Supramolecular hydrogen-bonding patterns of cocrystallized active pharmaceutical ingredient (API) phloroglucinol and N-heterocycles

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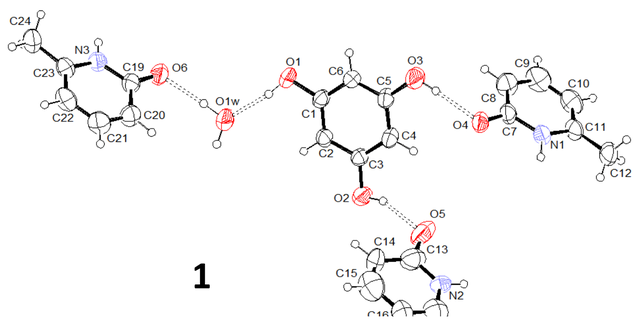
OBJECTIVE:

To synthesize 5 Cocrystals of the drug model phloroglucinol (PHL, 1,3,5- trihydroxybenzene, pKa 8,45) containing pyridine/pyrimidine/pyrazine derivatives as co-formers: (2-hydroxy-6-methyl-pyridine (**1**), 2,4-dimethyl-6-hydroxy-pyrimidine (**2**), 4-phenyl-pyridine (**3**), 2-hydroxy-pyridine (**4**), and 2,3,5,6- tetramethylpyrazine (**5**). The choice of these conformer molecules finds its justification by the fact that the heterocyclic skeleton containing nitrogen atom is the basis of many essential pharmaceuticals and of many physiologically active natural products. Pyrimidines, for instance, has great biological and medicinal significance; actually, 2nd and 4th position keto group substitution or amino substitution or mixed keto, amino groups substitution leads to anticancer, antiviral, antibacterial, antifungal, and treatment of respiratory tract infection and liver disorder. Methylpyrazines in particular are not uncommon in nature, and a typical source is maple syrup. Moreover, tetramethylpyrazine, also known as ligustrazine, is an antiinflammatory compound used to treat ischemic stroke or in the treatment of many neurological diseases because of its neuroprotective effect.

METHODOLOGY AND AHALYSES: Single crystals growth by evaporation, Liquid crystallization, Single-Crystal X-Ray Diffraction



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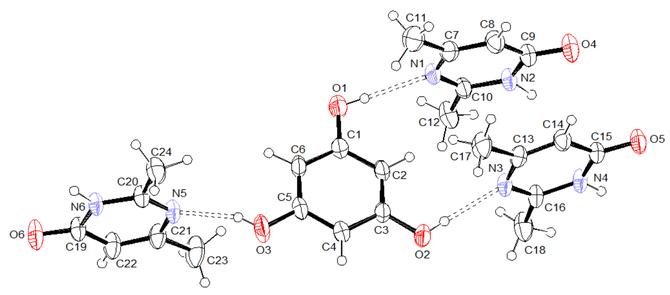

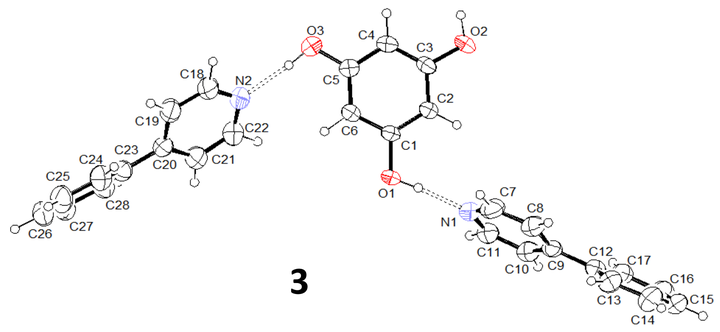

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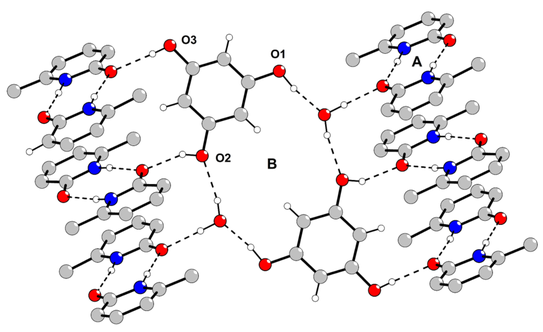

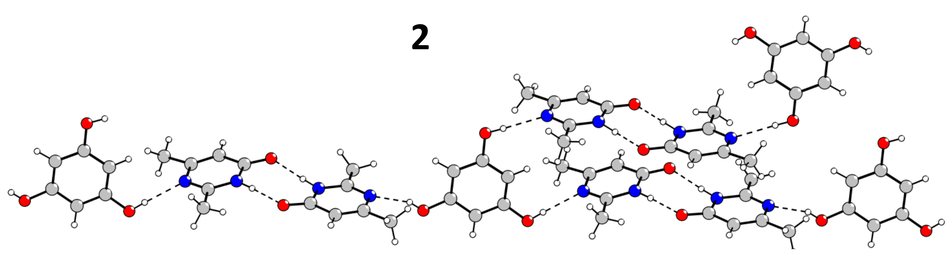

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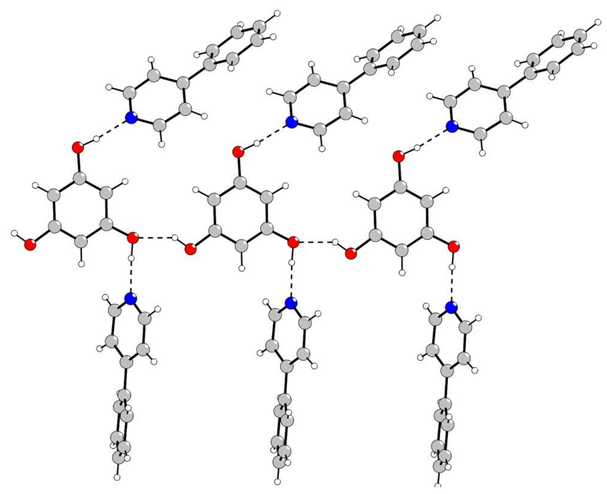

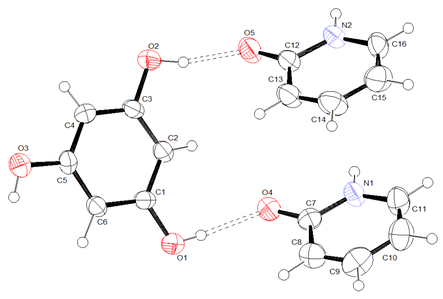

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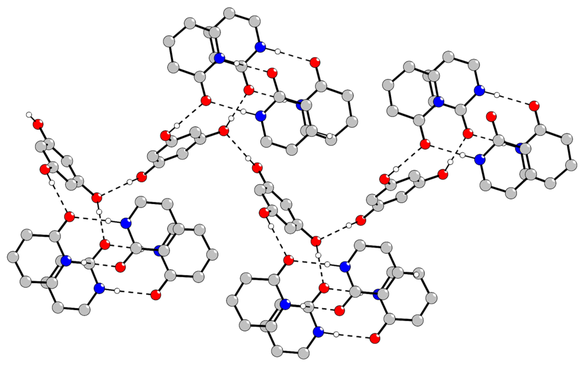

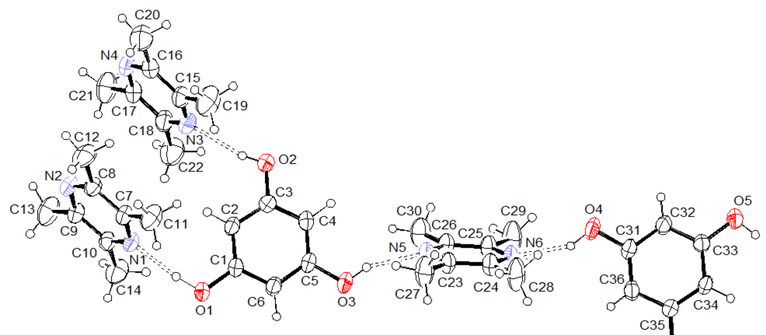

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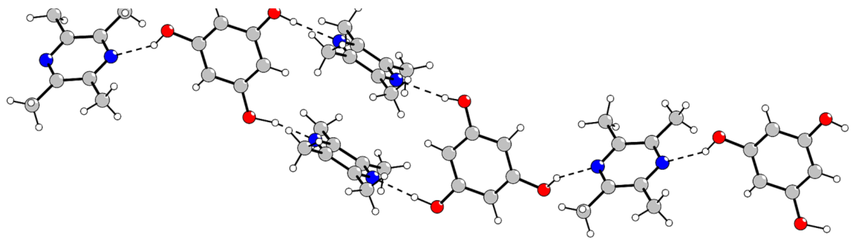
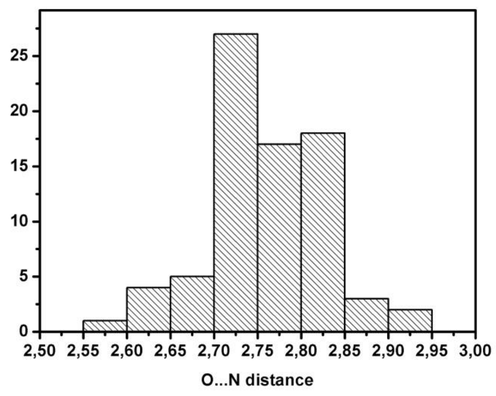
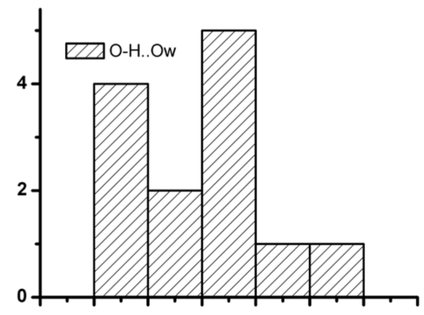
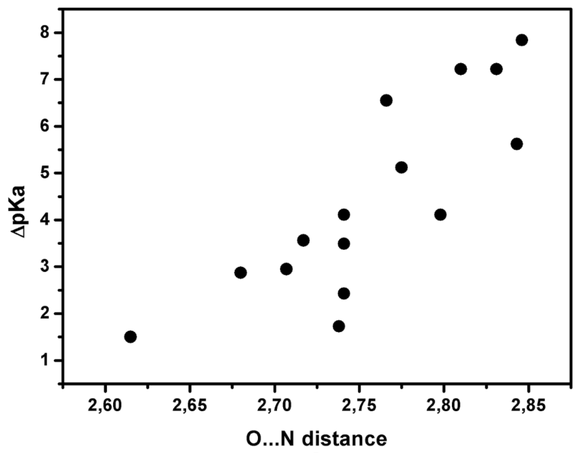




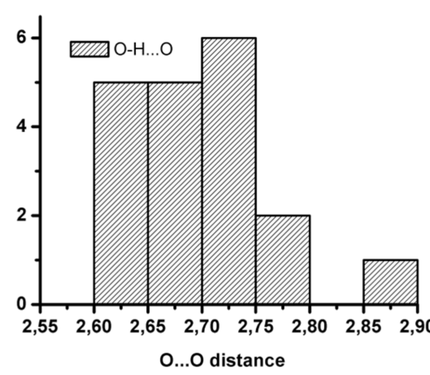


CONCLUSION:

- ✓ The OH group, that in principle can act both as an H-bonding donor or acceptor, forms preferably O-H...N interactions whose strength can be reasonably predicted on the base of the pKa equalization principle;
- ✓ The packing modes of the PHL-cocrystals are predictable and conserved when the coformer molecules has only one or two H-bonding acceptor groups. In this case, the final packing architecture and the PHL-coformer stoichiometric ratio are strictly connected to the size and shape of the coformer molecule.
- ✓ Hydrated form compromise packaging efficiency



ΔpK_a vs N…O distances (Å) in PHL CCs



Donor-…Acceptor distances (Å) in O-H…X (X=N,O) hydrogen bonding interactions found in PHL CCs

REFERENCES:

Cvetkovski, A, et al., *Acta Cryst.* (2016). B72

From Molecules to materials: 1ST Workshop on Benchmarking Solid State properties Warsaw. Poland 9-11 September CA22107 BEST-CSP