Comparison of ^{19}F-NMR and ^{14}C measurements for the assessment of ADME of BYL719 (Alpelisib) in humans.

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Drug Metabolism and Disposition

SUPPLEMENTAL DATA

METHODS

Synthesis of [14C]BYL719

As a starting material to the synthesis of [14C]BYL719 acetamido-4-methylthiazole-2-14C was used (**2**) provided by ChemDepo. Heck coupling of 4-bromo-2-(1,1,1-trifluoro-2-methylpropan-2-yl)pyridine (**1**) with **2** in the presence of palladium acetate, tritertbutylphosphoniumtetrafluoroborate and cesium carbonate in dimethylformamide provided acetamide intermediate (**3**). The acetamide was deprotected using 2N solution of HCl in ethanol. The resulting amine (**4**) reacted with phenylchloroformate (**5**) in tetrahydrofurane in the presence of Hunig's base (N,N-diisopropylethylamine) afforded carbamates derivatives (**6** and **7**) which were coupled to L-prolinamide (**8**) afforded crude [14C]BYL719 (**9**). Last coupling was done in N,N-dimethylacetamide in the presence of catalytic amount of triethylamine. Purification of crude material by flash chromatography on silica gel followed by the suspension of evaporated fractions of interest in ethanol, filtration and drying of the filter cake provided very pure drug substance - [14C]BYL719 (**10**). Starting from 102.0 mCi of 2-acetamido-4-methylthiazole-2-14C, 31.1 mCi of (S)-N1-(4-methyl-5-(2-(1,1,1-trifluoro-2- methylpropan-2-yl)pyridin-4-yl)thiazol-2-^{14}C-2-yl)pyrrolidine-1,2-dicarboxamide was obtained. The overall yield of the synthesis was 30.5%.

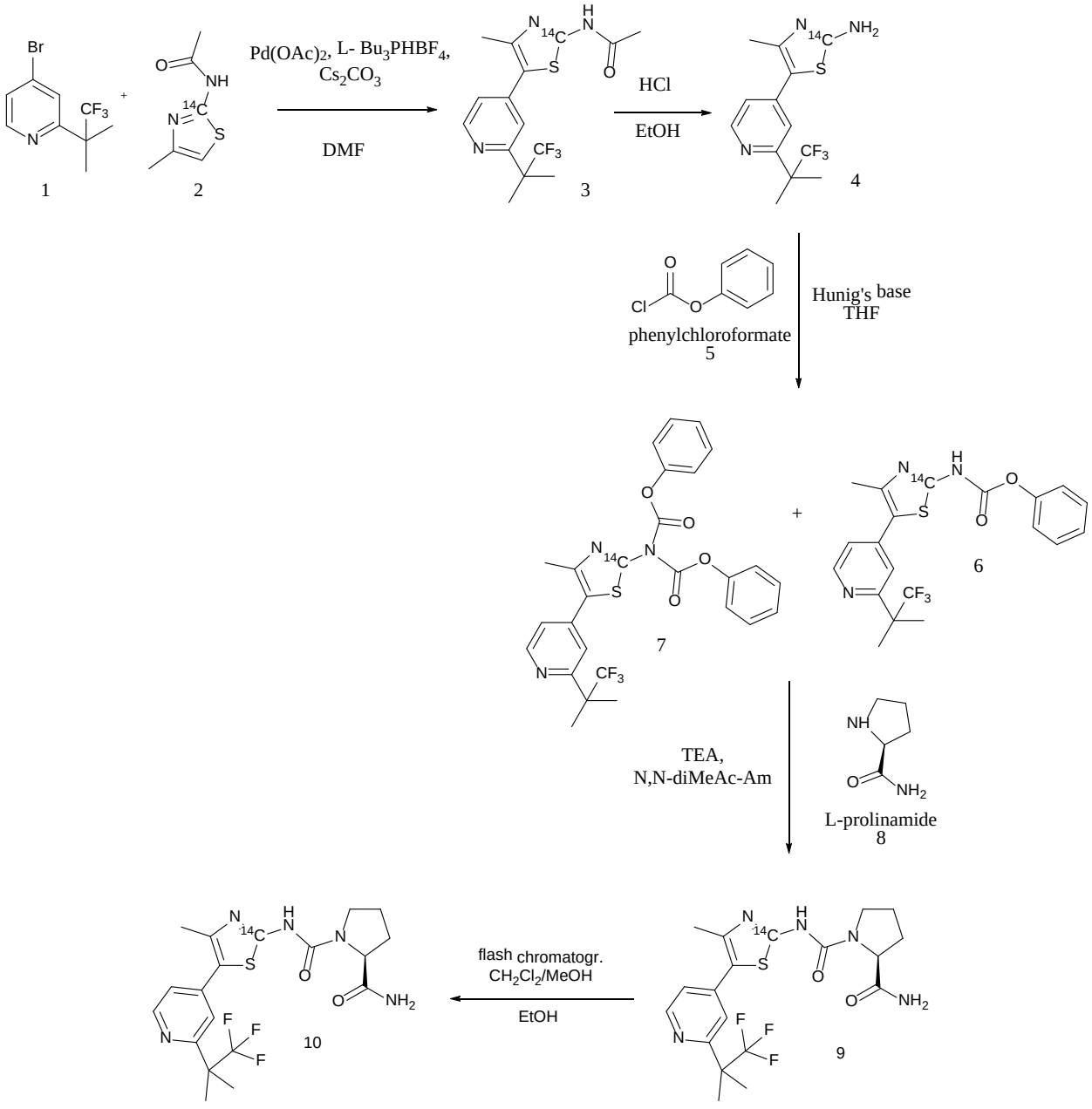

Figure S1. Synthetic scheme for [^{14}C]BYL719 (Alpelisib)

Synthesis of metabolite M4

The synthesis of metabolite M4 follows the same pathway as BYL719 (Furet et al, 2013) except for the last step which is replaced as follows (Figure S2):

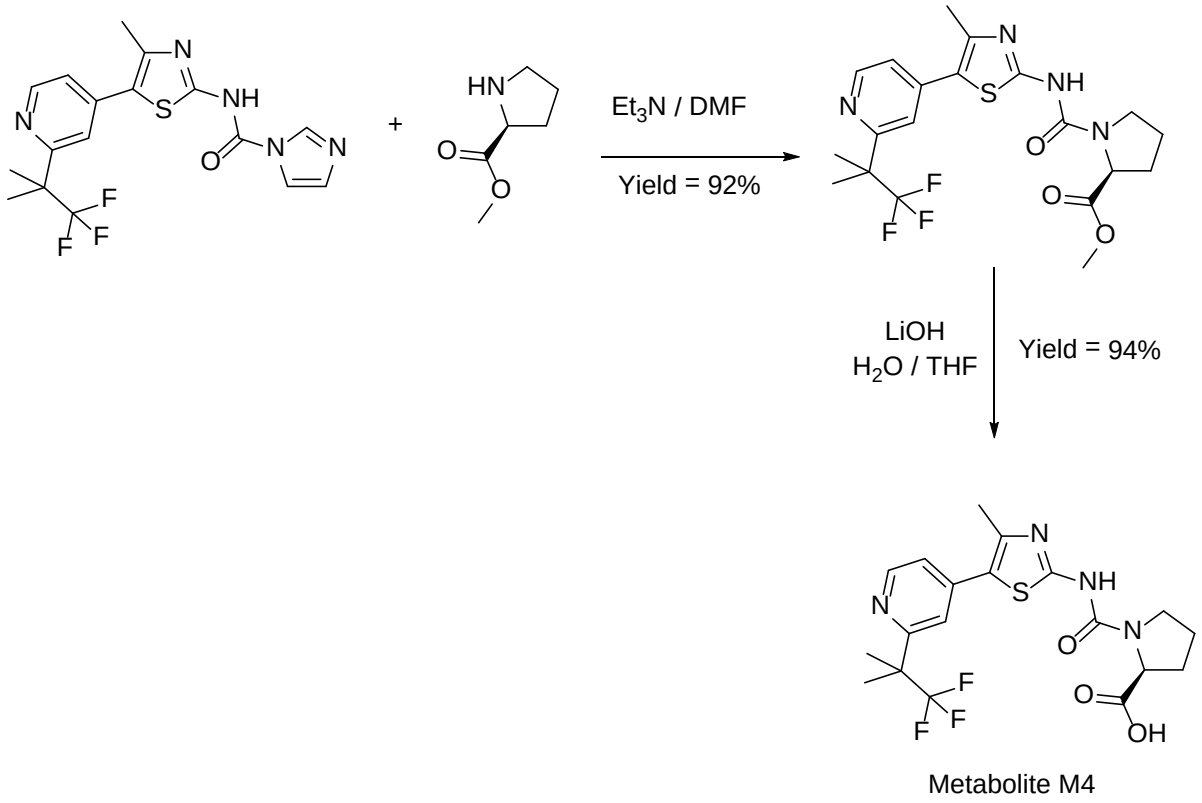

Figure S2. Synthetic scheme (last 2 steps) for metabolite M4. Preceding steps are published in Furet et al, 2013.

References

Furet P, Guagnano V, Fairhurst RA, Imbach-Weese P, Bruce I, Knapp M, Fritsch C, Blasco F, Blanz J, Aichholz R, Hamon J, Fabbro D, Caravatti G. (2013). Discovery of NVP-BYL719 a potent and selective phosphatidylinositol-3 kinase alpha inhibitor selected for clinical evaluation. Bioorg Med Chem Lett **23**: 3741-3748.