Development of Aminooxazoline Xanthene-based β-Amyloid Cleaving Enzyme (BACE1) Inhibitors with Improved Selectivity Towards Cathepsin D (CatD)

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Alzheimer's disease (AD) is a neurodegenerative disorder that currently affects 36 million people worldwide. It therefore represents one of the largest unmet medical needs in neuroscience today. The β-amyloid cleaving enzyme (BACE1) is considered a prime therapeutic target due to its genetically-verified, detrimental role in the initiation and progression of the disease. As part of an ongoing effort at Amgen to develop a disease-modifying therapy for AD, we have previously used the aminooxazoline xanthene (AOX) scaffold to generate potent and orally efficacious BACE1 inhibitors.[1] While AOX-based BACE1 inhibitors demonstrating robust reduction of CSF and brain Aβ levels, both in rat and non-human primates, were identified with acceptable cardiovascular safety margins, a retinal pathological finding in advanced rat toxicological studies demanded further investigation. It has been widely postulated that such retinal toxicity might be related to off-target inhibition of Cathepsin D (CatD), a closely related aspartyl protease.[2] Here we report the development of AOX-based BACE1 inhibitors with improved selectivity towards CatD utilizing a structure- and property-based approach to gain further insight into the observed ocular toxicity.

(1) (a) *J. Med. Chem.* **2014**, *57*, 9811-9831. (b) *J. Med. Chem.* **2014**, *57*, 9796-9810. (c) *ACS Med. Chem. Lett*. **2015**, *6*, 210-215. (d) *J. Med. Chem.* **2012**, *55*, 9156-9159. (e) *Bioorg. Med. Chem. Lett.* **2015**, *25*, 767-774

(2) *Toxicol. Pathol.* **2014**, 0192623314553804 (published on-line)