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MARK Inhibitors: Declaring a No-Go Decision on a Chemical Series Based on Extensive DMPK Experimentation

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Abstract: Attempts to optimize pharmacokinetic properties in a promising series of pyrrolopyrimidinone MARK inhibitors for the treatment of Alzheimer's disease are described. A focus on physical properties and ligand efficiency while prosecuting this series afforded key tool compounds that revealed a large discrepancy in the rat *in vitro–in vivo* DMPK (Drug Metabolism / Pharmacokinetics) correlation. These differences prompted an *in vivo* rat disposition study employing a radiolabeled representative of the series, and the results from this experiment justified the termination of any further optimization efforts.

Alzheimer's disease (AD) represents a huge unmet medical need for the healthcare industry: the number of people suffering from this disease is expected to reach 13-16 million people in the United States alone by the year 2050.[1] There are no disease-modifying therapies currently available, despite numerous attempts at their development. At present, the industry is exploring a range of approaches, from the pre-clinical space through late stage development.[2] The major physiological markers of AD are the presence of abnormal deposits in the brain: 1) plaques primarily made up of amyloid-β protein and 2) neurofibrillary tangles (NFTs) composed of the protein tau. As such, many therapeutic strategies are based on reducing the number and severity of these lesions. Tau protein is highly expressed in neurons, where it is involved in stabilizing microtubules. There are multiple phosphorylation sites on tau and the extent of tau phosphorylation determines the strength of this association, thus hyperphosphorylated tau has a weaker affinity for microtubules.[3] One therapeutic approach is to decrease the phosphorylation of tau through inhibiting the kinases involved in the phorphorylation process, leading to less unbound tau and thus less of a chance for the aggregation into NFTs. Multiple kinases are known to phosphorylate tau and many have been examined as possible targets for AD.[4] Among them are the microtubule-affinity regulating kinases (MARK),[5] a family consisting of 4 isoforms (MARK1-4) that phosphorylate tau at key serine residues and promote detachment from microtubules.

The previous paper described the structure guided design of a series of pyrrolopyrimidinone MARK family inhibitors, culminating in the selective compound **1**.[6] This was an excellent tool compound that allowed hypotheses about the pharmacological effect of a selective MARK inhibitor to be tested in *in vitro* systems. However, the DMPK properties of **1**, specifically the greater than hepatic clearance rate in multiple