27O-ISMS38

Discovery of Novel 1,3-Oxazine BACE1 (β-Secretase) Inhibitors: Incorporation of an Olefin Bond to Mitigate P-gp Efflux Leading to Robust Aβ Reduction

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Accumulation of Aβ peptides is a hallmark of Alzheimer's disease (AD) and a causal factor in the pathogenesis of AD. β-Secretase (BACE1) is a key enzyme responsible for producing Aβ peptides, and thus agents that inhibit BACE1 would be beneficial for disease-modifying treatment of AD. Our hit-to-lead SAR following HTS identified 1,3-dihydro-oxazine **1** as a lead; however, its high P-gp efflux translated into no significant potency *in vivo*. Additionally, **1** had the drawback of a high hERG potential. Therefore, we initiated efforts to address these issues.

Lowering pKa on the amidine was an approach to mitigating P-gp efflux and hERG inhibition. Although Roche reduced the pKa by introducing fluorine atoms, we hypothesized that incorporation of an olefin bond could also achieve this. As expected, the oxazine **2** with an olefin bond displayed a reduced pKa, translating into an attenuated P-gp efflux. Optimization at the 6-position led to the discovery of compound **3** with robust Aβ reduction both in mice and dogs. Importantly, though **3** remains an issue with respect to hERG, a significant safety margin over the dog EC_{50} value was observed in a cardiovascular safety study *in vivo*.

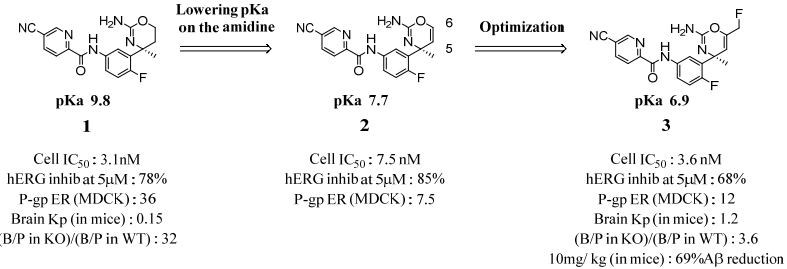

Figure. SAR of the oxazine with an olefin bond