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Informatics approaches to solid form stability

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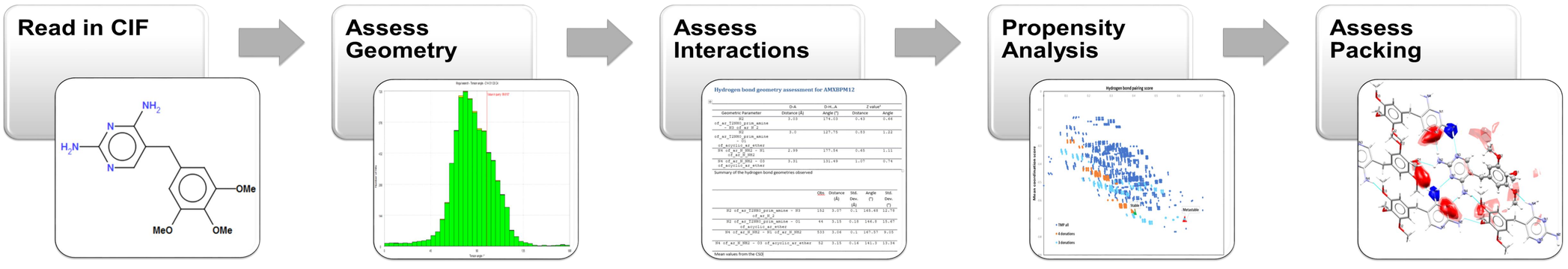
INTRODUCTION

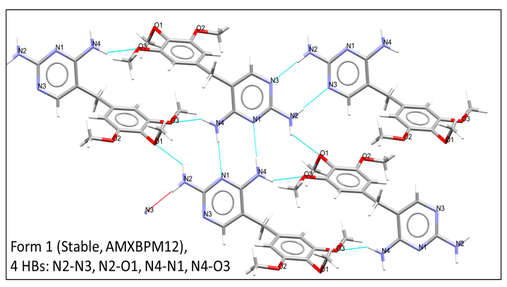
Solid form selection of an Active Pharmaceutical Ingredient (API) is a key stage in the drug product development process. Uncontrolled crystal form polymorphism can have a critical impact on pharmaceutical drug product robustness, exemplified by Ritonavir and Rotigotine[1]. Harnessing the structural chemistry knowledge derived from nearly one million entries in the Cambridge Structural Database (CSD)[2], we have applied state-of-the-art structural informatics tools found in *CSD-Materials* to 'health-check'[3] the antibiotic drug Trimethoprim[4]. These tools allow the risk of polymorphism to be assessed through a statistical analysis of intramolecular geometry and intermolecular interactions, complementing experimental studies through a deep understanding of the qualities of the structure.

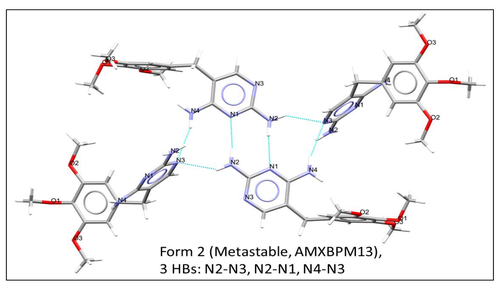


'Health-check' workflow

CRYSTAL STRUCTURE ANALYSIS

Trimethoprim (TMP) is a well-known antifolate drug and one of the most widely used broad-spectrum antibiotics. There are various salts, hydrates, solvates and multi-component systems of TMP, including four anhydrous polymorphs, many of which can be found in the CSD. The work described here focuses on two polymorphs of TMP, Form 1 (stable, AMXBPM12) and Form 2 (metastable, AMXBPM13)[4]. TMP has 2 hydrogen bond donors, (N2 and N4) and 5 hydrogen bond acceptors (N1, N3, O1, O2 and O3).



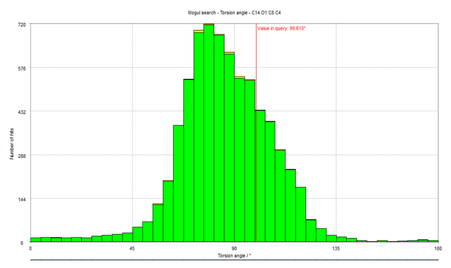


Hydrogen bonding in Form 1 and Form 2 is shown

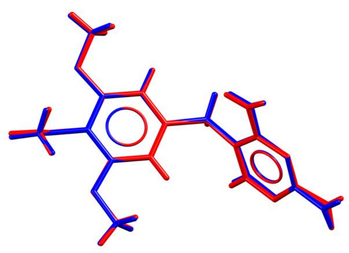
MOGUL ANALYSIS

Mogul is a library of molecular geometries derived from the CSD and provides information on the preferred values of bond lengths, valence angles, torsion angles and ring conformations. Mogul assessment was carried out on the two polymorphs of TMP; all geometric parameters were found to lie within normal CSD distributions, nothing was identified as unusual.

Molecule overlay of the two forms of TMP indicates no conformational differences.



Torsional distribution: C14-O1-C8-C4

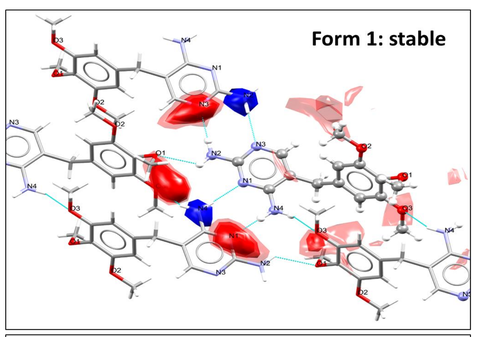


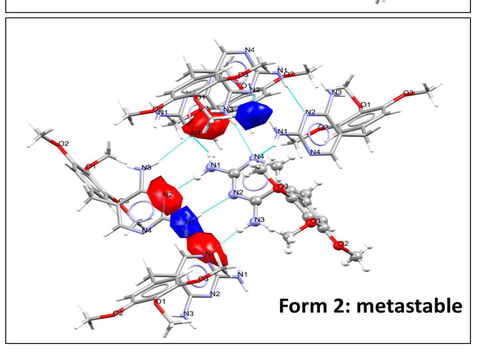
Molecule overlay of Form 1 (Red) and Form 2 (Blue)

FULL INTERACTION MAPS

Full Interaction Mapping allows a visual assessment of how the crystal packing environment can satisfy the interactions of the functional groups of a molecule. The satisfaction of donor-acceptor pairings is evaluated based on the intermolecular geometry.

The Full Interaction Maps for the two polymorphs of TMP indicate the packing environment shows a good match to the expected geometries of hydrogen bonding interactions for the stable Form 1 (AMXBPM12) compared with the metastable Form 2 (AMXBPM13) .





HYDROGEN BOND PROPSENSITY (HBP)

The HBP tool calculates probabilities for bond pairings to form in the target system based on a statistical model built from relevant structures in the CSD. The likelihood of hydrogen bond formation (propensity) is combined with how often a functional group is observed to participate in a given number of hydrogen bonds (coordination score) to generate plausible alternative structures. The intermolecular interactions of TMP Forms 1 and 2 were assessed using the HBP tool. The chart indicates that the hydrogen bonding network observed in Form 1 is the best outcome when both amine donors behave optimally.

Donor	Acceptor	Propensity	AMXBPM13 H-bond	AMXBPM12 H-bond
N2 of ar_T2NO_amine	N3 of ar_N_2	**0.71**	Yes	Yes
N4 of ar_N_NH2	N3 of ar_N_2	**0.62**	Yes	
N2 of ar_T2NO_amine	N1 of ar_N_NH2	**0.56**	Yes	
N4 of ar_N_NH2	N1 of ar_N_NH2	**0.46**		Yes
N2 of ar_T2NO_amine	O1 of ar_methoxy	**0.25**		Yes
N2 of ar_T2NO_amine	O2 of ar_methoxy	**0.24**		
N2 of ar_T2NO_amine	O3 of ar_methoxy	**0.24**		
N4 of ar_N_NH2	O1 of ar_methoxy	**0.18**		
N4 of ar_N_NH2	O2 of ar_methoxy	**0.18**		
N4 of ar_N_NH2	O3 of ar_methoxy	**0.18**		Yes
N2 of ar_T2NO_amine	N2 of ar_T2NO_amine	**0.04**		
N2 of ar_T2NO_amine	N4 of ar_N_NH2	**0.03**		
N4 of ar_N_NH2	N2 of ar_T2NO_amine	**0.02**		
N4 of ar_N_NH2	N4 of ar_N_NH2	**0.02**		

Results from the HBP calculation for the D/A pairings of TMP Form 1 and Form 2. Propensity can take a value between 0 and 1; 0 indicates the interaction will never be observed and 1 indicates the interaction will always be observed.

Atom (D/A)	=0	=1	=2	=3
N2	0.020	0.369	**0.574**	0.036
N4	0.053	0.407	**0.519**	0.021
N1	0.125	**0.836**	0.039	0.000
N2	**0.956**	0.044	0.000	0.000
N3	0.031	**0.901**	0.068	0.000
N4	**0.983**	0.017	0.000	0.000
O1	0.799	**0.201**	0.000	0.000
O2	**0.858**	0.142	0.000	0.000
O3	0.839	**0.161**	0.000	0.000

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Coordination tables for TMP Form 1 (stable) and Form 2 (metastable) respectively. Coloured entries reflect the observed outcomes; red indicates sub-optimal outcome and green indicates optimal outcome.

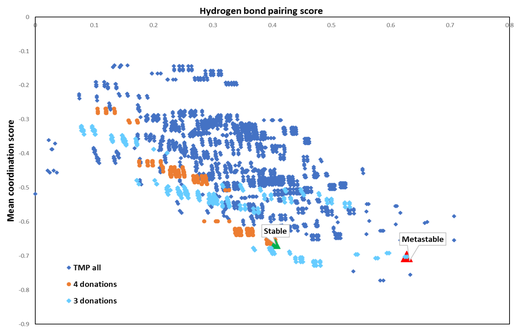

Chart showing possible combinations of D-A pairings of TMP, ranked in terms of propensity and coordination. Observed stable Form1 (green) and metastable Form 2 (red) are highlighted.

CONCLUSION

Trimethoprim is a highly complex system as shown by the 'health-check'. The combination of informatics tools - crystal structure analysis, Mogul analysis, the use of Full Interaction Maps and the calculation of hydrogen bond propensities - confirm that solid Form 1 of TMP is the most stable form, when both amine donors donate twice. This system has a high risk of polymorphism, which is reflected by the number of known forms of Trimethoprim.

REFERENCES

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3. N. Feeder *et al.*, Pharm Pharmacology, 2015, 67, 857-868
4. A. Nangia *et al.*, *Cryst. Growth Des.* 2015, 15, 1745-1756