers.

Keywords: sulfadrugs, tautomers, cocrystals