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Use of Structural Informatics for Selection of MCL1 Clinical Drug Candidate AZD5991

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Purpose

Two structurally similar molecules, AZD5991 and AZ4448, were evaluated in parallel as Mcl-1 drug candidates during the drug discovery stage1. Because the two compounds showed only slight differences in preclinical efficacy, toxicological or DMPK properties, assessment of pharmaceutical characteristics became the primary factor in choosing a drug candidate for further development. The work presented here discusses an innovative approach using structural informatics to assess the developability of a drug candidate to rationalize candidate selection.

Methods

Intrinsic solubility determination, formulation testing, solid form characterization, and single crystal structure analysis were carried out for both compounds. To assess and understand pharmaceutical property differences at the molecular level, structural informatics techniques based on representative forms of AZD5991 (Form A monohydrate) and AZ4448 (Form C anhydrous) were analyzed and applied using Mercury 4.0.0 from CSD (Cambridge Structural Database).

Results

Despite only slight differences in efficacy, toxicological and DMPK properties, the two structurally similar Mcl-1 candidate molecules, AZD5991 and AZ4448, were found to display significant differences in pharmaceutical properties such as intrinsic solubility and gelling behavior in aqueous solution.

Successful elucidation of 3-dimensional crystal structures of AZD5991 and AZ4448 revealed uniquely different hydrogen bonding motifs and crystal packing between the two molecules. The crystal structure of AZ4448 shows distinct pattern of intermolecular H-bonding and different packing density.

Conclusion

Structural informatics from single crystal structures showed that the subtle difference between the two structurally similar molecules results in distinct intermolecular hydrogen bonding behavior. Particularly, intermolecular hydrogen bonding formation impacts molecular conformation and crystal packing, which lead to different crystalline forms with distinct pharmaceutical properties.

Elucidation of structural information at the molecular level provides interpretation of experimental observations. We demonstrate how structural informatics played a significant role to verify and explain the observed empirical differences in pharmaceutical properties of the two compounds. More importantly, better understanding of solubility and formulation behaviours based on structural informatics helped the team select AZD5991 as the drug candidate for clinical evaluation.

Keywords: AZD5991, MCL1, Structural Informatics, Single Crystal Structures, Drug Candidate Selection