Synthesis of a Stable Labelled Isotopomer of the CSF-1R Kinase Inhibitor BLZ945 and its Chemical Epimerization to the Pharmacologically Active cis-Isomer

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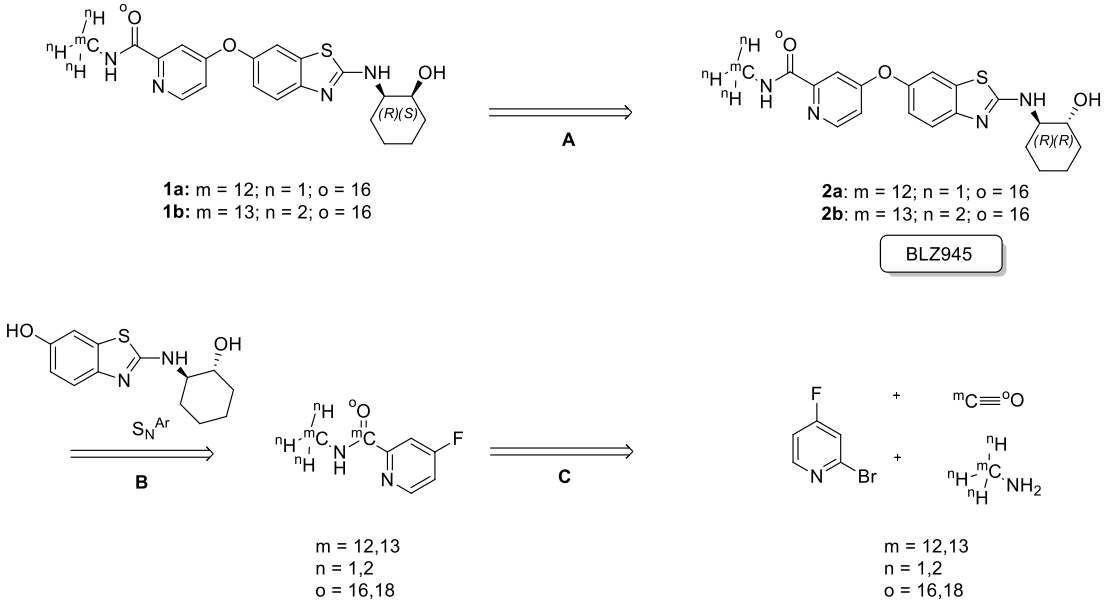
BLZ945 (**2a**), bearing a (1R,2R)-hydroxycyclohexylamino residue on C(2) of its benzothiazol core moiety, is a low molecular weight inhibitor of the colony stimulating factor 1 receptor (CSF-1R), which binds the cytokine M-CSF. Kinase inhibitors of this membrane protein found on macrophages have the potential to prevent metastasis in certain types of cancer. Recently, ten metabolites of BLZ945 were characterized after in-vitro incubation with human liver microsomes, hepatocyctes and recombinant P450[1]. Amongst these, the cis-isomer **1a** was identified as pharmacologically active. It was shown that the cis-metabolite **1a** accounted for 24% intrinsic clearance in human hepatocytes justifying the initiative to synthesize the stable labelled analytical standards **1a** and **2b**.

Here we present the development of a new synthesis of the isotopomer **2b.** Introduction of the label was achieved *via* amino-carbonylation of 2-bromo-4-fluoro-pyridine using a Xanthphos-based catalyst system with activation[2] (retro-step C). Nucleophilic aromatic substitution on this stable labelled building block used the enantiomerically pure hydroxyl-benzothiazol from our archive[3] (retro-step **B)**, followed by Mitsunobu epimerization to yield the cis-isomer **1b** (retro-step **A)**. Based on mechanistic studies with ^{18}O-labelling, we present indirect spectroscopic evidence for the presence of an activated intermediate in the Buchwald-Heck cycle.



[1] Krauser JA, Jin Y, Walles M *et al*. Xenobiotica **2015**, 45(2), 107.
[2] Martinelli JR, Watson DA, Buchwald SL et al.; J. Org. Chem., **2008**, 73, 7102. Baburajan P, Elango KP, Tetrahedron Letters **2014**, 55, 3525.
[3] Pfister KB, Wagman, AS, Ng S *et al*. Patent WO 2008/144062 A1.