Discovery and process development of Mosperafenib: The next-generation brain permeable paradox breaker BRAF inhibitor

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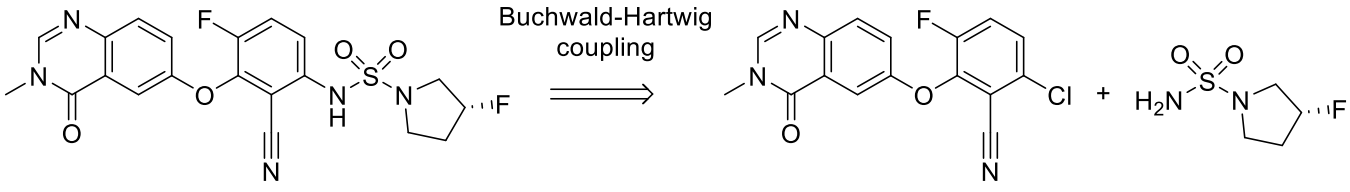
In a search for new and superior treatments for BRAF-mutant tumors we investigated several classes of BRAF V600E binders and their potential for conversion into new inhibitors without paradoxical RAF activation. Because of this effect, current marketed treatments for BRAF V600E dependent tumors consist of a BRAF inhibitor given in combination with a MEK inhibitor to prevent subsequent formation of secondary neoplastic lesions. In the course of these studies, Mosperafenib was discovered as a new BRAF inhibitor with very good molecular properties, high selectivity and excellent preclinical antitumor activity, absence of paradoxical activation, and therefore the prospect for a highly efficient monotherapy for BRAF V600E dependent tumors which included potential control of brain metastases due to high brain permeability [1].



Given the anticipated high demand for the drug substance to support both clinical studies and commercial supply, establishing a robust, scalable, and sustainable process became a critical priority early in the project. Efforts focused on resolving key challenges in the original synthetic route. Major developments included implementation of a Buchwald-Hartwig coupling in the final synthetic step, along with improvement of the process to the sulfonamide building block **2**. The new approach significantly reduced solvent usage, the PMI factor, and the number of unit operations, while delivering the final drug substance with higher yield and purity.

[1] Wichmann J. *et al*., *Clin Cancer Res,* **2022**, *28 (4)*, 770–780.