Polymorphism and Solubility Studies in Early Drug Development: The Account of MBQ-167

Jocelyn M. Jiménez-Cruz,[1,2] Cornelis P. Vlaar,[1] Torsten Stelzer,[1,2*] and Vilmalí López-Mejías[2,3*]

[1]Department of Pharmaceutical Sciences, University of Puerto Rico, Medical Sciences Campus, San Juan, Puerto Rico, 00936, USA

[2]Crystallization Design Institute, Molecular Sciences Research Center, University of Puerto Rico, San Juan, Puerto Rico, 00926, USA

[3]Department of Chemistry, University of Puerto Rico, Río Piedras Campus, San Juan, Puerto Rico, 00931, USA

*Email: torsten.stelzer@upr.edu
*Email: vilmali.lopez@upr.edu

Abstract.

Herein, we report on the solubility[1] and polymorphism[2] of MBQ-167 (9-ethyl-3-(5-phenyl-1H-1,2,3- triazol-3-yl)-9H-carbazole), a small molecule dual inhibitor of Rac and Cdc42, currently undergoing preclinical trials as a potential treatment for metastatic cancer. Solubility measurements of "as received" MBQ-167 were performed employing the polythermal method in eight neat solvents (acetonitrile, 1-butanol, 2-butanol, ethanol, ethyl acetate, methanol, 1-propanol, and 2-propanol) and two binary solvent mixtures (ethyl acetate + heptane and ethanol + water) at a temperature range between 278.15 and 333.15 K. The results showed that the solubility of MBQ-167 increases with increasing temperature in these neat solvents. In the binary solvent mixtures, the solubility of MBQ-167 increases with increasing temperature and decreases with increasing mass fraction of anti-solvent (heptane or water). No solvent-mediated polymorphic phase transitions were observed while performing the solubility studies, and no other solid forms were detected after the recrystallization in the solvents and solvent mixtures at this stage in the investigation. We also set out to investigate the polymorphic behavior of MBQ-167 and report the existence of two polymorphs. MBQ-167 forms I and II were obtained by the recrystallization from ethanol and 33% *(v/v)* heptane in ethyl acetate, respectively. Thermal analysis, employing mainly differential scanning calorimetry, revealed that MBQ-167 form I displays a single average melting point (T_m = 153.43 C, ΔH_{fus} = 7.17 kcal/mol) while form II (T_m = 129.89, ΔH_{fus} = 4.89 kcal/mol) undergoes an exothermic phase transition (T_m = 143.1, ΔH_{fus} = -1.3 kcal/mol) to form I, making MBQ-167 form I the thermodynamically stable form. The application of the Burger-Ramberger rules for assigning thermodynamic relationships in polymorphic pairs, indicates that this system is monotropic and confirms that MBQ-167 form I is the thermodynamically stable form. The structure of both polymorphs was elucidated by single crystal X-ray diffraction. MBQ-167 form I crystallizes in the orthorhombic (*Pbca*) space group, while MBQ-167 form II crystallizes in a monoclinic ($P2_1/n$) space group. MBQ-167 form II (metastable form) presents the most planar conformation along the significant torsion angles identified for MBQ-167. Additionally, a Hirshfeld surface analysis confirms that van der Waals contacts are the primary interactions and only subtle differences in short contacts help differentiate these polymorphs. These findings

support the notion that polymorphism is prevalent in organic molecules and that one should invest time and money probing possible polymorphs, particularly in early development as in the case of MBQ-167 to avoid unfortunate surprises during the development and manufacturing of active pharmaceutical ingredients.

References.

(1) Jiménez Cruz, J. M.; Vlaar, C. P.; López-Mejías, V.; Stelzer, T. Solubility Measurements and Correlation of MBQ-167 in Neat and Binary Solvent Mixtures. *J. Chem. Eng. Data* **2021**, *66* (1), 832–839. https://doi.org/10.1021/acs.jced.0c00908.

(2) Jiménez Cruz, J. M.; Vlaar, C. P.; Stelzer, T.; López-Mejías, V. Polymorphism in Early Development: The Account of MBQ-167. *Int. J. Pharm.* **2021**, *608* (August), 121064. https://doi.org/10.1016/j.ijpharm.2021.121064.